Study Report

P3-C2-002, P4-C2-001

DARWIN EU® - Drug Utilisation Study of prescription opioids

05/01/2026

Version 3.0

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Public

CONTENTS

Study title[1]	DARWIN EU® - Drug utilisation study of prescription opioids
Study report version	V3.0
Date	05/01/2026
EU PAS number	P3-C2-002: EUPAS1000000479 P4-C2-001: EUPAS1000000615
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	The objectives of this study were: 1. 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. 2. To assess the characteristics of new opioid users, indications, and treatment duration overall and in individuals with history of cancer/no history of cancer stratified by calendar year and country.
Countries of study	P3-C2-002: Estonia, Belgium, The Netherlands, France, Spain, Denmark, Norway P4-C2-001: Croatia, Germany, Hungary, Finland, Italy, Portugal, Sweden
Authors	Amy Lam (a.lam@darwin-eu.org), Annika Jödicke (a.jodicke@darwin-eu.org), Mike Du (m.du@darwin-eu.org), Edward Burn (e.burn@darwin-eu.org)

[1] This is a routine repeated study from P2-C1-002 (EUPAS105641).

1. TITLE

DARWIN EU® - Drug Utilisation Study of prescription opioids

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
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 source	**Names**	**Data Partner Organisation***
P3-C2-002		
IQVIA LPD Belgium	Gargi Jadhav Isabella Kaczmarczyk Akram Mendez Dina Vojinovic	IQVIA
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun Monika Roberta Korcinska Handest	Danish Medicines Agency
EBB	Raivo Kolde Marek Oja Ami Sild	University of Tartu
CDW Bordeaux	Romain Griffier Guillaume Verdy	CHU Bordeaux
IPCI	Katia Verhamme	Erasmus MC
NLHR	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo
IMASIS	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	Consorci Mar Parc de Salut Barcelona
SIDIAP	Talita Duarte Salles Irene López Sánchez Agustina Giuliodori Picco Anna Palomar Cros	IDIAP JGol

P4-C2-001		
NAJS	Karlo Pintarić Helena Ivanković Anamaria Jurčević Jakov Vuković Pero Ivanko	Croatian Institute of Public Health
FinOMOP-ACI Varha	Tommi Kauko Mikael Högerman Annika Pirnes Otto Ettala Arho Virkki Pia Tajanen-Doumbouya	Hospital District of Southwest Finland
InGef RDB	Raeleesha Norris Alexander Harms Annika Vivirito	Institut für angewandte Gesundheitsforschung Berlin GmbH
SUCD	Ágota Mészáros Zsolt István Bagyura Loretta Zsuzsa Kiss Tibor Héja	Semmelweis University
POLIMI	Gianluigi Galli Mauro Bucalo Vittoria Ramella Gabriele Guazzardi	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
EMDB-ULSEDV	Luís Ruano Firmino Machado	Clinical Academic Center Egas Moniz Health Alliance
HI-SPEED	Huiqi Li Fredrik Nyberg Nicklas Pihlström Rickard Ljung	Läkemedelsverket

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

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 were

1. 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/data source during the study period.
2. To determine duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing overall and in individuals with history of cancer/no history of cancer, all stratified by calendar year and country/data source.

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 individuals registered in the respective data sources on 1st of January of each year in the period 2012–2024 (or the latest available, whichever comes first), with at least 1 year of prior data availability (not applicable in hospital data sources) 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, whichever comes first), with at least 1 year of data availability (not applicable in hospital data sources), 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, whichever comes first), with at least 1 year of data availability (not applicable in hospital data sources), 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

P3-C2-002

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

P4-C2-001

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Finland: Auria Clinical Informatics (FinOMOP-ACI Varha)
3. Germany: InGef Research Database (InGef RDB)
4. Hungary: Semmelweis University Clinical Data (SUCD)
5. Italy: Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI)
6. Portugal: Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB-ULSEDV)
7. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

Data analyses

Population-level and Patient-level drug utilisation analyses were conducted in all data sources, with no calculation of duration being conducted for EBB, NAJS, InGef RDB, and EMDB-ULSEDV.

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 205,461 individuals (IQVIA LPD Belgium), 2,183,760 individuals (DK-DHR), 60,286 individuals (EBB), 274,026 individuals (CDW Bordeaux), 484,556 individuals (IPCI), 1,888,433 individuals (NLHR), 132,762 individuals (IMASIS), and 2,204,608 individuals (SIDIAP) were identified as new opioid users during the study period of 2012–2024 in P3-C2-002.

In addition, 1,341,765 individuals (NAJS), 266,327 individuals (FinOMOP-ACI Varha), 2,505,705 individuals (InGef RDB), 17,709 individuals (SUCD), 24,821 individuals (POLIMI), 89,900 individuals (EMDB-ULSEDV), and 2,585,592 individuals (HI-SPEED) were identified as new opioid users during the study period of 2012–2024 in P4-C2-001.

In general, over the past decade, the incidence of opioid use remained stable across most of the primary care or national registries data sources, while a decreasing trend was observed in NAJS, DK-DHR, InGef RDB, IPCI, and HI-SPEED. An increasing trend in overall opioid use was observed in EBB and all hospital data sources, except CDW Bordeaux. Among all included data sources, 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 for incidence.

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

Incidence and prevalence showed a marked decrease during the COVID-19 period (2020–2021), particularly for weak opioids, such as codeine or tramadol, and particularly among primary care or nationwide data sources (except EBB). However, opioid usage returned to the pre-COVID-19 level in most of these data sources, or even higher in hospital data sources from 2022 onwards. The trend was highly driven by non-cancer opioid use, while the dip during the COVID-19 period was substantially less pronounced for cancer opioid use.

When further stratified by opioid potency and route of administration, an increasing trend of potent opioid use was observed in DK-DHR, IPCI, and EBB among the primary care or nationwide data sources, and in all hospital data sources considering the number of opioid record counts, both in individuals with and without a history of cancer.

Higher incidence and prevalence of injectable opioids was observed in hospital data sources (IMASIS and CDW Bordeaux), while those of transdermal opioid use were highest in IPCI. 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 data sources were, in descending order, tramadol, codeine, oxycodone, ethylmorphine, morphine, noscapine, tilidine, dihydrocodeine, pholcodine, and fentanyl. Among these, 3 of them (fentanyl, morphine, oxycodone) were potent opioids. When considering the top 10 most frequently prescribed opioid ingredients in each data source, codeine, tramadol, oxycodone, and fentanyl were in top 10 most frequently prescribed opioid list in all the included data sources, while morphine was on the list in 14 out of 15 data sources, buprenorphine in 12 out of 15 data sources, and tapentadol in 9 out of 15 data sources. Among the primary care or nationwide data sources, an increasing trend of tramadol use was observed in SIDIAP (before 2017) and EBB, while a decreasing trend was observed in NAJS, InGef RDB, HI-SPEED, and substantially in DK-DHR. An increasing incidence in oxycodone prescriptions was observed in all hospital data sources and in IQVIA LPD Belgium, DK-DHR, EBB, IPCI, and NLHR. Incidence of morphine use were also increasing in all included data sources. A substantial increase in tapentadol incidence was observed in SIDIAP and IMASIS in the early study period before 2016 and remained at high level.

Patient-level opioid use

Among the new opioid users, more women than men received opioid prescriptions across all included data sources, except CDW Bordeaux. The median age of opioid new users ranged from 49 to 66 years. Among the new opioid users, 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 2.6–31.4%, compared to 1.8–48.4% of individuals who had a record of malignant neoplastic disease within 1 year prior to starting

opioids. When considering medication use within 1 year prior to the opioid use, 38.0–88.6% of new opioid users were prescribed with anti-inflammatory and anti-rheumatic agents.

The median duration for a first treatment episode with opioids ranged from 1 to 21 days in hospital data sources and from 6 to 18 days in primary care or nationwide data sources.

As the actual indication was not recorded in our data sources, we used recent recordings of conditions/diagnoses/procedures prior to new opioid prescriptions as proxies for potential indications: Most of the potential indications were pain-related or cough-related conditions. Procedures in hospital data sources recorded in the immediate time before opioid prescriptions included chest x-rays (suggestive of chest symptoms or findings), intravenous anaesthesia (suggestive of surgical procedures), and radiography other than chest x-rays (indicative for operative procedures, diagnostic and interventional radiology).

Conclusion

In general, over the past decade, the incidence of opioid use remained stable across most of the primary care or national registries data sources, while a decreasing trend was observed in DK-DHR, IPCI, InGef RDB, and NAJS. An increasing trend in overall opioid use was observed in EBB and all hospital data sources, except CDW Bordeaux. Most of the opioid prescriptions were recorded in individuals 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 in most primary care or nationwide data sources or even higher in hospital data sources from 2022 onwards, with the trend highly driven by non-cancer opioid use.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
FinOMOP-ACI Varha	Auria Clinical Informatics
ATC	Anatomical Therapeutic Chemical
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of 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
EMDB-ULSEDV	Egas Moniz Health Alliance database - Entre o Douro e Vouga
GP	General Practitioner
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
InGef RDB	InGef Research Database
IPCI	Integrated Primary Care Information Project
LPD	Longitudinal Patient Database
N/A	Not applicable
NAJS	Croatian National Public Health Information System
NLHR	Norwegian Linked Health Registry
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
POLIMI	Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
SIDIAP	The Information System for the Development of Research in Primary Care
SUCD	Semmelweis University Clinical Data
WHO	World Health Organisation

5. AMENDMENTS AND UPDATES

Number	Date	Section of studyprotocol	Amendment or update	Reason
Version 1.0	02/12/2025	N/A	Updated from routine-repeated study report (P3-C2-002, EUPAS1000000479)	This is a routine-repeated study.

Comparison with Previous Protocols

	P2-C1-002 (EUPAS105641)	P3-C2-002 (EUPAS1000000479)	P4-C2-001 (EUPAS1000000615)
Study period	2012–2022	2012–2024	2012–2024
Data partner			
Belgium: IQVIA LPD Belgium	*	*	
Croatia: NAJS			*
Denmark: DK-DHR		*	
Estonia: EBB	*	*	
Finland: FinOMOP-ACI Varha	[a]		*
France: CDW Bordeaux	*	*	
Germany: InGef RDB			*
Germany: IQVIA DA Germany	*		
Hungary: SUCD			*
Italy: POLIMI			*
The Netherlands: IPCI	*	*	
Norway: NLHR		*	
Portugal: EMDB-ULSEDV			*
Spain: IMASIS		*	
Spain: SIDIAP	*	*	
Sweden: HI-SPEED			*
Reference study protocol	N/A	P2-C1-002 (EUPAS105641)	P3-C2-002 (EUPAS1000000479)
Changes from reference study protocol	N/A	- Exposure: Add opioid use with history of cancer/no history of cancer - Patient-level DUS: change large scale characterisation to pre-defined list of conditions and medications - Indication: consider procedures for possible	Protocol was updated as mentioned in the P3-C2-002 study report *deviation from study protocol* section - Prior data availability: no longer require 1-year prior data availability in hospital data source - Assessment window for baseline characteristics: change from [-Inf, -366], [-365,

	P2-C1-002 (EUPAS105641)	P3-C2-002 (EUPAS1000000479)	P4-C2-001 (EUPAS1000000615)
		indication in hospital data source - Sensitivity analysis: remove 6-month washout period	-181], [-180, -1], [ID, ID] to [-Inf, -366], [-365, ID] - Type of cancer for cohort characteristics: update lymphoma with broad definition instead of separate Hodgkin lymphoma and non-Hodgkin lymphoma

CDW Bordeaux= Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA DA = IQVIA Disease Analyzer, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.
a. FinOMOP-ACI Varha was included in the protocol of initial study P2-C1-002 (EUPAS105641) but did not conduct the study.

6. MILESTONES

Study deliverable	Timelines (planned)	Timelines (actual)
Final Study Protocol	02/06/2025	02/06/2025
Creation of Analytical code	May 2025	Sept 2025
Execution of Analytical Code on the data	June – July 2025	12/09/2025
Draft Study Report	31/08/2025	02/12/2025
Final Study Report	To be confirmed by EMA	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) provides 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 aimed to 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) and P3-C2-002 (EUPAS1000000479), EMA requested a routine repeated study to include additional data sources and more recent data, which are presented alongside the results from P3-C2-002 in this report.

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/data source during the study period.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All individuals registered in the respective data sources on 1st of January of each year in the period 2012–2024 (or the latest available, whichever comes first), with at least 1 year of prior data availability (not applicable in hospital data sources) 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, whichever comes first), with at least 1 year of data availability (not applicable in hospital data sources), 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, whichever comes first.
Setting:	Inpatient and outpatient setting using data from the following 15 data sources: P3-C2-002 IQVIA LPD Belgium [Belgium], DK-DHR [Denmark], EBB [Estonia], CDW Bordeaux [France], IMASIS [Spain], SIDIAP [Spain], IPCI [The Netherlands], NLHR [Norway] P4-C2-001 NAJS [Croatia], FinOMOP-ACI Varha [Finland], InGef RDB [Germany], SUCD [Hungary], POLIMI [Italy], EMDB-ULSEDV [Portugal], HI-SPEED [Sweden]
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 individuals with history of cancer/no history of cancer, all stratified calendar year and country/data source.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of opioids overall and in individuals with history of cancer/no history of cancer in the period between 1/1/2012 and 31/12/2024 (or latest date available, whichever comes first), with at least 1 year of prior data availability (not applicable in hospital data sources), 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 new 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, whichever comes first.
Setting:	Inpatient and outpatient setting using data from the following 15 data sources: P3-C2-002 IQVIA LPD Belgium [Belgium], DK-DHR [Denmark], EBB [Estonia], CDW Bordeaux [France], IMASIS [Spain], SIDIAP [Spain], IPCI [The Netherlands], NLHR [Norway] P4-C2-001 NAJS [Croatia], FinOMOP-ACI Varha [Finland], InGef RDB [Germany], SUCD [Hungary], POLIMI [Italy], EMDB-ULSEDV [Portugal], HI-SPEED [Sweden]
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 individuals with history of cancer/no history of cancer (1) overall, (2) for the 10 most frequent opioids in each data source, (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.

ATC = Anatomical Therapeutic Chemical, CDW Bordeaux= Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

9. RESEARCH METHODS

9.1. Study type and study design

A cohort study was conducted using routinely-collected health data from 15 data sources (8 data sources in P3-C2-002; 7 data sources in P4-C2-001). 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

DUS = Drug utilisation study

9.2. Study setting and data sources

This study was conducted using routinely collected data from 15 data sources from 14 European countries. All data sources were previously mapped to the OMOP CDM.

P3-C2-002

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

P4-C2-001

1. Croatia: Croatian National Public Health Information System (NAJS)
2. Finland: Auria Clinical Informatics (FinOMOP-ACI Varha)
3. Germany: InGef Research Database (InGef RDB)
4. Hungary: Semmelweis University Clinical Data (SUCD)
5. Italy: Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI)
6. Portugal: Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB-ULSEDV)
7. Sweden: Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

Information on the data sources 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 data sources from the initial study P2-C1-002 and included 10 additional data sources (3 in P3-C2-002, 7 in P4-C2-001). The selection of data sources for this study was performed based on data reliability and relevance for the research question and feasibility counts.

Among all these 15 data sources, 9 data sources (P3-C2-002: IQVIA LPD Belgium, DK-DHR, EBB, IPCI, NLHR, SIDIAP; P4-C2-001: NAJS, InGef RDB, HI-SPEED) included records from primary care and outpatient specialist care where opioids are expected to be prescribed, while 6 of them also included data from hospitals (P3-C2-002: DK-DHR, EBB, NLHR; P4-C2-001: NAJS, InGef RDB, HI-SPEED). The other 6 data sources were hospital data sources (P3-C2-002: CDW Bordeaux, IMASIS; P4-C2-001: FinOMOP-ACI Varha, POLIMI, EMDB-ULSEDV, SUCD), where opioids were expected to be initiated and prescribed in inpatient setting, outpatient use following hospital discharge, and outpatient use for specialist care.

Table 3. Description of data sources.

Country	Name of Data source	Justification for Inclusion	Health Care setting	Type of Data	Number of active individuals	Data lock for the last update
P3-C2-002						
Belgium	IQVIA LPD Belgium	Data source covered primary care / outpatient specialist care setting where opioid prescriptions were issued.	Primary care, outpatient specialist care	EHR	0.2 million	30/09/2024
Denmark	DK-DHR	Data source covered secondary care specialist setting where opioid prescriptions were issued.	Community pharmacy, secondary care specialist	EHR	5.96 million	07/11/2024
Estonia	EBB	Data source covered primary care setting where opioid prescriptions were issued.	Biobank	Claims data	0.2 million	31/12/2022
France	CDW Bordeaux	Data source covered hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	0.2 million	04/03/2025
The Netherlands	IPCI	Data source covered primary care where opioid prescriptions were issued.	Primary care	EHR	1.25 million	30/06/2024
Norway	NLHR	Data source covered primary care and secondar care specialists where opioid prescriptions were issued.	Primary care, secondary care specialist, hospital inpatient care	Registries, EHR	6.95 million	31/12/2023
Spain	IMASIS	Data source covered secondary care specialists where opioid prescriptions were issued.	Secondary care specialist, hospital inpatient	EHR	0.1 million	20/09/2024
Spain	SIDIAP	Data source covered primary care / outpatient specialist care setting where opioid prescriptions were issued.	Primary care	EHR	6.0 million	30/06/2023
P4-C2-001						

Country	Name of Data source	Justification for Inclusion	Health Care setting	Type of Data	Number of active individuals	Data lock for the last update
Croatia	NAJS	Data source contained records from primary care GP, secondary specialist, and hospital inpatient care where opioid prescriptions were issued.	Primary care GP, secondary care specialist, hospital inpatient care	Registry	4.3 million	30/01/2025
Finland	FinOMOP-ACI Varha	Data source covered secondary care specialist and hospital inpatient care where opioid prescriptions were issued.	Secondary care specialist, hospital inpatient care	EHR	0.18 million	06/04/2025
Germany	InGef RDB	Data source contained claims data from primary care (GP and specialist), secondary care specialist, and hospital inpatient care where opioid prescriptions were issued.	Primary care (GP, specialist), secondary care specialist, hospital inpatient care	Claims data	7.7 million	31/12/2024
Hungary	SUCD	Data source contained records from secondary care specialist and hospital inpatient care where opioid prescriptions were issued.	Secondary care specialist, hospital inpatient care[a]	EHR	227 thousand	31/03/2025
Italy	POLIMI	Data source contained records from secondary care specialist and hospital inpatient care where opioid prescriptions were issued.	Secondary care specialists, hospital inpatient care[b]	EHR	104 thousand	29/04/2025
Portugal	EMDB-ULSEDV	Data source covered both inpatient and outpatient records from secondary care where opioid prescriptions were used	Secondary care specialist, hospital inpatient care[c]	EHR	101 thousand	20/10/2025
Sweden	HI-SPEED	Data source contained records from primary care GP, secondary care specialist, and hospital inpatient care where opioid prescriptions were issued.	Primary care GPs, secondary care specialists, hospital inpatient care	Registry	10.6 million	30/08/2024

CDW Bordeaux= Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EHR = Electronic heath record, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, GP=General practitioner, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

a. For drug records, only outpatient prescription records and part of the inpatient prescription records were available in SUCD.
b. For drug records, only inpatient prescription records were available in POLIMI.
c. For drug records, only outpatient prescription records were available in EMDB-ULSEDV.

Data source description (P3-C2-002)

IQVIA Longitudinal Patient Database Belgium (IQVIA LPD 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.

Danish Data Health Registries (DK-DHR)

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).

Estonian Biobank (EBB)

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.

Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)The clinical data warehouse of the Bordeaux University Hospital (CDW Bordeaux) 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).[7]

Integrated Primary Care Information Project (IPCI)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[8] The selection of 374 GP practices is representative of the entire country. The database contains records from 3.0 million (as of 01-2025) patients out of a Dutch population of 17M starting in 1996[8]. 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[8].

Norwegian Linked Health Registry data (NLHR)

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)

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, which 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.

Information System for Research in Primary Care (SIDIAP)

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 individuals 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.

Data source description (P4-C2-001)

Croatian National Public Health Information System (NAJS)

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health (CIPH). NAJS enables data collecting, processing, recording, managing, and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse, and others. The median observation period is 9.3 years.

Auria Clinical Informatics (FinOMOP-ACI Varha)

The data covers the patient register at the Hospital District of Southwest Finland (HDSF), containing Turku University Hospital, which is one of the five university hospitals in Finland. It covers the public specialist health care and most emergency health care in the area of Southwest Finland (Varsinais-Suomi) for all demographic groups. The data is utilized for scientific research from the data lake in the HDSF under the Finnish legislation (The Act on Secondary Use of Health and Social Data). The most relevant data domains are patients, visits, inpatient episodes, diagnoses, laboratory results, procedures, medication, pathology, radiology, radiotherapy, chemotherapy, obstetrics, and narrative patient reports, however there are also other data domains available. The median observation period is 8.4 years.

InGef Research Database (InGef RDB)

The InGef database comprises anonymized longitudinal claims data of about 10 million individuals across 50 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensings of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef database is dynamic in nature, i.e., claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data. All ambulatory diagnosis records are recorded by calendar quarter, with diagnosis date set to the first date of calendar quarter.

Semmelweis University Clinical Data (SUCD)

Semmelweis University is the largest provider of health care services in Hungary. Most of the departments cater for the most serious cases and patients requiring complex treatment, thus making the university a national health care provider. The overwhelming majority of patient data originates from Hungary, mainly from central region of the country: Budapest and Pest County. The database contains approximately 2 million individual patients across all care settings of the University since 2011. The hospital information system (MedSolution) is an integrated IT system provides functional support for inpatient and outpatient

care processes and serves as an integrated platform for different diagnostic areas, and in some specific area it supports the registration of medications. It supports all kinds of hospital work processes from admission to discharge. The outpatient module serves as a platform for the registration of activities related to care episode within the outpatient specialist care. During the care provision data related to health state of the patient, the diagnosis, the documentation of requested examinations and medical consultations, prescribed medication, final reports and performed interventions are recorded. The functions of the inpatient module assist the care provision within the inpatient settings. It documents the health state of the patient at admission and during the hospital stay, along with the anamnesis, diagnosis, the performed examinations and interventions, hospital final reports and provided medication in some are of care provision such as chemotherapy. Among other modules the diagnostic module registers the requested laboratory and imaging examinations and records the laboratory results. The median observation period is 266 days.

Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI)

Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, known simply as Policlinico of Milan, is a general hospital that can count on important excellence in different areas of care with a strong interdisciplinary focus. Given its nature as IRCCS – Institute for Research, Hospitalization and Health Care - in addition to care, it carries out biomedical and health research activities of a clinical and translational nature, involving the rapid transfer of therapies from the laboratories to the bedside of the sick person. The research activity is conducted in the different fields of medicine, from neurology to cardiology, from transplantation to hematology, to excellence of care in gynecology, neonatology, geriatrics, and rare diseases. Our DWH was born a few years ago with the aim of helping researchers in identifying patient cohorts and in obtaining large amounts of data for their studies more easily. A few years later, thanks to the EHDEN Project, we were also able to introduce the CDM OMOP. Currently the DWH contains data from Hospitalization, Outpatients visits, Laboratory test, Therapies, Radiology, Anatomic Pathology, and a REDCap instance for non-profit studies. The median observation period is 121 days.

Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB-ULSEDV)

Unidade Local de Saúde de Entre Douro e Vouga (ULSEDV) is an integrated public medical care centre comprising both primary, secondary, and tertiary healthcare. It fully serves approximately 274.000 patients of the municipalities of Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva. The ULSEDV includes 32 primary care centres assisted by three hospitals (Hospital de São Sebastião, Hospital São João da Madeira, and Hospital São Miguel), however the current database contains only hospital data. The median observation period is 9.5 years.

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED)

The Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED) study is a nationwide linked multi-register, regularly updated, observational study for timely response over time to scientific questions around effectiveness and safety of approved drugs that can arise suddenly, requiring rapid evidence for timely regulatory action - to protect patients' health and lives. The study data covers the whole Swedish population (about 10 million), with data on specialist care (National Patient Register), drug use (Prescribed Drug Register), cause of death (Cause-of-Death Register), sociodemographic data, and selected clinical data. Most data start from 2015; prescription drug data is available from 2018. The study population and all data are updated quarter yearly. HI-SPEED builds on the predecessor project SCIFI-PEARL (Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage) that was initiated in 2020 to conduct research on Covid-19 and pandemic-relations (https://www.gu.se/en/research/scifi-pearl). The median observation period is 9.7 years.

9.3. Study period

The study period spanned from the 1st of January 2012 or earliest data available, until the earliest of either 31st December 2024 or the respective latest date of data availability of the respective data sources.

9.4. Follow-up

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

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

Study population names	Time Anchor Description	Number of entries	Type of entry	Washout window	Care Setting	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
All individuals from the data source eligible for the study – Analysis of prevalent use	Individuals present in the data source during the study period and with at least 1 year of valid data source history (prior data availability requirement not applicable in hospital data source)	Multiple	Prevalent	N/A	IP and OP	N/A	N/A	Overall, substance, strength, route	N/A	N/A
All individuals from the data source eligible for the study – Analysis of incident use	Individuals present in the data source during the study period and with at least 1 year of valid data source history (prior data availability requirement not applicable in hospital data source)	Multiple	Incident	[-365 to ID]	IP and OP	N/A	N/A	Overall, substance, strength, route	N/A	N/A

ID = index date, IP = inpatient, N/A = not applicable, OP = outpatient

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) or 2) date at which they have a year of prior history recorded (not applied for hospital data sources). 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 individual ends.

An example of entry and exit into the denominator population is 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 contributes 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 data source (the end of observation period). Lastly, person ID 5 has two observation periods in the data source. 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.

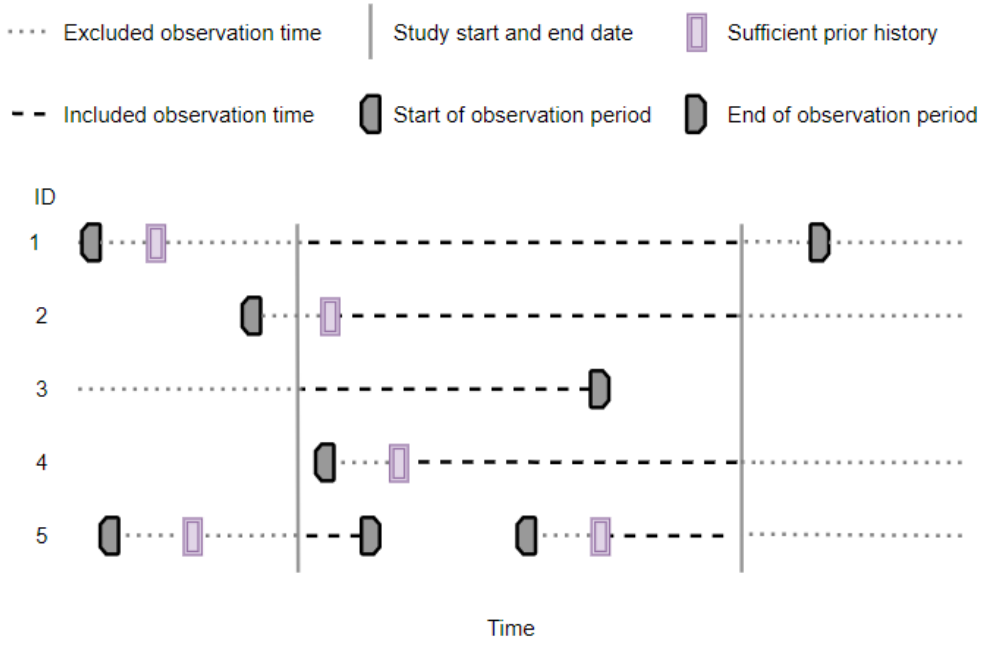

Figure 1. Included observation time for the denominator population.

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 data sources). 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, whichever comes first), with at least 1 year of prior data availability (not applicable in hospital data sources), 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 data source) 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 data source 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 data sources	N/A	N/A
Prior data source history of 1 year (not applicable in hospital data source)	Study individuals were 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 data sources (not applicable in hospital data source)	N/A	N/A
Washout period	New users were 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 data sources	N/A	N/A

N/A = not applicable.

9.6. Variables

9.6.1. Exposure

For this study, the exposure of interest was the prescription or dispensation (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 7**.

Table 6. Exposure of interest.

Substance Name	Strength*	No record counts in data sources expected based on feasibility		Substance Name	Strength*	No record counts in data sources 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		

Substance Name	Strength*	No record counts in data sources expected based on feasibility		Substance Name	Strength*	No record counts in data sources expected based on feasibility
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 names	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 study protocol.[a]	[-365 to ID]	Calendar year	Biobank, primary, and secondary care	RxNorm	N/A	All individuals present in the data source during the study period (except hospital data sources)	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 study protocol. 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.[a]	[-365 to ID]	Calendar year	Biobank, primary, and secondary care	RxNorm	N/A	All individuals present in the data source during the study period (except hospital data sources)	Previous opioid use	N/A	N/A

ID = index date, N/A = not applicable.

a. Exposure was based on dispensation data in EBB, DK-DHR, NLHR, InGef RDB, and HI-SPEED, and prescription data in other data sources.

9.6.2. Outcome

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 were used: 1–10, 11–20, 21–30 […] , and >80
- Sex: male or female
- History of cancer: yes or no (for outcome stratification: this covariate was used to define opioid prescriptions/dispensations in individuals with/without history of cancer (numerator) in the overall population (denominator))

The following covariates were used for the patient-level drug utilisation study, with detailed definition given in **Tabe 8**.

- 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, leukaemia, 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 data sources) and procedures (hospital data sources only) recorded in the month/week before/at the date of treatment start. The top 10 most frequent (clinically relevant) comorbidities from large-scale patient characterisation recorded (1) at index date (primary definition), (2) in the week before index date (sensitivity analysis), and (3) in the month before index date (sensitivity analysis) 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 comorbidities 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	Individuals 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 covariates by pre-defined conditions/medications of interest.	Counts	Demographics, comorbidities and comedication within anytime to 366 days before index date (ID), 365 days before ID to ID	Biobank, primary and secondary, care	SNOMED, RxNorm	N/A	Individuals with new use during the study period	N/A	N/A

ID = index date, N/A = not applicable.

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 of study protocol.

9.8. Data transformation

All data sources 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 data source 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 (including combinations and products for all indications), (3) by strength (weak/potent opioids) for those opioids where strength is labelled by the WHO, and (4) by route (oral, transdermal, or parenteral) for overall opioids 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**. 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%.

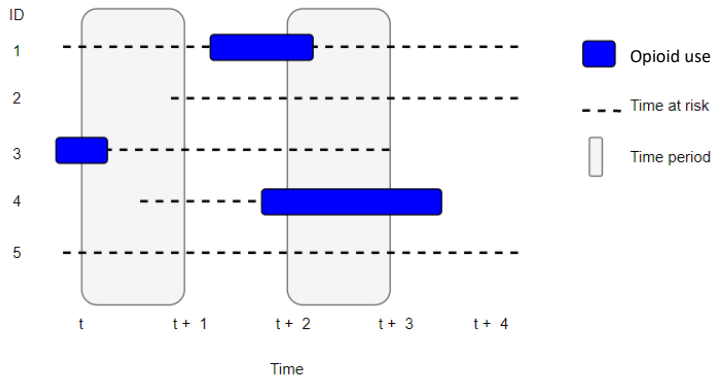

Figure 2. Illustration for prevalence estimation.

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. 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 new 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.

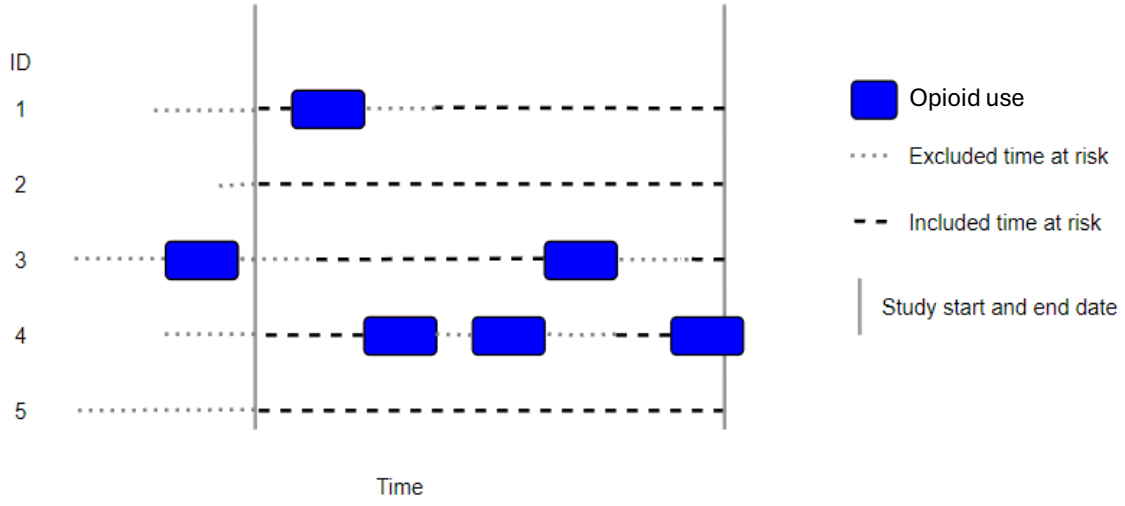

Figure 3. Illustration for incidence estimation.

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

For each concept extracted before/at index date, the number of individuals (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 data sources) and procedures (hospital data sources only) recorded at the date of treatment start/ in the week/month before treatment start. The number of individuals (N, %) with a record of the respective indication was provided.

Drug exposure calculations

Drug eras were defined as follows: Exposure started at date of the first prescription, e.g., the index date the individual entered the cohort. For each prescription, the estimated duration of use was retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions were combined into continuous exposed episodes (drug eras) using the following specifications: Two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤7 days.

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 data sources 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 data source. Before study initiation, test runs of the analyses were performed on a subset of the data sources and quality control checks were performed. Once all the tests passed, the final study codes package was released in the version-controlled Study Repository for execution against all the participating data sources.

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

The study results of all data sources were checked, after which they were made available to the team, and the dissemination phase started. All results were locked and timestamped for reproducibility and transparency.

Cell suppression was applied as required by data sources to protect individuals' 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

DUS = drug utilisation study.

9.9.3. Sensitivity analysis

Table 10. Sensitivity analyses – rationale, strengths, and limitations.

	What is being varied? How?	Why?	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

9.9.4. Deviations from the protocol

P3-C2-002

- 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 data sources often utilise the admission of patients to start the observation period. Therefore, individuals without prior visit to the hospital 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 data sources. Therefore, the 1-year prior data availability requirement was not applied to hospital data sources.
- 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 an individual belonged to a practice (i.e., contributed to the denominator) can only be made for dates between the first and last visit of the individual. This has a strong impact towards the data source 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 data source. To mitigate this, we did not conduct the analyses of incidence and prevalence within the 6 months before the last data availability in the data source.
- Drug records in NLHR were only available from 2018 on. 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 data sources.

P4-C2-001

- Data on outpatient drug records in IMASIS were only available since 2016, and therefore, estimation on incidence and prevalence (except for **Section 12.2.1. Objective 1. Population-level drug utilisation: Overview**) should be interpreted from the year of 2016 to ensure the completeness of data source.
- Hospital data in NAJS were only available for the period 2017–2022, and therefore, estimation on incidence and prevalence (except for **Section 12.2.1. Objective 1. Population-level drug utilisation: Overview**) should be interpreted for the period 2017–2022 to ensure the completeness of data source.

10. DATA MANAGEMENT

All data sources 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 data source 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 data source 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 *DataQualityDashboard* 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 data source. The results from the diagnostics provided detailed information related to drug dose, form, and days of supply, which informed us whether a data source 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.

12. RESULTS

All the results are available in a Shiny App: EUPAS1000000615, including additional stratifications not presented in the main report.

12.1. Participants

The study included approximately 56 million individuals across 15 data sources from 14 European countries. There were 670,162 individuals from IQVIA LPD Belgium, 6,766,607 individuals from DK-DHR, 209,576 individuals from EBB, 2,186,170 individuals from CDW Bordeaux, 2,487,567 individuals from IPCI, 5,625,017 individuals from NLHR, 827,455 individuals from IMASIS, and 7,482,435 individuals from SIDIAP eligible for the incidence analysis from P3-C2-002. The current study report also included 4,579,521 individuals from NAJS, 705,576 individuals from FinOMOP-ACI Varha, 9,632,705 individuals from InGef RDB, 2,195,922 individuals from SUCD, 1,056,346 individuals from POLIMI, 457,830 individuals from EMDB-ULSEDV, and 11,019,043 individuals from HI-SPEED eligible for the incidence analysis from P4-C2-002.

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[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
P3-C2-002				
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
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	-178,040	863,043	14,841	670,162
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	-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

Reason	Variable name[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
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	-68,497	278,585	512	209,576
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	-179,147	2,367,960	2,643	2,186,170
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	-450,577	2,983,001	44,857	2,487,567
NLHR				

Reason	Variable name[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
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	-1,526,861	7,319,973	131,641	5,652,017
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	-118,875	946,989	659	827,455
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	-2,596,600	10,137,445	58,410	7,482,435

Reason	Variable name[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
P4-C2-001				
NAJS				
Starting population		*4,853,340*		*4,853,340*
Missing year of birth	0	4,853,340	0	4,853,340
Missing sex	0	4,853,340	0	4,853,340
No observation time available during study period	79,002	4,773,808	79,002	4,773,808
Prior history requirement not fulfilled during study period	93,824	4,679,984	93,824	4,679,984
Starting analysis population		*4,679,984*		*4,679,984*
Apply washout criteria of 365 days	-1,387,501	6,067,485	100,463	4,579,521
FinOMOP-ACI Varha				
Starting population		*855,446*		*855,446*
Missing year of birth	0	855,446	0	855,446
Missing sex	0	855,446	0	855,446
No observation time available during study period	143,444	711,083	143,444	711,083
Prior history requirement not fulfilled during study period	0	711,083	0	711,083
Starting analysis population		*711,082*		*711,082*
Apply washout criteria of 365 days	-237,091	948,173	5,506	705,576
InGef RDB				
Starting population		*10,512,283*		*10,512,283*
Missing year of birth	0	10,512,283	0	10,512,283
Missing sex	0	10,512,283	0	10,512,283
No observation time available during study period	268,554	10,243,728	268,554	10,243,728
Prior history requirement not fulfilled during study period	502,439	9,741,289	502,439	9,741,289

Reason	Variable name[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
Starting analysis population		*9,741,289*		*9,741,289*
Apply washout criteria of 365 days	-2,455,852	12,197,141	108,584	9,632,705
SUCD				
Starting population		*2,335,088*		*2,335,088*
Missing year of birth	0	2,335,088	0	2,335,088
Missing sex	0	2,335,088	0	2,335,088
No observation time available during study period	139,050	2,196,038	139,050	2,196,038
Prior history requirement not fulfilled during study period	0	2,196,038	0	2,196,038
Starting analysis population		*2,196,038*		*2,196,038*
Apply washout criteria of 365 days	-7,114	2,203,152	116	2,195,922
POLIMI				
Starting population		*1,716,255*		*1,716,255*
Missing year of birth	0	1,716,255	0	1,716,255
Missing sex	0	1,716,255	0	1,716,255
No observation time available during study period	659,592	1,056,663	659,592	1,056,663
Prior history requirement not fulfilled during study period	0	1,056,663	0	1,056,663
Starting analysis population		*1,056,663*		*1,056,663*
Apply washout criteria of 365 days	-8,826	1,065,489	317	1,056,346
EMDB-ULSEDV				
Starting population		*575,079*		*575,079*
Missing year of birth	0	575,079	0	575,079
Missing sex	0	575,079	0	575,079
Cannot satisfy age criteria during the study period based on year of birth	999	574,080	999	574,080

Reason	Variable name[a]			
	Excluded records	Number records	Excluded individuals	Number individuals
No observation time available during study period	115,792	458,288	115,792	458,288
Prior history requirement not fulfilled during study period	0	458,288	0	458,288
Starting analysis population		*458,288*		*458,288*
Apply washout criteria of 365 days	-92,765	551,053	458	457,830
HI-SPEED				
Starting population		*11,739,647*		*11,739,647*
Missing year of birth	0	11,739,647	0	11,739,647
Missing sex	0	11,739,647	0	11,739,647
No observation time available during study period	503,912	11,235,735	503,912	11,235,735
Prior history requirement not fulfilled during study period	48,465	11,187,270	48,465	11,187,270
Starting analysis population		*11,187,270*		*11,187,270*
Apply washout criteria of 365 days	-2,139,639	13,326,909	168,227	11,019,043

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

a. The '**Number records'** and **'Number individuals'** for the row '*starting population*' and '*starting analysis population'* were the starting number of records/individuals. The **'Number records/individuals'** for the row with exclusion reason were the number of records/individuals after exclusion for that particular reason. In some data sources, multiple records were observed from one individual for '*starting population*'. This is due to the definition of observation period in the respective data source (e.g., ending observation period when the individual 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 individual 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

12.2.1. Objective 1. Population-level drug utilisation

Overview

The study included approximately 14 million new opioid users from 14 European countries. A total number of 205,461 individuals (IQVIA LPD Belgium), 2,183,760 individuals (DK-DHR), 60,286 individuals (EBB), 274,026 individuals (CDW Bordeaux), 484,556 individuals (IPCI), 1,888,433 individuals (NLHR), 132,762 individuals (IMASIS), and 2,204,608 individuals (SIDIAP) were identified as new opioid users during the study period of 2012–2024 in P3-C2-002. A further total number of 1,341,765 individuals (NAJS), 266,327 individuals (FinOMOP-ACI Varha), 2,505,705 individuals (InGef RDB), 17,709 individuals (SUCD), 24,821 individuals (POLIMI), 89,900 individuals (EMDB-ULSEDV), and 2,585,592 individuals (HI-SPEED) were identified as new opioid users during the study period of 2012–2024 in P4-C2-001.

The numbers of new opioid users with no history of cancer ranged from 9,085 (SUCD) to 2,426,600 (HI-SPEED), and with history of cancer ranged from 5,326 (IQVIA LPD Belgium) to 300,743 (DK-DHR) (**Table 12**). The proportion of new opioid users with no history of cancer ranged from 51.3% (SUCD) to 98.8% (IQVIA LPD Belgium), and with history of cancer ranged from 2.6% (IQVIA LPD Belgium) to 50.3% (SUCD).

Table 12. Number of new opioid users during the study period 2012–2024.

			Number of individuals with new opioid prescription[a]		
	Year included	Number of included individuals in denominator	Overall	without a history of cancer in 1 year before prescription	with a history of cancer in 1 year before prescription
P3-C2-002					
IQVIA LPD Belgium	2015–2024	670,162	205,461	202,947 (98.8%)	5,326 (2.6%)
DK-DHR	2012–2024	6,766,607	2,183,760	2,061,948 (94.4%)	300,743 (13.8%)
EBB	2012–2022	209,576	60,286	56,367 (93.5%)	6,413 (10.6%)
CDW Bordeaux	2012–2024	2,186,170	274,026	225,300 (82.2%)	55,979 (20.4%)
IPCI	2012–2024	2,487,567	484,556	458,775 (94.7%)	54,010 (11.1%)
NLHR	2019–2023	5,625,017	1,888,433	1,781,024 (94.3%)	195,511 (10.4%)
IMASIS	2012–2024	827,455	132,762	120,275 (90.6%)	21,560 (16.2%)
SIDIAP	2012–2023	7,482,435	2,204,608	2,155,971 (97.8%)	126,915 (5.8%)
P4-C2-001					
NAJS	2016–2024	4,579,521	1,341,765	1,230,842 (91.7%)	205,342 (15.3%)
FinOMOP-ACI Varha	2012–2024	705,576	266,327	248,372 (93.3%)	33,932 (12.7%)
InGef RDB	2016–2024	9,632,705	2,505,705	2,400,954 (95.8%)	209,717 (8.4%)

SUCD	2012–2024	2,195,922	17,709	9,085 (51.3%)	8,906 (50.3%)
POLIMI	2018–2024	1,056,346	24,821	18,527 (74.6%)	6,765 (27.3%)
EMDB-ULSEDV	2012–2024	457,830	89,900	88,583 (98.5%)	3,018 (3.4%)
HI-SPEED	2019–2024	11,019,043	2,585,592	2,426,600 (93.9%)	277,904 (10.7%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

a. The percentage of individuals with or without a history of cancer within 1 year before the new opioid prescription was calculated as the proportion of the overall new opioid users in each data source. The summed counts of individuals with or without a 1-year history of cancer may exceed the total number of new opioid users, as individuals can be reclassified after the washout period and the applied 1-year cancer definition.

Some data sources showed an increase of incidence (**Figure 4**) towards the end of study period. A drop in incidence (**Figure 4**) and prevalence (**Figure 5**) of overall opioid use was observed during the period of 2020–2021 in IQVIA LPD Belgium, NAJS, CDW Bordeaux, IPCI, NLHR, SIDIAP, IMASIS, and HI-SPEED. Other than these two observations, most data sources showed a stable trend in overall incidence (**Figure 4**) and prevalence (**Figure 5**) over years.

