ANESTHESIOLOGY®

# Global Trends in Analgesic Opioid Use in Pregnancy: A Retrospective Cohort Study

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*ANESTHESIOLOGY 2025; 142:1100–13*

## ABSTRACT

**Background:** Pain is common during pregnancy, yet there are few contemporary studies of opioid use in pregnancy. This study aimed to describe prescription analgesic opioid use during pregnancy across four regions: Oceania (New South Wales, Australia, and New Zealand), North America (Ontario, Canada, and United States), Northern Europe (Denmark, Finland, Iceland, Norway, Sweden, and United Kingdom), and East Asia (Hong Kong, South Korea, and Taiwan).

**Methods:** A common protocol was applied to population-based data to measure analgesic opioid dispensing or prescriptions during pregnancy before birth in 2000 to 2020. The populations captured included those with public and private insurance in the United States, a sample of primary care practices in the United Kingdom, and whole-of-population cohorts in the remainder of the locations. This study examined prevalence of use, defined as at least one dispensing or prescribing and estimated trends over time. Use by sociodemographic and pregnancy characteristics is described.

**Results:** Among a total of 20,306,228 pregnancies, 1,115,853 (55 per 1,000) had at least one analgesic opioid dispensing or prescription, ranging from 4 per 1,000 in the United Kingdom to 191 per 1,000 in the U.S. publicly insured population. The greatest relative decrease in prevalence was observed in Hong Kong (prevalence ratio, 0.2; 95% CI, 0.1 to 0.2 between 2005 and 2020), and the greatest increase was in Iceland (prevalence ratio, 4.4; 95% CI, 3.7 to 5.2 between 2004 and 2017). Codeine and tramadol were among the three most prevalent opioids in most populations. In a sensitivity analysis defining opioid use as two or more opioid -dispensing or -prescribing events, the prevalence of opioid use across populations was 17 per 1,000.

**Conclusions:** In this large multinational study, wide global variation in the prevalence of analgesic opioid use in pregnancy was observed, yet patterns of use by sociodemographic and pregnancy characteristics were relatively consistent. Analgesic opioid use remained stable or downward trending over time in most, but not all, countries.

(ANESTHESIOLOGY 2025; 142:1100–13)

## EDITOR'S PERSPECTIVE

### What We Already Know about This Topic

- There have been major shifts in the prescribing of opioid and non-opioid analgesics globally over the past two decades.
- Pain during pregnancy is common, but global data regarding the epidemiology of analgesic opioid use during pregnancy are limited.

### What This Article Tells Us That Is New

- Between 2000 and 2020, among 20,306,228 pregnancies across 12 countries and 4 regions, 1,115,853 pregnancies (55 per 1,000) had at least one analgesic opioid dispensing or prescription.
- Analgesic opioid use varied widely, ranging from 4 per 1,000 in the United Kingdom to 191 per 1,000 in the U.S. publicly insured population.
- Opioid use decreased in Hong Kong (prevalence ratio from earliest to latest years of 0.2); the U.S. publicly insured population (0.4); Finland (0.5); the U.S. privately insured population (0.6); Ontario, Canada (0.6); Denmark (0.6); and Sweden (0.8). There was a relative increase in opioid use in Iceland (prevalence ratio from earliest to latest year of 4.4), the United Kingdom (3.4), New Zealand (2.0), and Norway (1.2). There was no net change in opioid use in New South Wales, Australia; Taiwan; and South Korea.

This article is featured in "This Month in ANESTHESIOLOGY," page A1. This article is accompanied by an editorial on p. 992. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has a visual abstract.

Submitted for publication May 12, 2024. Accepted for publication February 3, 2025. Published online first on February 13, 2025.

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 ANESTHESIOLOGY 2025; 142:1100–13. DOI: 10.1097/ALN.0000000000005418

The article processing charges were funded by the University of New South Wales.

Over the last two decades, major changes in prescription analgesic opioid use have occurred worldwide. Use has been driven by paradigm shifts in managing noncancer pain, leading to dramatic global increases in opioid consumption between 2000 and 2010.[1] Since then, prevalence of opioid use has stabilized or declined in high-consuming countries, such as Germany, the United States, and Canada, while continuing to rise in other high-income countries including Spain, Portugal, and Switzerland.[2]

Population-level increases in opioid use are likely to have translated to increased use of analgesic opioids during pregnancy. Pain in pregnancy is common with low back pain and pelvic pain reported in greater than 70% of pregnancies.[3] Nonetheless, guidelines to assist clinicians in pharmacologic pain management during pregnancy are lacking. Evidence suggests that paracetamol (acetaminophen) is appropriate for mild to moderate pain, while repeated use of nonsteroidal anti-inflammatories should be minimized during early pregnancy and avoided after 20 weeks of pregnancy.[4,5] However, there is little guidance on the use of analgesic opioids. Acute pain is the most common reason for opioid use in pregnancy.[6–8] Chronic pain conditions have also become more common in pregnancy as average maternal age and comorbidities have increased.[7]

Opioids readily cross the placenta[9] posing a theoretical risk of teratogenic and neurotoxic effects to the growing fetus, which could lead to congenital anomalies,[10] perinatal morbidity and mortality,[11,12] and child and adolescent neurodevelopmental disorders.[13] Neonatal opioid withdrawal syndrome is a well recognized risk of opioid use during pregnancy.[14] Studies have also raised concerns regarding the prevalence of opioid overdose during pregnancy in the United States, United Kingdom, and Canada.[15–18] Notably, comedication of opioids with psychotropic medications has

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been associated with increased risk of overdose and death, resulting in a U.S. Food and Drug Administration (Silver Spring, Maryland) black box warning.[19,20]

Evidence relating to the patterns of analgesic opioid use during pregnancy is lacking from countries outside North America and Scandinavia.[7,21–23] Therefore, we aimed to describe global trends in analgesic opioid use during pregnancy (from the last menstrual period to birth) using population-based data from 13 countries in four global regions: Oceania (New South Wales, Australia, and New Zealand), North America (Ontario, Canada, and United States), Northern Europe (Denmark, Finland, Iceland, Norway, Sweden, and United Kingdom), and East Asia (Hong Kong, South Korea, and Taiwan). Specifically, we aimed to quantify analgesic opioid use between 2000 and 2020 by opioid type, pregnancy period, sociodemographic and pregnancy characteristics, and comedication with psychotropics.

## Materials and Methods

### Study Populations and Data Sources

In this study, we used a common protocol to examine analgesic opioid use in pregnancy across 14 populations in 13 countries. We aimed to capture pregnancies resulting in live or still births between January 2000 and December 2020, but the period of observation varied across populations depending on data availability (table 1).

