SUPPLEMENTAL MATERIAL

Off-label Use of Domperidone Among Postpartum Women in Canada: A Multi-database Cohort Study

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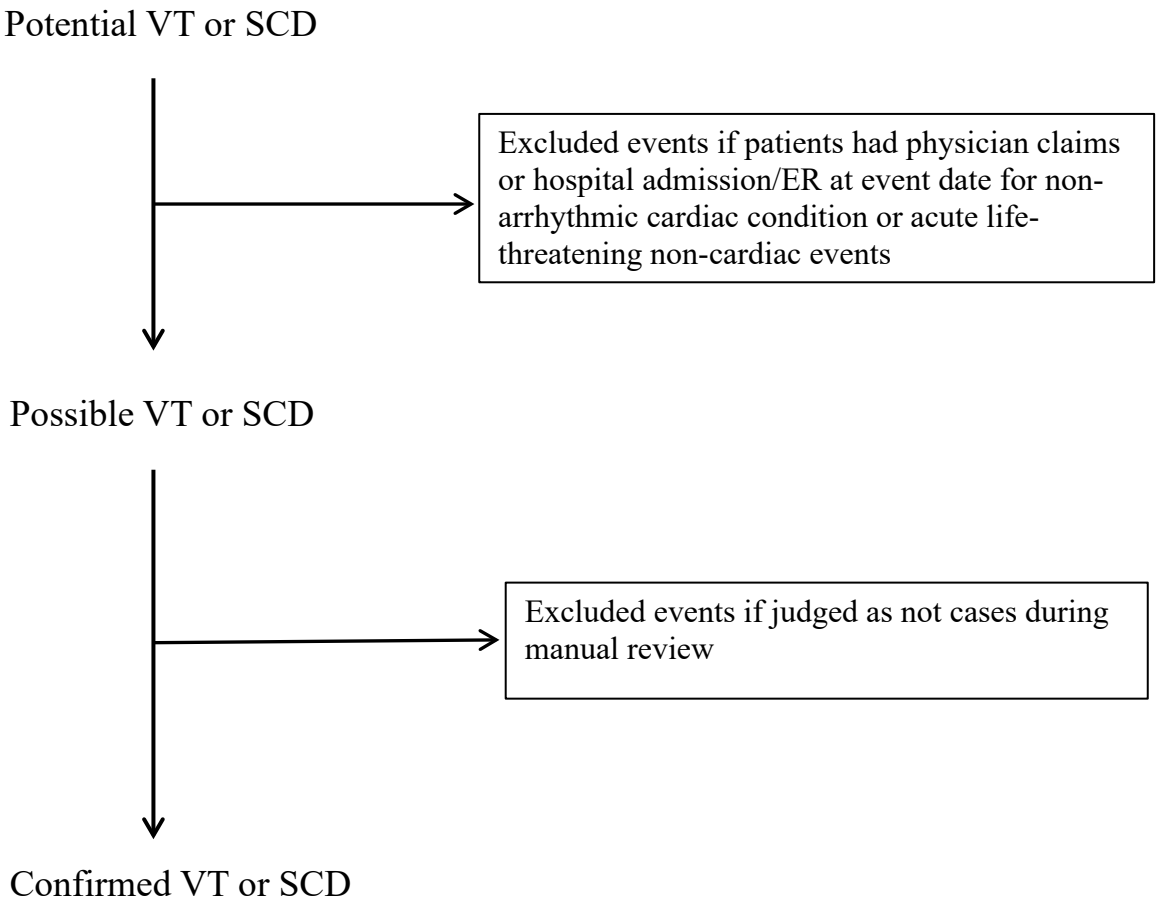

We first identified all women with a first recorded diagnosis of VT or SCD (defined using Canadian version of International Statistical Classification of Disease and Related Health Problems, 10th Revision [ICD-10-CA] diagnostic codes) (1) in hospitalization, emergency room, or vital statistics data during the 180 days after cohort entry; these records represented *potential* VT/SCD events. From these potential events, we then used hospitalization, emergency room, vital statistics, and outpatient billing data to exclude records with diagnostic codes (International Classification 9th Revision [ICD-9-CM] or ICD-10-CA codes in all sites, with Ontario's outpatient billing data using modified ICD-8 codes) (1-3) indicating non-arrhythmic cardiac events or acute life-threatening non-cardiac events (Supplementary Table 2), with the remaining events

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representing *possible* VT/SCD events. These remaining events then underwent manual review of their electronic administrative health records (including recorded diagnoses, procedures, and medication dispensing), blinded to exposure status, to further exclude events that did not meet the definition of SCD or VT.

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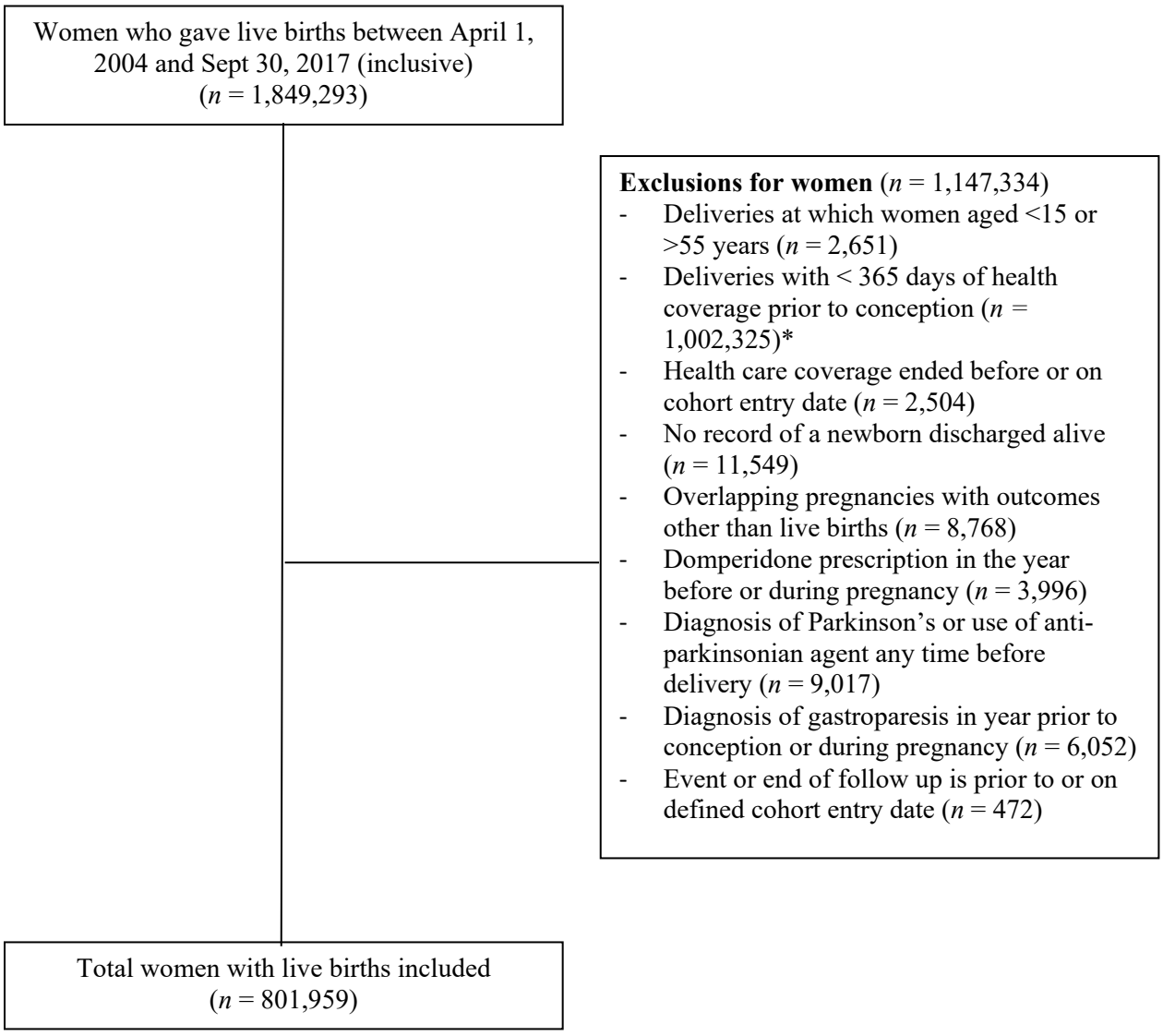

* The exclusion of observations with <365 days of health coverage was predominantly driven by Ontario, which was restricted to social assistance data.

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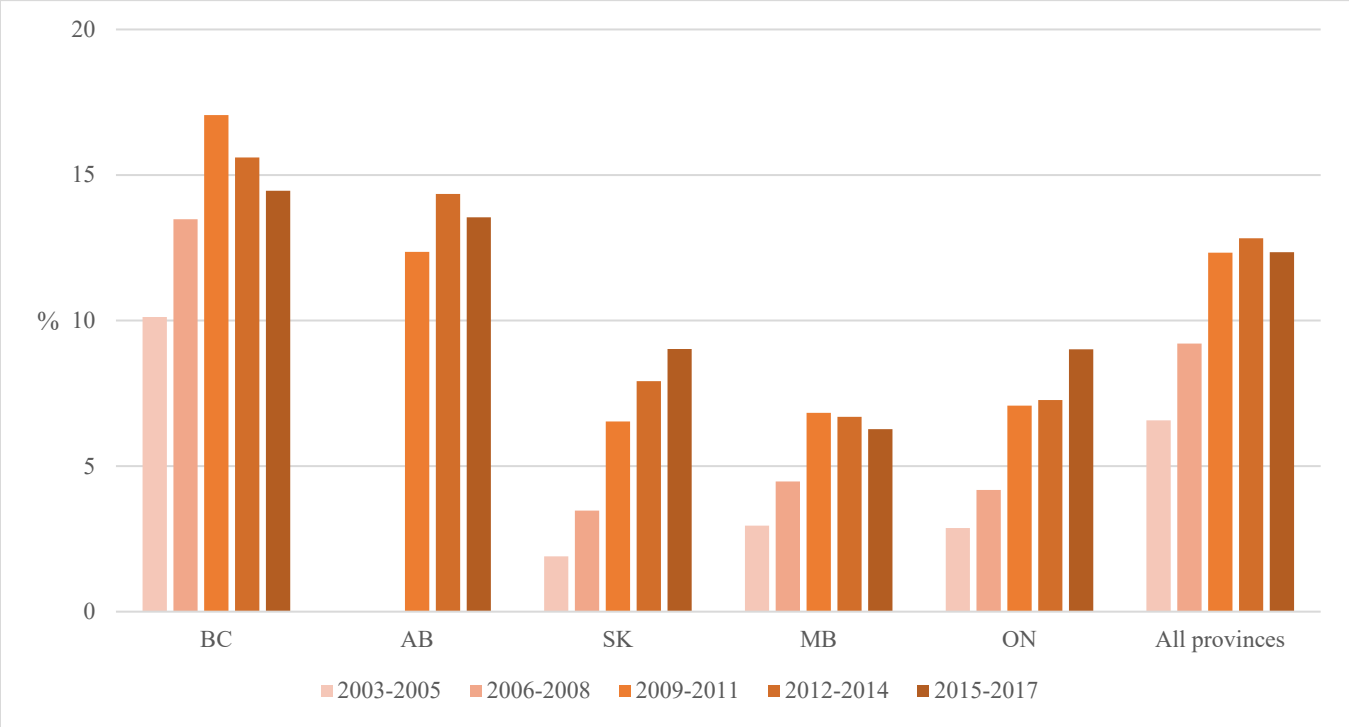

Abbreviations: BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario.

