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Knee Pain Severity Rather Than Structural Damage is a Risk Factor for Incident Widespread Pain: The Multicenter Osteoarthritis (MOST) Study

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Abstract

Objectives—To examine the longitudinal relation of knee pain, radiographic osteoarthritis (ROA), symptomatic knee OA (SxOA) and knee pain severity to incident widespread pain (WSP).

Methods—The Multicenter Osteoarthritis Study is a longitudinal cohort of persons with or at risk of knee OA. Participants were characterized with regards to consistent frequent knee pain (CFKP), ROA (Kellgren & Lawrence grade 2), SxOA, and knee pain severity at the 60-month visit (baseline). WSP was defined as pain above and below the waist, on both sides of the body and axially, using a standard homunculus, excluding knee pain. Incident WSP was defined as presence of WSP at 84 months among those who were free of WSP at baseline. We assessed the relation of baseline ROA, SxOA, CFKP and knee pain severity, respectively, to incident WSP using logistic regression, adjusting for potential confounders including models with and without pain severity.

Results—At baseline 1129 subjects were eligible for analysis (age mean, SD 66.7, 7.8; BMI 30.1, 5.8 kg/m²; 52% women). ROA in either knee [aOR 0.90 (0.63, 1.30) p=0.587] was not

associated with incident WSP. Baseline bilateral CFKP [adjusted Odds ratio (aOR) 2.35 (1.37, 4.03)], and bilateral SxOA [aOR 2.11 (1.04, 4.24)] and knee pain severity (worst knee) [aOR 1.11 (1.05, 1.17) $p < 0.001$] were significantly associated with incident WSP.

Conclusion—CFKP, SxOA and Knee pain severity increased the risk of developing WSP independent of structural pathology. These results suggest that knee pain and not structural pathology contributes to the onset of WSP.

Keywords

widespread pain; knee pain; osteoarthritis

Musculoskeletal pain disorders are leading causes of pain and disability worldwide.¹ These disorders can affect joints in isolation, regionally or be widespread throughout multiple areas of the body. Widespread pain (WSP) is thought to have a greater impact on an individual's life than single site or regional pain syndromes, and WSP is associated with less healthy aging.² The effects of WSP manifest in poor mental and physical functioning,³ morbidity,⁴ and mortality,⁵ thereby leading to a greater economic healthcare burden.^{4,6} Prevalence of WSP in adults (> 18 years) ranges from 7- 22%,⁷ and 8-33% in older adults (> 60 years) globally.⁸ Of note, WSP is commonly found in people with osteoarthritis (OA).⁹ OA of the knee is one of the most common musculoskeletal pain disorders, affecting up to 28% of older adults,¹⁰ and is a leading cause of disability.¹¹

Despite the personal and economic burden of WSP, its etiology is poorly understood. Longitudinal studies examining risk factors for onset of WSP report poor sleep, cognitive decline, anxiety, older age, multi-joint OA (defined as those with a documented physician consultation for OA and who had pain in at least two sites of either the hands, hips, knees or feet), health-related quality of life, baseline pain status and a family history of chronic pain as putative risk factors.^{9,12} Although both modifiable and non-modifiable risk factors have been identified, the mechanisms by which these risk factors may contribute to WSP have not been explored.^{9,12} In regards to pain progressing from local or regional to widespread, one hypothesis proposes that minor but persistent nociceptive peripheral input may result in WSP due to sensitization of the central nervous system.^{13,14} This would suggest that peripheral structural painful pathology, such as that seen in knee OA, could contribute to the development of WSP. However, a cross-sectional study of people with knee OA demonstrated an association of high pain severity and a low grade (2) of radiographic knee osteoarthritis (ROA),¹⁵ suggesting that perhaps pain itself rather than structural pathology may contribute to WSP. However, given the cross-sectional nature of the data, it is unclear as to whether WSP itself was contributing to the knee pain severity. No longitudinal studies have examined the time course of knee OA and WSP to determine if knee OA and its specific components (i.e., structural pathology, pain, and/or the combination of the two) are risk factors for WSP. Clearly, uncertainty exists regarding the etiologic mechanisms for WSP.

