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A domain-oriented approach to characterizing movement-evoked pain

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Abstract

Introduction: Movement-evoked pain (MEP) impacts a substantial proportion of US adults living with chronic pain. Evidence suggests that MEP is influenced by numerous biopsychosocial factors and mediated by mechanisms differing from those of spontaneous pain. However, both characteristic and mechanistic knowledge of MEP remain limited, hindering effective diagnosis and treatment.

Objectives: We asked (1) can chronic pain, functional, psychosocial, and behavioral measures be grouped into descriptive domains that characterize MEP? and (2) what relationships exist between biopsychosocial factors across multiple domains of MEP?

Methods: We formed 6 characteristic domains from 46 MEP-related variables in a secondary analysis of data from 178 individuals (aged 45–85 years) with knee pain. Ratings of pain during 3 functional activities (ie, Balance, Walking, Chair Stand) were used as primary MEP variables. Pearson correlations were calculated to show linear relationships between all individual domain variables. Relationships between variables were further investigated through weighted correlation network analysis.

Results: We observed a unique combination of pain characteristics associated with MEP apart from general pain. Notably, minutes doing physical activity were inversely associated with multiple variables within 4 of the 6 domains. Weighted correlation network analysis largely supported our classification of MEP domains. Additional interdomain relationships were observed, with the strongest existing between MEP, Mechanical Pain, and Multiple Pain Characteristics and Symptoms. Additional relationships were observed both within and between other domains of the network.

Conclusion: Our analyses bolster fundamental understanding of MEP by identifying relevant mechanistic domains and elucidating biopsychosocial and interdomain relationships.

Keywords: Chronic pain, Movement-evoked pain, Knee osteoarthritis, Quantitative sensory testing

1. Introduction

Osteoarthritis (OA) significantly interferes with physical activity, resulting in long-term disability for over 500 million adults worldwide.[7,22] Osteoarthritis pain often worsens with activity or movement of specific joints,[5,9] presenting a unique opportunity to investigate the role of movement-evoked pain (MEP) in high-impact chronic pain populations. In fact, research of individuals with OA suggests that different mechanisms mediate MEP vs spontaneous pain.[6] Scholars posit a need to expand outcomes to include MEP,[2,6,30] and elucidating characteristics of MEP is critical to understanding the pathogenesis, diagnostic and prognostic values, and specific treatment targets of MEP.

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

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Several reviews address current understanding of MEP,[12,20,30] being described as "pain during walking,"[23] "pain that is brought on or aggravated by movement and or stimulation,"[30] or more descriptively as "pain triggered or exacerbated by active or passive movement and clearly differentiated from background, ongoing, spontaneous pain."[1,6] The definition was most recently expanded to "pain that is acutely provoked and experienced in response to active or passive movement of the involved tissues," such as naturally occurring or experimentally standardized active range of motion, muscle contraction, or any form of physical or daily activity.[12]

Earlier studies of MEP primarily involved postsurgical pain.[28,30] However, numerous biopsychosocial factors interact to influence MEP, prompting investigators to assess MEP in people with chronic pain, including shoulder pain, knee OA, whiplash,[24,35] low back pain, and other musculoskeletal conditions.[2,5,8,30] Movement-evoked pain is influenced by several factors leading to considerable interindividual variability, including cognitive and pain modulatory predictors of MEP such as kinesiophobia,[5] pain catastrophizing,[29] and temporal summation.[35] Associations between stigma, perceived injustice, and MEP severity have also been observed.[27] Cruz-Almeida et al.[7] identified 3 distinct clusters of individuals with knee pain based on MEP and functional performance: highest function/minimal MEP, moderate function/mild MEP, and lowest function/severe MEP. These groups differed significantly across multiple measures of psychological functioning, clinical and experimental pain sensitivity, and pain-related interference and disability. In a recent editorial, Crow et al.[6] noted limitations in mechanistic understanding of MEP and chronic pain, in-general, due to the complexity of interactions between the variables above, among others. Many previous studies, including the current study, are limited by the absence of premovement pain ratings. Premovement and postmovement pain rating differentials would permit more precise characterization of MEP. Despite this limitation, we conducted complex analyses of numerous, multimodal pain-related variables to describe MEP.

The purpose of this study was to develop a preliminary multidomain mechanistic characterization of MEP in individuals with OA by answering the following research questions:

(1) Can chronic pain, functional, psychosocial, and behavioral measures be grouped into descriptive domains that thoroughly characterize MEP?
(2) What relationships exist between biopsychosocial factors across multiple domains of MEP (what are the unique contributions of biopsychosocial factors for MEP?)

2. Methods

2.1. Study design and sample

A secondary analysis was conducted on data collected from 178 individuals with knee pain who participated in the Understanding Pain and Limitations in Osteoarthritic Disease-2 (UPLOAD-2) Study, at the University of Florida and the University of Alabama at Birmingham. The parent study sought to understand ethnic/race group differences in knee pain related to OA, disability, and altered pain processing in non-Hispanic Black/African American and non-Hispanic White adults between ages 45 and 85 years. A detailed description of the screening and inclusion/exclusion criteria has been previously published.[1,3,33]

2.2. Study procedures and measures

Variables were selected from physical performance assessments, quantitative sensory testing (QST), and clinical and psychosocial measures utilized in the parent study. Based on our and other previous studies examining multiple biopsychosocial predictors of MEP, we proposed 7 exploratory domains to describe the presentation of MEP in individuals with chronic knee pain: 1. Mechanical Factors, 2. Modulatory Mechanisms, 3. Multiple Pain Characteristics and Symptoms, 4. Mobility-Limiting Function, 5. Mediating and Moderating Factors, 6. Pain Management Strategies, and 7. Molecular and Neural Structures (**Table 1**). For this analysis, we examined 6 of the 7 domains, with the intention of reporting on molecular and neural data in future publications.

