Dynamics of the opioid crisis in the Netherlands

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PART 2

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

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CHAPTER 5

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

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Abstract

Objective

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

Design

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

Results

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

Conclusion

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

Research in context

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

Introduction and rationale

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

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

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

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

Methods

Setting, participants, and data sources

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

Pharmacy claims data

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

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

Hospital admissions and deaths registry

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

Variables

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

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

Outcomes

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

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

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

Statistical Methods

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

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

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

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

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

Restriction analyses

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

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

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

Data Linkage

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

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

Results

Participants

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

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

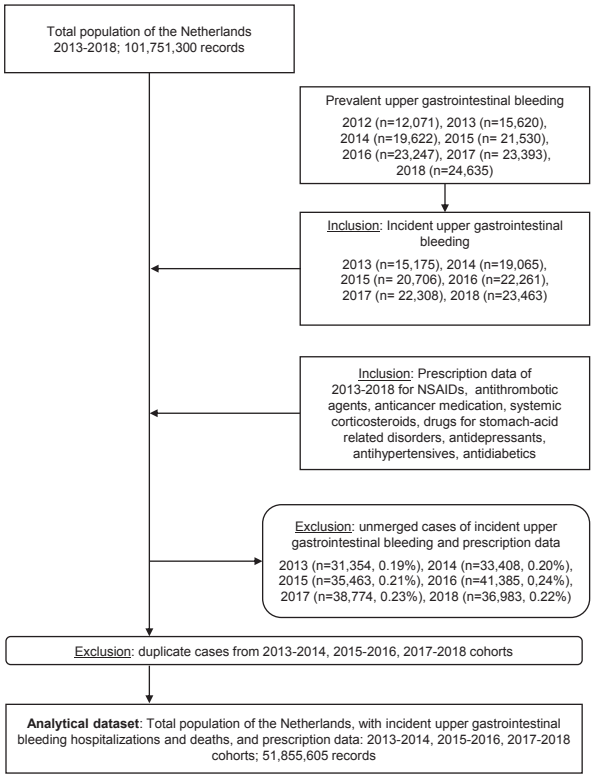

Figure 1. Flow diagram of merging of datasets, the Netherlands, from 2013 to 2018

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

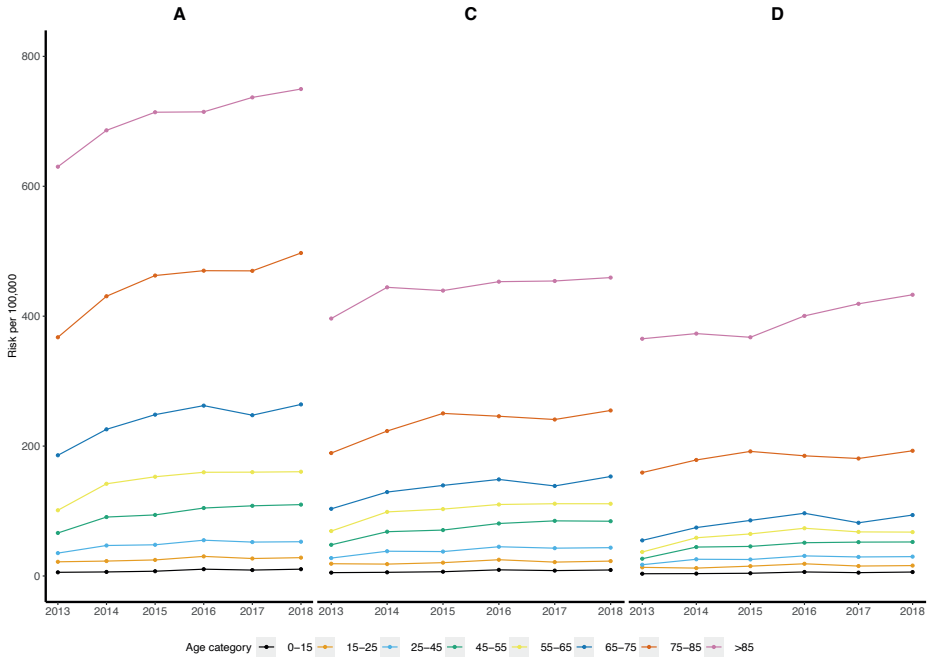

Figure 2. The age-specific risk of severe upper gastrointestinal bleeding in three different subgroups, the Netherlands, from 2013 to 2018

