

**Response to: 'Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women' by Gao et al.**

We would like to thank Gao et al for their interest in our paper 'Painful knee but not hand osteoarthritis is an independent predictor of mortality over 23 years follow-up of a population-based cohort of middle-aged women'. (1)

Gao et al highlighted a number of issues related to a discordance between pain and radiographic changes and sensitivity of the pain assessment. Although a single definition of knee osteoarthritis (KOA) remains elusive, the presence of knee pain is the main symptom of knee osteoarthritis(OA)(2-4) and there is still a strong relationship between pain and ROA. (5, 6) Notwithstanding this, a substantial number of patients with radiographic knee osteoarthritis (ROA) are asymptomatic. Although OA is the most common 'source' of knee pain in ROA, it is true, as pointed out by Gao et al. that many other diagnoses may be judged to account for a patient's symptoms including bursitis, tendinopathies and overuse injuries. In this cohort of middle aged to elderly women, we feel that these alternative causes will not be prevalent. We defined pain as the presence of side-specific knee pain in the preceding month, and painful radiographic KOA as knee specific pain and presence of ROA. We have performed additional analyses to further address the queries of Gao et al.

We analysed symptomatic ROA (SROA) using a definition of pain as present for at least 15 days in the last month, which is commonly used in the literature.(7, 8) Of the original painful ROA group, 49% fulfilled the new pain criteria, and a further 21% reported knee pain on 6-14 days in the in the preceding month. Both, the Kaplan-Meier survival plot (presented below) and hazard ratio for all-cause mortality in the model adjusted for age (2.06 (95% CI 1.14 to 3.72)) for symptomatic ROA was very similar to the one presented in our paper for painful ROA group. In the fully adjusted model a similar trend was seen with a HR of 1.6 (95% CI 0.77 to 3.44), but it was not statistically significant, most likely due to a small number women in the SROA group (n=28). Furthermore, we excluded from analyses any participants with joint pain due to other diseases that are or might be

associated with a decrease in average life expectancy including inflammatory arthritis (n=43). We are confident that the association with mortality in our paper is in women with painful radiographic KOA.

Gao et al mentioned a number of interesting points related to the consequences of KOA or its treatment. Our question related to whether women with KOA suffered or had an increased risk of premature mortality. As such we adjusted for known potential confounders, but we felt that consequences and treatment of KOA would be on the causal pathway of the association and that by adjusting for them we would induce a bias toward the null hypothesis. Hence we did not include them in our model. We agree that it is likely that individuals with KOA are more sedentary and have poor cardiovascular fitness. We therefore performed a sensitivity analysis looking at crude measures of physical activity and found that it did not attenuate the findings, but we accept that the reliability and validity of a single question is limited. We also found no substantial differences in the results when women who underwent knee replacement (from any of the knee subgroups) were excluded during the follow-up.

Although as noted by Gao et al, increased mortality of the painful ROA group compared to the control group could be potentially explained by the higher mean age and BMI. Age and BMI were adjusted for in our multivariable models. Furthermore the painless ROA group (Pain-/ROA+), with similar characteristics, in the fully adjusted model showed no positive association with excess mortality.

Similar to previous studies, we found that knee subgroups with ROA (Pain+ and Pain-) were more likely to have radiographic hand OA as well.(9) We decided not to include radiographic hand OA in the knee analyses as it has not been an independent risk factor associated with any excess mortality in this or previous study using Cox proportional hazards models adjusted for known cardiovascular risk factors.(10) The ability of our statistical model to explain significant mortality differences in hand OA analyses gives us confidence that our models were adjusted for all-important covariates. This included baseline NSAID use, occupation, age, BMI, typical cardiovascular risk factors, past physical activity, existing CVD disease. Despite the understandable desire to include as many potential variables as possible in regression analysis, overfitting of the model can be a real problem.

Prospective changes of the risk factors in each subgroup, differences in inflammatory markers, adipokines and health status including future risk of falls and fractures are very interesting new research questions emerging from our findings, and we are planning to investigate them in the future. We agree that it is plausible that painful KOA is an early sign of metabolic dysregulation, leading to CVD problems(11) and this will be a focus of future research.

