

## Letters

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## Proton pump inhibitors and osteoporosis-related fractures

In an important and interesting study, Laura Targownik and colleagues<sup>1</sup> state that the effect of exposure to proton pump inhibitors on osteoporosis-related fractures might be “similar in size to [the effect of] other established osteoporotic-fracture risk factors, such as smoking, low body mass index and excessive alcohol intake.” However, the authors did not take any of these factors into account in their analysis. Were the case and control groups comparable in terms of these 3 variables? If not, what is the role of these variables in the observed associations? For example, people who use proton pump inhibitors might be less likely to be active smokers because of gastroesophageal reflux disease but, at the same time, they could be more likely to have a history of smoking than people who do not use this class of drugs.

This may have an impact (of unknown magnitude) on the estimation of the effect of proton pump inhibitors.

This study relies on the analysis of administrative data, which were probably collected for purposes quite distinct from research into the causes of osteoporosis. This does not mean that such data are inadequate for health research, but that we should be more critical about the inferences drawn from them.

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**Competing interests:** None declared.

## REFERENCE

1. Targownik LE, Lix LM, Metge CJ, et al. Use of

proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008;179:319-26.

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## Two of the authors respond:

We thank Mathieu Forster for his interest in our article.<sup>1</sup> He expressed concern about the possible influence of unmeasured variables, specifically smoking status, alcohol use and body mass index, on the association that we observed between use of proton pump inhibitors and the development of osteoporosis-related fractures. For an unmeasured variable to influence the results of the study, it would have to be associated both with the outcome of interest in the unexposed cohort and with the exposure of interest. It has previously been established that smoking, excessive alcohol use and low body mass index are associated with higher risk for osteoporosis and osteoporosis-related fractures,<sup>2-4</sup> but for these factors to influence (positively or negatively) the relation between proton pump inhibitor use and osteoporosis-related fractures, they would also have to be independently associated with the use of proton pump inhibitors.

There are currently very little data available to confirm a relation between proton pump inhibitor use and any of the above factors. A recently published analysis of long-term use of proton pump inhibitors suggests a lack of a relation between use of proton pump inhibitors and both smoking and body

mass index.<sup>5</sup> However, smoking and alcohol use are both positively associated with gastroesophageal reflux disease, the most common indication for proton pump inhibitor therapy. Conversely, gastroesophageal reflux disease is also strongly associated with obesity,<sup>6</sup> which is in fact protective against osteoporosis and osteoporosis-related fractures. Given the likelihood that these influences have opposing effects, it is very likely that the overall effect of these unmeasured variables on the detected association is minimal. We agree that further studies are required to determine whether the association between use of proton pump inhibitors and the development of osteoporosis and osteoporosis-related fractures is truly causal.

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**Competing interests:** Laura Targownik has served on the national advisory board for AstraZeneca Canada. None declared for William Leslie.

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1. Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. *CMAJ* 2008;179:319-26.
2. De Laet C, Kanis JA, Oden A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int* 2005;16:1330-8.
3. Kanis JA, Johansson H, Johnell O, et al. Alcohol

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