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, for example, non-steroidal 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 hospitalisation), contingent on medication prescription, is unknown.

Design We conducted a cohort study using Dutch national statistics on pharmacy claims, hospitalisation and mortality between 2013 and 2018. We explored the incidence of sex-specific and age-specific severe UGIB in four (sub)populations: (A) total population, (B) without a filled prescrption for NSAIDs, (C) without filled prescriptions for 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% CI 197 to 201) in 2013–2014 and 260 (95% CI 258 to 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 with 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 a relationship between reduced prescribing of NSAIDs and the incidence of severe UGIB in the Netherlands since 2013. The relationship was also not observed when we removed the effect of risk factors.

INTRODUCTION AND RATIONALE

Non-steroidal 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, gastro-intestinal disturbances, increased risk of

Summary box

What is already known about this subject?
► Upper gastrointestinal bleeding (UGIB) has many risk factors including medications, such as non-steroidal 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.

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 2–4 fold 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, for example, 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. 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 hypothesise 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, for example, anticoagulants, as well as medication that can be bought over-the-counter.[13] Despite this, we hypothesised 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-dependent 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 nationwide cohort study using several anonymised datasets from Statistics Netherlands (CBS) covering the total population of the Netherlands (about 17.1 million residents) between 1 January 2013 and 31 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 pseudo-anonymised identifiers that ensure deterministic dataset linkage on an individual level (the dataset linkage and merging strategy is presented in online supplemental figure 1).

