



HAL
open science

Pain-phenotyping in osteoarthritis: Current concepts, evidence, and considerations towards a comprehensive framework for assessment and treatment

F. Saxer, A. Hollinger, M.F. Bjurström, P.G. Conaghan, T. Neogi, M. Schieker, Francis Berenbaum

► To cite this version:

F. Saxer, A. Hollinger, M.F. Bjurström, P.G. Conaghan, T. Neogi, et al.. Pain-phenotyping in osteoarthritis: Current concepts, evidence, and considerations towards a comprehensive framework for assessment and treatment. *Osteoarthritis and Cartilage Open*, 2024, 6 (1), pp.100433. 10.1016/j.ocarto.2023.100433 . hal-04405762

HAL Id: hal-04405762

<https://hal.sorbonne-universite.fr/hal-04405762>

Submitted on 19 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Pain-Phenotyping in Osteoarthritis: Current Concepts, Evidence, and Considerations towards a Comprehensive Framework for Assessment and Treatment

Saxer F^{1, 2*}, Hollinger A^{1, 3*}, Bjurström MF⁴, Conaghan PG⁵, Neogi T⁶, Schieker M^{1, 7}, Berenbaum F^{8 #}

¹ Novartis Institutes for Biomedical Research, Novartis Campus, 4002 Basel, Switzerland; (Saxer, Franziska franziska.saxer@novartis.com; Hollinger, Alexa alexa.hollinger@novartis.com; Schieker, Matthias matthias.schieker@novartis.com)

² Medical Faculty, University of Basel, 4002 Basel, Switzerland

³ Intensive Care Unit, Department of Acute Medicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

⁴ Department of Surgical Sciences, Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden (Martin Flores Bjurström martin.flores.bjurstrom@uu.se)

⁵ Leeds Institute of Rheumatic & Musculoskeletal Medicine, University of Leeds and NIHR Leeds Biomedical Research Centre, UK (Conaghan, Philip P.Conaghan@leeds.ac.uk)

⁶ Clinical Epidemiology Research and Training Unit and Rheumatology, Boston University School of Medicine Epidemiology, Boston University School of Public Health (Neogi, Tuhina tneogi@bu.edu)

⁷ Medical Faculty, Ludwig-Maximilians-University, Munich, 80336, Germany.

⁸ Department of Rheumatology, Sorbonne Université, INSERM CRSA, AP- HP Hopital Saint Antoine, Paris France (Berenbaum, Francis francis.berenbaum@aphp.fr)

* These authors contributed equally

corresponding author:

Prof. Francis Berenbaum

Email: francis.berenbaum@aphp.fr

1 **Pain-Phenotyping in Osteoarthritis: Current Concepts,**

2 **Evidence, and Considerations towards a Comprehensive**

3 **Framework for Assessment and Treatment**

4 **Abstract**

5 Objectives: Pain as central symptom of osteoarthritis (OA) needs to be addressed as part
6 of successful treatment. The assessment of pain as feature of disease or outcome in
7 clinical practice and drug development remains a challenge due to its
8 multidimensionality and the plethora of confounders. This article aims at providing
9 insights into our understanding of OA pain-phenotypes and suggests a framework for
10 systematic and comprehensive assessments.

11 Methods: This narrative review is based on a search of current literature for various
12 combinations of the search terms “pain-phenotype” and “knee OA” and summarizes
13 current knowledge on OA pain-phenotypes, putting OA pain and its assessment into
14 perspective of current research efforts.

15 Results: Pain is a complex phenomenon, not necessarily associated with tissue damage.
16 Various pain-phenotypes have been described in knee OA. Among those a phenotype
17 with high pain levels not necessarily matching structural changes and a phenotype with
18 low pain levels and impact are relatively consistent. Further subgroups can be
19 differentiated based on patient reported outcome measures, assessments of
20 comorbidities, anxiety and depression, sleep, activity and objective measures such as
21 quantitative sensory testing.

22 Conclusions: The complexity of both OA as disease and pain in OA prompt the definition
23 of a set of variables that facilitate assessments comparable across studies to maximize
24 our understanding of pain, as central concern for the patient.

25

26 Key words: phenotypes, osteoarthritis, osteoarthritis pain, drug development, patient

27 reported outcomes

28

29

30 **Abbreviations**

31	ADAMTS5	A disintegrin and metalloproteinase with thrombospondin motifs 5
32	CPM	Conditioned pain modulation
33	FDA	Food and drug administration
34	NGF	Nerve growth factor
35	NMDA	N-methyl-D-aspartate
36	OA	Osteoarthritis
37	PRO	Patient reported outcome
38	QST	Quantitative sensory testing
39	PPT	Pressure pain thresholds
40	TS	Temporal summation
41	WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

42

43

44 **Introduction**

45 Osteoarthritis (OA) is a complex multifactorial disease and global health care challenge
46 affecting more than 500 million people.¹ Not only is OA a major cause of reduction in
47 quality of life and activities of daily living, with substantial socio-economic impact,^{2,3} but
48 has also been associated with increased mortality.⁴ Total joint replacement is typically
49 the 'last resort' but approximately 20% of patients remain symptomatic after the
50 procedure.⁵ In the absence of treatments that can halt or reverse the OA process, and
51 despite much research over decades, there remains a huge unmet medical need.

52

53 For a "treatment of OA" claim for a medication that targets the underlying
54 pathophysiology, regulatory authorities require benefits on how patients feel, function
55 or (their joints) survive.⁶ While structural changes are objectively quantifiable, validly
56 assessing non-structural outcomes (i.e., pain or function) remains complex.

57 Previous research has established the concept of OA-phenotypes.^{7,8} i.e., the existence of
58 observable patient characteristics that systematically differ between groups of patients
59 affected by OA. Phenotyping thereby allows a stratification of a heterogeneous patient
60 population and may be reflective of different underlying pathologic mechanisms
61 defining different endotypes.^{9,10} The existence of different OA pain-phenotypes¹¹ adds
62 an additional layer of complexity.

63 This narrative review aims at summarizing key concepts of pain-phenotyping,
64 presenting current evidence. Pain is the most important symptom of OA and its
65 treatment central to patients' well-being. The manuscript tries to capture the complexity
66 of OA-pain that underlines the need for personalized and targeted management
67 approaches based on a better understanding of pain-phenotypes and underlying
68 mechanisms. We argue that a better understanding of these aspects is crucial for

69 designing meaningful future trials and measuring treatment success. The ultimate goal
70 is to establish a framework for systematic and comparable pain assessments in OA
71 patients, with the intention of developing and allocating targeted treatments that meet
72 patients' and societies' expectations.

73

74

75 **Pathophysiology of pain in OA**

76 Pain is defined as “an unpleasant sensory and emotional experience associated with, or
77 resembling that associated with, actual or potential tissue damage”.¹² This definition
78 underlines the complex interaction of pain triggers with biological, psychological and
79 social factors (see Supplementary Table 1).¹³ This definition also makes abundantly
80 clear that the absence of a structural correlate does not disqualify a sensation as pain,
81 and that pain can persist despite the normalization of structure. It remains unclear why
82 or which patients transition from acute to persistent or chronic pain.¹⁴ In principle,
83 chronicity should be assumed in most OA patients with a typical pain duration of >6
84 months; indeed a “chronic pain” phenotype is consistently reported.^{15, 16}

85

86 Pain perception, processing and transition to chronic pain are the result of experience-
87 driven neuro-structural changes¹⁷, neuro-immunologic crosstalk^{18, 19} and (epi)genetic
88 mechanisms.^{20, 21} In principle, pain perception occurs in several “morphologic layers”.
89 Peripheral joint nociceptors are activated by mechanical, thermal or chemical stimuli
90 such as cytokines or chemokines released as part of inflammatory processes and
91 cartilage degradation in OA. This can also trigger vascularization and ingrowth of
92 additional nociceptors perpetuating the stimulus.²² Continuous or repetitive stimulation
93 of nociceptors can reduce activation thresholds leading to peripheral sensitization with

94 primary hyperalgesia (an abnormally increased sensitivity to pain at the site of tissue
95 damage) or allodynia (pain from otherwise non-noxious stimuli such as light touch),
96 which may be present in OA.¹⁶ Nociceptor activity is transmitted via C-fibers (slow,
97 burning pain) or A-delta fibers (fast, sharp pain) to the cell body situated in the dorsal
98 root ganglion of the spinal cord. The activity is further transmitted to higher systems,
99 whereas inhibitory and excitatory influences from the local cellular environment as well
100 as thalamic centers, brainstem and cerebral cortex modulate the pain perception^{17, 23},
101 explaining the interrelation between pain and affect^{17, 24}, but also the impact from
102 expectation, observed in placebo and nocebo phenomena^{25, 26}.

