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REVIEW ARTICLE

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Implications of the changing epidemiology of inflammatory bowel disease in a changing world

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Abstract

The epidemiology of inflammatory bowel disease (IBD) has undergone considerable shifts since its emergence in the Western world over a century ago, especially in the last few decades, with increasing global burden of disease. IBD incidence continues to rise in developed countries in all age groups which is contributing to compounding prevalence. Further, IBD incidence is rising sharply in Asia and other recently developed and developing countries. In this review, we discuss the implications of changing trends of IBD epidemiology. First, changing patterns provide insights into IBD causes, as they occur concurrent with shifts in the environment, cultures, and attitudes. Understanding the impact of the environment on IBD risk can help towards prediction and prevention strategies. Second, we must prepare healthcare systems for the rising burden of IBD and address it at various levels towards improving outcomes and health, overall.

KEYWORDS
Crohn's disease, epidemiology, inflammatory bowel disease, prevention, ulcerative colitis

INTRODUCTION

The epidemiology of inflammatory bowel disease (IBD) has undergone considerable shifts since its emergence in the Western world over a century ago.[1,2] IBD incidence is sharply increasing in developing and recently developed countries. IBD incidence continues to rise in developed countries among children and older age groups, which is contributing to compounding prevalence.[3–5] Previously believed to be a disease of children and young adults, IBD is increasingly being reported in older individuals and the elderly.[5] Further, IBD incidence is rising at an alarming rate in recently developed and developing countries.[2]

In this review, we discuss the implications of changing trends of IBD epidemiology. First, these patterns provide insights into IBD causes as they occur concurrent with shifts in the environment, cultures, and attitudes. Second, we must prepare for the rising burden of IBD and address it at various levels, guided by the principles of disease prevention.

UNDERSTANDING NONGENETIC IBD RISK FACTORS

IBD causality has been a subject of immense research over the last decades paving the way for insights into IBD pathogenesis. Genome

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wide association study have identified important polymorphisms towards IBD risk.[6] However, there is marked heterogeneity in risk variants across populations and limited concordance within families, including between monozygotic twins.[7,8] The rise of IBD has been in parallel with industrialization and major shifts in the environment.[2,9] Immigration from a developing country to a western country is associated with an increase in the risk of IBD and other immune mediated diseases.[10,11] These indirect data corroborate the role of nongenetic factors towards IBD. Here, we categorize them into factors pertaining to the environment, lifestyle, and health (Figure 1).

The environment

Traditional epidemiological studies leveraging questionnaire and register data have been informative in understanding individual-level risk factors, but a study of more ubiquitous environmental exposures has become possible only recently, when advanced and innovative analytical techniques came to the forefront. Geographic information system leverages geographic data, obtained via satellites, to quantify environmental variables such as specific pollutants, greenspace, and biodiversity. These variables, transformed into indices, can be measured by location and time, leading to a quantification of the dose and duration of these exposures and modeling of outcomes as a function of these factors.

Leveraging GIS data, in a population-based study from Ontario, early life exposure to pollution (reactive oxygen species) was associated with later risk of IBD.[12] Residential green space during the early life period was found to be protective against IBD in a dose-dependent manner.[13] These data are consistent with other reports on the protective effect of greenspace on health and mortality.[14–16] Relatedly, blue space, a measure of water bodies, was protective against IBD in an analysis of the UK Biobank data.[17] The mechanisms through which environmental health may be causally related to human health are not well-elucidated, but improved immune tolerance, lower stress levels, improved diet and physical activity and lower exposure to pollutants may be some potential mechanisms. Certainly, various chemicals, ubiquitous in the urban world, are linked with downstream risk of adverse health outcomes.[18] For example, per- and polyfluoroalkyl substances (PFAS) are endocrine disruptive chemical ubiquitous and long-lasting in the environment implicated in many diseases.[19] PFAS may also have a role in IBD, although data are conflicting.[20,21] Heavy metals are also important health mediators of disease. In a pilot study, on mass spectrometric analysis of deciduous teeth, prenatal lead exposure was associated with future risk of IBD.[22]

Lifestyle

Urbanization and cultural shifts have led to vast changes in diet, habits, activity, and stress. Chronic disease states, including IBD, parallel these shifts. Here, we discuss the lifestyle factors that are most consistently linked with IBD.

