

## **Supplementary Files**

This appendix has been provided by the authors to give readers additional information about their work.  
Supplement to: Anick Bérard, Jin-Ping Zhao, Odile Sheehy. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: An updated analysis of the Quebec Pregnancy Cohort.

**Table S1. ICD-9 and ICD-10 codes for diagnoses of depression and anxiety, and other cognitive disorders**

<b>ICD-10</b>	<b>ICD-9</b>
<b>Episodic Mood disorders (296)</b>	
F309	2960
F300	2960
F301	2960
F308	2960
F302	2960
F338	2961
F334	2961
F333	2961
F332	2961
F331	2961
F330	2961
F328	2961
F322	2961
F339	2961
F323	2961
F310	2962
F311	2962
F312	2962
F315	2963
F314	2963
F313	2963
F380	2964
F316	2964
F317	2965
F319	2965
F318	2966
F381	2966
F319	2967
F317	2967
F348	2968
F388	2968
F349	2969
F39	2969
<b>Neurotic disorders (300)</b>	
F410	3000
F413	3000
F418	3000
F411	3000
F419	3000
F447	3001
F448	3001
F445	3001
F446	3001
F449	3001
F444	3001
F680	3001
F440	3001
F443	3001
F442	3001
F441	3001
F402	3002

**Table S1. ICD-9 and ICD-10 codes for diagnoses of depression and anxiety, and other cognitive disorders**

<b>ICD-10</b>	<b>ICD-9</b>
F401	3002
F400	3002
F408	3002
F409	3002
F429	3003
F428	3003
F422	3003
F420	3003
F421	3003
F320	3004
F480	3005
F480	3005
F481	3006
F452	3007
F450	3008
F488	3008
F451	3008
F99	3009
F489	3009
<b>Adjustment reaction (309)</b>	
F432	3090
F930	3092
F438	3098
<b>Depressive disorder, not elsewhere classified</b>	
F530	3119
F329	3119

ICD-9, International Classification of Diseases, Ninth Revision;  
ICD-10, International Classification of Diseases, 10<sup>th</sup> Revision.

---

**Table S2. Antidepressant Medications**

---

<b>Antidepressant Medication Class</b>	<b>Antidepressant Generic Name</b>
SSRI	Citalopram Fluoxetine Fluvoxamine Paroxetine Sertraline
SNRI	Venlafaxine
TCA	Amitriptyline Clomipramine Desipramine Doxepin Imipramine Nortriptyline Trimipramine
Bupropion	Bupropion excluding Zyban
Other	Bupirone Mirtazapine Trazodone Moclobémide L-tryptophane

---

SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor, TCA, tricyclic antidepressant.

**Table S3. ICD-9 and ICD-10 Diagnostic codes used to identify major congenital malformation by organ system.**

<b>Congenital malformation</b>	<b>ICD-9 diagnostic codes</b>	<b>ICD-10 diagnostic codes</b>
Major congenital malformations overall	740-759 excluding minor congenital malformations (743.6, 744.1, 744.2-744.4, 744.8, 744.9, 747.0, 747.5, 750.0, 752.4, 752.5, 754.6, 755.0, 755.1, 757.2-757.6, 757.8, 757.9)	Q00-Q89 excluding minor congenital malformations (Q10, Q162, Q17-Q182, Q184-Q189, Q250, Q270, Q381, Q515, Q516, Q520-Q527, Q53, Q664-Q666, Q69, Q70, Q81-Q84, Q950-Q952, Q954, Q955, Q959)
Nervous system	740-742	Q00-Q07
Eye, ear, face and neck	743-744	Q10-Q18
Circulatory system	745-747	Q20-Q28
Respiratory system	748	Q30-Q34
Digestive system	749-751	Q35-Q45
Genital organs	752	Q50-Q56
Urinary system	753	Q60-Q64
Musculoskeletal system	754-756	Q65-Q79
Other congenital malformations	757 and 759	Q80-Q89
Cardiac malformations	745-746	Q20-Q22
Ventricular/atrial septal defect	745.4 and 745.5	Q21.0-Q21.2
Omphalocele	756.7	Q79.2
Craniosynostosis	756.0	Q75
Cleft palate	749	Q35-Q37

ICD-9, International Classification of Disease, Ninth Revision; ICD-10, International Classification of Disease, 10<sup>th</sup> Revision.