Understanding whether having knee pain, knee OA structural pathology, or the combination of the two leads to WSP is valuable as it can lead to more timely targeted interventions for pain management that may help mitigate the development and effects of WSP. It would also

provide insights into why knee pain or knee OA structural pathology may be comorbid in a substantial proportion. We therefore examined the longitudinal relation of knee pain, ROA, symptomatic knee OA (SxOA) and knee pain severity to incident WSP in a large prospective cohort.

Materials and Methods

Study sample

The Multicenter Osteoarthritis Study is a longitudinal cohort that enrolled 3026 community dwelling adults between the ages of 50–79 years who had or were at risk of developing knee OA. Subjects were recruited from Birmingham, Alabama and Iowa City, Iowa, and the surrounding areas, and were assessed at 0-month, 30-month, 60-month and 84-month study visits. Details of the cohort have been published elsewhere.¹⁶ The study protocol was approved by the institutional review boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco and Boston University Medical Center and was in compliance with the Helsinki Declaration. All participants gave informed written consent. The current sample comprised participants who attended the 60-month visit (baseline for this study) and who followed up at the 84-month visit. Participants who had a total knee replacement by 60 months were excluded from this study.

Widespread pain assessment

The definition of WSP was operationalized as requiring pain to be present in each of the following areas: above (1) and below (2) the waist, on both sides of the body (right (3) and left (4)) and axially (5), excluding the knee (given our focus on knee OA and knee pain), using a validated standard homunculus.¹⁷ The operationalization of this definition was as per other large cohort studies. Those who did not meet this definition were classified as not having WSP. Incident WSP was defined as the presence of WSP at 84 months among those who did not meet the WSP criteria at 60 months.

Consistent frequent knee pain, radiographic osteoarthritis, symptomatic osteoarthritis and knee pain severity assessments

Consistent frequent knee pain (CFKP) was defined as a participant answering ‘yes’ to having knee pain on most days during the past month at the 60-month telephone screen and also at the clinic visit that occurred on average one month later. If either knee met the definition for CFKP, that participant was considered to have CFKP. Bilateral weight-bearing fixed-flexion posteroanterior radiographs and lateral weight-bearing radiographs of the knee were obtained at each study visit. Radiographic severity in the tibiofemoral joint was graded by two experienced readers blinded to clinical data according to Kellgren and Lawrence (KL) criteria (0–4)^{18,19} Any disagreements between readers were adjudicated by a third reader along with the first 2 readers to reach consensus. The inter-rater reliability weighted kappa for the KL grade was 0.80. A participant was defined as having radiographic OA (ROA) based on the presence of tibiofemoral OA KL grade ≥ 2. A participant was defined as having symptomatic knee OA (SxOA) if either knee had ROA plus CFKP in the same knee. Within each phenotype subjects were also characterized based on the number of knees affected (none, unilateral, or bilateral). Knee pain severity was measured using the Western

Ontario and McMaster Universities Osteoarthritis Index pain subscale (0-20 score range) on a knee-specific basis.²⁰ Higher scores on the WOMAC indicate greater pain. The higher of the two ratings was used to indicate worst knee pain in each subject.

Potential confounders

Potential confounders identified in the literature included comorbidities, depressive symptoms, pain catastrophizing, pain severity, physical activity, sleep, and fatigue. Age, sex, body mass index (BMI), and study site were also adjusted for. All were collected at baseline (60 mo). BMI (kg/m^2) was calculated (weight in kilograms divided by height in meters) from measurements taken by trained and certified staff at the 60-month clinic visit. Pain catastrophizing was measured using one item from the Coping Strategies Questionnaire. Use of the brief one-item scale has been shown to be valid and reliable.²¹ The item is scored between 0-6 with higher scores indicating greater frequency of the behaviour. Those with a score ≥ 1 were categorized as having catastrophizing. The Physical Activity Scale for the Elderly (PASE) is a validated measure consisting of 20 items asking about frequency of the activity. Responses range from 0-3 with higher numbers indicating a greater frequency of physical activity.²² These responses are then transformed according to validated regression equations to achieve a total activity score. Sleep was measured on a 4-point Likert scale (very bad to very good sleep) in response to the following question: During the past 7 days, how would you rate your sleep quality overall? Those indicating very bad or bad sleep were designated as having bad quality sleep. Fatigue was measured on a numeric rating scale (0-10) using the following question: During the past 7 days, what number between 0 and 10 best describes your usual level of fatigue? Higher numbers indicated higher levels of fatigue. Participants completed a modified version of the Charlson Comorbidity Index, a validated, self-reported measure of comorbid conditions.²³ The Center for Epidemiologic Studies Depression Scale (CES-D) was utilized as a measure of depressive symptoms.²⁴ A score of 16 or greater has been used as an indicator of depressive symptoms.²⁴ KL grade was assessed in both knees and the higher of the two grades was used as an indicator of worst KL grade.¹⁸

