Global, regional, and national trends in opioid analgesic consumption from 2015 to 2019: a longitudinal study

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Summary

Background Previous studies have reported an extremely unbalanced global access to opioid analgesics. We aimed to determine contemporary trends and patterns of opioid analgesic consumption at the global, regional, and national levels.

Methods We analysed the global pharmaceutical sales data of 66 countries or regions from the IQVIA-Multinational Integrated Data Analysis System database on opioid analgesics between 2015 and 2019. Opioid analgesic consumption was measured in milligram morphine equivalent per 1000 inhabitants per day (MME per 1000/day). The global, regional, and national trend changes were estimated using linear regressions. Factors associated with consumption patterns and trend changes were explored in multivariable linear regression analyses.

Findings Overall opioid analgesic sales in the 66 countries or regions increased from 27·52 MME per 1000/day (16·63–45·54) in 2015 to 29·51 MME per 1000/day (17·85–48·79) in 2019 (difference per year 3·96%, 95% CI 0·26 to 7·80). Sales reduced yearly in North America (–12·84%; 95% CI –15·34 to –10·27) and Oceania (–2·96%; –4·20 to –1·70); increased in South America (28·69%; 7·18 to 54·53), eastern Europe (7·68%; 3·99 to 11·49), Asia (5·74%; 0·61 to 11·14), and western and central Europe (1·64%; 0·52 to 2·78); and did not differ in Africa or central America and the Caribbean. The global opioid consumption patterns were associated with country-level Human Development Index (p=0·040), cancer death rate excluding leukaemia (p=0·0072), and geographical location (p<0·0001). In 2019, opioid analgesic consumption ranged from 0·01 MME per 1000/day to 5·40 MME per 1000/day in the 17 countries and regions in the lowest consumption quartile, despite high income levels and cancer death rates in some of them.

Interpretation Global opioid analgesic consumption increased from 2015 to 2019. The trend changes were distinctive across regions, which could reflect the different actions in response to known issues of opioid use and misuse. Disparities in opioid analgesic consumption remained, indicating potential inadequate access to essential pain relief in countries with low consumption.

Funding None.

Introduction

Opioid analgesics have been listed as an essential class of medicine for acute pain, cancer-related pain, and palliative care by WHO since 1977.[1] Although the importance of opioid analgesics has been emphasised ever since, concerns about inequity in opioid analgesic consumption remain worldwide.[2,3] Between 2011 and 2013, more than 95% of global opioid analgesic use occurred in a small number of high-income countries, accounting for only 15% of the global population.[3] In these countries where opioid analgesics have been readily available for decades, the over-reliance on prescription opioids for treatment of non-cancer pain was thought to contribute to the widespread non-medical use of opioids.[4,5] Such misuse of opioids has resulted in an epidemic of iatrogenic harms, including opioid dependence and overdose-related deaths.[6] However, the use of opioid analgesics in other parts of the world is disproportionately low and does not meet the basic needs for pain control.[3] Reasons for the restricted access to opioid analgesics in these regions were often multifactorial, including but not limited to financial, policy, cultural, and perceptual factors.[3,5] The issues with the global opioid analgesic consumption were recognised by the UN General Assembly 2016 on the World Drug Problem (UNGASS 2016), urging all governments to improve the control and supply of opioid analgesics to tackle this global drug problem.[7]

Existing knowledge about the global trends of opioid analgesic use mainly comes from a study of opioid analgesic use from 2001 to 2013,[3] using the International Narcotics Control Board (INCB) data reported in terms of the defined daily dose (DDD) for statistical purposes. Concepts of opioid crises and opioid epidemic have emerged as a result of understanding the trends in use, leading to various stewardship initiatives to ensure appropriate use of opioid analgesics.[5,8] The objectives of our study are to describe the global opioid analgesic

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Research in context

Evidence before this study

We searched PubMed without language restriction for articles published between Jan 1, 2001, and Oct 1, 2021, using the following search term: ((Global) AND (((Opioid) OR (Opiate)) AND ((Consumption) OR (Use))) AND (Trend)). We identified 259 records through the search. We reviewed the search results, the reference lists, and the International Narcotic Control Board (INCB) technical reports from 2015 to 2019 for evidence on the global trends in opioid analgesic consumption or use.
Two studies characterised the global trends in opioid analgesic use before this study, with one studying the period from 1980 to 2011, and the other from 2001 to 2013. Both previous studies used survey data from the INCB reports. Their findings suggested that global use of opioid analgesics has increased substantially from 2000 to 2013, but the increase was mostly driven by the high-income countries. During 2000–13, the consumption in low-income and middle-income regions did not have a substantial increase and was low, resulting in large disparities in the global opioid analgesic consumption.

Added value of this study

In our study of 66 countries and regions between 2015 and 2019 (5 years), we conducted an analysis on the contemporary trends and patterns of opioid analysis consumption at the global, regional, and national levels using global pharmaceutical sales data. We found an overall increase in opioid analgesic consumption worldwide. Our results showed that the consumption decreased in high-consumption regions like North America and Oceania; increased in low-consumption to middle-consumption regions like South America, eastern Europe, Asia, and western and central Europe; and was very low in Africa and central America and the Caribbean without significant change from 2015 through to 2019. We provided an updated ranking of the population-standardised opioid analgesic consumption in milligram morphine equivalent for individual countries and regions in 2019. This study provided opioid consumption rates, particularly in low-income and middle-income countries that can be used to support plans for future national, regional, and global public health policies.
We identified 17 countries with the lowest population-standardised consumption of opioid analgesics. Some of them had particularly high cancer prevalence and cancer death rates (eg, Kazakhstan), which might have the most unmet need for palliative care.

Implications of all the available evidence

Despite changes in some regional trends, the consumption of opioid analgesics remains disparate worldwide.
The discrepancies between opioid analgesic consumption and cancer prevalence in the low-consumption countries could be indicative of inadequate access to essential pain relief. These results can be used to evaluate the effects of national and international initiatives and policies on opioid analgesics.
The findings reinforce the need to recognise palliative care and pain relief as a public health priority and support initiatives to tackle the global gap in opioid access. Further regulatory actions are needed to promote adequate access to opioid analgesics worldwide, with a particular focus on the countries with very low consumption. The data call for global policies to integrate palliative care and pain relief into health-care systems, promote end-of-life care education, and strengthen staff training to reduce preventable pain and suffering in millions of patients worldwide.

consumption pattern between 2015 and 2019, to evaluate any further changes during the post-UNGASS 2016 era, and to explore country-level factors (eg, development index, economic status, geographical location, and cancer epidemiology), which could be associated with opioid analgesic consumption.

