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MULTIPLE NONSPECIFIC SITES OF JOINT PAIN OUTSIDE THE KNEES DEVELOP IN PERSONS WITH KNEE PAIN

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Abstract

Objective—Many persons with knee pain have joint pain outside the knee but despite the impact and high frequency of this pain, its distribution and causes have not been studied. Those studying gait abnormalities have suggested that knee pain causes pain in adjacent joints but pain adaptation strategies are highly individualized.

Methods—We studied persons age 50-79 years with or at high risk of knee osteoarthritis drawn from two community-based cohorts, the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative and followed for 5-7 years. We excluded those with knee pain at baseline and compared those who developed and did not develop knee pain at the first follow-up examination (the index visit). We examined pain on most days at joint regions outside the knee in examinations after the

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index visit. Logistic regression analyses examined the risk of joint specific pain adjusted for age, sex, BMI, depression with sensitivity analyses excluding those with widespread pain.

Results—In the combined cohorts, there were 693 persons with index visit knee pain vs. 2793 without it. 79.6% of those with bilateral and 63.8% of those with unilateral knee pain had pain during follow-up in a joint region outside the knee vs. 49.9% of those without knee pain. An increased risk of pain was present in most extremity joint sites without a predilection for specific sites. Results were unchanged when those with widespread pain were excluded.

Conclusions—Persons with chronic knee pain are at increased risk of pain in multiple joints in no specific pattern.

Keywords

knee pain; cohort study; joint pain

Painful knee osteoarthritis (OA) affects approximately 12% of persons age 55 and over (1) and the figure is roughly double this for chronic knee pain. The vast majority of studies of patients with painful knee OA report on just knees with little attention to other joints that might be symptomatic. As noted by Shakoor et al.,(2) patients with unilateral hip OA are at high risk of developing the same disease in the other hip and the contralateral knee, complications thought to be due to modifications of loading to avoid pain in the affected hip. Kraus et al.(3) reported that pain commonly developed in the ipsilateral ankle in persons with knee OA. While adjacent joints have been hypothesized as most often affected by knee pain,(4) Hodges and Tucker (5) suggest that each person's adaptive response to avoiding joint pain may be unique, making it hard to identify expected patterns of pain.

Compared with those who have few sites of pain outside the knees, those with multiple sites of pain have worse physical function,(6-8) are at risk of needing multiple joint arthroplasties, and are more likely to have buckling and falling.(9, 10) Multiple sites of joint pain could result from altered joint loading subsequent to the development of knee pain, a predisposition to generalized osteoarthritic changes, or from altered central pain processing.(11) We are unaware of any previous comprehensive investigations of the distribution of pain outside the knee.

After confirming that persons with knee pain are more likely to be afflicted with other joint pain than persons without knee pain, we examined the locations of joint pain to determine whether persons with knee pain had a predilection for specific sites of pain, examining sites previously reported to be at high risk in persons with painful knee OA, including the ankle and hip, extending our inquiry even to upper extremity joints. In sensitivity analyses, we removed persons with widespread pain to make sure our findings were not driven primarily by this group. The investigation may provide insights into how to prevent sequelae, disability and costs of chronic knee pain and osteoarthritis.

METHODS

We took advantage of the Multicenter Osteoarthritis (MOST) Study and the Osteoarthritis Initiative (OAI), both large cohort studies of persons with or at risk of knee pain and OA. In both studies, a homunculus was shown to subjects at each examination asking about pain at sites outside the knee (see Figure 1).

MOST Study

The MOST cohort includes persons with or at high risk of symptomatic knee OA recruited from the communities of Birmingham, Alabama and Iowa City, Iowa. 3,026 subjects aged 50-79 at baseline were recruited at baseline with follow-up visits at 30, 60 and 84 months. Eligibility has been detailed elsewhere (http://most.ucsf.edu/studyoverview.asp).

