

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

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SUPPLEMENTARY MATERIAL

Supplementary Figure 1. **Data linkage strategy**

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

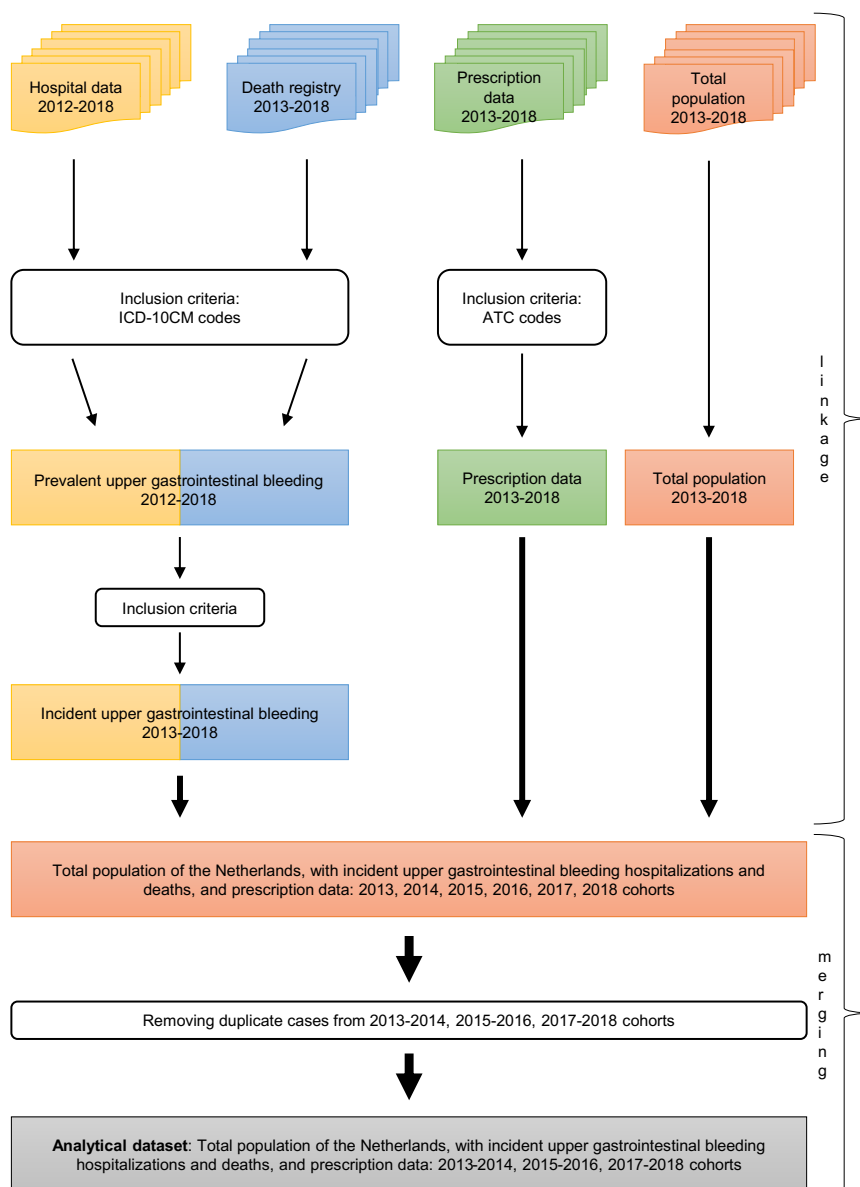
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Supplementary Figure 3. **The risk of severe upper gastrointestinal bleeding in women compared to men in different groups of residents who were unexposed to any risk factors (subgroup D), the Netherlands, from 2013 to 2018**

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	Model 1	Model 2
				event/100,000 inhabitants (95% CI)	odds ratio (95% CI)	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)
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

