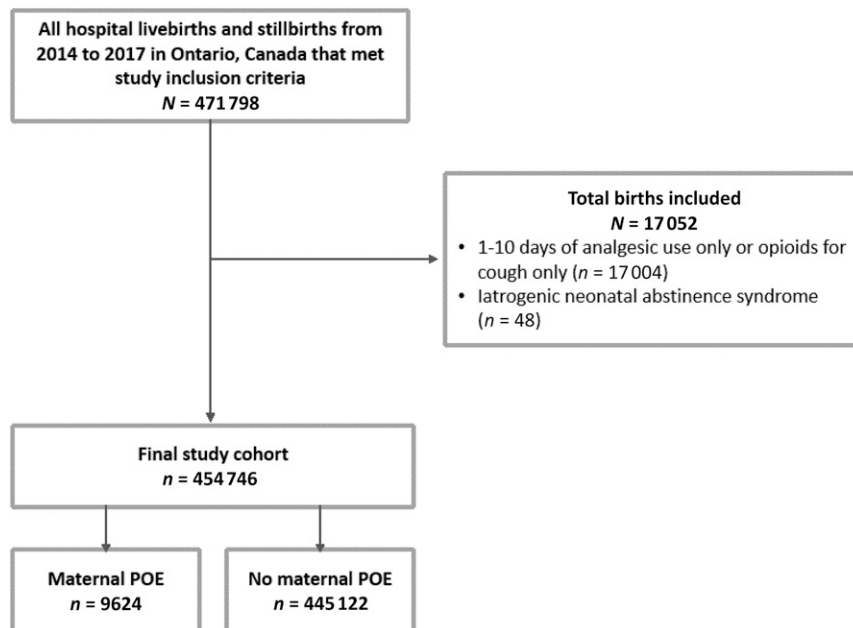


## Supplemental Information



### SUPPLEMENTAL FIGURE 2

Flowchart of the cohort formation of hospital livebirths and stillbirths in Ontario, 2014–2017.

**SUPPLEMENTAL TABLE 5** Technical Definitions of Comparative Measures of Opioid Use in Pregnancy From Existing Studies Using Administrative Data

Study (Country)	Measure	Data Source(s)	Technical Definition	Technical Definition Used to Replicate Measure
Haight et al <sup>3</sup> 2018 (United States)	Maternal OUD at delivery hospitalization	Maternal hospital records	Opioid dependence ICD-9-CM 304.00–304.03, 304.70–304.73 and nondependent opioid abuse ICD-9-CM 305.50–305.53	ICD-10 F11 at delivery hospitalization
Kozhimannil et al <sup>49</sup> 2019 (United States)	Maternal OUD (dependence or poisoning) at delivery hospitalization and no adverse effects in therapeutic opioid use	Maternal hospital records	OUD ICD-9 304.00, 304.01, 304.02, 305.50, 305.51, 305.52, 965.00, 965.01, 965.02, 965.09. Excluded ICD-9 304.03, E850.0, E850.1, E850.2, E935.0, E935.1, E935.2	ICD-10 F11, T40.00, T40.1-T40.4, T40.6 not Y45 at delivery hospitalization
Krans et al <sup>50</sup> 2019 (United States)	Maternal OUD in pregnancy (conception to birth)	Maternal hospital records	OUD ICD-9 304.0X, 304.7X, 305.50, 305.51, 305.52	ICD-10 F11 during pregnancy
Patrick et al <sup>11</sup> 2015 (United States)	Any prescription opioid dispensed in pregnancy (analgesic or OAT)	Outpatient prescription claims	Any prescription opioid fill	1+ prescription opioid analgesic or OAT during pregnancy
Sujan et al <sup>47</sup> 2019 (Sweden)	Any prescription opioid analgesic dispensed in pregnancy (excluding exposure to OAT)	Prescribed Drug Register	Any prescription opioid analgesic for pain fill (excluding OAT prescriptions)	1+ prescription opioid analgesic dispensed during pregnancy (excluding OAT prescriptions)
Falk et al <sup>48</sup> 2017 (Canada)	Any prescription opioid analgesic dispensed in pregnancy	Drug Program Information Network	Any prescription opioid fill (excluding methadone)	1+ prescription opioid analgesic dispensed during pregnancy
Filteau et al <sup>4</sup> 2018 (Canada)	NAS	Newborn hospital records	ICD-10 P96.1	ICD-10 P96.1

Definitions were replicated as closely as possible; however, in some cases, there was not a direct conversion from ICD-9 to ICD-10. ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

