

Supplemental Online Content

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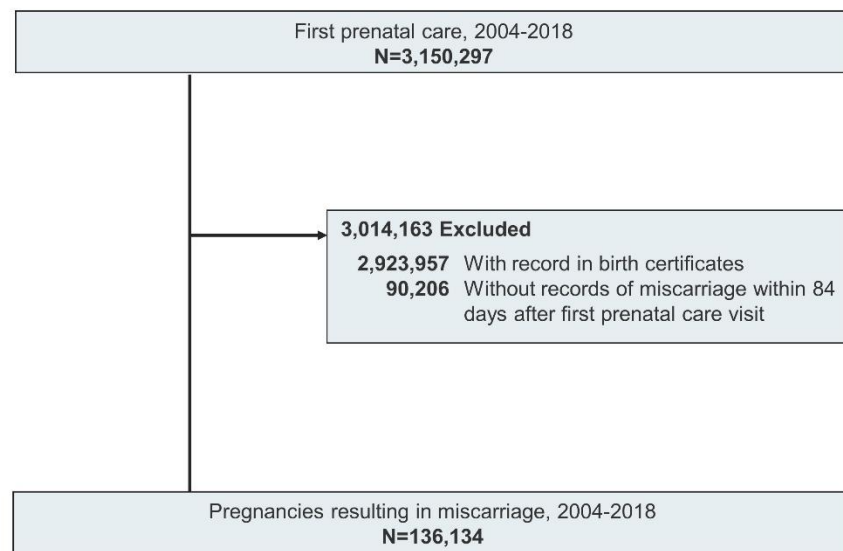
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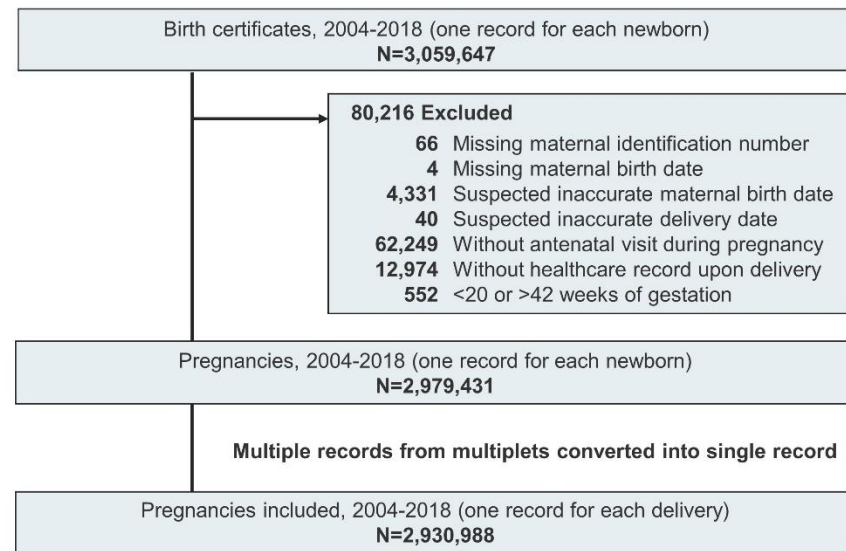
This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure 1. Flow chart of study population selection