2.2.1. Domain 1: mechanical factors

2.2.1.1. Handgrip dynamometry

Handgrip dynamometry assessed grip strength, measured in kilograms. The participant was seated with their elbow tucked to the midaxillary line and flexed to 90° as they squeezed the dynamometer. Six total measurements were taken, alternating between hands each measurement. Participants rated their hand/forearm pain during the handgrip procedure using a numerical rating scale (NRS) of 0 to 100, where 0 = no pain sensation and 100 = the most intense pain sensation imaginable.

2.2.1.2. Knee extension dynamometry

Knee extension dynamometry measured non–weight-bearing, isometric, lower extremity strength. The participant was seated with legs hanging at 80 to 90° and arms crossed over the chest. The participant extended the knee against a handheld dynamometer placed anteriorly above the ankle, pressing against the dynamometer with maximal effort. Three measurements were taken from each leg. Participants rated knee pain evoked during knee extension using an NRS of 0 to 100.

2.2.1.3. Wrist tenderness

Wrist tenderness, bony enlargements, deviation in alignment of fingers, and swelling were assessed by a nurse or trained staff member. Each wrist and all fingers were then independently flexed and then passively, mildly hyperextended to assess pain and tenderness. Manual pressure was simultaneously applied to the medial and lateral aspect of the first carpometacarpal (CMC), each proximal interphalangeal joint (PIP), and distal interphalangeal joint (DIP) independently to further assess joint tenderness. Presence of joint tenderness was coded as yes or no (binary outcome).

2.2.2. Domain 2: modulatory mechanisms

2.2.2.1. Heat pain threshold index

Heat Pain Threshold (HPT) Index was derived using a computer-controlled Medoc PATHWAY Pain & Sensory Evaluation System with a 16 Å~16 mm Advanced Thermal stimulator applied to the medial tibiofemoral joint line and femoral condyle of the most painful knee and ipsilateral ventral forearm. Thermode temperature increased from 32°C at 0.5°C/second intervals until the participant pressed a button indicating the onset of pain. An average of 3 HPT trials was used as an index for analysis.

Table 1

Proposed domains of movement-evoked pain.

DOMAIN #	DOMAIN NAME	OPERATIONAL DEFINITION	CHARACTERISTICS	PROPOSED FACTORS
1	**Mechanical Factors**	Pain associated with muscle activity, changes in joint angle, and/or internal/external forces such as compression, torsion, and strain acting upon tissue	Not always solely explained by nociception or mechanical allodynia; associated with passive or active manipulation (contraction or stretch) or movement.	• Handgrip Pain • Lower Leg Extension Pain • Wrist Tenderness
2	**Modulatory Mechanisms**	Facilitatory and inhibitory processes of the peripheral and central nervous pain that are evoked by constant or intermittent movement	Inhibition, facilitation, conditioned pain modulation, temporal summation, aftersensations, hyperalgesia	***Quantitative Sensory Testing*** • Cold Pain • Heat Pain Temporal Summation • Heat Pain Threshold Index • Pressure Pain Index • Punctate Pain Index • Punctate Pain Temporal Summation • Conditioned pain modulation • Pain Persistence
3	**Multiple Pain Characteristics and Symptoms**	MEP may be associated with multiple pain features assessed via retrospective self-report which could arise from nociceptive, neuropathic, and/or nociplastic inputs [13].	***Pain characteristics, including intensity, frequency, bodily distribution, and pain qualities.*** ***Pain interference and functional impacts.*** .	***Pain Features***• Number of Pain Sites • GCPS - Intensity • GCPS - Interference • WOMAC - Total Score • WOMAC - Pain Score ***Pain Qualities*** • SF-MPQ-2 - Neuropathic • painDETECT
4	**Mobility-Limiting Function**	Pain, or the perceived risk of pain, that inhibits fine or gross motor control (neuromuscular), range of motion (ROM) or the ability to initiate movement.	Includes (but not limited to) reduction of tolerance to active or passive manipulation of the extremity, postural transition and ambulation. May limit functional activities.	• SPPB - Balance function • SPPB - Chair Stand function • SPPB - Gait speed • SPPB - Total Function Score
5	**Mediating/Moderating Factors**	Mediators and moderators are variables reflecting processes that either facilitate the decrease or increase in sensation of pain.	Compounds; behaviors, mood, beliefs, and brain state; and social determinates of health which influence the perception of the sensation of pain.	• PANAS - Negative Affect • PANAS - Positive Affect • PROMIS - Depression • PROMIS - Anxiety • PROMIS - Sleep • PSQI
6	**Management Strategies**	Behaviors, strategies, treatment, and skills applied to gain control over pain, discomfort, and/or unpleasant sensations.	The patient's attitudes, beliefs, level of knowledge of the factors responsible for the experience of pain.	• IVC - Active Coping • IVC - Passive Coping • IPAQ - Moderate Intensity Activity • IPAQ - Vigorous Intensity Activity • IPAQ - Walk 10+ Minutes Per Day • IPAQ - Minutes Walking • IPAQ - Hours Sitting Weekday • IPAQ - Minutes Sitting/Laying Time
7	**Molecular and Neural Structures**	Processes that facilitate or inhibit the systemic processes of inflammation, nociception, and brain activity associated with MEP	Can be measured using multiple biological substrates: brain, blood, urine, and other biologics	N/A to this analysis

We operationalized MEP as pain experienced in response to weight-bearing movement of the knee joint structures during physical activities.

2.2.2.2. Heat pain temporal summation

Heat pain temporal summation (TS) was measured at the medial tibiofemoral condyles and joint line of the most painful knee and ipsilateral forearm using the CHEPS thermode of the PATHWAY system. The thermode was moved between trials to avoid sensitization/habituation of cutaneous nociceptors. Participants rated their heat pain using an NRS (0−100). Stimulations lasted <1 second with a 2.5-second interstimulus interval with target temperature of 44°C. If a subject gave a rating of 100, the procedure was stopped. The first pain rating was subtracted from the fifth pain rating as the change score.

