# Defining gene–lifestyle interactions in inflammatory bowel disease

**Letter: Modifiable lifestyle factors for the prevention of inflammatory bowel disease**

**Authors:** Jianhui Zhao[1*], Jie Chen[1*], Yuhao Sun[1], Shuai Yuan[2], Judith Wellens[3,4], Rahul Kalla[5], Evropi Theodoratou[6,7], Xue Li[1], Jack Satsangi[3]

[1] Department of Big Data in Health Science School of Public Health, and Center of Clinical Big Data and Analytics of The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

[2] Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

[3] Translational Gastroenterology Unit, Nuffield Department of Medicine, Experimental Medicine Division, University of Oxford, John Radcliffe Hospital, Oxford, UK

[4] KU Leuven Department of Chronic Diseases and Metabolism, Translational Research Center for Gastrointestinal Disorders (TARGID), Leuven, Belgium

[5] Edinburgh IBD Science Unit, Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK

[6] Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK.

[7] Cancer Research UK Edinburgh Centre, Medical Research Council Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK.

*Joint first authors. Correspondence to: Xue Li, xueli157@zju.edu.cn

Recently, Lopes *et al* quantified the effect of modifiable lifestyle factors in inflammatory bowel diseases (IBD) prevention using population attributable risk (PAR), and reported that 42.9% of Crohn's disease (CD) cases and 44.4% of ulcerative colitis (UC) cases could have been prevented by lifestyle interventions. This interesting result was based on six prospective cohorts including three US cohorts with 208,070 participants and three large European cohorts that were used for validation [1]. Undoubtedly, this well-performed study illustrates the possible merits of lifestyle modification as a prevention strategy for IBD.

However, we would like to argue that lifestyle modification as such cannot be uncoupled from the genetic background. Although the importance of genetic susceptibility in the development of IBD is widely accepted [2], this was unfortunately not assessed in Lopes et al 's study. We recently conducted a prospective cohort study on the UK Biobank in >450,000 individuals, and found that genetic risk and unhealthy lifestyle categories were independently associated with CD and UC risk without evidence of multiplicative interaction[3]. This indicated that over a 12-year period, individuals with the highest genetic risk and an unhealthy lifestyle had a probability of developing CD and UC that was approximately five times higher than those with the lowest genetic risk and a healthy lifestyle. Moreover, a heathy lifestyle was shown to some extent to mitigate against high genetic risk. This research presents evidence for genetically stratifying the risk of IBD and advocates for multimodal lifestyle modifications aimed at the highest genetic risk patients to prevent IBD.

Interestingly, both Lopes et al and Sun et al have shown that diet constitutes a significant risk factor in the development of IBD. Fruit and vegetables, fibre, red meat and n3:n6 polyunsaturated fatty acids (PUFAs) were considered to be important factors with regard to IBD risk in the study of Lopes *et al* throughout a detailed literature review[1]. Indeed, our study reveals that adherence to a healthy diet could have prevented 6.32% of CD and 4.68% of UC cases[3]. However, due to variations in dietary patterns across regions and the diverse ingredients in foods, the complexity of the relationship between diet and the development of IBD cannot be underestimated. Although no interaction between genetic risk and general unhealthy lifestyle was observed in our study, an increasing amount of evidence indicates that diet may play a significant role in the development of IBD, especially in individuals who are genetically predisposed to the condition[4]. Research that examines the interplay between diet and genetically-influenced variations in functionally-annotated genes offers

valuable information about potential biological pathways that could explain how diet plays a role in the development and progression of IBD. For example, Khalili et al. reported that amidst women carrying the GG genotype and TT genotype of rs1801274 in the *FCGR2A* gene, a significant decrease and increase in the risk of UC was observed with an increase in heme iron intake, respectively [5]. Besides, our recent study found that intake of ultra-processed foods (UPFs) is associated with higher incidence of CD after correcting for several confounding factors (including genetic risk), but not with UC [6]. Although the mechanisms of this phenomenon are still unclear, gene–diet interaction analyses might contribute to elucidate potential biological mechanisms underpinning the association between diet, genetics and IBD as well as pave the way towards precision nutrition [7].

In conclusion, we agree that modifiable lifestyle factors and genetic factors are likely to provide new insights into the development and prevention of IBD. However, further efforts are needed to identify and validate the interaction between dietary ingredients and genetic variants to gain a more comprehensive understanding of the relationship between IBD and diet. Additionally, analyses for specific ingredients of food based on genetically-influenced variations and dietary patterns can help delineate subgroups of individual who are most likely to benefit from nutritional interventions.

## Reference


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