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 analysis\(^2\) 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.\(^3\) For example, the proportion mediated is considered to be highly variable, particularly with small sample sizes and uncertain indirect and direct effect estimates.\(^3\)

Therefore, the main conclusions of the study should primarily be informative for explaining where the indirect effect broke down.\(^3\) In Bacon’s study, cartilage thickness 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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Funding AGC is supported by the University of New South Wales Prince of Wales Clinical School Postgraduate Research Scholarship and a NeuRa PhD Candidature Supplementary Scholarship. HL is supported by a National Health and Medical Research Council fellowship and by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS Foundation Trust.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

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To cite Cashin AG, McAuley JH, Lee H. Ann Rheum Dis Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2020-218139

Received 28 May 2020
Accepted 31 May 2020


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