Antidepressant Exposure During Pregnancy and Congenital Malformations: Is There an Association? A Systematic Review and Meta-Analysis of the Best Evidence

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ABSTRACT

Objective: Depression is often not optimally treated during pregnancy, partially because of conflicting data regarding antidepressant medication risk. This meta-analysis was conducted to determine whether antenatal antidepressant exposure is associated with congenital malformations and to assess the effect of known methodological limitations.

Data Sources: EMBASE, CINAHL, PsycINFO, and MEDLINE were searched from their start dates to June 2010. Keywords of various combinations were used, including, but not limited to *depressive/mood disorder*, *pregnancy*, *antidepressant drug/agent*, *congenital malformation*, and *cardiac malformation*.

Study Selection: English language studies reporting congenital malformations associated with antidepressants were included. Of 3,074 abstracts reviewed, 735 studies were retrieved and 27 studies were included.

Data Extraction: Two reviewers working independently assessed article quality. Data on use of any antidepressant, including fluoxetine and paroxetine specifically, were extracted. Outcomes included congenital malformations, major congenital malformations, cardiovascular defects, septal heart defects (ventral septal defects and atrial septal defects), and ventral septal defects only.

Results: Nineteen studies were above quality threshold and make up the primary meta-analyses. Pooled relative risks (RRs) were derived by using random-effects methods. Antidepressant exposure was not associated with congenital malformations (RR = 0.93; 95% CI, 0.85–1.02; $P = .113$) or major malformations (RR = 1.07; 95% CI, 0.99–1.17; $P = .095$). However, increased risk for cardiovascular malformations (RR = 1.36; 95% CI, 1.08–1.71; $P = .008$) and septal heart defects (RR = 1.40; 95% CI, 1.10–1.77; $P = .005$) were found; the RR for ventral septal defects was similar to septal defects, although not significant (RR = 1.54; 95% CI, 0.71–3.33; $P = .274$). Pooled effects were significant for paroxetine and cardiovascular malformations (RR = 1.43; 95% CI, 1.08–1.88; $P = .012$). These results are contrasted with those addressing methodological limitations but are typically consistent.

Conclusions: Overall, antidepressants do not appear to be associated with an increased risk of congenital malformations, but statistical significance was found for cardiovascular malformations. Results were robust in several sensitivity analyses. Given that the RRs are marginal, they may be the result of uncontrolled confounders. Although the RRs were statistically significant, none reached clinically significant levels.

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The consequences of a major depressive episode during pregnancy include effects on the mother, her infant, and family.[1–3] Although treatment is essential, the use of antidepressant medication during pregnancy has been found to be lower than other times of the life cycle.[4] One of the contributing factors for poor uptake of pharmacologic interventions appears to be concerns regarding the safety of antidepressant exposure for the fetus.[5] For example, preliminary reports of neonatal cardiovascular malformations following paroxetine exposure in early pregnancy[6] led to both the US Food and Drug Administration[6a] and Health Canada[6b] issuing advisories in 2005 warning about potential risks associated with the use of antidepressants during pregnancy. However, the warnings suggested a direct conflict between safety of the fetus and a mother's need for antidepressant medication, perhaps without regard to the documented negative effects of untreated depression on pregnancy outcomes.[3,7]

The results of prior meta-analyses have been conflicting. Several have found no evidence of increased risk of major congenital malformations above the baseline[8–10] rate, which has been widely cited as 1%–3% for any pregnancy in North America[11–14] and less than 4% for minor congenital malformations.[15] The most recent meta-analyses did report an increased risk for congenital malformations[16] and cardiac malformations[13,16] with paroxetine exposure specifically. Unfortunately, many individual studies have serious methodological limitations[17] that were not taken into account in the previous meta-analyses. For example, raw data unadjusted for confounders were used or studies were based on convenience samples. Furthermore, it is important to note the distinction between statistical significance and clinical significance when interpreting scientific evidence for clinical practice implications. The aim of this study was to synthesize the available data on congenital malformations, including cardiac, in infants of mothers who took antidepressant medications during pregnancy. In order to address the methodological limitations of the available research, we excluded studies below a quality threshold, used adjusted data where possible, examined for the effect of exposure contamination with any

Clinical Points

- Antidepressants do not appear to be associated with an increased risk of congenital malformations overall.
- Antidepressants may be associated with cardiovascular malformations.
- Clinical significance does not always follow from statistical significance, and clinicians must consider the risks of depressive illness prior to making any treatment decisions.

antidepressant use in the control group, and examined the influence of whether or not the samples were population based or obtained by convenience.

DATA SOURCES AND STUDY SELECTION

Following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,[18] 2 professional librarians with expertise in the areas of psychopharmacology and psychiatry independently conducted literature searches. A variety of keyword combinations were utilized, such as *depressive/mood disorder; pregnancy/pregnancy trimesters; tricyclic antidepressant drugs; antidepressant drug/agent; selective serotonin reuptake inhibitors, SSRIs; monoamine oxidase inhibitors; prenatal or antenatal, infant/outcomes; congenital malformation, cardiac malformation* (see supplementary material for full list of keywords). Strategies were based on the subject headings specific to the individual databases searched, combined with appropriate keywords and keyword phrases, and truncated if necessary. Concepts were combined with Boolean operators (AND, OR) to either broaden "like" concepts (OR) or narrow them (AND) to ensure more than 1 concept was included in the results. The explode feature (available for all of the databases searched, with the exception of MEDLINE In-Process and Scopus) was also used to broaden like concepts. The databases used included MEDLINE (Ovid), MEDLINE In-Process (Ovid) to access current literature (keyword searching only), PsycINFO (American Psychological Association; Ovid), CINAHL (Nursing and Allied Health), EMBASE (Excerpta Medica, Elsevier; Ovid), and Scopus (Elsevier) to access current literature (keyword searching only). The databases were searched from their start date to June 30, 2010. Reference lists of reviews and meta-analyses were also searched for further articles, but none were found.

Inclusion and Exclusion Criteria

Cohort and case-control studies published in English were eligible for inclusion if they (1) reported original data and at least 1 malformation of interest, (2) reported on any pharmacologic antidepressant agent exposure (ie, selective serotonin reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors), (3) had a nonexposed comparison group of pregnant women for the antidepressant examined, and (4) provided sufficient data to calculate an effect size. Abstracts and conference proceedings were excluded, and unpublished data were not searched because the volume of potentially eligible studies would have made doing so infeasible. Outcomes of interest were identified by the research team as well as the advisory committee of key stakeholders for this program of research, which included representatives from psychiatry, family medicine, obstetrics, neonatology, public health, patient advocacy, and policy. The following outcomes were included in this meta-analysis: any congenital malformation, major congenital malformation (structural defects present at birth that have surgical, medical, or cosmetic significance or a significant effect on function or social acceptability[15,19]), cardiovascular malformation, septal cardiac defect (atrial septal defects or ventral septal defects), and ventral septal defects only as defined by the authors of the original publication. When more than 1 study had been published on the same cohort, we selected the study with the largest number of cases of malformations within each malformation outcome.

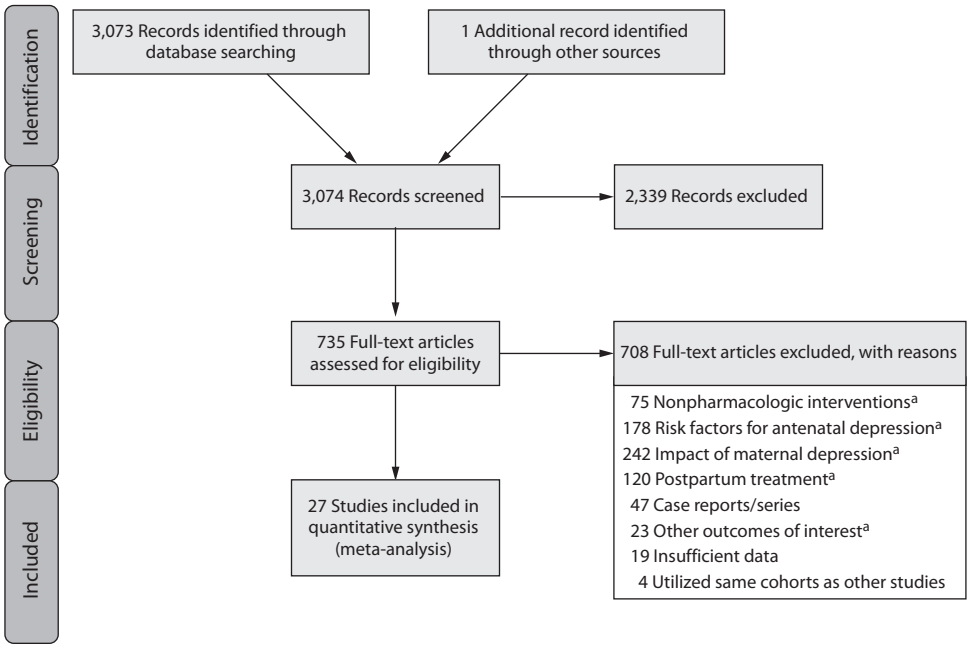
DATA EXTRACTION

The study was part of a larger research program developing a reference guide for physicians to assist in treatment discussions regarding antidepressant use during pregnancy with their patients. The data extraction and quality assessment processes for this program of research have been previously published.[7] Two independent research assistants completed the screening for all articles by their title and abstract, and eligible articles were retrieved. Data extraction forms were completed for all eligible studies and were based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[20] checklist. Data extracted included source, study design, participants (sample, control, demographics, and clinical characteristics), inclusion/exclusion criteria, antidepressants examined, dosage, duration of exposure, primary and secondary outcomes, outcome assessment methods, and loss to follow-up. Authors of original publications were sent requests for raw data if not provided in the article. Eight authors were contacted and 3 replied. Of these, 1 was unable to share data because of confidentiality issues, 1 was not able to meet our timeline, and the last 1 did not respond to our request for further clarification.

