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Constipation and risk of cardiovascular diseases: a Danish population-based matched cohort study

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ABSTRACT

Objectives To assess the risks of myocardial infarction, stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter and heart failure in patients with constipation compared with a general population cohort.

Design Population-based matched cohort study.

Setting All Danish hospitals and hospital outpatient clinics from 2004 to 2013.

Participants Patients with a constipation diagnosis matched on age, sex and calendar year to 10 individuals without constipation from the general population.

Main outcomes measures Comorbidity-adjusted and medication-adjusted hazard ratios (aHRs) for cardiovascular outcomes based on Cox regression analysis.

Results 83 239 patients with constipation were matched to 832 384 individuals without constipation. The median age at constipation diagnosis was 46.5% and 41% were men. Constipation was strongly associated with venous thromboembolism (aHR 2.04, 95% CI 1.89 to 2.20), especially splanchnic venous thrombosis (4.23, 95% CI 2.45 to 7.31). Constipation was also associated with arterial events, including myocardial infarction (1.24, 95% CI 1.14 to 1.35), ischaemic stroke (1.50, 95% CI 1.41 to 1.60), haemorrhagic stroke (1.46, 95% CI 1.26 to 1.69), peripheral artery disease (1.34, 95% CI 1.20 to 1.50), atrial fibrillation or atrial flutter (1.27, 95% CI 1.20 to 1.34) and heart failure (1.52, 95% CI 1.42 to 1.62). The associations were strongest during the first year after the constipation diagnosis and strengthened with an increased number of laxative prescriptions.

Conclusions Constipation was associated with an increased risk of several cardiovascular diseases, in particular venous thromboembolism.

Strengths and limitations of this study

► The population-based design within the setting of a tax-supported universal healthcare system limited selection bias.
► We only included constipated patients in contact with the healthcare system, which may limit the generalisability.
► The positive predictive value of the constipation diagnosis in the Danish National Patient Registry has not been examined in detail, but was confirmed by the treating physician and therefore assumed high.
► Cardiovascular diagnoses generally have very high positive predictive values in the Danish National Patient Registry.
► Despite the use of several approaches to control for and examine the potential impact of confounding, unmeasured confounding cannot be entirely excluded.

INTRODUCTION

Constipation causes substantial morbidity worldwide[1 2] and is one of the most prevalent conditions presenting to general practitioners, medical specialists and surgeons across subspecialties.[3] The prevalence of constipation ranges from 3% to 79% in various adult populations depending on age, sex and the definition of constipation.[2 4–9] Among patients hospitalised for cardiovascular disease, the prevalence of constipation is approximately 50%.[10]

Constipation and cardiovascular diseases share common risk factors, including age,[8] use of non-aspirin non-steroidal anti-inflammatory drugs,[11] diabetes mellitus, depression,[12] lack of physical exercise[13] and low dietary fibre intake.[13] However, a substantial proportion of cardiovascular diseases cannot be explained by traditional cardiovascular risk factors.[14] Constipation may be a risk factor for cardiovascular diseases via several putative mechanisms. Disturbances in the gut microbiome are common in patients with constipation[15] and have been associated with arterial stiffness,[16] increased blood pressure,[17] atherosclerotic cardiovascular diseases[18–20] and heart failure.[21] However, the associations have not been investigated specifically in constipated patients with dysbiosis. In addition, strain at stool and associated mental stress increase the blood pressure,[10] which is a risk factor for atherosclerotic, haemorrhagic and arrhythmic cardiovascular diseases.[22 23]

Information on the association between constipation and cardiovascular disease is currently limited. Two studies have examined this association, both focusing only on atherosclerotic cardiovascular disease and relying on self-reported constipation. In a cohort of postmenopausal women, only severe constipation was associated with a 1.2-fold increased risk of atherosclerotic cardiovascular disease.[24] In a cohort of US veterans, constipation was associated with a 1.1-fold increased risk of coronary heart disease and a 1.2-fold increased risk of ischaemic stroke.[25]

Considering the sheer number of patients with constipation,[3] any association with cardiovascular disease would have public health interest. Therefore, we conducted a large population-based cohort study of patients with a first-time diagnosis of constipation to examine the subsequent risk of common cardiovascular diseases compared with risks in a matched general population cohort.

METHODS
Setting and design
We conducted this population-based cohort study in Denmark, which had a cumulative population of 6 482 126 inhabitants during the study period. The Danish National Health Service provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners and hospitals.[26] Accurate and unambiguous linkage of all registries in Denmark is possible at the individual level using the unique central personal registry number assigned to each Danish citizen at birth and to residents on immigration.[27]

Patients with constipation
Selection of patients is presented in the study flowchart (figure 1). We used the Danish National Patient Registry (DNPR)[28] to identify all patients with a first-time inpatient or outpatient hospital diagnosis of constipation during the study period (1 July 2004 to 30 November 2013). The DNPR has recorded information on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995.[28] Each hospital discharge or outpatient clinic visit is recorded with one primary diagnosis (ie, the main reason for admission) and one or more secondary diagnoses classified according to the International Classification of Diseases, Eighth Revision (ICD-8) through 1993 and 10th Revision (ICD-10) thereafter.[28] We identified patients with constipation using both the primary and secondary inpatient and outpatient diagnoses. We excluded patients with a previous or concurrent inpatient or outpatient diagnosis of any of the study outcomes (myocardial infarction, ischaemic or haemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter and heart failure). The index date was defined as the date of first hospital admission with constipation (for inpatients) or the date of the first hospital clinic visit with a constipation
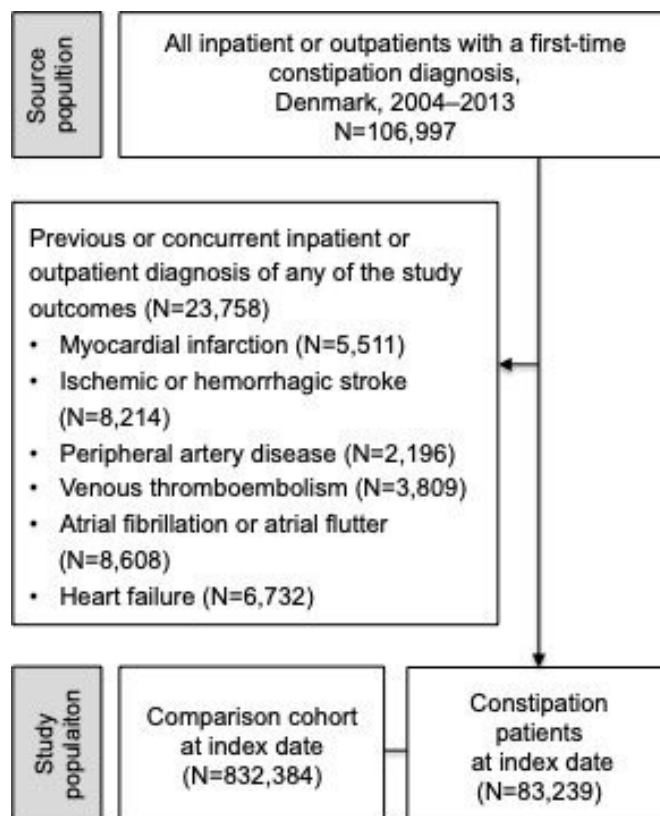

