Average symptom trajectories following incident radiographic knee osteoarthritis: data from the Osteoarthritis Initiative

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INTRODUCTION
Observations by Felson et al.1 support the hypothesis that disease progression in knee osteoarthritis (OA) follows a pattern of inertia in which knees showing recent incident change in X-ray are at higher risk of further X-ray progression. Given well-documented structure–pain discordance in OA, it is less clear whether patients’ reported experience of pain and function follow a similar pattern. This is important since the experience of symptoms and functional limitation drive help-seeking and should therefore feature in preventive strategies based on early diagnosis.

In a previous analysis of repeated-measures data in a cohort of adults at high risk of knee OA, we found that symptoms began to appear or worsen, on average, 2–3 years prior to the first appearance of incident radiographic knee OA.

What is already known about this subject?
In adults at high risk of knee osteoarthritis (OA) symptoms begin to appear or worsen, on average, 2–3 years prior to the first appearance of incident radiographic knee OA.

Key messages
What does this study add?
- We extended these findings forward in time and demonstrated that following an increase in the risk of symptoms prior to the incidence of radiographic knee OA, this risk does not continue to increase in the period up to 5 years after incidence.
- Patients undergoing an underlying transition in OA disease state may experience episodic symptom worsening but this does not inevitably presage further symptom decline in the short-to-medium term.

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METHODS

Data set

We used data from the Osteoarthritis Initiative (OAI) \(^3\) (available for public access at http://www.oai.ucsf.edu/). Between 2004 and 2006, 3284 participants aged 45–79 years were enrolled in the ‘incidence subcohort’ of the OAI if they were at high risk of developing symptomatic ROA. Individuals with rheumatoid arthritis or other inflammatory arthritis were excluded. Measures recorded from self-complete questionnaires, personal interviews, physical examinations and plain radiography were collected on enrolment and were repeated at annual clinic visits. All participants signed informed consent, and the study was approved by the institutional review board.

Selection of participants

Cases were defined as knees without symptoms (defined as knee pain, aching or stiffness: more than half the days of a month, past 12 months) on enrolment into the OAI, which had developed incident ROA (KL grade \(\geq 2\), defined as the new onset of combined definite osteophyte and joint space narrowing in the tibiofemoral joint \(^4\) (ascertained from fixed-flexion knee radiographs), at any of the first four annual follow-up visits. Cases were assigned a common baseline time point, \(t_0\), corresponding to when incident ROA was first identified. Knees that were surgically replaced were censored at the last visit before the knee replacement was recorded.

Outcome measures

Outcomes, measured annually up to 3 years before and 5 years after incident ROA, were the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC\(^5\)), Knee injury and Osteoarthritis Outcome Score (KOOS\(^6\)), Pain, Physical Function and Stiffness subscales and Knee injury and Osteoarthritis Outcome Score (KOOS\(^6\)), Other Symptoms subscales (dichotomised into at least one item in the subscale rated ‘moderate’, ‘severe’ or ‘extreme’ vs all items in the subscale rated ‘none’ or ‘mild’) and 34 individual items from the WOMAC and KOOS scales (dichotomised: ‘none’/‘mild’ vs ‘moderate’/‘severe’/‘extreme’; see ref. \(^2\)). For the current analyses, we used the knee-specific subscale scores and individual items as previously studied in the prodromal phase.\(^2\)

Statistical analysis

Trajectories of the probabilities of symptoms over time were estimated with random intercept multilevel logistic regression models,\(^7\) adjusting for age and gender, treating each knee as an individual case while accounting for correlation between knees within people. Complete case analysis was performed.

RESULTS

One hundred and sixty-nine cases of incident ROA were recorded in 161 participants during the first 4 years of follow-up of the OAI cohort (68, 31, 47 and 23 knees at years 1, 2, 3 and 4, respectively). At cohort entry: mean

