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ORIGINAL RESEARCH ARTICLE

International Trends in Opioid Prescribing by Age and Sex from 2001 to 2019: An Observational Study Using Population-Based Databases from 18 Countries and One Special Administrative Region

Adrienne Y. L. Chan[1,2,3,4] · Shahram Bahmanyar[5] · Kebede Beyene[6] · Greta Bushnell[7] · Bruce Carleton[8] · Amy Hai Yan Chan[6] · Sharon Cook[9] · Stephen Crystal[9] · Kari Furu[10,11] · Svetla Gadzhanova[12] · Patricia García Poza[13] · Rosa Gini[15] · Sabrina Giometto[14] · Jeff Harrison[6] · Ulrike Haug[16,17] · Christine Hsu[18] · Harpa Lind Hjördísar Jónsdóttir[19,20] · Joe Kai[21] · Øystein Karlstad[10] · Ju Hwan Kim[22,23] · Kiyoshi Kubota[24] · Edward Chia-Cheng Lai[25,39] · Hyesung Lee[36] · Wallis C. Y. Lau[1,2,26] · Kathy H. Li[8] · Ersilia Lucenteforte[37] · Géric Maura[27] · Anke Neumann[27] · Virginia Pate[18] · Anton Pottegård[28] · Nadeem Qureshi[21] · Lotte Rasmussen[28] · Johan Reutfors[5] · Elizabeth E. Roughead[12] · Leena Saastamoinen[29] · Tsugumichi Sato[30] · Oliver Scholle[16] · C. C. M. Schuiling-Veninga[4] · Chin-Yao Shen[25,39] · Ju-Young Shin[22,23,31] · Til Stürmer[18] · Katja Taxis[4] · Marco Tuccori[32,33,38] · Stephen Weng[21] · Kirstie H. T. W. Wong[34] · Helga Zoega[20] · Kenneth K. C. Man[1,2,26] · Ian C. K. Wong[1,2,3,35]

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Abstract

Objective To characterize multinational trends and patterns of opioid analgesic prescribing by sex and age.

Design, Setting, and Participants We studied opioid analgesic prescribing from 2001 to 2019 with common protocol using population-based databases from eighteen countries and one special administrative region.

Main Outcome Measures We measured opioid prescribing by geographical region, sex and age, estimating annual prevalent, incident, and nonincident opioid prescribing per 100 population with a 95% confidence interval (CI) and meta-analyzed the multinational and regional opioid prescribing with a random-effects model. Time trends were reported through average annual absolute changes, estimated using linear mixed models. We further explored the effect of sex and age on prevalent opioid prescribing in the multivariable analysis.

Results Over 248 million individuals were included. Pooled multinational opioid prescribing prevalence was 9.0% amongst included countries/regions. Opioid prescribing prevalence in 2015 ranged from 2.7% in Japan to 19.7% in Iceland. Average annual absolute changes in opioid prescribing prevalence per year ranged from − 1.53% (95% CI − 2.06, − 1.00; United States Medicaid) to + 1.24% (95% CI 1.02, 1.46; South Korea). Pooled multinational incident opioid prescribing (4.9%; 95% CI 4.1, 5.9) was higher than pooled multinational nonincident opioid prescribing (3.7%; 95% CI 2.9, 4.8). The female sex and older age were associated with higher opioid prescribing. Main limitations of this study include the absence of data from study duration or individuals not covered by the data sources and the lack of information on medication adherence and indication.

Conclusions Opioid prescribing remains unbalanced across geographical regions; however, results suggest a tendency to convergence across countries/regions. Differences in opioid prescribing by sex and age were identified.

1 Introduction

The use of prescription opioid analgesics (hereafter referred to as opioids) presents a controversial clinical challenge worldwide. Pain is among the most common symptoms presented clinically [1]. In particular, chronic pain continues to be a serious global public health problem with vast unmet needs for relief [2]. Conditions and symptoms, such as lower back pain, migraine, and other musculoskeletal disorders constitute the leading causes of disability worldwide, with prevalence estimates of chronic pain ranging from 11 to >60% [1, 3]. Pain management guidelines vary depending on the types of pain (nociceptive, neuropathic, nociplastic), etiologies, and clinical specialties involved [1]. Opioids are the reference standard for acute pain and the mainstay analgesic therapy for moderate to severe pain related to cancer and end-of-life care [1]. Although opioids

Extended author information available on the last page of the article

Key Points

Opioid prescribing patterns varied widely across countries but showed signs of convergence over time, with decreases in high-use countries and increases in low-use ones.

Women and older adults were more likely to be prescribed opioids, highlighting important demographic differences in pain treatment practices.

Differences in opioid prescribing between countries suggest potential inequalities in access or risk, underscoring the need for balanced, evidence-based pain management policies.

were recommended for chronic noncancer pain in the early 2000s, it is now recognized that they may do more harm than good if mismanaged [4].

While long-term use of opioids can lead to dependence and abuse, which can be fatal [5], global opioid use saw exponential growth over the past decades [6]. A recent study using pharmaceutical sales data from 66 countries/regions found that global opioid consumption continued to increase between 2015 and 2019 [7]. However, sales data do not provide information on who is using opioids, while designs of prior studies do not allow comparisons between countries and sub-populations to be drawn. This creates challenges when formulating targeted interventions for specific patient groups that may be at risk of opioid overconsumption and harm.

A cross-regional comparison of opioid prescribing with respect to patients' demographics is therefore needed to identify areas where improvements are needed and ultimately help to reduce the negative consequences associated with opioid over- or under-use. Using patient-level electronic health data with a common protocol approach, we aim to characterize the multinational trends and patterns of opioid prescribing overall and by patients' sex and age across 18 countries and one special administrative region (SAR).

2 Methods

2.1 Study design

We used a common protocol to study opioid prescribing in 20 participating sites from 18 different countries and one SAR across six geographical regions: East Asia (Hong Kong, Japan, South Korea, and Taiwan), Oceania (Australia and New Zealand), North America (Canada and two data sources in the USA, Medicaid and a privately insured sample referred to as MarketScan), Northern Europe (Denmark, Finland, Iceland, Norway, and Sweden), Western Europe (France, Germany, the Netherlands, and the United Kingdom (UK)), and Southern Europe (Italy and Spain). Each site contributed data for the study period, between 1 January 2001 and 31 December 2019, subject to the data availability of their respective databases. Details about the databases are shown in Table 1 and eTable 1 in the Supplement.

