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Chronic constipation as a risk factor for colorectal cancer: results from a nationwide, case-control study

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Abstract

Background and Aims: Prolonged colon transit times may increase contact time between potential carcinogens in the stool and the colonic mucosa. Nonetheless, previous studies have yielded conflicting results connecting chronic constipation with risk of CRC. We examined the association between chronic constipation and later CRC.

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Author Contributions: KS and JFL wrote the first draft of the paper. KS, JS and JFL conceived and designed the study with input from the other authors. JFL supervised the project. JFL and KS funded the study. JS carried out the statistics. All authors interpreted the data and contributed to the writing of the paper. All authors revised and approved the final version.

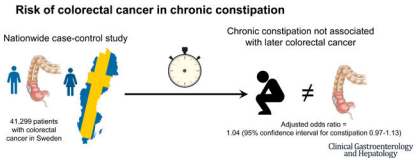
Data Transparency Statement: Other researchers can apply for our data through the Swedish National Board of Health and Welfare, and through the individual Swedish histopathology departments.

Methods: In this nationwide case-control study, we identified 41,299 CRC cases by colorectal biopsy in Sweden between July 2007 and December 2016 and matched them to 203,181 age- and sex-matched controls from the general population. We compared odds of earlier chronic constipation (defined as ≥2 laxative prescriptions in the Prescribed Drug Register with ≥6 months between first-last prescription) between CRC cases and controls using logistic regression. In separate analyses, we compared odds of earlier constipation between CRC cases and sibling comparators, but also examined earlier risk of having an inpatient/outpatient specialty diagnosis of chronic constipation prior to CRC.

Results: Overall, 3,943 patients with CRC met our criteria for chronic constipation prior to CRC. The crude proportion of chronic constipation in CRC patients was 9.5% compared to 8.8% in controls. After multivariable adjustment, there was a modest association between chronic constipation and later CRC (OR=1.10, 95% CI=1.06–1.14) that vanished using sibling comparators to control for residual confounding (OR=1.04, 95% CI=0.97–1.13). In a sensitivity analysis of 126,650 CRC patients diagnosed 1989–2016, we found no association with earlier chronic constipation diagnosed in inpatient/outpatient specialty clinics (OR=0.88, 95% CI=0.75–1.04).

Conclusions: In a nationwide case-control study, chronic constipation was not associated with later CRC.

Graphical Abstract



Keywords

constipation; colon cancer; colorectal cancer; histopathology; colonoscopy

INTRODUCTION

Chronic constipation affects an estimated 15% of the adult population worldwide,[1] and is more likely to occur in those of lower socioeconomic status (SES) and increasing age.[2] Similarly, colorectal cancer (CRC) is diagnosed in approximately 1 in 10 individuals globally,[3] with increased risk in persons of low SES and with advancing age.[4] Mechanistically, prolonged colon transit times may increase contact time between potential carcinogens in the stool and the colonic mucosa,[5] but whether chronic constipation is a risk factor for CRC remains controversial.[2] Moreover, constipation can be a symptom of CRC, keeping the possibility open that previous positive associations may be a result of reverse causation.

Current guidelines do not recommend a colonoscopy for chronic constipation in the absence of alarm symptoms,[6] though most groups acknowledge that chronic constipation may portend an increased risk for CRC.[7, 8] The evidence suggesting this link comes from many

sources of varying methodology,[9–15] with far fewer studies suggesting a lack of association between chronic constipation and CRC.[16–19] The majority of these studies have not been strictly population-based[9, 10, 12, 15, 19] or used bowel movement frequency as a surrogate for chronic constipation.[12–14, 17, 20]

Understanding the potential link between chronic constipation and CRC could have important implications for population-based screening initiatives given the high prevalence of both conditions. CRC is the second leading global cause of cancer mortality, and incidence rates are four times higher in the developed world compared to developing countries.[3] This translates to significant financial considerations; in Sweden alone, 9% of patients with chronic constipation will undergo a colonoscopy per year.[21]

In a nationwide histopathology register-based study including all CRC cases in Sweden, we examined the potential association between chronic constipation and later CRC.

METHODS

In this nationwide case-control study we matched CRC cases with controls from the Swedish general population to explore if earlier constipation was a risk factor for CRC.