Methods

Data sources

This study used the global opioid analgesic sales data from the IQVIA-Multinational Integrated Data Analysis System (MIDAS) database. IQVIA uses national sample surveys throughout the pharmaceutical sales distribution channels—from manufacturers and wholesalers to retail and hospital pharmacies—to estimate the total sales volume of opioid analgesics. In some countries, the volume of drugs sold in retail and hospital pharmacies are also obtained. The average coverage of MIDAS data was reported as 88%.[9,10] IQVIA-MIDAS either captures sales for the entire market or projects sales for panels with less than 100% sector coverage (appendix pp 4–5).

See Online for appendix

The IQVIA-MIDAS database has been validated against external data sources[11] and is used to evaluate the multinational consumption of various medicines, including psychotropic drugs, antibiotics, cardiovascular drugs, and dementia drugs.[9,10,12–14]

All countries with opioid analgesics sales data available from IQVIA via their data collection network were included in the study. Data on the sales of opioid analgesics were collected from 66 countries or regions in the IQVIA-MIDAS database, including two aggregated regions for which only aggregated data were available in the database: central America and west Africa. The included countries and regions were divided into the following continents or subcontinents: Africa, America (North), America (central and the Caribbean), America (South), Asia, Europe (west and central), Europe (east), and Oceania based on their geographical locations as defined by the UN.[15] These continents and subcontinents have been previously reported to have different opioid use patterns.[3]

Additional yearly country and region-level variables were obtained from other data sources (appendix p 3).

Opioid analgesics and measurements

Opioid analgesics in this study included products classified as N02A (narcotics) in the Anatomical Therapeutic Chemical system defined by the European Pharmaceutical Market Research Association (EphMRA). Opioid medicines that are predominantly used for treatment of opioid dependence (eg, buprenorphine, levomethadone, and methadone) were excluded from the

	MME/TID in 2015 (95% CI)*	MME/TID in 2019 (95% CI)*	Average annual percentage change (95% CI)	p value
Worldwide	27·52 (16·63 to 45·54)	29·51 (17·85 to 48·79)	3·96 (0·26 to 7·80)	0·036
Africa	1·62 (0·13 to 19·61)	0·96 (0·03 to 35·18)	–16·45 (–40·96 to 18·25)	0·29
Egypt	0·70	0·61	–4·29 (–8·09 to –0·33)	0·041
Morocco	0·95	1·46	12·41 (–4·10 to 31·77)	0·10
South Africa	18·68	14·52	–3·76 (–18·03 to 13·00)	0·50
Tunisia	11·65	12·70	2·20 (1·10 to 3·32)	0·0078
West Africa†	0·08	0·01	–61·54 (–96·80 to 362·30)	0·31
America (central and the Caribbean)	6·95 (0·02 to 2244·86)	7·71 (0·04 to 1456·07)	1·87 (–3·18 to 7·18)	0·44
Central America‡	1·50	2·05	4·73 (–11·67 to 24·18)	0·45
Mexico	1·20	1·48	6·38 (1·67 to 11·30)	0·023
Puerto Rico	185·93	151·46	–5·12 (–9·70 to –0·31)	0·043
America (North)	1450·99 (672·57 to 3130·66)	853·46 (229·89 to 3168·46)	–12·84 (–15·34 to –10·27)	<0·0001
Canada	1580·67	987·60	–11·61 (–13·78 to –9·39)	<0·0001
USA	1331·99	737·51	–14·06 (–20·03 to –7·63)	0·0068
America (South)	0·56 (0·07 to 4·33)	1·58 (0·29 to 8·60)	28·69 (7·18 to 54·53)	0·0085
Argentina	3·88	3·84	–0·95 (–4·87 to 3·13)	0·51
Brazil	8·23	6·94	–1·75 (–12·21 to 9·97)	0·65
Chile	0·35	0·66	15·44 (6·77 to 24·81)	0·010
Colombia	0·90	0·80	–1·60 (–13·58 to 12·04)	0·72
Ecuador	0·13	4·23	142·21 (29·24 to 353·95)	0·021
Peru	0·01	1·26	210·50 (48·02 to 551·33)	0·017
Uruguay	17·41	27·25	10·79 (6·86 to 14·88)	0·0029
Venezuela	0·03	0·02	–18·32 (–50·41 to 34·53)	0·29
Asia	5·87 (2·32 to 14·88)	7·47 (2·88 to 19·37)	5·74 (0·61 to 11·14)	0·029
India	1·39	3·45	24·45 (2·05 to 51·78)	0·039
Japan	142·05	274·87	14·16 (–9·91 to 44·65)	0·17
Kazakhstan	5·00	5·40	–5·54 (–32·15 to 31·51)	0·62
Lebanon	3·65	7·04	20·34 (–1·18 to 46·54)	0·058
Mainland China	6·48	8·99	8·49 (7·18 to 9·81)	<0·0001
Pakistan	4·88	3·71	–4·46 (–17·16 to 10·18)	0·38
Philippines	0·97	1·23	5·01 (–2·34 to 12·90)	0·12
Saudi Arabia	4·65	1·24	–24·32 (–54·68 to 26·39)	0·18
South Korea	4·72	13·96	30·28 (26·39 to 34·29)	0·0001
Taiwan	63·68	66·50	2·48 (–4·04 to 9·44)	0·32
Thailand	6·10	6·94	2·52 (–6·24 to 12·09)	0·44
Turkey	25·37	24·19	–1·19 (–2·13 to -0·24)	0·028
United Arab Emirates	0·41	0·79	14·87 (2·81 to 28·36)	0·029
Europe (eastern)	28·90 (12·95 to 64·47)	38·14 (20·91 to 69·57)	7·68 (3·99 to 11·49)	0·0001
Belarus	21·93	26·59	3·60 (–6·93 to 15·32)	0·37
Bosnia and Herzegovina	43·08	47·93	2·87 (–0·04 to 5·86)	0·052
Bulgaria	48·82	47·98	–1·43 (–5·89 to 3·23)	0·40
Croatia	86·72	104·10	5·41 (2·46 to 8·45)	0·010
Romania	49·50	62·05	5·71 (3·75 to 7·71)	0·0025
Russia	6·77	14·99	27·53 (4·97 to 54·95)	0·029
Serbia	63·63	66·68	1·30 (–1·78 to 4·47)	0·28
Ukraine	5·71	11·35	19·51 (12·80 to 26·62)	0·0022

(Table continues on next page)