103 Based on the above mechanisms, primarily three types of pain have been discerned
104 (with some overlap) in OA:

105 I) Nociceptive pain is triggered by tissue damage and often responsive to NSAIDs.²⁷ Pain
106 in OA was thought to be purely nociceptive²⁸ with inflammation as potential
107 pathophysiologic trigger and driver of pain.^{29, 30} The innate immune system,³¹ and
108 especially macrophages play crucial roles in knee OA-pain through induction of
109 inflammatory mediators,³² growth factors³³ and proteinases,³⁴ and are reciprocally
110 stimulated via nociceptor-secreted neuropeptides.³⁵ They also impact pain processing at
111 the level of dorsal root ganglia and literature supports their role in pain sensitization
112 and neuropathic pain.^{36, 37} Preclinical animal models evaluating anti-ADAMTS5 (a
113 disintegrin and metalloproteinase with thrombospondin motifs 5),³⁸ or antibodies
114 targeting Toll-like Receptors^{39, 40} in knee OA support the idea of neuroinflammatory
115 mechanisms in OA-pain. Similarly, the neurotrophin NGF (nerve growth factor) has been
116 implicated in OA-pain and inflammation^{33, 41}. NGF is increased in OA joints and
117 promising clinical results for pain relief have been reported in humans and animals⁴²⁻⁴⁴.
118 NGF is released in response to mechanical stress and inflammation⁴⁵, its role in the

119 context of inflammation however is not fully understood yet⁴⁶, which may explain the
120 safety concerns that finally led to a negative benefit risk evaluation for an anti-NGF
121 antibody by the FDA (food and drug administration)⁴⁷. In addition, histamine receptors
122 have been implicated in nociception and chronic pain. Subtypes are expressed in the
123 peripheral and central nervous system and play a role in the modulation of nociceptive
124 transmission. ⁴⁸

125

126 II) Nociplastic pain is a result of central dysregulation and sensitization, and refers to
127 “pain that arises from altered nociception despite no clear evidence of actual or
128 threatened tissue damage causing the activation of peripheral nociceptors or evidence
129 for disease or lesion of the somatosensory system causing the pain” (IASP
130 (International Association for the Study of Pain) definition).^{12, 49, 50} Yet, links between
131 disease duration and measures of central sensitization seem weak ⁵¹ and most patients
132 improve markedly after joint replacement, suggesting a peripheral driver of the pain
133 experience. ⁵²

134 Nociplastic pain is decoupled from the pathology at the joint level though also associated
135 with neuroimmunologic changes. In view of the impact of central pain modulation,
136 treatments such as patient education, sleep hygiene, and psychological treatment ⁵³ or,
137 centrally acting substances such as NMDA (N-methyl-D-aspartate) antagonists ⁵³,
138 cannabis-based medicines⁵⁴, tricyclic antidepressants, 5-hydroxytryptamine–
139 noradrenaline reuptake inhibitors and gabapentinoids^{53 55} may be beneficial as adjuncts
140 in improving this type of pain. Similarly, sympatholytics may be beneficial in nociplastic
141 and possibly neuropathic pain. ⁵³

142

143 III) Neuropathic pain is typically associated with structural nerve damage⁵⁶, the
144 morphologic correlate of which currently remains elusive in OA and may be related to
145 comorbidities rather than OA (e.g., diabetes, lumbar radiculopathy, etc.). A recent
146 matched pair approach in a cohort of knee OA patients suggested a potential
147 neuropathic pain component in 8.2% (based on PainDETECT). These patients differed
148 from their likely non-neuropathic counterparts (matched for pain intensity) in having a
149 higher degree of functional impairment and more painful joints but generally less
150 pronounced radiographic joint changes.⁵⁷

151

152 **Methods**

153 This narrative review is based on a non-systematic search of current literature in Ovid
154 MEDLINE® using the search terms “pain-phenotype” and “knee osteoarthritis” in
155 various combinations to identify articles covering the area of interest. To evaluate
156 potential surrogate measures for pain-phenotypes PubMed ® was searched for
157 biomarkers evaluated in the context of OA. The search was then expanded to cross-
158 referenced biomarkers and interventions.

159

160 **Studies examining knee OA pain-phenotypes**

161 The relevance of the different mechanisms for pain perception in OA underlines the
162 importance of distinguishing the predominant pain type or mechanism for a successful
163 treatment allocation especially in relation to nociceptive vs non-nociceptive pain. This
164 distinction can be achieved via pain-phenotyping, i.e., the differentiation of patient
165 clusters based on observable traits associated with differences in pain experience.

166

167 *Table 1 may be placed here*

168

169 Various studies have used phenotyping approaches to characterize pain-phenotypes in
170 OA as summarized in Table 1. Murphy et al.⁵⁸ cross-sectionally evaluated the co-
171 occurrence of centrally mediated symptoms in older adults with hip or knee OA and
172 identified three pain-phenotypes. Those with the highest pain levels also showed high
173 levels of depression and fatigue, low sleep quality and a high burden of comorbidities
174 potentially indicating a higher overall impact from central mechanisms of pain
175 perception. Patients in this cluster had the highest disease impact on health-related
176 quality of life. The second cluster had intermediate levels of depression and fatigue, low
177 levels of pain and good sleep, possibly indicative of a mixed peripheral and central pain-
178 phenotype. The third cluster had overall low levels of pain, fatigue or depression, but a
179 poor sleep quality. This could be patients with a predominantly nociceptive pain type.⁵⁸
180 However, because this evaluation was cross-sectional, directionality and mechanisms
181 cannot be discerned.

182 Finan et al.⁵⁹ also evaluated patient reported outcome (PRO) information on
183 anxiety/depression symptoms, sleep and pain catastrophizing but included the
184 congruence between pain and structural changes versus quantitative sensory testing
185 (QST). They dichotomized pain (cut-off 4.22 out of 20 on WOMAC (Western Ontario and
186 McMaster Universities Osteoarthritis Index) pain subscale score) and radiographic
187 grade (Kellgren-Lawrence 1 and 2 vs. 3 and 4) resulting in four combinations. The high-
188 pain groups trended towards higher impact in psychosocial function, which was
189 significant for patients with high-pain and low radiographic grade. The most notable
190 finding was that the high-pain and low Kellgren-Lawrence group exhibited
191 hypersensitivity on several QST modalities at unaffected anatomic sites, suggesting a

192 propensity towards central pain sensitization. In contrast, the other discordant group
193 with low-pain and high-Kellgren-Lawrence were the least pain-sensitive.⁵⁹
194 Similarly, Egsgaard et al.⁶⁰ aimed at identifying pain profiles in patients with OA based
195 on psychological measures, QST, Kellgren-Lawrence grade and biomarkers. Compared
196 to controls, the four resultant clusters had higher disease impact on physical
197 functioning, quality of life and pain response. In the order of pain impact (low to high),
198 the cluster of patients with overall low pain sensitivity and higher CPM (conditioned
199 pain modulation) than controls had the lowest pain. The next lowest pain cluster
200 showed increased temporal summation at the arm only (TS) and CPM and pressure pain
201 thresholds (PPT) comparable to controls, potentially indicative of an early stage of
202 chronification. Two clusters showed reduced PPTs, enhanced TS and reduced CPM. In
203 addition, one of those clusters was characterized by greater hyperalgesia, lower general
204 health and pain catastrophizing. While both of these clusters showed alterations in pain
205 thresholds quantifiable with QST, the one additionally affected by lower general health
206 and pain catastrophizing reported the highest values on the three WOMAC subscales,
207 suggesting an additive effect on pain experience.⁶⁰
208 In addition to psychological measures, radiographic OA grade and patient
209 characteristics, Kittelson et al. included extensor strength in their approach to pain-
210 phenotyping of the OAI (osteoarthritis initiative) database⁶¹, as well as a community
211 sample that comprised participants with symptomatic OA and healthy older adults as
212 controls.⁶² In both samples they identified four pain-phenotypes, one primarily
213 characterized by a high burden of comorbidities, one by a high level of psychological
214 distress and pain, and one with high extensor strength and a low overall burden of
215 disease. Participants from the community sample in this latter group often had a history
216 of knee trauma or surgery.⁶² A fourth pain-phenotype was identified in both analyses; in

217 the OAI, this fourth phenotype was characterized by a high proportion of joint line and
218 pes anserine tenderness⁶¹. In the community sample, the fourth phenotype was
219 differentiated by low target knee PPTs.⁶²

220

221 Reducing heterogeneity due to differences in OA severity, Frey-Law et al.⁶³ analysed
222 pain-phenotypes in patients scheduled for knee arthroplasty and identified five
223 phenotypes based on psychological assessments, patient characteristics, QST, pain
224 characteristics, function and quality of life. One pain-phenotype exhibited low pain
225 sensitivity but high PPTs at the target knee. Another exhibited average pain sensitivity
226 to all tested stimuli. In contrast, three clusters showed high sensitivity to pain. These
227 three clusters differed in their sensitivity to TS, heat and pressure pain, and punctate
228 pain, respectively. There was no relevant impact from the other evaluated
229 characteristics except a predominance of males in the low pain group. Interestingly, in
230 the high pain sensitivity group, high punctate and high heat and pressure pain
231 sensitivity translated into higher clinical pain levels, while TS did not ⁶³.

232 Evaluating thermal measures of QST as potential indicators of central sensitization and
233 neuropathic pain and their correlation with pain levels, pain characteristics and
234 function, Wright et al.⁶⁴ compared a community sample of patients with painful knee OA
235 to pain-free volunteers. Patients with OA displayed lower PPTs than pain-free
236 volunteers at the index knee but not at other sites. In addition, patients with OA showed
237 cold pressure pain on average at higher temperatures than pain-free controls at the
238 index and contralateral knee, as well as a distant site. This cold hyperalgesia was
239 pronounced in a subgroup of 44% of patients. These patients also had a tendency
240 towards reduced thresholds for pressure and thermal pain at sites other than the target
241 knee, higher pain levels, higher functional impact and higher PainDETECT scores.

242 Despite the differences in QST between the groups, there were no differences in
243 psychological impact.⁶⁴

244 In the only longitudinal study to date to assess pain susceptibility by Carlesso et al.⁶⁵,
245 four distinct phenotypes were identified among people with or at risk of knee OA who
246 were free of persistent knee pain at baseline. Interestingly, the group that was the most
247 sensitized based upon PPT measures had a 2-fold higher risk of developing persistent
248 knee pain compared with the group that had the least sensitization based upon PPT and
249 TS. Further, the group that exhibited TS was not at increased risk for developing
250 persistent knee pain.⁶⁵ The other factors that were examined (i.e., widespread pain, pain
251 catastrophizing, depressive symptoms, poor sleep) did not differentiate between the
252 groups, and thus did not contribute to risk of developing persistent knee pain.

