Inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC), are chronic debilitating diseases that occur in populations around the world. The diseases can manifest at any age, and therefore represent a clinical challenge for pediatricians, internists, family practitioners, and sur-
geons. The underlying etiology is thought to be multifactorial. There is a well-defined genetic contribution to the diseases, but this does not fully explain the epidemiology. Environmental factors, including the composition of the gut microbiota, are also important. This review will focus on the relationship between IBD and other environmental factors, such as diet, infections, and medications.

**Incidence and Prevalence of IBD**

Studies of the incidence and prevalence of IBD were recently summarized in a review by Cosnes et al. [1]. Within North America, the prevalence of CD is approximately 44–201 per 100,000, with increasing incidence until approximately age 30. Similarly, estimates of the prevalence of UC range from 37.5 to 238 per 100,000, with incidence increasing until approximately age 40. Although early research suggested a bimodal pattern of incidence with a second peak later in life, this has not been consistently observed.

There is wide geographic variability in the incidence and prevalence of IBD. High incidence rates have been observed in the United Kingdom, Northern Europe, Canada, and the United States. The incidence of IBD is generally lower in the Asia-Pacific region, with the exception of Australia [2]. In many regions, there is evidence of increased incidence and prevalence as one moves further from the equator [3]. Similar patterns have been seen with other immune-mediated diseases such as psoriasis and multiple sclerosis [4, 5].

Globally, there is evidence of increasing incidence of CD and UC over time [6]. Furthermore, the rising incidence of IBD in Western countries has generally predated that in developing nations. In general, the incidence of UC has risen before that of CD within any given area. For example, in 2012, the ratio of UC to CD in Asia was 2.0, while in Australia it was 0.5 [2].

The rising incidence of UC and CD across the world, but earlier in developed nations, has contributed to the hypothesis that ‘westernization’ of our lifestyle has led to the increased incidence of IBD. Before focusing on the specific evidence that supports an association between a Western lifestyle and the development of IBD, it is important to consider possible alternative explanations for the geographic patterns that have emerged. The most obvious alternative explanation is that improved access to healthcare and improved diagnostic tools led to more frequent diagnosis of IBD. It is possible that some patients with mild IBD who previously went undiagnosed throughout their entire life are now diagnosed because of greater availability of colonoscopy and cross-sectional imaging modalities. Increased awareness of IBD by clinicians could also contribute to rising incidence rates. Likewise, cultural norms may have evolved in some re-
regions, such that there is greater willingness to discuss one’s bowel symptoms. Each of these could contribute to an apparent increased incidence and prevalence even if there were truly no change in the epidemiology of these diseases.

Arguing against detection bias is the observation that incidence rates of numerous other immune-mediated diseases have also increased in a pattern similar to IBD [7–10]. Diseases such as asthma and psoriasis are diagnosed without the need for invasive or expensive tests. Given the frequent co-occurrence of immunologic diseases, it seems more likely that one or more environmental factors have contributed to the rising incidence rates of all of these diseases [11, 12].

This review will focus on several hypotheses related to the changing epidemiology of IBD, with a specific focus on environmental factors. Although the human gut microbiome can be considered an environmental factor, this will not be addressed in detail in this review, as it is the focus of another chapter in this book. Likewise, the important contribution of genetics to the epidemiology of IBD will not be discussed in detail since this will also be covered in another chapter.

**Emigration**

Some of the regional variation in incidence and prevalence of IBD is likely due to genetic factors. Increased access to care and diagnostic tests could also lead to higher incidence rates in more industrially developed nations. A recent systematic review demonstrated significantly higher incidence rates for both CD and UC among urban populations [13]. The strength of association was greater for CD than UC, although there was significant heterogeneity in each analysis without an obvious explanation. In addition to greater access to healthcare, environmental factors such as diet, pollution, climate, hygiene, and crowding may also contribute to these differences, and would be associated with urban residence.

