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A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight

Hsiang Huang, MD, MPH[1], **Shane Coleman, MD, MPH**[2], **Jeffrey A. Bridge, PhD**[3], **Kimberly Yonkers, MD**[4], and **Wayne Katon, MD**[2]

[1]Department of Psychiatry, Cambridge Health Alliance, Harvard Medical School, Cambridge, MA

[2]Department of Psychiatry & Behavioral Sciences, University of Washington Medical School, Seattle, WA

[3]Department of Pediatrics and The Research Institute at Nationwide Children's Hospital, The Ohio State University, Columbus, OH

[4]PMS and Perinatal Psychiatric Research Program, Yale University, New Haven, CT

Keywords

antidepressants; pregnancy; prenatal; antenatal; adverse birth outcomes; low birth weight; preterm birth

Introduction

Depression is a prevalent condition in pregnancy affecting up to 13% of women (1). Untreated antenatal depression is associated with poor self-care during pregnancy, risk of post-partum depression, risk of impaired maternal-infant attachment, and delays in infant development when it persists into the post-partum period (2, 3). Available treatments for depressive disorders include psychotherapeutic interventions and antidepressant medications such as selective serotonin inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Although psychotherapy may be a reasonable treatment option for mild to moderate depression, antidepressants are often required for the effective treatment of severe maternal depression (4, 5). Recent estimates of antidepressant exposure among pregnant women range from 3% to 13% (6, 7).

Preterm birth (PTB) and low birth weight (LBW) occur at national rates of 12.2% and 8.2%, respectively (8). Several studies over the past two decades have attempted to characterize the relationship between antidepressant use in pregnancy and risk of adverse birth outcomes

Corresponding Author: Hsiang Huang, MD, MPH, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge, MA 02139, Phone: 617-575-5772 Fax: 617-665-2521 hhuang@cha.harvard.edu.

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(9). However, in general, the observational studies published to date have provided inconsistent and sometimes conflicting findings on the relationship between antidepressant exposure and LBW and PTB. Differences in study design (prospective, retrospective), patient populations (patients recruited from mental health settings, patients identified from registries), comparator groups (non-depressed or depressed controls), and sample sizes make it difficult to interpret the variability of findings. Many studies are also limited in their ability to adequately control for important potential confounding variables such as smoking, substance abuse, medical conditions (such as pregnancy induced hypertension and gestation diabetes), and depression severity—all of which have been found to be independently associated with adverse birth outcomes (10, 11).

A recent meta-analysis has shown that although antidepressant use in pregnancy was not associated with spontaneous abortion, exposure was significantly associated with both preterm delivery and low birth weight (12). The goal of this meta-analysis is to add to the literature by further examining this association (e.g. reproductive outcomes of depressed women who are treated with antidepressants of any type during pregnancy), adding eight studies published after June 2010 (the end of the above systematic review). We also examine how the quality and study design of these previous studies influence the outcomes reported in this meta-analysis via sensitivity analyses.

Methods

Search strategy for identification of studies

We searched for English and non-English language articles via MEDLINE, CINAHL, PyschINFO, and reference lists of review papers. The electronic search included studies from the respectively databases' start dates and ended on December 1, 2012. We used the following keywords and their combinations: *antidepressant, selective serotonin reuptake inhibitor, SSRI, pregnancy, antenatal, prenatal, birthweight, birth weight, preterm, prematurity, gestational age, fetal growth restriction, intrauterine growth restriction,* and *small-for-gestational age*. Published English-language and non-English language studies were included in this meta-analysis if they provided the relative risk or adequate data for the calculation of an effect size as an odds ratio between antidepressant use and an adverse birth outcome (i.e. LBW or PTB). Included studies could be either prospective or retrospective. Studies were excluded if they lacked the outcomes of interest. Authors H.H. and S.C. contacted authors of studies that reported outcomes of interest as continuous variables for information to calculate effect sizes as odds ratios.