2.2.2.3. Pressure pain threshold

Pressure pain threshold (PPT) was assessed on the medial tibiofemoral condyles and joint line of the most affected knee, the ipsilateral quadriceps, forearm, and trapezius using a handheld digital pressure algometer (AlgoMed; Medoc) applied at a constant rate of 30 kPa/second. Order of testing was counterbalanced and randomized. Participants pressed a button to indicate the onset of pain. Pressure pain thresholds were repeated 3 times on each site to create a mean PPT for that site. The maximum pressure for the knee was 600 kPa and 1000 kPa for other sites. Maximum pressures were based on safety considerations for our knee pain participants. For individuals reaching maximum pressure levels without reporting pain, a value of 600/1000 was assigned.

2.2.2.4. Punctate pain index and temporal summation

Punctate pain index and TS were assessed by mechanical stimulation using a calibrated nylon monofilament with 300 g of force. Punctate testing was performed on the patella of the index knee and the dorsum of the ipsilateral hand in randomized order. Participants rated pain after a single contact. Immediately following the single stimulus, a series of 10 stimuli were administered at a rate of one contact per second and participants rated the greatest pain intensity experienced during the series. The sequence was then repeated at the same site. Pain was rated by NRS (0–100) and averaged separately by site. Temporal summation for each sequence was computed by subtracting the single-trial rating from the rating obtained after 10-stimuli.

2.2.2.5. Conditioned pain modulation

Conditioned pain modulation (CPM) was assessed as in our prior studies.[32,33] First, a single PPT at the left trapezius muscle was measured as a baseline test stimulus. Then, participants submerged their right hand up to the wrist in a cold water bath for 60 seconds as a conditioning stimulus. Temperatures were maintained at 12°C (+0.1°C) by a refrigeration unit (Neslab) that constantly circulated water to prevent warming around the immersed hand. When the hand had been submerged for 30 seconds, participants rated cold pain intensity rating (0–100) and a second PPT was applied to the trapezius. At 60 seconds, the hand was removed from the bath and a final cold pain rating and PPT were obtained. Conditioned pain modulation was computed by subtracting the baseline PPT from the PPT obtained during cold immersion such that positive numbers reflect pain inhibition.

2.2.2.6. Pain persistence assesses

Pain persistence assesses, "on average, for what percent of your waking day do you experience pain in your knee?" as a clinical measure of pain modulation, specifically pain inhibition and facilitation. Percent, ranging from 0 to 100, is based on a 24-hour day.

2.2.3. Domain 3: multiple pain characteristics and symptoms

The following measures provide insight into different pain characteristics and symptoms.

2.2.3.1. Number of pain sites

The number of pain sites was determined from a list of sites, such as head/jaw, neck, shoulder, upper back, low back, knees, legs, and ankles. The number of self-reported body locations with pain was totaled.

2.2.3.2. Graded chronic pain scale

Graded chronic pain scale (GCPS) measures knee pain severity over the past 6 months through 7 items related to pain intensity and pain-related interference of activities. Responses are used to calculate "Pain Grade," a combination of characteristic pain intensity (0–100 scale) and pain-related disability (0–6 scale), the latter representing both the degree and duration of pain-related disability. Grade 0 reflects no pain; Grade 1 reflects low intensity (<50) and low disability (<3); Grade 2 reflects high intensity (≥50) and low disability (<3); Grade 3 reflects high disability (3–4) moderately limiting (regardless of intensity); and Grade 4 reflects high disability (5–6) severely limiting (regardless of intensity).

2.2.3.3. Western Ontario and McMaster Universities Osteoarthritis Index

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) assesses knee pain, stiffness, and physical function over the prior 48 hours.[37] Higher scores indicate greater levels of pain, stiffness, and functional limitations.

2.2.3.4. Short Form McGill Pain Questionnaire-2

Short Form McGill Pain Questionnaire-2 (SF-MPQ-2) includes 22 descriptors of pain and related symptoms. Respondents rated the intensity of each descriptor as it related to their knee pain, from 0 (none) to 10 (worst possible).[10] Responses were summed to generate an overall score. Higher scores indicate greater levels of pain severity.

2.2.3.5. painDETECT

painDETECT is a questionnaire used to delineate between nociceptive and neuropathic pain. A version previously validated for adults with knee OA was used.[17] Scores range from 0 to 38, 0 to 12 indicates nociceptive pain, 13 to 18 indicates possible neuropathic pain components, and 19 to 38 indicates neuropathic pain.

2.2.3.6. Radiographic knee osteoarthritis

Radiographic knee OA was determined using anterior–posterior and lateral radiographs of the index knee. Study rheumatologists interpreted the radiographs to obtain a Kellgren–Lawrence (KL) score ranging from 0 (no joint changes) to 4 (severe joint changes).

2.2.4. Domain 4: mobility-limiting function

2.2.4.1. Short physical performance battery

Short physical performance battery (SPPB) consists of 3 measures of lower-extremity function and mobility: standing balance, ability to rise from a chair unassisted, and 4-meter walking speed. This is a well-validated instrument.[14] Total scores range from 0 to 12, with higher scores indicating better functional performance.

2.2.5. Domain 5: mediating and moderating factors

2.2.5.1. Positive and negative affect scale

Positive and negative affect scale (PANAS) comprised 20-items rated on a 5-point scale.[36] Higher scores on positive items indicate higher trait positive affect, while higher scores on negative items indicate higher negative affect.

