Maternal Anxiety During Pregnancy and the Association With Adverse Perinatal Outcomes:

Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This systematic review and meta-analysis examined the association between maternal antenatal anxiety (AA) and a range of perinatal outcomes.

Data Sources: Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, PsycINFO, CINAHL, Embase, and the Cochrane Library were searched to May 31, 2016, using controlled vocabulary and keywords (eg, *prenatal*, *anxiety*, *preterm*).

Study Selection: Perinatal outcomes of women with and without AA (diagnosed or self-reported using validated scale) derived from English language, prospectively collected data were included. 1,458 abstracts were reviewed, 306 articles were retrieved, and 29 articles were included.

Data Extraction: Two independent reviewers extracted data and assessed quality. Random-effects models were utilized for outcomes (≥ 3 studies). Subanalyses examined potential effect moderators including study quality and diagnostic versus self-reported anxiety among others.

Results: Antenatal anxiety was associated with increased odds for preterm birth (pooled odds ratio [OR] = 1.54; 95% confidence interval [CI], 1.39 to 1.70, 16 studies) and spontaneous preterm birth (OR = 1.41; 95% CI, 1.13 to 1.75), lower mean birth weight (mean difference = −55.96 g; 95% CI, −93.62 to −18.31 g), increased odds for low birth weight (OR = 1.80; 95% CI, 1.48 to 2.18), earlier gestational age (mean difference = −0.13 wk; 95% CI, −0.22 to −0.04 wk), increased odds for being small for gestational age (OR = 1.48; 95% CI, 1.26 to 1.74), and smaller head circumference (mean difference = −0.25 cm; 95% CI, −0.45 to −0.06 cm). Heterogeneity between studies was not significant for most outcomes. Subanalyses for birth weight found women with diagnosed anxiety had infants with significantly lower birth weight ($P < .03$) compared to those identified with rating scales (although both subanalyses were significant [$P < .01$]). Associations between anxiety and preeclampsia, cesarean delivery, and Apgar scores were nonsignificant.

Conclusions: Antenatal anxiety is associated with multiple adverse perinatal outcomes and is not benign. The impact of treating anxiety on these associations is unknown.

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Anxiety disorders are widespread psychiatric disorders appearing across the lifespan, including during pregnancy (the pooled prevalence during pregnancy is 15.2% for any anxiety disorder and 22.9% for anxiety symptoms).[1] Some studies suggest elevated rates of certain anxiety disorders such as generalized anxiety disorder (8.5%–9.5%)[2,3] compared to rates in the general population (3.1%)[4] over 1 year. As the disorders are common, understanding their effects on maternal and infant outcomes is important, yet studies to date[5,6] have not provided uniform conclusions, resulting in a lack of information critical to evidence-based treatment decisions for anxiety during pregnancy.

Attention has historically focused on perinatal depression. For example, one systematic review[7] noted 14 studies examining the effect of maternal depression on preterm birth (PTB) and only 4 studies examining maternal anxiety. Although research is beginning to focus on antenatal anxiety, syntheses of its impact on perinatal outcomes have not kept pace. To date, meta-analyses of the effects of anxiety during pregnancy have been narrowly focused on preterm birth[8,9] and low birth weight,[9] and while 2 systematic reviews[10,11] have addressed a broader range of outcomes, results were inconsistent and, with newer published work, need to be readdressed. Given the high prevalence of antenatal anxiety and the preliminary recognition of its negative effect on maternal and infant outcomes, it is important to systematically summarize the literature across diverse outcomes.

Our work addresses the significant gap in the literature by extending previous meta-analytic work to include a broad range of clinically relevant outcomes. The purpose of this systematic review

Clinical Points

- Treatment decisions for women with anxiety during pregnancy must consider the risks of anxiety itself on mothers and their infants, yet current understanding of these risks is incomplete.
- Anxiety during pregnancy is associated with several negative birth outcomes, and pregnant women should therefore be screened for anxiety and be informed about these risks.

and meta-analysis was to synthesize available data on the association between exposure to antenatal anxiety and the risk of various perinatal outcomes. We pooled results from studies comparing outcomes in pregnancies exposed and unexposed to maternal anxiety. Moreover, we examined the potential effect of variables that may account for heterogeneity as modifying variables on outcomes such as a diagnosis of anxiety versus anxiety measured by rating scales, among others.

METHODS

Search Strategy and Selection Criteria

We conducted a systematic review and meta-analyses following the guidelines of the Meta-Analysis Of Observational Studies in Epidemiology group,[12] using methods previously described.[13] Briefly, the review was guided by an advisory committee of key stakeholders. Independent literature searches were conducted by 2 professional librarians with expertise in psychiatry and psychopharmacology. As part of a broader search for studies of the impact of antenatal anxiety and medication use, 1 librarian searched Ovid MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, PsycINFO, CINAHL, Embase, and the Cochrane Library from their start date to May 31, 2016. Keywords included, but were not limited to, *anxiety/phobia, posttraumatic stress disorder, panic disorder, obsessive compulsive disorder, pregnancy, prenatal or antenatal, congenital malformations, cardiac malformation, preterm birth or premature delivery, low birth weight, birth weight, gestational age, Apgar, NICU, neonatal/infant outcomes, delivery outcomes,* and *preeclampsia*. The second experienced medical information specialist's search strategy was developed and tested through an iterative process in consultation with the review team, and the same databases were searched. This core strategy was reviewed prior to execution by another senior information specialist using the Evidence Based Checklist for the Peer Review of Electronic Search Strategies.[14] Strategies utilized a combination of controlled vocabulary (eg, *pregnancy*, *anxiety disorders*) and keywords (eg, *prenatal*, *anxiety*, *preterm*) (full search strategy available from the authors upon request). Vocabulary and syntax were adjusted across databases. Results were limited to the English language, removing animal-only records and opinion pieces. Reference lists of reviews and meta-analyses were also searched. We followed the PRISMA statement for reporting systematic reviews and meta-analyses.[15]

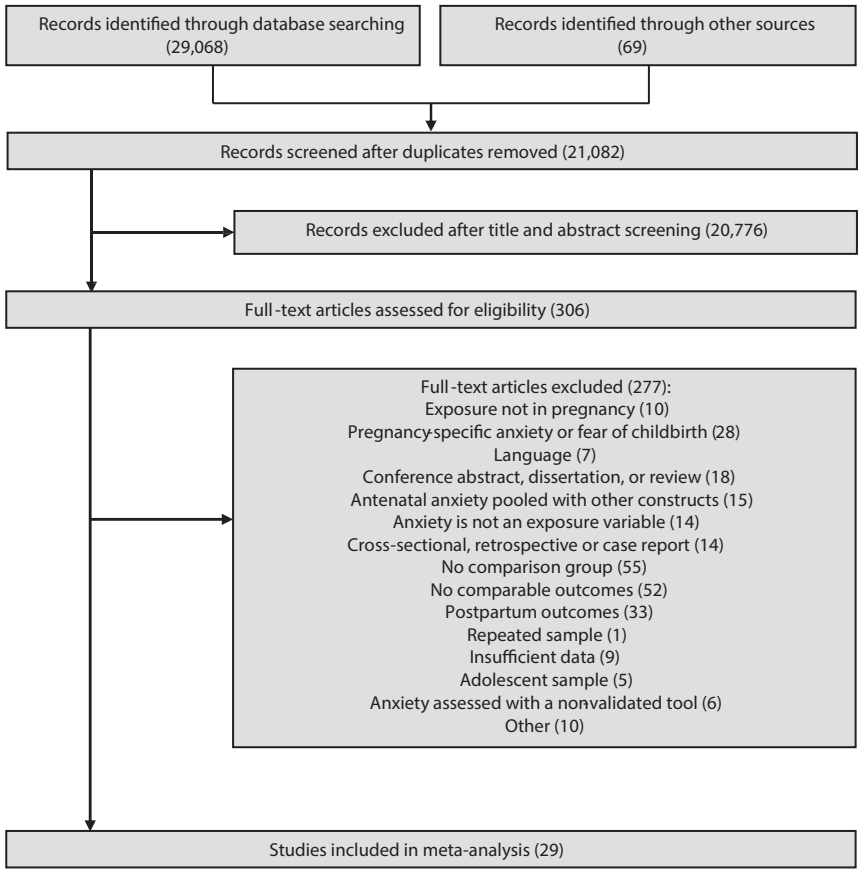
Original prospectively collected data with an assessment of maternal anxiety any time during pregnancy and an unexposed comparison group of pregnant women without anxiety were considered. Maternal anxiety required either a clinical diagnosis of any anxiety disorder or use of a validated self-report anxiety measure with a cutoff score for high anxiety. Pregnancy-specific or pregnancy-related anxiety was not considered, as it is believed to represent a distinct concept not well measured by current scales.[16] Outcomes in the infant or mother in the gestational and delivery periods were acceptable. When a sample was repeated in more than one publication, the article providing the most valid data relevant to our research question was chosen. One article presented 2 time points; as both were from the second trimester, the second time point with the larger sample size was used. For cases in which antenatal anxiety was assessed using multiple self-report measures, data representing the largest sample size were included. We excluded studies that pooled antenatal and postpartum anxiety scores, studies with adolescent samples, abstracts, conference proceedings, and unpublished data. Two reviewers independently screened all titles and abstracts and retrieved all eligible studies. Requests for raw data, clarification of methodology, or data analysis were sent to 9 authors; 4 responses were received.

Data Analysis

The quality assessment and data extraction methods were based on previously published methodology developed by our team.[13] Two reviewers conducted quality assessments and extracted data. Disagreements were resolved on a case-by-case basis by discussion with the study leads (S.G., L.G.), until consensus was reached. Study quality was assessed with the Systematic Assessment of Quality in Observational Research (SAQOR),[13] adapted from the Downs and Black[17] checklist and the Newcastle-Ottawa Scale.[18] Articles were assessed under the following categories: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences/control for confounders. Based on the SAQOR criteria and a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system,[19] each article was assigned a quality rating of high, moderate, low, or very low quality, further dichotomized into "above quality threshold" (high, moderate, and low) and "below quality threshold" (very low).

Data extraction procedures were based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[20] Extracted data included authors, year of publication, source country, details of study design, participants (sample, control, demographics, and clinical characteristics), inclusion/exclusion criteria, method and type of anxiety assessment, timing of anxiety assessment, outcomes and their assessment methods and definitions, statistical adjustment for confounders, and loss to follow-up. Adjusted estimates with their variances were extracted when available; when adjusted estimates were not provided in the published data, we calculated crude odds ratios or mean differences and sample variances. Before

Figure 1. Identification of Studies for Inclusion in the Meta-Analysis of the Association of Antenatal Anxiety With Perinatal Outcomes



calculating the odds ratio for studies that included cells with a 0 count, we added 0.5 to these cells. Data were extracted by one reviewer and checked by another and the primary author (S.G.); disagreements were resolved by the primary author. Outcomes were as defined by the authors of the original publication.

DerSimonian and Laird[21] random effects models were used to pool estimates of the odds ratio for binary outcomes and the weighted mean difference for continuous outcomes. In the few instances in which relative risks were given, they were treated as odds ratios, given that events were typically rare. We visually inspected funnel plots portraying individual study estimates (on the log scale for odds ratios) against their standard error to assess for the possibility of publication bias. The Egger weighted regression method was used to formally test for publication bias.[22] Cochrane Q and visual inspection of forest plots were used to assess between-study heterogeneity, which was then quantified by I^2, the percentage of the observed between-study variance in effects that is in excess of what is expected due to chance. Larger values of I^2 suggest that the effect varies quantitatively from study to study. The amount of heterogeneity may be characterized as low, moderate, or high ($I^2 = 25\%$, 50%, or 75%, respectively).[23] However I^2 does not indicate qualitative variation, whether the direction of the effect varies—high heterogeneity in the size of an effect can still exist in the context of a large degree of certainty about the direction of the effect.

