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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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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									
<i>Congenital malformations</i>									
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	
<i>Major malformations</i>									
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	
<i>Cardiovascular malformations</i>									
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	
<i>Septal heart defects</i>									
Studies above quality threshold	3	2,788	226,272	0.97	0.47 to 2.03	0.940	0.668	0.0	

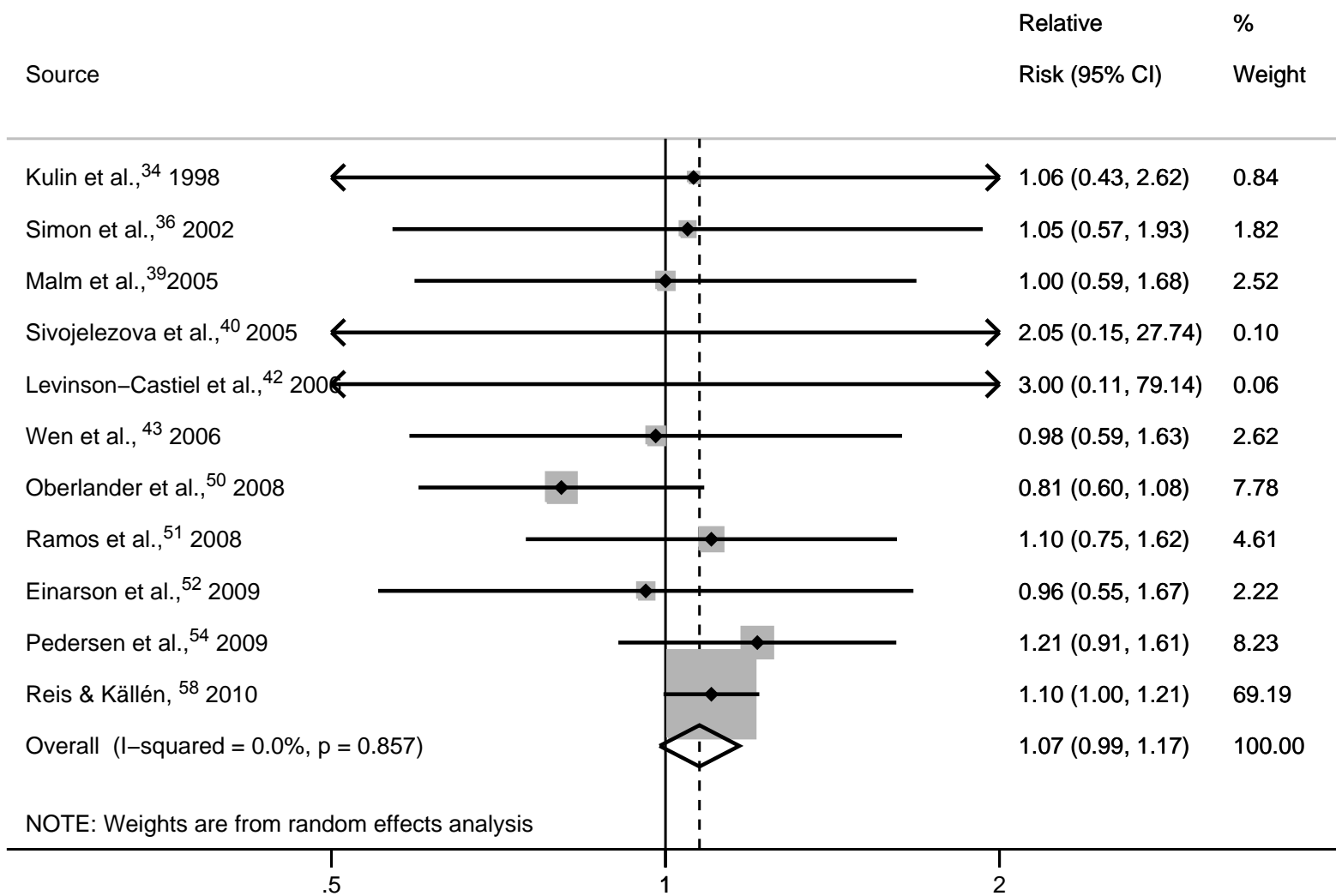
Supplementary eTable 1. Exposure to Paroxetine or Fluoxetine and risk of malformations: Meta-analyses results (continued)

