

What Is the Role of the Environment (Exposome) in Inflammatory Bowel Disease?

Carlotta Zennaro

Editorial Assistant

Citation: EMJ Gastroenterol. 2022;11[Suppl 1]:20-22. DOI/10.33590/emjgastroenterol/22F0317-2. <https://doi.org/10.33590/emjgastroenterol/22F0317-2>



OPENING Day 2 of the 17th Congress of European Crohn's and Colitis Organisation (ECCO), James Lindsay, Professor of Inflammatory Bowel Disease, Barts Health NHS Trust, London, UK, and The London School of Medicine, Queen Mary University of London, UK, discussed the influence of the environment on the risk of developing inflammatory bowel disease (IBD). The presentation discussed the pathways that mediate environmental impact on IBD as well as the limitations of presently available research, giving a valuable insight into what future studies could be conducted to ultimately determine the role of environmental factors in IBD.

The present understanding of IBD, an inflammatory disease, which includes Crohn's disease (CD) and ulcerative colitis (UC), is that the condition arises from an immune response to micro-organisms of the intestinal flora in genetically susceptible individuals. In addition to disease pathogenesis, other important aspects such as progression, extraintestinal manifestations, and immunogenicity to therapies, are yet to be well understood. While the genetics base is clear, it does not account for the discordance of disease in monozygotic twins, the increased incidence in second generation immigrants, or the rapid increase in IBD cases in the last 50 years. In light of these observations, Lindsay expressed the importance of examining the role of the environment, which, he stressed,

does not comprise a single factor, but a multitude of factors that are likely to impact disease onset and natural history.

INFLUENCE OF ENVIRONMENTAL EXPOSURE ON DISEASE ONSET

Lindsay presented a range of epidemiological studies that have proven fundamental when examining the impact of environmental factors on disease onset. An umbrella review, which examined over 71 environmental factors in 53 separate meta-analyses, found that breastfeeding had a protective effect on both CD and UC.¹ Additionally, Lindsay shared the findings of a study assessing the effect of



"An interesting new report revealed that antibiotic exposure over time might change the risk of developing antidrug antibodies with anti-TNF therapy in animal models, displaying a clear link between environment and disease natural history."

ultra-processed foods consumption in a cohort of nurses. In a total of 245,112 participants, there was incidence of both CD (369 cases) and UC (488 cases), with a median age of onset of 56 years, demonstrating that the intake of ultra-processed food was associated with an increased risk of incident CD but not UC, when corrected for a range of confounding factors.² The presentation also included an overview of a mechanistic introductory research that examined the dietary intake of foods linked to markers of inflammation. Such foods, termed empirical dietary inflammatory pattern (EDIP) foods were linked to an increased risk of CD.³ Lindsay highlighted the significance of the study in demonstrating the effect of dietary changes: individuals who started with a low intake of EDIP foods but moved to a high intake of EDIP foods had the same risk of developing CD as those who always had a high intake of high EDIP foods.

Despite the obvious value of epidemiological studies, Lindsay emphasised the importance of recognising their limitations and having a solid understanding of the methodologies used. Firstly, timing is essential when analysing results. For instance, the positive effect of breastfeeding is not observed in a cohort with an average age of >30; however, in a cohort of children, such protective effect is evident.⁴ Secondly,

Lindsay said that definitions are pivotal. This is particularly obvious when analysing diet as an impact factor, particularly regarding the ability of questionnaires to define ultra-processed foods versus other refined foods.

PATHWAYS LINK EXPOSOME TO DISEASE AETIOLOGY AND NATURAL HISTORY

The determination of the mechanistic pathways that might drive the impact on the mucosal immune system is critical. Lindsay suggested such pathways would include changes in intestinal permeability, signalling through “environmental sensors,” and modifying the epigenetic control of gene transcription.

