Published in final edited form as:
Arthritis Care Res (Hoboken). 2014 November ; 66(11): 1673–1679. doi:10.1002/acr.22359.

Knee Injuries Are Associated with Accelerated Knee Osteoarthritis Progression: Data from the Osteoarthritis Initiative

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Abstract

Objective—We aimed to evaluate if a recent knee injury was associated with accelerated knee osteoarthritis (KOA) progression.

Methods—In the Osteoarthritis Initiative (OAI) we studied participants free of KOA on their baseline radiographs (Kellgren-Lawrence [KL]<2). We compared three groups: 1) individuals with accelerated progression of KOA: defined as having at least one knee that progressed to end-stage KOA (KL Grade 3 or 4) within 48 months, 2) common KOA progression: at least one knee increased in radiographic scoring within 48 months (excluding those defined as accelerated KOA), and 3) no KOA: no change in KL grade in either knee. At baseline, participants were asked if their knees had ever been injured and at each annual visit they were asked about injuries during the prior 12 months. We used multinomial logistic regressions to determine if a new knee injury was associated with the outcome of accelerated KOA or common KOA progression after adjusting for age, sex, body mass index, static knee malalignment, and systolic blood pressure.

Results—A knee injury during the total observation period was associated with accelerated KOA progression (n=54, odds ratio [OR]=3.14) but not common KOA progression (n=187, OR=1.08). Furthermore, a more recent knee injury (within a year of the outcome) was associated with accelerated (OR=8.46) and common KOA progression (OR=3.12).

Conclusion—Recent knee injuries are associated with accelerated KOA. Most concerning is that certain injuries may be associated with a rapid cascade towards joint failure in less than one year.

While knee osteoarthritis is typically a slowly progressive disorder, it has recently been appreciated that 5 to 17% of knees have a rapid progression of structural damage (e.g. from normal to end-stage disease within 4 years) (1, 2). Characterization of the structural aspects of this phenomenon and its risk factors may provide insights into the nature of osteoarthritis progression and allow us to identify an at-risk subset for intervention. Identification of knee osteoarthritis phenotypes, such as those with accelerated knee osteoarthritis progression, may allow us to refine sampling for clinical studies (2-5) and develop interventions targeted at specific subtypes.

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The authors have no other conflicts of interest with regard to this work.

Individuals with a history of joint trauma are 3 to 6 times more likely to develop knee osteoarthritis (6, 7) and are diagnosed approximately 10 years earlier than individuals without a history of joint trauma (8). Within 5 years of injury, knees have structural changes reflective of altered joint health (e.g., altered cartilage composition, altered bone structure) (9-12). Knee injuries are a strong risk factor for knee osteoarthritis and may distinguish knees with accelerated knee osteoarthritis from common knee osteoarthritis progression or knees with no knee osteoarthritis. We aimed to evaluate if a recent knee injury was associated with accelerated knee osteoarthritis. Furthermore, we conducted preliminary analyses to determine if participants with accelerated knee osteoarthritis progression, common knee osteoarthritis progression, and no knee osteoarthritis differed based on key baseline characteristics, which we selected *a priori*. These preliminary analyses helped us verify which variables should be adjusted for in our primary analyses.

Patients and Methods

To assess the association between recent knee injuries and accelerated knee osteoarthritis we used data from the Osteoarthritis Initiative (OAI). The OAI is a multicenter observational cohort study of knee osteoarthritis that collected longitudinal clinical and image data (13) as well as biospecimens from 4,796 participants over an eight-year follow-up period. The primary variables (presence of radiographic knee progression and knee injuries) were from baseline and the first four annual OAI visits (months 0 to 48). OAI data are available for public access (14).

Participant Selection

Among participants with no baseline radiographic knee osteoarthritis (Kellgren-Lawrence [KL] Grade<2) in either knee (n = 1,930) we evaluated three groups that we defined based on radiographic definitions of OA: 1) accelerated knee osteoarthritis: at least one knee progressed to end-stage knee osteoarthritis (KL Grade 3 or 4) within 48 months, 2) common knee osteoarthritis progression: at least one knee increased in radiographic scoring within 48 months (excluding those defined as accelerated knee osteoarthritis progression), and 3) no knee osteoarthritis: no change in KL grade in either knee at baseline and 48-month follow-up. We omitted 364 (18.9%) individuals from the analyses because missing radiographic data made it impossible to determine group assignment (19 potential individuals with common knee osteoarthritis progression, 345 potential individuals with no knee osteoarthritis).

