Research

Prescribed opioid analgesics in early pregnancy and the risk of congenital anomalies: a population-based cohort study

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Abstract

Background: Recent data suggest an increased risk of congenital anomalies with prenatal exposure to opioid analgesics. We sought to further quantify the risk of anomalies after opioid analgesic exposure during the first trimester in a population-based cohort study.

Methods: Using administrative health data from Ontario, we followed 599 579 gestational parent–infant pairs from singleton pregnancies without opioid use disorder. We identified opioid analgesics dispensed in the first trimester and congenital anomalies diagnosed during the first year of life. We estimated propensity score–adjusted risk ratios (RRs) between first trimester exposure (any opioid analgesic and specific agents) and congenital anomalies (any anomaly, organ system anomalies, major or minor anomalies and specific anomalies).

Results: The prevalence of congenital anomalies was 2.8% in exposed infants and 2.0% in unexposed infants. Relative to unexposed infants, we observed elevated risks among those who were exposed for some anomaly groups, including gastrointestinal anomalies (any opioid analgesic: adjusted RR 1.46, 95% confidence interval [CI] 1.15–1.85; codeine: adjusted RR 1.53, 95% CI 1.12–2.09; tramadol: adjusted RR 2.69, 95% CI 1.34–5.38) and several specific anomalies, including ankyloglossia (any opioid: adjusted RR 1.88, 95% CI 1.30–2.72; codeine: adjusted RR 2.14, 95% CI 1.35–3.40). These findings persisted in sensitivity analyses.

Interpretation: Although the absolute risk of congenital anomalies was low, our findings add to accumulating data that suggest a small increased risk of some organ system anomalies and specific anomalies with first trimester exposure to opioid analgesics. These findings further quantify the potential risks associated with prenatal exposure to opioid analgesics to inform treatment choices for pain in pregnancy.

Opioid use in pregnancy is a public health concern,[1–5] with 2%–4% of pregnancies exposed to prescribed opioid analgesics.[6–8] Opioid analgesics cross the placenta and have potential to cause fetal harm.[9]

Evidence concerning the safety of opioid analgesics for pain in pregnancy is discrepant and limited.[10–13] Recent studies with Medicaid and private insurance health data from the United States suggested small increases in minor congenital anomalies and oral cleft anomalies with prenatal exposure to opioid analgesics.[10,14] Some studies have reported an increased risk of any anomaly,[15,16] heart anomalies,[7,16–18] spina bifida,[7,19,20] oral cleft anomalies,[10,15,21] gastroschisis[7] and clubfoot[16,22,23] with exposure. Other studies, however, have found no association with any anomaly,[22,24] major[10,14,19,22,24,25] or minor[14] anomalies, neural tube anomalies,[10,19,22,26] clubfoot[10] or heart anomalies.[8,15,19,22,27,28] Discrepant findings likely arise from different methodologies, including definitions of exposure and anomalies evaluated. Some studies included pregnant people with exposure to opioid agonist therapy and, therefore, opioid use disorder.[20,22,23] Many studies captured exposure through maternal self-report.[7,8,15–18,20–24,26,28,29] Others predominantly included births before 1990,[8,15,17,18,21,25,27,28] preventing evaluation of current medications. Only 2 population-based cohort studies have been conducted.[22,24]

Therefore, we undertook a population-based cohort study to estimate associations between opioid analgesic exposure during the first trimester and congenital anomalies using health administrative data capturing all narcotic prescriptions during pregnancy.

Methods

Study design and data sources

We constructed a population-based cohort of deliveries using administrative health data of the single-payer health care system in Ontario, Canada, held at ICES. We identified parent–infant pair

records for all live births and stillbirths at more than 20 weeks' gestation delivered at Ontario hospitals with an estimated date of confinement between Apr. 7, 2013 (280 d from implementation of the Narcotic Monitoring System [NMS]), and Mar. 31, 2018, in MOMBABY, a validated database of linked parent–infant records. We used estimated date of confinement rather than delivery date to prevent overselection of preterm births and, thus, anomalies.[30] To reduce confounding, we excluded pregnant people with opioid use disorder or opioid overdose within 2 years before delivery or those treated with methadone or buprenorphine for opioid use disorder.[1,31,32] We also excluded pairs without a valid Ontario health card, pairs with unsuccessful record linkage, pregnant people aged 50 and older, those with multiple fetuses and pregnancies exposed to opioid analgesics during the second or third trimester, but not the first.

Exposure

We captured exposure using records of prescribed prenatal opioid analgesics in the NMS database. Established in July 2012 through the Ontario Narcotics Strategy, the NMS records information on controlled drug prescriptions issued to Ontario residents, regardless of payment method. The exposure of interest was to opioid analgesics during the first trimester, defined as a prescription fill date between the estimated date of conception (following a validated algorithm;[33] Appendix 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.211215/tab-related-content) and less than 14 weeks' gestation. We classified exposure as any opioid analgesic and specific agents. The referent group was unexposed to any opioid analgesic during the index pregnancy period.

Outcomes

We identified congenital anomalies diagnosed within the first year of life using diagnosis codes from the Canadian version of the *International Classification of Diseases, 10th Revision* in the Hospital Discharge Abstract Database, the Same Day Surgery Database and the National Ambulatory Care Reporting System Database, which record mandatory hospital submissions (Appendix 1, Supplemental eTable 1). As in other studies,[34–36] we classified anomalies using the algorithm from the Metropolitan Atlanta Congenital Defects Program, a surveillance system of the US Centers for Disease Control and Prevention (Appendix 1, Supplemental eTable 2).[37,38] We defined anomalies as major (of medical or surgical importance) or minor (associated with minor medical or cosmetic significance). We classified them as any anomaly, by organ system, major or minor[37] and specific anomalies if at least 5 infants with the anomaly were exposed.

Confounders

We computed high-dimensional propensity scores (HDPS) for parent–infant pairs to ensure similarity of pairs by exposure. This method was developed for pharmacoepidemiologic administrative health data studies[39] and has been used with ICES data.[6,40,41] Briefly, using the HDPS algorithm, candidate covariates in the year before conception were identified empirically in the health care claims databases we selected (Appendix 1, Supplemental eTable 1). We prioritized covariates by their potential to control for confounding, and integrated them into an exposure propensity score.[39] We forced the following a priori confounders into the HPDS: gestational parent age, parity, socioeconomic status quintile, Elixhauser comorbidity score, diabetes, obesity, hypertension, pain, other prescribed psychotropic medications (only data on benzodiazepines or barbiturates were available in the NMS), and year of delivery. The resultant HDPS (between 0 and 1) for each parent–infant pair represents their probability of being treated with opioid analgesics conditional on the confounders. We further stabilized the HDPS to account for extreme weights.[42]

Statistical analysis

Given the large study size, we compared gestational parent–infant characteristics by exposure with standardized differences; we considered differences greater than 0.10 statistically meaningful.[43] We estimated risk ratios (RR) between opioid analgesic exposure during the first trimester and any congenital anomaly, organ system anomalies, major or minor anomalies, and specific anomalies using a log-binomial regression model. We estimated adjusted risk ratios using inverse probability of treatment weighting with HDPS.

