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Laslett, LL, Otahal, P, Hensor, EMA et al. (2 more authors) (2016) Knee Pain Predicts Subsequent Shoulder Pain and the Association Is Mediated by Leg Weakness: Longitudinal Observational Data from the Osteoarthritis Initiative. Journal of Rheumatology, 43 (11). pp. 2049-2055. ISSN 0315-162X

https://doi.org/10.3899/jrheum.160001

UNDERSTANDING THE BIOMECHANICAL 'SPREAD' OF JOINT PAIN – KNEE PAIN PREDICTS SUBSEQUENT SHOULDER PAIN, AND THE ASSOCIATION IS MEDIATED BY LEG WEAKNESS: LONGITUDINAL OBSERVATIONAL DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Abstract

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

Methods: Associations between persistent knee pain (pain in one or two knees over years 0-3 versus no persistent pain) and incident shoulder pain at year 4 were examined in participants from the longitudinal NIH Osteoarthritis Initiative (OAI). Associations were assessed using log multinomial modelling, adjusted for age, sex, BMI, depression score, other lower limb pain and baseline leg weakness (difficulty standing from a sitting position).

Results: In older adults with clinically significant knee 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 joint after knees (28.5%). Persistent pain in 1 or 2 knees increased risk of bilateral shoulder pain at year 4 (1 knee RR 1.59 (95% CI 0.97, 2.61); 2 knees RR 2.02 (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 (0.75, 2.77)), indicating mediation by functional leg weakness.

Conclusions: 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.

Key words: Osteoarthritis; Pain, Shoulder Disorders, Knee, Biomechanics

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LLL was funded by an OARSI Young Investigator Scholarship whilst 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).

SRK, EMAH and PGC are funded in part by the Arthritis Research UK Experimental Osteoarthritis Treatment Centre (Ref 20083) and the NIHR Leeds Musculoskeletal Biomedical Research Unit. This article/paper/report presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

The OAI is a public–private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

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Number of Words/Characters in abstract: 239

Article word count: ~2850

Short running footline: Knee pain predicts shoulder pain

Introduction

Musculoskeletal pain is common in the community, affecting 45-66% of adults[1-3], with prevalence of pain at most sites increasing with advancing age[1, 4]. Knees are amongst the most commonly reported sites of joint pain in older people[1], perhaps the most common[2, 5, 6]. Whilst a single joint can be affected, typically multiple joints are involved[2, 5, 7, 8]. The median number of affected joint sites in older adults is reportedly four[5, 6]. People with greater numbers of painful joints report higher levels of pain intensity in the affected joints[9], increased functional difficulty[5], increased likelihood of having more days absent from work due to 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, as 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 health care workers over one year demonstrates 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 any mechanisms as to how this 'spread' of pain might occur.

From multiple clinical observations, we hypothesised that increasing numbers of painful joints is related to pain-associated muscle loss in one 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 precedes pain in others. We then aimed to investigate whether knee pain predicts subsequent development of shoulder pain, and if so, to assess our a priori hypothesis, to assess whether any such association is mediated by functional leg muscle weakness, in a cohort of older adults with painful knees from the NIH Osteoarthritis Initiative (OAI).

Methods

Study design, setting and participants

Data used in this research were obtained from the OAI, a publicly available multi-centre population-based observational cohort study of people with knee OA or at risk of knee OA, available for public access at http://www.oai.ucsf.edu/. Specific datasets used are detailed in Supplementary Table 1. The OAI comprises data on persons aged 45-79 years. We included participants in the Progression sub-cohort (persons with existing knee OA; n=1,390), and the Incidence sub-cohort (persons with risk factors for knee OA; n=3,284)[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 MRI, 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 four 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 neither, one 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 two 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 also at years 1–3. Study participants who did not meet criteria for persistent pain in neither, 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 neither, one, or two shoulders at baseline; and incident shoulder pain if they had no shoulder pain at baseline, but reported pain in one or two shoulders at year 4, which was the last time point where data was collected on symptoms from the homunculus.

Assessment of confounders

Data on demographic confounders, anthropometry (including body mass index), 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), were collected from study participants using standard protocols[19] and from the most up–to–date data sources (see Appendix (**Error! Reference source not found.**)). Where only one knee was painful, data on difficulty rising from sitting was used from the persistently painful knee; otherwise responses were averaged over two 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 one-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 (two–tailed) and using Stata 12.0 and Stata 13.0. Analysis of variance was used to compare differences in means.

Associations between persistent knee pain during years zero to three and incident shoulder pain at year 4 were assessed using log multinomial modelling[20]. Covariates included age, sex, BMI, and CES-D depression score (baseline and change at 4 years), 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 centred. Mediation was explored by comparison of the confounder-adjusted models with and without the addition of potential mediators.