253 Heat and cold hyperalgesia have recently further been evaluated by Carlesso et al.⁶⁶ in
254 an analysis of pain-phenotypes in patients presenting with knee OA. The analysis was
255 based on the IMMPACT recommendations for pain-phenotyping, i.e., “pain variability,
256 intensity and qualities, somatization, anxio-depressive symptoms, sleep, fatigue, pain
257 catastrophizing, neuropathic pain, and quantitative sensory tests”.⁶⁷ The three pain
258 classes separated based on PRO information (consistent high, intermediate or low
259 disease impact). The results for QST were less clear. Temperature sensitivity and PPTs
260 separated the least affected from the two other classes. Only TS was significantly
261 different for all the classes.⁶⁶ TS has also been demonstrated to separate clusters in
262 other cohorts^{59, 60, 63, 65}, and to potentially predict acute postoperative pain intensity and
263 chronic postsurgical pain.^{68, 69}

264 Two studies evaluated clinical pain-phenotyping and included imaging. In a community
265 sample of older adults, Pan et al. identified three subgroups of patients with knee pain.⁷⁰
266 A predominantly female class including patients with high local pain, a high burden of

267 emotional problems and limited structural changes was identified, while another class
268 was dominated by males with low disease impact but definite structural changes. The
269 third class was healthy overall with limited signs of structural OA and low levels of knee
270 pain, assumed by the authors to comprise participants with early OA. Pain levels
271 between the high and low pain groups consistently differed over 10.7 years and were
272 not necessarily correlated with the presence of radiographic signs of OA.

273 In another cohort study of community dwelling adults, Burston et al.⁷¹ evaluated the
274 impact of anxiety and depression on incident knee pain. They report an odds ratio (OR)
275 of 1.71 for incident knee pain at twelve months in individuals with baseline anxiety
276 (adjusted for depression), and a 1.66 OR in patients with baseline depression (adjusted
277 for anxiety). These insights complement a preclinical OA model that demonstrated
278 astrocyte activation as potential correlate of altered pain perception in animals with
279 elevated baseline anxiety-like behaviour reversible after introducing a centrally acting
280 anxiolytic.⁷¹

281

282 In summary, the above-described studies clearly demonstrate the existence of several
283 OA pain-phenotypes, which seem differentiable based on objective measures and PRO
284 information. Many approaches suggest a low pain-phenotype as well as a phenotype
285 with high pain perception and impact. Interestingly, few articles on OA and OA pain-
286 phenotypes specifically report pes anserine tenderness^{61, 72, 73}, which may confound OA-
287 pain perception and OA pain-phenotyping.

288 Furthermore, the observed differences and similarities in previous OA-phenotyping
289 analyses underline the importance of the choice of input variables for the allocation of
290 clusters in phenotyping.⁷² The observed differences in pain perception and pain-
291 phenotypes do not necessarily correlate with the extent of radiographic changes. There

292 seems to be a certain overlap between structural OA and OA pain-phenotypes if imaging
293 is included as an input variable.^{61, 62, 70, 72} Whether imaging information dominates
294 differences between phenotypes, or if pain-phenotypes are associated with structural
295 changes assessed on imaging merits further investigation.

296 To further differentiate pain-phenotypes, the degree of altered neurobiological
297 signalling appears to be particularly relevant; specific questionnaires and QST measures,
298 especially TS and PPTs or thermal sensitivity appear to be important.

299

300 *Limitations of existing tools to identify OA pain-phenotypes*

301

302 Pain measurement in OA studies primarily focuses on questionnaires that inquire about
303 the intensity, pain on movement and a limited range of pain characteristics to capture
304 the pain experience (Supplementary Table 1). However, most of these questionnaires do
305 not differentiate the underlying pain mechanism(s) at play in any given individual.

306 Further highlighting the complexity of OA, numerous biomarkers (as potential
307 indicators of pathophysiologic mechanisms in OA) and interventions have been
308 evaluated in the context of structural and symptom (pain) OA outcomes (Supplemental
309 Table 2). Patients with different pain-pheno- and endotypes may report similar pain
310 intensity and dimensions. These pain measures therefore may not be suitable to
311 categorize patients but should be used as outcome measures to explore treatment
312 effects. To identify different pain-pheno- and -endotypes, assessments should include
313 clinical/biological information as well as medical history (e.g., burden of comorbidities,
314 signs of dysfunctional pain experience or pain quality, sleep, anxiety and depression,
315 physical activity and assessment of somatosensory function by QST, see Supplemental
316 Table 3). Given the above-described convergence of structural OA and OA pain-

317 phenotypes if imaging or performance measures are added to the clustering, the
318 selection of input variables has to be carefully considered.

319 Comorbidity impacts pain ⁷⁴ and various measures are used to estimate the burden of
320 comorbidity (comprehensively summarized by Stirland et al. ⁷⁵). It is however vital to
321 consider a score's "original purpose and the outcomes for which it is validated". ⁷⁵
322 Scores developed to predict mortality (e.g., Charlson Comorbidity Index) may be
323 unsuitable to reflect the burden of comorbidity and its impact on physical functioning.

324 Affective states such as anxiety, depression or pain catastrophizing influence pain
325 modulation and perception of pain. While there are diagnostic criteria and tools to
326 identify and grade anxiety and depression, a consensus regarding how to measure
327 catastrophizing has not yet been reached. ⁷⁶ Measures of emotional dysregulation or
328 positive and negative affect can also be useful. ^{77, 78} Kinesiophobia has been reported as
329 predictor of disability impacting quality of life in various pain conditions; it has been
330 associated with chronic pain and thus may also present a useful addition. ^{79, 80}

331 Exercise can positively influence pain ⁸¹; pain and activity may have a reciprocal
332 relationship in some individuals; it may therefore be misleading to assess one without
333 the other. ^{82, 83} This results in methodologic challenges. Objective performance tests are
334 subject to day-to-day variability and reflect what patients are able to do under
335 observation rather than what they habitually do in their free-living environment. The
336 domain of activity, in the future, may best be captured using digital devices that allow
337 the measurement of indicators in the free-living environment like step count, activities
338 at a certain heart rate or radius of mobility. Similarly, objective assessment of sleep
339 structure may be obtained using wearable technology. ^{84, 85} Measuring elements of sleep
340 is increasingly recognized as an important aspect to understanding the pain experience
341 since sleep and pain are also closely inter-related; pain may disrupt sleep, and sleep

342 disturbance negatively impacts descending pain inhibitory pathways, heightens pain
343 sensitivity and attenuates opioid analgesia.^{84, 86-88} These examples underline the
344 importance of systematically assessing pain and potential confounders in an integrative
345 approach.

346

347 **Considerations for a broader collection of pain measures**

348 This summary highlights the complexity of the pain experience as multidimensional
349 physical and psychological phenomenon, as well as of the plethora of assessment tools.

350 It also suggests the existence of different patterns of observable traits, OA pain-
351 phenotypes, which likely reflect different underlying mechanisms contributing to the
352 overall pain experience. Striving for the development of a personalized and targeted
353 management of OA, pain is a critical factor, and central to patients' well-being. OA-pain
354 is associated with multiple pathophysiological mechanisms reflected in distinct pheno-
355 and endotypes. This implies the need to systematically define those pain-pheno- and
356 -endotypes independent of the underlying OA pheno- and -endotype.

357

358 We therefore suggest the systematic collection of additional pain-related data, such as
359 pain quality, including potential signs of sensitization and other altered neurobiological
360 mechanisms, burden of comorbidity, presence of anxio-depressive psychopathology,
361 sleep quality and physical activity as a minimal set of assessments. Other aspects such as
362 pain catastrophizing, kinesiophobia, dysregulation of affect, etc. may play an important
363 role. At the moment there is however less consensus about their independent relevance
364 and optimal tools for the assessment of these concepts. Similarly, the potential
365 application of this additional pain-related data necessitates further evaluation. The
366 individual use of the PRO information could lead to unnecessary fragmentation of the

367 patient population. The use of patient response or patient characteristics patterns in
368 form of phenotypes for subgroup analyses or treatment allocation though could support
369 drug development. Pain-phenotyping could be specifically valuable to discriminate
370 treatments without any effect on pain, from those that target specific pain processes.
371 QST allows valuable additional insights into pain processing. Necessary expertise,
372 equipment and time for valid assessments may be challenging, thereby impacting the
373 implementability of comprehensive QST protocols in large multicenter trials.
374 Nevertheless, future research may guide the construction of targeted somatosensory
375 assessment-batteries based on their discriminative value e.g., in combination with PROs,
376 which would allow a broad implementation and add relevant scientific value to OA
377 trials.

378

379 One challenge has been the comparability of various PROs that focus on slightly different
380 clinical domains. Georgopoulos et al. have recently demonstrated, that harmonized
381 results of the 4 most widely used PROs for pain assessment produce similar patient
382 acceptable symptom states and are thus comparable.⁸⁹ To increase our knowledge
383 about pain-phenotypes from published and future studies, a similar concept to generally
384 interpret and compare PRO results could be applied, leveraging established cut off
385 values⁷¹. Alternatively cut off values such as tertiles or quartiles of the original score
386 range could be used.⁶⁵ The latter approach is based on the assumption, that for a score
387 e.g., ranging from 0-100 with 100 denoting high impact from a given pathology, people
388 who score between 0-25 or 0-33 are less likely to be impacted, compared to those
389 scoring between 66-100 or 75-100. While on a granular level, the different scores may
390 convey different nuances of patient experience (and thus allow focus in a specific
391 project), a separation in tertiles or quartiles in principle allows the clear identification of

392 highly vs marginally affected individuals for comparison with other studies. This could
393 also facilitate the implementation of systematic PRO-based assessments in clinical
394 practice to allow individualized treatment approaches.

