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## Osteoarthritis and mortality: Answering questions or questioning answers?

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In this issue of *Epidemiology*, Turkiewicz et al<sup>1</sup> report on their careful analysis which adds to the growing literature evaluating the link between osteoarthritis and time to death. In 2008, a systematic review noted “moderate evidence” supporting the notion that osteoarthritis is associated with an accelerated time to death.<sup>2</sup> Studies published since 2008 either support e.g.<sup>3</sup> or refute e.g.<sup>4</sup> the findings of the systematic review. In the present work, Turkiewicz et al<sup>1</sup> conclude that there is no association between osteoarthritis and time to death. Interestingly, they reach this conclusion despite reporting a hazard ratio less than one (0.87) and a precise 95% confidence interval (0.85–0.89). So what then do we believe?

The advantages of the current study relative to prior research are many. Previous work has been limited by small cohorts with the expected lack of precision.<sup>2</sup> With the approximately 1.3 million residents of the Skåne region of Sweden, the authors were able to identify approximately 80,000 residents with evidence of osteoarthritis. Clearly the authors have the advantage of sample size. Having a population-based cohort study to some extent removes the potential for selection biases that may have plagued previous research. The design of the study also permitted the authors to follow the cohort for a longer period of time (an average of 10 years) than some of the previous studies. The available data sources also allowed authors to accurately identify the date of death, thus reducing the attrition and biases that may occur with loss to follow-up. Lastly, the authors used the same data to confirm the known positive association between rheumatoid arthritis and accelerated time to death. In doing so, they assert that the results from the rheumatoid arthritis analyses support the validity of the findings regarding osteoarthritis and mortality.

Despite these strengths, concerns about misclassification of osteoarthritis are real in the context of studies that use healthcare administrative data. The authors cite work conducted on a subset of the population which indicated a high positive predictive value, but the likelihood of “false negatives” is a threat to the current study. In studies of the prevalence of

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### Conflicts of Interest:

The authors report no conflicts of interest relevant to this work. Dr. Lapane has served as a paid consultant to Janssen Pharmaceuticals / JEN Associates, GlaxoSmithKline, and HarmonYX on projects related to schizophrenia, lupus, and pharmacogenetic testing, respectively.

osteoarthritis, those that relied on radiographic data for the operational definition of osteoarthritis produced the highest prevalence estimates whereas studies that used self-reported data or symptoms yielded comparable prevalence estimates.<sup>5</sup> Administrative data sources lack measures of the severity of osteoarthritis and potential underlying cause of osteoarthritis (e.g. obesity or trauma). The potential for systematic differences in who was classified as having osteoarthritis to those who may have osteoarthritis, but do not seek care, exists. The likelihood that such differences are also risk factors for mortality cannot be easily dismissed. To address these concerns, Turkiewicz et al<sup>1</sup> offer an extensive array of thoughtfully executed sensitivity analyses, each confirming the primary findings and ruling out (as best as is possible with administrative health care data) these alternative explanations for the observed findings.

Nevertheless, osteoarthritis is a progressive disease for which there is no cure. Traditionally, symptom relief has been a primary goal and, towards that end, clinical guidelines<sup>6</sup> support both the use of pharmacological and non-pharmacological approaches. Many strategies that may help with symptom relief are available without a healthcare provider prescription. In Sweden, the extent to which persons with osteoarthritis eventually see a physician as a measure of last resort is unclear. It is curious that the average age at diagnosis in the present study was 70–72 years whereas in the United States the mean age at osteoarthritis diagnosis is 53 years.<sup>7</sup> It is probable that persons presenting for health care encounters that are coded as osteoarthritis have had the disease for some time. Whether the differences in age at diagnosis impact the estimate of effect itself or simply the generalizability of the findings is unclear.

That leads us to another question. To what extent can these findings be generalized beyond Sweden? Consider the major risk factors for osteoarthritis: genetic factors, obesity, and trauma. Although the prevalence of obesity is increasing in Sweden,<sup>8</sup> it is likely much less than other countries overwhelmed by the obesity epidemic. In the United States, an estimated ~26%–52% reduction in the incidence of symptomatic knee osteoarthritis would occur if obesity were eliminated.<sup>9</sup> Not likely so in Sweden. It is possible that the diagnosis of osteoarthritis in the administrative health care data in countries like the United States represents a proxy of overweight/obesity and thus is predictive of mortality. In Sweden, a diagnosis of osteoarthritis in health care data may be indicative of a healthier lifestyle. It was interesting to note that the median number of visits to a physiotherapist within a year of follow-up was less than one in the current study. This seems contrary to the typical recommended 8–12 weeks of therapy<sup>10</sup> but may suggest differences in the disease severity in the study setting. Although the authors attempted to adjust for differences in co-morbidities, they quite rightly remained cautious in their interpretation of their data. Their additional sensitivity analyses relating to the potential for unmeasured confounding likely guided their caution.

At the end of the day, what do we make of the contradictory findings? In patients with rheumatoid arthritis, the consistent findings of accelerated time to death have resulted in increased surveillance of cardiovascular risk factors. Despite the contradictory evidence base, it would be prudent for healthcare providers of persons with osteoarthritis to take a holistic approach to treating them as people, rather than treating a disease. For researchers,

the study by Turkiewicz et al<sup>1</sup> provides a template for how best to thoughtfully and comprehensively explore alternative explanations for observed estimates and calling it as they see it, rather than being seduced by statistical significance.

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