Studies of people who move between regions of differing IBD incidence and prevalence provide an opportunity to assess the impact of environmental factors on the risk of developing IBD. Several investigators have examined the incidence of IBD within Israel because Jews residing in Western countries are known to have an increased incidence of IBD. In early studies from Israel, immigrants to Israel had higher incidence rates than did Israeli-born populations [14–16]. However, by late 1980s, the incidence and prevalence of CD was comparable among Jews in southern Israel regardless of whether the patient or the patient’s father was born in Israel, Asia, Africa, Europe or America [17]. In contrast, the prevalence was much lower among Arab Israelis, which could be due to genetic or environmental differences since during this time period the Israeli Bedouin population led a lifestyle ‘more characteristic of Third World countries’ [17].
More recent data from Sweden suggest that the incidence of IBD is generally lower in first-generation immigrants, but by the second generation is comparable to that of the Swedish population [18]. Taking advantage of a unique population-based registry, Li et al. [18] observed that the incidence of CD was significantly lower among all first-generation immigrants, and that this was most evident among immigrants from Africa (SIR 0.54, 95% CI: 0.37–0.77), Asia (SIR 0.64, 95% CI: 0.54–0.74), Baltic countries (SIR 0.45, 95% CI: 0.23–0.79) and Latin America (SIR 0.43, 95% CI: 0.28–0.63). Only among those from Latin America was there a significantly lower incidence rate of CD among second-generation immigrants. Generally, similar results were observed for UC, with second generation incidence rates for most immigrants being similar to that of the Swedish population, while second-generation immigrants from southern and Eastern Europe continued to have lower incidence rates. Notably, if both parents were immigrants from the same country, the second generation continued to have a lower incidence of CD. Whether this is due to greater retention of lifestyle customs from the parents’ native land or other reasons is unknown.

Leicester, UK, is home to a large south Asian immigrant population. In the 1990s, the incidence of UC in Leicester was higher among south Asian immigrants than among those of European ancestry [19]. The distribution of disease differed between first- and second-generation immigrants, with proctitis being most common among first-generation immigrants whereas extensive colitis was more common among the second generation. It is likely that the second generation would have assimilated to the Western culture more than their parents, supporting a hypothesis that environmental factors not only influence incidence rates but could also influence disease phenotype.

Dietary differences are often cited as a contributor to the increased incidence of IBD among immigrants from Asia or Africa to Western nations. However, not all studies support this hypothesis. For example, Carr and Mayberry [19] observed that immigrants from south Asia to Leicester, UK, who developed UC were more likely to follow a traditional vegetarian diet than immigrants who did not follow a vegetarian diet.

Barreiro-de Acosta et al. [20] took a different approach to this question by studying people from the Galicia area of Spain where people often emigrate to other countries to find work and then return to Spain at a later time. Patients newly diagnosed with IBD while living in Galicia were more likely to have emigrated to a foreign land and returned than control subjects. Furthermore, the association was qualitatively stronger among those who had emigrated to industrialized European countries (OR 1.91, p = 0.02) than to Latin America (OR 1.48, p = 0.32). The association was somewhat stronger for UC (OR 2.24, p < 0.01)
than for CD (OR 1.56, p = 0.15). These data support the hypothesis that changes in environmental exposures that result from emigration may influence the risk of developing IBD.

The changing incidence of IBD during the last half century has occurred too fast to be attributable to changes in the underlying gene pool. Far more likely is that changes to our environment have led to the ‘epidemic’ of immune-mediated diseases and IBD in particular. That immigrants from low-incidence regions to high-incidence regions typically continue to have lower incidence rates for the first generation but comparable incidence rates to natives of their new home by the second generation suggests that early exposure to environmental factors may be important.

### Obesity and Physical Activity

People living in Western societies are typically less physically active and have easier access to food than our predecessors. This has led to an epidemic of obesity, including childhood obesity. One hypothesis is that the reduced physical activity and subsequent obesity could contribute to increasing incidence rates of IBD. Indeed, prior studies have documented that visceral adipose tissue produces inflammatory cytokines such as tumor necrosis factor-α and that obesity is associated with increased gut permeability [21]. Furthermore, several studies have suggested that obese patients with CD are more likely to undergo surgery [22, 23]. However, evidence linking physical activity and obesity to new-onset IBD is generally lacking. The strongest evidence comes from the European Investigation into Cancer and Nutrition (EPIC) study [24]. This prospective cohort study found no evidence that physical activity, total caloric intake or obesity was associated with new-onset CD or UC. The study included mostly middle-age and older adults, so it is possible that physical activity and obesity could still impact the incidence of these diseases in children.

