

## Joint Injury in Young Adults and Risk for Subsequent Knee and Hip Osteoarthritis

Allan C. Gelber, MD, MPH, PhD; Marc C. Hochberg, MD, MPH; Lucy A. Mead, ScM; Nae-Yuh Wang, MS, PhD; Fredrick M. Wigley, MD; and Michael J. Klag, MD, MPH

**Background:** Knee and hip injuries have been linked with osteoarthritis in cross-sectional and case-control studies, but few prospective studies have examined the relation between injuries in young adults and risk for later osteoarthritis.

**Objective:** To prospectively examine the relation between joint injury and incident knee and hip osteoarthritis.

**Design:** Prospective cohort study.

**Setting:** Johns Hopkins Precursors Study.

**Participants:** 1321 former medical students.

**Measurements:** Injury status at cohort entry was recorded when the mean age of participants was 22 years. Injury during follow-up and incident osteoarthritis were determined by using self-administered questionnaires. Osteoarthritis was confirmed by symptoms and radiographic findings.

**Results:** Over a median follow-up of 36 years, 141 participants

reported joint injuries (knee alone [ $n = 111$ ], hip alone [ $n = 16$ ], or knee and hip [ $n = 14$ ]) and 96 developed osteoarthritis (knee alone [ $n = 64$ ], hip alone [ $n = 27$ ], or knee and hip [ $n = 5$ ]). The cumulative incidence of knee osteoarthritis by 65 years of age was 13.9% in participants who had a knee injury during adolescence and young adulthood and 6.0% in those who did not ( $P = 0.0045$ ) (relative risk, 2.95 [95% CI, 1.35 to 6.45]). Joint injury at cohort entry or during follow-up substantially increased the risk for subsequent osteoarthritis at that site (relative risk, 5.17 [CI, 3.07 to 8.71] and 3.50 [CI, 0.84 to 14.69] for knee and hip, respectively). Results were similar for persons with osteoarthritis confirmed by radiographs and symptoms.

**Conclusions:** Young adults with knee injuries are at considerably increased risk for osteoarthritis later in life and should be targeted in the primary prevention of osteoarthritis.

*Ann Intern Med.* 2000;133:321-328.

For author affiliations, current addresses, and contributions, see end of text.

Osteoarthritis is a major contributor to functional impairment and reduced independence in older adults (1–4). It is the leading cause of arthritis in the United States, affecting an estimated 21 million persons (5), and has substantial economic impact (6, 7). History of an injury to a joint, particularly at the knee and hip, is associated with an increased risk for osteoarthritis in cross-sectional and case-control studies (8–11). Such studies, however, may overestimate this relation because persons with symptomatic osteoarthritis may be more likely to recall a past injury or to interpret early symptoms of osteoarthritis as indicative of joint injury. A prospective cohort study can address this weakness by determining exposure status before the outcome develops. To date, prospective studies have examined the relation between history of joint injury and osteoarthritis in middle-aged persons and senior citizens (12, 13), but not in young adults. However, many athletic injuries occur in high school and college. In addition, joint trauma may be a more common cause of osteoarthritis than has been previously recognized (14). We performed a prospective cohort study of 1321 young adults to examine the risk for knee

and hip osteoarthritis associated with joint injury during young adult life.

### Methods

#### Study Participants

The Johns Hopkins Precursors Study was designed by the late Caroline Bedell Thomas, MD, to identify precursors of the aging process (15). A total of 1337 medical students, members of the graduating classes of 1948 through 1964 at the Johns Hopkins University School of Medicine in Baltimore, Maryland, enrolled in the study. The cohort was 91% male and 97% white; the mean age was 22 years. At entry, participants underwent a standard history and examination, including assessment of musculoskeletal disorders, history of trauma, level of physical activity, and measurement of weight and height. Body mass index was calculated as weight in kilograms divided by height in meters squared. In addition, participants were asked to categorize their level of physical training during the past month as “none,” “little,” “moderate,” or “much,” as described elsewhere (16). Since graduation, participants

have been followed prospectively with annual self-administered questionnaires to detect incident disease and to update risk factor status over time. At the time that baseline data were collected, it was not customary to obtain informed consent. After establishment of the Joint Committee on Clinical Investigation at Johns Hopkins, the follow-up protocol was reviewed and approved.