Figure 1 Study flowchart. Because several patients had more than one previous or concurrent diagnosis of the study outcomes, the sum of these exceeds the number of patients excluded (23 758).

diagnosis (for outpatients). The ICD and Anatomical Therapeutic Chemical (ATC) codes used in this study are provided in online supplementary table S1.

Many patients with constipation are managed solely in primary care and not captured in hospital-based registries. Therefore, we performed a separate analysis in which we redefined the constipation cohort to also include prescriptions for laxatives. In this cohort including patients from general practice, we defined the constipation index date as the date of a hospital diagnosis or the date of a second prescription for laxatives, whichever occurred first. A second prescription was required to ensure that constipation was ongoing.

To evaluate the impact of constipation severity on the risk of study outcomes, we categorised patients based on the number of prescriptions for laxatives redeemed from 1 year prior to 3 months after the constipation diagnosis: low-intensity use corresponding to 0–1 prescriptions and high-intensity use corresponding to ≥2 prescriptions. For this purpose, we used data from the Danish National Health Service Prescription Database established in 2004.[29] For each prescription redeemed after 2004, the patient's central personal registry number, the amount and type of drug prescribed according to the ATC classification system and the date the drug was dispensed have been transferred electronically from community pharmacies to the Prescription Database. To avoid conditioning

on the future, the index date in this analysis was changed to 3 months after the constipation diagnosis or the matching date for individuals in the general population comparison cohort.[30]

General population comparison cohort

To put constipation into a population context, we created a comparison cohort from the general population using the Danish Civil Registration System. This system has recorded all changes in vital status and migration for the entire Danish population since 1968, with daily electronic updates.[27] For each patient in the constipation cohort, up to 10 individuals from the general population were randomly selected from the Civil Registration System and matched on sex and single year of age during the calendar year of the patient's constipation diagnosis. We selected 10 individuals for each constipation patient, as this approach would not be associated with extra expense and helped ensure adequate precision of our estimates, including in subcohorts. We used matching with replacement (ie, individuals from the general population comparison cohort could be matched with more than one patient with constipation).[31] Each member of the comparison cohort was assigned an index date corresponding to the date of admission or outpatient visit for the corresponding patient with constipation. All members of the comparison cohort were required to be alive on the date the corresponding patient was diagnosed with constipation. We included only comparison cohort members with no previous hospital-based diagnosis of the study outcomes or previous constipation diagnoses. Individuals from the comparison cohort who were diagnosed with constipation during follow-up were transferred to the constipation cohort at that point and follow-up was discontinued in the comparison cohort.

Cardiovascular outcomes

The outcomes were specified a priori according to hypotheses proposed in the introduction and included first-time myocardial infarction, ischaemic or haemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter and heart failure. These conditions were ascertained using all available primary and secondary inpatient and outpatient diagnoses recorded in the DNPR. We separately analysed the anatomical locations of venous thromboembolisms (ie, deep venous thrombosis, pulmonary embolism or splanchnic venous thrombosis). To explore underlying mechanisms, we assessed the risk of unprovoked and provoked venous thromboembolism; provoked was defined on the basis of a diagnosis of malignancy any time before the venous thromboembolism, or pregnancy, fracture/trauma or surgery within 90 days before the venous thromboembolism (online supplementary table S2).[32] Registration of cardiovascular diagnoses in the DNPR is accurate, with validation studies consistently reporting positive predictive values >80% for most conditions.[33] As approximately two-thirds of all unspecified strokes are known to be ischaemic strokes,[34] we classified unspecified strokes as ischaemic strokes.

Covariables

Using the full hospital history (inpatient and outpatient diagnoses) recorded in the DNPR before the index date, we obtained information on the following potential constipation-related conditions:[12] hypothyroidism, hyperthyroidism, pregnancy within 90 days, depression, Parkinson's disease, multiple sclerosis, colon, rectal and anal cancer, other gastrointestinal cancers, Crohn's disease, ulcerative colitis and paralytic ileus. In addition, we collected data on several cardiovascular risk factors: chronic pulmonary disease (as a measure of chronic smoking exposure), valvular heart disease, diabetes mellitus, hypertension, hypercholesterolemia, obesity, chronic kidney disease, liver disease and alcoholism-related disorders. We also retrieved information on medication use within 90 days preceding the index date from the Danish National Health Service Prescription Database,[29] including medications that can induce constipation[12] (iron supplements, opioids, calcium channel blockers, anticholinergic drugs, dopaminergic drugs, tricyclic antidepressants, diuretics, aspirin and non-steroidal anti-inflammatory drugs) and cardiovascular drugs (vitamin K antagonists, direct oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, P2Y12 inhibitors, digoxin, amiodarone, nitrates and statins).

Statistical analysis

We tabulated the distributions of the covariables for the constipation cohort and the general population cohort for comparison. We followed both cohorts from the index dates until the date of myocardial infarction, ischaemic stroke, haemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter, heart failure, emigration, death or end of follow-up (30 November 2013). After an initial event, we continued to follow patients for subsequent cardiovascular events to avoid informative censoring and to understand the full spectrum and extent of cardiovascular morbidity associated with constipation. We calculated and graphically illustrated the cumulative incidence per 1000 persons for each outcome for 0–1 year, >1–5 years, >5–10 years and 0–10 years, accounting for the competing risk of death.[35] We then used matching factor-stratified (conditional) Cox proportional hazards regression analysis[36] to compute hazard ratios adjusted (aHRs) for the categorical variables listed in table 1. To examine potential disparities in risk in subgroups of patients, the results were stratified by sex, age group, constipation-related conditions and drugs, type of hospital contact (inpatient/outpatient), type of diagnosis (primary/secondary) and number of cardiovascular risk factors (0, 1, ≥2). Using log-log plots, we examined potential deviations from the proportionality of hazard assumption in the analysed follow-up periods. We found no violations of the assumption.