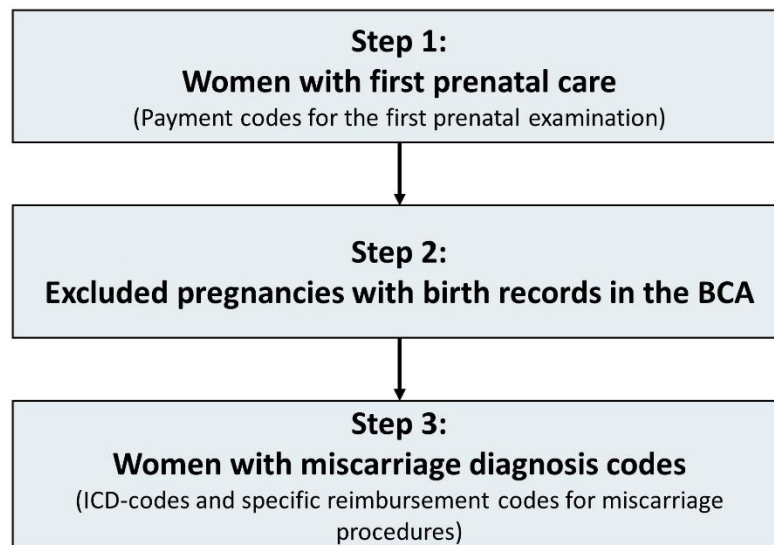
Pregnancies resulting in miscarriage



Pregnancies resulting in births



eFigure 2. Algorithms for miscarriage definition



For miscarriage cases, we utilized a robust algorithm, informed by clinical insights from obstetricians, to define them in our study.

Step 1: Women with first prenatal care

In Taiwan, every pregnant woman is entitled to ten free prenatal examinations paid for by the government (1): two in the first trimester, two in the second trimester, and four in the third trimester. A very high proportion of Taiwanese pregnant women thus undergo examinations according to the government-provided schedule. In our approach to defining those with miscarriage, we used the payment code for the first prenatal examination for initial identification.

Step 2: Excluded pregnancies with birth records in the BCA

In step 2, we excluded pregnancies with birth records in the BCA. In Taiwan, birth registration within seven days of delivery is mandatory. This approach ensures that there are no live births or stillbirths (≥ 20 weeks of gestational age) in those with miscarriage.

Step 3: Women with miscarriage diagnosis codes

Finally, we used diagnosis codes for identification of miscarriage, which, according to previous studies using other databases, have a high positive predictive value (PPV) for identifying miscarriages.

Reference:

1. Maternal Health Education Handbook. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. <https://health99.hpa.gov.tw/material/6852>. Accessed 9, September, 2023.

eTable 1. Data sources

National Birth Certificate Application (BCA) database from 2004 to 2018
<p>The BCA records all live births and stillbirths with gestational age of more than 20 weeks or birth weight more than 500 grams. In Taiwan, birth registration within seven days of delivery is mandatory. A validation study of the BCA database reported a low percentage of missing information and high levels of validity and reliability of documented birth-related information. The data on each pregnancy and delivery are provided by obstetricians, and information for newborns is provided by pediatricians. Data in the BCA database include demographic characteristics, gestational age in weeks, birth date of newborns, singleton or multiple pregnancy, and birth outcomes.</p>
National Health Insurance (NHI) database from 2002 to 2019
<p>The NHI database comprises anonymized health insurance claims for visits, procedures, and prescriptions for more than 99% of the population in Taiwan (~23 million). For each healthcare encounter, the following information was recorded: dates of outpatient visits, admissions, and discharges; type of medical care (outpatient or inpatient visits); prenatal care (e.g., for each pregnant woman, ten routine prenatal care visits are provided free of charge: two visits during the first trimester, two visits during the second trimester, and six visits during the third trimester); prescription medications dispensed designated by World Health Organization (WHO) Anatomical Therapeutic Chemical codes; and diagnostic codes according to the International Classification of Diseases, 9th Edition (ICD-9 CM) for those before 2016, or the 10th edition (ICD-10 CM) for those since 2016.</p>