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

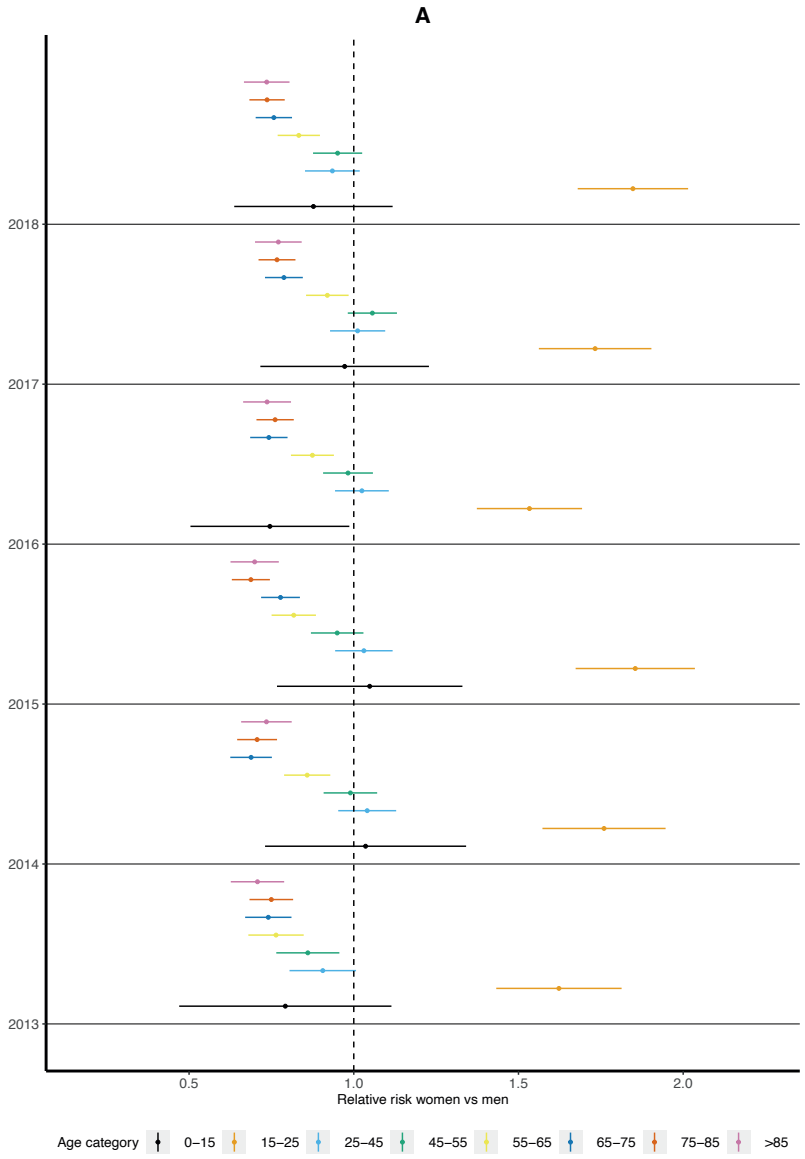

Figure 3. The risk of severe upper gastrointestinal bleeding in women compared to men in different age groups of the total population (subgroup A), the Netherlands, from 2013 to 2018