Registers and covariates

Demographic data (dates of birth and death, immigration/emigration, sex, age, county of residence, and education) from all study participants were retrieved from the Total Population Register[22] and the longitudinal integrated database for health insurance and labor market studies (LISA) using an individual's PIN.[23] Data were linked to the Swedish Patient Register[24] to obtain data on inpatient and outpatient medical encounters.

Within the study population we determined medical comorbidities in the last five years prior to study entry using relevant ICD-8, ICD-9, and ICD-10 codes (Table S2) prospectively recorded in routine clinical practice to determine presence of cardiovascular disease (CVD), diabetes, and neurologic disease (Table S2) both at any point up to CRC diagnosis and within 5 years of CRC diagnosis date or index date. Cancer diagnoses (excluding CRC) were determined from the Swedish Cancer Register.[25]

Source database

Patients with a colorectal biopsy consistent with CRC were identified through the Epidemiology Strengthened by histopathology Reports in Sweden (ESPRESSO) study, a histopathology-based cohort consisting of 6.1 million gastrointestinal (GI) pathology reports collected across Sweden's 28 pathology departments from 1965–2017.[26] Between 2015 and 2017, the cohort was assembled by collecting all Swedish histopathology data from GI tract sites accompanied by information on date of biopsy, topography (location of biopsy), and morphology. Each biopsy sample is categorized according to an individual's personal identity number (PIN), and includes information on date of birth and sex. Through linkage with individual PINs, it is possible to follow individuals over time across available Swedish registers (see below), and link data to information on healthcare diagnoses according to International Classification of Diseases (ICD) codes. Individuals with histopathology

data are matched with up to five controls from the general population (without GI histopathology) as well as all siblings.

Definition of CRC

CRC was defined according to relevant SNOMED codes (Table S1) in the ESPRESSO cohort between July 2007 and December 2016. Patients were excluded from analyses if they were diagnosed with inflammatory bowel disease (since patients with this disease often undergo screening for CRC and this may bias the results) or precancerous polyps (since their presence may indicate that constipation is secondary to the lesion rather than preceding it) at any time before the biopsy/CRC diagnosis date or if diagnosed with CRC ≥3 months before the biopsy date using the Cancer Register (Figure 1; for definitions see Appendix). CRC patients were also excluded if they had emigrated out of Sweden before the biopsy date or had immigrated to Sweden <2 years before their biopsy (and thus would not have complete data on constipation). Identical exclusion criteria were applied to matched reference controls.

Definition of Chronic Constipation

Because no ICD code for chronic constipation exists (as opposed to “any constipation”), we defined chronic constipation as:

- **a.** Having ≥2 earlier records of laxatives (Anatomical Therapeutic Chemical (ATC) code A06A*) with ≥6 months between first-last prescription *plus*
- **b.** The first prescription ≥2 years before the CRC diagnosis (or matching date for controls) *plus*
- **c.** The second laxative prescription needed to occur ≥6 months before the CRC diagnosis or matching date.

We required the first laxative prescription to occur ≥2 years before the CRC diagnosis (or matching date for controls) and the second prescription ≥6 months before the CRC diagnosis or matching date in order to account for potential reverse causation where constipation could be a presenting symptom of CRC. The former requirement (1st prescription ≥2 years) explains why we started our inclusion of CRC in July 2007. The Swedish Prescribed Drug Register began in July 2005, so only two years later could any CRC patient fulfill our exposure requirements.

We performed several sensitivity analyses making use of the Swedish Patient Register to test several stricter definitions of constipation: *(a)* ⩾2 visits ever for any constipation using the ICD-9 code 564.xx or the ICD-10 code K59.xx in inpatient or non-primary outpatient care starting in 1987 (when ICD-9 was introduced in Sweden). Similar to the main analysis, we required the first constipation diagnosis to occur ⩾2 years before the CRC diagnosis (or matching date for controls), and the second constipation diagnosis needed to occur ⩾6 months before the CRC diagnosis or matching date (*main sensitivity analysis*). *(b)* ⩾2 visits for constipation with ⩽12 months between any 2 constipation diagnoses (must not be the 1st and 2nd constipation diagnosis). *(c)* ⩾2 visits for constipation within 12 month period (as in #1) + two prescriptions of laxatives (ATC code A06A*) during an 18-month period starting

6 months before the index date (the date of the first health care contact with constipation as a primary diagnosis) as previously described.[21] "Two dispatches" corresponds to 6 months of constipation medication, which is sufficient to satisfy the chronicity condition of the Rome III/IV criteria.[27]

Controls

Index individuals with CRC were matched *at the time of diagnosis/biopsy* on age, sex, calendar year and county with up to five controls from the Swedish general population[22] with index date set as the date of CRC diagnosis (Figure 1).

