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METHODS

Study Design & Data Sources
ICES is an independent, non-profit research institute with designation under the Ontario Personal Health Information Protection Act to collect and analyze healthcare data for Ontario residents, without consent, for health system research.

Exposure
The prenatal period was determined by obstetric gestational age from the maternal record in MOMBABY. For pairs for whom this was unavailable (N = 2035), gestational age from the infant record in MOMBABY was used. If neither was available in MOMBABY (N = 1363), infants with or without an ICD-10-CA preterm indicator were assigned a gestational age of 35 and 39 weeks, respectively, following a validated algorithm.[33]

Outcome
We manually mapped ICD-10-CA codes to the six-digit modified British Pediatric Association codes used by the Metropolitan Atlanta Congenital Defects Program (MACDP). Unspecified and other ICD-10-CA codes were mapped to the corresponding 'NOS' (not otherwise specified) and 'NEC' (not elsewhere classified) MACDP codes, respectively; 'unspecified' codes correspond to diagnoses that cannot be specified further from the medical record, and 'other' codes correspond to diagnoses that do not fit within a general code. A pediatrician (AG) and perinatal epidemiologist (MMW) reviewed the MACDP and ICD-10-CA matching and the resultant list of anomalies.

HDPS
In addition to the *a priori* covariates, variables from the following databases were used as inputs to the HDPS macro to create a propensity score that well balanced exposed and unexposed pairs: 1) diagnostic codes from physician visits in the year prior to pregnancy (OHIP database), 2) diagnostic codes from emergency department visits in the year prior to pregnancy (NACRS database), 3) inpatient diagnostic codes from the hospital discharge abstract in the year prior to pregnancy (CIHI database), and 4) prescription medications excluding opioid analgesics in the year prior to pregnancy (ODB database, available for ODB recipients only).

Statistical Analysis
We report anomalies with six or fewer cases as 5-6 due to ICES privacy restrictions.

eTable 1. Details of study data sources.

Database	Description	Variables captured
Discharge Abstract Database (DAD)	Mandatory discharge abstract submissions from all acute inpatient facilities in Ontario.	ICD-10-CA diagnosis codes, maternal conditions (diabetes, obesity, hypertension), maternal pain diagnosis, Elixhauser comorbidity score.
National Ambulatory Care Reporting System Database (NACRS)	Records of all hospital-based and community-based outpatient care, including day surgery, outpatient clinics, and emergency department visits.	
Ontario Health Insurance Plan Claims Database (OHIP)	Records of universal coverage for medical services to all Ontario residents.	
Same Day Surgery Database (SDS)	Records information for all same day surgical procedures.	
MOMBABY	Linked maternal and infant hospital records (abstracted from DAD).	Gestational weeks (maternal and infant), infant sex, maternal age at delivery, number of prior live births, multiple births, delivery date.
Narcotics Monitoring System (NMS)	Collects mandatory information on all prescriptions of controlled drugs issued to Ontario residents, regardless of payment method.	Drug identification number, description of the product, dispensing date, quantity of drug dispensed, estimated number of days supplied.
Registered Person's Database	Contains demographic information on all Ontario residents registered under the Ontario Health Insurance Plan (OHIP).	Maternal socioeconomic status determined by neighbourhood income quintile using postal code at delivery. Income quintiles were assigned within census areas by the average household size-adjusted income of each neighbourhood.

eTable 2. Conditional diagnosis code inclusion criteria.

Specific anomaly (ICD-10-CA)	Conditional criteria
Tetralogy of Fallot (Q213)	Do not code the individual components of TOF separately. The individual components are pulmonary or RV flow tract stenosis (Q221), VSD (Q210), dextropositioned or overriding aorta (Q2030).
Plagiocephaly (Q673) Dolichocephaly (Q672)	Never code if craniosynostosis is present (Q750).
Ebstein's anomaly (Q225)	Do not code tricuspid atresia (Q224) separately, it is a component of Ebstein's anomaly.
Patent Ductus Arteriosus (Q250)	If >=36 weeks gestation always include; if <36 weeks gestation never include.
Inguinal hernia (K400, K401, K402, K403, K404, K409)	If >=36 weeks gestation and female, then always include; If <36 weeks gestation or male, then never include.
Torsion of testis (N4400, N4401, N4402, N4408)	Never code testicular torsion acquired postnatally.

eTable 3. Number of Major and Minor Anomalies among Pregnancies Exposed During the First Trimester Compared with Unexposed Pregnancies.

