



Diagnostic yield of endoscopy in irritable bowel syndrome: a nationwide prevalence study 1987–2016

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Abstract

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Specific 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.

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Declaration of interests

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Introduction: Symptoms of irritable bowel syndrome (IBS) are common reasons for endoscopic procedures. We examined the yield of colonoscopy and upper endoscopy in IBS for several organic diseases.

Methods: Matched population-based prevalence study in Sweden. We identified 21,944 participants diagnosed with IBS from 1987–2016 undergoing colonoscopy with a biopsy from all of Sweden's 28 pathology departments within 6 months of diagnosis. We compared prevalence of histopathology-proven diagnoses of inflammatory bowel disease (IBD), colorectal cancer, precancerous polyps, and microscopic colitis between patients recently diagnosed with IBS and matched controls without IBS (n=81,101) undergoing colonoscopy. We also compared prevalence of celiac disease between patients diagnosed with IBS (n=9,965) and matched controls (n=45,584) undergoing upper endoscopy with biopsy. IBS patients were also compared to their siblings. Conditioned logistic regression estimated adjusted odds ratios (aORs).

Results: Biopsy-proven IBD was seen in 1.6% of IBS and in 5.9% of controls (aOR=0.21; 95% CI=0.19–0.24). The prevalence of precancerous polyps was 4.1% vs. 13.0% (aOR=0.28; 95% CI=0.26–0.30), colorectal cancer 0.8% vs. 6.3% (aOR=0.17; 95% CI=0.14–0.20) and celiac disease 1.9% vs. 3.4% (aOR=0.54; 95% CI=0.47–0.63). Conversely, the prevalence of microscopic colitis was 2.9% vs. 1.7% (aOR=1.77; 95% CI=1.61–1.95), with higher prevalence in older patients and patients with IBS with diarrhea. Yield of colonoscopy for precancerous polyps, colorectal cancer, and microscopic colitis increased by age. Our findings were consistent using unaffected siblings as the comparator group.

Discussion: The diagnostic yield of upper endoscopy and colonoscopy for organic disease is low in patients with a first-time diagnosis of IBS, though increases with age.

Keywords

colonoscopy; functional GI disease; healthcare utilization; histopathology; esophagogastroduodenoscopy

INTRODUCTION

Irritable bowel syndrome (IBS) affects 11.2% of the global population,[1] with significant impacts on patients' quality of life despite no increased risk of mortality.[2] Among this sizeable population, there is a disproportionate number of patients <50 years[1] who would not traditionally meet criteria for endoscopy, still IBS patients accounted for up to 36% of gastroenterology consultations in one catchment area,[3] with most US patients undergoing at least one outpatient procedure the year of diagnosis,[4] with 28.7% of colonoscopies in those <50 performed in patients with IBS.[5] Procedure rates are similarly high in less procedure-incentivized payment systems. Between 63–84% of IBS patients in Europe will undergo a diagnostic procedure, with more than 1/3 undergoing colonoscopy.[6]

High endoscopic utilization persists despite some evidence that colonoscopy is unlikely to reveal structural disease. In a prospective trial of 466 non-constipated, suspected IBS patients undergoing colonoscopy, the rate of structural disease was no greater than controls. [7] Contrasting data, however, suggest an increased risk of structural disease on colonoscopy

in IBS patients without alarm symptoms,[8–10] microscopic colitis being the most likely ‘missed’ diagnosis in some cohorts.[11–13]

Similarly disparate findings are found when examining the use of upper endoscopy to exclude celiac disease in patients with IBS symptoms, though a more recent meta-analysis showed an increased risk of biopsy-proven celiac disease[14]—though only one small, population-based study was included.[15] Limitations to the existing literature include retrospective or non-population-based design,[9, 12] limited numbers of IBS patients without alarm symptoms,[7, 8, 12, 15] and lack of inclusion of patients with IBS without diarrhea. Thus, the role of endoscopic evaluation of typical IBS remains uncertain.

We used a nationwide histopathology register to examine the overall risk of structural gastrointestinal disease (inflammatory bowel disease, microscopic colitis, precancerous colon polyps, colorectal cancer, celiac disease) in a large cohort of individuals with IBS undergoing upper endoscopy and colonoscopy with biopsy compared to matched comparators undergoing the same investigations for other reasons.

MATERIALS and METHODS

We compared the first gastrointestinal biopsy after IBS diagnosis to first gastrointestinal biopsy in individuals without a prior IBS diagnosis, and calculated the prevalence of inflammatory bowel disease, pre-cancerous polyps, colorectal cancer (CRC), microscopic colitis, and celiac disease according to IBS status.

Source database with outcome data

IBS patients were selected from the ESPRESSO study, a histopathology-based cohort consisting of gastrointestinal pathology reports collected across Sweden’s 28 pathology departments from 1965–2017.[16]

For this study, biopsy results from individuals with IBS and matched controls were categorized according to the Systematized Nomenclature of Medicine (SNOMED) pathology codes originating from their endoscopic procedure to define our outcomes: inflammatory bowel disease, colorectal cancer, microscopic colitis, and celiac disease (Table S1). The SNOMED codes for inflammatory bowel disease (in conjunction with ICD codes), microscopic colitis and celiac disease have all been validated and found to have positive predictive values 95%.[17–19] Precancerous polyps were categorized into non-advanced (tubular adenomas and sessile serrated polyps) or advanced (tubulovillous adenomas, villous adenomas, or any adenoma with cellular dysplasia) on the basis of histology only without reference to size (not available from ESPRESSO database). Our prior validation study indicated a high accuracy for identification of serrated polyps, with a positive predictive value of 95%.[20]