eTable 2. Definitions of covariates using for the disease risk score calculation

Co-morbidities	ICD9-CODE	ICD10- Code
Sleep disorder or psychiatric medical conditions		
Anxiety	300.0x, 300.2x, 300.3x, 309.81	F40.xx-F43.xx
Insomnia	307.31,307.42, 309.49, 780.51, 780.52	G47.xx, F51.xx
Depression	296.2x, 296.3x, 311.xx, 300.4x	F32.xx-F34.xx
Schizophrenia	295.xx	F20.xx, F21.xx, F25.xx
Epilepsy	345.xx	G40.xx
Bipolar disorder	296.0x, 296.1x, 296.4x-296.8x	F30.xx, F31.xx
Life style factors		
Overweight/Obesity	278.0x	E66.xx
Tobacco use	305.1x	F172.xx
Alcohol abuse	291.xx, 303.xx, 305.0x	F10.xx
Drug abuse	304.xx, 305.2x–305.9x, 648.3x	F11.xx-F16.xx, F18.xx, F19.xx
Chronic comorbidities		
Hypertension	401.xx–405.xx	I10.xx-I13.xx, I15.xx
Hyperlipidemia	272.0x-272.4x, 272.9x	E78.0x-E78.5x
Diabetes mellitus	250.xx	E10.xx-E14.xx
Chronic congestive heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	I11.0x, I13.0x,I13.2x,I50.xx
Chronic ischemic heart disease	412.xx–414.xx	I20.xx, I25.xx
Congenital heart disease	745.0x–747.4x, 648.5x	Q20.xx-Q26.xx, O99.4x
Cardiac valvular disease	394.xx–397.xx, 424.xx	I05.xx-I09.xx, I34.xx-I39.xx
Asthma	493.xx	J44.xx, J45.xx
Hyperthyroidism	242.xx	E05.xx
Chronic renal disease	581.xx–583.xx, 585.xx, 587.xx, 588.xx	N02.2x, N03.xx-N05.xx, N08.xx, N17.1x, N17.2x, N18.xx, N25.xx
Human immunodeficiency virus	42.xx, V08.xx	B20.xx, B24.xx, O98.7x, Z21.xx, Z22.6x
Sickle cell disease	282.4x, 282.6x	D56.xx, D57.xx
Systemic lupus erythematosus	710.0x	M32.xx

eTable 3. Study outcome: ICD codes and specific reimbursement codes

The rationale for using a broader range of codes to define miscarriage is twofold. First, the codes we utilized were recommended by obstetricians. In Taiwan, the government funds ten free prenatal examinations, providing pregnant women with more opportunities to receive medical care and examinations. Consequently, if there are any indications (even suspicious sign such as 640 Hemorrhage in early pregnancy) of a miscarriage, the diagnostic codes we used are likely to be given. Second, we aimed to include all potential cases from the beginning. Since we can only define miscarriages from around 8 weeks of gestation until week 20, a timeframe during which more than half of all miscarriages have already occurred, we sought to include a larger study population to mitigate the reduced statistical power associated with a small sample size.

Miscarriage	Description
ICD codes	ICD-9-CM: 631.xx, 632.xx, 634.xx, 637.xx, 640.xx ICD-10-CM: O02.xx, O03.xx, O20.xx
Reimbursement codes in Taiwan	81001C: Removal of hydatidiform mole
	81006C: D&C (\leq 12.week)
	81007C: D&C (>12.week)
	81007CA: Septic abortion treatment
	81008B: Abortion, therapeutic transabdominal
	81009C: Medical induction for fetal death
	81010C: Medical induction for fetal death
	81012B: Destruction of the dead fetus
	81022B: Septic abortion treatment
	81030C: Dilution and evacuation after induction failure

eTable 4. Study medication category and ATC codes

Medication Category	Agents	ATC Codes
Long-acting benzodiazepines (half-life >24 h)	Clonazepam	N03AE01
	Diazepam	N05BA01
	Chlordiazepoxide	N05BA02
	Medazepam	N05BA03
	Bromazepam	N05BA08
	Clobazam	N05BA09
	Prazepam	N05BA11
	Nordazepam	N05BA16
	Cloxazolam	N05BA22
	Oxazolam	N05BA91
	Nitrazepam	N05CD02
	Flunitrazepam	N05CD03
	Brotizolam	N05CD09
Short-acting benzodiazepines (half-life ≤24 h)	Oxazepam	N05BA04
	Clorazepate	N05BA05
	Lorazepam	N05BA06
	Alprazolam	N05BA12
	Fludiazepam	N05BA17
	Flurazepam	N05CD01
	Estazolam	N05CD04
	Triazolam	N05CD05
	Lormetazepam	N05CD06
	Temazepam	N05CD07
	Midazolam	N05CD08
Nimetazepam	N05CD15	

