Study Report Phase II C1-002

31/10/2023

Version 3.0

TABLE OF CONTENTS

Table of contents **2**

1. DESCRIPTION OF STUDY TEAM **6**

2. DATA SOURCES **7**

3. ABSTRACT **8**

4. LIST OF ABBREVIATIONS **11**

5. AMENDMENTS AND UPDATES **11**

6. MILESTONES **11**

7. RATIONALE AND BACKGROUND **12**

8. RESEARCH QUESTION AND OBJECTIVES **13**

9. RESEARCH METHODS **15**

9.1 Study Type and Study Design 15
9.2 Study Setting and Data Sources 15
9.3 Study Period 18
9.4 Follow-up 18
9.4.1 Population-level Utilization of opioids 18
9.4.2 Patient-level Utilisation of opioids 19
9.5 Study Population with in and exclusion criteria 19
9.5.1 Population-level Utilisation of opioids 19
9.5.2 Patient-level Utilisation of opioids 19
9.6 Variables 21
9.6.1. Exposure/s 21
9.6.2. Outcome/s 23
9.6.3. Other covariates, including confounders, effect modifiers and other variables 23
9.7 Sample size 25
9.8 Data transformation 25
9.9 Statistical Methods 25
9.9.1 Patient privacy protection 25
9.9.2 Statistical model specification and assumptions of the analytical approach considered 25
9.9.3 Methods to derive parameters of interest 26
9.9.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence 27
9.9.5 Methods to control for potential sources of bias 28
9.9.6 Methods to deal with missing data 29
9.9.7 Description of sensitivity analyses 29
9.9.8 Evidence synthesis 29
9.10 Deviations from the protocol 29

10. DATA MANAGEMENT **30**

10.1. Data management 30
10.2. Data storage and protection 30

11. QUALITY CONTROL **30**

12. RESULTS **31**

12.1.1. Participants 31
Table 12.1.1 Number of participants in each source population 31
12.1.2. Descriptive Data 32
12.1.3. Outcome Data 32
12.1.4. Main Results 32
Incidence rates of opioids over time 32
Incidence rates of opioids over time by age group 40
Incidence rates of opioids over time by sex 48
Prevalence of opioids over time 56
Prevalence of opioids over time by age group 62
Prevalence of opioids over time by sex 70
12.1.5 Other Analysis 78
12.2. Patient-level DUS 78
12.2.1. Participants 78
12.2.2. Descriptive Data 78
Demographic Characteristics 78
Treatment duration 78
12.2.3. Outcome Data 89
12.2.4. Main Results 89
Indication 89
Large-Scale patient characterisation 90
12.2.5 Other Analysis 113

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 113

14 DISCUSSION 113
14.1 Key Results 113
14.2 Limitations of the research methods 114
14.3 Results in context 115
14.4 Generalisability 115
14.5 Other information 116

15 CONCLUSION 116

16 REFERENCES 117

17 ANNEXES 118

Document History

Version	Date	Description
V1.0	18/09/2023	**Final version for EMA review**
V2.0	13/10/2023	**Revised version addressing EMA comments**
V3.0	31/10/2023	**Revised version for archiving**

Study Title	DARWIN EU® - Drug utilization study of prescription opioids.
Study Report Version identifier	V3.0
Dates Study Report updates	31/10/2023
EU PAS register number	EUPAS 105641
Active substance	Opioids (substances listed in ATC classes N01AH, N02A and R05DA) namely: Acetyldihydrocodeine, Alfentanil, Anileridine, Bezitramide, Butorphanol, Buprenorphine, Codeine, Dezocine, Dimemorfan, Dextromethorphan, Dextromoramide, Dextropropoxyphene, Dihydrocodeine, Ethylmorphine, Fentanyl, Hydrocodone, Hydromorphone, Ketobemidone, Meptazinol, Meperidine (Pethidine), Methadone, Morphine, Nicomorphine, Normethadone, Nalbuphine, Noscapine, Oliceridine, Opium, Oxycodone, Oxymorphone, Papaveretum, Pentazocine, Phenazocine, Phenoperidine, Pholcodine, Pirinitramide, Propoxyphene, Remifentanil, Sufentanil, Tapentadol, Thebacon, Tilidine, Tramadol; Naloxone; Buprenorphine/Naloxone, Oxycodone/Naloxone, Pentazocine/Naloxone, Tilidine/Naloxone
Medicinal product	NA
Research question and objectives	This study aims to assess the incidence and prevalence of prescription opioids for the period 2012-2022, stratified by age, sex, calendar year and country, as well as characterisation of new users, indications and treatment duration stratified by calendar year and country
Country(-ies) of study	Estonia, Germany, Belgium, The Netherlands, France, Spain
Author(s)	Dr. Annika Jödicke Dr. Junqing (Frank) Xie

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigators	Junqing (Frank) Xie Annika Jödicke	University of Oxford
Data Scientists	Martí Català Sabaté Yuchen Guo Mike Du	University of Oxford
Epidemiologists	Daniel Prieto Alhambra	University of Oxford Erasmus MC
Statistician	NA	
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	James Brash	IQVIA
	Talita Duarte Salles	IDIAP JGol
	Raivo Kolde	University of Tartu
	Mees Mosseveld	Erasmus MC
	Romain Griffier	CHU Bordeaux

*Data partners' role is only to execute code at their data source, and they don't have an investigator role.

2. DATA SOURCES

This study was conducted using routinely collected data from 6 databases in 6 European. All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
4. Estonian Biobank (EBB), Estonia
5. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Detailed information on data source is described below.

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
The Netherlands	IPCI	Primary care	EHR	1.39 million	1/12/2022
France	CHUBX	Secondary care (in and outpatients)	EHR	2.13 million	1/3/2023
Spain	SIDIAP	Primary care	EHR	5.8 million	1/6/2022
Belgium	IQVIA LPD Belgium	outpatient specialist care	EHR	0.4 million	1/1/2022
Germany	IQVIA DA Germany	outpatient specialist care	EHR	8.5 million	1/9/2022
Estonia	EBB	Biobank	Claims data	0.2 million	31/3/2021

EHR = Electronic Heath record. Exposure is based on prescription data.

3. ABSTRACT

Title

DARWIN EU® Drug Utilisation Study of prescription opioids.

Rationale and Background

Prescription opioids, while effective for managing severe pain, have led to a public health crisis due to misuse, addiction, and overdose, particularly in the US. Recently, concerns have been growing in Europe due to increasing opioid use and related mortality. Factors such as chronic pain, mental health disorders, and advanced age can exacerbate misuse and the development of dependence. Given the potential for global use of opioids, enhanced surveillance and in-depth research into opioid utilization patterns are imperative. Drug utilization studies using a Common Data Model (CDM) can generate data from different data sources to supplement European opioid monitoring systems, providing more granular information to inform evidence-based decisions.

Research question and Objectives

The objectives of this study were

1. To investigate the annual incidence and annual period prevalence of use of opioids (overall, and by active drug substance, strength (weak/potent opioids) and route (oral, transdermal or parenteral)), stratified by calendar year, age, sex and country/database during the study period 2012-2022.
2. To determine the duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing, overall and stratified by calendar year and country/database.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilization study on opioids)
- New drug user cohort study (Objective 2, Patient-level drug utilization analyses regarding summary characterisation, indication of opioid use, and duration)

Population

Population-level utilization of opioids: All people registered in the respective databases on 1st of January of each year in the period 2012-2022 (or the latest available, whatever came first), with at least 1 year of prior data availability, participated in the population-level analysis (period prevalence calculation in Objective 1). Therefore, children aged <1 year were excluded.

New users of opioids in the period between 1/1/2012 and 31/12/2022 (or latest date available, whatever came first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12 months [or 6 months for sensitivity analyses], were included for incidence rate calculations in Objective 1.

Patient-level drug utilization: New users of opioids in the period between 1/1/2012 and 31/12/2022 (or latest date available, whatever came first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12months [6 months], were included for patient-level drug utilisation analyses.

Variables

Drug of interest: Opioids (substances listed in ATC classes N01AH, N02A and R05DA); naloxone; and fixed naloxone-opioid combinations.

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
4. Estonian Biobank (EBB), Estonia
5. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

No sample size has been calculated as this is a descriptive study.

Data analyses

Population-level opioid use: Annual incidence rate per 100,000 person years and annual period prevalence were estimated in the general population across all databases.

Patient-level opioid use: Large-scale patient-level characterization was conducted at and before index date, including patient demographics, and history of comorbidities and comedication. Frequency of potential indications at index date, and in the immediate time before was calculated. Treatment duration was estimated for the first treatment era and the minimum, p25, median, p75, and maximum were provided.

For all analyses a minimum cell count of 5 was used when reporting results, with any smaller counts reported as <5.

Results

Population level DUS

In general, over the past decade, the incidence of opioid use has either slightly decreased or remained stable across most of the databases, with the exception of the EBB. Prescriptions of new opioids decreased during the COVID-19 pandemic in 2020 and 2021. This decrease was mirrored by an increase in 2022, although longer follow-up will be needed to ascertain the trend in opioid prescriptions after the pandemic.

Weaker opioids such as codeine and tramadol accounted for the majority of new opioid prescriptions, followed by more potent substances such as morphine and fentanyl. Oral administration was the primary route of administration. Furthermore, older individuals had a substantially higher rate of opioid use compared to younger adults, and a consistently higher rate of opioid prescriptions was seen in women compared to men in the outpatient databases.

The trends and patterns observed in opioid prevalent use closely mirrored those of incident use. A distinction, however, is the time lag between changes in incidence and their manifestation in prevalence. Consequently, opioid use prevalence remained more stable compared to incidence estimates.

Patient-level DUS

A total of 138,171 new opioid users from CHUBX hospital [France]; 53,344 new opioid users from EBB biobank [Estonia]; and new opioid users from primary and secondary outpatient care including 440,849 from IPCI [The Netherlands]; 1,248,388 from IQVIA DA Germany [Germany]; 207,754 from IQVIA LPD

Belgium [Belgium] and 2,023,867 new opioid users from SIDIAP [Catalonia, Spain] were included between 2012 and 2022.

Median age of new opioid users ranged between 50 and 57 across all databases, with users of potent opioids tending to be older compared to users of weak opioids. More women than men were prescribed opioids in primary care and EBB, whereas no difference was seen in hospital inpatient data from CHUBX.

Treatment duration varied greatly by setting: Median duration of any new opioid prescription was 2 days in the CHUBX hospital, and ranged between 9 and 20 days for primary care and outpatient specialist care settings. Treatment duration varied greatly for different opioid substances, typically displaying a week, 2 weeks or a month of treatment. In SIDIAP, average treatment durations for potent opioids were substantially longer than for weak opioids.

The most commonly recorded conditions to define potential indications comprised respiratory conditions (e.g. cough, acute upper respiratory infections) and pain-related conditions (e.g. back pain, traumatic injury) for both primary care and outpatient specialist care databases. Hospital diagnoses included “Complications of surgical procedures” and “pain”. Cough-related conditions were more frequently recorded prior to treatment initiation with codeine (e.g. 20% in IQVIA DA Germany), whereas pain-related conditions were frequently recorded before tramadol and the potent opioids morphine and oxycodone (e.g. 6.5% and 9.4% “chronic pain”, in IQVIA Germany respectively).

Conclusion

In the latest decade, the rate of new opioid prescriptions has remained relatively stable or even declined slightly, with the exception of Estonia. Prescriptions of new opioids decreased during the COVID-19 pandemic in 2020 and 2021. This decrease was mirrored by an increase in 2022, although longer follow-up will be needed to ascertain the trend in opioid prescriptions after the pandemic.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EBB	Estonian Biobank
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
ID	Index date
IPCI	Integrated Primary Care Information Project
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
NA				

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Final Study Protocol	27/06/2023	27/06/2023
Creation of Analytical code	07/2023	07/2023
Execution of Analytical Code on the data	08/2023	08/2023
Interim Study Report (if applicable)	NA	NA
Final Study Report	18/09/2023	18/09/2023
Revised study report	13/10/2023	13/10/2023
Draft Manuscript (if agreed on)		
Final Manuscript (if agreed on)		

7. RATIONALE AND BACKGROUND

Prescription opioids are important medications recommended to treat acute and chronic moderate to severe pain but can lead to complex and interconnecting health and social issues related to misuse, abuse, dependence, addiction, overdose, and drug diversion. Abuse of prescription opioids, in particular, is an ongoing public health crisis in the US. By 2016 of all patients with a fatal overdose, 25% were due to prescription opioids[1]. This alarming trend has manifested in the US through distinct waves of opioid-related challenges over several decades, with the most recent wave starting around 2013. Within this latest wave, synthetic opioids, particularly the illicit production of fentanyl, have emerged as a primary focal point of concern and investigation in the US[2].

While no similar concern was observed in Europe in a review from 2015[3], recent studies suggest an increasing trend in the use of prescription opioids[4] and opioid-use related mortality. Surveillance of prescribing trends could potentially identify emerging issues.[3]

Clinical use of prescription opioids may also lead to some of the concerns above. Patients with chronic pain may develop dependence and addiction due to prolonged prescription opioid exposure leading to drug tolerance and a need for increased dose or opioid strength[5]. Similarly, patients with mental health disorders are at increased risk of initiation and prolonged opioid treatments. Moreover, older adults are more susceptible to the adverse effects of opioids, yet they typically have more comorbidities leading to painful conditions[6 7]. There is an need to describe the current utilization patterns of opioids among the general population..

A drug utilization study of prescription opioids based on a Common Data Model (CDM) will provide information on the trends of prescription opioids and the characteristics of prescription opioid users in Europe. By supplementing the conventional European monitoring systems for aggregated opioid consumption, this study will offer detailed data on these drugs including their strength and route of administration, thereby enabling well-informed, evidence-based decision-making.

8. RESEARCH QUESTION AND OBJECTIVES

Table 8.1: Primary research question and objective

Objectives:	To investigate the annual incidence and annual period prevalence of use of opioids (overall, and by active drug substance, strength (weak/potent opioids) and route (oral, transdermal or parenteral)), stratified by calendar year, age, sex and country/database during the study period 2012-2022.
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All people registered in the respective databases on 1st of January of each year in the period 2012-2022 (or the latest available, whatever came first), with at least 1 year of prior data availability, participated in the population-level analysis (period prevalence estimation). Therefore, children aged <1year were excluded. New users of opioids in the period between 1/1/2012 and 31/12/2022 (or latest date available, whatever came first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12 months [6 months], were included for incidence rate estimations.
Exposure:	Opioids (substances listed in ATC classes N01AH, N02A and R05DA), as well as naloxone, and fixed combinations (i.e. buprenorphine and naloxone, oxycodone and naloxone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on a pre-specified calendar time point, namely the 1st of January for each calendar year between 2012-2022 for the estimation of annual incidence/prevalence rates. End of follow-up was defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (e.g. 31st December 2022), whatever came first.
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: EBB [Estonia], IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CHUBX [France]
Main measure of effect:	Incidence and Prevalence

Table 8.2: Secondary research question and objective

Objectives:	To determine the duration of the first treatment era of opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing, all stratified calendar year and country/database.
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	New users of opioids in the period between 1/1/2012 and 31/12/2022 (or latest date available, whatever came first), with at least 1 year of prior data availability, and no use of the respective opioid in the previous 12 months [6 months], were included for patient-level drug utilisation analyses.
Exposure:	Opioids (substances listed in ATC classes N01AH, N02A and R05DA), as well as naloxone, and fixed combinations (i.e. buprenorphine and naloxone, oxycodone and naloxone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up started on the date of incident opioid prescription (index date). End of follow-up was defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2022), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 6 data sources: EBB [Estonia], IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CHUBX [France]
Main measure of effect:	Large-scale characterisation for new opioid users (1) overall, (2) for the most frequent opioids in each database, (3) by strength, (4) by route. Indications, based on a high-level approach considering the most frequent conditions recorded in the month/week before/at the date of treatment start, that could potentially be indications for opioids (e.g. conditions related to pain or cough) Duration of opioid use (first treatment era) expressed as minimum, p25, median, p75, and maximum days.

9. RESEARCH METHODS

9.1 Study Type and Study Design

Retrospective cohort studies were conducted. The study comprises two consecutive parts:

1. A population-based cohort study was conducted to address objective 1, assessing the prevalence and incidence of the respective opioids of interest.
2. A new drug user cohort was used to address objective 2; to characterize individual-level opioid utilization in terms of summary patient characteristics, indication and duration of use.

9.2 Study Setting and Data Sources

This study was conducted using routinely collected data from 6 databases in 6 EU countries. All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
4. Estonian Biobank (EBB), Estonia
5. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
6. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Detailed information on data sources is described in **Table 9.1**.

Table 9.1. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
The Netherlands	IPCI	Database covers primary care / outpatient specialist care setting where opioid prescriptions are issued.	Primary care	EHR	1.39 million	1/12/2022
France	CHUBX	Database covers hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	2.13 million	1/3/2023
Spain	SIDIAP	Databases covers primary care / outpatient specialist care setting where opioid prescriptions are issued.	Primary care	EHR	5.8 million	1/6/2022
Belgium	IQVIA LPD Belgium		outpatient specialist care	EHR	0.4 million	1/1/2022
Germany	IQVIA DA Germany		outpatient specialist care	EHR	8.5 million	1/9/2022
Estonia	EBB	Database covers primary care setting where opioid prescriptions are issued.	Biobank	Claims data	0.2 million	31/3/2021

LPD = Longitudinal Patient Database, DA = Disease Analyzer, EHR = Electronic Heath record. Exposure is based on prescription data.

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[8] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996[8]. The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval for this study was obtained from the Governance Board[8].

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[9]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Approval for this study was granted by both SIDIAP's Scientific and Ethics Committee.

Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).[10]

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants ("gene donors" >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population. Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor.

Longitudinal Patient Database (LPD) Belgium, Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[11]. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

9.3 Study Period

The study period was from the 1st of January 2012 until the earliest of 31st December 2022 or the latest date of data availability of the respective databases.

9.4 Follow-up

9.4.1 Population-level Utilization of opioids

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants in the denominator population began contributing person time on the respective study start date (1st January 2012). Participants stopped contributing person time at the earliest date of the following: 1) study end date (31st December 2022) or 2) end of available data in each of the data sources (date of last data extraction) or 3) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population is shown in Figure 9.1. In this example, person ID 1 has already sufficient prior history before the study start date and observation period ends after the study end date, so will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

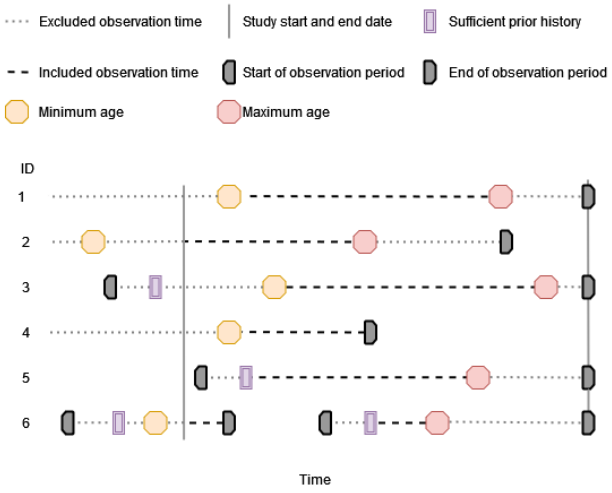


Figure 9.1. Included observation time for the denominator population

9.4.2 Patient-level Utilisation of opioids

Participants were followed up from the day of therapy initiation, i.e. the date of the first prescription of opioids (index date), until the earliest of loss to follow-up, end of data availability, death, or end of continuous exposure.

9.5 Study Population with in and exclusion criteria

9.5.1 Population-level Utilisation of opioids

The study cohort comprised all individuals present in the period 2012-2022 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion.

Additional eligibility criteria were applied for the calculation of incidence rates: New users had a first prescription of opioids in the period between 1/1/2012 and 31/12/2022 (or latest date available, whatever comes first), with at least 1 year of prior data availability, and no use of the respective opioid in the previous 365days [180days]. The operational definition is detailed in Table 9.2.

9.5.2 Patient-level Utilisation of opioids

All new users of opioids, after 365days [180days] of no use of the specific opioid /substance /strength/ route, in the period between 01/01/2012 and 31/12/2022 (or latest date available), with at least 365 days of visibility prior to the date of their first opioid prescription. The operational definition is detailed in Table 9.3.

Table 9.2: Operational Definition of Time 0 (index date) and other primary time anchors

Criterion	Details	Order of application	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2012-2022 (or the latest available)	All individuals present in the period 2012-2022 (or the latest available)	N/A	N/A	Biobank, primary and secondary care	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	Biobank, primary and secondary care	N/A	N/A	All individuals within the selected databases	N/A	N/A
Washout period	New users will be required to have not used opioids/ the specific opioid substance /strength/ route 3650days [180days] before a “new” prescription	After	365 days, [180 days]	Biobank, primary and secondary care	N/A	N/A	All individuals within the selected databases	N/A	N/A

Table 9.3: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristic /validation	Source for algorithm
Observation period in the database during the period 2012-2022 (or the latest available, whatever comes first)	See under inclusion criterion	After	N/A	Biobank, primary and secondary care	N/A	N/A	All individuals within the selected databases	N/A	N/A

9.6 Variables

9.6.1. Exposure/s

For this study, the exposure of interest is use (during study period) of opioids (all substances listed under ATC classes N01AH, N02A and R05DA), naloxone and fixed opioid-naloxone combinations.

Opioids were grouped
(1) Overall
(2) by drug substance (incl. combinations and products for all indications)
(3) by strength (weak/potent opioids) for those opioids where strength is labelled by the WHO
(4) by route (oral, transdermal or parenteral) for overall opioids.

A list of opioids is described in Table 9.4. Details of exposure are described in Table 9.5.

Table 9.4: Exposure of interest

Substance Name	Strength*	No record counts in databases expected based on feasibility	Substance Name	Strength*	No record counts in databases expected based on feasibility
acetyldihydrocodeine			noscapine		
alfentanil			oliceridine		X
anileridine		X	opium		
bezitramide		X	oxycodone	potent	
butorphanol		X	oxymorphone	potent	X
buprenorphine	potent		papaveretum		
codeine	weak		pentazocine		
dezocine		X	phenazocine		
dimemorfan		X	phenoperidine		X
dextromethorphan			pholcodine		
dextromoramide			pirinitramide		
dextropropoxyphene		X	propoxyphene		
dihydrocodeine			remifentanil		
ethylmorphine			sufentanil		
fentanyl	potent		tapentadol	potent	
hydrocodone	weak	X	thebacon		
hydromorphone	potent		tilidine		
ketobemidone			tramadol	weak	
meptazinol					
meperidine (pethidine)			naloxone		
methadone	potent				
morphine	potent		buprenorphine/naloxone		
nicomorphine		X	oxycodone/naloxone		
normethadon		X	pentazocine/naloxone		
nalbuphine			tilidine/naloxone		

*according to the WHO Analgesic Ladder (WHO Analgesic Ladder - StatPearls - NCBI Bookshelf (nih.gov))

Table 9.5: Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Overall opioids, substance, strength, route	Code lists in Appendix 1	[-365 to ID, -180 to ID]	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period	Previous opioid use	N/A	N/A

9.6.2. Outcome/s

N/A

9.6.3. Other covariates, including confounders, effect modifiers and other variables

9.6.3.1 Covariates for stratification in population-level drug utilisation study:

- Calendar year
- Age: 10-year age bands will be used: 1-10, 11-20, 21-20 […] , and >80
- Sex: male, female, missing

9.6.3.2 Covariates for patient-level drug utilisation study:

- Large-scale characterisation of baseline characteristics: the operational definition of the covariates is described in the Table 9.6 below. Index date is the date of the (first) incident prescription during the study period.
- Indication: We used a high-level approach considering the most frequent conditions recorded in the month/week before/at the date of treatment start. As a proxy for "indication", we evaluated the 50 most frequently co-morbidities recorded at the day of a new opioid prescription (window "0"), in week (7days) before start of new opioid treatment (window "7") and in the month (30days) before start of new opioid treatment (window "30"). Out of those, the 10 most frequent conditions that could be proxies for potential indications were selected.

Table 9.6 Exposure details

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Large-scale summary characteristics of new users	Large-scale patient-level characterization with regard to baseline co-variates	Counts	Demographics, co-morbidities and co-medication at index date (ID), and within anytime to 366 days before ID, 365 to-181days before ID, and 180 to 1day before ID	Biobank, primary and secondary care	SNOMED, RxNorm	N/A	Persons with new use during the study period	N/A	N/A
Indication of Use	Top 10 most frequent co-morbidities from large-scale patient characterization	Counts	At index date and as sensitivity analyses in windows around index date (ID): [-7, ID] and [-30, ID]	Biobank, primary and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A

9.7 Sample size

No sample size has been calculated as this is a descriptive study.

9.8 Data transformation

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources or on a simulated set of patients and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results.

The study results of all data sources were checked after which they were made available to the team in the Digital Research Environment and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.2 Complete Catalogue of Standard Analyses which describes the type of analysis in function of the study type.

Table 9.7 Description of Study Types and Type of analysis

STUDY TYPE	TYPE OF ANALYSIS
Population Level DUS	- Population-based incidence rates - Population-based prevalence
Patient Level DUS	- Characterization of patient-level baseline covariates for opioid users - Percentages of indications - Descriptive statistics of treatment duration of opioids

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 (and <20 for IQVIA LPD Belgium) were suppressed.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilization[12]" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence[13]" package for the population-level estimation of drug utilisation.

Drug exposure calculations

This document represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network.

Drug eras were defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 7 days. The time between the two joined eras was considered as exposed by the first era as shown in **Figure 2**, first row. Note: dose is not considered for this study.

Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 1: Gap era joint mode

If two eras start at the same date, the overlapping period was considered exposed by both. We did not consider repetitive exposure.

New user cohorts

New users were selected based on their first prescription of the respective drug of interest after the start of the study. For each patient, at least 365 days of data availability was required prior to that prescription. New users were required to not have been exposed to the drug of interest for at least 365days (180days) prior the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 365 days (180days) of no use, the whole exposure is eliminated.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. We used 10-year age bands for stratification for population-level analyses: 1-10,11-20, 21-20 […] and >80.

Characterisation of patient-level features

Large scale patient characterisation before/on index date (= date of prescription) was provided for different classifications for opioids [as introduced in section 9.6.1 "Exposures"], namely for (1) opioids overall, (2) the most frequent opioids in each database, (3) weak/potent opioids and (4) transdermal/oral/parenteral opioids, stratified for database/country. Co-variates were extracted for the following time intervals: Concepts in the "condition" and "drug" domain will be assessed for anytime to -366 days [conditions only], -365days to -181days, -180 to -1 day before index date, and at index date.

Indication

Indications were assessed based on a high-level approach considering the most frequent conditions recorded at the date of treatment start/ in the week/month before treatment start.

9.9.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Population-level drug utilisation study

Prevalence and incidence calculations were conducted separately for (1) opioids overall, (2) by drug substance (incl. combinations and products for all indications), (3) by strength (weak/potent opioids) for those opioids where strength is labelled by the WHO and (4) by route (oral, transdermal or parenteral) for overall opioids.

Prevalence calculations

Prevalence was calculated as annual period prevalence which summarises the total number of individuals who use the drug of interest during a given year divided by the population at risk of getting exposed during that year. Therefore, period prevalence gives the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals will be calculated.

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants are opioid users giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants being an opioid user, giving a prevalence of 20%.

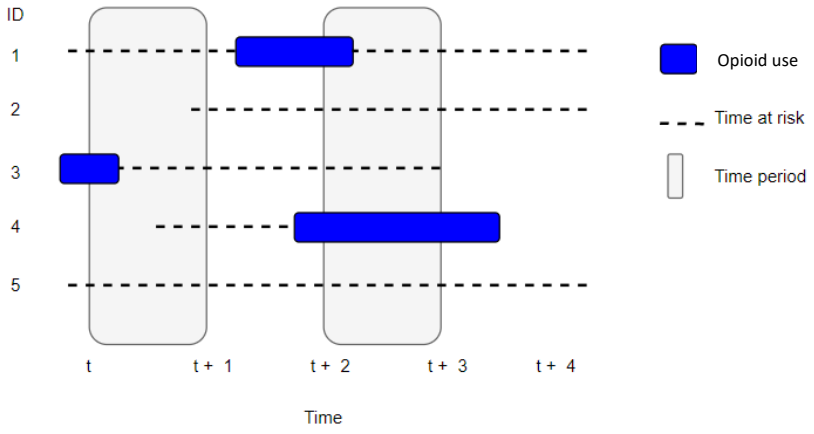


Figure 2: Period prevalence example

Incidence calculations

Annual incidence rates of the opioid of interest were calculated as the of number of **new users** after 356days (180days as sensitivity analysis) of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) were excluded. Those study participants who enter the denominator population then contributed time at risk up to their first prescription during the study period. Or if they do not have a drug exposure, they contributed time at risk up as described above in section 9.3 (study period and end of follow-up). Incidence rates were provided with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of opioid use is shown below in **Figure 4**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of opioid. Patient ID 2 and 5 are not seen to use opioid and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time at risk starting at the day when the washout period of a previous exposure, before study start, has ended before the next exposure of opioid is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of opioid count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.

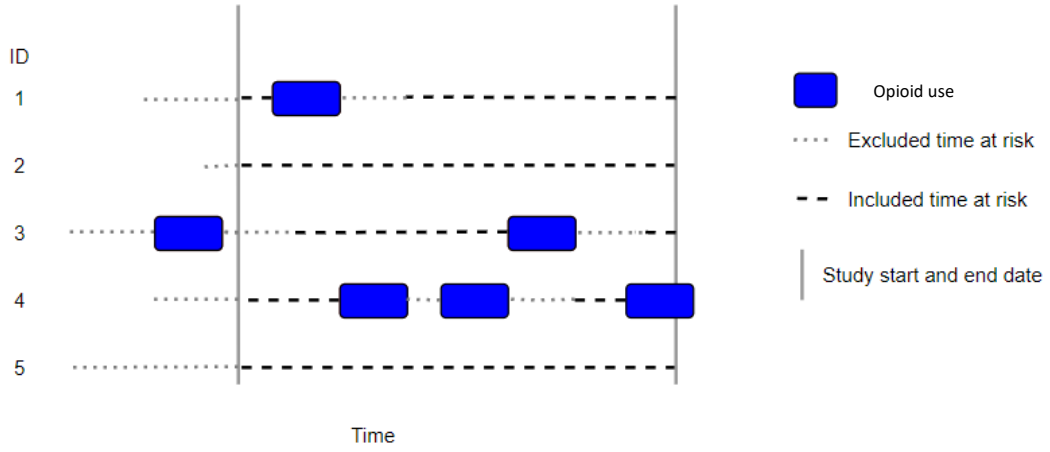


Figure 3: Incidence example

Patient-level drug utilisation study

New drug user patient-level characteristics on/before index date

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows will be provided.

Indication

Indications will be assessed based on a high-level approach considering the 10 most frequent conditions recorded at the date of treatment start/ in the week/month before treatment start. The number of persons (N, %) with a record of the respective indication will be provided.

Treatment duration

Treatment duration will be calculated as the duration of the first treatment era of the opioid of interest during the study period. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided

9.9.5 Methods to control for potential sources of bias

NA

9.9.6 Methods to deal with missing data

For the drug utilisation studies we assumed that the absence of a prescription record meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that that condition was not presented for the individual.

9.9.7 Description of sensitivity analyses

Table 9.8 describes the sensitivity analyses.

Table 1.8 Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Washout window to define new/incident user	Length of washout window	Washout window of 1 year might be too long as opioids can be used for acute conditions	Number of new users might increase with shorter washout period of 180 days	Washout period of 180days might be too short
Window to assess indication of use	Indication of use will be explored at index date (ID), and in a period of [-30 to ID] days of the index date and in a period from [-7 to ID] days before index date	Indication of use might not always be recorded on the date of prescription of the opioid of interest	Proportion of patients with an indication of use might increase.	Potential misclassification of indication of use if the disease code registered in the week/month before has nothing to do with prescription of the opioid of interest

9.9.8 Evidence synthesis

Results from analyses described are presented separately for each database and no meta-analysis of results was conducted.

9.10 Deviations from the protocol

Large-scale characterisation: Large-scale characterisation has been conducted for all substances, not only for the “top 10” most frequent opioids. Results are available in an interactive web application.

10. DATA MANAGEMENT

10.1. Data management

All databases have previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

This analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for this study report.

10.2. Data storage and protection

For this study, participants from various EU member states and from the UK processed personal data from individuals which was collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results. All and any results with n<5 participants were suppressed using cell suppression to minimise risk of reidentification.

The output files were stored in the DARWIN EU Data transfer zone. These output files did not contain any data that allow identification of subjects included in the study. The DTZ implemented further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with

expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion was used based on the CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). A pharmacist reviewed the codes of the opioids of interest. This software allowed the user to define a search strategy and using this then queried the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, DrugExposureDiagnostics[14] was run to assess the use of different codes across the databases contributing to the study.

The study code was based on two R packages developed for DARWIN EU to (1) estimate Incidence and Prevalence[13] and (2) characterize drug utilization[12] using the OMOP common data model.

12. RESULTS

All results are available in an interactive web-application ("shiny app") at https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access

12.1 Population-level DUS

The main results from population-level opioid and naloxone utilisation are presented below. Additional analyses including stratifications for calendar year, or sensitivity analyses using a shorter washout period of 180days to define "new users" are presented in the "shiny app".

12.1.1. Participants

Table 12.1.1 describes the number of people included in each database for each calendar year during the study period (2012 to 2022). The average annual cohort size amounted to 499,401 in CHUBX, 207,858 in EBB, 1,126,241 in IPCI, 7,786,831 in IQVIA DA Germany, 401,934 in IQVIA LPD Belgium and 5,866,879 in SIDIAP.

Table 12.1.1 Number of participants in each source population

	Database					
Year	**CHUBX**	**EBB**	**IPCI**	**IQVIA DA Germany**	**IQVIA LPD Belgium**	**SIDIAP**
2012	497250	209457	832447	6288553		5971079
2013	521128	209147	855669	6857308		5877660
2014	540221	208819	843181	7365979		5862354
2015	551943	208477	977125	7781577	371720	5815508
2016	556300	208136	1154419	8101992	398950	5810545
2017	552294	207761	1205130	8577400	412832	5817815
2018	539365	207420	1224679	8806240	415709	5836019
2019	514972	207016	1250665	8679416	418743	5863956
2020	474148	206489	1320435	8522922	420387	5914749
2021	412381	205860	1366065	7998682	412745	5899112
2022	333415	209457	1358843	6675076	364387	5971079
Average	499401	207858	1126241	7786831	401934	5866879

12.1.2. Descriptive Data

Descriptive data on new opioid users is provided in the patient level analyses section (12.2.2).

12.1.3. Outcome Data

Outcome data is provided in the "Main Results" section below (12.1.4).

12.1.4. Main Results

Incidence rates of opioids over time

In general, over the past decade, the incidence of opioid use has either slightly decreased or remained stable across most of the databases, with the exception of the Estonian Biobank (EBB). Prescriptions of new opioids decreased during the COVID-19 pandemic in 2020 and 2021. This decrease was mirrored by an increase in 2022, although longer follow-up will be needed to ascertain the trend in opioids prescriptions after the pandemic.

Weaker opioids such as codeine and tramadol accounted for the majority of new opioid prescriptions, followed by more potent substances such as morphine and fentanyl. Oral administration was the primary route of administration. Furthermore, older individuals had a substantially higher rate of opioid use compared to younger adults, and a consistently higher rate of opioid prescriptions was seen in women compared to men in the outpatient databases.

Figures 12.1.4.1 to 12.1.4.7 illustrate incidence rates for opioids including stratifications. As incidence rates varied greatly between individual substances, Figures 12.4.4 – 12.4.6 combine different substances with similar incidence rates. All details, including the number of events, population and person-years for each calendar year, and database can be found in the shiny app (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

Figure 12.1.4.1 - Incidence rates of any new opioid treatments between 2012 and 2022

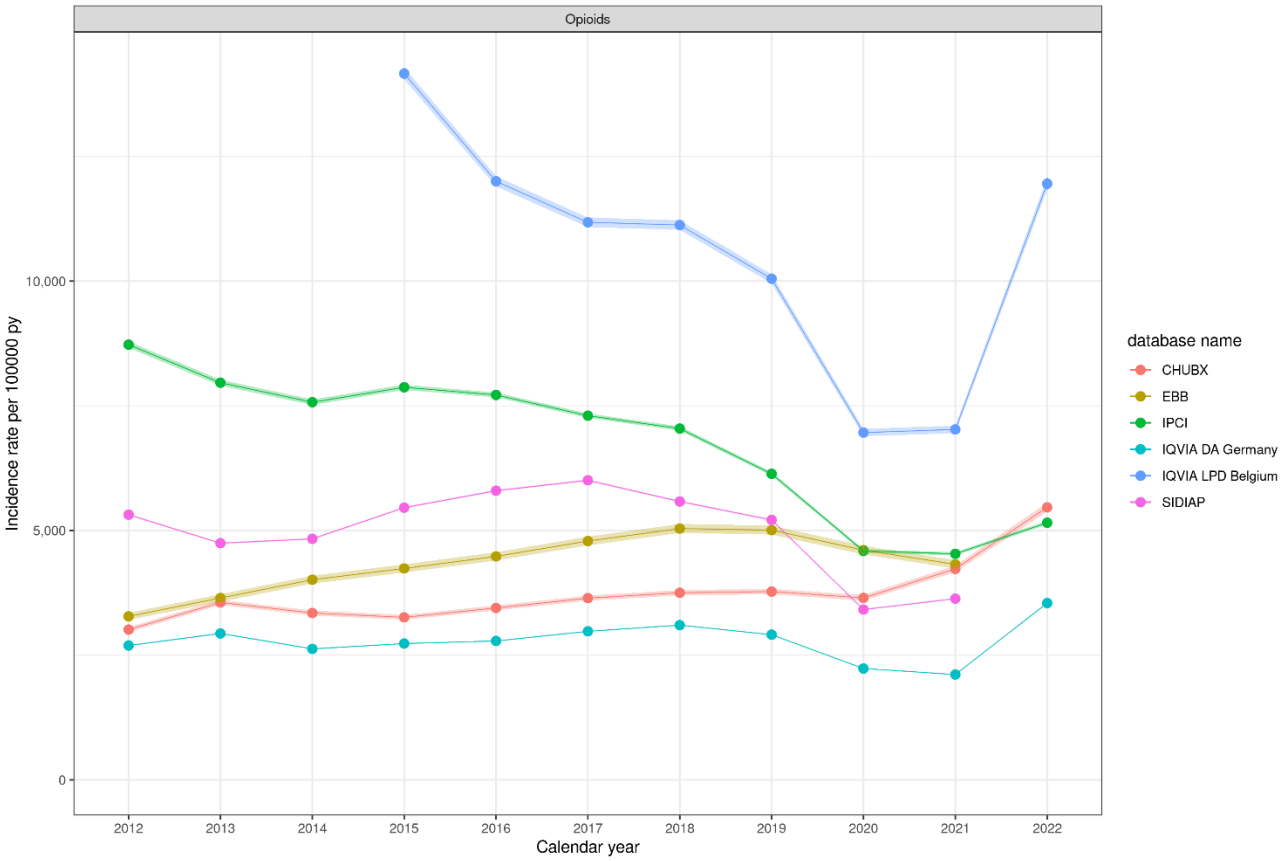


Figure 12.1.4.1 shows the incidence rate (IR) of new opioid treatments between 2012 to 2022.
CHUBX [France]: The IRs in general fluctuated throughout the years, with an increase from 2020 to 2022 when it reached an IR of 5,464 per 100,000 person-years.
In EBB [Estonia]: There was a steady increase in IR until 2018, reaching an IR of 5,039 per 100,000 person-years. From 2019, the IR decreased again to 4,321/100,000 person-years in 2021.
IPCI [Netherlands]: The IR showed a gradual decline from 8,725/100,000 person-years in 2012 to 4,532/100,000 person-years in 2021.
In SIDIAP [Spain], the IR increased slightly over the years from 2013 until a peak in 2017 at 6,006/100,000 person-years, followed by a declining trend reaching 3,415/100,000 person-years in 2020, and a slight increase in the following year.
IQVIA DA Germany [Germany], the IR was fairly stable over time until 2019. In 2020 and 2021 the IR decreased, followed by an increase again in 2022 up to 3,544/100,000 person-years. The incidence of overall opioid use was highest in IQVIA LBD Belgium [Belgium] starting with an incidence rate of 14,160/100,000 person-years in 2015, followed by a decline to an IR of 6,963/100,000 person-years in 2020 and an increase to 11,952/100,000 person-years in 2022.