Definition of IBS

We first identified all individuals undergoing a colonoscopy with biopsy (Table S1) in the ESPRESSO cohort and excluded those whose histopathology samples came from a surgical resection (Table S2). We used ICD codes to identify individuals within this cohort with a

diagnosis of IBS (ICD-9 564B; ICD-10 K58) in inpatient or non-primary outpatient care within 6 months *before* their upper endoscopy or colonoscopy with biopsy from 1987–2016 (1987 corresponding to the first year that the ICD-9 codes were introduced in Sweden). Both IBS patients and their matched controls (see below) were excluded from all analyses if at baseline they had an earlier diagnosis of celiac disease, microscopic colitis, precancerous polyps, or colorectal cancer (Table S1) up until –7 days from the index biopsy since these disorders may lead to false-positive IBS diagnoses (Figures 1 and 2). The 7-day window was selected because biopsy specimens may have been assigned a date a few days after the actual biopsy despite the diagnosis being coded a few days prior. For inflammatory bowel disease specifically, we required a concomitant ICD diagnosis of inflammatory bowel disease from –7 days to +365 days from the biopsy to ensure a true diagnosis. Using alternative inclusion criteria, we examined risk of a colorectal cancer diagnosis among patients in the ESPRESSO cohort regardless of previous history of precancerous polyps.

Patients with IBS were divided into those with diarrhea predominance (IBS-D) and those without diarrhea predominance (IBS non-D)(see ICD codes in Table S1).

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[21] and the longitudinal integrated database for health insurance and labor market studies (LISA) using an individual's PIN.[22] Data were linked to the Swedish Patient Register[23] to obtain data on inpatient and outpatient medical encounters. The diagnostic validity of the national patient register is generally 85–95%[23] with high validity seen for IBS.[24]

Controls

Index individuals with IBS were matched on age, sex, and county with up to five controls from the ESPRESSO cohort who also underwent upper endoscopy or colonoscopy with biopsy in the same calendar year.

Siblings

IBS patients were also compared to their siblings without IBS. Siblings were identified from the ESPRESSO cohort and underwent upper endoscopy or colonoscopy within 5 years of each other. Sibling comparisons allowed us to examine the influence of intrafamilial confounding.

Covariates

Within the study population we determined medical comorbidities related to overall health status in the last five years prior to study entry using ICD-8/9/10 codes prospectively recorded in routine clinical practice to determine presence of diabetes, cardiovascular disease, neurologic disease, and cancer (Table S3).

Statistical Analysis

We calculated crude prevalence for each histopathology-defined outcome and used conditional logistic regression to estimate multivariable-adjusted odds ratios (OR) and 95% confidence intervals (CI).

Because colonoscopy is more commonly used as a diagnostic for those with IBS-D, we also performed an analysis according to disease subtype (IBS-D and IBS non-D). Additionally, we performed stratified analyses according to age, quantifying the risk a traditional age-appropriate screening population (≥50 years old) vs those <50 years old. We also used a logistic regression model to estimate the prevalence of organic disease by age on a continuous scale, where age was included as a natural cubic spline function (with knots at percentiles 5%, 27.5%, 50%, 72.5%, and 95%). To account for possible temporal bias over time, we performed a subanalysis restricted to outcomes diagnosed in 2002 (the Swedish outpatient register was introduced in 2001) or later. To evaluate for increasing of a shift from right-sided to left-sided colorectal cancers,[25] we also evaluated the location of the CRC cases diagnosed in the cohort using location codes when available.

All analyses were conditioned on matching factors (sex, age, county, year of biopsy), except in siblings where we conditioned on matching set within family. We further adjusted for baseline medical comorbidities (cancer other than colorectal cancer, diabetes, cardiovascular disease including myocardial infarction, and neurologic disease) as well as for education. A sensitivity analysis additionally adjusted for presence of family history (in a parent or sibling) of inflammatory bowel disease, colorectal cancer, or celiac disease. 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 (Protocol 2014/1287–31/4). Informed consent was waived by the board since the study was strictly register-based.[26]

RESULTS

Yield of colonoscopy in IBS

We identified 25,764 patients diagnosed with IBS 1987–2016 followed by a colonoscopy within 6 months (Figure 1). After exclusions, there were 21,944 patients with IBS who were matched to 81,101 patients (with 97,468 biopsies; each IBS biopsy was linked to a non-IBS control biopsy) without IBS undergoing colonoscopy.

The average time interval between the IBS diagnosis and colonoscopy was 0.7 (SD 1.3) months. Table 1 shows the characteristics of study participants according to IBS status. Both IBS patients and matched controls were predominantly female with a mean age in the mid-40s. Compared to matched controls, IBS patients were less likely to have a preexisting diagnosis of cancer (excluding colorectal cancer) prior to colonoscopy. IBS was the primary diagnosis in the pre-colonoscopy clinical encounter almost 90% of the time, with IBS-D as the predominant subtype among the IBS cohort (62.4%). We also compared 1,240 IBS patients with their siblings (n=1,415).

Among all IBS patients, the diagnostic yield for the specified organic diseases was 9.3%, falling to 5.1% among those <50 years old (16.3% for those ≥50 years old). A summary of the absolute yield of colonoscopy and upper endoscopy for the studied diseases in IBS by age is found in Figure 3. The odds of organic disease in IBS relative to comparators is found in Figure S1.