eTable 5. Characteristics of cases and controls before matched

	Case, N (%)	Control, N (%)	Standardized difference
Total	136,134	2,930,988	
Age at pregnancy, mean (SD)	30.61 (5.91)	29.94 (4.95)	0.1236
Psychiatric medical conditions			
Anxiety	1,439 (1.06)	19,576 (0.67)	0.0421
Insomnia	1,774 (1.30)	19,869 (0.68)	0.0632
Depression	1,247 (0.92)	12,954 (0.44)	0.0577
Schizophrenia	111 (0.08)	1,199 (0.04)	0.0164
Epilepsy	153 (0.11)	2,806 (0.10)	0.0052
Bipolar	161 (0.12)	1,519 (0.05)	0.0228
Lifestyle factors			
Obesity	102 (0.07)	2,164 (0.07)	0.0004
Tobacco use	92 (0.07)	1,548 (0.05)	0.0060
Alcohol use	35 (0.03)	386 (0.01)	0.0090
Drug abuse	22 (0.02)	539 (0.02)	-0.0017
Chronic comorbidities			
Hypertension	652 (0.48)	15,252 (0.52)	-0.0059
Hyperlipidemia	470 (0.35)	6,120 (0.21)	0.0260
Diabetes mellitus	574 (0.42)	17,303 (0.59)	-0.0238
Chronic congestive heart failure	24 (0.02)	447 (0.02)	0.0019
Chronic ischemic heart disease	70 (0.05)	1,268 (0.04)	0.0038
Congenital heart disease	73 (0.05)	18,398 (0.63)	-0.0986
Cardiac valvular disease	198 (0.15)	8,959 (0.31)	-0.0338
Asthma	600 (0.44)	20,882 (0.71)	-0.0359
Hyperthyroidism	741 (0.54)	22,824 (0.78)	-0.0289
Chronic renal disease	130 (0.10)	4,432 (0.15)	-0.0159
Human immunodeficiency virus	7 (0.01)	970 (0.03)	-0.0202
Sickle cell disease	67 (0.05)	11,229 (0.38)	-0.0719
Systemic lupus erythematosus	231 (0.17)	3,687 (0.13)	0.0114
Medication use			
Antidepressants	3544 (2.6)	41,540 (1.42)	0.0846
Opioid analgesics	2,705 (1.99)	39,899 (1.36)	0.0488
Anticonvulsants	896 (0.66)	12,643 (0.43)	0.0308
Z-hypnotics	5303 (3.90)	4696 (0.16)	0.2674
Other anxiolytics	4,958 (3.64)	80,842 (2.76)	0.0502

Antipsychotics	2,083 (1.53)	27,004 (0.92)	0.0553
Antihypertensive drug	146 (0.11)	2,582 (0.09)	0.0061
Anti-diabetic drug	1,118 (0.82)	16,336 (0.56)	0.0319
Lipid modifying agents	502 (0.37)	5,510 (0.19)	0.0343
Healthcare utilization			
Outpatient visits, >5	56,807 (41.73)	1,105,506 (37.72)	0.0820
Inpatient visits, >1	5,838 (4.29)	6,412 (0.22)	0.2768

eTable 6. Characteristics of cases between risk period and reference period (31-58 days before the LMP)

