Association between prescription opioid use and unplanned intensive care unit admission and mortality in the adult population of the Netherlands: a registry study

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Pain

Association between prescription opioid use and unplanned intensive care unit admission and mortality in the adult population of the Netherlands: a registry study

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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.

Conclusions: 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.

Keywords: all-cause mortality; opioid prescription status; population-based cohort; prior opioid use; real-world data; registry-based data set; unplanned ICU admission

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.

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Widespread opioid use in the USA has caused a national health crisis, 'the opioid epidemic',[1] which cost 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.

Outcome measures

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 analysis

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). 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

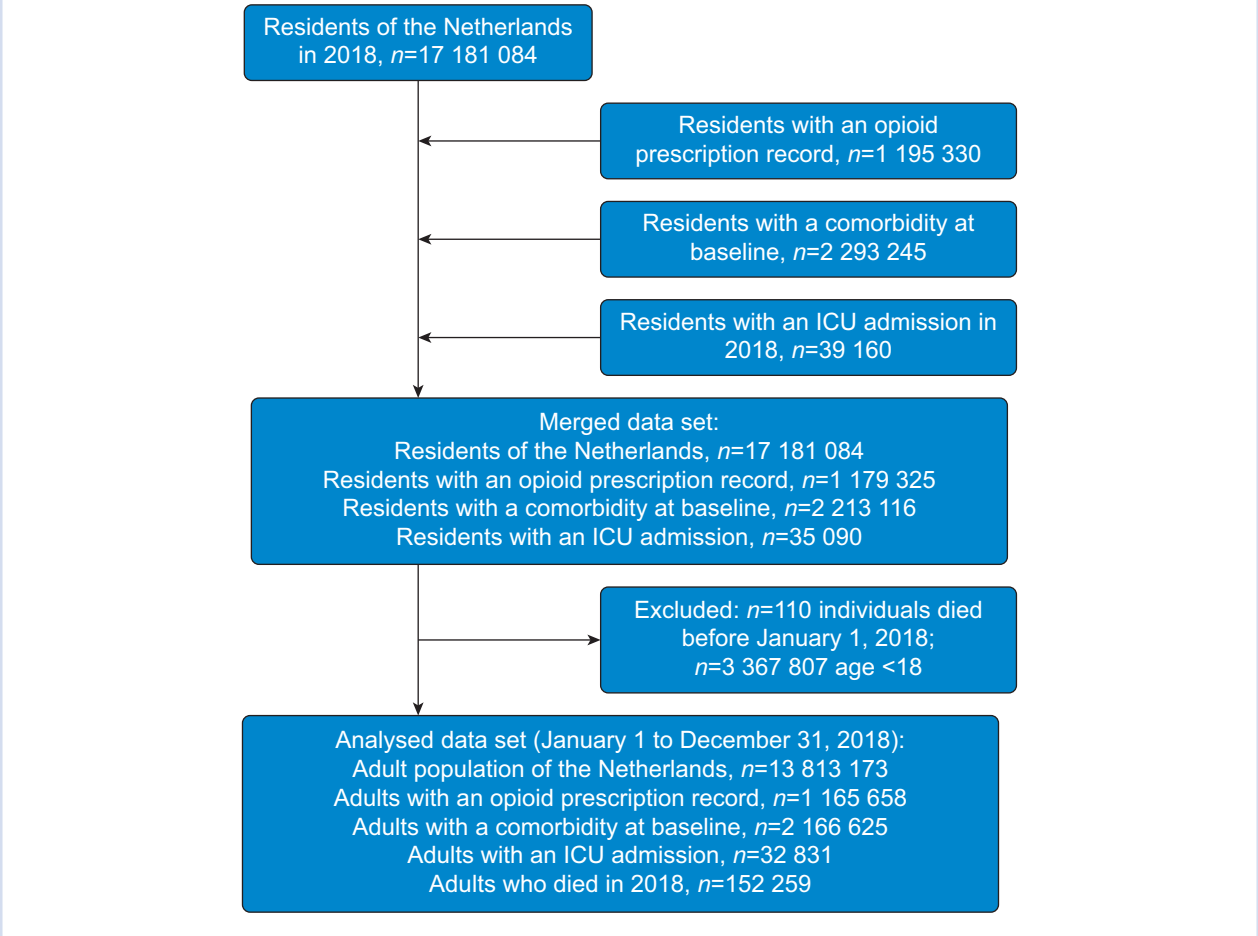


Fig 1. Inclusion and exclusion of individuals in the data set.

