Knee Pain Predicts Subsequent Shoulder Pain and the Association Is Mediated by Leg Weakness: Longitudinal Observational Data from the Osteoarthritis Initiative

Laura L. Laslett, Petr Otahal, Elizabeth M.A. Hensor, Sarah R. Kingsbury, and Philip G. Conaghan

ABSTRACT. Objective. To assess whether the "spread" of joint pain is related to pain-associated muscle loss in 1 joint leading to increased loading and subsequent pain in other joints.

Methods. Associations between persistent knee pain (pain in 1 or 2 knees over 0–3 years vs no persistent pain) and incident shoulder pain at Year 4 were examined in participants from the longitudinal National Institutes of Health Osteoarthritis Initiative. Associations were assessed using log multinomial modeling, adjusted for age, sex, body mass index, depression score, other lower limb pain, and baseline leg weakness (difficulty standing from a sitting position).

Results. In older adults with clinically significant knee osteoarthritis (OA) or at risk of knee OA (n = 3486), the number of painful joints increased yearly, from 2.1 joints (95% CI 2.0–2.2) at baseline increasing by 5.2% (95% CI 2.2–8.3) at Year 4. Shoulders were the next most commonly affected joints after knees (28.5%). Persistent pain in 1 or 2 knees increased risk of bilateral shoulder pain at Year 4 [1 knee: relative risk (RR) 1.59, 95% CI 0.97–2.61; 2 knees: RR 2.02, 95% CI 1.17–3.49] after adjustment for confounders. Further adjustment for leg weakness attenuated effect sizes (1 knee: RR 1.13, 95% CI 0.60–2.11; 2 knees: RR 1.44, 95% CI 0.75–2.77), indicating mediation by functional leg weakness.

Conclusion. Spread of joint pain is not random. Persistently painful knees predict new bilateral shoulder pain, which is likely mediated by leg weakness, suggesting that biomechanical factors influence the spread of pain. (First Release October 1 2016; J Rheumatol 2016;43:2049–55; doi:10.3899/jrheum.160001)

Key Indexing Terms:
OSTEOARTHRITIS PAIN SHOULDER DISORDERS KNEE BIOMECHANICS

Musculoskeletal pain is common in the community, affecting 45%–66% of adults[1,2,3], with prevalence of pain at most sites increasing with advancing age[1,4]. Knees are among the most commonly reported sites of joint pain in older people[1], perhaps the most common[2,5,6]. While a single joint can be affected, multiple joints are typically involved[2,5,7,8]. The median number of affected joint sites in older adults is reportedly 4[5,6]. People with greater numbers of painful joints

From the Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia; Leeds Institute of Rheumatic and Musculoskeletal Medicine, and UK National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, UK.

L.L. Laslett was funded by an Osteoarthritis Research International Young Investigator Scholarship while at the University of Leeds. She is also supported by an Arthritis Australia – Australian Rheumatology Association Heald Fellowship and a National Health and Medical Research Council Early Career Fellowship (Clinical Research Fellowship; GNT1070586). This study was supported by an Arthritis Research UK project grant (ref 20800), the Arthritis Research UK Experimental Osteoarthritis Treatment Centre (ref 20083), and the NIHR Leeds Musculoskeletal Biomedical Research Unit. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the Department of Health. The Osteoarthritis Initiative (OAI) is a public-private partnership composed of 5 contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the US National Institutes of Health, a branch of the US Department of Health and Human Services and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories, Novartis Pharmaceuticals Corp., GlaxoSmithKline, and Pfizer. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use dataset, and does not necessarily reflect the opinions or views of the OAI investigators, the National Institutes of Health, or the private funding partners.

L.L. Laslett, GDPH, PhD, Postdoctoral Research Fellow, Menzies Institute for Medical Research, University of Tasmania, and Visiting Scholar, Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds; P. Otahal, BSc, GDipSc, Statistician, Menzies Institute for Medical Research, University of Tasmania; E.M. Hensor, PhD, Biostatistician, Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds; S.R. Kingsbury, PhD, Postdoctoral Research Fellow, Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds; P.G. Conaghan, FRACP, FRCP, PhD, Professor of Musculoskeletal Medicine, Leeds Institute of Rheumatic and Musculoskeletal Medicine and NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds.

Address correspondence to Professor P.G. Conaghan, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, Leeds LS7 4SA, UK. E-mail: P.Conaghan@leeds.ac.uk

Accepted for publication July 7, 2016.

report higher levels of pain intensity in the affected joints[9], increased functional difficulty[5], increased likelihood of having more days absent from work because of sickness each year[10], and poorer quality of life both cross-sectionally[11,12] and longitudinally[11,13], equivalent to a dose response for pain.

