Association between osteoporosis and statins therapy: the story continues

It was with great interest that we read the study conducted by Leutner *et al*[1] that investigated the relationship between the use of statins and osteoporosis. As identified in the correspondence by Shih-Wei Lai, there is a long-standing interest in the relationship between statins and bone, with numerous observational studies identifying a protective effect; however, results are inconsistent.[2–4] In their study, Leutner *et al* identified that the use of statins was associated with an impressive 3.62-fold increased risk of being diagnosed with osteoporosis, and this association was observed in both men (OR 3.35) and women (OR 3.90. However, we note that if the crude ORs are calculated on the data matched for age and sex (derived from table 1 of the manuscript), the association between statin use and osteoporosis disappears with ORs of 1. Matching is one method to avoid the influence of confounding.[5] Due to the large difference between the reported ORs and the matched numbers, we are unsure how age and sex were included in the authors logistic regression model.

The authors further identify a very impressive dose-response relationship, which is identified in figure 2 of the manuscript. While we agree with the conclusion that it is highly important for future studies to consider the individual statins and dosage when examining the risk of osteoporosis, we would like to make an addition to consider statin potency. In the conclusion, the authors propose that the mediating effect of statins on bone is the inhibition of sex hormones via HMG-CoA reductase inhibition. However, we note that the inhibition of the synthesis of cholesterol influencing sex-hormones, based on HMG-Co-A-reductase inhibition, would also be affected by varying potencies of different statins.[6–8] Thus, we would not expect the results to be similar at identical average daily doses. Rather, simvastatin >40 mg would be comparable to 20 mg atorvastatin and 10 mg rosuvastatin. When comparing the results in the current study at these doses, the dose-dependent relationship becomes less clear. As a result, we postulate that within the drug, dose-response is likely a result of confounding by indication, whereby sicker (eg, frailer) patients who are prescribed higher statin doses are also more likely to be at risk for having a diagnosis of osteoporosis.[9] This confounding is intensified when non-users are the referent group.

While the authors draw a strong conclusion regarding the relationship between statins and osteoporosis, we believe that the impressive results are likely a product of unmeasured confounding. Moreover, due to the nature of a cross-sectional design, the authors cannot demonstrate a temporal relationship between statin use and osteoporosis diagnosis, nor were they able to assess time on therapy to assess a biologically plausible relationship.[10] To conclude that there is a dose-dependent relationship between statins and osteoporosis, these methodological issues need to be addressed. Thus, we believe that the results reported in this study should be interpreted with great caution.

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Contributors AMB and SW contributed to the conception of the article, initiated the draft of the article and approved the final draft submitted.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

Competing interests SW is a member of the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Burden AM, Weiler S. *Ann Rheum Dis* 2021;**80**:e204.

Received 31 October 2019
Accepted 2 November 2019
Published Online First 19 November 2019

Linked

► http://dx.doi.org/10.1136/annrheumdis-2019-216627

Ann Rheum Dis 2021;**80**:e204. doi:10.1136/annrheumdis-2019-216574

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