Definitions, epidemiology, and risk factors for inflammatory bowel disease

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Literature review current through: **Sep 2023.**
This topic last updated: **Sep 06, 2023.**

INTRODUCTION

Inflammatory bowel disease (IBD) is comprised of two major disorders: ulcerative colitis and Crohn disease. Ulcerative colitis affects the colon, whereas Crohn disease can involve any component of the gastrointestinal tract from the mouth to the perianal area. These disorders have somewhat different pathologic and clinical characteristics, but with substantial overlap; their pathogenesis remains poorly understood. (See "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease".)

The definition, epidemiology, and risk factors for IBD will be reviewed here. The clinical manifestations, diagnosis, and treatment of ulcerative colitis are discussed separately:

- (See "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults".)
- (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis".)
- (See "Management of the hospitalized adult patient with severe ulcerative colitis".)
- (See "Management of moderate to severe ulcerative colitis in adults".)

The clinical manifestations, diagnosis, and treatment of Crohn disease are discussed separately:

- (See "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults".)
- (See "Overview of the medical management of mild (low risk) Crohn disease in adults".)

- (See "Medical management of moderate to severe Crohn disease in adults".)

The epidemiology of IBD in children is presented in more detail separately. (See "Clinical presentation and diagnosis of inflammatory bowel disease in children", section on 'Epidemiology'.)

DEFINITIONS

Ulcerative colitis — Ulcerative colitis is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon. It almost invariably involves the rectum, and the extent often involves more proximal portions of the colon in a continuous fashion. Different terms have been used to describe the degree of involvement [1,2]:

- Ulcerative proctitis refers to disease limited to the rectum (within 18 cm of the anal verge, distal to the rectosigmoid junction)
- Ulcerative proctosigmoiditis refers to disease limited to the rectum and sigmoid colon and not involving the descending colon
- Left-sided colitis is defined as disease that extends beyond the rectum, from the sigmoid colon and as far proximally as the splenic flexure
- Extensive colitis refers to disease extending proximal to the splenic flexure

The severity of ulcerative colitis is generally classified as mild, moderate, or severe disease; however, the definitions of disease activity may vary depending on the specific index or score being used [1,3-5]. In addition to clinical parameters, practice guidelines stratify patients into either a low- or high-risk category by assessing inflammatory status to estimate the risk of long-term sequelae (eg, colectomy). The assessment of disease activity, severity, and risk is discussed in more detail separately. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Disease activity, severity, and risk'.)

Crohn disease — Crohn disease is characterized by transmural inflammation and by skip areas of involvement (ie, segments of normal-appearing bowel interrupted by areas of disease). The transmural inflammatory nature of Crohn disease may lead to fibrosis and strictures and to obstructive clinical presentations that are not typically seen in patients with ulcerative colitis. Transmural inflammation may also result in sinus tracts, giving rise to microperforations and fistula formation.

Crohn disease most commonly involves the ileum and proximal colon; however, any part of the gastrointestinal tract may be affected. (See "Clinical manifestations, diagnosis, and prognosis of

Crohn disease in adults".)

The assessment of disease activity, severity, and risk for patients with Crohn disease is discussed in more detail separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Assessing disease activity, severity, and risk'.)

GENETIC FACTORS

There are two issues related to genetic factors in IBD: factors that increase the susceptibility to IBD and genetic syndromes that are associated with an increased risk of IBD. These issues are discussed separately. (See "Genetic factors in inflammatory bowel disease".)

EPIDEMIOLOGY

Geographic and time trends — The prevalence of IBD has been increasing globally with variations by geographic region [6-8]. The number of individuals affected by IBD across the globe increased from 3.7 million in 1990 to 6.8 million in 2017 [7]. At a regional level, the highest age-standardized prevalence rates of IBD were observed in North America (422.0 cases per 100,000 population), while the lowest age-standardized prevalence rates were observed in the Caribbean (6.7 cases per 100,000 population).

The incidence and prevalence of Crohn disease and ulcerative colitis appear to be lower in Asia and the Middle East; however, in some newly industrialized countries in Africa, Asia, and South America, the incidence of IBD has been rising [9-11]. In a large systematic review of population-based studies on the incidence of Crohn disease and ulcerative colitis, the following temporal trends were noted: in Brazil, the annual percentage change (APC) increased for Crohn disease by 11.1 percent (95% CI 4.8-17.8) and for ulcerative colitis by 14.9 percent (95% CI 10.4-19.6), and in Taiwan, the APC increased for Crohn disease by 4 percent (95% CI 1.0-7.1) and for ulcerative colitis by 4.8 percent (95% CI 1.8-8.0) [11].

There seems to be a north-to-south gradient with higher incidence rates of both Crohn disease and ulcerative colitis in northern locations compared with southern latitudes [12,13]. This trend may be related to less sunlight and vitamin D exposure as risk factors for IBD [14-17]. (See 'Dietary factors' below.)