Within the context of painful joints due to rheumatoid arthritis, the site of the second affected joint is random, as might be expected for a systemic disease affecting all synovial joints[14]. However, there is some evidence that the pattern of involvement of different joints is not random for osteoarthritic pain. Persons having a hip or knee replacement were likely to have a second or subsequent joint replacement of the lower limbs (25%) over 9 years[15]. However, use of joint replacement as an outcome measure is complex because rates of joint replacement are predicted by socioeconomic factors and patient willingness to undergo surgery[16] as well as by somatic factors, such as pain[16,17], severity of radiographic damage, and effusion[17]. Observational data of middle-aged female healthcare workers over 1 year demonstrate that chronic knee pain predicts new chronic low back pain (OR 3.14, 95% CI 1.74–5.70), but not chronic neck/ shoulder pain after adjustment for demographic and work-related factors (OR 1.79, 95% CI 0.88–3.63)[18]. However, that study did not explore how this "spread" of pain might occur.

From multiple clinical observations, we hypothesized that an increase in the number of painful joints is related to pain-associated muscle loss in 1 joint, leading to increased loading and subsequent pain in other joints. For example, in people with knee pain, the commonly related loss of leg muscle strength leads to increased reliance on upper limbs for daily activities, such as getting out of chairs and cars or using stairs (requiring use of rails). If this "biomechanical spread" of joint pain is true, it would provide a critical point for interventions that could prevent the subsequent cascade of painful joints.

Our study, therefore, aimed to assess whether the number of painful joints increases over time, and if so, whether pain in certain joints preceded pain in others. We then aimed to investigate whether knee pain predicted subsequent development of shoulder pain, and if so, to assess our *a priori* hypothesis — to assess whether any such association was mediated by functional leg muscle weakness — in a cohort of older adults with painful knees from the US National Institutes of Health Osteoarthritis Initiative (OAI).

MATERIALS AND METHODS

Study design, setting, and participants. Data used in our research were obtained from the OAI, a publicly available multicenter population-based observational cohort study of people with knee osteoarthritis (OA) or at risk of knee OA (available at www.oai.ucsf.edu). Specific datasets used are detailed in Supplementary Table 1 (available online at jrheum.org). The OAI consists of data on persons aged 45–79 years. We included participants in the Progression subcohort (persons with existing knee OA, n = 1390) and the Incidence subcohort (persons with risk factors for knee OA, n = 3284)[19].

Persons were excluded from entering the OAI if they had inflammatory arthritis, severe joint space narrowing (JSN) in both knees, unilateral knee joint replacement and severe JSN in the contralateral knee, inability to undergo magnetic resonance imaging or to provide a blood sample, required use of walking aids excepting a single straight cane ≤ 50% of the time, or were unwilling to provide informed consent. Patients were recruited at 4 clinical sites, and were assessed yearly. The study was approved by the institutional review boards at each of the sites. All participants gave informed consent.

Exposure: Persistent knee pain. OAI participants were classified as having persistent pain in either 1 or both knees based on data from years 0–3 (Figure 1). Those with persistently sore knees had knee pain, aching, or stiffness on more than half of the days in the past 30 days at baseline and on at least 2 occasions in that same knee over years 1–3 based on data from the Screening Visit Workbook (P01KPR30CV, P01KPL30CV) and Follow-up Visit Interviews in the Joint Symptoms datasets. Participants were defined as not having persistently sore knees if they reported not having knee pain, aching, or stiffness on more than half of the days in the past 30 days at baseline and

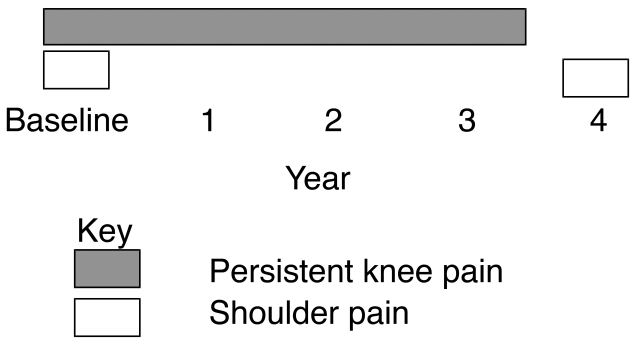

Figure 1. Timing of data points used to determine associations between knee pain and new shoulder pain.