**Table S4. ICD-9 and ICD-10 codes as well as medication codes for diagnoses of comorbidities: hypertension, diabetes, asthma, thyroid disease.**

### **Hypertension**

ICD-9 codes: 4010-4059, 6420-6429 and 7962

ICD-10 codes: I100, I101, I150, I151, I152, I158, I159, O10, O11, O12, O13, O14, O15 and O16

Medication generic codes: 10751, 6136, 4524, 41564, 45625, 37742, 45520, 45463, 43670, 46325, 46315, 47355, 47199, 46319, 45243, 38275, 46763, 46780, 40563, 42162, 39016, 45408, 8229, 44866, 38314, 47006, 45624, 42708, 46388, 46469, 47751, 45532, 43228, 47247, 40550, 46573, 47440, 47049, 42071, 47056, 47320, 45476, 45572, 47002, 45576, 47040, 47117, 46258, 47449, 45629, 47301, 47079, 46216, 47655, 47250, 46529, 47309, 46760, 47412, 47389, 47534, 47532, 46459, 47282, 47354, 47135, 46284, 46441, 47207, 47763, 47764, 47333, 46587, 47413, 46418, 47259, 47369, 9100, 46572, 3562, 4173, 41759, 41772, 4537, 1976, 43397, 19440, 41772, 38158, 38197, 9763, 47609, 47706, 47823 with formulation not in the following codes: 1479, 1624, 2204, 2233, 2784, 2813, 3480, 5365, 5599

### **Diabetes**

ICD-9 codes: 2500-2509, 2714 and 7902

ICD-10 codes: E10-E14 and R730

Medication generic codes: 47151, 46300, 5824, 47208, 47357, 46568, 46810, 1937, 4264, 47427, 46799, 46056, 47329, 15184, 9672, 4238, 47429, 46678, 47392, 46642, 47371, 47715, 46862, 47652, 46798, 47424, 46322, 47206, 44164, 45511, 45531, 47615, 47586, 47536, 47426, 4832, 4888, 18296, 18309, 39484, 18322, 39497, 18335, 18348, 39458, 39120, 46538, 39133, 46537, 39146, 39159, 39172, 39185, 46536, 39523, 43735, 41655, 43033, 44151, 44476, 44489, 44502, 44996, 45405, 45534, 45415, 45483, 45535, 46592, 46602, 46603, 46607, 47004

### **Asthma**

ICD-9 codes : 4930, 4931, 4933, 4934, 4935, 4936, 4937, 4938 and 4939

ICD-10 codes: J450, J458, J451 and J459

Medication generic codes: 364, 46428, 47428, 46800, 39419, 47315, 2223, 3380, 3406, 3419, 38548, 47231, 47271, 46430, 43124, 46640, 47186, 46302, 5083, 5096, 5109, 5070, 45555, 46752, 47303, 47302, 46467, 47033, 45563, 46463, 6721, 43475, 47153, 46299, 45547, 10530, 33634, 46737, 47335, 46597, 47112, 46247, 34180, 9464, 46847, 9490, 9503, 44944, 47266, 46401, 47428, 45581 or 780, 45499, 38730, 47213, 47050, 46435, 9737, 47626 with formulation in the following codes: 1305, 1334, 1856, 1885, 1972, 2610, 2639, 5563, 5564, 5584, 5619, 5634, 5563