Pharmacy claims data

Prescription reimbursement claims were collected for all residents of the Netherlands entitled to pharmaceutical care, that is, those ensured by the basic health insurance, which is n=17 163 404 (99.9%) residents in 2018.[14] The Dutch Healthcare Institute provides 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 encounter, 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, clinical modification) 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 haemorrhage (K25.0), acute gastric ulcer with perforation (K25.1), acute gastric ulcer with haemorrhage and perforation (K25.2), acute duodenal ulcer with haemorrhage (K26.0), acute duodenal ulcer with perforation (K26.1), acute duodenal ulcer with both haemorrhage and perforation (K26.2), acute peptic ulcer with haemorrhage, site unspecified (K27.0), acute peptic ulcer with perforation, site unspecified (K27.1), acute peptic ulcer with both haemorrhage and perforation, site unspecified (K27.2), acute gastrojejunal ulcer with haemorrhage (K28.0), acute gastrojejunal ulcer with perforation (K28.1), acute gastrojejunal ulcer with both haemorrhage and perforation (K28.2), acute haemorrhagic gastritis (K29.0), haematemesis (K92.0), melaena (K92.1) and unspecified gastrointestinal haemorrhage (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 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, SD) per one calendar year 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% CI. CIs were calculated based on the standard errors of the estimate, assuming normal distribution.[24] All estimates were calculated per 1 and per 2 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 five 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 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 eight 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).
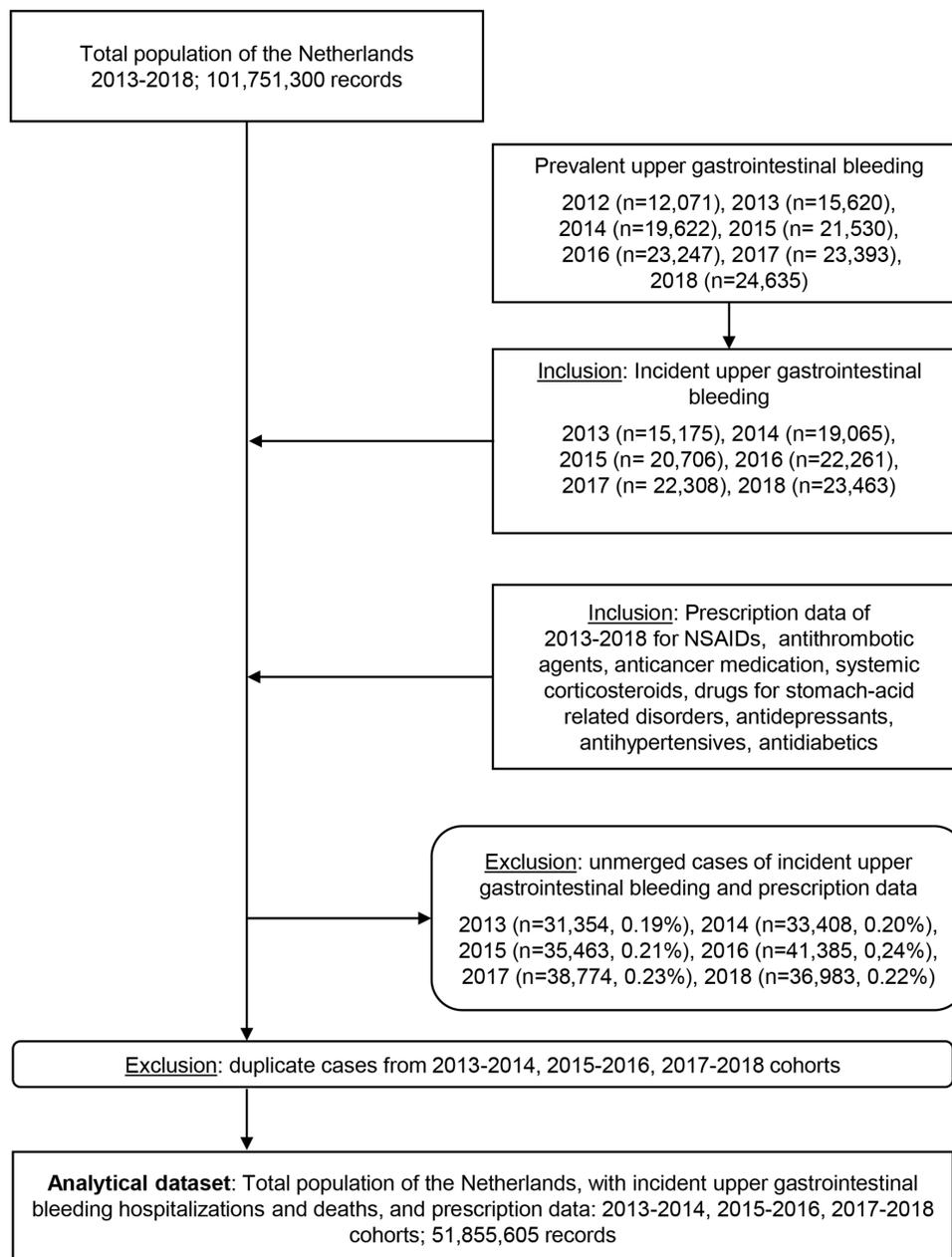
Then, we restricted the population to residents that did not fill a prescription for NSAIDs (subgroup B), and third to individuals to whom neither NSAIDs nor antithrombotic agents were prescribed (subgroup C). In the second analysis we removed the effect of NSAIDs prescription, because we were interested 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 homogeneous 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 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 (online supplemental table 1). Therefore, we decided to perform a complete case analysis.

TheStrengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist for cohort studies is included in the Appendix. All statistical analyses were performed with SPSS for Windows, release V.25.0 (SPSS). Figures were created with R studio (A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing,

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┌─────────────────────────────────┐
│ Total population of the Netherlands │
│ 2013-2018; 101,751,300 records   │
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┌─────────────────────────────────────┐
│ Prevalent upper gastrointestinal     │
│ bleeding                              │
│ 2012 (n=12,071), 2013 (n=15,620),    │
│ 2014 (n=19,622), 2015 (n= 21,530),   │
│ 2016 (n=23,247), 2017 (n= 23,393),   │
│ 2018 (n=24,635)                       │
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│ Inclusion: Incident upper gastrointestinal │
│ bleeding                              │
│ 2013 (n=15,175), 2014 (n=19,065),    │
│ 2015 (n= 20,706), 2016 (n=22,261),   │
│ 2017 (n= 22,308), 2018 (n=23,463)    │
└─────────────────────────────────────┘

