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**Supplement Article**

# Epidemiology of Inflammatory Bowel Disease across the Ages in the Era of Advanced Therapies

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## Abstract

**Background and Aims:** The incidence of inflammatory bowel diseases [IBD] has risen over the past decade to become a global issue. The objectives of this review were to describe the incidence and/or prevalence of IBD in the era of advanced therapies, and to describe the association between environmental risk factors and both pathogenesis and disease course across the ages.

**Methods:** We performed a search of English language publications listed in PubMed regarding the epidemiology of IBD and key environmental factors implicated in IBD from January 2000 to December 2023.

**Results:** Annual incidence rates varied by geographical region with IBD estimates ranging from 10.5 to 46.14 per 100 000 in Europe, 1.37 to 1.5 per 100 000 in Asia and the Middle East, 23.67 to 39.8 per 100 000 in Oceania, 0.21 to 3.67 per 100 000 in South America, and 7.3 to 30.2 per 100 000 in North America. The burden of IBD among children and adolescents, and older people is rising globally. Key environmental factors implicated in IBD pathogenesis include exposure to tobacco smoking, antibiotics, non-steroidal anti-inflammatory drugs, oral contraceptives, infections, and ultra-high processed foods. Breastfeeding and a high-quality diet rich in fruit, vegetables, fish, and other fibre sources are important protective factors. Smoking has consistently been shown to negatively impact disease outcomes for Crohn's disease.

**Conclusion:** The epidemiology of IBD has undergone considerable change in recent decades, with an increase in the burden of disease worldwide. Optimally studying and targeting environmental triggers in IBD may offer future opportunities for disease modification.

**Key Words:** Epidemiology; risk factors; inflammatory bowel disease

## 1. Introduction

Since its first description nearly a century ago in the Western population, the epidemiology of inflammatory bowel disease [IBD] has undergone considerable shifts and it has emerged as a truly global disease over the last two decades.[1]

The global burden of disease is increasingly influenced by the conditions and effects of globalization, including the worldwide dissemination of both infectious and non-infectious public health risks.[2] The impacts on daily life associated with globalization have induced discernible and tangible health consequences in practically all countries around the world. Today's increasing health risks in the Global South are closely related to urbanization and altered lifestyles, especially air pollution, unhealthy diets, physical inactivity, smoking, and excessive alcohol use.[2] The changes in working and living habits and their consequences for physical, mental, and social health contribute to the global harmonization of diseases. In many developing and emerging countries, this is associated with a double burden of disease due to the simultaneous occurrence of infectious and non-communicable diseases.[2]

More than 10 years ago, before the era of advanced therapies [biologics and novel small molecule drugs], a systematic literature review evaluated data from 167 studies from Europe [1930–2008], 52 studies from Asia and the Middle East [1950–2008], and 27 studies from North America [1920–2004].[3] The incidence of IBD was increasing or stable in virtually every region of the world that had been studied.[3] The incidence and prevalence of IBD were highest in westernized nations.

By 2020, the newly industrialized countries/regions of Asia and Latin America had seen a rapid rise in incidence.[4] The emergence of IBD in these traditionally low-prevalence regions suggested that the development of IBD might be influenced by environmental risk factors.[3] The increasing incidence of IBD in newly industrialized countries indicates a potential influence of a Western lifestyle, urbanization, and industrialization on risk.[5] Association studies have shown a number of environmental risk factors for IBD, including cigarette smoking, antibiotic use, breastfeeding, and appendectomy.[5] Several environmental factors [smoking prevention,

breastfeeding, a diet high in fibre, judicious use of antibiotics] can be targeted to reduce the incidence of IBD, but different populations [e.g. children, older patients] with different risk factors might require interventions at different time points.[5]

In this context, this narrative review of population-based studies had three main objectives: first, to describe the incidence and/or prevalence of IBD in the era of advanced therapies; second, to explore the association between environmental risk factors and pathogenesis and the effect on disease course over a patient's lifetime; and third, to discuss key exposome-based interventions that may prevent or attenuate disease onset and offer a true opportunity for disease modification.

## 2. Methods

To identify relevant articles for this narrative review, a MEDLINE literature search was conducted through the PubMed platform for articles published in the English language between January 2000 and December 2023. The following search terms were used 'inflammatory bowel disease', 'Crohn's disease', 'ulcerative colitis', 'epidemiology', 'incidence', 'prevalence', 'risk factors', 'lifestyle', 'smoking', 'environment', 'diet', and 'exposome.' Secondary references of the retrieved articles were reviewed to identify publications not captured by the electronic search. For key epidemiology studies included in this review, the following data were extracted: first author, year of publication, population, country, period, incidence, prevalence, need for surgery, hospitalization, and mortality. The incidence of IBD was reported using incidence rates, defined as the number of cases in a population over the person-years at risk in the population. The prevalence of IBD was reported as the number of prevalent cases in a defined region per 100 000 population.

## 3. Epidemiology of IBD across the ages

We reviewed the evidence regarding the epidemiology of IBD in the era of biologics and small molecule inhibitors [Figure 1]. Supplementary Table 1 summarizes the main characteristics of the key epidemiological studies, which were published between 2006 and 2023. Seventeen studies were specifically conducted in paediatric and adolescent populations.[6–22] The 42 incidence studies [Europe,[7,9,13–15,18,19,21,23–34] Asia and the Middle East,[6,10,17,20,35–40] North America,[16,22,41,42] Oceania,[37,43–45] and South America[46–48]] and the 16 prevalence studies [Europe,[24,26,28,30,31,49] North America,[22,50–52] South America,[46,47,53] Asia and the Middle East,[39] and Oceania[44]] were conducted in different geographical regions.