2.2 Data collection

Study population comprised all individuals during the study period grouped by age: 0–5, 6–11, 12–18, 19–30, 31–40, 41–50, 51-65 years, and 66 years or older. Age was defined as the mid-year age (i.e., on 1 July in the year of the date of medication record) except for Finland, Norway, Germany, Iceland, and US Medicaid where end-of-year age was used.

The primary outcome was the annual rate of opioid prescribing, calculated as the number of individuals who received at least one opioid prescription or dispensing in a calendar year per 100 population. The term "opioid prescribing" is used throughout the manuscript for consistency, but refers broadly to either prescribing or dispensing, depending on data availability (eTable 1). Where possible, the total number of individuals covered by the database at mid-year served as the denominator to calculate annual opioid prescribing for each site. For databases with universal coverage, population data were used. The numerator was defined as the number of unique individuals with at least one opioid record within each calendar year [8]. Medication records were extracted from prescribing or dispensing datasets for each individual, and a person was counted once per year regardless of the number of opioid records. Age-specific opioid prescribing data were not available for the Netherlands, for persons aged over 65 years in the two US sites, persons aged over 74 years in Japan, and persons aged over 18 years in Canada.

2.3 Ethics approval

Ethical approval for each data source was obtained by individual sites (eTable 2, Supplement).

2.4 Medication definition

To identify opioid prescribing, we examined the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification codes (eTable 3, Supplement) in the medication records [9]. Each site determined opioids that are used as analgesics according to local prescribing practices. We defined prevalent opioid users as individuals with at least one opioid record in each calendar year. Among prevalent uses, incident opioid users were defined as individuals with

Table 1 Data source characteristics, by site

Country/region	Name of database	Start and end year of available data	Health system or data source	Database coverage (% national population)
Australia	Australian pharmaceutical benefits scheme 10% sample	2012–2018[a]	Universal	~2.5 million (10%)
Canada	British Columbia PharmaNet (age <19)	2001–2017	Universal within the region	1.3 million children (~3.7%)
Denmark	The Danish National Prescription Registry	2001–2018	Universal	5.7 million (100%)
Finland	The Finnish Prescription Registry	2001–2018	Universal	5.5 million (100 %)
France	National Health Data System (système national des données de santé)	2006–2018	Universal	66.5 million (~100%)
Germany	German Pharmacoepidemiological Research Database	2004–2017	Publicly insured people	~16 million (20%)
Hong Kong	Hong Kong Clinical Data Analysis and Reporting System	2001–2019	Universal	~7 million (100%)
Iceland	Icelandic Prescription Medicines Register	2003–2018	Universal	0.4 million (~100%)
Italy	Tuscan Regional Administrative Healthcare databases	2004–2019	Universal within the region	3.7 million (6.18%)
Japan	Japanese Medical Data Center Database (Age <75)	2005–2018	Commercially insured people	7.3 million (6.1%)
The Netherlands	IADB.NL database	2008–2017	Universal	0.8 million (4.7%)
New Zealand	National data collections[b]	2008–2018	Universal	4.6 million (96%)
Norway	Norwegian Prescription Database	2004–2018	Universal	5.2 million (100%)
South Korea	National Health Insurance Service - National Sample Cohort	2002–2015	Universal	~1 million (~2.2%)
Spain	Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria	2005–2018	Universal	9.4 million (20%)
Sweden	The Swedish Prescribed Drug Register	2006–2019	Universal	~10 million (100%)
Taiwan	National Health Insurance Database	2001–2016	Universal	~23 million (99.9%)
United Kingdom	Clinical Practice Research Datalink–GOLD and Aurum datasets	2001–2018	UK General Practices (Primary care centres)	~35 million (13 %)
United States (MarketScan)	MarketScan Commercial Claims and Encounters (Age <65)	2001–2018	Commercially insured people	~27 million (8.4%)
United States (Medicaid)	MarketScan Multi-state Medicaid Database (Age <65)	2013–2018	Publicly insured people	16.2 million (5.1%)

[a]July 2012 onwards for all medicines (January 2006 onwards for subsidised medicines ~80% of total)

[b]Pharmaceutical Collection—Pharms Data (dispensing data); National Non-Admitted Patient Collection (outpatient/ED visit data); National Minimum Dataset (hospital inpatient data); Primary Health Organisation (PHO) enrolment collection (primary care data); National Health Index (NHI) data (age/sex data)

an opioid record in a calendar year (from 1 January to 31 December) and no opioid record in the preceding calendar year of the observed prescription/dispensing using a fixed one-year window as a wash-out period. We subtracted the number of incident users from prevalent users to identify nonincident users (eFig. 1, Supplement).

2.5 Data analysis

Each site provided aggregated data to the primary authors (A.Y.L.C. and K.K.C.M.). We expressed the annual measures (prevalent-, incident-, and nonincident-prescribing) of opioid

prescribing as a percentage of the total population covered by each site in a given calendar year. We calculated the site-specific annual measures of opioid prescribing with a 95% confidence interval (CI) by Poisson method [8]. Multinational and regional pooled measures were estimated of opioid prescribing in 2015 for overall, and by sex and age categories by meta-analyses with random-effects [8]. Female-to-male ratios of opioid prescribing by site were calculated by dividing the annual opioid prescribing rate in females by the corresponding rate in males in 2015. The year 2015 was chosen as it was the only common year for all sites.

We used a linear regression model to test for time trends throughout the study period. We fitted one model per study site, with year as the only predictor variable in the model [8]. We assessed relative changes between consecutive years in opioid prescribing as percentage change for each site. The multinational trend changes were estimated using linear mixed models with random-effects for site-level effects. We included geographical region, sex, and age in the multivariable linear mixed model to investigate their effects on opioid prescribing prevalence.

All statistical analyses were conducted using Statistical Analysis System (SAS) v9.4 (SAS Institute, Cary, NC, USA) and R Foundation for Statistical Computing version 3.6.0 (Vienna, Austria) with 5% significance level.