Sensitivity analysis

Sensitivity analyses included redefining the exposure period to include the 4 weeks before conception to evaluate possible misclassification; excluding individuals with opioid analgesic use in the year before pregnancy for possible confounding; analyzing individuals with more than 1 pregnancy, for which at least 1 was exposed and 1 was unexposed, to evaluate confounding; excluding infants born earlier than 37 weeks' gestation (for analysis of atrial septal defect, hypertrophic pyloric stenosis, ankyloglossia possibly related to prematurity); and stratifying by sex for effect measure modification (for hypertrophic pyloric stenosis). Additionally, we estimated adjusted risk differences to provide information on absolute effect size. Finally, we used 2 methods to explore the likely effect of potential unmeasured confounding. First, we determined the effect of an unmeasured confounder needed to fully account for our observed increased risk.[44] Second, we used simple bias analysis[45] to further remove possible unmeasured confounding arising from incomplete data on prenatal medications; we used estimates from previous studies (confounder–outcome association 1.5–3.0, and prevalence of psychotropic medication use by exposure group).[46]

Ethics approval

This study was approved by the Queen's University Health Sciences Research Ethics Board.

Results

Of 651 180 births in Ontario during the study period, 599 579 (92.1%) were included in the study cohort (Figure 1). The 599 579 pregnancies occurred among 491 060 individuals, 111 055 (22.6%) of whom were nulliparous. Of the 599 579 pregnancies, 11 903 (2.0%) were exposed to opioid analgesics. Most

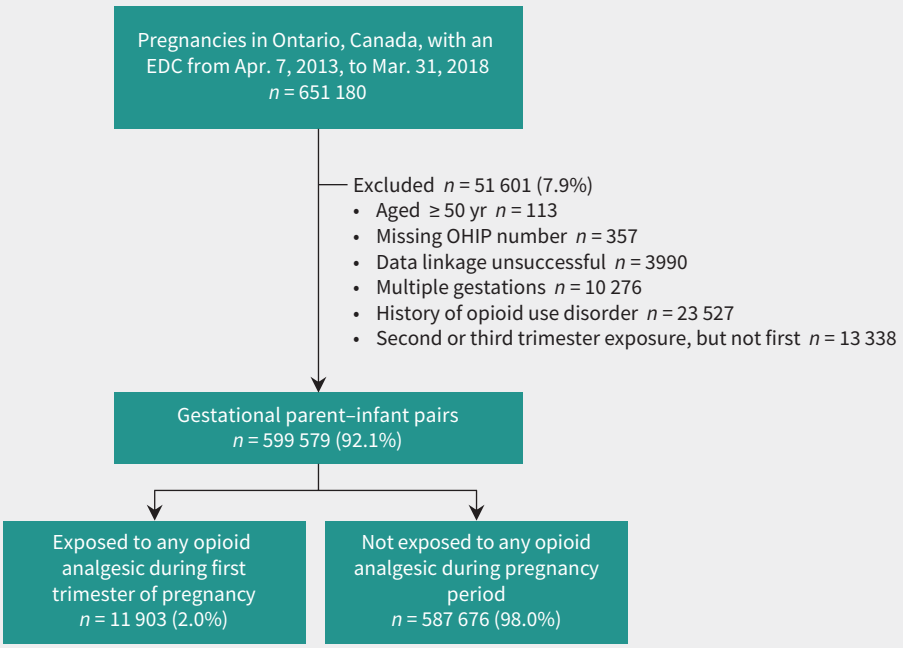

Figure 1: Flow chart of cohort creation. Note: EDC = estimated date of conception, OHIP = Ontario Health Insurance Plan.

pairs were exposed during the first trimester only (*n* = 9023, 75.8%) with 1195 (10.0%) exposed all 3 trimesters; the mean duration of exposure was 4.3 (standard deviation 9.2) weeks. Specific agents included codeine (*n* = 6524), oxycodone (*n* = 2885), hydromorphone (*n* = 1824), tramadol (*n* = 781), morphine (*n* = 670), fentanyl (*n* = 75), meperidine (*n* = 56) and others (*n* = 41). Standardized differences (Table 1) showed that exposed pairs were more likely to have been prescribed opioid analgesics in the year before pregnancy (47.6% v. 10.1%), to have a prescription for other psychotropics (8.4% v. 1.4%), and to have an Elixhauser comorbidity score of 1 or more (2.2% v. 0.7%) than those who were unexposed. Those exposed were also more likely to have a prior maternal diagnosis of pain (26.3% v. 9.8%), particularly lower back pain (20.9% v. 7.9%). Most covariates were balanced after HDPS weighting, except for history of opioid analgesic use and prescribed psychotropics.

Overall, 12 260 (2.0%) infants received a congenital anomaly diagnosis in the first year of life; 329 (2.8%) of 11 903 exposed infants received a diagnosis of an anomaly, compared with 11 931 (2.0%) of 587 676 unexposed infants. The number of anomalies per infant was similar by exposure group; 230 (69.9%) exposed infants with anomalies had 1 anomaly, compared with 7973 (66.8%) of those unexposed (Appendix 1, Supplemental eTable 3).

Figure 2 shows the unadjusted and adjusted RRs between exposure to opioid analgesics in the first trimester and any anomaly. After HDPS adjustment, infants exposed to any opioid analgesic had a small, elevated risk of any congenital anomaly (adjusted RR 1.14, 95% confidence interval [CI] 1.01–1.28) for an adjusted prevalence difference of 2.9 per 1000 infants (Appendix 1, Supplemental eTable 4). We observed an increased risk of any anomaly with exposure to morphine (adjusted RR 1.89, 95% CI 1.28–2.79) and tramadol (adjusted RR 1.79, 95% CI 1.23–2.60).

When classified by organ system and specific anomalies (Figure 3, Figure 4 and Figure 5), exposure was associated with increased risks of cardiovascular anomalies (with morphine), neoplasms and tumours (with tramadol), gastrointestinal (with any opioid analgesic and with codeine) and genital anomalies (with oxycodone). The risk of urinary anomalies was lower with any opioid analgesic exposure (adjusted RR 0.63, 95% CI 0.41–0.96) and higher with tramadol (adjusted RR 2.95, 95% CI 1.22–7.14).

