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Progression of osteoarthritis as a state of inertia

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Abstract

Objectives—To test whether knees which recently developed disease were at higher risk for subsequent x-ray progression than knees which had been stable, suggesting that recent change produces further change and recent stability yields subsequent stability (a pattern of inertia).

Methods—We used central readings of the annual posteroanterior x-rays obtained in the Osteoarthritis Initiative (OAI) focusing on change in Kellgren and Lawrence (KL) grade and change in semiquantitative joint space. We examined whether knees that had developed incident disease (KL grade 2) were at higher risk of subsequent progression than knees that were already grade 2 and had had stable disease. We combined data from multiple examinations. Using generalised estimating equations to adjust for the correlation between knees, we carried out logistic regression evaluating the risk for disease progression testing incident versus stable disease adjusting for age, sex, body mass index, physical activity, quadriceps strength and mechanical alignment.

Results—1562 OAI subjects with grade 2 disease had a mean age of 61.8 years, mean BMI of 29.4, and 61.7% were women. Of knees with stable disease, 4.1% showed progression within the next 12 months in KL grade versus 13.7% in those with incident disease (adjusted OR 4.0; 95% CI 2.4 to 6.7). For progression of joint space loss, we found a similar relation with incident versus stable disease (adjusted OR 5.3; 95% CI 3.6 to 7.9).

Conclusions—Knee osteoarthritis radiographic progression follows a pattern of inertia. Factors that trigger the transition from stable disease to progression should be sought.

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Competing interests None.

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INTRODUCTION

Once osteoarthritis (OA) begins in a joint, identifying the factors which accelerate disease progression is critical as these factors might be targets for disease modification. Further, if some knees were shown to have an accelerated pace of progression, these might be targeted in clinical trials testing new agents. Identifying risk factors for progression might also lead to a better understanding of the biology of disease such that if a risk factor were identified, its impact on disease biology could be uncovered and that could, in turn, provide insights into how and why the disease worsens.

OA is thought to be generally 'slowly progressive' with some patients having stabilisation of disease. Reviews of the topic of progression have suggested that there is often a dichotomy between those who experience slow progression of disease and those whose disease is stable over time. Kirwan and Elson[1] have suggested phases of disease worsening followed by periods of joint stability and have suggested that these phases could be identified by biomarkers such as positive bone scans. Progression studies have almost always limited themselves to one baseline and one follow-up radiograph or imaging evaluation; it necessarily follows that studies could not evaluate whether there were phases of progression and stability rather than just a continuous slow deterioration in joint structure. Since the studies have not generally had repeated assessments of disease structure such as repeated x-rays or MRIs, it has not been possible to evaluate this phasic hypothesis or test others about disease progression.

In terms of risk factors for progression, a recent best evidence synthesis[2] reported frustratingly few consistent risk factors for disease worsening. Among consistent factors tied with disease progression in the knee were generalised OA and serum hyaluronic acid. These authors and others[3,4] have noted that such major factors as age, gender and body mass index have not been consistently tied to progression of disease even though increased weight has clearly and consistently been noted as a risk factor for new onset disease.[3] To our knowledge, no one has examined whether recent disease worsening or disease development affects the subsequent rate of disease progression.

The Osteoarthritis Initiative (OAI), a study whose protocol included annual x-rays on subjects, provides a unique opportunity to examine the pattern of disease worsening in knee OA. If there were phases of disease as previously suggested, disease activity might be followed by more disease activity, and stability might be superseded by more stability. The principle of inertia, a fundamental principle of classical physics, refers to resistance of any object to change in its state of motion or rest. If disease worsening fits a pattern of inertia, then if it is unchanging, it will remain unchanged and if it is progressing, it will continue to progress. Based on previous anecdotal observations from earlier OA cohort studies where our group was responsible for reading serial x-rays, we hypothesised that OA worsening would fit a pattern of inertia. If this hypothesis were true, then persons at high risk of future progression could be identified as those with recent onset or worsening of disease and could be the focus of disease treatment and prevention efforts.

