Gastrointestinal Infection Increases Odds of Inflammatory Bowel Disease in a Nationwide Case–Control Study

Jordan E. Axelrad,[*,‡] Ola Olén,[§,‖,¶] Johan Askling,[¶] Benjamin Lebwohl,[‡] Hamed Khalili,[#] Michael C. Sachs,[¶] and Jonas F. Ludvigsson[‡,**,‡‡,§§]

*Inflammatory Bowel Disease Center, Division of Gastroenterology, Department of Medicine, NYU Langone Health, New York, New York; [‡]Division of Digestive and Liver Disease, Department of Medicine, Columbia University Medical Center, New York, New York; [§]Sachs' Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden; [‖]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [¶]Clinical Epidemiology Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [#]Inflammatory Bowel Disease Center, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; **Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden; [‡‡]Department of Pediatrics, Orebro University Hospital, Orebro, Sweden; and [§§]Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

BACKGROUND & AIMS: **Gastrointestinal infections have been associated with later development of inflammatory bowel diseases (IBD). However, studies have produced conflicting results. We performed a nationwide case–control study in Sweden to determine whether gastroenteritis is associated with the development of Crohn's disease (CD) or ulcerative colitis (UC).**

METHODS: **Using the Swedish National Patient Register, we identified 44,214 patients with IBD (26,450 with UC; 13,387 with CD; and 4377 with IBD-unclassified) from 2002 to 2014 and matched them with 436,507 individuals in the general population (control subjects). We then identified patients and control subjects with reported episodes of gastroenteritis (from 1964 to 2014) and type of pathogen associated. We collected medical and demographic data and used logistic regression to estimate odds ratios (ORs) for IBD associated with enteric infection.**

RESULTS: **Of the patients with IBD, 3105 (7.0%) (1672 with UC, 1050 with CD, and 383 with IBD-unclassified) had a record of previous gastroenteritis compared with 17,685 control subjects (4.1%). IBD cases had higher odds for an antecedent episode of gastrointestinal infection (aOR, 1.64; 1.57–1.71), bacterial gastrointestinal infection (aOR, 2.02; 1.82–2.24), parasitic gastrointestinal infection (aOR, 1.55; 1.03–2.33), and viral gastrointestinal infection (aOR, 1.55; 1.34–1.79). Patients with UC had higher odds of previous infection with Salmonella, *Escherichia coli*, Campylobacter, or *Clostridium difficile* compared to control subjects. Patients with CD had higher odds of previous infection with Salmonella, Campylobacter, Yersinia enterocolitica, *C difficile*, amoeba, or norovirus compared to control subjects. Increasing numbers of gastroenteritis episodes were associated with increased odds of IBD, and a previous episode of gastroenteritis remained associated with odds for IBD more than 10 years later (aOR, 1.26; 1.19–1.33).**

CONCLUSIONS: **In an analysis of the Swedish National Patient Register, we found previous episodes of gastroenteritis to increase odds of later development of IBD. Although we cannot formally exclude misclassification bias, enteric infections might induce microbial dysbiosis that contributes to the development of IBD in susceptible individuals.**

Keywords: Epidemiology; Risk Factor; Microbiome; Immune Response.

Abbreviations used in this paper: aOR, adjusted odds ratio; CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease unclassified; ICD, International Classification of Disease; OR, odds ratio; UC, ulcerative colitis.

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The intestinal microbiome regulates mucosal immunity through several homeostatic pathways and is influenced by a variety of factors including genetics of the host, diet, infection, and medications.[1] Any disturbance to this dynamic homeostasis between microbiota and the immune response may result in disease. Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), develops from a combination of genetic susceptibility and environmental factors that elicits a deleterious inflammatory response.[2] Intestinal dysbiosis is thought to be a major environmental factor in the pathogenesis and maintenance of IBD.[3,4] Enteric infection is a common cause of dysbiosis and is frequently identified in patients with IBD.[5–8]

Several studies have demonstrated a link between enteric infection, functionally altered commensal bacteria, and the development of IBD. An increased risk of IBD was observed in patients with a previous episode of acute gastroenteritis, including *Salmonella* or *Campylobacter jejuni* (Table 1).[9–15] However, in a national registry-based study from Denmark, both CD and UC were more common not only following an episode of gastroenteritis with a culture positive for *Salmonella* or *Campylobacter*, but also after a negative stool test, suggesting detection bias.[15] This latter study, however, did not evaluate the impact of patients without culture data, viral gastroenteritis, or recurrent gastroenteritis; the influence of antimicrobial therapies; or fully account for study design limitations, such as the fact that cultures were largely obtained to rule out potential alternative causes for chronic or recurrent diarrhea rather than to identify the causative agent of an episodic acute enteric infection.[15,16]

We aimed to evaluate the association between IBD and an antecedent episode of acute gastroenteritis encompassing multiple bacterial, parasitic, and viral infections, with species-specific coding, using the Swedish nationwide patient register.

What You Need to Know

Background

Gastrointestinal infection has been implicated in the subsequent development of inflammatory bowel disease (IBD), however, studies have reported conflicting data.

Findings

In this nationwide, population-based, case-control study of 44,214 patients with IBD and 436,507 matched general population controls using the Swedish patient register from 1964-2014, previous exposure to a gastrointestinal infection, including bacterial, viral, and parasitic pathogens, was a significant predictor of the subsequent development of IBD (aOR 1.64, 1.57-1.71).

Implications for patient care

Enteric infections, including viral infections, may trigger gut microbial dysbiosis and contribute to the development of IBD in susceptible individuals.

Methods

Study Population

We identified all people in Sweden with a diagnosis of IBD in the Swedish Patient Register (inpatient care since 1964, and nonprimary outpatient care since 2002) using International Classification of Disease (ICD) codes. For each patient with IBD, we randomly selected up to 10 control subjects without IBD from the Swedish Population Register matched for sex, year of birth, and place of residence.[17]

Gastroenteritis

Gastroenteritis (bacterial, parasitic, viral, and not otherwise defined) was defined by ICD codes prospectively recorded in inpatient and outpatient specialty care from 1964 to 2014 (Supplementary Table 1).

Inflammatory Bowel Disease

We used previously validated registry definitions to ascertain incident cases of IBD by restricting our population to patients with at least 2 visits or admissions to hospital listing a diagnosis of IBD.[18] We used the first visit as date of IBD onset. Subtype of IBD (UC, CD, and IBD unclassified [IBD-U]) was based on the first 2 diagnostic listings (Supplementary Table 2). Phenotype of IBD (extent of UC and localization and behavior of CD) was defined using the Montreal classification (Supplementary Table 3).

Covariates

Surgery. To study the potential confounding of previous gastrointestinal surgery on incident IBD, we recorded a history of colectomy and other bowel surgery. We used dates of surgery from inpatient care (from 1964 onward) and from outpatient specialist care (from 1997 onward) (Supplementary Table 4).

Autoimmune disease. We also recorded a history of autoimmunity (includes asthma, rheumatoid arthritis, psoriasis, multiple sclerosis, autoimmune thyroiditis, diabetes mellitus type 1, or vasculitis).[19] We identified diagnoses from inpatient care (1964 onward) and from outpatient specialist care (2001 onward) using ICD coding (Supplementary Table 5).

Drugs. To study whether the risk of IBD was influenced by treatment of gastroenteritis with antibiotics, we used the Swedish Prescribed Drug Register (started on

Table 1. Gastroenteritis and Risk of Subsequent IBD

Study	Study location and period	Study population	Patient-years or years of follow-up	Number of exposed individuals	Number of IBD diagnoses	Risk assessment (95% CI)
Garcia Rodriguez, 2006	United Kingdom, 1992–2001	94,013	325,743	43,013 (all GE)	64 (UC) 40 (CD)	UC: HR, 2.3 (1.5–3.6; all GE) CD: HR, 3.1 (1.7–5.7; all GE)
Porter, 2008	United States, 1999–2006	14,665	Max 7 y per patient	828 (all GE)	115 (UC) 88 (CD)	UC: OR, 1.4 (1.1–1.7; all GE) CD: OR, 1.5 (1.2–2.0; all GE)
Gradel, 2009	Denmark, 1991–2003	39,264	Max 15 y per patient	6685 (*Campylobacter*)	79 (UC)	UC: HR, 2.8 (1.7–4.6; *Salmonella*) HR, 3.0 (1.9–4.9; *Campylobacter*)
				6463 (*Salmonella*)	29 (CD)	CD: HR, 2.5 (1.0–6.3; *Salmonella*) HR, 3.3 (1.6–7.0; *Campylobacter*)
Jess, 2011	Denmark, 1992–2008	NR	94,264,447	49,420 (*Campylobacter*)	487 (UC)	UC: IRR, 3.0 (2.6–3.4; *Salmonella*) IRR, 2.6 (2.3–3.0; *Campylobacter*)
				41,628 (*Salmonella*)	161 (CD)	CD: IRR, 2.2 (1.7–2.7; *Salmonella*) IRR, 2.2 (1.8–2.7; *Campylobacter*)
Porter, 2017	United States, 2001–2009	82,107	470,060	18 (all GE, in IBD only)	49 (UC) 58 (CD)	UC: HR, 2.9 (1.4–6.0; all GE) CD: HR, 1.1 (0.5–2.5; all GE)
Axelrad, 2018	Sweden, 2002–2014	480,721	Max 12 y per patient	20,790 (all GE)	1672 (UC) 1050 (CD) 383 (IBD-U)	UC: 1.6 (1.5–1.7; all GE) CD: 1.7 (1.6–1.8; all GE) IBD-U: 2.0 (1.7–2.2; all GE)

CD, Crohn's disease; CI, confidence interval; GE, gastroenteritis; HR, hazard ratio; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; IRR, incidence rate ratio; NR, not reported; OR, odds ratio; UC, ulcerative colitis.