We used nationwide data in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden), South Korea, Taiwan, and New Zealand; state or province-wide data from New South Wales, Australia and Ontario, Canada, the most populous states in their respective countries; and territory-wide data from Hong Kong. These data capture the entire population in their respective regions. As of 2015, the United Kingdom data represent pregnancies from primary care and 7% of the United Kingdom population. These data are considered representative of the United Kingdom population when compared to national census data in terms of age, sex, ethnicity, socioeconomic status, and body mass index, but only capture mothers and babies who were both registered with a primary care physician. Hence, babies who die soon after birth are unlikely to be captured because they are unlikely to be registered.[28,29] The U.S. Medicaid data set represents publicly insured people, which includes people with limited income and resources in the United States, and the U.S. Market Scan data set represents privately insured people from a sample of commercial insurers (table 1).

To identify medication use in pregnancy, we used dispensing records in all populations except Taiwan, South Korea, and the United Kingdom, for which we used prescribing records. Analgesic opioids and psychotropics were classified according to Anatomical Therapeutic Chemical codes[30] in all populations but New Zealand (chemical identification codes), Hong Kong and the United Kingdom (British National Formulary chapter codes), Ontario (drug identification numbers), and United States (generic drug name). We restricted to outpatient community opioid use in all populations except Australia, where dispensing from private hospitals was inseparable from community dispensing. To ensure complete capture of dispensing or prescription data, we included pregnancies of all women with continuous residency or insurance coverage in each population of interest, from at least 90 days before the start of pregnancy (defined as last menstrual period) to 1 month after birth. Further details regarding the data sources, population capture, covered time periods, and identification of medication use are described in table 1.

### Analgesic Opioid Use

In the primary analysis, we defined analgesic opioid use as at least one dispensing or prescription during the following periods: prepregnancy (90 days before last menstrual period to last menstrual period minus 1 day), anytime in pregnancy (last menstrual period to birth), early pregnancy (last menstrual period to 90 days of gestation), and late pregnancy (91 days of gestation to birth). For each population, we included all analgesic opioids that were available locally during the period of observation (supplemental table 1, https://links.lww.com/ALN/D890). As our focus was use of opioids for analgesic purposes, we excluded opioids dispensed or prescribed as part of opioid agonist therapy for the treatment of opioid dependence according to Anatomical Therapeutic Chemical code (NO7BC) or the unique country code where Anatomical Therapeutic Chemical code was not used. This exclusion was not possible in New Zealand; hence, analgesic use may be overestimated in this population.

### Pregnancy Characteristics

Where available, we examined the following characteristics for all pregnancies: year of birth, maternal age, parity, multifetal pregnancy, gestational age at birth, body mass index in early pregnancy, cohabitation status, and socioeconomic status. Information on socioeconomic status was derived from available data for each population as described in supplemental table 2 (https://links.lww.com/ALN/D890). For each of these variables, we reported the number of observations with missing values.

### Psychotropic Comedication

Where possible, we identified pregnancy periods in which both opioids and psychotropics were dispensed or prescribed to quantify the number of pregnancies subject to potential safety concerns or drug–drug interactions. We considered the following psychotropics: anxiolytics, hypnotics, and sedatives (hereafter referred to as *sedatives*), antiepileptics, antipsychotics (excluding prochlorperazine as its main therapeutic indication is for nausea), antidepressants

**Table 1.** Study Populations and Data Source Descriptions.

| Region | Dates of Coverage | General Data Source Information | Description of Source for Pregnancy Data | Description of Source for Medication Data |
|---|---|---|---|---|
| New South Wales, Australia | July 1, 2012, to December 31, 2019 | Administrative and claims data, probabilistically linked data based on name, date of birth, sex and address; population-based statewide data | New South Wales Perinatal Data Collection; all pregnancies resulting in livebirth, or stillbirth of at least 20 weeks' gestation or at least 400 g birthweight | Pharmaceutical Benefits Scheme data (national pharmaceutical dispensing claims data); subsidized prescription drugs dispensed in outpatient settings and private hospitals |
| New Zealand | January 1, 2005, to March 31, 2020 | New Zealand Ministry of Health's National Collections[24]; individual-level data in the collections are linked using a unique patient identifier, the National Health Index; population-based nationwide data | Deliveries of live and stillborn infants of at least 20 weeks' gestation included in the New Zealand Pregnancy Cohort (derived from several National Collections, including the National Maternity Collection, Mortality Collection, National Minimum Dataset [hospitalizations], Laboratory Claims Collection) | Pharmaceutical Collection; all dispensings of government-funded prescription drugs from community pharmacies |
| United States, MarketScan | January 1, 2003, to December 31, 2020 | Merative MarketScan Commercial Claims and Encounters Database Healthcare claims for privately insured individuals, enrolled in more than 100 commercial health insurance programs that provide comprehensive coverage for more than 25 million members annually with active policies located throughout the United States; data linked on a unique enrollment identifier | All mother–infant linked pregnancies resulting in live birth and continuously enrolled in health plan from 3 months before pregnancy until 1 month after delivery; gestational age is estimated based on the presence/absence of International Classification of Diseases code for preterm birth[25] | All dispensed, reimbursed prescription drugs in outpatient settings |
| United States, Medicaid | January 1, 2000, to December 31, 2018 | Medicaid Analytic eXtract Database/Transformed Medicaid Statistical Information System Analytic Files Healthcare claims for publicly insured individuals in all 50 states and the District of Columbia; these data currently cover almost 50% of births in the United States and includes people with less financial resources with an over-representation of adolescents and young women, African Americans, and disabled persons; data linked on a unique enrollment identifier | All mother–infant linked pregnancies resulting in live birth and continuously enrolled in Medicaid from 3 months before pregnancy until 1 month after delivery; gestational age is estimated based on the presence/absence of International Classification of Diseases codes for preterm birth[25] | All dispensed, reimbursed prescription drugs in outpatient settings |
| Ontario, Canada | July 1, 2013, to March 31, 2021 | Population-based health administrative databases housed at Institute for Clinical Evaluative Sciences, an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement; all data sets were linked using unique encoded identifiers and analyzed at Institute for Clinical Evaluative Sciences; population based statewide data | MOMBABY data set links the Canadian Institute for Health Information Discharge Abstract Database inpatient admission records of delivering mothers and their newborns using a validated algorithm at Institute for Clinical Evaluative Sciences to capture all livebirths and stillbirths in Ontario hospitals | The Narcotics Monitoring System captures all controlled substances dispensed from community pharmacies regardless of payer from July 2012 onwards |
| United Kingdom | January 1, 2005, to December 31, 2020 | The Clinical Practice Research Datalink GOLD database (primary care database); includes 7% of the total United Kingdom population[26]; only captures mothers and babies who were both registered with a primary care physician; hence, babies who die soon after birth are unlikely to be captured as they are unlikely to be registered | All records relating to pregnancy outcomes of any type (live births, stillbirths, and early pregnancy losses) are extracted; the date of each woman's first pregnancy outcome is estimated using the records identified; records relating to the timing of the start of pregnancy (first day of last menstrual period) and additional data from general practice records are used to estimate pregnancy start dates[26,27] | Prescription records of all drugs prescribed in general practice |
| Iceland | January 1, 2003, to December 31, 2017 | Nationwide population health registers linked by personal identity numbers | Medical Birth Register; all pregnancies resulting in the delivery of a live-born infant or stillbirths from week 22 of gestation | National Prescription Medicines Register; all dispensed prescription drugs in outpatient settings |
| Finland | January 1, 2005, to December 31, 2020 | Nationwide population health registers linked by personal identity numbers | Medical Birth Register; all pregnancies resulting in the delivery of a live-born infant or stillbirths from week 22 of gestation | All dispensed, reimbursed prescription drugs in outpatient settings |