We thank Gao et al. for their interest in our paper.

**Correspondence** to Dr Stefan Kluzek, Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, University of Oxford, Old Rd, Oxford OX3 7LD, United Kingdom; stefankluzek@doctors.net.uk

**Contributors** Kluzek S<sup>1,2</sup>, Sanchez-Santos MT<sup>1,2</sup>, Leyland KM<sup>1,2</sup>, Judge A<sup>1,3</sup>, Newton J<sup>1,2</sup>, Arden NK<sup>1,2,3</sup>

### **Author Affiliations**

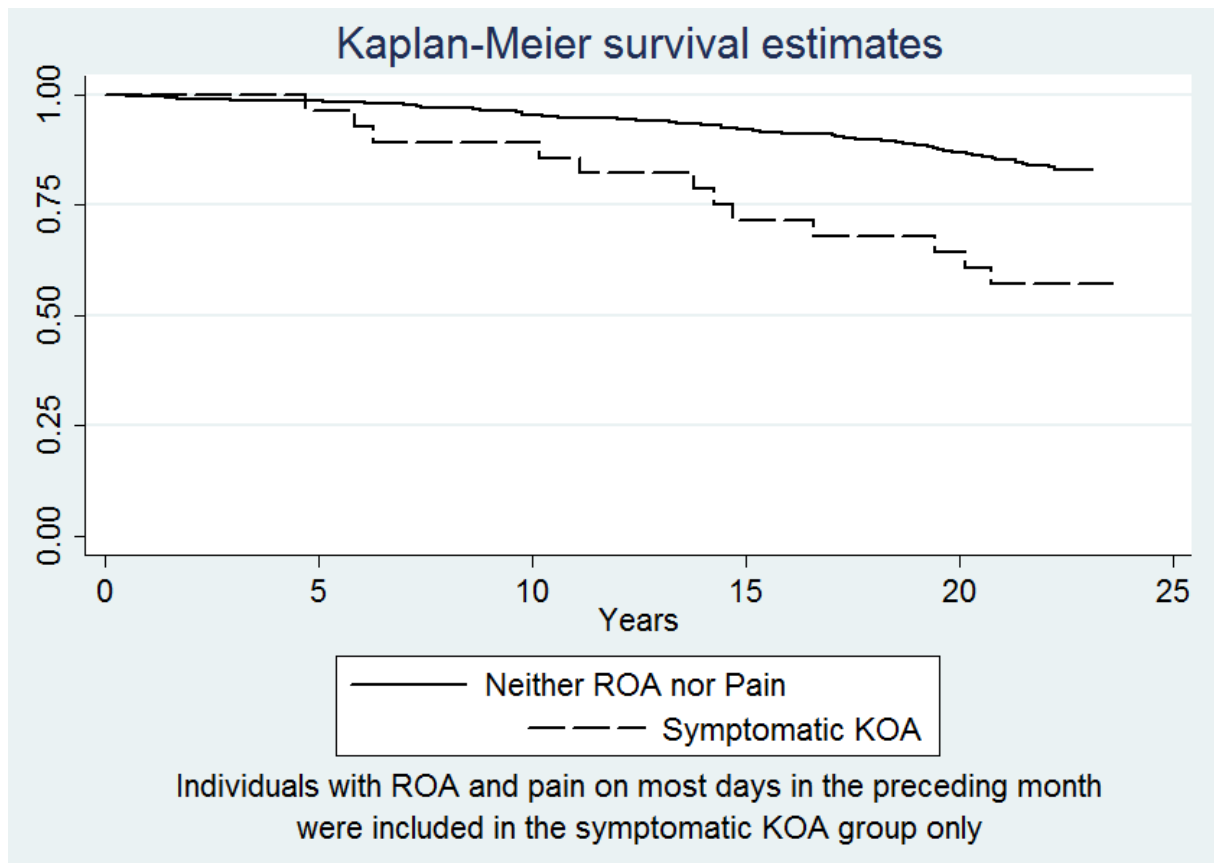
1 Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK

2 Arthritis Research UK Centre for Sport, Exercise and Osteoarthritis, University of Oxford, Oxford, UK

3 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, UK

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**Competing interests** None declared.



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