Breastfeeding influences offspring immune modulation, microbiome establishment, and risk of many chronic diseases later in life. In a systematic review of 35 epidemiological studies, being breastfed was associated with a protective effect against CD and UC (OR 0.71, 95% CI 0.59, 0.85 and 0.78, 0.67, 0.91, respectively) in a dose dependent manner, and across populations.[23] Mechanistic data further corroborate this association; for example, human milk oligosaccharides, modulate offspring gut microbiome and mucosal immune maturation.[24] In addition, formula feeds, the typical alternative to breastfeeding, contain emulsifiers and other synthetic molecules, which are implicated in intestinal inflammation and host-microbe interactions.[25,26]

Recent data have substantiated the role of modern and urban diets in IBD. In a prospective cohort from 21 countries including 116,087 individuals, consumption of ultra-processed foods was associated with incident IBD in a dose dependent manner (HR 1.82, 95% CI 1.22, 2.72 for ≥5 servings/day compared to <1 serving/day, p_{trend} = 0.006).[27] Data from the Nurses' Health Study corroborated

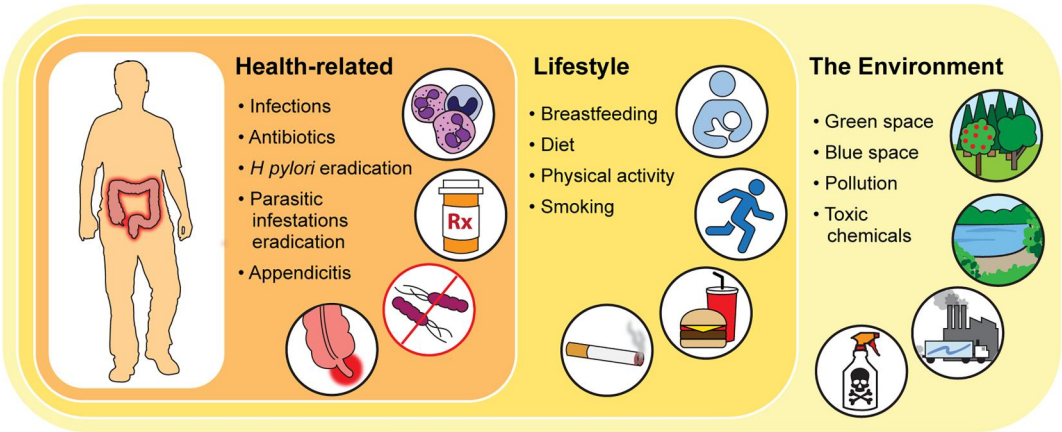

FIGURE 1 Environmental, lifestyle and health-related risk factors implicated in IBD risk. IBD, inflammatory bowel disease

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these findings.[28] Mechanistic data add further support; synthetic emulsifiers, such as carboxymethycellulose and polysorbate-80, are implicated in disrupting the intestinal mucosal barrier in mice as well as in humans in a pilot clinical trial.[25,29] Food coloring agents, for example, Red 40 and Yellow 6, have been linked with intestinal inflammation in mice models with augmented IL-23 expression.[26] Conversely, Mediterranean diet, which is rich in naturally-sourced and wholesome foods such as vegetables, fruits, fish and nuts, was protective against CD in a Swedish cohort (p_{trend} = 0.03).[30] Dietary factors have significant downstream metabolic implications.[31]

Next, smoking is associated with CD risk, disease progression, and reduced response to biologics.[32,33] In the context of UC, the data are less clear. Prenatal exposure to smoke has been linked with offspring IBD risk in multiple studies.[34–36] Smoking later in childhood also increases the risk of both CD and UC.[36] The effect of smoking on IBD risk is likely to be mediated through epigenetic alterations, at least in part. Certainly, there are indirect lines of evidence to support this. Smoking is a strong risk factor for downstream DNA methylation changes.[37,38] These are, in turn, implicated in IBD risk.[39,40]

Other lifestyle factors such as stress, anxiety, and lack of physical activity, which are ingrained in the modern and urban society, are also implicated in IBD risk. In a Nurses' Health Cohort of over 3 million person years follow up physical activity was associated with a protective effect against CD (p_{trend} = 0.02).[41] Whether these risk factors may themselves be causal, or a surrogate for other exposures, is yet to be teased out.

