Musculoskeletal
Research Paper

OPEN

PAIN REPORTS

Central aspects of pain associated with physical activity: results from the Investigating Musculoskeletal Health and Wellbeing cohort

Stephanie Louise Smith[a,b,c,d,*], Muhammad Umar Habib[a,b], Wendy J. Chaplin[a,b,c,d,e], Bonnie Millar[a,b,d], Daniel F. McWilliams[a,b,c,d], David Andrew Walsh[a,b,c,d,f]

Abstract

Background: Knee pain reduces activity, while inactivity can increase pain. The central nervous system modulates both pain and activity. The 8-item Central Aspects of Pain (CAP) questionnaire measures self-reported symptoms associated with current and future knee pain severity and psychophysical evidence of central pain sensitivity. The objective was to explore associations between CAP and physical inactivity in people with knee pain.

Methods: Participants from the Investigating Musculoskeletal Health and Wellbeing cohort who reported their knee as their most troublesome joint with numerical rating scale pain severity ≥1/10 completed questionnaires at baseline and 12 months addressing demographic and clinical characteristics, CAP questionnaire, and physical inactivity (Frail Non-Disabled questionnaire item). Chi-squared, correlations and multivariable logistic regression were performed.

Results: Seven hundred twenty-two participants provided baseline data and 404 longitudinal data. Higher baseline CAP scores were associated with higher baseline pain severity {OR: 1.25 (95% confidence interval [CI]: 1.02–1.53); $P = 0.032$} and physical inactivity (OR: 1.18 [95% CI: 1.11–1.25]; $P < 0.001$). Increasing CAP scores over 12 months were associated with becoming physically inactive (OR: 1.16 [95% CI: 1.01–1.32]; $P = 0.032$). The effects of CAP on physical inactivity were not fully explained by pain severity nor by any single characteristic of widespread pain distribution, emotional or cognitive factors, sleep disturbance, or fatigue.

Conclusion: Central aspects of pain questionnaire displays cross-sectional and longitudinal associations with physical inactivity. Central nervous system manifestations of pain appear to link pain with physical activity and may be more important than pain severity.

Keywords: Pain, Physical activity, Barriers, Central pain hypersensitivity, Knee

1. Introduction

Pain is a leading cause of disability and a risk factor for deteriorating physical activity,[16,30] making activities of daily living difficult.[12] Individuals adopt avoidance strategies, which hinder participation.[25,32] Pain resolution results in minor increases in physical activity,[31] suggesting that factors other than the sensory experience of pain contribute to its adverse effects on physical activity.

Osteoarthritis is a leading cause of knee pain and significantly contributes to years lived with disability.[22] Therapeutic exercise is recommended as the first-line treatment for osteoarthritis.[49]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

[a] Pain Centre Versus Arthritis, University of Nottingham, Nottingham, United Kingdom, [b] Academic Rheumatology, Injury, Recover and Inflammation Science, School of Medicine, University of Nottingham, Nottingham, United Kingdom, [c] Advanced Pain Discovery Platform, University of Nottingham, Nottingham, United Kingdom, [d] NIHR Biomedical Research Centre, University of Nottingham, Nottingham, United Kingdom, [e] School of Health Sciences, University of Nottingham, Nottingham, United Kingdom, [f] Sherwood Forest Hospitals NHS Foundation Trust, Rheumatology, Mansfield, Nottingham, United Kingdom

**Corresponding author. Address: Academic Rheumatology, Pain Centre Versus Arthritis, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham NG5 1PB, United Kingdom. Tel.: +44115 823 1942. E-mail address: Stephanie.Smith2@Nottingham.ac.uk (S.L. Smith).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 10 (2025) e1268

http://dx.doi.org/10.1097/PR9.0000000000001268

Exercise has demonstratable benefits, including reducing pain and pain sensitivity,[28] and improving function and quality of life for individuals with osteoarthritis.[23,24]

Physical activity is defined as any bodily movement produced by skeletal muscle that requires energy expenditure, referring to all movements, including during leisure time or as part of a person's work, such as exercise and transport.[70] Increasing physical activity, or moving more, may reduce all-cause mortality and the risk of several chronic medical conditions.[65] Physical activity can also help prevent or treat anxiety and depression.[42] Despite current guidelines, individuals with osteoarthritis typically have lower physical activity levels than the general population.[61]

Pain is an unpleasant sensory and emotional experience associated with the interplay between potential or threatened tissue damage and the processing of nociceptive signals by peripheral and central nervous systems (CNS). Distorted sensory processing in the CNS can amplify pain because of altered inhibitory and facilitatory pain pathways and long-term potentiation of neural synapses.[64] This altered pain processing has been associated with diverse characteristics, including fatigue,[37] disability,[26] mood disturbance, anxiety and depression,[26] neuropathic-like symptoms,[9,47] sleep disturbance,[62] catastrophising,[44] and widespread pain distribution.[35] Physical activity can moderate pain sensitivity in healthy individuals,[6,20,50,51] whereby greater physical activity levels are associated with less pain sensitivity.[6,20] Exercise therapies also aim to improve pain sensitivity.[28]

Nociplastic pain is defined as pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of disease or lesions of the somatosensory system causing pain.[29] Central sensitisation, an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input,[29] might contribute to nociplastic pain. Although nociplastic classification criteria also include comorbidities, including the characteristics such as sleep disturbance, fatigue, and cognitive problems. The Central Aspects of Pain (CAP) questionnaire was designed to reflect central pain mechanisms now referred to as nociplasticity. It was initially developed and validated in individuals with knee pain[2] and subsequently modified to be used by people with pain from other joints.[43] The CAP questionnaire consists of 8 items, each significantly associated with quantitative sensory testing (QST) evidence of central pain sensitivity. The 8 items loaded to a single unitary factor, which was more closely correlated with QST than is any of the original characteristics measured by questionnaires from which the CAP items were derived.[2–4] High CAP scores were associated with worse knee pain prognosis even after adjusting for baseline pain severity, suggesting that nociplasticity might be a barrier to improving pain.[4]

Characteristics that have been associated with CAP scores and nociplasticity have also been associated with physical inactivity. Such characteristics include fatigue,[21,48] neuropathic-like symptoms,[54] and catastrophising.[38,69] We hypothesised that CAP measures a state that acts as a barrier to physical activity. This study aimed to evaluate the associations between CAP and self-reported physical inactivity using cross-sectional data and longitudinal analyses over 12 months from a cohort of individuals with knee pain.

2. Methods

2.1. Study population

Data analysed were from the Investigating Musculoskeletal Health and Wellbeing (IMH&W) prospective cohort study.[45] Investigating Musculoskeletal Health and Wellbeing was designed to measure and characterise the development and progression of pain, frailty, and disability in adults with musculoskeletal problems in the East Midlands region of the United Kingdom. Data were from the first 5,500 people recruited into IMH&W between June 2018 and February 2020 who had completed the FRAIL questionnaire[46] at baseline and 12 months later were included. The study was approved by the Central London Research Ethics Committee (REC ref: 18/L.O./0870) and registered on clinicaltrails.gov (NCT03696134). Participants completed postal consent forms and questionnaires returned without consent forms implied consent. Individuals who reported the "knee" as the most bothersome joint based on the question, "Over the past 4 weeks, where was your most bothersome joint pain or aching feeling?" with pain levels ≥ 1 on the numerical rating scale (NRS) and answered the Frail Non-Disabled (FiND)[10] physical activity question at baseline and at 12 months were included.

2.2. Investigating musculoskeletal health and well-being variables

The IMH&W questionnaire captured participant characteristics (eg, age, sex, BMI, alcohol, and smoking status) and previous joint replacement at baseline. Socioeconomic status was calculated based on postcode using indices of multiple deprivation.[52] Average pain intensity in the most troublesome joint in the past 4 weeks was assessed on a 0 to 10 NRS using the question, "Over the past 4 weeks, how intense was your average pain or the average aching feeling in your most bothersome joint, where 0, is 'no pain' and 10 is 'pain as bad as could be'?".

