Study Report

P3-C2-002

DARWIN EU® Drug Utilisation Study of prescription opioids

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Version 2.0

Contents

Study title	DARWIN EU® - Drug utilisation study of prescription opioids
Study report version	V2.0
Date	28/05/2025
EU PAS number	EUPAS1000000479
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	N/A
Research question and objectives	This study aims to assess the incidence and prevalence of prescription opioids for the period 2012-2024, stratified by history of cancer/no history of cancer and age, sex, calendar year and country, as well as characterisation of new users, indications and treatment duration overall and in people with history of cancer/no history of cancer stratified by calendar year and country
Countryies of study	Estonia, Belgium, The Netherlands, France, Spain, Denmark, Norway
Author(s)	Amy Lam, Annika Jödicke, Mike Du, Edward Burn

[1] This is a routine repeated study from P2-C1-002 (EUPAS105641, https://catalogues.ema.europa.eu/node/3796).

TITLE

DARWIN EU® - Drug Utilisation Study of prescription opioids

1. DESCRIPTION OF STUDY TEAM

Study team role(s)	Name(s)	Organisation(s)
Principal Investigator(s)	Amy Lam	University of Oxford
Data Scientist(s)	Mike Du Edward Burn	University of Oxford
Clinical Epidemiologist	Annika Jödicke Junqing (Frank) Xie	University of Oxford
Study Manager	Natasha Yefimenko	Erasmus MC
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
Local Study Coordinator/Data Analyst	Gargi Jadhav Isabella Kaczmarczyk Akram Mendez Dina Vojinovic	IQVIA
	Talita Duarte Salles Irene López Sánchez Agustina Giuliodori Picco Anna Palomar Cros	IDIAP JGol
	Raivo Kolde Marek Oja Ami Sild	University of Tartu
	Katia Verhamme	Erasmus MC
	Romain Griffier Guillaume Verdy	CHU Bordeaux
	Claus Møldrup Elvira Bräuner Susanne Bruun Monika Roberta Korcinska Handest	Danish Medicines Agency
	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	Consorci Mar Parc de Salut Barcelona
	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

2. DATA SOURCES

Country	Name of Database	Health Care setting	Type of Data	Number of active subjects	Calendar period covered by each data source
The Netherlands	IPCI	Primary care	EHR	1.25 million	January 2012 – June 2024
France	CDW Bordeaux	Secondary care (in and outpatients)	EHR	0.2 million	January 2012 – December 2024
Spain	SIDIAP	Primary care	EHR	6.0 million	January 2012 – June 2023
Belgium	IQVIA LPD Belgium	Primary care, outpatient specialist care	EHR	0.2 million	September 2015 – September 2024
Estonia	EBB	Biobank	Claims data	0.2 million	January 2012 – December 2022
Denmark	DK-DHR	Community pharmacy, secondary care specialist	EHR	5.96 million	January 2012 – November 2024
Norway	NLHR	Primary care, secondary care specialist, hospital inpatient care	Registries, EHR	6.95 million	January 2019 – December 2023
Spain	IMASIS	Secondary care specialist, hospital inpatient	EHR	0.1 million	January 2012 – July 2024

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 spread of this issue, enhanced surveillance and in-depth research into opioid utilisation patterns are imperative. A drug utilisation study using a Common Data Model (CDM) is a promising approach to supplement European opioid monitoring systems, providing more granular data to inform evidence-based decisions on this complex topic.

Research question and Objectives

The objectives of this study are

(i) To investigate the annual incidence and annual period prevalence of use of opioids (overall, active drug substance, strength (weak/strong opioids) and route (oral, transdermal or parenteral), stratified by history of cancer/no history of cancer and for calendar year, age, sex and country/database during the study period.

(ii) To determine duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing overall and in people with history of cancer/no history of cancer, all stratified by calendar year and country/database.

Research Methods

Study design

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

Population

Population-level utilisation of opioids: All people registered in the respective databases on 1st of January of each year in the period 2012-2024 (or the latest available, whatever comes first), with at least 1 year of prior data availability (not applicable in hospital databases), were included in the population-level analysis (period prevalence calculation in Objective 1).

New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability (not applicable in hospital databases), and with no use of the respective opioid in the previous 12 months, were included for incidence rate calculations in Objective 1.

Patient-level drug utilisation: New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability (not applicable in hospital databases), and with no use of the respective opioid in the previous 12 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. Estonian Biobank (EBB), Estonia
2. IQVIA LPD Belgium, Belgium
3. Integrated Primary Care Information Project (IPCI), The Netherlands
4. The Information System for Research in Primary Care (SIDIAP), Spain
5. Clinical Data Warehouse for Bordeaux University Hospital (CDW Bordeaux), France
6. Danish Data Health Registries (DK-DHR), Denmark
7. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
8. Norwegian Linked Health Registry (NLHR), Norway

Data analyses

Population-level and Patient-level DUS analyses were conducted in all databases, with no calculation of duration being conducted for EBB.

Population-level opioid use: Annual period prevalence of opioid use and annual incidence rates per 100,000 person years were estimated.

Patient-level opioid use: A summary of patient-level characteristics based on a list of pre-defined conditions/medications of interest was conducted at index date, including patient demographics, and history of comorbidities and comedication. Frequency of indication at index date, and in the immediate time before were calculated. Cumulative treatment duration was estimated for the first treatment era and the minimum, p25, median, p75, and maximum was provided. For all analyses a minimum cell count of 5 was be used when reporting results, with any smaller counts noted as <5.

Results

Population-level opioid use

A total number of 274,026 individuals (CDW Bordeaux), 2,183,760 individuals (DK-DHR), 60,286 individuals (EBB), 132,762 individuals (IMASIS), 484,556 individuals (IPCI), 205,461 individuals (IQVIA LPD Belgium), 1,888,433 individuals (NLHR) and 2,204,608 individuals (SIDIAP) were identified as incident opioid users during the study period of 2012-2024.

In general, over the past decade, the incidence of opioid use has either slightly decreased or remained stable across most of the databases. An increasing trend was seen for EBB and the 2 hospital databases IMASIS and CDW Bordeaux, of which the increase in hospital database could be potentially driven by a sharp decrease in the denominator population. DK-DHR and IPCI had a decreasing trend in prescription opioid incidence over the study period. Among all included databases, IQVIA-LPD Belgium had the highest incidence of overall opioid use during the study period. Prevalence of overall opioid use showed similar trend and pattern as seen in incidence.

The majority of opioid prescriptions/dispensation were recorded in people who did not have a history of cancer in the year before prescription. Therefore, trends and pattern in overall opioid use aligned closely with non-cancer opioid use and were predominantly oral formulations.

Incidence and prevalence showed a marked decrease during the COVID-19 period (2020-2021), particularly for weak opioids such as codeine or tramadol. However, opioid usage returned to the pre-COVID-19 level or even higher in all databases from 2022 onwards. The trend was highly driven by non-cancer opioid use, while the drop during COVID-19 period was much less substantial for cancer opioid use.

When further stratified by opioid potency and route of administration, an increasing trend of potent opioid use was observed in EBB and IMASIS, both in people with and without a history of cancer.

Injectable opioids were predominantly used in hospitals (IMASIS, CDW Bordeaux) and transdermal opioid use. Trend and pattern of oral opioid use were similar to the pattern of weak opioid use in general.

When considering opioid use by ingredient, the top ten most frequently used opioid ingredients across all databases were, in descending order, tramadol, codeine, morphine, oxycodone, ethylmorphine, opium, dextromethorphan, fentanyl, buprenorphine and tapentadol. Among these opioid ingredients, five of them (buprenorphine, fentanyl, morphine, oxycodone, tapentadol) were potent opioids. Incidence of morphine use increased in all included databases and most databases showed an increase in the incidence of tramadol use over the study period, except DK-DHR that showed a decreasing trend in tramadol use.

Patient-level opioid use

Among new opioid users, there were more women than men receiving opioid prescriptions across all included databases except CDW Bordeaux. The median age of opioid incident users ranged from 49 to 62years. Among those starting opioids, the proportion of individuals with a record of malignant neoplastic disease any time before and up to 1 year prior to the new opioid prescription ranged from 2.6-13.6%, compared to 1.8-19.1% with a record within 1 year prior starting opioids. When considering medication use within 1 year prior to the opioid use, 38.0-73.7% of incident opioid users were prescribed with anti-inflammatory and anti-rheumatic agents.

The median duration for a first treatment episodes with opioids ranged from 1 day in hospitals to 11 days in primary care databases.

As the actual indication was not recorded in our databases, we used the recent recording of conditions/diagnoses/procedures prior to new opioid prescriptions as proxies for potential indications: Most of the possible indications were pain-related or cough-related conditions. Procedures in hospital databases recorded in the immediate time before opioid prescriptions included chest x-rays (suggestive of chest symptoms or findings) diagnostic radiography during the operative procedure (suggestive of post-operative pain) and local excision of breast lesion (suggestive of operative procedure and post-operative pain).

Conclusion

In recent years, an increasing trend in overall opioid use was observed in EBB and IMASIS, while decreasing trend was observed in DK-DHR and IPCI. Most of the opioid prescriptions were recorded in people without a recent history of cancer, suggesting indications for non-cancer use. There was a decrease in opioid use during the COVID-19 period (2020-2021), particular for weak opioids. Opioid usage returned to the pre-COVID-19 levels or even higher from 2022 onwards, with the trend highly driven by non-cancer opioid use.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACI VARHA	Auria Clinical Informatics VARHA
CDM	Common Data Model
CDW Bordeaux	Bordeaux University Hospital
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug Utilisation 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
IMASIS	Institut Municipal Assistència Sanitària Information System
IPCI	Integrated Primary Care Information Project
NLHR	Norwegian Linked Health Registry
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 studyprotocol	Amendment orupdate	Reason
Version 1.0	06/02/2025	N/A	Update from initial study protocol (P2-C1-002, EUPAS105641)	This is a routine-repeated study.

Comparison with Previous Protocols

	P2-C1-002 (EUPAS105641)	P3-C2-002 (Current study protocol)
Study period	2012-2022	2012-2024
Data partner		
EBB [Estonia]	*	*
IQVIA DA Germany [Germany]	*	
IQVIA LPD Belgium [Belgium]	*	*
SIDIAP [Spain]	*	*
IPCI [The Netherlands]	*	*
CDW BORDEAUX [France]	*	*
ACI VARHA [Finland]	*	
DK-DHR [Denmark]		*
IMASIS [Spain]		*
NLHR [Norway]		*
Reference study protocol	N/A	P2-C1-002 (EUPAS105641)
Changes from reference study protocol	N/A	- Exposure: Addition of analyses of opioid use in people with history of cancer/no history of cancer - New user characterisation: Instead of large scale characterisation, a pre-defined list of conditions and medications was used - Indication: procedures were included to explore possible indications in hospital database - Sensitivity analysis: removal of 6-month washout period - Hospital databases: No requirement of 365days of prior data availability

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Draft Study Protocol	17/01/2025	22/01/2025
Final Study Protocol	31/01/2025	03/03/2025
Creation of Analytical code	February 2025	23/01/2025
Execution of Analytical Code on the data	February 2025	25/02/2025
Draft Study Report	March 2025	15/04/2025
Final Study Report	To be confirmed	To be confirmed

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 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 by 2015, recent studies in Europe, suggest an increasing trend in the use of prescription opioids and opioid-use related mortality. Given that drug markets are increasingly global, the insufficient surveillance of these trends could potentially overlook the indicators of burgeoning 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[4]. Similarly, patients with mental health disorders are at increased risk of initiation and prolonged opioid treatments and their consequences. Moreover, older adults are more susceptible to the adverse effects of opioids, yet they typically have more pain management requirements due to accumulating a range of chronic disorders leading to painful conditions[5]. There is an imperative need for further investigation to describe the utilisation patterns of opioids among this demographic[6].

A drug utilisation study of prescription opioids based on a Common Data Model (CDM) will provide useful 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 in addressing this multifaceted topic.

Following the completion of P2-C1-002 (EUPAS105641, https://catalogues.ema.europa.eu/node/3796), EMA requested a routine repeated study to include additional databases and more recent data.

8. RESEARCH QUESTION AND OBJECTIVES

Table 1. Primary and secondary research questions and objectives.

A. **Primary research question and objective**

Objective:	To investigate the annual incidence and annual period prevalence of use of opioids (overall, active drug substance, strength (weak/strong opioids), route (oral, transdermal or parenteral)), stratified by history of cancer and calendar year, age, sex and country/database during the study period.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All people registered in the respective databases on 1st of January of each year in the period 2012-2024 (or the latest available, whatever comes first), with at least 1 year of prior data availability (not applicable in hospital databases), were included in the population-level analysis (period prevalence calculation in Objective 1). New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability (not applicable in hospital databases), and no use of the respective opioid in the previous 12 months, were included for incidence rate calculations in Objective 1.
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 1st of January for each calendar year between 2012-2024 for the calculation 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, whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 8 data sources: EBB [Estonia], IQVIA LPD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CDW Bordeaux [France], DK-DHR [Denmark], IMASIS [Spain], NLHR [Norway]
Main measure of effect:	Incidence and prevalence of opioid use

B. **Secondary research question and objective**

Objective:	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 overall and in people with history of

	cancer/no history of cancer, all stratified calendar year and country/database.
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	New users of opioids overall and in people with history of cancer/no history of cancer in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of prior data availability (not applicable in hospital databases), and no use of the respective opioid in the previous 12 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 and/or dispensation (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, whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 8 data sources: EBB [Estonia], IQVIA LPD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CDW Bordeaux [France], DK-DHR [Denmark], IMASIS [Spain], NLHR [Norway]
Main measure of effect:	Duration of opioid use (first treatment era) expressed as minimum, p25, median, p75, and maximum days. Summary patient-level characterisation by list of pre-defined conditions/medications of interest for new opioid users overall and in people with history of cancer/no history of cancer (1) overall, (2) for the 10 most frequent opioids in each database, (3) by strength, (4) by route. Indications, based on a high-level approach considering the most frequent conditions and procedures recorded in the month/week before/at the date of treatment start.

9. RESEARCH METHODS

9.1 Study type and study design

A cohort study was conducted using routinely-collected health data from 8 databases. The study comprised 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 characterise individual-level opioid utilisation in terms of summary patient characteristics, indication and duration of use.

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Patient Level DUS	New drug/s user cohort	Off the shelf

9.2 Study setting and data sources

This study was conducted using routinely collected data from 8 databases from 7 European countries. All databases were previously mapped to the OMOP CDM.

1. Estonian Biobank (EBB), Estonia
2. IQVIA LPD Belgium, Belgium
3. Integrated Primary Care Information Project (IPCI), The Netherlands
4. The Information System for Research in Primary Care (SIDIAP), Spain
5. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
6. Danish Data Health Registries (DK-DHR), Denmark
7. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
8. Norwegian Linked Health Registry (NLHR), Norway

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described below and in **Table 3**.

Fit for purpose: This study was repeated in 5 out of the 7 databases from the initial study P2-C1-002 and included 3 additional databases. The selection of databases for this study was performed based on data reliability and relevance for the research question and feasibility counts.

6 databases included records from primary care and outpatient specialist care where opioids are expected to be prescribed. 2 databases were covering in-and outpatient records from hospitals, where opioids were expected to be initiated and prescribed for outpatient use following hospital discharge.

Table 3. Description of 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 where opioid prescriptions are issued.	Primary care	EHR	1.25 million	30/06/2024
France	CDW Bordeaux	Database covers hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	0.2 million	04/03/2025
Spain	SIDIAP	Databases covers primary care / outpatient specialist care setting where opioid prescriptions are issued.	Primary care	EHR	6.0 million	30/06/2023
Belgium	IQVIA LPD Belgium		Primary care, outpatient specialist care	EHR	0.2 million	30/09/2024
Estonia	EBB	Database covers primary care setting where opioid prescriptions are issued.	Biobank	Claims data	0.2 million	31/12/2022
Denmark	DK-DHR	Database covers secondary care specialist setting where opioid prescriptions are issued.	Community pharmacy, secondary care specialist	EHR	5.96 million	07/11/2024
Norway	NLHR	Database covers primary care and secondar care specialists where opioid prescription are issued.	Primary care, secondary care specialist, hospital inpatient care	Registries, EHR	6.95 million	31/12/2023
Spain	IMASIS	Database covers secondary care specialists where opioid prescription are issued.	Secondary care specialist, hospital inpatient	EHR	0.1 million	20/09/2024

IPCI = Integrated Primary Care Information Project; CDW Bordeaux= Bordeaux University Hospital, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, DA = Disease Analyzer, EBB = Estonian Biobank, EHR = Electronic Heath record, DK-DHR = Danish Data Health Registries, NLHR = Norwegian Linked Health Registry data, IMASIS = Institut Municipal Assistència Sanitària Information. Exposure was based on dispensation data in EBB, DK-DHR and NLHR, and prescription data in other databases.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[7] The selection of 374 GP practices is representative of the entire country. The database contains records from 3.0 million (as of 01-2025) patients out of a Dutch population of 17M starting in 1996[7]. The median follow-up is 4.6 years as of 01/2025. 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 needs to be obtained for each study from the Governance Board[7].

Bordeaux University Hospital (CDW Bordeaux), 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).[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 15.5 years as of 01/2025. 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. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

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.

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.

Danish Data Health Registries (DK-DHR), Denmark

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The present database has access to the following registries for the entire Danish population of 5.9 million persons from 1/1/1995: the Central Person Registry, the National Patient Registry, the Register of Pharmaceutical Sales, the National Cancer Register, the Cause of Death registry, the Clinical Laboratory Information Register, COVID-19 test and Vaccination Registries, and the complete vaccination registry. The median follow-up is 21.7 years (as of 01/2025).

Norwegian Linked Health Registry data (NLHR), Norway

Norway has a universal public health care system consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants. Many population-based health registries were established in the 1960s with use of unique personal identifiers facilitating linkage between registries. Data from registries includes information about the pregnancy, diagnosis in secondary care (e.g., hospital), diagnosis and contact in primary care (e.g, GPs and outpatient specialists), all medications dispensed outside of hospitals, test results of communicable diseases (e.g., Sars-Cov-2), and records on vaccinations. The median follow-up is 16 years (as of 01/2025).

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. The information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, that are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The average follow-up period per patient is 6.4 years.

9.3 Study period

The study period will be from the 1st of January 2012 until the earliest of either 31st December 2024 or the respective latest date of data availability of the respective databases.

9.4 Follow-up

For the population-level analyses for incidence and prevalence, individuals will contribute person-time from the date they have reached at least 365 days of data availability (not applicable in hospital database) (**Table 4**).

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study – Analysis of Prevalent Use	Patient present in the database during the study period and with at least 1 year of valid database history (prior data availability requirement not applicable in hospital database)	Multiple	Prevalent	n/a	IP and OP	n/a	n/a	Overall, substance, strength, route	n/a	n/a
All patients from the database eligible for the study – Analysis of incident use	Patient present in the database during the study period and with at least 1 year of valid database history (prior data availability requirement not applicable in hospital database)	Multiple	Incident	[-365 to ID]	IP and OP	n/a	n/a	Overall, substance, strength, route	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable, ID = index date

Both incidence and prevalence required 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 date of the latest of the following: 1) study start date (1st January 2012), 2) date at which they have a year of prior history recorded (not applied for hospital databases). Participants stopped contributing person time at the earliest date of the following: 1) study end date (31st December 2024) or 2) end of available data in each of the data sources or 3) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population was shown in **Figure 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.

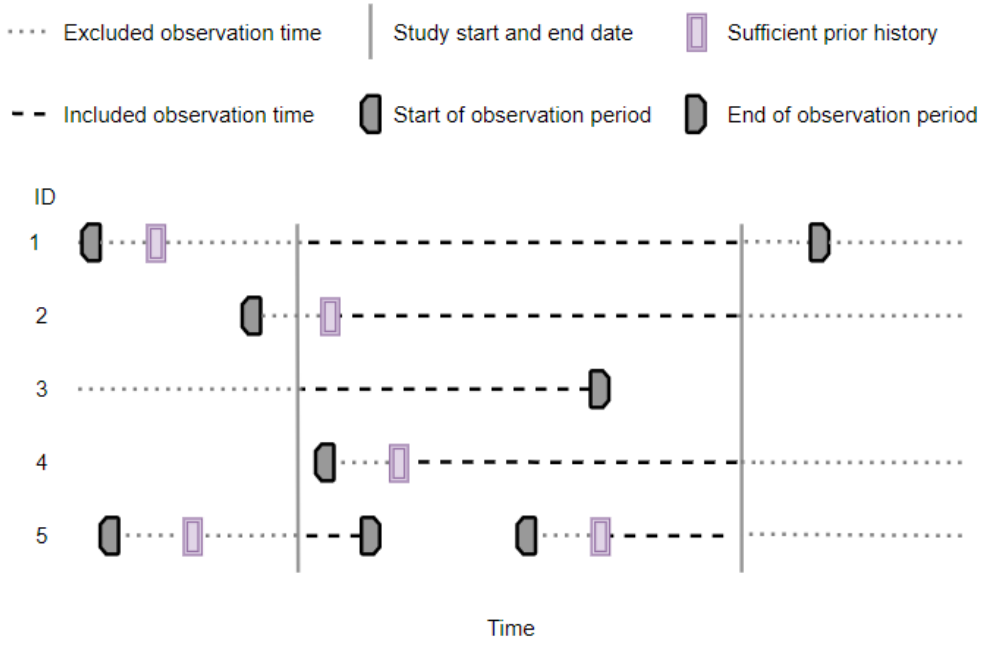

Figure 1. Included observation time for the denominator population.

9.5 Study population with in and exclusion criteria

The study cohort for population-level utilisation of opioids comprised all individuals present in the period 2012-2024 (or the latest available), with at least 365 days of data availability before the day they became eligible for study inclusion (not applicable in hospital databases). 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 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of prior data availability (not applicable in hospital databases), and no use of the respective opioid in the previous 12 months.

For patient-level utilisation of opioids, all new users of opioids, after 365 days of no use of the specific opioid /substance /strength/ route, in the period between 1/1/2012 and 31/12/2024 (or latest date available), with at least 365 days of visibility prior to the date of their first opioid prescription (not applicable in hospital database) were included.

Table 5. Operational definitions of inclusion criteria.

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 2012-2024 (or the latest available)	All individuals present in the period 2012-2024 (or the latest available)	N/A	N/A	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year (not applicable in hospital database)	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases (not applicable in hospital database)	N/A	N/A
Washout period	New users will be required to have not used opioids/ the specific opioid substance /strength/ route 365 days before a “new” prescription	After	365 days	primary care, secondary care (i.e in- and outpatient specialist 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 was the prescription (during study period) of opioids, naloxone and fixed opioid-naloxone combinations.

Opioids were grouped

(1) Overall
(2) by drug substance (including 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

This list of opioids is described in **Table 6**. Details of exposure were described in **Table 6**.

Table 6. 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				phenoperidine		X
dextromethorphan				pholcodine		
dextromoramide				pirinitramide		
dextropropoxyphene		X		propoxyphene		
dihydrocodeine				remifentanil		
ethylmorphine				sufentanil		
fentanyl	potent			tapentadol	potent	
hydrocodone	weak			thebacon		
hydromorphone	potent			tilidine		
ketobemidone				tramadol	weak	
meptazinol						
meperidine (pethidine)				naloxone		
methadone	potent					
morphine	potent			buprenorphine/naloxone		
nicomorphine				oxycodone/naloxone		
normethadon		X		pentazocine/naloxone		
nalbuphine				tilidine/naloxone		

*Drug strength has been assigned bases on the WHO analgesic ladder (https://www.ncbi.nlm.nih.gov/books/NBK554435/):
weak opioids (hydrocodone, codeine, tramadol),
potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone)

Table 7. 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	Preliminary code lists provided in Table 5.	[-365 to ID]	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period (except hospital databases)	Previous opioid use	N/A	N/A
Opioid use (overall, strength, route) with history of cancer/no history of cancer	Preliminary code lists provided in Table 5. History of cancer defined as cancer-related observation or condition within 1 year before index date or use of antineoplastic treatment within 1 year before index date.	[-365 to ID]	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period (except hospital databases)	Previous opioid use	N/A	N/A

9.6.2 Outcome/s

None.

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

The following covariates were used for the stratification in population-level drug utilisation study.

- Calendar year
- Age: 10-year age bands will be used: 1-10, 11-20, 21-30 […] , and >80
- Sex: male or female
- History of cancer: yes or no (for outcome stratification)

The following covariates were used for the patient-level drug utilisation study.

- Baseline characteristics given by the list of pre-defined conditions/medications of interest: the operational definition of the included covariates were as follows: anxiety, asthma, autoimmune disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, dementia, depressive disorder, diabetes, gastro-oesophageal reflux disease, heart failure, HIV, hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, ovarian cancer, leukemia, multiple myeloma, breast cancer, endometrial cancer, lymphoma, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism. Covariates for the baseline medications were pre-defined as follows: agents acting on the renin-angiotensin system, antibacterials for systemic use, antidepressants, antiepileptics, anti-inflammatory and antirheumatic products, antineoplastic agents, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, drugs for acid related disorders, drugs for obstructive airway diseases, drugs used in diabetes, hormonal contraceptives, immunosuppressants, lipid modifying agents, psycholeptics, psychostimulants. Index date was the start of the (first) incident prescription during the study period.
- Indication: We used a high-level approach considering the most frequent conditions (all databases) and procedures (hospital databases only) recorded in the month/week before/at the date of treatment start. The top 10 most frequent (clinically relevant) co-morbidities from large-scale patient characterisation recorded (1) at index date [primary definition] and (2) in the week before index date, (2) in the month before index date [sensitivity analyses] were provided as proxies for indication.

Table 8. Operational definitions of covariates.

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
Indication of Use	Top 10 most frequent co-morbidities and procedures from large-scale patient characterisation	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
Summary characteristics of new users by list of pre-defined conditions/medications of interest	Patient-level characterisation with regard to baseline co-variates by pre-defined conditions/medications of interest.	Counts	Demographics, co-morbidities and co-medication within anytime to 366 days before index date (ID), 365 days before ID to ID	Biobank, primary and secondary care	SNOMED, RxNorm	N/A	Persons with new use during the study period	N/A	N/A

9.7 Study size

No sample size had been calculated as this is a descriptive study. Prevalence and incidence of opioid use among the study population were estimated as part of Objective 1. Feasibility counts were provided in the Appendix.

9.8 Data transformation

All databases were mapped 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 is 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 returned the results set which only contained aggregated data. The results from each of the contributing data sites were combined in tables and figures for the study report.

9.9 Statistical methods

9.9.1 Main summary measures

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, (4) by route (oral, transdermal or parenteral) for overall opioids and stratified by history of cancer.

Prevalence calculations

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

An illustration of the calculation of period prevalence is shown below in **Figure 2.** Illustration for prevalence estimation. 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%.

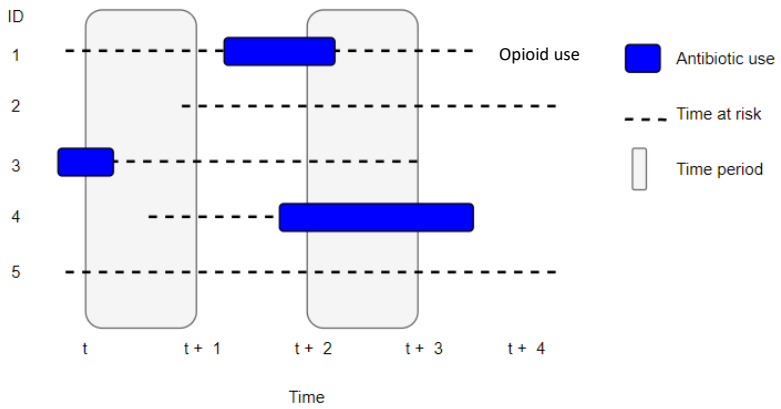

Figure 2. Illustration for prevalence estimation.

Incidence calculations

Annual incidence rates of the opioid of interest were calculated as the of number of **new users** after 356 days 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 entered 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 9.2.2 (study period and end of follow-up). Incidence rates were given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of opioid use is shown below in **Figure 3**. 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.