Demographics — Demographic factors including age, sex, and race/ethnicity have been described in population-based studies [14,18,19]:

- **Age** – The age of onset for many patients with ulcerative colitis and Crohn disease is between 15 and 30 years, although IBD can present at any age. Some studies suggest a bimodal age distribution for both disorders with a possible second peak between 50 and 80 years of age [19,20]. It is not clear whether this second peak relates to greater susceptibility to disease with older age, the late expression of an earlier environmental exposure, or higher rates of health care utilization in older persons.

  There also appear to be differences in overall incidence of Crohn disease by age. In a study using data from the Rochester Epidemiology Project, young adults (ie, the 20- to 29-year-old age group) had the highest incidence of Crohn disease (16.6 cases per 100,000 person-years) compared with other age groups [6].

  In addition, the overall incidence of pediatric-onset IBD has been increasing over time [21].

- **Sex** – Small differences in IBD incidence by sex have been reported. There is a slight female predominance in adult-onset Crohn disease, which suggests that hormonal factors may play a role in disease expression. In contrast, there may be a slight male predominance in ulcerative colitis [6,22]. In a study using data from the Rochester Epidemiology Project, male sex was associated with a higher incidence rate of ulcerative colitis compared with female sex (12.8 versus 8.8 cases per 100,000 person-years) [6].

- **Race and ethnicity** – Both ulcerative colitis and Crohn disease are more common in Jewish compared with non-Jewish populations [23,24]. The incidence of IBD is lower in Hispanic populations and Black populations compared with White populations [15,25,26].

  However, ethnic and racial differences may be related to environmental and lifestyle factors as well as due to underlying genetic differences [13,27-29]. As an example, in a large population-based study in Denmark, the risk of IBD was lower in first-generation immigrants compared with individuals from Denmark (incidence rate ratio [IRR] 0.76, 95% CI 0.74-0.79); however, the risk of IBD was not significantly different for second-generation immigrants [29]. The potential associations of IBD with specific genes or major histocompatibility complex loci are discussed separately. (See "Genetic factors in inflammatory bowel disease".)

CLINICAL RISK FACTORS

Lifestyle factors

Smoking — Smoking is a risk factor for Crohn disease but not for ulcerative colitis [30,31]. While the basis for this dichotomy has yet to be resolved, nicotine and/or smoking byproducts may directly affect mucosal immune responses, smooth muscle tone, gut permeability, and microvasculature [32].

- **Crohn disease** – Smoking is associated with an increased risk of Crohn disease. In a cohort study including over 200,000 women, both current and former smokers were more likely to develop Crohn disease compared with those who had never smoked (hazard ratio [HR] 1.9, 95% CI 1.4-2.5 and HR 1.4, 95% CI 1.05-1.73, respectively) [31].

  Smoking also increases the risk complications from Crohn disease (eg, strictures, fistula) and the need for surgery [30,33,34].

- **Ulcerative colitis** – Data suggest that current smoking is not a risk factor for and may lower the risk of developing ulcerative colitis [30,35]. In a cohort study including over 200,000 women, the risk of ulcerative colitis was not significantly different for current smokers compared with those who had never smoked, while former smokers had an increased risk of ulcerative colitis as compared with lifetime nonsmokers (HR 1.6, 95% CI 1.3-1.9) [31]. The increase in risk associated with smoking cessation may be explained by loss of the protective effect of smoking, which then precipitates the onset of or unmasks the symptoms of ulcerative colitis.

  Cigarette smoking may also influence the course of ulcerative colitis [36]. Smoking cessation in patients with ulcerative colitis is associated with an increase in disease activity and risk of hospitalization.

Physical activity — Physical activity has been associated with a decrease in risk of Crohn disease, but not ulcerative colitis [37,38]. In two large prospective cohort studies including 194,711 women who provided data on physical activity, the risk of Crohn disease but not ulcerative colitis was inversely associated with physical activity (hazard ratio [HR] Crohn disease highest fifth of physical activity as compared with lowest fifth 0.64, 95% CI 0.44-0.94) [37]. The absolute risk of Crohn disease and ulcerative colitis among women in the highest fifth of physical activity was 6 and 8 events per 100,000 person-years as compared with 16 and 11 events per 100,000 person-years among women in the lowest fifth of physical activity, respectively. Limited data also suggest that physical activity is associated with a reduction in disease activity in patients with an established diagnosis of Crohn disease [39].

Dietary factors — Data from epidemiologic studies suggest that dietary factors may play a role in the risk of developing IBD:

- Fiber – High intake of dietary fiber, particularly from fruit and cruciferous vegetables, has been associated with a decrease in risk of Crohn disease but not ulcerative colitis [40-42].

- Fats – Increased dietary intake of total fat, animal fat, and polyunsaturated fatty acids has been correlated with an increased incidence of ulcerative colitis and Crohn disease [41,43,44] and relapse in patients with ulcerative colitis [45]. In addition, a higher intake of omega-3 fatty acids and a lower intake of omega-6 fatty acids has been associated with a lower risk of developing Crohn disease [46].