3 Results

3.1 Prevalence

Our study included a total of 248 million individuals across the study sites (Table 1). The pooled multinational prevalence of opioid prescribing in 2015 was 9.0% (95% CI 7.4, 11.0; eFig. 2, Supplement). Pooled regional opioid prescribing prevalence was highest in Oceania (13.4%; 95% CI 12.0, 14.9), followed by Northern Europe (10.8%; 95% CI 9.1, 12.7), North America (10.4%; 95% CI 8.2, 13.0), Southern Europe (9.4%; 95% CI 6.5, 13.8), and Western Europe (9.1%; 95% CI 5.0, 16.6); East Asia had the lowest opioid prescribing prevalence (5.2%; 95% CI 3.1, 8.7). Site-specific opioid prescribing prevalence ranged from 2.7% in Japan (95% CI 2.7, 2.71) to 19.7% in Iceland (95% CI 19.5, 19.8).

3.2 Time trends of opioid prescribing prevalence

Trends of opioid prescribing prevalence differed in magnitude and direction across sites. Opioid prescribing prevalence increased across all East Asian sites and decreased across all North American sites during the study period. To better understand this heterogeneity, countries could be broadly grouped into three patterns, early high and declining, late but sustained increase, and relatively stable with modest fluctuations, based on their overall trajectory between 2001 and 2019 (Fig. 1). First, countries with high opioid prescribing prevalence at the beginning of the study period and experienced substantial declines over time, which includes both US data sources and Canada. In particular, the greatest annual average absolute reduction in opioid prescribing prevalence was observed in the US Medicaid (− 1.53%; 95% CI − 2.06, − 1.00; Table 2). Second, opioid prescribing in some countries began at low or moderate levels but rose steadily over time South Korea had the highest annual average absolute increase in opioid prescribing prevalence (+ 1.24%; 95% CI + 1.02, + 1.46). Third, most countries in Northern and Western European countries, including Denmark, Norway, Sweden, France, and the UK experienced relatively consistent levels of opioid prescribing over time or only modest changes.

Despite these groupings, opioid prescribing prevalence fluctuated over the study years in most sites (Fig. 1; eTable 4, Supplement). The greatest annual relative increase in opioid prescribing was observed in Finland between 2008 and 2009 (+ 133%; 95% CI + 132, + 134), followed by South Korea between 2007 and 2008 (+ 93.2%; 95% CI + 90.9, + 95.5). The greatest annual relative decrease in opioid prescribing was observed in Finland from 2004 to 2005 (− 51.6%; 95% CI − 51.2, − 52.0), followed by US Medicaid (− 19.8%; 95% CI − 19.6, − 20.1) and US MarketScan (− 18.8%; 95% CI − 18.7, − 18.9) both noted between 2017 and 2018. Many countries also observed a relative reduction in opioid prescribing between 2017 and 2018 (Denmark, Iceland, the UK, Finland, Italy, New Zealand, Sweden, Norway, and France; eTable 4, Supplement). Over the study period, the range of opioid use prevalence narrowed from 0.7% (Hong Kong) to 21.0% (US MarketScan) in 2001 to 2.2% (Japan) to 18.1% (France) in 2018. Multinational opioid use remained unchanged (average annual absolute change: 0.005%, 95% CI − 0.007, +0.02) from 2001 to 2019.

3.3 Incident and nonincident opioid prescribing

Multinational annual incident opioid prescribing was 4.9% (95% CI 4.1, 5.9; eFig. 3, Supplement) whereas multinational annual nonincident opioid prescribing was 3.7% (95% CI2.9%,4.8%; eFig. 4, Supplement). The rates of incident opioid prescribing increased throughout the study period in all East Asian sites and were heterogeneous across other regions (Table 2). Nonincident opioid prescribing was significantly reduced in all North American sites during the study period where a sharp decline was observed in both US sites and remained heterogeneous in other geographical regions, ranging from − 1.55% per year (95% CI − 1.89,

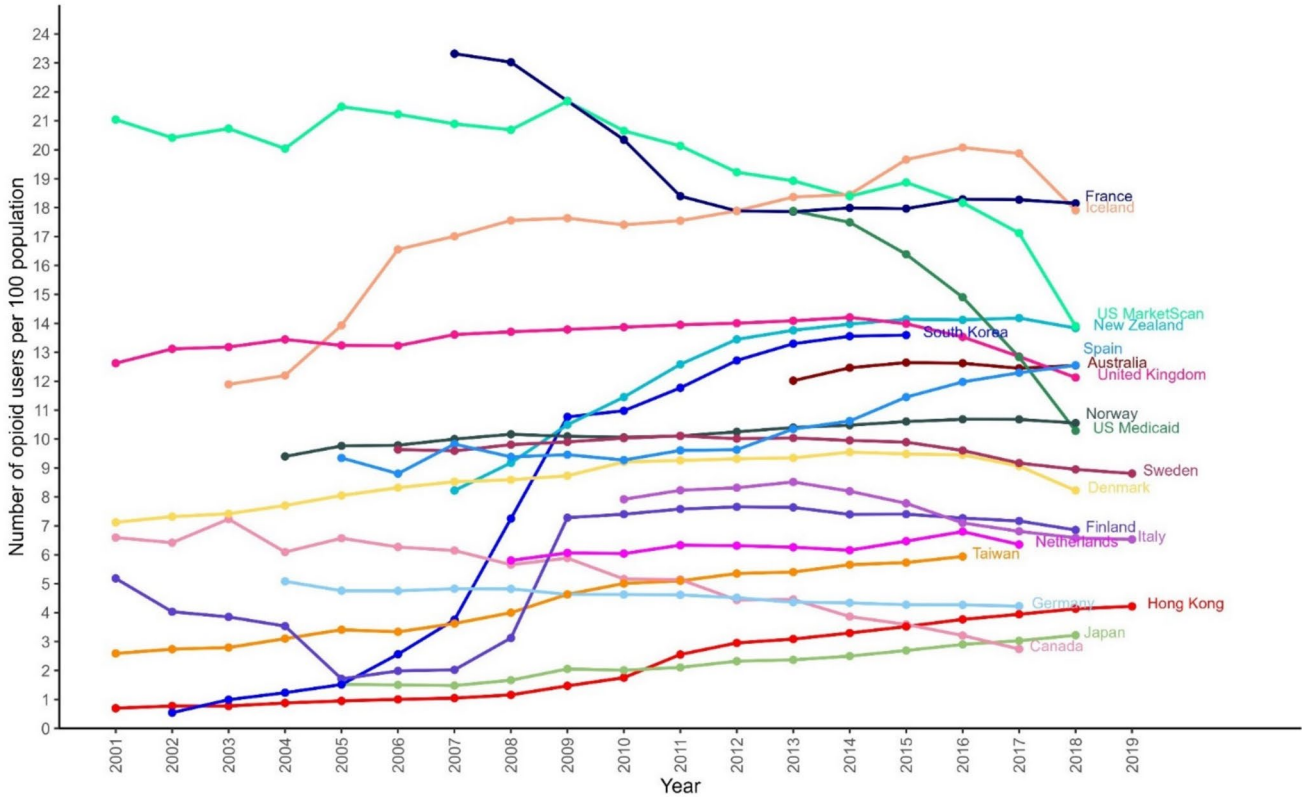

Fig. 1. Trends of opioid prescribing prevalence, 2001–2019. US, United States.

