Maternal opioid treatment after delivery and risk of adverse infant outcomes: population based cohort study

Jonathan S Zipursky,[1,2,3] Tara Gomes,[2,4,5,6] Karl Everett,[2] Andrew Calzavara,[2] J Michael Paterson,[2,4] Peter C Austin,[2,3,4] Muhammad M Mamdani,[2,4,5,6] Joel G Ray,[2,4,5,7] David N Juurlink[1,2,3,4]

For numbered affiliations see end of the article

Correspondence to: J S Zipursky Jonathan.Zipursky@sunnybrook.ca (ORCID 0000-0002-9776-807X)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2023;380:e074005 http://dx.doi.org/10.1136/bmj-2022-074005

Accepted: 13 February 2023

ABSTRACT

OBJECTIVE

To examine whether maternal opioid treatment after delivery is associated with an increased risk of adverse infant outcomes.

DESIGN

Population based cohort study.

SETTING

Ontario, Canada.

PARTICIPANTS

865 691 mother-infant pairs discharged from hospital alive within seven days of delivery from 1 September 2012 to 31 March 2020. Each mother who filled an opioid prescription within seven days of discharge was propensity score matched to a mother who did not.

MAIN OUTCOME MEASURES

The primary outcome was hospital readmission of infants for any reason within 30 days of their mother filling an opioid prescription (index date). Infant related secondary outcomes were any emergency department visit, hospital admission for all cause injury, admission to a neonatal intensive care unit, admission with resuscitation or assisted ventilation, and all cause death.

RESULTS

85 675 mothers (99.8% of the 85 852 mothers prescribed an opioid) who filled an opioid prescription within seven days of discharge after delivery were propensity score matched to 85 675 mothers who did not. Of the infants admitted to hospital within 30 days, 2962 (3.5%) were born to mothers who filled an opioid prescription compared with 3038 (3.5%) born to mothers who did not. Infants of mothers who were prescribed an opioid were no more likely to be admitted to hospital for any reason than infants of mothers who were not prescribed an opioid (hazard ratio 0.98, 95% confidence interval 0.93 to 1.03) and marginally more likely to be taken to an emergency department in the subsequent 30 days (1.04, 1.01 to 1.08), but no differences were found for any other adverse infant outcomes and there were no infant deaths.

CONCLUSIONS

Findings from this study suggest no association between maternal opioid prescription after delivery and adverse infant outcomes, including death.

WHAT IS ALREADY KNOWN ON THIS TOPIC

All opioids pass into breast milk, albeit in amounts not expected to cause respiratory or central nervous system depression in nursing infants

Isolated reports describe opioid toxicity in breastfed infants, hypothesised to reflect the ingestion of large quantities of opioids in breast milk

WHAT THIS STUDY ADDS

This population based study found that infants born to mothers prescribed opioids after delivery were at no greater risk of hospital readmission shortly after birth than infants born to mothers who were not prescribed opioids

The risk of emergency room visits was marginally increased in infants of mothers who filled an opioid prescription

No differences were, however, found for a range of other serious outcomes, including infant death

Introduction

Most mothers in North America initiate breastfeeding in the immediate postpartum period.[1] All opioids pass into breast milk in small amounts, although not in quantities expected to cause respiratory or central nervous system depression in nursing infants.[2-4] Isolated reports describe opioid toxicity in breastfed infants,[3] which some authors have hypothesised reflects the ingestion of large quantities of opioids in breast milk. However, the plausibility of these reports—and one high profile case in particular[5-7]—has been repeatedly questioned,[3-11] and two related articles were recently retracted by the editors of the journals in which they were published.[12]

Owing in part to ongoing regulatory warnings arising from case reports,[13-16] concerns remain about the possibility of breastfeeding related opioid toxicity in infants. This uncertainty might undermine postpartum analgesia and generate unnecessary anxiety for parents. Whether maternal opioid use while breastfeeding truly presents a risk to newborn infants remains the subject of debate. Using eight years of comprehensive population based healthcare data, we examined whether there was an association between maternal opioid prescription after delivery and short term increased risks of adverse outcomes in infants.

Methods

Study setting

This population based retrospective cohort study was conducted in mothers who gave birth between September 2012 and March 2020 in Ontario, Canada (population 14.7 million in 2020). Ontario residents have universal access to physician services and hospital care, and health records can be tracked using well established, routinely collected administrative health data.

Data sources

We identified births in Ontario between 1 September 2012 and 31 March 2020 using the ICES MOMBABY database, which identifies more than 98% of all Ontario births and allows linkage of mother-infant pairs.[17] Postpartum opioid prescriptions were identified using the Narcotics Monitoring System database, which contains detailed information on all prescriptions for opioids and other controlled drugs dispensed from community pharmacies, regardless of payer.[18] This database, launched in July 2012, contains detailed information on drug names, dispensing dates, drug quantities, and number of days of drug supplied. The data are regularly used in studies examining prescription opioid use in Ontario.[18-21]

Data on hospital admissions were obtained from the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed diagnostic and procedural information for all hospital admissions in Ontario.[22] We used the National Ambulatory Care Reporting System database to obtain information on emergency department visits of infants. Basic personal information was obtained from the Ontario Health Insurance Plan's Registered Persons Database, a registry of all Ontarians eligible for health insurance.[23 24] Details on mental health related hospital admissions were obtained using the Ontario Mental Health Reporting System database, and we used Ontario Health Insurance Plan's Claims History database to identify claims for outpatient physician services. The aforementioned databases are held and analysed in anonymised form at ICES (formerly Institute for Clinical Evaluative Sciences) and have been used extensively to study drug safety.[25-28]

Identification of participants

Our cohort comprised mothers who gave birth to a liveborn infant in a hospital in Ontario, Canada between 1 September 2012 and 31 March 2020. We restricted the analysis to singleton pregnancies so that each mother's prescription history could be related to the health of a single infant. The requirement was that each mother-infant pair should have been discharged from hospital alive within seven days of delivery, because extended hospital stays could reflect prematurity or complications that might impact the likelihood of a maternal opioid prescription or subsequent hospital admission of an infant. Only mother-infant pairs discharged from hospital on the same date were included. If mothers gave birth multiple times over the study period, we only analysed the first delivery. We excluded those who filled any opioid prescription, including buprenorphine or methadone, in the 100 days preceding the index prescription. To minimise the possibility of pregnancy misclassification, we excluded women younger than 12 years or older than 60 years.

