Title: Osteoarthritis pain phenotypes: how best to cut the cake?

Category: Invited Editorial

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Main Text

Heterogeneity within clinical populations raises challenges and opportunities for improving treatment. Osteoarthritis (OA) treatments often adhere to the 'one size fits all' utilitarian approach, suggesting that everyone will gain the greatest benefit from the same treatment. However, OA is a heterogeneous condition, with multiple pathologies driving different outcomes. No single outcome is necessarily equally important for all people. Increasingly recognised as a disease of the whole joint, OA affects articular cartilage, subchondral bone and synovium, resulting in a clinical syndrome in which pain is predominant.

Pain itself is symptomatically and mechanistically heterogeneous. It may be intermittent or constant. It may occur with movement, weight-bearing, or at rest. Pain may reflect both nociceptive drive from joint tissue pathology, and neuronal sensitisation, in the peripheral and the central nervous systems. The balance between components of this complex pathology and symptomatology may vary between individuals and within an individual across time, from early to established and end-stage disease. Furthermore, OA flares may exacerbate this complex interplay between pathology and symptoms.

Given this heterogeneity, it is unsurprising that existing treatments do not relieve all OA pain. It might be that we have not yet discovered the key that links OA pathology with symptoms, but it seems increasingly likely that a single key does not exist. There might be subgroups within the OA population (Figure 1). Each subgroup might have a unique constellation of OA pathology and symptoms, have a different prognosis, and respond to different interventions. Such phenotypic subgroups might be stable over time, amounting to separate diagnostic groups that, in our ignorance, we currently lump under the OA umbrella. Alternatively, patients might transition between phenotypic subgroups representing different disease stages.

Even this concept of phenotypic groupings might be oversimplistic. Rather than segregating between discrete subgroups, patient characteristics might vary across continuous multidimensional spectra. Every individual might represent a unique subgroup, and optimal care might need to be truly personalised. Homogenous disease populations, phenotypic subgroups and continuously distributed characteristics require different therapeutic approaches. A single treatment might work equally well for all people with the same diagnosis, or only for those who fit within a specific phenotypic subgroup. Risk scores might best address multidimensional phenotypes that blend into each other if they reliably indicate the individual's chances of benefit or harm.

Latent class analysis can disentangle OA heterogeneity and measure the certainty with which discrete phenotypic subgroups exist. It can help identify the key characteristics that define those subgroups, and enable allocation of individuals to each subgroup with measurable degrees of certainty. These subgroups can then be subcharacterised regarding demographics, clinical features, prognosis and treatment response. Latent class models might reflect differences in disease severity, indicating those who stand to gain the most from any treatment. At their most informative, latent classes might indicate mechanistic subgroups that will respond differently to different treatments.

The paper by Neelapala *et al.* [1] uses latent class analysis to define pain phenotypic subgroups in OA. Their approach is refreshingly broad, including a wide range of phenotypic characteristics. Their Model A, in essence, replicates previously defined chronic pain phenotypes[2]. Mechanistically, Model A might reflect central nervous system sensitisation and psychosocial aspects of pain, a group of characteristics that we have referred to as Central Aspects of Pain[3]. Within Model A, the three identified classes suggest different mechanistic underpinnings, particularly related to differences in pain processing. Class 1 might reflect altered central nervous system afferent signalling, class 2 spinal cord facilitation of nociceptive signalling, and class 3 alterations in descending modulatory controls from the brainstem. Whereas some people cleanly fit into a single class, some individuals

seem to straddle across two or more classes (Figure 1). The reporting of model statistics is important for the interpretation of this.

Neelapala *et al.*'s[1] findings illustrate an important aspect of the latent class approach: the nature of the identified phenotypic subgroups depends on the characteristics included in the modelling. Their model B interestingly includes additional variables, including quadriceps strength, walking speed, and comorbidities. The choice of variables included often depends on the characteristics measured in the host study (in this case, the Multicenter Osteoarthritis (MOST) study), and usually has a theoretical or empirical association with the outcome of interest (in this case, OA pain). The subjective selection of variables introduces bias and influences the revealed phenotypic subgroups. Other research has found that strength, speed, and comorbidities are each associated with pain in cross-sectional and longitudinal analyses[4-6]. Therefore, inclusion in a `'pain' phenotypic model may be justified. Model B produces different phenotypic groupings compared to Model A, and participants in Model A did not directly map onto Model B classes. These differences further highlight the heterogeneity and multidimensionality of OA as a clinical syndrome.