No. of Anomalies	Unexposed (N%)			Exposed (N%)		
	Any[a] (N = 11 931)	Major (N = 9264)	Minor (N = 3762)	Any[a] (N = 329)	Major (N = 247)	Minor (N = 112)
1	7973 (66.8%)	5440 (58.7%)	2533 (67.3%)	230 (69.9%)	151 (61.1%)	79 (70.5%)
>1	3958 (33.2%)	3824 (41.3%)	1229 (32.7%)	99 (30.1%)	96 (38.9%)	33 (29.5%)

[a]The sum of 'Major' and 'Minor' anomalies do not sum to the 'Any congenital anomaly' total. This is because pregnancies are only represented once under 'Any congenital anomaly' but may be represented under both 'Major' and 'Minor' anomaly columns if they have >1 anomaly.

eTable 4. Marginal Risk Differences of Anomalies per 1000 in Pregnancies Exposed During the First Trimester Compared with Unexposed Pregnancies.

Anomaly	Exposure[a]	No. of Infants	No. of infants with anomaly	Marginal Risk Difference per 1000 (95% CI)	
				Unadjusted	Adjusted with HDPS
Any congenital anomaly	None	587 676	11 931	1.0	1.0
	Any	11 903	329	7.3 (4.4, 10.3)	2.9 (0.1, 5.7)
	Codeine	6524	160	1.9 (0.5, 8.0)	2.1 (-1.5, 5.8)
	Morphine	670	25	17.0 (2.7, 31.4)	18.2 (3.2, 33.1)
	Hydromorphone	1824	49	6.6 (-0.9, 14.0)	2.5 (-4.6, 9.5)
	Oxycodone	2885	87	9.9 (3.6, 16.1)	2.8 (-2.9, 8.6)
	Tramadol	781	38	28.4 (13.3, 43.4)	16.0 (2.4, 29.6)
Major anomalies	None	587 676	9264	1.0	1.0
	Any	11 903	247	5.0 (2.4, 7.6)	0.7 (-1.7, 3.1)
	Codeine	6524	121	2.8 (-0.5, 6.1)	>0.1 (-3.1, 3.1)
	Morphine	670	20	14.1 (1.2, 27.0)	16.6 (2.8, 30.3)
	Hydromorphone	1824	33	2.3 (-3.8, 8.5)	-2.4 (-7.8, 3.0)
	Oxycodone	2885	66	7.1 (1.6, 12.6)	-0.5 (-5.2, 4.2)
	Tramadol	781	30	22.6 (9.2, 36.1)	14.8 (2.2, 27.3)
Minor anomalies	None	587 676	3762	1.0	1.0
	Any	11 903	112	3.0 (1.3, 4.8)	1.8 (0.1, 3.5)
	Codeine	6524	49	1.1 (-1.0, 3.2)	2.0 (-0.3, 4.3)
	Morphine	670	5-6[b]	2.6 (-4.6, 9.7)	3.3 (-4.3, 10.9)
	Hydromorphone	1824	21	5.1 (0.2, 10.0)	5.7 (0.6, 10.8)
	Oxycodone	2885	32	4.7 (0.9, 8.5)	3.5 (-0.3, 7.2)
	Tramadol	781	12	9.0 (0.3, 17.6)	3.9 (-3.5, 11.2)
Cardiovascular	None	587 676	3130	1.0	1.0
	Any	11 903	83	1.6 (0.1, 3.2)	0.7 (-0.8, 2.1)
	Codeine	6524	45	1.6 (-0.4, 3.6)	1.0 (-0.9, 3.0)
	Morphine	670	7	5.1 (-2.6, 12.8)	6.6 (-1.8, 15.0)
	Hydromorphone	1824	8	-0.9 (-4.1, 2.1)	-1.1 (-4.1, 2.0)
	Oxycodone	2885	20	1.6 (-1.4, 4.6)	-1.9 (-4.1, 0.3)
	Tramadol	781	11	8.8 (0.5, 17.0)	2.4 (-4.0, 8.7)
Gastrointestinal	None	587 676	2395	1.0	1.0
	Any	11 903	79	2.6 (1.1, 4.0)	1.9 (0.4, 3.3)
	Codeine	6524	41	2.2 (0.3, 4.1)	2.2 (0.2, 4.1)
	Morphine	670	8	7.9 (-0.4, 16.1)	4.3 (-2.8, 11.4)
	Hydromorphone	1824	7	-0.2 (-3.1, 2.6)	0.4 (-2.8, 3.5)
	Oxycodone	2885	20	2.9 (-0.2, 5.9)	0.6 (-2.0, 3.2)
	Tramadol	781	10	8.7 (0.8, 16.6)	6.9 (-0.7, 14.5)
Musculoskeletal	None	587 676	1997	1.0	1.0
	Any	11 903	54	1.1 (-0.1, 2.4)	0.1 (-1.1, 1.2)
	Codeine	6524	26	0.6 (-0.9, 2.1)	0.8 (-0.8, 2.4)
	Hydromorphone	1824	9	1.5 (-1.7, 4.8)	1.7 (-1.7, 5.0)
	Oxycodone	2885	16	2.1 (-0.6, 4.9)	1.8 (-0.9, 4.6)
Genital	None	587 676	1247	1.0	1.0
	Any	11 903	28	0.2 (-0.6, 1.1)	0.1 (-0.7, 1.0)
	Codeine	6524	12	>0.1 (-1.3, 0.8)	-0.4 (-1.5, 0.6)
	Oxycodone	2885	11	1.7 (-0.6, 3.9)	2.9 (0.2, 5.6)