2.2.5.2. Patient-reported outcomes measurement information system

Patient-reported outcomes measurement information system (PROMIS) Anxiety & Depression, SF v1.1 for Global Health, and Sleep Disturbances instrument were completed.[4,15,33,34] The anxiety & depression scale asks how often specific feelings have been experienced over the previous 7 days using a 5-point Likert scale (*never*, *rarely*, *sometimes*, *often, always*). The global health questionnaire also employs a 5-point Likert scale to report aspects of physical and mental health (*poor, fair, good, very good, excellent)*, as well as a 0 to 10 scale to report pain over the previous 7 days (no pain to worst imaginable pain). The sleep disturbance instrument uses a 5-point Likert scale to rate sleep quality (*very poor, poor, fair, good, very good*) and restfulness, sleep problems, and difficulty falling asleep (*not at all, a little bit, somewhat, quite a bit, very much)* over the previous 7 days.

2.2.5.3. Pittsburgh sleep quality index

Pittsburgh sleep quality index (PSQI) includes 19 self-report questions assessing 7 components of sleep quality: subjective rating, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.[3] Questions from each component are assigned a score of 0 to 3 (0 = no difficulty to 3 = severe difficulty) based on their sum, and then, all component scores are summed to obtain a global PSQI score (0–21). Higher global scores indicate greater sleep dysfunction.

2.2.6. Domain 6: management strategies

2.2.6.1. In vivo coping questionnaire

In vivo coping questionnaire (IVC) is a 10-item questionnaire measuring the degree to which participants use various strategies to actively or passively cope with experimental pain.[11]

2.2.6.2. International physical activity questionnaire

International physical activity questionnaire (IPAQ) is a 27-item instrument assessing the level of activity in individuals 15 to 69 years.[16] Activity is measured in duration and frequency over the previous 7 days (0–7 days). Walking, moderate-intensity activity, vigorous-intensity activity, walking at least 10 or more minutes, and number of hours sitting/laying subscores are calculated across 5 domains and then summed to generate an overall score. Higher scores indicate higher levels of activity. The sample mean was calculated, and participant outcomes were compared according to standard deviation.

2.2.7. Movement-evoked pain

Immediately following each of the 3 lower-extremity performance tasks (balance, chair stand, and walking) on the SPPB, participants were asked to rate their knee pain using an NRS 0 to 100. This measure of MEP has been used in previous studies of adults with OA and chronic low back pain.[2,25,32]

2.3. Statistical analysis

All analyses were performed using R Statistical Software (v4.1.3; R Core Team 2021). Before analysis, missing values and covariates with >20% missing rates were excluded. Pain ratings of 3 SPPB subscales (balance, chair stands, walking) represented our primary MEP measures; participants with missing values were also excluded from the analysis. The final analyses included 178 participants and 46 variables across the 6 domains.

To eliminate confounding effects, age, sex, race, and study site were regressed out for each of the 46 variables, residuals were derived for the following analysis. Linear, logistic, 0, or ordinal models were built to evaluate the associations of 4 covariates with the continuous, binary, or multilevel variable, respectively. Then, the residual was calculated for each variable by subtracting the effects of 4 covariates. Residuals for multilevel variables were calculated by a surrogate approach.[13,21]

Pearson correlations between all domain variables were computed. Simple correlations in a heat map range from −1 to +1, correlations close to 1 are more positively correlated. Red indicates a close correlation, and blue signifies a more distant and negative relationship. We then performed a Weighted Correlation Network Analysis (WCNA) to detect correlations of continuous variables among the 6 domains. As an unbiased approach, WCNA has been widely applied in gene expression data and multiomics data analysis and is demonstrably effective in analyzing large quantitative data sets beyond these applications.[26,38] To construct the coexpression network, we calculated a correlation matrix containing all pairwise, biweight midcorrelations between all pairs of variables included in the network analysis. The biweight midcorrelation is a more robust measure of correlation compared with Pearson correlation implemented in R package WCNA.[18] To construct signed network, the correlation matrix was converted into an adjacency matrix using function $f(x) = (0.5 + 0.5x)^{\beta}$ where x was the correlation of 2 variables and the selection of soft-threshold power β was based on the Scale-Free Topology Criterion (model fitting index $R^2 > 0.75$). A high power was selected to suppress low correlations that may be due to noise, penalize weaker connections, and strengthen stronger connections. Next, topological overlap matrix (TOM) was computed, and the topological overlap dissimilarity matrix (1-TOM) was used to generate the network dendrogram. Variables were hierarchically clustered using the distance measure, and modules were determined by choosing a height cutoff for the resulting dendrogram by using the dynamic tree-cutting algorithm, selecting a minimal module size of 4 and a merge cut height of 0.1. Variables within the same module are highly correlated. We designated modules A, B, C, and D (as opposed to colors) as to not confuse modules with the color-coded MEP domains that the individual nodes represent.

Table 2

Participant characteristics and movement-evoked pain ratings.

Characteristics	Total N = 178
Age	57.9 ± 7.9
Gender	
Male	65 (36.5)
Female	113 (63.5)
Ethnicity and race	
Non-Hispanic Black	90 (50.6)
Non-Hispanic White	88 (49.4)
Site	
UF	115 (64.6)
UAB	63 (35.4)
KL score (index knee)	
0	79 (44.4%)
1	26 (14.6%)
2	23 (12.9%)
3	15 (8.4%)
4	29 (16.3%)
Missing	6 (3.4%)
Movement-evoked pain	
SPPB Balance pain	19.0 ± 24.3
SPPB Chair stand pain	26.0 ± 28.0
SPPB Walk pain	21.7 ± 27.8

Continuous variables were expressed as mean ± standard deviation and qualitative variables were expressed as n (%).

KL, Kellgren–Lawrence; SPPB, short physical performance battery; UAB, University of Alabama-Birmingham; UF, University of Florida.

3. Results

3.1. Demographics

There is no significant difference between characteristics of the included and excluded participants in this study, except that KL scores and SPPB pain scores significantly lower in the participants free of OA (Table S1, http://links.lww.com/PR9/A232). The final sample included 178 individuals with or at risk for knee OA, where 44% had a KL score of zero. Participants were middle-aged (57.9 ± 7.9), and the majority were women (63.5%; **Table 2**). Self-identified ethnicity and race group assignment was near evenly distributed with 53% non-Hispanic White and 46% non-Hispanic Black participants. There were statistically more participants enrolled at University of Florida compared with University of Alabama-Birmingham ($P = 0.0137$).

