Figure 3. Mediation by osteophytes on the associations between total cartilage

Mediator	change in total knee pain β (95% CI)	P	change in weight-bearing pain β (95% CI)	P	change in non-weight-bearing pain β (95% CI)	P
LTF osteophyte						
Indirect effect	**-2.52 (-5.24, -0.69)**	**<0.01**	**-1.74 (-3.49, -0.48)**	**<0.01**	**-0.96 (-2.09, -0.17)**	**0.02**
Direct effect	-3.79 (-13.66, 5.77)	0.44	-4.75 (-11.34, 1.31)	0.13	-0.28 (-4.54, 3.92)	0.88
Total effect	-6.30 (-16.31, 3.29)	0.19	**-6.49 (-13.54, -0.33)**	**0.04**	-1.24 (-5.64, 3.00)	0.53
Proportion mediated%	NA		**27%**		NA	
MTF osteophyte						
Indirect effect	-1.64 (-4.17, 0.25)	0.10	-1.04 (-2.71, 0.13)	0.09	**-0.67 (-1.72, 0.08)**	0.09
Direct effect	-4.66 (-14.13, 4.17)	0.29	-5.45 (-12.06, 1.04)	0.10	-0.56 (-4.73, 3.85)	0.81
Total effect	-6.30 (-15.81, 2.56)	0.16	**-6.49 (-13.45, -0.11)**	**0.04**	-1.24 (-5.40, 2.97)	0.59
Proportion mediated%	NA		NA		NA	
Patellar osteophyte						
Indirect effect	**-3.16 (-6.29, -0.97)**	**<0.01**	**-1.93 (-4.04, -0.48)**	**<0.01**	**-1.26 (-2.61, -0.27)**	**<0.01**
Direct effect	-3.14 (-12.55, 6.18)	0.49	-4.56 (-11.03, 1.60)	0.15	0.02 (-4.26, 4.10)	0.99
Total effect	-6.30 (-15.86, 2.99)	0.17	**-6.49 (-13.18, -0.31)**	**0.04**	-1.24 (-5.42, 2.85)	0.54
Proportion mediated%	NA		**30%**		NA	

volume and changes in knee pain scores
Adjusted for age, sex, BMI and vitamin D supplement.
Statistically significant associations were shown in bold.
LTF, lateral tibiofemoral; MTF, medial tibiofemoral

Figure 2. Mediation by osteophytes on the associations between cartilage defects and changes in knee pain scores

Mediator	change in total knee pain β (95% CI)	P	change in weight-bearing pain β (95% CI)	P	change in non-weight-bearing pain β (95% CI)	P
LTF osteophyte						
Indirect effect	**1.74 (0.15, 3.44)**	**0.03**	**1.26 (0.24, 2.36)**	**0.02**	0.48 (-0.28, 1.26)	0.22
Direct effect	1.78 (-1.40, 4.93)	0.28	0.79 (-1.38, 2.98)	0.49	1.03 (-0.50, 2.52)	0.15
Total effect	**3.53 (0.52, 6.34)**	**0.02**	**2.05 (0.14, 4.12)**	**0.04**	**1.51 (0.23, 2.81)**	**0.02**
Proportion mediated%	**49%**		**62%**		NA	
MTF osteophyte						
Indirect effect	0.84 (-0.94, 2.81)	0.36	0.62 (-0.60, 1.91)	0.29	0.22 (-0.56, 1.04)	0.56
Direct effect	2.68 (-0.80, 6.27)	0.13	1.43 (-0.72, 3.53)	0.19	1.29 (-0.23, 2.84)	0.10
Total effect	**3.53 (0.53, 6.66)**	**0.02**	**2.05 (0.08, 4.06)**	**0.04**	**1.51 (0.26, 2.89)**	**0.02**
Proportion mediated%	NA		NA		NA	
Patellar osteophyte						
Indirect effect	**1.95 (0.70, 3.32)**	**<0.01**	**1.24 (0.45, 2.16)**	**<0.01**	**0.70 (0.12, 1.35)**	**0.01**
Direct effect	1.58 (-1.45, 4.76)	0.30	0.81 (-1.11, 2.71)	0.41	0.81 (-0.41, 2.06)	0.21
Total effect	**3.53 (0.60, 6.55)**	**0.02**	**2.05 (0.09, 3.99)**	**0.04**	**1.51 (0.36, 2.74)**	**0.01**
Proportion mediated%	**55%**		**61%**		**46%**	