METHODS

Study sample

The OAI study is a longitudinal cohort study of risk factors for incidence and progression of OA. Men and women aged 45–79 years with or at a high risk of knee OA were recruited from four sites in the USA: Columbus, Ohio; Providence, Rhode Island; Baltimore, Maryland; and Pittsburgh, Pennsylvania (www.oai.ucsf.edu). Eligibility for OAI required either that the subject already had at least one knee with symptomatic knee OA (frequent pain and Kellgren and Lawrence grade 2 or greater in the same knee) or was at a high risk of getting symptomatic OA by dint of risk factor status: they had either frequent knee pain without x-ray OA, were overweight, had a history of major knee injury or knee surgery, had a family history of knee replacement for OA, Heberden's nodes or were currently engaged in frequent knee bending activities. Assessment was carried out annually including questions on knee pain and x-rays. Risk factor assessments included weight and height, age, sex, isometric quadriceps strength, and physical activity using the Physical Activity Survey for the Elderly (PASE) questionnaire.

Radiographic methods and scoring

In the OAI, subjects obtained posteroanterior weight bearing knee radiographs annually using a Synaflexer frame (Synarc, San Francisco, California, USA) to create a fixed standardised and reproducible knee position. This protocol has been shown to provide reproducible estimates of joint space and provide consistency in terms of the image of the knee over time.[56]

X-ray readings were carried out centrally at Boston University by a team of three readers. For each ID, all x-rays from a subject were read paired. The baseline film was identified as such but the other films in the sequence were blinded to order. Each of the two readers (PA and BS) read all x-rays from all subjects. If there was a disagreement as to whether the knee at any time point had radiographic OA (Kellgren and Lawrence grade 2 or greater) or if between time points there was disagreement as to whether there was a worsening of disease (defined either as an increase in Kellgren and Lawrence grade or as an increase in joint space narrowing grade), the reading was adjudicated by a panel of three readers including the two who read the films (PA and BS) and one other reader (DTF). A consensus reading was arrived at when at least two of the three readers agreed. Most of the adjudication was carried out by the third reader alone and if he disagreed with both readers or could not determine which of the two readers were correct, the film was evaluated at the adjudication panel by all the three readers. Approximately 5% of all subject images came to this panel. Because of the large change required in a joint space width to progress a whole integer in score (eg, from grade 0 to 1, 1 to 2 or 2 to 3), we created a partial grade narrowing scoring system that allowed us to characterise change in joint space width when that change was clear-cut but did not reach an integer change threshold (for details, see[7]). For example, if a baseline knee had a medial joint space score of 1 and medial narrowing had clearly progressed in a subsequent image but the subsequent narrowing did not reach the threshold for grade 2 narrowing according to the OARSI Atlas,[8] then we gave that subsequent knee a partial grade (eg, 1.5) between 1 and 2. In previous work,[7] we have validated these partial

grades by showing that they corresponded to other measures of worsening such as malalignment, cartilage loss and others. The blinding to sequence of the x-rays prevented the readers from inferring that prior change would lead to subsequent change, making it impossible for them to confirm or deny the hypothesis being tested here. Agreement was high when the same knee films were sent repeatedly by the coordinating centre (for Kellgren and Lawrence grade, weighted κ=0.75, p<0.0001; for medial JS grade, weighted κ=0.745, p<0.0001; and for lateral JS grade, weighted κ=0.855, p<0.0001).

Case definitions and index exam

Cases of incident radiographic OA were defined according to Felson *et al*[9] as the new onset of a combination of joint space narrowing and osteophytes. New cases at the time they developed incident disease would, by definition, be Kellgren and Lawrence grade 2 or greater. For the purposes of this analysis, we defined an index exam as the exam when the follow-up evaluation of disease progression started. The exposure group of interest was knees that developed new incident disease within the 12 months before the index exam and that had scores at the index exam of Kellgren and Lawrence grade 2. The non-exposed group consisted of all the other knees that had a Kellgren and Lawrence grade 2 score at that index exam but that had not changed in the year before the index exam (we shall call these stable knees). For example, for an analysis of risk of progression/worsening between 12 and 24 months, 12 months would be the index exam and we would examine knees that had developed incident disease from 0 to 12 months and compare these with knees which had stable Kellgren and Lawrence scores of 2 at 0 and 12 months. Knees with stable disease could be used repeatedly in this analysis, with index dates conceivably at 12, 24 and even 36 months.

