

Appendix: Antidepressant Use in Pregnancy and the Risk of Cardiac Defects

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Table S1 Antidepressant Medications

Antidepressant Medication Class	Antidepressant Generic Name
SSRI	Citalopram
	Escitalopram
	Fluoxetine
	Fluvoxamine
	Paroxetine
	Sertraline
SNRI	Duloxetine
	Venlafaxine
Bupropion	Bupropion
TCA	Amitriptyline
	Amoxapine
	Clomipramine
	Desipramine
	Doxepin
	Imipramine
	Maprotiline
	Nortriptyline
	Protriptyline
	Trimipramine
	Other
Nefazodone	
Selegiline	
Trazodone	

Table S2 ICD-9 Diagnostic codes used to identify cardiac malformation

ICD-9 Diagnosis	
Other cardiac malformation*	
745	Bulbus Cordis Anomalies And Anomalies Of Cardiac Septal Closure
745.0x	Common Truncus
745.1x	Transposition Of Great Vessels
745.10	Complete Transposition Of Great Vessels
745.11	Double Outlet Right Ventricle
745.12	Corrected Transposition Of Great Vessels
745.19	Other Transposition Of Great Vessels
745.2x	Tetralogy Of Fallot
745.3x	Common Ventricle
745.6x	Endocardial Cushion Defects
745.60	Endocardial Cushion Defect Unspecified Type
745.61	Ostium Primum Defect
745.69	Other Endocardial Cushion Defects
745.7x	Cor Biloculare
745.8x	Other Bulbus Cordis Anomalies And Anomalies Of Cardiac Septal Closure
745.9x	Unspecified Defect Of Septal Closure
746	Other Congenital Anomalies Of Heart
746.00	Congenital Pulmonary Valve Anomaly Unspecified
746.1x	Tricuspid Atresia And Stenosis Congenital
746.2x	Ebstein's Anomaly
746.3x	Congenital Stenosis Of Aortic Valve
746.5x	Congenital Mitral Stenosis
746.7x	Hypoplastic Left Heart Syndrome
746.8	Other Specified Congenital Anomalies Of Heart
746.80	Subaortic Stenosis Congenital
746.82	Cor Triatriatum
746.84	Congenital Obstructive Anomalies Of Heart Not Elsewhere Classified
746.85	Coronary Artery Anomaly Congenital
746.86	Congenital Heart Block
746.87	Malposition Of Heart And Cardiac Apex
746.89	Other Specified Congenital Anomalies Of Heart
747	Other Congenital Anomalies Of Circulatory System
747.1x	Coarctation Of Aorta
747.10	Coarctation Of Aorta (Preductal) (Postductal)
747.11	Interruption Of Aortic Arch
747.2x	Other Congenital Anomalies Of Aorta
747.20	Congenital Anomaly Of Aorta Unspecified

747.21	Congenital Anomalies Of Aortic Arch
747.22	Congenital Atresia And Stenosis Of Aorta
747.29	Other Congenital Anomalies Of Aorta
747.4x	Congenital Anomalies Of Great Veins
747.40	Congenital Anomaly Of Great Veins Unspecified
747.41	Total Anomalous Pulmonary Venous Connection
747.42	Partial Anomalous Pulmonary Venous Connection
747.49	Other Anomalies Of Great Veins

Persistent Fetal Circulation

747.83

746.9x	Unspecified Congenital Anomaly Of Heart
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Right Ventricular Outflow Obstruction

746.01	Atresia Of Pulmonary Valve Congenital
746.09	Other Congenital Anomalies Of Pulmonary Valve
746.83	Infundibular Pulmonic Stenosis Congenital
747.3x and no preterm delivery codes in first 60 days following delivery	Congenital Anomalies Of Pulmonary Artery, Pulmonary Artery Coarctation And Atresia, Pulmonary Arteriovenous Malformation, Other Anomalies Of Pulmonary Artery And Pulmonary Circulation
746.02 and no preterm delivery codes in first 60 days following delivery	Stenosis of pulmonary valve congenital

Ventricular Septal Defects

745.4x	Ventricular Septal Defect
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* 747.81 (Anomalies of cerebrovascular system) typically indicates a maternal malformation and was therefore excluded

Table S3 Cardiac procedure and surgery codes used in the outcome definition

ICD-9	Description
35.x	Operations on valves and septa of heart
36.x	Operations on vessels of heart
37.x except for 37.94	Other operations on heart and pericardium
38.x except for 38.18, 38.91, 38.92, 38.93, 38.94, 38.95, 38.98, 38.99	Incision, excision, and occlusion of vessels
39.x except for 39.27, 39.50, 39.95, 39.98	Other operations on vessels
CPT-4	Description
00560	ANESTHESIA FOR PROCEDURES ON HEART, PERICARDIAL SAC, AND GREAT VESSELS OF CHEST; WITHOUT PUMP OXYGENATOR
00561	ANESTHESIA FOR PROCEDURES ON HEART, PERICARDIAL SAC, AND GREAT VESSELS OF CHEST; WITH PUMP OXYGENATOR, YOUNGER THAN 1 YEAR OF AGE
00563	ANESTHESIA FOR PROCEDURES ON HEART, PERICARDIAL SAC, AND GREAT VESSELS
33300-35190	Various cardiac surgeries/procedures.
92992	ATRIAL SEPTECTOMY OR SEPTOSTOMY; TRANSVENOUS METHOD, BALLOON (EG, RASHKIND TYPE) (INCLUDES CARDIAC CATHETERIZATION)
92993	ATRIAL SEPTECTOMY OR SEPTOSTOMY; BLADE METHOD (PARK SEPTOSTOMY) (INCLUDES CARDIAC CATHETERIZATION)
93530	RIGHT HEART CATHETERIZATION, FOR CONGENITAL CARDIAC ANOMALIES
93531	COMBINED RIGHT HEART CATHETERIZATION AND RETROGRADE LEFT HEART CATHETERIZATION, FOR CONGENITAL CARDIAC ANOMALIES
93532	COMBINED RIGHT HEART CATHETERIZATION AND TRANSSEPTAL LEFT HEART CATHETERIZATION THROUGH INTACT SEPTUM WITH OR WITHOUT RETROGRADE LEFT HEART CATHETERIZATION, FOR CONGENITAL CARDIAC ANOMALIES
93533	COMBINED RIGHT HEART CATHETERIZATION AND TRANSSEPTAL LEFT HEART CATHETERIZATION THROUGH EXISTING SEPTAL OPENING, WITH OR WITHOUT RETROGRADE LEFT HEART CATHETERIZATION, FOR CONGENITAL CARDIAC ANOMALIES

Table S4 Dose levels for individual antidepressant medications based on Goodman & Gilman's usual dose range

Class	Drug	Low Strength (mg/day)	Medium Strength (mg/day)	High Strength
SSRI	Citalopram	<20	≥20 and ≤30	>30
	Escitalopram	<10	≥10 and ≤15	>15
	Fluoxetine	<20	≥20 and ≤30	>30
	Fluvoxamine	<100	≥100 and ≤150	>150
	Paroxetine	<20	≥20 and ≤30	>30
	Sertraline	<100	≥100 and ≤125	>125
SNRI	Venlafaxine	<75	≥75 and ≤150	>150
	Duloxetine	<80	≥80 and ≤90	>90
Bupropion	Bupropion	<200	≥200 and ≤250	>250
TCA	Amoxapine	<200	≥200 and ≤250	>250
	Desipramine	<100	≥100 and ≤150	>150
	Maprotiline	<100	≥100 and ≤125	>125
	Nortriptyline	<75	≥75 and ≤112.5	>112.5
	Amitriptyline	<100	≥100 and ≤150	>150
	Clomipramine	<100	≥100 and ≤150	>150
	Doxepin	<100	≥100 and ≤150	>150
	Imipramine	<100	≥100 and ≤150	>150
	Trimipramine	<75	≥75 and ≤150	>150
	Protriptyline	<15	≥15 and ≤30	>30
Other	Mirtazapine	<15	≥15 and ≤30	>30
	Nefazodone	<200	≥200 and ≤300	>300
	Trazodone	<150	≥150 and ≤175	>175
	Selegiline	<10	10	>10

Dose levels were defined according to Goodman & Gilman's usual dose (mg/day)¹: low < lowest usual dose, medium ≤ the midpoint of the usual dose range, high > the midpoint of the usual dose range.