Adjusted for age, sex, BMI and vitamin D supplement.
Statistically significant associations were shown in bold.
LTF, lateral tibiofemoral; MTF, medial tibiofemoral

Figure 3. Mediation by osteophytes on the associations between total cartilage

Mediator	change in total knee pain β (95% CI)	P	change in weight-bearing pain β (95% CI)	P	change in non-weight-bearing pain β (95% CI)	P
LTF osteophyte						
Indirect effect	**-2.52 (-5.24, -0.69)**	**<0.01**	**-1.74 (-3.49, -0.48)**	**<0.01**	**-0.96 (-2.09, -0.17)**	**0.02**
Direct effect	-3.79 (-13.66, 5.77)	0.44	-4.75 (-11.34, 1.31)	0.13	-0.28 (-4.54, 3.92)	0.88
Total effect	-6.30 (-16.31, 3.29)	0.19	**-6.49 (-13.54, -0.33)**	**0.04**	-1.24 (-5.64, 3.00)	0.53
Proportion mediated%	NA		**27%**		NA	
MTF osteophyte						
Indirect effect	-1.64 (-4.17, 0.25)	0.10	-1.04 (-2.71, 0.13)	0.09	**-0.67 (-1.72, 0.08)**	0.09
Direct effect	-4.66 (-14.13, 4.17)	0.29	-5.45 (-12.06, 1.04)	0.10	-0.56 (-4.73, 3.85)	0.81
Total effect	-6.30 (-15.81, 2.56)	0.16	**-6.49 (-13.45, -0.11)**	**0.04**	-1.24 (-5.40, 2.97)	0.59
Proportion mediated%	NA		NA		NA	
Patellar osteophyte						
Indirect effect	**-3.16 (-6.29, -0.97)**	**<0.01**	**-1.93 (-4.04, -0.48)**	**<0.01**	**-1.26 (-2.61, -0.27)**	**<0.01**
Direct effect	-3.14 (-12.55, 6.18)	0.49	-4.56 (-11.03, 1.60)	0.15	0.02 (-4.26, 4.10)	0.99
Total effect	-6.30 (-15.86, 2.99)	0.17	**-6.49 (-13.18, -0.31)**	**0.04**	-1.24 (-5.42, 2.85)	0.54
Proportion mediated%	NA		**30%**		NA	

volume and changes in knee pain scores
Adjusted for age, sex, BMI and vitamin D supplement.
Statistically significant associations were shown in bold.
LTF, lateral tibiofemoral; MTF, medial tibiofemoral

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PAIN SEVERITY ACROSS HAND OSTEOARTHRITIS PHENOTYPES BASED ON A BIOPSYCHOSOCIAL APPROACH

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Purpose: Hand osteoarthritis (OA) pain is both heterogeneous and multifactorial, involving biological, psychological and social aspects extending beyond the OA disease process. Different phenotypes may have different prognosis and may require different treatments. Hence, the identification of such phenotypes may be clinically important. Currently, no previous studies have examined the presence of different hand OA phenotypes. Therefore, the purpose of this study was to explore classes based on a biopsychosocial framework as possible phenotypes in a hand OA population, and examine whether pain severity differ between the classes.

Methods: These cross-sectional analyses included 300 participants from the Nor-Hand study, a hospital-based cohort study. To examine the biological domain, OA severity was evaluated by obtaining bilateral hand radiographs that were scored according to a modified Kellgren-Lawrence scale (grade 0-4). A sum score of all hand joints was calculated (range: 0-128). Central pain sensitization was examined by quantitative sensory testing including pressure pain thresholds (PPTs) (kg/cm^2) at the tibialis anterior and trapezius muscle and temporal summation (TS) at the at the distal radioulnar joint (difference between first and peak measure of 5th or 10th tap). BMI (kg/m^2) was calculated based on measured height and weight. Comorbidity burden was assessed by a self-administered comorbidity questionnaire (range: 0-45). Sleep disturbances were self-reported on a 1-5 scale. The psychological domain was captured by three questionnaires; the Hospital Depression and Anxiety Scale (HADS, range: 0-42), the Pain Catastrophizing Scale (PCS, range: 0-52) and the Arthritis Self-Efficacy Scale (ASES, range: 10-100). Finally, to assess the social domain the participants reported highest degree of completed education (7 categories), current status of work (6 categories) and relationship (5 categories). Variables used for comparison across the classes included age, sex and pain severity, where pain severity during the last 24 hours was self-reported on two Numeric Rating Scales (NRS) for hand pain and for overall bodily pain (scale: 0-10). Latent class analysis (LCA) was used to identify groups of participants based on their responses on the measurements and questionnaires across the biopsychosocial domains. Posterior fit statistics of Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) were used to determine the optimal number of classes. Differences in age, sex and pain outcomes between classes were assessed by one-way ANOVAs and chi-squared tests.

