Dynamics of the opioid crisis in the Netherlands

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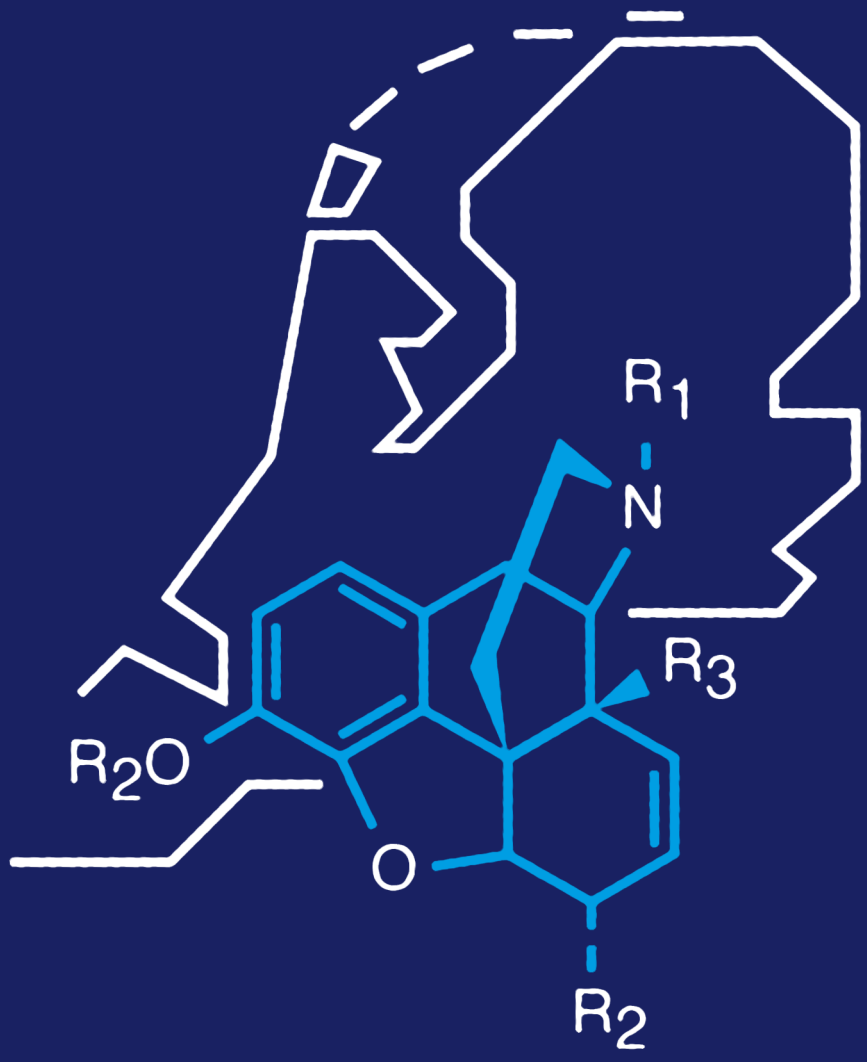

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CHAPTER 1

Introduction

The main aim of this thesis is to assess the prevalence of opioid use and associated health sequalae in the general population of the Netherlands between 2013 and 2018, and to characterize different (sub)populations of individuals who received an opioid prescription and those who suffered from many opioid-related adverse effects. To assess the breadth of problematic opioid use in the Netherlands we put the results of our analysis into context of other European countries and the United States. We also aimed to explore possible reasons for changing prescribing practice of analgesic medication within the Dutch health care system.

Opioids in the treatment of pain

The latex of the opium poppy, ***P. Somniferum L.,*** remains the commercial source of naturally occurring and semi-synthetic opioids [1]. These alkaloids have long been used for their effects for therapeutic and spiritual purposes [2]. Opioids hold a unique position in modern medicine; they are one of the World Health Organization's (WHO) essential medications [3], but are also considered narcotics and are thus controlled in most countries [4]. The therapeutic use of opioids long precedes our understanding of their mechanism of action or discovery of endogenous opioid receptors and ligands [5]. Endogenous opioid receptor ligands, β-endorphin, leu-enkephalin and met-enkephalin to name a few, act agonistically on mu (MOP), kappa (KOP), delta (DOP), and nociceptin receptor (NOP) opioid receptor subtypes [6]. Opioid receptors are ubiquitously present in a human body: they are scattered throughout the central nervous system and are present in many other tissues, including immune cells [7–10].

Binding of an opioid to an opioid receptor, particularly to a MOP subtype, produces analgesia, respiratory depression, pupil constriction, reduced gastrointestinal motility, euphoria (dysphoria and hallucination are induced by activation of the KOP receptor), sedation and physical dependence, and addiction [11]. Due to their modulative effects on nociception, opioids are used in pharmacotherapy of acute and chronic pain [12]. However, one of the most dangerous side-effect of their use is opioid-

induced respiratory depression that may lead to a fatal outcome (without prompt administration of an opioid antagonist)[13]. Apart from naturally occurring morphine and codeine, oxycodone, fentanyl, buprenorphine, and tramadol (either alone or in a fixed combination with paracetamol) are some of the most commonly prescribed opioid medications [14]. Together with non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, opioids constitute the WHO pain ladder [15], a guideline to step-wise approach to treatment of (cancer) pain.

The Opioid Epidemic

The opioid epidemic refers to an ongoing health-care crisis involving opioid use in the United States (US). In 1999, when Centers for Disease Control and Prevention started monitoring opioid overdose deaths [16], 6.1 people per 100,000 standard population died. This mortality rate increased to 19.8 per 100,000 standard population in 2016, when over 40,000 people died of an opioid overdose death [17]. This is more than the annual incidence of fatal car accidents [18]. The fatality rate was so high that a national health-care emergency was declared in 2016. To mitigate the burden of the opioid epidemic, the US government assigned approximately 115 billion US dollars for overdose prevention programs in 2017 alone [19]. Despite the efforts made, the US opioid epidemic has had a profound effect on the US society [20]. Over the course of twenty years, the type of opioids misused and abused has changed; it started with commonly prescribed opioids, was followed by heroin, and is now mostly attributed to synthetic opioids (mostly fentanyl), either prescribed or illicitly manufactured, and again to commonly prescribed opioids [21]. The use of opioids in the general US population is now at an all-time high – between February 2022 and March 2023 more than 100,000 individuals died due to an opioid overdose [22].

The leading cause behind the opioid overdose deaths is a cardiac arrest secondary to an opioid-induced respiratory depression, but there are other, not as hazardous side-effects of opioid use, but nonetheless with a great potential to do harm. It has been demonstrated that individuals who use or abuse opioids are in danger of serious injury due to falling and are more likely to cause a car crash [23,24]. Opioid users may also be at higher risk of infection, either by decreased motility of gastrointestinal tract or due to involvement of opioids in the regulation of immunity [25,26], and they are also at risk for developing physical dependence and addiction [27]. There is no opioid, used legally or illegally, neither short- or long-acting [28], in any type of pharmaceutical formulation

[29] that does not lead to physical dependence with prolonged use and may lead to development of an addiction under certain conditions.

Defining the vulnerable population at highest risk for opioid use, misuse, and abuse, and those at risk for an opioid overdose death in the US setting has proven to be quite challenging. Depending on whether we are aiming to identify population at risk for misuse or those who died from an overdose, socio-demographic characteristics may be diverse. In addition, the type of opioid misused or abused, either prescribed or illicitly obtained, adds an another layer of complexity to the research question. For example, older white women are more likely to receive a prescription for an opioid [30], whereas younger black men and younger white men most often die from an opioid overdose [31]. Commonly prescribed opioids are most likely to be abused by white middle aged men, thus leading to an opioid overdose [32], but illegally obtained opioids are involved in opioid overdose death of young white boys and men [33]. There is, however, no doubt that individuals with any prior addiction disorder, are at a great risk of developing an opioid use disorder [34].

Statistics Netherlands

The Centraal Bureau voor Statistiek (Statistics Netherlands) is a national statistics agency in the Netherlands. The agency collects, sorts, combines, and curates data on many topics, such as finances, demographics, and health. The raw data originates from many different sources and includes information on all Dutch residents [35]. This means more than 16 million rows of data [36]. (The reader is advised to refer to Table 1 for data availability for this thesis.) Apart from conducting their own research, the Statistics Netherlands offers their data collections to external researchers, but not before a review of a research proposal [37]. The data for which the access was granted cannot and should not be used for any other research questions that are not outlined in the protocol. The greatest strength of the collected information is in the possibility of linking various data sources by individual identifiers. These meaningless codes allow for merging of the data on an individual level, but cannot disclose the identity of an individual [35]. This opens many possibilities for research: new connections between seemingly unrelated topics can be observed and rare events that require great statistical power to be assessed are readily identifiable.

Table 1. An overview of the datasets available for this thesis

Dataset Name	Dataset Description	Calendar years
Medicijntab [38]	Reimbursed dispensed prescription medications on ATC-level 5	2006-2018
Medicijntab_Opioids[a]	Reimbursed dispensed prescription opioids on ATC level-4	2006-2018
Gbapersoontab [35]	Demographic characteristics of Dutch residents	1994-2022
Lmrbasis, Lbzbasistab [39,40]	Hospital admissions (including overnight observations) in public health centers, excluding outpatient visits	1995-2012 2003-2018
Lmr_Diagn, Lbzdiagnosentab [40,41]	Diagnoses of hospital admissions (including primary and secondaries), coded according to the ICD-(9)10 classification	1995-2012 2003-2018
Doodoorztab [42]	Causes of death of individuals who were residents of the Netherlands at the time of death, coded according to the ICD-10 classification	2013-2018
Inhatab [43]	Household income derived from income taxes	2011-2020
Gezondheidsmonitor [44]	National survey on adults (≥ 19 years old) about various health-related topics	2012-2016
Gezondheidsenquête [45]	National survey (all ages) about various health-related topics	2014-2017

ATC, anatomic therapeutic classification of the World Health Organization; ICD, international classification of diseases. [a] Dataset available upon request.

This table outlines the registers analyzed for the purpose of this thesis. The available registers are shortly described and the coverage in terms of calendar years are provided. For further reading about the data please refer to the respective references. These datasets are also further described in the following chapters.

Outline of this thesis

This thesis is divided in two general sections, **Part 1** and **Part 2** that address two distinct aims. In **Part 1**, we seek to assess prevalence of prescription opioid use and associated health sequalae in the general population of the Netherlands, and to characterize opioid users. Therefore, in **Chapter 2**, we determine the annual prevalence of opioid use and hospital admissions and deaths associated with opioid use, in the total population of the Netherlands between 2013 and 2017. We also identify socio-demographic and health-related risk factors. In **Chapter 3**, we further investigate the observed trend in opioid use and two possible reasons behind it and we explore the severity of opioid poisoning and assess the illicit opioid use in a hospital setting. In **Chapter 4**, we investigate relationship between opioid use and unplanned admission to the intensive care unit and all-cause mortality. Here we also identify predictors of both outcomes.

In **Part 2**, we aim to investigate possible explanations for increasing opioid use in the Netherlands. For this, in **Chapter 5**, we investigate whether decrease in prescribing of non-steroidal anti-inflammatory drugs (result that we obtained in Chapter 3) leads to a decrease in upper gastrointestinal bleeding which frequently associated with medication use. In **Chapter 6**, we compare prescribing rates of individual

analgesic medications in the Netherland to those in Slovenia, a country in European Union that is known for its stringent prescribing rules for opioids. Last, in **Chapter 7**, we summarize historical events that brought about the US opioid epidemic, we explore potential of opioids to promote misuse and abuse, we present challenges in pharmacoepidemiologic research into opioid effects, and we discuss opioid epidemic prevention strategies.

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PART 1

Assessing trends in opioid use and serious health outcomes in the general population of the Netherlands

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CHAPTER 2

Opioid prescription patterns and risk factors associated with opioid use in the Netherlands

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Ajda Bedene, Willem M. Lijfering, Marieke Niesters, Monique van Velzen, Frits R. Rosendaal, Marcel L. Bouvy, Albert Dahan, Eveline L.A. van Dorp

Abstract

Importance

An increase in opioid prescription was noted in the Netherlands. It is vital to identify risk factors for opioid prescription to ensure that health interventions remain appropriately targeted.

Objectives

To determine the prevalence of opioid prescriptions and adverse events associated with opioids, and to identify risk factors associated with opioid prescription in the Dutch population.

Design, Setting, and Participants

This cohort study used national statistics from the Netherlands from January 1, 2013, to December 31, 2017, including the full Dutch population of 16,779,575 people in 2013 and 17,081,507 people in 2017. Data from the Dutch Health Monitor surveys of 2012 and 2016 were also included. Databases were anonymized prior to analysis. All analyses were performed between December 2018 and February 2019.

Exposure

Opioid prescription.

Main outcomes and measures

The main outcomes were the dynamics of opioid prescriptions, hospital admissions for opioid overdose, and opioid overdose mortalities. The secondary outcome was risk factors associated with opioid prescription.

Results

In 2013, 814,211 individuals (4.9% of the total population) received an opioid prescription. In 2017, 1,027,019 individuals (6.0% of the total population) received at least 1 opioid prescription (mean [SD] age, 59.3 [18.5] years; 613 203 [59.7%] women). The rate of hospital admissions for opioid overdose was 9.2 per 100,000 inhabitants in 2013 and 13.1 per 100,000 inhabitants in 2017 (relative risk, 1.43 [95% CI, 1.34-1.52]). Similarly, an increased risk of opioid overdose death was observed, from 0.83 per 100,000 inhabitants in 2013 to 1.2 per 100,000 inhabitants in 2017 (relative risk, 1.49 [95% CI, 1.20-1.85]). Based on data from the 2012 Dutch Health Monitor survey, risk

factors associated with opioid prescription included being older than 65 years (odds ratio [OR], 4.20 [95% CI, 3.98-4.43]), having only a primary school education (OR, 3.62 [95% CI, 3.46-3.77]), being widowed (OR, 3.30 [95% CI, 3.13-3.49]), reporting always feeling symptoms of depression (OR, 3.77 [95% CI, 3.41-4.18]), and reporting poor or very poor physical health (OR, 10.40 [95% CI, 10.01- 10.81]). Self-reported back pain (OR, 4.34 [95% CI, 4.23-4.46]) and rheumatoid arthritis or fibromyalgia (OR, 3.77 [95% CI, 3.65-3.90]) were also associated with opioid prescription. However, unemployment (OR, 1.05 [95% CI, 0.96-1.13]) was not associated with opioid prescription, and alcohol use disorder (OR, 0.76 [95% CI, 0.73-0.80]) was negatively associated with opioid prescription.

Conclusion and Relevance

This study found that opioid prescriptions have increased in the Netherlands. Although the risk of adverse events is still relatively low, there is an urgent need to review pain management to prevent a further increase in opioid prescription.

Introduction

Opioids have been used for medicinal, recreational and religious purposes for more than 5,000 years [1]. In modern medicine, opioids are still the cornerstone of pain pharmacotherapy, e.g., in the management of postoperative acute pain and chronic pain associated with cancer [2–4]. An increasing body of evidence shows an increase in the prescription rate of opioids in the treatment of chronic pain not associated with cancer. This puts large numbers of individuals at risk for the potentially life-threatening adverse effects of opioids [5,6].

In the United States, a rapid increase in opioid use has been observed [7], and the proportion of US residents who filled at least one opioid prescription increased from 4.9% in 2006 to 17.4% in 2017 [8,9]. In 2015, approximately 2 million people in the United States experienced prescription opioid use disorder (i.e., addiction)[10], and there were approximately 400,000 opioid overdose deaths between 1999 and 2017 [11].

In 2015, about half a million citizens (3% of the population) received at least one oxycodone or fentanyl prescription, a 67% increase (approximately 200,000 individuals)

compared with 2012 [12]. Information on the dynamics of opioid prescription in the Netherlands is needed to prevent an increase in opioid overdose mortalities. Therefore, the aims of this study were to identify opioid prescription patterns, and changes in hospital admissions for opioid overdoses and opioid overdose mortality in the Netherlands, and to examine risk factors associated with opioid prescription in a large repeated national health survey.

Methods

The institutional review board of the anesthesiology department and intensive care unit of the Leiden University Medical Center approved the study and waived participant consent because we used deidentified data. Analyses were conducted between December 2018 and February 2019. We analyzed several anonymized databases from Statistics Netherlands covering the total population of the Netherlands. Statistics Netherlands collects information from several databases on prescription reimbursement data, hospital admission data with diagnosis, and mortality data on all causes of death and allows linkage on an individual level.

To identify opioid prescription, hospital admissions for opioid overdose, and opioid overdose mortalities, we performed an analysis including all individuals who lived in the Netherlands between January 1, 2013 and December 31, 2017. To identify risk factors associated with opioid prescriptions, and in all other analyses, we included participants of the September to November 2012 [13], and the September to November 2016 Dutch Health Monitor (DHM) survey [14].

Opioid prescription in the total Dutch population through time

Opioid reimbursement data were collected for all residents of the Netherlands registered in the municipal population register and entitled to pharmaceutical care (i.e., basic health insurance). These data come from the Health Care Insurance Board [15]. Opioids prescribed in hospitals and dispensed from outpatient or community pharmacies, or in care homes are collected in national reimbursement data, but medicines dispensed in hospitals are not. Opioids were classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification code N02A [16].

Hospital admissions for opioid overdose and opioid overdose deaths in the total Dutch population

The Dutch Hospital Data [17], a nationwide register of all inpatient hospital admissions and all hospital specialist outpatient clinical and emergency department visits since 2013, contains information about hospital admissions for opioid overdose. Each record contains the date of hospital inpatient and outpatient encounters, the discharge date, and discharge diagnoses. Diagnoses are coded according to the International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10CM) [18]. Hospital admissions for opioid overdose were identified with the F11 and T40 code series [19]. The Dutch Register of Causes of Death records all deaths in the Netherlands based on death certificates [20], encoded according to the ICD-10CM [18]. Opioid overdose deaths were classified with codes X40-45, Y10-15, Y47 and Y49 [21].

Characteristics of all participants and of individuals who received opioid prescriptions in the DHM

The DHM is a national health survey on well-being at a detailed subpopulation level [13,14]. The questionnaire was sent out by all Municipal Health Services to different random subsets of the population from September to November 2012 and from September to November 2016. Residents of the Netherlands aged 19 years or older were approached [13,14].

The DHM is a self-reported survey that includes educational level; marital status; lifestyle habits; employment; self-perceived physical health; ability to meet financial needs; body mass index (BMI), calculated as weight in kilograms divided by height in meters squared; frequency of feelings of depression; and severity of feeling of loneliness (based on an 11-point scale by de Jong-Gierveld et al [22]). Chronic disorders (e.g., history of cancer, headache or migraine, neck or shoulder pain, back pain, osteoarthritis of the hip or knee, and rheumatoid arthritis or fibromyalgia) were only queried in the 2012 DHM. Age, sex, immigration status (i.e., native, first generation, or second generation [based on the birth certificate]), and income data were obtained by Statistics Netherlands from the municipal registers, and household income data (based on quintile level) were obtained through tax records. We linked the 2012 and 2016 DHM data with national prescription reimbursement data.

Risk factors Associated with Opioid Prescription Among Participants in the DHM

Individuals surveyed in the 2012 and 2016 DHMs were considered opioid exposed if they filled at least 1 opioid prescription in that year. Opioid prescriptions were compared between the 2016 and 2012 DHMs.

The DHM oversampled individuals older than 65 years, which hampers direct translation to the total population. Therefore, we estimated age-specific risk rates of opioid prescription based on the age distribution of the Dutch population in a sensitivity analysis.

We investigated the characteristics of those receiving no, 1, 2 to 4, or 5 or more opioid prescriptions in the past 12 months in the 2012 DHM survey. Detailed information about the number of opioid prescriptions was available for the years 2012 through 2016 but not yet for 2017. 1 opioid prescription was considered a proxy for acute pain, and 5 or more opioid prescriptions was considered a proxy for chronic pain.

Trajectories of Individuals with Opioid Prescription in the 2012 DHM

We followed individuals who received an opioid prescription in the 2012 DHM for subsequent prescriptions, excluding those who died before January 1, 2013. By linking to the national reimbursement database, we assessed whether participants who had received an opioid prescription in 2012 filled at least 1 opioid prescription from 2013 to 2016, including prescription renewals (more than 1 opioid prescription). We stratified participants of 2012 DHM by self-reported morbidity (i.e., having cancer or having chronic noncancer pain in 12 months prior to the survey) for the longitudinal analysis of opioid prescription (adjusted for mortality) by linking national prescription and mortality database.

Statistical Analysis

To identify opioid prescription rate, hospital admissions for opioid overdose, and opioid overdose deaths, we obtained descriptive statistics for all residents living in the Netherlands between January 1, 2013 to December 31, 2017. Opioid prescriptions are shown as absolute numbers and as a proportion of the total population per calendar year. Findings are also presented as relative risk (RRs) with 95% confidence interval (CIs) that were calculated under the Poisson distribution assumption. Hospital admissions for opioid overdose and opioid overdose deaths are presented as number per 100,000

inhabitants per calendar year and as RRs with 95% CIs compared with 2013, the reference year. Similar descriptive analyses were performed in the 2012 and 2016 DHMs. To highlight risk factors associated with opioid prescription, we performed logistic regression analysis in the 2012 DHM. In the comparison of the 2016 DHM with the 2012 DHM, findings were adjusted for age, sex, level of education, standardized household income and marital status by logistic regression. Results are presented as odds ratios (ORs) with 95% CIs. We also performed a longitudinal analysis for opioid prescription from 2013 onwards, stratified by self-reported cancer and chronic noncancer pain.

Individuals with missing data for the relevant variables in the 2012 and 2016 DHMs were excluded from the analysis. For total population characteristics, there were no missing data, nor were individuals lost to follow-up. All statistical analyses were performed with SPSS Statistics version 24.0 (IBM).

Results

Opioid prescription, hospital admissions for opioid overdose, and opioid overdose deaths among the total Dutch population

Among the total population of 16,779,575 people in the Netherlands in 2013, 814,211 individuals (4.9%) received an opioid prescription. The number of opioid prescriptions increased to 1,027,019 of 17,081,507 people (6.0%) in 2017, a 24% relative increase. The mean (SD) age of individuals who received an opioid prescription was 59.3 (18.5) years in 2017; 613,203 women (59.7%) and 413,816 men (40.3%) received an opioid prescription (Table 1).

Table 1. Opioid prescription changes, hospital admissions for opioid overdose and opioid overdose deaths in the Netherlands from 2013 to 2017

	Opioid prescription[a]		Hospital admissions for opioid overdose, per 100,000[b]		Opioid overdose deaths, per 100,000c	
	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)	No. (%)	RR (95% CI)
2013 (n=16779575)	814211 (4.9)	1.00 (reference)	1537 (9.2)	1.00 (reference)	139 (0.8)	1.00 (reference)
2014 (n=16829290)	863110 (5.1)	1.06 (1.05-1.06)	1619 (9.6)	1.05 (0.98-1.13)	139 (0.8)	1.00 (0.79-1.26)
2015 (n=16900726)	921754 (5.5)	1.12 (1.12-1.13)	1801 (10.7)	1.16 (1.09-1.25)	158 (0.9)	1.13 (0.90-1.42)
2016 (n=16979120)	975979 (5.8)	1.18 (1.18-1.19)	2115 (12.5)	1.36 (1.27-1.45)	187 (1.1)	1.33 (1.07-1.66)
2017 (n=17081507)	1027019 (6.0)	1.24 (1.24-1.24)	2236 (13.1)	1.43 (1.34-1.52)	211 (1.2)	1.49 (1.20-1.85)

Abbreviation: RR, relative risk; CI confidence intervals

[a] identified by World Health Organization Anatomical Therapeutic Chemical classification code N02A.

[b] identified by International Statistical Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10CM) codes F11 and T40 series.

[c] identified by (ICD-10CM) codes X40-45, Y10-15, Y47 and Y49.

We identified an increase in hospital admissions for opioid overdose. This rate was 9.2 per 100,000 inhabitants in 2013 and 13.1 per 100,000 inhabitants in 2017 (RR, 1.43, [95% CI, 1.34-1.52]). Similarly, an increased risk of opioid overdose death was observed, from 0.83 per 100,000 inhabitants in 2013 to 1.2 per 100,000 inhabitants in 2017 (RR, 1.49; [95% CI, 1.20-1.85])(Table 1).

Characteristics of all participants and of individuals who received opioid prescriptions in the 2012 and 2016 DHMs

The response rate of the 2012 DHM varier between 45% and 50% per Municipal Health Service. In the 2016 DHM, more people were contacted, but at 40%, the response rate was slightly lower than in 2012. The 2012 DHM contained records for 387,195 individuals (mean [SD] age, 57.3 [18.0] years; 211,281 [54.6%] women), and the 2016 DHM contained records for 457,153 individuals (mean [SD] age, 60.3 [17.3] years; 247,116 [54%1] women). There was an overlap of 17,502 individuals (2.1%) between 2012 and 2016 DHMs, whereas 826,846 individuals (97.9%) were unique.

Characteristics of participants in the 2012 and 2016 DHM survey are presented in Table 2. In the 2012 DHM, 29,553 individuals (7.6%) received an opioid prescription (mean [SD] age, 64.8 [15.6] years; 8,546 [8.8%] women). Of these, 16,140 (54.6%) received more than 1 opioid prescription (eTable 1 in the Supplement). In the 2016 DHM, 37,458 individuals (8.2%) received an opioid prescription (mean [SD] age, 67.1 [14.4] years; 22,864 [9.3%] women).

Table 2. Characteristics of all participants and of individuals who received opioid prescriptions in the 2012 and 2016 Dutch Health Monitor Surveys

Characteristic	No./Total No. (%)			
	2012		2016	
	Overall	Received N02A Prescription	Overall	Received N02A Prescription
Total	**387195 (100)**	**29553/387195 (7.6)**	**457153 (100)**	**37458/457153 (8.2)**
Sex				
Men	175914/387195 (45)	11007/175914 (6.3)	210037/457153 (46)	14594/210037 (6.9)
Women	211281/387195 (55)	18546/211281 (8.8)	247116/457153 (54)	22864/247116 (9.3)
Age group, years				
19-35	53519/376384 (14)	1492/53519 (2.8)	50097/457153 (11)	1370/50097 (2.7)
35-45	43166/376384 (12)	1957/43166 (4.5)	40134/457153 (8.8)	1753/40134 (4.4)
45-55	56275/376384 (15)	3456/56275 (6.1)	60105/457153 (13)	3679/60105 (6.1)
55-65	60617/376384 (16)	4480/60617 (7.4)	71548/457153 (16)	5510/71548 (7.7)
> 65	162807/376384 (43)	17485/162807 (11)	235269/457153 (52)	25146/235269 (11)
Highest level of education				
Primary school	37138/373998 (10)	5080/37138 (14)	31823/425731 (7.5)	4602/31823 (15)
High school, underclassman[a]	131079/373998 (35)	12387/131079 (10)	141231/425731 (33)	14849/141231 (11)
High School, upperclassman[b]	105863/373998 (28)	6432/105863 (6.1)	130099/425731 (31)	9056/130099 (7.0)
College or more	99918/373998 (27)	4196/99918 (4.2)	122578/425731 (29)	5825/122578 (4.8)
Immigration status				
Native (Dutch)	335103/387195 (87)	25181/335103 (7.5)	397808/457153 (87)	32472/397808 (8.2)
First generation	28163/387195 (7.3)	2457/28163 (8.7)	32101/457153 (7.0)	2674 /32101 (8.3)
Second generation	23927/387195 (6.2)	1914/23927 (8.0)	27244/457153 (6.0)	2312/27244 (8.5)
Standardized household income, quintile[c]				
First	39072/384843 (10)	3659 /39072 (9.4)	37996/454276 (8.3)	3832/37996 (10)
Second	74437/384843 (19)	8127/74437 (11)	90475/454276 (20)	11142/90475 (12)
Third	82154/384843 (21)	6653/82154 (8.1)	100440/454276 (22)	8542/100440 (8.5)
Fourth	91375/384843 (24)	5916/91375 (6.5)	109165/454276 (24)	7439/109165 (6.8)
Fifth	97805/384843 (25)	5119/97805 (5.2)	116200/454276 (25)	6385/116200 (5.5)
Marital status				
Married or in partnership	262953/370390 (71)	18655/262953 (7.1)	316264/445961 (71)	24162/316264 (7.6)
Unmarried or single	42944/370390 (11)	1858/42944 (4.3)	46600/445961 (10)	2179/46600 (4.7)
Divorced	23424/370390 (6.3)	2389/23424 (10)	30862/445961 (6.9)	3177/30862 (10)
Widowed	41069/370390 (11)	5334/41069 (13)	52235/445961 (12)	6942/52235 (13)
Smoking status				
Nonsmoker	146773/363454 (40)	9152/146773 (6.2)	172754/424548 (41)	11452/172754 (6.6)
Former smoker	144863/363454 (40)	12007/144863 (8.3)	182754/424548 (43)	16538/182754 (9.0)
Current smoker	71818/363454 (20)	6058/71818 (8.4)	69040/424548 (16)	6443/69040 (9.3)
Comorbidity during the past 12 months				
Cancer	11026/369384 (3.0)	2108/11026 (19)	NA	NA
Headache or migraine	47634/334901 (14)	4940/47634 (10)	NA	NA
Neck or shoulder pain	39242/337196 (12)	6819 /39242 (17)	NA	NA
Back pain	42699/337289 (13)	9163/42699 (22)	NA	NA
Arthrosis of the hip or knee	72142/338617 (21)	11895/72142 (17)	NA	NA

Table 2. Characteristics of all participants and of individuals who received opioid prescriptions in the 2012 and 2016 Dutch Health Monitor Surveys *(continued)*

Characteristic	No./Total No. (%)			
	2012		2016	
	Overall	Received N02A Prescription	Overall	Received N02A Prescription
Total	**387195 (100)**	**29553/387195 (7.6)**	**457153 (100)**	**37458/457153 (8.2)**
Rheumatoid arthritis or fibromyalgia	24761/336003 (7.4)	5274/24761 (21)	NA	NA
Feelings of depression				
Always	2404/365277 (0.7)	467/2404 (19)	2943/436725 (0.7)	627/2943 (21)
Often	8979/365277 (2.5)	1442/8979 (16)	10872/436725 (2.5)	1864/10872 (17)
Sometimes	36730/365277 (10)	4368/36730 (12)	46831/436725 (11)	6186/46831 (13)
Rarely	89587/365277 (25)	7591/89587 (8.5)	116461/436725 (27)	10221/116461 (8.8)
Never	227577/365277 (62)	13666/227577 (6.0)	259618/436725 (59)	16617/259618 (6.4)
Feeling of lonelinessd				
Not lonely	216407/358213 (60)	467/216407 (19)	239971/450146 (57)	16285/239971 (6.8)
Somewhat lonely	114222/358213 (32)	1442/114222 (16)	144307/450146 (34)	13026/144307 (9.0)
Lonely	17980/358213 (5.0)	4368/17980 (12)	23816/450146 (5.7)	2908/23816 (12)
Very lonely	9604/358213 (2.7)	7591/9604 (8.5)	12695/450146 (3.0)	1754/12695 (14)
Ability to meet financial needs				
No difficulties	160284/363596 (44)	9615/160284 (6.0)	217319/421510 (52)	14036/217319 (6.5)
Just able	138441/363596 (38)	10718/138441 (7.7)	147605/421510 (35)	12973/147605 (8.8)
Some difficulties	49777/363596 (14)	5141/49777 (10)	44072/421510 (11)	5274/44072 (12)
Great difficulties	15094/363596 (4.2)	2129/15094 (14)	12514/421510 (3.0)	1955/12514 (16)
Other variables				
Heavy drinkere	30585/357491 (8.6)	1791/30585 (5.9)	34682/423970 (8.2)	2304/34682 (6.6)
Lives alone	70210/341606 (21)	7533/70210 (11)	95136/446588 (21)	10604/95136 (11)
Unemployed	8369/349560 (2.4)	636/8369 (7.6)	8571/407636 (1.9)	625/8571 (7.3)
Physical health				
Very good or good	276830/382208 (72)	11265/276830 (4.1)	323416/451423 (72)	14318/323416 (4.4)
Fair	89435/382208 (23)	12776/89435 (14)	107125/451423 (24)	15866/107125 (15)
Poor or very poor	15943/382208 (4.2)	4880/15943 (31)	20882/451423 (4.6)	6698/20882 (32)
BMI				
< 18.5	5061/371808 (1.4)	506/5061 (10)	5642/435892 (1.3)	588/5642 (10)
18.5-20	13845/371808 (3.6)	768/13845 (5.7)	15186/435892 (3.5)	963/15186 (6.3)
20-25	159525/371808 (43)	9344/159525 (5.9)	180510/435892 (41)	11105/180510 (6.2)
25-30	143098/371808 (39)	11198/143098 (7.8)	168617/435892 (39)	13788/168617 (8.2)
> 30	50639/371808 (14)	6120/50639 (12)	65937/435892 (15)	8662/65937 (13)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); N02A, World Health Organization Anatomical Therapeutic Chemical classification code for an opioid; NA, not available.

[a] Junior secondary vocational education (i.e., MAVO or LBO in the Dutch educational system).

[b] Senior secondary general education, university preparatory education, or senior secondary vocational education (i.e., HAVO, VWO, or MBO, respectively, in the Dutch educational system).

[c] First indicates incomes in the lowest 20% and fifth indicates incomes in the highest 20% of all reported incomes.

[d] Measured using the scale by de Jong-Gierveld etal. [22]

[e] Defined as at least 4 units of alcohol for women or 6 units of alcohol for men per day at least once per week.

Risk factors associated with opioid prescription in DHMs

Risk factors associated with opioid prescription are presented in Table 3. Among others, we found that being older than 65 years (OR, 4.20 [95% CI, 3.98-4.43]), being a woman (OR, 1.44 [95% CI, 1.41-1.48]), having only completed primary school (OR, 3.62 [95% CI, 3.46-3.77]), being divorced (OR, 2.51 [95% CI, 2.36-2.67]) or widowed (OR, 3.30 [95% CI, 3.13-3.49]), smoking (OR, 1.39 [95% CI, 1.34-1.43]), or having a BMI greater than 30 (OR, 2.28 [95% CI, 2.11-2.46]) were associated with opioid prescription in the 2012 DHM. Other individual characteristics associated with opioid prescription were back pain (OR, 4.34 [95% CI, 4.23-4.46]), rheumatoid arthritis or fibromyalgia (OR, 3.77 [95% CI, 3.65-3.90]), cancer (OR, 3.00 [95% CI, 2.86-3.15]). Factors related to emotional well-being and stress, such as increased feelings of depression (always vs never: 3.77 [95% CI, 3.41-4.18]), increased severity of feelings of loneliness (very lonely vs not lonely: OR, 2.39 [95% CI, 2.25-2.54]), and having difficulty meeting financial needs (great difficulties vs no difficulties: OR, 2.57 [95% CI, 2.45-2.71]) were also associated with increased risk of opioid prescription with increasing severity. Individuals who reported poor physical health status had increased odds of opioid prescription compared with individuals who reported good physical health (OR, 10.4 [95% CI, 10.0-10.8]). We did not find an association of opioid prescription with being unemployed (OR, 1.05 [95% CI, 0.96-1.13]), unhealthy alcohol use, defined as at least 4 units of alcohol for women or 6 units of alcohol for men per day at least once per week, was negatively associated with opioid prescription (OR, 0.76 [95% CI, 0.73-0.80]). Opioids were prescribed more than once during the year for more than 50% of individuals who received a prescription, with the highest number of repeated prescriptions groups in which we also found the highest ORs (eTable 1 in the Supplement).

Table 3. Risk factors associated with opioid prescription in the 2012 Dutch health monitor survey and increase in opioid prescription in the 2016 Dutch Health Monitor survey

	Odds ratio (95% CI)	
Factor	2012 N02A Prescription	2016 vs 2012 N02A Prescription, Adjusted[a]
Total	1.00 (reference)	1.05 (1.03-1.06)
Sex		
Men	1.00 (reference)	1.06 (1.03-1.09)
Women	1.44 (1.41-1.48)	1.04 (1.02-1.06)
Age group, years		
19-35	1.00 (reference)	1.05 (0.97-1.14)
35-45	1.66 (1.55-1.77)	1.04 (0.97-1.11)
45-55	2.28 (2.15-2.43)	1.05 (1.00-1.11)
55-65	2.78 (2.62-2.95)	1.08 (1.03-1.13)
> 65	4.20 (3.98-4.43)	1.04 (1.01-1.06)
Highest level of education		
Primary school	3.62 (3.46-3.77)	1.06 (1.01-1.11)
High school, underclassman[b]	2.38 (2.30-2.47)	1.06 (1.04-1.09)
High School, upperclassman[c]	1.48 (1.42-1.54)	1.04 (1.00-1.07)
College or more	1.00 (reference)	1.01 (0.97-1.06)
Immigration status		
Native (Dutch)	1.00 (reference)	1.06 (1.04-1.08)
First generation	1.18 (1.13-1.23)	0.94 (0.88-1.00)
Second generation	1.07 (1.02-1.12)	1.01 (0.95-1.08)
Standardized household income, quintile[d]		
First	1.87 (1.79-1.96)	1.07 (1.02-1.13)
Second	2.22 (2.14-2.30)	1.11 (1.07-1.14)
Third	1.60 (1.54-1.66)	1.00 (0.97-1.04)
Fourth	1.25 (1.21-1.30)	1.01 (0.97-1.05)
Fifth	1.00 (reference)	1.02 (0.98-1.06)
Marital status		
Married or in partnership	1.69 (1.61-1.77)	1.05 (1.03-1.07)
Unmarried or single	1.00 (reference)	1.02 (0.95-1.09)
Divorced	2.51 (2.36-2.67)	1.00 (0.94-1.06)
Widowed	3.30 (3.13-3.49)	1.06 (1.01-1.10)
Smoking status		
Nonsmoker	1.00 (reference)	1.03 (0.99-1.06)
Former smoker	1.36 (1.32-1.40)	1.07 (1.04-1.09)
Current smoker	1.39 (1.34-1.43)	1.07 (1.03-1.12)
Comorbidity during the past 12 months[e]		
Cancer	3.00 (2.86-3.15)	NA
Headache or migraine	1.48 (1.43-1.53)	NA
Neck or shoulder pain	3.00 (2.92-3.10)	NA
Back pain	4.34 (4.23-4.46)	NA
Arthrosis of the hip or knee	3.33 (3.24-3.41)	NA

Table 3. Risk factors associated with opioid prescription in the 2012 Dutch health monitor survey and increase in opioid prescription in the 2016 Dutch Health Monitor survey *(continued)*

	Odds ratio (95% CI)	
Rheumatoid arthritis or fibromyalgia	3.77 (3.65-3.90)	NA
Feelings of depression		
Always	3.77 (3.41-4.18)	1.09 (0.94-1.25)
Often	3.00 (2.82-3.18)	1.06 (0.97-1.14)
Sometimes	2.11 (2.04-2.19)	1.08 (1.04-1.13)
Rarely	1.45 (1.41-1.49)	1.01 (0.97-1.04)
Never	1.00 (reference)	1.02 (0.99-1.05)
Feeling of loneliness[f]		
Not lonely	1.00 (reference)	1.04 (1.02-1.07)
Somewhat lonely	1.38 (1.34-1.41)	1.04 (1.01-1.07)
Lonely	2.06 (1.96-2.16)	0.99 (0.93-1.06)
Very lonely	2.39 (2.25-2.54)	1.01 (0.93-1.09)
Ability to meet financial needs		
No difficulties	1.00 (reference)	1.05 (1.02-1.08)
Just able	1.32 (1.28-1.35)	1.09 (1.06-1.12)
Some difficulties	1.81 (1.74-1.87)	1.09 (1.04-1.14)
Great difficulties	2.57 (2.45-2.71)	1.09 (1.02-1.17)
Other variables[g]		
Heavy drinker[h]	0.76 (0.73-0.80)	1.04 (0.98-1.12)
Lives alone	1.69 (1.64-1.74)	1.03 (1.00-1.06)
Unemployed	1.05 (0.96-1.13)	0.96 (0.85-1.08)
Physical health		
Very good or good	1.00 (reference)	1.04 (1.01-1.07)
Fair	3.93 (3.83-4.04)	1.03 (1.00-1.06)
Poor or very poor	10.4 (10.0-10.8)	1.08 (1.03-1.13)
BMI		
< 18.5	1.84 (1.64-2.07)	0.93 (0.81-1.07)
18.5-20	1.00 (reference)	1.02 (0.92-1.07)
20-25	1.03 (0.96-1.11)	1.01 (0.98-1.04)
25-30	1.41 (1.30-1.52)	1.03 (0.99-1.05)
> 30	2.28 (2.11-2.46)	1.09 (1.05-1.13)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); N02A, World Health Organization Anatomical Therapeutic Chemical classification code for an opioid; NA, not available.

[a] Adjusted for age, sex, level of education, standardized household income, and marital status.

[b] Junior secondary vocational education (i.e., MAVO or LBO in the Dutch educational system).

[c] Senior secondary general education, university preparatory education, or senior secondary vocational education (HAVO, VWO, or MBO, respectively, in the Dutch educational system).

[d] First indicates incomes in the lowest 20% of all reported incomes, and fifth indicates incomes in the highest 20%.

[e] Compared with not having any of the listed comorbidities.

[f] Measured using the scale by de Jong-Gierveld et al. [22]

[g] Compared with nonheavy drinker, not living alone, and employed.

[h] Defined as at least 4 units of alcohol for women or 6 units of alcohol for men per day at least once per week.

Opioid prescriptions increased between the 2012 DHM and the 2016 DHM (adjusted OR, 1.05 [95% CI, 1.03-1.06]). Risk factors associated with opioid prescription that were identified in the 2012 DHM were also associated with opioid prescription in the 2016 DHM. Furthermore, groups that were not associated with increased risk of opioid prescription in the 2012 DHM were more likely to receive an opioid prescription in the 2016 DHM, as most ORs were higher than 1.00. Opioid prescription rates in the 2012 and 2016 DHM survey were similar to those of the whole country when stratified by age (eTable 2 in the Supplement).

Risk factors for single and multiple opioid prescriptions among participants in the 2012 DHM

We classified participants according to the number of prescriptions they filled in the 2012 DHM. Among 29,553 individuals who filled at least 1 opioid prescription in the 2012 DHM, 13,413 (45.4%) filled only 1 opioid prescription, 8,928 (30.2%) filled 2 to 4 prescriptions, and 7,212 (24.4%) filled 5 or more opioid prescriptions (eTable 3 in the Supplement). Risk factors associated with 1, 2 to 4, and 5 or more opioid prescriptions are presented in Table 4 (crude numbers are presented in eTable 4 in the Supplement). Repeated prescriptions were associated with previously identified risk factors for opioid prescription, and 5 or more prescriptions were particularly associated with these same risk factors, such as being older than 65 years (OR, 10.9 [95% CI, 9.27-12.8]), having great difficulty meeting financial needs (OR 3.42 [95% CI, 3.13-3.74]), having only a primary school education (OR, 6.26 [95% CI, 5.73-6.84]), being divorced (OR, 2.90 [95% CI, 2.55-3.29) or widowed (OR, 4.68 [95% CI, 4.20-5.22]), and having comorbidities (cancer: OR, 4.22 [95% CI, 3.91-4.56]; back pain: OR, 7.44 [95% CI, 7.10-7.81]; arthrosis of the hip or knee: OR, 4.90 [95% CI, 4.67-5.13]; rheumatoid arthritis or fibromyalgia: OR, 5.55 [95% CI, 5.25-5.85]).