We considered mothers to have used an opioid if they filled a prescription for morphine, codeine, hydromorphone, oxycodone, tramadol, or fentanyl between delivery and up to seven days after discharge from hospital. We matched each mother who filled an opioid prescription to one who did not on propensity score.[29] Mothers who filled an opioid prescription after delivery were matched to those who did not on age (±1 year), calendar year of delivery (±1 year), mode of delivery, and the logit of the propensity score using greedy nearest neighbour matching without replacement and a caliper width of 0.2 of the standard deviation of the logit of the propensity score.[30] We defined the index date as the date on which the opioid prescription was filled after discharge, or date of discharge if the prescription was filled before discharge. Mothers who had filled an opioid prescription were excluded if we were unable to match them with mothers who had not filled an opioid prescription.

A simulated index date was assigned to mothers who did not fill an opioid prescription after delivery. To generate this date, we first calculated a variable denoting the time from hospital discharge to opioid prescription for all mothers who received one. Random index dates were then assigned to the mothers who had not received an opioid prescription based on the frequency distribution of that variable. We matched mothers with an opioid prescription to mothers without an opioid prescription to equalise the time between hospital discharge date and the index date for each pair. Mother-infant pairs were further excluded if infants were readmitted to hospital before the index date.

Readmission of infants

We followed all infants until 30 days after the index date assigned to the mothers. The primary outcome was readmission of an infant to hospital for any reason within 30 days of the index date. Data were also collected on the main diagnoses for readmission of infants by opioid prescription category (filled or not filled) using ICD-10 (international classification of diseases, 10th revision) codes, grouped according to the diagnosis most likely to be the cause of readmission. We calculated rate ratios with 95% confidence intervals comparing the main five causes of admission, with infants of mothers not prescribed opioids as the reference group.

A series of secondary outcomes were examined individually in infants within 30 days of the index date, including visits to an emergency department for any reason, hospital admission for injury of any type, admission to a neonatal intensive care unit, hospital admission with resuscitation or assisted ventilation, and death. For infants with multiple outcomes of the same type during follow-up, we only considered the first occurrence. Finally, because codeine has been the focus of most of the recent literature in this subject, we performed a prespecified subgroup analysis limited to mothers who were dispensed codeine, and their matched controls.

Statistical analysis

Standardised differences were used to compare baseline characteristics between mothers who filled

an opioid prescription and those who did not, along with their infants, before and after propensity score matching.[31] We estimated the propensity score using a logistic regression model in which filling an opioid prescription after delivery was regressed on measured maternal, infant, and delivery characteristics. Standardised differences <0.1 generally indicate good balance between groups for a given covariate.[32]

The primary analysis used Cox proportional hazards regression, with infants of mothers who did not fill an opioid prescription being the reference group. Hazard ratios are reported along with 95% confidence intervals, with a two tailed type 1 error rate of 0.05 used as the threshold for statistical significance. To account for matching of the sample, we used a robust variance estimator to obtain the standard errors used to obtain tests of statistical significance and 95% confidence intervals.[33 34] We censored outcomes at 30 days after the index date and we censored mother-infant pairs if a mother who initially did not fill an opioid prescription subsequently did in the 30 days after the index date; in such instances, we censored matched infants on the date of that prescription.

To test the proportional hazards assumption, we plotted the log(–log(survival)) over log(time) for both study groups for the primary outcome and secondary outcomes, and the functions were approximately parallel (see supplementary figure S5). To confirm results, we performed prespecified sensitivity analyses using modified Poisson regression to estimate relative risks. Modified Poisson regression can be used to analyse prospective data with a binary primary outcome and generates relative risks rather than odds ratios.[35 36]

We also generated estimates of absolute risk differences for each outcome using the Kaplan-Meier method to compare mother-infant pairs in both study groups at 30 days. Using bootstrap methods of 2000

