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Shoulder Symptom Trajectories Over Four Years: Data From a Longitudinal Study on Osteoarthritis

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Objective. Limited data exist on the natural history of shoulder symptoms. We aimed to describe longitudinal patterns of shoulder symptoms and determine risk factors for incidence and persistence.

Methods. Data from Osteoarthritis Initiative participants observed annually for four years were used to describe shoulder symptom (yes/no, side) incidence and prevalence using descriptive analyses. Regression analyses investigated the association among three shoulder symptoms outcomes (persistent, incident, and intermittent) and clinical factors. Latent class growth analysis (LCGA) identified trajectories in those reporting pain at one or more time point.

Results. In total, 4,796 participants (58% women, mean age 61.2 years) were included. Baseline shoulder symptom prevalence was 22%; 32% of these reported bilateral symptoms. In those reporting right symptoms, 260 of 1,886 (14%) had persistent symptoms. Those with persistent symptoms had worse baseline and four-year clinical status (poorer function, mental health, and quality of life). In regression analysis, persistent symptoms were associated with sleep disturbance (adjusted odds ratio [aOR] 1.97, 95% confidence interval [95% CI] 1.49–2.62), work absenteeism (aOR 2.16, 95% CI 1.38–2.62), lower limb weakness (aOR 1.76, 95% CI 1.37–2.27), multiple-site joint symptoms (≥3 joints excluding shoulders) (aOR 4.90, 95% CI 2.79–8.58) and White race (aOR 1.39, 95% CI 1.04–1.88). Lower limb weakness was also associated with incident symptoms; no variables were associated with intermittent symptoms. LCGA identified two trajectories: the trajectory with high probability for symptoms (9% of LCGA analysis cohort) showed similar relationships to clinical variables as in the persistent symptoms group.

Conclusion. In this large, four-year study, persistent shoulder symptoms were common and associated with worse clinical outcomes. At least one risk factor for incident symptoms is modifiable.

INTRODUCTION

Shoulder symptoms (pain and functional impairment) are one of the most common musculoskeletal complaints worldwide, with a lifetime prevalence of 6.7%.[1] Causes of shoulder symptoms include rotator cuff disease, osteoarthritis, and adhesive capsulitis. Importantly for our aging society, shoulder symptoms increase with age. They are associated with significant morbidity, with a large socio-economic burden. In the United Kingdom, shoulder-related health costs are estimated to be £345 million.[2] There are very limited data on the long-term natural history of shoulder symptoms. A survey of 125 primary care patients in the United Kingdom showed that 50% of people continued to have symptoms at 18 months, although 43% of patients were lost to follow-up.[3]

The treatment of shoulder symptoms remains limited and includes glucocorticoid injections, physiotherapy, or surgery. However, current treatments have not been shown to improve the long-term outcomes of shoulder symptoms. Steroid injections alone or in combination with physiotherapy do not improve six-month outcomes in shoulder symptoms compared to physiotherapy alone, although they may improve short-term

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SIGNIFICANCE & INNOVATIONS

- This is the largest and longest study of shoulder symptoms with regular follow-up.
- The study demonstrated that persistent symptoms were associated with sleep disturbance, work absenteeism, lower limb weakness, multiple-site joint symptoms, and White race.
- We found lower limb weakness was associated with incident symptoms, highlighting a potential modifiable risk factor.

outcomes.[4] Physiotherapy may provide improvements, although longer-term benefits are uncertain.[5] The number of UK shoulder and arm operations has almost doubled to more than 66,000 in the past decade, although this may relate to traumatic causes and conditions affecting joints and tissues other than the shoulder.[6] However, despite this increase, shoulder surgery for subacromial shoulder symptoms has not been shown to provide benefit.[7] A recent study has shown that knee pain may predict incident shoulder pain at four years, mediated by leg weakness[8] and presumably related to consequent reliance on upper limbs or shoulders when getting out of chairs, climbing stairs, or similar activities. This suggests that lower limb functional impairment may play a role in development of shoulder pain.[9]

To develop treatment for patients with shoulder symptoms, especially if early intervention is to be considered, the identification of poor prognostic groups is needed. This study aimed to describe shoulder symptoms and their trajectories over a four-year period in participants enrolled in a large prospective cohort, the Osteoarthritis Initiative (OAI), and to evaluate risk factors for incident and persistent symptoms.