At each visit, subjects were asked about pain or discomfort in or around each knee on most days (defined as at least half of the days of the month). We label this frequent knee pain. They were also shown the homunculus with appendicular joints circled and enlarged images of the hands and feet where additional sites were circled and asked if they had pain or discomfort in any of these joints on most days. At each examination, weight and height were measured, and depressive symptoms were assessed using the CES-D.(12)

The Osteoarthritis Initiative (OAI)

The OAI is a longitudinal cohort study of risk factors for incidence and progression of OA. 4,796 subjects age 45-69 years with or at high risk of symptomatic knee OA were recruited from four sites, Columbus, Ohio; Providence, Rhode Island; Baltimore, Maryland; and Pittsburgh, Pennsylvania. if they did not already have symptomatic OA, they had to have at least one risk factor for its occurrence (13) (for details of eligibility and examinations see http://oai.epi-ucsf.org/datarelease). Each annual clinic visit included questions on frequent knee pain or discomfort, the CES-D and a measurement of height and weight. Furthermore, the same homunculus was shown annually to subjects, although in OAI, this figure left out the hips, which were asked about separately; to assess the hip, we used data from this separate hip pain question which was phrased, “During the past 12 months, have you had pain, aching, or stiffness in your left (right) hip on most days for at least one month?” To be consistent with OAI, we used a similar hip pain specific question in the MOST Study rather than the homunculus.

Defining knee pain and subsets with symptomatic knee OA and knee symptoms without OA

In both studies, subjects were asked about pain in either knee on most days of the past month. If they responded in the affirmative for either knee, we classified them as having pain in that knee.

In both studies, x-rays were acquired using the same technique and were read by the same readers using the same protocol.(14) Radiographic OA (ROA) was present when a knee showed Kellgren and Lawrence grade 2 or greater, which was defined as possible joint space narrowing and definite osteophytosis.(15) Subjects were characterized as having symptomatic knee OA when they had frequent knee pain and a Kellgren and Lawrence grade >=2 on radiograph in that knee. Among those without ROA, those with knee pain were handled differently than those without knee pain because those with knee pain are extremely likely to have MRI features suggestive of OA.(16) We characterized them as having knee pain without OA, but in our analyses, we combined the two groups with knee pain. We were interested in whether there was pain in other joints after the onset (or recurrence) of knee pain. We focused on two groups, those with knee pain vs. those without knee symptoms.

Defining an index visit and index knee pain

To address questions about whether persons with knee pain had pain outside the knee, we excluded subjects with prevalent knee pain at baseline because the coexistence of knee and other joint pain made it impossible to identify the first site of pain. We thereafter focused on persons who either did not have knee pain at either the baseline or first follow-up visit (the comparison group) or those who had knee pain recorded for the first time at the first follow-up examinations in MOST and OAI, which we will label the index visit. We will refer to the latter subjects as having index knee pain and, while they did not report knee pain at baseline, some of them may have had knee pain at some point before the baseline examination and others developed incident knee pain at the index exam. For our purposes, both recurrent knee pain and incident knee pain and their potential consequences are of interest.

Defining sites of articular pain outside the knee

In each study, subjects indicated on the homunculus which joint regions were painful on most days. While subjects with pain outside the knee at the index examination were eligible for the study, we excluded sites of prevalent pain and counted a site as eligible for incident pain in a location only if s/he did not have prevalent pain there at the index exam. We first defined incident pain as development of pain at any of the follow-up visits (starting after the index visit) up to 84-month visit in the MOST Study or 72-month visit in the OAI Study. We then used a stricter definition of incident pain as development of pain at half or more of the follow-up visits. For both approaches, we examined the incidence of pain in joint regions other than the ipsilateral knee. For the two sides of the same joint region (e.g. left and right hip), we considered them as ipsilateral or contralateral to the symptomatic knee at the index visit. Among subjects without incident knee pain, we randomly assigned an index knee. Since pain in the hip region might not represent pain from the hip joint, we subsetted hip pain into that localized to the groin or front of the thigh in which pain likely emanates from the hip joint (17)

Analysis approach

We assessed the frequency and distribution of painful sites in persons with index knee pain and those without it. After describing the frequency of pain in joints outside the knee and because we could not characterize ipsi- or contralateral incident pain in persons with bilateral knee symptoms, persons with pain in both knees at the index visit were excluded (see Figure 2). When we examined the risk of overall joint pain or of lower vs. upper extremity pain, we excluded incident contralateral knee pain from our analysis to equalize the number of eligible joint regions in those with and without knee pain. (i.e., we focused on incident joint symptoms outside the knees). Ultimately, 14 joints (2 each of feet, ankles, hips, hands, wrists, elbows, shoulders) were eligible but for each person, joint regions with prevalent symptoms at the index visit were excluded as incident painful sites and tested as confounders.