It is widely known that factors such as pregnancy, breastfeeding, and diet influence disease through changes in the microbiota. However, this begs the question of whether such changes are a causative factor or a result of disease. One of the largest sibling cohort studies, involving thousands of siblings of patients with CD followed up over time, looked to address this question. The results showed that people who subsequently developed CD were more likely to have antimicrobial antigens.⁵ This result highlighted the role of alterations in intestinal microbiota

“Environmental exposure has a major impact on the risk of developing IBD. There are well-defined pathways that mediate this impact.”

prior to disease onset, suggesting an aetiological impact. The study also emphasised the effect of permeability changes in disease onset: patients who had increased gut permeability and siblings who had increased gut permeability were significantly more likely to develop disease than those who did not.

There might also be environmental factors that have an impact on the mucosal immune system, independently to gut microbiota. There are many environmental sensing molecules, of which the most well described is the aryl hydrocarbon receptor (AHR), which has a range of ligands present in our diets. The presence of these AHR ligands is associated with protective immune responses, including protective intraepithelial lymphocytes and innate lymphoid cells. Research in animal models demonstrates that mice deficient in AHR develop more severe disease and that mice fed an AHR ligand-free diet also develop more severe IBD.⁶

A large study looking at modifications in the epigenome of patients with IBD compared with controls showed the effect of methylation on disease onset. The report found that IBD-associated hypermethylation in a key promoter (*TXK*) region negatively correlates with gene expression in cluster of differentiation 8+ T cells, which subsequently drives disease.⁷

IMPACT OF EXPOSOME ON NATURAL HISTORY OF INFLAMMATORY BOWEL DISEASE

According to Lindsay, the impact of the exposome on IBD natural history is much harder to investigate due to the debate of cause versus association. The best studied factor that influences natural history of disease is smoking. Smoking increases the risk of a CD flare, increases risk of first surgery, and increases risk of disease recurrence after first surgery. On the contrary, quitting smoking improves the outcomes from the perspective of inflammatory

flares and risk of subsequent surgeries. An interesting new report revealed that antibiotic exposure over time might change the risk of developing antidrug antibodies with anti-TNF therapy in animal models, displaying a clear link between environment and disease natural history.⁸

In his closing remarks, Lindsay explained that: “Environmental exposure has a major impact on the risk of developing IBD. There are well-defined pathways that mediate this impact.” However, special attention needs to be paid to the evaluation of epidemiological studies to understand the exact methodology and whether the results are pointing to cause or association. According to Lindsay: “It will be through robust intervention studies that we will get the assessment of the true impact of the exposome.” ■

References

1. Piovani D et al. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology*. 2019;157(3):647-59.e4.
2. Lo C-H et al. Ultra-processed foods and risk of Crohn's disease and ulcerative colitis: a prospective cohort study. *Clin Gastroenterol Hepatol*. 2021;DOI:10.1016/j.cgh.2021.08.031.
3. Lo C-H et al. Dietary inflammatory potential and risk of Crohn's disease and ulcerative colitis. *Gastroenterology*. 2020;159(3):873-83.e1.
4. Barclay AR et al. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *J Pediatr*. 2009;155(3):421-6.
5. Lee S-H et al. Anti-microbial antibody response is associated with future onset of Crohn's disease independent of biomarkers of altered gut barrier function, subclinical inflammation, and genetic risk. *Gastroenterology*. 2021;161(5):1540-51.
6. Li Y et al. Exogenous stimuli maintain intraepithelial lymphocytes via aryl hydrocarbon receptor activation. *Cell*. 2011;147(3):629-40.
7. Ventham NT et al.; IBD BIOM Consortium, IBD CHARACTER Consortium. Integrative epigenome-wide analysis demonstrates that DNA methylation may mediate genetic risk in inflammatory bowel disease. *Nat Commun*. 2016;7:13507.
8. Gorelik Y et al. Antibiotic use differentially affects the risk of anti-drug antibody formation during anti-TNF α therapy in inflammatory bowel disease patients: a report from the epi-IIRN. *Gut*. 2022;71(2):287-95.