395

396 The legacy of numerous failed trials, the increasing cost pressure on healthcare systems,
397 and the public and individual health burden of OA are concerning. Given the increase in
398 mechanistic understanding, the field is under a certain pressure to develop medicines
399 that address patients' symptoms and halt or reverse OA. One prerequisite for the
400 development of worthwhile treatments is the establishment of clinical endpoints that
401 provide a meaningful reflection of disease modification and long-term patient benefit.
402 This can only be accomplished if we better understand and measure pain in OA which
403 could also give further insights in the pain structure relationship. However, to achieve
404 real progress, data need to be comparable. Systematic generation of data that allow OA
405 pain-phenotyping may be one piece of the puzzle towards a "treatment of OA".

406

407 **Acknowledgements**

408 We thank Shafaq S Shaikh for her help in compiling the various patient reported outcome
409 measures and the insightful discussions including also Christel Naujocks and Daniel
410 Kuessner. We also thank all colleagues, labs and patients who by their work and trial
411 participation helped to generate these insights.

412

413 **Author contributions**

414 AH and FS have collected the information for the tables and performed literature
415 research. All authors have been involved in the analysis and interpretation of the data
416 and contributed to the final manuscript.

417

418 **Role of the funding source**

419 The manuscript has been developed as part of a medical fellowship by AH founded by
420 Novartis Biomedical Research. Also, FS and MS have received salaries from Novartis
421 during the work on this manuscript.

422 The funder had no influence on the study design, data interpretation or publication
423 strategy.

424

425 **Competing interests**

426 Franziska Saxer is employee and shareholder of Novartis, she is affiliated to the University
427 Basel and member of the European Union Medical Devices - Expert Panel section
428 Orthopaedics, traumatology, rehabilitation, rheumatology

429 Alexa Hollinger is a medical fellow at Novartis, she is affiliated with the University Hospital
430 Basel and the University of Basel.

431 Martin Flores Bjurström has no competing interests to declare

432 Philip G Conaghan reports consultancies or speakers bureaus for AbbVie, AstraZeneca,
433 EliLilly, GlaxoSmithKline, Grunenthal, Janssen, Levicept, Merck, Novartis, Pfizer, Stryker
434 and UCB. Philip G Conaghan is supported in part through the NIHR Leeds Biomedical
435 Research Centre. The views expressed are those of the author and not necessarily those of the
436 NHS, the NIHR or the Department of Health.

437 Tuhina Neogi reports consultancies for Pfizer-Eli Lilly, Novartis

438 Matthias Schieker is employee and shareholder of Novartis and owner LivImplant GmbH

439 Francis Berenbaum reports consultancies from AstraZeneca, Grunenthal, GSK, Eli Lilly,
440 Nordic Bioscience, Novartis, Pfizer, Servier, Peptinov, 4P Pharma, 4Moving Biotech.

441 Honoraria for lectures from Pfizer, Viatrix. Stock owner of 4Moving Biotech

442

443 **REFERENCES**

444

- 445 1. "Collaborative-Global Burden of Disease Network". Global Burden of Disease
446 Study 2019 results. vol. 2022. <https://vizhub.healthdata.org/gbd-results/2020>.
- 447 2. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of
448 osteoarthritis. *Nat Rev Rheumatol* 2014; 10: 437-441.
- 449 3. Araujo IL, Castro MC, Daltro C, Matos MA. Quality of Life and Functional
450 Independence in Patients with Osteoarthritis of the Knee. *Knee Surg Relat Res*
451 2016; 28: 219-224.
- 452 4. Nuesch E, Dieppe P, Reichenbach S, Williams S, Iff S, Juni P. All cause and disease
453 specific mortality in patients with knee or hip osteoarthritis: population based
454 cohort study. *BMJ* 2011; 342: d1165.
- 455 5. Beswick AD, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of
456 patients report long-term pain after total hip or knee replacement for
457 osteoarthritis? A systematic review of prospective studies in unselected patients.
458 *BMJ Open* 2012; 2: e000435.
- 459 6. Kim Y, Levin G, Nikolov NP, Abugov R, Rothwell R. Concept Endpoints Informing
460 Design Considerations for Confirmatory Clinical Trials in Osteoarthritis. *Arthritis*
461 *Care Res (Hoboken)* 2020.
- 462 7. Mobasheri A, Kapoor M, Ali SA, Lang A, Madry H. The future of deep phenotyping
463 in osteoarthritis: How can high throughput omics technologies advance our
464 understanding of the cellular and molecular taxonomy of the disease? *Osteoarthr*
465 *Cartil Open* 2021; 3: 100144.
- 466 8. Mobasheri A, Saarakkala S, Finnila M, Karsdal MA, Bay-Jensen AC, van Spil WE.
467 Recent advances in understanding the phenotypes of osteoarthritis. *F1000Res*
468 2019; 8.
- 469 9. Angelini F, Widera P, Mobasheri A, Blair J, Struglics A, Uebelhoer M, et al.
470 Osteoarthritis endotype discovery via clustering of biochemical marker data. *Ann*
471 *Rheum Dis* 2022; 81: 666-675.
- 472 10. Mobasheri A, van Spil WE, Budd E, Uzieliene I, Bernotiene E, Bay-Jensen AC, et al.
473 Molecular taxonomy of osteoarthritis for patient stratification, disease
474 management and drug development: biochemical markers associated with
475 emerging clinical phenotypes and molecular endotypes. *Curr Opin Rheumatol*
476 2019; 31: 80-89.
- 477 11. Carlesso L, Neogi T. Identifying pain susceptibility phenotypes in knee
478 osteoarthritis. *Clin Exp Rheumatol* 2019; 37.
- 479 12. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised
480 International Association for the Study of Pain definition of pain: concepts,
481 challenges, and compromises. *Pain* 2020; 161: 1976-1982.
- 482 13. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices,
483 and new advances. *Lancet* 2021; 397: 2082-2097.
- 484 14. Nijs J, Lahousse A, Kapreli E, Bilika P, Saracoglu I, Malfliet A, et al. Nociceptive Pain
485 Criteria or Recognition of Central Sensitization? Pain Phenotyping in the Past,
486 Present and Future. *J Clin Med* 2021; 10.
- 487 15. Dell'Isola A, Allan R, Smith SL, Marreiros SS, Steultjens M. Identification of clinical
488 phenotypes in knee osteoarthritis: a systematic review of the literature. *BMC*
489 *Musculoskelet Disord* 2016; 17: 425.

- 490 16. Arendt-Nielsen L. Pain sensitisation in osteoarthritis. *Clin Exp Rheumatol* 2017;
491 35 Suppl 107: 68-74.
- 492 17. Kuner R, Kuner T. Cellular Circuits in the Brain and Their Modulation in Acute
493 and Chronic Pain. *Physiol Rev* 2021; 101: 213-258.
- 494 18. Department of Clinical Sciences Lund SoAaIC, Lund University, Faculty of
495 Medicine. Doctoral Dissertation Series 2021:100. ISBN 978-91-8021-107-9.
- 496 19. Hiraga SI, Itokazu T, Nishibe M, Yamashita T. Neuroplasticity related to chronic
497 pain and its modulation by microglia. *Inflamm Regen* 2022; 42: 15.
- 498 20. Olesen AE, Nielsen LM, Feddersen S, Erlenwein J, Petzke F, Przemeczek M, et al.
499 Association Between Genetic Polymorphisms and Pain Sensitivity in Patients
500 with Hip Osteoarthritis. *Pain Pract* 2018; 18: 587-596.
- 501 21. Barowsky S, Jung JY, Nesbit N, Silberstein M, Fava M, Loggia ML, et al. Cross-
502 Disorder Genomics Data Analysis Elucidates a Shared Genetic Basis Between
503 Major Depression and Osteoarthritis Pain. *Front Genet* 2021; 12: 687687.
- 504 22. Fu K, Robbins SR, McDougall JJ. Osteoarthritis: the genesis of pain. *Rheumatology*
505 (Oxford) 2018; 57: iv43-iv50.
- 506 23. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. *Nat Rev*
507 *Neurosci* 2016; 18: 20-30.
- 508 24. Garland EL. Pain processing in the human nervous system: a selective review of
509 nociceptive and biobehavioral pathways. *Prim Care* 2012; 39: 561-571.
- 510 25. Turk DC, Fillingim RB, Ohrbach R, Patel KV. Assessment of Psychosocial and
511 Functional Impact of Chronic Pain. *J Pain* 2016; 17: T21-49.
- 512 26. Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and
513 nocebo effects. *Swiss Med Wkly* 2020; 150: w20340.
- 514 27. da Costa BR, Pereira TV, Saadat P, Rudnicki M, Iskander SM, Bodmer NS, et al.
515 Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid
516 treatment for knee and hip osteoarthritis: network meta-analysis. *BMJ* 2021;
517 375: n2321.
- 518 28. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis
519 of pain. *Rheum Dis Clin North Am* 2008; 34: 623-643.
- 520 29. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not
521 osteoarthrosis!). *Osteoarthritis Cartilage* 2013; 21: 16-21.
- 522 30. Vincent TL. IL-1 in osteoarthritis: time for a critical review of the literature.
523 *F1000Res* 2019; 8.
- 524 31. Miller RJ, Malfait AM, Miller RE. The innate immune response as a mediator of
525 osteoarthritis pain. *Osteoarthritis Cartilage* 2020; 28: 562-571.
- 526 32. Miller RE, Miller RJ, Malfait AM. Osteoarthritis joint pain: the cytokine connection.
527 *Cytokine* 2014; 70: 185-193.
- 528 33. Malfait AM, Miller RE, Miller RJ. Basic Mechanisms of Pain in Osteoarthritis:
529 Experimental Observations and New Perspectives. *Rheum Dis Clin North Am*
530 2021; 47: 165-180.
- 531 34. Chen Y, Jiang W, Yong H, He M, Yang Y, Deng Z, et al. Macrophages in
532 osteoarthritis: pathophysiology and therapeutics. *Am J Transl Res* 2020; 12: 261-
533 268.
- 534 35. Geraghty T, Winter DR, Miller RJ, Miller RE, Malfait AM. Neuroimmune
535 interactions and osteoarthritis pain: focus on macrophages. *Pain Rep* 2021; 6:
536 e892.
- 537 36. Ioan-Facsinay A. Initiating pain in osteoarthritis (OA): is it the mast cell?
538 *Osteoarthritis Cartilage* 2018; 26: 1-3.