┌─────────────────────────────────────┐
│ Inclusion: Prescription data of       │
│ 2013-2018 for NSAIDs, antithrombotic  │
│ agents, anticancer medication, systemic │
│ corticosteroids, drugs for stomach-acid │
│ related disorders, antidepressants,   │
│ antihypertensives, antidiabetics      │
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│ Exclusion: unmerged cases of incident │
│ upper gastrointestinal bleeding and   │
│ prescription data                     │
│ 2013 (n=31,354, 0.19%), 2014 (n=33,408, 0.20%), │
│ 2015 (n=35,463, 0.21%), 2016 (n=41,385, 0,24%), │
│ 2017 (n=38,774, 0.23%), 2018 (n=36,983, 0.22%)  │
└─────────────────────────────────────┘

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│ Exclusion: duplicate cases from 2013-2014, 2015-2016, 2017-2018 cohorts │
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│ Analytical dataset: Total population of the Netherlands, with incident upper gastrointestinal │
│ bleeding hospitalizations and deaths, and prescription data: 2013-2014, 2015-2016, 2017-2018 │
│ cohorts; 51,855,605 records          │
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Figure 1 Flow diagram of merging of datasets, the Netherlands, from 2013 to 2018. Datasets were merged based on unique pseudoanonymised 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 one calendar year and 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 calendar year 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 online supplemental file 1. ATC, Anatomical Therapeutic Chemical; ICD-10, International Statistical Classification of Diseases, 10th revision; NSAIDs, non-steroidal anti-inflammatory drugs.

Vienna, Austria, https ://www.R-proje ct.org), using *R* package *ggplot2* V.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, three cohorts, that is, 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

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	17 112 982	17 269 164	17 473 459
Age, mean (SD)	41.76 (23.18)	42.19 (23.32)	42.54 (23.43)
Age categories, n (%)			
0–15	2 867 188 (16.75)	2 815 725 (16.30)	2 776 878 (15.89)
15–25	2 079 263 (12.15)	2 105 049 (12.19)	2 138 442 (12.24)
25–45	4 368 952 (25.53)	4 299 213 (24.90)	4 305 414 (24.64)
45–65	4 755 790 (27.79)	4 834 007 (27.99)	4 880 562 (27.93)
>65	3 041 779 (17.77)	3 215 170 (18.62)	3 372 163 (19.30)
Sex, n (%)			
Men	8 482 826 (49.57)	8 568 391 (49.62)	8 679 186 (49.67)
Women	8 630 156 (50.43)	8 700 773 (50.38)	8 794 273 (50.33)
Received a prescription for a medication			
NSAIDs, n (%)	4 094 856 (23.93)	3 906 368 (22.62)	3 735 730 (21.38)
Antithrombotic agents, n (%)	1 962 912 (11.47)	2 033 817 (11.78)	2 091 111 (11.97)
Anticancer medication, n (%)	247 017 (1.44)	226 766 (1.31)	223 665 (1.28)
Systemic corticosteroids, n (%)	1 243 385 (7.27)	1 336 613 (7.74)	1 378 921 (7.89)
Drugs for stomach-acid disorders, n (%)	2 377 506 (13.89)	2 535 825 (14.68)	2 603 371 (14.90)
Antidepressants, n (%)	1 223 285 (7.15)	1 242 787 (7.20)	1 256 602 (7.19)
Antihypertensives, n (%)	3 419 241 (19.98)	3 454 098 (20.00)	3 484 030 (19.94)
Antidiabetic medication, n (%)	854 240 (4.99)	867 259 (5.02)	877 046 (5.02)

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, for example, could have used NSAIDs and antithrombotic agents at the same time in a given year.
ATC, Anatomical Therapeutic Chemical; NSAIDs, non-steroidal anti-inflammatory drugs.

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).

About 4 million (22%) of residents received at least one NSAID prescription in a 2-year period, which was closely followed by antihypertensive medication (20%), and drugs for stomach-acid related disorders (about 14% of the population). The prevalence of presribed medication 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 above-mentioned analyses were repeated annually, and showed similar results (online supplemental table 2).

