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# Prodromal symptoms in knee osteoarthritis: a nested case–control study using data from the Osteoarthritis Initiative

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SUMMARY

*Objective:* In order to gain a better understanding of the timing of emergent symptoms of osteoarthritis, we sought to investigate the existence, duration and nature of a prodromal symptomatic phase preceding incident radiographic knee osteoarthritis (ROA).

*Design:* Data were from the incidence cohort of the Osteoarthritis Initiative (OAI) public use datasets. Imposing a nested case–control design, ten control knees were selected for each case of incident tibiofemoral ROA between 2004 and 2010 from participants aged 45–79 years. Candidate prodromal symptoms were Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS) subscale scores and individual items, available up to 4 years prior to the time of incident ROA. Multi-level models were used to estimate the length of the prodromal phases.

*Results:* The prodromal phase for subscale scores ranged from 29 months (KOOS Other Symptoms) to 37 months (WOMAC Pain). Pain and difficulty on activities associated with higher dynamic knee loading were associated with longer prodromal phases (e.g., pain on twisting/pivoting (39 months, 95% confidence interval: 13, 64) vs pain on standing (25 months: 7, 42)).

*Conclusions:* Our analysis found that incident ROA is preceded by prodromal symptoms lasting at least 2–3 years. This has potential implications for understanding phasic development and progression of osteoarthritis and for early recognition and management.



## Introduction

Osteoarthritis has a substantial impact on the health of individuals and populations worldwide[1,2]. Symptoms often precede the appearance on plain radiographs of features traditionally used to define disease incidence (e.g., marginal osteophytes, joint space narrowing)[3–5], implying the existence of a potentially detectable 'prodromal phase' (period of premonitory symptoms) in the transition from pre-radiographic to radiographic stages of osteoarthritis. In the pre-radiographic stage, magnetic resonance imaging reveals lesions in articular cartilage, subchondral bone, bone marrow, and meniscus that appear to be associated with symptoms[6–8], suggesting a range of plausible sources of pain in this hypothesised prodromal phase. The investigation of prodromes has been an important focus for research in several recurrent-relapsing and chronic long-term conditions[9–12] where its significance is seen in terms of the prospects of early intervention, targeted search for biomarkers, understanding pathogenesis and the process of developing illness or disease, and enriched sampling for efficient trial design. These are also major concerns in osteoarthritis research and our desire to understand the contribution of simple patient-reported information to these goals was a strong motivation behind the current study. However, until recently it was not possible to undertake a prospective investigation of the timing of symptom changes before the occurrence of gross pathological changes on radiographs due to the lack of longitudinal studies that have obtained sufficiently frequent repeated images of the joint and measures of symptoms in persons at risk of developing radiographic knee osteoarthritis (ROA).

The Osteoarthritis Initiative (OAI) was established in 2001. It is a nationwide, multi-centre, longitudinal, prospective observational study of knee osteoarthritis, funded by private-public partnership,

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and developed to provide a unique publicly accessible research resource[13]. In a nested case–control analysis using data from participants enrolled between 2004 and 2006 and with annual plain radiography and measures of symptoms, we hypothesised that the incidence of ROA would be preceded by an increase in symptoms in which the symptoms that were earliest to appear and that had the strongest association with future incidence would be those experienced during more demanding activities involving high mechanical loads on the knee[14].

## Methods

### *Study setting and population*

The study population comprises participants of the OAI 'incidence sub-cohort'[15]. Between 2004 and 2006, 3,284 persons aged 45–79 years and at high risk of developing ROA were enrolled at 4 recruitment centers (Baltimore, MD; Pawtucket, RI; Columbus, OH; Pittsburgh, PA) from a combination of focused mailings, websites, and local advertisements, presentations and meetings. Potential participants were screened by telephone and clinic visit and were enrolled in the incidence sub-cohort if they did not have symptomatic ROA in either knee but were at high risk according to the presence of predetermined age-specific combinations of known risk factors (e.g., frequent knee symptoms, overweight, knee surgery). Individuals with an existing diagnosis of rheumatoid arthritis or other inflammatory arthritis were excluded. Extensive data were collected from participants at enrolment including self-complete questionnaires, personal interview, physical examination and plain radiography. Measures are repeated at annual clinic visits (94%, 89%, 85%, and 80% successfully followed up at 1, 2, 3, and 4 years respectively). All participants signed informed consent, and the study was approved by the institutional review board. Data used in the preparation of this article were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. Specific datasets used were: "enrollees; version 18", "outcomes99; version 3", "allclinical00; version 0.2.2", "allclinical01; version 1.2.1", "allclinical03; version 3.2.1", "allclinical05; version 5.2.1", "allclinical06; version 6.2.1", "physexam00; version 0.2.2", "physexam01; 1.2.1", "physexam03; 3.2.1", "physexam05; version 5.2.1", "physexam06; version 6.2.1", "subjectchar00; version 0.2.2", "subjectchar01; version 1.2.1", "subjectchar03; version 3.2.1", "subject char05; version 5.2.1", "subjectchar06; version 6.2.1", "medhist00; version 0.2.2", "jointsx00; version 0.2.2", "kxr_sq_bu00; version 0.6", "kxr_sq_bu01; version 1.6", "kxr_sq_bu03; version 3.5", "kxr_sq_bu05; version 5.5" and "kxr_sq_bu06; version 6.3".