Self-Reported Knee Injury

At baseline, participants were asked during an initial eligibility interview: “Have you ever injured your right knee badly enough to limit your ability to walk for at least two days?”. A similar question was asked for the left knee. At each annual visit participants were asked “Since your last annual visit to the OAI clinic about 12 months ago, have you injured your right knee badly enough to limit your ability to walk for at least two days?”. A similar question was asked for the left knee. Among individuals with accelerated or common knee osteoarthritis progression we focused on injuries to the knee that progressed. Among

individuals with no knee osteoarthritis we evaluated if the participant had a knee injury to either knee.

We focused on injuries at 4 time points: 1) prior to the OAI baseline, 2) during the total observation period, 3) within one year of the study outcome, and 4) between 1 and 2 years prior to the study outcome. We defined the study outcome visit for each group as follows: 1) accelerated knee osteoarthritis: the first visit with a KL grade of 3 or 4, 2) common knee osteoarthritis progression: the first visit with an increase in KL grade, and 3) no KOA: the 48-month OAI visit. The total observation period was defined as beginning at the OAI baseline and ending at the visit with the study outcome (ranging from 12 months to 48 months). For example if a participant had a knee with KL=1 at baseline and year one, KL=2 at year 3, and KL=3 at year 4, they would meet criteria for the accelerated group, and year 4 would be the outcome study visit. However, if a participant's knee stayed at KL=2 at 48 months, they would be considered to have common knee osteoarthritis and year 3 would be the study outcome visit. Finally, if the participant stayed at KL=1, then year 4 would be the study outcome visit.

Knee Radiographs

Weight-bearing, bilateral, fixed-flexion, posterior-anterior knee radiographs were obtained at baseline and the first 4 annual OAI visits. Central readers, who were blinded to sequence of follow-up radiographs, scored the paired images for KL Grades (0 to 4). The agreement for these readings (read-reread) was good (weighted kappa (intra-rater reliability) = 0.70 to 0.78). These KL grades are publicly available (Files: kXR_SQ_BU00_SAS (version 0.6) , kXR_SQ_BU01_SAS(version 1.6) , kXR_SQ_BU03_SAS(version 3.5), kXR_SQ_BU05_SAS(version 5.5) and kXR_SQ_BU06_SAS (version 6.3) (14)).

Clinical Data

Demographic, anthropometric, and other participant demographic characteristics, which we selected *a priori*, were acquired based on a standard protocol (data and protocol are publicly available (14)).

At the OAI baseline visit, research staff measured static knee alignment with a goniometer while the participant stood with feet approximately shoulder-width apart and toes directed straight ahead. The staff positioned the goniometer based on a standard protocol: 1) goniometer's axis was proximal to the tibial tuberosity in line with the knee joint line, 2) distal arm of the goniometer was aligned with the tibia and pointed towards the center of the ankle, and 3) proximal arm of the goniometer was aligned with the mid thigh. Normal alignment was defined as 0 degrees and any deviation was defined as varus or valgus malalignment.

Statistical Analyses

We first evaluated the distribution of baseline descriptive characteristics among the three groups with Chi-square tests or analyses of variance (with Tukey HSD post-hoc comparisons as needed). Based on the initial analyses we entered baseline descriptive characteristics that may distinguish individuals with accelerated knee osteoarthritis (i.e.,

variables with p values < 0.10 and a sufficient sample size) into a multinomial stepwise logistic regression model to determine if they were associated with accelerated knee osteoarthritis progression as an outcome compared with no knee osteoarthritis or common knee osteoarthritis progression.

For our primary analyses, we used multinomial logistic regressions to determine if a history of knee injury or a new knee injury was associated with the outcome of accelerated or common knee osteoarthritis progression before and after adjusting for age, sex, body mass index (BMI), presence of static knee malalignment, and systolic blood pressure. We also conducted a secondary analysis by replicating these analyses with 71 additional individuals who had accelerated knee osteoarthritis but their contralateral knee had prevalent knee osteoarthritis at baseline. This permitted us to explore our hypothesis in a larger sample size.

