

Supplementary Online Content

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eTable 1. List of Known Fetotoxic Prescribed Medications Excluded

eTable 2. List of Diagnostic Codes (*ICD-9* and *ICD-10*) and Medications Used for the Covariates

eTable 3. Number of Prescription Filled During Early Pregnancy by Pregnancy

eTable 4. Distribution of the Number of Pregnancies Exposed to Specific Benzodiazepine Agents

eTable 5. Distribution of Duration of Prescriptions Filled and Quantity of Pills Dispensed by Benzodiazepine Specific Agents

eTable 6. Association Between Short and Long-acting Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion

eTable 7. Association Between Mean Daily Dose of Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion

eMethods. Sensitivity Analyses

eTable 8. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the Variable Prior Pregnancy Categorized by Termination (Childbirth, Planned/Induced Abortion, Spontaneous Abortion)

eTable 9. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion Among Women With Mood and Anxiety Disorders Diagnosis in the 12 Months Before LMP Until Index Date

eTable 10. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With Pregnancies of Women With Only 1 Prescription Filled Prior to Pregnancy Who Overlap the LMP Considered as Unexposed

eTable 11. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With Only Pregnancies of Women Who Filled 2 or More Prescription of Benzodiazepine Were Considered as Exposed

eTable 12. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion Removing Benzodiazepine Prescription Filled in the 7 Days Prior to the Index Date (Date of the Spontaneous Abortion)

eTable 13. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the General Practitioner Visits Dichotomized Regarding the Purpose of Consultation (Mental Disorders vs. Other Disorders)

eTable 14. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the New Definition of Mood and

Anxiety Disorder Proposed by the Canadian Chronic Disease Surveillance System
(CCDSS)

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. List of Known Fetotoxic Medications Excluded

Class	Denomination commune
systemic retinoids	isotretinoin, acitretin, etretinate, tretinoin (retinoic acid), retinol, retinal, adapalene, bexarotene, tazarotene
antiepileptics	Acetazolamide, carbamazepin, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, valproic acid, rufinamide, sodium divalproex, sodium valproate, topiramate, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin, zonisamide
anti-thyroid drugs	Methimazole, propylthiouracil
anti-coagulants	Warfarin
tetracycline derivative	Nicoumalone, doxycyclin, minocyclin, streptomycin, tetracycline
angiotensin converting enzyme (ACE) inhibitors	Benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, verapamil
androgens	Danazol, testosterone, methyltestosterone
antineoplastic agents	Anastrozole, bicalutamide, busereline, busulfan, chlorambucil, cyclophosphamide, estramustine, etoposide, exemestane, fluorouracil, flutamide, gosereline, hydroxyurea, ifosfamide, interferon alfa-2B, interferon alfa-2B (without albumine), letrozole, leuprolide (acetate), melphalan, mercaptopurine, methotrexate, nilutamide, procarbazine, tamoxifen, thioguanine, tretinoin, triptoreline
others	Amiodarone, diethylstilbestrol, dihydroergotamine, fluconazole, leflunomide, lithium (carbonate), lithium (citrate), methotrexate, penicillamine, cyclophosphamide, misoprostol, diclofenac/misoprostol, quinine
statins	Atorvastatine calcique, amlodipine/atorvastatine calcique, cerivastatine, fluvastatine sodium, lovastatine, lovastatine/nicotinic acid, pravastatine sodium, pravastatine sodium/AAS, rosuvastatine calcique, simvastatine
angiotensin-receptor blocker (ARB)	Candesartan, candesartan/HCTZ, eprosartan, eprosartan/HCTZ, irbesartan, irbesartan/HCTZ, losartan, losartan/HCTZ, olmesartan, olmesartan/HCTZZ, telmisartan, telmisartan/HCTZ, valsartan, valsartan/HCTZ

eTable 2. List of Diagnostic Codes (*ICD-9* and *ICD-10*) and Medications Used for the Covariates

Hypertension

ICD-9 codes: 401.0-405.9, 642.0-642.9 and 796.2

ICD-10 codes: I10.0, I10.1, I15.0, I15.1, I15.2, I15.8, I15.9, O10, O11, O12, O13, O14, O15 and O16

Medication generic codes:

Generic name	Quebec generic code
Clonidine	10751
Methyldopa	6136
Hydralazine	4524
Minoxidil	41564
Doxazosine	45625
Prazosin	37742
Terazosin	45520
Acebutolol	45463
Atenolol	43670 - 46325 - 46315
Bisoprolol	47355
Carvedilol	47199 - 46319
Labetalol	45243
Metoprolol	38275 - 46763 - 46780
Nadolol	40563
Oxprenolol	42162
Pindolol	39016
Pindolol-HCTZ	45408
Propranolol	8229
Sotalol	44866
Timolol	38314
Amlodipine	47006
Amlodipine/Atorvastatine	47609
Felodipine	45624
Nifedipine	42708 - 46388 - 46469
Nifedipine-AAS	47751

Nimodipine	45532
Diltiazem	43228 - 47247
Verapamil	40550 - 46573
Verapamil-Trandolapril	47440
Benazepril	47049
Captopril	42071
Cilazapril	47056
Cilazapril-HCTZ	47320
Enalapril	45476
Enalapril-HCTZ	45572
Fosinopril	47002
Lisinopril	45576
Lisinopril-HCTZ	47040
Perindopril	47117 - 46258
Perindopril-Indapamide	47449
Quinapril	45629
Quinapril-HCTZ	47301
Ramipril	47079 - 46216
Ramipril-HCTZ	47655
Trandolapril	47250
Trandolapril/Verapamil	47440
Candesartan	46529 - 47309
Candesartan-HCTZ	46760 - 47412
Eprosartan	47389
Eprosartan-HCTZ	47534 - 47532
Irbesartan	46459 - 47282
Irbesartan-HCTZ	47354
Losartan	47135 - 46284 - 46441
Losartan-HCTZ	47207
Olmesartan medoxomil	47763
Olmesartan medoxomil-HCTZ	47764
Telmisartan	47333 - 46587
Telmisartan-HCTZ	47413
Telmisartan/Amlodipine	47889
Valsartan	46418 - 47259
Valsartan-HCTZ	47369
Spirolactone	9100 - 46572
Ethacryniqué	3562
Furosemide	4173
Amiloride	41759
Amiloride-HCTZ	41772
Hydrochlorothiazide	4537
Chlorthalidone	1976

Indapamide	43397
Metolazone	19440
Amiloride-HCTZ	41772
Spirolactone-HCTZ	38158
Triamterene-HCTZ	38197
Triamterene	9763
Amlodipine-Atorvastatine	47609
Aliskirene	47706
Aliskirene-HCTZ	47823
Excluding the medication with the following formulation:	
Formulation	Code
Ophthalmic powder	1479
Ophthalmic ointment	1624
Ophthalmic solution	2204
Ophthalmic and Optic Solution	2233
Ophthalmic suspension	2784
Ophthalmic and Optic Suspension	2813
Ophthalmic Irrigation Solution	3480
Ophthalmic gel	5365
Ophthalmic Gel Solution	5599

Diabetes

ICD-9 codes: 250.0-250.9, 271.4 and 790.2

ICD-10 codes: E10-E14 and R73.0

Medication generic codes:

Generic name	Quebec generic code
Metformin	5824 - 47208
Glucagon	4238
Chlorpropamide	1937
Glyburide	4264
Tolbutamide	9672 - 15184
Gliclazide	46056 - 47329
Glimepiride	46799 - 47427
Acarbose	46300 - 47151
Pioglitazone	46678 - 47392
Rosiglitazone	47371 - 46642
Rosiglitazone/Metformine	46862
Rosiglitazone/Glimepiride	47652
Nateglinide	46810
Repaglinide	47357 - 46568
Saxagliptine	47817
Sitagliptine	47715
Sitagliptine/Metformine	47807 - 47832
Insulin aspart	46798 - 47424