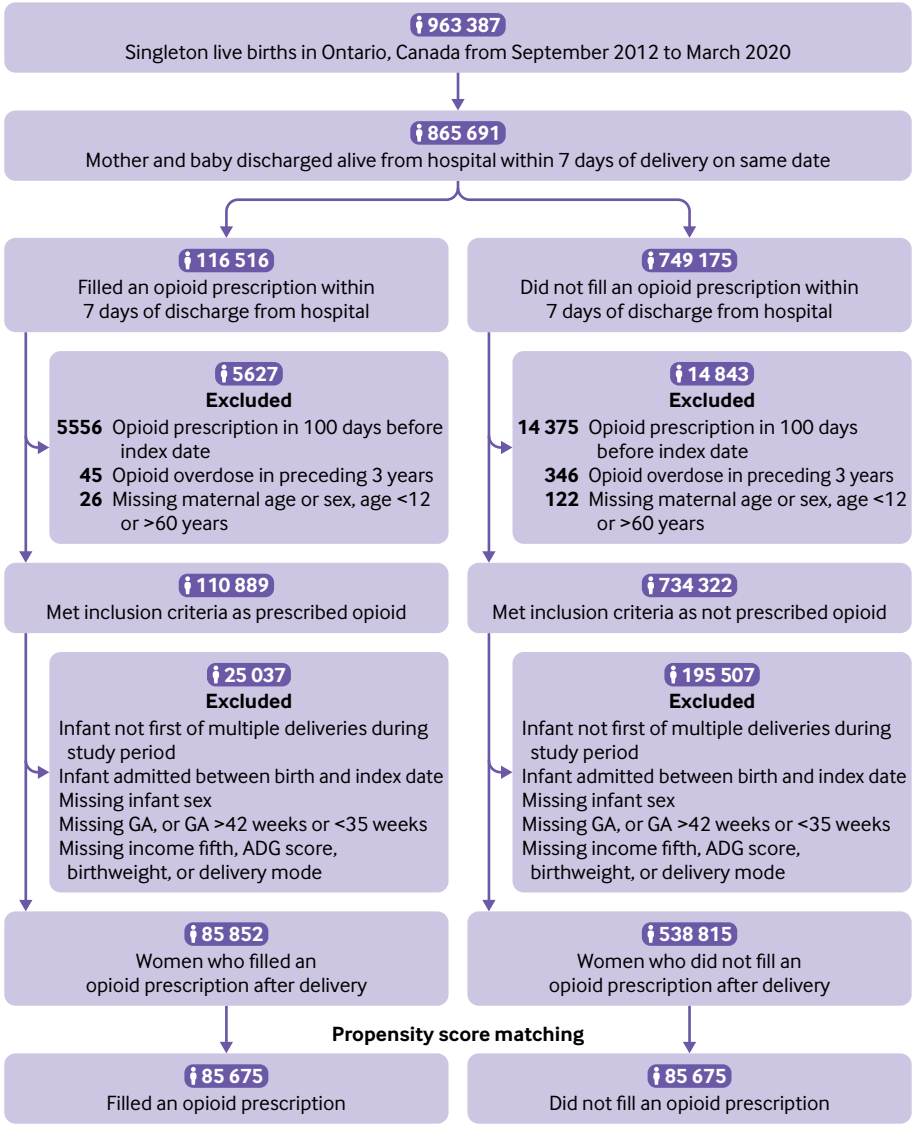


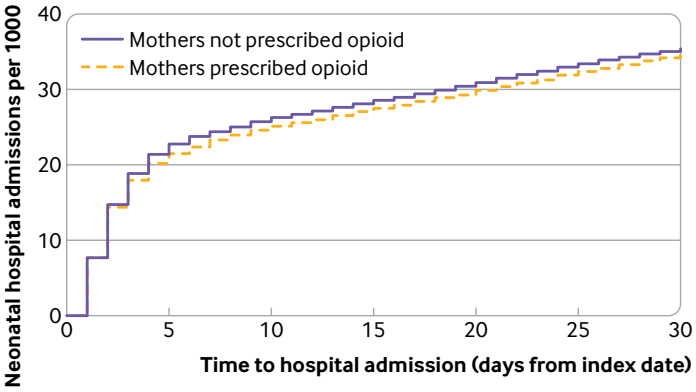
Fig 1 | Flow of participants through cohort. ADG=aggregated diagnosis groups (defined using the Johns Hopkins ACG System version 10)[37]; GA=gestational age

Table 1 | Characteristics of mother-infant pairs on the basis of maternal opioid prescription seven days after delivery, before and after propensity score matching. Values are number (percentage) unless stated otherwise

