Response to: 'Correspondence on 'Systemic evaluation of the relationship between psoriasis, psoriatic arthritis and osteoporosis: observational and Mendelian randomisation study' by Lee

We appreciate Dr Young Ho Lee's interest in our study on the relationship between psoriatic arthritis (PsA) and osteoporosis,[1] and thank him for the comments brought in his letter.[2]

Over the past few years, several methods were developed to deal with the pleiotropic effect of instrumental single-nucleotide polymorphisms (SNPs) in Mendelian randomisation (MR) analysis, such as inverse variance-weighted (IVW), MR Egger, the weighted median,[3] weighted (simple) mode-based[4] and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO).[5] However, the limitation of each method should be acknowledged.[6] The weighted median method estimated some SNPs as invalid instruments, but still kept at least half were valid instruments for the causal effect estimate to be unbiased. The advantage of this approach was the improved precision with reduced type 1 error compared with MR Egger, but less accuracy of IVW. In our study, we applied all the methods mentioned above, and the results complemented with each other that PsA had no causal effect on low bone mineral density (BMD).

However, in the large-scale observational study with UK biobank dataset, we found that PsA somehow associated with low BMD. Therefore, we started to think about how the inconsistent results between MR analysis and observational study could be explained. We speculated some secondary factors such as physical activity and medication treatments (methotrexate and ciclosporin) could rise this observational association, but this association was not genetically determined.[7] In the following conditional analysis and mediation analysis, we indeed observed that medication treatments might be the secondary factor causing the observational association. Therefore, we suggested that patients with PsA should be screened for BMD and proper management should be provided to reduce the fracture risk, especially for those who received treatment with methotrexate or ciclosporin. However, large-scale randomised controlled trial study was still needed to clarify the adverse effect of the methotrexate treatment. And we agreed that we should balance the treatment effect and the adverse effect of methotrexate.

In addition, we used quantitative ultrasound estimated BMD at heel as the outcome in our study. Although previous studies showed that quantitative ultrasound was also proven as a good predictor for the fracture risk,[8–11] BMD measured by dual-energy X-ray absorptiometry (DXA) was the golden standard in clinical practice. In UK biobank, only about ~5000 individuals had been measured by DXA; it is worth to check the association between PsA and BMD in the future if the DXA data are available for the ~500 000 individuals.

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