(*Continued*)

**Table 1.** (Continued)

| Region | Dates of Coverage | General Data Source Information | Description of Source for Pregnancy Data | Description of Source for Medication Data |
|---|---|---|---|---|
| Norway | January 1, 2005, to December 31, 2020 | Nationwide population health registers linked by personal identity numbers | Medical Birth Register; all pregnancies resulting in the delivery of a live-born infant or stillbirths from week 12 of gestation; for this study, including only live-born infants or stillbirths from 22 weeks | Norwegian Prescribed Drug Registry; all dispensed prescription drugs in outpatient settings |
| Sweden | July 1, 2006, to December 31, 2019 | Nationwide population health registers linked by personal identity numbers | Medical Birth Register; all pregnancies resulting in the delivery of a live-born infant or stillbirths from week 28 of gestation or from week 22 of gestation (July 1, 2008 onwards) | Prescribed Drug Register; all dispensed prescription drugs in outpatient settings |
| Denmark | January 1, 2001, to December 31, 2020 | Publicly available central registration of medication use; nationwide population health data | All pregnancies that resulted in a live birth or stillborn child after 22 weeks of gestation | All dispensed, reimbursed prescription drugs in outpatient settings |
| Taiwan | January 1, 2009, to December 31, 2020 | National Health Insurance Research Database; population-based nationwide data | Birth certificate application; all pregnancies resulting in the delivery of a live-born infant, or stillbirths from week 20 of gestation or body weight of at least 500 g | All prescribed and reimbursed prescription drugs in outpatient settings |
| South Korea | January 1, 2009, to December 31, 2020 | Health Insurance Review and Assessment Database; population-based nationwide data | All pregnancies that resulted in live births that were identified using procedure codes of delivery | All prescribed and reimbursed prescription drugs in outpatient settings |
| Hong Kong | January 1, 2005, to December 31, 2020 | Clinical Data Analysis and Reporting System; population-based statewide data | All pregnancies in public hospitals resulting in live birth or stillbirth are directly identified in the database | All dispensed prescription drugs in public outpatient settings |

and psychostimulants, and attention-deficit/hyperactivity disorder medications (supplemental table 3, https://links.lww.com/ALN/D890). For each psychotropic class, we quantified the number of pregnancies in which at least one opioid was dispensed or prescribed within the same period (early or late pregnancy) as the psychotropic.

## Data Analysis

For each population, we quantified the number of pregnancies in which any opioid was dispensed or prescribed, as well as the top three most prevalent opioids. We expressed this number as a prevalence per 1,000 pregnancies in each respective population. We further stratified these analyses by year of birth and pregnancy period.

To assess the relative change in use of analgesic opioids over time, we calculated the prevalence ratios with log-binomial 95% CI between the first and last year of available data for each population by fitting a log-binomial model using the first year as the reference. We also quantified the total number of opioid dispensings or prescriptions across each pregnancy (1, 2, 3, 4, 5, or more) and reported each category as a percentage of the total number of pregnancies in which an opioid was dispensed or prescribed. Finally, we identified the number of pregnancies with comedication of each class of psychotropic as defined above, expressed as prevalence per 1,000 pregnancies.

We performed a sensitivity analysis requiring two or more opioid dispensings or prescriptions, rather than one or more, as the definition of analgesic opioid use. This aimed to reduce the chance that a dispensed or prescribed opioid was not consumed. For this sensitivity analysis, we reported annual prevalence of opioid use and the overall prevalence of the top three most prevalent opioids in each population expressed per 1,000 pregnancies. All analyses were performed with R version 4.2.3.[31] A data analysis and statistical plan was written, date-stamped, and recorded in the investigators' files before the data were accessed. The data in this article are reported in accordance with the STROBE RECORD–Pharmacoepidemiology checklist.

## Ethics Approvals

The study was approved by institutional ethical and/or data protection review boards in each population (supplemental table 4, https://links.lww.com/ALN/D890).

# Results

Among a total of 20,306,228 pregnancies, 1,225,077 (55 per 1,000 pregnancies) had a recorded analgesic opioid dispensing or prescription. The total prevalence of opioid use when all available study years were combined, varied between populations, from 4 per 1,000 in the United Kingdom to 191 per 1,000 in the U.S. publicly insured population, but the majority clustered between 15 and 88 per 1,000 with an