### Assessment of Injury

Injury was defined as a report of trauma to the knee or hip joint, including internal derangement and fracture. During the baseline assessment, knee and hip injuries that occurred before graduation from medical school and the year of their occurrence were recorded. Postgraduation injuries were assessed by annual morbidity questionnaires. During every 5-year follow-up period, at least 86% of the living participants responded at least once to the questionnaires. Injuries were assigned diagnosis codes according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (17). Diagnoses included torn meniscus (code 836.2); torn knee ligament (code 844.9); tibial fracture (code 823.8); femoral fracture (code 821.01); fibular fracture (code 823.81); patellar fracture (code 822); broken leg, site not otherwise specified (code 827.0); knee injury, not otherwise specified (code 959.7); gunshot wound (code 891); hemarthrosis (code 844.9); shin splints (code 844.9); and hip dislocation (code 836.5).

### Incidence of Osteoarthritis

The methods used to determine osteoarthritis incidence in this cohort have been described elsewhere (18). Briefly, all participants were mailed annual morbidity questionnaires. Before 1985, respondents were queried about the development of “physical and musculoskeletal disorders.” Since 1985, follow-up morbidity questionnaires have contained the specific question, “Have you ever had arthritis?” and have asked those who respond affirmatively to “provide the type of arthritis, year of onset, and treatment received.” An event of osteoarthritis was defined as the self-report of osteoarthritis or degenerative arthritis in response to the questionnaire. The incidence date was determined by the reported year of osteoarthritis onset. Two rheumatologists reviewed each report of osteoarthritis, assigned ICD-9-CM codes (17) to the most specific arthritis site reported by the respondent, and excluded inflammatory arthritides. For this analysis, only osteoarthritis at the

knee (code 715.96) and hip (code 715.95) were included as outcomes.

In 1995, all surviving participants who had previously reported osteoarthritis were mailed a more detailed questionnaire. They were asked, “Have you had pain in or around the knee, including back of the knee, on most days for at least 1 month?” and “Have you had pain in or around either hip joint, including the buttock, groin, and side of upper thigh, on most days for at least 1 month?” These symptom-related questions were used to screen for knee and hip osteoarthritis, respectively, in the National Health and Nutrition Examination Survey (NHANES) (19). Respondents were also asked whether they had undergone radiographic evaluation of their knees and hips and whether radiography revealed osteophytes, joint space narrowing, subchondral cysts, or bony sclerosis (the radiographic hallmarks of osteoarthritis) (20).

### Statistical Analysis

The association between baseline characteristics and injury status was assessed by using the Student *t*-test for continuous variables and the chi-square test for categorical variables. These data are presented both for the entire cohort and separately by sex. Injury was the independent variable in the survival analysis; age was the time variable. Knee and hip osteoarthritis were examined as separate outcomes. The relation of a joint injury at baseline to the incidence of osteoarthritis was examined by using Kaplan-Meier analysis (21). The log-rank statistic was used to test whether the cumulative incidence of osteoarthritis differed according to injury status at cohort entry (22). In addition, Cox proportional hazards analysis was used to estimate the independent risk for osteoarthritis associated with a joint injury. Cox models were constructed for injury status at cohort entry and over follow-up, modeled as a time-dependent covariate. We adjusted for age at graduation, sex, body mass index, and level of physical activity, each of which was determined at baseline, to evaluate for possible confounding. In this cohort, body mass index at enrollment was more predictive of future osteoarthritis than average or most recent body mass index during follow-up (18). These analyses were performed for all reported events of knee and hip osteoarthritis and for cases confirmed by both characteristic symptoms and radiographic findings. Hazard ratios are reported as relative risks with 95% CIs. Statistical significance was defined as an  $\alpha$  level equal to

**Table 1. Baseline Characteristics of 1321 Men and Women according to Joint Injury at Cohort Entry or during Follow-up**

Variable	Participants with Injury (n = 141)*	Participants without Injury (n = 1180)	Men with Injury (n = 129)	Men without Injury (n = 1071)	Women with Injury (n = 12)	Women without Injury (n = 109)
Mean age at graduation $\pm$ SD, y	26.6 $\pm$ 2.8	26.3 $\pm$ 2.4	26.5 $\pm$ 2.7	26.4 $\pm$ 2.4	28.2 $\pm$ 4.0	26.0 $\pm$ 2.0†
Mean weight $\pm$ SD, kg‡	76.4 $\pm$ 9.5	73.9 $\pm$ 10.9†	77.6 $\pm$ 8.6	75.3 $\pm$ 10.0§	62.0 $\pm$ 7.4	59.3 $\pm$ 8.4
Mean height $\pm$ SD, m‡	1.81 $\pm$ 0.06	1.79 $\pm$ 0.08	1.82 $\pm$ 0.05	1.81 $\pm$ 0.07	1.70 $\pm$ 0.07	1.66 $\pm$ 0.07
Mean body mass index $\pm$ SD, kg/m <sup>2</sup> ‡	23.4 $\pm$ 2.4	22.9 $\pm$ 2.6§	23.5 $\pm$ 2.4	23.0 $\pm$ 2.6§	21.6 $\pm$ 2.3	21.4 $\pm$ 2.3
Physically active, n (%)	69 (58)	464 (48)§	64 (58)	435 (49)	5 (56)	29 (36)
Ever cigarette smokers, n (%)¶	76 (56)	572 (53)	68 (55)	523 (53)	8 (67)	49 (53)

\* One hundred eleven participants had a knee injury alone, 16 had a hip injury alone, and 14 had an injury at both the knee and hip joints.