− 1.21%) in US Medicaid to + 0.86% per year (95% CI 0.72, 1.00) in South Korea. In most sites, incident opioid prescribing had similar time trends with nonincident prescribing, except in Iceland and the US MarketScan (Fig. 2; eTable 5, Supplement). More people were incident opioid users than nonincident users in most sites, except in the US (MarketScan and Medicaid), South Korea, and Sweden.

3.4 Sex and age differences of opioid prescribing

The pooled multinational opioid prescribing prevalence was 10.2% (95% CI 8.3, 12.4) in females and 7.8% (95% CI 6.4, 9.5) in males (eFigs. 5-6, Supplement). The overall female-to-male ratio amongst opioid users was 1.33:1. Ratios of female-to-male opioid users ranged from 1.06:1 in Hong Kong to 1.64:1 in US Medicaid. Among incident opioid users, UK had the highest female-to-male ratio (2.39:1). In nonincident opioid users, Italy and Spain had the highest female-to-male ratios of 1.98:1 and 1.92:1, respectively (Fig. 3; eTable 6, Supplement).

When stratified by age, the pooled multinational opioid prescribing prevalence was 1.2% (95% CI 0.8, 1.7) in children and adolescents (>19 years; eFig. 7, Supplement). US MarketScan had the highest pediatric opioid prescribing (7.6%; 95% CI 7.6, 7.7). In adults (19–65 years), the pooled multinational opioid prescribing prevalence was 10.2% (95% CI 7.8, 13.2; eFig. 8, Supplement). US Medicaid had the highest opioid prescribing in adults (33.7%; 95% CI 33.6, 33.7), followed by Iceland, US MarketScan, and France. Hong Kong had the lowest opioid prescribing in adults (2.9%; 95% CI 2.9, 2.9). In older adults (> 65 years), the pooled multinational prevalence of opioid prescribing was 18.8%(95% CI 16.0, 22.2; eFig. 9, Supplement). Iceland had the highest opioid prescribing in older adults 35.0% (95% CI 34.5, 35.6), followed by the UK, South Korea, and France. In the multivariable analysis, the female sex ($p < 0.0001$), use in North America ($p = 0.001$), and older age ($p < 0.0001$) were associated with higher opioid prescribing (eTable 7, Supplement; eFig. 10, Supplement).

4 Discussion

This study is the most comprehensive study conducted to date to observe opioid prescribing trends over 19 years in 20 different study sites. We noted marked geographical differences in opioid prescribing with signs of convergence toward 2019. In most countries, there were more incident opioid users than nonincident users, more opioid users were female than male, and opioid prescribing increased with age. The dissimilar trends and patterns suggest varied

Table 2 Annual absolute changes in opioid prescribing (per 100 population) over the study period

Country/region	Years covered	Average absolute change per year, % (95%CI); *p* value		
		Prevalent use[a]	Incident use[a]	Nonincident use[a]
East Asia				
Hong Kong	2001–2019	**0.23 (0.20; 0.26); < 0.001**	**0.10 (0.08; 0.12); < 0.001**	**0.14 (0.12; 0.15); < 0.001**
Japan	2005–2018	**0.14 (0.12; 0.15); < 0.001**	**0.11 (0.07; 0.15); < 0.001**	0.03 (− 0.01; 0.08); 0.11
South Korea	2002–2015	**1.24 (1.02; 1.46); < 0.001**	**0.43 (0.31, 0.55); < 0.001**	**0.86 (0.72; 1.00); < 0.001**
Taiwan	2001–2016	**0.25 (0.22; 0.27); < 0.001**	**0.15 (0.13; 0.17); < 0.001**	**0.10 (0.09; 0.12); < 0.001**
Oceania				
Australia	2013–2018	0.07 (− 0.06; 0.21); 0.21	− 0.05 (− 0.12; 0.01); 0.08	0.05 (− 0.01; 0.11); 0.08
New Zealand	2007–2018	**0.52 (0.34; 0.71); < 0.001**	**0.22 (0.09; 0.34); < 0.01**	**0.24 (0.16; 0.31); < 0.001**
North America				
Canada	2001–2017	**− 0.25 (− 0.30; − 0.21); < 0.001**	**− 0.21 (− 0.25; − 0.17); < 0.001**	**− 0.04 (− 0.05; − 0.08); < 0.001**
United States (MarketScan)	2001–2018	**− 0.28 (− 0.40; − 0.16); < 0.001**	0.05 (− 0.03; 0.14); 0.22	**− 0.33 (− 0.42; − 0.25); < 0.001**
United States (Medicaid)	2013–2018	**− 1.53 (− 2.06; − 1.00); < 0.01**	− 0.25 (− 0.52; 0.03); 0.07	**− 1.55 (− 1.89; − 1.21); < 0.001**
Northern Europe				
Denmark	2001–2018	**0.12 (0.07; 0.17); < 0.001**	**0.04 (0.02; 0.07); < 0.01**	**0.08 (0.06; 0.10); < 0.001**
Finland	2001–2018	**0.30 (0.15; 0.46); < 0.001**	**0.14 (0.03; 0.25); 0.02**	**0.16 (0.11; 0.22); < 0.001**
Iceland	2003–2018	**0.44 (0.29; 0.59); < 0.001**	**0.18 (0.07; 0.28); < 0.01**	**0.21 (0.16; 0.27); < 0.001**
Norway	2004–2018	**0.08 (0.06; 0.10); < 0.001**	**0.04 (0.03; 0.05); < 0.001**	**0.03 (0.02; 0.04); < 0.001**
Sweden	2006–2019	**− 0.06 (− 0.11; − 0.01); 0.028**	**− 0.03 (− 0.04; − 0.02); < 0.001**	− 0.05 (− 0.09; 0.001); 0.06
Western Europe				
France	2007–2018	**− 0.48 (− 0.71; − 0.24); < 0.01**	**− 0.12 (− 0.23; − 0.02); 0.03**	**− 0.28 (− 0.46; − 0.11); < 0.01**
Germany	2004–2017	**− 0.06 (− 0.07; − 0.05); < 0.001**	**− 0.08 (− 0.09; − 0.07); < 0.001**	**0.023 (0.015; 0.03); < 0.001**
The Netherlands	2008–2017	**0.07 (0.03; 0.12); < 0.01**	0.03 (− 0.01; 0.07); 0.11	**0.04 (0.02; 0.06); <0.01**
United Kingdom	2001–2018	0.02 (− 0.04; 0.07); 0.54	0.01 (− 0.03; 0.05); 0.54	0.005 (− 0.01; 0.02); 0.59
Southern Europe				
Italy	2010–2019	**− 0.22 (− 0.32; − 0.12); < 0.01**	**− 0.21 (− 0.27; − 0.15); < 0.001**	− 0.01 (− 0.7; 0.04); 0.59
Spain	2005–2018	**0.27 (0.19; 0.35); < 0.001**	**0.06 (0.01; 0.12); 0.02**	**0.21 (0.17; 0.24); < 0.001**