**Table 2.** Characteristics of Pregnant Women with Prescription Opioid Use

| Characteristic | Australia | New Zealand | U.S. Private | U.S. Public | Canada | United Kingdom | Denmark | Finland | Iceland | Norway | Sweden | Taiwan | Korea | Hong Kong |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Total pregnancies, N | 623,668 | 911,004 | 1,795,012 | 2,522,490 | 970,720 | 2,207,405 | 1,167,500 | 647,430 | 60,324 | 921,588 | 1,483,887 | 2,133,972 | 4,317,032 | 544,196 |
| Prevalence of opioid use (per 1,000 pregnancies)* | 65 | 79 | 88 | 191 | 39 | 4 | 15 | 36 | 132 | 32 | 41 | 9 | 37 | 5 |
| Age | | | | | | | | | | | | | | |
| ≤ 19 yr | 79 | 74 | 119 | 138 | 42 | 2 | | 26 | 110 | 30 | 26 | 8 | 58 | 7 |
| 20–24 yr | 91 | 95 | 117 | 208 | 49 | 5 | | 35 | 125 | 36 | 40 | 9 | 45 | 7 |
| 25–29 yr | 68 | 87 | 92 | 214 | 38 | 7 | | 35 | 127 | 31 | 39 | 8 | 35 | 5 |
| 30–34 yr | 57 | 71 | 82 | 194 | 35 | 7 | | 35 | 134 | 30 | 39 | 8 | 34 | 5 |
| 35–39 yr | 58 | 69 | 87 | 171 | 38 | 7 | | 39 | 146 | 35 | 45 | 9 | 41 | 5 |
| ≥ 40 yr | 62 | 72 | 92 | 148 | 44 | 8 | | 40 | 156 | 41 | 50 | 10 | 52 | 8 |
| Parity | | | | | | | | | | | | | | |
| 0 | 54 | 68 | 89 | 184 | 33 | 2 | | 33 | 109 | 29 | 35 | | 37 | 5 |
| 1 | 61 | 88 | 78 | 223 | 37 | 4 | | 35 | 144 | 32 | 39 | | 35 | 5 |
| 2 | 80 | 76 | 71 | 237 | 48 | 5 | | 42 | 148 | 38 | 50 | | 41 | 7 |
| ≥ 3 | 112 | 86 | 79 | 198 | 61 | 6 | | 42 | 165 | 48 | 63 | | 55 | 15 |
| Data missing | 73 | | | | 30 | 8 | | 48 | | | | | | |
| Multifetal | 76 | 91 | 135 | 220 | 47 | 5 | | 40 | 178 | 34 | 60 | | 57 | 6 |
| Gestational age | | | | | | | | | | | | | | |
| ≤ 32 weeks | 70 | 81 | 119 | 198 | 52 | 1 | | 30 | 116 | 39 | 50 | 12 | | 6 |
| 33–36 weeks | 86 | 93 | 118 | 226 | 58 | 10 | | 44 | 157 | 46 | 60 | 10 | | 6 |
| ≥ 37 weeks | 63 | 78 | 85 | 188 | 37 | 6 | | 36 | 131 | 32 | 40 | 9 | | 5 |
| Socioeconomic status (low to high) | | | | | | | | | | | | | | |
| 1 | 82 | 87 | | | 45 | | | 32 | 152 | 51 | 55 | 9 | 82 | 5 |
| 2 | 82 | 85 | | | 41 | | | 43 | 130 | 38 | 46 | 9 | 36 | 5 |
| 3 | 63 | 75 | | | 37 | | | 43 | 119 | 26 | 31 | 9 | | 6 |
| 4 | 57 | 72 | | | 35 | | | 32 | 125 | | | 9 | | 6 |
| 5 | 45 | 67 | | | 33 | | | | | | | 8 | | |
| Data missing | 47 | 33 | | | 35 | | | | | 21 | 25 | 5 | | |
| Relationship status | | | | | | | | | | | | | | |
| Not cohabiting | | | | | | | | 42 | 156 | 51 | 47 | | | |
| Cohabiting | | | | | | | | 35 | 127 | 31 | 40 | | | |
| Data missing | | | | | | | | 23 | 164 | 35 | | | | |
| Body mass index | | | | | | | | | | | | | | |
| < 18 kg/m$^2$ | 56 | 67 | | | | | | 32 | 143 | 33 | 33 | | | |
| 18–29.9 kg/m$^2$ | 56 | 76 | | | | | | 33 | 160 | 31 | 37 | | | |
| ≥ 30 kg/m$^2$ | 102 | 113 | | | | | | 53 | 237 | 53 | 61 | | | |
| Data missing | 65 | 52 | | | | | | 31 | 108 | 30 | 42 | | | |

Denmark provided data on the proportion of opioid exposed pregnancies overall and per year, but no other measures. Australia is limited to New South Wales, and Canada is limited to Ontario.

*Number of pregnancies with prescription opioid use expressed as per 1,000 pregnancies in each stratum.

aggregate value of 55 per 1,000 (table 2). In sensitivity analyses defining opioid use as two or more opioid dispensings or prescriptions, the total prevalence of opioid use across populations was reduced from 55 per 1,000 to 17 per 1,000 (supplemental fig. 1, https://links.lww.com/ALN/D890). However, the overall patterns in opioid use across countries and top three most prevalent opioids were generally consistent with our primary analyses (supplemental table 7, https://links.lww.com/ALN/D890).

From the earliest to latest years, Hong Kong had the greatest relative decrease in opioid use, with a prevalence ratio of 0.2 (95% CI, 0.1 to 0.2; fig. 1; supplemental table 5, https://links.lww.com/ALN/D890). Opioid use also decreased in the U.S. publicly insured population (prevalence ratio, 0.4; 95% CI, 0.3 to 0.5); Finland (prevalence ratio, 0.5; 95% CI, 0.5 to 0.5); the U.S. privately insured population (prevalence ratio, 0.6; 95% CI, 0.5 to 0.6); Ontario, Canada (prevalence ratio, 0.6; 95% CI, 0.6 to 0.6); Denmark (prevalence ratio, 0.6; 95% CI, 0.6 to 0.7); and Sweden (prevalence ratio, 0.8; 95% CI, 0.8 to 0.9). There was a relative increase in opioid use in Iceland, the United Kingdom, New Zealand, and Norway, with prevalence ratios of 4.4 (95% CI, 3.7 to 5.2), 3.4 (95% CI, 2.9 to 3.9), 2.0 (95% CI, 1.5 to 2.8), and 1.2 (95% CI, 1.1 to 1.3) respectively. There was no net change in opioid use in New South Wales (Australia), Taiwan, and South Korea, all with prevalence ratios of 1 and 95% CI crossing 1.

We observed substantial variation by country in the three most prevalent opioids used in pregnancy (fig. 2). Codeine was featured in the top three opioids used in most populations followed by tramadol, although hydrocodone was the most prevalent in the U.S. publicly and privately insured populations.

The prevalence of analgesic opioid use was elevated among pregnancies of younger women (19 to 29 yr) in Australia, New Zealand, North America, and South Korea, but more prevalent among pregnancies of older women (35 years and older) in the United Kingdom, Hong Kong, and the Nordic countries (table 2). We observed a wide variation between populations in opioid use in multifetal pregnancies ranging from 5 per 1,000 in the United Kingdom to 220 per 1,000 in the U.S. publicly insured population, which reflected use in pregnancy overall. In terms of gestational age at birth, opioid use in pregnancy was most prevalent in pregnancies resulting in birth at 33 to 36 weeks of gestation. Prevalence of use tended to be higher among pregnancies of women with a lower socioeconomic status across populations; while socioeconomic status was not available for the U.S. populations, this is also consistent with higher use in the socioeconomically disadvantaged U.S. publicly insured population compared to the privately insured U.S. population. Where captured, analgesic opioid use in pregnancy increased with increasing body mass index and was more prevalent among pregnancies of women not cohabiting with a partner.

Among pregnancies with recorded analgesic opioid use, the majority only had one opioid dispensing or prescription during pregnancy, ranging from 59% in the U.S. publicly insured population to 81% in Finland and South Korea; while a small proportion had five or more opioid dispensings or prescriptions during pregnancy, ranging from 1% in South Korea to 13% in the United Kingdom (table 3).