Table 1. Change in total number of joints in the whole OAI cohort (n = 3486) and in those with at least 1 painful joint at each visit (n = 1573) by year. Mean number of affected joints at baseline is 2.1 (2.0–2.2) in the whole cohort and 3.9 (3.8–4.1) among those with ≥ 1 painful joint at each visit. Values are ratio of means* (95% CI) unless otherwise specified.

Time	Whole Cohort, n = 3486			At Least 1 Painful Joint, n = 1573		
	Unadjusted	Adjusted**	p	Unadjusted	Adjusted**	p
Baseline	Reference		—	Reference		—
Yr 1	1.023 (0.994–1.054)	1.024 (0.995–1.055)	0.11	1.033 (0.999–1.069)	1.034 (0.999–1.070)	0.06
Yr 2	1.012 (0.983–1.043)	1.016 (0.986–1.047)	0.29	1.024 (0.989–1.060)	1.026 (0.991–1.062)	0.15
Yr 3	1.030 (1.000–1.061)	1.036 (1.006–1.066)	**0.02**	1.034 (1.000–1.070)	1.039 (1.004–1.075)	**0.03**
Yr 4	1.047 (1.017–1.078)	1.052 (1.022–1.083)	**< 0.001**	1.062 (1.027–1.099)	1.068 (1.032–1.105)	**< 0.001**

* Incident rate ratio. ** Adjusted for age, sex, BMI, and CES-D score. Significant data are in bold face. OAI: Osteoarthritis Initiative; BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale.

also at years 1–3. Study participants who did not meet the criteria for persistent pain in the left, right, or both knees were excluded.

Outcome: Shoulder pain. OAI participants were classified as having shoulder pain or no shoulder pain (defined as shoulder pain, aching, or stiffness for more than half the days in the past 30 days) based on symptoms from the homunculus in the Screening Visit Workbook (P01OJPNLS, P01OJPNRS, P01OJPNNO) and Follow-up Visit Interviews in the Joint Symptoms datasets.

Participants were defined as having prevalent shoulder pain if they had shoulder pain in either 1 or 2 shoulders at baseline, and incident shoulder pain if they had no shoulder pain at baseline, but reported pain in 1 or 2 shoulders at Year 4, which was the last timepoint when data were collected on symptoms from the homunculus.

Assessment of confounders. Data were collected from study participants using standard protocols[19] and from the most up-to-date data sources (Supplementary Table 1, available online at jrheum.org). Data were on demographic confounders; anthropometry [including body mass index (BMI)]; questionnaires [including the Center for Epidemiologic Studies Depression Scale (CES-D), range 0–57]; item 3 of the physical function scale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; version 3.1), which asks the patient, "Think about the difficulty you had in doing the following daily physical activities due to arthritis in your knee. What degree of difficulty do you have rising from sitting?" (no difficulty/mild/moderate/severe/extreme difficulty); and pain (yes/no) at other joints (neck, back, shoulders, elbows, wrists, hands, hips, ankles, feet). Where only 1 knee was painful, data on difficulty rising from sitting were used from the persistently painful knee; otherwise, responses were averaged over 2 knees. Number of painful joints (neck, back, shoulders, elbows, wrists, hands, hips, knees, ankles, feet) was calculated at each visit.

Statistical methods. Changes in the number of joints were assessed using mixed-effects Poisson regression, using an unstructured covariance matrix and adjusting for demographic confounders (age, sex, BMI, and depression score). Comparisons between observed and expected frequencies of painful joint sites were assessed using 1-sample chi-square tests.

Primary hypotheses were tested using all available data on participants who met the entry criteria at baseline. Statistical significance was determined using a p value ≤ 0.05 (2–tailed) and using Stata 12.0 and Stata 13.0. ANOVA was used to compare differences in means.

Associations between persistent knee pain during years 0 to 3 and incident shoulder pain at Year 4 were assessed using log multinomial modeling[20]. Covariates included age, sex, BMI, CES-D (baseline and change at 4 yrs), other lower limb pain (presence/absence of pain in the hips, ankles, or feet), and leg weakness, defined as difficulty standing from a sitting position at baseline (WOMAC function subscale 3). Continuous covariates were centered. Mediation was analyzed by comparison of the confounder-adjusted models with and without the addition of potential mediators.

The number of patients available for our analysis was limited to those who had been recruited to the OAI; therefore, no sample size calculations were performed. Sensitivity analyses were conducted to determine the effect of participant dropout during the study, using inverse probability weighting[21]. Probability of response (inclusion in our study) was estimated from a logistic regression model with independent variables: race, smoking status, comorbidities, and death rates to 4 years.