Data extraction

Adverse birth outcomes—Two authors (H.H. and S.C.) reviewed all studies. A standardized eligibility and quality of study coding sheet were designed a priori (13). Of the 222 published studies reviewed, 28 met the inclusion criteria. Fifteen studies on LBW (<2500g) and 28 studies on PTB (<37 weeks gestational age) were included in this meta-analysis (Table 1).

Methodologic quality assessment—H.H. and S.C. rated each of the studies independently and assigned a quality score to each of the studies selected for this meta-analysis according to guidelines described by Downs and Black (14). We used a consensus approach and resolved differences in scoring prior to assigning a final quality score. The quality measure was based on the following indicators: whether characteristics of patients were clearly described, whether measures of antidepressant exposure were reliable and valid, the degree of adjustment for multiple potential confounding variables in analyses, whether measurement and adjustment for depression severity was made, the study

representativeness of the potential population, and sample size. The total quality scores ranged from 0–13.

Analysis

The association between antidepressant exposure in the antenatal period and adverse birth outcome was examined using relative risks (RRs). To do this, we considered odds ratios (ORs) as surrogates for RRs because when outcomes undergoing study are relatively uncommon, the relative odds approximate RRs (2). Each study's RR was weighted according to the inverse of its variance using random-effects models in order to calculate a pooled RR. Ninety-five percent confidence intervals (95% CIs) were calculated for each study result and for the pooled estimates. Statistical analyses were performed using Comprehensive Meta-analysis version 2.2 (Biostat, Englewood, New Jersey).

Heterogeneity of effect size was assessed using the Cochran Q χ^2 statistic ($P \leq .10$) and the I^2 statistic, which indicates the percentage of variation in the effect size estimate attributable to heterogeneity rather than sampling error (15). Random-effects models were used in all analyses because the Q statistic and the I^2 statistic indicated substantial heterogeneity of effect size in the primary analyses examining the association between antidepressant exposure and each adverse birth outcome. Random-effects meta-regression analyses and moderator analyses were conducted to determine whether four study characteristics could explain variability across studies: (1) methodological quality of studies; (2) drug type (SSRI vs. other or mixed); (3) control status (depressed, mixed, or non-depressed); and (4) study design (prospective vs. retrospective). "Leave-one-out" analyses were conducted by iteratively deleting each study and calculating the resulting effect size (16).

Publication bias was assessed visually using a funnel plot and quantitatively using a regression procedure to measure funnel plot asymmetry (17). The trim-and-fill method by Duval and Tweedie (18, 19) was used to adjust for potential publication bias. This method assesses asymmetry in the funnel plot, imputes the number of suspected missing studies, and recalculates the adjusted pooled effect size estimate. The adjusted result can be used as a sensitivity analysis to indicate the extent to which publication bias may affect the pooled estimate (2, 20).

Results

The retrieval and selection strategy is shown in Figure 1. Of the 222 citations found to meet the initial search criteria, 52 full-text articles were assessed for eligibility, and 28 articles were ultimately included in this analysis. Table 1 provides the characteristics of these studies. Further information was requested from 12 authors (of 16 studies) of whom six authors responded with two of these authors providing data allowing two additional studies to be included in the meta-analysis.

Association between antidepressant use in pregnancy and adverse birth outcomes

Low birth weight—Fifteen studies evaluated the association between antenatal antidepressant use and LBW with RRs ranging from 0.62 to 8.33 (Table 2). Using the random-effects model, antenatal antidepressant exposure was significantly associated with LBW (RR= 1.44, 95% CI: 1.21–1.70). Nine of the studies found no significant association. Significant heterogeneity across studies was noted (Q_{14}= 37.1; P=.001; I^2 = 62%).

Preterm birth—Twenty-eight studies evaluated the association between antenatal antidepressant exposure and PTB with RRs ranging from 0.40 to 11.70 (Table 2). Using the random-effects model, antenatal antidepressant exposure was significantly associated with

PTB (RR: 1.69, 95% CI: 1.52–1.88). Nine of the studies found no significant association. Significant heterogeneity across studies was noted (Q_{27}=49.4; P=.005; I^2 = 45%).