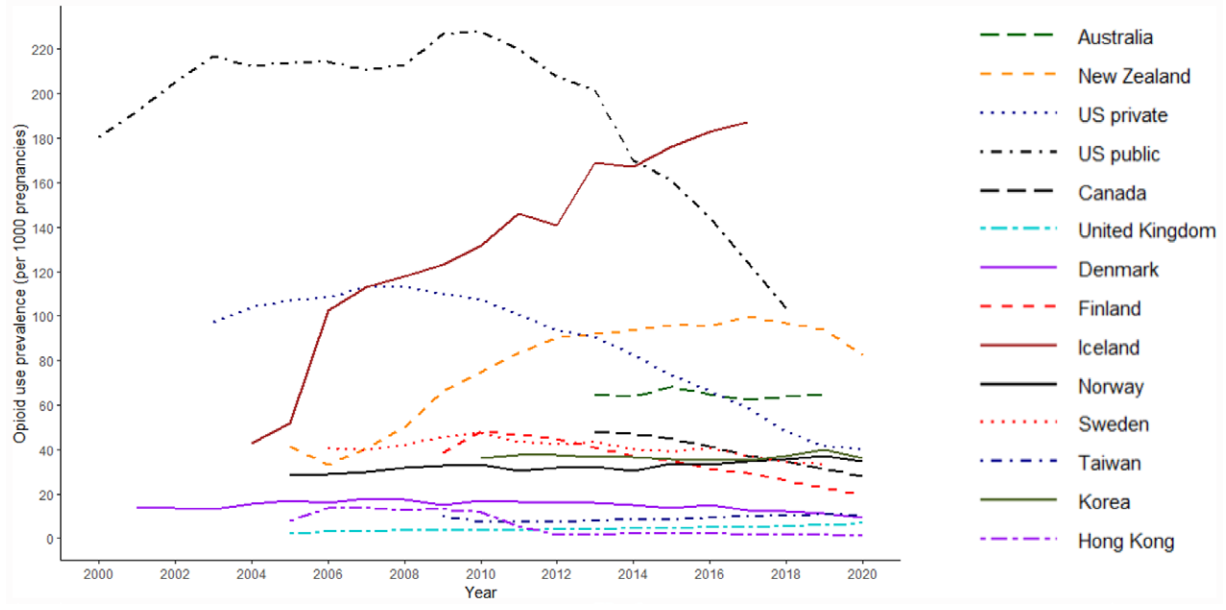


**Fig. 1.** Prevalence (per 1,000 pregnancies) of prescription opioid use during pregnancy by region and year. Note that Australia is limited to New South Wales and Canada is limited to Ontario.

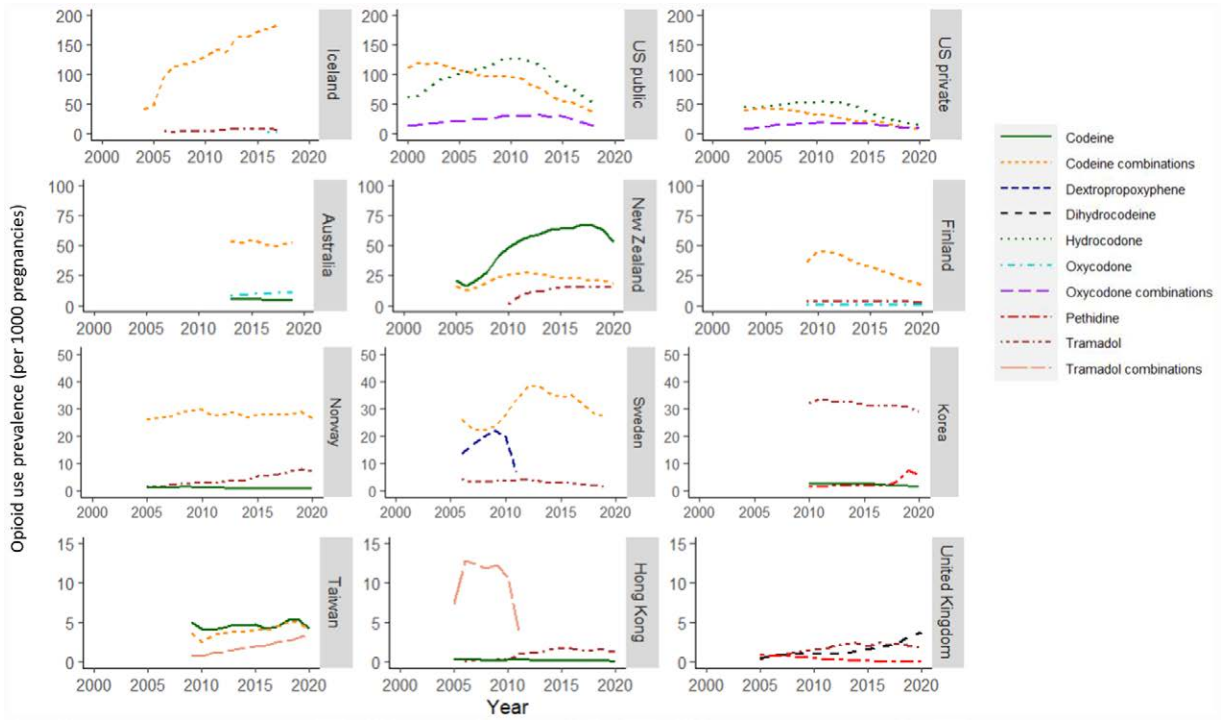


**Fig. 2.** Prevalence (per 1,000 pregnancies) of top three opioids in pregnancy by region. Note that Australia is limited to New South Wales and Canada is limited to Ontario.

**Table 3.** Percentage of Pregnancies with Any Opioid Use by the Number of Opioid Dispensings/Prescriptions

| Number of opioid dispensings/ prescriptions during pregnancy | Pregnancies with Any Opioid Use, % | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Australia | New Zealand | U.S. Private | U.S. Public | Canada | United Kingdom | Finland | Iceland | Norway | Sweden | Taiwan | Korea | Hong Kong |
| 1 | 77 | 79 | 74 | 59 | 76 | 66 | 81 | 75 | 79 | 73 | 79 | 81 | 79 |
| 2 | 12 | 12 | 14 | 18 | 12 | 13 | 10 | 15 | 11 | 13 | 9 | 13 | 13 |
| 3 | 4 | 3 | 4 | 8 | 4 | 5 | 3 | 4 | 3 | 5 | 2 | 4 | 4 |
| 4 | 2 | 1 | 2 | 4 | 2 | 3 | 2 | 2 | 2 | 2 | 2 | 1 | 2 |
| ≥ 5 | 5 | 4 | 5 | 11 | 7 | 13 | 4 | 4 | 5 | 7 | 7 | 1 | 2 |

Australia is limited to New South Wales, and Canada is limited to Ontario.

Across all populations (except Denmark, for which data were not available), the prevalence of opioid use was highest in late pregnancy, followed by early, and lowest for opioid use in early and late pregnancy (fig. 3). Opioid use generally decreased in pregnancy relative to prepregnancy except for the U.S. populations, in which more people had opioids dispensed/prescribed during both prepregnancy and pregnancy compared to prepregnancy alone (fig. 4).

Across all populations, psychotropic comedication with antidepressants or sedatives was most common followed by antipsychotics, antiepileptics, and attention-deficit/hyperactivity disorder medications (fig. 5). Iceland had the highest prevalence of psychotropic comedication, followed by Australia for antidepressants and antipsychotics, U.S. privately insured population for sedatives and attention-deficit/hyperactivity disorder medications, and Finland for antiepileptics. These data were not available for Canada and Denmark.