Table 1 Characteristics of patients with constipation and members of the general population comparison cohort

	Constipation cohort, n=83239	Comparison cohort, n=832384
Median age, years (25th–75th percentile)	46.5 (8.6–69.8)	46.5 (8.6–69.8)
Age groups, years		
<55	47645 (57.2)	476547 (57.3)
55–64	9440 (11.3)	94572 (11.4)
65–74	10877 (13.1)	108741 (13.1)
≥75	15277 (18.4)	152524 (18.3)
Male	34138 (41.0)	341374 (41.0)
Year of constipation diagnosis/index date		
2004–2008	30751 (36.9)	307510 (36.9)
2009–2013	52488 (63.1)	524874 (63.1)
Type of constipation diagnosis		
Primary diagnosis	54074 (65.0)	–
Secondary diagnosis	29165 (35.0)	–
Type of hospital contact for constipation		
Inpatient	44851 (53.9)	–
Outpatient	38388 (46.1)	–
Constipation-related conditions		
Hypothyroidism	1226 (1.5)	6167 (0.7)
Hyperthyroidism	1244 (1.5)	9463 (1.1)
Pregnancy within 90 days of the index date	678 (0.8)	2629 (0.3)
Depression	2237 (2.7)	6921 (0.8)
Parkinson's disease	644 (0.8)	1856 (0.2)
Multiple sclerosis	588 (0.7)	1477 (0.2)
Colon, rectal and anal cancer	3459 (4.2)	7005 (0.8)
Other gastrointestinal cancers	1901 (2.3)	1037 (0.1)
Crohn's disease, ulcerative colitis, paralytic ileus	3873 (4.7)	8892 (1.1)
Cardiovascular risk factors		
Chronic pulmonary disease	23204 (27.9)	163581 (19.7)
Valvular heart disease	946 (1.1)	6590 (0.8)
Diabetes mellitus	5366 (6.4)	33563 (4.0)
Hypertension	8929 (10.7)	54132 (6.5)
Hypercholesterolemia	1826 (2.2)	10972 (1.3)
Obesity	3340 (4.0)	17399 (2.1)
Chronic kidney disease	1220 (1.5)	5062 (0.6)
Liver disease	1308 (1.6)	4428 (0.5)
Alcoholism-related disorders	2776 (3.3)	10832 (1.3)
Drugs associated with constipation*		
Iron supplements	128 (0.2)	87 (0.0)
Opioids	17172 (20.6)	30089 (3.6)
Calcium channel blockers	5445 (6.5)	49499 (5.9)
Anticholinergic drugs	366 (0.4)	998 (0.1)
Dopaminergic drugs	1041 (1.3)	4064 (0.5)
Tricyclic antidepressants	2328 (2.8)	5471 (0.7)

Continued

Table 1 Continued

	Constipation cohort, n=83 239	Comparison cohort, n=8 32 384
Diuretics	9967 (12.0)	69 706 (8.4)
Aspirin	6000 (7.2)	49 569 (6.0)
Non-steroidal anti-inflammatory drugs	10 154 (12.2)	52 753 (6.3)
Cardiovascular drugs*		
Vitamin K antagonists and direct oral anticoagulants	298 (0.3)	2637 (0.3)
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	8078 (9.7)	81 854 (9.8)
Beta-blockers	3854 (4.6)	38 630 (4.6)
P2Y12 inhibitors	353 (0.4)	2019 (0.2)
Digoxin	293 (0.4)	2800 (0.3)
Amiodarone	22 (0.0)	52 (0.0)
Nitrates	978 (1.2)	5477 (0.7)
Statins	5549 (6.7)	53 432 (6.4)

Data are reported as n (%) unless otherwise specified.
*Redeemed prescription within ≤90 days before the index date.

Sensitivity analyses

We performed several sensitivity analyses to test the robustness of our study findings. First, to improve the specificity of the stroke diagnosis, we implemented a stricter definition of stroke, requiring a CT or MRI scan of the brain in the record of the incident hospital contact for stroke. Second, because 'unspecified stroke' diagnoses were classified in the main analysis as ischaemic strokes, as the most likely subtype,[34] we repeated the analysis with separate assessments of specified ischaemic stroke and unspecified stroke to test the validity of this assumption. Third, as a bias analysis, we calculated E-values for estimates of myocardial infarction and venous thromboembolism as representative outcomes and the corresponding lower limit of the 95% CI during 0–10 years of follow-up. The E-value is the minimum strength of the confounder association with both exposure and outcome that must be present, *above and beyond the measured covariates*, for an unmeasured confounder to explain away an association. This allowed us to assess how strong an unmeasured confounder (eg, immobilisation) would have to be to explain away the observed exposure-outcome association.[37]

All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA). The data, analytic methods and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Such disclosure would conflict with the regulations for use of Danish healthcare data.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

The study included 83 239 patients in the constipation cohort and 832 384 individuals in the matched general population comparison cohort. Median age at constipation diagnosis was 46.5 (IQR 8.6–69.8) years, and 41% of the study population were men. The constipation cohort had an expected higher prevalence of constipation-related conditions and associated drug use and a slightly higher prevalence of cardiovascular risk factors and associated drug use compared with the general population comparison cohort (table 1).

Constipation and cardiovascular disease risk

The cumulative incidence per 1000 persons after 10 years of follow-up in the constipation cohort compared with the general population cohort was 17 vs 20 for myocardial infarction, 30 vs 31 for ischaemic stroke, 6 vs 6 for haemorrhagic stroke, 15 vs 10 for peripheral artery disease, 21 vs 15 for venous thromboembolism, 42 vs 54 for atrial fibrillation or atrial flutter and 30 vs 30 for heart failure (figure 2). The cumulative incidence of myocardial infarction, ischaemic stroke and atrial fibrillation or atrial flutter was lower in the constipation cohort because of the competing risk of death.