The risk of major anomalies was elevated with exposure to morphine (adjusted RR 2.05, 95% 1.34–3.13, Figure 4) and tramadol (adjusted RR 1.94, 95% CI 1.28–2.92). Associations with specific major anomalies included atrial septal defect (with tramadol), ventricular septal defect (with codeine), pulmonary artery stenosis (with any opioid analgesic and with codeine) and hypertrophic pyloric stenosis (with any opioid analgesic, codeine and morphine). The risk of minor anomalies was elevated with exposure to any opioid analgesic, codeine, hydromorphone and oxycodone, and the risk of ankyloglossia was elevated with any opioid analgesic and codeine (Figure 5).

Specific agents associated with multiple anomalies included tramadol (with atrial septal defect, neoplasms and tumours, gastrointestinal anomalies and urinary anomalies), codeine (with gastrointestinal anomalies, ankyloglossia, hypertrophic pyloric stenosis, ventricular septal defect and pulmonary artery stenosis) and morphine (with cardiovascular anomalies and hypertrophic pyloric stenosis). Only oxycodone was associated with a single anomaly group (genital anomalies).

Table 1: Characteristics of pregnancies exposed to opioid analgesics in the first trimester, compared with pregnancies unexposed during the pregnancy period in Ontario, Canada, 2013–2018

	Before weighting			After weighting		
Characteristic	No. (%) exposed *n* = 11 903	No. (%) unexposed *n* = 587 676	Standardized difference	No. (%) exposed	No. (%) unexposed	Standardized difference*
Opioid analgesic use in the year before pregnancy	5662 (47.6)	59 108 (10.1)	0.91	3757 (31.6)	61 941 (10.5)	0.533
Maternal age at delivery, yr						
< 20	245 (2.1)	12 049 (2.1)	0.001	245 (2.1)	12 047 (2.1)	0.000
20–24	1502 (12.6)	60 568 (10.3)	0.073	1459 (12.3)	61 001 (10.4)	0.059
25–29	3135 (26.3)	158 052 (26.9)	0.013	3203 (26.9)	157 967 (26.9)	0.001
30–34	4021 (33.8)	218 741 (37.2)	0.072	4132 (34.7)	218 263 (37.1)	0.051
≥ 35	3000 (25.2)	138 266 (23.5)	0.039	2864 (24.1)	138 339 (23.5)	0.012
Year of delivery						
2013	2023 (17.0)	91 418 (15.6)	0.039	1874 (15.7)	91 384 (15.6)	0.005
2014	2510 (21.1)	117 456 (20.0)	0.027	2219 (18.6)	117 947 (20.1)	0.036
2015	2505 (21.0)	117 114 (19.9)	0.028	2426 (20.4)	117 241 (20.0)	0.010
2016	2398 (20.2)	118 223 (20.1)	0.001	2514 (21.1)	117 947 (20.1)	0.026
2017	2087 (17.5)	118 402 (20.1)	0.067	2371 (19.9)	118 231 (20.1)	0.004
2018	380 (3.2)	25 063 (4.3)	0.057	500 (4.2)	24 976 (4.3)	0.003
SES quintile at delivery						
1–2 (lowest)	5863 (49.3)	250 350 (42.6)	0.133	5118 (43.0)	251 702 (42.8)	0.003
3	2394 (20.1)	120 650 (20.5)	0.010	2406 (20.2)	120 356 (20.5)	0.007
4	2131 (17.9)	120 826 (20.6)	0.067	2422 (20.4)	120 297 (20.5)	0.003
5 (highest)	1515 (12.7)	95 909 (16.3)	0.102	1957 (16.4)	95 321 (16.2)	0.006
Maternal conditions†						
Diabetes	453 (3.8)	9446 (1.6)	0.136	312 (1.9)	14 457 (1.7)	0.019
Obesity	571 (4.8)	14 093 (2.4)	0.129	268 (2.62)	12 811 (2.5)	0.010
Hypertension	482 (4.0)	12 547 (2.1)	0.110	1383 (2.25)	60 354 (2.2)	0.005
Maternal pain diagnosis†						
Any	3131 (26.3)	57 393 (9.8)	0.440	1383 (11.6)	603 540 (10.3)	0.034
Lower back	2491 (20.9)	46 146 (7.9)	0.379	1096 (9.2)	48 601 (8.3)	0.036
Migraine	451 (3.8)	5256 (0.9)	0.192	160 (1.3)	5642 (1.0)	0.019
Chronic	364 (3.1)	5163 (0.9)	0.157	135 (1.1)	5524 (0.9)	0.017
Other	239 (2.0)	1897 (0.3)	0.158	58 (0.5)	2233 (0.4)	0.004
Limb	196 (1.6)	2880 (0.5)	0.113	74 (0.6)	3467 (0.6)	0.006
Arthritis	76 (0.6)	1617 (0.3)	0.054	30 (0.3)	1645 (0.3)	0.002
Facial	47 (0.4)	891 (0.2)	0.047	19 (0.2)	940 (0.2)	0.003
Elixhauser comorbidity score ≥ 1†	266 (2.2)	4083 (0.7)	0.13	105 (0.9)	4349 (0.7)	0.016
Previous live birth	2001 (16.8)	109 054 (18.6)	0.05	2237 (18.8)	108 720 (18.5)	0.007
Other prescribed psychotropic medications‡	998 (8.4)	7934 (1.4)	0.33	480 (4.0)	8580 (1.5)	0.158

Note: HDPS = high-dimensional propensity scores, NMS = Narcotic Monitoring System, SES = socioeconomic status.
*Standardized differences were weighted using inverse probability of treatment weighting with HDPS.
†In the year before pregnancy.
‡Data on other prescribed psychotropic medications were available only for barbiturates and benzodiazepines in the NMS database. No exposed pregnant people were prescribed barbiturates; 17 unexposed pregnant people were prescribed barbiturates.

Anomaly	Exposure*	No. of infants	No. of infants with anomaly	RR (95% CI) Unadjusted	RR (95% CI) Adjusted
Any congenital anomaly	None	587 676	11 931	1.00	1.00
	Any	11 903	329	1.37 (1.23–1.53)	1.14 (1.01–1.28)
	Codeine	6524	160	1.21 (1.04–1.42)	1.10 (0.94–1.30)
	Morphine	670	25	1.87 (1.25–2.79)	1.89 (1.28–2.79)
	Hydromorphone	1824	49	1.33 (1.00–1.77)	1.12 (0.82–1.53)
	Oxycodone	2885	87	1.50 (1.21–1.86)	1.14 (0.89–1.46)
	Tramadol	781	38	2.47 (1.78–3.42)	1.79 (1.23–2.60)

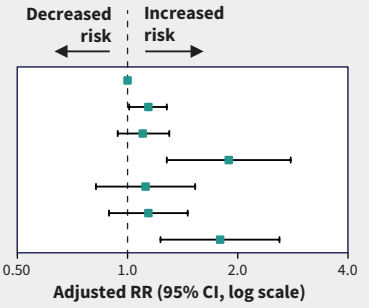

Figure 2: Forest plot of the risk of any congenital anomaly in pregnancies exposed to opioid analgesics in the first trimester compared with those not exposed during the pregnancy period, by specific agent. We adjusted estimates using inverse probability of treatment weighting with high-dimensional propensity scores. *We present data on specific opioid analgesic agents where at least 5 infants with the anomaly were exposed. Note: CI = confidence interval, RR = risk ratio.