## Discussion

In this large population-based study covering greater than 20 million pregnancies across 14 populations in 13 countries, we provide contemporary evidence on global trends

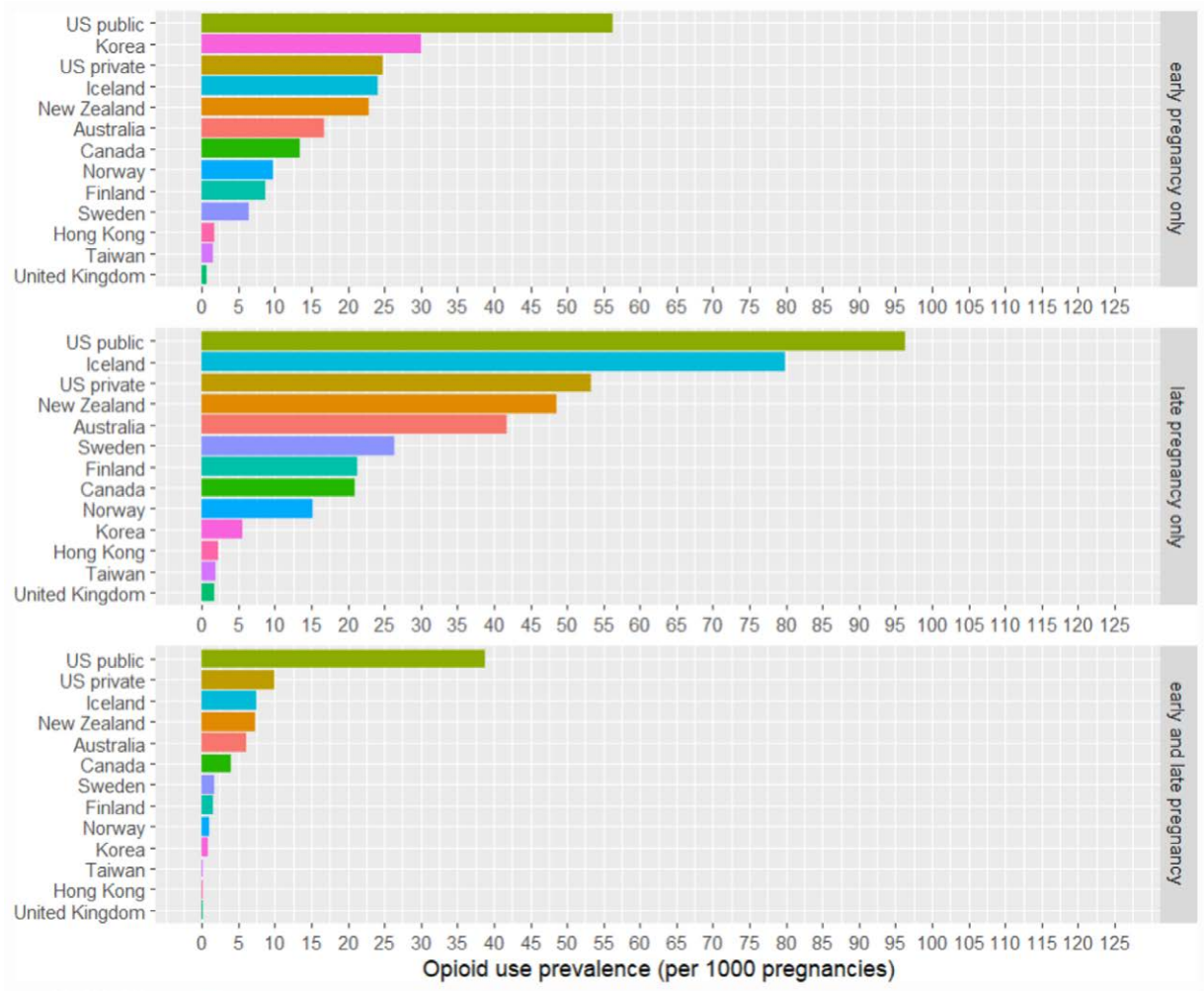


**Fig. 3.** Prevalence (per 1,000 pregnancies) of prescription opioid use by pregnancy period and region. "Early pregnancy" is defined as the time from the last menstrual period to 90 days of gestation. "Late pregnancy" is defined as the time from 91 days of gestation to birth. Data were not available for Denmark. Note that Australia is limited to New South Wales and Canada is limited to Ontario.

in analgesic opioid use in pregnant women. We observed substantial variation in prevalence of analgesic opioid use and in changes over time, with the greatest relative decrease in Hong Kong and the greatest increase in Iceland. In general, changes in the prevalence of opioid use in pregnancy mirrored changes in consumption of opioids in the general populations of the respective countries.[1,2]

The prevalence of opioid use in the United Kingdom and Hong Kong was substantially lower than in other countries. In Hong Kong, this is consistent with relatively lower opioid prescribing in the general population, and in the United Kingdom, it may relate to clinical practice or the primary health care population sampled. Given there were no substantial changes in clinical practice in these regions over the study period, trends in the prevalence of opioid use in pregnancy recorded here reflect actual trends in these regions.

Consistent with our findings where available, previous studies have described associations between opioid use in pregnancy and obesity,[22,32,33] low socioeconomic status,[22,32–34] and psychiatric comorbidity and psychotropic comedication.[23,35–38] These, along with smoking and somatic comorbid conditions, are potential confounders to consider in studies examining the causal association of opioid exposure in pregnancy with perinatal and early childhood adverse outcomes.

Our observations that codeine and tramadol, including combinations with other analgesics, were the most common opioids in pregnancy are consistent with previous studies across Europe.[22,39] Consistent with previous U.S. studies, prevalence was highest for hydrocodone in our U.S. populations.[40] These use patterns reflect the recommendations from regulators regarding risk of these medications during pregnancy and the postpartum period, as well as the