Table 4. Risk factors associated with number of opioid prescriptions in the 2012 Dutch Health Monitor

Factor	Odds Ratio (95% CI)		
	1 N02A Prescription	**2-4 N02A Prescription**	**≥ 5 N02A Prescription**
Sex			
Men	1.00 (reference)	1.00 (reference)	1.00 (reference)
Women	1.27 (1.22-1.31)	1.43 (1.37-1.50)	1.72 (1.64-1.81)
Age group, years			
19-35	1.00 (reference)	1.00 (reference)	1.00 (reference)
35-45	1.47 (1.35-1.61)	1.80 (1.58-2.06)	2.30 (1.89-2.79)
45-55	1.77 (1.63-1.91)	2.62 (2.32-2.96)	4.27 (3.58-5.09)
55-65	1.97 (1.82-2.12)	3.41 (3.04-3.83)	5.63 (4.75-6.68)
> 65	2.43 (2.28-2.60)	5.13 (4.61-5.70)	10.9 (9.3-12.8)
Highest level of education			
Primary school	2.28 (2.14-2.43)	3.70 (3.43-3.99)	6.26 (5.73-6.84)
High school, underclassman[a]	1.86 (1.77-1.95)	2.45 (2.30-2.62)	3.41 (3.14-3.70)
High School, upperclassman[b]	1.35 (1.28-1.43)	1.45 (1.35-1.56)	1.79 (1.63-1.96)
College or more	1.00 (reference)	1.00 (reference)	1.00 (reference)
Immigration status			
Native (Dutch)	1.00 (reference)	1.00 (reference)	1.00 (reference)
First generation	1.24 (1.17-1.32)	1.25 (1.16-1.34)	0.93 (0.85-1.02)
Second generation	1.08 (1.00-1.15)	1.03 (0.95-1.13)	1.09 (0.99-1.20)
Standardized household income, quintile[c]			
First	1.42 (1.33-1.52)	1.88 (1.74-2.03)	2.91 (2.66-3.18)
Second	1.53 (1.45-1.61)	2.25 (2.11-2.40)	3.75 (3.47-4.05)
Third	1.36 (1.30-1.44)	1.58 (1.47-1.69)	2.14 (1.97-2.33)
Fourth	1.15 (1.09-1.21)	1.25 (1.17-1.34)	1.51 (1.38-1.65)
Fifth	1.00 (reference)	1.00 (reference)	1.00 (reference)
Marital status			
Married or in partnership	1.54 (1.44-1.65)	1.86 (1.70-2.04)	1.68 (1.52-1.87)
Unmarried or single	1.00 (reference)	1.00 (reference)	1.00 (reference)
Divorced	1.95 (1.79-2.14)	2.88 (2.57-3.23)	2.90 (2.55-3.29)
Widowed	2.18 (2.02-2.36)	3.56 (3.22-3.94)	4.68 (4.20-5.22)
Smoking status			
Nonsmoker	1.00 (reference)	1.00 (reference)	1.00 (reference)
Former smoker	1.26 (1.21-1.31)	1.40 (1.34-1.48)	1.42 (1.34-1.50)
Current smoker	1.25 (1.19-1.32)	1.38 (1.30-1.47)	1.57 (1.47-1.67)
Comorbidity during the past 12 months			
Cancer	2.03 (1.88-2.20)	2.64 (2.43-2.87)	4.22 (3.91-4.56)
Headache or migraine	1.39 (1.32-1.45)	1.42 (1.34-1.50)	1.60 (1.51-1.70)
Neck or shoulder pain	2.12 (2.02-2.21)	2.92 (2.78-3.07)	3.94 (3.74-4.15)
Back pain	2.31 (2.21-2.41)	4.17 (4.00-4.37)	7.44 (7.10-7.81)
Arthrosis of the hip or knee	2.23 (2.15-2.31)	3.25 (3.12-3.39)	4.90 (4.67-5.13)
Rheumatoid arthritis or fibromyalgia	2.31 (2.20-2.43)	3.40 (3.22-3.60)	5.55 (5.25-5.85)
Feelings of depression			
Always	2.04 (1.72-2.42)	3.58 (3.02-4.24)	6.69 (5.70-7.84)

Table 4. Risk factors associated with number of opioid prescriptions in the 2012 Dutch Health Monitor *(continued)*

Factor	Odds Ratio (95% CI)		
	1 N02A Prescription	**2-4 N02A Prescription**	**≥ 5 N02A Prescription**
Often	1.89 (1.72-2.07)	2.77 (2.50-3.07)	5.10 (4.62-5.62)
Sometimes	1.54 (1.46-1.62)	2.05 (1.93-2.18)	3.25 (3.04-3.47)
Rarely	1.22 (1.17-1.27)	1.44 (1.36-1.51)	1.95 (1.84-2.06)
Never	1.00 (reference)	1.00 (reference)	1.00 (reference)
Feeling of loneliness[d]			
Not lonely	1.00 (reference)	1.00 (reference)	1.00 (reference)
Somewhat lonely	1.17 (1.13-1.22)	1.44 (1.38-1.52)	1.66 (1.57-1.75)
Lonely	1.51 (1.41-1.63)	2.11 (1.95-2.30)	2.84 (2.60-3.10)
Very lonely	1.68 (1.53-1.84)	2.17 (1.95-2.42)	3.78 (3.42-4.18)
Ability to meet financial needs			
No difficulties	1.00 (reference)	1.00 (reference)	1.00 (reference)
Just able	1.21 (1.16-1.26)	1.35 (1.29-1.42)	1.43 (1.35-1.52)
Some difficulties	1.54 (1.46-1.62)	1.78 (1.67-1.89)	2.18 (2.04-2.34)
Great difficulties	1.90 (1.76-2.05)	2.53 (2.32-2.76)	3.42 (3.13-3.74)
Other variablese			
Heavy drinker[f]	0.87 (0.81-0.93)	0.82 (0.75-0.89)	0.53 (0.47-0.60)
Lives alone	1.27 (1.22-1.33)	1.72 (1.64-1.81)	2.36 (2.24-2.48)
Unemployed	1.12 (1.00-1.25)	1.15 (1.00-1.32)	0.77 (0.64-0.93)
Physical health			
Very good or good	1.00 (reference)	1.00 (reference)	1.00 (reference)
Fair	2.45 (2.36-2.54)	4.07 (3.88-4.27)	8.71 (8.17-9.29)
Poor or very poor	3.41 (3.20-3.63)	8.51 (7.98-9.07)	33.4 (31.2-35.9)
BMI			
< 18.5	1.41 (1.18-1.69)	1.97 (1.58-2.45)	2.20 (1.80-2.68)
18.5-20	1.00 (reference)	1.00 (reference)	1.00 (reference)
20-25	1.08 (0.97-1.21)	1.17 (1.01-1.35)	0.82 (0.72-0.95)
25-30	1.42 (1.28-1.59)	1.69 (1.46-1.95)	1.06 (0.93-1.22)
> 30	1.99 (1.77-2.23)	2.77 (2.39-3.21)	1.94 (1.68-2.23)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); N02A, World Health Organization Anatomical Therapeutic Chemical classification code for an opioid.

[a] Junior secondary vocational education (ie, MAVO or LBO in the Dutch educational system).

[b] Senior secondary general education, university preparatory education, or senior secondary vocational education (HAVO, VWO, or MBO, respectively, in the Dutch educational system).

[c] First indicates incomes in the lowest 20% of all reported incomes, and fifth indicates incomes in the highest 20%.

[d] Measured using the scale by de Jong-Gierveld et al. [22]

[e] Compared with nonheavy drinker, not living alone, and employed.

[f] Defined as at least 4 units of alcohol for women or 6 units of alcohol for men per day at least once per week.

Trajectories of individuals with opioid prescriptions in the 2012 DHM

We followed participants of the 2012 DHM by linking them to national prescription statistics (Table 5). Of 386,470 participants who responded to 2012 DHM, 29,553 participants (7.6%) received an opioid prescription, which increased to 33,626 participants (9.1%) in 2016. Opioid prescription prevalence increased from 7.6% in 2012 to 12.2% in 2013 and to 22.7% in 2016, meaning that 22.7% of participants in the 2012 DHM had received an opioid prescription during the 4-year follow-up. We stratified participants in the 2012 DHM by cancer pain vs noncancer pain history.

Table 5. Trajectories of individuals with opioid prescription in the 2012 Dutch Health Monitor survey stratified by self-reported cancer or noncancer pain[a]

	No. (%)			
	2013 (n=386470)	**2014 (n=381818)**	**2015 (n=376667)**	**2016 (n=370747)**
Opioid prescription incidence, past 12 months	28929 (7.5)	30476 (8.0)	32405 (8.6)	33626 (9.1)
Opioid prescription prevalence, past 4 years	47289 (12)	60841 (16)	73155 (19)	84195 (23)
Death since 2012, n (%)	4652 (1.2)	5151 (1.3)	5920 (1.6)	6432 (1.7)
Cancer pain,	10830 (2.8)	9880 (2.6)	9202 (2.4)	8681 (2.3)
Opioid prescription incidence, past 12 months	2054 (19)	1701 (17)	1615 (18)	1531 (18)
RR (95% CI)	1.00 (reference)	0.91 (0.85-0.97)	0.93 (0.87-0.99)	0.93 (0.87-0.99)
1 opioid prescription	524 (4.8)	484 (4.9)	489 (5.3)	444 (5.0)
> 1 opioid prescription	1530 (14)	1217 (12)	1126 (12)	1087 (13)
Opioid prescription prevalence, past 4 years	3157 (29)	3163 (32)	3300 (36)	3458 (40)
RR (95% CI)	1.00 (reference)	1.10 (1.05-1.15)	1.23 (1.17-1.29)	1.37 (1.30-1.43)
Death since 2012	950 (8.7)	678 (6.9)	521 (5.6)	490 (5.6)
Noncancer pain[b]	143357 (37)	141348 (37)	139165 (37)	136674 (37)
Opioid prescription incidence, past 12 months	17481 (12)	17895 (13)	18766 (13)	19233 (14)
RR (95% CI)	1.00 (reference)	1.04 (1.02-1.06)	1.11 (1.08-1.13)	1.15 (1.13-1.18)
1 opioid prescription	6785 (4.7)	6514 (4.6)	6608 (4.7)	6528 (4.8)
> 1 opioid prescription	10696 (7.5)	11381 (8.1)	12158 (8.7)	12705 (9.3)
Opioid prescription prevalence, past 4 years	28259 (20)	34958 (25)	40838 (29)	45775 (33)
RR (95% CI)	1.00 (reference)	1.25 (1.24-1.27)	1.49 (1.47-1.51)	1.71 (1.67-1.72)
Death since 2012	2009 (1.4)	2183 (1.5)	2491 (1.8)	2787 (2.0)

Abbreviation: RR, relative risk; CI, confidence intervals.

[a] Of 387,195 individuals enrolled in the 2012 Dutch Health Monitor survey, 725 (0.2%) died before January 1, 2013. Percentages shown are cumulative incidences of those who were alive on January 1 per calendar year unless otherwise specified.

[b] Noncancer pain was identified as self-reported headache or migraine, neck or shoulder pain, backpain, arthrosis of hip or knee, or rheumatoid arthritis or fibromyalgia.

Of 11,026 participants who reported having cancer in 2012, 2,108 (19.1%) received an opioid prescription in 2012. By 2013, 2,054 individuals with cancer pain (19.0%) had received an opioid prescription in the past year, and this rate further decreased to 1,531 individuals (17.6%) in 2016 (RR, 0.93 [95% CI, 0.87- 0.99]). In 2013, 17,481 of 143,357 participants with noncancer pain (12.2%) reimbursed an opioid prescription, and by 2016, 19,233 of 136,674 participants with noncancer pain (14.1%) had reimbursed an opioid prescription (RR, 1.15 [95% CI, 1.13-1.18]). In 2016, opioid prescription prevalence at the 4-year follow-up was 39.8% (3,458 participants) among the group with cancer pain (RR, 1.37 [95% CI, 1.30-1.43]) and 33.5% (44 775 participants) among the group with noncancer pain (RR, 1.71 [95% CI, 1.67-1.72]).

Discussion

In this study using data with national coverage, we found an increase in opioid prescriptions in the Netherlands from 2012 to 2017. In addition, hospital admissions for opioid overdose and opioid overdose mortality increased during this same period. Several risk factors associated with opioid prescription were identified from 2 large national health surveys in 2012 and 2016.

The increase in opioid prescription, from 4.9% to 6.0% overall, occurred in all age groups, including opioid-naive individuals. This finding was consistent with results from the Dutch Foundation for Pharmaceutical Statistics [12], which reported an increase in the number of opioid prescriptions from 2008 to 2016. One of the reasons for the increase may be the introduction of the Dutch National Patient Safety Program, which evaluates hospital performance and patient satisfaction in all hospitals in the Netherlands. One of the benchmarks for hospital performance is postoperative pain and its effective treatment [23,24]. This may encourage physicians to prescribe more analgesics to combat patient pain scores more effectively. Another important aspect may be the reintroduction of oxycodone in postoperative pain management guidelines in 2013 [25]. Oxycodone has high abuse potential and has been among the drugs most frequently involved in opioid overdoses [26]. Another possible reason for the increase in opioid prescriptions could be that Dutch physicians may feel that there are no viable alternatives to opioids for the treatment of moderate to severe pain, particularly because of increased awareness of possible gastrointestinal and cardiac adverse effects associated with nonsteroidal anti-inflammatory drugs [25,27,28].

The increase in hospital admissions for opioid overdose and opioid overdose mortality is a cause for concern. However, these numbers are still considerably lower than those reported in the literature, mainly from the United States [10,29,30]. There are important differences in the organization of health care between the Netherlands and the United States, and this might account for the difference in morbidity rates. Because of the higher population density (and, concomitantly, health care facility density) in the Netherlands, access to health care is fast and relatively easy. People in need of emergency medical care can generally be reached by emergency medical services within a short time (<15 minutes [31]) and thus can receive appropriate treatment quickly.

We were unable to identify specific risk factors for hospital admissions for opioid overdose or opioid overdose deaths because of the low absolute number of such incidents. However, the increase in opioid prescription in the Netherlands coincided with opioid-related morbidity and mortality between 2013 and 2017. This suggests that risk factors associated with opioid prescription may also be associated with opioid-related morbidity and mortality.

We identified several risk factors associated with opioid prescription in the Netherlands. To our knowledge, earlier studies [11,30,32] on risk factors associated with opioid prescription did not include the Dutch population. Previously identified risk factors associated with opioid prescription include older age (>55 years), female sex [8], smoking [33], alcohol consumption [34,35], obesity [36], lower socioeconomic status [37], unemployment, and depression and anxiety [38,39]. Most of the risk factors identified in our study were consistent with these, although there were some important differences. We confirmed that female sex, older age, lower socioeconomic status, smoking, and obesity were associated with an increased risk of opioid prescription. Additionally, we observed that poor self- perceived health, depressive symptoms and loneliness, lower household income, and being divorced or widowed were associated with opioid prescription. Other studies have reported an association of alcohol consumption [40], ethnicity [41], and unemployment [42] with opioid prescription. We were unable to replicate these findings in our study population.

We found a high number of opioid prescriptions among individuals who self-reported pain symptoms unrelated to cancer. Participants with back pain, rheumatoid arthritis, or fibromyalgia had a similar or even higher prevalence of opioid prescription than

participants with cancer pain. During the course of several years, as noted in our longitudinal analysis (Table 5), we saw an increasing prevalence of opioid use among participants who reported noncancer pain, whereas the opioid prescription prevalence among participants with cancer pain remained fairly constant. This suggests a high prescription rate for chronic noncancer pain, despite a lack of evidence for effectiveness of prolonged opioid use [43,44]. Long-term opioid therapy is associated with increased risk of opioid use disorder or dependence and of occurrence of adverse events, including opioid overdose mortality [44].

Limitations

There were several limitations to our study. We did not have individual Anatomical Therapeutic Chemical classification codes for the opioids used, so we were unable to differentiate between strong and weak opioids or direct vs controlled-release preparations, nor could we comment on trends in individual drugs. We identified prolonged opioid use, but we have no data available for the total days of supply and individual doses (and therefore, the morphine milligram equivalents). In addition, the comorbidity survey was only included in the 2012 DHM, so calculations for the risk of opioid prescription through time for these conditions could not be made.

The response rates for the 2012 and 2016 DHMs were not optimal (response rates, 40%-45%), which leads to the question of whether the results can be extrapolated to the total Dutch population. However, since the sampling strategy and population characteristics (mean age and sex distribution) of individuals who were approached in the DHMs were similar, a comparison between the 2 DHMs is valid. Furthermore, when we compared opioid use in the Netherlands stratified by age, results of opioid use in the 2012 and 2016 DHMs were similar to the use of opioids in the whole country as assessed by national data from the Statistics Netherlands, indicating that the low response rates had not biased the results.

Except for the 2012 and 2016 DHMs, all databases used in this study were national statistics data, meaning they contained information about all residents of the Netherlands. However, the DHM is a national survey performed every 4 years that invites approximately 1 million citizens to complete it. Although approximately 40%

of approached individuals actually responded to the survey, the total population of respondents is high (approximately 400 000 individuals).

Conclusions

In conclusion, we found that the number of opioid prescriptions in the Netherlands was increasing. Further research is needed to identify the exact opioids being prescribed and the possible causes for the increase, as well as establishing populations at risk. Currently, the risks of hospital admission for opioid overdose and opioid overdose death are still low, but they are increasing; therefore, prescription of opioids should be monitored closely, and measures should to be taken to prevent a possible opioid epidemic in the Netherlands.

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Supplement to: Opioid prescription patterns and risk factors associated with opioid use in the Netherlands

eTable 1. Characteristics of individuals receiving opioid prescription and more than 1 opioid prescription in the DHM (2012-2016)

	2012 Rx, N02A n (%)	2016 Rx, N02A n (%)	2012 > 1 Rx, N02A n (%)	2016 > 1 Rx, N02A n (%)
Total	29553 (7.6)	37458 (8.2)	16140 (55)	22167 (59)
Sex				
Men	11007 (6.3)	14594 (6.9)	5665 (52)	8257 (57)
Women	18546 (8.8)	22864 (9.3)	10475 (57)	13910 (61)
Age group, years				
19-35	1492 (2.8)	1370 (2.7)	515 (35)	544 (40)
35-45	1957 (4.5)	1753 (4.4)	806 (41)	831 (47)
45-55	3456 (6.1)	3679 (6.1)	1668 (48)	1962 (53)
55-65	4480 (7.4)	5510 (7.7)	2341 (52)	3115 (57)
> 65	17485 (11)	25146 (11)	10436 (60)	15715 (63)
Highest level of education				
Primary school	5080 (14)	4602 (15)	3209 (63)	3062 (67)
High school, underclassman[a]	12387 (10)	14849 (11)	6956 (56)	9158 (62)
High School, upperclassman[b]	6432 (6.1)	9056 (7.0)	3196 (50)	5030 (56)
College or more	4196 (4.2)	5825 (4.8)	1922 (46)	3020(52)
Immigration status				
Native (Dutch)	25181 (7.5)	32472 (8.2)	13817 (54)	19260 (59)
First generation	2457 (8.7)	2674 (8.3)	1279 (52)	1506 (56)
Second generation	1914 (8.0)	2312 (8.5)	1043 (55)	1401 (61)
Standardized household income				
First quintile	3659 (9.4)	3832 (10)	2131 (58)	2433 (64)
Second quintile	8127 (11)	11142 (12)	5008 (62)	7258 (65)
Third quintile	6653 (8.1)	8542 (8.5)	3566 (54)	5050 (59)
Fourth quintile	5916 (6.5)	7439 (6.8)	3003 (51)	4113 (55)
Fifth quintile	5119 (5.2)	6385 (5.5)	2398 (47)	3255 (51)
Marital status				
Married/partnership	18655 (7.1)	24162 (7.6)	9738 (52)	13782 (57)
Unmarried/single	1858 (4.3)	2179 (4.7)	900 (48)	1187 (55)
Divorced	2389 (10)	3177 (10)	1389 (58)	1976 (62)
Widowed	5334 (13)	6942 (13)	3388 (64)	4610 (66)
Smoking				
Non-smoker	9152 (6.2)	11452 (6.6)	4774 (52)	6567 (43)
Former smoker	12007 (8.3)	16538 (9.0)	6605 (55)	9772 (59)
Current smoker	6058 (8.4)	6443 (9.3)	3391 (56)	3951 (61)
Comorbidity over the last 12 months				
Cancer	2108 (19)	NR	1378 (65)	NR
Headache/migraine	4940 (10)	NR	2779 (56)	NR

eTable 1. Characteristics of individuals receiving opioid prescription and more than 1 opioid prescription in the DHM (2012-2016) *(continued)*

	2012 Rx, N02A n (%)	2016 Rx, N02A n (%)	2012 > 1 Rx, N02A n (%)	2016 > 1 Rx, N02A n (%)
Neck/shoulder pain	6819 (17)	NR	4307 (63)	NR
Back pain	9163 (22)	NR	6272 (68)	NR
Arthrosis hip/knee	11895 (17)	NR	7467 (63)	NR
Rheumatoid arthritis/ fibromyalgia	5274 (21)	NR	3509 (67)	NR
Feelings of depression				
Always	467 (19)	627 (21)	322 (69)	454 (72)
Often	1442 (16)	1864 (17)	938 (65)	1302 (70)
Sometimes	4368 (12)	6186 (13)	2673 (61)	4027 (65)
Rarely	7591 (8.5)	10221 (8.8)	4287 (57)	6101 (60)
Never	13666 (6.0)	16617 (6.4)	6723 (49)	9064 (55)
Feeling of loneliness, De Jong Gierveld scale				
Not lonely (0-2 points)	13581 (6.3)	16285 (6.8)	6813 (50)	9051 (56)
Somewhat lonely (3-8 points)	9636 (8.4)	13026 (9.0)	5464 (57)	7917 (61)
Lonely (9-10 points)	2175 (12)	2908 (12)	1337 (62)	1886 (65)
Very lonely (11 points)	1326 (14)	1754 (14)	833 (62)	1170 (67)
Able to make ends meet				
No difficulties	9615 (6.0)	14036 (6.5)	4931 (51)	7845 (56)
Just able	10718 (7.7)	12973 (8.8)	5864 (57)	7687 (59)
Some difficulties	5141 (10)	5274 (12)	2942 (57)	3375 (64)
Great difficulties	2129 (14)	1955 (16)	1311 (62)	1323 (68)
Miscellaneous				
Heavy drinker[c]	1791 (5.9)	2304 (6.6)	869 (49)	1238 (54)
Lives alone	7533 (11)	10604 (11)	4658 (62)	6870 (65)
Unemployed	636 (7.6)	625 (7.3)	321 (54)	336 (54)
Physical health				
Very good/ good	11265 (4.1)	14318 (4.4)	4521 (40)	6613 (46)
Fair	12776 (14)	15866 (15)	7628 (60)	10068 (64)
Poor/ very poor	4880 (31)	6698 (32)	3630 (74)	5141 (77)
Body mass index, kg/m2				
< 18.5	506 (10)	588 (10)	323 (64)	433 (74)
18.5-20	768 (5.7)	963 (6.3)	419 (55)	599 (62)
20-25	9344 (5.9)	11105 (6.2)	4879 (52)	6345 (57)
25-30	11198 (7.8)	13788 (8.2)	5986 (54)	7868 (57)
> 30	6120 (12)	8662 (13)	3580 (59)	5417 (63)

N02A denotes ATC classification code for an opioid, Rx denotes prescription, NR denotes not reported

[a] MAVO, LBO (Dutch educational system)

[b] HAVO, VWO, MBO (Dutch educational system)

[c] 4(women)/6(men) glasses of alcohol per day at least once a week

eTable 2. Opioid prescription in the Netherlands, stratified by age groups

	% of the population (% opioid use)			
	2013	**2014**	**2015**	**2016**
Age group, years				
15-25	12 (1.4)	12 (1.5)	12 (1.7)	12 (1.7)
25-45	26 (3.4)	26 (3.5)	25 (3.9)	25 (4.0)
45-65	28 (6.4)	28 (6.7)	28 (7.1)	28 (7.5)
> 65	17 (11.8)	17 (12.5)	18 (12.7)	18 (13.4)

Table shows individuals in the Netherlands, who reimbursed opioid prescription in the year of concern (2013-2016), stratified by age groups.

eTable 3. Number of individuals, who reimbursed 1, 2-4 or more than 4 opioid prescriptions in 2016 vs 2012, the DHM

Opioid Prescriptions, n	**2012 Rx N02A, n (%)**	**2016 Rx N02A, n (%)**	**2016 vs 2012 Rx N02A, OR (95% CI)[a]**
1	13413 (45)	15291 (41)	1 (reference)
2-4	8928 (30)	12147 (32)	1.18 (1.14-1.23)
≥ 5	7212 (24)	10020 (27)	1.19 (1.15-1.25)

OR denotes odds ratio, CI denotes confidence interval

Total number of individuals, who reimbursed opioid prescriptions for the year 2012, n=29553 and for the year 2016, n=37458.

N02A denotes ATC classification code for an opioid, Rx denotes prescription

[a] Adjusted for age, sex, level of education, standardized household income and marital status.

eTable 4. Characteristics of individuals, who reimbursed 1, 2-4 or more than 4 opioid prescriptions, or no opioid prescription: the DHM 2012

	n (%)	**0 Rx N02A, n (%)**	**1 Rx N02A, n (%)**	**2-4 Rx N02A, n (%)**	**≥ 5 Rx N02A, n (%)**
Total	387195	357642 (92)	13413 (3.5)	8928 (2.3)	7212 (1.9)
Sex					
Men	175914	164907 (94)	5342 (3.0)	3297 (1.9)	2368 (1.3)
Women	211281	192735 (91)	8071 (3.8)	5631 (2.7)	4844 (2.3)
Age group, years					
19-35	53519	52027 (97)	977 (1.8)	361 (0.7)	154 (0.3)
35-45	43166	41209 (96)	1151 (2.7)	522 (1.2)	284 (0.7)
45-55	56275	52819 (94)	1788 (3.2)	983 (1.7)	685 (1.2)
55-65	60617	56137 (93)	2139 (3.5)	1372 (2.3)	969 (1.6)
> 65	162807	145322 (89)	7049 (4.3)	5476 (3.4)	4960 (3.0)
Highest level of education					
Primary school	37138	32058 (86)	1871 (5.0)	1608 (4.3)	1601 (4.3)
High school, underclassman[a]	131079	118692 (91)	5431 (4.1)	3820 (2.9)	3136 (2.4)
High School, upperclassman[b]	105863	99431 (94)	3236 (3.1)	1851 (1.7)	1345 (1.3)

eTable 4. Characteristics of individuals, who reimbursed 1, 2-4 or more than 4 opioid prescriptions, or no opioid prescription: the DHM 2012 *(continued)*

	n (%)	0 Rx N02A, n (%)	1 Rx N02A, n (%)	2-4 Rx N02A, n (%)	≥ 5 Rx N02A, n (%)
College or more	99918	95722 (96)	2274 (2.3)	1208 (1.2)	714 (0.7)
Immigration status					
Native (Dutch)	335103	309922 (93)	11364 (3.4)	7579 (2.3)	6238 (1.9)
First generation	28163	25706 (91)	1178 (4.2)	790 (2.8)	489 (1.7)
Second generation	23927	22013 (92)	871 (3.6)	559 (2.3)	484 (2.0)
Standardized household income					
First quintile	39072	35413 (91)	1528 (3.9)	1117 (2.9)	1014 (2.6)
Second quintile	74437	66310 (89)	3119 (4.2)	2538 (3.4)	2470 (3.3)
Third quintile	82154	75501 (92)	3087 (3.8)	1983 (2.4)	1583 (1.9)
Fourth quintile	91375	85459 (94)	2913 (3.2)	1757 (1.9)	1246 (1.4)
Fifth quintile	97805	92686 (95)	2721 (2.8)	1510 (1.5)	888 (0.9)
Marital status					
Married/partnership	262953	244298 (93)	8917 (3.4)	5623 (2.1)	4115 (1.6)
Unmarried/single	42944	41086 (96)	958 (2.2)	498 (1.2)	402 (0.9)
Divorced	23424	21035 (90)	1000 (4.3)	765 (3.3)	624 (2.7)
Widowed	41069	35735 (87)	1946 (4.7)	1648 (4.0)	1740 (4.2)
Smoking					
Non-smoker	146773	137621 (94)	4378 (3.0)	2701 (1.8)	2073 (1.4)
Former smoker	144863	132856 (92)	5402 (3.7)	3716 (2.6)	2889 (2.0)
Current smoker	71818	65760 (92)	2667 (3.7)	1816 (2.5)	1575 (2.2)
Comorbidity over the last 12 months					
Cancer	11026	8918 (81)	730 (6.6)	621 (5.6)	757 (6.9)
Headache/ migraine	47634	42694 (90)	2161 (4.5)	1469 (3.1)	1310 (2.8)
Neck/ shoulder pain	39242	32423 (83)	2512 (6.4)	2153 (5.5)	2154 (5.5)
Back pain	42699	33536 (79)	2891 (6.8)	2937 (6.9)	3335 (7.8)
Arthrosis hip/ knee	72142	60247 (84)	4428 (6.1)	3731 (5.2)	3736 (5.2)
Rheumatoid arthritis/ fibromyalgia	24761	19487 (79)	1765 (7.1)	1619 (6.5)	1890 (7.6)
Feelings of depression					
Always	2404	1937 (81)	145 (6.0)	148 (6.2)	174 (7.2)
Often	8979	7537 (84)	504 (5.6)	434 (4.8)	504 (5.6)
Sometimes	36730	32362 (88)	1695 (4.6)	1331 (3.6)	1342 (3.7)
Rarely	89587	81996 (92)	3304 (3.7)	2298 (2.6)	1989 (2.2)
Never	227577	213911 (94)	6943 (3.1)	4098 (1.8)	2625 (1.2)
Feeling of loneliness, De Jong Gierveld scale					
Not lonely (0-2 points)	216407	202826 (94)	6768 (3.1)	3982 (1.8)	2831 (1.3)
Somewhat lonely (3-8 points)	114222	104586 (92)	4172 (3.7)	3012 (2.6)	2452 (2.1)
Lonely (9-10 points)	17980	15805 (88)	838 (4.7)	685 (3.8)	652 (3.6)
Very lonely (11 points)	9604	8278 (86)	493 (5.1)	375 (3.9)	458 (4.8)
Able to make ends meet					
No difficulties	160284	150669 (94)	4684 (2.9)	2835 (1.8)	2096 (1.3)
Just able	138441	127723 (92)	4854 (3.5)	3290 (2.4)	2574 (1.9)

eTable 4. Characteristics of individuals, who reimbursed 1, 2-4 or more than 4 opioid prescriptions, or no opioid prescription: the DHM 2012 ***(continued)***

	n (%)	**0 Rx N02A, n (%)**	**1 Rx N02A, n (%)**	**2-4 Rx N02A, n (%)**	**≥ 5 Rx N02A, n (%)**
Some difficulties	49777	44636 (90)	2199 (4.4)	1543 (3.1)	1399 (2.8)
Great difficulties	15094	12965 (86)	818 (5.4)	657 (4.4)	654 (4.3)
Miscellaneous					
Heavy drinker[c]	30585	28794 (94)	922 (3.0)	566 (1.9)	303 (1.0)
Lives alone	70210	62677 (89)	2875 (4.1)	2340 (3.3)	2318 (3.3)
Unemployed	8369	7733 (92)	315 (3.8)	209 (2.5)	112 (1.3)
Physical health					
Very good/ good	276830	265565 (96)	6744 (2.4)	3215 (1.2)	1306 (0.5)
Fair	89435	76659 (86)	5148 (5.8)	4082 (4.6)	3546 (4.0)
Poor/ very poor	15943	11063 (69)	1250 (7.8)	1449 (9.1)	2181 (13.7)
Body mass index, kg/m2					
< 18.5	5061	4555 (90)	183 (3.6)	142 (2.8)	181 (3.6)
18.5-20	13845	12717 (94)	349 (2.5)	195 (1.4)	224 (1.6)
20-25	159525	150181 (94)	4465 (2.8)	2689 (1.7)	2190 (1.4)
25-30	143098	131900 (92)	5212 (3.6)	3461 (2.4)	2525 (1.8)
> 30	50639	44519 (88)	2540 (5.0)	1976 (3.9)	1604 (3.2)

N02A denotes ATC classification code for an opioid, Rx denotes prescription

[a] MAVO, LBO (Dutch educational system)

[b] HAVO, VWO, MBO (Dutch educational system)

[c] 4(women)/6(men) glasses of alcohol per day at least once a week

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CHAPTER 3

Causes and consequences of the opioid epidemic in the Netherlands: a population-based cohort study

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Abstract

Over the past decade opioid use has risen globally. The causes and consequences of this increase, especially in Europe, are poorly understood. We conducted a population-based cohort study using national statistics on analgesics prescriptions, opioid poisoning hospital admissions and deaths in the Netherlands from 2013 to 2017. Pain prevalence and severity was determined by using results of 2014-2017 Health Interview Surveys. Between 2013 and 2017 the proportion of residents receiving opioid prescription rose from 4.9% to 6.0%, and the proportion of those receiving NSAIDs decreased from 15.5% to 13.7%. Self-reported pain prevalence and severity remained constant, as 44.7% of 5,119 respondents reported no pain-impeded activities-of-daily-living in 2014 (aRR, 1.00 [95% CI, 0.95-1.06] in 2017 vs 2014). Over the observation period, the incidence of opioid poisoning hospitalization and death increased from 8.6 to 12.9 per 100,000 inhabitants. The incidence of severe outcomes related to opioid use increased, as 3.9% of 1,343 hospitalized for opioid poisoning died in 2013 and 4.6% of 2,055 in 2017. We demonstrated that NSAIDs prescription decreased and opioid prescription increased in the Netherlands since 2013, without an increase in pain prevalence and severity. Consequently, the incidence of severe outcomes related to opioids increased.

Introduction

Opioid prescription and associated medical complications have increased over the recent years, particularly in the United States but also in Europe [1,2]. Around 800,000 individuals in the Netherlands received an opioid prescription in 2013, which increased to over one million individuals (6.0% of the total population) in 2017. Hospital admissions for opioid poisoning increased from 9.2 per 100,000 inhabitants in 2013 to 13.1 per 100,000 inhabitants in 2017, and opioid-related mortality increased 50% over the same four-year period [2].

Causes for the increased frequency of opioid prescription have not been studied in Europe, although different explanations have been proposed [2]. The first cause could be an increased demand for analgesic prescription due to increasing pain prevalence in the population, possibly due to ageing and concomitantly increased morbidity [3,4]. Nationwide data from the United States have indeed shown that people after the mid-1990s gradually reported increased frequency of pain [5]. A second reason could be a shift from nonsteroidal anti-inflammatory drugs (NSAIDs) to opioids prescription. Recently an increasing number of scientific publications have raised awareness that NSAIDs users are at increased risk for adverse events and interactions with other pharmaceutical agents [6,7]. Simultaneously, the Dutch pain guidelines reintroduced oxycodone in analgesic clinical practice [8]. Indeed, preliminary data from the Netherlands showed a peak of NSAIDs use in 2011-2012, followed by a decrease, while concurrently an increase in oxycodone use has been noted [9]. However, it is unknown whether the increase in opioid prescription is paralleled by a similar decrease in NSAIDs prescriptions, which could offer an explanation of the opioid crisis.

Together with the increased opioid prescription, an increase in opioid related fatalities, hospitalization and death due to opioid poisoning, was observed. However, information whether hospitalization and death associated with opioid use were also boosted by an increase in illicit opioid use is currently unknown for the Netherlands. Studies from the United States have shown that wide-spread use of prescription opioids in the community preceded illegal opioid trade [10,11]. The latter introduces an additional risk for severe outcomes, such as overdose, as users of illicit opioids are not monitored [12]. Therefore, we assessed, among those who were hospitalized or died due to opioid poisoning, how many had not been reimbursed for an opioid prescription, which indicates either in-hospital administration or illicit use. Furthermore, we examined

different outcomes of opioid poisoning, i.e., death, prolonged hospitalization or complete recovery, in order to estimate whether the opioid crisis deepened since 2013.

We aimed to explore two possible causes for increased opioid prescription in the Netherlands: increased pain prevalence and severity, and decreased NSAIDs prescription. Furthermore, we estimated consequences of increased opioid prescription such as hospital admission and death due to opioid poisoning on a population level. The causes and consequences of increased opioid prescription warrant knowledge on precautions needed to be made to prevent further increase in opioid-related fatalities.

Methods

Participants

We conducted a population-based cohort study in the Netherlands. Detailed method descriptions have previously been reported [2]. In brief, we performed analyses into prescription reimbursement data, hospitalization, and mortality data using several anonymized databases from Statistics Netherlands (CBS) covering the total population of the Netherlands between 2013 and 2017 [13–16]. Furthermore, we used data from the national Health Interview Surveys, "Gezondheidsenquête" (GE) from the years 2014-2017 (also collected by the CBS) [17]. Datasets were linked on an individual level, based on the unique anonymized identifiers.

The institutional review board of the Anesthesiology Department and Intensive Care Unit of the Leiden University Medical Center approved the study in CBS and waived participant consent.

Pain prevalence and severity

Information on pain perception was included in the GE surveys from 2014 to 2017. The GE is an annual national survey that covers health-related lifestyle choices of Dutch residents [17]. Since 2013, the GE surveys have been conducted as part of the European Health Interview Survey (EHIS) and direct comparisons between the yearly GEs can be made for the years 2014-2017 [18,19]. The survey is sent to a random subset of the population of around 15,000 individuals each year, with response rates between 60 and 65% [17]. Over the four-year period around 38,000 individuals participated in the survey.

To explore the prevalence and severity of pain in the population, we investigated pain-impeded activities of daily living (ADL). Pain-impeded ADL was defined as the level of performance of daily activities (including outdoor and household chores) hindered by pain in the past four weeks [17]. Pain-impeded ADL was asked on a five-point Likert scale, with the categories: "not at all", "somewhat", "moderate", "much", and "extreme". Due to a low number of respondents in the "much", and "extreme" categories, these two groups were merged into the category "much and extreme".

Analgesic prescription

Prescription reimbursement data were collected for all Dutch residents entitled to pharmaceutical care, i.e., those with health insurance, which is 99.9% of all Dutch residents [20]. The Dutch Health Care Institute (ZINL) provides these data to the CBS. Analgesics dispensed from outpatient, community pharmacies, and in residential homes for elderly are collected in the national reimbursement database, whereas medicines dispensed in hospitals and nursing homes are not [14].

Opioid prescriptions were classified according to the ATC (the WHO drug classification system) code N02A and further stratified by natural (N02AA) and synthetic (N02AZ) opioids [21]. Morphine (N02AA01), hydromorphone (N02AA03), nicomorphine (N02AA04), and oxycodone (N02AA05) were classified as natural opioid (N02AA), and pethidine (N02AB02), fentanyl (N02AB03), dextromoramide (N02AC01), piritramide (N02AC03), pentazocine (N02AD01), buprenorphine (N02AE01), codeine with paracetamol (N02AJ06), tramadol with paracetamol (N02AJ13), tramadol (N02AX02), tapentadol (N02AX06), and other opioids (N02AX52) were classified as synthetic opioid (N02AZ) [22]. NSAIDs were classified according to ATC code M01A [21]. Individuals were considered exposed to prescription drugs when they filled at least one prescription per studied calendar year.

Hospital admissions and deaths related to opioid use

The Dutch Hospital Database contains information about all-cause hospital admissions and the Register of Causes of Death records all-causes of death. Each hospital admission record contains the date of hospital inpatient and outpatient encounters, the discharge date, and the discharge diagnoses [15,16]. Diagnoses and deaths are coded within the CBS according to the International Statistical Classification of Diseases and Related Health Problems (ICD, 10th revision) of the WHO [23].

Hospital admissions and deaths registered as due to opioid-related disorders, adverse events of opioid use and opioid overdose were defined as opioid poisoning (see Supplement online) [24]. Opioid poisoning cases were selected based on first hospital admission or death, whichever occurred first, per studied calendar year.

Statistical analysis

We present descriptive statistics for all Dutch residents between 2013 and 2017 on opioid prescriptions, hospital admissions and mortality. Individuals, who received opioid or NSAIDs prescriptions are presented as counts and as a proportion of the total population per calendar year. Hospital admissions, deaths, and also prescriptions are presented as number per 100,000 inhabitants per calendar year and as risk ratios with 95% confidence interval (CI) compared with the reference year (2013). Risk ratios were adjusted for age and sex (aRR) with direct standardization; age was divided in 5 categories (0-15, 15-25, 25-45, 45-65, ≥65 years), and further stratified by sex with weights from the total Dutch population of 2013. Similar analyses were performed on the 2014-2017 GE cohorts where the selected reference group was the 2014 GE cohort, whence the weights for standardization analysis were selected. To investigate whether GE surveys were a valid representation of the total population, we linked GEs data with the prescription datafiles of the same calendar year, and performed frequency analysis into opioid and NSAIDs prescription among respondents of the GEs.

Missing data

Individuals with missing data in the pain-impeded ADL variable in the GEs were dropped from the analysis (n=4,569, 46.5% in 2017). In 2013, 8 (0.6%) hospitalization cases due to opioid poisoning had missing information about residence before and destination after hospitalization. In 2014, 31 (2.2%) cases had missing information about residence before hospitalization due to opioid poisoning, and 29 (2.0%) cases had missing information about destination after hospital admission due to opioid poisoning. After 2014, there were no missing data. There were no missing data for the total population characteristics and no individuals were lost in the linkage process.

Hospital admissions and deaths related to opioid use

To study the impact of increased opioid prescription we performed several analyses. First, we estimated opioid poisoning per calendar year (either leading to hospitalization or death). Then we stratified opioid poisoning cases in two categories: whether individuals received opioid prescription or none in the same calendar year. This

provides insight in severe outcomes—defined as death, or consequent transfer to another health facility after being hospitalized for opioid poisoning—related to prescription opioid use versus in-hospital or illicit opioid use. Second, we explored residence status prior to hospitalization. Those who were transferred from another health facility to a hospital for an opioid poisoning were considered poisoned whilst being hospitalized, which provides information about in-hospital opioid use. Third, we assessed the severity of opioid poisoning per calendar year by following-up patients after their hospitalization. We classified three main outcomes of opioid poisoning: returning home, prolonged institutionalization, or death. Those who were able to return to their own living environment were considered to have experienced a milder form of poisoning. Those who were transferred to another health facility were considered prolongedly institutionalized due to a more severe poisoning. Individuals who were transferred to a psychiatric hospital were considered having an opioid addiction. Patients who died after being hospitalized for opioid poisoning were considered having experienced an opioid overdose.

The STROBE statement checklist for cohort studies is included in the Supplement online. All statistical analyses were performed with SPSS for Windows, release 24.0 (SPSS, Chicago, IL, USA). Figures were created with R studio (A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org), using ***R*** package ***ggplot2*** version 3.2.1 [25].

Results

Description of the studied populations

For the evaluation of analgesic prescription practice and consequences of changes thereof we studied 2 populations: the total Dutch population between 2013 and 2017, and the GE survey participants between 2014 and 2017.

For the total Dutch population, among the 16,779,575 (mean age, 40.8 years) residents in 2013, 8,472,236 (50.5%) were women. In 2017, 8,606,405 (50.4%) were women for a total population of 17,081,507 (mean age, 41.6 years) (see Supplementary Table S1 online).

In the GE cohorts, 9,516 GE respondents were included in 2014 (mean [SD] age, 40.4 [23.7] years, 4,879 women, 51.3%). In 2017, 9,826 GE respondents were included (mean [SD] age, 41.7 [24.1] years, 4,978 women, 50.7%) (see Supplementary Table S1 online).

Is there an increase in pain prevalence and severity?

The missing proportion for pain-impeded ADL in GE cohorts was approximately 46% and the level of missingness did not change between 2014 and 2017 (Table 1). Most of the respondents of the 2014-2017 GE surveys reported "not at all" (44.7% in 2014 and 44.3% in 2017) difficulties with pain-impeded ADL. Approximately the same proportion of the respondents of the 2014-2017 GE surveys had "moderate" (10.1% in 2014 and 9.6% in 2017) and "much and extreme" (9.0% in 2014 and 9.5% in 2017) levels of difficulty with ADL due to pain (Table 1). The age and sex-adjusted risk ratio (aRR) for "not at all" category in 2017 vs 2014 was 1.00; [95% confidence interval (CI), 0.95-1.06], and for "much and extreme" was 1.04; [95% CI, 0.91-1.18] (Table 1).

Table 1. Pain-impeded activities of daily living among the respondents of GE surveys, from 2014 to 2017

		2014 (n=9516)	2015 (n=9358)	2016 (n=9165)	2017 (n=9826)
Pain impeded activitiesof daily living					
Not at all	No./ Total No. (%)	2287/5119 (44.7)	2191/5021 (43.6)	2117/4947 (42.8)	2330/5257 (44.3)
	aRR (95% CI)*	1 (reference)	0.97 (0.92-1.03)	0.96 (0.90-1.02)	1.00 (0.95-1.06)
Somewhat	No./ Total No. (%)	1857/5119 (36.3)	1861/5021 (37.1)	1819/4947 (36.8)	1923/5257 (36.6)
	aRR (95% CI)*	1 (reference)	1.02 (0.96-1.09)	1.01 (0.95-1.08)	1.01 (0.94-1.07)
Moderate	No./ Total No. (%)	516/5119 (10.1)	502/5021 (10.0)	511/4947 (10.3)	506/5257 (9.6)
	aRR (95% CI)*	1 (reference)	1.00 (0.88-1.13)	1.02 (0.91-1.16)	0.94 (0.83-1.06)
Much and extreme	No./ Total No. (%)	459/5119 (9.0)	467/5021 (9.3)	500/4947 (10.1)	498/5257 (9.5)
	aRR (95% CI)*	1 (reference)	1.04 (0.91-1.18)	1.12 (0.99-1.28)	1.04 (0.91-1.18)
Missing	No. (%)	4397 (46.2)	4337 (46.3)	4218 (46.0)	4569 (46.5)
	aRR (95% CI)*	1 (reference)	1.01 (0.97-1.06)	1.01 (0.97-1.05)	1.02 (0.98-1.06)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; GE, Health Interview Survey; NSAIDs, nonsteroidal anti-inflammatory drugs

* adjusted for age and sex with direct standardization; 2014 cohort was selected as a reference population in the GE survey.

Changed analgesic prescription practice

Between 2013 and 2017 there was a 20% increase in opioid prescriptions (814,211, 4.9% in 2013; 1,027,019, 6.0% in 2017; aRR, 1.20; [95% CI, 1.20-1.20]) (Figure 1 and Supplementary Table S2 online). Stratified analysis showed that natural opioids contributed most to that increase since their use more than doubled (1.1% in 2013, and 2.5% in 2017,

aRR, 2.23; [95% CI, 2.22-2.24], whereas prescriptions of synthetic opioids prescription decreased slightly (3.8% in 2013, and 3.5% in 2017, aRR, 0.90; [95% CI, 0.90-0.90]). Between 2013 and 2017 the proportion of individuals who received NSAIDs prescriptions decreased (15.5% in 2013, and 13.7% in 2017, aRR, 0.88; [95% CI, 0.88-0.88]).

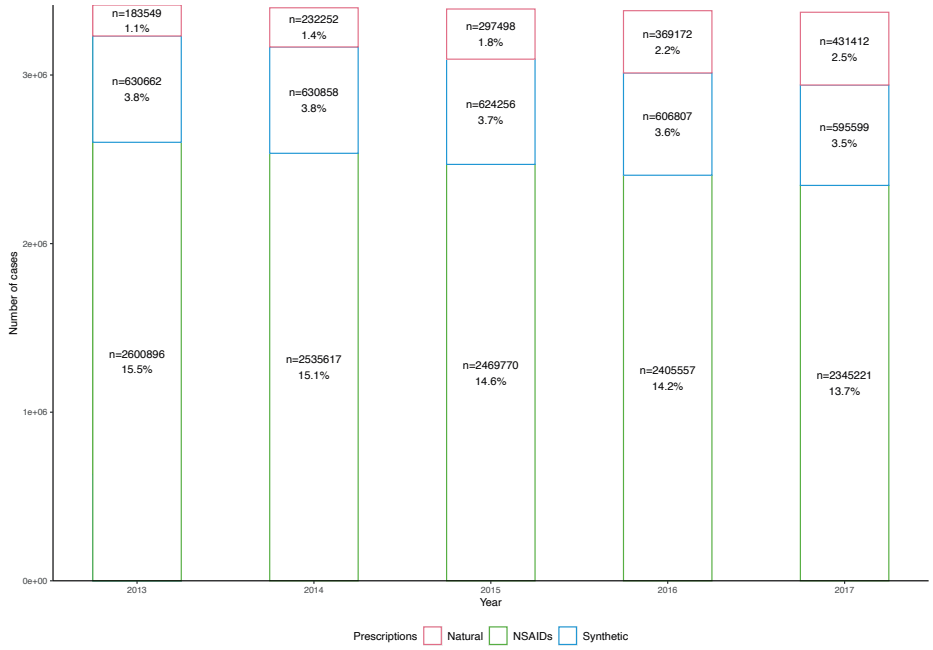

Figure 1. Opioid (overall and stratified by natural and synthetic), and NSAIDs prescription cases in the Netherlands, from 2013 to 2017

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs. Individuals, who reimbursed opioid prescriptions were selected by ATC code N02A (natural, N02AA; synthetic N02AZ), NSAIDs prescriptions by ATC code M01A.

