The Effect of Widespread Pain on Knee Pain Worsening, Incident Knee Osteoarthritis (OA), and Incident Knee Pain: The Multicenter OA (MOST) Study

Lisa C. Carlesso, Jingbo Niu, Neil A. Segal, Laura A. Frey-Law, Cora E. Lewis, Michael C. Nevitt, and Tuhina Neogi

ABSTRACT. Objective. Whether widespread pain (WSP) affects the risk of developing knee pain or knee osteoarthritis (OA) is unknown and could enhance understanding of pain mechanisms in OA.
Methods. Subjects from the Multicenter OA (MOST) study, a US National Institutes of Health–funded prospective cohort of older adults with or at risk of knee OA, were characterized regarding WSP, defined as pain above and below the waist on both sides of the body and axially using a standard homunculus, excluding knee pain at 60 months (baseline). Followup occurred 2 years later. We assessed the relation of WSP to odds of knee pain worsening (≥ 2-point increase in the Western Ontario and McMaster Universities Arthritis Index pain subscale) using logistic regression, and to odds of incident radiographic knee OA (ROA; Kellgren-Lawrence arthritis scale ≥ grade 2 of either knee among those free of ROA at baseline) and incident consistent frequent knee pain (CFKP; knee pain on most days during the past month among participants free of knee pain at baseline) in 1 or both knees using multinomial regression adjusting for potential confounders.
Results. There were 1752 participants available for analysis [mean age (SD) 67.0 yrs (7.7), body mass index 30.5 kg/m² (5.9), 59% women]. Baseline presence of WSP was not associated with worsened knee pain (adjusted OR 1.15, 95% CI 0.89–1.48, p = 0.30), ROA (adjusted OR 0.86, 95% CI 0.46–1.63, p = 0.65), or incident CFKP (adjusted OR 1.69, 95% CI 0.96–2.96, p = 0.07).
Conclusion. WSP was not significantly associated with worsening knee pain, incident ROA, or CFKP. Development of knee pain and ROA does not appear to be influenced by underlying WSP. (First Release March 1 2017; J Rheumatol 2017;44:493–8; doi:10.3899/jrheum.160853)

Key Indexing Terms:
WIDESPREAD PAIN   KNEE PAIN   OSTEOARTHRITIS

Osteoarthritis (OA) of the knee is one of the most common musculoskeletal pain disorders and is a leading cause of disability[1]. The prevalence of knee OA is 37% in people aged ≥ 45 years[2,3], and it is symptomatic in up to 17% of those with radiological evidence of OA[3]. Despite its prevalence and burden, the etiology of OA pain is not well understood. Some studies have suggested that widespread pain (WSP) may be associated with increased pain and decreased function[4] in those living with knee OA[5,6], and more generally contributes to poor mental and physical functioning[7], morbidity[8], and mortality[9].

The tendency of pain to become widespread is thought to be the result of elevated sensitivity of the central nervous system[10], associated with increasing intensity and duration

of pain[11]. Dysfunction in the central processing of pain can occur through the alterations of both ascending and descending pathways, resulting in diffuse hyperalgesia and/or allodynia, thus potentiating the onset or increased severity of knee pain[12]. We have recently shown that in people with or at risk of knee OA, knee pain severity is predictive of the development of WSP 2 years later[13]. However, it is unknown whether a bidirectional relationship may exist. The literature examining the association between WSP and knee pain has been largely cross-sectional. WSP was associated with greater prevalence of consistent versus inconsistent knee pain in 1 study[6], and others have shown a stronger association between WSP and knee pain with increasing structural severity of OA[14], as well as an association of WSP with a combination of high knee pain severity and low-grade structural severity of OA[15]. One longitudinal study by Jinks, *et al*[16] found an association of multijoint pain (≥ 2 joints) with incident knee pain. However, these studies did not adjust for important potential confounders such as pain catastrophizing[17], quality of sleep[18], or fatigue[19], and varying definitions of WSP were used, making direct comparisons difficult.