### 3.1. Adult patients with IBD

The annual incidence rates varied by geographical region with IBD estimates ranging from 10.5 to 46.14 per 100 000 in Europe, 1.37 to 1.5 per 100 000 in Asia and the Middle East, 23.67 to 39.8 per 100 000 in Oceania, 0.21 to 3.67 per 100 000 in South America, and 7.3 to 30.2 per 100 000 in North America. Crohn's disease [CD] estimates ranged from 4.1 to 22.78 per 100 000 in Europe, 0.09 to 3.6 per 100 000 in Asia and the Middle East, 13.23 to 26.0 per 100 000 in Oceania, and 0.04 to 0.64 per 100 000 in South America, and ulcerative colitis [UC] estimates ranging from 3.0 to 23.36 per 100 000 in Europe, 0.69 to 5.0 per 100 000 in Asia and the Middle East, 7.33 to 17.25 per 100 000 in Oceania, and 0.16 to 2.99 per 100 000 in South America. These included incidence rates for the periods from 2000 to 2020 for European studies, 2001 to 2013 for Asian and Middle Eastern studies, 2011 to 2018 for Oceanian studies, and 2000 to 2019 for South American studies.

For prevalence studies, the IBD estimates ranged from 187 to 832 per 100 000 in Europe, 1.83 to 70.1 per 100 000 in South America, and 214.9 to 478.4 per 100 000 in North America. The CD estimates ranged from 61.6 to 178 per 100 000 in Europe, 0.34 to 14.9 per 100 000 in South America, and 146 to 201 per 100 000 in North America. The UC estimates ranged from 99.84 to 191.4 per 100 000 in Europe, 1.45 to 60.1 per 100 000 in South America, and 202 to 238 per 100 000 in North America. The study periods from which these prevalence rates were derived were from 2000 to 2020 for European studies, 2000 to 2019 for South American studies, and 2003 to 2016 for North American studies.

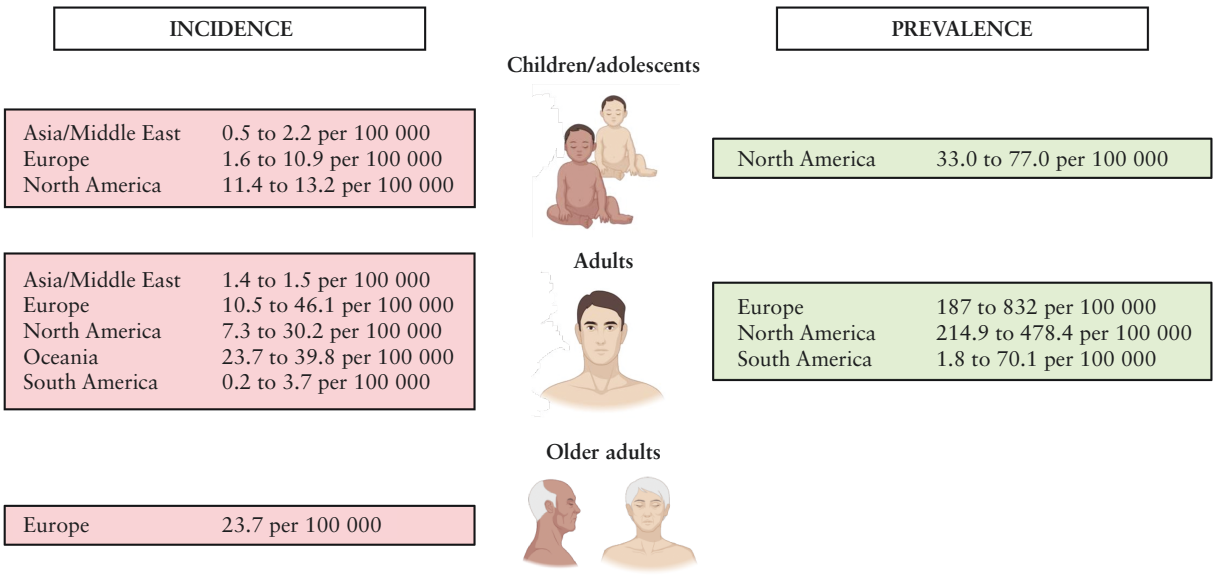


**Figure 1.** Epidemiology of inflammatory bowel disease across age groups. Figure created with BioRender.

Comparison of population-based data reveals that the incidence of IBD has risen rapidly in the East while plateauing in the West.[54] However, the compounding prevalence of IBD in the West is increasing and is driven by the incidence of IBD exceeding mortality rates.[5] The clinical presentation and disease course of IBD differ between East and West with more patients in the East presenting with complicated disease.[54]

### 3.2. Paediatric and adolescent patients with IBD

The annual incidence rates varied by geographical region, with IBD estimates ranging from 1.59 to 10.9 per 100 000 in Europe, 0.47 to 2.16 per 100 000 in Asia and the Middle East, and 11.4 to 13.2 per 100 000 in North America, CD estimates ranging from 1.7 to 6.8 per 100 000 in Europe, 0.19 to 1.53 per 100 000 in Asia and the Middle East, and 6.0 to 7.9 per 100 000 in North America, and UC estimates ranging from 0.88 to 3.87 per 100 000 in Europe, 0.13 to 0.38 per 100 000 in Asia and the Middle East, and 4.1 to 4.2 per 100 000 in North America. The study periods from which these incidence rates were derived ranged from 2000 to 2018 for European studies, 1998 to 2021 for Asian and Middle Eastern studies, and 2005 to 2009 for North American studies.

