

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

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Abbreviations: CAP-Knee – Central Aspects of Pain in the Knee; OA – Osteoarthritis; CS – Central Sensitisation; QST - Quantitative Sensory Testing; MRI - Magnetic Resonance Imaging; PPT - Pressure Pain Detection Thresholds; TS - Temporal Summation; CPM - Conditioned Pain Modulation; IMHW - Investigating Musculoskeletal Health and Wellbeing; DIF - Differential item functioning; CFI - Comparative Fit Index; TFI - Tucker Fit Index; RMSEA - Root Mean Square Error of Approximation; ACR – American College of Rheumatology.

ABSTRACT

OBJECTIVES: Pain is the prevailing symptom of knee osteoarthritis. Central sensitisation creates discordance between pain and joint pathology. We previously reported a central pain mechanisms trait derived from 8 discrete characteristics: neuropathic-like pain, fatigue, cognitive-impact, catastrophising, anxiety, sleep disturbance, depression, and pain distribution. We here validate and show that an 8-item questionnaire, Central Aspects of Pain in the Knee (CAP-Knee) is associated both with sensory and affective components of knee pain severity.

METHODS: Participants with knee pain were recruited from the Investigating Musculoskeletal Health and Wellbeing study in the East Midlands, UK. CAP-Knee items were refined following cognitive interviews. Psychometric properties were assessed in 250 participants using Rasch-, and factor-analysis, and Cronbach's alpha. Intra-class correlation coefficients tested repeatability. Associations between CAP-Knee and McGill Pain questionnaire pain severity scores using linear regression.

RESULTS: CAP-Knee targeted the knee pain sample well. Cognitive interviews indicated that participants interpreted CAP-Knee items in diverse ways aligned to their intended meanings. Fit to the Rasch model was optimised by rescaling each item, producing a summated score from 0-16. Internal consistency was acceptable (Cronbach's alpha=0.74) and test-retest reliability excellent ($ICC_{2,1}=0.91$). Each CAP-Knee item contributed uniquely to one discrete 'Central Mechanisms trait' factor. High CAP-Knee scores were associated with worse overall knee pain intensity and with each of sensory and affective McGill Pain Questionnaire scores.

CONCLUSION: CAP-Knee is a simple and valid self-report questionnaire, which measures a single 'Central Mechanisms' trait, and may help identify and target centrally-acting treatments aiming to reduce the burden of knee pain.

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INTRODUCTION

In individuals with knee osteoarthritis (OA), joint pathology only weakly predicts the pain severity [1], and up to 20% of people with severe OA report unsatisfactory pain relief following arthroplasty that replaces the affected joint [2]. Central pain mechanisms act through the central nervous system to augment knee pain severity [3], and predict poor outcome following peripherally targeted treatments such as arthroplasty [4]. Central sensitisation is one such central mechanism, defined as 'increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input' [5]. Pain is a sensory and emotional experience, and not only a neuronal response. Therefore central factors other than nociceptive neuronal activity might augment pain, including changes in brain connectivity or appraisal. The extent to which central mechanisms augment knee pain varies between individuals. Treatments that target central pain mechanisms can reduce knee pain severity [6], and might improve response to peripherally targeted treatments [7].

Quantitative sensory testing (QST) or magnetic resonance imaging (MRI) approaches assess complex pathophysiological central mechanisms such as Central Sensitization (CS) or other higher brain mechanisms linked to central pain mechanisms [5]. Self-report questionnaires also assess manifestations linked to central mechanisms (including psychological and somatic disturbances), and are less resource-intensive and feasible during normal clinical encounters. However, a comprehensive, validated mechanism-based self-report questionnaire is not currently available to identify people with knee pain that is importantly augmented by central pain mechanisms.

Responses to questionnaires addressing individual characteristics of anxiety, depression, catastrophizing, cognitive-impact, sleep, fatigue, pain distribution and neuropathic-like pain have each been associated with experimental markers of CS (including QST and neuroimaging biomarkers), and with pain outcomes in people with knee pain [2, 8-12], or some other chronically painful conditions [7, 13]. We previously selected 8 self-report items, each representing one of these 8 characteristics based on expert opinion (at least moderate agreement between experts on relevance to central pain mechanisms in knee OA), strength of association with the scales measuring the component characteristic, and with Pressure Pain detection Threshold (PPT) at a site distal to the affected knee (taken as an indicator of

central sensitisation) [9]. We showed by factor analytic approaches, that these 8 items contributed to a single underlying trait [9]. This 'Central Mechanisms' trait was associated with PPT at a distal site, and with knee pain severity more strongly than was any one of the 8 characteristics alone [9], and was a better predictor of future knee pain than other clinical predictors [8]. Existing questionnaires, including the short-form Central Sensitization Inventory and the Generalized Pain Questionnaire which were originally designed to assess central sensitivity syndromes such as fibromyalgia [14, 15] omit important characteristics that have been associated with QST-evidence of central pain mechanisms in people with knee pain. These include neuropathic-like pain qualities and cognitive-impact [9, 12, 16-19].

Clinical decision support tools have potential to greatly enhance a clinician's ability to carefully subgroup patients, and inform mechanism-based treatment allocation in primary care settings. Employing such tools could inform choice of tailored stratified treatment pathways for individuals with knee OA pain. However, such tools are not widely available for widespread use in clinical practice.