In summary, over the course of 10 years, the incidence of new opioid use was broadly stable up until 2018. During the pandemic period, a decline in opioid use is seen followed by an increase in 2022.

Figure 12.1.4.2 - Incidence rates of oral, transdermal, and parenteral opioids between 2012 and 2022

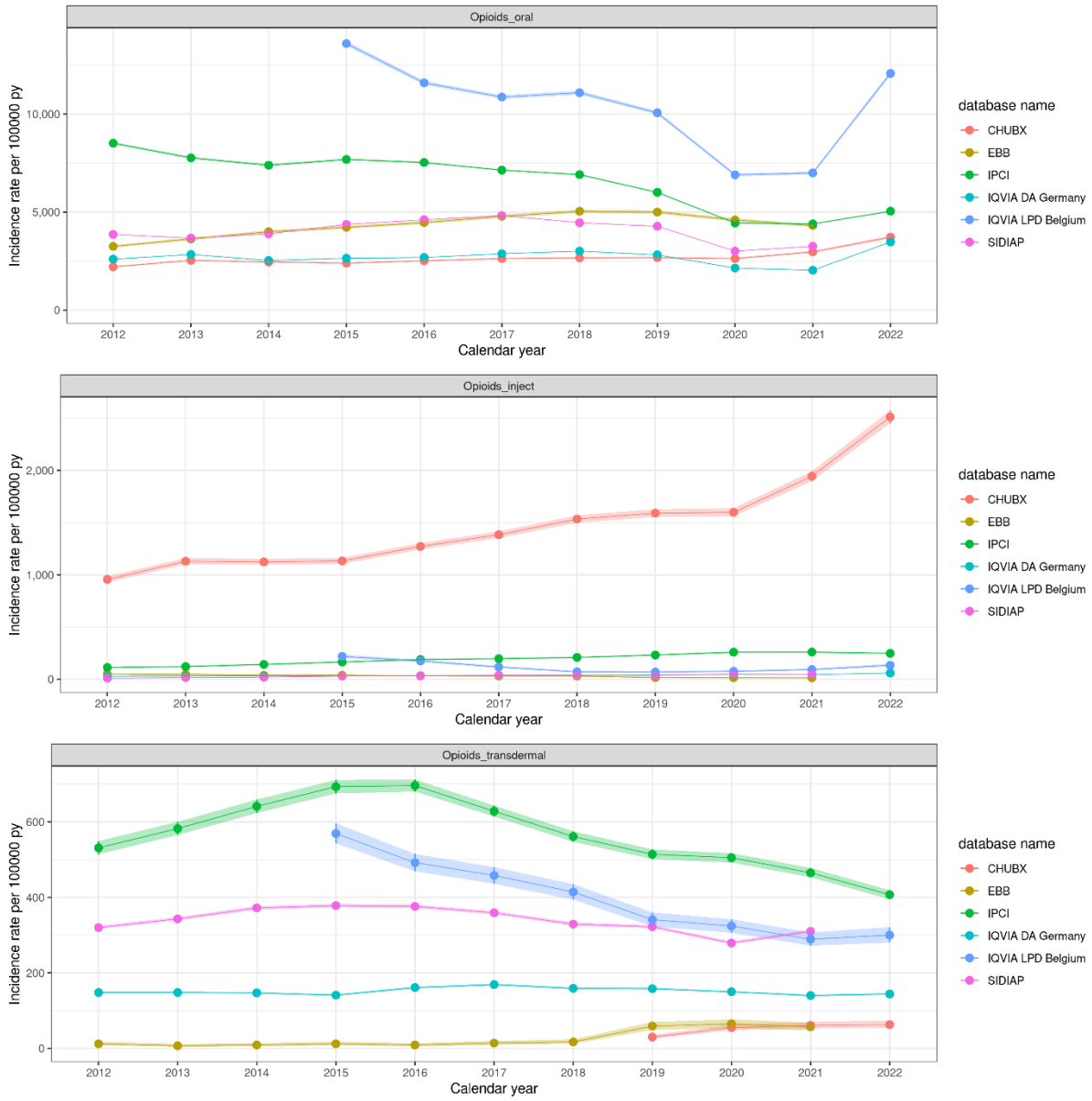
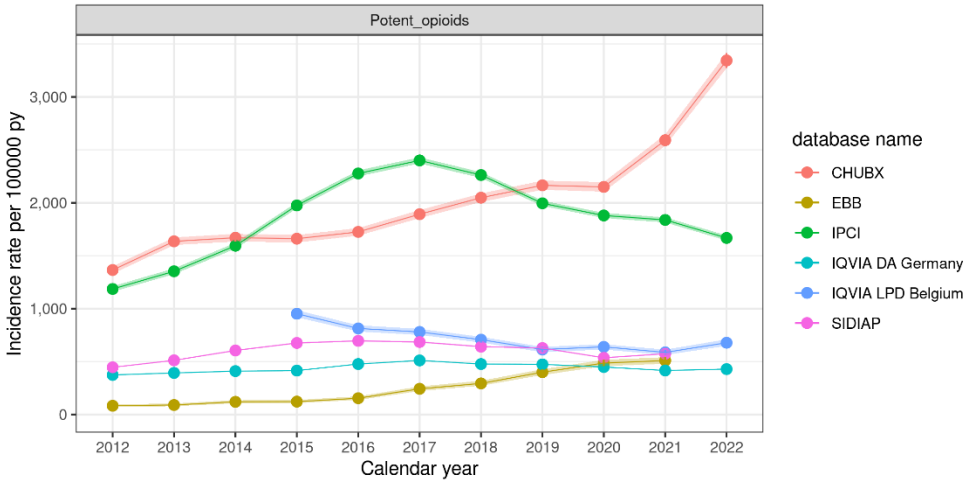


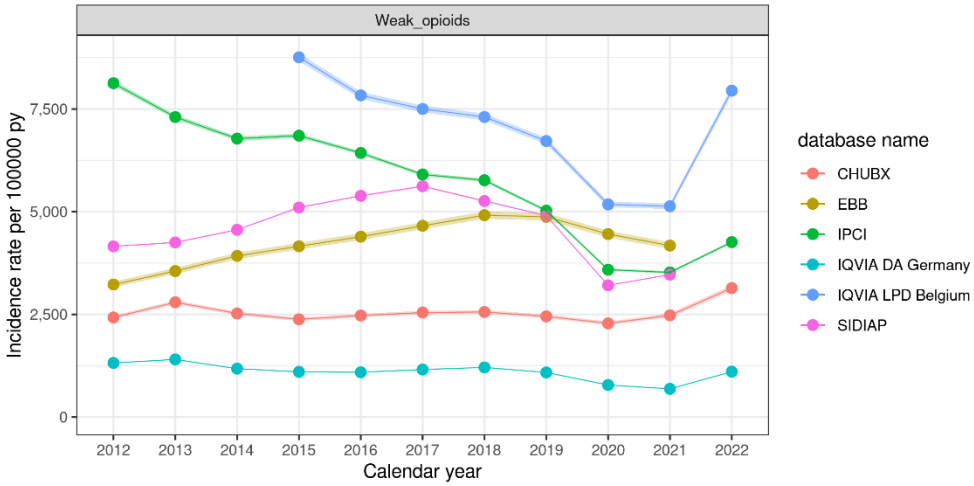
Figure 12.1.4.2 shows the IR of opioids, grouped by different administration routes. In general, oral opioids had the highest incidence, ranging between 2668/100,000pys in CHUBX and 11,091/100,000pys for IQVIA LPD Belgium in 2018, and driving the overall trend of opioid usage.

Both transdermal and parenteral opioids showed lower and relatively stable usage over the years in primary care and secondary outpatient care. While parenteral opioids might be less used in outpatient care, results from CHUBX inpatient data show that the use of parenteral opioids gradually increased, particularly between 2020 and 2022.

Figure 12.1.4.3- Incidence rates of weak and potent opioids between 2012 and 2022



*Potent opioids comprise the following substances: Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone, Oxymorphone, Tapentadol.



*Weak opioids comprise the following substances: Codeine, Hydrocodone, Tramadol

Figure 12.1.4.3 shows the IR of opioids based on their potency. Overall, weak opioids were initiated more frequently compared to potent opioids, driving the overall trend for new opioid treatments.

The incidence of potent opioid use was notably higher in CHUBX and IPCI compared to other databases, with a particular increase in use from 2020 onwards in CHUBX.

Figure 12.1.4.4- Incidence rates of *most* frequent opioids (substances) between 2012 and 2022

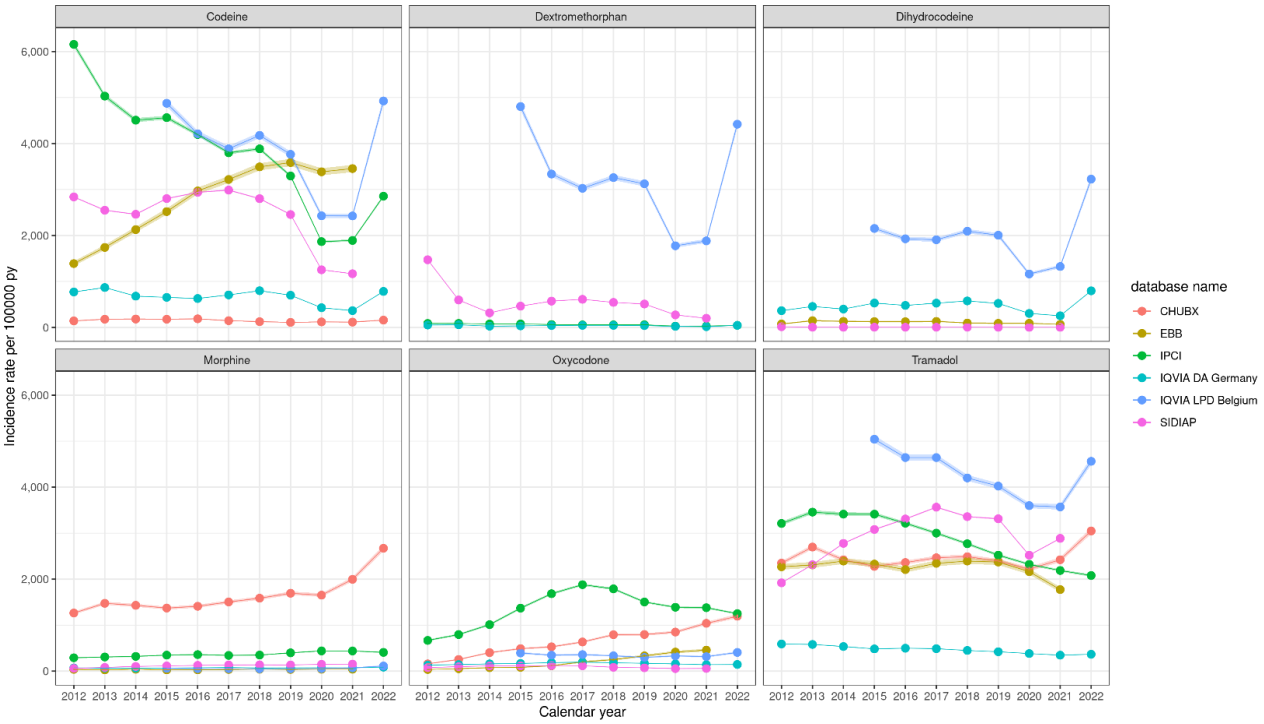


Figure 12.1.4.4 shows the incidence rates of the most frequently prescribed opioid substances. Codeine and tramadol were generally the most frequently initiated opioids. IR of codeine substantially decreased in IPCI and LPD Belgium before 2019, whereas an increase was seen for EBB before the COVID-19 pandemic. Lower incidence rates during the pandemic in 2020/2021 were seen for the outpatient primary and secondary care databases, but not for CHUBX and EBB. Morphine was most commonly used in hospital (CHUBX). Similar to codeine, IR for tramadol decreased over time in IPCI, LPD Belgium. However, new prescriptions for tramadol increased from 2012-2017 in SIDIAP, and decreased again up until 2020. Conversely, morphine and oxycodone remained consistent in most databases, except for an increase in CHUBX.

Figure 12.1.4.5- Incidence rates of less frequently prescribed opioid substances between 2012 and 2022



Figure 12.1.4.5 shows the incidence rates for less frequently used opioid substances. Among those, fentanyl was most frequently used across all databases and incidence remained relatively stable over time during the study period. Noscapine and tilidine were initiated predominantly and with increasing frequency in IQVIA DA Germany, with a particularly sharp increase from 2021 to 2022.

Figure 12.1.4.6- Incidence rates of least frequently prescribed opioid substances between 2012 and 2022

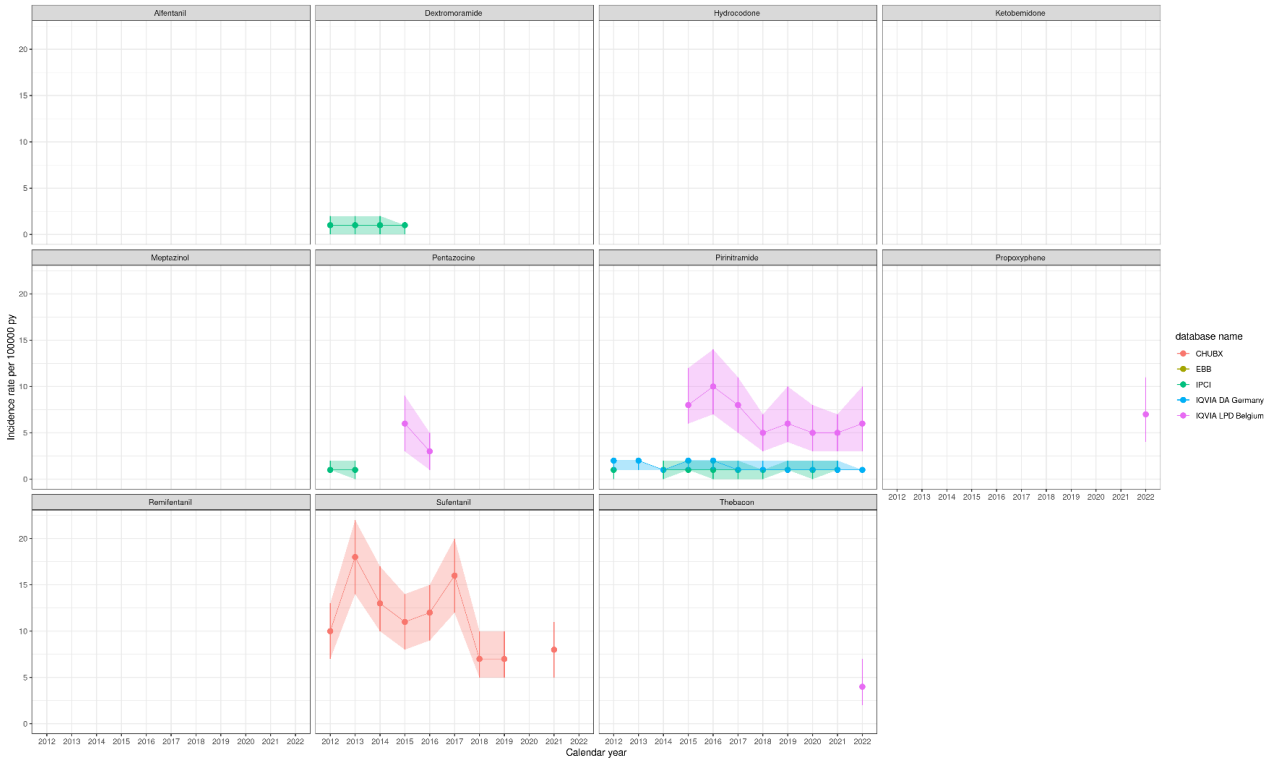


Figure 12.1.4.6 shows the incidence rates of the least frequently prescribed opioid substances. The majority of those opioids were not commonly prescribed, with some only used in specific settings (i.e. sufentanil in hospital CHUBX). No results are shown if either no exposure was captured or we were unable to report as counts were <5.

Figure 12.1.4.7- Incidence rates of naloxone use between 2012 and 2022

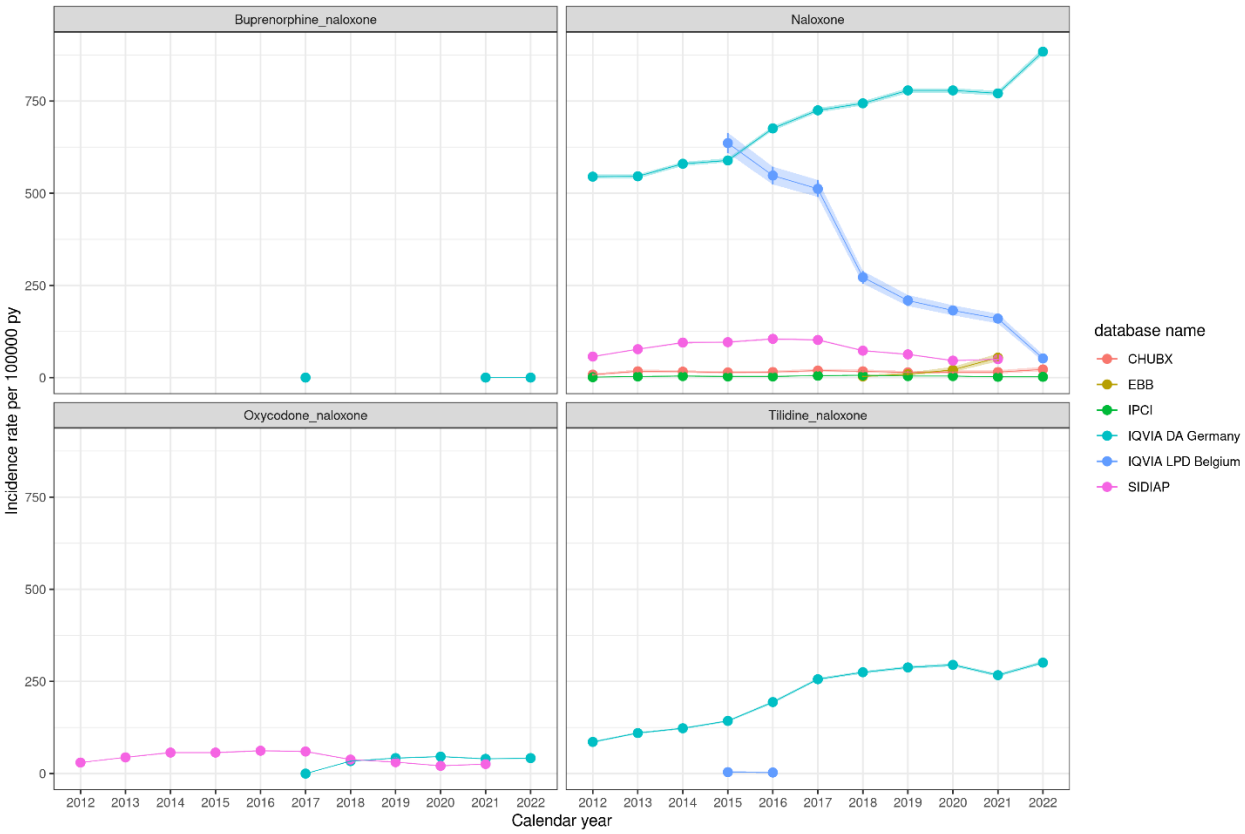


Figure 12.1.4.7 shows the incidence rates of naloxone use (substance level) and fixed combinations. An increasing incidence in naloxone was observed in IQVIA DA Germany, while there was a decline in IQVIA LBD Belgium. In other databases, naloxone use remained consistently lower and incidence appeared to fall in SIDIAP from 2017 and slightly rise in recent years in EBB.

Incidence rates of opioids over time by age group

Incidence rates for opioids gradually increased with increasing age, with substantially higher incidences of opioid use seen in older age groups across all datasets.

Figure 12.1.4.8 shows the incidence of overall opioid use stratified by age groups from 2012 to 2022. Incidence rates were gradually increasing with increasing age, with substantially higher incidences of opioid use seen in older age groups across all datasets. Notably, the IPCI and SIDIAP datasets had the largest difference in the incidence rates between the oldest and youngest age groups, while the IQVIA DA Germany dataset showed smaller differences between these age groups. These trends were consistently observed in the breakdown of data on opioid use categorized by administration method: oral (Figure 12.1.4.9), transdermal (Figure 12.1.4.10), and parenteral (Figure 12.1.4.11), as well as by potency: weak (Figure 12.1.4.12) and potent (Figure 12.1.4.13).

Opioid prescribing was also observed in children aged 1 to 10 and was largely driven by oral opioid prescribing. In general children aged 1 to 10 had the lowest incidence of opioid prescribing apart from in IQVIA Germany were children aged 1 to 10 had the highest incidence. This was driven by prescriptions of noscapine for the treatment of cough in that age group.

In a similar way, Figure 12.1.4.14 shows the rate of naloxone use by age from 2012 to 2022. This data also indicates a notable variation in use across different age groups, particularly in the IQVIA DA Germany.

More detailed data can be found in the shiny web-application (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

Figure 12.1.4.8 - Incidence rates of overall opioids between 2012 and 2022 stratified by age group.

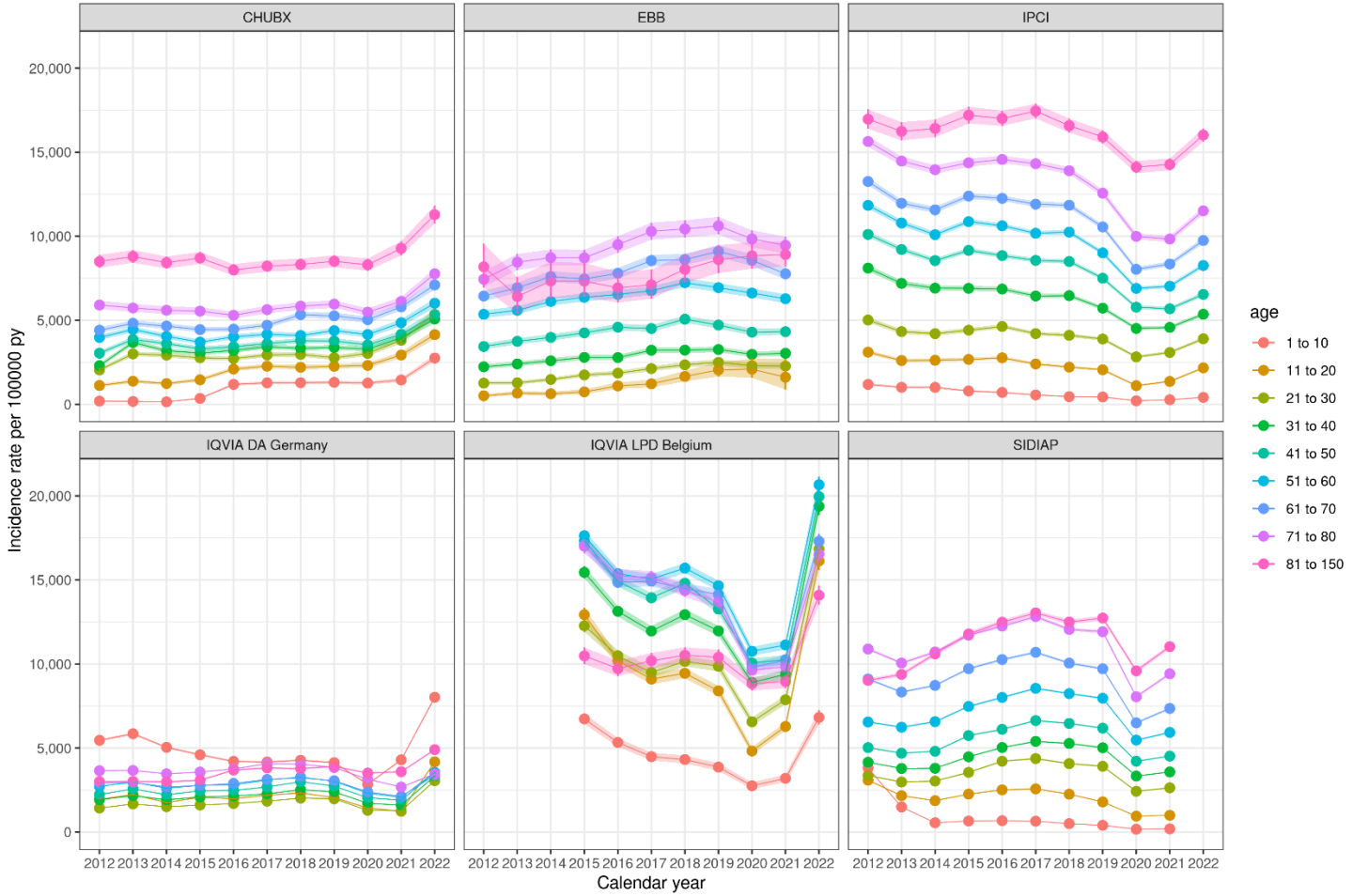


Figure 12.1.4.9 - Incidence rates of oral opioids use between 2012 and 2022 stratified by age group.

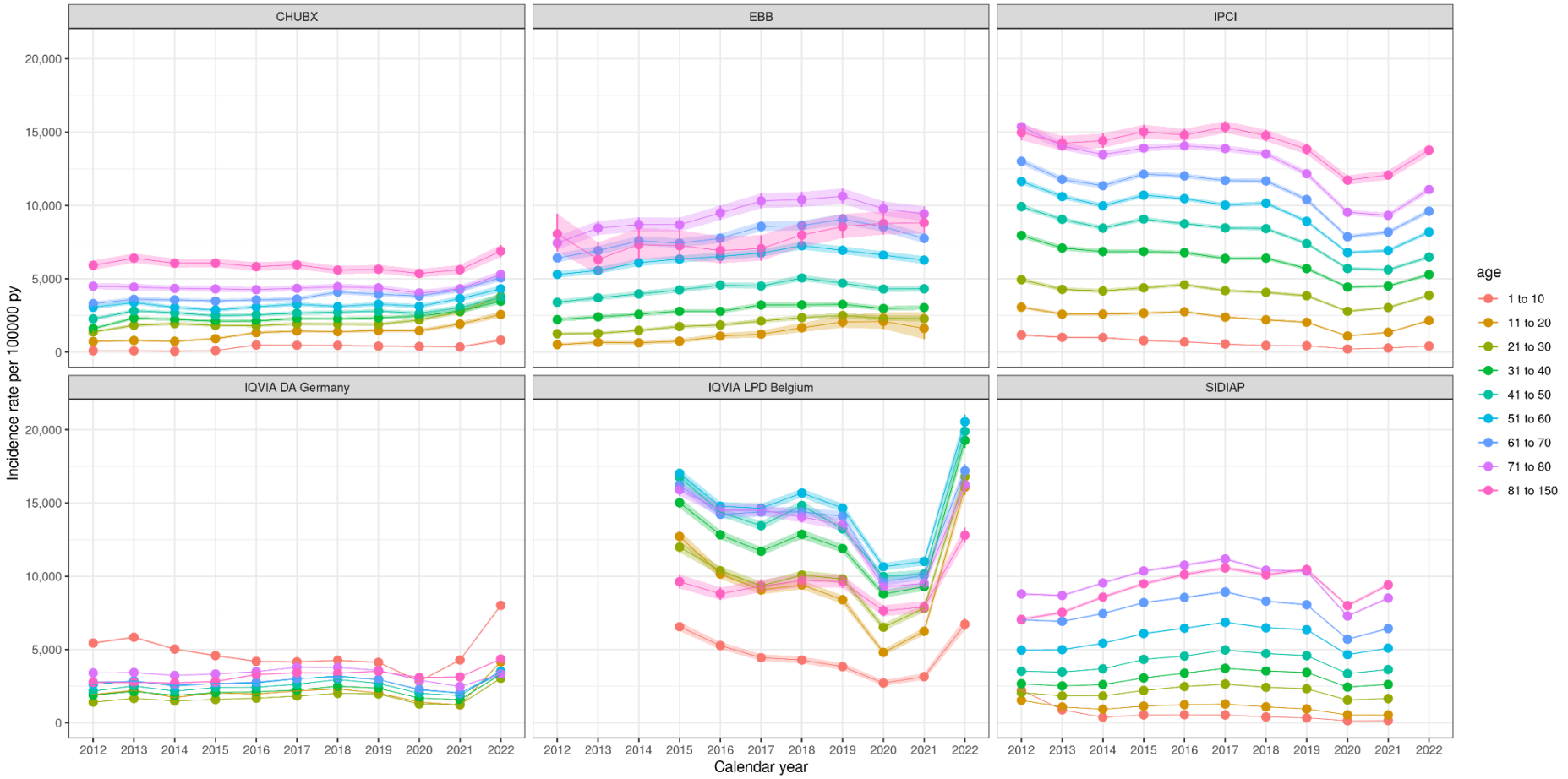


Figure 12.1.4.10 - Incidence rates of transdermal opioids use between 2012 and 2022 stratified by age group.

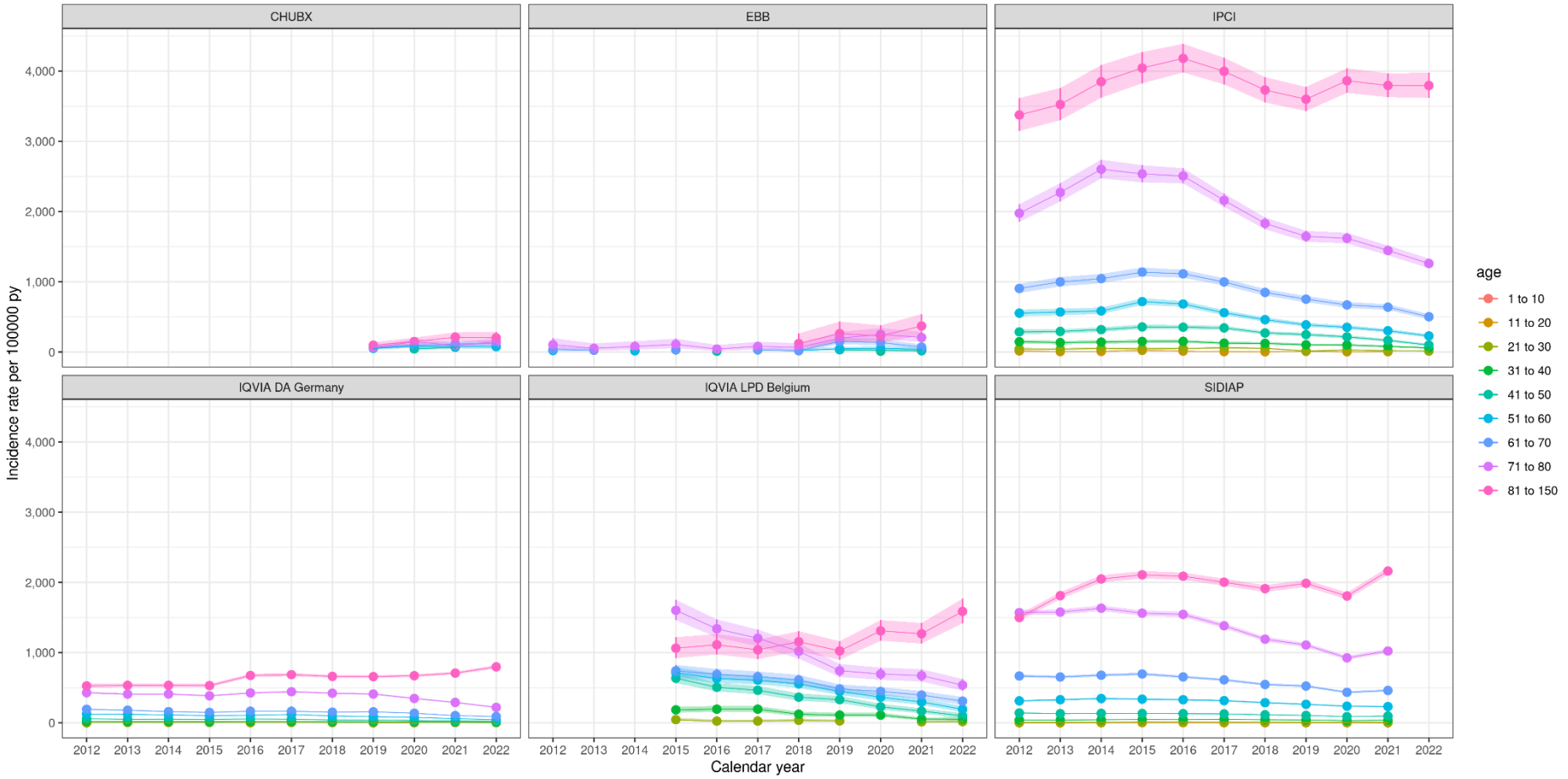


Figure 12.1.4.11 - Incidence rates of parenteral opioids use between 2012 and 2022 stratified by age group.

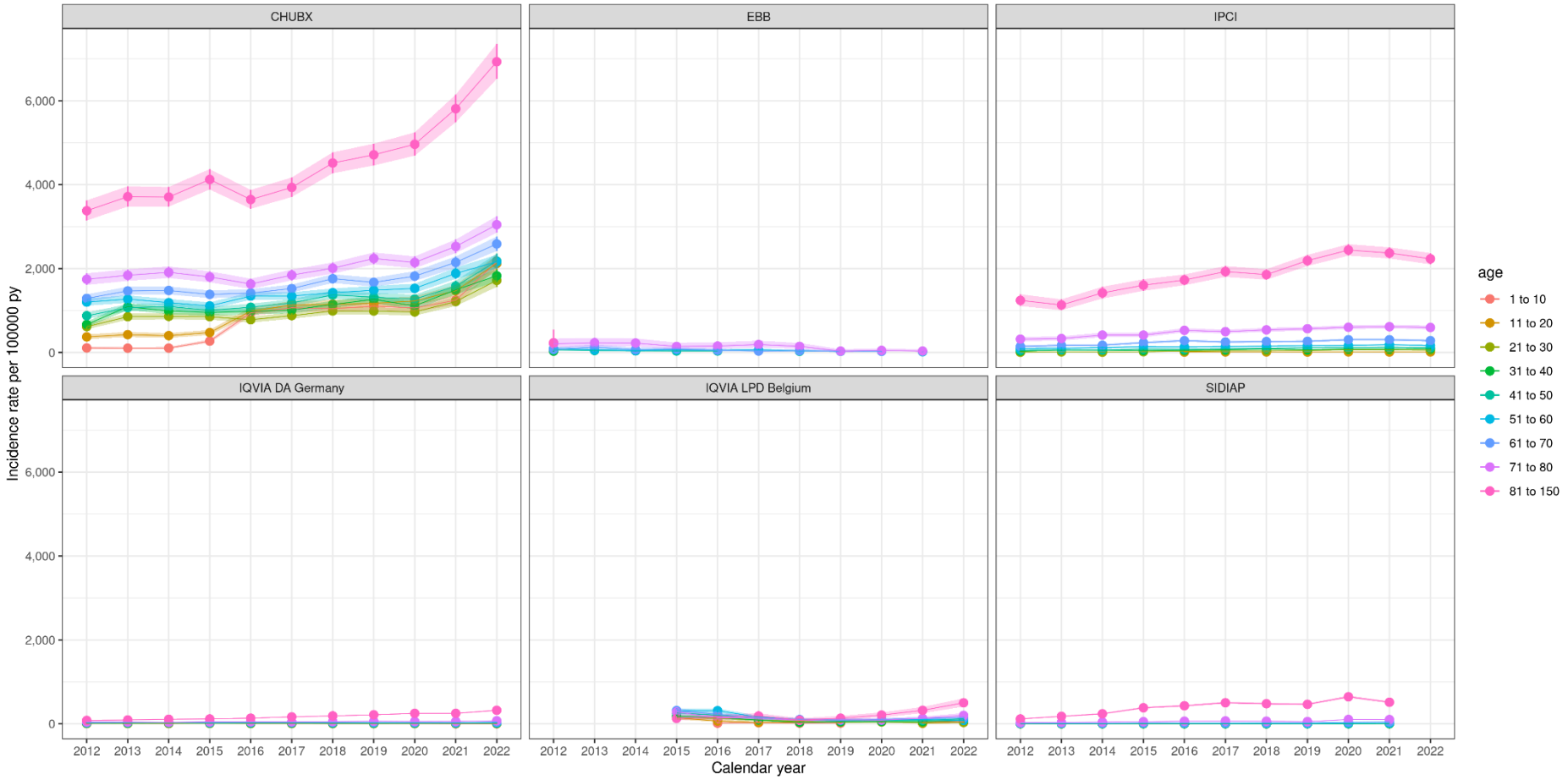


Figure 12.1.4.12- Incidence rates of weak opioids use between 2012 and 2022 stratified by age group.