- Vitamin D – Data suggest that vitamin D intake is inversely associated with risk of Crohn disease and that vitamin D deficiency is common among patients with IBD [16,47].

- Other dietary factors - Dietary emulsifiers and additives appear to play a role in changes in the microbiome and risk for IBD [48].

Dietary interventions to improve nutrition and eliminate food triggers for patients with IBD are discussed separately. (See "Nutrition and dietary management for adults with inflammatory bowel disease".)

Food antigens are thought to trigger an immunologic response resulting in the development of IBD; however, specific pathogenic antigens have not been identified [49].

Sleep duration — Sleep deprivation has been associated with an increased risk of incident ulcerative colitis and of disease flares in patients with IBD [50,51]. A prospective cohort study evaluated sleep duration in 151,871 women and the incidence of IBD [50]. During a follow-up of 2,292,849 person-years, there were 191 incident cases of Crohn disease and 230 cases of ulcerative colitis (incidence 8 per 100,000 and 10 per 100,000 person-years, respectively). Women with reported sleep duration of <6 or >9 hours per day had a higher risk of ulcerative colitis compared with women with reported sleep durations of seven to eight hours per day (odds ratio [OR] 1.5, 95% CI 1.1-2.1, and OR 2.1, 95% CI 1.4-2.9, respectively). In contrast, sleep duration did not modify the risk of Crohn disease. Further studies are needed to explore the mechanisms by which sleep may influence intestinal inflammation and if modification of sleep duration can decrease the risk of IBD.

Infection and the immune response — Infection and the immune response have been implicated in the pathogenesis of IBD. Studies have identified roles for both host and microbial factors in the pathogenesis of IBD, ultimately leading to inappropriate immune responses to intestinal microbes, and this is discussed in more detail separately [52]. (See "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease".)

While no specific pathogen has been consistently implicated in the development of IBD, the following clinical studies evaluated the role of infection:

- Gastroenteritis – Several observational studies have suggested an association between acute gastroenteritis and the development of IBD [53-56]. As an example, a case control study included over 3000 patients with incident IBD and over 11,000 controls [53]. After excluding patients who had acute gastroenteritis within six months of IBD diagnosis and adjusting for potential confounders, the risk of IBD was higher in patients with a prior episode of acute gastroenteritis compared with controls (OR 1.4; 95% CI 1.2-1.7).

  An increased risk of developing IBD was also found in a population-based cohort study of 13,148 patients with documented Salmonella or Campylobacter gastroenteritis when compared with a matched control group (1.2 versus 0.5 percent, HR 2.9, 95% CI 2.2-3.9) [54]. While the increased risk was highest during the first year after infection, it remained elevated during 15 years of follow-up.

- Other infectious pathogens – A number of studies have evaluated the possible role of several infectious agents (eg, mycobacteria, viruses, fungi) in the pathogenesis of IBD; however, no specific pathogen has been identified as a causal factor [57-61].

Medications

Antibiotics — While antibiotic use has been associated with IBD, it is unclear if this is a causal association [62-67]. In a meta-analysis of 11 observational studies that included 7208 patients diagnosed with IBD, antibiotic exposure was associated with an increased risk of Crohn disease (OR 1.74, 95% CI 1.35-2.23) but not ulcerative colitis [63]. In a case-control study including nearly 24,000 patients with IBD, antibiotic use was associated with higher risk for diagnosis of IBD compared with no antibiotic use after adjusting for other risk factors (adjusted OR 1.88, 95% CI 1.79-1.98) [65]. The role of antibiotics in the treatment of IBD is discussed separately. (See "Overview of the medical management of mild (low risk) Crohn disease in adults", section on 'Antibiotics' and "Management of Crohn disease after surgical resection", section on 'Antibiotics' and "Management of acute and chronic pouchitis".)

NSAIDs — Nonsteroidal antiinflammatory drugs (NSAIDs) may increase risk for developing IBD, but the magnitude of the risk appears small [68-70]. For example, in a cohort study including over 70,000 women, NSAID use for at least 15 days per month increased the risk of ulcerative colitis (HR 1.87, 95% CI 1.16-2.99) and for Crohn disease (HR 1.59, 95% CI 0.99-2.56) compared with no NSAID use [68]. However, the absolute increase in risk was small (absolute difference 7 cases per 100,000 person-years for ulcerative colitis and 6 cases per 100,000 person-years for Crohn disease).

While NSAIDs are associated with intestinal mucosal injury, some patients with IBD can tolerate NSAIDs, particularly when they are given in low doses (eg, ibuprofen ≤200 mg daily, naproxen <220 mg daily) [71,72]. NSAID-induced mucosal injury and the use of NSAIDs for patients with arthritis associated with IBD are discussed separately. (See "NSAIDs: Adverse effects on the distal small bowel and colon" and "Treatment of arthritis associated with inflammatory bowel disease".)