Siblings

CRC patients were also compared to their siblings. Siblings were identified through the Total Population Register.[22] Sibling comparisons allowed us to assess the potential association between chronic constipation and later CRC with further control for unmeasured confounding (siblings share more genetic and early environmental factors than matched controls).

Statistical Analysis

We used conditional logistic regression to estimate unadjusted and multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI) for having an earlier record of chronic constipation.

Although data were collected on comorbidities as above, we did not adjust for medical comorbidities in the regression; since matching occurred at the time of CRC diagnosis, matching on comorbidities would mean adjusting for comorbidities at the time of CRC diagnosis and therefore after the onset of constipation—thus potentially over-adjusting any association between chronic constipation and CRC.

All analyses were conditioned on matching factors (sex, age, county, year of biopsy), except in siblings where we conditioned on matching set within family instead of adjusted for the above four matching variables. We further adjusted for level of education (<9, 9–12, >12 years or missing). Statistics were carried out using SAS statistical software v9.4. A p-value <0.05 was considered statistically significant. The study was approved by the Stockholm Ethics Review Board. Informed consent was waived by the board since the study was strictly register-based.[28]

RESULTS

We identified 48,264 cases of CRC from 2007–2016 with a biopsy report demonstrating CRC (Figure 1). After exclusions there remained 41,299 CRC patients who were matched to 203,181 controls (Figure 1).

Both CRC patients and matched controls had a mean age in the 71.8 with slight male predominance (Table 1). Compared to matched controls without CRC, CRC patients were more likely to be diagnosed with CVD, non-CRC cancers, and diabetes.

Main results

Overall, 3,943 patients with CRC met our criteria for chronic constipation. The crude proportion of chronic constipation in CRC patients was 9.5% compared to 8.8% in matched controls. Conditioning on matching set, and adjusting for education there was a modest association between chronic constipation and later CRC (OR=1.10, 95% CI=1.06–1.14) (Table 2). The association between chronic constipation and later CRC did differ according to age category (p for interaction <0.001), level of education (p for interaction <0.001), and year of colon cancer diagnosis (p for interaction 0.013), though the effect size differences were small.

When comparing 17,818 CRC patients to their siblings (n=37,610)(Tables 3 and 4), the crude proportion of chronic constipation in CRC patients was 7.0% compared to 6.6% in siblings. CRC patients were no more likely to have chronic constipation than their siblings (OR=1.04, 95%CI=0.97–1.13).

Sensitivity analyses

In sensitivity analyses defining chronic constipation as ≥2 visits ever for any constipation in inpatient or non-primary outpatient care starting in 1987, we identified 126,650 cases of biopsy-verified CRC from 1989–2016. After exclusions there remained 111,125 CRC patients who were matched to 547,773 controls (Figure S1).

Overall, the number of patients meeting criteria for chronic constipation was greatly reduced. The crude proportion of chronic constipation in CRC patients was 0.16% compared to 0.18% in matched controls. Conditioning on matching set, and adjusting for education there was no association between chronic constipation and later CRC (OR=0.88, 95% CI=0.75–1.04)(Table S3). Additional sensitivity analyses found no association between CRC and chronic constipation, when the latter was the main diagnosis of their encounters. Further alternative definitions of chronic constipation including II) ≥2 visits for constipation within 12 months between any 2 constipation diagnoses or III) ≥2 visits for constipation within 12 months between any 2 constipation diagnoses with ≥2 prescriptions of laxatives during an 18-month period starting 6 months before the index date (since 2008) similarly demonstrated no increased risk for chronic constipation in CRC: OR=1.01, 95%CI=0.86–1.18 and OR=1.18, 95CI=0.88–1.57, respectively. Varying the time between the two visits for constipation to short (6–12 months), medium (1–5 years), and long (≥5 years) also showed no increased likelihood of chronic constipation in patients with CRC).