The Central Aspects of Pain (CAP)—knee questionnaire was previously developed and validated in people with knee pain[2–4] and subsequently modified from "knee" to "joint" for generalisability across musculoskeletal conditions.[43] The CAP questionnaire consists of 8 items associated with neuropathic-like symptoms, fatigue, cognitive impact, catastrophising, anxiety, sleep, depression, and pain distribution.[2–4] Items 1 to 7 are Likert scales and scored as never = 0, sometimes = 1, often/always = 2, with item 7 reverse scored. Item 8 body manikin was scored as knee pain only = 0, knee plus other pain below the waist = 2, providing a summated CAP score from 0 to 16.[3]

Self-reported physical inactivity was classified using the self-reported Frail Non-Disabled (FiND) questionnaire item "Which is your level of physical activity?".[10] Participants reported their levels of physical activity as either "Regular (at least 2–4 hours per week)" or "None or mainly sedentary." This question has demonstrated moderate agreement with physical/sedentary activity based on cut scores of sedentary activity <383 kcal/wk for men and <270 kcal/wk for women.[10]

2.3. Data analysis

Descriptive statistics for continuous or ordinal variables are reported as median and interquartile ranges (IQR), categorical variables as frequencies, and differences as mean and 95% confidence interval (95% CI). Minimal clinically important difference (MCID) was calculated as $0.5 \times$ SD for baseline scores rounded up to the nearest integer for CAP and pain NRS. Chi-squared and point-biserial Spearman (ρ) or Pearson (r) correlations were performed to assess cross-sectional and longitudinal associations at baseline and 12 months. Confounders were predefined as age, sex and BMI, chi-squared and point-biserial Spearman (ρ) or Pearson (r) correlations explored additional covariates of joint replacement, alcohol intake, and smoking status. Bivariate and multivariable logistic regression with confounders assessed the associations between baseline or change in CAP scores or pain NRS (continuous measure calculated as change from baseline to 12 months) with physical inactivity or change in physical inactivity at 12 months (change in physical activity as change from active to inactive or vice versa).

Secondary analysis explored if individual components of CAP better explained the association with physical activity. Bivariate logistic regression models examined associations with physical inactivity at baseline or changes in physical inactivity at 12 months. Multivariable logistic regressions explored whether associations between individual CAP items and inactivity at baseline could fully explain observed associations between CAP and inactivity. All analyses were performed using summarytools,[13] psych,[57] glm2,[41] dplyr,[68] tidyverse,[67] pander,[15] epitools,[7] and gmodels[66] packages in R statistical software (v4.2.2)[56] within the RStudio software (rstudio.com) with alpha set at 0.05.

This is a secondary analysis of data. Two-tailed logistic regression post hoc power calculation for the primary model of change in CAP and NRS associated with becoming active/sedentary. Based on a sample size of N = 404, log odds ratio = 0.464, proportion = 0.054, alpha = 0.05, normal distribution, multicollinearity = 0.375, probability of the outcome occurring (y = 1) in the treatment/exposure (x = 1) under the null hypothesis = 0.079, unstandardised regression coefficient for the predictor of interest = 0.462, and unstandardised regression coefficient for the reference group = 0 indicated 71% power.

3. Results

Of 5,500 IMH&W participants, 722 were eligible for the current study at baseline, of whom 404 participants also self-reported physical activity data at 12 months (**Fig. 1**). Participants with follow-up data reported similar characteristics at baseline to those of the entire baseline population (**Table 1**). For the 404 participants with follow-up data, the median (range) age was 72 (64–77) years, BMI 27.6 (24.8–31.6) kg/m^2, NRS pain 6 (4–8), and CAP 7 (5–11); 5 people with bilateral knee pain reported unilateral joint replacement. Of these, 177 (44%) reported bilateral knee pain at baseline. The minimal clinically important difference (0.5 × 3.6 = ±1.8) for CAP scores was 2 units and for NRS (0.5 × 2.1 = ±1.1) was 1 unit. Twenty-six percent (n = 106) were inactive at baseline.

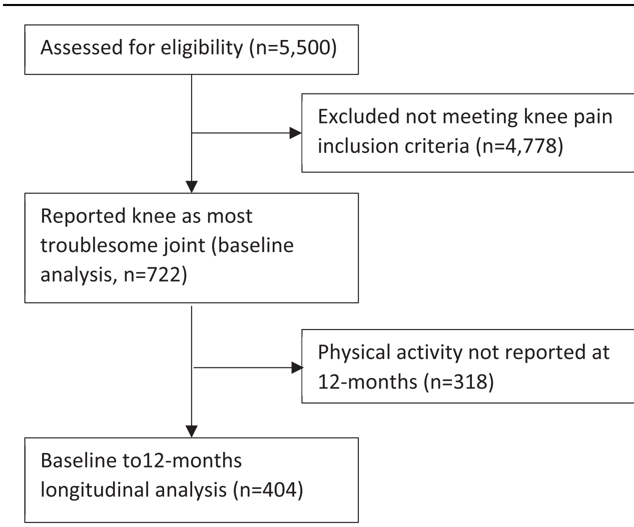

Figure 1. Consort diagram showing participant flow through the study.

3.1. Cross-sectional associations with physical inactivity at baseline

Higher pain NRS and CAP were associated with self-reported physical inactivity at baseline (n = 722, **Table 2**). Higher pain NRS was associated with higher CAP scores at baseline ($\rho = 0.63$, $P < 0.001$). Physical inactivity was associated with higher BMI (r = 0.18, $P < 0.001$) but not significantly associated with age (r = 0.05, P = 0.182), sex (χ^2 = 0.75, P = 0.386), previous joint replacement (χ^2 = 2.08, P = 0.149), alcohol consumption (χ^2 = 1.42, P = 0.234), nor smoking status (χ^2 = 1.78, P = 0.140). When adjusted for predefined confounders (age, sex, and BMI), associations of pain NRS or CAP with physical inactivity remained significant and of similar magnitude to bivariate analyses. When pain NRS and CAP were entered into a single regression model, CAP (but not pain NRS) remained significantly associated with physical inactivity (**Table 2**).

3.2. Longitudinal associations with 12-month physical inactivity

Of the 404 participants who reported physical activity data at baseline and 12 months, 74 (18%) reported being physically inactive both at baseline, and at 12 months, 262 (65%) were active at both time points, 36 (9%) transitioned from active to inactive, and 32 (8%) from inactive to active. Group mean pain NRS was similar between baseline and 12 months (mean difference: 0.20 [95% CI: −0.02 to 0.42]; P = 0.068). Ninety-six participants (25%) displayed pain increases (NRS ≥1) and 66 (17%) decreases (≤−1), whereas 228 (58%) indicated no change in pain NRS between baseline and 12 months. Mean CAP scores were slightly but significantly higher at 12 months compared with baseline (mean difference: 0.64 [95% CI: 0.27–1.00]; $P < 0.001$). Seventy-two participants (22%) displayed an improvement (decrease ≤ −2) in CAP scores, and 122 (36%) indicated an increase ≥2 in CAP scores. By contrast, for 141 participants (42%), the difference in CAP scores between baseline and 12 months did not exceed the MCID of 2. Baseline and 12-month physical inactivity were strongly intercorrelated (χ^2 = 131.52, $P <$ 0.001). Associations of baseline variables with 12-month physical inactivity replicated associations with baseline inactivity (see Table S1, supplemental digital content, http://links.lww.com/PR9/A301).

Increases in CAP scores between baseline and 12 months were associated with an increased likelihood of those physically active at baseline becoming physically inactive at 12 months (**Table 3**). Changes in pain NRS were not significantly associated with changes in physical activity at 12 months (**Table 3**). When pain NRS and CAP scores were included in a single model, a change in CAP scores was associated with becoming physically inactive 12 months, and a change in CAP and baseline NRS and CAP were associated with becoming physically active (**Table 3**). Baseline physical activity was not associated with CAP (OR: 1.78 [95% CI: 0.21–15.50]; P = 0.599) or NRS (OR: 0.35 [95% CI: 0.06–1.75]; P = 0.199) at 12 months.

Associations between CAP and physical inactivity were not fully explained by any single CAP item (see Tables S2 and S3, supplemental digital content, http://links.lww.com/PR9/A301). In bivariate cross-sectional baseline analyses, fatigue-associated (OR: 1.82 [95% CI: 1.32–2.52]; $P < 0.001$) and depression-associated (OR: 1.77 [95% CI: 1.36–2.31]; $P < 0.001$) items were

Table 1

Baseline participant characteristics.

	Knee most troublesome joint (n = 722)	Knee most troublesome joint with 12-mo physical activity data (n = 404)
Demographics		
Sex; n (% female)	396 (55%)	219 (54%)
Age, y	72 (65–77)	72 (65–77)
BMI (kg/m^2)	28.1 (24.8–31.6)	27.7 (24.7–31.0)
Previous total knee replacement, n (%)	12 (2%)	5 (1%)
Bilateral knee pain	335 (46%)	177 (44%)
Alcohol consumption		
<3 units per day, n (%)	634 (88%)	354 (88%)
≥3 units per day, n (%)	88 (12%)	50 (12%)
Smoking status		
Never, n (%)	327 (45%)	184 (45%)
Ex-smoker, n (%)	357 (49%)	201 (50%)
Current smoker, n (%)	38 (5%)	19 (5%)
Socioeconomic status (10 least deprived, 1 most deprived)	8 (5–9)	8 (5–9)
Physical activity		
Active, n (%)	502 (70%)	298 (74%)
Inactive, n (%)	220 (30%)	106 (26%)
Pain measures		
NRS (possible range 1–10)	6 (4–8)	6 (4–7)
CAP (possible range 0–16)	8 (5–11)	7 (5–10)

Baseline characteristics of participants contributing data to the current study. The subgroup who provided both baseline and follow-up data displayed baseline characteristics similar to the total baseline population. Data are median (interquartile range) or n (%).
BMI, body mass index; NRS, pain numerical rating scale; CAP, Central Aspects of Pain.

associated with inactivity. No individual baseline CAP item was significantly associated with 12-month inactivity (see Table S2, supplemental digital content, http://links.lww.com/PR9/A301). Baseline CAP remained significantly associated with greater baseline inactivity in separate multivariable models adjusted for each CAP item (aORs: 1.09–1.20, see Table S3, supplemental digital content, http://links.lww.com/PR9/A301). Only the baseline depression item remained significantly associated with baseline inactivity after adjustment for CAP (aOR: 1.60 [95% CI: 1.12–2.30]; $P = 0.011$).