3.2. Movement-evoked pain

Movement-evoked pain was represented by pain experienced during balance (19.0 ± 24.3), chair stand (26.0 ± 28.0), and walking (21.7 ± 27.8) during the SPPB (**Table 2**). No significant association was observed between SPPB pain scores and KL indices (**Fig. 1**, all $P > 0.05$ from the Kruskal–Wallis test).

3.3. Correlations of variables across 6 domains

Descriptive summary of variables within each domain are presented in **Table 3**. A heatmap of factors in the 6 domains depicted positive correlations between MEP and variables in domain 1 (mechanical), 3 (multiple pain characteristics), 5 (mediating/moderating factors), and 6 (management strategies) (**Fig. 2**). With the exception of wrist tenderness, all mechanical pain factors were associated with MEP. Pearson correlations further showed that MEP variables were associated with multiple pain characteristics and symptoms ($P < 0.001$). Short physical performance battery walk and chair pain were associated with single punctate pain, but no other QST variable. In vivo coping active coping was associated with SPPB balance pain only, while PROMIS sleep scores were associate with SPPB walk pain only. Although beyond the scope of our objectives, relationships of both directions were observed among multiple additional variables, underscoring the interrelation of biobehavioral factors contributing to pain.

3.4. Weighted correlation network analysis

A total of 178 individuals and 46 variables were clustered into 5 modules (A–E) based on their correlations (**Fig. 3**). Module A included correlations among the largest grouping of variables. Movement-evoked pain variables were highly correlated with mechanical factors and modulatory mechanisms. Moderate correlations were observed among each MEP measure and leg strength pain. Weaker relationships emerged with select factors from modulatory mechanisms, excluding CPM and pain persistence. As indicated in Modules B-E, MEP was not associated with any variables in Domains 3 to 6 (ie, mixed types of pain symptoms, management, mobility-limiting function, and mediating/moderating factors). Instead, variables in the other 4 domains were highly correlated with those within the same domain.

4. Discussion

This is the first exploratory, multimodal measurement characterizing MEP using explicit domains to describe the relationships among biopsychosocial factors. Our network analysis illustrates strong linkage among the 3 MEP variables, reflecting a clearly defined MEP condition that is separate from (but correlated with)

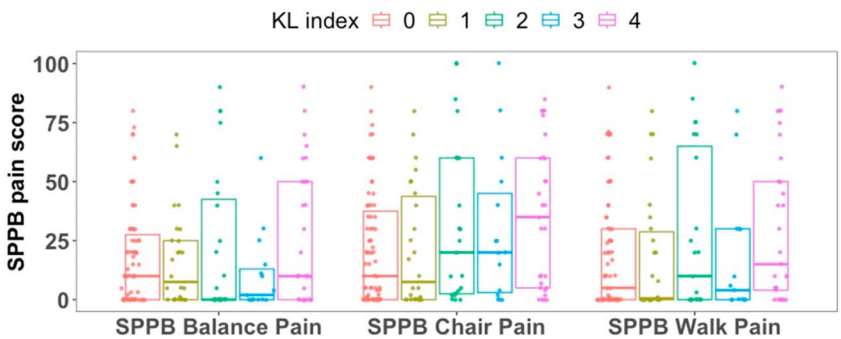

Figure 1. Boxplot for KL Index Scores and MEP Ratings. SPPB pain scores are not significantly associated with KL indices (all $P > 0.05$ from the Kruskal–Wallis test). KL, Kellgren–Lawrence; MEP, movement-evoked pain; SPPB, short physical performance battery.

Table 3

Descriptive statistics of domain variables.