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									
<i>Congenital malformations</i>									
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	
<i>Major malformations</i>									
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	
<i>Cardiovascular malformations</i>									
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	
<i>Septal heart defects</i>									

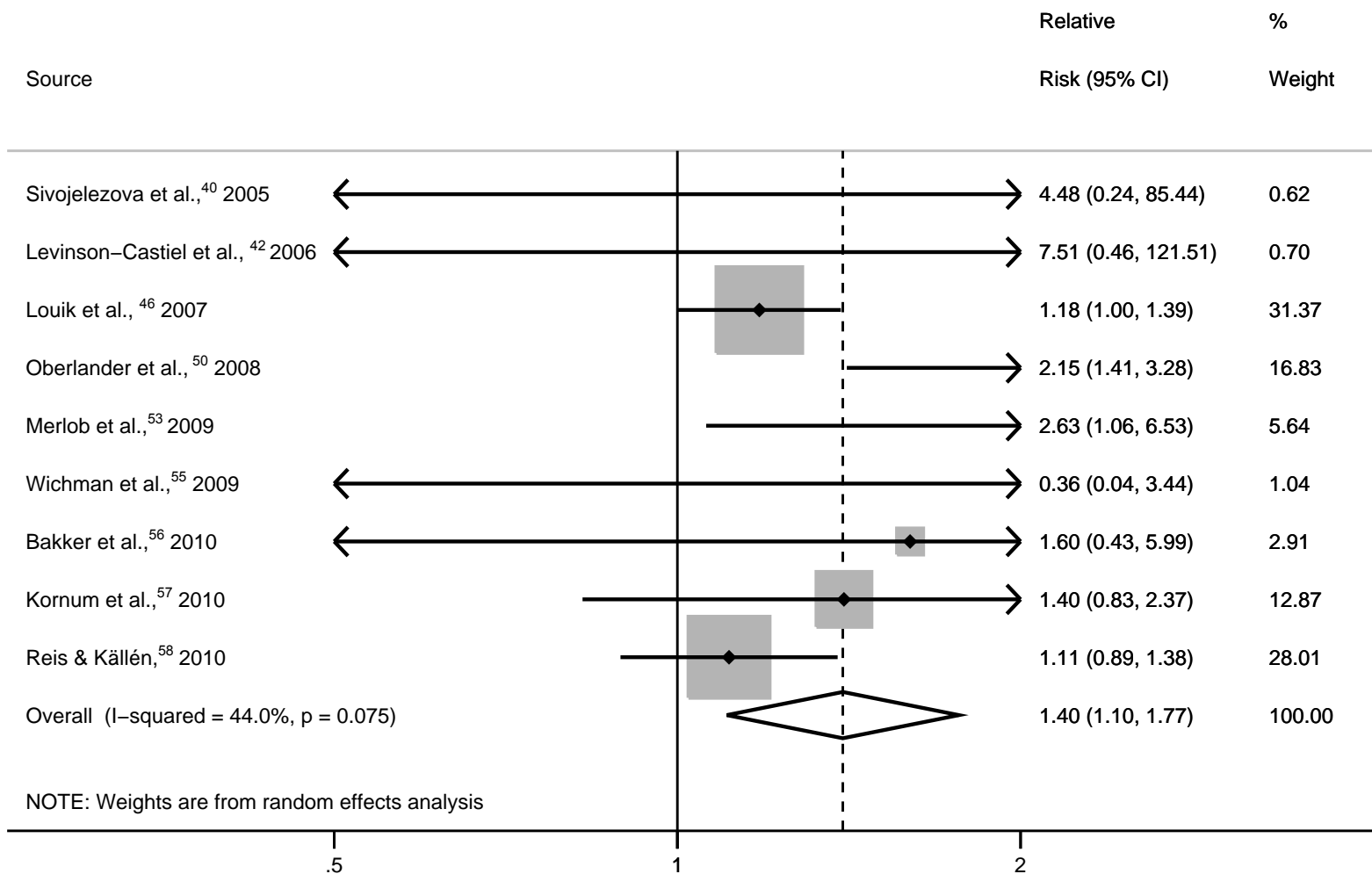
Studies above quality threshold	2 ^a	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0
Studies above quality threshold, no antidepressants in controls	2 ^a	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	0.0
Studies above quality threshold with adjusted data	2 ^a	2,546	224,937	1.18	0.65 to 2.14	0.581	0.458	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