In sensitivity analyses (Table 2), when including exposure 4 weeks before conception or excluding individuals with exposure to opioid analgesics before pregnancy, results were unchanged from the primary analyses. Among 2980 individuals with at least 1 exposed and 1 unexposed pregnancy, exposure to any opioid analgesic was associated with an increased risk of any anomaly (adjusted RR 1.13, 95% CI 0.83–1.55). An increased risk of ankyloglossia and hypertrophic pyloric stenosis with exposure to any opioid analgesic remained when restricting to term infants. We observed a stronger association between any opioid analgesic exposure and hypertrophic pyloric stenosis in female infants (adjusted RR 3.97, 95% CI 2.11–7.50) than male infants (adjusted RR 1.49, 95% CI 0.92–2.41). For confounding to fully account for our observed increased risk, most observed associations required risk ratios greater than 3 between the possible unmeasured confounder and the exposure and anomalies (Appendix 1, Supplemental eTable 5). Most findings persisted after further adjustment for possible unmeasured confounding (Appendix 1, Supplemental eTable 6).

Interpretation

In this population-based cohort of 599 579 parent–infant pairs, the prevalence of congenital anomalies was 204.4 per 10 000 infants; this is lower than the prevalence of 430.5 per 10 000 infants in the 2014 general Canadian pregnancy population.[47] Although the overall risk was low, we observed an increased risk of any congenital anomaly with tramadol,[16] and a previously unreported risk with morphine. An association with oxycodone was observed only when including exposure 4 weeks before conception. Associations with any anomaly, however, are less informative: any anomaly is a crude classification and may not capture differences in etiology.[48]

Previous studies reported elevated risks of heart anomalies with first trimester exposure to any opioid analgesic,[7] codeine[7,17,18] and tramadol,[16] but others reported no association with any opioid analgesic[8,10,15,19,22] or codeine.[10,19,22,27,28] A US case–control study reported increased risks of specific heart anomalies with periconceptional or first trimester exposure to opioid analgesics compared with acetaminophen.[29] Like others,[7,16–18] we observed associations with some cardiovascular anomalies; however, these did not persist in bias analysis.

Few studies have evaluated hypertrophic pyloric stenosis,[15,16,22] a major stomach anomaly leading to gastric outlet obstruction that requires surgery;[49] we observed an increased risk with any opioid analgesic, codeine and morphine. We observed a stronger association among female infants than male infants, which persisted in bias analysis. Hypertrophic pyloric stenosis is more common in male than female infants.[50,51] It is unknown why the baseline risk differs by sex; similarly, we cannot explain why sex would modify associations with exposure to opioid analgesics. This observation may be hypothesis-generating rather than suggestive of opioid analgesic teratogenicity.

Others have observed associations with exposure to codeine in the second and third trimesters and to oxycodone in the third trimester.[14] We observed an elevated risk of minor anomalies with any opioid analgesic, codeine, oxycodone and hydromorphone; associations were strongest for hydromorphone in bias analysis. We noted associations between any opioid analgesic and codeine with ankyloglossia, commonly known as tongue-tie, which is sometimes treated with release of the frenulum. We also observed other elevated risks: gastrointestinal anomalies with any opioid analgesic, codeine and tramadol; genital anomalies with oxycodone; and neoplasms and tumours and urinary anomalies with tramadol. We attribute the observed lower risk of urinary anomalies with any opioid analgesic to type I error. The difficulty of accurate exposure measurement is that etiology and time of organogenesis can vary within an organ system, which could reduce the specificity of estimated associations.[48]

Multiple sensitivity analyses suggested that misclassification of exposure or anomalies likely did not account for our results. Our HDPS adjustment attenuated some estimates, but elevated associations remained for some anomalies. Consistent with others,[10] our quantitative bias analysis estimated that an unmeasured confounder would have to be strongly associated with exposure and anomalies to fully account for associations. To correct estimates for possible unmeasured confounding from psychotropic medications (only benzodiazepines and barbiturates are available in the NMS and