### *Selection of cases and controls*

We sampled knees that developed incident ROA during follow-up up to 4 years, which were without knee symptoms on most days at enrolment, in order to control for the potential effect of the control group being entered into the OAI for different 'at risk' factors than the cases. Incident ROA, ascertained from fixed-flexion knee radiographs repeated at annual visits, was defined as the new onset of combined definite osteophyte and joint space narrowing in the tibiofemoral joint[16]. This outcome definition is the same as that used in previous studies investigating early disease biomarkers[17], and has been found to be associated with increased risk of further future disease progression[18]. The annual visit at which incident ROA was first identified was denoted in our analysis as time-zero (t0). Initially, the parameter of interest was the incidence rate ratio and so for each case knee, we used concurrent sampling[19] to select 10 control knees, matched for annual visit but not side (left/right) of the incident knee. Under this approach, matched odds ratios estimate incidence rate ratios[20].

### *Potential prodromal symptoms*

Information on potential prodromal symptoms was available at each annual visit from two well-validated and recommended knee-specific self-complete questionnaires[21]: the Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC LK 3.1[22]) and the Knee injury and Osteoarthritis Outcome Score (KOOS[23]). The WOMAC questionnaire comprises items on Pain on activity (5 items, summative subscale score 0–20), Stiffness (2 items, 0–8), and Physical Functioning (17 items, 0–68) with higher scores indicating more severe problems. The KOOS comprises items, with some overlapping content with WOMAC, on Pain (9 items), Other Symptoms (7 items), Function in Daily Living (17 items), Function in Sport and Recreation (5 items), and Knee-related Quality of Life (4 items) which are reverse-scored to provide 0–100 subscale scores with lower scores indicating more severe problems. For both measures all questions were answered separately for each knee with response options typically 'none/mild/moderate/severe/extreme', and the timeframe being 'within the past 7 days'. In our study we used some of these subscale scores (WOMAC Pain, Physical Function and Stiffness, and KOOS Pain and Other Symptoms), categorised as 1 if they had indicated moderate/severe/extreme symptoms on at least 1 of the individual items in the scale and 0 if not, due to the non-normal distribution of the subscale scores, as well as a selection of individual items from these measures (dichotomised into none/mild vs moderate/severe/extreme or never/rarely vs sometimes/often/always) and pain on most days of the month in the last 12 months, to explore the nature of prodromal symptoms. The timing of symptom report was anchored to the timing of incident ROA, i.e., symptoms reported 1, 2, 3, and 4 years before incident ROA were denoted by t0-1, t0-2, t0-3, and t0-4.

### *Statistical analysis*

All analyses were completed in Stata/MP 13.1 (Stata Corporation, TX, USA). The data was set up as survival time data which was then converted to case–control data using the -sttocc- command. Conditional logistic regression, with standard errors adjusted (clustered sandwich estimator) for the clustering between knees within the same person, was used to provide initial estimates of the crude associations between outcome at each time point, i.e., incident ROA, and either subscale scores or dichotomised items. Subscale scores and individual items that differed significantly (Wald test, $P < 0.05$) between cases and controls 1 year before incident ROA, i.e., t0-1, were considered for further modelling. Multi-level logistic regression models were then fitted using the -runmlwin- command[24,25] to estimate the trajectories of the probability of scoring at least 1 item 'moderate', 'severe' or 'extreme' in each subscale and the probability of scoring 'moderate', 'severe', or 'extreme' for each individual item in turn over time for cases and controls, as repeated measures of symptoms were nested within knees and knees were nested within people. The length of prodrome was estimated as the time at which the odds ratio equalled unity, i.e., cases had no increased odds of scoring higher for that subscale/item compared to controls (see Web Appendix). The probabilities of a case and of a control scoring moderate, severe or extreme (or sometimes, often or always) at each time were plotted for each item.

Each model included the same factors: a dummy variable for case–control status, time of visit before t0 measured continuously in years, a product term for interaction between case–control status and time, age measured continuously centred on the mean, sex and a constant term. Time was considered as a non-linear effect