†  $P < 0.01$  by *t*-test or chi-square analysis according to injury status, for the total cohort, for men, or for women.

‡ Based on data from 1180 men and 118 women.

§  $P < 0.05$  by *t*-test or chi-square analysis according to injury status, for the total cohort, for men, or for women.

|| Based on data from 1000 men and 89 women.

¶ Based on data from 1103 men and 105 women.

0.05 using a two-tailed test. We conducted a sensitivity analysis to assess the potential effect of an omitted covariate on the association between joint injury and subsequent osteoarthritis.

### Role of the Funding Sources

The funding sources did not have a role in the collection, analysis, or interpretation of the data or in the decision to submit the study for publication.

### Results

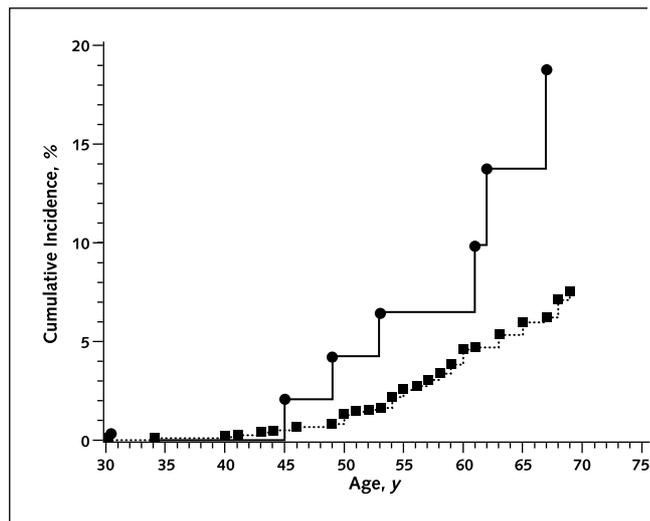
At graduation from medical school, the average age of the 1216 men and 121 women in the cohort was 26 years. Our analysis is based on events reported through 30 November 1995 and represents a median follow-up of 36 years. Information at baseline or during follow-up was available for 1321 participants, who form the basis of our longitudinal analysis.

At the end of follow-up in 1995, the mean age of the cohort  $\pm$  SD was 61.4  $\pm$  8.9 years. Overall, 141 participants had a joint injury (knee alone [ $n = 111$ ], hip alone [ $n = 16$ ], or injuries at both sites [ $n = 14$ ]) before or after graduation. Table 1 shows the baseline characteristics of the cohort according to injury status at the end of follow-up. Proportions of men and women with joint injury were similar ( $P > 0.2$ , chi-square test). Participants were generally lean, 49% were physically active, and 54% smoked cigarettes. Men who had a joint injury were heavier at baseline than men who were injury-free, but both groups of men were similar in age, level of physical activity, and smoking status. Women with injury were, on average, 2 years older at baseline than those without injury.

At baseline, 47 men (3.9%) reported a knee injury and 12 men (1.0%) reported a hip injury. The mean age at which the injuries occurred was 16 years. Knee injuries included 10 tibial fractures, 3 fibular fractures, 4 femoral fractures, 2 patellar fractures, and 9 otherwise unspecified leg fractures. In addition, 8 men incurred trauma resulting in torn knee cartilage, 2 had torn knee ligaments, 2 had knee injuries resulting from gunshot wounds, 1 had traumatic hemarthrosis, 1 had joint dislocation, 1 had shin splints, and 4 had otherwise unspecified knee injuries. Of men with a knee injury, 4 reported that they were injured while playing football, 2 each reported that they were injured while playing basketball or participating in athletics, and 1 each reported that he was injured while horseback riding, bicycling, skiing, playing volleyball, wrestling, playing baseball, or playing tennis. Knee trauma also resulted from motor vehicle accidents ( $n = 3$ ) and falls ( $n = 2$ ). At baseline, 4 of the 121 women (3.3%) had a history of knee injuries and 1 (0.8%) had a history of hip injuries.