Regardless of the potential for WSP to affect development of knee pain, it is also important to understand whether WSP can contribute to the development of structural pathology. The literature base regarding the association of WSP with incident knee OA is lacking, and evidence regarding potential mechanisms that may account for the relationship are conflicting and complex. For example, WSP is known to limit physical activity[20]. In a longitudinal study, McBeth, *et al*[20] reported that those with WSP were twice as likely to have lower levels of physical activity or to be engaging in less than 20 min of exercise in the past month at followup more than 2 years later[20]. Because physical activity helps promote cartilage volume while limiting the occurrence of cartilage defects (in the absence of knee injury)[21], it is thought that this may decrease the risk of knee OA. This would suggest that people with WSP may have an increased risk of developing incident knee OA because of lower levels of physical activity. However, studies have reported varying results of physical activity on incident knee OA including no effect[22,23], a protective effect[24], or an increased risk[25]. Alternatively, it is speculated that WSP may lead individuals to limit excessive joint loading, which could potentially be beneficial. Slower walking speeds are associated with lower knee joint and ground reaction forces[26], and faster walking speeds are associated with increased knee joint loading[27], which in theory suggest that slower walking may lead to a lower incidence of knee OA. However, 1 longitudinal study presented results contrary to this hypothesis by demonstrating that people with faster walking speeds had a lower incident of knee OA[28].

In a study comparing the effect of pain location versus pain severity on lower extremity physical function, Eggermont, *et al*[29] reported a significant trend in walking speeds, with those having WSP being the slowest versus those with multisite, single site, or no pain. Given these conflicting results and the limited evidence of the association of WSP with incident knee OA, clarification of the association of WSP with incident knee OA is warranted.

Understanding whether having WSP can lead to new onset or worsening of knee pain or the development of knee OA structural pathology is valuable because it can lead to more timely targeted interventions for pain management that may help mitigate the detrimental effects of WSP on knee pain or knee OA. We therefore examined the longitudinal relation of WSP to worsening of knee pain severity, incident knee pain, and radiographic knee OA (ROA) in a large prospective cohort.

MATERIALS AND METHODS

Study sample. The Multicenter Osteoarthritis Study is a US National Institutes of Health–funded, longitudinal cohort that initially enrolled 3026 community-dwelling adults between the ages of 50 and 79 years who had or were at risk of developing knee OA. Subjects were recruited from 2 sites — Birmingham, Alabama, and Iowa City, Iowa, USA. They were assessed at the 0-month, 30-month, 60-month, and 84-month study visits. Initial recruitment occurred between 2003 and 2005. Details of the cohort have been published elsewhere[30]. The study protocol was approved by the Institutional Review Boards (IRB) at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco, and Boston University Medical Center. All participants gave written informed consent. The current sample consisted of participants who attended the 60-month visit (the baseline for our study because this was the first time that several confounding variables were measured) and who attended the followup visit at 84 months.

Exposure: WSP. The definition of WSP required pain to be present in each of the following regions: above and below the waist, on both sides of the body, and axially, using participants' pain drawings on a validated standard homunculus[31]. Given our focus on knee OA and knee pain, we did not include knee pain in the definition of WSP (i.e., other lower extremity pain was required). Therefore, participants had to have at least 3 painful joints to be classified as having WSP. Those who met the definition were classified as having WSP and those who did not were classified as not having WSP.

Outcomes: Worsening knee pain, consistent frequent knee pain (CFKP), and ROA. Knee pain severity was assessed at each study visit using the pain subscale (scores range from 0–20) of the valid and reliable Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Likert version)[32]. Participants were classified as having worsening of knee pain if they reported an increase in pain of ≥ 2 points in either knee at 84 months compared with baseline knee pain at 60 months. For the WOMAC pain subscale, a 2-point change has been shown to be the minimal clinically important difference[33].