**SUPPLEMENTAL TABLE 6** Methods Used in the Current Study to Describe Opioid Exposure and Other Variables

Measure	Definition	Timing	Data Source
Maternal POE	Any prescription opioid during pregnancy or opioid-related hospital care during pregnancy or NAS	Conception to delivery; newborn birth episode; readmission within 14 d of life	NMS, DAD, NACRS, OHMRS
Maternal prenatal prescription opioid use			
Any maternal prenatal prescription opioid	Any prescription dispensed for 11+ days of an opioid analgesic or 1+ days for methadone or buprenorphine for OAT	Conception to delivery	NMS ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = NMS">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = NMS</a> )
Any maternal prenatal prescription for opioid analgesic for pain	11+ cumulative days supplied of opioid analgesics for pain (morphine, codeine, oxycodone, hydrocodone, hydromorphone, meperidine, tramadol, methadone, buprenorphine, fentanyl, tapentadol)	Conception to delivery	NMS
Any maternal prenatal prescription for OAT	1+ prescription for methadone or buprenorphine for OAT	Conception to delivery	NMS
Any maternal prescription for methadone	1+ prescription for methadone for OAT	Conception to delivery	NMS
Any maternal prescription for buprenorphine	1+ prescription for buprenorphine for OAT		
Opioid-related hospital care			
Maternal opioid-related hospital care	ICD-10 F11, T40.0-T40.4, T40.6, DSM-5 304.00, 305.50, Y45.0	2 y before conception; 6 mo before conception; pregnancy (conception to discharge of the delivery record; Pregnancy not including delivery record (conception to the day before delivery admission); delivery record (admission to discharge of the delivery record)	DAD ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = DAD">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = DAD</a> ), NACRS ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = NACRS">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = NACRS</a> ), OHMRS ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = OHMRS">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = OHMRS</a> )
Newborn hospital records with NAS	ICD-10 P96.1: withdrawal from maternal drugs of addiction, ICD-10 P04.4: infant affected by maternal drugs of addiction	Newborn birth episode; readmission within 14 d of life	DAD
OUD (hospital care)	ICD-10 F11 or DSM-5 304.00, 305.50	Conception to delivery	NACRS, DAD, OHMRS
OUD (hospital care or prescription)	ICD-10 F11 OR DSM-5 304.00, 305.50 OR 1+ prescription for methadone or buprenorphine for OAT	Conception to delivery	NACRS, DAD, OHMRS, NMS
Maternal substance use-related hospital care		2 y before conception; 6 mo before conception; pregnancy (conception to discharge of the delivery record; Pregnancy not including delivery record (conception to the day before delivery admission); delivery record (admission to discharge of the delivery record)	
Any tobacco	ICD-10 F17, T65.2, Z72.0, Z71.6, OHIP DXCODE 305		DAD, NACRS, OHIP ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = OHIP">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = OHIP</a> )
Any alcohol	OHIP DXCODE: 291, 303, ICD10CA G62.1, G31.2, G72.1, I42.6, K29.2, K85.2, K70, K86.0, E24.4, F10, X45, X65, Y15, T51, R78.0, Y90, Y91, Z72.1, Z71.4		DAD, NACRS, OHIP
Any nonopioid use	Any cannabis, any cocaine, any multidrug, ICD-10 F13, F15, T43, F16, T40.8, T40.9, F18		DAD, NACRS, OHIP
Any cannabis	ICD-10 F12, T40.7		DAD, NACRS, OHIP
Any cocaine	ICD-10 F14, T40.5, R78.2		DAD, NACRS, OHIP
Any multidrug use	ICD-10 F19		DAD, NACRS, OHIP