Insulin aspart/ Insulin aspart protamine	
Insulin glulisine	47749
Insulin isophane bio-synthetic	44164
Insulin lispro	46322 - 47206
Insulin zinc cristalline bio-synthetic	44489
Insulins zinc cristalline and isophane bio-synthetic	45531
Insulin aspart/Insulin aspart protamine	47615
Insulin detemir	47586
Insulin glargine	47536
Insulin lispro/Insulin lispro protamine	47426
Insulin globine zinc	4823
Insulin sulfate	4888
Insulin zinc cristalline (porc)	18296
Insulin protamine zinc (beef)	18309
Insulin protamine zinc (porc)	18322
Insulin isophane (porc)	18335
Insulin isophane (beef)	18348
Insulin slow release (beef and porc)	39120
Insulin isophane (beef and porc)	39133
Insulin protamine zinc (beef and porc)	39146
Insulin semi-slow release (beef and porc)	39159
Insulin ultra-slow release (beef and porc)	39172
Insulin crystal zinc (beef and porc)	39185
Insulin isophane (beef)	39458
Insulin protamine zinc (beef)	39484
Insulin protamine zinc (porc)	39497
Insulin crystal zinc (beef)	39523
Insulin slow release (porc)	41655
Insulin crystal zinc (porc)/ Insulin isophane (porc)	43033
Insulin crystal zinc (beef)	43735
Insulin isophane semi-synthetic of human sequence	44151
Insulin slow release semi-synthetic of human sequence	44476
Insulin crystal zinc semi-synthetic of human sequence	44502
Insulin ultra-slow release semi-synthetic of human sequence	44996
Insulins isophane and crystal zinc semi-synthetics of human sequence	45405
Insulin slow release bio-synthetic of human sequence	45415
Insulin ultra-slow release bio-synthetic of human sequence	45483
Insulins isophane and crystal zinc bio-synthetic of human sequence	45511
Insulins crystal zinc and isophane semi-synthetics of human sequence	45534
Insulin crystal zinc (beef and porc)	46536
Insulin isophane (beef and porc)	46537
Insulin slow release (beef and porc)	46538
Insulin isophane(human)/ Insulin injectable (human)	46592
Insulin isophane (human)	46602
Insulin injectable (human)	46603
Insulin lispro/Insulin isophane (human)	46607
Insulin crystal zinc (porc)	47004
Insulin lispro/ Insulin lispro protamine	47426

Alogliptine	48018
Alogliptine/Metformine	48017
Canagliflozine	48013
Dipagliflozine	n.a.
Glidazide	n.a.
Glimepiride	47427-46779
Linagliptine	47881
Linagliptine/Metformine	47965
Liraglutine	n.a.

Asthma

ICD-9 codes: 493.0, 493.1, 493.3, 493.4, 493.5, 493.6, 493.7, 493.8 and 493.9

ICD-10 codes: J45.0, J45.8, J45.1 and J45.9

Medication generic codes

Generic name	Quebec generic code
Aminophylline	364, 46428
Beclomethasone	780*
Budesonide	45499*
Budesonide/ formoterol	47428, 46800
Cromoglicate sodium	39419, 47315
Cromoglicate disodium	2223
Epinephrine	3380
Epinephrine	3406
Epinephrine racemic	3419
Fenoterol	38548
Flunisolide	38730*
Fluticasone	47050*, 46435*
Formoterol	47231*
Formoterol	47271, 46430
Formoterol / budesonide	47428
Ipratropium (bromure)	43124, 46640
Ipratropium (bromure)/ salbutamol (sulfate)	47186, 46302
Isoproterenol (chlorhydrate)	5083
Isoproterenol (chlorhydrate)/ phenylephrine (bitartrate)	5096
Isoproterenol (chlorhydrate)/ phenylephrine (chlorhydrate)	5109
Isoproterenol (sulfate)	5070
Ketotifene (fumarate)	45555, 46752
Montelukast sodium	47303, 47302, 46467
Nedocromil sodium	47033, 45563, 46463
Orciprenaline (sulfate)	6721
Oxtriphylline	43475
Pirbuterol (acetate)	47153, 46299
Procaterol hemihydrate (chlorhydrate)	45547
Salbutamol	10530
Salbutamol (sulfate)	33634, 46737
Salmeterol (xinafoate) / fluticasone (propionate)	47335, 46597
Salmeterol (xinafoate)	47112, 46247
Terbutaline (sulfate)	34180
Theophylline	9464, 46847, 9490, 9503
Theophylline/dextrose	44944
Triamcinolone (acetonide)	9737*
Zafirlukast	47266, 46401
Ciclesonide	47626
Mometasone	45581, 47299
Mometasone/Formeterol	47884, 47914
Zolair	n.a.

1 For code with a* use only the following formulations:

Formulation	Code
Powder aerosol	1305
Powder aerosol with applicator	1334
Aerosol solution	1856
Aerosol solution with applicator	1885
Solution for Inhalation	1972
Suspension aerosol	2610
Suspension aerosol with applicator	2639
Inhalation powder with applicator	5563
Inhalation powder	5564
Oral spray	5584
Gel	5619
Powder for solution for inhalation	5634

2

3 **Depression and anxiety**

4 ICD-9 codes: 296, 309, 311, 300.0 and 300.4

5 ICD-10 codes: F30, F31, F32, F33, F34, F38, F39, F40, F41 and F43

6 Medication generic codes:

Generic name	Quebec generic code
Citalopram	46543 - 47317
Escitalopram	47553
Fluoxetine	45504
Fluvoxamine	45633
Paroxetine	46164 - 47061
Sertraline	45630
Viibryd	NA
Desvenlafaxine	NA
Duloxetine	47714
Milnacipran	NA
Venlafaxine	46244 - 47118
Isocarboxazid	5018
Phenelzine	7280
Tranlycypromine	9698
Amitriptyline	442 - 429 - 46836
Amoxapine	43696
Clomipramine	14781
Desipramine	2522
Doxepin	3198
Imipramine	4784
Maprotiline	37443
Nortriptyline	46835 - 6578
Protriptyline	8294

Trimipramine	9906
Bupropion	46435 - 47285
Buspirone	45609
Maprotiline	37443
Mirtazapine	46744 - 47408
Reboxetine	NA
Trazodone	43137
Vilazodone	NA
Moclobemide	46427 - 47005
L-tryptophane	42058
Nefazodone	46235 - 47093

7

8 **Thyroid diseases**

9 ICD-9 codes: 244.0-244.9 and 242.9

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

11 Medication generic codes:

Generic name	Quebec generic code
Levothyroxine sodium	5252 - 46574
Liothyronine sodium/ levothyroxine sodium	33842
Liothyronine sodium	5317 - 46457 - 46474
Methimazole	40836
Propylthiouracile	8242

12

13 **Tobacco dependence**

14 ICD-9 codes: 305.0, 305.1 and 649.0

15 ICD-10 codes: F17, O99.33, Z71.6, and Z72.0

16

17 **Alcohol dependence**

18 ICD-9 codes: 303, 305.0 and 980

19 ICD-10 codes: F10, O99.31

20 **Other drugs dependence**

21 ICD-9 codes: 304.0, 304.2, 304.3, 304.4, 304.5, 304.6, 304.7, 304.8 and 304.9

22 ICD-10 codes: F11, F12, F14, F15, F16, F18, F19

23

eTable 3. Number of Prescription Filled During Early Pregnancy by Pregnancy	
Number of prescription filled	Number of pregnancies
1	897 (77.1%)
2	162 (13.9%)
3	43 (3.7%)
4	30 (2.6%)
5	11 (1.0%)
6 or more	20 (1.7%)

24

eTable 4. Distribution of the Number of Pregnancies Exposed to Specific Benzodiazepine Agents	
Benzodiazepine agent	Number of pregnancies exposed
<i>Monotherapy</i>	<i>1,128 (97.0%)</i>
Lorazepam	563
Clonazepam	200
Oxazepam	150
Alprazolam	91
Temazepam	26
Bromazepam	39
Flurazepam	21
Diazepam	26
Chlordiazepoxide	7
Triazolam	5
<i>Bitherapy</i>	<i>35 (3%)</i>
Lorazepam and clonazepam	14
Lorazepam and alprazolam	5
Lorazepam and oxazepam	3
Lorazepam and temazepam	2
Lorazepam and nitrazepam	1
Clonazepam and oxazepam	4
Clonazepam and alprazolam	1
Clonazepam and diazepam	1
Alprazolam and oxazepam	2
Alprazolam and temazepam	1
Oxazepam and flurazepam	1

eTable5. Distribution of Duration of Prescriptions Filled and Quantity of Pills Dispensed by Benzodiazepine Specific Agents			
	Total number of prescription filled	Duration of prescription filled	Quantity of pills provided by prescription filled
Benzodiazepine agents	Mean ± SD - Median [min-max;Q3]		
Overall benzodiazepines	1,715	16.5 ± 11.0 - 15 [1-90;30]	24.3 ± 21.7 - 20 [1-180;30]
Lorazepam	768	14.5 ± 11.3 - 10 [1-65;30]	19.2 ± 16.9 - 15 [1-100;30]
Clonazepam	402	16.8 ± 11.1 - 15 [1-90;30]	28.1 ± 22.9 - 21 [1-180;30]
Oxazepam	211	20.8 ± 9.6 - 20 [1-45;30]	23.5 ± 13.0 - 30 [1-90;30]
Alprazolam	149	18.9 ± 10.3 - 15 [2-40;30]	43.2 ± 38.6 - 30 [2-180;60]
Temazepam	44	17.4 ± 9.0 - 15 [6-30;30]	20.6 ± 10.4 - 20 [7-42;30]
Bromazepam	43	20.6 ± 11.6 - 20 [3-60;30]	26.3 ± 11.0 - 30 [10-60;30]
Flurazepam	40	19.1 ± 10.0 - 20 [4-30;30]	20.8 ± 8.4 - 20 [4-30;30]
Diazepam	28	14.6 ± 10.6 - 10 [1-30;30]	20.1 ± 19.3 - 15 [1-90;30]
Chlordiazepoxide	20	12.5 ± 10.8 - 7 [3-30;25]	38.0 ± 24.6 - 28 [12-90;44]
Triazolam	9	1.1 ± 0.3 - 1 [1-2;1]	1.1 ± 0.3 - 1 [1-2;1]
Nitrazepam	1	n.a.	n.a.
SD = standard deviation; min = minimum; max = maximum; Q3 = third percentile.			