	MME/TID in 2015 (95% CI)*	MME/TID in 2019 (95% CI)*	Average annual percentage change (95% CI)	p value
(Continued from previous page)				
Europe (western and central)	322·24 (226·29to 458·89)	346·85 (250·76 to 479·77)	1·64 (0·52 to 2·78)	0·0045
Austria	776·54	747·98	–0·91 (–1·32 to –0·49)	0·0061
Belgium	705·01	705·69	–0·20 (–1·36 to 0·97)	0·62
Czech Republic	309·24	376·58	5·14 (3·80 to 6·50)	0·0011
Denmark	991·23	860·81	–3·62 (–5·72 to –1·48)	0·013
Estonia	42·97	74·74	10·83 (–3·63 to 27·46)	0·10
Finland	404·17	367·57	–2·14 (–3·33 to –0·94)	0·011
France	412·92	437·95	1·47 (0·66 to 2·29)	0·010
Germany	881·40	879·04	–0·17 (–0·67 to 0·33)	0·36
Greece	106·66	125·64	5·13 (1·58 to 8·81)	0·019
Hungary	198·46	203·04	0·44 (–1·01 to 1·91)	0·41
Ireland	372·26	417·14	2·47 (0·11 to 4·89)	0·045
Italy	286·58	344·29	4·87 (1·82 to 8·02)	0·014
Latvia	75·71	98·25	7·40 (1·78 to 13·33)	0·017
Lithuania	80·44	80·49	–0·06 (–0·76 to 0·64)	0·80
Luxembourg	339·01	201·56	–12·77 (–15·27 to –10·20)	0·0001
Netherlands	617·71	717·34	4·12 (–0·81 to 9·30)	0·077
Norway	651·33	719·37	2·29 (0·84 to 3·75)	0·015
Poland	105·01	131·43	5·46 (0·92 to 10·19)	0·031
Portugal	211·16	355·97	13·43 (10·73 to 16·19)	<0·0001
Slovakia	204·03	215·79	0·95 (–1·52 to 3·48)	0·31
Slovenia	248·11	204·50	–5·05 (–6·76 to –3·30)	0·0029
Spain	675·04	863·14	6·15 (3·74 to 8·61)	0·0037
Sweden	614·20	572·16	–1·83 (–2·70 to –0·94)	0·0073
Switzerland	773·84	897·60	3·68 (1·81 to 5·59)	0·0080
UK	706·81	638·72	–2·63 (–4·86 to –0·34)	0·035
Oceania	656·29 (52·30 to 8235·42)	580·85 (55·14 to 6118·67)	–2·96 (–4·20 to –1·70)	0·0009
Australia	869·71	754·88	–3·40 (–5·85 to –0·88)	0·024
New Zealand	495·25	446·94	–2·52 (–4·88 to –0·10)	0·045

MME/TID=milligram morphine equivalent per 1000 inhabitants per day. *Worldwide and regional estimates with 95% CI were calculated by pooling the estimates from individual countries using a random-effects model. †Data were aggregated from Benin, Burkina Faso, Cameroon, Chad, Côte d'Ivoire, Gabon, Guinea, Mali, Nigeria, Republic of Congo, Senegal, and Togo. ‡Data was aggregated from Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama.

Table: **Worldwide, regional, and national levels of opioid analgesic consumption in 2015 and 2019 and average annual percentage change in consumption**

study because we could not infer the indications of the consumed products.[3] The list of opioid analgesics are available in the appendix (p 6).

Opioid analgesic sales data were used as a proxy for consumption of the medicine by patients. The crude sales volumes of opioid analgesic were measured in a standard unit (SU) in the IQVIA-MIDAS database, with one SU defined as a single tablet, capsule, or ampoule, or vial, or 5 mL oral suspension. To allow direct comparisons of opioid analgesics of different potencies and formulations, we converted the quantities of consumption from SU into morphine milligram equivalents (MMEs) for each opioid-containing product. Where the strength or formulation of the opioid product is missing, they were imputed based on the respective information of the most sold product of the same drug in that country and region during the same year.[9] The detailed methods and list of imputed formulations are available in the appendix (pp 7–8). The MME conversion factors of the opioid analgesics were collected from various sources and the details are available in the appendix (p 6).

Statistical analysis

The main measure was the population-standardised rate of opioid consumption, expressed as MME per 1000 inhabitants per day (MME per 1000/day). The global and regional consumption levels were computed by pooling the estimates from individual countries using a random-effects model.

The time trend of opioid analgesic consumption was evaluated at global, regional, and national levels across the study period. At country and region level, the average annual change in percentage MME per 1000/day and

95% CI was estimated using a linear regression model, with log-transformed consumption in MME per 1000/day as the dependent variable, and year as the independent variable. Natural logarithm transformation was performed on consumption as it showed a non-linear relationship with time. The worldwide and regional trend changes were estimated using linear mixed models, controlling for within-country or region correlations, and assuming the correlations between years were auto-correlated. The trend change was expressed as average annual percentage change, calculated by [exp(the coefficient of the year variable)−1]×100%. Additional analyses were conducted by including country and region's yearly GDP per capita, Human Development Index (HDI), leukaemia death rate, cancer (except leukaemia) death rate, and cancer (except leukaemia) prevalence in the linear mixed model to investigate their effects on opioid use. All factors (GDP, HDI, and cancer epidemiology) included in the models were log-transformed. The statistical significance level was set at $p<0·05$ for any associations between covariates and opioid analgesic consumption. All analyses were conducted using SAS (version 9.4).

Six sensitivity analyses were conducted. First, we conducted an analysis in which only strong opioid analgesics, defined as an opioid that is indicated for moderate and severe pain following WHO guidelines,[16] were included (appendix p 6). Second, we evaluated the unadjusted and adjusted global trend changes excluding the two aggregated regions (central America and west Africa). Third, we included buprenorphine, methadone, and levomethadone products under N02A classification in the analysis. Fourth, we restricted our analysis to include the 48 countries that had sales data available from both hospital and retail sectors in the database (appendix pp 4–5). Fifth, we repeated the multivariable analysis for the main analysis with untransformed covariates. Finally, we compared the average consumption data in 2015–16 with 2018–19.

Role of the funding source

There was no funding source for this study.

Results

In our data, all 66 countries or regions captured sales from the retail sector, and 48 (73%) of 66 countries or regions captured sales from both the retail sector and hospitals.

Opioid analgesic consumption increased from 2015 to 2019 among the 66 countries and regions included, which represent approximately 74·5% of the global population (table). The average annual increase globally was 3·96% (95% CI 0·26–7·80), from 27·52 MME per 1000/day (16·63–45·54) in 2015 to 29·51 MME per 1000/day (17·85–48·79) in 2019. The trends of opioid analgesic consumption varied between regions (table, figure 1; appendix p 18). A reduction in consumption was observed in North America and in Oceania. Annual increases in consumption were observed in South America, eastern Europe, Asia, and western and central Europe. Trends of consumption did not differ significantly in Africa or central America and the Caribbean.