**SUPPLEMENTAL TABLE 6** Continued

Measure	Definition	Timing	Data Source
<b>Social factors</b>			
Social assistance recipient	Ontario Drug Benefit program as proxy. Plan code: Ontario Disability Support Program OR Ontario Works	2 y before conception; pregnancy (date of conception to discharge of the delivery record)	ODB ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = ODB">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = ODB</a> )
Homelessness as noted on health care records	The record meets any following criteria: (1) DAD: ICD-10 Z590 or homeless = Y or postal code = XX, (2) NACRS: ICD-10 Z590 or residence type = homeless or postal code = XX, (3) OMHRS: usual residence = homeless (with or without shelter)	2 y before conception; pregnancy (date of conception to discharge of the delivery record)	DAD, NACRS, OMHRS
Health care received while involved with the criminal justice system as noted on health care records	The record meets any following criteria: (1) institution in OHIP with type= Correctional Centre, (2) institution in DAD with type= Correctional Centre and referred from law enforcement, (3) institution in NACRS with type= Correctional Centre and referred from a legal service, (4) Last 4 digits of X65 in OMHRS with type= Correctional Centre.	2 y before conception; pregnancy (date of conception to discharge of the delivery record)	OHIP, DAD, NACRS, OMHRS
Violence-related health care event	ICD-10: X85-X99, Y00-Y09, Y871, T740-T749	2 y before conception; pregnancy (date of conception to discharge of the delivery record)	NACRS, DAD
<b>Demographics</b>			
Maternal age at first delivery (y)		Index delivery	MOMBABY ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = MOMBABY">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = MOMBABY</a> )
Maternal age at current delivery (y)		Index delivery	MOMBABY
3+ previous livebirths	No. previous livebirths derived from all mom's records	Index delivery	MOMBABY
Area-level low-income (quintile 1)	Groups: Q1 (lowest) to Q5 (highest), missing (represents suppressed) was added to Q1	Conception	RPDB ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = RPDB">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = RPDB</a> ), PCCF+
Rural residence	<10 000 residents	Conception	PCCF+
Immigrant to Canada		Conception	IRCC Permanent Resident Database ( <a href="https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = CIC">https://datadictionary.ices.on.ca/Applications/DataDictionary/Library.aspx?Library = CIC</a> )
<b>Prepregnancy morbidity</b>			
High medical comorbidities	Johns Hopkins ADG score of 10+	2 y preconception	DAD, NACRS, OHIP
Pain (low back pain, joint pain, migraine/headache, rheumatoid arthritis, fibromyalgia, joint pain, chronic pancreatitis, peripheral neuropathy, sickle cell disease and renal calculus)	ICD-10: M54.5 (low back pain) or Abdominal pain (R10), G43, G44 (migraine/headache), rheumatoid arthritis (ICES-derived cohort), M79.7 (fibromyalgia), M25.5, M25.50-M25.59, K07.63, K07.69 (joint pain), K86.0, K86.1 (chronic pancreatitis), E10.41, E11.41, E13.41, E14.41 (peripheral neuropathy), D57.1, D57.2, D57.3, D57.8 (sickle cell disease), N20.0, N20.1, N20.2, N20.9, N21.0, N21.1, N21.8, N21.9, N22.0, N22.8 (renal calculus)	2 y preconception	DAD, NACRS
Prepregnancy diabetes	Database: DAD, OHIP, ICD-10: E10, E11, E13, E14 or OHIP: 250	2 y preconception	DAD, OHIP
Chronic hypertension	ICD-10: I10, I15, O10, O11 or OHIP: 401	2 y preconception	DAD, OHIP
Asthma (5 y preconception)		5 y preconception	ICES-derived cohort
Any mental health and addiction hospitalization or ED visit	ICD-10 (DAD/NACRS) DX10CODE1 = F06-F99 or DX10CODE2-DX10CODE10 = X60-X84,	2 y preconception, pregnancy	DAD, NACRS, OMHRS

SUPPLEMENTAL TABLE 6 Continued

Measure	Definition	Timing	Data Source
	Y10-Y19, Y28 when DX10CODE1 is not F06-F99; ICD-9-CM (OMHRS). Any OMHRS (including missing, except for 290.X, 294.X in primary diagnosis). If primary diagnosis missing and provisional = 17, exclude; OMHRS before 2016–2017, any OMHRS (including missing, except for 290.X, 294.X in primary diagnosis). If primary diagnosis missing and provisional = 2, exclude		
Pregnancy-related variables			
No fetal ultrasound by 20 wk	OHIP FEECODE: J157-J160, J457–460	Conception to delivery	OHIP
No prenatal care visit in the first trimester	Fee code in (A, K, P003, P004, P005) and billed by a physician with specialty code 00 (General Practice), or Code 20 (Obstetrics and Gynecology)	Conception to delivery	OHIP
Multiple births	Multiple gestation	Index delivery	DAD, MOMBABY
Cesarean delivery	CCI code 5MD60	Index delivery	DAD
Assisted vaginal delivery	CCI code 5MD53, 5MD54, 5MD55	Index delivery	DAD
Stillbirth	Any stillbirth delivery by mother from 20 wk gestation onward	Index delivery	DAD, MOMBABY
Livebirths			
Female sex	Infant sex	Index delivery	MOMBABY
Gestational age at birth (wk)	Newborn gestational wks (if missing gestational weeks from the maternal records was used)	Index delivery	MOMBABY
Small for gestational age birth weight <10th percentile	Same-sex, same-gestational-age birth weight below the 10th percentile	Index delivery	DAD, MOMBABY
Small for gestational age birth weight less than fifth percentile	Same-sex, same-gestational-age birth weight below the fifth percentile	Index delivery	DAD, MOMBABY
NICU admission	Admission to the NICU	Newborn birth episode	DAD
Infant's length of stay of the birth episode	No. days from birth to discharge	Newborn birth episode	DAD
Infant discharged to social services at birth	Discharged or transferred to other ambulatory care, palliative care or hospice, addiction treatment center, jails, infants and children discharged or detained by social services) or social services or Z622 OR Z762	Newborn birth episode	DAD

ADG, Aggregated Diagnosis Group; DAD, Discharge Abstract Database; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; IRCC, Immigration, Refugees and Citizenship Canada Permanent Resident; NACRS, National Ambulatory Care Reporting System; NMS, Narcotic Monitoring System; ODB, Ontario Drug Benefit; OHIP, Ontario Health Insurance Plan; OMHRS, Ontario Mental Health Reporting System.