eTable 6. Association Between Short and Long-acting Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion

Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date	284 (1.05)	624 (0.46)	2.30 (1.98-2.67)	1.81 (1.55-2.12)	< 0.001
Short-acting benzodiazepines ^a	98 (0.36)	178 (0.13)			< 0.001
Long-acting benzodiazepines ^b			2.64 (2.03-3.43)	1.73 (1.31-2.28)	
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)			< 0.001
SSRIs ^c alone	289 (1.06)	874 (0.65)	1.64 (1.49-1.81)	1.29 (1.16-1.43)	< 0.001
SNRIs ^d alone	129 (0.48)	313 (0.23)	1.81	1.43	< 0.001
Tricyclics ^e alone	136 (0.50)	266 (0.20)	1.70 (1.47-1.97)	1.30 (1.12-1.51)	0.007
Others ⁷ alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.83 (1.46-2.30)	0.002
Combined antidepressants	22 (0.08)				
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	2.48 (1.98-3.10)	1.94 (1.54-2.45)	0.009
Typical ^g alone	4 (0.01)	584 (0.43)			0.48
Atypical ^h alone		22 (0.02)	2.02 (1.64-2.49)	1.35 (1.09-1.69)	
Combined antipsychotics			0.54 (0.34-0.85)	0.47 (0.30-0.75)	
			2.03 (1.73-2.38)	1.26 (1.06-1.50)	
			0.96 (0.28-3.28)	0.64 (0.18-2.23)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858 (76.83)	113,292 (84.35)	1.00	1.00	
35-39			1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.11 (2.92-3.31)	< 0.001
Welfare recipient	1,954 (7.20)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.45
Urban dweller	6,592 (24.28)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
Emergency visit and/or hospitalization	22,426 (82.60)	110,978 (82.63)			
Health care utilization in the 12-month before LMP until index date	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.17 (1.13-1.21)	< 0.001

Psychiatrist visit	365 (1.34)	1,210 (0.90)	1.52 (1.34- 1.73)	1.07 (0.94- 1.22)	
General practitioner (GP) visits					
0	14,192				0.39
1-2	(52.27)	72,006	1.00	1.00	< 0.001
3 or more	3,885 (14.31)	(53.61)	1.05 (0.99- 1.11)	1.03 (0.97- 1.09)	
Number of other specialists visits	9,072 (33.92)	22,281			
0		(16.59)	1.36 (1.29- 1.43)	1.17 (1.11- 1.23)	0.16
1	17,239	40,018			0.03
2 or more	(63.50)	(29.30)			
	2,273 (8.37)		1.00	1.00	
	7,637 (28.13)	86,772	0.98 (0.93- 1.04)	0.96 (0.91- 1.02)	
		(64.61)			
		12,268	1.16 (1.11- 1.20)	1.05 (1.01- 1.10)	
		(9.13)			
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475	1.38 (1.32- 1.44)	1.17 (1.11- 1.23)	< 0.001
Mood and anxiety disorders	15 (0.06)	(7.80)			0.55
Insomnia		54 (0.04)	1.46 (0.79- 2.71)	1.22 (0.64- 2.32)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66- 0.78)	0.69 (0.64- 0.76)	< 0.001
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607	1.20 (1.13- 1.28)	1.18 (1.10- 1.26)	< 0.001
Diabetes	1,022 (3.76)	(4.17)			0.23
Asthma	5,001 (18.46)	4,957	0.99 (0.92- 1.06)	1.05 (0.97- 1.13)	< 0.001
Thyroid disorders	1,467 (5.40)	(3.69)			0.003
Tobacco dependence	696 (2.56)	20,788	1.22 (1.18- 1.27)	1.18 (1.13- 1.22)	< 0.001
Alcohol dependence	258 (0.95)	(15.48)			0.02
Other drugs dependence	373 (1.37)	7,581	0.92 (0.87- 0.98)	0.91 (0.85- 0.97)	0.04
		(5.64)			
		2,381	1.44 (1.31- 1.57)	1.28 (1.16- 1.41)	
		(1.77)			
		727 (0.54)	1.73 (1.48- 2.01)	1.22 (1.03- 1.45)	
		(0.91)			
		1,227	1.47 (1.30- 1.67)	1.15 (1.01- 1.32)	
		(0.91)			
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50- 0.54)	0.47 (0.45- 0.48)	< 0.001
Pregnancy in the 12-month before LMP	1,693 (6.24)	(43.89)			< 0.001
		6,246	1.39 (1.31- 1.48)	1.22 (1.14- 1.30)	
		(4.65)			
^a Short-acting benzodiazepines included alprazolam, bromazepam, lorazepam, oxazepam, temazepam and triazolam. ^b Long-acting benzodiazepines included chlordiazepoxide, clobazam, clonazepam, diazepam, flurazepam and nitrazepam. ^c SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.					

^dSNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.

^eTricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.

^fOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^gTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^hAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

eTable 7. Association Between Mean Daily Dose of Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion					
Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Mean daily dose of study medications exposure from LMP until index date					
1-5 mg/day	202 (0.74)	470 (0.35)	2.17 (1.82-2.58)	1.73 (1.44-2.08)	< 0.001
6-20 mg/day	163 (0.60)	300 (0.22)	2.70 (2.20-3.31)	1.96 (1.59-2.43)	< 0.001
more than 20 mg/day	10 (0.04)	18 (0.01)	3.22 (1.41-7.34)	2.55 (1.08-6.01)	0.03
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)			< 0.001
SSRIs ^a alone	289 (1.06)	874 (0.65)			0.001
SNRIs ^b alone	129 (0.48)	313 (0.23)	1.64 (1.49-1.81)	1.28 (1.15-1.43)	< 0.001
Tricyclics ^c alone	136 (0.50)	266 (0.20)	1.70 (1.47-1.97)	1.29 (1.11-1.50)	< 0.001
Others ^d alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.81 (1.44-2.28)	0.009
Combined antidepressants					
Antipsychotics exposure from LMP until index date	22 (0.08)	191 (0.14)	2.06 (1.67-2.57)	1.81 (1.44-2.28)	0.002
Typical ^e alone	251 (0.92)	584 (0.43)	2.48 (1.98-3.10)	1.94 (1.53-2.44)	0.009
Atypical ^f alone	4 (0.01)	22 (0.02)	2.02 (1.64-2.49)	1.34 (1.08-1.68)	0.47
Combined antipsychotics					
			0.54 (0.34-0.85)	0.47 (0.30-0.75)	
			2.03 (1.73-2.38)	1.26 (1.06-1.50)	
			0.96 (0.28-3.28)	0.63 (0.18-2.21)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858 (76.83)	113,292 (84.35)	1.00	1.00	
35-39	4,337 (15.97)	17,101 (12.73)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	1,954 (7.20)	3,912 (2.91)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	6,592 (24.28)	22,426 (82.60)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.42
Urban dweller		29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
		110,978 (82.63)			