Moderators of Outcome

Moderator analyses were conducted to explore sources of heterogeneity (Table 3). In LBW studies, although the omnibus test was not statistically significant, studies that used a depressed control group without antidepressant exposure yielded larger pooled RRs than studies that used mixed controls (Q_1=4.30, P=.038). Similarly, PTB studies that used a depressed control group without antidepressant exposure yielded larger RRs than studies that used either mixed controls (Q_1=10.45, P=.001) or non-depressed controls (Q_1=4.35, P=.037). In PTB studies, heterogeneity among studies was reduced by the addition of the control group moderator (depressed: Q_3= 2.01; P=.57; I^2 = 0%; mixed: Q_{10}= 17.42; P=.07; I^2 = 43%; non-depressed: Q_2= 18.17; P=.11; I^2 = 34%). Drug type, study design, control for depression severity, and study quality were not significant moderators of LBW or PTB.

Leave-One-Out Analyses

Sensitivity analyses revealed that no single study unduly influenced the pool risk ratio estimates of the association between antenatal antidepressant exposure and LBW and PTB.

Publication bias

In PTB studies, visual inspection of the funnel plot in which each study's effect size (as measured by log RR) was plotted against the standard error and showed marked asymmetry, suggesting that studies with negative findings may not have been published; evidence of possible publication bias was confirmed using the regression intercept approach (17) (P=.001). As shown in Table 4, the trim-and-fill adjusted RRs for PTB, while generally lower than the unadjusted RRs, are robust to the effects of publication bias. There was no evidence of publication bias for LBW studies.

Discussion

This systematic review found that antidepressant exposure during pregnancy was associated with significant increased risks of LBW and PTB. A prior meta-analysis by Lattimore (2005) in which nine studies were included also examined this relationship and showed a non-significant increase in risk for PTB (OR: 1.85, 95% CI: 0.79–4.29), but a stronger association for an increase in risk for LBW (OR: 3.64, 95% CI: 1.01–13.08) (21). One explanation for the differences found between our study and the Lattimore study is that the inclusion criteria used in each study differed (we included all studies with the outcomes of interest—both prospective and retrospective—while the Lattimore study included only prospective studies). A more recent meta-analysis by Ross et. al, that reviewed studies completed through 2010 also confirmed the existence of a statistically significant relationship between antidepressant exposure in pregnancy and both LBW and PTB (12). However, Ross and colleagues emphasized that the differences found between women exposed to antidepressants versus those not exposed on gestational age (approximately three days shorter) and birth weight (approximately 75 grams lower) were small and of questionable clinical significance.

There is some evidence that the length of exposure or timing of exposure during certain trimesters may influence antidepressants' effects on fetal development and subsequent birth outcomes. An early study by Chambers and colleagues found that late fluoxetine exposure was associated with PTB and LBW compared with earlier exposure (22). Other work suggests that the timing of (23) or duration of (24) antidepressant exposure influences the risk of these outcomes. Findings from a recent study by Wisner and colleagues also

suggested that the timing of exposure may affect birth outcomes (23). They found that mothers taking an antidepressant throughout pregnancy were more likely to have PTB infants than those exposed partially or not at all during pregnancy. On the other hand, a study by Oberlander and colleagues that used propensity score matching on population-based data of pregnant women showed that longer antidepressant exposure duration during pregnancy and *not* timing of exposure was associated with LBW (24). Antidepressant dosing has also been implicated as a factor in affecting adverse birth outcomes. For instance, a recent study that examined antidepressant dosing found that pregnant women exposed to high doses of antidepressants were five-fold more likely to have PTBs than those who were exposed to low-medium doses (25).

These results must be tempered by results of a recent meta-analysis that found that the illness of depression was also associated with risk of LBW and PTB (2). Moreover, Wisner and colleagues have shown that both persistent depressive symptoms throughout pregnancy as well as antidepressant exposure were independent risk factors for LBW and PTB (23). Tapering antidepressants in pregnant women with histories of depression has also been shown to be associated with a significantly higher risk of relapse compared to women remaining on antidepressant treatment (26). Lack of depression treatment in pregnancy increases the likelihood that depression will continue into the postpartum period with attendant suffering of the mother and possible complications in maternal-infant bonding, delayed developmental milestones, and subsequent behavioral problems (27).