Experience with the cyclooxygenase-2 (COX-2) selective inhibitors in patients with IBD is limited. Although small case series suggested an increased risk of exacerbation of IBD [73,74], randomized controlled trials have demonstrated no significant increase in disease activity or relapse in patients treated with short-term COX-2 selective inhibitors [75,76].

The association of NSAIDs with IBD may be due to several mechanisms. Cyclooxygenase-mediated disruption of the intestinal epithelial barrier associated with NSAID use can affect the interaction between the gut microbiome and immune cells in the intestine lining. In addition, NSAIDs alter platelet aggregation, the release of inflammatory mediators, and microvascular response to stress, which are key events in the pathogenesis of IBD. (See "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease".)

Oral contraceptives and hormone replacement — Oral contraceptives and hormone replacement therapy may increase the risk for developing IBD; however, the risk appears to be small [77-79]:

- In a meta-analysis of 14 studies including 75,815 premenopausal women, oral contraceptive use was associated with a higher risk of ulcerative colitis (relative risk [RR] 1.3, 95% CI 1.1-1.5) and Crohn disease (RR 1.5, 95% CI 1.3-1.7) compared with no oral contraceptive use [77].

- In a prospective cohort study of 108,844 postmenopausal women, hormone replacement therapy was associated with an increased risk of ulcerative colitis but not Crohn disease [78]. The risk of ulcerative colitis was increased among both current and past users compared with women who had never used postmenopausal hormone therapy (HR current users 1.7, 95% CI, 1.1-2.7; HR past users 1.7, 95% CI, 1.0-2.7). The risk of ulcerative colitis increased with longer duration of hormone use and decreased with time since discontinuation.

The risks associated with oral contraceptives and hormone replacement therapy are discussed separately. (See "Menopausal hormone therapy: Benefits and risks" and "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Gastrointestinal disorders'.)

The mechanism by which oral contraceptives or hormone replacement therapy increase the risk of IBD is unclear, but it may involve thrombotic effects on the microvasculature or the effect of estrogen in enhancing the inflammatory response [80].

Isotretinoin — An association between isotretinoin, used in the treatment of acne vulgaris, and IBD has been suggested by case reports [81,82]. While an association may be biologically plausible based on the pleiotropic effects of isotretinoin on the innate and adaptive intestinal immunoregulatory capacity, observational studies evaluating this association have yielded variable results [83-90].

Potentially confounding the association of isotretinoin use and the development of IBD is the fact that many patients with acne who are treated with isotretinoin have also been treated with oral tetracycline class antibiotics, which some data suggest may be associated with the development of IBD [64,88]. (See 'Antibiotics' above and "Oral isotretinoin therapy for acne vulgaris".)

Other factors

- **Appendectomy** — The relationship between appendectomy and IBD depends on whether the diagnosis is Crohn disease or ulcerative colitis:
  - Crohn disease – Some studies have suggested that the risk of Crohn disease is increased after appendectomy [91]. However, a meta-analysis suggested that the apparent increased risk may be due to a misdiagnosis in patients with incipient Crohn disease [92].
  - Ulcerative colitis – Data suggest that appendectomy may lower the risk of developing ulcerative colitis, while the mechanism of the protective effect is unknown [56,93-95]. In a case-control study including 212,963 patients who underwent appendectomy, the risk of developing ulcerative colitis was lower for patients with appendicitis or mesenteric lymphadenitis compared with controls (adjusted HR 0.58, 95% CI 0.38-0.87) [94]. However, the risk of ulcerative colitis was not lower for patients with nonspecific abdominal pain who underwent appendectomy compared with controls.
- **Psychological factors** – Studies examining the association between psychological factors and the risk of developing IBD have yielded inconsistent results [96-100]. However, stress may have a role in the exacerbation of symptoms in patients with established IBD, possibly via activation of the enteric nervous system and the production of proinflammatory cytokines [101,102]. (See "Medical management of low-risk adult patients with mild to moderate ulcerative colitis", section on 'Anxiety/depression screening'.)

- **Obesity** – It is unclear if obesity is associated with an increased risk of developing IBD [103,104]. However, accumulation of intra-abdominal fat may contribute to mucosal inflammation, thereby affecting the clinical course in patients with established IBD [105]. In a study of patients with Crohn disease, anoperineal complications occurred earlier in patients with obesity. In addition, patients with obesity were more likely to develop active disease (OR 1.5, 95% CI 1.1-2.1) and to require hospitalization (OR 2.4, 95% CI 1.6-3.5) [106].