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

In the total Dutch population, the 2 years' worth cumulative incidence of severe UGIB was 199 per 100 000 inhabitants (95% CI 197 to 201) in 2013–2014, and in 2017–2018 it was 260 per 100 000 inhabitants (95% CI 258 to 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 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 lower than in the total population, but the trend of severe UGIB over calendar time did not change (model 2, age-adjusted and sex-adjusted OR, 1.26 (95% CI 1.24 to 1.28) comparing 2017–2018 with 2013–2014) (table 2).

The cumulative incidence of severe UGIB over 2 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-adjusted and sex-adjusted OR, 1.29 (95% CI 1.26 to 1.32) comparing 2017–218 with 2013–2014).

Last, when we restricted the total Dutch population to residents who did not fill any prescriptions for NSAIDs, antithrombotic agents, anticancer medication, drugs for stomach-acid related disorders, antidepressants,

Table 2 Risk of severe UGIB 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 OR (95% CI)	Model 2 OR (95% CI)
A	2013–2014	34 071	17 112 982	199.09 (196.99 to 201.22)	1 (reference)	1 (reference)
	2015–2016	42 732	17 269 164	247.45 (245.11 to 249.80)	1.24 (1.23 to 1.26)	1.21 (1.20 to 1.23)
	2017–2018	45 516	17 473 459	260.49 (258.11 to 262.89)	1.31 (1.29 to 1.33)	1.25 (1.24 to 1.27)
B	2013–2014	23 029	13 018 126	176.90 (174.63 to 179.20)	1 (reference)	1 (reference)
	2015–2016	29 562	13 362 796	221.23 (218.72 to 223.76)	1.25 (1.23 to 1.27)	1.21 (1.19 to 1.23)
	2017–2018	32 503	13 737 729	236.60 (234.04 to 239.18)	1.34 (1.32 to 1.36)	1.26 (1.24 to 1.28)
C	2013–2014	10 837	11 678 227	92.80 (91.07 to 94.56)	1 (reference)	1 (reference)
	2015–2016	14 062	11 935 659	117.82 (115.88 to 119.78)	1.27 (1.24 to 1.30)	1.24 (1.21 to 1.27)
	2017–2018	15 338	12 229 473	125.42 (123.45 to 127.42)	1.35 (1.32 to 1.39)	1.29 (1.26 to 1.32)
D	2013–2014	4217	9 354 526	45.08 (43.72 to 46.44)	1 (reference)	1 (reference)
	2015–2016	5779	9 514 371	60.74 (59.17 to 62.31)	1.35 (1.30 to 1.40)	1.31 (1.26 to 1.37)
	2017–2018	6164	9 731 023	63.34 (61.76 to 64.92)	1.41 (1.35 to 1.46)	1.34 (1.29 to 1.39)

All medications were identified through prescription reimbursement data, based on their ATC codes. People might have received several medications in a given year, for example, could have used NSAIDs and antithrombotic agents at the same time. Incident cases of severe UGIB were identified based on ICD-10CM codes in the hospital admission and death registry.
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.
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 (categorised), and sex imbalances between the cohorts.
ATC, Anatomical Therapeutic Chemical; ICD-10, International Statistical Classification of Diseases, 10th revision; NSAIDs, non-steroidal anti-inflammatory drugs; UGIB, upper gastrointestinal bleeding.

antihypertensives or antidiabetic medication (subgroup D) the biennial cumulative incidence was about four 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-adjusted and sex-adjusted OR, 1.34 (95% CI 1.29 to 1.39)) (table 2). All of the above-mentioned analyses were repeated annually, and showed similar results (online supplemental 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 2A). 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, onine supplemental figure 2, online supplemental figure 3).