Health care utilization in the 12-month before LMP until index date	15,279	70,872	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Emergency visit and/or hospitalization	(56.28)	(52.77)			0.33
Psychiatrist visit	365 (1.34)	1,210 (0.90)	1.52 (1.34-1.73)	1.07 (0.94-1.22)	
General practitioner (GP) visits					0.43
0	14,192 (52.27)	72,006 (53.61)	1.00	1.00	< 0.001
1-2					
3 or more	3,885 (14.31)		1.05 (0.99-1.11)	1.02 (0.97-1.08)	
Number of other specialists visits	9,072 (33.92)	22,281 (16.59)	1.36 (1.29-1.43)	1.17 (1.11-1.24)	0.25
0					0.002
1	17,239 (63.50)	40,018 (29.30)			
2 or more	2,273 (8.37)	86,772 (64.61)	1.00	1.00	
	7,637 (28.13)	12,268 (9.13)	0.98 (0.93-1.04)	0.97 (0.91-1.02)	
		35,265 (26.26)	1.16 (1.11-1.20)	1.07 (1.02-1.12)	
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475 (7.80)	1.38 (1.32-1.44)	1.16 (1.11-1.22)	< 0.001
Mood and anxiety disorders	15 (0.06)	54 (0.04)	1.46 (0.79-2.71)	1.22 (0.64-2.32)	0.55
Insomnia					
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181 (3.86)	0.71 (0.66-0.78)	0.69 (0.64-0.76)	< 0.001
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607 (4.17)	1.20 (1.13-1.28)	1.18 (1.11-1.27)	< 0.001
Diabetes	1,022 (3.76)	4,957 (3.69)	0.99 (0.92-1.06)	1.05 (0.98-1.14)	0.22
Asthma	5,001 (18.46)	20,788 (15.48)	1.22 (1.18-1.27)	1.17 (1.13-1.22)	< 0.001
Thyroid disorders	1,467 (5.40)	7,581 (5.64)	0.92 (0.87-0.98)	0.91 (0.85-0.97)	0.003
Tobacco dependence	696 (2.56)	2,381 (1.77)	1.44 (1.31-1.57)	1.28 (1.16-1.42)	< 0.001
Alcohol dependence	258 (0.95)	727 (0.54)	1.73 (1.48-2.01)	1.22 (1.03-1.44)	0.02
Other drugs dependence	373 (1.37)	1,227 (0.91)	1.47 (1.30-1.67)	1.15 (1.01-1.32)	0.04
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943 (43.89)	0.52 (0.50-0.54)	0.47 (0.45-0.48)	< 0.001
Pregnancy in the 12-month before LMP	597 (2.2)	2,614 (1.95)	2.08 (1.72-2.51)	1.78 (1.46-2.16)	< 0.001
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.					

^bSNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.

^cTricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

33 **eMethods. Sensitivity Analyses**

34

35 **Methods**

36 Since it recognized that the risk of spontaneous abortion is higher among women with prior spontaneous
37 abortions compared to women with previous deliveries, we categorized the prior pregnancies in the year
38 before the first day of gestation as prior spontaneous abortion, prior planned abortions, and prior delivery in
39 the year before. Second, to take into account the underlying indication, we performed a sensitivity analysis
40 among pregnancies of women with a history of mood and anxiety disorders based on ICD-9 and ICD-10
41 diagnosis codes. Third, to investigate potential exposure misclassifications, we also used restricted definitions
42 of exposure. Since benzodiazepines are prescribed as occasional or as needed medications, we first considered
43 pregnancies of women who had only one benzodiazepine prescription filled prior the LMP with duration that
44 overlapped the LMP as unexposed. Second, we only considered pregnancies of women with two or more
45 benzodiazepine prescription filled during early pregnancy as exposed. Finally, to take into account the
46 possibility of receiving benzodiazepine for impending spontaneous abortion, we excluded all prescription
47 filled in the 7 days prior to the index date (date of the spontaneous abortion).

48 As many women are being followed for mental health problems by a general practitioner, we also
49 dichotomized the covariate on medical visits as general practitioner visit for mood and anxiety disorders, and
50 general practitioner visit for other reasons. Finally, as the definition of mood and anxiety disorders based on
51 diagnostic codes recorded in the RAMQ and MED-ECHO databases was not validated, which could
52 potentially bias results, we performed another sensitivity analysis, using the Canadian Chronic Disease
53 Surveillance System (CCDSS) definition of mood and anxiety disorders. The CCDSS use the ICD-9 codes:
54 296, 300 and 311, and the ICD-10 codes: F30-F48 and F68 for the identification of the mood and anxiety
55 disorders.³⁹

56

57

58 39. *Government of Canada Report from the Canadian Chronic Disease Surveillance System: Mood and*
59 *Anxiety Disorders in Canada, 2016. Available at: [https://www.canada.ca/en/public-](https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-canadian-chronic-disease-surveillance-system-mood-anxiety-disorders-canada-2016.html#a3)*
60 *health/services/publications/diseases-conditions/report-canadian-chronic-disease-surveillance-system-mood-*
61 *anxiety-disorders-canada-2016.html#a3. Accessed Janvier 20, 2019.*

62

63

64

65 **Statistical analyses**

66

67 We performed several sensitivity analyses to evaluate the robustness of our estimates. These were performed
68 using the overall incident benzodiazepine exposure in early pregnancy model. First, we estimated the
69 association between benzodiazepine exposure and spontaneous abortion adjusting for categories of prior
70 pregnancies (childbirth, planned/induced abortion or spontaneous abortion). Second, to take into account the
71 underlying indication, we estimated the association only among pregnancies of women with a history of mood
72 and anxiety disorders based on ICD-9 and ICD-10 diagnostic codes. Third, we evaluated the robustness of our
73 incident exposure definition using three additional definitions of exposure: 1) considering pregnancies of
74 women with only one prescription filled prior to pregnancy but with duration overlapping the LMP as
75 unexposed; 2) considering only pregnancies of women who filled at least two prescriptions of benzodiazepines
76 during pregnancy as exposed; and 3) considering pregnancies of women with only one prescription filled in
77 the 7 days before index date (date of spontaneous abortion) but after the 1st day of LMP as unexposed. We
78 performed three independent conditional regression models using each new definition of exposure. Moreover,
79 we performed a sensitivity analysis stratifying on the reason for general practitioner visit (visits for mood and
80 anxiety disorders; of for other reasons) to improve the specificity of the physician consultation. Finally, we
81 estimated the association between benzodiazepine and spontaneous abortion using the mood and anxiety
82 disorders definition provided by the CCDSS.³⁹

83

84 **Results**

85

86 Adjusting for prior pregnancy history as a categorical variable, the association between benzodiazepine
87 exposure and the risk of spontaneous abortion remained unchanged (aOR 1.85; 95% CI 1.61-2.13) (eTable 8,
88 Supplement). In the restricted analysis among pregnancies with a history of mood and anxiety disorders, we
89 observed a stronger association between benzodiazepine exposure and spontaneous abortion (aOR 2.85; 95%
90 CI 1.72-4.72; 198 exposed cases) (eTable 9, Supplement). However, the confidence interval included the point
91 estimate of the association found in the main analysis, which was suggesting that mood and anxiety disorders
92 were not effect modifiers in our study.

93

94 The estimates of the association between benzodiazepine exposure and spontaneous abortion were similar for
95 each sensitivity analysis performed using the additional exposure definitions. First, considering pregnancies of

96 women with only one benzodiazepine prescription filled prior to pregnancy but with duration overlapping the
97 LMP as unexposed (aOR 1.97; 95% CI 1.69-2.29; 321 exposed cases) (eTable 10, Supplement); second,
98 considering exposure as at least two prescription filled during pregnancy (aOR 1.89; 95% CI 1.43-2.48; 101
99 exposed cases) (eTable 11, Supplement); and, considering pregnancies of women with only one prescription
100 filled in the 7 days prior to index date but after LMP as unexposed (aOR 1.89; 95% CI 1.63-2.20; 324
101 exposed cases) (eTable 12, Supplement).

102
103 The estimate of the association in the sensitivity analysis stratified on the reason for the general practitioner's
104 visit also remained unchanged (aOR 1.83; 95% CI 1.60-2.11; 375 exposed cases) (eTable 13, Supplement).