EARLY LIFE EXPOSURES

The relationship of breastfeeding or early life exposure to antibiotics with inflammatory bowel disease is discussed separately. (See "Infant benefits of breastfeeding", section on 'Long-term benefits' and "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease", section on 'Role of microbes'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ulcerative colitis in adults" and "Society guideline links: Crohn disease in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Crohn disease in adults (The Basics)" and "Patient education: Ulcerative colitis in adults (The Basics)")

- Beyond the Basics topics (see "Patient education: Crohn disease (Beyond the Basics)" and "Patient education: Ulcerative colitis (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Background** – Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn disease (see 'Definitions' above):

  - Ulcerative colitis is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon. It almost invariably involves the rectum, and the extent often involves more proximal portions of the colon in a continuous fashion.

  - Crohn disease is characterized by transmural inflammation that may lead to fibrosis and strictures and may result in sinus tracts, giving rise to microperforations and fistula formation. Crohn disease most commonly involves the ileum and proximal colon; however, any part of the gastrointestinal tract may be affected.

- **Genetic factors** – There are two issues related to genetic factors in IBD: factors that increase the susceptibility to IBD and genetic syndromes that are associated with an increased risk of IBD. These issues are discussed separately. (See "Genetic factors in inflammatory bowel disease".)

- **Epidemiology** – The number of individuals affected by IBD across the world increased from 3.7 million in 1990 to 6.8 million in 2017. In North America, the age-standardized prevalence rate of IBD was 422 cases per 100,000 population. (See 'Geographic and time trends' above.)

  The age of onset for many patients with ulcerative colitis and Crohn disease is between 15 and 30 years, although IBD can present at any age. Some studies suggest a bimodal age distribution for both disorders with a possible second peak between 50 and 80 years. (See 'Demographics' above.)

- **Clinical risk factors** – Cigarette smoking increases the risk for Crohn disease but may lower the risk of developing ulcerative colitis. (See 'Smoking' above.)

Nonsteroidal antiinflammatory drugs (NSAIDs) may increase the risk for developing IBD, but the magnitude of the risk appears small. (See 'NSAIDs' above.)

NSAID-induced mucosal injury and the use of NSAIDs for patients with IBD-associated arthritis are discussed separately. (See "NSAIDs: Adverse effects on the distal small bowel and colon" and "Treatment of arthritis associated with inflammatory bowel disease".)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Paul Rutgeerts, MD (deceased), who contributed as a section editor for UpToDate in Gastroenterology.

REFERENCES

1. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol 2005; 19 Suppl A:5A.
2. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006; 55:749.
3. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med 1987; 317:1625.
4. de Jong MJ, Huibregtse R, Masclee AAM, et al. Patient-Reported Outcome Measures for Use in Clinical Trials and Clinical Practice in Inflammatory Bowel Diseases: A Systematic Review. Clin Gastroenterol Hepatol 2018; 16:648.
5. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol 2019; 114:384.
6. Shivashankar R, Tremaine WJ, Harmsen WS, Loftus EV Jr. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol 2017; 15:857.
7. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020; 5:17.

8. Agrawal M, Christensen HS, Bøgsted M, et al. The Rising Burden of Inflammatory Bowel Disease in Denmark Over Two Decades: A Nationwide Cohort Study. Gastroenterology 2022; 163:1547.
9. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012; 142:46.
10. Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology 2013; 145:158.
11. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 2017; 390:2769.
12. Nerich V, Monnet E, Etienne A, et al. Geographical variations of inflammatory bowel disease in France: a study based on national health insurance data. Inflamm Bowel Dis 2006; 12:218.
13. Khalili H, Huang ES, Ananthakrishnan AN, et al. Geographical variation and incidence of inflammatory bowel disease among US women. Gut 2012; 61:1686.
14. Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007; 5:1424.
15. Sonnenberg A, McCarty DJ, Jacobsen SJ. Geographic variation of inflammatory bowel disease within the United States. Gastroenterology 1991; 100:143.
16. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology 2012; 142:482.
17. Nerich V, Jantchou P, Boutron-Ruault MC, et al. Low exposure to sunlight is a risk factor for Crohn's disease. Aliment Pharmacol Ther 2011; 33:940.
18. Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. Inflamm Bowel Dis 2007; 13:254.
19. Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. Am J Gastroenterol 2006; 101:1559.
20. Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. Gastroenterology 1991; 100:350.