Inflammatory bowel disease—The crude prevalence of inflammatory bowel disease was lower in patients with IBS than in controls (1.6% vs. 5.9%)(Table 2). Conditioning on matching variables (age, sex, county, and calendar period), and adjusting for potential confounders including education and baseline medical comorbidities, patients with IBS were at 79% decreased risk of inflammatory bowel disease (aOR=0.21; 95% CI=0.19–0.24) (Table 2). Risk of inflammatory bowel disease did not vary significantly with sex or comorbidities (Table S4a).

Colorectal cancer—The crude prevalence of colorectal cancer was 0.8% in patients with IBS compared to 6.3% in controls. This corresponded to an 83% decreased risk of colorectal cancer in IBS (aOR=0.17; 95% CI 0.14–0.20)(Table 2). Risk of diagnosing colorectal cancer in IBS patients similarly did not vary significantly by age or sex. (Table S4b). Also when restricting our cohort to IBS patients aged ≥50 years, we did see a lower prevalence of colorectal cancer compared to matched controls (Table 2). Age affected prevalence estimates significantly. The proportion of colorectal cancer in IBS patients was 0–0.1% for those <40 years old compared to 3.8% for those ≥70 (Table S4b). There was no clear trend toward increasing left-sided colon cancers in our cohort (Table S7), though ESPRESSO contains a high proportion of codes that do not specify left- or right-sided CRC location and are therefore listed as unspecified.

Microscopic colitis—The crude prevalence of microscopic colitis was increased in IBS patients in comparison to matched controls (2.9% vs. 1.7%), which corresponded to an adjusted OR of 1.77 (95% CI 1.61–1.95). Overall, older women with IBS had an increased prevalence of microscopic colitis as well as those diagnosed with IBS with diarrhea (IBS-D) prior to colonoscopy (Table S4c). Among those IBS patients ≥50 years old, the risk of microscopic colitis was greater (OR=2.36; 95% CI 2.09–2.66) compared to controls than in those <50 years old (OR=1.16; 95% CI 0.99–1.36)(P for interaction <0.001)(Table 2). Again, age affected prevalence estimates significantly: the proportion of IBS patients having microscopic colitis was 0.9–1.6% in those <40 years old compared to 8.2% in those ≥70 (Table S4c).

Precancerous polyps—IBS patients had a lower yield of precancerous polyps on colonoscopy than comparators (4.1% vs. 13.0%), including lower prevalence of non-advanced and advanced adenomas (Table 2). The adjusted risk of any precancerous polyps was 72% lower in IBS (aOR=0.28; 95% CI 0.26–0.30), with similar findings for non-advanced and advanced adenomas. The estimates were similar across subgroups divided by age, sex, years of biopsy, comorbidity, and IBS subtype (Table S4d). Similar trends were seen for non-advanced and advanced adenoma subgroups (Tables S4e and S4f).

Yield of upper endoscopy in celiac disease

We identified 11,662 patients diagnosed with IBS 1987–2016 who had an upper endoscopy within 6 months (Figure 2). After exclusions, there were 9,965 patients with IBS who were matched to 42,584 patients (with 46,313 biopsies) without IBS undergoing upper endoscopy.

The average time interval from IBS diagnosis to upper endoscopy was 1.2 (SD 1.5). Table 1 shows the characteristics of study participants according to IBS status. Similar to the patients undergoing colonoscopy, both IBS patients and matched controls were predominantly female with a mean age in the mid-40s. IBS was the primary diagnosis in the pre-colonoscopy clinical encounter 83.9% of the time, with IBS-D as the predominant subtype among the IBS cohort.

Celiac disease—The crude prevalence of celiac disease in IBS was 1.9% compared to 3.4% in matched controls, which translated to a 46% decreased risk of celiac disease (aOR=0.54; 95 CI 0.47–0.63) (Table 2). The prevalence of positive biopsies for celiac was about the same as the general population above age 50 and significantly lower below age 30. (Table S4g).

An IBS diagnosis prior to upper endoscopy was associated with a 53% decreased risk of celiac disease on biopsy compared to siblings (OR= 0.43; 95% CI 0.20–0.89), but this was attenuated by adjustment for confounders (including age and sex)(aOR=0.47; 95 CI 0.19–1.18) with a wide CI likely due to small patient number (Table 2).

Sibling analyses—Sibling analyses confirmed the main analyses above (Table 2).

Analysis by endoscopy date—A subanalysis accounting for date of colonoscopy or upper endoscopy (as a possible source of temporal bias) evaluating patients diagnosed in 2002 and later confirmed the main analyses (Table S5).

Role of family history—For diseases with a strong heritable component (inflammatory bowel disease, colorectal cancer, and celiac disease), additional adjustment for family history of these diseases in a parent or sibling did not materially alter our effect estimates (Table S6).

DISCUSSION

In this nationwide, population-based survey of over 21,000 newly-diagnosed IBS patients undergoing colonoscopy with biopsy and over 9,900 newly-diagnosed IBS patients undergoing upper endoscopy with biopsy, we found an overall low diagnostic yield of inflammatory bowel disease, precancerous polyps, colorectal cancer, and celiac disease. Practically, the lower risk translates to only 1 out of 132 individuals with IBS undergoing colonoscopy being diagnosed with colorectal cancer. Conversely, patients initially diagnosed with IBS who later underwent colonoscopy were more likely to be diagnosed with microscopic colitis (especially older patients with IBS-D) than comparators undergoing colonoscopy for other indications. However, the absolute diagnostic yield was similarly low.