Table S5 Cohort characteristics for SSRIs; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	SSRI	Unexposed	SSRI	Unexposed
N	46,144	885,115	36,778	180,564
Age, mean (SD)	25.59 (5.94)	23.85 (5.75)	25.54 (5.96)	25.32 (53.09)
Year of delivery, N (%)				
2000-2002	8,103 (17.56)	187,511 (21.19)	5,822 (15.83)	29,134 (16.13)
2003-2005	24,652 (53.42)	426,522 (48.19)	19,534 (53.11)	95,448 (52.86)
2006-2007	13,389 (29.02)	271,082 (30.63)	11,422 (31.06)	55,982 (31.00)
Race, N (%)				
White	34,098 (73.89)	339,144 (38.32)	27,299 (74.23)	136,506 (75.60)
Black	5,438 (11.78)	313,369 (35.40)	4,193 (11.40)	19,380 (10.73)
Hispanic	4,145 (8.98)	164,317 (18.56)	3,261 (8.87)	15,017 (8.32)
Other or unknown	2,463 (5.34)	68,285 (7.71)	2,025 (5.51)	9,661 (5.35)
Multipara, N (%)	36,910 (79.99)	706,656 (79.84)	28,937 (78.68)	142,588 (78.97)
Multiple gestation, N (%)	1,780 (3.86)	31,258 (3.53)	1,377 (3.74)	6,711 (3.72)
Preterm birth, N (%) ⁽²⁾	6,470 (14.02)	98,886 (11.17)	5,250 (14.27)	25,299 (14.01)
Antidepressant indications, N (%)				
Depression	36,783 (79.71)	180,564 (20.40)	36,778 (100.00%)	180,564 (100.00%)
Other mental health disorders	4,430 (9.60)	17,325 (1.96)	3,907 (10.62)	19,389 (10.74)
Pain related diagnoses	4,376 (9.48)	24,527 (2.77)	3,634 (9.88)	18,232 (10.10)
Sleep disorders	1,487 (3.22)	3,319 (0.38)	1,236 (3.36)	6,419 (3.55)
Premenstrual tension syndrome	175 (0.38)	453 (0.05)	102 (0.28)	519 (0.29)
Smoking	2,451 (5.31)	17,769 (2.01)	2,154 (5.86)	10,634 (5.89)
Chronic fatigue syndrome	3,603 (7.81)	20,623 (2.33)	2,919 (7.94)	14,806 (8.20)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	2.76 (6.51)	0.24 (2.04)	3.46 (7.12)	3.31 (20.25)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	SSRI	Unexposed	SSRI	Unexposed
Number of inpatient depression diagnoses	0.05 (0.26)	0.00 (0.06)	0.06 (0.29)	0.06 (0.98)
Chronic maternal illness, N (%)				
Hypertension	1,656 (3.59)	12,573 (1.42)	1,319 (3.59)	6,606 (3.66)
Diabetes	1,288 (2.79)	10,628 (1.20)	997 (2.71)	4,957 (2.75)
Gestational diabetes	494 (1.07)	5,483 (0.62)	375 (1.02)	1,854 (1.03)
Epilepsy	412 (0.89)	2,388 (0.27)	343 (0.93)	1,783 (0.99)
Renal disease	76 (0.16)	819 (0.09)	64 (0.17)	325 (0.18)
Other psychotropic medications, N (%)				
Anticonvulsants	7,353 (15.93)	31,681 (3.58)	6,654 (18.09)	33,599 (18.61)
Antipsychotics	9,534 (20.66)	48,657 (5.50)	8,621 (23.44)	42,987 (23.81)
Anxiolytics	3,148 (6.82)	8,189 (0.93)	2,895 (7.87)	14,320 (7.93)
Benzodiazepines	14,560 (31.55)	49,063 (5.54)	12,856 (34.96)	63,100 (34.95)
Other hypnotics	13,277 (28.77)	115,608 (13.06)	11,540 (31.38)	56,323 (31.19)
Barbiturates	3,764 (8.16)	26,030 (2.94)	3,097 (8.42)	15,756 (8.73)
Other medications, N (%)				
Antidiabetics	1,682 (3.65)	15,364 (1.74)	1,303 (3.54)	6,449 (3.57)
Antihypertensives	6,814 (14.77)	54,170 (6.12)	5,588 (15.19)	28,078 (15.55)
Suspected teratogenics	3,508 (7.60)	26,967 (3.05)	2,806 (7.63)	14,345 (7.94)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.47 (3.35)	1.45 (2.10)	3.56 (3.41)	3.47 (13.03)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S6 Cohort characteristics for TCAs; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	TCA	Unexposed	TCA	Unexposed
N	5,954	885,115	3,314	180,562
Age, mean (SD)	26.68 (6.29)	23.85 (5.75)	26.95 (6.25)	26.53 (85.51)
Year of delivery, N (%)				
2000-2002	1,292 (21.70)	187,511 (21.19)	575 (17.35)	31,159 (17.26)
2003-2005	3,012 (50.59)	426,522 (48.19)	1,711 (51.63)	92,942 (51.47)
2006-2007	1,650 (27.71)	271,082 (30.63)	1,028 (31.02)	56,461 (31.27)
Race, N (%)				
White	3,746 (62.92)	339,144 (38.32)	2,328 (70.25)	126,497 (70.06)
Black	1,105 (18.56)	313,369 (35.40)	464 (14.00)	25,725 (14.25)
Hispanic	697 (11.71)	164,317 (18.56)	308 (9.29)	16,979 (9.40)
Other or unknown	406 (6.82)	68,285 (7.71)	214 (6.46)	11,361 (6.29)
Multipara, N (%)	4,883 (82.01)	706,656 (79.84)	2,644 (79.78)	143,805 (79.64)
Multiple gestation, N (%)	247 (4.15)	31,258 (3.53)	148 (4.47)	7,964 (4.41)
Preterm birth, N (%) ⁽²⁾	825 (13.86)	98,886 (11.17)	512 (15.45)	27,928 (15.47)
Antidepressant indications, N (%)				
Depression	3,328 (55.90)	180,564 (20.40)	3,314 (100.00%)	180,562 (100.00%)
Other mental health disorders	591 (9.93)	17,325 (1.96)	395 (11.92)	21,287 (11.79)
Pain related diagnoses	1,787 (30.01)	24,527 (2.77)	1,012 (30.54)	54,289 (30.07)
Sleep disorders	340 (5.71)	3,319 (0.38)	231 (6.97)	12,013 (6.65)
Premenstrual tension syndrome	9 (0.15)	453 (0.05)	3 (0.09)	178 (0.10)
Smoking	343 (5.76)	17,769 (2.01)	236 (7.12)	12,424 (6.88)
Chronic fatigue syndrome	458 (7.69)	20,623 (2.33)	282 (8.51)	15,674 (8.68)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	1.58 (4.89)	0.24 (2.04)	2.80 (6.27)	2.67 (21.82)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	TCA	Unexposed	TCA	Unexposed
Number of inpatient depression diagnoses	0.03 (0.22)	0.00 (0.06)	0.05 (0.29)	0.05 (1.24)
Chronic maternal illness, N (%)				
Hypertension	346 (5.81)	12,573 (1.42)	205 (6.19)	10,743 (5.95)
Diabetes	273 (4.59)	10,628 (1.20)	157 (4.74)	8,395 (4.65)
Gestational diabetes	62 (1.04)	5,483 (0.62)	38 (1.15)	2,115 (1.17)
Epilepsy	69 (1.16)	2,388 (0.27)	46 (1.39)	2,450 (1.36)
Renal disease	25 (0.42)	819 (0.09)	19 (0.57)	867 (0.48)
Other psychotropic medications, N (%)				
Anticonvulsants	1,297 (21.78)	31,681 (3.58)	926 (27.94)	48,207 (26.70)
Antipsychotics	1,169 (19.63)	48,657 (5.50)	891 (26.89)	48,026 (26.60)
Anxiolytics	379 (6.37)	8,189 (0.93)	337 (10.17)	17,636 (9.77)
Benzodiazepines	1,911 (32.10)	49,063 (5.54)	1,473 (44.45)	79,140 (43.83)
Other hypnotics	1,919 (32.23)	115,608 (13.06)	1,340 (40.43)	72,374 (40.08)
Barbiturates	1,059 (17.79)	26,030 (2.94)	617 (18.62)	32,907 (18.23)
Other medications, N (%)				
Antidiabetics	321 (5.39)	15,364 (1.74)	185 (5.58)	10,027 (5.55)
Antihypertensives	1,470 (24.69)	54,170 (6.12)	920 (27.76)	49,374 (27.34)
Suspected teratogenics	614 (10.31)	26,967 (3.05)	373 (11.26)	19,629 (10.87)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	4.66 (3.88)	1.45 (2.10)	5.17 (4.13)	4.61 (23.94)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S7 Cohort characteristics for SNRIs; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	SNRI	Unexposed	SNRI	Unexposed
N	6,904	885,115	6,010	180,564
Age, mean (SD)	26.30 (5.70)	23.85 (5.75)	26.26 (5.69)	25.87 (87.94)
Year of delivery, N (%)				
2000-2002	833 (12.07)	187,511 (21.19)	683 (11.36)	20,982 (11.62)
2003-2005	3,686 (53.39)	426,522 (48.19)	3,170 (52.75)	95,203 (52.73)
2006-2007	2,385 (34.55)	271,082 (30.63)	2,157 (35.89)	64,380 (35.65)
Race, N (%)				
White	5,592 (81.00)	339,144 (38.32)	4,903 (81.58)	147,859 (81.89)
Black	539 (7.81)	313,369 (35.40)	449 (7.47)	13,803 (7.64)
Hispanic	431 (6.24)	164,317 (18.56)	357 (5.94)	10,404 (5.76)
Other or unknown	342 (4.95)	68,285 (7.71)	301 (5.01)	8,497 (4.71)
Multipara, N (%)	5,675 (82.20)	706,656 (79.84)	4,905 (81.61)	147,525 (81.70)
Multiple gestation, N (%)	268 (3.88)	31,258 (3.53)	228 (3.79)	6,919 (3.83)
Preterm birth, N (%) ⁽²⁾	1,004 (14.54)	98,886 (11.17)	885 (14.73)	26,437 (14.64)
Antidepressant indications, N (%)				
Depression	6,014 (87.11)	180,564 (20.40)	6,010 (100.00%)	180,564 (100.00%)
Other mental health disorders	747 (10.82)	17,325 (1.96)	693 (11.53)	20,277 (11.23)
Pain related diagnoses	906 (13.12)	24,527 (2.77)	802 (13.34)	23,041 (12.76)
Sleep disorders	288 (4.17)	3,319 (0.38)	249 (4.14)	7,500 (4.15)
Premenstrual tension syndrome	15 (0.22)	453 (0.05)	13 (0.22)	342 (0.19)
Smoking	441 (6.39)	17,769 (2.01)	417 (6.94)	12,388 (6.86)
Chronic fatigue syndrome	680 (9.85)	20,623 (2.33)	577 (9.60)	17,132 (9.49)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	3.51 (7.15)	0.24 (2.04)	4.02 (7.51)	3.83 (37.97)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	SNRI	Unexposed	SNRI	Unexposed
Number of inpatient depression diagnoses	0.06 (0.30)	0.00 (0.06)	0.07 (0.32)	0.06 (1.40)
Chronic maternal illness, N (%)				
Hypertension	261 (3.78)	12,573 (1.42)	232 (3.86)	7,047 (3.90)
Diabetes	212 (3.07)	10,628 (1.20)	183 (3.04)	5,430 (3.01)
Gestational diabetes	86 (1.25)	5,483 (0.62)	76 (1.26)	2,251 (1.25)
Epilepsy	59 (0.85)	2,388 (0.27)	52 (0.87)	1,606 (0.89)
Renal disease	14 (0.20)	819 (0.09)	14 (0.23)	404 (0.22)
Other psychotropic medications, N (%)				
Anticonvulsants	1,698 (24.59)	31,681 (3.58)	1,591 (26.47)	47,539 (26.33)
Antipsychotics	1,959 (28.37)	48,657 (5.50)	1,865 (31.03)	55,912 (30.97)
Anxiolytics	648 (9.39)	8,189 (0.93)	609 (10.13)	18,426 (10.20)
Benzodiazepines	2,869 (41.56)	49,063 (5.54)	2,638 (43.89)	77,104 (42.70)
Other hypnotics	2,464 (35.69)	115,608 (13.06)	2,258 (37.57)	67,338 (37.29)
Barbiturates	705 (10.21)	26,030 (2.94)	622 (10.35)	18,933 (10.49)
Other medications, N (%)				
Antidiabetics	313 (4.53)	15,364 (1.74)	272 (4.53)	7,968 (4.41)
Antihypertensives	1,242 (17.99)	54,170 (6.12)	1,090 (18.14)	32,799 (18.16)
Suspected teratogenics	670 (9.70)	26,967 (3.05)	577 (9.60)	17,581 (9.74)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	4.06 (3.62)	1.45 (2.10)	4.13 (3.66)	3.95 (22.06)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S8 Cohort characteristics for other antidepressants; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Other	Unexposed	Other	Unexposed
N	7,055	885,115	6,021	180,564
Age, mean (SD)	26.40 (6.45)	23.85 (5.75)	26.26 (6.43)	25.90 (94.62)
Year of delivery, N (%)				
2000-2002	1,454 (20.61)	187,511 (21.19)	1,127 (18.72)	33,638 (18.63)
2003-2005	3,541 (50.19)	426,522 (48.19)	3,038 (50.46)	90,360 (50.04)
2006-2007	2,060 (29.20)	271,082 (30.63)	1,856 (30.83)	56,566 (31.33)
Race, N (%)				
White	4,894 (69.37)	339,144 (38.32)	4,246 (70.52)	127,199 (70.45)
Black	1,134 (16.07)	313,369 (35.40)	904 (15.01)	27,378 (15.16)
Hispanic	565 (8.01)	164,317 (18.56)	467 (7.76)	13,633 (7.55)
Other or unknown	462 (6.55)	68,285 (7.71)	404 (6.71)	12,355 (6.84)
Multipara, N (%)	5,274 (74.76)	706,656 (79.84)	4,436 (73.68)	132,568 (73.42)
Multiple gestation, N (%)	297 (4.21)	31,258 (3.53)	253 (4.20)	7,434 (4.12)
Preterm birth, N (%) ⁽²⁾	1,141 (16.17)	98,886 (11.17)	964 (16.01)	27,053 (14.98)
Antidepressant indications, N (%)				
Depression	6,039 (85.60)	180,564 (20.40)	6,021 (100.00%)	180,564 (100.00%)
Other mental health disorders	1,070 (15.17)	17,325 (1.96)	966 (16.04)	29,121 (16.13)
Pain related diagnoses	844 (11.96)	24,527 (2.77)	731 (12.14)	21,751 (12.05)
Sleep disorders	510 (7.23)	3,319 (0.38)	408 (6.78)	12,872 (7.13)
Premenstrual tension syndrome	9 (0.13)	453 (0.05)	7 (0.12)	238 (0.13)
Smoking	490 (6.95)	17,769 (2.01)	440 (7.31)	13,321 (7.38)