Sixty-two men and 7 women developed knee osteoarthritis, and 27 men and 5 women developed hip osteoarthritis. The mean  $\pm$  SD ages at onset of knee and hip osteoarthritis were 57  $\pm$  8 years and 59  $\pm$  6 years, respectively. The cumulative incidence of knee osteoarthritis by 65 years of age was 6.3% and the cumulative incidence of hip osteoarthritis was 2.9%. Fifty-two of 60 male participants (87%) who had reported knee osteoarthritis and were alive in 1995 returned the detailed osteoarthritis questionnaire. Of these 52 men, 43 (83%) had current symptoms, signs (including crepitus or tenderness at the joint margin), or radiographic features of knee osteoarthritis; 6 (12%) had undergone knee replacement surgery. Besides

**Figure.** Cumulative incidence of knee osteoarthritis according to injury status at cohort entry.



Kaplan-Meier plots are shown for participants with joint injury (circles) and those without joint injury (squares) at cohort entry.  $P = 0.0045$  (log-rank test).

joint replacement, 20 additional men with knee osteoarthritis (38%) had other surgical procedures, including arthroscopic meniscectomy and osteotomy. Similarly, 24 of 26 male participants (92%) who were alive in 1995 and had reported hip osteoarthritis returned the detailed questionnaire. Of these 24 men, 19 (79%) had current symptoms (including pain with flexion or internal rotation at the hip) or radiographic features of hip osteoarthritis; 10 (42%) had undergone hip replacement surgery. Fifty percent of the participants were currently using aspirin or other nonsteroidal anti-inflammatory drugs as medical therapy for their osteoarthritis. Compared with the remainder of the cohort, participants with osteoarthritis exhibited significantly greater limitations in their activities of daily living, including climbing stairs, bending, kneeling

and stooping, and walking more than 1 mile (data not shown).

We first examined the relation between injuries in young adult life (before graduation) and subsequent development of osteoarthritis. The cumulative incidence of knee osteoarthritis by 65 years of age was 13.9% among participants with a history of knee injury at baseline and 6.0% among those without ( $P = 0.0045$ , log-rank test) (Figure). The average time to clinically apparent osteoarthritis in participants with a knee injury at baseline was  $22 \pm 13$  years. These early knee injuries were associated with a nearly threefold increase (relative risk, 2.95 [CI, 1.35 to 6.45]) in risk for future symptomatic knee osteoarthritis. In contrast, none of the 13 men and women with a hip injury before graduation later developed hip osteoarthritis.

Next, we examined the association between joint injury at baseline or during follow-up and development of osteoarthritis. After graduation, an additional 68 men and 6 women incurred a new knee injury and 14 men and 3 women incurred a new hip injury, yielding a total of 125 persons with knee injuries and 30 persons with hip injuries throughout the study period. The cumulative incidence of knee and hip injury by 65 years of age was 11.0% and 2.2%, respectively. Knee injury occurred at a mean age of 36 years, and hip injury occurred at a mean age of 37 years. Six of the 125 participants with knee injury developed osteoarthritis concurrent with or before the injury. Of the remaining 119 participants, 20 developed osteoarthritis after the injury occurred (7.5 events per 1000 person-years of follow-up) (Table 2). In contrast, the incidence of knee osteoarthritis among 1202 participants without knee injury was 1.2 events per 1000 person-years of follow-up. The relation between a previous hip injury and incidence of hip osteoarthritis during follow-up was similar to that observed for knee osteoarthritis. Two of the 30 participants with hip

**Table 2.** Incidence of Knee and Hip Osteoarthritis Associated with a Joint Injury at Baseline or during Follow-up in 1321 Men and Women

Variable	Participants with Knee Injury (n = 119)*	Participants without Knee Injury (n = 1202)	Participants with Hip Injury (n = 28)*	Participants without Hip Injury (n = 1293)
Mean follow-up $\pm$ SD, y	34.5 $\pm$ 8.0	34.5 $\pm$ 8.8	35.6 $\pm$ 8.3	34.8 $\pm$ 8.7
Participants with osteoarthritis, n	20	49	2	30
Person-years of follow-up, n	2667	41 412	634	44 962
Osteoarthritis incidence per 1000 person-years (95% CI)	7.5 (4.9–11.6)	1.2 (0.9–1.6)	3.2 (0.9–11.5)	0.7 (0.5–1.0)

\* Participants with joint injury and without previous osteoarthritis who were followed for later development of osteoarthritis. Participants whose joint injury occurred after osteoarthritis developed are not included.