Results: We identified 4 different classes (Table 1): Class 1 (n=53, 18%) had relatively low levels of OA severity, psychological distress and comorbidity burden, and a high proportion of participants with a university education, working and living with a partner. Class 2 (n=103, 34%) had higher levels of OA severity and comorbidity burden than the other classes. They had low levels psychological distress, high self-efficacy, and relatively high frequency of participants with university education and working. Class 3 (n=119, **40**%) had relatively low OA severity, but more pain sensitization, high frequency of sleep problems and psychological distress, including low self-efficacy. Class 4 (n=25, 8%) had lower OA severity and more pain sensitization, psychological distress, and sleep problems than the other classes. This class displayed lowest levels of self-efficacy and lowest frequencies of participants with a university education and working. Entropy was calculated to assess the precision for assigning the participants to their most likely class (0.84). Differences between the classes are further detailed in Table 1. When we compared the four different classes (Table 2), we found that hand pain severity differed between the classes. Pain intensity in both hands and overall bodily pain was lowest in Class 2 and highest in Class 4. Class 4 was also characterized by having the lowest age.Class 1 held the highest proportion of men (n=14; 29%), although not significantly different from the other classes.

Conclusions: Four distinct potential phenotypes of hand OA that differed in hand pain severity were identified using biopsychosocial measures. Hand OA phenotypes with higher levels of pain sensitization, comorbidities, psychological and social burden tended to have more severe hand pain than persons with lower levels of these factors. Additionally, the phenotypes with lowest OA severity reported the highest pain severity which may reflect the discordance between OA severity and pain experience. Biopsychosocial factors are likely of importance in defining hand OA phenotypes, and treatment tailored to phenotypes may present a possibility for improved clinical outcomes. However, these potential phenotypes need to be validated in independent patient cohorts.

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USING ADVANCED STATISTICAL AND GRAPHICAL METHODS TO DEVELOP A MULTI-DOMAIN INDEX OF MOVEMENT-EVOKED PAIN

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Purpose: Movement-evoked pain (MEP) has emerged as a unique type of pain that substantially impacts general pain and functional outcomes

in musculoskeletal conditions. MEP is triggered or exacerbated by active or passive movement and is clearly differentiated from background, spontaneous or rest pain. However, our understanding of the mechanisms and correlates of MEP remain limited. The purpose of this study was to develop and validate a multi-domain mechanistic characterization of MEP in adults with clinical symptoms of knee osteoarthritis.
Methods: A secondary analysis of an observational study was conducted on data collected from individuals with knee pain at the University of Florida and the University of Alabama at Birmingham. The parent study investigated ethnic/race group differences in knee OA-related pain, disability, and altered pain processing in non-Hispanic Blacks and non-Hispanic Whites between 45-85 years of age. A battery of questionnaires (e.g., WOMAC, Graded Chronic Pain Scale [GCPS], etc.), quantitative sensory testing (QST), and functional activities (e.g. Short Physical Performance Battery [SPPB]) were used to gather data about pain and movement. Six domains were proposed to characterize the nature of MEP: mechanical qualities, modulatory mechanisms (QST), mixed types of pain (nociceptive, nociplastic, neuropathic), mobility-limiting factors (SPPB function), mediating/moderating factors (e.g., affect, sleep, etc.), and management interventions (e.g., coping, exercise, etc.). Our primary outcome measure was MEP, a composite measure of pain ratings gathered during the three components of the SPPB test-balance, walking, and unassisted chair stands. First, we applied principal component analysis (PCA) to condense the three SPPB pain measures into one variable. The first principal component (PC), a linear combination of the three SPPB pain measures, retained most of the variation in the data. Second, we examined the association of MEP with characteristic chronic pain intensity (GCPS) using Pearson's correlation. Then, we applied a novel network analysis, Mixed Graphical Modeling (MGM), to measure the partial correlation among pairs of variables from 6 domains (or networks) given all the other variables. MGM eliminated spurious associations between variables and revealed new associations adjusting for covariates (age, sex, and race). Associations identified in the network model were expected to provide insights into the direct interdependencies among 6 domains.
Results: A total of 178 individuals were included in the PCA and mean age was 57.9 (SD= 7.9). The first PC preserved 90.6% of the data's variation. There was significant correlation between PC and the GCPS characteristic pain intensity (r=0.61), suggesting collinearity and critical overlap in MEP and chronic pain intensity as concepts. To examine relationship between function scores and pain measures, unadjusted correlations found significant relationships between each SPPB pain measure and only SPPB walking, while the adjusted correlation analysis demonstrated that only SPPB balance pain was significantly associated with SPPB walking score. In univariate analyses, the PC was associated with nearly all variables from the 6 domains. The MGM (N= 134) revealed positive associations between select networks of factors. For example, the three SPPB pain measures were significantly associated with the mechanical domain (i.e., lower leg strength pain) and only one measure in the management domain, vigorous daily exercise. The other domains were uniquely correlated. Modulatory mechanisms were associated with the management and mixed types of pain domains. Mediating and moderating factors, such as sleep and positive affect, were associated with management domain factors of walking.
Conclusions: MEP is a complex concept and type of pain. In our sample, MEP showed significant associations with general chronic pain intensity and mechanical factors, which likely represents nociceptive pain. While the univariate analyses revealed numerous associations between MEP and variables in the 6 domains, adjustment in the MGM may have attenuated those associations. More research is needed to validate our models and expand the types of variables within each domain for a more precise and comprehensive characterization of MEP.