July 1, 2005) to identify antibiotic prescribing. A dispensation of a prescribed antimicrobial agent within 2 weeks following a diagnosis of gastroenteritis was considered targeted therapy (Supplementary Table 6).

First-degree relatives. To study the potential confounding of a family history of IBD, we identified all first-degree relatives of patients with IBD and their matched control subjects.

Statistics

To estimate the odds ratios (ORs) of IBD associated with enteric infection, we used logistic regression adjusted for the matching variables sex, age, birth year, and place of residence, and further adjusted for previous gastrointestinal surgery, autoimmune disease, and family history of IBD. For patients with diagnoses for multiple pathogens, any potential association was assessed for each pathogen. We excluded exposures $\leq$6 months of IBD to decrease detection bias.

To further assess the risk of IBD, we divided the time since gastroenteritis into $\geq$6 months to <1 year, 1 to <5 years, 5 to <10 years, and $\geq$10 years. We investigated a possible dose–response relationship between number of episodes of gastroenteritis and a diagnosis of IBD. Further latency analyses for gastroenteritis were performed excluding those exposures recorded within 12, 24, and 36 months.

We also analyzed stratum-specific ORs for variables regarding the exposure restricted to availability in the registry, such as season of exposure, antibiotics, and hospitalization.

From 1964 to 2001, incident cases of IBD were identified only in inpatient care and these data were excluded from the main analysis. From 2001 (when the register started including outpatient care), incident cases of IBD constituted a mixture of inpatient and outpatient cases. Consequently, we analyzed the years 1964–2001 and 2002–2014 separately. In sensitivity analyses, we restricted data to gastrointestinal infections diagnosed in a department of infectious disease or pediatrics, departments with a higher acuity of patient care and knowledge base of gastroenteritis. We then further divided these exposures to those identified in inpatient data (1964–2014) and those identified in outpatient data (2001–2014).

To assess the potential for misclassification of gastrointestinal infection as IBD, we performed several sensitivity analyses. We examined the proportion of patients with multiple diagnostic listings for IBD and the proportion of patients followed for more than 12 months who have had a dispensed prescription of an IBD medication. Finally, we performed a probabilistic sensitivity analysis to assess bias caused by differential misclassification of IBD.[20] This was parameterized in terms of the positive predictive values of IBD, that is the probability of truly having IBD given our register-based definition is positive, separately among gastroenteritis cases and control subjects. The negative predictive values were assumed to be 1. The analysis was run for 5000 iterations for the main analysis looking at the association between gastroenteritis and IBD, adjusted for the matching variables.

Statistical analyses were performed using R statistical software (version 3.5.0, R Foundation for Statistical Computing, Vienna, Austria). This study was approved by the Ethics Review Board in Stockholm (2007/785-31/5; 2011/1509- 32; 2015/0004-31).

Results

We identified 44,214 patients with IBD (26,450 with UC, 13,387 with CD, and 4377 with IBD-U) and 436,507 control subjects matched for sex, age, year of birth, and place of residence, from 2002 to 2014 (Table 2). There was a slight male predominance (51.2%) and median age of IBD diagnosis was 39 years (interquartile range, 25–58).

Of patients with IBD, 3105 (7.0%; UC, 1672 [6.3%]; CD, 1050 [7.8%]; IBD-U, 383 [8.8%]) were exposed to a previous episode of gastroenteritis compared with 17,685 (4.1%) control subjects (Table 3). Median age at first gastroenteritis was 22 (interquartile range, 3–42) for patients with IBD and 7 (interquartile range, 1–31) for control subjects. Among those with a prior episode of gastroenteritis, most were hospitalized for the episode (77.6% IBD vs 83.5% control subjects) and experienced only 1 episode (76.7% IBD vs 79.3% control subjects). Of patients diagnosed with gastrointestinal infection from 2005 to 2014, only a small minority were dispensed a prescription for outpatient antimicrobials for an episode of gastroenteritis (3.7% IBD vs 1.5% control subjects).

In sensitivity analysis, we did not find significant misclassification of gastrointestinal infection as IBD (Supplementary Table 7). In our probabilistic sensitivity analysis, the positive predictive value among cases were samples from a beta distribution with a mean of 0.8 and standard deviation 0.076, and for control subjects it was a beta distribution with mean 0.93 and standard deviation 0.08. Under this extreme scenario in which there is a 13% difference in the classification accuracy of IBD between gastroenteritis cases and control subjects, we found that this did not nullify our main results. The average OR over the 5000 iterations was 1.48, with a 2.5% quantile of 1.07 and 97.5% quantile of 1.99 over the iterations, suggesting that differential misclassification of IBD by gastroenteritis infection does not severely impact our findings.

Most episodes of gastroenteritis were not defined by a specific pathogen (2492 [80.3%] in IBD vs 14,572 [82.4%] control subjects). Among those with pathogen-specific coding, bacteria were the most common (527 [1.19%] IBD vs 2429 [0.56%] control subjects), followed by viral (275 [0.62%] IBD vs 1563 [0.36%] control

Table 2. Baseline Characteristics of All Incident Cases of IBD in Sweden Between 2002 and 2014 and Control Subjects Matched for Sex, Age, Year of Birth, and Place of Residence

Variable	Control subjects, n (%)	IBD, n (%)	UC, n (%)	CD, n (%)	IBD-U, n (%)
Total	436,507	44,214	26,450 (59.8)	13,387 (30.3)	4377 (9.9)
Males	223,648 (51.2)	22,659 (51.2)	13,878 (52.5)	6569 (49.1)	2212 (50.5)
Females	212,859 (48.8)	21,555 (48.8)	12,572 (47.5)	6818 (50.9)	2165 (49.5)
Age of first IBD diagnosis or entry into study					
Median (IQR)	39 (25–58)	39 (25–58)	40 (27–58)	36 (22–56)	41 (24–61)
Mean (SD)	42 (20)	42 (20)	43 (19)	40 (20)	43 (22)
<6	2185 (0.5)	219 (0.5)	105 (0.4)	75 (0.6)	39 (0.9)
6 to <10	4202 (1)	421 (1.0)	185 (0.7)	189 (1.4)	47 (1.1)
10 to <18	40,002 (9.2)	4016 (9.1)	1795 (6.8)	1733 (12.9)	488 (11.1)
18 to <40	178,776 (40.9)	18,014 (40.7)	10,977 (41.5)	5450 (40.7)	1587 (36.3)
40 to <60	116,578 (26.7)	11,807 (26.7)	7456 (28.2)	3273 (24.4)	1078 (24.6)
≥60	94,764 (21.7)	9737 (22.0)	5932 (22.4)	2667 (19.9)	1138 (26.0)
Year of first diagnosis or study entry					
2010–2014	160,876 (36.9)	16,256 (36.8)	8995 (34.0)	5036 (37.6)	2225 (50.8)
2006–2009	137,357 (31.5)	13,917 (31.5)	8445 (31.9)	4159 (31.1)	1313 (30.0)
2002–2005	138,274 (31.7)	14,041 (31.8)	9010 (34.1)	4192 (31.3)	839 (19.2)
Maximum Montreal classification at diagnosis	—	—			
N Paris classified			26,400	12,636	4372
E1 (proctitis)			5825 (22.1)	—	—
E2 (left-sided colitis)			5715 (21.6)	—	—
E3 or E4 (pancolitis)			6014 (22.8)	—	—
EX (extent not defined)			8845 (33.5)	—	—
L1 (terminal ileum)			—	3680 (29.1)	—
L2 (colonic)			—	2711 (21.5)	—
L3/LX (ileocecal or not defined)			—	6244 (49.4)	—
B1 (nonstricturing/nonpenetrating)			—	12,302 (97.4)	—
B2 (stricturing)			—	255 (2.0)	—
B3 (penetrating)			—	79 (0.6)	—
P (perianal disease modifier)			—	796 (6.3)	—
Complications of IBD					
Extraintestinal manifestations	28 (0.0)	592 (1.3)	289 (1.1)	253 (1.9)	50 (1.1)
Primary sclerosing cholangitis	12 (0.0)	412 (0.9)	314 (1.2)	57 (0.4)	41 (0.9)
Bowel surgery before diagnosis of IBD					
Small bowel resection	678 (0.2)	363 (0.8)	73 (0.3)	276 (2.1)	14 (0.3)
Colonic resection	2579 (0.6)	1338 (3.0)	432 (1.6)	783 (5.8)	123 (2.8)
Other bowel surgery	7248 (1.7)	1013 (2.3)	385 (1.5)	526 (3.9)	102 (2.3)
Personal history of autoimmune disease before IBD	30,368 (7.0)	4913 (11.1)	2576 (9.7)	1683 (12.6)	654 (14.9)
Asthma	14,550 (3.3)	2245 (5.1)	1141 (4.3)	799 (6.0)	305 (7.0)
Rheumatoid arthritis	3513 (0.8)	746 (1.7)	368 (1.4)	284 (2.1)	94 (2.1)
Psoriasis	4685 (1.1)	1001 (2.3)	511 (1.9)	354 (2.6)	136 (3.1)
Multiple sclerosis	855 (0.2)	110 (0.3)	66 (0.2)	28 (0.2)	16 (0.4)
Autoimmune thyroiditis	614 (0.1)	67 (0.2)	32 (0.1)	27 (0.2)	8 (0.2)
Diabetes mellitus type 1	5280 (1.2)	663 (1.5)	398 (1.5)	176 (1.3)	89 (2.0)
Vasculitis	2935 (0.7)	613 (1.4)	315 (1.2)	210 (1.6)	88 (2.0)
First-degree relative with IBD	17,829 (4.9)	5145 (13.6)	3004 (13.4)	1671 (14.5)	470 (12.5)
UC	12,052 (3.3)	3652 (9.7)	2435 (10.8)	882 (7.7)	335 (8.9)
CD	7855 (2.1)	2454 (6.5)	1088 (4.8)	1123 (9.8)	243 (6.5)

