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Reply to Newman et al., “Response to Epidemiology of Inflammatory Bowel disease in men with high-risk homosexual activity”

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We thank Newman *et al.*[1] for the interest in our recent letter[2]; however, we strongly disagree with the statement that our work has ‘significant methodological flaws’. Firstly, in regard to inference of sexual behavior from billing codes, we would like to point out that prior studies have used these codes to analyze administrative datasets[3]. We acknowledge the possibility of biases inherent to large database studies that use the electronic medical record (EHR), including the potential for misdiagnoses, inaccurate coding, and documentation errors. However, administrative claims documenting sexual orientation are coded by clinicians, the diagnoses relying on provision of patient-derived information and providers’ decisions, which can also be impacted by failure to divulge sexual activity, and may represent an important potential limitation for future prospective studies that should obviously be performed to either support or negate the current findings. Overall, we believe that our study employed best available methodologies and has important scientific validity.

Other methodological criticisms by Newman *et al.* are unsubstantiated and may be due to a misconception of TriNetX. In regard to the use of billing codes for IBD diagnosis, previous reports have also used international classification of disease (ICD) codes for epidemiological studies[4,5]. As pointed out by the authors, a single ICD-9 billing code for Crohn’s disease was validated with a positive predictive value (PPV) of 18–67% in a past study, where validation was performed from 1999–2001[6]; more recent studies, however, have found a higher PPV of up to 88%[7]. To address the risk of identifying false positive patients by relying on a single instance of an ICD code in a patient’s EHR, TriNetX incorporates a Natural Language Processing Model, as previously proposed[8,9] that aims to both correct

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potentially erroneous diagnoses as well as include diagnoses that are only entered in physicians' and pathology reports, as well as clinical and discharge records. Regarding 'timing in relation to IBD diagnosis,' timing is included within the TriNetX advanced online platform that was used for our analyses, with any diagnosis of IBD strictly occurring after a sexual behavior code was noted. Finally, in the original report we presented un-matched analyses due to length limitations; however, we also performed matching for confounding variables, with consistent results that retain high statistical significance.

In conclusion and importantly, the terms 'homosexual and heterosexual high-risk sexual activities' were used in accordance with ICD-10 code nomenclature and the terminology outlined in the same 2022 National Academies report cited by the authors[10]. Nonetheless, we strictly used these descriptors only when referring to the ICDs, since this terminology certainly does not reflect that used by the authors of our letter. Although we disagree with several of the comments made by Newman *et al.*, we hope that the dialogue started herein will lead to a call for changing the nomenclature of the billing codes and avoid use of derogatory terminology. In this context, we would like to strongly emphasize that the results of our analyses were not meant and should never be used to stigmatize sexual and gender minority individuals. On the contrary, we hope that our work will afford the following benefits: 1) increase health care access and equity in gastroenterology for the LGBTQIA+ patient population by focusing on the incidence and pathogenic mechanisms of IBD in these individuals; 2) promote the opening of specialized and dedicated GI clinics for LGBTQIA+ patients; 3) provide a better understanding of novel pathogenic mechanisms of IBD in a diverse patient population that will benefit the entire IBD community; and 4) develop novel personalized medical treatments based on manipulation of the gut microbiome, possibly by probiotics, metabolite therapy and diet interventions.

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