Table 2

Baseline cross-sectional associations with physical inactivity (active = 0, inactive = 1, n = 722).

	Odds ratio	95% confidence interval		*P*
		Lower	Upper	
Bivariate analyses				
Baseline CAP (0–16)	**1.20**	**1.14**	**1.26**	**<0.001**
Baseline pain NRS (0–10)	**1.25**	**1.16**	**1.36**	**<0.001**
CAP multivariable				
Baseline CAP (0–16)	**1.19**	**1.13**	**1.25**	**<0.001**
Age (y)	**1.03**	**1.01**	**1.05**	**0.001**
Sex (female)	1.06	0.74	1.51	0.753
BMI (kg/m^2)	**1.07**	**1.03**	**1.11**	**<0.001**
Pain NRS multivariable				
Baseline NRS (0–10)	**1.21**	**1.11**	**1.32**	**<0.001**
Age (y)	**1.03**	**1.01**	**1.04**	**0.004**
Sex (female)	0.97	0.68	1.37	0.842
BMI (kg/m^2)	**1.07**	**1.04**	**1.11**	**<0.001**
Combined multivariable				
Baseline CAP (0–16)	**1.18**	**1.11**	**1.25**	**<0.001**
Baseline NRS (0–10)	1.03	0.93	1.15	0.545
Age (y)	**1.03**	**1.01**	**1.05**	**0.001**
Sex (female)	1.07	0.75	1.53	0.709
BMI (kg/m^2)	**1.07**	**1.03**	**1.10**	**<0.001**

Bivariate associations are presented between Central Aspects of Pain (CAP) or pain numerical rating scale (NRS) and physical inactivity. Multivariable models adjusted for baseline CAP or/and NRS, in addition to predefined covariates of age, sex, and body mass index (BMI).
Statistically significant associations are shown in bold.

Higher baseline pain NRS was associated with increased CAP scores between baseline and 12 months (OR: 1.77 [95% CI: 1.17–2.68] per unit increase in pain NRS; $P = 0.007$). Higher baseline CAP scores were associated with increases in pain NRS at 12 months (OR: 1.25 [95% CI: 1.02–1.53] per unit increase in pain CAP; $P = 0.032$), and greater increases in CAP scores were associated with greater increases in NRS pain between baseline and 12 months (OR: 1.25 [95% CI: 1.18–1.34] per unit increase in CAP score; $P < 0.001$).

4. Discussion

This study examined associations between self-reported physical inactivity and central aspects of pain in people with knee pain. Central Aspects of Pain and pain NRS were each associated with self-reported physical inactivity in baseline bivariate cross-sectional analyses. Only CAP remained significantly related to physical inactivity after adjusting for confounders. In people physically active at baseline, increased CAP scores at 12 months was associated with becoming physically inactive, and increased pain NRS could not wholly explain this association. Central aspects of pain, therefore, might act as barriers to continuing physical activity, over and above any effect of pain severity. Conversely, low physical activity may lead to worsening nociplasticity.

Chronic pain is a complex sensory and emotional experience linked to evidence of widespread CNS dysfunction. CAP scores are associated with each of the 8 characteristics represented by its items; neuropathic-like pain, anxiety, depression, catastrophising, cognitive impact, sleep disturbance, fatigue, and widespread pain distribution. No single item explains the associations of CAP scores with pain severity[2] nor, we show here, with physical inactivity. We propose that CAP measures nociplasticity, an aspect of CNS dysfunction that might contribute to pain sensitivity. Our current data indicate that nociplasticity might also contribute to inactivity, over and above its effects on pain.

In people who were active at baseline, increasing CAP over 12 months was associated with becoming inactive. These findings demonstrate that, for some participants, CAP measures

Table 3

Associations between baseline or 12-mo change in pain NRS and CAP with 12-mo change in physical activity.

	Become inactive (0 = active baseline and follow-up, 1 = active baseline then inactive follow-up)				Become active (0 = inactive baseline and follow-up, 1 = inactive baseline then active follow-up)			
	Odds ratio	95% confidence interval		*P*	Odds ratio	95% confidence interval		*P*
		Lower	Upper			Lower	Upper	
Bivariate analyses								
Baseline CAP	1.05	0.95	1.17	0.339	0.96	0.86	1.07	0.488
Baseline pain NRS	1.15	0.97	1.35	0.106	1.07	0.87	1.32	0.488
CAP change	**1.16**	**1.03**	**1.30**	**0.012**	0.89	0.78	1.01	0.065
NRS change	1.12	0.94	1.33	0.195	1.00	0.83	1.21	0.995
CAP change multivariable								
CAP change	**1.16**	**1.01**	**1.32**	**0.032**	0.90	0.77	1.05	0.193
Baseline CAP	1.05	0.91	1.22	0.489	0.94	0.79	1.11	0.464
Age (y)	1.03	0.98	1.09	0.237	0.97	0.92	1.02	0.269
Sex (female)	1.54	0.62	3.79	0.352	**3.38**	**1.05**	**10.93**	**0.042**
BMI (kg/m^2)	**1.14**	**1.06**	**1.23**	**<0.001**	1.03	0.94	1.13	0.502
NRS change multivariable								
NRS change	1.25	0.99	1.57	0.055	1.02	0.82	1.26	0.891
Baseline NRS	1.25	1.00	1.58	0.051	1.07	0.84	1.38	0.575
Age (y)	**1.02**	**0.97**	**1.07**	**0.407**	0.97	0.93	1.02	0.229
Sex (female)	1.03	0.45	2.35	0.944	**4.67**	**1.57**	**13.90**	**0.005**
BMI (kg/m^2)	**1.13**	**1.05**	**1.22**	**<0.001**	0.99	0.91	1.08	0.896
Full multivariable								
CAP change	**1.20**	**1.04**	**1.38**	**0.013**	**0.79**	**0.66**	**0.94**	**0.007**
NRS change	1.15	0.89	1.50	0.285	1.24	0.94	1.62	0.128
Baseline CAP	1.05	0.89	1.25	0.552	**0.80**	**0.65**	**0.99**	**0.039**
Baseline NRS	1.29	0.96	1.72	0.089	**1.52**	**1.06**	**2.17**	**0.022**

Bivariate associations are presented for baseline or change in Central Aspects of Pain (CAP) or pain numerical rating scale (NRS) with changing physical activity. Increases in CAP scores and NRS were allocated positive values so that an OR >1.0 indicates that an increase in CAP or NRS was associated with an increased likelihood of becoming active or inactive. Multivariable models are presented for changes in CAP or NRS, and adjusted for baseline CAP or NRS, as well as predefined covariates of age, sex, and body mass index (BMI), or change in both CAP and NRS.
Statistically significant associations are shown in bold.

a changeable state rather than a fixed trait and that changing CAP scores might have biological importance by influencing physical inactivity. This also raises the possibility that CAP scores might be amenable to therapeutic interventions, that CAP might measure the effects of such interventions, and that reducing CAP scores might help prevent or reverse physical inactivity.

Central Aspects of Pain should not be considered the only (or necessarily the most important) moderator of physical activity. We showed that responses to the depression item in the CAP questionnaire were associated with physical inactivity, over and above any effect of CAP itself. Depressive symptoms might, for example, be associated with reduced motivation to remain physically active.[27] Furthermore, only changes in CAP were related to becoming less physically active not CAP at baseline. Therefore, other factors influencing physical activity and CAP, such as injury or disease activity, may explain these changes. It is possible that increases in CAP scores are a consequence rather than (or as well as) cause of decreased physical activity. Exercise and physical activity might moderate central pain processing and thereby reduce nociplasticity.[11]

Pain resulting from altered CNS processing may play a role in being physically inactive in individuals with knee pain. Nociplasticity might be associated with an increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input (central sensitisation),[1] although central sensitisation cannot be directly measured in humans. Quantitative sensory testing evidence of central sensitisation has been associated with fatigue, catastrophising, widespread pain, neuropathic symptoms, mood, sleep, and widespread pain.[9,26,35,37,44,47,62] Furthermore, some of these characteristics are recognised as part of the IASP nociplastic pain classification criteria.[34] Fatigue, mood disturbance, and catastrophising have been associated previously with physical inactivity.[42,48,53,54,69] Rather than pain intensity, these characteristics might influence participation in physical activity and explain the associations we show between CAP and physical inactivity. Catastrophising and mood disturbance might lead to activity avoidance beliefs and behaviours,[17,39,40,60] and a fear of causing greater pain and or damage might lead to physical inactivity.