Bold indicates *p*-value < 0.05 (two-sided)

[a]We defined prevalent opioid users as individuals with at least one opioid record in each calendar year, incident opioid users as individuals with an opioid record in each calendar year and no opioid record in the preceding calendar year of the observed prescription/dispensing. We subtracted the number of incident users from prevalent users to approximate the number of non-incident users. We used a linear regression model to test time trends by estimating the annual average absolute changes in opioid prescribing per 100 population throughout the study period. We fitted one model per study site, with year as the only predictor variable in the model

opioid prescribing approaches and potential differences in opioid access across and within geographical regions, sexes, and age groups.

4.1 Varied but potentially converging opioid prescribing

In our study, multinational opioid prescribing was converging from 2001 to 2019, i.e., decreased in countries with high use at the beginning of the study period and increased in sites with low use. This pattern suggests that the tension between concerns about under-treatment and the risk of opioid-related harms is slowly being resolved by a more middle-ground pattern. Our results align closely with the observation in a study using country-level consumption data, reaffirming that opioid prescribing decreased in historically high-use countries, while increasing in previously low-use settings since the early 2010s [7]. Despite this being an encouraging observation, there were concerns about people being abruptly cut off from long-term pain treatment in

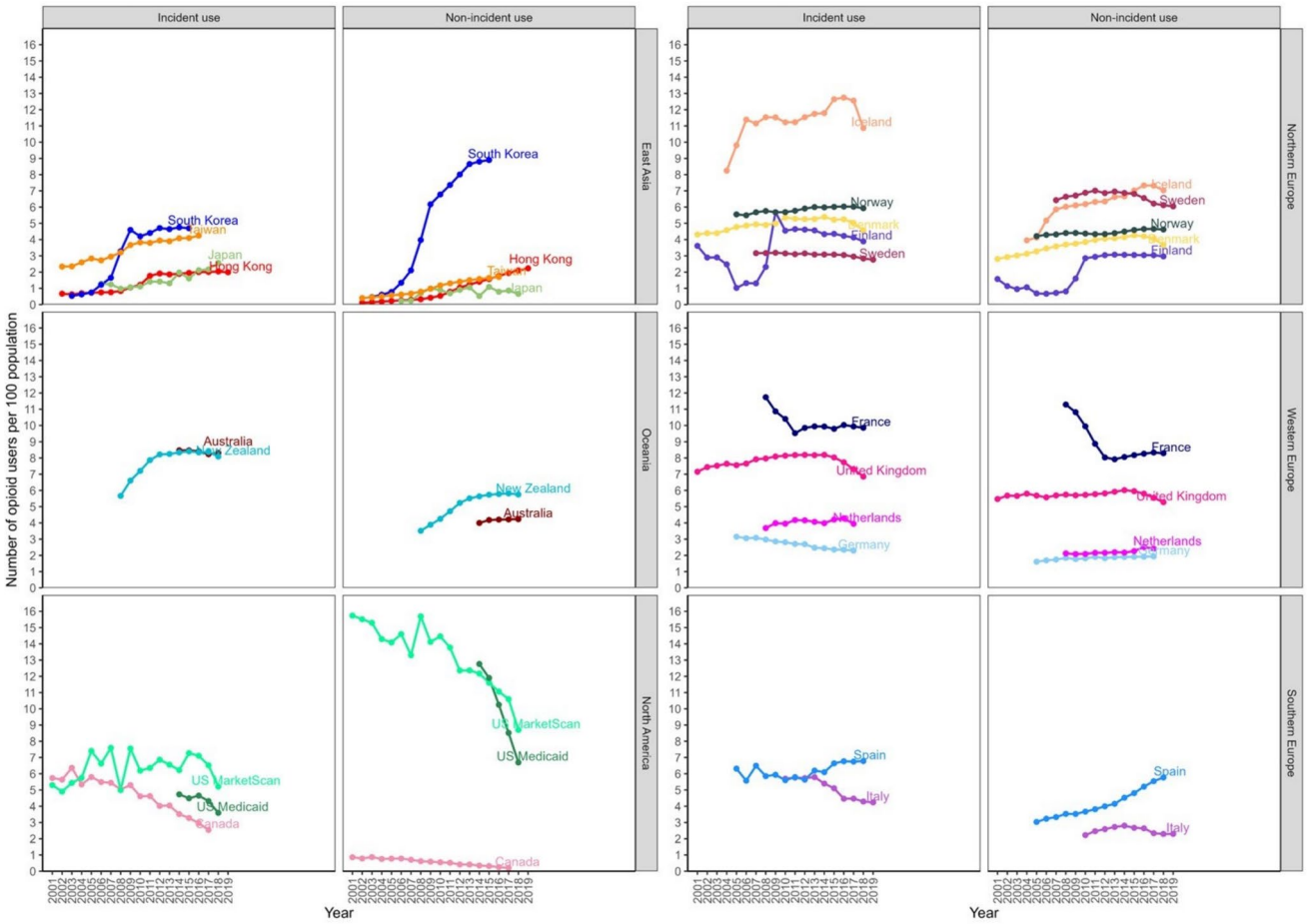

Fig. 2. Trends of incident and nonincident opioid prescribing, 2001–2019. We defined prevalent opioid users as individuals with at least one opioid record in each calendar year, incident opioid users as individuals with an opioid record in each calendar year and no opioid record in the preceding calendar year of the observed prescription/dispensing. We subtracted the number of incident users from prevalent users to approximate the number of nonincident users. For US MarketScan, nonincident use included prevalent opioid users and opioid users without enrolment in the prior year