DISCUSSION

In this study, in which we had full access to national Dutch registry data on pharmacy claims, hospitalisations and mortality between 1 January 2013 and 31 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
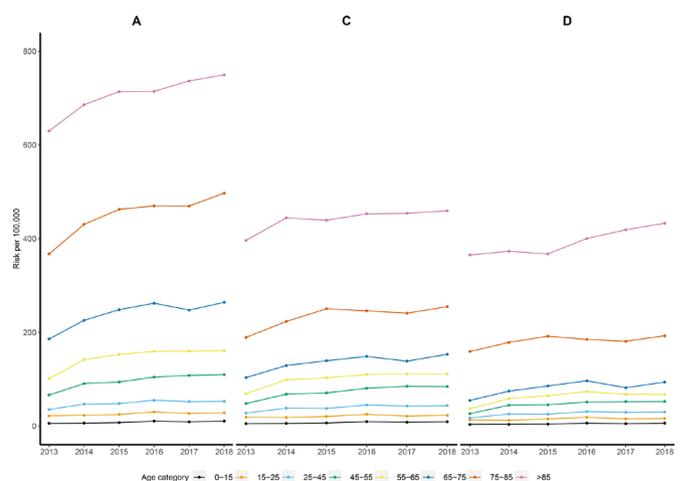
Figure 2 The age-specific risk of severe upper gastrointestinal bleeding in three different subgroups, the Netherlands, from 2013 to 2018. Figure shows age-specific annual cumulative incidence of severe upper gastrointestinal bleeding per 100 000 inhabitants in three different scenarios: (A) total population, (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.
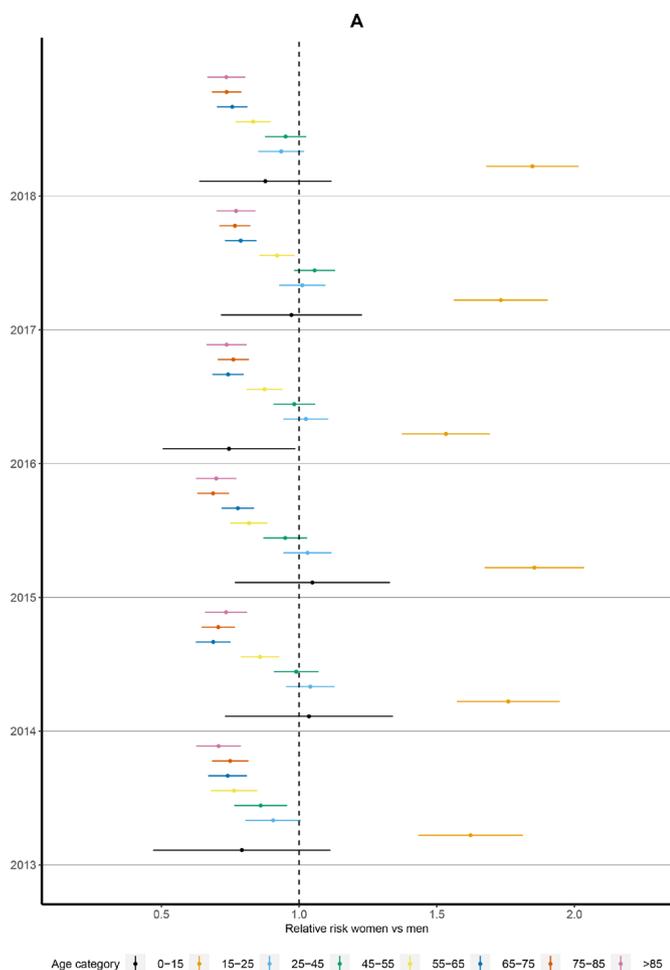
Figure 3 The risk of severe upper gastrointestinal bleeding (UGIB) in women compared with men in different age groups of the total population (subgroup A), the Netherlands, from 2013 to 2018 figure shows crude relative risks of annual incidence of severe UGIB in women compared with men (male sex was the reference group) among different age groups in the total Dutch population .

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 corrected 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, that is, 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 use of NSAIDs 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 3 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 dysmenorrhoea (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, prescribed 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 use of NSAIDs, 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 dysmenorrhoea and other afflictions.

Limitations

This research has some methodological issues that warrant a comment. First, there was some data lost when merging 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 (online supplemental table 1).

Second, prescription information on NSAIDs and other medications was only available on the third 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 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 (eg, 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 UGIB since then.

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