Physical activity is recommended to prevent and manage painful conditions such as arthritis, and physical activity might moderate pain. It has been suggested that physical activity can influence affective pain networks more than sensory pain networks[59] and decrease central excitability while increasing central inhibition of nociceptive transmission.[36] Physical activity might reduce pain sensitivity in people without chronic pain,[6,19,20,36,50,51,59] across different pain conditions.[8,18] Conversely, amplification of pain signals (pain hypersensitivity) as a result of altered CNS processing can lead to functional limitations.[11] Nociplasticity has been shown to affect physical activity and physical function,[58] potentially through the avoidance of movements, neural adaptations in the sensory and motor areas, and neurophysiological and neuromuscular changes.[11,58] Our longitudinal findings are consistent with either nociplasticity altering activity levels or activity levels altering nociplasticity.

The impacts of central aspects of pain and physical inactivity might be bidirectional, and optimal interventions might address both concurrently. It seems that reductions in pain sensitivity alone may be insufficient to reverse physical inactivity because decreasing CAP scores were not associated with increased activity in those who were inactive at baseline. In individuals with a reduction of at least −2 (MCID) in CAP scores, only 6 (5%) became active, 12 (10%) became sedentary, and 99 (85%) did not change their activity levels. Similarly, removing the peripheral nociceptive drive in osteoarthritis by joint replacement surgery often does not alone lead to a return to physical activity.[5] Treatments that solely target pain sensitivity might help people maintain their physical activity but might be insufficient to increase physical activity and quality of life for those who are already inactive. Current NICE guidelines recommend therapeutic exercise as a first-line treatment for osteoarthritis knee pain[45] to improve pain and function.[63] Although exercise has been shown to be beneficial for improving nociplasticity,[28] more holistic biopsychosocial approaches may be required to enable individuals who are not currently active to undertake exercise and increase physical activity. Combining therapeutic exercise with cognitive behavioural therapy, which targets pain sensitivity, the associated characteristics, and function, might be more beneficial in reducing the impact on physical activity from pain sensitivity.

This study has several limitations. Physical activity was self-reported based on the categorical FiND questionnaire item "What is your level of physical activity?" Participants reported whether they undertook "regular (at least 2–4 hours per week)" or "none or mainly sedentary" physical activity. Although previously validated against gait speed,[10] this dichotomous outcome may fail to take into account all activities, such as travel to work and household chores, and might underestimate or overestimate the true prevalence of physical inactivity.[55] Changing physical activity might also be difficult to detect based on the above definition, and more granular data could be measured by self-report or directly measured physical activity. Increased or new activity may take some time to be considered regular. Direct measures of physical activity also have limitations of participant burden, cost, and the need for specialised training,[55] with no gold standard, making them difficult to use in extensive cohort studies like IMH&W. We found that low physical activity was associated with higher BMI, and BMI was adjusted in our multivariable models. However, we were unable to explore all potential confounders, such as pain duration, change in medication, injury or treatment between time points, which might explain some of the observed associations. Minimal clinically important difference was used to determine if participants had important changes in NRS or CAP between baseline and 12 months. Minimal clinically important difference was estimated using the "distribution-based" approach (SD $\times$ 0.5), which has some limitations compared with the "gold standard", "anchor-based" approach. The "distribution-based" approach lacks clinical context to define what constitutes meaningful change; it is also sensitive to the characteristics of the sample, eg, baseline severity, sample size, and heterogeneity.[14,33] This was an exploratory study with multiple analyses, increasing the risk of type I errors. Post hoc power calculations indicated that the study showed 71% power; additional dedicated studies need to confirm these results.

In conclusion, as measured by CAP, central aspects of pain display cross-sectional and longitudinal associations with physical inactivity. Increasing CAP scores were associated with becoming physically inactive at 12 months, but a decrease in CAP scores was not significantly associated with becoming active. Central aspects seem to link pain with physical inactivity and may be more important than pain severity itself in posing a barrier to maintaining physical activity in people with knee pain. Addressing central aspects might help people with chronic knee pain remain active.

Disclosures

The authors have no conflict of interest to declare.

Acknowledgements

The authors want to acknowledge the time and effort of the study participants and IMH&W staff. In the first instance, data requests for IMH&W data may be directed to david.walsh@nottingham.ac.uk. The study analysis plan is not preregistered. No specific funding was received from any bodies in the public, commercial, or not-for-profit sectors to perform the work described in this article. D. A. Walsh received research grants, consultancy, and speaker honoraria from Pfizer Ltd, UCB Pharma, Orion Corporation, GlaxtonSmithKline Research and Development, Eli Lilly Company, Grunenthal GmbH, Contura International A/S, AbbVie Inc, and Medscape International. D. F. McWilliams has grant support from Eli Lilly, Pfizer, and UCB.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A301.

Article history:
Received 14 November 2024
Received in revised form 31 January 2025
Accepted 24 February 2025
Available online 18 April 2025

References

[1] Classification of chronic pain. In: Merskey H, Bogduk N, editors. Description of chronic pain syndromes and definitions of pain terms. Washington, DC: IASP Press, 2012.
[2] Akin-Akinyosoye K, Frowd N, Marshall L, Stocks J, Fernandes GS, Valdes A, McWilliams DF, Zhang W, Doherty M, Ferguson E, Walsh DA. Traits associated with central pain augmentation in the Knee Pain in the Community (KPIC) cohort. PAIN 2018;159:1035–44.
[3] Akin-Akinyosoye K, James RJE, McWilliams DF, Millar B, das Nair R, Ferguson E, Walsh DA. The Central Aspects of Pain in the Knee (CAP-Knee) questionnaire; a mixed-methods study of a self-report instrument for assessing central mechanisms in people with knee pain. Osteoarthritis Cartilage 2021;29:802–14.
[4] Akin-Akinyosoye K, Sarmanova A, Fernandes GS, Frowd N, Swaithes L, Stocks J, Valdes A, McWilliams DF, Zhang W, Doherty M, Ferguson E, Walsh DA. Baseline self-report "central mechanisms" trait predicts persistent knee pain in the Knee Pain in the Community (KPIC) cohort. Osteoarthritis Cartilage 2020;28:173–81.
[5] Almeida GJ, Khoja SS, Piva SR. Physical activity after total joint arthroplasty: a narrative review. Open Access J Sports Med 2018;9:55–68.
[6] Andrzejewski W, Kassolik K, Brzozowski M, Cymer K. The influence of age and physical activity on the pressure sensitivity of soft tissues of the musculoskeletal system. J Bodyw Mov Ther 2010;14:382–90.
[7] Aragon TJ. Epitools: epidemiology tools. The Comprehensive R Archive Network. Available at: https://cran.rproject.org/web/packages/epitools/epitools.pdf. Accessed July 31, 2022.
[8] Belavy DL, Van Oosterwijck J, Clarkson M, Dhondt E, Mundell NL, Miller CT, Owen PJ. Pain sensitivity is reduced by exercise training: evidence from a systematic review and meta-analysis. Neurosci Biobehav Rev 2021;120:100–8.
[9] Blikman T, Rienstra W, Van Raay JJAM, Dijkstra B, Bulstra SK, Stevens M, Van Den Akker-Scheek I. Neuropathic-like symptoms and the association with joint-specific function and quality of life in patients with hip and knee osteoarthritis. PLoS One 2018;13:e0199165.
[10] Cesari M, Demougeot L, Boccalon H, Guyonnet S, Abellan Van Kan G, Vellas B, Andrieu S. A self-reported screening tool for detecting community-dwelling older persons with frailty syndrome in the absence of mobility disability: the FiND questionnaire. PLoS One 2014;9:e101745.
[11] Chimenti RL, Frey-Law LA, Sluka KA. A mechanism-based approach to physical therapist management of pain. Phys Ther 2018;98:302–14.
[12] Clynes MA, Jameson KA, Edwards MH, Cooper C, Dennison EM. Impact of osteoarthritis on activities of daily living: does joint site matter? Aging Clin Exp Res 2019;31:1049–56.
[13] Comtois D. summarytools: Tools to Quickly and Neatly Summarize Data. R package version 1.1.3, 2025. Available at: https://github.com/dcomtois/summarytools. Accessed January 3, 2022.
[14] Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56:395–407.
[15] Daróczi G, Tsegelskyi R. pander: An R 'Pandoc' Writer. R package version 0.6.7, 2025. Available at: https://github.com/rapporter/pander. Accessed January 3, 2025.