eTable 4. Marginal Risk Differences of Anomalies per 1000 in Pregnancies Exposed During the First Trimester Compared with Unexposed Pregnancies (continued).

Anomaly	Exposure[a]	No. of Infants	No. of infants with anomaly	Marginal Risk Difference per 1000 (95% CI)	
				Unadjusted	Adjusted with HDPS
Urinary	None	587 676	1351	1.0	1.0
	Any	11 903	32	0.4 (-0.5, 1.3)	-1.1 (-1.9, -0.3)
	Codeine	6524	12	-0.5 (-1.5, 0.6)	-0.6 (-1.6, 0.4)
	Hydromorphone	1824	7	1.5 (-1.3, 4.4)	-0.8 (-2.6, 1.0)
	Oxycodone	2885	10	1.2 (-1.0, 3.3)	0.2 (-1.7, 2.2)
	Tramadol	781	5-6[b]	4.1 (-1.5, 9.7)	4.5 (-1.5, 10.5)
Neoplasms & tumours	None	587 676	886	1.0	1.0
	Any	11 903	22	0.3 (-0.4, 1.1)	0.2 (-0.6, 1.0)
	Codeine	6524	11	0.2 (-0.8, 1.2)	0.1 (-0.9, 1.1)
	Tramadol	781	5-6[b]	4.9 (-0.7, 10.5)	5.6 (-0.5, 11.7)
Central nervous system	None	587 676	735	1.0	1.0
	Any	11 903	21	0.5 (-0.2, 1.3)	0.0 (-0.7, 0.7)
	Codeine	6524	7	-0.2 (-1.0, 0.6)	-0.4 (-1.1, 0.3)
	Oxycodone	2885	8	1.5 (-0.4, 3.4)	0.9 (-0.9, 2.6)
Chromosomal	None	587 676	607	1.0	1.0
	Any	11 903	17	0.4 (-0.3, 1.1)	0.1 (-0.6, 0.7)
	Codeine	6524	11	0.7 (-0.3, 1.7)	0.3 (-0.6, 1.2)
Oral clefts	None	587 676	610	1.0	1.0
	Any	11 903	16	0.3 (-0.4, 1.0)	-0.3 (-0.8, 0.2)
	Codeine	6524	7	0.0 (-0.8, 0.8)	-0.7 (-1.1, -0.2)
	Tramadol	781	5-6[b]	5.4 (-0.2, 11.0)	0.5 (-2.4, 3.3)
Respiratory	None	587 676	373	1.0	1.0
	Any	11 903	8	>0.1 (-0.4, 0.5)	-0.2 (-0.6, 0.1)
Eye	None	587 676	278	1.0	1.0
	Any	11 903	9	0.3 (-0.2, 0.8)	0.2 (-0.3, 0.7)
	Codeine	6524	5-6[b]	0.3 (-0.4, 1.0)	0.3 (-0.4, 1.0)
Ear, face and neck	None	587 676	283	1.0	1.0
	Any	11 903	7	0.1 (-0.3, 0.5)	-0.1 (-0.5, 0.2)

[a]We present data on specific opioid analgesic agents where at least 5 infants with the anomaly were exposed.
[b]Due to ICES privacy restrictions, we report anomalies with six or fewer cases as 5-6.

eTable 5. Estimated association of an unmeasured confounder between any opioid analgesic exposure and the particular anomaly needed to fully explain the observed association in our population-based cohort.