MATERIALS AND METHODS

Participants and outcome definition. We used data from the publicly available OAI, a multicenter prospective observational study involving 4,796 individuals with, or at risk of, knee osteoarthritis with clinical, radiologic, and other data collected at baseline and annual follow-up visits, available at https://data-archive.nimh.nih.gov/oai. The specific eligibility risk factors and ethical issues are described in detail in the *Osteoarthritis Initiative Study Protocol*.[10] Ethical approval for collecting all participant information was provided by the OAI. At each study site the institutional review board (IRB) approved the study, and informed consent was given by all patients. The OAI study and public use of clinical and imaging data was approved by the committee on Human Research, University of California, San Francisco (IRB approval number 10-00532). Shoulder symptoms were self-reported and assessed annually from baseline to 48 months of follow-up. Shoulder symptoms were reported separately using a joint manikin for the left and right shoulder as binary yes or no according to the question "Do you have pain, aching, or stiffness on most days? By most days, we mean more than half the days of a month." For the current secondary analysis, data from all 4,796 OAI participants, using both shoulders per participant at five consecutive time points (baseline to year 4), were used.

Demographics and risk factors. The covariates considered in the study were age, sex, race, smoking status, Medical Outcomes Study Short Form 12 (SF-12) health assessment, depression, sleep disturbance, comorbidities, employment status, self-reported joint pain, and lower limb weakness described in more detail below.

Age was kept as a continuous variable in years, sex was coded as binary (male or female), and race was categorized as White or non-White (Black or African American, Asian, and other non-White were combined into non-White). Smoking status was categorized into "current/former" and "never smoked."

The SF-12 is a validated generic health related quality of life instrument that covers eight health domains (physical functioning, social functioning, role-physical, role-emotional, mental health, energy/vitality, pain, and general health perception). It also generates a Physical Component Summary (PCS-12) scale score and a Mental Health Component Summary Scale Score. The two components (mental health and physical health) were assessed separately in our study.

Depression was measured using the long form 20-Item Center for Epidemiological Studies Depression (CES-D) scale (range 0–57). The recommended screening threshold of ≥16 is used to identify depressive symptoms. The frequency of restless sleep was evaluated by participants' responses to a question on the CES-D scale, which asked participants how often in the past week their sleep was restless, with the following response options: rarely (rarely or none of the time; <1 day), some (some or a little of the time; 1–2 days), moderate or much (occasionally or a moderate amount of time; 3–4 days), and most (most or all of the time; 5–7 days). The last two categories were combined in our study. The presence of comorbid conditions was assessed using a validated self-administered questionnaire modeled on the Charlson comorbidity index.

Assessment of working status and absence from work were assessed using the current employment status question with the following four responses: works for pay, unpaid work for family business, not working in part due to health, and not working for other reasons.

Pain in other regions such as back, neck, wrist, foot, and ankle were self-reported and were summed to define multiple joint pain. The definition of pain, for example, in the elbow, was "elbow pain, aching or stiffness: more than half the days, past 30 days." This was similarly worded for the other regions. A proxy for lower limb weakness was defined based on the OAI question regarding difficulty standing from sitting in the last 7 days, coded as none,

mild, moderate, severe, and extreme; this was discretized to "none" and "present" for our study.

We also considered whether health insurance could affect the outcomes with participants potentially not accessing health care for financial reasons; however, on exploration of the data, we found that 98% of participants had some form of health insurance.

Statistical analyses. *Descriptive statistics.* Summary statistics were used to describe the baseline characteristics, including prevalence and incidence of shoulder symptoms. We categorized participants into three outcomes. The main outcome was "persistent shoulder symptoms" defined as symptoms at four or more time points in the same shoulder, "incident symptoms" defined as any shoulder symptoms reported from year 2 in a previously symptom-free shoulder, and intermittent shoulder symptoms defined as a discrete episode of shoulder symptoms during the follow-up, preceded or followed by a symptom-free interval. The distribution of different variables across these outcomes was assessed using descriptive statistics and compared to participants with no shoulder symptoms throughout the full OAI sample. Longitudinally, we described the different patterns of shoulder symptoms possible over time (n = 32 possible patterns per side) and reported these as proportions.

Regression models. The association among the three shoulder symptoms outcomes (persistent, incident, and intermittent) with risk factors—age, body mass index (BMI), sex, smoking status, sleep disturbance, employment, multiple-site joint symptoms, and lower limb weakness—were assessed at baseline, separately for each outcome using multivariable logistic regression models. These analyses were performed at the individual level. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Latent growth curve analyses. All 4,796 OAI participants at five consecutive time points were considered for latent class growth analysis (LCGA) modeling to assess if any trajectories of shoulder symptoms existed. LCGA was conducted using Mplus software V.8.1. A total of 1,886 participants who self-reported right shoulder symptoms at one or more time point were included in the LCGA analysis sample. Following preliminary analysis involving latent growth curve modeling in which shoulder pain was modeled using different approaches (linear, quadratic), the linear model was selected as the most appropriate model for the LCGA.