Organ system	Exposure*	No. of infants	No. of infants with anomaly†	RR (95% CI) Unadjusted	RR (95% CI) Adjusted
Cardiovascular	None	587 676	3130	1.00	1.00
	Any	11 903	83	1.31 (1.05–1.63)	1.13 (0.89–1.43)
	Codeine	6524	45	1.30 (0.97–1.74)	1.19 (0.88–1.63)
	Morphine	670	7	1.97 (0.94–4.16)	2.23 (1.10–4.52)
	Hydromorphone	1824	8	0.82 (0.41–1.65)	0.79 (0.39–1.63)
	Oxycodone	2885	20	1.30 (0.84–2.03)	0.64 (0.34–1.24)
	Tramadol	781	11	2.68 (1.47–4.84)	1.45 (0.63–3.31)
Gastrointestinal	None	587 676	2395	1.00	1.00
	Any	11 903	79	1.63 (1.30–2.04)	1.46 (1.15–1.85)
	Codeine	6524	41	1.55 (1.13–2.11)	1.53 (1.12–2.09)
	Morphine	670	8	2.95 (1.47–5.94)	2.05 (0.88–4.77)
	Hydromorphone	1824	7	0.94 (0.45–1.98)	1.09 (0.54–2.20)
	Oxycodone	2885	20	1.71 (1.10–2.65)	1.15 (0.65–2.00)
	Tramadol	781	10	3.17 (1.70–5.92)	2.69 (1.34–5.38)
Musculoskeletal	None	587 676	1997	1.00	1.00
	Any	11 903	54	1.34 (1.02–1.75)	1.02 (0.76–1.37)
	Codeine	6524	26	1.17 (0.80–1.73)	1.25 (0.85–1.82)
	Hydromorphone	1824	9	1.45 (0.75–2.80)	1.49 (0.77–2.88)
	Oxycodone	2885	16	1.64 (1.00–2.68)	1.53 (0.90–2.60)
Genital	None	587 676	1247	1.00	1.00
	Any	11 903	28	1.11 (0.76–1.61)	1.07 (0.73–1.58)
	Codeine	6524	12	0.87 (0.49–1.53)	0.79 (0.43–1.45)
	Oxycodone	2885	11	1.80 (0.99–3.26)	2.36 (1.37–4.06)
Urinary	None	587 676	1351	1.00	1.00
	Any	11 903	32	1.17 (0.82–1.66)	0.63 (0.41–0.96)
	Codeine	6524	12	0.80 (0.45–1.41)	0.74 (0.41–1.35)
	Hydromorphone	1824	7	1.67 (0.79–3.52)	0.66 (0.20–2.19)
	Oxycodone	2885	10	1.51 (0.81–2.82)	1.10 (0.52–2.35)
	Tramadol	781	5–6	2.80 (1.16–6.75)	2.95 (1.22–7.14)
Neoplasms and tumours	None	587 676	886	1.00	1.00
	Any	11 903	22	1.23 (0.80–1.87)	1.14 (0.73–1.78)
	Codeine	6524	11	1.12 (0.62–2.03)	1.07 (0.58–1.98)
	Tramadol	781	5–6	4.27 (1.77–10.31)	4.71 (1.98–11.17)
Central nervous system	None	587 676	735	1.00	1.00
	Any	11 903	21	1.41 (0.91–2.18)	1.01 (0.61–1.68)
	Codeine	6524	7	0.86 (0.41–1.81)	0.67 (0.29–1.57)
	Oxycodone	2885	8	2.22 (1.11–4.46)	1.70 (0.74–3.89)
Chromosomal	None	587 676	607	1.00	1.00
	Any	11 903	17	1.38 (0.85–2.24)	1.06 (0.61–1.85)
	Codeine	6524	11	1.63 (0.90–2.97)	1.28 (0.65–2.53)
Oral clefts	None	587 676	610	1.00	1.00
	Any	11 903	16	1.30 (0.79–2.13)	0.73 (0.37–1.41)
	Codeine	6524	7	1.03 (0.49–2.18)	0.36 (0.10–1.29)
	Tramadol	781	5–6	6.20 (2.56–14.99)	1.46 (0.23–9.50)
Respiratory	None	587 676	373	1.00	1.00
	Any	11 903	8	1.06 (0.53–2.13)	0.64 (0.26–1.60)
Eye	None	587 676	278	1.00	1.00
	Any	11 903	9	1.60 (0.82–3.11)	1.40 (0.69–2.82)
	Codeine	6524	5–6	1.62 (0.67–3.93)	1.68 (0.70–4.06)
Ear, face and neck	None	587 676	283	1.00	1.00
	Any	11 903	7	1.22 (0.58–2.59)	0.71 (0.26–1.93)

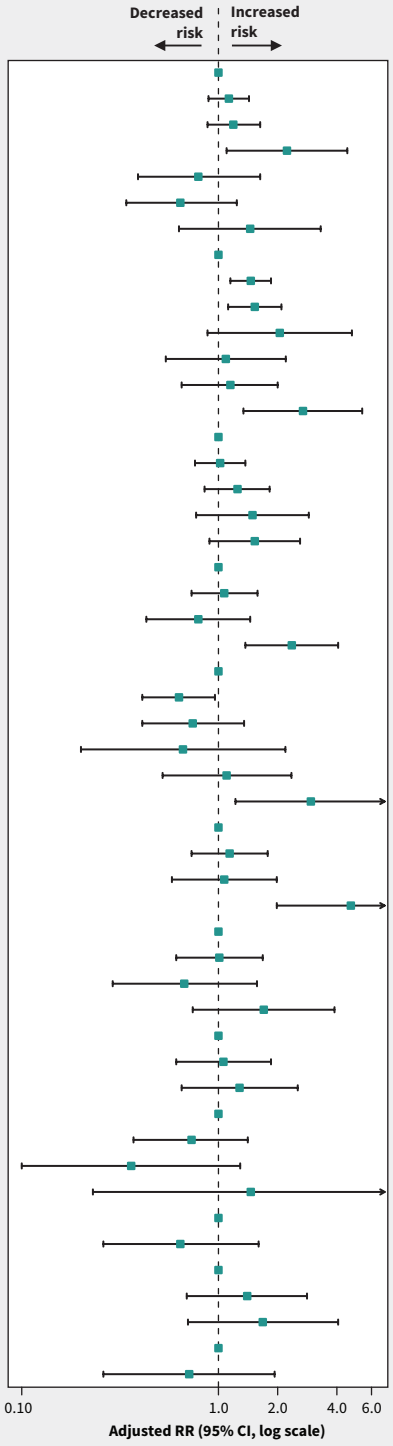

Figure 3: Forest plot of the risk of congenital anomalies in pregnancies exposed to opioid analgesics in the first trimester compared with those not exposed during the pregnancy period, classified by organ system. We adjusted estimates using inverse probability of treatment weighting with high-dimensional propensity scores. *We present data on specific opioid analgesic agents where at least 5 infants with the anomaly were exposed. †Given ICES privacy restrictions, we report anomalies with 6 or fewer cases as 5–6. Note: CI = confidence interval, RR = risk ratio.