Individuals who only received an opioid prescription as analgesic increased with nearly 30% between the 2013 and 2017 (2.4% in 2013 and 3.2% in 2017; aRR, 1.28, [95% CI, 1.27-1.29]), those who received an opioid and NSAIDs prescription increased slightly (2.5% in 2013 and 2.8% in 2017; aRR, 1.12 [95% CI, 1.12-1.13]), whereas the number of individuals who only received NSAIDs prescription decreased (13.0% in 2013 and 10.9% in 2017; aRR, 0.83 [95% CI, 0.83-0.83]) (Figure 2 and Supplementary Table S3 online). The number of individuals with neither of these analgesic prescriptions remained stable from 2013 to 2017 (aRR, 1.02; [95% CI, 1.01-1.02], reference year 2013).

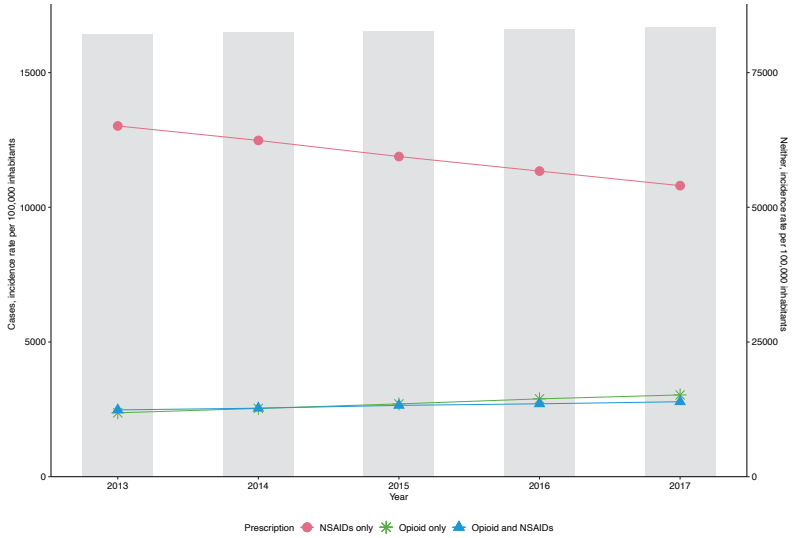

Figure 2. Opioid and NSAIDs prescription cases (stratified by concomitant and single prescription) and those with neither of these analgesic prescriptions in the Netherlands, from 2013 to 2017

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs. Individuals, who reimbursed opioid prescriptions were selected by ATC code N02A (natural, N02AA; synthetic N02AZ), NSAIDs prescriptions by ATC code M01A. Prescription cases are presented as incidence rates per 100,000 inhabitants per observed calendar year. Primary axis presents incidence of analgesics prescription, and the secondary axis shows the incidence of those with neither of analgesics prescription.

Impact of increased opioid prescription on opioid poisoning

The frequency of opioid poisoning increased with nearly 50% between 2013 and 2017 (n=1,440, 8.6 per 100,000 inhabitants in 2013, and n=2,200, 12.9 per 100,000 inhabitants in 2017; aRR, 1.48; [95% CI, 1.39-1.59]) (Table 2). The frequency of opioid poisoning related to opioid prescriptions, nearly doubled after 2013 (3.4 and 6.6 per 100,000 inhabitants in 2013 and 2017, respectively; aRR, 1.89; [95% CI, 1.71-2.09]). The number of individuals who were hospitalized or died because of opioid poisoning, but had not filled a prescription at a pharmacy also increased, indicative of increase in illicit use (5.2 and 6.3 per 100,000 inhabitants in 2013 and 2017, respectively; aRR, 1.22; [95% CI, 1.11-1.33]). From 2016, the frequency of opioid poisoning among those who had received prescription opioids was equal/slightly surpassed that of those without a prescription (6.0 and 6.1 per 100,000 inhabitants, respectively in 2016 and 6.6 and 6.3 per 100,000 inhabitants, respectively in 2017). Patients with opioid poisoning without an opioid prescription were younger and more often male (mean [SD] age, 45.6 [17.8] years; n=711 (66.3%) men) than poisoning cases related to opioid prescription (mean [SD] age, 56.4 [17.6] years; n=514 (45.6%) men).

Table 2. Hospitalization and death of opioid poisoning, stratified by receiving opioid prescription in the Netherlands, from 2013 to 2017

		2013 (n=16779575)	2014 (n=16829290)	2015 (n=16900726)	2016 (n=16979120)	2017 (n=17081507)
Opioid poisoning	No. (per 100,000)	1440 (8.6)	1499 (8.9)	1742 (10.3)	2049 (12.1)	2200 (12.9)
	aRR (95% CI)*	1 (reference)	1.03 (0.96-1.11)	1.19 (1.11-1.28)	1.39 (1.30-1.49)	1.48 (1.39-1.59)
Opioid prescription	No. (per 100,000)	572 (3.4)	696 (4.1)	844 (5.0)	1018 (6.0)	1127 (6.6)
	aRR (95% CI)*	1 (reference)	1.20 (1.08-1.35)	1.44 (1.30-1.60)	1.73 (1.56-1.92)	1.89 (1.71-2.09)
	Mean age (SD), years	56.1 (15.9)	57.8 (16.6)	57.3 (16.8)	55.9 (16.9)	56.4 (17.6)
	Male, No. (%)	289 (50.5)	337 (48.4)	411 (48.7)	467 (45.9)	514 (45.6)
	Female, No. (%)	283 (49.5)	359 (51.6)	433 (51.3)	551 (54.1)	613 (54.4)
In-hospital and illegal opioid use	No. (per 100,000)	868 (5.2)	803 (4.8)	898 (5.3)	1031 (6.1)	1073 (6.3)
	aRR (95% CI)*	1 (reference)	0.92 (0.84-1.02)	1.03 (0.94-1.13)	1.17 (1.07-1.28)	1.22 (1.11-1.33)
	Mean age (SD), years	46.6 (16.4)	46.9 (16.2)	46.9 (16.9)	46.9 (18.1)	45.6 (17.8)
	Male, No. (%)	564 (65.0)	534 (66.5)	583 (64.9)	658 (63.8)	711 (66.3)
	Female, No. (%)	304 (35.0)	269 (33.5)	315 (35.1)	373 (36.2)	362 (33.7)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval

* adjusted for age and sex with direct standardization; the 2013 total Dutch population cohort was selected as a reference.

Opioid poisoning cases were derived from hospitalization and death dataset for the year in concern, and duplicate cases were filtered out. ICD-10CM codes used to identify opioid poisoning are reported in the Supplement online. Opioid prescriptions were identified by ATC code N02A.

Table 3. Residence before and destination after hospitalization for opioid poisoning in the Netherlands, from 2013 to 2017

		2013 (n=16779575)	2014 (n=16829290)	2015 (n=16900726)	2016 (n=16979120)	2017 (n=17081507)
Opioid poisoning (Hospital cases)	No. (per 100,000)	1351 (8.1)	1432 (8.5)	1638 (9.7)	1933 (11.4)	2055 (12.0)
	aRR (95% CI)*	1 (reference)	1.05 (0.98-1.13)	1.19 (1.11-1.28)	1.40 (1.31-1.50)	1.48 (1.38-1.58)
Residence before hospital admission	Total No.	1343	1401	1638	1933	2055
Own living environment	No. (%)	1279 (95.2)	1332 (95.1)	1567 (95.7)	1816 (93.9)	1943 (94.5)
(Other) hospital[a]	No. (%)	35 (2.6)	48 (3.4)	41 (2.5)	76 (3.9)	80 (3.9)
Other[b]	No. (%)	29 (2.2)	21 (1.5)	30 (1.8)	41 (2.1)	32 (1.6)
Destination after hospital discharge	Total No.	1343	1403	1638	1933	2055
Own living environment	No. (%)	1085 (80.8)	1106 (78.8)	1260 (76.9)	1473 (76.2)	1523 (74.1)
	RR (95% CI)	1 (reference)	0.98 (0.90-1.06)	0.95 (0.88-1.03)	0.94 (0.87-1.02)	0.92 (0.85-0.99)
Institutionalization	No. (%)	205 (15.3)	245 (17.5)	312 (19.0)	379 (19.6)	438 (21.3)
	RR (95% CI)	1 (reference)	1.14 (0.95-1.38)	1.25 (1.05-1.49)	1.28 (1.08-1.52)	1.40 (1.18-1.65)
Psychiatric hospital	No. (%)	41 (3.1)	57 (4.1)	66 (4.0)	89 (4.6)	129 (6.3)
	RR (95% CI)	1 (reference)	1.33 (0.89-1.99)	1.32 (0.89-1.95)	1.51 (1.04-2.18)	2.06 (1.45-2.92)
(Other) hospital[c]	No. (%)	40 (3.0)	38 (2.7)	51 (3.1)	75 (3.9)	75 (3.6)
	RR (95% CI)	1 (reference)	0.91 (0.58-1.42)	1.05 (0.69-1.58)	1.30 (0.89-1.91)	1.23 (0.83-1.80)
Other[d]	No. (%)	124 (9.2)	150 (10.7)	195 (11.9)	215 (11.1)	234 (11.4)
	RR (95% CI)	1 (reference)	1.16 (0.91-1.47)	1.29 (1.03-1.61)	1.20 (0.97-1.50)	1.23 (0.99-1.53)
Death	No. (%)	53 (3.9)	52 (3.7)	66 (4.0)	81 (4.2)	94 (4.6)
	RR (95% CI)	1 (reference)	0.94 (0.64-1.38)	1.02 (0.71-1.47)	1.06 (0.75-1.50)	1.16 (0.83-1.62)

Abbreviations: aRR, adjusted risk ratio; RR, risk ratio; CI, confidence interval

*adjusted for age and sex with direct standardization; 2013 cohort was selected as a reference.

[a] academic, general, categorical, psychiatric

[b] rehabilitation institution, nursing/residential home, other institutions, hospital abroad, born in this hospital, origin unknown

[c] academic, general, categorical

[d] rehabilitation institution, nursing/residential home, other institutions, hospital abroad, hospice, destination unknown

In 2017, most of the opioid poisoning cases (n=1,943 out of total of 2,055; 94.5%) experienced disease onset outside of hospital, and 80 (3.9%) individuals experienced it whilst being hospitalized (Table 3). In 2013, the majority of individuals with opioid poisoning (1,085/1,343; 80.8%) were discharged home. That proportion decreased to 74.1% (1,523/2,055) in 2017 (RR, 0.92; [95% CI, 0.85-0.99]). However, an increasing number of patients were transferred from a hospital to another care facility after an opioid poisoning (205/1,343 (15.3%) in 2013, and 438/2,055 (21.3%) in 2017; RR, 1.40; [95% CI, 1.18-1.65]). Among these, transfers to a psychiatric hospital increased most in relative numbers (n=41 (3.1%) patients in 2013, and n=129 patients (6.3%) in 2017; RR, 2.06; [95% CI, 1.45-2.92]). Fatalities due to opioid poisoning also increased substantially, both in absolute numbers, and as a proportion of those with opioid poisoning, indicating an increase in severity of these cases (53/1,343 cases (3.9%) in 2013, and 94/2,055 cases (4.6%) in 2017; RR, 1.16; [95% CI, 0.83-1.62])

Opioid poisoning cases were identified in the hospitalization dataset by the ICD-10CM codes reported in the Supplement online

Discussion

We previously reported an increase in opioid prescription and related fatalities in the Netherlands from 2013 to 2017 [2]. In the present study, based on national statistics, and annual population-wide national surveys we further elaborated on causes and consequences of the increase in opioid use. We found a shift from NSAID prescription to opioid prescription, without an overall increase in need for pain treatment. Over the four-year period, opioid prescriptions increased by 20%, whereas opioid poising increased by nearly 50%. The increase in opioid prescriptions was mainly due to a large increase in the use of natural opioids. The severity of opioid poisoning also increased, since there were more opioid-related deaths among those admitted with opioid poisoning, and the number of those who were consequently transferred to the other care facilities had risen.

The increase in opioid prescriptions was mainly due to an increase in natural opioid prescriptions (N02AA), namely, morphine, hydromorphone, and especially oxycodone, and not in synthetic opioid prescriptions (N02AZ). At the same time a decrease in

NSAIDs prescription rate has been observed, although still a large proportion of residents (13.7% of the total population) received an NSAIDs prescription in 2017. Of note, NSAIDs are not only prescribed, but are also sold over the counter in the Netherlands [26–28].We demonstrated, that a recent increase in opioid prescription cannot be sufficiently explained by increase in prevalence and severity of pain, but that changed analgesic prescription practice, defined as a shift from NSAIDs to opioids prescription, is the most probable reason for opioid epidemic in the Netherlands. The change in analgesic prescription practice subsequently stemmed from a concurrent introduction of oxycodone by revised Dutch pain treatment guidelines [8], and restriction of NSAIDs use due to their common adverse events by the scientific community [29,30].

We considered suspicion bias in the observed increase of opioid-related fatalities [31]. When suspicion bias would have been the explanation for the increased rate of opioid-related fatalities, an increase in hospital admission and death due to opioid poisoning would have been restricted to those receiving an opioid prescription in the same calendar year. However, the increase also included individuals who had not received opioid prescriptions. These individuals most probably had acquired the drugs illegally, since we found a few in-hospital poisoning (3.9% of all opioid poisonings in 2017). Furthermore, those who had not received an opioid prescription were considerably younger (mean age difference was ten years) compared with those receiving opioid prescriptions and mostly males (65% of all opioid poisoning cases in those not having prescription), which further supports our finding that among those who had not received an opioid prescription, opioid poisoning occurred due to illicit opioid use. These observations render suspicion bias as an explanation for the observed increased rate of opioid poisoning unlikely. Furthermore, this finding is consistent with reports on the opioid epidemic from the United States that showed that widespread opioid use leads to widespread opioid addiction (either prescription or illegal use), with gradual increase in severity of consequences (fatal or non-fatal opioid poisoning) [32].

Opioid use and opioid overdose deaths are increasing in most countries in the European union [33–37]. However, the situation of pharmacologic pain relief in the Netherlands is somewhat different compared with other European countries. For instance, Danish and British pain guidelines advocate NSAIDs as first line treatment, and are far more stringent in opioid prescription compared to the Dutch pain guideline [38,39]. Furthermore, a ***decrease*** in prescription opioid use has been noted since 2016

in the United Kingdom [40]. Specifically, in the United Kingdom and in Denmark, tramadol is the most frequently prescribed opioid, and not natural opioids, such as oxycodone (the opioid that is advocated by Dutch pain guidelines in favour of NSAIDs) [41,42]. This reinforces our finding that a changed analgesic prescription practice, which was preceded by pain guidelines, is indeed responsible for the recent opioid epidemic in the Netherlands. In addition, we showed that, over time, more patients in the Netherlands suffered from prescription opioid poisoning than from illegal opioid poisoning, while in the United Kingdom the far majority of patients have opioid poisoning related with heroin use, i.e., illegal opioid poisoning [33], further supporting the evidence that the opioid epidemic in the Netherlands is for a large part iatrogenic.

This research has some methodological issues that warrant commenting. First, to estimate pain prevalence and severity we used results of national health surveys. All other outcomes were identified in the Dutch national statistics. Second, the question related to pain prevalence was missing in 46% of participants. As we consider it unlikely that the missingness was at random, while at the same time the amount of missingness was large, we decided not to impute missing values. However, we consider it unlikely that the reason for missingness changed over the observation period and the level of missingness did not change between 2014 and 2017. Third, non-response bias cannot be excluded as survey response rates ranged between 60 to 65%, depending on the year. Although, this is an acceptable response rate of questionnaires in social sciences [43], it may have affected our results. However, population characteristics of survey participants were similar to the total Dutch population from 2014 to 2017 (see the Supplementary Table S1 online), as well as participants were randomly sampled. Therefore, it is unlikely that the results of the national survey are not representative of the whole population. Nevertheless, the missing data may render the absolute numbers of individuals reporting pain inaccurate, where an overestimate seems most likely. Additionally, the frequency of opioid and NSAIDs prescription among the respondents of surveys was similar to the frequency of opioid and NSAIDs prescription in the total Dutch population (see the Supplementary Table S4 online). Fourth, we did not have the detailed prescription information to enable us to identify individual active substances, dosing, and pharmaceutical dosage forms. Fifth, we only performed research into opioid and NSAIDs prescriptions, but not into other analgesic agents, such as antidepressants and antiepileptic agents, as those are mostly used for neuropathic pain [44]. Sixth, NSAIDs are also available as an over-the-counter medication, and the information about the proportion of the population exposed to them is unknown.

Although, the NSAIDs prescription decreased between 2013 and 2017 in the Netherlands, that does not necessarily imply that the total exposure to NSAIDs in the total population decreased, because NSAIDs are also available over the counter. Lastly, hospital diagnosis and deaths were ICD-10 coded by the CBS and the accuracy of these codes is not known.

In conclusion, the opioid prescription rate is increasing in the Netherlands, without an increase in pain prevalence and severity. This increase is mainly related to natural opioid use, while at the same time NSAIDs prescription is decreasing. This shift in analgesic prescription practice was accompanied by the increase and the worsening of opioid toxicity, which was related to prescription opioids and increased illicit use of opioids. The changed analgesic pharmacotherapy strategy in the Netherlands has potentially exposed more individuals to toxic effects of opioid use, and without taking any measures to prevent further deterioration of pain management, it doesn't seem that rate of opioid-related fatalities will decline any time soon.

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Supplement to: Causes and consequences of the opioid epidemic in the Netherlands: a population-based cohort study

STROBE Statement —Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(***a***) Indicate the study's design with a commonly used term in the title or the abstract	1
		(***b***) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(***a***) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-10
		(***b***) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-10
Statistical methods	12	(***a***) Describe all statistical methods, including those used to control for confounding	8,9
		(***b***) Describe any methods used to examine subgroups and interactions	8,9
		(***c***) Explain how missing data were addressed	8,9
		(***d***) If applicable, explain how loss to follow-up was addressed	NA
		(***e***) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA

	Item No	Recommendation	Page No
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

International Statistical Classification of Diseases and Related Health Problems, 10th revision of the World Health Organization used to identify opioid-related complications in the Hospital and Mortality data, the Netherlands, from 2013 to 2017

ICD-10CM opioid poisoning	
F11.0	Acute intoxication
F11.1	Harmful use
F11.2	Dependence syndrome
F11.3	Withdrawal state
F11.4	Withdrawal state with delirium
F11.5	Psychotic disorder
F11.6	Amnesic syndrome
F11.7	Residual and late-onset psychotic disorder
F11.8	Other mental and behavioural disorders
F11.9	Unspecified mental and behavioural disorder
T40.0	Opium poisoning
T40.1	Heroin poisoning
T40.2	Poisoning by other opioids
T40.3	Methadone poisoning
T40.4	Poisoning by other synthetic narcotics
T40.6	Poisoning by other and unspecified narcotics

Supplementary Table S1. Characteristics of the study population: total Dutch population and the GE survey cohort, from 2013 to 2017

		2013	**2014**	**2015**	**2016**	**2017**
The total Dutch population	No.	16779575	16829290	16900726	16979120	17081507
	Mean age, years	40.8	41.0	41.3	41.5	41.6
	Male, No. (%)	8307339 (49.5)	8334385 (49.5)	8372858 (49.5)	8417135 (49.6)	8475102 (49.6)
	Female, No. (%)	8472236 (50.5)	8494905 (50.5)	8527868 (50.5)	8561985 (50.4)	8606405 (50.4)
The GE cohort	No.	NA	9516	9358	9165	9826
	Mean age (SD), years	NA	40.4 (23.7)	40.7 (23.5)	41.0 (23.7)	41.7 (24.1)
	Male, No. (%)	NA	4637 (48.7)	4609 (49.3)	4455 (48.6)	4848 (49.3)
	Female, No. (%)	NA	4879 (51.3)	4749 (50.7)	4710 (51.4)	4978 (50.7)

Abbreviations: SD, standard deviation; NA, not available

Supplementary Table S2. Age- and sex- adjusted relative risks and incidence rates for opioid prescription cases, overall and stratified by natural and synthetic, and NSAIDs prescription cases in the Netherlands, from 2013 to 2017

		2013 (n=16779575)	2014 (n=16829290)	2015 (n=16900726)	2016 (n=16979120)	2017 (n=17081507)
Opioid prescription	No.	814211	863110	921754	975979	1027019
	aIR (per 100,000, 95% CI)*	4850 (4840-4860)	5080 (5070-5090)	5351 (5340-5362)	5597 (5586-5608)	5819 (5808-5831)
	aRR (95% CI)*	1 (reference)	1.05 (1.04-1.05)	1.10 (1.10-1.11)	1.15 (1.15-1.16)	1.20 (1.20-1.20)
Natural	No.	183549	232252	297498	369172	431412
	aIR (per 100,000, 95% CI)*	1090 (1090-1100)	1360 (1360-1370)	1723 (1716-1729)	2111 (2105-2118)	2437 (2430-2444)
	aRR (95% CI)*	1 (reference)	1.25 (1.24-1.25)	1.57 (1.57-1.58)	1.93 (1.92-1.94)	2.23 (2.22-2.24)
Synthetic	No.	630662	630858	624256	606807	595599
	aIR (per 100,000, 95% CI)*	3760 (3750-3770)	3710 (3700-3720)	3628 (3619-3637)	3485 (3477-3494)	3382 (3374-3391)
	aRR (95% CI)*	1 (reference)	0.99 (0.98-0.99)	0.97 (0.96-0.97)	0.93 (0.92-0.93)	0.90 (0.90-0.90)
NSAIDs prescription	No.	2600896	2535617	2469770	2405557	2345221
	aIR (per 100,000, 95% CI)*	15500 (15480-15520)	15030 (15010-15040)	14532 (14514-14550)	14050 (14032-14068)	13587 (13570-13604)
	aRR (95% CI)*	1 (reference)	0.97 (0.97-0.97)	0.94 (0.94-0.94)	0.91 (0.90-0.91)	0.88 (0.88-0.88)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; aIR, adjusted incidence rate; NSAIDs, nonsteroidal anti-inflammatory drugs

*adjusted for age and sex with direct standardization; the 2013 total Dutch population cohort was selected as a reference.

Individuals, who reimbursed opioid prescriptions were selected by ATC code N02A (natural, N02AA; synthetic N02AZ), NSAIDs prescriptions by ATC code M01A.

Supplementary Table S3. Age- and sex- adjusted relative risks and incidence rates for opioid prescription vs NSAIDs prescription cases, stratified by concomitant and only prescription, in the Netherlands, from 2013 to 2017

Opioid prescription	NSAIDs prescription		2013 (n=16779575)	2014 (n=16829290)	2015 (n=16900726)	2016 (n=16979120)	2017 (n=17081507)
Yes	No	No.	398029	432597	469045	508907	542168
		aIR (per 100,000, 95% CI)*	2372 (2365-2379)	2535 (2527-2542)	2703 (2695-2711)	2890 (2883-2898)	3036 (3028-3044)
		aRR (95% CI)*	1 (reference)	1.07 (1.06-1.07)	1.14 (1.13-1.14)	1.22 (1.21-1.22)	1.28 (1.27-1.29)
Yes	Yes	No.	416182	430513	452709	467072	484851
		aIR (per 100,000, 95% CI)*	2480 (2473-2488)	2543 (2535-2550)	2648 (2640-2655)	2706 (2699-2714)	2783 (2775-2791)
		aRR (95% CI)*	1 (reference)	1.03 (1.02-1.03)	1.07 (1.06-1.07)	1.09 (1.09-1.10)	1.12 (1.12-1.13)
No	Yes	No.	2184714	2105103	2017061	1938485	1860370
		aIR (per 100,000, 95% CI)*	13020 (13003-13037)	12483 (12466-12499)	11884 (11868-11900)	11344 (11328-11360)	10804 (10788-10819)
		aRR (95% CI)*	1 (reference)	0.96 (0.96-0.96)	0.91 (0.91-0.91)	0.87 (0.87-0.87)	0.83 (0.83-0.83)
No	No	No.	13780650	13861007	13961911	14064656	14194118
		aIR (per 100,000, 95% CI)*	82128 (82084-82171)	82440 (82396-82483)	82765 (82722-82809)	83059 (83016-83103)	83377 (83333-83420)
		aRR (95% CI)*	1 (reference)	1.00 (1.00-1.00)	1.01 (1.01-1.01)	1.01 (1.01-1.01)	1.02 (1.01-1.02)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; aIR, adjusted incidence rate; NSAIDs, nonsteroidal anti-inflammatory drugs

*adjusted for age and sex with direct standardization; the 2013 total Dutch population cohort was selected as a reference.

Individuals, who reimbursed opioid prescriptions were selected by ATC code N02A (natural, N02AA; synthetic N02AZ), NSAIDs prescriptions by ATC code M01A.

Supplementary Table S4. Opioid and NSAIDs prescription rate among respondents of GE surveys, from 2014 to 2017

		2014 (n=9516)	2015 (n=9358)	2016 (n=9165)	2017 (n=9826)
Opioid prescription	No./ Total No. (%)	447/9516 (4.70)	468/9358 (5.00)	504/9165 (5.50)	576/9826 (5.86)
	aRR (95% CI)*	1 (reference)	1.05 (0.93-1.20)	1.15 (1.02-1.31)	1.19 (1.05-1.34)
Pain impeded activities of daily living					
Not at all	No./ Total No. (%)	70/2287 (3.06)	76/2191 (3.47)	75/2117 (3.54)	94/2330 (4.03)
	aRR (95% CI)*	1 (reference)	1.15 (0.83-1.59)	1.17 (0.84-1.62)	1.27 (0.93-1.74)
Somewhat	No./ Total No. (%)	94/1857 (5.06)	112/1861 (6.02)	119/1819 (6.54)	143/1923 (7.44)
	aRR (95% CI)*	1 (reference)	1.17 (0.89-1.54)	1.29 (0.98-1.68)	1.38 (1.06-1.79)
Moderate	No./ Total No. (%)	92/516 (17.83)	74/502 (14.74)	85/511 (16.63)	99/506 (19.57)
	aRR (95% CI)*	1 (reference)	0.81 (0.60-1.10)	0.95 (0.70-1.27)	1.05 (0.79-1.39)
Much and extreme	No./ Total No. (%)	130/459 (28.32)	135/467 (28.91)	159/500 (31.8)	166/498 (33.33)
	aRR (95% CI)*	1 (reference)	1.01 (0.79-1.29)	1.13 (0.89-1.42)	1.18 (0.93-1.48)
Missing	No./ Total No. (%)	60/4397 (1.36)	69/4337 (1.59)	66/4218 (1.56)	74/4569 (1.62)
NSAIDs prescription	No./ Total No. (%)	1378/9516 (14.48)	1317/9358 (14.07)	1314/9165 (14.34)	1339/9826 (13.63)
	aRR (95% CI)*	1 (reference)	0.96 (0.89-1.03)	0.98 (0.91-1.06)	0.93 (0.86-1.00)
Pain impeded activities of daily living					
Not at all	No./ Total No. (%)	334/2287 (14.60)	278/2191 (12.69)	286/2117 (13.51)	299/2330 (12.83)
	aRR (95% CI)*	1 (reference)	0.87 (0.75-1.03)	0.93 (0.79-1.09)	0.87 (0.75-1.02)
Somewhat	No./ Total No. (%)	377/1857 (20.30)	399/1861 (21.44)	362/1819 (19.9)	398/1923 (20.70)
	aRR (95% CI)*	1 (reference)	1.06 (0.92-1.22)	0.98 (0.85-1.13)	1.00 (0.87-1.15)
Moderate	No./ Total No. (%)	168/516 (32.56)	146/502 (29.08)	141/511 (27.59)	163/506 (32.21)
	aRR (95% CI)*	1 (reference)	0.89 (0.71-1.11)	0.84 (0.67-1.05)	0.96 (0.77-1.19)
Much and extreme	No./ Total No. (%)	173/459 (37.69)	187/467 (40.04)	200/500 (40.00)	182/498 (36.55)
	aRR (95% CI)*	1 (reference)	1.03 (0.84-1.27)	1.04 (0.85-1.28)	0.96 (0.78-1.18)
Missing	No./ Total No. (%)	326/4397 (7.41)	307/4337 (7.08)	324/4218 (7.68)	297/4569 (6.50)

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; GE, Health Interview Survey; NSAIDs, nonsteroidal anti-inflammatory drugs

*adjusted for age and sex with direct standardization; 2014 cohort was selected as a reference population in the GE survey.

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CHAPTER 4

The association of opioid use with risk of ICU admission and mortality in the adult Dutch population: a registry study

Published in British journal of anaesthesia. 2022 Aug;129(2):254-262

Ajda Bedene, Willem M. Lijfering, M. Sesmu Arbous, Frits R. Rosendaal, Albert Dahan, Eveline L.A. van Dorp

Abstract

Background

Opioid overdoses are increasing in the Netherlands, and there may be other harms associated with prescription opioid use. We investigated the relationship between prescription opioid use and unplanned ICU admission and death.

Methods

This is an analysis of linked government registries of the adult Dutch population (age >18 years) alive on January 1, 2018. The co-primary outcomes were ICU admission and death up to 1 year. Crude event rates and event-specific adjusted hazard rates (aHRs) with 95% confidence intervals (CIs) were calculated using multivariable analysis for people with and without exposure to an opioid prescription.

Results

We included 13,813,173 individuals, of whom 32,831 were admitted to the ICU and 152,259 died during the 1-year follow-up. Rates of ICU admission and death amongst people who reimbursed an opioid prescription were 5.87 and 62.2 per 1000 person-years, and rates of ICU admission and death in those without a prescription were 2.03 and 6.34, respectively. Exposed individuals had a higher rate of both ICU admission (aHR 2.53; 95% CI: 2.45-2.60) and death (aHR 7.11; 95% CI: 7.02-7.19) compared with unexposed individuals. Both outcomes were more frequent amongst prescription opioid users across a range of subgroups.

Conclusion

The rate of ICU admission and death was higher amongst prescription opioid users than non-users in the full cohort and in subgroups. These findings represent an important public health concern.

Editor's key points

- The epidemic of prescription opioid and gabapentinoid use was first identified in the USA but is now a problem in many high-income countries.
- In some cases, addiction to prescription drugs evolves into addiction to illegal 'recreational' drugs.
- Whilst most exposure occurs in the community, many individuals are first introduced to prescription opioids in secondary care, for instance after surgery.
- The findings of this study suggest an important association between prescription opioid use, intensive care admission, and death even after adjustment for baseline risk factors.

Introduction

Widespread opioid use in the United States has caused a national health crisis, "the opioid epidemic" [1], which took almost 92,000 lives in 2020 [2,3]. Several other countries have also reported a rising number of opioid prescriptions over the past decade [4–6]. We have shown previously that prescription opioid use in the Netherlands increased by about 20% over the past few years, with an increased incidence of side-effects, such as opioid overdose, although to a lesser extent than in the USA. [7,8].

The burden of opioid use extends beyond overdose/ poisoning. Opioid use is also associated with constipation and other gastrointestinal disturbances, dizziness, lowered consciousness, and possible immune system modulation [9]. People taking prescription opioids may have an increased risk of falls and traffic accidents, and may therefore be at greater risk of ICU admission and death [10–13]. However, it is unclear whether in the Netherlands and Europe, these observations relate to other socio-demographic risk factors, rather than prescription opioid use itself [14], given most available evidence comes from the USA and Canada [13,15–19].

In this study, we offer a Dutch perspective on the association between prescription opioid use and serious adverse health outcomes. We hypothesised that opioid use is

associated with an increased risk of unplanned ICU admission and all-cause mortality in the adult population of the Netherlands, alive on January 1, 2018. Furthermore, we investigated other possible explanatory variables, such as duration of treatment and socio-demographic factors, which might provide an alternative explanation for observed associations.

Methods

Setting and participants

We conducted a nationwide cohort study of linked data registries from Statistics Netherlands (Centraal Bureau voor de Statistiek), a Dutch government agency that collects and manages a wide range of data on all Dutch residents (17.5 million inhabitants). As the individual identities were not disclosed, participant consent was waived by the Medical Ethical Review Committee of Leiden University Medical Center (reference number: G21.048). We analysed data from October 9, 2016 (1 year and 12 weeks before the study start date of January 1, 2018) until December 31, 2018 (after which data were unavailable). The final cohort for analysis included all adult residents of the Netherlands who were alive on January 1, 2018 (index date). Individuals who died before January 1, 2018 or were younger than 18 years were excluded from the cohort. A detailed description of the inclusion criteria and variable definitions are provided in the Supplementary material.

Exposure status

Individuals were considered exposed when they reimbursed at least one opioid prescription between 12 weeks before the study start date (January 1, 2018) and December 31, 2018. We assessed exposure from 12 weeks before the start of the follow-up period to ensure temporality between exposure and outcome, and because opioids are not usually prescribed on a single prescription in the Netherlands for longer than 12 weeks. Time at risk in days was calculated from the date the first prescription was reimbursed to the end of the follow-up period for the two exposure groups. Generally, postoperative opioids are prescribed for a 2-week duration in the Netherlands. However, there are many exceptions; opioids may be prescribed for a few days only or for several months (usually for chronic non-malignant pain). Considering the findings of the Consortium to Study Opioid Risks and Trends (CONSORT) study [20], we defined chronic opioid use as when individuals reimbursed five or more opioid prescriptions

from October 9, 2017 to December 31, 2018. For assessing the risk of events depending on the duration of opioid use, we defined distinct categories of opioid users first time, intermittent, and chronic. We defined categories based on the date of reimbursement relative to the index date and the number of opioid prescriptions. Further details on variable definition are provided in the Supplementary material.

Outcomes

The co-primary outcomes were unplanned ICU admission and all-cause mortality up to 1 year. To estimate the risk of these outcomes, individuals were followed from January 1, 2018 until an outcome event occurred (the date of admission to the ICU or date of death, or the end of the 1-year follow-up, December 31, 2018). ICU admission was defined as having been registered as admitted to ICU in the Dutch Hospital Data registry, the data holder [21]. We provide a detailed variable description in the Supplementary material. Planned ICU admission related to a planned surgical procedure was excluded as an outcome event because these individuals receive significant quantities of opioids but under close medical supervision [22,23], but they may have an increased mortality risk related to surgery [24]. ICU admission was considered an endpoint when death and ICU admission occurred on the same date. However, death is a competing event of ICU admission and was treated as such in the analysis.

Other explanatory variables

We considered several other variables, which may be associated with the co-primary outcomes and with opioid prescription status. Before the analysis, we selected a list of potential confounding variables, based on clinical experience and data availability (specifically comorbid disease). From the population register, we extracted date of birth, sex, and immigration status. We calculated age on index date and stratified it into several categories. Immigration status was defined and divided into three categories using terminology defined by Statistics Netherlands [25]. Comorbidities at index date were identified through pharmacy claims in 2017. Prescribed medications were used as a proxy for an indication. (Anatomical Therapeutic Chemical [ATC] codes for these definitions can be found in the Supplementary material.) Socio-economic factors, standardised private household income, and primary source of income were derived from 2017 tax records.

Data sources and linkage

We analysed data from registries describing opioid prescription reimbursement, hospital admissions, mortality, administrative factors, and household income. We provide a detailed description of the listed registries in the Supplementary material, including the proportion of the population included. We linked the aforementioned data sets based on unique pseudo-anonymised identifiers. These identifiers were created by Statistics Netherlands to allow for deterministic linkage whilst protecting the privacy of individuals.

Statistical methods

Baseline characteristics are given as proportions of the total study population. The median follow-up period was calculated using a reversed Kaplan-Meier method. The absolute risk of ICU admission and death is presented by counts and time at risk of the event expressed in person-years, shown separately for opioid exposure status. Cox regression models were constructed with opioid prescription status as a time-varying covariate, where not being exposed to opioids was taken as a reference and ICU admission (Models 1 and 2) and death (Models 3 and 4) as endpoints. The competing risk of death was considered in the estimation of the risk of ICU admission (Models 1 and 2). For all models, we present unadjusted hazard rate (HR) ratios (Models 1 and 3) and adjusted hazard rate (aHR) ratios, where we corrected for the influence of age, sex, immigration status, comorbidities, main source of income, and standardised household income in quintiles (Models 2 and 4), where applicable. Finally, we investigated the association of the duration of opioid use and other explanatory variables with outcomes, conditional on the opioid prescription status. To explore this, we analysed subgroups of the study population depending on the duration of opioid use and other explanatory variables of interest, and further divided them based on opioid prescription status. We then compared incident rates of the co-primary outcomes (separately for ICU admission and death) according to opioid prescription status in all subgroups by Cox regression models. Data analysis was performed in R (a language and environment for statistical computing; R Core Team, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org; version 3.6.2) with packages survival (version 3.2.13) and ggplot 2 (version 3.3.5) [26,27]. This analysis is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [28].

Results

Population characteristics

In total, 1,179,325 residents out of 1,195,330 (98.6%) with a registered opioid prescription were linked to the total population cohort (Fig 1). For unplanned ICU admission, the percentage of linkage was 89.6% (35,090 individuals out of 39,160), and for comorbidities it was 96.5% (2,213,116 individuals out of 2,293,245). We excluded all unlinked individuals and those younger than 18 years (3,367,807) or those who died before January 1, 2018 (110 people).

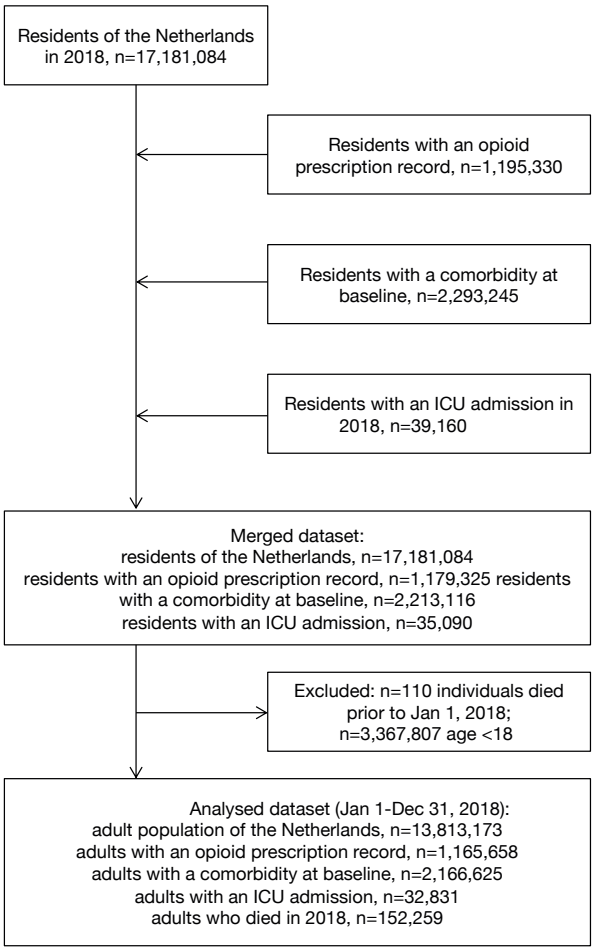


Figure 1. Inclusion and exclusion of individuals in the data set

In 2018, 1,165,658 (8.4%) of 13,813,173 eligible adult residents received an opioid prescription, 32,831 (0.2%) residents were admitted to the ICU, and 152,259 (1.1%) died within 1 year. The median follow-up period was 365 days. The study population consisted of 7,011,126 (51%) women and 6,802,047 (49%) men (Table 1). Some people with records in the opioid prescription reimbursement registry, unplanned ICU admissions from the hospital registry, and comorbidities identified through the prescription reimbursement registry could not be linked to the total population of the Netherlands (17,181,084 people in 2018).

Table 1. Characteristics of adult residents of the Netherlands included in the analysis

	Adult residents, No. (%)
Total	13813173
Sex	
Men	6802047 (49.2)
Women	7011126 (50.8)
Age group, years	
18-35	3653069 (26.4)
35-45	2061585 (14.9)
45-55	2546367 (18.4)
55-65	2295143 (16.6)
65-75	1878043 (13.6)
75-85	1002751 (7.26)
> 85	376215 (2.72)
Immigration status	
Native	10711308 (77.5)
First generation	1932006 (14.0)
Second generation	1169859 (8.47)
Comorbidity	
Depression	1001059 (7.25)
Other psychiatric conditions	587935 (4.26)
Cancer	143491 (1.04)
Diabetes	785933 (5.69)
Chronic viral infection	105132 (0.76)
Main source of income	
Wage	9111520 (66.0)
Welfare	1138361 (8.24)
Pension	3297809 (23.9)
Other *	265483 (1.92)
Household income, quintile	
First	2007038 (14.5)
Second	2332282 (16.9)
Third	2651616 (19.2)
Fourth	2925798 (21.2)

Table 1. Characteristics of adult residents of the Netherlands included in the analysis *(continued)*

	Adult residents, No. (%)
Fifth	3339781 (24.2)
No identified income	104038 (0.75)
Institutionalised	234396 (1.70)
Student grant	218224 (1.58)

Total number of individuals in 2018 is n=17,181,084, of these n=110 have died before January 1, 2018 and were excluded from the analysis. The total number that is reported in the table is the number of adults in the Dutch population of 2018. The table shows descriptive statistics for all adult residents included in the study. The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown.

Association between opioid use, duration of opioid use, and ICU admission or death

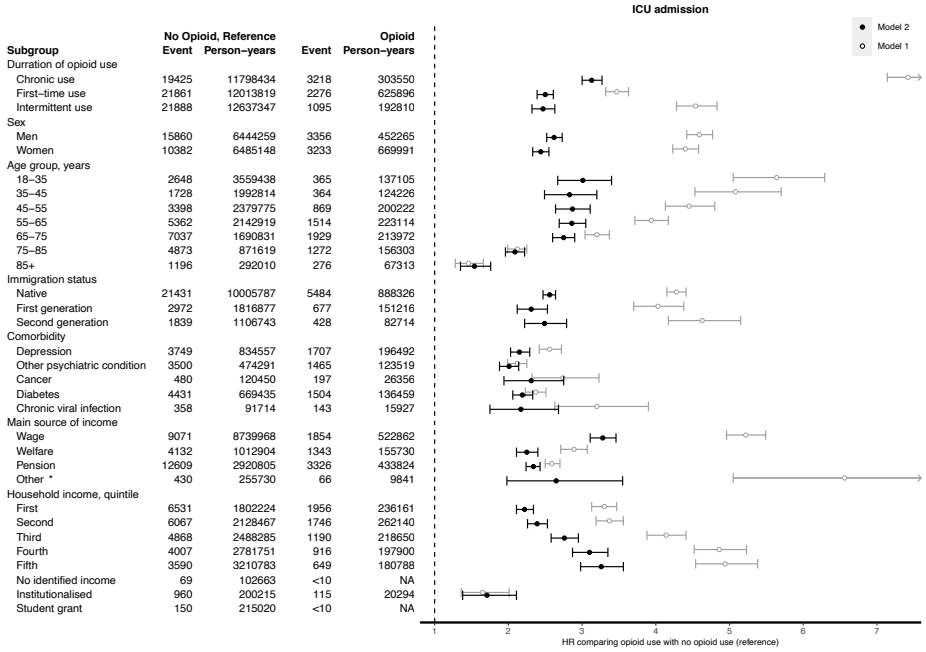
There were 6,589 ICU admissions registered for 1,122,256 person-years amongst opioid users (5.9 per 1000 person-years) and 26,242 ICU admissions for 12,929,407 person-years amongst non-users (2.0 per 1000 person-years). Amongst adult residents using opioids, the mortality rate was 62 per 1000 person-years, and amongst those not using opioids it was 6.3 per 1000 person-years (i.e., 70,248 deaths in 1,129,399 person-years and 82,011 deaths in 12,938,602 person-years in opioid users and non-users, respectively). To clarify how the multivariable models were constructed, we report estimates for individual covariates for the full cohort in Table 2 and for subgroups in Supplementary Tables 1-14. For the total adult Dutch population, the rate of ICU admission was higher amongst opioid users than non-users (HR 4.29 [95% confidence interval {CI}: 4.18-4.41]; aHR 2.53 [95% CI: 2.45-2.60]). An increased rate of ICU admission was consistently present across groups of chronic opioid users, first-time opioid users, and intermittent users when compared with non-opioid users (aHR 3.13 [95% CI: 3.00-3.27] for chronic use, 2.50 [95% CI: 2.39-2.61] for first-time use, and 2.47 [95% CI: 2.32-2.63] for intermittent use) (Fig 2). The HR of death (obtained through Models 3 and 4) was greater amongst opioid users compared with non-opioid users (HR 14.9 [95% CI: 14.7-15.0]; aHR 7.11 [95% CI: 7.02-7.19]). Again, an increased mortality rate was consistently observed within groups of opioid users, defined by the duration of treatment, compared with no use (aHR 7.15 [95% CI: 7.03-7.27] for chronic use, aHR 8.49 [95% CI: 8.34-8.64] for first-time opioid use, and aHR 4.32 [95% CI: 4.20-4.44] for intermittent use) (Fig 3).