Statistical analyses

We evaluated the relation of CFKP, ROA SxOA, and knee pain severity, respectively, at 60 months to incident WSP using logistic regression. We also examined the relation of bilateral and unilateral involvement for each of CFKP, ROA, and SxOA compared with neither knee having the condition. All models were adjusted for age, sex, BMI, comorbidities, physical activity, clinic site, depressive symptoms, pain catastrophizing, sleep, and fatigue. We also adjusted for KL grade in the CFKP and knee pain severity models and knee pain severity in the CFKP, ROA and SxOA models. Additionally, we ran models for CFKP, ROA and SxOA with and without adjustment for pain severity, as the mere presence of pain and the severity of pain may have different effects in the case of CFKP and SxOA, whereas with ROA we sought to obtain an estimate of the effects of structural pathology without consideration for pain severity.

For a sensitivity analysis, we evaluated the effect of each exposure from the parent study baseline (0 months) on incident WSP at 84 months, excluding those who had a TKR, and

with similar adjustment of covariates with the exception of pain catastrophizing, sleep and fatigue as these variables were first collected at 60 months. We performed these additional analyses to improve precision, capturing more endpoints over a longer period of time. All analyses were performed using SAS 9.3 (SAS Institute, Gary, North Carolina, USA).

Results

There were 2330 subjects who attended the 60-mo clinic visit, which was the baseline study visit for this study. Of these, 163 were excluded for having total knee replacement, 852 already fulfilled the criteria for WSP and 186 did not return to or had incomplete data at the 84-month visit, leaving 1129 subjects without WSP at this baseline visit for analysis (Table 1). Mean age was (67 years), mean BMI (30 kg/m²), and the majority were female (52%). At 84 months 181 (16.1%) had developed WSP.

CFKP and risk of WSP

When adjusted for knee pain severity, the baseline presence of CFKP with either knee was associated with a non-significant 30% higher incidence of WSP 2 years later among those with CFKP in either knee compared with those who did not have CFKP [adjusted OR 1.30 (0.83, 2.06)]. The baseline presence of unilateral or bilateral CFKP was associated with 13% and 68% higher incidence of WSP, respectively, compared with those who did not have CFKP, albeit not significantly. In models without knee pain severity added, CFKP in both knees or either knee was significantly associated with a 135% [adjusted OR 2.35 (1.37, 4.03)] and 76% [adjusted OR 1.76 (1.18, 2.62)] higher incidence of WSP 2 years later, respectively, compared with those who did not have CFKP. Baseline presence of unilateral CFKP was associated with a non-significant 45% higher incidence of WSP compared with those who did not have CFKP (see Table 2).

ROA and risk of WSP

When knee pain severity was included in the model, those with baseline ROA in either knee did not have an increased risk of incident WSP compared with those who did not have ROA [adjusted OR 0.76 (0.52, 1.12)]. Both baseline unilateral ROA and bilateral ROA had a non-significant 29% and 18% lower risk respectively of incident WSP compared with those without ROA. Similarly, when knee pain severity was removed from the model, there were no significant findings with either unilateral, bilateral or either knee with ROA, however values were more indicative of parity between those with and without ROA (see Table 2).

SxOA and risk of WSP

Similarly, neither presence of baseline SxOA in either knee [adjusted OR 0.91 (0.54, 1.51)], or unilateral [adjusted OR 0.77 (0.43, 1.37)], or bilateral SxOA [adjusted OR 1.35 (0.63, 2.91)] were significantly associated with risk of incident WSP compared with those without SxOA when the models were adjusted for knee pain severity. In models without adjustment for knee pain severity, bilateral SxOA was significantly associated with a 111% increased risk of incident WSP [adjusted OR 2.11 (1.04, 4.24)]. Neither the presence of SxOA in either knee or unilaterally was significantly associated with incident WSP (see Table 2).