Major congenital anomalies	Exposure*	No. of infants	No. of infants with anomaly†	RR (95% CI) Unadjusted	RR (95% CI) Adjusted
Any major congenital anomalies	None	587 676	9264	1.00	1.00
	Any	11 903	247	1.32 (1.16–1.50)	1.04 (0.91–1.20)
	Codeine	6524	121	1.18 (0.98–1.41)	1.00 (0.82–1.22)
	Morphine	670	20	1.92 (1.23–3.00)	2.05 (1.34–3.13)
	Hydromorphone	1824	33	1.15 (0.81–1.62)	0.85 (0.56–1.27)
	Oxycodone	2885	66	1.46 (1.14–1.87)	0.97 (0.71–1.32)
	Tramadol	781	30	2.49 (1.73–3.59)	1.94 (1.28–2.92)
Specific major anomalies (ICD-10-CA)					
Atrial septal defect (Q211)	None	587 676	1961	1.00	1.00
	Any	11 903	53	1.34 (1.02–1.76)	1.22 (0.91–1.62)
	Codeine	6524	28	1.29 (0.89–1.87)	1.15 (0.78–1.72)
	Oxycodone	2885	13	1.35 (0.78–2.34)	0.79 (0.38–1.66)
	Tramadol	781	9	3.48 (1.80–6.73)	2.28 (0.99–5.25)
Ventricular septal defect (Q210)	None	587 676	849	1.00	1.00
	Any	11 903	23	1.34 (0.88–2.03)	1.18 (0.75–1.85)
	Codeine	6524	14	1.49 (0.88–2.52)	1.59 (0.95–2.67)
	Oxycodone	2885	5–6	1.20 (0.50–2.89)	0.61 (0.17–2.21)
Patent ductus arteriosus (Q250)	None	587 676	748	1.00	1.00
	Any	11 903	21	1.39 (0.90–2.14)	1.05 (0.63–1.75)
Stenosis of pulmonary artery (Q256)	None	587 676	311	1.00	1.00
	Any	11 903	13	2.06 (1.19–3.60)	1.81 (0.99–3.31)
	Codeine	6524	7	2.03 (0.96–4.29)	2.16 (1.03–4.51)
Atrioventricular septal defect (Q212)	None	587 676	209	1.00	1.00
	Any	11 903	5–6	1.42 (0.63–3.19)	0.92 (0.33–2.55)
Tetralogy of Fallot (Q213)	None	587 676	226	1.00	1.00
	Any	11 903	8	1.75 (0.86–3.54)	0.85 (0.30–2.36)
Cleft lip (Q36)	None	587 676	311	1.00	1.00
	Any	11 903	12	1.91 (1.07–3.39)	1.25 (0.61–2.57)
	Codeine	6524	5–6	1.45 (0.60–3.51)	0.64 (0.17–2.46)
Cleft palate, unspecified (Q359)	None	587 676	205	1.00	1.00
	Any	11 903	5–6	1.20 (0.50–2.92)	0.88 (0.31–2.54)
Cleft palate with cleft lip (Q37)	None	587 676	223	1.00	1.00
	Any	11 903	7	1.55 (0.73–3.29)	0.82 (0.30–2.26)
Congenital hypertrophic pyloric stenosis (Q400)	None	587 676	728	1.00	1.00
	Any	11 903	32	2.17 (1.52–3.10)	1.93 (1.32–2.82)
	Codeine	6524	21	2.60 (1.69–4.02)	2.17 (1.34–3.51)
	Morphine	670	5–6	6.06 (2.51–14.66)	4.03 (1.35–12.03)
	Oxycodone	2885	5–6	1.40 (0.58–3.38)	1.61 (0.68–3.79)
Hypospadias, balanic (Q540)	None	587 676	394	1.00	1.00
	Any	11 903	10	1.25 (0.67–2.35)	0.65 (0.27–1.58)
	Codeine	6524	5–6	1.14 (0.47–2.76)	0.75 (0.25–2.25)
Hypospadias, unspecified (Q549)	None	587 676	211	1.00	1.00
	Any	11 903	5–6	1.17 (0.48–2.84)	0.76 (0.25–2.33)
Congenital hydronephrosis (Q620)	None	587 676	505	1.00	1.00
	Any	11 903	9	0.88 (0.46–1.70)	0.42 (0.20–0.91)
	Codeine	6524	5–6	0.89 (0.37–2.15)	0.45 (0.13–1.59)
Craniosynostosis (Q750)	None	587 676	299	1.00	1.00
	Any	11 903	7	1.16 (0.55–2.45)	1.22 (0.58–2.56)
Down syndrome, unspecified (Q909)	None	587 676	349	1.00	1.00
	Any	11 903	10	1.42 (0.75–2.65)	1.27 (0.65–2.50)
	Codeine	6524	5–6	1.55 (0.69–3.47)	1.11 (0.43–2.92)

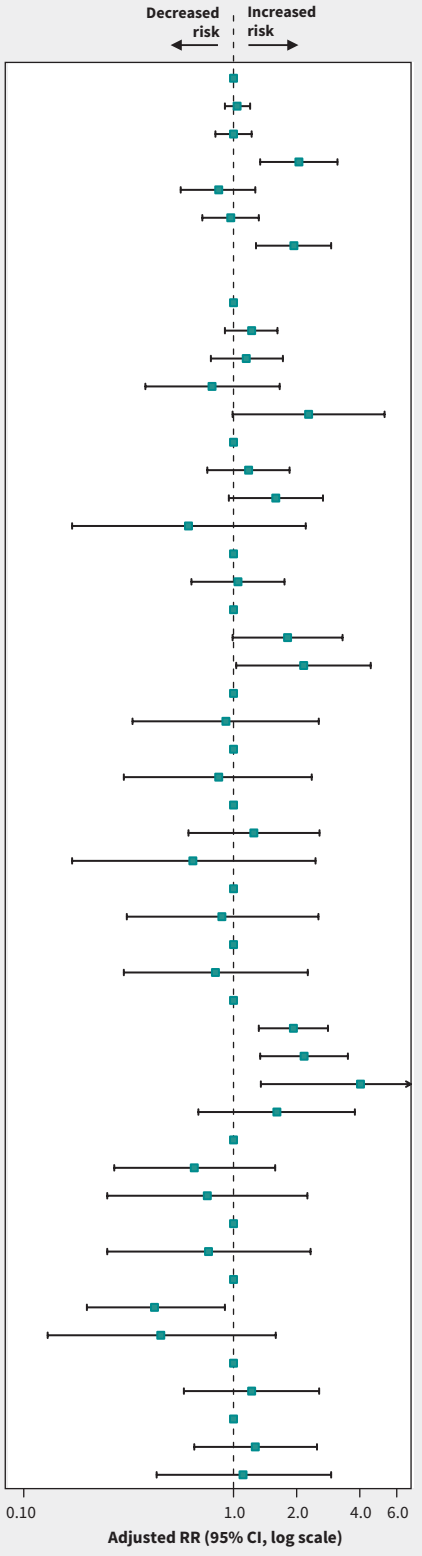

Figure 4: Forest plot of the risk of specific major congenital anomalies in pregnancies exposed to opioid analgesics in the first trimester compared with those not exposed during the pregnancy period, by specific agent. We adjusted estimates using inverse probability of treatment weighting with high-dimensional propensity scores. *We present data on specific opioid analgesic agents where at least 5 infants with the anomaly were exposed. †Given ICES privacy restrictions, we report anomalies with 6 or fewer cases as 5–6. Note: CI = confidence interval, ICD-10-CA = diagnostic code from the Canadian version of the *International Classification of Diseases, 10th Revision*, RR = risk ratio.