countries with a sharp decline [10]. Patients may be at risk of withdrawal or seek opioids from nonregulated sources that are not captured in administrative datasets, especially if supportive interventions, such as psychological and nonpharmacological services, were not available [11]. This challenge has been particularly salient in the USA, given pressures on physicians to reduce prescribing, resulting in a sharp reduction in opioid use relative to other countries [12].

Nonetheless, similar to earlier studies, opioid use remained unbalanced across and within geographical regions over the study period [6, 13, 14]. In Europe, opioid prescribing prevalence ranged from 4.3% in Germany to 19.7% in Iceland, a quadruple difference. East Asia had the lowest regional opioid prescribing prevalence. Sites with low prescribing should examine if barriers to opioid access including poor physical availability and practical accessibility, cultural biases, or restrictive regulations, should be addressed [2]. Conversely, the potentially excessive number of users in countries with high opioid prescribing suggests that a large proportion of patients could be at risk of opioid-related harm [5]. While opioid prescribing in each site is influenced by differences in health systems, opioid availability, pain prevalence, and regulatory policies, given that the human development indexes of our study sites were similar [15], this raises questions about how much variability in clinical opioid prescribing is reasonable and whether or not at least some degree of the identified heterogeneity should be reconciled.

4.2 Incident and nonincident opioid prescribing in different sites

To identify the people at higher risk of opioid-related morbidities and mortality (i.e. those with more frequent opioid exposure), we further classified prevalent users into incident and nonincident users. More people were incident opioid users than nonincident users, except in the USA, South