Anomaly	Risk Ratio
Any congenital anomaly	1.54
Minor congenital anomalies	1.83
Gastrointestinal anomaly	2.28
Stenosis of pulmonary artery	3.02
Ankyloglossia	3.17
Hypertrophic pyloric stenosis	3.27
Hypertrophic pyloric stenosis (female infants)	7.40

Vanderweele and Ding, Ann Int Med 2017[1]

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding.

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Neoplasms & Tumours and Tramadol	4.71 (1.98-11.17)	4.58 (1.92-10.85)	0.009	0.068	1.5
		4.45 (1.87-10.55)	0.040	0.160	1.5
		4.39 (1.84-10.40)	0.055	0.207	1.5
		4.45 (1.87-10.55)	0.009	0.068	2
		4.22 (1.78-10.01)	0.040	0.160	2
		4.12 (1.73-9.76)	0.055	0.207	2
		4.22 (1.77-10.01)	0.009	0.068	3
		3.85 (1.62-9.14)	0.040	0.160	3
		3.70 (1.55-8.77)	0.055	0.207	3
Congenital Hypertrophic Pyloric Stenosis and Morphine	4.03 (1.35-12.03)	3.92 (1.31-11.69)	0.009	0.068	1.5
		3.81 (1.28-11.36)	0.040	0.160	1.5
		3.75 (1.26-11.20)	0.055	0.207	1.5
		3.81 (1.28-11.37)	0.009	0.068	2
		3.61 (1.21-10.79)	0.040	0.160	2
		3.52 (1.18-10.52)	0.055	0.207	2
		3.61 (1.21-10.78)	0.009	0.068	3
		3.30 (1.10-9.84)	0.040	0.160	3
		3.16 (1.06-9.44)	0.055	0.207	3
Urinary Anomalies and Tramadol	2.95 (1.22-7.14)	2.87 (1.19-6.94)	0.009	0.068	1.5
		2.79 (1.15-6.74)	0.040	0.160	1.5
		2.75 (1.14-6.65)	0.055	0.207	1.5
		2.79 (1.15-6.75)	0.009	0.068	2
		2.64 (1.09-6.40)	0.040	0.160	2
		2.58 (1.07-6.24)	0.055	0.207	2
		2.64 (1.09-6.40)	0.009	0.068	3
		2.41 (1.00-5.84)	0.040	0.160	3
		2.32 (0.96-5.60)	0.055	0.207	3
Gastrointestinal Anomalies and Tramadol	2.69 (1.34-5.38)	2.61 (1.30-5.23)	0.009	0.068	1.5
		2.54 (1.27-5.08)	0.040	0.160	1.5
		2.50 (1.25-5.01)	0.055	0.207	1.5
		2.54 (1.27-5.08)	0.009	0.068	2
		2.41 (1.20-4.82)	0.040	0.160	2
		2.35 (1.17-4.70)	0.055	0.207	2
		2.41 (1.20-4.82)	0.009	0.068	3
		2.20 (1.10-4.40)	0.040	0.160	3
		2.11 (1.05-4.22)	0.055	0.207	3
Genital Anomalies and Oxycodone	2.36 (1.37-4.06)	2.29 (1.33-3.94)	0.009	0.068	1.5
		2.23 (1.29-3.83)	0.040	0.160	1.5
		2.20 (1.28-3.78)	0.055	0.207	1.5
		2.23 (1.29-3.84)	0.009	0.068	2
		2.12 (1.23-3.64)	0.040	0.160	2
		2.06 (1.20-3.55)	0.055	0.207	2
		2.11 (1.23-3.64)	0.009	0.068	3
		1.93 (1.12-3.32)	0.040	0.160	3
		1.85 (1.08-3.19)	0.055	0.207	3

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding (continued).