After adjusting for the covariables, constipation was associated with a 1.2–2-fold increased risk of cardiovascular disease during 0–10 years of follow-up (myocardial infarction: aHR 1.24, 95% CI 1.14 to 1.35; ischaemic stroke: aHR 1.50, 95% CI 1.41 to 1.60; haemorrhagic stroke: aHR 1.46, 95% CI 1.26 to 1.69; peripheral artery disease: aHR 1.34, 95% CI 1.20 to 1.50; venous thromboembolism: aHR 2.04, 95% CI 1.89 to 2.20; atrial fibrillation or atrial flutter: aHR 1.27, 95% CI 1.20 to 1.34; heart failure: aHR 1.52, 95% CI 1.42 to 1.62; figure 3). The risks
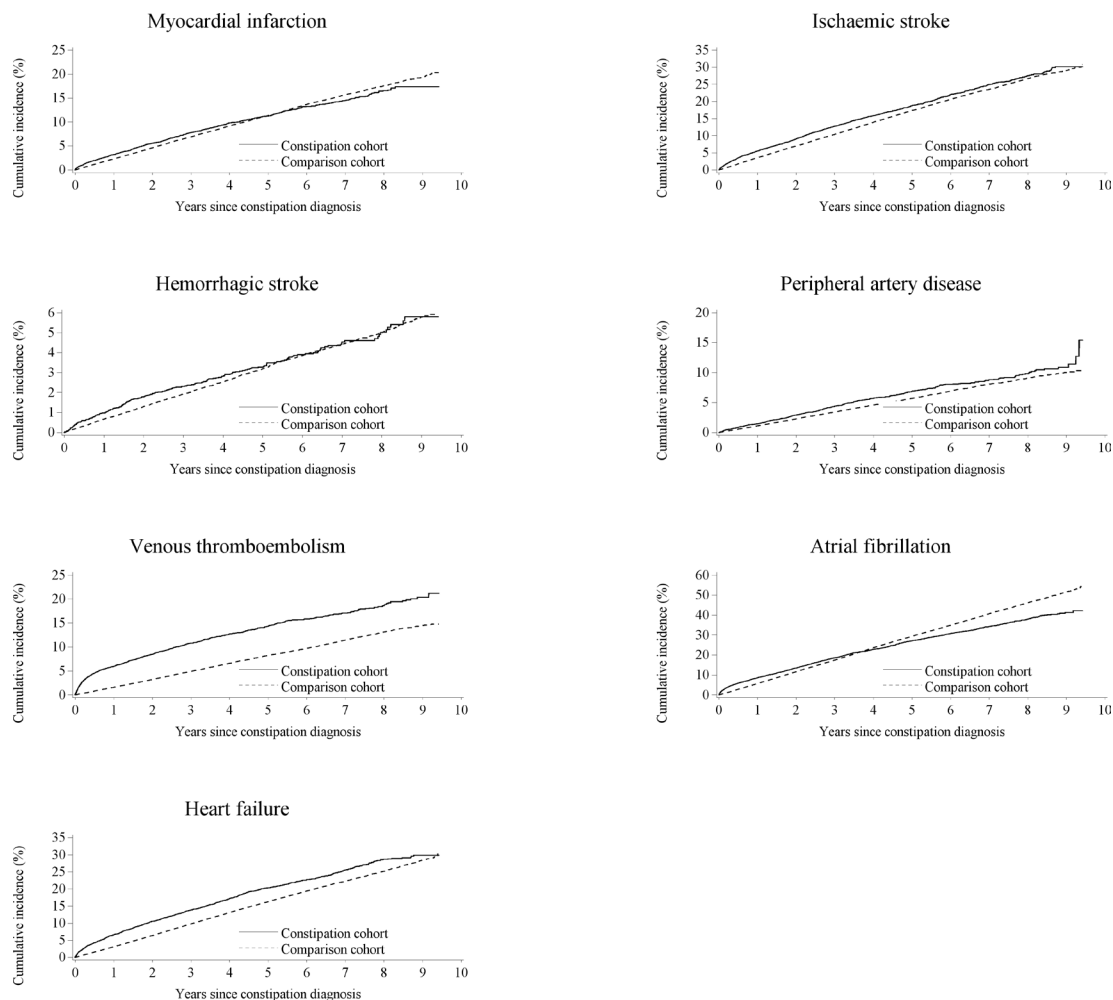
Figure 2 Cumulative risk (%) of myocardial infarction, ischaemic and haemorrhagic stroke, peripheral artery disease, venous thromboembolism, atrial fibrillation or atrial flutter and heart failure among patients with constipation and members of the general population comparison cohort.

were similar for deep venous thrombosis and pulmonary embolism but markedly higher for splanchnic venous thrombosis (aHR 4.23, 95% CI 2.45 to 7.31). The risks were only slightly higher for provoked venous thromboembolism than for unprovoked venous thromboembolism (online supplementary table S3).

The excess risk of cardiovascular disease was highest during the first year following the diagnosis of constipation, with a 1.5-fold increased risk of myocardial infarction, an approximately 1.7-fold increased risk of ischaemic stroke, haemorrhagic stroke and atrial fibrillation or atrial flutter and a 1.2-fold increased risk of peripheral artery disease. The risk was even higher for venous thromboembolism (3.5-fold) and heart failure (2.2-fold). During >1–5 years of follow-up, constipation was persistently associated with myocardial infarction (1.2-fold increased risk), ischaemic and haemorrhagic stroke (1.4-fold increased risk), peripheral artery disease and venous thromboembolism (1.5-fold increased risk), heart failure (1.3-fold increased risk) and marginally with atrial fibrillation or atrial flutter (1.1-fold increased risk). During >5–10 years of follow-up, constipation was associated primarily with ischaemic

stroke (1.5-fold increased risk) and venous thromboembolism (1.3-fold increased risk) and marginally with haemorrhagic stroke and heart failure (figure 3).

When we included prescriptions for laxatives in the definition of constipation, the constipation cohort increased to 109 915 patients, 24% of whom were identified through prescription redemption. Using this expanded definition of constipation did not change the associations for any outcomes (table 2).