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis.

subjects), and then parasitic enteric infections (38 [0.09%] IBD vs 210 [0.05%] control subjects) (Supplementary Table 8).

After adjusting for previous bowel surgery, other autoimmune disease, or first-degree relative with IBD, any antecedent episode of gastrointestinal infection (adjusted OR [aOR], 1.64; 1.57–1.71), any bacterial gastrointestinal infection (aOR, 2.02; 1.82–2.24), any parasitic gastrointestinal infection (aOR, 1.55; 1.03–2.33), and any viral gastrointestinal infection (aOR, 1.55; 1.34–1.79) predicted a higher OR of IBD compared with control subjects (Table 4). In terms of predicting IBD subtypes, only any antecedent parasitic gastrointestinal infection lost significance for UC (aOR, 1.27; 0.72–2.25) and IBD-U (aOR, 2.02; 0.58–7.04). Similar associations between gastroenteritis and IBD were found when analyzing data excluded data from 1964 to 2001 (data not shown).

Table 3. Characteristics of Study Population Stratified by IBD Subtype

Variable	Control subjects, n (%)	IBD, n (%)	UC, n (%)	CD, n (%)	IBD-U, n (%)
Previous episode of gastroenteritis					
Unexposed	418,822 (95.9)	41,109 (93.0)	24,778 (93.7)	12,337 (92.2)	3994 (91.2)
Exposed	17,685 (4.1)	3105 (7.0)	1672 (6.3)	1050 (7.8)	383 (8.8)
Exposed					
Age of first gastroenteritis exposure					
Median (IQR)	7 (1–31)	22 (3–42)	23 (3–41)	21 (3–40)	22 (2–48)
Mean (SD)	19 (22)	26 (23)	26 (23)	25 (23)	27 (25)
<6	8632 (48.8)	1001 (32.2)	519 (31.0)	349 (33.2)	133 (34.7)
6 to <10	841 (4.8)	129 (4.2)	63 (3.8)	50 (4.8)	16 (4.2)
10 to <18	1080 (6.1)	206 (6.6)	114 (6.8)	77 (7.3)	15 (3.9)
18 to <40	4085 (23.1)	950 (30.6)	541 (32.4)	308 (29.3)	101 (26.4)
40 to <60	1727 (9.8)	473 (15.2)	251 (15.0)	158 (15.0)	64 (16.7)
≥60	1320 (7.5)	346 (11.1)	184 (11.0)	108 (10.3)	54 (14.1)
Hospitalized for an episode of gastroenteritis[a]	14,772 (83.5)	2409 (77.6)	1287 (77.0)	816 (77.7)	306 (79.9)
Season of episode of gastroenteritis					
Spring	5256 (29.7)	835 (26.9)	464 (27.8)	271 (25.8)	100 (26.1)
Summer	3424 (19.4)	689 (22.2)	365 (21.8)	245 (23.3)	79 (20.6)
Fall	3482 (19.7)	665 (21.4)	359 (21.5)	229 (21.8)	77 (20.1)
Winter	5523 (31.2)	916 (29.5)	484 (28.9)	305 (29.0)	127 (33.2)
Number of episodes of gastroenteritis					
1	14,032 (79.3)	2383 (76.7)	1306 (78.1)	785 (74.8)	292 (76.2)
2	2943 (16.6)	507 (16.3)	257 (15.4)	182 (17.3)	68 (17.8)
3	385 (2.2)	121 (3.9)	63 (3.8)	44 (4.2)	14 (3.7)
4	242 (1.4)	56 (1.8)	31 (1.9)	20 (1.9)	5 (1.3)
>4	83 (0.5)	38 (1.2)	15 (0.9)	19 (1.8)	4 (1.1)
Antibiotic exposure for an episode of gastroenteritis[b]	258 (1.5)	114 (3.7)	56 (3.3)	48 (4.6)	10 (2.6)
Penicillin V	21 (0.1)	2 (0.1)	2 (0.1)	0	0
Beta-lactamase antibiotics other than penicillin V	19 (0.1)	4 (0.1)	3 (0.2)	1 (0.1)	0
Cephalosporins	15 (0.1)	1 (0.0)	1 (0.1)	0	0
Sulfonamides	10 (0.1)	6 (0.2)	2 (0.1)	4 (0.4)	0
Macrolides	18 (0.1)	7 (0.2)	2 (0.1)	2 (0.2)	3 (0.8)
Quinolones	80 (0.5)	36 (1.2)	18 (1.1)	16 (1.5)	2 (0.5)
Vancomycin, oral	9 (0.1)	4 (0.1)	2 (0.1)	2 (0.2)	0
Metronidazole	103 (0.6)	67 (2.2)	32 (1.9)	29 (2.8)	6 (1.6)
Tinidazole	6 (0.0)	3 (0.1)	2 (0.1)	1 (0.1)	0

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; IQR, interquartile range; SD, standard deviation; UC, ulcerative colitis.

[a]From 1964 to 2001, incident cases of IBD represented inpatient care only. From 2001, when the register started including outpatient care, incident cases of IBD constituted a mixture of inpatient and outpatient cases.

[b]Antibiotic prescribing within 14 days of a diagnosis for gastroenteritis.

There were no major differences when restricting data to gastrointestinal infections diagnosed in a department of infectious disease or pediatrics. Enteric infection remained significantly associated with IBD when further dividing exposures to those identified in inpatient data (1964–2014; aOR, 1.49; 1.42–1.57) and those identified in outpatient data (2001–2014; aOR, 2.45; 2.26–2.66). Stratifying by family history, enteric infection was similarly associated with IBD between patients with a first-degree relative with IBD (aOR, 1.66; 1.32–2.09) and without a first-degree relative with IBD (aOR, 1.66; 1.59–1.74). In addition, excluding all patients with bowel surgery before the index date, there were no changes to the results with any antecedent episode of gastrointestinal infection predicting a higher OR of IBD compared with control subjects (aOR, 1.63; 1.56–1.71).

In examining the impact of bacterial versus viral enteric infection, compared with 459,931 patients without a previous episode of gastroenteritis, previous viral and bacterial gastrointestinal infection predicted the highest OR of IBD (60; aOR, 3.15; 1.62–6.11) followed by bacterial gastrointestinal infection only (2896; aOR, 2.04; 1.84–2.27), and viral gastrointestinal infection only (1778; aOR, 1.56; 1.35–1.81).

Certain pathogens predicted a higher OR of IBD and specific IBD subtypes compared with other pathogens (Figure 1, Table 4). A previous episode of *Salmonella* (aOR, 1.49; 1.15–1.94), *Escherichia coli* (aOR, 2.94; 1.27–6.83), *Campylobacter* (aOR, 1.86; 1.32–2.61), and *Clostridium difficile* (aOR, 4.02; 2.94–5.49) predicted a higher OR of UC. A previous episode of *Salmonella* (aOR, 1.82; 1.26–2.62), *Campylobacter* (aOR, 1.87; 1.13–3.11), *Yersinia enterocolitica* (aOR, 9.59; 3.04–30.3), *C difficile*

Table 4. Crude OR and aOR and 95% CIs for IBD in Relation to a History of Gastroenteritis Compared With Reference Individuals Adjusted for Previous Bowel Surgery, Other Autoimmune Disease, or First-Degree Relative With IBD