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Atrial Septal Defect and Tramadol	2.28 (0.99-5.25)	2.21 (0.96-5.10)	0.009	0.068	1.5
		2.15 (0.94-4.96)	0.040	0.160	1.5
		2.12 (0.92-4.89)	0.055	0.207	1.5
		2.15 (0.94-4.96)	0.009	0.068	2
		2.04 (0.89-4.71)	0.040	0.160	2
		1.99 (0.87-4.59)	0.055	0.207	2
		2.04 (0.89-4.70)	0.009	0.068	3
		1.87 (0.81-4.30)	0.040	0.160	3
		1.79 (0.78-4.12)	0.055	0.207	3
Cardiovascular Anomalies and Morphine	2.23 (1.10-4.52)	2.17 (1.07-4.39)	0.009	0.068	1.5
		2.11 (1.04-4.27)	0.040	0.160	1.5
		2.08 (1.02-4.21)	0.055	0.207	1.5
		2.11 (1.04-4.27)	0.009	0.068	2
		2.00 (0.99-4.05)	0.040	0.160	2
		1.95 (0.96-3.95)	0.055	0.207	2
		2.00 (0.99-4.05)	0.009	0.068	3
		1.82 (0.90-3.70)	0.040	0.160	3
		1.75 (0.86-3.55)	0.055	0.207	3
Congenital Hypertrophic Pyloric Stenosis and Codeine	2.17 (1.34-3.51)	2.11 (1.30-3.41)	0.009	0.068	1.5
		2.05 (1.27-3.32)	0.040	0.160	1.5
		2.02 (1.25-3.27)	0.055	0.207	1.5
		2.05 (1.27-3.32)	0.009	0.068	2
		1.95 (1.20-3.15)	0.040	0.160	2
		1.90 (1.17-3.07)	0.055	0.207	2
		1.94 (1.20-3.15)	0.009	0.068	3
		1.78 (1.10-2.87)	0.040	0.160	3
		1.70 (1.05-2.76)	0.055	0.207	3
Stenosis of Pulmonary Artery and Codeine	2.16 (1.03-4.51)	2.10 (1.00-4.38)	0.009	0.068	1.5
		2.04 (0.97-4.26)	0.040	0.160	1.5
		2.01 (0.96-4.20)	0.055	0.207	1.5
		2.04 (0.97-4.26)	0.009	0.068	2
		1.94 (0.92-4.04)	0.040	0.160	2
		1.89 (0.90-3.94)	0.055	0.207	2
		1.94 (0.92-4.04)	0.009	0.068	3
		1.77 (0.84-3.69)	0.040	0.160	3
		1.70 (0.81-3.54)	0.055	0.207	3
Ankyloglossia and Codeine	2.14 (1.35-3.40)	2.08 (1.31-3.30)	0.009	0.068	1.5
		2.02 (1.28-3.21)	0.040	0.160	1.5
		1.99 (1.26-3.17)	0.055	0.207	1.5
		2.02 (1.28-3.21)	0.009	0.068	2
		1.92 (1.21-3.05)	0.040	0.160	2
		1.87 (1.18-2.97)	0.055	0.207	2
		1.92 (1.21-3.05)	0.009	0.068	3
		1.75 (1.10-2.78)	0.040	0.160	3
		1.68 (1.06-2.67)	0.055	0.207	3

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding (continued).