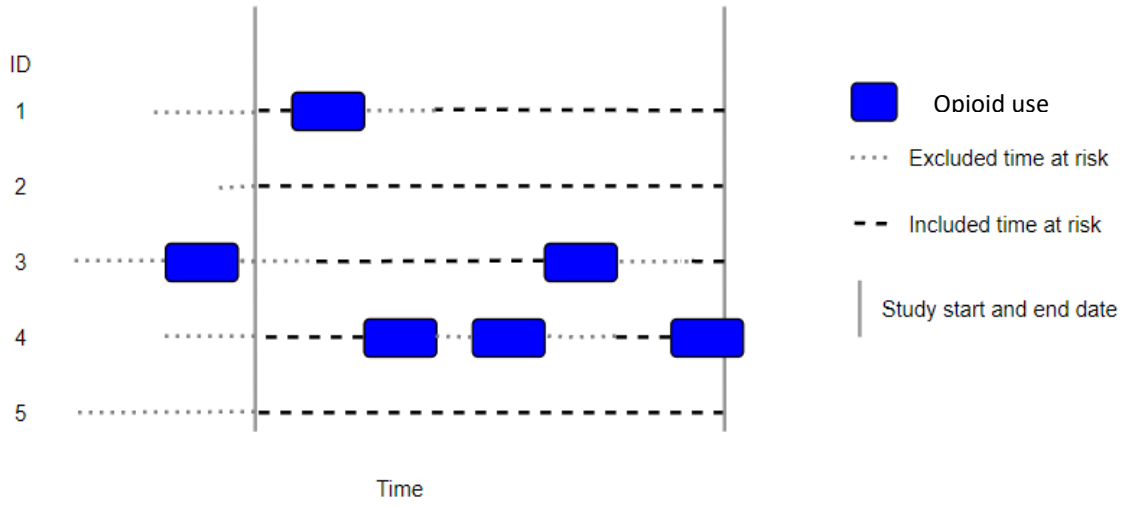

Figure 3. Illustration for incidence estimation.

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 was provided.

Indication

Indications were assessed based on a high-level approach considering the 10 most frequent conditions (all databases) and procedures (hospital databases only) 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 was provided.

Treatment duration

Treatment duration was calculated as the duration of the first treatment era of the opioid of interest during the study period. Treatment duration was summarised 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 was not provided.

9.9.2 Main statistical methods

Analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed. Once all the tests were passed, 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 review and approved the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations were performed, and additional fine tuning of the code base was needed. A service desk was available during the study execution for support.

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 can start. All results were locked and timestamped for reproducibility and transparency.

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 was reported as <5.

Details on type of analysis were given in **Table 9**.

Table 9. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates - Population-based prevalence of use of a drug/drug class
Patient Level DUS	Off-the-shelf	- Characterisation of patient-level features - Large-scale characterisation for indication/s - Estimation of minimum, p25, median, p75, and maximum treatment duration

9.9.4 Sensitivity analysis

Table 10. 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
Window to assess indication of use	Indication of use was 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

9.9.5 Deviations from the protocol

- In the protocol, at least 1 year of prior data availability was required to be included for the population-level utilisation of opioids. However, hospital database utilise the admission of patients to start the observation period. For individuals without prior visit to the hospital, they would not be included in the study cohort as planned in the protocol given the 365 days of prior observation requirement, leading to substantial loss of individuals in the hospital databases. Therefore, the 1-year prior data availability requirement was not applied to hospital databases.
- IQVIA LPD Belgium defined the observation period based on patient visit rather than records of registration with practice and/ or death record. Therefore, the assumption that a patient belonged to a practice (i.e. contributed to the denominator) can only be me made for dates between the first and last visit of the patient. This has a strong impact towards the database end resulting in a reduced denominator as the full denominator depends on the frequency of visits including future visits that have not yet taken place, which could lead to increase in prevalence or incidence towards the end of data availability in the database. To mitigate this, we did not conduct the analyses of incidence and prevalence within the 6 months before the last data availability in the database.
- Drug records in NLHR were only available since 2018, therefore the prevalent use of opioids would appear as incident use. For this reason, population DUS in NLHR would only be started from 2019 despite fulfilling the 1-year prior data availability requirement.
- Sensitivity analysis with washout period of 180 days was removed in the routinely repeated study. For this reason, assessment window for baseline characteristic was updated from [-Inf, -366], [-365, -181], [-180, -1], [ID, ID] to [-Inf, -366], [-365, ID].
- Type of cancer for characterising cancer opioid users was updated, changing from separate Hodgkin lymphoma and non-Hodgkin lymphoma to lymphoma as a broad group.
- It was stated in protocol that opioid exposure was based on prescription data. It has now been updated that exposure was based on dispensation data in EBB, DK-DHR and NLHR, and prescription data in other databases.

10. DATA MANAGEMENT

All databases had previously mapped their data to the OMOP common data model. This enabled the use of standardised analytics and using DARWIN EU 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.

The analytic code for this study was written in R and used standardised analytics. Each data partner executed the study code against their database containing patient-level data, and then returned the results (csv files) which only contained aggregated data. The results from each of the contributing data sites were combined in tables and figures for the study report.

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 data partners ran 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.

Before executing the study code, we used the DrugExposureDiagnostics R Package (https://darwin-eu.github.io/DrugExposureDiagnostics/) to summarise the ingredient specific drug exposure data of each database. The results from the diagnostics provided detailed information related to drug dose, form, and days of supply, which informed us whether a database have sufficient information for the patient level DUS analysis.

When defining cohorts for cancer history, a systematic search of possible codes for inclusion has been identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). This software allows the user to define a search strategy and using this, then query the vocabulary tables of the OMOP common data model to find potentially relevant codes.

The study code is available on GitHub: darwin-eu-studies/P3-C2-002-RR-DUS-Opioids.

12. RESULTS

All the results are available in a shiny app: data.darwin-eu.org/p3-c2-002opioid/, including additional stratifications not presented in the main report.

12.1 Participants

The study included 2,186,170 individuals from CDW Bordeaux, 6,766,607 individuals from DK-DHR, 209,576 individuals from EBB, 2,487,567 individuals from IPCI, 7,482,435 individuals from SIDIAP, 827,455 individuals from IMASIS, 670,162 individuals from IQVIA LPD Belgium and 5,625,017 individuals from NLHR eligible for the incidence analysis.

Attrition of the study population for incidence of overall opioids use is provided in **Table 11**.:

Table 11. Attrition table of denominator for the incidence of overall opioid use.

Reason	Variable name			
	Excluded records	Number records	Excluded subjects	Number subjects
CDW Bordeaux				
Starting population		*2,363,709*		*2,363,709*
Missing year of birth	0	2,363,709	0	2,363,709
Missing sex	1,255	2,362,454	1,255	2,362,454
Cannot satisfy age criteria during the study period based on year of birth	1,188	2,361,266	1,188	2,361,266
No observation time available during study period	172,447	2,188,819	172,447	2,188,819
Prior history requirement not fulfilled during study period	0	2,188,819	0	2,188,819
No observation time available after applying age, prior observation and, if applicable, target criteria	6	2,188,813	6	2,188,813
Starting analysis population		*2,188,813*		*2,188,813*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-179,147	2,367,960	2,643	2,186,170
DK-DHR				
Starting population		*9,235,411*		*8,593,356*
Missing year of birth	0	9,235,411	0	8,593,356
Missing sex	0	9,235,411	0	8,593,356
No observation time available during study period	1,747,887	7,487,524	1,339,441	7,253,915
Prior history requirement not fulfilled during study period	449,390	7,038,134	372,690	6,881,225
Starting analysis population		*7,038,134*		*6,881,225*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-2,812,016	9,850,150	114,618	6,766,607
EBB				
Starting population		*211,725*		*211,725*
Missing year of birth	0	211,725	0	211,725
Missing sex	0	211,725	0	211,725
No observation time available during study period	1,637	210,088	1,637	210,088
Prior history requirement not fulfilled during study period	0	210,088	0	210,088
Starting analysis population		*210,088*		*210,088*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-68,497	278,585	512	209,576

Reason	Variable name			
	Excluded records	Number records	Excluded subjects	Number subjects
IPCI				
Starting population		*2,954,616*		*2,954,616*
Missing year of birth	0	2,954,616	0	2,954,616
Missing sex	0	2,954,616	0	2,954,616
No observation time available during study period	99,069	2,855,547	99,069	2,855,547
Prior history requirement not fulfilled during study period	323,123	2,532,424	323,123	2,532,424
Starting analysis population		*2,532,424*		*2,532,424*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-450,577	2,983,001	44,857	2,487,567
SIDIAP				
Starting population		*8,553,325*		*8,553,325*
Missing year of birth	0	8,553,325	0	8,553,325
Missing sex	0	8,553,325	0	8,553,325
No observation time available during study period	733,570	7,819,755	733,570	7,819,755
Prior history requirement not fulfilled during study period	278,910	7,540,845	278,910	7,540,845
Starting analysis population		*7,540,845*		*7,540,845*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-2,596,600	10,137,445	58,410	7,482,435
IMASIS				
Starting population		*1,747,852*		*1,747,852*
Missing year of birth	0	1,747,852	0	1,747,852
Missing sex	0	1,747,852	0	1,747,852
No observation time available during study period	919,738	828,114	919,738	828,114
Prior history requirement not fulfilled during study period	0	828,114	0	828,114
Starting analysis population		*828,114*		*828,114*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-118,875	946,989	659	827,455
IQVIA LPD BELGIUM				
Starting population		*1,094,334*		*1,094,334*
Missing year of birth	0	1,094,334	0	1,094,334
Missing sex	0	1,094,334	0	1,094,334
No observation time available during study period	15,538	1,078,796	15,538	1,078,796

Reason	Variable name			
	Excluded records	**Number records**	**Excluded subjects**	**Number subjects**
Prior history requirement not fulfilled during study period	393,793	685,003	393,793	685,003
Starting analysis population		*685,003*		*685,003*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-178,040	863,043	14,841	670,162
NLHR				
Starting population		*6,148,772*		*6,114,138*
Missing year of birth	0	6,148,772	0	6,114,138
Missing sex	0	6,148,772	0	6,114,138
No observation time available during study period	139,138	6,009,634	118,504	5,995,634
Prior history requirement not fulfilled during study period	216,522	5,793,112	211,976	5,783,658
Starting analysis population		*5,793,112*		*5,783,658*
Apply washout criteria of 365 days (note, additional records may be created for those with an outcome)	-1,526,861	7,319,973	131,641	5,652,017

Remarks: The '**Number records'** and **'Number subjects'** for the row '*starting population*' and '*starting analysis population'* were the starting number of records/subjects. The **'Number records/subjects'** for the row with exclusion reason were the number of records/subjects after exclusion for that particular reason. In some databases, multiple records were observed from one person for '*starting population*'. This is due to the definition of observation period in the respective database (e.g. ending observation period when the person emigrates and starting another new observation period when the person returns). Please note that it is possible to have more **'Number records'** after applying washout criteria, e.g. the person who discontinued from exposure for more than 365 days would return as a new record and contribute to denominator population. For the addition in **'Number records'** after applying the washout criteria, it was presented as a negative number in the '**Excluded records'** column.

12.2 Main results

Objective 1. Population-level drug utilisation

A total number of 274,026 individuals (CDW Bordeaux), 2,183,760 individuals (DK-DHR), 60,286 individuals (EBB), 132,762 individuals (IMASIS), 484,556 individuals (IPCI), 205,461 individuals (IQVIA LPD Belgium), 1,888,433 individuals (NLHR) and 2,204,608 individuals (SIDIAP) were identified as incident opioid users during the study period of 2012-2024.

The numbers of incident opioid users with no history of cancer ranged from 56,367 (EBB) to 2,155,971 (SIDIAP), and that with history of cancer ranged from 5,326 (IQVIA LPD Belgium) to 300,743 (DK-DHR) (**Table 12**).

Table 12. Number of incident opioids users during the study period 2012-2024.

	Year included	N (included subjects (denominator))	N (subjects with new opioid prescription)		
			Overall	…without a history of cancer in 1 year before prescription	…with a history of cancer in 1 year before prescription
CDW Bordeaux	2012-2024	2,186,170	274,026	225,300	55,979
DK-DHR	2012-2024	6,766,607	2,183,760	2,061,948	300,743
EBB	2012-2022	209,576	60,286	56,367	6,413
IMASIS	2012-2024	827,455	132,762	120,275	21,560
IPCI	2012-2024	2,487,567	484,556	458,775	54,010
IQVIA LPD Belgium	2015-2024	670,162	205,461	202,947	5,326
NLHR	2019-2023	5,625,017	1,888,433	1,781,024	195,511
SIDIAP	2012-2023	7,482,435	2,204,608	2,155,971	126,915

OVERALL OPIOIDS USE

Incidence

Incidence of overall opioid use (Error! Reference source not found.) was highest in IQVIA LPD Belgium, s tarting at 12,757/100,000 person-years in 2016 to 15,366/100,000 person-years in 2023.

EBB was starting as the lowest incidence of overall opioid use in 2012 at the incidence of 2,410. However, the incidence gradually increased over years and reached 6,627 in 2022.

DK-DHR was starting with the second highest incidence of overall opioid use in 2012 at 6,590, while the incidence decreased over time and became the lowest among all included databases in 2023 at 4,526.

All databases, except for EBB, showed a dip in incidence of overall opioid use during the COVID-19 pandemic period of 2020-2021. However, from 2022 onwards incidence rates returned to the pre-pandemic levels or even higher. Without considering the period of 2020-2021, there was an increasing trend in incidence of overall opioid use in CDW Bordeaux, EBB, IMASIS and IQVIA LPD Belgium, a slightly decreasing trend in IPCI, and a substantial decrease in DK-DHR over time.

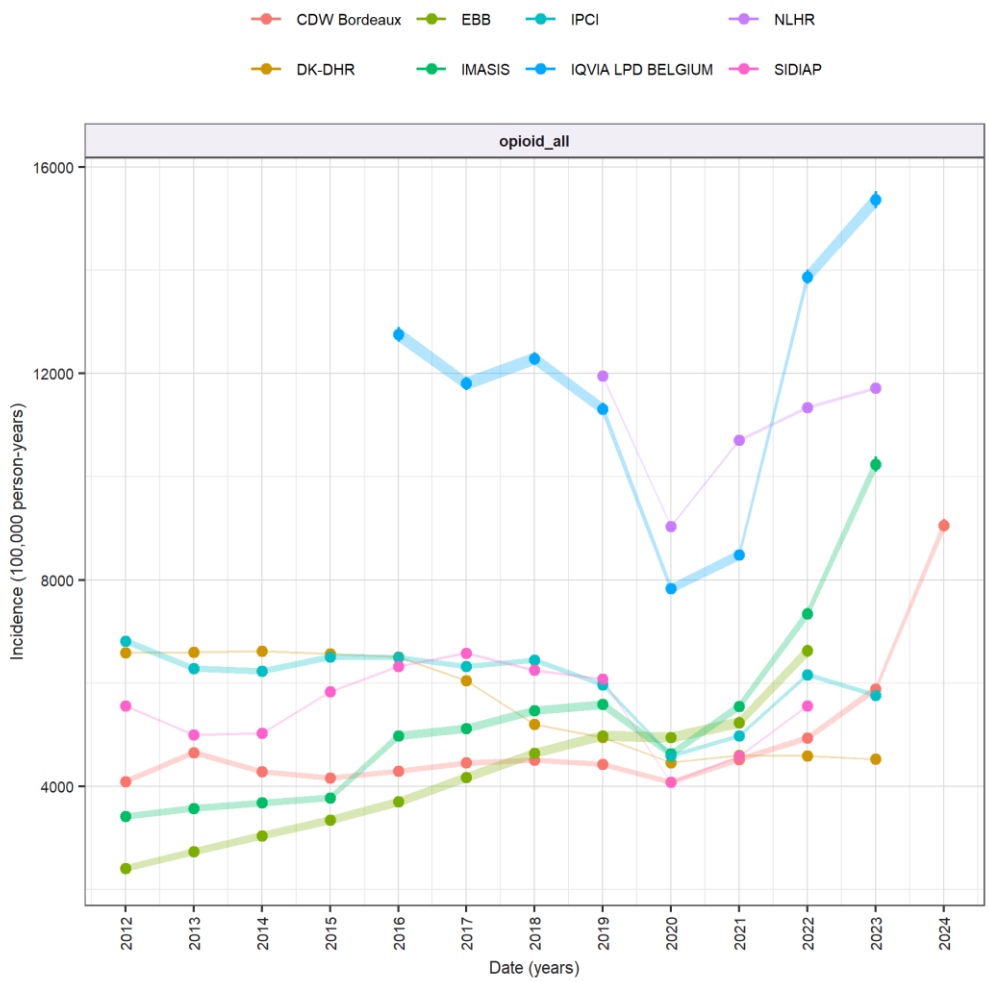

Figure 4. Incidence of opioids (all), overall.

Remark: As shown in **Figure 5**, incidence of opioid use had increased by 2-fold in CDW Bordeaux (4,096 in 2012 to 9,057 in 2024) and by 3-fold in IMASIS (3,416 in 2012 to 10,242 in 2023). Both IMASIS and CDW Bordeaux are hospital databases and defined the observation period by visits and records. An increase in

incidence of overall opioid use was observed in CDW Bordeaux from 2022 to 2024 and in IMASIS from 2021 to 2023. When considering the number of opioid users and number of denominators for the incidence analysis, there was a drop in the number of people included in the denominator population during 2022-2023 in IMASIS and between 2023-2024 in CDW Bordeaux (**Figure 5**). This might have led to the increase in the estimates incidence rates in 2023 and 2024 for both hospital databases.

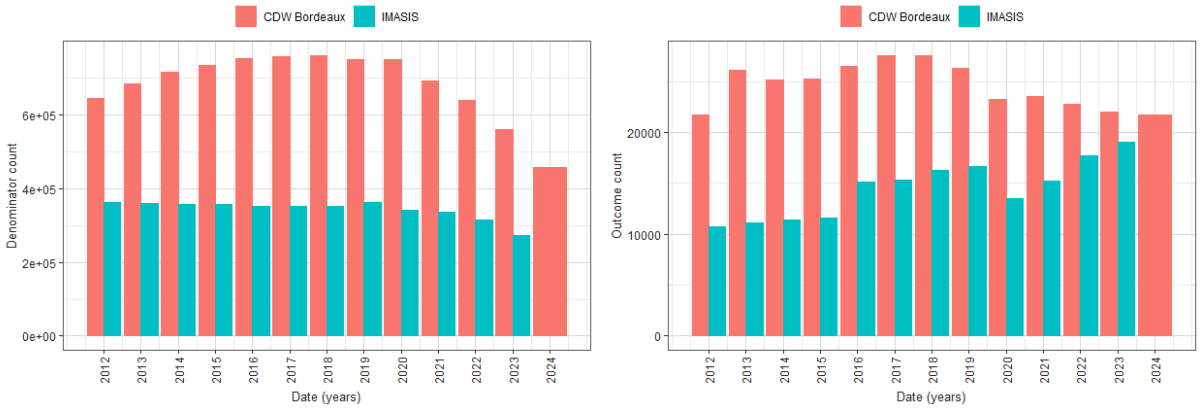

Figure 5. Denominator counts and number of prescriptions in CDW Bordeaux and IMASIS.

Left panel: Denominator counts in CDW Bordeaux (red) and IMASIS (green) over time
Right panel: Number of prescriptions in CDW Bordeaux (red) and IMASIS (green) over time

However, for the period up until 2021 we observed an increasing trend in opioid prescription in IMASIS and (less pronounced) in CDW Bordeaux.

IQVIA LPD Belgium also shared the same problem on observation period defined by records and therefore there remained a sharp decrease in denominator and inflation in incidence during 2022-2023.

In contrast, the incidence of overall opioid use in EBB increased steadily over the year from 2012 to 2022. The number of opioid users increased from 4,916 in 2012 to 12,370 in 2022 with the denominator population remained rather stable.

Overall opioids use, stratified by history of cancer

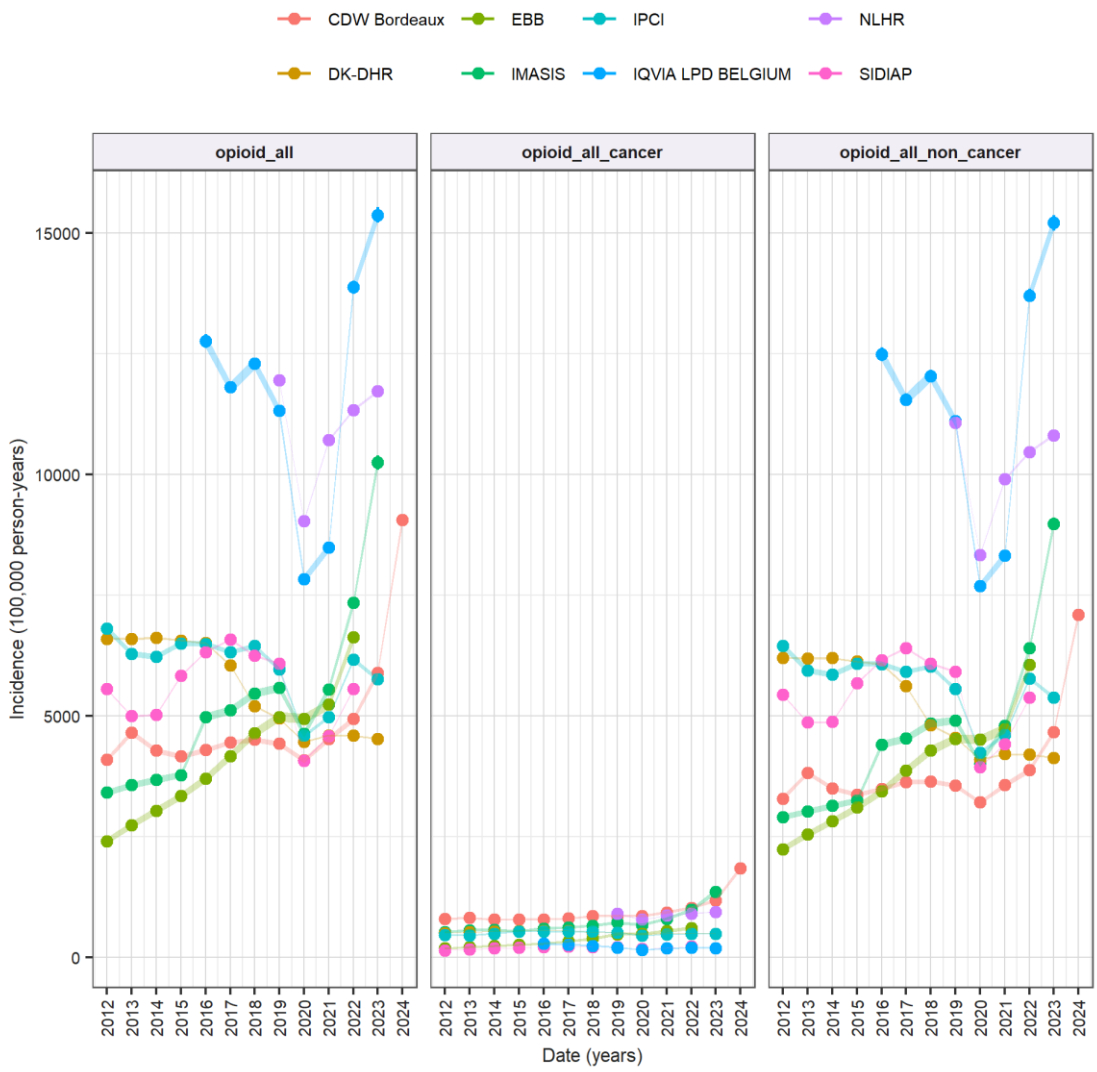

Figure 6. Incidence of opioids all, stratified by history of cancer.

As shown in **Figure 6**, the incidence of overall opioid prescriptions was dominated by prescriptions without a history of cancer.

When considering the opioid use with a record of recent history of cancer (**Figure 7**), the dip in incidence during the COVID-19 pandemic period of 2020-2021 was less prominent compared to that of non-cancer opioid use. **Figure 7** shows the incidence rates in more detail.

There was an increase in incidence of cancer opioids in CDW Bordeaux, EBB and IMASIS, decreasing trend in IQVIA LPD Belgium, while remaining stable in DK-DHR, IPCI and SIDIAP. When comparing the incidence of cancer opioid use across the different databases, the distribution and ranking was different from that of overall opioid use. IQVIA LPD Belgium had a lower incidence of cancer opioid use (291/100,000 person-years in 2016 to 198/100,000 person-years in 2023). Contrary to the highest incidence of non-cancer opioid use among all included database, IQVIA LPD Belgium had the lowest incidence of cancer opioid since 2019. SIDIAP had the lowest incidence of cancer opioid use when starting in 2012 (151) and remained as the

second lowest in 2022 (230). CDW Bordeaux had the highest incidence of cancer opioid use (801 in 2012 to 1,850 in 2024).

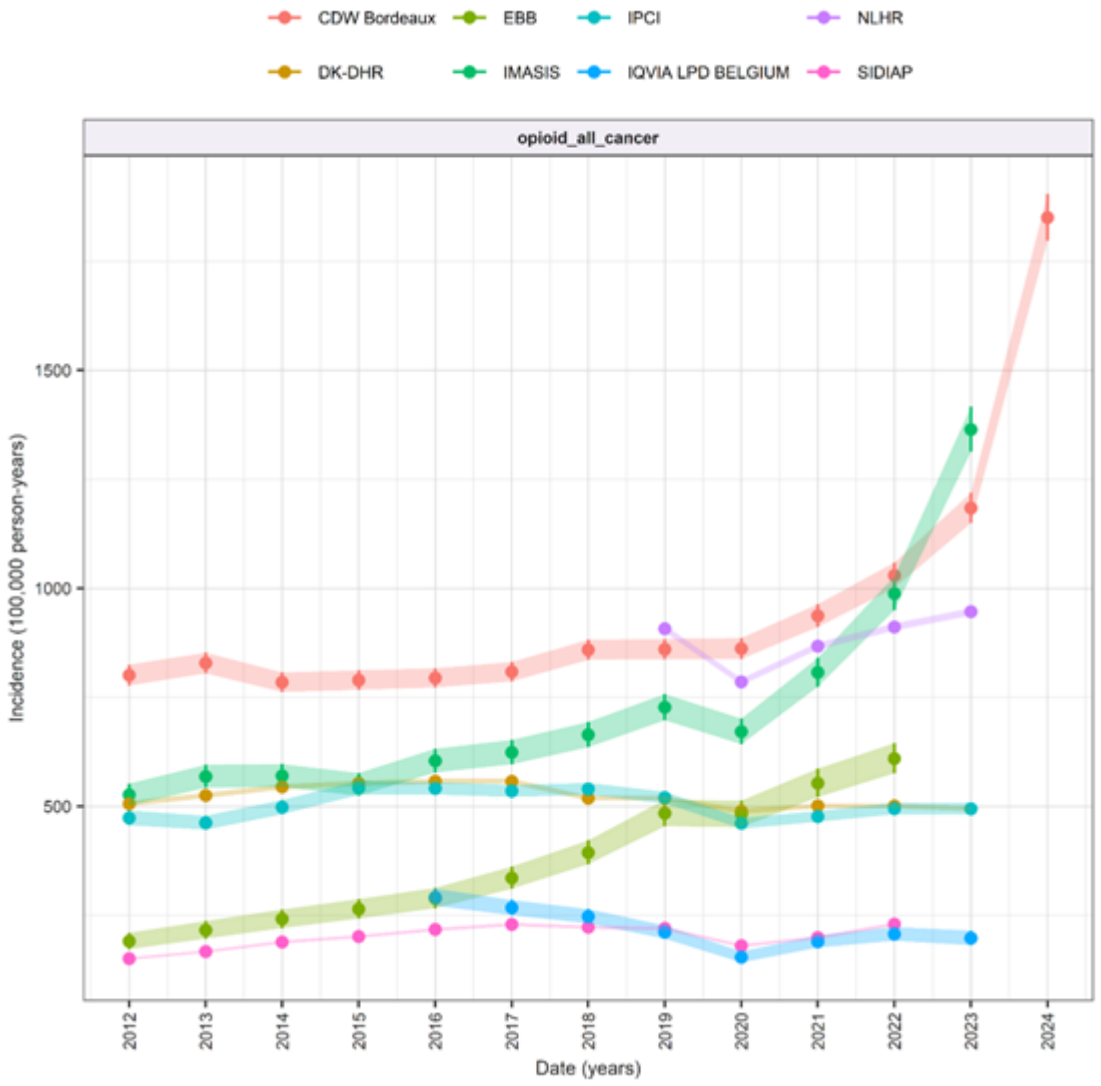

Figure 7. Incidence of opioids with recent record of cancer.

An increase in incidence of opioids with history of cancer was observed in CDW Bordeaux, EBB and IMASIS, whereas there was a decreasing trend in IQVIA LPD Belgium. Incidence remained largely stable in DK-DHR, IPCI and SIDIAP.

When comparing the incidence of cancer opioid use across the different databases, highest incidence rates were seen in hospital databases as expected. Contrary to the highest incidence of opioid prescriptions without cancer history among all included databases, IQVIA LPD Belgium had the lowest incidence of opioid prescriptions with cancer history since 2019. SIDIAP had the lowest incidence of cancer opioid use when starting in 2012 (151) and remained as the second lowest in 2022 (230). CDW Bordeaux had the highest incidence of cancer opioid use (801 in 2012 to 1,850 in 2024).

Prevalence

The prevalence of overall opioid use shared similar pattern to incidence (**Figure 8**).