Our analysis focused on whether change in the year prior to the index exam predicted subsequent change in a knee and to carry out this analysis, we needed to select annual examinations where there was a prior and a subsequent x-ray. OAI obtained x-rays at 0, 12, 24, 36 and 48 months but the first and last time points were not usable for our purposes since they did not have either an antecedent (baseline) or follow-up (48 months) examination in which to test our theory. Thus, we focused on the 12-, 24- and 36-month examinations. Progression was defined when Kellgren and Lawrence grade increased or a new knee replacement occurred after the index exam. Progression in joint space narrowing was defined as present if either medial or lateral joint space developed a higher score or a new knee replacement occurred at follow-up. In addition to testing grade 2 incident knees versus stable knees, we also evaluated whether antecedent joint space loss resulting in grade 2 disease at the index exam was a risk factor for subsequent joint space loss. Further, we evaluated whether antecedent change either in Kellgren and Lawrence grade or in joint space predicted not just the change in the year after the index exam, but the subsequent year.

Statistical analysis

We carried out logistic regression using knee specific status as the exposure with generalised estimating equations used to adjust for the correlation between knees. We combined data from multiple examinations characterising the knee status at each examination and its prior change to test its risk for subsequent change. In addition to crude analyses, we carried out

analyses adjusted for age, sex, race, body mass index and clinic site. In some studies, malalignment has been shown[1011] to be a powerful risk factor for disease progression, but long limb films used to assess mechanical alignment were not available in all OAI subjects and were obtained at different examinations. Further, since alignment changes with the development of OA, we could not use malalignment status at the 12-month exam to stand in for its status at later examinations. Therefore, to examine malalignment, we limited analyses to only the examination at which long limb films were acquired and for only those limbs and knees with a mechanical axis measurement. To compare covariates in those with incident versus stable disease, we used t tests and χ^2 as appropriate.

Because of concerns that knees with recent incident disease may have more advanced (severe) disease than those with persistent prevalent disease due to the requirement for incidence that both joint space narrowing (JSN) and osteophytes be present and that at least one of these be a new finding, we carried out additional analyses in which we required that knees tested for risk of progression had Kellgren and Lawrence grade 2 and a joint space narrowing grade of 1 at the index exam, so that the stable knees had Kellgren and Lawrence (KL) grade 2 and JSN grade of 1 prior to the index exam.

Last, we used a different approach, a latent variable mixed effects model, to examine the correlation among knee specific change in joint space narrowing during different time intervals. The latent variables were baseline maximal JSN score and change of maximal JSN score during each 12-month interval. The measure of interest for this analysis was derived from the covariance matrix between random effects of latent variables.

RESULTS

When we examined knees that had recently developed incident OA and Kellgren and Lawrence grade 2 versus those that had had Kellgren and Lawrence grade 2 (table 1), we found that their ages and average body mass indices were similar. There were a slightly greater number of women in those with recent development of incident OA and the proportion of knees that were affected by knee pain was modestly higher in those with recent incident OA than with knees where the Kellgren and Lawrence grade had been present in earlier films. Neither the percentage of knees with pain nor knee pain severity based on a visual analogue scale assessment was significantly different in the group with incident versus stable OA. There were also no significant differences between groups in quadriceps strength. Clinical centre A showed fewer incident cases (p=0.065) than the other centres. We saw similar differences between the two groups when we looked at knees with recent joint space narrowing worsening versus no change in joint space narrowing.

We first tested our inertia hypothesis by examining knees with Kellgren and Lawrence grade 2 comparing those knees which had recently developed incident OA versus those which had had stable OA. Of 139 knees with incident Kellgren and Lawrence grade 2, 19 (13.7%) developed a higher Kellgren and Lawrence grade in the year after the index exam versus only 4.1% of those which had had a stable grade (see table 2). This translated into an adjusted OR for progression of Kellgren and Lawrence grade of 4.0 (95% CI 2.4 to 6.7) (see table 2).

The likelihood of Kellgren and Lawrence worsening increased in the initial 12 months after the index exam, and it remained modestly increased in the period 12–24 months after the index exam (see table 3).