To examine whether unilateral index knee pain predisposed to incident pain in specific lower extremity joint regions, we carried out logistic regression for each joint region with the dependent variable incident pain in that region. Age, BMI, sex, depressive symptoms, count of painful joints among the 14 eligible joints at the index visit and the cohort (MOST or OAI) were adjusted in the models. To test whether specific joint regions were at higher risk of pain than others, we performed a logistic regression analysis in which each site within a person was used as an observation, with the dependent variable incident pain at the joint region, and a generalized estimating equation (GEE) method was used to account for the dependence of painful sites within subjects. The logistic regression predictors included index knee pain, joint site, and an interaction term testing incident pain in that joint site vs. the other joints. Other predictors included the covariates listed above. We carried out sensitivity analyses removing persons from the analysis who met ACR criteria for widespread pain (18) defined as axial pain PLUS pain in right and left sided joints PLUS pain in upper and lower extremity joints. Lastly, we assessed whether follow-up data after the index exam were missing completely at random (MCAR) according to Little's test.(19). This chi-square test compares index visit values of key variables between subjects who have follow-up data and those who do not. For this analysis we included all subjects eligible for incident pain at any non-knee joint and evaluated MCAR by the key variables of number of painful joints at the index visit, BMI and depression, while adjusting for study (MOST or OAI), age, sex, and knee pain.

RESULTS

In MOST, 281 persons had index knee pain (of whom 168 had new unilateral pain) vs. 852 persons without knee pain at the index visit (see Figure 2 and Table 1). Those with knee pain were slightly older, more likely to be female, had on average a higher BMI and were more likely to have depressive symptoms than those without pain. In the OAI study, there were 412 subjects with knee pain at the index exam (of whom 241 had unilateral knee pain) and 1,941 who did not have knee pain at that exam. As in MOST, those with symptomatic OA had a higher mean BMI and were more likely to have depressive symptoms than those without pain (Table 1).

In both MOST and OAI, prevalent pain in joint regions outside the knee was common at the index exam. The mean number of joint regions outside the knee that were painful was 2.3/14 in those with knee pain vs. 1.3/14 in those without it ($p<.001$). Those with bilateral knee pain had more painful joint regions (2.9) than persons with unilateral knee pain (1.9). For those with bilateral knee pain, 79.6% percent had pain outside the knee, whereas 63.8% percent of those with unilateral pain had pain elsewhere. Of those with no index visit knee pain, 49.9% had pain elsewhere.

After excluding subjects with widespread pain at the index visit, those with index knee pain still had more sites of pain than those without it ($p<.001$). For those with bilateral knee pain, 65.1% percent had pain outside the knee, whereas 48.0% percent of those with unilateral pain had pain elsewhere. Of those with no index visit knee pain, 39.6% had pain elsewhere.

We then focused on persons developing unilateral knee pain at the index visit vs. those without it. We found an increase in prevalent joint pain in multiple joints in upper and lower extremity sites. We addressed the risk of hip pain in the groin or front of the thigh, which we characterized as hip joint pain. Among those with incident knee pain, we found an increased risk of ipsilateral (aOR = 2.3 (1.7, 3.0)) but not contralateral (aOR 1.2 (0.9, 1.6)) prevalent hip joint pain.

Of 1137 subjects with index visit knee pain in MOST, 1020 (89.7%) attended at least one subsequent examination and provided information on pain outside the knee. In OAI, of 2280 subjects, 2182 (95.7%) had follow-up data. Those lost to follow-up were not different from those with follow-up on sex, race, BMI, or depressive symptoms but in both studies those lost were more likely to be older than those who had follow-up. The longest possible follow-up for MOST was 54 months and for OAI, it was 60 months after the index visit.

After excluding prevalent sites of pain, we then addressed the location of new onset joint pain at follow-up in persons with and without knee pain at the index visit. The knee pain group more often developed new onset pain in other previously pain-free joint regions than the group without index knee pain. Persons with knee pain had an average of 2.6 joints with new onset pain out of 12.1 eligible joints vs. 2.0/12.7 eligible joints for those without knee pain (adjusted odds ratio 1.3 (95%CI 1.2, 1.4)) (Table 2). For incident pain in at least half the follow-up visits, those with knee pain had an average of 1.6/12.1 eligible joints with new onset pain compared with 1.0/12.7 eligible joints in those without knee pain (adjusted odds ratio 1.4 (95% CI 1.2,1.5)) (Table 3).