**Table 3. Relative Risk for Future Knee and Hip Osteoarthritis Associated with Joint Injury at Baseline or during Follow-up\***

Model	Knee Injury		Hip Injury	
	Cases	Relative Risk (95% CI)	Cases	Relative Risk (95% CI)
	<i>n</i>		<i>n</i>	
Unadjusted				
All cases	69	5.17 (3.07–8.71)	32	3.50 (0.84–14.69)
Confirmed cases	39	8.89 (4.69–16.87)	19	2.89 (0.39–21.75)
Age-adjusted				
All cases	69	5.17 (3.07–8.71)	32	3.38 (0.81–14.21)
Confirmed cases	39	8.90 (4.69–16.89)	19	2.86 (0.38–21.50)
Adjusted for physical activity				
All cases	56	5.04 (2.82–9.02)	25	5.78 (1.36–24.57)
Confirmed cases	32	8.76 (4.32–17.78)	15	4.80 (0.63–36.55)
Adjusted for body mass index, physical activity				
All cases	56	5.02 (2.81–8.98)	25	6.01 (1.40–25.86)
Confirmed cases	32	8.72 (4.29–17.71)	15	4.25 (0.55–32.60)
Adjusted for age, sex, body mass index, physical activity				
All cases	56	5.01 (2.80–8.97)	–†	
Confirmed cases	32	8.54 (4.20–17.37)	–†	

\* Joint injury was modeled as a time-dependent covariate (Cox proportional hazards analysis).

† Number of events was insufficient for analysis.

injury developed osteoarthritis before the injury occurred. Of the remaining 28 participants, 2 who were injured after graduation later developed hip osteoarthritis (3.2 events per 1000 person-years) (Table 2). In contrast, 30 of 1293 participants without previous hip injury developed incident hip osteoarthritis (0.7 event per 1000 person-years).

The association between a previous injury (incurred throughout the study period) and future osteoarthritis was further examined by modeling injury as a time-dependent covariate. Knee injury, at baseline or during follow-up, substantially increased the risk for subsequent knee osteoarthritis (relative risk, 5.17 [CI, 3.07 to 8.71]) (Table 3). This increase in risk for knee osteoarthritis persisted after adjustment for age, sex, body mass index, and level of physical activity at baseline. When the analysis was repeated and confined to persons with symptomatic and radiographic evidence of osteoarthritis, the point estimate of the risk associated with previous knee injury was greater than for all cases.

Time-dependent hip injury was associated with a threefold increase in risk for future hip osteoarthritis (relative risk, 3.50 [CI, 0.84 to 14.69]) (Table 3). Because relatively few participants developed hip osteoarthritis—fewer than 50% of those who developed knee osteoarthritis—the confidence intervals surrounding the risk estimates were wide. When the model was adjusted for physical activity, the risk estimate nearly doubled and was of border-

line statistical significance. In exploratory analyses to investigate the influence of physical activity on this association, the risk for hip osteoarthritis associated with time-dependent hip injury varied by physical activity status. The relative risk for osteoarthritis associated with hip injury was 9.72 (CI, 1.12 to 84.45) in the group that was physically active at baseline and 4.92 (CI, 0.63 to 38.38) in the group that was not. Because the study included few cases of hip osteoarthritis, the confidence intervals around these estimates were wide.

A sensitivity analysis was conducted to determine how severe a potential missing confounder would have to be to affect the results. We found that the risk for knee osteoarthritis associated with joint injury decreased only modestly with a confounder (omitted covariate) that was related to the exposure (knee injury) with an odds ratio greater than 2.5 and to the outcome (knee osteoarthritis) with a relative risk greater than 3.

## Discussion

In this cohort study of former medical students who were enrolled in their twenties, joint injury was related to a substantial increased risk for future knee osteoarthritis. In addition, injury at the knee and hip joints during follow-up resulted in a greater incidence of later osteoarthritis at that joint. Our findings also indicate that the risk for

knee osteoarthritis associated with previous injury is not explained by confounding due to heavier body weight or higher level of physical activity in young adulthood.

Cross-sectional studies have shown that a history of joint injury is related to knee and hip osteoarthritis (23, 24). For example, a history of knee fracture, severe knee sprain, or swelling in NHANES participants was associated with prevalent knee osteoarthritis (odds ratio, 16.3 at the right knee and 10.9 at the left knee) (8). A similarly strong association was observed in a population-based case-control study in Bristol, United Kingdom (25). In addition, Finnish former soccer players and weight lifters with knee osteoarthritis were more likely to have a history of knee injury than former athletes without osteoarthritis (26). With regard to hip osteoarthritis, prevalence data from NHANES yielded age-adjusted odds ratios of 24.2 for history of hip trauma among men and 4.17 for history of hip trauma among women (9). Greater risk for hip osteoarthritis in persons with a history of lower-limb injury was also observed in Finnish and English population-based case-control studies (10, 11).