Table 2. Hazard ratio estimates for individual covariates in multivariable Cox regression models for ICU admission and death within 1 year

	ICU admission			Death		
Covariates	**Events, No.**	**Person-years**	**Model 2 aHR (95% CI)**	**Events, No.**	**Person-years**	**Model 4 aHR (95% CI)**
Sex						
Men	19216	6896524	1(reference)	73868	6906128	1(reference)
Women	13615	7155139	0.59 (0.58-0.61)	78391	7161873	0.58 (0.57-0.59)
Age group, years						
18-35	3013	3696543	1(reference)	1241	3698222	1(reference)
35-45	2092	2117041	1.12 (1.06-1.19)	1661	2118212	2.22 (2.06-2.40)
45-55	4267	2579997	1.76 (1.68-1.85)	5470	2582322	5.67 (5.32-6.04)
55-65	6876	2366034	2.69 (2.57-2.81)	14092	2369614	14.2 (13.4-15.1)
65-75	8966	1904803	4.28 (4.02-4.55)	28605	1909138	44.8 (42.1-47.7)
75-85	6145	1027923	4.83 (4.52-5.16)	44656	1030603	102 (95.5-109)
> 85	1472	359324	3.17 (2.92-3.44)	56534	359889	242 (226-258)
Immigration status						
Native	26915	10894114	1(reference)	132400	10907491	1(reference)
First generation	3649	1968093	0.72 (0.69-0.74)	11523	1969912	0.67 (0.66-0.69)
Second generation	2267	1189457	0.96 (0.91-1.00)	8336	1190598	0.98 (0.95-1.00)
Comorbidity						
Depression	5456	1031049	1.36 (1.32-1.41)	21258	1033804	0.88 (0.86-0.89)
Other psychiatric conditions	4965	597810	2.11 (2.04-2.18)	25627	600318	1.59 (1.56-1.62)
Cancer	677	146805	1.13 (1.05-1.22)	7706	147142	1.61 (1.56-1.65)
Diabetes	5935	805894	1.76 (1.71-1.81)	27220	808704	1.13 (1.12-1.15)
Chronic viral infection	501	107641	1.53 (1.40-1.67)	2340	107886	1.43 (1.36-1.50)
Main source of income						
Wage	10925	9262830	1(reference)	17825	9268795	1(reference)
Welfare	5475	1168634	1.87 (1.79-1.95)	9583	1171506	1.19 (1.16-1.22)
Pension	15935	3354629	1.15 (1.10-1.21)	120703	3361910	0.78 (0.75-0.80)
Other *	496	265570	1.52 (1.37-1.68)	4148	265790	2.24 (2.15-2.33)
Household income, quintile						
First	8487	2038385	1.97 (1.89-2.06)	49205	2042193	3.41 (3.33-3.49)
Second	7813	2390607	1.54 (1.48-1.60)	26886	2394585	1.15 (1.12-1.17)
Third	6058	2706935	1.39 (1.33-1.44)	17655	2710062	1.16 (1.14-1.19)
Fourth	4923	2979651	1.20 (1.16-1.26)	12900	2982258	1.07 (1.04-1.10)
Fifth	4239	3391571	1(reference)	11244	3393812	1(reference)
No identified income	78	104246	0.87 (0.68-1.12)	274	104285	1.85 (1.63-2.10)
Institutionalised	1075	220509	1.91 (1.77-2.05)	34023	220963	7.43 (7.24-7.64)
Student grant	158	219758	1.22 (1.04-1.44)	72	219844	1.32 (1.04-1.68)

In this table, we show hazard ratio estimates of all covariates included in the two multivariable models, Models 2 and 4, that were built to estimate the risk of ICU admission and death. Here, it is also evident which category within variable was defined as reference. For example, the age category 18-35 yr was taken as a reference to estimate age effect estimates. The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics

Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. aHR, adjusted hazard rate; CI, confidence interval.



Subgroup	No Opioid, Reference Event	Person–years	Opioid Event	Person–years
Durration of opioid use				
Chronic use	19425	11798434	3218	303550
First–time use	21861	12013819	2276	625896
Intermittent use	21888	12637347	1095	192810
Sex				
Men	15860	6444259	3356	452265
Women	10382	6485148	3233	669991
Age group, years				
18–35	2648	3559438	365	137105
35–45	1728	1992814	364	124226
45–55	3398	2379775	869	200222
55–65	5362	2142919	1514	223114
65–75	7037	1690831	1929	213972
75–85	4873	871619	1272	156303
85+	1196	292010	276	67313
Immigration status				
Native	21431	10005787	5484	888326
First generation	2972	1816877	677	151216
Second generation	1839	1106743	428	82714
Comorbidity				
Depression	3749	834557	1707	196492
Other psychiatric condition	3500	474291	1465	123519
Cancer	480	120450	197	26356
Diabetes	4431	669435	1504	136459
Chronic viral infection	358	91714	143	15927
Main source of income				
Wage	9071	8739968	1854	522862
Welfare	4132	1012904	1343	155730
Pension	12609	2920805	3326	433824
Other *	430	255730	66	9841
Household income, quintile				
First	6531	1802224	1956	236161
Second	6067	2128467	1746	262140
Third	4868	2488285	1190	218650
Fourth	4007	2781751	916	197900
Fifth	3590	3210783	649	180788
No identified income	69	102663	<10	NA
Institutionalised	960	200215	115	20294
Student grant	150	215020	<10	NA

Figure 2. Association between opioid use and ICU admission in different subgroups of the total population

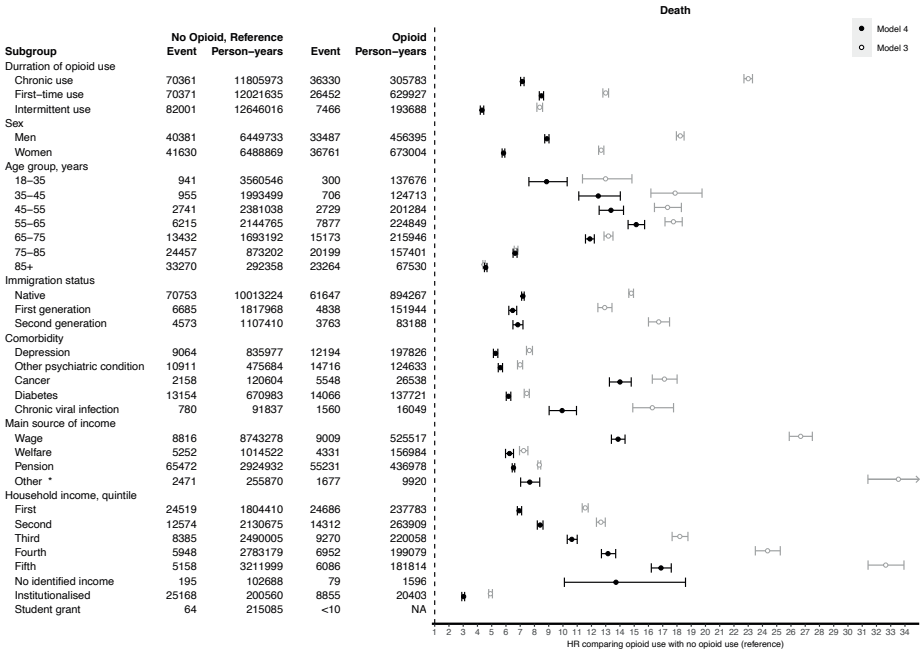
The graph shows unadjusted and adjusted estimates in subgroups of age, sex, comorbidities, primary source of income, and household income in quintiles. (The first quintile is the lowest income group.) Here, we also report number of events and cumulative number of person-years for each exposure group (opioid use and no opioid use). Model 1 was a cause-specific univariable Cox regression model, where ICU admission was entered as a dependent variable and opioid prescription status as a time-varying independent variable. In this model, the competing risk of death was considered. Model 2 was a multivariable model, where age, sex, immigration status, comorbidity, main source of income, and household income in quintiles were included as covariates. In this model, the competing risk of death was considered. The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Risk factors for ICU admission and death

The rate of ICU admission was increased amongst opioid users compared with non-users in all subgroups (e.g., by age, sex, and household income) (Fig 2). The rate of ICU admission was higher in men than in women (Table 2), but the HR ratio was elevated for opioid use in both sexes (aHR 2.62 [95% CI: 2.52-2.73] for men; aHR 2.44 [95% CI:

2.33-2.55] for women). The HR ratio of ICU admission in users compared with non-users was similar between categories of immigration status, comorbidities, and main source of income (Fig 2). The rate of ICU admission increased with age (Table 2), but the aHR ratio of ICU admission appeared largest in the youngest age group (aHR 1.54 [95% CI: 1.35-1.76] for age group >85 yr; aHR 3.01 [95% CI: 2.67-3.40] for the 18-35 age group). Whereas the rate of ICU admission was in general lowest in the most affluent socio-economic class (Table 2), the aHR opioid use was largest in this group (aHR for first quintile, least affluent group, 2.22 [95% CI: 2.11-2.34] and for fifth quintile, most affluent group, 3.26 [95% CI: 2.98-3.56]) (Fig 2).

The rate of death was increased amongst opioid users compared with non-users across subgroups (Fig 3). In contrast with the ICU admission HR ratio, the HR ratio for death associated with opioid use was higher amongst men than women (aHR 8.87 [95% CI: 8.72-9.02] for men; aHR 5.83 [95% CI: 5.73-5.92] for women) (Figs 2 and 3). In different age groups, the aHR ratio of death was highest within the 55-65 yr group (aHR 15.1 [95% CI: 14.6-15.7]) (Fig 3), although the number of deaths increased with age (Tables 1 and 2). We observed no difference in the mortality HR ratio within categories of immigration status, but it was approximately twice as high in the wage group of main sources of income than in the welfare group (aHR 13.9 [95% CI: 13.4-14.4] for wage; aHR 6.25 [95% CI: 5.97-6.53] for welfare). The mortality rate was greater amongst patients with cancer who are using opioids compared with patients with cancer who are not using opioids (aHR 14.095% CI: 13.3-14.8]), and in patients with depression who are using opioids compared with patients with depression who are not using opioids (aHR 5.27 [95% CI: 5.12-5.43]) (Fig 3).



Subgroup	No Opioid, Reference Event	Person–years	Opioid Event	Person–years
Durration of opioid use				
Chronic use	70361	11805973	36330	305783
First–time use	70371	12021635	26452	629927
Intermittent use	82001	12646016	7466	193688
Sex				
Men	40381	6449733	33487	456395
Women	41630	6488869	36761	673004
Age group, years				
18–35	941	3560546	300	137676
35–45	955	1993499	706	124713
45–55	2741	2381038	2729	201284
55–65	6215	2144765	7877	224849
65–75	13432	1693192	15173	215946
75–85	24457	873202	20199	157401
85+	33270	292358	23264	67530
Immigration status				
Native	70753	10013224	61647	894267
First generation	6685	1817968	4838	151944
Second generation	4573	1107410	3763	83188
Comorbidity				
Depression	9064	835977	12194	197826
Other psychiatric condition	10911	475684	14716	124633
Cancer	2158	120604	5548	26538
Diabetes	13154	670983	14066	137721
Chronic viral infection	780	91837	1560	16049
Main source of income				
Wage	8816	8743278	9009	525517
Welfare	5252	1014522	4331	156984
Pension	65472	2924932	55231	436978
Other *	2471	255870	1677	9920
Household income, quintile				
First	24519	1804410	24686	237783
Second	12574	2130675	14312	263909
Third	8385	2490005	9270	220058
Fourth	5948	2783179	6952	199079
Fifth	5158	3211999	6086	181814
No identified income	195	102688	79	1596
Institutionalised	25168	200560	8855	20403
Student grant	64	215085	<10	NA

Figure 3. Association between opioid use and death in different subgroups of the total population

The graph shows results of univariable and multivariable Cox regression models in different subgroups of opioid use, sex, age, comorbidities, primary source of income, and household income in quintiles. (The first quintile is the lowest income group.) We also report number of events and cumulative number of person-years for each exposure group (opioid use and no opioid use). In the figure, we do not show the results of the unadjusted model for the 'no identified income' category of household income. The estimate was obtained by applying Model 3 in individuals with reported no identified income (restriction of the full cohort). Model 3 was a univariable Cox regression model, where death was entered as a dependent variable and opioid prescription status as a time-varying independent variable. Model 4 was a multivariable model, where age, sex, immigration status, comorbidity, main source of income, and household income in quintiles were entered as covariates. The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Discussion

We provide evidence for an association between prescription opioid use and both unplanned ICU admission and death in the adult population of the Netherlands. Residents who are prescribed opioids are two-to eight-fold more likely to experience both outcomes, and the association is stronger in some socio-demographic subgroups.

We also observed a positive correlation between the number of completed opioid prescriptions and the rate of both outcomes. The rate of ICU admission was highest amongst individuals who reimbursed five or more prescriptions and were considered chronic users.

Several recent papers have described an association between prescribed opioid use and opioid overdose deaths in Europe. A recent case-crossover study, including 1.7 million opioid users identified in the UK primary care database, demonstrated that almost 75% of opioid overdosed individuals received an opioid prescription in the year before death [10]. Similarly, a German insurance database study, covering 5 million residents, showed that patients on long-term opioid therapy were at higher risk for all-cause mortality than patients on other types of analgesics [29]. We show that these findings can be extrapolated to the general population, given the increased all-cause mortality risk associated with opioid use in the whole adult population of the Netherlands.

Although several studies on the use of opioids after ICU admission have been published in recent years, the evidence on use of opioids before ICU admission is limited [15,17,30]. Munch and colleagues [31] showed in a large cohort study of patients in ICU in Denmark that current opioid use in the pre-admission period led to a higher mortality risk than in the opioid-naive individuals. Similar conclusions were drawn in cohort studies of patients in ICU from Sweden and the USA. [19,30]. However, these studies do not explore the association between opioid use and the risk of ICU admission, but merely include prior opioid use as a risk factor for poor outcomes. Some studies investigated the association between opioid use and the risk of ICU admission attributable to opioid overdose alone [13,32], but opioids can lead to more life-threatening situations, such as traumatic injury and an increased incidence of infection, and in some cases overdose is falsely classified as cardiac or respiratory arrest. We have included all unplanned ICU admissions in the Dutch population, allowing a broader interpretation.

Interestingly, for both co-primary outcomes (ICU admission and death), the HR ratios comparing opioid users with non-users varied somewhat within levels of grouping variables (i.e., age, sex, main source of income, and household income in quintiles) and were most prominent in those groups with the lowest baseline risk. However, regardless of the investigated subgroup, the rate of unplanned ICU admission and

death was always elevated when opioid users were compared with non-users, as effects estimates were all greater than one. Furthermore, we observed an increased rate of ICU admission and death across the different groups of opioid users. The rates for both outcomes were most increased in the chronic opioid use group compared with the non-exposed group. The same was found for relative rates (HR ratios) for ICU admission; however, when we adjusted for predefined covariates and the outcome considered was death, the estimate for chronic use was attenuated so much so that the mortality HR ratio for first-time users surpassed it. We note that this inconsistency in estimated relative rates of ICU admission and death may be partially explained by differences in confounding factors in subgroups of opioid users. (For example, chronic users may have more comorbidities than first-time users.) In this project, such confounding was not explored but may be of interest for future research.

There are some limitations to our study. First, our data on exposure are subject to some uncertainty. We only have information on whether individuals have reimbursed an opioid prescription, not whether patients ingested the medication. Neither do we have information on the type, dose, and indication of prescribed opioids and on illicit opioid use. When an individual is exposed to illicit opioids only, he or she would be classified as unexposed, which would lead to seemingly increased rates in the unexposed and ultimately to an underestimation of the treatment effect estimate. Additionally, we assumed individuals exposed from the date they received an opioid prescription to the end of the follow-up, which most probably leads to a treatment effect underestimation. Furthermore, caution is needed in the interpretation of the data on comorbidities. Comorbidity status was defined as patients having filled a prescription for medication for that said disease. This has undoubtedly introduced misclassification. For example, we used anti-cancer medication as a proxy for having cancer, which means we may have missed individuals who underwent radiotherapy or inpatient chemotherapy. However, the estimated prevalence of cancer and the prevalence of depression, diabetes, and chronic viral infections correspond to those found in other studies [33–36]. The use of antidepressants as a proxy for having depression also comes with a caveat, which is that we might wrongly classify people using antidepressants for other indications (most notably chronic pain). Finally, it is important to interpret the hazard ratios of those classified as 'other psychiatric condition' with care, as the ATC coding for this group includes ATC code for benzodiazepines. Concomitant use of benzodiazepines is a definite risk factor for an opioid overdose [37]. Our findings, although associations appear to be strong, are not definitive. In the interpretation of

the study results, we advise caution because we cannot confirm that the relationship between opioid use and ICU admission or death is causal. It is possible that opioid prescription status is a proxy for ill health, which in itself heightens the risk of ICU admission and death. This relationship was demonstrated previously: those who reported poor physical health were 10 times more likely to be prescribed an opioid [8], and their risk of fatal and non-fatal opioid poisoning is increased compared with fit individuals [38,39].

In conclusion, the 1-year risk of ICU admission and death is increased in individuals exposed to prescription opioids compared with unexposed individuals. Awareness of the elevated risks of increasing opioid use is important for healthcare professionals prescribing these drugs. Opioids are of essential importance in modern medicine, but they should be used prudently and prescribed with care, and their users should be regularly monitored for potential adverse events.

Acknowledgements

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STROBE Statement —Checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1, 2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5, Supp
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5, Supp
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5, 6, 7 Supp
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supp
Bias	9	Describe any efforts to address potential sources of bias	6, 7
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5, 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7, 8
		(*b*) Describe any methods used to examine subgroups and interactions	7, 8
		(*c*) Explain how missing data were addressed	7 ,8
		(*d*) If applicable, explain how loss to follow-up was addressed	7 ,8
		(*e*) Describe any sensitivity analyses	7 ,8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	9

	Item No	Recommendation	Page No
Outcome data	15*	Report numbers of outcome events or summary measures over time	9, 10
Main results	16	(***a***) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, 10
		(***b***) Report category boundaries when continuous variables were categorized	9, 10
		(***c***) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9, 10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12, 13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12, 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org

Supplement to: The association of opioid use with risk of ICU admission and mortality in the Dutch population

Supplement to methods: description of the data sources

The population register, household income register, pharmacy claims register, hospital admissions register and mortality register are some of the many registries collected and curated by Statistics Netherlands. This governmental company has access to all personal information in registries that is de-identified by their personnel, upon which individuals are assign unique identifiers that allow for linkage between different registries. The company ensures data completeness and quality.

Access to the data can be granted to an applicant after the approval of the proposal. The registered applicant is required to sign confidentiality agreement and vows to protect the privacy of individuals. Then, the access to the data is granted through secured environment. When all analyses are performed, the results and the code used to obtain them are checked by Statistics Netherlands, and all cells containing less than ten (n = 10) events need to be removed before the output is granted.

Description of Data Sources

In this study we linked data from different registries, population register, household income register, pharmacy claims register, hospital admissions register, and mortality register. We here describe registers and their coverage of the total population.

Population register

Demographic characteristics, for example, date of birth, were collected for all individuals—residents and non-residents—who were registered at the Basic Persons Registry. Residents are by definition of Statistics Netherlands registered individuals, and non-residents are individuals who either no longer reside in the Netherlands or never did but have a relationship with the government, for example, emigrants still earning income in the Netherlands or seasonal workers [1].

Registration is mandatory in the Netherlands; without it even simple daily tasks are impossible. For example, acquiring a new telephone number is impossible without the registration number. The register is regularly updated and the final version is submitted annually. As per recommendation of the Statistics Netherlands, we utilised the 2019 version of the register [1].

Household income register

At the beginning of every year all Dutch residents (on average 17 million) earning an income need to submit a tax return for the preceding year to the Tax and Customs Administration. Based on a tax return the number of Dutch residents, the standardised private household income, and the main source of income is estimated. For the estimation of the latter all taxable income sources are considered, as well as age and a composition of a household [2].

Pharmacy claims register

Information on prescribed medication was collected for all residents of the Netherlands who are eligible for pharmaceutical care that is covered by the basic health insurance, 'Zorgverzekeringswet' [3]. It is mandatory for almost all residents to be insured by the basic health insurance; n=17,173,600 individuals of the total n=17,181,084 registered residents in 2018 (99.9% of the population) were insured by the basic health insurance [4].

An insured resident can file an insurance claim for the covered medications by Dutch law; which is then collected by The Dutch Health Care Institute ("Zorginstituut Nederland") and provided to Statistics Netherlands [3,5]. The pharmacy claims register contains information on medications dispensed to residents in outpatient pharmacies, community pharmacies, and in residential care homes for elderly whereas in-hospital medication use and medication use in nursing homes is not registered [3,5]. Medications, found in this register, are recorded and classified according to the of the World Health Organization Anatomical Chemical Classification (ATC) system [6].

Hospital admission register

National Basic Registration Hospital Care is an external registration of hospital admissions that is managed by the Dutch Hospital Data. Information on all patient admissions to general hospitals, university hospitals, and a few categorical hospitals is collected, but information on private centres is not [5,7]. Registered hospital admissions could be inpatient, one-day admissions, and prolonged observations without overnight stay, whereas outpatient encounters are not recorded.

Dutch Hospital Data provides data to Statistics Netherlands, that links these records to the population registry; only records that could be uniquely linked to the population registry are preserved (the linkage was deterministic in 99.7% of records in 2018).

Each record contains information on admission and discharge date, discharge clinical diagnoses, main medical procedure and main medical specialty of a doctor discharging a patient. From 2018 onwards the Dutch Hospital Data provided two additional variables indicating the admission to the intensive care unit (ICU) [7].

Mortality register

All-causes of death of individuals registered at the Basic Persons Registry are recorded by the Dutch Register of Causes of Death. Statistics Netherlands processes information about a deceased individual in which the information from the cause of death certificate is considered and then cross-checked with the information from the Basic Persons Registry. This improves the accuracy of the obtained data [8].

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Supplement to Methods. Operational definitions of variables used for the exposure, confounders, eligibility and outcomes

Variable	Values	Definitions	Time of the assessment [-)
Eligibility			
Age ≥ 18	0/1	Age derived from the date of birth. Day of birth was 1 for all residents.	January 1, 2018
Alive on January 1, 2018	0/1	Date of death was extracted from the population registry.	Any date older than January 1, 2018
Exposure			
Current opioid use	0/1	Filled a prescription for an opioid, ATC code: "N02AZ" or "N02AA	October 9, 2017 - December 31, 2018
Prior opioid use	0/1	Filled a prescription for an opioid, ATC code: "N02AZ" or "N02AA	October 9, 2016 - October 9, 2017
Number of opioid prescriptions	Integer	The number of prescriptions per individual was retrieved from the number of unique dates of prescription and opioid type.	October 9, 2017 - December 31, 2018
First-time opioid use	0/1	Filled a first prescription for an opioid during the "current" window; not considered "prior" users, ATC code: "N02AZ" or "N02AA	October 9, 2017 - December 31 2018
Chronic opioid use	0/1	Filled five or more prescriptions for an opioid; whether there is prior use was considered irrelevant, ATC code: "N02AZ" or "N02AA	October 9, 2017 - December 31, 2018
Intermittent opioid use	0/1	Filled a prescription for an opioid, but less than five prescriptions, ATC code: "N02AZ" or "N02AA	October 9, 2016 - October 9, 2017, October 9, 2017- December 31, 2018
Covariates			
Age	Decimal	Age on January 1, 2018 derived from the date of birth. Day of birth was 1 for all residents.	January 1, 2018
Age categorized	18-35/ 35-45/ 45-55/ 55-65/ 65-75/ 75-85/ ≥ 85	Age on January 1, 2018 derived from the date of birth. Day of birth was 1 for all residents.	January 1, 2018
Sex	Male/ Female	Registered sex of a resident. In the event of gender change, the last applicable gender is recorded. When unknown, registered as female.	January 1, 2018
Immigration status	Native/First generation/ Second generation	Registered immigration status of a resident	January 1, 2018
Depression	0/1	Filled a prescription for an antidepressant, ATC code: "N06A"	January 1, 2017 - January 1, 2018

Supplement to Methods. Operational definitions of variables used for the exposure, confounders, eligibility and outcomes *(continued)*

Variable	Values	Definitions	Time of the assessment [-)
Other psychiatric condition	0/1	Filled a prescription for an antipsychotic, ATC code: "N05A", or an anxiolytic, ATC code: "N05B", or hypnotics and sedative, ATC code: "N05C"	January 1, 2017 - January 1, 2018
Cancer	0/1	Filled a prescription for an anti-cancer medication, ATC code: "L01" or "L02"	January 1, 2017 - January 1, 2018
Diabetes	0/1	Filled a prescription for an antidiabetic medication, ATC code: "A10"	January 1, 2017 - January 1, 2018
Chronic viral infection	0/1	Filled a prescription for a direct antiviral medication, ATC code: "J05A"	January 1, 2017 - January 1, 2018
Standardized private household income	1st/ 2nd/ 3rd/ 4th/ 5th quintile and institutionalised/ student grant/ no identified income	Standardized private household income obtained through tax records	January 1, 2017 - January 1, 2018
Primary source of household income	Wage/ Welfare/ Pension/ Other (Student grant, property income, no identified income)	Primary source of household income obtained through tax records	January 1, 2017 - January 1, 2018
Outcomes			
Admission to the intensive care unit	0/1	Admission to the intensive care unit was registered by the data holder when the hospital admission and the intensive care unit admission occurred on the same date	January 1, 2018 – January 1, 2019
All-causes of death	0/1	Date of death was extracted from the population registry	January 1, 2018 – January 1, 2019

Supplementary Table 1. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of duration of opioid treatment

	ICU admission		
	Subgroup, duration of opioid us		
	Chronic use (yes vs no)	**First-time use (yes vs no)**	**Intermittent use (yes vs no)**
Covariates	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**
Sex			
Men	1 (reference)	1 (reference)	1 (reference)
Women	0.59 (0.58-0.61)	0.58 (0.56-0.59)	0.60 (0.59-0.62)
Age group, years			
18-35	1 (reference)	1 (reference)	1 (reference)
35-45	1.11 (1.04-1.19)	1.10 (1.03-1.17)	1.10 (1.03-1.17)
45-55	1.72 (1.62-1.82)	1.74 (1.65-1.84)	1.71 (1.62-1.81)
55-65	2.59 (2.46-2.74)	2.71 (2.57-2.85)	2.64 (2.50-2.78)
65-75	4.18 (3.89-4.50)	4.47 (4.17-4.80)	4.47 (4.16-4.80)
75-85	4.92 (4.55-5.33)	5.40 (5.01-5.83)	5.53 (5.12-5.98)
$\geq$ 85	3.20 (2.90-3.54)	3.78 (3.44-4.16)	4.00 (3.63-4.40)
Immigration status			
Native	1 (reference)	1 (reference)	1 (reference)
First generation	0.75 (0.71-0.78)	0.74 (0.71-0.77)	0.74 (0.71-0.78)
Second generation	0.96 (0.91-1.01)	0.96 (0.91-1.01)	0.97 (0.92-1.02)
Comorbidity			
Depression	1.38 (1.33-1.44)	1.41 (1.35-1.47)	1.42 (1.37-1.48)
Other psychiatric conditions	2.16 (2.08-2.26)	2.22 (2.12-2.32)	2.36 (2.26-2.46)
Cancer	1.11 (1.01-1.23)	1.14 (1.03-1.25)	1.08 (0.98-1.20)
Diabetes	1.77 (1.71-1.84)	1.83 (1.76-1.89)	1.88 (1.81-1.94)
Chronic viral infection	1.43 (1.27-1.60)	1.46 (1.30-1.64)	1.64 (1.47-1.83)
Main source of income			
Wage	1 (reference)	1 (reference)	1 (reference)
Welfare	1.97 (1.87-2.07)	1.90 (1.81-1.99)	1.97 (1.87-2.06)
Pension	1.21 (1.14-1.29)	1.16 (1.09-1.23)	1.16 (1.09-1.23)
Other *	1.52 (1.35-1.72)	1.49 (1.33-1.67)	1.56 (1.39-1.75)
Household income, quintile			
First	2.07 (1.97-2.18)	1.98 (1.89-2.08)	2.12 (2.02-2.23)
Second	1.58 (1.51-1.66)	1.53 (1.46-1.60)	1.61 (1.53-1.69)
Third	1.40 (1.33-1.47)	1.36 (1.30-1.43)	1.41 (1.35-1.48)
Fourth	1.20 (1.14-1.27)	1.18 (1.12-1.24)	1.19 (1.13-1.25)
Fifth	1 (reference)	1 (reference)	1 (reference)
No identified income	0.90 (0.68-1.19)	0.88 (0.67-1.15)	0.90 (0.68-1.19)
Institutionalised	2.11 (1.94-2.29)	2.12 (1.96-2.30)	2.25 (2.07-2.44)
Student grant	1.26 (1.05-1.52)	1.31 (1.10-1.55)	1.38 (1.15-1.65)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 2. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of sex

	ICU admission	
	Subgroup, sex	
	Men	**Women**
	Model 2 aHR (95% CI)	**Model 2 aHR (95% CI)**
Sex		
Men	NA	NA
Women	NA	NA
Age group, years		
18-35	1 (reference)	1 (reference)
35-45	1.19 (1.10-1.29)	1.04 (0.95-1.13)
45-55	1.96 (1.84-2.09)	1.54 (1.43-1.66)
55-65	3.17 (2.98-3.37)	2.15 (2.00-2.31)
65-75	5.08 (4.69-5.51)	3.33 (3.02-3.67)
75-85	6.02 (5.51-6.57)	3.54 (3.19-3.92)
≥ 85	4.50 (4.03-5.03)	2.16 (1.91-2.45)
Immigration status		
Native	1 (reference)	1 (reference)
First generation	0.74 (0.71-0.78)	0.69 (0.65-0.73)
Second generation	1.00 (0.95-1.06)	0.90 (0.84-0.96)
Comorbidity		
Depression	1.20 (1.14-1.26)	1.52 (1.45-1.59)
Other psychiatric conditions	1.92 (1.83-2.02)	2.35 (2.24-2.46)
Cancer	1.06 (0.95-1.18)	1.17 (1.05-1.31)
Diabetes	1.66 (1.60-1.73)	1.91 (1.82-2.00)
Chronic viral infection	1.58 (1.41-1.77)	1.46 (1.27-1.68)
Main source of income		
Wage	1 (reference)	1 (reference)
Welfare	1.91 (1.82-2.02)	1.82 (1.71-1.94)
Pension	1.19 (1.11-1.27)	1.12 (1.04-1.22)
Other *	1.39 (1.21-1.59)	1.71 (1.48-1.99)
Household income, quintile		
First	1.89 (1.79-2.00)	2.09 (1.95-2.24)
Second	1.53 (1.45-1.61)	1.58 (1.47-1.68)
Third	1.37 (1.30-1.44)	1.41 (1.32-1.51)
Fourth	1.16 (1.10-1.23)	1.28 (1.19-1.37)
Fifth	1 (reference)	1 (reference)
No identified income	0.88 (0.64-1.21)	0.89 (0.61-1.31)
Institutionalised	2.08 (1.89-2.28)	1.83 (1.62-2.05)
Student grant	0.95 (0.73-1.23)	1.50 (1.21-1.86)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 3. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different age groups

	ICU admission						
	Subgroup, age in years						
	18-35	**35-45**	**45-55**	**55-65**	**65-75**	**75-85**	**> 85**
Covariates	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)
Sex							
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.79 (0.73-0.84)	0.73 (0.67-0.8)	0.68 (0.64-0.72)	0.58 (0.55-0.61)	0.56 (0.54-0.59)	0.53 (0.51-0.56)	0.48 (0.43-0.53)
Age group, years							
18-35	NA	NA	NA	NA	NA	NA	NA
35-45	NA	NA	NA	NA	NA	NA	NA
45-55	NA	NA	NA	NA	NA	NA	NA
55-65	NA	NA	NA	NA	NA	NA	NA
65-75	NA	NA	NA	NA	NA	NA	NA
75-85	NA	NA	NA	NA	NA	NA	NA
≥ 85	NA	NA	NA	NA	NA	NA	NA
Immigration status							
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.7 (0.62-0.78)	0.77 (0.69-0.87)	0.64 (0.59-0.70)	0.65 (0.60-0.70)	0.78 (0.72-0.84)	0.87 (0.80-0.96)	0.85 (0.67-1.07)
Second generation	0.90 (0.82-1.00)	0.87 (0.75-1.01)	0.88 (0.77-1.00)	0.90 (0.81-1.00)	1.03 (0.94-1.13)	1.04 (0.94-1.15)	1.00 (0.78-1.27)
Comorbidity							
Depression	2.30 (2.05-2.58)	1.49 (1.31-1.68)	1.38 (1.27-1.50)	1.32 (1.23-1.41)	1.28 (1.20-1.36)	1.10 (1.02-1.20)	1.08 (0.91-1.28)
Other psychiatric conditions	5.13 (4.57-5.76)	3.32 (2.92-3.78)	2.31 (2.10-2.54)	2.00 (1.85-2.15)	1.79 (1.67-1.93)	1.42 (1.30-1.56)	1.05 (0.87-1.26)
Cancer	1.20 (0.64-2.23)	2.26 (1.46-3.50)	1.62 (1.22-2.14)	1.23 (1.00-1.52)	1.12 (0.98-1.28)	1.05 (0.91-1.19)	0.83 (0.63-1.09)
Diabetes	8.33 (7.21-9.62)	3.18 (2.70-3.76)	2.40 (2.18-2.64)	1.77 (1.66-1.89)	1.71 (1.63-1.80)	1.41 (1.33-1.50)	1.22 (1.07-1.39)
Chronic viral infection	1.92 (1.44-2.56)	1.95 (1.42-2.67)	1.49 (1.17-1.90)	1.74 (1.46-2.07)	1.34 (1.12-1.60)	1.28 (1.03-1.61)	1.49 (0.95-2.35)

Supplementary Table 3. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different age groups *(continued)*

	ICU admission						
	Subgroup, age in years						
	18-35	**35-45**	**45-55**	**55-65**	**65-75**	**75-85**	**> 85**
Main source of income							
Wage	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Welfare	1.86 (1.64-2.10)	2.39 (2.06-2.77)	1.80 (1.62-1.99)	1.58 (1.47-1.69)	0.99 (0.86-1.15)	0.91 (0.64-1.28)	NA
Pension	1.51 (1.16-1.96)	2.16 (1.65-2.83)	2.25 (1.92-2.64)	1.39 (1.29-1.51)	0.82 (0.77-0.88)	0.72 (0.64-0.82)	0.71 (0.52-0.95)
Other *	1.87 (1.47-2.37)	1.15 (0.6-2.2)	1.35 (0.94-1.94)	1.22 (0.98-1.53)	0.91 (0.73-1.13)	1.17 (0.92-1.47)	1.39 (0.88-2.19)
Household income, quintile							
First	1.56 (1.36-1.8)	1.88 (1.56-2.26)	2 (1.78-2.25)	1.9 (1.74-2.08)	2.18 (2-2.38)	1.92 (1.71-2.15)	2.62 (2.01-3.42)
Second	1.44 (1.26-1.65)	1.74 (1.47-2.07)	1.73 (1.55-1.94)	1.58 (1.45-1.73)	1.68 (1.55-1.81)	1.34 (1.20-1.50)	1.66 (1.27-2.16)
Third	1.29 (1.13-1.47)	1.53 (1.30-1.80)	1.59 (1.43-1.76)	1.48 (1.36-1.60)	1.38 (1.28-1.50)	1.19 (1.06-1.34)	1.60 (1.22-2.11)
Fourth	1.05 (0.92-1.20)	1.32 (1.12-1.56)	1.27 (1.15-1.40)	1.31 (1.21-1.41)	1.13 (1.04-1.23)	1.14 (1.01-1.29)	1.63 (1.23-2.17)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	0.58 (0.36-0.92)	1.87 (0.78-4.48)	1.40 (0.75-2.62)	1.66 (1.04-2.65)	NA	NA	NA
Institutionalised	2.60 (2.11-3.21)	3.45 (2.65-4.50)	3.50 (2.88-4.26)	3.12 (2.65-3.67)	3.13 (2.68-3.65)	1.24 (1.03-1.48)	0.78 (0.57-1.07)
Student grant	1.16 (0.96-1.42)	NA	NA	NA	NA	NA	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 4. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of immigration status

	ICU admission		
	Subgroup, immigration status		
	Native	**First generation**	**Second generation**
Covariates	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**
Sex			
Men	1 (reference)	1 (reference)	1 (reference)
Women	0.59 (0.58-0.60)	0.61 (0.57-0.65)	0.57 (0.53-0.62)
Age group, years			
18-35	1 (reference)	1 (reference)	1 (reference)
35-45	1.06 (0.99-1.13)	1.44 (1.25-1.66)	1.10 (0.93-1.29)
45-55	1.73 (1.64-1.83)	1.95 (1.71-2.24)	1.66 (1.42-1.94)
55-65	2.64 (2.51-2.79)	2.76 (2.41-3.16)	2.51 (2.17-2.91)
65-75	4.20 (3.91-4.50)	4.54 (3.84-5.37)	4.10 (3.30-5.09)
75-85	4.71 (4.37-5.08)	5.50 (4.56-6.63)	4.52 (3.56-5.73)
$\geq$ 85	3.16 (2.88-3.45)	3.37 (2.53-4.49)	2.88 (2.07-4.01)
Immigration status			
Native	NA	NA	NA
First generation	NA	NA	NA
Second generation	NA	NA	NA
Comorbidity			
Depression	1.40 (1.36-1.45)	1.08 (0.97-1.21)	1.32 (1.16-1.50)
Other psychiatric conditions	2.08 (2.01-2.16)	2.01 (1.81-2.23)	2.53 (2.23-2.87)
Cancer	1.12 (1.03-1.22)	1.40 (1.04-1.87)	1.09 (0.79-1.52)
Diabetes	1.72 (1.67-1.78)	1.85 (1.71-2.01)	2.01 (1.78-2.27)
Chronic viral infection	1.49 (1.35-1.65)	1.71 (1.37-2.13)	1.63 (1.18-2.25)
Main source of income			
Wage	1 (reference)	1 (reference)	1 (reference)
Welfare	1.98 (1.89-2.08)	1.69 (1.53-1.88)	1.82 (1.58-2.10)
Pension	1.14 (1.07-1.20)	1.37 (1.19-1.58)	1.26 (1.03-1.55)
Other *	1.51 (1.35-1.69)	1.41 (1.07-1.87)	1.50 (1.04-2.17)
Household income, quintile			
First	2.06 (1.96-2.16)	1.51 (1.31-1.73)	1.69 (1.44-1.99)
Second	1.55 (1.48-1.62)	1.31 (1.13-1.51)	1.56 (1.34-1.81)
Third	1.40 (1.34-1.46)	1.41 (1.21-1.63)	1.15 (0.98-1.35)
Fourth	1.21 (1.15-1.26)	1.08 (0.92-1.28)	1.29 (1.10-1.51)
Fifth	1 (reference)	1 (reference)	1 (reference)
No identified income	1.49 (1.05-2.10)	0.58 (0.37-0.91)	NA
Institutionalised	1.77 (1.63-1.92)	2.74 (2.21-3.39)	1.95 (1.49-2.55)
Student grant	1.24 (1.03-1.50)	1.13 (0.72-1.77)	1.05 (0.65-1.70)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 5. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different comorbidities

	ICU admission				
	Subgroup, comorbidities				
	Depression	**Other psychiatric conditions**	**Cancer**	**Diabetes**	**Chronic viral infection**
Covariates	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)
Sex					
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.77 (0.73-0.82)	0.81 (0.77-0.86)	0.55 (0.47-0.64)	0.67 (0.64-0.71)	0.57 (0.48-0.69)
Age group, years					
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	0.68 (0.60-0.76)	0.74 (0.67-0.83)	1.69 (0.80-3.59)	0.47 (0.39-0.58)	1.10 (0.72-1.68)
45-55	0.80 (0.72-0.88)	0.78 (0.70-0.86)	1.69 (0.86-3.33)	0.48 (0.41-0.56)	1.21 (0.82-1.79)
55-65	1.04 (0.94-1.15)	0.94 (0.85-1.04)	1.90 (0.98-3.68)	0.54 (0.46-0.62)	2.03 (1.41-2.92)
65-75	1.44 (1.24-1.66)	1.18 (1.02-1.38)	2.22 (1.09-4.52)	0.86 (0.73-1.02)	2.12 (1.28-3.51)
75-85	1.26 (1.07-1.48)	0.95 (0.80-1.12)	2.41 (1.17-4.94)	0.84 (0.71-1.00)	2.16 (1.26-3.71)
≥ 85	0.69 (0.55-0.86)	0.43 (0.34-0.54)	1.45 (0.68-3.11)	0.51 (0.41-0.63)	1.56 (0.78-3.11)
Immigration status					
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.53 (0.48-0.59)	0.57 (0.52-0.63)	0.95 (0.71-1.29)	0.72 (0.67-0.77)	0.74 (0.57-0.95)
Second generation	0.83 (0.74-0.93)	0.85 (0.76-0.94)	0.95 (0.68-1.33)	1.00 (0.90-1.11)	0.95 (0.68-1.34)
Comorbidity					
Depression	NA	1.34 (1.27-1.42)	1.63 (1.34-1.99)	1.20 (1.12-1.29)	1.07 (0.86-1.35)
Other psychiatric conditions	2.32 (2.19-2.45)	NA!	1.37 (1.07-1.75)	1.55 (1.43-1.68)	2.20 (1.74-2.78)
Cancer	1.30 (1.09-1.55)	0.93 (0.74-1.15)	NA	1.03 (0.86-1.22)	1.02 (0.60-1.75)
Diabetes	1.73 (1.61-1.86)	1.56 (1.45-1.69)	1.48 (1.22-1.81)	NA	2.16 (1.71-2.73)
Chronic viral infection	1.30 (1.07-1.57)	1.47 (1.22-1.78)	1.24 (0.73-2.11)	1.67 (1.38-2.02)	NA

Supplementary Table 5. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different comorbidities *(continued)*

	ICU admission				
	Subgroup, comorbidities				
	Depression	**Other psychiatric conditions**	**Cancer**	**Diabetes**	**Chronic viral infection**
Main source of income					
Wage	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Welfare	1.45 (1.33-1.58)	1.45 (1.33-1.59)	1.36 (0.95-1.95)	1.45 (1.31-1.60)	1.48 (1.09-2.00)
Pension	1.09 (0.96-1.25)	1.14 (1.00-1.31)	1.29 (0.88-1.87)	0.96 (0.86-1.08)	1.23 (0.81-1.87)
Other *	1.54 (1.17-2.04)	1.86 (1.41-2.47)	NA	1.49 (1.13-1.97)	2.67 (1.45-4.91)
Household income, quintile					
First	1.49 (1.33-1.67)	1.50 (1.31-1.71)	1.82 (1.36-2.43)	1.73 (1.54-1.93)	1.91 (1.35-2.71)
Second	1.20 (1.08-1.34)	1.26 (1.11-1.44)	1.36 (1.04-1.79)	1.36 (1.22-1.52)	1.78 (1.29-2.47)
Third	1.16 (1.04-1.30	1.27 (1.12-1.46)	1.33 (1.01-1.75)	1.23 (1.10-1.37)	1.74 (1.26-2.42)
Fourth	1.16 (1.03-1.30)	1.19 (1.03-1.36)	1.24 (0.93-1.64)	1.16 (1.03-1.30)	1.29 (0.91-1.83)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	1.46 (0.76-2.81)	1.68 (0.96-2.94)	NA	NA	NA
Institutionalised	1.41 (1.17-1.70)	1.40 (1.18-1.67)	NA	1.29 (1.05-1.59)	2.60 (1.36-4.97)
Student grant	1.58 (1.10-2.26)	1.44 (0.99-2.09)	NA	1.82 (1.03-3.23)	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 6. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of main source of income

	ICU admission			
	Subgroup, main source of income			
	Wage	**Welfare**	**Pension**	**Other**
Covariates	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**	**Model 2 aHR (95% CI)**
Sex				
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.65 (0.62-0.67)	0.70 (0.66-0.74)	0.52 (0.51-0.54)	0.77 (0.64-0.92)
Age group, years				
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	1.01 (0.94-1.09)	1.19 (1.07-1.31)	1.57 (1.09-2.27)	1.32 (0.79-2.22)
45-55	1.75 (1.65-1.85)	1.35 (1.24-1.49)	2.90 (2.15-3.92)	2.16 (1.40-3.33)
55-65	2.83 (2.67-3.01)	1.69 (1.55-1.84)	2.89 (2.21-3.77)	3.31 (2.19-4.98)
65-75	5.43 (5.01-5.90)	2.29 (1.98-2.66)	3.54 (2.72-4.59)	5.23 (3.35-8.17)
75-85	7.17 (6.29-8.17)	2.78 (2.00-3.88)	4.06 (3.12-5.28)	8.96 (5.68-14.1)
≥ 85	5.15 (3.88-6.83)	NA	2.87 (2.19-3.74)	5.91 (3.39-10.3)
Immigration status				
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.75 (0.7-0.79)	0.53 (0.5-0.57)	0.84 (0.79-0.89)	0.58 (0.43-0.78)
Second generation	0.97 (0.9-1.04)	0.72 (0.65-0.8)	1.03 (0.96-1.10)	0.83 (0.59-1.18)
Comorbidity				
Depression	1.74 (1.64-1.84)	1.21 (1.14-1.3)	1.22 (1.17-1.29)	1.54 (1.15-2.06)
Other psychiatric conditions	2.98 (2.79-3.19)	2.3 (2.16-2.44)	1.63 (1.55-1.72)	3.29 (2.45-4.41)
Cancer	1.34 (1.13-1.60)	1.06 (0.8-1.41)	1.09 (0.99-1.19)	NA
Diabetes	2.33 (2.18-2.48)	1.95 (1.81-2.1)	1.54 (1.48-1.60)	2.41 (1.80-3.22)
Chronic viral infection	1.77 (1.52-2.07)	1.48 (1.23-1.79)	1.37 (1.20-1.57)	2.87 (1.66-4.98)
Main source of income				
Wage	NA	NA	NA	NA
Welfare	NA	NA	NA	NA
Pension	NA	NA	NA	NA
Other *	NA	NA	NA	NA
Household income, quintile				
First	1.85 (1.72-1.99)	1.59 (1.24-2.03)	2.14 (2.00-2.29)	2.10 (1.54-2.86)
Second	1.58 (1.49-1.68)	1.32 (1.03-1.70)	1.57 (1.47-1.67)	1.04 (0.62-1.75)
Third	1.42 (1.35-1.50)	1.32 (1.02-1.70)	1.33 (1.24-1.43)	0.93 (0.61-1.41)
Fourth	1.20 (1.14-1.26)	1.28 (0.97-1.68)	1.17 (1.08-1.26)	0.92 (0.60-1.42)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	NA	NA	NA	1.35 (0.92-1.98)
Institutionalised	2.29 (1.68-3.12)	2.38 (1.84-3.09)	1.39 (1.24-1.56)	4.06 (2.82-5.83)
Student grant	0.99 (0.78-1.26)	2.49 (1.53-4.05)	NA!	2.47 (1.53-3.97)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 7. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of household income in quintiles