RESULTS

Change in number of painful joints by year. Patients were selected if they had full covariate data at baseline and joint pain data available at baseline, Year 4, and at least 2 of the intervening years. The number selected was 3486, mean (± SD) age 61 ± 9.0 years, 57% women, BMI 28.6 ± 4.7, median (interquartile range) depression score 4 (2–9). The geometric mean number of painful joints at baseline was 2.1. Number of painful joints increased by 2.4%, 1.6%, 3.6%, and 5.2% at years 1–4, respectively, compared with baseline (Table 1), with effect sizes becoming statistically significant by Year 3. However, our analysis included

Table 2. Distribution of demographic characteristics of participants with OAI by incidence of shoulder pain at Year 4. Baseline data unless otherwise indicated. Values are mean (SD) unless otherwise specified.

Characteristics	Neither Shoulder, n = 1291	One Shoulder, n = 176	Both Shoulders, n = 88	p
No. persistently painful knees, yrs 0–3				**< 0.001**
None	894 (69.2)	104 (59.1)	43 (48.9)	
1 knee*	242 (18.7)	42 (23.9)	24 (27.3)	
Both knees	155 (12.0)	30 (17.0)	21 (23.9)	
Female, %	44.7	41.5	33.0	**0.08**
Age, yrs	61.4 (9.1)	61.6 (9.3)	61.6 (8.6)	0.91
BMI, kg/m^2	28.1 (4.7)	28.6 (5.0)	29.0 (4.9)	0.15
Difficulty standing from sitting**	0.5 (0.77)	0.7 (0.8)	1.0 (1.0)	**< 0.001**
CES-D score	5.3 (5.73)	7.0 (7.26)	6.8 (7.08)	**< 0.001**
Prevalence of hip, ankle, or foot pain, %	29.6	37.5	44.3	**0.006**
Leg used to kick ball				0.35
Right leg	91.3	91.9	92.2	
Left leg	7.3	6.6	5.9	
Both legs	1.3	1.4	2.0	
Change in BMI	0.20 (1.88)	0.10 (1.78)	0.13 (2.23)	0.99
Change in depression score	0.6 (5.62)	0.4 (7.94)	3.1 (7.14)	**< 0.001**

* Averaged over both knees, or for the sore knee if only 1 knee is painful. ** Difficulty standing from sitting is subscale 3 of the WOMAC function scale. Statistical significance is p ≤ 0.05 and in bold face. OAI: Osteoarthritis Initiative; BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

patients who never developed pain or who had intermittent symptoms, with no painful joints at some timepoints; this resulted in patterning in the model deviance residuals. Restricting the analysis to patients with at least 1 painful joint (any joint) at each timepoint (n = 1573) eliminated this issue, and the same pattern of increasing painful joint count was observed. Painful joint count increased from a geometric mean of 3.9 at baseline by 3.4% (–0.1% to 7.0%), 2.6% (–1.0% to 6.2%), 3.9% (0.4% to 7.5%), and 6.8% (3.2% to 10.5%) at years 1–4, respectively, compared with baseline (Table 1).

Does pain in certain joints precede pain in others? To investigate whether the pattern of joint pain development was random or whether some joints were more likely to become painful before others, we focused on patients who had no joint pain at baseline but later went on to develop pain in a single joint type, uni- or bilaterally (n = 448). If the development of joint pain was random, each joint type would be equally likely to be affected (expected frequency for each of the 10 joint types = 10%). In fact, the pattern was nonrandom (chi-square = 213.88, $p < 0.001$) with pain being more likely to develop first in the knee (22.8%), hand (20.5%), or shoulder (14.7%; Figure 2).

We then focused on patients with knee pain at baseline that persisted over 1–4 years, who had no pain in other joint types at baseline but later developed pain in 1 additional joint type, uni- or bilaterally (n = 70). The frequency of subsequent involvement was expected to be 7.8% for the remaining 9 joint types; however, the pattern of joint pain spread was found to be nonrandom, with pain more likely to develop next in the shoulder (28.6%), hand (18.6%), or hip (15.6%, chi-square = 39.29, $p < 0.001$; Figure 3).