Domain	Variable	Category	Entire cohort
1 - Mechanical Factors	Handgrip Pain L		13.6 ± 19.9
1 - Mechanical Factors	Handgrip Pain R		13.9 ± 20.6
1 - Mechanical Factors	Leg Pain L		15.6 ± 22.0
1 - Mechanical Factors	Leg pain R		17.2 ± 22.4
1 - Mechanical Factors	Wrist Tenderness L	0	139 (78.1%)
1 - Mechanical Factors	Wrist Tenderness L	1	39 (21.9%)
1 - Mechanical Factors	Wrist Tenderness R	0	142 (79.8%)
1 - Mechanical Factors	Wrist Tenderness R	1	36 (20.2%)
2 - Modulatory Mechanisms	QST Cold Index		0.0 ± 1.0
2 - Modulatory Mechanisms	QST Heat Pain Threshold Index		0.0 ± 0.8
2 - Modulatory Mechanisms	QST Heat Pain TS Index		0.0 ± 0.8
2 - Modulatory Mechanisms	QST Pressure Pain Index		0.0 ± 0.9
2 - Modulatory Mechanisms	QST Single Punctate Pain Index		0.0 ± 0.9
2 - Modulatory Mechanisms	QST Punctate TS		0.0 ± 0.8
2 - Modulatory Mechanisms	CPM		50.8 ± 70.2
2 - Modulatory Mechanisms	Pain Persistence		48.6 ± 31.3
3 - Multiple Pain Characteristics and Symptoms	Number of Pain Sites		5.7 ± 3.7
3 - Multiple Pain Characteristics and Symptoms	GCPS Interference		47.7 ± 30.4
3 - Multiple Pain Characteristics and Symptoms	GCPS Pain Intensity		55.7 ± 23.2
3 - Multiple Pain Characteristics and Symptoms	GCPS Pain Grade	1	56 (31.8%)
3 - Multiple Pain Characteristics and Symptoms	GCPS Pain Grade	2	38 (21.6%)
3 - Multiple Pain Characteristics and Symptoms	GCPS Pain Grade	3	51 (29%)
3 - Multiple Pain Characteristics and Symptoms	GCPS Pain Grade	4	31 (17.6%)
3 - Multiple Pain Characteristics and Symptoms	WOMAC Total		36.0 ± 19.8
3 - Multiple Pain Characteristics and Symptoms	WOMAC Pain		7.8 ± 4.3
3 - Multiple Pain Characteristics and Symptoms	SF-MPQ-2 Neuropathic		1.8 ± 2.1
3 - Multiple Pain Characteristics and Symptoms	painDETECT Total		10.7 ± 7.1
3- Multiple Pain Characteristics and Symptoms	KL Score	0	79 (44.4%)
4 - Mobility-Limiting Function	SPPB Balance		3.7 ± 0.7
4 - Mobility-Limiting Function	SPPB Chair Stand		2.0 ± 1.2
4 - Mobility-Limiting Function	SPPB Walking		3.7 ± 0.6
4 - Mobility-Limiting Function	SPPB Total		9.4 ± 1.7
5 - Mediating and Moderating Factors	PANAS Negative Affect		16.4 ± 6.7
5 - Mediating and Moderating Factors	PANAS Positive Affect		34.8 ± 7.8
5 - Mediating and Moderating Factors	PROMIS Anxiety Raw		13.8 ± 5.8
5 - Mediating and Moderating Factors	PROMIS Depression Raw		13.2 ± 6.4
5 - Mediating and Moderating Factors	PROMIS Sleep		17.8 ± 7.6
5 - Mediating and Moderating Factors	PSQI Sleep Duration	0	44 (25.1%)
5 - Mediating and Moderating Factors	PSQI Sleep Duration	1	53 (30.3%)
5 - Mediating and Moderating Factors	PSQI Sleep Duration	2	66 (37.7%)
5 - Mediating and Moderating Factors	PSQI Sleep Duration	3	12 (6.9%)
6 - Management Strategies	IVC Active Coping		2.6 ± 0.8
6 - Management Strategies	IVC Passive Coping		2.8 ± 1.3
6 - Management Strategies	IPAQ Days Mod. Activity	0	36 (21.1%)
6 - Management Strategies	IPAQ Days Mod. Activity	1	20 (11.7%)
6 - Management Strategies	IPAQ Days Mod. Activity	2	22 (12.9%)
6 - Management Strategies	IPAQ Days Mod. Activity	3	29 (17%)
6 - Management Strategies	IPAQ Days Mod. Activity	4	23 (13.5%)
6 - Management Strategies	IPAQ Days Mod. Activity	5	17 (9.9%)
6 - Management Strategies	IPAQ Days Mod. Activity	6	2 (1.2%)
6 - Management Strategies	IPAQ Days Mod. Activity	7	22 (12.9%)
6 - Management Strategies	IPAQ Minutes Mod. Activity		68.0 ± 88.6
6 - Management Strategies	IPAQ Days Vig. Activity	0	42 (24.6%)
6 - Management Strategies	IPAQ Days Vig. Activity	1	25 (14.6%)
6 - Management Strategies	IPAQ Days Vig. Activity	2	21 (12.3%)
6 - Management Strategies	IPAQ Days Vig. Activity	3	30 (17.5%)
6 - Management Strategies	IPAQ Days Vig. Activity	4	15 (8.8%)
6 - Management Strategies	IPAQ Days Vig. Activity	5	16 (9.4%)
6 - Management Strategies	IPAQ Days Vig. Activity	6	7 (4.1%)
6 - Management Strategies	IPAQ Days Vig. Activity	7	15 (8.8%)
6 - Management Strategies	IPAQ Minutes Vig. Activity		80.8 ± 122.2
6 - Management Strategies	IPAQ Days Walk 10+ Min.	0	2 (1.1%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	1	10 (5.7%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	2	15 (8.5%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	3	18 (10.2%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	4	11 (6.2%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	5	19 (10.8%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	6	13 (7.4%)
6 - Management Strategies	IPAQ Days Walk 10+ Min.	7	88 (50%)
6 - Management Strategies	IPAQ Minutes Walk Day		101.9 ± 144.1
6 - Management Strategies	IPAQ Hours Sitting Weekday		5.2 ± 3.7
6 - Management Strategies	IPAQ Minutes Sitting/Laying		314.9 ± 226.5