Frequent knee pain was assessed at each study visit. CFKP was defined as a participant answering "yes" to having knee pain on most days during the past month at the telephone screen 1 month prior to the clinic visit and again at the clinic visit. If either knee met the definition for CFKP, that participant was considered to have CFKP. Incident CFKP was defined as the presence of CFKP at 84 months among those who did not have CFKP at 60 months.

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 2 experienced readers blinded to clinical data according to the Kellgren-Lawrence arthritis grading scale (KL) criteria (0–4)[34,35]. Any disagreements between readers were adjudicated by a third reader along

with the first 2 readers to reach consensus. The interrater reliability weighted κ for the KL grade was 0.80. A participant was defined as having incident ROA based on the presence of tibiofemoral OA, KL grade ≥ 2, at 84 months among those who did not have ROA at the 60-month clinic visit (baseline for our study).

Potential confounders. Potential confounders including age, sex, body mass index (BMI), comorbidities, depressive symptoms, pain catastrophizing, pain severity, physical activity, sleep, fatigue, and study site were collected at baseline (60 mos). BMI (kg/m^2) was calculated from measurements taken by trained and certified staff at the 60-month clinic visit. Participants completed a modified version of the Charlson Comorbidity Index, a validated, self-reported measure of comorbid conditions[36]. The Center for Epidemiologic Studies Depression Scale was used as a measure of depressive symptoms[37]. A score of 16 or greater has been used as an indicator of depressive symptoms[37]. Pain catastrophizing was measured using 1 item from the Coping Strategies Questionnaire. Use of the brief 1-item scale has been shown to be valid and reliable[38]. The item is scored between 0 and 6 with higher scores indicating greater frequency of the behavior. Pain catastrophizing was defined as being present if the score was ≥ 1. Knee pain severity was measured using the WOMAC pain subscale (0–20 score range) on a knee-specific basis[32]. Higher scores on the WOMAC indicate greater pain. The higher of the 2 ratings was used to indicate worst knee pain in each subject. The Physical Activity Scale for the Elderly is a validated measure consisting of 20 items asking about the frequency of each activity[39]. These responses are then transformed according to the New England Research Institute's validated regression equations to achieve a total activity score. Sleep was assessed with the following question: "During the past 7 days, how would you rate your sleep quality overall?" with responses ranging from "very bad" to "very good" on a 4-point Likert scale. Those indicating "bad" or "very bad" sleep were classified as having bad 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 a higher level of fatigue.

Statistical analyses. We evaluated the association between WSP and worsening knee pain using logistic regression. We also examined the relation of WSP to bilateral and unilateral involvement for each of the incident ROA and incident CFKP compared with either knee having the condition using multinomial regression. Those who had a knee replacement over the course of our study were considered to have experienced the outcomes of worsening pain severity and CFKP, and were considered to have incident ROA. All models were adjusted for age, sex, BMI, comorbidities, physical activity, and clinic site, while the model was also adjusted for depressive symptoms, pain catastrophizing, fatigue, sleep, and ROA when worsening knee pain and CFKP were the outcome, and for WOMAC pain severity when ROA was the outcome. We also conducted a sensitivity analysis to evaluate the effect of WSP from the parent study baseline (0 mo) on worsening knee pain, incident CFKP, and incident ROA at 84 months, with similar adjustment of potential confounders with the exception of pain catastrophizing, sleep, and fatigue because these variables were first collected at 60 months. The sensitivity analyses were conducted to improve precision by assessing greater endpoints over a longer period of time. All analyses were performed using SAS 9.3 (SAS Institute).

Ethics. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. All subjects gave informed consent to participate in this research. Approval for this secondary analysis was granted by the Boston University Medical Center IRB (# H-27296).

RESULTS

There were 1752 subjects eligible for worsened knee pain [mean age (SD) 67.0 yrs (7.7), BMI 30.5 kg/m^2 (5.9), and 59% women], 815 eligible subjects for analysis of incident

CFKP [mean age (SD) 66.9 yrs (7.4), BMI 29.5 kg/m^2 (5.2), 54% women], and 675 for incident ROA [mean age 65.6 yrs (7.4), BMI 28.9 kg/m^2 (4.7), 60% women; Table 1].