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

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

Discussion

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

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

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

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

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

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

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

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

Limitations

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

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

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

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

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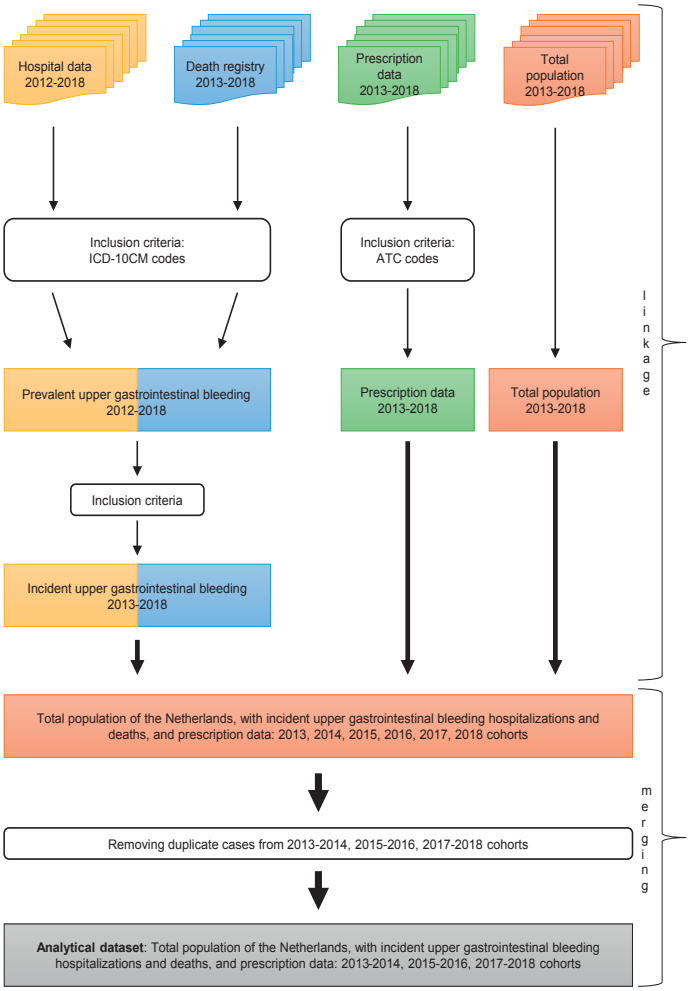
Supplement to: Risk of drug-related upper gastrointestinal bleeding in the total population of the Netherlands: a time-trend analysis



Supplementary Figure 1. Data linkage strategy

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

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

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

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

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

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

	2013	2014	2015	2016	2017	2018
Total, n	16779442	16829289	16900726	16979120	17081506	17181084
Age, mean [SD]	41.29 [22.97]	41.53 [23.03]	41.76 [23.10]	41.95 [23.16]	42.12 [23.23]	42.30 [23.28]
Age categories, n (%)						
0-15	2676566 (15.95)	2647191 (15.73)	2619145 (15.5)	2595233 (15.28)	2578067 (15.09)	2559103 (14.89)
15-25	2042172 (12.17)	2050432 (12.18)	2058861 (12.18)	2069566 (12.19)	2086033 (12.21)	2101106 (12.23)
25-45	4286532 (25.55)	4232031 (25.15)	4201191 (24.86)	4188101 (24.67)	4195813 (24.56)	4221792 (24.57)
45-65	4735716 (28.22)	4773582 (28.36)	4810241 (28.46)	4839257 (28.50)	4853937 (28.42)	4853361 (28.25)
>65	3038456 (18.11)	3126053 (18.58)	3211288 (19.00)	3286963 (19.36)	3367657 (19.72)	3445722 (20.06)
Sex, n (%)						
men	8307302 (49.51)	8334418 (49.52)	8372983 (49.54)	8417298 (49.57)	8475255 (49.62)	8527129 (49.63)
women	8472140 (50.49)	8494871 (50.48)	8527743 (50.46)	8561822 (50.43)	8606251 (50.38)	8653955 (50.37)
Received a prescription for a medication						
NSAIDs, n (%)	2593528 (15.46)	2527462 (15.02)	2461396 (14.56)	2395910 (14.11)	2335794 (13.67)	2286139 (13.31)
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Abbreviations: SD, standard deviation; NSAIDs, nonsteroidal anti-inflammatory drugs. All medications were identified through prescription reimbursement data, based on their ATC codes per calendar year. Identified medications: NSAIDs (ATC code: M01A), antithrombotic agents (B01A), anticancer medication (L01, L02), systemic corticosteroids (H02A, H02B), drugs for stomach-acid related disorders (A02A, A02B, A02X), antidepressants (N06A), antihypertensives (C02, C03, C07, C08, C09), antidiabetic medication (A10). People might have received several medications in a given year, e.g., could have used NSAIDs and antithrombotic agents at the same time in a given year.