Does persistent knee pain predict shoulder pain? Participants with persistent knee pain in 0, 1, or 2 knees and no baseline

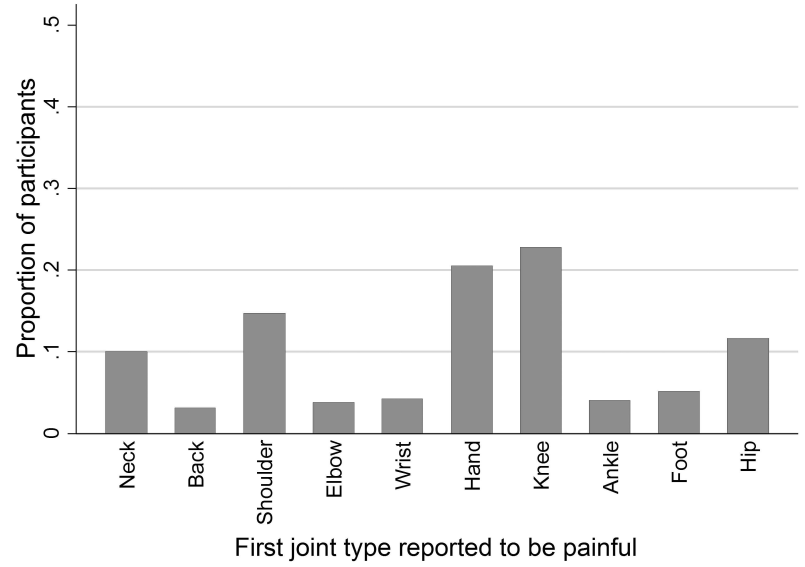

Figure 2. Joint type first reported to be painful in Osteoarthritis Initiative participants with no pain at baseline who later reported pain in a single joint type uni- or bilaterally (n = 448).

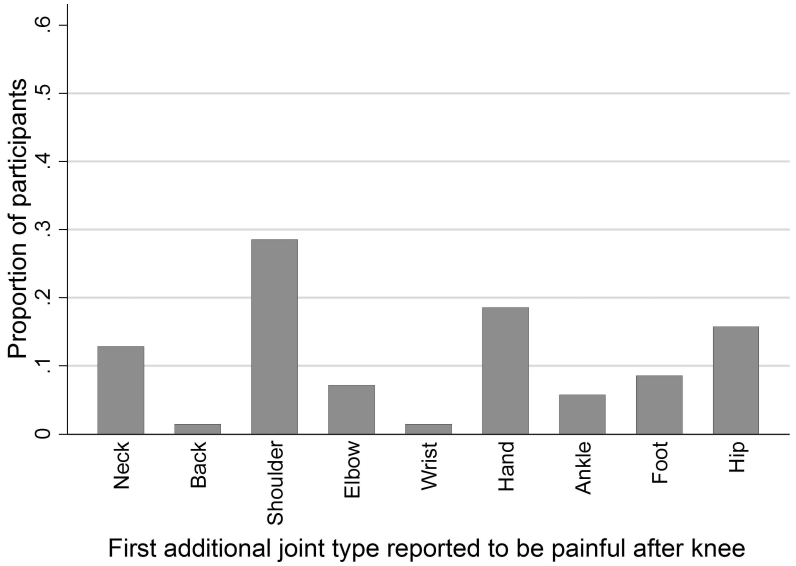

Figure 3. First joint type to subsequently be reported painful in Osteoarthritis Initiative participants with at least 1 painful knee at baseline who later reported pain in a single additional joint type uni- or bilaterally (n = 70).

shoulder pain (n = 1555) were aged 61.4 ± 9.1 years, 56% women, and with a mean BMI of 28.2 ± 4.7. Participants who had more difficulty standing from a seated position, higher depression scores, and pain in additional lower limb joints at baseline were more likely to develop shoulder pain at Year 4 (all $p < 0.001$; Table 2).

Persistent pain in 1 or 2 knees increased the risk of unilateral shoulder pain at Year 4 in univariable associations [1 knee: relative risk (RR) 1.36, 95% CI 0.98–1.91; 2 knees: RR 1.46, 95% CI 0.999–2.13], but while the effect size was similar after adjustment for confounders (Models 2 and 3), associations were no longer statistically significant. Age, sex, and BMI were not statistically significant in the model; therefore, no further analyses were conducted to investigate the potential for effect modification.