**SUPPLEMENTAL TABLE 7** Maternal and Neonatal Characteristics by ICD-10 Diagnostic Codes P96.1 and P04.4

Characteristic	P96.1, <i>n</i> = 3239	P04.4, <i>n</i> = 1234
Of the mother		
Any documented maternal opioid use in the current pregnancy <sup>a</sup>	2391 (73.8)	597 (48.4)
Maternal prescription opioid use in the current pregnancy		
Any prescription opioid	2233 (69.0)	514 (41.7)
Opioid analgesic for pain, 11+ days	391 (12.1)	100 (8.1)
OAT	1938 (59.8)	427 (34.6)
Methadone	1668 (51.5)	331 (26.8)
Buprenorphine	330 (10.2)	113 (9.2)
Opioid-related hospital care in the current pregnancy		
Maternal opioid-related care, conception to birth	898 (27.7)	283 (22.9)
Maternal opioid-related care, pregnancy (excluding delivery)	196 (6.1)	54 (4.4)
Maternal opioid-related care, delivery hospitalization	785 (24.2)	256 (20.7)
Newborn opioid-related care, P96.1	3239 (100.0)	171 (13.9)
Newborn opioid-related care, P04.4	171 (5.3)	1234 (100.0)
OUD (hospital or OAT prescription)	2151 (66.4)	526 (42.6)
Mental health and addiction-related hospital care within 2 y preconception, up to birth		
Any opioid	1158 (35.8)	361 (29.3)
Any tobacco	449 (13.9)	176 (14.3)
Any alcohol	337 (10.4)	170 (13.8)
Any nonopioid or multidrug use	806 (24.9)	356 (28.8)
Any cannabis	173 (5.3)	95 (7.7)
Any cocaine	193 (6.0)	99 (8.0)
Any multidrug use	511 (15.8)	193 (15.6)
Any mental health and addiction hospitalization or ED visit	914 (28.2)	347 (28.1)
Demographics around the current pregnancy		
Maternal age at first delivery, y, mean (SD)	22.5 (5.3)	21.9 (5.3)
Maternal age at current birth, y, mean (SD)	28.2 (5.3)	27.0 (5.7)
Area-level low-income quintile	1538 (47.5)	612 (49.6)
Rural residence	714 (22.0)	337 (27.3)
Immigrant to Canada	62 (1.9)	32 (2.6)
3+ previous livebirths	697 (21.5)	261 (21.2)
Social variables within 2 y preconception, up to birth		
Social assistance recipient	2273 (70.2)	745 (60.4)
Homelessness	107 (3.3)	49 (4.0)
Involvement in the criminal justice system	325 (10.0)	106 (8.6)
Violence-related health care event	278 (8.6)	126 (10.2)
Infant discharged to social services at birth	433 (13.4)	162 (13.1)
Of the pregnancy and newborn		
Female sex	1362 (42.1)	546 (44.2)
Gestational age at birth, weeks		
23–31	51 (1.6)	51 (4.1)
32–36	582 (18.0)	187 (15.2)
37–42	2606 (80.5)	996 (80.7)
Small for gestational age birth weight <10th percentile	644 (19.9)	230 (18.6)
Small for gestational age birth weight less than fifth percentile	359 (11.1)	137 (11.1)
NICU admission	2426 (74.9)	606 (49.1)
Mean (SD) length of stay in the birth hospitalization, d	15.7 (14.7)	10.2 (16.9)
No fetal ultrasound at 18–20 wk gestation	741 (22.9)	271 (22.0)
No prenatal care visit in the first trimester	351 (10.8)	223 (18.1)

Included are all live hospital births in Ontario, Canada, 2014–2017. All data are presented as a number (%) unless otherwise indicated. P96.1: Withdrawal from maternal drugs of addiction. P04.4: Infant affected by maternal drugs of addiction. Missing data included sex P96.1, *n* = 231 (7.1%) and P04.4 *n* = 107 (8.7%).

<sup>a</sup> Defined as any prescription opioid during pregnancy (11+ days of opioid analgesic or methadone or buprenorphine) or any opioid-related hospital care. Groups are not mutually exclusive.