	Before propensity score matching			After propensity score matching		
Characteristic	Opioid (n=85 852)	No opioid (n=538 815)	Standardised difference	Opioid (n=85 675)	No opioid (n=85 675)	Standardised difference
Maternal						
Median (IQR) age (years)	32 (28-35)	31 (27-34)	0.196	32 (28-35)	32 (28-35)	0.000
Income fifth:						
1 (lowest)	17 545 (20.4)	121 561 (22.6)	0.052	17 522 (20.5)	17 635 (20.6)	0.003
2	16 662 (19.4)	110 673 (20.5)	0.028	16 646 (19.4)	16 842 (19.7)	0.006
3	17 145 (20.0)	112 245 (20.8)	0.021	17 113 (20.0)	17 274 (20.2)	0.005
4	18 702 (21.8)	109 866 (20.4)	0.034	18 652 (21.8)	18 537 (21.6)	0.003
5 (highest)	15 798 (18.4)	84 470 (15.7)	0.073	15 742 (18.4)	15 387 (18.0)	0.011
Rural residence	7251 (8.4)	48 200 (8.9)	0.018	7242 (8.5)	7029 (8.2)	0.009
Year of delivery:						
2012	4702 (5.5)	33 126 (6.1)	0.029	4687 (5.5)	4635 (5.4)	0.003
2013	14 041 (16.4)	96 402 (17.9)	0.041	14 006 (16.3)	14 066 (16.4)	0.002
2014	13 237 (15.4)	88 222 (16.4)	0.026	13 220 (15.4)	13 220 (15.4)	0.000
2015	11 608 (13.5)	72 700 (13.5)	0.001	11 589 (13.5)	11 611 (13.6)	0.001
2016	10 984 (12.8)	63 870 (11.9)	0.029	10 960 (12.8)	10 919 (12.7)	0.001
2017	10 098 (11.8)	59 810 (11.1)	0.021	10 080 (11.8)	10 129 (11.8)	0.002
2018	9938 (11.6)	56 217 (10.4)	0.037	9921 (11.6)	9899 (11.6)	0.001
2019	9149 (10.7)	55 407 (10.3)	0.012	9126 (10.7)	9151 (10.7)	0.001
2020	2095 (2.4)	13 061 (2.4)	0.001	2086 (2.4)	2045 (2.4)	0.003
Median (IQR) No of previous live births	0 (0-1)	0 (0-1)	0.080	0 (0-1)	0 (0-1)	0.004
Primigravid	51 868 (60.4)	305 050 (56.6)	0.077	51 724 (60.4)	51 626 (60.3)	0.002
Mental health diagnosis	10 353 (12.1)	50 543 (9.4)	0.087	10 279 (12.0)	9534 (11.1)	0.027
Substance misuse diagnosis	1116 (1.3)	6301 (1.2)	0.012	1107 (1.3)	1004 (1.2)	0.011
Median (IQR) ADG score	8 (6-11)	8 (6-10)	0.268	8 (6-11)	8 (6-11)	0.008
Hypertension	10 334 (12.0)	44 976 (8.3)	0.122	10 291 (12.0)	10 074 (11.8)	0.008
Diabetes	10 259 (11.9)	51 107 (9.5)	0.080	10 243 (12.0)	10 341 (12.1)	0.004
Delivery						
Mode of delivery:						
Vaginal						
Spontaneous	11 572 (13.5)	371 999 (69.0)	1.367	11 550 (13.5)	11 550 (13.5)	0.000
Operative	4923 (5.7)	55 013 (10.2)	0.166	4864 (5.7)	4864 (5.7)	0.000
Caesarean	69 357 (80.8)	111 803 (20.7)	1.502	69 261 (80.8)	69 261 (80.8)	0.000
Median (IQR) gestational age (weeks)	39 (38-40)	39 (38-40)	0.121	39 (38-40)	39 (38-40)	0.004
Episiotomy	5754 (6.7)	65 198 (12.1)	0.186	5673 (6.6)	5988 (7.0)	0.015
Perineal tear:						
1st/2nd degree	8828 (10.3)	268 509 (49.8)	0.956	8819 (10.3)	8555 (10.0)	0.010
3rd/4th degree	2746 (3.2)	21 252 (3.9)	0.04	2675 (3.1)	2679 (3.1)	0.000
Median (IQR) No of days to index	0 (0-0)	0 (0-0)	0.018	0 (0-0)	0 (0-0)	0.000
Severe maternal morbidity	1724 (2.0)	4395 (0.8)	0.101	1717 (2.0)	1672 (2.0)	0.004
Median (IQR) hospital length of stay post delivery (days)	2 (2-2)	1 (1-2)	0.890	2 (2-2)	2 (2-2)	0.017
Infant						
Female sex	40 859 (47.6)	267 558 (49.7)	0.041	40 780 (47.6)	40 631 (47.4)	0.003
Median (IQR) birthweight (g)	3435 (3115-3770)	3373 (3075-3685)	0.126	3434 (3115-3770)	3432 (3111-3765)	0.006
Complications at birth:						
Chorioamnionitis	79 (0.1)	178 (0.0)	0.024	79 (0.1)	62 (0.1)	0.007
Chromosomal anomaly	19 (0.0)	129 (0.0)	0.001	19 (0.0)	20 (0.0)	0.001
Congenital anomaly	1679 (2.0)	8421 (1.6)	0.03	1669 (1.9)	1623 (1.9)	0.004
Congenital viral illness	1-5*	9-13*	0.003	0	0	NA
Other diseases of prematurity	598 (0.7)	3750 (0.7)	0.00	592 (0.7)	581 (0.7)	0.002
Neonatal haemorrhage	67 (0.1)	479 (0.1)	0.004	67 (0.1)	63 (0.1)	0.002
Kernicterus	1-5*	1-5*	0.003	0	0	NA
Assisted ventilation	3080 (3.6)	12 292 (2.3)	0.077	3070 (3.6)	2943 (3.4)	0.008
Necrotising enterocolitis	1-5*	1-5*	0.003	0	0	NA
NICU admission	6220 (7.2)	22 594 (4.2)	0.132	6202 (7.2)	6133 (7.2)	0.003
Respiratory distress	3781 (4.4)	15 067 (2.8)	0.086	3768 (4.4)	3680 (4.3)	0.005
Sepsis	100 (0.1)	434 (0.1)	0.011	100 (0.1)	102 (0.1)	0.001
Intrauterine hypoxia/asphyxia	281 (0.3)	1056 (0.2)	0.026	277 (0.3)	252 (0.3)	0.005
Periventricular leukomalacia or intraventricular haemorrhage	6 (0.0)	27 (0.0)	0.003	6-10*	1-5*	0.001

ADG=aggregated diagnosis groups defined using the Johns Hopkins ACG System version 10[37]; IQR=interquartile range; NA=not applicable; NICU=neonatal intensive care unit.
*Exact cell sizes suppressed because of institutional privacy regulations.

independent samples, we calculated confidence intervals for the risk difference. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC).



No of infants at risk

No opioid	85 675	83 835	83 315	82 880	82 566	82 257	82 003
Opioid	85 675	83 940	83 407	82 969	83 648	82 336	82 065

Fig 2 | Cumulative incidence curves for all cause hospital admission in infants by maternal opioid prescription

Patient and public involvement

No patients or members of the public were involved in the design, conduct, or interpretation of the study, owing to the retrospective and deidentified nature of the data as well as ICES privacy restrictions.

Results

Full cohort

Overall, we identified 963 387 singleton live births from 1 September 2012 to 31 March 2020 in Ontario, Canada (fig 1). Of the 624 667 mothers identified after exclusions, 85 852 (13.7%) filled an opioid prescription within seven days of discharge after delivery and 538 815 (86.3%) did not. The percentage of mothers who filled an opioid prescription differed based on mode of delivery, and the proportion declined gradually over the study interval (see supplementary figure S1). Most opioid prescriptions issued after delivery were for oxycodone (42.0%), morphine (19.3%), codeine (19.9%), and hydromorphone (12.0%). The types of opioids dispensed to mothers after delivery has changed over time from 2012 to 2020, as evidenced by a trend towards fewer prescriptions for codeine and increasingly more prescriptions for oxycodone, morphine, and hydromorphone (see supplementary figure S2). The median total dispensed dose of opioid prescriptions was 135.0 morphine milligram equivalents (interquartile range (IQR) 90-150), and the median number of days for drugs supplied was 3 (IQR 2-4).

Propensity score matched cohort

After propensity score matching, we identified 85 675 (99.8% of the 85 852 mothers successfully matched to a control) mothers who filled an opioid prescription and an equal number who did not, with good balance across baseline characteristics (table 1).