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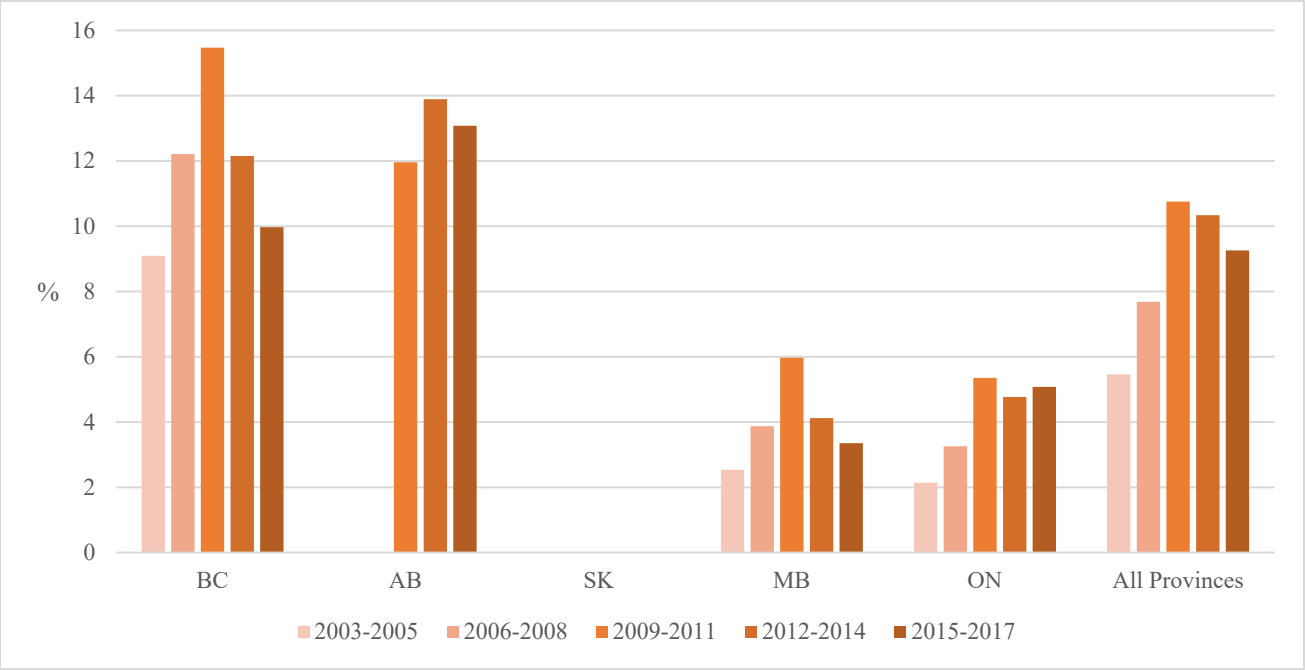

Note: Saskatchewan was excluded from the dose >30 mg analyses as data regarding dosage were not available**.**
Abbreviations: BC: British Columbia; AB: Alberta; SK: Saskatchewan; MB: Manitoba; ON: Ontario.

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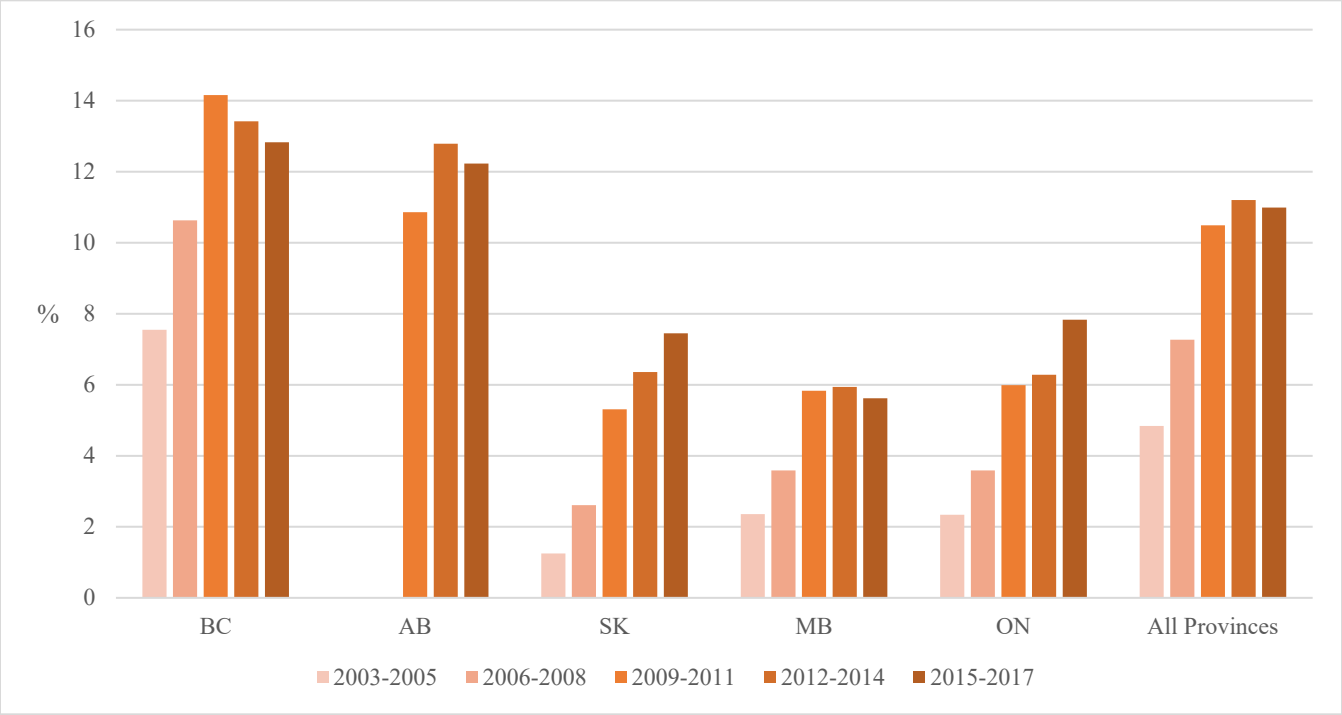

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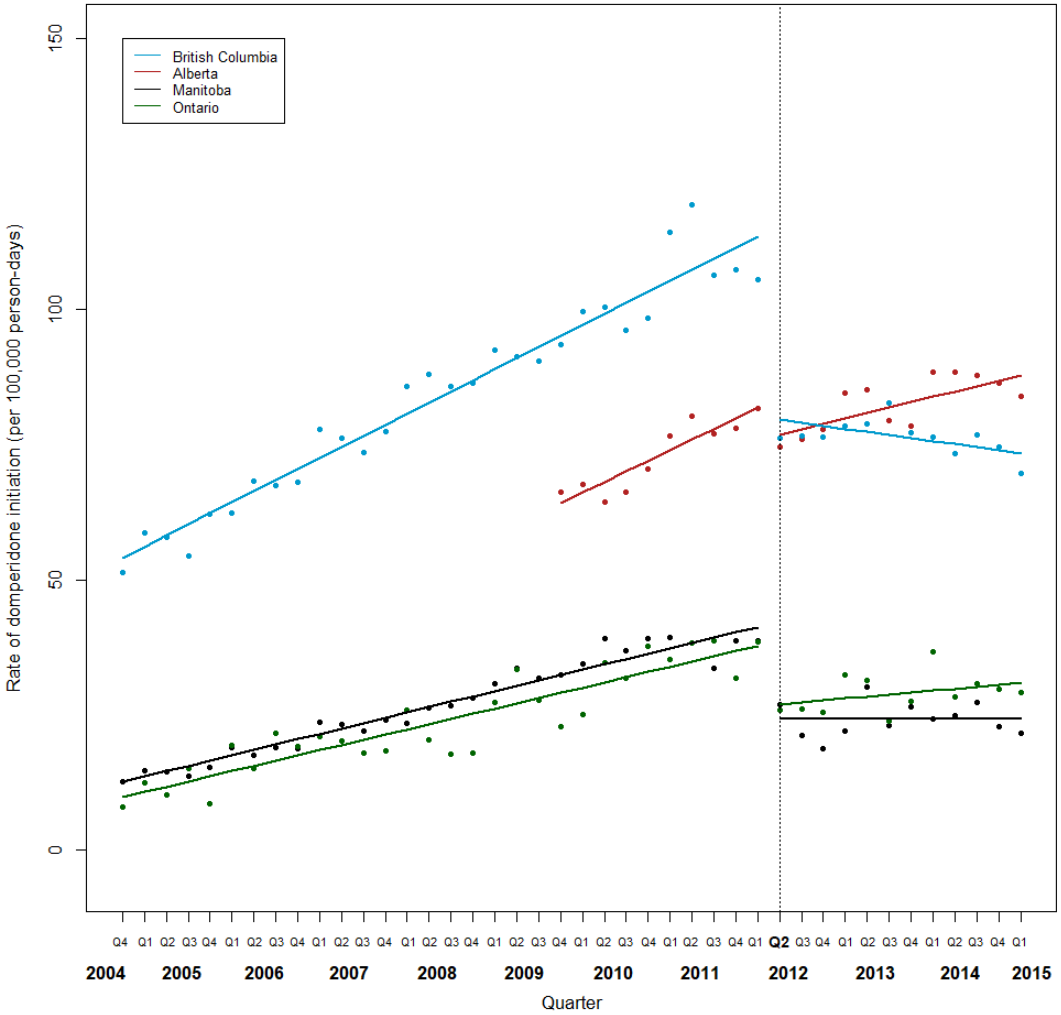

Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-33.3 (-39.9, -26.7)	-2.6 (-3.4, -1.8)
Alberta	-6.0 (-12.2, 0.2)	-0.9 (-2.1 0.2)
Manitoba	-17.1 (-20.8, -13.3)	-1.0 (-1.4, -0.5)
Ontario	-11.1 (-16.4, -5.9)	-0.6 (-1.2, 0.0)
All Provinces	-16.8 (-28.2, -5.4) I^2= 94.6% Tau^2= 127.22	-1.3 (-2.1, -0.4) I^2= 83.4% Tau^2= 0.639

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses

* Impact is measured in initiators per 100,000 person-days.

† Change in slope is measured in initiators per 100,000 person-days per quarter.