	Risk period (N=134,864)	Reference period (N=134,864)	SD
Psychiatric medical conditions			
Anxiety	720 (0.53)	922 (0.68)	-0.0193
Insomnia	938 (0.70)	1148 (0.85)	-0.0178
Depression	534 (0.40)	747 (0.55)	-0.0230
Schizophrenia	83 (0.06)	76 (0.06)	0.0021
Epilepsy	101 (0.07)	71 (0.05)	0.0088
Bipolar	83 (0.06)	104 (0.08)	-0.0059
Lifestyle factors			
Obesity	53 (0.04)	57 (0.04)	-0.0015
Tobacco use	78 (0.06)	50 (0.04)	0.0095
Alcohol use	25 (0.02)	35 (0.03)	-0.0050
Drug abuse	21 (0.02)	26 (0.02)	-0.0028
Chronic comorbidities			
Hypertension	699 (0.52)	342 (0.25)	0.0427
Hyperlipidemia	280 (0.21)	299 (0.22)	-0.0030
Diabetes mellitus	676 (0.50)	328 (0.24)	0.0424
Chronic congestive heart failure	11 (0.01)	10 (0.01)	0.0008
Chronic ischemic heart disease	36 (0.03)	51 (0.04)	-0.0062
Congenital heart disease	54 (0.04)	26 (0.02)	0.0121
Cardiac valvular disease	162 (0.12)	122 (0.09)	0.0091
Asthma	292 (0.22)	399 (0.30)	-0.0157
Hyperthyroidism	715 (0.53)	393 (0.29)	0.0373
Chronic renal disease	859 (0.64)	98 (0.07)	0.0950
Human immunodeficiency virus	146 (0.11)	≤3 (0.00)	0.0456
Sickle cell disease	336 (0.25)	28 (0.02)	0.0622
Systemic lupus erythematosus	222 (0.16)	157 (0.12)	0.0129
Medication use			
Antidepressants	1069 (0.79)	1475 (1.09)	-0.0311
Opioid analgesics	294 (0.22)	452 (0.34)	-0.0223
Anticonvulsants	322 (0.24)	371 (0.28)	-0.0072
Z-hypnotics	1064 (0.79)	1321 (0.98)	-0.0204
Other anxiolytics	487 (0.36)	1055 (0.78)	-0.0559
Antipsychotics	581 (0.43)	652 (0.48)	-0.0078

Antihypertensive drug	263 (0.20)	70 (0.05)	0.0408
Anti-diabetic drug	631 (0.47)	684 (0.51)	-0.0056
Lipid modifying agents	200 (0.15)	306 (0.23)	-0.0182

eTable 7. Characteristics of cases between risk period and reference period (181-208 days before the LMP)

	Risk period (N=134,864)	Reference period (N=134,864)	SD
Psychiatric medical conditions			
Anxiety	720 (0.53)	869 (0.64)	-0.0144
Insomnia	938 (0.70)	1021 (0.76)	-0.0072
Depression	534 (0.40)	694 (0.51)	-0.0176
Schizophrenia	83 (0.06)	71 (0.05)	0.0037
Epilepsy	101 (0.07)	75 (0.06)	0.0075
Bipolar	83 (0.06)	110 (0.08)	-0.0075
Lifestyle factors			
Obesity	53 (0.04)	46 (0.03)	0.0027
Tobacco use	78 (0.06)	61 (0.05)	0.0056
Alcohol use	25 (0.02)	22 (0.02)	0.0017
Drug abuse	21 (0.02)	24 (0.02)	-0.0017
Chronic comorbidities			
Hypertension	699 (0.52)	353 (0.26)	0.0412
Hyperlipidemia	280 (0.21)	252 (0.19)	0.0047
Diabetes mellitus	676 (0.50)	318 (0.24)	0.0438
Chronic congestive heart failure	11 (0.01)	7 (0.01)	0.0036
Chronic ischemic heart disease	36 (0.03)	47 (0.03)	-0.0047
Congenital heart disease	54 (0.04)	36 (0.03)	0.0073
Cardiac valvular disease	162 (0.12)	114 (0.08)	0.0111
Asthma	292 (0.22)	346 (0.26)	-0.0082
Hyperthyroidism	715 (0.53)	371 (0.28)	0.0403
Chronic renal disease	859 (0.64)	80 (0.06)	0.0982
Human immunodeficiency virus	146 (0.11)	≤3 (0.00)	0.0451
Sickle cell disease	336 (0.25)	33 (0.02)	0.0608
Systemic lupus erythematosus	222 (0.16)	162 (0.12)	0.0118
Medication use			
Antidepressants	1069 (0.79)	1412 (1.05)	-0.0266
Opioid analgesics	294 (0.22)	550 (0.41)	-0.0340
Anticonvulsants	322 (0.24)	398 (0.30)	-0.0109
Z-hypnotics	1064 (0.79)	1261 (0.94)	-0.0158
Other anxiolytics	487 (0.36)	1001 (0.74)	-0.0515
Antipsychotics	581 (0.43)	677 (0.50)	-0.0104