Hospital admission of infants

In the primary analysis, 2962 (3.5%) children born to mothers who filled an opioid prescription were admitted to hospital in the subsequent 30 days, compared with 3038 (3.5%) children born to mothers who did not fill an opioid prescription. Among those admitted to hospital, the median time from index date to admission was 3 days (IQR 2-12) in infants of mothers prescribed opioids and 3 days (IQR 2-11) in infants of mothers not prescribed opioids (P=0.54). Infants of mothers prescribed opioids were no more likely than infants of mothers not prescribed opioids to be readmitted to hospital in the 30 days after the index date (hazard ratio 0.98, 95% confidence interval 0.93 to 1.03; fig 2 and table 2). This finding corresponds to an absolute risk difference of 0.08% (95% confidence interval −0.06% to 0.22%). We found consistent results in a sensitivity analysis using modified Poisson regression (see supplementary table S2).

The main five reasons for readmission in infants did not differ meaningfully between the two study groups, with the exception of jaundice (fig 3). Hospital admissions for jaundice were less common among infants born to mothers who filled an opioid prescription compared with infants born to mothers who did not (rate ratio 0.84, 95% confidence interval 0.78 to 0.90).

Secondary outcomes

In secondary analyses, we examined the association between postpartum opioid prescriptions and adverse infant outcomes in the ensuing 30 days. Infants born to mothers prescribed opioids after delivery were slightly more likely to be taken to the emergency department in the subsequent 30 days (hazard ratio 1.04, 1.01 to 1.08; table 2) compared with infants born to mothers not prescribed opioids, corresponding to an absolute risk increase of 0.41% (95% confidence interval 0.17% to 0.63%). However, in addition to no difference in the risk of hospital admission for any cause, we found no association between a postpartum opioid prescription and infant admission to a neonatal intensive care unit (hazard ratio 1.12, 0.94 to 1.32), admission with resuscitation or assisted ventilation (0.87, 0.60 to 1.26), or admission with injury (1.24, 0.92 to 1.67) (table 2). For each of the secondary outcomes, results were again consistent in analyses using modified Poisson regression (see supplementary table S2). During nearly five million person days of follow-up no infant deaths occurred.

Codeine and infant hospital admission

Overall, 17 037 mothers who filled a codeine prescription were matched on propensity score to an equal number of mothers who did not. The personal characteristics of these groups were similar to those of participants in the primary analysis, with acceptable balance on baseline characteristics (see supplementary table S1). In this analysis, 474 (2.8%) infants born to mothers who filled a codeine prescription were admitted to hospital in the subsequent 30 days,

Table 2 | Association between maternal postpartum opioid prescriptions and adverse infant outcomes

Outcomes in infants	No (%) of events in infants: Maternal opioid prescription (n=85 675)	No maternal opioid prescription (n=85 675)	Hazard ratio (95% CI)	P value
Primary outcome				
Admission to hospital	2962 (3.46)	3038 (3.55)	0.98 (0.93 to 1.03)	0.36
Secondary outcomes				
Emergency department visit	9053 (10.6)	8714 (10.2)	1.04 (1.01 to 1.08)	0.004
Admission to NICU	287 (0.33)	256 (0.30)	1.12 (0.94 to 1.32)	0.20
Admission with resuscitation or assisted ventilation	53 (0.03)	61 (0.04)	0.87 (0.60 to 1.26)	0.45
Admission with injury	99 (0.12)	80 (0.09)	1.24 (0.92 to 1.67)	0.15
Death	0	0	NA	NA

CI=confidence interval; NA=not applicable; NICU=neonatal intensive care unit.

compared with 638 (3.7%) infants born to mothers who did not fill an opioid prescription. Compared with infants born to mothers who were not prescribed an opioid, those born to mothers prescribed codeine were less likely to be admitted to hospital in the 30 days after the index date (hazard ratio 0.74, 95% confidence interval 0.66 to 0.83, see supplementary figure S3). This corresponded to an absolute risk reduction of 0.96% (95% confidence interval 0.68% to 1.23%).

Supplementary figure S4 shows the main five diagnosis categories for hospital admission of infants in the codeine subgroup. Admissions for jaundice (rate ratio 0.50, 95% confidence interval 0.41 to 0.61) and feeding difficulties (0.50, 0.30 to 0.83) were less common among infants of mothers who filled a codeine prescription than among infants of mothers who did not fill a codeine prescription. No significant differences were found in readmission rates for the other main diagnostic categories.

Discussion

This population based study with data spanning almost eight years and including more than 80 000 infants born to mothers prescribed opioids after delivery (mainly caesarean) found that infants were at no greater risk of readmission shortly after birth than infants born to mothers who were not prescribed opioids. We found a marginally increased risk of visits to an emergency department in infants of mothers who filled an opioid prescription, but no significant differences in a range of adverse infant outcomes and no infant deaths.

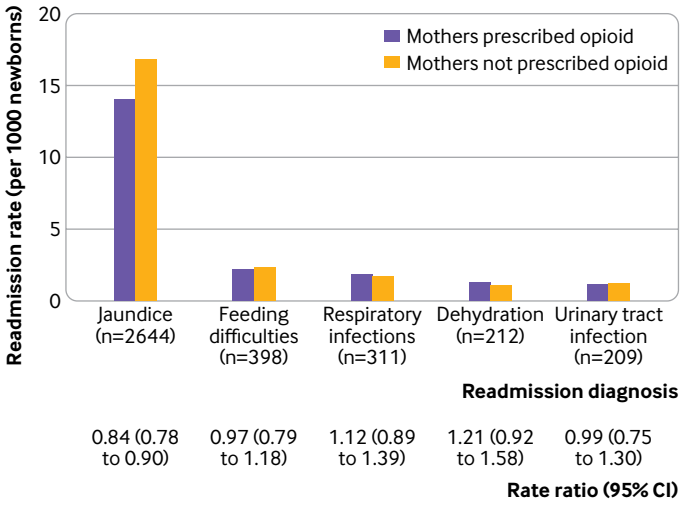


Fig 3 | Main five reasons for readmission to hospital in 2962 infants of mothers prescribed an opioid after index delivery and 3038 infants of mothers not prescribed an opioid. CI=confidence interval