Chronic fatigue syndrome	485 (6.87)	20,623 (2.33)	411 (6.83)	12,348 (6.84)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	4.57 (8.72)	0.24 (2.04)	5.30 (9.14)	5.13 (42.62)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Other	Unexposed	Other	Unexposed
Number of inpatient depression diagnoses	0.09 (0.36)	0.00 (0.06)	0.10 (0.38)	0.09 (1.99)
Chronic maternal illness, N (%)				
Hypertension	305 (4.32)	12,573 (1.42)	262 (4.35)	7,715 (4.27)
Diabetes	210 (2.98)	10,628 (1.20)	176 (2.92)	5,461 (3.02)
Gestational diabetes	82 (1.16)	5,483 (0.62)	71 (1.18)	2,070 (1.15)
Epilepsy	72 (1.02)	2,388 (0.27)	65 (1.08)	2,038 (1.13)
Renal disease	13 (0.18)	819 (0.09)	12 (0.20)	277 (0.15)
Other psychotropic medications, N (%)				
Anticonvulsants	1,981 (28.08)	31,681 (3.58)	1,821 (30.24)	53,981 (29.90)
Antipsychotics	2,281 (32.33)	48,657 (5.50)	2,095 (34.79)	62,963 (34.87)
Anxiolytics	705 (9.99)	8,189 (0.93)	645 (10.71)	19,653 (10.88)
Benzodiazepines	2,827 (40.07)	49,063 (5.54)	2,572 (42.72)	76,068 (42.13)
Other hypnotics	2,712 (38.44)	115,608 (13.06)	2,440 (40.52)	70,953 (39.30)
Barbiturates	718 (10.18)	26,030 (2.94)	616 (10.23)	18,677 (10.34)
Other medications, N (%)				
Antidiabetics	263 (3.73)	15,364 (1.74)	219 (3.64)	6,702 (3.71)
Antihypertensives	1,306 (18.51)	54,170 (6.12)	1,127 (18.72)	33,226 (18.40)
Suspected teratogenics	676 (9.58)	26,967 (3.05)	575 (9.55)	17,475 (9.68)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	4.23 (3.80)	1.45 (2.10)	4.28 (3.80)	4.02 (23.99)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S9 Cohort characteristics for bupropion; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Bupropion	Unexposed	Bupropion	Unexposed
N	8,856	885,115	6,691	180,563
Age, mean (SD)	26.02 (5.89)	23.85 (5.75)	26.02 (5.93)	25.71 (67.21)
Year of delivery, N (%)				
2000-2002	1,273 (14.37)	187,511 (21.19)	802 (11.99)	21,948 (12.16)
2003-2005	4,564 (51.54)	426,522 (48.19)	3,372 (50.40)	90,761 (50.27)
2006-2007	3,019 (34.09)	271,082 (30.63)	2,517 (37.62)	67,854 (37.58)
Race, N (%)				
White	6,932 (78.27)	339,144 (38.32)	5,267 (78.72)	142,667 (79.01)
Black	857 (9.68)	313,369 (35.40)	589 (8.80)	16,047 (8.89)
Hispanic	624 (7.05)	164,317 (18.56)	488 (7.29)	12,544 (6.95)
Other or unknown	443 (5.00)	68,285 (7.71)	347 (5.19)	9,305 (5.15)
Multipara, N (%)	7,228 (81.62)	706,656 (79.84)	5,360 (80.11)	144,399 (79.97)
Multiple gestation, N (%)	327 (3.69)	31,258 (3.53)	257 (3.84)	6,995 (3.87)
Preterm birth, N (%) ⁽²⁾	1,205 (13.61)	98,886 (11.17)	934 (13.96)	26,440 (14.64)
Antidepressant indications, N (%)				
Depression	6,704 (75.70)	180,564 (20.40)	6,691 (100.00%)	180,563 (100.00%)
Other mental health disorders	931 (10.51)	17,325 (1.96)	804 (12.02)	21,992 (12.18)
Pain related diagnoses	817 (9.23)	24,527 (2.77)	681 (10.18)	18,129 (10.04)
Sleep disorders	283 (3.20)	3,319 (0.38)	235 (3.51)	6,521 (3.61)
Premenstrual tension syndrome	24 (0.27)	453 (0.05)	18 (0.27)	520 (0.29)
Smoking	885 (9.99)	17,769 (2.01)	625 (9.34)	16,896 (9.36)
Chronic fatigue syndrome	733 (8.28)	20,623 (2.33)	576 (8.61)	15,736 (8.71)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	2.85 (6.59)	0.24 (2.04)	3.75 (7.34)	3.62 (28.30)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Bupropion	Unexposed	Bupropion	Unexposed
Number of inpatient depression diagnoses	0.04 (0.24)	0.00 (0.06)	0.06 (0.27)	0.05 (1.22)
Chronic maternal illness, N (%)				
Hypertension	354 (4.00)	12,573 (1.42)	263 (3.93)	6,853 (3.80)
Diabetes	261 (2.95)	10,628 (1.20)	191 (2.85)	5,090 (2.82)
Gestational diabetes	104 (1.17)	5,483 (0.62)	79 (1.18)	2,002 (1.11)
Epilepsy	26 (0.29)	2,388 (0.27)	22 (0.33)	628 (0.35)
Renal disease	15 (0.17)	819 (0.09)	13 (0.19)	343 (0.19)
Other psychotropic medications, N (%)				
Anticonvulsants	1,750 (19.76)	31,681 (3.58)	1,579 (23.60)	42,823 (23.72)
Antipsychotics	2,092 (23.62)	48,657 (5.50)	1,892 (28.28)	51,526 (28.54)
Anxiolytics	589 (6.65)	8,189 (0.93)	518 (7.74)	14,028 (7.77)
Benzodiazepines	2,663 (30.07)	49,063 (5.54)	2,356 (35.21)	62,641 (34.69)
Other hypnotics	2,690 (30.37)	115,608 (13.06)	2,318 (34.64)	62,600 (34.67)
Barbiturates	774 (8.74)	26,030 (2.94)	653 (9.76)	17,403 (9.64)
Other medications, N (%)				
Antidiabetics	379 (4.28)	15,364 (1.74)	293 (4.38)	7,799 (4.32)
Antihypertensives	1,389 (15.68)	54,170 (6.12)	1,114 (16.65)	29,878 (16.55)
Suspected teratogenics	768 (8.67)	26,967 (3.05)	590 (8.82)	16,000 (8.86)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.69 (3.48)	1.45 (2.10)	3.88 (3.54)	3.66 (16.31)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S10 Cohort characteristics for paroxetine; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Paroxetine	Unexposed	Paroxetine	Unexposed
N	11,126	885,115	8,748	180,564
Age, mean (SD)	26.04 (5.93)	23.85 (5.75)	26.02 (5.95)	25.72 (57.84)
Year of delivery, N (%)				
2000-2002	2,588 (23.26)	187,511 (21.19)	1,859 (21.25)	38,514 (21.33)
2003-2005	6,307 (56.69)	426,522 (48.19)	4,992 (57.06)	103,230 (57.17)
2006-2007	2,231 (20.05)	271,082 (30.63)	1,897 (21.69)	38,820 (21.50)
Race, N (%)				
White	7,935 (71.32)	339,144 (38.32)	6,282 (71.81)	130,651 (72.36)
Black	1,351 (12.14)	313,369 (35.40)	1,013 (11.58)	20,365 (11.28)
Hispanic	1,236 (11.11)	164,317 (18.56)	962 (11.00)	19,551 (10.83)
Other or unknown	604 (5.43)	68,285 (7.71)	491 (5.61)	9,997 (5.54)
Multipara, N (%)	9,145 (82.19)	706,656 (79.84)	7,099 (81.15)	146,650 (81.22)
Multiple gestation, N (%)	470 (4.22)	31,258 (3.53)	362 (4.14)	7,432 (4.12)
Preterm birth, N (%) ⁽²⁾	1,543 (13.87)	98,886 (11.17)	1,227 (14.03)	24,924 (13.80)
Antidepressant indications, N (%)				
Depression	8,763 (78.76)	180,564 (20.40)	8,748 (100.00%)	180,564 (100.00%)
Other mental health disorders	955 (8.58)	17,325 (1.96)	816 (9.33)	16,736 (9.27)
Pain related diagnoses	1,080 (9.71)	24,527 (2.77)	871 (9.96)	18,043 (9.99)
Sleep disorders	356 (3.20)	3,319 (0.38)	280 (3.20)	5,712 (3.16)
Premenstrual tension syndrome	29 (0.26)	453 (0.05)	18 (0.21)	377 (0.21)
Smoking	536 (4.82)	17,769 (2.01)	465 (5.32)	9,664 (5.35)
Chronic fatigue syndrome	863 (7.76)	20,623 (2.33)	703 (8.04)	14,471 (8.01)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	2.47 (5.91)	0.24 (2.04)	3.13 (6.49)	3.04 (18.19)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Paroxetine	Unexposed	Paroxetine	Unexposed
Number of inpatient depression diagnoses	0.04 (0.23)	0.00 (0.06)	0.05 (0.26)	0.05 (0.81)
Chronic maternal illness, N (%)				
Hypertension	436 (3.92)	12,573 (1.42)	360 (4.12)	7,326 (4.06)
Diabetes	322 (2.89)	10,628 (1.20)	232 (2.65)	4,840 (2.68)
Gestational diabetes	122 (1.10)	5,483 (0.62)	97 (1.11)	1,937 (1.07)
Epilepsy	95 (0.85)	2,388 (0.27)	72 (0.82)	1,503 (0.83)
Renal disease	18 (0.16)	819 (0.09)	13 (0.15)	263 (0.15)
Other psychotropic medications, N (%)				
Anticonvulsants	1,533 (13.78)	31,681 (3.58)	1,348 (15.41)	28,228 (15.63)
Antipsychotics	2,010 (18.07)	48,657 (5.50)	1,777 (20.31)	36,954 (20.47)
Anxiolytics	827 (7.43)	8,189 (0.93)	739 (8.45)	15,097 (8.36)
Benzodiazepines	3,940 (35.41)	49,063 (5.54)	3,417 (39.06)	68,755 (38.08)
Other hypnotics	3,116 (28.01)	115,608 (13.06)	2,645 (30.24)	54,295 (30.07)
Barbiturates	914 (8.22)	26,030 (2.94)	741 (8.47)	15,265 (8.45)
Other medications, N (%)				
Antidiabetics	379 (3.41)	15,364 (1.74)	286 (3.27)	5,971 (3.31)
Antihypertensives	1,695 (15.23)	54,170 (6.12)	1,355 (15.49)	27,895 (15.45)
Suspected teratogenics	813 (7.31)	26,967 (3.05)	623 (7.12)	13,274 (7.35)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.51 (3.37)	1.45 (2.10)	3.58 (3.43)	3.45 (12.94)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S11 Cohort characteristics for sertraline; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Sertraline	Unexposed	Sertraline	Unexposed
N	14,040	885,115	11,056	180,564
Age, mean (SD)	25.33 (5.90)	23.85 (5.75)	25.29 (5.93)	25.12 (51.80)
Year of delivery, N (%)				
2000-2002	2,329 (16.59)	187,511 (21.19)	1,679 (15.19)	27,936 (15.47)
2003-2005	7,611 (54.21)	426,522 (48.19)	5,911 (53.46)	96,405 (53.39)
2006-2007	4,100 (29.20)	271,082 (30.63)	3,466 (31.35)	56,223 (31.14)
Race, N (%)				
White	10,359 (73.78)	339,144 (38.32)	8,169 (73.89)	135,160 (74.85)
Black	1,715 (12.22)	313,369 (35.40)	1,304 (11.79)	20,367 (11.28)
Hispanic	1,223 (8.71)	164,317 (18.56)	967 (8.75)	15,123 (8.38)
Other or unknown	743 (5.29)	68,285 (7.71)	616 (5.57)	9,914 (5.49)
Multipara, N (%)	11,131 (79.28)	706,656 (79.84)	8,605 (77.83)	141,034 (78.11)
Multiple gestation, N (%)	515 (3.67)	31,258 (3.53)	386 (3.49)	6,334 (3.51)
Preterm birth, N (%) ⁽²⁾	1,988 (14.16)	98,886 (11.17)	1,593 (14.41)	25,143 (13.92)
Antidepressant indications, N (%)				
Depression	11,074 (78.87)	180,564 (20.40)	11,056 (100.00%)	180,564 (100.00%)
Other mental health disorders	1,296 (9.23)	17,325 (1.96)	1,150 (10.40)	18,634 (10.32)
Pain related diagnoses	1,261 (8.98)	24,527 (2.77)	1,058 (9.57)	17,330 (9.60)
Sleep disorders	453 (3.23)	3,319 (0.38)	381 (3.45)	6,015 (3.33)
Premenstrual tension syndrome	46 (0.33)	453 (0.05)	26 (0.24)	440 (0.24)
Smoking	765 (5.45)	17,769 (2.01)	654 (5.92)	10,736 (5.95)
Chronic fatigue syndrome	1,087 (7.74)	20,623 (2.33)	876 (7.92)	14,326 (7.93)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	2.66 (6.08)	0.24 (2.04)	3.36 (6.65)	3.31 (20.74)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Sertraline	Unexposed	Sertraline	Unexposed
Number of inpatient depression diagnoses	0.05 (0.25)	0.00 (0.06)	0.06 (0.28)	0.05 (0.88)
Chronic maternal illness, N (%)				
Hypertension	481 (3.43)	12,573 (1.42)	375 (3.39)	6,179 (3.42)
Diabetes	389 (2.77)	10,628 (1.20)	310 (2.80)	4,933 (2.73)
Gestational diabetes	143 (1.02)	5,483 (0.62)	108 (0.98)	1,742 (0.96)
Epilepsy	123 (0.88)	2,388 (0.27)	105 (0.95)	1,778 (0.98)
Renal disease	26 (0.19)	819 (0.09)	24 (0.22)	352 (0.20)
Other psychotropic medications, N (%)				
Anticonvulsants	2,013 (14.34)	31,681 (3.58)	1,819 (16.45)	29,932 (16.58)
Antipsychotics	2,704 (19.26)	48,657 (5.50)	2,417 (21.86)	39,871 (22.08)
Anxiolytics	895 (6.37)	8,189 (0.93)	808 (7.31)	13,383 (7.41)
Benzodiazepines	4,030 (28.70)	49,063 (5.54)	3,527 (31.90)	57,111 (31.63)
Other hypnotics	3,984 (28.38)	115,608 (13.06)	3,424 (30.97)	55,699 (30.85)
Barbiturates	1,091 (7.77)	26,030 (2.94)	892 (8.07)	14,657 (8.12)
Other medications, N (%)				
Antidiabetics	499 (3.55)	15,364 (1.74)	389 (3.52)	6,214 (3.44)
Antihypertensives	1,982 (14.12)	54,170 (6.12)	1,615 (14.61)	26,705 (14.79)
Suspected teratogenics	1,101 (7.84)	26,967 (3.05)	874 (7.91)	14,263 (7.90)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.39 (3.34)	1.45 (2.10)	3.48 (3.40)	3.36 (12.26)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