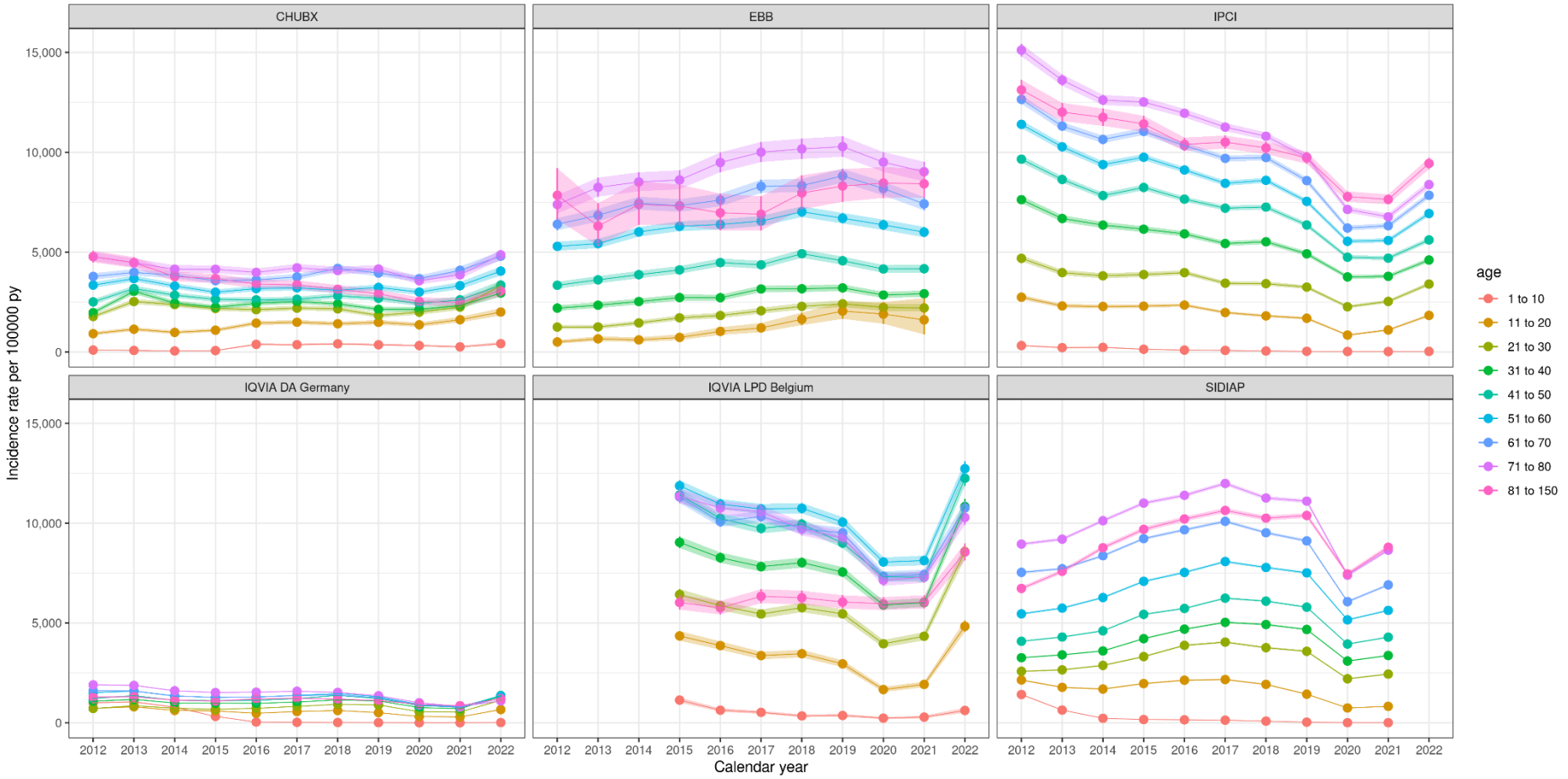


Figure 12.1.4.13- Incidence rates of potent opioids use between 2012 and 2022 stratified by age group.

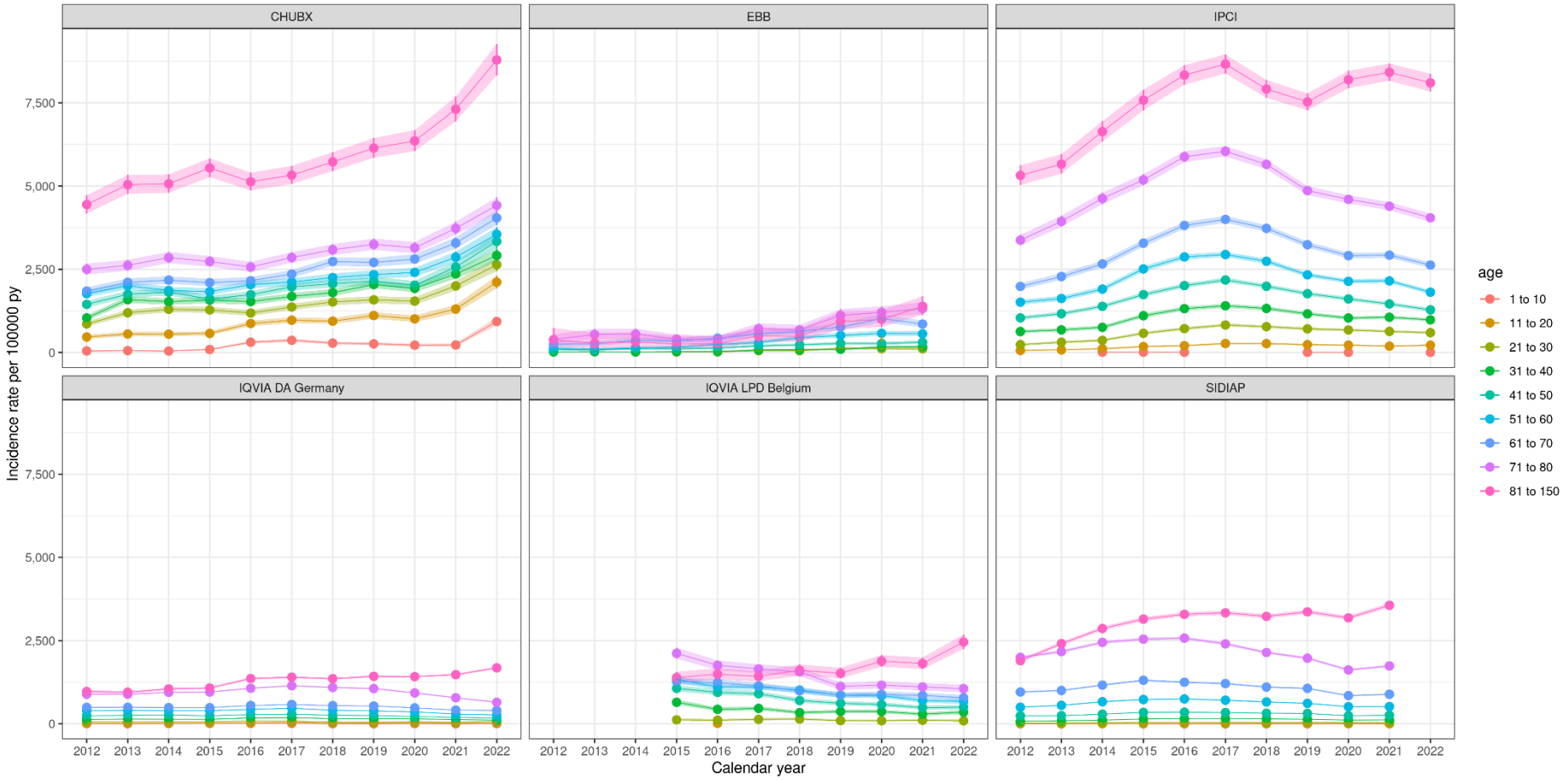
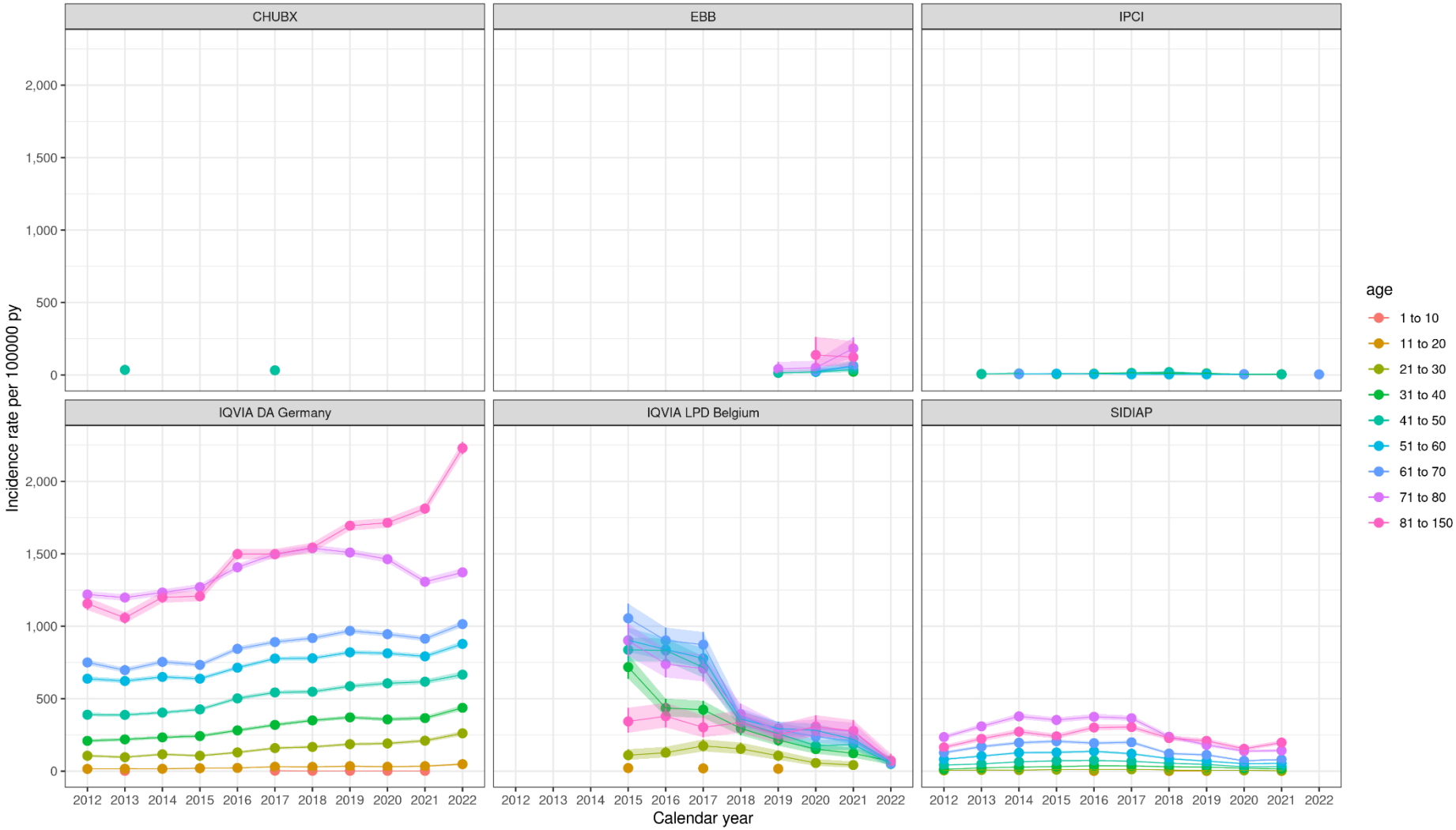


Figure 12.1.4.14- Incidence rates of naloxone use between 2012 and 2022 stratified by age group.



Incidence rates of opioids over time by sex

Figure 12.1.4.15 shows the incidence of overall opioid use stratified by sex from 2012 to 2022. In general, women had consistently higher rates of overall opioid use compared to men, a pattern that is found across all databases except for CHUBX where incidence of overall opioid use was higher in men and in IQVIA Germany where incidence was similar in women and men. This remains consistent in the breakdown of data on opioid use based on different administration for oral (Figure 12.1.4.16) opioids whilst the incidence of transdermal opioids (Figure 12.1.4.17) was highest in women in all databases apart from EBB and CHUBX where incidence was similar. Similar distributions to overall opioid prescribing were observed as well with different potencies, categorized as weak (Figure 12.1.4.19) and potent (Figure 12.1.4.20). However, an exception can be seen in the case of parenteral opioid use (Figure 12.1.4.18), where the usage rates between women and men are roughly equivalent. Similarly, Figure 12.1.4.21 shows that naloxone incidence is higher among women compared to men.

More detailed data can be found in the shiny app (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

Figure 12.1.4.15 - Incidence rates of overall opioids between 2012 and 2022 stratified by sex.

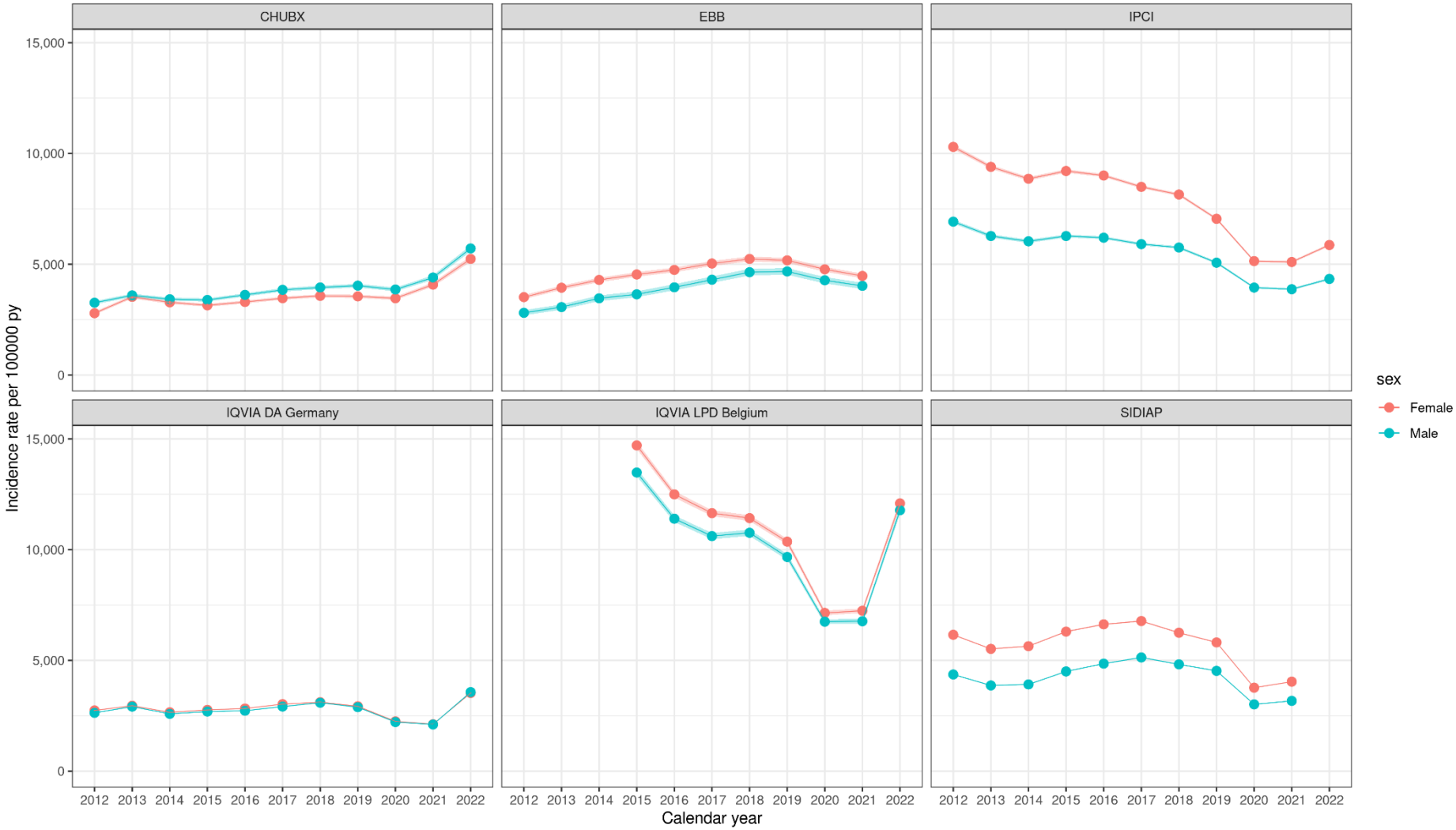


Figure 12.1.4.16 - Incidence rates of oral opioids between 2012 and 2022 stratified by sex.

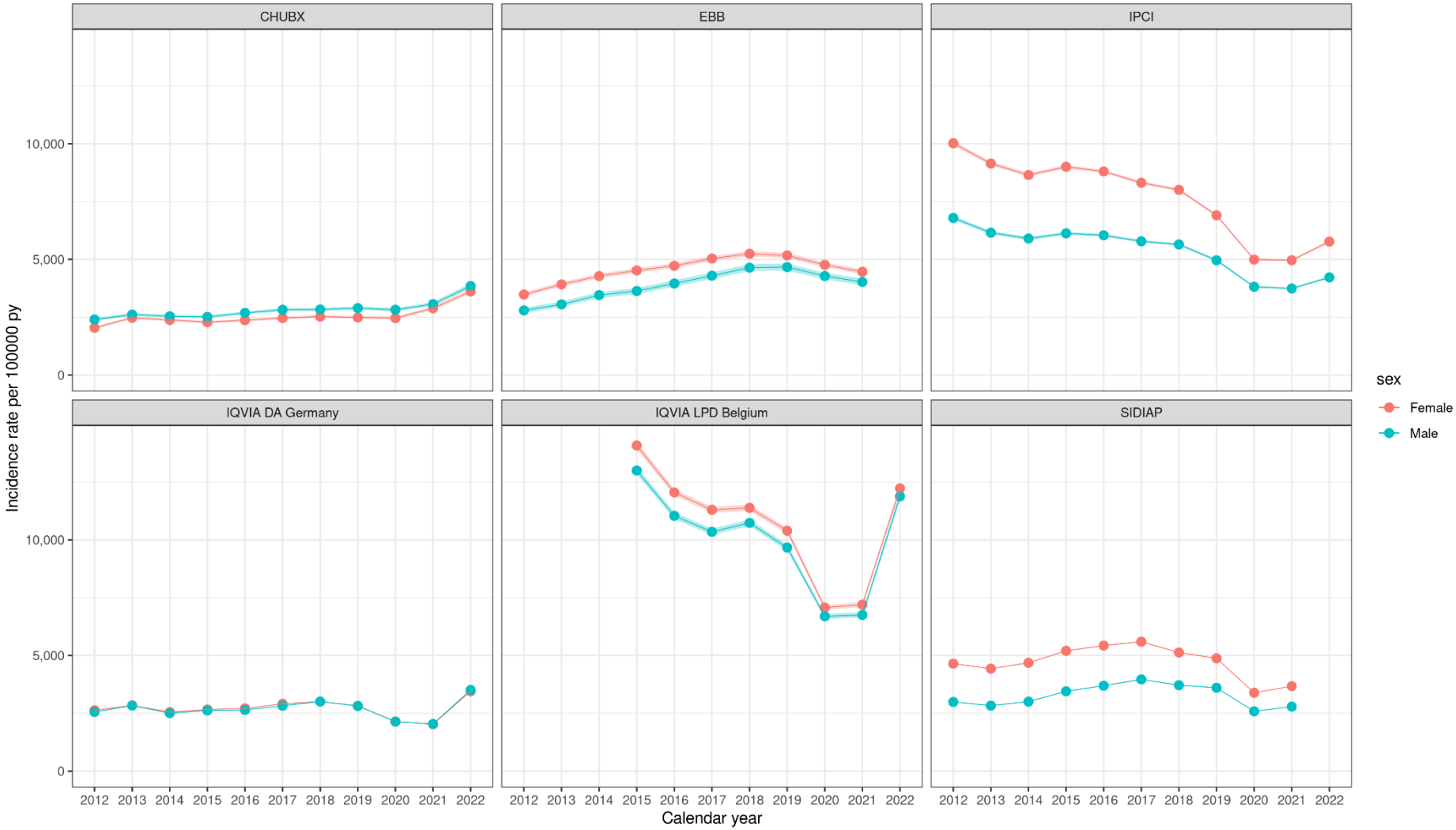


Figure 12.1.4.17 - Incidence rates of transdermal opioids between 2012 and 2022 stratified by sex.

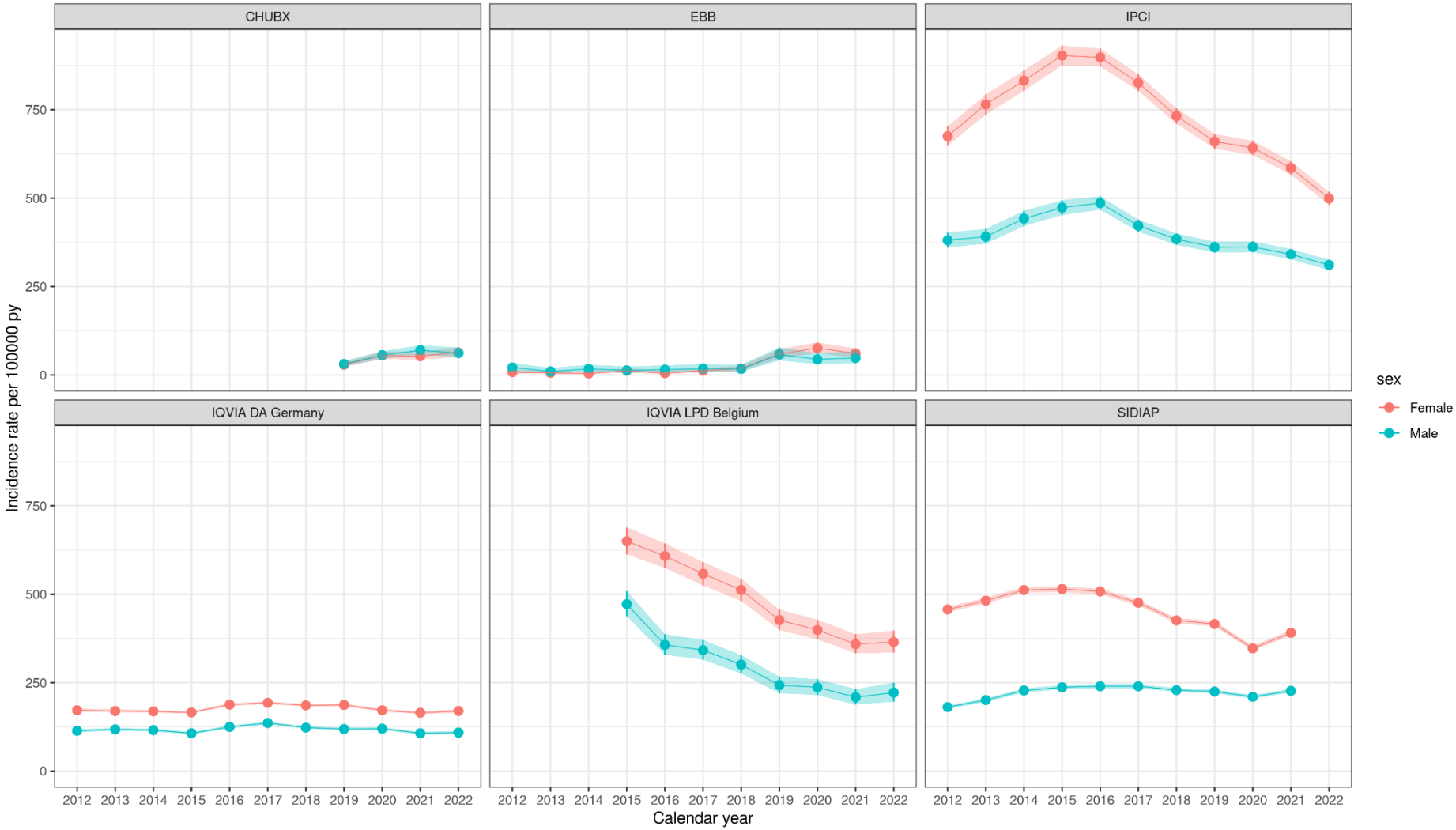


Figure 12.1.4.18 - Incidence rates of parenteral opioids between 2012 and 2022 stratified by sex.

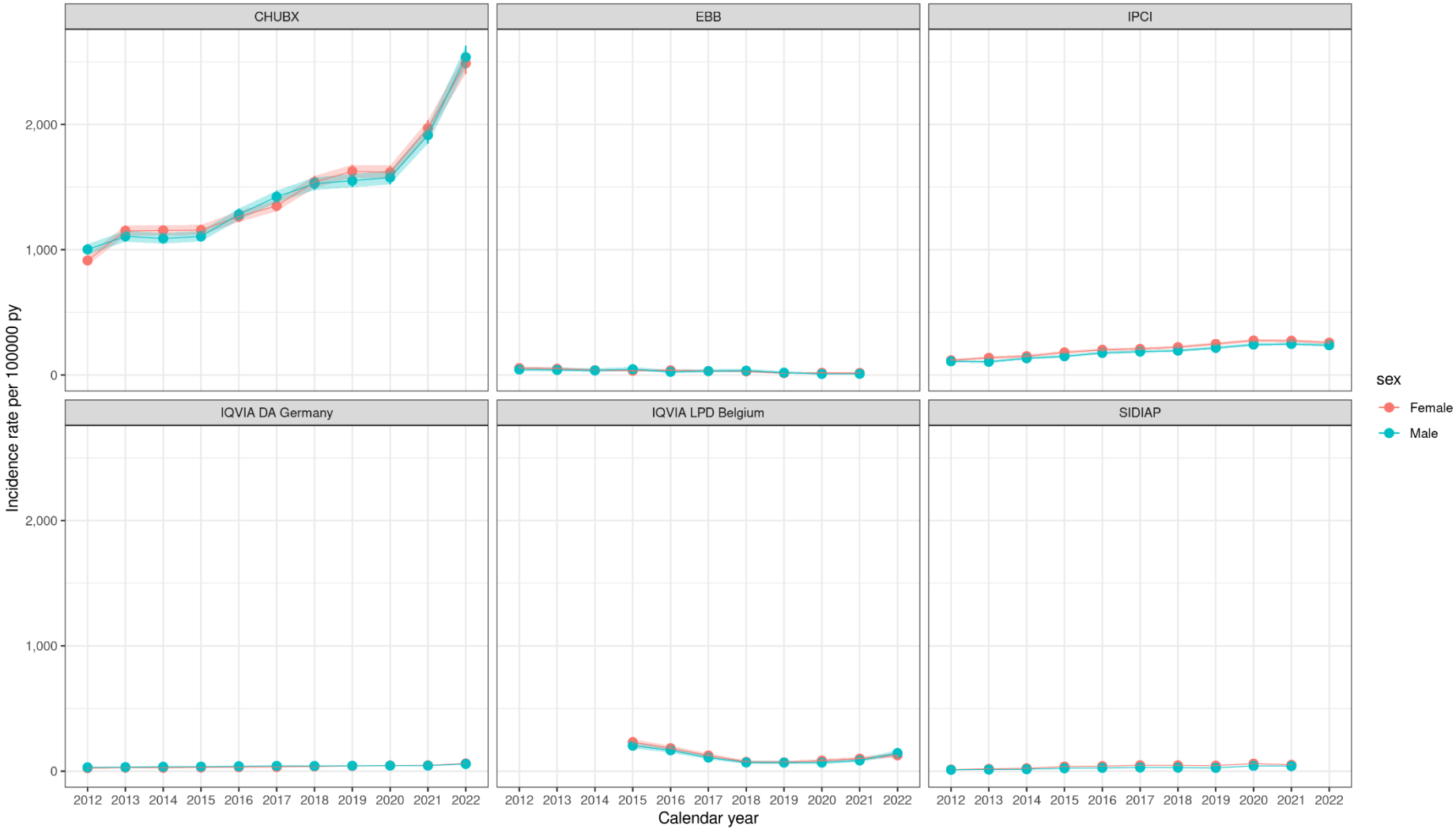


Figure 12.1.4.19- Incidence rates of weak opioids between 2012 and 2022 stratified by sex.

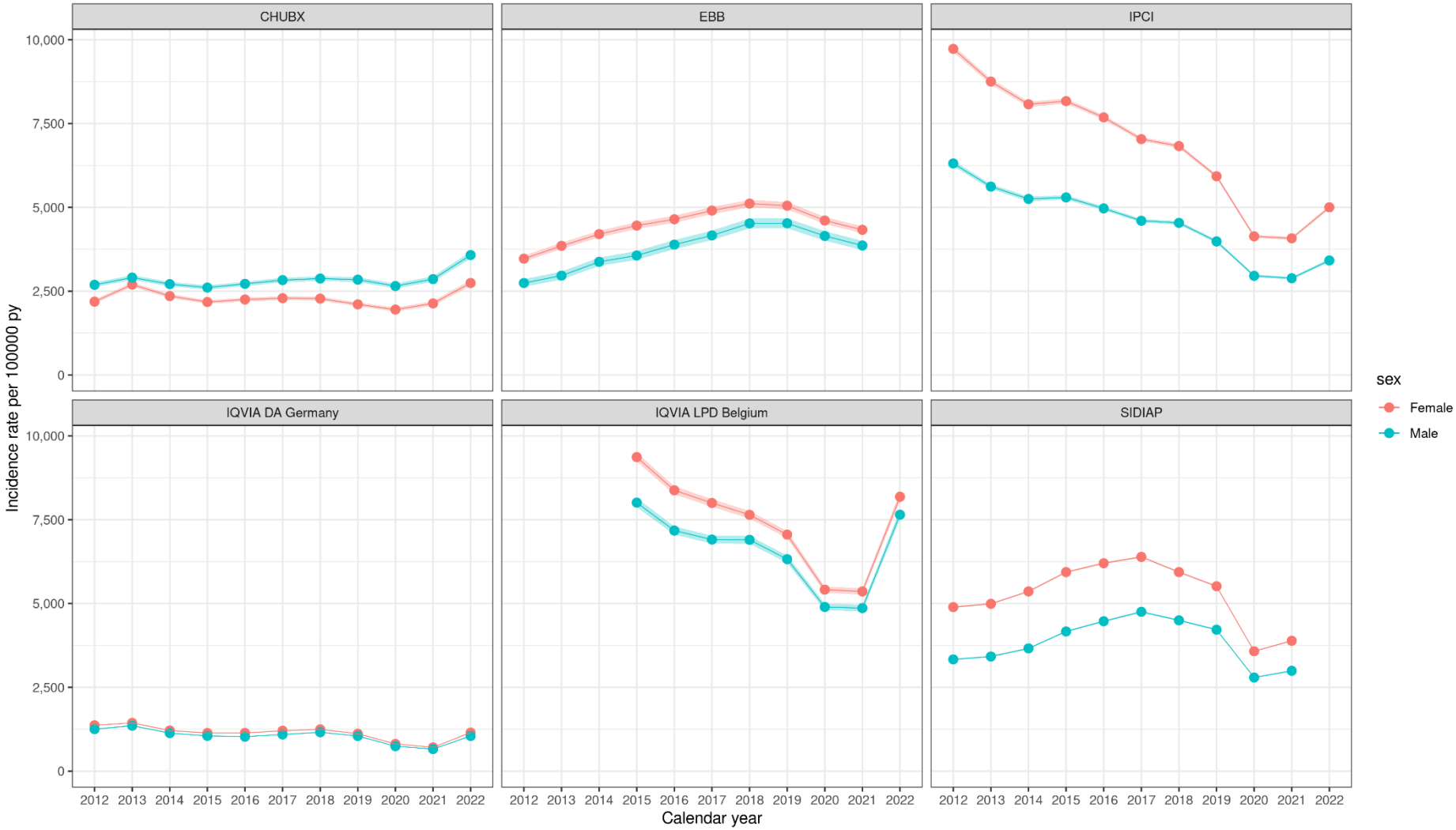


Figure 12.1.4.20- Incidence rates of potent opioids between 2012 and 2022 stratified by sex.

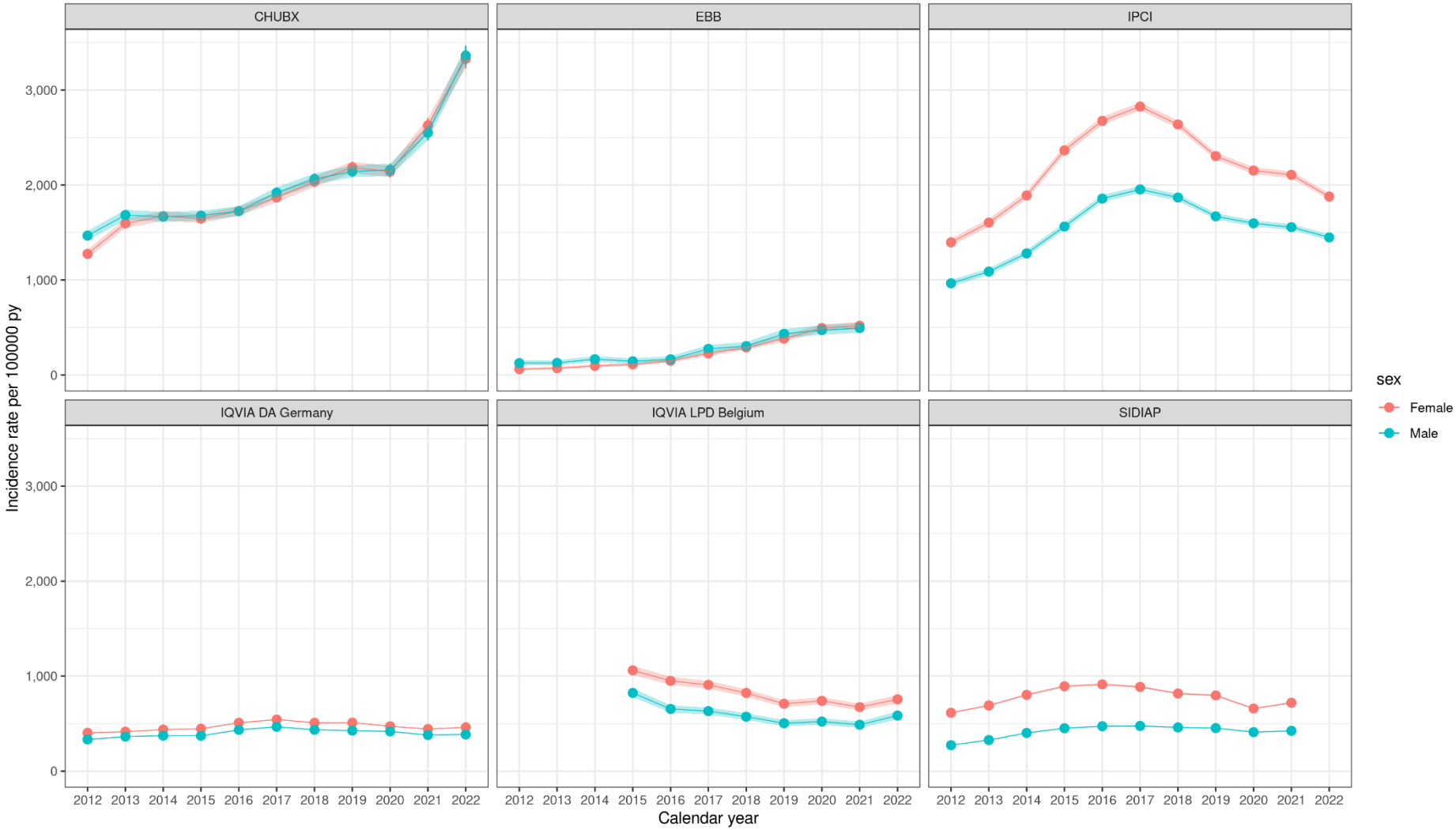
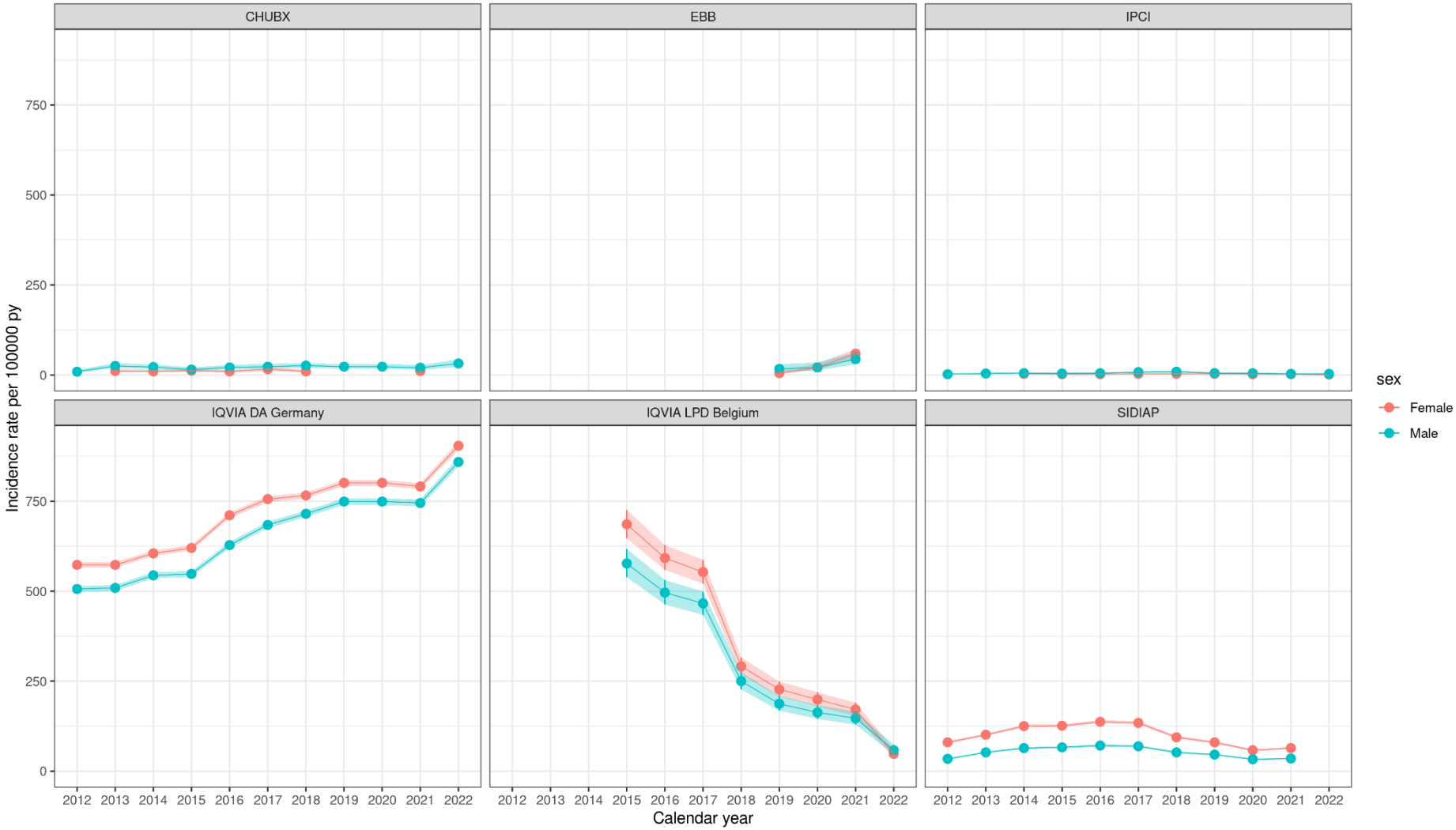


Figure 12.1.4.21- Incidence rates of naloxone between 2012 and 2022 stratified by sex.