Quality Assessment

The Systematic Assessment of Quality in Observational Research (SAQOR)[7] tool used for this investigation was developed by our team and based on previously published quality assessment tools (Downs and Black[21] and the Newcastle-Ottawa Scale[22]) and adapted to assess study quality in this area of research. Nineteen aspects of each study under the following categories were evaluated by outcome: (1) sample, (2) control group, (3) quality of exposure/outcome measure, (4) follow-up, and (5) distorting influences. Specifically, the distorting influences category included whether analyses controlled for confounders such as depression, other psychotropic medications, smoking, alcohol, or illicit drug use. On the basis of the aforementioned criteria, we assigned a final quality rating of high, moderate, low, or very

Figure 1. Identification of Independent Studies for Inclusion in Meta-Analysis (adapted from PRISMA 2009 flow diagram[30])



[a]Other outcomes of interest in our research program.

low using a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[23] Studies were then categorized as "above quality threshold" (high, moderate, or low quality) or "below quality threshold" (very low quality). Results of the data extraction and quality assessment were compared between raters for each study, with any differences resolved through consensus by the principal investigators.

Statistical Analyses

Adjusted risk estimates were preferred when these were available, and odds ratios (ORs) and relative risks (RRs) were considered as equivalent measures of risk. We calculated ORs from the raw number of cases and controls when no such risk estimate was reported. For each outcome, we calculated 1 estimate of the OR for malformations for each article and pooled these risks across studies using random-effects models.[24] We added 0.5 to cells with 0 cases when calculating the OR.[25] All analyses were conducted on the log scale. Visual inspection of funnel plots depicting the risk estimates (on the log scale) against their standard error and Egger regression-based test[26] were used to assess publication bias. Cochrane Q and I^2 were used to quantify between-study heterogeneity.[27,28] I^2 may be interpreted as the proportion of the total variance due to between-study heterogeneity. For studies reporting multiple exposure or control groups, these groups were combined in order to calculate a single risk estimate for each study where possible, if they were independent. For each outcome, our main analysis consisted of the pooled risk for the studies determined to be above quality threshold; further, we excluded studies that included some antidepressants in their control group (for example, when only selective serotonin reuptake inhibitor [SSRI] use was used as the exposure group but other antidepressants were not assessed and controls could have been, and in some cases were reported to have been, exposed to any antidepressants in their pregnancy) and also reran the analysis with articles that matched or adjusted their data in any way. Because of the generally low study quality, we also estimated the pooled risk excluding all convenience samples. We selected 2 specific antidepressants (fluoxetine and paroxetine) for a separate analysis of their effect on malformations where sufficient data were available, as more information was available for them compared to others. All analyses were conducted with Stata statistical software, version 10.1 (StataCorp LP)[29] and similar to our other work in Ross et al.[30]

RESULTS

Of the 3,074 abstracts reviewed, 2,339 were excluded based on title and abstract. In total, 735 articles were retrieved and assessed for eligibility and 31 articles met the inclusion criteria (Figure 1).[31] Of these, 4 articles were excluded because they were duplicate analyses of studies already included in our quantitative analysis, leaving 27 studies[32–58] for a quantitative analysis (Table 1). Nineteen of the 27 studies were above the quality threshold, whereas 8 were below. Most studies reported data on more than 1 outcome (14 above quality threshold reported on any congenital malformation, 11 on any major malformation, 13 on any cardiovascular malformation, 9 on any septal cardiac defect [atrial septal defects or ventral septal defects], and 5 on ventral septal defects specifically). Eleven studies used a convenience sample, while 16 studies used either a

Table 1. Study Characteristics of 27 Studies in the Congenital Malformations Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders[a]	Drug	Results	Outcome Definition
Pastuszak et al,[32] 1993[b,c,d,e,f,g]	B	Canada, United States	Fluoxetine, n = 128 and 74 TCA, n = 74 NTC, n = 128	Matched for age and date of consultation (collected data on alcohol and smoking, and reported groups had "similar distribution")	Fluoxetine, TCA	Major malformations: 2% in fluoxetine vs 1.8% in NTC (P = .38) and 3.4% in fluoxetine, 0% in TCA, vs 3% in NTC (P = .8)[h] Cardiac malformations: fluoxetine, 1 VSD event; TCA, 0 events; NTC, 1 VSD event[h]	
Chambers et al,[33] 1996[b,c,g]	B	United States	Fluoxetine, n = 164 NTC, n = 226	(Collected data on alcohol, smoking, and other drugs)	Fluoxetine	Major malformations: 5.5% in fluoxetine vs 4.0% in NTC (P = .63)	Major malformations: structural defect with cosmetic or functional importance seen in less than 4% of the general population
Kulin et al,[34] 1998[b,c,d,g,i]	A	Canada, United States	SSRI, n = 267 NTC, n = 267	Groups "matched" (No difference between groups for alcohol or age, parity, or previous spontaneous abortion)	Sertraline, paroxetine, fluvoxamine, fluoxetine	Major malformations: 4.1% in SSRI vs 3.8% in NTC (RR = 1.06; 95% CI, 0.43 to 2.62; P = .91) Cardiac malformations: SSRI , 2 cardiac events; NTC, 4 cardiac events	Major malformations: structural or functional anomalies with significant medical or social consequences
Einarson et al,[35] 2001[b,c,d,g]	B	Canada, United States, Italy, Brazil	Venlafaxine, n = 150 SSRI, n = 150 NTC, n = 150	(Reported no significant difference for age, alcohol and smoking)	Venlafaxine, fluoxetine, paroxetine, sertraline, fluvoxamine	Major malformations: 1.6% in venlafaxine, 2.4% in SSRI vs 0.7% in NTC (P = .89) Venlafaxine vs NTC (OR = 2.21; 95% CI, 0.20 to 24.69; P = .93) Venlafaxine vs SSRI (OR = 0.66; 95% CI, 0.11 to 3.99; P = .99)[h] Cardiac malformations: venlafaxine, 0 events; SSRI, 1 event; NTC, 1 event[h]	Major malformations: any anomaly with adverse effect on the function or social acceptability of the individual
Simon et al,[36] 2002[b,c,d,i]	A	United States	SSRI, n = 185; control, n = 185 TCA, n = 209; control, n = 209	Matched for maternal age, year of delivery, length of enrollment in health plan, lifetime antidepressant prescriptions filled and refilled, lifetime history of psychiatric treatment (compared smoking, alcohol, other drug use)	Fluoxetine, fluvoxamine, sertraline, paroxetine, amitriptyline, imipramine, doxepin, nortriptyline, protriptyline, desipramine	Major malformations: SSRI vs control (OR = 1.36; 95% CI, 0.56 to 3.30), TCA vs control (OR = 0.82; 95% CI, 0.35 to 1.95)[h] Minor malformations: SSRI vs control (OR = 1.14; 95% CI, 0.56 to 2.31), TCA vs control (OR = 0.76; 95% CI, 0.37 to 1.58)[h] Cardiac malformations: 0.5% in TCA vs 1.0% in unexposed (OR = 0.50; 95% CI, 0.05 to 5.53), 2.2% in SSRI vs 0.0% in unexposed[h]	
Einarson et al,[37] 2003[b,c,d,e,f,g]	B	Canada, United States, Italy	Trazodone/ nefazodone, n = 147 Nonteratogenic antidepressants, n= 147 NTC, n = 147	Matched for timing of call to Teratogen Information Service (compared age, smoking, alcohol use)	Trazodone, nefazodone, other nonteratogenic antidepressants	Major malformations: 1.6% in nefazodone/ trazodone, 2.4% in other nonteratogenic antidepressants vs 3.0% in NTC (P = .75)[h] Cardiac malformations: trazodone/ nefazodone, 0 events; other antidepressants, 1 VSD event; NTC, 1 VSD event[h]	Major malformations: any anomaly with adverse effect on the function or social acceptability of the individual
Chun-Fai-Chan et al,[38] 2005[b,c,g]	B	Canada, United States, United Kingdom	Bupropion, n = 91 Other antidepressant, n = 89 NTC, n = 89	Matched for age, alcohol use, smoking	Bupropion, other antidepressants	Major malformations: 0 in bupropion, 1 in other antidepressants vs 2 in NTC (P = .51)[h]	