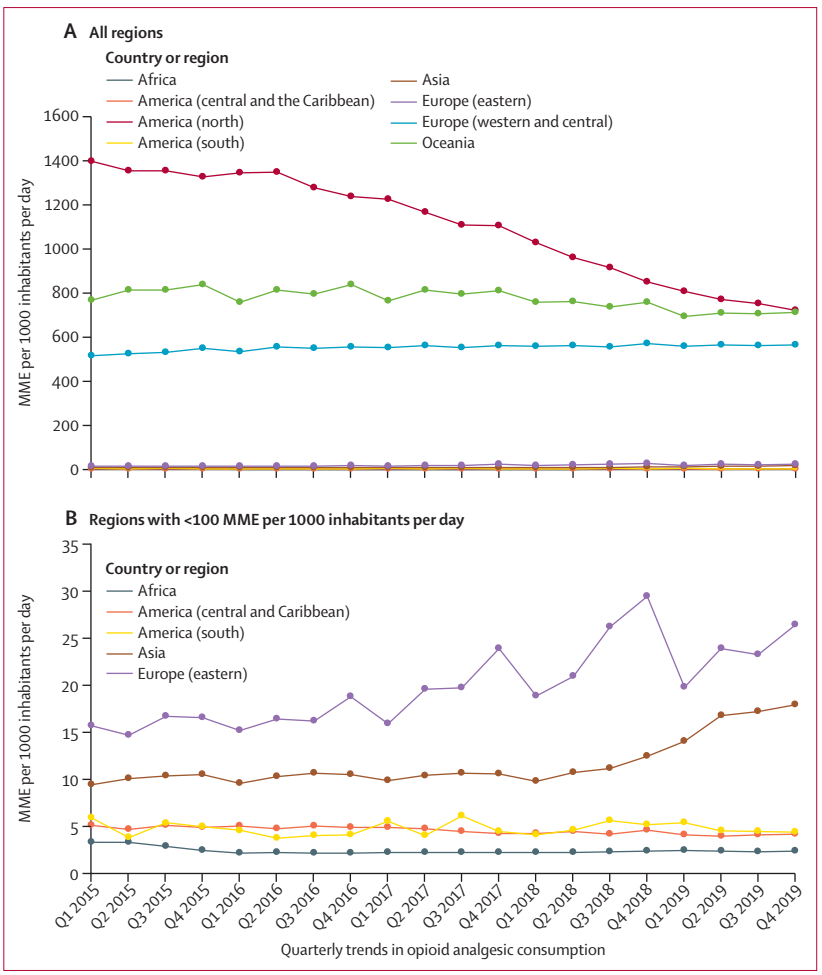

Figure 1: **Quarterly trends in opioid analgesic consumption at the regional level between 2015 and 2019**
(A) all regions (B) regions with less than 100 MME per 1000/day. MME per 1000/day=milligram morphine equivalent per 1000 inhabitants per day.

The levels of opioid analgesic consumption varied greatly by country and region throughout the study period. In 2015, we found a high level (>200 MME per 1000/day) of opioid analgesic consumption rate in North America (1450·99 MME per 1000/day; 95% CI 672·57–3130·66), Oceania (656·29 MME per 1000/day; 52·30–8235·42), and western and central Europe (322·24 MME per 1000/day; 226·29–458·89; table). Despite decreases in consumption in North America and Oceania, these three regions still contributed a large proportion of the global consumption in 2019. Consumption remained low in other parts of the world, even for those with the increasing trends between 2015 and 2019 (figure 2).

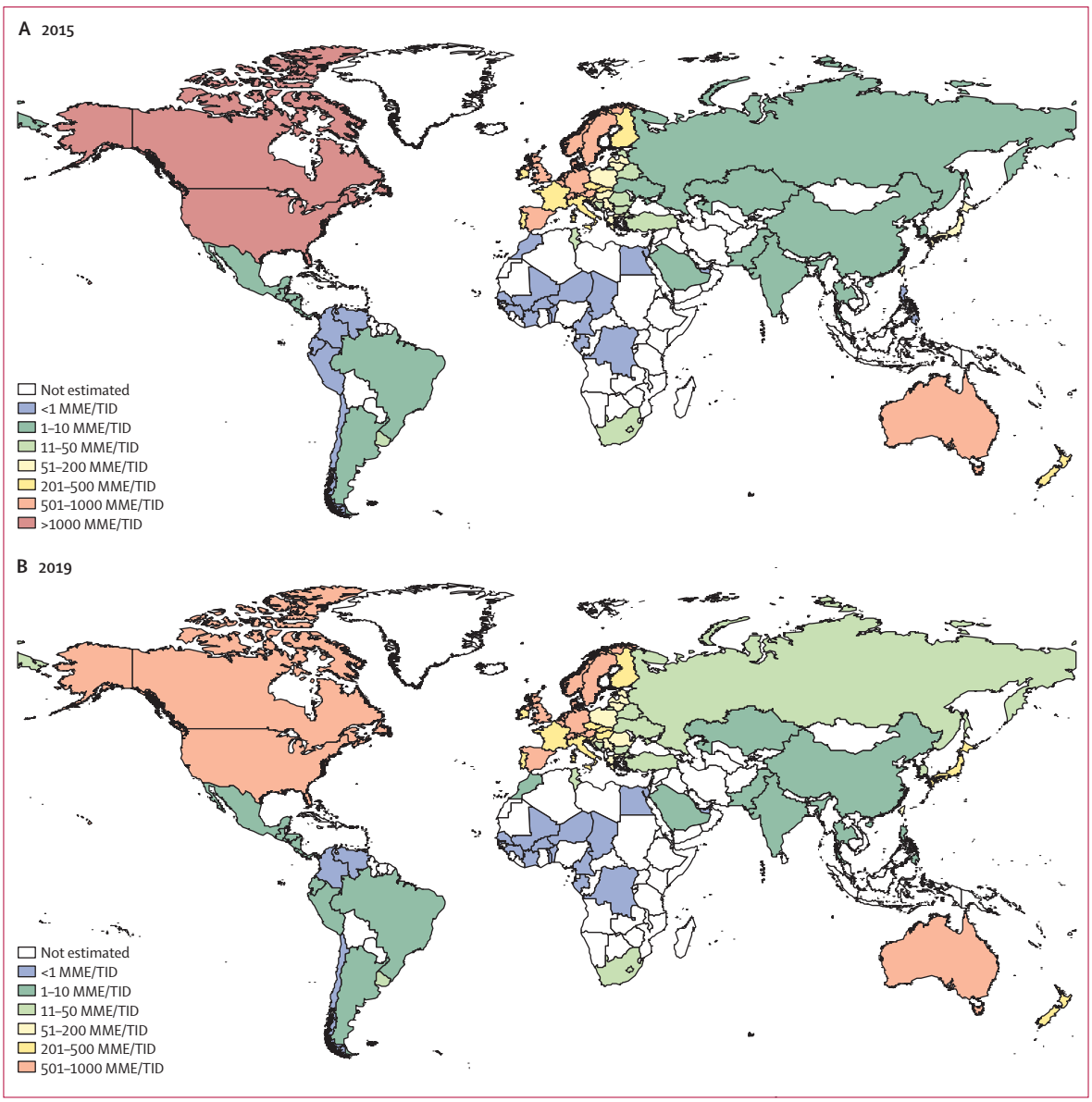

Figure 2: **Worldwide consumption of opioid analgesics in 2015 and 2019**
MME per 1000/day=milligram morphine equivalent per 1000 inhabitants per day.