Table S12 Cohort characteristics for fluoxetine; overall unadjusted and depression restricted adjusted. Medicaid Analytic eXtract, 2000-2007.

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Fluoxetine	Unexposed	Fluoxetine	Unexposed
N	11,048	885,115	8,664	180,563
Age, mean (SD)	25.74 (6.06)	23.85 (5.75)	25.63 (6.08)	25.36 (58.53)
Year of delivery, N (%)				
2000-2002	2,171 (19.65)	187,511 (21.19)	1,519 (17.53)	32,147 (17.80)
2003-2005	5,505 (49.83)	426,522 (48.19)	4,305 (49.69)	89,644 (49.65)
2006-2007	3,372 (30.52)	271,082 (30.63)	2,840 (32.78)	58,772 (32.55)
Race, N (%)				
White	8,083 (73.16)	339,144 (38.32)	6,332 (73.08)	133,050 (73.69)
Black	1,240 (11.22)	313,369 (35.40)	979 (11.30)	19,931 (11.04)
Hispanic	1,070 (9.69)	164,317 (18.56)	828 (9.56)	16,691 (9.24)
Other or unknown	655 (5.93)	68,285 (7.71)	525 (6.06)	10,891 (6.03)
Multipara, N (%)	8,834 (79.96)	706,656 (79.84)	6,791 (78.38)	141,601 (78.42)
Multiple gestation, N (%)	421 (3.81)	31,258 (3.53)	320 (3.69)	6,592 (3.65)
Preterm birth, N (%) ⁽²⁾	1,513 (13.69)	98,886 (11.17)	1,205 (13.91)	24,844 (13.76)
Antidepressant indications, N (%)				
Depression	8,680 (78.57)	180,564 (20.40)	8,664 (100.00%)	180,563 (100.00%)
Other mental health disorders	1,149 (10.40)	17,325 (1.96)	1,003 (11.58)	20,741 (11.49)
Pain related diagnoses	1,052 (9.52)	24,527 (2.77)	846 (9.76)	17,464 (9.67)
Sleep disorders	339 (3.07)	3,319 (0.38)	286 (3.30)	6,066 (3.36)
Premenstrual tension syndrome	81 (0.73)	453 (0.05)	44 (0.51)	868 (0.48)
Smoking	583 (5.28)	17,769 (2.01)	509 (5.87)	10,394 (5.76)
Chronic fatigue syndrome	861 (7.79)	20,623 (2.33)	689 (7.95)	14,561 (8.06)
Proxies for depression severity, mean (SD)				
Number of outpatient depression diagnoses	2.78 (6.64)	0.24 (2.04)	3.52 (7.25)	3.45 (24.58)

