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Environmental protective and risk factors in an at-risk population of subsequent Crohn's Disease

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Title page:

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CCC GEM, Crohn's and Colitis Canada Genetic, Environmental, Microbial; CD, Crohn's disease; DC, dietary clusters; FCP, fecal calprotectin; OmpC, anti - Escherichia coli outer membrane porin C

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Authors' contributions:

DN: conceptualization, writing – original draft, writing – review & editing

FF: writing – review & editing, supervision

FC: conceptualization, writing – review & editing, supervision

Dear Editors,

We read with great interest the article by Turpin et al. [1] who evaluated whether long-term dietary clusters (DC) were associated with gut microbiome compositions as well as gut inflammation assessed by fecal calprotectin (FCP) in a cohort of healthy first-degree relatives of Crohn's disease (CD) patients. They found that DC3 resembling the Mediterranean diet was associated with 1) a lower abundance of Ruminococcus, Dorea, and Campylobacter and an increase of Faecalibacterium and 2) a lower proportion of individuals with increased FCP at both cutoffs of 100 and 250μg/g. Undoubtedly, this study provided important evidence for the role of diet and gut microbiome in at-risk populations. However, as this study is part of the Crohn's and Colitis Canada Genetic, Environmental, Microbial (CCC GEM) Project the following issues are worth further analysis.

First, as certain Western dietary components have been associated with increased risk of CD [2, 3] and DC1 resembles the Western diet it would be interesting to investigate whether this association is also confirmed in a population already at risk.

Second, as antibiotics can alter the composition of the human gut microbiota [4], antibiotic-associated dysbiosis affects the ability of the gut microbiota to control intestinal inflammation upon fecal microbiota transplantation in experimental colitis models [5] and exposure to antibiotics increases the risk of subsequent CD [6] it would be useful to account in the analysis for the potential confounding effects of exposure to antibiotics.

Third, smoking is a well-recognized risk factor for CD [6] and it is associated with gut microbiota composition alterations [7]. Similarly to antibiotics, it would be worthwhile considering smoking as a potential confounder.

Fourth, Lee et al. previously reported from the CCC GEM cohort that the presence, more than 3 years before diagnosis, of 2 or more antibodies against microbial antigens (anti-

Saccharomyces cerevisiae, anti-OmpC, anti-A4-Fla2, anti-FlaX, anti-CBir1) was associated with a higher risk of developing CD. Interestingly, this association remained significant even after adjusting for potential confounders like FCP, gut barrier function, C- reactive protein, and CD-polygenic risk score. [8] It would be interesting to assess whether there is a significantly different prevalence of antibodies against microbial antigens in DC1 compared to DC2 and DC3 after adjusting for FCP. It is noteworthy that DC3 on FCP and high antibodies on CD development resulted in similar (47% vs 42%) percentages of the total effect in the causal mediation analysis.

Finally, congratulations to the Author's team for the intense work required to carry out such a cohort. CCC GEM will certainly contribute to understanding the preclinical and early stages of CD.

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