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Epidemiologic studies for osteoarthritis: new versus conventional study design approaches

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Current insights into osteoarthritis epidemiology

Osteoarthritis (OA) is the most common form of arthritis. Symptomatic knee OA occurs in approximately 13% of persons who are aged 60 and older [1]. Its prevalence is approximately 6.1% for knees (unpublished data) in U.S. adults who are aged 30 and older; thus, approximately 12 million persons have symptomatic knee OA. Because, of its prevalence, knee OA has a formidable impact on the burden of disability in older Americans. OA is ranked as either the top or second leading cause of disability among elders [2].

Epidemiology is the study of the occurrence of disease in populations and its association with characteristics of people and their environments. Epidemiologic studies have provided much information about the occurrence of OA. Disease in the knee is common, especially among the aged; hip OA is less prevalent in most populations than disease in the knee; and for disease in the hand, radiographic OA is nearly universal in older people, whereas symptoms are less frequent. Studies have also shown that, for most joints, women who are older

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than 50 have a higher incidence and prevalence of disease than men. Throughout the United States and Europe, the prevalence of OA and its societal burden in terms of disability and economic costs is high. These critical data serve one important role of epidemiologic studies, to estimate disease impact and the need for resource allocation.

A second major goal of epidemiologic studies is to evaluate risk factors for disease, thereby, identifying those individuals and groups who are at greatest risk, providing insights into disease biology, and suggesting ways to prevent or treat disease. The identification of a link between high blood pressure and high cholesterol with heart disease provides an excellent example as to how epidemiologic observations can be transformed into prevention opportunities and treatments that, in turn, lead to a decrease in disease incidence and mortality. Heart disease mortality has decreased as a consequence of epidemiologic insights.

For OA, understanding whether and why certain groups are at high risk offers similar opportunities for prevention or treatment. Persons who are overweight are at high risk of disease, especially in the knee and hip [3–5]. The strong relationship of knee OA with obesity provided evidence that excess loading likely causes disease and suggests that weight loss may treat it. Also, OA, especially in the hips and hands, often is inherited. Understanding the biology of specific allelic variations that increase the risk of disease in affected families will provide opportunities for prevention and treatment.

Racial and ethnic differences often provide clues about disease causation. Until recently, little strong evidence existed that there were racial disparities in the occurrence of OA in the United States, although Jordan and colleagues [6] reported that, compared with whites who had disease, African Americans often are more disabled by OA and tend to have more severe disease.

A recent epidemiologic study that compared the prevalence of knee, hip, and hand OA among elders in Beijing to similar population groups in the United States showed that hip OA is exceedingly rare in China [7], whereas knee OA is prevalent, especially in Chinese women, despite their comparative thinness [8]. Insights into the reasons for these dramatic racial and ethnic differences will likely provide insights into what causes OA in these joints.

Limitations of current studies

Too few cases to study risk factors for disease onset

Despite valuable information from epidemiologic evidence about risk factors for OA, insights have been limited. Until now, epidemiologic studies have focused on samples that were recruited randomly from the general population (or recruited without over sampling those who had OA). This has been necessary to estimate disease incidence and prevalence. Although some studies have been large, with samples ranging from 1000 to more than 5000 subjects, rates of

incident disease (or new onset cases per year) are low in the general population because OA takes many years to develop and is not universal [9]. It is difficult and expensive to follow these cohorts for the 10 to 15 years that is needed to observe large numbers of new cases of OA. To get enough cases for study, epidemiologists have defined disease using the radiograph, although only half of persons who have radiographic disease have frequent joint pain. From a public health standpoint, the development of symptomatic OA is far more important and its determinants may differ from those of radiographic disease.

Combined with findings from animal studies and basic science insights, these epidemiologic studies have provided hints that a variety of modifiable factors influence the occurrence of OA. Among these are dietary factors, particular types of physical activity, and high or low bone mineral density [1]. Even with several thousand subjects, the ability of epidemiologists to evaluate these important and potentially modifiable risk factors definitively is limited, because of the low rate of new disease occurrence and because each of these risk factors is measured with considerable noise, which creates frequent misclassification of a person's status. For example, because physical activity varies from week to week and questionnaires that evaluate it have imperfect reproducibility, the evaluation of the effect of specific levels of activity and of specific activities on OA is especially difficult [10,11].