Comparison with other studies

Our findings indicate that readmission of infants to hospital is no more likely among those born to mothers prescribed opioids after delivery than among those born to mothers not prescribed opioids after delivery. Adverse events were rare in the infants and most tended to occur shortly after initial hospital discharge. Moreover, these findings are concordant with a previous study in Ontario involving nearly 8000 mothers in receipt of social assistance who filled a postpartum prescription for codeine.[38] Our study extends this work by examining all in-hospital deliveries in Ontario, all opioid prescriptions rather than just for codeine, and all prescriptions regardless of payer. Our findings are also consistent with the observation that millions of mothers in North America and hundreds of thousands of new mothers are prescribed opioids after delivery each year.[39] Despite these findings, no convincing reports have been published of serious opioid toxicity in infants associated with breastfeeding.[3]

The basis of the lower risk of hospital admission in infants born to mothers prescribed codeine is unclear but might be explained by unmeasured confounding. Prescribers might issue codeine to mothers after delivery in situations deemed to be particularly safe and in ways not captured by the factors we included in the propensity score. In addition, based on earlier warnings, codeine may be preferentially prescribed to mothers who are less likely to breastfeed. Indeed, increased rates of formula feeding in this group could explain why we observed a lower rate of readmissions for jaundice (eg, less breastfeeding related jaundice) and feeding difficulties in infants born to mothers who received codeine. We acknowledge that if mothers who were prescribed opioids are less likely to breastfeed, this would affect our study's ability to detect a true association between maternal opioid use and opioid toxicity in infants.

As outlined in a recent review, concerns about opioid toxicity in breastfed infants seem to be

doi: 10.1136/bmj-2022-074005 | *BMJ* 2023;380:e074005 | the bmj

unsubstantiated.[3] Most of the postulated risks are based on poorly documented historical reports and relate specifically to maternal codeine use. In mothers, overactivity of cytochrome P450 isoform 2D6 (CYP2D6), the enzyme responsible for codeine's bioactivation to morphine, was postulated as the mechanism responsible for toxicity in infants. The theory postulated was that mothers with gene duplications leading to overexpression of CYP2D6 generated greater amounts of morphine, which then passed into breast milk and placed infants at risk. However, our work and that of others has shown that maternal CYP2D6 genotype is unlikely to have a meaningful impact on the risk of opioid toxicity in breastfed infants.[3 11] Maternal and infant drug clearance are more important determinants of drug accumulation in infants.[3 11] In addition, the amount of drug ingested during breastfeeding is usually estimated by the relative infant dose, which represents the average daily dose of drug ingested expressed as a percentage of the weight adjusted average maternal daily dose.[2] All opioids fall well below the safety cut-off for relative infant dose (<10%) during breastfeeding.[2 4]

Our findings should not be construed as an endorsement of liberal postpartum opioid use. Until recently, theoretical risks to infants associated with opioid use in mothers after delivery have greatly overshadowed the much more likely risks to mothers.[4] Although adequate treatment of postpartum pain is essential and for some mothers other analgesics will not be appropriate, clinicians and patients should use caution when initiating opioids after delivery. Untreated maternal pain can interfere with self-care, baby care, and infant bonding and is associated with increased rates of postpartum depression and chronic persistent pain.[40]

Recent observational studies of mothers after delivery have also characterised important adverse maternal outcomes associated with new opioid use. These include persistent opioid use in the year after delivery and serious opioid related events, including initiation of opioid maintenance treatment, overdose, and even death.[41-43] These maternal events, although rare, are serious and could also indirectly impact the health of infants. Our findings help clarify that providers should focus on the potential risks of postpartum opioid treatment as they relate to mothers and their infants rather than to infants alone. Evidence based guidelines for the management of postpartum pain would help in this regard.

Strengths and limitations of this study

This study has several limitations. Firstly, we used administrative data to identify filled opioid prescriptions, and therefore information on the extent to which the drugs were taken and the use of other common postpartum analgesics, including non-steroidal anti-inflammatory drugs and paracetamol (acetaminophen), was lacking. Secondly, we lacked information on breastfeeding status. In North America, however, more than 80% of mothers attempt breastfeeding.[1] In Ontario, more than 90% of mothers initiate breastfeeding, and a similar number continue to do so two months after delivery.[44] For this reason we intentionally selected a short follow-up period (30 days) to assess infant outcomes. Our cohort is, however, likely to include mothers who were (and were not) breastfeeding to various degrees. We acknowledge that avoidance or minimisation of breastfeeding in mothers using opioids after delivery would limit our ability to detect any true association between maternal postpartum opioid use and opioid toxicity in infants.

Thirdly, we were unable to identify opioids used for analgesia during delivery and before hospital discharge, and we lacked data on use of non-prescription opioids. In Canada, 8 mg codeine tablets can be purchased from pharmacies. We suspect that such purchases are uncommon in the first month after delivery, especially when prescription opioids are so easily obtained. Moreover, we postulate that use of non-prescription opioids might be more common in the mothers who were not prescribed postpartum opioids, which would likely bias our results to the null. In addition, mothers might occasionally receive a small supply of opioids at hospital discharge to take home. Although we were not able to capture this practise in our data, we anticipate that the volume of these take home prescriptions would be small enough not to have clinical impact.

Fourthly, some of our results may be affected by residual confounding as we were unable to account for all potential factors associated with maternal receipt of a postpartum opioid prescription. However, we used propensity score matching to minimise confounding due to measured covariates. Fifthly, by requiring opioid prescriptions to be filled within a week of delivery, our study mainly comprised mothers who underwent caesarean delivery. Sixthly, we were unable to account for the estimated >3000 (about 2%) births that occur out of hospital each year in Ontario.[45] Finally, our study was conducted in a setting in which mothers and infants have universal access to healthcare, and the generalisability of our findings to other settings is unknown.