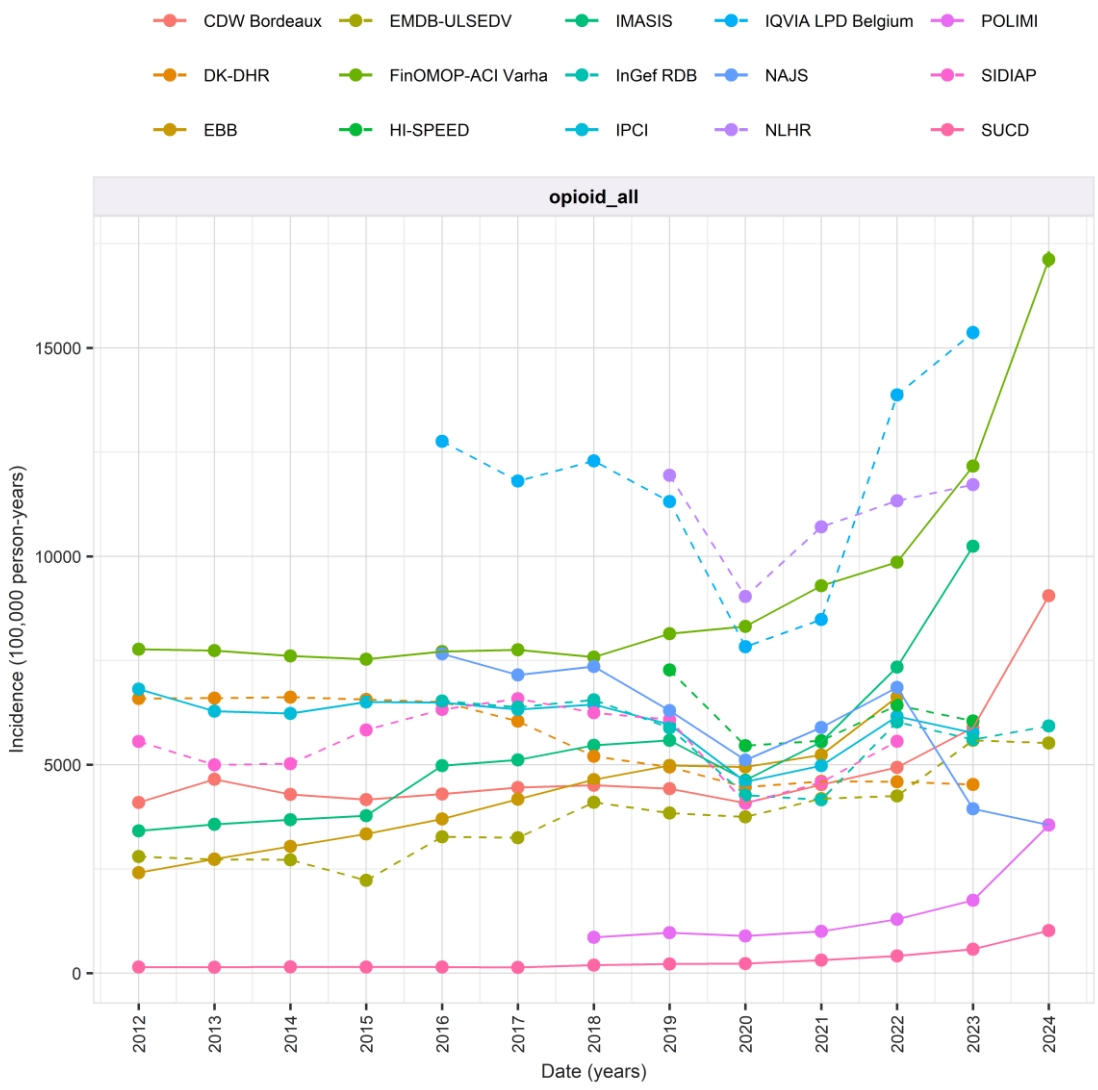

Figure 4. Incidence of overall opioid use.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

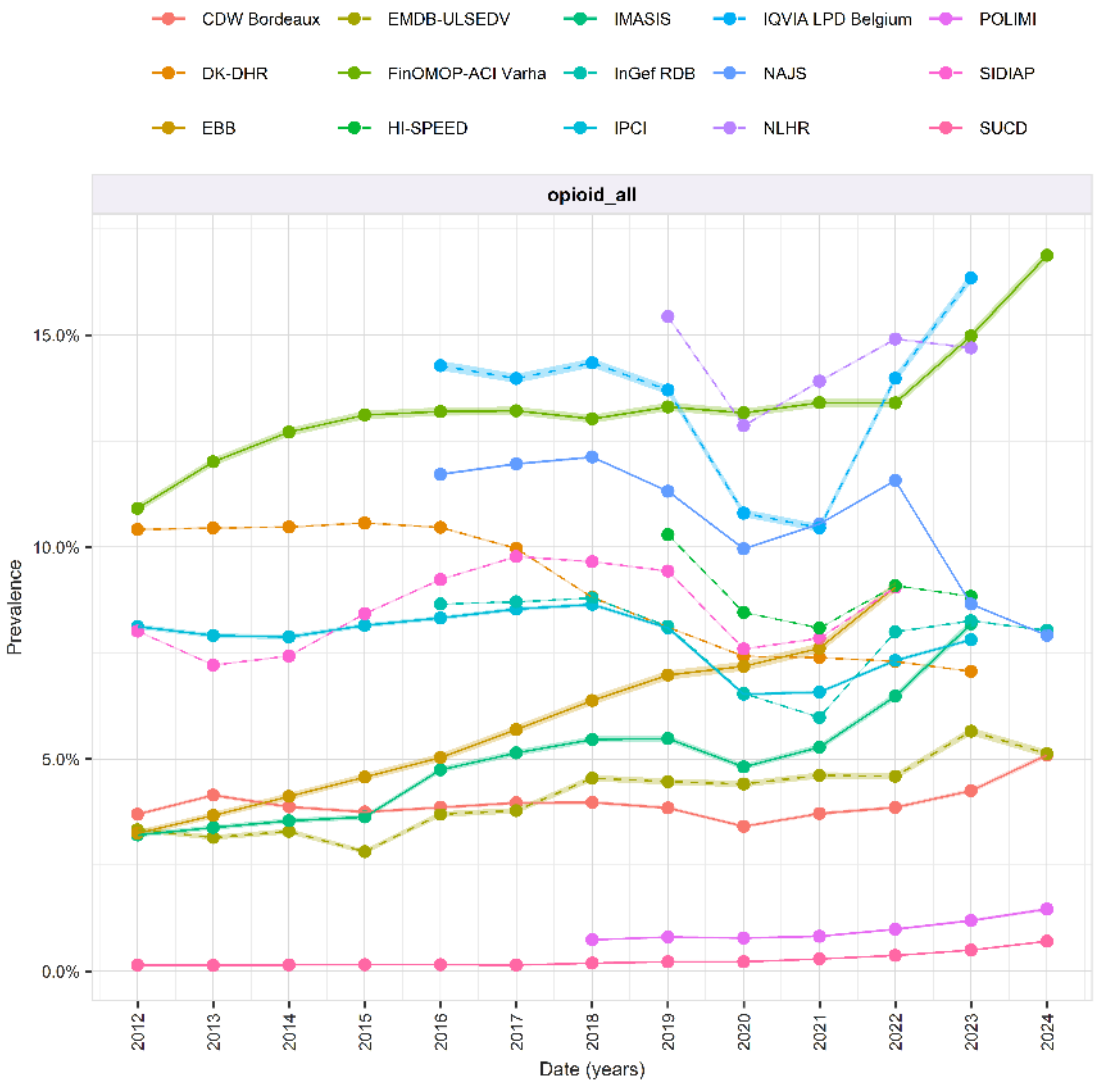

Figure 5. Prevalence of overall opioid use.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

Several considerations need to be taken into account when describing and interpreting the results presented above:

Seven data sources, including all 6 hospital data sources (FinOMOP-ACI Varha, CDW Bordeaux, SUCD, POLIMI, EMDB-ULSEDV, IMASIS) and IQVIA LPD Belgium, defined the observation period based on visit records rather than registration with a practice and/or death records. As a result, individuals in these data sources contributed to the denominator only between their first and last recorded visits. This approach led to a reduced denominator toward the end of the study period, as the denominator definition depended entirely on visit frequency, and future visits could not be captured. Consequently, both prevalence and, more markedly, incidence estimates were inflated toward the end of the study period. To avoid misinterpretation of the population-level DUS results in these data sources, separate graphs with the counts of denominators and numerators were presented.

Some data sources were incomplete for certain study periods, leading to fluctuations in the estimated incidence and prevalence of opioid use. These results with fluctuation should therefore not be interpreted as true trends of opioid use in those data sources. In IMASIS, while the incidence and prevalence remained relatively stable between 2012–2015 and 2016–2019, there was a noticeable increase from 2015 to 2016. This was due to the addition of hospital data into the IMASIS data source in 2016, resulting in a sudden rise in opioid records during that year (**Figure 6**). Similarly, NAJS showed a drop in both incidence and prevalence from 2022 to 2023, with this low level persisting into 2024. Data from secondary care were only available in NAJS for the years 2017–2022. Although the inclusion of secondary care data in 2017 did not lead to major changes, there was a clear drop in opioid records in 2023 (**Figure 6**), which led to systematically lower and underestimated incidence and prevalence of overall opioid use for 2023–2024. To prevent misinterpretation of opioid use trends, data points corresponding to periods with incomplete data sources were censored from the subsequent result and discussion sections.

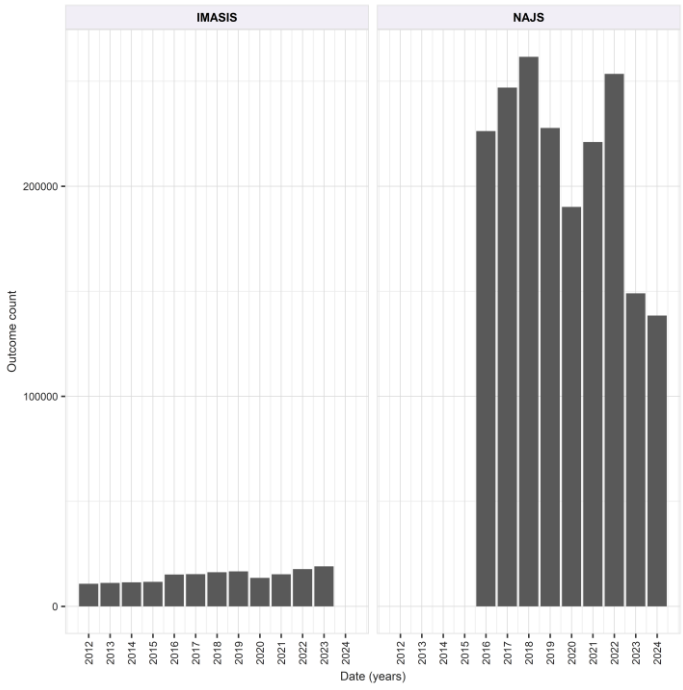

Figure 6. Number of overall opioid record counts in IMASIS and NAJS.

IMASIS = Institut Municipal Assistència Sanitària Information, NAJS = Croatian National Public Health Information System.

For SUCD, POLIMI, and EMDB-ULSEDV, data on opioid prescriptions were available only from either inpatient or outpatient settings, while the denominator included all individuals with any hospital visit. As a result, estimates from incidence/prevalence analyses could not be reliably interpreted, as the data were not representative of overall opioid use within the institution. However, since the data availability in each of these data sources remained consistent over the study years, population-level DUS results for SUCD, POLIMI, and EMDB-ULSEDV were reported and discussed separately. Trends in opioid use were interpreted with a focus on the specific inpatient or outpatient settings covered by each data source to ensure appropriate interpretation of the results.

Overall Opioid Use

For better interpretation of results, reporting on incidence and prevalence of opioid use were grouped by type of data sources: primary care/national registries, hospital data sources with complete coverage, and hospital data sources with partial coverage.

Incidence of overall opioid use (**Figure 7**) was highest in IQVIA LPD Belgium, starting at 12,757/100,000 person-years in 2016 to 15,366/100,000 person-years in 2023. Without considering SUCD, POLIMI, and EMDB-ULSEDV, EBB had 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 data sources in 2023 at 4,526.

When we consider the type of data sources, all primary care and nationwide data sources, except for EBB, showed a dip in incidence of overall opioid use during the COVID-19 pandemic period of 2020–2021 (**Figure 7A**). 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 EBB and IQVIA LPD Belgium, a slightly decreasing trend in NAJS, InGef RDB, IPCI, and HI-SPEED, and a substantial decrease in DK-DHR over time.

As mentioned previously, IQVIA LPD Belgium defined observation period based on visit records and therefore there was a sharp decrease in denominator (**Figure 8A**) and inflation in incidence during 2022–2023. The number of overall opioid record counts (**Figure 8B**) returned to pre-COVID 19 level in 2022–2023.

In contrast to IQVIA LPD Belgium, 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.

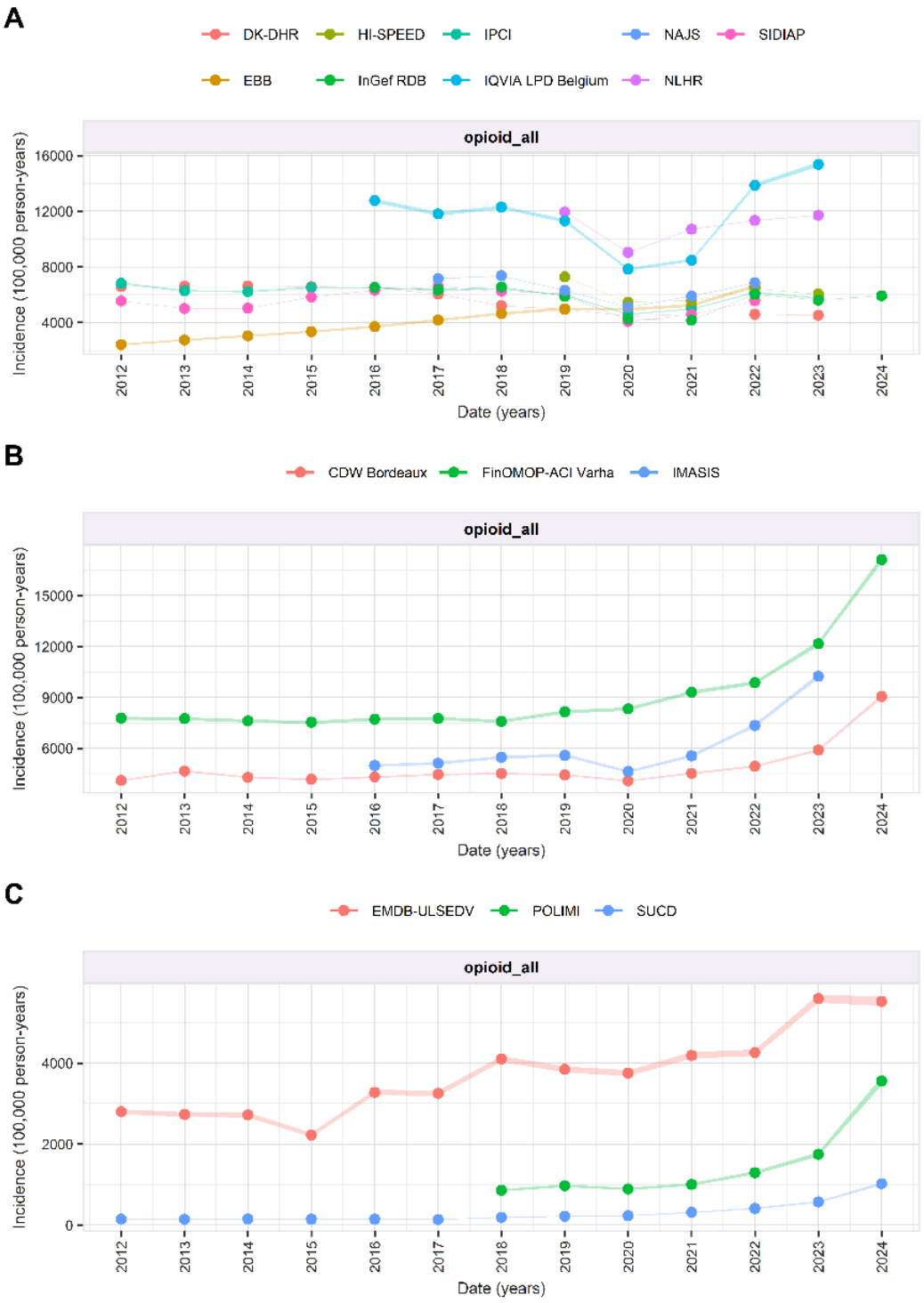

Figure 7. Incidence of overall opioid use, in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

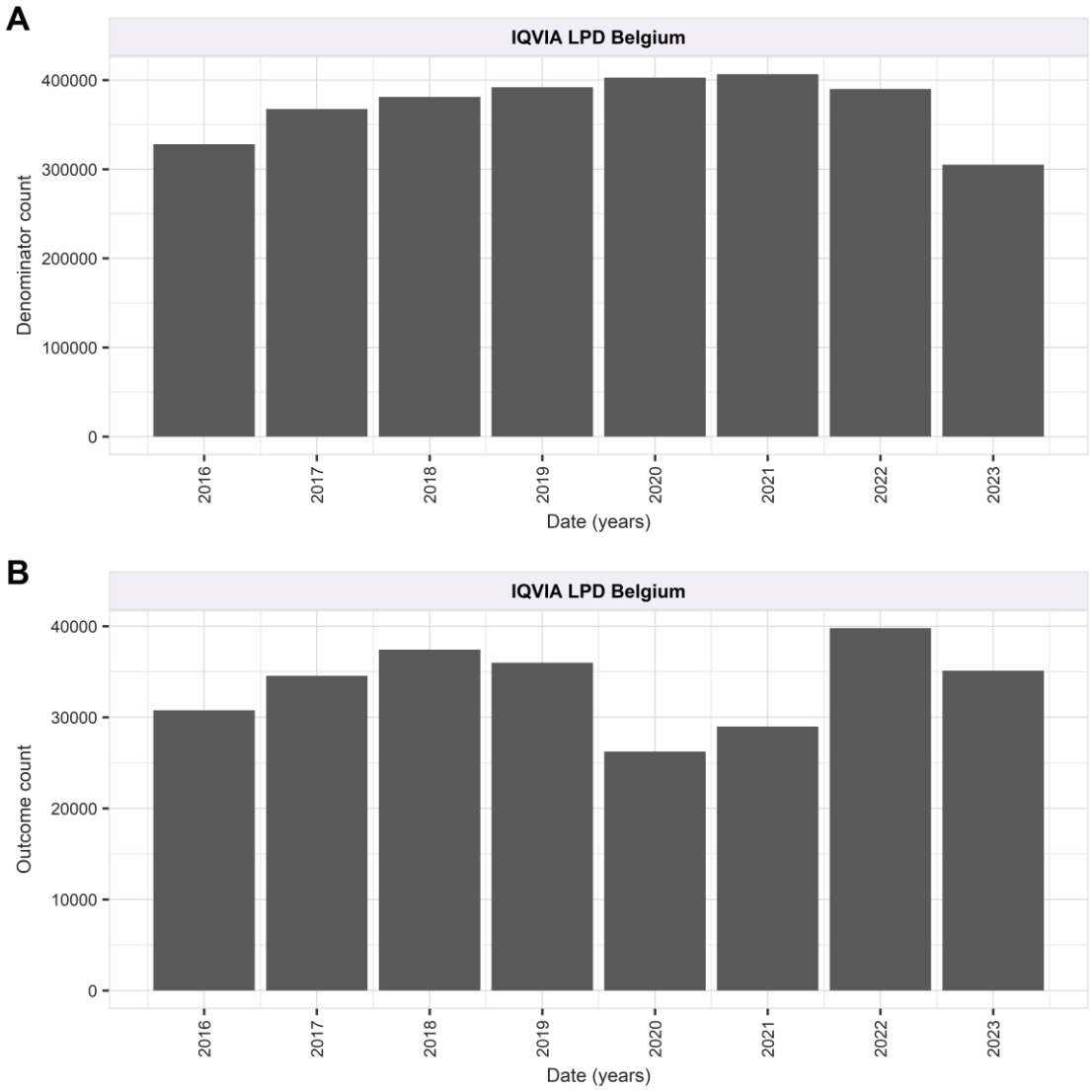

Figure 8. Number of (A) denominator counts and (B) overall opioid record counts in IQVIA LPD Belgium.

IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium.

All hospital data sources, including SUCD, POLIMI, and EMDB-ULSEDV, showed an increasing trend in incidence of overall opioid use. As shown in **Figure 7B**, incidence of opioid use had increased by 2-fold in CDW Bordeaux (4,096 in 2012 to 9,057 in 2024), FinOMOP-ACI Varha (7,771 in 2012 to 17,121 in 2024), and IMASIS (4,979 in 2016 to 10,242 in 2023). Incidence of opioid use increased by 2-fold in EMDB-ULSEDV, 4-fold in POLIMI, and 7-fold in SUCD over the study period. All three data sources are hospital data sources and defined the observation period by visits and records. When considering the number of denominators for the incidence analysis in hospital data sources (**Figure 9A**), there was a drop in the number of individuals included in the denominator population towards the end of study period in all hospital data sources. This might contribute to the increase in the estimates of incidence rates towards the end of study period consistently observed in all hospital data sources.

When we also considered number of opioid record counts in hospital data sources (**Figure 9B**), an increasing trend of opioid use was observed in FinOMOP-ACI Varha and IMASIS, as well as in SUCD, POLIMI, and EMDB-ULSEDV. Therefore, increase in overall opioid new use in these data sources should not be interpreted as solely the artefact of reducing denominator.

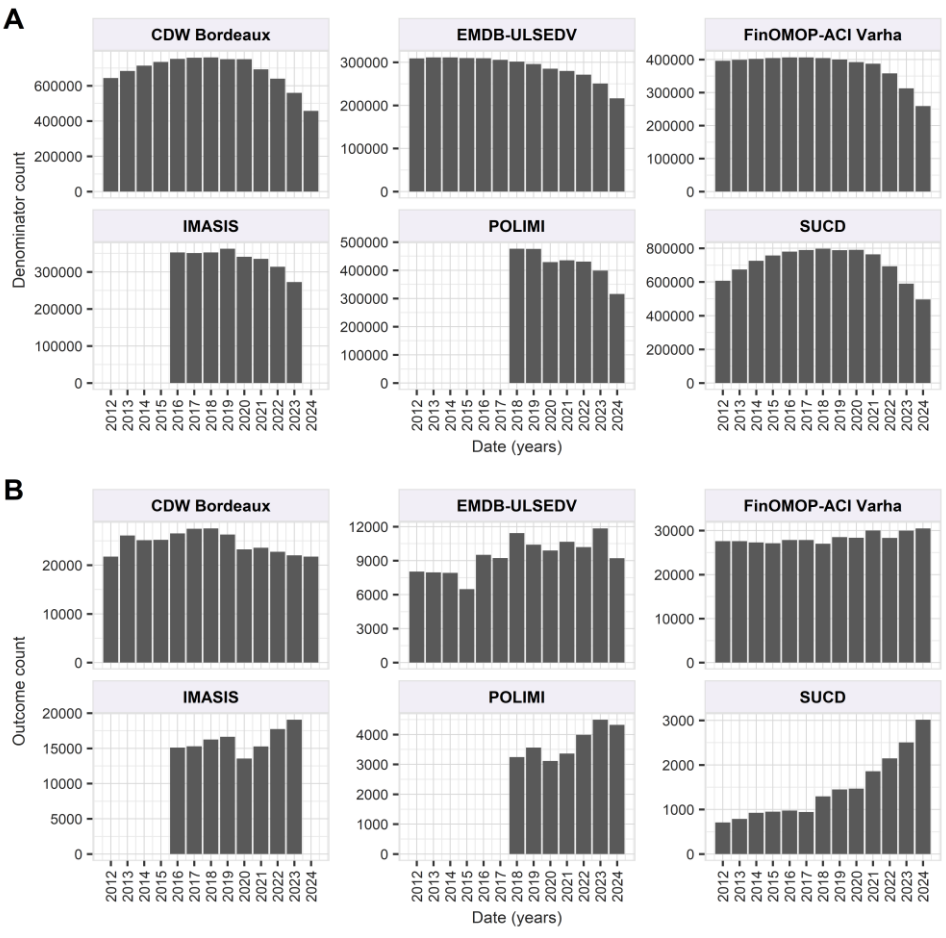

Figure 9. Number of (A) denominator counts and (B) overall opioid record counts in hospital data sources.

CDW Bordeaux = Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

The prevalence of overall opioid use shared similar pattern to incidence (**Figure 10**).

Among the primary care and nationwide data source, highest prevalence was observed in IQVIA LPD Belgium (13.7–16.3% during the study period, excluding 2020–2021) and NLHR (14.7–15.4%, excluding 2020–2021) (**Figure 10A**). Lowest prevalence was observed in EBB for study period 2012–2019. Increasing trend in prevalence of overall opioid use was observed in EBB and IQVIA LPD Belgium. After considering the denominator issues in data sources, increasing trend in prevalence of overall opioid use was observed in EBB, from 3.3% in 2012 to 9.1% in 2022.

Among all the hospital data sources (except SUCD, POLIMI, and EMDB-ULSEDV), FinOMOP-ACI Varha had the highest prevalence of overall opioid use, ranging from 10.9% to 16.9%. CDW Bordeaux had the lowest prevalence of overall opioid use since 2016 (3.9–5.1%). Increasing trend in prevalence of overall opioid use was observed in all hospital data sources (**Figure 10B**, **Figure 10C**). Similar to incidence of overall opioid use, an increasing number of prevalent opioid users was observed in SUCD, POLIMI, EMDB-ULSEDV, and IMASIS over the time of study period (**Figure 11**). However, FinOMOP-ACI Varha showed a decreasing number of prevalent opioid users towards the end of study period (**Figure 11**), contrary to the increasing number of overall opioid records (**Figure 9B**).

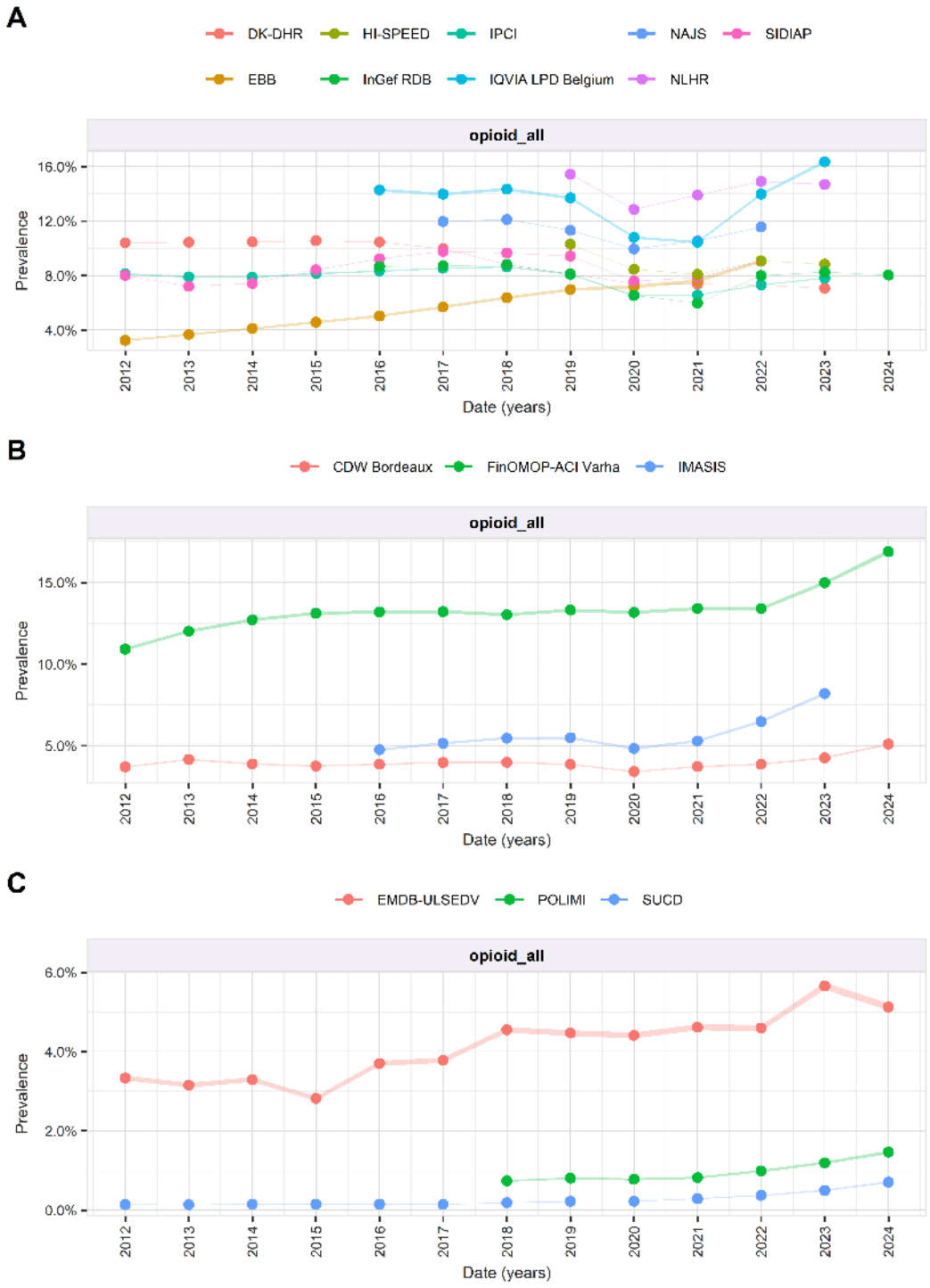

Figure 10. Prevalence of overall opioid use, overall, in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

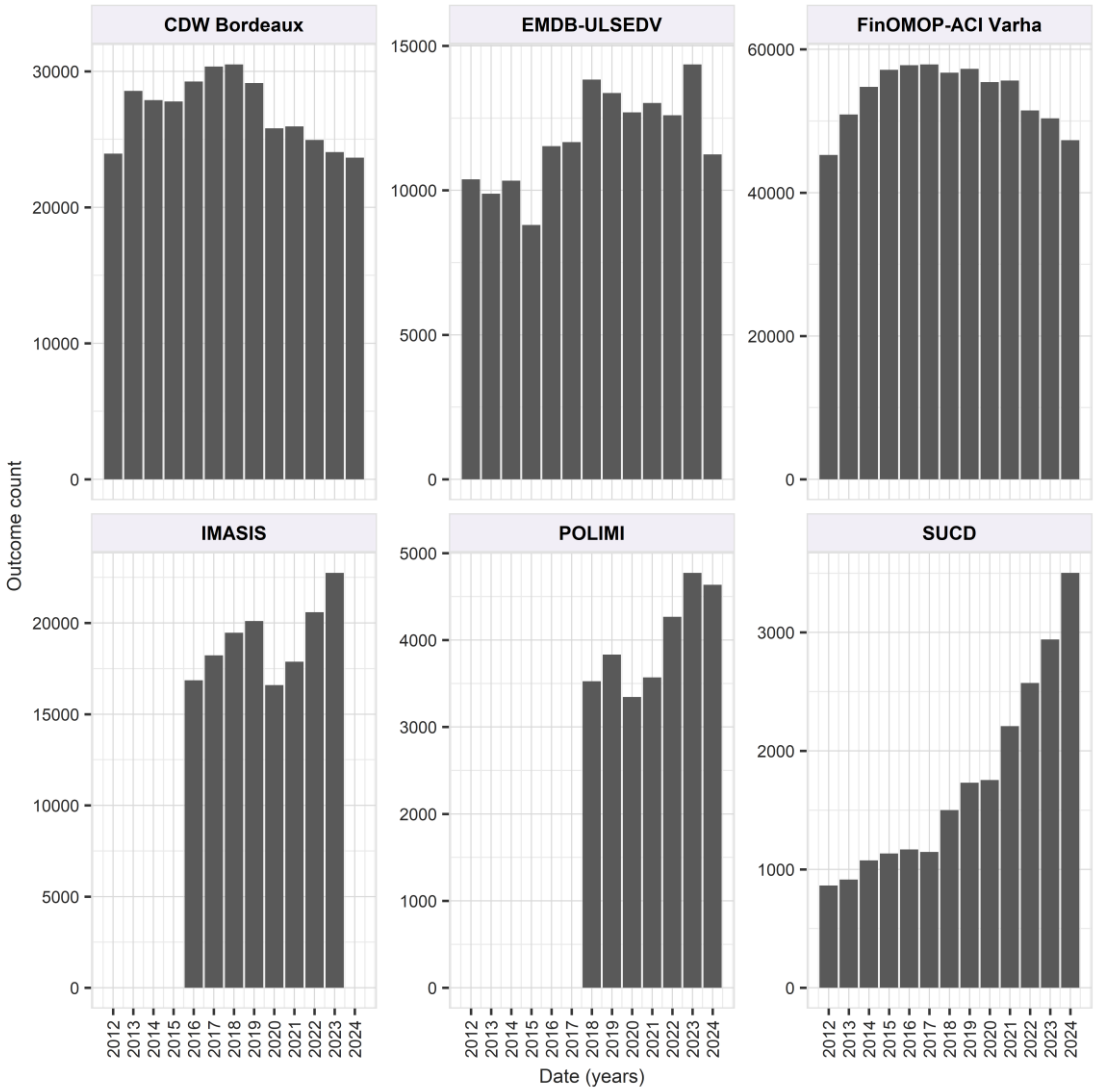

Figure 11. Number of prevalent opioid users in hospital data sources.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

Opioid Use by History of Cancer

The incidence of overall opioid prescriptions was dominated by prescriptions in people without a history of cancer, regardless of type of data sources (**Figure 12**). This explained the highly similar trend and pattern of non-cancer opioid use with overall opioid use. When considering the opioid use with a record of recent history of cancer, the dip in incidence during the COVID-19 pandemic period of 2020–2021 was less prominent compared to that of non-cancer opioid use.

Among the primary care and nationwide data sources (**Figure 12A**), NLHR had the highest prevalence of cancer opioid use (ranging from 907/100,000 person-years to 946/100,000 person-years, excluding 2020–2021) while IQVIA LPD Belgium had a lower incidence of cancer opioid use (291 in 2016 to 198 in 2023). Contrary to the highest incidence of non-cancer opioid use, 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). There was an increase in incidence of cancer opioids in EBB, decreasing trend in IQVIA LPD Belgium, while remaining stable in NAJS, DK-DHR, IPCI, SIDIAP, and HI-SPEED.

Among the hospital data sources (except SUCD, POLIMI, and EMDB-ULSEDV), CDW Bordeaux had the highest incidence of cancer opioid use (801 in 2012 to 1,850 in 2024), while IMASIS had the lowest (604 in 2016 to 1364 in 2023) (**Figure 12B**). Incidence of cancer opioids increased in all hospital data sources, including SUCD, POLIMI and EMDB-ULSEDV (**Figure 12B**, **Figure 12C**). The increasing cancer opioid use in FinOMOP-ACI Varha, SUCD, POLIMI, EMDB-ULSEDV, and IMASIS was supported with the increasing number of cancer opioid record counts over the study period (**Figure 13**).

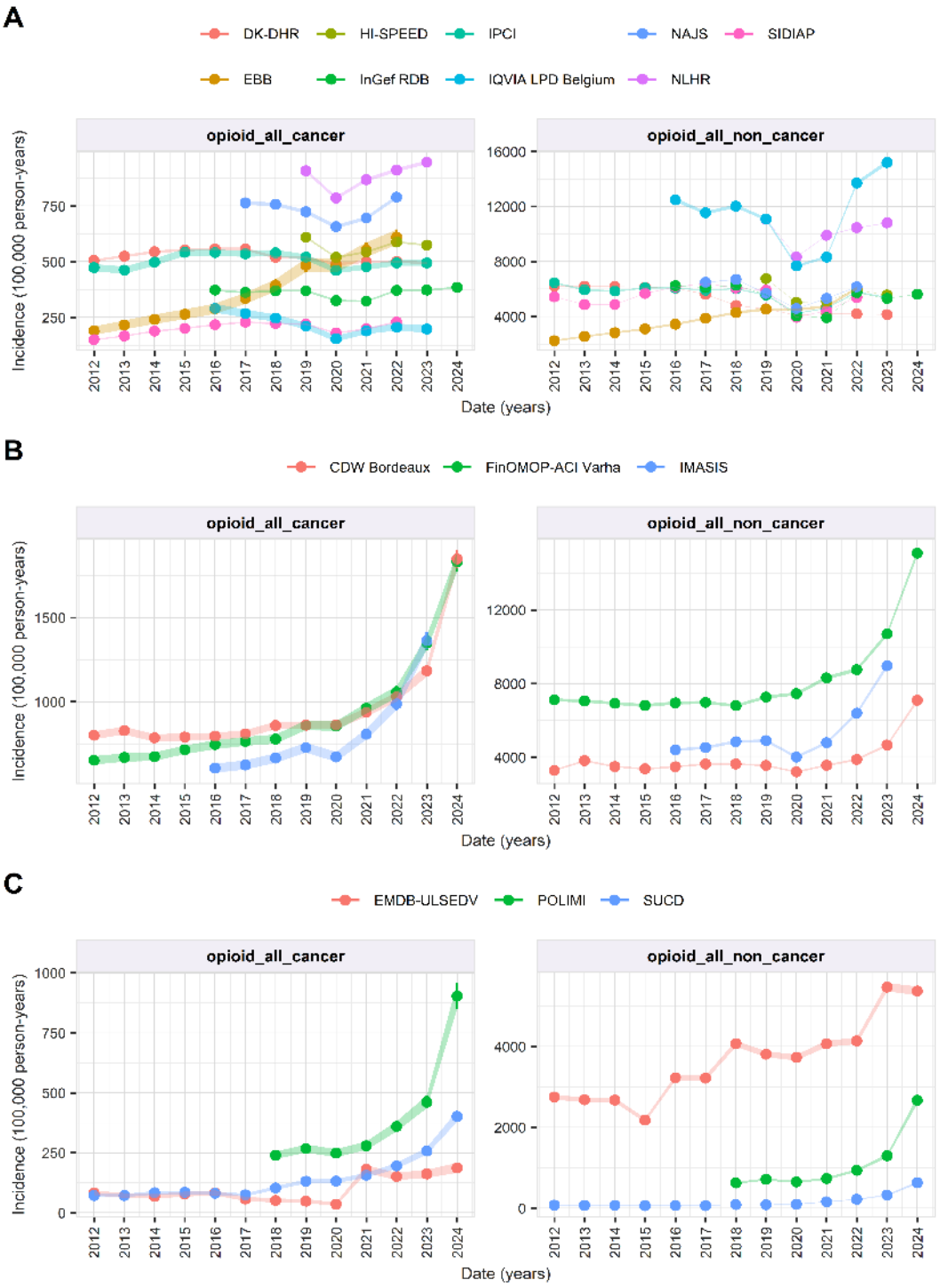

Figure 12. Incidence of opioid use, stratified by history of cancer, in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

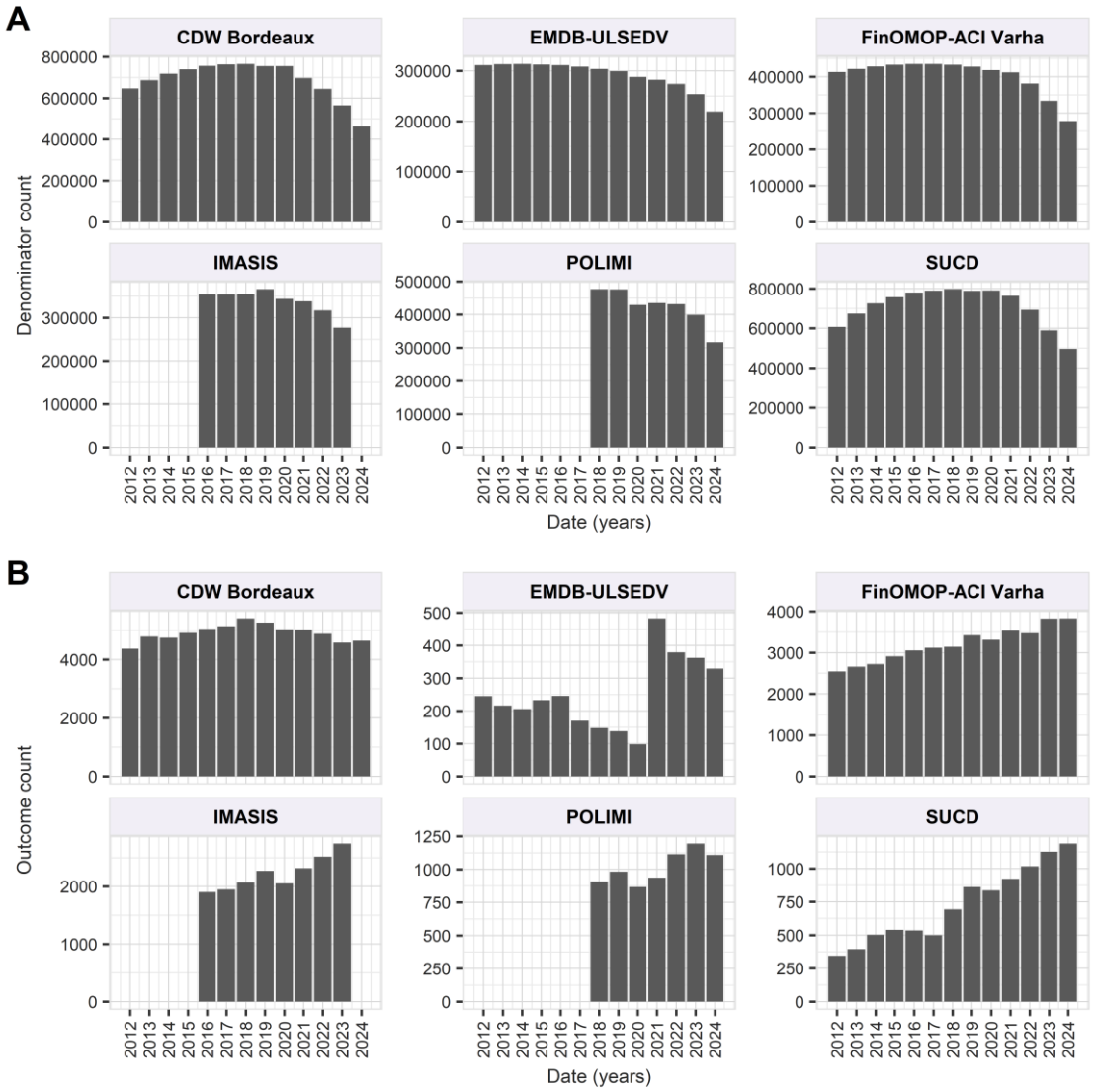

Figure 13. Number of (A) denominator counts and (B) cancer opioid record counts in hospital data sources.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

The prevalence of cancer opioid use shared a similar trend and pattern with incidence in most data sources (**Figure 14**). Among the primary care and nationwide data sources, NLHR and NAJS had the highest prevalence of cancer opioid use, while that remained low in SIDIAP and IQVIA Belgium throughout the study period (**Figure 14A**). Unlike in incidence, FinOMOP-ACI Varha had the highest prevalence of cancer opioid use in hospital data sources (except SUCD, POLIMI, and EMDB-ULSEDV) (**Figure 14B**). This might be suggestive of sustained cancer opioid use in FinOMOP-ACI Varha.

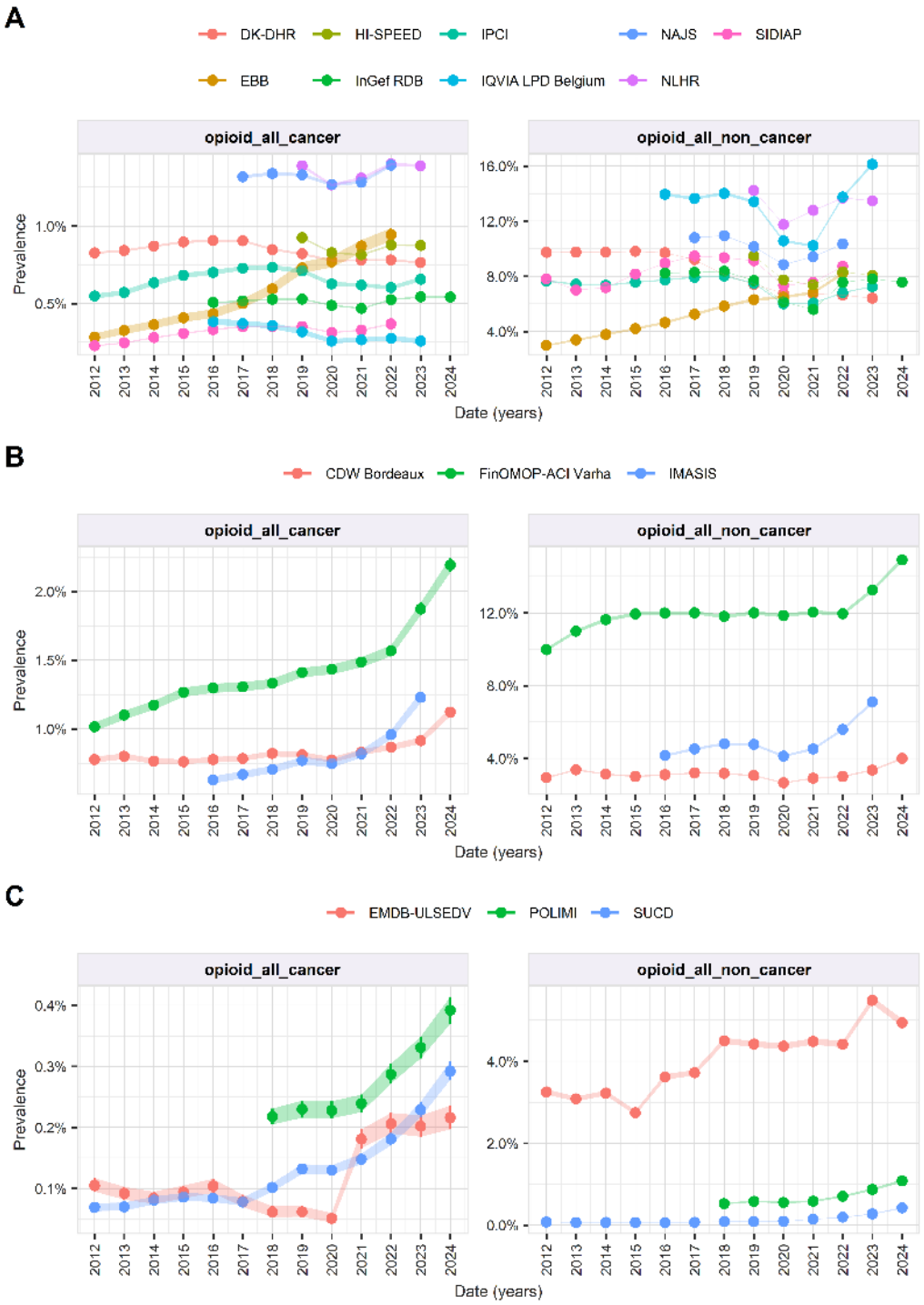

Figure 14. Prevalence of opioid use, stratified by history of cancer, in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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Opioid Use by Potency

Differences in incidence rate estimates and pattern were observed when stratified by opioid potency. Despite this, opioid use remained dominated by non-cancer opioid use regardless of potency (**Figure 15**).