WSP and odds of worsening knee pain. In the 549 people with WSP at baseline (60 mos), 170 (31.0%) also had worsening knee pain. The presence of WSP at baseline was associated with a nonstatistically significant 15% higher odds of worsening knee pain (adjusted OR 1.15, 95% CI 0.89–1.48, p = 0.30) at 84 months compared with those without WSP at baseline.

WSP and odds of CFKP. The baseline presence of WSP was associated with a nonstatistically significant 69% increased odds of incident CFKP 2 years later compared with those without WSP (adjusted OR 1.69, 95% CI 0.96–2.96, p = 0.07). WSP was also associated with nonstatistically significant increased odds of incident unilateral and bilateral CFKP (Table 2).

WSP and odds of ROA. Baseline WSP was associated with a nonstatistically significant 14% lower odds of incident ROA (adjusted OR 0.86, 95% CI 0.46–1.63, p = 0.65). There was not a statistically significant association between WSP and either incident unilateral or bilateral ROA compared with no ROA (Table 2).

Sensitivity analyses. As with our primary analyses, the findings for knee pain worsening and the incident ROA groups (data not shown) were similar. However, WSP at 0 month was significantly associated with about double the odds of incident CFKP 7 years later compared with those who did not have CFKP (adjusted OR 2.05, 95% CI 1.35–3.13, p = 0.008) and in those with unilateral CFKP compared with those without CFKP (adjusted OR 2.19, 95% CI 1.37–3.50, p = 0.0001). The presence of WSP was associated with a nonstatistically significant 73% higher incidence of bilateral CFKP. Given this result, we reran the main incident CFKP model (i.e., 60–84 mos) without pain catastrophizing, fatigue, and sleep. A significant association of WSP was found in those with incident CFKP (adjusted OR 1.90, 95% CI 1.10–3.29, p = 0.022) compared with those without CFKP, indicating that pain catastrophizing, fatigue, and sleep were attenuating the effect of WSP over a 2-year time frame. There were no statistically significant findings for either unilateral or bilateral incident CFKP.

DISCUSSION

In contrast to previous largely cross-sectional studies, we found no association of WSP with knee pain, defined as either worsening of knee pain severity or incident CFKP after 2 years. We also demonstrated that WSP is not predictive of the development of structural pathology of OA at the knee over a 2-year window.

Our findings differ from those of some prior studies. Most of the prior studies have been cross-sectional, potentially having reverse causation bias, and have included subjects with

Table 1. Baseline participant characteristics. Values are mean (SD) unless otherwise specified.

Characteristics	All Eligible for Knee Pain Worsening, n = 1752	With WSP, n = 549	Without WSP, n = 1203	Eligible for Incident CFKP, n = 815	Eligible for Incident ROA, n = 675
Age, yrs	67.0 (7.7)	67.3 (7.6)	66.9 (7.7)	66.9 (7.4)	65.6 (7.4)
BMI, kg/m^2	30.5 (5.9)	31.2 (6.1)	30.1 (5.8)	29.5 (5.2)	28.9 (4.7)
Female, n (%)	1032 (58.9)	395 (71.9)	637 (53.0)	441 (54.1)	402 (59.6)
Comorbidities, median (IQR)	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)
PASE physical activity, 0–400	182.3 (88.6)	170.6 (84.3)	187.6 (90.0)	186.3 (87.6)	184.2 (85.2)
WOMAC pain severity, 0–20	3.6 (3.7)	5.6 (3.8)	2.7 (3.2)	1.3 (1.8)	2.4 (2.9)
CES-D depressive symptoms, 0–60	6.8 (7.3)	9.9 (8.8)	5.3 (5.9)	5.4 (6.1)	6.4 (6.9)
Pain catastrophizing, n (%)	852 (48.6)	360 (65.6)	492 (40.9)	323 (39.6)	288 (42.7)
Fatigue, 0–10	3.3 (2.4)	4.3 (2.4)	2.8 (2.2)	2.7 (2.2)	3.1 (2.4)
Sleep bad, n (%)	310 (17.7)	147 (26.8)	163 (13.5)	108 (13.3)	116 (17.2)
Whole knee ROA, n (%)	963 (58.5)	320 (61.4)	643 (57.1)	356 (44.9)	—