LCGA then identified trajectories of shoulder pain reporting over 48 months. The fit of the trajectories was tested for two to five trajectory classes, with the most optimal model chosen based on a combination of fit indices and model interpretability. The fit indices used were Akaike information criteria (AIC), Bayesian information criteria (BIC), Vuong–Lo–Mendell–Rubin likelihood ratio test (LRT), and bootstrap likelihood ratio test (BLRT). Significant LRT and BLRT for k groups ($P < 0.05$) indicate that the fit of the specific model is an improvement over a model with k – 1 groups. Entropy indices (ranging 0–1) were checked to ensure the quality and reliability of the classification. After determining the number of trajectories, the best possible or optimal model was also determined by considering the usefulness of the latent classes (>5% in each class) and inspecting the trajectory shapes for similarity, as well as the posterior probabilities of group membership from each individual. Each study participant had two shoulders included in the OAI cohort; however, LCGA methodology is unable to account for the within-person correlations. Therefore, the right shoulder from each participant was selected. Sensitivity analyses were undertaken to compare the optimal number of trajectory classes selected using data from the left shoulder and, secondly, limiting the data to only participants reporting no pain at sites deemed closely related to the shoulder anatomically (hand or finger pain, elbow pain, and wrist pain). Having determined the optimal number of trajectory classes, the baseline shoulder-specific, comorbid, and sociodemographic characteristics of each trajectory class were compared descriptively, and tests for differences were performed using either *t*-tests or chi-square tests, depending on their distribution.

RESULTS

Baseline findings. A total of 4,796 participants were included, with a mean ± SD age of 61.2 ± 9.2 years; 58% were women, 79% reported as White race, and the median BMI (interquartile range) was 28.3 (25.1–31.7). Lower limb weakness was seen in more than 25% of participants, whereas 56% of participants reported multiple-site symptoms at three or more other joints (excluding the shoulders) (Table 1). The prevalence of left and right shoulder symptoms was 13.5% (645 of 4,796) and 15.9% (762 of 4,796), respectively, at baseline in the whole OAI cohort, with 22% (1,065 of 4,796) overall prevalence of unilateral or bilateral symptoms. In those reporting symptoms exclusively on one side at baseline (unilateral, n = 723 of 4,796, 15%), the same symptomatic side was reported as symptomatic at 48 months in 209 of 723 (29%) participants. Bilateral shoulder involvement was common in those reporting shoulder symptoms at baseline (n = 342 of 1,065, 32%), and this persisted in 89 of 342 (26%) participants at 48 months.

At the individual level, persistent shoulder symptoms in either shoulder was reported by 343 of 2,375 participants (14%) reporting pain at one or more time point. When compared to those without shoulder symptoms throughout follow-up, these participants were more likely to have more depressive symptoms, sleep disturbance, worse physical health, and proportionally greater multiple-site symptom involvement and lower limb weakness (Table 1). Over the four-year study period, incidence of shoulder symptoms was 16% in the OAI cohort; intermittent symptoms were reported by 14% of participants.

Table 1. Baseline characteristics of the different shoulder patterns investigated*

Characteristic	Full OAI sample, N = 4,796	Participants with persistent symptoms, n = 343	Participants with intermittent symptoms, n = 678	No shoulder symptoms throughout, n = 2,421	Incidence of shoulder symptoms, n = 777
Age, mean ± SD	61.16 ± 9.19	61.19 ± 9.01	61.20 ± 9.32	61.13 ± 9.20	61.26 ± 9.08
Sex, female, n (%)	2,804 (58)	196 (57)	393 (58)	1,407 (58)	435 (56)
BMI, median (IQR)	28.3 (25.1–31.7)	29.05 (25.8–32.4)	28.4 (25.4–31.8)	27.9 (24.8–31.4)	28.5 (25.3–31.7)
Race, non-White, n (%)	3,790 (21)	93 (27)	166 (25)	410 (17)	149 (19)
Smoking status: current/ former, n (%)	2,232 (47)	178 (52)	326 (48)	1,060 (44)	390 (51)
PASE, mean (SD)	160.83 (82.48)	162.83 (85.49)	154.90 (84.77)	162.19 (81.19)	164.10 (84.83)
Current employment (works for pay), n (%)	2,943 (62)	183 (53)	402 (60)	1,534 (63)	478 (62)
Comorbidities: 2+, n (%)	507 (11)	44 (13)	73 (11)	205 (8)	64 (8)
Mental health (SF-12), n (%)	53.60 (8.12)	52.45 (9.36)	53.22 (8.40)	54.05 (7.61)	53.77 (7.59)
Physical health (SF-12), n (%)	48.83 (9.18)	43.80 (10.28)	47.18 (9.24)	50.59 (8.21)	48.97 (8.94)
Depression score,[a] median (IQR)	4 (2–9)	7 (3–12)	5 (2–10)	4 (1–8)	4 (2–9)
Had restless sleep, n (%)	800 (17)	99 (29)	120 (18)	328 (14)	134 (17)
Multiple-site joint symptoms,[b] median	3	5	3	2	3
MJP categories, n (%)					
0 joints	532 (11)	15 (4)	54 (8)	365 (15)	77 (10)
1–2 joints	1,567 (33)	44 (13)	176 (26)	953 (39)	252 (32)
3+ joints	2,697 (56)	284 (83)	448 (66)	1,103 (46)	448 (58)
Lower limb weakness,[c] n (%)	1,309 (27)	148 (43)	230 (34)	527 (22)	237 (31)