We then examined whether the same was true of worsening of joint space narrowing. We limited this examination to those knees with grade 2 at the index date and in those knees, we separated those whose joint spaces had worsened in the previous year versus those which had stable joint space scores. Of 167 knees with recent worsening in joint space narrowing and Kellgren and Lawrence grade 2 at the index date, 43 (25.8%) showed a further worsening of joint space narrowing in the 12 months after the index exam (see table 4). This compares with only 6.1% of knees in which the joint space narrowing grade (0 or 1) had been stable before the index exam. Joint space narrowing progression prior to the index exam conferred an increased risk of joint space narrowing progression in the 12 months after the index exam (adjusted OR of 5.3 (93% CI 3.6 to 7.9)). Joint space narrowing prior to the index exam conferred an increased risk of joint space narrowing progression in the 12 months after the index exam and increased the risk of worsening joint space narrowing interval from 12 to 24 months after the index exam. For example, a knee that went at baseline from a joint space narrowing of 0 to 1 at 12 months had a higher risk of worsening joint space narrowing between 24 and 36 months than a knee which between baseline and 1 year had a joint space narrowing score that was constant at both times.

Only a subset of knees had mechanical axis of the limb assessed at one of the exams in OAI. When we adjusted these analyses additionally for mechanical alignment measured in these limbs, we found no change in the OR for progression, suggesting that mechanical alignment at the time of the Kellgren and Lawrence grade and the beginning of follow-up did not confound the increased risk that we noted.

We also repeated all analyses using knees that had Kellgren and Lawrence grade 2 and joint space narrowing scores of 1 at the index exam. The results were unchanged (data not shown).

We carried out latent variable analyses to examine the correlations of joint space loss at one interval versus others. The 0–12-month joint space loss was correlated with the 12–24-month loss ($r=0.65$, $p<0.0001$) and the 0–12-month loss was modestly correlated with the 24–36-month loss ($r=0.38$, $p=0.0002$) and 36–48-month loss ($r=0.33$, $p=0.0012$).

DISCUSSION

Our findings confirm our hypothesis that the structural course of OA fits a pattern of inertia. For knees that have been experiencing radiographic deterioration at least in terms of joint space narrowing, there is likely to be further worsening defined as further narrowing for 12 and 24 months afterward. For knees with disease that has been stable, it is likely that they will remain stable.

Our data do not necessarily support the hypothesis that OA progression is phasic, that is, that some progression occurs and then there is stability followed by another period of

progression. Rather, our data suggest that, after some incipient event which propels disease worsening, a long period of disease progression transpires.

Our findings have implications for the study of risk factors and of disease progression in OA. First, they suggest that it is possible to identify knees that are at a substantial increased risk of ongoing progression but that to do so one needs historical information about recent progression. Second, it suggests that there are likely to be risk factors that propel this process, a process which often may lead from early to end-stage disease in a few years. Identifying such factors could, in theory, abrogate structural progression in a substantial minority of knees. If one focused for example on preventing joint space loss, table 4 suggests of 348 knees with joint space loss over a 1 year period of time (305+43), 43 or 12.4% belong to this phenotype in which progression extends from a year prior. Our findings could be identifying a subset of knees in which deterioration occurs at a high rate over at least 2–3 years.

Our findings also speak to the evaluation and scoring of radiographs in knee OA. First, they point out that both Kellgren and Lawrence grades and joint space narrowing scores represent artificial mileposts that imperfectly measure disease progression on a continuum. Also, the effect we saw was better detected by evaluating joint space change on the radiographs than it was by examining Kellgren and Lawrence grade, a matter we have recently discussed.[9] Osteophytes alone, which sometimes define Kellgren and Lawrence grades, may not be as meaningful as measures of progression of even of disease state as is joint space narrowing when acquired using a standardised approach. Osteophytes can appear to change with small changes in the rotation in an image and rotational positioning is difficult to standardise.

While a one-time measurement of mechanical alignment did not attenuate the effect we found, changes in alignment as disease develops could be a major cause of the rapid disease progression we identified. Such changes must be considered along with possible changes in inflammatory state of the joint or other factors as causes of this rapid progression subset.

Our study is limited in that it relies on radiographs which are an imperfect way of evaluating structural pathology within the knee. It is likely that in the future an evaluation of the same phenomenon can occur using MRI. Also, our study was carried out in an older population with a high prevalence of obesity. It remains to be seen whether a similar pattern of progression would be seen in a younger, thinner population.