Regardless of the statistical significance of the Q statistic for an outcome, we explored sources of heterogeneity through subgroup analyses as they were planned a priori. These subgroup analyses examined within-group effects and between-group differences in pooled effects based on the following study characteristics: (1) study quality above versus below threshold; (2) anxiety identification using clinical diagnosis versus validated self-report measure with cutoff score; (3) adjusted versus unadjusted estimates; (4) antenatal assessment time; (5) registry versus non-registry data; and (6) source country. Additional subgroup analyses were completed for the following outcomes when data were available: (1) controlling for depression (preterm birth); (2) effect of specific anxiety diagnoses (preterm birth); (3) adjustment for gestational age (birth weight); and (4) percentile threshold (small for gestational age). Fixed-effects models were used in analyses with < 3 articles. Statistical analyses were completed with the metafor package in R (3.3.2) and similar to our other work.[24] Forest plots were generated with Review Manager (RevMan) 5.3 for Windows (Review Manager version 5.3, Cochrane Collaboration, http://tech.cochrane.org/revman).

RESULTS

Of the 1,458 articles for which abstracts were reviewed, 1,152 were excluded based on title and abstract. Of the remaining 306 retrieved and assessed articles, 29 studies met the inclusion criteria (Figure 1) and were included in meta-analyses[5,6,25–51]; 16 were above quality threshold and 13 were below. Detailed study characteristics are provided in Table 1. Suitable data were available for a total of 11 outcomes.

In 16 pooled studies, maternal antenatal anxiety was significantly associated with preterm birth (odds ratio [OR] = 1.54; 95% CI, 1.39 to 1.70; $P < .0001$; Figure 2A). Heterogeneity across studies was not significant ($Q_{15} = 11.71$, $P = .70$; $I^2 = 0\%$) as were none of the moderator variables (Table 2). Five studies with women experiencing antenatal posttraumatic stress disorder/symptoms specifically pooled to an OR similar to the main analyses and no heterogeneity (OR = 1.41; 95% CI, 1.20 to 1.67, $P < .01$). Regarding spontaneous preterm birth, 5 studies pooled to a significant effect (OR = 1.41; 95% CI, 1.13 to 1.75; $P < .01$; Figure 2B), similar in magnitude to the main analysis, without heterogeneity. Interestingly, the moderators registry/non-registry data and source country crossed the significance threshold (both $Q_1 = 3.80$, $P = .05$), but the subgroups contained only 2 or 3 studies, while identification of anxiety by diagnostic versus non-diagnostic (self-report) measures approached borderline significance ($Q_1 = 3.23$, $P = .07$); the remainder of the moderator analyses were not significant (Table 2).

Antenatal anxiety was associated with lower infant birth weight (continuous variable, 12 studies, mean difference = −55.96 g; 95% CI, −93.62 to −18.31 g; $P = .004$; Figure 2C). Significant heterogeneity across studies was present, accounting for 47% of the variance ($Q_{11} = 20.83$, $P = .04$; $I^2 = 47\%$). Infants of mothers experiencing diagnosed clinical anxiety were lower in birth weight than those whose mothers' anxiety was assessed using a self-reported measure (mean difference = −143.47 g [95% CI, −240.27 to −46.67 g] versus −30.42 g [−51.87 to −8.97 g]; $Q_1 = 4.99$, $P = .03$; Table 2). An additional subanalysis examining adjustment for gestational age as a potential moderator was not significant.

The outcome "low birth weight" (typically defined as < 2,500 g, 11 studies, OR = 1.80; 95% CI, 1.48 to 2.18; $P < .00001$; Figure 2D) was significant, but heterogeneity across studies was not ($Q_{10} = 10.19$, $P = .42$; $I^2 = 2.0\%$). Although data from non-registry studies pooled to a considerably higher odds ratio (2.09) compared to registry studies (1.42) with a significant moderator ($Q_1 = 3.75$, $P = .05$), both subanalyses were significant (Table 2).

Among 8 studies, gestational age (GA) at birth pooled to a significant effect (mean difference = −0.13 weeks; 95% CI, −0.22 to −0.04, $P = .004$; Figure 2E). Heterogeneity was not significant ($Q_7 = 7.11$, $P = .42$; $I^2 = 2\%$), nor were any of the subgroup analyses (Table 2). The variable "small for gestational age" (SGA) was significantly associated with maternal anxiety (7 studies, OR = 1.48; 95% CI, 1.26 to 1.74; $P < .0001$; Figure 2F). Heterogeneity was not significant ($Q_6 = 3.05$, $P = .80$; $I^2 = 0\%$), nor were any of the moderators (Table 2) including the definition of SGA (birth weight below 15th, 10th, or 2.5th percentile for GA). Smaller head circumference was also a significant outcome (4 studies, mean difference = −0.25 cm; 95% CI, −0.45 to −0.06 cm; $P = .012$. Figure 2G), and heterogeneity across studies was not significant ($Q_3 = 2.27$, $P = .52$; $I^2 = 0\%$), nor were there any significant moderators (Table 2).

Apgar scores at 1 and 5 minutes did not pool to significant estimates. Four studies (OR = 1.70, 95% CI, 0.90 to 3.23; $P = .10$; Figure 3A) with minimal heterogeneity were used for the 1-minute score ($Q_3 = 4.83$, $P = .18$; $I^2 = 38\%$) and 5 studies for the 5-minute outcome (OR = 2.68; 95% CI, 0.75 to 9.67; $P = .13$; Figure 3B); heterogeneity was slightly greater for the latter analysis ($Q_4 = 8.91$, $P = .06$; $I^2 = 55\%$). Exposure to prenatal maternal anxiety was not significantly associated with preeclampsia (4 studies, OR = 3.30; 95% CI, 0.56 to 19.37; $P = .19$; Figure 3C); however, there was significant heterogeneity across studies, accounting for 78% of the variance ($Q_3 = 13.63$, $P < .01$; $I^2 = 78\%$). None of the moderator subanalyses were significant (Table 2).

Based on 4 studies, exposure to antenatal anxiety was not associated with delivery by cesarean section (OR = 1.01, 95% CI, 0.46 to 2.25; $P = .97$; Figure 3D), although there was significant heterogeneity accounting for 82.1% of the variance ($Q_3 = 20.26$, $P < .01$; $I^2 = 85.0\%$). A number of moderator variables emerged as significant, including adjustment for confounders, anxiety assessment time, use of registry versus non-registry data, and country (Table 2), but the majority of subanalyses contained too few studies. When there was a sufficient number of studies in the subanalysis for meaningful interpretation (ie, > 3 studies), the ORs were not significant.

The assessment of publication bias was possible only for preterm birth, low birth weight, and birth weight, as data were not sufficient to produce a funnel plot for other outcomes. There was no evidence of asymmetry based on visual inspection, and the Egger test was not statistically significant for the aforementioned outcomes.

DISCUSSION

To our knowledge, this is the first meta-analysis to examine a wide range of perinatal outcomes in relation to maternal anxiety during pregnancy. We found significant associations between antenatal anxiety and 7 of the 11 perinatal outcomes including preterm and spontaneous preterm birth, low birth weight and birth weight, gestational age, small for gestational age, and head circumference at birth. These observed associations were consistently significant, with little heterogeneity and few moderators significantly affecting the relationship. Only in studies that examined birth weight did we find significant between-studies heterogeneity among those that included a clinical diagnosis of anxiety versus those that included a self-report measure. This was also seen (albeit at a trend level) in the analysis for spontaneous preterm birth and is a noteworthy

Table 1. Study Details of 29 Studies Included in the Meta-Analysis

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Andersson et al,[25] 2004[A]; Sweden	Anxious in second trimester: n = 64 Not anxious: n = 1,261	Inclusion: undergoing routine second trimester ultrasound, singleton, live births, complete medical records Exclusion: malformation of the fetus, "missed spontaneous abortion at the ultrasound examination," "inability to read and understand the questionnaire," not consenting, and bipolar disorder (diagnosed with PRIME-MD) Use of antenatal psychotropic medication was possible (2 noted), as was comorbidity	Diagnosis: PRIME-MD, 1–2 weeks after ultrasound, telephone interview (included anxiety not otherwise specified, a subthreshold diagnosis, found to be the most common diagnosis)	All outcomes adjusted for age, marital status, SES, smoking habits, and BMI	PTB: < 37 weeks' completed gestation Spontaneous PTB: "rupture of membranes and/or premature labor before 37 completed weeks of gestation" LBW: BW < 2,500 g SGA: BW below 2.5th percentile for expected weight for GA in Sweden (boys: 3,629 g; girls: 3,505 g) Apgar 5 min: < 4 Apgar 1 min: < 4	PTB: 3/64 in anxious vs 65/1,261 in not anxious (aOR = 1.02; 95% CI, 0.3 to 3.45) Spontaneous PTB: 1/64 vs 37/1,261 (aOR = 0.61; 95% CI, 0.08 to 4.61) LBW: 2/64 vs 28/1,261 (aOR = 1.66; 95% CI, 0.36 to 7.75) SGA: 2/64 vs 18/1,261 (aOR = 1.32; 95% CI, 0.26 to 6.66) Apgar 5: 0/64 vs 4/1,261 (aOR = 0.06; 95% CI not given) Apgar 1: 2/64 vs 15/1,261 (aOR = 3.82; 95% CI, 0.82 to 17.82)
Berle et al,[26] 2005[B]; Norway[#]	Anxious during pregnancy: n = 71 Not anxious: n = 609	Inclusion: women who participated in the HUNT-2 population survey and who gave birth within 40 weeks after participating Exclusion: none stated Use of antenatal psychotropic medication was possible (≤ 3 in each trimester), as was comorbidity	HADS score ≥ 8 – used as caseness for HADS-defined anxiety disorder	PTB, LBW, Apgar 5 min and Apgar 1 min outcomes: unadjusted Adjusted data not presented, authors stated adjustment had no effect on results	PTB: < 37 weeks (259 days) LBW: BW < 2,500 g Apgar 5 min: < 8 Apgar 1 min: < 8	PTB: 3 in anxious vs 19 in not anxious (OR = 1.24; 95% CI, 0.62 to 2.8) LBW: 4/71 vs 17/609 (OR = 2.08; 95% CI, 0.68 to 6.36) Apgar 5 min: 4/71 vs 8/609 (OR = 4.49; 95% CI, 1.32 to 15.29) Apgar 1 min: 10/71 vs 41/609 (OR = 2.27; 95% CI, 1.08 to 4.76)
Bindt et al,[27] 2013[A]; Côte d'Ivoire and Ghana	Anxious in third trimester: n = 102 Not anxious: n = 614	Inclusion: third trimester, residing within distance of 5 km of hospitals and live births Exclusion: <18 years of age, multiple pregnancies, chronic physical diseases, severe pregnancy complications due to diabetes, hemorrhage, hypertension, preeclampsia (ie, low-obstetric risk cohort only) Antenatal psychotropic medication not prescribed but unknown if preexisting, comorbidity possible	Generalized Anxiety Disorder 7-item Scale score ≥ 10	PTB outcome adjusted for country, SES, and maternal vaginal infection BW outcome adjusted for country, SES, maternal age, child sex LBW, GA, Apgar 5 min, head circumference, and C-section outcomes were unadjusted	PTB: GA < 37 weeks LBW: BW < 2,500 g Apgar 5 min: < 7 C-section	PTB: 5/102 in anxious vs 16/614 in not anxious (aOR = 1.8; 95% CI, 0.6 to 5.5) LBW: 0/102 vs 12/614 BW, mean (SD), g: 3,191.2 (426.5) in anxious vs 3,168.8 (443.5) in not anxious (β = 17.1; 95% CI, −74.6 to 108.7, *P* = .72) GA, mean (SD), wk: 39.5 (2.1) in anxious vs 39.6 (1.9) in not anxious Head circumference, mean (SD), cm: 33.2 (1.5) in anxious vs 33.4 (1.8) in not anxious Apgar 5 min: 2/102 vs 0/614 C-section: 20/102 vs 111/614