Results

Baseline Participant Characteristics

Individuals with accelerated knee osteoarthritis (n = 54) tended to be older and have greater baseline BMI and systolic blood pressure (see Table 1). Specifically, in the post hoc analyses we found that individuals with accelerated knee osteoarthritis were older than those with common knee osteoarthritis progression (p = 0.02) and had a greater BMI than those with no knee osteoarthritis (p = 0.01). The frequency of static knee malalignment was not different between individuals with accelerated knee osteoarthritis and the other two groups but individuals with no knee osteoarthritis were more likely to have knee malalignment than individuals with common knee osteoarthritis progression (p = 0.01). None of the post-hoc analyses supported a difference in systolic blood pressures among the groups. Only baseline age (odds ratio [OR] = 1.04, 95% confidence interval [CI] = 1.01 to 1.08; per year) and BMI (OR = 1.10, 95% CI = 1.03 to 1.17; per kg/m^2) were associated with accelerated knee osteoarthritis progression compared with those with no knee osteoarthritis. In comparison with individuals with common knee osteoarthritis, only age was associated with developing accelerated knee osteoarthritis progression (OR = 1.05, 95% CI = 1.01 to 1.09; per year). Accelerated knee osteoarthritis progression was not associated with a history of injury prior to OAI baseline (see Table 2).

New Knee Injuries

A knee injury during the total observation period was associated with accelerated knee osteoarthritis (odds ratio [OR] = 3.37, 95% CI = 1.82 to 6.25) but not common knee osteoarthritis progression (OR = 0.99, 95% CI = 0.61 to 1.61, see Table 2). Furthermore, a recent knee injury (within the year of meeting the study outcome) was associated with accelerated (OR = 9.22, 95% CI = 4.50 to 18.90) and common knee osteoarthritis progression (OR = 3.04, 95% CI = 1.66 to 5.58). Our analyses among individuals with no history of knee injury prior to the OAI baseline and the secondary analysis supported our primary findings.

Discussion

Knee injuries are an important risk factor for knee osteoarthritis and may lead to an early onset of knee osteoarthritis (6-8). Our findings further support the hypothesis that knee injuries may be an important risk factor for the development of accelerated knee osteoarthritis. Perhaps most concerning is that certain injuries may initiate or coincide with a rapid cascade towards joint failure that may occur in less than one year. Thirteen out of the 17 individuals with accelerated knee osteoarthritis and a knee injury during the total observation period experienced their injury in the year prior to developing end-stage osteoarthritis (KL ≥ 3; definite joint space narrowing). Therefore, the first year after an injury may be an important time frame to differentiate those susceptible to accelerated knee osteoarthritis, common knee osteoarthritis progression, or no knee osteoarthritis. Despite an emphasis on a hypothesis that injuries cause accelerated osteoarthritis, an alternative explanation for our findings is that the onset of accelerated knee osteoarthritis increases the risk of injury. If this is true, this could create a vicious cycle where accelerated knee osteoarthritis leads to an injury, which subsequently leads to another phase of accelerated knee osteoarthritis. If we can identify which injuries are associated with accelerated and common knee osteoarthritis progression then this may enable us to recognize these potential phenotypes.

The odds of having knee osteoarthritis after joint trauma are 3 to 6 times higher than an individual without a history of knee injury (6, 7). During the total observation period, we observed similar odds ratios for individuals who developed accelerated knee osteoarthritis; but, this was not the case for individuals with common knee osteoarthritis progression. Future research to determine why some patients develop accelerated knee osteoarthritis after a knee injury while others develop common knee osteoarthritis progression or no knee osteoarthritis will be instrumental in identifying individuals at highest risk for structural progression after an acute knee injury. Individuals with accelerated knee osteoarthritis tended to be older and more obese; therefore, obesity and age may be important factors. However, after we adjusted for age and BMI the association between knee injury and accelerated knee osteoarthritis was still significant.

While the association between recent knee injury and accelerated knee osteoarthritis progression is independent of age and BMI we could not explore some important factors in this study: the type, severity, mechanism, subsequent treatment of the knee injury. An individual with an anterior cruciate ligament tear and cartilage damage or meniscal pathology (including partial meniscectomy) is more likely to have radiographic knee osteoarthritis later in life than an individual with an isolated anterior cruciate ligament tear (15-18). Furthermore, certain types of meniscal pathology (e.g., meniscal root injuries) may be associated with spontaneous osteonecrosis and thus accelerated joint degeneration (19, 20). While certain injuries may predispose a knee to accelerated osteoarthritis, the role of subsequent treatment (e.g., surgery, rehabilitation, return-to-activity timeline) at modifying the risk of osteoarthritis remains poorly understood. Now that we verified that knee injuries are associated with accelerated knee osteoarthritis we need to determine the type, severity, and mechanism of the injury as well as subsequent treatment so that we can better understand who and why some injuries are associated with accelerated knee ostearthritis.