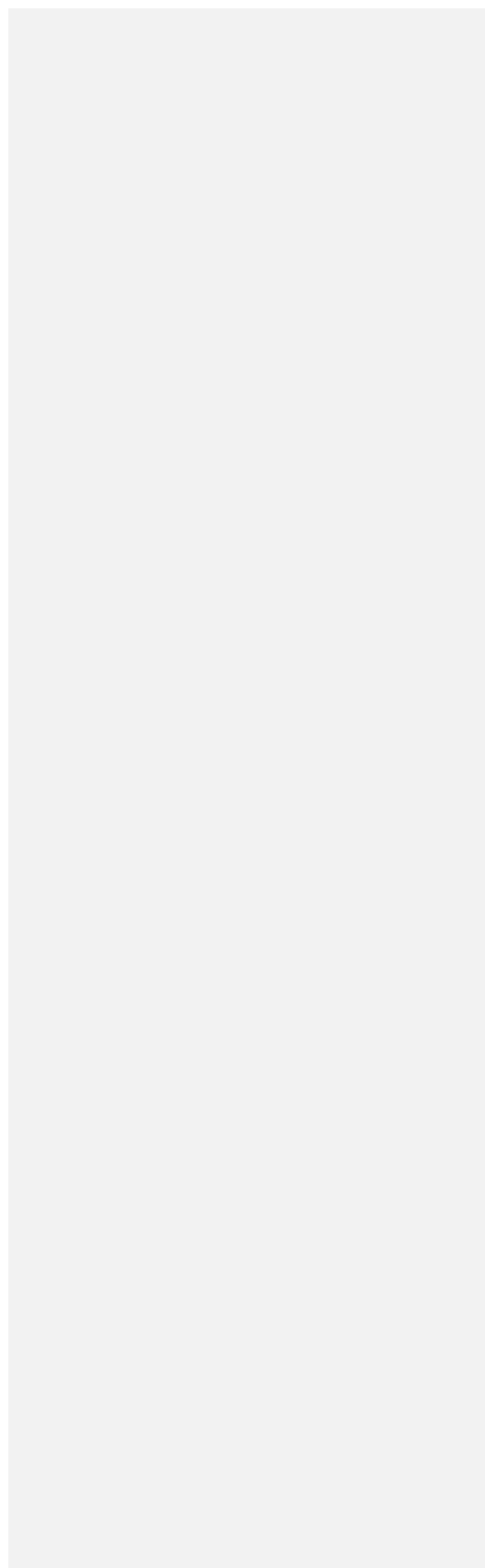
- 539 37. Miller RE, Tran PB, Das R, Ghoreishi-Haack N, Ren D, Miller RJ, et al. CCR2
540 chemokine receptor signaling mediates pain in experimental osteoarthritis. *Proc*
541 *Natl Acad Sci U S A* 2012; 109: 20602-20607.
- 542 38. Miller RE, Tran PB, Ishihara S, Larkin J, Malfait AM. Therapeutic effects of an anti-
543 ADAMTS-5 antibody on joint damage and mechanical allodynia in a murine
544 model of osteoarthritis. *Osteoarthritis Cartilage* 2016; 24: 299-306.
- 545 39. Miller RE, Scanzello CR, Malfait AM. An emerging role for Toll-like receptors at
546 the neuroimmune interface in osteoarthritis. *Semin Immunopathol* 2019; 41:
547 583-594.
- 548 40. Sharma N, Drobinski P, Kayed A, Chen Z, Kjølgaard-Petersen CF, Gantzel T, et al.
549 Inflammation and joint destruction may be linked to the generation of cartilage
550 metabolites of ADAMTS-5 through activation of toll-like receptors. *Osteoarthritis*
551 *Cartilage* 2020; 28: 658-668.
- 552 41. Malfait AM, Miller RE, Block JA. Targeting neurotrophic factors: Novel approaches
553 to musculoskeletal pain. *Pharmacol Ther* 2020; 211: 107553.
- 554 42. Miller RE, Block JA, Malfait AM. Nerve growth factor blockade for the
555 management of osteoarthritis pain: what can we learn from clinical trials and
556 preclinical models? *Curr Opin Rheumatol* 2017; 29: 110-118.
- 557 43. FDA. FDA Approves Novel Treatment to Control Pain in Cats with Osteoarthritis,
558 First Monoclonal Antibody Drug for Use in Any Animal Species. Press
559 Announcements, vol. 20232022.
- 560 44. FDA. FDA Approves First Monoclonal Antibody for Dogs with Osteoarthritis Pain.
561 CVM Updates, vol. 20232023.
- 562 45. Pecchi E, Priam S, Gosset M, Pigenet A, Sudre L, Liguillon MC, et al. Induction of
563 nerve growth factor expression and release by mechanical and inflammatory
564 stimuli in chondrocytes: possible involvement in osteoarthritis pain. *Arthritis Res*
565 *Ther* 2014; 16: R16.
- 566 46. Minnone G, De Benedetti F, Bracci-Laudiero L. NGF and Its Receptors in the
567 Regulation of Inflammatory Response. *Int J Mol Sci* 2017; 18.
- 568 47. Tanezumab
569 Monoclonal Antibody Against Nerve Growth Factor. FDA Advisory Committee Meeting.
570 <https://www.fda.gov/media/146926/download>: FDA 2021.
- 571 48. Obara I, Telezhkin V, Alrashdi I, Chazot PL. Histamine, histamine receptors, and
572 neuropathic pain relief. *Br J Pharmacol* 2020; 177: 580-599.
- 573 49. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al. Do we need a
574 third mechanistic descriptor for chronic pain states? *Pain* 2016; 157: 1382-1386.
- 575 50. Soni A, Wanigasekera V, Mezue M, Cooper C, Javaid MK, Price AJ, et al. Central
576 Sensitization in Knee Osteoarthritis: Relating Presurgical Brainstem
577 Neuroimaging and PainDETECT-Based Patient Stratification to Arthroplasty
578 Outcome. *Arthritis Rheumatol* 2019; 71: 550-560.
- 579 51. Neogi T, Frey-Law L, Scholz J, Niu J, Arendt-Nielsen L, Woolf C, et al. Sensitivity
580 and sensitisation in relation to pain severity in knee osteoarthritis: trait or state?
581 *Ann Rheum Dis* 2015; 74: 682-688.
- 582 52. Pinedo-Villanueva R, Khalid S, Wylde V, Goberman-Hill R, Soni A, Judge A.
583 Identifying individuals with chronic pain after knee replacement: a population-
584 cohort, cluster-analysis of Oxford knee scores in 128,145 patients from the
585 English National Health Service. *BMC Musculoskelet Disord* 2018; 19: 354.
- 586 53. Yong RJ, Nguyen M, Nelson E, Urman RD. *Pain Medicine : An Essential Review*. 1st
587 ed. Cham: Springer International Publishing 2017.