Subgroup analyses
In analyses stratified by the intensity of laxative use before and immediately after the constipation diagnosis, we observed stronger associations with a higher intensity of laxative use for all outcomes, except for peripheral artery disease (table 3). The association was particularly strengthened in patients with high-intensity versus low-intensity use for the outcomes ischaemic stroke (3.2-fold and 1.4-fold, respectively) and venous thromboembolism (5.2-fold and 1.7-fold, respectively). The associations were similar among women and men (online supplementary table S4) and generally attenuated with increasing age
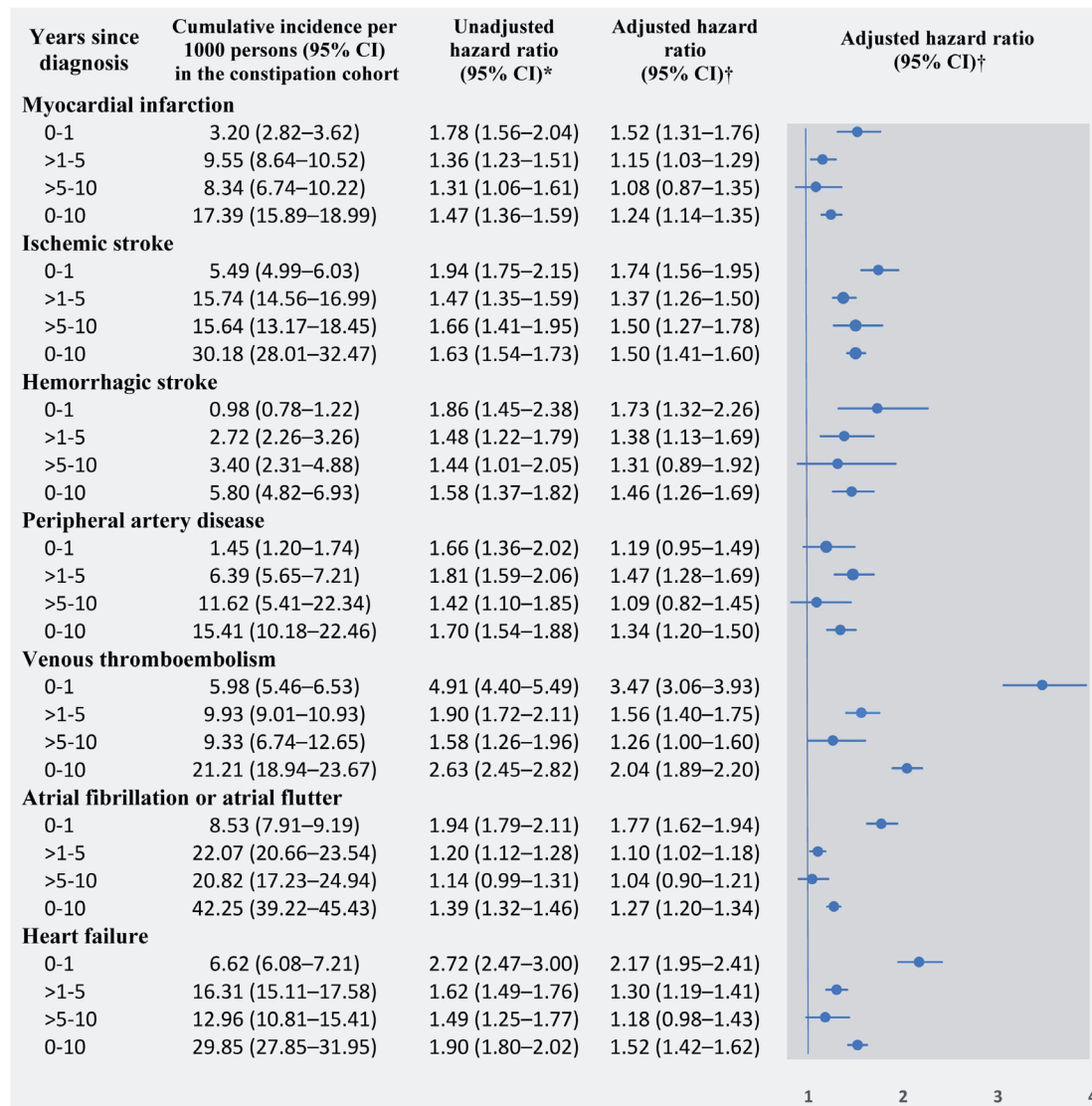
Years since diagnosis	Cumulative incidence per 1000 persons (95% CI) in the constipation cohort	Unadjusted hazard ratio (95% CI)*	Adjusted hazard ratio (95% CI)†	Adjusted hazard ratio (95% CI)†
Myocardial infarction				
0-1	3.20 (2.82–3.62)	1.78 (1.56–2.04)	1.52 (1.31–1.76)	
>1-5	9.55 (8.64–10.52)	1.36 (1.23–1.51)	1.15 (1.03–1.29)	
>5-10	8.34 (6.74–10.22)	1.31 (1.06–1.61)	1.08 (0.87–1.35)	
0-10	17.39 (15.89–18.99)	1.47 (1.36–1.59)	1.24 (1.14–1.35)	
Ischemic stroke				
0-1	5.49 (4.99–6.03)	1.94 (1.75–2.15)	1.74 (1.56–1.95)	
>1-5	15.74 (14.56–16.99)	1.47 (1.35–1.59)	1.37 (1.26–1.50)	
>5-10	15.64 (13.17–18.45)	1.66 (1.41–1.95)	1.50 (1.27–1.78)	
0-10	30.18 (28.01–32.47)	1.63 (1.54–1.73)	1.50 (1.41–1.60)	
Hemorrhagic stroke				
0-1	0.98 (0.78–1.22)	1.86 (1.45–2.38)	1.73 (1.32–2.26)	
>1-5	2.72 (2.26–3.26)	1.48 (1.22–1.79)	1.38 (1.13–1.69)	
>5-10	3.40 (2.31–4.88)	1.44 (1.01–2.05)	1.31 (0.89–1.92)	
0-10	5.80 (4.82–6.93)	1.58 (1.37–1.82)	1.46 (1.26–1.69)	
Peripheral artery disease				
0-1	1.45 (1.20–1.74)	1.66 (1.36–2.02)	1.19 (0.95–1.49)	
>1-5	6.39 (5.65–7.21)	1.81 (1.59–2.06)	1.47 (1.28–1.69)	
>5-10	11.62 (5.41–22.34)	1.42 (1.10–1.85)	1.09 (0.82–1.45)	
0-10	15.41 (10.18–22.46)	1.70 (1.54–1.88)	1.34 (1.20–1.50)	
Venous thromboembolism				
0-1	5.98 (5.46–6.53)	4.91 (4.40–5.49)	3.47 (3.06–3.93)	
>1-5	9.93 (9.01–10.93)	1.90 (1.72–2.11)	1.56 (1.40–1.75)	
>5-10	9.33 (6.74–12.65)	1.58 (1.26–1.96)	1.26 (1.00–1.60)	
0-10	21.21 (18.94–23.67)	2.63 (2.45–2.82)	2.04 (1.89–2.20)	
Atrial fibrillation or atrial flutter				
0-1	8.53 (7.91–9.19)	1.94 (1.79–2.11)	1.77 (1.62–1.94)	
>1-5	22.07 (20.66–23.54)	1.20 (1.12–1.28)	1.10 (1.02–1.18)	
>5-10	20.82 (17.23–24.94)	1.14 (0.99–1.31)	1.04 (0.90–1.21)	
0-10	42.25 (39.22–45.43)	1.39 (1.32–1.46)	1.27 (1.20–1.34)	
Heart failure				
0-1	6.62 (6.08–7.21)	2.72 (2.47–3.00)	2.17 (1.95–2.41)	
>1-5	16.31 (15.11–17.58)	1.62 (1.49–1.76)	1.30 (1.19–1.41)	
>5-10	12.96 (10.81–15.41)	1.49 (1.25–1.77)	1.18 (0.98–1.43)	
0-10	29.85 (27.85–31.95)	1.90 (1.80–2.02)	1.52 (1.42–1.62)	