Knee pain severity and risk of WSP

Lastly, baseline knee pain severity was significantly associated with increased risk of incident WSP, such that each point higher on the 0 to 20 WOMAC pain subscale was associated with a 14% increased risk of incident WSP [adjusted OR per subscale unit increase 1.11 (1.05, 1.17) $p < 0.001$; crude OR 1.14].

Sensitivity Analyses

In the sensitivity analyses, we evaluated incidence of WSP over 84 months. As with our primary analyses, the findings for ROA, knee pain severity and those of SxOA that were adjusted for pain severity were similar (data not shown), even though adjustment for the potential confounders of sleep, fatigue and catastrophizing was not possible since they were not available at baseline. However, when pain severity was removed from the SxOA model, the presence of SxOA at study inception was significantly associated with an increased risk of incident WSP in those with unilateral [adjusted OR 1.55(1.08, 2.23)], bilateral [adjusted OR 1.47 (0.80, 2.71)], or either knee [adjusted OR 1.53(1.10, 2.13)] compared with those without SxOA. These estimates were approximately 20% higher than those without adjustment for pain severity (data not shown). In subjects with CFKP, all estimates in the model without adjustment for pain severity were significantly associated with incident WSP, with unilateral [adjusted OR 1.76(1.26,2.47)] and SxOA in either knee [adjusted OR 1.80(1.33,2.45)] having 76% and 80 % increased risk, respectively. As with SxOA, estimates without pain severity adjustment were higher (approximately 25%).

Discussion

The objective of our study was to determine the relation of CFKP, ROA, SxOA and knee pain severity to the risk of incident WSP two years later. Our results indicate that of the four phenotypes analyzed, only knee pain severity regardless of structural damage was significantly associated with WSP. These findings demonstrate that a localized pain condition, such as knee OA, is a risk factor for the later development of WSP. Neither CFKP, ROA nor SxOA, independent of pain severity, contributed to the development of WSP, suggesting that just the mere presence of pain nor structural pathology are factors in the development of WSP in people with knee OA; rather, it is pain severity itself that is most important. When adjustment for knee pain severity was removed from our models, significant associations with WSP were found for bilateral CFKP, SxOA and CFKP in either knee, suggesting that the symptoms in these phenotypes contribute to risk of WSP in relation to their associated pain severity. The significant association of bilateral symptoms may represent the effects of the summation of pain, leading to heightened pain sensitivity acting centrally on the nervous system. Further, greater pain severity increases the risk for the subsequent development of WSP. These results build on previous cross-sectional analyses and clarify the contribution of pain versus structural damage to the development of WSP. To our knowledge this is the first study to examine these relationships longitudinally in people with or at risk of knee OA.

Previous cross-sectional analyses that have investigated the relationship of WSP and severity of knee pain support our findings. Riddle and Stratford¹⁵ evaluated people with different

levels of knee pain and ROA and reported that those with high pain severity and low ROA grade (2) were more likely to report WSP than those with either low pain severity and high ROA grade (3), high pain severity and high grade ROA, or low pain severity and low grade ROA. Importantly, the sample consisted of those who had average knee pain 20 out of 100 on a visual analog scale in the past month potentially biasing the sample mean of knee pain severity upwards. Similar findings have been reported by others regarding the severity of knee pain²⁵ and WSP, including a dose response relationship²⁶. These findings in combination with our results are consistent with the central sensitivity syndrome hypothesis²⁷; the longitudinal nature of our study supports the direction of the relationship.

Few studies have examined predictors of WSP. In an experimental study using delayed onset muscle soreness in a young, healthy population, Niederstrasser²⁸ reported that the initial pain intensity experienced with the fatiguing eccentric exercise was not predictive of WSP 24 hours later. However, the healthy sample, the acute, temporary nature of the initial pain stimulus, and the short time frame to evaluate for onset of WSP, are not necessarily relevant to the population or the chronic pain stimulus associated with OA. In line with our current findings, a longitudinal, population-based study of risk factors for the onset of WSP⁹ reported that those having higher baseline pain and regional pain had a significant 10% increased risk of incident WSP.