DISCUSSION

In this nationwide, population-based study of over 40,000 individuals with CRC—representing virtually all CRC cases in Sweden over a decade—we found only a modest association between chronic constipation and later CRC—that vanished when we compared CRC cases to sibling comparators, thereby taking intrafamilial confounding into account. A sensitivity analysis of 126,000 CRC cases diagnosed 1989–2016 found no association with earlier inpatient or non-primary outpatient care-diagnosed constipation. Varying the

definition of chronic constipation did not materially alter our findings even in the setting of prolonged (≥5 years) duration of symptoms, and ORs consistently remained around 1.

Fear of the potential adverse effects of constipation has had a strong and enduring grip on the popular imagination,[29] and the potential impact on risk of CRC is no exception. In fact, the literature to date has largely suggested that these fears are at least modestly founded with the largest and most recent study demonstrating an incidence risk ratio of 1.2 (95%CI 1.07–1.35), representing 1,434 CRC cases in a much larger (n=28,854) population of chronic constipation patients.[15] Almost 30% of these cases occurred in the first two years after diagnosis of constipation, raising the concern for reverse causation—that is that constipation was a sign of rather than a risk factor for CRC.

While CRC is a common malignancy, the incidence in a population is relatively small over time. By identifying almost all CRC cases in Sweden *a priori* and then looking at the occurrence of chronic constipation earlier, we were able to identify over 40,000 CRC cases. The next largest study identified 1,207 CRC cases over a 13.3-year period,[18] though notably also did not identify an increased risk of CRC with chronic constipation.

The high prevalence of both CRC and chronic constipation implies that any data connecting the two could have significant financial implications. Unlike the United States, most countries in Europe and worldwide do not have colonoscopy-based CRC screening program.[30] Any suggestion that individuals with chronic constipation represent a population that may need extra surveillance could generate a significant increase in need for colonoscopy with perceived risk of CRC thought to drive colonoscopy utilization.[31] In fact, fear of CRC is higher in both women and those with comorbid anxiety,[32, 33] the same population that is disproportionately affected by chronic constipation.[1, 2]

We did observe effect modification for the association between chronic constipation and risk of later CRC across age, level of education, and year of CRC diagnosis, though the magnitude of the effects would be small. Although there is an increased effect size seen in some of the younger ages, increased education levels, and later years of CRC diagnosis, the effect sizes are virtually identical for those with and without CC.

Our study has several notable strengths. Most importantly, it represents analysis of almost 40 times more CRC cases than ever previously assembled, with strict linkage to histopathology data to confirm diagnosis. Patients who successfully seek care for constipation may be more likely to see specialists and undergo more diagnostic procedures with corresponding increases in CRC detection. By using a population-based cohort with CRC as the starting point, we were able to ensure that any association with constipation was not merely a reflection of diagnostic access bias since all CRC cases in Sweden are included in the analysis. The ability to leverage sibling analyses to further account for residual confounding further strengthens our case that the association between chronic constipation and CRC is most likely null. We were also careful to account for potential reverse causation where constipation reflects a symptom of CRC rather than a risk factor, by using an exclusion period where the first laxative dispensation or constipation diagnosis needed to occur ≥2 years prior to the CRC diagnosis with the second dispensation or diagnosis ≥6 months

before the CRC diagnosis. Extensive sensitivity analyses varying the definition of chronic constipation (including one where we extended our study period to 1989–2016) did not significantly alter our results.

In any observational study, there is a risk of residual confounding. Although data were collected on comorbidities as per Table 1, we did not adjust for medical comorbidities in our final analysis. Matching comorbidities at the time of CRC diagnosis would introduce an additional source of bias, as we would be accounting for comorbidities were potentially diagnosed after the onset of constipation. Our use of sibling comparisons allowed us to examine the influence of intrafamilial confounding associated with shared genetic and early environmental factors on chronic constipation and CRC. In the absence of a chronic constipation diagnostic code, there may be some misclassification of patients using the laxative prescription surrogate, and some patients may obtain laxatives over-the-counter without a prescription. However, we conducted several sensitivity analyses using diagnostic codes alone or in combination with laxative dispensations to examine the effects of more rigorous definitions of chronic constipation with similar results. Most importantly, the prevalence of chronic constipation in our cohort (8.8–9.5%) compares favorably with the prevalence of chronic constipation in Sweden using the most recent Rome IV definitions derived a self-completed questionnaire (10.3%, 95%CI 9.0—11.6), respectively).[34] Finally, Sweden represents a single country with a homogenous population such that our findings may have more limited generalizability. However, during the study period, Sweden's colon cancer screening methodology was similar to most countries in Europe and elsewhere and has not used a colonoscopy-based program.