These studies, however, have several limitations. When the exposure (injury) and outcome (osteoarthritis) are assessed at the same point in time, it is difficult to discern which occurred first. Injury may result from an unsteady, mechanically impaired knee and may not predate the development of osteoarthritis. In addition, the knee pain and impaired function caused by existing osteoarthritis may influence recollection of previous injury or lead to misinterpretation of early symptoms of osteoarthritis as indicative of an injury, resulting in an overestimation of risk. Prospective studies, in which risk factor status is ascertained before subsequent development of the outcome, are not vulnerable to these biases. Data from the Framingham Osteoarthritis Study, in which a history of knee injury was assessed at a mean age of 71 years and again 8 years later, yielded few reports of injury and inconsistent results that were not statistically significant (13). Our analyses compared the incidence of knee and hip osteoarthritis in a cohort of young adults who were not selected on the basis of collegiate or professional athletic status. This longitudinal cohort study extends previous reports by using prospectively collected data and is not susceptible to the previously discussed biases. Knee injury sustained at a mean age of 16 years was associated with an increased lifetime incidence of subsequent knee osteoarthritis.

Our study has several limitations. It included only a

small number of women because the cohort was assembled from 1948 to 1964, when women made up only 10% of entering medical school classes. Because of this small number, we could not meaningfully analyze sex-specific risk in women. Our results are strictly applicable only to physicians and may not be generalizable to persons in other occupations. However, if the frequency of joint injury is greater in other populations and is associated with a similar lifetime risk for future osteoarthritis, our data may underestimate the burden of osteoarthritis associated with joint injury in the general population. Information on family history and other possible risk factors for osteoarthritis was not incorporated into the study protocol when this cohort was initiated; therefore, we were unable to consider all potential confounders. In addition, relatively few persons had knee and hip osteoarthritis, which limited the statistical power and yielded wide CIs. The risk could also have been overestimated if persons with a joint injury were more apt to recognize early symptoms and seek radiographic evaluation. The Precursors Study participants, however, are known to be highly accurate in their self-report of chronic diseases, including cardiovascular disease (27) and gout (28). Although radiographs were not obtained on all incident events, approximately 80% of participants with self-reported osteoarthritis responded affirmatively to symptom-based screening questions (29) or reported having radiography that demonstrated the hallmarks of osteoarthritis (20). The association between injury and knee osteoarthritis was as strong or stronger when confirmed cases were used as the outcome. Further support for the validity of self-reported osteoarthritis comes from a study of community residents in Australia. In this study, osteoarthritis was confirmed 81% of the time after examination by trained metrologists (30) using the American College of Rheumatology criteria (31).

The joint is a complex organ, made up of periarticular and subchondral bone, articular cartilage, synovial membrane, joint capsule, and periarticular musculature. Deleterious effects of trauma that compromise the structural integrity of one or more of these joint constituents are implicated in the development of osteoarthritis (32–34). Harmful forces inflicted on a joint during an injury lead to cartilage breakdown, trabecular microfracture, and bone remodeling (35, 36). It is noteworthy that knee osteoarthritis is induced in animal models by transection of the anterior cruciate ligament or by injury to the meniscus (37, 38). Joint injury may also adversely affect muscle tissue as

a direct result of the injury or indirectly through disuse atrophy during convalescence. Moreover, weakness of the quadriceps muscle is related to both prevalent and incident knee osteoarthritis (39, 40).

Novel drug treatments for osteoarthritis are currently being developed (41). Some of these drugs are understood to have a chondroprotective effect, including inhibition of degradative metalloproteinases. Such agents may stabilize or reverse the course of an early osteoarthritic joint. Persons with a risk factor linked to the development of osteoarthritis are suitable participants for such investigational therapy (42).

Our findings strongly demonstrate that adolescents and young adults with traumatic injury to the knee joint, as well as persons with knee and hip injuries incurred during middle age, are at substantially increased risk for osteoarthritis at the same joint later in life. Such persons constitute a high-risk group and are an ideal population to target for primary prevention of osteoarthritis. Physicians who encounter a young patient with a knee or hip injury should consider recommending joint-stabilizing braces and temporary modification of high-impact exercise to minimize further damage. In addition, physicians should advocate use of proper sports equipment under safe conditions to prevent joint injuries and decrease their long-term sequelae.

From Johns Hopkins University, University of Maryland, and Veterans Affairs Medical Center, Baltimore, Maryland.

Presented in part at the 60th National Scientific Meeting of the American College of Rheumatology, Orlando, Florida, 19–22 October 1996.

**Acknowledgment:** The authors thank the members of the Precursors Study, whose dedicated participation over 47 years has made this work possible.