Health-related

Infections have been implicated in IBD risk across studies.[42,43] In particular, gastrointestinal bacterial infections such as Salmonella and Campylobacter species have been associated with IBD; however detection bias is likely to play a role in this association.[44,45] Conversely, *Helicobacter pylori* may have a protective role against IBD. In a Taiwanese study, H. pylori eradication, after adjusting for antibiotic use, was associated with increased risk of immune mediated diseases, including IBD.[46] This may be potentially mediated by a direct tolerogenic effect, or an indirect effect via regulation of the gut microbiome and mucosal homeostasis.[47,48] These data emphasize "the hygiene hypothesis" which refers to altered immune tolerance with improving hygiene.[49]

Antibiotic use across all age groups has been linked with an increased risk of IBD in a dose-dependent manner. In a population-based cohort study, we reported that ≥3, but not fewer, courses of antibiotics during pregnancy increased UC risk in the offspring by 45% (aHR 1.45, 95% CI 1.06, 2.00).[50] Consistent findings were reported in a nested case-control study of an Italian birth cohort.[51] Increasing number of antibiotics courses also increase IBD risk among those ≥60 years of age.[52] Broad-spectrum antibiotics may lead to greater risk compared to narrow-spectrum antibiotics.[53] These data implicate antibiotic-mediated gut microbiome disruption in IBD pathogenesis.[54] In a recent population-based study, early life exposure to mebendazole, a broad spectrum antihelminthic agent, was associated with a 32% increased risk of adult-onset UC (aHR 1.33, 95% CI 1.13, 1.56), but not CD.[55]

Appendicitis and appendectomy have been implicated in IBD risk. In a Swedish cohort study, appendectomy at age <20 years for appendicitis or mesenteric lymphadenitis was associated with a lower risk of UC.[56] Similar results were reported upon combining data from Swedish and Danish registers.[57] Interestingly, in a Danish cohort study of familial units, individuals with first-degree relatives with appendicitis, but not own history of appendicitis, at age <20 years had a lower risk of UC. This risk was even lower in those with family history of UC.[58] These data bring into question the role of appendicitis, including shared risk factors for appendicitis, rather than appendectomy, in modulating IBD risk. Further, appendicitis and appendectomy are also reported to modulate UC course.[59]

Timing of exposure: The early life period versus later in life

Additional important considerations are the timing of exposure as well as the timing of disease onset. The early life period, which extends from the prenatal period to early childhood, is a critical window for immune development and microbiome establishment, and exposures during this period confer a long-lasting effect on the offspring.[60,61] This hypothesis, known as the Developmental Origins of Health and Disease, is relevant to IBD. Many of the exposures described above are operative during the early life period.[42,50] Conversely, older onset IBD may have different underlying mechanisms, for example, age related immune senescence.[62]

RESPONSE TO THE RISING IBD BURDEN

IBD is a life course disease, often occurs in children and young adults, and it has no cure. It is associated with complications such as infections, hospitalizations, surgeries, and cancer.[63,64] IBD leads to adverse impact on mental health and on disability.[65,66] The management of IBD involves long-term use of biologics and small molecules, and complex surgeries, each of which incurs substantial healthcare costs. The direct healthcare costs attributed to an IBD patient are estimated to be three times those attributed to a non-IBD patient, and with increasing trends over the years.[67] Further, IBD is associated with indirect societal costs which can be more occult and pervasive.[68]

As the incidence and prevalence of IBD continue to rise, including and especially in developing countries, the urgency to prepare healthcare systems and mitigate its impact cannot be overstated. Strategies towards IBD prediction and prevention are important in the larger public health and economic context. Here, we can apply the principles of disease prevention, analogous to what is done in other chronic diseases such as diabetes and cardiovascular disease, to manage the impact of IBD.[69] Such preventive strategies

