Response by Abrahami et al to letter regarding article 'Proton pump inhibitors and risk of colorectal cancer'

We thank Chen Dong *et al*[1] for their interest in our study on the use of proton pump inhibitors (PPIs) and colorectal cancer incidence.[2] We have responded to their comments as follows.

While there may be some differences between PPI and histamine-2 receptor antagonist (H2RA) users, these two drug classes are used across similar indications in the real-world setting.[3] Thus, the use of H2RAs as an active comparator provides a clinically meaningful comparison for physicians deciding whether to treat patients with gastric disorders with a PPI or H2RA. This is certainly a better approach than comparing PPI users to non-users. Furthermore, we included all approved and off-label indications for acid suppressant drug use in our propensity score models to minimise residual confounding by disease severity. After applying propensity score weights, our population was well balanced on all measured confounders, suggesting a strong similarity between our two study populationstable 1. Overall, the use of H2Ras as an active comparator was a

major strength of our paper, which was not considered in many previous studies.

The authors suggest using patients who discontinued PPIs as an alternative comparator group. However, such a comparison group would be problematic if treatment discontinuation is related to the outcome of interest. Furthermore, this approach would necessarily compare PPI users with varying treatment lengths and thus include prevalent users, introducing well-known biases in pharmacoepidemiology.[4] The use of a new-user, active comparator design mitigates these biases by capturing patients newly diagnosed with gastric disorders (and having similar stages of disease severity) while eliminating biases related to the inclusion of 'survivors'.

The authors suggest conducting a dose–response analysis to compare patients using different doses of the same PPI drug. Given that comparing drugs with different potencies is not recommended, we conducted a secondary analysis using the WHO defined daily dose definition,[5] where all PPI prescriptions were converted to omeprazole equivalents. We observed a dose–response relationship, with higher dose equivalents associated with an increased risk of colorectal cancer.

We want to take this opportunity to clarify our secondary exposure definition. All secondary exposures were calculated using time-varying exposure definitions, which were updated at each person-day of follow-up. These analyses showed stronger associations between PPI use and colorectal cancer incidence with longer durations of use. Indeed, the time-since initiation analysis was consistent with the other exposure definitions, in that only the highest category of use (greater than 4 years) was associated with an increased risk of colorectal cancer (HR 1.19, 95% CI 1.03 to 1.34).

Finally, regarding the missing variables highlighted by the authors, unfortunately, the clinical practice research datalink does not consistently record such information. However, it is unclear that these variables meet the traditional definition for confounding, as they are unlikely associated with PPI prescribing. Nonetheless, the high dimensional propensity score analysis, which empirically selected an additional 200 covariates, may capture variables that are proxies for some of the variables highlighted by the authors. Reassuringly, results from this sensitivity analysis were highly consistent with our main findings.

Devin Abrahami,[1,2,3] **Laurent Azoulay**[1,2,4]

[1]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada
[2]Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[3]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA
[4]Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada

Correspondence to Dr Laurent Azoulay, Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada; laurent.azoulay@mcgill.ca

Contributors DA and LA wrote the response. Both authors approved the final version of the letter and agreed to be accountable for its accuracy.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests LA served as a consultant for Janssen and Pfizer for work unrelated to this study. DA has no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; there are no other relationships or activities that could appear to have influenced the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Abrahami D, Azoulay L. *Gut* 2022;**71**:1690–1691.

Received 11 November 2021
Accepted 17 November 2021
Published Online First 2 December 2021

Linked

► http://dx.doi.org/10.1136/gutjnl-2021-326139

Gut 2022;**71**:1690–1691. doi:10.1136/gutjnl-2021-326544

ORCID iD
Laurent Azoulay http://orcid.org/0000-0001-5162-3556

REFERENCES

1 Chen Dong Y-HL, Tan T-Y, Yao C-C. Correspondence to proton pump inhibitors and risk of colorectal cancer. *Gut* 2022;71:1690.
2 Abrahami D, McDonald EG, Schnitzer ME, *et al*. Proton pump inhibitors and risk of colorectal cancer. *Gut* 2022;71:111–8.
3 Abrahami D, McDonald EG, Schnitzer M, *et al*. Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study. *BMJ Open* 2020;10:e041529.
4 Yoshida K, Solomon DH, Kim SC. Active-comparator design and new-user design in observational studies. *Nat Rev Rheumatol* 2015;11:437–41.
5 WHO collaborating centre for drug statistics methodology: definition and general considerations, 2018. Available: https://www.whocc.no/ddd/definition_and_general_considera/