We therefore have developed a simple questionnaire (Central Aspects of Pain in the Knee; CAP-Knee) comprising self-report items measuring each of the 8 characteristics which contribute to the Central Mechanisms trait in people with knee pain. We hypothesised that this Central Mechanism trait is associated with both sensory and emotional components of knee pain. We show that CAP-Knee is interpreted appropriately, psychometrically valid and reliable, and associated with sensory and affective components of pain severity in people with knee pain.

METHODS

Study design

A mixed methods, cross-sectional observational study combining thematic analysis of interviews with people with knee pain, with quantitative analysis of questionnaire psychometric properties and external validity.

Participants and recruitment

Eligible participants were aged ≥ 40 years, reported knee pain on most days for the past month, provided informed consent, and could communicate in English. Participants were

excluded if they reported having an inflammatory arthritis such as Rheumatoid Arthritis. Details of participant recruitment are provided in Figure 1.

Small samples (5-15 participants) may fail to uncover common problems in questionnaire evaluation studies, thus a default sample size of 30 participants is endorsed for cognitive interviews [20-22]. Recruitment ended when data saturation had been reached, and the research team confirmed when no new themes emerged.

All participants contributing to Rasch or repeatability analysis reported that their knee was their most bothersome joint pain, and that their knee pain had lasted ≥ 4 weeks. Participants were recruited from those consenting to further contact participating in the Investigating Musculoskeletal Health and Wellbeing (IMH&W) study (clinicaltrials.gov NCT03696134) [23]. For Rasch analysis, data from 250-500 participants may provide accurate and stable person and item estimates, as well as a good balance for statistical interpretation of the fit statistics [24]. Additionally, it is recommended that a minimum sample size for repeatability studies should be 50 [25]. Thus, for the Rasch study and the nested repeatability study, complete data for 250 participants were included.

IMH&W participants were recruited from GP surgeries, or a database of participants in previous studies undertaken by the University of Nottingham who had consented to be contacted with information about future research. Ethical approval for interviews was obtained from the Nottingham Research Ethics Committee 2 (17/EM/0480), and for nested recruitment and questionnaire analysis from the London Central Research Ethics Committee (18/LO/0870).

Self-report questionnaire assessment

Data for age, sex, weight and height, physician-diagnosed conditions, CAP-Knee questionnaire, and question groups 1-20 from the McGill Pain Questionnaire [26] were collected by self-report from all participants. Weight and height were used to calculate body mass index (BMI) [27]. Participants were asked to state the joint with the most bothersome pain, and to rate its severity on an 11-point Likert scale ('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?'). In the current study, items originally selected from a larger item pool used in the Knee Pain in the Community study [28] were

reworded and response options modified to provide a consistent structure and response format across the newly developed questionnaire. The final version of the CAP-Knee following item refinement is shown in Figure 2.

The CAP-Knee questionnaire comprises 8 items which assess each of the 8 characteristics linked to Central Mechanisms of knee pain. Each of the items originated from established questionnaires measuring Neuropathic-like pain [29], Fatigue [30], Cognitive impact [31], Catastrophizing [32], Anxiety and Depression [33], Sleep disturbance [34], and Pain distribution [35].

Cognitive interviews

KAA conducted all cognitive interviews at the University of Nottingham. Eligibility was confirmed by asking participants “Have you had knee pain on most days of the last month?” and knee OA clinical classification used American College of Rheumatology (ACR) criteria [36]. Participants completed the CAP-Knee questionnaire immediately before the interview.

Interviews used probing techniques that were standardised according to an interview guide (Supplement 1). To elicit difficulties or comments related to interpretation of questionnaire items [37], probes were developed for each of the four-stage question response model, including stages of comprehension, retrieval, judgement and response formulation [38]. Interviews were audio-recorded, transcribed verbatim using a transcription service, and transcription accuracy was checked against recordings.

The full text of each transcript was coded and analysed with the aid of the NVivo 12 qualitative software programme [39]. Transcripts were iteratively analysed in groups of 5 or 6 until data saturation was achieved. Throughout qualitative analyses, disagreements or questions were discussed and interpretations were validated within the research team (KAA, DAW, RdN, EF), to minimise the influence of researcher subjectivity and preconceptions on identifying potential themes [40]. Following assessment of the original version of the CAP-Knee (Supplementary Figure 1), a further wave of 5 cognitive interviews after revision of CAP-Knee items was undertaken using the above procedures.

Content analysis adopted a summative approach seeking to assign codes and sub-codes across participant responses within each transcript, following Tourangeau’s question response model [37]. In order to guide item revision, problems were identified based on

sub-codes of each main code of comprehension (completely-, partially or not aligned to the researchers' intended meaning of each item), retrieval (no-, partial- and complete-retrieval difficulty), judgement (certain initial or uncertain initial response) and response formulation (consistent or inconsistent) - supplement 2. One researcher (KAA) categorised each participant based on quotes contributing to sub-codes across each item [41]. An item was revised if (i) emerging themes were not aligned with researcher's interpretation, and (ii) the item was not well understood by a majority of participants (including complete non-alignment, complete retrieval difficulty, uncertain initial response and no response consistency) [42].

Thematic analyses also informed item revision by assessing the range of interpretations provided by participants for each CAP-Knee item. An inductive approach to thematic analysis was used to identify themes that were exhaustive and mutually exclusive. Analysis of the transcripts followed a sequential process [43] allowing the researcher to search for themes and patterns across the entire dataset, rather than within participant interviews. Themes were extracted according to DeSantis and Ugarriza [44]. Identified themes were reduced or expanded to account for various interpretations, and meaning was attributed to the interpretation and experiences expressed by participants about each item [45].