WSP: widespread pain; CFKP: consistent frequent knee pain; ROA: radiographic knee osteoarthritis; BMI: body mass index; IQR: interquartile range; PASE: Physical Activity Scale for the Elderly; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; CES-D: Center for Epidemiologic Studies Depression Scale.

Table 2. Risk of WSP to incident CFKP and ROA. Values are n (%) unless otherwise specified.

Incident CFKP	Risk among Subjects without WSP, n = 669	Risk among Subjects with WSP, n = 146	Crude OR, WSP vs without WSP, Reference	Adjusted OR* (95% CI), WSP vs without WSP, Reference	p
Either knee affected, vs none affected	69 (10.3)	27 (18.5)	1.97	1.69 (0.96–2.96)	0.07
One knee	55 (8.2)	18 (12.3)	1.65	1.58 (0.83–3.02)	0.17
Both knees	14 (2.1)	9 (6.2)	3.24	1.82 (0.64–5.16)	0.26

Incident ROA	Risk among Subjects without WSP, n = 475	Risk among Subjects with WSP, n = 200	Crude OR, WSP vs without WSP, Reference	Adjusted OR† (95% CI), WSP vs without WSP, References	p
Either knee affected, vs none affected	43 (9.1)	22 (11.0)	1.24	0.86 (0.46–1.63)	0.65
One knee	38 (8.0)	21 (10.5)	1.34	0.99 (0.51–1.92)	0.97
Both knees	5 (1.1)	1 (0.5)	0.49	0.23 (0.02–2.53)	0.23

* Adjusted for age at 60 months, sex, BMI, comorbidities, physical activity, clinic site, ROA either knee, depressive symptoms, catastrophizing, sleep, and fatigue. † Adjusted for age at 60 months, sex, BMI, comorbidities, physical activity, clinic site, and knee pain severity. WSP: widespread pain; ROA: radiographic knee osteoarthritis; CFKP: consistent frequent knee pain; BMI: body mass index.

both WSP and preexisting knee pain[14,15]. Some have alluded to a potential dose-response relationship between number of painful joints and knee pain severity[40,41]. The 1 prior longitudinal study focused on multijoint pain, defined as ≥ 2 joints[16]. Our stricter definition required at least 3 painful joints, in addition to a painful knee joint. Thus, our results, when considered with those of Jinks, *et al*[16], suggest that a dose-response relationship does not exist. While the longitudinal results of our study do not support the idea that WSP is involved in the development of worsening pain, incident pain, or ROA, a previous longitudinal analysis in this cohort has shed some light on the sequential relationships of knee pain and knee OA to WSP, demonstrating that knee pain severity is predictive of the development of WSP[13]. However, when the results of our sensitivity analysis are considered, the notion that the relationship between these variables may be bidirectional in certain circumstances cannot be excluded.

Although we found no association longitudinally, with longer duration of followup, there was a suggestion of increased odds of CFKP. However, comparable sensitivity analyses (i.e., important confounders removed) conducted between 60 and 84 months demonstrated that the confounders attenuated the effect of WSP on CFKP and may explain, in part, why prior cross-sectional studies, which also did not adjust for those factors, were positive. However, our analyses cannot confirm the precise involvement of pain catastrophizing, sleep quality, or fatigue as confounders or mediators. For example, it is possible that WSP could cause any of these variables, which in turn could lead to incident CFKP. Given the 5-year difference in time frames, and the inability to adjust for confounders since study baseline, we cannot rule out the possibility that duration of WSP may have had an effect. We are unaware of any other studies that have prospectively studied the relationship between WSP and incident

ROA. While our findings in this regard were nonsignificant, the direction of the effect estimates suggests that WSP may have a protective effect on the development of ROA. This would support the hypothesis that WSP may lead to lower loads transmitted to the knee, such as through decreased walking speed and/or other strategies used by those with WSP. At this juncture, such interpretation is speculative.