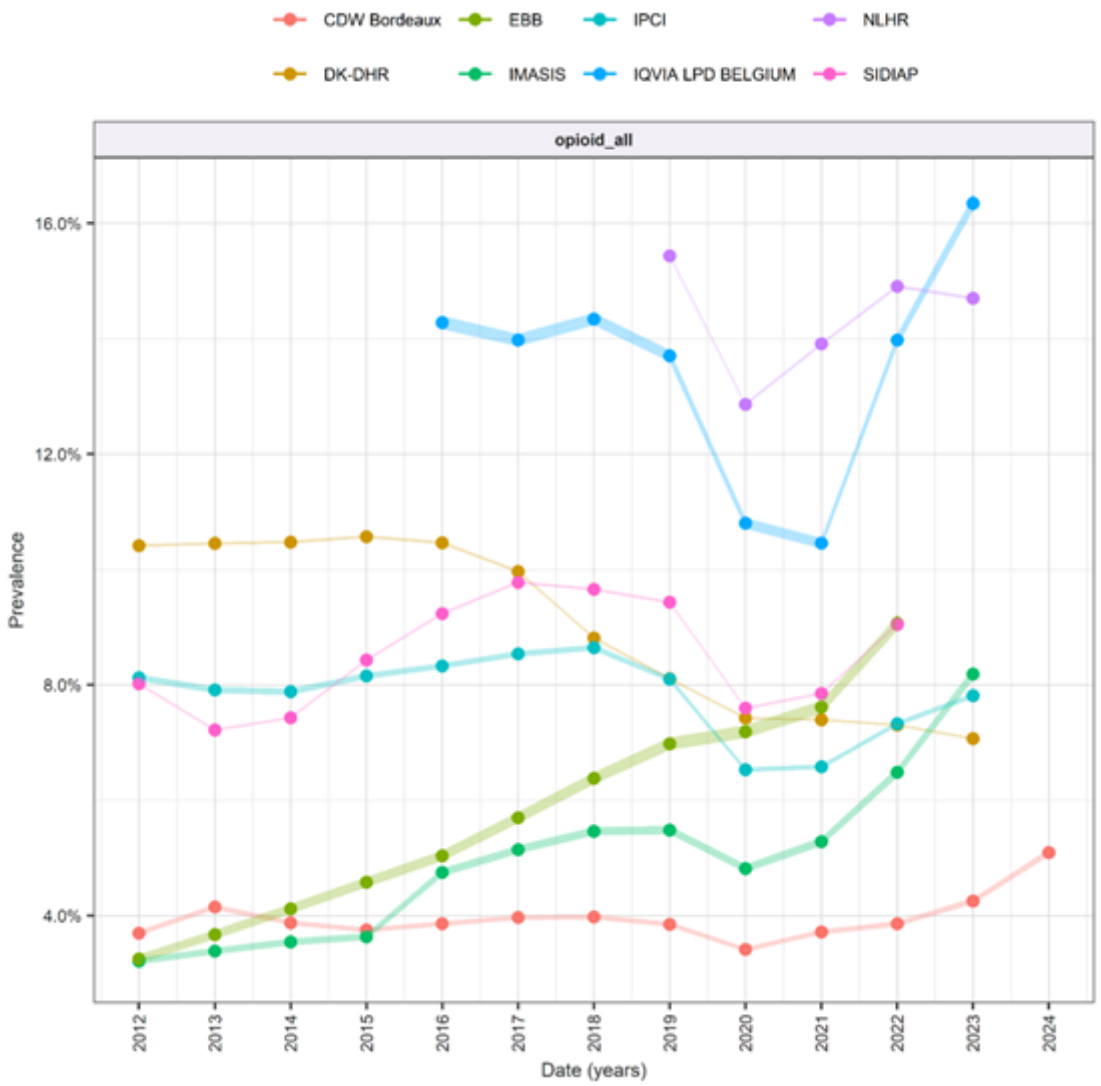

Figure 8. Prevalence of opioids all, overall.

Highest prevalence was observed in IQVIA LPD Belgium (ranging from 13.7% to 16.3% during the study period excluding 2020-2021) and NLHR (14.7-15.4% excluding 2020-2021). IMASIS had the lowest prevalence of overall opioid use during the early study period in 2012-2015 (3.2-3.6%) while CDW Bordeaux had the lowest prevalence of overall opioid use since 2016 (3.9-5.1%). Increase trend in prevalence of overall opioid use was observed in CDW Bordeaux, EBB, IMASIS and IQVIA LPD Belgium. After considering the denominator issues in databases, increasing trend in prevalence of overall opioid use was observed in EBB and IMASIS.

When considering the opioid use with/without history of cancer individually (**Figure 9, Figure 10**), NLHR had the highest prevalence of cancer opioid use among all databases, while that remained low in SIDIAP and IQVIA Belgium.

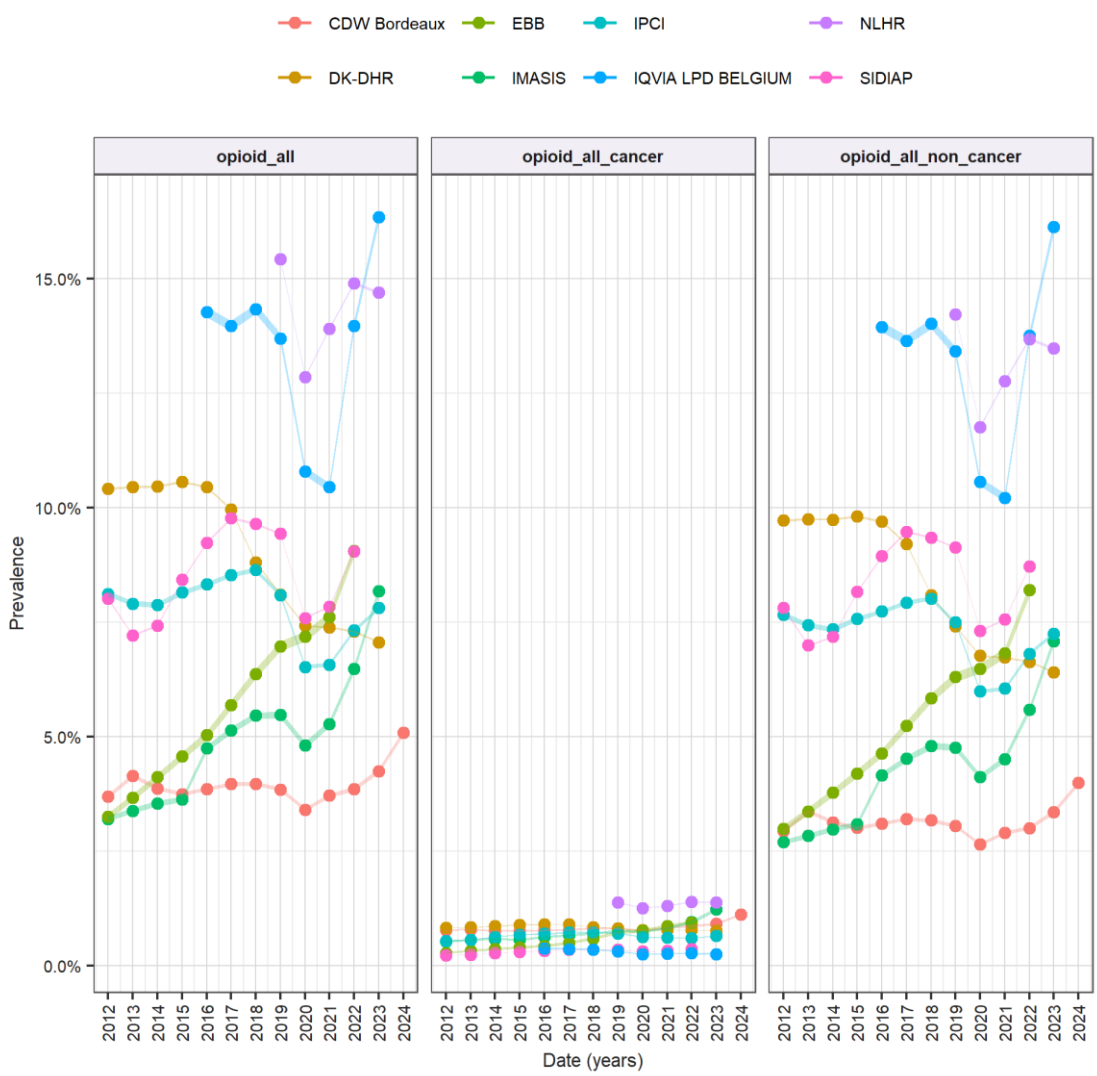

Figure 9. Prevalence of opioids all, overall and stratified by history of cancer.

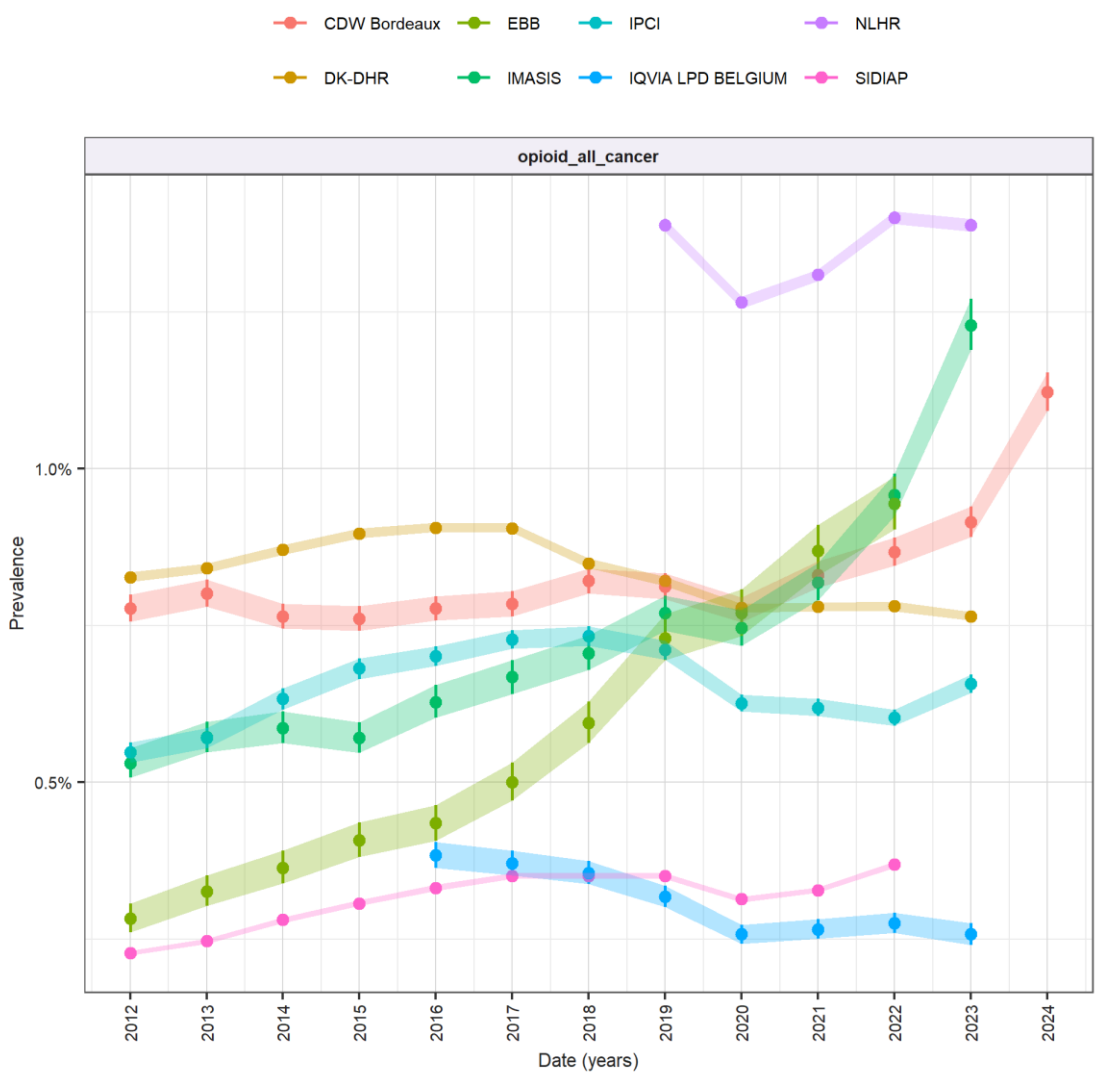

Figure 10. Prevalence of opioids with cancer.

Opioids by potency

Differences in incidence rate estimates and pattern were observed when stratified by opioid potency. Despite such, opioid use remained dominated by non-cancer opioid use regardless of potency. (**Figure 11**)

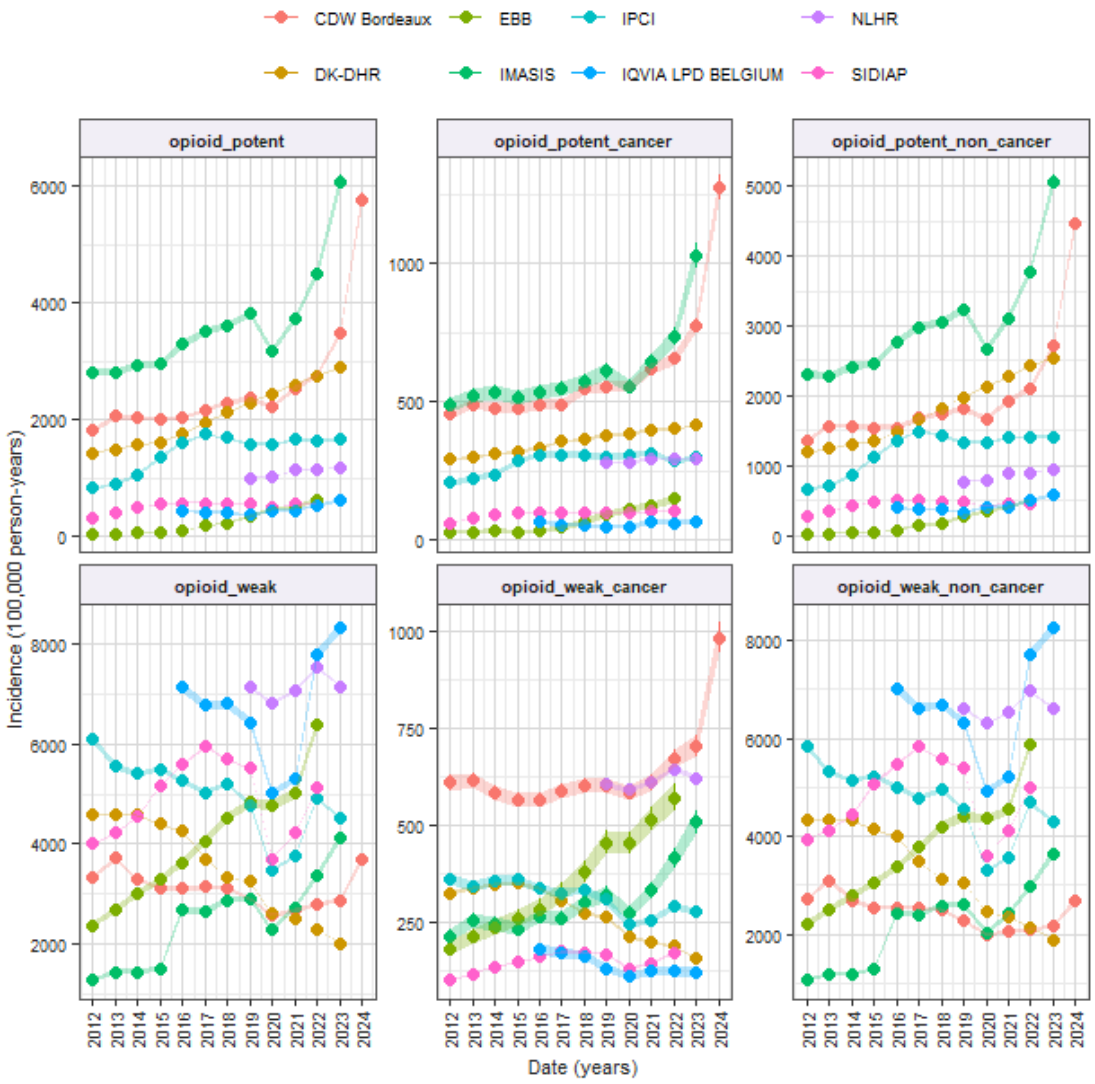

Figure 11. Incidence of opioids by potency, overall and stratified by cancer.

Incidence of weak opioid use shared similar pattern as incidence of overall opioid prescriptions. The dipping of trend during 2020-2021 was consistent in all databases except EBB, which showed an ongoing increasing trend, and DK-DHR, which showed an ongoing decreasing trend. In general, increasing trend of incidence of weak opioids was observed in EBB and IMASIS (after taking into account of denominator issue), while decreasing trend was observed in DK-DHR and IPCI. IQVIA LPD Belgium (ranging from 6,443/100,000 person-years in 2019 to 8,330/100,000 person-years in 2023 excluding 2020-2021) and NLHR (ranging from 7,150 in 2019 to 7,164 in 2023) were among the highest incidence of weak opioid prescriptions. IMASIS was starting with the lowest incidence of weak opioids use among all databases at 1,279 in 2012 but increased to 4,141 in 2023, while that in DK-DHR was dropping from 4,579 in 2012 to 2,007 in 2023 and becoming the lowest among all databases towards end of the study period. The incidence of weak opioid use increased by 2- to 3-fold in EBB and IMASIS while that in DK-DHR dropped by half.

The dipping trend in incidence of potent opioids during 2020-2021 was only observed in CDW Bordeaux and IMASIS. Increasing trend of potent opioid use was observed in all included databases, including both cancer potent opioid use and non-cancer potent opioid use. Highest incidence of potent opioid use was observed in IMASIS, with the incidence increased from 2,797 in 2012 to 3,731 in 2021 and further up to 6,068 in 2023 during the study period. The three databases with the lowest incidence were respectively EBB (42 in 2012 to 637 in 2022), IQVIA LPD Belgium (450 in 2016 to 633 in 2023) and SIDIAP (320 in 2012 to 542 in 2022).

When comparing incidence within the same database, IMASIS showed a higher incidence of potent opioid use than weak opioid. DK-DHR had a higher incidence in weak opioid use than potent opioid use when starting in 2012, but the incidence of potent opioid use became higher and taking over since 2021 while the difference of incidence between the two potency groups continued to diverge over time. Similarly CDW Bordeaux was starting with higher incidence in weak opioid use than potent opioid use, while incidence of potent opioid use overtook weak opioid use since 2022. Lower incidence of potent opioid use than weak opioid use was observed consistently in all other databases. Apart from CDW Bordeaux and DK-DHR, IPCI also showed an increasing trend in potent opioid use and decreasing trend in weak opioid use.

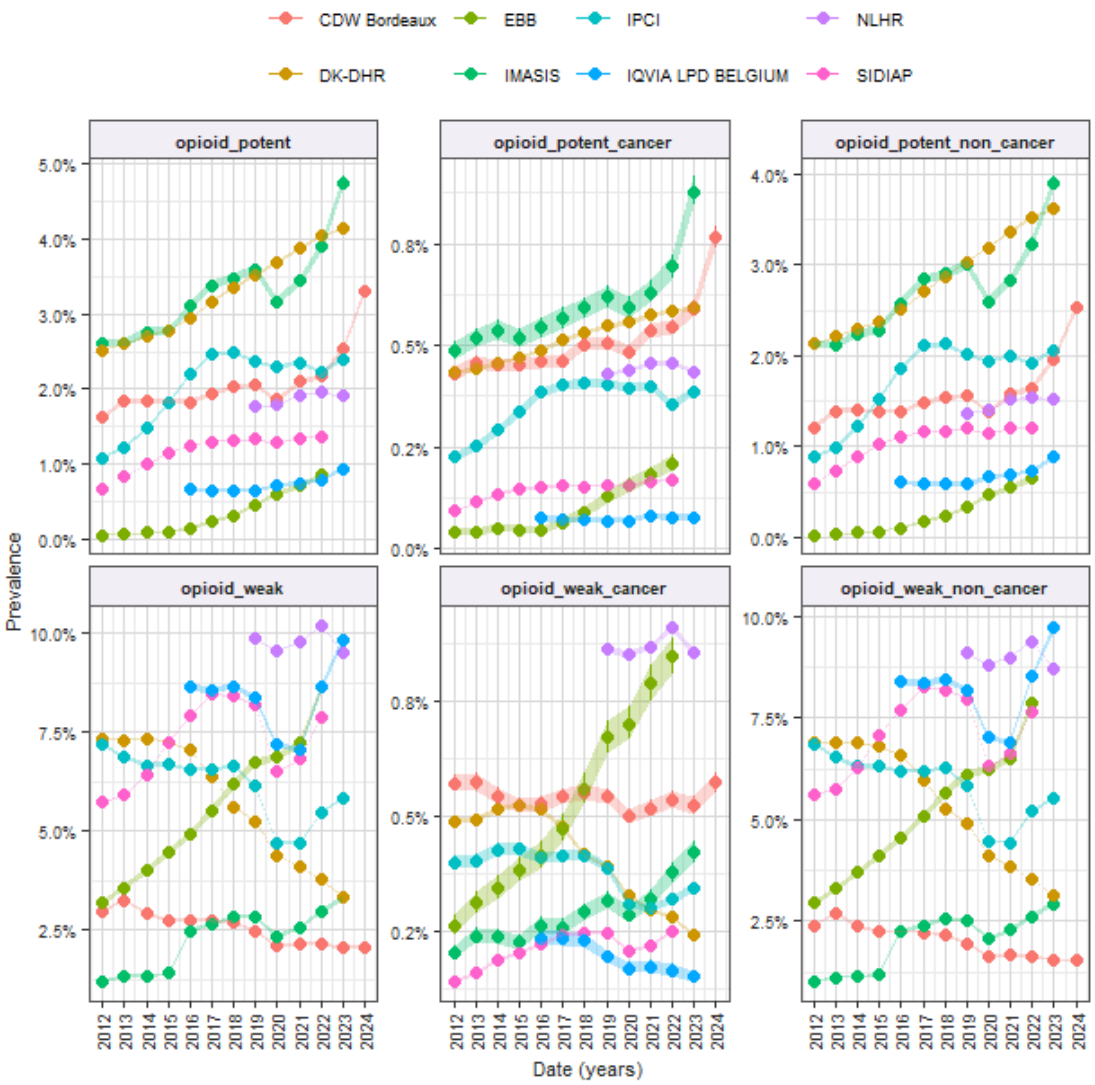

Figure 12. Prevalence of opioids by potency, overall and stratified by history of cancer.

Prevalence of opioid prescriptions when stratified by potency shared similar trend and pattern as in incidence (**Figure 12**). Prevalence of potent opioid use was the highest in IMASIS (2.6% in 2012 to 4.7% in 2023) and DK-DHR (2.5% in 2012 to 4.1% in 2023), and prevalence was the lowest in EBB (0.06% in 2012 to 0.9% in 2022). Prevalence of weak opioid use was highest in NLHR (9.9% in 2019 to 10.2% in 2022), while it was overtaken by IQVIA LPD Belgium in 2023 (9.8%). Lowest prevalence of weak opioid use was observed in IMASIS (1.2% in 2012 to 3.3% in 2023) and CDW Bordeaux (3.0% in 2012 to 2.1% in 2024).

Opioids by route of administration

Different trends and pattern of incidence rates were observed when opioid prescriptions were stratified by route of administration, with highest incidence rates being observed for oral formulations (**Figure 13**). When comparing incidence between different routes within the same database, the incidence of oral opioids was consistently higher than that of injectable opioid and transdermal opioid use in all databases except for IMASIS and CDW Bordeaux (both CDW Bordeaux and IMASIS are hospital databases).

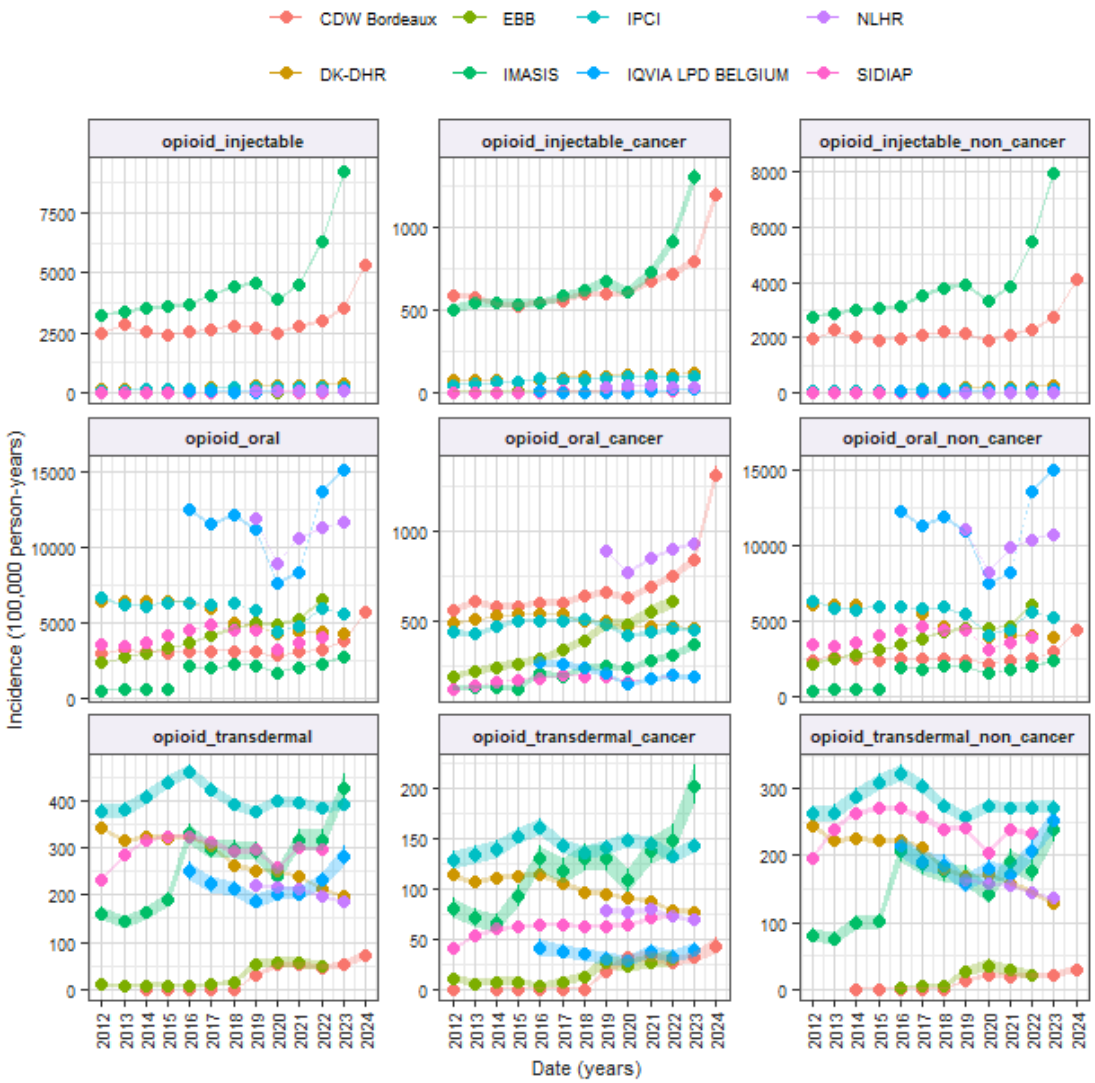

Figure 13. Incidence of opioids by routes, overall and stratified by history of cancer.

Trends and pattern of incidence of oral opioid use followed closely with the overall opioid a weak opioids group. Dipping in incidence during 2020-2021 was less prominent for injectable opioids and transdermal opioids compared to oral opioids. Dipping of incidence was only observed in IMASIS for injectable opioids, and IMASIS and SIDIAP for transdermal opioids (**Figure 13**).

Incidence of oral opioids was highest in IQVIA LPD Belgium (ranging from 11,175/100,000 person-years to 15,132/100,000 person-years excluding 2020-2021) and in NLHR (ranging from 11,266 to 11,869 excluding 2020-2021). Lowest incidence of oral opioids was observed in IMASIS, ranging from 555 to 2,761.

When considering the use of injectable opioids, the incidence was much higher in IMASIS (increasing from 3,262 in 2012 to 9,192 in 2023) and CDW Bordeaux (increasing from 2,516 in 2012 to 5,340 in 2024), compared to the other databases (ranging from 11 to 381 over the whole study period across all databases). However, an increasing trend in incidence of injectable opioids was observed in all databases except in EBB.

Incidence of transdermal opioids was the highest in IPCI, ranging from 376 to 462 during the study period, while that being overtaken by IMASIS in 2023 with an incidence of 428. Despite a 5-fold increase in the prescription of transdermal opioids in EBB (10 in 2012 to 50 in 2022), it remained at the lowest level, together with CDW Bordeaux, among all the databases. Incidence of transdermal opioids was increasing over years in CDW Bordeaux, EBB and IMASIS, while it was decreasing in DKK-DHR and NLHR.