		IBD			UC			CD			IBD-U		
Gastrointestinal infection	Controls subjects exposed	IBD exposed	OR (95% CI)	aOR (95% CI)	UC exposed	OR (95% CI)	aOR (95% CI)	CD exposed	OR (95% CI)	aOR (95% CI)	IBD-U exposed	OR (95% CI)	aOR (95% CI)
Gastrointestinal infection	17,685	3105	1.80 (1.73–1.87)	1.64 (1.57–1.71)	1672	1.66 (1.58–1.75)	1.55 (1.47–1.65)	1050	1.96 (1.83–2.10)	1.67 (1.55–1.81)	383	2.10 (1.87–2.36)	1.96 (1.73–2.22)
Bacterial gastrointestinal infection	2429	527	2.15 (1.96–2.37)	2.02 (1.82–2.24)	290	1.95 (1.72–2.22)	1.87 (1.62–2.14)	178	2.57 (2.18–3.03)	2.25 (1.86–2.72)	59	2.19 (1.65–2.90)	2.16 (1.57–2.96)
Parasitic gastrointestinal infection	210	38	1.79 (1.26–2.52)	1.55 (1.03–2.33)	19	1.46 (0.90–2.37)	1.27 (0.72–2.25)	16	2.47 (1.43–4.28)	2.07 (1.06–4.02)	3	1.64 (0.48–5.59)	2.02 (0.58–7.04)
Viral gastrointestinal infection	1563	275	1.75 (1.54–1.99)	1.55 (1.34–1.79)	130	1.54 (1.28–1.85)	1.47 (1.20–1.80)	100	1.98 (1.60–2.46)	1.59 (1.24–2.03)	45	2.04 (1.48–2.82)	1.78 (1.23–2.57)
Not defined if viral or bacterial	14,572	2492	1.74 (1.67–1.82)	1.58 (1.51–1.65)	1345	1.61 (1.52–1.71)	1.50 (1.41–1.60)	837	1.86 (1.73–2.01)	1.59 (1.46–1.73)	310	2.14 (1.89–2.43)	1.98 (1.73–2.27)
Bacteria													
Typhoid/paratyphoid	57	2	0.35 (0.08–1.41)	0.19 (0.03–1.40)	0	—	—	1	0.66 (0.09–4.98)	0.45 (0.05–4.24)	1	2.46 (0.27–22.0)	—
Salmonella	787	134	1.68 (1.40–2.02)	1.61 (1.32–1.96)	74	1.54 (1.21–1.97)	1.49 (1.15–1.94)	44	1.95 (1.41–2.69)	1.82 (1.26–2.62)	16	1.71 (1.01–2.92)	1.74 (0.99–3.07)
Shigella	132	19	1.42 (0.88–2.30)	1.37 (0.81–2.29)	12	1.50 (0.82–2.75)	1.56 (0.84–2.89)	6	1.38 (0.59–3.23)	0.99 (0.33–2.96)	1	0.98 (0.13–7.70)	1.13 (0.14–9.24)
Escherichia coli	39	7	2.03 (0.95–4.34)	2.06 (0.91–4.66)	7	2.57 (1.12–5.90)	2.94 (1.27–6.83)	1	1.65 (0.20–13.7)	—	0	—	—
Campylobacter	362	76	2.07 (1.62–2.66)	1.91 (1.46–2.49)	46	2.00 (1.46–2.75)	1.86 (1.32–2.61)	23	2.35 (1.49–3.70)	1.87 (1.13–3.11)	7	1.81 (0.81–4.07)	1.98 (0.81–4.83)
Yersinia enterocolitica	32	12	3.71 (1.91–7.21)	3.76 (1.87–7.57)	5	2.91 (1.07–7.89)	2.61 (0.87–7.83)	6	7.42 (2.57–21.4)	9.59 (3.04–30.3)	1	1.42 (0.17–11.5)	1.24 (0.15–10.3)
Clostridium difficille	355	148	4.11 (3.39–4.98)	4.10 (3.25–5.19)	82	3.95 (3.06–5.11)	4.02 (2.94–5.49)	46	4.28 (3.03–6.06)	4.25 (2.79–6.47)	20	4.38 (2.58–7.44)	4.32 (2.17–8.60)
Other bacterial infection	508	112	2.18 (1.77–2.67)	2.08 (1.67–2.59)	57	1.77 (1.33–2.34)	1.75 (1.30–2.36)	43	3.00 (2.13–4.22)	2.50 (1.71–3.66)	12	2.47 (1.31–4.65)	2.76 (1.41–5.41)
Bacterial food poisoning	198	27	1.34 (0.90–2.01)	1.38 (0.89–2.16)	16	1.36 (0.80–2.29)	1.49 (0.84–2.63)	8	1.27 (0.61–2.66)	1.04 (0.43–2.52)	3	1.48 (0.44–4.98)	1.82 (0.52–6.33)
Parasite													
Amoeba	87	19	2.15 (1.31–3.54)	2.09 (1.15–3.80)	9	1.81 (0.89–3.68)	1.94 (0.84–4.49)	9	3.17 (1.50–6.73)	2.81 (1.11–7.14)	1	0.99 (0.13–7.72)	1.36 (0.17–10.9)
Giardia	113	18	1.57 (0.96–2.58)	1.14 (0.62–2.09)	11	1.55 (0.82–2.93)	1.01 (0.46–2.24)	6	1.69 (0.71–4.03)	1.37 (0.47–3.96)	1	1.23 (0.15–9.82)	1.47 (0.18–12.1)
Cryptosporidium	4	0	—	—	0	—	—	0	—	—	0		
Isospora	1	0	—	—	0	—	—	0	—	—	0	—	—
Other parasitic infection	17	2	1.16 (0.27–5.04)	1.43 (0.32–6.47)	0	—	—	1	3.30 (0.34–31.7)	2.89 (0.28–30.3)	1	9.97 (0.62–160)	6.81 (0.39–120)

Table 4. Continued

Gastrointestinal infection	Controls subjects exposed	IBD			UC			CD			IBD-U		
		IBD exposed	OR (95% CI)	aOR (95% CI)	UC exposed	OR (95% CI)	aOR (95% CI)	CD exposed	OR (95% CI)	aOR (95% CI)	IBD-U exposed	OR (95% CI)	aOR (95% CI)
Virus													
Rotavirus	235	27	1.14 (0.77–1.70)	0.90 (0.58–1.40)	15	1.14 (0.67–1.95)	0.83 (0.45–1.54)	8	0.95 (0.46–1.96)	0.76 (0.35–1.68)	4	1.99 (0.68–5.84)	2.14 (0.71–6.42)
Norovirus	157	28	1.75 (1.17–2.61)	1.88 (1.10–3.22)	13	1.45 (0.81–2.59)	1.74 (0.85–3.57)	11	2.85 (1.45–5.57)	3.19 (1.28–7.96)	4	1.26 (0.44–3.57)	1.13 (0.22–5.68)
Adenovirus	11	3	2.71 (0.76–9.72)	2.41 (0.65–9.00)	2	3.32 (0.67–16.4)	3.22 (0.64–16.1)	1	1.98 (0.23–17.0)	1.22 (0.11–13.6)	0	—	—
Other viral infection	1338	250	1.86 (1.62–2.13)	1.68 (1.45–1.96)	115	1.60 (1.31–1.95)	1.60 (1.29–1.98)	94	2.21 (1.77–2.77)	1.80 (1.39–2.32)	41	2.04 (1.45–2.85)	1.73 (1.17–2.56)

aOR, adjusted odds ratio; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; OR, crude odds ratio; UC, ulcerative colitis.

(aOR, 4.25; 2.79–6.47), *Amoeba* (aOR, 2.81; 1.11–7.14), and *norovirus* (aOR, 3.19; 1.28–7.96) predicted a higher OR of CD. Focusing on *C difficile*, compared with 477,765 individuals without any bacterial gastrointestinal infection, those with *C difficile* had the highest OR of IBD (503; aOR, 4.13; 3.27–5.21), whereas those with any bacteria excluding *C difficile* had an increased OR of IBD, but at a lower effect (2453; aOR, 1.73; 1.54–1.95).

In further sensitivity analysis, we did not find any evidence to suggest that the validity of an IBD diagnosis differed between cases with or without a previous history of *Y enterocolitica* (proportion with 3 or more IBD diagnoses 79.6% without exposure to *Yersinia*, 75.0% with exposure to *Yersinia*) or prescription for an IBD medication (79.6% without exposure to *Yersinia*, 75.0% with exposure to *Yersinia*).

After considering time between gastroenteritis and a diagnosis of IBD, stratifying by different time periods, a previous episode of gastroenteritis remained a significant predictor of IBD at any age and season of exposure, and at more than 10 years following the episode (aOR, 1.26; 1.19–1.33; Table 5). In terms of *C difficile*, a previous episode of gastroenteritis remained a significant predictor of IBD at more than 10 years (aOR, 2.45; 1.26–4.76; Supplementary Table 9). Antimicrobial therapy for an episode, although rare, predicted a higher OR of IBD (aOR, 4.16; 3.26–5.32). In addition, increasing episodes of gastroenteritis predicted a higher OR of IBD with more than 4 episodes predicting the highest OR of IBD (aOR, 3.73; 2.43–5.73; Table 5, Supplementary Figure 1*A*). This association persisted after excluding patients with gastroenteritis exposures within 12, 24, and 36 months within a diagnosis of IBD (Supplementary Figure 1*B*–1*D*).

In terms of IBD characteristics, previous exposure to gastroenteritis predicted the highest OR of very early onset IBD, age less than 6 years (aOR, 3.26; 2.20–4.84), and late onset IBD, age greater than 60 (aOR, 2.23; 1.97–2.51), and all phenotypes except penetrating (aOR, 0.50; 0.06–3.87) and perianal disease (aOR, 1.32; 0.99–1.74; Supplementary Table 10).