To our knowledge, these results represent the largest, population-based analysis of the yield of endoscopy in IBS with the benefit of pathology confirmation of disease findings. The economic impacts of our finding are potentially substantial given the high prevalence of IBS across global societies with high direct healthcare costs.[6] In Europe, a third of IBS patients will undergo colonoscopy,[27] and almost 30% of colonoscopies in the US performed in patients under 50 are performed for IBS.[5]

Existing data have been mixed as to the yield of endoscopic procedures in IBS.

In a community-based colon cancer screening cohort (n=9,160 with IBS) in Taiwan demonstrated an approximately 20% increased risk of colonic adenomas and colorectal cancer.[10] Two other Taiwan-based cohorts found an increased risk of colorectal cancer (compared to randomly-selected controls[28] and expected cancer rate[29]) among IBS patients in the first one to two years after diagnosis that attenuated afterward. Data from a Danish registry with large numbers of IBS patients (n=57,851) demonstrated a similar trend with increased risk of colorectal cancer early on after IBS diagnosis followed by a decreased risk in later years.[30]

Our findings are consistent with other studies looking at the diagnostic yield of colonoscopy. In their prospective study of 466 suspected IBS patients undergoing colonoscopy compared to controls undergoing screening or surveillance colonoscopy, Chey *et al* found decreased rates of colonic adenomas and colorectal cancers and adenomas compared to controls. [7] They also found no significantly-increased risk of inflammatory bowel disease or microscopic colitis, though there were few cases of each overall. In a random population of 1,220 Swedish patients undergoing colonoscopy, the prevalence of inflammatory bowel disease was 1.8% and 0.4% among those with and without IBS symptoms, respectively.[31]

A small, uncontrolled study did demonstrate a 4.6% risk of microscopic colitis among 87 IBS patients,[12] and meta-analyses incorporating larger numbers of patients have not suggested an increased risk of microscopic colitis in IBS.[11, 13] Our own data more definitively establish the low risk of a microscopic colitis diagnosis overall among patients with IBS undergoing colonoscopy, though the odds of diagnosis was increased compared to matched comparators—especially among those diagnosed with IBS-D and in older patients. The difference in diagnostic yield by age is striking: 1 in 80 IBS patients <40 years old undergoing colonoscopy will be diagnosed with microscopic colitis compared to 1 in 12 among those 70 years old.

Our data suggest a decreased yield of celiac disease among patients with IBS undergoing upper endoscopy with biopsy, though we would argue that the availability and excellent test characteristics of celiac serology testing may decrease the yield of patients with IBS undergoing upper endoscopy. Many of these patients would likely have undergone serologic testing prior to their clinicians making a diagnosis of IBS. However, our celiac disease prevalence of 1.9% is not substantially lower than the 3.3% celiac prevalence from a meta-analysis performed among those with positive celiac serologies undergoing duodenal biopsy. [14] Moreover, a multicenter study of 492 IBS patients without constipation undergoing serology and confirmatory endoscopy demonstrated a similar yield of celiac disease between the IBS population and controls.[32]

Our study had several strengths which bolster our conclusions. It is the largest study to date utilizing a population-based approach for IBS data with diagnoses of interest confirmed by pathology, minimizing the risk of misclassification bias. By including over 103,000 patients undergoing colonoscopy with biopsy and more than 52,000 patients undergoing upper endoscopy with biopsy, we were able to prospectively capture less common diagnoses in significant quantity including inflammatory bowel disease, colorectal cancer, and celiac disease. Well-validated Swedish registers[33] ensure minimal loss to follow up, and the availability of matched siblings also undergoing endoscopic evaluation confirms our main findings in those with similar genetic and environmental backgrounds.

We acknowledge several limitations. Sweden does not have a nationwide colorectal cancer screening program, and thus our IBS cohort may represent a more severe subset of disease with symptoms bothersome enough to merit endoscopic evaluation. The majority of IBS patients will not seek care for their disease.[34] We also acknowledge that some patients presenting with IBS-like symptoms would have avoided a clinical diagnosis of IBS by virtue of some historical or diagnostic feature such as fecal calprotectin for inflammatory bowel disease, or alarm symptoms for colorectal cancer. We also relied on a single diagnostic code for identification of IBS patients, which may introduce misclassification bias. Nevertheless, the ICD system is thought to have strong validity in IBS[24] and conditioning the IBS diagnosis on having an associated gastrointestinal biopsy also likely increases data validity and reduces the risk of transcription error in ICD coding. Finally, because cases of structural GI disease were matched to controls at the time of biopsy, we are unable to evaluate the yield of endoscopy in patients diagnosed with IBS after an endoscopic procedure or those with IBS who never underwent endoscopy.

In summary, we show that the diagnostic yield of upper endoscopy and colonoscopy is relatively low in patients with a first-time diagnosis of IBS. Age of IBS diagnosis is clearly an important factor, and we demonstrate an increasing yield of diagnostic colonoscopy for both colorectal cancer and microscopic colitis in older patients. Because IBS is a disease primarily diagnosed in the young, this data importantly highlights the low yield of endoscopic evaluations in this population. Our findings support a symptom-based diagnostic approach to IBS not involving endoscopy, saving healthcare expenditures and minimizing patient risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

CI confidence interval

OR	Odds ratio
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome

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HIGHLIGHTS

- Symptoms of irritable bowel syndrome (IBS) are common reasons for endoscopic procedures
- We examined the yield of colonoscopy and upper endoscopy in IBS in a large cohort
- Inflammatory bowel disease, precancerous polyps, colorectal cancer, and celiac disease were all less common in IBS compared to controls
- Microscopic colitis was more common in IBS patients
- The yield of upper endoscopy and colonoscopy for organic disease is low in patients with a first-time diagnosis of IBS