Our study has several strengths and limitations to consider. The prospective design of our investigation in this population provides the first longitudinal evidence, to our knowledge, regarding the association of WSP (defined in a validated manner) on worsening knee pain, incident knee pain, and incident knee ROA. We were able to adjust for important confounders; however, the possibility of residual confounding remains as with any observational study. We did not consider an intermediate stage of regional pain (i.e., those with multi-joint pain, but not meeting the WSP criteria). Because previous work has reported an association of multijoint pain (i.e., ≥ 2 joints) and incident knee pain, we cannot rule out that this association may exist in our cohort and may have diminished our ability to detect a difference relative to those with no other joint pain. Last, our primary analyses considered only a 2-year followup. The influence of WSP on worsening knee pain, incident knee pain, and incident knee ROA may require a longer followup to delineate its influence more clearly, as is suggested by the secondary analyses. However, that no significant influence was observed over a 2-year window suggests a relatively weak effect of WSP on knee OA overall.

We found no association between WSP and worsening knee pain, incident knee pain, or incident knee ROA over 24 months. Our current study suggests that the effect of pain sensitivity associated with WSP itself may not necessarily lead to the worsening or onset of knee pain or knee structural pathology. The results of our sensitivity analyses provide an opportunity for future studies to clarify the involvement of pain catastrophizing, sleep quality, or fatigue as confounders or mediators in this relationship.

REFERENCES

1. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351-8.
2. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. J Rheumatol 2006;33:2271-9.
3. Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172-80.
4. McBeth J, Lacey RJ, Wilkie R. Predictors of new-onset widespread pain in older adults: results from a population-based prospective cohort study in the UK. Arthritis Rheum 2014;66:757-67.
5. White DK, Felson DT, Niu J, Nevitt MC, Lewis CE, Torner JC, et al. Reasons for functional decline despite reductions in knee pain: the Multicenter Osteoarthritis Study. Phys Ther 2011;91:1849-56.
6. Neogi T, Nevitt MC, Yang M, Curtis JR, Torner J, Felson DT. Consistency of knee pain: correlates and association with function. Osteoarthritis Cartilage 2010;18:1250-5.
7. Lacey RJ, Belcher J, Rathod T, Wilkie R, Thomas E, McBeth J. Pain at multiple body sites and health-related quality of life in older adults: results from the North Staffordshire Osteoarthritis Project. Rheumatology 2014;53:2071-9.
8. Kadam UT, Thomas E, Croft PR. Is chronic widespread pain a predictor of all-cause morbidity? A 3 year prospective population based study in family practice. J Rheumatol 2005;32:1341-8.
9. Nitter AK, Forseth KØ. Mortality rate and causes of death in women with self-reported musculoskeletal pain: results from a 17-year follow-up study. Scand J Pain 2013;4:86-92.
10. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10:895-926.
11. Arendt-Nielsen L, Graven-Nielsen T. Translational musculoskeletal pain research. Best Pract Res Clin Rheumatol 2011;25:209-26.
12. Fingleton C, Smart K, Moloney N, Fullen BM, Doody C. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:1043-56.
13. Carlesso LC, Segal N, Curtis JR, Wise BL, Law LF, Nevitt M, et al. Knee pain severity rather than structural damage is a risk factor for incident widespread pain: the Multicenter Osteoarthritis (MOST) study. Arthritis Care Res 2016; Sep 16 (E-pub ahead of print).
14. Schiphof D, Kerkhof HJ, Damen J, de Klerk BM, Hofman A, Koes BW, et al. Factors for pain in patients with different grades of knee osteoarthritis. Arthritis Care Res 2013;65:695-702.
15. Riddle DL, Stratford PW. Knee pain during daily tasks, knee osteoarthritis severity, and widespread pain. Phys Ther 2014;94:490-8.
16. Jinks C, Jordan KP, Blagojevic M, Croft P. Predictors of onset and progression of knee pain in adults living in the community. A prospective study. Rheumatology 2008;47:368-74.
17. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, et al. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis Rheum 2003;48:2916-22.
18. McBeth J, Wilkie R, Bedson J, Chew-Graham C, Lacey RJ. Sleep disturbance and chronic widespread pain. Curr Rheumatol Rep 2015;17:469.
19. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407-17.
20. McBeth J, Nicholl BI, Cordingley L, Davies KA, Macfarlane GJ. Chronic widespread pain predicts physical inactivity: results from the prospective EPIFUND study. Eur J Pain 2010;14:972-9.
21. Urquhart DM, Tobing JF, Hanna FS, Berry P, Wluka AE, Ding C, et al. What is the effect of physical activity on the knee joint? A systematic review. Med Sci Sports Exerc 2011;43:432-42.
22. Felson DT, Niu J, Clancy M, Sack B, Aliabadi P, Zhang Y. Effect of recreational physical activities on the development of knee osteoarthritis in older adults of different weights: the Framingham Study. Arthritis Rheum 2007;57:6-12.
23. Mork PJ, Holtermann A, Nilsen TI. Effect of body mass index and physical exercise on risk of knee and hip osteoarthritis: longitudinal data from the Norwegian HUNT Study. J Epidemiol Community Health 2012;66:678-83.
24. Hart DJ, Doyle DV, Spector TD. Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. Arthritis Rheum 1999;42:17-24.
25. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum 1997;40:728-33.