### Diet and the Risk of IBD

The bowel lumen is continually exposed to numerous antigens, including the food that we consume and the enormous population of organisms that compose the gut microbiome. Although obesity and higher total caloric intake do not appear to increase the risk of IBD, selected micro- and macronutrients, additives, or contaminants could influence the risk through a variety of pathways. Proposed mechanisms through which diet could influence the incidence of IBD in-
clude direct dietary antigens, altering the gut microbiome, influencing gene expression, and affecting gastrointestinal permeability [25].

Our first diet is typically breast milk or infant formula. Breastfeeding is more common in less developed areas where there typically has been a lower incidence of IBD. In addition to secreted immunoglobulins, breast milk contains a number of anti-infective and anti-inflammatory compounds, including caseins, whey proteins, growth factors, and milk fat globule proteins (reviewed in detail by Chatterton [26]). Furthermore, breastfeeding has been shown to alter the composition of the neonatal gut microbiota [27]. Numerous studies have examined the relationship between breastfeeding and the subsequent risk for IBD. A recent meta-analysis observed that breastfed newborns had a lower incidence of childhood onset IBD (pooled odds ratio 0.69, p = 0.02) [28]. Although separate analyses of CD and UC did not identify statistically significant reductions in the incidence, the magnitude of the effect for both diseases was comparable to that observed for IBD. These data support a role for the earliest dietary exposures in the risk of developing IBD.

Lending further support to the role of early diet in the risk for IBD is the observation that even among children, new onset of IBD is uncommon during the first year of life and therefore prior to the introduction of table food [29]. Following the introduction of table food, there is a dramatic alteration in the composition of the gut microbiome [30]. Given the likely important role of the gut microbiome in the etiology of IBD, it is logical that early-life food exposures could also impact the risk for IBD. Unfortunately, data on the relationship between early-life diet and risk for IBD are generally lacking.

Several investigators have examined the association of long-term dietary patterns and the risk of incident IBD [reviewed in 25, 31]. Most recently, the authors of a systematic review came to the conclusions that high dietary intakes of total fats, PUFAs, omega-6 fatty acids, and meat were associated with an increased risk of CD and UC; high fiber and fruit intakes were associated with decreased CD risk, and high vegetable intake was associated with decreased UC risk [31]. These are briefly discussed below.

One of the earliest hypotheses related to sugar intake. Although most studies have been potentially flawed by the challenges of recalling pre-illness dietary patterns and/or failure to account for confounders such as smoking, several investigators have observed associations between sucrose and other sugars and the incidence of CD and UC [32–35]. Subsequent studies have focused on other dietary components. Most studies have found a positive association between dietary protein and both CD and UC, although this was only statistically significant in a few [35, 36]. Numerous studies have also examined fiber, most not identifying an association with new-onset IBD [25]. Fruit intake was significant-
ly associated with a lower incidence of CD in several studies [37, 38], but not in any of 8 studies of UC [reviewed in 31]. Both meat and egg consumption have been associated with UC in several studies [33, 36, 39, 40], but these have generally not been associated with CD [31].

Dietary fat has been examined in multiple observational studies, but a few prospective studies deserve particular notice. The EPIC study collected data on dietary patterns at baseline and identified cases of UC diagnosed at least 18 months after the dietary assessment [41]. Compared to non-IBD patients, those with UC had higher consumption of the n-6 PUFA linoleic acid with evidence of a dose response. Those in the highest quartile of intake had more than a 2-fold increased risk of UC. Linoleic acid is converted to arachidonic acid and incorporated into cell membranes from which they can be released and converted to prostaglandins, leukotrienes, and thromboxanes. Linoleic acid is found in high concentrations in red meat, cooking oils and polyunsaturated margarines. In contrast, high intake of the n-3 PUFA docosahexaenoic acid was inversely associated with new-onset UC. Importantly, the Denmark-EPIC subcohort obtained gluteal adipose biopsies at baseline and were able to measure the n-6 PUFA arachidonic acid in the gluteal adipose tissue. Again, those in the highest quartile had the greatest incidence of subsequent UC (RR = 3.1 with a positive dose response) [42]. This study is particularly important as it used pre-disease tissue levels rather than relying on dietary recalls to assess exposure. Thus, it validated the findings from dietary recalls using pre-disease biomarkers. New data from the Nurses’ Health Study cohorts have partially reproduced the findings of the EPIC cohort [43]. A food frequency questionnaire was used to assess dietary patterns every 4 years, and participants were followed prospectively for 26 years. In this cohort, cumulative energy-adjusted intake of total fat, saturated fats, unsaturated fats, n-6 and n-3 PUFAs was not associated with incident diagnosis of CD or UC. However, greater consumption of long-chain n-3 PUFAs (docosahexaenoic acid, eicosapentaenoic acid, and docosahexaenoic acid) and a higher ratio of n-3:n-6 PUFAs appeared protective against development of UC.