Compared with persons without knee pain, new onset pain in joints outside the knee increased in the group with knee pain for most ipsilateral and contralateral joints. This was true for incident joint region pain at any follow-up examination (Table 2) and for joint region pain occurring in at least half of the later examinations (Table 3). The exceptions were pain in the wrists and hands and in the legs; exceptions were the ipsilateral hip and contralateral ankle and foot. There was no clear-cut predilection for pain in any specific lower extremity joint region. When we divided the index knee pain group into those with ROA and those without ROA, findings were similar.

We found that those with knee pain had similar risk of new onset hip pain localized to the groin or front of the thigh at any visit in both ipsilateral side (adjusted OR 1.1 (95% CI 0.8, 1.5)) and contralateral (adjusted OR = 1.2 (0.9, 1.6)). The findings were similar for pain occurring during at least half the follow-up visits (Table 3).

When we added interaction terms testing whether any specific site was at increased risk in those with unilateral index knee pain (in both the analyses of any pain during follow-up and pain in at least half the exams of follow-up), we found no significant interactions, suggesting that even though most sites showed a significantly higher probably of pain in those with knee pain, no specific site was at increased risk compared with other sites.

When we excluded persons with widespread pain at the index visit, our results were unchanged. There were no specific joint sites of pain in this group.

Little's test had a chi-square test statistic of 8.0 on 7 degrees of freedom and was non-significant (p=0.34), indicating that subjects without follow-up were not substantially different from subjects with follow-up. To underscore this result, the mean number of non-knee painful sites was 1.3 for those with follow-up and 1.5 for subjects without, and the median was 1 in both groups.

DISCUSSION

In this first investigation of the association of knee pain with pain in multiple other sites, we confirmed that those with painful knees were more likely to have multiple other sites of joint pain than persons without knee pain. More importantly, our results suggest that there was a modest increase in risk of pain for most joints, with no site-specific risks.

As to why persons with knee OA have multiple sites of pain, Farquhar and colleagues (4) suggested that impairments in other lower extremity joints occur in those with chronic knee pain as a consequence of gait modifications made by those with painful knees and these modifications gradually cause damage to other joints. These authors contend that this damage leaves patients disabled even after a TKR ‘cures’ their originally affected knee. Indeed, Mundermann et al (20) noted that, given gait alterations in severe knee OA, adjacent hips and ankles are likely to be damaged. Interestingly Gillam et al,(21) in a large-scale follow-up of knee replacement subjects in Australia and Norway did not find a consistent predilection for ipsi- vs. contralateral later hip replacements. Since damage to other joints is likely cumulative, evidence that these account for multi-joint pain in those with knee OA would constitute a powerful argument for early treatment of knee OA to prevent this damage. Our results do not necessarily support the argument that in persons with knee pain, aberrant loading by altered movement patterns induces pain in only nearby joints.

Our findings suggest that the sites affected are more than just hip and ankle and that there is no special predilection for pain in these locations. Hodges and Tucker (5) suggest that pain adaptation strategies (e.g. avoiding knee pain by changing loading across the painful knee) are unique to each individual. As they note, “rather than a stereotypical change that is the same in all conditions... the nervous system has a range of options to achieve the goal of protection” (from pain). One person with knee pain may increase loading of the contralateral hip, whereas another uses their arms to partly weight bear to arise from a chair and climb stairs.”

Obviously, there are other potential explanations for the co-occurrence of multiple sites of musculoskeletal pain in persons with painful knee OA. While this study cannot differentiate specific underlying mechanisms, this finding supports either a predilection for osteoarthritic changes at multiple joint sites and/or raises the possibility that nervous system driven pain sensitization increases the risk not only of widespread pain but even of regional pain. Since symptomatic OA is unusual in some of these painful sites (e.g. elbow, shoulder, ankle), pain sensitization would seem a more likely explanation. Central sensitization is a proven feature of advanced OA.(22, 23) During OA pain, the entire nociceptive system is sensitized and thresholds for pain drop throughout the body, making it likely that articular stimuli that would usually not be painful, become so. It is also possible that pain adaptation strategies cited above cause excessive loading to an area outside the knee and this area becomes painful in part from sensitization. Widespread pain may be the extreme end of a continuum of pain sensitization, and our findings persisted unchanged even when we excluded those with widespread pain.(24)

Since the phenomenon of multiple musculoskeletal comorbidities is disabling and potentially preventable, it is important to investigate causes so as to develop preventive strategies. Prevention opportunities might exist if those with knee pain alone can be identified at an early point in their disease.