Incidence of weak opioid use shared similar pattern as incidence of overall opioid prescriptions. The dipping of trend during 2020–2021 was consistent in most primary care and nationwide data sources (**Figure 15A**). 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. Incidence of weak opioid use in DK-DHR was dropping from 4,579 in 2012 to 2,007 in 2023 and becoming the third lowest among all data sources towards end of the study period. InGef RDB and HI-SPEED had the lowest incidence of weak opioid use among the primary care and nationwide data sources. In terms of the trend of incidence of weak opioid use along the study period, an ongoing increasing trend was observed in EBB, while an ongoing decreasing trend was observed in DK-DHR and HI-SPEED. In general, increasing trend of incidence of weak opioids was observed in EBB, while decreasing trend was observed in DK-DHR, IPCI, NAJS, InGef RDB, and HI-SPEED. The incidence of weak opioid use increased by 2- to 3-fold in EBB, while that in DK-DHR and HI-SPEED dropped by half.

Among the hospital data sources (excluding SUCD, POLIMI, and EMDB-ULSEDV), FinOMOP-ACI Varha had the highest incidence of weak opioid use (**Figure 15B**). When considering the trend of weak opioid use among all hospital data sources (**Figure 15B**, **Figure 15C**), increasing trend of incidence was observed in SUCD, POLIMI, and EMDB-ULSEDV, while decreasing trend was observed in FinOMOP-ACI Varha, with the support by the number of weak opioid record counts over the study period (**Figure 16**).

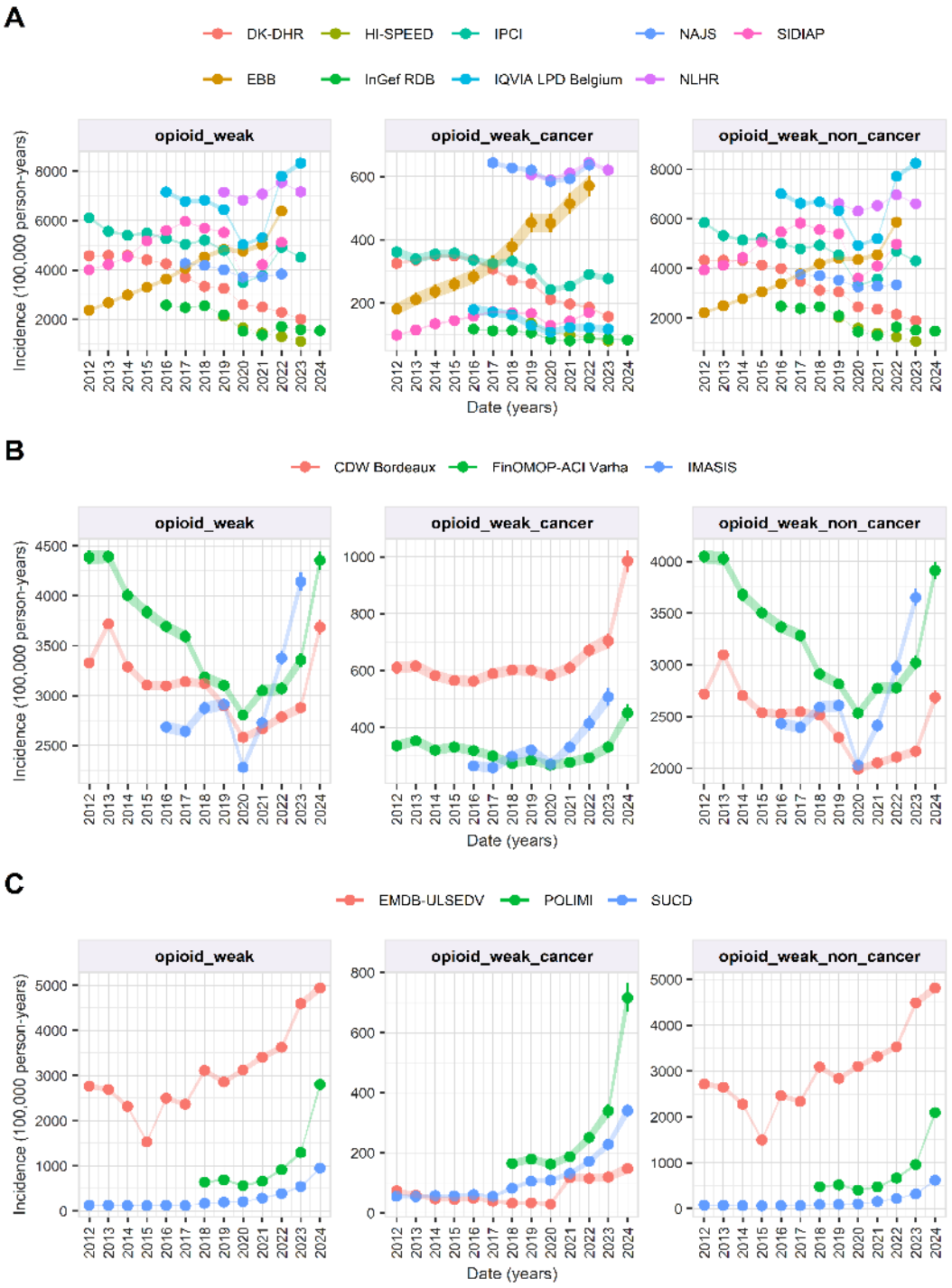

Figure 15. Incidence of weak opioid use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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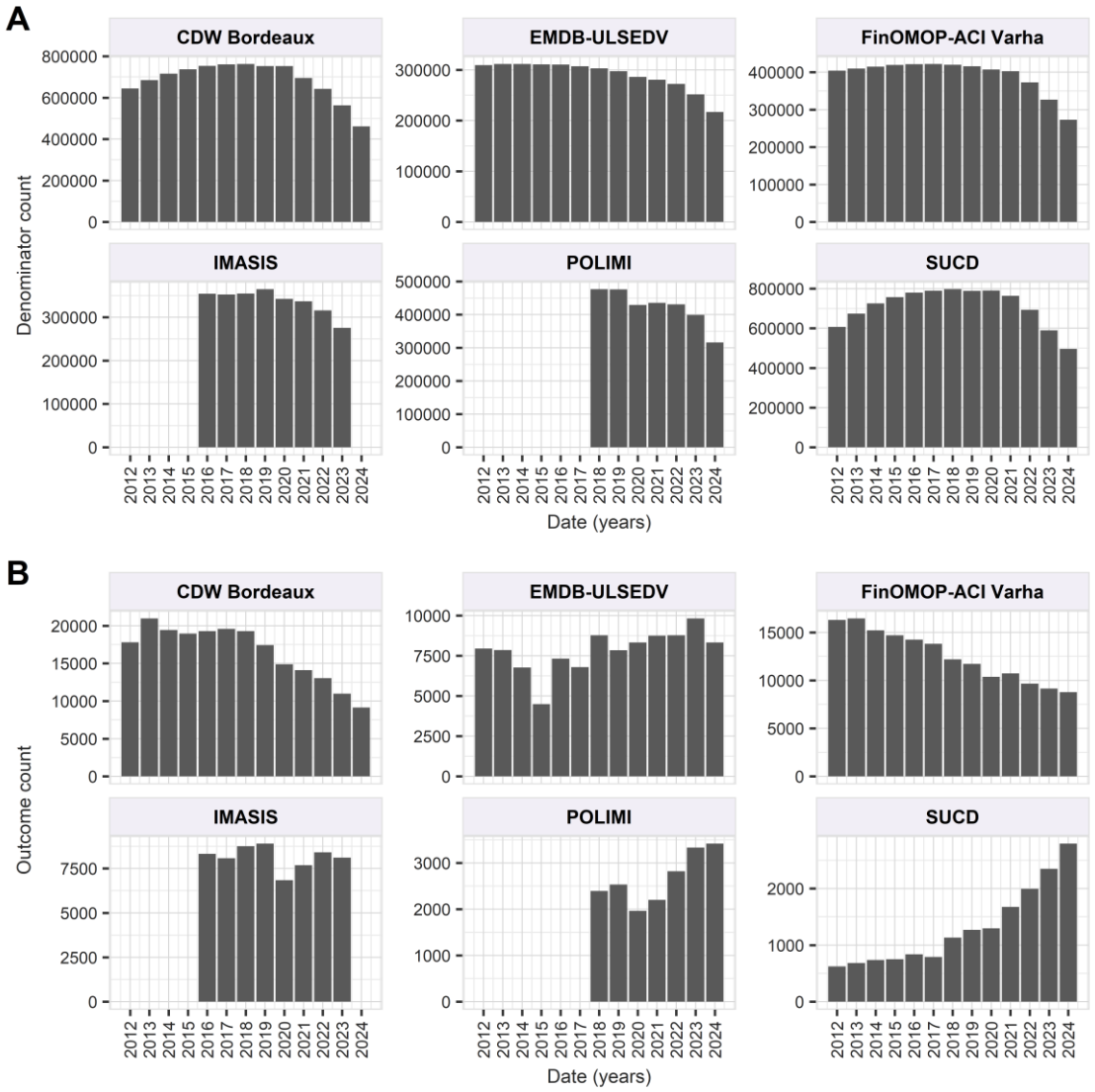

Figure 16. Number of (A) denominator counts and (B) weak opioid record counts in hospital data sources.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

Contrary to incidence of overall opioid use or weak opioid use, the dipping trend in incidence of potent opioids during 2020–2021 was only observed in HI-SPEED, but not other primary care or nationwide data sources (**Figure 17A**). Among the primary care or nationwide data sources, HI-SPEED had the highest incidence of potent opioid use, ranging from 2,911 to 3,297 over the study period. EBB (42 in 2012 to 637 in 2022) and NAJS (269 in 2017 to 215 in 2022) were among the lowest in terms of incidence of potent opioid use. Increasing trend of potent opioid use was observed in most primary care or nationwide data sources, except in HI-SPEED, InGef RDB, and NAJS, of which incidence of potent opioid use remained stable over years. The trend was similar in both cancer potent opioid use and non-cancer potent opioid use.

Among all the hospital data sources, excluding SUCD, POLIMI, and EMDB-ULSEDV (**Figure 17B**), highest incidence of potent opioid use was observed in FinOMOP-ACI Varha. Considering the incidence of potent opioid use among all hospital data sources (**Figure 17B**, **Figure 17C**), the dipping pattern of potent opioid use during 2020–2021 was observed in CDW Bordeaux, IMASIS and EMDB-ULSEDV. When we further considered both the incidence of potent opioid use and number of potent opioid record counts (**Figure 18**), increasing use of potent opioid was observed in all hospital data sources.

When comparing incidence within the same data source, IMASIS, FinOMOP-ACI Varha, and HI-SPEED 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 started 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 data sources. Apart from CDW Bordeaux and DK-DHR, IPCI and FinOMOP-ACI Varha also showed an increasing trend in potent opioid use and decreasing trend in weak opioid use.

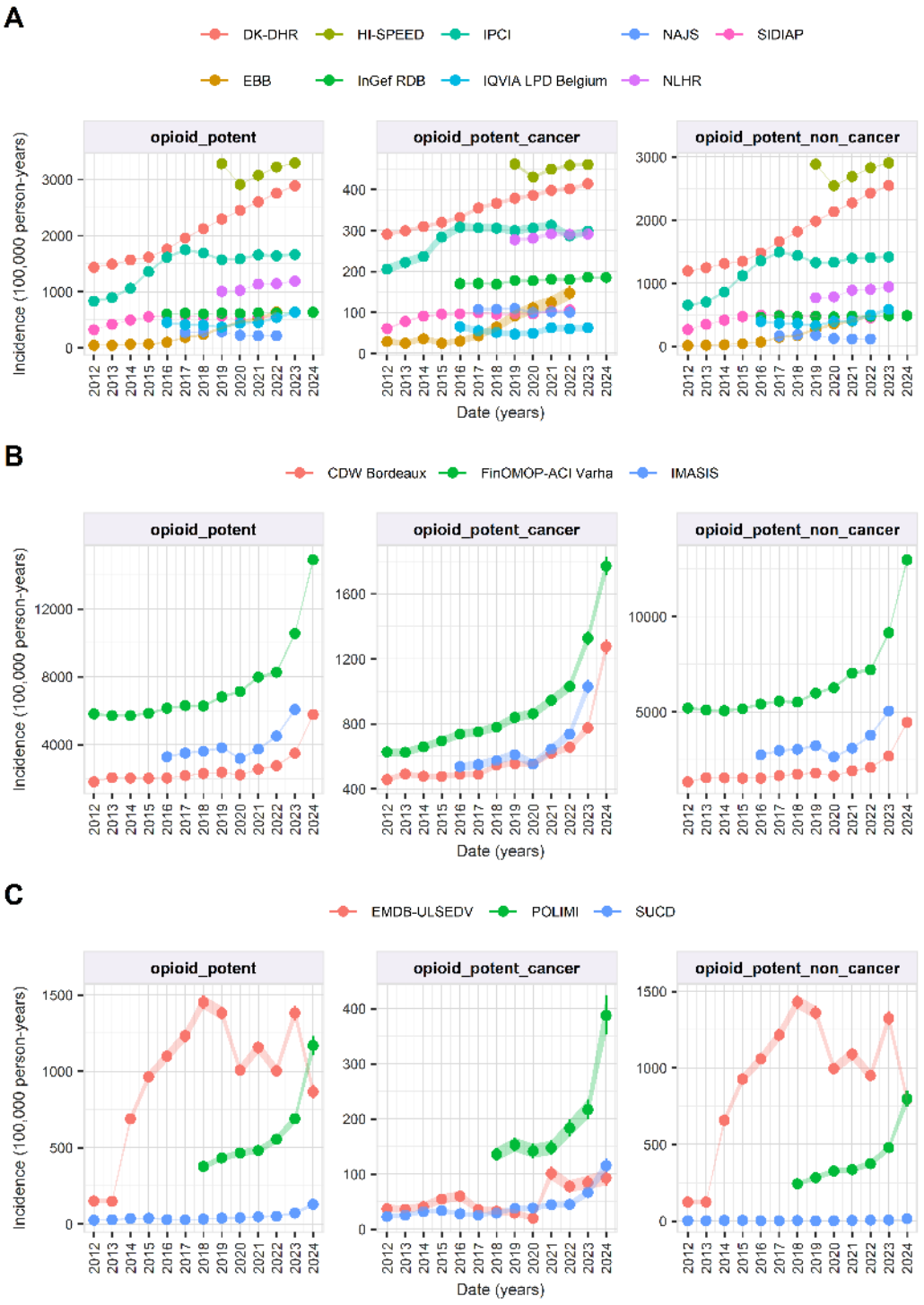

Figure 17. Incidence of potent opioid use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

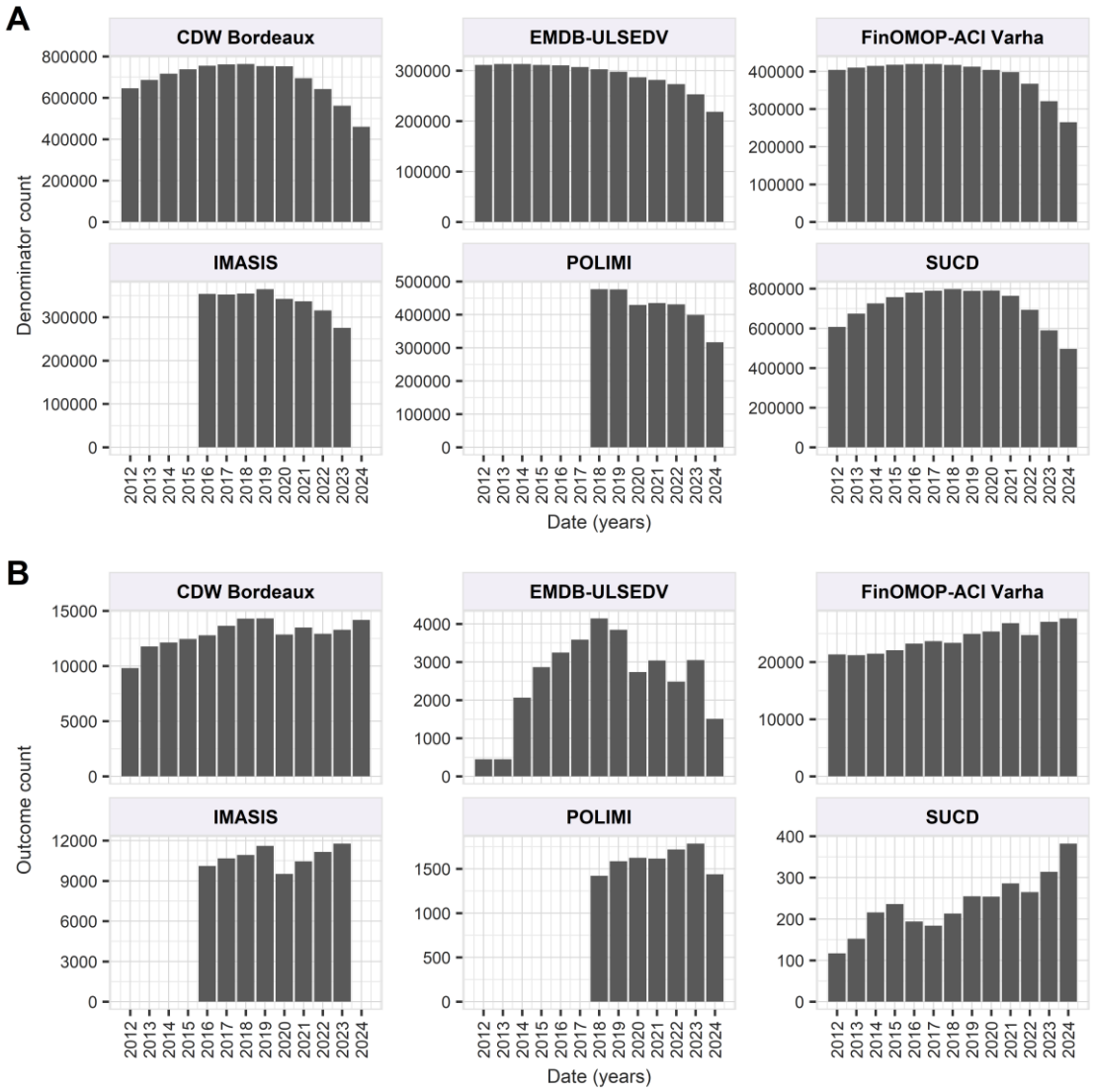

Figure 18. Number of (A) denominator counts and (B) potent opioid record counts in hospital data sources.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

Prevalence of opioid prescriptions when stratified by potency shared similar trend and pattern as in incidence (**Figure 19, Figure 20**).

Prevalence of weak opioid use was highest in NLHR (9.9% in 2019 to 10.2% in 2022) among the primary care and nationwide data sources (**Figure 19A**). Lowest prevalence of weak opioid use was observed in InGef RDB (3.2% in 2016 to 2.0% in 2024) and HI-SPEED (3.5% in 2019 to 2.0% in 2023). Among the hospital data sources (excluding SUCD, POLIMI, and EMDB-ULSEDV), the highest prevalence of weak opioid use was observed in FinOMOP-ACI Varha, while it was similarly low in IMASIS and CDW Bordeaux (**Figure 19B**).

Prevalence of potent opioid use was the highest in HI-SPEED (ranging from 4.3% to 4.7%) among the primary care and nationwide data sources and the lowest in EBB (0.06% in 2012 to 0.9% in 2022) and NAJS (0.4% in 2016 to 0.3% in 2024) (**Figure 20A**). Prevalence of potent opioid use, among the hospital data sources, excluding SUCD, POLIMI, and EMDB-ULSEDV, was the highest in FinOMOP-ACI Varha and the lowest in CDW Bordeaux (**Figure 20B**).

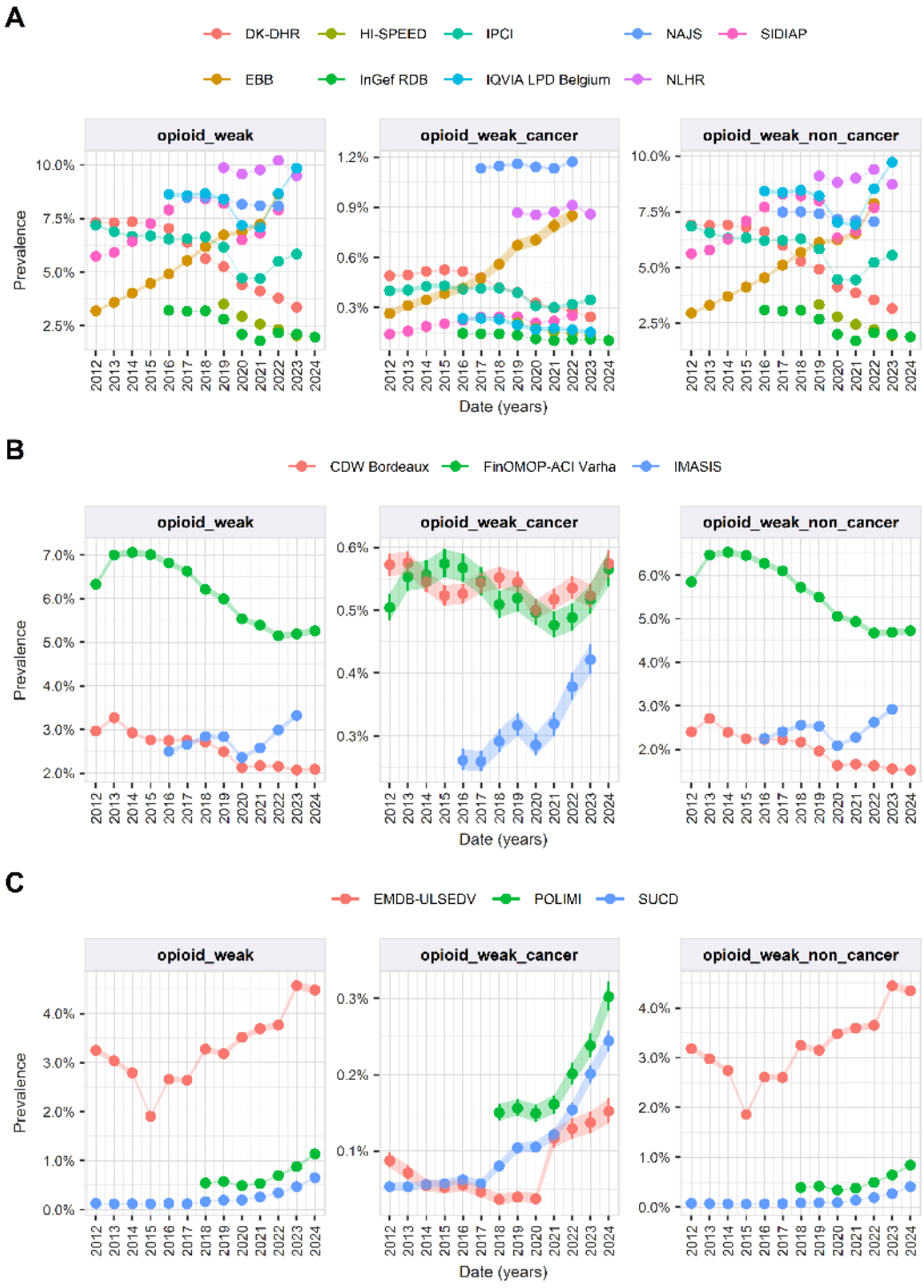

Figure 19. Prevalence of weak opioid use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

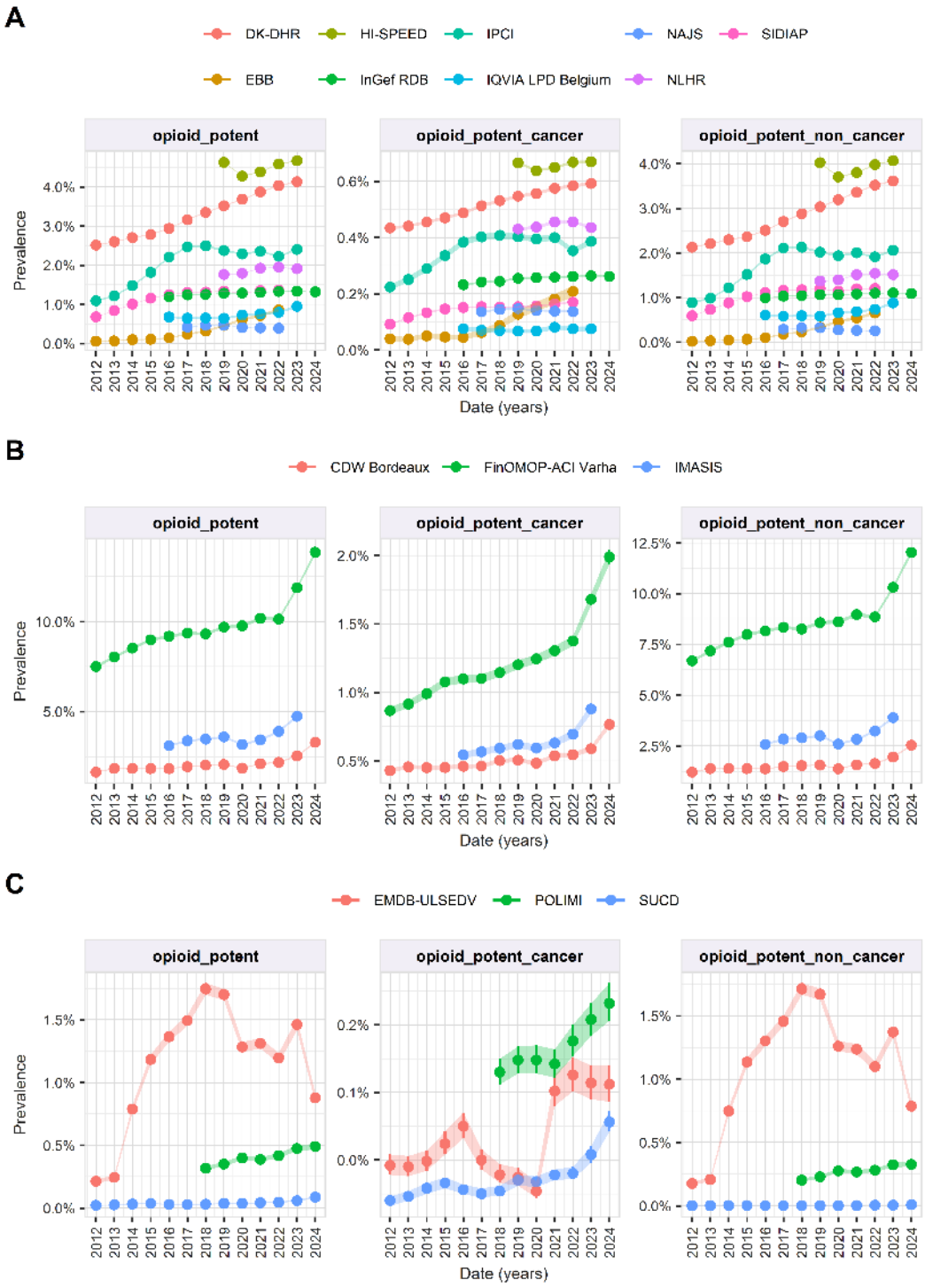

Figure 20. Prevalence of potent opioid use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage .

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

Opioid Use 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 21**). When comparing incidence between different routes within the same data source, the incidence of oral opioids was consistently higher than that of injectable opioid and transdermal opioid use in all data sources, except for IMASIS and POLIMI, which are both hospital data sources.

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 and NAJS for injectable opioids and in IMASIS and SIDIAP for transdermal opioids.

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) in primary care and nationwide data sources, while that of oral opioids was lowest in HI-SPEED (ranging from 1,879 to 2,025) (**Figure 21A**). Incidence of oral opioid use was similarly high in FinOMOP-ACI Varha and CDW Bordeaux considering hospital data sources, excluding SUCD, POLIMI and EMDB-ULSEDV (**Figure 21B**).

When considering the use of injectable opioids, the incidence was much higher in IMASIS and CDW Bordeaux compared to the other data sources. However, an increasing trend in incidence of injectable opioids was observed in all data sources, except in EBB, NAJS, NLHR, and HI-SPEED.

Incidence of transdermal opioids was the highest in IPCI, ranging from 376 to 462 during the study period, which was overtaken by IMASIS in 2023 with an incidence of 428, a possible reason being due to inflated incidence with reduced denominator. 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 data sources. Incidence of transdermal opioids was increasing over years in CDW Bordeaux, EBB, and IMASIS, while it was decreasing in DK-DHR, NLHR, and HI-SPEED.

Prevalence of oral opioid prescriptions was highest in NLHR (14.5-15.2% excluding 2020-2021) and IQVIA LPD Belgium (ranging from 13.3–16.0% excluding 2020–2021), with it being lowest in IMASIS (0.5–2.4%) and CDW Bordeaux (2.4–3.3%), without considering SUCD, POLIMI, and EMDB-ULSEDV (**Figure 22**). Prevalence of injectable opioids was the highest in IMASIS, ranging from 3.0% to 7.1%, and the lowest in SIDIAP, EBB, HI-SPEED, and FinOMOP-ACI Varha (<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 data sources. EBB and CDW Bordeaux had the lowest prevalence of transdermal opioids (<0.1%).

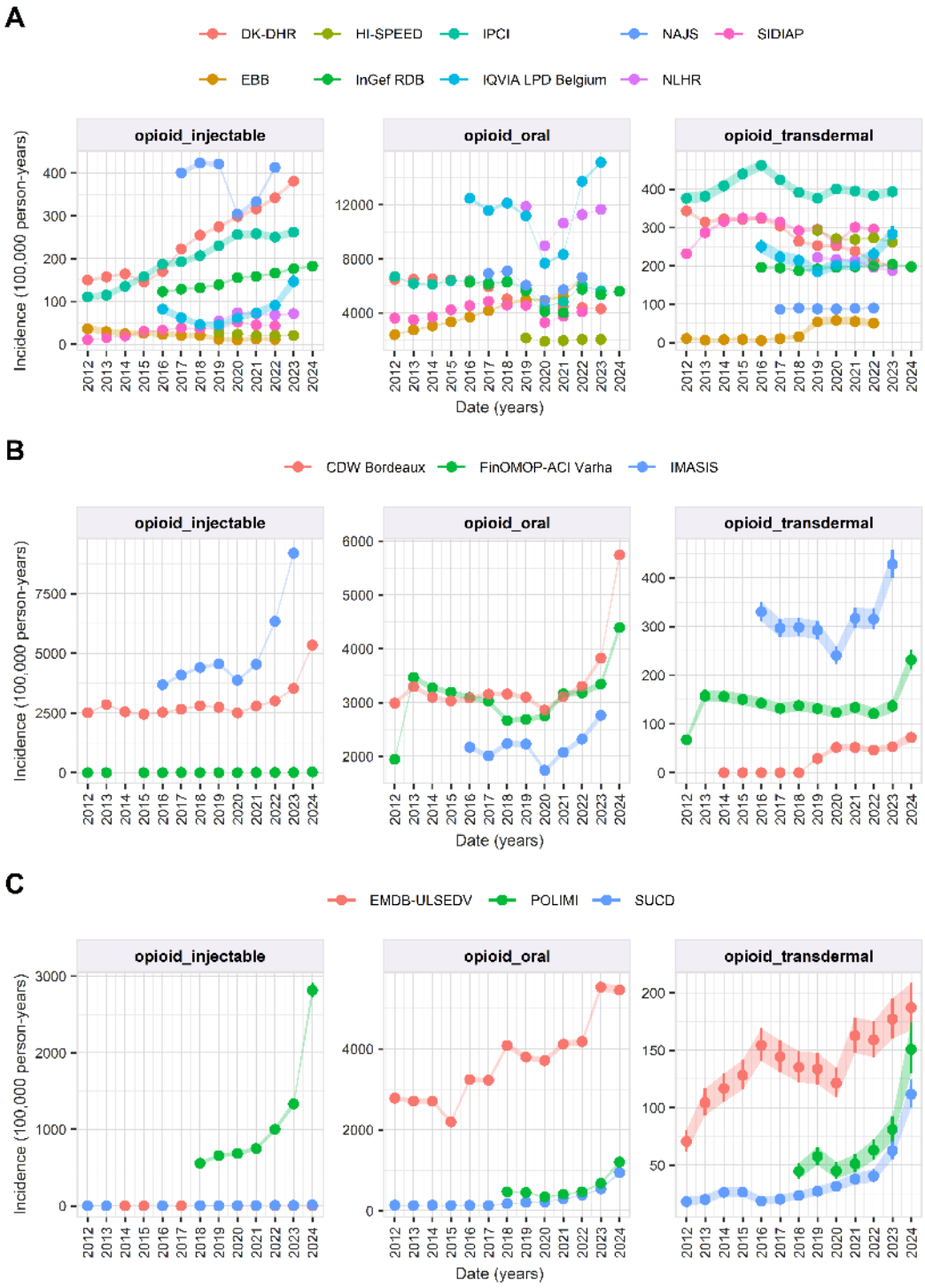

Figure 21. Incidence of opioid use by route of administration in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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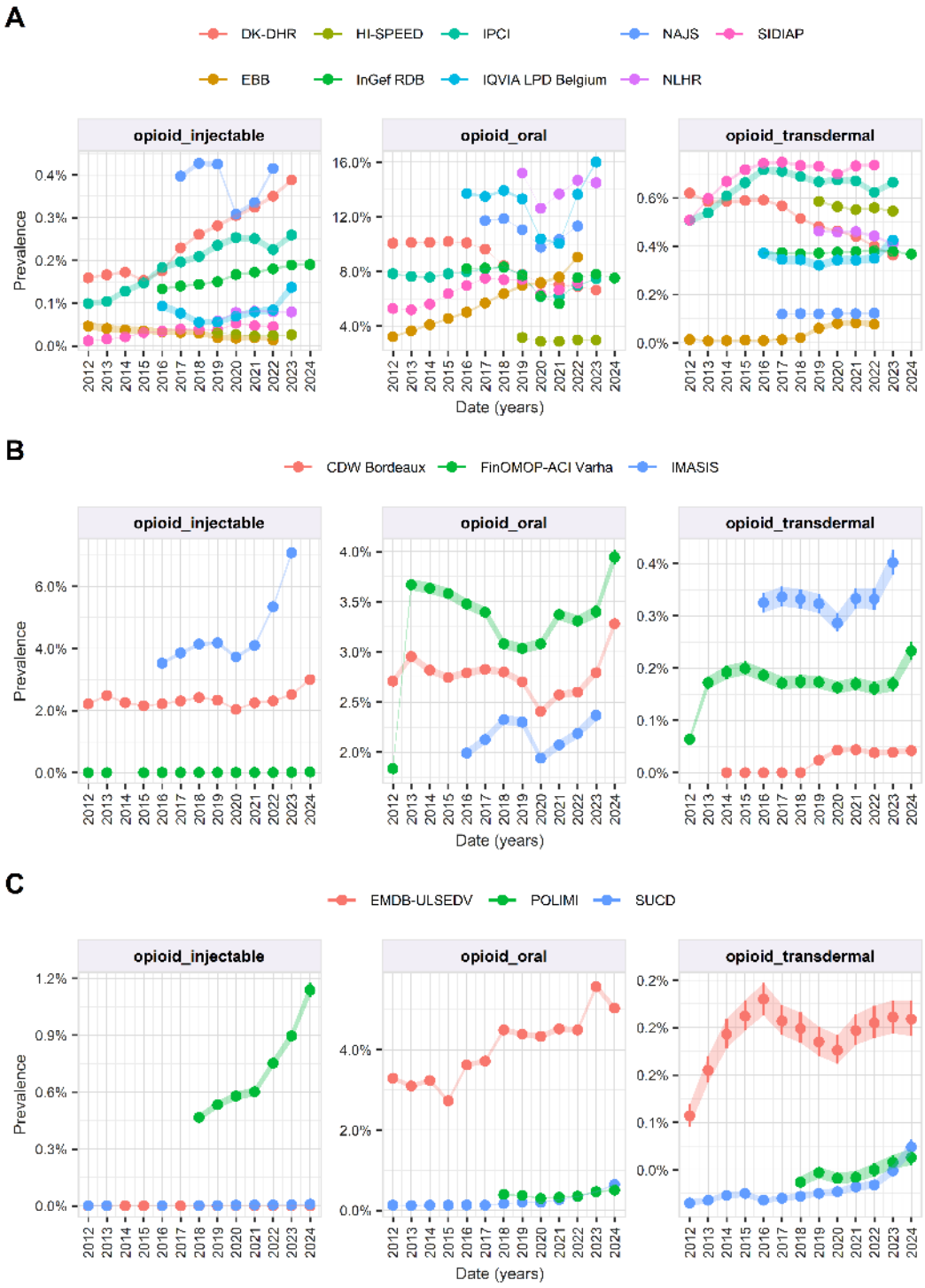

Figure 22. Prevalence of opioid use by route of administration in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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Opioid Use by Ingredient

The top 10 most frequently prescribed opioid ingredients across all data sources were, in descending order, tramadol, codeine, oxycodone, ethylmorphine, morphine, noscapine, tilidine, dihydrocodeine, pholcodine, and fentanyl. Among these, 3 of them (fentanyl, morphine, oxycodone) were potent opioids.

When we individually considered the top 10 most frequently prescribed opioid ingredients in each data source (**Table 13**), codeine, tramadol, oxycodone, and fentanyl had been in top 10 most frequently prescribed opioid list in all the included data sources, while morphine was on the list in 14 out of 15 data sources, buprenorphine in 12 out of 15 data source, and tapentadol in 9 out of 15 data sources. Incidence of tramadol, oxycodone, fentanyl, morphine, buprenorphine, and tapentadol use were reported separately in primary care or nationwide data sources (**Figure 23A**) and hospital data sources (**Figure 23B, Figure 23C**).

Tramadol was the most commonly prescribed opioid in 4 out of 9 primary care or nationwide data sources, and in 4 out of 6 hospital data sources. Among the primary care or nationwide data sources, NAJS had the highest incidence of tramadol use among all data sources despite a decreasing trend over years, decreasing from 4,256 in 2017 to 3,831 in 2022. Increasing trend of tramadol use was observed in SIDIAP (before 2017) and EBB, while that remained steady over years in IPCI and NLHR. A decreasing trend was observed in NAJS, InGef RDB, HI-SPEED, and substantially in DK-DHR (dropping from 3,408 in 2012 to 929 in 2023). Among the hospital data sources, without considering the increased incidence of tramadol use in the last two years of study period within each data source, use of tramadol was generally steady in CDW Bordeaux, IMASIS, and FinOMOP-ACI Varha, while a slow increasing trend was observed in POLIMI and SUCD over the steady period. The trend of tramadol use was fluctuating in EMDB-ULSEDV.

An increasing incidence in **oxycodone** prescriptions was observed in all hospital data sources and in IQVIA LPD Belgium, DK-DHR, EBB, IPCI, and NLHR. Among the primary care or nationwide data sources, HI-SPEED had the highest incidence of oxycodone use, with incidence ranging from 2,623 to 2,971. Among the hospital data sources, FinOMOP-ACI Varha had the highest incidence of oxycodone use, with rate increasing from 5,509 in 2012 to 7,955 in 2022. The sharp increase of incidence from 2022 to 2024 in FinOMOP-ACI Varha might be a result of incidence inflation due to the drop in denominator, however the number of oxycodone record count was also increasing during the time, which might suggest an actual increasing use of oxycodone in the hospital during 2022–2024. While most data sources 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 IPCI among the primary care or nationwide data sources (incidence ranging from 282 to 376) and in IMASIS among the hospital data sources (incidence increasing from 2,600 in 2016 to 2,919 in 2021). Among the primary care or nationwide data sources, incidence of fentanyl use was increasing in IPCI and SIDIAP before the year of 2016 and remained steady afterwards, while incidence was steadily decreasing in NAJS, DK-DHR, NLHR, and HI-SPEED. Steadily increasing trend of fentanyl use was observed along the whole study period in EBB and all hospital data sources.

Incidence of **morphine** prescriptions were increasing in all data sources except in HI-SPEED and NAJS. Among the primary care or nationwide data sources, the incidence of morphine use was the highest in DK-DHR, increasing from 1,013 to 2,296 over the study period, while that was lowest in EBB (ranging from 19 to 51) and NAJS (ranging from 30 to 36). Among the hospital data sources, incidence rate of morphine use was the highest in CDW Bordeaux (ranging from 1,701/100,000 person-years in 2012 to 2,122/100,000 person-years in 2022), followed by IMASIS (ranging from 1,281 in 2012 to 1,628 in 2022).

Most primary care or nationwide data sources showed a decreasing trend in **buprenorphine** new prescriptions over the years, except for EBB (increasing from 4 in 2018 to 36 in 2020 and dropping to 12 in 2022). Among these data sources, HI-SPEED had the highest incidence of buprenorphine use, with the incidence ranging from 211 to 224. Incidence of buprenorphine use dropped from 224 (2012) to 110 (2023)

in DK-DHR and from 174 (2019) to 148 (2023) in NLHR, while incidence of that remained steady in HI-SPEED. Among the hospital data sources, the use of buprenorphine was the highest in FinOMOP-ACI Varha, with incidence increasing from 286 in 2012 to 328 in 2022.

A substantial increase in **tapentadol** incidence was observed in SIDIAP and IMASIS in the 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). Among the primary care or nationwide data sources, NLHR had an incidence of tapentadol use increasing from 82 in 2019 to 134 in 2023. Use of tapentadol remained at a steady level in InGef RDB, ranging from 72 to 93 over the study period. NAJS showed an increasing trend of use from 77 in 2017 to 95 in 2019, while decreasing from 2019 onwards, reaching 53 in 2022. Other data sources had a rather steady level of incidence of tapentadol. Incidence of tapentadol ranged from 12 in DK-DHR to 23 in IPCI in 2023. Among the hospital data sources, EMDB-ULSEDV, despite having only partial drug records from the institution, had the highest incidence of tapentadol use, ranging from 609 to 1,263 over the study period.

Prevalence of individual opioid ingredient use followed closely with the incidence (**Figure 24**).

Table 13. Top ten most frequently prescribed opioid ingredients in descending order within each individual data source.

Primary Care or Nationwide Data Source				
IQVIA LPD Belgium	**NAJS**	**DK-DHR**	**EBB**	**InGef RDB**
tramadol	tramadol	tramadol	codeine	tilidine
codeine	pholcodine	**morphine**	tramadol	noscapine
dextromethorphan	**fentanyl**	codeine	**oxycodone**	codeine
dihydrocodeine	**tapentadol**	**oxycodone**	dihydrocodeine	dihydrocodeine
ethylmorphine	**buprenorphine**	opium	**morphine**	tramadol
oxycodone	sufentanil	**fentanyl**	**fentanyl**	**oxycodone**
pholcodine	meperidine	**buprenorphine**	**buprenorphine**	**morphine**
fentanyl	**morphine**	dextromethorphan	**methadone**	**fentanyl**
tilidine	**oxycodone**	ketobemidone	meperidine	**hydromorphone**
noscapine	codeine	**methadone**		**tapentadol**
IPCI	**NLHR**	**SIDIAP**	**HI-SPEED**	
codeine	codeine	tramadol	**oxycodone**	
tramadol	ethylmorphine	codeine	ethylmorphine	
oxycodone	tramadol	dextromethorphan	codeine	
morphine	**oxycodone**	**fentanyl**	**morphine**	
fentanyl	**buprenorphine**	**tapentadol**	**buprenorphine**	
noscapine	**morphine**	**morphine**	tramadol	
buprenorphine	**tapentadol**	dimemorfan phosphate	**fentanyl**	
dextromethorphan	**fentanyl**	**oxycodone**	ketobemidone	
tapentadol	ketobemidone	**buprenorphine**	noscapine	
methadone	noscapine	noscapine	**tapentadol**	

Hospital Data Source					
FinOMOP-ACI Varha	**CDW Bordeaux**	**IMASIS**	**SUCD***	**POLIMI***	**EMDB-ULSEDV***
oxycodone	tramadol	**fentanyl**	tramadol	tramadol	tramadol
codeine	**morphine**	tramadol	**fentanyl**	**morphine**	**tapentadol**
tramadol	**oxycodone**	**morphine**	codeine	codeine	codeine
fentanyl	opium	alfentanil	**oxycodone**	**oxycodone**	**fentanyl**
alfentanil	nalbuphine	sufentanil	dihydrocodeine	**fentanyl**	**buprenorphine**
buprenorphine	codeine	remifentanil	morphine	**tapentadol**	**morphine**
morphine	**buprenorphine**	codeine	**hydromorphone**	**methadone**	**oxycodone**
ethylmorphine	**fentanyl**	**tapentadol**	ethylmorphine	**buprenorphine**	**hydromorphone**
meperidine	**methadone**	**oxycodone**	**buprenorphine**	meperidine	dextromethorphan
hydromorphone	sufentanil	**methadone**	dextromethorphan	sufentanil	

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* SUCD, POLIMI, and EMDB-ULSEDV are hospital data sources with partial coverage.