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Broekman et al,[28] 2014[B]; Singapore	Anxious in 26th–28th weeks of gestation: n = 155 (fifth quintile, STAI score > 87) Low anxiety score: n = 180 (first quintile, STAI score ≤ 53)	Inclusion: naturally conceiving women, of Chinese, Malay, or Indian ethnicity (parental ethnic background homogeneous too; homogeneous ethnicity of the child, "ie, all the 6 persons are from the same race"), Singaporean citizen or Singapore permanent resident of age ≥ 18 years, intending to deliver in the involved hospitals and to live in Singapore for 5 years following, attending the first trimester antenatal ultrasound scan, delivered infant at term (gestational age of 37–40 weeks) Exclusion: major medical complications (eg, type 1 diabetes and cancer), taking psychotropic medication, women with complicated obstetric complications (stillbirths, in vitro fertilization, multiple births), did not receive a mental health screening, women with missing gestational age data Comorbidity possible	STAI score > 87, reflecting the top quintile	BW and head circumference outcomes adjusted for ethnicity; maternal age at infant birth; income; history in pregnancy of hypertension, diabetes, cigarette smoking, and alcohol use and maternal height		BW, mean (SE), g: 3,265.81 (92.9) in anxious vs 3,323.14 (94.4) in not anxious Head circumference, mean (SE), cm: 34.49 (0.31) vs 34.26 (0.31) in not anxious
Brouwers et al,[29] 2001[B]; Netherlands	High anxiety in third trimester: n = 20 Not high anxiety: n = 85 GA: total N = 102, group n not given	Inclusion: women with adequate free thyroxine at 12 weeks' gestation, stratified random sampling further used to get to n = 131 Exclusion: Gemelli (multiple births), gestational diabetes, fertility issues history, premature delivery, missing data; 1 woman and 1 child excluded because of death, another because of repeated suicidal behavior Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-state score ≥ 39 or STAI-trait score ≥ 37, reflecting > 1 SD above the mean, or both	BW, GA, Apgar 5 min, and Apgar 1 min outcomes were unadjusted (confound data collected for other analyses)	Apgar 5 min: < 8 Apgar 1 min: < 6	BW, mean (SD), g: boys, 3,458 (473) and girls, 3,402 (496) in anxious vs boys, 3,510 (537) and girls, 3,497 (604) in not anxious GA, mean (SD), wk: 39.4 (2.1) vs 39.8 (1.4) Apgar 5 min: 0/20 vs 0/85 Apgar 1 min: 0/20 vs 0/85
Chen et al,[30] 2010[B]; Taiwan[#]	Anxious during pregnancy and within 2 years prior to delivery: n = 317 Not anxious: n = 1,585 (randomly selected, matched 5:1 for age, year of birth, gestational hypertension, diabetes, coronary heart disease, renal disease)	Inclusion: (see *ICD* code description) Exclusion: diagnosed with any other type of mental illness (schizophrenia, major depression, substance abuse/dependence) from *ICD-9-CM* codes 290–319, or other chronic disease, except gestational diabetes, hypertension, hyperlipidemia, renal disease, and coronary heart disease Antenatal use of psychotropic medication unknown	*ICD* code for panic disorder (*ICD-9-CM* code 300.01) ≥ once during pregnancy and 3 consensus previous codes	LBW, PTB, SGA outcomes adjusted for infant sex, parity, age of mother, maternal educational level, difference in parents ages, mother's marital status, monthly income, gestational hypertension, diabetes, renal disease, hyperlipidemia, coronary heart disease Preeclampsia outcome adjusted for same as above outcomes with the addition of father's education level instead of difference in parents' age	PTB: < 37 weeks LBW: BW < 2,500 g SGA: BW below 10th percentile for GA Preeclampsia: preeclampsia	PTB: 31/317 in anxious vs 113/1,585 in not anxious (aOR = 1.43; 95% CI, 0.94 to 2.19) LBW: 22/317 vs 83/1,585 (aOR = 1.28; 95% CI, 0.78 to 2.09) SGA: 63/317 vs 223/1,585 (aOR = 1.56; 95% CI, 1.13 to 2.14) Preeclampsia: 5/317 vs 20/1,585 (aOR = 1.14; 95% CI, 0.42 to 3.09)

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Clavarino et al,[31] 2010[B]; Australia	Anxious during pregnancy: n = 630 (combined "anxiety during pregnancy but not after," n = 298, and "anxiety all the time," n = 332) Not anxious: n = 2,965 Anxiety in pregnancy measured "… on average 18 weeks of gestation"	Inclusion: live, singleton births Exclusion: none stated Antenatal use of psychotropic medication unknown, comorbidity possible	7-item anxiety subscale of the Delusions Symptoms-States Inventory State of Anxiety and Depression score above the 90th percentile	LBW outcome: unadjusted (confound data collected for other analyses)	LBW: < 2,500 g	LBW: 28.19% of LBW babies were exposed to anxiety during pregnancy (12.75% of the LBW babies were exposed to "anxiety during pregnancy but not after" + 15.44% of LBW babies were exposed to "anxiety all the time") vs 61.74% of LBW babies were not exposed to anxiety in pregnancy
Crandon,[32] 1979[B]; England	High anxiety in third trimester: n = 34 Not high anxiety: n = 112	Inclusion: women in third trimester of pregnancy who have spoken English since childhood Exclusion: none stated Antenatal use of psychotropic medication unknown, comorbidity unknown	Institute for Personality and Ability Testing Anxiety Self-Analysis Form score ≥ 7	Preeclampsia outcome: unadjusted	Preeclampsia: "any persisting diastolic blood pressure of 90 mm Hg or more, provided it developed after the 24th week, in a patient without prior hypertension"	Preeclampsia: 9/34 in anxious vs 2/112 in not anxious
Field et al,[33] 2010[B]; USA	Anxious in second trimester: n = 77 Not anxious: n = 345	Inclusion: none stated Exclusion: < 18 years of age, multiple fetuses, HIV/AIDS status, or medical complications. Also excluded bipolar disorder, schizophrenia or related psychotic disorders, and depressive disorder (diagnosed with SCID) Comorbid depression excluded in data used Antenatal use of psychotropic medication unknown in anxious group	SCID for *DSM-IV* anxiety diagnoses	PTB ("prematurity") and BW outcomes: unadjusted (confound data collected for other analyses)	PTB: "prematurity"	PTB: 10.2% in anxious vs 6.0% in not anxious BW, mean (SD), g: 3,195.76 (347.75) vs 3,352.17 (448.26)
Field et al,[34] 2003[B]; USA	High anxiety in second trimester: n = 66 Low anxiety: n = 66	Inclusion and exclusion: none stated. Recruited at first prenatal visit at about 20 weeks Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-trait score > 38, reflecting a median split	LBW outcome: unadjusted (confound data collected for other analyses)	LBW: < 2,500 g	LBW: 34% in anxious vs 12% in not anxious ($\chi^2 = 7.80$, $P < .01$)
Goldenberg et al,[35] 1991[B]; USA	High vs low anxiety in second trimester: n = not clear Total group possible n = 1,545	Inclusion: "mixed black-white indigent group of women who delivered between 1986 and 1988," multiparous, with known risk factors for IUGR (smoking, use of alcohol, low maternal weight and height, and past LBW infant) Exclusion: multiple births Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-trait; "after observing the range of scores on each scale, the groups were divided into high and low categories"	Adjusted for "maternal cigarette smoking, educational level, age, height, and weight"	SGA: "infants born weighing < the 15th percentile BW for GA based on Alabama standards for race, infant sex, and parity" Categorized as IUGR by original authors	SGA: aOR = 1.47 (95% CI, 1.05 to 2.05) Categorized as SGA in our analyses
Groome et al,[36] 1995[B]; USA	High anxiety in third trimester: n = 9 Low anxiety in third trimester: n = 9	Inclusion: pregnant, nonsmoking, between 38 and 40 weeks' gestation Exclusion: "any maternal or fetal complication, including hypertension (chronic or pregnancy-related), diabetes mellitus (preexisting or gestational), suspected fetal growth restriction, a fetal structural anomaly on ultrasound, or a maternal history of substance abuse" Antenatal use of psychotropic medication unknown, comorbidity unknown	STAI median split, specific cutoff score used not stated	BW outcome: unadjusted		BW, mean (SD), g: 3,648 (464) in anxious and 3,514 (403) in low anxiety

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Henrichs et al,[37] 2010[A]; Netherlands	Anxious at 20 weeks: n = 937 Not anxious: n = 5,376	Inclusion: Generation R cohort, due dates between April 2002 and January 2006, living in the Rotterdam area Exclusion: fetal deaths and twin pregnancies, and for those with multiple pregnancies, data on second or third pregnancy enrolled excluded Antenatal use of psychotropic medication unknown, comorbidity possible	Anxiety subscale of the Brief Symptom Inventory, top 15%	BW outcome adjusted for GA at birth, "fetal sex, maternal age, height, BMI, education level, ethnicity, smoking during pregnancy, parity, gestational diabetes, hypertension in pregnancy, preeclampsia," and family stress		BW: β = −37.73 (95% CI, −69.22 to −6.25)
Ibanez et al,[38] 2012[B]; France	Anxious at 24–28 weeks: n = 135 Not anxious: n = 1,154	Inclusion: women who were less than 20 weeks' pregnant Exclusion: multiple pregnancy, history of diabetes, not able to read French, planning to deliver in other maternity ward, planning to leave study region (within next 3 years), stillbirth, fetal malformation, and high prenatal depressive symptoms (measured by Center for Epidemiologic Studies Depression Scale at 24–28 weeks' gestation) Comorbid depression excluded in data used Antenatal use of psychotropic medication unknown	STAI-state score ≥ 37, reflecting the 80th percentile	Analyses differed in adjustments and may have included: newborn's sex, maternal age, education level, parity, pre-pregnancy BMI, prenatal smoking, hypertension during pregnancy, the maternity unit, and gestational age	PTB: < 37 weeks SGA: BW below the 10th customized percentile Spontaneous preterm birth: spontaneous preterm labor or preterm premature rupture of membranes	PTB: 8/135 in anxious vs 58/1,154 in not anxious (aOR = 1.14; 95% CI, 0.52 to 2.49) SGA: 20/135 vs 129/1,154 (aOR = 1.26; 95% CI, 0.75 to 2.13) BW, mean (SD), g: 3,256 (540) vs 3,278 (484) (adjusted mean [SD]: 3,180 [540] in anxious vs 3,185 [481] in not anxious) GA, mean (SD), wk: 39.1 (2.1) vs 39.3 (1.6) [adjusted mean (SD): 38.6 (2.2) in anxious vs 38.8 (1.6) in not anxious] Spontaneous PTB: 3/135 in anxious vs 34/1,154 in not anxious (aOR = 0.74; 95% CI, 0.22 to 2.45)
Khashan et al,[39] 2014[A]; Ireland (recruitment from New Zealand, Australia, 3 centers in United Kingdom, Ireland)	Anxious in second trimester: n = 531 Not anxious in second trimester: n = 1,836 Data used from 20 ± 1 weeks of gestation	Inclusion: nulliparous, healthy women, singleton pregnancies Exclusion: none stated Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-short form score: top 10th percentile vs lowest 25th percentile	SGA analyses adjusted for: BMI, age, smoking, family income, maternal education, ethnicity," plus "cluster effect" (ie, site)	SGA: "BW below the 10th customized percentile"	SGA: 80/531 in anxious vs 184/1,836 in not anxious (aOR = 1.45; 95% CI, 1.13 to 1.86)