continued

Table 1 (continued). Study Characteristics of 27 Studies in the Congenital Malformations Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders[a]	Drug	Results	Outcome Definition
Malm et al,[39] 2005[b,c,i]	A	Finland	SSRI, n = 1,398 Control, n = 1,782	Matched for year of pregnancy ending, age, parity, geographic area, social status Adjusted for maternal age, smoking, low social status, nulliparity, purchase of other reimbursed drugs	Citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine	Major malformations: SSRI vs control (AOR = 1.0; 95% CI, 0.6 to 1.7; $P = .4$)	Major congenital anomalies: significant congenital structural anomaly, congenital hypothyroidism, or chromosomal defect Minor anomalies were not included
Sivojelezova et al,[40] 2005[b,c,d,e,g,i]	A	Canada	Citalopram, n = 108 Other SSRIs, n = 115 NTC, n = 118	Matched for maternal age, gestational age at time of recruitment (collected data on alcohol, smoking, and other drugs)	Citalopram, other SSRIs	Major malformations: 0.9% in citalopram, 2.6% in other SSRIs vs 0.8% in NTC ($P = .52$)[h] Cardiac malformations: citalopram, 1 ASD event; other SSRIs, 2 cardiac events (1 ASD); NTC, 0 events[h]	Major malformations: structural and/or functional anomalies requiring surgical correction or altering social acceptability of the child
Djulus et al,[41] 2006[b,c,g]	B	Canada, United States, Israel, Australia, Italy, United Kingdom	Mirtazapine, n = 104 Other antidepressant, n = 104 NTC, n = 104	Matched for maternal age at time of conception, tobacco use, alcohol use, gestational age at the first contact, chronic conditions	Mirtazapine, other antidepressants	Major malformations: 1.9% in mirtazapine, 1.0% in other antidepressants vs 1.9% in NTC; mirtazapine vs other antidepressants ($P = .50$); mirtazapine vs NTC ($P = .69$)[h]	Major malformations: structural abnormality that was lethal, required medical or surgical treatment, or was of importance cosmetically and would affect quality of life. Excluded genetic disorders and chromosomal defects
Levinson-Castiel et al,[42] 2006[b,c,d,e,f,i]	A	Israel	SSRI, n = 60 Unexposed, n = 60	Matched for sex, gestational age, mode of delivery, birth weight (excluded other medications, recreational drugs, alcohol, conditions or congenital anomalies affecting the central nervous system, preterm infants)	Any SSRI	Major malformations: 5% in SSRI vs 1.7% in unexposed ($P = .60$) Cardiac malformations: SSRI, 2 VSD events; unexposed, 0 events	
Wen et al,[43] 2006[b,c]	A	Canada	SSRI, n = 972 Unexposed, n = 3,878	Matched for year of birth, type of institute at birth, first 3 digits of mother's postal code Adjusted for maternal age, parity, drug dependence, multigestation, receipt of provincial social assistance	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	Major malformations: SSRI vs unexposed (AOR = 0.98; 95% CI, 0.59 to 1.64) Minor malformations: SSRI vs unexposed (AOR = 1.02; 95% CI, 0.69 to 1.51)[h]	*ICD-9* codes used to identify malformations (major and minor)
Davis et al,[44] 2007[b,d,i]	A	United States	SSRI, n = 805 Unexposed, n = 49,031 TCA, n = 167 Unexposed, n = 49,669	Stratified by health system, maternal age, birth season	SSRIs, TCAs	One or more malformation risk: SSRIs (RR = 0.97; 95% CI, 0.81 to 1.16); TCAs (RR = 0.86; 95% CI, 0.57 to 1.30)[h] Cardiac malformations: SSRI, 17 cardiac events; TCA, 2 cardiac events[h]	Used *ICD-9* codes and reviewed charts for 3 categories of congenital anomalies
Källén and Olausson,[45] 2007[b,i]	A	Sweden	SSRI, n = 6,555 Unexposed, n = 873,876	Adjusted for year of birth, maternal age, parity, smoking, previous miscarriages	Paroxetine, fluoxetine, citalopram, sertraline, fluvoxamine, escitalopram	Congenital malformations: SSRI (AOR = 0.89; 95% CI, 0.79 to 1.07)	Utilized definitions by the Swedish health registers (some used *ICD* codes), chromosomal anomalies excluded

continued

Table 1 (continued). Study Characteristics of 27 Studies in the Congenital Malformations Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders[a]	Drug	Results	Outcome Definition
Louik et al,[46] 2007[d,e,i]	A	Canada, United States	Infants with birth defects, n = 9,849 Infants without birth defects, n = 5,860	Adjusted for maternal age, race/ethnic group, education, year of last menstrual period, study center, smoking, alcohol, family history of birth defect, prepregnancy BMI, parity, seizures, diabetes mellitus, hypertension, infertility, use of folic acid	SSRI, non-SSRI antidepressants	Cardiac malformations: SSRIs (AOR = 1.2; 95% CI, 0.9 to 1.6); non-SSRIs (AOR = 0.8; 95% CI, 0.5–1.5)[h] Septal heart defects: SSRIs (AOR = 1.2; 95% CI, 0.8 to 1.8), non-SSRIs (AOR = 1.1; 95% CI, 0.6 to 2.4)[h]	*ICD-9-CM* codes
Boucher et al,[47] 2008[b,d,e,f]	B	Canada	Any antidepressant, n = 73 Unexposed, n = 73	Matched for same hospital, gestational age, and date at delivery (No group difference for smoking, alcohol, or age)	Citalopram, paroxetine, sertraline, fluoxetine, fluvoxamine, venlafaxine, amitriptyline, trazodone, mirtazapine	Congenital malformations: 3% in any antidepressant vs 5% in unexposed ($P = .68$) Cardiac malformations: exposed, 1 VSD event; unexposed, 0 events	
Diav-Citrin et al,[48] 2008[b,c,d,g]	B	Israel, Italy, Germany	Paroxetine, n = 463 Fluoxetine, n = 346 NTC, n = 1,467	Adjusted cardiac analysis for gestational age at call, maternal age, smoking, previous miscarriages, origin, concomitant psychiatric medications, multifetal gestation, SSRI dose	Paroxetine, fluoxetine	Major malformations: 5.2% in paroxetine, 4.7% in fluoxetine vs 2.5% in NTC ($P < .05$)[h] Cardiac malformations: 2.0% in paroxetine, 2.8% in fluoxetine vs 0.6% in NTC ($P < .05$) (paroxetine exposed: AOR = 2.66; 95% CI, 0.80–8.90) (fluoxetine exposed: AOR = 4.47; 95% CI, 1.31–15.27)[h]	Major anomalies: structural abnormalities with serious surgical, medical, or cosmetic consequences. Significant neurodevelopmental or functional abnormalities were classified as major anomalies when they necessitated special education or interventions
Einarson et al,[49] 2008[d,g,i]	A	Canada, United States, Italy, Switzerland, Australia, Germany, Israel, Finland	Paroxetine, n = 1,174 NTC, n = 1,174	(Reported "similar characteristics," including smoking and alcohol use)	Paroxetine	Cardiac malformations: 0.7% in paroxetine vs 0.7% in NTC (OR = 1.1; 95% CI, 0.36 to 2.78)	
Oberlander et al,[50] 2008[b,c,d,e,f]	A	Canada	SSRI, n = 2,625 Unexposed, n = 107,320	Adjusted for age, prenatal care visits, diagnosis of depression in year before pregnancy, number of psychiatric visits and physician visits in year before pregnancy, diseases and complications of pregnancy, depression in first trimester, prescription fill after pregnancy known	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine	Major malformations: 2.9% in SSRI vs 3.1% in unexposed (regression adjusted risk difference = −0.61; 95% CI, −1.44 to 0.21) Cardiac malformations: SSRI, 17 events vs control, 512 events (regression adjusted risk difference = 0.21, 95% CI, −0.14 to 0.55) Septal heart defects: SSRI, 12 events (6 VSD events); control, 294 events (219 VSD events) (VSD: regression adjusted risk difference = 0.10; 95% CI, −0.12 to 0.33)	Major congenital anomalies identified by *ICD-9* codes (740.0–759.9) Excluded specific minor anomalies

continued

Table 1 (continued). Study Characteristics of 27 Studies in the Congenital Malformations Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders[a]	Drug	Results	Outcome Definition
Ramos et al,[51] 2008[b,c]	A	Canada	Any antidepressant, n = 1,101 Unexposed, n = 1,228	Adjusted for maternal age, receiving welfare, urban dweller, living alone, psychiatric disorders and comorbidities unrelated to psychiatric disorders before and during pregnancy, diabetes and hypertension before and during pregnancy, baby's gender, year of pregnancy, prenatal visits	SSRI, TCA, bupropion, mirtazapine, moclobemide, nefazodone, trazodone, venlafaxine	Major malformations: any antidepressant (AOR = 1.10; 95% CI, 0.75 to 1.62)	*ICD-9* codes
Einarson et al,[52] 2009[b,c,g,i]	A	Canada	Any antidepressant, n = 928 NTC, n = 928	Matched for maternal age, smoking, alcohol use	Bupropion, citalopram, escitalopram, fluvoxamine, nefazodone, paroxetine, mirtazapine, fluoxetine, trazodone, venlafaxine, sertraline	Major malformations: 2.5% in any antidepressant vs 2.6% in NTC (risk ratio = 0.96; 95% CI, 0.55 to 1.67)	
Merlob et al,[53] 2009[d,e,f]	A	Israel	SSRI, n = 235 Unexposed, n = 67,636	(Collected data on smoking and alcohol)	Paroxetine, fluoxetine, citalopram, escitalopram, sertraline, fluvoxamine, venlafaxine	Cardiac malformations: 3.4% in SSRI vs 1.6% in unexposed (RR = 2.17; 95% CI, 1.07 to 4.39; $P = .023$) Septal heart defects: exposed, 6 VSD events; unexposed, 656 VSD events	Screened infants with heart murmurs for cardiac malformations (excluded cases of congenital syndromes) Functional murmurs, isolated persistent foramen ovale, peripheral pulmonic stenosis, and patent ductus arteriosus excluded
Pedersen et al,[54] 2009[c,i]	A	Denmark	SSRI, n = 1,370 Unexposed, n = 493,113	Adjusted for age, year, income, marital status, smoking	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine	Major malformations: SSRI exposure (AOR = 1.21; 95% CI, 0.91 to 1.62; NS)	*ICD-10* codes Malformations detected at birth for live-born infants or within year 1 after birth were considered
Wichman et al,[55] 2009[d,e,f]	A	United States	Exposed, n = 808 Unexposed, n = 24,406		Citalopram, escitalopram, paroxetine, fluoxetine, sertraline, venlafaxine	Cardiac: 0.4% in exposed vs 0.8% in unexposed ($P = .23$) VSD: 0.0% in exposed vs 0.1% in unexposed ($P > .99$)	Congenital heart disease—abnormality in cardiocirculatory function or structure, present at birth. VSD—hole within the septum between the heart ventricles Heart disease diagnosed immediately following birth and prior to discharge home included

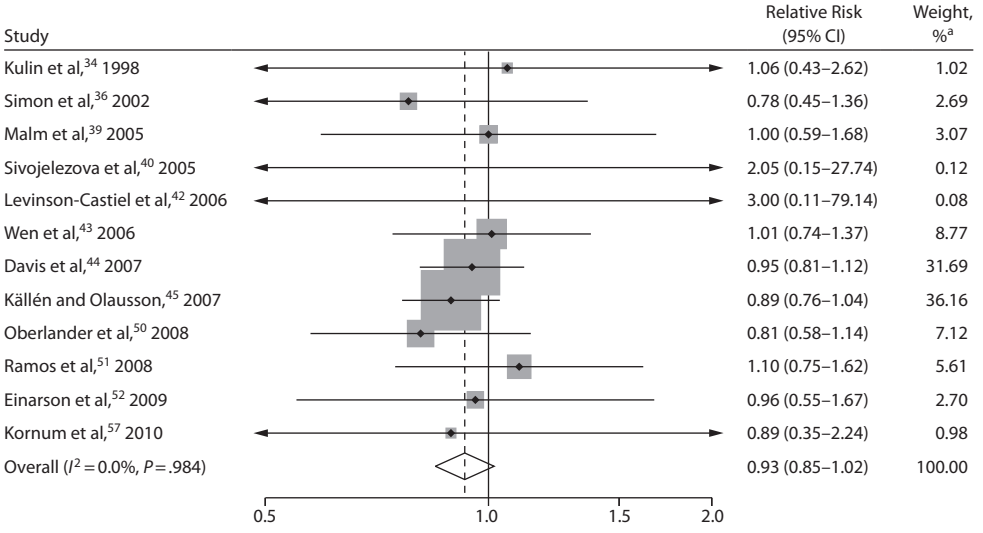
continued

Table 1 (continued). Study Characteristics of 27 Studies in the Congenital Malformations Meta-Analyses