* BMI, body mass index; IQR, interquartile range; MJP, multiple joint pain; OAI, Osteoarthritis Initiative; PASE, Physical Activity Scale for the Elderly; SF-12, Medical Outcomes Study Short Form 12.
[a] Depression was measured using the long form 20-Item Center for Epidemiological Studies Depression scale.
[b] Symptoms in other regions such as back, neck, wrist, foot and ankle, hip, and knee were self-reported and summed to classify multiple joint symptoms.
[c] Lower weakness was defined based on the OAI question on the difficulty of standing from sitting in the last 7 days coded as none, mild, moderate, severe, and extreme and was discretized to none and present.

In analyses by side (joint-level), in the 1,886 participants who reported right shoulder symptoms at least once at any time point, 509 participants (27%) reported symptoms in at least three of the five study time points, with 14% reporting persistent symptoms. Approximately 5% of participants reported right shoulder symptoms at all five time points (Supplementary Table S1). Similar findings were seen in the left: 1,647 participants reported left shoulder symptoms at one or more time point, with 178 of these (11%) classified as having persistent left shoulder symptoms. Approximately 70% reported multisite joint symptoms in addition to shoulder symptoms.

Logistic regression findings. Persistent symptoms were associated with female sex, White race, sleep disturbance, work absenteeism due to health reasons, lower limb weakness, and having multiple-site joint symptoms, all $P < 0.05$ (Table 2). For instance, men had reduced odds (23% less likely) of reporting persistent symptoms compared to women, those of non-White race were less likely to report persistent symptoms (OR 0.71, 95% CI 0.53–0.96) compared to those of White race, and those with lower limb weakness were approximately twice as likely to report persistent symptoms than those without muscle weakness (OR 1.76, 95% CI 1.37–2.27). Having multiple-site joint symptoms in three or more nonshoulder sites was associated with increased odds of reporting shoulder symptoms (Table 2). For incident symptoms, only lower limb weakness was statistically significant (Table 2), whereas none of the variables investigated were associated with intermittent symptoms. Exploratory analyses (separately for left and right shoulder) showed consistent results to the main study findings, with increased odds of reporting persistent symptoms in those with multiple-site joint symptoms and lower limb weakness; similar findings were also seen for those with bilateral shoulder symptoms (results not shown).

LCGA analyses findings. A total of 1,886 participants self-reported right shoulder symptoms at one or more time point. Their baseline characteristics did not differ from those of the full cohort (Table 3). Compared to those with no pain at any time point, those with pain at all time points were more likely to be non-White race, have multiple joint involvement, more comorbidities, and be in less physical health as per SF-12 scores (all $P < 0.001$) (Table 3). Those developing "incident" shoulder pain did not appear to have different characteristics from the full cohort (Table 3).

We identified two trajectories of shoulder symptoms over four years (Figure 1; Table 4). The two-class solution was considered the best fit because it returned a statistically significant BLRT and Lo-Mendell-Rubin likelihood ratio test, had high entropy, had

Table 2. Multivariable logistic regression model for persistent and incident shoulder symptoms*