The decision to initiate or remain on antidepressant treatment in pregnant women should be based on risk-benefit ratio and should occur in the context of shared decision making between the patient and her physician. It is certainly reasonable in many women, given concerns about both depression and SSRI use being linked to adverse birth outcomes, to initiate treatment with an evidence-based psychotherapy such as interpersonal therapy or cognitive behavioral therapy and potentially adding an antidepressant for non-response. However, the highest risk of depression during pregnancy is in low-income populations which often have the greatest barriers to finding psychotherapeutic services due to limitations in insurance coverage for mental health issues. There are also limitations in being able to pay out-of-pocket costs since co-pays are generally higher for mental health services. Lastly, low-income patients face a multitude of difficulties in attending mental health visits including taking time off from work, obtaining childcare services, and transportation costs.

Strengths of this study include the development of a coding sheet for inclusion and methodological quality *a priori*. We also aimed to characterize the quality of studies based on their ability to control important confounding factors such as the severity of depression, smoking, and alcohol use which all affect birth outcomes. We were able to extend the findings of our colleagues Ross et. al, (12) by including eight additional studies that have been published since 2011.

The main limitation of our study is exclusion of studies based on our selection criteria. For instance, studies in which only the means of birth weight or gestational age were provided were not included in our study if authors did not reply to our request for additional data (14 studies were excluded). Furthermore, the included studies varied widely in design, type of population, control group, and methods. Most importantly, few studies were able to control for all potential confounding factors that are associated with the exposure (antidepressant use) and events (PTB and LBW). Pregnant women with depression have significantly more pregnancy-related somatic symptoms (28) which likely lead to more physician visits, are more likely to take over-the-counter and allopathic medicines for these somatic symptoms, have more comorbid medical illnesses preceding pregnancy such as hypertension (29), and have higher rates of smoking, higher BMIs and use of illicit substances. Moreover, women

with greater depression severity and persistence of depression are more likely to receive antidepressant treatment (confounding by indication) and few studies controlled for severity or persistence of depression. More prospective epidemiologic studies that control for all these potential confounding factors as well as severity of depression are needed to better describe the strength of association between antenatal antidepressant exposure and PTB and LBW.

Conclusions

Antidepressant use during pregnancy may significantly increase the risk for preterm birth and low birth weight. Our finding highlights the need for a careful examination of the risk-benefit ratio when considering the initiation or maintenance of antidepressant therapy in pregnant women with depression.