105
106 Finally, the association between benzodiazepines and spontaneous abortion remained unchanged in the
107 sensitivity analysis using the CCDSS³⁹ definition of mood and anxiety disorder (aOR 1.86; 95% CI 1.62-2.14;
108 375 exposed cases) (eTable 14, Supplement).

eTable 8. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the Variable Prior Pregnancy Categorized by Termination (Childbirth, Planned/Induced Abortion and Spontaneous Abortion)					
Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date Benzodiazepines (overall)	375 (1.38)	788 (0.59)	2.39 (2.10-2.73)	1.85 (1.61-2.13)	< 0.001
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.29 (1.16-1.43)	< 0.001
SSRIs ^a alone	129 (0.48)	874 (0.65)	1.70 (1.47-1.97)	1.30 (1.11-1.51)	< 0.001
SNRIs ^b alone	136 (0.50)	313 (0.23)	2.06 (1.67-2.57)	1.83 (1.46-2.29)	0.008
Tricyclics ^c alone	146 (0.54)	266 (0.20)	2.48 (1.98-3.10)	1.94 (1.54-2.45)	0.002
Others ^d alone	22 (0.08)	350 (0.26)	2.02 (1.64-2.49)	1.35 (1.08-1.70)	0.008
Combined antidepressants	22 (0.08)	350 (0.26)	0.54 (0.34-0.85)	0.47 (0.30-0.75)	0.48
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	2.03 (1.73-2.38)	1.26 (1.06-1.50)	
Typical ^e alone	4 (0.01)	584 (0.43)	0.96 (0.28-3.28)	0.64 (0.18-2.23)	
Atypical ^f alone		22 (0.02)			
Combined antipsychotics		22 (0.02)			
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858 (76.83)	113,292 (84.35)	1.00	1.00	
35-39	4,337 (15.97)	17,101 (12.73)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	1,954 (7.20)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	6,592 (24.28)	3,912 (2.91)	1.16 (1.12-1.19)	1.06 (1.03-1.10)	0.47
Urban dweller	22,426 (82.60)	29,112 (21.68)	1.00 (0.96-1.03)	1.01 (0.98-1.05)	
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Psychiatrist visit	365 (1.34)				0.33

General practitioner (GP) visits					
0	14,192	1,210	1.52 (1.34-	1.07 (0.93-	0.47
1-2	(52.27)	(0.90)	1.73)	1.22)	< 0.001
3 or more	3,885 (14.31)	72,006	1.00	1.00	
Number of other specialists visits	9,072 (33.92)	(53.61)	1.05 (0.99-	1.02 (0.97-	
0		22,281	1.11)	1.08)	0.18
1	17,239	(16.59)	1.36 (1.29-	1.16 (1.10-	0.002
2 or more	(63.50)	40,018	1.43)	1.22)	
	2,273 (8.37)	(29.30)			
	7,637 (28.13)		1.00	1.00	
		86,772	0.98 (0.93-	0.96 (0.91-	
		(64.61)	1.04)	1.02)	
		12,268	1.16 (1.11-	1.06 (1.01-	
		(9.13)	1.20)	1.11)	
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475	1.38 (1.32-	1.16 (1.11-	< 0.001
Mood and anxiety disorders	15 (0.06)	(7.80)	1.44)	1.22)	0.56
Insomnia		54 (0.04)	1.46 (0.79-	1.21 (0.64-	
			2.71)	2.32)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66-	0.69 (0.64-	< 0.001
		(3.86)	0.78)	0.75)	
Co-morbidities in the 12-month before LMP until index date	1,336 (4.92)	5,607	1.20 (1.13-	1.19 (1.11-	< 0.001
Hypertension	1,022 (3.76)	(4.17)	1.28)	1.27)	0.19
Diabetes	5,001 (18.46)	4,957	0.99 (0.92-	1.05 (0.98-	< 0.001
Asthma	1,467 (5.40)	(3.69)	1.06)	1.14)	0.003
Thyroid disorders	696 (2.56)	20,788	1.22 (1.18-	1.18 (1.13-	< 0.001
Tobacco dependence	258 (0.95)	(15.48)	1.27)	1.22)	0.02
Alcohol dependence	373 (1.37)	7,581	0.92 (0.87-	0.91 (0.85-	0.04
Other drugs dependence		(5.64)	0.98)	0.97)	
		2,381	1.44 (1.31-	1.28 (1.16-	
		(1.77)	1.57)	1.42)	
		727 (0.54)	1.73 (1.48-	1.22 (1.03-	
		1,227	2.01)	1.44)	
		(0.91)	1.47 (1.30-	1.15 (1.01-	
			1.67)	1.32)	
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50-	0.47 (0.45-	< 0.001
In the 12-month before LMP	597 (2.2)	(43.89)	0.54)	0.48)	0.95
Prior childbirth	952 (3.51)	2,614	1.16 (1.06-	1.00 (0.90-	< 0.001
Prior planned/induced abortion	179 (0.66)	(1.95)	1.28)	1.10)	< 0.001
Prior spontaneous abortion		3,307	1.46 (1.35-	1.32 (1.22-	
		(2.46)	1.58)	1.43)	
		406 (0.30)	2.08 (1.72-	1.77 (1.46-	
			2.51)	2.15)	

^aSSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

^bSNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.

^cTricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

eTable 9. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion Among Pregnancies of Women With Mood and Anxiety Disorders Diagnosis in the 12 Months Before LMP Until Index Date

Characteristic	Spontaneous abortion n=3,419	Controls n=12,533	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date	198 (5.79)	372 (2.97)	3.24 (2.03-5.18)	2.85 (1.72-4.72)	<0.001
Benzodiazepines (overall)					
Antidepressants exposure from LMP until index date	403 (11.79)	1,245 (9.93)	1.29 (1.00-1.68)	1.16 (0.87-1.54)	0.31
SSRIs ^a alone	182 (5.32)	563 (4.49)	1.68	1.54	0.88
SNRIs ^b alone	26 (0.76)	50 (0.40)	1.32 (0.87-2.01)	1.04 (0.66-1.63)	0.22
Tricyclics ^c alone	72 (2.11)	119 (0.95)	2.01	1.63	0.39
Others ^d alone	112 (3.28)	274 (2.19)	1.46 (0.52-4.10)	2.03 (0.66-6.28)	0.57
Combined antidepressants	5 (0.15)		2.00 (0.99-4.05)	1.40 (0.65-3.02)	0.27
Antipsychotics exposure from LMP until index date	160 (4.68)	45 (0.36)	4.05	3.02	0.08
Typical ^e alone	4 (0.12)	366 (2.92)	1.82 (1.12-2.94)	1.17 (0.69-1.98)	0.33
Atypical ^f alone		16 (0.13)			
Combined antipsychotics			0.45 (0.09-2.27)	0.37 (0.07-2.16)	
			1.74 (1.12-2.71)	1.55 (0.94-2.54)	
			0.62 (0.06-7.00)	0.23 (0.01-4.74)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	2,705 (79.12)	10,675 (85.18)	1.00	1.00	
35-39	501 (14.65)	1,445 (11.53)	1.19 (0.95-1.50)	1.37 (1.07-1.75)	0.01
40 or more	213 (6.23)	3,333 (26.59)	1.50	1.75	0.001
Welfare recipient	988 (28.90)	10,461 (83.47)	2.12 (1.36-3.33)	2.23 (1.38-3.61)	0.19
Urban dweller	2,859 (83.62)		1.23 (1.02-1.48)	1.15 (0.93-1.41)	0.08
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	2,333 (68.24)	8,055 (64.27)	1.28 (1.06-1.54)	1.25 (1.01-1.55)	0.04
Psychiatrist visit	288 (8.42)	921 (7.35)	1.32 (0.98-1.79)	1.19 (0.86-1.66)	0.30
General practitioner (GP) visits	1,473 (43.08)				

0	185 (5.41)	5,489			0.01
1-2	1,761 (51.51)	(43.80)	1.00	1.00	0.21
3 or more		941 (7.51)	0.43 (0.23-0.81)	0.41 (0.21-0.81)	
Number of other specialists visits	1,962 (57.39)	6,103			
0	292 (8.54)	(48.70)	0.77 (0.44-1.37)	0.68 (0.37-1.25)	0.33
1	1,165 (34.07)				0.03
2 or more		7,440	1.00	1.00	
		(59.36)	1.27 (0.92-1.75)	1.19 (0.84-1.68)	
		1,065	1.37 (1.07-1.75)	1.37 (1.04-1.80)	
		(8.50)			
		4,028			
		(32.14)			
≥ one diagnostic of insomnia in the 12-month before LMP until index date	7 (0.20)	17 (0.14)	0.67 (0.11-3.99)	0.67 (0.10-4.62)	0.68
Folic acid exposure in the 6-months before LMP until index date	98 (2.87)	583 (4.65)	0.61 (0.37-0.99)	0.72 (0.43-1.20)	0.20
Co-morbidities in the 12-month before LMP until index date	241 (7.05)	741 (5.91)	1.11 (0.80-1.55)	1.17 (0.81-1.68)	0.41
Hypertension	130 (3.80)	504 (4.02)	1.55	1.68	0.04
Diabetes	915 (26.76)	2,843	0.69 (0.45-1.06)	0.62 (0.40-0.98)	0.38
Asthma	231 (6.76)	(22.68)	1.06	0.98	0.52
Thyroid disorders	161 (4.71)	890 (7.10)	1.22 (1.01-1.48)	1.10 (0.89-1.36)	0.69
Tobacco dependence	88 (2.57)	414 (3.30)	1.48	1.36	0.63
Alcohol dependence	143 (4.18)	191 (1.52)	0.90 (0.65-1.26)	0.89 (0.63-1.27)	0.95
Other drugs dependence		408 (3.26)	1.20 (0.80-1.82)	1.10 (0.68-1.79)	
			1.43 (0.78-2.62)	1.20 (0.57-2.55)	
			1.32 (0.83-2.09)	0.98 (0.59-1.65)	
Pregnancy follow-up by gynecologist or obstetrician	1,053 (30.80)	5,569	0.54 (0.45-0.65)	0.51 (0.41-0.62)	<0.001
Spontaneous abortion in the 12-month before LMP	28 (0.82)	(44.43)	2.00 (0.72-5.57)	2.17 (0.73-6.39)	0.16
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. ^b SNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine. ^c Tricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine. ^d Other antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone. ^e Typical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol. ^f Atypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.					