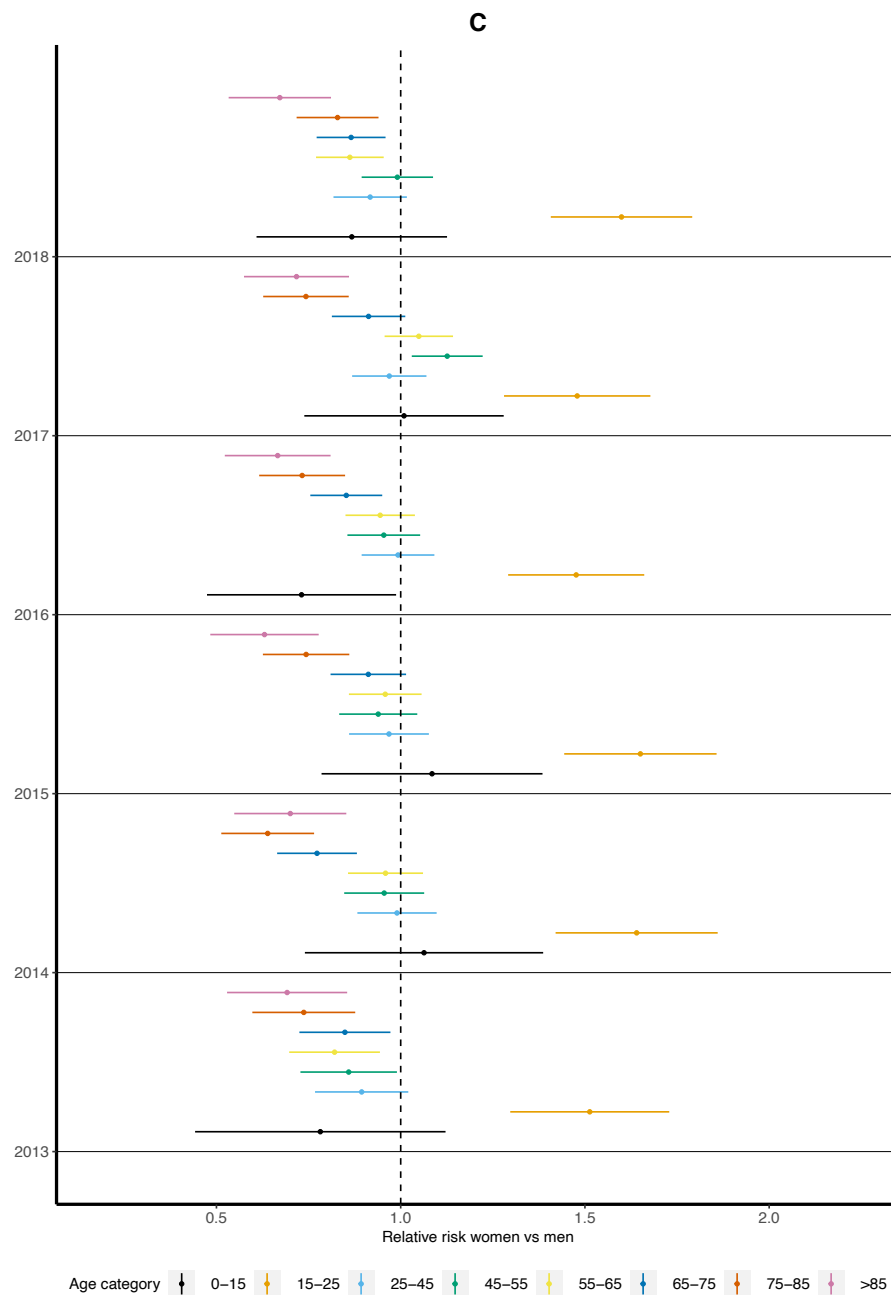


Figure shows crude relative risks of annual incidence of severe upper gastrointestinal bleeding in women compared to men (male sex was the reference group) in different age groups among those residents who were unexposed to prescribed nonsteroidal anti-inflammatory drugs and antithrombotic agents (subgroup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