Figure 3 Risk of cardiovascular events among patients with constipation relative to the general population cohort. *Controlled for matching factors (age, sex and calendar year) by study design. †Controlled for matching factors (age, sex and calendar year) by study design and adjusted for hypothyroidism, hyperthyroidism, pregnancy within 90 days before the index date, depression, Parkinson's disease, multiple sclerosis, colon, rectal and anal cancer, other gastrointestinal cancers, Crohn's disease, ulcerative colitis, paralytic ileus, chronic pulmonary disease, valvular heart disease, diabetes mellitus, hypertension, hypercholesterolemia, obesity, chronic kidney disease, liver disease, alcoholism-related disorders, medications associated with constipation (iron supplements, opioids, calcium channel blockers, anticholinergic drugs, dopaminergic drugs, tricyclic antidepressants, diuretics, aspirin and non-steroidal anti-inflammatory drugs) and cardiovascular drugs (vitamin K antagonists, direct oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, P2Y12 inhibitors, digoxin, amiodarone, nitrates and statins).

(online supplementary table S5). With the exception of haemorrhagic stroke, the associations were stronger in patients with inpatient diagnoses of constipation than in patients with outpatient diagnoses (online supplementary table S6). When restricting to patients with a primary diagnosis of constipation, the associations remained, though marginally attenuated compared with patients with secondary diagnoses of constipation (online supplementary table S7). The associations were slightly weakened in patients diagnosed with constipation-related conditions or who used drugs that can cause constipation (online supplementary table S8). However,

the risks of myocardial infarction, ischaemic stroke and haemorrhagic stroke were higher in patients with constipation who used non-steroidal anti-inflammatory drugs. When restricting the analysis to patients with no cardiovascular risk factors at baseline, the results remained largely unchanged. Only the risk of myocardial infarction increased with an increasing burden of cardiovascular risk factors at baseline (online supplementary table S9).

Sensitivity analyses
In separate analyses of unspecified stroke and specified ischaemic stroke, the associations were moderately

Table 2 Risk of cardiovascular events among patients with constipation relative to the general population cohort, redefining constipation as a hospital diagnosis or ≥2 prescriptions for laxatives, whichever came first

Years since diagnosis	No. at risk/no. of events in the constipation cohort	Cumulative incidence per 1000 persons in the constipation cohort (95% CI)	Unadjusted HR (95% CI)*	Adjusted HR (95% CI)†
Myocardial infarction				
0–1	109 915/337	3.25 (2.92 to 3.62)	1.86 (1.66 to 2.09)	1.49 (1.30 to 1.72)
>1–5	71 896/517	9.93 (9.09 to 10.84)	1.38 (1.25 to 1.51)	1.15 (1.04 to 1.28)
>5–10	26 358/137	8.99 (7.44 to 10.78)	1.45 (1.21 to 1.75)	1.20 (0.97 to 1.48)
0–10	109 915/991	16.70 (15.42 to 18.06)	1.53 (1.43 to 1.63)	1.25 (1.15 to 1.35)
Ischaemic stroke				
0–1	109 915/545	5.26 (4.84 to 5.72)	1.90 (1.74 to 2.09)	1.74 (1.56 to 1.93)
>1–5	71 738/787	15.37 (14.30 to 16.50)	1.36 (1.26 to 1.47)	1.27 (1.17 to 1.38)
>5–10	26 188/220	15.54 (13.28 to 18.08)	1.47 (1.27 to 1.70)	1.42 (1.21 to 1.66)
0–10	109 915/1552	27.05 (25.28 to 28.91)	1.53 (1.45 to 1.62)	1.42 (1.34 to 1.51)
Haemorrhagic stroke				
0–1	109 915/105	1.02 (0.84 to 1.23)	2.15 (1.74 to 2.65)	1.77 (1.37 to 2.29)
>1–5	72 027/158	3.00 (2.55 to 3.51)	1.46 (1.23 to 1.73)	1.22 (1.01 to 1.48)
>5–10	26 553/49	3.50 (2.49 to 4.81)	1.68 (1.22 to 2.30)	1.47 (1.03 to 2.10)
0–10	109 915/312	5.60 (4.80 to 6.52)	1.68 (1.48 to 1.89)	1.40 (1.22 to 1.61)
Peripheral artery disease				
0–1	109 915/139	1.35 (1.14 to 1.59)	1.45 (1.22 to 1.74)	1.27 (1.03 to 1.57)
>1–5	71 957/319	6.21 (5.54 to 6.94)	1.64 (1.46 to 1.85)	1.38 (1.21 to 1.58)
>5–10	26 407/79	9.76 (5.18 to 17.06)	1.45 (1.14 to 1.85)	1.19 (0.91 to 1.57)
0–10	109 915/537	12.47 (9.08 to 16.77)	1.56 (1.42 to 1.71)	1.32 (1.19 to 1.46)
Venous thromboembolism				
0–1	109 915/720	6.87 (6.38 to 7.38)	5.56 (5.07 to 6.09)	3.44 (3.06 to 3.88)
>1–5	71 800/533	10.26 (9.40 to 11.18)	1.92 (1.74 to 2.11)	1.61 (1.45 to 1.79)
>5–10	26 352/124	10.10 (7.76 to 12.96)	1.50 (1.24 to 1.82)	1.15 (0.93 to 1.44)
0–10	109 915/1377	21.27 (19.45 to 23.21)	2.84 (2.68 to 3.02)	2.04 (1.90 to 2.19)
Atrial fibrillation or atrial flutter				
0–1	109 915/892	8.55 (8.01 to 9.13)	2.01 (1.87 to 2.16)	1.71 (1.56 to 1.86)
>1–5	71 621/1142	22.41 (21.12 to 23.77)	1.21 (1.14 to 1.29)	1.10 (1.03 to 1.18)
>5–10	26 110/281	21.06 (17.82 to 24.71)	1.12 (0.99 to 1.27)	1.08 (0.94 to 1.24)
0–10	109 915/2315	39.20 (36.76 to 41.74)	1.42 (1.36 to 1.49)	1.26 (1.20 to 1.32)
Heart failure				
0–1	109 915/652	6.29 (5.83 to 6.79)	2.71 (2.49 to 2.96)	2.08 (1.88 to 2.31)
>1–5	71 722/824	16.17 (15.07 to 17.33)	1.59 (1.47 to 1.71)	1.26 (1.16 to 1.37)
>5–10	26 237/201	13.75 (11.70 to 16.06)	1.43 (1.23 to 1.67)	1.13 (0.95 to 1.35)
0–10	109 915/1677	27.55 (25.87 to 29.30)	1.88 (1.78 to 1.98)	1.46 (1.37 to 1.55)