21. Kuenzig ME, Fung SG, Marderfeld L, et al. Twenty-first Century Trends in the Global Epidemiology of Pediatric-Onset Inflammatory Bowel Disease: Systematic Review. Gastroenterology 2022; 162:1147.
22. Loftus EV Jr, Silverstein MD, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gut 2000; 46:336.
23. Mayberry JF, Judd D, Smart H, et al. Crohn's disease in Jewish people--an epidemiological study in south-east Wales. Digestion 1986; 35:237.
24. Karlinger K, Györke T, Makö E, et al. The epidemiology and the pathogenesis of inflammatory bowel disease. Eur J Radiol 2000; 35:154.
25. Calkins BM, Lilienfeld AM, Garland CF, Mendeloff AI. Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci 1984; 29:913.
26. Roth MP, Petersen GM, McElree C, et al. Geographic origins of Jewish patients with inflammatory bowel disease. Gastroenterology 1989; 97:900.
27. Damas OM, Avalos DJ, Palacio AM, et al. Inflammatory bowel disease is presenting sooner after immigration in more recent US immigrants from Cuba. Aliment Pharmacol Ther 2017; 46:303.
28. Benchimol EI, Mack DR, Guttmann A, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. Am J Gastroenterol 2015; 110:553.
29. Agrawal M, Corn G, Shrestha S, et al. Inflammatory bowel diseases among first-generation and second-generation immigrants in Denmark: a population-based cohort study. Gut 2021; 70:1037.
30. Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 2006; 81:1462.
31. Higuchi LM, Khalili H, Chan AT, et al. A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. Am J Gastroenterol 2012; 107:1399.
32. Johnson GJ, Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. Aliment Pharmacol Ther 2005; 21:921.
33. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. Gastroenterology 2001; 120:1093.
34. Louis E, Michel V, Hugot JP, et al. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. Gut 2003; 52:552.

35. Boyko EJ, Perera DR, Koepsell TD, et al. Effects of cigarette smoking on the clinical course of ulcerative colitis. Scand J Gastroenterol 1988; 23:1147.

36. Beaugerie L, Massot N, Carbonnel F, et al. Impact of cessation of smoking on the course of ulcerative colitis. Am J Gastroenterol 2001; 96:2113.

37. Khalili H, Ananthakrishnan AN, Konijeti GG, et al. Physical activity and risk of inflammatory bowel disease: prospective study from the Nurses' Health Study cohorts. BMJ 2013; 347:f6633.

38. Wanner M, Martin BW, Autenrieth CS, et al. Associations between domains of physical activity, sitting time, and different measures of overweight and obesity. Prev Med Rep 2016; 3:177.

39. Jones PD, Kappelman MD, Martin CF, et al. Exercise decreases risk of future active disease in patients with inflammatory bowel disease in remission. Inflamm Bowel Dis 2015; 21:1063.

40. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology 2013; 145:970.

41. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. Am J Gastroenterol 2011; 106:563.

42. Abegunde AT, Muhammad BH, Bhatti O, Ali T. Environmental risk factors for inflammatory bowel diseases: Evidence based literature review. World J Gastroenterol 2016; 22:6296.

43. Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. Inflamm Bowel Dis 2005; 11:154.

44. Geerling BJ, Dagnelie PC, Badart-Smook A, et al. Diet as a risk factor for the development of ulcerative colitis. Am J Gastroenterol 2000; 95:1008.

45. Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut 2004; 53:1479.

46. Amre DK, D'Souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol 2007; 102:2016.

47. Del Pinto R, Pietropaoli D, Chandar AK, et al. Association Between Inflammatory Bowel Disease and Vitamin D Deficiency: A Systematic Review and Meta-analysis. Inflamm Bowel Dis 2015; 21:2708.

48. Bancil AS, Sandall AM, Rossi M, et al. Food Additive Emulsifiers and Their Impact on Gut Microbiome, Permeability, and Inflammation: Mechanistic Insights in Inflammatory Bowel Disease. J Crohns Colitis 2021; 15:1068.

49. Chapman-Kiddell CA, Davies PS, Gillen L, Radford-Smith GL. Role of diet in the development of inflammatory bowel disease. Inflamm Bowel Dis 2010; 16:137.
50. Ananthakrishnan AN, Khalili H, Konijeti GG, et al. Sleep duration affects risk for ulcerative colitis: a prospective cohort study. Clin Gastroenterol Hepatol 2014; 12:1879.
51. Ali T, Madhoun MF, Orr WC, Rubin DT. Assessment of the relationship between quality of sleep and disease activity in inflammatory bowel disease patients. Inflamm Bowel Dis 2013; 19:2440.
52. Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. Nat Rev Immunol 2008; 8:458.
53. Porter CK, Tribble DR, Aliaga PA, et al. Infectious gastroenteritis and risk of developing inflammatory bowel disease. Gastroenterology 2008; 135:781.
54. 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.
55. García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. Gastroenterology 2006; 130:1588.
56. López-Serrano P, Pérez-Calle JL, Pérez-Fernández MT, et al. Environmental risk factors in inflammatory bowel diseases. Investigating the hygiene hypothesis: a Spanish case-control study. Scand J Gastroenterol 2010; 45:1464.
57. Wakefield AJ, Ekbom A, Dhillon AP, et al. Crohn's disease: pathogenesis and persistent measles virus infection. Gastroenterology 1995; 108:911.
58. Haslam N, Mayberry JF, Hawthorne AB, et al. Measles, month of birth, and Crohn's disease. Gut 2000; 47:801.
59. Feller M, Huwiler K, Stephan R, et al. Mycobacterium avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. Lancet Infect Dis 2007; 7:607.
60. Iizuka M, Chiba M, Yukawa M, et al. Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease. Gut 2000; 46:163.
61. Chassaing B, Darfeuille-Michaud A. The commensal microbiota and enteropathogens in the pathogenesis of inflammatory bowel diseases. Gastroenterology 2011; 140:1720.
62. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics and new diagnoses of Crohn's disease and ulcerative colitis. Am J Gastroenterol 2011; 106:2133.
63. Ungaro R, Bernstein CN, Gearry R, et al. Antibiotics associated with increased risk of new-onset Crohn's disease but not ulcerative colitis: a meta-analysis. Am J Gastroenterol 2014;

109:1728.