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OPIOID USE PRIOR TO TOTAL KNEE REPLACEMENT: COMPARATIVE ANALYSIS OF TRENDS IN ENGLAND AND SWEDEN

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Purpose: Opioids are still frequently used in the pain management of knee osteoarthritis (OA), despite increasing evidence of limited effectiveness, increased morbidity and mortality, as well as risk of addiction. Our aim was to describe and compare trends in the frequency of opioid use in patients with knee OA in England and Sweden in the 10 years prior to total knee replacement (TKR).
Methods: We identified 47,045 patients, aged 45 years and over, from the English national database (Clinical Practice Research Datalink Aurum) and 5,955 patients from the regional Swedish database (Skåne Healthcare register), all undergoing TKR between 2015 and 2019. 1:1 controls, matched on age, sex, and either practice (England) or residential area (Sweden) were randomly selected by risk-set sampling. For each included person, we retrieved information on all prescribed opioids. We estimated the annual prevalence and prevalence rates ratio (PRR) of opioid use in the 10 years prior to TKR (or matched index date for controls) using Poisson regression. In secondary analyses, opioids were stratified by strength (weak/strong), and patterns of use (prevalence and PRR) were explored in the 12-month period (0-3, 4-6, 7-9, and 10-12 months) preceding TKR to investigate the opioid use shortly prior to surgery.
Results: The proportion of patients with OA prescribed *any* opioid prior to TKR increased towards the date of surgery from 24% to 44% in England, and from 16% to 33% in Sweden, between 10 and 1 years prior to TKR. The prevalence increased gradually from 10 to 3 years, and then sharply rose in the 2 years preceding surgery (Figure 1). Opioid use among controls in both countries was relatively stable, resulting in an increasing PRR, between 1.6 to 2.7 and 1.6 to 2.6, in England and Sweden respectively, 10 to 1 years prior to TKR. Whilst the prevalence of prescribed opioids was higher in England, a majority of cases and controls were using weak opioids (e.g. Codeine and Dihydrocodeine), whereas in Sweden, the proportion using strong opioids (e.g. Tramadol and Morphine) was greater. The PRR of prescribed strong opioids increased from 1.6 to 2.3 in England, and from 1.6 to 2.6 in Sweden, 10 to 1 years preceding TKR. The PRR of prescribed weak opioids increased from 1.6 to 2.7 in England, and from 1.6 to 2.9 in Sweden, 10 to 1 years preceding TKR. No relevant cohort or period effects were observed in either country.

The mean of VAS and WOMAC, Synovial thickness comparison between pre-treatment, 1st, 2nd, 4th week

Pain VAS	TDM + NSAID	Placebo	P-value
Pre-treatment	4.64	3.80	0.927
1st week	2.75	2.8	0.916
2nd week	1.94	2.6	0.014
4th week	1.42	2.1	0.037
WOMAC score	**TDM + NSAID**	**Placebo**	**P-value**
Pre-treatment	9.04	6.63	0.183
1st week	5.59	6.01	0.713
2nd week	3.88	5.76	0.073
4th week	3.33	5.69	0.015
Synovial thickness	**TDM + NSAID**	**Placebo**	**P-value**
Pre-treatment	2.93	2.92	0.927
1st week	2	3.01	0.869
2nd week	1.86	2.74	0.014
4th week	1.81	2.65	0.004