Antihypertensive drug	263 (0.20)	73 (0.05)	0.0399
Anti-diabetic drug	631 (0.47)	582 (0.43)	0.0054
Lipid modifying agents	200 (0.15)	273 (0.20)	-0.0129

eTable 8. Associations between pregnancy benzodiazepine use and the risk of miscarriage: case-time-control design

	Reference period: 31-58 days before the LMP			Reference period: 181-208 days before the LMP		
	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)
Overall benzodiazepine						
CCO cases	1,307	2,778	0.47 (0.44-0.50)	1,502	2,806	0.54 (0.50-0.57)
CCO controls	623	2,490	0.25 (0.23-0.27)	753	2,386	0.32 (0.29-0.34)
CTC ratio	-	-	1.88 (1.70-2.08)	-	-	1.69 (1.52-1.87)
Long-acting benzodiazepine						
CCO cases	581	1,329	0.44 (0.40-0.48)	677	1,358	0.50 (0.46-0.55)
CCO controls	276	1,217	0.23 (0.20-0.27)	354	1,202	0.30 (0.26-0.33)
CTC ratio	-	-	1.91 (1.60-2.28)	-	-	1.67 (1.44-1.93)
Short-acting benzodiazepine						
CCO cases	937	1,834	0.51 (0.47-0.55)	1,083	1,883	0.58 (0.54-0.62)
CCO controls	452	1,610	0.28 (0.25-0.31)	555	1,579	0.35 (0.32-0.39)
CTC ratio	-	-	1.82 (1.59-2.08)	-	-	1.66 (1.47-1.87)

CCO=case crossover; CTC=case-time-control

eTable 9. Associations between pregnancy benzodiazepine use and the risk of miscarriage: subgroup analyses

	Reference period: 31-58 days before the LMP			Reference period: 181-208 days before the LMP		
	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)
The five most commonly benzodiazepine use						
<i>Alprazolam</i>						
CCO cases	424	801	0.53 (0.47-0.60)	499	871	0.57 (0.51-0.64)
CCO controls	210	690	0.30 (0.26-0.36)	275	668	0.41 (0.36-0.47)
CTC ratio	-	-	1.77 (1.44-2.17)	-	-	1.39 (1.17-1.66)
<i>Diazepam</i>						
CCO cases	228	536	0.43 (0.37-0.50)	242	553	0.44 (0.38-0.51)
CCO controls	103	494	0.21 (0.17-0.26)	118	452	0.26 (0.21-0.32)
CTC ratio	-	-	2.05 (1.58-2.66)	-	-	1.69 (1.31-2.19)
<i>Lorazepam</i>						
CCO cases	237	560	0.42 (0.36-0.49)	288	536	0.54 (0.47-0.62)
CCO controls	150	478	0.31 (0.26-0.38)	179	466	0.38 (0.32-0.46)
CTC ratio	-	-	1.35 (1.06-1.73)	-	-	1.42 (1.13-1.79)
<i>Oxazolam</i>						
CCO cases	136	353	0.39 (0.32-0.47)	149	346	0.43 (0.36-0.52)
CCO controls	65	281	0.23 (0.18-0.30)	73	263	0.28 (0.32-0.36)
CTC ratio	-	-	1.70 (1.23-2.33)	-	-	1.54 (1.27-1.86)
<i>Fludiazepam</i>						
CCO cases	242	334	0.73 (0.61-0.86)	261	358	0.73 (0.62-0.86)
CCO controls	77	324	0.24 (0.19-0.31)	92	316	0.29 (0.23-0.37)
CTC ratio	-	-	3.04 (2.26-4.10)	-	-	2.52 (1.89-3.36)