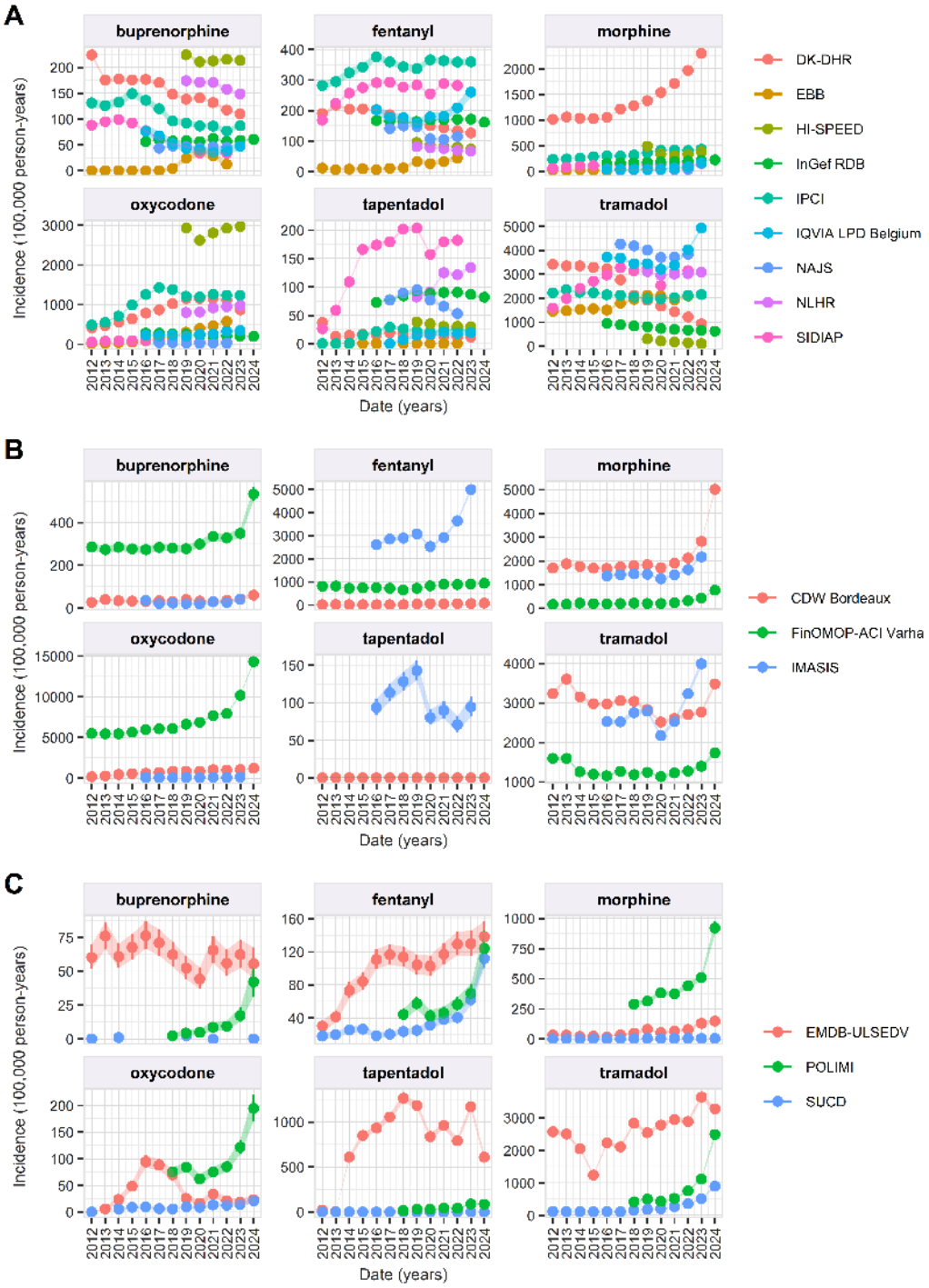

Figure 23. Incidence of buprenorphine, fentanyl, morphine, oxycodone, tapentadol, and tramadol use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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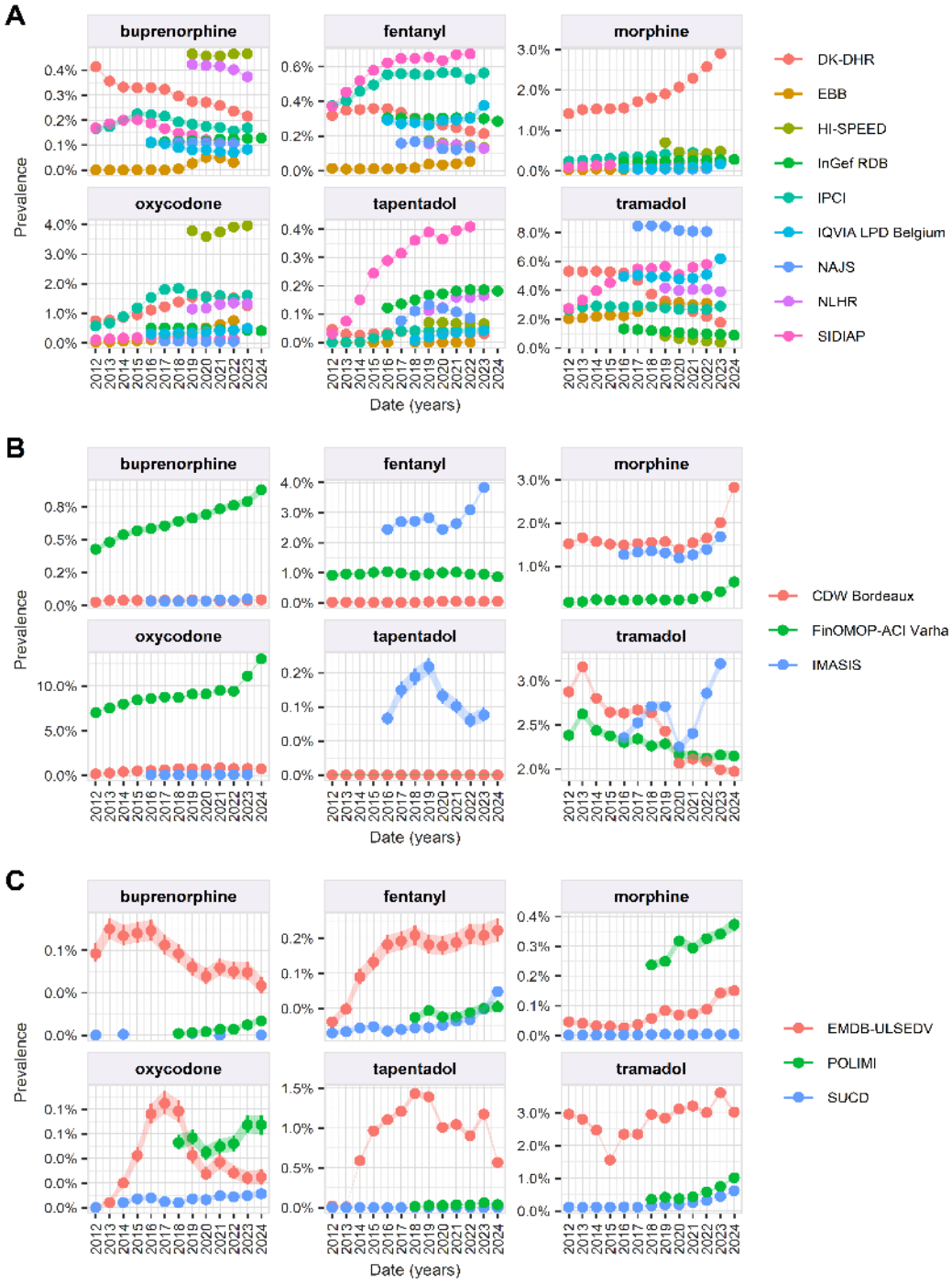

Figure 24. Prevalence of buprenorphine, fentanyl, morphine, oxycodone, tapentadol, and tramadol use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

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Naloxone and Opioid-Naloxone Combination Use

Among the primary care or nationwide data sources (**Figure 25A**), the highest incidence of naloxone use was observed in InGef RDB, with incidence increasing from 1,194 in 2016 to 1,746 in 2024. Apart from InGef RDB, there was also increasing trend in naloxone use in NLHR, EBB, HI-SPEED, and a decreasing trend in SIDIAP, IQVIA LPD Belgium, DK-DHR, and NAJS. The use of naloxone in NLHR, SIDIAP, and HI-SPEED was largely influenced by oxycodone-naloxone combination use, whereas in IQVIA LPD Belgium and InGef RDB, it was mainly dominated by the tilidine-naloxone combination. The combination use of buprenorphine and naloxone has remained steady in recent years.

Among the hospital data sources (**Figure 25B**, **Figure 25C**), the highest incidence of naloxone use was observed in FinOMOP-ACI Varha, with incidence increasing from 468 in 2012 to 2,766 in 2022, while incidence of naloxone use remained below 200 for all other hospital data sources during the study period. Apart from FinOMOP-ACI Varha, incidence of naloxone use was also increasing in IMASIS and POLIMI. In POLIMI and EMDB-ULSEDV, the use of naloxone was highly dominated by oxycodone-naloxone combination.

Prevalence of naloxone use was presented in **Figure 26**. In general, trend and pattern in prevalence of naloxone use followed closely to incidence of naloxone use.

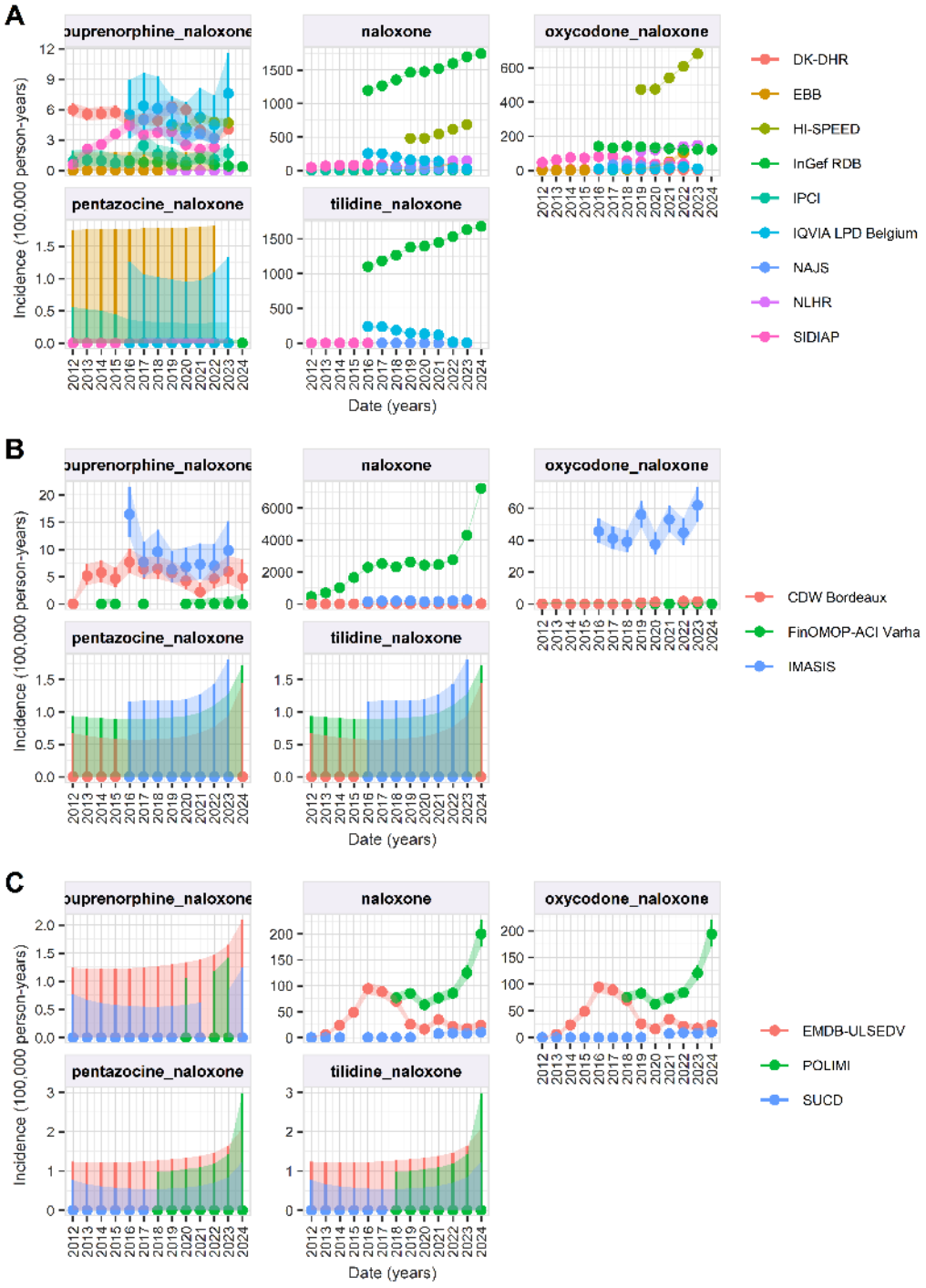

Figure 25. Incidence of naloxone and opioid-naloxone combination use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

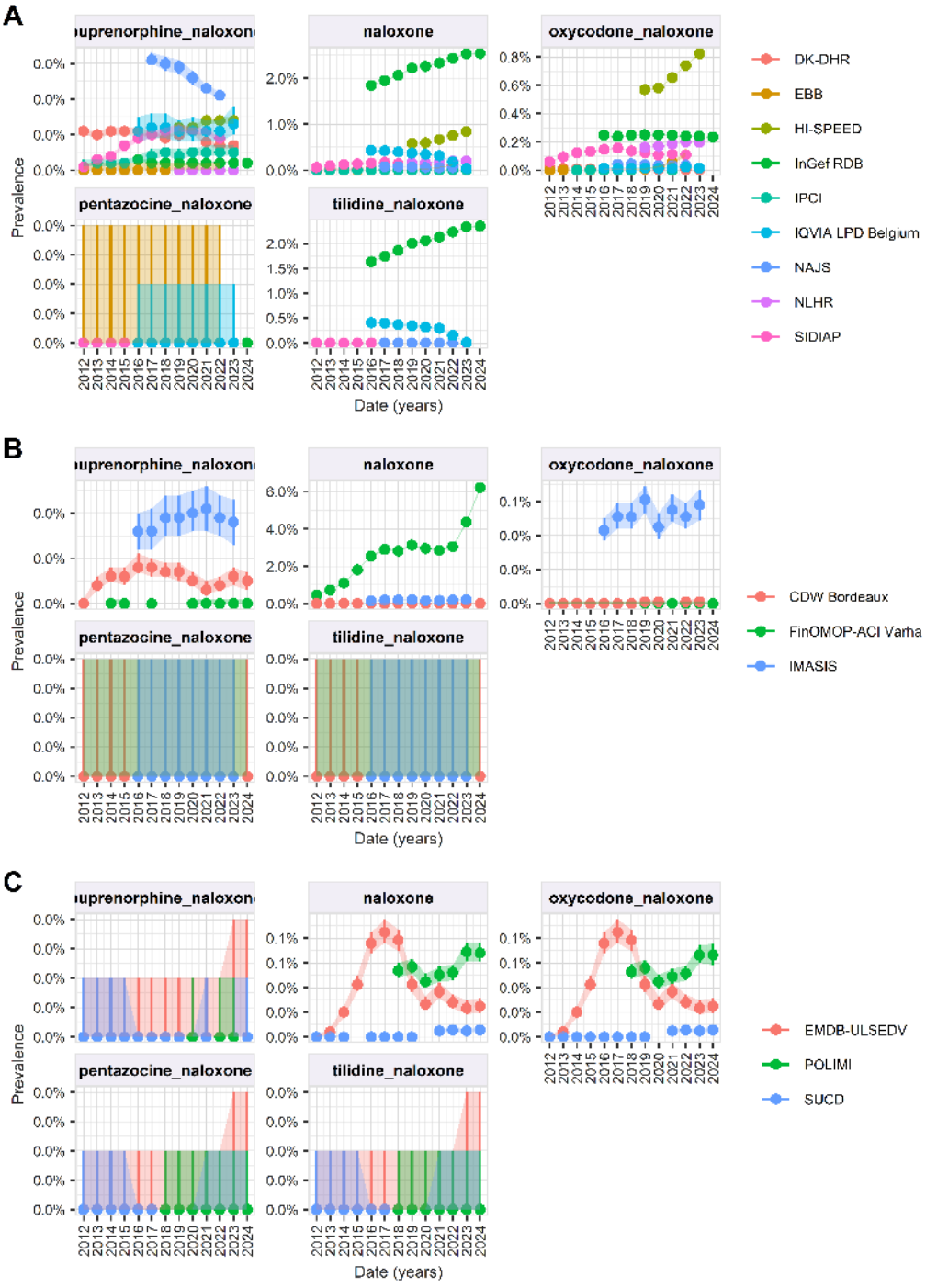

Figure 26. Prevalence of naloxone and opioid-naloxone combination use in (A) primary care or national registries, (B) hospital data sources with complete coverage, and (C) hospital data sources with partial coverage.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IMASIS = Institut Municipal Assistència Sanitària Information, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SIDIAP = The Information System for the Development of Research in Primary Care, SUCD = Semmelweis University Clinical Data.

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 data source. In general, incidence (**Figure 27**, **Figure 28**) and prevalence (**Figure 29**, **Figure 30**) of opioid use increased with age, except in InGef RDB, in which they started with a high incidence of opioid use in the population aged 10 years or below. The use of opioids in age group 0–10 years in InGef RDB was highly driven by noscapine, while use of noscapine was not common in other included data sources. The incidence and prevalence of opioid use dropped in age group 11–20 years in InGef RDB compared to that in age group 0–10 years, while that increased with age, as in other data sources, from the age group 11–20 years.

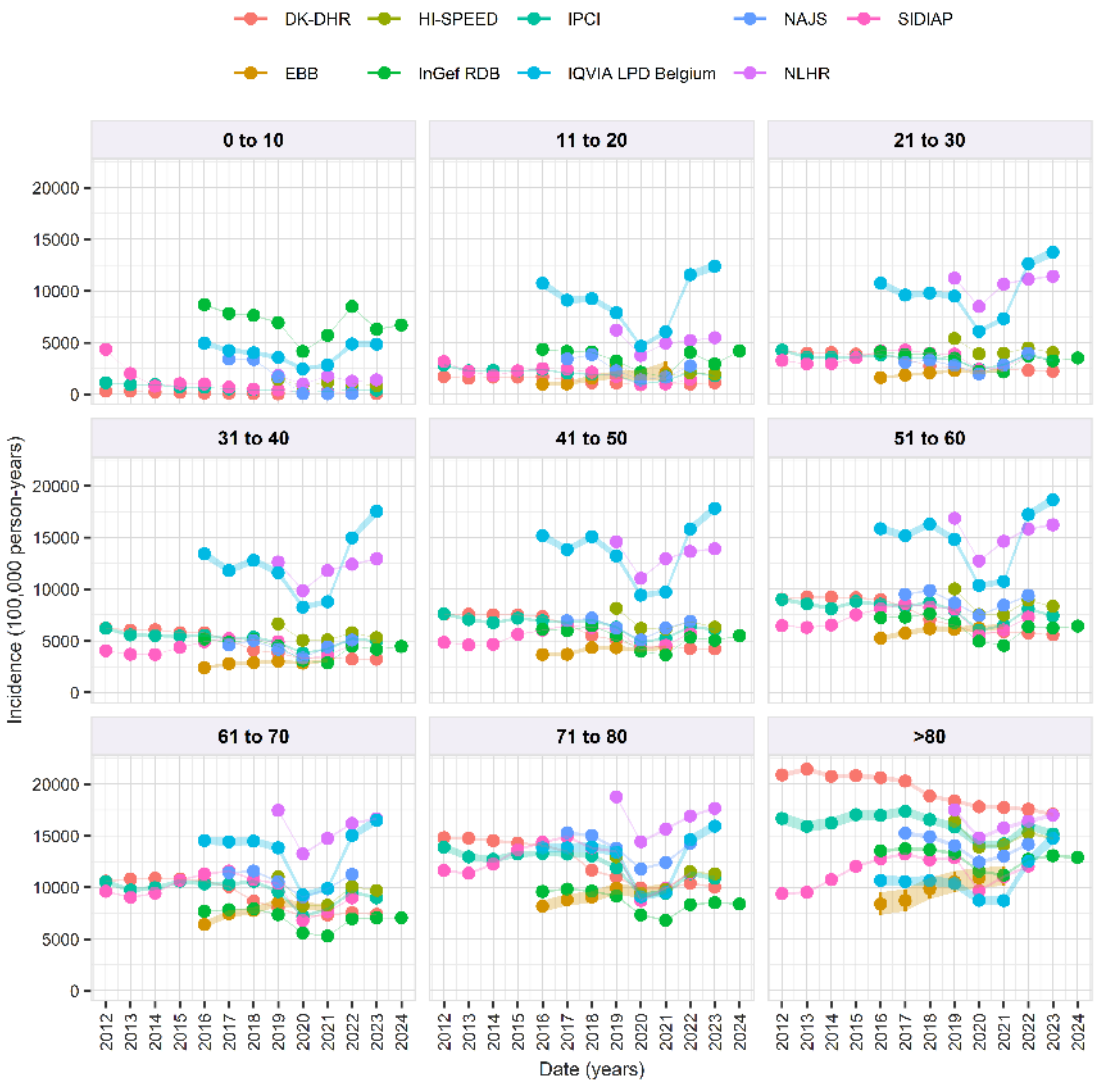

Figure 27. Incidence of overall opioid use in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

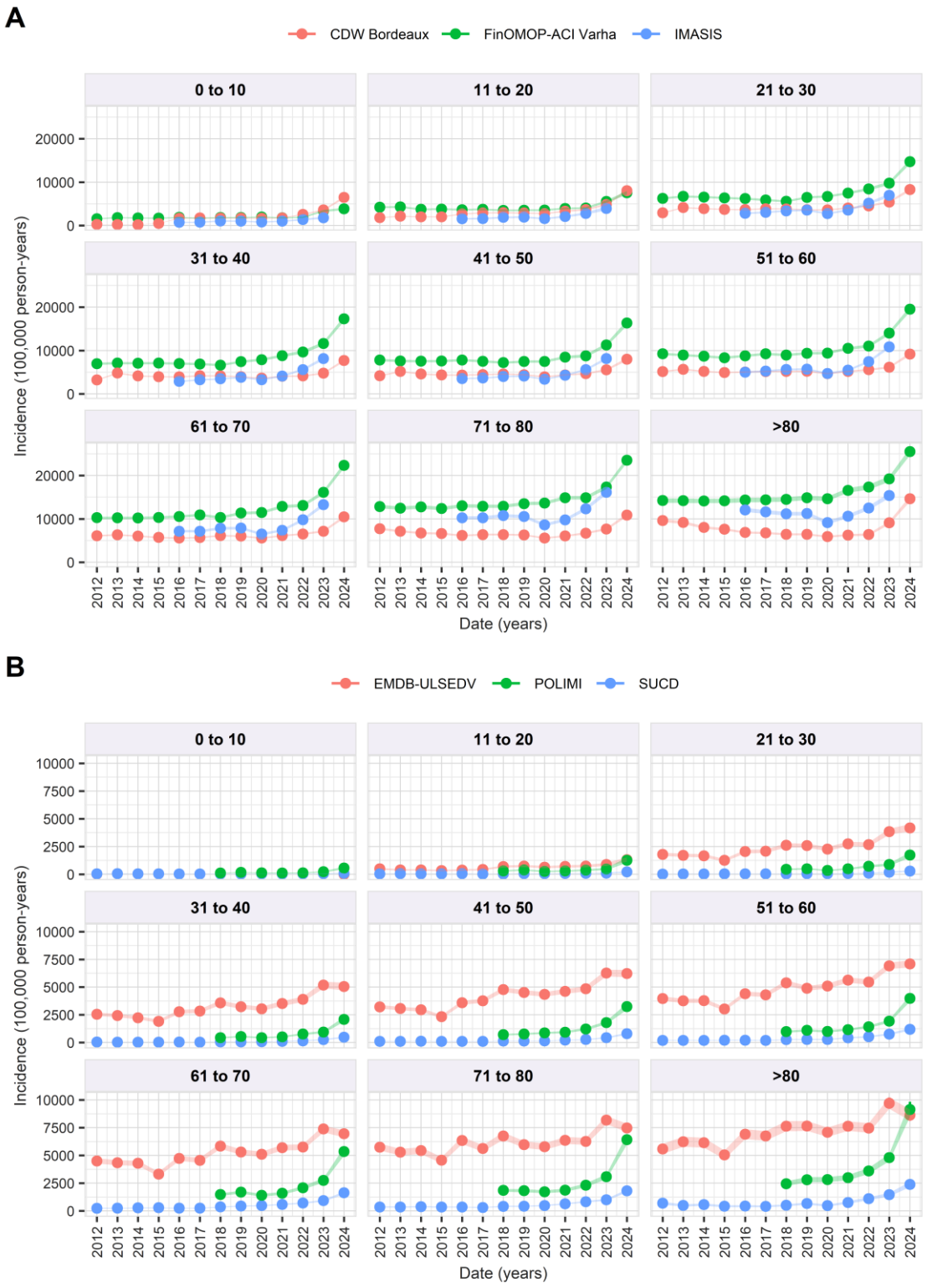

Figure 28. Incidence of overall opioid use in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

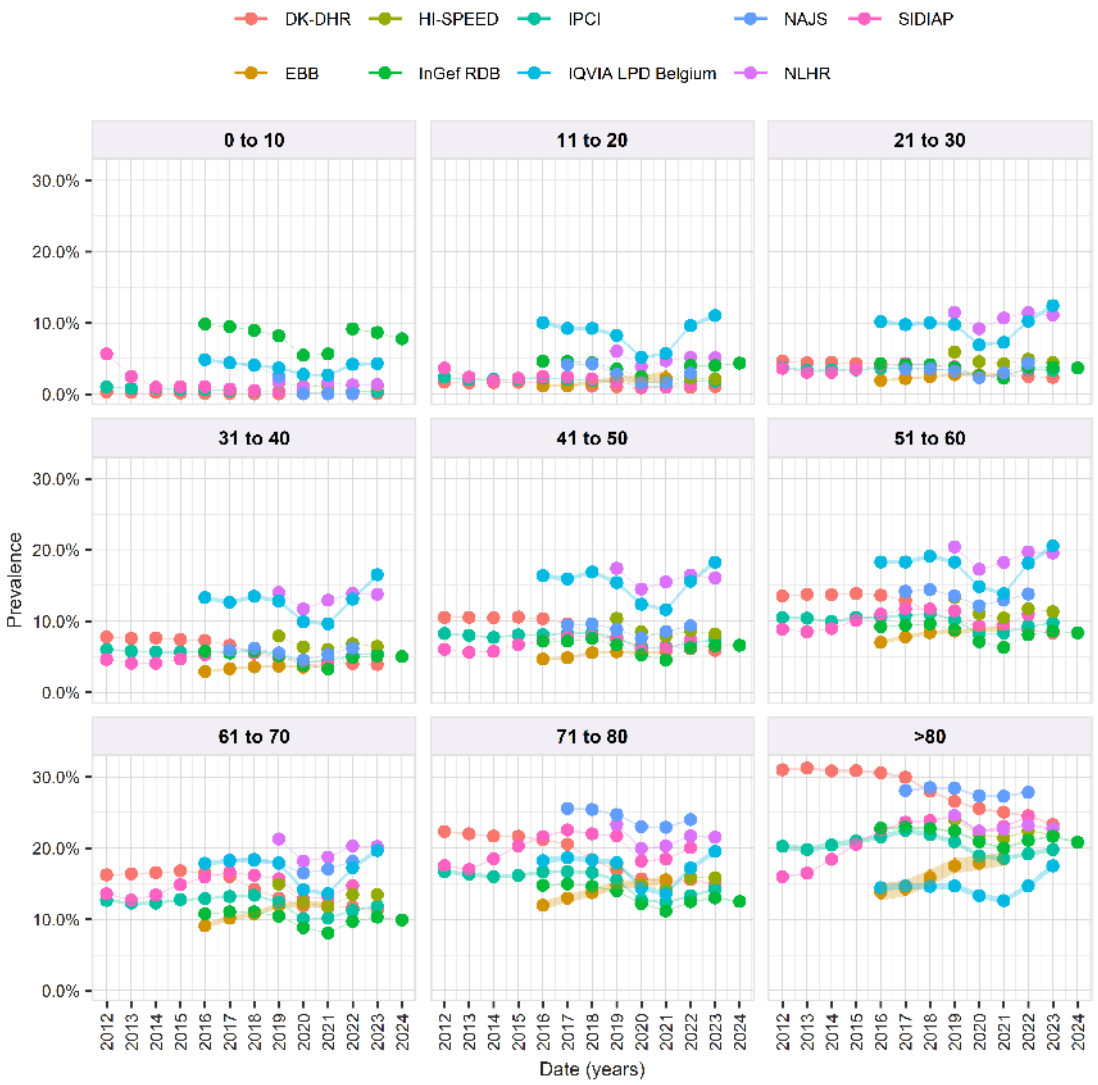

Figure 29. Prevalence of overall opioid use in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

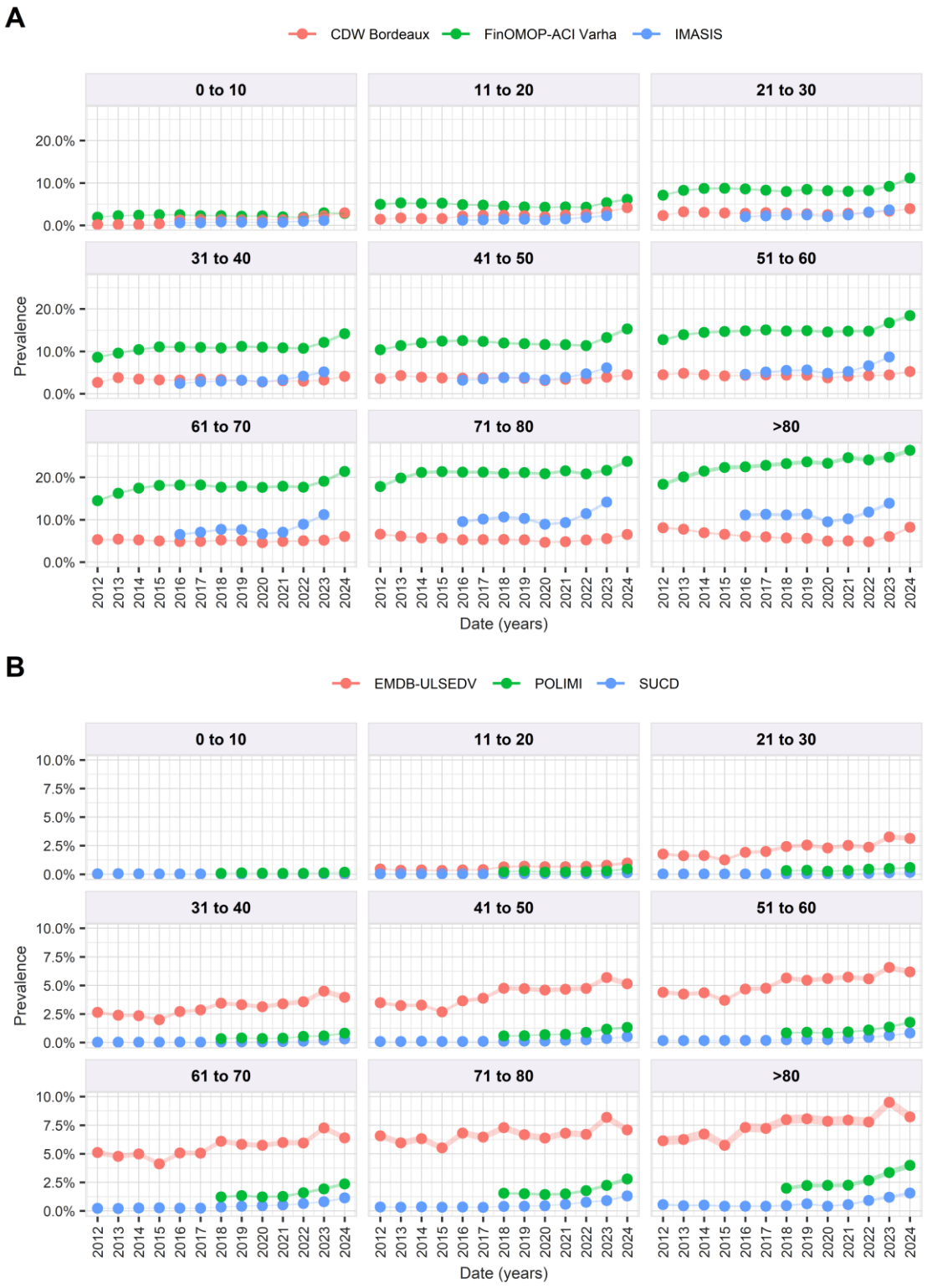

Figure 30. Prevalence of overall opioid use in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

Opioid Use by History of Cancer, Stratified by Age

When considering the opioid prescriptions with history of cancer stratified by age, InGef RDB (**Figure 31**), CDW Bordeaux, and FinOMOP-ACI Varha (**Figure 32**) had the higher incidence among younger and middle-aged groups, while NLHR had the higher incidence among older aged groups. InGef RDB had the highest prevalence among younger aged group, FinOMOP-ACI Varha and NLHR having the highest prevalence among the middle aged group, while NLHR and NAJS had the highest prevalence among older age groups (**Figure 33**, **Figure 34**).

In the age group 0–10 years the highest incidence of cancer opioid use was observed in InGef RDB, ranging from 109 to 262/100,000 person-years over the study period. FinOMOP-ACI Varha had higher incidence in younger adult, ranging from 77–464 in the age group 21–30 years to 163–737 in the age group 31–40 years. CDW Bordeaux had higher incidence of cancer opioid use consistently among younger age groups (ranging from 33–244 in the age group 11–20 years to 168–505 in the age group 31–40 years) and among middle-aged groups (increasing from 523–1,177 in the age group 41–50 years to 1,818–3,865 in the age group 61–70 years). In NLHR, the incidence of opioids with cancer increased from 394–495 in the age group 41–50 years to 3,547–4,104 in individuals aged above 80, while prevalence of opioids with cancer increased from 0.6–0.7% in the age group 41–50 years to 5.5–5.8% in individuals aged above 80.

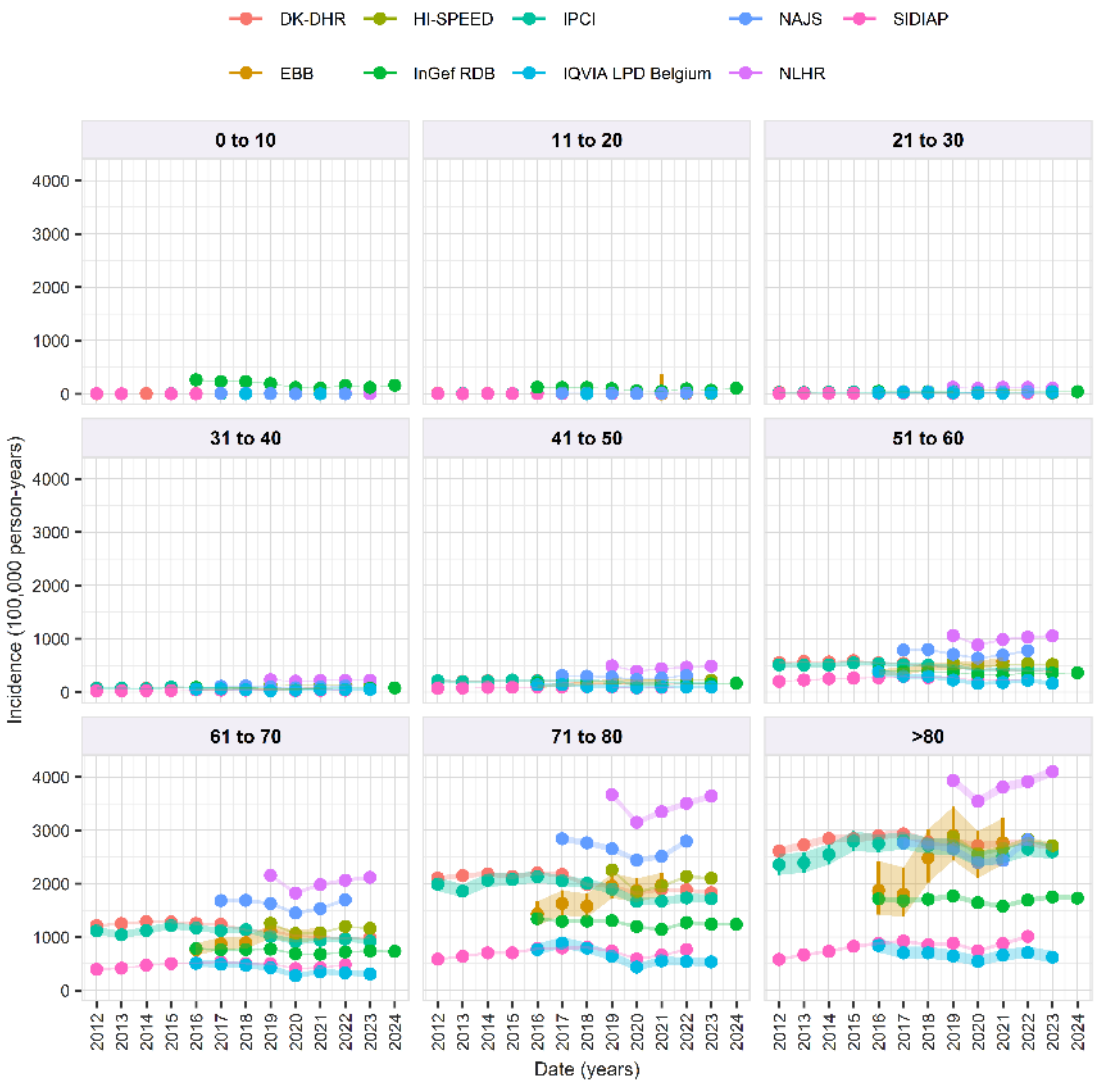

Figure 31. Incidence of opioid use with history of cancer in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

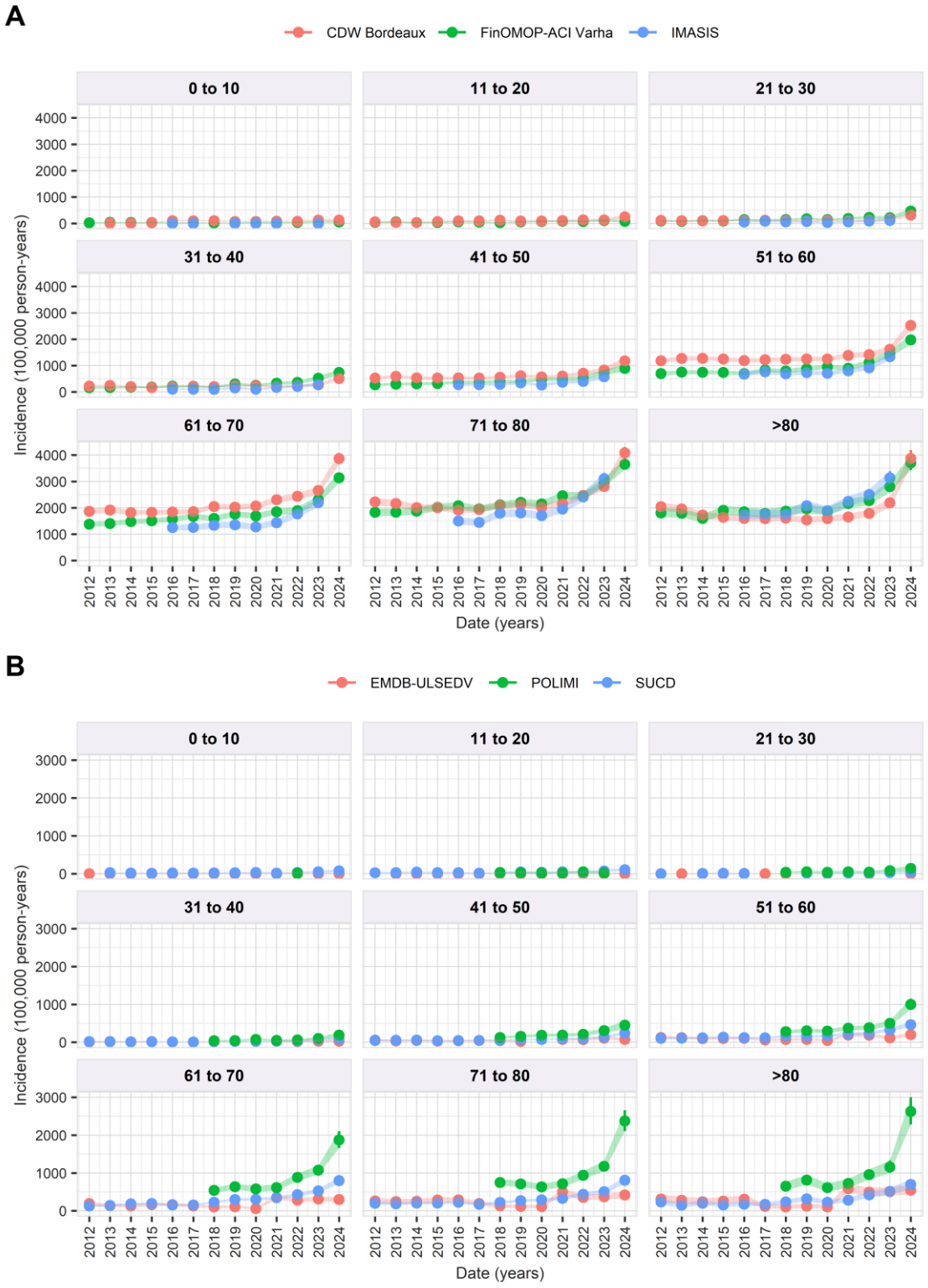

Figure 32. Incidence of opioid use with history of cancer in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

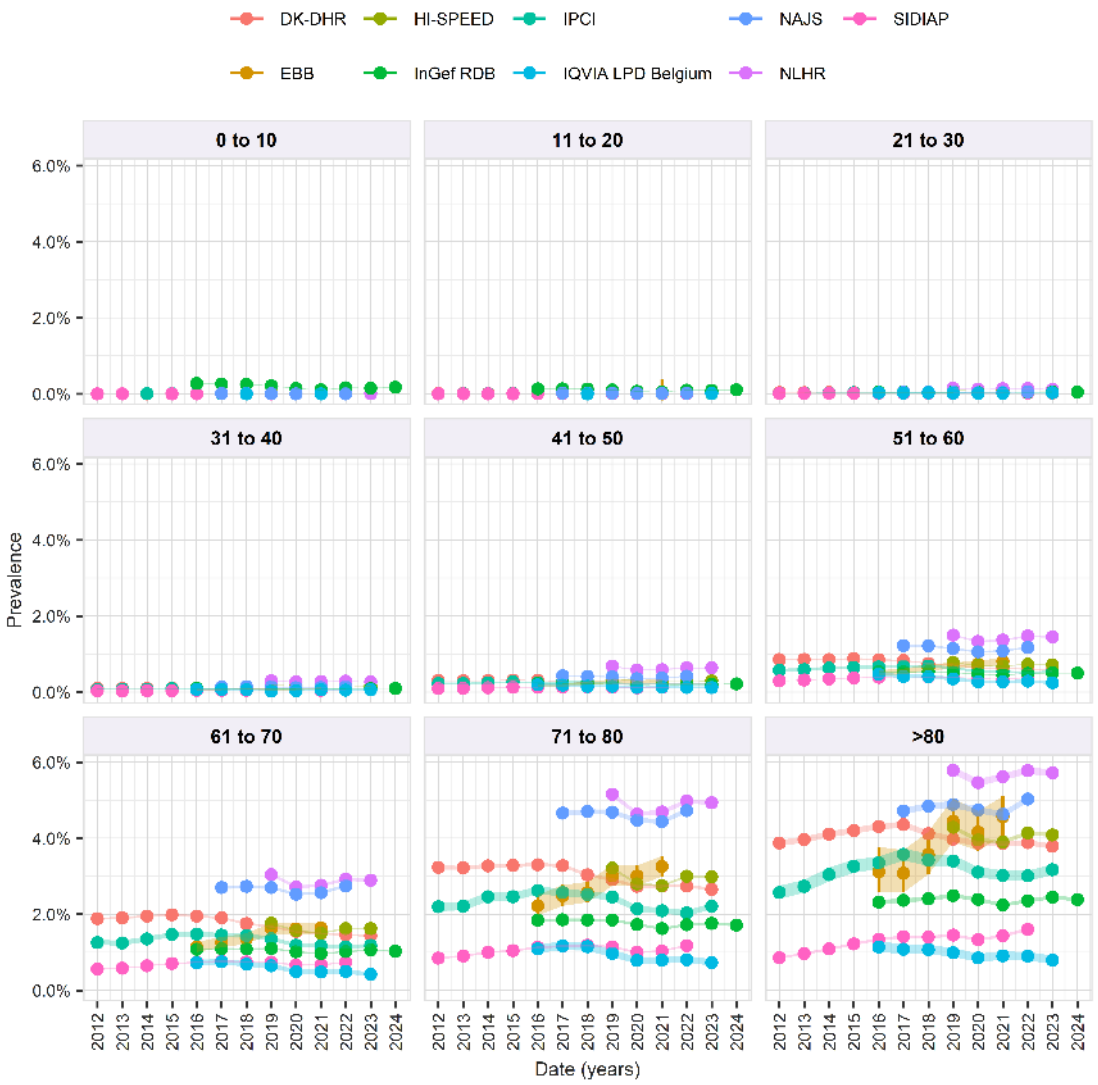

Figure 33. Prevalence of opioid use with history of cancer in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

Figure 34. Prevalence of opioid use with history of cancer in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

For the incidence of opioid without cancer history stratified by age, InGef RDB and IQVIA LPD Belgium had the highest incidence in younger age groups among the primary care or nationwide data sources (**Figure 35**). In the InGef RDB aged 0–10 group, the incidence of non-cancer opioid use decreased from 8,450 in 2016 to 6,797 in 2019. The incidence dipped to 4,054 in 2020 and returned up high at 8,364 in 2022. A similar pattern was also observed in IQVIA LPD Belgium in the 11–20 age group. Without considering the period of 2020 and 2021, the incidence of non-cancer opioid use in IQVIA LPD Belgium aged 11–20 group 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. Considering the hospital data sources, FinOMOP-ACI Varha had the highest incidence of non-cancer opioid use across all the age groups (**Figure 36**).

