

Dear Editor:

Thank you for consideration of our review article regarding the interactions between obesity and IBD. We hope we have addressed the concerns of our reviewers, as noted below:

Regarding reviewer 01574245's comments:

The language polishing that was noted has been corrected. Thank you for pointing this out. We removed several paragraphs from the pharmacology section that we agree were not particularly germane (having to do with pharmacokinetics), and we also removed all of the rodent studies mentioned in the section concerning adipokines.

Regarding reviewer 00036825's comments, we added a paragraph regarding some interactions between diabetes and IBD, as we agree that information is interesting in the context of the overall theme of this review. Regarding this reviewer's suggestion to add information about dietary factors that might overlap between obesity and IBD (such as observations that high fat diets may be associated with an increased risk of IBD), we do make a comment to that regard in the opening paragraph. The challenge in delving too much into that area is that 1) there are multiple other reviews of the epidemiology of IBD as it relates to diet, and 2) trying to link in a broad sense diet to obesity is in itself an exhaustive topic. We feel that this would almost mandate its own separate review, and would be too extensive to appropriately cover in this particular review. Similarly, observations regarding increased gut permeability—perhaps modulated at the level of the microbiota—in obesity are largely driven by murine studies, and based on the recommendation of other reviewers to avoid excessive inclusion of animal studies given the scope of this review, we felt it was inappropriate to add at this point. We did add further discussion to the epidemiology section as the discrepancy between the EPIC cohort's findings in comparison to the NHS study findings (as well as a Danish registry that confirmed the latter), as being driven largely by differences in the age and sex distribution of the cohorts, and we agree that that is an important distinction to outline.

Finally, regarding reviewer 03474015's comments, we added language in the epidemiology section regarding the interaction of age and sex with obesity in IBD. In the section on obesity and IBD outcomes we added another sentence to clarify the confusing paragraph and offer an explanation for the apparent discrepant results of the studies we cited. We also discuss in the body of the paper regarding possible differences between obese and non-obese IBD patients in regard to disease location and behavior. In the section on obesity as a pro-inflammatory state, we added a sentence about the role of substance P in inducing expression of pro-inflammatory cytokines in mesenteric pre-adipocytes. Many of the articles cited (Flores et al., Krane et al., Guardado et al., etc) were already included in this review's references.

We appreciate the feedback of the reviewers and the editor in strengthening this manuscript and hope that we have addressed your concerns with our revision.

Regards,

Jason W. Harper and Timothy L. Zisman