Canada, the USA, Australia, New Zealand, and 13 west European countries were the 17 countries in the highest quartile of opioid consumption in 2019, ranging from 987·60 MME per 1000/day in Canada to 376·58 MME per 1000/day in the Czech Republic (table, figure 3). There were 17 countries and regions in the lowest quartile of opioid analgesic consumption: west Africa, Venezuela, Egypt, Chile, the United Arab Emirates, Colombia, Philippines, Saudi Arabia, Peru, Morocco, Mexico, central America, India, Pakistan, Argentina, Ecuador, and Kazakhstan, with the consumption ranging from 0·01 MME per 1000/day in west Africa to 5·40 MME per 1000/day in Kazakhstan (table, figure 3).

In multivariable analysis, in which yearly GDP per capita, HDI, geographical location, and cancer epidemiology of each country and region were adjusted, the worldwide trend over the years in opioid analgesic consumption was –1·03% per year (95% CI –4·86 to 2·95). We found geographical location (continent; p<0·0001) was associated with opioid analgesic consumption, where countries in Oceania and North America had higher consumption than other regions regardless of HDI or cancer epidemiology. HDI (p=0·040) and cancer (except leukaemia) death rate (p=0·0072) were positively correlated with the consumption, whereas cancer (except leukaemia) prevalence

(p=0·78), leukaemia death rate (p=0·67), or GDP per capita (p=0·11) were not associated with the trends. The associations of each factor differed by regions, where the opioid analgesic consumption was associated with HDI within western and central Europe (p=0·017), cancer (except leukaemia) death rate among countries within Africa (p=0·0058) and Asia (p=0·035), and cancer (except leukaemia) prevalence (p=0·0002) and leukaemia death rate (p=0·0001) within South America. No factors were found to be associated with opioid analgesic consumption in countries in eastern Europe (figures 4, 5; appendix pp 19–22).

Results from the analysis on strong opioid analgesics showed a smaller and statistically non-significant annual change in global consumption (0·36% [–2·76 to 3·58; p=0·82]). The trends of strong opioid analgesics at regional level were generally consistent with those of overall opioid consumption, except for South America. The increasing trend observed in overall opioid consumption was not found in the strong opioid analgesics in South America from 2015 to 2019 (average annual change –3·76% per year; 95% CI –12·07 to 5·33; appendix pp 9–10, p 23). In a sensitivity analysis excluding the aggregated data of west Africa and central America (full data not shown), the unadjusted average annual change for global opioid analgesic consumption was 5·58% (2·77 to 8·46), and adjusted average annual change was 0·71% (–2·27 to 3·79). The sensitivity analyses for opioid analgesics including N02A buprenorphine, methadone, and levomethadone products (appendix pp 11–12, 24), and countries and regions with market share data from both retail and hospital sectors (appendix pp 13–14, 25) showed similar results on the global and regional trends of opioid analgesic consumption to the main analysis. The results from the multivariable analysis with untransformed factors (appendix p 15) and the analysis comparing consumption from 2015–16 to 2018–19 (appendix pp 16–17) yielded consistent results with the main analysis.

Discussion

Using a database of opioid analgesic sales data in 66 countries and regions from 2015 to 2019, we found an overall increase of 4% annually in the global opioid analgesic consumption. The consumption declined in high-consumption regions including North America and Oceania, and increased in low-to-middle consumption regions, such as Asia and eastern Europe. However, disparities in opioid analgesic consumption remained across the world. The discrepancies between the very low opioid analgesic consumption and high cancer death rate or cancer prevalence in particular countries (eg, Kazakhstan) might indicate potentially inadequate access to opioid analgesics as essential pain control.

The increase in opioid analgesic consumption worldwide was associated with the rising global HDI and increasing cancer death rates. This finding is consistent with previous evidence that the development level of the country or region was the main determinant of opioid analgesic access,[3,17] and advanced cancer was the major health condition requiring opioid analgesic treatment.[5,18]