	ICU admission					
	Household income, quintile					
	First	**Second**	**Third**	**Fourth**	**Fifth**	**Institutionalised**
Covariates	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)	Model 2 aHR (95% CI)
Sex						
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.64 (0.61-0.67)	0.56 (0.53-0.58)	0.57 (0.54-0.6)	0.61 (0.58-0.65)	0.57 (0.53-0.61)	0.73 (0.64-0.83)
Age group, years						
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	1.19 (1.07-1.31)	1.19 (1.03-1.37)	1.06 (0.93-1.22)	1.13 (0.98-1.31)	0.91 (0.78-1.06)	1.25 (0.97-1.61)
45-55	1.57 (1.43-1.72)	1.94 (1.72-2.20)	1.93 (1.72-2.16)	1.94 (1.72-2.18)	1.65 (1.46-1.86)	1.63 (1.30-2.06)
55-65	2.06 (1.89-2.25)	2.77 (2.46-3.12)	3.04 (2.72-3.40)	3.36 (3.00-3.75)	2.80 (2.51-3.13)	2.21 (1.77-2.76)
65-75	3.13 (2.75-3.55)	3.91 (3.35-4.55)	4.75 (4.12-5.48)	4.98 (4.31-5.75)	4.78 (4.17-5.47)	2.88 (1.89-4.39)
75-85	3.50 (3.06-4.01)	4.09 (3.50-4.79)	5.55 (4.76-6.46)	6.81 (5.81-7.98)	6.54 (5.55-7.70)	1.43 (0.90-2.26)
≥ 85	2.65 (2.26-3.09)	2.94 (2.47-3.52)	4.37 (3.60-5.30)	5.78 (4.67-7.14)	3.90 (2.97-5.12)	0.50 (0.31-0.81)
Immigration status						
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.60 (0.57-0.64)	0.74 (0.68-0.81)	0.87 (0.79-0.96)	0.77 (0.69-0.87)	0.89 (0.78-1.00)	0.92 (0.76-1.11)
Second generation	0.80 (0.74-0.87)	1.06 (0.97-1.16)	0.85 (0.77-0.95)	1.11 (1.00-1.24)	1.00 (0.89-1.13)	0.92 (0.73-1.16)
Comorbidity						
Depression	1.24 (1.17-1.31)	1.25 (1.17-1.33)	1.37 (1.27-1.48)	1.63 (1.49-1.78)	1.77 (1.60-1.96)	1.43 (1.19-1.72)
Other psychiatric conditions	2.05 (1.94-2.16)	1.95 (1.82-2.09)	2.39 (2.19-2.60)	2.46 (2.22-2.73)	2.55 (2.25-2.88)	1.55 (1.32-1.82)
Cancer	1.04 (0.88-1.24)	1.05 (0.91-1.22)	1.19 (1.00-1.40)	1.24 (1.03-1.50)	1.23 (1.00-1.52)	NA
Diabetes	1.68 (1.59-1.78)	1.66 (1.57-1.76)	1.77 (1.65-1.90)	2.02 (1.86-2.20)	2.17 (1.97-2.40)	1.42 (1.17-1.74)
Chronic viral infection	1.39 (1.17-1.65)	1.55 (1.29-1.85)	1.72 (1.40-2.10)	1.46 (1.15-1.86)	1.46 (1.14-1.88)	2.11 (1.21-3.67)

Supplementary Table 7. Hazard ratio estimates for all covariates of a multi-variable model (model 2), estimating the risk of admission to the intensive care unit in different categories of household income in quintiles *(continued)*

	ICU admission					
	Household income, quintile					
	First	**Second**	**Third**	**Fourth**	**Fifth**	**Institutionalised**
Main source of income						
Wage	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Welfare	2.11 (1.96-2.28)	1.81 (1.64-1.99)	1.68 (1.51-1.87)	1.78 (1.54-2.05)	1.68 (1.31-2.16)	2.5 (1.82-3.44)
Pension	1.64 (1.45-1.85)	1.33 (1.17-1.51)	1.01 (0.90-1.13)	1.00 (0.89-1.12)	1.03 (0.92-1.14)	2.03 (1.20-3.42)
Other *	1.63 (1.35-1.97)	1.10 (0.68-1.78)	1.01 (0.70-1.48)	1.05 (0.71-1.56)	1.25 (1.02-1.52)	2.43 (1.59-3.72)
Household income, quintile						
First	NA	NA	NA	NA	NA	NA
Second	NA	NA	NA	NA	NA	NA
Third	NA	NA	NA	NA	NA	NA
Fourth	NA	NA	NA	NA	NA	NA
Fifth	NA	NA	NA	NA	NA	NA
No identified income	NA	NA	NA	NA	NA	NA
Institutionalised	NA	NA	NA	NA	NA	NA
Student grant	NA	NA	NA	NA	NA	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 8. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of duration of opioid treatment

	Death		
	Subgroup, duration of opioid us		
	Chronic use (yes vs no)	**First-time use (yes vs no)**	**Intermittent use (yes vs no)**
Covariates	**Model 4 aHR (95% CI)**	**Model 4 aHR (95% CI)**	**Model 4 aHR (95% CI)**
Sex			
Men	1 (reference)	1 (reference)	1 (reference)
Women	0.59 (0.58-0.60)	0.61 (0.60-0.62)	0.63 (0.62-0.64)
Age group, years			
18-35	1 (reference)	1 (reference)	1 (reference)
35-45	2.24 (2.07-2.44)	1.94 (1.77-2.12)	1.97 (1.8-2.16)
45-55	5.97 (5.57-6.40)	4.90 (4.54-5.28)	4.86 (4.5-5.24)
55-65	14.8 (13.9-15.8)	12.1 (11.3-13.0)	11.7 (10.9-12.5)
65-75	47.3 (44.2-50.7)	50.5 (46.9-54.3)	50.1 (46.6-53.9)
75-85	107 (99.3-114)	141 (131-152)	143 (133-154)
≥ 85	230 (214-247)	384 (357-414)	367 (341-396)
Immigration status			
Native	1 (reference)	1 (reference)	1 (reference)
First generation	0.71 (0.69-0.73)	0.68 (0.66-0.69)	0.69 (0.67-0.71)
Second generation	0.98 (0.96-1.01)	0.99 (0.96-1.02)	1.01 (0.98-1.04)
Comorbidity			
Depression	0.83 (0.81-0.85)	0.99 (0.97-1.01)	1.04 (1.02-1.07)
Other psychiatric conditions	1.51 (1.48-1.55)	1.61 (1.57-1.65)	1.69 (1.65-1.72)
Cancer	1.65 (1.60-1.70)	1.27 (1.22-1.32)	1.22 (1.17-1.27)
Diabetes	1.10 (1.08-1.12)	1.18 (1.16-1.20)	1.23 (1.21-1.26)
Chronic viral infection	1.50 (1.41-1.59)	1.22 (1.13-1.32)	1.38 (1.29-1.48)
Main source of income			
Wage	1 (reference)	1 (reference)	1 (reference)
Welfare	1.25 (1.21-1.29)	1.41 (1.36-1.46)	1.39 (1.34-1.44)
Pension	0.75 (0.72-0.77)	0.68 (0.65-0.70)	0.63 (0.61-0.66)
Other *	2.09 (1.99-2.19)	1.98 (1.88-2.09)	1.96 (1.86-2.06)
Household income, quintile			
First	3.61 (3.51-3.72)	4.14 (4.02-4.27)	4.54 (4.39-4.68)
Second	1.24 (1.20-1.27)	1.30 (1.26-1.34)	1.37 (1.33-1.42)
Third	1.24 (1.20-1.28)	1.25 (1.21-1.29)	1.30 (1.25-1.34)
Fourth	1.11 (1.08-1.15)	1.09 (1.05-1.13)	1.12 (1.08-1.16)
Fifth	1 (reference)	1 (reference)	1 (reference)
No identified income	1.91 (1.66-2.19)	2.60 (2.25-3.01)	2.55 (2.20-2.96)
Institutionalised	8.29 (8.03-8.55)	11.3 (10.9-11.6)	12.4 (11.9-12.8)
Student grant	1.39 (1.08-1.80)	1.91 (1.48-2.45)	1.94 (1.51-2.50)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 9. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of sex

	Death	
	Subgroup, sex	
	Men	**Women**
Covariates	**Model 4 aHR (95% CI)**	**Model 4 aHR (95% CI)**
Sex		
Men	NA	NA
Women	NA	NA
Age group, years		
18-35	1 (reference)	1 (reference)
35-45	1.93 (1.76-2.13)	2.73 (2.41-3.09)
45-55	4.63 (4.27-5.01)	7.55 (6.78-8.41)
55-65	11.4 (10.5-12.2)	19.8 (17.9-22.0)
65-75	31.3 (28.9-33.9)	71.6 (64.3-79.7)
75-85	71.0 (65.9-77.0)	160 (143-178)
≥ 85	170 (157-184)	381 (342-424)
Immigration status		
Native	1 (reference)	1 (reference)
First generation	0.68 (0.66-0.70)	0.66 (0.64-0.68)
Second generation	0.97 (0.94-1.01)	0.98 (0.94-1.01)
Comorbidity		
Depression	0.94 (0.92-0.97)	0.85 (0.83-0.87)
Other psychiatric conditions	1.82 (1.77-1.87)	1.46 (1.43-1.49)
Cancer	1.53 (1.47-1.59)	1.64 (1.58-1.71)
Diabetes	1.15 (1.13-1.18)	1.11 (1.08-1.13)
Chronic viral infection	1.53 (1.43-1.63)	1.31 (1.22-1.40)
Main source of income		
Wage	1 (reference)	1 (reference)
Welfare	1.34 (1.29-1.39)	0.96 (0.92-1.00)
Pension	1.03 (0.99-1.07)	0.54 (0.52-0.56)
Other *	2.46 (2.32-2.61)	1.87 (1.76-1.99)
Household income, quintile		
First	2.84 (2.75-2.93)	4.09 (3.94-4.24)
Second	1.26 (1.22-1.30)	1.02 (0.98-1.06)
Third	1.16 (1.13-1.20)	1.15 (1.10-1.20)
Fourth	1.04 (1.01-1.08)	1.09 (1.05-1.14)
Fifth	1 (reference)	1 (reference)
No identified income	1.99 (1.70-2.32)	1.60 (1.28-2.00)
Institutionalised	6.35 (6.11-6.60)	8.53 (8.20-8.87)
Student grant	1.20 (0.88-1.63)	1.53 (1.04-2.26)

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 10. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different age groups

	Death						
	Subgroup, age in years						
	18-35	**35-45**	**45-55**	**55-65**	**65-75**	**75-85**	**> 85**
Covariates	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)
Sex							
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.43 (0.38-0.48)	0.59 (0.53-0.65)	0.61 (0.57-0.64)	0.57 (0.55-0.59)	0.55 (0.54-0.57)	0.54 (0.53-0.55)	0.62 (0.61-0.63)
Age group, years							
18-35	NA	NA	NA	NA	NA	NA	NA
35-45	NA	NA	NA	NA	NA	NA	NA
45-55	NA	NA	NA	NA	NA	NA	NA
55-65	NA	NA	NA	NA	NA	NA	NA
65-75	NA	NA	NA	NA	NA	NA	NA
75-85	NA	NA	NA	NA	NA	NA	NA
> 85	NA	NA	NA	NA	NA	NA	NA
Immigration status							
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.70 (0.58-0.83)	0.66 (0.58-0.76)	0.52 (0.48-0.57)	0.58 (0.55-0.62)	0.61 (0.58-0.63)	0.68 (0.65-0.70)	0.83 (0.79-0.86)
Second generation	0.77 (0.65-0.91)	0.73 (0.61-0.86)	0.90 (0.80-1.00)	1.04 (0.97-1.12)	1.01 (0.96-1.07)	0.97 (0.93-1.01)	0.96 (0.92-1.01)
Comorbidity							
Depression	1.70 (1.39-2.08)	0.90 (0.78-1.05)	0.82 (0.76-0.89)	0.78 (0.74-0.82)	0.91 (0.87-0.94)	0.89 (0.86-0.92)	0.80 (0.78-0.83)
Other psychiatric conditions	4.30 (3.51-5.26)	3.29 (2.85-3.81)	2.30 (2.13-2.50)	2.04 (1.94-2.14)	1.91 (1.84-1.98)	1.62 (1.57-1.67)	1.23 (1.20-1.26)
Cancer	6.25 (4.15-9.42)	5.97 (4.52-7.87)	5.62 (4.93-6.39)	3.41 (3.13-3.71)	2.19 (2.08-2.31)	1.68 (1.61-1.75)	1.13 (1.08-1.18)
Diabetes	2.04 (1.39-3.00)	1.79 (1.44-2.23)	1.51 (1.37-1.65)	1.29 (1.23-1.36)	1.26 (1.22-1.30)	1.13 (1.10-1.16)	0.97 (0.95-1.00)
Chronic viral infection	2.43 (1.65-3.58)	3.30 (2.54-4.28)	1.81 (1.52-2.16)	2.12 (1.91-2.35)	1.79 (1.64-1.95)	1.23 (1.13-1.34)	0.87 (0.79-0.96)
Main source of income							
Wage	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)

Supplementary Table 10. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different age groups *(continued)*

	Death						
	Subgroup, age in years						
	18-35	**35-45**	**45-55**	**55-65**	**65-75**	**75-85**	**> 85**
Welfare	1.40 (1.16-1.68)	1.47 (1.24-1.73)	1.33 (1.21-1.45)	1.18 (1.12-1.24)	0.83 (0.76-0.90)	0.95 (0.85-1.07)	0.69 (0.62-0.78)
Pension	2.49 (1.80-3.44)	6.30 (5.21-7.61)	4.40 (3.94-4.91)	2.05 (1.95-2.16)	0.81 (0.78-0.85)	0.46 (0.44-0.48)	0.32 (0.31-0.34)
Other *	1.52 (1.06-2.16)	2.57 (1.64-4.03)	1.73 (1.33-2.25)	1.67 (1.46-1.92)	1.89 (1.71-2.08)	1.47 (1.36-1.59)	1.16 (1.08-1.25)
Household income, quintile							
First	2.97 (2.39-3.71)	2.34 (1.92-2.86)	2.73 (2.47-3.02)	2.46 (2.31-2.61)	3.43 (3.26-3.60)	3.19 (3.04-3.34)	4.07 (3.87-4.29)
Second	1.28 (1.01-1.63)	1.24 (1.02-1.51)	1.26 (1.13-1.40)	1.26 (1.18-1.34)	1.31 (1.25-1.37)	1.15 (1.10-1.21)	1.04 (0.98-1.09)
Third	1.48 (1.20-1.84)	1.12 (0.93-1.34)	1.12 (1.02-1.23)	1.11 (1.05-1.19)	1.20 (1.14-1.26)	1.15 (1.09-1.21)	1.14 (1.08-1.21)
Fourth	1.10 (0.88-1.38)	1.03 (0.85-1.25)	1.00 (0.91-1.10)	1.03 (0.97-1.10)	1.09 (1.03-1.14)	1.05 (1.00-1.11)	1.06 (1.00-1.13)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	2.49 (1.44-4.31)	3.22 (1.81-5.71)	4.43 (3.08-6.38)	3.05 (2.38-3.91)	1.89 (1.16-3.08)	1.31 (0.81-2.13)	0.71 (0.43-1.17)
Institutionalised	5.68 (4.20-7.67)	7.34 (5.64-9.55)	9.79 (8.51-11.3)	11.7 (10.7-12.7)	14.3 (13.4-15.3)	10.8 (10.3-11.4)	6.37 (6.05-6.71)
Student grant	1.72 (1.28-2.31)	NA	NA	NA	NA	NA	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 11. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of immigration status

	Death		
	Subgroup, immigration status		
	Native	**First generation**	**Second generation**
Covariates	**Model 4 aHR (95% CI)**	**Model 4 aHR (95% CI)**	**Model 4 aHR (95% CI)**
Sex			
Men	1 (reference)	1 (reference)	1 (reference)
Women	0.58 (0.57-0.59)	0.59 (0.57-0.61)	0.57 (0.55-0.6)
Age group, years			
18-35	1 (reference)	1 (reference)	1 (reference)
35-45	2.14 (1.96-2.34)	2.39 (1.98-2.89)	2.19 (1.76-2.73)
45-55	5.47 (5.08-5.90)	5.25 (4.43-6.23)	6.54 (5.45-7.86)
55-65	13.4 (12.5-14.4)	13.5 (11.4-15.9)	17.8 (15.1-21.0)
65-75	42.8 (39.7-46.1)	39.9 (33.7-47.2)	56.8 (47.1-68.5)
75-85	96.0 (89.2-104)	100 (84.6-119)	120 (99-146)
≥ 85	226 (209-244)	287 (242-341)	272 (224-331)
Immigration status			
Native	NA	NA	NA
First generation	NA	NA	NA
Second generation	NA	NA	NA
Comorbidity			
Depression	0.87 (0.86-0.89)	0.88 (0.82-0.94)	0.95 (0.89-1.03)
Other psychiatric conditions	1.57 (1.54-1.60)	1.73 (1.63-1.84)	1.65 (1.54-1.76)
Cancer	1.57 (1.52-1.61)	2.24 (1.99-2.51)	1.77 (1.58-1.99)
Diabetes	1.14 (1.12-1.16)	1.10 (1.05-1.15)	1.24 (1.17-1.32)
Chronic viral infection	1.39 (1.32-1.46)	1.77 (1.54-2.03)	1.58 (1.32-1.88)
Main source of income			
Wage	1 (reference)	1 (reference)	1 (reference)
Welfare	1.28 (1.24-1.32)	1.08 (1.01-1.17)	1.17 (1.05-1.30)
Pension	0.78 (0.75-0.80)	0.88 (0.82-0.95)	0.75 (0.66-0.85)
Other *	2.32 (2.22-2.43)	1.64 (1.41-1.91)	2.05 (1.73-2.43)
Household income, quintile			
First	3.58 (3.49-3.67)	1.89 (1.73-2.06)	3.86 (3.50-4.26)
Second	1.15 (1.12-1.18)	1.03 (0.94-1.13)	1.25 (1.13-1.39)
Third	1.16 (1.13-1.19)	1.06 (0.97-1.17)	1.32 (1.19-1.46)
Fourth	1.06 (1.04-1.09)	1.01 (0.91-1.12)	1.23 (1.10-1.37)
Fifth	1 (reference)	1 (reference)	1 (reference)
No identified income	2.51 (2.12-2.99)	1.27 (0.99-1.64)	3.13 (1.96-4.99)
Institutionalised	7.46 (7.25-7.68)	6.24 (5.64-6.91)	9.33 (8.34-10.4)
Student grant	1.16 (0.86-1.55)	1.82 (1.08-3.07)	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 12. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different comorbidities

Covariates	Death				
	Subgroup, comorbidities				
	Depression	Other psychiatric conditions	Cancer	Diabetes	Chronic viral infection
	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)
Sex					
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.52 (0.51-0.54)	0.54 (0.52-0.55)	0.54 (0.52-0.57)	0.54 (0.52-0.57)	0.53 (0.48-0.58)
Age group, years					
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	1.28 (1.08-1.53)	1.63 (1.40-1.90)	1.88 (1.18-3.01)	1.88 (1.18-3.01)	2.88 (1.81-4.60)
45-55	2.61 (2.25-3.04)	3.07 (2.69-3.50)	3.89 (2.58-5.87)	3.90 (2.59-5.89)	3.92 (2.55-6.03)
55-65	5.62 (4.86-6.49)	6.49 (5.73-7.36)	6.23 (4.17-9.29)	6.28 (4.21-9.36)	10.5 (7.01-15.9)
65-75	13.7 (11.7-16.1)	14.0 (12.2-16.1)	9.52 (6.33-14.3)	9.64 (6.41-14.5)	17.5 (11.3-27.2)
75-85	27.0 (23.3-32.0)	26.0 (22.6-30.0)	16.0 (10.6-24.0)	16.0 (10.7-24.0)	24.0 (15.5-38.0)
≥ 85	58.0 (50.0-69.0)	50.0 (44.0-58.0)	30.0 (20.0-45.0)	30.0 (20.0-46.0)	45.0 (29.0-71.0)
Immigration status					
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.60 (0.57-0.64)	0.61 (0.58-0.64)	0.90 (0.81-1.00)	0.91 (0.82-1.00)	0.71 (0.62-0.82)
Second generation	1.02 (0.96-1.09)	0.93 (0.88-0.99)	1.01 (0.90-1.12)	1.00 (0.90-1.12)	0.99 (0.83-1.17)
Comorbidity					
Depression	NA	0.80 (0.78-0.82)	0.86 (0.80-0.93)	0.86 (0.80-0.93)	0.79 (0.70-0.88)
Other psychiatric conditions	1.64 (1.59-1.69)	NA	1.64 (1.53-1.77)	1.65 (1.53-1.77)	1.97 (1.77-2.21)
Cancer	1.69 (1.58-1.81)	1.57 (1.47-1.67)	NA	NA	1.78 (1.49-2.13)
Diabetes	1.25 (1.21-1.29)	1.14 (1.10-1.18)	1.07 (1.00-1.14)	NA	1.12 (1.00-1.26)
Chronic viral infection	1.28 (1.16-1.41)	1.45 (1.32-1.59)	1.25 (1.05-1.49)	1.25 (1.05-1.49)	NA

Supplementary Table 12. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different comorbidities *(continued)*

Covariates	Death				
	Subgroup, comorbidities				
	Depression	Other psychiatric conditions	Cancer	Diabetes	Chronic viral infection
	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)
Main source of income					
Wage					
Welfare	0.82 (0.76-0.87)	0.66 (0.62-0.70)	0.84 (0.72-0.96)	0.83 (0.72-0.96)	0.90 (0.75-1.07)
Pension	0.97 (0.89-1.05)	0.85 (0.79-0.91)	0.83 (0.74-0.93)	0.83 (0.74-0.93)	1.17 (0.96-1.42)
Other *	3.23 (2.88-3.62)	2.76 (2.49-3.07)	1.88 (1.57-2.24)	1.87 (1.57-2.24)	2.78 (2.06-3.74)
Household income, quintile					
First	2.50 (2.34-2.67)	1.95 (1.83-2.07)	2.2 (2.01-2.41)	2.21 (2.02-2.43)	2.22 (1.89-2.61)
Second	0.83 (0.77-0.89)	0.72 (0.67-0.76)	0.91 (0.83-1)	0.91 (0.83-1.00)	0.94 (0.79-1.11)
Third	0.93 (0.87-1.00)	0.87 (0.81-0.93)	0.95 (0.86-1.04)	0.95 (0.86-1.04)	0.99 (0.84-1.18)
Fourth	0.97 (0.91-1.05)	0.93 (0.87-1.00)	0.96 (0.87-1.06)	0.96 (0.87-1.06)	0.99 (0.84-1.18)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	1.29 (0.87-1.92)	0.76 (0.51-1.12)	NA	0.62 (0.19-2.01)	NA
Institutionalised	3.62 (3.36-3.89)	2.65 (2.48-2.83)	2.47 (2.17-2.81)	2.49 (2.19-2.83)	3.01 (2.37-3.83)
Student grant	0.98 (0.52-1.86)	NA	NA	NA	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

Supplementary Table 13. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of main source of income

Covariates	Death			
	Subgroup, main source of income			
	Wage	Welfare	Pension	Other
	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)
Sex				
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.69 (0.67-0.71)	0.61 (0.58-0.64)	0.55 (0.54-0.56)	0.69 (0.64-0.75)
Age group, years				
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	1.82 (1.65-2.00)	2.17 (1.90-2.48)	5.47 (3.75-7.97)	4.41 (2.94-6.61)
45-55	4.67 (4.30-5.06)	5.07 (4.52-5.69)	10.3 (7.24-14.6)	7.85 (5.48-11.25)
55-65	11.6 (10.7-12.5)	10.2 (9.14-11.4)	11.6 (8.31-16.4)	14.1 (10.1-19.7)
65-75	35.8 (32.8-38.9)	24.1 (21.2-27.4)	16.3 (11.6-22.8)	86.2 (62.2-120)
75-85	125 (115-137)	103 (88.7-120)	35.0 (25.3-50.0)	252 (182-349)
≥ 85	447 (407-492)	261 (222-307)	84.0 (60.0-118)	514 (371-712)
Immigration status				
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.69 (0.65-0.72)	0.45 (0.42-0.48)	0.71 (0.70-0.73)	0.41 (0.36-0.47)
Second generation	0.97 (0.91-1.04)	0.88 (0.81-0.95)	0.98 (0.95-1.00)	0.93 (0.80-1.08)
Comorbidity				
Depression	0.95 (0.91-1.00)	0.77 (0.73-0.82)	0.88 (0.86-0.89)	1.05 (0.92-1.20)
Other psychiatric conditions	2.78 (2.64-2.94)	1.70 (1.62-1.79)	1.48 (1.46-1.51)	1.42 (1.24-1.62)
Cancer	2.66 (2.44-2.91)	2.92 (2.58-3.29)	1.49 (1.45-1.54)	1.32 (1.10-1.59)
Diabetes	1.29 (1.22-1.35)	1.23 (1.16-1.30)	1.10 (1.08-1.12)	1.34 (1.19-1.52)
Chronic viral infection	1.84 (1.63-2.08)	1.81 (1.59-2.06)	1.29 (1.22-1.36)	1.75 (1.34-2.28)
Main source of income				
Wage	NA	NA	NA	NA
Welfare	NA	NA	NA	NA
Pension	NA	NA	NA	NA
Other *	NA	NA	NA	NA
Household income, quintile				
First	3.33 (3.15-3.52)	2.84 (2.36-3.42)	3.10 (3.01-3.19)	10.8 (9.68-12.1)
Second	1.58 (1.50-1.67)	1.30 (1.08-1.58)	0.99 (0.97-1.03)	3.57 (3.08-4.15)
Third	1.17 (1.12-1.23)	1.05 (0.86-1.28)	1.03 (0.99-1.06)	1.24 (1.05-1.46)
Fourth	1.04 (0.99-1.08)	1.06 (0.86-1.31)	0.95 (0.92-0.99)	1.10 (0.92-1.31)
Fifth	1 (reference)	1 (reference)	1 (reference)	1 (reference)
No identified income	NA	NA	NA	7.33 (6.14-8.76)
Institutionalised	3.63 (2.87-4.59)	8.88 (7.34-10.7)	6.85 (6.63-7.07)	18.1 (15.8-20.8)
Student grant	1.40 (0.99-1.97)	NA	NA	5.71 (3.49-9.34)

Supplementary Table 14. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of household income in quintiles

Covariates	Death						
	Household income, quintile						
	First	Second	Third	Fourth	Fifth	No income	Institutionalised
	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model aHR (95% CI)
Sex							
Men	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Women	0.66 (0.64-0.67)	0.39 (0.38-0.4)	0.50 (0.48-0.51)	0.56 (0.54-0.58)	0.59 (0.56-0.61)	0.49 (0.38-0.64)	0.77 (0.75-0.78)
Age group, years							
18-35	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
35-45	2.11 (1.87-2.39)	2.46 (1.98-3.06)	1.71 (1.41-2.07)	2.02 (1.65-2.48)	2.10 (1.7-2.58)	3.76 (2.27-6.23)	2.92 (2.20-3.89)
45-55	5.30 (4.77-5.89)	6.23 (5.16-7.53)	4.25 (3.62-5.00)	4.78 (4.03-5.66)	5.12 (4.31-6.08)	7.24 (4.51-11.6)	8.67 (6.81-11.0)
55-65	11.1 (10.0-12.3)	17.7 (14.8-21.2)	11.8 (10.1-13.7)	12.8 (10.9-15.1)	12.6 (10.7-14.8)	11.9 (7.42-19.2)	25.2 (20.1-31.7)
65-75	39.6 (35.5-44.2)	50.3 (41.5-61.0)	31.4 (26.7-36.8)	35.8 (30.3-42.3)	31.2 (26.3-36.9)	31.9 (17.5-58.0)	96.3 (76.7-121)
75-85	81.0 (72.7-91.0)	101 (83.2-123)	72 (61.3-85)	87 (73.3-103)	82.0 (68.9-98.0)	92 (49.9-169)	191 (152-240)
$\geq$ 85	249 (223-278)	240 (197-292)	188 (160-222)	240 (201-285)	221 (185-264)	186 (93-372)	288 (229-362)
Immigration status							
Native	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
First generation	0.53 (0.52-0.55)	0.82 (0.78-0.87)	0.88 (0.82-0.94)	0.89 (0.82-0.96)	0.93 (0.86-1.00)	0.38 (0.28-0.50)	0.80 (0.76-0.84)
Second generation	0.96 (0.92-1.00)	0.94 (0.89-0.99)	0.99 (0.93-1.06)	1.01 (0.94-1.09)	0.87 (0.8-0.95)	0.90 (0.56-1.45)	1.00 (0.95-1.05)
Comorbidity							
Depression	0.91 (0.89-0.94)	0.92 (0.89-0.96)	0.95 (0.90-1.00)	1.02 (0.96-1.08)	1.03 (0.96-1.10)	1.35 (0.84-2.19)	0.76 (0.73-0.78)
Other psychiatric conditions	1.71 (1.67-1.76)	1.95 (1.88-2.03)	2.33 (2.22-2.45)	2.65 (2.50-2.81)	2.88 (2.69-3.07)	1.65 (1.00-2.71)	1.02 (0.99-1.05)
Cancer	1.51 (1.44-1.58)	1.83 (1.74-1.93)	1.88 (1.76-2.00)	2.08 (1.93-2.24)	2.25 (2.07-2.44)	NA	0.92 (0.85-0.99)
Diabetes	1.18 (1.15-1.21)	1.24 (1.2-1.27)	1.33 (1.28-1.38)	1.38 (1.31-1.45)	1.41 (1.33-1.50)	1.42 (0.90-2.24)	0.87 (0.84-0.90)
Chronic viral infection	1.37 (1.26-1.48)	1.48 (1.34-1.63)	1.59 (1.42-1.79)	1.66 (1.46-1.89)	1.89 (1.66-2.15)	NA	0.85 (0.73-0.99)

Supplementary Table 14. Hazard ratio estimates for all covariates of a multi-variable model (model 4), estimating the risk of death in different categories of household income in quintiles *(continued)*

Covariates	Death						
	Household income, quintile						
	First	Second	Third	Fourth	Fifth	No income	Institutionalised
	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI)	Model aHR (95% CI)
Main source of income							
Wage	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	NA	1 (reference)
Welfare	1.17 (1.12-1.24)	0.96 (0.89-1.04)	0.99 (0.91-1.09)	1.12 (0.99-1.25)	1.12 (0.92-1.35)	NA	3.05 (2.51-3.71)
Pension	0.77 (0.72-0.83)	0.63 (0.57-0.69)	0.78 (0.73-0.84)	0.78 (0.74-0.83)	0.94 (0.88-0.99)	NA	1.93 (1.57-2.37)
Other *	3.17 (2.94-3.41)	3.01 (2.59-3.50)	1.21 (1.03-1.42)	1.08 (0.91-1.27)	1.06 (0.95-1.18)	NA	6.74 (5.48-8.29)
Household income, quintile							
First	NA	NA	NA	NA	NA	NA	NA
Second	NA	NA	NA	NA	NA	NA	NA
Third	NA	NA	NA	NA	NA	NA	NA
Fourth	NA	NA	NA	NA	NA	NA	NA
Fifth	NA	NA	NA	NA	NA	NA	NA
No identified income	NA	NA	NA	NA	NA	NA	NA
Institutionalised	NA	NA	NA	NA	NA	NA	NA
Student grant	NA	NA	NA	NA	NA	NA	NA

The variable 'Household income' refers to standardised private household income. The first quintile category is the lowest income group, and the fifth quintile is the most affluent group. Immigration status was defined and divided into three categories by Statistics Netherlands. *The other category of main source of income. This category includes primary source of income from a student grant, property income, and when household income is unknown. HR, hazard rate; N/A, not available.

R1
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R3
R2O
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R2

PART 2

Investigating possible explanations for an increase in opioid use in the Netherlands

R1
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CHAPTER 5

Risk of drug-related upper gastrointestinal bleeding in the total population of the Netherlands: a time-trend analysis

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Abstract

Objective

Many prescribed and over-the-counter medications, ***e.g.***, nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with upper gastrointestinal bleeding (UGIB). Recently, a decrease in prescribing of NSAIDs was observed in the Netherlands, but whether a similar decreasing trend could be observed in the incidence of severe UGIB (either fatal or requiring hospitalization), contingent on medication prescription, is unknown.

Design

We conducted a cohort study using Dutch national statistics on pharmacy claims, hospitalization and mortality between 2013 and 2018. We explored the incidence of sex- and age-specific severe UGIB in four (sub)populations: A) total population, B) without filled NSAIDs prescriptions, C) without filled NSAIDs and antithrombotic agents, D) without any risk factors for UGIB.

Results

The cumulative incidence of severe UGIB did not decrease throughout the study period, regardless of the subgroup analysis. In the total population, it was 199 per 100,000 inhabitants [95% confidence interval (CI), 197-201] in 2013-2014 and 260 [95% CI, 258-263] in 2017-2018. The absolute risk of severe UGIB was 50% lower in the subgroup B than in the full cohort. It decreased further by 50% in the subgroup D when compared to subgroup B. The risk of severe UGIB was 1.5-1.9-fold higher in young women than in young men; an indication of over-the-counter NSAIDs use being more prevalent in women than men in this age group.

Conclusion

We found no evidence to support the relationship between the prescribing of NSAIDs and the incidence of severe UGIB in the Netherlands since 2013. The relationship was not observed when we removed the effect of risk factors.

Research in context

- What is already known about this subject? The upper gastrointestinal bleeding (UGIB) has many risk factors including medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs). Recently a decrease in prescribing of NSAIDs was noted in the Netherlands but whether a similar trend can be observed in the incidence of UGIB is unknown.
- What are the new findings? There is no evidence for the association between the prescribing of NSAIDs and the incidence of severe UGIB in the Netherlands between 2013 and 2018. The relationship was not observed in the absence of any potential risk factors. This finding may indicate high prevalence of over-the-counter NSAIDs use.
- How might it impact on clinical practice in the foreseeable future? Monitoring and potentially restricting the use of over-the-counter NSAIDs is warranted.

Introduction and rationale

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most prescribed medications in the Netherlands [1]. The therapeutic actions of NSAIDs, have been linked to inhibition of the cyclo-oxygenase enzymes (COX)-2 isoform, while side effects, gastrointestinal disturbances, increased risk of cardiovascular events and renal complications, are thought to be mediated by the inhibition of the COX-1 isoform [2,3]. The annual incidence of upper gastrointestinal bleeding (UGIB) is approximately 100 per 100,000 residents, and about 10% of hospitalised patients die within 30 days [4,5]. Various observational studies have reported two- to fourfold increased risk of UGIB in NSAIDs users compared with non-users [6–8].

These serious side effects of NSAIDs may have motivated a change in their prescribing, e.g. the 2013 Dutch clinical guideline on postoperative pain management that advocates caution when prescribing NSAIDs [9]. Previous studies demonstrated that the number of Dutch residents who filled a prescription for NSAIDs fell by 200,000 between 2013 and 2017 [10,11]. However, it remains unknown whether a recent decrease in prescribing of NSAIDs brought about a change in the prevalence of UGIB

in the total population of the Netherlands. In 2003 van Leerdam et al reported that the incidence rate of UGIB hospital admissions decreased between 1993-1994 and 2000 in the Amsterdam area, the Netherlands [12]. To our knowledge no studies have been conducted on time-trends of incident UGIB in the Netherlands on a national level.

One could hypothesize that a decrease in prescribing of NSAIDs would lead to a decrease in the incidence of UGIB. Not only are prescribed NSAIDs associated with this side effect, but also many other prescription drugs, e.g., anticoagulants, as well as medication that can be bought over-the-counter [13]. Despite this, we hypothesized that the incidence of severe UGIB, either fatal or requiring hospital admission, is associated with the decreased prescribing rate of NSAIDs. To investigate this hypothesis, we set out to determine the (sex- and age-dependent) incidence of severe UGIB in the Netherlands between 2013 and 2018, contingent on prescription medication use.

Methods

Setting, participants, and data sources

We conducted a nation-wide cohort study using several anonymized datasets from Statistics Netherlands (CBS) covering the total population of the Netherlands (about 17.1 million residents) between 1st January 2013 and 31st December 2018. We merged prescription reimbursement datasets, hospital admission datasets, and the mortality register of different calendar years into one analytical dataset based on unique anonymized identifiers that ensure deterministic dataset linkage on an individual level (the dataset linkage and merging strategy is presented in Supplementary Figure 1). This study was exempt from the Medical Ethical Review Committee of Leiden University Medical Center after a review (reference number: G20.054).

Pharmacy claims data

Prescription reimbursement claims were collected for all residents of the Netherlands entitled to pharmaceutical care, i.e., those ensured by the basic health insurance, which is n=17,163,404 (99.9%) residents in 2018 [14]. The Dutch Health Care Institute (ZIN) provides the medication claims data to CBS. Medication dispensed from outpatient and community pharmacies, as well as in residential homes for the elderly are collected in the national reimbursement database, however medicines dispensed from hospital pharmacies for in-hospital patient care and pharmaceutical care in nursing homes

are not registered [15]. In this registry medications are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [16].

Hospital admissions and deaths registry

The Dutch Hospital Data contains information about all hospital admissions, and the Dutch Register of Causes of Death registers all-cause deaths [17,18]. Each record of the hospital admission data contains the date of hospital encounters, the discharge date, and discharge diagnoses [19,20]. Hospital admission diagnoses and causes of deaths are coded according to the International Statistical Classification of Diseases and Related Health Problems (ICD, 10th revision) of the WHO [21].

Variables

Apart from NSAIDs (M01A), we identified antithrombotic agents (B01A) that are considered a risk factor for UGIB, and for which a prescription is required in the Netherlands. There are many other prescribed medications as well as medical conditions that are considered risk factors for UGIB. In this project we considered corticosteroids for systemic use (H02A, H02B), anticancer medication (L01, L02), drugs for (stomach) acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), and antidiabetic medication (A10). Use of corticosteroids, antidepressants, particularly selective serotonin reuptake inhibitors, and some antihypertensive medications have shown to be associated with UGIB in monotherapy and in combinations with other medications [13]. Having received a prescription for an anticancer medication, drugs for acid related disorder, or antidiabetic disorder, were considered as proxies for having a medical condition which we considered important comorbidities that are associated with elevated risk of UGIB.

Individuals were considered exposed to a prescribed medication when they filled at least one prescription per one studied calendar years (which was also analysed per two consecutive calendar years). In the main analysis the variables and the outcome were estimated per two calendar years, whereas estimates evaluated per annum can be found in the Supplement. Each medication group described above was treated as an individual variable in the analysis.

Outcomes

We defined severe UGIBs as those that were fatal or required hospital admission, and we selected a range of UGIB ICD-10CM codes that were previously found to be

associated with prescribed medications in four different primary care databases of the Netherlands, Italy and Denmark [22]. These ICD-10CM codes are: acute gastric ulcer with hemorrhage (K25.0), acute gastric ulcer with perforation (K25.1), acute gastric ulcer with hemorrhage and perforation (K25.2), acute duodenal ulcer with hemorrhage (K26.0), acute duodenal ulcer with perforation (K26.1), acute duodenal ulcer with both hemorrhage and perforation (K26.2), acute peptic ulcer with hemorrhage, site unspecified (K27.0), acute peptic ulcer with perforation, site unspecified (K27.1), acute peptic ulcer with both hemorrhage and perforation, site unspecified (K27.2), acute gastrojejunal ulcer with hemorrhage (K28.0), acute gastrojejunal ulcer with perforation (K28.1), acute gastrojejunal ulcer with both hemorrhage and perforation (K28.2), acute hemorrhagic gastritis (K29.0), haematemesis (K92.0), melaena (K92.1), and unspecified gastrointestinal hemorrhage (K92.2).

Severe UGIB was identified based on the first hospital admission or death, whichever occurred first, per studied calendar year. Severe UGIB events were identified per calendar year, and were incident when individuals did not have the same diagnosis registered in the preceding 12 months. The risk of recurrent UGIB is highest within first 12 months after the diagnosis and decreases with time [23].

Statistical Methods

To identify the prevalence of prescribed medications and demographic characteristics, we performed descriptive statistics for all people residing in the Netherlands between 2013 and 2018. We presented this information in absolute numbers and as a proportion of the total population (we also show mean age and corresponding standard deviation) per one- and two-calendar years. Incident severe UGIB was presented in the absolute manner as cumulative biennial and annual incidence per 100,000 inhabitants with 95% confidence intervals (CI). Confidence intervals were calculated based on the standard errors of the estimate using a traditional formula [24]. All estimates were calculated per one and per two years' time-frame. The biennial analysis was performed to account for random fluctuations in the occurrence of disease outcomes, which may be present as was previously shown in other population-based studies [25–27].

Univariable (Model 1) and multivariable (Model 2) logistic regression was used to study the relationship between time frame (from 2013 to 2018) and the incident severe UGIB, where the 2013-2014 (or 2013 in the annual analysis) calendar time was taken as a reference. Relationship between calendar time and incident severe UGIB

was considered confounded by age and sex, because over time population ages and there are slight changes in sex distribution. Therefore, we corrected the estimate of incident UGIB over calendar time for age (stratified into 5 age categories: 0-15, 15-25, 25-45, 45-65, ≥65 years), and sex (stratified by female and male sex). Results of logistic regression models were presented as odds ratios (OR) with 95% CI.

The association between calendar year and severe UGIB could also be affected by changes in ethnical structure and sociodemographic variables, however, the Netherlands did not recently undergo major political, environmental or other changes that could potentially impact these risk factors of severe UGIB between 2013 and 2018.

We also explored the incidence of severe UGIB depending on age and sex differences. For this analysis, we stratified the population by sex (stratified by female and male sex) and age (stratified into 8 age categories: 0-15, 15-25, 25-45, 45-55, 55-65, 65-75, 75-85, ≥85 years), and we compared the absolute risk of severe UGIB in women relative to men in different age groups over observation period.

Restriction analyses

To study the association between several medication prescriptions and the cumulative incidence of severe UGIB in a given calendar year we repeated the same above-mentioned statistical analysis in four different (sub)populations. These subpopulations were created by restriction. First, we analysed the total population of the Netherlands (group A).

Then, we restricted the population to residents that did not fill a prescription for NSAIDs (subgroup B), and third to individuals to whom neither NSAIDs nor antithrombotic agents were prescribed (subgroup C). In the second analysis we removed the effect of NSAIDs prescription, because we were interested in the incidence of severe UGIB independent from prescribed NSAIDs. Similarly, in the second restriction—when we restricted for NSAIDs and antithrombotic agents—we intended to investigate the risk of severe UGIB that cannot be explained by these two most important risk factors. However, individuals could still receive a prescription for any other medication that is a risk factor for UGIB; the observed incidence of severe UGIB in the subgroup B and C is isolated from the effect of prescribed NSAIDs and NSAIDs and antithrombotic agents, respectively, but not from any other prescribed or over-the-counter medications.

Last, we restricted the total Dutch population to those individuals who did not fill a prescription for any of the above-mentioned prescribed medications (subgroup D). We considered this group to be risk factor free. This way, we aimed to estimate the effect of over-the-counter NSAIDs use, and its association with UGIB. We were particularly interested in the risk of UGIB in the young (less than 25 years old) because other risk factors and competing risks of severe UGIB are largely absent in this rather homogenous age group. We expected to find a larger risk of severe UGIB in young women (aged 15-25 years) compared with men in the same age group since it is more likely that women are using more over-the-counter NSAIDs to treat the menstrual pain [28–31].

Data Linkage

Some data on the prescription reimbursement, and severe UGIB could not be merged to the population registry. In order to investigate whether the data loss could introduce bias in our study we calculated cumulative proportions for the variables and the outcome of this study in the merged and in the unmerged data. Then, we compared whether linkage in the variables and in the outcome changed over observation time. The proportion of the non-linked records did not vary for any of the relevant variables in this analysis throughout the observational period (Supplementary Table 1). Therefore, we decided to perform a complete case analysis.

The STROBE statement checklist for cohort studies is included in the Appendix. All statistical analyses were performed with SPSS for Windows, release 25.0 (SPSS, Chicago, IL, USA). Figures were created with R studio (A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https ://www.R-proje ct.org), using ***R*** package ***ggplot2*** version 3.2.125 [32].

Results

Participants

In this study all people residing in the Netherlands between 2013 and 2018 were included. A total of 217,367 records (0.21% of 101,751,300 records) could not be linked. The proportion of the non-linked records did not vary between 2013 and 2018 (from 0.19% to 0.24%) (Figure 1). For the primary analyses, 3 cohorts, i.e., 2013-2014, 2015-2016, and 2017-2018 were created. Of 17,112,982 residents (mean age [SD], 41.76

[23.18]) in 2013-2014, 8,630,156 (50.43%) were women. The number of residents in the following years increased slightly (n=17,269,164 and n=17,473,459 individuals in 2015-2016 and 2017-2018, respectively), as did age, while the sex distribution remained largely unchanged (Table 1).