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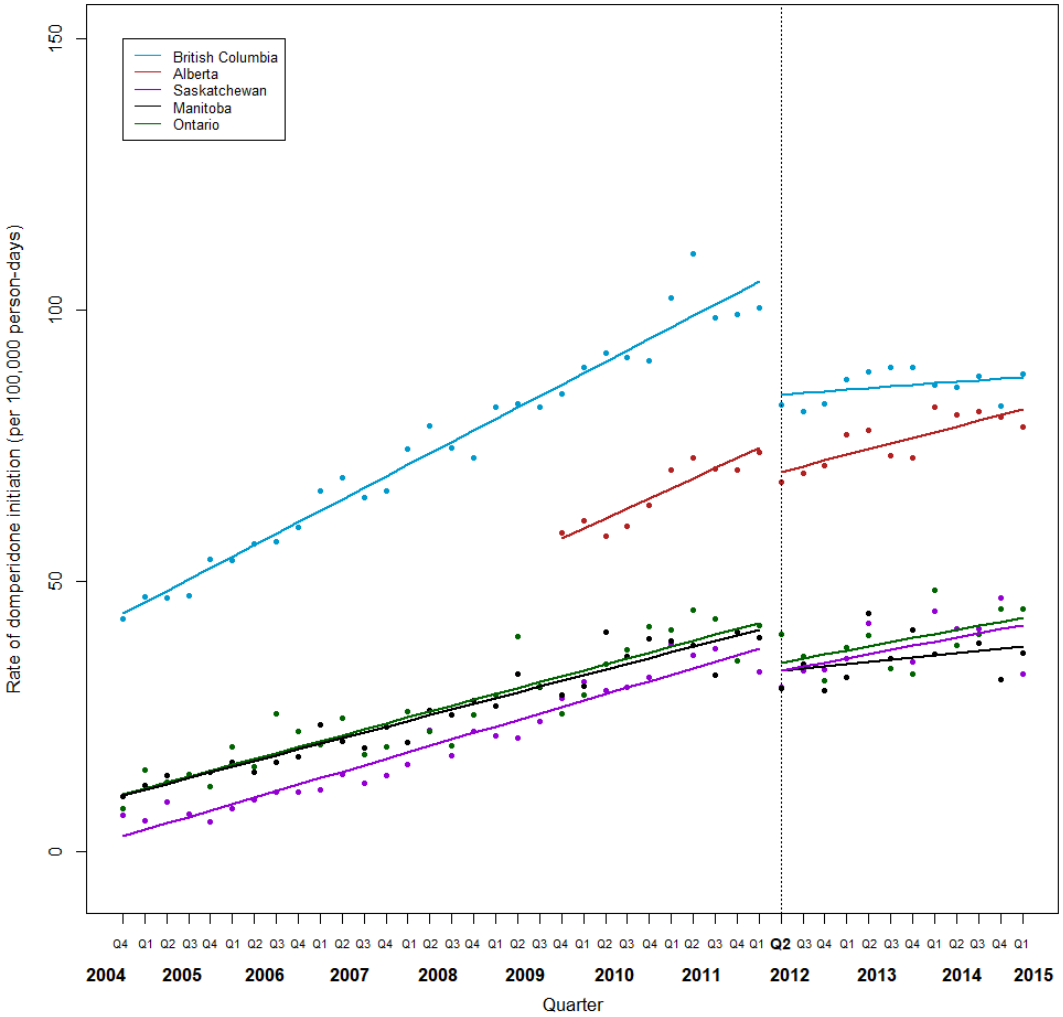

Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-21.1 (-26.5, -15.7	-1.8 (-2.5, -1.1)
Alberta	-5.4 (-10.7, -0.1)	-0.8 (-1.7, 0.1)
Saskatchewan	-4.8 (-9.5, -0.1)	-0.4 (-1.0, 0.2)
Manitoba	-7.9 (-12.1, -3.7)	-0.6 (-1.2, -0.1)
Ontario	-8.0 (-14.3, -1.8)	-0.3 (-1.1, 0.4)
All Provinces	-9.4 (-15.2, -3.6) I^2= 84.6% Tau^2= 37.12	-0.8 (-1.3, -0.3) I^2= 68.2% Tau^2= 0.243

* Impact is measured in initiators per 100,000 person-days.
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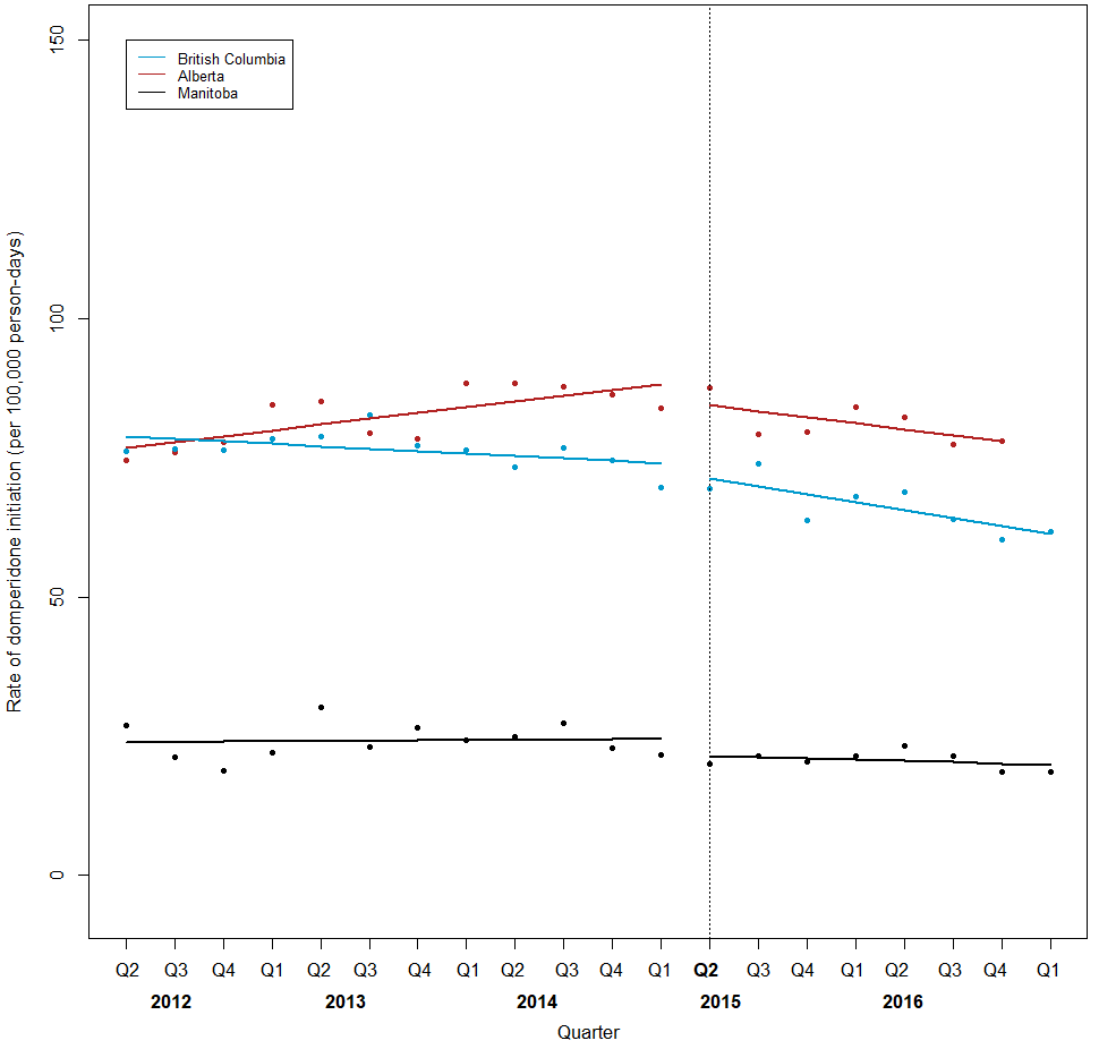

Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	-1.2 (-6.7, 4.3)	-1.0 (-2.0, 0.01)
Alberta	-2.6 (-9.5, 4.3)	-2.1 (-3.5, -0.7)
Manitoba	-2.8 (-8.1, 2.6)	-0.3 (-1.3, 0.7)
All Provinces	-2.7 (-5.5, 1.2) I^2= 0.0% Tau^2= 0.00	-1.0 (-2.0, -0.1) I^2= 53.1% Tau^2= 0.373

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses. Ontario was excluded from this analysis due to insufficient data available post-advisory.

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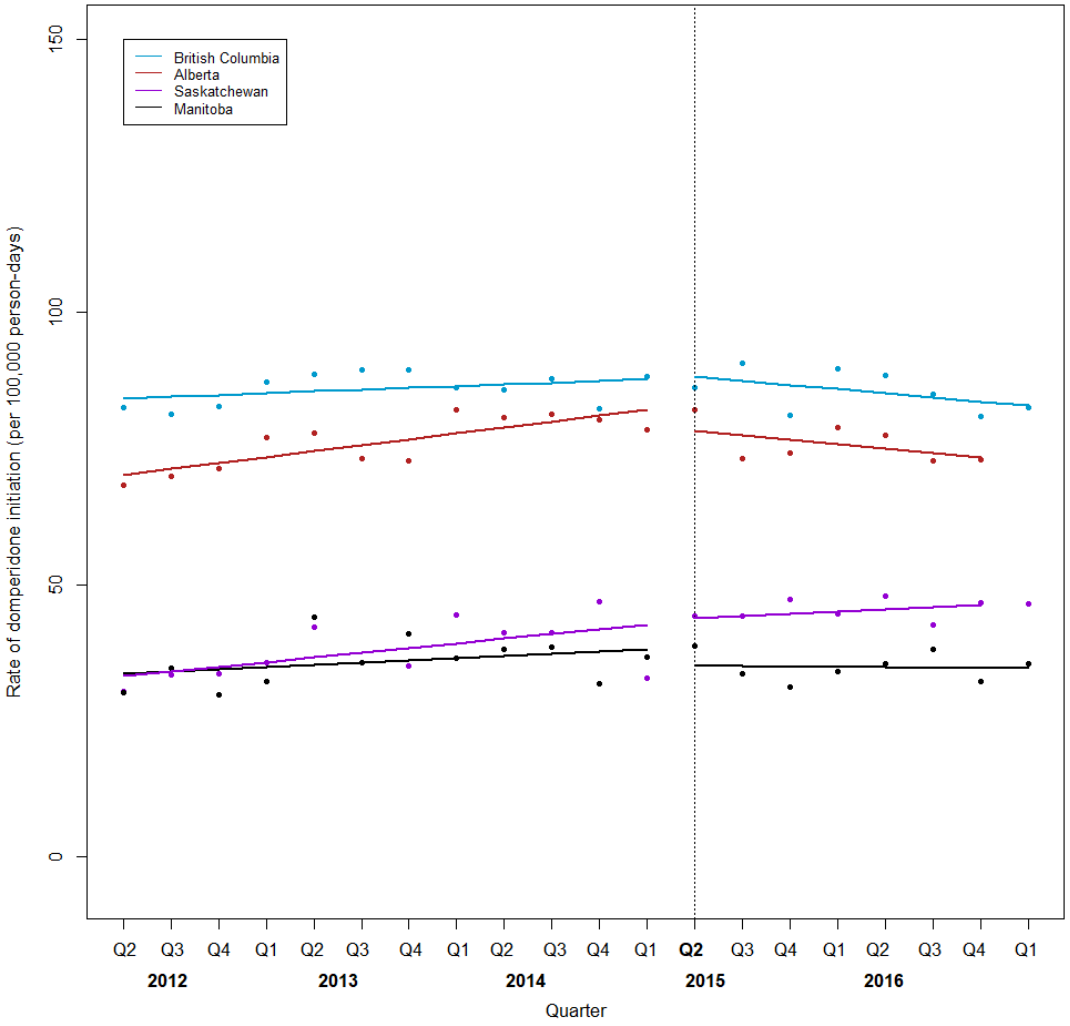

Province	Immediate Impact (95% CI)*	Change in Slope (95% CI)†
British Columbia	1.3 (-4.6, 7.1)	-1.1 (-2.2, -0.0)
Alberta	-2.9 (-8.7 2.9)	-1.9 (-3.1, -0.7)
Saskatchewan	0.8 (-4.6, 6.3)	-0.5 (-1.5, 0.5)
Manitoba	-3.0 (-9.6, 3.6)	-0.5 (-1.7, 0.7)
All Provinces	-0.8 (-3.7, 2.2) I^2= 0.0% Tau^2=0.00	-1.0 (-1.6, -0.3) I^2= 25.4% Tau^2= 0.108

Note: Ontario was excluded from this analysis due to insufficient data available post-advisory.