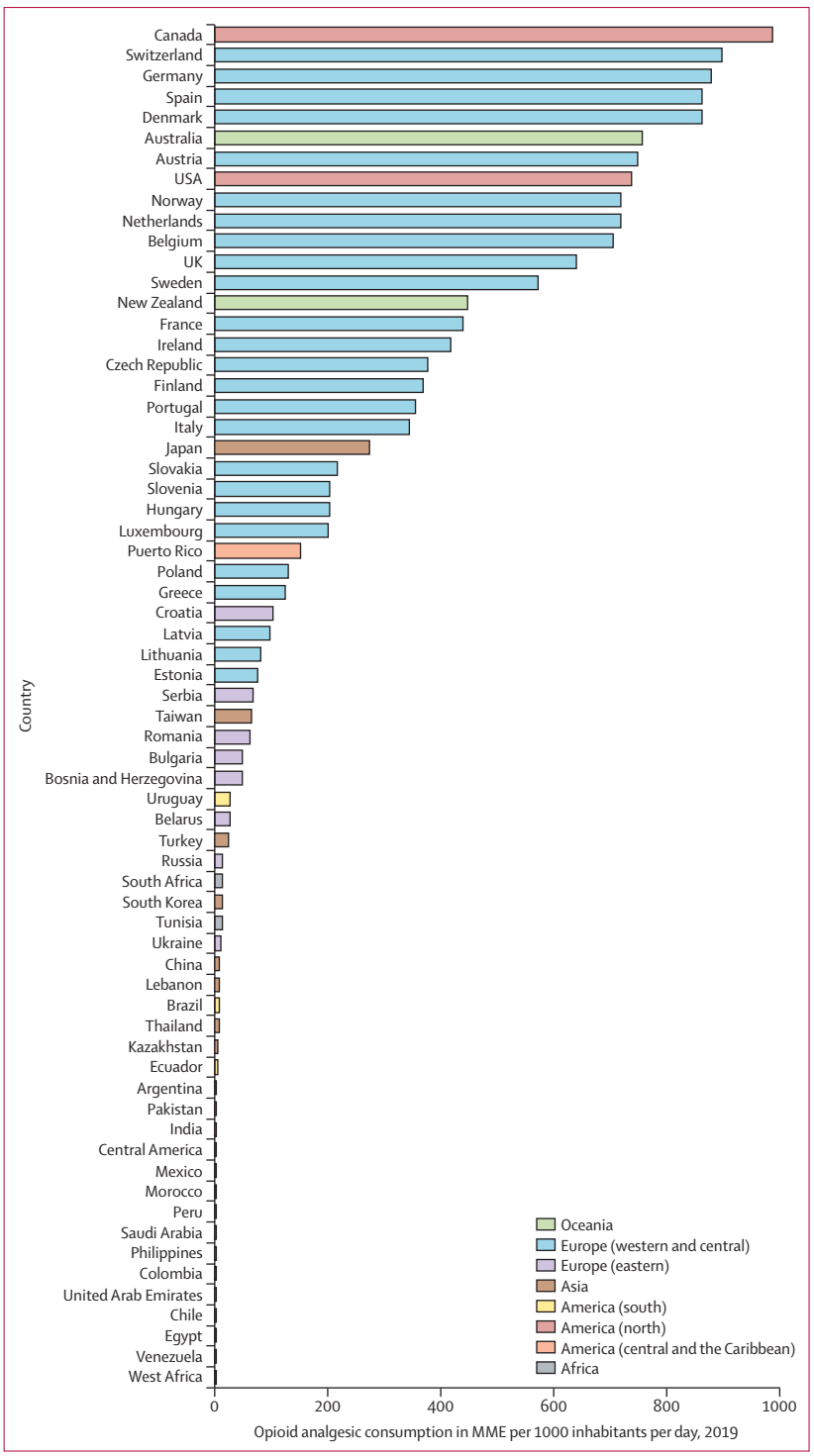

Figure 3: **Rankings of opioid analgesic consumption for individual countries and regions in 2019**
MME=milligram morphine equivalent.

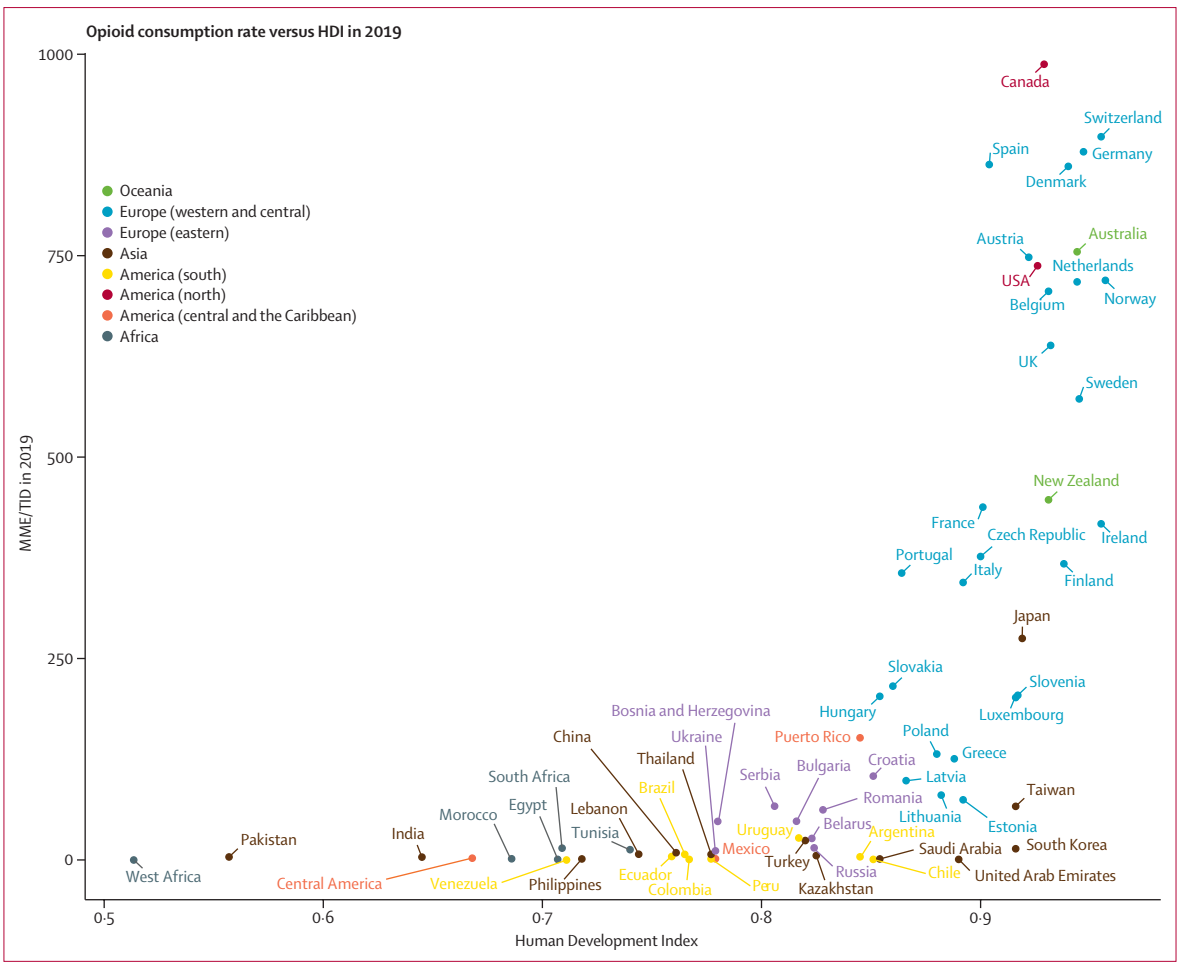

Figure 4: **Plot of individual country or regions' opioid analgesic consumption rate by Human Development Index in 2019**
This figure shows the patterns of opioid analgesic consumption rate in relation to the Human Development Index (HDI) for each country and region. HDI is a summary measure of human development which ranges between 0 and 1. MME per 1000/day=milligram morphine equivalent per 1000 inhabitants per day.