- 588 54. Bennici A, Mannucci C, Calapai F, Cardia L, Ammendolia I, Gangemi S, et al. Safety
589 of Medical Cannabis in Neuropathic Chronic Pain Management. *Molecules* 2021;
590 26.
- 591 55. Leaney AA, Lyttle JR, Segan J, Urquhart DM, Cicuttini FM, Chou L, et al.
592 Antidepressants for hip and knee osteoarthritis. *Cochrane Database of Systematic*
593 *Reviews* 2022.
- 594 56. Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the
595 nervous system to damage. *Annu Rev Neurosci* 2009; 32: 1-32.
- 596 57. van Helvoort EM, Welsing PMJ, Jansen MP, Gielis WP, Loef M, Kloppenburg M, et
597 al. Neuropathic pain in the IMI-APPROACH knee osteoarthritis cohort: prevalence
598 and phenotyping. *RMD Open* 2021; 7.
- 599 58. Murphy SL, Lyden AK, Phillips K, Clauw DJ, Williams DA. Subgroups of older
600 adults with osteoarthritis based upon differing comorbid symptom presentations
601 and potential underlying pain mechanisms. *Arthritis Res Ther* 2011; 13: R135.
- 602 59. Finan PH, Buenaver LF, Bounds SC, Hussain S, Park RJ, Haque UJ, et al.
603 Discordance between pain and radiographic severity in knee osteoarthritis:
604 findings from quantitative sensory testing of central sensitization. *Arthritis*
605 *Rheum* 2013; 65: 363-372.
- 606 60. Egsgaard LL, Eskehave TN, Bay-Jensen AC, Hoeck HC, Arendt-Nielsen L.
607 Identifying specific profiles in patients with different degrees of painful knee
608 osteoarthritis based on serological biochemical and mechanistic pain
609 biomarkers: a diagnostic approach based on cluster analysis. *Pain* 2015; 156: 96-
610 107.
- 611 61. Kittelson AJ, Stevens-Lapsley JE, Schmiede SJ. Determination of Pain Phenotypes
612 in Knee Osteoarthritis: A Latent Class Analysis Using Data From the
613 Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2016; 68: 612-620.
- 614 62. Kittelson AJ, Schmiede SJ, Maluf K, George SZ, Stevens-Lapsley JE. Determination
615 of Pain Phenotypes in Knee Osteoarthritis Using Latent Profile Analysis. *Pain Med*
616 2021; 22: 653-662.
- 617 63. Frey-Law LA, Bohr NL, Sluka KA, Herr K, Clark CR, Noiseux NO, et al. Pain
618 sensitivity profiles in patients with advanced knee osteoarthritis. *Pain* 2016; 157:
619 1988-1999.
- 620 64. Wright A, Benson HAE, Will R, Moss P. Cold Pain Threshold Identifies a Subgroup
621 of Individuals With Knee Osteoarthritis That Present With Multimodality
622 Hyperalgesia and Elevated Pain Levels. *Clin J Pain* 2017; 33: 793-803.
- 623 65. Carlesso LC, Segal NA, Frey-Law L, Zhang Y, Na L, Nevitt M, et al. Pain
624 Susceptibility Phenotypes in Those Free of Knee Pain With or at Risk of Knee
625 Osteoarthritis: The Multicenter Osteoarthritis Study. *Arthritis Rheumatol* 2019;
626 71: 542-549.
- 627 66. Carlesso LC, Feldman DE, Vendittoli PA, LaVoie F, Choiniere M, Bolduc ME, et al.
628 Use of IMMPACT Recommendations to Explore Pain Phenotypes in People with
629 Knee Osteoarthritis. *Pain Med* 2022.
- 630 67. Edwards RR, Dworkin RH, Turk DC, Angst MS, Dionne R, Freeman R, et al. Patient
631 phenotyping in clinical trials of chronic pain treatments: IMMPACT
632 recommendations. *Pain* 2016; 157: 1851-1871.
- 633 68. Sangesland A, Storen C, Vaegter HB. Are preoperative experimental pain
634 assessments correlated with clinical pain outcomes after surgery? A systematic
635 review. *Scand J Pain* 2017; 15: 44-52.
- 636 69. van Helmond N, Aarts HM, Timmerman H, Olesen SS, Drewes AM, Wilder-Smith
637 OH, et al. Is Preoperative Quantitative Sensory Testing Related to Persistent

- 638 Postsurgical Pain? A Systematic Literature Review. *Anesth Analg* 2020; 131:
639 1146-1155.
- 640 70. Pan F, Tian J, Cicuttini F, Jones G, Aitken D. Differentiating knee pain phenotypes
641 in older adults: a prospective cohort study. *Rheumatology (Oxford)* 2019; 58:
642 274-283.
- 643 71. Burston JJ, Valdes AM, Woodhams SG, Mapp PI, Stocks J, Watson DJG, et al. The
644 impact of anxiety on chronic musculoskeletal pain and the role of astrocyte
645 activation. *Pain* 2019; 160: 658-669.
- 646 72. Demanse D, Saxer F, Lustenberger P, Tankó LB, Nikolaus P, Rasin I, et al.
647 Unsupervised machine-learning algorithms for the identification of clinical
648 phenotypes in the Osteoarthritis Initiative database. *Semin Arthritis Rheum*
649 2023; 58.
- 650 73. McGonagle D, Hermann KG, Tan AL. Differentiation between osteoarthritis and
651 psoriatic arthritis: implications for pathogenesis and treatment in the biologic
652 therapy era. *Rheumatology (Oxford)* 2015; 54: 29-38.
- 653 74. Dominick CH, Blyth FM, Nicholas MK. Unpacking the burden: understanding the
654 relationships between chronic pain and comorbidity in the general population.
655 *Pain* 2012; 153: 293-304.
- 656 75. Stirland LE, Gonzalez-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ
657 TC. Measuring multimorbidity beyond counting diseases: systematic review of
658 community and population studies and guide to index choice. *BMJ* 2020; 368:
659 m160.
- 660 76. Petrini L, Arendt-Nielsen L. Understanding Pain Catastrophizing: Putting Pieces
661 Together. *Front Psychol* 2020; 11: 603420.
- 662 77. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of
663 positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988; 54: 1063-
664 1070.
- 665 78. Koechlin H, Coakley R, Schechter N, Werner C, Kossowsky J. The role of emotion
666 regulation in chronic pain: A systematic literature review. *J Psychosom Res* 2018;
667 107: 38-45.
- 668 79. Boersma K, Linton SJ. How does persistent pain develop? An analysis of the
669 relationship between psychological variables, pain and function across stages of
670 chronicity. *Behav Res Ther* 2005; 43: 1495-1507.
- 671 80. Alshahrani MS, Reddy RS, Tedla JS, Asiri F, Alshahrani A. Association between
672 Kinesiophobia and Knee Pain Intensity, Joint Position Sense, and Functional
673 Performance in Individuals with Bilateral Knee Osteoarthritis. *Healthcare (Basel)*
674 2022; 10.
- 675 81. Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior
676 predicts endogenous pain modulation in older adults. *Pain* 2017; 158: 383-390.
- 677 82. Trudeau J, Van Inwegen R, Eaton T, Bhat G, Paillard F, Ng D, et al. Assessment of
678 pain and activity using an electronic pain diary and actigraphy device in a
679 randomized, placebo-controlled crossover trial of celecoxib in osteoarthritis of
680 the knee. *Pain Pract* 2015; 15: 247-255.
- 681 83. Lo GH, Song J, McAlindon TE, Hawker GA, Driban JB, Price LL, et al. Validation of a
682 new symptom outcome for knee osteoarthritis: the Ambulation Adjusted Score
683 for Knee pain. *Clin Rheumatol* 2019; 38: 851-858.
- 684 84. Smith MT, Mun CJ, Remeniuk B, Finan PH, Campbell CM, Buenaver LF, et al.
685 Experimental sleep disruption attenuates morphine analgesia: findings from a
686 randomized trial and implications for the opioid abuse epidemic. *Sci Rep* 2020;
687 10: 20121.

- 688 85. Fabbri M, Beracci A, Martoni M, Meneo D, Tonetti L, Natale V. Measuring
689 Subjective Sleep Quality: A Review. *Int J Environ Res Public Health* 2021; 18.
690 86. Smith MT, Edwards RR, McCann UD, Haythornthwaite JA. The effects of sleep
691 deprivation on pain inhibition and spontaneous pain in women. *Sleep* 2007; 30:
692 494-505.
- 693 87. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and
694 a path forward. *J Pain* 2013; 14: 1539-1552.
- 695 88. Irwin MR, Olmstead R, Bjurstrom MF, Finan PH, Smith MT. Sleep Disruption and
696 Activation of Cellular Inflammation Mediate Heightened Pain Sensitivity: A
697 Randomized Clinical Trial. *Pain* 2022.
- 698 89. Georgopoulos V, Smith S, McWilliams DF, Steultjens MPM, Williams A, Price A, et
699 al. Harmonising knee pain patient-reported outcomes: a systematic literature
700 review and meta-analysis of Patient Acceptable Symptom State (PASS) and
701 individual participant data (IPD). *Osteoarthritis Cartilage* 2022.
702

Table 1: Summary of key OA pain-phenotyping studies



Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Murphy et al.⁵⁸ 2011	older adults (≥65y) with hip or knee OA and signs of primary fatigue	129 (69% knee OA)	relationship among pain, fatigue, and physical activity	na	Hierarchical agglomerative cluster analysis Cross sectional Community sample	Patient Characteristics	61% female Age: 72.2 (+/-9.8), range 65 to 90 y BMI: 30.5 +/-5.9 kg/m ² , range 21.5 to 49.9 Self-reported duration of pain (months) 132.1 (146.5) range 0 to 708	no significant differences in patient characteristics
						Brief Fatigue Inventory	BFI total 4.5 (2.0) range 0.25 to 8.75	Cluster I: 36% highest scores on all measures - high stiffness, high disability, TUG 13.5 +/- 8.9
						WOMAC	WOMAC pain 7.9 (3.4) range 2 to 20 WOMAC stiffness 3.3 (1.7) range 0 to 8 WOMAC disability 20.9 (10.3) range 3 to 42	Cluster II: 30% subclinical depression, moderate fatigue, moderate illness burden, overall low pain, low sleep disturbance - stiffness moderate, disability low, TUG 10.5 +/-2.1 s
						- 5 times daily NRS pain assessment - Illness burden (41 somatic symptoms) - Timed up-and-go test - Activity measured via Actiwatch - Pittsburgh Sleep Quality Index (PSQI) - Center for Epidemiologic Studies Depression Scale (CES-D)		Cluster III: 34% relevant sleep disturbance, mild pain, low fatigue and depression scores, low illness burden - low stiffness, moderate disability, TUG 10.2 +/- 2.3s