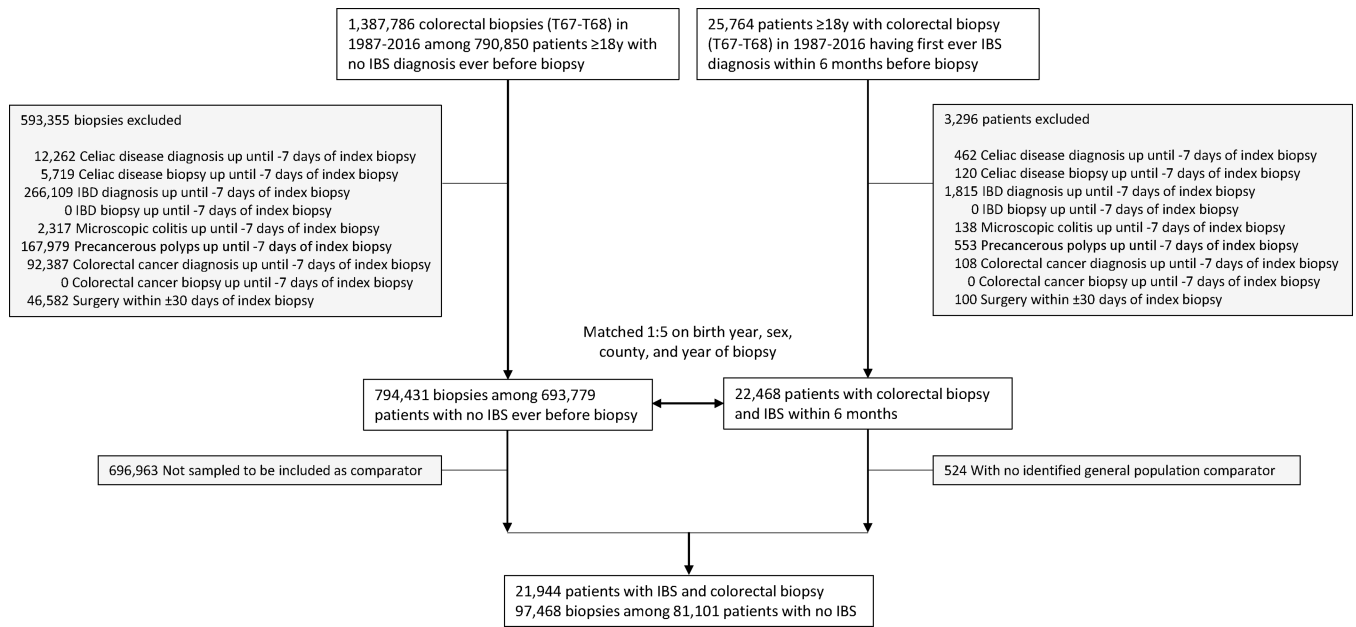


Figure 1. Flow chart of identified IBS patients undergoing colonoscopy and their matched controls IBS, irritable bowel syndrome; IBD, inflammatory bowel disease

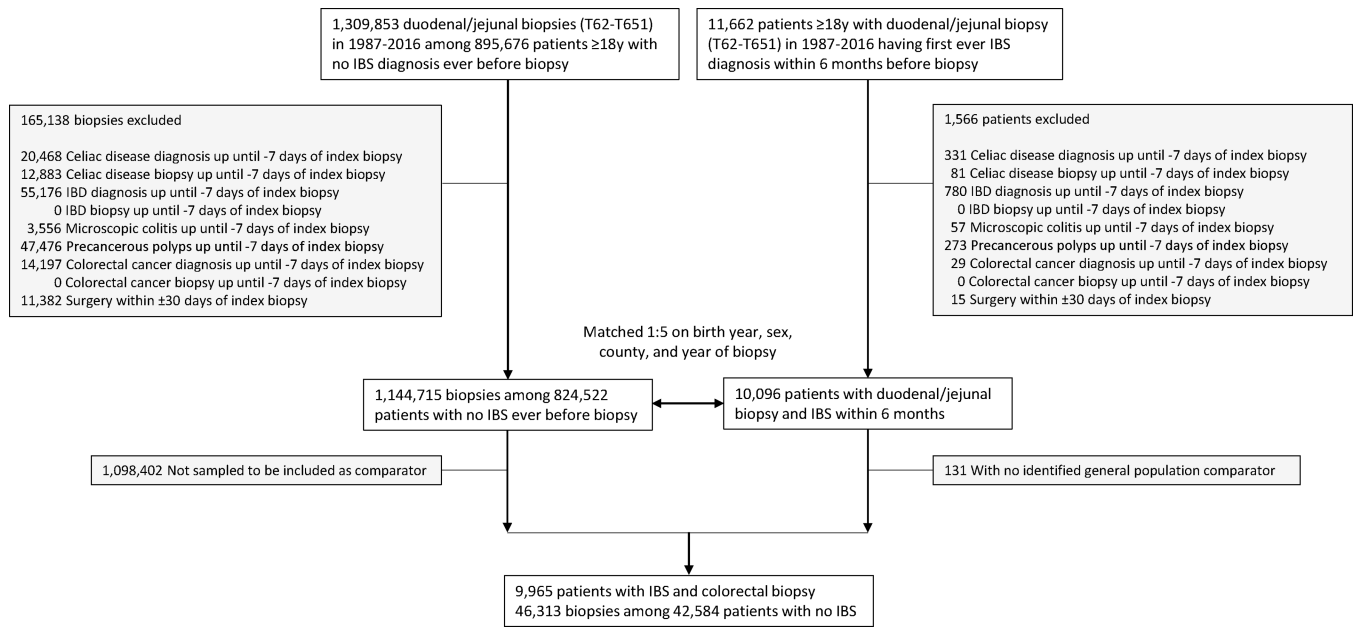


Figure 2. Flow chart of identified IBS patients undergoing upper endoscopy and their matched controls
IBS, irritable bowel syndrome; IBD, inflammatory bowel disease