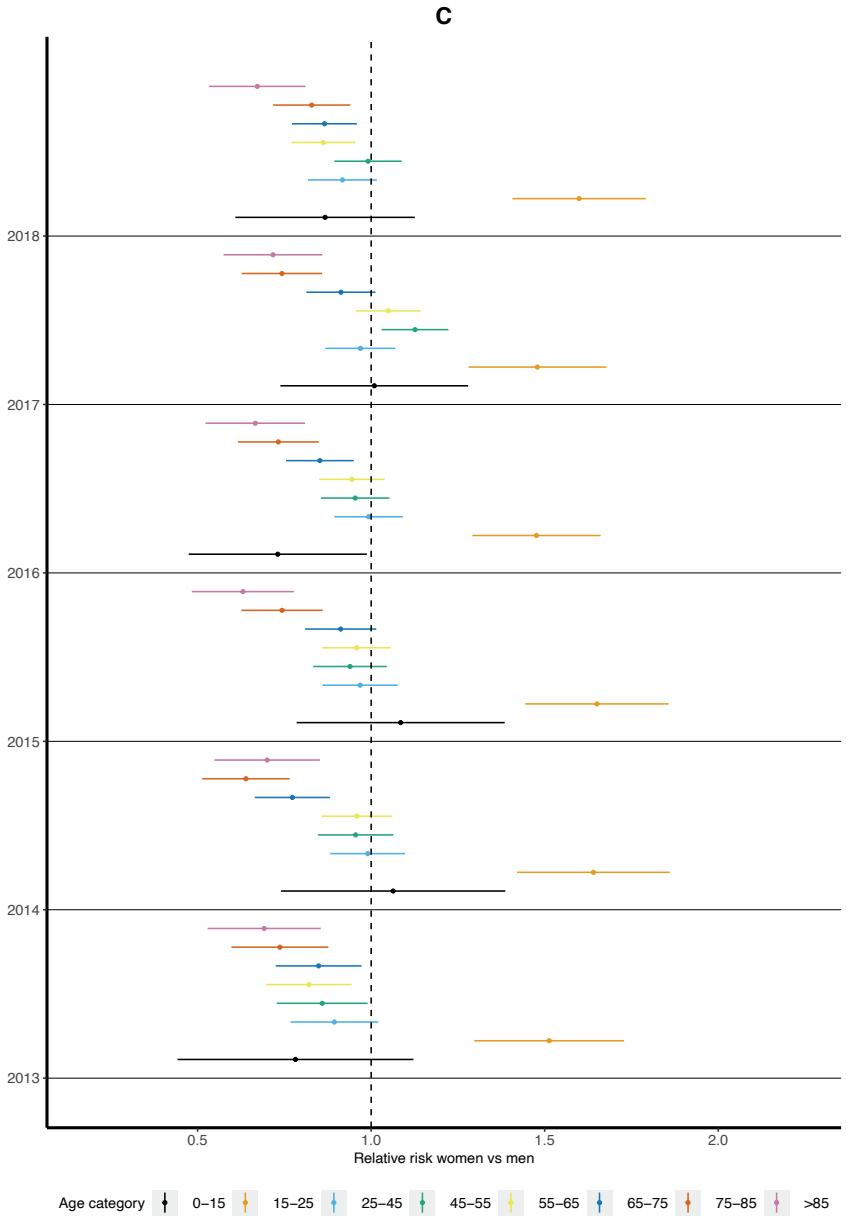
Supplementary Table 3. Risk of severe upper gastrointestinal bleeding in four different subgroups, the Netherlands, from 2013 to 2018