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Fluoxetine	Unexposed	Fluoxetine	Unexposed
Number of inpatient depression diagnoses	0.06 (0.30)	0.00 (0.06)	0.07 (0.33)	0.07 (1.57)
Chronic maternal illness, N (%)				
Hypertension	350 (3.17)	12,573 (1.42)	264 (3.05)	5,473 (3.03)
Diabetes	285 (2.58)	10,628 (1.20)	218 (2.52)	4,520 (2.50)
Gestational diabetes	113 (1.02)	5,483 (0.62)	81 (0.93)	1,756 (0.97)
Epilepsy	97 (0.88)	2,388 (0.27)	83 (0.96)	1,736 (0.96)
Renal disease	19 (0.17)	819 (0.09)	17 (0.20)	346 (0.19)
Other psychotropic medications, N (%)				
Anticonvulsants	1,841 (16.66)	31,681 (3.58)	1,641 (18.94)	34,132 (18.90)
Antipsychotics	2,447 (22.15)	48,657 (5.50)	2,175 (25.10)	45,738 (25.33)
Anxiolytics	709 (6.42)	8,189 (0.93)	648 (7.48)	13,377 (7.41)
Benzodiazepines	3,268 (29.58)	49,063 (5.54)	2,853 (32.93)	58,600 (32.45)
Other hypnotics	3,041 (27.53)	115,608 (13.06)	2,616 (30.19)	53,989 (29.90)
Barbiturates	825 (7.47)	26,030 (2.94)	673 (7.77)	14,435 (7.99)
Other medications, N (%)				
Antidiabetics	400 (3.62)	15,364 (1.74)	306 (3.53)	6,319 (3.50)
Antihypertensives	1,612 (14.59)	54,170 (6.12)	1,290 (14.89)	26,640 (14.75)
Suspected teratogenics	832 (7.53)	26,967 (3.05)	682 (7.87)	14,062 (7.79)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.38 (3.32)	1.45 (2.10)	3.49 (3.41)	3.34 (13.03)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

**Table S13 Cohort characteristics for all antidepressants combined; overall unadjusted and depression restricted adjusted.
Medicaid Analytic eXtract, 2000-2007.**

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Any Antidepressant ⁽³⁾	Unexposed	Any Antidepressant	Unexposed
N	64,389	885,115	49,527	180,422
Age, mean (SD)	25.71 (5.96)	23.85 (5.75)	25.65 (5.97)	25.41 (51.75)
Year of delivery, N (%)				
2000-2002	11,221 (17.43)	187,511 (21.19)	7,596 (15.34)	28,089 (15.57)
2003-2005	33,826 (52.53)	426,522 (48.19)	25,884 (52.26)	93,925 (52.06)
2006-2007	19,342 (30.04)	271,082 (30.63)	16,047 (32.40)	58,408 (32.37)
Race, N (%)				
White	47,221 (73.34)	339,144 (38.32)	36,898 (74.50)	136,968 (75.92)
Black	7,982 (12.40)	313,369 (35.40)	5,679 (11.47)	19,523 (10.82)
Hispanic	5,709 (8.87)	164,317 (18.56)	4,227 (8.53)	14,402 (7.98)
Other or unknown	3,477 (5.40)	68,285 (7.71)	2,723 (5.50)	9,528 (5.28)
Multipara, N (%)	51,660 (80.23)	706,656 (79.84)	39,011 (78.77)	142,607 (79.04)
Multiple gestation, N (%)	2,505 (3.89)	31,258 (3.53)	1,905 (3.85)	6,930 (3.84)
Preterm birth, N (%) ⁽²⁾	8,988 (13.96)	98,886 (11.17)	7,086 (14.31)	25,650 (14.22)
Antidepressant indications, N (%)				
Depression	49,553 (76.96)	180,564 (20.40)	49,527 (100.00%)	180,422 (100.00%)
Other mental health disorders	6,271 (9.74)	17,325 (1.96)	5,390 (10.88)	19,932 (11.05)
Pain related diagnoses	7,094 (11.02)	24,527 (2.77)	5,416 (10.94)	20,434 (11.33)
Sleep disorders	2,254 (3.50)	3,319 (0.38)	1,789 (3.61)	7,108 (3.94)
Premenstrual tension syndrome	205 (0.32)	453 (0.05)	126 (0.25)	475 (0.26)
Smoking	3,805 (5.91)	17,769 (2.01)	3,135 (6.33)	11,698 (6.48)
Chronic fatigue syndrome	5,011 (7.78)	20,623 (2.33)	3,938 (7.95)	14,791 (8.20)
Proxies for depression severity, mean (SD)				

Characteristic	Overall cohort, unadjusted		Depression restricted cohort, Accounting for PS strata ⁽¹⁾	
	Any Antidepressant ⁽³⁾	Unexposed	Any Antidepressant	Unexposed
Number of outpatient depression diagnoses	2.65 (6.40)	0.24 (2.04)	3.44 (7.10)	3.27 (20.18)
Number of inpatient depression diagnoses	0.05 (0.25)	0.00 (0.06)	0.06 (0.29)	0.05 (0.83)
Chronic maternal illness, N (%)				
Hypertension	2,410 (3.74)	12,573 (1.42)	1,842 (3.72)	6,861 (3.80)
Diabetes	1,870 (2.90)	10,628 (1.20)	1,378 (2.78)	5,124 (2.84)
Gestational diabetes	694 (1.08)	5,483 (0.62)	519 (1.05)	1,900 (1.05)
Epilepsy	530 (0.82)	2,388 (0.27)	428 (0.86)	1,713 (0.95)
Renal disease	118 (0.18)	819 (0.09)	99 (0.20)	348 (0.19)
Other psychotropic medications, N (%)				
Anticonvulsants	11,227 (17.44)	31,681 (3.58)	9,933 (20.06)	36,861 (20.43)
Antipsychotics	13,719 (21.31)	48,657 (5.50)	12,275 (24.78)	45,143 (25.02)
Anxiolytics	4,338 (6.74)	8,189 (0.93)	3,955 (7.99)	14,643 (8.12)
Benzodiazepines	20,257 (31.46)	49,063 (5.54)	17,705 (35.75)	64,523 (35.76)
Other hypnotics	18,892 (29.34)	115,608 (13.06)	16,065 (32.44)	58,554 (32.45)
Barbiturates	5,798 (9.00)	26,030 (2.94)	4,535 (9.16)	17,360 (9.62)
Other medications, N (%)				
Antidiabetics	2,471 (3.84)	15,364 (1.74)	1,852 (3.74)	6,827 (3.78)
Antihypertensives	10,092 (15.67)	54,170 (6.12)	7,965 (16.08)	29,786 (16.51)
Suspected teratogenics	5,174 (8.04)	26,967 (3.05)	3,994 (8.06)	15,157 (8.40)
Number of distinct prescription drugs, excluding antidepressants, mean (SD)	3.57 (3.38)	1.45 (2.10)	3.66 (3.45)	3.57 (12.54)

⁽¹⁾ To account for PS, the untreated observations were weighted using the distribution of the treated among PS strata

⁽²⁾ Relates to current pregnancy

⁽³⁾ The total number of exposed pregnancies is less than the sum of pregnancies across exposure groups due to polytherapy.

Table S14 Absolute risk for congenital cardiac malformations in women with and without antidepressant exposure by class; depression restricted cohort. Medicaid Analytic eXtract, 2000-2007.

Exposure groups	Any cardiac malformation		RVOTO		VSD		Other cardiac malformation		
	Total	Events	Risk (/10,000)	Events	Risk (/10,000)	Events	Risk (/10,000)	Events	Risk (/10,000)
Unexposed	180,564	1,497	82.9	246	13.6	751	41.6	743	41.2
All antidepressants	49,553	460	92.8	69	13.9	211	42.6	259	52.3
SSRI	36,783	341	92.7	53	14.4	155	42.1	189	51.4
Paroxetine	8,763	71	81.0	13	14.8	28	32.0	40	45.7
Sertraline	11,074	106	95.7	17	15.4	50	45.2	57	51.5
Fluoxetine	8,680	84	96.8	12	13.8	41	47.2	45	51.8
TCA	3,328	27	81.1	<11	15.0	15	45.1	13	39.1
SNRI	6,014	69	114.7	12	20.0	34	56.5	37	61.5
Other	6,039	64	106.0	<11	8.3	26	43.1	40	66.2
Bupropion	6,704	57	85.0	10	14.9	26	38.8	37	55.2

Table S15 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women with conventional PS and high-dimensional PS adjustment; restricted to women with depression diagnosis. Medicaid Analytic eXtract 2000-2007.