It might be noted that incidence increased the risk of progression between 12 and 24 months after the index date but that the finding was not statistically significant. Numbers of knees followed were smaller, making the dichotomous outcome of progression challenged by sample size. When we looked at the same issue using latent variable analyses, we found a strong statistically significant relationship between earlier incidence and joint space loss starting 12 months after index ($r=0.38$, $p=0.0002$) and even starting 24 months after index date ($r=0.33$, $p=0.0012$). We suggest that joint space loss predicts later joint space as long as 2–3 years later. Even so, the course of OA usually is longer than 2–3 years and our window on the disease is still relatively short. Also, our knees with stable disease must have been incident cases at one time, so that their disease trajectory slowed.

It is possible that knees with Kellgren and Lawrence grade 2 which had recently changed had more severe disease than knees with Kellgren and Lawrence grade 2 whose course had been static. Previous work has shown that progression occurs more rapidly and is more likely in those with severe structural disease than in those with milder disease.[12,13] In additional analyses in which we held Kellgren and Lawrence grade and joint space narrowing grade constant in those at the index exam, we found no difference in results.

We[14] and others[15] have written that accurately identifying risk factors for disease progression is formidably difficult especially in OA.[14] There are two major reasons underlying the problems in studying progression. First, diseased joints all have risk factors for incidence and these are likely to be the same as risk factors for progression; thus, a risk factor may spuriously fail to show effects on progression even when it increases the risk of incidence (eg, see Niu *et al*[3] and the relation of obesity to OA progression). This first problem relates to why real risk factors for progression are not detected as such but the factor we have studied clearly shows an increased risk of progression. Second, in studies of risk factors for progression, there may be a 'horse racing' phenomenon[16] in which knees with a possible risk factor for progression have more severe prevalent disease than other knees, and those with more severe prevalent disease are more likely to progress.[13] Most OA progression studies include joints with prevalent grade 2 and 3 and those with grade 3 or more advanced disease, could, to use the horse racing analogy, be farther along in the race and therefore, closer to the finish line. We have tried to adjust for this possibility by limiting our analyses to grade 2 Kellgren and Lawrence prevalent disease and even carried out secondary analyses in which we required knees at the index date have both KL grade 2 and a narrowing grade of 1. Even so, we cannot exclude the possibility that recent incidence increases the apparent risk of progression because knees with recent incidence have worse structural disease than knees with persistent prevalent disease.

In summary, the course of knee OA follows a pattern of inertia. Knees that are progressing are far more likely to continue to progress than knees which have been stable in terms of structural deterioration. These findings have broad implications for our understanding of the biology of disease and for the identification of a rapidly progressive subcohort of disease and provide opportunities for the investigation of factors which propel rapid deterioration.

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Table 1

Characteristics of knees in the study according to whether there was prior change

	All	By KL grade change in the year before the index exam		By JSN change in the year before the index exam	
		Constant KL=2	Incident OA	No JSN increase	JSN increase
	2037 knees (1562 subjects)	1898 knees (1427 subjects)	139 knees (135 subjects)	1948 knees (1476 subjects)	167 knees (146 subjects)
Baseline age, year, mean (SD)	61.8 (9.0)	61.8 (9.0)	61.3 (8.6)	61.7 (9.0)	62.3 (8.8)
Baseline BMI, kg/m^2, mean (SD)	29.4 (4.8)	29.4 (4.8)	29.3 (4.3)	29.4 (4.8)	28.7 (4.6)
N (%) female	963 (61.7)	869 (60.9)	94 (69.6)	904 (61.3)	59 (68.6)
N (%) Whites	1227 (78.6)	1115 (78.2)	112 (83.0)	1150 (78.0)	77 (89.5)
Baseline PASE, mean (SD)	158.3 (82.0)	158.6 (82.7)	156.1 (74.5)	158.5 (82.1)	155.7 (82.1)
Baseline/12-month quadriceps strength,* mean (SD)	325.8 (128.2)	324.5 (128.0)	343.0 (130.1)	324.9 (128.3)	337.2 (126.6)
Clinical centre					
A	260 (16.7)	246 (17.24)	14 (10.4)	250 (16.9)	10 (11.6)
B	317 (20.3)	287 (20.11)	30 (22.2)	298 (20.2)	19 (22.1)
C	454 (29.1)	420 (29.43)	34 (25.2)	427 (28.9)	27 (31.4)
D	388 (24.8)	343 (24.04)	45 (33.3)	364 (24.7)	24 (27.9)
E	143 (9.2)	131 (9.18)	12 (8.9)	137 (9.3)	6 (7.0)
N (%) knee pain more than half the days of a month in the past 12 months at the index visit	632 (31.2)	584 (30.9)	48 (34.8)	601 (31.0)	31 (35.2)
N (%) knee pain more than half the days of a month in the past 30 days at the index visit	567 (28.0)	5252 (27.8)	42 (30.4)	542 (27.9)	25 (28.4)
Knee pain severity in the past 30 days, scale 0–10, mean (SD), at the index visit	2.6 (2.7)	2.6 (2.7)	2.5 (2.6)	2.6 (2.7)	2.8 (2.7)

