

## Response to: ‘Correspondence on ‘Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study’ by Zheng

We thank Dr Zheng for his comments on our recently published article in the *Annals of the Rheumatic Diseases* entitled ‘Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study’.<sup>1,2</sup> Our main goal in this study was to bring more clinical insight into the simultaneous use of these two common medications in patients with rheumatoid arthritis (RA), that is, oral glucocorticoids (GCs) and proton pump inhibitors (PPIs), using data from a large primary care database and pharmacoepidemiological methodologies.

Our results showed that there was an interaction in the risk of osteoporotic (OP) fractures with concomitant use of oral GCs and PPIs in patients with RA. Based on the adjusted hazard ratios and according to the formula proposed by Rothman *et al.*,<sup>3</sup> the relative excess risk due to interaction (RERI) was:  $1.60 - 1.23 - 1.22 + 1 = 0.15$ . We now have also calculated the CIs and the statistical significance of this index using the method proposed by Hosmer and Lemeshow.<sup>4,5</sup> The lower and upper limits of the 95% CI of the RERI were  $-0.16$  and  $0.45$ , respectively, and the *p* value was  $0.36$ . This means, although we observed a 15% more risk of OP fracture with concomitant use of oral GCs and PPIs in addition to the single use of each drug versus non-use of both, this additive interaction was not statistically significant.

As we discussed in our paper, there is currently no proven biological mechanism for an action of PPIs on bone or falling,<sup>6</sup> while the effects of GCs on bone and the musculoskeletal system are quite established. Our secondary analyses (ie, lower fracture risk with long-term or higher daily doses of PPIs compared with short-term or lower daily doses) did not support the few proposed potential mechanisms, such as hypochlorhydria and calcium malabsorption, or an increased fall risk due to malabsorption of magnesium or vitamin B<sub>12</sub>. This is important to consider when interpreting a potential additive interaction between oral GCs and PPIs on fracture risk. Without this basic knowledge, it would be extremely difficult to confer any conclusions on a plausible synergistic action of these two drugs, since it would sound more as a methodological reasoning rather than a clinical explanation.

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**Correction notice** This article has been corrected since it published Online First. Reference 3 has been corrected.

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### REFERENCES

- 1 Abtahi S, Driessen JHM, Burden AM, *et al.* Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2021;**80**:423–31.
- 2 Zheng B. Correspondence on ‘Concomitant use of oral glucocorticoids and proton pump inhibitors and risk of osteoporotic fractures among patients with rheumatoid arthritis: a population-based cohort study’. *Ann Rheum Dis* 2023;**82**:e93.
- 3 Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. In: *Chapter 16, application of stratified analysis methods: analyses of biologic interactions*. 3<sup>rd</sup> ed. Philadelphia (PA, USA): Lippincott Williams & Wilkins, 2008: 298–9.
- 4 Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology* 1992;**3**:452–6.
- 5 Li R, Chambless L. Test for additive interaction in proportional hazards models. *Ann Epidemiol* 2007;**17**:227–36.
- 6 Andersen BN, Johansen PB, Abrahamsen B. Proton pump inhibitors and osteoporosis. *Curr Opin Rheumatol* 2016;**28**:420–5.