In summary, in this large population-based cohort of patients with CRC diagnosed over a period of 9 years, previous chronic constipation was no more common in CRC patients than in matched controls. Our findings will hopefully offer clarity to providers struggling to balance previously discordant data on this topic with real patient concerns about risk of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosures:

KS has received research support from AstraZeneca, Ironwood, and Urovant, has served as a speaker for Shire, and has served as a consultant to Arena, Gelesis, GI Supply, Synergy, and Shire. JFL coordinates a study on behalf of the Swedish IBD quality register (SWIBREG). This study has received funding from Janssen. OO has been PI for projects (unrelated to the current paper) at KI partly financed by investigator-initiated grants from Janssen and Pfizer.

Abbreviations:

CI	confidence interval.

GI	Gastrointestinal.
OR	Odds ratio.
CRC	colorectal cancer.

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WHAT YOU NEED TO KNOW

Background:

Prolonged colon transit times may increase contact time between potential carcinogens in the stool and the colonic mucosa. Previous studies have yielded conflicting results connecting chronic constipation with risk of colorectal cancer.

Findings:

In a large, nationwide case-control study accounting for 41,299 colorectal cancer cases, we found no association between chronic constipation and later colorectal cancer.

Implications for Clinical Care:

These findings may alleviate patient fears and result in cost savings by avoiding unnecessary testing in chronic constipation patients likely to undergo colonoscopy as part of their workup for symptoms.