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Finan et al. ⁵⁹ 2013	Baseline of study to evaluate psychological treatments in OA patients with/without insomnia	113	Association between self-reported levels of pain with measures of central sensitization in the absence of moderate-to-severe radiographic evidence of pathologic changes of knee OA	na.	cross-sectional multivariate general linear modeling	Patient Characteristics	66.7% female Age: 61.05 +/- 8.93 y BMI: 30.94 +/- 5.85 kg/m ²	<p><u>Low pain/low knee OA grade (21.2%)</u>; overall lowest BMI</p> <p><u>High pain/high knee OA grade (28.3%)</u>; reduced distant (and local) PPT vs low pain groups, high rate of depression, anxiety, sleep disturbance and pain catastrophizing, overall highest BMI</p> <p><u>Low pain/high knee OA grade (23.90%)</u>; overall oldest group</p>
						<ul style="list-style-type: none"> • STAI • CES-D • PCS • PSQI • Radiographic disease severity (Kellgren/Lawrence) • QST <ul style="list-style-type: none"> • PPT • CPT • Mechanical phasic pain • Thermal phasic pain • Sensitivity to tonic pain • CPM 	<p><u>High pain/low knee OA grade (26.5%)</u>; significantly increased pain response to distant mechanical phasic stimuli and thermal phasic pain compared to high knee OA groups, reduced distant PPT vs low pain groups, high rate of depression, anxiety, sleep disturbance and pain catastrophizing, overall youngest group</p> <p>no differences in CPM or QST measures locally, education and income as significant covariates</p>	

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Egsgaard ⁶⁰ et al. 2015	full spectrum from no clinical OA to clinical OA, randomly selected from pre-existing database 40-80y controls with no OA and little or no pain	280 (216:64)	identification of knee pain profiles identification of marker patterns correlating to pain profiles	non-OA knees largely independent of pain	Principal Components Analysis (PCA) with clustering using Ward's method with squared Euclidean distance	Patient Characteristics	64% female Age: 61.7 +/- 10.0 y BMI: 33.9 +/- 7.0 kg/m ²	Principal components: PC1: physical health questionnaires PC2: peripheral, central, and spreading sensitization, PC3: biochemical markers, PC4: pain catastrophizing, PC5: temporal summation.
						<ul style="list-style-type: none"> • OA grade • Comorbidities • Number of painful joints • Pain duration • Pain localization • WOMAC • Lequesne functional index • EQ-5D • Pain catastrophizing • QST <ul style="list-style-type: none"> • PPT • TS • CPM • Biomarkers <ul style="list-style-type: none"> • VICM • CIM • CRP • CRPM • CIIIM 	<p>Profile A (12.5%): moderate impact on WOMAC/ Lequesne, low to moderate catastrophizing, near normal TS, high CPM and PPT as potential sign of resilience, still reduced QoL</p> <p>Profile B (27.3%): moderate impact on WOMAC/ Lequesne, low to moderate catastrophizing, near normal TS, moderate CPM but reduced PPT, reduced QoL</p> <p>Profile C (39.4%): moderate impact on WOMAC/ Lequesne, low to moderate catastrophizing, increased TS, reduced CPM and</p>	

								<p>PPT, reduced QoL, CRP near normal</p> <p>Profile D (18.9%): higher impact on WOMAC and especially Lequesne, increased catastrophizing, increased TS, reduced CPM and PPT, reduced QoL</p> <p>Profile E (1.9%): outlier cluster, not reported in detail</p> <p>controls low impact on WOMAC/Lequesne, moderate CPM and PPT, low TS</p>
--	--	--	--	--	--	--	--	---

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Kittelson et al. ⁶¹ 2016	OAI from the incident and progression cohort	3494	Knee OA pain-phenotypes based on 1) knee OA pathology 2) psychological distress 3) altered pain neurophysiology 4) relation to patient characteristics	na	Latent Class Analysis cross sectional cluster analysis (4-year follow-up visit) with some longitudinal information	Patient Characteristics	OA 59.2% female Age: 64.9 +/-9.0 y BMI: 28.9 +/- 5.0 kg/m ²	Class 1: on average older than all other classes, higher proportion of females, slowest walking speed, high level of comorbidities Class 2: on average older than class 3/4, high levels of knee joint tenderness, weak extensor strength and high proportion of pes anserine tenderness Class 3: highest pain level, psychological distress, highest number of painful sites and more severe radiographic OA Class 4: mild radiographic OA, low levels of pain and comorbidity, highest average extensor strength
						<ul style="list-style-type: none"> Numeric Pain Rating Scale (NPRS) WOMAC Radiographic severity of knee OA MVIC Tenderness of the knee joint Modified Charlson Comorbidity Index Number of pain sites (as surrogate for central sensitization) CES-D Modified version of the coping strategies questionnaire-catastrophizing subscale 20-meter timed walking test at self-selected walking speed Health seeking behavior (unstructured question) 	similar symptom duration and health seeking behavior	
Kittelson et al. ⁶² 2021	Recruitment from community (healthy elderly) and orthopaedic clinics (OA patients)	183 (152:31)	Knee OA pain-phenotypes based on 1) multimorbidity 2) psychological distress 3) pain sensitivity	healthy community dwelling elders	Latent Profile Analysis Cross sectional Community sample	Patient Characteristics	OA 64.5% female, control 64.5% female Age: OA 65.2 +/- 8.5 y, control 64.9 +/- 9.0 y	Group 1 (9% of pt with knee pain): characterized by high FCI scores (upper gastrointestinal, osteoporosis, heart disease, asthma), slower walking speed than group 2/4 ("weakness and

	50-85y		4) knee impairment or pathology				BMI: OA 30.2 +/- 6.0 kg/m ² , control 26.7 +/- 4.6 kg/m ²	heightened pain sensitivity with multimorbidity") Group 2 (63% of pt with knee pain): low PCS and FCI (vs group 1 and 3), higher target knee PPT and lower extensor strength than healthy elderly or group 4 ("weakness and heightened pain sensitivity") Group 3 (11% of pt with knee pain): characterized by pain catastrophizing, higher pain ratings than group 2/4 ("weakness and heightened pain sensitivity with pain associated distress") Group 4 (17% of pt with knee pain): characterized by high PPT vs all other groups, otherwise similar to healthy elderly, highest proportion of pt with previous knee surgery or trauma ("normal strength, low pain sensitivity")
						<ul style="list-style-type: none"> • Visual analog scale (VAS) • WOMAC pain • ICOAP • Normalized knee extensor strength at maximum voluntary isometric contraction (MVIC) • Functional Comorbidity Index (FCI) • Pain Catastrophizing Scale (PCS) • Walking speed • Health seeking behaviour (unstructured question) • Symptom duration • QST <ul style="list-style-type: none"> • PPT (target knee) 	similar symptom duration and health seeking behavior	
						<i>Tampa Scale for Kinesiophobia, modified Charlson Comorbidity Index, PPT (regional/distant), Radiographic Severity of Knee Osteoarthritis, CES-D evaluated but excluded based on weaker correlation with pain intensity (Spearman correlations)</i>		

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Frey-Law et al. ⁶³ 2017	Baseline of TANK (TENS After New Knee) study NCT01364870 ≥30y scheduled for primary total knee joint replacement	218	QST pain sensitivity profiles in advanced knee OA	na	Principal Components Analysis (PCA) and Principal Axis Factoring (PAF) with clustering using Ward's method with squared Euclidean distance	Patient Characteristics	54.6% female (50% in control group) Age: not reported BMI: not reported	<p>Low Pain Sensitivity Profile (18.3%): low QST based standardized pain sensitivity before and after adjustment for age and sex</p> <p>Average Pain Sensitivity Profile (38.5%): average QST based standardized pain sensitivity, after adjustment for age and sex more pronounced difference in PPT and HPT vs low pain sensitivity cluster</p> <p>High Pain Sensitivity Profile temporal summation (20.6%): isolated high TS with low values for other qualities, effect pronounced after adjustment</p> <p>High Pain Sensitivity Profile high heat and pressure pain (17.9%): before adjustment, after adjustment similar to average pain sensitivity cluster with TS as main discriminator, higher pain levels than pure TS cluster also in KOOS, at rest, gait and range of movement</p> <p>High Pain Sensitivity Profile high punctate pain (4.5%): average for all qualities (especially) after adjustment except punctate pain with highest</p>
						<ul style="list-style-type: none"> • Pain intensity (rest and movement) via 21-point NRS • Pain duration • Analgesic medication • State-Trait Anxiety Inventory (STAI) anxiety subscale • Geriatric Depression Scale (GDS), 5-item version • PCS • KOOS • SF-36 • QST <ul style="list-style-type: none"> • PPT • HPT and HPTol • Punctate Pain Intensity via VAS • TS via tonic heat stimulus 		

Commented [MB1]: Especially?

								<p>pain levels also in KOOS, at rest, gait and range of movement</p> <p>no relevant impact from other assessments apart from sex. Men were allocated predominant in low pain sensitivity cluster. After adjustment higher pain sensitivity for non-white and/or hispanic individuals</p>
--	--	--	--	--	--	--	--	--

Commented [MB2]: Maybe rephrase to avoid misunderstanding. As I understand it, men are predominant in the low pain sens. cluster.