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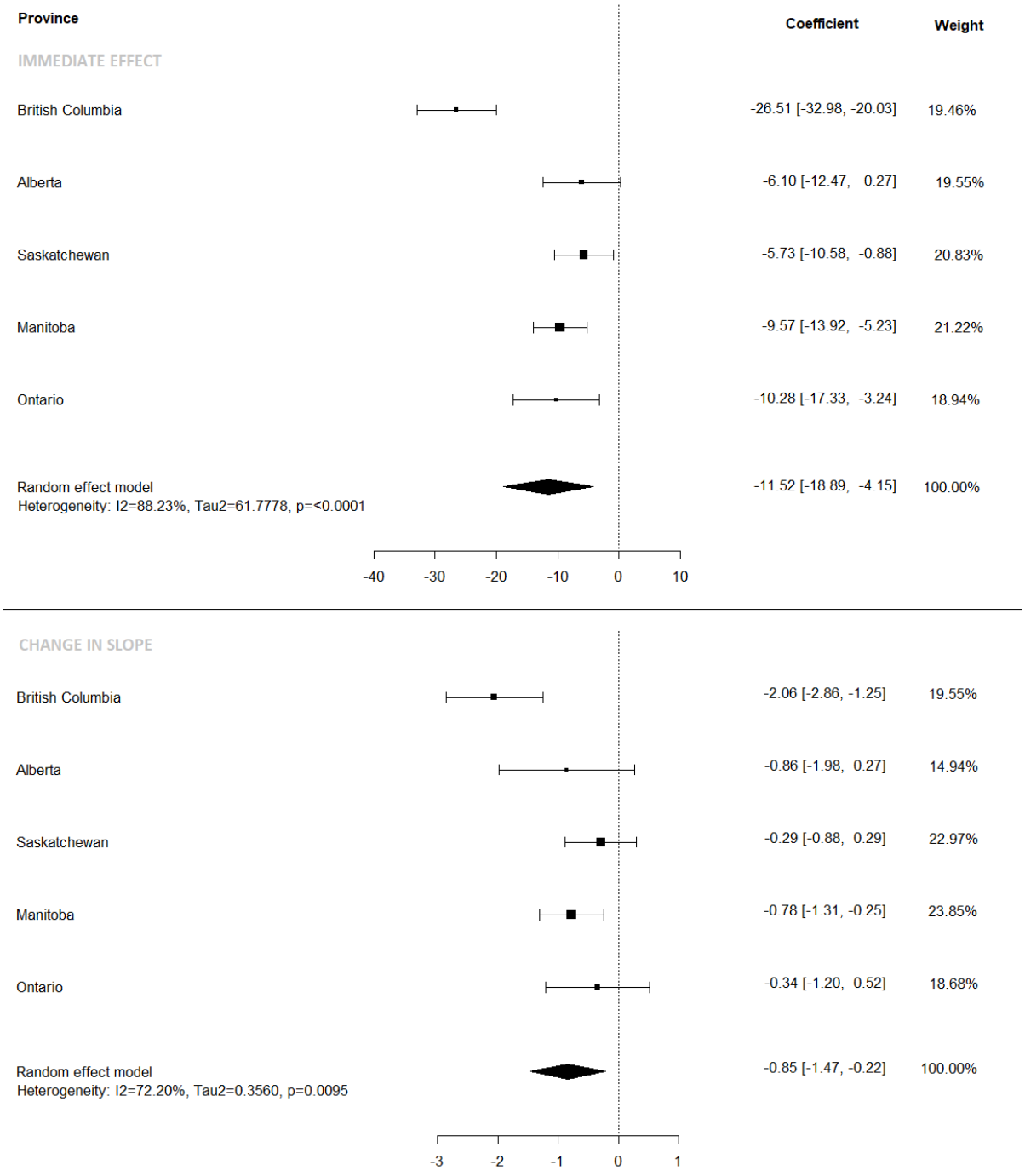

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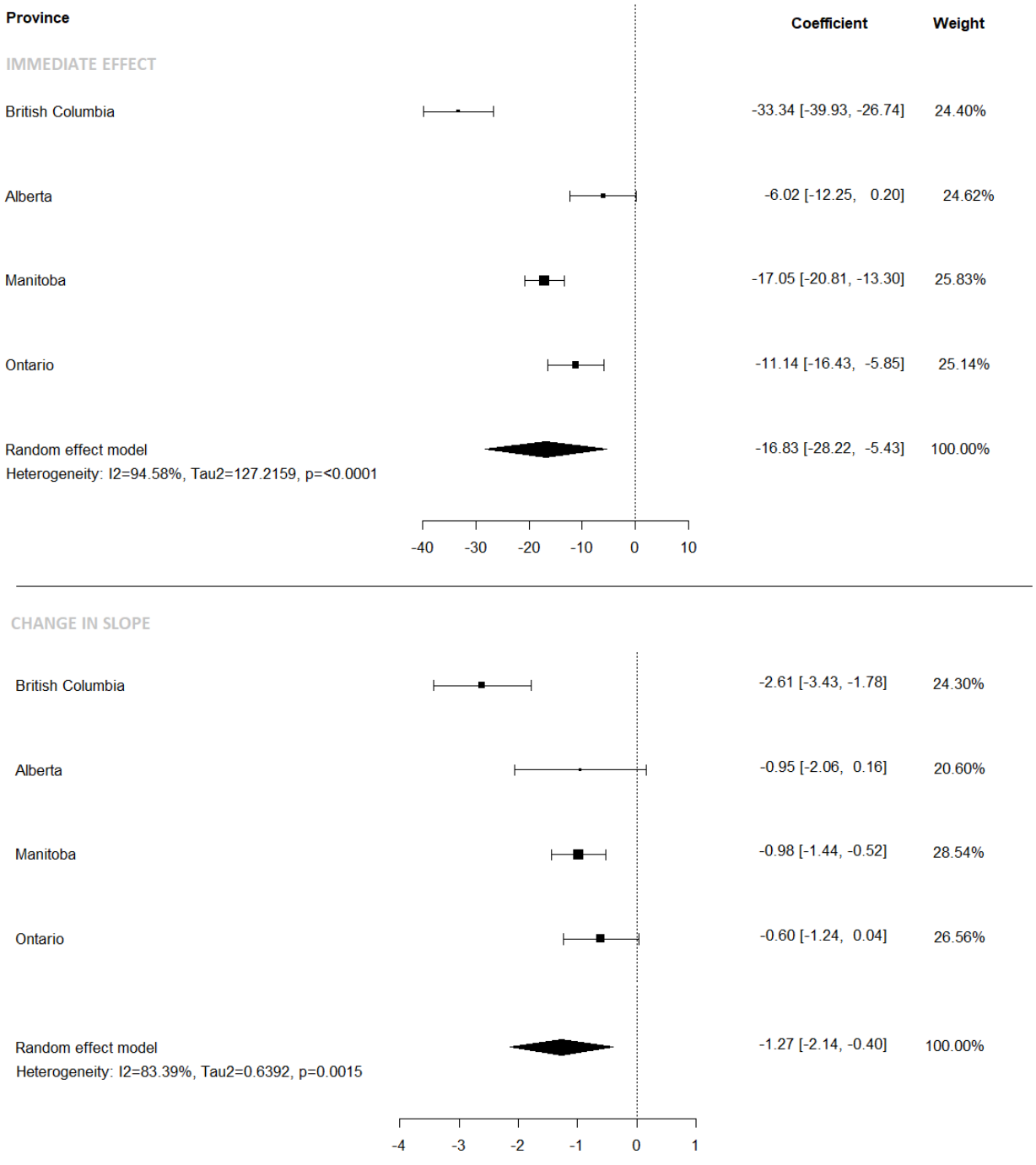

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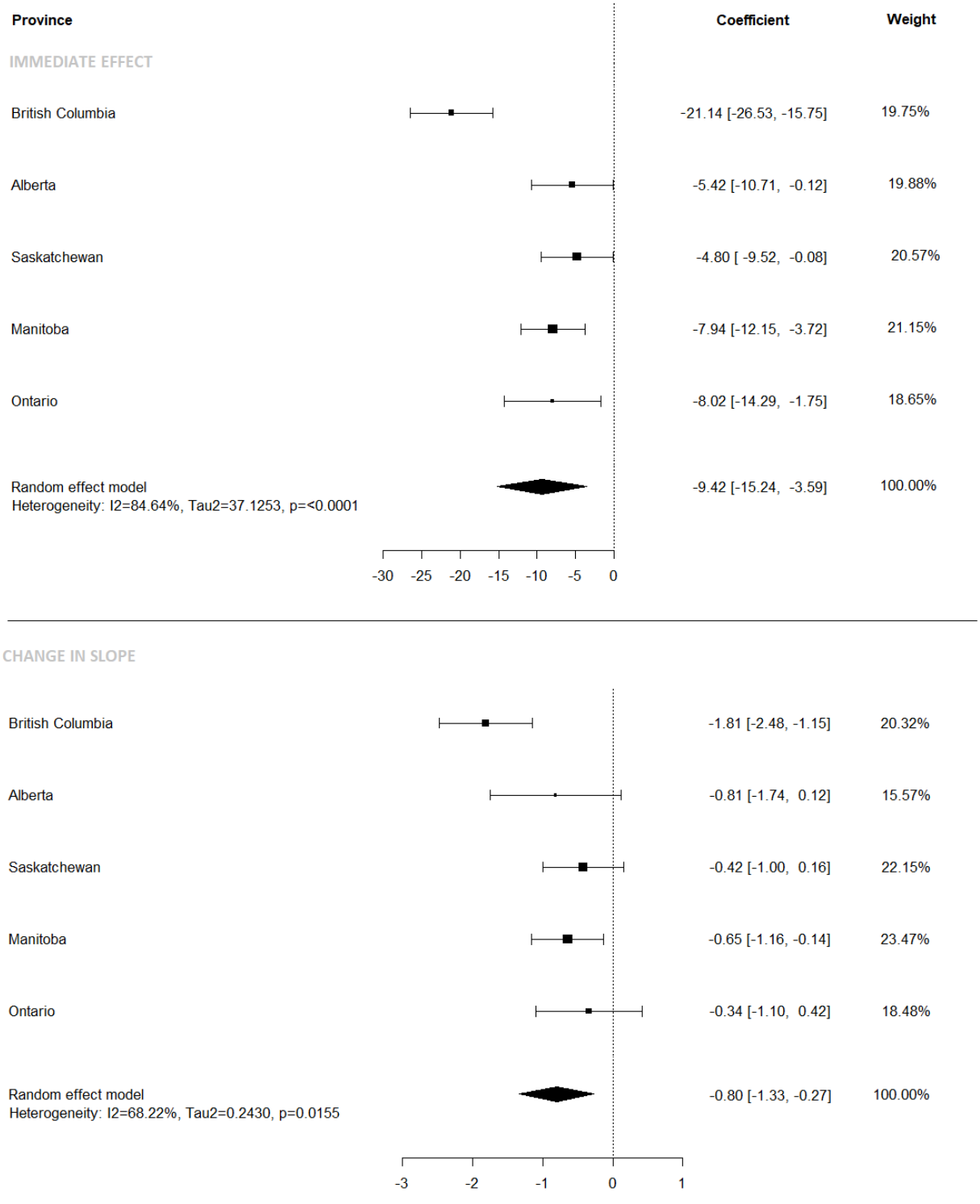