Exposure	Depression Restricted and PS Stratification					Depression Restricted and hdPS Stratification*				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
Any cardiac malformation										
ANTIDEP	49,527	180,422	460	1,496	1.02 (0.90, 1.15)	49,553	180,563	460	1,497	1.04 (0.92, 1.18)
SSRI	36,778	180,564	341	1,497	1.06 (0.93, 1.22)	36,783	180,564	341	1,497	1.08 (0.94, 1.23)
PAROXETINE	8,748	180,564	71	1,497	0.94 (0.73, 1.21)	8,756	180,564	71	1,497	0.93 (0.72, 1.19)
SERTRALINE	11,056	180,564	106	1,497	1.09 (0.88, 1.34)	11,045	180,564	106	1,497	1.06 (0.86, 1.32)
FLUOXETINE	8,664	180,563	84	1,497	1.14 (0.90, 1.44)	8,676	180,563	84	1,497	1.10 (0.87, 1.40)
TCAS	3,314	180,562	27	1,497	0.77 (0.52, 1.14)	3,287	180,547	27	1,497	0.72 (0.48, 1.08)
SNRIS	6,010	180,564	69	1,497	1.20 (0.91, 1.57)	5,999	180,564	69	1,497	1.20 (0.91, 1.56)
OTHER	6,021	180,564	64	1,497	1.21 (0.91, 1.60)	6,039	180,564	64	1,497	1.16 (0.87, 1.53)
BUPROPION	6,691	180,563	57	1,497	0.92 (0.69, 1.22)	6,698	180,563	57	1,497	0.95 (0.71, 1.26)
Other cardiac malformation										
ANTIDEP	49,527	180,422	259	742	1.15 (0.97, 1.36)	49,553	180,564	259	743	1.19 (1.01, 1.40)
SSRI	36,778	180,564	189	743	1.19 (0.99, 1.43)	36,783	180,561	189	743	1.21 (1.00, 1.45)
PAROXETINE	8,748	180,564	40	743	1.10 (0.78, 1.55)	8,751	180,564	40	743	1.08 (0.77, 1.52)
SERTRALINE	11,056	180,564	57	743	1.19 (0.89, 1.59)	11,069	180,564	57	743	1.19 (0.89, 1.59)
FLUOXETINE	8,664	180,563	45	743	1.23 (0.89, 1.70)	8,655	180,563	45	743	1.22 (0.88, 1.69)
TCAS	3,314	180,562	13	743	0.79 (0.45, 1.40)	3,296	180,564	13	743	0.69 (0.38, 1.24)
SNRIS	6,010	180,564	37	743	1.31 (0.90, 1.90)	6,001	180,564	37	743	1.36 (0.94, 1.97)
OTHER	6,021	180,564	40	743	1.65 (1.15, 2.37)	6,039	180,564	40	743	1.67 (1.17, 2.39)
BUPROPION	6,691	180,563	37	743	1.16 (0.81, 1.67)	6,687	180,564	37	743	1.26 (0.88, 1.81)
RVOTO										
ANTIDEP	49,527	180,422	69	246	0.92 (0.67, 1.25)	49,553	180,559	69	246	0.91 (0.67, 1.24)
SSRI	36,778	180,564	53	246	0.99 (0.70, 1.38)	36,783	180,564	53	246	0.99 (0.70, 1.38)
PAROXETINE	8,748	180,564	13	246	1.07 (0.59, 1.93)	8,760	180,564	13	246	1.03 (0.57, 1.85)
SERTRALINE	11,056	180,564	17	246	1.12 (0.67, 1.88)	11,064	180,564	17	246	1.08 (0.64, 1.82)

Exposure	Depression Restricted and PS Stratification					Depression Restricted and hdPS Stratification*				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
FLUOXETINE	8,664	180,563	12	246	0.93 (0.50 , 1.72)	8,676	180,564	12	246	0.87 (0.47, 1.63)
TCAS	3,314	180,562	<11	246	0.94 (0.37 , 2.36)	3,298	180,563	<11	246	0.88 (0.35, 2.23)
SNRIS	6,010	180,564	12	246	1.06 (0.55 , 2.05)	6,005	180,564	12	246	1.06 (0.55, 2.04)
OTHER	6,021	180,564	<11	246	0.61 (0.24 , 1.52)	6,039	180,564	<11	246	0.54 (0.21, 1.35)
BUPROPION	6,691	180,563	<11	246	1.09 (0.56 , 2.10)	6,696	180,564	<11	246	1.07 (0.55, 2.08)
VSD										
ANTIDEP	49,527	180,422	211	751	0.95 (0.79 , 1.14)	49,553	180,557	211	751	0.96 (0.80, 1.15)
SSRI	36,778	180,564	155	751	0.98 (0.81 , 1.20)	36,783	180,564	155	751	0.99 (0.81, 1.21)
PAROXETINE	8,748	180,564	28	751	0.73 (0.49 , 1.09)	8,760	180,564	28	751	0.73 (0.49, 1.08)
SERTRALINE	11,056	180,564	50	751	1.04 (0.76 , 1.41)	11,065	180,564	50	751	0.98 (0.72, 1.34)
FLUOXETINE	8,664	180,563	41	751	1.12 (0.80 , 1.57)	8,676	180,563	41	751	1.04 (0.74, 1.46)
TCAS	3,314	180,562	15	751	0.86 (0.50 , 1.47)	3,304	180,564	15	751	0.85 (0.50, 1.46)
SNRIS	6,010	180,564	34	751	1.24 (0.85 , 1.82)	5,993	180,564	34	751	1.18 (0.80, 1.73)
OTHER	6,021	180,564	26	751	0.99 (0.64 , 1.53)	6,039	180,564	26	751	0.91 (0.59, 1.40)
BUPROPION	6,691	180,563	26	751	0.88 (0.58 , 1.34)	6,696	180,564	26	751	0.86 (0.57, 1.31)

* The predefined covariates along with 200 empirically identified potential confounding variables were included in the high dimensional propensity score

Table S16 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women, stratified by age and race; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
Age	<30					>=30				
ANTIDEP	37,346	153,127	325	1240	1.00 (0.87, 1.15)	12,190	27,373	135	257	1.09 (0.85, 1.39)
SSRI	27,923	153,189	244	1240	1.05 (0.90, 1.23)	8,824	27,375	97	257	1.13 (0.87, 1.49)
PAROXETINE	6,446	153,187	50	1240	0.95 (0.70, 1.29)	2,295	27,368	21	257	0.98 (0.60, 1.58)
SERTRALINE	8,527	153,185	72	1240	1.00 (0.78, 1.29)	2,517	27,375	34	257	1.30 (0.88, 1.93)
FLUOXETINE	6,492	153,187	62	1240	1.17 (0.89, 1.54)	2,156	27,375	22	257	1.09 (0.68, 1.75)
TCAS	2,247	153,178	20	1240	0.91 (0.58, 1.44)	1,053	27,366	<11	257	0.55 (0.25, 1.22)
SNRIS	4,426	153,186	52	1240	1.26 (0.93, 1.72)	1,555	27,375	16	257	0.98 (0.56, 1.73)
OTHER	4,252	153,189	42	1240	1.22 (0.87, 1.71)	1,747	27,375	22	257	1.22 (0.74, 2.03)
BUPROPION	4,917	153,187	37	1240	0.87 (0.61, 1.23)	1,759	27,374	20	257	1.13 (0.68, 1.86)
Race	Non-caucasian					Caucasian				
ANTIDEP	12,629	84,302	94	678	0.87 (0.68, 1.12)	36,915	96,254	366	819	1.09 (0.94, 1.25)
SSRI	9,477	84,302	76	678	0.94 (0.71, 1.23)	27,286	96,166	265	817	1.11 (0.95, 1.31)
PAROXETINE	2,457	84,294	14	678	0.69 (0.40, 1.21)	6,274	96,259	57	819	1.06 (0.79, 1.41)
SERTRALINE	2,875	84,301	30	678	1.11 (0.74, 1.67)	8,160	96,262	76	819	1.07 (0.83, 1.37)
FLUOXETINE	2,324	84,300	17	678	0.89 (0.53, 1.50)	6,324	96,262	67	819	1.23 (0.94, 1.60)
TCAS	979	84,272	<11	677	0.57 (0.23, 1.39)	2,332	96,252	22	819	0.89 (0.57, 1.38)
SNRIS	1,082	84,299	<11	678	0.48 (0.19, 1.23)	4,896	96,262	64	819	1.34 (1.01, 1.78)
OTHER	1,753	84,300	11	678	0.67 (0.35, 1.27)	4,245	96,262	52	819	1.45 (1.06, 1.99)
BUPROPION	1,404	84,294	12	678	1.13 (0.62, 2.05)	5,271	96,262	45	819	0.91 (0.66, 1.26)

Formal statistical tests provided no evidence of treatment effect heterogeneity (all p-values ≥ 0.05). Conclusions about the presence/absence of effect-measure modification are not based on the findings from formal statistical tests, but on a comparison of the effect estimates across exposure groups.

Table S17 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women, stratified by low, medium, and high dose; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	<i>FIRST DOSE</i>					<i>HIGHEST DOSE</i>				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
<i>Low Dose</i>										
ANTIDEP	12,327	180,564	106	1,497	0.92 (0.74, 1.14)	10,893	180,564	94	1,497	0.92 (0.74, 1.15)
SSRI	5,742	180,558	54	1,497	1.10 (0.83, 1.46)	5,524	180,534	51	1,497	1.06 (0.79, 1.42)
PAROXETINE	1,068	180,533	14	1,497	1.59 (0.93, 2.72)	1,069	180,530	13	1,497	1.44 (0.83, 2.52)
SERTRALINE	3,706	180,540	35	1,497	1.09 (0.77, 1.54)	3,952	180,549	36	1,497	1.06 (0.75, 1.49)
FLUOXETINE	800	180,532	<11	1,496	0.29 (0.07, 1.18)	856	180,531	<11	1,497	0.42 (0.13, 1.31)
TCAS	1,874	180,533	16	1,497	0.79 (0.47, 1.31)	2,122	180,550	18	1,497	0.79 (0.49, 1.28)
SNRIS	854	180,516	<11	1,496	1.07 (0.56, 2.08)	895	180,544	11	1,497	1.11 (0.58, 2.11)
OTHER	2,517	180,556	28	1,497	1.20 (0.80, 1.80)	2,920	180,561	35	1,497	1.33 (0.92, 1.92)
BUPROPION	3,435	180,559	19	1,497	0.62 (0.39, 0.99)	4,089	180,563	27	1,497	0.73 (0.49, 1.09)
<i>Medium dose</i>										
ANTIDEP	20,442	180,564	201	1,497	1.10 (0.92, 1.30)	21,046	180,564	204	1,497	1.08 (0.91, 1.28)
SSRI	16,489	180,564	163	1,497	1.12 (0.93, 1.34)	17,432	180,564	171	1,497	1.11 (0.93, 1.33)
PAROXETINE	3,925	180,553	28	1,497	0.80 (0.54, 1.18)	4,158	180,560	30	1,497	0.81 (0.56, 1.19)
SERTRALINE	3,962	180,554	49	1,497	1.33 (0.98, 1.80)	4,573	180,564	55	1,497	1.25 (0.94, 1.68)
FLUOXETINE	4,338	180,552	44	1,496	1.25 (0.91, 1.71)	4,987	180,562	51	1,497	1.23 (0.92, 1.66)
TCAS	114	178,949	<11	1,487	<0.001 (<0.001, >999.999)	145	179,612	<11	1,495	0.61 (0.08, 4.50)
SNRIS	3,095	180,562	25	1,496	0.86 (0.56, 1.31)	3,323	180,561	32	1,496	1.01 (0.69, 1.48)
OTHER	1,041	180,541	11	1,497	1.09 (0.58, 2.03)	1,203	180,547	14	1,497	1.22 (0.69, 2.14)
BUPROPION	127	180,489	<11	1,495	1.67 (0.39, 7.17)	161	180,532	<11	1,496	1.29 (0.30, 5.52)
<i>High dose</i>										
ANTIDEP	5,413	180,564	56	1,497	1.12 (0.83, 1.50)	6,240	180,564	65	1,497	1.12 (0.84, 1.47)
SSRI	4,529	180,561	41	1,497	0.96 (0.69, 1.35)	5,185	180,561	48	1,497	0.99 (0.72, 1.36)
PAROXETINE	1,120	180,515	13	1,495	1.23 (0.70, 2.16)	1,303	180,542	16	1,497	1.35 (0.80, 2.25)