For the three North American prevalence studies, the IBD estimates ranged from 33.0 to 77.0 per 100 000, the CD estimates ranged from 19.7 to 28.0 per 100 000, and the UC estimates ranged from 31.6 to 45.9 per 100 000. The burden of IBD among children and adolescents is rising globally.

The Global Burden of Disease [GBD] data describe the state of IBD in children and adolescents, from 1990 to 2019, in 204 countries and territories.[55] Their recent epidemiological analysis showed that incidence cases of IBD increased from 20 897.4 (95% confidence interval [CI] 17 008.6–25 520.2) in 1990 to 25 658.6 [95% CI 21 268.5–31 075.6] in 2019, representing a 22.78% increase, and mortality cases of IBD decreased from 2756.5 [95% CI 1162.6–4484.9] in 1990 to 1208.0 [95% CI 802.4–1651.4] in 2019, representing a 56.17% decrease.[55]The age at which children are being diagnosed with IBD is decreasing.[56]

### 3.3. Older patients with IBD

Older patients now represent the largest growing patient population with IBD.[57] Whilst in 2010, patients aged 65 years and older represented less than 20% of the overall IBD population,[58] current estimates suggest that this group now represents up to 30% in the UK and Canada for example.[59,60] Amongst these, 20% are adult-onset older IBD patients [diagnosed at a younger age and now ageing with IBD][61–63] and 15% are older adult-onset IBD patients,[3,64,65] defined by a new IBD diagnosis above the age of 60 years. One European study evaluated incidence rates in a population of elderly onset IBD patients, with IBD incidence rate of 23.66 per 100 000, CD incidence rate of 6.23 per 100 000, and UC incidence rate of 17.43 per 100 000.[29]

### 3.4. Surgery rates

Surgery rates ranged from 5.8 to 25% in CD, and 2 to 6.6% in UC in European studies, 7.7 to 46.1% in CD, and 1.6 to 7.1% in UC in Asian and Middle Eastern studies, 22.5 to 46.1% in CD, and 2.8 to 7.1% in UC in North American studies, and 2.9 to 62.5% in CD, and 2.8 to 37.5% in UC in South American studies. In the paediatric and adolescent population, surgery rates ranged from 2.7 to 14.6%.

### 3.5. Hospitalization rates

In the included studies, hospitalization for IBD rates ranged from 43 to 46% in Europe, 31.9 to 55.5% in North America, 31.9 to 55.5% in Asia, and 19.6 to 39.5% in South America. Recently, a systematic review showed that hospitalization rates for IBD are stabilizing in countries in North America, Western Europe, and Oceania, whereas newly industrialized countries [Asia, Eastern Europe, and Latin America] have rapidly increasing hospitalization rates, contributing to an increasing burden on global healthcare systems.[66]

## 4. The exposome in IBD

Advances in genomics over the past two decades have helped identify key pathways implicated in the pathogenesis and pathophysiology of IBD.[67] The hereditability of IBD has been demonstrated through familial studies examining IBD risk among first-degree relatives and twins, and genome-wide association studies have highlighted more than 250 susceptibility loci with their functional consequences for intestinal barrier function and both innate and adaptive T cell immunity.[68–72] Although genetic susceptibility remains the strongest risk factor for IBD, it only partly explains disease variance. Susceptibility loci explain ~13.1% and 8.2% of the variance in disease liability for CD and UC, respectively.[70] It is widely accepted that the missing heritability problem is largely driven by external environmental factors and their convoluted interactions with the genome and the intestinal microbiome that modify the risk of developing IBD and its subsequent disease course.[67] The effect of multiple environmental factor exposures may account for the rising global incidence and explain the aforementioned evolving epidemiological trends. The geographical variation in these trends may be due to the exposure of similar environmental risk factors in populations that may share genetic commonalities. Geographical epidemiological variability has been described both intercontinentally and also within certain individual countries.[73] In Europe, for example, although the rapidly rising incidence rates in the east are now similar to those in the west, other persistent differences include a less complicated disease at diagnosis, decreased need for surgery in CD, and lower rates of colorectal cancer in UC compared to the west.[74] Within individual countries, such as the USA, France, Portugal, Spain, and Italy, there is a north–south disease gradient for incidence, whereas Canada demonstrates an east–west disease gradient; these differences are probably due to differing environmental exposures.[73]

The term ‘exposome’ first entered the medical lexicon in 2005 to describe the life-course of environmental and lifestyle factor exposures from the pre-natal period right through childhood and adulthood.[75] Studying the exposome is complicated but has been broadly approached in three ways: recalling risk factors and lifestyle choices over a lifetime compared to matched healthy controls, an ‘-omics’ approach after disease onset to detect cellular-level changes through biospecimens obtained at specified time intervals, and directly studying a potential causative factor through a hypothesis-driven manner with the aim of establishing causality. In this section we describe some of the key environmental factors implicated in IBD, which are stratified by the age groups in which they have been studied in the era of advanced therapies over the past 20 years. This is summarized in Table 1 and Figure 2.