eTable 10. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With Pregnancies of Women With Only 1 Prescription Filled Prior to Pregnancy Who Overlap the LMP Considered as Unexposed

Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date	321 (1.18)	632 (0.47)	2.52 (2.18-2.91)	1.97 (1.69-2.29)	< 0.001
Benzodiazepines (overall)					
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.29 (1.16-1.43)	< 0.001
SSRIs ^a alone	289 (1.06)	874 (0.65)	1.81	1.43	< 0.001
SNRIs ^b alone	129 (0.48)	313 (0.23)	1.70 (1.47-1.97)	1.30 (1.12-1.51)	< 0.001
Tricyclics ^c alone	136 (0.50)	266 (0.20)	1.97	1.51	0.007
Others ^d alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.81 (1.44-2.28)	
Combined antidepressants	22 (0.08)		2.48 (1.98-3.10)	1.97 (1.56-2.48)	0.002
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	3.10	2.48	0.006
Typical ^e alone	4 (0.01)	584 (0.43)	2.02 (1.64-2.49)	1.35 (1.09-1.69)	0.47
Atypical ^f alone		22 (0.02)			
Combined antipsychotics			0.54 (0.34-0.85)	0.47 (0.30-0.75)	
			2.03 (1.73-2.38)	1.28 (1.07-1.52)	
			0.96 (0.28-3.28)	0.63 (0.18-2.21)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858	113,292	1.00	1.00	
35-39	(76.83)	(84.35)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	1,954 (7.20)				< 0.001
Urban dweller	6,592 (24.28)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.42
	22,426 (82.60)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
		110,978 (82.63)			
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Psychiatrist visit	365 (1.34)				0.33

General practitioner (GP) visits					
0	14,192	1,210	1.52 (1.34-1.73)	1.07 (0.94-1.22)	0.44
1-2	(52.27)				< 0.001
3 or more	3,885 (14.31)	72,006	1.00	1.00	
Number of other specialists visits	9,072 (33.92)	(53.61)	1.05 (0.99-1.11)	1.02 (0.97-1.08)	0.26
0		22,281			
1	17,239	(16.59)	1.36 (1.29-1.43)	1.17 (1.11-1.24)	0.002
2 or more	(63.50)	40,018			
	2,273 (8.37)	(29.30)	1.00	1.00	
	7,637 (28.13)	86,772	0.98 (0.93-1.04)	0.97 (0.91-1.02)	
		(64.61)			
		12,268	1.16 (1.11-1.20)	1.07 (1.03-1.12)	
		(9.13)			
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475	1.38 (1.32-1.44)	1.17 (1.11-1.22)	< 0.001
Mood and anxiety disorders	15 (0.06)	(7.80)			0.57
Insomnia		54 (0.04)	1.46 (0.79-2.71)	1.21 (0.63-2.31)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66-0.78)	0.69 (0.64-0.76)	< 0.001
Co-morbidities in the 12-month before LMP until index date	1,336 (4.92)	5,607	1.20 (1.13-1.28)	1.18 (1.10-1.27)	< 0.001
Hypertension	1,022 (3.76)	(4.17)			0.22
Diabetes	5,001 (18.46)	4,957	0.99 (0.92-1.06)	1.05 (0.97-1.13)	< 0.001
Asthma	1,467 (5.40)	(3.69)			0.003
Thyroid disorders	696 (2.56)	20,788	1.22 (1.18-1.27)	1.17 (1.13-1.22)	< 0.001
Tobacco dependence	258 (0.95)	(15.48)			0.02
Alcohol dependence	373 (1.37)	7,581	0.92 (0.87-0.98)	0.91 (0.85-0.97)	0.04
Other drugs dependence		(5.64)			
		2,381	1.44 (1.31-1.57)	1.28 (1.16-1.42)	
		(1.77)			
		727 (0.54)	1.73 (1.48-2.01)	1.22 (1.03-1.44)	
		(0.91)	1.47 (1.30-1.67)	1.15 (1.01-1.32)	
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50-0.54)	0.47 (0.45-0.48)	< 0.001
Spontaneous abortion in the 12-month before LMP	597 (2.2)	(43.89)			< 0.001
		2,614	2.08 (1.72-2.51)	1.78 (1.46-2.16)	
		(1.95)			
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. ^b SNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine. ^c Tricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.					

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

eTable 11. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With Only Pregnancies of Women Who Filled 2 or More Prescription of Benzodiazepine Were Considered as Exposed					
Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date Benzodiazepines (overall)	101 (0.37)	165 (0.12)	3.02 (2.32-3.92)	1.89 (1.43-2.48)	< 0.001
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.31 (1.18-1.46)	< 0.001
SSRIs ^a alone	289 (1.06)	874 (0.65)	1.81	1.46	< 0.001
SNRIs ^b alone	129 (0.48)	313 (0.23)	1.70 (1.47-1.97)	1.31 (1.13-1.52)	< 0.001
Tricyclics ^c alone	136 (0.50)	266 (0.20)	1.97	1.52	0.003
Others ^d alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.84 (1.47-2.31)	
Combined antidepressants	22 (0.08)		2.48 (1.98-3.10)	1.97 (1.56-2.48)	0.002
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	3.10	2.48	0.008
Typical ^e alone	4 (0.01)	584 (0.43)	2.02 (1.64-2.49)	1.40 (1.12-1.74)	0.46
Atypical ^f alone		22 (0.02)			
Combined antipsychotics			0.54 (0.34-0.85)	0.48 (0.30-0.76)	
			2.03 (1.73-2.38)	1.26 (1.06-1.50)	
			0.96 (0.28-3.28)	0.62 (0.18-2.18)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858	113,292	1.00	1.00	
35-39	(76.83)	(84.35)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	1,954 (7.20)				< 0.001
Urban dweller	6,592 (24.28)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.11)	0.45
	22,426 (82.60)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Psychiatrist visit	365 (1.34)				0.34

General practitioner (GP) visits					
0	14,192	1,210	1.52 (1.34-	1.07 (0.93-	0.42
1-2	(52.27)	(0.90)	1.73)	1.22)	< 0.001
3 or more	3,885 (14.31)	72,006	1.00	1.00	
Number of other specialists visits	9,072 (33.92)	(53.61)	1.05 (0.99-	1.02 (0.97-	
0		22,281	1.11)	1.08)	0.26
1	17,239	(16.59)	1.36 (1.29-	1.17 (1.11-	0.002
2 or more	(63.50)	40,018	1.43)	1.24)	
	2,273 (8.37)	(29.30)			
	7,637 (28.13)		1.00	1.00	
		86,772	0.98 (0.93-	0.97 (0.91-	
		(64.61)	1.04)	1.03)	
		12,268	1.16 (1.11-	1.07 (1.03-	
		(9.13)	1.20)	1.12)	
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475	1.38 (1.32-	1.17 (1.12-	< 0.001
Mood and anxiety disorders	15 (0.06)	(7.80)	1.44)	1.24)	0.58
Insomnia		54 (0.04)	1.46 (0.79-	1.20 (0.63-	
			2.71)	2.29)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66-	0.70 (0.64-	< 0.001
		(3.86)	0.78)	0.76)	
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607	1.20 (1.13-	1.18 (1.10-	< 0.001
Diabetes	1,022 (3.76)	(4.17)	1.28)	1.26)	0.21
Asthma	5,001 (18.46)	4,957	0.99 (0.92-	1.05 (0.97-	< 0.001
Thyroid disorders	1,467 (5.40)	(3.69)	1.06)	1.13)	0.003
Tobacco dependence	696 (2.56)	20,788	1.22 (1.18-	1.18 (1.13-	< 0.001
Alcohol dependence	258 (0.95)	(15.48)	1.27)	1.22)	0.02
Other drugs dependence	373 (1.37)	7,581	0.92 (0.87-	0.91 (0.85-	0.04
		(5.64)	0.98)	0.97)	
		2,381	1.44 (1.31-	1.28 (1.16-	
		(1.77)	1.57)	1.42)	
		727 (0.54)	1.73 (1.48-	1.23 (1.04-	
		1,227	2.01)	1.45)	
		(0.91)	1.47 (1.30-	1.13 (1.01-	
			1.67)	1.33)	
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50-	0.47 (0.45-	< 0.001
Spontaneous abortion in the 12-month before LMP	597 (2.2)	(43.89)	0.54)	0.48)	< 0.001
		2,614	2.08 (1.72-	1.78 (1.46-	
		(1.95)	2.51)	2.16)	
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.					
^b SNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.					
^c Tricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.					