Trend in prevalence of opioid prescriptions without history of cancer (**Figure 37**, **Figure 38**) generally aligns with the incidence rates. Prevalence of non-cancer opioid use in aged 0–10 group remain the highest in InGef RDB, with a range of 5.3–9.5% over the study period. 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 and NAJS remained at a level above 20% from 2017 in aged above 80.

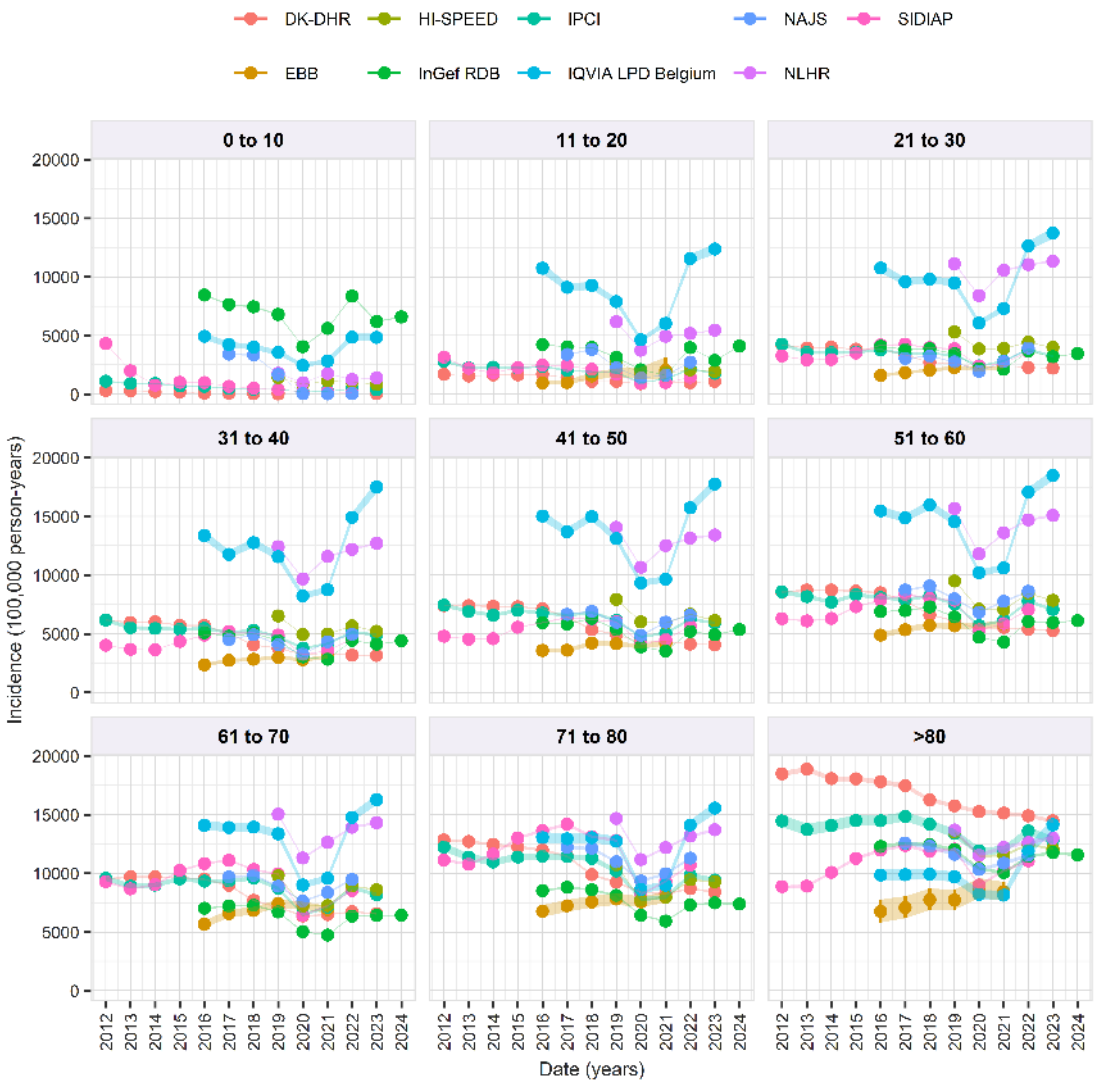

Figure 35. Incidence of opioid use without history of cancer in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

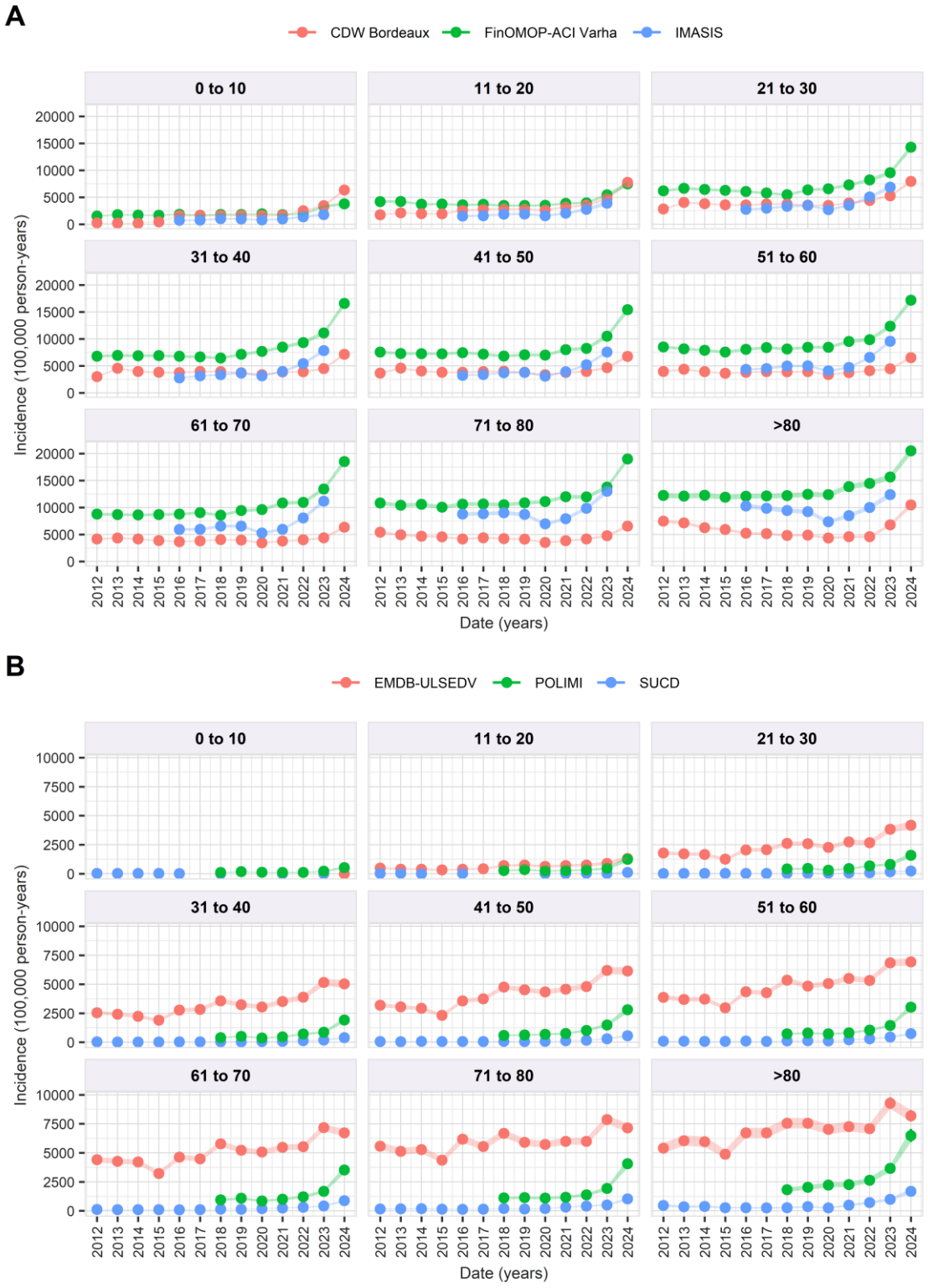

Figure 36. Incidence of opioid use without history of cancer in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

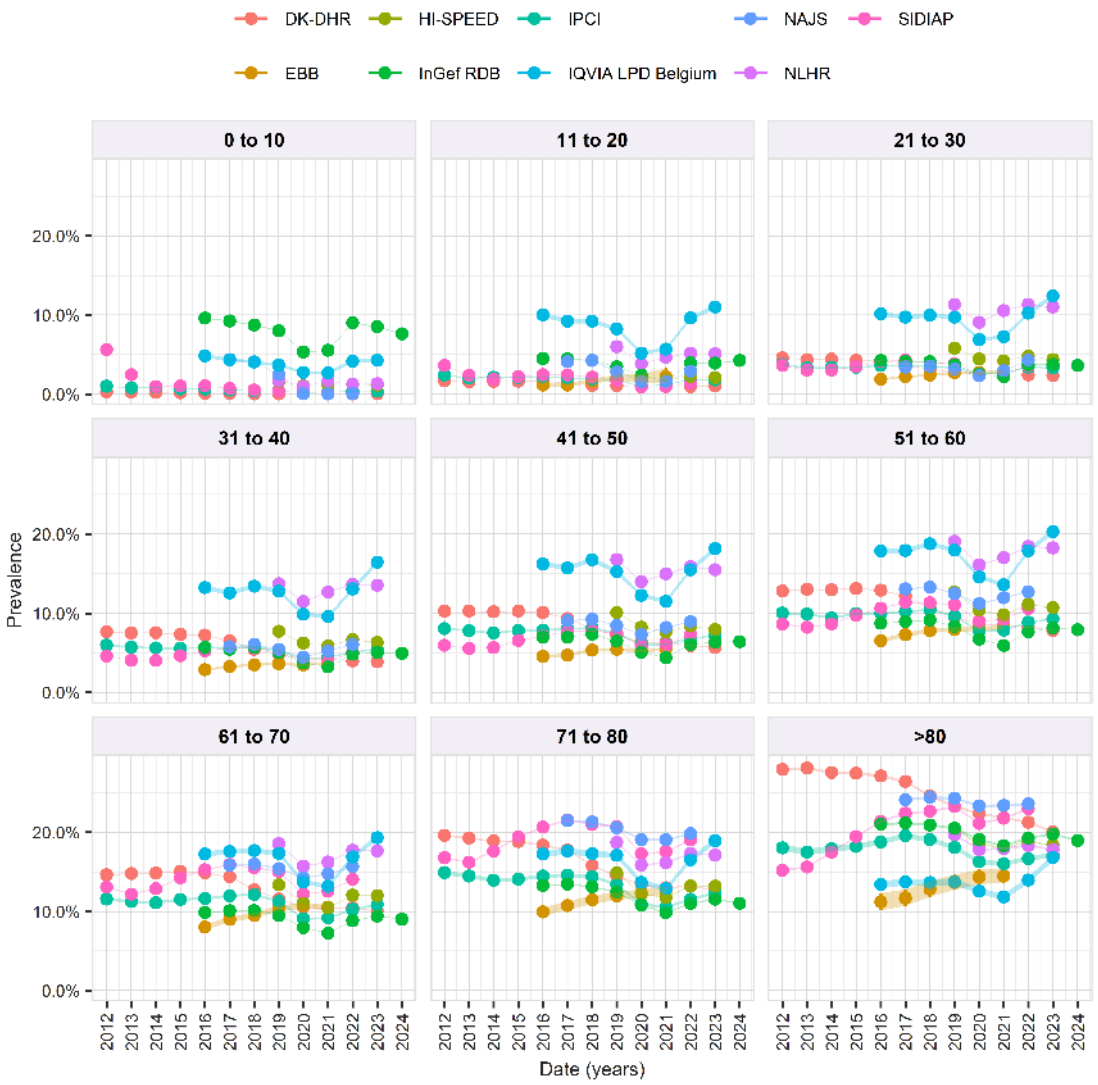

Figure 37. Prevalence of opioid use without history of cancer in primary care or national registries, stratified by age.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

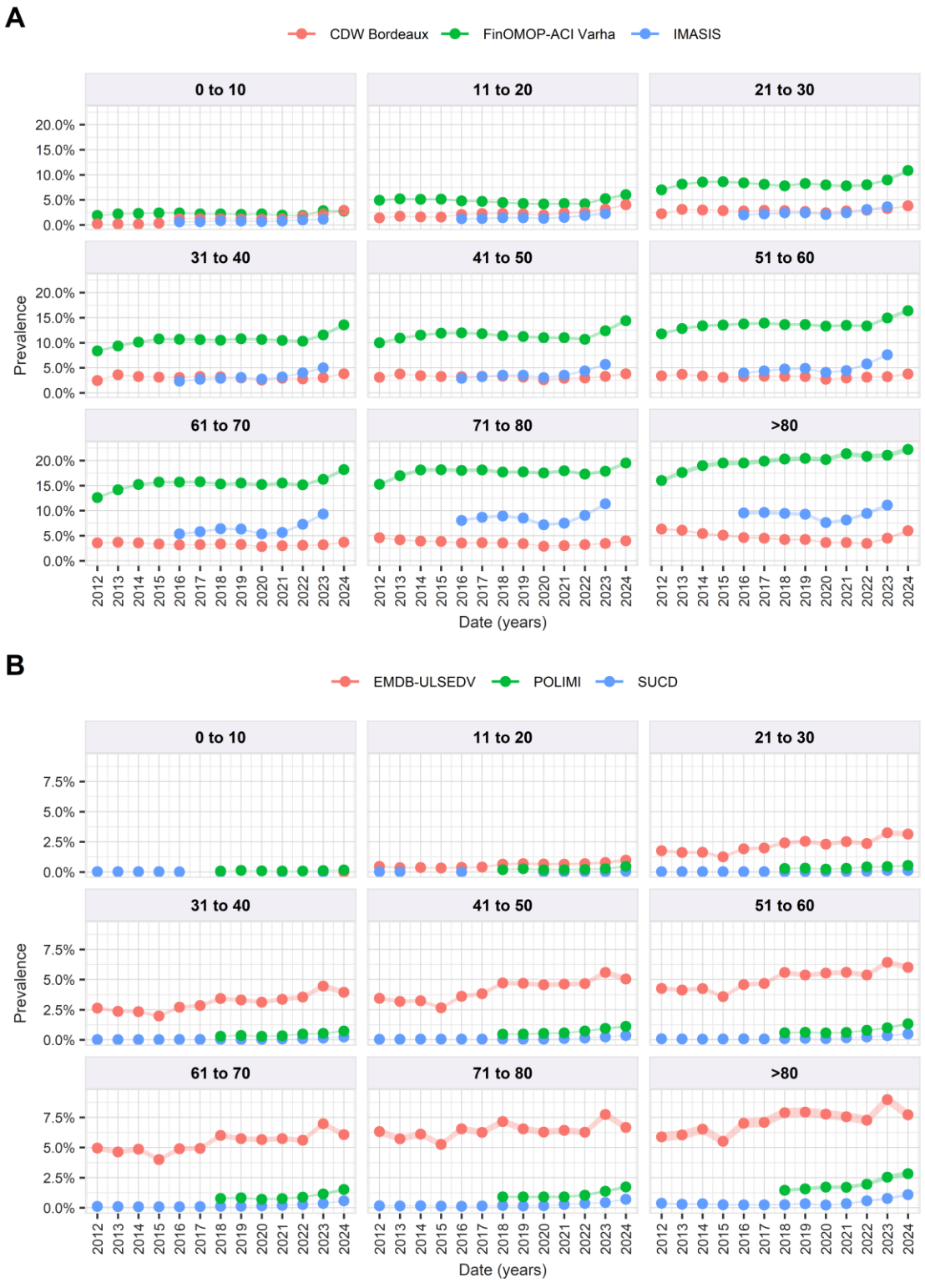

Figure 38. Prevalence of opioid use without history of cancer in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by age.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

Overall Opioid Use and Opioid Use by History of Cancer, Stratified by Sex

Higher incidence of opioid prescriptions was observed in women compared to men across all primary care or nationwide data sources (**Figure 39**). In hospital data sources, incidence of opioid use was higher in men compared to women in CDW Bordeaux, IMASIS, and POLIMI (**Figure 40**). A similar pattern was observed with prevalence of opioid use stratified by sex (**Figure 41**, **Figure 42**).

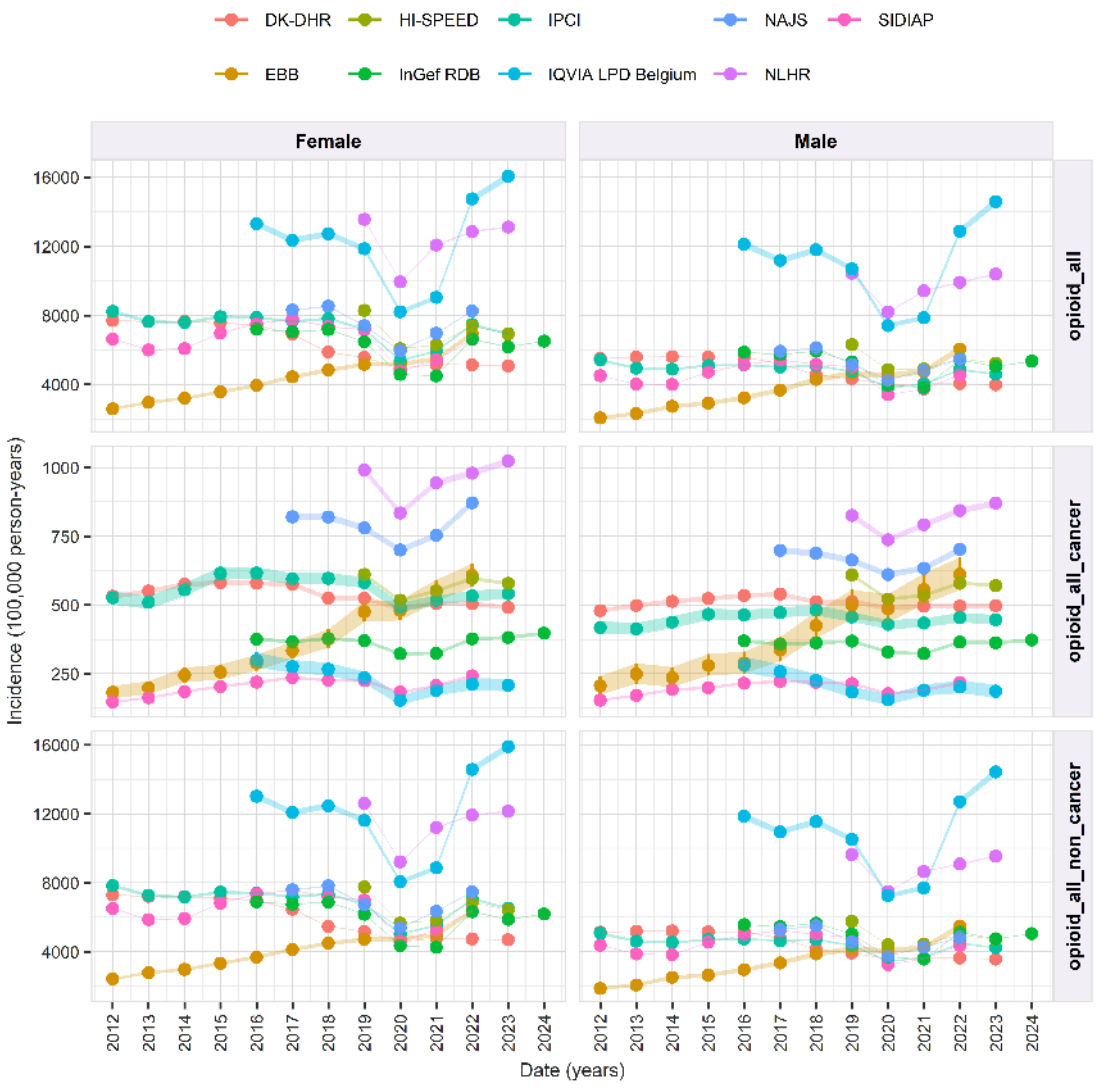

Figure 39. Incidence of opioid use in primary care or national registries, stratified by sex.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

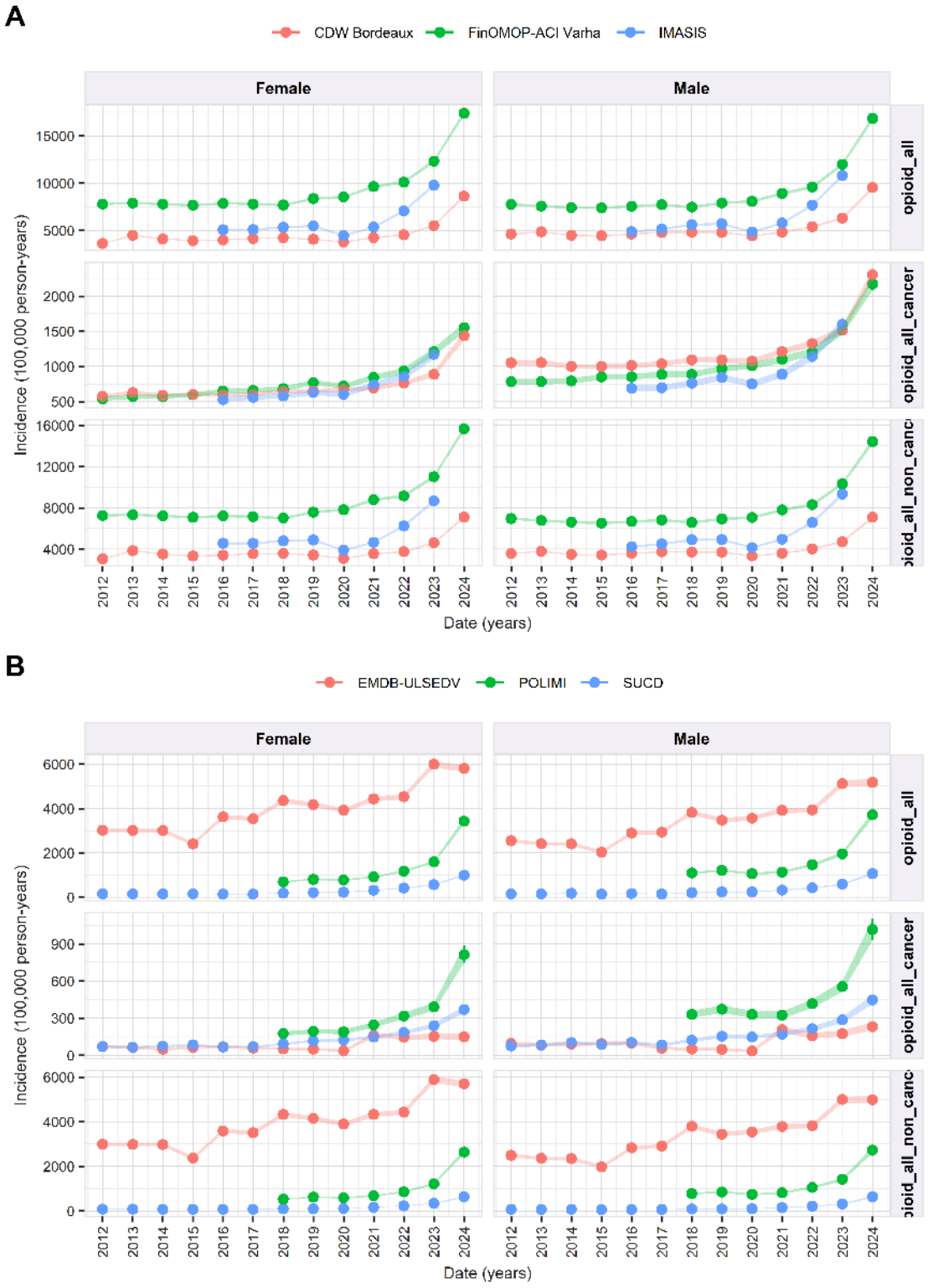

Figure 40. Incidence of opioid use in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by sex.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

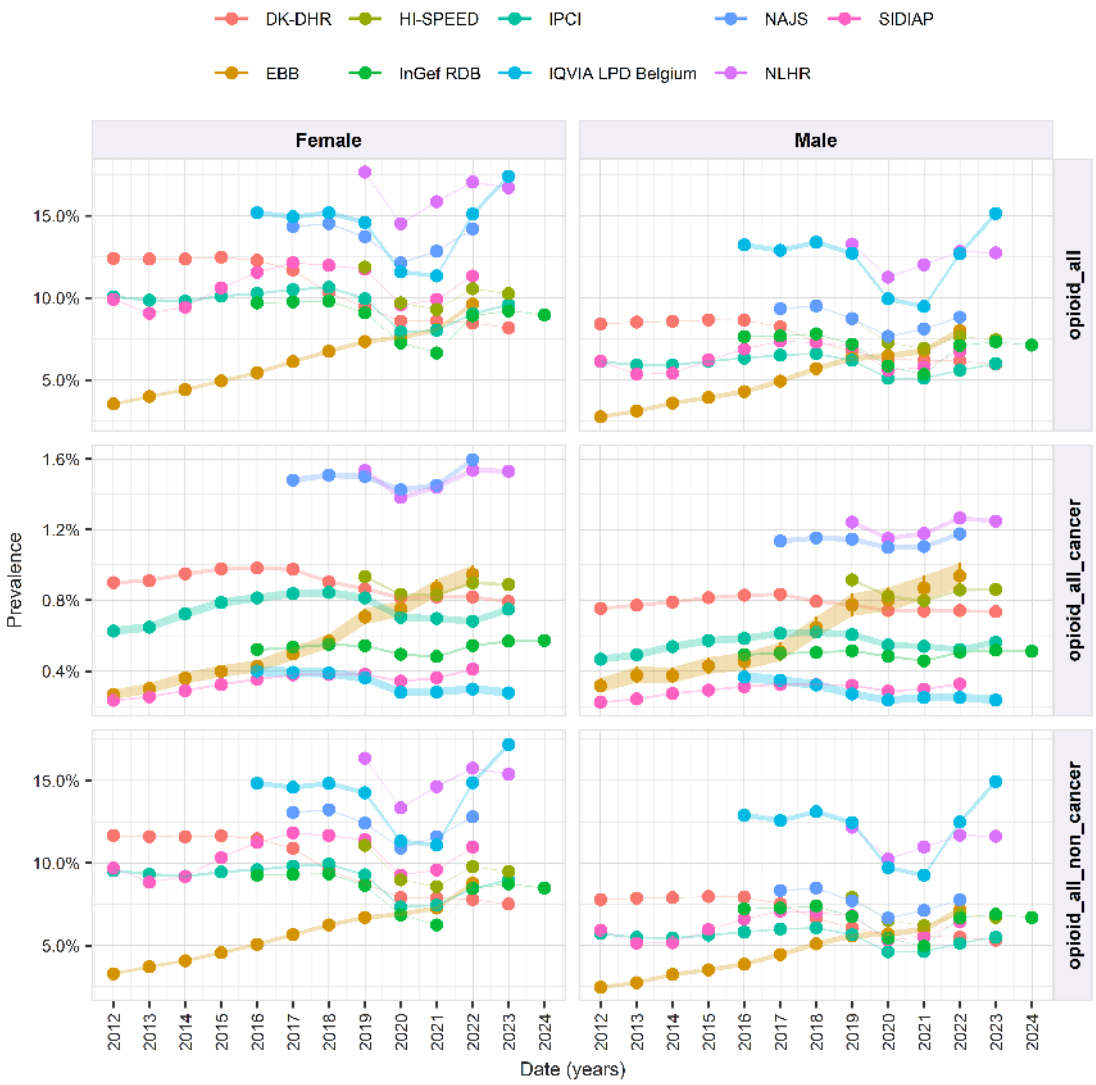

Figure 41. Prevalence of opioid use in primary care or national registries, stratified by sex.

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

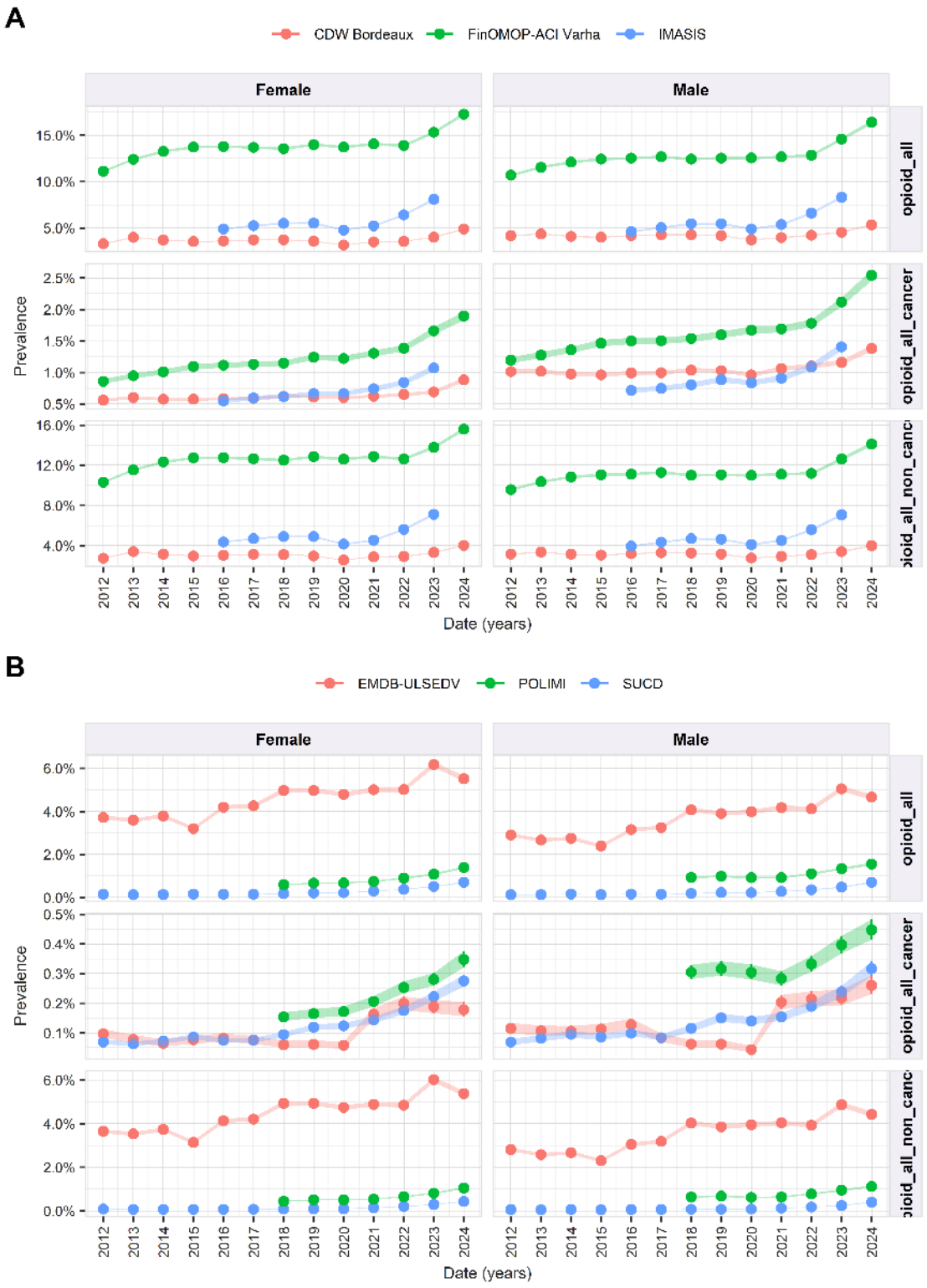

Figure 42. Prevalence of opioid use in (A) hospital data sources with complete coverage and (B) hospital data sources with partial coverage, stratified by sex.

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

12.2.2. Objective 2. Patient-level characterisation and DUS

Cohort characteristics

Patient-level characterisation of new opioid users during 2012–2024 are presented in **Table 14** for primary care or nationwide data sources and in **Table 15** for hospital data sources. 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 data sources, except CDW Bordeaux. The proportion of women ranged from 51.0% in POLIMI to 60.1% in IPCI, while it was 49.1% in CDW Bordeaux.

Median age of new opioid users ranged from 49 [IQR 33–64] in NLHR to 66 [54–75] in SUCD.

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 31.4% in SUCD, and that within malignant neoplastic disease recorded within 1 year prior to the new opioid prescription ranged from 1.8% in IQVIA LPD Belgium to 48.4% in CDW Bordeaux.

When considering the medication use within 1 year prior to the new opioid prescription, 38.0% (CDW Bordeaux) to 88.6% (FinOMOP-ACI Varha) 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 data sources (1 [1–5] day in IMASIS and 2 [1–5] days in CDW Bordeaux) to a week or more in the primary care or nationwide data source (e.g., 11 [7–11] days in SIDIAP, 18 [10–29] days in HI-SPEED). Despite being a hospital data source, SUCD had a median duration of the first treatment episode of opioids at 21 [11–31] days, as the drug records were mostly outpatient prescription records in the data source.

Table 14. Patient level characterisation of new opioid users in primary care or national registries.