*Controlled for matching factors (age, sex, calendar year) by study design.
†Controlled for matching factors (age, sex and calendar year) by study design and adjusted for hypothyroidism, hyperthyroidism, pregnancy within 90 days of the index date, depression, Parkinson's disease, multiple sclerosis, colon, rectal and anal cancer, other gastrointestinal cancers, Crohn's disease, ulcerative colitis, paralytic ileus, chronic pulmonary disease, valvular heart disease, diabetes mellitus, hypertension, hypercholesterolemia, obesity, chronic kidney disease, liver disease, alcoholism-related disorders, medications associated with constipation (iron supplements, opioids, calcium channel blockers, anticholinergic drugs, dopaminergic drugs, tricyclic antidepressants, diuretics, aspirin and non-steroidal anti-inflammatory drugs) and cardiovascular drugs (vitamin K antagonists, direct oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, P2Y12 inhibitors, digoxin, amiodarone, nitrates and statins).

higher for unspecified stroke. When we restricted the analysis to stroke diagnoses confirmed by CT or MRI of the brain during the incident hospital contact for stroke, the results remained unchanged (online supplementary table S10). For myocardial infarction (aHR 1.24, 95% CI 1.14 to 1.35), the E-value was 1.79 (E-value for lower limit

Table 3 Risk of cardiovascular events among patients with constipation relative to the general population cohort, by use of laxatives in the constipation cohort from 1 year before to 3 months after the constipation diagnosis*

	Cumulative incidence per 1000 persons in the constipation cohort (95% CI)		Adjusted HR (95% CI)†	
	0 to 1 prescriptions for laxatives (n=68 698)	≥2 prescriptions for laxatives (n=3125)	0–1 prescriptions for laxatives (n=68 698)	≥2 prescriptions for laxatives (n=3125)
Myocardial infarction	17.88 (16.20 to 19.69)	12.78 (7.59 to 20.36)	1.17 (1.07 to 1.28)	2.40 (1.05 to 5.49)
Ischaemic stroke	31.08 (28.63 to 33.68)	19.59 (12.47 to 29.37)	1.39 (1.30 to 1.49)	3.22 (1.72 to 6.03)
Haemorrhagic stroke	6.10 (4.99 to 7.40)	4.05 (1.82 to 8.12)	1.41 (1.20 to 1.65)	4.59 (1.09 to 19.36)
Peripheral artery disease	16.83 (10.82 to 25.08)	7.28 (2.34 to 18.29)	1.38 (1.22 to 1.55)	0.88 (0.20 to 3.89)
Venous thromboembolism	19.54 (16.99 to 22.35)	28.15 (19.60 to 39.11)	1.66 (1.52 to 1.82)	5.15 (2.63 to 10.08)
Atrial fibrillation or atrial flutter	42.44 (39.00 to 46.08)	25.93 (18.42 to 35.44)	1.12 (1.06 to 1.19)	1.37 (0.76 to 2.45)
Heart failure	29.58 (27.36 to 31.94)	23.27 (14.67 to 35.10)	1.36 (1.26 to 1.46)	1.76 (0.90 to 3.42)

The dash (–) indicates insufficient data for an estimate.

*The analysis was performed as a landmark analysis, starting follow-up 3 months after the constipation diagnosis.

†Controlled for matching factors (age, sex and calendar year) by study design and adjusted for hypothyroidism, hyperthyroidism, pregnancy within 90 days before the index date, depression, Parkinson's disease, multiple sclerosis, colon, rectal and anal cancer, other gastrointestinal cancers, Crohn's disease, ulcerative colitis, paralytic ileus, chronic pulmonary disease, valvular heart disease, diabetes mellitus, hypertension, hypercholesterolemia, obesity, chronic kidney disease, liver disease, alcoholism-related disorders, medications associated with constipation (iron supplements, opioids, calcium channel blockers, anticholinergic drugs, dopaminergic drugs, tricyclic antidepressants, diuretics, aspirin and non-steroidal anti-inflammatory drugs) and cardiovascular drugs (vitamin K antagonists, direct oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, P2Y12 inhibitors, digoxin, amiodarone, nitrates and statins).

NSAIDs, non-steroidal anti-inflammatory drugs.

of 95% CI=1.54). For venous thromboembolism (aHR 2.04, 95% CI 1.89 to 2.20), the E-value was 3.50 (E-value for lower limit of 95% CI=3.19).

DISCUSSION

In this nationwide, matched, population-based cohort study with a virtually complete follow-up of 83 239 patients with constipation, we showed that constipation was associated with an increased risk of all cardiovascular outcomes in the short term and primarily associated with venous thromboembolism and ischaemic stroke beyond 5 years of follow-up. The associations were generally stronger for venous than arterial events and strongest for splanchnic venous thrombosis. The associations were strengthened in patients with more intense use of laxatives, especially for the outcomes ischaemic stroke and venous thromboembolism. When applying a redefined algorithm for our constipation cohort using prescriptions for laxatives in order to capture presumably milder cases of constipation in primary care, our results were similar to the results of the main analysis. We observed an increasing risk of cardiovascular outcomes with decreasing age, presumably due to a low absolute risk of in younger age groups, where the relative effect of constipation is more pronounced.

Comparison with other studies

Two American studies have focused on constipation as a risk factor for cardiovascular disease, both examining only atherosclerotic cardiovascular disease.[24 25] In a prospective cohort of 73 047 community-dwelling postmenopausal women enrolled in the Women's Health Initiative in the USA, constipation was reported among 35%. After adjusting for confounding factors, only severe constipation remained moderately associated with a composite outcome of atherosclerotic cardiovascular events, with an aHR of 1.23 (95% CI 1.03 to 1.47).[24] In contrast, in a cohort of 3 359 653 US veterans, 7% reported constipation. Patients with constipation (versus without) had aHRs of 1.11 (95% CI 1.08 to 1.14) for coronary heart disease and 1.19 (95% CI 1.15 to 1.22) for ischaemic stroke. Patients taking 1 and ≥2 types of laxatives (versus none) experienced a similarly increased risk.[25] In both studies, constipation was self-reported, which is less specific than symptom-based criteria.[7] Therefore, the constipation cases were likely milder than the physician-evaluated, hospital-based cases included in our study. This could explain why patients with self-perceived constipation had only a modestly increased risk of cardiovascular events. Another cohort study examined the association between self-reported bowel movement frequency and risk of cardiovascular disease (coronary heart disease or stroke) among participants in the Nurses' Health Study in the USA.[38] The study included 86 289 women and followed them for up to 30 years. After adjustment, the study found no association with incident cardiovascular disease.