Our data also showed a distinctive geographical pattern of opioid analgesic consumption independent of HDI and cancer death rates. One previous study reported a similar variation in opioid analgesic use by continents in clinical trial settings, in which patients in Asia and eastern Europe were more likely to be undertreated with opioids for pain control than were patients in North America.[19] The differences persisted despite the standardised treatment protocols. It might suggest there are other more deeply ingrained factors affecting pain-control practice in different regions of the world. Attitudes of physicians and patients towards pain management has been identified as one of the main factors affecting opioid use.[3,19]

Countries within the same geographical regions are likely to share similar beliefs towards the use of opioid analgesics. For example, the Arab countries, such as the United Arab Emirates, had one of the lowest estimates of opioid analgesic consumption worldwide despite the high incomes and HDI. The low consumption could be partly explained by the low cancer death rates, but cultural and religious principles in these countries could have also shaped governments' and individuals' attitudes towards opioid analgesics and restricted their use in practice.[20] In other instances, countries and regions with similar geographical locations and cultural backgrounds might still have different patterns of opioid analgesic consumption (eg, the consumption was ten times higher in Taiwan than in mainland China), which could be due to the variations in the provision of pain services.[21,22] Overall, the development status and cancer death rate might not be the only factors shaping a country or region's opioid analgesic consumption pattern. The optimal national opioid usage would require effective policies regulating the availability, affordability, and attitudes of prescribers, patients, and policy makers towards opioid analgesics.[3]

Our findings could be interpreted in the context of initiatives over the last decade to regulate opioid analgesic consumption in many regions.[3,8] The initiatives differ

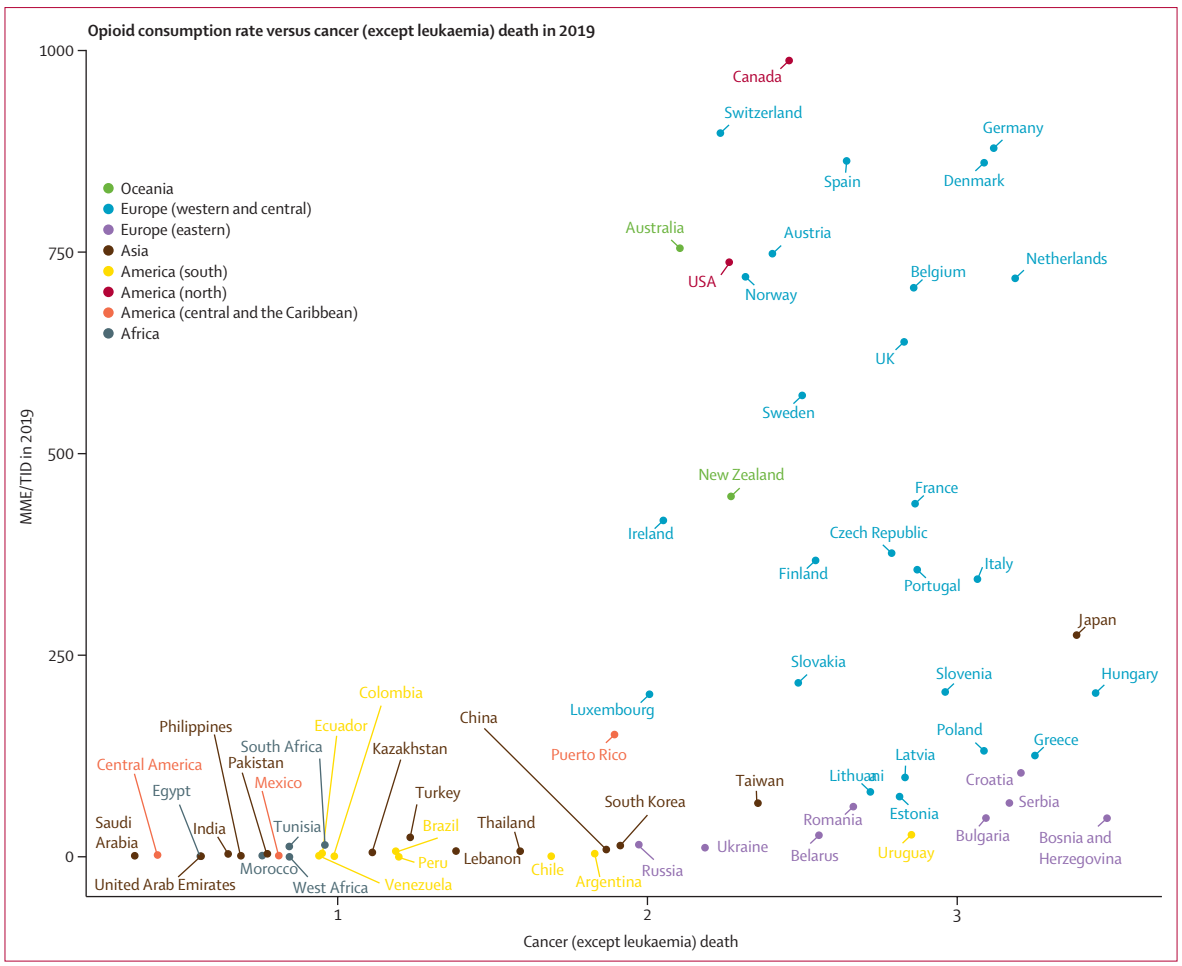

Figure 5: **Plot of individual country or regions' opioid analgesic consumption rate by cancer (except leukaemia) death rate in 2019**
Cancer death rates were measured as the number of cancer deaths per 1000 population. MME per 1000/day=milligram morphine equivalent per 1000 inhabitants per day.

largely by country because different countries are facing different challenges in promoting the appropriate use of opioid analgesics. North America was the region that was most severely affected by the opioid epidemic, having an estimated prevalence of opioid use disorder of over 1000 cases per 100 000 people in 2016 (three-fold higher than the global average). With the increased awareness of opioid misuse,[7,23,24] a combination of strategies, including opioid prescribing guidelines and laws, the prescription drug monitoring programmes, and professional and public education programmes were introduced in the USA to reduce inappropriate opioid prescribing.[25,26] However, while overprescribing and addiction must be addressed, there are concerns about the potential negative effects of these programmes, such as increased illicit use of opioids and more patients being undertreated or untreated for pain.[27,28] We were unable to examine these effects as we do not have information on illicit opioid consumption or the appropriateness of the opioid prescription. Further research is warranted to fully evaluate the public health implications of the strategies. In other regions (eg, Asia and eastern Europe), the accessibility to opioid analgesics has increased. This could reflect the increasing recognition of the short supply of essential opioid analgesics for pain control in low-income and middle-income countries over the past decade,[3,29] and resultant international[5,8] and national initiatives[30] that have been undertaken to promote opioid availability in such regions. For example, in mainland China, the National Health and Family Planning Commission has launched the nationwide Good Pain Management Programme, which emphasised the use of opioid analgesics for cancer pain relief.[31] In addition, the Commission has led many joint initiatives including training sessions for professional, patient education, and publishing pain management guidelines, which might all contribute to the increased, appropriate, opioid consumption in the country.[32,33]

Our study highlighted several trends. First, the increase in consumption of opioid analgesics in South

America did not persist when we restricted the analysis to the use of strong opioid analgesics. This finding could suggest that the availability of strong opioid analgesics, which are essential for managing moderate to severe pain, could still be restricted. Second, a continued increase in high opioid analgesic consumption was seen for some western European countries, such as Norway, Spain, and Switzerland. Several European countries have overtaken the USA and become high consumers of opioid analgesics, behind Canada. Conversely, in the 17 countries or regions with the lowest consumption in 2019, notable differences existed between opioid analgesic consumption and cancer epidemiology. These disparities could be indicative of poor access to pain relief by patients with cancer pain. Urgent improvements in the access to opioid analgesics in these countries are of paramount importance to meet patients' needs for pain relief. Overall, although the gaps in opioid consumption between countries have been reduced, disparities remained and could be of concern, requiring further actions.

