

Response to: 'Does it make sense to investigate whether the offspring of people with a total knee replacement for severe primary knee osteoarthritis have a higher risk of worsening knee pain?' by Lei *et al*

We would like to thank Lei *et al*¹ for their interest in and comments on our paper on the higher risk of worsening knee pain in the offspring with a family history of knee osteoarthritis (OA) as compared with control with no family history.²

First, we agree that the correlation between the radiographic OA and the presence of pain is weak and not significant in this cohort. Our group has published much of the research on this area and what does contribute to pain. Our contention is that radiographic OA is of limited significance and papers from this cohort show that. The MRI scans show many structural changes within the knee long before radiographic OA develops and these are related to knee pain.³ This suggests that knee pain as an outcome would be of greater importance than radiographic OA in early disease. Additionally, we also have recently published our results on the genetic contribution to the progression of radiographic OA⁴ as well as knee structural changes in MRI,⁵ finding that offspring have a greater risk of the progression of radiographic OA and increases in multiple knee structural abnormalities.

Second, with regard to knee injury, we did the analyses by excluding those with knee injury at baseline. We observed similar results (total knee pain, OR=2.11, 95% CI 1.03 to 4.32) and therefore reported the results after adjustment for knee injury rather than exclude subjects with a consequent decrease in power. Third, we entitled our paper as worsening knee pain because the majority of people (>60%) experienced an increase in knee pain over 8 years, especially in the offspring. Further, we found that offspring have a higher proportion of incident knee pain and also have a higher proportion with progression of knee pain. This was further supported in the multi-variable analyses that offspring had an increased risk of incidence (OR=2.90, 95% CI 1.14 to 7.38) and progression (OR=2.61, 95% CI 1.04 to 6.51) of total knee pain.

Fourth, it seems that Lei *et al* are not totally clear about the study design. This study was an age-matched and sex-matched case-control study at baseline where 'cases' were defined as offspring of people with total knee replacement (TKR) for primary knee OA, whereas 'controls' in this study were randomly selected individuals with no family history of knee OA. Although the current study was a follow-up study, the prevalence of knee pain in the offspring or controls is still comparable in that the participants were a subsample of the baseline case-control study and the prevalence calculation was based on our population rather than the study design.

Finally, in the paper, we discussed and acknowledged several potential confounders in an observational setting as it is very hard to measure or collect some data due to budgetary considerations or our understanding at the time when the study was

designed. We did not have information on pain medication; however, we do not believe that this would change our results because this is a younger cohort with a low prevalence of knee OA and there were only three people undergoing TKR at 10 years. In addition, we have considered many possible confounders such as physical activity and employment. The analyses were repeated by adding these factors into model, finding that the results did not change. We do not believe that sample size of this study is small as this is the largest and longest MRI study to date and reports numerous statistically significant results.

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