### **Thyroid diseases**

ICD-9 codes : 2440-2449 and 2429

ICD-10 codes : E01, E02, E03 and E05

Medication generic codes: 5252, 46574, 5317, 46457, 46474, 33842, 40836 and 8242

Table S5. Comparisons between pregnancies included and excluded in the study.	Pregnancies not meeting eligibility criteria:						
	Study population n=18,487	More than one antidepressants used during the 1 <sup>st</sup> trimester n=529	Multiple pregnancies n=186	Unmatched pregnancies with ISQ database n=954	Fetotoxic drug exposure during the 1 <sup>st</sup> trimester n=552	Chromosomal abnormalities only n=42	Minor birth defect only n=425
<b>Characteristics</b>	<b>No. (%)</b>						
<b>Measured on the first day of gestation:</b>							
Maternal age (years), mean ( $\pm$ SD)	27.8 $\pm$ 5.7	29.3 $\pm$ 5.7	28.5 $\pm$ 5.6	28.2 $\pm$ 6.0	29.4 $\pm$ 6.2	29.1 $\pm$ 6.7	27.7 $\pm$ 5.4
Urban dweller, n (%)	15,382 (83.2)	459 (86.8)	158 (85.0)	836 (84.6)	452 (81.9)	33 (78.6)	356 (83.8)
Welfare recipient, n (%)	6,169 (33.4)	281 (53.1)	75 (40.3)	431 (45.2)	256 (46.4)	17 (40.4)	149 (35.0)

**Table S6. List of fetotoxic drug used in those excluded from the study population.**

	Number of pregnancies exposed
<b>Medication</b>	
Valproic acid divalproex	135
Lithium	99
Carbamazepine	68
Clomiphene	60
Misoprostol	29
Atorvastatin	28
Phenytoin	21
Conjugated estrogens	12
Propylthiouracil	11
Warfarine	11
Pravastatine	10
Ramipril	9
Irbesartan	7
Enalapril	6
Methimazole	6
Vitamin A	6
Candesartan	5
Cilazapril	5
Perindopril	5
Phenobarbital	5
Quinalapril	5
Valsartan	5
Dihydroergotamine	4
Losatan/HCTZ	4
Quinine	4
Simvastatine	4
Amethopterine	3
Fosinopril	3
Isotretinoin	3
Leuprolide	3
Telmisartan	3
Acitretin	2
Cerivastatin	2
Irbesartan/HCTZ	2
Lisinopril	2
Losartan	2
Lovastatine	2
Rovustatine	2
Valsartan/HCTZ	2
Candersartan/HCTZ	1

Cilazapril/HCTZ	1
Fluvastatin	1
Fourouracil	1
Penicillamine	1
Testosterone	1
Trandopril	1

---

Note: 552 pregnancies were excluded from the study population because of exposures to fetotoxic drugs during the first trimester (see Figure 1). Given that some pregnancies were exposed to more than one fetotoxic drugs, the total exceeds 552.



**TABLE S7.** Type of antidepressant use during the 1<sup>st</sup> trimester of pregnancy and the risk of major congenital malformations as well as organ specific malformations in a cohort of depressed pregnant women using 95% and 99% confidence intervals.