Prevalence of opioids over time

The trends and patterns observed in opioid prevalent use generally mirrored those of incident use. A significant distinction, however, is the time lag between changes in incidence and their manifestation in prevalence and opioid use prevalence remained more stable compared to incidence estimates.

Figures 12.1.4.22 to 12.1.4.42 illustrate prevalence for opioids including stratifications. As prevalence varied greatly between individual substances, Figures 12.4.25 – 12.4.26 combine different substances with similar prevalence. Substances not included in Figures 12.4.25 – 12.4. had very low prevalence (<0.5% or <5 prescriptions), or were not prescribed at all. All details, including the number of events, population and person-years for each calendar year, and database can be found in the shiny app (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

Figure 12.1.4.22 – Prevalence of overall opioid use between 2012 and 2022.

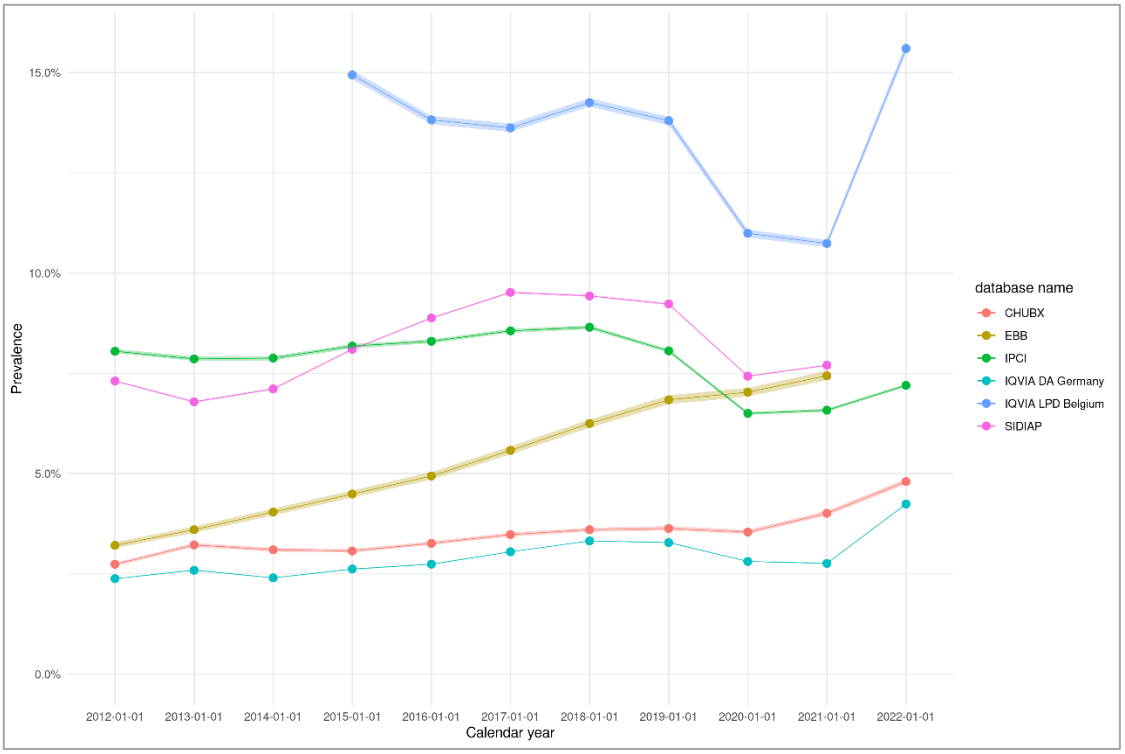


Figure 12.1.4.22 shows the prevalence of overall opioid use between 2012 to 2022 across databases. In CHUBX, there was a small, but gradual increase in the prevalence of opioid use, rising from 2.7% in 2012 to 4.8% in 2022. The EBB reported an almost linear upwards trend in this period, increasing from 3.2% in 2012 to 7.4% in 2022. In contrast, IPCI had a relatively steady prevalence until 2018, at around 8.6%, followed by a decline. In SIDIAP, highest prevalence was seen in 2017 at 9.5%, which then stabilized before falling in 2021 and 2022. IQVIA DA Germany reported fluctuating prevalence rates throughout the decade. IQVIA LBD Belgium shown a falling annual prevalence until 2020/2021, but saw an increase in 2022. Overall, IQVIA LBD Belgium has the highest reported opioid prevalence, while IQVIA DA Germany has the lowest.
Prevalence dropped during the early pandemic in 2020 for LPD Belgium, IPCI, SIDIAP and DA Germany, but slightly increased in EBB and CHUBX.

Figure 12.1.4.23 - Prevalence of oral, transdermal, and parenteral opioids between 2012 and 2022.

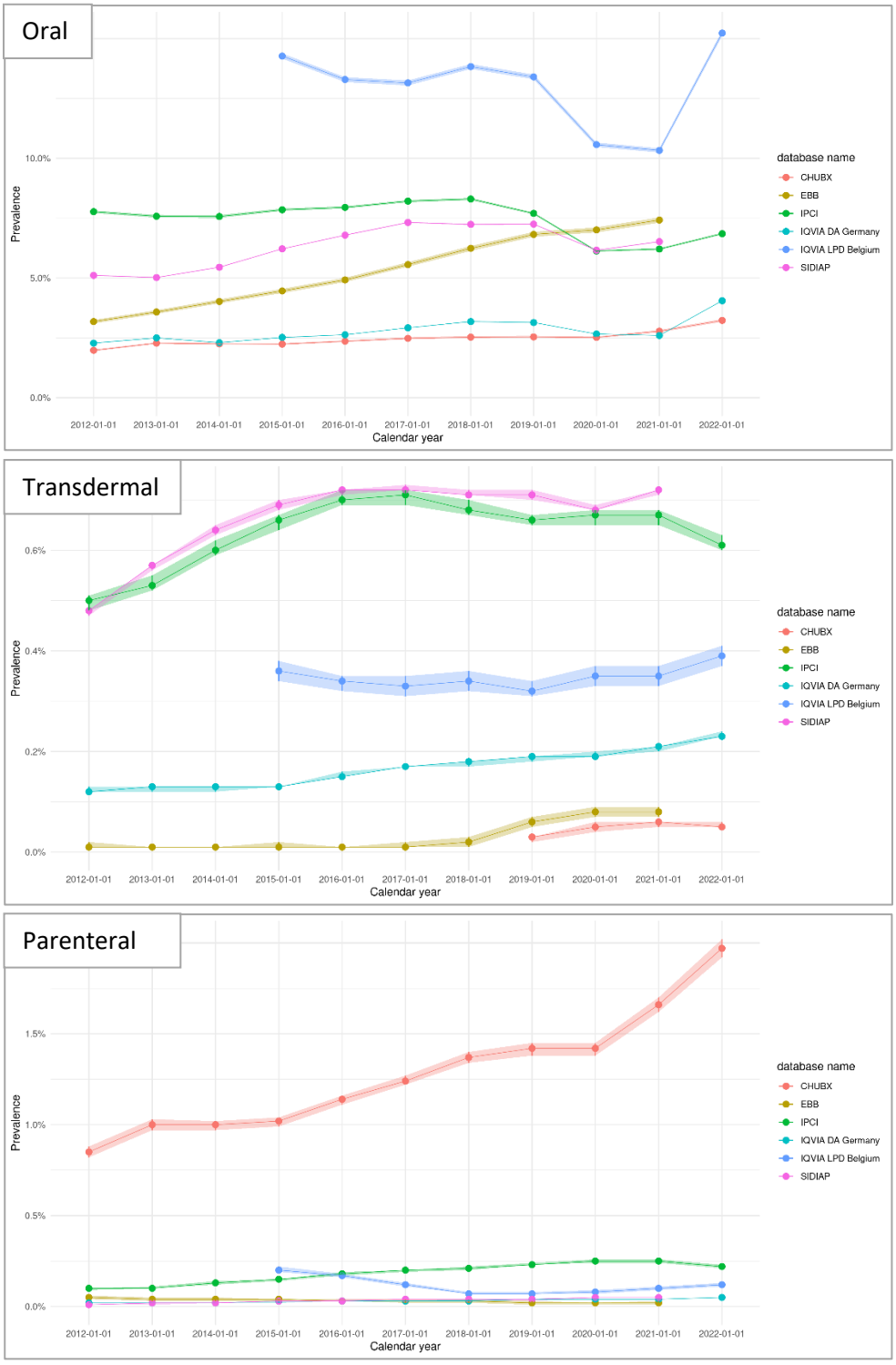
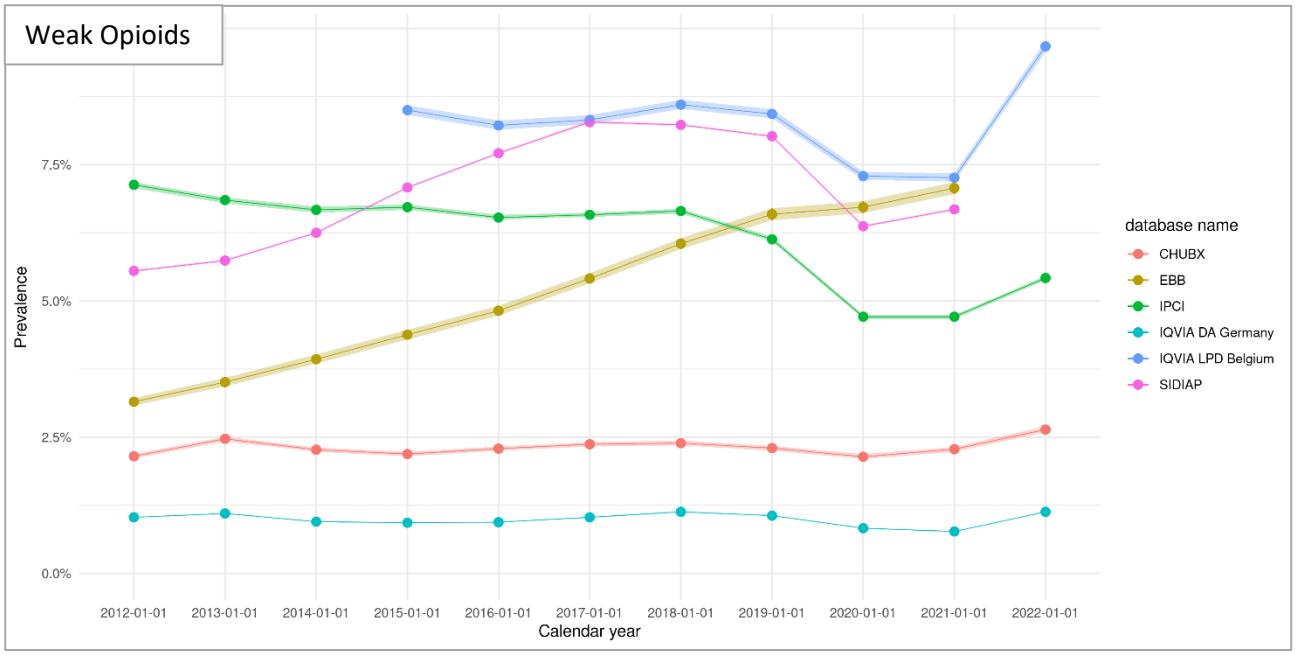


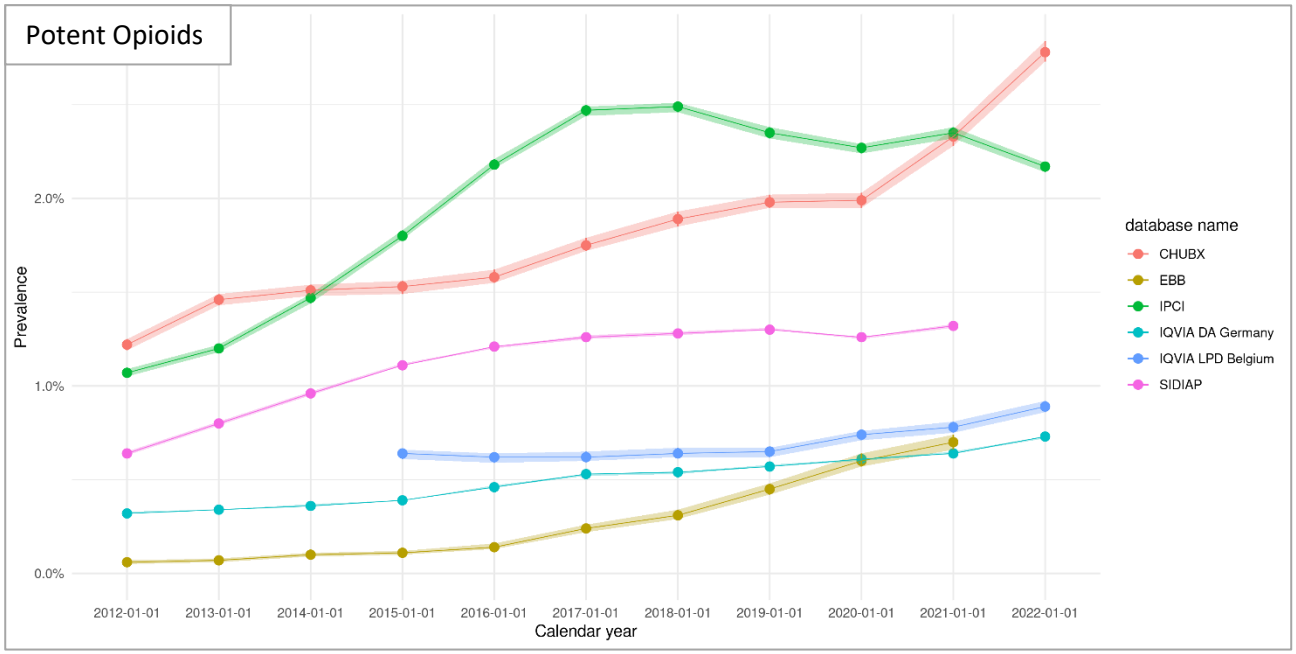
Figure 12.1.4.23 shows the prevalence of opioids, grouped by different routes of administration. Overall, oral opioids had the highest prevalence, driving the overall trend of opioid usage. Both transdermal and parenteral opioids showed lower and relatively stable usage over the years. However, there was an exception in CHUBX, where the prevalent use of parenteral opioids gradually increased.

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Figure 12.1.4.24- Prevalence of weak and potent opioids between 2012 and 2022.



*Weak opioids comprise the following substances: Codeine, Hydrocodone, Tramadol



*Potent opioids comprise the following substances: Buprenorphine, Fentanyl, Hydromorphone, Methadone, Morphine, Oxycodone, Oxymorphone, Tapentadol.

Figure 12.1.4.24 shows prevalence of opioids based on their potency. Overall, weak opioids were used more frequently than potent opioids in the primary and secondary care outpatient databases. For CHUBX, the prevalence of prescriptions of weak opioids was fairly stable over time, whereas the prevalence of potent opioids gradually increased from 2012 to 2022.

Figure 12.1.4.25- Prevalence of most commonly prescribed opioids (substances) between 2012 and 2022.

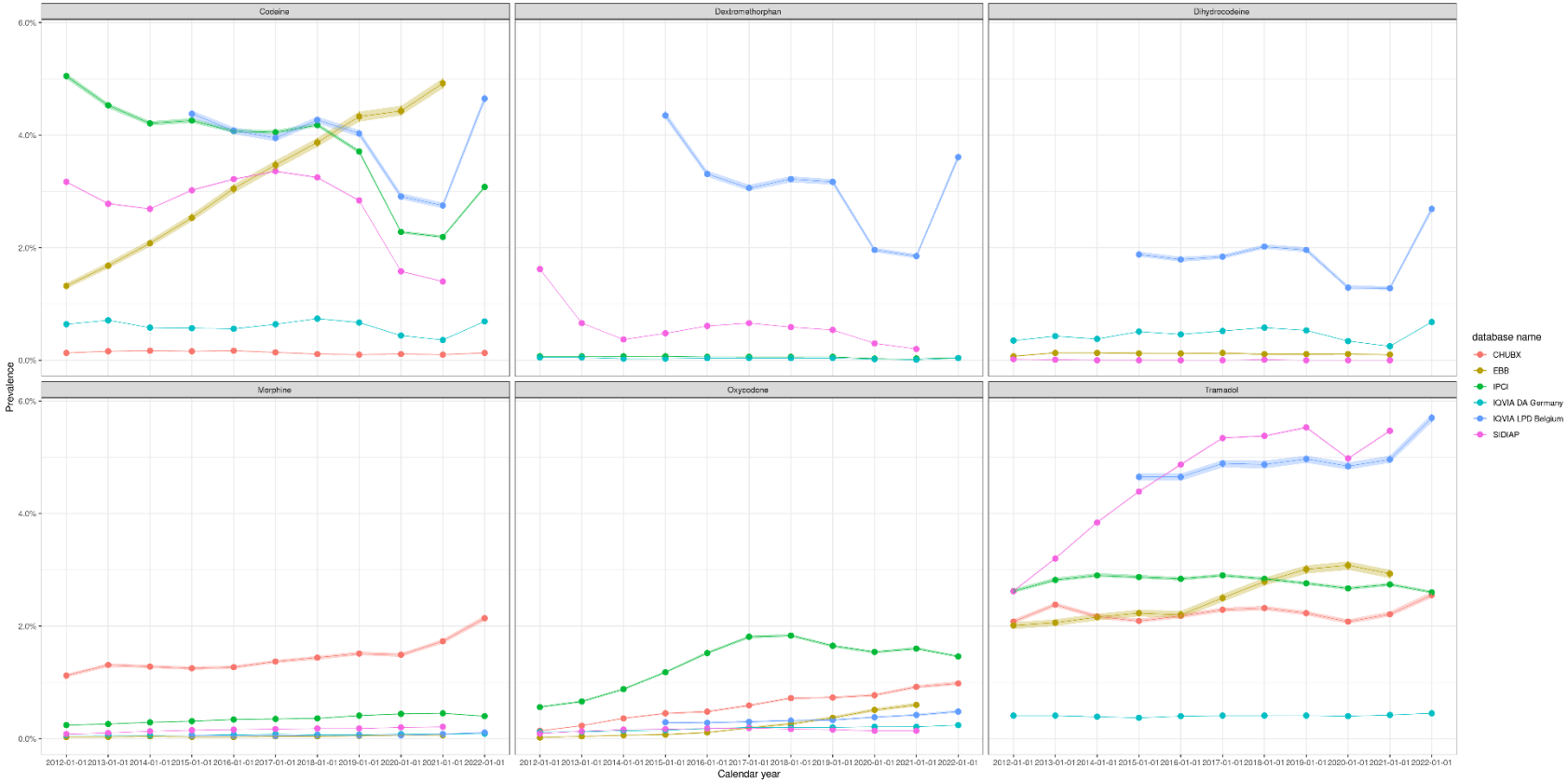


Figure 12.1.4.25 shows the prevalence of the most commonly prescribed opioid substances. Codeine and tramadol were the most commonly used opioids. Prevalence of codeine increased steadily over time in EBB, while it gradually decreased in IPCI. A pronounced fall in prevalence was reported from 2018 to 2020 in LPD Belgium, IPCI and SIDIAP. Prevalence of tramadol use increased from 2012 to 2019 in SIDIAP, whereas it remained largely stable over time in all other databases. Prevalence of morphine and oxycodone increased gradually in CHUBX.

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Figure 12.1.4.26- Prevalence of less commonly prescribed opioids (substances) between 2012 and 2022.

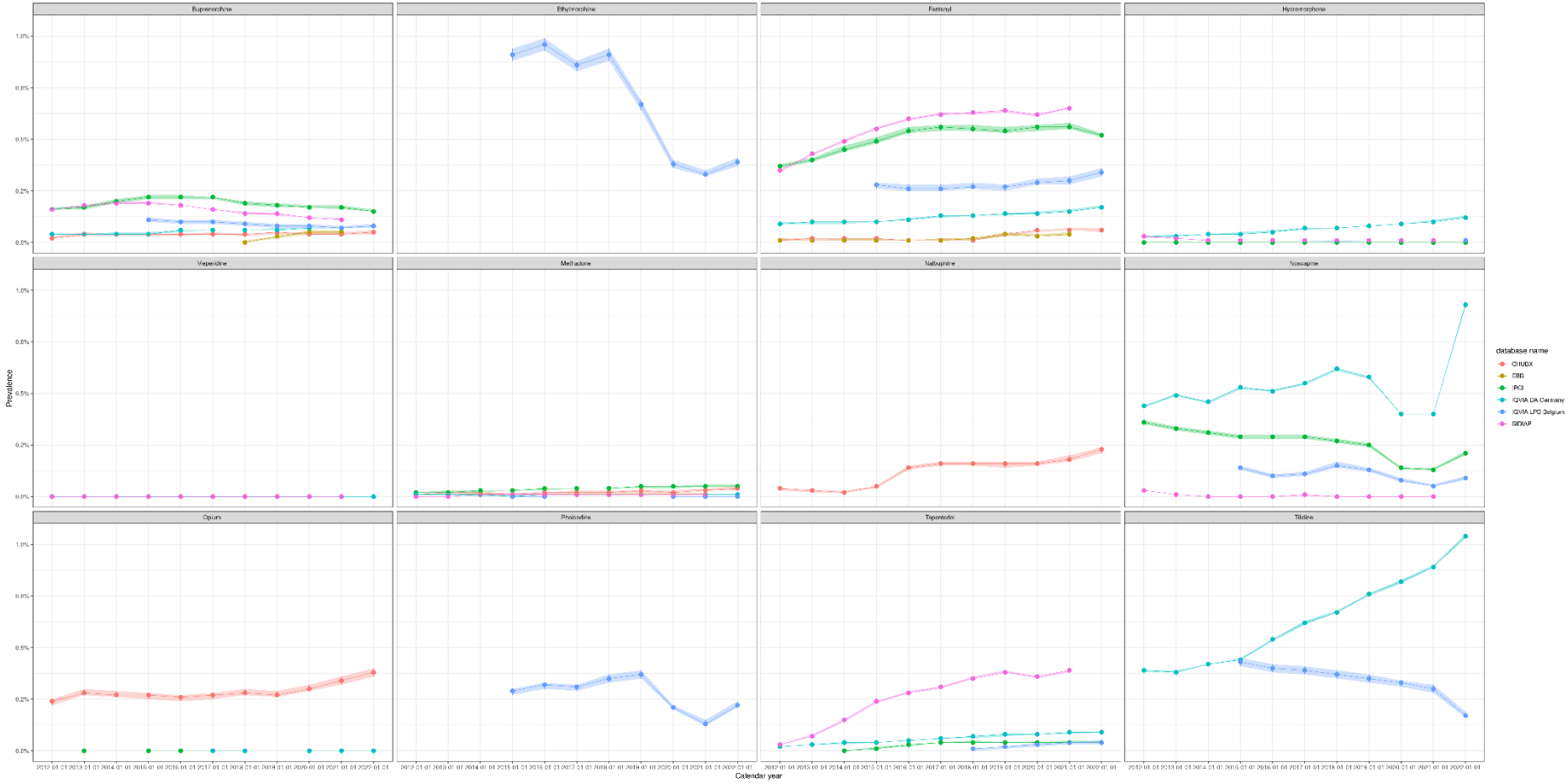


Figure 12.1.4.26 shows the prevalence of less frequently used opioids. Among those, fentanyl was most common used across all databases, with a relatively stable prevalence over time. Prevalence of noscapine and tilidine increased in IQVIA DA Germany.

Figure 12.1.4.28- Prevalence of naloxone use between 2012 and 2022.

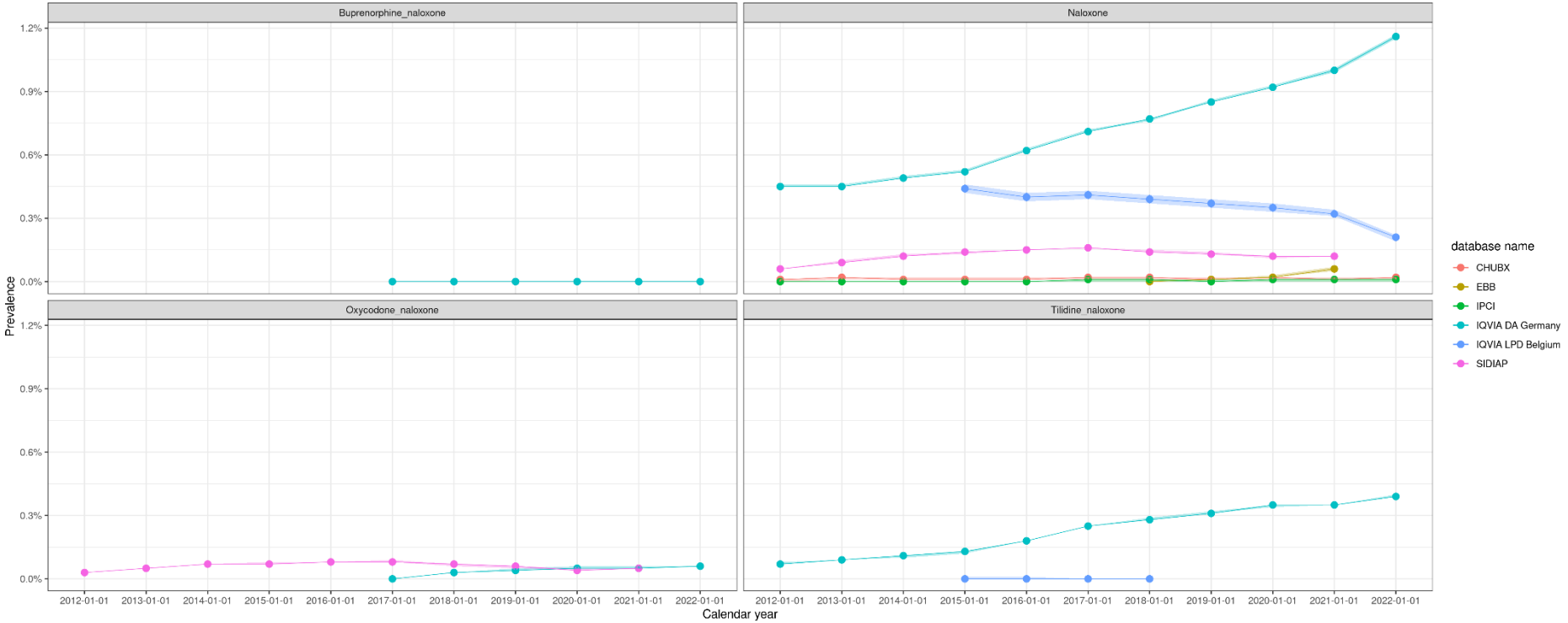


Figure 12.1.4.28 shows the prevalence of naloxone (substance) and prevalence of fixed opioid-naloxone combinations. An increase in naloxone use was reported in IQVIA DA Germany. In other databases, the prevalence of naloxone remained consistently low.

Prevalence of opioids over time by age group

Figure 12.1.4.29 shows the prevalence of overall opioid use by age group from 2012 to 2022. Prevalence gradually increased with advanced age, with substantially higher rates of opioid use seen in older age groups across all datasets. Notably, the IPCI and SIDIAP datasets had the most pronounced difference in the prevalence between the oldest and youngest age groups, while the IQVIA DA Germany dataset had a much smaller difference between age groups. These trends were consistently observed in the breakdown of data on opioid use categorized by administration method: oral (Figure 12.1.4.30), transdermal (Figure 12.1.4.31), and parenteral (Figure 12.1.4.32), as well as by potency: weak (Figure 12.1.4.33) and potent (Figure 12.1.4.34).

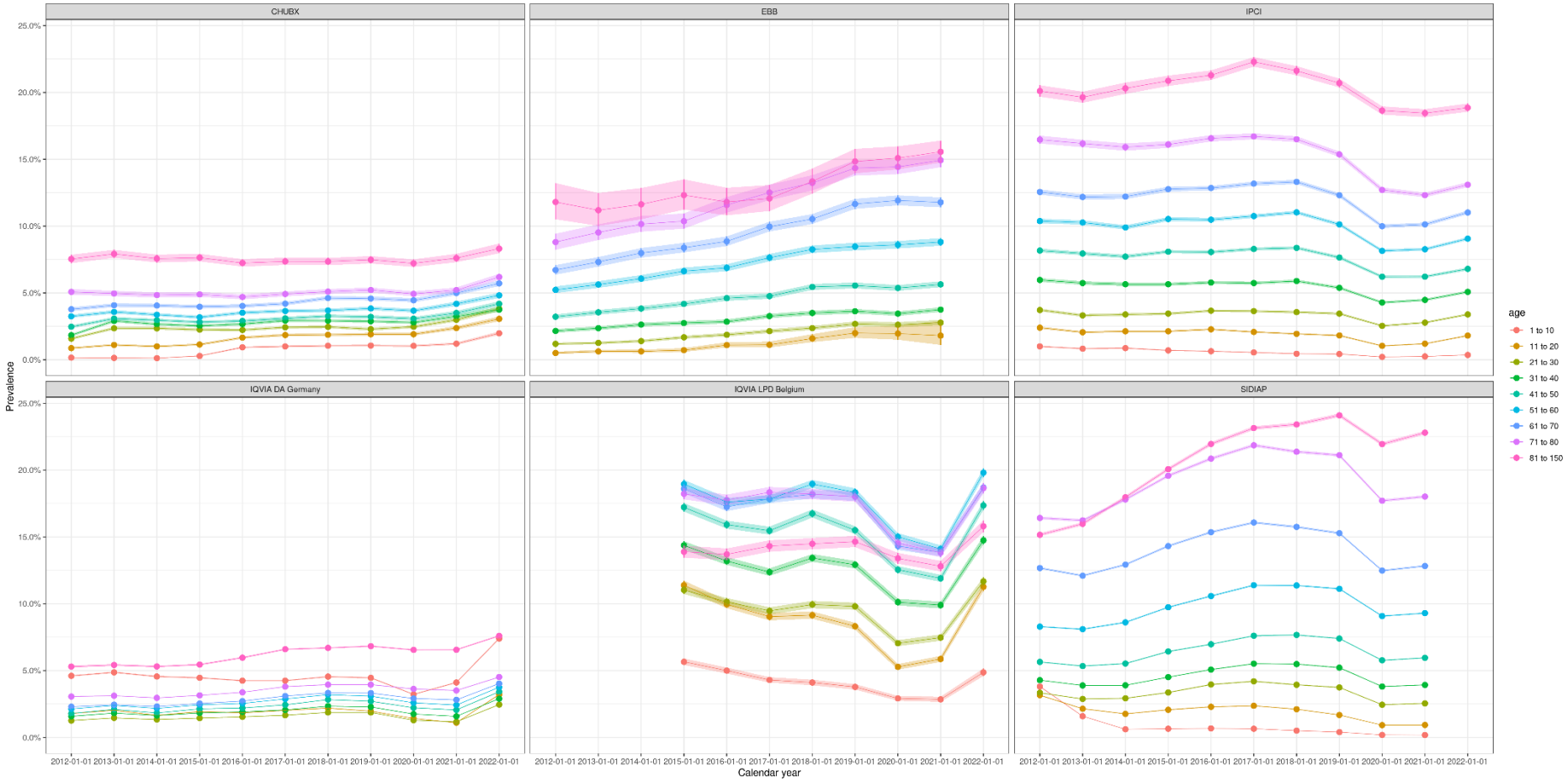
High prevalence of opioid use as reported in young children (age group 1-10) for IQVIA DA Germany, which is predominantly driven by prescriptions of noscapine.

Figure 12.1.4.35 shows the prevalence of naloxone use by age from 2012 to 2022. There was also a notable variation in use across different age groups, particularly in the IQVIA DA Germany.

More detailed data can be found in the shiny app (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

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Figure 12.1.4.29 - Prevalence of overall opioids between 2012 and 2022 stratified by age group.



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Figure 12.1.4.30 - Prevalence of oral opioids between 2012 and 2022 stratified by age group.

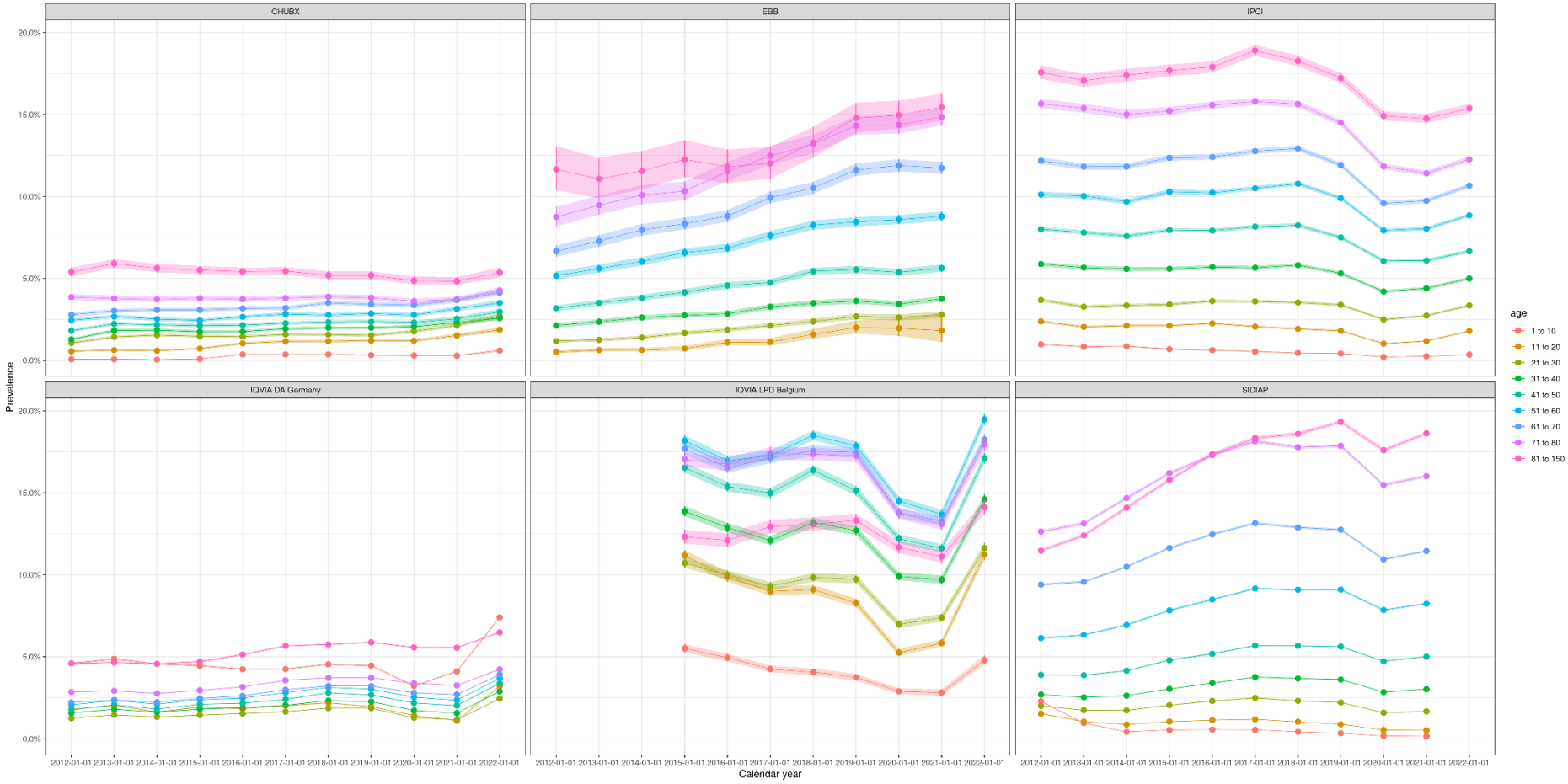


Figure 12.1.4.31 - Prevalence of transdermal opioids between 2012 and 2022 stratified by age group.