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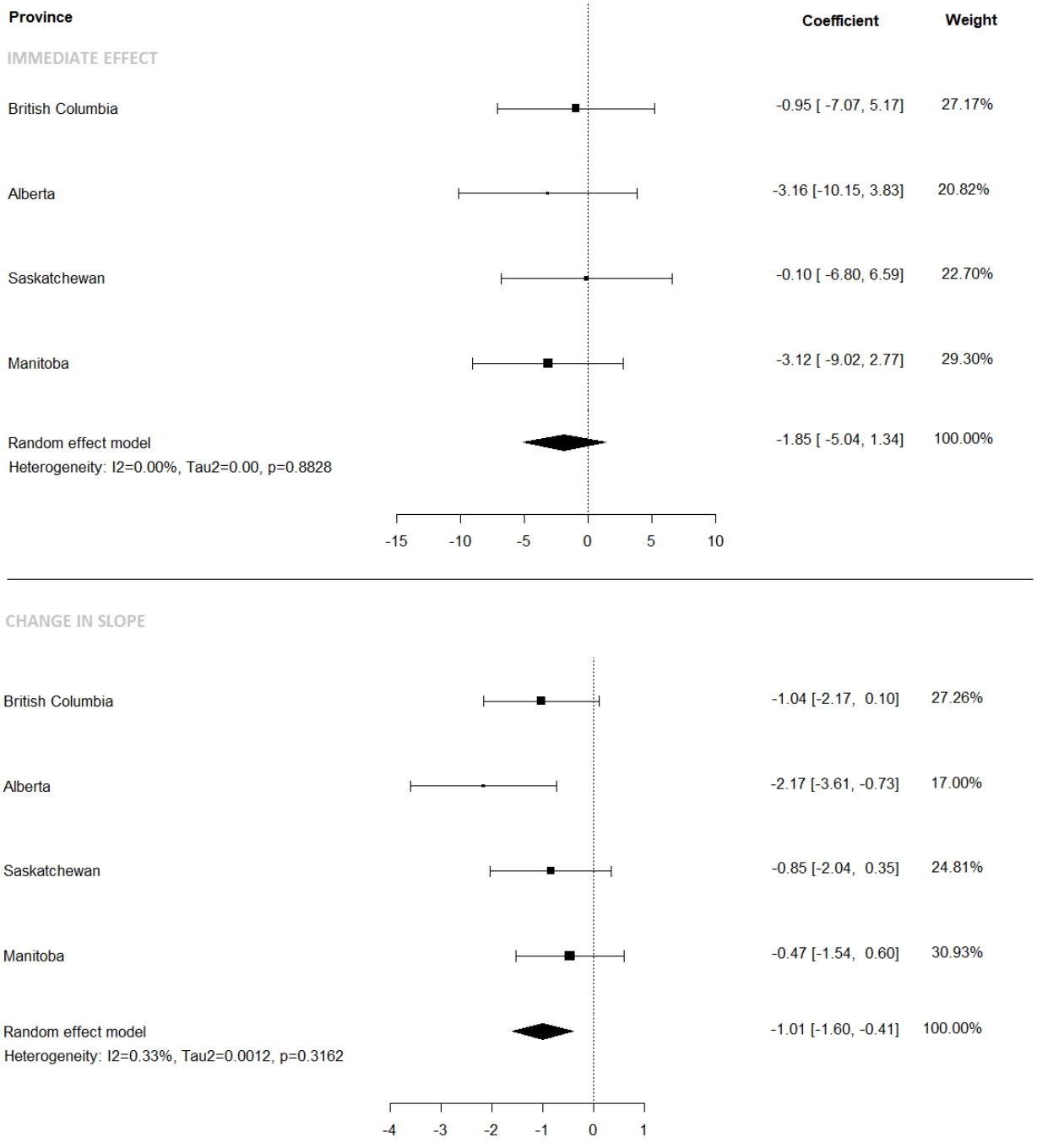

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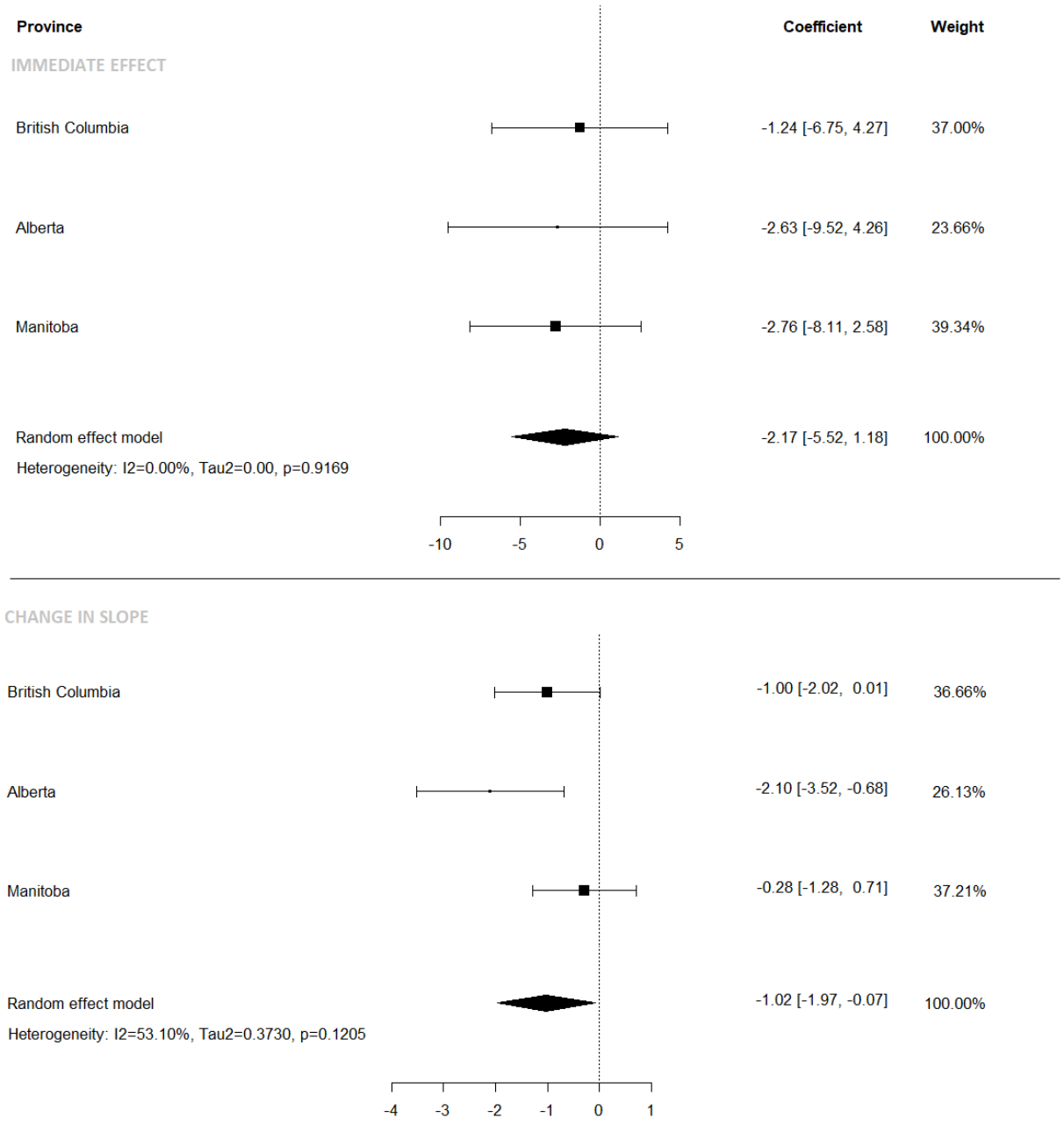

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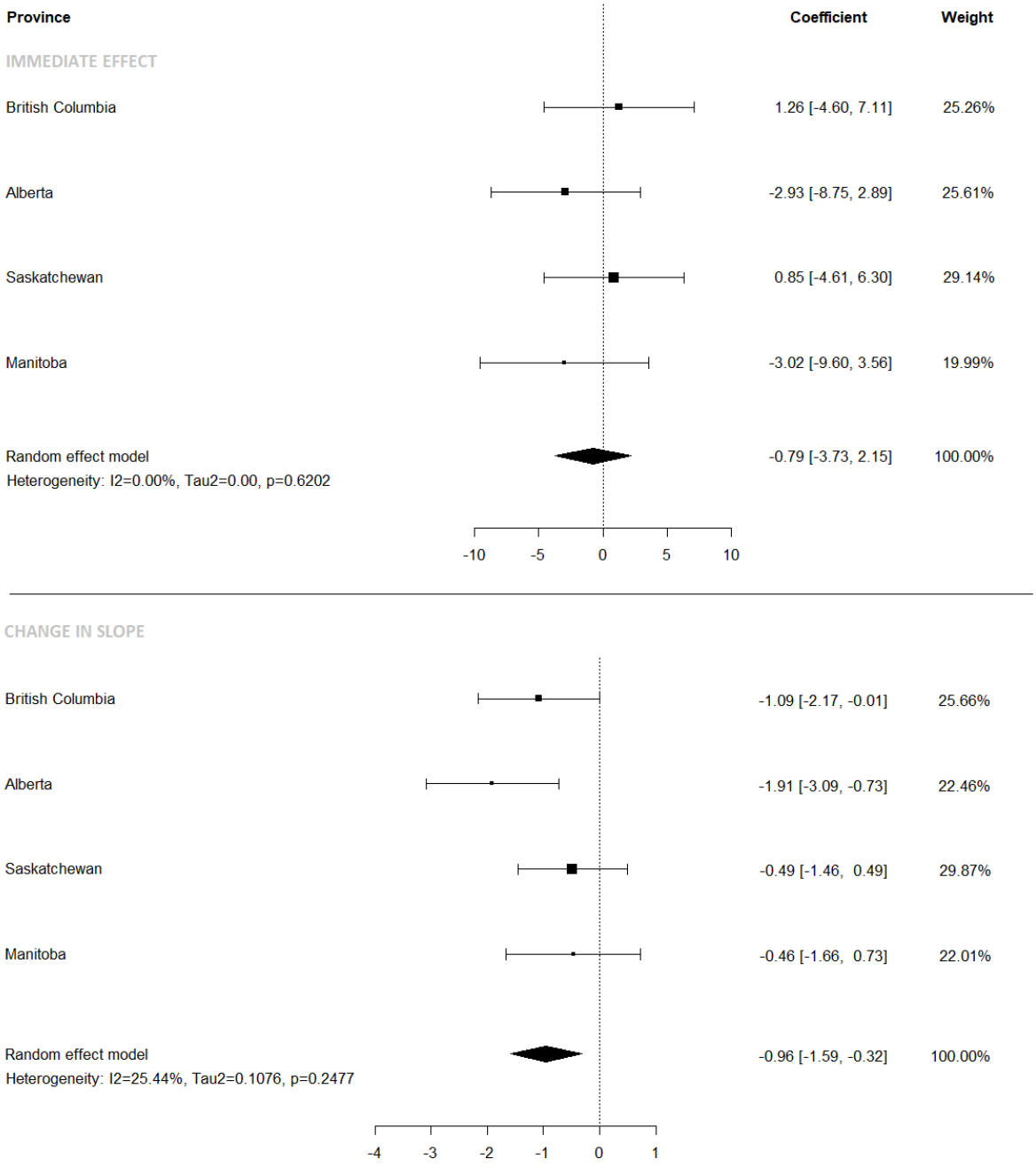