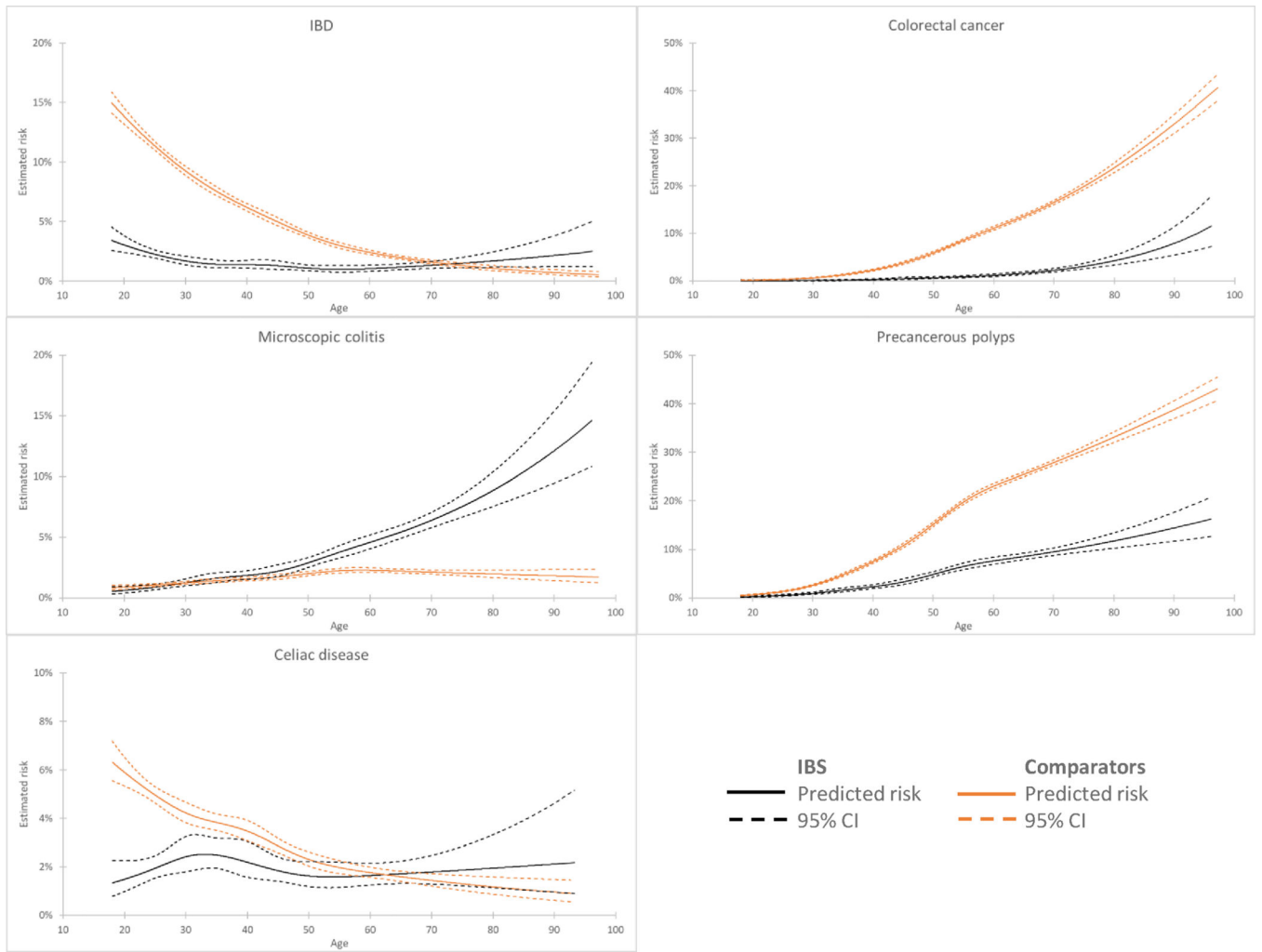


Figure 3. Spline regressions showing estimated yield of organic disease diagnosis by colonoscopy (for inflammatory bowel disease, colorectal cancer, microscopic colitis, and precancerous polyps) or upper endoscopy (for celiac disease) by age
IBS, irritable bowel syndrome; IBD, inflammatory bowel disease

Table 1.