There are a variety of hypotheses as to why a diet low in fiber and high in meat and refined sugars would be associated with an increased incidence of IBD. A high-fiber diet reduces intestinal transit time and therefore reduces the amount of time that the gut mucosa may come in contact with dietary antigens. However, this seems an artificially simple explanation given that over the course of a lifetime, there is extensive exposure of the gut mucosa to dietary antigens, regardless of the composition of the diet. Both CD and UC occur in regions of the gastrointestinal tract with the highest concentration of microorganisms, and the gut microbiome is believed to be a central contributor to the pathogenesis. Long-term diet is associated with alteration in the composition of the gut microbiota,
including bacteria, viruses, microeukaryotes, and archaea [44, 45]. However, it remains unknown what microorganisms are most influential in the etiology of IBD. Interestingly, the prebiotic inulin has been associated with an increase in the abundance of *Faecalibacterium prausnitzii* in 2 studies [46, 47]. *F. prausnitzii* has been associated with reduced relapse rates after ileocolonic resection [48]. Given that after surgery the intestine is temporarily ‘healed’, this raises the hypothesis that insoluble fibers may influence the risk of developing IBD through modulation of the gut microbiota. Diet could also influence the incidence of IBD by altering the composition of fecal bile acids. Fat consumption, particularly meat, leads to greater concentration of secondary bile acids [49]. In animal models, consumption of milk-derived saturated fat leads to the production of taurine-conjugated bile acids, which further leads to an increase in sulphate-reducing bacteria *Bilophila wadsworthia*, which in turn can produce greater amounts of the potentially mucosal toxic hydrogen sulfide and which may directly influence antigen-presenting cells leading to production of inflammatory cytokines [50, 51]. Finally, it is conceivable that the relationship between diet, the gut microbiome, and IBD may be mediated through a metabolic product of the microbiota [52]. A similar model has been proposed for other diseases, such as cardiovascular disease [53]. While data from animal models lend credence to this hypothesis for IBD [52], more definitive evidence in humans is needed.

**Infections and Antibiotic Exposure**

In addition to diet, other factors can influence the composition of the gut microbiome. Antibiotics and enteric infections have been a focus of several studies of risk factors for IBD. Much research has focused on atypical mycobacterial infections (*Mycobacterium avium* subspecies *paratuberculosis*, MAP) given the similarity of CD to Johne’s disease in cattle. Two systematic reviews of these studies observed that patients with CD were more likely than healthy controls or patients with UC to have evidence of prior MAP infection whether assessed by PCR or ELISA [54, 55]. However, several questions remain regarding the causal nature of this association. Most notable is whether CD or the genetics of CD could predispose patients to colonization or infection with MAP [56]. For example, Marks et al. [57] have demonstrated impaired ability of patients with CD to respond to breaches of the mucosa and local infection, which could contribute to granuloma formation. Furthermore, a well-designed clinical trial of long-term treatment with antibiotics targeted at *Mycobacterium* failed to produce long-term changes in the natural history of CD, albeit the participants in this study were not limited to those with documented prior MAP
Interestingly, the proportion achieving remission at week 16 was higher in the antibiotic arm than in the placebo arm, raising questions about the role of antibiotics in managing acute exacerbations of CD.