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Site	Start and end dates of data available per site	Databases				
		Population	Drug data and dispensing captured	Prescription drug claims	Hospitalization data	Outpatient billing data
British Columbia	April 1, 2004 – March 31, 2017	All	Dispensing (All)	PharmaNet	CIHI Discharge Abstract Database ICD-9: 1994-2002; ICD-10: Since 2002	Healthideas (ICD-9)
Alberta	April 1, 2009 – December 31, 2016	≥18 years	Dispensing (Public)	Pharmaceutical Information Network Dispenses	CIHI Discharge Abstract Database	Practitioner Claims (ICD-9)
Saskatchewan	April 1, 2004 – September 30, 2017	All	Dispensing (Public)	Prescription Drug Plan Historical Claims	CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10 Since Apr 2002:	Medical Services Branch (ICD-9)
Manitoba	April 1, 2004 – March 31, 2017	All	Dispensing (All)	Drug Program Information Network	Hospital Abstracts User Manual Database (prior to April 1, 2004) Discharge abstract data/Manitoba Abstract Data Elements Database (since April 1, 2004) ICD-9: Apr 1979 to Mar 2004 ICD-10: Since Apr 2004	Manitoba Health Medical- Physician Services (ICD-9)
Ontario	April 1, 2004 – December 31, 2015	Social assistance recipients	Dispensing (Public)	Ontario Drug Benefit Plan Database	CIHI Discharge Abstract Database ICD-9: Until Mar 2002; ICD-10: Since Apr 2002	Ontario Health Insurance Plan (OHIP) Claims History Database (Modified ICD-8)

Abbreviations: CIHI: Canadian Institute for Health Information; ICD: International Classification of Disease (1-3)

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Supplemental Table 2. Codes indicating non-arrhythmic cardiac event and acute life-threatening non-cardiac event.

	ICD 9	ICD 10
Non- arrhythmic cardiac causes		
Acute myocardial infarction	410.x	I21.x, I22.x
Acute ischemic heart disease	411.x, 413.x	I20.x, I23.x, I24.x
Myocarditis	422.x	I40.x, I41
Endocarditis	421.x	I33.x, I39
Aortic dissection/rupture	441.0, 441.1, 441.3, 441.5, 441.6	I71.0, I71.1, I71.3, I71.5, I71.8
Haemopericardium, cardiac tamponade	785.51, 423.0, 423.3	R57.0, I31.2
Acute life-threatening non-cardiac events		
Pulmonary Embolism	415.1	I26.x
Gastro-Intestinal Bleeding	530.21, 530.82, 531.0-531.2, 532.0-532.2, 533.0-533.2, 534.0-534.2, 456.0, 456.20, 578x	K22.8, K25.0-K25.2, K26.0-K26.2, K27.0-K27.2, K28.0-K28.2, I85.0, K92.0-K92.2
Peritonitis	567.x	K65.x
Stroke	430, 431, 433.x, 434.x	I60.x, I61.x, I62.x, I63.x
Metastatic cancer (1 month before)	196.x-198.x	C77.x-C79.x
Suicide	E950.x-E953.x, E954, E955.x, E956, E957.x, E958x	X60.x-X84.x
Pulmonary edema, distress syndrome, respiratory failure	518.4, 518.5x, 518.81, 518.82	J80, J96.0

Note: The conditions listed here are those for which events can be excluded without manual review. They are not meant to be an all-inclusive list of codes for the exclusion of potential events during manual review.
ICD: International Classification of Disease (1, 2)

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Supplemental Table 3. Operational definitions of patient characteristics.

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
Time interval between delivery and first domperidone prescription (days)	-	-	-	0-15 days 16-30 days 31-45 days > 45 days	-
Age	-	-	-	1: 15-19 2: 20-24 3: 25-29 4: 30-34 5: 35-39 6: 40-44 7: 45-55	Measured at cohort entry
	-	-	-	Continuous	Measured at cohort entry
Overweight or obese	278.0*	E66.x	-	0: No 1: Yes	Look back period is 5 years before index conception
Alcohol-related comorbidities	291.x* 303.x* 571.0* 571.1 571.2 571.3 535.3	F10x K70x K29.2 G31.2 G62.1 G72.1 I42.6 E24.4 K85.2 K86.0 Z50.2 Z71.4	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Income quintile	-	-	-	1st (highest) 2nd 3rd 4th 5th (lowest) Missing	Look back period is 5 years before cohort entry

Appendix 1, as supplied by the authors. Appendix to: Moriello C, Paterson JM, Reynier P, et al; the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Off-label postpartum use of domperidone in Canada: a multidatabase cohort study. *CMAJ Open* 2021. doi: 10.9778/cmajo.20200084. Copyright © 2021 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.

Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
Previous history of arrhythmia or conductions disorders	426.x* 427.x*	I45.x I49.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Any insertion of a pacemaker or defibrillator	V45.01 V45.02	Z95.0 Z95.810	-	0: No 1: Yes	Look back period is 5 years before cohort entry Note: please also use the following CCI procedure codes to identify insertion of pacemaker: 1.HB.53.x 1.HD.53.x 1.HZ.53.x
Hypertension	401.x* 402.x* 403.x* 404.x 405.x	I10 I11.x I12.x I13.x I15.x I16.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Cardiomyopathy	425.x	I42.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Left ventricular hypertrophy	429.3	I51.7	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Heart failure	428.x*	I50.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Ischemic heart disease	410.x* 411.x 412* 413.x* 414.x	I20.x I21.x I22.x I23.x I24.x I25.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Valvular heart disease	394.x* 395.x 396.x 397.0 397.1	I07.1 I07.2 I07.8 I34.x I35.x I36.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		I37.x I38 I39			
Asthma	493.x*	J45.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Diabetes	249.x 250.x*	E08.x E09.x E10.x E11.x E13.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hyperlipidemia	272.0* 272.1 272.2 272.3 272.4	E78.0x E78.1 E78.2 E78.3 E78.4 E78.5	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Depression	292.84 296.2x 296.3x 296.5x 298.0 311*	F32.x F33.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Epilepsy	345.x*	G40.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Cerebrovascular disease	430 431 432.x* 433.x 434.x 435.x* 436* 437.x* 438.x	I60.x I61.x I62.x I63.x I65.x I66.x I67.x I68.x I69.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		G45			
Peripheral vascular disease	440.x* 441.x 443.x 444.x 448.x	I70.x I71.x I73.x I74.x I78.x I79.x K55.1	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hepatic diseases	070.x 570 571.x* 572.x 573.x*	B16.x B17.x B18.x B19.x K70.x K71.x K72.x K73.x K74.x K75.x K76.x K77	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Renal diseases	250.4 403.x* 404.x 580.x* 581.x* 582.x 583.x 584.x* 585.x* 586 587	E11.2 E13.2 I12.x I13.x N00.x N01.x N02.x N03.x N04.x N05.x N06.x N07.x N08 N10	-	0: No 1: Yes	Look back period is 5 years before cohort entry

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
		N11.x N12 N15.x N16 N18.x N19.x			
Hypokalemia	276.8	E87.6	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hypocalcemia	275.41	E83.51	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Hypomagnesemia	275.2	E83.42	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Schizophrenia	295.x*	F20.x	-	0: No 1: Yes	Look back period is 5 years before cohort entry
Multi-fetal gestation	651.x*	O30.x	-	0: No 1: Yes	Measure during index pregnancy
Parity≥1	-	-	-	0: No 1: Yes 2: Unknown	Measure during index pregnancy Note: If this variable is not available in your dataset, please use the following DAD variables to define it: (1) Previous livebirths (2) Previous term deliveries (3) Previous pre-term deliveries
Gestational age	-	-	-	1. Continuous 2. Categorical as, <=37 weeks 38-42 weeks >=43 weeks	Measure at delivery
Caesarian section	669.7x	O82	-	0: No 1: Yes	Measure at delivery Please also use the following procedure codes to check for caesarean section,

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
					CCI: 5MD60* CCP: 86* ICD9: 74* ICD-10-CA: 5.MD.60*
Gestational diabetes	648.0x 648.8x	O24.4	-	0: No 1: Yes	Measure during index pregnancy
Hypertensive disorders of pregnancy	642.x	O13.x	-	0: No 1: Yes	Measure during index pregnancy
Postpartum hemorrhage	666.x*	O72.x	-	0: No 1: Yes	Measure during the time interval between (and including) the day of delivery and 14 days after delivery
Complications of anesthesia during labour and delivery	668.x	O74.x	-	0: No 1: Yes	Measure at delivery
Antepartum hemorrhage	641.x	O46.x	-	0: No 1: Yes	Measure during index pregnancy
Infections or sepsis after childbirth	670.x	O85 O86.x	-	0: No 1: Yes	Measure during the time interval between delivery and 14 days after delivery
Anti-arrhythmic drugs	-	-	C01AA05 C01EB10 C01BA C01BB C01BC C01BD C01BG C07AA C07AB C07AG C08DA C08DB	0: No 1: Yes	Any use in the year before conception and during pregnancy
Statins	-	-	C10AA C10BA C10BX	0: No 1: Yes	Any use in the year before conception and during pregnancy
Antihypertensive medications	-	-	C02 C03	0: No 1: Yes	Any use in the year before conception and during pregnancy

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
			C07 C08 C09		
Proton pump inhibitors	-	-	A02BC A02BD01 A02BD02 A02BD03 A02BD04 A02BD06 A02BD07 B01AC56 M01AE52	0: No 1: Yes	Any use in the year before conception and during pregnancy
Antipsychotic medications	-	-	N05A	0: No 1: Yes	Any use in the year before conception and during pregnancy
Hospitalized in the year before conception	-	-	-	0: No 1: Yes	Note: 1) Please extract this information from the Hospital Discharge Abstract Database (DAD). 2) The length of hospital stay should be at least 1 day
Number of clinic visit in the year before conception	-	-	-	Categorical as 0 1-3 4 and more	
Hospitalized during pregnancy	-	-	-	0: No 1: Yes	Note: 1) Please extract this information from the Hospital Discharge Abstract Database (DAD). 2) The length of hospital stay should be at least 1 day
Number of clinic visit during pregnancy	-	-	-	Categorical as 0 1-3	

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Covariate	ICD-9	ICD-10	ATC	Variable coding	Comments
				4 and more	

* Denotes codes used for outpatient data by sites with only 3-digit physician billing data. ICD: International Classification of Disease (1, 2).

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Supplemental Table 4. Baseline characteristics of deliveries overall and by use of domperidone in the six months immediately postpartum.