Discussion

In this nationwide, population-based, case-control study of 480,721 patients spanning 1964–2014, previous exposure to a gastrointestinal infection predicted the development of IBD. This association persisted over time and increased with repeated episodes of gastroenteritis. Certain pathogens, such as *C difficile*, *Campylobacter*, and *Salmonella*, yielded the strongest association with IBD, findings that remained significant at more than 10 years following the infection.

There are numerous data suggesting a role for enteric infections in promoting gastrointestinal microbial dysbiosis and subsequently, the intestinal inflammation that characterizes IBD.[5,6,21–24] During an enteric infection in

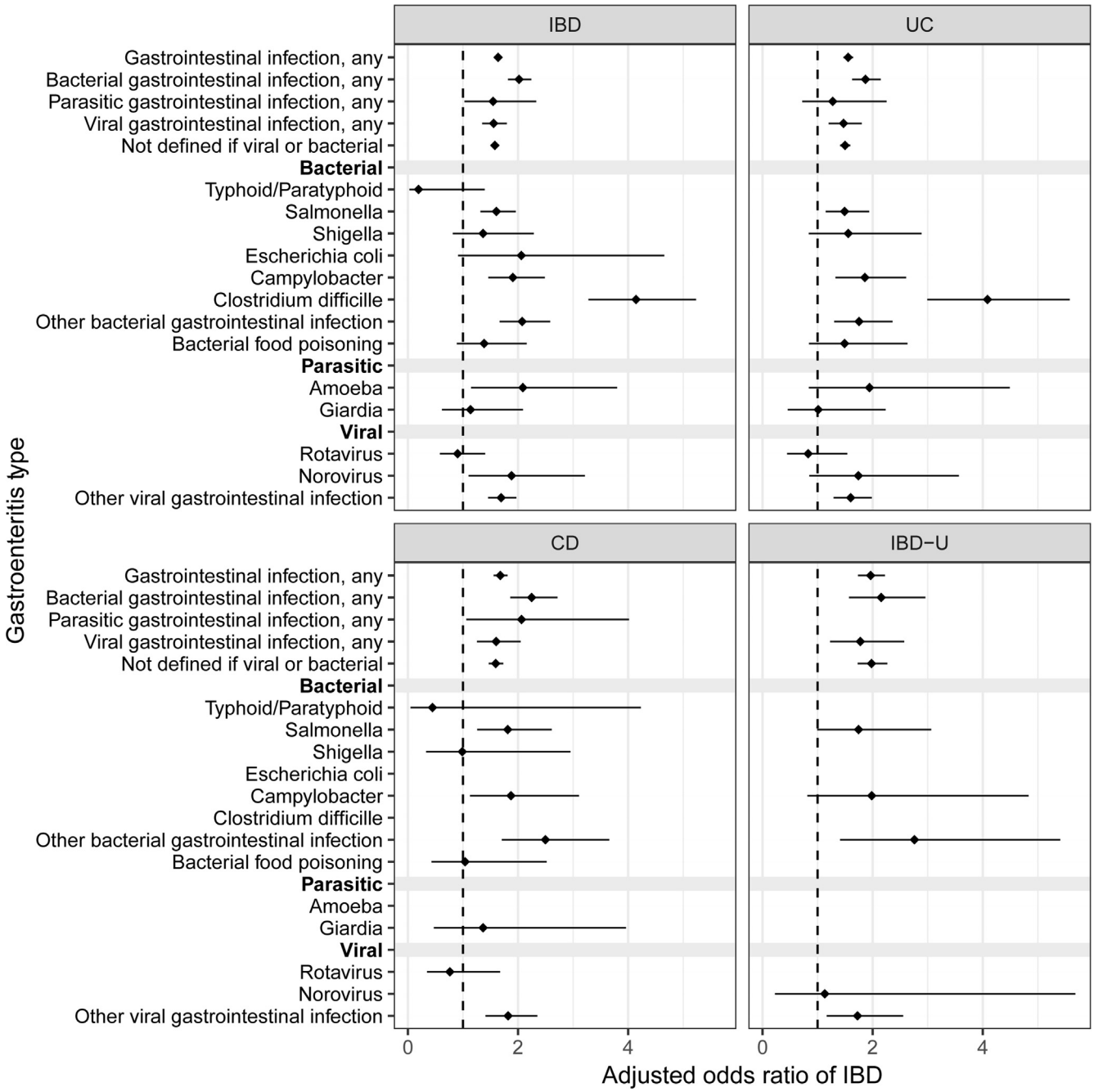


Figure 1. Gastrointestinal infection and risk of IBD. Forest plots of adjusted odds ratios and 95% confidence intervals for IBD, UC, CD, and IBD-U, in patients with a history of specific gastrointestinal pathogens compared with reference individuals adjusted for previous bowel surgery, other autoimmune disease, or first-degree relative with IBD.

mice models, tolerance to commensals is lost and microbiota-specific T cells differentiate to inflammatory effector cells, which also form memory cells that are phenotypically and functionally consistent with pathogen-specific T cells, suggesting that during an acute gastrointestinal infection, the immune response to commensals parallels the response to pathogens.[24] *Salmonella enterica* Typhimurium was shown to cause gastrointestinal inflammation in mice, which persisted after pathogen clearance and irreversibly escalated in severity with repeated infections.[6] These data confirmed a pathogenic origin of chronic intestinal inflammation using models of human gastroenteritis, and are consistent with our data not only suggesting a role for *Salmonella*, but also for repeated episodes of gastroenteritis.

C difficile is unique in this analysis in that infection is rare in healthy hosts, typically requiring a preexisting altered gut microbiome to colonize, expand, and result in disease. Through multiple mechanisms, it is a cause and consequence of profound microbial dysbiosis.[1,25] Given the gut microbial conditions necessary for *C difficile*, infection may represent patients at risk for IBD because of previous depletion of key microbial functions rather than a direct effect of *C difficile* infection. These factors

Table 5. Crude OR and aOR and 95% CIs for the Association Between Characteristics of Gastroenteritis and IBD Adjusted for Previous Bowel Surgery, Other Autoimmune Disease, or First-Degree Relative With IBD

Variable	Control subjects exposed (n = 17,685)	IBD exposed (n = 3105)	OR (95% CI)	aOR (95% CI)
Time from gastroenteritis to IBD				
≥6 mo to <1 *y*	422	253	5.95 (5.09–6.96)	5.89 (4.93–7.04)
1 to <5 *y*	2625	736	2.80 (2.58–3.04)	2.66 (2.42–2.92)
5 to <10 *y*	2521	464	1.83 (1.66–2.02)	1.67 (1.50–1.86)
≥10 y	12,117	1652	1.37 (1.30–1.44)	1.26 (1.19–1.33)
Age of first gastroenteritis exposure				
<6	8632	1001	1.16 (1.09 –1.24)	1.09 (1.01–1.16)
6 to <10	841	129	2.36 (2.25 –2.48)	2.21 (2.09–2.33)
10 to <18	1080	206	1.90 (1.64–2.21)	1.80 (1.55–2.10)
18 to <40	4085	950	2.33 (2.17–2.50)	2.24 (2.08–2.42)
40 to <60	1727	473	2.72 (2.45–3.01)	2.55 (2.27–2.87)
≥60	1320	346	2.60 (2.31–2.93)	2.53 (2.10–3.06)
Hospitalization for episode of gastroenteritis	14,772	2409	1.65 (1.58–1.73)	1.49 (1.42–1.57)
Season of episode of gastroenteritis				
Spring	5256	835	1.59 (1.48–1.71)	1.43 (1.32–1.55)
Summer	3424	689	2.01 (1.85–2.18)	1.81 (1.66–1.98)
Fall	3482	665	1.90 (1.75–2.07)	1.75 (1.60–1.92)
Winter	5523	916	1.66 (1.55–1.78)	1.52 (1.41–1.63)
Episodes of gastroenteritis				
1	14,032	2383	1.74 (1.67–1.82)	1.61 (1.53–1.69)
2	2943	507	1.77 (1.61–1.94)	1.53 (1.38–1.70)
3	385	121	3.22 (2.63–3.95)	2.65 (2.11–3.32)
4	242	56	2.37 (1.77–3.17)	2.05 (1.49–2.80)
>4	83	38	4.67 (3.18–6.86)	3.73 (2.43–5.73)
Outpatient antimicrobial therapy for episode of gastroenteritis, including *Clostridium difficile*	258	114	4.38 (3.51–5.46)	4.16 (3.26–5.32)
No outpatient antimicrobial therapy for episode of gastroenteritis	17,427	2991	1.76 (1.69–1.83)	1.60 (1.53–1.67)

aOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; OR, crude odds ratio.

may also explain the persistent risk of IBD at more than 10 years following the infection.

There have been several studies examining the potential role of viruses in the pathogenesis of CD.[23,26,27] In animal models, norovirus infection in the setting of a polymorphism in the CD susceptibility autophagy gene *ATG16L1* produced intestinal pathology resembling CD in mice.[22,23] The ability of norovirus infection to induce TH1 immune responses provides a potential explanation for the selective association with CD, which typically displays a stronger TH1 signature compared with UC.[22]

In addition, the median age of gastroenteritis exposure differed substantially between control subjects and patients with IBD, 7 and 22 years, respectively. It is perhaps this exposure to enteric infection relatively later in life that may direct an increased risk of IBD, or lack of exposure earlier in life that may influence immune tolerance. Moreover, considering this differential in age of exposure in patients with IBD, using matched control subjects, it may limit our analysis of patients with very early onset IBD.