Article	Quality Threshold	Country	Sample Size	Confounders[a]	Drug	Results	Outcome Definition
Bakker et al,[56] 2010[d,e,f]	A	Netherlands	Exposed, n = 16 Unexposed, n = 1,266	Adjusted for year of birth (compared age, smoking, alcohol, number of other characteristics)	Paroxetine	Cardiac malformations: 10 events in exposed cases (AOR = 1.5; 95% CI, 0.5 to 4.0; *P* = .476) Septal heart defects: exposed, 4 (AOR = 1.6; 95% CI, 0.4 to 5.6; *P* = .493) VSD: exposed, 1 (AOR = 0.5; 95% CI, 0.1 to 4.2; *P* = .528)	*ICD-9* and *ICD-10*
Kornum et al,[57] 2010[b,d,e,i]	A	Denmark	SSRI, n = 2,062 Non-SSRI antidepressant, n = 358 Unexposed, n = 213,712	Adjusted for smoking, maternal age, birth order, birth year	Paroxetine, fluoxetine, sertraline, citalopram, escitalopram, non-SSRI antidepressant	Congenital malformations: 5.1% in SSRI, 3.5% in unexposed (AOR = 1.3; 95% CI, 1.1 to 1.6); non-SSRI exposure (AOR = 0.5; 95% CI, 0.2 to 1.1)[h] Cardiac malformations: 1.3% in SSRI vs 0.7% in unexposed (AOR = 1.7; 95% CI, 1.1 to 2.5)[h] Septal heart defects: SSRI, 18 events (AOR = 1.4; 95% CI, 0.8 to 2.3); non-SSRI, 0 events[h]	*ICD*-8 and *ICD-10* codes Malformations had to be registered within the first year of life and a singleton birth, excluded chromosomal anomalies
Reis and Källén,[58] 2010[c,d,e,i]	A	Sweden	SSRI, n = 10,170 TCA, n = 1,662 SNRI, n = 1,351 MAOI, n = 37 Unexposed, n = 1,236,053	Adjusted for year of birth, maternal age, parity, smoking, BMI	SSRIs, TCAs, SNRIs, MAOIs	Severe malformations: TCAs (AOR = 1.36; 95% CI, 1.07 to 1.72), SSRIs (AOR = 1.08; 95% CI, 0.97 to 1.21), SNRIs (AOR = 1.00; 95% CI, 0.73 to 1.37), antidepressants (AOR = 1.10; 95% CI, 1.00–1.22) Cardiac malformations: TCAs (AOR = 1.63; 95% CI, 1.12 to 2.36), SSRIs (AOR = 0.99; 95% CI, 0.82 to 1.20), SNRIs (AOR = 1.33; 95% CI, 0.84 to 2.09), antidepressants (AOR = 1.11; 95% CI, 0.94–1.30) Septal heart defects: TCAs (AOR = 1.84; 95% CI, 1.13 to 2.97), SSRIs (AOR = 1.00; 95% CI, 0.77 to 1.29), SNRIs (AOR = 1.26; 95% CI, 0.63 to 2.26), antidepressants (AOR = 1.11; 95% CI, 0.89–1.38)	*ICD-9* and *ICD-10* codes Excluded preauricular appendix, patent ductus (preterm infant), tongue tie, single umbilical artery, hip subluxation, and nevus, undescended testicle. Considered these conditions common, recorded variably and of lower significance clinically

[a]Refers to matching, exclusions, or adjusted data for outcome of interest. Individual studies may have collected or compared groups on other characteristics or adjusted data on other outcomes.
[b]Included in our any congenital malformations meta-analysis.
[c]Included in our major malformations meta-analysis.
[d]Included in our cardiovascular malformations meta-analysis.
[e]Included in our septal heart defects meta-analysis.
[f]Included in our ventral septal defects meta-analysis.
[g]Convenience sample.
[h]We combined the drug groups in our analyses.
[i]Included in no antidepressant exposure in control group analysis.
Abbreviations: A = above quality threshold; AOR = adjusted odds ratio; ASD = atrial septal defects; B = below quality threshold; *ICD-8* = *International Classification of Diseases, Eighth Revision*; *ICD-9-CM* = *International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10* = *International Classification of Diseases, Tenth Revision*; MAOI = monoamine oxidase inhibitor; NS = nonsignificant; NTC = nonteratogen control; OR = odds ratio; RR = relative risk; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; VSD = ventral septal defects.

Figure 2. Exposure to Any Antidepressant and the Risk of Congenital Malformations: Meta-Analysis Results for Studies Above the Quality Threshold



[a]Weights are from random effects analysis.

population- or hospital-based sample. Of all studies available, 13 clearly stated that no antidepressants were used in the control group and 21 reported adjusted data or applied matching. Information on fluoxetine was available from 0 to 7 studies depending on the outcome, and 0–8 studies were available for paroxetine.

Congenital Malformations

Overall, we pooled results from 12 studies* that were above quality threshold; the RR for congenital malformations was 0.93 (95% CI, 0.85–1.02; P = .113; Figure 2). Results were similar when studies were restricted to those studies that clearly excluded antidepressants from the control group. When studies with any adjustment were analyzed, all the studies regardless of quality, or 10 studies that did not use convenience samples (regardless of study quality), yielded similar results, with RRs ranging from 0.92 to 0.95 (Table 2). The RRs from the meta-analyses with the individual antidepressants (fluoxetine and paroxetine) were similar in magnitude (ranging from 1.02 to 1.15) and not statistically significant (Supplementary eTable 1).

Major Congenital Malformations

When only major malformations were analyzed, the pooled risk was small and not significant for the studies that were above quality threshold (RR = 1.07; 95% CI, 0.99–1.17; P = .095; Supplementary eFigure 1). Overall, the RRs for the other analyses were small, between 1.07 and 1.10 (Table 2), but statistically significant depending on the subanalysis conducted. Results were not significant for any of the analyses for paroxetine use; however, the risk associated with the use of fluoxetine was similar to the overall analyses, with slightly higher RRs between 1.20 and 1.29 (Supplementary eTable 1).

Cardiovascular Malformations

With regard to cardiovascular malformations (13 studies above quality threshold) as the disease outcome, the pooled RR was small (RR = 1.36; 95% CI, 1.08–1.71; P = .008; Figure 3) but statistically significant in all analyses, ranging from 1.26 to 1.39 (see Table 2). One study[58] in particular had a strong influence on the results because of its sample size, detailed exposure measurement, and moderate study quality and was included in most subanalyses. Few studies were available for analyses stratified by medication. The risk associated with paroxetine was slightly higher (RR = 1.43; 95% CI, 1.08–1.88; P = .012; RRs between 1.43–1.47) and consistently statistically significant. The risk associated with fluoxetine was slightly lower and not statistically significant (RRs from 1.17 to 1.33; Supplementary eTable 1).

Septal Heart Defects (atrial septal defects or ventral septal defects)

Results involving the 9 studies above quality threshold indicated a significant association between exposure to antidepressants during pregnancy and an increased risk for any septal heart defect (atrial septal defects or ventral septal defects) (RR = 1.40; 95% CI, 1.10–1.77; P = .005; Supplementary eFigure 2). In subanalyses, the RRs were similar to the findings for any cardiovascular malformation (RRs between 1.17 and 1.40; Table 2) and statistically significant. Two studies[46,58] had a particularly strong influence on the pooled estimate. There was no evidence suggesting that paroxetine or fluoxetine were associated with septal defects (Supplementary eTable 1); however, only 3 and 2 studies, respectively, were available for such an analysis.

*Pedersen et al[54] and Reis and Källén[58] were excluded from this analysis, as these studies were population based and from the same country as Kornum et al[57] and Källén and Olausson,[45] respectively.

Table 2. Exposure to Any Antidepressant and Risk of Malformation: Meta-Analyses Results