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

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

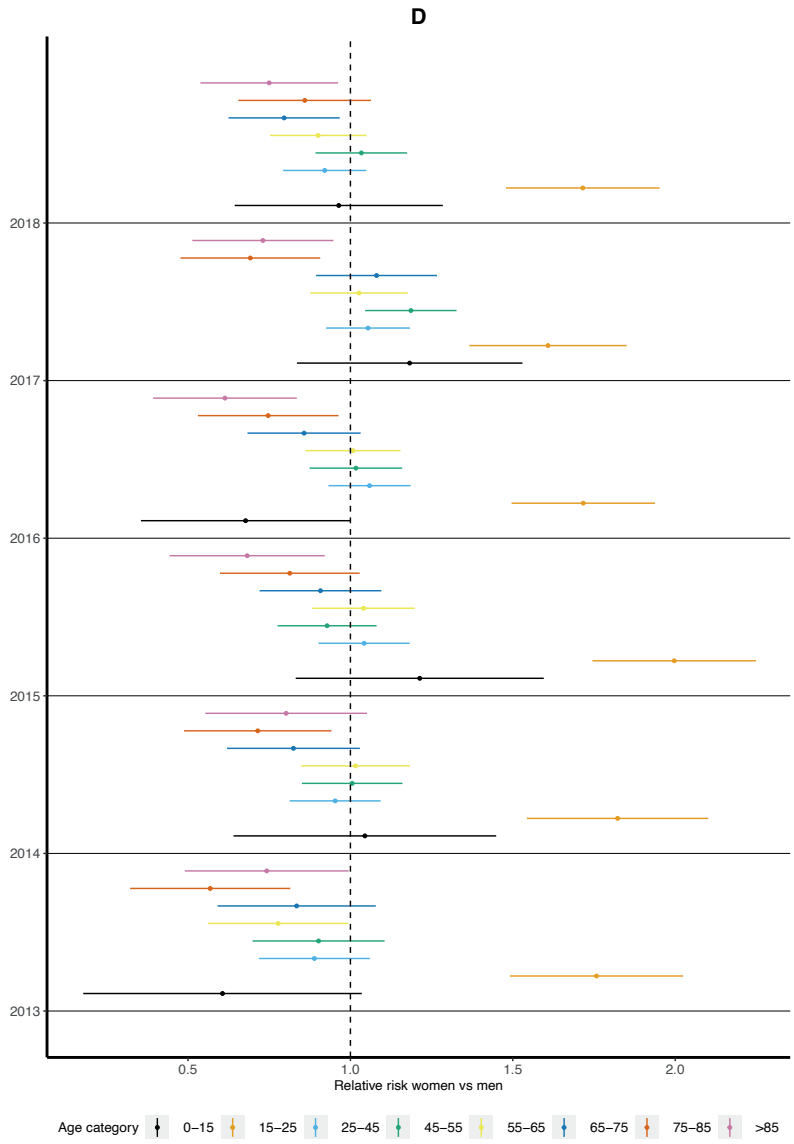
Subgroup	Calendar Year	No.	Total No.	Cumulative incidence event/100,000 inhabitants (95% CI)	Model 1 odds ratio (95% CI)	Model 2 odds ratio (95% CI)
D	2013	2351	10429604	22.54 (21.63-23.45)	1.00 (reference)	1.00 (reference)
	2014	3237	10469429	30.92 (29.85-31.98)	1.37 (1.30-1.45)	1.35 (1.28-1.43)
	2015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

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



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

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



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

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