We do not contend that the reports of pain in each of these joint regions represent arthritis in that region. For example, hip pain may be frequently due to trochanteric bursitis. Whether reported pain is due to arthritis or another source of musculoskeletal pain is not critical, as pain is the primary source of loss of function and disability.(25)

There are important limitations to our work. First, we cannot be sure that what we labeled as incident joint pain in fact is new onset. Joint pains wax and wane, and it is possible that our 'incident sites of pain' represent pain recurrence in some cases. The clinical and functional effect is the same even if 'new sites' of pain occasionally are recurrences. Also most subjects in our study had multiple sites of pain both at baseline and at the index visit; identifying a subcohort without any sites of pain outside the knee left us too few subjects to carry out these analyses. This latter limitation speaks to the high prevalence of multiple joint pains in older adult cohorts. Also, aberrant loading was not examined in subjects so that our explanations regarding loading are speculative. We also note that at the index exam persons with knee pain already had more sites of pain outside the knee than persons without it, so that they had less of a chance to develop pain in multiple sites. We note that, for individual pain sites we examined only sites that were not painful at the index exam Lastly, because we could not determine ipsi- vs. contralateral pain sites, we did not examine the distribution of pain in those with bilateral knee pain at the index visit.

In conclusion, persons with frequently painful knees often develop pain in joints outside the knee. The specific joint regions at increased risk likely vary by person. The heightened risk of pain likely occurs for many reasons including pain avoidance, pain sensitivity and generalized osteoarthritis.

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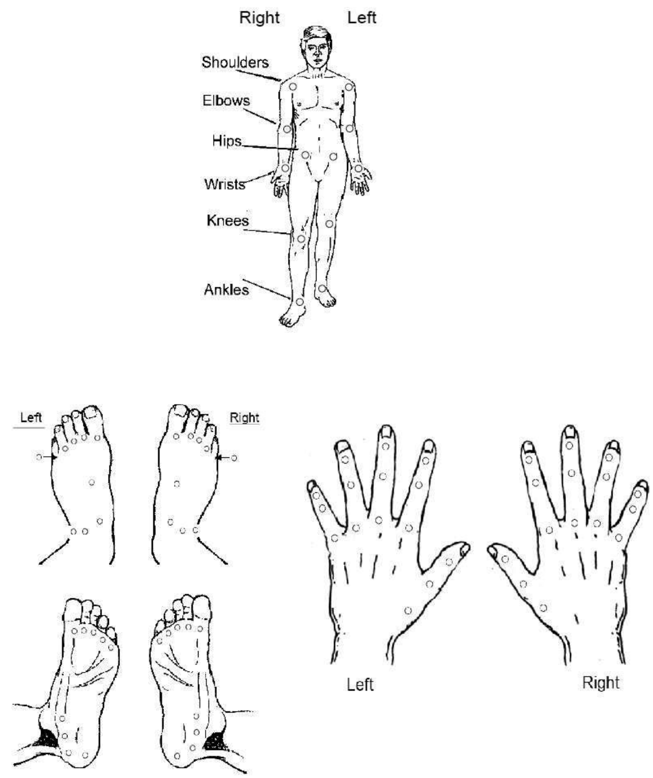