Prevalence of opioids by routes is shown in **Figure 14**.

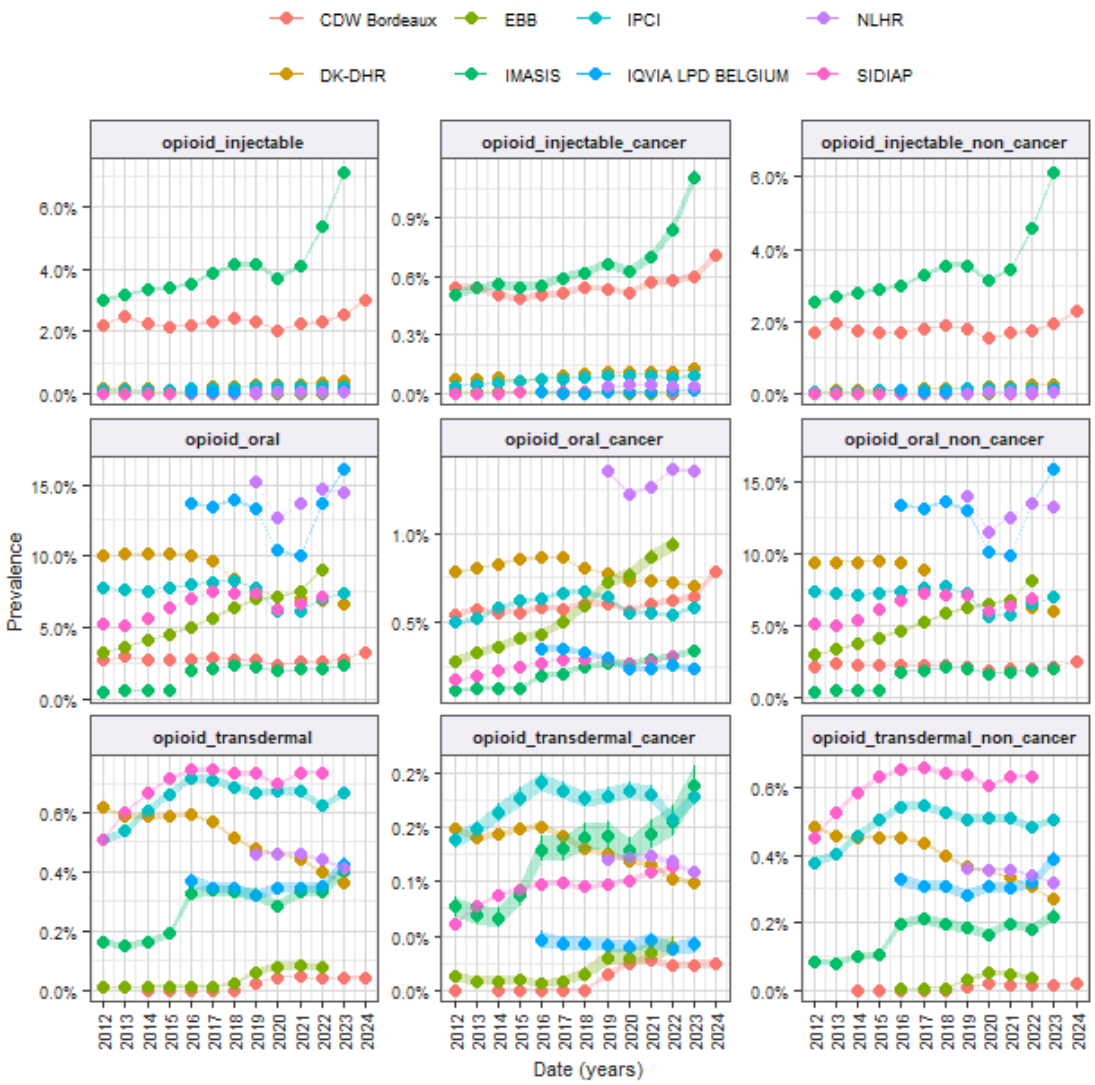

Figure 14. Prevalence of opioids by routes, overall and stratified by history of cancer.

Prevalence of oral opioid prescriptions was highest in IQVIA LPD Belgium (ranging from 13.3-16.0% excluding 2020-2021) and NLHR (14.5-15.2% excluding 2020-2021), with prevalence being lowest in IMASIS (0.5-2.4%) and CDW Bordeaux (2.4-3.3%). (**Figure 14**) Prevalence of injectable opioids was the highest in IMASIS, ranging from 3.0% to 7.1%, and the lowest in SIDIAP and EBB (<0.1% throughout the whole study period). Prevalence of transdermal opioids was similarly high in SIDIAP and IPCI, ranging from 0.5-0.7% for both databases. EBB and CDW Bordeaux had the lowest prevalence of transdermal opioids (<0.1%).

Opioids by ingredient

The top 10 most frequently prescribed opioid ingredients across all databases were, in descending order, tramadol, codeine, morphine, oxycodone, ethylmorphine, opium, dextromethorphan, fentanyl, buprenorphine and tapentadol. Among these, 5 of them (buprenorphine, fentanyl, morphine, oxycodone, tapentadol) were potent opioids.

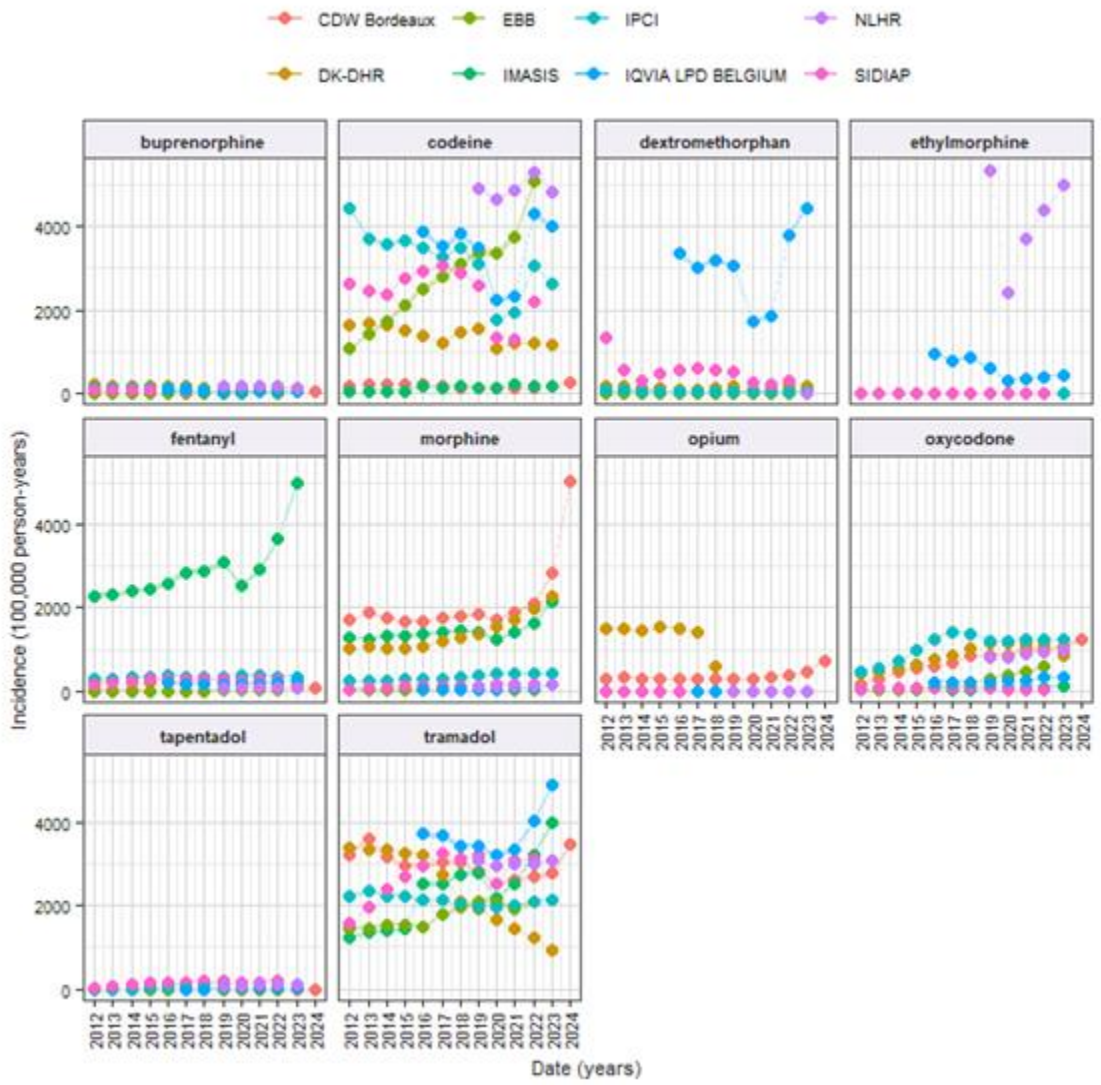

Figure 15. Incidence of opioids by ingredient.

Incidence of **morphine** prescriptions were increasing in all databases (**Figure 15**). Morphine incidence rates were highest in CDW Bordeaux (ranging from 1,701/100,000 person-years to 5,019/100,000 person-years excluding the 2020-2021), IMASIS (ranging from 1,281 to 2,168 excluding the 2020-2021) and DK-DHR (ranging from 1,013 to 2,296 excluding the 2020-2021) and lowest in EBB, ranging from 19 to 51.

Almost all databases, except SIDIAP, showed increasing incidence in **oxycodone** prescriptions. IPCI had the highest incidence of oxycodone prescriptions: rates increased from 487 in 2012, reaching the peak at 1426 in 2017 and maintained stably high at 1,234 in 2023. DK-DHR had the second highest incidence of oxycodone prescriptions, increasing from 412 in 2012 to 1156 in 2019, remained stable until 2022 and dropped to 868 in 2023. While NLHR, IQVIA LPD Belgium and IMASIS showed steady increase in incidence of oxycodone, a substantial increase was observed in EBB from 49 in 2015 to 579 in 2022 and in CDW Bordeaux from 184 in 2012 to 1,240 in 2024.

Fentanyl was most commonly prescribed in IMASIS, with incidence increasing from 2,297 to 4,996 over the study period. The incidence of fentanyl use ranged from 6-44 in EBB to 282-376 in IPCI, with the trend remaining steady over time.

A substantial increase in **tapentadol** incidence was observed in SIDIAP and IMASIS in early study period before 2016 and remained at high level (SIDIAP: ranging 166-203 during 2015-2022 excluding 2020-2021; IMASIS: ranging 71-143 during 2016-2023 excluding 2020-2021). NLHR had an incidence of tapentadol use increasing from 82 in 2019 to 134 in 2023. Other databases had a rather steady level of incidence of tapentadol. Incidence of tapentadol ranged from 12 in DK-DHR to 23 in IPCI in 2023.

Most databases showed a decreasing trend in **buprenorphine** incident prescriptions over the years, except for IMASIS (increasing from 19 in 2020 29 in 2021 and further up to 40 in 2023) and EBB (increasing from 4 in 2018 to 36 in 2020 and dropping to 12 in 2022). Incidence of buprenorphine use, in the two databases with the highest incidence, dropped from 224 (2012) to 110 (2023) in DK-DHR and from 174 (2019) to 148 (2023) in NLHR.

Tramadol was the most commonly prescribed opioid. Most databases showed an increase in the incidence of tramadol prescriptions over the study period, except DK-DHR. Tramadol prescriptions in CDW Bordeaux, IPCI and NLHR remained stable over time. IQVIA LPD Belgium had the highest incidence of tramadol among all databases, with incidence ranging from 3,718 in 2016 to 4,919 in 2023, while that in DK-DHR was dropping from 3,408 in 2012 to 929 in 2023.

Prevalence of individual opioid ingredient use followed closely with the incidence (**Figure 16**).

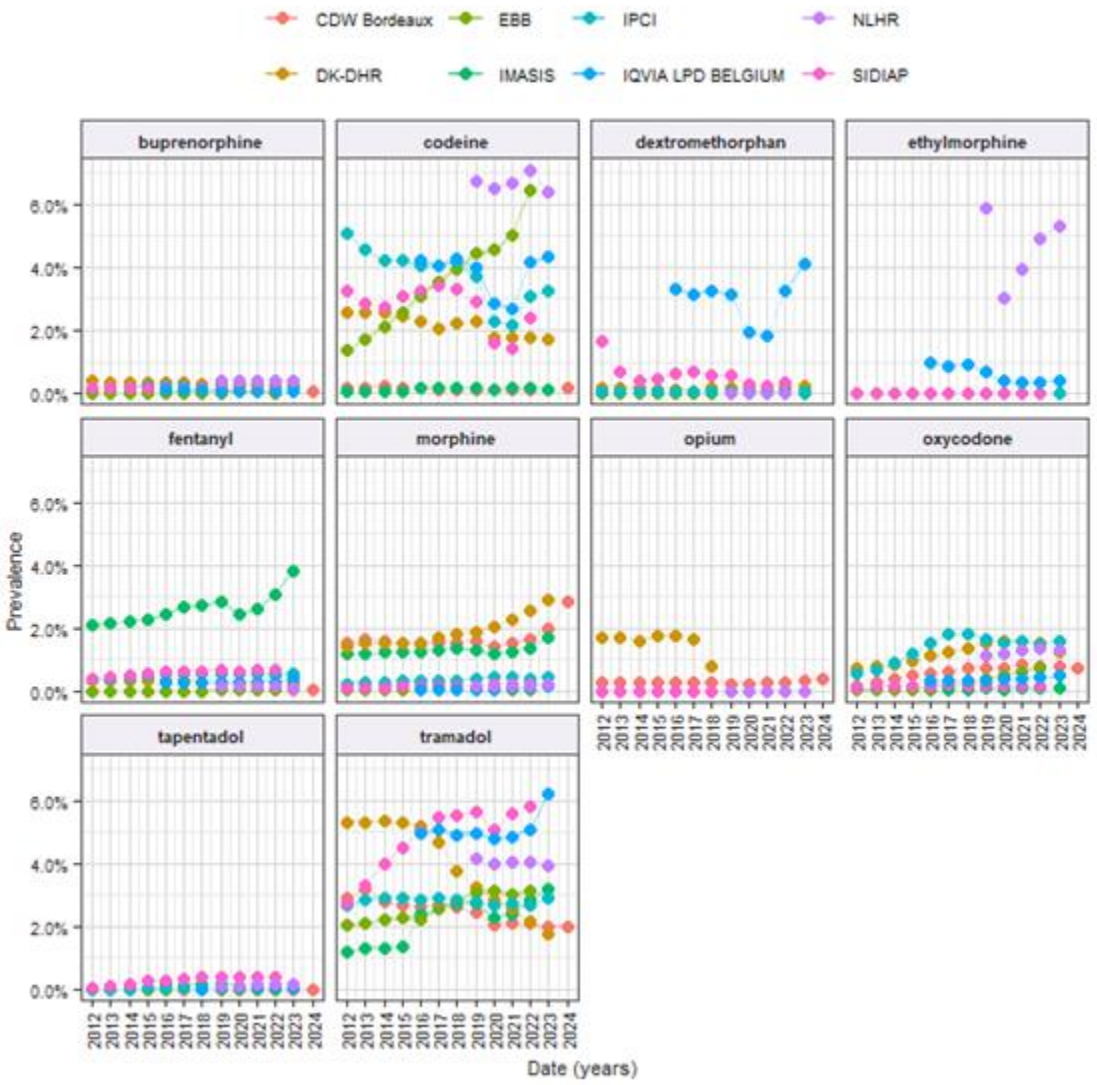

Figure 16. Prevalence of opioids by ingredient.

Naloxone and opioid-naloxone combination use

There has been an increasing trend in the use of naloxone in IMASIS, NLHR, and EBB, and a decreasing trend in SIDIAP and IQVIIA LPD Belgium (**Figure 17, Figure 18**). The use of naloxone in NLHR and SIDIAP was largely influenced by oxycodone-naloxone combination use, whereas in IQVIA LPD Belgium, it was mainly dominated by the tilidine-naloxone combination. The combination use of buprenorphine and naloxone has remained steady in recent years.

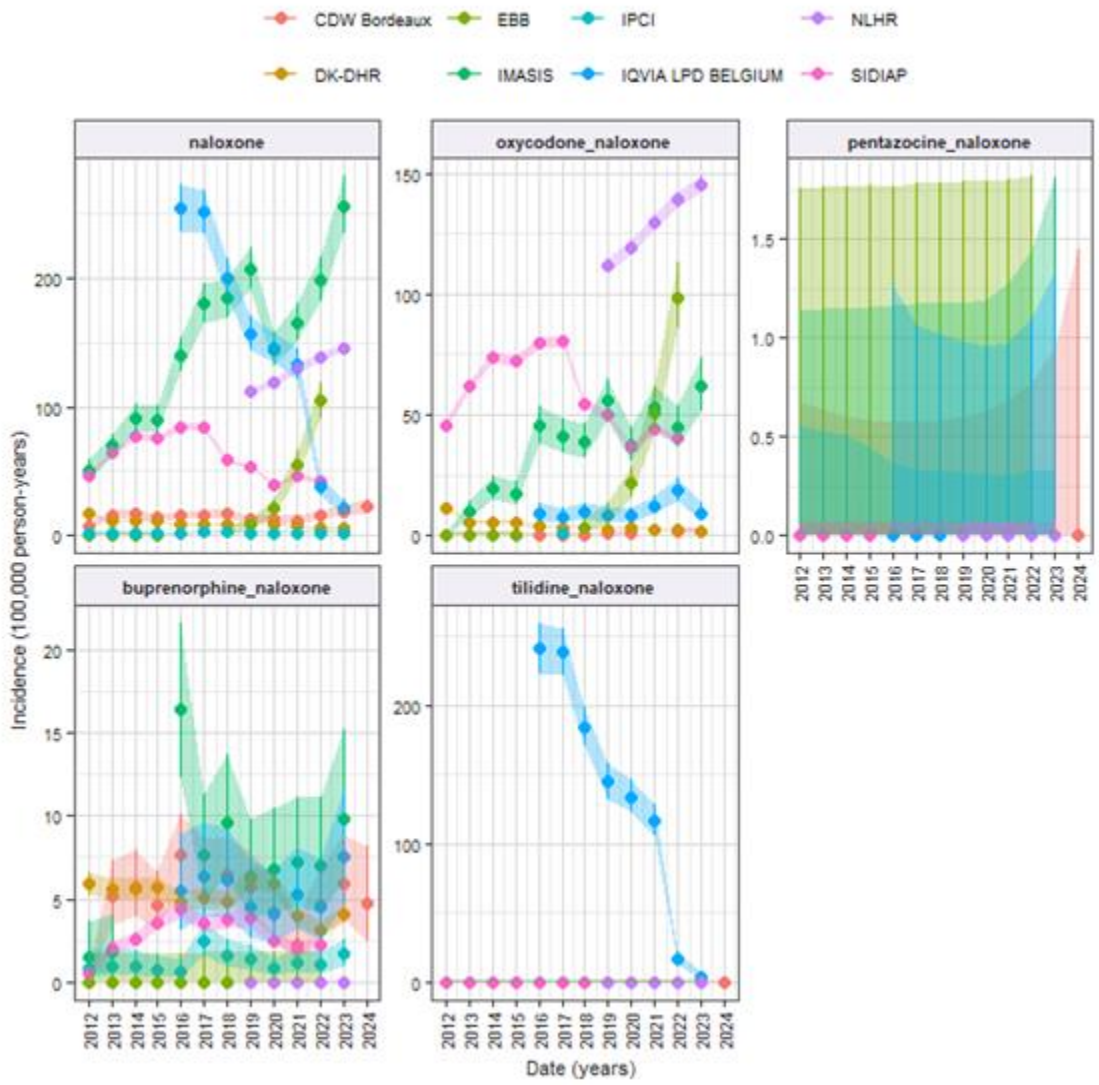

Figure 17. Incidence of naloxone and opioid-naloxone combination use.

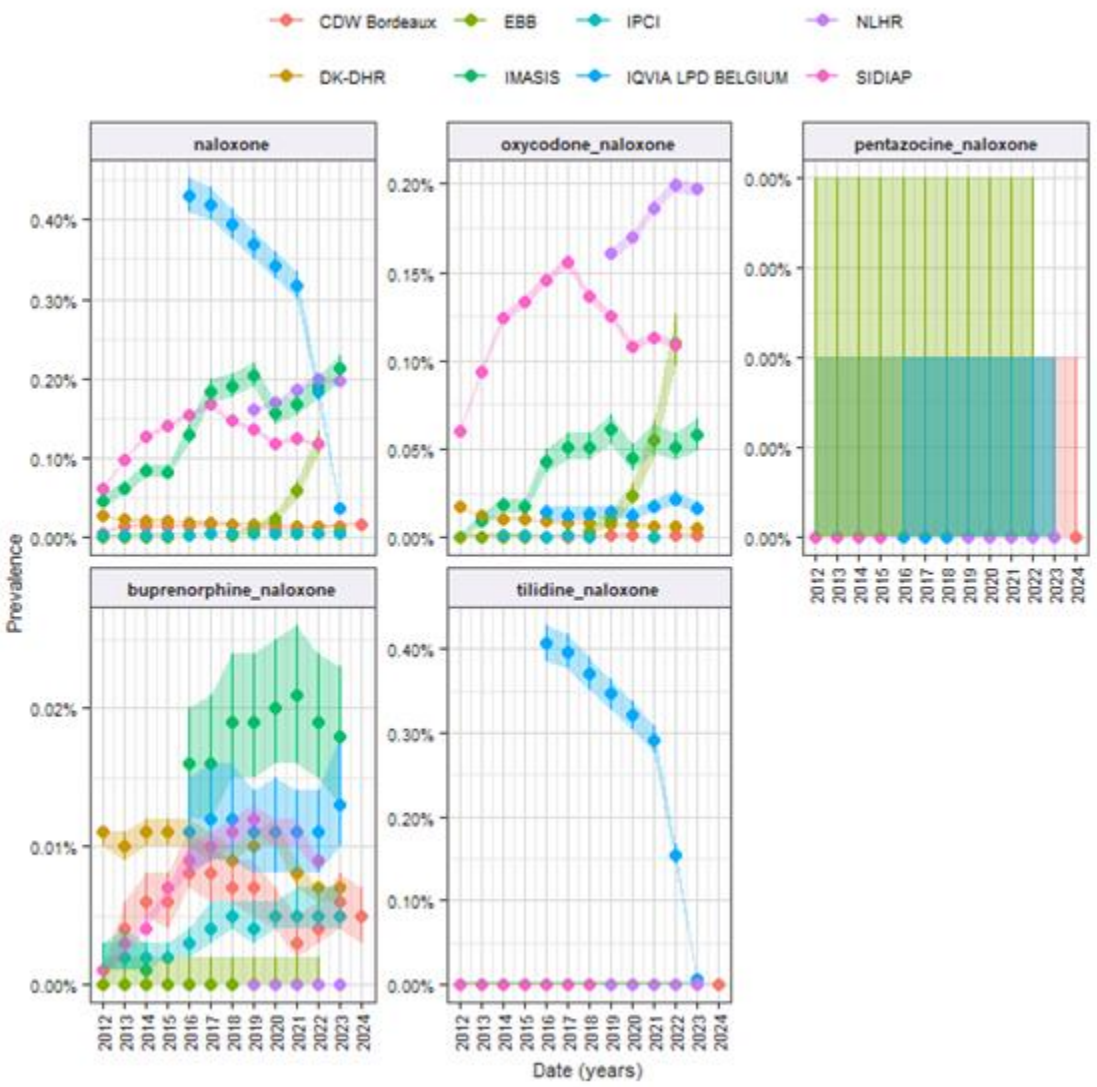

Figure 18. Prevalence of naloxone and opioid-naloxone combination use.

Overall opioid use stratified by age

When stratified the analysis by age groups, similar pattern in trends of opioid prescriptions were observed across different age groups within each database. In general, incidence (**Figure 19**) and prevalence (**Figure 20**) of opioid use increased with age. The increase was more prominent in DK-DHR, IPCI and SIDIAP.

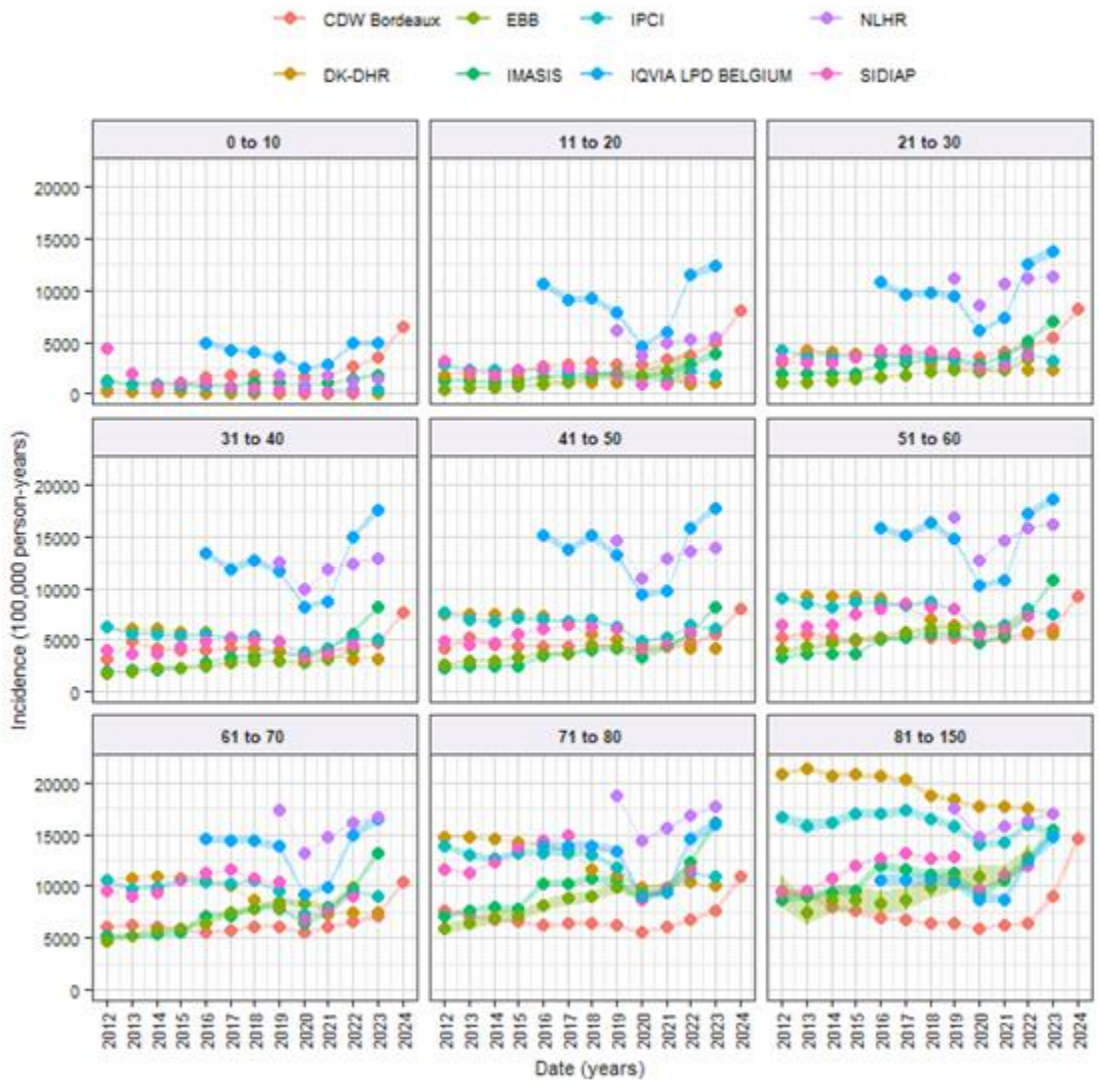

Figure 19. Incidence of opioids stratified by age.