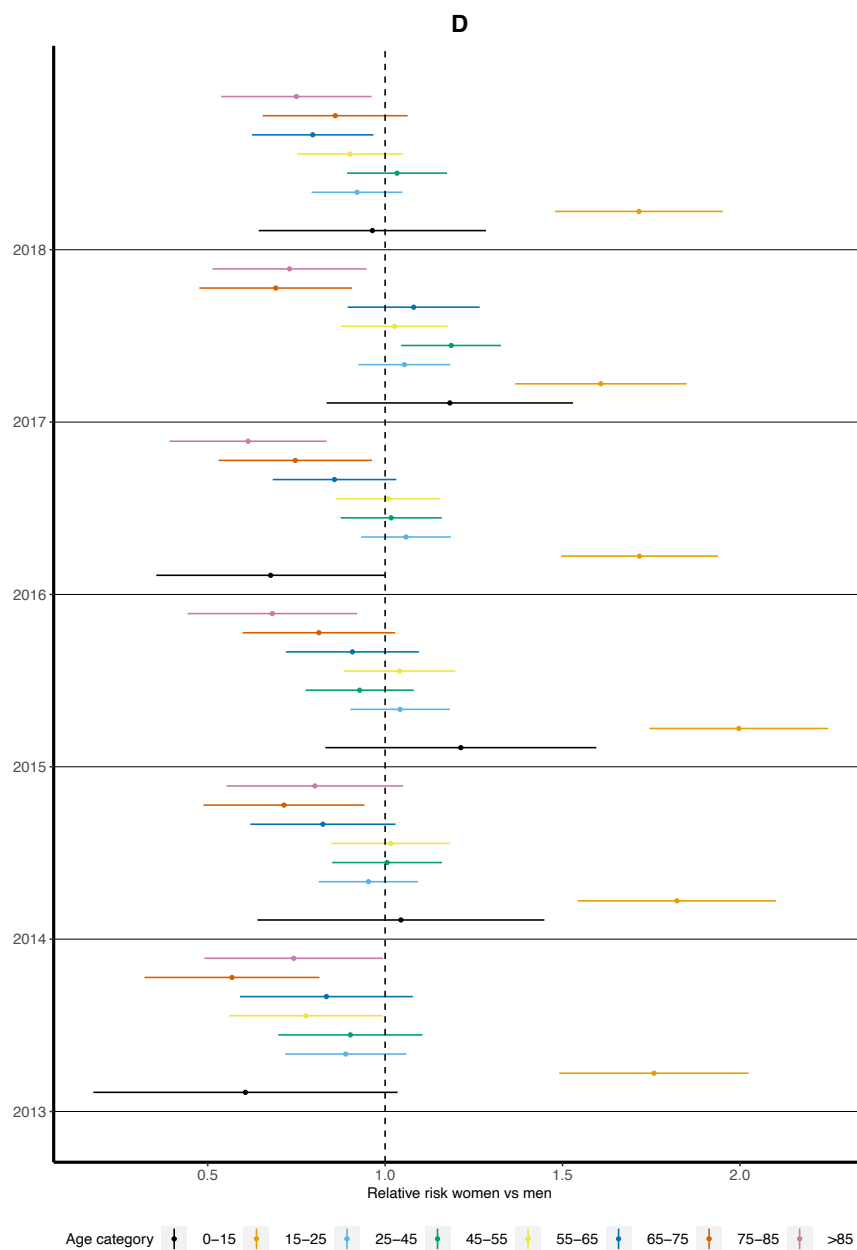


Figure shows crude relative risks of annual incidence of severe upper gastrointestinal bleeding in women compared to men (male sex was the reference group) in different age groups among those residents without any medication that is either a risk factor for upper gastrointestinal bleeding or the indication 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.