(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).

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

There were 6589 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).

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 14.0

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

	Adult residents, *n* (%)
Total	13 813 173
Sex	
Men	6 802 047 (49.2)
Women	7 011 126 (50.8)
Age group (yr)	
18–35	3 653 069 (26.4)
35–45	2 061 585 (14.9)
45–55	2 546 367 (18.4)
55–65	2 295 143 (16.6)
65–75	1 878 043 (13.6)
75–85	1 002 751 (7.26)
≥85	376 215 (2.72)
Immigration status	
Native	10 711 308 (77.5)
First generation	1 932 006 (14.0)
Second generation	1 169 859 (8.47)
Comorbidity	
Depression	1 001 059 (7.25)
Other psychiatric conditions	587 935 (4.26)
Cancer	143 491 (1.04)
Diabetes mellitus	785 933 (5.69)
Chronic viral infection	105 132 (0.76)
Main source of income	
Wage	9 111 520 (66.0)
Welfare	1 138 361 (8.24)
Pension	3 297 809 (23.9)
Other*	265 483 (1.92)
Household income, quintile	
First	2 007 038 (14.5)
Second	2 332 282 (16.9)
Third	2 651 616 (19.2)
Fourth	2 925 798 (21.2)
Fifth	3 339 781 (24.2)
No identified income	104 038 (0.75)
Institutionalised	234 396 (1.70)
Student grant	218 224 (1.58)