Exposure	<i>FIRST DOSE</i>					<i>HIGHEST DOSE</i>				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
SERTRALINE	63	180,521	<11	1,497	1.29 (0.18, 9.46)	86	180,498	<11	1,496	0.98 (0.13, 7.23)
FLUOXETINE	682	180,510	<11	1,496	0.59 (0.22, 1.61)	811	180,539	<11	1,497	0.55 (0.22, 1.39)
TCAS ⁽¹⁾										
SNRIS	161	180,501	<11	1,496	0.71 (0.10, 5.11)	196	180,507	<11	1,496	1.68 (0.52, 5.48)
OTHER	99	180,488	<11	1,496	1.11 (0.15, 8.39)	124	180,481	<11	1,496	1.07 (0.15, 7.81)
BUPROPION	649	180,517	13	1,496	2.18 (1.22, 3.91)	797	180,549	14	1,496	1.87 (1.06, 3.30)

⁽¹⁾ No patients were treated with this dose

Table S18 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women, varying the exposure definitions; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp	
Exposed: ≥1 Dispensing during the first trimester					
ANTIDEP	29,056	181,164	282	1,503	1.09 (0.94, 1.26)
SSRI	28,168	181,164	270	1,503	1.11 (0.95, 1.29)
PAROXETINE	6,543	181,163	59	1,503	1.04 (0.79, 1.37)
SERTRALINE	8,617	181,164	92	1,503	1.19 (0.95, 1.49)
FLUOXETINE	6,660	181,164	60	1,503	1.06 (0.80, 1.40)
TCAS	2,281	181,157	19	1,503	0.78 (0.48, 1.25)
SNRIS	4,442	181,164	46	1,503	1.03 (0.75, 1.43)
OTHER	4,264	181,164	50	1,503	1.31 (0.95, 1.80)
BUPROPION	5,058	181,164	43	1,503	0.93 (0.67, 1.28)
Exposed: ≥2 Dispensings during the first trimester					
ANTIDEP	17,834	181,164	188	1,503	1.14 (0.95, 1.36)
SSRI	11,430	181,164	116	1,503	1.14 (0.92, 1.41)
PAROXETINE	2,602	181,152	28	1,503	1.24 (0.84, 1.84)
SERTRALINE	3,164	181,159	34	1,503	1.17 (0.82, 1.67)
FLUOXETINE	2,419	181,154	25	1,503	1.21 (0.80, 1.83)
TCAS	654	181,124	<11	1,502	0.93 (0.43, 2.02)
SNRIS	1,966	181,153	26	1,502	1.34 (0.87, 2.05)
OTHER	1,285	181,161	18	1,503	1.50 (0.90, 2.51)
BUPROPION	1,409	181,144	18	1,503	1.35 (0.82, 2.21)
Reference group: No exposure throughout pregnancy					
ANTIDEP	49,553	168,783	460	1,402	0.99 (0.87, 1.13)
SSRI	36,759	169,029	341	1,403	1.04 (0.91, 1.20)
PAROXETINE	8,757	169,028	71	1,403	0.92 (0.71, 1.20)
SERTRALINE	11,059	169,029	106	1,403	1.04 (0.84, 1.29)
FLUOXETINE	8,655	169,029	84	1,403	1.09 (0.86, 1.39)

Exposure	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp	
TCAS	3,314	169,028	27	1,403	0.73 (0.49, 1.10)
SNRIS	6,009	169,029	69	1,403	1.11 (0.84, 1.47)
OTHER	6,006	169,029	64	1,403	1.15 (0.86, 1.53)
BUPROPION	6,697	169,029	57	1,403	0.87 (0.66, 1.17)

Table S19 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women, varying the outcome definitions; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	Inpatient diagnosis of cardiac malformation					12 months follow-up to ascertain cardiac malformation ⁽¹⁾				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
Any cardiac malformation										
ANTIDEP	49,527	180,422	335	1,128	0.96 (0.83, 1.11)	33,275	116,987	169	517	0.98 (0.80, 1.20)
SSRI	36,778	180,564	249	1,129	1.00 (0.85, 1.17)	24,918	117,042	116	517	0.91 (0.72, 1.15)
PAROXETINE	8,748	180,564	50	1,129	0.84 (0.62, 1.14)	6,274	117,040	17	517	0.53 (0.32, 0.89)
SERTRALINE	11,056	180,564	78	1,129	1.02 (0.80, 1.31)	7,507	117,042	43	517	1.16 (0.83, 1.62)
FLUOXETINE	8,664	180,563	66	1,129	1.18 (0.90, 1.54)	5,671	117,040	24	517	0.75 (0.48, 1.16)
TCAS	3,314	180,562	18	1,129	0.66 (0.41, 1.08)	2,217	117,034	17	517	1.33 (0.80, 2.23)
SNRIS	6,010	180,564	48	1,129	1.05 (0.76, 1.45)	4,007	117,042	27	517	1.25 (0.81, 1.93)
OTHER	6,021	180,564	51	1,129	1.26 (0.92, 1.73)	3,988	117,042	17	517	0.93 (0.56, 1.57)
BUPROPION	6,691	180,563	43	1,129	0.89 (0.64, 1.24)	4,295	117,042	26	517	1.12 (0.73, 1.71)
Other cardiac malformation										
ANTIDEP	49,527	180,422	205	608	1.10 (0.91, 1.33)	33,275	116,987	100	263	1.08 (0.82, 1.41)
SSRI	36,778	180,564	154	609	1.16 (0.95, 1.43)	24,918	117,042	64	263	0.93 (0.68, 1.27)
PAROXETINE	8,748	180,564	31	609	1.03 (0.70, 1.51)	6,274	117,040	<11	263	0.41 (0.19, 0.89)
SERTRALINE	11,056	180,564	50	609	1.25 (0.92, 1.71)	7,507	117,042	23	263	1.14 (0.72, 1.81)
FLUOXETINE	8,664	180,563	39	609	1.31 (0.92, 1.85)	5,671	117,040	18	263	1.04 (0.62, 1.75)
TCAS	3,314	180,562	<11	609	0.69 (0.35, 1.37)	2,217	117,034	<11	263	1.43 (0.73, 2.79)
SNRIS	6,010	180,564	25	609	1.04 (0.66, 1.63)	4,007	117,042	19	263	1.58 (0.93, 2.67)
OTHER	6,021	180,564	35	609	1.79 (1.22, 2.64)	3,988	117,042	13	263	1.31 (0.71, 2.40)
BUPROPION	6,691	180,563	29	609	1.09 (0.72, 1.64)	4,295	117,042	15	263	1.17 (0.66, 2.05)
RVOTO										
ANTIDEP	49,527	180,422	44	166	0.81 (0.55, 1.19)	33,275	116,987	42	130	0.95 (0.63, 1.43)
SSRI	36,778	180,564	32	166	0.80 (0.52, 1.23)	24,918	117,042	32	130	0.98 (0.63, 1.54)
PAROXETINE	8,748	180,564	<11	166	1.06 (0.52, 2.15)	6,274	117,040	<11	130	0.90 (0.39, 2.11)
SERTRALINE	11,056	180,564	<11	166	0.64 (0.29, 1.40)	7,507	117,042	12	130	1.36 (0.72, 2.58)

Exposure	Inpatient diagnosis of cardiac malformation					12 months follow-up to ascertain cardiac malformation ⁽¹⁾				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
FLUOXETINE	8,664	180,563	<11	166	0.98 (0.48 , 2.00)	5,671	117,040	<11	130	0.84 (0.37 , 1.93)
TCAS	3,314	180,562	<11	166	0.78 (0.24 , 2.53)	2,217	117,034	<11	130	1.25 (0.38 , 4.13)
SNRIS	6,010	180,564	<11	166	0.93 (0.40 , 2.14)	4,007	117,042	<11	130	0.73 (0.26 , 2.04)
OTHER	6,021	180,564	<11	166	0.70 (0.25 , 1.95)	3,988	117,042	<11	130	0.26 (0.04 , 1.90)
BUPROPION	6,691	180,563	<11	166	1.60 (0.81 , 3.14)	4,295	117,042	<11	130	1.59 (0.77 , 3.30)
VSD										
ANTIDEP	49,527	180,422	139	537	0.84 (0.67 , 1.04)	33,275	116,987	74	251	0.89 (0.66 , 1.21)
SSRI	36,778	180,564	101	537	0.86 (0.67 , 1.09)	24,918	117,042	52	251	0.84 (0.59 , 1.18)
PAROXETINE	8,748	180,564	18	537	0.62 (0.38 , 1.02)	6,274	117,040	<11	251	0.36 (0.15 , 0.83)
SERTRALINE	11,056	180,564	34	537	0.94 (0.65 , 1.36)	7,507	117,042	18	251	0.97 (0.58 , 1.62)
FLUOXETINE	8,664	180,563	29	537	1.09 (0.73 , 1.63)	5,671	117,040	<11	251	0.52 (0.25 , 1.06)
TCAS	3,314	180,562	<11	537	0.77 (0.40 , 1.49)	2,217	117,034	<11	251	1.35 (0.66 , 2.73)
SNRIS	6,010	180,564	24	537	1.15 (0.74 , 1.81)	4,007	117,042	<11	251	0.98 (0.49 , 1.96)
OTHER	6,021	180,564	17	537	0.88 (0.52 , 1.49)	3,988	117,042	<11	251	0.92 (0.43 , 1.96)
BUPROPION	6,691	180,563	15	537	0.68 (0.40 , 1.17)	4,295	117,042	11	251	0.96 (0.50 , 1.84)

⁽¹⁾ 65% of original cohort size

Table S20 Probabilistic bias analyses comparing the risk for cardiac malformations between exposed and unexposed women, using the positive predictive value (PPV) for any cardiac malformation from the internal validation study; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	Conventional Analyses ⁽¹⁾				Probabilistic Bias Analyses ⁽²⁾				
	Lower bound CI ⁽³⁾	OR	Upper bound CI	Width CI	Lower bound CI	OR	Upper bound CI	Width CI	Change from conventional analyses
AD	0.90	1.02	1.15	1.28	0.92	1.06	1.22	1.33	3.8
SSRI	0.94	1.09	1.24	1.32	0.95	1.11	1.31	1.38	4.2
PARO	0.84	1.11	1.43	1.69	0.87	1.15	1.54	1.77	4.8
SERTR	0.86	1.08	1.36	1.57	0.86	1.12	1.48	1.72	9.7
FLUOX	0.89	1.13	1.44	1.61	0.88	1.19	1.56	1.78	10.7
TCAS	0.39	0.66	1.13	2.93	0.36	0.65	1.20	3.34	14.2
SNRIS	0.83	1.13	1.52	1.84	0.89	1.24	1.73	1.95	5.9
OTHER	0.90	1.24	1.70	1.89	0.95	1.35	1.92	2.02	7.0
BUPRO	0.63	0.87	1.22	1.93	0.62	0.91	1.28	2.07	7.2

⁽¹⁾ Adjustment for continuous PS, rather than PS-stratification as used in the primary analyses. The adjustment method was changed to allow a direct comparison with results from the probabilistic bias analysis which does not allow for PS-stratification.