Statistical analysis

Based on our previous study [9] and prior to Rasch analysis, CAP-Knee items 1 to 7 were scored 0 to 3 according to responses 'never', 'sometimes', 'often', or 'always'. Item 8 was allocated a binary score of '0' or '3' based on pain reported at one knee, plus any other additional region below the waist, by shading on the pain distribution manikin [9]. All subsequent analyses used Rasch transformed scores according to findings made in the current study.

Rasch analysis

Rasch analysis was performed as described in a previous study [46], using the Test Analysis Modules (TAM) package within the R programmer software [47]. *Differential item functioning* (DIF) was explored for sex (males and females) and age (<64 years, 64–71 years and over 71 years), using the Mantel-Haenszel test. Residual Mean Square (MNSQ) values between 0.7 and 1.3 were deemed acceptable fit residuals for each item response category [48]. Where disordered response thresholds were observed, items were re-scored by

collapsing appropriate adjacent response options [49, 50]. The person separation index (PSI) was calculated to estimate measurement reliability of CAP-Knee, with PSI = >0.70 set as the cut-off for reliability [51, 52].

Confirmatory Factor Analysis (CFA) and floor/ceiling effects

To determine whether CAP-Knee data fit a one-factor model, CFA within a structural Equation Modelling (SEM) framework used *MPlus* version 7.4 [53] as previously described [9]. Floor and ceiling effects were considered present if >15% of respondents achieved the lowest/highest possible scores (50).

Reliability and associations with knee pain

Reliability was assessed using Stata 14.2 [54]. Item-redundancy and internal-consistency were investigated by calculating Cronbach's alpha (α), with values < 0.70 indicating poor internal consistency, and values >0.90 indicating item redundancy [55]. Test-retest reliability was assessed by Intra-class Correlation Coefficient ($ICC_{2,1}$) [56].

MPQ responses were summed to give a single score for knee pain intensity, and summated ranks of descriptive terms within groups 1-10 and 11-15 were used to derive sensory and affective pain subscales respectively [26]. Associations between CAP-Knee scores and MPQ total scores for knee pain severity were calculated using Pearson correlation coefficients, and between CAP-Knee and McGill Pain Questionnaire scores using Spearman's rho.

Multivariable linear regressions were used for associations between CAP-Knee and pain scales, and were adjusted for age, BMI and sex.

RESULTS

CAP-Knee items interpretation

Twenty-two cognitive interviews were conducted (participant characteristics in Table 1), comprising 4 transcript groups, at which point data saturation was achieved. Mean interview duration was 29 min (range 16 to 57 min). Twenty-one participants (95%) fulfilled ACR clinical classification criteria for knee OA, of whom 11 (52%) had bilateral knee OA. Participant interpretation of all items in the final CAP-Knee questionnaire aligned well with their intended meanings (Table 2), although participants interpreted each item according to multiple constructs. Table 3 provides example quotes for each theme and sub-theme.

Fatigue and sleep items were interpreted as discrete constructs by most participants, although five attributed fatigue to sleep disturbance. Most (n=13) participants described the fatigue item in terms of physical exertion as a source of fatigue. Seven participants attributed fatigue to other causes (older age, medical problems including thyroid problems, diabetes, and fibromyalgia, or medication). Fatigue was also described in terms of a need to rest in order to obtain relief (n=8). Sleep disturbance was related to knee pain or discomfort (n=16) while trying to sleep, but also to the impact of other painful sites (n=7). Participants often described their sleep disturbance by reference to aids that they used to help them sleep (n=8), including pharmacological analgesics or sleeping pills, or non-pharmacological aids such as cushions placed between their knees.

The cognitive item was described in terms of task distraction (n=10) or hypervigilance (n=12). The catastrophizing item was interpreted in terms of causes and consequences of knee pain (n=11), or of avoidance behaviours (n=9).

The anxiety item was related to 3 subthemes, fear for the integrity of their knee (n=7), fear of falling over (n=6), and fear of future disability (n=3). The depression item was related to aspects of both social (n=11) and physical (n=14) functioning that participants no longer enjoyed.

The pain distribution manikin was variously interpreted by participants, who indicated different qualities or diagnoses for pain at different sites and at different times (n=14), or indicated sites of pain for which they had sought professional help (n=9), or which had different impacts on their life (n=5).

The neuropathic-like pain item in the developmental questionnaire was not well understood by 59% of participants (Table 2). Participants referred to weather-induced pain or thermotherapy which were not aligned with the intended meaning of thermal allodynia. The rewritten item in the final CAP-Knee questionnaire (Figure 1) references an example of tangible physical stimulus: 'Cold or heat (e.g. bath water) on my knee was painful', and was understood well by all participants.

Rasch modelling, scale and item responses

Baseline characteristics for study participants across the interview and Rasch/repeatability studies are shown in Table 1. Likelihood ratio test showed significant differences ($p < 0.001$)

between the partial credit formulation and the rating scale model. The partial credit formulation therefore was used, thereby avoiding assumption of uniform threshold distance across all items.