64. Margolis DJ, Fanelli M, Hoffstad O, Lewis JD. Potential association between the oral tetracycline class of antimicrobials used to treat acne and inflammatory bowel disease. Am J Gastroenterol 2010; 105:2610.
65. Nguyen LH, Örtqvist AK, Cao Y, et al. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. Lancet Gastroenterol Hepatol 2020; 5:986.
66. Oh SJ, Kim HJ, Lee CK, Big Data Research Group (BDRG) of the Korean Society of Gastroenterology. A dose-dependent increase in the risk of inflammatory bowel disease after exposure to broad-spectrum antibiotics: A national population study in Korea. Aliment Pharmacol Ther 2023; 58:191.
67. Narula N, Wong ECL, Pray C, et al. Associations of Antibiotics, Hormonal Therapies, Oral Contraceptives, and Long-Term NSAIDS With Inflammatory Bowel Disease: Results From the Prospective Urban Rural Epidemiology (PURE) Study. Clin Gastroenterol Hepatol 2023; 21:2649.
68. Ananthakrishnan AN, Higuchi LM, Huang ES, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. Ann Intern Med 2012; 156:350.
69. Felder JB, Korelitz BI, Rajapakse R, et al. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. Am J Gastroenterol 2000; 95:1949.
70. Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2006; 4:196.
71. Bonner GF, Walczak M, Kitchen L, Bayona M. Tolerance of nonsteroidal antiinflammatory drugs in patients with inflammatory bowel disease. Am J Gastroenterol 2000; 95:1946.
72. Bonner GF, Fakhri A, Vennamaneni SR. A long-term cohort study of nonsteroidal anti-inflammatory drug use and disease activity in outpatients with inflammatory bowel disease. Inflamm Bowel Dis 2004; 10:751.
73. Reinisch W, Miehsler WP, Dejaco C, et al. Treatment of peripheral arthropathy in IBD with Rofecoxib, a selective COX-2 inhibitor (abstract). Gastroenterology 2001; 120:A277.
74. Mahadevan U, Loftus EV Jr, Tremaine WJ, Sandborn WJ. Safety of selective cyclooxygenase-2 inhibitors in inflammatory bowel disease. Am J Gastroenterol 2002; 97:910.
75. El Miedany Y, Youssef S, Ahmed I, El Gaafary M. The gastrointestinal safety and effect on disease activity of etoricoxib, a selective cox-2 inhibitor in inflammatory bowel diseases. Am

J Gastroenterol 2006; 101:311.

76. Sandborn WJ, Stenson WF, Brynskov J, et al. Safety of celecoxib in patients with ulcerative colitis in remission: a randomized, placebo-controlled, pilot study. Clin Gastroenterol Hepatol 2006; 4:203.
77. Cornish JA, Tan E, Simillis C, et al. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. Am J Gastroenterol 2008; 103:2394.
78. Khalili H, Higuchi LM, Ananthakrishnan AN, et al. Hormone therapy increases risk of ulcerative colitis but not Crohn's disease. Gastroenterology 2012; 143:1199.
79. García Rodríguez LA, González-Pérez A, Johansson S, Wallander MA. Risk factors for inflammatory bowel disease in the general population. Aliment Pharmacol Ther 2005; 22:309.
80. Cutolo M, Capellino S, Sulli A, et al. Estrogens and autoimmune diseases. Ann N Y Acad Sci 2006; 1089:538.
81. Bankar RN, Dafe CO, Köhnke A, Babu PS. Ulcerative colitis probably associated with isotretinoin. Indian J Gastroenterol 2006; 25:171.
82. Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. Ann Pharmacother 2001; 35:1214.
83. Bernstein CN, Nugent Z, Longobardi T, Blanchard JF. Isotretinoin is not associated with inflammatory bowel disease: a population-based case-control study. Am J Gastroenterol 2009; 104:2774.
84. Crockett SD, Porter CQ, Martin CF, et al. Isotretinoin use and the risk of inflammatory bowel disease: a case-control study. Am J Gastroenterol 2010; 105:1986.
85. Reddy D, Siegel CA, Sands BE, Kane S. Possible association between isotretinoin and inflammatory bowel disease. Am J Gastroenterol 2006; 101:1569.
86. Shale M, Kaplan GG, Panaccione R, Ghosh S. Isotretinoin and intestinal inflammation: what gastroenterologists need to know. Gut 2009; 58:737.
87. Crockett SD, Gulati A, Sandler RS, Kappelman MD. A causal association between isotretinoin and inflammatory bowel disease has yet to be established. Am J Gastroenterol 2009; 104:2387.
88. Alhusayen RO, Juurlink DN, Mamdani MM, et al. Isotretinoin use and the risk of inflammatory bowel disease: a population-based cohort study. J Invest Dermatol 2013; 133:907.
89. Etminan M, Bird ST, Delaney JA, et al. Isotretinoin and risk for inflammatory bowel disease: a nested case-control study and meta-analysis of published and unpublished data. JAMA