[16] De Rooij M, Van Der Leeden M, Heymans MW, Holla JFM, Häkkinen A, Lems WF, Roorda LD, Veenhof C, Sanchez-Ramirez DC, De Vet HCW, Dekker J. Prognosis of pain and physical functioning in patients with knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care Res 2016;68:481–92.

[17] Dekker J, Boot B, van der Woude LH, Bijlsma JW. Pain and disability in osteoarthritis: a review of biobehavioral mechanisms. J Behav Med 1992; 15:189–214.

[18] Elkhabir AA, Mcwilliams DF, Smith S, Chaplin W, Salimian M, Georgopoulos V, Kouraki A, Walsh DA. Effects of exercise on indices of central sensitisation in humans: a systematic review and network meta-analysis. Osteoarthritis Cartilage 2023;31:S377.

[19] Ellingson L, Stegner A, Schwabacher I, Koltyn K, Cook D. Exercise strengthens central nervous system modulation of pain in fibromyalgia. Brain Sci 2016;6:8.

[20] Ellingson LD, Colbert LH, Cook DB. Physical activity is related to pain sensitivity in healthy women. Med Sci Sports Exerc 2012;44:1401–6.

[21] Fawole HO, Felson DT, Frey-Law LA, Jafarzadeh SR, Dell'Isola A, Steultjens MP, Nevitt MC, Lewis CE, Riskowski JL, Chastin SFM. Is the association between physical activity and fatigue mediated by physical function or depressive symptoms in symptomatic knee osteoarthritis? The Multicenter Osteoarthritis Study. Scand J Rheumatol 2021;50: 372–80.

[22] Ferrari AJ, Santomauro DF, Aali A, Abate YH, Abbafati C, Abbastabar H, Abd Elhafeez S, Abdelmasseh M, Abd-Elsalam S, Abdollahi A, Abdullahi A, Abegaz KH, Abeldaño Zuñiga RA, Aboagye RG, Abolhassani H, Abreu LG, Abualruz H, Abu-Gharbieh E, Abu-Rmeileh NM, Ackerman IN, Addo IY, Addolorato G, Adebiyi AO, Adepoju AV, Adewuyi HO, Afyouni S, Afzal S, Afzal S, Agodi A, Ahmad A, Ahmad D, Ahmad F, Ahmad S, Ahmed A, Ahmed LA, Ahmed MB, Ajami M, Akinosoglou K, Akkaif MA, Al Hasan SM, Alalalmeh SO, Al-Aly Z, Albashtawy M, Aldridge RW, Alemu MD, Alemu YM, Alene KA, Al-Gheethi AAS, Alharrasi M, Alhassan RK, Ali MU, Ali R, Ali SSS, Alif SM, Aljunid SM, Al-Marwani S, Almazan JU, Alomari MA, Al-Omari B, Altaany Z, Alvis-Guzman N, Alvis-Zakzuk NJ, Alwafi H, Al-Wardat MS, Al-Worafi YM, Aly S, Alzoubi KH, Amare AT, Amegbor PM, Ameyaw EK, Amin TT, Amindarolzarbi A, Amiri S, Amugsi DA, Ancuceanu R, Anderlini D, Anderson DB, Andrade PP, Andrei CL, Ansari H, Antony CM, Anwar S, Anwar SL, Anwer R, Anyanwu PE, Arab JP, Arabloo J, Arafat M, Araki DT, Aravkin AY, Arkew M, Armocida B, Arndt MB, Arooj M, Artamonov AA, Aruleba RT, Arumugam A, Ashbaugh C, Ashemo MY, Ashraf M, Asika MO, Askari E, Astell-Burt T, Athari SS, Atorkey P, Atout MMDW, Atreya A, Aujayeb A, Ausloos M, Avan A, Awotidebe AW, Awuviry-Newton K, Ayala Quintanilla BP, Ayuso-Mateos JL, Azadnajafabad S, Azevedo RMS, Babu AS, Badar M, Badiye AD, Baghdadi S, Bagheri N, Bah S, Bai R, Baker JL, Bakkannavar SM, Bako AT, Balakrishnan S, Bam K, Banik PC, Barchitta M, Bardhan M, Bardideh E, Barker-Collo SL, Barqawi HJ, Barrow A, Barteit S, Barua L, Bashiri Aliabadi S, Basiru A, Basu S, Basu S, Bathini PP, Batra K, Baune BT, Bayileyegn NS, Behnam B, Behnoush AH, Beiranvand M, Bejarano Ramirez DF, Bell ML, Bello OO, Beloukas A, Bensenor IM, Berezvai Z, Bernabe E, Bernstein RS, Bettencourt PJG, Bhagavathula AS, Bhala N, Bhandari D, Bhargava A, Bhaskar S, Bhat V, Bhatti GK, Bhatti JS, Bhatti MS, Bhatti R, Bhutta ZA, Bikbov B, Bishai JD, Bisignano C, Bitra VR, Bjørge T, Bodolica V, Bodunrin AO, Bogale EK, Bonakdar Hashemi M, Bonny A, Bora Basara B, Borhany H, Boxe C, Brady OJ, Bragazzi NL, Braithwaite D, Brant LC, Brauer M, Breitner S, Brenner H, Brown J, Brugha T, Bulamu NB, Buonsenso D, Burkart K, Burns RA, Busse R, Bustanji Y, Butt ZA, Byun J, Caetano Dos Santos FL, Calina D, Cámera LA, Campos-Nonato IR, Cao C, Capodici A, Carr S, Carreras G, Carugno A, Carvalho M, Castaldelli-Maia JM, Castañeda-Orjuela CA, Castelpietra G, Catapano AL, Cattaruzza MS, Caye A, Cegolon L, Cembranel F, Cenderadewi M, Cerin E, Chakraborty PA, Chan JSK, Chan RNC, Chandika RM, Chandrasekar EK, Charalampous P, Chattu VK, Chatzimavridou-Grigoriadou V, Chen AW, Chen A-T, Chen CS, Chen H, Chen NM, Cheng ETW, Chimed-Ochir O, Chimoriya R, Ching PR, Cho WCS, Choi S, Chong B, Chong YY, Choudhari SG, Chowdhury R, Christensen SWM, Chu D-T, Chukwu IS, Chung E, Chung E, Chutiyami M, Claassens MM, Cogen RM, Columbus A, Conde J, Cortesi PA, Cousin E, Criqui MH, Cruz-Martins N, Dadras O, Dai S, Dai X, Dai Z, Dalaba MA, Damiani G, Das JK, Das S, Dashti M, Dávila-Cervantes CA, Davletov K, De Leo D, Debele AT, Debopadhaya S, Decleene NK, Deeba F, Degenhardt L, Del Bo'C, Delgado-Enciso I, Demetriades AK, Denova-Gutiérrez E, Dervenis N, Desai HD, Desai R, Deuba K, Dhama K, Dharmaratne SD, Dhingra S, Dias Da Silva D, Diaz D, Diaz LA, Diaz MJ, Dima A, Ding DD, Dirac MA, Do THP, Do Prado CB, Dohare S, Dominguez R-MV, Dong W, Dongarwar D, D'Oria M, Dorsey ER, Doshmangir L, Dowou RK, Driscoll TR, Dsouza HL, Dsouza V, Dube J, Dumith SC, Duncan BB, Duraes AR, Duraisamy S, Durojaiye OC, Dzianach PA, Dziedzic AM, Eboreime E, Ebrahimi A, Edinur HA, Edvardsson D, Eikemo TA, Eini