The summary item-fit statistics from analyses of CAP-Knee scores with four response levels per item indicated misfit to the Rasch model, with significant item-trait interaction [$X^2(df) = 63(28)$; $p < 0.001$] (Table 4). The cognitive-impact item showed misfit (Table 5). CAP-Knee was well targeted, but the sleep disturbance item exhibited disordering of the step difficulty (i.e. the difficulty of a higher step was lower than that of its adjacent lower step), displaying a disordered response threshold (Supplementary Figure 2). Principal Components Analysis of the residuals found that all eight items loaded on the first component. Eleven (4% [Binomial CI: 2%-8%]) of 246 t-tests were significant (Table 4). Four items (neuropathic-like pain, fatigue, anxiety and depression) showed misfit for outfit values in one or more response options (Table 5). CAP-Knee item residuals demonstrated no correlations ($r < 0.3$) between items. None of the items exhibited non-uniform DIF for age or sex. None of the items showed uniform-DIF for age, however, the pain distribution item showed uniform-DIF ($p = 0.03$) for sex.

CAP-Knee analysis was modified by collapsing response categories until the thresholds demonstrated sequential levels of severity. Merging the highest categories 3 ('*Always*') and 2 ('*Often*') for the first seven items produced a scale that performed better than using four response levels (Tables 4 and 5, Figure 1). The final scale, in which each item was allocated a score from 0 to 2 using collapsed responses (possible total score range; 0 to 16) was unidimensional, with no local item dependency observed, although the pain distribution item still showed uniform-DIF for sex. The Rasch-transformed CAP-Knee scoring regime is shown in Supplement 3.

Confirmatory factor analysis and reliability

Factor analysis confirmed the one-factor model (comparative fit index = 0.98; Tucker Lewis Index = 0.97; model $X^2(df) = 38(20)$; root mean square error of approximation = 0.08). All eight items loaded significantly on to the single latent factor, which we named 'Central Mechanisms' (Table 6). Cronbach's alpha was 0.74. Of the respondents, one (0.4%) had the minimum CAP-Knee score of 0, and two (0.8%) had the maximum score of 16. Pairs of complete questionnaires were obtained from each of 76 of 105 participants who completed

the CAP-Knee the second time for the reliability study (Table 1). The median interval between the first and second assessments was 20 days (IQR 17 to 24 days). The reliability intra-class correlation coefficient ($ICC_{2,1}$) was 0.91 (95% CI 0.86 to 0.94).

Association of CAP-Knee scores with knee pain severity

We hypothesised that because central mechanisms augment nociceptive pain from the knee, CAP-Knee would be associated with both sensory and emotional components of knee pain in participants who reported knee as their most painful joint ($n=169$).

Higher CAP-Knee scores were indeed associated with knee pain severity, measured using a 0-11 Likert scale ($r=0.62$, $p<0.001$). Associations between knee pain severity and CAP-Knee scores remained significant in a multivariable linear regression model which included age, sex and BMI as covariates ($B=0.33$ (95% CI 0.25 – 0.41), $p<0.001$). CAP-Knee was also positively associated with total McGill Pain Questionnaire scores ($\rho=0.61$ (95% CI 0.59 – 0.64), $p<0.001$), as well as with each subscale for Affective or Sensory Pain ($\rho = 0.62$ (95% CI 0.59 – 0.63), $p<0.001$; $\rho = 0.47$ (95% CI 0.35 – 0.51), $p<0.001$, respectively). Affective and Sensory subscale scores were positively correlated with each other ($\rho = 0.48$ (95% CI 0.44 – 0.52), $p<0.001$) and linear regression including both subscales as covariates showed significant associations of CAP-Knee scores with each of Affective and Sensory scores (Affective: $B= 0.65$ (95% CI 0.44 – 0.85), $p<0.001$; Sensory: $B=0.14$ (95% CI 0.06-0.21), $p<0.001$).

DISCUSSION

We show that a Central Mechanisms trait, measured by a psychometrically validated CAP-Knee questionnaire was associated both with sensory and affective components of knee pain [8, 9]. CAP-Knee items were understood well by people with knee pain, aligned to our mechanistic model of central pain augmentation. CAP-Knee scores were strongly associated with worse knee pain, consistent with contributions from central mechanisms to both sensory and affective pain components. CAP-Knee is suitable for use in research measuring the Central Mechanisms trait to develop, target and evaluate treatments that aim to reduce the burden of knee pain by reducing central pain augmentation.

The current study confirms our previous findings in another participant cohort that items addressing each of 8 characteristics of neuropathic-like pain, fatigue, cognitive-impact,

catastrophizing, anxiety, sleep disturbance, depression, and pain distribution contribute to a single 'Central Mechanisms' trait [9]. We show here that the Central Mechanisms trait as measured by CAP-Knee is associated with each of the sensory and affective subscales of the MPQ. This supports an integrative model of knee pain in which central mechanisms contribute both to its severity and to its psychological impact. We have also identified heterogeneous participant interpretations of CAP-Knee items, although interpretations aligned well to our mechanistic model of central pain augmentation. Each of these participant-centred interpretations might be indicative of central pain mechanisms, and each also reflects an area of concern to people with knee pain. These findings highlight the diversity and impact of knee pain within the study population.

Rasch analyses demonstrated that respondents might have difficulty distinguishing between response categories 'often' and 'always'. Scoring transformation that collapsed these responses (each scored 2) resolved disordered thresholds, improved the Rasch properties of the CAP-Knee, and met the Rasch assumption for unidimensionality of the latent trait of Central Mechanisms measured by the CAP-Knee, without otherwise impairing CAP-Knee's psychometric properties. We therefore suggest use of these Rasch transformed scores in future studies to aid longitudinal tracking of the Central Mechanisms trait, or as an outcome measure using parametric analyses. The good measurement properties of CAP-Knee demonstrated here are prerequisite for its use as a mechanistic outcome tool measuring the ability of an intervention to reduce central pain mechanisms.

