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

We read with great interest the published paper by Xia *et al*¹ which provided an in-depth analysis regarding the relationship between psoriasis, psoriatic arthritis (PsA) and osteoporosis. By comprehensively analysing the datasets from three Genome-Wide Association Studies and UK Biobank, the authors concluded that the association between PsA and estimated bone mineral density (eBMD)/osteoporosis/fracture was not genetically determined but secondary (eg, treatment with methotrexate or ciclosporin). Although the conclusion was drawn based on very stringent confounders controlling, there are a few points in this study that are worth mentioning.

First, typically, many background characteristics should be controlled in an observational study, especially with large datasets. In association analysis part, only seven confounders (ie, age, height, weight, smoking, drinking, regular physical activity and medication treatments) were controlled. It is well established that psoriasis/PsA is a systemic inflammatory disorder that is associated with several comorbidities, for example, cardiovascular disease^{2,3} and metabolic syndrome (namely, diabetes mellitus, obesity, hypertension and dyslipidaemia).^{4,5} These comorbidities may also have residual confounding effect on the association between psoriasis, PsA and osteoporosis.

Second, we noted that there were a total of 432 513 psoriasis/controls and 428 455 PsA/controls in UK data-1 dataset, the baseline imbalance presumably existed between psoriasis/PsA cases and controls. Although this is not a concern to consider running multivariable linear/logistic regression, it is convincing to clarify and eliminate the imbalance to testify and strengthen the regression. It is preferable to use propensity score methods for confounder controlling,⁶ though it will cause the reduction of sample size, it has been widely accepted and used in other observational studies.^{7,8}

Third, the information about medication treatment (mainly refers to methotrexate and ciclosporin in the text) should be described more detailed, especially the ciclosporin. Because ciclosporin is recommended for the management of skin psoriasis,⁹ however, it is not put forward in the EULAR recommendations for the management of PsA,¹⁰ because lack of convincing efficacy.^{11,12} More importantly, disease activity is another issue that should be addressed when interpreting the relationship between psoriasis, PsA and osteoporosis. Evidence suggests that there is a high prevalence of osteoporosis in patients with spondyloarthritis,¹³ and patients with high disease severity are prone to suffering from more comorbidities, including osteoporosis.¹⁴ Additionally, disease activity is an important factor affecting medication because PsA cases with high disease activity tend to take more methotrexate and/or ciclosporin. Therefore, high disease activity seems to be a contributor for taking methotrexate or ciclosporin, and then for osteoporosis, which exactly explain that PsA cases, rather than psoriasis, was found to contribute to lower eBMD in this study.

Last but not least, in Mendelian randomisation approach part, multiple sensitivity methods were used to explore horizontal pleiotropy, however, linkage disequilibrium, other key issue of Mendelian randomisation analysis, should be taken into consideration to avoid false positive of causal effects. New evidence showed that linkage disequilibrium is widespread in naïve

phenome-wide association studies of proteins, and nearly 31.5% associations, which being supported by evidence from Mendelian randomisation, however, were not supported by results of colocalisation analyses.¹⁵

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