Congenital malformations		Crude Prevalence	Adjusted* Prevalence		
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	(99% CI)	
Major congenital malformations overall	Non exposed	1.00	1.00		
	Paroxetine	1.39 (1.15-1.68)	1.24 (0.99-1.55)	(0.79-1.66)	
	Sertraline	1.13 (0.83-1.55)	1.09 (0.80-1.50)	(0.72-1.66)	
	Citalopram	1.41 (1.11-1.78)	1.36 (1.08-1.73)	(1.00-1.86)	
	Fluoxetine	0.83 (0.51-1.35)	0.80 (0.49-1.31)	(0.42-1.53)	
	Fluvoxamine	0.63 (0.23-1.75)	0.63 (0.23-1.77)	(0.16-2.44)	
	Venlafaxine	1.12 (0.89-1.41)	1.10 (0.87-1.38)	(0.81-1.48)	
	Tricyclic antidepressants	1.23 (0.91-1.67)	1.16 (0.86-1.56)	(0.78-1.72)	
	Other antidepressants	0.96 (0.61-1.52)	0.93 (0.59-1.47)	(0.51-1.70)	
	Nervous system	Non exposed	1.00	1.00	
Paroxetine		1.37 (0.75-2.49)	1.34 (0.74-2.42)	(0.31-2.93)	
Sertraline		1.79 (0.73-4.38)	1.72 (0.69-4.26)	(0.52-5.69)	
Citalopram		1.32 (0.57-3.02)	1.28 (0.55-2.93)	(0.43-3.82)	
Fluoxetine		0.68 (0.10-4.80)	0.64 (0.09-4.52)	(0.05-8.40)	
Fluvoxamine		2.39 (0.33-17.05)	2.44 (0.33-18.11)	(0.18-34.12)	
Venlafaxine		1.20 (0.55-2.59)	1.19 (0.55-2.58)	(0.43-3.30)	
Tricyclic antidepressants		0.68 (0.17-2.72)	0.60 (0.15-2.38)	(0.10-3.69)	
Other antidepressants		1.34 (0.33-5.40)	1.21 (0.30-4.89)	(0.19-7.60)	
Eye, ear, face and neck		Non exposed	1.00	1.00	
	Paroxetine	0.76 (0.31-1.88)	0.75 (0.30-1.86)	(0.23-2.48)	
	Sertraline	0.47 (0.07-3.40)	0.44 (0.06-3.18)	(0.03-5.96)	
	Citalopram	1.18 (0.43-3.23)	1.13 (0.41-3.09)	(0.30-4.25)	
	Fluoxetine	0.91 (0.13-6.47)	0.85 (0.12-5.94)	(0.07-11.00)	
	Venlafaxine	0.70 (0.22-2.22)	0.70 (0.22-2.19)	(0.15-3.16)	
	Tricyclic antidepressants	2.74 (1.19-6.30)	2.45 (1.05-5.72)	(0.80-7.48)	
	Other antidepressants	1.80 (0.44-7.36)	1.71 (0.41-7.15)	(0.26-11.23)	
	Circulatory system	Non exposed	1.00	1.00	
		Paroxetine	1.17 (0.83-1.65)	1.13 (0.79-1.60)	(0.71-1.79)
Sertraline		1.31 (0.75-2.30)	1.25 (0.71-2.19)	(0.60-2.61)	
Citalopram		1.31 (0.84-2.06)	1.27 (0.81-1.99)	(0.70-2.30)	
Fluoxetine		0.56 (0.18-1.76)	0.52 (0.16-1.65)	(0.11-2.38)	
Fluvoxamine		2.06 (0.64-6.61)	2.00 (0.62-6.47)	(0.42-9.39)	
Venlafaxine		0.78 (0.47-1.30)	0.77 (0.46-1.27)	(0.39-1.49)	
Tricyclic antidepressants		1.04 (0.56-1.91)	0.96 (0.52-1.77)	(0.43-2.15)	
Other antidepressants		0.94 (0.38-2.31)	0.88 (0.36-2.13)	(0.27-2.82)	