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

eTable 12. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion Removing Benzodiazepine Prescription Filled in the 7 Days Prior to the Index Date (Date of Spontaneous Abortion)

Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date Benzodiazepines (overall)	324 (1.19)	643 (0.48)	2.47 (2.15-2.89)	1.89 (1.63-2.20)	< 0.001
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.29 (1.16-1.43)	< 0.001
SSRIs ^a alone	129 (0.48)	874 (0.65)	1.70 (1.47-1.97)	1.30 (1.11-1.51)	< 0.001
SNRIs ^b alone	136 (0.50)	313 (0.23)	2.06 (1.67-2.57)	1.82 (1.45-2.29)	0.007
Tricyclics ^c alone	146 (0.54)	266 (0.20)	2.48 (1.98-3.10)	1.95 (1.54-2.46)	0.002
Others ^d alone	22 (0.08)	350 (0.26)	2.02 (1.64-2.49)	1.36 (1.09-1.69)	0.009
Combined antidepressants	22 (0.08)	350 (0.26)	0.54 (0.34-0.85)	0.48 (0.30-0.76)	0.47
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	2.03 (1.73-2.38)	1.26 (1.06-1.50)	
Typical ^e alone	4 (0.01)	584 (0.43)	0.96 (0.28-3.28)	0.63 (0.18-2.20)	
Atypical ^f alone		22 (0.02)			
Combined antipsychotics		22 (0.02)			
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858 (76.83)	113,292 (84.35)	1.00	1.00	
35-39			1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	1,954 (7.20)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.43
Urban dweller	6,592 (24.28)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Psychiatrist visit	365 (1.34)				0.34

General practitioner (GP) visits					
0	14,192	1,210	1.52 (1.34-	1.07 (0.93-	0.43
1-2	(52.27)	(0.90)	1.73)	1.22)	< 0.001
3 or more	3,885 (14.31)	72,006	1.00	1.00	
Number of other specialists visits	9,072 (33.92)	(53.61)	1.05 (0.99-	1.02 (0.97-	
0		22,281	1.11)	1.08)	0.26
1	17,239	(16.59)	1.36 (1.29-	1.17 (1.11-	0.002
2 or more	(63.50)	40,018	1.43)	1.24)	
	2,273 (8.37)	(29.30)			
	7,637 (28.13)		1.00	1.00	
		86,772	0.98 (0.93-	0.97 (0.91-	
		(64.61)	1.04)	1.02)	
		12,268	1.16 (1.11-	1.07 (1.03-	
		(9.13)	1.20)	1.12)	
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475	1.38 (1.32-	1.17 (1.11-	< 0.001
Mood and anxiety disorders	15 (0.06)	(7.80)	1.44)	1.23)	0.56
Insomnia		54 (0.04)	1.46 (0.79-	1.21 (0.63-	
			2.71)	2.31)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66-	0.69 (0.64-	< 0.001
		(3.86)	0.78)	0.76)	
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607	1.20 (1.13-	1.18 (1.10-	< 0.001
Diabetes	1,022 (3.76)	(4.17)	1.28)	1.27)	0.22
Asthma	5,001 (18.46)	4,957	0.99 (0.92-	1.05 (0.97-	< 0.001
Thyroid disorders	1,467 (5.40)	(3.69)	1.06)	1.13)	0.003
Tobacco dependence	696 (2.56)	20,788	1.22 (1.18-	1.17 (1.13-	< 0.001
Alcohol dependence	258 (0.95)	(15.48)	1.27)	1.22)	0.02
Other drugs dependence	373 (1.37)	7,581	0.92 (0.87-	0.91 (0.85-	0.04
		(5.64)	0.98)	0.97)	
		2,381	1.44 (1.31-	1.28 (1.16-	
		(1.77)	1.57)	1.42)	
		727 (0.54)	1.73 (1.48-	1.22 (1.03-	
		1,227	2.01)	1.44)	
		(0.91)	1.47 (1.30-	1.16 (1.01-	
			1.67)	1.32)	
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50-	0.47 (0.45-	< 0.001
Spontaneous abortion in the 12-month before LMP	597 (2.2)	(43.89)	0.54)	0.48)	< 0.001
		2,614	2.08 (1.72-	1.78 (1.46-	
		(1.95)	2.51)	2.16)	
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.					
^b SNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.					
^c Tricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.					

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

eTable 13. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the General Practitioner Visits Dichotomized Regarding the Purpose of Consultation (Mood and Anxiety Disorders vs Other Reasons)					
Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date	375 (1.38)	788 (0.59)	2.47 (2.15-2.89)	1.83 (1.60-2.11)	< 0.001
Benzodiazepines (overall)					
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.28 (1.15-1.43)	< 0.001
SSRIs ^a alone	289 (1.06)	874 (0.65)	1.81	1.43	< 0.001
SNRIs ^b alone	129 (0.48)	313 (0.23)	1.70 (1.47-1.97)	1.29 (1.11-1.50)	< 0.001
Tricyclics ^c alone	136 (0.50)	266 (0.20)	1.97	1.50	0.009
Others ^d alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.82 (1.45-2.29)	
Combined antidepressants	22 (0.08)		2.48 (1.98-3.10)	1.94 (1.53-2.45)	0.001
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	3.10	2.45	0.01
Typical ^e alone	4 (0.01)	584 (0.43)	2.02 (1.64-2.49)	1.34 (1.09-1.67)	0.45
Atypical ^f alone		22 (0.02)			
Combined antipsychotics			0.54 (0.34-0.85)	0.47 (0.29-0.75)	
			2.03 (1.73-2.38)	1.25 (1.05-1.48)	
			0.96 (0.28-3.28)	0.62 (0.18-2.17)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858	113,292	1.00	1.00	
35-39	(76.83)	(84.35)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	1,954 (7.20)				< 0.001
Urban dweller	6,592 (24.28)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.41
	22,426 (82.60)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
Health care utilization in the 12-month before LMP until index date					
Emergency visit and/or hospitalization	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Psychiatrist visit	365 (1.34)				0.25

