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'

I read with great interest the article published by Abtahi *et al* recently.[1] The authors aimed to investigate the association between concomitant use of oral glucocorticoids (GCs) and proton pump inhibitors (PPIs) and the risk of osteoporotic fractures among patients with rheumatoid arthritis.[1] The study showed that concomitant current use of oral GCs and PPIs was associated with increased risk of osteoporotic fractures compared with non-use (adjusted HR: 1.60, 95% CI: 1.35 to 1.89). Both oral GC and PPI use alone were also associated with increased risk of osteoporotic fracture compared with non-use (adjusted HR: 1.23, 95% CI: 1.03 to 1.47 (oral GC use alone); adjusted HR: 1.22, 95% CI: 1.05 to 1.42 (PPI use alone)). The authors concluded that there was an interaction in the risk of osteoporotic fractures with concomitant use of oral GCs and PPIs because the osteoporotic fracture risk associated with the current use of oral GCs or PPIs alone was statistically different from concomitant use (Wald test $p<0.05$). However, the current analyses in the study are insufficient to reach a conclusion regarding the interaction between oral use of GC and PPI.

If there is interaction between two factors, the effect of one factor on the outcome should be different across strata of the other factor, and vice versa.[2] In the study by Abtahi *et al*,[1] if there is interaction between oral use of GC and PPI, the combined effect of GC and PPI (ie, 1.60) should be larger than the sum of the individual effects of GC and PPI. The sum of the individual effects of GC and PPI are 1.45 ((1.23–1)+(1.22–1)+1) or 1.50 (1.23×1.22) on the basis of additive scale or multiplicative scale, respectively. It has been suggested that when biologic interaction is examined, additive scale should be used.[2 3] Therefore, Abtahi *et al* should test if the HR of 1.60 is statistically different from 1.45, instead of statistically different from 1.23 (oral GC use alone) and 1.22 (PPI use alone).

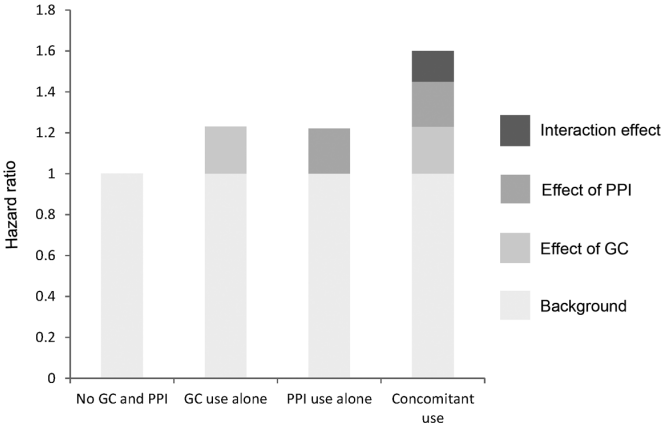

Figure 1 The interaction effect between GC and PPI. GC, glucocorticoid; PPI, proton pump inhibitors.

There are three measures for interaction as departure from additivity. Relative excess risk due to interaction (RERI), as the most commonly used one, is 0.15 (1.60–1.23–1.22+1) in this study. An RERI of 0 indicates exact additivity and thus no interaction on an additive scale.[2 3] Therefore, an RERI of 0.15 indicates that there is interaction on an additive scale between oral use of GC and PPI on the risk of osteoporotic fractures. Figure 1 shows the interaction effect between oral use of GC and PPI. However, the 95% CI for RERI should be calculated to see if the interaction effect is statistically significant.

In conclusion, the current analyses in the study are insufficient to reach a conclusion regarding the interaction between oral use of GC and PPI. I recommend the authors to calculate the measures such as RERI and its 95% CI to see whether the interaction is truly exist between oral use of GC and PPI on the risk of osteoporotic fractures.

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