Previous population-based studies of gastrointestinal infection and the subsequent development of IBD have yielded conflicting data.[9–15] Although surveillance, misclassification, and detection bias may have contributed to our findings, we do not believe they contribute to our findings more than marginally. First, we excluded any diagnoses of IBD within 6 months of a diagnosis of gastroenteritis and repeated this analysis for repeated episodes, excluding patients diagnosed with IBD within 12, 24, and 36 months of an exposure. Second, to further address potential differential misclassification, our analyses were designed a priori and we performed sensitivity analyses demonstrating that IBD diagnoses were equally valid with or without a previous history of gastroenteritis in general and specifically in cases of *Y enterocolitica*. We also showed that results did not change when restricting analyses to gastroenteritis diagnosed in the department of infectious diseases or pediatrics, suggesting that both our exposures and outcomes are valid. Our probabilistic sensitivity analysis suggested that differential misclassification of IBD by gastroenteritis infection did not significantly impact our findings. Third, although any diagnosis of gastroenteritis was linked to IBD, it varied significantly by type of pathogen and IBD subtype. However, because most exposures were not defined by a pathogen, caution may be warranted when interpreting our pathogen-specific results. Lastly, the increased risk of IBD

persisted for more than 10 years following the infection. Given that long period between exposure and outcome, it is unlikely that this merely reflects diagnostic delay of underlying IBD, and instead suggests a true association.

Given these findings, we hypothesize that enteric infections, including viral infections, may trigger gut microbial dysbiosis or, in the case of *C difficile*, identify patients with existing dysbiosis and/or exacerbate underlying dysbiosis, and contribute to the development of IBD. Our findings may further elucidate the role of enteric infectious in the development of IBD, and help clinicians identify patients at risk for IBD.

There are several strengths to the present study including our large number of participants with virtually complete follow-up using a national patient register. Furthermore, we used matched control subjects from the general population, enabling us to adjust for important potential confounders. These data were obtained from the Swedish Patient Register, which has nationwide follow-up since 1987, and a recent validation study in this register found a positive predictive value for IBD of 93%.[18]

There are several limitations to the present study including lack of culture data or specific pathogen diagnoses for most gastroenteritis events and most gastroenteritis cases occurred in the inpatient setting, possibly limiting generalizability. However, it is likely that episodes coded as "other viral gastrointestinal infection" likely represented norovirus or rotavirus and would only increase our effect size.[28] There are no formal validation studies regarding ICD coding of gastrointestinal infections in Swedish register. In addition, we were unable to obtain presenting clinical symptoms associated with a visit for gastroenteritis. Moreover, only outpatient prescribing of antimicrobials is available through the Swedish Prescribed Drug Register since mid-2005, and therefore, inpatient antimicrobial prescribing patterns were not available for analysis. In addition, we did not have detailed information on smoking history, previous antibiotic exposures, or disease severity in our study population. We used ICD codes recorded prospectively in clinical practice as proxies for disease extent and disease behavior, using the Montreal classification, but we have not yet validated the use of ICD codes for disease extent and behavior in clinical practice. Finally, we had limited power to assess risk of IBD associated with specific pathogens and urge caution when interpreting these findings.

In summary, in this nationwide, population-based study using the Swedish patient register, previous exposure to a gastrointestinal infection was associated with the subsequent development of IBD. Although we cannot formally exclude surveillance, misclassification, or detection bias, this association varied by type of pathogen, persisted over time, and increased with repeated episodes of gastroenteritis, consistent with growing translational data on dysbiotic triggers in IBD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.09.034.

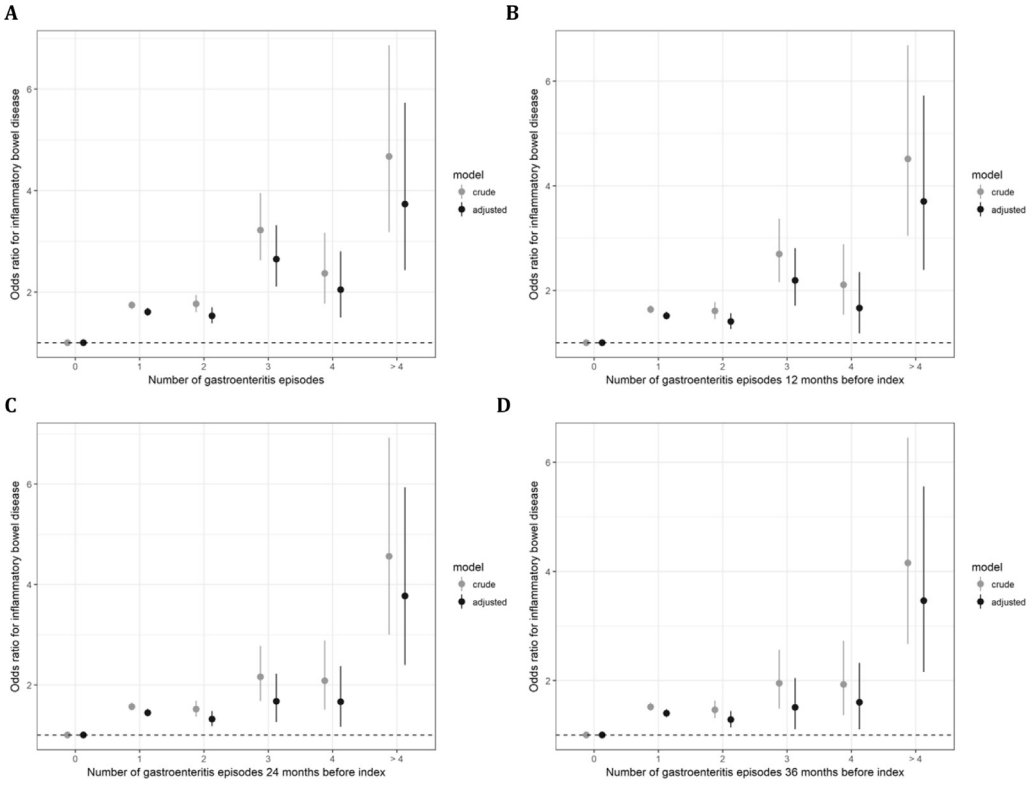
References

1. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol 2014;16:1024–1033.
2. Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. Annu Rev Immunol 2010;28:573–621.
3. Joeris T, Müller-Luda K, Agace WW, et al. Diversity and functions of intestinal mononuclear phagocytes. Mucosal Immunol 2017;10:845–864.
4. Dubinsky M, Braun J. Diagnostic and prognostic microbial biomarkers in inflammatory bowel diseases. Gastroenterology 2015;149:1265–1274.
5. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature 2012;491:119–124.
6. Yang WH, Heithoff DM, Aziz PV, et al. Recurrent infection progressively disables host protection against intestinal inflammation. Science 2017;358(6370).
7. Axelrad JE, Joelson A, Green PHR, et al. Enteric infections are common in patients with flares of inflammatory bowel disease. Am J Gastroenterol 2018;113:1530–1539.
8. Axelrad JE, Joelson A, Nobel YR, et al. Enteric infection in relapse of inflammatory bowel disease: the utility of stool microbial PCR testing. Inflamm Bowel Dis 2017;23:1034–1039.
9. Gradel KO, Nielsen HL, Schønheyder HC, et al. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. Gastroenterology 2009;137:495–501.
10. Keithlin J, Sargeant J, Thomas MK, et al. Systematic review and meta-analysis of the proportion of *Campylobacter* cases that develop chronic sequelae. BMC Public Health 2014;14:1203.
11. Castaño-Rodríguez N, Kaakoush NO, Lee WS, et al. Dual role of *Helicobacter* and *Campylobacter* species in IBD: a systematic review and meta-analysis. Gut 2017;66:235–249.
12. Porter CK, Tribble DR, Aliaga PA, et al. Infectious gastroenteritis and risk of developing inflammatory bowel disease. Gastroenterology 2008;135:781–786.
13. Porter CK, Welsh M, Riddle MS, et al. Epidemiology of inflammatory bowel disease among participants of the Millennium Cohort: incidence, deployment-related risk factors, and antecedent episodes of infectious gastroenteritis. Aliment Pharmacol Ther 2017;45:1115–1127.
14. García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. Gastroenterology 2006;130:1588–1594.
15. Jess T, Simonsen J, Nielsen NM, et al. Enteric *Salmonella* or *Campylobacter* infections and the risk of inflammatory bowel disease. Gut 2011;60:318–324.
16. Riddle MS, Porter CK. Detection bias and the association between inflammatory bowel disease and *Salmonella* and *Campylobacter* infection. Gut 2012;61:635.
17. Ludvigsson JF, Almqvist C, Bonamy A-KE, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125–136.

