Defining osteoarthritis: a moving target

The challenge of disease definition in osteoarthritis (OA) continues to grow. As described by Pereira et al., in a recent issue of Osteoarthritis and Cartilage (OAC), there are substantial differences in prevalence and incidence estimates when defining OA by radiographic changes alone, as symptomatic OA (requiring a combination of both symptoms and radiographic change) or as self-reported OA, using patient/participant self-report of a previous OA diagnosis. The authors find, not surprisingly to those in the field, a higher prevalence of radiographic OA in comparison to the symptomatic definitions. What may be more surprising is the close relationship between symptomatic OA, which requires both radio-graphs and a report of symptoms, and self-reported OA, requiring perhaps only a single question, both having a prevalence ~10–40% lower than that estimated based on radiographic OA. The estimates are most dissimilar for hand OA, which has a remarkably high radiographic prevalence on the order of 50%, but is symptomatic in 15% and reported by only 5% in the pooled estimates. In contrast, the prevalence estimates for hip OA are more comparable, with a radiographic prevalence of 15%, symptomatic prevalence of 6%, and was reported by 7% of subjects (Fig. 1).

As discussed by the authors, even these three seemingly straightforward definitions are highly variable across studies. Radiographic OA can be determined based on one of many available scoring systems, including the Kellgren–Lawrence scale, assessment of individual radiographic features such as osteophytes or joint space narrowing and their combinations, or quantitative assessment of joint space width. These measures are most commonly applied to the knee, and may be less reliable at other joint sites. Hand OA, in particular, is a challenge to define. Should one distal interphalangeal joint with a Kellgren-Lawrence grade ≥2 define OA of the hand, or should multiple, bilateral joint involvement be required? While Pereira et al. have necessarily combined different radiographic definitions to achieve their goal of pooled prevalence estimates, such differences in radiographic definition are likely responsible for the greater variation demonstrated in the forest plots (Pereira et al., Figures 2–5) among radiographic OA prevalence estimates compared to symptomatic or self-report estimates.

The concept of symptomatic OA is attractive to clinicians, as it seems to represent the best of both worlds, by combining information on structural damage with the patient’s symptoms. However, by defining symptomatic OA as requiring radiographic changes and symptoms in the same joint, all of the issues noted above for radiographic definitions remain, with the added question of how symptoms should be defined. What is the time frame? The last year, month, week? How frequently should symptoms have occurred over that time? Are we concerned only with pain, or also with aching and stiffness? How should we quantify severity? These questions only multiply when progression, in addition to presence of disease, is considered.

Self-report definitions have the distinct advantage of not requiring a clinical examination or imaging studies, making them a good option for large population studies and studies in community settings, but are also problematic. Many individuals are not aware of their clinical diagnosis and may have other forms of arthritis, or arthralgias, and not OA. There may even be confusion in patient’s minds between OA and other non-arthritic diseases, such as osteoporosis. An assumption that one’s pain is due to OA may be made when in reality there is a tendinopathy, bursitis, impingement, or other soft tissue condition. It is therefore very compelling that the estimates for self-reported OA prevalence, at all sites, in the Pereira et al. report closely mirrored those for symptomatic OA, which is a much more burdensome assessment.

Another important consideration for prevalence studies is the population being assessed. While population-based studies use methods (standardization, census weighting, enumeration, etc) to ensure generalizability, studies of disease frequency using hospital or clinic-based groups of patients may have characteristics unique to that group that may not be representative of true population prevalence. Pereira et al. mention this issue and report a sensitivity analysis to estimate the influence of prevalence estimates from “hospital-based” compared to other studies. Further review of the studies considered “hospital-based” by the authors shows that some of these were in fact population-based while others were convenience samples of clinic or hospital patients. A clearer definition of “hospital-based studies” or perhaps a sensitivity analysis comparing the studies that were population-based to those that were not, may help to better understand these differences. A related issue is the wide variation among ethnic groups for OA at different joint sites, which makes pooled estimates across populations, although appealing, not particularly informative.
While radiographic, symptomatic, and self-report have been the most commonly utilized ways to define incident and prevalent OA to date; there are multitudes of other potential ways to define OA. These include definitions based on other imaging modalities, such as the magnetic resonance imaging (MRI) definition currently under development\(^2\) or ultrasound-based determinations\(^5\). Clinical definitions vary across studies, and phenotypic definitions including combinations of joints may be considered in addition to single joints\(^2,12\). Clinical definitions such as those of the American College of Rheumatology are based primarily on history and examination findings, such as pain, aching, or stiffness, crepitus, and bony enlargement, without requiring radiographs for confirmation of the diagnosis\(^13\). Alternative phenotypic definitions could be based on risk factors, such as injury, obesity, or malalignment, or on outcomes such as performance measures or functional limitations.

So what phenotypes and/or disease definitions are important in OA? It likely depends on the question to be answered. For clinicians, symptoms are paramount, as symptoms, not radiographic or other imaging changes, bring a person to the doctor. For bone and cartilage researchers, structural and microstructural changes are most important and may provide clues into pathogenesis and mechanisms of disease initiation and progression. Those developing drugs and performing clinical trials may be interested in symptom and/or structural modification. Groups studying systemic outcomes, such as serum/urine biomarkers and genetic markers, have a particular challenge to face. While these systemic markers are often used in association with a local phenotype, such as a Kellgren–Lawrence grade of 2 or more in a given joint, or a total joint replacement, such systemic measurements must reflect the whole person and not just a single joint. Therefore, while challenging, it may be more reasonable to use a measure of whole-body disease burden in such studies. For structural change, this might include multiple joint radiographic assessments, while for symptomatic or pain, assessments at the person-level would include the other complexities that influence pain, such as mood, coping strategies, catastrophizing behavior, support, socioeconomic status, etc. For researchers, it is essential to consider the phenotype to be assessed in a given study, and to collect all of the relevant information to define that phenotype, whether it is of incidence, prevalence, progression, psychosocial factors, or genetic influence. This also highlights the need for readers of the literature in OA to be aware of the phenotype being used, how it was determined/defined, and the assumptions that were made, in order to better understand the implications of the study.

**Author contributions**

Both Dr. Nelson and Dr. Jordan contributed to the conception and design of this report, drafted and revised the manuscript, and provided final approval of the submitted version.

**Conflict of interest statement**

The authors have no competing interests or financial disclosures in relation to this work.

**References**


A.E. Nelson*, J.M. Jordan*  
Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, 3300 Doc J. Thurston Building, Campus Box 7280, Chapel Hill, NC 27599-7280, United States  
* Address correspondence and reprint requests to: A.E. Nelson, Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, 3300 Doc J. Thurston Building, Campus Box 7280, Chapel Hill, NC 27599-7280, United States. Tel: 1-919-966-0553; Fax: 1-919-966-1739.  
E-mail addresses: aenelson@med.unc.edu (A.E. Nelson); joanne_jordan@med.unc.edu (J.M. Jordan)