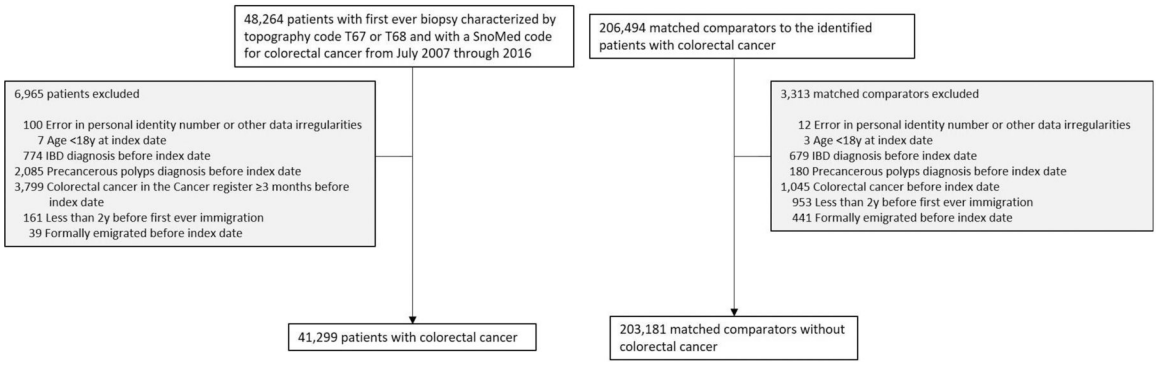

Figure 1:
Flow chart of identified patients and their matched comparators

Table 1

Baseline characteristics of study cohort

Characteristic	Colorectal cancer (n=41,299)	Matched comparators (n=203,181)
Female, no. (%)	19 508 (47.2%)	95 951 (47.2%)
Male, no. (%)	21 791 (52.8%)	107 230 (52.8%)
Age		
Mean (SD)	71.8 (11.5)	71.8 (11.5)
Median (IQR)	72.9 (64.8–80.3)	72.8 (64.8–80.3)
Range, min-max	18.1–100.0	18.3–99.9
Categories, no. (%)		
18y – <30y	75 (0.2%)	337 (0.2%)
30y – <40y	372 (0.9%)	1 799 (0.9%)
40y – <50y	1 452 (3.5%)	7 084 (3.5%)
50y – <60y	4 119 (10.0%)	20 294 (10.0%)
60y – <70y	10 708 (25.9%)	52 952 (26.1%)
≥70y	24 573 (59.5%)	120 715 (59.4%)
Country of birth, no. (%)		
Nordic country	38 314 (92.8%)	187 630 (92.3%)
Other	2 985 (7.2%)	15 549 (7.7%)
Missing	0	2 (0.0%)
Level of education, no. (%)		
≤9 years	15 919 (38.5%)	77 794 (38.3%)
10–12 years	15 979 (38.7%)	77 552 (38.2%)
>12 years	8 961 (21.7%)	44 752 (22.0%)
Missing	440 (1.1%)	3 083 (1.5%)
Year of colon cancer/Index year, no. (%)		
July 2007–2010	16 412 (39.7%)	80 830 (39.8%)
2011–2013	13 746 (33.3%)	67 637 (33.3%)
2014–2016	11 141 (27.0%)	54 714 (26.9%)
Disease history ever before index date, no. (%)		
Cardiovascular disease (CVD)	22 949 (55.6%)	94 208 (46.4%)
Myocardial infarction (MI)	3 278 (7.9%)	16 319 (8.0%)
Cardiovascular disease in inpatient care	20 120 (48.7%)	78 927 (38.8%)
Cancer (excluding CRC)	13 418 (32.5%)	41 775 (20.6%)
Cancer (excluding CRC) using the Cancer register only	8 794 (21.3%)	33 802 (16.6%)
Diabetes	5 516 (13.4%)	19 427 (9.6%)
Neurologic disease	8 306 (20.1%)	40 351 (19.9%)
None of the above	11 161 (27.0%)	77 205 (38.0%)
Disease history within 5 years before index date, no. (%)		
Cardiovascular disease (CVD)	19 031 (46.1%)	66 229 (32.6%)
Myocardial infarction (MI)	1 450 (3.5%)	6 244 (3.1%)
Cardiovascular disease in inpatient care	15 941 (38.6%)	49 553 (24.4%)

Characteristic	Colorectal cancer (n=41,299)	Matched comparators (n=203,181)
Cancer (excluding CRC)	10 026 (24.3%)	24 237 (11.9%)
Cancer (excluding CRC) using the Cancer register only	3 862 (9.4%)	12 562 (6.2%)
Diabetes	5 030 (12.2%)	15 998 (7.9%)
Neurologic disease	4 606 (11.2%)	21 103 (10.4%)
None of the above	15 824 (38.3%)	113 770 (56.0%)

CRC, colorectal cancer.

Table 2

Prevalence and odds ratio of constipation in patients with colorectal cancer and matched comparators

Group	N exposed (% with constipation)		Odds ratio* (95%CI)	Odds ratio** (95%CI)
	CRC with constipation	Comparators with constipation		
Overall	3 943 (9.5%)	17 887 (8.8%)	1.10 (1.06–1.14)	1.10 (1.06–1.14)
Sex				
Female	2 376 (12.2%)	10 604 (11.1%)	1.12 (1.07–1.18)	1.13 (1.07–1.18)
Male	1 567 (7.2%)	7 283 (6.8%)	1.06 (1.00–1.13)	1.07 (1.01–1.13)
Age				
18y – <30y	5 (6.7%)	0	-	-
30y – <40y	6 (1.6%)	17 (0.9%)	1.83 (0.70–4.80)	2.08 (0.78–5.58)
40y – <50y	43 (3.0%)	111 (1.6%)	1.93 (1.34–2.77)	1.91 (1.33–2.75)
50y – <60y	159 (3.9%)	542 (2.7%)	1.51 (1.26–1.81)	1.51 (1.25–1.81)
60y – <70y	661 (6.2%)	2 276 (4.3%)	1.47 (1.34–1.61)	1.47 (1.34–1.61)
≥70y	3 069 (12.5%)	14 941 (12.4%)	1.01 (0.97–1.05)	1.01 (0.97–1.05)
Country of birth				
Nordic country	3 630 (9.5%)	16 342 (8.7%)	1.10 (1.06–1.14)	1.10 (1.06–1.14)
Other	313 (10.5%)	1 545 (9.9%)	1.24 (0.95–1.64)	1.25 (0.95–1.64)
Level of education				
≤9 years	1 621 (10.2%)	8 275 (10.6%)	0.95 (0.89–1.02)	0.95 (0.89–1.02)
10–12 years	1 487 (9.3%)	6 028 (7.8%)	1.25 (1.16–1.35)	1.25 (1.16–1.35)
>12 years	765 (8.5%)	3 116 (7.0%)	1.18 (1.04–1.34)	1.18 (1.04–1.34)
Year of colon cancer/Index year				
July 2007–2010	1 008 (6.1%)	4 943 (6.1%)	1.00 (0.93–1.08)	1.01 (0.94–1.08)
2011–2013	1 480 (10.8%)	6 431 (9.5%)	1.16 (1.09–1.23)	1.16 (1.09–1.23)
2014–2016	1 455 (13.1%)	6 513 (11.9%)	1.12 (1.05–1.19)	1.12 (1.05–1.19)
Disease history within 5 years before index date, no. (%)				
Cardiovascular disease (CVD)	2 629 (13.8%)	10 283 (15.5%)	0.87 (0.82–0.92)	0.87 (0.83–0.92)
Cancer (excluding CRC)	1 210 (12.1%)	3 395 (14.0%)	0.93 (0.83–1.04)	0.93 (0.83–1.04)
Diabetes	745 (14.8%)	2 513 (15.7%)	0.90 (0.76–1.08)	0.91 (0.76–1.09)
Neurologic disease	823 (17.9%)	4 046 (19.2%)	0.78 (0.67–0.91)	0.78 (0.67–0.91)
None of the above	763 (4.8%)	5 188 (4.6%)	1.23 (1.12–1.35)	1.23 (1.12–1.35)