18. Jakobsson GL, Sternegård E, Olén O, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scand J Gastroenterol 2017;52:216–221.
19. Wilson JC, Furlano RI, Jick SS, et al. Inflammatory bowel disease and the risk of autoimmune diseases. J Crohns Colitis 2016;10:186–193.
20. Fox MP, Lash TL, Greenland S. A method to automate probabilistic sensitivity analyses of misclassified binary variables. Int J Epidemiol 2005;34:1370–1376.
21. Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. Curr Opin Immunol 2011;23:473–480.
22. Matsuzawa-Ishimoto Y, Shono Y, Gomez LE, et al. Autophagy protein ATG16L1 prevents necroptosis in the intestinal epithelium. J Exp Med 2017;214:3687–3705.
23. Cadwell K, Patel KK, Maloney NS, et al. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell 2010;141:1135–1145.
24. Hand TW, Dos Santos LM, Bouladoux N, et al. Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science 2012;337:1553–1556.
25. Sokol H, Jegou S, McQuitty C, et al. Specificities of the intestinal microbiota in patients with inflammatory bowel disease and *Clostridium difficile* infection. Gut Microbes 2018;9:55–60.
26. Sartor RB, Wu GD. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. Gastroenterology 2017;152:327–339.
27. Hubbard VM, Cadwell K. Viruses, autophagy genes, and Crohn's disease. Viruses 2011;3:1281–1311.
28. Axelrad JE, Joelson A, Nobel Y, et al. The distribution of enteric infections utilizing stool microbial polymerase chain reaction testing in clinical practice. Dig Dis Sci 2018;63:1900–1909.

Reprint requests
Address requests for reprints to: Jordan E. Axelrad, MD, MPH, 240 East 38th Street, 23rd Floor, New York, New York 10016. e-mail: Jordan.Axelrad@nyulangone.org; fax: (212) 263–3096.

Conflicts of interest
The authors disclose no conflicts.



Supplementary Figure 1. Episodes of gastroenteritis and risk of inflammatory bowel disease. Forest plots of crude and adjusted odds ratios and 95% confidence intervals for IBD in patients with a history of multiple episodes of gastroenteritis compared with reference individuals adjusted for previous bowel surgery, other autoimmune disease, or first-degree relative with IBD. (*A*) Excluding patients diagnosed with IBD within 6 months of their first episode of gastroenteritis. (*B*) Excluding patients diagnosed with IBD within 12 months of their first episode of gastroenteritis. (*C*) Excluding patients diagnosed with IBD within 24 months of their first episode of gastroenteritis. (*D*) Excluding patients diagnosed with IBD within 36 months of their first episode of gastroenteritis.

Supplementary Table 1. ICD Codes Representing Different Types of Gastrointestinal Infections

Class of gastroenteritis	Infectious agent	ICD-7	ICD-8	ICD-9	ICD-10 code
Infectious diseases of the GI tract	Any	040-049	000-009	001-009	A00-A09
Bacterial infections	Typhoid/paratyphoid	040-041	001-002	002	A01
	Salmonella	042	003	003	A02
	Shigella	045	004	004	A03
	Escherichia coli	—	008,0	008A	A04.0-A04.4
	Campylobacter	—	—	008E	A04.5
	Yersinia enterocolitica	—	—	008E	A04.6
	Clostridium difficille	—	—	008E	A04.7
	Other bacterial infection	—	008,2-008,3	008F	A04 (except A04.0-A04.7)
	Bacterial food poisoning	049	005	005	A05
Parasitic infections	*Amoeba*	046	006	006	A06
	Giardia	047,02	007,10	007B	A07.1
	Cryptosporidium	—	—	—	A07.2
	Isospora	—	—	—	A07.3
	Other protozoic GI infections	047 (except 047,02)	007 (except 007,10)	007 (except than 007B)	A07 (except A07.1-A07.3)
Viral infections	*Rotavirus*	—	—	008L	A08.0
	Norovirus	—	—	—	A08.1
	Adenovirus	—	—	008H	A08.2
	Other viral GI infection	—	008,8-008,9	008M (except 008L, 008H)	A08 (except A08.0-A08.2)
Infectious disease, not otherwise defined	Not defined if viral or bacterial	048, 571, 764, 785,6	008 (except 008,0; 008,2; 008,3), 009	008, 008W, 009	A09

GI, gastrointestinal; ICD, International Classification of Disease.

Supplementary Table 2. ICD Codes Defining IBD

	ICD-7	ICD-8	ICD-9	ICD-10
	1964–1968	1969–1986	1987–1996	1997 onward
UC	572,20; 572,21; 578,03	563,10; 563,99; 569,02	556	K51
CD	572,00; 572,09	563,00	555	K50
IBD-U	UC+CD	UC+CD	UC+CD	UC+CD, K52.3

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; ICD, International Classification of Disease; UC, ulcerative colitis.

Supplementary Table 3. Definitions and Diagnostic Codes Used to Define UC and CD According to the Paris Classifications Since the Start of ICD-10 (1997)

UC	Extent	Diagnostic codes
E1	Ulcerative proctitis	K51.2
E2	Left-sided UC	K51.3; K51.5
E3 or E4	Extensive UC	K51.0
EX	Extent not defined	K51.4; K51.8; K51.9
CD	Location/behavior	Diagnostic codes
L1 (location)	Small bowel disease or terminal ileitis	K50.0
L2	Colon	K50.1
L3/LX	Ileocecal CD or location not defined	K50.8, K50.9
B1 (behavior)	Nonstricturing, nonpenetrating	None of the ICD-codes for B2 or B3.
B2	Stricturing	Crohn's disease AND any of the following codes (K56.5; K56.6; K56.7; K62.4)
B3	Penetrating	Crohn's disease AND any of the following diagnostic codes (K63.0, K63.2, K31.6, N82.3, N82.3, N82.4) OR any of the following surgical procedure codes (JFA76, JFA86).
P	Perianal disease modifier	Crohn's disease AND any of the following diagnostic codes: (K60.3, K60.4, K60.5, K61.0, K61.1, K61.2, K61.3, K61.4, K62.4) OR any of the following surgical procedure codes: (JHD20, JHD30, JHD33, JHD50, JHD60, JHD63, JHA00, JHA20, JHW96)

CD, Crohn's disease; UC, ulcerative colitis.

Supplementary Table 4. Surgery ICD Codes Associated With IBD

Surgery codes	5/6th edition	7th edition (KKÅ97)
Years	1963–1996	1997–2016
Resection of small bowel		
Small bowel resection	4630-4631	JFB00-01
Enteroanastomosis	4631	JFC00-01
Stricture-plasty to the small bowel		JFA60
Resection of the colon		
Left-sided hemicolectomy	4640	JFB43-44
Right-sided hemicolectomy	4641	JFB30-31
Ileocecal resection	4642	JFB20-21
Resection of the transverse colon	4643	JFB40-41
Resection of the colon sigmoideum	4644	JFB46-47,
Other type of partial colon resection	4649	JFB50-51
Other type of partial colon or small bowel resection		JFB33-34, JFB96-97
Other colon resection with colostomy and distal closure		JFB63-64, JGB10-11
Resection of the sigmoid colon with sigmoidostomy and closure of the rectum	4713	JFB60-61
Colectomy and ileostomy with closure of the rectum	4651	JFH10
Laparoscopic colectomy and ileostomy		JFH11
Other colectomy		JFH96
Colectomy with ileorectal anastomosis	4650	JFH00
Laparoscopic colectomy with ileorectal anastomosis		JFH01
Ileorectal anastomosis		JFC40
Laparoscopic ileorectal anastomosis		JFC41
Colectomy, rectal mucosectomy and ileoanal anastomosis *without* ileostomy		JFH30
Colectomy, rectal mucosectomy and ileoanal anastomosis *and* ileostomy		JFH33
Mucosectomy and ileoanal anastomosis after previous colectomy	4654	JGB50
Extirpation of rectum or making of an ileoanal anastomosis after previous colectomy		JGB60
Proctocolectomy with continent ileostomy, Kock	4653	JFH40
Proctocolectomy with ileostomy	4652	JFH20
Rectal resection	4820-4828	JGB
Other bowel surgery		
Other operation of the small bowel and/or colon	4660-4668, 4700-4739, 4790-4798	JFW96
Other laparoscopic operation of the small bowel and/or colon		JFW97
Appendectomy		JEA00-JEA10

IBD, inflammatory bowel disease; ICD, International Classification of Disease.

Supplementary Table 5. ICD Codes Associated With Autoimmune Disease

	ICD-7	ICD-8	ICD-9	ICD-10
	1964–1968	1969–1986	1987–1996	1997 onward
Asthma	241	493	493	J45
Rheumatoid arthritis	722	712	714	M05, M06, M08, M09
Psoriasis	706	696	696	M07, L40, L41
Multiple sclerosis	345	340	340	G35
Autoimmune thyroiditis	—	245	245	E06.3
Diabetes mellitus type 1	—	—	—	E10
Vasculitis	—	446	446, 710	M30, M31, M32, M33, M34, M35, M36

ICD, International Classification of Disease.