Baseline characteristics of patients with irritable bowel syndrome (IBS) and matched controls

Characteristic	Patients undergoing colonoscopy		Patients undergoing upper endoscopy		Patients undergoing colonoscopy compared to siblings	
	IBS (n=21,944)	Matched controls (n=97,468)	IBS (n=9,965)	Matched controls (n=46,313)	IBS (n=1,240)	Siblings (n=1,415)
Women, no. (%)	15 213 (69.3%)	68 358 (70.1%)	7 199 (72.2%)	33 990 (73.4%)	876 (70.6%)	790 (55.8%)
Men, no (%)	6 731 (30.7%)	29 110 (29.9%)	2 766 (27.8%)	12 323 (26.6%)	364 (29.4%)	625 (44.2%)
Age, years						
Mean (SD)	44.7 (17.0)	45.7 (17.0)	41.9 (16.8)	42.5 (16.8)	48.3 (15.6)	50.1 (16.2)
Median (IQR)	43.2 (30.0–57.7)	44.8 (30.9–58.9)	39.3 (27.3–54.2)	40.2 (27.6–55.1)	50.4 (35.3–61.1)	52.6 (36.3–63.8)
Range, min-max	18.0–96.1	18.0–97.2	18.0–93.3	18.0–92.7	18.1–81.9	18.3–80.5
Categories, no. (%)						
18y - <30y	5 495 (25.0%)	22 750 (23.3%)	3 110 (31.2%)	13 957 (30.1%)	215 (17.3%)	225 (15.9%)
30y - <40y	4 137 (18.9%)	17 360 (17.8%)	2 013 (20.2%)	9 045 (19.5%)	177 (14.3%)	186 (13.1%)
40y - <50y	4 015 (18.3%)	17 673 (18.1%)	1 713 (17.2%)	8 063 (17.4%)	223 (18.0%)	222 (15.7%)
50y - <60y	3 637 (16.6%)	17 084 (17.5%)	1 447 (14.5%)	7 007 (15.1%)	287 (23.1%)	294 (20.8%)
60y - <70y	2 775 (12.6%)	13 527 (13.9%)	995 (10.0%)	4 922 (10.6%)	257 (20.7%)	344 (24.3%)
70y	1 885 (8.6%)	9 074 (9.3%)	687 (6.9%)	3 319 (7.2%)	81 (6.5%)	144 (10.2%)
Country of birth, no (%)						
Nordic country	19 982 (91.1%)	86 388 (88.6%)	8 953 (89.8%)	38 520 (83.2%)	1 213 (97.8%)	1 378 (97.4%)
Other	1 961 (8.9%)	11 078 (11.4%)	1 012 (10.2%)	7 791 (16.8%)	27 (2.2%)	37 (2.6%)
Level of education, no (%)						
9 years	4 159 (19.0%)	19 632 (20.1%)	1 803 (18.1%)	10 097 (21.8%)	249 (20.1%)	356 (25.2%)
10–12 years	10 636 (48.5%)	45 079 (46.3%)	4 839 (48.6%)	21 604 (46.6%)	571 (46.0%)	651 (46.0%)
>12 years	7 032 (32.0%)	32 051 (32.9%)	3 255 (32.7%)	14 168 (30.6%)	419 (33.8%)	403 (28.5%)
Missing	117 (0.5%)	706 (0.7%)	68 (0.7%)	444 (1.0%)	1 (0.1%)	5 (0.4%)
Year of index biopsy, no. (%)						
1987–1996	428 (2.0%)	1 641 (1.7%)	380 (3.8%)	1 653 (3.6%)	6 (0.5%)	23 (1.6%)
1997–2006	8 447 (38.5%)	37 373 (38.3%)	4 229 (42.4%)	19 788 (42.7%)	446 (36.0%)	470 (33.2%)
2007–2011	7 473 (34.1%)	33 367 (34.2%)	3 151 (31.6%)	14 663 (31.7%)	480 (38.7%)	522 (36.9%)
2012–2016	5 596 (25.5%)	25 087 (25.7%)	2 205 (22.1%)	10 209 (22.0%)	308 (24.8%)	400 (28.3%)
1997	21 516 (98.0%)	95 827 (98.3%)	9 585 (96.2%)	44 660 (96.4%)	1 234 (99.5%)	1 392 (98.4%)
Months between IBS diagnosis and index biopsy						
Mean (SD)	0.7 (1.3)		1.2 (1.5)		0.8 (1.3)	
Median (IQR)	0.1 (0.0–0.9)		0.4 (0.0–1.9)		0.1 (0.0–0.9)	
Range, min-max	0.0–6.0		0.0–6.0		0.0–6.0	
Disease history within 5 years before biopsy, no (%)						

Characteristic	Patients undergoing colonoscopy		Patients undergoing upper endoscopy		Patients undergoing colonoscopy compared to siblings	
	IBS (n=21,944)	Matched controls (n=97,468)	IBS (n=9,965)	Matched controls (n=46,313)	IBS (n=1,240)	Siblings (n=1,415)
Cardiovascular disease (CVD)	3 635 (16.6%)	17 424 (17.9%)	1 440 (14.5%)	6 517 (14.1%)	225 (18.1%)	313 (22.1%)
Cardiovascular disease in inpatient care	2 051 (9.3%)	10 032 (10.3%)	846 (8.5%)	4 326 (9.3%)	125 (10.1%)	190 (13.4%)
Cancer (excluding CRC)	725 (3.3%)	9 779 (10.0%)	285 (2.9%)	2 485 (5.4%)	50 (4.0%)	156 (11.0%)
Diabetes	791 (3.6%)	3 857 (4.0%)	314 (3.2%)	1 905 (4.1%)	56 (4.5%)	80 (5.7%)
Neurologic disease	2 114 (9.6%)	7 875 (8.1%)	892 (9.0%)	3 524 (7.6%)	138 (11.1%)	148 (10.5%)
IBS subtype (in biopsies 1997), no. (%)						
IBS with diarrhea	13 434 (62.4%)		5 260 (54.9%)		796 (64.5%)	
IBS without diarrhea	8 057 (37.4%)		4 309 (45.0%)		436 (35.3%)	
IBS unspecified	25 (0.1%)		16 (0.2%)		2 (0.2%)	
IBS as main diagnosis, no. (%)						
Yes	19 615 (89.4%)		8 363 (83.9%)		1 086 (87.6%)	
No	2 329 (10.6%)		1 602 (16.1%)		154 (12.4%)	
Deaths, no. (%)						
30 days after index date	15 (0.1%)	244 (0.3%)	10 (0.1%)	181 (0.4%)	0	4 (0.3%)
90 days after index date	40 (0.2%)	708 (0.7%)	31 (0.3%)	427 (0.9%)	1 (0.1%)	14 (1.0%)
365 days after index date	148 (0.7%)	2 079 (2.1%)	84 (0.8%)	1 122 (2.4%)	4 (0.3%)	29 (2.0%)

