Changes in synovitis and bone marrow lesions may not mediate the effect of cartilage loss on joint pain in osteoarthritis

We read with interest the recent article by Bacon *et al*¹ that used mediation analysis² to understand the process by which cartilage loss changes joint pain. Given considerable investment in treatments that focus on chondroprotection, this is an important topic and the findings from this study have potential to inform patient management. The authors concluded that a small, non-clinically important effect of cartilage loss on joint pain was mediated by synovitis. To ensure this study accurately informs future research and practice, we ask the authors to clarify the reporting and interpretation of their results.

The results presented in tables 3 and 4 do not support the authors conclusion that synovitis mediated the effect of cartilage loss on joint pain. The 95% CIs for all of the indirect effects presented include the null. If correct, these indirect effects and their precision estimates clearly demonstrate that in this study, there was no evidence that synovitis and bone marrow lesions mediate the effect of cartilage loss on joint pain. We suspect the authors might have used the 'proportion mediated' estimates to draw their conclusions. However, in most settings, the indirect effect estimate is a more robust measure than the proportion mediated.³ Although the proportion mediated is intuitive for interpretation, it is subject to a number of limitations.⁴ For example, the proportion mediated is considered to be highly variable, particularly with small sample sizes and uncertain indirect and direct effect estimates.⁵ Therefore, the main conclusions of the study should primarily reflect the indirect effect, rather than the proportion mediated. We urge the authors to consider this and revise their conclusions appropriately.

We also have some concerns about the accuracy of the numbers presented in tables 3 and 4. The point estimates of the proportion mediated for synovitis are identical for both exposures (0.1 and 0.05 mm cartilage thickness loss) despite differences in their indirect and total effect estimates. If we assume that the proportion mediated is simply the ratio of the indirect effect and the total effect, on the difference scale,⁶ the proportion mediated should be 15.1% for 0.1 mm and 12.5% for 0.05 mm in table 3, and 25.0% for 0.1 mm and 20.0% for 0.05 mm in table 4. It would be helpful if the authors could verify these estimates or clearly state how the proportion mediated was estimated if they used a different method.

Finally, when mediators fail to explain a mechanism, the path specific exposure–mediator and mediator–outcome effects can be informative for explaining where the indirect effect broke down.³ In Bacon's study, cartilage thickness may not be associated with synovitis or bone marrow lesions, or these mediators may not be associated with the outcome joint pain, or both. We encourage the authors to consider reporting these path specific effects to provide readers with a better understanding for why

cartilage loss does not have an effect on joint pain via synovitis and bone marrow lesions.

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