**Grant Support:** In part by grants from the National Institutes of Health (AG-01760, KO8 AR-01939) and a Postdoctoral Fellowship award from the Arthritis Foundation.

**Requests for Single Reprints:** Allan C. Gelber, MD, MPH, PhD, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205.

**Requests To Purchase Bulk Reprints (minimum, 100 copies):** Barbara Hudson, Reprints Coordinator; phone, 215-351-2657; e-mail, bhudson@mail.acponline.org.

**Current Author Addresses:** Dr. Gelber: Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7500, Baltimore, MD 21205.

Dr. Hochberg: University of Maryland School of Medicine, 10 South Pine Street, MSTF 8-34, Baltimore, MD 21201.

Ms. Mead and Dr. Wang: The Precursors Study, 2024 East Monument Street, Suite 2-200, Baltimore, MD 21205.

Dr. Wigley: Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 7300, Baltimore, MD 21205.

Dr. Klag: Johns Hopkins University School of Medicine, 2024 East Monument Street, Suite 2-600, Baltimore, MD 21205.

**Author Contributions:** Conception and design: A.C. Gelber, M.C. Hochberg, L.A. Mead, M.J. Klag.

Analysis and interpretation of the data: A.C. Gelber, M.C. Hochberg, L.A. Mead, N. Wang, F.M. Wigley, M.J. Klag.

Drafting of the article: A.C. Gelber, M.C. Hochberg, M.J. Klag.

Critical revision of the article for important intellectual content: A.C. Gelber, M.C. Hochberg, L.A. Mead, N. Wang, F.M. Wigley, M.J. Klag.

Final approval of the article: A.C. Gelber, M.C. Hochberg, L.A. Mead, N. Wang, F.M. Wigley, M.J. Klag.

Provision of study materials or patients: L.A. Mead, M.J. Klag.

Statistical expertise: L.A. Mead, N. Wang.

Obtaining of funding: A.C. Gelber, M.J. Klag.

Administrative, technical, or logistic support: M.J. Klag.

Collection and assembly of data: A.C. Gelber, M.C. Hochberg, L.A. Mead, M.J. Klag.

## References

1. **Cremer P, Hochberg MC.** Osteoarthritis. *Lancet.* 1997;350:503-8.
2. **Yelin EH, Felts WR.** A summary of the impact of musculoskeletal conditions in the United States. *Arthritis Rheum.* 1990;33:750-5.
3. **Cunningham LS, Kelsey JL.** Epidemiology of musculoskeletal impairments and associated disability. *Am J Public Health.* 1984;74:574-9.
4. **Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al.** The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health.* 1994;84:351-8.
5. **Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al.** Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-99.
6. **Gabriel SE, Crowson CS, Campion ME, O'Fallon WM.** Indirect and nonmedical costs among people with rheumatoid arthritis and osteoarthritis compared with nonarthritic controls. *J Rheumatol.* 1997;24:43-8.
7. **Gabriel SE, Crowson CS, Campion ME, O'Fallon WM.** Direct medical costs unique to people with arthritis. *J Rheumatol.* 1997;24:719-25.
8. **Davis MA, Ettinger WH, Neuhaus JM, Cho SA, Hauck WW.** The association of knee injury and obesity with unilateral and bilateral osteoarthritis of the knee. *Am J Epidemiol.* 1989;130:278-88.
9. **Tepper S, Hochberg MC.** Factors associated with hip osteoarthritis: data from the First National Health and Nutrition Examination Survey (NHANES-I). *Am J Epidemiol.* 1993;137:1081-8.
10. **Heliövaara M, Makela M, Impivaara O, Knekt P, Aromaa A, Sievers**