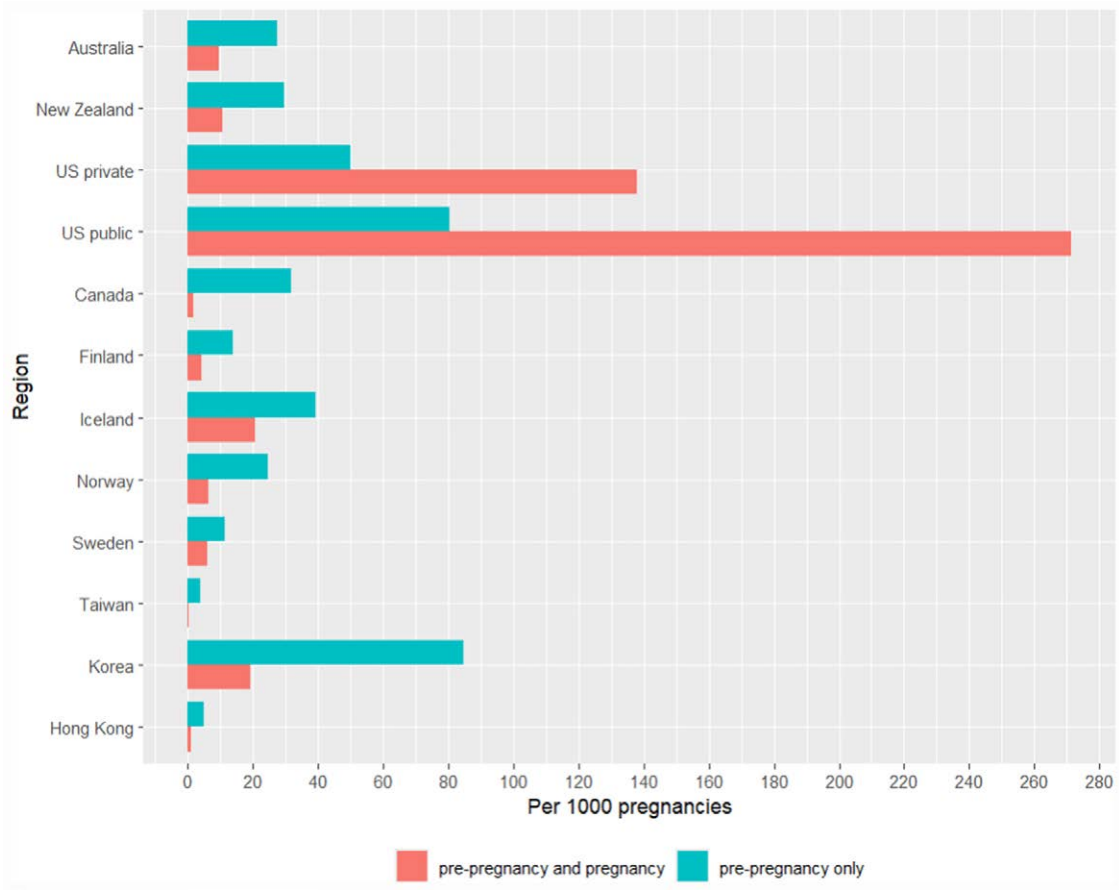


**Fig. 4.** Prevalence (per 1,000 pregnancies) of prescription opioid use prepregnancy only and both prepregnancy and pregnancy. "Prepregnancy" is defined as the time from 90 days before the last menstrual period to the last menstrual period minus 1 day. Note that Australia is limited to New South Wales and Canada is limited to Ontario.

relative prevalence of use in the general population. Future pregnancy safety studies should focus on these high prevalence opioids.

We found variable opioid use across pregnancy periods but generally less use in pregnancy than immediately before pregnancy. This likely reflects caution from women and prescribers about medication use leading to less initiation during pregnancy or more discontinuation of prepregnancy use.[41] Conversely, the relatively higher opioid use during pregnancy in both U.S. data sets may represent a relatively greater continuation of opioid use before pregnancy into pregnancy and/or relatively more opioid initiation during pregnancy compared to other countries, but this requires further investigation. Greater opioid use in late compared to early pregnancy may be a consequence of late pregnancy covering a longer period than early. However, if may also be due to the higher prevalence of painful conditions such as low back and pelvic pain as pregnancy progresses[42] and few effective alternatives for pain control in late pregnancy.

To date, most studies about opioid-associated overdose deaths during pregnancy have not differentiated illicit from analgesic opioids, and so the true risk of analgesic opioids alone is unclear.[15,17,18,43] In our data, there were few pregnancies in which an opioid was dispensed or prescribed more than once during pregnancy, suggesting intermittent use for pain. Higher-dose analgesic opioid use and use with sedatives has been associated with increased risk of overdose and death in the nonpregnant population, and these risks are likely to translate to pregnancy.[19,44] While we were only able to measure the number of opioid dispensings or prescriptions rather than dose, our observations that five or more opioid dispensings/prescriptions were received during 1 to 13% of pregnancies and between less than 1% and 32% were comedicated with sedatives indicate wide international variation yet significant subgroups at higher risk of adverse events.

The ability to measure opioid use across the 14 populations in greater than 20 million pregnancies along with women's sociodemographic and pregnancy characteristics raises opportunities for future research collaboration across countries. This could be achieved *via* distributed analyses such as those used by the Canadian Network of

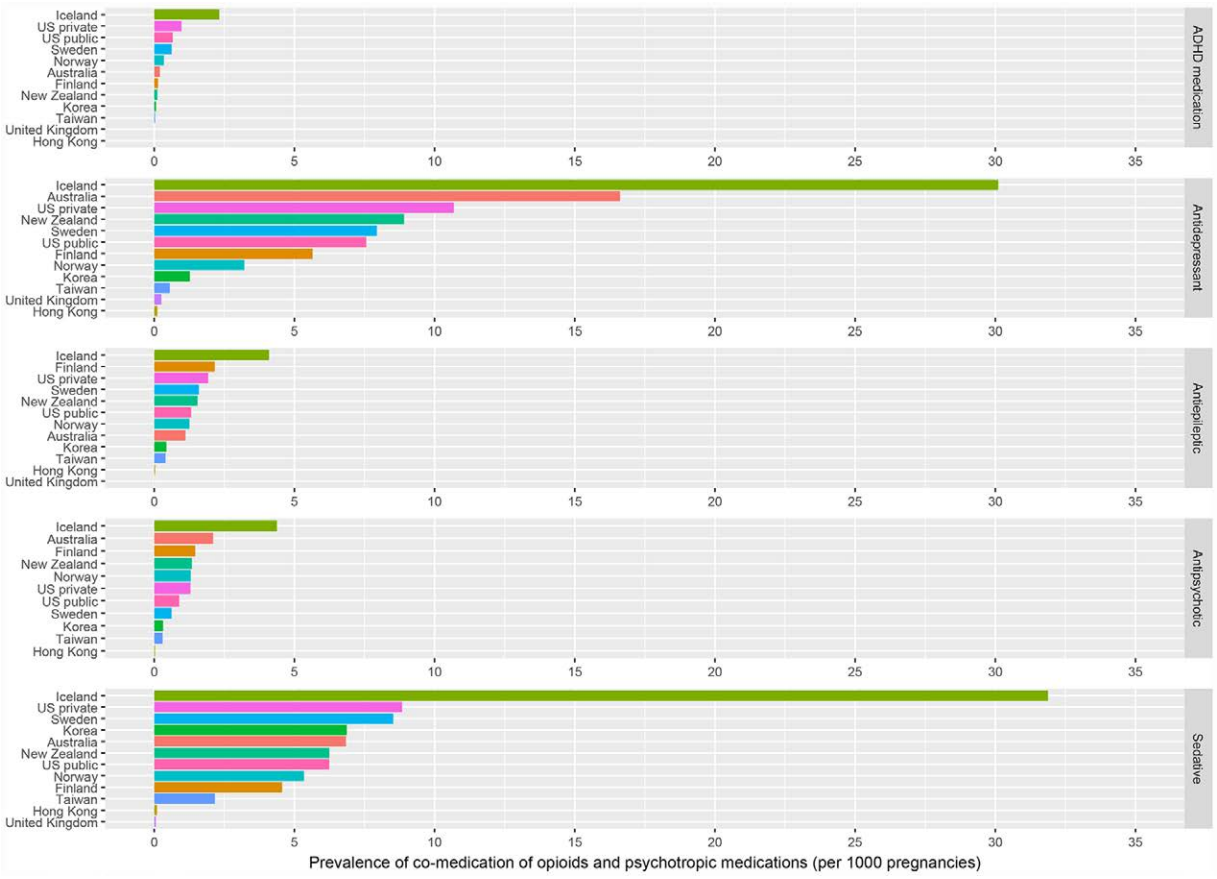


**Fig. 5.** Prevalence (per 1,000 pregnancies) of psychotropic comedication with prescription opioids by region. "Comedication" was defined as one or more opioid dispensing or prescription and one or more dispensing or prescription of the above psychotropics within either early pregnancy (last menstrual period to 90 days of gestation) or late pregnancy (91 days of gestation to birth). "Sedative" includes sedatives, anxiolytics, and hypnotics. Data were not available for Denmark or Ontario, Canada. Australia is limited to New South Wales. ADHD, attention-deficit and hyperactivity disorder.