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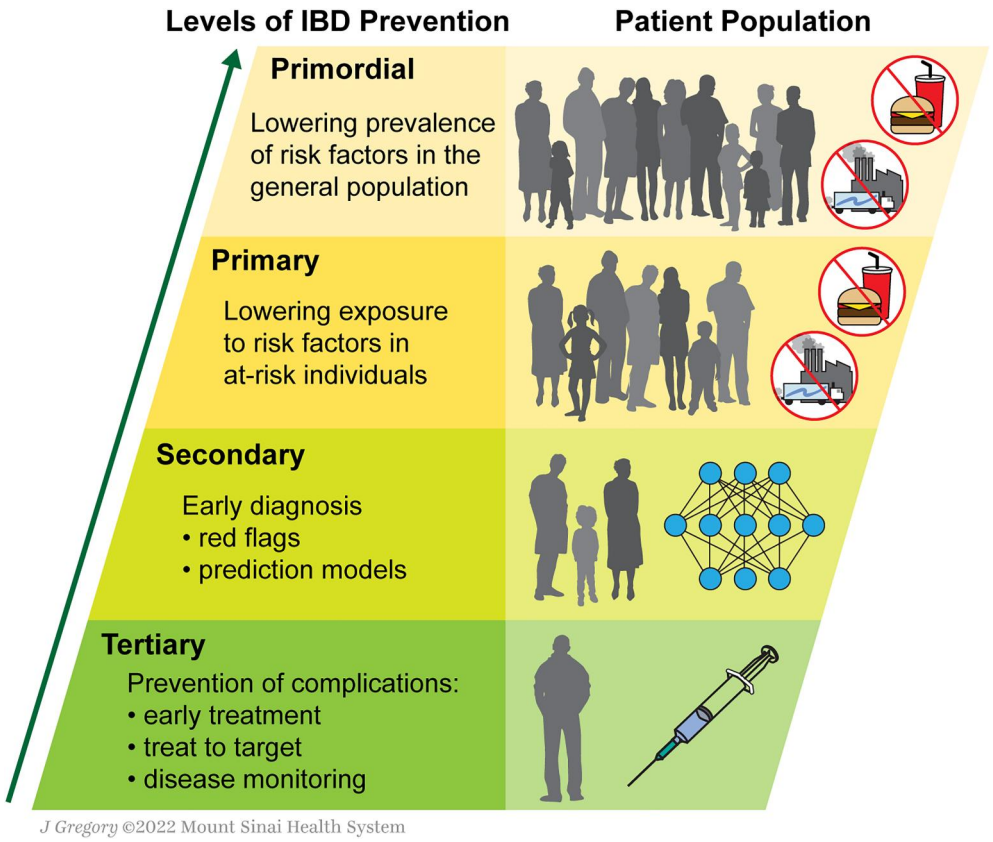

FIGURE 2 Levels of IBD prevention. IBD, inflammatory bowel disease

are also relevant to other immune mediated diseases, which have significant overlap during the preclinical phase.[70] We lead the discussion with tertiary prevention, a goal that is largely achieved, and move towards primordial prevention, which we aspire to achieve (Figure 2).

Tertiary prevention: Early IBD treatment

Robust data demonstrate that early treatment of IBD is critical to prevent complications. In a meta-analysis of CD clinical trials and real world data, treatment with biologics within 2 years of diagnosis was associated with higher rates of remission and mucosal healing compared to late or non-biologic treatment.[71] Treat-to-target is a key concept in IBD; the STRIDE2 guidelines advocate to strive for clinical, endoscopic and biomarker remission in CD and UC.[72] In the long-term follow up data from the CALM trial, patients with recently-diagnosed CD who achieved deep remission at 1 year had a lower risk of disease progression compared to patients who did not.[73] Like CD, UC is also a progressive disease; while data on long-term outcomes with early therapy are lacking, it is reasonable to institute early and adequate treatment to lower the risk of colectomy and colorectal cancer.[74] IBD in older individuals warrants additional considerations around frailty, comorbid conditions, and medications interactions.[75]