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Lilliecreutz et al,[40] 2011[A]; Sweden	Anxious in second trimester: n = 110 Not anxious in second trimester: n = 220 (randomly stratified for age and parity) Screened at 12–16 weeks of gestation (not clear when diagnosis made)	Inclusion: women approached in 12th–16th week of pregnancy Exclusion: inability to understand Swedish, and women with intrauterine fetal death, twins, and cesarean deliveries due to preeclampsia 3 women using selective serotonin reuptake inhibitors (1 in index and 2 in control group)	Injection Phobia Scale Anxiety score ≥ 20 was used to screen, followed by diagnosis of blood and injection phobia according to *DSM-IV* criteria (by phone)	PTB, cesarean section, SGA, breastfeeding, and preeclampsia outcomes were adjusted for "sociodemographic factors," smoking and psychiatric history (but unclear which are the "sociodemographic factors") GA outcome unadjusted (did conduct adjusted analysis but only *P* value presented)	PTB: < 37 completed weeks of gestation SGA: "BW less than 2 SD below the mean weight for gestational length according to Swedish standard" Preeclampsia: preeclampsia C-section: acute cesarean section and elective cesarean section	PTB: 8/110 in anxious vs 5/220 in not anxious (aOR = 3.58; 95% CI, 1.01 to 12.67; *P* = .047) SGA: 5/110 vs 1/220 (aOR = 6.45; 95% CI, 1.05 to 39.50; *P* = .044) GA, mean (SD), wk: 39.1 (2.2) vs 39.5 (1.8) (*P* = .079) Preeclampsia: 6/110 vs 2/220 (aOR = 10.39; 95% CI, 1.84 to 58.56; *P* = .008) C-section: 19/106 vs 34/220
McDonald et al,[41] 2014[B]; Canada	Anxious in second trimester: n = 445 Not anxious in second trimester: n = 2,429	Inclusion: less than 24 weeks and 6 days' gestation age at the time of recruitment, at least 18 years of age, receiving prenatal care in Calgary, and able to complete the questionnaires in English Exclusion: baby losses (both miscarriages and neonatal/infant loss) Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-state score ≥ 40	PTB outcome was unadjusted (confound data collected for other analyses)	PTB: < 37 weeks' gestation (we combined data on early preterm, < 34 weeks, and late preterm births, 34–36 weeks)	PTB: 47/445 in anxious vs 153/2,429 in not anxious
Männistö et al,[42] 2016[A]; USA	Anxious in pregnancy: n = 689 No psychiatric disorder: n = 206,996	Inclusion: all deliveries between the years 2002 and 2008 at 12 clinical centers with 19 hospitals Exclusion: multifetal pregnancies, errors of identification Comorbid depression (and other psychiatric disorders studied) excluded in data used Antenatal use of psychotropic medication unknown 90.9% provided single data point (ie, 1 pregnancy)	*ICD-9* code for anxiety state diagnosis (*ICD-9* code 300.0) as per electronic medical records or maternal discharge summaries	PTB outcome: adjusted for maternal age, BMI, insurance, marital status, prenatal smoking, prenatal alcohol use or substance abuse, parity, other chronic maternal diseases, clinical site, and other psychiatric disorders in pregnancy	PTB: < 37 weeks' gestation Spontaneous PTB: preterm labor or premature rupture of membranes	PTB: aOR = 1.68; 95% CI, 1.41 to 2.01 Spontaneous PTB: aOR = 1.73; 95% CI, 1.36 to 2.2 (data provided by K. Grantz, MD, personal communication in electronic form, October 13, 2017)
Nasreen et al,[43] 2010[A]; Bangladesh	Anxious in third trimester: n = 149 Not anxious in third trimester: n = 434	Inclusion: singleton, term births Exclusion: emigration from study area, intrauterine death, abortion Antenatal use of psychotropic medication unknown, comorbidity possible	STAI-trait ≥ 46, reflecting the 75th percentile	LBW outcome adjusted for poor household economic status, maternal malnutrition, emotional support during pregnancy, and joint family C-section, BW, and GA outcomes were unadjusted	LBW: < 2,500 g C-section: instrumental by cesarean section	LBW: 43/149 in anxious vs 65/434 in not anxious (aOR = 2.08; 95% CI, 1.32 to 3.29) BW, mean (SD), g: 2,800 (500) vs 2,900 (400) GA, mean (SD), wk: 40.1 (1.4) vs 40 (1.3) C-section: 5/149 vs 31/434

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
O'Donnell et al,[44] 2014[A]; England	High anxiety at 32 weeks: n = 1,213 Low anxiety: n = 6,731	Inclusion: Avon Longitudinal Study of Parents and Children cohort, women residing in Avon, estimated date of delivery April 1, 1991, to December 31, 1992 Exclusion: low birth weight (< 1,500 g), birth before 32 weeks gestation Antenatal use of psychotropic medication unknown, comorbidity possible	Crown Crisp Experiential Index score—top 15% of the sample, specific cutoff score used not provided	GA and BW outcomes were unadjusted (confound data collected for other analyses)		BW, mean (SD), g: 3,431 (511) in anxious vs 3,449 (502) in not anxious GA, mean (SD), wk: 39.47 (1.62) vs 39.6 (1.56)
Pavlov et al,[45] 2014[A]; Israel[#]	Anxious during pregnancy: n = 224 Not anxious during pregnancy: n = 256,088	Inclusion: all deliveries between the years 1989 and 2010 Exclusion: multiple pregnancies, lacking prenatal care Antenatal use of psychotropic medication unknown, comorbidity unknown	"Diagnosis of anxiety disorder was recorded by the admitting physician from the referral information. The diagnosis was made according to the charts, by a psychiatrist or a family physician. All current anxiety diagnoses were included." Anxiety diagnosis criteria unclear but included following author clarification	PTB and cesarean section outcomes adjusted for: maternal age, ethnicity, smoking (preterm only), induction of labor, hypertensive disorders, and diabetes mellitus, premature rupture of membranes, placental abruption, gestational age, and previous C-section (last 3 C-sections only) LBW, Apgar 5 min, and Apgar 1 min outcomes were unadjusted	PTB: preterm labor below 37 weeks and preterm birth LBW: < 2,500 g Apgar 5 min: < 7 Apgar 1 min: < 7 C-section: cesarean section	PTB: 34/224 in anxious vs 20,256/256,088 in not anxious (aOR = 1.92; 95% CI, 1.32 to 2.8) LBW: 25/224 vs 20,487/256,088 Apgar 5 min: 5/224 (2.2%) vs 7,667/256,088 (3%) (OR = 0.74, *P* = .504) Apgar 1 min: 15/224 (6.7%) vs 16,655/256,088 (6.5%) (OR = 1.032, *P* = .907) C-section: 71/224 (31.7%) vs 34,807/256,088 (13.6%) (OR = 2.95, *P* < .001; aOR = 2.5; 95% CI, 1.82 to 3.46)
Peacock et al,[46] 1995[A]; England	High anxiety in second trimester: n = 280 Not high: n = 917 (assessed at "booking"—assumed to be second trimester)	Inclusion: "women booking for antenatal care at St George's Hospital between August 1982 and March 1984," white women Exclusion: poor ability to speak English, age < 15 years, insulin-dependent diabetes mellitus, multiple pregnancy, presentation > 24 weeks' gestation, macerated stillbirths, and severe congenital malformations Antenatal use of psychotropic medication unknown, comorbidity possible	General Health Questionnaire anxiety subscale score ≥ 7	PTB or spontaneous PTB ("spontaneous preterm birth; < 37 completed weeks gestation") outcome was unadjusted (confound data collected for other analyses)	PTB/spontaneous PTB: spontaneous PTB (< 37 weeks' gestation)	PTB: 19/280 in anxious vs 63/917 in not anxious
Rogal et al,[5] 2007[A]; USA	Anxious during pregnancy: n = 31 Not anxious during pregnancy: n = 1,079	Inclusion: "current pregnancy, ability to speak English or Spanish, and enrollment at one of the included prenatal care clinics" Exclusion: none stated Antenatal use of psychotropic medication unknown	PTSD: MINI	PTB and LBW outcomes adjusted for age, race, language, substance use in pregnancy, major depression, minor depression, and panic disorder (psychiatric disorders diagnosed by MINI) GA and BW outcomes were unadjusted	PTB: < 37 weeks LBW: < 2,500 g	PTB: 5/31 (16.1%) in anxious vs 76/1,079 (7.0%) in not anxious; aOR = 2.72; 95% CI, 0.91 to 8.14 LBW: 2/31 (6.5%) vs 70/1,079 (6.5%); aOR = 0.87; 95% CI, 0.18 to 4.17 BW, mean (SD), g: 3,279.1 (519.5) vs 3,288.8 (539.0); *P* = .92 GA, mean (SD), wk: 38.6 (1.8) vs 39.1 (2.0); *P* = .27

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Seng et al,[47] 2011[B]; USA	Anxious during pregnancy: n = 98 Not anxious during pregnancy (and not exposed to trauma and no history of PTSD symptoms): n = 277	Inclusion: age greater than 18 years, expecting first child, able to speak English, initiating prenatal care before 28 weeks Exclusion: miscarriage or elective abortion subsequent to screening interview, multiple gestation, fetal demise, stillbirth or neonatal death Antenatal use of psychotropic medication unknown, comorbidity possible	PTSD: "standardized psychiatric diagnostic interview" using "computer-assisted telephone interview" technology	PTB, LBW, BW, and GA outcomes were unadjusted (confound data collected for other analyses)	PTB: < 37 completed weeks' gestation LBW: < 2,500 g	PTB: 22/98 (22.4%) in anxious vs 48/277 (17.3%) in not anxious LBW: 13/98 (13.3%) vs 24 (8.7%) BW, mean (SD), g: 3,053 (682) vs 3,274 (628) GA, mean (SD), wk: 38.7 (2.8) vs 39.1 (2.5)
Shaw et al,[6] 2014[A]; USA[#]	Anxious during pregnancy: n = 1,679 Not anxious during pregnancy: n = 13,285	Inclusion: all VHA-reimbursed deliveries in fiscal years 2000–2012 Exclusion: women without VHA encounters before delivery, deliveries resulting from irreconcilable data Antenatal use of psychotropic medication existed, comorbidity possible	PTSD: active PTSD cases (diagnosis in any encounter(s) within 9 months before delivery). VHA uses the validated screening instrument (the primary care PTSD screen) plus clinical diagnosis (consistent with *ICD-9-CM* code 309.81)	PTB or spontaneous PTB adjusted for age, race, deployment history, and multiple gestation (data found in Appendices, available online)	PTB: spontaneous onset of delivery before 37 weeks (*ICD-9-CM* diagnosis code 644.2) Spontaneous PTB: spontaneous preterm delivery	PTB: aOR = 1.41; 95% CI, 1.18 to 1.69 Using data for active PTSD within 9 months
Sjöström et al,[48] 1997[A]; Sweden	High anxiety in third trimester: n = 14 Low anxiety in third trimester: n = 23	Inclusion: attending the municipal antenatal clinic in Malmo, Sweden (1988–1989) (subgroup of a larger sample of 93 consecutive nulliparous women); healthy woman; speaking Swedish fluently; no regular medication; and singleton pregnancy Exclusion: delivered before the planned Doppler ultrasound examination at 37 weeks, did not attend the Doppler ultrasound examination for practical reasons, incomplete data concerning stress variables in the third trimester, difficulties in locating middle cerebral artery at the ultrasound examination Comorbidity unknown	STAI-state score ≥ 35 (we combined "low" (20–30) and "medium" (31–34) groups to be the control/not anxious group) [STAI used in this study but larger N in highly anxious STAI-state group used]	BW, SGA and head circumference outcomes: unadjusted (confound data collected for other analyses)	SGA: BW less than 2 SD below the mean of normal	SGA: 1/14 in anxious vs 1/23 in not anxious BW, mean (SD), g: 3,749.3 (678.1) vs 3758.2 (361.2), and 3542.5 (356.6) Head circumference, mean (SD), cm: 35.1 (1.5) vs 35.8 (0.9) and 35.7 (0.6) Low and medium groups were combined for a weighted mean
Teixeira et al,[49] 1999[A]; England	Anxious in third trimester: n = 32 Not anxious in third trimester: n = 68	Inclusion: pregnant women at parentcraft classes with singleton pregnancies between 28 and 32 weeks of gestation Exclusion: "medical disease, including known preeclampsia or antepartum hemorrhage, smoking, previous adverse obstetric outcome such as preterm delivery and small for gestational age baby, assisted conception, abnormal volume of amniotic fluid or abnormal velocity waveforms from the umbilical artery, known small for gestational age fetus (< 5th percentile) on a previous scan, multiple pregnancy," incomplete questionnaires, and unclear uterine velocity waveforms Antenatal use of psychotropic medication unknown as was comorbidity	STAI-trait score > 40 (STAI used but we used STAI-trait score data because they had a larger n)	Preeclampsia outcome was unadjusted		Preeclampsia: 0/32 in anxious vs 4/68 in not anxious

(continued)

Table 1 (continued).