Dose analysis						
CCO cases						
DDD<1.0	932	2,202	0.43 (0.40-0.47)	1,090	2,195	0.50 (0.47-0.54)
1.0≤DDD	375	576	0.61 (0.54-0.69)	412	609	0.65 (0.58-0.73)
CCO controls						
DDD<1.0	482	1,979	0.24 (0.22-0.27)	579	1,894	0.31 (0.28-0.34)
1.0≤DDD	141	511	0.26 (0.22-0.31)	174	492	0.35 (0.30-0.41)
CTC ratio						
DDD<1.0	-	-	1.79 (1.57-2.04)	-	-	1.61 (1.43-1.82)
1.0≤DDD	-	-	2.35 (1.90-2.90)	-	-	1.86 (1.53-2.25)

CCO=case crossover; CTC=case-time-control

eTable 10. Associations between pregnancy benzodiazepine use and the risk of miscarriage: sensitivity analyses

	Reference period: 31-58 days before the LMP			Reference period: 181-208 days before the LMP		
	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)	Exposed to the risk period only	Expose to the reference period only	Odds ratio (95%CI)
Time window of 7 days						
CCO cases	687	1,426	0.48 (0.44-0.53)	751	1,357	0.55 (0.51-0.61)
CCO controls	309	1,201	0.26 (0.23-0.29)	319	1,197	0.27 (0.24-0.30)
CTC ratio	-	-	1.85 (1.59-2.14)	-	-	2.04 (1.77-2.35)
Time window of 14 days						
CCO cases	946	1,991	0.48 (0.44-0.51)	1,058	1,993	0.53 (0.49-0.57)
CCO controls	401	1,777	0.23 (0.20-0.25)	444	1,677	0.27 (0.24-0.29)
CTC ratio	-	-	2.09 (1.83-2.39)	-	-	1.96 (1.74-2.22)
Time window of 56 days						
CCO cases	2,247	3,903	0.58 (0.55-0.61)	2,592	4,068	0.64 (0.61-0.67)
CCO controls	1,388	3,421	0.41 (0.38-0.43)	1,627	3,261	0.50 (0.48-0.53)
CTC ratio	-	-	1.41 (1.31-1.53)	-	-	1.28 (1.20-1.37)
Exposure redefined as dispensing ≥ 14 days						
CCO cases	560	1,229	0.46 (0.41-0.50)	719	1,357	0.53 (0.48-0.58)
CCO controls	331	1,065	0.31 (0.28-0.35)	465	1,178	0.40 (0.36-0.44)
CTC ratio	-	-	1.48 (1.28-1.72)	-	-	1.33 (1.15-1.52)
≥2 prescription dispensed						
CCO cases	525	1,090	0.29 (0.26-0.33)	418	1,051	0.22 (0.20-0.25)
CCO controls	223	891	0.11 (0.10-0.13)	161	830	0.08 (0.07-0.10)
CTC ratio			2.54 (2.11-3.07)			2.67 (2.16-3.29)
≥2 diagnoses of miscarriage						

CCO cases	756	1,808	0.42 (0.38-0.46)	891	1,839	0.49 (0.45-0.53)
CCO controls	418	1,646	0.25 (0.23-0.28)	512	1,571	0.33 (0.30-0.36)
CTC ratio	-	-	1.68 (1.46-1.93)	-	-	1.48 (1.31-1.68)
Redefined miscarriage						
CCO cases	728	1,735	0.42 (0.39-0.46)	836	1,797	0.47 (0.43-0.51)
CCO controls	383	1,665	0.23 (0.21-0.26)	463	1,607	0.29 (0.26-0.32)
CTC ratio	-	-	1.83 (1.60-2.09)	-	-	1.62 (1.42-1.85)
Adjusted for time-varying confounders*						
CCO cases	1,307	2,778	0.51 (0.48-0.55)	1,502	2,806	0.57 (0.53-0.60)
CCO controls	623	2,490	0.28 (0.26-0.31)	753	2,386	0.36 (0.33-0.40)
CTC ratio	-	-	1.82 (1.63-2.04)	-	-	1.58 (1.41-1.78)
Negative control: redefine risk period						
CCO cases	2,550	2,383	1.07 (1.01-1.13)	2,376	2,241	1.06 (1.00-1.12)
CCO controls	2,140	1,906	1.12 (1.05-1.19)	1,893	1,785	1.06 (0.99-1.13)
CTC ratio	-	-	0.96 (0.88-1.04) ^a	-	-	1.00 (0.92-1.09) ^b