Our current study is subject to some limitations. Characteristics additional to those 8 measured by CAP-Knee, some as yet unidentified, might additionally contribute to central pain mechanisms. Our study might be affected by sources of bias. Study participants were recruited through the IMH&W survey, which itself recruited from a range of sources in order to optimize the generalizability of our findings. However, different participant samples might have given different results. CAP-Knee was completed following postal receipt by participants, a key advantage if to be used in epidemiological research or surveys.

While previous work demonstrates that the Central Mechanisms trait performs fairly across age, sex and BMI groups, the current work identified DIF by sex for the pain distribution item. This finding reflects previous work which identified women are more likely to report greater widespread pain [57, 58]. The pain distribution item contributed least to the Central

Mechanisms trait identified in this study. In both our current and previous study [9], the distribution item loaded less strongly to the Central Mechanisms trait factor than did other items, suggesting that pain distribution might less reliably indicate central pain mechanisms than do other characteristics. However, based on our earlier data and an extensive literature indicating that widespread pain, as, for example, in fibromyalgia, is associated with central sensitisation, we recommend retention of the 'Pain Distribution' item within CAP-Knee.

Ours is a cross-sectional investigation, and future longitudinal research should determine whether CAP-Knee equals or improves upon outcome prediction by other measures of central pain mechanisms, such as QST [59]. CAP-Knee might also help identify areas of concern for people with knee pain, but does not include items addressing characteristics of additional concern to patients (e.g. swelling or stiffness) that were not linked to central pain mechanisms. CAP-Knee might be useful as an outcome measure to evaluate treatments aiming to reduce central pain mechanisms, but was not designed as a patient-centred outcome measure. Application of CAP-Knee as a stratification tool would require future work to determine clinically relevant cut-off scores, for example, to determine subgroups with knee pain who will have poor pain prognosis, or respond to a drug or psychological intervention designed to modify central pain mechanisms. CAP-Knee would require further validation before use in conditions other than knee pain. Combination of CAP-Knee with other predictors of poor pain prognosis might best identify people most likely to benefit from interventions which target central pain mechanisms [8].

In conclusion, our findings indicate the heterogeneous nature and impact of knee pain. We describe and validate the CAP-Knee questionnaire, suitable for measuring the Central Mechanisms trait in people with knee pain. We have demonstrated construct validity of the CAP-Knee as a measure of the Central Mechanisms trait, and shown convergent validity of the CAP-Knee with existing sensory and affective measures. Eight self-report items are related to 8 discrete characteristics of neuropathic-like pain, fatigue, cognitive-impact, catastrophising, anxiety, sleep disturbance, depression, and pain distribution. CAP-Knee is short, easy and inexpensive to administer, either by post or face:face, and was easily understood by people with knee pain. CAP-Knee is suitable for further development as a

stratification tool to identify people who might most benefit from new or established treatments designed to reduce augmentation of knee pain by the central nervous system.

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CONTRIBUTIONS

Kehinde Akin-Akinyosoye, Daniel McWilliams, Roshan das Nair, Eamonn Ferguson and David A Walsh contributed to the conception and design of the interview study. Kehinde Akin-Akinyosoye, Daniel McWilliams, Bonnie Millar, Eamonn Ferguson and David A Walsh contributed to the conception and design of the IMH&W study. Kehinde Akin-Akinyosoye collected the data. Kehinde Akin-Akinyosoye and Richard E James contributed to the coding the interview data. Kehinde Akin-Akinyosoye performed the statistical and qualitative analysis. Kehinde Akin-Akinyosoye, Daniel McWilliams, Roshan das Nair, Eamonn Ferguson and David A Walsh contributed to the data interpretation. All authors critically reviewed and edited the manuscript and approved the final version.

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CONFLICTS OF INTEREST

Kehinde Akin-Akinyosoye: None declared

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FIGURE LEGENDS

FIGURE 1: THE CAP-KNEE QUESTIONNAIRE (FINAL VERSION).

FIGURE 2: RECRUITMENT FLOWCHART FOR THE QUANTITATIVE AND QUALITATIVE ASSESSMENT SUB-STUDIES.

+ 39 out of 50 individuals responding to study between December 2017 and June 2018 consented to further contact and were therefore screened for study eligibility.

*489 people who had provided baseline questionnaire data to the IMHW study between May 2018 and December 2018 were screened for inclusion, of whom 250, each registered with one of 32 different general practices within the East Midlands region, met the eligibility criteria for this study.

#Data from the first 250 participants who completed the CAP-Knee within the IMW&H study and met the inclusion criteria for psychometric assessment of the CAP-Knee were assessed. To test repeatability, 193 of the 250 participants were mailed within 7-days of receipt of their questionnaires with an invitation to complete the CAP-Knee questionnaire a second time. 105 of the 193 participants completed and returned the CAP-Knee questionnaire a second time.

TABLES

Table 1. Characteristics of study participants.

Characteristic (units or possible score range)	Total study population (n=250)	Knee most painful joint (n=169)	Reliability subgroup (n=76)	Interviews (n=22)⁺
Age (y)	71 (64 – 77)	71 (64 – 77)	71 (66 – 78)	66 (59 - 74)
Female sex	158 (63%)	96 (58%)	49 (72%)	15 (68%)
BMI (kg.m ⁻²)	28 (25 – 32)	27 (24-32)	28 (24 – 32)	30 (27-35)
CAP-Knee (0-16)*	7 (5-10)	7 (5-10)	7 (5-9)	6 (4-8)
Joint pain (0-10)	6 (4-8)	6 (4-7)	5 (4-7)	6 (4-7)
McGill total (0-78)	16 (9-25)	16 (8-25)	14 (9-22)	10 (6-11)
McGill affective (0-14)	1 (0-3)	1 (0-2)	0 (0-2)	0 (0-0)
McGill sensory (0-42)	11 (6-16)	11 (6-15)	10 (7-13)	7 (4-11)

Data are median and interquartile range (IQR) or n (%).

