Response to: 'Correspondence on 'Systemic evaluation of the relationship between psoriasis, psoriatic arthritis and osteoporosis: observational and Mendelian randomisation study" by Cui *et al*

We would like to thank the interests and comments from Cui *et al*[1] on our study[2] entitled 'Systemic evaluation of the relationship between psoriasis, psoriatic arthritis and osteoporosis: observational and Mendelian randomization study'. Here, we responded the comments point by point.

First, the potential confounders we included were age, sex, height, weight, smoking status, drinking status, regular physical activity and mediation treatment. The selected confounders were known potentially to have effect on the outcome (bone mineral density, BMD),[3] and were typically recorded in UK Biobank dataset. The mediation analysis suggested that 63% of the effect of psoriatic arthritis (PsA) on BMD were mediated by treatment with methotrexate or ciclosporin; thus, there were many other unmeasured confounders to be discovered. In addition, we excluded participants if they were diagnosed with one of the potential secondary causes of osteoporosis including multiple sclerosis, Crohn's disease, ulcerative colitis, hyperthyroidism, lupus erythematosus and rheumatoid arthritis.[2]

Second, we agree that propensity score matching could be a complementary to multivariable linear/logistic regression. Here, we conducted additional propensity score matching analysis by using the 'MatchIt' Package in R (method ='nearest', ratio=1), after we obtained the matched dataset, we implemented liner regression model with the confounders in the same three ways as our previous study.[2] Compared with the previous study,[2] we found similar results for psoriasis and BMD (model 0, p=0.88; model 1, p=0.90; model 2, p=0.30), and for PsA and BMD (model 0, p=0.005; model 1, p=0.008; model 2, p=0.45).

Third, the ciclosporin, a calcineurin inhibitor, was recommended by 2018 American College of Rheumatology/National Psoriasis Foundation guideline as oral small molecule for the treatment of PsA[4]; however, the European League Against Rheumatism did not recommend ciclosporin for PsA treatment.[5] In our dataset, there were 121 individuals and 6 individuals who taken methotrexate and ciclosporin in 4904 psoriasis cases, respectively. There were 288 individuals and 3 individuals who taken methotrexate and ciclosporin medications in 847 psoriasis cases, respectively. On the other hand, we agree that the disease activity is an important factor affecting the use of medication,[6] just like Cui *et al*[1] mentioned, methotrexate or ciclosporin were more likely prescribed to patients with high disease activity, which exactly explain that PsA cases, rather than psoriasis, was found to be associated with lower eBMD.

Finally, we did consider the linkage disequilibrium in the reverse-direction mendelian randomisation (MR) analysis. By using the 'clump_data()' function on each chromosome in 'TwoSampleMR' package,[7] we selected 973 single nucleotide polymorphisms (SNPs) as instrumental variables out of 1103 genome wide significant BMD SNPs,[8] we chose the SNP with the lower p value if there was LD (r^2 >0.05) between two significant SNPs. While we did not consider linkage disequilibrium of the instrumental variables for psoriasis (60 SNPs) and PsA (25 SNPs), just as Budu-Aggrey *et al*[9] did in their analysis. Here, when applied the 'clump_data()' function described above, there were one SNP rs112768831 and six SNPs (rs113633694, rs142422776, rs145699582, rs149014202, rs189254950, rs918520) removed for the psoriasis MR analysis and PsA MR analysis, respectively. Still, we found no evidence to show association of genetically increased psoriasis and PsA risk with BMD (p=0.21and p=0.83, respectively, by using the inverse-variance weighted MR method).

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