Respiratory system	Non exposed	1.00	1.00	
	Paroxetine	0.98 (0.43-2.23)	0.95 (0.41-2.21)	(0.32-2.88)
	Fluoxetine	1.93 (0.47-7.90)	1.93 (0.47-7.85)	(0.30-12.24)
	Venlafaxine	2.25 (1.13-4.50)	2.17 (1.07-4.38)	(0.86-5.48)
	Tricyclic antidepressants	0.96 (0.24-3.91)	0.90 (0.22-3.61)	(0.14-5.62)
	Other antidepressants	1.91 (0.47-7.82)	1.79 (0.44-7.32)	(0.28-11.42)
Digestive system	Non exposed	1.00	1.00	
	Paroxetine	0.97 (0.55-1.71)	0.96 (0.54-1.71)	(0.45-2.05)
	Sertraline	1.15 (0.47-2.83)	1.13 (0.46-2.77)	(0.35-3.68)
	Citalopram	1.16 (0.57-2.37)	1.13 (0.55-2.32)	(0.44-2.91)
	Fluoxetine	0.88 (0.22-3.58)	0.87 (0.21-3.56)	(0.14-5.55)
	Venlafaxine	0.91 (0.45-1.85)	0.89 (0.44-1.83)	(0.35-2.29)
	Tricyclic antidepressants	2.70 (1.49-4.89)	2.55 (1.40-4.66)	(1.16-5.63)
	Other antidepressants	0.44 (0.06-3.10)	0.42 (0.06-2.98)	(0.03-5.55)
Genital organs	Non exposed	1.00	1.00	
	Paroxetine	0.80 (0.42-1.53)	0.79 (0.41-1.52)	(0.33-1.87)
	Sertraline	0.97 (0.35-2.72)	0.90 (0.31-2.61)	(0.22-3.65)
	Citalopram	0.93 (0.41-2.13)	0.86 (0.37-1.99)	(0.28-2.60)
	Fluoxetine	0.50 (0.07-3.45)	0.50 (0.07-3.35)	(0.04-6.14)
	Venlafaxine	0.74 (0.30-1.81)	0.69 (0.29-1.67)	(0.22-2.21)
	Tricyclic antidepressants	1.24 (0.51-3.01)	1.12 (0.46-2.72)	(0.35-3.60)
	Other antidepressants	0.91 (0.23-3.58)	0.83 (0.21-3.27)	(0.14-5.05)
Urinary system	Non exposed	1.00	1.00	
	Paroxetine	0.46 (0.19-1.13)	0.47 (0.19-1.14)	(0.15-1.51)
	Sertraline	0.86 (0.27-2.73)	0.86 (0.27-2.71)	(0.19-3.91)
	Citalopram	0.18 (0.03-1.28)	0.18 (0.02-1.26)	(0.01-2.35)
	Fluoxetine	0.55 (0.08-3.94)	0.56 (0.08-4.00)	(0.04-7.46)
	Venlafaxine	1.43 (0.75-2.73)	1.43 (0.75-2.73)	(0.61-3.34)
	Tricyclic antidepressants	0.83 (0.26-2.60)	0.80 (0.25-2.57)	(0.17-3.72)
	Other antidepressants	0.54 (0.08-3.91)	0.54 (0.08-3.86)	(0.04-7.19)
Musculoskeletal system	Non exposed	1.00	1.00	
	Paroxetine	1.02 (0.75-1.37)	1.01 (0.75-1.37)	(0.68-1.51)
	Sertraline	1.06 (0.64-1.76)	1.03 (0.62-1.71)	(0.53-2.01)
	Citalopram	1.96 (1.44-2.68)	1.92 (1.40-2.62)	(1.27-2.89)
	Fluoxetine	1.00 (0.49-2.04)	0.99 (0.48-2.01)	(0.39-2.52)
	Fluvoxamine	0.88 (0.21-3.58)	0.87 (0.21-3.57)	(0.14-5.56)
	Venlafaxine	1.32 (0.95-1.84)	1.30 (0.93-1.80)	(0.84-2.00)
	Tricyclic antidepressants	0.88 (0.51-1.51)	0.84 (0.49-1.44)	(0.41-1.71)
	Other antidepressants	0.85 (0.40-1.83)	0.83 (0.39-1.80)	(0.30-2.29)
Cardiac malformations	Non exposed	1.00	1.00	
	Paroxetine	1.49 (1.11-2.00)	1.45 (1.12-1.88)	(0.87-2.03)