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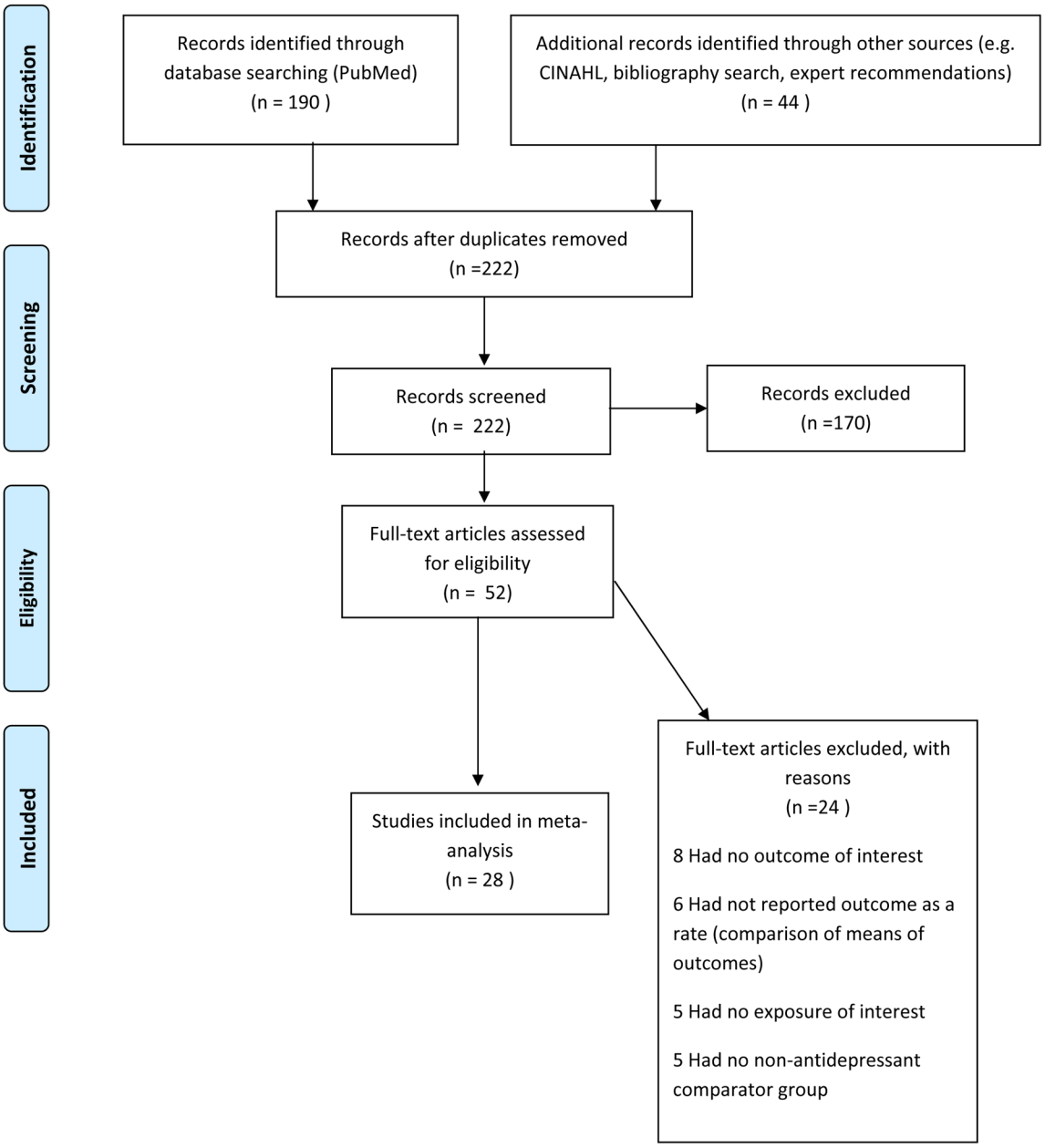

Figure 1.
Identification of independent studies for inclusion in the meta-analysis (from PRISMA flow diagram guidelines)