CRC, colorectal cancer.

*Conditioned on matching set (age, sex, county, and calendar period);

**Conditioned on matching set and further adjusted for education

Table 3

Baseline characteristics of CRC patients compared to siblings

Characteristic	Colorectal cancer (n=17,818)	Matched siblings (n=37,610)
Female, no. (%)	8 007 (44.9%)	18 444 (49.0%)
Male, no. (%)	9 811 (55.1%)	19 166 (51.0%)
Age		
Mean (SD)	65.8 (9.6)	64.4 (9.8)
Median (IQR)	67.4 (60.7–72.7)	65.7 (58.8–71.4)
Range, min-max	18.1–84.8	18.1–84.5
Categories, no. (%)		
18y – <30y	52 (0.3%)	155 (0.4%)
30y – <40y	275 (1.5%)	557 (1.5%)
40y – <50y	969 (5.4%)	2 583 (6.9%)
50y – <60y	2 808 (15.8%)	7 428 (19.8%)
60y – <70y	6 994 (39.3%)	15 285 (40.6%)
≥70y	6 720 (37.7%)	11 602 (30.8%)
Country of birth, no. (%)		
Nordic country	17 655 (99.1%)	37 294 (99.2%)
Other	163 (0.9%)	315 (0.8%)
Missing	0	1 (0.0%)
Level of education, no. (%)		
≤9 years	5 570 (31.3%)	12 152 (32.3%)
10–12 years	7 526 (42.2%)	16 083 (42.8%)
>12 years	4 671 (26.2%)	8 841 (23.5%)
Missing	51 (0.3%)	534 (1.4%)
Year of colon cancer/Index year, no. (%)		
July 2007–2010	6 121 (34.4%)	13 329 (35.4%)
2011–2013	6 100 (34.2%)	12 762 (33.9%)
2014–2016	5 597 (31.4%)	11 519 (30.6%)
Disease history ever before index date, no. (%)		
Cardiovascular disease (CVD)	8 227 (46.2%)	13 845 (36.8%)
Myocardial infarction (MI)	941 (5.3%)	1 857 (4.9%)
Cardiovascular disease in inpatient care	6 872 (38.6%)	10 800 (28.7%)
Cancer (excluding CRC)	5 255 (29.5%)	7 577 (20.1%)
Cancer (excluding CRC) using the Cancer register only	3 289 (18.5%)	6 541 (17.4%)
Diabetes	2 084 (11.7%)	2 817 (7.5%)
Neurologic disease	3 513 (19.7%)	7 568 (20.1%)
None of the above	5 957 (33.4%)	16 568 (44.1%)
Disease history within 5 years before index date, no. (%)		
Cardiovascular disease (CVD)	6 575 (36.9%)	8 620 (22.9%)
Myocardial infarction (MI)	399 (2.2%)	616 (1.6%)
Cardiovascular disease in inpatient care	5 202 (29.2%)	5 764 (15.3%)