E, Ekholuenetale M, Ekundayo TC, El SayedI, El Tantawi M, Elbarazi I, Elemam NM, Elgohary GMT, Elhadi M, Elmeligy OAA, Elnahas G, Elshaer M, Elsohaby I, Engelbert Bain L, Erkhembayar R, Eshrati B, Estep K, Fabin N, Fagbamigbe AF, Falzone L, Fareed M, Farinha CSES, Faris MEM, Faro A, Farrokhi P, Fatehizadeh A, Fauk NK, Feigin VL, Feng X, Fereshtehnejad S-M, Feroze AH, Ferreira N, Ferreira PH, Fischer F, Flavel J, Flood D, Flor LS, Foigt NA, Folayan MO, Force LM, Fortuna D, Foschi M, Franklin RC, Freitas A, Fukumoto T, Furtado JM, Gaal PA, Gadanya MA, Gaidhane AM, Gaihre S, Galali Y, Ganbat M, Gandhi AP, Ganesan B, Ganie MA, Ganiyani MA, Gardner WM, Gebi TG, Gebregergis MW, Gebrehiwot M, Gebremariam TBB, Gebremeskel TG, Gela YY, Georgescu SR, Getachew Obsa A, Gething PW, Getie M, Ghadiri K, Ghadirian F, Ghailan KY, Ghajar A, Ghasemi M, Ghasempour Dabaghi G, Ghasemzadeh A, Ghazy RM, Gholamrezanezhad A, Ghorbani M, Ghotbi E, Gibson RM, Gill TK, Ginindza TG, Girmay A, Glasbey JC, Göbölös L, Godinho MA, Goharinezhad S, Goldust M, Golechha M, Goleij P, Gona PN, Gorini G, Goulart AC, Grada A, Grivna M, Guan S-Y, Guarducci G, Gubari MIM, Gudeta MD, Guha A, Guicciardi S, Gulati S, Gulisashvili D, Gunawardane DA, Guo C, Gupta AK, Gupta B, Gupta I, Gupta M, Gupta R, Gupta VB, Gupta VK, Gupta VK, Gutiérrez RA, Habibzadeh F, Habibzadeh P, Haddadi R, Hadi NR, Haep N, Hafezi-Nejad N, Hafiz A, Hagins H, Halboub ES, Halimi A, Haller S, Halwani R, Hamilton EB, Hankey GJ, Hannan MA, Haque MN, Harapan H, Haro JM, Hartvigsen J, Hasaballah AI, Hasan I, Hasanian M, Hasnain MS, Hassan A, Haubold J, Havmoeller RJ, Hay SI, Hayat K, Hebert JJ, Hegazi OE, Heidari G, Helfer B, Hemmati M, Hendrie D, Henson CA, Hezam K, Hiraike Y, Hoan NQ, Holla R, Hon J, Hossain MM, Hosseinzadeh H, Hosseinzadeh M, Hostiuc M, Hostiuc S, Hsu JM, Huang J, Hugo FN, Hushmandi K, Hussain J, Hussein NR, Huynh CK, Huynh H-H, Hwang B-F, Iannucci VC, Ihler AL, Ikiroma AI, Ikuta KS, Ilesanmi OS, Ilic IM, Ilic MD, Imam MT, Immurana M, Irham LM, Islam MR, Islam SMS, Islami F, Ismail F, Ismail NE, Isola G, Iwagami M, Iwu CCD, Iyer M, Jaafari J, Jacobsen KH, Jadidi-Niaragh F, Jafarinia M, Jaggi K, Jahankhani K, Jahanmehr N, Jahrami H, Jain A, Jain N, Jairoun AA, Jaiswal A, Jakovljevic M, Jatau AI, Javadov S, Javaheri T, Jayapal SK, Jayaram S, Jee SH, Jeganathan J, Jeyakumar A, Jha AK, Jiang H, Jin Y, Jonas JB, Joo T, Joseph A, Joseph N, Joshua CE, Jozwiak JJ, Jürisson M, K V, Kaambwa B, Kabir A, Kabir Z, Kadashetti V, Kalani R, Kalankesh LR, Kaliyadan F, Kalra S, Kamenov K, Kamyari N, Kanagasabai T, Kandel H, Kanmanthareddy AR, Kanmodi KK, Kantar RS, Karaye IM, Karim A, Karimi SE, Karimi Y, Kasraei H, Kassel MB, Kauppila JH, Kawakami N, Kayode GA, Kazemi F, Kazemian S, Keikavoosi-Arani L, Keller C, Kempen JH, Kerr JA, Keshtkar K, Kesse-Guyot E, Keykhaei M, Khajuria H, Khalaji A, Khalid A, Khalid N, Khalilian A, Khamesipour F, Khan A, Khan I, Khan M, Khan MA, Khanmohammadi S, Khatab K, Khatami F, Khatatbeh MM, Khater AM, Khayat Kashani HR, Khidri FF, Khodadoust E, Khormali M, Khorrami Z, Kifle ZD, Kim MS, Kimokoti RW, Kisa A, Kisa S, Knudsen AKS, Kocarnik JM, Kochhar S, Koh HY, Kolahi A-A, Kompani F, Koren G, Korzh O, Kosen S, Koulmane Laxminarayana SL, Krishan K, Krishna V, Krishnamoorthy V, Kuate Defo B, Kuddus MA, Kuddus M, Kuitunen I, Kulkarni V, Kumar M, Kumar N, Kumar R, Kurmi OP, Kusuma D, Kyu HH, La Vecchia C, Lacey B, Ladan MA, Laflamme L, Lafranconi A, Lahariya C, Lai DTC, Lal DK, Lalloo R, Lallukka T, Lám J, Lan Q, Lan T, Landires I, Lanfranchi F, Langguth B, Laplante-Lévesque A, Larijani B, Larsson AO, Lasrado S, Lauriola P, Le H-H, Le LKD, Le NHH, Le TDT, Leasher JL, Ledda C, Lee M, Lee PH, Lee S-W, Lee SW, Lee W-C, Lee YH, Legrand KE, Lenzi J, Leong E, Leung J, Li M-C, Li W, Li X, Li Y, Li Y, Lim L-L, Lim SS, Lindstrom M, Linn S, Liu G, Liu R, Liu S, Liu W, Liu X, Liu X, Llanaj E, Lo C-H, López-Bueno R, Loreche AM, Lorenzovici L, Lozano R, Lubinda J, Lucchetti G, Lunevicius R, Lusk JB, Lv H, Ma ZF, Machairas N, Madureira-Carvalho ÁM, Magaña Gómez JA, Maghazachi AA, Maharjan P, Mahasha PW, Maheri M, Mahjoub S, Mahmoud MA, Mahmoudi E, Majeed A, Makris KC, Malakan Rad E, Malhotra K, Malik AA, Malik I, Malta DC, Manla Y, Mansour A, Mansouri P, Mansournia MA, Mantilla Herrera AM, Mantovani LG, Manu E, Marateb HR, Mardi P, Martinez G, Martinez-Piedra R, Martini D, Martins-Melo FR, Martorell M, Marx W, Maryam S, Marzo RR, Mathangasinghe Y, Mathieson S, Mathioudakis AG, Mattumpuram J, Maugeri A, Mayeli M, Mazidi M, Mazzotti A, Mcgrath JJ, Mckee M, Mckowen ALW, Mcphail MA, Mehrabani-Zeinabad K, Mehrabi Nasab E, Mekene Meto T, Mendoza W, Menezes RG, Mensah GA, Mentis A-FA, Meo SA, Meresa HA, Meretoja A, Meretoja TJ, Mersha AM, Mestrovic T, Mettananda KCD, Mettananda S, Michalek IM, Miller PA, Miller TR, Mills EJ, Minh LHN, Mirijello A, Mirrakhimov EM, Mirutse MK, Mirza-Aghazadeh-Attari M, Mirzaei M, Mirzaei R, Misganaw A, Mishra AK, Mitchell PB, Mittal C, Moazen B, Moberg ME, Mohamed J, Mohamed MFH, Mohamed NS, Mohammadi E, Mohammadi S, Mohammed H, Mohammed S,