⁺Following examination of both knees across participants, 21 (95%) fulfilled the ACR clinical classification criteria for knee OA at any joint, of which 10 (48%) had unilateral OA, and 11/21 (50%) had bilateral OA.

*Rasch transformed scored.

Table 2: Themes and subthemes identified for each item included within the CAP-Knee Scale

Item	Participants with responses related to codes of poor item function	Key theme (number of participants contributing to theme)	Subtheme (number of participants contributing to subtheme)
1. Neuropathic-like pain (‘Cold or heat touching my knee was painful’)*	10 (59%)	Thermal allodynia (n=12) Weather induced pain (n=9) ω Thermotherapy (n=5) ω	-
Item 1 revised: Neuropathic-like pain (‘Cold or heat (e.g. bath water) on my knee was painful ’)*	1 (20%)	Thermal allodynia (n=5)	-
2. Fatigue (‘I generally felt tired’)	5 (23%)	Source of fatigue (n=17) Fatigue relief (n=8)	Physical exertion (n=13) Sleep disturbance (n=5) Other fatigue sources (n=7)
3. Cognitive-impact (‘Knee pain stopped me concentrating on what I was doing’)	7 (32%)	Task distraction (n=10) Hypervigilance (n=12)	-
4. Catastrophizing (‘I kept thinking about how much my knee hurts’)	1 (5%)	Causes and consequences (n=11) Avoidance behaviours (n=9)	-
5. Anxiety (‘In general, I got sudden feelings of panic’)	0 (0%)	Fear (n=15)	Fear of what happens in the knee (n=7) Fear of falling over (n=6) Fear for the future (n=3)
6. Sleep (‘Knee pain affected my sleep’)	2 (9%)	Sleep disturbance (n=21)	Knee pain interrupting sleep (n=16)

			Other painful sites disturbing sleep (n=7)
		Use of sleeping aids (n=8)	-
7. Depression	2 (9%)	Social function (n=11)	-
("I generally still enjoyed the things I used to enjoy")		Physical limitation (n=14)	
	0 (0%)		
8. Pain Distribution			Nature of pain (n=14)
("The final question is about 'pain that you may have had in any part of your body, please shade in the diagram below to indicate where you have suffered any pain for most days in the last 4 weeks. And by pain, we mean aching and discomfort, but we don't mean pain due to feverish illnesses such as flu.")		Painful sites (n=17)	Impact of pain (n=5) Help-seeking experiences (n=9)

* All themes emerged from discussions across all participants (n=22), except for the neuropathic-like pain item where the original item in the developmental questionnaire was used in the first 3 rounds of interviews (n=17), and the revised item used in the final (4th) round of interviews (n=5).

Ω - themes not aligned with intended meaning of the item by the researchers.

Table 3: Participant quotes supporting themes and subthemes identified for each item included within the CAP-Knee Scale

Item	Key theme (Participant Quote)	Subtheme (Participant Quote)
1. Neuropathic-like pain	<p>Thermal allodynia (“Well if I put something too cold on it, it really seizes the knee.” –Interview 1)</p> <p>Weather induced pain (“So you know when it’s been winter and the cold from the winter makes my leg ache worse!” – Interview 10)</p> <p>Thermotherapy (“...because I think hot water sometimes will ease it [knee pain] but it doesn’t at times.” –Interview 19)</p>	-
2. Fatigue (“I generally felt tired”)	<p>Source of fatigue</p> <p>Fatigue relief (“Well sometimes it tires you out. If it’s aching it does make you tired. So, yeah, I just sit down and rest.” – Interview 9)</p>	<p>Physical exertion (“...in the p stimulation doing work and</p> <p>Sleep disturbance (“Sometime – Interview 20”)</p> <p>Other fatigue sources (“But So it’s a combination thing, I</p> <p>-</p>
3. Cognitive-impact (“Knee pain stopped me concentrating on what I was doing”)	<p>Task distraction (“Um, probably say if you’re sitting writing or something, would you be able to concentrate if your knee was hurting you? And if you ask me that, I would probably say I would be able to concentrate to begin with and then my knee would niggle away at me. I’d have to stop writing and get up and straighten my legs and then go back to it, yeah.” – Interview 11)</p> <p>Hypervigilance (“But if say I wanted to get up and go to the toilet, I have to think about it. You know what I mean? So anything you’re doing, it’s kind of there.” – Interview 2)</p>	-
4. Catastrophizing (“I kept thinking about how much my knee hurts”)	<p>Causes and consequences (“...I sometimes wonder if that [step exercise] damaged my knee! Because I used to go all the time.” – Interview 7)</p> <p>Avoidance behaviours (“Um, well if I’m sitting in, say I’m relaxing, and if I move my leg over it’ll start hurting so I’m thinking about, you know, I’ve got to keep still, you know...” – Interview 21)</p>	-
5. Anxiety	<p>Fear</p>	<p>Fear of what happens in the sometimes it feels as though Interview 1)</p>

Table 4. Summary item-person interaction statistics for CAP-Knee using the partial credit model

Model	X ² (df)	P value	Item fit residual (mean)	Item fit residual (SD)	Person fit residual (mean)	Person fit residual (SD)	PSI	Percentage of significant t-tests (95% CI)
Scores not Rasch transformed	63 (28)	<0.05	0.79	1.35	0.01	1.09	0.8	4.43% (2.23% to 7.79%)
Scores Rasch transformed	52 (28)	<0.05	0.19	1.34	0.02	1.28	0.73	4.43% (2.23% to 7.79%)
Ideal value	-	>0.05	0	1	0	1	≥0.70	<5%

Rasch transformation comprised collapsing responses 'Often' and 'Always' each scored 2, whereas non-transformed scores were 'Often'=2, 'Always'=3. PSI; Person Separation Index. N=250.