Article; Country	Sample Size	Inclusion/Exclusion Criteria	Anxiety Classification	Confounders/Adjustments	Outcome Definitions	Results
Xiong et al,[50] 2008[A]; USA	Anxious during pregnancy: n = 13 Not anxious during pregnancy: n = 285 Timing in pregnancy not clear	Inclusion: women from New Orleans and Baton Rouge, pregnant during Hurricane Katrina or became pregnant immediately after the hurricane, speaking English, planning to deliver at the study hospitals, > 18 years old, (for New Orleans) resident of area before the storm, and (for Baton Rouge) not having extensive experience of the hurricane (evacuating or having a relative die) Exclusion: none stated Antenatal use of psychotropic medication unknown, comorbidity possible	PTSD Checklist–Civilian Version "a cutoff value of 50 was used to define PTSD"	PTB and LBW outcomes adjusted for maternal age, race, education, parity, smoking, marital status, alcohol use, family income, and history of LBW	PTB: gestational age < 37 weeks LBW: BW < 2,500 g	PTB: 1/13 in anxious vs 28/285 in not anxious (aOR = 0.8; 95% CI, 0.1 to 6.39) LBW: 3/13 vs 26/285 (aOR = 3.1; 95% CI, 0.79 to 12.6)
Yonkers et al,[51] 2014[A]; USA	Anxious during pregnancy: n = 129 Not anxious during pregnancy: n = 2,525	Inclusion: > 18 years, < 17 weeks of pregnancy. "Offered participation to women who had used an antidepressant, experienced a major depressive episode in the last 5 years, or experienced a traumatic event and had symptoms of reexperiencing the trauma. We also randomly selected one third of women without these characteristics to participate as non-exposed comparison." Exclusion: multiple pregnancy, insulin dependent diabetes, did not speak English or Spanish, no access to a telephone, plans to relocate, plans to terminate pregnancy	PTSD: Modified PTSD Symptom Scale, *DSM-III-R* diagnosis generated (data on other diagnoses available)	PTB outcome adjusted for age, race/ethnicity, education, any cigarette use during pregnancy, illegal drug use during pregnancy, heavy alcohol use during pregnancy, psychotropic drug use during pregnancy (serotonin reuptake inhibitors and benzodiazepines), and prior pregnancy outcomes	PTB: delivery prior to 37 completed weeks of pregnancy	PTB: 23/129 in anxious vs 202/2,525 in not anxious (aOR = 1.22; 95% CI, 0.57 to 2.61)

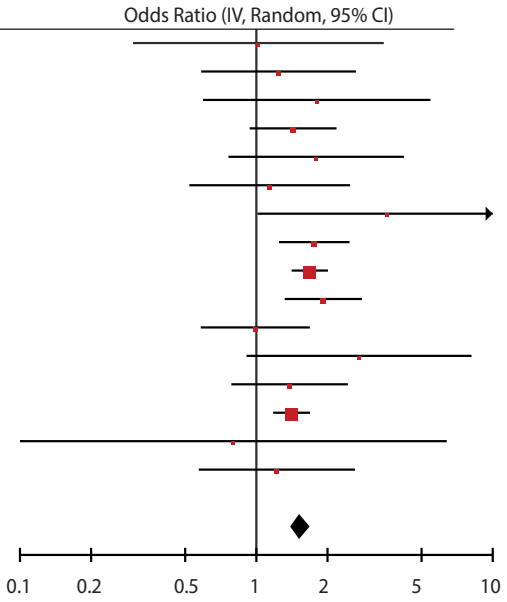
[A]Above quality threshold.
[B]Below quality threshold.
[#]Registry data used.
Abbreviations: aOR = adjusted odds ratio; BMI = body mass index; BW = birth weight; CI = confidence interval; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; *DSM-IV* = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; GA = gestational age; HADS = Hospital Anxiety and Depression Scale; HUNT-2 = The Nord-Trøndelag Health Study; *ICD* = *International Classification of Diseases*; *ICD* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; IUGR = intrauterine growth restriction; LBW = low birth weight; MINI = Mini-International Neuropsychiatric Interview; PRIME-MD = Primary Care Evaluation of Mental Disorders; PTB = preterm birth; PTSD = posttraumatic stress disorder; SCID = Structured Clinical Interview for *DSM-IV*; SES = socioeconomic status; SGA = small for gestational age; STAI = State-Trait Anxiety Index; UK = United Kingdom; USA = United States of America; VHA = Veterans Health Administration.

Figure 2. Significant Pool Associations Between Antenatal Anxiety and Perinatal Outcomes

A. Preterm Birth Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	0.7	1.02 (0.30 to 3.46)
Berle et al, 2005[26]	1.8	1.24 (0.58 to 2.64)
Bindt et al, 2013[27]	0.8	1.80 (0.59 to 5.45)
Chen et al, 2010[30]	5.6	1.43 (0.94 to 2.18)
Field et al, 2010[33]	1.4	1.79 (0.76 to 4.21)
Ibanez et al, 2012[38]	1.6	1.14 (0.52 to 2.49)
Lilliecreutz et al, 2011[40]	0.6	3.58 (1.01 to 12.68)
McDonald et al, 2014[41]	8.4	1.76 (1.25 to 2.48)
Männistö et al, 2016[42]	31.8	1.68 (1.41 to 2.01)
Pavlov et al, 2014[45]	7.0	1.92 (1.32 to 2.80)
Peacock et al, 1995[46]	3.5	0.99 (0.58 to 1.68)
Rogal et al, 2007[5]	0.8	2.72 (0.91 to 8.13)
Seng et al, 2011[47]	3.1	1.38 (0.78 to 2.44)
Shaw et al, 2014[6]	30.9	1.41 (1.18 to 1.69)
Xiong et al, 2008[50]	0.2	0.80 (0.10 to 6.39)
Yonkers et al, 2014[51]	1.7	1.22 (0.57 to 2.61)
Total (95% CI)	**100.0**	**1.54 (1.39 to 1.70)**

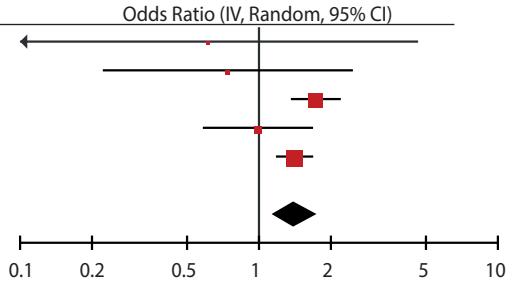
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{15} = 11.71$ ($P = .70$); $I^2 = 0\%$
Test for overall effect: $Z = 8.50$ ($P < .00001$)



B. Spontaneous Preterm Birth Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	1.1	0.61 (0.08 to 4.63)
Ibanez et al, 2012[38]	3.1	0.74 (0.22 to 2.47)
Männistö et al, 2016[42]	36.6	1.73 (1.36 to 2.20)
Peacock et al, 1995[46]	13.4	0.99 (0.58 to 1.68)
Shaw et al, 2014[6]	45.7	1.41 (1.18 to 1.69)
Total (95% CI)	**100.0**	**1.41 (1.13 to 1.75)**

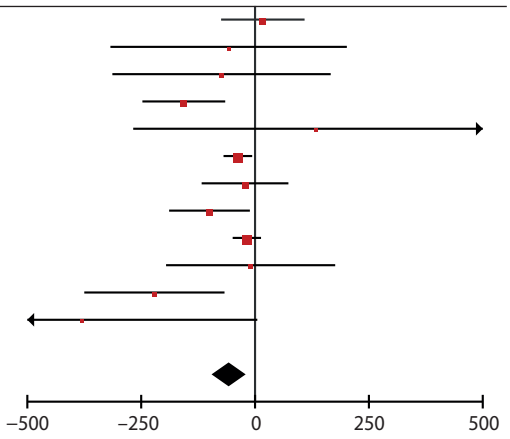
Heterogeneity: $\tau^2 = 0.02$; $\chi^2_4 = 6.04$ ($P = .20$); $I^2 = 34\%$
Test for overall effect: $Z = 3.08$ ($P = .002$)



C. Birth Weight (grams) Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Mean Difference (IV, Random, 95% CI)
Bindt et al, 2013[27]	10.3	17.10 (−74.55 to 108.75)
Broekman et al, 2014[28]	1.9	−58.00 (−317.59 to 201.59)
Brouwers et al, 2001[29]	2.3	−73.58 (−313.29 to 166.14)
Field et al, 2010[33]	10.4	−156.41 (−247.35 to −65.47)
Groome et al, 1995[36]	0.9	134.00 (−267.52 to 535.52)
Henrichs et al, 2010[37]	22.2	−37.73 (−69.21 to −6.25)
Ibanez et al, 2012[38]	9.8	−22.00 (−117.28 to 73.28)
Nasreen et al, 2010[43]	10.7	−100.00 (−188.67 to −11.33)
O'Donnell et al, 2014[44]	22.3	−18.00 (−49.16 to 13.16)
Rogal et al, 2007[5]	3.6	−9.70 (−195.38 to 175.98)
Seng et al, 2011[47]	4.9	−221.00 (−374.95 to −67.05)
Sjöström et al, 1997[48]	0.9	−380.66 (−766.30 to 4.98)
Total (95% CI)	**100.0**	**−55.96 (−93.62 to −18.31)**

Heterogeneity: $\tau^2 = 1405.49$; $\chi^2_{11} = 20.83$, ($P = .04$); $I^2 = 47\%$
Test for overall effect: $Z = 2.91$ ($P = .004$)



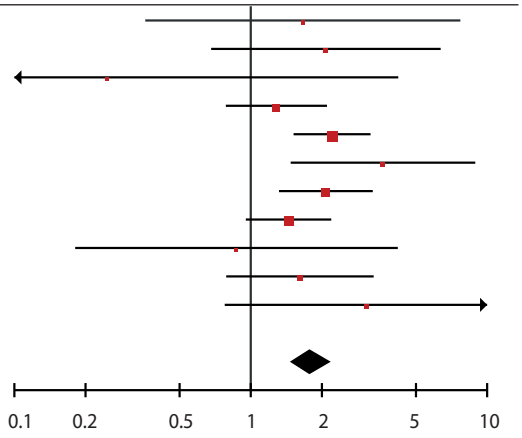
(continued)

Figure 2 (continued).

D. Low Birth Weight Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	1.6	1.66 (0.36 to 7.70)
Berle et al, 2005[26]	3.0	2.08 (0.68 to 6.36)
Bindt et al, 2013[27]	0.5	0.25 (0.01 to 4.21)
Chen et al, 2010[30]	15.2	1.28 (0.78 to 2.10)
Clavarino et al, 2010[31]	25.6	2.21 (1.52 to 3.21)
Field et al, 2003[34]	4.7	3.63 (1.48 to 8.91)
Nasreen et al, 2010[43]	17.6	2.08 (1.32 to 3.28)
Pavlov et al, 2014[45]	21.0	1.44 (0.95 to 2.19)
Rogal et al, 2007[5]	1.5	0.87 (0.18 to 4.19)
Seng et al, 2011[47]	7.3	1.61 (0.79 to 3.31)
Xiong et al, 2008[50]	2.0	3.10 (0.78 to 12.38)
Total (95% CI)	**100.0**	**1.80 (1.48 to 2.18)**

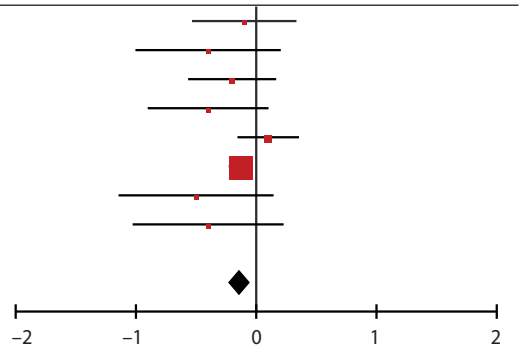
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{10} = 10.19$, ($P = .42$); $I^2 = 2\%$
Test for overall effect: $Z = 5.88$ ($P < .00001$)



E. Gestational Age (weeks) Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Mean Difference (IV, Random, 95% CI)
Bindt et al, 2013[27]	4.1	−0.10 (−0.53 to 0.33)
Brouwers et al, 2001[29]	2.2	−0.40 (−1.00 to 0.20)
Ibanez et al, 2012[38]	5.8	−0.20 (−0.57 to 0.17)
Lilliecreutz et al, 2011[40]	3.1	−0.40 (−0.90 to 0.10)
Nasreen et al, 2010[43]	11.7	0.10 (−0.16 to 0.36)
O'Donnell et al, 2014[44]	69.2	−0.13 (−0.23 to −0.03)
Rogal et al, 2007[5]	1.9	−0.50 (−1.14 to 0.14)
Seng et al, 2011[47]	2.0	−0.40 (−1.03 to 0.23)
Total (95% CI)	**100.0**	**−0.13 (−0.22 to −0.04)**

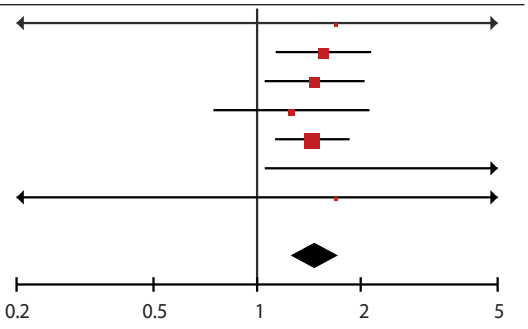
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_7 = 7.11$ ($P = .42$); $I^2 = 2\%$
Test for overall effect: $Z = 2.92$ ($P = .003$)