Our study complements the literature by examining patients with physician-diagnosed constipation in a population-based, nationwide setting and comparing with matched individuals from the general population. In contrast to previous studies, we also examined the association with venous thromboembolism. Moreover, we included a wide range of separately analysed

cardiovascular outcomes, beyond atherosclerotic disease, while retaining the precision of the effect estimates in several subgroup analyses.

Potential mechanisms

Putative mechanisms through which constipation may increase cardiovascular risk are likely multifactorial and may differ by type of outcome. Increased risk of venous events may be related to shared risk factors, such as physical inactivity and obesity. This could explain the observation of a markedly higher risk of splanchnic venous thrombosis compared with deep venous thrombosis and pulmonary embolism.

Decreased gut motility in patients with constipation may cause dysbiosis of the microbiota.[21] Recently, the contributory role of the gut microbiota in the development of atherosclerosis and cardiovascular disease has been observed consistently in several large clinical cohorts.[18–20] The increased transit time in constipated patients may further facilitate the translocation of proinflammatory cytokines from gut bacteria and result in heightened inflammatory responses as well as oxidative stress.[21] Thus, patients with constipation may sustain a state of systemic low-grade inflammation,[21] which accelerates the development of atherosclerosis.[39] Such a mechanism may explain the association between constipation and disease development in distant cardiovascular beds and underlie our observation of an increased risk of myocardial infarction, ischaemic stroke and peripheral arterial disease. In a recent paper,[40] a positive association between constipation and various gastrointestinal cancers has been established. This may partly explain our observation of a much higher risk of splanchnic venous thrombosis than deep venous thrombosis and pulmonary embolism. Increased blood pressure, a universal cardiovascular risk factor, may also be at the root of the observed association with various cardiovascular diseases. Constipation leads to straining at stool, which has been associated with transient increases in blood pressure.[10] Moreover, chronic constipation induces psychological stress,[41] which may increase blood pressure. All of the above mechanisms are presumably related temporally to the peak of constipation symptoms, which likely occurs at time of diagnosis. This may explain our observation of highest cardiovascular risk during the first year after the constipation diagnosis.

We observed an increased risk for all outcomes in patients with more intense use of laxatives, except for peripheral artery disease. This may reflect more severe constipation in these patients; however, confounding by indication may also partly underlie this observation. As an example, patients with severe pain from cancer or ischaemic heart disease may become constipated from morphine use, which in turn may drive the more intense use of laxatives.

Though we analysed each cardiovascular outcome separately, it is likely that relationships exist between them; for example, a first occurrence of myocardial infarction may drive the development of heart failure. Similarly, all cardiovascular outcomes in our study, except heart failure and haemorrhagic stroke, require anticoagulation or antithrombotic therapy, which may mediate the increased risk of haemorrhagic stroke observed in our study.

Reverse causation is possible for outcomes with the potential for slow onset and a long prediagnostic phase, that is, certain cases of heart failure and atrial fibrillation or flutter. Both diseases can lead to dyspnoea and decreased activity, which in turn can induce constipation.[13] The remaining outcomes of the study are characterised by acute onset, specific symptoms and severe course and are unlikely to precede constipation undiagnosed.

Strengths and weaknesses of the study

Several strengths and limitations should be considered when interpreting our results. The population-based design within the setting of a tax-supported universal healthcare system with complete follow-up of all patients largely eliminated selection bias stemming from selective inclusion of specific hospitals, health insurance systems or income levels.[27] The positive predictive value of the DNPR data is high for diagnoses of myocardial infarction (97%), ischaemic stroke (97%), haemorrhagic stroke (88%), peripheral artery disease (91%), venous thromboembolism (88%) and atrial fibrillation or atrial flutter (95%), but somewhat lower for heart failure (80%).[28 33 42] Constipation diagnoses in the DNPR are based on an evaluation by the treating physician. Therefore, the positive predictive value is assumed to be high, whereas sensitivity and other aspects of validity may be lower.

Surveillance and detection bias cannot be excluded. However, most outcomes included in the study are characterised by acute onset and a severe clinical course, making them less susceptible to surveillance bias. Furthermore, we observed no compensatory deficit in estimates for any outcome during >1–5 years of follow-up. Such deficits would be expected if detection bias was present during the first year of follow-up.

We used several approaches to control for and examine the potential impact of confounding. We adjusted our analyses for a wide range of conditions and drugs associated with constipation, as well as cardiovascular and life style diseases and associated drugs. Our results remained largely unchanged in analyses restricted to patients with no cardiovascular risk factors at baseline, indicating that confounding by cardiovascular comorbidity may not be prominent. However, a degree of unmeasured confounding may be expected by physical inactivity and dietary habits, which are risk factors for both constipation and cardiovascular disease.[13] Moreover, obesity was incompletely captured (4.0% in the constipation cohort and 2.1% in the comparison cohort), and residual confounding by obesity is possible despite adjusting for associated lifestyle conditions. The derived E-values indicating the strength of association with both the exposure and the outcome needed by an unmeasured confounder to potentially (as a maximum) explain away selected representative findings for myocardial infarction and

venous thromboembolism (aHR 1.24 and 2.04) were relative large (E-values 1.79 and 3.50). For example, the association between obesity and constipation is 1.10 (95% CI 0.69 to 1.75);[43] therefore, residual confounding by obesity is unlikely to be an important confounder. However, multiple unmeasured confounders may in concert explain our results to an unknown degree.

Conclusion

Constipation was associated with an increased risk of the most common cardiovascular diseases. The strongest associations were observed for venous thromboembolism.

Contributors JS, KA, HG and HTTS conceived the study idea and designed the study. JS directed the analyses, which were carried out by SKS and PS. All authors participated in the discussion and interpretation of the results. JS reviewed the literature, organised the writing and wrote the initial drafts. All authors critically revised the manuscript for intellectual content and approved the final version. HTTS is the guarantor.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Danish Data Protection Agency (record number: 2006-53-1396). Informed consent and approval from an ethics committee are not required for registry-based studies according to Danish legislation.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. No additional data are available.

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