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Table 1

Characteristics of studies included in the meta-analysis

Trial	Year	Exposure	Controls	Trial design	Sample size	RR (95% CI)	RR (95% CI)	Quality Score	Controlled for Depression Severity
						LBW	PTB		
Grzeskowiak (30)	**2012**	SSRI	Dep	retrospective	1787	2.26 (1.31–3.91)	2.68 (1.83–3.93)	8	No
El Marroun (31)	**2012**	SSRI	non-Dep	prospective	7126	1.65 (0.77–3.56)	2.14 (1.08–4.25)	9	No
Klieger-Grossmann (32)	**2012**	escitalopram	non-Dep	prospective	425	4.51 (1.43–18.69)	2.21 (0.92–5.68)	7	No
Nordeng (33)	**2012**	various AD	mixed	prospective	62204	0.62 (0.33–1.16)	1.21 (0.87–1.69)	11	Yes
Yonkers (34)	**2012**	SSRI	non-Dep	prospective	2432		1.62 (1–2.5)	9	Yes
Colvin (35)	**2011**	SSRI	non-Dep	retrospective	96698	1.4 (1.25–1.56)	1.43 (1.24–1.65)	8	No
Latendresse (36)	**2011**	SSRI	Mixed	retrospective	100		11.7 (2.2–60.7)	7	Yes
Roca (25)	**2011**	SSRI	non-Dep	retrospective	252	1.37 (0.46–3.81)	3.44 (1.30–9.11)	7	No
Einarson (37)	**2010**	various AD	non-Dep	retrospective	1856		1.7 (1.18–2.45)	6	No
Lewis (38)	**2010**	SSRI or SNRI	mixed	prospective	54	8.33 (1.11–62.67)	4.52 (0.47–43.41)	9	Yes
Reis (39)	**2010**	SSRI	Mixed	retrospective	1068177	1.13 (0.97–1.31)	1.45 (1.31–1.63)	6	No
Lund (40)	**2009**	SSRI	non-Dep	prospective	52099	0.63 (0.15–2.67)	2.02 (1.29–3.16)	7	No
Toh (41)	**2009**	SSRI	mixed	retrospective	5796		1.27 (0.59–2.76)	8	No
Wisner (23)	**2009**	SSRI	non-Dep	prospective	179		5.43 (1.98–14.84)	9	No
Maschi (42)	**2008**	various AD	Mixed	prospective	1400	1.18 (0.53–2.41)	2.31 (1.14–4.63)	3	No
Davis (43)	**2007**	SSRI	Mixed	retrospective	50710		1.45 (1.25–1.68)	3	No
Lennestal (44)	**2007**	SNRI	Mixed	retrospective	860215	1.12 (0.74–1.68)	1.6 (1.19–2.15)	8	No
Pearson (45)	**2007**	various AD	non-Dep	retrospective	252		1.07 (0.4–2.67)	4	No
Suri (46)	**2007**	various AD	Dep	prospective	71		3.5 (0.4–165.11)	11	Yes
Djulus (47)	**2006**	mirtazapine	non-Dep	prospective	208		5.43 (1.11–51.83)	7	No
Wen (48)	**2006**	SSRI	Mixed	retrospective	4850	1.58 (1.19–2.11)	1.57 (1.28–1.92)	7	No
Sivojelezova (49)	**2005**	citalopram	non-Dep	prospective	264		2.31 (0.71–8.71)	6	No
Kallen (50)	**2004**	various AD	Mixed	prospective	563656	1.98 (1.55–2.52)	1.96 (1.60–2.41)	9	No
Casper (51)	**2003**	SSRI	Dep	prospective	44		0.4 (0.005–33.99)	11	Yes
Simon (52)	**2002**	SSRI	Dep	retrospective	370	2.73 (0.92–8.09)	4.38 (1.57–12.22)	8	No

Trial	Year	Exposure	Controls	Trial design	Sample size	RR (95% CI)	RR (95% CI)	Quality Score	Controlled for Depression Severity
						LBW	**PTB**		
Ericson (53)	**1999**	various AD	Mixed	retrospective	281728	1.32 (0.96–1.80)	1.43 (1.14–1.8)	4, 6	No
Chambers (22)	**1996**	fluoxetine	non-Dep	prospective	290		2.65 (0.98–6.89)	3	No
Pastuszak (54)	**1993**	fluoxetine	non-Dep	prospective	256		0.85 (0.22–3.09)	2	No

Table 2

Effect of Antenatal Antidepressant Exposure on Outcomes of Low Birth Weight and Preterm Birth

				Heterogeneity		
Outcome	**No. of Studies**	**Relative Risk[‖] % (95% CI)**	***P* Value**	**Q_{df} Within**	***P* Value**	**% Variance Explained**
Low Birth Weight	15	1.44 (1.21–1.70)	<.001	37.1_{14}	.001	62
Preterm Birth	28	1.69 (1.52–1.88)	<.001	49.4_{27}	.005	45

Abbreviations: No. indicates number; CI, confidence interval; df, degrees of freedom.

[‖]Pooled effect size estimated using the random-effects model.