Persistent pain in 1 or 2 knees increased risk of bilateral shoulder pain at Year 4 after adjustment for demographic factors (1 knee: RR 1.65, 95% CI 1.01–2.72; 2 knees: RR 2.27, 95% CI 1.34–3.85 in Model 2; Table 3). Associations attenuated slightly after further adjustment for lower limb pain (1 knee: RR 1.59, 95% CI 0.97–2.61; 2 knees: RR 2.02, 95% CI 1.17–3.49 in Model 3; Table 3). Further attenuation of effect sizes in Model 4 indicates that the association between knee pain and the development of shoulder pain was mediated by leg weakness (Model 4). We analyzed this association further by examining the putative causal pathway between baseline knee pain and new shoulder pain at Year 4. Knee pain was associated with increased risk of leg weakness in univariate associations (1 knee: $\beta = 1.16$, 95% CI 1.08–1.24; 2 knees: $\beta = 1.21$, 95% CI 1.11–1.30). In turn, weakness predicts incident shoulder pain (1 shoulder: RR 1.21, 95% CI 1.06–1.36; 2 shoulders: RR 1.46, 95% CI 1.25–1.71 for univariate associations). While these associations could indicate either confounding or mediation, investigations of the association between baseline knee pain and new shoulder pain adjusting only for weakness indicate mediation[22] because weakness is statistically significant in a model including both knee pain and weakness. RR for unilateral pain were as follows: 1 knee: 1.14, $p = 0.52$; 2 knees: 1.16, $p = 0.54$. In this same model, weakness is statistically significant at the $p = 0.1$ level (RR 1.19, $p = 0.09$). RR for new bilateral pain were as follows: 1 knee 1.29, $p = 0.39$, and 2 knees 1.54, $p = 0.18$. Weakness was statistically significant in this same model (RR 1.41, $p = 0.01$; Supplementary Figure 1, available online at jrheum.org).

Sensitivity analyses: Knee pain to shoulder pain. Using inverse probability weighting in the log multinomial regressions demonstrated similar results (Model 2: 1 shoulder, 1 knee: RR 1.29, 95% CI 0.9–1.84; 1 shoulder, 2 knees: RR 1.39, 95% CI 0.92-2.11; 2 shoulders, 1 knee: RR 1.65, 95% CI 0.98–2.77; 2 shoulders, 2 knees: RR 2.14, 95% CI 1.24–3.67), suggesting that missing data had not substantially altered the results.

We varied the leg used to assess difficulty standing from a seated position. Using the data from the non-matched knee gave similar effect sizes to Model 3 for both unilateral and bilateral shoulder pain, suggesting mediation through the weakest leg and most painful knee rather than the contralateral knee.

We further adjusted Model 2 for use of analgesic medications, which were used by 22% of the cohort overall. Use of these medications was not statistically significant for either new unilateral or bilateral pain at Year 4, and did not change effect sizes, suggesting that use of analgesic medications did not affect risk of new shoulder pain in our analyses.

We also ran log multinomial models with an additional predictor term for OAI participants who had intermittent pain (pain on < 3 occasions from years 0–4) in either knee. These participants were not at increased risk of incident shoulder pain in either 1 (RR 1.07, 95% CI 0.81–1.4, $p = 0.63$) or 2 shoulders (RR 1.04, 95% CI 0.81–1.4, $p = 0.86$) after adjustment for demographic factors (Model 2) and after 4 years of observation.

Table 3. Associations between knee pain and incident shoulder pain at Year 4 in OAI participants without baseline shoulder pain. Values are for the painful knee if only 1 sore knee, averaged otherwise.

Variables	Model 1: Univariable, n = 1555		Model 2: Adjusted for Demographic Factors, n = 1521		Model 3: Additionally Adjusted for Lower Limb Pain, n = 1521		Model 4: Additionally Adjusted for Functional Leg Weakness, n = 1520	
	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p	RR (95% CI)	p
Incident unilateral shoulder pain								
1 knee	1.36 (0.98–1.91)	0.069	1.24 (0.87–1.76)	0.232	1.21 (0.85–1.72)	0.288	0.89 (0.57–1.38)	0.594
2 knees	1.46 (0.999–2.13)	**0.050**	1.33 (0.89–1.99)	0.160	1.28 (0.85–1.93)	0.239	0.92 (0.56–1.5)	0.724
Incident bilateral shoulder pain								
1 knee	1.89 (1.16–3.06)	**0.010**	1.65 (1.01–2.72)	**0.046**	1.59 (0.97–2.61)	0.066	1.13 (0.60–2.11)	0.707
2 knees	2.47 (1.50–4.07)	**< 0.001**	2.27 (1.34–3.85)	**0.002**	2.02 (1.17–3.49)	**0.010**	1.44 (0.75–2.77)	0.274