	Sertraline	1.19 (0.63-2.25)	1.14 (0.60-2.15)	(0.49-2.63)
	Citalopram	1.18 (0.71-1.97)	1.15 (0.69-1.92)	(0.59-2.25)
	Fluoxetine	0.45 (0.11-1.82)	0.42 (0.10-1.73)	(0.07-2.71)
	Fluvoxamine	2.45 (0.76-7.87)	2.44 (0.75-7.95)	(0.52-11.54)
	Venlafaxine	0.81 (0.47-1.40)	0.80 (0.47-1.38)	(0.39-1.64)
	Tricyclic antidepressants	1.12 (0.59-2.13)	1.05 (0.55-1.99)	(0.45-2.44)
	Other antidepressants	0.89 (0.33-2.42)	0.84 (0.31-2.27)	(0.23-3.10)
Ventricular/atrial septal defect	Non exposed	1.00	1.00	
	<b>Paroxetine</b>	1.43 (1.17-1.75)	1.39 (1.00-1.93)	(0.64-2.12)
	Sertraline	1.36 (0.69-2.65)	1.33 (0.68-2.60)	(0.55-3.21)
	Citalopram	1.41 (0.83-2.39)	1.39 (0.82-2.36)	(0.69-2.79)
	Fluoxetine	0.57 (0.14-2.30)	0.55 (0.14-2.27)	(0.09-3.55)
	Fluvoxamine	2.03 (0.49-8.36)	2.10 (0.51-8.71)	(0.32-13.66)
	Venlafaxine	0.74 (0.39-1.39)	0.73 (0.39-1.39)	(0.32-1.70)
	Tricyclic antidepressants	1.14 (0.56-2.32)	1.10 (0.54-2.24)	(0.43-2.81)
	Other antidepressants	1.14 (0.42-3.08)	1.11 (0.41-2.97)	(0.30-4.06)
Cranyosynostosis	Non exposed	1.00	1.00	
	Paroxetine	1.44 (0.69-2.99)	1.53 (0.72-3.25)	(0.57-4.12)
	Sertraline	2.24 (0.82-6.16)	2.29 (0.83-6.36)	(0.60-8.78)
	Citalopram	3.89 (2.06-7.35)	3.95 (2.08-7.52)	(1.69-9.22)
	Fluoxetine	1.07 (0.15-7.65)	1.14 (0.16-8.21)	(0.08-15.35)
	Venlafaxine	1.38 (0.56-3.43)	1.41 (0.57-3.52)	(0.42-4.70)
	Tricyclic antidepressants	1.06 (0.26-4.36)	1.05 (0.25-4.37)	(0.16-6.88)
	Other antidepressants	1.05 (0.15-7.63)	1.15 (0.16-8.42)	(0.08-15.82)

Note: Ventricular/atrial septal defects are a sub-set of cardiac malformations; Results are provided when defects were identified for the antidepressant type in the study population (if 0 outcome identified).

\*Adjusted for maternal age, welfare status, diabetes, hypertension, asthma and other medication uses including benzodiazepines as well as health care utilization in the year prior and during the first trimester.

**Table S8.1.** Results of the probabilistic sensitivity analyses correcting for misclassification of antidepressant exposure during the first trimester and the risk of major congenital malformation with sensitivity and specificity drawn from trapezoidal distribution

<b>Analysis</b>	<b>OR 2.5 percentile</b>	<b>OR median estimate</b>	<b>OR 97.5 percentile</b>
<b>Conventional analysis</b>	0.99	1.11	1.25
<b>Non-differential sensitivity analysis</b>			
Sensitivity only	1.09	1.23	4.11
Sensitivity and random error	1.04	1.25	4.03

**Table S8.2.** Results of the probabilistic sensitivity analyses correcting for misclassification of major congenital malformation during the first 6 months of baby's life and the probability to be exposed to antidepressant medications during the first trimester with sensitivity and specificity drawn from trapezoidal distribution

<b>Analysis</b>	<b>OR 2.5 percentile</b>	<b>OR median estimate</b>	<b>OR 97.5 percentile</b>
<b>Conventional analysis</b>	0.99	1.11	1.25
<b>Differential sensitivity analysis</b>			
Sensitivity only	0.43	3.70	55.15
Sensitivity and random error	0.43	3.72	54.06