	Overall (n = 1,190,987)	Domperidone (n = 137,401)	No domperidone (n = 1,053,586)
Age (years), mean ± SE	28.6 ± 0.6	29.6 ± 0.4	28.5 ± 0.6
15-19, n (%)	54,061 (4.5)	2,811 (2.1)	51,250 (4.9)
20-24, n (%)	194,958 (16.4)	15,196 (11.1)	179,762 (17.1)
25-29, n (%)	352,403 (29.6)	37,625 (27.4)	314,778 (29.9)
30-34, n (%)	371,580 (31.2)	48,234 (35.1)	323,346 (30.7)
35-39, n (%)	179,903 (15.1)	26,979 (19.6)	152,924 (14.5)
40-44, n (%)	36,084 (3.0)	6,088 (4.4)	29,996 (2.9)
45-55, n (%)	1,998 (0.2)	468 (0.3)	1,530 (0.2)
Person days follow up (sum of person days for each outcome			
Composite of VT/SCD	207,301,730	24,138,820	183,162,910
VT	207,301,722	24,138,820	183,162,952
SCD	207,302,489	24,138,952	183,163,537
All-cause mortality	207,302,598	24,138,952	183,163,646
Comorbidities, n (%)			
Asthma	120,088 (10.1)	16,441 (12.0)	103,647 (9.5)
Hyperlipidemia	8,398 (0.7)	1,339 (1.0)	7,048 (0.7)
Epilepsy	1,1037 (0.9)	1,308 (1.0)	9,729 (0.9)
Cerebrovascular disease	5,176 (0.4)	736 (0.5)	4,440 (0.4)
Peripheral vascular disease	12,403 (1.0)	1,753 (1.3)	10,650 (1.0)
Hepatic disease	20,351 (1.7)	2,678 (2.0)	17,673 (1.7)
Renal disease	21,852 (1.8)	2,527 (1.8)	19,325 (1.8)
Schizophrenia	3,967 (0.3)	404 (0.3)	3,563 (0.3)
Hypokalemia	2,854 (0.2)	315 (0.2)	2,539 (0.2)
Hypocalcemia	63 (0.0)	*s*	60 (0.0)
Hypomagnesemia	85 (0.0)	10 (0.0)	75 (0.0)

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	Overall (n = 1,190,987)	Domperidone (n = 137,401)	No domperidone (n = 1,053,586)
Complication of pregnancy or childbirth, n (%)			
Gestational diabetes	48,554 (4.1)	8,798 (6.4)	39,756 (3.8)
Hypertensive disorders of pregnancy	88,351 (7.4)	14,750 (10.7)	73,601 (7.0)
Postpartum hemorrhage	116,351 (9.8)	14,861 (10.8)	101,490 (9.6)
Complications of anesthesia during labor and delivery	10,633 (0.8)	1,675 (1.2)	8,958 (0.9)
Antepartum hemorrhage	55,560 (4.7)	8,491 (6.2)	47,069 (4.5)
Infections or sepsis after childbirth	15,289 (1.3)	2,450 (1.8)	12,839 (1.2)
Hospitalized year before conception, n (%)			
No	1,045,263 (87.8)	125,510 (91.4)	919,753 (87.3)
Yes	145,724 (12.2)	11,891 (8.7)	133,833 (12.7)
Number of physician visits in year before conception, n (%)			
0	109,466 (9.2)	8,777 (6.4)	100,689 (9.6)
1 to 3	248,062 (20.8)	22,885 (16.7)	225,177 (21.4)
4 and more	833,459 (70.0)	105,739 (77.0)	727,720 (69.1)
Hospitalized during pregnancy, n (%)			
No	744,178 (62.5)	77,846 (56.7)	666,332 (63.2)
Yes	446,809 (37.5)	59,555 (43.3)	387,254 (36.8)
Number of clinic visits during pregnancy, n (%)			
0	3,861 (0.3)	138 (0.1)	3,723 (0.4)
1 to 3	14,709 (1.2)	383 (0.3)	14,326 (1.4)
4 and more	1,172,417 (98.4)	136,880 (99.6)	1,035,537 (98.3)

Abbreviations: SCD: sudden cardiac death; SE: standard error; VT: ventricular tachyarrhythmia; s: Suppressed to protect patient privacy
Note: women were permitted to contribute multiple observations to the study cohort

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Supplemental Table 5. Distribution of dosage of first domperidone treatment episode by province and calendar period.

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
British Columbia				
N of observations	63,608	37,682	15,207	10,719
Mean ± SD, mg	60.9 ± 26.4	65.7 ± 26.0	55.8 ± 24.4	51.3 ± 26.8
Median, mg	61	80	57	40
First quartile, mg	40	40	30	30
Third quartile, mg	80	80	80	71
Frequency, n (%)				
0-10 mg	163 (0.3)	74 (0.2)	47 (0.3)	42 (0.4)
11-20 mg	982 (1.5)	474 (1.3)	272 (1.8)	236 (2.2)
21-30 mg	10,321 (16.2)	3,329 (8.8)	3,546 (23.3)	3,446 (32.1)
31-40 mg	10,903 (17.1)	6,087 (16.2)	2,932 (19.3)	1,884 (17.6)
41-50 mg	2,296 (3.6)	1,279 (3.4)	539 (3.5)	478 (4.5)
51-60 mg	6,789 (10.7)	3,323 (8.8)	1,946 (12.8)	1,520 (14.2)
61-70 mg	2,767 (4.4)	1,754 (4.7)	580 (3.8)	433 (4.0)
71-80 mg	21,798 (34.3)	16,510 (43.8)	3,752 (24.7)	1,536 (14.3)
≥81 mg	7,589 (11.9)	4,852 (12.9)	1,593 (10.5)	1,144 (10.7)
Alberta				
N of observations	51,953	17,275	20.960	13,718
Mean ± SD, mg	63.3 ± 41.5	65.4 ± 39.9	63.9 ± 42.0	59.8 ± 42.3
Median, mg	60	62	60	56
First quartile, mg	40	40	40	30
Third quartile, mg	80	80	80	80
Frequency, n (%)				
0-10 mg	291 (0.6)	60 (0.3)	126 (0.6)	105 (0.8)
11-20 mg	926 (1.8)	245 (1.4)	416 (2.0)	265 (1.9)
21-30 mg	10,209 (19.7)	2,643 (15.3)	4,151 (19.8)	3,415 (24.9)

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	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
31-40 mg	10,871 (20.9)	3,837 (22.2)	4,394 (21.0)	2,640 (19.2)
41-50 mg	1,119 (2.2)	379 (2.2)	447 (2.1)	293 (2.1)
51-60 mg	4,659 (9.0)	1,455 (8.4)	1,810 (8.6)	1,394 (10.2)
61-70 mg	1,376 (2.6)	456 (2.6)	549 (2.6)	371 (2.7)
71-80 mg	14,357 (27.6)	5,464 (31.6)	5,576 (26.6)	3,317 (24.2)
≥81 mg	8,145 (15.7)	2,736 (15.8)	3,491 (16.7)	1,918 (14.0)
Manitoba				
N of observations	9,220	4,919	2,495	1,806
Mean ± SD, mg	57.9 ± 25.6	65.7 ± 25.2	50.1 ± 23.3	47.3 ± 22.4
Median, mg	60	80	40	38
First quartile, mg	30	40	30	30
Third quartile, mg	80	80	68	60
Frequency, n (%)				
0-10 mg	41 (0.4)	6 (0.1)	21 (0.8)	14 (0.8)
11-20 mg	177 (1.9)	51 (1.0)	68 (2.7)	58 (3.2)
21-30 mg	2,330 (25.3)	604 (12.3)	939 (37.6)	787 (43.6)
31-40 mg	1,191 (12.9)	697 (14.2)	303 (12.1)	191 (10.6)
41-50 mg	253 (2.7)	99 (2.0)	84 (3.4)	70 (3.9)
51-60 mg	1,231 (13.4)	571 (11.6)	385 (15.4)	275 (15.2)
61-70 mg	250 (2.7)	108 (2.2)	83 (3.3)	59 (3.3)
71-80 mg	2,744 (29.8)	2,189 (44.5)	370 (14.8)	185 (10.2)
≥81 mg	1,003 (10.9)	594 (12.1)	242 (9.7)	167 (9.2)
Ontario				
N of observations	3,110	1,781	1,126	203
Mean ± SD, mg	57.0 ± 28.7	59.1 ± 28.4	54.8 ± 29.0	51.0 ± 28.5
Median, mg	50	60	40	40
First quartile, mg	30	31	30	30
Third quartile, mg	80	80	80	69

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	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
Frequency, n (%)				
0-10 mg	20 (0.6)	11 (0.6)	*s*	*s*
11-20 mg	115 (3.7)	63 (3.5)	43 (3.8)	9 (4.4)
21-30 mg	776 (25.0)	355 (19.9)	345 (30.6)	76 (37.4)
31-40 mg	562 (18.1)	354 (19.9)	181 (16.1)	27 (13.3)
41-50 mg	94 (3.0)	49 (2.8)	*s*	*s*
51-60 mg	380 (12.2)	213 (12.0)	144 (12.8)	23 (11.3)
61-70 mg	91 (2.9)	53 (3.0)	30 (2.7)	8 (3.9)
71-80 mg	422 (13.6)	310 (17.4)	97 (8.6)	15 (7.4)
≥81 mg	650 (20.9)	373 (20.9)	243 (21.6)	34 (16.8)

Abbreviation: SD: standard deviation, S: suppressed to protect patient privacy.

Note: Saskatchewan does not have access to dosage data and was thus excluded from dosage analyses.

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Supplemental Table 6. Distribution of duration of first domperidone treatment episode by province and calendar period.

	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
British Columbia				
N of observations	63,608	37,682	15,207	10,719
Mean ± SD, days	44.2 ± 39.3	41.7 ± 38.0	47.8 ± 41.5	48.2 ± 39.9
Median, days	30	30	30	30
First quartile, days	21	17	25	28
Third quartile, days	56	50	60	60
Frequency, n (%)				
≤7 days	2,117 (3.3)	1,489 (4.0)	431 (2.8)	197 (1.8)
8-14 days	8,606 (13.5)	5,919 (15.7)	1,676 (11.0)	1,011 (9.4)
15-21 days	6,021 (9.5)	3,990 (10.6)	1,200 (7.9)	831 (7.8)
22-28 days	5,386 (8.5)	3,532 (9.4)	1,128 (7.4)	726 (6.8)
29-35 days	19,286 (30.3)	10,472 (27.8)	5,050 (33.2)	3,764 (35.1)
36-42 days	2,281 (3.6)	1,362 (3.6)	492 (3.2)	427 (4.0)
43+ days	19,911 (31.3)	10,918 (29.0)	5,230 (34.4)	3,763 (35.1)
Alberta				
N of observations	51,953	17,275	20.960	13,718
Mean ± SD, days	63.3 ± 41.5	65.4 ± 39.9	63.9 ± 42.0	59.8 ± 42.3
Median, days	30	30	30	30
First quartile, days	28	26	28	30
Third quartile, days	60	60	60	62
Frequency, n (%)				
≤7 days	1,236 (2.4)	446 (2.6)	483 (2.3)	307 (2.2)
8-14 days	4,452 (8.6)	1,649 (9.5)	1,776 (8.5)	1,027 (7.5)
15-21 days	3,660 (7.0)	1,190 (6.9)	1,536 (7.3)	934 (6.8)
22-28 days	3,712 (7.1)	1,361 (7.9)	1,485 ()7.1	866 (6.3)