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Major Anomalies and Morphine	2.05 (1.34-3.13)	1.99 (1.30-3.04)	0.009	0.068	1.5
		1.94 (1.27-2.96)	0.040	0.160	1.5
		1.91 (1.25-2.91)	0.055	0.207	1.5
		1.94 (1.27-2.96)	0.009	0.068	2
		1.84 (1.20-2.81)	0.040	0.160	2
		1.79 (1.17-2.74)	0.055	0.207	2
		1.84 (1.20-2.80)	0.009	0.068	3
		1.68 (1.10-2.56)	0.040	0.160	3
		1.61 (1.05-2.46)	0.055	0.207	3
Major Anomalies and Tramadol	1.94 (1.28-2.92)	1.88 (1.24-2.84)	0.009	0.068	1.5
		1.83 (1.21-2.76)	0.040	0.160	1.5
		1.81 (1.19-2.72)	0.055	0.207	1.5
		1.83 (1.21-2.76)	0.009	0.068	2
		1.74 (1.15-2.62)	0.040	0.160	2
		1.70 (1.12-2.55)	0.055	0.207	2
		1.74 (1.15-2.62)	0.009	0.068	3
		1.59 (1.05-2.39)	0.040	0.160	3
		1.52 (1.00-2.29)	0.055	0.207	3
Congenital Hypertrophic Pyloric Stenosis and Any Opioid	1.93 (1.32-2.82)	1.87 (1.28-2.74)	0.009	0.068	1.5
		1.82 (1.25-2.66)	0.040	0.160	1.5
		1.80 (1.23-2.63)	0.055	0.207	1.5
		1.82 (1.25-2.66)	0.009	0.068	2
		1.73 (1.18-2.53)	0.040	0.160	2
		1.69 (1.15-2.46)	0.055	0.207	2
		1.73 (1.18-2.53)	0.009	0.068	3
		1.58 (1.08-2.31)	0.040	0.160	3
		1.52 (1.04-2.21)	0.055	0.207	3
Any Congenital Anomaly and Morphine	1.89 (1.28-2.79)	1.84 (1.24-2.71)	0.009	0.068	1.5
		1.79 (1.21-2.64)	0.040	0.160	1.5
		1.76 (1.19-2.60)	0.055	0.207	1.5
		1.79 (1.21-2.64)	0.009	0.068	2
		1.69 (1.15-2.50)	0.040	0.160	2
		1.65 (1.12-2.44)	0.055	0.207	2
		1.69 (1.15-2.50)	0.009	0.068	3
		1.55 (1.05-2.28)	0.040	0.160	3
		1.48 (1.00-2.19)	0.055	0.207	3
Minor Anomalies and Hydromorphone	1.89 (1.23-2.89)	1.84 (1.19-2.81)	0.009	0.068	1.5
		1.79 (1.16-2.73)	0.040	0.160	1.5
		1.76 (1.15-2.69)	0.055	0.207	1.5
		1.79 (1.16-2.73)	0.009	0.068	2
		1.69 (1.10-2.59)	0.040	0.160	2
		1.65 (1.08-2.53)	0.055	0.207	2
		1.69 (1.10-2.59)	0.009	0.068	3
		1.55 (1.01-2.36)	0.040	0.160	3
		1.48 (0.97-2.27)	0.055	0.207	3

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding (continued).

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Ankyloglossia and Any Opioid	1.88 (1.30-2.72)	1.83 (1.26-2.64)	0.009	0.068	1.5
		1.78 (1.23-2.57)	0.040	0.160	1.5
		1.75 (1.21-2.53)	0.055	0.207	1.5
		1.78 (1.23-2.57)	0.009	0.068	2
		1.69 (1.17-2.44)	0.040	0.160	2
		1.64 (1.14-2.38)	0.055	0.207	2
		1.68 (1.16-2.44)	0.009	0.068	3
		1.54 (1.06-2.23)	0.040	0.160	3
		1.48 (1.02-2.14)	0.055	0.207	3
Stenosis of Pulmonary Artery and Any Opioid	1.81 (0.99-3.31)	1.76 (0.96-3.22)	0.009	0.068	1.5
		1.71 (0.94-3.13)	0.040	0.160	1.5
		1.69 (0.92-3.08)	0.055	0.207	1.5
		1.71 (0.94-3.13)	0.009	0.068	2
		1.62 (0.89-2.97)	0.040	0.160	2
		1.58 (0.87-2.89)	0.055	0.207	2
		1.62 (0.89-2.97)	0.009	0.068	3
		1.48 (0.81-2.71)	0.040	0.160	3
		1.42 (0.78-2.60)	0.055	0.207	3
Any Congenital Anomaly and Tramadol	1.79 (1.23-2.60)	1.74 (1.19-2.53)	0.009	0.068	1.5
		1.69 (1.16-2.46)	0.040	0.160	1.5
		1.67 (1.15-2.42)	0.055	0.207	1.5
		1.69 (1.16-2.46)	0.009	0.068	2
		1.60 (1.10-2.33)	0.040	0.160	2
		1.56 (1.08-2.27)	0.055	0.207	2
		1.60 (1.10-2.33)	0.009	0.068	3
		1.46 (1.01-2.13)	0.040	0.160	3
		1.41 (0.97-2.04)	0.055	0.207	3
Ventricular Septal Defect and Codeine	1.59 (0.95-2.67)	1.54 (0.92-2.59)	0.009	0.068	1.5
		1.50 (0.90-2.52)	0.040	0.160	1.5
		1.48 (0.88-2.49)	0.055	0.207	1.5
		1.50 (0.90-2.52)	0.009	0.068	2
		1.43 (0.85-2.39)	0.040	0.160	2
		1.39 (0.83-2.33)	0.055	0.207	2
		1.42 (0.85-2.39)	0.009	0.068	3
		1.30 (0.78-2.18)	0.040	0.160	3
		1.25 (0.75-2.10)	0.055	0.207	3
Minor Anomalies and Oxycodone	1.54 (1.05-2.26)	1.50 (1.02-2.20)	0.009	0.068	1.5
		1.45 (0.99-2.13)	0.040	0.160	1.5
		1.43 (0.98-2.10)	0.055	0.207	1.5
		1.45 (0.99-2.14)	0.009	0.068	2
		1.38 (0.94-2.03)	0.040	0.160	2
		1.35 (0.92-1.98)	0.055	0.207	2
		1.38 (0.94-2.03)	0.009	0.068	3
		1.26 (0.86-1.85)	0.040	0.160	3
		1.21 (0.82-1.77)	0.055	0.207	3