Analysis	No. of Studies	No. of Cases	Total Sample Size	Relative Risk	95% CI	*P* Value	*P* Value for Heterogeneity	I^2 (%)	*P* Value for Publication Bias
Congenital malformations									
Studies above quality threshold	12	52,572	1,223,210	0.93	0.85–1.02	.113	.984	0.0	
Studies above quality threshold, no antidepressants in controls	9	48,675	1,102,717	0.92	0.83–1.02	.115	.988	0.0	
Studies above quality threshold with adjusted data	12	52,572	1,223,210	0.93	0.85–1.02	.113	.984	0.0	
All studies	20	52,687	1,226,756	0.95	0.87–1.04	.308	.684	0.0	.439
All studies excluding convenience samples	10	52,506	1,220,536	0.92	0.84–1.01	.099	.953	0.0	
Major malformations									
Studies above quality threshold	11	56,334	1,940,124	1.07	0.99–1.17	.095	.857	0.0	
Studies above quality threshold, no antidepressants in controls	8	52,605	1,817,081	1.10	1.01–1.21	.032	.986	0.0	
Studies above quality threshold with adjusted data	11	56,334	1,940,124	1.07	0.99–1.17	.095	.857	0.0	
All studies	18	56,443	1,943,538	1.09	1.01–1.18	.033	.666	0.0	.984
All studies excluding convenience samples	8	56,262	1,936,142	1.08	0.99–1.17	.091	.650	0.0	
Cardiovascular malformations									
Studies above quality threshold	13	20,444	1,547,012	1.36	1.08–1.71	.008	.134	31.1	
Studies above quality threshold, no antidepressants in controls	9	17,945	1,338,913	1.33	1.02–1.75	.037	.147	33.9	
Studies above quality threshold with adjusted data	10	19,128	1,450,406	1.35	1.07–1.70	.011	.181	28.6	
All studies	18	20,473	1,550,271	1.26	1.07–1.47	.005	.313	11.8	.238
All studies excluding convenience samples	11	20,419	1,542,707	1.39	1.09–1.79	.009	.089	39.1	
Septal heart defects									
Studies above quality threshold	9	10,195	1,703,561	1.40	1.10–1.77	.005	.075	44.0	.144
Studies above quality threshold, no antidepressants in controls	5	8,954	1,494,368	1.17	1.03–1.33	.013	.527	0.0	
Studies above quality threshold with adjusted data	7	9,509	1,608,759	1.35	1.08–1.68	.009	.105	42.9	
All studies	12	10,200	1,704,652	1.37	1.11–1.69	.003	.168	28.2	.173
All studies excluding convenience samples	9	10,194	1,703,049	1.40	1.10–1.77	.006	.073	44.3	
Ventral septal defects									
Studies above quality threshold	5	1,096	207,467	1.54	0.71–3.33	.274	.232	28.4	.557
Studies above quality threshold, no antidepressants in controls	1[a]	2	120	7.51	0.46–121.51	.155			
Studies above quality threshold with adjusted data	3	410	114,382	1.39	0.48–4.07	.542	.275	22.6	
All studies	8	1,101	208,316	1.67	0.94–2.97	.081	.473	0.0	.565
All studies excluding convenience samples	6	1,097	207,613	1.65	0.81–3.36	.168	.294	18.4	

[a]Insufficient number of studies for meta-analyses.

Ventral Septal Defects

Results for ventral septal defects were similar to any cardiac malformations (RR = 1.54; 95% CI, 0.71–3.33; *P* = .274; Supplementary eFigure 3), but they were not statistically significant; the few studies that investigated this outcome were generally small and reported very few or sometimes no case in either the exposure or the comparison group (Table 2). There were not enough studies to conduct a meta-analysis stratified by paroxetine or fluoxetine.

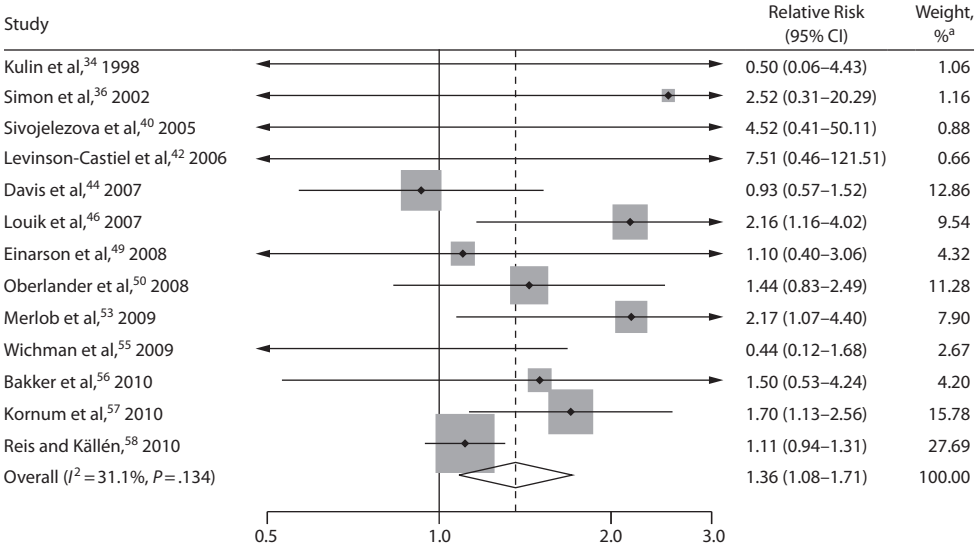
Publication Bias and Influential Studies

When the analyses were repeated with all identified studies regardless of study quality, we found very similar results. We did not find evidence for the presence of publication bias in any of our analyses (see Table 2). When we recalculated the pooled risk, excluding studies one by one, 1 study[58] was found to have had a particular influence on the derived pooled risk. This finding was most apparent for cardiac outcomes, for which exclusion of this study resulted in a slightly higher risk. For all other analyses, the estimate was well within the pooled CIs.

DISCUSSION

We conducted a systematic review and meta-analysis of the literature, examining associations between the use of any antidepressant and rates of overall congenital malformations, overall major congenital malformations, and, more specifically, cardiac malformations (as defined by the authors of the individual articles; see Table 1). Furthermore, on the basis of the available data for cardiac outcomes, we were then able to examine possible associations with antidepressant exposure and septal defects, as well as ventral septal defects alone. In addition to any antidepressant, we were also able to conduct analyses on 2 individual antidepressant medications (paroxetine and fluoxetine). These 2 medications were chosen on the basis of available evidence for meta-analyses on the outcomes of interest; the evidence reflects the focus of previously published literature. We found no evidence that

Figure 3. Exposure to Any Antidepressant and the Risk of Cardiovascular Malformations: Meta-Analysis Results for Studies Above the Quality Threshold



[a]Weights are from random effects analysis.

antidepressants were associated with congenital malformations or major malformations in our primary analyses. Results were generally confirmed in several subanalyses, although there was an indication that antidepressants in general and, more specifically, fluoxetine exposure was associated with major congenital malformations. It is important to consider that these classifications of congenital and major malformations include many different malformations with different timelines of development, which can potentially confound relationships with a specific malformation, if one exists.[54] It is also important to note that we were able to analyze only 2 specific antidepressants, and so we cannot draw conclusions regarding the safety of other individual antidepressant drugs that we did not examine separately. Any antidepressant exposure was found to be associated with cardiac malformations in general. More specifically, when we looked at septal heart defects, we also found any antidepressant exposure to be associated. However, it is important to consider that statistical significance is not equivalent to clinical significance. There were only a few studies with which to further examine categorizations of cardiac malformations, and these studies had a small number of cases. We were able to analyze only ventral septal defects as a subcategory of septal defects, and these analyses were not significant, although the RRs were similar. Further research of high methodological quality is needed to confirm the results presented here.

There may be different associations between specific antidepressants and malformations. For example, antidepressants as a whole were associated with risk for any cardiac malformation, as was paroxetine, yet fluoxetine was not. Regardless of whether a class or individual effect exists, it is important to note that, overall, these results are largely reassuring, as even the nonsignificant meta-analyses did not return an RR higher than 1.67, with the highest significant one being 1.47, which is below the 2-fold increase benchmark that has been cited for clinical significance in this field.[52] The findings also are relieving, as depression during pregnancy is common, with rates as high as 20% being reported,[59] and 1.8%–2.1% of pregnancies having reported exposure to an SSRI,[60,61] among the most frequently used of the antidepressants in pregnancy.[62]

As far as we are aware, our study is the first meta-analysis to report a small increase in major malformations with fluoxetine, the oldest of the SSRIs in use. Note, however, that this was not a consistent finding, as our main analysis, which was with the higher quality studies, was not significant, although it was reduced to 4 studies. Several meta-analyses previously did report an increased risk for cardiovascular malformations with paroxetine (ie, Bar-Oz et al,[13] Wurst et al[16]) but, unlike Wurst et al,[16] we did not find an increased risk for congenital malformations with this drug. Ours is the first meta-analysis, to our knowledge, to specifically examine the type of malformation implicated, and our results suggest that septal heart defects are associated with antidepressant exposure. However, although paroxetine was associated with cardiovascular malformations in general, it was not associated with septal heart defects in our analysis. Isolated ventricular malformations are a common type of congenital cardiovascular malformation, with an incidence rate of approximately 2%–5%.[63] These are typically small muscular defects, though they can be large or complex, and are often asymptomatic and/or close spontaneously early on and thus are frequently not detected.[63] Atrial septal defects, on the other hand, are less common[63] and are approximately 7% of congenital cardiac lesions.[64] As there are more severe and less severe types, some will require surgical intervention in infancy to avoid negative outcomes,[65] while others close spontaneously.[63] In contrast to the majority of ventricular septal defects that do close by the first year, it is often the atrial septal defects that are not diagnosed early and present in adulthood.[63] Previous research suggested that the inclusion of common reversible

heart defects such as the ventral ones may inflate any existing association found with antidepressant exposure.[13,49,52,63] We attempted to differentiate between atrial septal defects and ventral septal defects, but there were not enough studies. Although our ventral septal defects analysis was not significant, the RRs were in a similar range to the overall septal defects analysis, which was significant. Note that the CIs were wide for the ventral septal defects-only analyses, and, thus, perhaps the results are biased. Sources of uncontrolled bias leading to the marginal increased risk for septal defects may include detection bias.[13] Women with depression may be more likely to have an ultrasound and echocardiogram in pregnancy and after birth. They may also have an increased use of health care services due to the depression itself or due to the publicity surrounding the risks of congenital malformations with SSRIs. Furthermore, many more women with depression may request diagnostic testing of their infants compared to healthy mothers.[13] All of the aforementioned potential sources of bias could increase the chance of false detection of an increased risk for septal defects and SSRI exposure. More research is certainly needed that focuses on these types of malformations, with the goal of determining whether an association with the type of cardiovascular effect exists, if it is dependent on a particular drug, or if indeed it is a class effect.