Characteristic	Colorectal cancer (n=17,818)	Matched siblings (n=37,610)
Cancer (excluding CRC)	3 991 (22.4%)	3 774 (10.0%)
Cancer (excluding CRC) using the Cancer register only	1 475 (8.3%)	2 144 (5.7%)
Diabetes	1 891 (10.6%)	2 089 (5.6%)
Neurologic disease	1 891 (10.6%)	3 304 (8.8%)
None of the above	8 161 (45.8%)	24 872 (66.1%)

CRC, colorectal cancer.

Table 4

Prevalence and odds ratio of constipation in patients with colorectal cancer and siblings

Group	N exposed (% with constipation)		Odds ratio* (95%CI)	Odds ratio** (95%CI)
	CRC with constipation	Comparators with constipation		
Overall	1 254 (7.0%)	2 468 (6.6%)	1.05 (0.97–1.13)	1.04 (0.97–1.13)
Sex				
Female	736 (9.2%)	1 511 (8.2%)	1.04 (0.91–1.18)	1.03 (0.91–1.18)
Male	518 (5.3%)	957 (5.0%)	1.06 (0.92–1.23)	1.07 (0.92–1.24)
Age				
18y – <30y	4 (7.7%)	0	-	-
30y – <40y	5 (1.8%)	6 (1.1%)	0.65 (0.06–6.60)	0.65 (0.06–6.61)
40y – <50y	30 (3.1%)	54 (2.1%)	1.70 (0.86–3.37)	1.70 (0.86–3.38)
50y – <60y	104 (3.7%)	240 (3.2%)	1.15 (0.82–1.60)	1.17 (0.83–1.64)
60y – <70y	417 (6.0%)	884 (5.8%)	1.10 (0.93–1.29)	1.11 (0.94–1.31)
≥70y	694 (10.3%)	1 284 (11.1%)	0.90 (0.80–1.01)	0.89 (0.79–1.00)
Country of birth				
Nordic country	1 239 (7.0%)	2 448 (6.6%)	1.04 (0.97–1.13)	1.04 (0.97–1.12)
Other	15 (9.2%)	20 (6.3%)	1.12 (0.49–2.58)	1.11 (0.48–2.55)
Level of education				
≤9 years	401 (7.2%)	890 (7.3%)	0.89 (0.75–1.05)	0.89 (0.75–1.05)
10–12 years	533 (7.1%)	1 014 (6.3%)	1.24 (1.07–1.45)	1.24 (1.07–1.45)
>12 years	311 (6.7%)	543 (6.1%)	1.11 (0.90–1.36)	1.11 (0.90–1.36)
Year of colon cancer/Index year				
July 2007–2010	221 (3.6%)	411 (3.1%)	1.14 (0.95–1.36)	1.14 (0.95–1.36)
2011–2013	478 (7.8%)	882 (6.9%)	1.14 (1.00–1.29)	1.13 (1.00–1.28)
2014–2016	555 (9.9%)	1 175 (10.2%)	0.94 (0.84–1.06)	0.94 (0.84–1.06)
Disease history within 5 years before index date, no. (%)				
Cardiovascular disease (CVD)	705 (10.7%)	1 169 (13.6%)	0.78 (0.67–0.90)	0.78 (0.67–0.91)
Cancer (excluding CRC)	363 (9.1%)	518 (13.7%)	0.70 (0.51–0.95)	0.70 (0.51–0.95)
Diabetes	222 (11.7%)	300 (14.4%)	1.18 (0.80–1.75)	1.17 (0.79–1.74)
Neurologic disease	305 (16.1%)	581 (17.6%)	0.85 (0.58–1.25)	0.85 (0.57–1.26)

Group	N exposed (% with constipation)		Odds ratio* (95%CI)	Odds ratio** (95%CI)
	CRC with constipation	Comparators with constipation		
None of the above	328 (4.0%)	867 (3.5%)	1.13 (0.95–1.34)	1.10 (0.93–1.31)

CRC, colorectal cancer.

*Conditioned on matching set (family);

**Conditioned on matching set and further adjusted for education