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

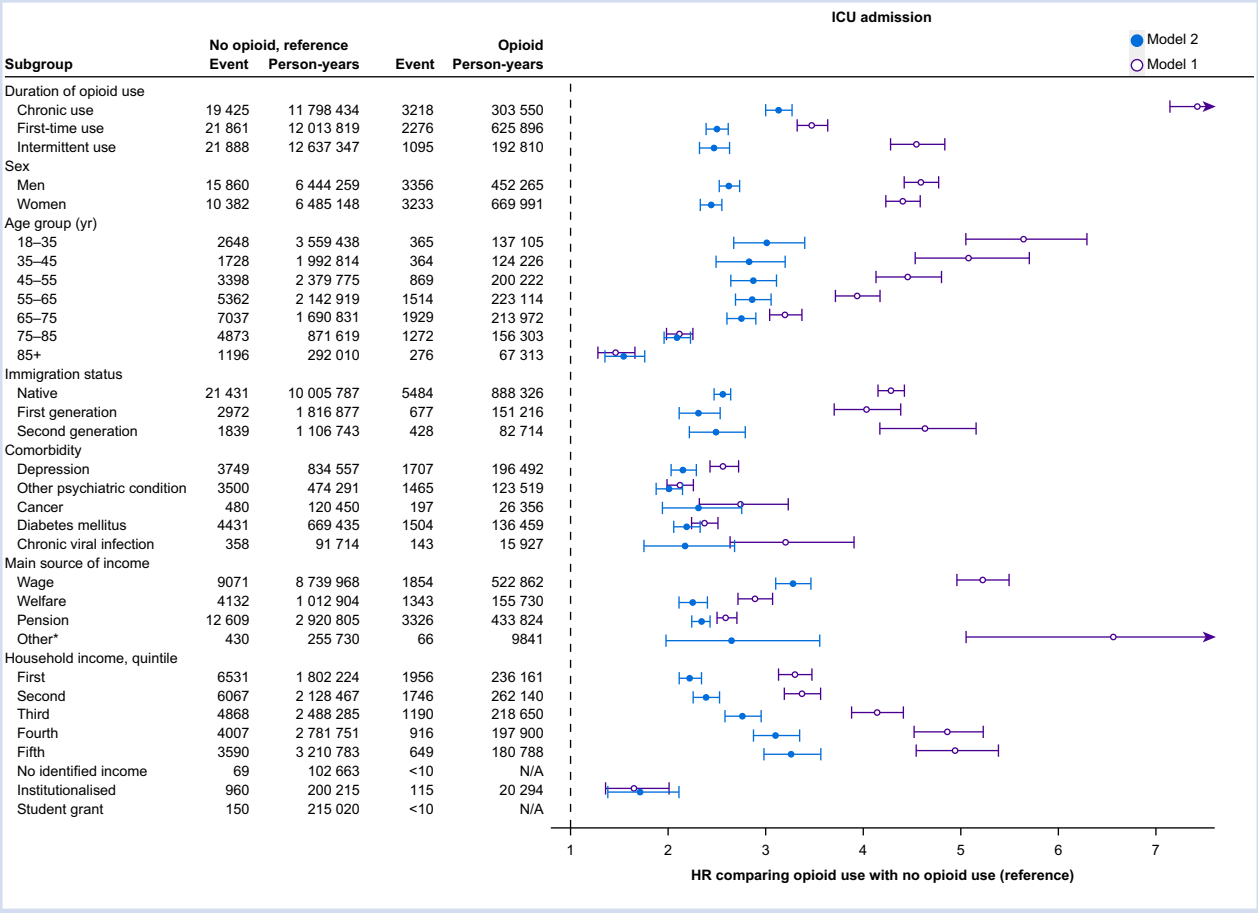
Covariates	ICU admission			Death		
	Events, *n*	Person-years	Model 2, aHR (95% CI)	Events, *n*	Person-years	Model 4, aHR (95% CI)
Sex						
Men	19 216	6 896 524	1 (reference)	73 868	6 906 128	1 (reference)
Women	13 615	7 155 139	0.59 (0.58–0.61)	78 391	7 161 873	0.58 (0.57–0.59)
Age group (yr)						
18–35	3013	3 696 543	1 (reference)	1241	3 698 222	1 (reference)
35–45	2092	2 117 041	1.12 (1.06–1.19)	1661	2 118 212	2.22 (2.06–2.40)
45–55	4267	2 579 997	1.76 (1.68–1.85)	5470	2 582 322	5.67 (5.32–6.04)
55–65	6876	2 366 034	2.69 (2.57–2.81)	14 092	2 369 614	14.2 (13.4–15.1)
65–75	8966	1 904 803	4.28 (4.02–4.55)	28 605	1 909 138	44.8 (42.1–47.7)
75–85	6145	1 027 923	4.83 (4.52–5.16)	44 656	1 030 603	102 (95.5–109)
≥85	1472	359 324	3.17 (2.92–3.44)	56 534	359 889	242 (226–258)
Immigration status						
Native	26 915	10 894 114	1 (reference)	132 400	10 907 491	1 (reference)
First generation	3649	1 968 093	0.72 (0.69–0.74)	11 523	1 969 912	0.67 (0.66–0.69)
Second generation	2267	1 189 457	0.96 (0.91–1.00)	8336	1 190 598	0.98 (0.95–1.00)
Comorbidity						
Depression	5456	1 031 049	1.36 (1.32–1.41)	21 258	1 033 804	0.88 (0.86–0.89)
Other psychiatric conditions	4965	597 810	2.11 (2.04–2.18)	25 627	600 318	1.59 (1.56–1.62)
Cancer	677	146 805	1.13 (1.05–1.22)	7706	147 142	1.61 (1.56–1.65)
Diabetes mellitus	5935	805 894	1.76 (1.71–1.81)	27 220	808 704	1.13 (1.12–1.15)
Chronic viral infection	501	107 641	1.53 (1.40–1.67)	2340	107 886	1.43 (1.36–1.50)
Main source of income						
Wage	10 925	9 262 830	1 (reference)	17 825	9 268 795	1 (reference)
Welfare	5475	1 168 634	1.87 (1.79–1.95)	9583	1 171 506	1.19 (1.16–1.22)
Pension	15 935	3 354 629	1.15 (1.10–1.21)	120 703	3 361 910	0.78 (0.75–0.80)
Other*	496	265 570	1.52 (1.37–1.68)	4148	265 790	2.24 (2.15–2.33)
Household income, quintile						
First	8487	2 038 385	1.97 (1.89–2.06)	49 205	2 042 193	3.41 (3.33–3.49)
Second	7813	2 390 607	1.54 (1.48–1.60)	26 886	2 394 585	1.15 (1.12–1.17)
Third	6058	2 706 935	1.39 (1.33–1.44)	17 655	2 710 062	1.16 (1.14–1.19)
Fourth	4923	2 979 651	1.20 (1.16–1.26)	12 900	2 982 258	1.07 (1.04–1.10)
Fifth	4239	3 391 571	1 (reference)	11 244	3 393 812	1 (reference)
No identified income	78	104 246	0.87 (0.68–1.12)	274	104 285	1.85 (1.63–2.10)
Institutionalised	1075	220 509	1.91 (1.77–2.05)	34 023	220 963	7.43 (7.24–7.64)
Student grant	158	219 758	1.22 (1.04–1.44)	72	219 844	1.32 (1.04–1.68)