Table 3

Moderators of Effect of Antidepressant Exposure on Outcomes of Low Birth Weight and Preterm Birth

		Within Group					Effect of Moderator		
				Heterogeneity					
Moderator	**No. of Studies**	**Relative Risk‖ % (95% CI)**	***P* Value**	**Q_{df} Within**	***P* Value**	**% Variance Explained**	**Q_{df} Between**	***P* Value**	**% Variance Explained**
Low Birth Weight									
Drug Type									
SSRIs	9	1.48 (1.22–1.79)	<.001	17.9_8	.02	55	0.3_1	.57	1
Other/mixed antidepressants	6	1.31 (0.90–1.90)	.16	18.4_5	.003	73			
Study Design									
Retrospective	8	1.36 (1.18–1.57)	<.001	12.7_7	.08	45	0.2_1	.66	1
Prospective	7	1.54 (0.92–2.58)	.10	19.6_6	.003	69			
Control Group§									
Depressed	2	2.35 (1.44–3.83)	.001	0.1_1	.76	0			
Mixed	8	1.32 (1.03–1.68)	.03	25.8_7	.001	73	4.3_2	.12	12
Non-Depressed	5	1.53 (1.06–2.20)	.02	5.6_4	.23	29			
Control for Depression Severity									
Yes	2	1.89 (0.15–23.5)	.62	5.8_1	.02	83	0.0_1	.85	0
No	13	1.47 (1.26–1.72)	<.001	27.8_{12}	.006	57			
Preterm Birth									
Drug Type									
SSRIs	18	1.74 (1.52–2.00)	<.001	35.1_{17}	.006	52	0.4_1	.55	1
Other/mixed antidepressants	10	1.63 (1.38–1.93)	<.001	13.5_9	.14	33			
Study Design									

		Within Group					Effect of Moderator		
				Heterogeneity					
Moderator	**No. of Studies**	**Relative Risk‖ % (95% CI)**	***P* Value**	**Q_{df} Within**	***P* Value**	**% Variance Explained**	**Q_{df} Between**	***P* Value**	**% Variance Explained**
Retrospective	13	1.59 (1.42–1.78)	<.001	24.2_{12}	.02	50	2.6_{1}	.11	5
Prospective	15	1.91 (1.57–2.32)	<.001	18.1_{14}	.20	23			
Control Group‡									
Depressed	4	2.85 (2.00–4.07)	<.001	2.0_{3}	.57	0			
Mixed	11	1.55 (1.39–1.73)	<.001	17.4_{10}	.07	43	11.5_{2}	.003	23
Non-Depressed	13	1.84 (1.50–2.27)	<.001	18.2_{12}	.11	34			
Control for Depression Severity									
Yes	6	1.90 (1.07–3.38)	.03	10.1_{5}	.07	50	0.1_{1}	.70	0
No	22	1.70 (1.53–1.89)	<.001	39.0_{21}	.01	46			

Abbreviations: No. indicates number; CI, confidence interval; df, degrees of freedom.

‖Pooled effect size estimated using the random-effects model.

§Pairwise effect of moderator: depressed vs. mixed, Q_1=4.3, P=.04; depressed vs. non-depressed, Q_1=1.9, P=.17; mixed vs. non-depressed, Q_1=0.4, P=.51.

‡Pairwise effect of moderator: depressed vs. mixed, Q_1=10.4, P=.001; depressed vs. non-depressed, Q_1=4.4, P=.04; mixed vs. non-depressed, Q_1=2.1, P=.14.

Table 4

Comparison of Unadjusted Pooled Relative Risks and Trim-and-Fill Adjusted Pooled Relative Risks

Control Group	No. of Studies	Unadjusted Pooled RR (95% CI)†	Number of Missing Studies	Trim-and-Fill Adjusted Pooled RR (95% CI)‡
Overall	28	1.69 (1.52 to 1.88)	7	1.62 (1.44 to 1.82)
Depressed	4	2.85 (2.00 to 4.07)	0	2.85 (2.00 to 4.07)
Mixed	11	1.55 (1.40 to 1.73)	2	1.53 (1.36 to 1.74)
Non-Depressed	13	1.84 (1.50 to 2.27)	4	1.63 (1.29 to 2.05)

RR indicates relative risk; CI, confidence interval.

†Using random effects models.

‡Using random-random effects trim-and-fill models.