Our findings should also raise awareness that this research needs to include older adults with injuries and not just younger, physically active individuals that tend to be included in these studies (16, 21, 22).

Thirteen out of the 17 injuries among individuals with accelerated knee osteoarthritis and 18 out of 23 injuries among individuals with common knee osteoarthritis progression experienced their injury within the year of reaching their study outcome. This supports a hypothesis that the first year or two after an injury is an important time frame that may set a path to joint failure (23-25). This suggests that we will need to determine which type, severity, mechanism, or subsequent treatment of the knee injury predispose individuals to the onset of accelerated or common knee osteoarthritis progression and then attempt to recognize these injuries as soon as possible. If researchers want to pursue clinical trials among individuals that are at risk for progression then it may be ideal to recruit participants at the time of an injury.

While injuries may cause accelerated osteoarthritis, we cannot rule out that knee osteoarthritis progression (accelerated or common) may increase the risk of injury. This alternative hypothesis may explain why the association between injury and osteoarthritis progression (accelerated or common) is greater during the 12 months prior to the study outcome compared with the association found with injuries during the total observation period, which include time intervals with no osteoarthritis progression. Knee osteoarthritis and knee pain are associated with altered neuromuscular control (e.g., proprioception, muscle activation patterns)(26-28), which may increase the risk of injury or falls (29, 30). If osteoarthritis progression influences neuromuscular control then an individual may be more susceptible to knee injury. If this hypothesis is true, then it may be important for clinicians to monitor older patients who report a knee injury because it could be an indicator that the joint is experiencing the onset or progression of osteoarthritis. This could also introduce a vicious cycle where osteoarthritis progression may lead to a knee injury, which could further hasten the degenerative changes.

An acute injury may be a very important risk factor for accelerated knee osteoarthritis among this sample but we still need to better understand what triggered accelerated knee osteoarthritis among the 70% that did not suffer an acute knee injury during the total observation period. It's possible that some of these individuals suffered minor perturbations to the joint that may not have been reported as an injury but nonetheless compromised the integrity of joint tissues. Subsequently, these altered structures may have exposed the joint to repetitive overloading, which could further compromise other tissues like the subchondral bone and articular cartilage(31).

This study highlights the importance of knee injuries in the incidence of accelerated knee osteoarthritis but has several limitations. As noted previously, we lack granular detail about the knee injury and if joint structures could have been compromised during the total observation period despite the participant reporting that they had no new knee injuries. Conversely, many participants (n = 145) reported an injury despite no radiographic evidence of osteoarthritis progression (accelerated or common). This could be attributable to a lack of data regarding the type, severity, mechanism, or subsequent treatment of the knee injury and

limitations of self-reported injury data. Some individuals may have reported an injury that was not an intraarticular injury or only a minor injury that is not associated with knee osteoarthritis. These analyses were also limited to 54 individuals with incident accelerated knee osteoarthritis. We attempted to address this concern by conducting a secondary analysis among 71 additional individuals who had accelerated knee osteoarthritis but their contralateral knee had prevalent knee osteoarthritis at baseline. These analyses supported our primary finding. The limited sample size limits our ability to offer a precise odds ratio but it is unlikely to change our overall findings that knee injuries are associated with accelerated knee osteoarthritis. However, these findings may not be generalizable to the overall population since the OAI is not a populationbased cohort study. Future studies could pursue this research in population-based cohorts but we believe these findings will be confirmed since they complement the existing literature about the association between knee injuries and early onset knee osteoarthritis (8).

We often focus on the association of injuries and osteoarthritis later in life for a younger, physically active population but this study reminds us that even among older adults we need to pay attention to self-reported injuries. It is concerning that certain types or severities of injuries may be associated with a rapid cascade towards joint failure in less than one year. Future studies will need to explore if certain injuries are causing accelerated knee osteoarthritis and/or accelerated knee osteoarthritis is increasing the risk of injury. We must develop strategies to recognize this potential phenotype promptly after their injury and discover interventions to delay or prevent the onset of accelerated and common knee osteoarthritis progression.