[95% 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).

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.



Subgroup	No opioid, reference Event	Person-years	Opioid Event	Person-years
Duration of opioid use				
Chronic use	19 425	11 798 434	3218	303 550
First-time use	21 861	12 013 819	2276	625 896
Intermittent use	21 888	12 637 347	1095	192 810
Sex				
Men	15 860	6 444 259	3356	452 265
Women	10 382	6 485 148	3233	669 991
Age group (yr)				
18–35	2648	3 559 438	365	137 105
35–45	1728	1 992 814	364	124 226
45–55	3398	2 379 775	869	200 222
55–65	5362	2 142 919	1514	223 114
65–75	7037	1 690 831	1929	213 972
75–85	4873	871 619	1272	156 303
85+	1196	292 010	276	67 313
Immigration status				
Native	21 431	10 005 787	5484	888 326
First generation	2972	1 816 877	677	151 216
Second generation	1839	1 106 743	428	82 714
Comorbidity				
Depression	3749	834 557	1707	196 492
Other psychiatric condition	3500	474 291	1465	123 519
Cancer	480	120 450	197	26 356
Diabetes mellitus	4431	669 435	1504	136 459
Chronic viral infection	358	91 714	143	15 927
Main source of income				
Wage	9071	8 739 968	1854	522 862
Welfare	4132	1 012 904	1343	155 730
Pension	12 609	2 920 805	3326	433 824
Other*	430	255 730	66	9841
Household income, quintile				
First	6531	1 802 224	1956	236 161
Second	6067	2 128 467	1746	262 140
Third	4868	2 488 285	1190	218 650
Fourth	4007	2 781 751	916	197 900
Fifth	3590	3 210 783	649	180 788
No identified income	69	102 663	<10	N/A
Institutionalised	960	200 215	115	20 294
Student grant	150	215 020	<10	N/A

Fig 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.