Conclusions

This study found no association between maternal opioid prescription after delivery and several adverse infant outcomes, including death. Although we endorse caution in short term postpartum opioid use in selected mothers, clinicians and parents should be reassured that infants are at low risk of harm.

AUTHOR AFFILIATIONS

[1]Department of Medicine, Sunnybrook Health Sciences Centre, Toronto ON M4N 3M5, Canada

[2]ICES, Toronto, Ontario, Canada

[3]Sunnybrook Research Institute, Toronto, Ontario, Canada

[4]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

[5]Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Ontario, Canada

[6]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

[7]Department of Medicine, St Michael's Hospital, Toronto, Ontario, Canada

We thank IQVIA Solutions Canada for use of their Drug Information File. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Contributors: JSZ, TG, KE, AC, PA, JGR, and DNJ conceived and designed the study. JSZ, TG, KE, PA, JGR, and DNJ analysed and interpreted the data. JSZ and DNJ drafted the article. All authors revised the article critically for important intellectual content and gave final approval of the version to be published. All authors had access to the data in the study and take responsibility for the integrity of the data and accuracy of the analysis. JSZ and DNJ are the guarantors. JSZ attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long term Care. The research was funded by a Canadian Institute for Health Research project grant (PJT162139). JSZ was supported by the University of Toronto Department of Medicine Clinician Scientist Training Program and a Canadian Institute for Health Research Banting and Best Doctoral Award. PA is supported by a Mid-Career Investigator Award from the Heart and Stroke Foundation. TG is supported by a Tier 2 Canada Research Chair in Drug Policy Research and Evaluation. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: JSZ has received payments for medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids; DNJ is an unpaid member of Physicians for Responsible Opioid Prescribing (PROP). DNJ is also a member of the American College of Medical Toxicology. DNJ has received payment for lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids. TG is supported by a Canada Research Chair in Drug Policy Research and Evaluation and has received funding from the Ontario Ministry of Health.

Ethical approval: The use of the data in this project is authorised under section 45 of Ontario's Personal Health Information Protection Act and does not require review by a research ethics board. ICES is an independent, non-profit research institute with legal status under Ontario's health information privacy law that allows it to collect and analyse healthcare and personal data without consent for health system evaluation and improvement.

Data sharing: The dataset from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (eg, healthcare organisations and governments) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS (das@ices.on.ca). The full dataset creation plan and underlying analytical code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification. The study also used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from Canada Post and Statistics Canada.

The lead and senior authors (JSZ and DNJ, the manuscript's guarantors) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered), have been explained.

Dissemination to participants and related patient and public communities: Results of this study have been shared with the Ontario Ministry of Health and ICES. After publication, results will be shared with patients and relevant communities through the media, conference proceedings, and social media.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Centers for Disease Control and Prevention. Breastfeeding Report Card. CDC, 2020. https://www.cdc.gov/breastfeeding/data/reportcard.htm
2 Ito S. Opioids in Breast Milk: Pharmacokinetic Principles and Clinical Implications. *J Clin Pharmacol* 2018;58(Suppl 10):S151-63. doi:10.1002/jcph.1113.
3 Zipursky J, Juurlink DN. The Implausibility of Neonatal Opioid Toxicity from Breastfeeding. *Clin Pharmacol Ther* 2020;108:964-70. doi:10.1002/cpt.1882.
4 Zipursky J, Juurlink DN. Opioid use in pregnancy: An emerging health crisis. *Obstet Med* 2021;14:211-9. doi:10.1177/1753495X20971163.
5 Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006;368:704. doi:10.1016/S0140-6736(06)69255-6.
6 Madadi P, Koren G, Cairns J, et al. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician* 2007;53:33-5.
7 Madadi P, Koren G, Cairns J, et al. Maternal codeine is not safe for all breast-fed infants. [Retracted article.] *Can Pharm J* 2006;139:56-60. doi:10.1177/171516350613900610.
8 Bateman DN, Eddleston M, Sandilands E. Codeine and breastfeeding. *Lancet* 2008;372:625, author reply 626. doi:10.1016/S0140-6736(08)61266-0.
9 Ferner RE. Did the drug cause death? Codeine and breastfeeding. *Lancet* 2008;372:606-8. doi:10.1016/S0140-6736(08)61254-4.
10 Young M. Morphine in breast milk. *Can Fam Physician* 2007;53:1005-6, author reply 1005-6. https://www.ncbi.nlm.nih.gov/pubmed/17872775.
11 Willmann S, Edginton AN, Coboeken K, Ahr G, Lippert J. Risk to the breast-fed neonate from codeine treatment to the mother: a quantitative mechanistic modeling study. *Clin Pharmacol Ther* 2009;86:634-43. doi:10.1038/clpt.2009.151.
12 Pimlott N, Tsuyuki RT. Risks of maternal codeine intake in breastfed infants: a joint statement of retraction from *Canadian Family Physician* and the *Canadian Pharmacists Journal*. [Retracted article.] *Can Fam Physician* 2020;66:793-6.
13 Government of Canada. Health Canada Endorsed Important Safety Information on TYLENOL with Codeine products. Recalls and Safety Alerts. Government of Canada, 2008. https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2008/14526a-eng.php
14 European Medicines Agency. Codeine-containing medicines. Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation. EMA, 2013. https://www.ema.europa.eu/en/medicines/human/referrals/codeine-containing-medicines
15 US Food and Drug Administration. Use of Codeine and Tramadol Products in Breastfeeding Women - Questions and Answers. FDA, 2017. https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm118113.htm
16 Bryant AS, Miller RS, American College of Obstetricians and Gynecologists' Committee on Clinical Consensus–Obstetrics. Pharmacologic Stepwise Multimodal Approach for Postpartum Pain Management: ACOG Clinical Consensus No. 1. *Obstet Gynecol* 2021;138:507-17. doi:10.1097/AOG.0000000000004517
17 Fitzpatrick T, Wilton AS, Guttmann A. Development and validation of a simple algorithm to estimate common gestational age categories using standard administrative birth record data in Ontario, Canada. *J Obstet Gynaecol* 2021;41:207-11. doi:10.1080/01443615.2020.1726304.
18 ICES. Data Dictionary. Narcotic Monitoring System. 2018. https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx (accessed 7 Mar 2022).
19 Campbell TJ, Martins D, Tadrous M, et al. Dental Opioid Prescription Characteristics and the Risk of New, Persistent Use. *Am J Prev Med* 2021;60:831-9. doi:10.1016/j.amepre.2021.01.016.
20 Wunsch H, Hill AD, Fu L, et al. New Opioid Use after Invasive Mechanical Ventilation and Hospital Discharge. *Am J Respir Crit Care Med* 2020;202:568-75. doi:10.1164/rccm.201912-2503OC.
21 Gomes T, Campbell T, Tadrous M, Mamdani MM, Paterson JM, Juurlink DN. Initial opioid prescription patterns and the risk of ongoing use and adverse outcomes. *Pharmacoepidemiol Drug Saf* 2021;30:379-89. doi:10.1002/pds.5180.
22 Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto, Institute for Clinical Evaluative Sciences, 2006. https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information