[†] Both IBS patients and their matched controls were excluded from all analyses if at baseline they had an earlier diagnosis of inflammatory bowel disease, celiac disease, microscopic colitis, precancerous polyps or colorectal cancer up until -7 days from the index biopsy since these disorders may lead to false-positive IBS diagnoses.

*** Conditioned on matching set and further adjusted for age, sex, education and baseline medical comorbidities (cancer, diabetes, CVD, and neurologic disease)

Table 2.

Prevalence and odds ratio of inflammatory bowel disease (IBD), microscopic colitis, precancerous polyps, colorectal cancer and celiac disease in patients with IBS and matched controls as well as IBS and sibling comparators.

Group	N events (%) IBS	Comparators	Odds ratio* (95%CI)	Odds ratio** (95%CI)	Sibling comparatOdds ratio*** (95%CI)
Overall					
IBD	341 (1.6%)	5 796 (5.9%)	0.22 (0.20–0.25)	0.21 (0.19–0.24)	0.32 (0.19–0.53)
Colorectal cancer	166 (0.8%)	6 166 (6.3%)	0.10 (0.09–0.12)	0.17 (0.14–0.20)	0.13 (0.05–0.37)
Microscopic colitis	640 (2.9%)	1 649 (1.7%)	1.88 (1.71–2.06)	1.77 (1.61–1.95)	2.30 (1.30–4.08)
Precancerous polyps	902 (4.1%)	12 635 (13.0%)	0.28 (0.26–0.30)	0.28 (0.26–0.30)	0.23 (0.16–0.33)
Non advanced	669 (3.0%)	7 995 (8.2%)	0.35 (0.32–0.38)	0.34 (0.32–0.37)	0.23 (0.15–0.36)
Advanced	249 (1.1%)	5 042 (5.2%)	0.21 (0.18–0.24)	0.23 (0.20–0.26)	0.34 (0.19–0.60)
Celiac disease	192 (1.9%)	1 568 (3.4%)	0.54 (0.47–0.63)	0.54 (0.47–0.63)	0.47 (0.19–1.18)
Age <50y					
IBD	243 (1.8%)	4 902 (8.5%)	0.17 (0.15–0.20)	0.17 (0.15–0.20)	0.22 (0.11–0.45)
Colorectal cancer	24 (0.2%)	981 (1.7%)	0.10 (0.06–0.14)	0.21 (0.13–0.34)	-
Microscopic colitis	203 (1.5%)	782 (1.4%)	1.18 (1.01–1.38)	1.16 (0.99–1.36)	14.67 (0.37–578.5)
Precancerous polyps	229 (1.7%)	3 071 (5.3%)	0.31 (0.27–0.35)	0.32 (0.28–0.37)	0.19 (0.07–0.50)
Non advanced	177 (1.3%)	2 171 (3.8%)	0.35 (0.30–0.41)	0.35 (0.30–0.41)	0.17 (0.05–0.59)
Advanced	54 (0.4%)	961 (1.7%)	0.23 (0.18–0.31)	0.26 (0.19–0.34)	0.83 (0.18–3.74)
Celiac disease	136 (2.0%)	1 300 (4.2%)	0.45 (0.38–0.54)	0.46 (0.38–0.55)	0.27 (0.07–1.00)
Age 50y					
IBD	98 (1.2%)	894 (2.3%)	0.51 (0.42–0.63)	0.46 (0.38–0.58)	0.55 (0.13–2.30)
Colorectal cancer	142 (1.7%)	5 185 (13.1%)	0.10 (0.09–0.12)	0.16 (0.13–0.20)	0.14 (0.04–0.44)
Microscopic colitis	437 (5.3%)	867 (2.2%)	2.58 (2.29–2.91)	2.36 (2.09–2.66)	2.24 (1.14–4.42)
Precancerous polyps	673 (8.1%)	9 564 (24.1%)	0.27 (0.25–0.29)	0.27 (0.25–0.29)	0.20 (0.13–0.33)
Non advanced	492 (5.9%)	5 824 (14.7%)	0.36 (0.32–0.39)	0.34 (0.31–0.37)	0.25 (0.15–0.42)
Advanced	195 (2.4%)	4 081 (10.3%)	0.20 (0.18–0.24)	0.22 (0.19–0.25)	0.26 (0.13–0.55)
Celiac disease	56 (1.8%)	268 (1.8%)	1.04 (0.78–1.39)	1.00 (0.74–1.34)	0.47 (0.04–5.29)

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

** Conditioned on matching set and further adjusted for education and baseline medical comorbidities (cancer, diabetes, CVD, and neurologic disease).

*** Conditioned on matching set and further adjusted for age, sex, education and baseline medical comorbidities (cancer, diabetes, CVD, and neurologic disease).