More recent studies have examined common enteric infections. Among residents of Denmark, those with culture-documented \textit{Salmonella} or \textit{Campylobacter} infection were 2.9 times more likely to be subsequently diagnosed with IBD than a group of matched controls. The association was stronger during the first year of follow-up, but a subsequent diagnosis of IBD remained statistically more common even after excluding the first year [59]. Similar results have been observed in a second cohort from the UK [60], where a culture-documented bacterial gastroenteritis was 1.7 times more common among patients with UC and 3.7 times more common among patients with CD than in nondiseased controls. In a cohort of military personnel, Porter et al. [61] observed that those with documented gastroenteritis were also more likely to be subsequently diagnosed with IBD, with a somewhat stronger association for CD than for UC. These retrospective cohort studies could produce biased results if patients with confirmed infection were more likely to subsequently undergo workup for persistent symptoms after the infection resolved (detection bias) or if patients with clinically undiagnosed IBD tend to develop more severe infections than those without IBD (spectrum bias). Alternatively, it is possible that patients with a genetic predisposition to develop IBD are also more likely to develop enteric infections. Many of the genes associated with an increased risk for IBD control are linked to the innate and adaptive immune response to microorganisms [62, 63]. Thus, enteric infections may be a marker for those at increased risk for IBD without being part of the causal pathway.

Antibiotic exposure has also been associated with an increased risk of developing IBD, particularly CD (table 1). To prevent the risk of recall bias inherent

<table>
<thead>
<tr>
<th>First author</th>
<th>Selected classes</th>
<th>OR (95% CI)</th>
<th>Dose response for any antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Card [64]</td>
<td>cephalosporins</td>
<td>1.30 (0.81–2.09)</td>
<td>no</td>
</tr>
<tr>
<td></td>
<td>broad-spectrum penicillins</td>
<td>1.04 (0.77–1.42)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tetracyclines</td>
<td>1.72 (1.12–2.64)</td>
<td></td>
</tr>
<tr>
<td>Hviid [65]</td>
<td>broad-spectrum penicillins (within 3 months)</td>
<td>3.13 (1.33–7.40)</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>broad-spectrum penicillins (&gt;3 months before)</td>
<td>1.42 (0.67–2.99)</td>
<td></td>
</tr>
<tr>
<td>Kronman [66]</td>
<td>broad-spectrum penicillins</td>
<td>1.72 (1.32–2.24)</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>flouroquinolones</td>
<td>3.70 (2.25–6.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tetracyclines</td>
<td>1.05 (0.65–1.69)</td>
<td></td>
</tr>
<tr>
<td>Margolis [67]</td>
<td>tetracyclines</td>
<td>1.62 (1.04–2.53)</td>
<td>not tested</td>
</tr>
</tbody>
</table>
in asking people to recall their prior antibiotic exposure, several studies have relied on administrative or electronic health record data to define antibiotic exposure [64–68]. These studies have generally observed more frequent antibiotic exposure among patients who were later diagnosed with CD, but no association with subsequent diagnosis of UC (fig. 1). Because early antibiotic exposure may impact the long-term composition of the gut microbiome, several investigators have examined the impact of antibiotic exposure early in life. For example, Shaw et al. [68] observed that the odds of antibiotic exposure in the first year of life was 2.9 times greater among children subsequently diagnosed with IBD than among matched controls. Furthermore, there was evidence of a dose response with a stronger association among those with more courses of antibiotics.

Most studies of antibiotic exposure have focused on short-term use of antibiotics for common infections. Margolis studied the impact of long-term antibiotic exposure among patients with acne. Tetracyclines are the most commonly used antibiotics for acne, and exposure to tetracyclines was associated with a 60% increased incidence of CD but no significant increased incidence of UC. Thus, the association between antibiotic exposure and subsequent risk of CD but not UC appears to be unrelated to the indication for antibiotic therapy. Furthermore, this CD-specific association differs from that observed with prior enteric infections, where infection appears to be associated with both CD and UC.

No specific class of antibiotics has been consistently associated with incident CD (table 1). For example, while both Margolis and Card observed associations with tetracyclines, Kronman did not. Rather, Kronman observed an association with broad-spectrum penicillins, as did Hviid, but only in the first 3 months af-

![Fig. 1. Association of antibiotic exposure with subsequent IBD diagnosis.](image-url)
ter treatment. In contrast, Card observed no association with broad-spectrum penicillins. These inconsistencies potentially provide insight into the underlying biology behind the observed associations with CD. It seems unlikely that the association is related to a specific immunologic property of the antibiotics. One possibility is that the antibiotics alter the gut microbiota in a way that is specific to different populations. For example, the patterns of association were more similar among studies of children [65, 66] and among the studies of older patients [64, 67]. This may reflect a relationship between the risk of developing IBD and the different indications for antibiotics, which may differ by age.