Acknowledgments

Grant Support: These analyses were supported by a grant from the National Institute of Health (268201000020C-1-0-1). 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. 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. This work in part with resources at the VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (#CIN 13-413), at the Michael E. DeBakey VA Medical Center, Houston, TX. The views expressed in this article are those of the author(s) and do not necessarily represent the views of the Department of Veterans Affairs.

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Significance and Innovations

1. Older individuals and those with a recent knee injury may be more likely to develop accelerated knee osteoarthritis.
2. Recent knee injuries are frequently associated with a rapid cascade towards joint failure in less than one year.

Table 1

Baseline Descriptive Characteristics of Individuals with and without Accelerated Knee Osteoarthritis (KOA) Progression

	No KOA (n = 1325) n (%) or mean (SD)	Common KOA (n = 187) n (%) or mean (SD)	Accelerated KOA (n = 54) n (%) or mean (SD)	Univariate Analyses[1] p-value
Females	759 (57%)	122 (65%)	34 (63%)	0.093
Race other than white (n miss = 2)	177 (13%)	34 (18%)	8 (15%)	0.205
Age (years)	59.2 (9.2)	58.0 (8.3)[2]	61.8 (8.6)[2]	0.023
BMI (kg/m^2)	27.1 (4.4)[3]	27.8 (4.5)	28.9 (4.7)[3]	0.002
Abnormal weight circumference (n miss = 78)	847 (67%)	127 (73%)	40 (74%)	0.197
Systolic blood pressure (mm Hg)	121 (16)	118 (13)	123 (14)	0.047
Fallen in past 12mo (n miss = 27)	433 (33%)	63 (34%)	21 (41%)	0.479
Static knee malalignment (Varus or Valgus, n miss = 79)[4]	992 (79%)[5]	122 (70%)[5]	40 (74%)	0.020
History of knee surgery (n miss = 1)	132 (10.0%)	13 (7.0%)	2 (3.7%)	0.144
Socio-economic Status				
No health insurance that covers prescription (n miss = 23)	117 (9%)	12 (7%)	8 (16%)	0.126
Income < $50K (n miss = 52)	403 (31%)	48 (27%)	22 (43%)	0.087
Less than a college degree (n miss = 8)	434 (33%)	73 (40%)	16 (31%)	0.186
Self-Reported Health Assessments				
Frequent knee pain on most days of a month in past year (n miss = 1)	502 (38%)	77 (41%)	25 (46%)	0.344
WOMAC pain score	2.2 (2.8)	2.1 (2.6)	2.7 (3.0)	0.346
Charlson Comorbidity Score > 0 (n miss = 2)	264 (20%)	28 (15%)	14 (28%)	0.099
SF-12 Physical Summary Score (n miss = 13)	51.5 (7.8)	51.7 (7.6)	50.8 (9.7)	0.773
SF-12 Mental Summary Score (n miss = 13)	53.4 (7.5)	53.8 (7.5)	53.4 (7.7)	0.733
Depression score (CES-D; n miss = 11)	6.0 (6.3)	5.6 (6.1)	6.1 (5.9)	0.708
Physical activity score (PASE score; n miss = 7)	169 (82)	177 (82)	182 (91)	0.250
Other Joints				
Right hand bony enlargements (n miss = 20)	697 (53%)	107 (58%)	31 (57%)	0.498
Left hand bony enlargements (n miss = 21)	617 (47%)	93 (50%)	32 (59%)	0.191
Handy bony enlargements (either hand; n miss = 20)	776 (59%)	122 (66%)	37 (68%)	0.128
Any back pain, past 30 days (n miss = 2)	781 (59%)	99 (53%)	36 (67%)	0.134
Doctor diagnosed back OA (n miss = 55)	190 (15%)	30 (17%)	11 (22%)	0.346
Doctor diagnosed hip OA (n miss = 44)	94 (7%)	11 (6%)	5 (10%)	0.624
Doctor diagnosed hand OA (n miss = 44)	215 (17%)	21 (12%)	9 (18%)	0.200
Doctor diagnosed back, hip, or hand OA (n miss = 48)	357 (28%)	48 (26%)	19 (37%)	0.296