26. Zeni JA Jr, Higginson JS. Differences in gait parameters between healthy subjects and persons with moderate and severe knee osteoarthritis: a result of altered walking speed? Clin Biomech 2009;24:372-8.

27. Teixeira-Salmela LF, Nadeau S, Milot MH, Gravel D, Requião LF. Effects of cadence on energy generation and absorption at lower extremity joints during gait. Clin Biomech 2008;23:769-78.

28. Purser JL, Golightly YM, Feng Q, Helmick CG, Renner JB, Jordan JM. Association of slower walking speed with incident knee osteoarthritis-related outcomes. Arthritis Care Res 2012;64:1028-35.

29. Eggermont LH, Bean JF, Guralnik JM, Leveille SG. Comparing pain severity versus pain location in the MOBILIZE Boston study: chronic pain and lower extremity function. J Gerontol A Biol Sci Med Sci 2009;64:763-70.

30. Segal NA, Nevitt MC, Gross KD, Hietpas J, Glass NA, Lewis CE, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. PM R 2013;5:647-54.

31. Leveille SG, Zhang Y, McMullen W, Kelly-Hayes M, Felson DT. Sex differences in musculoskeletal pain in older adults. Pain 2005;116:332-8.

32. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.

33. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45:384-91.

34. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494-502.

35. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3 Suppl A:3-70.

36. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.

37. Radloff S. The CES-D scale: a self-report depression scale for research in the general population. Appl Psychol Meas 1977; 1:385-401.

38. Jensen MP, Keefe FJ, Lefebvre JC, Romano JM, Turner JA. One- and two-item measures of pain beliefs and coping strategies. Pain 2003;104:453-69.

39. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46:153-62.

40. Croft P, Jordan K, Jinks C. "Pain elsewhere" and the impact of knee pain in older people. Arthritis Rheum 2005;52:2350-4.

41. Kamaleri Y, Natvig B, Ihlebaek CM, Bruusgaard D. Localized or widespread musculoskeletal pain: does it matter? Pain 2008; 138:41-6.