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
Number records	-	N	286,251	1,914,779	3,592,890	89,135	3,403,179	686,566	2,458,504	3,367,282	3,230,699
Number individuals	-	N	205,461	1,341,765	2,183,760	60,286	2,505,705	484,556	1,888,433	2,204,608	2,585,592
Age	-	Median [Q25–Q75]	51 [34–64]	59 [44–71]	59 [44–72]	55 [42–66]	51 [31–64]	57 [43–70]	49 [33–64]	55 [40–70]	56 [38–71]
		Range	1 to 116	1 to 108	1 to 110	9 to 104	0 to 110	1 to 105	1 to 110	1 to 116	1 to 112
Sex	Female	N (%)	159,429 (55.70%)	1,141,632 (59.62%)	2,024,157 (56.34%)	61,513 (69.01%)	1,854,051 (54.48%)	412,494 (60.08%)	1,337,241 (54.39%)	1,975,922 (58.68%)	1,795,394 (55.57%)
	Male	N (%)	126,822 (44.30%)	773,147 (40.38%)	1,568,733 (43.66%)	27,622 (30.99%)	1,549,128 (45.52%)	274,072 (39.92%)	1,121,263 (45.61%)	1,391,360 (41.32%)	1,435,305 (44.43%)
Treatment duration (days)	-	Median [Q25–Q75]	7 [6–20]	30 [30–30] [a]	6 [3–13]	30 [30–30] [a]	30 [30–30] [a]	10 [7–15]	11 [5–14]	11 [7–31]	18 [10–29]
		Range	1 to 2,527	1 to 3,258	1 to 4,454	1 to 4,009	1 to 3,228	1 to 3,668	1 to 1,786	1 to 4,198	1 to 2,068
Comorbidities (anytime to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	32,339 (11.30%)	129,254 (6.75%)	278,420 (7.75%)	6,917 (7.76%)	74,858 (2.20%)	28,902 (4.21%)	141,320 (5.75%)	112,433 (3.34%)	87,995 (2.72%)
	Osteoporosis	N (%)	13,294 (4.65%)	169,840 (8.87%)	265,484 (7.39%)	7,069 (7.93%)	40,725 (1.20%)	16,996 (2.48%)	112,663 (4.58%)	171,904 (5.11%)	73,943 (2.29%)
	Gastro-oesophageal reflux disease	N (%)	40,998 (14.33%)	379,614 (19.83%)	72,215 (2.01%)	30,170 (33.85%)	22,083 (0.65%)	10,225 (1.49%)	119,724 (4.87%)	171,691 (5.10%)	82,496 (2.55%)
	Obesity	N (%)	14,672 (5.13%)	134,453 (7.02%)	374,731 (10.43%)	18,609 (20.88%)	191,155 (5.62%)	99,588 (14.51%)	201,692 (8.20%)	1,123,709 (33.37%)	179,642 (5.56%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Venous thromboembolism	N (%)	6,463 (2.26%)	69,189 (3.61%)	113,005 (3.15%)	7,398 (8.30%)	28,598 (0.84%)	14,404 (2.10%)	100,167 (4.07%)	73,545 (2.18%)	68,832 (2.13%)
	Dementia	N (%)	1,473 (0.51%)	21,233 (1.11%)	78,960 (2.20%)	629 (0.71%)	36,411 (1.07%)	4,999 (0.73%)	15,785 (0.64%)	43,146 (1.28%)	41,782 (1.29%)
	Pneumonia	N (%)	10,650 (3.72%)	166,203 (8.68%)	1,041,107 (28.98%)	17,295 (19.40%)	69,372 (2.04%)	42,090 (6.13%)	380,421 (15.47%)	165,136 (4.90%)	157,935 (4.89%)
	Hypothyroidism	N (%)	19,872 (6.95%)	204,525 (10.68%)	184,080 (5.12%)	10,971 (12.31%)	191,222 (5.62%)	20,725 (3.02%)	171,935 (6.99%)	213,079 (6.33%)	144,669 (4.48%)
	Inflammatory bowel disease	N (%)	2,062 (0.72%)	18,223 (0.95%)	74,305 (2.07%)	1,399 (1.57%)	15,699 (0.46%)	5,915 (0.86%)	36,112 (1.47%)	15,645 (0.46%)	42,946 (1.33%)
	Depressive disorder	N (%)	22,660 (7.92%)	321,716 (16.81%)	823,690 (22.93%)	34,625 (38.85%)	152,535 (4.48%)	39,211 (5.71%)	192,481 (7.83%)	342,112 (10.16%)	264,444 (8.19%)
	Malignant neoplastic disease	N (%)	7,518 (2.63%)	196,442 (10.26%)	461,196 (12.84%)	10,820 (12.14%)	145,804 (4.28%)	62,782 (9.15%)	311,737 (12.68%)	276,843 (8.22%)	335,561 (10.39%)
	Chronic kidney disease (with renal impairment)	N (%)	2,004 (0.70%)	49,678 (2.60%)	70,906 (1.97%)	2,769 (3.11%)	136,816 (4.02%)	31,114 (4.53%)	44,453 (1.81%)	181,700 (5.40%)	87,618 (2.71%)
	Chronic liver disease	N (%)	522 (0.18%)	18,212 (0.95%)	31,392 (0.87%)	2,286 (2.56%)	14,422 (0.42%)	1,679 (0.24%)	16,328 (0.66%)	32,146 (0.95%)	27,400 (0.85%)
	Asthma	N (%)	44,040 (15.39%)	136,327 (7.12%)	730,125 (20.32%)	15,264 (17.12%)	58,824 (1.73%)	47,478 (6.92%)	427,510 (17.39%)	144,805 (4.30%)	206,688 (6.40%)
	Stroke	N (%)	3,105 (1.09%)	43,293 (2.26%)	176,619 (4.92%)	2,140 (2.40%)	37,668 (1.11%)	14,698 (2.14%)	71,471 (2.91%)	63,439 (1.88%)	64,815 (2.01%)
	Chronic kidney disease	N (%)	1,767 (0.62%)	40,277 (2.10%)	49,025 (1.36%)	2,040 (2.29%)	106,078 (3.12%)	8,055 (1.17%)	30,522 (1.24%)	174,384 (5.18%)	64,788 (2.01%)
	Type 2 diabetes	N (%)	24,219 (8.47%)	294,914 (15.41%)	361,393 (10.06%)	10,738 (12.05%)	315,812 (9.28%)	75,865 (11.05%)	193,445 (7.87%)	501,018 (14.88%)	311,754 (9.65%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	HIV infection	N (%)	296 (0.10%)	724 (0.04%)	4,451 (0.12%)	198 (0.22%)	1,925 (0.06%)	400 (0.06%)	3,433 (0.14%)	7,733 (0.23%)	3,284 (0.10%)
	Rheumatoid arthritis	N (%)	2,551 (0.89%)	49,516 (2.59%)	90,082 (2.51%)	9,249 (10.38%)	23,611 (0.69%)	10,068 (1.47%)	119,135 (4.85%)	19,357 (0.57%)	43,413 (1.34%)
	Hypertension	N (%)	79,770 (27.88%)	1,018,587 (53.21%)	1,013,715 (28.21%)	44,975 (50.46%)	581,569 (17.09%)	129,274 (18.84%)	632,929 (25.75%)	645,785 (19.18%)	695,995 (21.54%)
	Myocardial infarction	N (%)	2,477 (0.87%)	40,268 (2.10%)	129,619 (3.61%)	2,121 (2.38%)	34,491 (1.01%)	15,457 (2.25%)	56,322 (2.29%)	37,855 (1.12%)	50,393 (1.56%)
	Anxiety	N (%)	45,043 (15.74%)	503,953 (26.33%)	417,951 (11.63%)	24,839 (27.87%)	70,412 (2.07%)	140,688 (20.50%)	673,111 (27.38%)	748,649 (22.23%)	406,401 (12.58%)
	Heart failure	N (%)	5,678 (1.98%)	69,777 (3.65%)	133,575 (3.72%)	20,732 (23.26%)	128,729 (3.78%)	14,596 (2.13%)	86,931 (3.54%)	74,316 (2.21%)	107,479 (3.33%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	25,569 (8.93%)	276,162 (14.42%)	11,296 (0.31%)	10,389 (11.66%)	8,619 (0.25%)	2,942 (0.43%)	48,186 (1.96%)	36,262 (1.08%)	29,481 (0.91%)
	Venous thromboembolism	N (%)	3,457 (1.21%)	45,290 (2.37%)	29,568 (0.82%)	1,593 (1.79%)	17,019 (0.50%)	6,601 (0.96%)	36,852 (1.50%)	17,979 (0.53%)	29,586 (0.92%)
	Obesity	N (%)	11,046 (3.86%)	93,969 (4.91%)	136,270 (3.79%)	9,707 (10.89%)	134,420 (3.95%)	85,244 (12.42%)	117,743 (4.79%)	734,905 (21.82%)	120,116 (3.72%)
	Malignant neoplastic disease	N (%)	5,082 (1.78%)	201,351 (10.52%)	284,526 (7.92%)	7,395 (8.30%)	139,162 (4.09%)	46,367 (6.75%)	185,912 (7.56%)	93,740 (2.78%)	236,011 (7.31%)
	Stroke	N (%)	2,181 (0.76%)	35,233 (1.84%)	41,087 (1.14%)	679 (0.76%)	19,064 (0.56%)	9,478 (1.38%)	35,738 (1.45%)	13,573 (0.40%)	28,447 (0.88%)
	Heart failure	N (%)	4,309 (1.51%)	65,940 (3.44%)	76,935 (2.14%)	10,383 (11.65%)	97,273 (2.86%)	10,967 (1.60%)	73,945 (3.01%)	22,310 (0.66%)	87,848 (2.72%)
	Chronic kidney disease	N (%)	1,211 (0.42%)	39,948 (2.09%)	38,097 (1.06%)	1,419 (1.59%)	92,667 (2.72%)	7,822 (1.14%)	21,326 (0.87%)	35,444 (1.05%)	58,965 (1.83%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Depressive disorder	N (%)	26,862 (9.38%)	363,514 (18.98%)	873,498 (24.31%)	36,061 (40.46%)	194,069 (5.70%)	46,189 (6.73%)	210,394 (8.56%)	379,507 (11.27%)	293,946 (9.10%)
	Anxiety	N (%)	25,341 (8.85%)	363,281 (18.97%)	123,893 (3.45%)	8,178 (9.17%)	34,285 (1.01%)	57,819 (8.42%)	185,628 (7.55%)	118,312 (3.51%)	184,106 (5.70%)
	Type 2 diabetes	N (%)	28,453 (9.94%)	336,975 (17.60%)	399,942 (11.13%)	11,510 (12.91%)	360,875 (10.60%)	83,060 (12.10%)	226,694 (9.22%)	533,449 (15.84%)	354,490 (10.97%)
	Pneumonia	N (%)	5,648 (1.97%)	83,689 (4.37%)	305,184 (8.49%)	2,769 (3.11%)	53,146 (1.56%)	19,611 (2.86%)	62,291 (2.53%)	38,106 (1.13%)	57,995 (1.80%)
	Chronic liver disease	N (%)	349 (0.12%)	12,372 (0.65%)	17,855 (0.50%)	711 (0.80%)	12,494 (0.37%)	909 (0.13%)	6,361 (0.26%)	3,725 (0.11%)	16,519 (0.51%)
	Chronic kidney disease (with renal impairment)	N (%)	1,383 (0.48%)	47,863 (2.50%)	49,843 (1.39%)	1,849 (2.07%)	119,797 (3.52%)	21,409 (3.12%)	32,837 (1.34%)	38,044 (1.13%)	75,852 (2.35%)
	Myocardial infarction	N (%)	1,873 (0.65%)	36,740 (1.92%)	20,755 (0.58%)	562 (0.63%)	14,649 (0.43%)	9,795 (1.43%)	26,403 (1.07%)	6,969 (0.21%)	17,031 (0.53%)
	Chronic obstructive pulmonary disease	N (%)	20,097 (7.02%)	94,619 (4.94%)	179,506 (5.00%)	2,562 (2.87%)	57,679 (1.69%)	19,768 (2.88%)	96,619 (3.93%)	20,517 (0.61%)	67,551 (2.09%)
	Hypothyroidism	N (%)	15,885 (5.55%)	163,019 (8.51%)	153,004 (4.26%)	7,191 (8.07%)	120,694 (3.55%)	10,938 (1.59%)	145,203 (5.91%)	27,299 (0.81%)	93,037 (2.88%)
	Asthma	N (%)	30,360 (10.61%)	99,621 (5.20%)	287,079 (7.99%)	7,685 (8.62%)	29,088 (0.85%)	24,478 (3.57%)	250,997 (10.21%)	20,498 (0.61%)	112,303 (3.48%)
	Rheumatoid arthritis	N (%)	1,549 (0.54%)	34,705 (1.81%)	47,493 (1.32%)	2,691 (3.02%)	14,830 (0.44%)	5,214 (0.76%)	80,001 (3.25%)	2,725 (0.08%)	32,364 (1.00%)
	HIV infection	N (%)	162 (0.06%)	591 (0.03%)	4,396 (0.12%)	113 (0.13%)	1,456 (0.04%)	253 (0.04%)	2,694 (0.11%)	572 (0.02%)	3,098 (0.10%)
	Osteoporosis	N (%)	8,155 (2.85%)	122,658 (6.41%)	182,277 (5.07%)	2,650 (2.97%)	31,643 (0.93%)	7,395 (1.08%)	67,022 (2.73%)	20,119 (0.60%)	47,318 (1.46%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Hypertension	N (%)	67,812 (23.69%)	987,189 (51.56%)	562,304 (15.65%)	37,798 (42.41%)	414,026 (12.17%)	78,664 (11.46%)	557,647 (22.68%)	75,776 (2.25%)	514,339 (15.92%)
	Dementia	N (%)	1,126 (0.39%)	22,066 (1.15%)	64,921 (1.81%)	275 (0.31%)	47,499 (1.40%)	4,641 (0.68%)	15,929 (0.65%)	11,864 (0.35%)	42,931 (1.33%)
	Inflammatory bowel disease	N (%)	1,414 (0.49%)	13,606 (0.71%)	35,652 (0.99%)	408 (0.46%)	8,941 (0.26%)	3,245 (0.47%)	21,034 (0.86%)	2,820 (0.08%)	30,819 (0.95%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	13,004 (4.54%)	61,779 (3.23%)	289,263 (8.05%)	12,287 (13.78%)	191,211 (5.62%)	30,311 (4.41%)	106,623 (4.34%)	390,712 (11.60%)	191,258 (5.92%)
	Diuretics	N (%)	16,777 (5.86%)	300,338 (15.69%)	683,229 (19.02%)	7,359 (8.26%)	423,852 (12.45%)	96,705 (14.09%)	122,316 (4.98%)	436,991 (12.98%)	508,543 (15.74%)
	Drugs used in diabetes	N (%)	23,862 (8.34%)	252,021 (13.16%)	345,254 (9.61%)	7,826 (8.78%)	302,861 (8.90%)	67,490 (9.83%)	182,842 (7.44%)	387,710 (11.51%)	326,684 (10.11%)
	Antithrombotics	N (%)	15,997 (5.59%)	185,982 (9.71%)	571,855 (15.92%)	8,799 (9.87%)	443,353 (13.03%)	100,291 (14.61%)	249,105 (10.13%)	377,774 (11.22%)	592,419 (18.34%)
	Drugs for obstructive airway diseases	N (%)	77,808 (27.18%)	304,490 (15.90%)	699,387 (19.47%)	17,082 (19.16%)	817,658 (24.03%)	178,794 (26.04%)	571,046 (23.23%)	868,844 (25.80%)	691,618 (21.41%)
	Psycholeptics	N (%)	66,662 (23.29%)	886,082 (46.28%)	612,110 (17.04%)	24,097 (27.03%)	271,920 (7.99%)	137,573 (20.04%)	495,883 (20.17%)	1,217,853 (36.17%)	717,071 (22.20%)
	Agents acting on renin angiotensin system	N (%)	52,033 (18.18%)	776,716 (40.56%)	954,029 (26.55%)	28,705 (32.20%)	977,371 (28.72%)	161,552 (23.53%)	463,209 (18.84%)	944,965 (28.06%)	846,262 (26.19%)
	Antineoplastic agents	N (%)	956 (0.33%)	22,477 (1.17%)	91,342 (2.54%)	869 (0.97%)	96,231 (2.83%)	6,003 (0.87%)	22,092 (0.90%)	26,400 (0.78%)	50,127 (1.55%)
	Antidepressants	N (%)	43,652 (15.25%)	172,851 (9.03%)	544,617 (15.16%)	14,204 (15.94%)	434,710 (12.77%)	78,665 (11.46%)	260,291 (10.59%)	694,995 (20.64%)	612,125 (18.95%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Antibacterials systemic	N (%)	121,253 (42.36%)	1,117,353 (58.35%)	1,576,594 (43.88%)	42,885 (48.11%)	1,611,201 (47.34%)	223,010 (32.48%)	809,681 (32.93%)	1,409,408 (41.86%)	984,188 (30.46%)
	Psychostimulants	N (%)	1,498 (0.52%)	77 (0.00%)	42,931 (1.19%)	407 (0.46%)	20,139 (0.59%)	6,900 (1.01%)	31,618 (1.29%)	36,103 (1.07%)	78,733 (2.44%)
	Immunosuppressants	N (%)	2,211 (0.77%)	21,899 (1.14%)	93,709 (2.61%)	2,385 (2.68%)	80,741 (2.37%)	12,346 (1.80%)	61,495 (2.50%)	44,960 (1.34%)	92,019 (2.85%)
	Antiinflammatory antirheumatic agents	N (%)	127,988 (44.71%)	1,191,721 (62.24%)	1,690,051 (47.04%)	54,344 (60.97%)	2,012,846 (59.15%)	277,284 (40.39%)	1,105,105 (44.95%)	2,482,258 (73.72%)	1,780,220 (55.10%)
	Calcium channel blockers	N (%)	19,484 (6.81%)	357,057 (18.65%)	581,826 (16.19%)	11,477 (12.88%)	400,948 (11.78%)	79,222 (11.54%)	215,658 (8.77%)	322,551 (9.58%)	506,806 (15.69%)
	Drugs acid related disorder	N (%)	81,293 (28.40%)	750,759 (39.21%)	1,148,425 (31.96%)	26,855 (30.13%)	1,045,727 (30.73%)	276,506 (40.27%)	489,795 (19.92%)	1,520,364 (45.15%)	782,203 (24.21%)
	Hormonal contraceptives (systemic)	N (%)	14,618 (5.11%)	26,924 (1.41%)	160,280 (4.46%)	4,258 (4.78%)	55,744 (1.64%)	16,896 (2.46%)	207,441 (8.44%)	60,254 (1.79%)	259,081 (8.02%)
	Lipid modifying agents	N (%)	54,441 (19.02%)	397,716 (20.77%)	876,161 (24.39%)	14,458 (16.22%)	525,890 (15.45%)	162,447 (23.66%)	444,559 (18.08%)	795,667 (23.63%)	640,001 (19.81%)
	Beta blocking agents	N (%)	47,514 (16.60%)	480,708 (25.11%)	533,310 (14.84%)	21,377 (23.98%)	661,318 (19.43%)	127,758 (18.61%)	265,891 (10.82%)	376,355 (11.18%)	597,975 (18.51%)
Cancer (anytime to 366 days prior)	Prostate cancer	N (%)	1,210 (0.42%)	19,824 (1.04%)	55,901 (1.56%)	1,177 (1.32%)	15,222 (0.45%)	6,005 (0.87%)	38,506 (1.57%)	29,909 (0.89%)	61,032 (1.89%)
	Breast cancer	N (%)	0 (0.00%)	0 (0.00%)	55,748 (1.55%)	190 (0.21%)	0 (0.00%)	10,207 (1.49%)	0 (0.00%)	41,194 (1.22%)	14,496 (0.45%)
	Multiple myeloma	N (%)	123 (0.04%)	2,316 (0.12%)	4,978 (0.14%)	95 (0.11%)	2,463 (0.07%)	542 (0.08%)	2,723 (0.11%)	2,644 (0.08%)	4,615 (0.14%)
	Pancreatic cancer	N (%)	84 (0.03%)	1,479 (0.08%)	3,000 (0.08%)	165 (0.19%)	2,345 (0.07%)	540 (0.08%)	1,928 (0.08%)	1,934 (0.06%)	2,636 (0.08%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Lymphoma	N (%)	184 (0.06%)	5,866 (0.31%)	14,652 (0.41%)	416 (0.47%)	6,264 (0.18%)	1,746 (0.25%)	9,951 (0.40%)	4,367 (0.13%)	11,162 (0.35%)
	Colorectal cancer	N (%)	605 (0.21%)	24,607 (1.29%)	53,041 (1.48%)	1,074 (1.20%)	16,016 (0.47%)	5,355 (0.78%)	26,220 (1.07%)	31,290 (0.93%)	23,847 (0.74%)
	Ovarian cancer	N (%)	65 (0.02%)	3,997 (0.21%)	7,777 (0.22%)	338 (0.38%)	2,757 (0.08%)	666 (0.10%)	4,986 (0.20%)	3,252 (0.10%)	3,820 (0.12%)
	Endometrial cancer	N (%)	70 (0.02%)	4,054 (0.21%)	2,485 (0.07%)	283 (0.32%)	2,117 (0.06%)	715 (0.10%)	3,077 (0.13%)	3,924 (0.12%)	1,196 (0.04%)
	Lung cancer	N (%)	391 (0.14%)	7,640 (0.40%)	18,328 (0.51%)	339 (0.38%)	3,609 (0.11%)	3,850 (0.56%)	10,455 (0.43%)	9,258 (0.27%)	9,255 (0.29%)
	Leukaemia	N (%)	317 (0.11%)	4,970 (0.26%)	12,558 (0.35%)	260 (0.29%)	4,598 (0.14%)	1,281 (0.19%)	6,052 (0.25%)	6,557 (0.19%)	9,319 (0.29%)
Cancer (365 to 0 days prior)	Multiple myeloma	N (%)	93 (0.03%)	2,558 (0.13%)	5,809 (0.16%)	111 (0.12%)	2,883 (0.08%)	518 (0.08%)	2,821 (0.11%)	1,188 (0.04%)	5,421 (0.17%)
	Lymphoma	N (%)	140 (0.05%)	5,991 (0.31%)	8,971 (0.25%)	369 (0.41%)	5,236 (0.15%)	1,447 (0.21%)	7,524 (0.31%)	1,182 (0.04%)	9,393 (0.29%)
	Prostate cancer	N (%)	844 (0.29%)	21,190 (1.11%)	37,469 (1.04%)	1,001 (1.12%)	10,804 (0.32%)	4,102 (0.60%)	28,029 (1.14%)	4,901 (0.15%)	47,716 (1.48%)
	Lung cancer	N (%)	320 (0.11%)	15,113 (0.79%)	27,259 (0.76%)	337 (0.38%)	6,489 (0.19%)	6,117 (0.89%)	12,131 (0.49%)	13,410 (0.40%)	14,273 (0.44%)
	Endometrial cancer	N (%)	48 (0.02%)	2,970 (0.16%)	14 (0.00%)	118 (0.13%)	1,401 (0.04%)	462 (0.07%)	1,574 (0.06%)	894 (0.03%)	788 (0.02%)
	Leukaemia	N (%)	211 (0.07%)	5,430 (0.28%)	11,446 (0.32%)	247 (0.28%)	4,768 (0.14%)	1,028 (0.15%)	5,100 (0.21%)	1,660 (0.05%)	9,168 (0.28%)
	Pancreatic cancer	N (%)	105 (0.04%)	4,479 (0.23%)	7,349 (0.20%)	183 (0.21%)	7,062 (0.21%)	1,450 (0.21%)	3,178 (0.13%)	3,651 (0.11%)	6,764 (0.21%)
	Breast cancer	N (%)	0 (0.00%)	0 (0.00%)	8,254 (0.23%)	30 (0.03%)	0 (0.00%)	6,707 (0.98%)	0 (0.00%)	7,843 (0.23%)	3,219 (0.10%)
	Ovarian cancer	N (%)	52 (0.02%)	4,347 (0.23%)	5,284 (0.15%)	212 (0.24%)	3,179 (0.09%)	677 (0.10%)	3,682 (0.15%)	1,109 (0.03%)	3,459 (0.11%)
	Colorectal cancer	N (%)	343 (0.12%)	29,341 (1.53%)	29,459 (0.82%)	795 (0.89%)	14,634 (0.43%)	4,520 (0.66%)	20,903 (0.85%)	9,055 (0.27%)	26,418 (0.82%)

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

a. Default prescription duration was 30 days in NAJS (1 day for secondary conciliatory care), EBB, and InGef RDB.

Table 15. Patient level characterisation of new opioid users in hospital data sources.

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
Number records	-	N	367,898	319,317	19,026	26,085	122,775	184,025
Number individuals	-	N	266,327	274,026	17,709	24,821	89,900	132,762
Age	-	Median [Q25–Q75]	59 [38–72]	55 [34–71]	66 [54–75]	63 [48–76]	58 [44–71]	62 [45–76]
		Range	0 to 117	0 to 108	0 to 101	0 to 105	2 to 105	0 to 108
Sex	Female	N (%)	199,787 (54.30%)	156,713 (49.08%)	11,314 (59.47%)	13,293 (50.96%)	70,033 (57.04%)	95,958 (52.14%)
	Male	N (%)	168,111 (45.70%)	162,597 (50.92%)	7,712 (40.53%)	12,792 (49.04%)	52,742 (42.96%)	88,067 (47.86%)
	None	N (%)	-	7 (0.00%)	-	-	-	-
Treatment duration (days)	-	Median [Q25–Q75]	11 [2–31]	2 [1–5]	21 [11–31]	4 [2–8]	31 [31–31] [a]	1 [1–5]
		Range	1 to 4,838	1 to 1,530	1 to 336	1 to 820	1 to 385	1 to 2,533
Comorbidities (anytime to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	7,886 (2.43%)	6,461 (3.36%)	1,181 (8.19%)	576 (3.66%)	2,009 (1.73%)	10,799 (6.93%)
	Osteoporosis	N (%)	4,424 (1.36%)	3,549 (1.85%)	1,544 (10.71%)	104 (0.66%)	1,410 (1.21%)	7,821 (5.02%)
	Gastro-oesophageal reflux disease	N (%)	11,073 (3.42%)	4,442 (2.31%)	1,495 (10.37%)	74 (0.47%)	649 (0.56%)	1,941 (1.25%)
	Obesity	N (%)	12,788 (3.94%)	13,682 (7.12%)	612 (4.24%)	210 (1.34%)	9,669 (8.32%)	25,179 (16.17%)
	Venous thromboembolism	N (%)	4,078 (1.26%)	4,560 (2.37%)	521 (3.61%)	209 (1.33%)	776 (0.67%)	2,965 (1.90%)
	Dementia	N (%)	4,438 (1.37%)	2,279 (1.19%)	158 (1.10%)	96 (0.61%)	423 (0.36%)	2,185 (1.40%)
	Pneumonia	N (%)	20,363 (6.28%)	8,878 (4.62%)	990 (6.87%)	1,152 (7.33%)	2,168 (1.86%)	8,573 (5.50%)
	Hypothyroidism	N (%)	13,258 (4.09%)	7,319 (3.81%)	711 (4.93%)	129 (0.82%)	1,134 (0.98%)	6,778 (4.35%)
	Inflammatory bowel disease	N (%)	6,228 (1.92%)	1,533 (0.80%)	339 (2.35%)	151 (0.96%)	242 (0.21%)	1,004 (0.64%)

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Depressive disorder	N (%)	20,497 (6.32%)	12,084 (6.29%)	1,126 (7.81%)	98 (0.62%)	7,771 (6.68%)	15,660 (10.06%)
	Malignant neoplastic disease	N (%)	27,971 (8.63%)	22,033 (11.47%)	4,523 (31.37%)	1,840 (11.70%)	5,299 (4.56%)	21,167 (13.59%)
	Chronic kidney disease (with renal impairment)	N (%)	7,005 (2.16%)	12,216 (6.36%)	1,439 (9.98%)	1,128 (7.17%)	1,634 (1.41%)	12,416 (7.97%)
	Chronic liver disease	N (%)	3,081 (0.95%)	4,275 (2.22%)	347 (2.41%)	842 (5.35%)	647 (0.56%)	6,405 (4.11%)
	Asthma	N (%)	17,864 (5.51%)	5,632 (2.93%)	516 (3.58%)	80 (0.51%)	2,040 (1.75%)	6,984 (4.48%)
	Stroke	N (%)	12,645 (3.90%)	4,313 (2.24%)	898 (6.23%)	205 (1.30%)	1,266 (1.09%)	3,826 (2.46%)
	Chronic kidney disease	N (%)	4,563 (1.41%)	8,909 (4.64%)	1,341 (9.30%)	753 (4.79%)	1,020 (0.88%)	8,701 (5.59%)
	Type 2 diabetes	N (%)	40,881 (12.61%)	14,740 (7.67%)	1,930 (13.39%)	1,077 (6.85%)	11,202 (9.63%)	26,792 (17.20%)
	HIV infection	N (%)	187 (0.06%)	1,251 (0.65%)	<5	38 (0.24%)	52 (0.04%)	1,733 (1.11%)
	Rheumatoid arthritis	N (%)	7,363 (2.27%)	1,692 (0.88%)	221 (1.53%)	45 (0.29%)	617 (0.53%)	1,225 (0.79%)
	Hypertension	N (%)	63,964 (19.73%)	38,252 (19.91%)	7,082 (49.12%)	1,608 (10.23%)	21,284 (18.30%)	46,311 (29.74%)
	Myocardial infarction	N (%)	9,969 (3.08%)	2,529 (1.32%)	302 (2.09%)	155 (0.99%)	1,134 (0.98%)	3,732 (2.40%)
	Anxiety	N (%)	17,168 (5.30%)	11,683 (6.08%)	1,059 (7.35%)	125 (0.79%)	2,856 (2.46%)	10,770 (6.92%)
	Heart failure	N (%)	12,416 (3.83%)	7,597 (3.95%)	1,172 (8.13%)	564 (3.59%)	2,327 (2.00%)	9,073 (5.83%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	2,220 (0.60%)	8,463 (2.65%)	1,423 (7.48%)	43 (0.16%)	145 (0.12%)	1,741 (0.95%)
	Venous thromboembolism	N (%)	1,783 (0.48%)	8,300 (2.60%)	625 (3.28%)	563 (2.16%)	191 (0.16%)	2,151 (1.17%)
	Obesity	N (%)	7,674 (2.09%)	38,563 (12.08%)	451 (2.37%)	319 (1.22%)	3,519 (2.87%)	34,968 (19.00%)

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Malignant neoplastic disease	N (%)	29,898 (8.13%)	61,076 (19.13%)	9,206 (48.39%)	6,570 (25.19%)	2,452 (2.00%)	23,319 (12.67%)
	Stroke	N (%)	6,546 (1.78%)	8,276 (2.59%)	710 (3.73%)	508 (1.95%)	258 (0.21%)	3,027 (1.64%)
	Heart failure	N (%)	9,216 (2.51%)	15,657 (4.90%)	1,500 (7.88%)	1,316 (5.05%)	1,033 (0.84%)	10,747 (5.84%)
	Chronic kidney disease	N (%)	3,468 (0.94%)	17,023 (5.33%)	1,822 (9.58%)	1,176 (4.51%)	511 (0.42%)	12,433 (6.76%)
	Depressive disorder	N (%)	22,354 (6.08%)	26,403 (8.27%)	803 (4.22%)	155 (0.59%)	8,825 (7.19%)	22,291 (12.11%)
	Anxiety	N (%)	6,290 (1.71%)	27,479 (8.61%)	834 (4.38%)	60 (0.23%)	557 (0.45%)	6,107 (3.32%)
	Type 2 diabetes	N (%)	63,039 (17.13%)	36,706 (11.50%)	3,229 (16.97%)	3,884 (14.89%)	12,897 (10.50%)	41,872 (22.75%)
	Pneumonia	N (%)	9,462 (2.57%)	16,179 (5.07%)	1,183 (6.22%)	2,850 (10.93%)	603 (0.49%)	6,316 (3.43%)
	Chronic liver disease	N (%)	2,112 (0.57%)	6,804 (2.13%)	334 (1.76%)	1,319 (5.06%)	154 (0.13%)	5,912 (3.21%)
	Chronic kidney disease (with renal impairment)	N (%)	5,453 (1.48%)	24,453 (7.66%)	2,103 (11.05%)	2,646 (10.14%)	766 (0.62%)	17,880 (9.72%)
	Myocardial infarction	N (%)	7,154 (1.94%)	3,018 (0.95%)	158 (0.83%)	289 (1.11%)	188 (0.15%)	3,541 (1.92%)
	Chronic obstructive pulmonary disease	N (%)	4,763 (1.29%)	16,434 (5.15%)	1,489 (7.83%)	761 (2.92%)	706 (0.58%)	10,901 (5.92%)
	Hypothyroidism	N (%)	4,720 (1.28%)	18,743 (5.87%)	563 (2.96%)	138 (0.53%)	358 (0.29%)	8,027 (4.36%)
	Asthma	N (%)	6,456 (1.75%)	11,828 (3.70%)	424 (2.23%)	62 (0.24%)	414 (0.34%)	6,429 (3.49%)
	Rheumatoid arthritis	N (%)	4,581 (1.25%)	3,260 (1.02%)	191 (1.00%)	54 (0.21%)	161 (0.13%)	1,034 (0.56%)
	HIV infection	N (%)	191 (0.05%)	1,179 (0.37%)	6 (0.03%)	80 (0.31%)	20 (0.02%)	2,014 (1.09%)
	Osteoporosis	N (%)	1,663 (0.45%)	5,841 (1.83%)	1,298 (6.82%)	98 (0.38%)	223 (0.18%)	8,083 (4.39%)
	Hypertension	N (%)	27,193 (7.39%)	96,335 (30.17%)	7,700 (40.47%)	1,372 (5.26%)	5,169 (4.21%)	53,810 (29.24%)

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Dementia	N (%)	2,266 (0.62%)	5,955 (1.86%)	293 (1.54%)	376 (1.44%)	264 (0.22%)	3,734 (2.03%)
	Inflammatory bowel disease	N (%)	5,154 (1.40%)	3,091 (0.97%)	304 (1.60%)	334 (1.28%)	46 (0.04%)	977 (0.53%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	37,506 (10.19%)	29,915 (9.37%)	1,502 (7.89%)	3,224 (12.36%)	8,024 (6.54%)	17,786 (9.66%)
	Diuretics	N (%)	59,489 (16.17%)	28,610 (8.96%)	3,112 (16.36%)	6,884 (26.39%)	4,640 (3.78%)	22,312 (12.12%)
	Drugs used in diabetes	N (%)	52,932 (14.39%)	24,036 (7.53%)	1,514 (7.96%)	3,542 (13.58%)	2,724 (2.22%)	24,939 (13.55%)
	Antithrombotics	N (%)	133,547 (36.30%)	87,763 (27.48%)	5,020 (26.38%)	14,640 (56.12%)	14,037 (11.43%)	63,112 (34.30%)
	Drugs for obstructive airway diseases	N (%)	69,653 (18.93%)	23,396 (7.33%)	1,009 (5.30%)	3,529 (13.53%)	6,396 (5.21%)	31,530 (17.13%)
	Psycholeptics	N (%)	143,282 (38.95%)	137,248 (42.98%)	2,650 (13.93%)	6,773 (25.97%)	16,480 (13.42%)	123,279 (66.99%)
	Agents acting on renin angiotensin system	N (%)	100,221 (27.24%)	31,714 (9.93%)	3,578 (18.81%)	6,368 (24.41%)	1,868 (1.52%)	21,838 (11.87%)
	Antineoplastic agents	N (%)	10,742 (2.92%)	10,391 (3.25%)	2,638 (13.87%)	934 (3.58%)	<5	4,320 (2.35%)
	Antidepressants	N (%)	48,366 (13.15%)	23,024 (7.21%)	1,067 (5.61%)	2,514 (9.64%)	6,893 (5.61%)	15,746 (8.56%)
	Antibacterials systemic	N (%)	137,519 (37.38%)	76,133 (23.84%)	5,223 (27.45%)	14,569 (55.85%)	33,016 (26.89%)	87,292 (47.43%)
	Psychostimulants	N (%)	2,568 (0.70%)	401 (0.13%)	437 (2.30%)	57 (0.22%)	77 (0.06%)	316 (0.17%)
	Immunosuppressants	N (%)	13,971 (3.80%)	8,135 (2.55%)	1,188 (6.24%)	1,418 (5.44%)	619 (0.50%)	3,914 (2.13%)
	Antiinflammatory antirheumatic agents	N (%)	325,843 (88.57%)	121,192 (37.95%)	7,588 (39.88%)	16,246 (62.28%)	69,562 (56.66%)	108,264 (58.83%)

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Calcium channel blockers	N (%)	52,484 (14.27%)	28,285 (8.86%)	1,767 (9.29%)	4,292 (16.45%)	1,089 (0.89%)	17,124 (9.31%)
	Drugs acid related disorder	N (%)	110,234 (29.96%)	110,242 (34.52%)	7,550 (39.68%)	22,527 (86.36%)	18,585 (15.14%)	99,074 (53.84%)
	Hormonal contraceptives (systemic)	N (%)	11,982 (3.26%)	436 (0.14%)	1,695 (8.91%)	12 (0.05%)	384 (0.31%)	1,360 (0.74%)
	Lipid modifying agents	N (%)	79,406 (21.58%)	44,664 (13.99%)	2,044 (10.74%)	4,438 (17.01%)	3,333 (2.71%)	23,405 (12.72%)
	Beta blocking agents	N (%)	91,810 (24.96%)	35,181 (11.02%)	3,431 (18.03%)	7,123 (27.31%)	2,975 (2.42%)	17,333 (9.42%)
Cancer (anytime to 366 days prior)	Prostate cancer	N (%)	7,316 (2.26%)	2,277 (1.19%)	281 (1.95%)	74 (0.47%)	584 (0.50%)	2,766 (1.78%)
	Breast cancer	N (%)	2,083 (0.64%)	354 (0.18%)	28 (0.19%)	175 (1.11%)	0 (0.00%)	3,514 (2.26%)
	Multiple myeloma	N (%)	607 (0.19%)	656 (0.34%)	219 (1.52%)	103 (0.66%)	21 (0.02%)	208 (0.13%)
	Pancreatic cancer	N (%)	193 (0.06%)	779 (0.41%)	211 (1.46%)	24 (0.15%)	81 (0.07%)	259 (0.17%)
	Lymphoma	N (%)	1,475 (0.45%)	1,301 (0.68%)	197 (1.37%)	92 (0.59%)	68 (0.06%)	635 (0.41%)
	Colorectal cancer	N (%)	3,155 (0.97%)	2,430 (1.26%)	836 (5.80%)	120 (0.76%)	879 (0.76%)	3,205 (2.06%)
	Ovarian cancer	N (%)	375 (0.12%)	235 (0.12%)	160 (1.11%)	20 (0.13%)	125 (0.11%)	276 (0.18%)
	Endometrial cancer	N (%)	170 (0.05%)	152 (0.08%)	30 (0.21%)	0 (0.00%)	28 (0.02%)	97 (0.06%)
	Lung cancer	N (%)	104 (0.03%)	1,877 (0.98%)	321 (2.23%)	71 (0.45%)	104 (0.09%)	1,103 (0.71%)
	Leukaemia	N (%)	989 (0.31%)	1,139 (0.59%)	242 (1.68%)	121 (0.77%)	60 (0.05%)	413 (0.27%)
Cancer (365 to 0 days prior)	Multiple myeloma	N (%)	642 (0.17%)	1,242 (0.39%)	491 (2.58%)	241 (0.92%)	18 (0.01%)	330 (0.18%)
	Lymphoma	N (%)	1,105 (0.30%)	2,628 (0.82%)	385 (2.02%)	194 (0.74%)	31 (0.03%)	657 (0.36%)
	Prostate cancer	N (%)	6,659 (1.81%)	4,575 (1.43%)	369 (1.94%)	301 (1.15%)	271 (0.22%)	2,378 (1.29%)

Variable name	Variable level	Estimate name	Data source					
			FinOMOP-ACI Varha	CDW Bordeaux	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Lung cancer	N (%)	214 (0.06%)	7,554 (2.37%)	1,036 (5.45%)	658 (2.52%)	139 (0.11%)	2,103 (1.14%)
	Endometrial cancer	N (%)	174 (0.05%)	447 (0.14%)	40 (0.21%)	0 (0.00%)	32 (0.03%)	244 (0.13%)
	Leukaemia	N (%)	1,172 (0.32%)	2,266 (0.71%)	521 (2.74%)	424 (1.63%)	24 (0.02%)	613 (0.33%)
	Pancreatic cancer	N (%)	758 (0.21%)	2,930 (0.92%)	1,032 (5.42%)	184 (0.71%)	122 (0.10%)	683 (0.37%)
	Breast cancer	N (%)	2,610 (0.71%)	301 (0.09%)	22 (0.12%)	441 (1.69%)	0 (0.00%)	3,007 (1.63%)
	Ovarian cancer	N (%)	350 (0.10%)	694 (0.22%)	318 (1.67%)	103 (0.39%)	36 (0.03%)	345 (0.19%)
	Colorectal cancer	N (%)	4,127 (1.12%)	7,021 (2.20%)	1,433 (7.53%)	530 (2.03%)	448 (0.36%)	3,207 (1.74%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

a. Default prescription duration was 31 days in EMDB-ULSEDV.

When analyses were stratified for history of cancer, new users of opioids with cancer history (**Table 16**, **Table 17**) were predominantly women (ranging from 50.1% to 64.8%), except for CDW Bordeaux, IMASIS, FinOMOP-ACI Varha, POLIMI, and EMDB-ULSEDV, whereas more men received new opioid prescriptions in these hospital data sources (ranging from 52.4% to 60.5%). The new opioid users with cancer history were older, with a median age ranging from 67 [57–75] in CDW Bordeaux to 73 [62–80] in HI-SPEED. When considering the type of cancer diagnosed within 1 year prior to opioid use, there were 6.8–17.3% of cancer opioid users with colorectal cancer, 0.7–12.8% with lung cancer, and 4.0–17.7% with prostate cancer. Median treatment duration ranged from 1 [1–6] day in IMASIS to 31 [11-106] days in SIDIAP.

Non-cancer opioid new users were generally younger (**Table 18**, **Table 19**), with median age ranging from 48 [32–63] in NLHR to 65 [51–76] in SUCD. 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 57.5% in NAJS) and anti-inflammatory and antirheumatic agents (ranging from 37.6% in CDW Bordeaux to 88.2% in FinOMOP-ACI Varha). 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 19 [10–29] days in HI-SPEED.

Table 16. Patient level characterisation of new users for opioids with history of cancer in primary care or national registries.

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
Number records	-	N	6,362	256,331	369,624	8,332	233,399	229,027	62,618	311,916	133,793
Number individuals	-	N	5,326	205,342	300,743	6,413	209,717	195,511	54,010	277,904	126,915
Age	-	Median [Q25–Q75]	70 [59–79]	70 [62–78]	72 [63–79]	67 [58–75]	67 [55–78]	70 [59–77]	71 [62–79]	73 [62–80]	70 [59–79]
		Range	3 to 109	1 to 105	1 to 107	18 to 101	1 to 105	1 to 105	1 to 106	1 to 111	1 to 109
Sex	Female	N (%)	3,558 (55.93%)	143,766 (56.09%)	190,660 (51.58%)	5,395 (64.75%)	118,592 (50.81%)	122,441 (53.46%)	35,134 (56.11%)	156,331 (50.12%)	68,838 (51.45%)
	Male	N (%)	2,804 (44.07%)	112,565 (43.91%)	178,964 (48.42%)	2,937 (35.25%)	114,807 (49.19%)	106,586 (46.54%)	27,484 (43.89%)	155,585 (49.88%)	64,955 (48.55%)
Days in cohort	-	Median [Q25–Q75]	10 [6–30]	30 [30–40] [a]	7 [3–16]	30 [30–30] [a]	30 [30–41] [a]	11 [4–17]	15 [9–30]	18 [10–37]	31 [11–106]
		Range	1 to 1,711	1 to 3,159	1 to 4,376	1 to 763	1 to 2,988	1 to 1,786	1 to 2,915	1 to 2,063	1 to 4,149
Comorbidities (inf to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	1,296 (20.40%)	29,480 (11.50%)	54,527 (14.75%)	1,200 (14.40%)	15,830 (6.78%)	31,536 (13.77%)	5,973 (9.54%)	19,834 (6.36%)	11,200 (8.37%)
	Osteoporosis	N (%)	824 (12.97%)	39,006 (15.22%)	46,583 (12.60%)	1,227 (14.73%)	7,689 (3.29%)	25,613 (11.18%)	3,331 (5.32%)	14,330 (4.59%)	10,607 (7.93%)
	Gastro-oesophageal reflux disease	N (%)	1,183 (18.62%)	65,293 (25.48%)	8,344 (2.26%)	3,255 (39.07%)	2,852 (1.22%)	17,458 (7.62%)	1,116 (1.78%)	10,930 (3.50%)	8,446 (6.31%)
	Obesity	N (%)	429 (6.75%)	19,363 (7.56%)	34,929 (9.45%)	1,823 (21.88%)	21,651 (9.28%)	17,544 (7.66%)	10,830 (17.30%)	17,103 (5.48%)	52,974 (39.60%)
	Venous thromboembolism	N (%)	368 (5.79%)	15,769 (6.15%)	20,254 (5.48%)	1,104 (13.25%)	6,234 (2.67%)	21,026 (9.18%)	2,612 (4.17%)	15,015 (4.81%)	5,222 (3.90%)
	Dementia	N (%)	99 (1.56%)	4,259 (1.66%)	8,069 (2.18%)	95 (1.14%)	4,120 (1.77%)	3,081 (1.35%)	767 (1.23%)	5,233 (1.68%)	2,953 (2.21%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Pneumonia	N (%)	499 (7.85%)	32,304 (12.60%)	136,290 (36.87%)	2,100 (25.20%)	13,395 (5.74%)	55,663 (24.30%)	6,354 (10.15%)	27,382 (8.78%)	8,837 (6.61%)
	Hypothyroidism	N (%)	756 (11.90%)	35,397 (13.81%)	24,454 (6.62%)	1,306 (15.67%)	26,788 (11.48%)	25,064 (10.94%)	2,499 (3.99%)	18,660 (5.98%)	9,007 (6.73%)
	Inflammatory bowel disease	N (%)	67 (1.05%)	3,305 (1.29%)	7,973 (2.16%)	173 (2.08%)	1,788 (0.77%)	4,387 (1.92%)	973 (1.55%)	6,322 (2.03%)	868 (0.65%)
	Depressive disorder	N (%)	680 (10.70%)	55,284 (21.57%)	87,143 (23.58%)	3,504 (42.05%)	14,827 (6.35%)	13,909 (6.07%)	3,562 (5.69%)	22,510 (7.22%)	15,805 (11.81%)
	Malignant neoplastic disease	N (%)	3,659 (57.59%)	146,982 (57.35%)	202,058 (54.67%)	5,651 (67.82%)	75,693 (32.43%)	147,159 (64.25%)	27,704 (44.25%)	158,644 (50.86%)	38,596 (28.85%)
	Chronic kidney disease (with renal impairment)	N (%)	220 (3.46%)	14,443 (5.64%)	15,221 (4.12%)	630 (7.56%)	27,975 (11.99%)	12,462 (5.44%)	5,522 (8.82%)	20,751 (6.65%)	14,536 (10.86%)
	Chronic liver disease	N (%)	27 (0.42%)	3,771 (1.47%)	5,399 (1.46%)	253 (3.04%)	2,962 (1.27%)	2,066 (0.90%)	273 (0.44%)	4,097 (1.31%)	2,558 (1.91%)
	Asthma	N (%)	1,064 (16.75%)	19,591 (7.64%)	75,440 (20.41%)	1,687 (20.25%)	6,199 (2.66%)	42,949 (18.75%)	4,525 (7.23%)	19,880 (6.37%)	4,760 (3.56%)
	Stroke	N (%)	205 (3.23%)	9,424 (3.68%)	29,467 (7.97%)	390 (4.68%)	5,613 (2.40%)	15,460 (6.75%)	2,651 (4.23%)	12,056 (3.87%)	4,867 (3.64%)
	Chronic kidney disease	N (%)	198 (3.12%)	11,886 (4.64%)	10,436 (2.82%)	485 (5.82%)	21,769 (9.33%)	8,154 (3.56%)	900 (1.44%)	15,288 (4.90%)	13,960 (10.43%)
	Type 2 diabetes	N (%)	978 (15.39%)	60,139 (23.47%)	54,056 (14.62%)	1,608 (19.30%)	41,522 (17.79%)	31,900 (13.93%)	11,048 (17.65%)	51,133 (16.39%)	32,729 (24.46%)
	HIV infection	N (%)	7 (0.11%)	95 (0.04%)	534 (0.14%)	13 (0.16%)	214 (0.09%)	404 (0.18%)	45 (0.07%)	362 (0.12%)	356 (0.27%)
	Rheumatoid arthritis	N (%)	133 (2.09%)	8,555 (3.34%)	12,824 (3.47%)	1,010 (12.12%)	3,719 (1.59%)	19,612 (8.56%)	1,474 (2.35%)	6,837 (2.19%)	965 (0.72%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Hypertension	N (%)	3,239 (50.98%)	188,902 (73.71%)	164,165 (44.41%)	5,982 (71.80%)	87,629 (37.55%)	116,158 (50.72%)	19,901 (31.79%)	126,222 (40.47%)	38,172 (28.53%)
	Myocardial infarction	N (%)	129 (2.03%)	8,442 (3.29%)	22,307 (6.04%)	415 (4.98%)	4,946 (2.12%)	11,389 (4.97%)	2,698 (4.31%)	8,894 (2.85%)	2,654 (1.98%)
	Anxiety	N (%)	1,293 (20.35%)	83,594 (32.62%)	39,800 (10.77%)	2,355 (28.26%)	7,125 (3.05%)	52,412 (22.88%)	12,143 (19.40%)	30,463 (9.77%)	25,449 (19.02%)
	Heart failure	N (%)	450 (7.08%)	17,424 (6.80%)	25,049 (6.78%)	3,478 (41.74%)	22,609 (9.69%)	21,904 (9.56%)	2,966 (4.74%)	23,084 (7.40%)	6,129 (4.58%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	964 (15.15%)	52,877 (20.63%)	1,590 (0.43%)	1,284 (15.41%)	2,138 (0.92%)	10,010 (4.37%)	384 (0.61%)	4,668 (1.50%)	2,108 (1.58%)
	Venous thromboembolism	N (%)	308 (4.84%)	12,748 (4.97%)	10,423 (2.82%)	375 (4.50%)	8,258 (3.54%)	11,823 (5.16%)	1,949 (3.11%)	10,924 (3.50%)	3,049 (2.28%)
	Obesity	N (%)	326 (5.12%)	13,015 (5.08%)	14,868 (4.02%)	922 (11.07%)	19,580 (8.39%)	8,690 (3.79%)	8,816 (14.08%)	12,753 (4.09%)	34,037 (25.44%)
	Malignant neoplastic disease [b]	N (%)	6,362 (100.00%)	251,907 (98.27%)	369,381 (99.93%)	8,332 (100.00%)	176,621 (75.67%)	229,027 (100.00%)	58,337 (93.16%)	286,484 (91.85%)	118,979 (88.93%)
	Stroke	N (%)	161 (2.53%)	7,905 (3.08%)	8,006 (2.17%)	138 (1.66%)	4,026 (1.72%)	8,234 (3.60%)	1,899 (3.03%)	6,098 (1.96%)	1,296 (0.97%)
	Heart failure	N (%)	385 (6.05%)	17,776 (6.93%)	15,873 (4.29%)	2,105 (25.26%)	25,478 (10.92%)	19,839 (8.66%)	2,512 (4.01%)	22,514 (7.22%)	2,324 (1.74%)
	Chronic kidney disease	N (%)	171 (2.69%)	13,458 (5.25%)	9,425 (2.55%)	412 (4.94%)	28,209 (12.09%)	7,023 (3.07%)	803 (1.28%)	15,700 (5.03%)	2,865 (2.14%)
	Depressive disorder	N (%)	863 (13.56%)	63,317 (24.70%)	95,674 (25.88%)	3,642 (43.71%)	22,356 (9.58%)	15,015 (6.56%)	4,203 (6.71%)	25,722 (8.25%)	18,186 (13.59%)
	Anxiety	N (%)	947 (14.89%)	64,910 (25.32%)	15,799 (4.27%)	885 (10.62%)	6,612 (2.83%)	12,975 (5.67%)	5,298 (8.46%)	16,398 (5.26%)	4,445 (3.32%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Type 2 diabetes	N (%)	1,140 (17.92%)	68,706 (26.80%)	60,555 (16.38%)	1,704 (20.45%)	49,685 (21.29%)	36,065 (15.75%)	12,169 (19.43%)	58,595 (18.79%)	35,691 (26.68%)
	Pneumonia	N (%)	341 (5.36%)	21,793 (8.50%)	59,159 (16.01%)	544 (6.53%)	19,057 (8.16%)	15,669 (6.84%)	3,519 (5.62%)	13,545 (4.34%)	3,578 (2.67%)
	Chronic liver disease	N (%)	25 (0.39%)	3,351 (1.31%)	4,002 (1.08%)	100 (1.20%)	4,334 (1.86%)	1,107 (0.48%)	192 (0.31%)	3,700 (1.19%)	586 (0.44%)
	Chronic kidney disease (with renal impairment)	N (%)	197 (3.10%)	16,419 (6.41%)	13,126 (3.55%)	517 (6.20%)	38,533 (16.51%)	11,830 (5.17%)	3,950 (6.31%)	21,523 (6.90%)	3,315 (2.48%)
	Myocardial infarction	N (%)	109 (1.71%)	7,332 (2.86%)	3,449 (0.93%)	102 (1.22%)	2,660 (1.14%)	5,347 (2.33%)	1,770 (2.83%)	3,342 (1.07%)	521 (0.39%)
	Chronic obstructive pulmonary disease	N (%)	1,048 (16.47%)	25,123 (9.80%)	41,849 (11.32%)	561 (6.73%)	20,916 (8.96%)	24,952 (10.89%)	4,414 (7.05%)	18,792 (6.02%)	2,743 (2.05%)
	Hypothyroidism	N (%)	683 (10.74%)	29,999 (11.70%)	22,130 (5.99%)	990 (11.88%)	30,191 (12.94%)	22,422 (9.79%)	1,394 (2.23%)	15,234 (4.88%)	1,495 (1.12%)
	Asthma	N (%)	704 (11.07%)	14,559 (5.68%)	33,908 (9.17%)	947 (11.37%)	5,269 (2.26%)	28,290 (12.35%)	2,334 (3.73%)	13,516 (4.33%)	665 (0.50%)
	Rheumatoid arthritis	N (%)	89 (1.40%)	6,016 (2.35%)	6,993 (1.89%)	282 (3.38%)	3,491 (1.50%)	13,353 (5.83%)	786 (1.26%)	5,515 (1.77%)	130 (0.10%)
	HIV infection	N (%)	<5	82 (0.03%)	534 (0.14%)	7 (0.08%)	274 (0.12%)	325 (0.14%)	35 (0.06%)	354 (0.11%)	55 (0.04%)
	Osteoporosis	N (%)	657 (10.33%)	28,376 (11.07%)	33,744 (9.13%)	483 (5.80%)	7,486 (3.21%)	15,148 (6.61%)	1,573 (2.51%)	10,206 (3.27%)	1,634 (1.22%)
	Hypertension	N (%)	2,969 (46.67%)	184,814 (72.10%)	100,845 (27.28%)	5,360 (64.33%)	103,409 (44.31%)	102,853 (44.91%)	12,566 (20.07%)	110,711 (35.49%)	4,622 (3.45%)
	Dementia	N (%)	95 (1.49%)	4,644 (1.81%)	7,747 (2.10%)	63 (0.76%)	7,700 (3.30%)	3,301 (1.44%)	827 (1.32%)	6,799 (2.18%)	1,011 (0.76%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Inflammatory bowel disease	N (%)	53 (0.83%)	2,434 (0.95%)	3,582 (0.97%)	55 (0.66%)	1,612 (0.69%)	2,355 (1.03%)	579 (0.92%)	5,169 (1.66%)	177 (0.13%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	639 (10.04%)	11,878 (4.63%)	46,676 (12.63%)	1,484 (17.81%)	34,427 (14.75%)	18,373 (8.02%)	4,936 (7.88%)	27,326 (8.76%)	23,091 (17.26%)
	Diuretics	N (%)	1,078 (16.94%)	73,791 (28.79%)	123,737 (33.48%)	1,497 (17.97%)	73,434 (31.46%)	30,230 (13.20%)	15,666 (25.02%)	93,507 (29.98%)	34,490 (25.78%)
	Drugs used in diabetes	N (%)	956 (15.03%)	53,287 (20.79%)	52,299 (14.15%)	1,184 (14.21%)	39,728 (17.02%)	27,896 (12.18%)	9,660 (15.43%)	51,588 (16.54%)	27,062 (20.23%)
	Antithrombotics	N (%)	1,122 (17.64%)	45,557 (17.77%)	98,084 (26.54%)	1,718 (20.62%)	75,152 (32.20%)	60,634 (26.47%)	16,777 (26.79%)	123,468 (39.58%)	37,092 (27.72%)
	Drugs for obstructive airway diseases	N (%)	1,899 (29.85%)	48,997 (19.11%)	89,172 (24.13%)	1,792 (21.51%)	65,937 (28.25%)	62,509 (27.29%)	18,393 (29.37%)	73,063 (23.42%)	43,824 (32.76%)
	Psycholeptics	N (%)	2,619 (41.17%)	155,350 (60.61%)	117,206 (31.71%)	3,418 (41.02%)	52,313 (22.41%)	87,872 (38.37%)	22,153 (35.38%)	114,509 (36.71%)	69,445 (51.90%)
	Agents acting on renin angiotensin system	N (%)	2,089 (32.84%)	143,940 (56.15%)	143,167 (38.73%)	4,025 (48.31%)	109,929 (47.10%)	82,404 (35.98%)	22,204 (35.46%)	133,118 (42.68%)	59,801 (44.70%)
	Antineoplastic agents [a]	N (%)	723 (11.36%)	26,002 (10.14%)	101,161 (27.37%)	865 (10.38%)	111,431 (47.74%)	19,754 (8.63%)	6,916 (11.04%)	55,957 (17.94%)	20,963 (15.67%)
	Antidepressants	N (%)	1,626 (25.56%)	28,748 (11.22%)	70,703 (19.13%)	1,410 (16.92%)	48,943 (20.97%)	31,624 (13.81%)	8,903 (14.22%)	69,022 (22.13%)	36,379 (27.19%)
	Antibacterials systemic	N (%)	3,036 (47.72%)	170,166 (66.39%)	210,286 (56.89%)	4,681 (56.18%)	129,765 (55.60%)	101,896 (44.49%)	27,247 (43.51%)	136,907 (43.89%)	72,792 (54.41%)
	Psychostimulants	N (%)	36 (0.57%)	7 (0.00%)	2,718 (0.74%)	39 (0.47%)	1,042 (0.45%)	982 (0.43%)	255 (0.41%)	4,430 (1.42%)	1,945 (1.45%)
	Immunosuppressants	N (%)	87 (1.37%)	4,080 (1.59%)	15,744 (4.26%)	258 (3.10%)	11,636 (4.99%)	10,512 (4.59%)	1,844 (2.94%)	16,270 (5.22%)	2,784 (2.08%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Antiinflammatory antirheumatic agents	N (%)	2,893 (45.47%)	166,664 (65.02%)	178,759 (48.36%)	5,332 (63.99%)	155,503 (66.63%)	111,277 (48.59%)	28,673 (45.79%)	193,456 (62.02%)	98,154 (73.36%)
	Calcium channel blockers	N (%)	923 (14.51%)	72,959 (28.46%)	93,693 (25.35%)	1,862 (22.35%)	51,001 (21.85%)	43,425 (18.96%)	11,964 (19.11%)	84,581 (27.12%)	23,456 (17.53%)
	Drugs acid related disorder	N (%)	2,951 (46.38%)	151,331 (59.04%)	184,496 (49.91%)	3,955 (47.47%)	138,912 (59.52%)	86,709 (37.86%)	38,004 (60.69%)	137,023 (43.93%)	100,119 (74.83%)
	Hormonal contraceptives (systemic)	N (%)	83 (1.30%)	10,799 (4.21%)	7,056 (1.91%)	131 (1.57%)	1,949 (0.84%)	7,825 (3.42%)	469 (0.75%)	9,902 (3.17%)	3,431 (2.56%)
	Lipid modifying agents	N (%)	2,293 (36.04%)	74,270 (28.97%)	132,781 (35.92%)	2,219 (26.63%)	65,913 (28.24%)	82,598 (36.06%)	22,980 (36.70%)	105,603 (33.86%)	49,295 (36.84%)
	Beta blocking agents	N (%)	2,155 (33.87%)	98,804 (38.55%)	89,792 (24.29%)	3,313 (39.76%)	86,348 (37.00%)	55,160 (24.08%)	18,739 (29.93%)	103,914 (33.31%)	25,944 (19.39%)
Cancer (inf to 366 days prior)	Prostate cancer	N (%)	679 (10.69%)	18,238 (7.12%)	35,129 (9.50%)	922 (11.07%)	6,615 (2.83%)	27,217 (11.88%)	3,362 (5.37%)	39,248 (12.58%)	3,697 (2.76%)
	Breast cancer	N (%)	0 (0.00%)	0 (0.00%)	32,528 (8.80%)	176 (2.11%)	0 (0.00%)	0 (0.00%)	5,792 (9.25%)	8,578 (2.75%)	11,915 (8.91%)
	Multiple myeloma	N (%)	69 (1.09%)	1,986 (0.77%)	4,472 (1.21%)	69 (0.83%)	2,014 (0.86%)	2,432 (1.06%)	378 (0.60%)	4,360 (1.40%)	424 (0.32%)
	Pancreatic cancer	N (%)	43 (0.68%)	1,191 (0.46%)	2,183 (0.59%)	86 (1.03%)	1,879 (0.81%)	1,355 (0.59%)	314 (0.50%)	1,855 (0.59%)	295 (0.22%)
	Lymphoma	N (%)	106 (1.67%)	5,181 (2.02%)	10,068 (2.72%)	304 (3.65%)	3,933 (1.69%)	7,269 (3.17%)	1,026 (1.64%)	8,345 (2.68%)	517 (0.39%)
	Colorectal cancer	N (%)	273 (4.30%)	21,448 (8.37%)	21,255 (5.75%)	635 (7.62%)	8,239 (3.53%)	16,108 (7.03%)	2,851 (4.55%)	10,971 (3.52%)	4,001 (2.99%)
	Ovarian cancer	N (%)	29 (0.46%)	3,303 (1.29%)	4,119 (1.11%)	200 (2.40%)	1,990 (0.85%)	3,076 (1.34%)	431 (0.69%)	2,213 (0.71%)	451 (0.34%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD Belgium	NAJS	DK-DHR	EBB	InGef RDB	NLHR	IPCI	HI-SPEED	SIDIAP
	Endometrial cancer	N (%)	34 (0.54%)	3,228 (1.26%)	500 (0.14%)	190 (2.28%)	777 (0.33%)	1,850 (0.81%)	306 (0.49%)	503 (0.16%)	437 (0.33%)
	Lung cancer	N (%)	166 (2.61%)	6,592 (2.57%)	13,024 (3.52%)	200 (2.40%)	2,909 (1.25%)	7,926 (3.46%)	2,408 (3.85%)	7,121 (2.28%)	1,502 (1.12%)
	Leukaemia	N (%)	170 (2.68%)	4,580 (1.79%)	10,058 (2.72%)	220 (2.64%)	3,549 (1.52%)	4,888 (2.13%)	804 (1.28%)	8,221 (2.64%)	897 (0.67%)
Cancer (365 to 0 days prior)	Multiple myeloma	N (%)	128 (2.01%)	3,583 (1.40%)	8,028 (2.17%)	140 (1.68%)	4,214 (1.81%)	3,563 (1.56%)	724 (1.16%)	6,759 (2.17%)	1,916 (1.43%)
	Lymphoma	N (%)	168 (2.64%)	7,011 (2.74%)	10,515 (2.84%)	414 (4.97%)	6,433 (2.76%)	8,619 (3.76%)	1,795 (2.87%)	10,880 (3.49%)	1,543 (1.15%)
	Prostate cancer	N (%)	986 (15.50%)	24,254 (9.46%)	44,123 (11.94%)	1,088 (13.06%)	14,648 (6.28%)	31,366 (13.70%)	4,808 (7.68%)	53,921 (17.29%)	5,964 (4.46%)
	Lung cancer	N (%)	492 (7.73%)	19,511 (7.61%)	38,027 (10.29%)	386 (4.63%)	8,322 (3.57%)	16,370 (7.15%)	7,976 (12.74%)	18,660 (5.98%)	17,175 (12.84%)
	Endometrial cancer	N (%)	58 (0.91%)	3,893 (1.52%)	21 (0.01%)	133 (1.60%)	1,765 (0.76%)	1,769 (0.77%)	571 (0.91%)	981 (0.31%)	1,168 (0.87%)
	Leukaemia	N (%)	237 (3.73%)	6,328 (2.47%)	13,007 (3.52%)	270 (3.24%)	5,659 (2.42%)	5,678 (2.48%)	1,252 (2.00%)	10,022 (3.21%)	2,143 (1.60%)
	Pancreatic cancer	N (%)	139 (2.18%)	5,816 (2.27%)	11,278 (3.05%)	214 (2.57%)	8,525 (3.65%)	4,292 (1.87%)	1,767 (2.82%)	8,486 (2.72%)	4,444 (3.32%)
	Breast cancer	N (%)	0 (0.00%)	0 (0.00%)	12,277 (3.32%)	39 (0.47%)	0 (0.00%)	0 (0.00%)	8,124 (12.97%)	4,055 (1.30%)	9,616 (7.19%)
	Ovarian cancer	N (%)	67 (1.05%)	5,201 (2.03%)	6,546 (1.77%)	232 (2.78%)	3,618 (1.55%)	4,325 (1.89%)	791 (1.26%)	4,192 (1.34%)	1,392 (1.04%)
	Colorectal cancer	N (%)	434 (6.82%)	34,408 (13.42%)	37,055 (10.03%)	879 (10.55%)	17,570 (7.53%)	24,868 (10.86%)	5,361 (8.56%)	31,114 (9.98%)	11,098 (8.29%)