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding (continued).

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Gastrointestinal Anomalies and Codeine	1.53 (1.12-2.09)	1.49 (1.09-2.03)	0.009	0.068	1.5
		1.45 (1.06-1.97)	0.040	0.160	1.5
		1.42 (1.04-1.95)	0.055	0.207	1.5
		1.45 (1.06-1.97)	0.009	0.068	2
		1.37 (1.00-1.87)	0.040	0.160	2
		1.34 (0.98-1.83)	0.055	0.207	2
		1.37 (1.00-1.87)	0.009	0.068	3
		1.25 (0.92-1.71)	0.040	0.160	3
		1.20 (0.88-1.64)	0.055	0.207	3
Gastrointestinal Anomalies and Any Opioid	1.46 (1.15-1.85)	1.42 (1.12-1.80)	0.009	0.068	1.5
		1.38 (1.09-1.75)	0.040	0.160	1.5
		1.36 (1.07-1.72)	0.055	0.207	1.5
		1.38 (1.09-1.75)	0.009	0.068	2
		1.31 (1.03-1.66)	0.040	0.160	2
		1.28 (1.01-1.62)	0.055	0.207	2
		1.31 (1.03-1.66)	0.009	0.068	3
		1.19 (0.94-1.51)	0.040	0.160	3
		1.15 (0.90-1.45)	0.055	0.207	3
Any Congenital Anomaly and Oxycodone (*including exposure four weeks before conception*)	1.31 (1.07-1.60)	1.27 (1.04-1.55)	0.009	0.068	1.5
		1.24 (1.01-1.51)	0.040	0.160	1.5
		1.22 (1.00-1.49)	0.055	0.207	1.5
		1.24 (1.01-1.51)	0.009	0.068	2
		1.17 (0.96-1.43)	0.040	0.160	2
		1.15 (0.94-1.40)	0.055	0.207	2
		1.17 (0.96-1.43)	0.009	0.068	3
		1.07 (0.88-1.31)	0.040	0.160	3
		1.03 (0.84-1.26)	0.055	0.207	3
Minor Anomalies and Codeine	1.31 (1.00-1.72)	1.27 (0.97-1.67)	0.009	0.068	1.5
		1.24 (0.94-1.62)	0.040	0.160	1.5
		1.22 (0.93-1.60)	0.055	0.207	1.5
		1.24 (0.94-1.62)	0.009	0.068	2
		1.17 (0.90-1.54)	0.040	0.160	2
		1.15 (0.87-1.50)	0.055	0.207	2
		1.17 (0.90-1.54)	0.009	0.068	3
		1.07 (0.82-1.41)	0.040	0.160	3
		1.03 (0.79-1.35)	0.055	0.207	3
Minor Anomalies and Any Opioid	1.26 (1.03-1.53)	1.22 (1.00-1.49)	0.009	0.068	1.5
		1.19 (0.97-1.45)	0.040	0.160	1.5
		1.17 (0.96-1.42)	0.055	0.207	1.5
		1.19 (0.97-1.45)	0.009	0.068	2
		1.13 (0.92-1.37)	0.040	0.160	2
		1.10 (0.90-1.34)	0.055	0.207	2
		1.13 (0.92-1.37)	0.009	0.068	3
		1.03 (0.84-1.25)	0.040	0.160	3
		0.99 (0.81-1.20)	0.055	0.207	3

eTable 6. Sensitivity results of simple bias analysis for possible unmeasured confounding (continued).