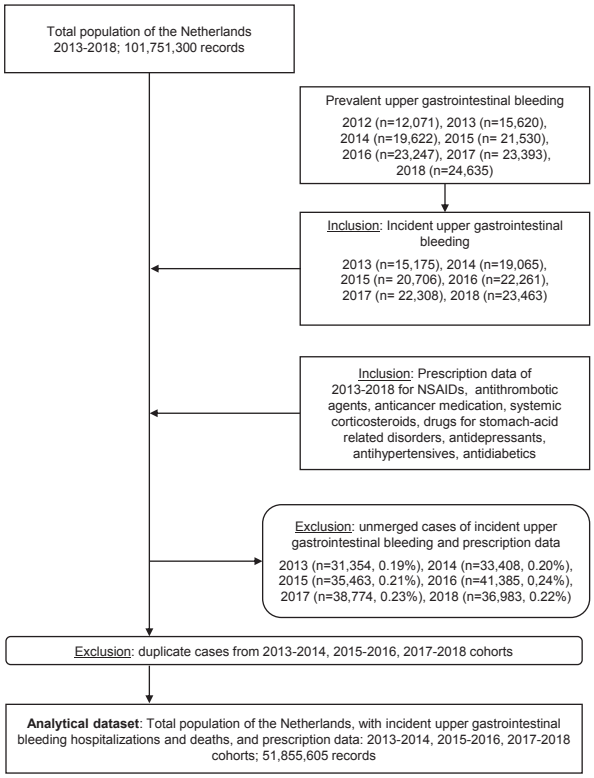

Figure 1. Flow diagram of merging of datasets, the Netherlands, from 2013 to 2018

Datasets were merged based on unique pseudo-anonymized identifier, which ensures deterministic linkage, and the year of occurrence. We performed complete case analysis.

All medications were identified through prescription reimbursement data based on their ATC codes per two calendar years. Identified medications: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B,

A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10).

Cases of severe upper gastrointestinal bleeding were identified based on ICD-10CM codes in the hospital admission and death registry per one- and two-calendar years. Description of inclusion criteria of incident severe upper gastrointestinal bleeding cases is described in detail in the methods section of the article. Results of data preparation can be found in Table 1. Detailed information on the excluded cases can be found in the Supplement.

Table 1. General characteristics of the study population, the Netherlands, in 2013-2014, 2015-2016, and 2017-2018

	2013-2014	**2015-2016**	**2017-2018**
Total, n	17112982	17269164	17473459
Age, mean [SD]	41.76 [23.18]	42.19 [23.32]	42.54 [23.43]
Age categories, n (%)			
0-15	2867188 (16.75)	2815725 (16.30)	2776878 (15.89)
15-25	2079263 (12.15)	2105049 (12.19)	2138442 (12.24)
25-45	4368952 (25.53)	4299213 (24.90)	4305414 (24.64)
45-65	4755790 (27.79)	4834007 (27.99)	4880562 (27.93)
>65	3041779 (17.77)	3215170 (18.62)	3372163 (19.30)
Sex, n (%)			
men	8482826 (49.57)	8568391 (49.62)	8679186 (49.67)
women	8630156 (50.43)	8700773 (50.38)	8794273 (50.33)
Received a prescription for a medication			
NSAIDs, n (%)	4094856 (23.93)	3906368 (22.62)	3735730 (21.38)
Antithrombotic agents, n (%)	1962912 (11.47)	2033817 (11.78)	2091111 (11.97)
Anticancer medication, n (%)	247017 (1.44)	226766 (1.31)	223665 (1.28)
Systemic corticosteroids, n (%)	1243385 (7.27)	1336613 (7.74)	1378921 (7.89)
Drugs for stomach-acid disorders, n (%)	2377506 (13.89)	2535825 (14.68)	2603371 (14.90)
Antidepressants, n (%)	1223285 (7.15)	1242787 (7.20)	1256602 (7.19)
Antihypertensives, n (%)	3419241 (19.98)	3454098 (20.00)	3484030 (19.94)
Antidiabetic medication, n (%)	854240 (4.99)	867259 (5.02)	877046 (5.02)

Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs. All medications were identified through prescription reimbursement data, based on their ATC codes per two calendar years. Identified medication: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10). People might have received several medications in a given year, e.g., could have used NSAIDs and antithrombotic agents at the same time in a given year.

About 4 million (22%) of residents received at least one NSAID prescription in a two-years' period, which was closely followed by antihypertensive medication (20%), and drugs for stomach-acid related disorders (about 14% of the population). The prevalence of medication prescriptions remained stable or increased during the observation period for all studied therapeutic groups, except NSAIDs which decreased (n=4,094,856 (23.93%) and n=3,735,730 (21.38%) in 2013-2014 and 2017-2018, respectively) (Table 1). All of the abovementioned analyses were repeated annually, and showed similar results (Supplementary Table **2**).

Risk of severe UGIB in the four different (sub)populations

In the total Dutch population, the two years' worth cumulative incidence of severe UGIB was 199 per 100,000 inhabitants [95% CI, 197-201] in 2013-2014, and in 2017-2018 it was 260 per 100,000 inhabitants [95% CI, 258-263] (Table 2). Throughout the observation period the risk of severe UGIB in the total Dutch population did not decrease, in fact, the odds of severe UGIB were increased by 25% when we compared the years 2017-2018 with years 2013-2014 (Table 2).

The cumulative incidence of severe UGIB in the restricted subpopulation of people not exposed to prescribed NSAIDs (subgroup B) was a bit lower than in the total population, but the trend of severe UGIB over calendar time did not change (Model 2, age- and sex-adjusted OR, 1.26 [95% CI, 1.24-1.28] comparing 2017-2018 with 2013-2014) (Table 2).

The cumulative incidence of severe UGIB over two years' time in the further restricted total population (to those individuals to whom neither NSAIDs nor antithrombotic agents were prescribed, subgroup C) was approximately 50% lower when compared with the full cohort, but again the relative risk estimates (where calendar times were compared) did not show a decrease of severe UGIB over time (Model 2, age- and sex-adjusted OR, 1.29 [95% CI, 1.26-1.32] comparing 2017-218 with 2013-2014).

Table 2. Risk of severe upper gastrointestinal bleeding in four different subgroups, the Netherlands, in 2013-2014, 2015-2016, and 2017-2018

Subgroup	Calendar Year	No.	Total No.	Cumulative incidence, event/100,000 inhabitants (95% CI)	Model 1 odds ratio (95% CI)	Model 2 odds ratio (95% CI)
A	2013-2014	34071	17112982	199.09 (196.99-201.22)	1.00 (reference)	1.00 (reference)
	2015-2016	42732	17269164	247.45 (245.11-249.80)	1.24 (1.23-1.26)	1.21 (1.20-1.23)
	2017-2018	45516	17473459	260.49 (258.11-262.89)	1.31 (1.29-1.33)	1.25 (1.24-1.27)
B	2013-2014	23029	13018126	176.90 (174.63-179.20)	1.00 (reference)	1.00 (reference)
	2015-2016	29562	13362796	221.23 (218.72-223.76)	1.25 (1.23-1.27)	1.21 (1.19-1.23)
	2017-2018	32503	13737729	236.60 (234.04-239.18)	1.34 (1.32-1.36)	1.26 (1.24-1.28)
C	2013-2014	10837	11678227	92.80 (91.07-94.56)	1.00 (reference)	1.00 (reference)
	2015-2016	14062	11935659	117.82 (115.88-119.78)	1.27 (1.24-1.30)	1.24 (1.21-1.27)
	2017-2018	15338	12229473	125.42 (123.45-127.42)	1.35 (1.32-1.39)	1.29 (1.26-1.32)
D	2013-2014	4217	9354526	45.08 (43.72-46.44)	1.00 (reference)	1.00 (reference)
	2015-2016	5779	9514371	60.74 (59.17-62.31)	1.35 (1.30-1.40)	1.31 (1.26-1.37)
	2017-2018	6164	9731023	63.34 (61.76-64.92)	1.41 (1.35-1.46)	1.34 (1.29-1.39)

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; UGIB, upper gastrointestinal bleeding. Subgroups: A) total population, B) restricted to the group of individuals without a prescription for NSAIDs, C) restricted to the group of individuals who did not receive a prescription for NSAIDs nor antithrombotic agents, D) restricted to the group of individuals without any medication that is either a risk factor for upper gastrointestinal bleeding or the indication for which the medication is prescribed is one. These are NSAIDs, antithrombotic agents, anticancer medication, systemic corticosteroids, drugs for stomach-acid related disorders, antidepressants, antihypertensives, antidiabetic medication. All medications were identified through prescription reimbursement data, based on their ATC codes. People might have received several medications in a given year, e.g., could have used NSAIDs and antithrombotic agents at the same time in a given year. Incident cases of severe upper gastrointestinal bleeding were identified based on ICD-10CM codes in the hospital admission and death registry. Model 1: logistic regression model where incident severe UGIB was entered as a dependant variable and calendar year as independent variable. Model 2: was Model 1 corrected for age (categorized), and sex imbalances between the cohorts.

Last, when we restricted the total Dutch population to residents who did not fill any prescriptions for NSAIDs, antithrombotic agents, anticancer medication, drugs for acid related disorders, antidepressants, antihypertensives, or antidiabetic medication (subgroup D) the biennial cumulative incidence was about 4-times lower than in the total Dutch population, and the trend of severe UGIB incidence remained unchanged when 2017-2018 was compared with 2013-2014 (Model 2, age- and sex-adjusted OR, 1.34 [95% CI, 1.29-1.39]) (Table 2). All of the abovementioned analyses were repeated annually, and showed similar results (Supplementary Table **3**).

In the following post hoc analyses, we observed that the cumulative incidence of severe UGIB increased with age (Figure 2). In the total Dutch population those aged more than 85 years had the highest cumulative incidence (625-700 per 100,000 per year) (Figure 2-A).

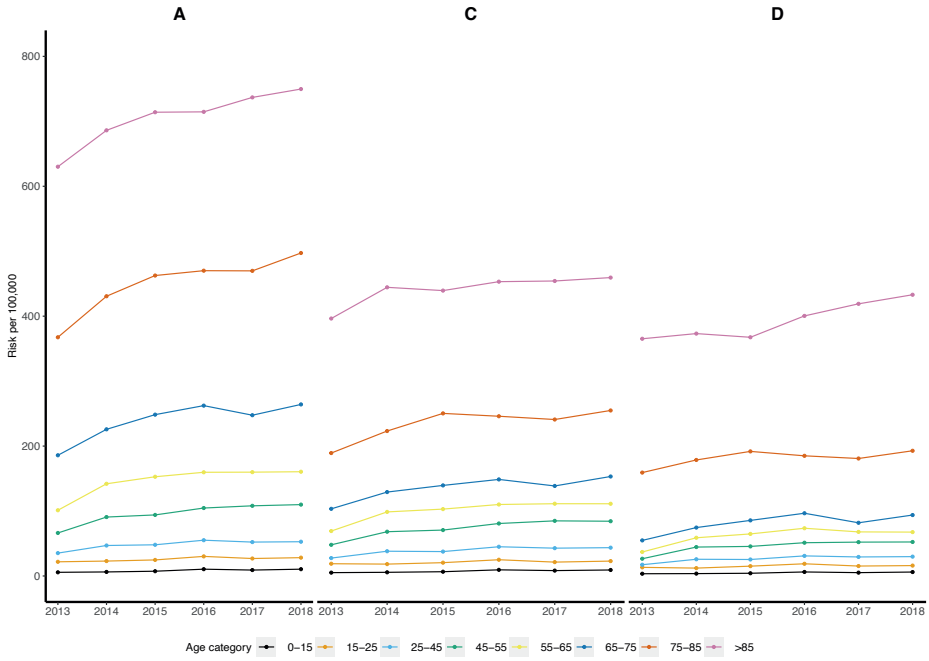

Figure 2. The age-specific risk of severe upper gastrointestinal bleeding in three different subgroups, the Netherlands, from 2013 to 2018

Figure shows age-specific annual cumulative incidence of severe upper gastrointestinal bleeding per 100,000 inhabitants in three different scenarios: A) total population, C) individuals who did not receive a prescription for nonsteroidal anti-inflammatory drugs nor antithrombotic agents, D) individuals without any risk factors of upper gastrointestinal bleeding.

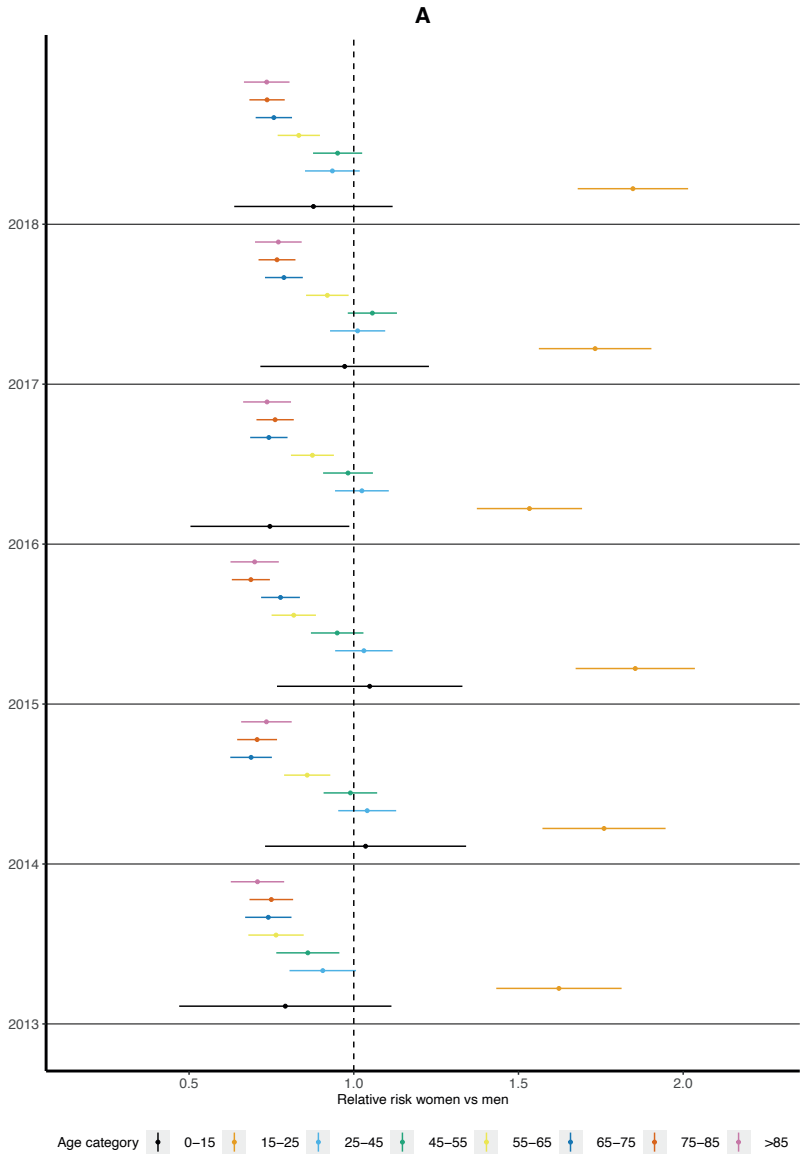

Figure 3. The risk of severe upper gastrointestinal bleeding in women compared to men in different age groups of the total population (subgroup A), the Netherlands, from 2013 to 2018

Figure shows crude relative risks of annual incidence of severe upper gastrointestinal bleeding in women compared to men (male sex was the reference group) among different age groups in the total Dutch population (subgroup A). The relative risks of severe UGIB in women compared with men in the observation period in individuals who did not receive a prescription for nonsteroidal anti-inflammatory drugs nor antithrombotic agents (subgroup C), and in individuals without any risk factors of upper gastrointestinal bleeding (subgroup D) can be found in the Supplement as Supplementary Figure 2 and Supplementary Figure 3, respectively.

The absolute risk of incident UGIB over the calendar time was lowest in 2013 for all age groups and slightly increased over the following years 2014-2018 (Figure 2). The risk of incident severe UGIB was generally lower in women than in men in all subgroups (Figure 3), except in the 15-25 years age group where women had approximately 1.75-fold higher risk of incident UGIB than men throughout the observation period (Figure 3, Supplementary Figure 2, Supplementary Figure 3).

Discussion

In this study, in which we had full access to national Dutch registry data on pharmacy claims, hospitalizations and mortality between 1st January 2013 and 31st December 2018, we did not find a decrease in the number of hospital admissions or deaths due to UGIB. If anything, a slight increase in the risk of severe UGIB was observed over the observation period, which may be due to a random low incidence of severe UGIB in 2013. For the other years the cumulative incidence of severe UGIB was remarkably similar across all age groups and restriction analyses we performed. This finding is contrary to our research hypothesis where we expected to find a decrease in severe UGIB between 2013 and 2018, together with the decline of the number of prescribed NSAIDs (not used for inpatient care or in patients admitted to nursing homes) in the total Dutch population over the same calendar time.

Various studies have identified medication groups that are associated with an increased risk of UGIB, of which, NSAIDs and antithrombotic agents are most strongly associated [6–8,13,33–39]. This is also what we found in our overall and age stratified analysis over calendar time. We observed that the yearly incidence of severe UGIB dropped by approximately 50% when we restricted our analysis to the population unexposed to prescribed NSAIDs or antithrombotic agents (Table 2). Even when we restricted the total Dutch population to those without any risk factors and correction for age and sex differences over time, we did not find a decrease in the risk of UGIB between 2013 and 2018, despite the decrease in prevalence of prescribed NSAIDs throughout this observation period (Table 1).

A possible explanation for this finding is that the Dutch residents are able to buy NSAIDs over-the counter, ***i.e.***, through drugstores, supermarkets, and online. The sale of over-the-counter NSAIDs is not limited by any guidelines, and is further endorsed

by commercials in the public domain. While the exact prevalence of over-the-counter NSAIDs use is unknown (as this is not registered), surveys have shown that it must be high. One survey found that approximately one in three residents buys at least one package of over-the-counter NSAIDs in a month time [40]. In another Dutch health survey, 8% of respondents had used NSAIDs in the last day, of which the majority had used the over-the-counter medication, and over 50% of respondents had used NSAIDs in the last three months [41,42].

From our results the risk of severe UGIB attributable to the over-the-counter use of NSAIDs cannot be inferred. First, UGIB is a multicausal disease where underlying pathology, medication use and diet are all related to the onset of the disease [43]. From our study, due to its design, we cannot fully distinguish which of the underlying factors led to severe UGIB. Second, even though we did take various risk factors into account by restriction, the remaining risk of severe UGIB is not necessarily only related to over-the-counter use of NSAIDs as there are likely many remaining (residual) explanatory variables, such as alcohol intake, smoking, or underlying ***Helicobacter pylori*** infection.

The presence of other possible explanations for the risk of severe UGIB becomes most apparent in our age and sex stratified analysis (Figure 3). It has been previously reported that male sex is a risk factor for UGIB [44], which was also true for our analysis when we stratified severe UGIB for sex only. However, further stratification for age revealed an interesting finding in the age group of 15-25 years—where the majority of people are free from any underlying severe disease—where women had a 1.5-1.9-fold increased risk of severe UGIB when compared with men. This increased risk in women was also present when we restricted the total Dutch population to the subpopulation without any risk factors for UGIB (subgroup D). Since in the 15-25 age group, it is more likely that women use NSAIDs more often than men as they self-treat primary dysmenorrhea (painful cramping of the uterus before or during a menstruation for which NSAIDs are the treatment of choice) [45–48]. Therefore, this increased risk of severe UGIB may be ascribed to over-the-counter NSAIDs use. It was demonstrated, that in the Netherlands, women use more NSAIDs, prescription and over-the-counter, than men [40,49], which further supports our finding.

This result, though interesting, should be viewed with caution because 1) it was a finding based on a post hoc analysis. 2) This is a result from an observational study where residual confounding might still play a role. 3) No such finding has been

reported previously (chance of a type I error) and 4) even if this risk can be fully explained by the over-the-counter NSAIDs use, the absolute risk of severe UGIB in this age group was very low and was not contrasted to the potential benefits of NSAIDs use as an analgesic in primary dysmenorrhea and other afflictions.

Limitations

This research has some methodological issues that warrant a comment. First, there was some data lost when merging the prescription reimbursement, hospital admission and mortality data to the dataset of the total population of the Netherlands. However, the total number of information lost (on average 0.21% of all records) was little and we consider this most likely to have occurred completely at random given that these errors were errors due to logistics. This was also indicated in a sensitivity analysis where we determined that the loss of data could not have led to bias (Supplementary Table 1).

Second, prescription information on NSAIDs and other medications was only available on the 3rd ATC level, and therefore we were not able to identify individual active substances. Third, we have no information for how long the NSAIDs were prescribed and/or used. However, short-term NSAIDs use has a poor association with gastrointestinal bleeding, and is mainly determined by the dose of the medication [50,51]. Fourth, our data only allowed us to investigate whether someone received a comedication in a given year, and not the amount of the comedication. Because there were no changes in prescribing policies or changes in reimbursement of any of the proposed prescribed medications in this period of time, we considered the use of comedication constant, but cannot comment on whether the amount of use (e.g., covered in prescriptions) could further attenuate the risk of severe UGIB.

Last, hospital diagnoses and deaths were ICD-10CM coded and the positive predictive values is unknown for this particular set of ICD-10CM codes in the CBS database. However, UGIB as outcome had an association with risk factors for gastrointestinal bleeding including age, NSAIDs and antithrombotic agents prescription, and sex, making it unlikely that the outcome of interest does not have a good positive predictive value. In addition, the annual cumulative incidences of gastrointestinal bleeding that we have found in our study are comparable with cumulative incidences reported in other studies [52].

In conclusion, we found no evidence of a relationship between the decrease in prevalence of NSAIDs prescriptions in 2013 and the steady trend in incidence of upper gastrointestinal bleeding since then.

Acknowledgments

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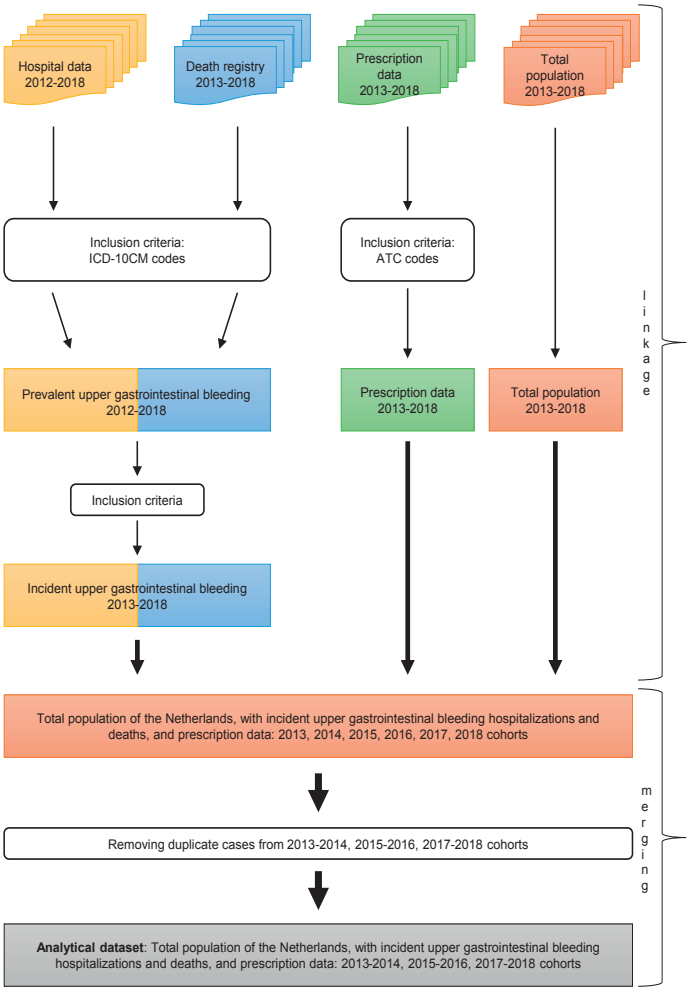
Supplement to: Risk of drug-related upper gastrointestinal bleeding in the total population of the Netherlands: a time-trend analysis



Supplementary Figure 1. Data linkage strategy

All medications were identified through prescription reimbursement data based on their ATC codes. Individuals were considered exposed when they received at least one prescription per calendar year. Identified medications: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10). Upper gastrointestinal bleeding cases were identified based on ICD-10CM codes in the hospital admission and death registry. Description of inclusion criteria of incident upper gastrointestinal bleeding cases is described in detail in the methods section of the article.

Supplementary Table 1. Comparison of merged and unmerged data, the Netherlands, from 2013 to 2018

	2013	2014	2015	2016	2017	2018
Merged						
Total No.	16779442	16829289	16900726	16979120	17081506	17181084
Incident upper gastrointestinal bleeding	15104 (0.09)	18967 (0.11)	20583 (0.12)	22149 (0.13)	22177 (0.13)	23339 (0.14)
Received a prescription for a medication						
NSAIDs, n (%)	2593528 (15.46)	2527462 (15.02)	2461396 (14.56)	2395910 (14.11)	2335794 (13.67)	2286139 (13.31)
Antithrombotic agents, n (%)	1682484 (10.03)	1712126 (10.17)	1739267 (10.29)	1771826 (10.44)	1798828 (10.53)	1825742 (10.63)
Anticancer medication, n (%)	175078 (1.04)	172634 (1.03)	155907 (0.92)	167794 (0.99)	150885 (0.88)	158829 (0.92)
Systemic corticosteroids, n (%)	758897 (4.52)	788039 (4.68)	831659 (4.92)	840608 (4.95)	852508 (4.99)	876619 (5.10)
Drugs for acid disorders, n (%)	1909798 (11.38)	2015757 (11.98)	2094243 (12.39)	2165561 (12.75)	2194367 (12.85)	2220974 (12.93)
Antidepressants, n (%)	986648 (5.88)	1003138 (5.96)	1020894 (6.04)	1026128 (6.04)	1028124 (6.02)	1043653 (6.07)
Antihypertensives, n (%)	3108997 (18.53)	3125074 (18.57)	3142348 (18.59)	3165057 (18.64)	3181763 (18.63)	3190664 (18.57)
Antidiabetic medication, n (%)	792709 (4.72)	799433 (4.75)	805087 (4.76)	810306 (4.77)	814704 (4.77)	818917 (4.77)
Unmerged						
Total No.	16779575	16829289	16900726	16979120	17081506	17181084
Incident upper gastrointestinal bleeding	15175 (0.09)	19065 (0.11)	20706 (0.12)	22261 (0.13)	22308 (0.13)	23463 (0.14)
Received a prescription for a medication						
NSAIDs, n (%)	2600896 (15.50)	2535617 (15.07)	2469770 (14.61)	2405557 (14.17)	2345221 (13.73)	2294707 (13.36)
Antithrombotic agents, n (%)	1684335 (10.04)	1714124 (10.19)	1741484 (10.30)	1774237 (10.45)	1801310 (10.55)	1828123 (10.64)
Anticancer medication, n (%)	175287 (1.04)	172818 (1.03)	156090 (0.92)	168001 (0.99)	151077 (0.88)	159030 (0.93)
Systemic corticosteroids, n (%)	760633 (4.53)	789742 (4.69)	833707 (4.93)	842734 (4.96)	854765 (5.00)	878874 (5.12)
Drugs for stomach-acid disorders, n (%)	1917421 (11.43)	2025393 (12.03)	2103756 (12.45)	2176234 (12.82)	2204899 (12.91)	2230141 (12.98)
Antidepressants, n (%)	988884 (5.89)	1005330 (5.97)	1023187 (6.05)	1028409 (6.06)	1030421 (6.03)	1046031 (6.09)
Antihypertensives, n (%)	3113050 (18.55)	3129329 (18.59)	3147010 (18.62)	3169924 (18.67)	3186908 (18.66)	3195665 (18.60)
Antidiabetic medication, n (%)	794062 (4.73)	800764 (4.76)	806614 (4.77)	811957 (4.78)	816487 (4.78)	820639 (4.78)

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs. Dataset was merged based on unique pseudo-anonymized identifier, which ensures deterministic linkage, and the year of occurrence. We performed complete case analysis in all other analyses based on "merged" data.

All medications were identified through prescription reimbursement data, based on their ATC codes per calendar year. Identified medications: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10). Upper gastrointestinal bleeding cases were identified based on ICD-10CM codes in the hospital admission and death registry per calendar year.

Supplementary Table 2. General characteristics of the study population, the Netherlands, from 2013 to 2018

	2013	2014	2015	2016	2017	2018
Total, n	16779442	16829289	16900726	16979120	17081506	17181084
Age, mean [SD]	41.29 [22.97]	41.53 [23.03]	41.76 [23.10]	41.95 [23.16]	42.12 [23.23]	42.30 [23.28]
Age categories, n (%)						
0-15	2676566 (15.95)	2647191 (15.73)	2619145 (15.5)	2595233 (15.28)	2578067 (15.09)	2559103 (14.89)
15-25	2042172 (12.17)	2050432 (12.18)	2058861 (12.18)	2069566 (12.19)	2086033 (12.21)	2101106 (12.23)
25-45	4286532 (25.55)	4232031 (25.15)	4201191 (24.86)	4188101 (24.67)	4195813 (24.56)	4221792 (24.57)
45-65	4735716 (28.22)	4773582 (28.36)	4810241 (28.46)	4839257 (28.50)	4853937 (28.42)	4853361 (28.25)
>65	3038456 (18.11)	3126053 (18.58)	3211288 (19.00)	3286963 (19.36)	3367657 (19.72)	3445722 (20.06)
Sex, n (%)						
men	8307302 (49.51)	8334418 (49.52)	8372983 (49.54)	8417298 (49.57)	8475255 (49.62)	8527129 (49.63)
women	8472140 (50.49)	8494871 (50.48)	8527743 (50.46)	8561822 (50.43)	8606251 (50.38)	8653955 (50.37)
Received a prescription for a medication						
NSAIDs, n (%)	2593528 (15.46)	2527462 (15.02)	2461396 (14.56)	2395910 (14.11)	2335794 (13.67)	2286139 (13.31)
Antithrombotic agents, n (%)	1682484 (10.03)	1712126 (10.17)	1739267 (10.29)	1771826 (10.44)	1798828 (10.53)	1825742 (10.63)
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Drugs for stomach-acid disorders, n (%)	1909798 (11.38)	2015757 (11.98)	2094243 (12.39)	2165561 (12.75)	2194367 (12.85)	2220974 (12.93)
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Antidiabetic medication, n (%)	792709 (4.72)	799433 (4.75)	805087 (4.76)	810306 (4.77)	814704 (4.77)	818917 (4.77)

Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs. All medications were identified through prescription reimbursement data, based on their ATC codes per calendar year. Identified medications: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10). People might have received several medications in a given year, e.g., could have used NSAIDs and antithrombotic agents at the same time in a given year.

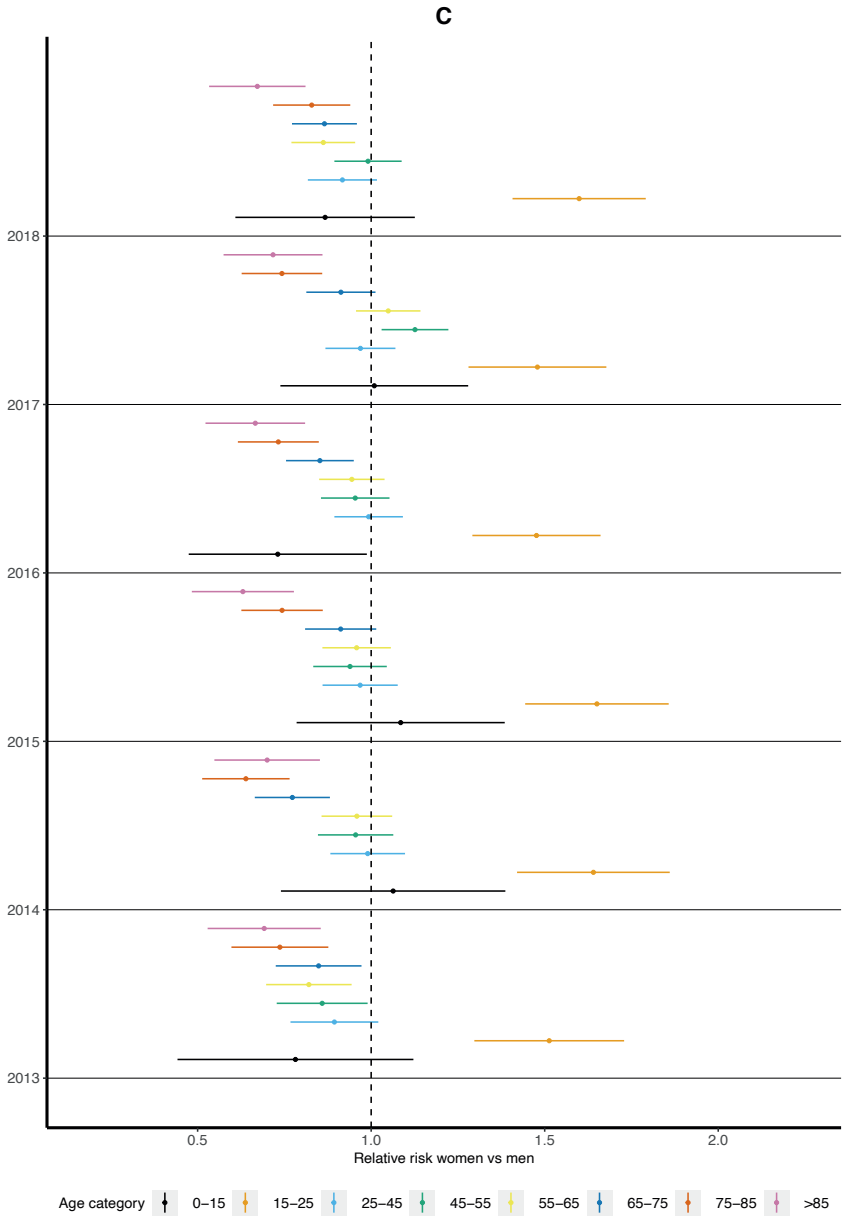
Supplementary Table 3. Risk of severe upper gastrointestinal bleeding in four different subgroups, the Netherlands, from 2013 to 2018

Subgroup	Calendar Year	No.	Total No.	Cumulative incidence event/100,000 inhabitants (95% CI)	Model 1 odds ratio (95% CI)	Model 2 odds ratio (95% CI)
A	2013	15104	16779442	90.01 (88.58-91.45)	1.00 (reference)	1.00 (reference)
	2014	18967	16829289	112.70 (111.10-114.31)	1.25 (1.23-1.28)	1.23 (1.21-1.26)
	2015	20583	16900726	121.79 (120.12-123.45)	1.35 (1.33-1.38)	1.32 (1.29-1.35)
	2016	22149	16979120	130.45 (128.73-132.17)	1.45 (1.42-1.48)	1.40 (1.37-1.43)
	2017	22177	17081506	129.83 (128.12-131.54)	1.44 (1.41-1.47)	1.38 (1.35-1.41)
	2018	23339	17181084	135.84 (134.10-137.58)	1.51 (1.48-1.54)	1.43 (1.40-1.46)
B	2013	11631	14185914	81.99 (80.50-83.48)	1.00 (reference)	1.00 (reference)
	2014	14649	14301827	102.43 (100.77-104.09)	1.25 (1.22-1.28)	1.23 (1.20-1.26)
	2015	16074	14439330	111.32 (109.60-113.04)	1.36 (1.33-1.39)	1.31 (1.28-1.35)
	2016	17469	14583210	119.79 (118.01-121.56)	1.46 (1.43-1.50)	1.40 (1.36-1.43)
	2017	17732	14745712	120.25 (118.48-122.02)	1.47 (1.43-1.50)	1.39 (1.35-1.42)
	2018	18690	14894945	125.48 (123.68-127.28)	1.53 (1.50-1.57)	1.43 (1.40-1.46)
C	2013	5808	12851369	45.19 (44.03-46.36)	1.00 (reference)	1.00 (reference)
	2014	7613	12931217	58.87 (57.55-60.20)	1.30 (1.26-1.35)	1.28 (1.24-1.33)
	2015	8153	13037289	62.54 (61.18-63.89)	1.38 (1.34-1.43)	1.35 (1.30-1.39)
	2016	9137	13140386	69.53 (68.11-70.96)	1.54 (1.49-1.59)	1.49 (1.44-1.54)
	2017	9091	13267028	68.52 (67.12-69.93)	1.52 (1.47-1.57)	1.45 (1.40-1.50)
	2018	9555	13385632	71.38 (69.95-72.81)	1.58 (1.53-1.63)	1.50 (1.45-1.55)

Supplementary Table 3. Risk of severe upper gastrointestinal bleeding in four different subgroups, the Netherlands, from 2013 to 2018 *(continued)*

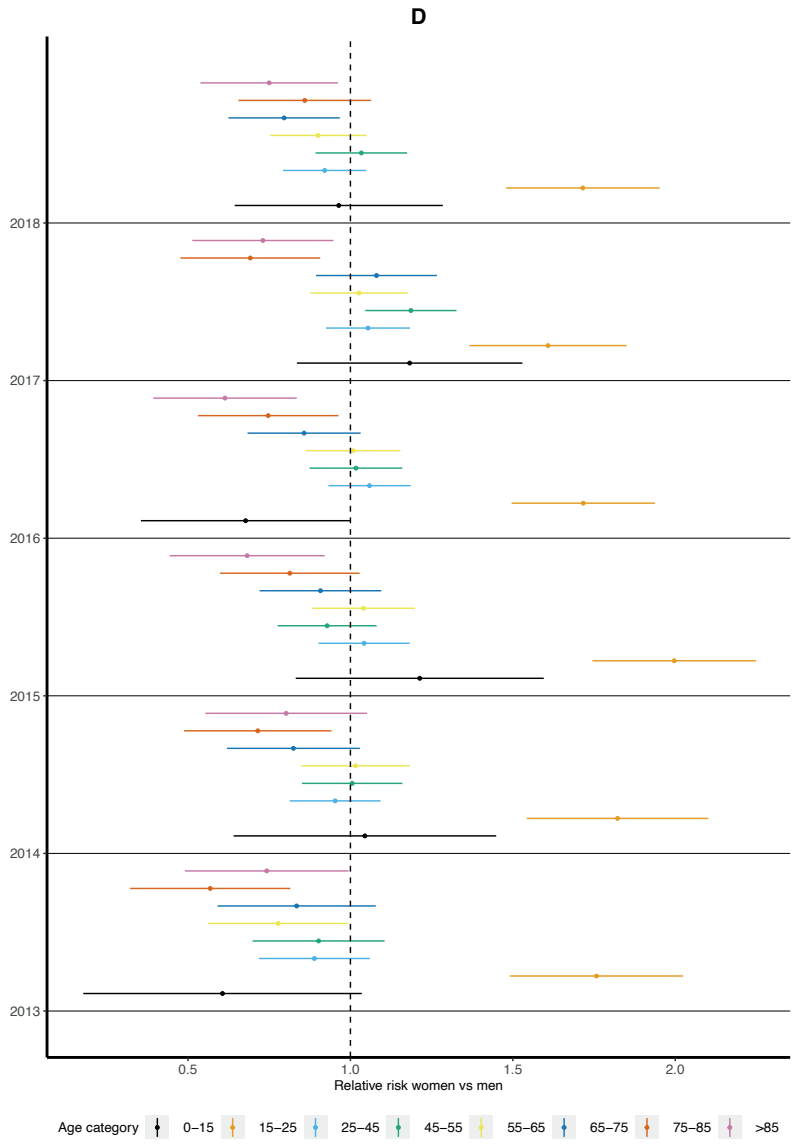
Subgroup	Calendar Year	No.	Total No.	Cumulative incidence event/100,000 inhabitants (95% CI)	Model 1 odds ratio (95% CI)	Model 2 odds ratio (95% CI)
D	2013	2351	10429604	22.54 (21.63-23.45)	1.00 (reference)	1.00 (reference)
	2014	3237	10469429	30.92 (29.85-31.98)	1.37 (1.30-1.45)	1.35 (1.28-1.43)
	2015	3496	10531701	33.20 (32.09-34.30)	1.47 (1.40-1.55)	1.44 (1.36-1.51)
	2016	4082	10592788	38.54 (37.35-39.72)	1.71 (1.63-1.80)	1.65 (1.57-1.74)
	2017	3909	10701190	36.53 (35.38-37.67)	1.62 (1.54-1.71)	1.55 (1.47-1.63)
	2018	4126	10786143	38.25 (37.09-39.42)	1.70 (1.61-1.79)	1.61 (1.53-1.69)

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; UGIB, upper gastrointestinal bleeding. Subgroups: A) total population, B) restricted to the group of individuals without a prescription for NSAIDs, C) restricted to the group of individuals who did not receive a prescription for NSAIDs nor antithrombotic agents, D) restricted to the group of individuals without any medication that is either a risk factor for upper gastrointestinal bleeding or the indication for which the medication is prescribed is one. These are NSAIDs, antithrombotic agents, anticancer medication, systemic corticosteroids, drugs for stomach-acid related disorders, antidepressants, antihypertensives, antidiabetic medication. All medications were identified through prescription reimbursement data, based on their ATC codes. People might have received several medications in a given year, e.g., could have used NSAIDs and antithrombotic agents at the same time in a given year. Incident cases of severe upper gastrointestinal bleeding were identified based on ICD-10CM codes in the hospital admission and death registry. Model 1: logistic regression model where incident severe UGIB was entered as a dependant variable and calendar year as independent variable. Model 2: was Model 1 corrected for age (categorized), and sex imbalances between the cohorts.



Supplementary Figure 2. The risk of severe upper gastrointestinal bleeding in women compared to men in different groups of residents who were unexposed to prescribed nonsteroidal anti-inflammatory drugs and antithrombotic agents (subgroup C), the Netherlands, from 2013 to 2018

Figure shows crude relative risks of annual incidence of severe upper gastrointestinal bleeding in women compared to men (male sex was the reference group) in different age groups among those residents who were unexposed to prescribed nonsteroidal anti-inflammatory drugs and antithrombotic agents (subgroup C).



Supplementary Figure 3. The risk of severe upper gastrointestinal bleeding in women compared to men in different groups of residents who were unexposed to any risk factors (subgroup D), the Netherlands, from 2013 to 2018

Figure shows crude relative risks of annual incidence of severe upper gastrointestinal bleeding in women compared to men (male sex was the reference group) in different age groups among those residents without any medication that is either a risk factor for upper gastrointestinal bleeding or the indication for which the medication is prescribed is one (subgroup D). These are NSAIDs, antithrombotic agents, anticancer medication, systemic corticosteroids, drugs for stomach-acid related disorders, antidepressants, antihypertensives, antidiabetic medication.

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CHAPTER 6

Comparison of two different analgesic prescription strategies and healthcare systems: Slovenia versus the Netherlands

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Abstract

Background

Prescribing practice of pain medication is changing in the Netherlands; opioids are used more often instead of nonsteroidal anti-inflammatory drugs (NSAIDs), therefore we aimed to compare the use of pain medication with Slovenia which has stringent prescribing rules for strong opioids.

Methods

We conducted a cohort study into national prescription databases of the Netherlands and Slovenia covering pharmacy claims between January 1, 2013 and December 31, 2019. In the analysis about 17 million Dutch and 2 million Slovenian residents were included.

Findings

The use of opioids and NSAIDs was higher in Slovenia than in the Netherlands. More frequent use of opioids in Slovenia could be almost entirely explained by weak opioids (about 6% of the population), whereas they were prescribed 50% less frequently in the Netherlands. The opioid use has increased by about 20% in the Netherlands (4.85% and 6.00% of the population in 2013 and 2018, respectively), and the majority of this increase could be explained by strong opioids (4.05% in 2018), specifically, by oxycodone whose use increased by more than 2-fold between 2013 and 2019. In comparison, oxycodone was seldomly used in Slovenia (about 0.3% of the population received a prescription in a year).

Interpretation

When medication use is controlled by stringent prescribing rules, like for strong opioids in Slovenia, the use is lower as compared to when such rules do not exist.

Introduction and rationale

The use of opioids has become wide-spread worldwide and the number of opioid overdoses have risen to such numbers that some countries proclaimed an opioid epidemic [1]. Causes of this increase in opioid use are not well known, but are probably multifactorial. Remarkably, the situation regarding opioid crisis differs between countries, and a probable reason for this is lack of harmonized pain relief guidelines. In 1996, the World Health Organization (WHO) published a revised guideline about the treatment of pain relief in patients with cancer, wherein the now established three-step pain ladder was introduced, which entails a stepwise approach to pain relief, starting with acetaminophen/paracetamol and ending, via nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids for mild to moderate pain, at opioids for moderate to severe pain as a last resort [2,3]. As a response to the uncontrolled rate of opioid overdoses in the United States, a new guideline by the Centers for Disease Control and Prevention was proposed in 2016, that provides recommendations regarding safety of opioid use in the treatment of chronic non-cancer pain [4]. A similar approach was taken by the National Institute for health and Care Excellence that announced a new guideline for chronic pain in 2021, but has not yet been published [5].

In the Netherlands, physicians follow the WHO pain ladder. The guide is supplemented by the pain standard of the general practitioners' society in the Netherlands, and the postoperative pain guideline that was revised in 2013. Since then, the prevalence of opioids and NSAIDs use has changed in the Netherlands. It has been previously reported by our group and others, that the opioid prescription prevalence increased from 814,211 individuals in 2013 to 1,027,019 individuals in 2017 who registered to at least one opioid prescription per calendar year [6,7], while the number of individuals with NSAIDs prescriptions has decreased by n = 255,675 individuals between 2013 and 2017 [8]. Based on the scientific literature it has been evident for some time that the use of NSAIDs is associated with increased risk of gastrointestinal, cardiac and renal complications [9–14], which may have encouraged physicians against NSAIDs prescribing. Moreover, in the 2013 edition of the Dutch postoperative pain guideline, special attention was given to novel opioid analgesic medications with oxycodone being one of them. The working group recommended prescribing morphine and piritramide in treatment of moderate to severe postoperative pain, but also oxycodone when oral intake is possible [9]. This advice may have encouraged Dutch physicians to consider oxycodone as a pain treatment option.