Current epidemiologic studies of OA have drawn from population samples and studying persons who are at low risk and at high risk of disease. The small number of cases of OA that develops over time provides limited statistical power to address the relationship of putative risk factors with disease. The problem of uncommon outcomes is compounded by imprecise risk factor assessments; when risk factors are measured with imprecision, larger sample sizes are needed to evaluate their relation with disease. One solution to the need for a large numbers of subjects to provide adequate numbers of new disease end points is to study risk factors for worsening of existing OA. Because such changes are more common and can be measured as continuous or ordinal variables, they provide a greater ability to observe associations between risk factors and disease outcomes. Implicit in this approach is the notion that factors that affect the course of disease are the same at the initial and later stages; however, several studies suggested that the risk factors for incident OA may be different from risk factors for progression. Therefore, studies of risk factors for disease progression in those who have preexisting disease may provide no information about the risk factors for incidence. To accumulate sufficient numbers of persons who have incident disease, the options are to study a huge sample of subjects repeatedly or to focus longitudinal studies on persons who are highly likely to develop disease. It would be wasteful to include expensive OA imaging tests in large-scale epidemiologic population studies if most subjects are not likely to develop clinically significant OA. A targeted approach that focuses on those who are at high risk is a more rational response to this study design conundrum.

Further, from a disease prevention standpoint, it is unlikely that population-wide efforts will be undertaken; instead, prevention efforts will be focused most

on those who already have OA or are at high risk because these persons would be motivated to undertake the prevention opportunities that are identified by epidemiologic studies. For example, if running were identified as a risk factor for OA, this does not mean that public health recommendations should discourage recreational running. Rather, for those who have early disease, running might be discouraged in favor of other forms of exercise.

Several unequivocally strong risk factors can be used to define a high-risk population, including female gender, older age, overweight, and having previous knee injury or knee surgery [1,3,4]. Further, rates of disease progression in those who have pre-existing OA are greater than incidence rates [9], but structural progression on radiograph is defined based on joint space loss; this is difficult to assess on radiographs of the knee. Progression of hip OA is easier to evaluate, given its more rapid progression and the ease with which progressive narrowing in the hip joint can be evaluated [12]. The high rates of total hip replacement for OA, at least in the United States, make the study of hip OA radiographic progression over several years challenging.

A problematic focus on radiographs

There are three central reasons why a focus on radiographic definitions of disease in epidemiologic studies of OA is not ideal. First, the concordance between structural OA and symptoms is poor; many persons who have radiographic disease—even severe disease—have few, if any, symptoms [13]. Others who have severe and disabling symptoms have only mild radiographic evidence of disease. Symptomatic OA should be a major focus of studies on preventing OA because symptomatic disease causes disability and has societal and public health impacts. Epidemiologic studies should focus on identifying risk factors for diseases that cause suffering and public health burdens; generally, structural OA does not unless it is accompanied by symptoms (structural OA—even without frequent symptoms—may alter gait and create mobility limitations but this is uncommon). Symptomatic OA, which is characterized by the combined presence of joint symptoms and evidence of OA pathology in symptomatic joints, should be the focus of epidemiologic inquiry for disease onset and disease progression. Because symptomatic OA is less common than radiographic disease, the challenge of designing studies that will provide an adequate number of end points for risk factor analyses is heightened.

Second, so disease prevalence rates could be compared with historical estimates and those from other geographic locations and to maximize the number of cases, OA epidemiologists have focused on the prevalence of radiographic findings of disease as their primary measure of disease occurrence. The existence of an accepted atlas for the characterization of disease that was developed by Kellgren and Lawrence has encouraged this disease definition. When change over time is the main focus, radiographs are less appealing than when disease prevalence is the target. Radiographs are insensitive to early disease onset [14]

and probably are insensitive to disease progression, in part because of their poor reproducibility. Radiographs, especially of the knee, have poor long-term reproducibility, which makes it difficult to distinguish radiographic change from changes in imaging [15]. Minor changes in positioning of the joint (eg, degree of flexion of the knee, rotation of the foot) can create dramatic changes in the appearance of a knee radiograph. Given the duration of epidemiologic studies, it is unlikely that the same radiograph technologist in the same location will perform the same radiograph. Even so, several epidemiologic studies [9,16,17] evaluated structural change in OA using radiography and reported valuable information; however, so much change must occur for the radiograph to display this change clearly that rates of absolute change have been low in most studies [9,15]. The development of protocols for flexed knee radiographs [18] has increased the reproducibility of radiographic evaluation, and consequently, increased the likelihood that important radiographic change can be detected; however, it has not increased the likelihood that radiographs will detect small, potentially clinically important, degrees of change. Further, reproducible positioning may require fluoroscopy which probably is unacceptable in large population studies because of its greater complexity and cost compared with plain radiography, its increased radiation exposure, and the variation in the availability of appropriate equipment from site to site. The poor sensitivity to change of conventional radiography constitutes another obstacle for epidemiologists who are studying risk factors for development or progression of OA.