F. Small for Gestational Age Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	0.3	1.69 (0.10 to 29.41)
Chen et al, 2010[30]	25.1	1.56 (1.13 to 2.15)
Goldenberg et al, 1991[35]	22.9	1.47 (1.05 to 2.05)
Ibanez et al, 2012[38]	9.4	1.26 (0.75 to 2.12)
Khashan et al, 2014[39]	41.2	1.45 (1.13 to 1.86)
Lilliecreutz et al, 2011[40]	0.8	6.45 (1.05 to 39.52)
Sjöström et al, 1997[48]	0.3	1.69 (0.10 to 29.41)
Total (95% CI)	**100.0**	**1.48 (1.26 to 1.74)**

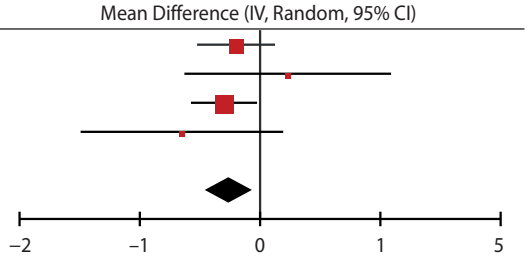
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_6 = 3.05$ ($P = .80$); $I^2 = 0\%$
Test for overall effect: $Z = 4.80$ ($P < .00001$)



G. Head Circumference (cm) Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Mean Difference (IV, Random, 95% CI)
Bindt et al, 2013[27]	37.3	−0.20 (−0.52 to 0.12)
Broekman et al, 2014[28]	5.3	0.23 (−0.63 to 1.09)
Nasreen et al, 2010[43]	51.9	−0.30 (−0.57 to −0.03)
Sjöström et al, 1997[48]	5.5	−0.65 (−1.49 to 0.19)
Total (95% CI)	**100.0**	**−0.25 (−0.45 to −0.06)**

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_3 = 2.27$ ($P = .52$); $I^2 = 0\%$
Test for overall effect: $Z = 2.52$ ($P = .01$)



Abbreviations: CI = confidence interval, IV = instrumental variables.

Table 2. Effect of Maternal Antenatal Anxiety on Perinatal Outcomes and Moderator Subanalyses

Analysis	No. of Studies	Within Group: Effect: Odds Ratio or Mean Difference (95% CI)[b]	Effect: *P* Value	Heterogeneity: Q_{df} Within	Heterogeneity: *P* Value	Heterogeneity: I^2 (Percentage of Variance Explained)	Effect of Moderator: Q_{df} Between	Effect of Moderator: *P* Value
Preterm Birth								
All studies	16	1.54 (1.39 to 1.70)	<.01	11.71_{15}	.70	0.0		
Study quality							0.02_1	.89
Above quality threshold	10	1.55 (1.35 to 1.77)	<.01	9.87_9	.36	9.0		
Below quality threshold	6	1.52 (1.23 to 1.88)	<.01	1.81_5	.87	0.0		
Diagnostic measure of anxiety							0.80_1	.37
Diagnostic	9	1.57 (1.41 to 1.76)	<.01	6.63_8	.58	0.0		
Not diagnostic	7	1.40 (1.11 to 1.77)	<.01	4.30_6	.64	0.0		
Any adjusted data							0.24_1	.62
Adjusted findings	11	1.56 (1.40 to 1.74)	<.01	7.86_{10}	.64	0.0		
Unadjusted findings	5	1.46 (1.15 to 1.84)	<.01	3.63_4	.46	0.0		
Anxiety assessment time							0.22_2	.89
Any time in pregnancy	9	1.55 (1.39 to 1.73)	<.01	5.56_8	.70	0.0		
Second trimester	5	1.51 (1.06 to 2.16)	.02	5.52_4	.24	28.0		
Third trimester	2	1.33 (0.70 to 2.52)	.39	0.44_1	.51	0.0		
Registry data							0.13_1	.71
Registry	5	1.56 (1.39 to 1.74)	<.01	3.62_4	.46	0.0		
Non-registry	11	1.49 (1.21 to 1.83)	<.01	7.98_{10}	.63	0.0		
Country							2.73_3	.43
North America	8	1.56 (1.39 to 1.75)	<.01	4.46_7	.73	0.0		
Europe	5	1.18 (0.83 to 1.67)	.35	3.47_4	.48	0.0		
Developing nations	1	1.80 (0.59 to 5.45)[b]	.30					
Other	2	1.68 (1.26 to 2.24)	<.01	1.04_1	.31	4.0		
Exclude depression							0.46_1	.50
Yes	5	1.60 (1.38 to 1.87)	<.01	1.86_4	.76	0.0		
No	11	1.49 (1.31 to 1.70)	<.01	9.38_{10}	.50	0.0		
Spontaneous Preterm Birth								
All studies	5	1.41 (1.13 to 1.75)	<.01	6.04_4	.20	34.0		
Study quality							1.13_1	.29
Above quality threshold	4	1.44 (1.16 to 1.79)	<.01	4.82_3	.19	38.0		
Below quality threshold	1	0.74 (0.22 to 2.47)[c]	.63					
Diagnostic measure of anxiety							3.23_1	.07
Diagnostic	3	1.52 (1.27 to 1.83)	<.01	2.56_2	.28	22.0		
Not diagnostic	2	0.94 (0.58 to 1.54)	.82	0.19_1	.67	0.0		
Any adjusted data							2.03_1	.15
Adjusted findings	4	1.49 (1.23 to 1.82)	<.01	3.88_3	.27	23.0		
Unadjusted findings	1	0.99 (0.58 to 1.68)[c]	.97					
Anxiety assessment time							3.95_2	.14
Any time in pregnancy	2	1.54 (1.26 to 1.87)	<.01	1.79_1	.18	44.0		
Second trimester	2	0.96 (0.57 to 1.61)	.88	0.20_1	.65	0.0		
Third trimester	1	0.74 (0.22 to 2.47)[c]	.63					
Registry data							3.80_1	.05
Registry	2	1.54 (1.26 to 1.87)	<.01	1.79_1	.18	44.0		
Non-registry	3	0.92 (0.58 to 1.48)	.74	0.35_2	.84	0.0		
Country							3.80_1	.05
North America	2	1.54 (1.26 to 1.87)	<.01	1.79_1	.18	44.0		
Europe	3	0.92 (0.58 to 1.48)	.74	0.35_2	.84	0.0		
Developing nations	0							
Other	0							
Birth Weight								
All studies	12	−55.96 (−93.62 to −18.31)	<.01	20.83_{11}	.04	47.0		
Study quality							2.34_1	.13
Above quality threshold	6	−32.88 (−64.87 to −0.89)	.04	7.43_5	.19	33.0		
Below quality threshold	6	−101.13 (−182.46 to −19.79)	.01	7.87_5	.16	36.0		
Diagnostic measure of anxiety							4.99_1	.03
Diagnostic	3	−143.47 (−240.27 to −46.67)	<.01	3.03_2	.22	34.0		
Not diagnostic	9	−30.42 (−51.87 to −8.97)	<.01	8.23_8	.41	3.0		
Any adjusted data							2.54_1	.11
Adjusted findings	4	−31.38 (−59.63 to −3.12)	.03	1.31_3	.73	0.0		
Unadjusted findings	8	−95.97 (−170.16 to −21.78)	.01	19.01_7	<.01	63.0		
Anxiety assessment time							1.63_2	.44
Any time in pregnancy	2	−121.99 (−328.65 to 84.67)	.25	2.95_1	.09	66.0		
Second trimester	2	−89.09 (−204.33 to 26.16)	.13	5.84_1	.02	83.0		
Third trimester	8	−28.96 (−64.37 to 6.45)	.11	7.85_7	.35	11.0		
Registry data								
Registry	0							
Non-registry	12	−55.96 (−93.62 to −18.31)	<.01	20.83_{11}	.04	47.0		

(continued)

Table 2 (continued).

Analysis	No. of Studies	Within Group: Effect: Odds Ratio or Mean Difference (95% CI)[b]	Within Group: Effect: *P* Value	Within Group: Heterogeneity: Q_{df} Within	Within Group: Heterogeneity: *P* Value	Within Group: Heterogeneity: I^2 (Percentage of Variance Explained)	Effect of Moderator: Q_{df} Between	Effect of Moderator: *P* Value
Country							3.03_3	.39
North America	4	−124.10 (−229.70 to −18.49)	.02	4.87_3	.18	38.0		
Europe	5	−29.05 (−51.51 to −6.59)	.01	4.12_4	.39	3.0		
Developing nations	2	−42.05 (−156.80 to 72.70)	.47	3.24_1	.07	69.0		
Other	1	−58.00 (−317.59 to 201.59)[c]	.66					
Adjusted for GA							1.28_1	.26
Yes	2	−36.18 (−66.08 to −6.29)	.02	0.09_1	.76	0.0		
No	10	−74.96 (−135.13 to −14.80)	.01	20.68_9	.01	56.0		
Low Birth Weight								
All studies	11	1.80 (1.48 to 2.18)	<.01	10.19_{10}	.42	2.0		
Study quality							0.33_1	.57
Above quality threshold	6	1.68 (1.26 to 2.23)	<.01	4.49_5	.48	0.0		
Below quality threshold	5	1.90 (1.38 to 2.61)	<.01	5.25_4	.26	23.7		
Diagnostic measure of anxiety							2.97_1	.09
Diagnostic	6	1.52 (1.17 to 1.99)	<.01	4.64_5	.46	0.0		
Not diagnostic	5	2.13 (1.62 to 2.81)	<.01	2.55_4	.64	0.0		
Any adjusted data							0.28_1	.60
Adjusted findings	5	1.67 (1.22 to 2.29)	<.01	3.39_4	.50	0.0		
Unadjusted findings	6	1.88 (1.39 to 2.56)	<.01	6.44_5	.27	22.3		
Anxiety assessment time							4.57_2	.10
Any time in pregnancy	6	1.47 (1.12 to 1.93)	<.01	2.27_5	.81	0.0		
Second trimester	3	2.33 (1.66 to 3.27)	<.01	1.21_2	.55	0.0		
Third trimester	2	1.16 (0.18 to 7.45)	.88	2.11_1	.15	52.6		
Registry data							3.75_1	.05
Registry	3	1.42 (1.05 to 1.93)	.03	0.61_2	.74	0.0		
Non-registry	8	2.09 (1.64 to 2.68)	<.01	5.79_7	.56	0.0		
Country							0.85_3	.84
North America	4	2.12 (1.23 to 3.66)	<.01	3.45_3	.33	13.0		
Europe	2	1.92 (0.78 to 4.75)	.16	0.05_1	.82	0.0		
Developing nations	2	1.16 (0.18 to 7.45)	.88	2.11_1	.15	52.6		
Other	3	1.64 (1.18 to 2.29)	<.01	3.64_2	.16	45.1		
Gestational Age								
All studies	8	−0.13 (−0.22 to −0.04)	<.01	7.11_7	.42	2.0		
Study quality							1.10_1	.30
Above quality threshold	5	−0.11 (−0.26 to 0.03)	.13	5.41_4	.25	26.0		
Below quality threshold	3	−0.28 (−0.56 to 0.00)	.05	0.47_2	.79	0.0		
Diagnostic measure of anxiety							3.18_1	.07
Diagnostic	3	−0.43 (−0.76 to −0.09)	.01	0.07_2	.97	0.0		
Not diagnostic	5	−0.11 (−0.20 to −0.03)	.01	3.86_4	.42	0.0		
Any adjusted data							0.11_1	.74
Adjusted findings	1	−0.20 (−0.57 to 0.17)[c]	.28					
Unadjusted findings	7	−0.13 (−0.26 to −0.01)	.03	6.97_6	.32	14.0		
Anxiety assessment time							3.20_2	.20
Any time in pregnancy	2	−0.45 (−0.90 to 0.00)	.05	0.05_1	.83	0.0		
Second trimester	1	−0.40 (−0.90 to 0.10)[c]	.12					
Third trimester	5	−0.11 (−0.20 to −0.03)	.01	3.86_4	.42	0.0		
Registry data								
Registry	8	−0.13 (−0.22 to −0.05)	<.01	7.11_7	.42	2.0		
Non-registry	0							
Country							4.62_2	.10
North America	2	−0.45 (−0.90 to 0.00)	.05	0.05_1	.83	0.0		
Europe	4	−0.15 (−0.24 to −0.06)	<.01	1.84_3	.61	0.0		
Developing nations	2	0.05 (−0.17 to 0.27)	.67	0.60_1	.44	0.0		
Other	0							
Small for Gestational Age								
All studies	7	1.48 (1.26 to 1.74)	<.01	3.05_6	.80	0.0		
Study quality							0.00_1	.95
Above quality threshold	4	1.49 (1.17 to 1.90)	<.01	2.58_3	.46	0.0		
Below quality threshold	3	1.47 (1.19 to 1.82)	<.01	0.45_2	.80	0.0		
Diagnostic measure of anxiety							0.39_1	.53
Diagnostic	3	1.72 (1.00 to 2.97)	.05	2.34_2	.31	14.7		
Not diagnostic	4	1.43 (1.19 to 1.73)	<.01	0.29_3	.96	0.0		
Any adjusted data							0.01_1	.92
Adjusted findings	6	1.48 (1.26 to 1.73)	<.01	3.02_5	.70	0.0		
Unadjusted findings	1	1.70 (0.10 to 29.53)[c]	.72					

(continued)

Table 2 (continued).