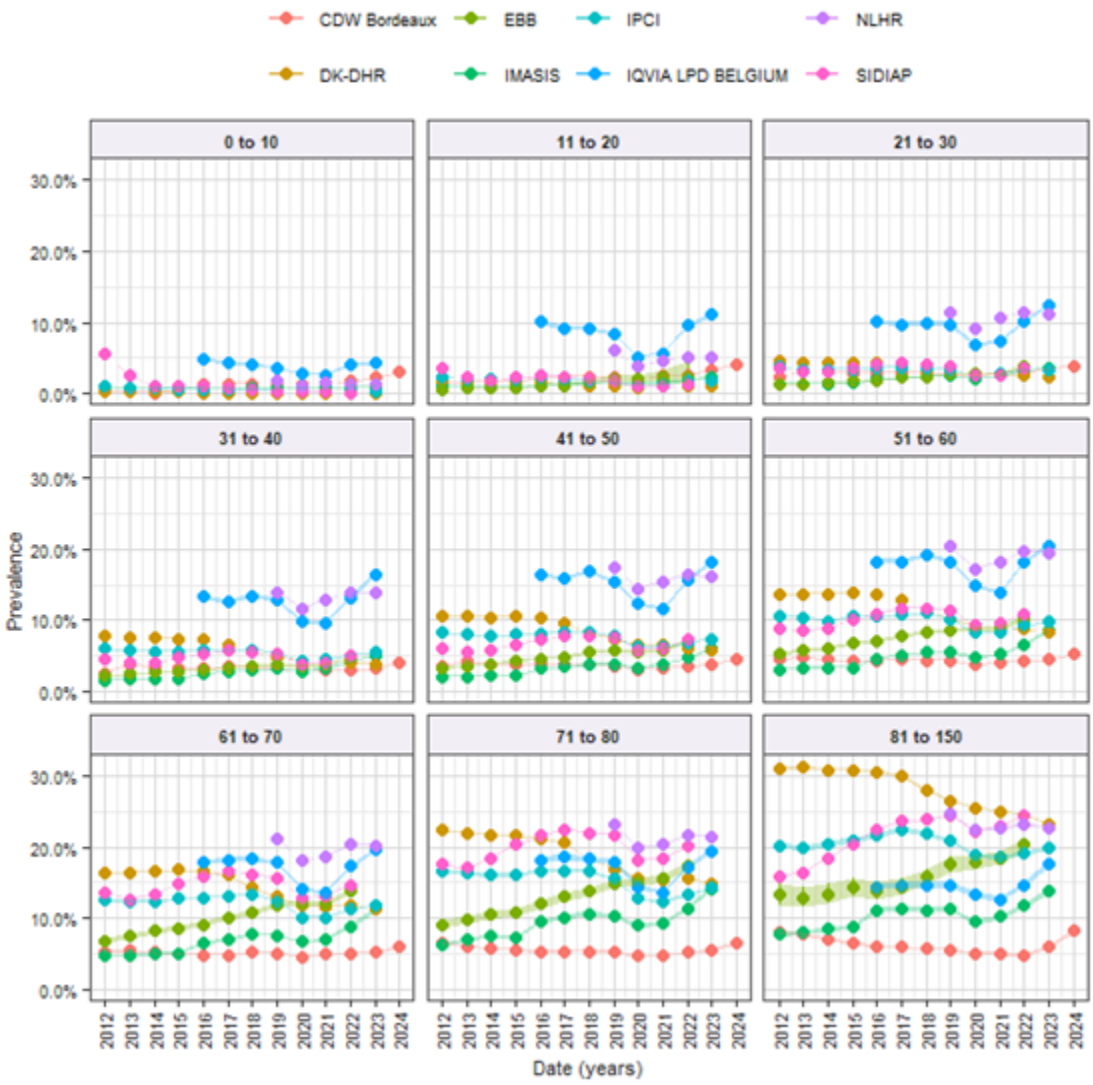

Figure 20. Prevalence of opioids stratified by age.

When considering the opioid prescriptions with history of cancer stratified by age, CDW Bordeaux and NLHR had the highest incidence in younger and middle-aged groups and older aged groups respectively (**Figure 21**). NLHR had the highest prevalence across all age groups (**Figure 22**). CDW Bordeaux had the highest incidence of cancer opioid use in younger age groups (ranging from 33-244/100,000 person-years in aged 11-20 to 168-505/100,000 person-years in aged 31-40) and in middle-aged groups (increasing from 523-1,177 in aged 41-50 to 1,818-3,865 in aged 61-40). In NLHR, the incidence of opioids with cancer increased from 394-495 in aged 41-50 to 3,547-4,104 in people aged above 80, while prevalence of opioids with cancer increased from 0.6-0.7% in aged 41-50 to 5.5-5.8% in people aged above 80.

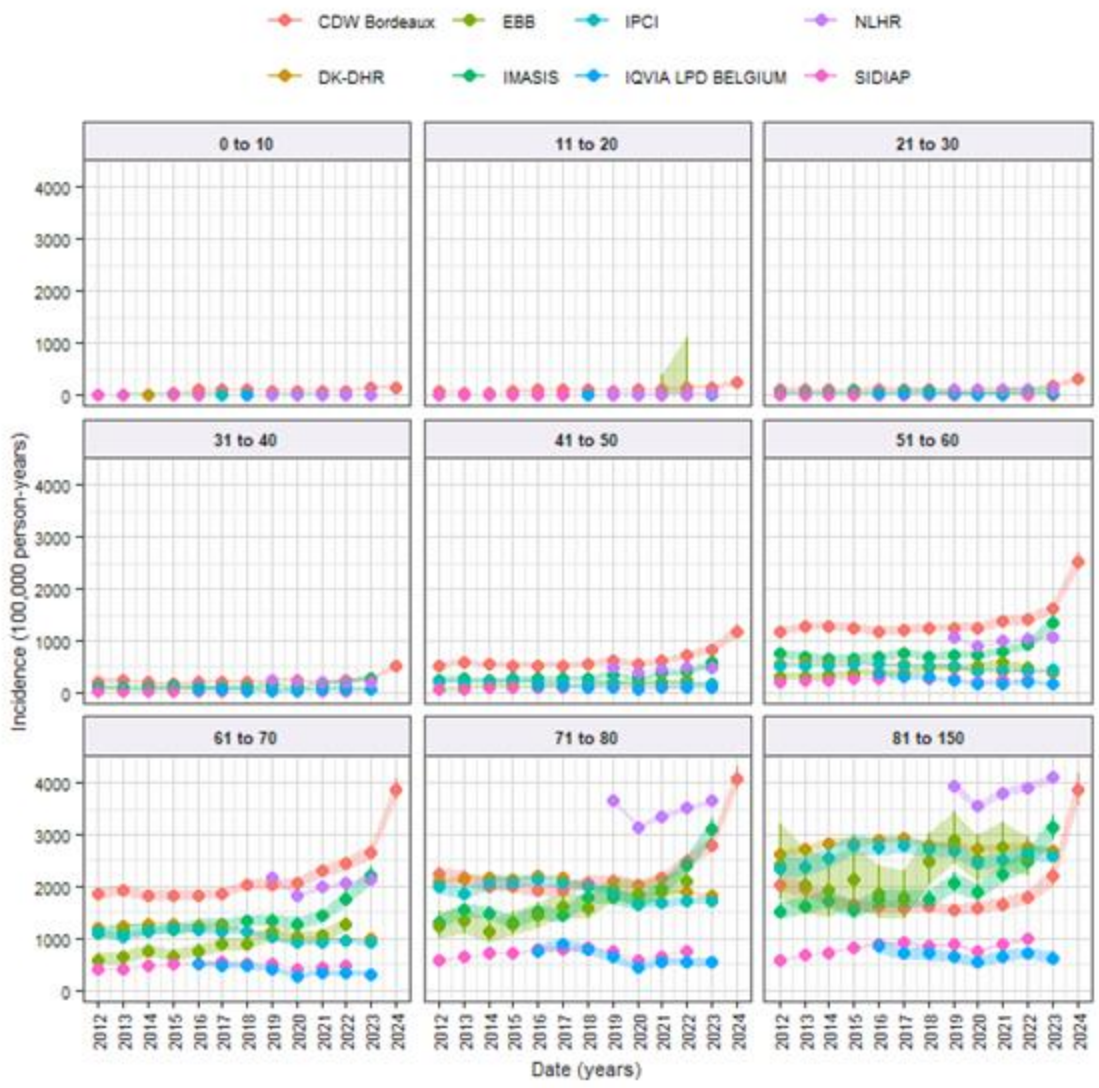

Figure 21. Incidence of opioids with history of cancer, stratified by age.

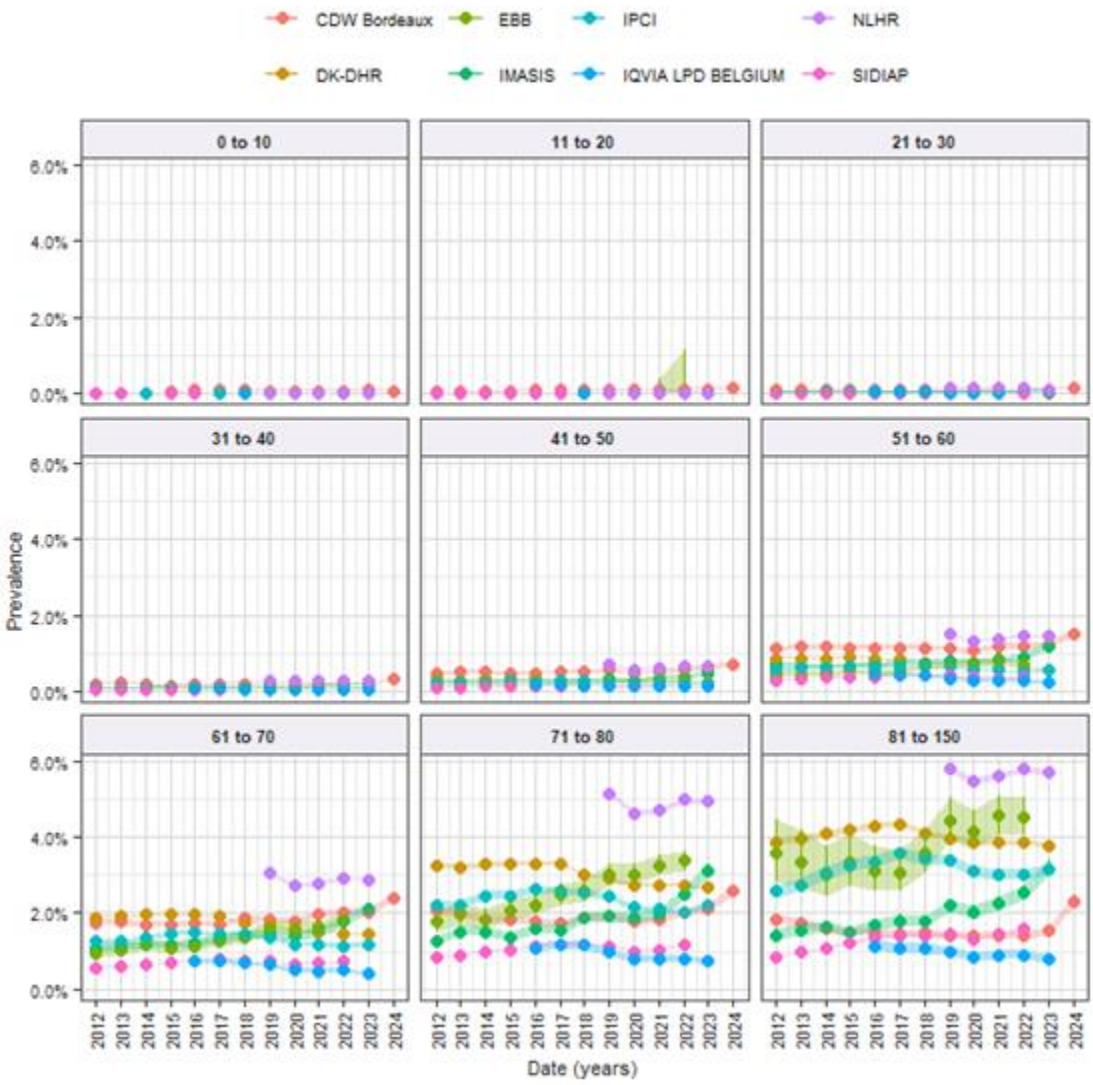

Figure 22. Prevalence of opioids with history of cancer, stratified by age.

For the incidence of opioid without cancer history stratified by age (**Figure 23**), IQVIA LPD Belgium had the highest incidence in younger age groups. In aged 0-10 group, the incidence of non-cancer opioid use decreased from 4,930 in 2016 to 3,558 in 2019. The incidence dipped to 2,457-2,829 during 2020-2021, and returned up high at 4,849 in 2022 and 4,833 in 2023. Without considering the period of 2020 and 2021, the incidence of non-cancer opioid use ranged from 7,895-12,365 in aged 11-20 to 14,565-18,478 in aged 51-60. NLHR also showed a high incidence of non-cancer opioid use in younger age groups, ranging from 4,929-6,175 in aged 11-20 to 13,604-15,668 in aged 51-60 without considering the incidence in 2020. IPCI and DK-DHR showed a significant increase in incidence of non-cancer opioid use with increasing age in older age groups. Without considering the period of 2020-2021, the incidence of non-cancer opioid use in IPCI increased from 8,191-9,587 in aged 61-70 to 12,808-14,851 in aged above 80. Incidence of non-cancer opioid use in DK-DHR doubled with increasing age, with that increasing from 6,371-9,701 in aged 61-70 to 14,473-18,864 in aged above 80.

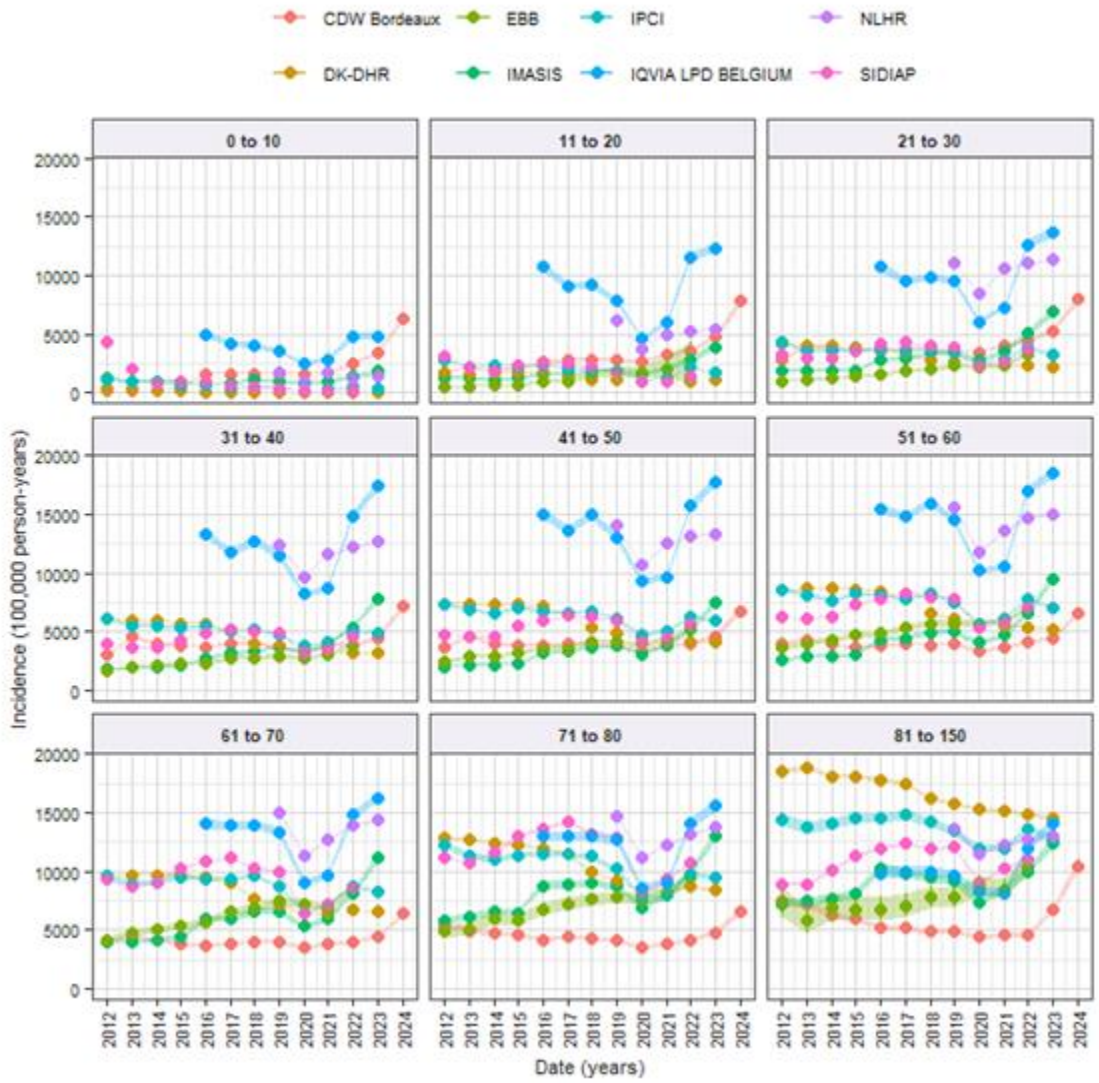

Figure 23. Incidence of opioids without history of cancer, stratified by age.

Trend in prevalence of opioid prescriptions without history of cancer (**Figure 24**) generally aligns with the incidence rates. Without considering the period of 2020-2021, the prevalence of non-cancer opioids in IQVIA LPD Belgium increased from 3.7-4.8% in aged 0-10 to 8.3-11.0% in aged 11-20, and further increased gradually to 17.9-20.3% in aged 51-60. In NLHR, without considering the estimate in 2020, the prevalence of non-cancer opioids increased from 4.7-6.0% in aged 11-20 to 10.6-11.3% in aged 21-30, and further up to 17.0-19.1% in aged 51-60. Prevalence of non-cancer opioids in DK-DHR, despite on decreasing trend over time in all age groups, increased with age, from 7.8-14.6% in aged 61-70 to 15.8-28.0% in aged above 80. Prevalence of non-cancer opioids in SIDIAP remained at a level above 20% from 2017.

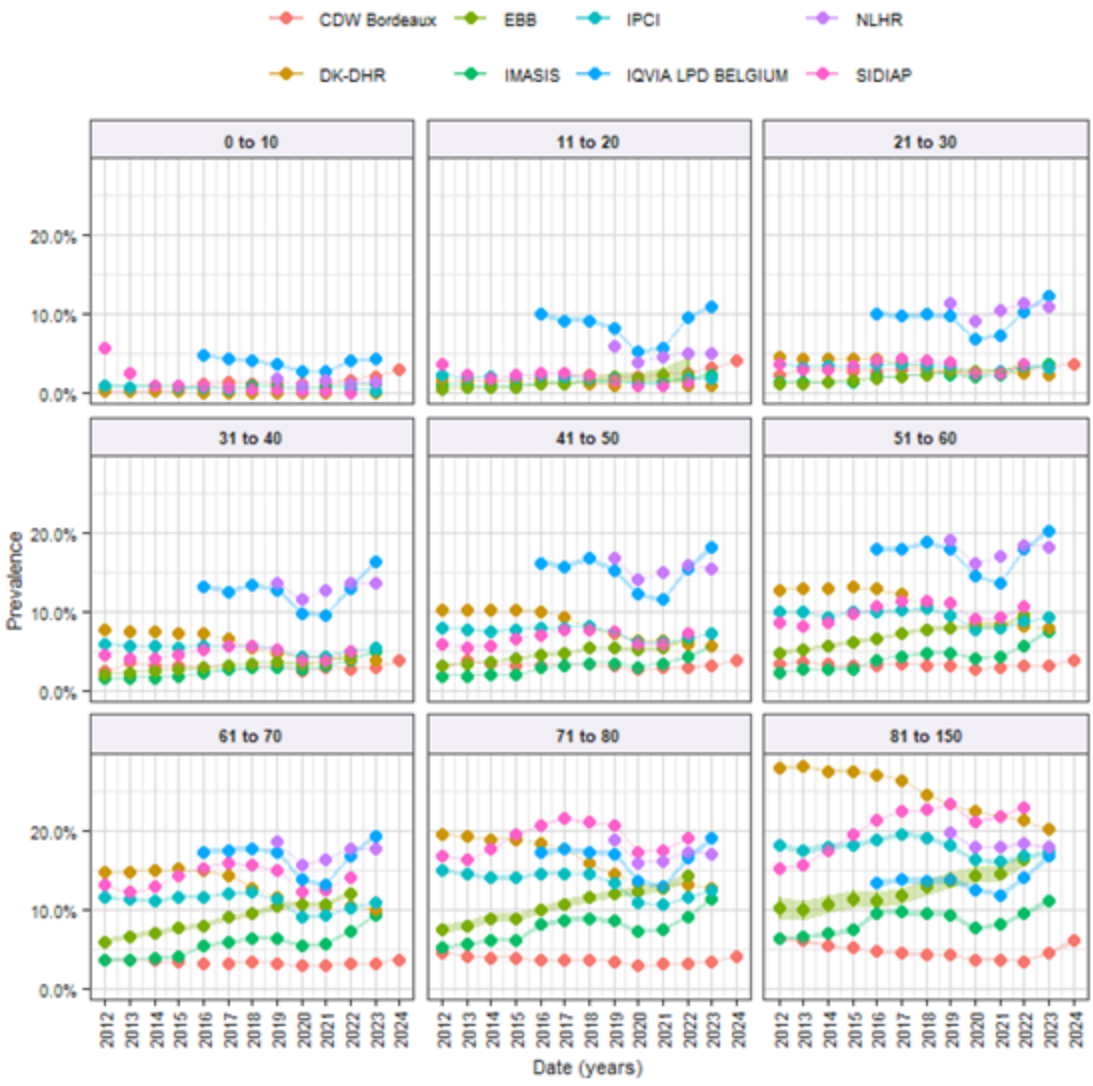

Figure 24. Prevalence of opioids without history of cancer, stratified by age.

Overall opioid use stratified by sex

Higher incidence of opioid prescriptions was observed in women compared to men across all databases, except for CDW Bordeaux and IMASIS where higher incidence of opioid use was observed in men. (**Figure 25** to **Figure 26**)

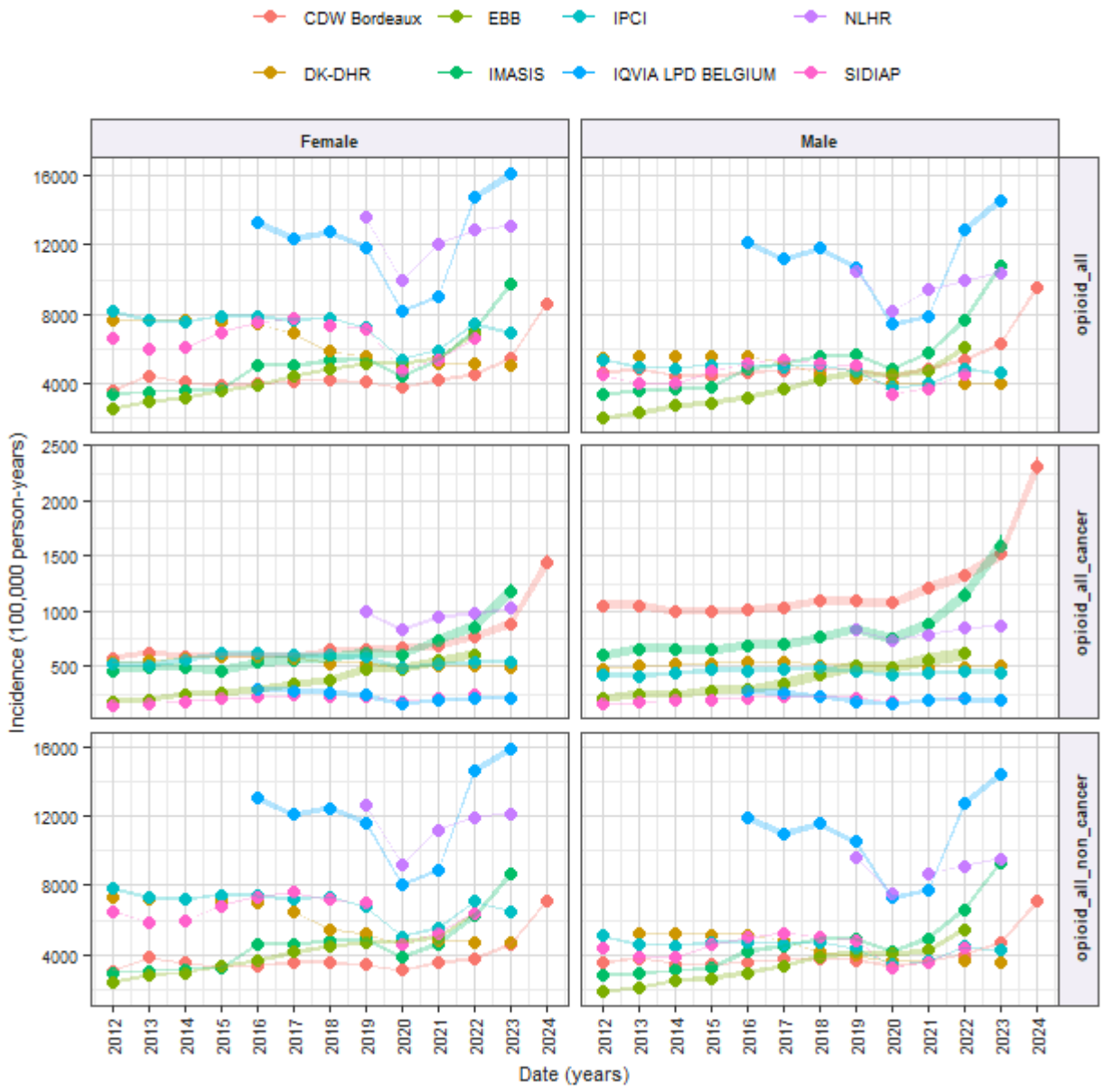

Figure 25. Incidence of opioid use stratified by sex.

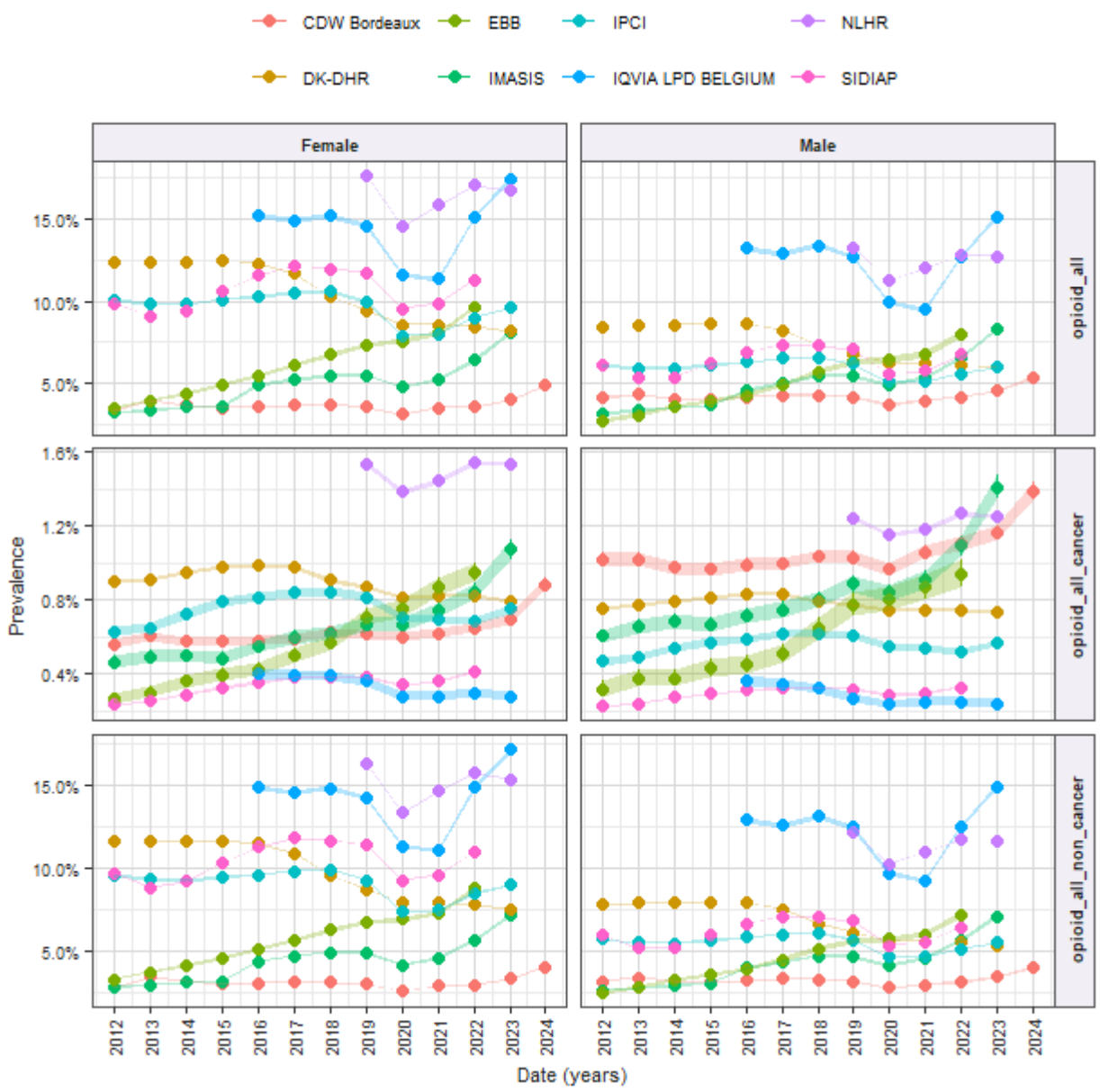

Figure 26. Prevalence of opioid use stratified by sex.