Secondary prevention: Early IBD diagnosis

Early diagnosis, an indispensable step towards early treatment, is highly relevant in the context of IBD. CD can be associated with varied and nonspecific symptoms, thereby leading to delay in diagnosis. In a Swiss cohort of IBD patients, adults with delay in CD diagnosis were more likely to present with strictures, fistulas and other complications.[76] Similarly, in data from France, delay in CD diagnosis by 13 months or longer was associated with an increased risk of surgery.[77] In order to minimize delay in diagnosis, Danese et al developed the Red Flag Index, a questionnaire of relevant signs and symptoms.[78] This, in combination with fecal calprotectin, has been validated as a tool for early CD diagnosis.[79]

Primary prevention: Decreasing IBD risk among at risk individuals

Primary prevention implies decreasing risk among at risk individuals thereby preventing the onset of disease. Genetic risk for IBD, represented by family history of IBD, particularly among first degree relatives, is considered one of the strongest risk factors for IBD.[80] Individuals with immune-mediated diseases such as lupus, rheumatoid arthritis and ankylosing spondylitis are at risk for IBD.[81] Parental history of an immune-mediated disease is also a risk factor for IBD.[82]

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Preclinical IBD, a period of immune dysfunction and microbiome perturbations at a subclinical level also represents the "at risk" state.[83] The Genetics, Environment, and Microbiome study has demonstrated that increased intestinal permeability among FDRs of individuals with CD is associated with increased risk of CD (HR 3.03, 95% CI, 1.64, 5.63) as long as 3 years prior to CD diagnosis.[84] In a pilot study of 13 individuals, the group identified a microbiome signature detectable via increased fecal proteolytic and elastase activity predictive of UC onset.[85] In a proteomic analysis of serum samples from military recruits, the PREDICTS (Proteomic Evaluation and Discovery in an IBD Cohort of Tri-Service Subjects) study identified that signatures pertaining to antimicrobial antigens, complement cascade, innate immunity, and glycosaminoglycan and lysosome metabolism up to 5 years prior to CD onset (areas under the receiver operating characteristic curve: 0.76 and 0.86, 5 years and 1 year before diagnosis, respectively).[86] Further, anti-granulocyte macrophage-colony stimulating factor antibodies predicted CD diagnosis, as well as complicated disease course.[87] These and other ongoing works are key to characterize preclinical IBD towards prediction and prevention.

The next step in primary prevention is to identify an intervention to prevent IBD onset in at risk individuals. Key features of such an intervention would be safety, effectiveness, and ease of administration. While these are early data, orally administered phage therapy targeting pathogenic *Klebsiella pneumoniae* strains attenuated inflammation in IBD models and were safe in healthy volunteers.[88] Further research in this area is eagerly awaited.

Primordial prevention: Decreasing prevalence of risk factors

Finally, the overarching goal would be to apply the principles of prevention to the general population and work towards decreasing the prevalence of risk factors for IBD and other chronic diseases. Towards that goal, we must take steps towards environmental justice, such as restricting fossil fuels use, minimizing pollution, implementing sustainable practice, and fighting climate change. These efforts are needed at individual, societal, country, and global levels. Relatedly, lifestyle changes such as healthful diets, minimizing intake of processed foods, avoiding smoking, and spending time in nature would be considerations, not only in the context of IBD, but also towards improving health overall.

CONCLUSION

In summary, the evolving epidemiology of IBD on a global scale provides important insights into IBD risk and pathogenesis. Environmental health is closely linked to IBD risk and outcomes, as is the case with other chronic diseases. As the burden of IBD changes, we must prepare healthcare systems globally to mitigate its impact through early diagnosis and early treatment. We are making strides in our vision of IBD prediction and prevention.

AUTHOR CONTRIBUTIONS

Manasi Agrawal: concept, literature search, drafting of manuscript and critical revision of the manuscript for important intellectual content; Tine Jess: concept, drafting of manuscript and critical revision of the manuscript for important intellectual content.

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CONFLICT OF INTEREST

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated. MA reports no conflict of interest. TJ reports no conflict of interest.

DATA AVAILABILITY STATEMENT

A data availability statement is not applicable here as this paper includes no original data.

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