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 Gong and Zhang and Lin *et al*

We read with much interest the two correspondences on our recently published paper by Lin *et al* and Gong and Zhang in the *Annals of the Rheumatic Diseases*.[1–3] We conducted a retrospective cohort study to evaluate the association between concomitant use of two commonly used medications in patients with rheumatoid arthritis (RA), that is, oral glucocorticoids (GCs) and proton pump inhibitors (PPIs), and risk of osteoporotic (OP) fractures. We used data from one of the largest primary care databases in the world, the Clinical Practice Research Datalink (CPRD). While this database is a rich source, it does have some inherent limitations.

The first question of both correspondences addresses one of these limitations of the CPRD, that is, the absence of any direct measure of RA disease activity in the database, such as the Disease Activity Score in 28 joints. The values of C reactive protein (CRP) were also not available for all patients, and if available, not for the whole follow-up period. Therefore, we decided not to include CRP in the analyses, considering our on-treatment study design and importance of having information on covariates during all person-times from patients for the entire follow-up. We were aware of this limitation and mentioned this in the paper. We also reported our strategy to overcome this by using proxies of RA disease activity, such as use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and five analgesics (including non-selective non-steroidal anti-inflammatory drugs, selective cyclooxygenase-2 inhibitors, paracetamol, opioids and tramadol). Based on the European Alliance of Associations for Rheumatology and the UK National Institute for Health and Care Excellence guidelines on RA management,[4 5] we assume that patients with RA would have been prescribed csDMARDs and analgesics according to the severity of the inflammation and pain that they had experienced. Thus, by considering these six covariates in the Cox regression model, we aimed to adjust (at least partly) for RA disease severity in our analyses.

Continuing with the effect of disease severity indicators on our risk estimates, questioned by Gong and Zhang, the frequency of use of some types of analgesics, such as opioids and tramadol, was higher among concomitant GC and PPI users at baseline versus non-users (data shown in table 1 in the manuscript). Nevertheless, we had an on-treatment study design and adjusted our final Cox regression model for use of analgesics and csDMARDs during follow-up, so any confounding effect from these proxies of disease severity have been taken into account in the fully adjusted analyses.

We agree with Lin *et al* that postmenopausal status is an important predisposing factor to primary osteoporosis and the resulting fractures. But there is little evidence to think that a postmenopausal status is associated with higher use of oral GCs or PPIs, as by definition a true confounder should be associated with both the exposure and outcome and does not lie in the causal pathway of this association.[6 7] We included hormone replacement therapy (HRT) in our primary list of covariates as an indirect measure of postmenopausal status. Not so many patients were on HRT at baseline (4.3% of concomitant users and 2.6% of non-users), and our univariate Cox regression models showed that HRT was not associated with a significant change in the beta coefficient of the main association (ie, >5%).

The association between statin use and fracture risk was not uniform in the literature. Meta-analyses of randomised controlled trials (RCTs) showed a neutral effect from statins on fracture risk.[8] But, many observational studies in the past two decades claimed surprisingly beneficial effects of statins on various adverse outcomes such as cancers, diabetes, respiratory diseases and fractures, which has been later found out to be explained by time-related biases or healthy-user bias.[9–12] Based on the stronger evidence from RCTs, we did not feel a necessity to add statins as a covariate in our study.

Regarding the last point by Lin *et al* on our inclusion and exclusion criteria for establishing our patient population, we should clarify that we used Thomas algorithm (updated by Muller *et al*) for selecting our study population within the CPRD and we only included those patients from the CPRD who had a definite RA diagnosis based on Thomas algorithm. The 17 111 patients who were excluded in the second step, as shown in figure 1 in the manuscript, were either those without a definite RA diagnosis or those who had a previous OP fracture or used oral GCs and/or PPIs in the 1-year look-back period.

Answering the last question by Gong and Zhang on GC dose changes and stratification of GC use, we can explain that the average duration of drug use was estimated based on the time between first and last drug exposure during the follow-up, and for this we did not consider the drug holidays or intervals. However, we carefully calculated the average daily use of oral GCs and PPIs, cumulative use of oral GCs and continuous duration of PPIs during follow-up, while accounting for drug dose changes. The average daily dose of oral GCs was calculated at each current GC use interval. When the average daily dose was ≤7.5 mg prednisolone equivalent dose (PED)/day, an interval (not patient) was classified as low GC use, when this was 7.6–14.9 mg PED/day, an interval was classified as medium GC use, and when the average daily dose was ≥15 mg PED/day, an interval was classified as high GC use. So, patients could move between the groups, depending on what was the most recent average daily GC exposure.

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