General practitioner (GP) visits for mood and anxiety disorders	25,836 (95.16)	1,210 (0.90)	1.52 (1.34-1.73)	1.08 (0.95-1.24)	0.31 < 0.001
0					
1-2	1,061 (3.91)	129,182 (96.19)	1.00	1.00	
3 or more	252 (0.93)	4,174 (3.11)	0.77 (0.72-0.83)	1.03 (0.97-1.09)	0.22
General practitioner (GP) visits for other reasons	15,256 (56.19)	949 (0.71)	0.74 (0.64-0.85)	1.18 (1.12-1.24)	0.41
0					
1-2	3,967 (14.61)	76,193 (56.73)	1.00	1.00	0.27
3 or more	7,926 (29.19)	12,268 (9.13)	1.06 (1.01-1.11)	1.05 (0.95-1.16)	0.002
Number of other specialists visits	17,239 (63.50)	22,446 (16.71)	0.84 (0.80-0.88)	0.93 (0.79-1.10)	
0					
1	2,273 (8.37)	35,666 (26.56)	1.00	1.00	
2 or more	7,637 (28.13)	86,772 (64.61)	0.98 (0.93-1.04)	0.97 (0.91-1.03)	
		12,268 (9.13)	1.16 (1.11-1.20)	1.07 (1.03-1.12)	
		35,265 (26.26)			
≥ one diagnostic in the 12-month before LMP until index date	2,681 (9.88)	10,475 (7.80)	1.38 (1.32-1.44)	1.21 (1.15-1.29)	< 0.001
Mood and anxiety disorders	15 (0.06)	54 (0.04)	1.46 (0.79-2.71)	1.22 (0.64-2.32)	0.55
Insomnia					
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181 (3.86)	0.71 (0.66-0.78)	0.69 (0.64-0.75)	< 0.001
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607 (4.17)	1.20 (1.13-1.28)	1.18 (1.11-1.27)	< 0.001
Diabetes	1,022 (3.76)	4,957 (3.69)	0.99 (0.92-1.06)	1.05 (0.97-1.13)	0.22
Asthma	5,001 (18.46)	20,788 (15.48)	1.22 (1.18-1.27)	1.17 (1.13-1.22)	< 0.001
Thyroid disorders	1,467 (5.40)	7,581 (5.64)	0.92 (0.87-0.98)	0.91 (0.85-0.97)	0.003
Tobacco dependence	696 (2.56)	2,381 (1.77)	1.44 (1.31-1.57)	1.28 (1.16-1.41)	< 0.001
Alcohol dependence	258 (0.95)	727 (0.54)	1.73 (1.48-2.01)	1.22 (1.03-1.44)	0.02
Other drugs dependence	373 (1.37)	1,227 (0.91)	1.47 (1.30-1.67)	1.15 (1.01-1.32)	0.04
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943 (43.89)	0.52 (0.50-0.54)	0.47 (0.45-0.48)	< 0.001
	597 (2.2)				< 0.001

Spontaneous abortion in the 12-month before LMP		2,614 (1.95)	2.08 (1.72- 2.51)	1.78 (1.47- 2.16)	
<p>^aSSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.</p> <p>^bSNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine.</p> <p>^cTricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.</p> <p>^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.</p> <p>^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.</p> <p>^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.</p>					

eTable 14. Association Between Benzodiazepine Incident Exposure During Early Pregnancy and the Risk of Spontaneous Abortion With the New Definition of Mood and Anxiety Disorder Proposed by the Canadian Chronic Disease Surveillance System (CCDSS)

Characteristic	Spontaneous abortion n=27,149	Controls n=134,305	Odds Ratio (OR)		P-value
			Crude 95%CI	Adjusted 95% CI	
Study medications exposure from LMP until index date	375 (1.38)	788 (0.59)	2.47 (2.15-2.89)	1.86 (1.62-2.14)	< 0.001
Benzodiazepines (overall)					
Antidepressants exposure from LMP until index date	628 (2.31)	1,897 (1.41)	1.64 (1.49-1.81)	1.30 (1.17-1.45)	< 0.001
SSRIs ^a alone	289 (1.06)	874 (0.65)	1.81	1.45	< 0.001
SNRIs ^b alone	129 (0.48)	313 (0.23)	1.70 (1.47-1.97)	1.31 (1.12-1.52)	< 0.001
Tricyclics ^c alone	136 (0.50)	266 (0.20)	1.97	1.52	0.005
Others ^d alone	146 (0.54)	350 (0.26)	2.06 (1.67-2.57)	1.82 (1.45-2.29)	
Combined antidepressants	22 (0.08)		2.48 (1.98-3.10)	1.97 (1.56-2.48)	0.001
Antipsychotics exposure from LMP until index date	251 (0.92)	191 (0.14)	3.10	2.48	0.008
Typical ^e alone	4 (0.01)	584 (0.43)	2.02 (1.64-2.49)	1.37 (1.10-1.71)	0.49
Atypical ^f alone		22 (0.02)			
Combined antipsychotics			0.54 (0.34-0.85)	0.47 (0.29-0.75)	
			2.03 (1.73-2.38)	1.27 (1.07-1.51)	
			0.96 (0.28-3.28)	0.65 (0.19-2.26)	
Demographic characteristics at LMP					
Maternal age (y)					
Less than 35	20,858	113,292	1.00	1.00	
35-39	(76.83)	(84.35)	1.38 (1.32-1.43)	1.55 (1.49-1.61)	< 0.001
40 or more	4,337 (15.97)	17,101 (12.73)	2.73 (2.57-2.90)	3.10 (2.91-3.30)	< 0.001
Welfare recipient	1,954 (7.20)				< 0.001
Urban dweller	6,592 (24.28)	3,912 (2.91)	1.16 (1.12-1.19)	1.07 (1.03-1.10)	0.41
	22,426 (82.60)	29,112 (21.68)	1.00 (0.96-1.03)	1.02 (0.98-1.05)	
Health care utilization in the 12-month before LMP until index date	15,279 (56.28)	70,872 (52.77)	1.15 (1.11-1.18)	1.18 (1.14-1.22)	< 0.001
Emergency visit and/or hospitalization					0.22
Psychiatrist visit	365 (1.34)				

General practitioner (GP) visits					
0	14,192	1,210	1.52 (1.34-	1.09 (0.95-	0.42
1-2	(52.27)	(0.90)	1.73)	1.24)	< 0.001
3 or more	3,885 (14.31)	72,006	1.00	1.00	
Number of other specialists visits	9,072 (33.92)	(53.61)	1.05 (0.99-	1.02 (0.97-	
0		22,281	1.11)	1.08)	0.24
1	17,239	(16.59)	1.36 (1.29-	1.18 (1.12-	0.003
2 or more	(63.50)	40,018	1.43)	1.24)	
	2,273 (8.37)	(29.30)			
	7,637 (28.13)		1.00	1.00	
		86,772	0.98 (0.93-	0.97 (0.91-	
		(64.61)	1.04)	1.02)	
		12,268	1.16 (1.11-	1.07 (1.02-	
		(9.13)	1.20)	1.12)	
		35,265			
		(26.26)			
≥ one diagnostic in the 12-month before LMP until index date	3,172 (11.68)	11,806	1.35 (1.29-	1.13 (1.07-	< 0.001
Mood and anxiety disorders (CCDSS definition)	15 (0.06)	(8.79)	1.41)	1.19)	0.55
Insomnia		54 (0.04)	1.46 (0.79-	1.22 (0.64-	
			2.71)	2.32)	
Folic acid exposure in the 6-months before LMP until index date	751 (2.77)	5,181	0.71 (0.66-	0.69 (0.64-	< 0.001
		(3.86)	0.78)	0.76)	
Co-morbidities in the 12-month before LMP until index date					
Hypertension	1,336 (4.92)	5,607	1.20 (1.13-	1.18 (1.11-	< 0.001
Diabetes	1,022 (3.76)	(4.17)	1.28)	1.27)	0.22
Asthma	5,001 (18.46)	4,957	0.99 (0.92-	1.05 (0.97-	< 0.001
Thyroid disorders	1,467 (5.40)	(3.69)	1.06)	1.13)	0.003
Tobacco dependence	696 (2.56)	20,788	1.22 (1.18-	1.18 (1.13-	< 0.001
Alcohol dependence	258 (0.95)	(15.48)	1.27)	1.22)	0.02
Other drugs dependence	373 (1.37)	7,581	0.92 (0.87-	0.91 (0.85-	0.04
		(5.64)	0.98)	0.97)	
		2,381	1.44 (1.31-	1.28 (1.16-	
		(1.77)	1.57)	1.42)	
		727 (0.54)	1.73 (1.48-	1.22 (1.03-	
		1,227	2.01)	1.44)	
		(0.91)	1.47 (1.30-	1.16 (1.01-	
			1.67)	1.32)	
Pregnancy follow-up by gynecologist or obstetrician	8,037 (29.60)	58,943	0.52 (0.50-	0.47 (0.45-	< 0.001
Spontaneous abortion in the 12-month before LMP	597 (2.2)	(43.89)	0.54)	0.48)	< 0.001
		2,614	2.08 (1.72-	1.78 (1.46-	
		(1.95)	2.51)	2.16)	
^a SSRI antidepressants included citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. ^b SNRI antidepressants included desvenlafaxine, duloxetine and venlafaxine. ^c Tricyclic antidepressants included amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline and trimipramine.					

^dOther antidepressants included bupropion, buspirone, L-tryptophan, maprotiline, mirtazapine, trazodone, moclobemide and nefazodone.

^eTypical antipsychotic agents included chlorpromazine, fluphenazine, flupentixol, haloperidol, loxapine, methotrimeprazine, pericyazine, perphenazine, pimozide, prochlorperazine, trifluoperazine and zuclopenthixol.

^fAtypical antipsychotic agents included aripiprazole, clozapine, olanzapine, risperidone, quetiapine and ziprasidone.

122
123