Mohammed S, Mohr RM, Mokdad AH, Molinaro S, Momtazmanesh S, Monasta L, Mondello S, Moodi Ghalibaf A, Moradi M, Moradi Y, Moradi-Lakeh M, Moraga P, Morawska L, Moreira RS, Morovatdar N, Morrison SD, Morze J, Mosapour A, Mosser JF, Mossialos E, Motappa R, Mougin V, Mouodi S, Mrejen M, Msherghi A, Mubarik S, Mueller UO, Mulita F, Munjal K, Murillo-Zamora E, Murlimanju B, Mustafa G, Muthu S, Muzaffar M, Myung W, Nagarajan AJ, Naghavi P, Naik GR, Nainu F, Nair S, Najmuldeen HHR, Nangia V, Naqvi AA, Narayana AI, Nargus S, Nascimento GG, Nashwan AJ, Nasrollahizadeh A, Nasrollahizadeh A, Natto ZS, Nayak BP, Nayak VC, Nduaguba SO, Negash H, Negoi I, Negoi RI, Nejadghaderi SA, Nesbit OD, Netsere HB, Ng M, Nguefack-Tsague G, Ngunjiri JW, Nguyen DH, Nguyen HQ, Niazi RK, Nikolouzakis TK, Nikoobar A, Nikoomanesh F, Nikpoor AR, Nnaji CA, Nnyanzi LA, Noman EA, Nomura S, Norrving B, Nri-Ezedi CA, Ntaios G, Ntsekhe M, Nurrika D, Nzoputam CI, Nzoputam OJ, Oancea B, Odetokun IA, O'Donnell MJ, Oguntade AS, Oguta JO, Okati-Aliabad H, Okeke SR, Okekunle AP, Okonji OC, Olagunju AT, Olasupo OO, Olatubi MI, Oliveira GMM, Olufadewa II, Olusanya BO, Olusanya JO, Omar HA, Omer GL, Omonisi AEE, Onie S, Onwujekwe OE, Ordak M, Orish VN, Ortega-Altamirano DV, Ortiz A, Ortiz-Brizuela E, Osman WMS, Ostroff SM, Osuagwu UL, Otoiu A, Otstavnov N, Otstavnov SS, Ouyahia A, Ouyang G, Owolabi MO, P AMP, Padron-Monedero A, Padubidri JR, Palicz T, Palladino C, Pan F, Pandi-Perumal SR, Pangaribuan HU, Panos GD, Panos LD, Pantea Stoian AM, Pardhan S, Parikh RR, Pashaei A, Pasovic M, Passera R, Patel J, Patel SK, Patil S, Patoulias D, Patthipati VS, Pawar S, Pazoki Toroudi H, Pease SA, Peden AE, Pedersini P, Peng M, Pensato U, Pepito VCF, Peprah EK, Peprah P, Perdigão J, Pereira MO, Perianayagam A, Perico N, Pesudovs K, Petermann-Rocha FE, Petri WA, Pham HT, Philip AK, Phillips MR, Pigeolet M, Pigott DM, Pillay JD, Piracha ZZ, Pirouzpanah S, Plass D, Plotnikov E, Poddighe D, Polinder S, Postma MJ, Pourtaheri N, Prada SI, Pradhan PMS, Prakash V, Prasad M, Prates EJS, Priscilla T, Pritchett N, Puri P, Puvvula J, Qasim NH, Qattea I, Qazi AS, Qian G, Rabiee RadM, Radhakrishnan RA, Radhakrishnan V, Raeisi Shahraki H, Rafferty Q, Raggi A, Raghav PR, Rahim MJ, Rahman MM, Rahman MHU, Rahman M, Rahman MA, Rahmani S, Rahmanian M, Rahmawaty S, Rajaa S, Ramadan MM, Ramasamy SK, Ramasubramani P, Ramazanu S, Rana K, Ranabhat CL, Rancic N, Rane A, Rao CR, Rao K, Rao M, Rao SJ, Rashidi M-M, Rathnaiah Babu G, Rauniyar SK, Rawaf DL, Rawaf S, Razo C, Reddy MMRK, Redwan EMM, Reifels L, Reiner JrRC, Remuzzi G, Renzaho AMN, Reshmi B, Reyes LF, Rezaei N, Rezaei N, Rezaei N, Rezaei Hachesu P, Rezaeian M, Rickard J, Rodrigues CF, Rodriguez JAB, Roever L, Ronfani L, Roshandel G, Rotimi K, Rout HS, Roy B, Roy N, Roy P, Rubagotti E, S NC, Saad AMA, Saber-Ayad MM, Sabour S, Sacco S, Sachdev PS, Saddik B, Saddler A, Sadee BA, Sadeghi E, Sadeghi M, Saeb MR, Saeed U, Safi SZ, Sagar R, Sagoe D, Saif Z, Sajid MR, Sakshaug JW, Salam N, Salami AA, Salaroli LB, Saleh MA, Salem MR, Salem MZY, Sallam M, Samadzadeh S, Samargandy S, Samodra YL, Samy AM, Sanabria J, Sanna F, Santos IS, Santric-Milicevic MM, Sarasmita MA, Sarikhani Y, Sarmiento-Suárez R, Sarode GS, Sarode SC, Sarveazad A, Sathian B, Sathyanarayan A, Satpathy M, Sawhney M, Scarmeas N, Schaarschmidt BM, Schmidt MI, Schneider IJC, Schumacher AE, Schwebel DC, Schwendicke F, Sedighi M, Senapati S, Senthilkumaran S, Sepanlou SG, Sethi Y, Setoguchi S, Seylani A, Shadid J, Shafie M, Shah H, Shah NS, Shah PA, Shahbandi A, Shahid S, Shahid W, Shahwan MJ, Shaikh MA, Shakeri A, Shalash AS, Sham S, Shamim MA, Shamshirgaran MA, Shamsi MA, Shanawaz M, Shankar A, Shannawaz M, Sharath M, Sharifan A, Sharifi-Rad J, Sharma M, Sharma R, Sharma S, Sharma U, Sharma V, Shastry RP, Shavandi A, Shayan AM, Shayan M, Shehabeldine AME, Shetty PH, Shibuya K, Shifa JE, Shiferaw D, Shiferaw WS, Shigematsu M, Shiri R, Shitaye NA, Shittu A, Shivakumar KM, Shivarov V, Shokati Eshkiki Z, Shool S, Shrestha S, Shuval K, Sibhat MM, Siddig EE, Sigfusdottir ID, Silva DAS, Silva JP, Silva LMLR, Silva S, Simpson CR, Singal A, Singh A, Singh BB, Singh H, Singh JA, Singh M, Singh P, Skou ST, Sleet DA, Slepak ELN, Solanki R, Soliman SSM, Song S, Song Y, Sorensen RJD, Soriano JB, Soyiri IN, Spartalis M, Sreeramareddy CT, Stark BA, Starodubova AV, Stein C, Stein DJ, Steiner C, Steiner TJ, Steinmetz JD, Steiropoulos P, Stockfelt L, Stokes MA, Subedi NS, Subramaniyan V, Suemoto CK, Suleman M, Suliankatchi AR, Sultana A, Sundström J, Swain CK, Szarpak L, Tabaee Damavandi P, Tabarés-Seisdedos R, Tabatabaei Malazy O, Tabatabaeizadeh S-A, Tabatabai S, Tabche C, Tabish M, Tadakamadla SK, Taheri AY, Taheri Soodejani M, Taherkhani A, Taiba J, Talaat IM, Talukder A, Tampa M, Tamuzi JL, Tan K-K, Tandukar S, Tang H, Tavakoli OliaeeR, Tavangar SM, Teimoori M, Temsah M-H, Teramoto M, Thangaraju P, Thankappan KR, Thapar R, Thayakaran R, Thirunavukkarasu S, Thomas N, Thomas NK, Thum CCC, Tichopad A, Ticoalu JHV, Tillawi T, Tiruye TY, Tobe-Gai R, Tonelli M, Topor-Madry R, Torre AE, Touvier M, Tovani-Palone MR, Tran JT, Tran MTN, Tran NM, Tran N-H, Trico D, Tromans SJ, Truyen TTTT, Tsatsakis A, Tsegay GM, Tsermpini EE, Tumurkhuu M, Tyrovolas S, Udoh A, Umair M, Umakanthan S, Umar TP, Undurraga EA, Unim B, Unnikrishnan B, Unsworth CA, Upadhyay E, Urso D, Usman JS, Vahabi SM, Vaithinathan AG, Van Den Eynde J, Varga O, Varma RP, Vart P, Vasankari TJ, Vasic M, Vaziri S, Vellingiri B, Venketasubramanian N, Veroux M, Verras G-I, Vervoort D, Villafañe JH, Violante FS, Vlassov V, Vollset SE, Volovat SR, Vongpradith A, Waheed Y, Wang C, Wang F, Wang N, Wang S, Wang Y, Wang Y-P, Ward P, Wassie EG, Weaver MR, Weerakoon KG, Weintraub RG, Weiss DJ, Weldemariam AH, Wells KM, Wen YF, Whisnant JL, Whiteford HA, Wiangkham T, Wickramasinghe DP, Wickramasinghe ND, Wilandika A, Wilkerson C, Willeit P, Wimo A, Woldegebreal DH, Wolf AW, Wong YJ, Woolf AD, Wu C, Wu F, Wu X, Wu Z, Wulf Hanson S, Xia Y, Xiao H, Xu X, Xu YY, Yadav L, Yadollahpour A, Yaghoubi S, Yamagishi K, Yang L, Yano Y, Yao Y, Yaribeygi H, Yazdanpanah MH, Ye P, Yehualashet SS, Yesuf SA, Yezli S, Yiğit A, Yiğit V, Yigzaw ZA, Yismaw Y, Yon DK, Yonemoto N, Younis MZ, Yu C, Yu Y, Yusuf H, Zahid MH, Zakham F, Zaki L, Zaki N, Zaman BA, Zamora N, Zand R, Zandieh GGZ, Zar HJ, Zarrintan A, Zastrozhin MS, Zhang H, Zhang N, Zhang Y, Zhao H, Zhong C, Zhong P, Zhou J, Zhu Z, Ziafati M, Zielińska M, Zimsen SRM, Zoladl M, Zumla A, Zyoud SH, Vos T, Murray CJL. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: a systema. Lancet 2024;403: 2133–61.