This study adds unique value to the body of literature regarding opioid analgesics utilisation. This study provides 5 years of recent data on the global consumption of opioids analgesics continuing from the last INCB study.[2,3] The INCB also reported estimates for opioid use in each country and region as 3-year averages over 2017–19 in the most recent annual report.[34] However, one should be cautious when comparing the results from this study to the INCB data because this study estimated the opioid use in MME whereas the INCB reported the results in defined daily dose (DDD) for statistical purposes. MME is a more accurate reflection of the clinical use of opioid analgesics than DDD.[3,35] There could be 0·6–7·1 times differences between these two measurements.[36] Hence, we provided a different ranking of countries in opioid use. When the INCB data was converted to measurements in MME based on the knowledge of the total weight of opioids consumed, the rankings of countries and regions became similar to our study (eg, Canada consumed more opioids than the USA).[5] Our trends are also comparable with other nationwide studies investigating opioid use within a similar time period, including studies in North America[26] and some European countries.[37,38] Of the 17 countries or regions that were in our lowest quartile of opioid consumption, all were also considered having inadequate or very inadequate consumption by INCB,[34] except Saudi Arabia, Argentina, Chile, and Colombia. Our estimates are anticipated to be lower because, unlike INCB, we excluded all buprenorphine, methadone, and levomethadone products. Also, not all the countries in the data have both retail and hospital coverage, although it will not affect the estimation of trends, which is our main objective. Nonetheless, the restricted access to opioid analgesics in these four countries has been suggested by other studies.[20,39,40] Further investigations are warranted to explore whether opioid access is adequate in these countries.

The study was strengthened by several methodological improvements from the previous study on the global trend of opioid use.[3] We used sales data on opioid analgesics, which could capture nearly all legally distributed opioid analgesics by the wholesalers that fell under the EphMRA definition, including the over-the-counter sales. We have detailed information on the strength and formulation of the opioid-containing products, which allowed us to calculate the opioid analgesic consumption volumes in MME.

This study has limitations. We used pharmaceutical sales data as a proxy for medication consumption. Imperfect estimation could arise from situations such as wastage of medicines, stockpiling, or cross-border distribution of drugs that left sold medications unconsumed.[41] However, this limitation is unlikely to have a large effect on the national and regional trends over time in opioid sales that we observed nor our overall conclusion. As we did not have data on individual opioid medications and the characteristics of individual patients, we were unable to study the association between patient characteristics and opioid analgesic consumption at the individual level, nor were we able to differentiate between appropriate use and inappropriate use of opioid analgesics. As a result, we excluded data on buprenorphine, levomethadone, and methadone because of their indication for opioid dependence disorders. As this is a descriptive, associational study with potential for unexplored variables, we cannot conclude a causal link between any factors and our observed opioid consumption trends. We did not investigate other qualitative factors, such as cultural attitudes towards opioid analgesics, that could impede access to the medications. We explored the potential unmet need in cancer pain relief only. However, even in countries with low cancer death rates, there could be a need for palliative care and pain control for other conditions than cancer, such as infections, trauma, and respiratory failure.[5] In addition, the log-transformation of the opioid analgesic sales data would tend to bring the trend estimates towards the null and underestimate the trend. Nevertheless, we still found strong time trends in many regions of the world. Although we studied 66 countries and regions representing 74·5% of the global population, our findings might not apply to countries that were not included in the study. Due to the low number of Caribbean countries available in the database, our results for central America and the Caribbean might not be entirely reflective of this subregion. Further studies are warranted to fully understand opioid use in Caribbean countries.

The analysis in this study has contributed to an improved understanding of the scale of the global gap in access to opioid analgesics, reinforcing the need to recognise it as a public health priority and support

initiatives to tackle it. We provided opioid consumption rates, particularly in low-income and middle-income countries, that can be used to support plans for future national, regional, and global public health policies. We have identified countries with very low consumption of opioid analgesics, despite the high cancer death rates or cancer prevalence in some of them (eg, Kazakhstan). These countries might have insufficient access to pain and palliative care, for which the reasons should be identified. Previous investigation in South America suggested over-regulation and poorly developed medical education were the main barriers that impaired access to opioid analgesics in the region.[40] Several international initiatives have been established to promote equity in global access to opioid analgesics for pain control in low and middle-income countries.[5,16] However, it was also well-recognised that the palliative care services started late and developed slowly in low and middle-income countries, and that many barriers to palliative care development still exist.[30,33] Therefore, the opioid analgesic consumption levels in these countries were still well below the global average. Continuous efforts by low and middle-income countries are needed to better integrate opioid analgesic use for pain control and palliative care into the health-care systems. This study can provide information to these countries to formulate public health policies regarding the use of opioid analgesics and serve as a baseline for the evaluation of these policies.

The overall consumption of opioid analgesics has increased in the 66 countries and regions over the 5 years between 2015 and 2019. The trend changes varied across regions with declines in the high-consumption countries and regions and increases in some low-consumption countries and regions. However, global disparities in opioid analgesic consumption still exist, and poor access to opioid analgesics in countries with low consumption might have resulted in unmet needs for pain relief of patients. International and national efforts are required to improve the availability of opioid analgesics in countries with a low consumption but a high cancer death rate and cancer prevalence. The data from this study reinforce the need to close the gap in opioid analgesic access as a public health priority and call for global policies to integrate palliative care and pain relief into health-care systems, promote end-of-life care education, and strengthen staff training to reduce preventable pain and suffering in millions of patients worldwide.

Contributors

ICKW and LW accessed and verified the underlying data, and all authors had accessed to the data. CJ, WCYL, and ICKW conceptualised the study. CJ and WCYL conducted the statistical analysis. CJ wrote the original draft under the supervision of WCYL and ICKW. All authors interpreted the data, and critically reviewed and commented on all other drafts. All authors have approved the submission of the manuscript.

Declaration of interests

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Data sharing

The underlying MIDAS data were provided by IQVIA under license. The terms of our agreement do not permit disclosure, sublicensing, or sharing of IQVIA MIDAS data. IQVIA will honour legitimate requests for MIDAS data from qualified researchers. Please contact IQVIA to seek approval for data access; a license fee might be applied.

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