Objective 2. Patient-level characterisation and DUS

Cohort characteristics

Patient-level characterisation of new opioid users during 2012-2024 are presented in **Table 13**. New opioid users were defined as no prescription of opioids within the prior 1 year.

There were consistently more women among the new opioid users compared to men across all included databases except CDW Bordeaux: The proportion of women ranged from 52.1% in IMASIS to 60.1% in IPCI, while CDW Bordeaux it was 49.1%.

Median age of new opioid users ranged from 49 [IQR 33-64] in NLHR to 62 [45-76] in IMASIS.

When considering the baseline comorbidities of new opioid users, the proportion of individuals with malignant neoplastic disease recorded at any time before 1 year prior to the opioid use ranged from 2.6% in IQVIA LPD Belgium to 13.6% in IMASIS, and that within 1 year prior to the opioid use ranged from 1.8% in IQVIA LPD Belgium to 19.1% in CDW Bordeaux.

When considering the medication use within 1 year prior to the new opioid prescription, 38.0% (CDW Bordeaux) to 73.7% (SIDIAP) of new opioid users were prescribed with anti-inflammatory and anti-rheumatic agents.

The median duration of the first treatment episode of opioids ranged from short durations of few days in the hospital databases (1 [1-5] day in IMASIS and 2 [1-5] days in CDW Bordeaux) to a week or more in the outpatient setting (e.g. 11 [7-11] days in SIDIAP).

Table 13. Patient level characterisation of new opioid users.

			CDM name							
Variable name	Variable level	Estimate name	CDW Bordeaux	DK-DHR	EBB	IMASIS	IPCI	IQVIA LPD BELGIUM	SIDIAP	NLHR
Number records	-	N	319,317	3,592,890	89,135	184,025	686,566	286,251	3,367,282	2,458,504
Number subjects	-	N	274,026	2,183,760	60,286	132,762	484,556	205,461	2,204,608	1,888,433
Age	-	Median [Q25 - Q75]	55 [34 - 71]	59 [44 - 72]	55 [42 - 66]	62 [45 - 76]	57 [43 - 70]	51.00 [34.00 - 64.00]	55 [40 - 70]	49 [33 - 64]
		Range	0 to 108	1 to 110	9 to 104	0 to 108	1 to 105	1.00 to 116.00	1 to 116	1 to 110
Sex	Female	N (%)	156,713 (49.08%)	2,024,157 (56.34%)	61,513 (69.01%)	95,958 (52.14%)	412,494 (60.08%)	159,429 (55.70%)	1,975,922 (58.68%)	1,337,241 (54.39%)
	Male	N (%)	162,597 (50.92%)	1,568,733 (43.66%)	27,622 (30.99%)	88,067 (47.86%)	274,072 (39.92%)	126,822 (44.30%)	1,391,360 (41.32%)	1,121,263 (45.61%)
	None	N (%)	7 (0.00%)	-	-	-	-	-	-	-
Treatment duration (days)	-	Median [Q25 - Q75]	2 [1 - 5]	6 [3 - 13]	30 [30 - 30]	1 [1 - 5]	10 [7 - 15]	7.00 [6.00 - 20.00]	11 [7 - 31]	11 [5 - 14]
		Range	1 to 1,530	1 to 4,454	1 to 4,009	1 to 2,533	1 to 3,668	1.00 to 2,527.00	1 to 4,198	1 to 1,786
Comorbidities (anytime to 366 days prior)	Myocardial infarction	N (%)	2,529 (1.32%)	129,619 (3.61%)	2,121 (2.38%)	3,732 (2.40%)	15,457 (2.25%)	2,477 (0.87%)	37,855 (1.12%)	56,322 (2.29%)
	Hypertension	N (%)	38,252 (19.91%)	1,013,715 (28.21%)	44,975 (50.46%)	46,311 (29.74%)	129,274 (18.84%)	79,770 (27.88%)	645,785 (19.18%)	632,929 (25.75%)
	Depressive disorder	N (%)	12,084 (6.29%)	823,690 (22.93%)	34,625 (38.85%)	15,660 (10.06%)	39,211 (5.71%)	22,660 (7.92%)	342,112 (10.16%)	192,481 (7.83%)
	Hypothyroidism	N (%)	7,319 (3.81%)	184,080 (5.12%)	10,971 (12.31%)	6,778 (4.35%)	20,725 (3.02%)	19,872 (6.95%)	213,079 (6.33%)	171,935 (6.99%)
	Dementia	N (%)	2,279 (1.19%)	78,960 (2.20%)	629 (0.71%)	2,185 (1.40%)	4,999 (0.73%)	1,473 (0.51%)	43,146 (1.28%)	15,785 (0.64%)
	Chronic kidney disease with renal impairment	N (%)	12,216 (6.36%)	70,906 (1.97%)	2,769 (3.11%)	12,416 (7.97%)	31,114 (4.53%)	2,004 (0.70%)	181,700 (5.40%)	44,453 (1.81%)

	Stroke	N (%)	4,313 (2.24%)	176,619 (4.92%)	2,140 (2.40%)	3,826 (2.46%)	14,698 (2.14%)	3,105 (1.09%)	63,439 (1.88%)	71,471 (2.91%)
	COPD	N (%)	6,461 (3.36%)	278,420 (7.75%)	6,917 (7.76%)	10,799 (6.93%)	28,902 (4.21%)	32,339 (11.30%)	112,433 (3.34%)	141,320 (5.75%)
	Inflammatory bowel disease	N (%)	1,533 (0.80%)	74,305 (2.07%)	1,399 (1.57%)	1,004 (0.64%)	5,915 (0.86%)	2,062 (0.72%)	15,645 (0.46%)	36,112 (1.47%)
	Rheumatoid arthritis	N (%)	1,692 (0.88%)	90,082 (2.51%)	9,249 (10.38%)	1,225 (0.79%)	10,068 (1.47%)	2,551 (0.89%)	19,357 (0.57%)	119,135 (4.85%)
	Chronic liver disease	N (%)	4,275 (2.22%)	31,392 (0.87%)	2,286 (2.56%)	6,405 (4.11%)	1,679 (0.24%)	522 (0.18%)	32,146 (0.95%)	16,328 (0.66%)
	Obesity	N (%)	13,682 (7.12%)	374,731 (10.43%)	18,609 (20.88%)	25,179 (16.17%)	99,588 (14.51%)	14,672 (5.13%)	1,123,709 (33.37%)	201,692 (8.20%)
	Malignant neoplastic disease	N (%)	22,033 (11.47%)	461,196 (12.84%)	10,820 (12.14%)	21,167 (13.59%)	62,782 (9.15%)	7,518 (2.63%)	276,843 (8.22%)	311,737 (12.68%)
	Osteoporosis	N (%)	3,549 (1.85%)	265,484 (7.39%)	7,069 (7.93%)	7,821 (5.02%)	16,996 (2.48%)	13,294 (4.65%)	171,904 (5.11%)	112,663 (4.58%)
	Heart failure	N (%)	7,597 (3.95%)	133,575 (3.72%)	20,732 (23.26%)	9,073 (5.83%)	14,596 (2.13%)	5,678 (1.98%)	74,316 (2.21%)	86,931 (3.54%)
	Chronic kidney disease	N (%)	8,909 (4.64%)	49,025 (1.36%)	2,040 (2.29%)	8,701 (5.59%)	8,055 (1.17%)	1,767 (0.62%)	174,384 (5.18%)	30,522 (1.24%)
	Anxiety	N (%)	11,683 (6.08%)	417,951 (11.63%)	24,839 (27.87%)	10,770 (6.92%)	140,688 (20.50%)	45,043 (15.74%)	748,649 (22.23%)	673,111 (27.38%)
	GERD	N (%)	4,442 (2.31%)	72,215 (2.01%)	30,170 (33.85%)	1,941 (1.25%)	10,225 (1.49%)	40,998 (14.33%)	171,691 (5.10%)	119,724 (4.87%)
	Venous thromboembolism	N (%)	4,560 (2.37%)	113,005 (3.15%)	7,398 (8.30%)	2,965 (1.90%)	14,404 (2.10%)	6,463 (2.26%)	73,545 (2.18%)	100,167 (4.07%)
	HIV infection	N (%)	1,251 (0.65%)	4,451 (0.12%)	198 (0.22%)	1,733 (1.11%)	400 (0.06%)	296 (0.10%)	7,733 (0.23%)	3,433 (0.14%)
	Pneumonia	N (%)	8,878 (4.62%)	1,041,107 (28.98%)	17,295 (19.40%)	8,573 (5.50%)	42,090 (6.13%)	10,650 (3.72%)	165,136 (4.90%)	380,421 (15.47%)
	Type 2 Diabetes	N (%)	14,740 (7.67%)	361,393 (10.06%)	10,738 (12.05%)	26,792 (17.20%)	75,865 (11.05%)	24,219 (8.47%)	501,018 (14.88%)	193,445 (7.87%)
	Asthma	N (%)	5,632 (2.93%)	730,125 (20.32%)	15,264 (17.12%)	6,984 (4.48%)	47,478 (6.92%)	44,040 (15.39%)	144,805 (4.30%)	427,510 (17.39%)

Comorbidities (365 days prior to index date)	Myocardial infarction	N (%)	3,018 (0.95%)	20,755 (0.58%)	562 (0.63%)	3,541 (1.92%)	9,795 (1.43%)	1,873 (0.65%)	6,969 (0.21%)	26,403 (1.07%)
	Venous thromboembolism	N (%)	8,300 (2.60%)	29,568 (0.82%)	1,593 (1.79%)	2,151 (1.17%)	6,601 (0.96%)	3,457 (1.21%)	17,979 (0.53%)	36,852 (1.50%)
	HIV infection	N (%)	1,179 (0.37%)	4,396 (0.12%)	113 (0.13%)	2,014 (1.09%)	253 (0.04%)	162 (0.06%)	572 (0.02%)	2,694 (0.11%)
	Chronic liver disease	N (%)	6,804 (2.13%)	17,855 (0.50%)	711 (0.80%)	5,912 (3.21%)	909 (0.13%)	349 (0.12%)	3,725 (0.11%)	6,361 (0.26%)
	Heart failure	N (%)	15,657 (4.90%)	76,935 (2.14%)	10,383 (11.65%)	10,747 (5.84%)	10,967 (1.60%)	4,309 (1.51%)	22,310 (0.66%)	73,945 (3.01%)
	Pneumonia	N (%)	16,179 (5.07%)	305,184 (8.49%)	2,769 (3.11%)	6,316 (3.43%)	19,611 (2.86%)	5,648 (1.97%)	38,106 (1.13%)	62,291 (2.53%)
	Chronic kidney disease with renal impairment	N (%)	24,453 (7.66%)	49,843 (1.39%)	1,849 (2.07%)	17,880 (9.72%)	21,409 (3.12%)	1,383 (0.48%)	38,044 (1.13%)	32,837 (1.34%)
	Obesity	N (%)	38,563 (12.08%)	136,270 (3.79%)	9,707 (10.89%)	34,968 (19.00%)	85,244 (12.42%)	11,046 (3.86%)	734,905 (21.82%)	117,743 (4.79%)
	Asthma	N (%)	11,828 (3.70%)	287,079 (7.99%)	7,685 (8.62%)	6,429 (3.49%)	24,478 (3.57%)	30,360 (10.61%)	20,498 (0.61%)	250,997 (10.21%)
	Malignant neoplastic disease	N (%)	61,076 (19.13%)	284,526 (7.92%)	7,395 (8.30%)	23,319 (12.67%)	46,367 (6.75%)	5,082 (1.78%)	93,740 (2.78%)	185,912 (7.56%)
	COPD	N (%)	16,434 (5.15%)	179,506 (5.00%)	2,562 (2.87%)	10,901 (5.92%)	19,768 (2.88%)	20,097 (7.02%)	20,517 (0.61%)	96,619 (3.93%)
	Hypothyroidism	N (%)	18,743 (5.87%)	153,004 (4.26%)	7,191 (8.07%)	8,027 (4.36%)	10,938 (1.59%)	15,885 (5.55%)	27,299 (0.81%)	145,203 (5.91%)
	Stroke	N (%)	8,276 (2.59%)	41,087 (1.14%)	679 (0.76%)	3,027 (1.64%)	9,478 (1.38%)	2,181 (0.76%)	13,573 (0.40%)	35,738 (1.45%)
	Inflammatory bowel disease	N (%)	3,091 (0.97%)	35,652 (0.99%)	408 (0.46%)	977 (0.53%)	3,245 (0.47%)	1,414 (0.49%)	2,820 (0.08%)	21,034 (0.86%)
	Type 2 Diabetes	N (%)	36,706 (11.50%)	399,942 (11.13%)	11,510 (12.91%)	41,872 (22.75%)	83,060 (12.10%)	28,453 (9.94%)	533,449 (15.84%)	226,694 (9.22%)
	Osteoporosis	N (%)	5,841 (1.83%)	182,277 (5.07%)	2,650 (2.97%)	8,083 (4.39%)	7,395 (1.08%)	8,155 (2.85%)	20,119 (0.60%)	67,022 (2.73%)
	Rheumatoid arthritis	N (%)	3,260 (1.02%)	47,493 (1.32%)	2,691 (3.02%)	1,034 (0.56%)	5,214 (0.76%)	1,549 (0.54%)	2,725 (0.08%)	80,001 (3.25%)

	GERD	N (%)	8,463 (2.65%)	11,296 (0.31%)	10,389 (11.66%)	1,741 (0.95%)	2,942 (0.43%)	25,569 (8.93%)	36,262 (1.08%)	48,186 (1.96%)
	Anxiety	N (%)	27,479 (8.61%)	123,893 (3.45%)	8,178 (9.17%)	6,107 (3.32%)	57,819 (8.42%)	25,341 (8.85%)	118,312 (3.51%)	185,628 (7.55%)
	Hypertension	N (%)	96,335 (30.17%)	562,304 (15.65%)	37,798 (42.41%)	53,810 (29.24%)	78,664 (11.46%)	67,812 (23.69%)	75,776 (2.25%)	557,647 (22.68%)
	Chronic kidney disease	N (%)	17,023 (5.33%)	38,097 (1.06%)	1,419 (1.59%)	12,433 (6.76%)	7,822 (1.14%)	1,211 (0.42%)	35,444 (1.05%)	21,326 (0.87%)
	Dementia	N (%)	5,955 (1.86%)	64,921 (1.81%)	275 (0.31%)	3,734 (2.03%)	4,641 (0.68%)	1,126 (0.39%)	11,864 (0.35%)	15,929 (0.65%)
	Depressive disorder	N (%)	26,403 (8.27%)	873,498 (24.31%)	36,061 (40.46%)	22,291 (12.11%)	46,189 (6.73%)	26,862 (9.38%)	379,507 (11.27%)	210,394 (8.56%)
Medications (365 days prior to index date)	Beta blocking agents	N (%)	35,181 (11.02%)	533,310 (14.84%)	21,377 (23.98%)	17,333 (9.42%)	127,758 (18.61%)	47,514 (16.60%)	376,355 (11.18%)	265,891 (10.82%)
	Psycholeptics	N (%)	137,248 (42.98%)	612,110 (17.04%)	24,097 (27.03%)	123,279 (66.99%)	137,573 (20.04%)	66,662 (23.29%)	1,217,853 (36.17%)	495,883 (20.17%)
	Antidepressants	N (%)	23,024 (7.21%)	544,617 (15.16%)	14,204 (15.94%)	15,746 (8.56%)	78,665 (11.46%)	43,652 (15.25%)	694,995 (20.64%)	260,291 (10.59%)
	Immunosuppressants	N (%)	8,135 (2.55%)	93,709 (2.61%)	2,385 (2.68%)	3,914 (2.13%)	12,346 (1.80%)	2,211 (0.77%)	44,960 (1.34%)	61,495 (2.50%)
	Antithrombotics	N (%)	87,763 (27.48%)	571,855 (15.92%)	8,799 (9.87%)	63,112 (34.30%)	100,291 (14.61%)	15,997 (5.59%)	377,774 (11.22%)	249,105 (10.13%)
	Psychostimulants	N (%)	401 (0.13%)	42,931 (1.19%)	407 (0.46%)	316 (0.17%)	6,900 (1.01%)	1,498 (0.52%)	36,103 (1.07%)	31,618 (1.29%)
	Hormonal contraceptives systemic	N (%)	436 (0.14%)	160,280 (4.46%)	4,258 (4.78%)	1,360 (0.74%)	16,896 (2.46%)	14,618 (5.11%)	60,254 (1.79%)	207,441 (8.44%)
	Drugs acid related disorder	N (%)	110,242 (34.52%)	1,148,425 (31.96%)	26,855 (30.13%)	99,074 (53.84%)	276,506 (40.27%)	81,293 (28.40%)	1,520,364 (45.15%)	489,795 (19.92%)
	Antiepileptics	N (%)	29,915 (9.37%)	289,263 (8.05%)	12,287 (13.78%)	17,786 (9.66%)	30,311 (4.41%)	13,004 (4.54%)	390,712 (11.60%)	106,623 (4.34%)
	Antibacterials systemic	N (%)	76,133 (23.84%)	1,576,594 (43.88%)	42,885 (48.11%)	87,292 (47.43%)	223,010 (32.48%)	121,253 (42.36%)	1,409,408 (41.86%)	809,681 (32.93%)
	Calcium channel blockers	N (%)	28,285 (8.86%)	581,826 (16.19%)	11,477 (12.88%)	17,124 (9.31%)	79,222 (11.54%)	19,484 (6.81%)	322,551 (9.58%)	215,658 (8.77%)

	Lipid modifying agents	N (%)	44,664 (13.99%)	876,161 (24.39%)	14,458 (16.22%)	23,405 (12.72%)	162,447 (23.66%)	54,441 (19.02%)	795,667 (23.63%)	444,559 (18.08%)
	Drugs used in diabetes	N (%)	24,036 (7.53%)	345,254 (9.61%)	7,826 (8.78%)	24,939 (13.55%)	67,490 (9.83%)	23,862 (8.34%)	387,710 (11.51%)	182,842 (7.44%)
	Antiinflammatory/ antirheumatic agents	N (%)	121,192 (37.95%)	1,690,051 (47.04%)	54,344 (60.97%)	108,264 (58.83%)	277,284 (40.39%)	127,988 (44.71%)	2,482,258 (73.72%)	1,105,105 (44.95%)
	Diuretics	N (%)	28,610 (8.96%)	683,229 (19.02%)	7,359 (8.26%)	22,312 (12.12%)	96,705 (14.09%)	16,777 (5.86%)	436,991 (12.98%)	122,316 (4.98%)
	Drugs for obstructive airway diseases	N (%)	23,396 (7.33%)	699,387 (19.47%)	17,082 (19.16%)	31,530 (17.13%)	178,794 (26.04%)	77,808 (27.18%)	868,844 (25.80%)	571,046 (23.23%)
	Agents acting on renin angiotensin system	N (%)	31,714 (9.93%)	954,029 (26.55%)	28,705 (32.20%)	21,838 (11.87%)	161,552 (23.53%)	52,033 (18.18%)	944,965 (28.06%)	463,209 (18.84%)
	Antineoplastic agents	N (%)	10,391 (3.25%)	91,342 (2.54%)	869 (0.97%)	4,320 (2.35%)	6,003 (0.87%)	956 (0.33%)	26,400 (0.78%)	22,092 (0.90%)
Cancer (anytime to 366 days prior)	Lung cancer	N (%)	1,877 (0.98%)	18,328 (0.51%)	339 (0.38%)	1,103 (0.71%)	3,850 (0.56%)	391 (0.14%)	9,258 (0.27%)	10,455 (0.43%)
	Endometrial cancer	N (%)	152 (0.08%)	2,485 (0.07%)	283 (0.32%)	97 (0.06%)	715 (0.10%)	70 (0.02%)	3,924 (0.12%)	3,077 (0.13%)
	Lymphoma	N (%)	1,301 (0.68%)	14,652 (0.41%)	416 (0.47%)	635 (0.41%)	1,746 (0.25%)	184 (0.06%)	4,367 (0.13%)	9,951 (0.40%)
	Ovarian cancer	N (%)	235 (0.12%)	7,777 (0.22%)	338 (0.38%)	276 (0.18%)	666 (0.10%)	65 (0.02%)	3,252 (0.10%)	4,986 (0.20%)
	Leukemia	N (%)	1,139 (0.59%)	12,558 (0.35%)	260 (0.29%)	413 (0.27%)	1,281 (0.19%)	317 (0.11%)	6,557 (0.19%)	6,052 (0.25%)
	Colorectal cancer	N (%)	2,430 (1.26%)	53,041 (1.48%)	1,074 (1.20%)	3,205 (2.06%)	5,355 (0.78%)	605 (0.21%)	31,290 (0.93%)	26,220 (1.07%)
	Pancreatic cancer	N (%)	779 (0.41%)	3,000 (0.08%)	165 (0.19%)	259 (0.17%)	540 (0.08%)	84 (0.03%)	1,934 (0.06%)	1,928 (0.08%)
	Multiple myeloma	N (%)	656 (0.34%)	4,978 (0.14%)	95 (0.11%)	208 (0.13%)	542 (0.08%)	123 (0.04%)	2,644 (0.08%)	2,723 (0.11%)
	Breast cancer	N (%)	354 (0.18%)	55,748 (1.55%)	190 (0.21%)	3,514 (2.26%)	10,207 (1.49%)	0 (0.00%)	41,194 (1.22%)	0 (0.00%)
	Prostate cancer	N (%)	2,277 (1.19%)	55,901 (1.56%)	1,177 (1.32%)	2,766 (1.78%)	6,005 (0.87%)	1,210 (0.42%)	29,909 (0.89%)	38,506 (1.57%)

Cancer (365 to 0 days prior to index date)	Endometrial cancer	N (%)	447 (0.14%)	14 (0.00%)	118 (0.13%)	244 (0.13%)	462 (0.07%)	48 (0.02%)	894 (0.03%)	1,574 (0.06%)
	Ovarian cancer	N (%)	694 (0.22%)	5,284 (0.15%)	212 (0.24%)	345 (0.19%)	677 (0.10%)	52 (0.02%)	1,109 (0.03%)	3,682 (0.15%)
	Lung cancer	N (%)	7,554 (2.37%)	27,259 (0.76%)	337 (0.38%)	2,103 (1.14%)	6,117 (0.89%)	320 (0.11%)	13,410 (0.40%)	12,131 (0.49%)
	Pancreatic cancer	N (%)	2,930 (0.92%)	7,349 (0.20%)	183 (0.21%)	683 (0.37%)	1,450 (0.21%)	105 (0.04%)	3,651 (0.11%)	3,178 (0.13%)
	Prostate cancer	N (%)	4,575 (1.43%)	37,469 (1.04%)	1,001 (1.12%)	2,378 (1.29%)	4,102 (0.60%)	844 (0.29%)	4,901 (0.15%)	28,029 (1.14%)
	Leukemia	N (%)	2,266 (0.71%)	11,446 (0.32%)	247 (0.28%)	613 (0.33%)	1,028 (0.15%)	211 (0.07%)	1,660 (0.05%)	5,100 (0.21%)
	Colorectal cancer	N (%)	7,021 (2.20%)	29,459 (0.82%)	795 (0.89%)	3,207 (1.74%)	4,520 (0.66%)	343 (0.12%)	9,055 (0.27%)	20,903 (0.85%)
	Lymphoma	N (%)	2,628 (0.82%)	8,971 (0.25%)	369 (0.41%)	657 (0.36%)	1,447 (0.21%)	140 (0.05%)	1,182 (0.04%)	7,524 (0.31%)
	Multiple myeloma	N (%)	1,242 (0.39%)	5,809 (0.16%)	111 (0.12%)	330 (0.18%)	518 (0.08%)	93 (0.03%)	1,188 (0.04%)	2,821 (0.11%)
	Breast cancer	N (%)	301 (0.09%)	8,254 (0.23%)	30 (0.03%)	3,007 (1.63%)	6,707 (0.98%)	0 (0.00%)	7,843 (0.23%)	0 (0.00%)

When analyses were stratified for history of cancer, new users of opioids with cancer history (**Table 14**) were predominantly women (ranging from 51.5% in SIDIAP to 64.8% in EBB), except for CDW Bordeaux and IMASIS whereas more men received new opioid prescriptions (39.5% and 53.5% respectively). The new opioid users with cancer history were older, with a median age ranging from 67 [57-75] in CDW Bordeaux to 72 [63-79] in DK-DHR. When considering the type of cancer diagnosed within 1 year prior to opioid use, there were 6.8-13.8% of cancer opioid users with colorectal cancer, 4.6-12.8% with lung cancer, and 4.5-15.5% with prostate cancer. Median treatment duration ranged from 1 [1-6] day in IMASIS to 31 [11-106] days in SIDIAP.

Non-cancer opioid incident users were generally younger (**Table 15**), with median age ranging from 48 [32-63] in NLHR to 61 [43-75] in IMASIS. There was a higher proportion of women (51.4% in CDW Bordeaux to 69.5% in EBB). Despite these individuals being on opioids defined as non-cancer use, the cohort included a certain proportion of individuals with history of cancer more than 1 year prior to opioid use, ranging from 1.8% in IQVIA LPD Belgium to 9.9% in IMASIS. Considering the medication use 1 year prior to non-cancer opioid initiation, there were high proportion of individuals being prescribed/dispensed with systemic antibacterial agents (ranging from 23.2% in CDW Bordeaux to 47.5% in EBB) and anti-inflammatory and antirheumatic agents (ranging from 37.6% in CDW Bordeaux to 73.8% in SIDIAP). The treatment duration of non-cancer opioid use was slightly shorter compared to that of cancer opioid, with a median ranging from 1 [1-4] day in IMASIS to 11 [7-31] days in SIDIAP.

Table 14. Patient level characterisation of new users for opioids with history of cancer.