Our sensitivity analysis revealed a difference in findings regarding the effect of unilateral knee pain (both models) on risk of incident WSP. These results suggest that adjustment for the confounders of pain catastrophizing, sleep and fatigue is important when interpreting the effect of the presence of unilateral knee pain on incident WSP and that the effect increases when the severity of knee pain is not considered. This may also explain why our primary results are in contrast to others. Schiphof, et al.²⁹ used a cross-sectional analysis to evaluate the association of various factors with knee pain, and with knee pain in combination with a range of KL grades (0-4). The authors reported that those with WSP were 4.4 times more likely to have knee pain, and that the risk of WSP was greatest in those with KL grades 3 or 4.²⁹ However, they only focused on pain presence, while knee pain severity, pain catastrophizing, sleep and fatigue were not accounted for; thus this likely accounts, in part, for the differences in our findings, in addition to theirs being cross-sectional. Schiphof et al.²⁹ did report a significant association of duration of knee pain with WSP and given the difference in duration of our two analyses (2 years versus 7) we cannot rule out that duration may be an important factor. It should be noted that 852 (36.6%) of our cohort had developed WSP at 60 months and only another 181 (16.1%) went on to develop WSP 2 years later. In our sensitivity analyses, there was an association with incident WSP when evaluated over a 84-month period. We chose the baseline for our study to be the 60-month visit to enable controlling for important potential confounders that were not available at the 0-month visit, but this led to the exclusion of individuals who had existing WSP at the 60-month visit. With the known genetic association of incident WSP,³⁰ and general issues with depletion of susceptibles, it is possible that the remaining participants who were free of WSP at the 60-month visit were less susceptible to the development of WSP, and this may account, in part, for our negative results. However, this issue should have affected the relation of pain severity to incident WSP. As we were able to find significant associations of pain severity with risk of WSP, this suggests that depletion of susceptibles does not primarily account for the lack

of association between the structural pathology-based phenotypes (i.e., ROA, SxOA) with risk of developing WSP when pain severity was accounted for. Thus, it appears that radiographic structural disease on its own does not increase the risk of developing WSP. Other notable differences between this study and ours are the longitudinal nature, thus establishing the sequential relationship of knee pain and knee OA to WSP and we separately assessed the effects of the presence of knee pain, knee pain severity and structural pathology.

The connection between WSP and pain severity may lie in the plasticity of the nociceptive system that is known to adapt centrally to peripheral input, often referred to as central sensitization³¹. The relationship of pain severity and central sensitization has been noted in other populations³² suggesting that persistent nociceptive signaling is important in the development of a sensitized nervous system¹⁴. Nociceptive signaling can also be influenced by the presence of inflammation, a known facilitator of pain in the knee joint³³. Inflammation increases the excitability of spinal neurons thus creating a centrally sensitized state³⁴ which is also maintained by pro-inflammatory cytokines that contribute to pain by directly acting on neurons and indirectly by promoting inflammation³⁵. While central sensitization is defined as “increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input”³⁶ and thus cannot be directly assessed in humans, it can manifest as heightened pain intensity³², widespread or referred pain, or decreased pain thresholds³¹.

Our study has several strengths and limitations to consider. The primary strength is the prospective nature of our investigation, establishing the first longitudinal results investigating risk factors for WSP in this population. We used a valid and frequently employed definition for WSP pain. Our analysis utilized three phenotypes frequently seen clinically as well as the consideration of knee pain severity and a sensitivity analysis suggested the role of certain confounders may be important. As with any observational study, there remains the possibility of residual confounding. We were not able to adjust for all potential confounders that have been reported in the literature (e.g., cognitive decline). The progression to WSP can be a progressive one whereby people transition from no pain or localized pain, to regional pain, to WSP.^{9,12} We did not consider an intermediate stage of regional pain (i.e., those with multiple pain sites but not meeting the WSP criteria); this may provide richer information about the associations we studied. Further, other prospective studies have reported that the presence of WSP fluctuated over several years, with people moving in and out of WSP^{37,38}. Thus, true incidence of WSP may be difficult to discern. Lastly, our time frame for follow-up of two years may not have been sufficient to detect WSP in some people.