Supplementary Table 6. Anatomic Therapeutic Chemical Codes Associated With Antimicrobials

Antimicrobial	Anatomic therapeutic chemical code
Penicillin V	J01CE
Beta-lactamase antibiotics other than penicillin V	J01CA
Cephalosporins	J01D
Sulfonamides	J01E
Macrolides	J01F
Quinolones	J01M
Vancomycin, oral	J01XA01, A07AA09
Metronidazole	J01XD01, P01AB01
Tinidazole	P01AB02

Supplementary Table 7. Sensitivity Analysis to Assess for Misclassification of Gastrointestinal Infection as IBD Based on Number of IBD Diagnoses and Prescription Data for an IBD Medication

Variable	Exposed to gastrointestinal infection, n (%)	Unexposed to gastrointestinal infection, n (%)
≥0.5 IBD diagnoses per year	3025 (97.6)	39,985 (97.5)
≥2 IBD diagnoses	2765 (89.0)	36,493 (88.8)
≥3 IBD diagnoses	2472 (79.6)	32,715 (79.6)
Any IBD medication prescription	2370 (76.9)	32,566 (79.8)

IBD, inflammatory bowel disease.

Supplementary Table 8. All Incident Cases of IBD in Sweden January 1, 2002, to December 31, 2014, and Reference Individuals From the General Population Matched for Sex, Age, Birth Year, and Place of Residence

ICD-code for gastrointestinal infections >6 mo before the index date, n (%)	Control subjects n (%)	IBD n (%)	UC n (%)	CD n (%)	IBD-U n (%)
Total in case-control analysis	436,507	44,214	26,450	13,387	4377
Gastrointestinal infection, any	17,685 (4.05)	3105 (7.02)	1672 (6.32)	1050 (7.84)	383 (8.75)
Bacterial gastrointestinal infection, any	2429 (0.56)	527 (1.19)	290 (1.09)	178 (1.33)	59 (1.35)
Parasitic gastrointestinal infection, any	210 (0.05)	38 (0.09)	19 (0.07)	16 (0.12)	3 (0.07)
Viral gastrointestinal infection, any	1563 (0.36)	275 (0.62)	130 (0.49)	100 (0.75)	45 (1.03)
Not defined if viral or bacterial	14,572 (3.34)	2492 (5.64)	1345 (5.09)	837 (6.25)	310 (7.08)
Bacteria					
Typhoid/paratyphoid	57 (0.01)	2 (0.00)	0	1 (0.01)	1 (0.02)
Salmonella	787 (0.18)	134 (0.30)	74 (0.30)	44 (0.33)	16 (0.37)
Shigella	132 (0.03)	19 (0.04)	12 (0.05)	6 (0.05)	1 (0.02)
Escherichia coli	39 (0.01)	7 (0.01)	7 (0.03)	1 (0.01)	0
Campylobacter	362 (0.08)	76 (0.17)	46 (0.17)	23 (0.17)	7 (0.16)
Yersinia enterocolitica	32 (0.01)	12 (0.03)	5 (0.02)	6 (0.05)	1 (0.02)
Clostridium difficille	355 (0.08)	148 (0.33)	82 (0.31)	46 (0.34)	20 (0.46)
Other bacterial gastrointestinal infection	508 (0.12)	112 (0.25)	57 (0.22)	43 (0.32)	12 (0.27)
Bacterial food poisoning	198 (0.05)	27 (0.06)	16 (0.06)	8 (0.06)	3 (0.07)
Parasite					
Amoeba	87 (0.02)	19 (0.04)	9 (0.03)	9 (0.07)	1 (0.02)
Giardia	113 (0.03)	18 (0.04)	11 (0.04)	6 (0.05)	1 (0.02)
Cryptosporidium	4 (0.00)	0	0	0	0
Isospora	1 (0.00)	0	0	0	0
Other parasitic gastrointestinal infection	17 (0.00)	2 (0.00)	0	1 (0.01)	1 (0.02)
Virus					
Rotavirus	235 (0.05)	27 (0.05)	15 (0.06)	8 (0.06)	4 (0.09)
Norovirus	157 (0.04)	28 (0.05)	13 (0.05)	11 (0.08)	4 (0.09)
Adenovirus	11 (0.00)	3 (0.01)	2 (0.01)	1 (0.01)	0
Other viral gastrointestinal infection	1338 (0.31)	250 (0.57)	115 (0.43)	94 (0.70)	41 (0.94)

NOTE. For patients with diagnoses for multiple pathogens, any potential association was assessed for each pathogen.
CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease-unclassified; ICD, International Classification of Disease; UC, ulcerative colitis.

Supplementary Table 9. Crude OR and aOR and 95% CIs for the Association Between Characteristics of *Clostridium difficile* and IBD Adjusted for Previous Bowel Surgery, Other Autoimmune Disease, or First-Degree Relative With IBD

Variable	Control subjects exposed (n = 355)	IBD exposed (n = 148)	OR (95% CI)	aOR (95% CI)
Time from *C difficile* to IBD				
≥6 months to <1 y	28	34	11.93 (7.23–19.7)	12.40 (6.45–23.8)
1 to <5 y	172	64	3.65 (2.74–4.86)	3.92 (2.78–5.53)
5 to <10 y	102	36	3.46 (2.37–5.06)	3.36 (2.08–5.40)
≥10 y	53	14	2.60 (1.44–4.68)	2.45 (1.26–4.76)
Age of first gastroenteritis exposure				
<6	13	8	6.16 (2.55–14.9)	5.22 (2.12–12.9)
6 to <10	1	140	4.03 (3.31–4.91)	4.04 (3.17–5.14)
10 to <18	4	6	15.0 (4.23–53.1)	14.5 (4.04–52.1)
18 to <40	53	39	7.31 (4.83–11.1)	6.55 (4.25–10.1)
40 to <60	99	39	3.87 (2.67–5.60)	3.67 (2.48–5.45)
≥60	185	56	2.95 (2.19–3.98)	2.28 (1.38–3.75)
Hospitalization for episode of *C difficile*	318	122	3.77 (3.06–4.65)	3.81 (2.94–4.93)
Season of episode of gastroenteritis				
Spring	91	41	4.42 (3.05–6.39)	4.23 (2.65–6.75)
Summer	80	25	3.07 (1.96–4.81)	3.76 (2.23–6.33)
Fall	99	34	3.37 (2.28–4.97)	2.73 (1.67–4.46)
Winter	85	48	5.55 (3.89–7.91)	5.87 (3.86–8.91)
Outpatient antimicrobial therapy for episode of *C difficile*	53	31	5.76 (3.70–8.97)	6.08 (3.71–9.98)

aOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; OR, crude odds ratio.

Supplementary Table 10. Crude OR and aOR and 95% CIs for Characteristics of IBD Based on Exposure History of Gastroenteritis

Variable	IBD unexposed (n = 41,109)	IBD exposed (n = 3105)	OR (95% CI)	aOR (95% CI)
Sex				
Male	21,194	1465	1.69 (1.60–1.79)	1.56 (1.47–1.66)
Female	19,915	1640	1.92 (1.81–2.02)	1.71 (1.61–1.82)
Age of first IBD diagnosis				
<6	175	44	3.24 (2.23–4.72)	3.26 (2.20–4.84)
6 to <10	354	67	2.06 (1.55–2.74)	1.97 (1.46–2.66)
10 to <18	3673	343	1.52 (1.35–1.71)	1.41 (1.25–1.60)
18 to <40	16,638	1376	1.50 (1.41–1.59)	1.40 (1.32–1.49)
40 to <60	11,142	665	2.34 (2.14–2.55)	2.15 (1.96–2.35)
≥60	9127	610	2.39 (2.19–2.62)	2.23 (1.97–2.51)
Year of IBD diagnosis or study entry				
2010–2014	14,877	1379	1.85 (1.74–1.96)	1.70 (1.59–1.81)
2006–2009	12,991	926	1.74 (1.62–1.87)	1.54 (1.43–1.67)
2002–2005	13,241	800	1.80 (1.67–1.94)	1.65 (1.51–1.79)
Maximum Paris classification at diagnosis				
E1 (proctitis)	5528	297	1.25 (1.11–1.42)	1.18 (1.03–1.34)
E2 (left-sided colitis)	5424	291	1.42 (1.25–1.62)	1.33 (1.16–1.52)
E3 or E4 (pancolitis)	5602	412	1.80 (1.61–2.00)	1.73 (1.54–1.94)
EX (extent not defined)	8176	669	2.02 (1.85–2.20)	1.85 (1.68–2.03)
L1 (terminal ileum)	3388	292	2.07 (1.82–2.36)	1.74 (1.50–2.02)
L2 (colonic)	2509	202	1.97 (1.68–2.30)	1.80 (1.52–2.13)
L3/LX (ileocecal or not defined)	5741	503	1.94 (1.75–2.14)	1.62 (1.45–1.80)
B1 (nonstricturing/nonpenetrating)	11,331	971	1.97 (1.83–2.11)	1.68 (1.56–1.82)
B2 (stricturing)	231	24	3.83 (2.35–6.24)	2.70 (1.28–5.69)
B3 (penetrating)	77	2	0.60 (0.14–2.61)	0.50 (0.06–3.87)
P (perianal disease modifier)	882	70	1.56 (1.20–2.02)	1.32 (0.99–1.74)
Complications of IBD				
Extraintestinal manifestations	547	45	2.27 (1.62–3.18)	1.77 (1.16–2.69)
Primary sclerosing cholangitis	380	32	1.68 (1.14–2.49)	1.47 (0.97–2.22)

aOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; OR, crude odds ratio.