Response to: 'Relation between cartilage loss and pain in knee osteoarthritis' by Wu *et al* and 'Changes in synovitis and bone marrow lesions may not mediate the effect of cartilage loss on joint pain in osteoarthritis' by Cashin *et al*

Our paper[1] was primarily focused on the small effect that preventing cartilage loss has on pain reduction. In an additional analysis, we noted that synovitis change mediated a small percentage of that effect, an effect that was not statistically significant. Cashin *et al*[2] suggested that our mediation results should be interpreted based on whether the 95% CIs for the indirect or mediation effects overlapped with the null (ie, was statistically significant). Like the American Statistical Association and leading methodology experts, we oppose drawing a binary conclusion based on whether a threshold is statistically significant. Crossing an arbitrary significance threshold does not convey the presence or absence of a 'real' effect. Therefore, we exercised caution and embraced uncertainty, rather than dichotomy, in our conclusions. We do, however, agree that estimates for indirect effects are more robust measures of mediation than estimates of per cent mediated.

With respect to the accuracy of the values in tables 3 and 4, the values in the table are correct but results of calculations were rounded to two decimal places for publication—this is the source of the confusion. From table 3, for the 0.1 mm exposure the full calculation is (0.04597)/(0.32578)=0.14110749, or 14.11% after rounding. For the 0.5 mm exposure, it is (0.02298)/(0.16289)=0.1410768, or 14.11% after rounding.

With respect to exposure–mediator and mediator–outcome effects, cartilage thickness loss (0.01 mm) was significantly associated with synovitis change over 24 months (estimate=0.09 (0.05,0.12) p<0.0001), while synovitis change was also associated with change in WOMAC pain (estimate=0.66 (0.40,0.93), p<0.0001), supporting our conclusion that synovitis may be acting as a mediator in this relationship. However, although change in bone marrow lesions (BMLs) was predictive of change in WOMAC pain over 24M, (estimate=0.11 (0.01,0.21), p=0.0295), cartilage thickness loss (0.1 mm) was not predictive of change in BMLs (estimate 0.08 (−0.01,0.17), p=0.0763).

In their letter, X-D *et al*ask about excluding knees with severe disease (Kellgren and Lawrence (KL) grade 4) from our analysis and raise questions about the appropriateness of the WOMAC survey as a tool to assess the relation of pain change with cartilage change.[3] Knees with severe disease (KL grade 4) have been excluded from almost all osteoarthritis (OA) trials examining structural effects of treatment. On radiographs, these knees have no joint space remaining in the most affected compartment and MRIs show no cartilage left in that location, making it impossible to preserve cartilage there. As for use of the WOMAC survey, we chose to examine WOMAC pain because it is the most widely used tool to assess pain in knee OA trials. Other pain surveys in OA tend to produce similar results to those of WOMAC pain. While we are not convinced that changes in other characteristics of pain, such as its persistence, would more strongly associate with cartilage loss than the WOMAC pain scale, we agree with X-D *et al* that this question is worth further exploration.

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