			CDM name							
Variable name	Variable level	Estimate name	CDW Bordeaux	DK-DHR	EBB	IMASIS	IPCI	IQVIA LPD BELGIUM	SIDIAP	NLHR
Number records	-	N	63,876	369,624	8,332	26,348	62,618	6,362	133,793	229,027
Number subjects	-	N	55,979	300,743	6,413	21,560	54,010	5,326	126,915	195,511
Age	-	Median [Q25 - Q75]	67 [57 - 75]	72 [63 - 79]	67 [58 - 75]	70 [59 - 79]	71 [62 - 79]	70.00 [59.00 - 79.00]	70 [59 - 79]	70 [59 - 77]
		Range	0 to 106	1 to 107	18 to 101	3 to 104	1 to 106	3.00 to 109.00	1 to 109	1 to 105
Sex	Female	N (%)	25,210 (39.47%)	190,660 (51.58%)	5,395 (64.75%)	12,265 (46.55%)	35,134 (56.11%)	3,558 (55.93%)	68,838 (51.45%)	122,441 (53.46%)
	Male	N (%)	38,663 (60.53%)	178,964 (48.42%)	2,937 (35.25%)	14,083 (53.45%)	27,484 (43.89%)	2,804 (44.07%)	64,955 (48.55%)	106,586 (46.54%)
	None	N (%)	-	-	-	-	-	-	-	-
Treatment duration (days)	-	Median [Q25 - Q75]	3 [1 - 7]	7 [3 - 16]	30 [30 - 30]	1 [1 - 6]	15 [9 - 30]	10.00 [6.00 - 30.00]	31 [11 - 106]	11 [4 - 17]
		Range	1 to 2,114	1 to 4,376	1 to 763	1 to 1,276	1 to 2,915	1.00 to 1,711.00	1 to 4,149	1 to 1,786
Comorbidities (anytime to 366 days prior to index date)	Myocardial infarction	N (%)	672 (1.77%)	22,307 (6.04%)	415 (4.98%)	723 (3.13%)	2,698 (4.31%)	129 (2.03%)	2,654 (1.98%)	11,389 (4.97%)
	Hypertension	N (%)	11,446 (30.07%)	164,165 (44.41%)	5,982 (71.80%)	9,238 (40.06%)	19,901 (31.79%)	3,239 (50.98%)	38,172 (28.53%)	116,158 (50.72%)
	Depressive disorder	N (%)	2,626 (6.90%)	87,143 (23.58%)	3,504 (42.05%)	2,575 (11.17%)	3,562 (5.69%)	680 (10.70%)	15,805 (11.81%)	13,909 (6.07%)

	Hypothyroidism	N (%)	2,173 (5.71%)	24,454 (6.62%)	1,306 (15.67%)	1,151 (4.99%)	2,499 (3.99%)	756 (11.90%)	9,007 (6.73%)	25,064 (10.94%)
	Dementia	N (%)	396 (1.04%)	8,069 (2.18%)	95 (1.14%)	350 (1.52%)	767 (1.23%)	99 (1.56%)	2,953 (2.21%)	3,081 (1.35%)
	Chronic kidney disease with renal impairment	N (%)	3,697 (9.71%)	15,221 (4.12%)	630 (7.56%)	2,846 (12.34%)	5,522 (8.82%)	220 (3.46%)	14,536 (10.86%)	12,462 (5.44%)
	Stroke	N (%)	962 (2.53%)	29,467 (7.97%)	390 (4.68%)	699 (3.03%)	2,651 (4.23%)	205 (3.23%)	4,867 (3.64%)	15,460 (6.75%)
	COPD	N (%)	2,321 (6.10%)	54,527 (14.75%)	1,200 (14.40%)	2,857 (12.39%)	5,973 (9.54%)	1,296 (20.40%)	11,200 (8.37%)	31,536 (13.77%)
	Inflammatory bowel disease	N (%)	249 (0.65%)	7,973 (2.16%)	173 (2.08%)	152 (0.66%)	973 (1.55%)	67 (1.05%)	868 (0.65%)	4,387 (1.92%)
	Rheumatoid arthritis	N (%)	381 (1.00%)	12,824 (3.47%)	1,010 (12.12%)	159 (0.69%)	1,474 (2.35%)	133 (2.09%)	965 (0.72%)	19,612 (8.56%)
	Chronic liver disease	N (%)	1,684 (4.42%)	5,399 (1.46%)	253 (3.04%)	1,481 (6.42%)	273 (0.44%)	27 (0.42%)	2,558 (1.91%)	2,066 (0.90%)
	Obesity	N (%)	3,917 (10.29%)	34,929 (9.45%)	1,823 (21.88%)	4,147 (17.98%)	10,830 (17.30%)	429 (6.75%)	52,974 (39.60%)	17,544 (7.66%)
	Malignant neoplastic disease	N (%)	16,669 (43.80%)	202,058 (54.67%)	5,651 (67.82%)	9,464 (41.04%)	27,704 (44.25%)	3,659 (57.59%)	38,596 (28.85%)	147,159 (64.25%)
	Osteoporosis	N (%)	946 (2.49%)	46,583 (12.60%)	1,227 (14.73%)	1,363 (5.91%)	3,331 (5.32%)	824 (12.97%)	10,607 (7.93%)	25,613 (11.18%)
	Heart failure	N (%)	1,922 (5.05%)	25,049 (6.78%)	3,478 (41.74%)	1,831 (7.94%)	2,966 (4.74%)	450 (7.08%)	6,129 (4.58%)	21,904 (9.56%)
	Chronic kidney disease	N (%)	2,549 (6.70%)	10,436 (2.82%)	485 (5.82%)	1,948 (8.45%)	900 (1.44%)	198 (3.12%)	13,960 (10.43%)	8,154 (3.56%)
	Anxiety	N (%)	3,475 (9.13%)	39,800 (10.77%)	2,355 (28.26%)	1,398 (6.06%)	12,143 (19.40%)	1,293 (20.35%)	25,449 (19.02%)	52,412 (22.88%)
	GERD	N (%)	1,269 (3.33%)	8,344 (2.26%)	3,255 (39.07%)	357 (1.55%)	1,116 (1.78%)	1,183 (18.62%)	8,446 (6.31%)	17,458 (7.62%)

	Venous thromboembolism	N (%)	1,546 (4.06%)	20,254 (5.48%)	1,104 (13.25%)	734 (3.18%)	2,612 (4.17%)	368 (5.79%)	5,222 (3.90%)	21,026 (9.18%)
	HIV infection	N (%)	366 (0.96%)	534 (0.14%)	13 (0.16%)	246 (1.07%)	45 (0.07%)	7 (0.11%)	356 (0.27%)	404 (0.18%)
	Pneumonia	N (%)	2,522 (6.63%)	136,290 (36.87%)	2,100 (25.20%)	1,930 (8.37%)	6,354 (10.15%)	499 (7.85%)	8,837 (6.61%)	55,663 (24.30%)
	Type 2 Diabetes	N (%)	4,355 (11.44%)	54,056 (14.62%)	1,608 (19.30%)	5,771 (25.02%)	11,048 (17.65%)	978 (15.39%)	32,729 (24.46%)	31,900 (13.93%)
	Asthma	N (%)	921 (2.42%)	75,440 (20.41%)	1,687 (20.25%)	850 (3.69%)	4,525 (7.23%)	1,064 (16.75%)	4,760 (3.56%)	42,949 (18.75%)
Comorbidities (365 days prior to index date)	Myocardial infarction	N (%)	537 (0.84%)	3,449 (0.93%)	102 (1.22%)	387 (1.47%)	1,770 (2.83%)	109 (1.71%)	521 (0.39%)	5,347 (2.33%)
	Venous thromboembolism	N (%)	3,320 (5.20%)	10,423 (2.82%)	375 (4.50%)	859 (3.26%)	1,949 (3.11%)	308 (4.84%)	3,049 (2.28%)	11,823 (5.16%)
	HIV infection	N (%)	373 (0.58%)	534 (0.14%)	7 (0.08%)	304 (1.15%)	35 (0.06%)	-	55 (0.04%)	325 (0.14%)
	Chronic liver disease	N (%)	2,970 (4.65%)	4,002 (1.08%)	100 (1.20%)	1,631 (6.19%)	192 (0.31%)	25 (0.39%)	586 (0.44%)	1,107 (0.48%)
	Heart failure	N (%)	3,542 (5.55%)	15,873 (4.29%)	2,105 (25.26%)	2,328 (8.84%)	2,512 (4.01%)	385 (6.05%)	2,324 (1.74%)	19,839 (8.66%)
	Pneumonia	N (%)	4,929 (7.72%)	59,159 (16.01%)	544 (6.53%)	1,577 (5.99%)	3,519 (5.62%)	341 (5.36%)	3,578 (2.67%)	15,669 (6.84%)
	Chronic kidney disease with renal impairment	N (%)	7,655 (11.98%)	13,126 (3.55%)	517 (6.20%)	4,501 (17.08%)	3,950 (6.31%)	197 (3.10%)	3,315 (2.48%)	11,830 (5.17%)
	Obesity	N (%)	9,773 (15.30%)	14,868 (4.02%)	922 (11.07%)	5,549 (21.06%)	8,816 (14.08%)	326 (5.12%)	34,037 (25.44%)	8,690 (3.79%)
	Asthma	N (%)	1,927 (3.02%)	33,908 (9.17%)	947 (11.37%)	902 (3.42%)	2,334 (3.73%)	704 (11.07%)	665 (0.50%)	28,290 (12.35%)
	Malignant neoplastic disease	N (%)	63,857 (99.97%)	369,381 (99.93%)	8,332 (100.00%)	26,348 (100.00%)	58,337 (93.16%)	6,362 (100.00%)	118,979 (88.93%)	229,027 (100.00%)

	COPD	N (%)	6,556 (10.26%)	41,849 (11.32%)	561 (6.73%)	3,485 (13.23%)	4,414 (7.05%)	1,048 (16.47%)	2,743 (2.05%)	24,952 (10.89%)
	Hypothyroidism	N (%)	5,457 (8.54%)	22,130 (5.99%)	990 (11.88%)	1,630 (6.19%)	1,394 (2.23%)	683 (10.74%)	1,495 (1.12%)	22,422 (9.79%)
	Stroke	N (%)	1,365 (2.14%)	8,006 (2.17%)	138 (1.66%)	457 (1.73%)	1,899 (3.03%)	161 (2.53%)	1,296 (0.97%)	8,234 (3.60%)
	Inflammatory bowel disease	N (%)	443 (0.69%)	3,582 (0.97%)	55 (0.66%)	181 (0.69%)	579 (0.92%)	53 (0.83%)	177 (0.13%)	2,355 (1.03%)
	Type 2 Diabetes	N (%)	10,925 (17.10%)	60,555 (16.38%)	1,704 (20.45%)	9,367 (35.55%)	12,169 (19.43%)	1,140 (17.92%)	35,691 (26.68%)	36,065 (15.75%)
	Osteoporosis	N (%)	1,490 (2.33%)	33,744 (9.13%)	483 (5.80%)	1,561 (5.92%)	1,573 (2.51%)	657 (10.33%)	1,634 (1.22%)	15,148 (6.61%)
	Rheumatoid arthritis	N (%)	733 (1.15%)	6,993 (1.89%)	282 (3.38%)	157 (0.60%)	786 (1.26%)	89 (1.40%)	130 (0.10%)	13,353 (5.83%)
	GERD	N (%)	2,601 (4.07%)	1,590 (0.43%)	1,284 (15.41%)	346 (1.31%)	384 (0.61%)	964 (15.15%)	2,108 (1.58%)	10,010 (4.37%)
	Anxiety	N (%)	8,941 (14.00%)	15,799 (4.27%)	885 (10.62%)	1,059 (4.02%)	5,298 (8.46%)	947 (14.89%)	4,445 (3.32%)	12,975 (5.67%)
	Hypertension	N (%)	27,569 (43.16%)	100,845 (27.28%)	5,360 (64.33%)	12,448 (47.24%)	12,566 (20.07%)	2,969 (46.67%)	4,622 (3.45%)	102,853 (44.91%)
	Chronic kidney disease	N (%)	5,130 (8.03%)	9,425 (2.55%)	412 (4.94%)	2,962 (11.24%)	803 (1.28%)	171 (2.69%)	2,865 (2.14%)	7,023 (3.07%)
	Dementia	N (%)	1,088 (1.70%)	7,747 (2.10%)	63 (0.76%)	663 (2.52%)	827 (1.32%)	95 (1.49%)	1,011 (0.76%)	3,301 (1.44%)
	Depressive disorder	N (%)	5,973 (9.35%)	95,674 (25.88%)	3,642 (43.71%)	3,956 (15.01%)	4,203 (6.71%)	863 (13.56%)	18,186 (13.59%)	15,015 (6.56%)
Medications (365 days prior to index date)	Beta blocking agents	N (%)	9,970 (15.61%)	89,792 (24.29%)	3,313 (39.76%)	3,950 (14.99%)	18,739 (29.93%)	2,155 (33.87%)	25,944 (19.39%)	55,160 (24.08%)
	Psycholeptics	N (%)	34,796 (54.47%)	117,206 (31.71%)	3,418 (41.02%)	19,993 (75.88%)	22,153 (35.38%)	2,619 (41.17%)	69,445 (51.90%)	87,872 (38.37%)

	Antidepressants	N (%)	6,204 (9.71%)	70,703 (19.13%)	1,410 (16.92%)	3,264 (12.39%)	8,903 (14.22%)	1,626 (25.56%)	36,379 (27.19%)	31,624 (13.81%)
	Immunosuppressants	N (%)	2,449 (3.83%)	15,744 (4.26%)	258 (3.10%)	531 (2.02%)	1,844 (2.94%)	87 (1.37%)	2,784 (2.08%)	10,512 (4.59%)
	Antithrombotics	N (%)	23,771 (37.21%)	98,084 (26.54%)	1,718 (20.62%)	13,238 (50.24%)	16,777 (26.79%)	1,122 (17.64%)	37,092 (27.72%)	60,634 (26.47%)
	Psychostimulants	N (%)	71 (0.11%)	2,718 (0.74%)	39 (0.47%)	45 (0.17%)	255 (0.41%)	36 (0.57%)	1,945 (1.45%)	982 (0.43%)
	Hormonal contraceptives systemic	N (%)	65 (0.10%)	7,056 (1.91%)	131 (1.57%)	312 (1.18%)	469 (0.75%)	83 (1.30%)	3,431 (2.56%)	7,825 (3.42%)
	Drugs acid related disorder	N (%)	31,006 (48.54%)	184,496 (49.91%)	3,955 (47.47%)	18,940 (71.88%)	38,004 (60.69%)	2,951 (46.38%)	100,119 (74.83%)	86,709 (37.86%)
	Antiepileptics	N (%)	8,784 (13.75%)	46,676 (12.63%)	1,484 (17.81%)	3,449 (13.09%)	4,936 (7.88%)	639 (10.04%)	23,091 (17.26%)	18,373 (8.02%)
	Antibacterials systemic	N (%)	18,075 (28.30%)	210,286 (56.89%)	4,681 (56.18%)	18,156 (68.91%)	27,247 (43.51%)	3,036 (47.72%)	72,792 (54.41%)	101,896 (44.49%)
	Calcium channel blockers	N (%)	8,288 (12.98%)	93,693 (25.35%)	1,862 (22.35%)	3,186 (12.09%)	11,964 (19.11%)	923 (14.51%)	23,456 (17.53%)	43,425 (18.96%)
	Lipid modifying agents	N (%)	12,396 (19.41%)	132,781 (35.92%)	2,219 (26.63%)	5,029 (19.09%)	22,980 (36.70%)	2,293 (36.04%)	49,295 (36.84%)	82,598 (36.06%)
	Drugs used in diabetes	N (%)	7,222 (11.31%)	52,299 (14.15%)	1,184 (14.21%)	6,464 (24.53%)	9,660 (15.43%)	956 (15.03%)	27,062 (20.23%)	27,896 (12.18%)
	Antiinflammatory/ antirheumatic agents	N (%)	25,563 (40.02%)	178,759 (48.36%)	5,332 (63.99%)	18,819 (71.42%)	28,673 (45.79%)	2,893 (45.47%)	98,154 (73.36%)	111,277 (48.59%)
	Diuretics	N (%)	7,977 (12.49%)	123,737 (33.48%)	1,497 (17.97%)	5,686 (21.58%)	15,666 (25.02%)	1,078 (16.94%)	34,490 (25.78%)	30,230 (13.20%)
	Drugs for obstructive airway diseases	N (%)	7,142 (11.18%)	89,172 (24.13%)	1,792 (21.51%)	8,392 (31.85%)	18,393 (29.37%)	1,899 (29.85%)	43,824 (32.76%)	62,509 (27.29%)
	Agents acting on renin angiotensin system	N (%)	9,013 (14.11%)	143,167 (38.73%)	4,025 (48.31%)	5,069 (19.24%)	22,204 (35.46%)	2,089 (32.84%)	59,801 (44.70%)	82,404 (35.98%)

	Antineoplastic agents	N (%)	9,505 (14.88%)	101,161 (27.37%)	865 (10.38%)	3,882 (14.73%)	6,916 (11.04%)	723 (11.36%)	20,963 (15.67%)	19,754 (8.63%)
Cancer (anytime to 366 days prior index date)	Lung cancer	N (%)	1,636 (4.30%)	13,024 (3.52%)	200 (2.40%)	709 (3.07%)	2,408 (3.85%)	166 (2.61%)	1,502 (1.12%)	7,926 (3.46%)
	Endometrial cancer	N (%)	113 (0.30%)	500 (0.14%)	190 (2.28%)	61 (0.26%)	306 (0.49%)	34 (0.54%)	437 (0.33%)	1,850 (0.81%)
	Lymphoma	N (%)	1,054 (2.77%)	10,068 (2.72%)	304 (3.65%)	354 (1.53%)	1,026 (1.64%)	106 (1.67%)	517 (0.39%)	7,269 (3.17%)
	Ovarian cancer	N (%)	180 (0.47%)	4,119 (1.11%)	200 (2.40%)	149 (0.65%)	431 (0.69%)	29 (0.46%)	451 (0.34%)	3,076 (1.34%)
	Leukemia	N (%)	1,003 (2.64%)	10,058 (2.72%)	220 (2.64%)	259 (1.12%)	804 (1.28%)	170 (2.68%)	897 (0.67%)	4,888 (2.13%)
	Colorectal cancer	N (%)	1,891 (4.97%)	21,255 (5.75%)	635 (7.62%)	1,557 (6.75%)	2,851 (4.55%)	273 (4.30%)	4,001 (2.99%)	16,108 (7.03%)
	Pancreatic cancer	N (%)	683 (1.79%)	2,183 (0.59%)	86 (1.03%)	150 (0.65%)	314 (0.50%)	43 (0.68%)	295 (0.22%)	1,355 (0.59%)
	Multiple myeloma	N (%)	606 (1.59%)	4,472 (1.21%)	69 (0.83%)	161 (0.70%)	378 (0.60%)	69 (1.09%)	424 (0.32%)	2,432 (1.06%)
	Breast cancer	N (%)	238 (0.63%)	32,528 (8.80%)	176 (2.11%)	1,400 (6.07%)	5,792 (9.25%)	0 (0.00%)	11,915 (8.91%)	0 (0.00%)
	Prostate cancer	N (%)	1,673 (4.40%)	35,129 (9.50%)	922 (11.07%)	1,599 (6.93%)	3,362 (5.37%)	679 (10.69%)	3,697 (2.76%)	27,217 (11.88%)
Cancer (365 to 0 days prior to index date)	Endometrial cancer	N (%)	465 (0.73%)	21 (0.01%)	133 (1.60%)	273 (1.04%)	571 (0.91%)	58 (0.91%)	1,168 (0.87%)	1,769 (0.77%)
	Ovarian cancer	N (%)	721 (1.13%)	6,546 (1.77%)	232 (2.78%)	408 (1.55%)	791 (1.26%)	67 (1.05%)	1,392 (1.04%)	4,325 (1.89%)
	Lung cancer	N (%)	7,878 (12.33%)	38,027 (10.29%)	386 (4.63%)	2,400 (9.11%)	7,976 (12.74%)	492 (7.73%)	17,175 (12.84%)	16,370 (7.15%)

	Pancreatic cancer	N (%)	3,066 (4.80%)	11,278 (3.05%)	214 (2.57%)	807 (3.06%)	1,767 (2.82%)	139 (2.18%)	4,444 (3.32%)	4,292 (1.87%)
	Prostate cancer	N (%)	4,740 (7.42%)	44,123 (11.94%)	1,088 (13.06%)	2,713 (10.30%)	4,808 (7.68%)	986 (15.50%)	5,964 (4.46%)	31,366 (13.70%)
	Leukemia	N (%)	2,329 (3.65%)	13,007 (3.52%)	270 (3.24%)	672 (2.55%)	1,252 (2.00%)	237 (3.73%)	2,143 (1.60%)	5,678 (2.48%)
	Colorectal cancer	N (%)	7,245 (11.34%)	37,055 (10.03%)	879 (10.55%)	3,641 (13.82%)	5,361 (8.56%)	434 (6.82%)	11,098 (8.29%)	24,868 (10.86%)
	Lymphoma	N (%)	2,768 (4.33%)	10,515 (2.84%)	414 (4.97%)	764 (2.90%)	1,795 (2.87%)	168 (2.64%)	1,543 (1.15%)	8,619 (3.76%)
	Multiple myeloma	N (%)	1,285 (2.01%)	8,028 (2.17%)	140 (1.68%)	385 (1.46%)	724 (1.16%)	128 (2.01%)	1,916 (1.43%)	3,563 (1.56%)
	Breast cancer	N (%)	317 (0.50%)	12,277 (3.32%)	39 (0.47%)	3,208 (12.18%)	8,124 (12.97%)	0 (0.00%)	9,616 (7.19%)	0 (0.00%)

Table 15. Patient level characterisation of new users for opioids without history of cancer.

			CDM name							
Variable name	Variable level	Estimate name	CDW Bordeaux	DK-DHR	EBB	IMASIS	IPCI	IQVIA LPD BELGIUM	SIDIAP	NLHR
Number records	-	N	258,511	3,349,560	82,390	161,445	645,024	282,114	3,280,105	2,299,573
Number subjects	-	N	225,300	2,061,948	56,367	120,275	458,775	202,947	2,155,971	1,781,024
Age	-	Median [Q25 - Q75]	50 [31 - 69]	57 [42 - 72]	53 [41 - 65]	61 [43 - 75]	56 [42 - 69]	50.00 [34.00 - 64.00]	55 [40 - 70]	48 [32 - 63]
		Range	0 to 108	1 to 110	9 to 104	0 to 108	1 to 105	1.00 to 116.00	1 to 116	1 to 110
Sex	Female	N (%)	132,807 (51.37%)	1,905,859 (56.90%)	57,236 (69.47%)	85,400 (52.90%)	390,791 (60.59%)	157,200 (55.72%)	1,933,754 (58.95%)	1,257,823 (54.70%)
	Male	N (%)	125,700 (48.62%)	1,443,701 (43.10%)	25,154 (30.53%)	76,045 (47.10%)	254,233 (39.41%)	124,914 (44.28%)	1,346,351 (41.05%)	1,041,750 (45.30%)
Treatment duration (days)	-	Median [Q25 - Q75]	2 [1 - 5]	6 [3 - 13]	30 [30 - 30]	1 [1 - 4]	10 [7 - 15]	7.00 [6.00 - 20.00]	11 [7 - 31]	11 [5 - 14]
		Range	1 to 1,530	1 to 4,454	1 to 4,009	1 to 2,533	1 to 3,668	1.00 to 2,527.00	1 to 4,198	1 to 1,785
Comorbidities (anytime to 366 days prior to index date)	Myocardial infarction	N (%)	1,946 (1.24%)	116,444 (3.48%)	1,817 (2.21%)	3,175 (2.33%)	13,660 (2.12%)	2,407 (0.85%)	36,206 (1.10%)	49,190 (2.14%)
	Hypertension	N (%)	27,766 (17.75%)	914,567 (27.30%)	40,268 (48.87%)	38,915 (28.55%)	116,465 (18.06%)	77,803 (27.59%)	622,255 (18.97%)	556,581 (24.20%)
	Depressive disorder	N (%)	9,778 (6.25%)	779,370 (23.27%)	31,981 (38.82%)	13,723 (10.07%)	37,186 (5.77%)	22,338 (7.92%)	333,452 (10.17%)	184,994 (8.04%)
	Hypothyroidism	N (%)	5,328 (3.41%)	169,507 (5.06%)	9,932 (12.05%)	5,908 (4.33%)	19,099 (2.96%)	19,425 (6.89%)	207,745 (6.33%)	156,074 (6.79%)

	Dementia	N (%)	1,924 (1.23%)	74,572 (2.23%)	569 (0.69%)	1,903 (1.40%)	4,511 (0.70%)	1,394 (0.49%)	41,115 (1.25%)	14,086 (0.61%)
	Chronic kidney disease with renal impairment	N (%)	8,946 (5.72%)	62,313 (1.86%)	2,313 (2.81%)	10,228 (7.50%)	27,746 (4.30%)	1,874 (0.66%)	173,145 (5.28%)	36,862 (1.60%)
	Stroke	N (%)	3,449 (2.20%)	159,578 (4.76%)	1,848 (2.24%)	3,285 (2.41%)	13,078 (2.03%)	2,981 (1.06%)	60,312 (1.84%)	62,088 (2.70%)
	COPD	N (%)	4,375 (2.80%)	249,800 (7.46%)	6,017 (7.30%)	8,569 (6.29%)	25,425 (3.94%)	31,641 (11.22%)	105,546 (3.22%)	123,187 (5.36%)
	Inflammatory bowel disease	N (%)	1,323 (0.85%)	70,074 (2.09%)	1,278 (1.55%)	889 (0.65%)	5,315 (0.82%)	2,017 (0.72%)	15,084 (0.46%)	33,563 (1.46%)
	Rheumatoid arthritis	N (%)	1,369 (0.88%)	84,124 (2.51%)	8,519 (10.34%)	1,103 (0.81%)	9,209 (1.43%)	2,475 (0.88%)	18,846 (0.57%)	108,987 (4.74%)
	Chronic liver disease	N (%)	2,743 (1.75%)	28,439 (0.85%)	2,068 (2.51%)	5,237 (3.84%)	1,497 (0.23%)	507 (0.18%)	30,452 (0.93%)	15,313 (0.67%)
	Obesity	N (%)	10,085 (6.45%)	356,470 (10.64%)	17,259 (20.95%)	21,993 (16.14%)	93,322 (14.47%)	14,447 (5.12%)	1,092,844 (33.32%)	191,659 (8.33%)
	Malignant neoplastic disease	N (%)	6,078 (3.89%)	323,839 (9.67%)	6,154 (7.47%)	13,426 (9.85%)	46,566 (7.22%)	5,128 (1.82%)	264,078 (8.05%)	207,057 (9.00%)
	Osteoporosis	N (%)	2,727 (1.74%)	242,297 (7.23%)	6,181 (7.50%)	6,800 (4.99%)	15,294 (2.37%)	12,809 (4.54%)	166,437 (5.07%)	98,263 (4.27%)
	Heart failure	N (%)	5,947 (3.80%)	119,704 (3.57%)	18,123 (22.00%)	7,670 (5.63%)	12,988 (2.01%)	5,424 (1.92%)	70,892 (2.16%)	74,189 (3.23%)
	Chronic kidney disease	N (%)	6,691 (4.28%)	43,051 (1.29%)	1,674 (2.03%)	7,212 (5.29%)	7,494 (1.16%)	1,649 (0.58%)	166,149 (5.07%)	25,574 (1.11%)
	Anxiety	N (%)	8,512 (5.44%)	397,737 (11.87%)	23,017 (27.94%)	9,704 (7.12%)	133,248 (20.67%)	44,362 (15.73%)	733,556 (22.36%)	640,787 (27.87%)
	GERD	N (%)	3,288 (2.10%)	67,684 (2.02%)	27,708 (33.63%)	1,682 (1.23%)	9,561 (1.48%)	40,326 (14.30%)	167,009 (5.09%)	108,548 (4.72%)
	Venous thromboembolism	N (%)	3,161 (2.02%)	100,884 (3.01%)	6,547 (7.95%)	2,393 (1.76%)	12,766 (1.98%)	6,253 (2.22%)	70,756 (2.16%)	86,681 (3.77%)

	HIV infection	N (%)	922 (0.59%)	4,095 (0.12%)	190 (0.23%)	1,546 (1.13%)	369 (0.06%)	293 (0.10%)	7,501 (0.23%)	3,181 (0.14%)
	Pneumonia	N (%)	6,637 (4.24%)	958,650 (28.62%)	15,626 (18.97%)	7,049 (5.17%)	38,321 (5.94%)	10,349 (3.67%)	160,028 (4.88%)	345,786 (15.04%)
	Type 2 Diabetes	N (%)	10,766 (6.88%)	329,731 (9.84%)	9,531 (11.57%)	22,288 (16.35%)	69,194 (10.73%)	23,671 (8.40%)	481,061 (14.67%)	173,394 (7.54%)
	Asthma	N (%)	4,817 (3.08%)	688,159 (20.54%)	14,008 (17.00%)	6,351 (4.66%)	44,922 (6.97%)	43,474 (15.42%)	142,140 (4.33%)	402,358 (17.50%)
Comorbidities (365 days prior to index date)	Myocardial infarction	N (%)	2,560 (0.99%)	18,559 (0.55%)	483 (0.59%)	3,259 (2.02%)	8,552 (1.33%)	1,804 (0.64%)	6,624 (0.20%)	23,012 (1.00%)
	Venous thromboembolism	N (%)	5,283 (2.04%)	22,138 (0.66%)	1,292 (1.57%)	1,455 (0.90%)	5,219 (0.81%)	3,251 (1.15%)	15,974 (0.49%)	28,658 (1.25%)
	HIV infection	N (%)	844 (0.33%)	4,035 (0.12%)	110 (0.13%)	1,769 (1.10%)	229 (0.04%)	161 (0.06%)	530 (0.02%)	2,484 (0.11%)
	Chronic liver disease	N (%)	4,066 (1.57%)	15,435 (0.46%)	631 (0.77%)	4,577 (2.84%)	768 (0.12%)	331 (0.12%)	3,267 (0.10%)	5,764 (0.25%)
	Heart failure	N (%)	12,572 (4.86%)	67,231 (2.01%)	8,819 (10.70%)	8,941 (5.54%)	9,448 (1.46%)	4,061 (1.44%)	20,884 (0.64%)	62,227 (2.71%)
	Pneumonia	N (%)	11,713 (4.53%)	268,470 (8.02%)	2,325 (2.82%)	5,035 (3.12%)	17,447 (2.70%)	5,429 (1.92%)	35,838 (1.09%)	52,802 (2.30%)
	Chronic kidney disease with renal impairment	N (%)	17,543 (6.79%)	41,688 (1.24%)	1,471 (1.79%)	14,258 (8.83%)	18,835 (2.92%)	1,250 (0.44%)	35,932 (1.10%)	25,407 (1.10%)
	Obesity	N (%)	29,409 (11.38%)	128,187 (3.83%)	9,026 (10.96%)	30,562 (18.93%)	80,105 (12.42%)	10,850 (3.85%)	715,193 (21.80%)	112,849 (4.91%)
	Asthma	N (%)	10,061 (3.89%)	268,680 (8.02%)	6,989 (8.48%)	5,725 (3.55%)	23,155 (3.59%)	29,954 (10.62%)	20,123 (0.61%)	234,961 (10.22%)
	Malignant neoplastic disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	COPD	N (%)	10,345 (4.00%)	156,946 (4.69%)	2,126 (2.58%)	8,119 (5.03%)	17,116 (2.65%)	19,523 (6.92%)	18,625 (0.57%)	82,482 (3.59%)