**Table 1.** Summary of environmental risk and protective factors influencing IBD development through the ages.

| Risk | Protective |
|---|---|
| **Prenatal and early childhood** | |
| • Prenatal maternal tobacco smoking [OR 1.5, 95% CI 1.2–1.9][76] | • Breastfeeding: CD [OR 0.7, 95% CI 0.6–0.9] and UC [OR 0.8, 95% CI 0.7–0.9][77] Risk of IBD further decreases with breastfeeding to 1 year versus 3 or 6 months |
| • Prenatal antibiotic exposure [OR 1.8, 95% CI 1.2–2.5][76] | |
| • Early life otitis media [OR 2.1, 95% CI 1.2–3.6][76] | • High-quality diet [increased intake of fish and vegetables] at 12 months of age[78] |
| **Adolescence and adulthood** | |
| • Urban living for CD [IRR 1.42, 95% CI 1.26–1.60][79] | • Exposure to farm animals, pets, and bed sharing[1] |
| • Non-steroidal anti-inflammatory drugs [OR 1.80, 95% CI 1.23–2.64][80] | • Fruit for UC and CD [OR 0.69, 95% CI 0.49–0.96][1] |
| • Oral contraceptives [greater risk with combined versus progesterone] [OR 2.17, 95% CI 1.70–2.77][80] | • Vegetables for UC [OR 0.71, 95% CI 0.58–0·88][1] |
| • Cigarette smoking in CD [OR 1.76, 95% CI 1.40–2.22][81] | • Cigarette smoking in UC—current smoking less likely to develop UC [OR 0.58, 95% CI 0.45–0.75][81,82] but smoking status after diagnosis does not affect disease course nor outcomes[83] |
| • Antibiotic use[84]—particularly in:<br>○ within the first 2 years of exposure<br>○ with antibiotics used to treat enteric infections<br>○ those >40 years of age | • Appendicectomy for UC [OR 0.39, 95% CI 0.29–0.52][85] which reduces the risk of developing UC by as much as 69% [95% CI 62–75%][86,87] |
| • Prior gastroenteritis [OR 1.55, 95% CI 1.47–1.65].[88,89] | • Presence of gastric *Helicobacter pylori* [OR 0.53, 95% CI 0.44–0.65][88] |
| • Ultra-high processed foods in CD [HR 1.70, 95% CI 1.23–2.35][90]<br>• Western and carnivorous dietary habits with increased fat intake[91,92] | • Fibre intake for CD [OR 0.59, 95% CI 0.39–0.90][93] |
| **Older adults [> 60 years]** | |
| • Antibiotic use[84] | • Mediterranean diet in CD [HR 0.42, 95% CI 0.22–0.80][94] |

Abbreviations: OR, odds ratio; CI, confidence interval; CD, Crohn's disease; UC, ulcerative colitis; HR, hazard ratio. Values specified are risks for IBD unless disease subtype specified.

## 5. Factors affecting the risk of developing IBD

### 5.1. Prenatal and early childhood exposures

Early life events are known to alter the risk of chronic disease development in later life, influenced by the complex interactions between the genome and the epigenome.[95] Epigenetic changes, such as DNA methylation or histone modification [by acetylation or methylation], can occur from environmental influences during critical developmental periods, leading to imprinting and increased susceptibility to IBD.

In a recent systematic review and meta-analysis, Agrawal *et al*. synthesized the findings of 114 case-control or cohort studies that reported an association between early life environmental exposures [prenatal to ≤5 years] and risk of developing IBD.[96] Prenatally, maternal tobacco smoking increased the odds of the infant developing IBD compared to those unexposed (odds ratio [OR] 1.5, 95% CI 1.2–1.9), although this association was not seen when analyses were stratified by disease type.[96] *In utero* exposure to antibiotics, particularly in the third trimester, also increased the odds of developing IBD [OR 1.8, 95% CI 1.2–2.5] though for antibiotic exposure during early childhood, there was a positive but non-significant trend.[96] Mode of delivery did not affect outcomes. Early life infections, particularly otitis media, have also been associated with the future risk of developing IBD [OR 2.1, 95% CI 1.2–3.6]. The maternal intestinal microbiota has been demonstrated to promote the maturation and development of the neonatal immune system, which may in part explain the above findings.[97] This is of key importance for immune-mediated inflammatory diseases such as IBD and should enable further research exploring environmental exposures at this critical stage of life.

Breastfeeding and a high-quality diet in infants were shown to reduce the risk of IBD. While earlier studies of lower quality in the pre-biologic era showed inconsistent results, more recent data demonstrate that breastfeeding is protective with a strong inverse association between breastfeeding in infancy and the subsequent development of IBD.[98,99] In a systematic review and meta-analysis by Xu *et al*. that included 7536 patients with CD, 7353 with UC, and 330 222 controls, breastfed babies had a reduced risk of CD [OR 0.7, 95% CI 0.6–0.9] and UC [OR 0.8, 95% CI 0.7–0.9].[99] There was a further reduction in the risk of CD [OR 0.2, 95% CI 0.1–0.5] and UC [OR 0.2, 95% CI 0.1–0.4] for babies who were breastfed for at least 12 months versus those fed for 3 or 6 months. At 12 months of age, a recent prospective study by Guo *et al*. established that a diet that consisted of a high intake of vegetables and fish was associated with a reduced risk of subsequent IBD.[76] However, an intake of sugar-sweetened beverages was associated with an increased risk of IBD.