Characteristic	Persistent symptoms (4 or more occasions)			Incident symptoms			Intermittent symptoms		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.00	0.99–1.02	0.270	1.00	0.99–1.00	0.928	1.00	0.99–1.00	0.811
Sex (ref. Female)	**0.77**	**0.60–0.98**	**0.036**	0.88	0.75–1.02	0.104	0.96	0.79–1.15	0.640
BMI	1.00	0.98–1.03	0.800	1.00	0.99–1.01	0.754	0.99	0.97–1.01	0.482
Race (ref. White)	**0.71**	**0.53–0.96**	**0.024**	1.17	0.95–1.43	0.140	1.01	0.81–1.25	0.959
Smoking status (ref. Nonsmokers)	1.17	0.92–1.49	0.204	1.17	0.94–1.37	0.054	0.92	0.77–1.11	0.393
Sleep disturbance[a] (ref. rarely get sleep disturbance)	**1.97**	**1.49–2.62**	**<0.001**	1.05	0.85–1.29	0.641	0.84	0.67–1.06	0.147
Not working due to health reasons[b] (ref. works for pay)	**2.16**	**1.38–3.39**	**<0.001**	0.91	0.63–1.21	0.620	0.87	0.60–1.26	0.465
Lower limb weakness[c] (ref. no weakness)	**1.76**	**1.37–2.27**	**<0.001**	**1.19**	**1.00–1.43**	**0.050**	1.10	0.90–1.34	0.346
MJP categories[d] (ref. zero category)									
1–2 joints	1.07	0.58–1.99	0.825	1.11	0.84–1.47	0.454	0.81	0.56–1.17	0.271
3+ joints	**4.90**	**2.79–8.58**	**<0.001**	1.14	0.87–1.50	0.340	0.81	0.57–1.14	0.141

* Bold text indicates significance. BMI, body mass index; CI, confidence interval; MJP, multiple joint pain; OR, odds ratio; ref., reference.
[a] The frequency of restless sleep was evaluated based on the sleep question from the Center for Epidemiological Studies Depression asking how often in the past week their sleep was restless.
[b] Assessment of working status and absence from work were assessed using the current employment status question with the following 4 responses: works for pay, unpaid work for family business, not working in part due to health, and not working for other reasons.
[c] Lower limb weakness was defined based on the OAI question on the difficulty standing from sitting in the last 7 days coded as none, mild, moderate, severe, and extreme and was discretized to none and present.
[d] Symptoms in other regions such as back, neck, wrist, foot and ankle, hip, and knee were self-reported and summed to classify multiple joint symptoms.

lower AIC and BIC than a one-class model, and the model converged with no warnings. All class sizes were >5% of the total number of participants included in the analysis (Supplementary Table S2). The posterior probability of correctly allocating participants into trajectory 1 and 2 was 98% and 75%, respectively, indicating that there was a 98% probability on average of each trajectory class being correctly classified. Supplementary Table S2 summarizes the model fit indices of the class models iteratively.

Trajectory 1 (n = 174, 9%) had "high probability of reporting symptoms," and trajectory 2 "low symptom reporting probability" (91%). Similarities were seen between those in

Table 3. Baseline characteristics of those included in or excluded from LCGA analysis*

Characteristic	Full OAI sample, N = 4,796	Participants included in the trajectory analyses, n = 1,886	Painful shoulder at 5 time points, n = 86	No painful shoulder throughout, n = 2,910	Incidence of shoulder pain, n = 1,575
Mental health (SF-12)	53.60 (8.12)	52.91 (8.77)	51.52 (10.57)	54.05 (7.63)	52.86 (8.69)
Physical health (SF-12)	48.83 (9.18)	46.75 (9.83)	**41.90 (10.81)**	**50.17 (8.47)**	47.18 (9.57)
Depression score, median (IQR)	4 (2–9)	5 (2–11)	**9 (4–13)**	**4 (1–8)**	5 (2–10)
Had restless sleep, n (%)	800 (17)	396 (21)	**32 (37)**	**304 (10)**	191(12)
Gender, female, n (%)	2,804 (58)	1,138 (60)	47 (55)	1,666 (57)	939 (60)
Race, non-White, n (%)	3,790 (21)	1,416 (25)	**27 (31)**	**534 (18)**	362 (23)
Age, mean ± SD	61.16 ± 9.19	61.30 ± 9.26	61.86 ± 8.34	61.06 ± 9.15	61.28 ± 9.26
PASE, mean (SD)	160.83 (82.48)	158.47 (83.65)	163.63 (85.61)	162.37 (81.69)	159.54 (83.29)
Smoking status: current/former, n (%)	2,232 (47)	972 (52)	41 (48)	1,290 (45)	780 (50)
MJP, median	1	1	**2**	**1**	1
MJP categories, n (%)					
0 painful joints	1,498 (31)	453 (24)	10 (12)	1,045 (36)	395 (25)
1–2 painful joints	2,838 (59)	1,154 (61)	47 (55)	1,684 (58)	962 (61)
3+ painful joints	460 (10)	279 (15)	29 (33)	181 (6)	218 (13)
Current employment (works for pay), n (%)	2,943 (62)	1,106 (59)	47 (55)	1,837 (63)	937 (60)
Comorbidities (CCI index): 2+, n (%)	507 (11)	198 (10)	**13 (15)**	**243 (8)**	164 (10)

* Bold values indicate significance. CCI, Charlson comorbidity index; IQR, interquartile range; LCGA, latent class growth analysis; MJP, multiple joint pain; OAI, Osteoarthritis Initiative; PASE, Physical Activity Scale for the Elderly; SF-12, Medical Outcomes Study Short Form 12.