Observational Drug Effect Studies[44] or a common data model such as that used by the International and Nordic Pregnancy drug Safety Studies (InPress and NorPreSS)[45,46] to increase the power to detect rare adverse perinatal and early childhood developmental outcomes and study the effect of individual opioids. Previous studies investigating the safety of opioids during pregnancy have often been limited by small sample sizes,[47,48] necessitating the aggregation of all opioids into a single category, despite their diverse pharmacologic properties. This approach overlooks the unique effects and risks associated with individual opioids, underscoring the importance of more granular research enabled by larger, collaborative data sets.

This study was subject to several limitations. The study analyses were based on dispensing data for all populations but the United Kingdom, Taiwan, and South Korea, which contributed prescribing records. While neither dispensings nor prescriptions indicate actual medication consumption or timing thereof, dispensing records are more proximal to this event. While it was the intention of this study to capture opioid use during pregnancy, we may capture opioid dispensings or prescribing records intended for use after birth. We anticipate most of this pre-emptive opioid dispensing or prescribing occurs in hospital and given this is not captured in our study, is unlikely to be driving opioid use recorded in our study. There was variation in population capture across countries, from full coverage in most instances to a representative sample of primary care prescribing in the United Kingdom and publicly insured people with low incomes and those with private health insurance from a sample of payers in the United States. While these factors may limit the accuracy and comparability of these findings, as well as generalizability to the entire country studied, the United Kingdom and U.S. data sets are considered representative samples of their respective countries. The study periods in which data were available differed, limiting the ability to compare trends in opioid prevalence over time. While recorded diagnoses before opioid dispensation or

prescription can be used to approximate indication and comorbidities, these were not consistently available across populations and so were not included in our analyses. Therefore, we cannot comment on the appropriateness of prescribing. Finally, while all populations used validated or established measures of socioeconomic status, definitions varied between populations, limiting direct comparability.

## Conclusions

We have described trends in opioid use in greater than 20 million pregnancies across 14 populations in 13 countries. We observed that opioid use was more common in late compared to early pregnancy and consistent with previous studies, in those with a lower socioeconomic status and higher body mass index. While most pregnancies with exposure to analgesic opioids involved only one dispensing/prescription, there was a small but significant proportion of pregnancies in some populations that received five or more opioid dispensings or prescriptions and comedication with sedatives. Only Iceland, New Zealand, the United Kingdom, and Norway had a net increase in opioid use over the study period; opioid use decreased in six other populations and remained stable in four. While many factors influence opioid use in pregnancy, this may in part reflect increased opioid stewardship activities in many countries and evolving knowledge around potential adverse events when used in pregnancy.

## Acknowledgments

The authors acknowledge the Canadian Institute for Health Information and the Ontario Ministry of Health for compiling and providing data and/or information on which parts of this study are based. In addition, this article used data adapted from the Statistics Canada Postal Code 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 Corporation (Ottawa, Canada) and Statistics Canada (Ottawa, Canada). The authors also thank IQVIA Solutions Canada Inc. for use of the Drug Information File. The New Zealand analyses were based on data provided by the New Zealand Ministry of Health. The authors thank the New South Wales Ministry of Health and the Australian Government Department of Health and Aged Care for the provision of data and gratefully acknowledge the assistance of the Center for Health Record Linkage and the Australian Institute of Health and Welfare Data Integration Unit in linking the data collections.

## Research Support

Supported by National Health and Medical Research Council Center of Research Excellence in Medications Intelligence (Canberra, Australia) grant No. 1196900 and National Health and Medical Research Council investigator grant No. 1196560 (to Dr. Brett) and by a University of New South Wales Scientia Program Award (to Dr. Zoega). Supported in part by Institute for Clinical Evaluative Sciences (Ontario, Canada), which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care, and by the Research Council of Norway through Centers of Excellence funding scheme project No. 262700. Also supported by Taiwan National Science and Technology Council grant No. 112-2628-B-006-003, Taiwan National Health Research Institutes grant No. NHRI-11A1-CG-CO-04-2225-1, and funds from the Taiwan Health and Welfare Data Science Center. Dr. Kelty has received funding from Medical Development International (Scoresby, Australia), and Dr. Leinonen has received funding from Innovative Medicines Initiative (Brussels, Belgium). Dr. Wong receives payment for work with the Institute for Health Research in England, the European Commission, the National Health and Medical Research Council in Australia, the European Union's Seventh Framework program for research and technological development, the Research Grants Council Hong Kong, and the Health and Medical Research Fund Hong Kong; receives consulting fees from the World Health Organization (Geneva, Switzerland); receives payment for expert testimony for appeal court in Hong Kong; serves on advisory committees for Member of Pharmacy and Poisons Board (Hong Kong); is a member of the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization; and is a member of the Advisory Panel on COVID-19 Vaccines of the Hong Kong Government. Dr. Man is funded by a C.W. Maplethorpe Fellowship, European Commission Horizon 2020, National Institute for Health and Care Research (United Kingdom), and the Hong Kong Research Grant Council.

## Competing Interests

Dr. Huybrechts has received grants from United BioSource LLC (King of Prussia, Pennsylvania) and Takeda (Tokyo, Japan) to Brigham and Women's Hospital (Boston, Massachusetts) unrelated to this work. Dr. Cesta has participated in research projects unrelated to this work funded by pharmaceutical companies, with all funds paid to the institution where they are employed. Dr. Wong has received research grants from Amgen (Thousand Oaks, California), Janssen, GSK, Novartis, Pfizer, Bayer, Bristol-Myers Squibb, and Takeda and consulting fees from IQVIA for projects unrelated to this work; they are also the nonexecutive director of Jacobson Medical in Hong Kong and are the founder and a director of Therakind Limited (London, United Kingdom), Advance Data Analytics for Medical Science Limited (Hong Kong), Asia Medicine Regulatory Affairs Services Limited, and OCUS Innovation Limited (Hong Kong, Ireland, and United Kingdom). The other authors declare no competing interests.

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## Supplemental Digital Content

Supplemental tables and figures, https://links.lww.com/ALN/D890

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