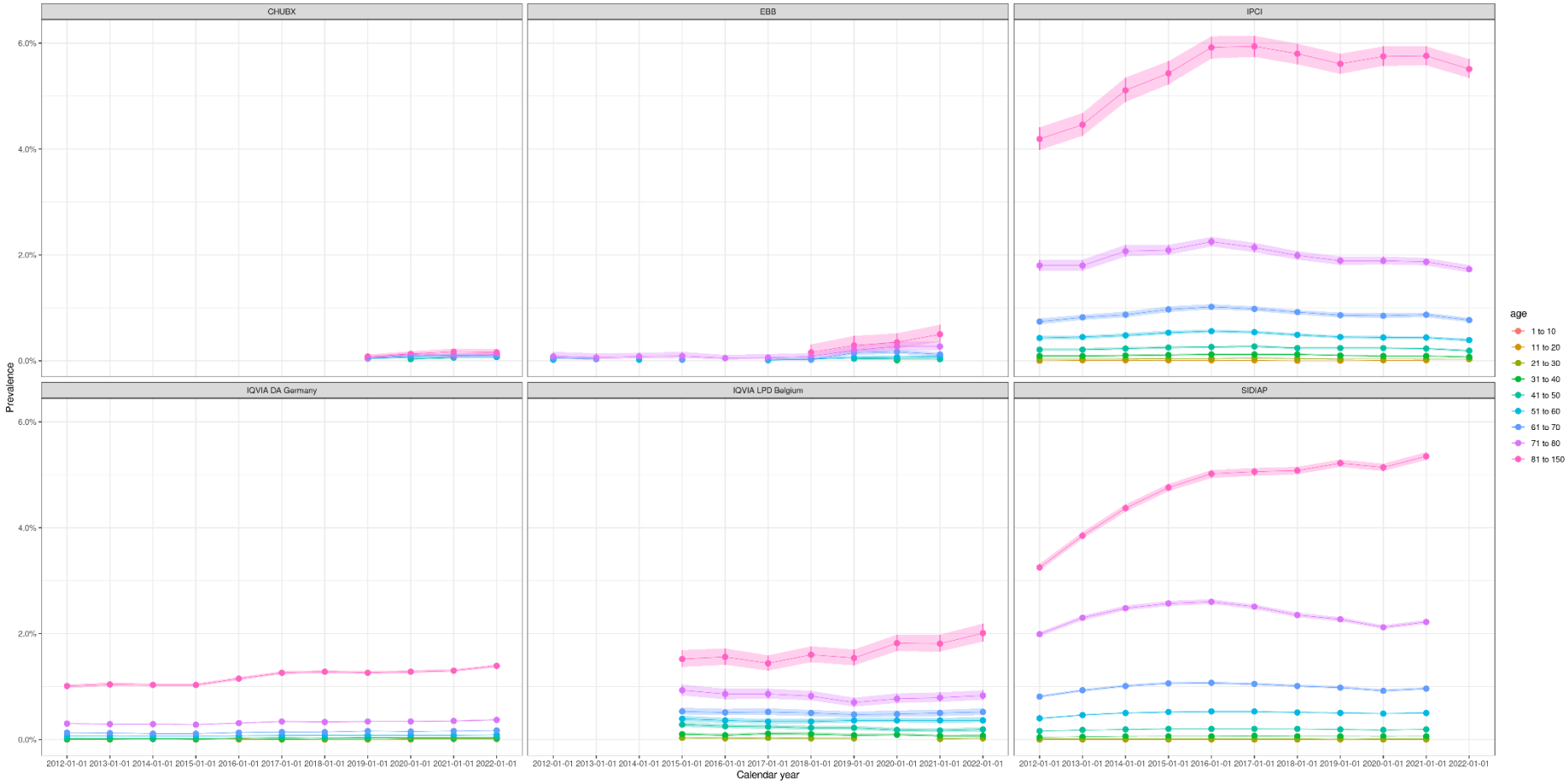


Figure 12.1.4.32 - Prevalence of parenteral opioids between 2012 and 2022 stratified by age group

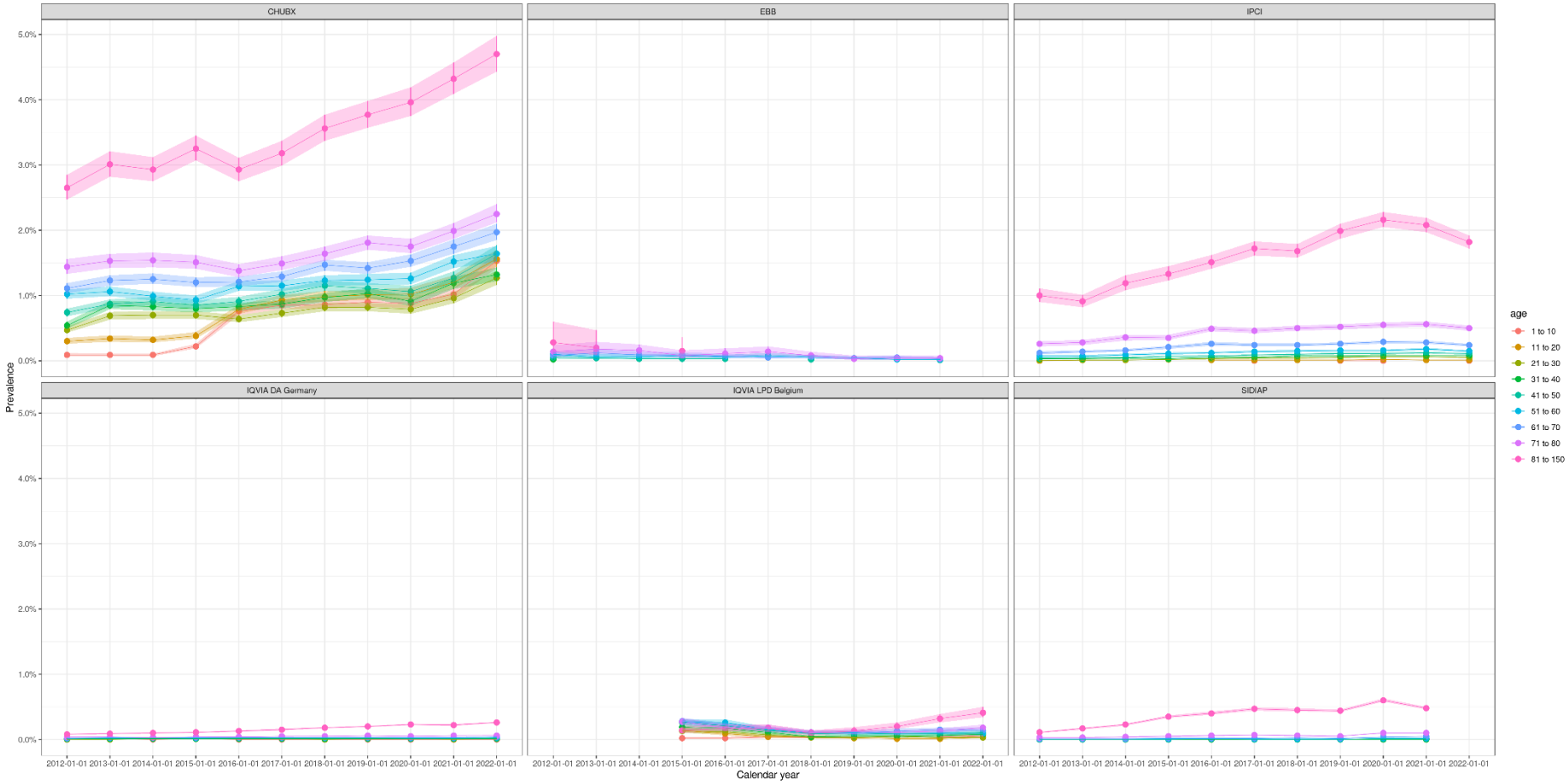


Figure 12.1.4.33- Prevalence of weak opioids between 2012 and 2022 stratified by age group

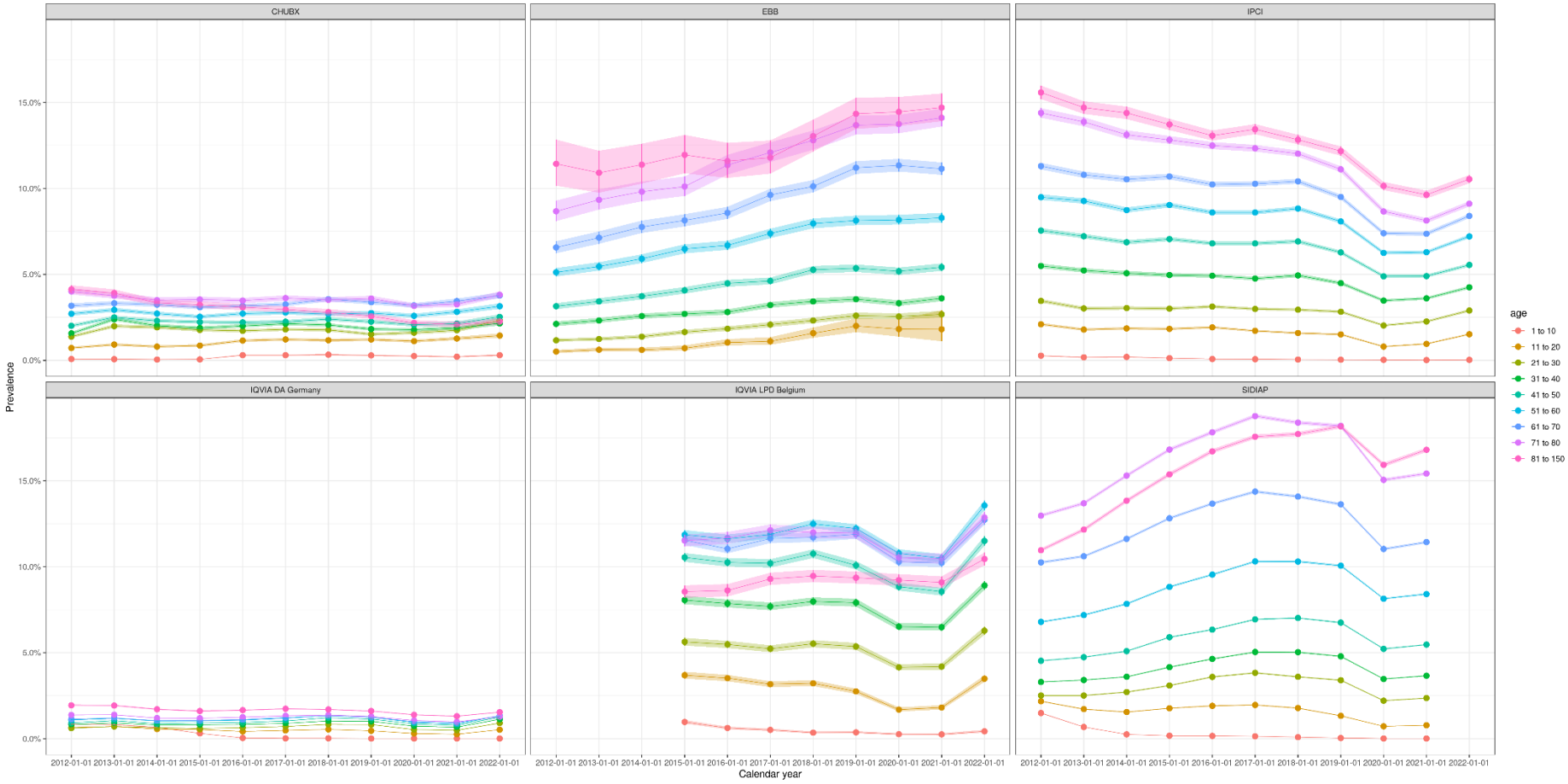


Figure 12.1.4.34- Prevalence of potent opioids between 2012 and 2022 stratified by age group.

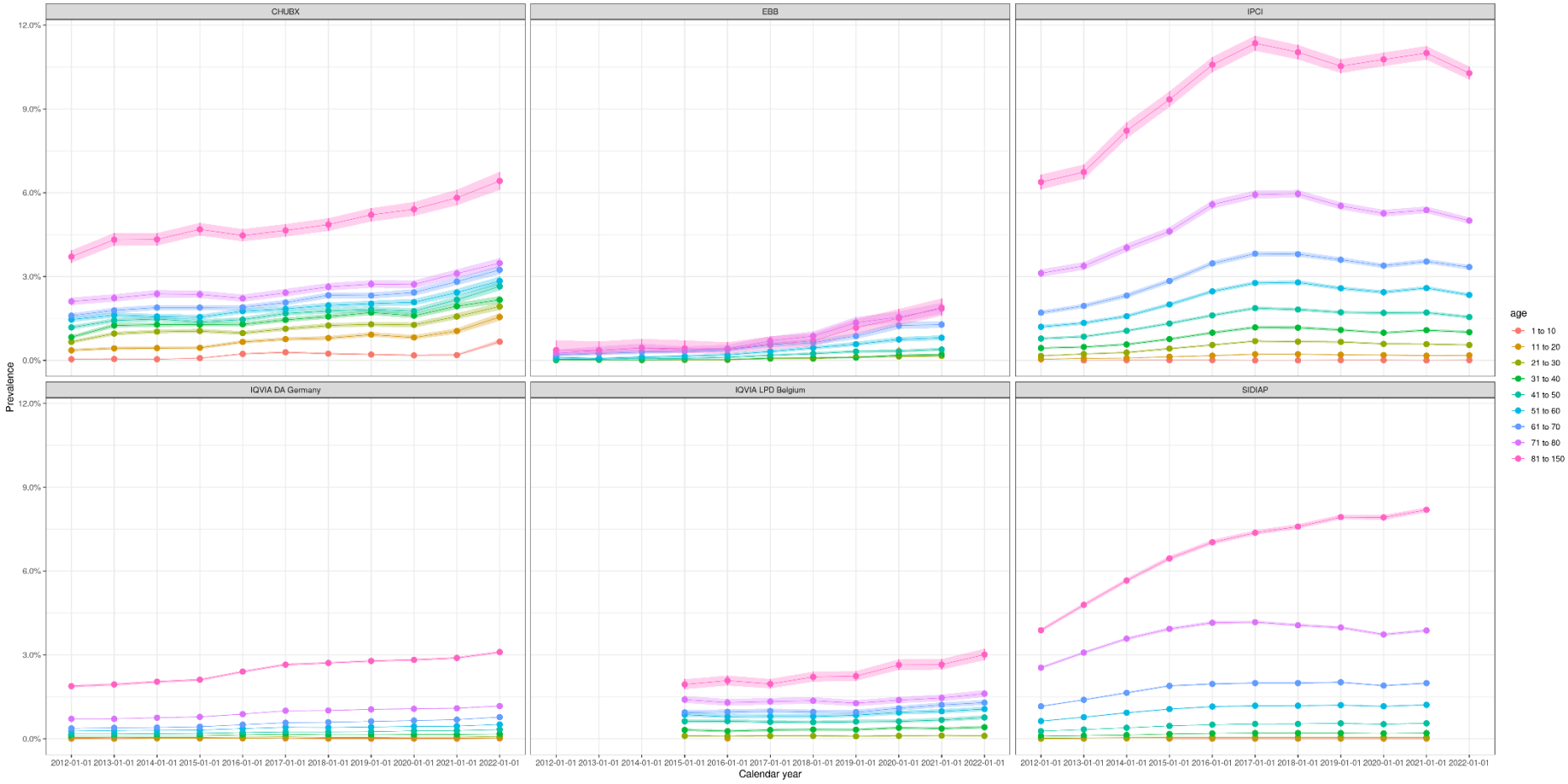
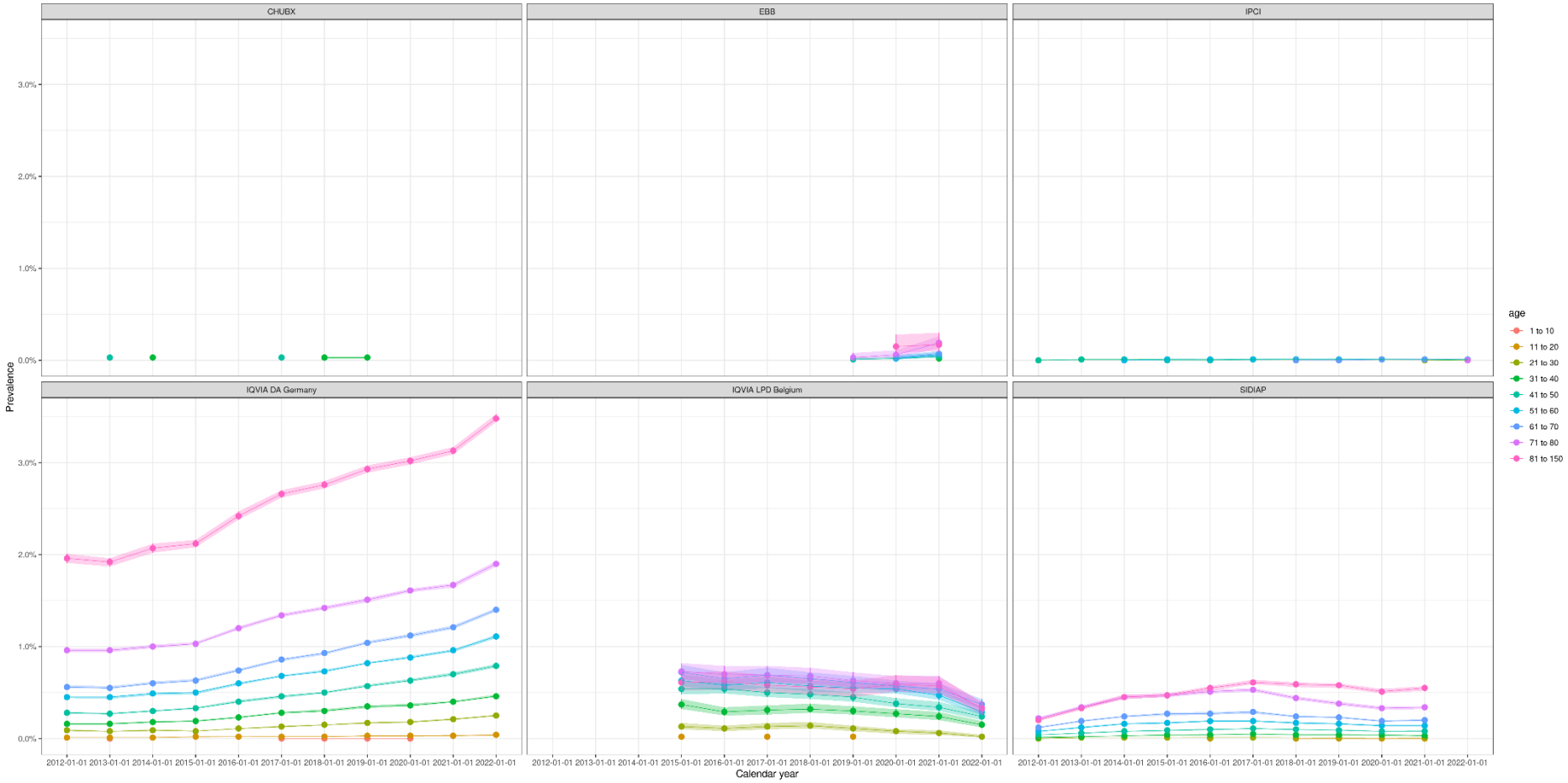


Figure 12.1.4.35- Prevalence of naloxone use between 2012 and 2022 stratified by age group.



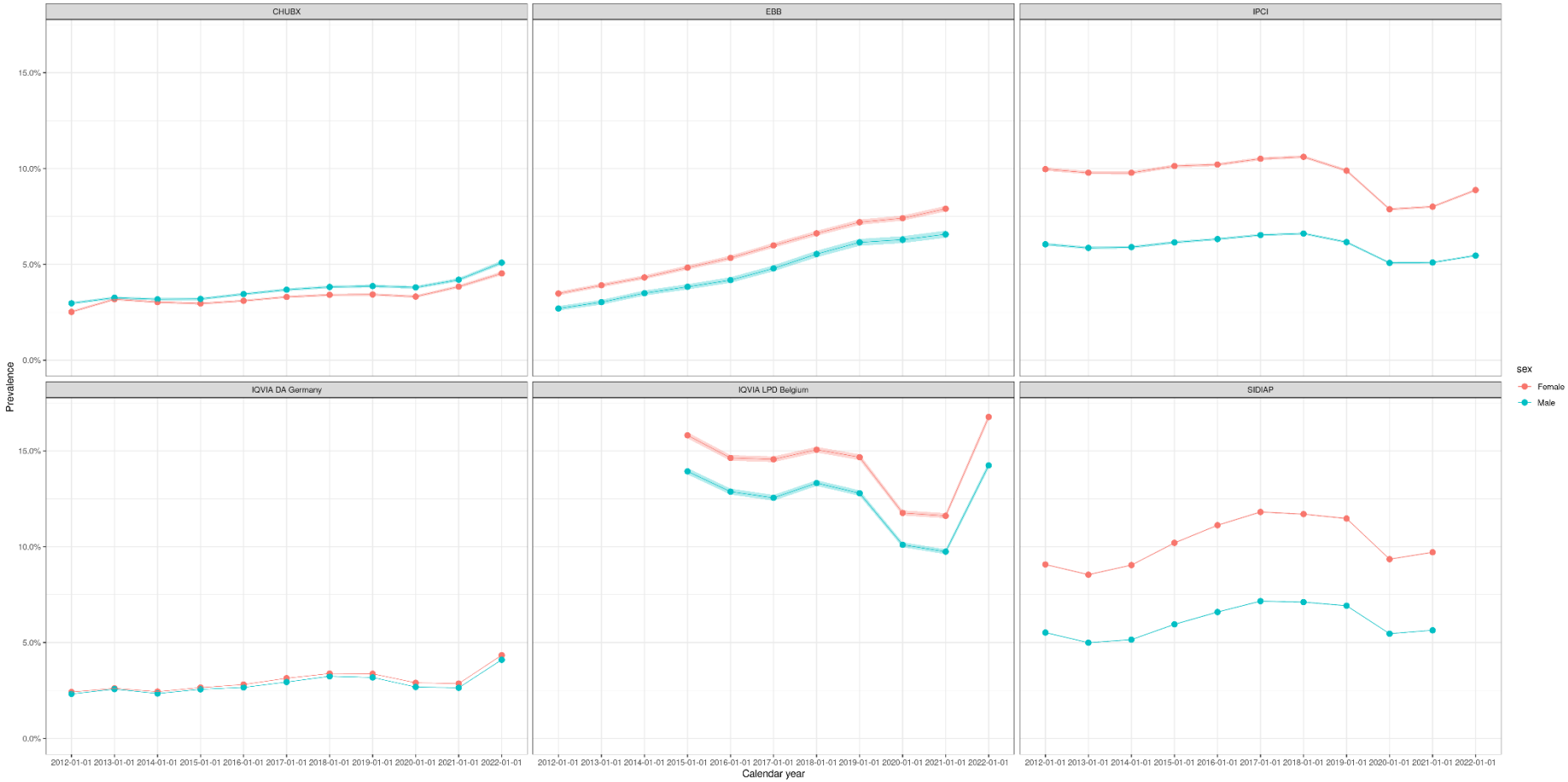
Prevalence of opioids over time by sex

Figure 12.1.4.36 shows the prevalence of overall opioid use stratified by sex from 2012 to 2022. In general, women consistently had higher rates of overall opioid use compared to men, a pattern that is found across various databases. This remains consistent in the breakdown of data on opioid use based on different administration including oral (Figure 12.1.4.37) and transdermal (Figure 12.1.4.38), as well as different potencies, categorized as weak (Figure 12.1.4.40) and potent (Figure 12.1.4.41). However, an exception can be seen in the case of parenteral opioid use (Figure 12.1.4.39), where the prevalent usage between women and men are roughly equivalent. Similarly, Figure 12.1.4.42 shows that naloxone prevalence is higher among women compared to men. For CHUBX, prevalence of opioid use was similar for men and women.

More detailed data can be found in the shiny app (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access).

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Figure 12.1.4.36 - Prevalence of overall opioid use between 2012 and 2022 stratified by sex.



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Figure 12.1.4.37 - Prevalence of oral opioid use between 2012 and 2022 stratified by sex.

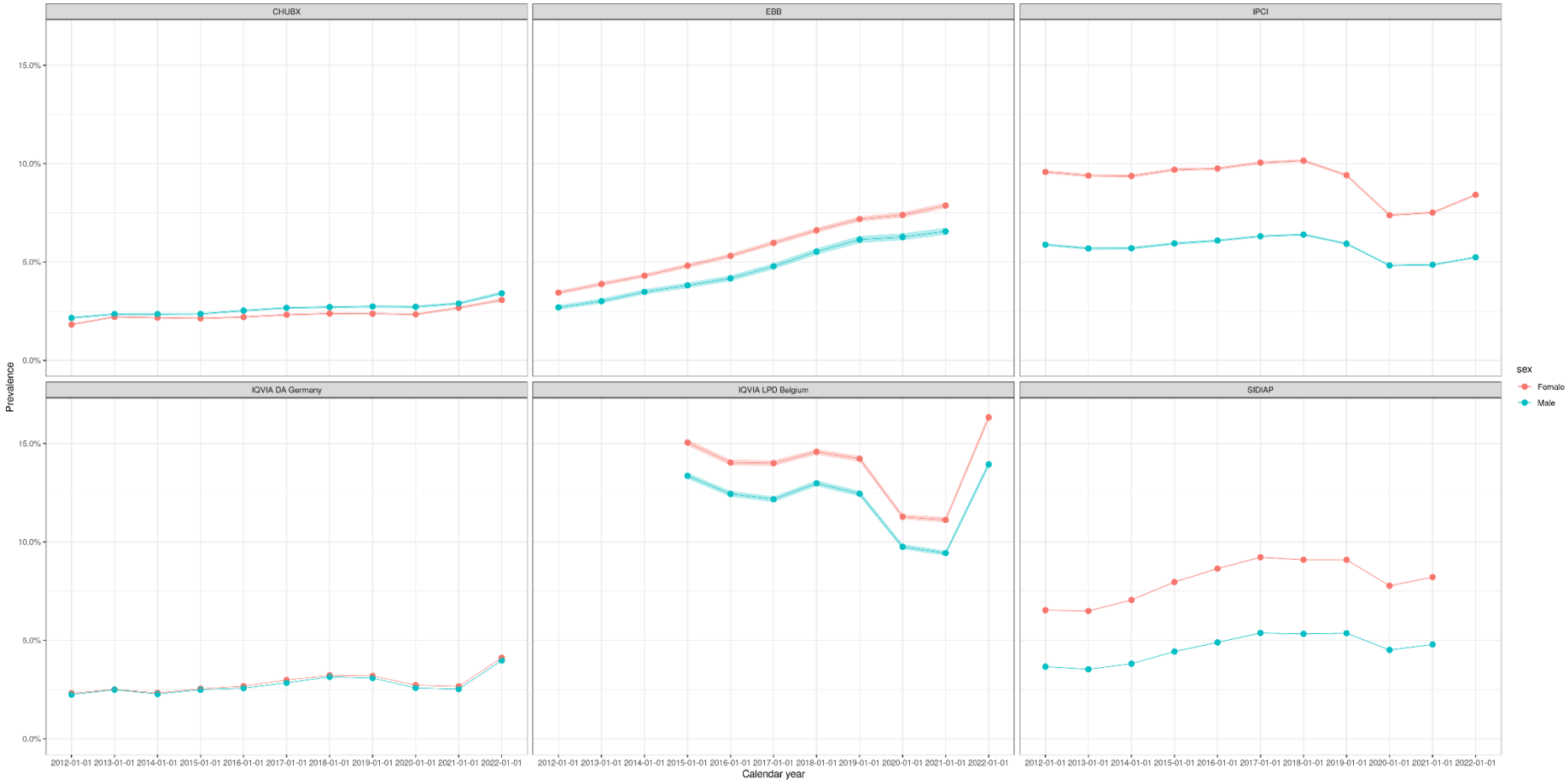


Figure 12.1.4.38 - Prevalence of transdermal opioid use between 2012 and 2022 stratified by sex.

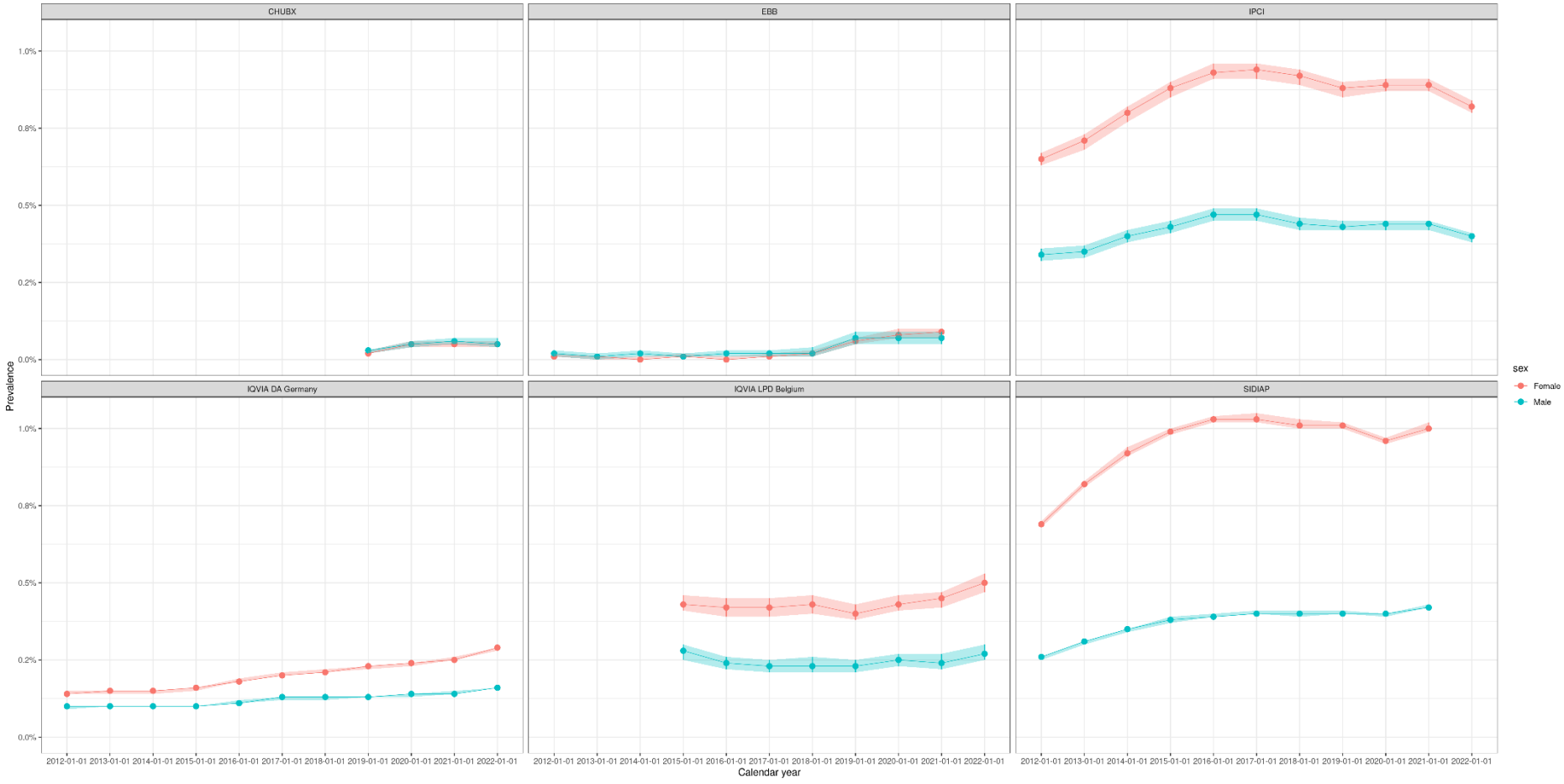


Figure 12.1.4.39 - Prevalence of parenteral opioids between 2012 and 2022 stratified by sex.

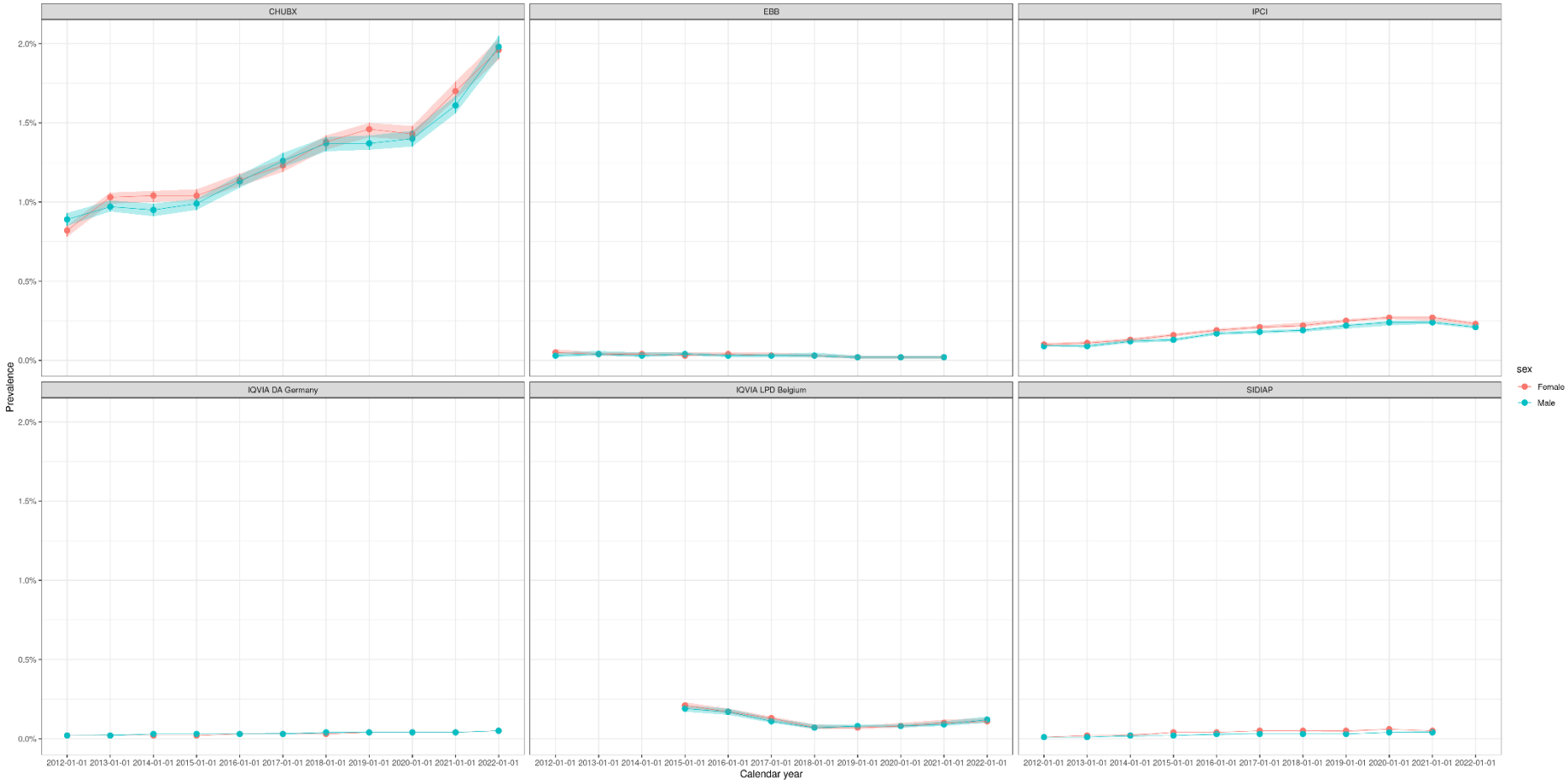


Figure 12.1.4.40- Prevalence of weak opioids between 2012 and 2022 stratified by sex.

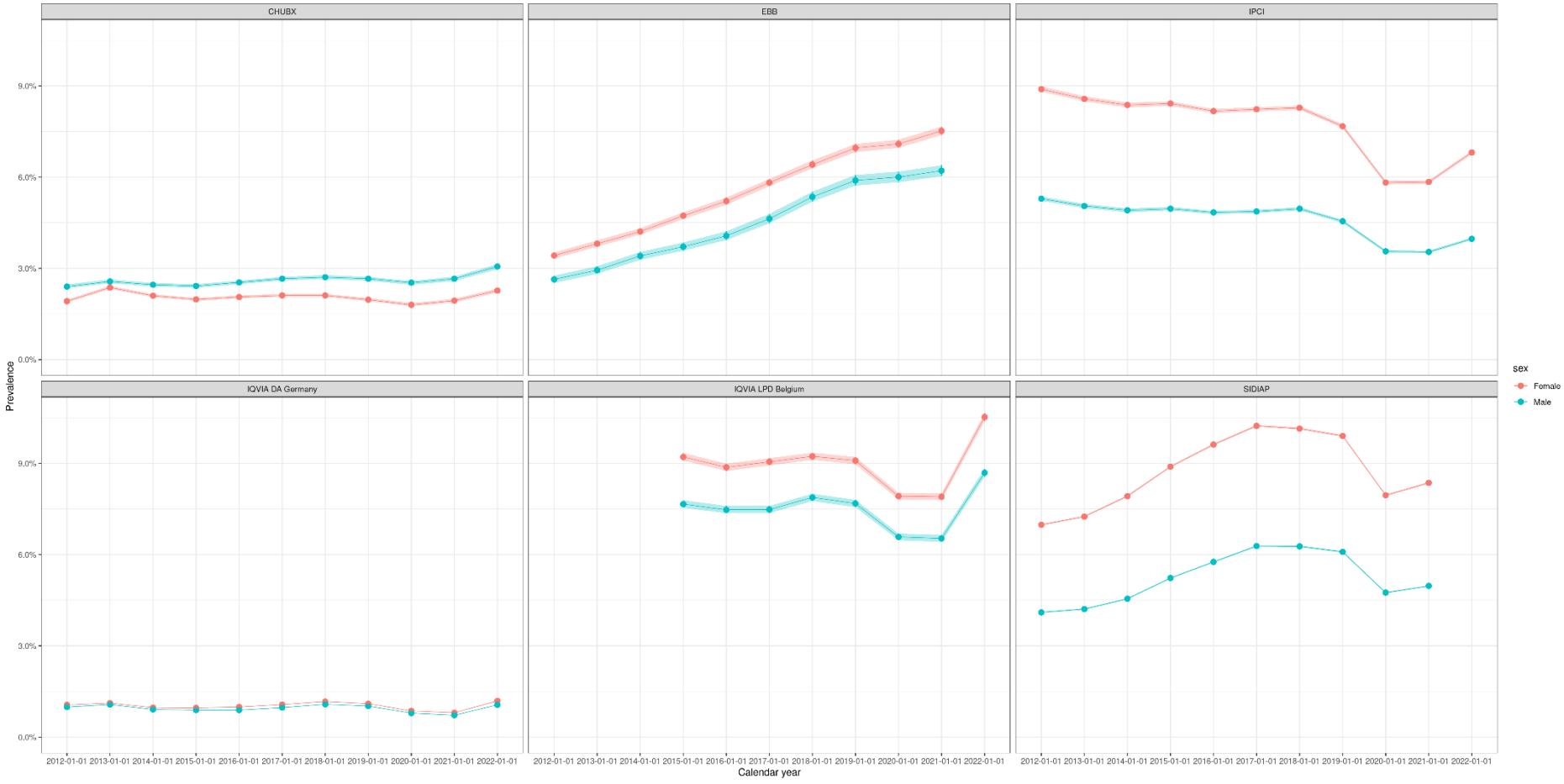


Figure 12.1.4.41- Prevalence of potent opioids between 2012 and 2022 stratified by sex.