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Wright et al. ⁶⁴ 2017	adults with painful knee OA pain-free volunteers (≥50y)	120 (80:40)	widespread cold, pressure, and heat hyperalgesia in OA patients differences in QST measures, levels of pain, pain characteristics, and perceived function in patients with wide-spread cold hyperalgesia	pain free control OA patients with and without wide-spread cold hyperalgesia	Standard statistics Cross sectional Community sample	Patient Characteristics	OA 55% female, control 60% female Age: OA 64, range 50 to 86 y; control 64, range 51 to 86 y OA 38% obese, control 10% obese	no significant differences in patient characteristics
						Brief Fatigue Inventory	BFI total 4.5 (2.0) range 0.25 to 8.75	<u>OA vs pain free:</u> sign. higher index knee PPT in OA (pressure hyperalgesia: 22.50% index knee, 16.25% contralat. knee, 3.75% distant site)
						WOMAC	OA WOMAC pain, 18.5/50 OA WOMAC function, 53.4/250	sign. higher CDT at index and contralat. knee (cold hypoesthesia 11.25% index knee, 17.50% contralat. knee, 17.50% distant site; cold hyperalgesia 47.50% index knee, 37.50% contralat. knee, 43.75% distant site)
						Short-Form Health Survey (SF-36)	43.75% (n=35) cold hyperalgesic based on 12.25°C cut off	sign. higher overall WDT in OA, no differences in HPT (heat hypoesthesia 11.25% index knee, 17.50% contralat. knee, 17.50% distant site; heat
						<ul style="list-style-type: none"> • PainDETECT • Pain quality assessment scale (PQAS) • QST • PPT • CDT • CPT • WDT • HPT 		

								<p>hyperalgesia 47.50% index knee, 37.50% contralat. knee, 43.75% distant site)</p> <p><u>Cold hyperalgesic vs non-hyperalgesic OA patients:</u></p> <p>sign. lower cold detection and cold pain threshold at all sites cold-hyperalgesic vs non-cold hyperalgesic OA patients, no difference between non-hyperalgesic OA patients vs pain-free controls</p> <p>sign. lower warmth detection threshold at index knee and distant site (cold hyperalgesic patients vs all others), sign. lower warmth detection threshold at contralateral knee (cold hyperalgesic patients vs pain free controls, but not vs other OA patients), lower heat pain threshold at all sites (cold hyperalgesic patients vs other OA patients), but no difference between cold hyperalgesic patients and controls.</p> <p>sign. higher index knee and contralat knee PPT, no sign. difference at distant site</p> <p>no differences in SF36 based on cold hyperalgesia in OA patients, higher WOMAC pain and disability in patients with cold</p>
--	--	--	--	--	--	--	--	---

								hyperalgesia, correlation between cold hyperalgesia and PainDETECT scores and surface and paradoxical subscores in pain quality assessment scale
--	--	--	--	--	--	--	--	--

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Pan et al. ⁷⁰ 2019	Recruitment from community (healthy elderly) and orthopedic clinics (OA patients) 50-85y	Tasmanian Older Adult Cohort Study	963	knee pain-phenotypes in an older population	Latent Class Analysis Cross sectional Community sample	Patient Characteristics	50% female (sampling strategy) Age: 62.8 +/- 7.4 y BMI: 27.7 +/- 4.6 kg/m ²	Class 1 (25%): highest proportion of females, on average more emotional problems, higher burden of comorbidity, more severe knee pain and more painful sites, lower knee structural damage, lower education
								Class 2 (20%): more males, higher level of education, fewer painful sites or structural knee abnormalities, lower levels of pain Class 3 (50%): overall lowest prevalence of knee pain, comorbidities, radiographic OA, structural damage and low BMI consistently WOMAC and painful sites Class 1 > Class 2 > Class 3 over average 10.7 y
						<ul style="list-style-type: none"> • WOMAC pain • Number of painful sites • MRI characteristics (cartilage defects, bone marrow lesions, effusion-synovitis) • Radiographic presence of knee OA • Education level • Single mental health item from the short form-8 • 4-item comorbidity questionnaire (heart attack, diabetes, hypertension, rheumatoid arthritis) 		

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Burston et al.⁷¹ 2019	participants from a community-based cohort study ≥40y	230 (130:100) 3274 for impact of anxiety (351 anxiety at baseline) on incident knee pain at 12 months 3767 for impact of knee pain (1020 with baseline knee pain) on incident anxiety at 12 months	associations between knee pain, pain spread, anxiety, and depression	Non-OA patients	Spearman correlation and linear regression	Patient Characteristics	OA 61.9% female, control 58.2% female Age: OA 60.27 +/- 9.61 y; control 63.06, +/- 8.88 y BMI: OA 27.1 +/- 4.56 kg/m ² , control 30.09 +/- 6.62 kg/m ²	<u>Impact of anxiety (25% of population)</u> anxiety sign. associated with all pain measures and PPTs after adj. for depression odds ratio (OR) for incident knee pain at 12 months in patients with anxiety 1.71 (adj. for depression) OR for incident anxiety at 12 months in patients with knee pain 1.18 (after adj. for depression) OR for incident anxiety at 12 months in patients with depression 3.20 <u>Impact of depression (10% of population)</u> OR for incident knee pain at 12 months in patients with depression 1.66 (adj. for anxiety)
						<ul style="list-style-type: none"> • HADS • Intermittent and Constant Osteoarthritis Pain scale (ICOAP) • Numeric Rating Scale (NRS) • OA severity (Kellgren-Lawrence) • QST • PPT 		

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Carlesso et al.⁶⁵ 2019	MOST population 50-79y having/at risk of developing knee OA without persistent knee pain	852	pain susceptibility phenotype (PSP) based on development of persistent pain at 2 years	na	Latent Class Analysis observational longitudinal	Patient Characteristics	55% female Age: 67y BMI: 29.5 kg/m ²	Pain susceptibility phenotypes (PSP) PSP 1 (34%): pressure pain sensitivity (~16–26%), facilitated TS (33–35%) PSP 2 (31%): pressure pain sensitivity (0–6%), facilitated TS (2–10%), 22% non-caucasian PSP 3 (23%): pressure pain sensitivity (75–89%), facilitated TS (53–58%), 74% female, higher risk of developing incident knee pain PSP 4 (12%): pressure pain sensitivity (0–4%), facilitated TS (82–90%), 26% female, 23% non-caucasian, mean age 70% no relevant differences in other aspects analyzed
						<ul style="list-style-type: none"> • Widespread pain index (WPI) • QST <ul style="list-style-type: none"> • PPT • TS • Coping Strategies Questionnaire (single item for pain catastrophizing) • - CES-D 		

Reference	Population	Sample Size (for comparative studies n of OA patients : n of controls)	Phenomenon	Comparator	Approach	Evaluation	Population Characteristics	Phenotypes/Groups
Carlesso et al.⁶⁶ 2022	orthopaedic specialist confirmed diagnosis of OA ≥40y	343	Pain-phenotype identification based on IMMPACT criteria	na	Latent Class Analysis observational longitudinal	Patient Characteristics	63% female Age: 64y BMI: 32kg/m ²	<p>Class 1 (49%): overall low scores in all assessed measures (i.e. low severity) or marginal signs of central sensitization according to QST</p> <p>Class 2 (40%): overall moderate scores in assessed measures, but high pain variability, mixed QST values</p> <p>Class 3 (11%): overall highest scores in assessed measures (except pain variability), QST values for PPT patella, TS, cold pain and CPM heat pain as indicator of relevant central sensitization</p> <p>decreasing function from class 1 to class 3 considering walk fast and climb stairs, no significant difference for sit stand</p> <p>increasing health care utilization of 44% and 240% for class 2 and 3 respectively compared to class 1</p>
						<ul style="list-style-type: none"> Modified Pain Detect Questionnaire Hospital Anxiety and Depression Scale (HADS) Patient Health Questionnaire-15 (self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic instrument) Pain Catastrophizing Scale Multidimensional Fatigue Inventory Pain variability (NRS 3 times via text for a week) Average pain intensity (NRS, recall 1 week) Pittsburgh Sleep Quality Index (PSQI) Short form McGill Pain Questionnaire 2 QST 		

						<ul style="list-style-type: none"> • <i>PPT</i> • <i>TS</i> • <i>CPT</i> • <i>HPT</i> • <i>CPM</i> (Conditioned pain modulation) • Self-report Charlson comorbidity index • Life Orientation Test-Revised scale (dispositional optimism) • Chronic Pain Self Efficacy Scale • Kellgren-Lawrence grade • Knee Injury and Osteoarthritis Outcomes Score (KOOS) activities of daily living subscale • Core measures of functional performance (1) transition from sit to stand, 2) walk fast and 3) climb stairs • Healthcare Utilization (via provincial insurance system in one vicinity) 		
--	--	--	--	--	--	--	--	--

Abbreviations:

pt: patients

BMI: Body Mass Index; BFI: Brief Fatigue Inventory; CES-D: Center for Epidemiologic Studies Depression Scale; FCI: Functional Comorbidity Index; GDS: Geriatric Depression Scale HADS: Hospital Anxiety and Depression Scale; ICOAP: Intermittent and Constant Osteoarthritis Pain scale KOOS: Knee Injury and Osteoarthritis Outcomes Score; MVIC: Normalized knee extensor strength at maximum voluntary isometric contraction; NRS: Numeric Rating Scale; NPRS: Numeric Pain Rating Scale PCS: Pain Catastrophizing Scale; PRIME-MD: Primary Care Evaluation of Mental Disorders; PQAS: Pain quality assessment scale; PSQI: Pittsburgh Sleep Quality Index; S F-36: Short-Form Health Survey; STAI: State-Trait Anxiety Inventory; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; QST: Quantitative Sensory Testing; CDT: Cold Detection Threshold; CPT: Cold Pain Threshold; CPM: Conditioned pain modulation; HPT: Heat Pain Threshold; HPTol: Heat Pain Tolerance; PPT: Pressure Pain Threshold; TS: Temporal Summation; WDT: Warmth Detection Threshold
CIM: Collagen I Metabolite; CIIIM: Sollaragen III Metabolite; CRP: C-Reactive Protein; CRPM: C-Reactive Protein Metabolite; VICM: Citrullinated Vimentin Fragment;