Table 5. Fit statistics for CAP-Knee items

Items	Scores not Rasch transformed				Scores Rasch transformed			
	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ	Difficulty logit	SE logit	Outfit MNSQ	Infit MNSQ
1. Neuropathic- like pain	2.03	0.11	0.86	0.91	1.6	0.12	0.86	0.92
2. Fatigue	-0.12	0.08	0.98	0.99	-0.99	0.11	0.94	0.94
3. Cognitive-impact	1.09	0.09	0.59	0.59	0.45	0.10	0.59	0.60
4. Catastrophizing	0.59	0.08	0.72	0.72	-0.09	0.10	0.73	0.75
5. Anxiety	2.39	0.12	0.85	0.94	1.96	0.13	0.88	0.93
6. Sleep disturbance	0.78	0.09	0.70	0.72	0.21	0.10	0.67	0.69
7. Depression	0.11	0.08	1.02	1.07	-0.64	0.10	0.93	1.02
8. Pain distribution	0.17	0.15	1.23	1.16	-0.45	0.16	1.37	1.19

Rasch transformation comprised collapsing responses 'Often' and 'Always' each scored 2, whereas non-transformed scores were 'Often'=2, 'Always'=3.. Negative difficulty logits indicate items that are easier to endorse, and positive measures indicate items that are more difficult to endorse. Cognitive-impact and sleep disturbance items displayed misfitting values for infit or outfit (MNSQ outside the range 0.7 to 1.3). N=250. MNSQ = Mean square residual; SE = Standard Error.

Table 6. Item loading for Rasch-transformed CAP-Knee scores

Characteristic: Item wording	Loading
1. Neuropathic-Like pain: Cold or heat (e.g. bath water) on my knee was painful	0.559**
2. Fatigue: I generally felt tired.	0.470**
3. Cognitive-impact: My knee pain stopped me concentrating on what I was.	0.864**
4. Catastrophizing: I kept thinking about how much my knee hurts.	0.748**
5. Anxiety: In general, I got sudden feelings of panic.	0.692**
6. Sleep disturbance: My knee pain affected my sleep.	0.736**
7. Depression: I generally still enjoyed the things I used to enjoy.	0.450**
8. Pain Distribution: This final question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last 4 WEEKS. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu.	0.158*

CFA of the Rasch-transformed CAP-Knee scores (responses for items 1-7 collapsed to 3 levels). **Loading;** factor loading coefficient for item loading to the singled 'Central Mechanisms' factor, n=250, ** p<0.01, * p<0.05.

SUPPLEMENT 1. INTERVIEW GUIDE FOR COGNITIVE INTERVIEW

Introduction

“Hello, my name is Kehinde Akin-Akinyosoye. I am a PhD student with the Arthritis Research UK Pain Centre at Nottingham University. Thank you for agreeing to participate in this interview. Your feedback will help us learn how people with knee pain interpret the questions within this questionnaire. The purpose for this interview is to find out your understanding of each question, particularly, how you come to understand these questions.”

“I will be recording the interview. Do I have your permission to record the interview?”

- If yes, start the recording equipment and read the consent form to the interviewee.
- If no, terminate the interview. Offer participant inclusion to the reliability study to the participant.

“Before we start, I just have a few things to tell you”.

“This interview will only take 30 minutes depending on how much you would like to say in answer to each question”

“If you would like to withdraw from the study and stop the interview at any time, then you can do so without giving a reason. If you would like to have a break during the interview, you are also free to do so. I will pause the audio recording at that point until we begin the interview again.”

“For this interview, I will hand you a blank version of the questionnaire. The questionnaire contains 8 questions which we will be discussing today. I will like you to complete this questionnaire, and I will then ask you about how you understood and responded to each question.

“Do you have any questions before we begin?”

- Answer any questions
- Hand over blank questionnaire to participant

“Please remember that there are no right or wrong answers, and what you say will not hurt my feelings. Feel free to say anything that you are thinking”

“Are you happy to go ahead with the interview?”

- If yes, begin interview: *“Okay, let’s begin with the first question”*
- If no, ask: *“Are there any concerns that you would like me to address?”*

Question 1:

Cold or heat touching my knee was painful (interviews 1-17) or **Cold or heat (e.g. bath water) on my knee was painful** (interviews 18-22)

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 2:

I generally felt tired

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 3:

My knee pain stopped me concentrating on what I was doing

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 4:

I kept thinking about how much my knee hurts

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 5:

In general, I got sudden feelings of panic

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 6:

My knee pain affected my sleep

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 7:

I generally still enjoyed the things I used to enjoy

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *““What were you thinking of when you answered the statement?”*

If participant shows difficulty responding: *“How did you go about deciding on which answer to pick?”*

- *“How sure are you of your answer?”*

Question 8:

This final question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last 4 WEEKS. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu

Probe:

- *“Can you tell me in your own words, what the statement means to you?”*

If participant shows difficulty responding: *“Can you repeat the question I just asked in your own words?”*

- *“What were you thinking of when you were shading in the picture?”*

If participant shows difficulty responding: *“How did you go about deciding on how to shade in the picture?”*

- *“Can you tell me how long have you felt pain in the areas that you shaded?”*
- *“How sure are you of your answer?”*

Closing

“That was my final question. I will now switch of the audio recording equipment.”