Strengths and Limitations

Perinatal researchers and clinicians have poor evidence-based information on effective treatments for perinatal women, as conducting the evidence-based gold standard, the randomized controlled trial, especially with pharmacological interventions, has ethical barriers among others.[66] Our reliance on observational studies and registries[67,68] may propagate biases, as they have methodological limitations; thus, we keenly await new studies for replication and to confirm previous results. One of the strengths of our analysis was our attention to study quality. We limited our analyses to studies determined to be above a certain threshold of quality, according to the SAQOR, excluding studies below that threshold. Further, we ran subanalyses to examine whether limiting the data to those studies that (1) confirmed no antidepressant use in the control group, (2) had any adjustments made to the data, or (3) did not use convenience sampling among all the studies influenced any of the study results. We found few differences associated with study quality, suggesting that the findings presented in our analysis are quite robust. One exception was our analysis for major congenital malformations. While the pooled risk measure was not statistically significant in our main analysis using only studies above our quality threshold, the pooled estimates became statistically significant in 2 subanalyses. Regardless of the statistical significance, however, it is important to note that the RRs increased from 1.07 to only 1.10. As such, a very small and only marginally significant effect was present, even in these secondary analyses. Thus, largely, differences were small when examining all available data versus studies above our quality threshold. This is noteworthy given the known methodological flaws in these data as well as our concerns with our inability to make definitive conclusions based on previous research.

A further strength of our work rests on the fact that we used adjusted or matched data where possible in our meta-analyses, as well as running subanalyses for studies with any adjustments. Research in the area has been criticized for not taking into account "non-iatrogenic confounders" in pregnancy.[17] Indeed, many studies either did not adjust for any confounders, including depression, or applied matching in very small samples, which makes it difficult to assess whether such matching was successful. However, the most influential studies were also the large ones, and thus heavily influenced the results; these studies did adjust for several potential confounders.[45,46,50,57,58] Thus, most of our pooled risk estimates were heavily influenced by studies that did use adjusted data, including our subanalyses. Although this is relieving to a certain extent, these studies used data from population-based registries; they provide better evidence than that provided by data derived from convenience samples, but they are not randomized controlled trials, which provide the best evidence. The absence of evidence from randomized controlled trials highlights the importance for more research. There seems to be a clear need for more studies of high methodological quality that clearly separate antidepressant exposure across intervention and control groups and accurately adjust for the potential confounding effect of other risk factors for malformations.

Our study was limited by the quality of the articles available to be synthesized in our meta-analyses. Often, the specific outcomes examined were not precisely operationalized by authors of the original studies. For example, many studies reported to be examining "malformations," but did not always specify whether they were major or minor. Studies often did not control for or assess if other psychotropic medications, in addition to antidepressants (ie, hypnotics), were used, the dose, or the timing of use during the pregnancy. We have noted that 1 of the most influential studies was Reis and Källén,[58] and, although it was above our quality threshold, it did not control for hypnotics or benzodiazepines. The size and study quality of the articles from the Swedish registries dominated the pooled effects, yet we did not actually have any knowledge of how many women took the medication as prescribed. A recent study by Källén et al[69] found that prescription data do not always accurately reflect use. Moreover, in another review[70] of how exposure to medication is classified in research utilizing administrative data, the authors concluded that there is tremendous uncertainty about the exposure. As fundamental factors, such as the dose of medication, timing of use during the perinatal period, duration of time the medication was taken, and the way in which women who discontinue using the medication at any point in pregnancy are dealt with in studies that use administrative data, the risk estimates may not be accurate.[70] Few studies included any information on diagnosis; that is, whether the medication was actually prescribed for depression. Antidepressants are also indicated for anxiety disorders, which are increasingly

recognized as common in pregnancy[13,71]; these disorders themselves are also associated with adverse birth outcomes, including lower birth weight,[72] placental abruption,[73] and decreased fetal activity.[74] Finally, we were not able to control for the effects of depression itself, and it is possible that the disease itself may be associated with malformations, perhaps via its association with inadequate prenatal care.[59] Malnourishment overall (poor diet quality) and vitamin deficiencies (such as folic acid) are associated with various congenital malformations, including neural tube defects, congenital heart defects, and orofacial clefts.[75,76] Depressed women are also more likely to smoke,[77] and not all studies controlled for smoking despite the known association of smoking with untoward effects.[78] Although our analysis was limited to what we deemed to be above quality threshold, and meta-analysis pools data so that conclusions can be reached with higher sample sizes, the original study limitations cannot be entirely ignored.[67]

The data on the effects of in utero antidepressant exposure have grown recently, and it is now time to pay closer attention to study design in our interpretation of these findings.[17,69,70] It will be possible for future research to operationalize the precise malformations to be investigated and not group all. Expanding upon proposed future designs,[17] the ideal study, aside from a sufficiently powered multisite randomized controlled trial, would examine the effects within 1 diagnostic group (ie, unipolar major depression of moderate to severe symptomatology), excluding or controlling for known confounders (ie, other medications, smoking or alcohol use), with similar timed exposure (ie, within the first month of the first trimester) and compared to (a) euthymic women without a history of depression and any current medication use and to (b) depressed women of similar severity who are not treated with antidepressant medication. Such a study would indeed be challenging to conduct, as the ethics of randomization into the treatment versus no medication treatment arm can be debated as well as the potential effects of nonmedication treatment on outcome; however, it would be able to provide many answers.

Implications

The decision to use antidepressants during pregnancy must take into account the severity of the illness, whether there is a risk for suicide in particular, and the likelihood of relapse if medication is discontinued.[2] This is especially important to consider in light of a small baseline risk for malformations in the general population, with a small increase in risk potentially associated with antidepressant exposure for some outcomes where the absolute risk remains low. Moreover, it still remains to be determined whether some antidepressants are safer to use than others, as we were able to examine only 2 individual antidepressants in our meta-analyses (paroxetine and fluoxetine), or whether a class effect does indeed exist. We did not find a risk for cardiac malformations with the use of fluoxetine, for example, but we did find an increased risk with the use of paroxetine. Note, however, that although it was significant, the RR was still below 1.5 in all subanalyses conducted. While we were able to examine only the drugs for which the most data were available, future studies should specifically examine sertraline and citalopram, as data are also accumulating for these commonly used drugs. Potential risks of antidepressant treatment must be considered in light of other evidence. As many as 68% of women recruited from psychiatric settings who discontinued antidepressant use during pregnancy have been found to relapse,[62] leaving both the woman and her infant vulnerable to the potential effects of untreated perinatal depression. Data derived from obstetric clinics did not demonstrate a clear link between risk of a depressive episode and the discontinuation of antidepressant medication during pregnancy.[79] However, the study did demonstrate that women with more severe illness (greater than 4 depressive episodes prior to pregnancy) are at high risk for recurrence, even after accounting for the use of antidepressant medication. Treatment decisions must weigh the effects of untreated maternal depression (both in the immediate and long term) for a mother and fetus against the potential adverse effects of antidepressant exposure on the fetus. Moreover, untreated depression can have tremendous impacts on quality of life and experience of pregnancy; these factors must also be taken into account when making treatment decisions.

SUMMARY OF RESULTS AND IMPORTANT CONSIDERATIONS

Results

Any antidepressant medication exposure

Significantly associated with:

- Cardiovascular malformations (RR = 1.36)
- Septal heart defects (atrial septal defects and ventral septal defects) (RR = 1.40)

Not significantly associated with:

- Congenital malformations (RR = 0.93)
- Major malformations (RR = 1.07)
  Significant when all studies included (RR = 1.09), but RR similar to the nonsignificant RR of higher quality studies only
- Ventral septal defects (RR = 1.54)
  Able to be analyzed only for exposure to any antidepressant

Paroxetine exposure

Significantly associated with:

- Cardiovascular malformations (RR = 1.43)

Not significantly associated with:

- Congenital malformations (RR = 1.03)
- Major malformations (RR = 1.11)
- Septal heart defects (RR = 0.97)

Fluoxetine exposure

Not significantly associated with:

- Congenital malformations (RR = 1.10)
- Major malformations (RR = 1.20)
  Significant when all studies included (RR = 1.25), but RR similar to the nonsignificant RR of higher quality studies only
- Cardiovascular malformations (RR = 1.17)
- Septal heart defects (RR = 1.18)

Considerations

(1) Congenital malformations and major malformations categories include a variety of malformations with different gestational timelines of development. The grouping of all malformations together may cause confounding of potential associations if they exist.
(2) Results seem robust, but uncontrolled confounders cannot be excluded. For example, we cannot be sure the medication exposure from data derived from administrative sources accurately reflects use.
(3) Because of limited data, we were able to examine only septal defects (atrial septal defects and ventral septal defects) and then ventral septal defects, but not atrial septal defects alone.
    - Although the ventral septal defects analysis was not significant, the RRs were similar to the RRs found in the septal defects analysis, which was significant, suggesting that a significant association may indeed exist for ventral septal defects, which may be evident with more research.
    - Alternatively, including common reversible heart defects, such as ventral septal defects, could increase the chance of finding an association.
    - There may be detection bias leading to a false detection of an association for antidepressant drugs and septal defects.
(4) On the basis of available data, we were able to analyze only 2 individual medications (paroxetine and fluoxetine), and so it was not possible to determine if there was a class effect or an individual drug effect or to determine the safety of other individual antidepressant drugs.
    - This bias in the available data on individual antidepressant medications also reflects previous research interests and foci.
(5) Few studies included any information on diagnosis. The effects of a major depressive episode must also be considered.
(6) Although there were statistically significant results, one must consider clinical significance.
    - None of the significant RRs found were above 1.47, and the clinically significant benchmark for this field has been cited as being a 2-fold increase.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), desipramine (Norpramin and others), doxepin (Silenor and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

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Author contributions: Conception and design: Drs Grigoriadis and Ross; data analysis and interpretation: Drs Grigoriadis, Ross, Roerecke, Rehm, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten and Mamisashvili; drafting or revision of the manuscript: Drs Grigoriadis, Roerecke, Rehm, Ross, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten and Mamisashvili; and approval of the final version of the manuscript for publication: Drs Grigoriadis, Ross, Roerecke, Rehm, Dennis, Koren, Steiner, Mousmanis, and Cheung and Mss VonderPorten and Mamisashvili. Drs Grigoriadis and Ross had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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

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Disclaimer: The views expressed here do not necessarily reflect those of the Ministry of Health and Long-Term Care.