Analysis	No. of Studies	Within Group: Effect — Odds Ratio or Mean Difference (95% CI)[b]	Effect — *P* Value	Heterogeneity — Q_{df} Within	Heterogeneity — *P* Value	Heterogeneity — I^2 (Percentage of Variance Explained)	Effect of Moderator — Q_{df} Between	Effect of Moderator — *P* Value
Anxiety assessment time							0.42_2	.81
Any time in pregnancy	1	1.55 (1.13 to 2.14)[c]	<.01					
Second trimester	4	1.48 (1.22 to 1.81)	<.01	2.57_3	.46	0.0		
Third trimester	2	1.27 (0.76 to 2.12)	.36	0.04_1	.84	0.0		
Registry data							0.13_1	.72
Registry	1	1.55 (1.13 to 2.14)[c]	<.01					
Non-registry	6	1.45 (1.21 to 1.75)	<.01	2.91_5	.71	0.0		
Country							0.14_2	.93
North America	1	1.48 (1.06 to 2.06)[c]	.02					
Europe	5	1.44 (1.16 to 1.80)	<.01	2.90_4	.58	0.0		
Developing nations	0							
Other	1	1.55 (1.13 to 2.14)[c]	<.01					
Definition of SGA							0.87_2	.65
<2.5th Percentile	3	2.49 (0.82 to 7.59)	.11	1.70_2	.43	0.0		
<10th Percentile	3	1.46 (1.21 to 1.75)	<.01	0.46_2	.80	0.0		
<15th Percentile	1	1.48 (1.06 to 2.06)[c]	.02					
Head Circumference								
All studies	4	−0.25 (−0.45 to −0.06)	.01	2.27_3	.52	0.0		
Study quality							1.29_1	.26
Above quality threshold	3	−0.28 (−0.48 to −0.08)	<.01	0.99_2	.61	0.0		
Below quality threshold	1	0.23 (−0.63 to 1.09)[c]	.60					
Diagnostic measure of anxiety								
Diagnostic	0							
Not diagnostic	4	−0.25 (−0.45 to −0.06)	.01	2.27_3	.52	0.0		
Any adjusted data							1.29_1	.26
Adjusted findings	1	0.23 (−0.63 to 1.09)[c]	.60					
Unadjusted findings	3	−0.28 (−0.48 to −0.08)	<.01	0.99_2	.61	0.0		
Anxiety assessment time								
Any time in pregnancy	0							
Second trimester	0							
Third trimester	4	−0.25 (−0.45 to −0.06)	.01	2.27_3	.52	0.0		
Registry data								
Registry	0							
Non-registry	4	−0.25 (−0.45 to −0.06)	.01	2.27_3	.52	0.0		
Country							2.06_2	.36
North America	0							
Europe	1	−0.65 (−1.49 to 0.19)[c]	.13					
Developing nations	2	−0.26 (−0.47 to −0.05)	.02	0.21_1	.64	0.0		
Other	1	0.23 (−0.63 to 1.09)[c]	.60					
Apgar 1 Minute								
All studies	4	1.70 (0.90 to 3.23)	.10	4.83_3	.18	38.0		
Study quality							0.25_1	.61
Above quality threshold	2	1.61 (0.48 to 5.44)	.44	2.49_1	.11	60.0		
Below quality threshold	2	2.32 (1.12 to 4.81)	.02	0.10_1	.75	0.0		
Diagnostic measure of anxiety							0.25_1	.61
Diagnostic	2	1.61 (0.48 to 5.44)	.44	2.49_1	.11	60.0		
Not diagnostic	2	2.32 (1.12 to 4.81)	.02	0.10_1	.75	0.0		
Any adjusted data							1.23_1	.27
Adjusted findings	1	3.82 (0.82 to 17.81)[c]	.24					
Unadjusted findings	3	1.48 (0.77 to 2.85)	.09	3.23_2	.20	38.0		
Anxiety assessment time							1.39_2	.50
Any time in pregnancy	2	1.46 (0.68 to 3.15)	.33	2.90_1	.09	65.0		
Second trimester	1	3.82 (0.82 to 17.81)[c]	.09					
Third trimester	1	4.33 (0.08 to 225.22)[c]	.47					
Registry data							1.38_1	.24
Registry	2	1.46 (0.68 to 3.15)	.33	2.90_1	.09	65.0		
Non-registry	2	3.88 (0.93 to 16.30)	.06	0.00_1	.95	0.0		
Country							4.41_1	.04
North America	0							
Europe	3	2.54 (1.32 to 4.91)	<.01	0.43_2	.81	0.0		
Developing nations	0							
Other	1	1.03 (0.61 to 1.74)[c]	.91					
Apgar 5 Minutes								
All studies	5	2.68 (0.75 to 9.67)	.13	8.91_4	.06	55.0		
Study quality							0.29_1	.59
Above quality threshold	3	2.35 (0.31 to 17.84)	.41	4.88_2	.09	59.0		
Below quality threshold	2	4.48 (1.39 to 14.42)	.01	0.00_1	.99	0.0		

(continued)

Table 2 (continued).

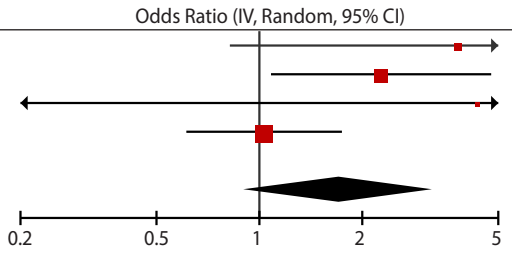
Analysis	No. of Studies	Within Group: Effect: Odds Ratio or Mean Difference (95% CI)[b]	Within Group: Effect: *P* Value	Within Group: Heterogeneity: Q_{df} Within	Within Group: Heterogeneity: *P* Value	Within Group: Heterogeneity: I^2 (Percentage of Variance Explained)	Effect of Moderator: Q_{df} Between	Effect of Moderator: *P* Value
Diagnostic measure of anxiety							7.31_1	<.01
Diagnostic	2	0.82 (0.35 to 1.91)	.64	0.59_1	.44	0.0		
Not diagnostic	3	5.53 (1.85 to 16.53)	<.01	1.01_2	.60	0.0		
Any adjusted data							0.01_1	.92
Adjusted findings	1	2.47 (0.13 to 47.31)[c]	.55					
Unadjusted findings	4	2.90 (0.63 to 13.32)	.17	8.84_{30}	.03	66.0		
Anxiety assessment time							1.71_2	.42
Any time in pregnancy	2	1.73 (0.30 to 10.10)	.54	5.46_1	.02	82.0		
Second trimester	1	2.47 (0.13 to 47.31)[c]	.55					
Third trimester	2	12.65 (1.10 to 145.44)	.04	0.46_1	.50	0.0		
Registry data							1.02_1	.31
Registry	2	1.73 (0.30 to 10.10)	.54	5.46_1	.02	82.0		
Non-registry	3	6.52 (0.99 to 42.77)	.05	1.15_2	.56	0.0		
Country							8.78_2	.01
North America	0							
Europe	3	4.13 (1.39 to 12.25)	.01	0.13_2	.94	0.0		
Developing nations	1	24.54 (1.10 to 548.11)[c]	.04					
Other	1	0.74 (0.30 to 1.80)[c]	.51					
Preeclampsia								
All studies	4	3.30 (0.56 to 19.37)	.19	13.63_3	<.01	78.0		
Study quality							0.12_1	.73
Above quality threshold	2	1.99 (0.05 to 74.04)	.71	4.48_1	.03	78.0		
Below quality threshold	2	4.43 (0.27 to 72.40)	.30	8.86_1	<.01	89.0		
Diagnostic measure of anxiety							0.00_1	.96
Diagnostic	2	3.06 (0.36 to 26.36)	.65	4.70_1	.03	79.0		
Not diagnostic	2	2.71 (0.04 to 190.30)	.31	6.42_1	.01	84.0		
Any adjusted data							0.00_1	.96
Adjusted findings	2	3.06 (0.36 to 26.36)	.31	4.70_1	.03	79.0		
Unadjusted findings	2	2.71 (0.04 to 190.30)	.65	6.42_1	.01	84.0		
Anxiety assessment time							4.72_2	.09
Any time in pregnancy	1	1.14 (0.42 to 3.09)[c]	.80					
Second trimester	1	10.39 (1.84 to 58.61)[c]	<.01					
Third trimester	2	2.71 (0.04 to 190.30)	.65	6.42_1	.01	84.0		
Registry data							1.70_1	.19
Registry	1	1.14 (0.42 to 3.09)[c]	.80					
Non-registry	3	5.32 (0.66 to 42.97)	.12	6.50_2	.04	69.0		
Country							1.70_1	.19
North America	0							
Europe	3	5.32 (0.66 to 42.97)	.12					
Developing nations	0							
Other	1	1.14 (0.42 to 3.09)[c]	.80					
Cesarean Delivery								
All studies	4	1.01 (0.46 to 2.25)	.97	20.26_3	<.01	85.0		
Study quality								
Above quality threshold	4	1.01 (0.46 to 2.25)	.97	20.26_3	<.01	85.0		
Below quality threshold	0							
Diagnostic measure of anxiety							2.22_1	.14
Diagnostic	2	1.82 (0.88 to 3.74)	.10	4.38_1	.04	77.2		
Not diagnostic	2	0.78 (0.33 to 1.83)	.56	2.55_1	.11	61.0		
Any adjusted data							10.76_1	<.01
Adjusted findings	1	2.50 (1.81 to 3.45)[c]	<.01					
Unadjusted findings	3	0.95 (0.59 to 1.54)	.84	3.10_2	.21	35.6		
Anxiety assessment time							9.20_2	.01
Any time in pregnancy	1	2.50 (1.81 to 3.45)[c]	<.01					
Second trimester	1	1.20 (0.65 to 2.21)[c]	.57					
Third trimester	2	0.78 (0.33 to 1.83)	.56	2.55_1	.11	61.0		
Registry data							10.76_1	<.01
Registry	1	2.50 (1.81 to 3.45)[c]	<.01					
Non-registry	3	0.95 (0.59 to 1.54)	.84	3.10_2	.21	35.6		
Country							9.20_2	.01
North America	0							
Europe	1	1.20 (0.65 to 2.21)[c]	.57					
Developing nations	2	0.78 (0.33 to 1.83)	.56	2.55_1	.11	61.0		
Other	1	2.50 (1.81 to 3.45)[c]	<.01					

[a]Developing nations include Bangladesh, Côte d'Ivoire, and Ghana; other countries include Australia, Israel, Singapore, and Taiwan.
[b]Pooled effect size estimated using random-effects model.
[c]Pooled effect size estimated using fixed-effects model.
Abbrevation: CI = confidence interval, SGA = small for gestational age.