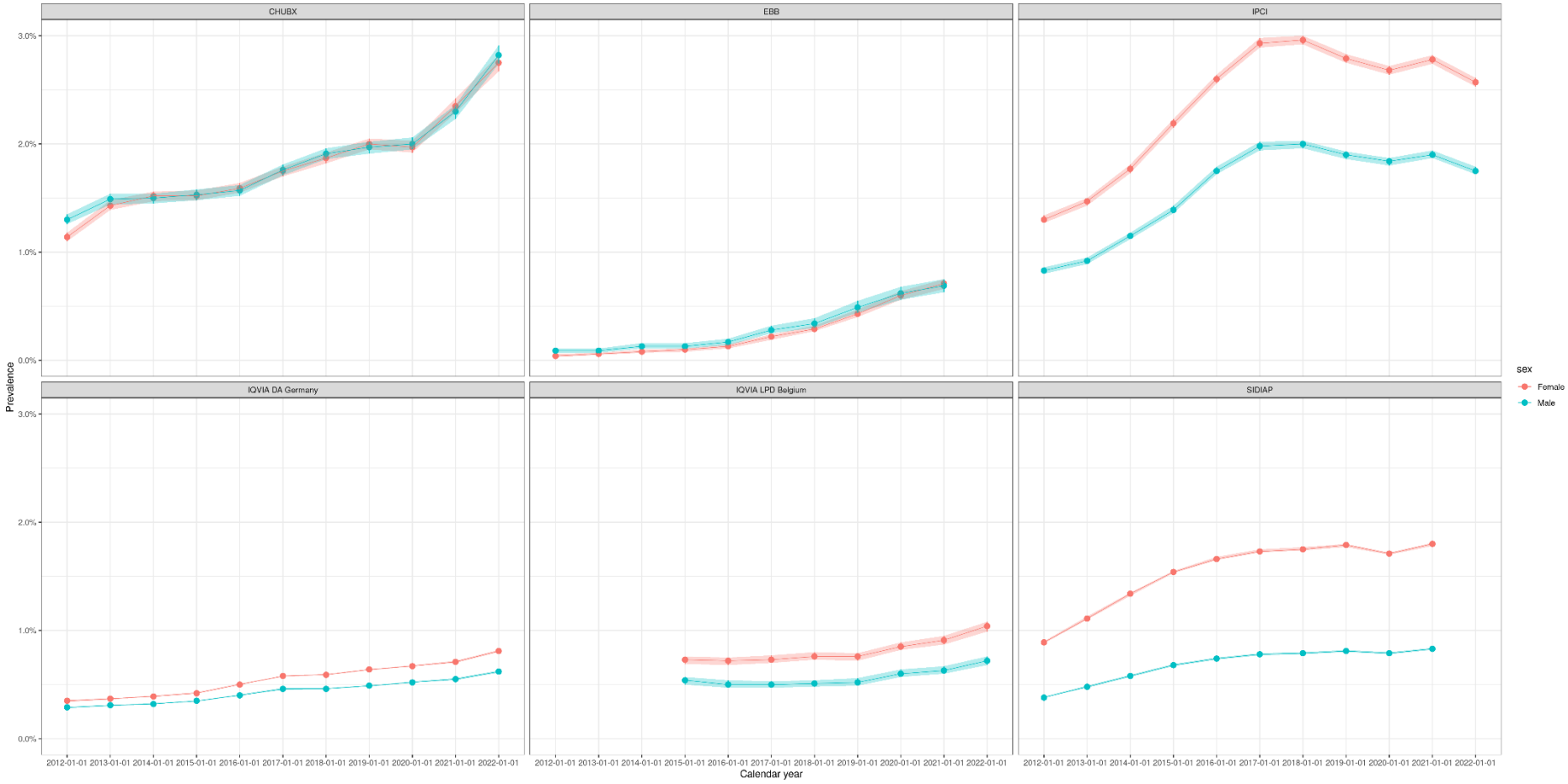
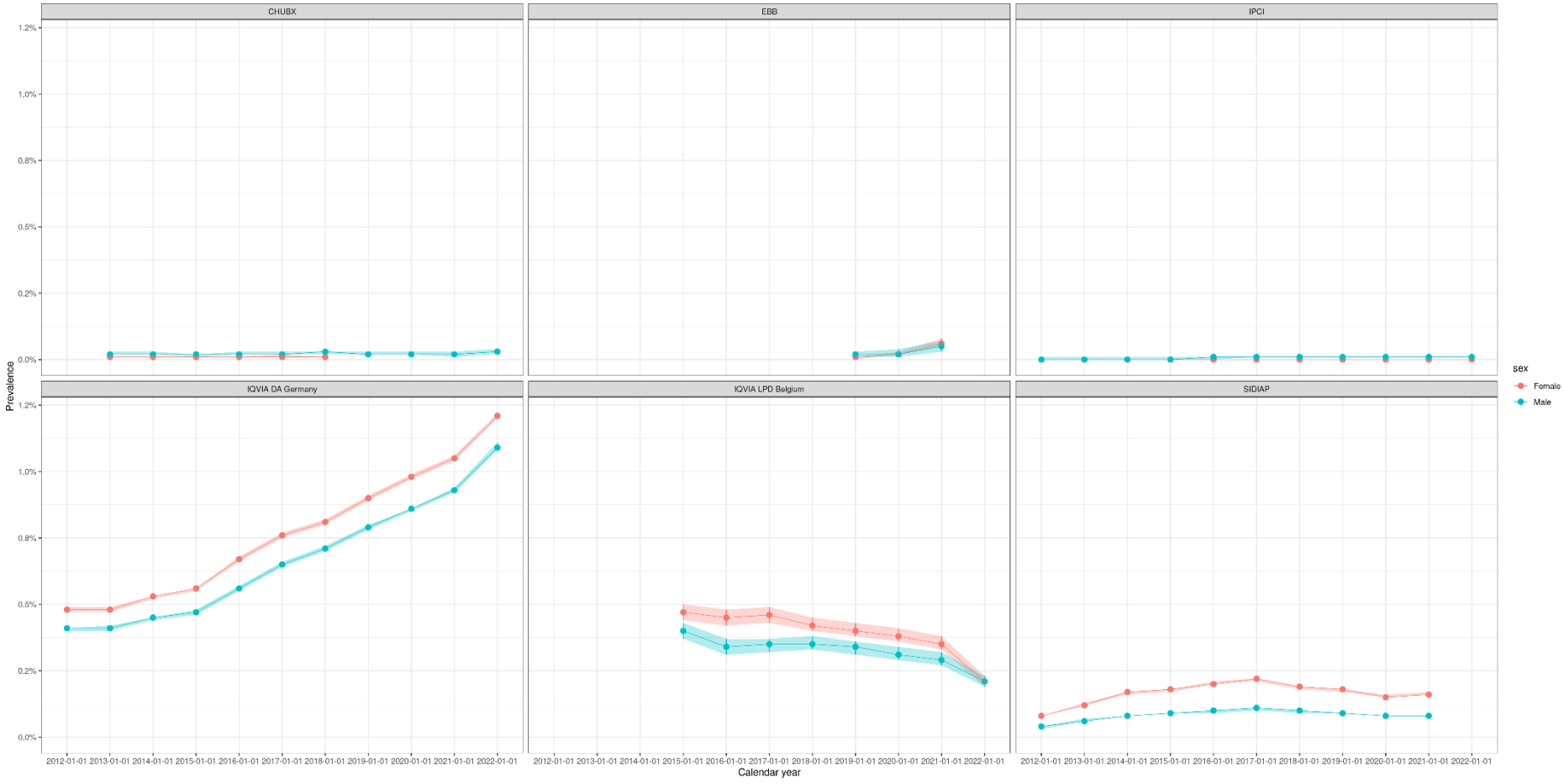


Figure 12.1.4.42- Prevalence of naloxone use between 2012 and 2022 stratified by sex.



12.1.5 Other Analysis

Additional analyses including stratifications for calendar year, or sensitivity analyses using a shorter washout period of 180 days to define "new users" for incidence rate estimation are presented in the shiny web application at https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access

12.2. Patient-level DUS

The main results from patient-level opioid and naloxone utilisation for new drug users are presented below. Additional analyses including stratifications for calendar year, or sensitivity analyses using a shorter washout period of 180 days to define "new users" are presented in the shiny web application at https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access

12.2.1. Participants

Between 2012 and 2022, more than 3.6 million people as captured in the 6 participating databases in this study started treatment with opioids. New users were defined as having at least one prescription of an opioid, without being opioid users in the year before treatment start. A total of 138,171 new opioid users from the inpatient setting were included from CHUBX [France]. In addition, 53,344 new opioid users were included from the EBB [Estonia], and 440,849; 1,248,388; 207,754 and 2,023,867 from primary care and outpatient specialist practices from IPCI [The Netherlands], IQVIA DA Germany [Germany], IQVIA LPD Belgium [Belgium] and SIDIAP [Catalonia, Spain]

12.2.2. Descriptive Data

Demographic Characteristics

Demographic characteristics (age, sex) of new opioid users during the whole study period are presented in Tables 12.2.2.1 – 12.2.2.4. Median age of new opioid users ranged between 50 and 57 across all databases. Users of transdermal or injectable opioids tended to be older than users of oral opioids. The average age was also higher in people who were prescribed potent opioids compared to weak opioids. However, opioid prescriptions were also reported for children.

More women than men were prescribed opioids in primary care (56-60% were women in IPCI, IQVIA DA Germany, IQVIA LPD Belgium and SIDIAP) and EBB (69% women). No difference in prescribing of any opioids between women and men was seen in hospital data from CHUBX.

Demographic characteristics (age, sex) of new naloxone users during the whole study period are presented in Table 12.2.2.5. Median age of new naloxone users ranged between 52 and 69 across all databases. More male naloxone users than female users were included from CHUBX and IPCI, whereas fewer men than women initiated naloxone in the other databases.

Characteristics stratified for calendar year are available in the web application (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access), as are characteristics of less frequently used opioids and sensitivity analyses (180days washout period prior to treatment start).

Treatment duration

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Treatment duration is presented as the duration of the first continuous treatment episode for a person in Tables 12.2.2.6 - 12.2.2.9. Treatment duration varied greatly by setting: Median duration of any new opioid prescription was 2 days in the hospital database from CHUBX, with treatment durations for the most common individual substances ranging between an median duration of 1 day for morphine and 8 days for buprenorphine (Table 12.2.2.9)

For primary care and outpatient specialist care settings, the median treatment duration for any opioid ranged between 9 days for LPD Belgium and 20 days for IQVIA DA Germany. For the EBB, the default duration for all prescriptions were set to 30days in the database, with more details on the actual prescription duration only becoming available in 2021. Therefore, the median duration is 30days for the overall study period 2012-2022 for EBB.

Treatment duration varied greatly for different opioid substances, typically displaying a week, 2 weeks or a month of treatment. In SIDIAP, average treatment durations for potent opioids were substantially longer than for weak opioids, with median durations of 75 days vs. 11 days, respectively. Moreover, treatment durations in outpatient care for transdermal opioids were longer than for oral opioids and injections.

Table 12.2.2.1 – Demographic characteristics of new users of opioids, overall

			Database					
Variable	**Level**	**Format**	CHUBX	EBB	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
number subjects		N	138,171	53,344	440,849	1,248,388	207,754	2,023,867
number records		N	166,275	76,111	609,727	1,638,442	294,219	3,007,253
age		median [q25 - q75]	57 [37 - 72]	54 [42 - 65]	57 [43 - 70]	54 [32 - 70]	50 [34 - 64]	55 [40 - 70]
sex	Female	N (%)	84,635 (50.90)	52,659 (69.19)	366,540 (60.12)	936,414 (57.15)	163,545 (55.59)	1,773,685 (58.98)
	Male	N (%)	81,638 (49.10)	23,452 (30.81)	243,187 (39.88)	700,624 (42.76)	130,674 (44.41)	1,233,568 (41.02)
	Missing	N (%)	<20 (NA)	NA	NA	1,404 (0.09)	NA	NA

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Table 12.2.2.2 – Demographic characteristics of new users of opioids between 2012 - 2022, by route of administration

Variable	Level	Format	Database					
			CHUBX	EBB	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
Oral								
number subjects		N	100,639	53,242	431,317	1,220,862	205,017	1,619,726
number records		N	117,856	75,903	596,907	1,603,128	290,242	2,283,741
age		median [q25 - q75]	58 [39 - 73]	54 [42 - 65]	57 [42 - 70]	54 [31 - 69]	50 [34 - 64]	58 [43 - 72]
sex	Female	N (%)	59,390 (50.39)	52,496 (69.16)	359,432 (60.22)	914,649 (57.05)	161,113 (55.51)	1,373,068 (60.12)
	Male	N (%)	58,465 (49.61)	23,407 (30.84)	237,475 (39.78)	687,259 (42.87)	129,129 (44.49)	910,673 (39.88)
	Missing	N (%)	<20 (NA)	NA	NA	1,220 (0.08)	NA	NA
Parenteral (injection)								
number subjects		N	58,543	390	21,686	22,275	2,777	19,062
number records		N	66,026	452	22,034	24,366	3,051	19,213
age		median [q25 - q75]	58 [35 - 75]	60 [51 - 69]	76 [62 - 86]	76 [59 - 85]	57 [43 - 71]	86 [77 - 91]
sex	Female	N (%)	35,148 (53.23)	310 (68.58)	11,863 (53.84)	13,455 (55.22)	1,675 (54.90)	11,621 (60.49)
	Male	N (%)	30,877 (46.76)	142 (31.42)	10,171 (46.16)	10,680 (43.83)	1,376 (45.10)	7,592 (39.51)
	Missing	N (%)	<20 (NA)	NA	NA	231 (0.95)	NA	NA
Transdermal								
number subjects		N	698	458	41,034	62,722	5,894	163,872
number records		N	709	471	44,374	66,926	6,604	178,949
age		median [q25 - q75]	69 [58 - 78]	69 [59 - 77]	76 [65 - 84]	80 [71 - 86]	74 [60 - 84]	76 [64 - 84]
sex	Female	N (%)	356 (50.21)	310 (65.82)	28,227 (63.61)	44,244 (66.11)	4,326 (65.51)	118,285 (66.10)
	Male	N (%)	353 (49.79)	161 (34.18)	16,147 (36.39)	22,502 (33.62)	2,278 (34.49)	60,664 (33.90)
	Missing	N (%)	NA	NA	NA	180 (0.27)	NA	NA

Table 12.2.2.3 – Demographic characteristics of new users of opioids between 2012 - 2022, by potency

Variable	Level	Format	Database					
			CHUBX	EBB	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
Weak Opioids								
number subjects		N	99,010	52,258	370,525	495,208	133,600	1,839,893
number records		N	114,567	74,280	504,910	616,484	178,994	2,714,607
age		median [q25 - q75]	56 [37 - 69]	54 [42 - 65]	56 [42 - 69]	56 [42 - 70]	53 [39 - 65]	56 [41 - 70]
sex	Female	N (%)	54,657 (47.71)	51,431 (69.24)	309,852 (61.37)	361,101 (58.57)	100,788 (56.31)	1,612,357 (59.40)
	Male	N (%)	59,909 (52.29)	22,849 (30.76)	195,058 (38.63)	254,914 (41.35)	78,206 (43.69)	1,102,250 (40.60)
	Missing	N (%)	<20 (NA)	NA	NA	469 (0.08)	NA	NA
Potent Opioids								
number subjects		N	76,748	3,869	139,108	176,110	11,392	270,888
number records		N	88,823	4,179	160,865	197,142	12,992	306,266
age		median [q25 - q75]	59 [40 - 75]	62 [51 - 71]	66 [52 - 78]	75 [61 - 83]	67 [53 - 80]	74 [61 - 83]
sex	Female	N (%)	47,034 (52.95)	2,664 (63.75)	93,731 (58.27)	120,047 (60.89)	7,988 (61.48)	196,871 (64.28)
	Male	N (%)	41,788 (47.05)	1,515 (36.25)	67,134 (41.73)	76,744 (38.93)	5,004 (38.52)	109,395 (35.72)
	Missing	N (%)	<20 (NA)	NA	NA	351 (0.18)	NA	NA

Table 12.2.2.4 – Demographic characteristics of new users of opioids between 2012 - 2022, 8 most frequently prescribed opioids

Variable	Level	Format	Database					
			CHUBX	EBB	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
Buprenorphine								
number subjects		N	1,060	182	11,156	21,645	1,470	39,118
number records		N	1,495	187	11,992	23,285	1,642	41,768
age		median [q25 - q75]	43 [35 - 50]	69 [58 - 78]	75 [62 - 84]	79 [67 - 85]	62 [48 - 77]	75 [62 - 82]
sex	Female	N (%)	310 (20.74)	140 (74.87)	8,646 (72.10)	15,420 (66.22)	1,033 (62.91)	30,705 (73.51)
	Male	N (%)	1,185 (79.26)	47 (25.13)	3,346 (27.90)	7,835 (33.65)	609 (37.09)	11,063 (26.49)
	Missing	N (%)	NA	NA	NA	30 (0.13)	NA	NA
Codeine								
number subjects		N	6,524	37,929	252,061	335,371	78,098	1,079,424
number records		N	6,913	49,981	330,738	418,923	98,520	1,406,449
age		median [q25 - q75]	58 [41 - 70]	54 [41 - 65]	56 [41 - 68]	53 [37 - 66]	50 [35 - 62]	50 [36 - 65]
sex	Female	N (%)	3,256 (47.10)	35,975 (71.98)	209,821 (63.44)	247,553 (59.09)	55,052 (55.88)	822,294 (58.47)
	Male	N (%)	3,657 (52.90)	14,006 (28.02)	120,917 (36.56)	171,158 (40.86)	43,468 (44.12)	584,155 (41.53)
	Missing	N (%)	NA	NA	NA	212 (0.05)	NA	NA
Dextromethorphan								
number subjects		N	24		4,770	24,862	74,604	298,651
number records		N	24		5,621	26,785	88,913	323,151
age		median [q25 - q75]	62 [43 - 74]		53 [40 - 65]	45 [24 - 60]	44 [24 - 61]	49 [30 - 67]
sex	Female	N (%)	<20 (NA)		3,593 (63.92)	14,725 (54.97)	48,650 (54.72)	193,539 (59.89)
	Male	N (%)	<20 (NA)		2,028 (36.08)	12,043 (44.96)	40,263 (45.28)	129,612 (40.11)
	Missing	N (%)	NA		NA	17 (0.06)	NA	NA
Dihydrocodeine								
number subjects		N	80	1,646	<5	258,330	43,195	2,869
number records		N	82	1,821	NA	319,834	52,936	2,996
age		median [q25 - q75]	66 [54 - 78]	57 [47 - 67]	NA [NA - NA]	52 [37 - 65]	51 [37 - 63]	45 [14 - 64]

sex	Female	N (%)	42 (51.22)	1,309 (71.88)	NA (NA)	187,146 (58.51)	30,936 (58.44)	1,768 (59.01)
	Male	N (%)	40 (48.78)	512 (28.12)	NA	132,343 (41.38)	22,000 (41.56)	1,228 (40.99)
	Missing	N (%)	NA	NA	NA	345 (0.11)	NA	NA
Fentanyl								
number subjects		N	1,271	313	35,805	48,516	5,003	146,614
number records		N	1,314	321	38,011	51,131	5,543	157,576
age		median [q25 - q75]	67 [56 - 78]	68 [59 - 77]	76 [65 - 84]	80 [71 - 86]	75 [61 - 84]	76 [64 - 84]
sex	Female	N (%)	616 (46.88)	194 (60.44)	23,306 (61.31)	32,916 (64.38)	3,613 (65.18)	99,585 (63.20)
	Male	N (%)	698 (53.12)	127 (39.56)	14,705 (38.69)	18,050 (35.30)	1,930 (34.82)	57,991 (36.80)
	Missing	N (%)	NA	NA	NA	165 (0.32)	NA	NA
Morphine								
number subjects		N	64,512	580	35,187	35,829	1,426	68,123
number records		N	73,325	608	36,713	38,462	1,508	70,097
age		median [q25 - q75]	59 [38 - 75]	65 [56 - 74]	72 [57 - 83]	75 [60 - 84]	71 [57 - 84]	78 [65 - 87]
sex	Female	N (%)	39,700 (54.14)	347 (57.07)	20,420 (55.62)	21,976 (57.14)	889 (58.95)	35,739 (50.99)
	Male	N (%)	33,624 (45.86)	261 (42.93)	16,293 (44.38)	16,332 (42.46)	619 (41.05)	34,358 (49.01)
	Missing	N (%)	<20 (NA)	NA	NA	154 (0.40)	NA	NA
Noscapine								
number subjects		N			25,887	307,830	3,280	3,415
number records		N			27,669	378,373	3,560	3,462
age		median [q25 - q75]			49 [16 - 68]	11 [5 - 44]	51 [34 - 64]	4 [2 - 11]
sex	Female	N (%)			16,717 (60.42)	201,060 (53.14)	1,954 (54.89)	1,811 (52.31)
	Male	N (%)			10,952 (39.58)	177,141 (46.82)	1,606 (45.11)	1,651 (47.69)
	Missing	N (%)			NA	172 (0.05)	NA	NA
Oxycodone								
number subjects		N	25,762	3,267	107,151	70,108	6,454	41,190
number records		N	27,977	3,519	122,233	76,579	7,213	43,853
age		median [q25 - q75]	66 [51 - 79]	61 [50 - 70]	64 [50 - 75]	72 [59 - 81]	63 [51 - 75]	70 [57 - 79]
sex	Female	N (%)	14,193 (50.73)	2,252 (64.00)	70,580 (57.74)	46,145 (60.26)	4,234 (58.70)	29,111 (66.38)
	Male	N (%)	13,784 (49.27)	1,267 (36.00)	51,653 (42.26)	30,355 (39.64)	2,979 (41.30)	14,742 (33.62)

	Missing	N (%)	NA	NA	NA	79 (0.10)	NA	NA

Table 12.2.2.5 – Demographic characteristics of people with new naloxone prescriptions between 2012 - 2022

			Database					
Variable	**Level**	**Format**	CHUBX	EBB	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
number subjects		N	643	180	197	308,979	4,865	34,432
number records		N	726	181	214	356,912	5,497	36,679
age		median [q25 - q75]	52 [38 - 77]	64 [50 - 74]	52 [40 - 63]	68 [55 - 79]	58 [46 - 71]	69 [56 - 79]
sex	Female	N (%)	254 (34.99)	122 (67.40)	68 (31.78)	212,469 (59.53)	3,340 (60.76)	24,179 (65.92)
	Male	N (%)	472 (65.01)	59 (32.60)	146 (68.22)	144,057 (40.36)	2,157 (39.24)	12,500 (34.08)
	Missing	N (%)	NA	NA	NA	386 (0.11)	NA	NA

Table 12.2.2.6 – Treatment duration of opioids between 2012 - 2022, overall

			Database					
Variable	**Level**	**Format**	CHUBX	EBB*	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
duration (days)		median [q25 - q75]	2 [1 - 5]	30 [30 - 30]	10 [7 - 15]	20 [7 - 30]	9 [5 - 25]	11 [7 - 31]
		range [min - max]	1 - 1,530	1 - 3,644	1 - 4,018	1 - 4,018	1 - 3,190	1 - 3,834

Table 12.2.2.7 – Treatment duration of opioids between 2012 - 2022, by route of administration

			Database					
Variable	**Level**	**Format**	CHUBX	EBB*	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
			Oral					
duration (days)		median [q25 - q75]	3 [1 - 6]	30 [30 - 30]	10 [7 - 15]	20 [7 - 30]	9 [5 - 25]	15 [7 - 56]
		range [min - max]	1 - 1,530	1 - 3,644	1 - 4,018	1 - 4,018	1 - 3,190	1 - 3,834
			Parenteral (injection)					
duration (days)		median [q25 - q75]	1 [1 - 1]	30 [30 - 30]	19 [7 - 43]	4 [2 - 4]	10 [6 - 35]	8 [5 - 13]
		range [min - max]	1 - 1,108	1 - 335	1 - 1,979	1 - 2,721	1 - 912	1 - 2,179
			Transdermal					
duration (days)		median [q25 - q75]	4 [1 - 9]	30 [26 - 53]	27 [15 - 55]	30 [30 - 60]	10 [5 - 30]	86 [30 - 230]
		range [min - max]	1 - 657	1 - 469	1 - 4,018	1 - 2,383	1 - 432	1 - 3,834

Table 12.2.2.8 – Treatment duration for new users of opioids between 2012 - 2022, by potency

Variable	Level	Format	Database					
			CHUBX	EBB*	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
Weak Opioids								
duration (days)		median [q25 - q75]	2 [1 - 4]	30 [30 - 30]	10 [8 - 15]	10 [1 - 20]	12 [6 - 30]	11 [7 - 31]
		range [min - max]	1 - 505	1 - 1,705	1 - 4,018	1 - 4,018	1 - 3,190	1 - 3,834
Potent Opioids								
duration (days)		median [q25 - q75]	1 [1 - 5]	30 [30 - 30]	15 [7 - 32]	30 [20 - 53]	15 [9 - 30]	75 [29 - 199]
		range [min - max]	1 - 1,742	1 - 3,644	1 - 4,018	1 - 4,018	1 - 1,557	1 - 3,834

Table 12.2.2.9 – Treatment duration for new users of opioids between 2012 - 2022, 8 most frequent opioids and naloxone

Variable	Level	Format	Database					
			CDW Bordeaux	EBB*	IPCI	IQVIA DA Germany	IQVIA LPD Belgium	SIDIAP
Buprenorphine								
duration (days)		median [q25 - q75]	8 [3 - 34]	30 [30 - 58]	28 [14 - 67]	30 [30 - 57]	10 [7 - 30]	61 [21 - 215]
		range [min - max]	1 - 1,165	3 - 469	1 - 2,830	1 - 3,286	1 - 360	1 - 3,834
Codeine								
duration (days)		median [q25 - q75]	3 [1 - 6]	30 [15 - 30]	10 [8 - 15]	8 [1 - 20]	7 [4 - 20]	7 [6 - 11]
		range [min - max]	1 - 505	1 - 1,065	1 - 1,959	1 - 4,018	1 - 1,818	1 - 3,834
Dextromethorphan								
duration (days)		median [q25 - q75]	2 [1 - 4]		14 [5 - 14]	7 [7 - 12]	6 [4 - 9]	8 [6 - 21]
		range [min - max]	1 - 11		1 - 662	1 - 4,018	1 - 819	1 - 3,817
Dihydrocodeine								
duration (days)		median [q25 - q75]	3 [2 - 5]	30 [30 - 30]	NA [NA - NA]	30 [30 - 30]	7 [6 - 20]	8 [6 - 21]
		range [min - max]	1 - 275	1 - 620	NA - NA	1 - 2,722	1 - 645	1 - 1,192

Fentanyl								
duration (days)		median [q25 - q75]	4 [1 - 9]	30 [18 - 50]	23 [14 - 50]	30 [30 - 60]	10 [5 - 30]	89 [31 - 225]
		range [min - max]	1 - 657	1 - 446	1 - 4,018	1 - 2,383	1 - 432	1 - 3,834
Morphine								
duration (days)		median [q25 - q75]	1 [1 - 3]	30 [30 - 40]	15 [7 - 34]	13 [4 - 30]	15 [7 - 56]	33 [11 - 91]
		range [min - max]	1 - 1,109	1 - 602	1 - 2,078	1 - 4,018	1 - 912	1 - 3,834
Noscapine								
duration (days)		median [q25 - q75]			12 [7 - 14]	7 [4 - 10]	5 [4 - 7]	8 [6 - 21]
		range [min - max]			1 - 438	1 - 462	1 - 387	1 - 643
Oxycodone								
duration (days)		median [q25 - q75]	3 [1 - 8]	30 [30 - 30]	12 [6 - 24]	25 [20 - 50]	28 [9 - 30]	69 [29 - 175]
		range [min - max]	1 - 1,519	1 - 1,706	1 - 3,909	1 - 4,018	1 - 1,118	1 - 3,834
Naloxone								
duration (days)		median [q25 - q75]	1 [1 - 7]	20 [10 - 30]	23 [12 - 89]	25 [10 - 50]	26 [10 - 60]	68 [29 - 176]
		range [min - max]	1 - 433	1 - 190	1 - 1,099	1 - 4,018	1 - 2,721	1 - 3,834

12.2.3. Outcome Data

See section 12.2.4 “Main Results” below.

12.2.4. Main Results

Indication

As a proxy for “indication”, we evaluated the 50 most frequent co-morbidities recorded at the day of a new opioid prescription (window “0”), in week (7days) before start of new opioid treatment (window “7”) and in the month (30days) before start of new opioid treatment (window “30”). Out of those, the 10 most frequent conditions that could be proxies for potential indications were selected.

Tables 12.2.4.1 – 12.2.4.15 present potential indications for opioids including surgery/procedures and related complications, headache, abdominal pain, chest pain, and cancer separately for each database. Table 12.2.4.16 presents potential indications for naloxone including opioid overdose, drug abuse or opioid dependence across all databases.

Overall, there was a high degree of missingness of recordings of potential indication. Among those conditions that could require opioid treatment and therefore can be considered as potential indications, predominant conditions varied by setting, opioid potency and route of administration.

Hospital diagnoses included “complications of surgical procedures” and localized pain.

For the EBB, most common relevant conditions were pain-related comorbidities such as “pain in spine”, “low back pain”, “osteoarthritis”, “polyarthropathy” and nerve root disorders for all routes of administration. Chronic intractable pain was a common condition recorded before start of treatment with potent opioids. Additional indications of respiratory conditions were seen for oral preparations and weak opioids, including “cough” and “acute upper respiratory infections”.

For primary care and outpatient specialist care databases, both “cough” and “acute upper respiratory infections” and pain-related conditions (i.e. back pain, joint pain, abdominal pain, traumatic injury) were among the most commonly recorded conditions indicating potential indications.

Cough-related conditions were frequently recorded prior to treatment initiation with codeine (e.g. 20% in IQVIA DA Germany), whereas pain-related conditions were frequently recorded before tramadol and the potent opioids morphine and oxycodone (e.g. 6.5% and 9.4% “chronic pain”, respectively).

For naloxone, hospital records frequently included conditions requiring naloxone use such as “Coma”, “Acute hypoxemic respiratory failure”, “Poisoning by psychotropic agent”, “Poisoning caused by opioid receptor agonist” and “Morphine overdose”. No specific indication were recorded in EBB, IQVIA Germany and IQVIA Belgium.

For ICPI, “Substance abuse” and “drug dependence” were commonly recorded prior to naloxone prescription. Opioid dependence was also recorded in SIDIAP prior to naloxone treatment.

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Large-Scale Patient Characterisation

Results from large scale characterization are presented in the interactive web application for all new opioid users overall, individual opioids in each database, by strength, and by route. Analyses were conducted separately for new users without previous prescriptions of the same opioid/route/potency within 180 and 365days before treatment start (https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access). A summary of findings is provided as follows:

Co-morbidities

Within 6 months prior to the initiation of opioids (any), chronic conditions such as cardiovascular disease, hypertension, hyperlipidemia, type 2 diabetes were most frequently recorded. For CHUBX, electrolyte imbalances, nausea/vomiting and constipation were common. In primary care and outpatient specialist care databases, potential indications for opioid treatment, including respiratory disease and cough, as well as back- and shoulder problems, pain and injury were among the most commonly recorded conditions alongside chronic cardiovascular conditions, diseases for the digestive track, sleep disorders and depression.

No substantial differences in the most common co-morbidities were seen for weak and potent opioids within the respective databases. Comorbidities for people with new prescriptions of oral opioids were comparable to overall opioid users. For parenteral opioid users in IPCI, more severe conditions (e.g. malignant tumor) and general health deterioration, fatigue and chronic pain were recorded compared to oral opioids.

Co-medication

The most common co-medication within the 6 months prior to start of new opioids (any) are non-opioid pain killers such as NSAIDs or acetaminophen. Heparin, proton pump inhibitors, electrolytes and cardiovascular drugs are commonly co-prescribed in the hospital setting. In the outpatient setting, amoxicillin, vitamin D, levothyroxine and corticosteroids were prescribed in addition to the previously mentioned drug classes.

When focused on potent opioids and weak opioids, similar comedications are being seen for both groups, except for tramadol and codeine being prescribed prior to potent opioids, and morphine prior to weak opioids in hospital.

No major differences were seen between injectables, oral and transdermal opioids. Tramadol, fentanyl, zopiclone and oxycodone were prescribed prior to injectable opioids, and tramadol and morphine were prescribed in hospital before initiation of oral and transdermal opioids. Gabapentin was commonly prescribed in EBB prior to transdermal opioids.