*Quadriceps strength from baseline was used. If strength was not assessed at the baseline visit, we used the 12-month value.

BMI, body mass index; JSN, joint space narrowing; KL, Kellgren and Lawrence; OA, osteoarthritis; PASE, Physical Activity Survey for the Elderly.

Table 2

Risk of progression in the year after index examination as a function of whether knee had incident versus stable disease in year prior to index examination*

KL grade change in the first 12-month period	N of knee-visits	N (%) of knees with KL grade progression in the second 12-month period	Unadjusted		Adjusting sex, race, baseline age, BMI, clinic site, PASE and quadriceps strength	
			OR (95% CI)	p Value	OR (95% CI)	p Value
0–1 to 2 (incident osteoarthritis)	139	19 (13.7)	3.7 (2.2 to 6.1)	<0.0001	4.0 (2.4 to 6.7)	<0.0001
2 to 2 (constant KL grade)	5008	206 (4.1)	1.0		1.0	

*For example, for a 12-month knee x-ray, we are comparing knees which developed incident KL grade 2 at 12 months with knees that had KL grade 2 at both baseline and 12 months. The 12-month period for this example would be the period from 12 to 24 months.

BMI, body mass index; KL, Kellgren and Lawrence; PASE, Physical Activity Survey for the Elderly.

Table 3

Risk of annual progression starting 12 months after index examination as a function of whether knee had incident versus stable disease in year prior to index examination

KL grade change in the first 12-month period	N of knees	N (%) of knees with KL grade progression in the third 12-month period	Unadjusted		Adjusting sex, race, baseline age, BMI, clinic site, PASE and quadriceps strength	
			OR (95% CI)	p Value	OR (95% CI)	p Value
0–1 to 2 (incident osteoarthritis)	93	7 (7.5)	1.8 (0.8 to 3.9)	0.15	2.0 (0.9 to 4.4)	0.10
2 to 2 (constant KL grade)	3173	138 (4.4)	1.0		1.0	

BMI, body mass index; KL, Kellgren and Lawrence; PASE, Physical Activity Survey for the Elderly.

Table 4

Risk of joint space narrowing progression after index examination as a function of whether knee had incident versus stable joint space loss in year prior to index examination

JSN increase in the 12-month period before the index exam	N of knee-visits	N (%) of knees with JSN progression in the year after the index exam*	Crude		Adjusting sex, race, baseline age, BMI, clinic site, PASE and quadriceps strength	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Yes	167	43 (25.8)	5.4 (3.7 to 7.9)	<0.0001	5.3 (3.6 to 7.9)	<0.0001
No	4979	305 (6.1)	1.0		1.0	
JSN increase in the 12-month period before the index exam		N (%) of knees with JSN progression in the year starting 12 months after the index exam†				
Yes	114	36 (31.6)	5.1 (3.2 to 8.1)	<0.0001	5.6 (3.5 to 8.8)	<0.0001
No	3314	224 (6.8)	1.0		1.0	

*12 months, 24 months and 36 months were the visits with KL grade=2.

†12 months and 24 months were the visits with KL grade=2. We could not use the 36-month index exam because follow-up radiographs with readings did not extend 24 months afterward.

BMI, body mass index; JSN, joint space narrowing; KL, Kellgren and Lawrence; PASE, Physical Activity Survey for the Elderly.