Association	aRR estimated (95% CI)	aRR corrected (95% CI)	p0	p1	RRc
Any Congenital Anomaly and Hydromorphone (*including exposure four weeks before conception*)	1.22 (0.95-1.56)	1.19 (0.92-1.52)	0.009	0.068	1.5
		1.15 (0.90-1.47)	0.040	0.160	1.5
		1.14 (0.88-1.45)	0.055	0.207	1.5
		1.15 (0.90-1.47)	0.009	0.068	2
		1.09 (0.85-1.40)	0.040	0.160	2
		1.07 (0.83-1.36)	0.055	0.207	2
		1.09 (0.85-1.40)	0.009	0.068	3
		1.00 (0.78-1.28)	0.040	0.160	3
		0.96 (0.75-1.22)	0.055	0.207	3
Atrial Septal Defect and Any Opioid	1.22 (0.91-1.62)	1.19 (0.88-1.57)	0.009	0.068	1.5
		1.15 (0.86-1.53)	0.040	0.160	1.5
		1.14 (0.85-1.51)	0.055	0.207	1.5
		1.15 (0.86-1.53)	0.009	0.068	2
		1.09 (0.82-1.45)	0.040	0.160	2
		1.07 (0.80-1.42)	0.055	0.207	2
		1.09 (0.82-1.45)	0.009	0.068	3
		1.00 (0.74-1.33)	0.040	0.160	3
		0.96 (0.71-1.27)	0.055	0.207	3
Any Congenital Anomaly and Codeine (*including exposure four weeks before conception*)	1.13 (0.99-1.29)	1.10 (0.96-1.25)	0.009	0.068	1.5
		1.07 (0.94-1.22)	0.040	0.160	1.5
		1.05 (0.92-1.20)	0.055	0.207	1.5
		1.07 (0.94-1.22)	0.009	0.068	2
		1.01 (0.89-1.16)	0.040	0.160	2
		0.99 (0.87-1.13)	0.055	0.207	2
		1.01 (0.89-1.16)	0.009	0.068	3
		0.92 (0.81-1.06)	0.040	0.160	3
		0.89 (0.78-1.01)	0.055	0.207	3
Any Congenital Anomaly and Any Opioid	1.14 (1.01-1.28)	1.11 (0.98-1.24)	0.009	0.068	1.5
		1.08 (0.95-1.21)	0.040	0.160	1.5
		1.06 (0.94-1.19)	0.055	0.207	1.5
		1.08 (0.95-1.21)	0.009	0.068	2
		1.02 (0.91-1.15)	0.040	0.160	2
		1.00 (0.88-1.12)	0.055	0.207	2
		1.02 (0.91-1.15)	0.009	0.068	3
		0.93 (0.83-1.05)	0.040	0.160	3
		0.89 (0.79-1.00)	0.055	0.207	3
Major Anomalies and Any Opioid	1.04 (0.91-1.20)	1.01 (0.88-1.17)	0.009	0.068	1.5
		0.98 (0.86-1.13)	0.040	0.160	1.5
		0.97 (0.85-1.12)	0.055	0.207	1.5
		0.98 (0.86-1.13)	0.009	0.068	2
		0.93 (0.82-1.08)	0.040	0.160	2
		0.91 (0.80-1.05)	0.055	0.207	2
		0.93 (0.82-1.08)	0.009	0.068	3
		0.85 (0.74-0.98)	0.040	0.160	3
		0.82 (0.71-0.94)	0.055	0.207	3

Abbreviations: aRR, Adjusted Risk Ratio: estimated in study and corrected for unmeasured confounding; p_1 prevalence of confounder in opioid analgesic exposed, p_0 prevalence of confounder in opioid analgesic unexposed; RR_c association between the confounder and the risk of anomaly.

References

1. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.