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

With great interest, I have read the article by Xia *et al*,[1] which evaluated the relationship between psoriasis, psoriatic arthritis (PsA) and osteoporosis. This Mendelian randomisation (MR) study suggests that the effect of PsA on osteoporosis is secondary, but not causal. However, it is important to discuss some methodological issues in MR. First, MR is a powerful tool for analysing causal relationships between exposures and outcomes because of minimisation of residual confounding.[2 3] However, MR is often vulnerable to bias resulting from pleiotropy.[2] Therefore, the use of a variety of robust methods working in diverse ways and relying on different assumptions has been recommended to derive valid inferences and assess the reliability of MR analyses.[4] In the MR-Egger test, the pleiotropic effects of single nucleotide polymorphisms (SNPs) on the outcome should be independent of the association between SNPs and exposure.[2] The weighted median method assumes that valid variants account for at least 50% of the total weight of the instrument.[5] The weighted median estimator has the benefit of preserving greater precision in the estimates, whereas the MR-Egger process results in loss of precision and power.[5] The authors should consider the weighted median method as a sensitivity analysis tool in this study. Second, patients with a low bone density at the calcaneus are at an increased risk of hip fracture. However, low bone density at the hip is a better predictor of hip fracture than bone density at other sites.[6] Similarly, bone density at the spine and hip measured using dual X-ray absorptiometry may be a more reliable predictor of spinal and hip fractures than bone density at other sites. In addition, the expected bone mineral density (BMD) is uncertain in most cases of osteoporosis diagnosed using ultrasonography.[7] Data on BMD measured using dual X-ray absorptiometry and fracture at the same site would give more accurate results. Third, it is necessary to determine the effect of disease-modifying antirheumatic drugs on bone metabolism as it is indicated in patients at a high risk of osteoporosis. The possible adverse effect of methotrexate (MTX), used for rheumatic diseases, on bone metabolism cannot be excluded in the study population despite controlling for factors such as concomitant therapies or disease type. However, the direct local effects of MTX on the bone must be weighed against the indirect anti-inflammatory effects of the drug.[8] Decreased systemic inflammation with MTX treatment in the study population appears to outweigh any direct local adverse effect that MTX may have on osteoblast and osteoclast function. Cohort and case–control studies have not demonstrated any substantial effects of MTX on BMD.[9] Many practitioners, including myself, do not believe that MTX treatment for rheumatic diseases has an adverse effect on bone density. It is imperative that the findings of this MR study be interpreted with caution considering the aforementioned methodological concerns.

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