### 5.2. Adolescence and adulthood

#### 5.2.1. Smoking

Cigarette smokers have a 2-fold increased risk of developing CD [OR 1.76, 95% CI 1.40–2.22],[100,101] but a reduced risk of developing UC [OR 0.58, 95% CI 0.45–0.75].[77,78,100] It is unclear if the observational associations with opposing risks of developing CD and UC reflect actual causal associations, confounding, or reverse causation.[102]

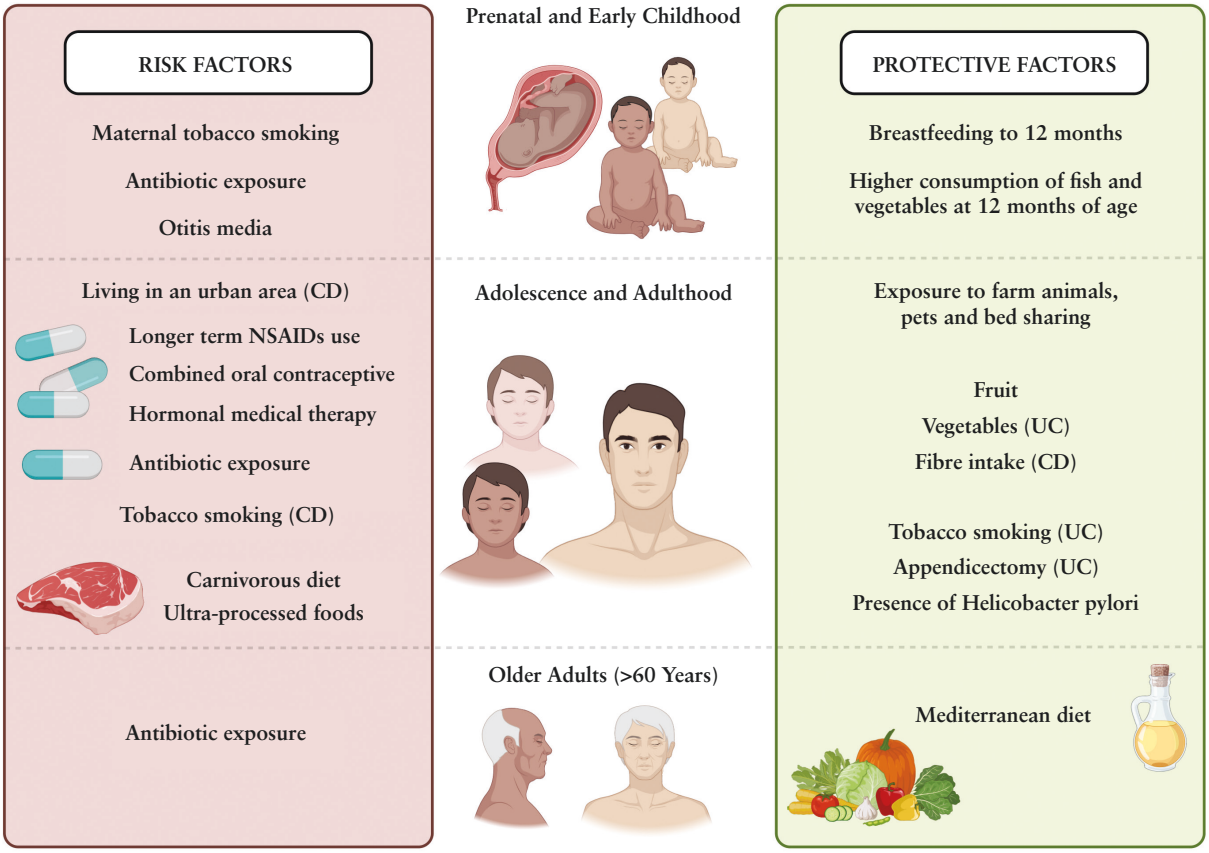


**Figure 2.** Key environmental factors implicated in inflammatory bowel disease. Figure created with BioRender.

### 5.2.2. Exposure to drugs and prior surgery

Antibiotics are known to disrupt the intestinal microbiome and, as described, increase the risk of IBD development with exposure in early life, particularly in the prenatal period and first year of infancy.[96] This association decreases, however, with increasing childhood age of exposure through to adolescence.[103] For adults, antibiotic exposure was also shown to increase the risk of IBD across all ages in a recent population-based cohort study with more than 87 million person-years of follow-up.[81] The highest risk of developing IBD occurred in patients aged 40–60 years (incidence rate ratio [IRR] 1.48, 95% CI 1.4–1.54). The risk was particularly magnified within the first 2 years of antibiotic exposure and after use of antibiotic classes often prescribed to treat gastrointestinal pathogens, such as nitroimidazoles and fluroquinolones.[81]

Other drugs frequently implicated in causing IBD include non-steroidal anti-inflammatory drugs [NSAIDs], the combined oral contraceptive pill [OCP], and hormone medical therapy. Previously, there had been mixed reports of the association of isotretinoin and IBD but a recent meta-analysis including >2.5 million participants showed no evidence of increased odds of developing UC or CD.[104] The PURE study by Narula *et al.* was a prospective cohort study of 133 137 adults who were followed up for a median period of 11 years, which assessed the association between medication use and the risk of developing IBD.[105] Here, NSAIDs increased the odds of incident IBD (adjusted OR [aOR] 1.80, 95% CI 1.23–2.64], which was further increased by long-term use [aOR 5.58, 95% CI 2.26–13.80]. Increased odds of IBD in the PURE study were also seen with previous or current OCP use [aOR 2.17, 95% CI 1.70–2.77] and with hormonal medication use [aOR 4.43, 95% CI 1.78–11.01].[105]