Minor congenital anomalies	Exposure*	No. of infants	No. of infants with anomaly†	RR (95% CI) Unadjusted	RR (95% CI) Adjusted
Any minor congenital anomalies	None	587 676	3762	1.00	1.00
	Any	11 903	112	1.47 (1.22–1.78)	1.26 (1.03–1.53)
	Codeine	6524	49	1.17 (0.89–1.56)	1.31 (1.00–1.72)
	Morphine	670	5–6	1.40 (0.63–3.13)	1.51 (0.69–3.31)
	Hydromorphone	1824	21	1.81 (1.17–2.78)	1.89 (1.23–2.89)
	Oxycodone	2885	32	1.74 (1.23–2.47)	1.54 (1.05–2.26)
	Tramadol	781	12	2.42 (1.37–4.29)	1.60 (0.78–3.28)
Specific minor anomalies (ICD-10-CA)					
Hemangioma of other sites (D1808)	None	587 676	324	1.00	1.00
	Any	11 903	8	1.22 (0.60–2.46)	1.44 (0.74–2.78)
	Codeine	6524	5–6	1.39 (0.57–3.36)	1.61 (0.70–3.70)
Plagiocephaly (Q673)	None	587 676	240	1.00	1.00
	Any	11 903	7	1.44 (0.68–3.05)	0.46 (0.19–1.13)
	Codeine	6524	5–6	1.88 (0.77–4.55)	1.46 (0.53–4.03)
Ankyloglossia (Q381)	None	587 676	794	1.00	1.00
	Any	11 903	30	1.87 (1.30–2.69)	1.88 (1.30–2.72)
	Codeine	6524	14	1.59 (0.94–2.70)	2.14 (1.35–3.40)
	Oxycodone	2885	10	2.57 (1.38–4.80)	1.79 (0.82–3.91)
Pilonidal cyst without abscess (L059)	None	587 676	210	1.00	1.00
	Any	11 903	5–6	1.41 (0.63–3.18)	0.67 (0.21–2.20)

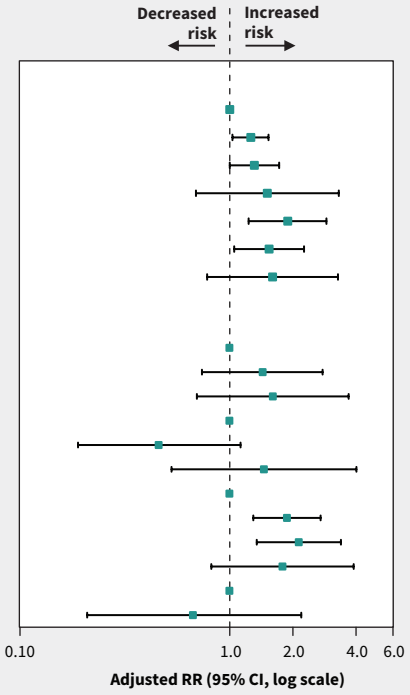

Figure 5: Forest plot of the risk of specific minor congenital anomalies in pregnancies exposed to opioid analgesics in the first trimester compared with those not exposed during the pregnancy period, by specific agent. We adjusted estimates using inverse probability of treatment weighting with high-dimensional propensity scores. *We present data on specific opioid analgesic agents where at least 5 infants with the anomaly were exposed. †Given ICES privacy restrictions, we report anomalies with 6 or fewer cases as 5–6. Note: CI = confidence interval, ICD-10-CA = diagnostic code from the Canadian version of the *International Classification of Diseases, 10th Revision*, RR = risk ratio.

were thus used as a proxy for other prenatal medications), we used psychotropic medication prevalence from a pregnant Medicaid population,[46] which was higher than what would be expected in our cohort. Most associations persisted, supporting the small increased risk observed by others.[10,14] Previous studies of administrative health data did not observe confounding from selective serotonin reuptake inhibitors or benzodiazepines in a high-risk cohort of pregnant people.[31]

Our methods improve upon some limitations of previous studies. Rather than using maternal recall, we used data from a central database that captures all prescriptions of controlled substances to capture prescriptions of opioid analgesics during pregnancy;[7,8,15–18,20,22–24,26,28,29,52] only a small proportion of NMS records (< 3%) were not linked. Our contemporary population-based study adds robust data to population-based studies from Sweden[22] and Norway.[24] Studies of Medicaid and private insurance beneficiaries often exclude many parent–infant pairs to ensure complete pregnancy coverage data;[10,14] this is not a concern with our data set. Further, we systematically identified anomalies using the classification system from the Metropolitan Atlanta Congenital Defects Program.

Limitations

We identified cases using diagnostic codes for billing, which may not be entirely accurate; the diagnosis and documentation of minor anomalies and those with subtle medical significance could be vulnerable to exposure-dependent recording bias. A small number of exposed infants with certain anomalies reduced precision, which could have led to spurious associations and prevented evaluation of some previously reported associations. Deliveries before 20 weeks' gestation were not recorded; therefore, early losses and terminations (potentially owing to anomalies) were not captured. Although we had extensive prescription data, we did not have data on over-the-counter pain medications that may have been used by pregnant people. Lastly, we determined exposure by the prescription fill date without further confirmation of use; this could have attenuated our associations. Future research investigating specific anomalies and agents is warranted, given the smaller number of exposed infants.

Conclusion

Although the absolute risk of anomalies was low, our study adds to those suggesting a small increased risk of congenital anomalies with exposure to opioid analgesics. Both the potential for harm or distress to the pregnant person as a consequence of forgoing treatment and the subsequent risk to the infant must be considered for effective treatment. These findings further quantify harms associated with prenatal exposure to opioid analgesics to inform treatment choices for pain in pregnancy.