The number of patients available for this analysis was limited to those who had been recruited to the OAI; therefore, no sample size calculations were performed. Sensitivity analyses were conducted in order to determine the effect of participant drop out during the study, using inverse probability weighting[21]. Probability of response (inclusion in the 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; n=3486, mean (± standard deviation) age 61±9.0, 57% female, BMI 28.6±4.7, median (1st quartile, 3rd quartile) 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 compared to baseline (**Error! Reference source not found.**), with effect sizes becoming statistically significant by year 3. However, this analysis included patients who never developed pain or who had intermittent symptoms, with no painful joints at some time-points; this resulted in patterning in the model deviance residuals. Restricting the analysis to patients with at least one painful joint (any joint) at each time-point (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%, 7.0%), 2.6% (-1.0%, 6.2%), 3.9% (0.4%, 7.5%) and 6.8% (3.2%, 10.5%) at years 1-4, compared to baseline (**Error! Reference source not found.**).

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 focussed 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 were 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 non-random (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 focussed 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 one 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 non-random, 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 shoulder pain (n=1555) were aged 61.4±9.1, years, 56% female, mean BMI 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) (**Error! Reference source not found.**).

Persistent pain in 1 or 2 knees increased the risk of unilateral shoulder pain at year 4 in univariable associations (1 knee 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 (RR 1.65 (95% CI 1.01, 2.72); RR 2.27 (1.34,

3.85) – model 2: **Error! Reference source not found.**). Associations attenuated slightly after further adjustment for lower limb pain (RR 1.59 (95% CI 0.97, 2.61); RR 2.02 (1.17, 3.49) – model 3: **Error! Reference source not found.**). 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 explored this association further by examining the putative causal pathway between baseline knee pain and new shoulder pain at year 4. Knee pain is associated with increased risk of leg weakness in univariate associations (1 knee: β=1.16; 95% CI 1.08, 1.24; 2 knees: β=1.21; 1.11, 1.30). In turn, weakness predicts incident shoulder pain (1 shoulder: relative risk (RR) 1.21; 1.06, 1.36; 2 shoulders: RR 1.46, 1.25,1.71: 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], as weakness is statistically significant in a model including both knee pain and weakness. Relative risks for unilateral pain are as follows: 1 knee RR 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). Relative risks for new bilateral pain are as follows: 1 knee RR 1.29, p=0.39; 2 knees RR 1.54, p=0.18. Weakness is statistically significant in this same model (RR 1.41, p=0.01) (See supplementary figure).

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 1.29 (95% CI 0.9, 1.84); 1 shoulder 2 knees 1.39 (0.92, 2.11); 2 shoulder, 1 knee RR 1.65 (0.98, 2.77); 2 shoulder 2 knees RR 2.14 (1.24, 3.67), suggesting that missing data has 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 gives 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 does 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 one (RR 1.07; 95% CI 0.81 to 1.4, p=0.63) or two shoulders (RR 1.04; 95% CI 0.81 to 1.4, p=0.86) after adjustment for demographic factors (Model 2) and after 4 years of observation.

Discussion

This 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 non-linear manner. Incidence peaked at the latest time point we examined. Spread of joint pain over time was not random, with shoulders the most common joint to become painful knees, in this longitudinal cohort of persons. Persistent pain in one 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 one 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 hypothesise that this might occur due to 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 as 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

suggests that the mediation is occurring through the weakest leg and most painful knee.

Our findings of spread of joint pain from one joint to another, is consistent with previous data on spread of chronic pain from one region to others[18], although that cohort consisted of females 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 is also consistent with other reports which 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 shows 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 this study include the large sample size of the OAI, the long duration of follow up (4 years for data on pain at other joints), the relatively low proportion of participants who had dropped out by year 4 (less than 20%), standardised measurement protocols, data collection over five different centres across the U.S., and the ability to adjust for known demographic / anthropometric[3], and psychological and psychosocial confounders[27, 28].

Limitations include the non–random nature of the sample, which limits generalizability to people with or at risk of developing knee OA, which is 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 follow up, 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 (eg chair stand time) were not suitable as measures as 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.

In conclusion, spread of joint pain over time is not random, with shoulders the most common painful joint following knees. The association between persistent pain in one or two knees and incident bilateral shoulder pain is mediated by functional lower limb weakness, suggesting 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 amongst persons with painful knees and reduce the accumulation of multiple site joint pains.

Acknowledgments

We thank the participants and the investigators of the OAI for their much valued participation in the study.

This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners

Ethics approval Committee on Human Research, University of California, San Francisco (IRB approval number 10-00532).

Competing interests

None of the authors have competing interests to declare.

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Figure Legends

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

Figure 2: Joint type first reported to be painful in OAI 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 OAI participants with at least one painful knee at baseline who later reported pain in a single additional joint type uni- or bilaterally (n=70)