FIGURE 1.
Homunculus

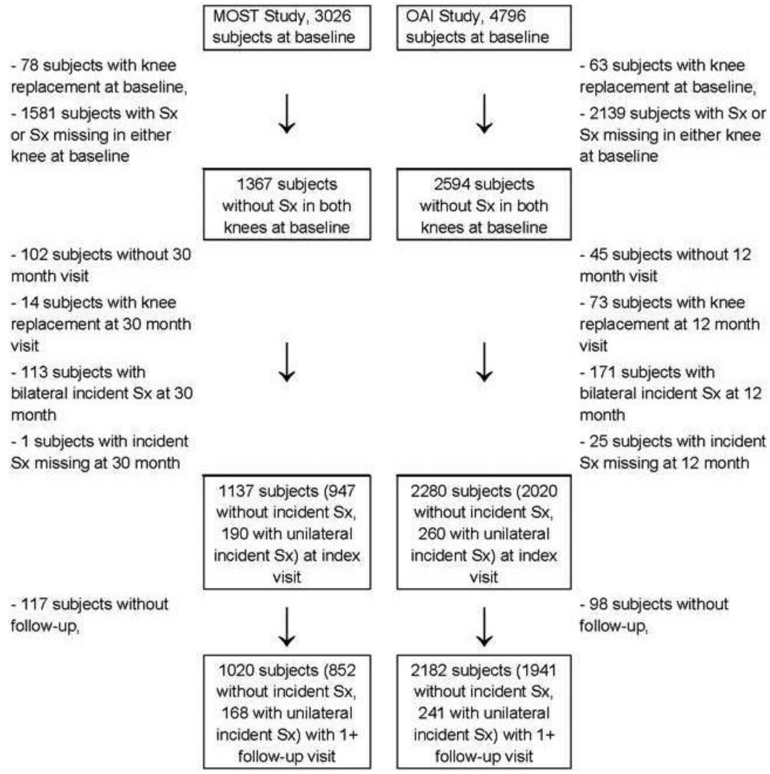

FIGURE 2.
Flowchart

TABLE 1

Characteristics of subjects studied from MOST and OAI at the index visit

	MOST Study		OAI Study	
	No incident knee pain#	**Unilateral incident knee pain#**	**No incident knee pain#**	**Unilateral incident knee pain#**
	N=852	**N=168**	**N=1941**	**N=241**
Age [Mean (SD)]W	64.3 (7.8)	65.6 (8.2)	62.2 (9.2)	62.6 (8.9)
Female	446 (52.4%)	105 (62.5%)	1124 (57.9%)	145 (60.2%)
BMI [Mean (SD)]	29.7 (5.1)	30.1 (5.2)	27.7 (4.7)	29.2 (4.9)
CES-D: Depressive Symptoms	71 (8.3%)	20 (11.9%)	135 (7.0%)	29 (12.1%)
Race, White	756 (88.7%)	138 (82.1%)	1692 (87.2%)	193 (80.1%)
Black	86 (10.1%)	25 (14.9%)	208 (10.7%)	41 (17.0%)
Other	10 (1.2%)	5 (3.0%)	22 (1.1%)	7 (2.9%)

*Depressive symptoms were defined as present when CES-D score was >=16 out of 20.(12)

#Those with no incident knee pain at the index visit also had no knee pain at baseline. Those with unilateral incident knee pain had no knee pain at baseline and reported it for the frst time at the index visit.

Table 2

Risk of incident pain in each joint region according to whether subject had incident unilateral knee pain: pain in any follow-up visit

Joint	Incident knee pain	Incident joint pain on ipsilateral side: Incident joint pain n/N(%)	Incident joint pain on ipsilateral side: Adjusted model[a] OR (95% CI)	Incident joint pain on contralateral side: Incident joint pain n/N(%)	Incident joint pain on contralateral side: Adjusted model[a] OR (95% CI)
Shoulder	None	483/2452 (19.7)	1.0	522/2485 (21.0)	1.0
	Unilateral	93/344 (27.0)	1.4 (1.1, 1.8)	101/346 (29.2)	1.4 (1.1, 1.9)
Elbow	None	190/2694 (7.1)	1.0	184/2684 (6.9)	1.0
	Unilateral	46/384 (12.0)	1.7 (1.2, 2.4)	42/385 (10.9)	1.6 (1.1, 2.4)
Wrist	None	264/2633 (10.0)	1.0	249/2621 (9.5)	1.0
	Unilateral	47/359 (13.1)	1.2 (0.8, 1.7)	53/378 (14.0)	1.2 (0.9, 1.7)
Hand	None	562/2318 (24.2)	1.0	552/2322 (23.8)	1.0
	Unilateral	92/312 (29.5)	1.2 (0.9, 1.5)	95/320 (29.7)	1.2 (0.9, 1.6)
Hip	None	527/2451 (21.5)	1.0	514/2423 (21.2)	1.0
	Unilateral	84/314 (26.8)	1.2 (0.9, 1.6)	95/338 (28.1)	1.2 (0.9, 1.6)
Hip pain in groin/front thigh	None	524/2501 (21.0)	1.0	500/2469 (20.3)	1.0
	Unilateral	77/321 (24.0)	1.1 (0.8, 1.5)	93/352 (26.4)	1.2 (0.9, 1.6)
Knee	None	n/a	n/a	745/2793 (26.7)	1.0
	Unilateral	n/a	n/a	163/409 (39.9)	1.6 (1.3, 2.0)
Ankle	None	280/2639 (10.6)	1.0	295/2635 (11.2)	1.0
	Unilateral	58/362 (16.0)	1.4 (1.0, 1.9)	58/375 (15.5)	1.2 (0.9, 1.6)
Foot	None	408/2616 (15.6)	1.0	414/2609 (15.9)	1.0
	Unilateral	93/356 (26.1)	1.5 (1.2, 2.0)	92/366 (25.1)	1.4 (1.0, 1.8)
Upper limb joints[b]	None	3006/20209 (14.9)	1.0		
	Unilateral	569/2828 (20.1)	1.3 (1.2, 1.6)		
Lower limb joints, excluding knees[b]	None	2438/15373 (15.9)	1.0		
	Unilateral	480/2111 (22.7)	1.3 (1.2, 1.5)		
Upper/lower limb joints excluding knees[b]	None	5444/35582 (15.3)	1.0		
	Unilateral	1049/4939 (21.2)	1.3 (1.2, 1.4)		