- K. Association of overweight, trauma and workload with coxarthrosis. A health survey of 7,217 persons. *Acta Orthop Scand*. 1993;64:513-8.
11. **Cooper C, Inskip H, Croft P, Campbell L, Smith G, McLaren M, et al.** Individual risk factors for hip osteoarthritis: obesity, hip injury, and physical activity. *Am J Epidemiol*. 1998;147:516-22.
  12. **Hart DJ, Doyle DV, Spector TD.** Incidence and risk factors for radiographic knee osteoarthritis in middle-aged women: the Chingford Study. *Arthritis Rheum*. 1999;42:17-24.
  13. **Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, et al.** Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum*. 1997;40:728-33.
  14. **Roos H, Lauren M, Adalberth T, Roos EM, Jonsson K, Lohmander LS.** Knee osteoarthritis after meniscectomy: prevalence of radiographic changes after twenty-one years, compared with matched controls. *Arthritis Rheum*. 1998;41:687-93.
  15. **Thomas CB.** Observations on some possible precursors of essential hypertension and coronary artery disease. *Bulletin of the Johns Hopkins Hospital*. 1951;89:419-41.
  16. **Deckers JW, Klag MJ, Seidler AJ, Mead LA.** Association of youthful and mid-life physical activity with subsequent development of cardiovascular disease [Abstract]. *Circulation*. 1990;82:III-259.
  17. Diseases: tabular list. In: Department of Health and Human Services. *The International Classification of Diseases, 9th Revision, Clinical Modification: ICD-9-CM, vol 1*. Washington, DC: U.S. Government Printing Office; 1980.
  18. **Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ.** Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. *Am J Med*. 1999;107:542-8.
  19. National Health and Nutrition Examination Survey (U.S.). *Basic Data on Arthritis in Knee, Hip, and Sacroiliac Joints, in Adults Ages 25-74 Years, United States, 1971-75*. Hyattsville, MD: National Center for Health Statistics; 1979.
  20. **Kellgren JH, Lawrence JS.** Radiological assessment of osteoarthrosis. *Ann Rheum Dis*. 1957;16:494-502.
  21. **Kaplan EL, Meier P.** Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*. 1958;53:457-81.
  22. **Peto R, Peto J.** Asymptotically efficient rank invariant procedures. *Journal of the Royal Statistical Society (A)*. 1972;135:185-207.
  23. **Hochberg MC, Lethbridge-Cejku M.** Epidemiologic considerations in the primary prevention of osteoarthritis. In: Hamerman D, ed. *Osteoarthritis: Public Health Implications for an Aging Population*. Baltimore: Johns Hopkins Univ Pr; 1997:169-86.
  24. **Felson DT, Zhang Y.** An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum*. 1998;41:1343-55.
  25. **Cooper C, McAlindon T, Coggon D, Egger P, Dieppe P.** Occupational activity and osteoarthritis of the knee. *Ann Rheum Dis*. 1994;53:90-3.
  26. **Kujala UM, Kettunen J, Paananen H, Aalto T, Battie MC, Impivaara O, et al.** Knee osteoarthritis in former runners, soccer players, weight lifters, and shooters. *Arthritis Rheum*. 1995;38:539-46.
  27. **Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, et al.** Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med*. 1993;328:313-8.
  28. **Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC.** Incidence and risk factors for gout in white men. *JAMA*. 1991;266:3004-7.
  29. **Comoni-Huntley J, Huntley RR, Feldman JJ, eds.** *Health Status and Well-Being of the Elderly: National Health and Nutrition Examination Survey-I, Epidemiologic Follow-up Study*. New York: Oxford Univ Pr; 1990.
  30. **March LM, Schwarz JM, Carfrae BH, Bagge E.** Clinical validation of self-reported osteoarthritis. *Osteoarthritis and Cartilage*. 1998;6:87-93.
  31. **Altman RD.** Criteria for classification of clinical osteoarthritis. *J Rheumatol Suppl*. 1991;27:10-2.
  32. **Rall KL, McElroy GL, Keats TE.** A study of long term effects of football injury to the knee. *Mo Med*. 1964;61:435-8.
  33. **Mankin HJ.** The reaction of articular cartilage to injury and osteoarthritis (first of two parts). *N Engl J Med*. 1974;291:1285-92.
  34. **Mankin HJ.** The reaction of articular cartilage to injury and osteoarthritis (second of two parts). *N Engl J Med*. 1974;291:1335-40.
  35. **Radin EL, Paul IL, Rose RM.** Role of mechanical factors in pathogenesis of primary osteoarthritis. *Lancet*. 1972;1:519-22.
  36. **Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al.** The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. *Arthritis Rheum*. 1999;42:483-9.
  37. **Altman RD, Kates J, Chun LE, Dean DD, Eyre D.** Preliminary observations of chondral abrasion in a canine model. *Ann Rheum Dis*. 1992;51:1056-62.
  38. **Little C, Smith S, Ghosh P, Bellenger C.** Histomorphological and immunohistochemical evaluation of joint changes in a model of osteoarthritis induced by lateral meniscectomy in sheep. *J Rheumatol*. 1997;24:2199-209.
  39. **Slemenda C, Brandt KD, Heilman DK, Mazucca S, Braunstein EM, Katz BP, et al.** Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med*. 1997;127:97-104.
  40. **Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazucca SA, Braunstein EM, et al.** Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? *Arthritis Rheum*. 1998;41:1951-9.
  41. **Creamer P, Dieppe PA.** Novel drug treatment strategies for osteoarthritis. *J Rheumatol*. 1993;20:1461-4.
  42. **Lequesne M, Brandt K, Bellamy N, Moskowitz R, Menkes CJ, Pelletier JP, et al.** Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol Suppl*. 1994;41:65-73.