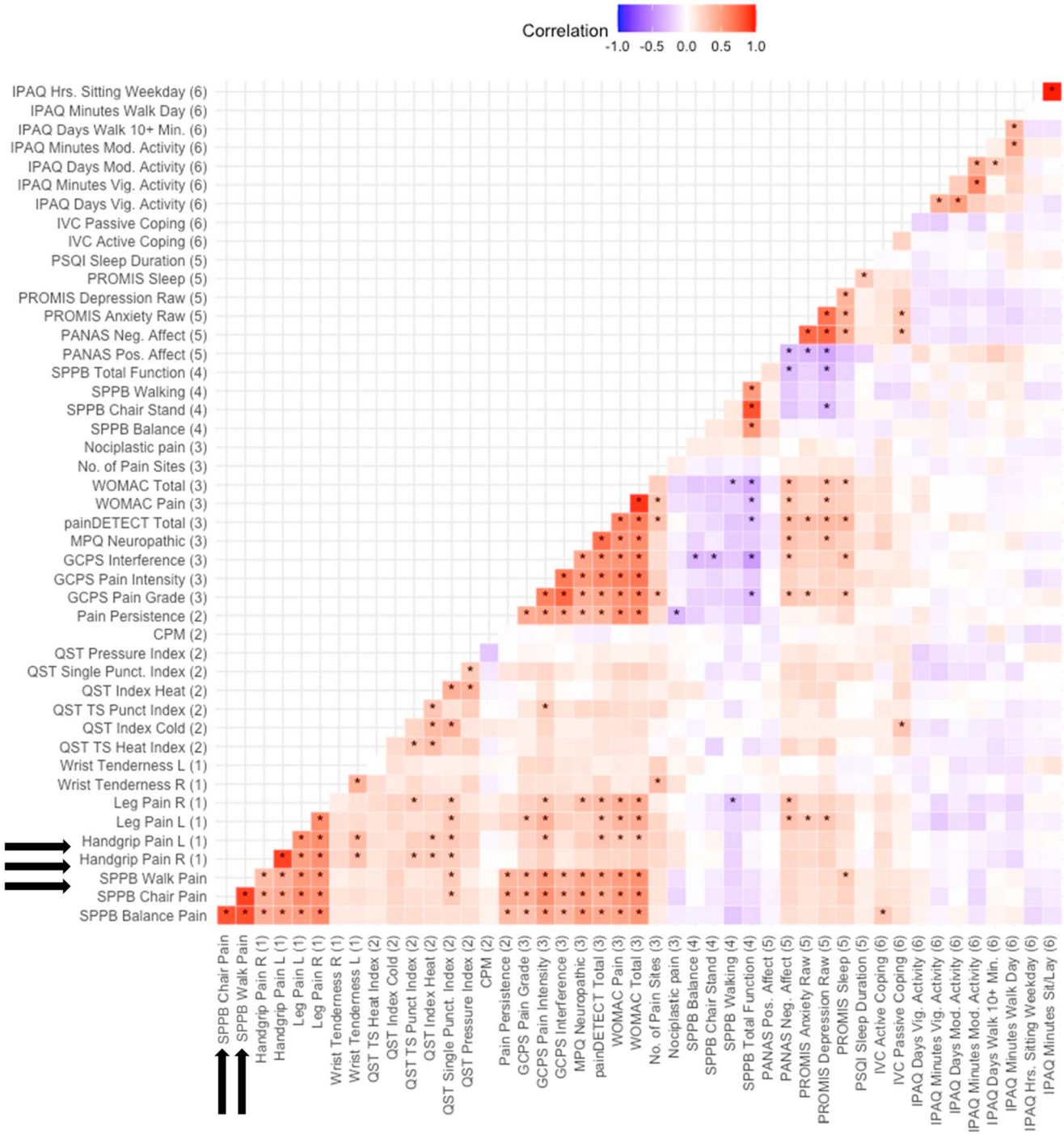

Figure 2. Heatmap of Correlations. The number in the parenthesis denotes the domain each variable belongs to. Figure shows correlations after regressing out age, sex, race, and study site. Multiple testing was conducted using Bonferroni correction. *Bonferroni adjusted-$P < 0.05$. Arrows indicate variables selected to represent movement-evoked pain.

other retrospective, self-report pain measures, such as the neuropathic pain (painDETECT) or chronic pain intensity and interference (GCPS). Weighted correlation network analysis results also largely support our novel, discrete domains. Module A included all Mechanical Pain (Domain 1) variables, demonstrating numerous interrelations of varying strength. Module A also contained 6 of 8 Modulatory Mechanisms (Domain 2), albeit exhibiting weak interrelation ($0.3 \leq \rho < 0.5$). Module B included all Multiple Pain Characteristics and Symptoms (Domain 3) with moderate to strong ($\rho \geq 0.5$) correlations.

While the relationship between domains 1 and 2 may appear intuitive on cursory observation, a strength of the WCNA lies within its ability to illustrate patterns of association between variables, both within and across domains that cannot be captured by pairwise relationships generated by the correlation analysis. Pain modulatory mechanisms are related to mechanical pain primarily through single punctate index scores comparable with studies reported by Overstreet et al.[25] that found temporal summation of mechanical pain induced by a weighted PinPrick stimulator was significantly associated with MEP in people with