Phenotypic subgroups presented by Neelapala *et al.*[1] might be only one way of viewing the OA population. Other variables might have revealed different phenotypic subgroups. For example, bone marrow lesions are more strongly associated with pain than meniscal extrusion[7]. OA populations have previously been subgrouped based on biochemical variables (e.g., cartilage, bone turnover, or inflammation markers)[2]. Social determinants might be strongly associated with high-impact chronic pain[8], but are often a blind spot for stratification. The OA population might be split into multiple overlapping phenotypic subgroups, each determined by different characteristics.

Empirically derived subgroups can inform a deeper understanding of the disease. Phenotypes may assemble combinations of characteristics with a directional or causal relationship with a clinical

outcome. Model A may represent a bidirectional or cyclical relationship between pain processing and worsening pain, where persistent or severe nociception causes changes in central nervous system processing, affecting pain persistence and severity. Muscle strength and walking speed are often considered secondary to pain[9]. However, changes in the central nervous system's neural drive to muscles also can alter muscle strength[10] and, therefore, gait and physical function. Alterations in gait and activity might reciprocally alter the central nervous system processing of nociceptive inputs[11]. Further exploration of the directionality and mechanisms that underpin relationships between patient characteristics and clinical outcomes will inform how phenotyping might influence diagnosis and treatment.

Phenotypic subgrouping might have the greatest clinical value if it can predict prognosis or response to a specific treatment. Neelapala *et al.*[1] found no association between their phenotypes and pain prognosis, but need not necessarily indicate that no such association exists. MOST is an observational cohort whose research protocol has not controlled treatment. We might expect that if a phenotypic subgroup were especially responsive to a treatment they receive, then allocation to that phenotype might predict a good outcome. Conversely, that phenotype might be associated with a poor outcome if such treatment is currently unavailable. Early research indicated that seropositivity was a poor prognostic marker in rheumatoid arthritis. However, with the advent of biological treatments that suppress immune-driven inflammation, seropositivity might predict good outcome[12]. OA phenotypic subgrouping might yet help define eligibility for clinical trials of targeted interventions and help to identify for whom such treatments might be most appropriate in clinical practice.

Phenotypic subgrouping might indicate different prognoses for different pain outcomes. Neelapala *et al.*[1] classified poor prognosis by a composite of increase ≥2 from baseline to 2 years follow up on a visual analogue scale assessing average pain over the past month, plus a shift from only intermittent

to constant pain, and an increase in the frequency of intermittent pain. For some individuals, increasingly widespread pain also might be important. Different phenotypic subgroups might predict different outcome characteristics that have different mechanistic underpinnings.

Suppose people are to be allocated to a subgroup. To recommend treatment, that allocation should be made with an acceptable level of confidence. Subgroups might be discreet, but, more often, overlap or merge into each other (Figure 1). For an individual on the boundary between subgroups, allocation might be reduced to tossing a coin. Should people who do not neatly fit one specific subgroup be allocated to a single subgroup, or simultaneously to multiple subgroups? If different phenotypes predict response to different treatments, should those who straddle subgroups be offered multiple treatments? At its most extreme, there might be continuity across a spectrum for each characteristic, whereby `risk scores' might be more helpful than drawing seemingly arbitrary boundaries between subgroups. Further research might build on the findings of Neelapala *et al*.[1] to determine whether other characteristics or measurement tools might more robustly allocate individuals into their identified subgroups. Indeed, unmeasured factors might more closely represent what mechanistically drives differences between subgroups.

Phenotypic subgrouping has promise in OA. As with all new disciplines, a range of methodological approaches have been adopted, some more robust than others[2, 13]. Characteristics used to define subgroups should ideally be defined in advance of data collection, and studies should be adequately powered for multiple subgroup analyses[14]. Even within patient subgroups there will remain inter-individual variation and individual patient preference.

To conclude, the paper by Neelapala *et al*. [1] is an object lesson in phenotypic subgrouping. It illustrates the strengths of this approach, and emphasises the likelihood that OA is a heterogenous condition rather than a single diagnosis. It also illustrates some of the weaknesses of latent class

analyses. The subgroups identified depend on the variables included in the models. They might point to clinically meaningful phenotypes, but represent only one way of looking at the population. Looking from different angles, using different clinical or biological, psychological or social characteristics, OA phenotypic subgroups might look very different. In the future, we may face an array of possible overlapping phenotypes. Being able to assess and make informed decisions requires skills in risk quantification and communication, and an understanding of the level of certainty and potential biases arising from variable selection during modelling. Ultimately, phenotypic subgroups are most useful if they can reliably determine prognosis and predict treatment response. As a bonus, they might provide insights into diagnosis and OA pain mechanisms.