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	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
29-35 days	18,976 (36.5)	6,211 (36.0)	7,591 (36.2)	5,174 (37.7)
36-42 days	15,21 (2.9)	479 (2.8)	614 (2.9)	428 (3.1)
43+ days	18,396 (35.4)	5,939 (34.4)	7,475 (35.7)	4,982 (36.6)
Saskatchewan				
N of observations	9,510	4,023	2,918	2,569
Mean ± SD, days	26.2 ± 15.7	26.4 ± 16.2	25.9 ± 15.6	25.9 ± 15.1
Median, days	20	22	20	20
First quartile, days	18	18	18	18
Third quartile, days	35	35	35	35
Frequency, n (%)				
≤7 days	597 (6.3)	297 (7.4)	176 (6.0)	124 (4.8)
8-14 days	1,309 (13.8)	596 (14.8)	390 (13.4)	323 (12.6)
15-21 days	3,005 (31.6)	1,071 (26.6)	970 (33.2)	964 (37.5)
22-28 days	1,822 (19.2)	913 (22.7)	541 (18.5)	368 (14.3)
29-35 days	577 (6.1)	145 (3.6)	208 (7.1)	224 (8.7)
36-42 days	506 (5.3)	232 (5.8)	139 (4.8)	135 (5.3)
43+ days	1,694 (17.8)	769 (19.1)	494 (16.9)	431 (16.8)
Manitoba				
N of observations	9,220	4,919	2,495	1,806
Mean ± SD, days	46.2 ± 38.9	42.6 ± 36.8	50.4 ± 41.1	50.4 ± 39.9
Median, days	30	30	30	30
First quartile, days	21	21	30	30
Third quartile, days	60	55	62	63
Frequency, n (%)				
≤7 days	304 (3.3)	205 (4.2)	68 (2.7)	31 (1.7)
8-14 days	993 (10.8)	632 (12.8)	202 (8.1)	159 (8.8)
15-21 days	1,090 (11.8)	740 (15.0)	198 (7.9)	152 (8.4)
22-28 days	387 (4.2)	217 (4.4)	108 (4.3)	62 (3.4)

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	All	Pre-Advisory (April 1, 2004 to March 2, 2012)	Between Advisories (March 3, 2012 to January 20, 2015)	Post-Advisory (January 21, 2015 to September 20, 2017)
29-35 days	2,825 (30.6)	1,315 (26.7)	871 (34.9)	639 (35.4)
36-42 days	492 (5.3)	300 (6.1)	112 (4.5)	80 (4.4)
43+ days	3,129 (33.9)	1,510 (30.7)	936 (37.5)	683 (37.8)
Ontario				
N of observations	3,110	1,781	1,126	203
Mean ± SD, days	35.8 ± 27.7	34.8 ± 27.4	36.7 ± 27.7	40.0 ± 29.0
Median, days	30	30	30	30
First quartile, days	22	20	28	28
Third quartile, days	33	30	34	49
Frequency, n (%)				
≤7 days	75 (2.4)	55 (3.1)	*s**	*s*
8-14 days	377 (12.1)	217 (12.2)	134 (11.9)	26 (12.8)
15-21 days	325 (10.5)	217 (12.2)	92 (8.2)	16 (7.9)
22-28 days	203 (6.5)	136 (7.6)	58 (5.2)	9 (4.4)
29-35 days	1,442 (46.4)	792 (44.5)	560 (49.7)	90 (44.3)
36-42 days	66 (2.1)	36 (36)	*s*	*s*
43+ days	622 (20.0)	328 (18.4)	238 (21.1)	56 (27.6)

Abbreviation: SD: standard deviation, s: suppressed to protect patient privacy.

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Supplemental Table 7. Interrupted time-series analyses modeling ln(prescription rate): Impact of 2012 Health Canada Advisory.

Province	Immediate Relative Change (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter	Relative Change in Slope (95% CI)	Relative Decrease in Slope of Geometric Mean of Initiation Rate per Quarter
All				
British Columbia	0.77 (0.71, 0.84)	30.0%	0.98 (0.97, 0.99)	2.5%
Alberta	0.93 (0.85, 1.001)	8.1%	0.99 (0.97, 1.001)	1.3%
Saskatchewan	0.78 (0.65, 0.94)	28.5%	0.96 (0.94, 0.98)	4.2%
Manitoba	0.74 (0.64, 0.86)	34.6%	0.97 (0.95, 0.99)	3.2%
Ontario	0.72 (0.58, 0.89)	38.9%	0.98 (0.95, 1.004)	2.3%
All Provinces	0.80 (0.72, 0.88) I^2= 67.8%	25.4%	0.98 (0.97, 0.98) I^2= 18.2%	2.5%
Dosage >30mg				
British Columbia	0.69 (0.63, 0.76)	45.1%	0.97 (0.95, 0.98)	3.5%
Alberta	0.92 (0.85, 1.001)	8.3%	0.99 (0.97, 1.0001)	1.5%
Manitoba	0.55 (0.46, 0.66)	80.7%	0.96 (0.94, 0.98)	4.3%
Ontario	0.64 (0.50, 0.81)	57.2%	0.97 (0.94, 0.99766)	3.2%
All Provinces	0.71 (0.53, 0.95) I^2= 93.2%	40.5%	0.97 (0.96, 0.98) I^2= 52.2%	3.0%
Duration >14 days				
British Columbia	0.78 (0.71, 0.85)	28.8%	0.97 (0.96, 0.98)	2.8%
Alberta	0.92 (0.86, 0.99675)	8.1%	0.99 (0.97, 0.999)	1.4%
Saskatchewan	0.75 (0.60, 0.93)	34.0%	0.95 (0.92, 0.98)	5.1%
Manitoba	0.72 (0.61, 0.85)	38.2%	0.97 (0.95, 0.99)	3.3%
Ontario	0.73 (0.58, 0.92)	36.6%	0.97 (0.95, 1.002)	2.6%
All Provinces	0.79 (0.71, 0.88) I^2= 68.8%	25.8%	0.97 (0.96, 0.98) I^2= 36.1%	2.7%

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Supplemental Table 8. Interrupted time-series analyses modeling ln(prescription rate): Impact of 2015 Health Canada Advisory.

Province	Immediate Relative Change (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter	Relative Change in Slope (95% CI)	Immediate Relative Decrease in Geometric Mean of Initiation Rate per Quarter
All				
British Columbia	0.99 (0.93, 1.05)	0.9%	0.99 (0.98, 1.001)	1.1%
Alberta	0.96 (0.89, 1.05)	3.7%	0.97 (0.96, 0.99)	2.6%
Saskatchewan	1.00 (0.87, 1.15)	0.1%	0.98 (0.96, 1.01)	1.9%
Manitoba	0.93 (0.80, 1.07)	8.1%	0.99 (0.96, 1.01)	1.2%
All Provinces	0.98 (0.93, 1.02) I^2=0.0%	2.3%	0.98 (0.98, 0.99) I^2=8.1%	1.6%
Dosage >30mg				
British Columbia	0.99 (0.92, 1.06)	1.4%	0.98 (0.97, 0.9979)	1.6%
Alberta	0.97 (0.89, 1.05)	3.1%	0.97 (0.96, 0.99)	2.6%
Manitoba	0.89 (0.71, 1.13)	11.8%	0.99 (0.94, 1.03)	1.5%
All Provinces	0.97 (0.92, 1.03) I^2= 0.0%	2.7%	0.98 (0.97, 0.99) I^2= 0.0%	1.9%
Duration >14 days				
British Columbia	1.01 (0.95, 1.09)	1.4%*	0.99 (0.97, 1.08)	1.3%
Alberta	0.96 (0.89, 1.04)	3.9%	0.98 (0.96, 0.99)	2.6%
Saskatchewan	1.02 (0.88, 1.18)	2.1%*	0.99 (0.96, 1.01)	1.4%
Manitoba	0.92 (0.76, 1.10)	9.0%	0.99 (0.95, 1.10)	1.4%
All Provinces	0.99 (0.94, 1.04) I^2= 0.0%	1.1%	0.98 (0.97, 0.99) I^2= 0.0%	1.7%

*Immediate increase in geometric mean of initiation rate.

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Supplemental Table 9. AIC values for linear and interrupted time series analysis models of the 2012 Health Canada advisories overall, for domperidone dose > 30 mg/day, and for durations of >14 days in the six months immediately postpartum in five Canadian provinces.

	Outcome: Prescription Rate		Outcome: ln(Prescription Rate)	
	Linear	Interrupted Time Series	Linear	Interrupted Time Series
All				
British Columbia	332.7	243.0	-47.0	-132.5
Alberta	124.9	122.8	-66.5	-70.2
Saskatchewan	242.1	234.6	-15.9	-55.3
Manitoba	259.1	215.8	-25.0	-78.7
Ontario	272.1	258.6	-10.2	-28.1
Dose > 30 mg/day				
British Columbia	350.4	242.4	-20.7	-123.7
Alberta	124.5	121.2	-65.7	-70.9
Manitoba	288.0	201.6	14.2	-64.0
Ontario	268.2	238.3	8.8	-17.2
Duration > 14 days				
British Columbia	317.1	228.4	-43.0	-130.0
Alberta	118.4	114.9	-67.2	-73.1
Saskatchewan	235.0	224.4	0.06	-39.0
Manitoba	251.2	221.6	-18.0	-59.8
Ontario	260.1	249.3	-6.7	-22.8

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Supplemental Table 10. AIC values for linear and interrupted time series analysis models of the 2015 Health Canada advisories overall, for domperidone dose > 30 mg/day, and for durations of >14 days in the six months immediately postpartum in four Canadian provinces.

	Outcome: Prescription Rate		Outcome: ln(Prescription Rate)	
	Linear	**Interrupted Time Series**	**Linear**	**Interrupted Time Series**
All				
British Columbia	110.5	111.3	-72.4	-71.6
Alberta	117.4	109.4	-51.2	-59.4
Saskatchewan	121.4	123.4	-33.8	-31.4
Manitoba	110.3	113.2	-37.6	-34.9
Dose > 30 mg/day				
British Columbia	107.9	108.0	-62.2	-63.1
Alberta	116.0	108.6	-51.4	-58.9
Manitoba	102.3	105.5	-23.9	-21.3
Duration >14 days				
British Columbia	108.9	110.4	-69.0	-67.5
Alberta	112.7	104.5	-51.8	-60.1
Saskatchewan	112.3	115.1	-33.9	-30.6
Manitoba	113.7	117.2	-29.5	-26.1

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Supplemental Table 11. Number of events and incidence rates of VT, SCD, and all-cause mortality in the six months immediately postpartum across the five participating provinces (2004-2017).

Endpoint	Number of events	Number of person-years of follow-up*	Incidence Rate (95% CI) †
Composite of VT/SCD	22	568,618.38	0.39 (0.25, 0.59)
VT	13	568,618.49	0.23 (0.13, 0.39)
SCD	10	568,620.46	0.18 (0.09, 0.33)
All-cause mortality	168	568,620.76	2.95 (2.54, 3.44)

Abbreviations: CI: confidence interval; SCD: sudden cardiac death; VT: ventricular tachyarrhythmia.
*Number of deliveries with livebirths: 1,190,987
†Incidence rates are expressed as event per 10,000 person-years.

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