Dynamics of the opioid crisis in the Netherlands

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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

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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).

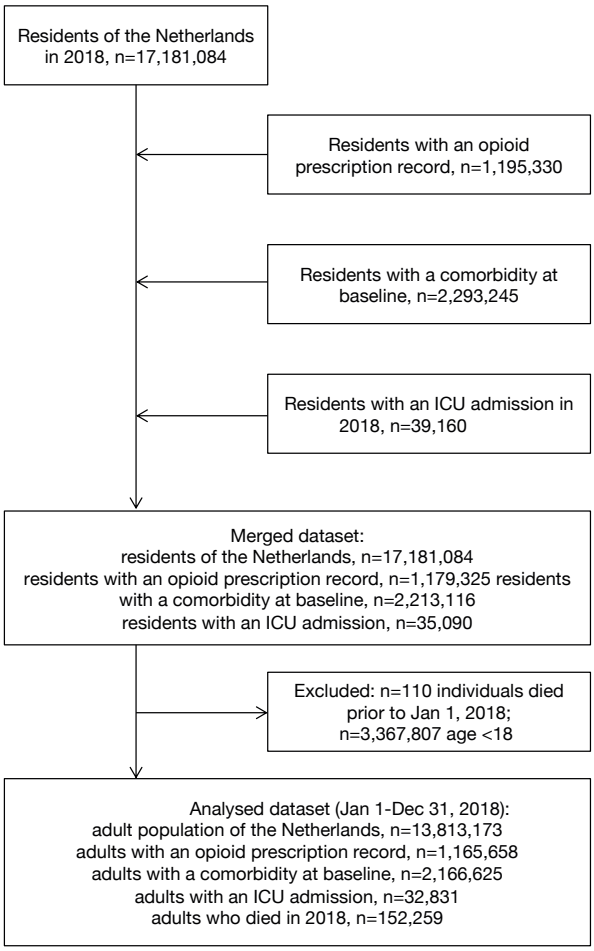


Figure 1. Inclusion and exclusion of individuals in the data set

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

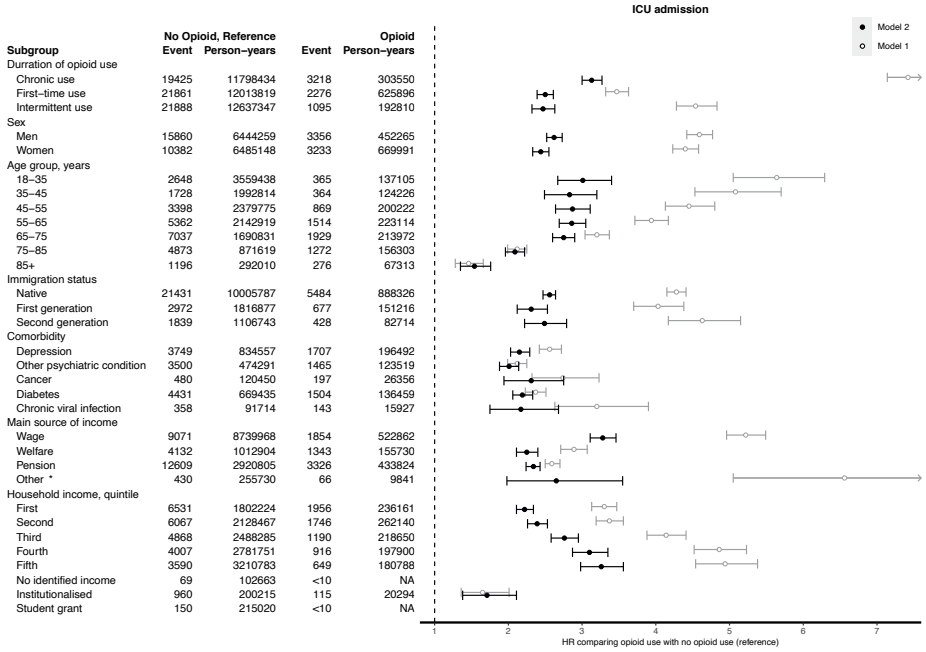
There were 6,589 ICU admissions registered for 1,122,256 person-years amongst opioid users (5.9 per 1000 person-years) and 26,242 ICU admissions for 12,929,407 person-years amongst non-users (2.0 per 1000 person-years). Amongst adult residents using opioids, the mortality rate was 62 per 1000 person-years, 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

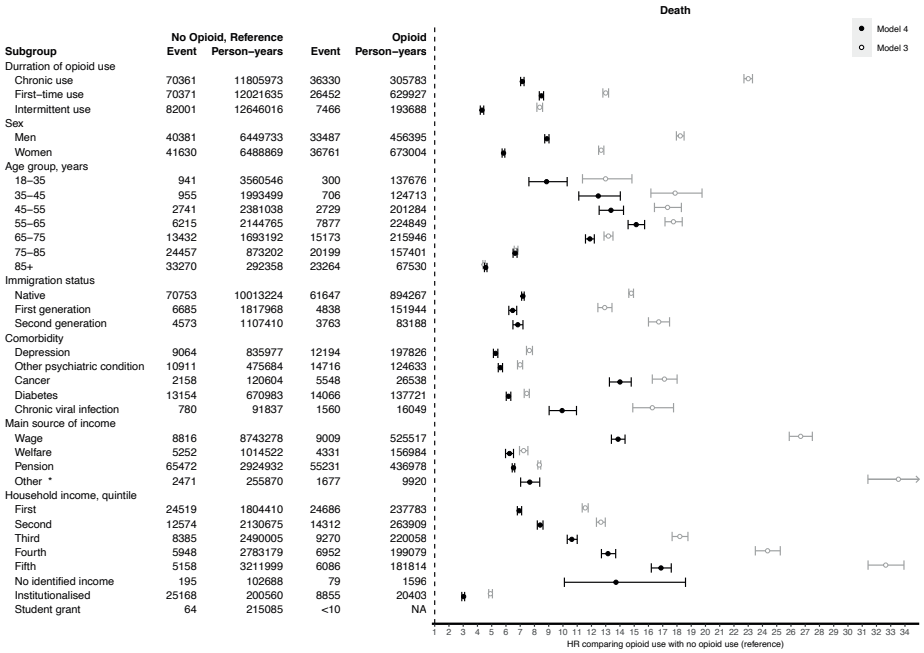
The graph shows unadjusted and adjusted estimates in subgroups of age, sex, comorbidities, primary source of income, and household income in quintiles. (The first quintile is the lowest income group.) Here, we also report number of events and cumulative number of person-years for each exposure group (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.