[a]Adjusting for age, gender, BMI, depression at the index visit, study and count of painful upper and lower limb joints at the index visit (excluding knees)

[b]Correlation among joints in a subject was controlled using generalized estimating equation

Table 3

Risk of incident pain in each joint region according to whether subject had incident unilateral knee pain: pain in at least half of follow-up visits

Joint		Incident joint pain on ipsilateral side		Incident joint pain on contralateral side	
	Incident knee pain	**Incident joint pain n/N(%)**	**Adjusted model[a] OR (95% CI)**	**Incident joint pain n/N(%)**	**Adjusted model[a] OR (95% CI)**
Shoulder	None	234/2452 (9.5)	1.0	267/2485 (10.7)	1.0
	Unilateral	57/344 (16.6)	1.5 (1.1, 2.1)	64/346 (18.5)	1.5 (1.1, 2.1)
Elbow	None	63/2694 (2.3)	1.0	67/2684 (2.5)	1.0
	Unilateral	23/384 (6.0)	2.1 (1.3, 3.6)	20/385 (5.2)	1.7 (1.0, 3.0)
Wrist	None	141/2633 (5.4)	1.0	126/2621 (4.8)	1.0
	Unilateral	27/359 (7.5)	1.1 (0.7, 1.7)	35/378 (9.3)	1.4 (0.9, 2.1)
Hand	None	313/2318 (13.5)	1.0	300/2322 (12.9)	1.0
	Unilateral	61/312 (19.6)	1.2 (0.9, 1.7)	62/320 (19.4)	1.3 (0.9, 1.7)
Hip	None	263/2451 (10.7)	1.0	256/2423 (10.6)	1.0
	Unilateral	44/314 (14.0)	1.1 (0.8, 1.6)	57/338 (16.9)	1.3 (1.0, 1.9)
Hip pain in Groin/front thigh	None	260/2501 (10.4)	1.0	242/2469 (9.8)	1.0
	Unilateral	37/321 (11.5)	0.9 (0.6, 1.4)	55/352 (15.6)	1.3 (1.0, 1.9)
Knee	None	n/a	n/a	426/2793 (15.3)	1.0
	Unilateral	n/a	n/a	108/409 (26.4)	1.6 (1.2, 2.0)
Ankle	None	135/2639 (5.1)	1.0	149/2635 (5.7)	1.0
	Unilateral	36/362 (9.9)	1.6 (1.0, 2.3)	40/375 (10.7)	1.4 (0.9, 2.0)
Foot	None	262/2616 (10.0)	1.0	275/2609 (10.5)	1.0
	Unilateral	69/356 (19.4)	1.6 (1.2, 2.3)	66/366 (18.0)	1.2 (0.9, 1.7)
Upper limb joints[b]	None	1511/20209 (7.5)	1.0		
	Unilateral	349/2828 (12.3)	1.4 (1.2, 1.7)		
Lower limb joints, excluding knees[b]	None	1340/15373 (8.7)	1.0		
	Unilateral	312/2111 (14.8)	1.3 (1.2, 1.5)		
Upper/lower limb joints excluding knees[b]	None	2851/35582 (8.0)	1.0		
	Unilateral	661/4939 (13.4)	1.4 (1.2, 1.5)		

[a]Adjusting for age, gender, BMI, depression at the index visit, study and count of painful upper and lower limb joints at the index visit (excluding knees)

[b]Correlation among joints in a subject was controlled using generalized estimating equation