	No KOA (n = 1325) n (%) or mean (SD)	Common KOA (n = 187) n (%) or mean (SD)	Accelerated KOA (n = 54) n (%) or mean (SD)	Univariate Analyses[1] p-value
Doctor diagnosed hand OA AND hip or back OA (n miss = 65)	101 (8%)	8 (4%)	3 (6%)	0.235
Pharmacological Interventions				
Either knee, used meds for pain, past 12mo (n miss = 2)	571 (43%)	86 (46%)	27 (50%)	0.490
Either knee, injection for arthritis, past 6m (n miss = 1)	13 (1%)	4 (2%)	2 (4%)	0.094
Take any pain medication today (for any pain)	124 (9%)	18 (10%)	8 (15%)	0.410
OTC NSAIDs for joint pain, past 30days (n miss = 3)	213 (16%)	27 (15%)	15 (28%)	0.059
Acetaminophen for joint pain, past 30 day (n miss = 2)	112 (9%)	12 (7%)	7 (13%)	0.303
Rx NSAIDs for joint pain, past 30days (n miss = 1)	56 (4%)	9 (5%)	1 (2%)	0.634
COXIBS for joint pain, past 30days	86 (7%)	9 (5%)	4 (7%)	0.641
Strong Prescription pain med for joint pain, past 30days	29 (2%)	3 (2%)	0 (0%)	0.485

Note.

1) Chi-squares and analyses of variance (with Tukey HSD post-hoc comparisons as needed).

2) Individuals with accelerated knee osteoarthritis were older than those with common knee osteoarthritis progression (p = 0.02).

3) Individuals with accelerated knee osteoarthritis had a greater BMI than those with no knee osteoarthritis (p = 0.01).

4) Static malalignment based on a clinical examination with a goniometer.

5) The frequency of static knee malalignment was not different between individuals with accelerated knee osteoarthritis and the other two groups but individuals with no knee osteoarthritis were more likely to have knee malalignment than individuals with common knee osteoarthritis progression (p = 0.01). CES-D = Center for Epidemiologic Study Depression Scale Score; PASE = Physical Activity Scale for the Elderly; OTC = over the counter; NSAIDs = nonsteroidal anti-inflammatory drugs; Rx = Prescription; COXIBS = COX-2 selective nonsteroidal anti-inflammatory drugs.

Table 2

Distribution of Knee Injuries among Individuals with and without accelerated knee osteoarthritis (KOA) progression

	No KOA (n=1325) REFERENCE GROUP	Common KOA (n=187)	Accelerated KOA (n=54)	Common KOA Unadjusted OR (95% CI)	Accelerated KOA Unadjusted OR (95% CI)	Common KOA Adjusted OR (95% CI)	Accelerated KOA Adjusted OR (95% CI)
History of knee injury before OAI baseline (n = 1554)	461 (35%)	52(28%)	16 (30%)	0.74 (0.52, 1.04)	0.78 (0.43, 1.42)	0.76 (0.53, 1.08)	0.84 (0.46, 1.54)
New Knee Injury							
Between 1 and 2 years prior to study outcome (n = 1441)[1]	54 (4%)	5 (5%)	2 (5%)	n/a	n/a	n/a	n/a
Within1 year of the study outcome (n = 1558)	39 (3%)	18 (10%)	13 (25%)	3.57 (1.99, 6.38)	10.97 (5.42, 22.17)	3.04 (1.66, 5.58)	9.22 (4.50, 18.90)
During total observation period (n = 1507)	145 (11%)	23 (13%)	17 (32%)	1.12 (0.70, 1.80)	3.67 (2.01, 6.70)	0.99 (0.61, 1.61)	3.37 (1.82, 6.25)
During total observation period among knees with no history of injury prior to baseline (n = 980)	76 (9%)	12 (9%)	9 (24%)	1.02 (0.54, 1.93)	3.13 (1.42, 6.88)	0.88 (0.45, 1.74)	2.97 (1.33, 6.65)

Notes.

1) Definition excludes those who developed common KOA or accelerated KOA at 12-months since the participants were not asked about recent injuries at the Osteoarthritis Initiative (OAI) baseline visit. n/a = not applicable (did not pursue multinomial logistic regression models). Odds ratios were adjusted for age, sex, body mass index (BMI), presence of static knee malalignment, and systolic blood pressure. OR = odds ratio, CI = confidence interval, OAI = Osteoarthritis Initiative.