With regard to previous surgery, appendicectomy confers a protective effect for UC and reduces the risk of incident diagnosis by as much as 69% [95% CI 62–75%], especially in patients operated on at ≤20 years of age for acute appendicitis.[106,107] Results of appendicectomy as a treatment option in medically refractive UC are controversial and outcomes from randomized controlled trials are eagerly awaited.[82,83,108,109] Evidence for the link between prior tonsillectomy and CD is tenuous given mixed results, and outcomes are likely to have been confounded by the need for repeated antibiotic exposure.[84,110]

### 5.2.3. Diet

The pro-colitogenic effects of intestinal dysbiosis and the amelioration of the inflammatory burden by modulation with faecal microbiota transplantation are well established.[80,86,111,112] Unravelling the tight interrelation between diet and host microbiome–immune responses is key and the westernized diet-associated gut dysbiosis is thought to be one of the main environmental factors responsible for the pathogenesis of IBD. Pre-clinical models have shown the deleterious impact of additives and specific nutrients to trigger and perpetuate gut inflammation. Epidemiological studies have associated a number of dietary components with IBD. Despite this, no specific dietary regimen is advocated for preventing disease onset or relapse in national or international consensus guidelines.

To prevent IBD onset, reducing consumption of ultra-processed foods [UPFs] is likely to be beneficial. UPF includes additives to preserve or enhance a food product, for example artificial sweeteners or emulsifiers.[87] A meta-analysis by Narula *et al.* that included >1 million patients with >13 million years of person-years follow-up across five cohort studies published between 2020 and 2022 showed an increased CD risk [but not UC] for those with a higher UPF intake (hazard ratio [HR] 1.71, 95% CI 1.37–2.14).[113] In a large prospective population-based cohort study, western dietary patterns with low fruit and vegetable consumption, and high intake of snacks and pre-prepared meals showed an increased likelihood of incident CD [OR 1.16, 95% CI 1.03–1.30].[114] A pattern comprising red meat, poultry, and processed meat was associated with increased risk of UC [OR 1.11, 95% CI 1.01–1.20].[114] Other important dietary factors include: soft drink consumption, which increased the risk of UC (relative risk [RR] 1.69, 95% CI 1.24–2.30), and sucrose intake, which increased the risk of developing both UC [RR 1.10, 95% CI, 1.02–1.18] and CD [RR 1.09, 95% CI 1.02–1.16].[115,116]

The adoption of the Mediterranean diet, which emphasizes plant-based foods, whole grains, and healthy fats, has been shown to reduce mortality from cardiovascular disease and cancer.[117] There is increasing interest and data to support the integration of this diet into IBD clinical practice.[118] Large-scale prospective studies have shown that adherence to the Mediterranean diet can reduce the risk of developing CD.[119,120] This is also applicable to studies observing the effect of various components of this diet. For example, a meta-analysis of 14 case-control studies showed that a higher consumption of fruit was inversely associated with the risk of developing UC [OR 0.69, 95% CI 0.49–0.96] and CD [OR 0.57, 95% CI 0.44–0.74], and a higher consumption of vegetables was associated with a reduced risk of UC [OR 0.71, 95% CI 0.58–0.88] but did not meet significance for CD.[121] A US-based prospective study showed that long-term fibre intake was associated with a 40% reduced risk of CD [OR 0.59, 95% CI 0.39–0.90] but not UC.[122]

#### 5.2.4. Environmental location, hygiene, and living conditions

Reduced exposure to antigenic stimuli can lead to reduced diversity and abundance of the intestinal microbiome with a greater proclivity to develop pro-inflammatory T-cell immune responses to later stimuli.[123] In an umbrella review of meta-analyses, Piovani *et al.* summarize the outcomes of several meta-analyses that examined the effect of urban–rural exposures on the development of IBD. In order of decreasing risk, urban living was found to be associated with CD [IRR 1.42, 95% CI 1.26–1.60], IBD [OR 1.35, 95% CI 1.15-1.58], and, to a lesser extent, UC [IRR 1.17, 95% CI 1.03–1.32].[90] In contrast, habitation in proximity to farm animals, having pets, and bed sharing were found to be protective against both CD and UC.[90]

### 5.3. Older patients with IBD

Patients with older-onset IBD usually have a more benign and less progressive disease course, potentially representing a distinct sub-type within the IBD spectrum.[91,124,125] Age-related physiological changes in the gastrointestinal tract, alongside gut dysbiosis in terms of reduced diversity and abundance, alterations in lifestyle, dietary intake, and reduced functionality of the host immune system could lead to the development of IBD.[126,127]

Assessments of the impact of environmental exposure on older IBD patients are limited compared to other age groups given the incidence and prevalence in this age group has only dramatically increased in the past decade. Detailed study is also hindered by the effects of polypharmacy and multiple comorbidities that afflict this age group, including impairment to both mobility and cognition. Nonetheless, exposure to antibiotics to treat enteric bacteria in those aged ≥60 years has been shown to increase the risk of developing IBD [IRR 1.47, 95% CI 1.42–1.53].[81] In terms of protective factors, two prospective studies showed that adopting and adhering to a Mediterranean diet was associated with a significantly lower risk of older-onset CD [HR 0.42, 95% CI 0.22–0.80] but not UC.[119]

## 6. Factors affecting the disease course of IBD

Data on exposures and the possible impact on the subsequent course of IBD are far more limited. Here, studies have been conducted in adults and therefore this section has not been further sub-stratified by age. The impact of disease relapse on patients and caregivers warrants the urgent need to pursue research strategies that delineate risk factors that negatively affect disease course.