Table 12.2.4.1 – **CHUBX:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Opioids (overall)		Parenteral		Oral		Transdermal	
Window	**Concept**	**%**	**Concept**	**%**	**Concept**	**%**	**Concept**	**%**
0	Headache	2.73	Complication of surgical procedure	3.00	Headache	2.48	Acquired absence of organ	3.82
	Complication of surgical procedure	2.66	Abdominal pain	2.78	Complication of surgical procedure	2.45	Anaemia in neoplastic disease	3.39
	Complication of procedure	2.38	Complication of procedure	2.52	Complication of procedure	2.2	Abdominal pain	3.25
	Acquired absence of organ	2.29	Acquired absence of organ	2.45	Acquired absence of organ	2.17	Complication of surgical procedure	2.97
	Coronary artery graft present	2.13	Acute pain	2.42	Coronary artery graft present	2.12	Complication of procedure	2.83
	Abdominal pain	2.08	Headache	1.79	Generalized ischemic myocardial dysfunction	1.66	Complication of procedure	2.83
	Low back pain	1.65	Coronary artery graft present	1.73	Low back pain	1.53		
	Acute pain	1.64	Low back pain	1.57	Chest pain	1.43		
	Generalized ischemic myocardial dysfunction	1.63	Secondary malignant neoplasm of bone	1.46	Acute pain	1.24		
	Chest pain	1.52	Acute abdomen	1.37	Pain in lower limb	1.22		
7	Complication of surgical procedure	6.44	Complication of surgical procedure	7.10	Complication of surgical procedure	7.66	Abdominal pain	12.87
	Complication of procedure	6.21	Complication of procedure	6.76	Complication of procedure	7.31	Acquired absence of organ	11.88
	Headache	5.45	Abdominal pain	6.17	Headache	6.18	Complication of procedure	10.89
	Acquired absence of organ	5.02	Acquired absence of organ	5.61	Acquired absence of organ	5.52	Secondary malignant neoplasm of bone	10.18
	Abdominal pain	4.4	Acute pain	5.29	Coronary artery graft present	4.89	Complication of surgical procedure	10.04
	Coronary artery graft present	4.4	Headache	3.83	Generalized ischemic myocardial dysfunction	4.2	Secondary malignant neoplasm of liver and intrahepatic bile duct	10.04
	Generalized ischemic myocardial dysfunction	3.77	Coronary artery graft present	3.58	Abdominal pain	4.01	Chronic pain	9.48
	Acute pain	3.51	Secondary malignant neoplasm of liver and intrahepatic bile duct	3.18	Chest pain	3.9	Chronic neuropathic pain	9.19
	Chest pain	3.29	Low back pain	3.06	Acute pain	3.86	Inflammatory disorder of digestive tract	8.91
	Low back pain	2.94	Generalized ischemic myocardial dysfunction	3.05	Low back pain	3.4	Secondary malignant neoplasm of lung	8.35
30	Complication of procedure	6.87	Complication of procedure	7.97	Complication of procedure	8.33	Abdominal pain	20.23
	Complication of surgical procedure	6.82	Complication of surgical procedure	7.9	Complication of surgical procedure	8.32	Anemia in neoplastic disease	18.81
	Headache	5.98	Abdominal pain	7.29	Headache	6.87	Acquired absence of organ	15.13

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	Acquired absence of organ	5.42	Acquired absence of organ	6.46	Acquired absence of organ	6.06	Complication of procedure	14.99
	Abdominal pain	4.92	Acute pain	5.83	Coronary artery graft present	5.22	Secondary malignant neoplasm of bone	13.01
	Coronary artery graft present	4.66	Headache	4.66	Abdominal pain	4.78	Complication of surgical procedure	13.01
	Generalized ischemic myocardial dysfunction	4.17	Coronary artery graft present	4.05	Generalized ischemic myocardial dysfunction	4.68	Secondary malignant neoplasm of liver and intrahepatic bile duct	12.59
	Chest pain	3.72	Anaemia in neoplastic disease	3.99	Chest pain	4.52	Inflammatory disorder of digestive tract	12.31
	Acute pain	3.69			Acute pain	4.2	Malignant adenomatous neoplasm	12.31
	Low back pain	3.19			Low back pain	3.77	Chronic pain	12.16

Table 12.2.4.2 – **CHUBX:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
Window	**Concept**	**%**	**Concept**	**%**	**Concept**	**%**
0	Complication of surgical procedure	2.91	Complication of surgical procedure	2.77	Complication of surgical procedure	3.66
	Acquired absence of organ	2.66	Complication of procedure	2.51	Acquired absence of organ	3.39
	Complication of procedure	2.62	Acquired absence of organ	2.47	Secondary malignant neoplasm of bone	3.16
	Abdominal pain	2.25	Abdominal pain	2.23	Complication of procedure	2.84
	Headache	2.1	Acute pain	2.13	Headache	2.69
	Coronary artery graft present	1.91	Low back pain	1.75	Coronary artery graft present	2.4
	Low back pain	1.9	Coronary artery graft present	1.73	Secondary malignant neoplasm of liver and intrahepatic bile duct	2.38
	Secondary malignant neoplasm of bone	1.66	Headache	1.72	Abdominal pain	2.07
	Chest pain	1.48	Chest pain	1.42	Secondary malignant neoplasm of lung	2.07
	Generalized ischemic myocardial dysfunction	1.46	Generalized ischemic myocardial dysfunction	1.37	Adverse effect of prosthetic device	1.99
7	Complication of surgical procedure	7.56	Complication of surgical procedure	7.12	Complication of surgical procedure	11.74
	Complication of procedure	7.17	Complication of procedure	6.93	Complication of procedure	9.76
	Acquired absence of organ	5.98	Acquired absence of organ	5.53	Acquired absence of organ	9.02
	Abdominal pain	5.16	Abdominal pain	4.97	Abdominal pain	6.42
	Acute pain	4.84	Acute pain	4.93	Headache	6.29
	Headache	4.58	Headache	3.92	Acute pain	5.78
	Coronary artery graft present	4.04	Coronary artery graft present	3.69	Coronary artery graft present	5.78

	Low back pain	3.58	Low back pain	3.36	Adverse effect of prosthetic device	5.45
	Pain in lower limb	3.43	Generalized ischemic myocardial dysfunction	3.18	Secondary malignant neoplasm of bone	5.36
	Generalized ischemic myocardial dysfunction	3.43	Chest pain	3.17	Anemia in neoplastic disease	5.29
30	Complication of surgical procedure	8.28	Complication of procedure	8.04	Complication of surgical procedure	13.53
	Complication of procedure	8.25	Complication of surgical procedure	7.87	Complication of procedure	12.03
	Acquired absence of organ	6.64	Acquired absence of organ	6.24	Acquired absence of organ	10.31
	Abdominal pain	6.06	Abdominal pain	5.85	Abdominal pain	8.29
	Headache	5.31	Acute pain	5.38	Headache	7.53
	Acute pain	5.2	Headache	4.67	Acute pain	6.76
	Coronary artery graft present	4.48	Coronary artery graft present	4.14	Anemia in neoplastic disease	6.66
	Generalized ischemic myocardial dysfunction	4.08	Generalized ischemic myocardial dysfunction	3.85	Coronary artery graft present	6.61
	Low back pain	4.05	Low back pain	3.84	Adverse effect of prosthetic device	6.26
	Pain in lower limb	4	Generalized ischemic myocardial dysfunction	3.18	Secondary malignant neoplasm of bone	5.93

Table 12.2.4.3 – **CHUBX:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		Codeine		Tramadol	
Window	**Concept**	**%**	**Concept**	**%**	**Concept**	**%**
0	Complication of surgical procedure	2.74	Headache	2.38	Complication of surgical procedure	2.80
	Headache	2.61	Acquired absence of organ	2.33	Headache	2.59
	Complication of procedure	2.27	Joint pain	1.82	Complication of procedure	2.30
	Coronary artery graft present	2.05	Coronary artery graft present	1.81	Coronary artery graft present	2.05
	Acquired absence of organ	1.87	Low back pain	1.51	Acquired absence of organ	1.85
	Abdominal pain	1.63	Generalized ischemic myocardial dysfunction	1.45	Abdominal pain	1.65
	Generalized ischemic myocardial dysfunction	1.48	Cough	1.43	Generalized ischemic myocardial dysfunction	1.47
	Adverse effect of prosthetic device	1.23	Complication of procedure	1.35	Adverse effect of prosthetic device	1.24
	Chest pain	1.22	Chest pain	1.27	Chest pain	1.21
	Low back pain	1.15	Malignant adenomatous neoplasm	1.23	Low back pain	1.12
7	Complication of surgical procedure	7.73	Headache	6.91	Complication of surgical procedure	7.89
	Complication of procedure	7.16	Acquired absence of organ	6.39	Complication of procedure	7.26
	Headache	5.73	Complication of procedure	5.53	Headache	5.67
	Acquired absence of organ	5.11	Complication of surgical procedure	4.76	Acquired absence of organ	5.1
	Coronary artery graft present	4.69	Coronary artery graft present	4.75	Coronary artery graft present	4.68

	Abdominal pain	4.29	Cough	4.46	Abdominal pain	4.37
	Generalized ischemic myocardial dysfunction	3.81	Chest pain	4.43	Generalized ischemic myocardial dysfunction	3.81
	Acute pain	3.31	Anemia in neoplastic disease	4.36	Acute pain	3.31
	Chest pain	3.22	Acute pain	4.2	Chest pain	3.19
	Adverse effect of prosthetic device	2.8	Malignant adenomatous neoplasm	4.14	Adverse effect of prosthetic device	2.85
30	Complication of surgical procedure	8.30	Headache	8.17	Complication of surgical procedure	8.46
	Complication of procedure	8.00	Complication of procedure	7.82	Complication of procedure	8.11
	Headache	6.28	Acquired absence of organ	7.70	Headache	6.23
	Acquired absence of organ	5.55	Complication of surgical procedure	6.29	Acquired absence of organ	5.53
	Coronary artery graft present	4.93	Cough	5.66	Coronary artery graft present	4.92
	Abdominal pain	4.82	Anemia in neoplastic disease	5.66	Abdominal pain	4.9
	Generalized ischemic myocardial dysfunction	4.2	Chest pain	5.58	Generalized ischemic myocardial dysfunction	4.18
	Chest pain	3.74	Coronary artery graft present	5.37	Chest pain	3.7
	Acute pain	3.62	Acute pain	5.3	Acute pain	3.62
	Adverse effect of prosthetic device	3.04	Generalized ischemic myocardial dysfunction	5.04	Adverse effect of prosthetic device	3.08

Table 12.2.4.4 – **EBB:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Opioids (overall)		Parenteral		Oral		Transdermal	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Nerve root disorder	10.49	Nerve root disorder	17.04	Nerve root disorder	10.48	Chronic intractable pain	23.14
	Cough	8.52	Pain in spine	12.83	Cough	8.55	Nerve root disorder	4.88
	Pain in spine	7.94	Intervertebral disc disorder	12.17	Pain in spine	7.93	Primary malignant neoplasm of prostate	4.03
	Intervertebral disc disorder	5.71	Low back pain	3.98	Intervertebral disc disorder	5.70	Osteoarthritis of hip	4.03
	Low back pain	5.39	Osteoarthritis of knee	3.98	Low back pain	5.39	Chronic pain	3.61
	Osteoarthritis of knee	3.62	Osteoarthritis of hip	3.76	Osteoarthritis of knee	3.62	Spinal stenosis	3.40
	Acute upper respiratory infection	3.19	Polyarthropathy	3.10	Acute upper respiratory infection	3.20	Primary malignant neoplasm of head of pancreas	3.18
	Osteoarthritis of hip	2.54	Lumbago with sciatica	2.88	Osteoarthritis of hip	2.54	Osteoarthritis of knee	2.76
	Polyarthropathy	2.32	Spinal stenosis	2.65	Polyarthropathy	2.32	Primary malignant neoplasm of lung	2.55
	Joint pain	2.15	Arthropathy	1.77	Joint pain	2.15	Primary malignant neoplasm of rectum	2.34
7	Nerve root disorder	11.60	Nerve root disorder	19.91	Nerve root disorder	11.59	Spinal stenosis	5.94
	Pain in spine	9.00	Pain in spine	14.82	Pain in spine	8.98	Chronic intractable pain	23.35

	Cough	8.62	Intervertebral disc disorder	14.16	Cough	8.65	Nerve root disorder	7.43
	Intervertebral disc disorder	6.37	Low back pain	5.97	Intervertebral disc disorder	6.35	Chronic pain	5.73
	Low back pain	6.26	Osteoarthritis of knee	4.87	Low back pain	6.27	Osteoarthritis of hip	4.88
	Osteoarthritis of knee	4.22	Osteoarthritis of hip	4.42	Osteoarthritis of knee	4.22	Primary malignant neoplasm of prostate	4.67
	Acute upper respiratory infection	3.89	Polyarthropathy	4.20	Acute upper respiratory infection	3.91	Anemia in neoplastic disease	3.82
	Osteoarthritis of hip	2.94	Lumbago with sciatica	3.32	Osteoarthritis of hip	2.94	Primary malignant neoplasm of head of pancreas	3.61
	Polyarthropathy	2.73	Spinal stenosis	2.88	Polyarthropathy	2.74	Spondylosis	3.61
	Joint pain	2.64	Inflammatory disorder of digestive tract	2.65	Joint pain	2.64	Intervertebral disc disorder	3.61
30	Nerve root disorder	13.22	Nerve root disorder	23.89	Nerve root disorder	13.21	Chronic intractable pain	24.84
	Pain in spine	10.52	Pain in spine	18.14	Pain in spine	10.49	Nerve root disorder	12.53
	Cough	8.80	Intervertebral disc disorder	16.59	Cough	8.83	Chronic pain	9.34
	Intervertebral disc disorder	7.38	Essential hypertension	12.17	Low back pain	7.38	Spinal stenosis	7.86
	Low back pain	7.37	Low back pain	8.19	Intervertebral disc disorder	7.36	Intervertebral disc disorder	7.22
	Osteoarthritis of knee	5.59	Osteoarthritis of knee	7.08	Osteoarthritis of knee	5.58	Osteoarthritis of hip	6.79
	Acute upper respiratory infection	5.18	with congestive heart failure	6.86	Acute upper respiratory infection	5.20	Inflammatory disorder of digestive tract	6.37
	Osteoarthritis of hip	3.8	Polyarthropathy	5.75	Osteoarthritis of hip	3.8	Osteoarthritis of knee	6.16
	Polyarthropathy	3.69	Inflammatory disorder of digestive tract	5.75	Polyarthropathy	3.7	Polyarthropathy	5.73
	Joint pain	3.58	Osteoarthritis of hip	5.53	Joint pain	3.58	Low back pain	5.31

Table 12.2.4.5 – **EBB:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Chronic intractable pain	12.20	Chronic intractable pain	9.05	Chronic intractable pain	12.45
	Nerve root disorder	6.84	Multiple myeloma	4.61	Nerve root disorder	7.33
	Primary gonarthrosis, bilateral	6.29	Primary malignant neoplasm of prostate	4.44	Primary gonarthrosis, bilateral	7.30
	Primary coxarthrosis, bilateral	5.98	Primary malignant neoplasm of lung	4.44	Primary coxarthrosis, bilateral	6.96
	Acquired valgus deformity of limb	4.62	Primary malignant neoplasm of lower lobe, bronchus or lung	3.78	Acquired valgus deformity of limb	5.48
	Intervertebral disc disorder	4.59	Anemia in neoplastic disease	3.62	Disorder of rotator cuff	5.40
	Disorder of rotator cuff	4.52	Primary malignant neoplasm of breast upper outer quadrant	3.29	Intervertebral disc disorder	5.03

	Osteoarthritis of hip	4.50	Primary malignant neoplasm of head of pancreas	3.13	Osteoarthritis of hip	4.86
	Osteoarthritis of knee	4.33	Primary malignant neoplasm of rectum	2.80	Osteoarthritis of knee	4.83
	Spinal stenosis	2.9	Malignant neoplasm, overlapping lesion of breast	2.8	Spinal stenosis	3.13
7	Chronic intractable pain	12.54	Chronic intractable pain	9.70	Chronic intractable pain	12.70
	Nerve root disorder	9.12	Anemia in neoplastic disease	5.76	Nerve root disorder	9.55
	Primary gonarthrosis, bilateral	6.94	Primary malignant neoplasm of lung	5.26	Primary gonarthrosis, bilateral	7.99
	Primary coxarthrosis, bilateral	6.84	Primary malignant neoplasm of prostate	5.10	Primary coxarthrosis, bilateral	7.84
	Intervertebral disc disorder	6.10	Multiple myeloma	4.77	Intervertebral disc disorder	6.68
	Osteoarthritis of hip	5.72	Nerve root disorder	4.11	Osteoarthritis of knee	6.42
	Osteoarthritis of knee	5.60	Primary malignant neoplasm of lower lobe, bronchus or lung	3.95	Osteoarthritis of hip	6.19
	Disorder of rotator cuff	4.93	Primary malignant neoplasm of head of pancreas	3.29	Disorder of rotator cuff	5.85
	Spinal stenosis	4.36	Primary malignant neoplasm of breast upper outer quadrant	3.29	Spinal stenosis	4.58
	Arthropathy	3.57	Malignant neoplasm, overlapping lesion of breast		Arthropathy	3.84
30	Nerve root disorder	13.26	Chronic intractable pain	11.18	Nerve root disorder	13.78
	Chronic intractable pain	13.11	Anemia in neoplastic disease	8.55	Chronic intractable pain	13.33
	Osteoarthritis of knee	10.24	Nerve root disorder	7.89	Osteoarthritis of knee	11.48
	Osteoarthritis of hip	9.62	Inflammatory disorder of digestive tract	6.09	Osteoarthritis of hip	10.51
	Intervertebral disc disorder	8.64	Primary malignant neoplasm of prostate	5.92	Primary gonarthrosis, bilateral	9.43
	Primary gonarthrosis, bilateral	8.28	Primary malignant neoplasm of lung	5.76	Intervertebral disc disorder	9.24
	Primary coxarthrosis, bilateral	7.92	Pain in spine	4.28	Primary coxarthrosis, bilateral	8.95
	Spinal stenosis	5.79	Primary malignant neoplasm of respiratory tract	4.28	Disorder of rotator cuff	6.45
	Disorder of rotator cuff	5.46	Low back pain	4.11	Spinal stenosis	5.97
	Arthropathy	5.22	Angina pectoris	4.11	Arthropathy	5.74

Table 12.2.4.6 – **EBB:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		Codeine		Tramadol	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Nerve root disorder	10.61	Cough	13.44	Nerve root disorder	15.68
	Cough	8.68	Nerve root disorder	8.52	Pain in spine	10.09
	Pain in spine	8.06	Pain in spine	6.55	Intervertebral disc disorder	8.67
	Intervertebral disc disorder	5.74	Acute upper respiratory infection	4.90	Low back pain	6.70

	Low back pain	5.50	Low back pain	4.66	Osteoarthritis of knee	4.57
	Osteoarthritis of knee	3.64	Intervertebral disc disorder	4.65	Osteoarthritis of hip	3.49
	Acute upper respiratory infection	3.24	Osteoarthritis of knee	3.34	Polyarthropathy	2.82
	Osteoarthritis of hip	2.5	Acute laryngitis and/or tracheitis	2.45	Backache	2.32
	Polyarthropathy	2.36	Polyarthropathy	2.22	Joint pain	2.27
	Joint pain	2.19	Joint pain	2.17	Arthropathy	1.94
7	Nerve root disorder	11.72	Cough	13.57	Nerve root disorder	17.37
	Pain in spine	9.13	Nerve root disorder	9.54	Pain in spine	11.65
	Cough	8.78	Pain in spine	7.42	Intervertebral disc disorder	9.70
	Intervertebral disc disorder	6.39	Acute upper respiratory infection	5.82	Low back pain	7.99
	Low back pain	6.39	Low back pain	5.44	Osteoarthritis of knee	5.40
	Osteoarthritis of knee	4.23	Intervertebral disc disorder	5.29	Osteoarthritis of hip	4.05
	Acute upper respiratory infection	3.95	Osteoarthritis of knee	3.93	Polyarthropathy	3.42
	Osteoarthritis of hip	2.89	Joint pain	2.63	Backache	2.91
	Polyarthropathy	2.77	Acute laryngitis and/or tracheitis	2.6	Joint pain	2.85
	Joint pain	2.68	Polyarthropathy	2.59	Spondylosis	2.5
30	Nerve root disorder	13.34	Cough	13.78	Nerve root disorder	19.61
	Pain in spine	10.66	Nerve root disorder	11.29	Pain in spine	13.75
	Cough	8.96	Pain in spine	8.93	Intervertebral disc disorder	11.14
	Low back pain	7.53	Acute upper respiratory infection	7.29	Low back pain	9.58
	Intervertebral disc disorder	7.41	Low back pain	6.67	Osteoarthritis of knee	7.18
	Osteoarthritis of knee	5.56	Intervertebral disc disorder	6.39	Osteoarthritis of hip	5.11
	Acute upper respiratory infection	5.24	Osteoarthritis of knee	5.27	Polyarthropathy	4.78
	Polyarthropathy	3.74	Joint pain	3.6	Joint pain	3.97
	Osteoarthritis of hip	3.7	Polyarthropathy	3.51	Arthropathy	3.54
	Joint pain	3.62	Osteoarthritis of hip	3.41	Backache	3.44

Table 12.2.4.7 – **IPCI:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Overall		Inject		Oral		Transdermal	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Cough	20.60	Urolithiasis	5.07	Cough	21.11	Finding of back	3.86
	Acute upper respiratory infection	5.43	Malignant tumor of lung	4.57	Acute upper respiratory infection	5.56	Low back pain	3.31
	Low back pain	3.13	Localized abdominal pain	4.03	Low back pain	3.15	Backache with radiation	3.06
	Finding of back	2.73	General health deterioration	3.22	Finding of back	2.74	Malignant tumor of lung	2.63
	Backache with radiation	2.70	Heart failure	3.19	Backache with radiation	2.73	Generalized aches and pains	2.12
	Finding of shoulder region	1.65	Generalized abdominal pain	1.94	Finding of shoulder region	1.67	General health deterioration	1.33

	Finding of region of thorax	1.15	Generalized aches and pains	1.80	Finding of region of thorax	1.16	Finding of lower limb	1.18
	Finding of neck region	1.09	Pneumonia	1.62	Finding of neck region	1.10	Fracture of vertebral column	1.12
	Finding of lower limb	0.87	Malignant tumor of pancreas	1.62	Finding of lower limb	0.87	Finding of hip region	1.12
	Traumatic injury	0.81	Malignant tumor of colon	1.5	Finding of knee region	0.8	Malignant tumor of pancreas	0.99
7	Cough	21.54	Malignant tumor of lung	5.71	Cough	22.07	Finding of back	5.49
	Acute upper respiratory infection	6.04	Urolithiasis	5.56	Acute upper respiratory infection	6.16	Low back pain	4.64
	Low back pain	3.73	Localized abdominal pain	5.26	Low back pain	3.75	Backache with radiation	3.97
	Finding of back	3.36	General health deterioration	5.24	Finding of back	3.36	Malignant tumor of lung	3.39
	Backache with radiation	3.18	Generalized aches and pains	3.30	Backache with radiation	3.21	Generalized aches and pains	2.69
	Finding of shoulder region	2.02	Generalized abdominal pain	2.76	Finding of shoulder region	2.04	General health deterioration	2.17
	Finding of region of thorax	1.50	Pneumonia	2.72	Finding of region of thorax	1.51	Finding of lower limb	1.87
	Finding of neck region	1.29	Malignant tumor of pancreas	2.06	Finding of neck region	1.31	Finding of hip region	1.69
	Traumatic injury	1.25	Malignant tumor of colon	1.9	Traumatic injury	1.23	Traumatic injury	1.58
	Finding of lower limb	1.16	Finding of back	1.89	Finding of lower limb	1.16	Fracture of vertebral column	1.54
30	Cough	22.18	General health deterioration	6.97	Cough	22.70	Finding of back	7.46
	Acute upper respiratory infection	6.63	Malignant tumor of lung	6.79	Acute upper respiratory infection	6.75	Low back pain	6.49
	Low back pain	4.25	Localized abdominal pain	6.62	Low back pain	4.26	Backache with radiation	5.26
	Finding of back	3.88	Urolithiasis	5.73	Finding of back	3.89	Malignant tumor of lung	4.38
	Backache with radiation	3.61	Urinary tract infectious disease	5.14	Backache with radiation	3.64	Generalized aches and pains	3.34
	Finding of shoulder region	2.55	Generalized aches and pains	4.32	Finding of shoulder region	2.57	General health deterioration	3.22
	Finding of region of thorax	1.97	Generalized abdominal pain	3.78	Finding of region of thorax	1.98	Finding of lower limb	3.05
	Traumatic injury	1.6	Traumatic injury	3.03	Finding of lower limb	1.16	Finding of hip region	2.7
	COVID-19	1.6	Finding of back	2.98	COVID-19	1.15	Traumatic injury	2.67
	Finding of lower limb	1.56	Malignant tumor of pancreas	2.35	Finding of knee region	1.03	Finding of region of thorax	2.32

Table 12.2.4.8 – **IPCI:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Backache with radiation	4.25	Urolithiasis	4.82	Backache with radiation	4.49
	Finding of back	3.49	Backache with radiation	3.28	Finding of back	3.43
	Low back pain	3.29	Malignant tumor of lung	3.25	Low back pain	3.19
	Urolithiasis	1.55	Localized abdominal pain	3.24	Finding of shoulder region	1.68
	Finding of shoulder region	1.54	Finding of back	2.71	Traumatic injury	1.45
	Localized abdominal pain	1.49	Low back pain	2.35	Lumbar hernia	1.43
	Traumatic injury	1.38	General health deterioration	2.09	Finding of lower limb	1.25
	Lumbar hernia	1.32	Generalized abdominal pain	1.54	Finding of hip region	1.20

	Finding of lower limb	1.27	Generalized aches and pains	1.53	Localized abdominal pain	1.16
	Finding of hip region	1.2	Lumbar hernia	1.13	Finding of region of thorax	1.14
7	Backache with radiation	5.50	Urolithiasis	5.36	Backache with radiation	5.87
	Finding of back	4.87	Localized abdominal pain	4.32	Finding of back	4.86
	Low back pain	4.53	Backache with radiation	4.26	Low back pain	4.47
	Traumatic injury	2.45	Malignant tumor of lung	4.09	Traumatic injury	2.64
	Localized abdominal pain	2.24	Finding of back	3.88	Finding of shoulder region	2.32
	Finding of shoulder region	2.13	General health deterioration	3.45	Localized abdominal pain	1.97
	Finding of lower limb	1.94	Low back pain	3.30	Finding of lower limb	1.96
	Urolithiasis	1.84	Generalized aches and pains	2.56	Lumbar hernia	1.92
	Finding of hip region	1.79	Generalized abdominal pain	2.21	Finding of hip region	1.83
	Lumbar hernia	1.73	Traumatic injury	1.8	Finding of region of thorax	1.74
30	Backache with radiation	6.58	Urolithiasis	5.56	Backache with radiation	7.07
	Finding of back	6.04	Localized abdominal pain	5.50	Finding of back	6.06
	Low back pain	5.65	Backache with radiation	5.14	Low back pain	5.62
	Traumatic injury	3.30	Malignant tumor of lung	5.01	Traumatic injury	3.48
	Localized abdominal pain	3.14	Finding of back	5.00	Finding of shoulder region	3.12
	Finding of shoulder region	2.89	General health deterioration	4.73	Localized abdominal pain	2.93
	Finding of lower limb	2.77	Low back pain	4.29	Finding of lower limb	2.80
	Finding of hip region	2.49	Generalized aches and pains	3.26	Finding of hip region	2.55
	Finding of region of thorax	2.44	Generalized abdominal pain	3.07	Finding of region of thorax	2.55
	Lumbar hernia	2.07	Traumatic injury	2.77	Lumbar hernia	2.31

Table 12.2.4.9 – **IPCI:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		Codeine		Tramadol	
Window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Cough	24.31	Cough	39.16	Low back pain	7.32
	Acute upper respiratory infection	6.18	Acute upper respiratory infection	9.87	Finding of back	6.14
	Low back pain	3.37	Common cold	1.39	Backache with radiation	6.07
	Finding of back	2.82	COVID-19	1.30	Finding of shoulder region	3.74
	Backache with radiation	2.68	Pneumonia	1.07	Finding of neck region	2.52
	Finding of shoulder region	1.77	Low back pain	0.81	Finding of region of thorax	2.11
	Finding of region of thorax	1.23	Finding of region of thorax	0.7	Finding of lower limb	1.84
	Finding of neck region	1.21	Finding of back	0.66	Finding of knee region	1.66
	Common cold	0.87	Pain in throat	0.54	Finding of hip region	1.56
	Finding of lower limb	0.87	Finding of shoulder region	0.5	Traumatic injury	1.43

7	Cough	25.40	Cough	40.85	Low back pain	8.56
	Acute upper respiratory infection	6.85	Acute upper respiratory infection	10.90	Finding of back	7.39
	Low back pain	3.95	COVID-19	1.95	Backache with radiation	7.10
	Finding of back	3.41	Common cold	1.63	Finding of shoulder region	4.49
	Backache with radiation	3.14	Pneumonia	1.45	Finding of neck region	2.92
	Finding of shoulder region	2.14	Low back pain	0.99	Finding of region of thorax	2.69
	Finding of region of thorax	1.57	Finding of region of thorax	0.92	Finding of lower limb	2.38
	Finding of neck region	1.41	Finding of back	0.86	Traumatic injury	2.08
	COVID-19	1.31	Pain in throat	0.77	Finding of knee region	2.04
	Finding of lower limb	1.13	Finding of shoulder region	0.63	Finding of hip region	2
30	Cough	26.07	Cough	41.72	Low back pain	9.45
	Acute upper respiratory infection	7.47	Acute upper respiratory infection	11.72	Finding of back	8.27
	Low back pain	4.46	COVID-19	2.56	Backache with radiation	7.90
	Finding of back	3.93	Common cold	1.80	Finding of shoulder region	5.34
	Backache with radiation	3.57	Pneumonia	1.78	Finding of neck region	3.34
	Finding of shoulder region	2.68	Low back pain	1.34	Finding of region of thorax	3.30
	Finding of region of thorax	2.03	Finding of region of thorax	1.34	Finding of lower limb	3.03
	COVID-19	1.8	Finding of back	1.22	Finding of knee region	2.65
	Finding of neck region	1.7	Finding of shoulder region	1.04	Traumatic injury	2.54
	Finding of lower limb	1.53	Pain in throat	0.95	Finding of hip region	2.46

Table 12.2.4.10 – **IQVIA DA Germany:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Overall		**Inject**		**Oral**		**Transdermal**	
Windows	**concept**	**%**	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Acute upper respiratory infection	14.25	Nerve root disorder	5.49	Acute upper respiratory infection	14.58	Chronic pain	13.02
	Cough	14.21	Chronic pain	4.67	Cough	14.55	Pain	3.51
	Nerve root disorder	3.71	Lumbago with sciatica	4.40	Nerve root disorder	3.69	Nerve root disorder	2.95
	Chronic pain	2.12	Low back pain	4.08	Acute pharyngitis	1.96	Chronic intractable pain	2.34
	Low back pain	1.93	Pain	2.70	Chronic pain	1.91	Spondylosis	1.56
	Acute pharyngitis	1.92	Spondylosis	2.43	Low back pain	1.9	Spinal stenosis	1.49
	Lumbago with sciatica	1.85	Intervertebral disc prolapse	2.21	Common cold	1.84	Pain disorder with psychological factor	1.38
	Common cold	1.8	Muscle pain	2.20	Lumbago with sciatica	1.83	Osteoarthritis of knee	1.33
	Intervertebral disc prolapse	1.35	Disorder of musculoskeletal system	1.8	Intervertebral disc prolapse	1.35	Low back pain	1.28
	Spondylosis	1.26	Chronic intractable pain	1.14	Spondylosis	1.24	Osteoarthritis of hip	1.14
7	Acute upper respiratory infection	15.61	Nerve root disorder	7.21	Acute upper respiratory infection	15.97	Chronic pain	14.22

	Cough	14.44	Chronic pain	6.07	Cough	14.79	Pain	4.22
	Nerve root disorder	4.37	Lumbago with sciatica	5.47	Nerve root disorder	4.33	Nerve root disorder	3.88
	Low back pain	2.29	Low back pain	5.27	Acute pharyngitis	2.28	Chronic intractable pain	2.61
	Chronic pain	2.28	Pain	3.44	Low back pain	2.25	Spondylosis	1.96
	Acute pharyngitis	2.23	Spondylosis	3.37	Lumbago with sciatica	2.15	Spinal stenosis	1.77
	Lumbago with sciatica	2.17	Disorder of musculoskeletal system	2.98	Common cold	2.08	Low back pain	1.75
	Common cold	2.03	Intervertebral disc prolapse	2.73	Chronic pain	2.06	Osteoarthritis of knee	1.75
	Intervertebral disc prolapse	1.55	Muscle pain	2.34	Intervertebral disc prolapse	1.55	Pain disorder with psychological factor	1.54
	Spondylosis	1.49	Secondary malignant neoplastic disease	1.58	Spondylosis	1.46	Osteoarthritis of hip	1.47
30	Acute upper respiratory infection	16.84	Nerve root disorder	8.83	Acute upper respiratory infection	17.22	Chronic pain	16.25
	Cough	14.70	Chronic pain	8.19	Cough	15.05	Chronic intractable pain	3.03
	Nerve root disorder	5.53	Lumbago with sciatica	6.30	Nerve root disorder	5.50	Spondylosis	2.92
	Low back pain	2.85	Low back pain	6.16	Low back pain	2.82	Low back pain	2.82
	Lumbago with sciatica	2.66	Spondylosis	4.31	Lumbago with sciatica	2.63	Osteoarthritis of knee	2.75
	Chronic pain	2.62	Pain	4.28	Acute pharyngitis	2.6	Spinal stenosis	2.47
	Acute pharyngitis	2.54	Disorder of musculoskeletal system	3.78	Chronic pain	2.4	Lumbago with sciatica	2.3
	Common cold	2.27	Intervertebral disc prolapse	3.41	Spondylosis	1.88	Osteoarthritis of hip	2.28
	Spondylosis	1.92	Muscle pain	2.47	Intervertebral disc prolapse	1.88	Pain disorder with psychological factor	1.95
	Intervertebral disc prolapse	1.88	Secondary malignant neoplastic disease	2.38	Disorder of musculoskeletal system	1.71	Intervertebral disc prolapse	1.73

Table 12.2.4.11 – **IQVIA DA Germany:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
Windows	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Chronic pain	10.09	Chronic pain	6.53	Chronic pain	9.38
	Nerve root disorder	4.38	Inflammatory disorder of digestive tract	3.61	Nerve root disorder	5.07
	Pain	2.86	Pain	2.97	Intervertebral disc prolapse	3.23
	Intervertebral disc prolapse	2.12	Disorder of intestine	1.93	Pain	2.66
	Spinal stenosis	1.96	Nerve root disorder	1.73	Spinal stenosis	2.56
	Lumbago with sciatica	1.79	Primary malignant neoplasm of respiratory tract	1.67	Lumbago with sciatica	2.18
	Spondylosis	1.75	Chronic intractable pain	1.50	Spondylosis	2.08
	Low back pain	1.67	Abdominal pain	1.46	Osteoarthritis of knee	2.07
	Chronic intractable pain	1.66	Secondary malignant neoplastic disease	1.27	Low back pain	2.03

	Osteoarthritis of knee	1.59	Secondary malignant neoplasm of bone	0.95	Intervertebral disc disorder	1.69
7	Chronic pain	10.89	Chronic pain	7.71	Chronic pain	10.05
	Nerve root disorder	5.46	Inflammatory disorder of digestive tract	3.98	Nerve root disorder	6.32
	Pain	3.29	Pain	3.61	Intervertebral disc prolapse	3.76
	Intervertebral disc prolapse	2.51	Nerve root disorder	2.37	Pain	2.99
	Lumbago with sciatica	2.32	Primary malignant neoplasm of respiratory tract	2.09	Spinal stenosis	2.95
	Spinal stenosis	2.28	Disorder of intestine	2.04	Lumbago with sciatica	2.81
	Low back pain	2.19	Chronic intractable pain	1.79	Low back pain	2.61
	Spondylosis	2.16	Secondary malignant neoplastic disease	1.76	Spondylosis	2.56
	Osteoarthritis of knee	1.92	Abdominal pain	1.67	Osteoarthritis of knee	2.37
	Chronic intractable pain	1.82	Secondary malignant neoplasm of bone	1.28	Intervertebral disc disorder	2
30	Chronic pain	12.44	Chronic pain	9.93	Chronic pain	11.71
	Nerve root disorder	7.79	Inflammatory disorder of digestive tract	4.78	Nerve root disorder	9.14
	Pain	3.99	Pain	4.57	Intervertebral disc prolapse	4.99
	Lumbago with sciatica	3.45	Nerve root disorder	3.85	Lumbago with sciatica	4.28
	Low back pain	3.41	Primary malignant neoplasm of respiratory tract	2.9	Low back pain	4.15
	Intervertebral disc prolapse	3.33	Secondary malignant neoplastic disease	2.66	Spinal stenosis	3.90
	Spondylosis	3.13	Chronic intractable pain	2.27	Spondylosis	3.73
	Spinal stenosis	2.99	Abdominal pain	2.14	Pain	3.68
	Osteoarthritis of knee	2.82	Secondary malignant neoplasm of bone	1.86	Osteoarthritis of knee	3.44
	Osteoarthritis of hip	2.21	Low back pain	1.79	Intervertebral disc disorder	2.65

Table 12.2.4.12 – **IQVIA DA Germany:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		**Codeine**		**Tramadol**	
Windows	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Acute upper respiratory infection	13.36	Cough	19.86	Nerve root disorder	10.21
	Cough	13.32	Acute upper respiratory infection	19.74	Low back pain	6.19
	Nerve root disorder	4.41	Acute pharyngitis	2.28	Lumbago with sciatica	5.88
	Low back pain	2.55	Common cold	1.91	Chronic pain	3.70
	Lumbago with sciatica	2.39	Upper respiratory tract infection due to	1.72	Intervertebral disc prolapse	3.50
	Acute pharyngitis	1.56	Nerve root disorder	1.52	Spondylosis	3.42
	Chronic pain	1.47	Acute laryngitis	1.49	Disorder of musculoskeletal system	2.82
	Spondylosis	1.43	Headache	1.34	Osteoarthritis of knee	2.44
	Intervertebral disc prolapse	1.36	Respiratory tract infection	1.22	Neck pain	2.06
	Common cold	1.3	Acute laryngotracheitis	1.08	Pain	2.01
7	Acute upper respiratory infection	14.78	Acute upper respiratory infection	21.79	Nerve root disorder	11.91

	Cough	13.61	Cough	20.27	Low back pain	7.22
	Nerve root disorder	5.19	Acute pharyngitis	2.71	Lumbago with sciatica	6.82
	Low back pain	2.98	Common cold	2.19	Chronic pain	4.05
	Lumbago with sciatica	2.77	Nerve root disorder	1.86	Intervertebral disc prolapse	4.04
	Acute pharyngitis	1.87	Acute laryngitis	1.7	Spondylosis	4.00
	Spondylosis	1.68	Headache	1.54	Disorder of musculoskeletal system	3.67
	Chronic pain	1.65	Respiratory tract infection	1.36	Osteoarthritis of knee	2.80
	Disorder of musculoskeletal system	1.65	Acute tonsillitis	1.26	Neck pain	2.44
	Intervertebral disc prolapse	1.58	Chronic sinusitis	1.22	Pain	2.23
30	Acute upper respiratory infection	15.96	Acute upper respiratory infection	23.28	Nerve root disorder	14.18
	Cough	13.90	Cough	20.63	Essential hypertension	10.68
	Nerve root disorder	6.54	Acute pharyngitis	3.09	Low back pain	8.43
	Low back pain	3.63	Nerve root disorder	2.79	Lumbago with sciatica	7.95
	Lumbago with sciatica	3.32	Common cold	2.42	Spondylosis	4.95
	Acute pharyngitis	2.15	Headache	1.86	Intervertebral disc prolapse	4.78
	Spondylosis	2.15	Acute laryngitis	1.85	Chronic pain	4.77
	Chronic pain	2.06	Acute tonsillitis	1.54	Disorder of musculoskeletal system	4.67
	Intervertebral disc prolapse	1.95	Inflammatory disorder of digestive tract	1.52	Osteoarthritis of knee	3.66
	Neck pain	1.73	Respiratory tract infection	1.46	Neck pain	3.03

Table 12.2.4.13 – **IQVIA LPD Belgium:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Overall		**Inject**		**Oral**		**Transdermal**	
window	**concept**	**%**	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Cough	26.56	Low back pain	15.77	Cough	27.02	Low back pain	20.14
	Common cold	13.32	Cough	14.26	Common cold	13.53	Pain	18.76
	Low back pain	10.03	Pain	13.01	Low back pain	9.90	Spondylosis	7.54
	Acute upper respiratory infection	9.76	Common cold	5.77	Acute upper respiratory infection	9.89	Polyarthropathy	6.01
	Pain	6.23	Acute tracheitis	5.18	Pain	6.09	Esophagitis	5.59
	Acute sinusitis	5.98	Lumbago with sciatica	4.62	Acute sinusitis	6.06	Backache	4.59
	Acute tracheitis	5.86	Esophagitis	3.64	Acute tracheitis	5.96	Lumbago with sciatica	4.41
	Acute pharyngitis	5.59	Acute upper respiratory infection	3.31	Acute pharyngitis	5.66	Neuralgia	3.74
	Acute laryngitis and/or tracheitis	3.23	Esophagitis	3.64	Acute laryngitis and/or tracheitis	3.29	Joint pain	3.36