⁽²⁾ Distribution for bias parameters corresponding to a PPV=75.1%: Sensitivity: Min=0.5, Mode=0.75, Max=1.0; Specificity: Min=0.9985, Mode=0.99875. Max=0.999

⁽³⁾ The CI represents a ‘simulation’ interval. The bias parameters are drawn from pre-specified triangular distributions; the draw is repeated over 1,000 iterations and results are accumulated to generate a frequency distribution. The simulation interval represents the 5th and the 95th percentile of the frequency distribution.

Quantification of the potential impact of missing terminations

Background:

The study cohort included live births only. Severe cardiac malformations that result in spontaneous abortions, stillbirths or pregnancy terminations for cardiac anomalies will therefore be missed. If a depletion of affected offspring occurred preferentially among women exposed to antidepressants versus the reference group of unexposed women (e.g., due to differences in prenatal care and screening, or differences in the propensity to terminate a pregnancy), studies restricted to live births would underestimate relative risks.

Methods:

We used the methods proposed by Greenland and Khoury^{2,3} to quantify the potential impact of missing terminations.

Observed (with selection bias)			“Truth” (without selection bias)		
	Case*	Non-case		Case*	Non-case
Exposed	A ₁	B ₁	Exposed	A ₁ /S ₁₁	B ₁ /S ₀₁
Unexposed	A ₀	B ₀	Unexposed	A ₀ /S ₁₀	B ₀ /S ₀₀

*: pregnancies with a cardiac malformation

A₁ = Total number of cases exposed
 A₀ = Total number of cases unexposed
 B₁ = Total number of non-cases exposed
 B₀ = Total number of non-cases unexposed

S₁₁=probability of case selection (survival) among exposed
 S₁₀=probability of case selection among unexposed
 S₀₁=probability of non-case selection among exposed
 S₀₀=probability of non-case selection among unexposed

The observed or apparent odds ratio (AOR) – in the presence of selection bias - is estimated as:
 (A₁B₀/A₀B₁)

The corrected odds ratio is estimated as:
 $[(A_1/S_{11})(B_0/S_{00})] / [(A_0/S_{10})(B_1/S_{01})] = (A_1B_0/A_0B_1) * (S_{10}S_{01}/S_{11}S_{00}) = AOR * (S_{10}S_{01}/S_{11}S_{00})$

It should be noted that bias will only occur if *both* the cardiac defect and the exposure affect pregnancy terminations; the selection probabilities would cancel out otherwise.

Values considered for the selection probabilities

- S₀₀: Around 48% of pregnancies are unintended, and the proportion of unintended pregnancies ending in abortion is around 45%.⁴ Only a small proportion of these terminated unintended pregnancies would carry a fetus with a major congenital malformation. Therefore, around 20% of pregnancies (slightly less than 0.48*0.45) are terminated for reasons other than congenital malformations (e.g. social reasons).

Informed by the literature, the probability of non-case selection among unexposed (S_{00}) was therefore assumed to be 80% (100%-20% [terminations due to social reasons]).

- S_{10} : Fewer than 20% of cardiac malformations are detected before 24 weeks of pregnancy, and less than 50% of those detected are terminated.⁵ It has been estimated that around 10% of all pregnancies with cardiac malformations are terminated in the US.⁶ Informed by these estimates, the probability of case selection among unexposed (S_{10}) was therefore assumed to be 70% (100% – 20% [terminations due to social reasons] – 10% [terminations due to cardiac malformations detected early]). In addition to considering the 70% best estimate based on the literature, we also evaluated the impact of lower selection probabilities among affected pregnancies (range considered: 50-70%).
- S_{01} , S_{11} : To explore the interaction of malformation status and exposure with respect to the selection probabilities, we assumed that antidepressant exposure would decrease or increase the selection probability by up to 20%. That is, $S_{01}=S_{00}+N\%$ and $S_{11}=S_{10}+N\%$ with N ranging from -20% to +20%.

This combination of the four selection probabilities resulted in broad ranges for the magnitude of the potential selection bias that were represented graphically. We evaluated the impact of these selection probabilities on the relative risk estimated for SSRIs and any cardiac malformation in the main analysis (OR=1.06, 95% CI 0.93-1.22), after restricting to women with depression and adjusting for other potential confounders.

The range of values for the selection probabilities considered in the sensitivity analyses are summarized in the table below:

	Selection probabilities			
	Pregnancies with cardiac malformations		Pregnancies without cardiac malformation	
	Unexposed (S_{10})	Exposed (S_{11})	Unexposed (S_{00})	Exposed (S_{01})
Figure 1A	50-70% (70% best estimate based on literature)	$S_{10}-20\%$ $S_{10}-10\%$ S_{10} $S_{10}+10\%$ $S_{10}+20\%$	80%	$S_{00}-20\%$ $S_{00}-10\%$ S_{00} $S_{00}+10\%$ $S_{00}+20\%$
Figure 1B	50-70% (70% best estimate based on literature)	$S_{10}-20\%$ $S_{10}-10\%$ S_{10} $S_{10}+10\%$ $S_{10}+20\%$	80%	80%

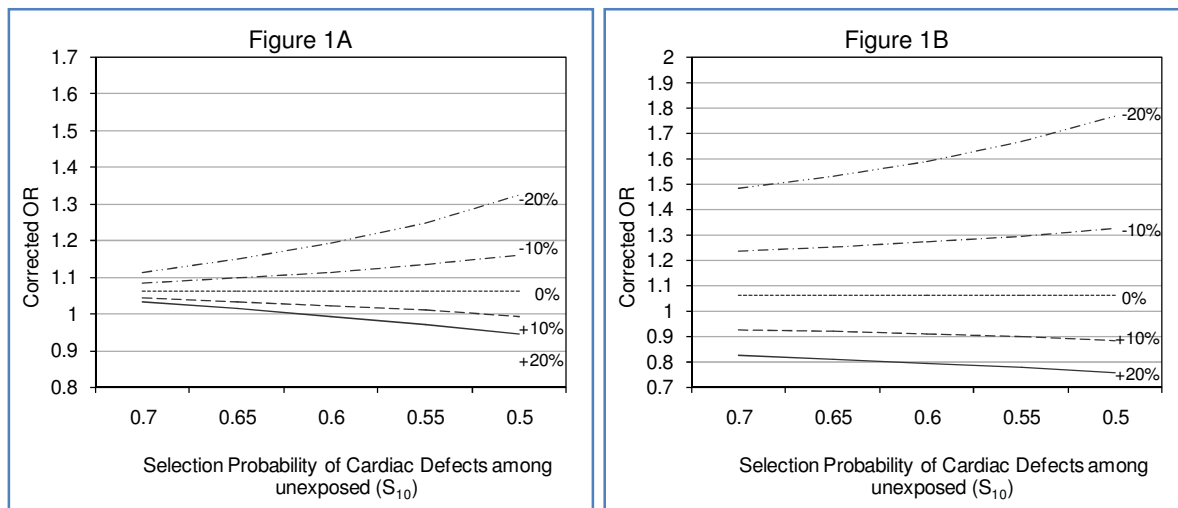
Results:

Figure 1A shows the range of plausible values for the corrected OR. Only under the most extreme scenarios of at least 45% of infants with cardiac malformations terminated among non-SSRI users and 65% terminated among SSRI users (top line) would the relative risk be larger than 1.2.

Figure 1B takes an even more extreme scenario where SSRI users have the same probability of terminating pregnancies for social reasons as non-SSRI users, but have a different probability of termination in the presence of cardiac malformations. Under these circumstances, if 30 to 50% of infants with cardiac malformations were terminated among non-SSRI users and 50 to 70% were terminated among SSRI users, the OR would reach the hypothesized 1.5 to 1.7 value (based on some meta-analyses of SSRIs and cardiac malformations)⁷.

It should be noted that the selection probabilities used here are most likely conservative estimates since we had restricted the study population to women with depression and had adjusted for other covariates. Such adjustment would reduce not only confounding but also selection bias if the adjusted factors were common causes of SSRI use and inclination to terminate (e.g. factors associated with depression). Also, the proportion of terminations would most likely be lower for cardiac malformations such as ventricular septal defects, which were the ones most commonly linked with SSRIs in earlier studies.

Figure 1 Corrected relative risk for the association between SSRI use during the first trimester and cardiac malformations in women with depression diagnosis. The graphs represent a range of plausible values for selection probabilities (1-probability of termination) among unexposed. The different lines represent the corrected relative risk for a range of higher or lower selection probabilities among SSRI users.



Conclusion:

In conclusion, findings from this sensitivity analysis show that the differences in the proportion of terminations among women with depression on SSRIs vs. those untreated within levels of covariates used in the adjustment would have to be unrealistically strong in order to dilute a relative risk of 1.5 or higher. Moreover, this selection bias would not explain the discrepancies with prior studies, since they also included live births preferentially.

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