Previous presentations: Preliminary results of this study were presented at the ▪ Motherisk Update 2012 (paper title: The effect of antidepressant medications on mothers and babies—an updated systematic analysis); May 23, 2012; Toronto, Ontario, Canada ▪ Canadian Psychiatric Association Conference (paper title: Evidence-based discussion guide for antidepressant treatment in depressed pregnant and postpartum women); October 13–15, 2011; Vancouver, British Columbia, Canada ▪ Canadian Institutes for Health Research, Innovations in Gender, Sex and Health Research Conference; (paper titles: (1) Effects of in utero exposure to antidepressant medication during pregnancy: a meta-analysis and (2) Short-term and long-term impact of untreated maternal depression on the child); November 22–23, 2010; Toronto, Ontario, Canada ▪ Canadian Psychiatric Association Conference; (paper title: Outcomes associated with antidepressant medication use during pregnancy: a meta-analysis); September 23–26, 2010; Toronto, Ontario, Canada ▪ 36th Annual Meeting of the North American Society for Psychosocial Obstetrics and Gynecology; (poster title: Preliminary results from the Reproductive Life Stages Algorithm Project: use of antidepressant medication during pregnancy and lactation: development of an evidence-based decision tool); February 10–13, 2010; Richmond, Virginia ▪ Organization for the Study of Sex Differences 3rd Annual Meeting; (poster title: An evidence-based algorithm to quantify risk-benefit decision-making for use of antidepressant medication during pregnancy and lactation); June 4–6, 2009; Toronto, Ontario, Canada ▪ 35th Annual Meeting of the North American Society for Psychosocial Obstetrics and Gynecology; (poster title: Use of antidepressant medication during pregnancy and lactation: development of an evidence-based decision

tool); February 4–7, 2009; New Haven, Connecticut ▪ Canadian College of Neuropsychopharmacology Annual Meeting; (poster, title: An evidence-based algorithm to quantify risk-benefit decision-making for use of antidepressant medication during pregnancy and lactation. Research in progress: current state of knowledge); June 6–9, 2008; Toronto, Ontario, Canada.

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Supplementary material: See accompanying pages.

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

Supplementary material follows this article.

THE JOURNAL OF CLINICAL PSYCHIATRY

Supplementary Material

Article Title: Antidepressant Exposure During Pregnancy and Congenital Malformations: Is There an Association? A Systematic Review and Meta-Analysis of the Best Evidence

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List of Supplementary Material for the article

1. **Keywords** Keywords
2. **eTable 1** Exposure to Paroxetine or Fluoxetine and risk of malformations: Meta: analyses results
3. **eFigure 1** Exposure to any antidepressant and the risk of major congenital malformations: meta-analysis results for studies above the quality threshold
4. **eFigure 2** Exposure to any antidepressant and the risk of septal heart defect: meta-analysis results for studies above the quality threshold
5. **eFigure 3** Exposure to any antidepressant and the risk of ventricular septal defect (VSD): meta-analysis results for studies above the quality threshold

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Keywords

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

Supplementary eTable 1. Exposure to Paroxetine or Fluoxetine and risk of malformations: Meta-analyses results

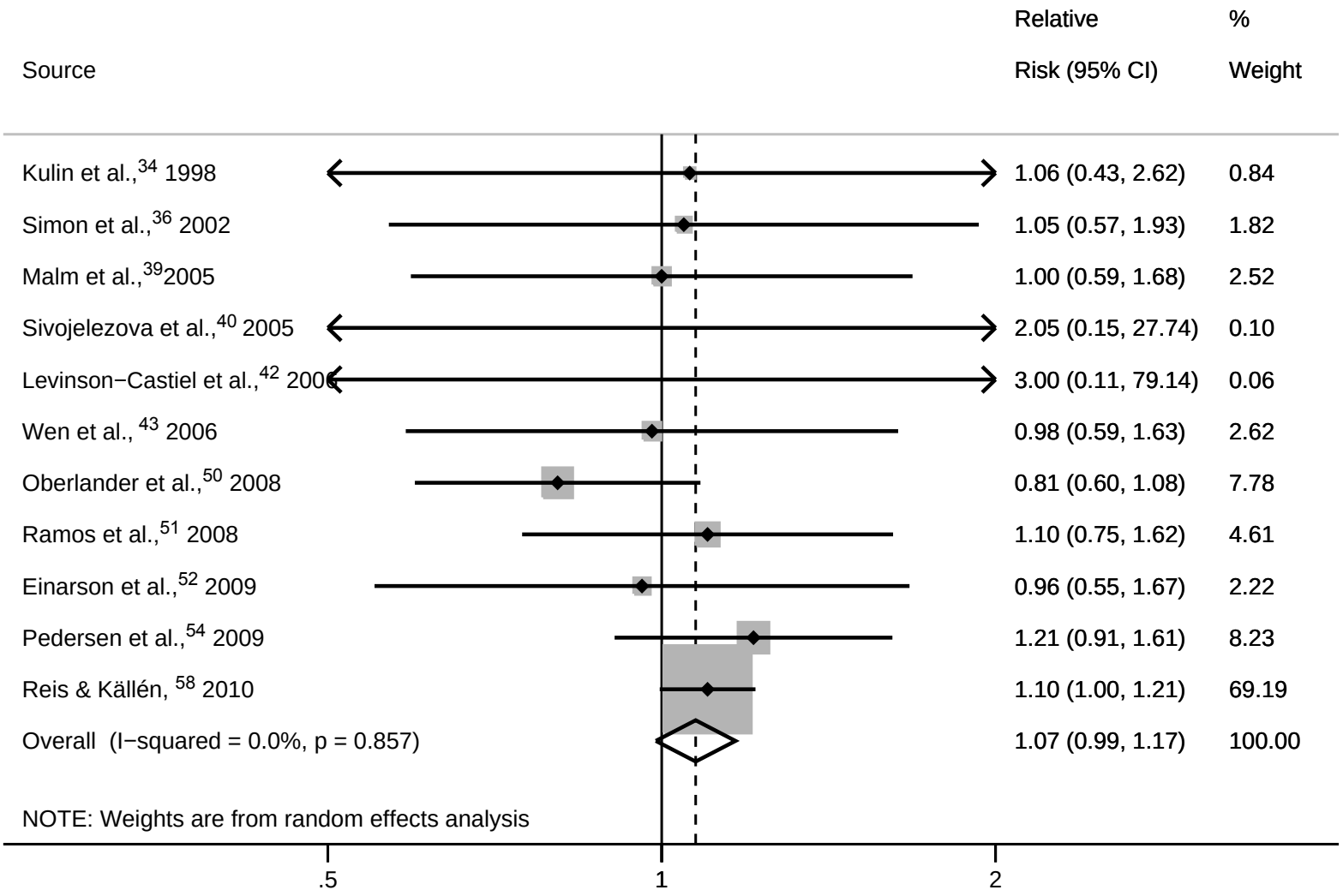
Analysis	No. of studies	No. of cases	Total sample size	RR	95% CI	*P* Value	*P* Value for Heterogeneity	I^2 (%)	*P* Value for Publication Bias
Paroxetine Exposure									
				Congenital malformations					
Studies above quality threshold	6	59,157	1,254,625	1.03	0.87 to 1.22	0.738	0.821	0.0	
Studies above quality threshold, no antidepressants in controls	4	55,570	1,140,614	1.02	0.83 to 1.26	0.819	0.760	0.0	
Studies above quality threshold with adjusted data	4	59,157	1,254,625	1.03	0.87 to 1.22	0.738	0.821	0.0	
All Studies	7	59,209	1,256,332	1.09	0.91 to 1.31	0.354	0.326	13.6	0.817
All studies excluding convenience samples	6	59,157	1,254,625	1.03	0.87 to 1.22	0.738	0.821	0.0	
				Major malformations					
Studies above quality threshold	5	55,557	1,900,864	1.11	0.88 to 1.39	0.377	0.322	14.4	
Studies above quality threshold, no antidepressants in controls	3	51,970	1,785,889	1.21	0.94 to 1.56	0.146	0.404	0.0	
Studies above quality threshold with adjusted data	5	55,557	1,900,864	1.11	0.88 to 1.39	0.377	0.322	14.4	
All Studies	6	55,609	1,902,571	1.20	0.91 to 1.57	0.190	0.136	40.3	0.958
All studies excluding convenience samples	5	55,557	1,900,864	1.11	0.88 to 1.39	0.377	0.322	14.4	
				Cardiovascular malformations					
Studies above quality threshold	7	18,579	1,639,065	1.43	1.08 to 1.88	0.012	0.899	0.0	
Studies above quality threshold, no antidepressants in controls	5	17,389	1,527,305	1.45	1.06 to 1.99	0.019	0.725	0.0	
Studies above quality threshold with adjusted data	6	18,562	1,635,544	1.46	1.09 to 1.94	0.011	0.856	0.0	
All Studies	8	18,594	1,640,772	1.47	1.12 to 1.93	0.005	0.867	0.0	0.338
All studies excluding convenience samples	6	18,562	1,635,544	1.45	1.09 to 1.94	0.011	0.856	0.0	
				Septal heart defects					
Studies above quality threshold	3	2,788	226,272	0.97	0.47 to 2.03	0.940	0.668	0.0	