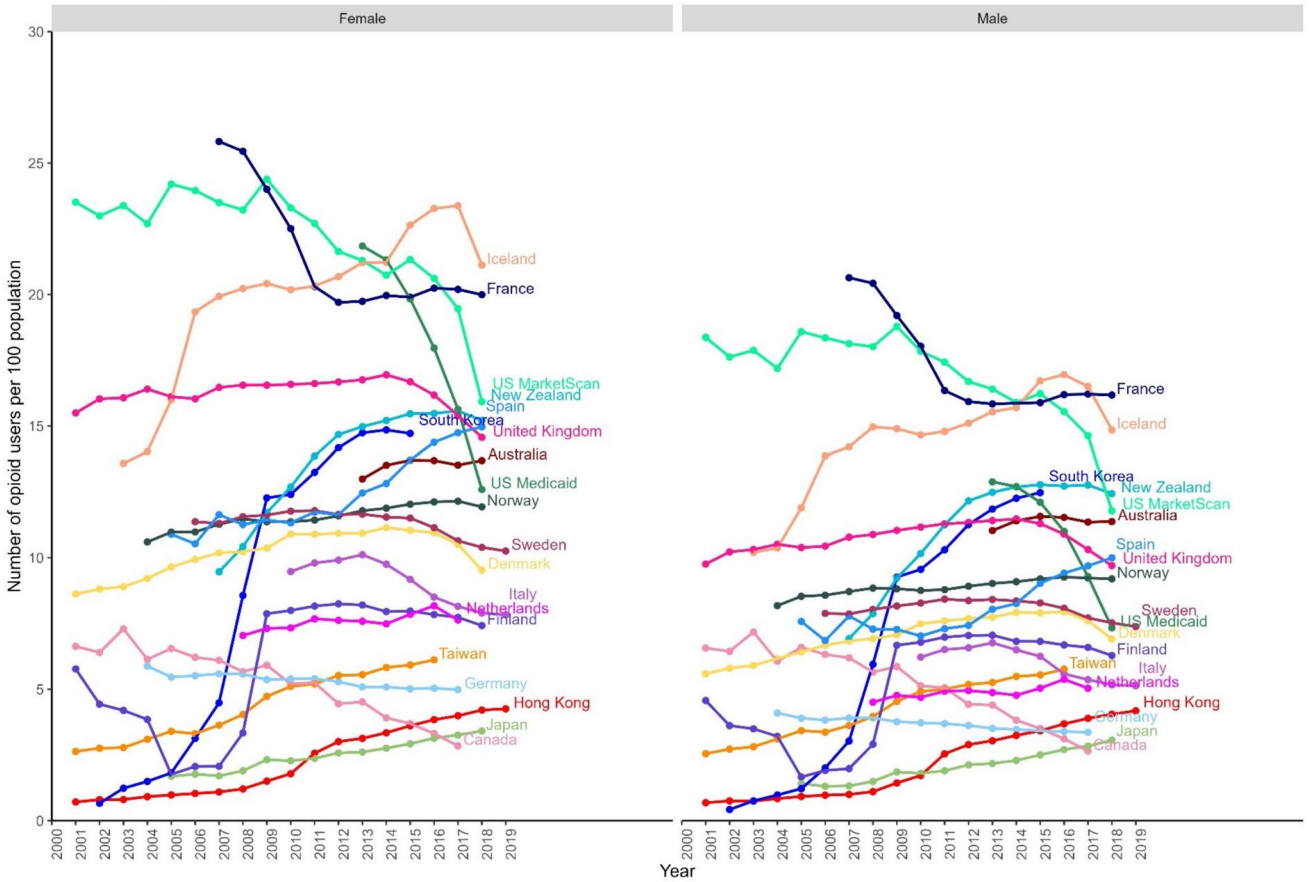

Fig. 3. Trends of opioid prescribing by sex, 2001–2019

Korea, and Sweden. Use of opioids to manage acute pain, cancer pain, and terminal pain is well-accepted clinically. However, their use for chronic noncancer pain remains controversial as potential harms outweigh the benefits.[16] In particular, nonincident opioid prescribing in South Korea was much higher than in other Asian sites. The sharp decline in nonincident use in North America suggests progress in restraining long-term use, a shift away from long-term use while countries where nonincident use is high and increasing relative to incident use like South Korea are concerning. Between the two US sites, a higher incident opioid prescribing was observed in individuals covered by private insurance than in Medicaid. While the observed differences between private and public reimbursed incident opioid prescribing could in part reflect potential differences in health, the direction of the finding was not as expected, given that Medicaid caters for the population with disability and greater health needs. People on Medicaid generally have poorer health and more chronic pain and would typically be thought to receive more opioids. The lower rates observed in our data suggest that other factors, not captured in administrative claims, may also play a role. There is evidence of racial, socioeconomic, and educational bias in opioid prescribing, with lower-income and less-educated individuals, many of whom are on Medicaid, receiving fewer prescriptions even when presenting with similar pain indications and severity as their privately insured counterparts [17]. Consequently, policies aimed at curbing opioid over-prescribing may have disproportionately impacted Medicaid populations, as reflected in our finding that the greatest average annual absolute reduction in opioid prescribing prevalence occurred among Medicaid recipients.

4.3 Sex and age differences in opioid prescribing

Sex differences in opioid prescribing were consistent across most data sources, where more females used opioids than males. This may be due to differences in pain conditions, pain experiences, and health-seeking behaviors [18–20]. Notably, females in the UK were twice as likely to be incident users of opioids than males, a much higher ratio than in other countries. Opioid prescribing also increased with age. The higher prevalence of chronic musculoskeletal and end-of-life conditions may explain the higher opioid prescribing in older adults when compared

with other age groups. High pediatric opioid prescribing in the US MarketScan data is also notable, at over six times the pooled average. This aligns with recent US studies showing that opioids remain commonly prescribed to children, especially for dental and postoperative procedures [21]. Other single-country studies have similarly reported higher rates of pediatric opioid prescribing in the USA compared with countries such as Denmark and Norway [22, 23]. By age 18, nearly one in five children have received at least one opioid prescription, raising concerns about the risk of later opioid misuse and unintended prolonged use [23]. The differences in opioid prescribing by sex and age may reflect the different pain management needs in each subpopulation [24–26]. Sex-related differences in opioid metabolism, hormones, body composition, and menstrual cycles, may contribute to differences in analgesic effect and safety profile of opioids [24]. Similarly, age- and gene-related pharmacodynamic and pharmacokinetic characteristics affect pain sensitivity, clinical efficacies, and occurrence of adverse events with opioid prescribing [25, 26]. Older adults, for instance, are more susceptible to side effects such as respiratory depression, impaired motor coordination, dizziness, and falls [27].

4.4 Strengths and limitations

This study presents the most comprehensive analysis to date of opioid prescribing by sex, age, and geographical location over 19 years in 20 different study sites. This study has several limitations. Firstly, although the common protocol enabled us to standardize the opioid prescribing and population measures evaluated in this study, heterogeneity of data sources did exist. For instance, the Icelandic register also captured drugs dispensed in nursing homes. This may inflate opioid prescribing rates when compared with a purely outpatient population. Also, opioid administration during hospitalization were often not captured. Secondly, we could not collect information on the indication of use and several opioids may have therapeutic indications beyond pain management. Thirdly, clinical practice differs, and the opioids included per site were different. Finally, we only assessed the number of people using opioids, not the volume of use.

Our results should be interpreted considering the regulatory interventions or guidelines changes during the study period. For example, the European Medicines Agency recommended the withdrawal of dextropropoxyphene in 2009 but the effect on opioid prescribing was largest in France in 2011 [28]. In Denmark, there were considerable media attention and regulatory actions since 2017 to decrease tramadol use and subsequently other opioids [29]. In Finland, there was a nationwide intervention in 2017 for decreasing paracetamol–codeine prescribing in large packages for new patients [30]. Reimbursement status of a medication may also affect the data captured. In Finland, paracetamol–codeine products were out of reimbursement status in the years where the greatest decrease was seen (2001–2008). However, they were still used despite not being captured in the prescription register. In the USA, the Centers for Disease Control and Prevention released key guidelines on opioid prescribing in 2016 amidst the epidemic of opioid overdoses and substance use disorders [31].

4.5 Implications and future research directions

Patients who suffer from pain symptoms and conditions require adequate pain relief while avoiding opioid-related harms such as addiction and overdose. However, decisions on pain management remain complex, particularly for patients who have become established on long-term opioid treatment [32]. Cross-disciplinary collaboration is needed to streamline evidence-based recommendations for different types of pains at different severity levels. To ensure adequate but prudent opioid prescribing, pain assessment should be routinely implemented. Other preventive measures to mitigate unintended misuse and diversion of opioids include setting realistic expectations about pain relief goals, promoting analgesia stewardship, highlighting the addictive properties of opioids, short prescription durations, providing novel delivery devices or routes of administration where appropriate, and follow-up of care after prescription with careful evaluation on the need for treatment continuation [33]. The WHO Analgesic Ladder also recommends first considering nonopioid analgesics where appropriate when administering pain treatment [34].

Our study identified clear differences in opioid prescribing by patient demographics—age, sex, and geographical regions. There is currently a paucity of research on the comparative safety and effectiveness of opioids for pain relief in specific populations, especially females, older adults, and nonCaucasians [27, 35]. Given the biopsychosocial differences that affect both opioid prescribing and responses, extrapolating treatment evidence from general populations may not be appropriate. Future safety and effectiveness evidence on opioid use, stratified into sex, age, and strong and weak opioids, should be generated with comprehensive information on potential influencing factors and categorized by clinical indication and comorbidities to inform safe prescribing in different subpopulations. Comparative studies incorporating biopsychosocial approaches to pain are also needed.

5 Conclusions

Our study suggests that multinational opioid prescribing was converging from 2001 to 2019, where opioid prescribing was decreasing in high-utilizing countries and was increasing in low-utilizing countries/regions. However, opioid prescribing

remained unbalanced across geographical locations with distinct differences by sex and age. Our findings highlight the need for more equitable, evidence-based pain management and research focused on underrepresented populations.