**Other Environmental Exposures of Interest**

**Mode of Delivery**

Much like the data on breast- and formula feeding, Cesarean versus vaginal delivery has been explored as a risk factor for developing IBD. The rate of C-section has increased substantially in recent decades and is known to impact the composition of the neonatal gut microbiota [69]. Vaginal delivery exposes the newborn to maternal vaginal and fecal flora whereas the gut of infants born via C-section is initially colonized with maternal skin flora [70]. Additional differences persist to at least 4 months of age [69]. Recently, Bager et al. [71] found that C-section was associated with a small but significantly increased incidence of IBD. In exploratory analyses, they observed that the increased risk appeared to decline with age and was particularly elevated if the C-section was performed emergently rather than electively. No clear difference in effect was apparent based on whether the mother or father had IBD.

**Appendectomy**

The finding that appendectomy, particularly for acute appendicitis, is associated with lower incidence rates of UC has been highly reproducible [72]. Data on the relation between appendectomy and CD are less consistent. For example, a recent meta-analysis demonstrated that the risk of CD was higher in the first 5 years following appendectomy but no effect was evident beyond 5 years [73]. Furthermore, there was substantial heterogeneity among the studies. The reason for the observed association between appendectomy and incident IBD is unclear. The appendix has been considered by some to be a reservoir for repopulating the gut microbiota if needed. Recent data suggest that the composition of the microbio-
ta within the appendix differs from that in stool. While Firmicutes are the dominant phylum, the appendix contains genera from several phyla that are not routinely found in stool [74]. *Fusobacterium nucleatum* abundance appeared to correlate with severity of inflammation of the appendix [74, 75]. Interestingly, *F. nucleatum* has also been found in patients with IBD [76, 77], thus potentially suggesting a link between appendectomy and UC via the gut microbiota. We have previously observed a borderline association of appendectomy with composition of the gut microbiota based on presence of different bacterial genera but not when accounting for relative abundance [44]. The complex biology of *F. nucleatum* and its interactions with other bacteria in the pathogenesis of gingivitis raises interesting yet complex hypotheses that could explain the strong association of appendectomy status and subsequent risk of developing IBD [78, 79]. Further studies specifically addressing this hypothesis are warranted.

**Sun Exposure and Vitamin D**

As noted previously, the incidence of IBD is higher in areas further from the equator. A potential explanation for this association is lower sun exposure leading to lower levels of vitamin D. Of course, vitamin D stores also depend on dietary intake. In France, people living in areas of high sun exposure have a lower incidence of CD, although the same association was not observed for UC [80]. Sun exposure is only one source of vitamin D. Another group of investigators estimated vitamin D stores based on self-reported dietary intake and sun exposure in the Nurses’ Health Study cohort. Those women with the predicted highest vitamin D levels had lower risks of both CD and UC, although this was not statistically significant for UC [81]. Dietary intake of vitamin D was associated with a reduced risk of UC (10% risk reduction for each 100 IU per day of intake) and a nonsignificant 7% reduction in CD incidence.

**Smoking**

Smoking is perhaps the best studied of the environmental factors, and these studies have yielded some of the most consistent results (table 2) [82–84]. Current smokers have an increased risk of developing new CD and have a worse outcome following surgery than people who never smoke. In contrast, their risk of developing UC is reduced, as long as they continue to smoke. However, former smokers have a higher incidence of UC than people who never smoked. This creates a paradox. If current smoking reduces the incidence of UC, why
would stopping smoking increase the incidence of UC? Surprisingly, little is known about this or why the epidemiology of smoking differs so dramatically between CD and UC. A simple hypothesis is that smoking predisposes to ileal disease and protects against colonic disease [85, 86]. However, the association with ileal CD is not uniform, and many patients with colonic CD are smokers. Granuloma are characteristic of CD, yet among patients with CD, smokers may be less likely to have granuloma than nonsmokers [87]. Interestingly, smoking is less common among patients with sarcoidosis, another granulomatous disease [88]. Some have suggested that smoking contributes to microthrombi which in turn may be part of the pathogenesis of CD. However, the mechanism behind the association is likely more complicated. Timing and mode of delivery of smoke exposure could also be important. Use of smokeless tobacco does not appear to predispose to CD [88], nor does passive smoke in utero or as a child [82].