	Esophagitis	3.19	Acute sinusitis	3.31	Esophagitis	3.19	Enthesopathy	3.04
7	Cough	26.65	Low back pain	16.65	Cough	27.12	Low back pain	21.12
	Common cold	13.67	Cough	14.65	Common cold	13.88	Pain	19.12
	Low back pain	10.25	Pain	13.83	Low back pain	10.14	Spondylosis	7.84
	Acute upper respiratory infection	9.93	Common cold	6.13	Acute upper respiratory infection	10.07	Polyarthropathy	6.16
	Pain	6.33	Acute tracheitis	5.24	Acute sinusitis	6.30	Esophagitis	5.92
	Acute sinusitis	6.22	Lumbago with sciatica	4.79	Pain	6.20	Backache	4.8
	Acute tracheitis	5.91	Esophagitis	4.03	Acute tracheitis	6.02	Lumbago with sciatica	4.59
	Acute pharyngitis	5.87	Acute sinusitis	3.67	Acute pharyngitis	5.94	Neuralgia	3.94
	Esophagitis	3.37	Spondylosis	3.51	Esophagitis	3.37	Joint pain	3.62
	Acute laryngitis and/or tracheitis	3.27	Acute upper respiratory infection	3.47	Acute laryngitis and/or tracheitis	3.33	Enthesopathy	3.21
30	Cough	26.87	Low back pain	18.49	Cough	27.33	Low back pain	23.67
	Common cold	14.20	Cough	15.24	Common cold	14.41	Pain	20.40
	Low back pain	10.86	Pain	15.08	Low back pain	10.78	Spondylosis	8.96
	Acute upper respiratory infection	10.24	Common cold	6.56	Acute upper respiratory infection	10.38	Esophagitis	7.12
	Acute sinusitis	6.68	Acute tracheitis	5.7	Acute sinusitis	6.77	Polyarthropathy	7.01
	Pain	6.61	Esophagitis	5.64	Pain	6.49	Lumbago with sciatica	5.24
	Acute pharyngitis	6.33	Lumbago with sciatica	5.18	Acute pharyngitis	6.40	Backache	5.19
	Acute tracheitis	6.03	Acute sinusitis	4.23	Acute tracheitis	6.13	Neuralgia	4.53
	Esophagitis	4.03	Spondylosis	4.1	Esophagitis	4.04	Joint pain	4.01
	Acute laryngitis and/or tracheitis	3.34	Acute upper respiratory infection	3.8	Acute laryngitis and/or tracheitis	3.4	Enthesopathy	3.56

Table 12.2.4.14 – **IQVIA LPD Belgium:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Pain	19.06	Pain	23.61	Pain	20.23
	Low back pain	18.93	Low back pain	12.67	Low back pain	19.35
	Spondylosis	5.95	Pain in limb	3.18	Lumbago with sciatica	6.83

	Lumbago with sciatica	5.50	Primary malignant neoplasm of respiratory tract	3.18	Spondylosis	5.63
	Esophagitis	5.34	Spondylosis	2.92	Esophagitis	5.57
	Polyarthropathy	4.56	Polyarthropathy	2.59	Polyarthropathy	3.98
	Backache	3.49	Secondary malignant neoplasm of bone	2.39	Cough	3.22
	Neuralgia	3.33	Primary malignant neoplasm of colon	2.39	Neuralgia	3.17
	Enthesopathy	2.92	Neuralgia	2.39	Enthesopathy	3.15
	Joint pain	2.89	Cough	2.32	Backache	3.04
7	Low back pain	19.91	Pain	25.53	Pain	20.66
	Pain	19.44	Low back pain	13.53	Low back pain	20.55
	Spondylosis	6.17	Pain in limb	3.32	Lumbago with sciatica	7.08
	Lumbago with sciatica	5.73	Primary malignant neoplasm of respiratory tract	3.25	Esophagitis	5.99
	Esophagitis	5.67	Spondylosis	3.18	Spondylosis	5.91
	Polyarthropathy	4.7	Polyarthropathy	2.92	Polyarthropathy	4.21
	Backache	3.67	Cough	2.92	Neuralgia	3.49
	Neuralgia	3.52	Neuralgia	2.92	Cough	3.44
	Joint pain	3.1	Secondary malignant neoplasm of bone	2.72	Backache	3.27
	Enthesopathy	3.05	Lumbago with sciatica	2.65	Enthesopathy	3.26
30	Low back pain	22.19	Pain	27.25	Low back pain	23.28
	Pain	20.69	Low back pain	16.18	Pain	22.27
	Spondylosis	7.07	Esophagitis	5.7	Lumbago with sciatica	7.94
	Esophagitis	7.04	Cough	4.24	Esophagitis	7.53
	Lumbago with sciatica	6.43	Polyarthropathy	3.98	Spondylosis	6.86
	Polyarthropathy	5.37	Pain in limb	3.98	Polyarthropathy	4.89
	Backache	4.09	Spondylosis	3.78	Cough	4.33
	Neuralgia	3.99	Bronchopneumonia	3.71	Neuralgia	4.19
	Joint pain	3.58	Primary malignant neoplasm of respiratory tract	3.65	Backache	3.85
	Cough	3.43	Superficial injury	3.51	Enthesopathy	3.73

Table 12.2.4.15 – **IQVIA LPD Belgium:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		Codeine		Tramadol	

window	concept	%	concept	%	concept	%
0	Low back pain	16.82	Cough	29.01	Low back pain	28.07
	Cough	15.01	Common cold	15.06	Pain	13.76
	Pain	9.57	Acute upper respiratory infection	9.50	Lumbago with sciatica	6.13
	Common cold	8.24	Acute tracheitis	8.37	Spondylosis	5.64
	Acute upper respiratory infection	5.23	Acute sinusitis	7.45	No matching concept	6.27
	Acute tracheitis	4.36	Acute pharyngitis	7.16	Pure hypercholesterolemia	6.18
	Acute sinusitis	4.29	Low back pain	6.05	Esophagitis	4.85
	Acute pharyngitis	4.07	Pain	5.91	Backache	3.79
	Esophagitis	3.87	Acute laryngitis and/or tracheitis	4.6	Joint pain	3.72
	Lumbago with sciatica	3.54	Headache	3.45	Polyarthropathy	3.15
7	Low back pain	17.15	Cough	29.23	Low back pain	28.56
	Cough	15.19	Common cold	15.58	Pain	13.90
	Pain	9.69	Acute upper respiratory infection	9.72	Lumbago with sciatica	6.26
	Common cold	8.57	Acute tracheitis	8.45	Spondylosis	5.79
	Disorders of initiating and maintaining sleep	6.23	Acute sinusitis	7.80	Esophagitis	5.10
	Acute upper respiratory infection	5.40	Acute pharyngitis	7.56	Backache	3.87
	Acute sinusitis	4.52	Low back pain	6.33	Joint pain	3.79
	Acute tracheitis	4.42	Pain	6.06	Polyarthropathy	3.23
	Acute pharyngitis	4.33	Acute laryngitis and/or tracheitis	4.66	Neck pain	3.17
	Esophagitis	4.08	Headache	3.53	Sciatica	3.12
30	Low back pain	17.92	Cough	29.62	Low back pain	29.55
	Cough	15.66	Common cold	16.35	Pain	14.29
	Pain	10.00	Acute upper respiratory infection	10.09	Lumbago with sciatica	6.56
	Common cold	9.23	Acute tracheitis	8.62	Spondylosis	6.16
	Acute upper respiratory infection	5.8	Acute sinusitis	8.46	Esophagitis	6.08
	Acute sinusitis	5.09	Acute pharyngitis	8.15	Joint pain	4.1
	Esophagitis	4.91	Low back pain	7.24	Backache	4.03
	Acute pharyngitis	4.81	Pain	6.52	Polyarthropathy	3.56
	Acute tracheitis	4.58	Acute laryngitis and/or tracheitis	4.76	Neck pain	3.37
	Lumbago with sciatica	3.82	Esophagitis	4.18	Sciatica	3.33

Table 12.2.4.16 – **SIDIAP:** Frequency of recording of conditions potentially reflecting an indication for new opioid prescriptions in 2012 - 2022, overall and by route of administration.

	Overall		Inject		Oral		Transdermal	
	concept	**%**	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Common cold	10.18	Traumatic AND/OR non-traumatic injury	3.64	Common cold	5.30	Chronic pain	1.42
	Cough	5.13		2.02	Cough	3.33	Low back pain	1.01
	Acute pharyngitis	2.40	Acute lower respiratory tract infection	1.07	Low back pain	2.97	Traumatic AND/OR non-traumatic injury	0.78
	Low back pain	2.25	Closed fracture of femur	0.68	Acute pharyngitis	1.48	Joint pain	0.70
	Acute lower respiratory tract infection	1.03	Coronavirus infection	0.58	Joint pain	1.07	Osteoarthritis	0.57
	Joint pain	0.83	Pain	0.54	Chest pain	0.89	Primary malignant neoplasm of respiratory tract	0.44
	Traumatic AND/OR non-traumatic injury	0.74	COVID-19	0.53	Traumatic AND/OR non-traumatic injury	0.88	Pain	0.41
	Chest pain	0.73	Chronic pain	0.47	Neck pain	0.88	Lumbago with sciatica	0.29
	Neck pain	0.67	Senile asthenia	0.46	Lumbago with sciatica	0.82	Osteoarthritis of hip	0.25
	Lumbago with sciatica	0.61	Abdominal pain	0.38	Acute lower respiratory tract infection	0.69	Secondary malignant neoplasm of bone	0.24
7	Common cold	10.94	Traumatic AND/OR non-traumatic injury	5.99	Common cold	5.88	Low back pain	1.81
	Cough	5.42	Acute lower respiratory tract infection	3.10	Low back pain	3.99	Chronic pain	1.52
	Low back pain	3.03	Patient dependence on care provider	2.59	Cough	3.56	Traumatic AND/OR non-traumatic injury	1.44
	Acute pharyngitis	2.66	Fever	1.88	Acute pharyngitis	1.67	Joint pain	0.97
	Acute lower respiratory tract infection	1.23	Coronavirus infection	1.28	Traumatic AND/OR non-traumatic injury	1.35	Primary malignant neoplasm of respiratory tract	0.64
	Traumatic AND/OR non-traumatic injury	1.13	COVID-19	1.09	Joint pain	1.33	Osteoarthritis	0.63
	Joint pain	1.04	Closed fracture of femur	1.08	Lumbago with sciatica	1.12	Lumbago with sciatica	0.5
	Chest pain	0.89	Senile asthenia	0.96	Neck pain	1.11	Pain	0.49

	Neck pain	0.85	Pain	0.84	Chest pain	1.08	Backache	0.39
	Lumbago with sciatica	0.84	Abdominal pain	0.83	Acute lower respiratory tract infection	0.85	Abdominal pain	0.39
30	Common cold	11.89	Traumatic AND/OR non-traumatic injury	8.26	Common cold	6.79	Low back pain	3.88
	Cough	5.81	Acute lower respiratory tract infection	5.68	Low back pain	5.36	Traumatic AND/OR non-traumatic injury	2.90
	Low back pain	4.12	COVID-19	2.18	Cough	3.94	Chronic pain	1.72
	Acute pharyngitis	3.01	Coronavirus infection	1.74	Traumatic AND/OR non-traumatic injury	2.15	Joint pain	1.58
	Traumatic AND/OR non-traumatic injury	1.84	Dysphagia	1.68	Acute pharyngitis	1.98	Primary malignant neoplasm of respiratory tract	1.16
	Acute lower respiratory tract infection	1.62	Abdominal pain	1.57	Joint pain	1.91	Lumbago with sciatica	1.07
	Joint pain	1.51	Closed fracture of femur	1.53	Neck pain	1.54	Abdominal pain	1.03
	Neck pain	1.21	Senile asthenia	1.51	Lumbago with sciatica	1.54	Sciatica	0.86
	Lumbago with sciatica	1.16	Common cold	1.21	Chest pain	1.34	Chest pain	0.79
	Chest pain	1.11	Chronic pain	1.06	Acute lower respiratory tract infection	1.22	Backache	0.79

Table 12.2.4.17 – **SIDIAP:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of potent opioids, incl. morphine and oxycodone in 2012 - 2022

	Potent		Morphine		Oxycodone	
window	**concept**	**%**	**concept**	**%**	**concept**	**%**
0	Chronic pain	1.16	Traumatic AND/OR non-traumatic injury	1.43	Low back pain	1.01
	Low back pain	1.15	Primary malignant neoplasm of respiratory tract	0.93	Chronic pain	0.85
	Traumatic AND/OR non-traumatic injury	0.84	Chronic pain	0.57	Traumatic AND/OR non-traumatic injury	0.53
	Joint pain	0.66	Acute lower respiratory tract infection	0.47	Joint pain	0.51
	Osteoarthritis	0.47	Secondary malignant neoplasm of bone	0.34	Lumbago with sciatica	0.44
	Primary malignant neoplasm of respiratory tract	0.45	Pain	0.33	Neuralgia	0.42
	Lumbago with sciatica	0.41	Primary malignant neoplasm	0.29	Osteoarthritis	0.34
	Sciatica	0.35	Low back pain	0.27	Sciatica	0.31

	Pain	0.34	Joint pain	0.26	Primary malignant neoplasm of respiratory tract	0.26
	Neuralgia	0.32	Abdominal pain	0.25	Prolapsed lumbar intervertebral disc	0.23
7	Low back pain	1.93	Traumatic AND/OR non-traumatic injury	2.69	Low back pain	1.71
	Traumatic AND/OR non-traumatic injury	1.50		1.64	Traumatic AND/OR non-traumatic injury	1.01
	Chronic pain	1.23	Primary malignant neoplasm of respiratory tract	1.51	Chronic pain	0.92
	Joint pain	0.91	Acute lower respiratory tract infection	1.25	Joint pain	0.72
	Lumbago with sciatica	0.65	Urinary tract infectious disease	1.06	Lumbago with sciatica	0.71
	Primary malignant neoplasm of respiratory tract	0.65	Chronic pain	0.73	Neuralgia	0.51
	Sciatica	0.55	Secondary malignant neoplasm of bone	0.66	Sciatica	0.49
	Osteoarthritis	0.52	Low back pain	0.6	Primary malignant neoplasm of respiratory tract	0.39
	Acute lower respiratory tract infection	0.42	Abdominal pain	0.58	Osteoarthritis	0.37
	Pain	0.41	COVID-19	0.54	Secondary malignant neoplasm of bone	0.32
30	Low back pain	3.76	Traumatic AND/OR non-traumatic injury	4.42	Low back pain	3.27
	Traumatic AND/OR non-traumatic injury	2.80	Patient dependence on care provider	4.22	Traumatic AND/OR non-traumatic injury	2.13
	Joint pain	1.47	Urinary incontinence	3.24	Lumbago with sciatica	1.34
	Chronic pain	1.37	Primary malignant neoplasm of respiratory tract	3.04	Joint pain	1.29
	Lumbago with sciatica	1.25	Urinary tract infectious disease	2.80	Chronic pain	1.14
	Primary malignant neoplasm of respiratory tract	1.17	Acute lower respiratory tract infection	2.63	Sciatica	1.04
	Sciatica	1.06	Abdominal pain	1.45	Primary malignant neoplasm of respiratory tract	0.85
	Acute lower respiratory tract infection	1.02	Low back pain	1.44	Abdominal pain	0.72
	Abdominal pain	0.95	Secondary malignant neoplasm of bone	1.37	Neuralgia	0.67
	Chest pain	0.71	COVID-19	1.12	Neck pain	0.6

Table 12.2.4.18 – **SIDIAP:** Frequency of recording of conditions potentially reflecting an indication for new prescriptions of weak opioids, incl. codeine and tramadol in 2012 - 2022

	Weak		Codeine		Tramadol	
window	**concept**	**%**	**concept**	**%**	**concept**	**%**

0	Common cold	9.51	Common cold	19.77	Low back pain	4.16
	Cough	4.56	Cough	9.57	Joint pain	1.47
	Low back pain	2.47	Acute pharyngitis	4.67	Neck pain	1.20
	Acute pharyngitis	2.28	Acute lower respiratory tract infection	1.94	Lumbago with sciatica	1.17
	Acute lower respiratory tract infection	0.95	Acute upper respiratory infection	1.31	Traumatic AND/OR non-traumatic injury	0.95
	Joint pain	0.90	Chest pain	0.95	Sciatica	0.87
	Chest pain	0.81	Acute tonsillitis	0.69	Renal colic	0.81
	Traumatic AND/OR non-traumatic injury	0.76	COVID-19	0.61	Knee pain	0.75
	Neck pain	0.74	Traumatic AND/OR non-traumatic injury	0.54	Chest pain	0.70
	Lumbago with sciatica	0.67	Low back pain	0.52	Shoulder joint pain	0.64
7	Common cold	10.24	Common cold	21.16	Low back pain	5.60
	Cough	4.84	Cough	10.13	Joint pain	1.84
	Low back pain	3.31	Acute pharyngitis	5.14	Lumbago with sciatica	1.61
	Acute pharyngitis	2.52	Acute lower respiratory tract infection	2.28	Neck pain	1.52
	Traumatic AND/OR non-traumatic injury	1.16	Acute upper respiratory infection	1.41	Traumatic AND/OR non-traumatic injury	1.51
	Acute lower respiratory tract infection	1.13	COVID-19	1.11	Renal colic	1.22
	Joint pain	1.13	Chest pain	1.08	Sciatica	1.17
	Chest pain	0.98	Acute tonsillitis	0.83	Knee pain	0.93
	Neck pain	0.94	Traumatic AND/OR non-traumatic injury	0.76	Chest pain	0.91
	Lumbago with sciatica	0.92	Low back pain	0.69	Backache	0.82
30	Common cold	11.15	Common cold	22.62	Low back pain	7.47
	Cough	5.24	Cough	10.79	Joint pain	2.60
	Low back pain	4.47	Acute pharyngitis	5.69	Traumatic AND/OR non-traumatic injury	2.42
	Acute pharyngitis	2.87	Acute lower respiratory tract infection	2.80	Lumbago with sciatica	2.20
	Traumatic AND/OR non-traumatic injury	1.87	COVID-19	1.70	Neck pain	2.07
	Joint pain	1.62	Acute upper respiratory infection	1.52	Sciatica	1.59
	Acute lower respiratory tract infection	1.50	Chest pain	1.29	Renal colic	1.44
	Neck pain	1.32	Traumatic AND/OR non-traumatic injury	1.29	Knee pain	1.35
	Lumbago with sciatica	1.26	Acute tonsillitis	1.11	Chest pain	1.20
	Chest pain	1.21	Low back pain	1.1	Backache	1.10

Table 12.2.4.19 – Frequency of recording of conditions potentially reflecting an indication for new prescriptions of naloxone in 2012 – 2022, across databases

	CHUBX		**EBB**		**IPCI**		**IQVIA DA Germany**		**IQVIA LPD Belgium**		**SIDIAP**	
Window	Concept	%	Concept	%	Concept	%	Concept	%	Concept	%	Concept	%

0	Coma	9.68			Substance abuse	7.48					Opioid dependence	0.49
	Acute hypoxemic respiratory failure	6.65			Drug dependence	5.14					Opioid-induced psychotic disorder with delusions	0.16
	Poisoning by psychotropic agent	6.50									Nonorganic insomnia	0.19
	Poisoning caused by opioid receptor agonist	6.07									Opioid-induced organic mental disorder	0.1
	Poisoning by benzodiazepine-based tranquilizer	5.92										
	Morphine overdose	5.64										
	Disorientated	5.2										
	Blood chemistry abnormal	3.61										
	Acute hypercapnic respiratory failure	3.18										
7	Morphine overdose	14.31			Substance abuse	7.48					Opioid dependence	0.53
	Disorientated	13.58			Drug dependence	5.14					Opioid-induced psychotic disorder with delusions	0.17
	Coma	12.28									Nonorganic insomnia	0.25
	Acute hypoxemic respiratory failure	11.13										
	Poisoning caused by opioid receptor agonist	7.66										
	Poisoning by psychotropic agent	7.51										
	Poisoning by benzodiazepine-based tranquilizer	7.08										
	Opioid dependence, on agonist therapy	5.49										
	Blood chemistry abnormal	5.35										
30	Disorientated	18.06			Substance abuse	7.94					Opioid dependence	0.56

	Morphine overdose	17.34			Drug dependence	5.61					Nonorganic insomnia	0.45
	Coma	13.01			Drug abuse	3.27						
	Acute hypoxemic respiratory failure	12.86			Opioid dependence	2.34						
	Poisoning caused by opioid receptor agonist	8.24										
	Poisoning by psychotropic agent	7.8										
	Poisoning by benzodiazepine-based tranquilizer	7.23										
	Opioid dependence, on agonist therapy	6.5										
	Blood chemistry abnormal	6.21										

12.2.5 Other Analysis

Additional analyses including stratifications for calendar year, or sensitivity analyses using a shorter washout period of 180days to define "new users" are presented in the shiny web application at https://data-dev.darwin-eu.org/connect/#/apps/e3479785-bf65-41e5-9777-84b4d1c5bd9f/access

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf)

Only in the case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14 DISCUSSION

14.1 Key Results

Population level DUS

In general, over the past decade, the incidence of opioid use has either slightly decreased or remained stable across most of the databases, with the exception of the EBB. Prescriptions of new opioids decreased during the COVID-19 pandemic in 2020 and 2021. This decrease was mirrored by an increase in 2022, although longer follow-up will be needed to ascertain the trend in opioids prescriptions after the pandemic.

Weaker opioids such as codeine and tramadol accounted for most of the observed opioid initiation, followed by more potent substances such as morphine and fentanyl. Oral administration was the primary route of administration. Furthermore, older individuals had a substantially higher rate of opioid use compared to younger adults, as well as women showing a consistently higher rate compared to men in the outpatient databases.

The trends and patterns observed in opioid prevalence closely mirrored those of incidence rates but with less fluctuation.

Patient-level DUS

A total of 138,171 new opioid users from CHUBX hospital [France]; 53,344 new opioid users from EBB biobank [Estonia]; and new opioid users from primary and secondary outpatient care including 440,849 from IPCI [The Netherlands]; 1,248,388 from IQVIA DA Germany [Germany]; 207,754 from IQVIA LPD Belgium [Belgium] and 2,023,867 new opioid users from SIDIAP [Catalonia, Spain] were included between 2012 and 2022.

The median age of new opioid users ranged between 50 and 57 across all databases, with users of potent opioids usually older compared to those of weak opioids. More women than men were prescribed opioids in primary care and EBB, whereas no difference was seen in hospital data from CHUBX.

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Treatment duration varied greatly by setting: Median duration of any new opioid prescription was 2 days in the CHUBX hospital, and ranged between 9 and 20 days for primary care and outpatient specialist care settings. Treatment duration varied greatly for different opioid substances, typically displaying a week, 2 weeks or a month of treatment. In SIDIAP, average treatment durations for potent opioids were substantially longer than for weak opioids.

The most commonly recorded conditions to define potential indications comprised respiratory conditions (e.g. cough, acute upper respiratory infections) and pain-related conditions (e.g. back pain, traumatic injury) for both primary care and outpatient specialist care databases. Hospital diagnoses included "Complications of surgical procedures" and "pain". Cough-related conditions were frequently recorded prior to treatment initiation with codeine, whereas pain-related conditions were frequently recorded before tramadol and the potent opioids morphine and oxycodone.

14.2 Limitations of the research methods

General limitations:

Data collection: This study leveraged routinely collected prescription and dispensation data within the scope of covered healthcare practices and databases. Certain combinations containing potential opioid substances like codeine, which are accessible over-the-counter in countries such as France, may not be fully captured. This could potentially result in an underestimation of the overall use of opioids and particular ingredients. However, the focus of the study was on prescription opioids.

Prescription fulfilment versus actual usage: The recorded prescription itself does not necessarily translate to the actual intake of the drug by the individuals. Assumptions about the actual use and duration of treatment had to be made in this study. We used well established methods to estimate treatment episode duration to overcome this issue. Despite this, the potential discrepancy in prescription and actual use is unlikely to affect the internal validity of the estimated trends observed in this study. Inpatient prescriptions were only available from CHUBX, but not in any of the other contributing databases.

Indication assessment: A critical limitation in describing indications was the lack of recorded codes that may represent indications for the prescriptions in all studied databases. Indication assessments were carried out through a proxy, using all conditions at the onset of therapy or the immediate time before. Indication may therefore be incomplete due to missing recordings, and recorded co-morbidities might be captured which do not necessarily present true indications for opioid initiation.

No stratification for indication (i.e. cough/pain) were conducted. Therefore, the overall incidence of prevalence could have been driven by both cough and pain medications. For instance, children aged 1-10 were frequently prescribed noscapin in IQVIA DA Germany (potentially also reflecting a shortage of other cough medications at that time), which lead to higher incidence rates of overall opioids in this age group compared to other age groups in DA Germany.

Database-specific limitations:

Estonian Biobank (EBB): The treatment duration in this database was not collected on and before 2021, and a default duration of 30 days was arbitrarily assigned to each prescription. Therefore, the overall treatment duration between 2012 – 2022 may not reflect the actual treatment duration for Estonia.

IQVIA DA Germany: In Germany, GPs do not act as gate keeper in the healthcare system. Therefore, patients can attend more than 1 practice contributing to DA Germany, and potentially receive opioid prescriptions from different practices.

14.3 Results in context

Population-level incidence and prevalence:

In terms of the broader trends of opioid consumption, the results show a slightly decreasing or stable incidence and prevalence of opioid use, with decreased incidence rates in 2020 and 2021. Prior studies indicate a rising trend in prescription opioid use across nearly all European countries *before the outbreak of the COVID-19 pandemic.* However, we acknowledge that direct comparisons of opioid epidemiology findings between our study and previous work are challenging due to significant heterogeneity in previous research. Previous studies predominantly used ecological/survey designs, studied aggregated drug consumption sources (typically obtaining numerator and denominator from different databases), covered earlier (pre-pandemic) calendar periods, included only a portion of opioids subtypes, and applied various definitions of opioid utilization metrics[15].

For instance, in a recent comprehensive ecological study, Pierce et al[4]. examined data from 25 European countries. Their results indicated an increase in prescription opioids consumption of 37% in Estonia, 123% in the Netherlands, and 38% in Germany between 2016-2018, compared to 2008-2010. In contrast, Belgium and France recorded a 9% decline during the same period. In a separate study, Kalkman et al[16]. utilized aggregated data from multiple Dutch databases, finding that oxycodone prescriptions increased from 574 per 100,000 inhabitants in 2008 to 2,568 in 2017. This marked increase significantly influenced the overall trend in the Netherlands. Meanwhile, in France, Keto et al[17]. reported steady PO prevalence using a nationwide register, observing between 120 and 160 dispensed opioids per 100,000 inhabitants from 2009 to 2017.

One notable gap in the existing literature is the lack of data on new opioid users. Many prior studies on opioid utilization relied heavily on summary statistics, without the granularity of individual-level information required to ascertain users who started opioid therapy. In contrast to prevalence data, our incidence findings show a decline in opioid initiation just before the pandemic in most countries from 2019 to 2020, offering an alternative view of opioid usage trends in Europe. This supports the broader expert consensus[18] that, unlike the U.S., Europe does not face a comparable opioid crisis in terms of magnitude and characteristics.

Uniquely, this study also assesses opioid utilization during and after the COVID-19 pandemic. We observed a decline in opioid use in 2020 compared to 2019, which then remained fairly stable in 2021. This reduction in incident prescriptions is likely due to disruptions and restrictions in routine healthcare, including the management of pain and other potential indications. However, there was a subsequent increase in opioid use after the pandemic, both in terms of incidence and prevalence, across all analysed databases. However, not all databases were able to provide data up to the end of 2022 and further studies will be required to understand whether this increase in the use of prescription opioids is a short-term rebound effect or a longer-term trend.

14.4 Generalisability

While our study comprised data from 6 European Countries and covers a wide range of settings (hospital in- and outpatient setting, outpatient specialist settings and primary care databases), findings from this study are not to be generalised to other countries or databases but only reflect the situation in the specific region and setting covered by the respective database. Settings with high use of opioids, such as nursing homes, palliative care facilities but also illegal use of prescription opioids are not covered in this study. Moreover,

patient populations particularly in hospitals vary based on the severity of conditions and health-related burden, which can impact the need for opioid prescriptions.

14.5 Other information

NA

15 CONCLUSION

In the latest decade, the rate of new opioid prescriptions has remained relatively stable or even declined slightly, with the exception of Estonia. Prescriptions of new opioids decreased during the COVID-19 pandemic in 2020 and 2021. This decrease was mirrored by an increase in 2022, although longer follow-up will be needed to ascertain the trend in opioids prescriptions after the pandemic.

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16 REFERENCES

1. Seth P, Scholl L, Rudd RA, Bacon S. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. MMWR Morb Mortal Wkly Rep. 2018;67(12):349-358. doi:10.15585/mmwr.mm6712a1. .
2. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Department of Health and Human Services. Annual Surveillance Report Of Drug-related Risks And Outcomes. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf. Accessed May 16, 2023. .
3. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? Current drug abuse reviews. 2015;8(1):3-14. doi:10.2174/1874473708011506111842l8. .
4. Pierce, M., Van Amsterdam, J., Kalkman, G., Schellekens, A., & Van den Brink, W. (2021). Is Europe facing an opioid crisis like the United States? An analysis of opioid use and related adverse effects in 19 European countries between 2010 and 2018. European Psychiatry, 64(1), E47. doi:10.1192/j.eurpsy.2021.2219.
5. Kennedy J, Wood EG, Wu C-H. Factors associated with frequent or daily use of prescription opioids among adults with chronic pain in the United States. The Journal of international medical research. 2023;51(1):3000605221149289. doi:10.1177/03000605221149289. .
6. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006;166(19):2087-2093. doi:10.1001/archinte.166.19.2087. .
7. Dufort A, Samaan Z. Problematic Opioid Use Among Older Adults: Epidemiology, Adverse Outcomes and Treatment Considerations. Drugs & Aging. 2021;38(12):1043-1053. doi:10.1007/s40266-021-00893-z. .
8. Vlug A, van der Lei J, Mosseveld B, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of information in medicine* 1999;38:339-44.
9. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, et al. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Informatics in primary care* 2011;19(3):135-45.
10. Brat GA, Weber GM, Gehlenborg N, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *NPJ Digit Med* 2020;3:109. doi: 10.1038/s41746-020-00308-0 [published Online First: 2020/08/31]
11. Rathmann W, Bongaerts B, Carius H, et al. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Ther* 2018;56(10):459-66.
12. Catala M, Du M, Guo Y, et al. DrugUtilisation: Summarise Patient-Level Drug Utilisation in Data Mapped to the OMOP Common Data Model [Available from: https://cran.r-project.org/web/packages/DrugUtilisation/index.html accessed 08/08/2023.
13. Edward Burn etal. IncidencePrevalence: Estimate Incidence and Prevalence using the OMOP Common Data Model.

Version: 0.3.0. Published: 2023-05-07 https://cran.r-project.org/web/packages/IncidencePrevalence/index.html.
14. Ger Inberg et al. Diagnostics for OMOP Common Data Model Drug Records: Package 'DrugExposureDiagnostics'. Version 0.4.1. Date/Publication 2023-03-13. https://cran.r-project.org/web//packages//DrugExposureDiagnostics/DrugExposureDiagnostics.pdf.

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15. Kalkman G, van den Brink W, Pierce M, et al. Monitoring Opioids in Europe: The Need for Shared Definitions and Measuring Drivers of Opioid Use and Related Harms. *Eur Addict Res (2022) 28 (3): 231–240*
16. Kalkman G, Kramers C, van Dongen R, et al. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. *The Lancet Public Health* 2019;4(10):E498-E505. doi: https://doi.org/10.1016/S2468-2667(19)30128-8
17. Keto, J., Heiskanen, T., Hamunen, K. et al. Opioid trends in Finland: a register-based nationwide follow-up study. Sci Rep 12, 7261 (2022). https://doi.org/10.1038/s41598-022-10788-7.
18. Kalkman G, Kramers C, van den Brink W, et al. The North American opioid crisis: a European perspective. *The Lancet* 2022;400(10361) doi: https://doi.org/10.1016/S0140-6736(22)01594-X

17 ANNEXES

Appendix I: List of Stand-alone Documents

Document title	Version	Date	
Medication code list	V1	18/09/2023	

Opioids and Naloxone: Individual substances incl. mono-preparations and combinations incl. the respective opioid/naloxone

Table 1 – Opioids

Concept name	Concept id	Standard?	Including all descendants?
Alfentanil	19059528	Yes	Yes
Anileridine	19032662	Yes	Yes
Bezitramide	37493802	Yes	Yes
Buprenorphine	1133201	Yes	Yes
Butorphanol	1133732	Yes	Yes
Codeine	1201620	Yes	Yes
Dextromethorphan	1119510	Yes	Yes
Dextromoramide	19021940	Yes	Yes
Dezocine	19088393	Yes	Yes
Dihydrocodeine	1189596	Yes	Yes
Dimemorfan	36852751	Yes	Yes
Ethylmorphine	19050414	Yes	Yes
Fentanyl	1154029	Yes	Yes
Hydrocodone	1174888	Yes	Yes
Hydromorphone	1126658	Yes	Yes
Ketobemidone	40798904	Yes	Yes
Meperidine	1102527	Yes	Yes
Meptazinol	19003010	Yes	Yes
Methadone	1103640	Yes	Yes
Morphine	1110410	Yes	Yes
Nalbuphine	1114122	Yes	Yes
Nicomorphine	37493805	Yes	Yes
Normethadone	19015787	Yes	Yes
Noscapine	19021930	Yes	Yes

Oliceridine	37002667	Yes	Yes
Opium	923829	Yes	Yes
Oxycodone	1124957	Yes	Yes
Oxymorphone	1125765	Yes	Yes
Papaveretum	19129648	Yes	Yes
Pentazocine	1130585	Yes	Yes
Phenazocine	19132884	Yes	Yes
Phenoperidine	19132889	Yes	Yes
Pholcodine	19024213	Yes	Yes
Pirinitramide	19134009	Yes	Yes
Propoxyphene	1153664	Yes	Yes
Remifentanil	19016749	Yes	Yes
Sufentanil	19078219	Yes	Yes
Tapentadol	19026459	Yes	Yes
Thebacon	40799139	Yes	Yes
Tilidine	19002431	Yes	Yes
Tramadol	1103314	Yes	Yes

Table 2 – Naloxone

Concept name	Concept id	Standard?	Including all descendants?
Naloxone	1114220	Yes	Yes

Weak and Potent Opioids

Table 3 – Weak Opioids

Concept name	Concept id	Standard?	Including all descendants?
Codeine	1201620	Yes	Yes
Hydrocodone	1174888	Yes	Yes
Tramadol	1103314	Yes	Yes

Table 4 – Potent Opioids

Concept name	Concept id	Standard?	Including all descendants?
Buprenorphine	1133201	Yes	Yes
Fentanyl	1154029	Yes	Yes
Hydromorphone	1126658	Yes	Yes
Methadone	1103640	Yes	Yes
Morphine	1110410	Yes	Yes
Oxycodone	1124957	Yes	Yes
Oxymorphone	1125765	Yes	Yes
Tapentadol	19026459	Yes	Yes

Opioids by route of administration

Table 5 – Routes of administration for all opioids

Route of administration	Dose Form	Including all descendants?
oral	Oral Granules, Sublingual Tablet, Oral Pellet, Chewable Extended Release Oral Tablet, Oral Flakes, Oral Gel, Oral Foam, Extended Release Oral Capsule, Oral Paste, Oral Strip, Extended Release Oral Tablet, Delayed Release Oral Tablet, Oral Cream, Powder for Oral Suspension, Oral Spray, Chewable Tablet, Granules for Oral Solution, Powder for Oral Solution, Oral Lozenge, Buccal Tablet, Oral Granules (Effervescents), Granules for Oral Suspension, Oral Solution, Chewing Gum, Oral Ointment, Oral Wafer, Oral Powder, Oral Suspension, Sustained Release Buccal Tablet, Disintegrating Oral Tablet, Effervescent Oral Tablet, Oral Capsule, Delayed Release Oral Capsule, Oral Tablet, Sublingual Powder, Delayed Release Oral Granules, Tablet for Oral Suspension, Oral Film, Sublingual Film, Buccal film	Yes
transdermal	Transdermal System, Medicated Patch	Yes
Parenteral (injection)	Auto-Injector, Prefilled Applicator, Intravenous Solution, Prefilled Syringe, Soft Tissue Injection Suspension, Intrathecal Suspension, Intraperitoneal Solution, Intratracheal Suspension, Extended Release Suspension, Intramuscular Solution, Pen Injector, Injection, Irrigation Solution, Intravenous Suspension, Injectable Foam, Intramuscular Prolonged Release Suspension, Injectable Suspension, Injectable Solution, Jet Injector	Yes

Naloxone: Fixed combinations

Table 6 – Buprenorphine

Concept id	Concept name	Domain id	Ingredient concept id
1970413	buprenorphine / naloxone Oral Tablet	drug	1114220
37498350	buprenorphine / naloxone Sublingual Film	drug	1114220
40015149	buprenorphine / naloxone Sublingual Tablet	drug	1114220
45776270	buprenorphine / naloxone Buccal Film	drug	1114220

Table 7 – Oxycodone

Concept id	Concept name	Domain id	Ingredient concept id
21160441	Naloxone / Oxycodone Oral Suspension	drug	1114220
36269469	Naloxone / Oxycodone Extended Release Oral Capsule	drug	1114220
41017321	Naloxone / Oxycodone Oral Tablet	drug	1114220
45774941	naloxone / oxycodone Extended Release Oral Tablet	drug	1114220

Table 8 – Pentazocine

Concept id	Concept name	Domain id	Ingredient concept id

40063474	naloxone / pentazocine Oral Tablet	drug	1114220

Table 9 – Tilidine

Concept id	Concept name	Domain id	Ingredient concept id
36264356	Naloxone / Tilidine Extended Release Oral Capsule	drug	1114220
36272016	Naloxone / Tilidine Topical Solution	drug	1114220
40063476	naloxone / tilidine Extended Release Oral Tablet	drug	1114220
40063477	naloxone / tilidine Oral Capsule	drug	1114220
41298261	Naloxone / Tilidine Oral Tablet	drug	1114220
43799912	Naloxone / Tilidine Oral Solution	drug	1114220