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

Subgroup	No opioid, reference Event	No opioid, reference Person-years	Opioid Event	Opioid Person-years
Duration of opioid use				
Chronic use	70 361	11 805 973	36 330	305 783
First-time use	70 371	12 021 635	26 452	629 927
Intermittent use	82 001	12 646 016	7466	193 688
Sex				
Men	40 381	6 449 733	33 487	456 395
Women	41 630	6 488 869	36 761	673 004
Age group (yr)				
18–35	941	3 560 546	300	137 676
35–45	955	1 993 499	706	124 713
45–55	2741	2 381 038	2729	201 284
55–65	6215	2 144 765	7877	224 849
65–75	13 432	1 693 192	15 173	215 946
75–85	24 457	873 202	20 199	157 401
85+	33 270	292 358	23 264	67 530
Immigration status				
Native	70 753	10 013 224	61 647	894 267
First generation	6685	1 817 968	4838	151 944
Second generation	4573	1 107 410	3763	83 188
Comorbidity				
Depression	9064	835 977	12 194	197 826
Other psychiatric condition	10 911	475 684	14 716	124 633
Cancer	2158	120 604	5548	26 538
Diabetes mellitus	13 154	670 983	14 066	137 721
Chronic viral infection	780	91 837	1560	16 049
Main source of income				
Wage	8816	8 743 278	9009	525 517
Welfare	5252	1 014 522	4331	156 984
Pension	65 472	2 924 932	55 231	436 978
Other*	2471	255 870	1677	9920
Household income, quintile				
First	24 519	1 804 410	24 686	237 783
Second	12 574	2 130 675	14 312	263 909
Third	8385	2 490 005	9270	220 058
Fourth	5948	2 783 179	6952	199 079
Fifth	5158	3 211 999	6086	181 814
No identified income	195	102 688	79	1596
Institutionalised	25 168	200 560	8855	20 403
Student grant	64	215 085	<10	N/A

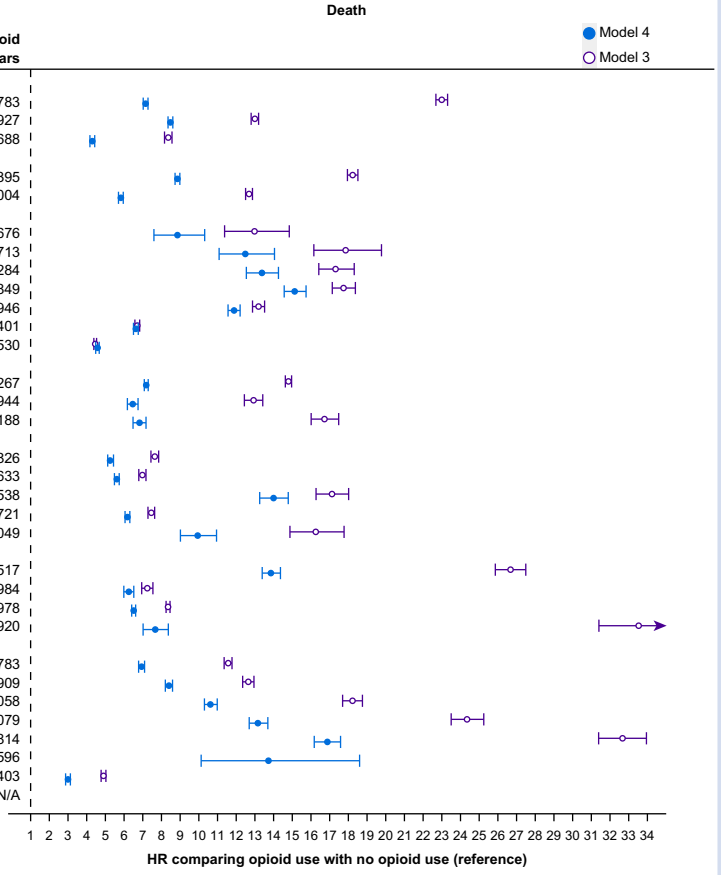


Fig 3. Association between opioid use and death in different subgroups of the total population. The graph shows results of univariable and multivariable Cox regression models in different subgroups of opioid use, sex, age, comorbidities, primary source of income, and household income in quintiles. (The 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.

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.

Authors' contributions

Study conception/design: all authors
Data analysis: AB, ELAvD
Data interpretation: all authors
Drafting of paper: AB, ELAvD
Critical revisions: all authors
Approval of final submitted version: all authors
AB and ELAvD had full access to the Statistics Netherlands data set. All authors agreed to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations of interest

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Appendix A. Supplementary data

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