Some data suggest that the effect of smoking varies among ethnic groups and by age. Lakatos et al. [89] recently demonstrated that the association of current smoking with CD and UC risk may be greater in young adults than in children or the elderly. Interestingly, the association of smoking with CD among Israelis has not been consistent with most other populations [90, 91]. This has led some to hypothesize that smoking may have less of an effect in a genetically high-risk population, although the association has been observed in other high-risk populations such as Sweden. Furthermore, some of the countries with low smoking rates, such as Canada and Sweden, also have the highest incidence of CD [3].

Table 2. Summary of meta-analyses of smoking and IBD

<table>
<thead>
<tr>
<th>Meta-analysis groups</th>
<th>CD Pooled OR</th>
<th>UC Pooled OR</th>
</tr>
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<tbody>
<tr>
<td>Adult current smoker [83]</td>
<td>1.76 (1.40–2.22)</td>
<td>0.58 (0.45–0.75)</td>
</tr>
<tr>
<td>Adult former smoker [83]</td>
<td>1.30 (0.97–1.76)</td>
<td>1.79 (1.37–2.34)</td>
</tr>
<tr>
<td>Childhood passive smoking [82]</td>
<td>1.10 (0.92–1.30)</td>
<td>1.01 (0.85–1.20)</td>
</tr>
<tr>
<td>Prenatal exposure [82]</td>
<td>1.10 (0.67–1.80)</td>
<td>1.11 (0.63–1.97)</td>
</tr>
<tr>
<td>Postoperative smoking – clinical recurrence [84]</td>
<td>2.15 (1.42–3.27)</td>
<td>not applicable</td>
</tr>
<tr>
<td>Postoperative smoking – surgical recurrence [84]</td>
<td>2.30 (1.29–4.08)</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

Conclusions

CD and UC are chronic and often debilitating diseases without a known cure. Understanding the environmental factors associated with the onset of IBD can provide insight into the underlying etiology of these diseases, and perhaps lead to ways to prevent or at least alter the natural history. Given the relatively low inci-
dence of disease, it is generally impractical to consider interventions targeted at the entire population with a goal of preventing disease onset. However, such interventions could be useful in high-risk populations. To that end, there is a need for better ability to identify high risk of populations using genetics and other biomarkers. Smoking, antibiotic use, and diet are potentially reversible risk factors for IBD. Recommendations to avoid smoking are appropriate for all people for numerous reasons. Antibiotic use should be limited to appropriate indications, a recommendation that too is appropriate for all populations. Detangling the relationship between diet, the gut microbiome and IBD raises the potential to reduce the incidence of IBD through dietary modification, an approach that might be considered among those at the highest risk (e.g. children of parents with IBD).

Although much progress has been made in describing the epidemiology of IBD, many questions remain unanswered. For example, why does the incidence of IBD increase with age but plateau after the 3rd or the 4th decade of life? If diet is associated with incidence of IBD, can the risk be altered by dietary modification? Why does smoking have opposite relationships with CD and UC? Are antibiotics directly causal or do the genetic risk factors for IBD increase the risk of enteric and other infections? Breakthroughs in sequencing techniques have allowed substantial advances in our understanding of the genetic and microbial epidemiology of IBD. Additional breakthroughs in related fields can be expected in the next decade. Because of the increasing complexity of the science, major breakthroughs will likely require close collaboration of population epidemiologists, nutritional epidemiologists, geneticists, microbiologists, immunologists, and mucosal biologists.

Disclosure Statement

Dr. Lewis has served as a consultant for Takeda, Rebiotix, Amgen, Millennium Pharmaceuticals, Prometheus, Lilly, Shire, AstraZeneca, Janssen Pharmaceuticals, Merck, MedImmune, and AbbVie. He has served on a Data and Safety Monitoring Board for clinical trials sponsored by Pfizer. He has received research support from Bayer, Shire, Centocor, Nestle, and Takeda.

References


60 Garcia Rodriguez LA, Ruigomez A, Panes J: Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. Gastroenterology 2006;130:1588–1594.