In Slovenia, physicians also follow national guidelines on non-cancer and cancer pain [15,16], which were based on the WHO pain ladder. The prevalence of analgesic prescriptions is routinely checked by the National Institute of Public Health for surveillance purposes [17]. In addition to this guideline, there are special prescribing rules that concern only "strong" opioids, which we define as all registered opioid medications that do not contain tramadol. In other words, "weak" opioids are those opioids that contain either tramadol or tramadol in combination with paracetamol, for which special prescribing rules do not apply. These special prescribing rules are: special hand-written prescription form in a duplicate, compulsory identification both at the doctor's office and in the pharmacy and required age more than 18 years to be able to fill the medication, prescription of the amount that lasts up to 30 days of persistent use, repeat prescription prohibited.

In the current study, we hypothesized that the prevalence of opioid use is lower in Slovenia than in the Netherlands, because of this strict prescription policy regarding strong opioids [18]. In contrast, we expected that the use of NSAIDs is higher in Slovenia compared with the Netherlands, because prescribing restrictions that pertain to strong opioids in Slovenia do not apply to this group of analgesic medication. Therefore, we set out to compare the prevalence of analgesic medications use in the total population of Slovenia and in the Netherlands between 2013 and 2019.

Methods

Setting and Participants

We conducted a nation-wide cohort study for which we analyzed national prescription datasets from the Netherlands and from Slovenia. Vital statistics of the Netherlands are managed by Statistics Netherlands, that collects information on all residents (about 17 million people). Prescription data of Slovenia are collected and managed by the Health Insurance Institute of Slovenia. In this dataset the whole population of Slovenia is covered which is about 2 million people. In this cohort study, we investigated data that pertain to the time between January 1st, 2013 and December 31st, 2019.

This study was exempt from the Medical Ethical Review Committee of Leiden University Medical Center (reference number: G21.033), as well as from the National Medical Ethics Committee of Slovenia after a review (reference number: 0120- 17/2021-3). All personal

information of participants in the Netherlands was identified by third parties prior to analysis. Authorized employee (M.U.) of the Health Insurance Institute of Slovenia had access to personal information of participants, and prepared identified aggregated data prior to analysis. This ensures that no personal information can be disclosed from the results.

Data Sources

The Netherlands

Statistics Netherlands

Prescription reimbursement data were collected for all Dutch residents entitled to pharmaceutical care, i.e., those insured by the basic health insurance which is mandatory by law and covers almost all residents, n = 17,163,404 (99.9%) in 2018 [19]. The Health Care Institute of the Netherlands collects prescription reimbursement data and provides it to Statistics Netherlands. Medication dispensed from outpatient, community pharmacies, and in residential homes for elderly are collected in the national reimbursement database, whereas medicine use in hospitals and in nursing homes is not collected [20]. In the prescription reimbursement database of Statistics Netherlands medications are classified according to the Anatomical Therapeutic Chemical Classification System (ATC) [21], and are made available on the 3rd level (4 position) of the ATC code. These data were at the time of the analysis (in December 2020) published up to and including 2019.

Medicine and Medical Devices Information Project (GIP)

Prescription reimbursement data does not contain information on the level of active substances, i.e., 5th level of the ATC classification, therefore we analyzed the open-source prescription data (GIP) provided by the Health Care Institute of the Netherlands [22]. The Institute is responsible for the content of the GIP data, keeping the data updated as well as its accuracy [23]. The GIP data contains information on all medications reimbursed under the basic health insurance [24]. The information that is publicly available on the GIP database may be used as desired, when the source of the information is declared [25].

Slovenia

Prescription data were collected for all residents of Slovenia entitled to the pharmaceutical care which is insured by the national health insurance that covered almost all residents (about 2 million, 99.97%) throughout the observation time. Prescription data records all medications dispensed from community pharmacies. Medicines used during hospitalization and during outpatient hospital or nursing home encounter are not recorded in this dataset. Note that magistral preparations containing opioids are not recorded in this dataset. All prescriptions for medications were identified based on the 5th level of the ATC classification.

Variables and Outcomes

We performed an analysis into national vital statistics of the Netherlands and of Slovenia, in which all citizens who resided in an individual country at the time of observation, i.e., between January 1st, 2013 and December 31st, 2019, were included. To obtain information on national vital statistics data we utilized publicly available data in both countries. Information on age (stratified into age groups) and sex for the Netherlands was obtained from "StatLine" of Statistics Netherlands [26], and the same information for Slovenia from Statistical Office of the Republic of Slovenia [27].

We identified individuals who received a prescription for a medication and also filled the prescription in a pharmacy. The number of those who received at least one prescription for an analgesic medication in a calendar year was used to calculate annual prevalence, which is the main outcome of this study. We investigated two analgesic medication groups that are represented in the WHO pain ladder, namely opioids, and NSAIDs. Opioid prescriptions were identified based on the ATC code N02A, and NSAIDs prescriptions based on the ATC code M01A. There are substantial differences in the availability of individual active substances in Slovenia and in the Netherlands, however, we classified opioid medications as "strong" and "weak", based on tramadol. When a medication contained tramadol, it was classified as a weak opioid, and otherwise as a strong opioid medication. These opioid groups were defined based on "Medicinal Products Act" in Slovenia, in order to compare the two countries. A comprehensive list of all registered active substances is available in the Supplementary Table 1.

Statistical Methods

We performed a descriptive analysis of the total population in the Netherlands, in Slovenia and in the European Union between 2013 and 2019, and calculated the

total number of residents living in each individual country. Then, we stratified the total population of each individual country by age, which was grouped into five age categories: from 0 to 14 years, from 15 to 24 years, from 25 to 44 years, from 45 to 64 years and more than 65 years, and sex. These results were presented as total numbers and as a proportion of the total population. Then, we identified the number of individuals to whom opioids, and NSAIDs were prescribed and calculated an annual prevalence percentage with corresponding 95% confidence interval (CI) for each individual country through the observation period. To explore time-trends of opioids, and NSAIDs prescriptions in each individual country we calculated relative risks (RR) with corresponding 95% CI in which we selected the calendar year 2013 as a reference. In order to make the annual prevalence calculations as well as the time- trend analysis comparable between the Netherlands and Slovenia, we corrected for demographic differences (age and sex) between these two countries with direct standardization where we utilized the population of European Union of 2013 as weights. We presented results of the latter analysis as standardized prevalence percentage with corresponding 95% CI, and standardized RR with corresponding 95% CI where we took the calendar year of 2013 as a reference. There were no individuals lost to follow-up nor were any data lost in the merging process.

All statistical analyses were performed with SPSS for Windows, release 25.0 (SPSS, Chicago, IL, USA). Figures were created with R studio (A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria, https://www.R- project.org), using R package ggplot2 version 3.2.125 [28]. The STROBE statement checklist for cohort studies was used to guide reporting of the findings.

Results

Participants

In the analysis, all residents of the Netherlands and Slovenia were included. There were n = 2,080,908 individuals registered in Slovenia in 2019. Of these, about a half were women (n = 1,042,252) (Table 1). The age structure was similar in both countries as 47.2% of the Dutch population of 2019 (n = 17,282,163), and 48.5% of the population of Slovenia of 2019 was older than 45 years. Women accounted for about 50% of the total Dutch population and of the Slovenian population throughout the observation period

Table 1. Population characteristics, the Netherlands, Slovenia, and the total population of European Union, from 2013 to 2019

	2013	2014	2015	2016	2017	2018	2019
Slovenia							
Total, No.	2058821	2061085	2062874	2064188	2065895	2066880	2080908
Age groups, years, No. (%)							
0-14	298095 (14.48)	301053 (14.61)	304310 (14.75)	306390 (14.84)	308594 (14.94)	310677 (15.03)	313706 (15.08)
15-24	215937 (10.49)	208493 (10.12)	202709 (9.83)	199154 (9.65)	195820 (9.48)	194130 (9.39)	194795 (9.36)
25-44	595959 (28.95)	592346 (28.74)	586705 (28.44)	581084 (28.15)	574065 (27.79)	565162 (27.34)	563159 (27.06)
45-64	596685 (28.98)	599087 (29.07)	599764 (29.07)	597458 (28.94)	596990 (28.90)	595649 (28.82)	596194 (28.65)
≥65	352145 (17.10)	360106 (17.47)	369386 (17.91)	380102 (18.41)	390426 (18.90)	401262 (19.41)	413054 (19.85)
Sex, No. (%)							
Women	1039760 (50.50)	1040211 (50.47)	1040645 (50.45)	1040855 (50.42)	1040770 (50.38)	1039839 (50.31)	1042252 (50.09)
Men	1019061 (49.50)	1020874 (49.53)	1022229 (49.55)	1023333 (49.58)	1025125 (49.62)	1027041 (49.69)	1038656 (49.91)
The Netherlands							
Total, No.	16779575	16829289	16900726	16979120	17081507	17181084	17282163
Age groups, years, No. (%)							
0-14	2877922 (17.15)	2850074 (16.94)	2827066 (16.73)	2799772 (16.49)	2781768 (16.29)	2762624 (16.08)	2739819 (15.85)
15-24	2049538 (12.21)	2058275 (12.23)	2070025 (12.25)	2084673 (12.28)	2101648 (12.30)	2116813 (12.32)	2131944 (12.34)
25-44	4333861 (25.83)	4287658 (25.48)	4242279 (25.10)	4217738 (24.84)	4214276 (24.67)	4222614 (24.58)	4255450 (24.62)
45-64	4693909 (27.97)	4714258 (28.01)	4753671 (28.13)	4791629 (28.22)	4824155 (28.24)	4839917 (28.17)	4840946 (28.01)
≥65	2824345 (16.83)	2919024 (17.34)	3007685 (17.80)	3085308 (18.17)	3159660 (18.50)	3239116 (18.85)	3314004 (19.18)
Sex, No. (%)							
Women	8472236 (50.49)	8494904 (50.48)	8527868 (50.46)	8561985 (50.43)	8606405 (50.38)	8654043 (50.37)	8701077 (50.35)
Men	8307339 (49.51)	8334385 (49.52)	8372858 (49.54)	8417135 (49.57)	8475102 (49.62)	8527041 (49.63)	8581086 (49.65)
European union							
Total, No.	505163008	507235091	508520205	510181874	511378572	512372000	513471676
Age groups, years, No. (%)							
0-14	79062512 (15.65)	79237403 (15.62)	79315276 (15.60)	79444690 (15.57)	79650613 (15.58)	79768888 (15.57)	79747760 (15.53)
15-24	58155625 (11.51)	57492742 (11.33)	56860113 (11.18)	56488882 (11.07)	55937539 (10.94)	55439958 (10.82)	55182710 (10.75)
25-44	138653493 (27.45)	137929625 (27.19)	136997167 (26.94)	136448198 (26.75)	135513904 (26.50)	134679168 (26.29)	133997808 (26.10)

Table 1. Population characteristics, the Netherlands, Slovenia, and the total population of European Union, from 2013 to 2019 *(continued)*

	2013	2014	2015	2016	2017	2018	2019
45-64	137344767 (27.19)	138548592 (27.31)	139343781 (27.40)	140066955 (27.45)	140798128 (27.53)	141343811 (27.59)	141781802 (27.61)
>65	91946611 (18.20)	94026729 (18.54)	96003868 (18.88)	97733149 (19.16)	99478388 (19.45)	101140175 (19.74)	102761596 (20.01)
Sex, No. (%)							
Women	258781338 (51.23)	259724441 (51.20)	260301222 (51.19)	260886459 (51.14)	261414441 (51.12)	261841054 (51.10)	262332762 (51.09)
Men	246381670 (48.77)	247510650 (48.80)	248218983 (48.81)	249295415 (48.86)	249964131 (48.88)	250530946 (48.90)	251138914 (48.91)

(Table 1). Demographic characteristics of both Slovenia and the Netherlands are similar to the population of European Union of 2013 that was selected to standardize the annual prevalence of different analgesic medications.

Annual prevalence of opioids and NSAIDs prescription

Generally, Slovenian residents received more pain medication compared to residents of the Netherlands (Figure 1).

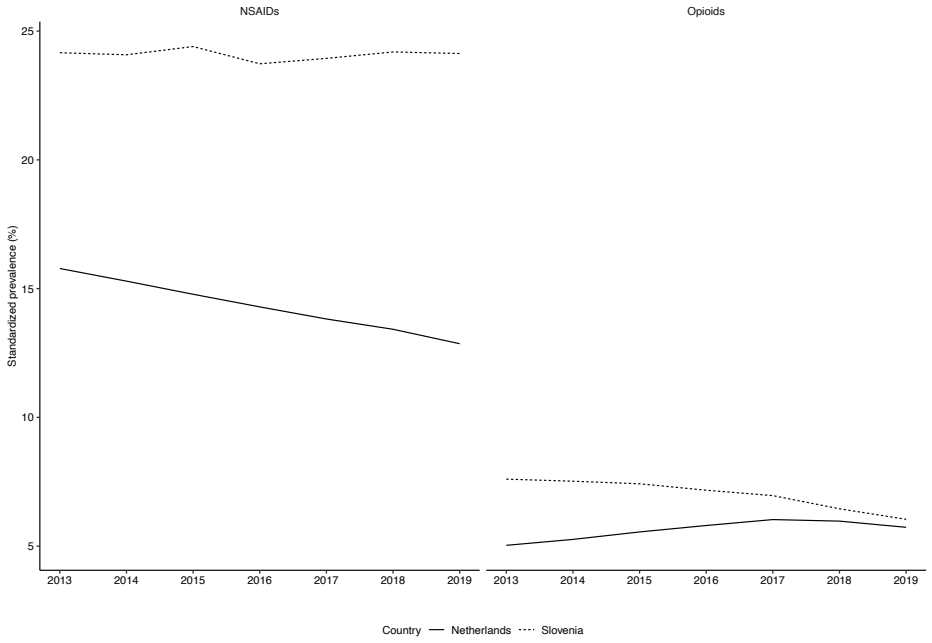

Figure 1. Standardized prevalence of opioid, NSAIDs and other analgesic medication use in the Netherlands and in Slovenia, from 2013 to 2018(9)

In Slovenia, 6.79% [95% CI, 6.75–6.82] of residents received at least one prescription for an opioid in 2018, which was 6.00% [95% CI, 5.99–6.01] in the Netherlands in the same calendar year. However, prescription opioid use is decreasing in Slovenia (standardized RR, 0.85 [95% CI, 0.84–0.85], comparing 2018 with 2013). In the Netherlands prescription opioid use is increasing over the time frame (standardized RR, 1.19 [95% CI, 1.18–1.19], comparing 2018 with 2013) (Figure 1, Supplementary Table **2**). The more frequent use of prescription opioids in Slovenia could be almost entirely explained by weak opioids

(~6%), whereas in the Netherlands weak opioids were less frequently prescribed (~3%) (Figures 2, 3). The majority of the increase in prescription opioid use in the Netherlands could be explained by strong opioids (RR, 1.70 [95% CI, 1.69–1.70]), specifically, by oxycodone that was prescribed to about 2% Dutch residents in 2019 (Figure 3). The prevalence of oxycodone prescription increased more than 2-fold between 2013 and 2019 in the Netherlands. In comparison, oxycodone was barely used in Slovenia throughout the observation period (about 0.3% of the population received a prescription for oxycodone in a year's time).

NSAIDs, nonsteroidal anti-inflammatory drugs. Opioids were identified based on the ATC code N02A, NSAIDs based on the M01A and other analgesic medication based on the N02B. Prevalence was corrected for age- and sex- differences between Slovenia in the Netherlands with direct standardization where we utilized the population of the European Union of 2013 as weights.

There were also differences between these two countries when comparing NSAIDs use (Figure 1). In 2018, about 25% of the Slovenian population and about 13% of the Dutch population received at least one prescription for NSAIDs medication (Figure 1, Supplementary Table 2). In the Netherlands the use of NSAIDs prescriptions has decreased since 2013 (standardized RR, 0.85 [95% CI, 0.85–0.85], comparing 2018 with 2013), whereas in Slovenia it remained unchanged throughout the observation time (standardized RR, 1.00 [95% CI, 1.00–1.01], comparing 2018 with 2013) (Figure 1, Supplementary Table 2).

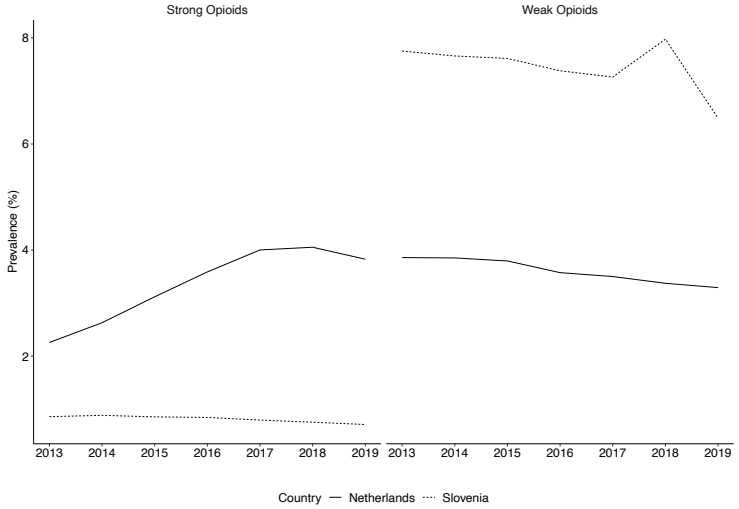

Figure 2. Prevalence of strong and weak opioids use in the Netherlands and in Slovenia, from 2013 to 2019

Opioids were identified based on the ATC code N02A, strong opioids were defined as all opioids except tramadol. There are differences in the availability of individual substances in each country. These differences can be found in the Supplementary Table 1.

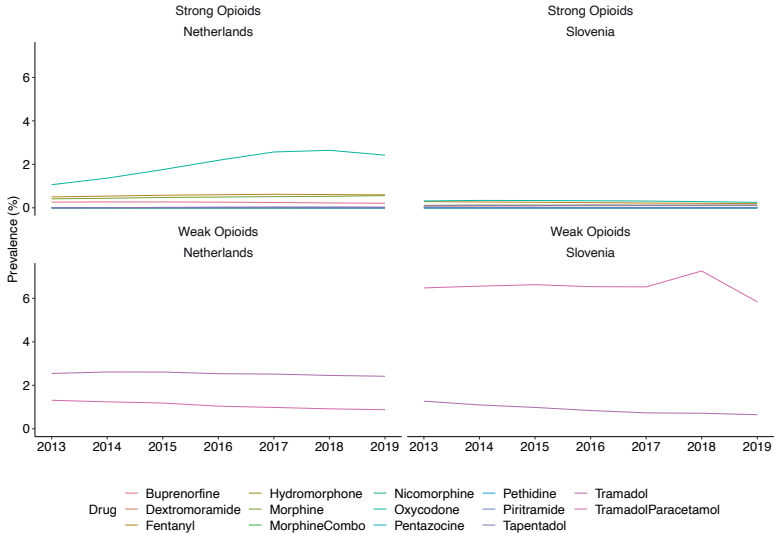

Figure 3. Prevalence of individual opioids in the Netherlands and in Slovenia, from 2013 to 2019

Opioids were identified based on the ATC code N02A, strong opioids were defined as all opioids except tramadol. There are differences in the availability of individual substances in each country. These differences can be found in the Supplementary Table 1.

Discussion

In this analysis we set out to compare the annual prevalence of pain medication use in Slovenia and in the Netherlands between January 1st, 2013 and December 31st, 2019. In order to make the comparison between these two countries accurate, we corrected pain medication use for demographic differences (age and sex) with direct standardization. We discovered that the annual prevalence of opioids, and NSAIDs, was higher in Slovenia compared with the Netherlands throughout the observation period. However, strong opioid use trends investigated between 2013 and 2019 pointed in the opposite direction when these two countries were compared.

Throughout the observation period, opioid use in Slovenia has decreased between 2013 and 2019 (standardized RR, 0.80 [95% CI, 0.79–0.80], 2019 compared with 2013, prevalence of opioid use in the general population was 6% in 2019), which could be in its entirety explained by a decrease in prescription of tramadol in combination with acetaminophen/paracetamol (n = 121,534, 5.84%). In the Netherlands the use of opioids has increased by 20% between 2013 and 2017 and plateaued out in 2018 (standardized RR, 1.19 [95% CI, 1.18–1.19] when comparing 2018 with 2013), and the prevalence of opioid use in the general population was 6% in 2018. The increase in opioid prescription in the Netherlands can be explained almost entirely by oxycodone (n = 418,707, 2.42% in 2019) and tramadol (n = 417,649, 2.42% in 2019) use. However, the use of tramadol has been steadily decreasing since 2013 (RR, 0.95 [95% CI, 0.95–0.95] comparing 2019 with 2013), whereas the use of oxycodone increased more than 2-fold (RR, 2.28 [95% CI, 2.27–2.29], comparing 2019 with 2013). Approximately the same proportion of residents received an opioid prescription in Slovenia in 2019 as in the Netherlands in 2018. This finding is in contrast with our hypothesis, where we expected that the use of opioid medications would be higher in the Netherlands than in Slovenia.

The analysis into individual opioid medications revealed that prescription of weak and strong opioids differed between countries. The following reasons can potentially explain these findings: First, in Slovenia prescribing of strong opioids is strictly regulated by the Medicinal Products Act and requires a special prescription form. This procedure is rather complicated and time-consuming, i.e., it needs to be in a paper format, either hand-written or printed, and an entry in the book of narcotics needs to be made, which ensures full traceability of the prescribed opioid [10,18]. In Figures 2,

3 we demonstrated that almost all opioid prescriptions in Slovenia can be explained by prescribing tramadol in combination with acetaminophen/paracetamol, which is a weak opioid (also in a lower dose) and therefore not strictly regulated. In contrast in the Netherlands, opioid prescription is not as strictly regulated compared to Slovenia with less time-consuming regulations. This suggests that applying strict prescription rules for strong opioids may lead to a lower prescription rate of strong opioids.

Second, in the Netherlands the prescription of strong opioids, especially oxycodone, is recommended as demonstrated on the example of the revised postoperative pain guideline [9]. This suggests that the threshold for receiving a prescription for a strong opioid is lower in the Netherlands compared to Slovenia. Additionally, many patients who receive tramadol experience gastrointestinal disturbances [29], which may have inspired Dutch physicians to prescribe less tramadol while at the same time oxycodone was advertised as a safer opioid option [30]; the use of oxycodone skyrocketed and the use of tramadol plateaued [31].

Third, the difference in opioid prescription can be explained by the difference between countries in the quantity and duration of the prescribed opioids. In Slovenia, physicians are not allowed to prescribe strong opioids for longer than 30 days. In contrast, there are no restrictions on the length of dosing imposed in the Netherlands [10,18]. Prescribing a strong opioid on repeat prescription enables a patient to have a continuous prolonged access to the opioid medication without consulting with a medical professional. Although, the pain guideline of the general practitioners' society in the Netherlands advises on evaluation of opioid use every 1–2 weeks [10], 16.8% of patients still received a prescription for a strong opioid for more than 90 days of consistent use [32].

We also observed differences in the use of NSAIDs between the two countries. Every one in four residents in Slovenia and about one in seven residents in the Netherlands received at least one prescription for NSAIDs medication in a year's time. The number of individuals to whom NSAIDs were prescribed has steadily decreased for the past decade in the Netherlands, while their use in Slovenia remained stable. A possible explanation for this could be that in the Netherlands physicians put greater emphasis on their unfavorable adverse events profile [8,33], as well as advise patients' to buy NSAIDs over-the-counter since the most clinically useful strength, 400mg,

is not reimbursed by the basic health insurance [24]. Furthermore, the increase in prescriptions of strong opioids may have led to less indications to prescribe NSAIDs.

To fully understand differences between Slovenia and the Netherlands we must also explore differences in healthcare systems. In Slovenia there is a great emphasis on prevention and complementary medicine, for example physical therapy, including exercise, hydro therapy, and psychological support [34]. In general, it is more acceptable to make use of treatments that may not be as cost effective in pain relief and may take longer time as compared to taking a pill, but they are in fact more patient-friendly. This is as opposed to the Netherlands where the healthcare system is cost-driven and this holistic approach has been partly cut from the healthcare budget [35]. Additionally, in the Netherlands standards of hospital care among others include level of pain as perceived by hospitalized patients. This means, that hospitals, according to a survey were able to keep their patients' pain levels low, were awarded with better rating compared to those hospitals where patients experienced more pain while hospitalized [36]. Hence, to achieve better hospital performance Dutch physicians may prescribe more strong pain medication to efficiently combat pain.

This research has some methodological issues that warrant a comment. First, we have no information about the indication for which the medication was prescribed, the amount, dose, nor for how long the medication was used. Therefore, calculation of defined daily doses as well as morphine milligram equivalents is not possible. Second, there may be other discrepancies, measured and unmeasured, between countries that could further explain differences in the use of pain relief medication, however such information is not known to us. Third, we do not have information on over-the-counter medication use, therefore use especially of NSAIDs is most probably underestimated. Opioids are in general not available as an over-the-counter medication; the only exception is codeine that can be bought as pain medication in small doses in Slovenia, and is available as antitussive medication in the Netherlands.

In conclusion, the use of strong opioids is increasing in the Netherlands and it is decreasing in Slovenia over the same time frame. The majority of opioid use in Slovenia can be explained by tramadol in combination with paracetamol, as opposed to the Netherlands where the majority of individuals receive either a prescription for oxycodone or tramadol. The use of strong opioids, especially, oxycodone is very low in Slovenia, whereas in the Netherlands use is high and increasing. One of the reasons for

differences in strong opioid use in both countries could be explained by differences in prescribing practice of strong opioids, which is very stringent in Slovenia and much more lenient in the Netherlands. We demonstrated that prescribing strategies of analgesic medication differ substantially between countries in Europe. It is our opinion that the field of guidelines in the treatment of pain warrant further inquiries to be able to achieve consensus in pain treatment and could become a foundation for harmonized guidelines.

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Supplement to: Comparison of two different analgesic prescription strategies and healthcare systems: Slovenia versus the Netherlands

Supplementary Table 1. Reimbursed pain medication in the Netherlands and in Slovenia from 2013 to 2019

ATC	INN	strong/weak opioid	Reimbursed in Slovenia	Reimbursed in the Netherlands
N02AA01	Morphine	strong	yes	yes
N02AA03	Hydromorphone	strong	yes	yes
N02AA04	Nicomorphine	strong	no	yes
N02AA05	Oxycodone	strong	yes	yes
N02AA51	Morphine combinations	strong	no	yes
N02AB02	Pethidine	strong	no	yes
N02AB03	Fentanyl	strong	yes	yes
N02AC01	Dextromoramide	strong	no	yes
N02AC03	Piritramide	strong	no	yes
N02AD01	Pentazocine	strong	no	yes
N02AE01	Buprenorphine	strong	yes	yes
N02AX06	Tapentadol	strong	yes	yes
N02AJ13	Tramadol with paracetamol	weak	yes	yes
N02AX02	Tramadol	weak	yes	yes
M01AA01	Phenylbutazone	NA	no	yes
M01AB01	Indomethacin	NA	yes	yes
M01AB05	Diclofenac	NA	yes	yes
M01AB08	Etodolac	NA	yes	no
M01AB16	Aceclofenac	NA	no	yes
M01AB55	Diclofenac, combinations	NA	yes	yes
M01AC01	Piroxicam	NA	no	yes
M01AC06	Meloxicam	NA	yes	yes
M01AE01	Ibuprofen	NA	yes	yes (not 400 mg)
M01AE02	Naproxen	NA	yes	yes
M01AE03	Ketoprofen	NA	yes	yes
M01AE11	Tiaprofenic acid	NA	no	yes
M01AE17	Dexketoprofen	NA	yes	yes
M01AE52	Naproxen and esomeprazole	NA	no	yes
M01AH01	Celecoxib	NA	yes	yes
M01AH05	Etoricoxib	NA	yes	yes
M01AX01	Nabumeton	NA	no	yes
M01AX17	Nimesulid	NA	yes	no

Abbreviations: ATC, anatomical therapeutic classification; INN, international non-proprietary name

Supplementary Table 2. (Standardized) prevalence of pain medication use, the Netherlands and Slovenia, 2013-2018(9)

Opioid prescriptions per country	Year	No.	Total No.	Prevalence (95% CI)	Prevalence (95% CI), standardized	RR (95% CI)	RR (95% CI), standardized
Slovenia	2013	155991	2058821	7.58 (7.54-7.61)	7.60 (7.56-7.64)	1 (reference)	1 (reference)
	2014	155961	2061085	7.57 (7.53-7.60)	7.52 (7.48-7.55)	1.00 (0.99-1.01)	0.99 (0.98-1.00)
	2015	155677	2062874	7.55 (7.51-7.58)	7.42 (7.38-7.45)	1.00 (0.99-1.00)	0.98 (0.97-0.98)
	2016	152348	2064188	7.38 (7.34-7.42)	7.17 (7.13-7.21)	0.97 (0.97-0.98)	0.94 (0.94-0.95)
	2017	149592	2065895	7.24 (7.21-7.28)	6.96 (6.92-6.99)	0.96 (0.95-0.96)	0.92 (0.91-0.92)
	2018	140301	2066880	6.79 (6.75-6.82)	6.45 (6.41-6.48)	0.90 (0.89-0.90)	0.85 (0.84-0.85)
	2019	133608	2080908	6.42 (6.39-6.45)	6.04 (6.01-6.07)	0.85 (0.84-0.85)	0.80 (0.79-0.80)
The Netherlands	2013	814211	16779575	4.85 (4.84-4.86)	5.03 (5.02-5.04)	1 (reference)	1 (reference)
	2014	863110	16829289	5.13 (5.12-5.14)	5.26 (5.25-5.28)	1.06 (1.05-1.06)	1.05 (1.04-1.05)
	2015	921763	16900726	5.45 (5.44-5.46)	5.55 (5.53-5.56)	1.12 (1.12-1.13)	1.10 (1.10-1.11)
	2016	975990	16979120	5.75 (5.74-5.76)	5.80 (5.79-5.81)	1.18 (1.18-1.19)	1.15 (1.15-1.16)
	2017	1027019	17081507	6.01 (6.00-6.02)	6.03 (6.01-6.04)	1.24 (1.24-1.24)	1.20 (1.19-1.20)
	2018	1030529	17181084	6.00 (5.99-6.01)	5.97 (5.96-5.99)	1.24 (1.23-1.24)	1.19 (1.18-1.19)
	2019	999699	17282163	5.78 (5.77-5.80)	5.73 (5.72-5.74)	1.19 (1.19-1.20)	1.14 (1.14-1.14)
NSAIDs prescriptions per country							
Slovenia	2013	500595	2058821	24.31 (24.26-24.37)	24.16 (24.09-24.23)	1 (reference)	1 (reference)
	2014	501206	2061085	24.32 (24.26-24.38)	24.08 (24.02-24.15)	1.00 (1.00-1.00)	1.00 (0.99-1.00)
	2015	509224	2062874	24.69 (24.63-24.74)	24.40 (24.33-24.46)	1.02 (1.01-1.02)	1.01 (1.01-1.01)
	2016	496742	2064188	24.06 (24.01-24.12)	23.73 (23.67-23.80)	0.99 (0.99-0.99)	0.98 (0.98-0.99)
	2017	502158	2065895	24.31 (24.25-24.37)	23.94 (23.87-24.00)	1.00 (1.00-1.00)	0.99 (0.99-0.99)
	2018	508271	2066880	24.59 (24.53-24.65)	24.19 (24.12-24.26)	1.01 (1.01-1.01)	1.00 (1.00-1.01)
	2019	510234	2080908	24.52 (24.46-24.58)	24.13 (24.06-24.20)	1.01 (1.01-1.01)	1.00 (0.99-1.00)

Supplementary Table 2. (Standardized) prevalence of pain medication use, the Netherlands and Slovenia, 2013-2018(9) *(continued)*

Opioid prescriptions per country	Year	No.	Total No.	Prevalence (95% CI)	Prevalence (95% CI), standardized	RR (95% CI)	RR (95% CI), standardized
The Netherlands	2013	2600896	16779575	15.50 (15.48-15.52)	15.78 (15.77-15.80)	1 (reference)	1 (reference)
	2014	2535617	16829289	15.07 (15.05-15.08)	15.29 (15.27-15.31)	0.97 (0.97-0.97)	0.97 (0.97-0.97)
	2015	2469770	16900726	14.61 (14.60-14.63)	14.78 (14.76-14.80)	0.94 (0.94-0.95)	0.94 (0.93-0.94)
	2016	2405557	16979120	14.17 (14.15-14.18)	14.29 (14.27-14.31)	0.91 (0.91-0.92)	0.91 (0.90-0.91)
	2017	2345221	17081507	13.73 (13.71-13.75)	13.82 (13.80-13.84)	0.89 (0.88-0.89)	0.88 (0.87-0.88)
	2018	2294707	17181084	13.36 (13.34-13.37)	13.42 (13.40-13.44)	0.86 (0.86-0.86)	0.85 (0.85-0.85)
	2019	2217218	17282163	12.83 (12.81-12.85)	12.86 (12.84-12.88)	0.83 (0.83-0.83)	0.81 (0.81-0.82)

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CHAPTER 7

Opioid epidemic: lessons learned and updated recommendations for misuse involving prescription versus non-prescription opioids

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Abstract

Introduction

In the past decades, the opioid crisis heavily impacted parts of the US society and has been followed by increase in use of opioids worldwide. It is of paramount importance that we explore the origins of the US opioid epidemic to develop best practices to tackle the rising tide of opioid overdoses.

Areas covered

In this expert review we discuss opioid (over)prescription, change in perception of pain, and false advertisement of opioid safety as the leading causes of the US opioid epidemic. Then, we review the evidence about opioid dependence and addiction potential, and provide current knowledge about predictors of aberrant opioid-related behavior. Lastly, we discuss different approaches that were considered or undertaken to combat the rising tide of opioid-related deaths by regulatory bodies, pharmaceutical companies and health-care professionals. For this expert review we considered published articles relevant to the topic under investigation that we retrieved from Medline or Google scholar electronic database.

Expert opinion

The opioid epidemic is a dynamic process with many underlying mechanisms. Therefore, no single approach may be best suited to combat it. In our opinion, the best way forward is to employ multiple strategies to tackle different underlying mechanisms.

Background on the opioid crisis

In the United States (US) and other countries worldwide, the use of opioids has risen substantially in the past couple of decades [1]. According to a survey conducted between 1998 and 2016 in Boston, Massachusetts, US, approximately 5% of their inhabitants, representative of the US general population, used an opioid in the seven days preceding the interview [2]. In addition, opioids were prescribed to about 6% of the Dutch population at some time during a one-year period (2017) [3], to about 8% of the population in any Scandinavian country per year (period from 2006 and 2017) [4], and to about 9% of the general population (of age between 16 and 59 years) in a year's time in England and Wales (between 2006 and 2019) [5]. Although the use of (prescribed and illicit) opioids in Europe (in absolute numbers) is not as widespread as in the US yet [6], it affects more people each year. According to the European Pain Federation (EFIC), there is no evidence of an opioid crisis across countries in Europe at the present time [6]. However, a clear association between the use of opioids and opioid-involved overdose deaths has been established [7], so the upward trend in prescribing rates warrants prudent opioid prescribing and close monitoring of opioid overdose deaths in Europe and elsewhere. Here, healthcare professionals play a key role as they alone can guarantee appropriate, safe opioid therapy, when necessary, educate patients about harms, and prevent opioid use when the risks outweigh the benefits and there is no clear indication for prescribing opioids.

In this expert review, we will first discuss the historic events leading to the opioid crisis in the US and its changing characteristics since 1999. The intention here is to understand and to reflect upon the events that jointly brought about the health care crisis in the US (as a case study). We will also discuss addictive properties of opioid medications and factors that are associated with opioid use disorder, although the evidence is not always unambiguous. Lastly, we will discuss the measures that were undertaken to combat the rising tide of opioid overdose deaths in the US, from which we can learn to best prevent the next health care crisis elsewhere.

The (three) waves of the US opioid epidemic

The opioid crisis in the US has been closely monitored since 1999. It is generally accepted that it consists of three distinct waves: a first wave since 1999, a second wave since 2010, and third wave from 2013 onwards (the three waves are depicted in Figure 1) [8–15]. The first wave of the crisis was characterized by an increase in death

rates by commonly prescribed opioids (prescription opioid line in Figure 1) [8,13]. The next wave of the crisis was triggered by an increase in heroin use [9], and the last wave was initiated by an increase in the use of synthetic opioids (fentanyl and congeners), obtained either by prescription or illicitly [10–12].

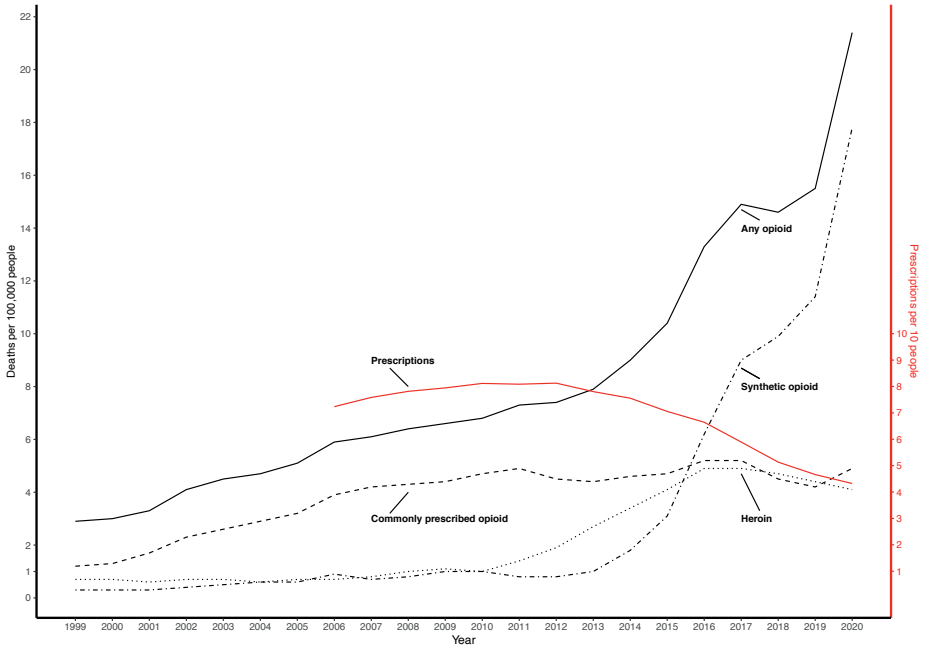

Figure 1. Opioid overdose deaths and opioid prescription rates in the United States, 1999-2019

Figure was created based on publicly available data provided by the Centers of Disease Control and Prevention, US [13,16]. A similar figure is freely available and can be found on the website of the Centers of Disease Control and Prevention. [17] This figure shows the age adjusted annual death rates using the direct method and standard population (n= 2,000 individuals) between 1999 and 2020. Deaths are classified using the International Classification of Diseases, Tenth Revision (ICD-10). Drug overdose deaths are identified using underlying cause of death codes X40-X44, X60-X64, X85, and Y10-Y14. Some deaths may involve multiple opioid drugs. Furthermore, with the red line and by the right-side y-axis the annual prescription rates of opioids per 10 US residents is depicted. The annual prescription rate was calculated based on the number of dispensed opioid prescriptions in a calendar time and the size of the US population.

In more recent years, the US opioid epidemic seems to have transformed once again. In 2018, a brief decrease in overdose deaths was followed by an increase (Figure 1) that persisted until and including 2020 (the last reported rate of opioid overdose deaths) when over 20 deaths per 100,000 individuals were reported [13,14]. Based on this finding, it has been proposed that another wave, the fourth wave, has commenced in the US [15]. The recent rise in overdose deaths has been characterized by use of stimulants, methamphetamine and cocaine, and by concomitant use of stimulants and opioids, still mostly synthetic (e.g., benzo dope, a combination of fentanyl and etizolam; tranq dope, a combination of fentanyl and xylazine) [18].

The US opioid crisis – the perfect storm

Available evidence suggests that the US opioid epidemic was initiated by (over) prescribing of opioids in the 1990s and 2000s [8,19]. Any increase in use of a substance is either stimulated by an increase in demand, e.g., people are in more pain and therefore require more analgesics, or supply has suddenly increased. In the first wave of the US opioid crisis both demand and supply were altered in a way that has resulted in widespread opioid use.

Changed perception of pain and false reassurance of opioid effectiveness and safety

Since the 1960s, many efforts have been made to prioritize pain management in patient care [20]. The World Health Organization (WHO) added opioids to the Model list of essential medicines in 1977, which further cemented the unique position opioids hold in modern medicine [21]. Later, in 1986, the Expert Committee on Cancer Pain Relief and Active Supportive Care introduced the WHO 'pain ladder' for the treatment of malignant pain [22]. The novelty of the WHO Pain ladder was in the stepwise approach to pain management – starting with a non-opioid analgesic, continuing with weak opioids for a mild to moderate pain, and as a last resort, strong opioids for moderate to severe pain. The end goal of the proposed approach was a pain-free patient [22]. Unfortunately, being completely pain-free is unattainable for many chronic pain-inducing conditions. Here, reduction of pain and thus quality of life improvement may be of greater importance to the patients [23–26].

A discussion about the efficacy and particularly the safety of opioids in the treatment of chronic non-malignant pain started with a rather short letter published in the ***New England Journal of Medicine*** in 1980, reporting that just 4 out of about 12,000

hospitalized patients (less than 0.1%), who received at least one opioid during their hospitalization and had no prior history of addiction, developed addiction [27]. Unfortunately, the message of this letter was misinterpreted by many, including pharmaceutical companies, and it was falsely assumed that addiction is rare in patients receiving opioids in all settings [28]. Thereafter, at a meeting of the American Pain Society (APS) in 1995, James Campbell gave a talk about benefits and safety of opioid analgesics in the treatment of chronic non-malignant pain [29]. Later that year, the APS published the 'Quality improvement guidelines for the treatment of acute and cancer pain', further cementing the 'safe and effective' policy of opioids in the treatment of chronic non-malignant pain [30]. Furthermore, the APS proclaimed pain as a "fifth vital sign" in 1996, joining body temperature, pulse rate, respiration rate, and blood pressure in the assessment of one's wellbeing, while other countries followed suit [31]. In 2001, the Joint Commission for Accreditation of Healthcare Organizations (JCAHO; from now on mentioned as the Joint Commission) published a new pain management standard that changed the standard of care by making adequate pain relief a patient's right, by improving education and training of healthcare professionals about pain relief, and by emphasizing the importance of qualitative pain assessment and safe pain management [32]. Although the intention of the JCAHO standard was not to overtreat pain, it did probably have such an effect [33]. A close reader may have noticed that the strategy to combat pain (including educational material) proposed by the WHO never concerned non-malignant pain, but it is still widely used as the goal for the treatment of any type of pain (including non-malignant pain) in medical schools worldwide. Only recently, new guidelines concerning just chronic non-malignant pain are being developed [34,35].

The APS had a key role in the US opioid epidemic – by advising 'safe and effective' opioid pain treatment they drove sales of opioid analgesics, manufactured by different pharmaceutical companies, including Purdue Pharma [36,37]. The APS was dissolved in 2019 after facing several lawsuits due to their financial ties with the pharmaceutical industry [38]. Furthermore, the pharmaceutical industry, particularly Purdue Pharma, employed an aggressive marketing strategy to promote oxycodone (OxyContin®) prescription for treatment of chronic non-malignant pain, while the addictive properties of the medication were downplayed. Addiction to OxyContin® was considered highly unlikely, a claim that was mostly based on the letter by Porter and Jick [27], as well as assumed because of the controlled-release formulation of OxyContin® [39]. However, it has been shown that controlled-release formulations do

not have favorable safety profiles over other formulations [40]. When controlled-release oxycodone was introduced in clinical practice in Ontario, Canada, the associated overdose mortality increased about five-fold between 2000 and 2003 [41]. Physicians were led to believe (by the pharmaceutical industry, and the medical and scientific community) that opioids have low addictive potential that provided false reassurance of opioid safety profile in the treatment of chronic non-malignant pain. This is considered to be one of the reasons behind the US opioid epidemic [28].

Further deterioration of opioid use

Given the above, it is evident that the stage was set for the supply of opioids to follow the increasing demand, creating the perfect storm. In addition to over-prescription of opioids, drug diversion, i.e., use for other purposes than intended by the prescribing physician, contributed to uncontrolled opioid use in the US [42,43]. Diversion happened both at the level of a patient and of a prescriber. First, the patients were able to acquire a prescription from a second physician when the initial opioid treatment was stopped by their personal physician ('doctor shopping') [44], and second, some medical professionals (physicians and pharmacists) identified the increased demand for opioids as an ideal business opportunity. They began selling opioid prescriptions and opioids themselves ('pill mills') [45]. However, the transition towards problematic opioid use did not stop there; patients to whom opioid were prescribed began distributing their analgesic medication to family and friends with an intention to help them ease their pain or for financial gains. Kennedy-Hendricks et al. [46] reported that about 20% of all participants in their study shared their prescribed opioids with others, mostly with the intention to help alleviate their pain. Abusers of prescription opioids considered their behavior to be safer compared with the use of illicit opioids, e.g., heroin, because their opioids were licensed by the medication authority and are therefore "legal". Furthermore, they contained predictable doses (unlike illicit drugs) so their overdose potential was considered lower [47].

Subsequently, probably due to prescription monitoring programs and efforts to close 'pill mills' [47], the use of heroin and synthetic opioids increased, and the number of opioids overdose deaths associated with them quadrupled (Figure 1) [13]. Initially, heroin and illicit synthetic opioids were used by those initially misusing prescription opioids [48]. However, the increase in demand did not go unnoticed by manufacturers of illicit drugs, and they increased the supply of illicit opioids. In 2015, first-time opioid users were 4-times as likely to initiate opioid use with heroin than they were in 2005

[49]. Since the first wave of the opioid epidemic in 1999, it has been estimated that collectively more than 800,000 people died from a drug overdose in the US [50]. Currently, opioids are the main cause of drug overdose deaths with opioid overdoses accounting for about 70% of all drug overdose deaths in 2019 [51]. In 2016 alone more than 60,000 lives were lost due to an opioid overdose, after which the US opioid epidemic was declared a national emergency by President Donald Trump [52,53].