Studies above quality threshold, no antidepressants in controls	2[a]	2,539	224,733	0.78	0.32 to 1.88	0.577	0.903	0.0	
Studies above quality threshold with adjusted data	3	2,788	226,272	0.97	0.47 to 2.03	0.940	0.668	0.0	
All Studies	3	2,788	226,272	0.97	0.47 to 2.03	0.940	0.668	0.0	0.967
All studies excluding convenience samples	3	2,788	226,272	0.97	0.47 to 2.03	0.940	0.668	0.0	
Fluoxetine Exposure									
				Congenital malformations					
Studies above quality threshold	4	52,221	1,202,620	1.10	0.84 to 1.44	0.498	0.215	32.9	
Studies above quality threshold, no antidepressants in controls	3	48,831	1,091,293	1.15	0.77 to 1.72	0.482	0.107	55.2	
Studies above quality threshold with adjusted data	4	52,221	1,202,620	1.10	0.84 to 1.44	0.498	0.215	32.9	
All Studies	7	52,289	1,204,878	1.15	0.92 to 1.45	0.220	0.321	14.3	0.200
All studies excluding convenience samples	4	52,221	1,202,620	1.10	0.84 to 1.44	0.498	0.215	32.9	
				Major malformations					
Studies above quality threshold	4	55,391	1,898,925	1.20	0.98 to 1.48	0.081	0.375	3.6	
Studies above quality threshold, no antidepressants in controls	3	52,001	1,786,981	1.29	1.03 to 1.61	0.025	0.518	0.0	
Studies above quality threshold with adjusted data	4	55,391	1,898,925	1.20	0.98 to 1.48	0.081	0.375	3.6	
All Studies	7	55,459	1,901,183	1.25	1.03 to 1.51	0.021	0.587	0.0	0.806
All studies excluding convenience samples	4	55,391	1,898,925	1.20	0.98 to 1.48	0.081	0.375	3.6	
				Cardiovascular malformations					
Studies above quality threshold	4	17,391	1,583,857	1.17	0.89 to 1.55	0.258	0.424	0.0	
Studies above quality threshold, no antidepressants in controls	3	16,874	1,474,754	1.19	0.83 to 1.72	0.338	0.247	28.5	
Studies above quality threshold with adjusted data	4	17,391	1,583,857	1.17	0.89 to 1.55	0.258	0.424	0.0	
All Studies	6	17,408	1,585,725	1.33	0.92 to 1.90	0.127	0.210	30.0	0.324
All studies excluding convenience samples	4	17,391	1,583,857	1.17	0.89 to 1.55	0.258	0.424	0.0	
				Septal heart defects					

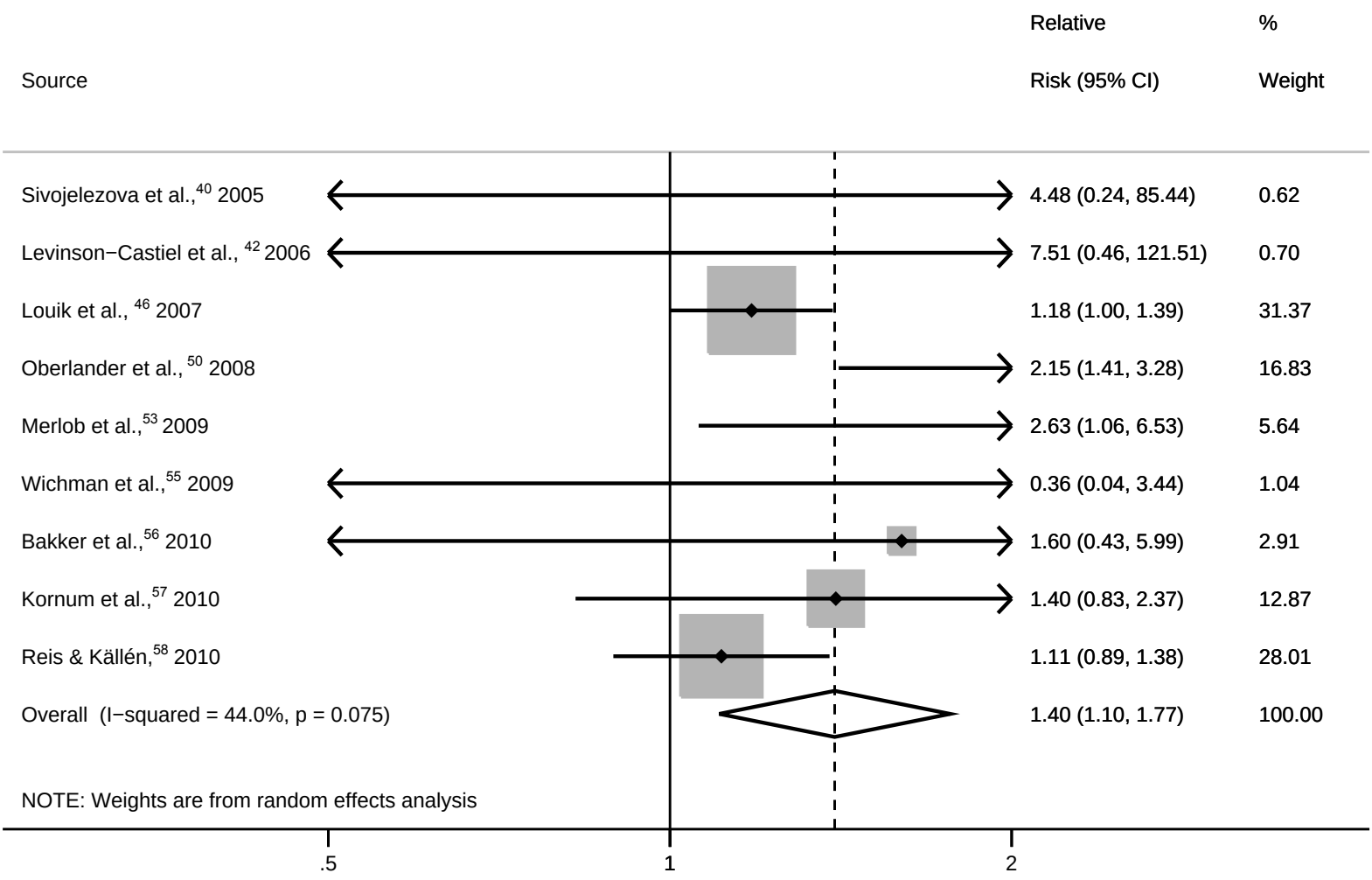
Studies above quality threshold	2[a]	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0
Studies above quality threshold, no antidepressants in controls	2[a]	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0
Studies above quality threshold with adjusted data	2[a]	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0
All Studies	2[a]	2,548	225,193	1.18	0.65 to 2.14	0.581	0.458	0.0
All studies excluding convenience samples	2[a]	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0

a. Insufficient number of studies for meaningful results from meta-analysis

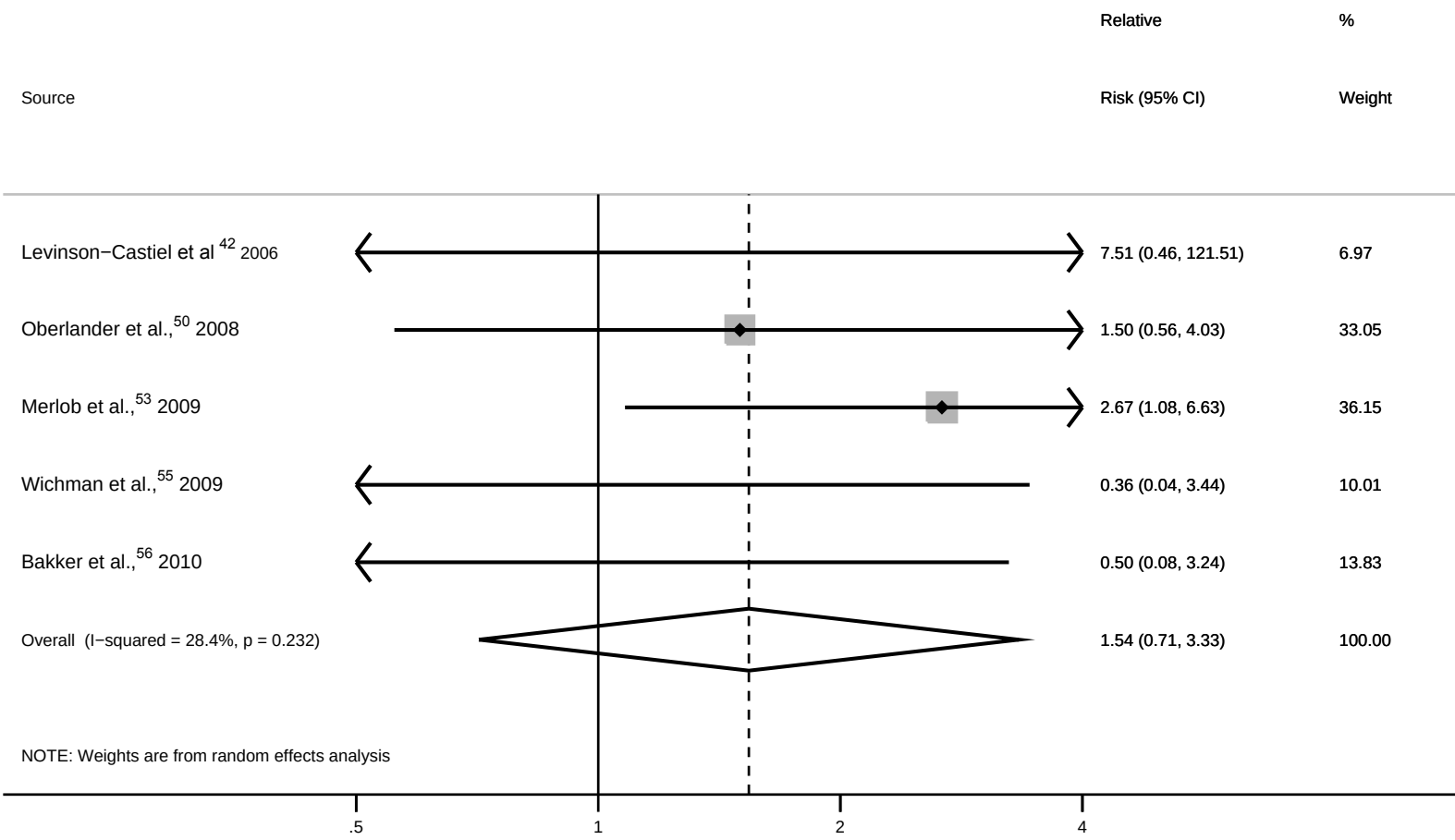
Abbreviations: RR= Relative Risk, 95% CI= 95% Confidence Interval



Supplementary eFigure 1. Exposure to any antidepressant and the risk of major congenital malformations: meta-analysis results for studies above the quality threshold. Abbreviations: see Figure 2.



Supplementary eFigure 2. Exposure to any antidepressant and the risk of septal heart defect: meta-analysis results for studies above the quality threshold. Abbreviations: see Figure 2.



Supplementary eFigure 3. Exposure to any antidepressant and the risk of ventricular septal defect (VSD): meta-analysis results for studies above the quality threshold. Abbreviations: see Figure 2.