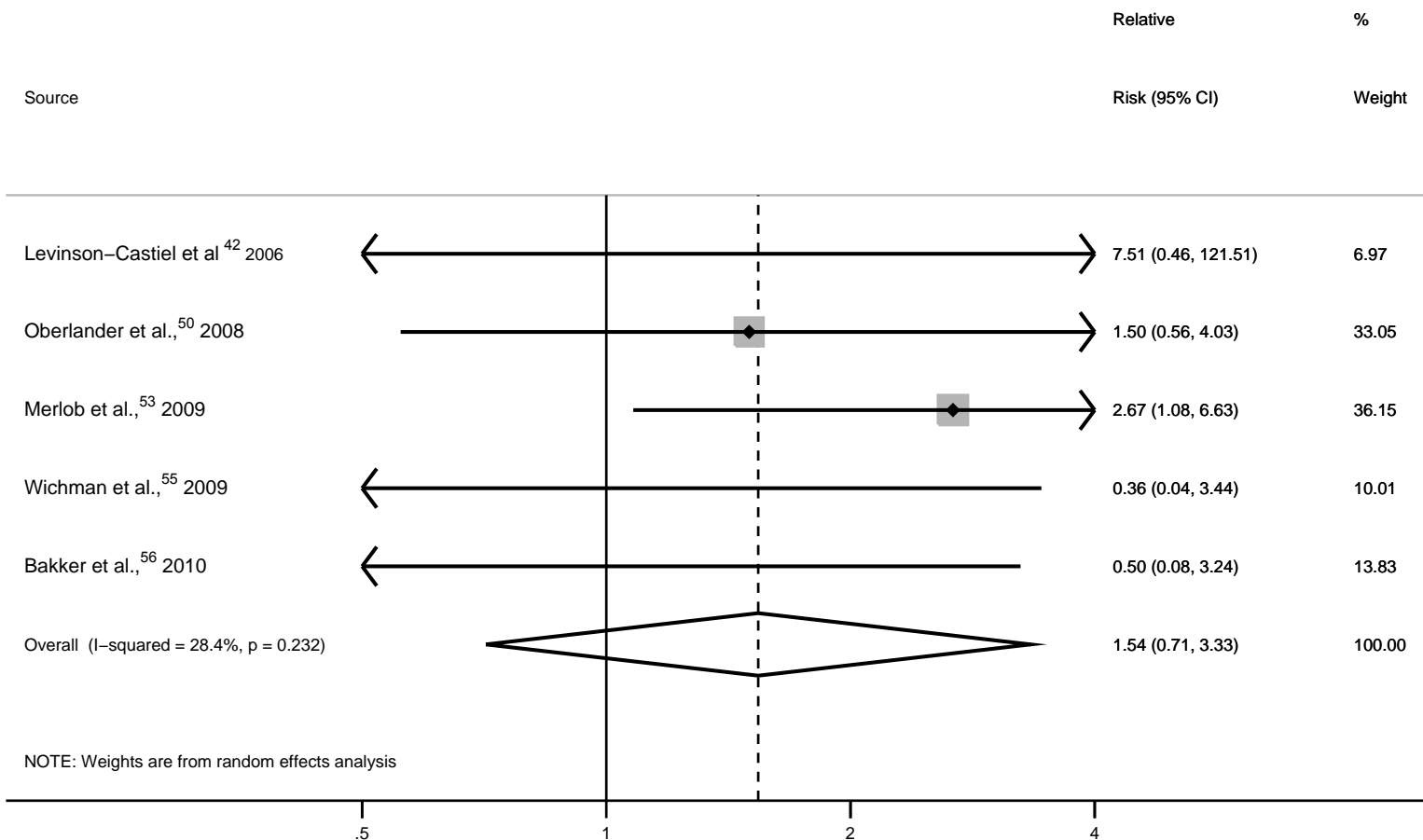
Abbreviations: RR= Relative Risk, 95% CI= 95% Confidence Interval



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.