Table 2 (part 1 of 2): Results of sensitivity analyses

Analysis	Exposure	No. of infants	No. of anomalies	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Restricting to pregnant people without opioid analgesic exposure in the previous year*					
Any congenital anomaly	None	528 568	10 483	1.00	1.00
	Any opioid analgesic	6241	172	1.40 (1.20–1.63)	1.25 (1.09–1.44)
	Codeine	3818	89	1.18 (0.96–1.46)	1.06 (0.87–1.29)
	Morphine	398	18	2.34 (1.46–3.76)	2.38 (1.61–3.53)
	Hydromorphone	976	28	1.46 (1.00–2.13)	1.38 (0.98–1.93)
	Oxycodone	1045	33	1.61 (1.14–2.28)	1.33 (0.98–1.79)
	Tramadol	293	11	1.93 (1.06–3.52)	1.77 (1.05–2.99)
Redefining exposure to include the first trimester or 4 weeks before conception					
Any congenital anomaly	None	582 560	11 793	1.00	1.00
	Any	17 019	467	1.37 (1.24–1.50)	1.14 (1.03–1.25)
	Codeine	9471	240	1.26 (1.11–1.43)	1.13 (0.99–1.29)
	Morphine	799	27	1.69 (1.15–2.49)	1.84 (1.29–2.64)
	Hydromorphone	2688	77	1.43 (1.14–1.79)	1.22 (0.95–1.56)
	Oxycodone	4049	116	1.43 (1.19–1.72)	1.31 (1.07–1.60)
	Tramadol	1227	49	2.01 (1.51–2.68)	1.66 (1.20–2.29)
By organ system†					
Cardiovascular	Any	3090 (0.5)	123 (0.7)	1.37 (1.14–1.64)	1.11 (0.91–1.35)
Gastrointestinal	Any	2367 (0.4)	107 (0.6)	1.55 (1.28–1.88)	1.45 (1.18–1.78)
Musculoskeletal	Any	1972 (0.3)	79 (0.5)	1.37 (1.10–1.72)	0.89 (0.70–1.14)
Genital	Any	1228 (0.2)	47 (0.3)	1.31 (0.98–1.76)	1.12 (0.81–1.55)
Urinary	Any	1333 (0.2)	50 (0.3)	1.28 (0.97–1.70)	0.68 (0.50–0.92)
Neoplasms and tumours	Any	878 (0.2)	30 (0.2)	1.17 (0.81–1.68)	0.93 (0.61–1.41)
Central nervous system	Any	726 (0.1)	30 (0.2)	1.42 (0.98–2.04)	1.02 (0.67–1.56)
Chromosomal	Any	598 (0.1)	26 (0.2)	1.49 (1.01–2.21)	1.10 (0.69–1.76)
Oral clefts	Any	604 (0.1)	22 (0.1)	1.25 (0.82–1.91)	0.92 (0.55–1.53)
Respiratory	Any	370 (0.1)	11 (0.1)	1.02 (0.56–1.85)	0.59 (0.26–1.31)
Eye	Any	272 (< 0.1)	15 (0.1)	1.89 (1.12–3.18)	1.55 (0.86–2.78)
Ear, face and neck	Any	274 (< 0.1)	16 (0.1)	2.00 (1.21–3.31)	1.40 (0.76–2.59)
Major congenital anomalies	Any	9160 (1.6)	351 (2.1)	1.32 (1.18–1.47)	1.05 (0.94–1.18)
Minor congenital anomalies	Any	3712 (0.6)	162 (1.0)	1.50 (1.28–1.76)	1.13 (0.95–1.33)
Specific major anomalies (ICD-10-CA)†					
Atrial septal defect (Q211)	Any	1934 (0.3)	80 (0.5)	1.42 (1.13–1.77)	1.18 (0.92–1.51)
Ventricular septal defect (Q210)	Any	839 (0.1)	33 (0.2)	1.35 (0.95–1.91)	1.19 (0.81–1.74)
Patent ductus arteriosus (Q250)	Any	738 (0.1)	31 (0.2)	1.44 (1.00–2.06)	0.97 (0.62–1.52)
Stenosis of pulmonary artery (Q256)	Any	307 (0.1)	17 (0.1)	1.90 (1.16–3.09)	1.47 (0.84–2.59)
Atrioventricular septal defect (Q212)	Any	206 (< 0.1)	9 (0.1)	1.50 (0.77–2.92)	0.63 (0.22–1.79)
Tetralogy of fallot (Q213)	Any	224 (< 0.1)	10 (0.1)	1.53 (0.81–2.88)	0.67 (0.26–1.77)
Cleft lip (Q36)	Any	309 (0.1)	14 (0.1)	1.55 (0.91–2.65)	1.16 (0.61–2.18)
Cleft palate, unspecified (Q359)	Any	205 (< 0.1)	5–6‡ (< 0.1)	0.83 (0.34–2.03)	0.60 (0.20–1.75)
Cleft palate with cleft lip (Q37)	Any	220 (< 0.1)	10 (0.1)	1.56 (0.83–2.93)	1.09 (0.50–2.36)
Congenital hypertrophic pyloric stenosis (Q400)	Any	44 (0.3)	716 (0.1)	2.11 (1.55–2.86)	1.99 (1.45–2.73)
Hypospadias, balanic (Q540)	Any	14 (0.1)	390 (0.1)	1.23 (0.72–2.09)	0.82 (0.42–1.60)

Table 2 (part 2 of 2): Results of sensitivity analyses

Analysis	Exposure	No. of infants	No. of anomalies	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Hypospadias, unspecified (Q549)	Any	7 (< 0.1)	209 (< 0.1)	1.15 (0.54–2.44)	0.68 (0.25–1.85)
Congenital hydronephrosis (Q620)	Any	15 (0.1)	499 (0.1)	1.03 (0.62–1.72)	0.34 (0.19–0.61)
Craniosynostosis (Q750)	Any	9 (0.1)	297 (0.1)	1.04 (0.53–2.01)	1.26 (0.68–2.34)
Down syndrome, unspecified (Q909)	Any	14 (0.1)	345 (0.1)	1.39 (0.81–2.37)	1.21 (0.67–2.18)
Specific minor anomalies (ICD-10-CA)					
Hemangioma of other sites (D1808)	Any	9 (0.1)	323 (0.1)	0.95 (0.49–1.85)	1.11 (0.59–2.08)
Plagiocephaly (Q673)	Any	10 (0.1)	237 (< 0.1)	1.44 (0.77–2.72)	0.22 (0.10–0.49)
Ankyloglossia (Q381)	Any	37 (0.2)	787 (0.1)	1.61 (1.16–2.24)	1.57 (1.12–2.22)
Pilonidal cyst without abscess (L059)	Any	8 (< 0.1)	208 (< 0.1)	1.32 (0.65–2.67)	0.71 (0.27–1.88)
Preterm births excluded (ICD-10-CA)					
Atrial septal defect (Q211)	None	551 987	1277	1.00	1.00
	Any	10 711	30	1.21 (0.84–1.74)	0.96 (0.65–1.44)
Ankyloglossia (Q381)	None	551 987	697	1.00	1.00
	Any	10 711	21	1.55 (1.01–2.40)	1.89 (1.27–2.81)
Hypertrophic pyloric stenosis (Q400)	None	551 987	662	1.00	1.00
	Any	10 711	28	2.18 (1.49–3.19)	1.93 (1.32–2.82)
Sex-specific models					
Female infants, hypertrophic pyloric stenosis	None	281 577	131	1.00	1.00
	Any	5687	5–6†	2.27 (1.00–5.15)	3.97 (2.11–7.50)
Male infants, hypertrophic pyloric stenosis	None	297 413	588	1.00	1.00
	Any	5981	25	2.12 (1.42–3.16)	1.49 (0.92–2.41)

Note: CI = confidence interval, ICD-10-CA = diagnostic code from the Canadian version of the *International Classification of Diseases, 10th Revision*, RR = risk ratio.
*109 859 participants had > 1 pregnancy. Of these, 106 290 were unexposed in all pregnancies, 589 were exposed in all pregnancies; 2980 had at least 1 exposed and 1 unexposed pregnancy and were included in the above result.
†Number (%) of infants reflects number of exposed infants among all 599 579 infants included in sensitivity analysis. Number (%) of anomalies reflects number of exposed infants with anomaly among 17 019 exposed infants with any congenital anomaly in sensitivity analysis. Reference group for RRs is infants with no opioid analgesic exposure.
‡Because of ICES privacy restrictions, we report anomalies with 6 or fewer cases as 5–6.

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