Figure 3. Nonsignificant Pooled Associations Between Antenatal Anxiety and Perinatal Outcomes

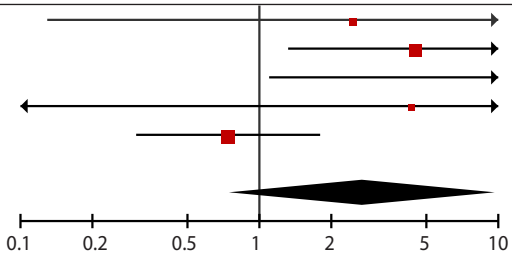
A. Low Apgar Scores at 1 Minute Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	13.8	3.82 (0.82 to 17.81)
Berle et al, 2005[26]	36.0	2.27 (1.08 to 4.77)
Brouwers et al, 2001[29]	2.5	4.33 (0.08 to 225.22)
Pavlov et al, 2014[45]	47.6	1.03 (0.61 to 1.74)
Total (95% CI)	**100.0**	**1.70 (0.90 to 3.23)**
Heterogeneity: $\tau^2 = 0.15$; $\chi^2_3 = 4.83$ ($P = .18$); $I^2 = 38\%$		
Test for overall effect: $Z = 1.63$ ($P = .10$)		



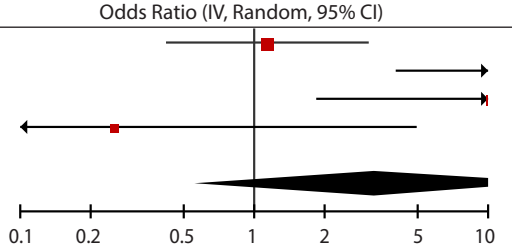
B. Low Apgar Scores at 5 Minutes Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Andersson et al, 2004[25]	13.1	2.47 (0.13 to 47.31)
Berle et al, 2005[26]	30.8	4.49 (1.32 to 15.28)
Bindt et al, 2013[27]	12.2	24.54 (1.10 to 548.10)
Brouwers et al, 2001[29]	8.4	4.33 (0.08 to 225.22)
Pavlov et al, 2014[45]	35.5	0.74 (0.30 to 1.80)
Total (95% CI)	**100.0**	**2.68 (0.75 to 9.67)**
Heterogeneity: $\tau^2 = 1.00$; $\chi^2_4 = 8.91$ ($P = .06$); $I^2 = 55\%$		
Test for overall effect: $Z = 1.51$ ($P = .13$)		



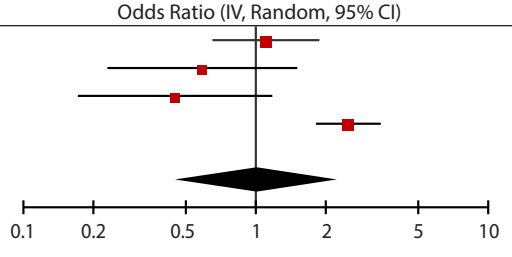
C. Preeclampsia Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Chen et al, 2010[30]	30.5	1.14 (0.42 to 3.09)
Crandon, 1979[32]	26.6	19.80 (4.03 to 97.34)
Lilliecreutz et al, 2011[40]	25.6	10.39 (1.84 to 58.61)
Teixeira et al, 1999[49]	17.3	0.25 (0.01 to 4.95)
Total (95% CI)	**100.0**	**3.30 (0.56 to 19.37)**
Heterogeneity: $\tau^2 = 2.41$; $\chi^2_3 = 13.63$ ($P = .003$); $I^2 = 78\%$		
Test for overall effect: $Z = 1.32$ ($P = .19$)		



D. Cesarean Section Delivery Following Exposure to Maternal Antenatal Anxiety

Study or Subgroup	Weight, %	Odds Ratio (IV, Random, 95% CI)
Bindt et al, 2013[27]	27.3	1.11 (0.65 to 1.88)
Lilliecreutz et al, 2011[40]	21.7	0.59 (0.23 to 1.51)
Nasreen et al, 2010[43]	21.4	0.45 (0.17 to 1.18)
Pavlov et al, 2014[45]	29.6	2.50 (1.81 to 3.45)
Total (95% CI)	**100.0**	**1.01 (0.46 to 2.25)**
Heterogeneity: $\tau^2 = 0.53$; $\chi^2_3 = 20.26$ ($P = .0002$); $I^2 = 85\%$		
Test for overall effect: $Z = 0.03$ ($P = .97$)		



Abbreviations: CI = confidence interval, IV = instrumental variables.

finding as it provides preliminary evidence for an effect of anxiety severity on low infant birth weight and spontaneous preterm birth. While we found no significant associations between antenatal anxiety and preeclampsia, cesarean delivery, or Apgar scores at 1 and at 5 minutes, these outcomes were examined based on 5 or fewer studies and the first 2 outcomes had significant heterogeneity across the included studies. Overall, our findings suggest a strong and robust association between maternal antenatal anxiety and adverse perinatal outcomes, leading to a broader understanding of the potential impact of antenatal anxiety that will inform screening and treatment decisions.

We assessed for the effects of moderator variables because of the known methodological limitations from observational studies and applied a rigorous quality assessment to separate studies based on quality, although we found study quality was not a significant source of heterogeneity. Our results were consistent with prior work, arguing for the strength of the relationship between antenatal anxiety and adverse outcomes previously summarized. Specifically, we replicated

the effects on risk of preterm birth (OR = 1.54), spontaneous preterm birth (OR = 1.41), and low birth weight (OR = 1.80), despite differing definitions of anxiety and the number of included studies. Previously, a pooled OR of 1.46 (based on 7 studies)[8] and a pooled RR of 1.50 (based on 12 studies)[9] were reported for preterm birth in association with antenatal anxiety. These prior meta-analyses[8,9] included measurement of anxiety as a continuous variable and pregnancy-specific anxiety, and one[9] included a retrospective study, which we excluded. We expand upon prior work by including more studies and a larger pooled sample size. Similarly, our low birth weight outcome yielded an effect comparable to that of a previous meta-analysis[9] (OR = 1.76), but again we included a greater number of studies (11 vs 6) with a larger pooled sample size.

To our knowledge, the association between antenatal anxiety and the variables of small for gestational age, gestational age, birth weight, and head circumference has not been previously summarized. It is not surprising that we found significant pooled effects, as those outcomes may be related to preterm birth and low birth weight, further reinforcing the strength of the relationship. In a previous meta-analysis,[24] we examined the effects of depression on diverse perinatal outcomes and did not find such consistent and numerous adverse delivery outcomes, speaking to the potentially more grave effects of antenatal anxiety. It has already been suggested that antenatal anxiety may be more prevalent than depression[52–55]; it appears the consequences of this disorder may also be more adverse as well.

The primary limitations of this study stem from methodological issues of the included original articles. The definition of anxiety by self-report varied across studies with respect to the scales and cutoff scores used. Even for the State-Trait Anxiety Inventory (STAI), the most commonly used measure of antenatal anxiety, the cutoff scores used were not uniform and only half of the studies employed the STAI-state suggested cutoff (39–40).[56] The category of diagnosed anxiety disorder was likewise a heterogeneous grouping. We included all types of anxiety disorders as there were not enough studies examining perinatal outcomes in association with specific anxiety disorders, other than for posttraumatic stress disorder (PTSD) and preterm birth. Additionally, we included 1 study with unclear diagnostic criteria,[44] as correspondence with the primary author confirmed an active clinical diagnosis of anxiety (E. Sheiner, MD, PhD, personal communication in electronic form, April 18, 2016). A study just published[57] that examined generalized anxiety disorder (GAD), panic disorder (PD), PTSD, and comorbidity of these disorders with major depression found significance for preterm birth only in the adjusted models for comorbid PTSD and depression but not for any of the individual disorders (although several unadjusted were significant) nor for any other delivery outcome. This is the same cohort as that in Yonkers et al,[51] included in our analyses, which also did not find significance for the individual disorders and preterm birth (but similarly was found for comorbid PTSD and major depression in adjusted models). Our main analyses included the nonsignificant Yonkers et al[51] data on PTSD only as we deemed this the most rigorous diagnostically (PD had a small sample size and the GAD diagnosis was based on only 1 month of symptoms instead of 6). There were enough data for us to investigate pooled PTSD data from several articles on preterm birth, and this analysis was similar to the main one and was significant. The timing of the anxiety assessments was also not consistent across the studies, and we grouped them by trimester. Our inclusion criteria specified that the initial assessment occur in pregnancy and we do not believe any occurred just prior to delivery, although some articles were vague in their descriptions (ie, Nasreen et al[43] assessed during the third trimester, and Shaw et al[6] included a diagnosis that was documented within 9 months before delivery). Most studies did not report on active treatments for anxiety, and thus we cannot confirm whether the associations between prenatal anxiety and outcomes truly reflect untreated anxiety. A majority of studies (22/29) did not report whether psychotropic medication was used, and only 1 study[51] controlled for psychotropic use and found evidence for an effect of antidepressants (same cohort published in 2017,[57] which found an effect for medications but not in adjusted models with individual anxiety disorders); psychotherapy use was equally not identified. Comorbidity was also not considered, and this may confound the data as anxiety is often seen with other disorders (eg, depression) and this may increase the chance of negative perinatal/neonatal outcomes, although to date data are not consistent.[33,38,42] For example, Männistö et al[42] reported an adjusted odds ratio for PTB in pregnant women with comorbid depression and anxiety that was higher than the adjusted odds ratio in association with any singular maternal psychiatric disorder (OR = 2.31, 1.93–2.78); a similar result was observed for spontaneous PTB (OR = 2.24, 1.73–2.91) (K. Grantz, MD, personal communication in electronic form, October 13, 2017). On the contrary, Ibanez et al[38] found no significant risk of PTB in pregnant women with comorbid depression and anxiety, but a significantly increased risk of spontaneous PTB. When statistical adjustments were made, different variables were used across studies, and given that certain factors (eg, smoking, SES) are known to be associated with both anxiety and negative perinatal outcomes, this inconsistency may have also confounded associations. Finally, we limited our search to English-language publications as we did not originally budget for translation costs, which may have biased the results. However, only 7 studies were excluded based on this criterion, and given the strength of the significant associations ($P < .0001$), any such bias is likely to minimally impact the results.

Additional research must address whether treatment of antenatal anxiety decreases the risk of adverse perinatal outcomes. Unfortunately there is a dearth of studies examining interventions to treat antenatal anxiety—eg, a recent systematic review and meta-analysis[58] found 28 trials for the treatment of prenatal depressive disorders and only 1 for the treatment of anxiety disorders. Nevertheless,

some treatments are common to both depressive and anxiety disorders and may suggest areas for initial research focus. For example, use of selective serotonin reuptake inhibitors (SSRIs) in pregnant women with psychiatric diagnoses has been associated with a lower risk for some negative perinatal outcomes; however, effects were outcome-specific (eg, PTB and cesarean section only) and require replication.[59] Research in this area is further complicated by the fact that medications to treat anxiety (SSRIs and benzodiazepines) have been associated with potential adverse effects[60,61]; evaluating the effect of non-pharmacologic treatments such as psychotherapy should also be a focus of future studies. Moreover, whether there exists a period of heightened susceptibility, or a differential impact of longer exposure to anxiety, should be the focus of future research. Although we did not find a significant effect for timing of anxiety as a moderator, few studies identified the trimester of anxiety assessment. Lastly, the potential underlying mechanisms linking antenatal anxiety with poor perinatal outcomes, while recently summarized elsewhere,[62] remain an important topic for further study as they may ultimately inform treatment optimization.

Our findings are clinically important given the high prevalence of anxiety in pregnancy, as previously noted, coupled with low treatment uptake. For example, a large US study[63] found that past-year pregnant women sought treatment for an anxiety disorder at nearly half the rate of non-pregnant women (6.1% versus 11.6%). The multiple adverse perinatal outcomes associated with antenatal anxiety highlight the need to both identify and manage pregnant women with high levels of anxiety, particularly those with the most severe forms of anxiety (eg, diagnosed anxiety disorders). Here, we provide data that will be useful to clinicians and patients in their decision making. Women with antenatal anxiety disorders have higher rates of psychotropic medication nonadherence compared to other prenatal psychiatric disorders,[64] and those declining medications have significantly more anxiety symptoms across pregnancy than those adherent to their medication regimen.[65] While psychological therapies are both first-line treatment for mild anxiety and the preferred modality for most women during pregnancy,[66] these treatments are nevertheless also linked with variable rates of adherence/attrition.[58] Along with our data, the preceding provides a strong argument for not only identifying antenatal anxiety but additionally addressing treatment preferences, barriers, and adherence in women with antenatal anxiety to mitigate potential adverse perinatal outcomes.

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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.