In conclusion, we found that the severity of knee pain and having bilateral symptomatic knee pain was a significant risk factor for incident WSP, indicating that localized pain can be involved in the development of WSP. In contrast, structural pathology independent of pain severity was not significantly associated with increased risk for incident WSP. These findings highlight the importance of pain symptomatology as an important factor that can contribute to the onset of WSP, suggesting a possible role for sensitization and the importance of adequately managing pain symptoms. Further, the underlying peripheral structural pathologic input appears to be unimportant relative to the resulting knee pain

severity in the subsequent development of WSP. These findings support the need to further explore mechanism-based management of pain³⁹ as a disease unto itself to avoid negative consequences of pain remaining untreated.

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Significance and Innovations

- In a longitudinal study of people with or at risk of knee osteoarthritis, baseline knee pain severity and bilateral symptomatic knee pain were associated with incident WSP, indicating that localized pain can develop into pain that is widespread. This work builds on findings from previous cross-sectional studies.
- In contrast, structural pathology independent of pain severity was not significantly associated with increased risk for incident WSP.
- These findings highlight the importance of pain symptomatology as an important factor that can contribute to the onset of WSP, suggesting a possible role for sensitization and the importance of adequately managing pain symptoms.

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Table 1

Baseline participant characteristics

Whole sample N=1129	
Age (yrs)– mean (sd)	66.7 (7.8)
BMI – (kg/m ²) mean (sd)	30.1 (5.8)
Female - N (%)	592 (52.5)
Depressive symptoms – (0-60) mean (sd)	5.2 (5.8)
Pain catastrophizing – N (%)	461 (40.8)
Comorbidities – N median (25th, 75th percentile)	0 (0,1)
Fatigue (0-10) – mean (sd)	2.8 (2.2)
Sleep bad – N (%)	149 (13.2)
PASE Physical activity (0-400) mean (sd)	188.0 (90.3)
WOMAC pain severity (0-20)– mean (sd)	2.7 (3.2)
Worst Kellgren-Lawrence grade 2 N (%)	587 (53.9)

Table 2

Relation of CFKP, ROA and SxOA to risk of incident widespread pain

# of knees	CFKP at baseline				ROA at baseline [†]				SxOA at baseline		
	Risk of Incident WSP n/N (%)	Crude OR	Adjusted OR	Risk of incident WSP n/N (%)	Crude OR	Adjusted OR	Risk of incident WSP n/N (%)	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Either Knee (vs. none)	63/272 (23.2)	1.88	* 1.30 (0.83, 2.06) ‡ 1.76 (1.18, 2.62)	100/593 (16.2)	1.13	‡ 0.76 (0.52, 1.12) ‡ 0.90 (0.63, 1.30)	38/163 (23.3)	1.74	* 0.91 (0.54, 1.51) ‡ 1.37 (0.89, 2.13)		
None (Referent)	118/855 (13.8)	1.0	1.0	70/460 (14.8)	1.0	1.0	135/906 (14.9)	1.0	1.0		
Unilateral	30/164 (19.6)	1.40	* 1.13 (0.67, 1.90) ‡ 1.45 (0.90, 2.35)	43/293 (14.1)	0.96	‡ 0.71 (0.45, 1.11) ‡ 0.81 (0.52, 1.25)	23/119 (19.3)	1.37	* 0.77 (0.43, 1.37) ‡ 1.14 (0.68, 1.91)		
Bilateral	33/108 (29.4)	2.75	* 1.68 (0.92, 3.08) ‡ 2.35 (1.37, 4.03)	57/300 (18.3)	1.31	‡ 0.82 (0.53, 1.28) ‡ 1.00 (0.66, 1.53)	15/44 (34.1)	2.95	* 1.35 (0.63, 2.91) ‡ 2.11 (1.04, 4.24)		

* Adjusting for age at 60 mo, sex, BMI, comorbidities, physical activity, clinic site, depressive symptoms, pain catastrophizing, sleep, fatigue, worst KL grade and knee pain severity.

† Adjusting for age at 60 mo, sex, BMI, comorbidities, physical activity, clinic site, depressive symptoms, pain catastrophizing, sleep, fatigue, and worst KL grade

‡ Adjusting for age at 60 mo, sex, BMI, comorbidities, physical activity, clinic site, depressive symptoms, pain catastrophizing, sleep, fatigue, and knee pain severity