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

a. History of cancer was defined as cancer-related observation or condition within 1 year before index date (inclusive), or use of antineoplastic agents within 1 year before index date (inclusive).
b. Default prescription duration was 30 days in NAJS (1 day for secondary conciliatory care), EBB, and InGef RDB.

Table 17. Patient level characterisation of new users for opioids with history of cancer in hospital data sources.

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
Number records	-	N	63,876	41,536	9,463	7,111	3,253	26,348
Number individuals	-	N	55,979	33,932	8,906	6,765	3,018	21,560
Age	-	Median [Q25–Q75]	67 [57–75]	69 [60–77]	67 [57–74]	68 [58–77]	69 [59–78]	70 [59–79]
		Range	0 to 106	0 to 101	0 to 98	0 to 100	17 to 102	3 to 104
Sex	Female	N (%)	25,210 (39.47%)	19,292 (46.45%)	5,302 (56.03%)	3,353 (47.15%)	1,548 (47.59%)	12,265 (46.55%)
	Male	N (%)	38,663 (60.53%)	22,244 (53.55%)	4,161 (43.97%)	3,758 (52.85%)	1,705 (52.41%)	14,083 (53.45%)
	None	N (%)	<5	-	-	-	-	-
Days in cohort	-	Median [Q25–Q75]	3 [1–7]	11 [2–44]	24 [11–31]	4 [2–10]	31 [31–31] [a]	1 [1–6]
		Range	1 to 2,114	1 to 4,761	1 to 381	1 to 497	1 to 263	1 to 1,276
Comorbidities (inf to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	2,321 (6.10%)	1,529 (4.06%)	577 (8.71%)	126 (2.88%)	129 (4.15%)	2,857 (12.39%)
	Osteoporosis	N (%)	946 (2.49%)	610 (1.62%)	446 (6.73%)	33 (0.76%)	52 (1.67%)	1,363 (5.91%)
	Gastro-oesophageal reflux disease	N (%)	1,269 (3.33%)	1,336 (3.55%)	521 (7.86%)	7 (0.16%)	20 (0.64%)	357 (1.55%)
	Obesity	N (%)	3,917 (10.29%)	1,198 (3.18%)	189 (2.85%)	42 (0.96%)	350 (11.25%)	4,147 (17.98%)
	Venous thromboembolism	N (%)	1,546 (4.06%)	833 (2.21%)	227 (3.43%)	70 (1.60%)	39 (1.25%)	734 (3.18%)
	Dementia	N (%)	396 (1.04%)	461 (1.22%)	36 (0.54%)	11 (0.25%)	22 (0.71%)	350 (1.52%)
	Pneumonia	N (%)	2,522 (6.63%)	3,155 (8.38%)	418 (6.31%)	311 (7.12%)	117 (3.76%)	1,930 (8.37%)
	Hypothyroidism	N (%)	2,173 (5.71%)	1,836 (4.87%)	238 (3.59%)	40 (0.92%)	42 (1.35%)	1,151 (4.99%)
	Inflammatory bowel disease	N (%)	249 (0.65%)	987 (2.62%)	115 (1.74%)	24 (0.55%)	9 (0.29%)	152 (0.66%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Depressive disorder	N (%)	2,626 (6.90%)	1,707 (4.53%)	336 (5.07%)	15 (0.34%)	256 (8.23%)	2,575 (11.17%)
	Malignant neoplastic disease	N (%)	16,669 (43.80%)	15,938 (42.31%)	3,993 (60.25%)	1,187 (27.17%)	1,241 (39.90%)	9,464 (41.04%)
	Chronic kidney disease (with renal impairment)	N (%)	3,697 (9.71%)	1,393 (3.70%)	387 (5.84%)	244 (5.59%)	124 (3.99%)	2,846 (12.34%)
	Chronic liver disease	N (%)	1,684 (4.42%)	399 (1.06%)	130 (1.96%)	444 (10.16%)	49 (1.58%)	1,481 (6.42%)
	Asthma	N (%)	921 (2.42%)	1,868 (4.96%)	194 (2.93%)	21 (0.48%)	68 (2.19%)	850 (3.69%)
	Stroke	N (%)	962 (2.53%)	1,889 (5.01%)	323 (4.87%)	47 (1.08%)	57 (1.83%)	699 (3.03%)
	Chronic kidney disease	N (%)	2,549 (6.70%)	954 (2.53%)	325 (4.90%)	122 (2.79%)	74 (2.38%)	1,948 (8.45%)
	Type 2 diabetes	N (%)	4,355 (11.44%)	7,039 (18.69%)	761 (11.48%)	345 (7.90%)	555 (17.85%)	5,771 (25.02%)
	HIV infection	N (%)	366 (0.96%)	30 (0.08%)	<5	8 (0.18%)	<5	246 (1.07%)
	Rheumatoid arthritis	N (%)	381 (1.00%)	1,004 (2.67%)	48 (0.72%)	7 (0.16%)	17 (0.55%)	159 (0.69%)
	Hypertension	N (%)	11,446 (30.07%)	10,987 (29.17%)	3,053 (46.07%)	416 (9.52%)	983 (31.61%)	9,238 (40.06%)
	Myocardial infarction	N (%)	672 (1.77%)	1,552 (4.12%)	104 (1.57%)	27 (0.62%)	72 (2.32%)	723 (3.13%)
	Anxiety	N (%)	3,475 (9.13%)	1,108 (2.94%)	330 (4.98%)	19 (0.43%)	113 (3.63%)	1,398 (6.06%)
	Heart failure	N (%)	1,922 (5.05%)	1,914 (5.08%)	404 (6.10%)	109 (2.50%)	149 (4.79%)	1,831 (7.94%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	2,601 (4.07%)	286 (0.69%)	609 (6.44%)	5 (0.07%)	21 (0.65%)	346 (1.31%)
	Venous thromboembolism	N (%)	3,320 (5.20%)	577 (1.39%)	382 (4.04%)	241 (3.39%)	54 (1.66%)	859 (3.26%)
	Obesity	N (%)	9,773 (15.30%)	747 (1.80%)	130 (1.37%)	41 (0.58%)	291 (8.95%)	5,549 (21.06%)
	Malignant neoplastic disease [b]	N (%)	63,857 (99.97%)	35,840 (86.29%)	9,383 (99.15%)	6,777 (95.30%)	3,252 (99.97%)	26,348 (100.00%)
	Stroke	N (%)	1,365 (2.14%)	799 (1.92%)	283 (2.99%)	65 (0.91%)	39 (1.20%)	457 (1.73%)
	Heart failure	N (%)	3,542 (5.55%)	1,491 (3.59%)	574 (6.07%)	241 (3.39%)	209 (6.42%)	2,328 (8.84%)
	Chronic kidney disease	N (%)	5,130 (8.03%)	827 (1.99%)	512 (5.41%)	185 (2.60%)	121 (3.72%)	2,962 (11.24%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Depressive disorder	N (%)	5,973 (9.35%)	1,851 (4.46%)	258 (2.73%)	26 (0.37%)	443 (13.62%)	3,956 (15.01%)
	Anxiety	N (%)	8,941 (14.00%)	309 (0.74%)	341 (3.60%)	11 (0.15%)	81 (2.49%)	1,059 (4.02%)
	Type 2 diabetes	N (%)	10,925 (17.10%)	10,394 (25.02%)	1,406 (14.86%)	1,329 (18.69%)	800 (24.59%)	9,367 (35.55%)
	Pneumonia	N (%)	4,929 (7.72%)	1,737 (4.18%)	646 (6.83%)	811 (11.40%)	143 (4.40%)	1,577 (5.99%)
	Chronic liver disease	N (%)	2,970 (4.65%)	330 (0.79%)	132 (1.39%)	788 (11.08%)	36 (1.11%)	1,631 (6.19%)
	Chronic kidney disease (with renal impairment)	N (%)	7,655 (11.98%)	1,208 (2.91%)	687 (7.26%)	613 (8.62%)	201 (6.18%)	4,501 (17.08%)
	Myocardial infarction	N (%)	537 (0.84%)	710 (1.71%)	36 (0.38%)	45 (0.63%)	19 (0.58%)	387 (1.47%)
	Chronic obstructive pulmonary disease	N (%)	6,556 (10.26%)	1,169 (2.81%)	917 (9.69%)	168 (2.36%)	148 (4.55%)	3,485 (13.23%)
	Hypothyroidism	N (%)	5,457 (8.54%)	1,011 (2.43%)	234 (2.47%)	44 (0.62%)	64 (1.97%)	1,630 (6.19%)
	Asthma	N (%)	1,927 (3.02%)	903 (2.17%)	197 (2.08%)	12 (0.17%)	53 (1.63%)	902 (3.42%)
	Rheumatoid arthritis	N (%)	733 (1.15%)	641 (1.54%)	42 (0.44%)	10 (0.14%)	19 (0.58%)	157 (0.60%)
	HIV infection	N (%)	373 (0.58%)	25 (0.06%)	<5	13 (0.18%)	7 (0.22%)	304 (1.15%)
	Osteoporosis	N (%)	1,490 (2.33%)	323 (0.78%)	346 (3.66%)	18 (0.25%)	43 (1.32%)	1,561 (5.92%)
	Hypertension	N (%)	27,569 (43.16%)	6,536 (15.74%)	3,667 (38.75%)	324 (4.56%)	960 (29.51%)	12,448 (47.24%)
	Dementia	N (%)	1,088 (1.70%)	385 (0.93%)	59 (0.62%)	38 (0.53%)	51 (1.57%)	663 (2.52%)
	Inflammatory bowel disease	N (%)	443 (0.69%)	935 (2.25%)	96 (1.01%)	35 (0.49%)	<5	181 (0.69%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	8,784 (13.75%)	6,170 (14.85%)	574 (6.07%)	1,094 (15.38%)	614 (18.87%)	3,449 (13.09%)
	Diuretics	N (%)	7,977 (12.49%)	11,640 (28.02%)	1,538 (16.25%)	2,424 (34.09%)	558 (17.15%)	5,686 (21.58%)
	Drugs used in diabetes	N (%)	7,222 (11.31%)	8,610 (20.73%)	576 (6.09%)	1,213 (17.06%)	280 (8.61%)	6,464 (24.53%)
	Antithrombotics	N (%)	23,771 (37.21%)	21,934 (52.81%)	3,004 (31.74%)	4,018 (56.50%)	894 (27.48%)	13,238 (50.24%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Drugs for obstructive airway diseases	N (%)	7,142 (11.18%)	9,824 (23.65%)	524 (5.54%)	1,118 (15.72%)	376 (11.56%)	8,392 (31.85%)
	Psycholeptics	N (%)	34,796 (54.47%)	22,493 (54.15%)	1,210 (12.79%)	2,109 (29.66%)	996 (30.62%)	19,993 (75.88%)
	Agents acting on renin angiotensin system	N (%)	9,013 (14.11%)	16,398 (39.48%)	1,366 (14.44%)	2,029 (28.53%)	170 (5.23%)	5,069 (19.24%)
	Antineoplastic agents [a]	N (%)	9,505 (14.88%)	12,353 (29.74%)	2,664 (28.15%)	968 (13.61%)	<5	3,882 (14.73%)
	Antidepressants	N (%)	6,204 (9.71%)	5,784 (13.93%)	416 (4.40%)	730 (10.27%)	655 (20.14%)	3,264 (12.39%)
	Antibacterials systemic	N (%)	18,075 (28.30%)	22,670 (54.58%)	2,751 (29.07%)	4,382 (61.62%)	1,687 (51.86%)	18,156 (68.91%)
	Psychostimulants	N (%)	71 (0.11%)	67 (0.16%)	173 (1.83%)	14 (0.20%)	<5	45 (0.17%)
	Immunosuppressants	N (%)	2,449 (3.83%)	2,670 (6.43%)	423 (4.47%)	432 (6.08%)	11 (0.34%)	531 (2.02%)
	Antiinflammatory antirheumatic agents	N (%)	25,563 (40.02%)	39,039 (93.99%)	3,947 (41.71%)	4,673 (65.72%)	1,872 (57.55%)	18,819 (71.42%)
	Calcium channel blockers	N (%)	8,288 (12.98%)	9,094 (21.89%)	619 (6.54%)	1,272 (17.89%)	85 (2.61%)	3,186 (12.09%)
	Drugs acid related disorder	N (%)	31,006 (48.54%)	18,742 (45.12%)	4,010 (42.38%)	6,422 (90.31%)	1,596 (49.06%)	18,940 (71.88%)
	Hormonal contraceptives (systemic)	N (%)	65 (0.10%)	717 (1.73%)	1,665 (17.59%)	7 (0.10%)	8 (0.25%)	312 (1.18%)
	Lipid modifying agents	N (%)	12,396 (19.41%)	12,853 (30.94%)	644 (6.81%)	1,435 (20.18%)	304 (9.35%)	5,029 (19.09%)
	Beta blocking agents	N (%)	9,970 (15.61%)	14,103 (33.95%)	1,357 (14.34%)	2,188 (30.77%)	247 (7.59%)	3,950 (14.99%)
Cancer (inf to 366 days prior)	Prostate cancer	N (%)	1,673 (4.40%)	4,685 (12.44%)	260 (3.92%)	27 (0.62%)	208 (6.69%)	1,599 (6.93%)
	Breast cancer	N (%)	238 (0.63%)	1,268 (3.37%)	18 (0.27%)	109 (2.50%)	0 (0.00%)	1,400 (6.07%)
	Multiple myeloma	N (%)	606 (1.59%)	486 (1.29%)	212 (3.20%)	97 (2.22%)	9 (0.29%)	161 (0.70%)
	Pancreatic cancer	N (%)	683 (1.79%)	148 (0.39%)	202 (3.05%)	11 (0.25%)	36 (1.16%)	150 (0.65%)
	Lymphoma	N (%)	1,054 (2.77%)	987 (2.62%)	186 (2.81%)	71 (1.63%)	14 (0.45%)	354 (1.53%)
	Colorectal cancer	N (%)	1,891 (4.97%)	1,909 (5.07%)	777 (11.72%)	57 (1.30%)	250 (8.04%)	1,557 (6.75%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Ovarian cancer	N (%)	180 (0.47%)	210 (0.56%)	155 (2.34%)	12 (0.27%)	29 (0.93%)	149 (0.65%)
	Endometrial cancer	N (%)	113 (0.30%)	54 (0.14%)	26 (0.39%)	0 (0.00%)	16 (0.51%)	61 (0.26%)
	Lung cancer	N (%)	1,636 (4.30%)	91 (0.24%)	301 (4.54%)	45 (1.03%)	52 (1.67%)	709 (3.07%)
	Leukaemia	N (%)	1,003 (2.64%)	710 (1.88%)	236 (3.56%)	92 (2.11%)	18 (0.58%)	259 (1.12%)
Cancer (365 to 0 days prior)	Multiple myeloma	N (%)	1,285 (2.01%)	751 (1.81%)	499 (5.27%)	246 (3.46%)	40 (1.23%)	385 (1.46%)
	Lymphoma	N (%)	2,768 (4.33%)	1,502 (3.62%)	392 (4.14%)	202 (2.84%)	39 (1.20%)	764 (2.90%)
	Prostate cancer	N (%)	4,740 (7.42%)	7,341 (17.67%)	377 (3.98%)	307 (4.32%)	345 (10.61%)	2,713 (10.30%)
	Lung cancer	N (%)	7,878 (12.33%)	303 (0.73%)	1,085 (11.47%)	679 (9.55%)	229 (7.04%)	2,400 (9.11%)
	Endometrial cancer	N (%)	465 (0.73%)	204 (0.49%)	43 (0.45%)	0 (0.00%)	41 (1.26%)	273 (1.04%)
	Leukaemia	N (%)	2,329 (3.65%)	1,315 (3.17%)	524 (5.54%)	428 (6.02%)	34 (1.05%)	672 (2.55%)
	Pancreatic cancer	N (%)	3,066 (4.80%)	1,058 (2.55%)	1,051 (11.11%)	191 (2.69%)	174 (5.35%)	807 (3.06%)
	Breast cancer	N (%)	317 (0.50%)	2,962 (7.13%)	23 (0.24%)	446 (6.27%)	0 (0.00%)	3,208 (12.18%)
	Ovarian cancer	N (%)	721 (1.13%)	431 (1.04%)	320 (3.38%)	105 (1.48%)	61 (1.88%)	408 (1.55%)
	Colorectal cancer	N (%)	7,245 (11.34%)	4,934 (11.88%)	1,442 (15.24%)	548 (7.71%)	564 (17.34%)	3,641 (13.82%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

a. Default prescription duration was 31 days in EMDB-ULSEDV.
b. History of cancer was defined as cancer-related observation or condition within 1 year before index date (inclusive), or use of antineoplastic agents within 1 year before index date (inclusive).

Table 18. Patient level characterisation of new users for opioids without history of cancer in primary care or national registries.

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
Number records	-	N	282,114	1,739,288	3,349,560	82,390	3,247,905	645,024	2,299,573	3,280,105	3,009,227
Number individuals	-	N	202,947	1,230,842	2,061,948	56,367	2,400,954	458,775	1,781,024	2,155,971	2,426,600
Age	-	Median [Q25–Q75]	50 [34–64]	58 [42–70]	57 [42–72]	53 [41–65]	50 [30–63]	56 [42–69]	48 [32–63]	55 [40–70]	54 [37–70]
		Range	1 to 116	1 to 108	1 to 110	9 to 104	0 to 110	1 to 105	1 to 110	1 to 116	1 to 112
Sex	Female	N (%)	157,200 (55.72%)	1,049,305 (60.33%)	1,905,859 (56.90%)	57,236 (69.47%)	1,776,604 (54.70%)	390,791 (60.59%)	1,257,823 (54.70%)	1,933,754 (58.95%)	1,689,787 (56.15%)
	Male	N (%)	124,914 (44.28%)	689,983 (39.67%)	1,443,701 (43.10%)	25,154 (30.53%)	1,471,301 (45.30%)	254,233 (39.41%)	1,041,750 (45.30%)	1,346,351 (41.05%)	1,319,440 (43.85%)
	None	N (%)	-	-	-	-	-	-	-	-	-
Days in cohort	-	Median [Q25–Q75]	7 [6–20]	30 [30–30] [a]	6 [3–13]	30 [30–30] [a]	30 [30–30] [a]	10 [7–15]	11 [5–14]	11 [7–31]	19 [10–29]
		Range	1 to 2,527	1 to 3,258	1 to 4,454	1 to 4,009	1 to 3,228	1 to 3,668	1 to 1,785	1 to 4,198	1 to 2,068
Comorbidities (inf to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	31,641 (11.22%)	111,289 (6.40%)	249,800 (7.46%)	6,017 (7.30%)	67,717 (2.09%)	25,425 (3.94%)	123,187 (5.36%)	105,546 (3.22%)	76,340 (2.54%)
	Osteoporosis	N (%)	12,809 (4.54%)	146,903 (8.45%)	242,297 (7.23%)	6,181 (7.50%)	38,706 (1.19%)	15,294 (2.37%)	98,263 (4.27%)	166,437 (5.07%)	66,472 (2.21%)
	Gastro-oesophageal reflux disease	N (%)	40,326 (14.30%)	338,689 (19.48%)	67,684 (2.02%)	27,708 (33.63%)	20,785 (0.64%)	9,561 (1.48%)	108,548 (4.72%)	167,009 (5.09%)	75,761 (2.52%)
	Obesity	N (%)	14,447 (5.12%)	122,787 (7.06%)	356,470 (10.64%)	17,259 (20.95%)	180,877 (5.57%)	93,322 (14.47%)	191,659 (8.33%)	1,092,844 (33.32%)	169,340 (5.63%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Venous thromboembolism	N (%)	6,253 (2.22%)	59,512 (3.42%)	100,884 (3.01%)	6,547 (7.95%)	24,919 (0.77%)	12,766 (1.98%)	86,681 (3.77%)	70,756 (2.16%)	58,643 (1.95%)
	Dementia	N (%)	1,394 (0.49%)	19,102 (1.10%)	74,572 (2.23%)	569 (0.69%)	34,801 (1.07%)	4,511 (0.70%)	14,086 (0.61%)	41,115 (1.25%)	38,523 (1.28%)
	Pneumonia	N (%)	10,349 (3.67%)	145,139 (8.35%)	958,650 (28.62%)	15,626 (18.97%)	62,485 (1.92%)	38,321 (5.94%)	345,786 (15.04%)	160,028 (4.88%)	140,396 (4.67%)
	Hypothyroidism	N (%)	19,425 (6.89%)	180,667 (10.39%)	169,507 (5.06%)	9,932 (12.05%)	176,529 (5.44%)	19,099 (2.96%)	156,074 (6.79%)	207,745 (6.33%)	132,808 (4.41%)
	Inflammatory bowel disease	N (%)	2,017 (0.72%)	16,135 (0.93%)	70,074 (2.09%)	1,278 (1.55%)	14,734 (0.45%)	5,315 (0.82%)	33,563 (1.46%)	15,084 (0.46%)	39,102 (1.30%)
	Depressive disorder	N (%)	22,338 (7.92%)	288,993 (16.62%)	779,370 (23.27%)	31,981 (38.82%)	146,410 (4.51%)	37,186 (5.77%)	184,994 (8.04%)	333,452 (10.17%)	251,211 (8.35%)
	Malignant neoplastic disease	N (%)	5,128 (1.82%)	86,957 (5.00%)	323,839 (9.67%)	6,154 (7.47%)	99,022 (3.05%)	46,566 (7.22%)	207,057 (9.00%)	264,078 (8.05%)	225,577 (7.50%)
	Chronic kidney disease (with renal impairment)	N (%)	1,874 (0.66%)	41,456 (2.38%)	62,313 (1.86%)	2,313 (2.81%)	123,979 (3.82%)	27,746 (4.30%)	36,862 (1.60%)	173,145 (5.28%)	74,503 (2.48%)
	Chronic liver disease	N (%)	507 (0.18%)	15,765 (0.91%)	28,439 (0.85%)	2,068 (2.51%)	12,772 (0.39%)	1,497 (0.23%)	15,313 (0.67%)	30,452 (0.93%)	24,951 (0.83%)
	Asthma	N (%)	43,474 (15.42%)	124,108 (7.14%)	688,159 (20.54%)	14,008 (17.00%)	55,880 (1.72%)	44,922 (6.97%)	402,358 (17.50%)	142,140 (4.33%)	194,797 (6.47%)
	Stroke	N (%)	2,981 (1.06%)	38,008 (2.19%)	159,578 (4.76%)	1,848 (2.24%)	34,573 (1.06%)	13,078 (2.03%)	62,088 (2.70%)	60,312 (1.84%)	56,845 (1.89%)
	Chronic kidney disease	N (%)	1,649 (0.58%)	33,631 (1.93%)	43,051 (1.29%)	1,674 (2.03%)	96,730 (2.98%)	7,494 (1.16%)	25,574 (1.11%)	166,149 (5.07%)	55,068 (1.83%)
	Type 2 diabetes	N (%)	23,671 (8.40%)	256,824 (14.77%)	329,731 (9.84%)	9,531 (11.57%)	292,284 (9.00%)	69,194 (10.73%)	173,394 (7.54%)	481,061 (14.67%)	278,046 (9.24%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	HIV infection	N (%)	293 (0.10%)	664 (0.04%)	4,095 (0.12%)	190 (0.23%)	1,813 (0.06%)	369 (0.06%)	3,181 (0.14%)	7,501 (0.23%)	3,074 (0.10%)
	Rheumatoid arthritis	N (%)	2,475 (0.88%)	45,240 (2.60%)	84,124 (2.51%)	8,519 (10.34%)	22,477 (0.69%)	9,209 (1.43%)	108,987 (4.74%)	18,846 (0.57%)	39,852 (1.32%)
	Hypertension	N (%)	77,803 (27.59%)	897,153 (51.59%)	914,567 (27.30%)	40,268 (48.87%)	533,272 (16.42%)	116,465 (18.06%)	556,581 (24.20%)	622,255 (18.97%)	611,956 (20.34%)
	Myocardial infarction	N (%)	2,407 (0.85%)	35,236 (2.03%)	116,444 (3.48%)	1,817 (2.21%)	31,886 (0.98%)	13,660 (2.12%)	49,190 (2.14%)	36,206 (1.10%)	44,786 (1.49%)
	Anxiety	N (%)	44,362 (15.73%)	451,816 (25.98%)	397,737 (11.87%)	23,017 (27.94%)	66,609 (2.05%)	133,248 (20.67%)	640,787 (27.87%)	733,556 (22.36%)	387,864 (12.89%)
	Heart failure	N (%)	5,424 (1.92%)	60,898 (3.50%)	119,704 (3.57%)	18,123 (22.00%)	118,671 (3.65%)	12,988 (2.01%)	74,189 (3.23%)	70,892 (2.16%)	93,366 (3.10%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	24,973 (8.85%)	242,375 (13.94%)	10,345 (0.31%)	9,439 (11.46%)	7,191 (0.22%)	2,688 (0.42%)	41,418 (1.80%)	34,968 (1.07%)	26,396 (0.88%)
	Venous thromboembolism	N (%)	3,251 (1.15%)	36,620 (2.11%)	22,138 (0.66%)	1,292 (1.57%)	10,651 (0.33%)	5,219 (0.81%)	28,658 (1.25%)	15,974 (0.49%)	21,558 (0.72%)
	Obesity	N (%)	10,850 (3.85%)	86,046 (4.95%)	128,187 (3.83%)	9,026 (10.96%)	123,810 (3.81%)	80,105 (12.42%)	112,849 (4.91%)	715,193 (21.80%)	112,163 (3.73%)
	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%)	0 (0.00%)
	Stroke	N (%)	2,074 (0.74%)	30,346 (1.74%)	35,740 (1.07%)	566 (0.69%)	16,138 (0.50%)	8,198 (1.27%)	30,586 (1.33%)	12,687 (0.39%)	24,008 (0.80%)
	Heart failure	N (%)	4,061 (1.44%)	56,068 (3.22%)	67,231 (2.01%)	8,819 (10.70%)	81,707 (2.52%)	9,448 (1.46%)	62,227 (2.71%)	20,884 (0.64%)	72,855 (2.42%)
	Chronic kidney disease	N (%)	1,092 (0.39%)	31,615 (1.82%)	32,327 (0.97%)	1,109 (1.35%)	75,574 (2.33%)	7,324 (1.14%)	16,992 (0.74%)	33,643 (1.03%)	48,311 (1.61%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Depressive disorder	N (%)	26,421 (9.37%)	325,407 (18.71%)	823,891 (24.60%)	33,303 (40.42%)	183,266 (5.64%)	43,815 (6.79%)	202,286 (8.80%)	369,466 (11.26%)	278,702 (9.26%)
	Anxiety	N (%)	24,820 (8.80%)	323,162 (18.58%)	115,368 (3.44%)	7,514 (9.12%)	29,761 (0.92%)	54,508 (8.45%)	178,228 (7.75%)	115,427 (3.52%)	174,106 (5.79%)
	Type 2 diabetes	N (%)	27,795 (9.85%)	292,889 (16.84%)	363,922 (10.86%)	10,222 (12.41%)	331,484 (10.21%)	75,594 (11.72%)	203,931 (8.87%)	511,394 (15.59%)	315,564 (10.49%)
	Pneumonia	N (%)	5,429 (1.92%)	68,756 (3.95%)	268,470 (8.02%)	2,325 (2.82%)	39,736 (1.22%)	17,447 (2.70%)	52,802 (2.30%)	35,838 (1.09%)	48,827 (1.62%)
	Chronic liver disease	N (%)	331 (0.12%)	10,103 (0.58%)	15,435 (0.46%)	631 (0.77%)	9,347 (0.29%)	768 (0.12%)	5,764 (0.25%)	3,267 (0.10%)	14,051 (0.47%)
	Chronic kidney disease (with renal impairment)	N (%)	1,250 (0.44%)	37,462 (2.15%)	41,688 (1.24%)	1,471 (1.79%)	95,077 (2.93%)	18,835 (2.92%)	25,407 (1.10%)	35,932 (1.10%)	61,019 (2.03%)
	Myocardial infarction	N (%)	1,804 (0.64%)	32,191 (1.85%)	18,559 (0.55%)	483 (0.59%)	12,938 (0.40%)	8,552 (1.33%)	23,012 (1.00%)	6,624 (0.20%)	14,648 (0.49%)
	Chronic obstructive pulmonary disease	N (%)	19,523 (6.92%)	78,845 (4.53%)	156,946 (4.69%)	2,126 (2.58%)	44,719 (1.38%)	17,116 (2.65%)	82,482 (3.59%)	18,625 (0.57%)	55,630 (1.85%)
	Hypothyroidism	N (%)	15,449 (5.48%)	142,473 (8.19%)	139,519 (4.17%)	6,397 (7.76%)	100,425 (3.09%)	9,979 (1.55%)	130,882 (5.69%)	26,307 (0.80%)	82,703 (2.75%)
	Asthma	N (%)	29,954 (10.62%)	90,655 (5.21%)	268,680 (8.02%)	6,989 (8.48%)	25,882 (0.80%)	23,155 (3.59%)	234,961 (10.22%)	20,123 (0.61%)	103,747 (3.45%)
	Rheumatoid arthritis	N (%)	1,498 (0.53%)	31,863 (1.83%)	44,239 (1.32%)	2,481 (3.01%)	13,231 (0.41%)	4,756 (0.74%)	73,395 (3.19%)	2,648 (0.08%)	29,381 (0.98%)
	HIV infection	N (%)	161 (0.06%)	542 (0.03%)	4,035 (0.12%)	110 (0.13%)	1,273 (0.04%)	229 (0.04%)	2,484 (0.11%)	530 (0.02%)	2,897 (0.10%)
	Osteoporosis	N (%)	7,720 (2.74%)	105,824 (6.08%)	166,522 (4.97%)	2,319 (2.81%)	28,209 (0.87%)	6,633 (1.03%)	59,339 (2.58%)	19,303 (0.59%)	41,729 (1.39%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Hypertension	N (%)	65,856 (23.34%)	868,179 (49.92%)	499,516 (14.91%)	33,595 (40.78%)	344,995 (10.62%)	70,233 (10.89%)	490,132 (21.31%)	72,519 (2.21%)	435,659 (14.48%)
	Dementia	N (%)	1,051 (0.37%)	19,594 (1.13%)	60,142 (1.80%)	233 (0.28%)	42,728 (1.32%)	4,087 (0.63%)	13,991 (0.61%)	11,180 (0.34%)	38,057 (1.26%)
	Inflammatory bowel disease	N (%)	1,376 (0.49%)	12,073 (0.69%)	33,562 (1.00%)	374 (0.45%)	7,904 (0.24%)	2,892 (0.45%)	19,689 (0.86%)	2,704 (0.08%)	27,597 (0.92%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	12,764 (4.52%)	54,440 (3.13%)	269,122 (8.03%)	11,297 (13.71%)	175,729 (5.41%)	28,300 (4.39%)	99,044 (4.31%)	380,463 (11.60%)	179,316 (5.96%)
	Diuretics	N (%)	16,122 (5.71%)	256,733 (14.76%)	611,241 (18.25%)	6,274 (7.62%)	381,786 (11.75%)	87,547 (13.57%)	105,139 (4.57%)	416,629 (12.70%)	448,207 (14.89%)
	Drugs used in diabetes	N (%)	23,304 (8.26%)	219,023 (12.59%)	313,686 (9.36%)	6,917 (8.40%)	279,197 (8.60%)	61,633 (9.56%)	165,239 (7.19%)	370,775 (11.30%)	292,313 (9.71%)
	Antithrombotics	N (%)	15,331 (5.43%)	158,608 (9.12%)	512,873 (15.31%)	7,457 (9.05%)	394,786 (12.16%)	89,829 (13.93%)	208,148 (9.05%)	354,438 (10.81%)	504,658 (16.77%)
	Drugs for obstructive airway diseases	N (%)	76,756 (27.21%)	273,127 (15.70%)	648,113 (19.35%)	15,701 (19.06%)	778,740 (23.98%)	168,344 (26.10%)	533,572 (23.20%)	843,212 (25.71%)	646,666 (21.49%)
	Psycholeptics	N (%)	65,204 (23.11%)	788,358 (45.33%)	544,273 (16.25%)	21,551 (26.16%)	237,931 (7.33%)	124,573 (19.31%)	445,940 (19.39%)	1,176,373 (35.86%)	647,575 (21.52%)
	Agents acting on renin angiotensin system	N (%)	50,726 (17.98%)	686,697 (39.48%)	864,263 (25.80%)	25,544 (31.00%)	909,487 (28.00%)	147,749 (22.91%)	408,919 (17.78%)	908,323 (27.69%)	754,961 (25.09%)
	Antineoplastic agents	N (%)	457 (0.16%)	83 (0.00%)	7,540 (0.23%)	60 (0.07%)	4,798 (0.15%)	403 (0.06%)	4,330 (0.19%)	10,815 (0.33%)	3,972 (0.13%)
	Antidepressants	N (%)	42,796 (15.17%)	156,442 (8.99%)	510,026 (15.23%)	13,207 (16.03%)	409,746 (12.62%)	74,369 (11.53%)	244,743 (10.64%)	675,334 (20.59%)	573,768 (19.07%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Antibacterials systemic	N (%)	119,446 (42.34%)	1,000,541 (57.53%)	1,442,757 (43.07%)	39,100 (47.46%)	1,525,299 (46.96%)	206,356 (31.99%)	743,024 (32.31%)	1,364,430 (41.60%)	890,266 (29.58%)
	Psychostimulants	N (%)	1,480 (0.52%)	72 (0.00%)	42,101 (1.26%)	375 (0.46%)	19,556 (0.60%)	6,743 (1.05%)	31,231 (1.36%)	35,034 (1.07%)	77,404 (2.57%)
	Immunosuppressants	N (%)	2,161 (0.77%)	19,903 (1.14%)	84,053 (2.51%)	2,198 (2.67%)	74,066 (2.28%)	11,349 (1.76%)	55,360 (2.41%)	43,222 (1.32%)	82,115 (2.73%)
	Antiinflammatory antirheumatic agents	N (%)	126,342 (44.78%)	1,074,518 (61.78%)	1,577,059 (47.08%)	50,173 (60.90%)	1,909,183 (58.78%)	259,741 (40.27%)	1,032,612 (44.90%)	2,420,629 (73.80%)	1,653,931 (54.96%)
	Calcium channel blockers	N (%)	18,941 (6.71%)	311,952 (17.94%)	524,121 (15.65%)	10,040 (12.19%)	370,367 (11.40%)	72,002 (11.16%)	187,556 (8.16%)	308,398 (9.40%)	448,924 (14.92%)
	Drugs acid related disorder	N (%)	79,601 (28.22%)	653,141 (37.55%)	1,039,832 (31.04%)	23,850 (28.95%)	958,089 (29.50%)	253,471 (39.30%)	435,793 (18.95%)	1,458,550 (44.47%)	693,449 (23.04%)
	Hormonal contraceptives (systemic)	N (%)	14,584 (5.17%)	18,072 (1.04%)	156,658 (4.68%)	4,148 (5.03%)	54,570 (1.68%)	16,632 (2.58%)	203,021 (8.83%)	58,167 (1.77%)	252,595 (8.39%)
	Lipid modifying agents	N (%)	52,983 (18.78%)	351,694 (20.22%)	794,689 (23.73%)	12,714 (15.43%)	486,673 (14.98%)	148,145 (22.97%)	390,096 (16.96%)	765,174 (23.33%)	567,971 (18.87%)
	Beta blocking agents	N (%)	46,181 (16.37%)	419,428 (24.11%)	478,548 (14.29%)	18,850 (22.88%)	608,467 (18.73%)	116,155 (18.01%)	231,459 (10.07%)	360,485 (10.99%)	528,828 (17.57%)
Cancer (inf to 366 days prior)	Prostate cancer	N (%)	697 (0.25%)	3,618 (0.21%)	27,788 (0.83%)	371 (0.45%)	12,458 (0.38%)	3,478 (0.54%)	15,491 (0.67%)	28,377 (0.87%)	30,218 (1.00%)
	Breast cancer	N (%)	0 (0.00%)	0 (0.00%)	30,873 (0.92%)	19 (0.02%)	0 (0.00%)	6,247 (0.97%)	0 (0.00%)	33,965 (1.04%)	7,401 (0.25%)
	Multiple myeloma	N (%)	82 (0.03%)	674 (0.04%)	860 (0.03%)	30 (0.04%)	1,359 (0.04%)	356 (0.06%)	461 (0.02%)	2,900 (0.09%)	726 (0.02%)
	Pancreatic cancer	N (%)	60 (0.02%)	529 (0.03%)	1,259 (0.04%)	98 (0.12%)	779 (0.02%)	328 (0.05%)	857 (0.04%)	1,982 (0.06%)	1,207 (0.04%)
	Lymphoma	N (%)	117 (0.04%)	1,355 (0.08%)	5,876 (0.18%)	136 (0.17%)	3,780 (0.12%)	1,034 (0.16%)	3,575 (0.16%)	4,264 (0.13%)	4,206 (0.14%)

Variable name	Variable level	Estimate name	Data source								
			IQVIA LPD BELGIUM	NAJS	DK-DHR	EBB	InGef RDB	IPCI	NLHR	SIDIAP	HI-SPEED
	Colorectal cancer	N (%)	434 (0.15%)	6,682 (0.38%)	39,551 (1.18%)	544 (0.66%)	10,795 (0.33%)	3,428 (0.53%)	14,096 (0.61%)	30,096 (0.92%)	16,896 (0.56%)
	Ovarian cancer	N (%)	52 (0.02%)	1,275 (0.07%)	4,442 (0.13%)	166 (0.20%)	1,033 (0.03%)	362 (0.06%)	2,424 (0.11%)	3,136 (0.10%)	2,091 (0.07%)
	Endometrial cancer	N (%)	49 (0.02%)	1,753 (0.10%)	2,200 (0.07%)	133 (0.16%)	1,720 (0.05%)	527 (0.08%)	1,638 (0.07%)	3,864 (0.12%)	894 (0.03%)
	Lung cancer	N (%)	326 (0.12%)	2,056 (0.12%)	9,291 (0.28%)	166 (0.20%)	1,519 (0.05%)	2,463 (0.38%)	4,153 (0.18%)	9,990 (0.30%)	3,753 (0.12%)
	Leukaemia	N (%)	181 (0.06%)	932 (0.05%)	3,630 (0.11%)	50 (0.06%)	1,901 (0.06%)	731 (0.11%)	1,649 (0.07%)	6,302 (0.19%)	2,020 (0.07%)

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, InGef RDB = InGef Research Database, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care.

a. Default prescription duration was 30 days in NAJS (1 day for secondary conciliatory care), EBB, and InGef RDB.