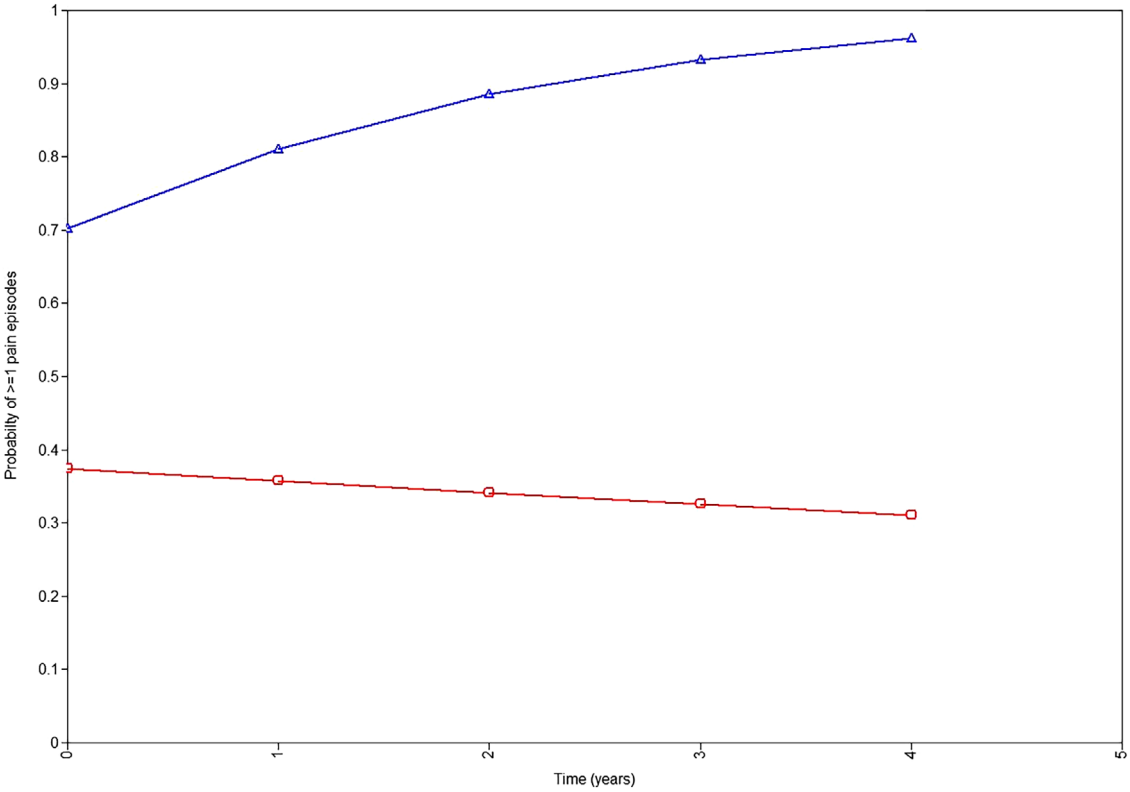

Figure 1. Shoulder pain trajectories (2-class solution).

trajectory 1 and the group defined as having persistent symptoms in terms of their demographics and clinical features (see Table 4).

Table 4 summarizes the demographics and clinical covariates between the two trajectories. We found statistically significant differences for the PCS-12 of the SF-12 measure, with those in trajectory class 1 more likely to have lower PCS-12 scores (mean difference 2.88; $P < 0.001$). Trajectory 1 was also characterized by having proportionally more people with multiple joint pain (26% vs 14%; $P < 0.001$). Participants in trajectory class