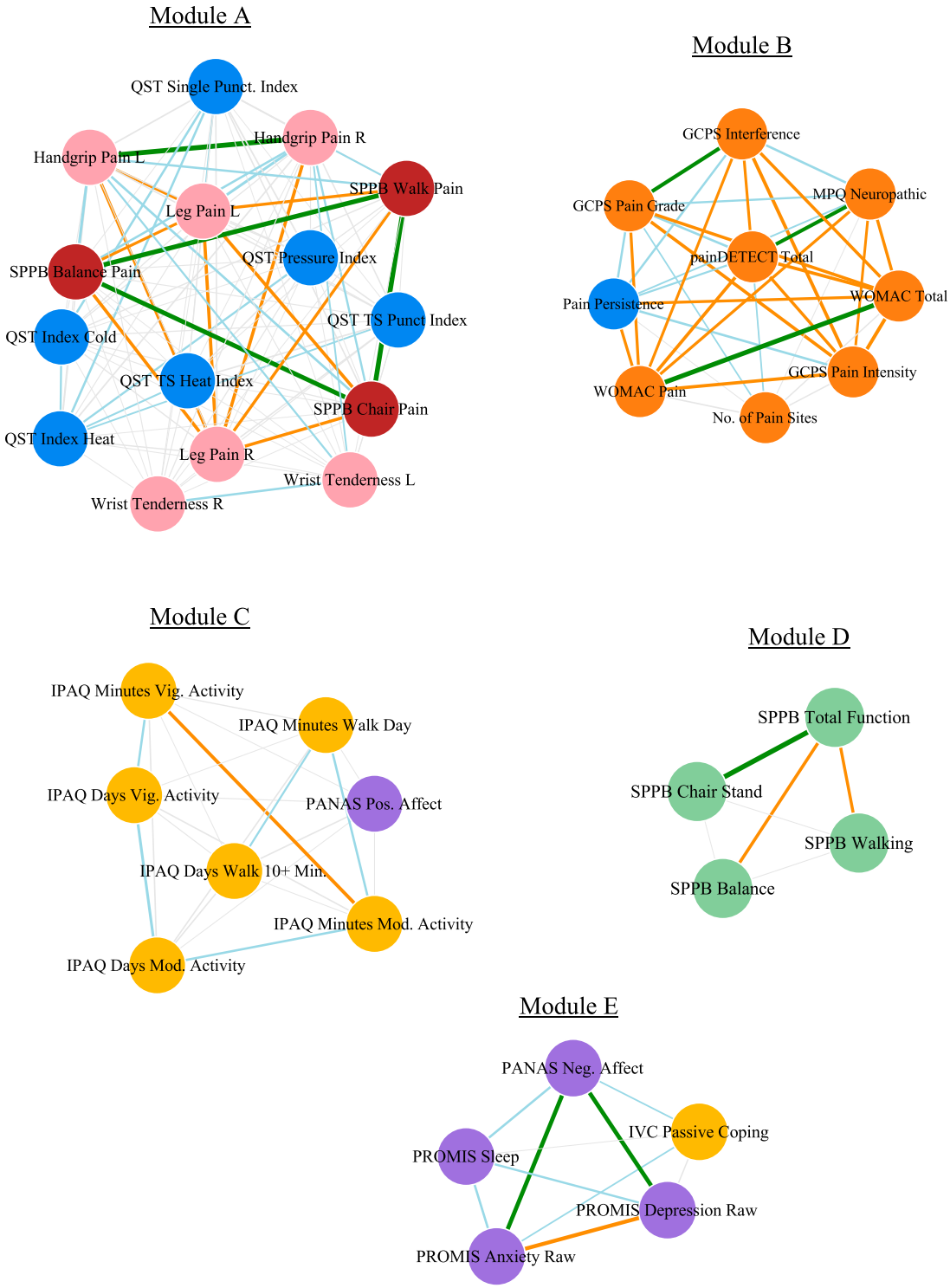

Figure 3. Variables within each domain are highly correlated and clustered into the same module by the Weighted Correlation Network Analysis (WCNA). The edge (ie, line) colors and thickness reflect the strength of correlation between variables, with green showing strong correlation ($\rho \geq 0.7$), followed by orange showing moderate correlation ($0.5 \leq \rho < 0.7$) and light blue indicating weak correlation ($0.3 \leq \rho < 0.5$). Thicker lines reflect stronger correlations. Correlations $\rho < 0.3$ are not shown. Variables clustered into the same module are all positively correlated. Module cluster colors correspond to domain colors in Table 1.

chronic low back pain. Nearly all other relationships between modulatory mechanisms and mechanical pain were indirect. These results underscore the complexity of characteristics associated with pain while disentangling the relationship between pain and function. One explanation is that intensity and temporal characteristics of tasks included in the SPPB may be insufficient to elicit levels of MEP experienced in real-world scenarios. The use of more comprehensive physical performance measures may be necessary to properly describe the relationship between physical function and MEP. It is unclear whether correlations between isolated variables (such as IVC Coping) indicate additional relationships between domains or suggest that

domains should be revised to include them. Exceptions to the domains may indicate the need to reassign or exclude variables that exhibit no (or weak) association to the remaining variables within their domain.

Chronic pain is a highly personal and individualized experience, presenting a mosaic of multiple features (ie, nociceptive, nociplastic, neuropathic), driven by unique mechanisms and influenced by numerous biopsychosocial factors. Conflation of MEP with other pain types continues to present a considerable barrier to proper pain diagnosis and treatment. Recent research has attempted to overcome this barrier by investigating individual characteristics thought to be associated with MEP to identify predictors. Our multidomain predictors are a precursor to generating a scorable, comprehensive index of MEP-related factors. Such an index could reveal an MEP-specific chronic pain signature to be used to (1) identify individuals at high risk for developing high-impact chronic pain or MEP, (2) as a baseline tool to determine potential prognosis or progression of disease-related MEP in clinical patients and research participants, and (3) identify responders to targeted treatments based on MEP profile. To optimize efficacy, treatment must target the appropriate mechanism(s). For example, several studies demonstrate that TENS can reduce MEP by activating endogenous pain inhibition.[8,19,28,29,34] Additional research is needed across other populations and variables to determine core factors characterizing the nature of MEP.

4.1. Limitations and conclusion

This analysis was exploratory in design and therefore should be interpreted in consideration of several limitations. Of note, we used a single disease exemplar (ie, individuals with or at risk for knee OA) to study MEP, of which 50% of the sample did not meet criteria for radiographic knee OA; thus, our findings should be interpreted and extrapolated to OA conditions cautiously. An additional domain including brain and blood biomarkers and sleep biometrics would likely yield a more robust characterization of MEP. Our MEP measures were based on only 3 physical activities. Movement-evoked pain measurement precision importantly hinges on assessing pain premovement/postmovement to determine change and the type and extent of the effect of movement on pain intensification. All these observations are limited in that premovement pain ratings were not collected to observe the direct effect of movement on pain. In addition, the IVC measures are not standard measures of coping or self-management since they only relate to what individuals experienced during QST; thus, they may have limited utility in understanding management of MEP. Owing to the immersion time and transient effects of CPM, the CPM protocol used does not allow sufficient time for multiple PPTs to be conducted and averaged. Single PPTs as used in this study may be subject to variability and reduce the precision and detection of CPM.

These limitations notwithstanding, our findings reaffirm that MEP is a distinct pain type with discernible unique characteristics. Network analysis demonstrates that chronic pain, functional, psychosocial, and behavioral measures can be grouped into domains that more clearly characterize MEP. Our work also serves as an initial excursion into analyzing nuanced patterns existing amongst biopsychosocial factors of MEP. Future research focused on the refinement of domain characteristics will enhance the effectiveness of applying the findings of our study.

Disclosures

The authors have no conflict of interest to declare.

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Data availability: The UPLOAD-2 data set may become available upon request to the Drs. Fillingim and Sibille.

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