Table 19. Patient level characterisation of new users for opioids without history of cancer in hospital data sources.

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
Number records	-	N	258,511	335,214	9,769	19,237	120,781	161,445
Number individuals	-	N	225,300	248,372	9,085	18,527	88,583	120,275
Age	-	Median [Q25–Q75]	50 [31–69]	57 [36–72]	65 [51–76]	60 [44–76]	57 [44–71]	61 [43–75]
		Range	0 to 108	0 to 117	1 to 101	0 to 105	2 to 105	0 to 108
Sex	Female	N (%)	132,807 (51.37%)	185,082 (55.21%)	6,124 (62.69%)	10,053 (52.26%)	69,117 (57.23%)	85,400 (52.90%)
	Male	N (%)	125,700 (48.62%)	150,132 (44.79%)	3,645 (37.31%)	9,184 (47.74%)	51,664 (42.77%)	76,045 (47.10%)
	None	N (%)	<5	-	-	-	-	-
Days in cohort	-	Median [Q25–Q75]	2 [1–5]	11 [2–31]	18 [8–31]	4 [2–7]	31 [31–31] [a]	1 [1–4]
		Range	1 to 1,530	1 to 4,838	1 to 335	1 to 820	1 to 385	1 to 2,533
Comorbidities (inf to 366 days prior)	Chronic obstructive pulmonary disease	N (%)	4,375 (2.80%)	6,793 (2.30%)	627 (7.88%)	463 (4.01%)	1,943 (1.70%)	8,569 (6.29%)
	Osteoporosis	N (%)	2,727 (1.74%)	4,003 (1.36%)	1,122 (14.11%)	75 (0.65%)	1,393 (1.22%)	6,800 (4.99%)
	Gastro-oesophageal reflux disease	N (%)	3,288 (2.10%)	10,135 (3.44%)	995 (12.51%)	68 (0.59%)	637 (0.56%)	1,682 (1.23%)
	Obesity	N (%)	10,085 (6.45%)	11,972 (4.06%)	431 (5.42%)	174 (1.51%)	9,477 (8.28%)	21,993 (16.14%)
	Venous thromboembolism	N (%)	3,161 (2.02%)	3,447 (1.17%)	301 (3.79%)	146 (1.26%)	757 (0.66%)	2,393 (1.76%)
	Dementia	N (%)	1,924 (1.23%)	4,072 (1.38%)	125 (1.57%)	86 (0.74%)	419 (0.37%)	1,903 (1.40%)
	Pneumonia	N (%)	6,637 (4.24%)	18,053 (6.12%)	599 (7.53%)	860 (7.44%)	2,125 (1.86%)	7,049 (5.17%)
	Hypothyroidism	N (%)	5,328 (3.41%)	11,902 (4.03%)	478 (6.01%)	91 (0.79%)	1,112 (0.97%)	5,908 (4.33%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Inflammatory bowel disease	N (%)	1,323 (0.85%)	5,520 (1.87%)	234 (2.94%)	130 (1.12%)	238 (0.21%)	889 (0.65%)
	Depressive disorder	N (%)	9,778 (6.25%)	19,304 (6.54%)	808 (10.16%)	83 (0.72%)	7,658 (6.69%)	13,723 (10.07%)
	Malignant neoplastic disease	N (%)	6,078 (3.89%)	14,394 (4.88%)	573 (7.21%)	718 (6.21%)	4,742 (4.15%)	13,426 (9.85%)
	Chronic kidney disease (with renal impairment)	N (%)	8,946 (5.72%)	6,003 (2.03%)	1,074 (13.51%)	909 (7.86%)	1,571 (1.37%)	10,228 (7.50%)
	Chronic liver disease	N (%)	2,743 (1.75%)	2,796 (0.95%)	222 (2.79%)	431 (3.73%)	625 (0.55%)	5,237 (3.84%)
	Asthma	N (%)	4,817 (3.08%)	16,546 (5.61%)	327 (4.11%)	59 (0.51%)	2,005 (1.75%)	6,351 (4.66%)
	Stroke	N (%)	3,449 (2.20%)	11,229 (3.81%)	591 (7.43%)	161 (1.39%)	1,229 (1.07%)	3,285 (2.41%)
	Chronic kidney disease	N (%)	6,691 (4.28%)	3,865 (1.31%)	1,037 (13.04%)	639 (5.53%)	973 (0.85%)	7,212 (5.29%)
	Type 2 diabetes	N (%)	10,766 (6.88%)	35,673 (12.09%)	1,194 (15.02%)	762 (6.59%)	10,900 (9.53%)	22,288 (16.35%)
	HIV infection	N (%)	922 (0.59%)	163 (0.06%)	<5	30 (0.26%)	51 (0.04%)	1,546 (1.13%)
	Rheumatoid arthritis	N (%)	1,369 (0.88%)	6,688 (2.27%)	175 (2.20%)	41 (0.35%)	616 (0.54%)	1,103 (0.81%)
	Hypertension	N (%)	27,766 (17.75%)	55,666 (18.87%)	4,119 (51.80%)	1,222 (10.57%)	20,719 (18.11%)	38,915 (28.55%)
	Myocardial infarction	N (%)	1,946 (1.24%)	8,848 (3.00%)	200 (2.52%)	131 (1.13%)	1,094 (0.96%)	3,175 (2.33%)
	Anxiety	N (%)	8,512 (5.44%)	16,391 (5.56%)	740 (9.31%)	106 (0.92%)	2,790 (2.44%)	9,704 (7.12%)
	Heart failure	N (%)	5,947 (3.80%)	11,057 (3.75%)	784 (9.86%)	461 (3.99%)	2,260 (1.98%)	7,670 (5.63%)
Comorbidities (365 days prior to index date)	Gastro-oesophageal reflux disease	N (%)	6,052 (2.34%)	2,030 (0.61%)	848 (8.68%)	39 (0.20%)	128 (0.11%)	1,471 (0.91%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Venous thromboembolism	N (%)	5,283 (2.04%)	1,412 (0.42%)	251 (2.57%)	336 (1.75%)	159 (0.13%)	1,455 (0.90%)
	Obesity	N (%)	29,409 (11.38%)	7,163 (2.14%)	328 (3.36%)	284 (1.48%)	3,340 (2.77%)	30,562 (18.93%)
	Malignant neoplastic disease	N (%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
	Stroke	N (%)	7,062 (2.73%)	5,990 (1.79%)	436 (4.46%)	448 (2.33%)	228 (0.19%)	2,657 (1.65%)
	Heart failure	N (%)	12,572 (4.86%)	8,262 (2.46%)	956 (9.79%)	1,093 (5.68%)	896 (0.74%)	8,941 (5.54%)
	Chronic kidney disease	N (%)	12,415 (4.80%)	2,884 (0.86%)	1,341 (13.73%)	1,012 (5.26%)	428 (0.35%)	10,095 (6.25%)
	Depressive disorder	N (%)	21,035 (8.14%)	21,072 (6.29%)	561 (5.74%)	130 (0.68%)	8,580 (7.10%)	19,207 (11.90%)
	Anxiety	N (%)	19,190 (7.42%)	6,094 (1.82%)	506 (5.18%)	53 (0.28%)	494 (0.41%)	5,277 (3.27%)
	Type 2 diabetes	N (%)	26,536 (10.26%)	55,345 (16.51%)	1,873 (19.17%)	2,638 (13.71%)	12,431 (10.29%)	34,309 (21.25%)
	Pneumonia	N (%)	11,713 (4.53%)	8,338 (2.49%)	557 (5.70%)	2,088 (10.85%)	511 (0.42%)	5,035 (3.12%)
	Chronic liver disease	N (%)	4,066 (1.57%)	1,884 (0.56%)	211 (2.16%)	558 (2.90%)	128 (0.11%)	4,577 (2.84%)
	Chronic kidney disease (with renal impairment)	N (%)	17,543 (6.79%)	4,624 (1.38%)	1,450 (14.84%)	2,080 (10.81%)	640 (0.53%)	14,258 (8.83%)
	Myocardial infarction	N (%)	2,560 (0.99%)	6,701 (2.00%)	123 (1.26%)	248 (1.29%)	175 (0.14%)	3,259 (2.02%)
	Chronic obstructive pulmonary disease	N (%)	10,345 (4.00%)	3,957 (1.18%)	612 (6.26%)	612 (3.18%)	600 (0.50%)	8,119 (5.03%)
	Hypothyroidism	N (%)	13,620 (5.27%)	4,047 (1.21%)	338 (3.46%)	96 (0.50%)	311 (0.26%)	6,732 (4.17%)
	Asthma	N (%)	10,061 (3.89%)	5,881 (1.75%)	236 (2.42%)	50 (0.26%)	372 (0.31%)	5,725 (3.55%)
	Rheumatoid arthritis	N (%)	2,616 (1.01%)	4,178 (1.25%)	150 (1.54%)	46 (0.24%)	148 (0.12%)	922 (0.57%)
	HIV infection	N (%)	844 (0.33%)	170 (0.05%)	<5	67 (0.35%)	15 (0.01%)	1,769 (1.10%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Osteoporosis	N (%)	4,547 (1.76%)	1,461 (0.44%)	980 (10.03%)	86 (0.45%)	191 (0.16%)	6,876 (4.26%)
	Hypertension	N (%)	70,483 (27.26%)	22,607 (6.74%)	4,160 (42.58%)	1,075 (5.59%)	4,473 (3.70%)	43,495 (26.94%)
	Dementia	N (%)	4,991 (1.93%)	1,994 (0.59%)	235 (2.41%)	342 (1.78%)	229 (0.19%)	3,176 (1.97%)
	Inflammatory bowel disease	N (%)	2,703 (1.05%)	4,512 (1.35%)	215 (2.20%)	307 (1.60%)	43 (0.04%)	843 (0.52%)
Medications (365 days prior to index date)	Antiepileptics	N (%)	21,951 (8.49%)	33,078 (9.87%)	958 (9.81%)	2,213 (11.50%)	7,869 (6.52%)	15,265 (9.46%)
	Diuretics	N (%)	21,623 (8.36%)	51,282 (15.30%)	1,647 (16.86%)	4,595 (23.89%)	4,379 (3.63%)	17,911 (11.09%)
	Drugs used in diabetes	N (%)	17,480 (6.76%)	46,624 (13.91%)	969 (9.92%)	2,409 (12.52%)	2,575 (2.13%)	19,756 (12.24%)
	Antithrombotics	N (%)	66,160 (25.59%)	117,397 (35.02%)	2,100 (21.50%)	10,818 (56.24%)	13,473 (11.15%)	52,415 (32.47%)
	Drugs for obstructive airway diseases	N (%)	16,964 (6.56%)	62,632 (18.68%)	521 (5.33%)	2,486 (12.92%)	6,184 (5.12%)	24,785 (15.35%)
	Psycholeptics	N (%)	104,795 (40.54%)	127,083 (37.91%)	1,498 (15.33%)	4,791 (24.91%)	16,030 (13.27%)	106,486 (65.96%)
	Agents acting on renin angiotensin system	N (%)	23,749 (9.19%)	87,720 (26.17%)	2,283 (23.37%)	4,425 (23.00%)	1,775 (1.47%)	17,947 (11.12%)
	Antineoplastic agents	N (%)	1,217 (0.47%)	1,724 (0.51%)	5 (0.05%)	<5	0 (0.00%)	936 (0.58%)
	Antidepressants	N (%)	17,569 (6.80%)	44,307 (13.22%)	676 (6.92%)	1,833 (9.53%)	6,645 (5.50%)	13,377 (8.29%)
	Antibacterials systemic	N (%)	59,839 (23.15%)	121,110 (36.13%)	2,571 (26.32%)	10,410 (54.11%)	31,995 (26.49%)	72,033 (44.62%)
	Psychostimulants	N (%)	337 (0.13%)	2,518 (0.75%)	278 (2.85%)	47 (0.24%)	76 (0.06%)	286 (0.18%)
	Immunosuppressants	N (%)	5,986 (2.32%)	12,095 (3.61%)	790 (8.09%)	1,038 (5.40%)	619 (0.51%)	3,516 (2.18%)

Variable name	Variable level	Estimate name	Data source					
			CDW Bordeaux	FinOMOP-ACI Varha	SUCD	POLIMI	EMDB-ULSEDV	IMASIS
	Antiinflammatory antirheumatic agents	N (%)	97,179 (37.59%)	295,500 (88.15%)	3,760 (38.49%)	11,793 (61.30%)	68,520 (56.73%)	92,304 (57.17%)
	Calcium channel blockers	N (%)	20,791 (8.04%)	45,681 (13.63%)	1,180 (12.08%)	3,104 (16.14%)	1,033 (0.86%)	14,777 (9.15%)
	Drugs acid related disorder	N (%)	81,325 (31.46%)	96,994 (28.93%)	3,673 (37.60%)	16,364 (85.07%)	17,712 (14.66%)	83,368 (51.64%)
	Hormonal contraceptives (systemic)	N (%)	379 (0.15%)	11,483 (3.43%)	55 (0.56%)	6 (0.03%)	380 (0.31%)	1,089 (0.67%)
	Lipid modifying agents	N (%)	33,284 (12.88%)	69,600 (20.76%)	1,436 (14.70%)	3,076 (15.99%)	3,179 (2.63%)	19,557 (12.11%)
	Beta blocking agents	N (%)	26,110 (10.10%)	81,352 (24.27%)	2,151 (22.02%)	5,039 (26.19%)	2,849 (2.36%)	14,284 (8.85%)
Cancer (inf to 366 days prior)	Prostate cancer	N (%)	670 (0.43%)	3,176 (1.08%)	24 (0.30%)	49 (0.42%)	453 (0.40%)	1,396 (1.02%)
	Breast cancer	N (%)	131 (0.08%)	1,011 (0.34%)	11 (0.14%)	70 (0.61%)	0 (0.00%)	2,361 (1.73%)
	Multiple myeloma	N (%)	58 (0.04%)	166 (0.06%)	10 (0.13%)	7 (0.06%)	23 (0.02%)	70 (0.05%)
	Pancreatic cancer	N (%)	113 (0.07%)	73 (0.02%)	12 (0.15%)	16 (0.14%)	63 (0.06%)	152 (0.11%)
	Lymphoma	N (%)	280 (0.18%)	597 (0.20%)	12 (0.15%)	21 (0.18%)	66 (0.06%)	336 (0.25%)
	Colorectal cancer	N (%)	630 (0.40%)	1,507 (0.51%)	65 (0.82%)	69 (0.60%)	763 (0.67%)	1,930 (1.42%)
	Ovarian cancer	N (%)	61 (0.04%)	201 (0.07%)	5 (0.06%)	8 (0.07%)	115 (0.10%)	159 (0.12%)
	Endometrial cancer	N (%)	45 (0.03%)	138 (0.05%)	5 (0.06%)	0 (0.00%)	19 (0.02%)	44 (0.03%)
	Lung cancer	N (%)	283 (0.18%)	32 (0.01%)	20 (0.25%)	32 (0.28%)	105 (0.09%)	522 (0.38%)
	Leukaemia	N (%)	153 (0.10%)	347 (0.12%)	6 (0.08%)	31 (0.27%)	50 (0.04%)	182 (0.13%)

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga, FinOMOP-ACI Varha = Auria Clinical Informatics, IMASIS = Institut Municipal Assistència Sanitària Information, POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SUCD = Semmelweis University Clinical Data.

a. Default prescription duration was 31 days in EMDB-ULSEDV.

Indication

Large scale characterisation on conditions recorded on the index date (**Table 20**, **Table 21**) was conducted to identify potential indications for the opioid prescription.

Conditions that were possibly indicative for baseline comorbidities were excluded. Most identified potential indications were pain-related or cough-related. Cough or cough-related conditions were the most commonly identified potential indications in IPCI (21%), IQVIA LPD Belgium (28%), NLHR (6%), SIDIAP (11%), and HI-SPEED (3%). Pain-related conditions were the most commonly identified indications in CDW Bordeaux (3%), DK-DHR (45%), EBB (10%), IMASIS (2%), FinOMOP-ACI Varha (6%), NAJS (17%), POLIMI (2%), and SUCD (4%).

For hospital data sources (CDW Bordeaux, IMASIS, FinOMOP-ACI Varha, POLIMI, SUCD, EMDB-ULSEDV), an additional large-scale characterisation on procedures recorded on the index date (**Table 22**) 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 CDW Bordeaux (7%), IMASIS (1%), POLIMI (16%), SUCD (2%), and EMDB-ULSEDV (10.1%), which was suggestive of chest symptoms or findings. The most common identified procedures relevant to opioid use in FinOMOP-ACI Varha was intravenous anaesthesia (16%), which was indicative for surgical procedures. 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. In POLIMI, SUCD, and EMDB-ULSEDV, the other identified procedures for possible indication for opioid use included mostly radiographs (indicative for operative procedures, diagnostic, and interventional radiology), while that in FinOMOP-ACI Varha was mostly anaesthesia-related.

Table 20. Large scale characterisation on conditions for identification of possible indication for opioid use in primary care or national registries.

IQVIA LPD Belgium		
Diagnosis name	**N**	**%**
Cough	81,556	28
Common cold	37,018	13
Low back pain	28,957	10
Acute upper respiratory infection	25,338	9
Acute bronchitis	22,597	8
Pain	19,466	7
Acute tracheitis	16,612	6
Influenza	15,319	5
Acute laryngitis and/or tracheitis	8,192	3
Lumbago with sciatica	5,962	2

NAJS		
Diagnosis name	**N**	**%**
Pain in spine	332,013	17
Cough	285,572	15
Acute upper respiratory infection	119,415	6
Lumbago with sciatica	109,269	6
Osteoarthritis of knee	75,742	4
COVID-19	61,757	3
Acute bronchitis	60,688	3
Intervertebral disc disorder	57,753	3
Common cold	51,826	3
Acute pharyngitis	49,621	3

DK-DHR		
Diagnosis name	**N**	**%**
Severe pain	1,620,526	45
Pain	1,537,220	43
Cough	655,029	18
Dry cough	110,294	3
Muscle pain	72,729	2
Pneumonia	46,547	1
Moderate pain	19,871	1
Neuropathic pain	18,338	1

EBB		
Diagnosis name	**N**	**%**
Nerve root disorder	9,154	10
Cough	8,684	10
Pain in spine	6,878	8
Intervertebral disc disorder	4,937	6
Low back pain	4,742	5
Osteoarthritis of knee	3,216	4
Acute bronchitis	3,181	4
Acute upper respiratory infection	2,938	3
Osteoarthritis of hip	2,247	3
Joint pain	1,994	2

NLHR		
Diagnosis name	**N**	**%**
Cough	152,401	6
Acute upper respiratory infection	143,519	6
Low back pain	75,353	3
Joint pain	66,764	3
Backache	48,870	2
Acute lower respiratory tract infection	47,521	2
Sciatica	37,498	2
COVID-19	27,781	1
Upper respiratory tract infection caused by Influenza virus	22,643	1
Pain in limb	21,642	1

IPCI		
Diagnosis name	**N**	**%**
Cough	141,371	21
Acute upper respiratory infection	36,748	5
Low back pain	21,176	3
Finding of back	19,037	3
Backache with radiating pain	18,555	3
Finding of shoulder region	11,345	2
Finding of region of thorax	8,055	1
Finding of neck region	7,390	1
Acute bronchitis	7,039	1
Finding of lower limb	6,109	1

HI-SPEED		
Diagnosis name	**N**	**%**
Cough	93,155	3
Acute upper respiratory infection	73,638	2
Pain	32,156	1
Acute bronchitis	20,607	1
Disorder of musculoskeletal system	18,605	1
Backache	17,509	1
Low back pain	17,470	1

SIDIAP		
Diagnosis name	**N**	**%**
Common cold	376,652	11
Cough	203,036	6
Low back pain	86,345	3
Upper respiratory tract infection due to Influenza	62,830	2
Acute lower respiratory tract infection	38,457	1
Joint pain	30,071	1
Acute bronchitis	26,557	1
Neck pain	25,246	1
Acute upper respiratory infection	23,828	1
Lumbago with sciatica	23,730	1

DK-DHR = Danish Data Health Registries, EBB = Estonian Biobank, HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage, IPCI = Integrated Primary Care Information Project, IQVIA LPD Belgium = IQVIA Longitudinal Patient Database Belgium, NAJS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = The Information System for the Development of Research in Primary Care. No condition was identified on the date of opioid use initiation in InGef RDB.

Table 21. Large scale characterisation on conditions for identification of possible indication for opioid use in hospital data sources.

CDW Bordeaux		
Diagnosis name	**N**	**%**
Complication of surgical procedure	9,490	3
Complication of procedure	8,367	3
Acute pain	6,761	2
Low back pain	4,767	1

FinOMOP-ACI Varha		
Diagnosis name	**N**	**%**
Injury whilst engaged in leisure activity	20,115	6
Osteoarthritis of knee	5,467	2
Low back pain	4,909	1
Acute appendicitis	4,051	1
Osteoarthritis of hip	3,983	1
Pneumonia	3,423	1
Fracture of neck of femur	3,089	1
Primary malignant neoplasm of prostate	2,979	1
Calculus of gallbladder without cholecystitis or cholangitis	2,709	1
Primary gonarthrosis, bilateral	2,585	1

SUCD		
Diagnosis name	**N**	**%**
Secondary malignant neoplasm of liver and intrahepatic bile duct	681	4
Intervertebral disc disorder	629	3
Primary malignant neoplasm of respiratory tract	607	3
Secondary malignant neoplasm of bone	581	3
Primary malignant neoplasm of breast	566	3
Nerve root disorder	508	3
Pain	486	3
Primary malignant neoplasm of pancreas	479	3
Lumbago with sciatica	477	3
Spondylosis	379	2

POLIMI		
Diagnosis name	**N**	**%**
Primary malignant neoplasm of liver	459	2
Uterine leiomyoma	363	1
Primary malignant neoplasm of prostate	210	1
Primary malignant neoplasm of respiratory tract	180	1
Bacterial pneumonia	175	1
Infective pneumonia	170	1
Kidney stone	165	1
Displacement of lumbar intervertebral disc without myelopathy	152	1
Acute pancreatitis	150	1
Ureteric stone	152	1

IMASIS		
Diagnosis name	**N**	**%**
Osteoarthritis of knee	3,618	2
Low back pain	1,817	1
Complication of surgical procedure	1,682	1
Primary malignant neoplasm of female breast	1,677	1
Fracture of bone	1,151	1

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Table 22. Large scale characterisation on procedures for identification of possible indication for opioid use in hospital data sources.

CDW Bordeaux		
Diagnosis name	**N**	**%**
Plain chest X-ray	23,417	7
Diagnostic radiography during operative procedure	16,175	5
Insertion of catheter into artery	10,968	3
Immunocytochemical procedure	10,402	3
Insertion of catheter for central venous pressure monitoring	10,394	3
Computed tomography of abdomen and pelvis with contrast	7,218	2
CT, 3-dimensional reconstruction	6,989	2
Interventional radiology	6,399	2
Cytopathology test	6,197	2
CT of brain without contrast	6,077	2

FinOMOP-ACI Varha		
Diagnosis name	**N**	**%**
Intravenous anesthesia	57,827	16
Maintenance of general anesthesia	56,575	15
Administration of general anesthetic	46,029	13
Inhalation general anesthesia	43,271	12
Spinal anesthesia	42,273	12
Lung X-ray	28,502	8
Local anesthesia	22,496	6
CT of abdomen	10,782	3
Standard chest X-ray	9,661	3
CT of head	9,374	3

POLIMI		
Diagnosis name	**N**	**%**
Plain chest X-ray	4,150	16
Laparoscopy	1,622	6
CT of abdomen without contrast	758	3
Computed tomography, head or brain; without contrast material	739	3
Computed tomography, head or brain; with contrast material	739	3
Other laparotomy	728	3
Thoracoscopy	658	3
CT of abdomen with contrast	628	2
Total abdominal hysterectomy	607	2
Standard chest X-ray	602	2

SUCD		
Diagnosis name	**N**	**%**
Plain chest X-ray	306	2
Echography of kidney	192	1
Injection of cytotoxic substance	182	1
Pelvic echography	173	1
US scan of bladder	148	1
Diagnostic radiography, combined PA and lateral	147	1

EMDB-ULSEDV		
Diagnosis name	**N**	**%**
Plain X-ray of chest	12,427	10
Radiologic examination, ribs, unilateral; 2 views	6,994	6
Radiography of hip	5,148	4
X-ray of bone of knee	4,655	4
Plain X-ray of abdomen	4,628	4
Radiologic examination, hip, unilateral; 1 view	3,038	3

IMASIS		
Diagnosis name	**N**	**%**
Plain Radiography of Chest	2,220	1
Fluoroscopy of Multiple Coronary Arteries using Low Osmolar Contrast	2,169	1
Local excision of lesion of breast	2,053	1
Introduction of Other Therapeutic Substance into Subcutaneous Tissue, Percutaneous Approach	2,050	1
Ligation and stripping of varicose vein of lower limb	1,888	1
Range of Motion and Joint Mobility Treatment of Musculoskeletal System - Lower Back / Lower Extremity	1,884	1

Diagnostic radiography of chest, combined PA and lateral	147	1	Radiologic examination, ankle; 2 views	2,684	2	Introduction of Analgesics, Hypnotics, Sedatives into Peripheral Vein, Percutaneous Approach	1,819	1
Radiography of prostate	100	1	X-ray of bone of foot	2,677	2	Repair of inguinal hernia with graft or prosthesis, not otherwise specified	1,802	1
Ultrasonography of abdomen	101	1	CT of head	2,510	2	Total knee replacement	1,530	1
US scan of abdomen and pelvis	101	1	Radiologic examination, shoulder; complete, minimum of 2 views	2,415	2	Supplement Abdominal Wall with Synthetic Substitute, Open Approach	1,458	1

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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 EUPAS1000000615.

13. DISCUSSION

13.1. Key results

Population-level opioid use

In general, over the past decade, the incidence of opioid use remained stable across most of the primary care or national registries data sources, while a decreasing trend was observed in NAJS, DK-DHR, InGef RDB, IPCI, and HI-SPEED. An increasing trend in overall opioid use was observed in EBB and all hospital data sources, except CDW Bordeaux. Among all included data sources, 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 individuals who did not have a history of cancer in the year before prescription, regardless of type of data sources. Therefore, trends and pattern in overall opioid use aligned closely with non-cancer opioid use and were predominantly driven by oral formulations.

Incidence and prevalence of opioid use showed a marked decrease during the COVID-19 period (2020–2021), particularly for weak opioids such as codeine or tramadol and particularly among primary care or nationwide data sources (except EBB). However, opioid usage returned to the pre-COVID-19 level in most primary care or nationwide data sources or even higher in hospital data sources 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 DK-DHR, IPCI, and EBB among the primary care or nationwide data sources, and in all hospital data sources considering the number of opioid record counts, both in individuals with and without a history of cancer. Higher incidence and prevalence of injectable opioids was observed in hospital data sources (IMASIS and CDW Bordeaux), while that of transdermal opioid use was the highest in IPCI. Increasing trend of injectable opioids was observed in most data sources except EBB, NAJS, NLHR, and HI-SPEED, while increasing trend of transdermal opioid use was observed in CDW Bordeaux, EBB, and IMASIS. 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 data sources were, in descending order, tramadol, codeine, oxycodone, ethylmorphine, morphine, noscapine, tilidine, dihydrocodeine, pholcodine, and fentanyl. Among these, 3 of them (fentanyl, morphine, oxycodone) were potent opioids.

Patient-level opioid use

Among new opioid users, there were more women than men receiving opioid prescriptions across all included data sources except CDW Bordeaux. The median age of opioid new users ranged from 49 to 66 years. 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 2.6–31.4%, compared to 1.8–48.4% with a record within 1 year prior starting opioids. When considering medication use within 1 year prior to the opioid use, 38.0–88.6% of new opioid users were prescribed with anti-inflammatory and anti-rheumatic agents.

The median duration for a first treatment episodes with opioids ranged from 1 to 21 days in hospital data sources, and from 6 to 18 days in primary care or nationwide data sources.

As the actual indication was not recorded in most data sources, 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 data sources recorded in the immediate time before opioid prescriptions included chest x-rays (suggestive of chest symptoms or findings), intravenous anaesthesia (suggestive of surgical procedures), and radiography other than chest x-rays (indicative for operative procedures, diagnostic and interventional radiology).

13.2. 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 individual 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 preparations for treatment of cough. 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 data sources. 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 included records of prevalent conditions/comorbidities. In addition, large scale characterisation on procedures identified not only the actual procedures which required use of opioids (e.g., surgical operation), but also the procedures indicative of underlying symptoms or conditions.

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 data source, which could impact on the definition of cancer or non-cancer opioid use. Furthermore, 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 (0.05–0.58%) 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 data sources, 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 from original study P2-C1-002, where we required 365 days of prior observation as inclusion criterion, leading to substantial loss of individuals in the hospital data source. To mitigate this problem, the 1-year prior data availability requirement was not applied to hospital data source.

Similarly, for the hospital data sources (CDW Bordeaux, IMASIS, FinOMOP-ACI Varha, EMDB-ULSEDV, SUCD, POLIMI), the observation period of individuals depended largely on their hospital inpatient/outpatient visits. The end date of the observation period was defined by the last recorded visit in these data sources. Consequently, there was a substantial decrease in the denominator population toward the end of the study period, leading to an apparent increase in incidence estimates. To address this issue and supplement the incidence/prevalence results, we included plots showing the number of denominator counts and number of incident/prevalent opioid users over the study period. This allows for interpretation of the results within these data sources. Moreover, since the observation period was defined by hospital visits, while such visits were more likely to involve individuals requiring medical care, this may have also artificially inflated the incidence and prevalence estimates.

Data from some hospital data sources (POLIMI, SUCD, EMDB-ULSEDV) were not complete, as drug records were not fully available from all inpatient and outpatient services. Details for each individual data source are specified in the respective section of the results. Therefore, estimates from the incidence and prevalence analyses should not be directly interpreted for these data sources. However, the observed trends in incidence and prevalence may still provide valuable insights within specific clinical settings, reflecting local prescribing practices and data capture characteristics.

In the current study, opioid use by route of administration was defined based on the dosage form of each concept. Therefore, the ability to identify the route of administration largely depended on the level of granularity in data mapping within each data source.

Data source-specific limitations

IQVIA LPD Belgium: The observation period of the individuals in this data source is calculated based on the last visit, observation, or interaction of the individual 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.

NAJS: Data from secondary care were only available for the year 2017–2022 in NAJS and therefore leading to a sudden drop of overall opioid use from 2022 to 2023. Interpretation of trend in opioid use in NAJS should take the availability of data into account. No explicit information on duration of drug exposure could be given in NAJS. A default duration of 30 days was assigned to each drug record, except for drug records in secondary conciliatory care where drug exposure of 1-day was assumed. Therefore, treatment duration could not be estimated in NAJS.

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.

InGef RDB: No explicit information on duration of drug exposure was given in InGef RDB. A default duration of 30 days was assigned to each drug record, and therefore treatment duration could not be estimated in InGef RDB. Condition records in InGef RDB were recorded only at the start of every quarter and therefore, indication derived by large scale characterisation on index date, and in prior one week or one month for sensitivity analysis, was not possible to be systematically carried out and interpreted.

SUCD: Only outpatient and part of the inpatient drug records were available, while the denominator population included all individuals with any records in the data source. Therefore, trends of opioid use in SUCD should be carefully interpreted with regards to the clinical settings where data was collected, while estimated value of incidence and prevalence should not be over-interpreted due to limited representativeness of results for the institution. Furthermore, as only part of the inpatient drug records

was available, some of the common opioid preparation used in hospital setting (e.g., injection opioids) were not frequently observed.

POLIMI: Only inpatient drug records were available, while the denominator population includes all individuals with any records (including outpatient visit and laboratory record) in the data source. Therefore, trend of opioid use in POLIMI should be carefully interpreted with regards to the clinical settings where data was collected, while estimated value of incidence and prevalence should not be over-interpreted due to limited representativeness of results for the institution.

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.

EMDB-ULSEDV: Only outpatient drug records were available, while the denominator population includes all individuals with any records (including hospitalisation) in the data source. Therefore, trend of opioid use in EMDB-ULSEDV should be carefully interpreted with regards to the clinical settings where data was collected, while estimated value of incidence and prevalence should not be over-interpreted due to limited representativeness of results for institution. As only outpatient drug records were available, use of some common opioid preparations used in hospital setting (e.g., injection opioids) was not observed. Also, no explicit information on duration of drug exposure was given in EMDB-ULSEDV. A default duration of 31 days was assigned to each drug record, and therefore treatment duration could not be estimated in EMDB-ULSEDV.

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.

13.3. 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 individuals 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 EBB and all hospital data sources except CDW Bordeaux, and decreasing trend in NAJS, DK-DHR, InGef RDB, IPCI, and HI-SPEED. This is a routine repeated study of initial opioid study (P2-C1-002, EUPAS105641). For the data sources that was included in the initial opioid study, including IQVIA LPD Belgium, EBB, CDW Bordeaux, IPCI, and SIDIAP), the trends and pattern for 2012–2022 followed closely with previous study findings. 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 in most primary care or nationwide data source, or even higher in hospital data sources, aligning with the findings on the opioid prescription previously reported. While the increasing trend towards the end of study period in IQVIA LPD Belgium and all hospital data sources (FinOMOP-ACI Varha, CDW Bordeaux, SUCD, POLIMI, EMDB-ULSEDV, IMASIS) could be an inflated results from the decrease in denominator owing to definitions of the observation period, a rising trend in EBB was seen. Previous study using Estonian nationwide prescription data also showed a 67% increase in

annual opioid prescribing rates during the period of 2011–2017.[15] It was reported an increase in codeine and potent opioids such as oxycodone and fentanyl of which results from the current study echoes with.

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.[16] 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.[17] 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 particular use of morphine and oxycodone, in Denmark warranted attention. Similarly, while the overall opioid use in Sweden was comparable to that in most other countries, Sweden had the highest use of potent opioids among all included primary care or nationwide data sources. Oxycodone was the most commonly identified opioid, with the highest number of incident records over the study period within the data source. This result aligns with previous findings showing the highest prevalence of oxycodone use among the three Scandinavian countries (Denmark, Norway, and Sweden).[18] Alongside the increasing use of oxycodone, there was also report of increasing oxycodone-related deaths.[19] A previous literature[18] suggested that the increase in oxycodone use may have been partly due to a morphine shortage.

While the overall trends and patterns were generally aligned between the incidence and prevalence of opioid use, we observed differences in the ranking of data sources within each outcome. For example, in FinOMOP-ACI Varha, there was a considerable difference between the incidence (7,771 to 17,121 per 100,000 person-years) and prevalence (10.9% to 16.9%) of overall opioid use. Another example was NAJS, where the incidence remained at below 8,000 per 100,000 person-years, but the prevalence of overall opioid use was consistently around 10–12% throughout the study period. The observation of a higher prevalence compared with incidence may be explained by repeated or sustained opioid use during the study period. Such users would not be identified as incident cases due to the one-year washout period definition, but such sustained opioid use could be captured through prevalence estimates. Although the median duration of opioid use remained short, it should be noted that we defined the treatment era by concatenating treatments separated by less than seven days (gap era definition as described in **Section 9.9.1. Drug Exposure Calculations**). Therefore, subsequent opioid prescriptions or dispensations that occur more than seven days after the previous prescription or dispensation would not be captured in the treatment duration estimation.

Trend and pattern of opioid use depend 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 data sources. However, it was observed that IPCI, as a primary care data source, had the highest incidence and prevalence of fentanyl use and the second highest incidence of fentanyl among primary care and nationwide data sources. 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 data source covering 96% of the Dutch population.[20] On the other hand, some of the included data sources (DK-DHR, NLHR, NAJS, and HI-SPEED) were national data source 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 data sources, 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, EUPAS105641). In this routinely repeated study, 3 new data sources (DK-DHR, IMASIS, NLHR) were included in P3-C2-002, and another 7 new data sources (FinOMOP-ACI Varha, EMDB-ULSEDV, HI-SPEED, InGef RDB, NAJS, POLIMI, SUCD) were included in P4-C2-001. Results from the hospital data sources, especially FinOMOP-ACI Varha, CDW Bordeaux, and IMASIS, showed similar trends, suggesting that the patterns of

opioid use in hospital settings were consistent across data sources. The data source setting of DK-DHR, NLHR, NAJS, and HI-SPEED was unique compared to the other included data sources in a way that they are both national-wide linked data sources 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 these nationwide data sources shared a similar trend of decrease in opioid use during COVID-19 as observed in other data sources, the overall trend of opioid use over years was unique to the data source 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 data sources were 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.[21, 22] 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.

The study systematically assessed opioid use across different countries. However, when interpreting the results, it is important to balance between ensuring access to pain relief medications and minimizing the risk of misuse. This requires evaluating the appropriateness of drug use, for example, whether prescriptions follow the principles of the pain medication ladder. Although trends in opioid use were observed, it should be noted that these findings were based on retrospective data. Therefore, fluctuations in trends might reflect temporary factors such as drug shortages during certain periods. Despite such, the study still provides valuable insights into opioid use across different clinical settings in the included European countries. Careful interpretation and continuous long-term monitoring of opioid use remain essential.

13.4. Generalisability

The study included data sources from 14 European countries (Belgium, Croatia, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, the Netherlands, Norway, Portugal, Spain, Sweden) 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 data source and should not be generalised to other countries or data sources. Settings with high use of opioids, such as nursing homes and palliative care facilities, were not covered in this study.

14. CONCLUSION

In general, over the past decade, the incidence of opioid use remained stable across most of the primary care or national registries data sources, while a decreasing trend was observed in NAJS, DK-DHR, InGef RDB, IPCI, and HI-SPEED. An increasing trend in overall opioid use was observed in EBB and all hospital data sources, except CDW Bordeaux. Most of the opioid prescriptions were prescribed to individuals with no 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 in most primary care or nationwide data sources, or even higher in hospital data sources from 2022 onwards.

15. REFERENCES

1. Seth P, Scholl L, Rudd RA, Bacon S. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. MMWR Morb Mortal Wkly Rep. 2018;67(12):349-358. doi:10.15585/mmwr.mm6712a1. .

2. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Department of Health and Human Services. Annual Surveillance Report Of Drug-related Risks And Outcomes. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf. Accessed May 16, 2023. .

3. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? Current drug abuse reviews. 2015;8(1):3-14. doi:10.2174/1874473708011506111842l8. .

4. Kennedy J, Wood EG, Wu C-H. Factors associated with frequent or daily use of prescription opioids among adults with chronic pain in the United States. The Journal of international medical research. 2023;51(1):3000605221149289. doi:10.1177/03000605221149289. .

5. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006;166(19):2087-2093. doi:10.1001/archinte.166.19.2087. .

6. Dufort A, Samaan Z. Problematic Opioid Use Among Older Adults: Epidemiology, Adverse Outcomes and Treatment Considerations. Drugs & Aging. 2021;38(12):1043-1053. doi:10.1007/s40266-021-00893-z. .

7. Brat GA, Weber GM, Gehlenborg N, Avillach P, Palmer NP, Chiovato L, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. NPJ Digit Med. 2020;3:109.

8. Vlug A, van der Lei J, Mosseveld B, van Wijk M, van der Linden P, MC S. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods of information in medicine. 1999;38:339-44.

9. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Informatics in primary care. 2011;19(3):135-45.

10. Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol. 2010;63(4):422-7.

11. United Nations Office on Drugs and Crime. World Drug Report 2022 - Drug Market Trends - Cannabis, Opioids. Austria: UNODC; 2022.

12. GBD 2016 Alcohol and Drug Use Collaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987-1012.

13. Shen J, Hua G, Li C, Liu S, Liu L, Jiao J. Prevalence, incidence, deaths, and disability-adjusted life-years of drug use disorders for 204 countries and territories during the past 30 years. Asian J Psychiatr. 2023;86:103677.

14. Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. "Every 'never' I ever said came true": transitions from opioid pills to heroin injecting. Int J Drug Policy. 2014;25(2):257-66.

15. Uusküla A, Raag M, Kurvits K, Laius O, Uusküla M, Oselin K. Trends in opioid prescribing in Estonia (2011-2017). Pharmacol Res Perspect. 2020;8(2):e00577.

16. Agardh EE, Allebeck P, Knudsen AKS, Aronsson AE, Flodin P, Eikemo TA, et al. Disease Burden Attributed to Drug use in the Nordic Countries: a Systematic Analysis for the Global Burden of Diseases,

Injuries, and Risk Factors Study 2019. International Journal of Mental Health and Addiction. 2025;23(1):618-49.

17. Danish Medicines Agency DMA. Opioid use in Denmark is decreasing. In: Danish Health Data Authority DMA, editor. 2020.

18. Rolová G, Skurtveit S, Handal M, Kurita GP, Lid TG, Odsbu I, Hoffmann M. Trends in opioid prescribing in Scandinavian countries from 2010 to 2023: Insights from multi-metric evaluation. Br J Clin Pharmacol. 2025.

19. Fugelstad A, Ågren G, Ramstedt M, Thiblin I, Hjelmström P. Oxycodone-related deaths in Sweden 2006-2018. Drug Alcohol Depend. 2022;234:109402.

20. Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. Lancet Public Health. 2019;4(10):e498-e505.

21. Häuser W, Morlion B, Vowles KE, Bannister K, Buchser E, Casale R, et al. European* clinical practice recommendations on opioids for chronic noncancer pain - Part 1: Role of opioids in the management of chronic noncancer pain. Eur J Pain. 2021;25(5):949-68.

22. Krčevski Škvarč N, Morlion B, Vowles KE, Bannister K, Buchsner E, Casale R, et al. European clinical practice recommendations on opioids for chronic noncancer pain - Part 2: Special situations. Eur J Pain. 2021;25(5):969-85.