<table>
<thead>
<tr>
<th>Time</th>
<th>WOMAC Pain</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
<th>WOMAC Physical Function</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
<th>KOOS Pain</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
<th>KOOS Other Symptoms</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t0</td>
<td>46 (27.2)</td>
<td>Ref.</td>
<td>1</td>
<td>37 (22.0)</td>
<td>Ref.</td>
<td>1</td>
<td>21 (25.3)</td>
<td>0.95 (0.46 to 1.98)</td>
<td>14 (16.9)</td>
<td>0.74 (0.34 to 1.65)</td>
<td>17 (20.8)</td>
<td>0.88 (0.41 to 1.87)</td>
</tr>
<tr>
<td>t0+1</td>
<td>36 (22.6)</td>
<td>0.74 (0.41 to 1.34)</td>
<td>26 (16.4)</td>
<td>0.63 (0.33 to 1.19)</td>
<td>23 (14.0)</td>
<td>0.75 (0.40 to 1.41)</td>
<td>28 (18.3)</td>
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<td>0.75 (0.40 to 1.41)</td>
</tr>
<tr>
<td>t0+2</td>
<td>32 (22.4)</td>
<td>0.87 (0.47 to 1.64)</td>
<td>25 (15.9)</td>
<td>0.60 (0.32 to 1.11)</td>
<td>16 (11.2)</td>
<td>0.72 (0.39 to 1.34)</td>
<td>21 (16.9)</td>
<td>0.68 (0.34 to 1.38)</td>
<td>21 (26.2)</td>
<td>0.42 (0.20 to 0.89)</td>
<td>26 (19.7)</td>
<td>0.83 (0.47 to 1.47)</td>
</tr>
<tr>
<td>t0+3</td>
<td>21 (25.3)</td>
<td>0.85 (0.46 to 1.63)</td>
<td>25 (15.9)</td>
<td>0.60 (0.32 to 1.11)</td>
<td>16 (11.2)</td>
<td>0.72 (0.39 to 1.34)</td>
<td>21 (16.9)</td>
<td>0.68 (0.34 to 1.38)</td>
<td>21 (26.2)</td>
<td>0.42 (0.20 to 0.89)</td>
<td>26 (19.7)</td>
<td>0.83 (0.47 to 1.47)</td>
</tr>
<tr>
<td>t0+4</td>
<td>12 (21.1)</td>
<td>0.64 (0.26 to 1.57)</td>
<td>9 (15.8)</td>
<td>0.63 (0.34 to 1.29)</td>
<td>8 (14.0)</td>
<td>0.54 (0.23 to 1.29)</td>
<td>7 (12.1)</td>
<td>0.42 (0.20 to 0.89)</td>
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<td>7 (12.1)</td>
<td>0.42 (0.20 to 0.89)</td>
</tr>
</tbody>
</table>

#KOOS, Knee injury and Osteoarthritis Outcome Score; OA, osteoarthritis; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index.
age 65.2 years (SD 9.2); 69% female; mean BMI 29.2 kg/m² (SD 4.6); 42.6% previous knee injury; 20.7% previous knee surgery; 72% with KL=1. Approximately 25% of knees had at least one symptom (individual item) present at t0 on each WOMAC subscales, reducing to ∼15% by t0+1 for Pain and Stiffness and 23% for Physical Functioning with little further change by t0+5 (Table 1).

The probability of having at least one symptom in each of the subscales generally stabilised or lessened following the initial prodromal phase with mostly non-significant associations of time after t0, for example, ORs for WOMAC Stiffness peak at t0 (OR at t0+1: 0.55 (95% CI 0.31 to 0.97)), suggesting that stiffness symptoms reduce in the year after incidence. Similar results were found across the individual items (data not shown). Two items to note were pain frequency (weekly or more; measured in KOOS), which increased greatly in the lead up to incident ROA and then decreased slightly, and audible joint sounds (sometimes or more; measured in KOOS), which had a much higher overall probability, and after increasing prior to incident radiographic OA, stabilised then increased again at 5 years (Figure 1). On removing knees which progressed to a higher KL grade up to 3 years after t0 (n=22, 13%), there was very little change to the trajectories (data not shown).

**DISCUSSION**

Following an increase in the risk of symptoms during the prodromal phase, this risk does not continue to increase in the period up to 5 years after the incidence of ROA. Instead, on most measures, it appears to stabilise or lessen, but not to prior levels. Reasons for the observed stabilisation or reduction of symptoms after incident ROA include the possible effect of treatment or, as alluded to by Hutton, a process of adaptation at the level of the joint and/or individual. An important caveat is that this may apply only in the absence of further disease progression since relatively few knees in this analysis progressed to KL grade ≥3 during the period of observation after incident ROA.

While undergoing the transition to incident ROA, a high proportion of knees were not at any time reported as having ‘moderate’ or worse symptoms: 50% of knees did not have ‘moderate’, ‘severe’ or ‘extreme’ symptoms on any individual items in the WOMAC Stiffness subscale; 36% on WOMAC Physical Function subscale; 43% on WOMAC Pain; 20% on KOOS Pain and 25% on KOOS Other Symptoms. Only 3–10% did not have even ‘mild’ symptoms on at least one item. The transition to incident ROA is therefore not entirely ‘silent’, but symptom changes may be subtle and may not trigger help-seeking. Rather than immediate clinical application, our findings serve to advance our understanding of the temporal relationship between symptom change and disease progression, raising the possibility of episodic symptom worsening in response to an underlying transition in disease state.

We have studied prodromal and postdromal symptom trajectories anchored around the transition to incident tibiofemoral ROA (KL grade ≥2). Extending this approach to earlier, preradiographic index events and states based on MRI and identifying preventable proximal triggers (eg, recent injury) is warranted.
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Competing interests None declared.

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REFERENCES


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