	Hypothyroidism	N (%)	13,620 (5.27%)	139,519 (4.17%)	6,397 (7.76%)	6,732 (4.17%)	9,979 (1.55%)	15,449 (5.48%)	26,307 (0.80%)	130,882 (5.69%)
	Stroke	N (%)	7,062 (2.73%)	35,740 (1.07%)	566 (0.69%)	2,657 (1.65%)	8,198 (1.27%)	2,074 (0.74%)	12,687 (0.39%)	30,586 (1.33%)
	Inflammatory bowel disease	N (%)	2,703 (1.05%)	33,562 (1.00%)	374 (0.45%)	843 (0.52%)	2,892 (0.45%)	1,376 (0.49%)	2,704 (0.08%)	19,689 (0.86%)
	Diabetes t2	N (%)	26,536 (10.26%)	363,922 (10.86%)	10,222 (12.41%)	34,309 (21.25%)	75,594 (11.72%)	27,795 (9.85%)	511,394 (15.59%)	203,931 (8.87%)
	Osteoporosis	N (%)	4,547 (1.76%)	166,522 (4.97%)	2,319 (2.81%)	6,876 (4.26%)	6,633 (1.03%)	7,720 (2.74%)	19,303 (0.59%)	59,339 (2.58%)
	Rheumatoid arthritis	N (%)	2,616 (1.01%)	44,239 (1.32%)	2,481 (3.01%)	922 (0.57%)	4,756 (0.74%)	1,498 (0.53%)	2,648 (0.08%)	73,395 (3.19%)
	GERD	N (%)	6,052 (2.34%)	10,345 (0.31%)	9,439 (11.46%)	1,471 (0.91%)	2,688 (0.42%)	24,973 (8.85%)	34,968 (1.07%)	41,418 (1.80%)
	Anxiety	N (%)	19,190 (7.42%)	115,368 (3.44%)	7,514 (9.12%)	5,277 (3.27%)	54,508 (8.45%)	24,820 (8.80%)	115,427 (3.52%)	178,228 (7.75%)
	Hypertension	N (%)	70,483 (27.26%)	499,516 (14.91%)	33,595 (40.78%)	43,495 (26.94%)	70,233 (10.89%)	65,856 (23.34%)	72,519 (2.21%)	490,132 (21.31%)
	Chronic kidney disease	N (%)	12,415 (4.80%)	32,327 (0.97%)	1,109 (1.35%)	10,095 (6.25%)	7,324 (1.14%)	1,092 (0.39%)	33,643 (1.03%)	16,992 (0.74%)
	Dementia	N (%)	4,991 (1.93%)	60,142 (1.80%)	233 (0.28%)	3,176 (1.97%)	4,087 (0.63%)	1,051 (0.37%)	11,180 (0.34%)	13,991 (0.61%)
	Depressive disorder	N (%)	21,035 (8.14%)	823,891 (24.60%)	33,303 (40.42%)	19,207 (11.90%)	43,815 (6.79%)	26,421 (9.37%)	369,466 (11.26%)	202,286 (8.80%)
Medications (365 days prior to index date)	Beta blocking agents	N (%)	26,110 (10.10%)	478,548 (14.29%)	18,850 (22.88%)	14,284 (8.85%)	116,155 (18.01%)	46,181 (16.37%)	360,485 (10.99%)	231,459 (10.07%)
	Psycholeptics	N (%)	104,795 (40.54%)	544,273 (16.25%)	21,551 (26.16%)	106,486 (65.96%)	124,573 (19.31%)	65,204 (23.11%)	1,176,373 (35.86%)	445,940 (19.39%)
	Antidepressants	N (%)	17,569 (6.80%)	510,026 (15.23%)	13,207 (16.03%)	13,377 (8.29%)	74,369 (11.53%)	42,796 (15.17%)	675,334 (20.59%)	244,743 (10.64%)

	Immunosuppressants	N (%)	5,986 (2.32%)	84,053 (2.51%)	2,198 (2.67%)	3,516 (2.18%)	11,349 (1.76%)	2,161 (0.77%)	43,222 (1.32%)	55,360 (2.41%)
	Antithrombotics	N (%)	66,160 (25.59%)	512,873 (15.31%)	7,457 (9.05%)	52,415 (32.47%)	89,829 (13.93%)	15,331 (5.43%)	354,438 (10.81%)	208,148 (9.05%)
	Psychostimulants	N (%)	337 (0.13%)	42,101 (1.26%)	375 (0.46%)	286 (0.18%)	6,743 (1.05%)	1,480 (0.52%)	35,034 (1.07%)	31,231 (1.36%)
	Hormonal contraceptives systemic	N (%)	379 (0.15%)	156,658 (4.68%)	4,148 (5.03%)	1,089 (0.67%)	16,632 (2.58%)	14,584 (5.17%)	58,167 (1.77%)	203,021 (8.83%)
	Drugs acid related disorder	N (%)	81,325 (31.46%)	1,039,832 (31.04%)	23,850 (28.95%)	83,368 (51.64%)	253,471 (39.30%)	79,601 (28.22%)	1,458,550 (44.47%)	435,793 (18.95%)
	Antiepileptics	N (%)	21,951 (8.49%)	269,122 (8.03%)	11,297 (13.71%)	15,265 (9.46%)	28,300 (4.39%)	12,764 (4.52%)	380,463 (11.60%)	99,044 (4.31%)
	Antibacterials systemic	N (%)	59,839 (23.15%)	1,442,757 (43.07%)	39,100 (47.46%)	72,033 (44.62%)	206,356 (31.99%)	119,446 (42.34%)	1,364,430 (41.60%)	743,024 (32.31%)
	Calcium channel blockers	N (%)	20,791 (8.04%)	524,121 (15.65%)	10,040 (12.19%)	14,777 (9.15%)	72,002 (11.16%)	18,941 (6.71%)	308,398 (9.40%)	187,556 (8.16%)
	Lipid modifying agents	N (%)	33,284 (12.88%)	794,689 (23.73%)	12,714 (15.43%)	19,557 (12.11%)	148,145 (22.97%)	52,983 (18.78%)	765,174 (23.33%)	390,096 (16.96%)
	Drugs used in diabetes	N (%)	17,480 (6.76%)	313,686 (9.36%)	6,917 (8.40%)	19,756 (12.24%)	61,633 (9.56%)	23,304 (8.26%)	370,775 (11.30%)	165,239 (7.19%)
	Antiinflammatory/ antirheumatic agents	N (%)	97,179 (37.59%)	1,577,059 (47.08%)	50,173 (60.90%)	92,304 (57.17%)	259,741 (40.27%)	126,342 (44.78%)	2,420,629 (73.80%)	1,032,612 (44.90%)
	Diuretics	N (%)	21,623 (8.36%)	611,241 (18.25%)	6,274 (7.62%)	17,911 (11.09%)	87,547 (13.57%)	16,122 (5.71%)	416,629 (12.70%)	105,139 (4.57%)
	Drugs for obstructive airway diseases	N (%)	16,964 (6.56%)	648,113 (19.35%)	15,701 (19.06%)	24,785 (15.35%)	168,344 (26.10%)	76,756 (27.21%)	843,212 (25.71%)	533,572 (23.20%)
	Agents acting on renin angiotensin system	N (%)	23,749 (9.19%)	864,263 (25.80%)	25,544 (31.00%)	17,947 (11.12%)	147,749 (22.91%)	50,726 (17.98%)	908,323 (27.69%)	408,919 (17.78%)
	Antineoplastic agents	N (%)	1,217 (0.47%)	7,540 (0.23%)	60 (0.07%)	936 (0.58%)	403 (0.06%)	457 (0.16%)	10,815 (0.33%)	4,330 (0.19%)

Cancer (anytime to 366 days priorindex date)	Lung cancer	N (%)	283 (0.18%)	9,291 (0.28%)	166 (0.20%)	522 (0.38%)	2,463 (0.38%)	326 (0.12%)	9,990 (0.30%)	4,153 (0.18%)
	Endometrial cancer	N (%)	45 (0.03%)	2,200 (0.07%)	133 (0.16%)	44 (0.03%)	527 (0.08%)	49 (0.02%)	3,864 (0.12%)	1,638 (0.07%)
	Lymphoma	N (%)	280 (0.18%)	5,876 (0.18%)	136 (0.17%)	336 (0.25%)	1,034 (0.16%)	117 (0.04%)	4,264 (0.13%)	3,575 (0.16%)
	Ovarian cancer	N (%)	61 (0.04%)	4,442 (0.13%)	166 (0.20%)	159 (0.12%)	362 (0.06%)	52 (0.02%)	3,136 (0.10%)	2,424 (0.11%)
	Leukemia	N (%)	153 (0.10%)	3,630 (0.11%)	50 (0.06%)	182 (0.13%)	731 (0.11%)	181 (0.06%)	6,302 (0.19%)	1,649 (0.07%)
	Colorectal cancer	N (%)	630 (0.40%)	39,551 (1.18%)	544 (0.66%)	1,930 (1.42%)	3,428 (0.53%)	434 (0.15%)	30,096 (0.92%)	14,096 (0.61%)
	Pancreatic cancer	N (%)	113 (0.07%)	1,259 (0.04%)	98 (0.12%)	152 (0.11%)	328 (0.05%)	60 (0.02%)	1,982 (0.06%)	857 (0.04%)
	Multiple myeloma	N (%)	58 (0.04%)	860 (0.03%)	30 (0.04%)	70 (0.05%)	356 (0.06%)	82 (0.03%)	2,900 (0.09%)	461 (0.02%)
	Breast cancer	N (%)	131 (0.08%)	30,873 (0.92%)	19 (0.02%)	2,361 (1.73%)	6,247 (0.97%)	0 (0.00%)	33,965 (1.04%)	0 (0.00%)
	Prostate cancer	N (%)	670 (0.43%)	27,788 (0.83%)	371 (0.45%)	1,396 (1.02%)	3,478 (0.54%)	697 (0.25%)	28,377 (0.87%)	15,491 (0.67%)

Indication

Large scale characterisation on conditions recorded on the index date (**Table 16**) was conducted to identify possible indication for the opioid prescription.

Conditions that were possibly indicative for baseline comorbidities were excluded. Most identified possible indications were pain-related or cough-related. Most commonly identified indication were cough or cough-related conditions in IPCI (21%), IQVIA LPD Belgium (28%), NLHR (6%) and SIDIAP (11%). Most commonly identified indications were “pain-related” conditions in CDW Bordeaux (3%), DK-DHR (45%), EBB (10%) and IMASIS (2%).

For hospital databases (CDW Bordeaux and IMASIS), an additional large-scale characterisation on procedures recorded on the index date (**Table 17**) was performed. Procedures which deemed irrelevant, such as possible indicative for baseline comorbidities (e.g. cataract-related procedures) and generic routine procedures (e.g. ECG monitoring and oxygen therapy), were excluded. The most common identified procedures relevant to opioid use was plain chest x-ray in both CDW Bordeaux (7%) and IMASIS (1%), which was suggestive of chest symptoms or findings. In CDW Bordeaux, the other procedures for possible indication for opioid use included radiography (indicative for operative procedures, diagnostic and interventional radiology), catheter insertion (indicative for operative procedures) and immunocytochemical procedure (indicative for testing for oncological conditions). The procedures identified in IMASIS included radiography (indicative for diagnostic and interventional radiology), surgical operation and therapeutic subcutaneous insertion.

Table 16. Large scale characterisation on conditions for identification of possible indication for opioid use (Part I).

CDW Bordeaux				DK-DHR				EBB				IMASIS		
Diagnosis name	N	%		**Diagnosis name**	**N**	**%**		**Diagnosis name**	**N**	**%**		**Diagnosis name**	**N**	**%**
Complication of surgical procedure	9,490	3		Severe pain	1,620,526	45		Nerve root disorder	9,154	10		Osteoarthritis of knee	3,618	2
Complication of procedure	8,367	3		Pain	1,537,220	43		Cough	8,684	10		Low back pain	1,817	1
Acute pain	6,761	2		Cough	655,029	18		Pain in spine	6,878	8		Complication of surgical procedure	1,682	1
Low back pain	4,767	1		Dry cough	110,294	3		Intervertebral disc disorder	4,937	6		Primary malignant neoplasm of female breast	1,677	1
				Muscle pain	72,729	2		Low back pain	4,742	5		Fracture of bone	1,151	1
				Pneumonia	46,547	1		Osteoarthritis of knee	3,216	4				
				Moderate pain	19,871	1		Acute bronchitis	3,181	4				
				Neuropathic pain	18,338	1		Acute upper respiratory infection	2,938	3				
								Osteoarthritis of hip	2,247	3				
								Joint pain	1,994	2				

Table 16. Large scale characterisation on conditions for identification of possible indication for opioid use (Part II).

IPCI				IQVIA Belgium				NLHR				SIDIAP		
Diagnosis name	**N**	**%**		**Diagnosis name**	**N**	**%**		**Diagnosis name**	**N**	**%**		**Diagnosis name**	**N**	**%**
Cough	141,371	21		Cough	81,556	28		Cough	152,401	6		Common cold	376,652	11
Acute upper respiratory infection	36,748	5		Common cold	37,018	13		Acute upper respiratory infection	143,519	6		Cough	203,036	6
Low back pain	21,176	3		Low back pain	28,957	10		Low back pain	75,353	3		Low back pain	86,345	3
Finding of back	19,037	3		Acute upper respiratory infection	25,338	9		Joint pain	66,764	3		Upper respiratory tract infection due to Influenza	62,830	2

Backache with radiating pain	18,555	3		Acute bronchitis	22,597	8		Backache	48,870	2		Acute lower respiratory tract infection	38,457	1
Finding of shoulder region	11,345	2		Pain	19,466	7		Acute lower respiratory tract infection	47,521	2		Joint pain	30,071	1
Finding of region of thorax	8,055	1		Acute tracheitis	16,612	6		Sciatica	37,498	2		Acute bronchitis	26,557	1
Finding of neck region	7,390	1		Influenza	15,319	5		COVID-19	27,781	1		Neck pain	25,246	1
Acute bronchitis	7,039	1		Acute laryngitis and/or tracheitis	8,192	3		Upper respiratory tract infection caused by Influenza virus	22,643	1		Acute upper respiratory infection	23,828	1
Finding of lower limb	6,109	1		Lumbago with sciatica	5,962	2		Pain in limb	21,642	1		Lumbago with sciatica	23,730	1

Table 17. Large scale characterisation on procedures for identification of possible indication for opioid use.

CDW Bordeaux				**IMASIS**		
Diagnosis name	**N**	**%**		**Diagnosis name**	**N**	**%**
Plain chest X-ray	23,417	7		Plain Radiography of Chest	2,220	1
Diagnostic radiography during operative procedure	16,175	5		Fluoroscopy of Multiple Coronary Arteries using Low Osmolar Contrast	2,169	1
Insertion of catheter into artery	10,968	3		Local excision of lesion of breast	2,053	1
Immunocytochemical procedure	10,402	3		Introduction of Other Therapeutic Substance into Subcutaneous Tissue, Percutaneous Approach	2,050	1
Insertion of catheter for central venous pressure monitoring	10,394	3		Ligation and stripping of varicose vein of lower limb	1,888	1
Computed tomography of abdomen and pelvis with contrast	7,218	2		Range of Motion and Joint Mobility Treatment of Musculoskeletal System - Lower Back / Lower Extremity	1,884	1
CT, 3-dimensional reconstruction	6,989	2		Introduction of Analgesics, Hypnotics, Sedatives into Peripheral Vein, Percutaneous Approach	1,819	1
Interventional radiology	6,399	2		Repair of inguinal hernia with graft or prosthesis, not otherwise specified	1,802	1
Cytopathology test	6,197	2		Total knee replacement	1,530	1
CT of brain without contrast	6,077	2		Supplement Abdominal Wall with Synthetic Substitute, Open Approach	1,458	1

Large scale characterisation on conditions and procedures recorded within 1 week and 1 month before index date were conducted as sensitivity analysis, with detailed results available on data.darwin-eu.org/p3-c2-002opioid/.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil 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 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 opioid use

In general, over the past decade, the incidence of opioid use has either slightly decreased or remained stable across most of the database: an increasing trend was seen for EBB and the 2 hospital databases IMASIS and CDW Bordeaux, with the latter potentially driven by a sharp decrease in the denominator population for the hospital databases. DK-DHR and IPCI had a decreasing trend in prescription opioid incidence over the study period. Among all included databases, IQVIA-LPD Belgium had the highest incidence of overall opioid use during the study period. Prevalence of overall opioid use showed similar trend and pattern as seen in incidence.

The majority of opioid prescriptions/dispensation were recorded in people who did not have a history of cancer in the year before prescription. Therefore, trends and pattern in overall opioid use aligned closely with non-cancer opioid use and were predominantly oral formulations.

Incidence and prevalence showed a marked decrease during the COVID-19 period (2020-2021), particularly for weak opioids such as codeine or tramadol. However, opioid usage returned to the pre-COVID-19 level or even higher in all databases from 2022 onwards. The trend was highly driven by non-cancer opioid use, while the drop during COVID-19 period was much less substantial for cancer opioid use.

When further stratified by opioid potency and route of administration, an increasing trend of potent opioid use was observed in EBB and IMASIS, both in people with and without a history of cancer.

Injectable opioids were predominantly used in hospitals (IMASIS, CDW Bordeaux) and transdermal opioid use. Trend and pattern of oral opioid use were similar to the pattern of weak opioid use in general.

When considering opioid use by ingredient, the top 10 most frequently used opioid ingredients across all databases were, in descending order, tramadol, codeine, morphine, oxycodone, ethylmorphine, opium, dextromethorphan, fentanyl, buprenorphine and tapentadol. Among these opioid ingredients, 5 of them (buprenorphine, fentanyl, morphine, oxycodone, tapentadol) were potent opioids. Incidence of morphine use were increasing in all included databases and most databases showed an increase in the incidence of tramadol use over the study period, except DK-DHR showing a decreasing trend in tramadol use.

Patient-level opioid use

Among new opioid users, there were more women than men receiving opioid prescriptions across all included databases except CDW BORDEAUX. The median age of opioid incident users ranged from 49 to 62years. Among those starting opioids, the proportion of individuals with a record of malignant neoplastic disease any time before and up to 1 year prior to the new opioid prescription ranged from 2.6-13.6%, compared to 1.8-19.1% with a record within 1 year prior starting opioids. When considering medication use within 1 year prior to the opioid use, 38.0-73.7% of incident opioid users were prescribed with anti-inflammatory and anti-rheumatic agents.

The median duration for a first treatment episodes with opioids ranged from 1 day in hospitals to 11 days in primary care databases.

As the actual indication was not recorded in most databases, we used the recent recording of conditions/diagnoses/procedures prior to new opioid prescriptions as proxies for potential indications: Most of the possible indications were pain-related or cough-related conditions. Procedures in hospital databases recorded in the immediate time before opioid prescriptions included chest x-rays (suggestive of chest symptoms or findings) diagnostic radiography during the operative procedure (suggestive of post-operative pain) and local excision of breast lesion (suggestive of operative procedure and post-operative pain).

14.2 Limitations of the research methods

General limitations

The study was informed by routinely collected health care data and so data quality issues must be considered. In this study in particular, misclassification is possible for drug exposures, as a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use are unavoidable. However, we used validated methods for the estimation of treatment duration, based on the concatenation of prescriptions and accounting for refill gaps.[10] Moreover, some opioid ingredients are accessible as over-the-counter drug in some countries, such as codeine in combination preparation for cough syrup. This could possibly result in underestimation of overall opioid use and particular ingredients. Therefore, interpretation of the study results should focus on the prescription of opioids.

The actual indication of opioid use is not explicitly recorded in most of the databases. Indication of drug use were only recorded in DK-DHR. To understand the possible indication of opioid use, we performed the large scale characterisation on conditions and procedures for the indication identification. However, this method was limited by incomplete or missing records, and including records of prevalent conditions/comorbidities.

Similarly, as the true indication of opioid use is not comprehensively recorded, a proxy of condition records of malignant neoplastic disease or prescription/dispensation of anti-neoplastic agents within 1 year prior to the opioid initiation was used to define the opioid use for cancer. This definition of cancer opioid depends highly on the data quality and availability of medical records, particular records of cancer. The practice of record input regarding prevalent cancer and cancer history may differ in different database, which could impact on the definition of cancer or non-cancer opioid use. Also, the current definition of cancer opioids refers to the opioid use with active cancer record, but in reality, cancer pain could be chronic in nature. Therefore, careful interpretation of the results on opioid use stratified by history of cancer is needed.

There was a small proportion (0.06-0.58%) of non-cancer opioid users receiving anti-neoplastic agents within 1 year prior to opioid use. This stems from the difference in defining cancer/non-cancer opioid use and identification of drug use. For the definition of cancer/non-cancer opioid use, in view of the consistency of definition and rules imposing on conditions and drug records, only start date of record was used. On the contrary, definition of baseline medication use takes into account of the duration of drug records. Therefore, for opioid users with antineoplastic agent use >365 days prior to opioid initiation and

continuing into 365 days prior to the opioid initiation, these individuals were defined as non-cancer opioid users with records of antineoplastic agent use within 365 days prior to opioid initiation.

In hospital databases, observation period of individuals starts when they made a visit or admission to the hospital. For individuals without prior visit to the hospital, they would not be included in the study cohort as planned in the protocol given the 365 days of prior observation requirement, leading to substantial loss of individuals in the hospital database. To mitigate this problem, the 1-year prior data availability requirement was not applied to hospital database.

Database-specific limitations

CDW Bordeaux and IMASIS: Both CDW Bordeaux and IMASIS are hospital databases, where observation period depends highly on the individual visit to the hospital. End date of observation period is defined by the last visit, and therefore there is substantial decrease in denominator towards the end of study period/observation period and increase in incidence estimates.

EBB: Treatment duration was not collected on and before 2021, and a default duration of 30 days was assigned to each drug record. Therefore, treatment duration could not be estimated in EBB.

IMASIS: Data regarding outpatient drug records were available since 2016 and therefore leading to a sudden increasing from 2015 to 2016 in the overall opioid use. Interpretation of trend in opioid use in IMASIS should take the availability of data into account.

IQVIA LPD Belgium: The observation period of the patients in this database is calculated based on the last visit, observation or interaction of the patient with the health care system. This methodology impacts the individuals considered “at risk” for the different medicines of interest of the study (i.e., the individuals included in the denominator populations) during the latest months of available data from the latest data lock, where healthy and/or non-frequent users of the health care system are typically not considered active. Consequently, the denominators used to calculate incidence of opioid initiation may present an artefactual decrease whilst incident users remain stable. To minimise the resulting artificial inflation of rates, we stopped the observation period of IQVIA-LPD Belgium 6 months before their data cut.

NLHR: Drug dispensing records were only availability since 2018. Prevalent use of opioid would be misclassified as incident use. For this reason, study period in NLHR started in 2019 instead.

14.3 Interpretation

Opioid use is a major global public health issue. According to the United Nations Office on Drugs and Crime (UNODC) World Drug Report 2022[11], there were 1.2% of global population aged 15-64 using opioids in 2020. The figure contained people using opiates and pharmaceutical opioids for non-medical purposes. Among these opioid users, half of them (prevalence 0.6%) received opiates, which included use of heroin, opium and non-medical use of codeine and morphine. Compared to the global figure, the prevalence of opioid use was 0.7% in Europe. Opioids have been known for its high abuse liability. According to Global Burden of Disease study, opioid dependence has been identified as the most common drug use disorder,[12] with opioids accounting for 80% of death attributable to drug use in 2019.[13] Given that non-medical use of pharmaceutical opioids increased with the rising number in opioid prescription for non-cancer pain management since 1997,[14] research is needed to comprehensively evaluate the trend and pattern of opioid use over time to inform relevant policy decision.

In this study, we observed an increasing trend in prevalence of overall opioid use in CDW Bordeaux, EBB, IMASIS and IQVIA LPD Belgium, and decreasing trend in DK-DHR and IPCI. The trend and pattern for 2012-2022 followed closely with the initial opioid study (P2-C1-002, DARWIN EU® Drug utilization study of prescription opioids | HMA-EMA Catalogues of real-world data sources and studies). Despite the decrease in the prevalence of opioid use during 2020-2021 possibly due to COVID-19, it is observed that the prevalence returned to the pre-COVID-19 level or even higher, aligning with the findings on the opioid

prescription previously reported.[15] While the increasing trend towards the end of study period in IQVIA LPD Belgium, CDW Bordeaux and IMASIS may be the artefact of decrease in denominator owing to definitions of the observation period, the rising trend in EBB warranted attention. Previous study using Estonian nationwide prescription data also showed a 67% increase in annual opioid prescribing rates during the period of 2011-2017.[16] It was reported an increase in codeine and potent opioids such as oxycodone and fentanyl of which results from the current study echoes with. Despite the incidence and prevalence estimates starting as the lowest rates among all included databases and remaining low compared to other countries such as Belgium and Norway, the drastic increase trend should be monitored.

Nordic countries have higher disease burden attributed to drug use compared to global and European figure, as we can observe the higher incidence and prevalence of opioid use in NLHR and DK-DHR.[17] While Norway had a declining disease burden due to drug use since 2001, that in Denmark persisted over years. These figures highlighted the importance of regulatory risk minimisation measure in Denmark during 2017-2018, which involved reporting the side effects for tramadol, and stricter dispensing status of tramadol and other opioids.[18] The impact of risk minimisation measures could be seen as in the significant decrease in overall opioid use and particularly weak opioids in the current study. Despite such, a steadily increasing prevalence of non-cancer potent opioids in Denmark warranted attention.

Trend and pattern of opioid use depends highly on the type of data source. For example, incidence and prevalence of injectable opioids was highest in IMASIS and CDW Bordeaux as both are hospital databases. However, it was observed that IPCI, as a primary care database, had the highest incidence and prevalence of oxycodone use and the second highest incidence of fentanyl among all included databases. This finding was supported by a previous study on substantially increasing number of prescription opioids, particularly oxycodone, in the Netherlands with the prescription data collected from national database covering 96% of the Dutch population.[19] On the other hand, some of the included databases (DK-DHR, NLHR) were national database in nature, with information from primary care, specialist care and inpatient care linked. This might also partly explain the higher incidence and prevalence of opioid use in NLHR compared to other databases, with higher incidence of ethylmorphine use presumably for cough treatment.

This is a routinely repeated study from the initial study on drug utilisation of opioids (P2-C1-002, DARWIN EU® Drug utilization study of prescription opioids | HMA-EMA Catalogues of real-world data sources and studies). In this routinely repeated study, 3 new data sources (DK-DHR, IMASIS, NLHR) were included. Results from IMASIS shared similar trend with CDW Bordeaux, suggesting that the pattern of opioid use in hospital settings aligns closely across databases. The database setting of DK-DHR and NLHR was unique compared to the other included databases in a way that they are both national-wide linked databases and therefore the pattern of opioid use is comprehensive and reflects highly at the country level while with minimal impact on drug use interpretation with regards to specific healthcare setting. While opioid use in both DK-DHR and NLHR shared a similar trend of decrease in opioid use during COVID-19 as observed in other databases, the overall trend of opioid use over years was unique to the database country, as shown in the substantial decrease in opioid use in DK-DHR with risk minimisation measure implemented in Denmark. In addition to the analysis we had in previous study, the current study further stratified the use of opioid by history of cancer within the prior 1 year. Results showed that most of the opioid prescriptions in the databases was for non-cancer use. Guidelines on opioid use mostly focus on cancer-related pain. In 2021, European clinical practice recommendations on opioids for chronic noncancer pain, commissioned by European Pain Federation, was published, extensively reviewed the evidence available on role of opioid in medical conditions and provided guidance for good clinical practice on prescribing opioids for non-cancer pain.[20,21] Therefore results from current study might provide insight in the distribution of opioid use in the European countries and help to understand and assist further evaluation on the appropriateness of opioid use according to the existing guidelines. After stratifying opioid use by the history of cancer, the decrease in opioid use during COVID-19 was highly driven by the opioid use without history of cancer, with such a pattern being much less substantial in cancer opioid use. This might also imply the difference and

prioritisation in healthcare service provision during pandemic and allow us to understand the impact of COVID-19 on opioid use in a broader term of healthcare service delivery.

14.4 Generalisability

The study included databases from seven European countries (France, Denmark, Estonia, Spain, the Netherlands, Belgium and Norway) covering different parts of Europe. The study also included data from diverse healthcare settings including primary care and specialist care, secondary care, and hospital inpatient care. However, findings from this study only reflect the situation in the specific region, setting and period covered by the respective database, and should not be generalised to other countries or databases. Settings with high use of opioids, such as nursing homes and palliative care facilities, are not covered in this study.

15. CONCLUSION

An increasing trend in overall opioid use was observed in EBB and IMASIS, while a decreasing trend was observed in DK-DHR and IPCI. Most of the opioid prescriptions were not prescribed to people with a history of cancer, which suggests they were prescribed for non-cancer related indications. There was a decrease in opioid prescriptions during the early COVID-19 period (2020-2021), in particular prescriptions of weak opioid and opioid with non-cancer related indications. However, rates of opioid prescriptions returned to the pre-COVID-19 level or even higher from 2022 onwards.

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