Table 4. Baseline characteristics of shoulder pain trajectory classes*

Characteristic	All participants selected for LCGA, N = 1,886	Class 1, n = 174 (9%)	Class 2, n = 1,712 (91%)	Exclusively shoulder pain group, class 1 (sensitivity analyses), n = 67
Mental health (SF-12)	52.92 (8.77)	52.20 (9.55)	52.99 (8.69)	52.82 (9.08)
Physical health (SF-12)	46.74 (9.82)	**44.13 (10.34)**	**47.02 (9.74)**	48.30 (9.40)
Depression score, median (IQR)	5 (2–11)	**7 (2–11)**	**5 (2–11)**	7 (3–11)
Had restless sleep, n (%)	396 (21)	**49 (28)**	**347 (20)**	16 (24)
Gender, female, n (%)	1,138 (60)	98 (56)	1,040 (61)	28 (42)
Race, non-White, n (%)	3,790 (21)	46 (26)	421 (25)	14 (21)
Age, mean ± SD	61.30 ± 9.26	61.89 ± 8.90	61.23 ± 9.29	62.48 ± 9.20
PASE, mean (SD)	158.47 (83.65)	160.35 (84.57)	158.28 (83.58)	177.25 (84.04)
Smoking status: current smoker, n (%)	942 (51)	84 (49)	858 (51)	31 (47)
MJP, median	1	1	1	N/A
MJP categories, n (%)				N/A
0 painful joints	458 (24)	28 (16)	425 (25)	
1–2 painful joints	1,154 (61)	100 (58)	1,054 (62)	
3+ painful joints	279 (15)	**46 (26)**	**233 (14)**	
Not in work (in part due to health), n (%)	141 (7)	**23 (13)**	**118 (7)**	6 (9)
Comorbidities (CCI index): 2+, n (%)	198 (11)	26 (15)	172 (10)	8 (12)

* Bold text indicates significance. CCI, Charlson comorbidity index; IQR, interquartile range; LCGA, latent class growth analysis; MJP, multiple joint pain; N/A, not applicable; PASE, Physical Activity Scale for the Elderly; SF-12, Medical Outcomes Study Short Form 12.

1 were also more likely to be off work due to health issues (13% vs 7%; $P < 0.001$). Although participants in trajectory class 1 had a slightly higher proportion of having at least two comorbidities (13% vs 9%), this was not statistically significant ($P = 0.05$).

Although we found a statistically significant difference among the mean depression scores between the trajectory groups (median scores 7.0 vs 5.0 for trajectory 1 and trajectory 2, respectively; $P < 0.01$) these differences were not clinically important. Based on a published cutoff for depressive symptoms (threshold = ≥16), trajectory 1 had 18% of participants classed as depressed compared to 15% in trajectory 2. Those in trajectory class 1 were more likely to report restless sleep (defined as three days or more) compared to those in trajectory 2 (28% vs 20%; $P < 0.001$).

When the trajectory analyses were repeated using data from the left shoulder for sensitivity analyses, the two-class solution was also found to be the optimal solution (trajectory 1 had 7% of participants, trajectory 2 had 93%). Model fit results were very similar to those from the right shoulder (see supplementary results).

DISCUSSION

We have demonstrated the prevalence and incidence of shoulder symptoms in a large, prospective cohort. We have also shown the risk factors for incident shoulder symptoms and factors associated with shoulder pain persistence over a four-year period. To the best of our knowledge, this is the largest and longest longitudinal observational study on patients reporting shoulder symptoms in which regular follow-up was undertaken.

Although this analysis was selected from a cohort with, or at risk of developing, knee osteoarthritis, our findings that prevalences of right and left shoulder symptoms (13.5% and 15.9%, respectively, at baseline and 22% prevalence if either side was considered) were similar to previous community-based shoulder studies.[1] This supports the face validity of our findings. The incidence of shoulder symptoms in our cohort, defined as reporting symptoms any time after baseline, was 16%. This is similar to previous studies in which incidence ranged from 0.9 to 29%.[1] Similar to previous studies, we found that women had a higher prevalence of shoulder symptoms compared to men, and symptoms increased with age.[1] Previous studies have been unable to demonstrate the intermittent nature of shoulder symptoms over a prolonged period. In the current four-year study, 14% of patients reported intermittent shoulder symptoms.

We found persistent symptoms were associated with female sex, sleep disturbance, work absenteeism due to health reasons, White race, lower limb weakness, and presence of multiple-site joint symptoms. There have been previous reviews evaluating prognostic factors for shoulder symptoms[11,12] that found higher symptom intensity and disability scores were associated with poorer long-term outcomes. Our study did not include continuous data on the level of symptoms or disability, but it included other markers, such as sleep disturbance and workplace absenteeism, which have been shown to be associated with high levels of symptoms.[13,14] There are few studies evaluating the ethnic differences in shoulder symptoms. We found that participants who are White are more likely to report persistent symptoms than non-White. There have been no studies evaluating race and its association with persistent shoulder symptoms, and further work is required to substantiate our findings from this predominantly White cohort.