Dermatol 2013; 149:216.

90. Rashtak S, Khaleghi S, Pittelkow MR, et al. Isotretinoin exposure and risk of inflammatory bowel disease. JAMA Dermatol 2014; 150:1322.
91. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy is followed by increased risk of Crohn's disease. Gastroenterology 2003; 124:40.
92. Kaplan GG, Jackson T, Sands BE, et al. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. Am J Gastroenterol 2008; 103:2925.
93. Rutgeerts P, D'Haens G, Hiele M, et al. Appendectomy protects against ulcerative colitis. Gastroenterology 1994; 106:1251.
94. Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. N Engl J Med 2001; 344:808.
95. Okazaki K, Onodera H, Watanabe N, et al. A patient with improvement of ulcerative colitis after appendectomy. Gastroenterology 2000; 119:502.
96. Lerebours E, Gower-Rousseau C, Merle V, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: A population-based case-control study. Am J Gastroenterol 2007; 102:122.
97. Ananthakrishnan AN, Khalili H, Pan A, et al. Association between depressive symptoms and incidence of Crohn's disease and ulcerative colitis: results from the Nurses' Health Study. Clin Gastroenterol Hepatol 2013; 11:57.
98. Li J, Nørgard B, Precht DH, Olsen J. Psychological stress and inflammatory bowel disease: a follow-up study in parents who lost a child in Denmark. Am J Gastroenterol 2004; 99:1129.
99. Schoultz M, Beattie M, Gorely T, Leung J. Assessment of causal link between psychological factors and symptom exacerbation in inflammatory bowel disease: a systematic review utilising Bradford Hill criteria and meta-analysis of prospective cohort studies. Syst Rev 2020; 9:169.
100. Jordi SBU, Lang BM, Auschra B, et al. Depressive Symptoms Predict Clinical Recurrence of Inflammatory Bowel Disease. Inflamm Bowel Dis 2022; 28:560.
101. Singh S, Graff LA, Bernstein CN. Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD? Am J Gastroenterol 2009; 104:1298.
102. Bitton A, Dobkin PL, Edwardes MD, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. Gut 2008; 57:1386.
103. Chan SS, Luben R, Olsen A, et al. Body mass index and the risk for Crohn's disease and ulcerative colitis: data from a European Prospective Cohort Study (The IBD in EPIC Study). Am J Gastroenterol 2013; 108:575.

104. Mendall MA, Gunasekera AV, John BJ, Kumar D. Is obesity a risk factor for Crohn's disease? Dig Dis Sci 2011; 56:837.

105. Desreumaux P, Ernst O, Geboes K, et al. Inflammatory alterations in mesenteric adipose tissue in Crohn's disease. Gastroenterology 1999; 117:73.

106. Blain A, Cattan S, Beaugerie L, et al. Crohn's disease clinical course and severity in obese patients. Clin Nutr 2002; 21:51.

Topic 4066 Version 47.0

Contributor Disclosures

Mark A Peppercorn, MD No relevant financial relationship(s) with ineligible companies to disclose. **Adam S Cheifetz, MD** Consultant/Advisory Boards: Abbvie [IBD]; Adiso [IBD]; Arena [IBD]; Artizan [IBD]; Bristol Myers Squibb [IBD]; Clario [IBD]; Food is Good [GI]; Fresenius Kabi [IBD]; Fzata [IBD]; Janssen [IBD]; Pfizer [IBD]; Procise [IBD]; Prometheus [IBD]; Samsung [IBD]; Spherix [IBD]; Takeda [IBD]. Speaker's Bureau: Abbvie [IBD]; Bristol Myers Squibb [UC]. All of the relevant financial relationships listed have been mitigated. **Sunanda V Kane, MD, MSPH** Grant/Research/Clinical Trial Support: Bristol Myers Squibb [IBD]. Consultant/Advisory Boards: Boehringer Ingelheim [IBD]; Bristol Myers Squibb [IBD]; Fresenius Kabi [IBD]; InveniAI [IBD]; Janssen [IBD]; Lilly [IBD]; Takeda [IBD]; Techlab [IBD]. Other Financial Interest: PredicaMed [Scientific Board]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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