However, opioid use is not only associated with fatal opioid overdoses but also with non-fatal opioid overdose [54], increased risk of motor vehicle accidents [55], falling from standing height [56], addiction [57], tolerance [58], and many more. Besides that, opioid use disorder impairs the physical and mental component of the quality of life [59], and causes members of the active population to miss on average 29 workdays per year (work absenteeism) compared with those without an opioid use disorder [60]. Finally, the cost of opioid epidemic in the US was estimated to be about one trillion US dollars in 2017 alone [61].

Although the decision to include opioids within the armamentarium of pain management for chronic non-malignant pain was not based on sound scientific evidence [34], opioids are often prescribed to treat pain not related to cancer for longer periods of time despite the clear and well-known association between prolonged opioid use (more than 3 months) and opioid dependence and abuse [62].

What makes opioids prone to abuse?

Modern medicine relies heavily on opioids; without opioids anesthesia and management of postoperative pain would be more difficult and perhaps even impossible. The chemical structure of opioids shares many similarities with endogenous opioid receptor ligands. These ligands specifically bind to opioid receptors that are ubiquitously present throughout the central nervous system [63–65]. The biologic effects of opioids are considerable, and the individual biologic response to them varies considerably [66–68]. The complexity and the role of the pharmacokinetics and pharmacodynamics of opioids in the development of analgesic and adverse effects has been given much attention in the literature and is discussed in detail elsewhere [69–72]. Here we provide an overview of the mechanisms that are involved in short- and long-term adaptations to repeated activation of opioid receptors and other targets,

to guide the discussion about the potential of opioids to produce tolerance and addiction.

Short- and long-term adaptations to opioid use

Tolerance

Cellular changes in response to opioids use begin immediately after the initial exposure. Opioids bind to opioid receptors, which are G-protein-coupled receptors, that upon activation regulate many downstream biochemical pathways [73]. Both cytoplasmic G-protein subunits of the receptor interact with several cellular-effector mechanisms, inhibiting adenylyl cyclase and voltage-gated calcium channels, and stimulating inwardly rectifying potassium channels (GIRKs) and phospholipase C beta (PLCB) [74,75]. Ultimately, these biochemical changes are inhibitory on a cellular level, but can produce diverse effects based on receptor location (i.e., at pre- or post-synaptic neurons) [74,76]. Although four different opioid receptor subtypes have been identified, the analgesic and adverse actions of morphine (and morphine-like agonists) require predominantly activation of the mu-opioid receptor (MOR) subtype, as demonstrated in knockout mice models [77].

Various receptor and cellular, short- and long-term, adaptations during (repeat) opioid exposure are associated with the development of tolerance. One such adaptation is receptor desensitization that can occur within seconds to minutes after the initial opioid exposure. This particular mechanism includes the cytoplasmic decoupling of the effector (G-protein) from the opioid receptor by phosphorylation (by different kinases) and recruitment of beta-arrestin (and other proteins) and is followed either by receptor endocytosis, degradation, or recovery [75,76,78]. Initially, the receptors are able to quickly recover from acute desensitization, but upon repeat activation (by prolonged opioid use) the recovery potential is attenuated and desensitization is accelerated, probably by up-regulation of intracellular kinases and beta-arrestin [76]. This ultimately shifts the equilibrium between active and desensitized MORs and eventually leads to acute and long-term tolerance [76,79]. Other mechanisms involved in development of opioid tolerance are increased adenylate cyclase activity, activation of N-methyl-D-aspartate (NMDA) receptors, and glia cell activation, that all strive to restore the signaling process despite continued opioid exposure [80,81].

Reward

The addictive potential of opioids most probably originates from long-term adaptations in neuronal circuits that receive input from dopaminergic midbrain neurons [82,83]. Natural rewards and addictive substances (including opioids) are able to influence behavior by increasing extracellular dopamine levels within the mesocorticolimbic system [75,84,85] that is involved in reward and establishment of behavioral changes necessary to experience reward [83]. After an initial surge in dopamine levels, the concentration of dopamine returns to baseline levels. However, it has been proposed that chronic exposure to addictive substances, changes the homeostatic dopamine set point outside of its normal range [86,87]. This hypothesis has been further supported by results from imagining studies [87,88]. In a positron emission tomography (PET) imaging study by Volkow et al. [88], it was observed that two weeks after discontinuation of substance use, dopamine levels in the basal ganglia were depleted in individuals with an opioid (heroin) use disorder.

Opioid use disorder: clinical considerations

Tolerance, defined as the need to increase drug dose over time to produce the same biologic effect, and physical dependence can develop within days of opioid treatment (short-term effects) [89]. Dependence is characterized by withdrawal symptoms that can present as irritability, dysphoria, insomnia, diarrhea, runny nose, shivering, loss of weight, tremor, writhing, agitation, and aggression [90,91], and may last for several days, even weeks [92]. Although the withdrawal symptoms upon discontinuation of opioids may be perceived as severe, they are not life-threatening and can be reduced by opioid tapering [34]. Furthermore, tolerance can not only affect opioid analgesia, but can also influence the adverse effect potential [93].

According to the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association [94], the clinical manifestation of opioid tolerance, dependence, and addiction is summarized in 'opioid use disorder' and defined as a disorder that "includes signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or, if another medical condition is present that requires opioid treatment, that are used in doses greatly in excess of the amount needed for that medical condition." [94]. The clinical picture will differ between patients depending on personal characteristics and the duration of opioid treatment, which is reflected in a wide range of symptoms included in the diagnostic criteria. Furthermore, when

opioids are used under appropriate medical supervision, symptoms of tolerance and withdrawal (dependence) are not considered in the evaluation of the disorder [94].

Until recently, it seemed improbable that an opioid use disorder (formerly named 'addiction') could be present in a clinical setting because the compulsive need for opioids, with disregard of any negative consequences, was rarely observed in patients [95]. However, dependence and complementary withdrawal symptoms are neither necessary nor sufficient for the manifestation of opioid use disorder in a clinical setting [96,97]. For example, it is common for dependence to occur without a concomitant opioid use disorder, in the treatment of malignant pain [98]. Still, recent evidence suggests that opioid use disorder may be common among cancer survivors and patients in remission [99,100]. Presence of substance use disorder in any clinical setting is not improbable and may very well be more prevalent than originally considered. In a 2015 review study [57], 38 different studies on opioid misuse and "addiction" from diverse clinical settings were included. The authors concluded that rates of "addiction" varied between 8% and 12% and appeared to be highest in pain clinics.

The probability of substance use disorder increases with the increase in their availability [101]. Above, we described that the availability and ease with which the substance can be procured, especially opioids, has increased considerably in the US since the 1990s [102]. Exposure is, in itself, the single most important risk factor for any substance use disorder, including obviously opioid use disorder. For example, it has been demonstrated by a large US population-based study that the respondents of the survey (n = 9,279) who use prescribed opioids had an increased risk (odds ratio of 3.1 after correcting for confounding variables) of any opioid misuse compared with nonusers [103]. Moreover, the daily dose of prescribed opioids, the number of filled opioid prescriptions, and prolonged opioid use are all positively associated with the risk of opioid misuse [104–106], although the benefit of prolonged exposure to opioids for the treatment of chronic non-malignant pain (in comparison to nonsteroidal anti-inflammatory agents, NSAIDs) has not been supported in a well conducted randomized clinical trial [107].

For advances in safe opioid treatment, it is of paramount importance to assess the individual patient's predisposition for opioid use disorder before an opioid is prescribed [108]. Furthermore, when prolonging opioid treatment is deemed necessary, the risk of

aberrant opioid-related behavior needs to be continuously evaluated and the opioid treatment properly tailored to ensure safe and effective treatment [109].

Who is at risk for opioid misuse, abuse and addiction?

Although not to prescribe opioids may protect from an opioid use disorder, in many clinical scenarios this option is simply not feasible and the uncontrolled pain itself may further exacerbate the potential for aberrant opioid-related behavior [110]. We must therefore prescribe opioids with careful consideration of the individual patient's characteristics [109,111].

Predictors of opioid use disorder

Several risk factors of aberrant opioid-related behavior have been identified. They may be grouped by demographic differences, psychiatric comorbidities (presence ***versus*** absence), substance misuse factors, and other factors [109,110].

Evidence on demographic factors of aberrant opioid-related behavior is particularly highly heterogeneous, and population, setting, and outcome definition dependent [112]. Although more women are being prescribed opioids than men [113], it appears that illicit opioid misuse is more prevalent in the younger age groups and is associated with male sex [114,115]. For example, when population-based data on opioid-related hospital admissions and deaths in the Netherlands were examined, it was found that patients with opioid prescriptions were on average ten years older and more often women (54.4 %) than in those without an opioid prescription (male sex in 66.3% of cases) [116]. Women are also more likely to report substance use and abuse than men, but that does not necessary translate into prevalence of misuse [117]. In addition to age and sex, other variables, for example, gender identity, ethnicity, marital and socio-economic status may be important, but the evidence is sparse, and many population groups were not included in studies [112].

An association between chronic pain, concurrent psychiatric comorbidities and opioid misuse has been identified [109]. A small double blind, placebo controlled randomized trial (n = 81 with a 25% drop out rate) on negative affect, a constellation of anxiety, depression, and a catastrophizing cognitive style, found that patients with chronic low back pain with high negative affect during six months of follow-up were likely to be

prescribed higher doses of opioids, had lesser improvement in pain, and greater rate of opioid misuse than those with low negative affect [118]. Depression in particular increases the risk of abuse of prescription opioids [119], but a similar increase in risk of prescription opioid abuse was also identified in patients with an anxiety disorder [120], panic attacks, post-traumatic stress disorder, and personality disorders [121]. However, a well-treated psychiatric disorder is considered a protective factor for opioid misuse in adolescents [19].

Above all other risk factors, a personal history of substance misuse and abuse preceding a long-term opioid treatment is a strong predictor of aberrant opioid-related behavior [122]. A study in which electronic health records were investigated for signs of opioid dependence in patients with chronic non-malignant pain, predicted an increased risk of current dependence, particularly in patients with a history of severe dependence and prescription opioid abuse (odds ratio 56) [123]. Personal history of any substance (alcohol, tobacco, marijuana) abuse is associated with an aberrant opioid-related behavior [124]. The non-opioid abusive substances serve as introductory drugs to prescription opioids. In a study in adolescent cannabis and tobacco users (age 14 years), a positive association with opioid use at age 19 years was identified [125]. Furthermore, it is now widely accepted that prescription opioids serve as a gateway drug toward abuse of heroin and other illicit opioids [48]. In the US, the majority of heroin users report having started their addiction trajectory with prescription opioids [48,126]. Besides the history of personal substance abuse, familial substance abuse is also an important risk factor [127]. In families where one of the parents was a current marijuana user, the offspring had higher risk of binge alcohol use, tobacco, and marijuana use [128].

Other risk factors of substance abuse include sexual abuse, particularly in the preadolescent period, legal problems and being a victim of an injury, as well as genetic factors (although genetic screening is currently not implemented in routine clinical practice) [122,129–131]. In a recent study, 55 pregnant women that were opioid users were interviewed about childhood trauma and abuse. When childhood sexual abuse was reported, the risk of current opioid misuse in pregnancy was increased (odds ratio 3.5) [132]. Similar findings were observed for any type of childhood abuse, including physical and emotional abuse [133]. As we already established that non-opioid abusive substances are often introductory drugs to prescription opioid misuse, it may be

worthwhile to enforce efforts of drug awareness and prevention programs in children of all ages.

Why are research findings on predictors of opioid misuse diverse?

There is much attention to research on the safety of opioid use. The breadth of provided evidence can be appreciated by quick Medline search; an algorithm consisting of keywords 'risk factors', 'opioid', 'misuse', 'addiction' and 'abuse' yields nearly 200,000 hits with exponential growth in number since the 1990s. However, the general lack of high-quality evidence and highly heterogenous findings have been recognized by many authors [112,134]. Findings not only depend on the internal validity of the study (considering confounding, information and selection bias), but also on the population under observation (children, adolescents, adults, elderly), country of origin (with differences in healthcare systems), year of research, setting (surgery, intensive care unit, pain clinic, street) and other, thus limiting generalizability of the study findings. Furthermore, conditional on the type of opioid misused (prescription or illicit drugs), the operational definition of the outcome under observation, and on the type of pain studied (malignant ***versus*** non-malignant pain ***versus*** no pain), predictors and other outcomes found to be associated with aberrant opioid-related behavior may differ substantially [112,135].

To improve our understanding of mechanisms behind opioid misuse, abuse, and addiction and to develop valid, useful clinical tools to aid in recognizing high risk patients in practice, we need to especially improve internal validity of opioid safety research, which is particularly challenging in observational studies, since clinical trials are mostly insufficiently powered to detect safety signals [136]. Based on our experience in conducting large-scale observational research on opioid safety, we recognized the presence of confounding by indication to be challenging to control for in this research field. Furthermore, the information on opioid use, outcomes, and other variables in registry-based studies is imperfect, which could have a profound impact on detecting safety signals [137].

The majority of opioid safety studies utilize an inactive comparator (no use) to study the safety profile of opioids. The 'no use' is there as an observational equivalent of a placebo control in a randomized clinical trial, however, in that setting the randomization ensures that if the two arms differ, it is only by chance. This does not hold for observation comparisons: patients to whom opioids were prescribed must be different from those

not requiring such medication; opioid users typically have an indication for opioid use. We can correct for these differences by controlling for them with various proposed techniques, e.g., multivariable regression models, propensity score adjustments, matching, but these may be insufficient at completely removing group differences in prognostic factors. Even though advanced methods have been proposed, e.g., high dimension propensity score, self-controlled series and external confounding adjustment [138–140], that are promising a high degree of control over measured and unmeasured (by proxy) confounding variables, they are seldom utilized [134]. Another approach would be to make use of an active comparator design [141]. However, it remains unclear what would the optimal comparator be in the research on opioid safety. A choice of an active comparator in opioid research very much depends on the research question, and even then, it may well be that one specific opioid (or another analgesic) is preferentially prescribed to more vulnerable patients that also have a poorer outcome prognosis.

Data utilized in opioid safety studies have rarely been collected for the purpose of scientific research. Therefore, we must assume a high variability in the reporting of opioid-related outcomes, opioid use, and other variables within and between medical centers. Although the information about opioid use is most often gained by examination of pharmacy claims which tend to be quite accurate, even the most sophisticated algorithms used to identify the duration of opioid treatment fail to address the issue of compliance with therapy being prescribed. Therefore, we do not know whether a patient actually ingested the medication, whether illicit opioids are used, or whether patients are buying opioids over the counter [134]. Although availability of opioids as an over the counter medicine may vary between countries, and the exposure prevalence due to over the counter opioids is assumed to be small compared with prescription opioids and may therefore not have substantial impact on the effect estimates [142], the structure of misclassification (and its association with other errors) introduced by over the counter use may be difficult to anticipate [143]. Similarly, various disease classifications (most often international classification of diseases, ICD) are utilized to identify outcomes and even populations in different settings and countries. For example, the F-series are not used for coding of drug-related deaths in the US, whereas in Europe this is standard practice [7]. When a new study, based on data collected in Europe, is being planned, but the code series from US are utilized, a serious underestimation of outcomes will occur. Furthermore, to identify individual opioid-related outcomes, a set of codes or even individual codes are used,

e.g., heroin poisoning. This may lead to serious misclassification, since the probability of accurate reporting may be reduced and the identification of individual opioid poisoning by a physician may be challenging (e.g., due to unreliable urine testing) [111,144,145]. Incomplete or missing information on the exposure, outcome, or other variables, and the underlying mechanism that led to the inaccurate information may have various consequences for the investigated outcome of interest that even most experienced researchers may misjudge [146], and therefore needs to be formally explored [147].

What can be done to prevent further escalation or another opioid crisis?

Many interventions have been developed to counter the opioid epidemic, but many of them only targeted misuse of prescription opioids. Therefore, despite the fact that the number of opioid prescriptions has declined for over a decade now, the number of opioid deaths in the US is still rising. This 'opioid paradox' [148] shows clearly that the myriad preventive measures that were implemented over that same decade, did not have the desired effect.

Regulatory solutions

Because the opioid crisis was initially perceived as a public health problem [149], many of the first preventive measures were legislative and regulatory, aimed at decreasing the number of prescriptions and indirectly the number of pills available for misuse. In several healthcare settings, prescription drug monitoring programs (PDMPs) were intensified or expanded. These mostly automated systems with usually state-wide coverage enable prescribers to check whether a patient has already received a recent prescription for a certain drug. Use of these PDMPs prior to prescription of a monitored drug is now mandatory in many parts of the US. This has limited the number of drugs prescribed [150,151]. However, PDMPs intentionally targeted the prescription rates of opioids and did not have an influence on non-medical use of opioids and might even unintentionally have increased the use of heroin and other illicit opioids [152].

An important, nationwide step was taken when the Centers for Disease Control (CDC) published their 'Opioid prescribing guideline' in 2016 [34], focused on the treatment of chronic non-malignant pain with opioids. This guideline gave a series

of recommendations on whether or not to initiate opioid therapy for chronic pain, on which opioids to prescribe (it states a preference for immediate release opioid formulations as opposed to extended release formulations), which dose and for how long to prescribe (as low a dose as possible for the shortest period of time), and how to assess the risk of opioid related harm (e.g., not prescribing to patients with a history of substance abuse, or concomitant use of benzodiazepines). Similarly, some countries in Europe updated or developed new prescription guidelines, as for example the Netherlands [153], and the United Kingdom [35], that either rely more heavily on opioids in the post-operative period (the Netherlands) or were developed specifically for chronic non-malignant pain and therefore support also non-pharmacological interventions.

In the wake of the US guidelines, which were first and foremost intended as a set of clinical recommendations, many US states implemented laws limiting the duration of opioid prescriptions, and in some cases even the dose that could be prescribed [154]. Furthermore, restrictions were placed on 'doctor shopping' [155], and high-volume prescribers were sent letters informing them of their unusual prescription behavior [156]. These legal limitations have affected the prescription rates of opioids (the red line in Figure 1) and although they might have curbed the increasing rate of opioid overdoses associated with prescribed opioids (Figure 1), they have done little so far to limit the overall number of overdose deaths (these are now mainly driven by illicit opioids), and the question remains whether they are effective at all [157].

Pharmacological solutions

Pharmacological solutions to the opioid problem have also been presented over the past two decades. When the first signs of opioid misuse were starting to surface, several new pharmacological opioid formulations, targeted at decreasing abuse potential (so called abuse deterrent formulations or ADFs), entered the market. Furthermore, novel opioid-receptor agonists and of course new formulations of naloxone became used.

Abuse Deterrent Formulations

There are several ways in which a drug can be formulated in an abuse deterrent way, as described by the Food and Drugs Administration (FDA) [158]: adding a physical or chemical barrier to the drug in question, combining agonist/antagonist combinations, decreasing a drug's likability by including aversive substances that deter users from

using the drug in large amounts, and novel technologies such as unconventional delivery systems or using prodrugs that can only be activated by ingestion.

The best-known example of the first category, adding a chemic-physical barrier, is a reformulation of OxyContin® (ADF OxyContin®). The drug was marketed with a new shell which made crushing and extraction of the drug difficult. This decreased the number of opioid overdoses due to oxycodone [159], but only for a short while. A plateau was reached within a few years after reformulation, for which there are several possible explanations. First, it is possible that users used different ways to ingest the drug (orally as opposed to snorting and injecting), which would eventually lead to the same incidence of oxycodone overdoses. It is also possible that users changed their drug preference, and simply started to snort and inhale/inject other types of opioids. This would then decrease the number of oxycodone overdoses, but not the number of overall opioid overdoses. It is important to note that the number of heroin overdoses rose between 2010 and 2014 [160]. A study into the abuse of ADF OxyContin® in a large cohort of patients with an opioid use disorder showed that in a subsample only a small percentage of users stopped abusing oxycodone altogether [161]. Some switched to a different drug (heroin) but most did not change their behavior after the reformulation. The evidence for a massive switch to heroin is inconclusive: one study reported that the odds of heroin initiation did not change after the introduction of ADF OxyContin® [162], others have shown no decrease in overall opioid overdose deaths after the introduction of ADF OxyContin® [163,164], consistent with the idea that users simply switched to other opioid drugs. After the introduction of ADF OxyContin® several other abuse deterrent formulations were marketed [165]. We note, however, that not all ADF formulations hold the same physico-chemical properties that facilitate or deter alternative routes of administration [165].

Another way of deterring abuse is by combining antagonists with agonists. This has an interesting pharmacological rationale. Naloxone, together with naltrexone still the most important opioid antagonist, has poor bioavailability when swallowed orally, due to its high first pass effect. An opioid user swallowing the tablet as intended, would not suffer from the effects of the added naloxone, but if one were to snort or inject a crushed tablet, naloxone would work and limit the opioid' effects or even cause withdrawal symptoms. The use of agonist/antagonist combinations to deter opioid misuses goes back even further than addition of a physico-chemical barrier: already in the early 2000s a combination tablet of buprenorphine and naloxone was released [166]. Since then,

several other formulations, combining oxycodone or morphine with either naloxone or naltrexone became available [165].

Opioid alternatives

There are few true alternatives to the use of opioids for moderate to severe pain. When non-steroidal anti-inflammatory drugs (NSAIDs) have fallen out of favor because of their undesirable cardiovascular side-effect profile or because of limitation in the healthcare budget assigned to this widely used medication group (as for example in the Netherlands [116]), there are few opioid alternatives to alleviate both acute and chronic pain. The ultimate goal in opioid research, finding an opioid with all the advantages but none (or fewer) of the disadvantages, has thus far proven elusive. The opioid analgesics currently available all exert their main actions through the mu-opioid receptor (MOR) as opposed to the kappa and delta opioid receptors [77,167]. This receptor activation is responsible for both the desired (analgesic) and unwanted (respiratory depressant) effects of opioids, and therefore for the overdose deaths. A new investigative pathway has opened up a possible future pain therapy – biased opioid receptor ligands. After mu opioid receptor (MOR) activation, the analgesic effect is mostly mediated through the activation of the G protein, while it is assumed (but not fully proven) that the majority of side effects, such as respiratory depression, are mediated through activation of an auxiliary cytoplasmic transduction MOR protein, beta-arrestin [168,169]. Any pharmacological compounds favoring the G protein pathway over the beta-arrestin pathway would theoretically have analgesic properties while lower risk of side-effects: the biased ligands. Several candidate molecules have been tested in pre-clinical and clinical trials [170,171], from which oliceridine was the first to receive FDA approval for in-hospital use.

Naloxone for home use

Finally, a different way of preventing the loss of life from opioid overdoses is to treat overdoses promptly. An opioid overdose is easily treated when discovered early. Administration of 0.4 to 4 mg of naloxone (via intravenous, intramuscular or intranasal routes), depending on the opioid used and dose, can reverse opioid-induced respiratory depression and thus prevent coma, cardiac arrest and death. The caveat here is the availability of naloxone – while naloxone is readily available in hospitals and physician practices, it is not available in those places where most overdoses happen. An idea already developed in the early years of this century [172,173], to provide communities with improvised naloxone kits for home use, was more widely introduced

in the early 2010s. In 2014, the WHO issued a guideline on community management of opioid overdose, stating 'Naloxone needs to be available to anyone likely to witness an opioid overdose in the pre-hospital setting' [174]. To this effect, so-called 'take home naloxone' formulations (THN), such as an auto-injector pen and a nasal spray were introduced. In their opioid prescription guideline, the CDC [175] and US Surgeon General Public Health Advisory [176] recommend prescribing any form of THN to any patient with a high risk of overdose (i.e., a patient with a history of overdose or opioid use disorder, a patient with a high opioid dose or concurrent benzodiazepine use, or any individual using illegal opioids). McDonald et al. [177] conducted a systematic review of the observational evidence available for THN schemes. Not only did they show that THN schemes are successful in decreasing opioid overdose deaths, but they also showed that they are cost-effective, have a low risk of adverse events and are easily implemented over a wide range of social settings. They therefore conclude that THN distribution should be introduced as a standard of care in prevention of opioid overdose deaths [177].

Patient-centered solutions

Patients' expectations of both their pain levels and the effect of the analgesic therapy should be carefully managed by the physician. Patient education in pain and pain therapy during a pre-operative visit might be able to help decrease opioid need after the surgery [178,179]. Similarly, someone who receives an opioid prescription for non-surgical pain, should be informed of possible side-effects and the potential for misuse, by both the prescriber and the pharmacist dispensing the medication [180,181]. Patient awareness of the risks of opioid use might help with decreasing opioid use and consequent misuse.

Tailoring prescriptions, for example post-surgery, to the specific patient will also help in reducing leftover pills [182–184]. Any pills left at home are a risk for non-medical use, be it for self-medication, or diversion to others. Patients are likely to hold on to their leftover pills, for their own or other people's future use [185]. Furthermore, return of opioid tablets to the pharmacy (or the hospital) should be as easy as possible, and might even need to be financially rewarded [148], also to decrease the number of pills available for misuse.

Expert opinion

As we have tried to demonstrate in this review, the opioid crisis is a complex problem, and there does not seem to exist one definite solution. Not only has the general opinion on pain and what amount of pain is bearable changed, but also doctors' attitudes and possibilities, as well as possibilities of healthcare facilities. The rise in the number of opioid-related fatalities continues year upon year and shows no sign of slowing. As physicians, we are at least partially responsible for this 'rising tide of deaths' [186], and it is therefore also our responsibility to help find a solution for this problem. However, modern medicine without opioids is currently unthinkable. We are limited in therapeutic options when a patient is in serious pain. Anesthesia without opioids is very difficult and possibly unsafe [187]. We need to convince ourselves, but also all of our colleagues, as well as our patients that there is a fine line between responsible opioid use and misuse. In this respect, it is important to note that the need for opioids in pain therapy is subject to a high amount of variability. It is therefore difficult to develop a one-size-fits-all strategy for opioid therapy in both acute and chronic non-malignant pain settings. It is of paramount importance that therapy is individualized, and a good relationship between patient and prescriber is key here. Initiation of opioid therapy warrants close contact between patient and physician to enable monitoring of opioid effect, possible side-effects or signs of misuse. Where possible, prescriptions should be short-termed and refills only possible after close contact with the physician. Ideally, opioids should only be used as a 'pain circuit breaker' in non-malignant pain, much like a course of antibiotics. Cancer pain patients should, on the other hand, have access to opioid therapy when required, also on a long-term basis, but again with careful consideration of appropriate opioid therapy and with acknowledging the side effects. Opioid use should not be, however, extended beyond the intended indication (for example, after cancer patients enter remission or are cured) to prevent opioid use disorder in this patient group. Where continuation of analgesic therapy is unavoidable in the treatment of non-malignant pain, possible alternatives for opioid therapy (such as NSAIDS and antidepressants or antiepileptics) should be considered. In this indication, prolonged opioid use should be avoided at all costs, as little scientific evidence has been provided to support continued opioid use in chronic non-malignant pain [107]. Additionally, when appropriate, complementary approaches such as physical therapy, psychological support and rehabilitation programs should be considered. Not only can these non-pharmacological treatments help in alleviating chronic non-malignant pain, but can also aid patients to deal with the pain and accept

it. It has been demonstrated that multidisciplinary approach to pain management is more beneficial for a patient than a conventional one. Patients treated by such a team reported having reduced pain intensity, improved psychological well-being, quality of sleep and physical functioning [188]. Furthermore, patient empowerment in the treatment of chronic non-malignant pain will provide the necessary information to the patient so they can make an informed decision about the initiation of the opioid treatment and be alerted for possible side effects [189]. Additionally, it can aid in detecting opioid misuse when an opioid is already prescribed [190]. Unfortunately, these alternative approaches are not always reimbursed by health insurance, nor are the lengthy patient consultations that are required.

As we have shown, due to the complexity of the opioid crisis, there is not one universal cure. A combination of measures, aimed at different underlying mechanisms behind the opioid crisis, and always in concordance with all parties involved, are the best way forward.

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CHAPTER 8

SUMMARY AND CONCLUSION

In this thesis we aimed to investigate patterns of opioid use, prescribed and illicitly obtained, and concomitant hazards, such as hospital admission and death due to opioid poisoning, in the general population of the Netherlands. We also sought to explore the possible explanations for these patterns and other consequences, and to identify (sub)populations with a high probability of receiving an opioid prescription. We discussed our findings in the context of other European countries and the United States to gain perspective in the seriousness of the opioid crisis in the Netherlands.

Summary of the main findings

In **Part 1,** we investigated the trends in prescribing of opioids and associated health outcomes, such as hospital admission and death due to opioid poisoning, unplanned ICU admission and all-cause mortality, in the general population of the Netherlands between 2013 and 2018. We also aimed to identify risk factors associated with opioid use and predictors of opioid-related side-effects. For this, we merged national registers on pharmacy claims, hospital admissions and mortality, with two large nation-wide surveys, and analyzed nation-wide individual patient data. The aims of this section were addressed in **Chapter 2**, **Chapter 3**, and **Chapter 4**.

In **Chapter 2**, we discovered an increasing trend in prevalence of opioid use in the Netherlands, with a concomitant increase in opioid-related hospital admission and deaths. By analyzing data from a repeated large national survey, we identified female sex, older age, lower socio-economic status, smoking, obesity, poor self-perceived health, depressive symptoms and loneliness, lower household income, being divorced and widowed to be associated with receiving an opioid prescription. Furthermore, survey respondents who reported having back pain, rheumatoid arthritis or fibromyalgia had a similar or slightly higher probability of receiving an opioid prescription than respondents who reported having cancer.

In the following **Chapter 3**, we explored the two possible explanations for the increasing trend in opioid prescribing and two probable consequences of it in the general Dutch population. For this, we utilized results from another national survey. We demonstrated no increase in prevalence and intensity of pain; however, we were able to confirm a decrease in prescriptions of nonsteroidal anti-inflammatory drugs (NSAIDs) as the most likely explanation for the increase in opioid use. The two consequences,

increased severity of opioid-related hospital admissions and increase in illegal opioid use, were both confirmed by our analysis.

In **Chapter 4** we aimed to investigate the relationship between prescription opioid use and a one-year risk of unplanned ICU admission and all-cause mortality to gain a broader perspective into many "hidden" effects of opioids. As an alternative explanation for the hypothesized positive association, we included socio-demographic variables, and co-morbidities in the analysis. To assure the correct sequence of events, meaning that opioids would always precede the observed two outcomes, we constructed Cox regression models where opioid exposure was entered as a time-varying variable, and all-cause mortality was considered a competing risk of unplanned ICU admission. Based on the constructed models and frequency analysis, we found an association between the use of prescription opioids and both outcomes. We also observed a positive association between the number of opioid prescriptions received and the risk of both outcomes, where having received five of more prescriptions yielded the highest estimates.

In **Part 2**, we aimed to explore possible explanations for the increase in the use of opioids in the Netherlands. Based on results obtained in **Chapter 3**, we understood that the prescribing rate of NSAIDs has decreased, but we did not yet understand why. So, in **Chapter 5**, we aimed to understand whether substituting NSAIDs for opioids, in order to prevent common NSAIDs-related side effects, such as gastrointestinal bleeding, is a successful public-health strategy. For this, we analyzed data from pharmacy claims register, hospital admission and death register of the total population of the Netherlands. Due to lack of details in the data that was available to us, we also included publicly available data by the Health Care Institute of the Netherlands for the collaboration with the Health Care Institute of Slovenia in **Chapter 6**. We concluded by reviewing existing evidence on the opioid epidemic in **Chapter 7**.

In **Chapter 5** we compiled a list of prescription medications of which the use can be linked to an increased risk of upper gastrointestinal bleeding, and removed their effects (partially or fully) on the risk of this outcome. Contrary to our hypothesis, we identified an increasing trend in the bi-annual and annual incidence of upper gastrointestinal bleeding associated with medication use. The trend remained even when the incidence of the outcome was investigated in a subpopulation where no one received a prescription for any of the high-risk medications. This led us to conclude that

another source of exposure to hazardous substances must exist, most probably over-the-counter NSAIDs medication, which conclusion was supported by our finding that young women showed a higher risk of the upper gastrointestinal bleeding than young men, where it is known that this is the group that buys most over the counter NSAIDs.

In **Chapter 6** we sought to compare the prevalence of prescription NSAIDs and opioid use, and explore their trends between 2013 and 2019 both in Slovenia and the Netherlands. To allow for a direct comparison between the two countries, we standardized the aggregated data of both countries by the direct method, using the 2013 population of the European Union as weights. We found higher prescription rates of both NSAIDs and opioids in Slovenia than in the Netherlands. However, while the trend for opioid prescriptions was decreasing in Slovenia, the trend was increasing in the Netherlands. For Slovenia, the majority of the opioids could be explained by tramadol, whereas, the majority of the increase in the Netherland was explained by oxycodone. This potent opioid is barely prescribed in Slovenia.

In **Chapter 7** we reviewed existing evidence on the United States opioid epidemic, with focus on the reasons behind the public health emergency. We also discussed different perspectives on the addictive potential of the opioids, including biochemical pathways, clinical presentation, with the focus on identifying vulnerable population. Based on our work with public health registers, we discussed struggles of pharmacoepidemiologic research of opioid safety. Last, we reviewed strategies that were undertaken in the US to combat the rising tide of opioid overdose deaths and we concluded with our expert opinion on best strategies to prevent a next opioid crisis.

In conclusion, the use of opioid is increasing in the Netherlands, which is reflected in an increase in complications associated with the use, such as hospital admission and death due to opioid poisoning. In addition to these direct hazards of opioid use, patients also face the risk of unplanned ICU admission and all-cause mortality. Dependent on socio-demographic characteristics and co-morbidities the risk of these outcomes may vary, but is unique to the general population of the Netherlands when compared to other countries.

Dutch summary

In dit proefschrift beoogden we patronen van opioïdengebruik, zowel voorgeschreven als illegaal verkregen, en bijkomende gevaren zoals ziekenhuisopname en overlijden als gevolg van opioïdenvergiftiging, te onderzoeken in de algemene bevolking van Nederland. Daarnaast hebben we zoveel mogelijk geprobeerd verklaringen voor deze patronen en andere gevolgen te verkennen en (sub)populaties met een hoog risico op het krijgen van een opioïderecept te identificeren. We bespraken onze bevindingen in de context van andere Europese landen en de VS om een beeld te krijgen van de ernst van de opioïdencrisis in Nederland.

Samenvatting van de belangrijkste bevindingen

In **Deel 1** onderzochten we trends in het voorschrijven van opioïden en daaraan gerelateerde gezondheidsuitkomsten, zoals ziekenhuisopname en overlijden als gevolg van opioïdevergiftiging, ongeplande IC-opnames en algemene mortaliteit. Voor dit gebruiken we de algemene bevolking van Nederland tussen 2013 en 2018. We wilden ook risicofactoren identificeren die verband houden met opioïdegebruik en voorspellers van opioïdegerelateerde bijwerkingen. Hiervoor combineerden we nationale registers van apotheekclaims, ziekenhuisopnames en sterfte met twee grootschalige nationale enquêtes en analyseerden we nationale individuele patiëntgegevens. De doelstellingen van dit deel werden behandeld in **Hoofdstuk 2**, **Hoofdstuk** 3 en **Hoofdstuk 4**.

In **Hoofdstuk 2** ontdekten we een toenemende trend in de prevalentie van opioïdegebruik in Nederland, met een gelijktijdige stijging van opioïdegerelateerde ziekenhuisopnames en sterfgevallen. Door gegevens van een vierjaarlijks uitgevoerde grootschalige nationale gezondheidsenquête te analyseren, identificeerden we vrouwelijk geslacht, oudere leeftijd, lager sociaal-economische status, roken, obesitas, zelfbeleefde slechte lichamelijke gezondheid, depressieve symptomen en eenzaamheid, lager huishoudinkomen, gescheiden zijn en het verlies van een echtgenoot als geassocieerd met het krijgen van een opioïderecept. Bovendien hadden ondervraagden die rugpijn, reumatoïde artritis of fibromyalgie rapporteerden, een vergelijkbare of iets hogere kans op het krijgen van een opioïderecept dan respondenten die meldden dat ze kanker hadden.

In **Hoofdstuk 3** onderzochten we mogelijke verklaringen voor de toenemende trend in het voorschrijven van opioïden en waarschijnlijke gevolgen ervan in de algemene Nederlandse bevolking. Hiervoor gebruikten we resultaten van een andere nationale enquête. We toonden geen toename aan in de prevalentie en intensiteit van pijn. We konden echter wel een afname in het aantal NSAID-voorschriften aanvoeren als de meest waarschijnlijke verklaring voor de toename van opioïdengebruik. Beide gevolgen, een toename van de ernst van opioïdegerelateerde ziekenhuisopnames en een toename van illegaal opioïdegebruik, werden bevestigd door onze analyse.

In **Hoofdstuk 4** beoogden we de relatie tussen het gebruik van voorgeschreven opioïden en het risico op ongeplande IC-opname enerzijds en overlijden binnen een jaar anderzijds te onderzoeken. Hiermee probeerden we om een breder perspectief te krijgen op de vele "verborgen" effecten van opioïden. Als alternatieve verklaring voor de veronderstelde positieve associatie, namen we sociodemografische variabelen en comorbiditeiten op in de analyse. Om de juiste volgorde van gebeurtenissen te waarborgen, wat betekende dat opioïden altijd de waargenomen twee uitkomsten zouden voorafgaan, construeerden we Cox-regressiemodellen waarbij opioïde-expositie werd ingevoerd als een variabele die in de tijd varieert, en overlijden door alle oorzaken werd beschouwd als een concurrerend risico van ongeplande IC-opname. Op basis van de geconstrueerde modellen en frequentieanalyse vonden we een associatie tussen het gebruik van voorgeschreven opioïden en beide uitkomsten. We observeerden ook een positieve correlatie tussen het aantal ontvangen opioïderecepten en het risico op beide uitkomsten, waarbij het ontvangen van vijf of meer recepten de hoogste schattingen opleverde.

In **Deel 2** beoogden we mogelijke verklaringen te verkennen voor de toename van het gebruik van opioïden in Nederland. Gebaseerd op resultaten verkregen in Hoofdstuk 3 begrepen we dat de voorschrijving van NSAID's was afgenomen, maar we begrepen nog niet waarom. Dus, in **Hoofdstuk 5**, beoogden we te begrijpen of het vervangen van NSAID's door opioïden, om veelvoorkomende bijwerkingen van NSAID's, zoals gastro-intestinale bloeding, te voorkomen een succesvolle volksgezondheidsstrategie is. Hiervoor analyseerden we gegevens uit het register voor geneesmiddelen vergoedingen, het ziekenhuisopname- en het sterfteregister van de totale bevolking van Nederland. Vanwege het gebrek aan details in de voor ons beschikbare gegevens, namen we ook openbaar beschikbare gegevens van het Zorginstituut Nederland op

voor de samenwerking met het Zorginstituut Slovenië in **Hoofdstuk 6**. We sloten af door bestaand bewijs over de opioïdenepidemie te herzien in **Hoofdstuk 7**.

In **Hoofdstuk 5** stelden we een lijst samen van voorgeschreven medicijnen waarvan het gebruik kan worden gekoppeld aan een verhoogd risico op bloedingen in het bovenste maag-darmkanaal en verwijderden hun effecten (gedeeltelijk of volledig) op het risico van uitkomst. In tegenstelling tot onze hypothese identificeerden we een toenemende trend in de tweejaarlijkse en jaarlijkse incidentie van bloedingen in het bovenste maag-darmkanaal in verband met medicijngebruik. De trend bleef zelfs bestaan wanneer de incidentie van de uitkomst werd onderzocht in een subpopulatie waar niemand een recept kreeg voor een van de medicijnen met een hoog bloedingsrisico. Dit leidde ons tot de conclusie dat er een andere bron van blootstelling aan gevaarlijke stoffen moet bestaan, hoogstwaarschijnlijk vrij verkrijgbare NSAID-medicatie, wat werd ondersteund door jonge vrouwen die een hoger risico hadden op bloedingen in het bovenste maag-darmkanaal dan jonge mannen.

In **Hoofdstuk 6** wilden we de prevalentie van voorgeschreven NSAID's en opioïdengebruik vergelijken en hun trends tussen 2013 en 2019 tussen Slovenië en Nederland verkennen. Om een directe vergelijking tussen de twee landen mogelijk te maken, standaardiseerden we de geaggregeerde gegevens van beide landen volgens de directe methode, met behulp van de bevolking van de Europese Unie van 2013 als gewichten. We vonden een hogere voorschrijfratio van zowel NSAID's als opioïden in Slovenië dan in Nederland. Terwijl de trend voor opioïdenrecepten afnam in Slovenië, was de trend stijgend in Nederland. Voor Slovenië kon de meerderheid van de opioïden worden verklaard door tramadol, terwijl de meerderheid van de toename in Nederland werd verklaard door oxycodon. Dit krachtige opioïde wordt nauwelijks voorgeschreven in Slovenië.

In **Hoofdstuk 7** herzagen we bestaand bewijs over de opioïdenepidemie in de Verenigde Staten, met de focus op de redenen achter de noodsituatie in de volksgezondheid. We bespraken ook verschillende perspectieven over het verslavende potentieel van opioïden, inclusief biochemische routes, klinische presentatie, met de focus op het identificeren van kwetsbare bevolkingsgroepen. Op basis van ons werk met registers voor de volksgezondheid bespraken we de uitdagingen van het farmaco-epidemiologisch onderzoek naar de veiligheid van opioïden. Tot slot bespraken we strategieën die in de VS zijn ondernomen om de toenemende golf van overdoses door

opioïden te bestrijden, en we concludeerden met ons deskundig advies over de beste strategieën om een volgende opioïdencrisis te voorkomen.

Samenvattend neemt het gebruik van opioïden toe in Nederland. Dit blijkt duidelijk uit de toename van complicaties geassocieerd met het gebruik, zoals ziekenhuisopname en overlijden als gevolg van opioïdenvergiftiging. Naast deze directe gevaren van opioïdengebruik lopen patiënten ook het risico op ongeplande IC-opname en algemene mortaliteit. Afhankelijk van sociodemografische kenmerken en comorbiditeiten kan het risico van deze uitkomsten meer uitgesproken zijn, maar het is uniek voor de algemene bevolking van Nederland in vergelijking met andere landen.

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Appendix

Publications

Bedene A, Lijfering WM, Niesters M, van Velzen M, Rosendaal FR, Bouvy ML, Dahan A, van Dorp ELA. Opioid Prescription Patterns and Risk Factors Associated With Opioid Use in the Netherlands. JAMA Netw Open. 2019;2:e1910223. doi: 10.1001/jamanetworkopen.2019.10223. PMID: 31461149; PMCID: PMC6716286.

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Bedene A, van Dorp ELA, Rosendaal FR, Dahan A, Lijfering WM. Risk of drug-related upper gastrointestinal bleeding in the total population of the Netherlands: a time-trend analysis. BMJ Open Gastroenterol. 2022;9:e000733. doi: 10.1136/bmjgast-2021-000733. PMID: 35012975; PMCID: PMC8753354.

Bedene A, Lijfering WM, Arbous MS, Rosendaal FR, Dahan A, van Dorp ELA. Association between prescription opioid use and unplanned intensive care unit admission and mortality in the adult population of the Netherlands: a registry study. Br J Anaesth. 2022;129:254-262. doi: 10.1016/j.bja.2022.05.009. Epub 2022 Jun 22. PMID: 35752474.

Bedene A, Strmljan A, van Dorp ELA, Udovič M, Lijfering WM, Niesters M, Rosendaal FR, Dahan A, Fürst J. Comparison of Two Different Analgesic Prescription Strategies and Healthcare Systems: Slovenia vs. the Netherlands. Front Pain Res (Lausanne). 2021;2:723797. doi: 10.3389/fpain.2021.723797. PMID: 35295498; PMCID: PMC8915570.

Bedene A, Dahan A, Rosendaal FR, van Dorp ELA. Opioid epidemic: lessons learned and updated recommendations for misuse involving prescription versus non-prescription opioids. Expert Rev Clin Pharmacol. 2022;15:1081-1094. doi: 10.1080/17512433.2022.2114898. Epub 2022 Sep 6. PMID: 36068971.

Not included in this thesis

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Bulder RMA, van der Vorst JR, van Schaik J, Bedene A, Lijfering WM, Bastiaannet E, Hamming JF, Lindeman JHN. Persistent High Long-term Excess Mortality after Elective AAA Repair Especially in Women: A Large Population-Based Study. Ann Surg. 2023. doi: 10.1097/SLA.0000000000006044. Epub ahead of print. PMID: 37497631.

Curriculum Vitae

Ajda Bedene was born in Ljubljana, Slovenia, on the 15th of February 1991. She earned her master's degree in pharmacy from the Faculty of Pharmacy, University of Ljubljana, in 2015. During her master's program, she conducted research for her thesis at the Department of Biochemistry at the Faculty of Pharmacy, and the results were subsequently published in a scientific journal.

In order to obtain her pharmaceutical care license, she completed an internship program at the Rehabilitation Institute of Slovenia – Soca. Following her training, she worked as a pharmacist at the institute for three years. Collaborating with colleagues, she developed a proposal for a clinical trial exploring the use of cannabinoids in patients with multiple sclerosis. Unfortunately, the proposal did not secure funding, leading her to pursue research opportunities in Leiden, the Netherlands.

Ajda embarked on a Ph.D. trajectory at Leiden University Medical Center, under the guidance of Prof. Dr. F.R. Rosendaal, Prof. Dr. A. Dahan, Dr. E.L.A. van Dorp, and Dr. W.M. Lijfering. Her research focused on opioid use and its associated health outcomes within the general Dutch population. Following the completion of her Ph.D., she integrated her research expertise and pharmaceutical knowledge in her professional journey. Currently, she is associated with the Central Committee on Research Involving Human Subjects (CCMO) in The Hague, where she assesses the quality of investigational medicinal products intended for use in clinical trials.

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The completion of this thesis marks a significant milestone, and I owe immense gratitude to the unwavering support of mentors, colleagues, friends, and family. In this section, I sincerely wish to convey my appreciation.

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Vid Prijatelj, my partner in crime, best friend, and biggest fan, your endless support has made this journey all the more rewarding. Thank you for doing the dishes!