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Declarations

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Ethics approval Each participating site followed the relevant local ethics and regulatory frameworks for study approval, namely, Australia: The External Requests Evaluation Committee (RMS0863); Canada: University of British Columbia Clinical Research Ethics Board (UW 19-762); Hong Kong: University of Hong Kong/ Hospital Authority Hong Kong West Cluster (UW20-051); Iceland: National Bioethics Committee (VSN-20-058); Norway: Regional Ethics Committee (REK) (REK sør-øst D, ref. 92144); New Zealand: Auckland Health Research Ethics Committee (26501); South Korea: Sungkyunkwan University Institutional Review Board (2019-05-006); Spain: CEIm-Regional de la Comunidad de Madrid (01/20); Taiwan: Taiwan National Cheng Kung University Hospital Institutional Review Board (A-ER-107-387); the United Kingdom: Independent Scientific Advisory Committee (19_169); and the United States: University of North Carolina Institutional Review Board (19-3195) and Rutgers, The State University of New Jersey ArtSci Institutional Review Board (Pro2020002048). Ethical approval is exempted in Denmark, Finland, France, Germany, Italy, the Netherlands, New Zealand, Sweden.

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Author contributions I.C.K.W., K.K.C.M., and A.Y.L.C. had full access to the aggregate analysis data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. I.C.K.W. and K.K.C.M. were responsible for the study concept, and I.C.K.W., K.K.C.M., and A.Y.L.C. were responsible for the study design. All authors were involved in the acquisition, statistical analysis, or interpretation of data. I.C.K.W., K.K.C.M., and A.Y.L.C. drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Data availability statement The aggregate-level datasets generated or analyzed during the current study are available from the corresponding author on reasonable request subject to agreement from the site-investigators and their respective data providers.

Code availability R codes and dataset adopted in this study are available on GitHub repository at https://github.com/adrienneylc/GOMAP-opioids.

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Authors and Affiliations

Adrienne Y. L. Chan[1,2,3,4] · Shahram Bahmanyar[5] · Kebede Beyene[6] · Greta Bushnell[7] · Bruce Carleton[8] · Amy Hai Yan Chan[6] · Sharon Cook[9] · Stephen Crystal[9] · Kari Furu[10,11] · Svetla Gadzhanova[12] · Patricia García Poza[13] · Rosa Gini[15] · Sabrina Giometto[14] · Jeff Harrison[6] · Ulrike Haug[16,17] · Christine Hsu[18] · Harpa Lind Hjördísar Jónsdóttir[19,20] · Joe Kai[21] · Øystein Karlstad[10] · Ju Hwan Kim[22,23] · Kiyoshi Kubota[24] · Edward Chia-Cheng Lai[25,39] · Hyesung Lee[36] · Wallis C. Y. Lau[1,2,26] · Kathy H. Li[8] · Ersilia Lucenteforte[37] · Géric Maura[27] · Anke Neumann[27] · Virginia Pate[18] · Anton Pottegård[28] · Nadeem Qureshi[21] · Lotte Rasmussen[28] · Johan Reutfors[5] · Elizabeth E. Roughead[12] · Leena Saastamoinen[29] · Tsugumichi Sato[30] · Oliver Scholle[16] · C. C. M. Schuiling-Veninga[4] · Chin-Yao Shen[25,39] · Ju-Young Shin[22,23,31] · Til Stürmer[18] · Katja Taxis[4] · Marco Tuccori[32,33,38] · Stephen Weng[21] · Kirstie H. T. W. Wong[34] · Helga Zoega[20] · Kenneth K. C. Man[1,2,26] · Ian C. K. Wong[1,2,3,35]

✉ Kenneth K. C. Man
kenneth.man@ucl.ac.uk

✉ Ian C. K. Wong
wongick@hku.hk

1 Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

2 Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Hong Kong Special Administrative Region, China Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, China

3 Aston Pharmacy School, Aston University, Birmingham, UK

4 Unit of PharmacoTherapy, -Epidemiology and -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

5 Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden

6 School of Pharmacy, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand

7 Rutgers School of Public Health, Piscataway, and the Rutgers Center for Pharmacoepidemiology and Treatment Science, Rutgers University, New Brunswick, NJ, USA

8 Division of Translational Therapeutics, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada

9 Center for Health Services Research, Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA

10 Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo, Norway

11 Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

12 Clinical and Health Sciences, Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, SA, Australia

13 Division of Pharmacoepidemiology and Pharmacovigilance, Spanish Agency of Medicines and Medical Devices (AEMPS), Madrid, Spain

14 Unit of Biostatistics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

15 Agenzia regionale di sanità della Toscana, Osservatorio di epidemiologia, Florence, Italy

16 Department of Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology-BIPS, Bremen, Germany

17 Faculty of Human and Health Sciences, University of Bremen, Bremen, Germany

18 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

19 Faculty of Psychology, University of Iceland, Reykjavík, Iceland

20 Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

21 Primary Care Stratified Medicine (PRISM) research group, School of Medicine, University of Nottingham, Nottingham, UK

22 School of Pharmacy, Sungkyunkwan University, Suwon, Gyeonggi-do, South Korea

23 Department of Biohealth Regulatory Science, Sungkyunkwan University, Seoul, South Korea

24 NPO Drug Safety Research Unit Japan, Tokyo, Japan

25 School of Pharmacy, Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan

[26] Research Department of Practice and Policy, UCL School of Pharmacy, Mezzanine Floor, BMA House, Entrance A, Tavistock Square, London WC1H 9JP, UK

[27] French National Health Insurance (Caisse Nationale de L'Assurance Maladie, Cnam), 50 Avenue du Pr. André Lemierre, 75 986 Paris Cedex 20, France

[28] Clinical Pharmacology, Pharmacy and Environmental medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark

[29] Research Unit, The Social Insurance Institution of Finland, Kela, PO Box 450, 00056 Helsinki, Finland

[30] Department of Pharmacy, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Noda, Japan

[31] Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea

[32] Unit of Adverse Drug Reactions Monitoring, University Hospital of Pisa, Pisa, Italy

[33] Unit of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[34] Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

[35] Macau University of Science and Technology, Hong Kong, Macau Special Administrative Region, China

[36] Department of Medical Informatics, Kangwon National University College of Medicine, Chuncheon, Korea

[37] Department of Statistics, Computer Sciences and Applications G. Parenti, University of Florence, Florence, Italy

[38] Department of Diagnostic and Public Health, University of Verona, Verona, Italy

[39] Population Health Data Center, National Cheng Kung University, Tainan, Taiwan