Switch off recording equipment

“Thank you for taking time to answer these questions and for your participation in the study. Please feel free to share any other comments that you haven’t shared to this point”

- Pause to allow the interviewee to share additional comments.

“If there are questions or concerns, please contact me on [telephone number].”

SUPPLEMENT 2. ITEM CODING SCHEME

Participant *comprehension* of each CAP-Knee item was determined by coding within themes that were identified through interview by reference to the researcher's intended meaning of that item (listed below). Comprehension was coded as completely aligned, partially aligned or completely non-aligned. *Retrieval difficulty* was coded as none, partial or complete, based on the extent to which participants directly addressed the intended meaning of the item, or instead referred to other aspects of the item before concluding their response to its intended meaning. For example, responses to item 1 were coded as partial retrieval difficulty if participants recalled event(s) not related as well as those that were related to hot or cold stimuli causing or not causing pain to the affected knee. *Judgement* was coded as 'certain' or 'uncertain' initial response according to whether the participant indicated during interview that they were certain or unsure whether they agreed with the response that they had provided on the hard copy CAP-Knee questionnaire prior to commencing the interview, and whether the questionnaire response matched their responses during the interview. For example, judgement was coded as 'uncertain' for item 1 for a participant who reported during interview that heat or cold on their knee sometimes produced pain, but who had responded "never" on the questionnaire, or if the participant was unable to decide on a response for the question. *Response consistency* was coded as 'Consistent' (only one response category checked per item), or 'Inconsistent' (no or >1 response category checked).

Codes were developed and validated by discussion between 2 researchers (KAA and RJEJ) until consensus was reached, using transcripts from 7 participants.

Item intended meanings

Neuropathic-like pain: 'Cold or heat touching my knee was painful' (interviews 1-17) or 'Cold or heat (e.g. bath water) on my knee was painful' (interviews 18-22)

Hypersensitivity to heat or cold applied to the knee, where stimulus intensity is lower than would normally be required to cause pain or damage, indicative of thermal allodynia (Phillips 2017). Application of a cold or hot stimulus that would normally not cause pain when in physical contact with unaffected areas, causes pain to the participant's knee.

Fatigue: 'I generally felt tired'

The enduring, subjective sensation of generalized tiredness or exhaustion, which may or may not be related to knee pain. Fatigue, or feeling tired is typically also described as feeling "rundown" or "knackered", physically and/or mentally.

Cognitive-impact: 'My knee pain stopped me concentrating on what I was doing'

Concentration is an attentional process that involves the ability to focus on the task at hand while ignoring distractions (Moran 2012). Knee pain might interfere with, interrupt, distract, or prevent someone from concentrating on something they were previously focused on.

Catastrophizing: 'I kept thinking about how much my knee hurts'

This item investigates the focused attention on knee pain, on its possible causes and consequences, as opposed to its solutions, indicative of ruminative thoughts (Hilt 2007) . This item seeks to identify the frequency of ruminative thoughts about having knee pain, and the knee pain experience.

Anxiety: ‘In general, I got sudden feelings of panic’

Panic is an extreme form of fear and anxiety, and is characterized by physical sensations, such as a racing heart, shortness of breath that lasts for a short period of time. Panic is a fear of unfamiliar situations, triggered by frightening thoughts, images, and sensations (Busch 1993) . This item seeks to identify whether the respondent has had feelings of panic, nervousness or unease, which might or might not be related to knee pain.

Sleep: ‘My knee pain affected my sleep’

This item investigates the frequency of knee pain disrupting sleep (nocturnal or daytime), including poor quality of sleep, insufficient or too much inefficient sleep, or interrupting sleep cycle.

Depression: ‘I generally still enjoyed the things I used to enjoy’

This item addresses a loss of interest or pleasure (Bartolomucci 2009) . Enjoyment is the feeling of pleasure, satisfaction or happiness that you have when you do or experience something that you like.

Pain distribution: ‘This final question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last 4 WEEKS. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu’

This item investigates location of pain, ache or discomfort across anatomical sites.

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SUPPLEMENT 3. CAP-KNEE RASCH-TRANSFORMED SCORING

Rasch-transformed scoring algorithm for CAP-Knee

Items 1-7

Never = 0

Sometimes = 1

Often =2

Always =2

Item 8: Pain distribution.

Manikin:

No shaded regions below waist = 0.

Only 1 knee shaded and no other regions below the waist = 0.

1 knee plus any additional shaded region below the waist = 2.

Both knees shaded = 2.

CAP-Knee score

Sum of items 1, 2, 3, 4, 5, 6, 7, 8

Range 0-16

FOOTNOTES

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Transparency Declaration

I, Kehinde Akin-Akinyosoye, affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study have been explained.

Ethics approval

Ethical approval for interviews was obtained from the Nottingham Research Ethics Committee 2 (17/EM/0480), and for nested recruitment and questionnaire analysis from the London Central Research Ethics Committee (18/LO/0870).

This study was conducted impartially by the researcher, independent of the project funder.

Participant consent

Written informed consent obtained.