We also found that lower limb weakness was a risk factor for incident shoulder symptoms at any time point. In a previous study, persistent pain in one or two knees increased the risk of bilateral shoulder pain at four years, and this finding was mediated by leg weakness defined by difficulty standing from a sitting position.[8] Quadriceps strengthening and other targeted measures aimed at reducing lower limb weakness may therefore offer an attractive therapeutic target to improve leg strength and reduce the risk of subsequent development of shoulder symptoms.

Latent growth analyses demonstrated evidence of two trajectories: those with high and increasing probability of reporting shoulder symptoms over time and those with low and decreasing probability of reporting shoulder symptoms over time. Other studies have found varying trajectory numbers.[15] A study by Hallman et al assessing trajectories of neck and/or shoulder symptoms identified through questionnaires among workers from cleaning, manufacturing, transportation and office work and administration (n = 748) over one year reported four clinical trajectories: low (asymptomatic, very low, low recovering), moderate fluctuating, strong fluctuating, severe persistent.[15] These extra trajectories may be explained by differences in statistical technique applied (our analysis involved latent growth curve analysis, a type of mixture modeling, unlike Hallman et al, who used latent class analysis); additionally, differences in frequency of data collection and length of follow-up (one year in that study versus four years in our study) may also account for these findings.

We found similar clinical and demographic factors associated with worse trajectories as a previous study.[15] Those in trajectory 1 were more likely to have lower levels of physical health, not work due to health reasons, and have multiple-site joint symptoms at baseline. As well as supporting our logistic regression findings, this is similar to findings from a previous trajectory study that found worse symptoms were associated with multiple-site symptoms, higher physical strain at work, absence from work, low levels of physical activity, and lower levels of self-rated health at baseline, although that study assessed both neck and shoulder.[15]

A strength of this work was the large sample size and the longitudinal data set with regular follow-up and low attrition rates. As of year 5, 80% of the OAI participants (n = 3,831) were still in the cohort, with completed clinic visits. For our trajectory analysis, we used an advanced analytical technique (LCGA) that offers several advantages compared to traditional clustering techniques

such as latent class analysis. Fixed information maximum likelihood missing data techniques methods in which parameters are estimated using all available observations in the data set were applied to minimize estimate biases. The selection of the optimal number of trajectory classes was based on both statistical and clinical considerations.

There are some limitations to our study. This study was conducted in a cohort selected for knee osteoarthritis, and there is a potential for selection bias. However, the prevalence and incidence of shoulder symptoms was similar to other studies derived from community cohorts, although the incidence was slightly higher in our study. Shoulder symptoms were self-reported every 12 months; more frequent sampling may have better reflected intermittent shoulder symptoms. Our analysis involved categorical outcomes as per OAI data collection, and our results were interpreted as probability of reporting shoulder symptoms; a study using a continuous measure of symptoms would provide patterns with more detail. This study evaluated data collecting shoulder symptoms (pain, aching, and stiffness), not just shoulder pain. The data did not contain symptom severity, symptom duration, or shoulder-specific functional outcomes. These findings may differ if pain was evaluated. Another limitation was that our proxy for lower limb weakness was classified according to self-reported difficulty in rising from a chair. This may be affected by multiple factors, such as back or hip pain, and this question may better represent overall lower limb strength or lower limb functional impairment and not correlate exclusively with having weak quadriceps muscles. We also acknowledge that for persistent pain models, some residual confounding may still be present even after covariate adjustments because these regression models at the individual level included people with bilateral symptoms, although this effect is likely small. Unfortunately, we were unable to report symptoms by handedness because this was not available in the data set.

Stratification models for targeting treatment at poor prognostic groups with musculoskeletal symptoms have previously shown improved health benefits and cost-savings.[16] Understanding the baseline factors associated with long-term shoulder symptoms and the different symptoms trajectories groups could have important clinical significance, as it could provide more personal care in terms of prognosis, targeting of treatment and monitoring.

In the largest and longest study of shoulder symptoms with regular follow-up, we showed that persistent shoulder symptoms were common and demonstrated factors associated with this. Lower limb weakness may potentially be a modifiable risk factor for incident shoulder symptoms. Although further longitudinal work from a shoulder-symptoms cohort is required to help substantiate these findings, our findings offer an opportunity for targeted therapy in the treatment and prevention of this common condition.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Professor Conaghan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tran, Dube, Kingsbury, Conaghan.

Analysis and interpretation of data. Tran, Dube, Kingsbury, Conaghan.

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