23 Wilkins R, Khan S. PCCF+ Version H User's Guide. Automated Geographic Coding Based on the Statistics Canada Postal Code Conversion Files, Including Postal Codes through October 2010. Catalogue 82F0086-XDB. Health Analysis Division, Statistics Canada, Ottawa, Jan 2011.
24 Iron K, Zagorski B, Sykora K, et al. Living and Dying in Ontario: An Opportunity for Improved Health Information: ICES Investigative Report. Toronto, Ontario, Canada, 2008. https://www.ices.on.ca/Publications/Atlases-and-Reports/2008/Living-and-dying-in-Ontario.
25 Antoniou T, Gomes T, Mamdani MM, et al. Trimethoprim-sulfamethoxazole induced hyperkalaemia in elderly patients receiving spironolactone: nested case-control study. *BMJ* 2011;343:d5228. doi:10.1136/bmj.d5228
26 Gomes T, Greaves S, van den Brink W, et al. Pregabalin and the Risk for Opioid-Related Death: A Nested Case-Control Study. *Ann Intern Med* 2018;169:732-4. doi:10.7326/M18-1136.
27 Finkelstein Y, Macdonald EM, Gonzalez A, Sivilotti MLA, Mamdani MM, Juurlink DN, Canadian Drug Safety And Effectiveness Research Network (CDSERN). Overdose Risk in Young Children of Women Prescribed Opioids. *Pediatrics* 2017;139:e20162887. doi:10.1542/peds.2016-2887.
28 Turner SD, Gomes T, Camacho X, et al. Neonatal opioid withdrawal and antenatal opioid prescribing. *CMAJ Open* 2015;3:E55-61. doi:10.9778/cmajo.20140065.
29 Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011;46:399-424. doi:10.1080/00273171.2011.568786.
30 Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150-61. doi:10.1002/pst.433.
31 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083-107. doi:10.1002/sim.3697.
32 Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med* 2007;26:734-53. doi:10.1002/sim.2580.
33 Cox DR. Regression Models and Life-Tables. *J R Stat Soc B* 1972;34:187-202. doi:10.1111/j.2517-6161.1972.tb00899.x.
34 Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. *Stat Med* 2013;32:2837-49. doi:10.1002/sim.5705.
35 Yelland LN, Salter AB, Ryan P. Performance of the modified Poisson regression approach for estimating relative risks from clustered prospective data. *Am J Epidemiol* 2011;174:984-92. doi:10.1093/aje/kwr183.
36 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702-6. doi:10.1093/aje/kwh090.
37 Johns Hopkins University ACG Case-Mix Adjustment System Version 10 [computer program]. Baltimore, MD: Johns Hopkins University School of Hygiene and Public Health; 2011.
38 Juurlink DN, Gomes T, Guttmann A, et al. Postpartum maternal codeine therapy and the risk of adverse neonatal outcomes: a retrospective cohort study. *Clin Toxicol (Phila)* 2012;50:390-5. doi:10.3109/15563650.2012.681052.
39 Osmundson SS, Min JY, Grijalva CG. Opioid prescribing after childbirth: overprescribing and chronic use. *Curr Opin Obstet Gynecol* 2019;31:83-9. doi:10.1097/GCO.0000000000000527.
40 Eisenach JC, Pan PH, Smiley R, Lavand'homme P, Landau R, Houle TT. Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. *Pain* 2008;140:87-94. doi:10.1016/j.pain.2008.07.011.
41 Peahl AF, Dalton VK, Montgomery JR, Lai YL, Hu HM, Waljee JF. Rates of New Persistent Opioid Use After Vaginal or Cesarean Birth Among US Women. *JAMA Netw Open* 2019;2:e197863. doi:10.1001/jamanetworkopen.2019.7863.
42 Osmundson SS, Min JY, Wiese AD, et al. Opioid Prescribing After Childbirth and Risk for Serious Opioid-Related Events: A Cohort Study. *Ann Intern Med* 2020;173:412-14. doi:10.7326/M19-3805.
43 Osmundson SS, Wiese AD, Min JY, et al. Delivery type, opioid prescribing, and the risk of persistent opioid use after delivery. *Am J Obstet Gynecol* 2019;220:405-7. doi:10.1016/j.ajog.2018.10.026.
44 Francis J, Mildon A, Stewart S, et al. Breastfeeding rates are high in a prenatal community support program targeting vulnerable women and offering enhanced postnatal lactation support: a prospective cohort study. *Int J Equity Health* 2021;20:71. doi:10.1186/s12939-021-01386-6.
45 Statistics Canada. Births, 2021. Statistics Canada, 2022. https://www150.statcan.gc.ca/n1/daily-quotidien/220928/dq220928d-eng.htm (accessed 19 Jan 2023).

Supplementary information: Additional methods, tables S1 and S2, and figure S1-S5