### 6.1. Smoking

Tobacco smoking is perhaps the most well-studied environmental factor for IBD and is well known for its detrimental impact on CD and for developing a more severe phenotype.[100,101] Quite how tobacco smoking impacts disease pathogenesis and disease course remains unclear but proposed mechanisms include mucosal damage, impaired mucosal immune responses, comprised blood flow, and modulation of the composition of gut microbiota by reducing bacterial species diversity.[94,128] Smokers with established CD have an increased risk of disease relapse, need for hospitalization, and need for surgical intervention.[93,129] Patients who are able to adhere to smoking cessation for more than 12 months run a more benign disease course comparable to those who have never smoked.[130] Although patients with UC have a reduced risk of developing disease as described above, smoking status after diagnosis does not appear to affect disease course or clinical outcomes.[77,78,100]

Most studies were conducted prior to or at the beginning of the advanced therapy era. Therefore, while is it difficult to ascertain to what extent immunosuppressive therapy is able to negate the deleterious consequences of smoking, tobacco smoking should be strongly discouraged with cessation support offered to those who require it given the well-known systemic effects. Moving forwards, observing how the shifting global patterns of tobacco smoking affect IBD epidemiology, disease phenotype, and treatment responsiveness will be important. For e-cigarette use, there are limited data but evidence so far does not point towards worse outcomes for patients with IBD.[131]

### 6.2. Psychological factors

There is evidence that psychological factors can contribute to IBD symptom flares. A prospective population-based study of 704 adults assessing triggers of symptomatic flares in IBD identified high perceived stress, low mood, and major

life events as trigger variables significantly associated with flares.[132] These findings were corroborated by another prospective study that identified perceived stress and avoidance coping as predictors of earlier relapse.[133] Sleep disturbance may also be implicated in disease flares. Ananthakrishnan *et al.* conducted a systematic review and found that among 1291 patients with CD, poor sleep had a 2-fold increase in risk of active disease at 6 months [aOR 2.0, 95% CI 1.45–2.76].[134] No increased risk of disease flare was seen with UC.

### 6.3. Medication

There is some evidence that medication can increase the risk of IBD flares. Lo *et al.* examined two nested case-control cohorts to explore associations between antibiotic types and IBD flare-ups, defined by steroid use and hospitalization episodes. The study found a significantly increased risk of disease relapse with exposure to quinolones [OR 3.0–3.8], antifungals [OR 1.5–2.3], agents against amoebiasis and protozoal infections [OR 2.0–3.2], intestinal anti-infectives [OR 2.1–2.3], and beta-lactam antibiotics [OR 1.4].[135] Data regarding NSAID use and disease relapse are mixed. Long *et al.* prospectively showed that regular NSAID use was associated with active CD but not UC, although it is difficult to determine if this is due to NSAIDs increasing CD activity or if NSAID use was a marker of sub-optimally controlled disease, i.e. NSAIDs being taken for pain due to active disease.[136] A previous systematic review showed no association between NSAID use and risk of UC or CD exacerbation.[137]

### 6.4. Diet

As well as reducing the risk of CD, the Mediterranean diet may also improve disease course in those with an existing diagnosis of IBD. Studies have shown inverse associations with disease activity and adherence.[85,138–142] Many of the suppositions of the impact of diet and IBD, but not all, have derived from observational studies. Establishing causality with dietary exposures poses unique challenges, which include difficulty quantifying intake and the confounding effect of other environmental factors and behaviours.[143] There is a need for robustly designed large-scale nutritional trials, akin to IBD drug trials, to disentangle disease variation and to accurately assess efficacy of nutritional therapy in adults with IBD. This is essential to address the current limitations of dietary intervention studies.[87]

It is important to recognize the widespread heterogeneity of all studies assessing environmental associations with IBD and that correlation does not equate to causation. Further, the mechanistic reasons behind the associations remain poorly understood. This highlights the need for further carefully designed and high-quality prospective studies to further explore causality and the effect of risk modification to achieve optimal patient outcomes.

## 7. Exposome-based intervention

Optimal study of environmental triggers in IBD requires a means of quantitatively measuring the frequency, duration, and extent of exposures within the critical window of vulnerability in carefully defined cohorts.[144] This involves identifying the signatures of exposure, namely measurable indicators of biological response to environmental factors, and how they relate to changes in biomarkers of disease onset, disease progression and response to therapy, which also need to be identified and qualified.[144]

Increased evidence supports the concept of a preclinical phase in IBD, which precedes clinical diagnosis, during which immune and inflammatory pathways are already altered.[145,146] Primary prevention is defined as prevention of disease development. Targeting the early pathogenic events that promote the development of IBD could prevent or attenuate disease onset and offer a true opportunity for disease modification.[145] One approach to the primary prevention of chronic diseases is via modification of lifestyle and dietary factors. Recently, in a prospective study across six US and European cohorts, a substantial burden of IBD risk may have been prevented through lifestyle modification.[120] The authors constructed modifiable risk scores based on established modifiable risk factors, including body mass index [BMI], smoking status, NSAID use, physical activity, and diet, which explored daily consumption of fruit and vegetables, fibre, n3:n6 polyunsaturated fatty acids [PUFAs], and red meat.[120] The authors highlight that adherence to low-risk factors may have prevented 42.9% of CD and 44.4% of UC cases.[120] Similarly, adherence to a healthy lifestyle may have prevented 61.1% of CD and 42.2% of UC cases.[120] Further prospective interventional studies are needed to determine whether lifestyle modification is effective for the primary prevention of IBD, particularly in high-risk populations and those with younger-onset disease.