Reference category: pain in neither knee, no incident shoulder pain. Model 2: adjusted for sex, age, BMI, depression score (as assessed by the CES-D scale), change in depression score. Model 3: further adjusted for pain in the hips, ankles, and feet at baseline. Model 4: further adjusted for weakness [difficulty standing from a sitting position at baseline (WOMAC function subscale 3)]. Significant data are in bold face. OAI: Osteoarthritis Initiative; RR: relative risk; BMI: body mass index; CES-D: Center for Epidemiologic Studies Depression Scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

DISCUSSION

Our longitudinal study demonstrated that the average number of painful joints increases over time in people with knee OA or at risk of knee OA in a nonlinear manner. Incidence peaked at the latest timepoint we examined. Spread of joint pain over time was not random, with shoulders being the most common joints to become painful after knee pain in this longitudinal cohort of persons. Persistent pain in 1 knee increased the risk of new bilateral shoulder pain by 127% (RR 2.27) after adjustment for demographic, anthropometric, and psychological confounders. These effects were mediated by functional leg weakness. This confirms that pain spreads from 1 joint site to others over time, and suggests that this spread may be influenced by biomechanical factors associated with loss of functional muscle capability. We hypothesize that this might occur because of the increased reliance on upper limbs for daily activities such as getting out of chairs and cars or using stairs (requiring use of rails) in people who have lost leg muscle strength. This would seem consistent with existing theoretical frameworks, including biomechanical interrelationships[23,24], which might be a consequence of abnormal joint loading[25,26] or altered lifting patterns[18].

We used item number 3 of the WOMAC function scale (difficulty standing from a sitting position) as the measure of lower limb weakness because it is related to functional difficulty for a given individual; this item defines a very important functional capability for everyday living. This was not collinear with knee pain (data not shown), suggesting that it measures aspects of functional difficulties beyond pain. Sensitivity analyses using the functional aspects of the non-painful knee in unilateral knee pain suggest that the mediation is occurring through the weakest leg and most painful knee.

Our findings of spread of joint pain from 1 joint to another are consistent with previous data on spread of chronic pain from 1 region to others[18], although that cohort consisted of women only, had much younger mean age than our cohort, had a time horizon of 1 year, and assessed regional rather than joint-related pain. Our data are also consistent with other reports that demonstrate that spread of pain in osteoarthritic–type cohorts is not random[14]; these are typically measured by joint replacements and include differences between ipsilateral and contralateral pain[14]. While our data show that incident pain in other limbs is not random, we did not observe effects related to the side at which pain occurred (contralateral/ipsilateral; data not shown), even after adjusting for dominant leg.

Strengths of our study include the large sample size of the OAI, the long duration of followup (4 yrs for data on pain at other joints), the relatively low proportion of participants who had dropped out by Year 4 (< 20%), standardized measurement protocols, data collection over 5 different centers across the United States, and the ability to adjust for known demographic/anthropometric[3], psychological, and psychosocial confounders[27,28].

Limitations include the nonrandom design of the sample, which limits generalizability to people with or at risk of developing knee OA (the underlying focus of the OAI), and the yearly frequency of the assessments. More frequent assessments would have provided a more complete understanding of the pattern of joint pain development. Study participants could report new pain in several joints at each followup, hampering our ability to observe shorter time period trends in the data. Additionally, using WOMAC item 3 (inability to rise from a chair) is an imperfect measure of leg weakness. However, other variables measuring similar aspects of weakness (e.g., chair stand time) were not suitable as measures because they did not allow differentiation between limbs. Additionally, we cannot rule out the effect of leg weakness being due to a factor that is collinear with leg weakness.

Spread of joint pain over time is not random, with shoulders the most common painful joint following knees. The association between persistent pain in 1 or 2 knees and incident bilateral shoulder pain is mediated by functional lower limb weakness, suggesting that biomechanical factors influence the spread of pain. Targeted measures aimed at reducing lower limb weakness may reduce the risk of pain developing in upper limb joints among persons with painful knees and reduce the accumulation of multiple site joint pains.

ACKNOWLEDGMENT

We thank the participants and the investigators of the Osteoarthritis Initiative for their much-valued participation in the study.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

REFERENCES

1. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain 2003;102:167-78.
2. Thomas E, Peat G, Harris L, Wilkie R, Croft PR. The prevalence of pain and pain interference in a general population of older adults: cross-sectional findings from the North Staffordshire Osteoarthritis Project (NorStOP). Pain 2004;110:361-8.
3. Zhai G, Blizzard L, Srikanth V, Ding C, Cooley H, Cicuttini F, et al. Correlates of knee pain in older adults: Tasmanian Older Adult Cohort Study. Arthritis Rheum 2006;55:264-71.
4. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis 1998;57:649-55.
5. Keenan AM, Tennant A, Fear J, Emery P, Conaghan PG. Impact of multiple joint problems on daily living tasks in people in the community over age fifty-five. Arthritis Rheum 2006;55:757-64.
6. Raja R, Kingsbury SR, Dube B, Hensor E, Hogg S, Conaghan P. Detailed clinical characteristics of people with chronic multiple-site joint pains and utilization of therapeutic interventions [abstract]. Intern Med J 2014;44:16.