[23] Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a cochrane systematic review. Br J Sports Med 2015;49:1554–7.

[24] Fransen M, Mcconnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;2014: CD007912.

[25] Gay C, Eschalier B, Levyckyj C, Bonnin A, Coudeyre E. Motivators for and barriers to physical activity in people with knee osteoarthritis: a qualitative study. Joint Bone Spine 2018;85:481–6.

[26] Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. PAIN 2019;160:1920–32.

[27] Glowacki K, Duncan MJ, Gainforth H, Faulkner G. Barriers and facilitators to physical activity and exercise among adults with depression: a scoping review. Ment Health Phys Activity 2017;13:108–19.

[28] Ibrahim A, McWilliams DF, Smith SL, Chaplin WJ, Salimian M, Georgopoulos V, Kouraki A, Walsh DA. Comparative effectiveness of various exercise interventions on central sensitisation indices: a systematic review and network meta-analysis. Ann Phys Rehabil Med 2025;68:101894.

[29] Intenational Association for the Study of Pain Terminology Working Group. IASP terminology. In: Loser JD, editor. Vol. 2025. Washington, DC: IASP Press, 2011.

[30] James RJE, Walsh DA, Ferguson E. Trajectories of pain predict disabilities affecting daily living in arthritis. Br J Health Psychol 2019;24: 485–96.

[31] Jinks C, Jordan K, Croft P. Osteoarthritis as a public health problem: the impact of developing knee pain on physical function in adults living in the community: (knest 3). Rheumatology (Oxford) 2007;46:877–81.

[32] Kanavaki AM, Rushton A, Efstathiou N, Alrushud A, Klocke R, Abhishek A, Duda JL. Barriers and facilitators of physical activity in knee and hip osteoarthritis: a systematic review of qualitative evidence. BMJ Open 2017;7:e017042.

[33] Klukowska AM, Vandertop WP, Schröder ML, Staartjes VE. Calculation of the minimum clinically important difference (MCID) using different methodologies: case study and practical guide. Eur Spine J 2024;33: 3388–400.

[34] Kosek E, Clauw D, Nijs J, Baron R, Gilron I, Harris RE, Mico JA, Rice ASC, Sterling M. Chronic nociplastic pain affecting the musculoskeletal system: clinical criteria and grading system. PAIN 2021;162:2629–34.

[35] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009;10:895–926.

[36] Law LF, Sluka KA. How does physical activity modulate pain? PAIN 2017; 158:369–70.

[37] Lazaridou A, Franceschelli O, Galenkamp L, Napadow V, Edwards R. The relationship between quantitative sensory testing (qst), mindfulness, fatigue, and pain in fibromyalgia. J Pain 2018;19:S35.

[38] Lazaridou A, Martel MO, Cornelius M, Franceschelli O, Campbell C, Smith M, Haythornthwaite JA, Wright JR, Edwards RR. The association between daily physical activity and pain among patients with knee osteoarthritis: the moderating role of pain catastrophizing. Pain Med 2019;20:916–24.

[39] Leon L, Redondo M, De Felipe SL, Garriguez D, Alcazar LA, Rodriguez-Rodriguez L. The role of fear-avoidance model on pain and disability in knee osteoarthritis patients. Arthritis Rheumatol 2018;70:1284–5.

[40] Lethem J, Slade PD, Troup JDG, Bentley G. Outline of a fear avoidance model of exaggerated pain perception>. Behav Res Ther 1983;21:401–8.

[41] Marschner IC. glm2: fitting generalized linear models with convergence problems. R Journal 2011;3:12–5.

[42] Martinsen EW. Physical activity in the prevention and treatment of anxiety and depression. Nordic J Psychiatry 2008;62:25–9.

[43] McWilliams DF, Georgopoulos V, Patel J, Millar B, Smith SL, Walsh DA. Validation of a questionnaire for central nervous system aspects of joint pain: the CAP questionnaire. Rheumatology (Oxford) 2024;18:keae342.

[44] Meints SM, Mawla I, Napadow V, Kong J, Gerber J, Chan S-T, Wasan AD, Kaptchuk TJ, Mcdonnell C, Carriere J, Rosen B, Gollub RL, Edwards RR. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. PAIN 2019;160:833–43.

[45] Millar B, McWilliams DF, Abhishek A, Akin-Akinyosoye K, Auer DP, Chapman V, Doherty M, Ferguson E, Gladman JRF, Greenhaff P, Stocks J, Valdes AM, Walsh DA. Investigating musculoskeletal health and wellbeing; a cohort study protocol. BMC Musculoskelet Disord 2020;21:182.

[46] Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging 2012;16:601–8.

[47] Moss P, Benson HAE, Will R, Wright A. Patients with knee osteoarthritis who score highly on the PainDETECT questionnaire present with multimodality hyperalgesia, increased pain, and impaired physical function. Clin J Pain 2018;34:15–21.

[48] Murphy SL, Alexander NB, Levoska M, Smith DM. The relationship between fatigue and subsequent physical activity among older adults with symptomatic osteoarthritis. Arthritis Care Res (Hoboken) 2013;65:1617–24.

[49] National Institute for Health Care Excellence. Osteoarthritis in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence (NICE), 2022.

[50] Naugle KM, Ohlman T, Naugle KE, Riley ZA, Keith NR. Physical activity behavior predicts endogenous pain modulation in older adults. PAIN 2017;158:383–90.

[51] Naugle KM, Riley JL. Self-reported physical activity predicts pain inhibitory and facilitatory function. Med Sci Sports Exerc 2014;46:622–9.

[52] Noble S, McLennan D, Noble M, Plunkett E, Gutacker N, Silk M, Gemma W. The English indices of deprivation 2019. Res Rep 2019;10:1–87.

[53] Penninx BWJH, Messier SP, Rejeski WJ, Williamson JD, Dibari M, Cavazzini C, Applegate WB, Pahor M. Physical exercise and the prevention of disability in activities of daily living in older persons with osteoarthritis. Arch Intern Med 2001;161:2309.

[54] Power JD, Perruccio AV, Gandhi R, Veillette C, Davey JR, Syed K, Mahomed NN, Rampersaud YR. Neuropathic pain in end-stage hip and knee osteoarthritis: differential associations with patient-reported pain at rest and pain on activity. Osteoarthritis Cartilage 2018;26:363–9.

[55] Prince SA, Adamo KB, Hamel M, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Activity 2008;5:56.

[56] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2021.

[57] Revelle W. Procedures for personality and psychological research. Evanston: Northwestern University, 2022.

[58] Rojas G, Orozco-Chavez I. Physical activity level and physical fitness in subjects with chronic musculoskeletal pain: a cross-sectional study. PeerJ 2024;12:e16880.

[59] Schnitzler A, Ploner M. Neurophysiology and functional neuroanatomy of pain perception. J Clin Neurophysiol 2000;17:592–603.

[60] Scopaz KA, Piva SR, Wisniewski S, Fitzgerald GK. Relationships of fear, anxiety, and depression with physical function in patients with knee osteoarthritis. Arch Phys Med Rehabil 2009;90:1866–73.

[61] Shih M, Hootman JM, Kruger J, Helmick CG. Physical activity in men and women with arthritis national health interview survey, 2002. Am J Prev Med 2006;30:385–93.

[62] Song J, Muhammad LN, Neogi T, Dunlop DD, Wohlfahrt A, Bolster MB, Bingham IIICO, Clauw DJ, Marder W, Lee YC. Pain sensitization as a potential mediator of the relationship between sleep disturbance and subsequent pain in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2023;75:778–84.

[63] Uthman OA, Van Der Windt DA, Jordan JL, Dziedzic KS, Healey EL, Peat GM, Foster NE. Exercise for lower limb osteoarthritis: systematic review incorporating trial sequential analysis and network meta-analysis. BMJ 2013;347:f5555.

[64] Villafañe JH. Exercise and osteoarthritis: an update. J Exerc Rehabil 2018;14:538–539.

[65] Warburton DER, Bredin SSD. Health benefits of physical activity: a systematic review of current systematic reviews. Curr Opin Cardiol 2017;32:541–56.

[66] Warnes GR, Bolker B, Lumley T, Johnson RC, Jain N, Schwartz M, Rogers J. gmodels: Various R Programming Tools for Model Fitting. R package version 2.19.1, 2024. Available at: https://CRAN.Rproject.org/package=gmodels. Accessed January 3, 2025.

[67] Wickham H, Averick M, Bryan J, Chang W, McGowan L, François R, Grolemund G, Hayes A, Henry L, Hester J, Kuhn M, Pedersen T, Miller E, Bache S, Müller K, Ooms J, Robinson D, Seidel D, Spinu V, Takahashi K, Vaughan D, Wilke C, Woo K, Yutani H. Welcome to the tidyverse. J Open Source Softw 2019;4:1686.

[68] Wickham H, François R, Henry L, Müller K, Vaughan D. dplyr: A Grammar of Data Manipulation. R package version 1.1.4.9000, 2025. Available at: https://github.com/tidyverse/dplyr. Accessed January 3, 2025.

[69] Wideman TH, Finan PH, Edwards RR, Quartana PJ, Buenaver LF, Haythornthwaite JA, Smith MT. Increased sensitivity to physical activity among individuals with knee osteoarthritis: relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. PAIN 2014;155:703–711.

[70] World Health Organisation. Physical activity. Available at: https://www.who.int/news-room/fact-sheets/detail/physical-activity. Accessed December 8, 2024.