Despite advances in the treatment of chronic IBD, induction and maintenance of remission are still difficult to achieve in a substantial proportion of patients. In this context, a growing number of patients choose alternative or complementary approaches to better control their symptoms. Recently, a group of international experts from the International Organization for the Study of Inflammatory Bowel Diseases voted on a series of consensus statements to inform the management of environmental and lifestyle factors in IBD.[147] The recommendations include avoiding traditional cigarette smoking in patients with CD or UC, screening for symptoms of depression, anxiety, and psychosocial stressors at diagnosis and during flares [with referral to mental health professionals when appropriate], and encouraging regular physical activity as tolerated as secondary prevention.[147] Patients using dietary approaches for treatment of their IBD should be encouraged to adopt diets that are best supported by evidence and involve monitoring for the objective resolution of inflammation.[147]

Studies have evaluated the impact of smoking cessation on the course of IBD. Cosnes *et al.* evaluated the benefit of smoking cessation in patients with CD.[130] Repeated counselling to stop smoking, with easy access to a smoking cessation programme, was given to 474 consecutive smokers with CD. Patients who stopped smoking for more than 1 year [quitters] were included in a prospective follow-up study, which compared disease course and therapeutic needs with two control groups, continuing smokers and non-smokers. During a median follow-up of 29 months [1–54 months], the risk of a flare-up in quitters did not differ from that in non-smokers and was lower than in continuing smokers. Need for steroids and for introduction or reinforcement of immunosuppressive therapy, respectively, were similar in quitters and non-smokers and increased in continuing smokers. The risk of surgery was not significantly different in the three groups. In a systematic review, smoking cessation was associated with a 65% reduction in the risk of a relapse as compared with continued smokers in CD.[148] Using nicotine replacement therapy and bupropion, there was an improved chance of success of up to 10%.[148]

Concerning diet, a randomized controlled trial compared exclusive enteral nutrition [EEN] with the CD exclusion diet [CDED], a whole-food diet coupled with partial enteral nutrition [PEN], designed to reduce exposure to dietary components that have adverse effects on the microbiome and intestinal barrier in children with mild to moderate CD.[79] CDED plus PEN was better tolerated than EEN in children with mild to moderate CD. Both diets were effective in inducing remission by week 6. The combination of CDED plus PEN induced sustained remission in a significantly higher proportion of patients than EEN. CDED was also assessed in adults with CD.[88] CDED with or without PEN was effective for induction and maintenance of remission in adults with mild-to-moderate biologic-naive CD.

Most data on the benefits of the complementary approaches are based on observational studies. Clinical trials are needed to evaluate the impact of holistic medicine on the IBD disease course, potentially in combination with drug treatments. Inconsistent efficacies of complementary and alternative medicines in turn could be related to variation in formulations between different brands/producers due to less stringent regulatory aspects as compared with medically approved therapies.[89] In addition, negative publication bias is a prevalent issue in the field of complementary and alternative approaches and can be addressed only by larger systemic changes to the academic ecosystem.[89] Fortunately, a multitude of controlled and uncontrolled trials are currently being performed and will aim to investigate the role of physical activity and dietary therapies in potentially improving quality of life, physical fitness, controlling inflammation, disease prevention, and progression.[89] For example, physical activity and exercise have been suggested to be elements in both the prevention and supplementary treatment of IBD; however, this is based on limited underpowered trials.[92] The IBD-FITT study is an open-label randomized clinical trial investigating the effect of a 12-week exercise intervention in adult patients with moderately active IBD on disease-specific health-related quality of life, disease activity by clinical scoring systems, and biomarkers.[92] This study will include 150 patients allocated to intervention and usual care.[92] The intervention will be based on a 12-week aerobic exercise programme and will include two supervised exercise sessions of 60 min per week, combined with one weekly home training session.[92] These trials may provide a new patient-active disease management approach.

## 8. Conclusion

The effect of exposure to multiple environmental factors could explain the worldwide increase in IBD incidence across the ages. It is expected that in 2030 the prevalence of IBD, CD, and UC will be significantly increasing with some of the highest rates of increase seen within the paediatric and the elderly populations.[60] Studies that seek to elucidate host–environment interactions in IBD and the precise effect of environmental exposures on the pathogenesis and subsequent disease course while considering the background genetic susceptibility remain high on the research priority agenda. The rapidly increasing incidence outside the Western world means that this research should reflect the diversity of ethnicities and geographical populations to better understand disease development in these communities. Longitudinal data obtained from IBD patients prior to or just after a diagnosis and before and after environmental exposure[s] are invaluable. Optimally studying and targeting environmental triggers in IBD may offer future opportunities for disease modification and, ultimately, prevention studies.

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## Author Contributions

BC and SH wrote the article and created figures and tables. LPB supervised the project. All the authors critically reviewed the manuscript content, and the final manuscript was approved by all the authors.

## Data Availability

The data underlying this article are available in the article.

## Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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