7. Leyland KM, Hart DJ, Javaid MK, Judge A, Kiran A, Soni A, et al. The natural history of radiographic knee osteoarthritis: a fourteen-year population-based cohort study. Arthritis Rheum 2012;64:2243-51.
8. Dawson J, Linsell L, Zondervan K, Rose P, Randall T, Carr A, et al. Epidemiology of hip and knee pain and its impact on overall health status in older adults. Rheumatology 2004;43:497-504.
9. Suri P, Morgenroth DC, Kwoh CK, Bean JF, Kalichman L, Hunter DJ. Low back pain and other musculoskeletal pain comorbidities in individuals with symptomatic osteoarthritis of the knee: data from the osteoarthritis initiative. Arthritis Care Res 2010;62:1715-23.
10. Haukka E, Kaila-Kangas L, Ojajarvi A, Miranda H, Karppinen J, Viikari-Juntura E, et al. Pain in multiple sites and sickness absence trajectories: a prospective study among Finns. Pain 2013; 154:306-12.
11. Laslett LL, Quinn SJ, Winzenberg TM, Sanderson K, Cicuttini F, Jones G. A prospective study of the impact of musculoskeletal pain and radiographic osteoarthritis on health related quality of life in community dwelling older people. BMC Musculoskelet Disord 2012;13:168.
12. Finney A, Healey EL, Lewis M, Ryan P, Dziedzic KS. Multisite peripheral joint pain in the community: prevalence and impact in the North West Midlands, United Kingdom (UK) [abstract]. Ann Rheum Dis 2013;72:A121.
13. Hoogeboom TJ, den Broeder AA, de Bie RA, van den Ende CH. Longitudinal impact of joint pain comorbidity on quality of life and activity levels in knee osteoarthritis: data from the Osteoarthritis Initiative. Rheumatology 2013;52:543-6.
14. Shakoor N, Block JA, Shott S, Case JP. Nonrandom evolution of end-stage osteoarthritis of the lower limbs. Arthritis Rheum 2002;46:3185-9.
15. Gillam MH, Lie SA, Salter A, Furnes O, Graves SE, Havelin LI, et al. The progression of end-stage osteoarthritis: analysis of data from the Australian and Norwegian joint replacement registries using a multi-state model. Osteoarthritis Cartilage 2013;21:405-12.
16. Hawker GA, Guan J, Croxford R, Coyte PC, Glazier RH, Harvey BJ, et al. A prospective population-based study of the predictors of undergoing total joint arthroplasty. Arthritis Rheum 2006; 54:3212-20.
17. Conaghan PG, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, et al. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. Ann Rheum Dis 2010;69:644-7.
18. Andersen LL, Clausen T, Carneiro IG, Holtermann A. Spreading of chronic pain between body regions: prospective cohort study among health care workers. Eur J Pain 2012;16:1437-43.
19. Nevitt MC, Felson DT, Lester G. The osteoarthritis initiative: protocol for the cohort study. [Internet. Accessed July 25, 2016.] Available from: oai.epi-ucsf.org/datarelease/docs/StudyDesign Protocol.pdf
20. Blizzard L, Hosmer DW. The log multinomial regression model for nominal outcomes with more than two attributes. Biom J 2007;49:889-902.
21. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res 2013;22:278-95.
22. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci 2000;1:173-81.
23. Murata Y, Takahashi K, Yamagata M, Hanaoka E, Moriya H. The knee-spine syndrome. Association between lumbar lordosis and extension of the knee. J Bone Joint Surg Br 2003;85:95-9.
24. Tsuji T, Matsuyama Y, Goto M, Yimin Y, Sato K, Hasegawa Y, et al. Knee-spine syndrome: correlation between sacral inclination and patellofemoral joint pain. J Orthop Sci 2002;7:519-23.
25. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986:34-40.
26. Frost HM. Perspectives: a biomechanical model of the pathogenesis of arthroses. Anat Rec 1994;240:19-31.
27. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain 2000;87:325-34.
28. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rheumatol 1999;26:1785-92.