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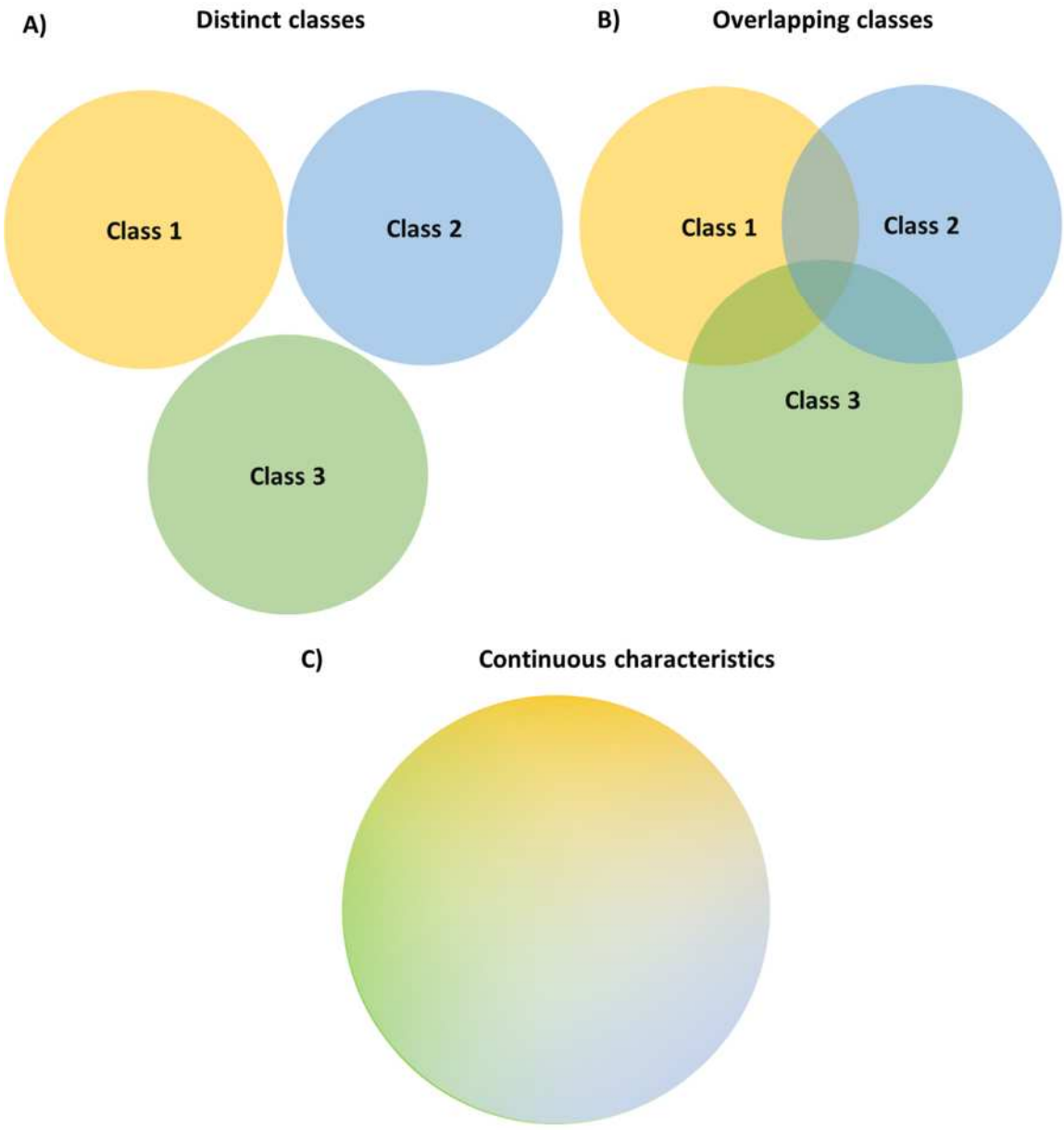
Figure 1.


A)
Distinct classes
Class 1
Class 2
Class 3
B)
Overlapping classes
Class 1
Class 2
Class 3
C)
Continuous characteristics