CCO=case crossover; CTC=case-time-control

*Adjustment for co-medication use (antidepressants, opioid analgesics, anticonvulsants, z-hypnotics, other anxiolytics)

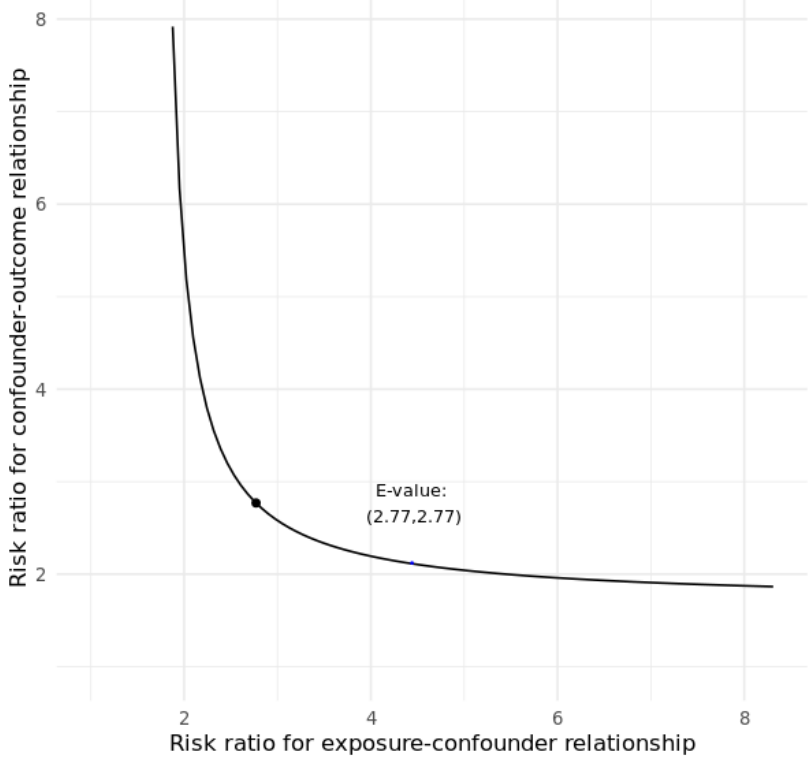
^aRisk period redefined as (LMP-31) to (LMP-58), and reference period remained as (LMP-181) to (LMP-208)

^aRisk period redefined as (LMP-91) to (LMP-118), and reference period remained as (LMP-181) to (LMP-208)

eTable 11. Calculating the E-value to assess the impact of unmeasured confounders

To further evaluate the potential effects of residual or unmeasured confounders, we calculated the E-values. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both the treatment and the outcome, conditional on the measured covariates, to explain away an observed association.

	OR	95% CI	E-value for point estimate	E-value for 95% CI
Overall benzodiazepine	1.69	1.52-1.87	2.77	2.41



Each point along the curve defines a joint relationship between the two sensitivity parameters that could potentially explain away the estimated effect. If one of the two parameters is smaller than the E-value, the other must be larger, as defined by the plotted curve.

The E-value of 2.77 for the benzodiazepine association indicates that an unmeasured confounder would need to have an aOR of 2.77 or greater with both the exposure and outcome to fully explain away the observed association. The lower bound of the CI for the E-value, at 2.41, suggests that the statistical significance of our findings is not likely to be entirely attributable to unmeasured confounders.