The last reason why a focus on radiographs in OA studies is problematic is because radiographs do not visualize many important joint structures whose pathology may be central to the study of OA. Some of this pathology may occur before the onset of full-blown symptomatic disease, and thus, be of importance in understanding disease onset, whereas other types of pathology may be found primarily in established disease and may have a role in the worsening of disease. Radiographs, if done carefully, accurately image bony abnormalities in OA (eg, osteophytes) and provide indirect evidence on cartilage loss through the evaluation of joint space narrowing. They do not image cartilage directly nor do they provide evidence of the integrity of menisci (in knees), labrum (in hips), or ligaments. Further, they provide little evidence on the existence of synovitis and imaging of effusions on radiograph is insensitive. Although bone is imaged, bone marrow lesions—which may be important sources of pain in OA and may increase the risk of disease worsening [19,20]—are not imaged on radiograph. Lastly, radiographs are two-dimensional images and usually are not tomographic. Thus, the three-dimensional extent of any pathology is difficult to gauge.

Although a primary focus on radiographs probably should be discouraged in future epidemiologic studies of OA, current disease definitions depend on radiographs. To compare disease prevalence and risk factor assessments, future studies will need a radiographic component. For these reasons, radiographs will need to be included in OA studies, but not as the primary outcomes.

One major alternative to radiographic evaluation of OA, MR imaging, has emerged. MR imaging directly visualizes most of the important anatomic structures in the knee, including hard and soft tissue structures. MR imaging is a promising outcome tool in the epidemiologic study of knee OA. MR imaging is able to delineate cartilage directly and, as a three-dimensional technique, can reveal the spatial pattern of loss. MR imaging can detect focal and diffuse cartilage changes and is less vulnerable to changes in joint position than radiography. MR imaging also can visualize damage in other soft-tissue structures in and around the joint—meniscal disruption, subchondral marrow lesions and synovitis—changes that may be linked to the occurrence of knee pain. MR imaging has been used successfully in some longitudinal studies of the natural history of cartilage loss [21,22].

Future studies of OA should include MR imaging and radiographic assessment of disease; the former to dissect the structural manifestations of disease and the latter to characterize disease as present or absent using standards that already are in wide use. As MR imaging becomes standardized with features of OA that are accepted, radiograph studies may become unnecessary.

A focus on nonmodifiable risk factors

The established risk factors for knee OA—older age, female gender, obesity, and inheritance—cannot be modified readily. Recent studies suggest that other risk factors exist, which, if modified, could decrease the prevalence and burden of this disease. These factors include specific types of physical activities, muscle weakness, proprioceptive deficits, and micronutrient deficiencies. Studies that evaluated these factors showed promising, but inconsistent or inconclusive, results. A large longitudinal study with well-developed measurement tools and standardized assessment of these risk factors is needed to demonstrate clearly whether factors like these are related genuinely to disease occurrence.

A major goal of epidemiologic studies of any disease is to identify risk factors that could be modified, thus preventing disease. Established epidemiologic cohorts have attempted to examine modifiable risk factors; however, the findings have not been, nor are they likely to be, definitive. Because the payoff for identifying modifiable risk factors may be a decrease in disease burden, studies with a better chance of determining their relation to disease are needed.

Limitations in comparing risk factors for incidence and progression

Several studies have suggested that risk factors for incident OA may be different from risk factors for progression. For example, in subjects who were followed 5 years, Cooper et al [23] reported that risk factors for incident

(30 cases) disease included obesity, Heberden's nodes, previous knee injury, and regular participation in outdoor sport; only obesity significantly affected the risk of progressive disease (49 cases). Brandt et al [24] reported in a longitudinal community-based study that quadriceps weakness increased the risk of radiographic incident knee OA (for women who developed incident OA [n = 14], quadriceps strength/kg body weight was 0.47 versus 0.57 in women who did not develop OA [P = .053]). Quadriceps weakness did not increase the risk of progressive knee OA. If risk factors for OA differed by stage of disease, then preventive strategies should be tailored to disease stage. Further, if risk factor profiles differed by stage of disease, that would provides important insights about disease biology.

There also may be distinct risk factors for OA progression. McAlindon et al [25] suggested that vitamin D and vitamin C deficiencies increased the risk of progressive, but not incident, radiographic disease. Lane et al [17] found that vitamin D deficiency was a risk factor for joint space loss in the hip. Zhang et al [26], using data from the Framingham Study, reported that high bone density was associated with a modest increase in the risk of incident disease; however, women (and men) who had high bone density were protected against progressive OA, especially joint space narrowing. Hart et al [27] also suggested that bone density may have opposite effects on OA incidence and progression.

In other chronic diseases (eg, heart disease), risk factors for incident and progressive disease are the same. There are at least four explanations for the findings that risk factors for incident and progressive disease differ. The first is that the studies that examined these risk factors do not have sufficient cases of incident and progressive disease to distinguish the risk factors for one from the other. The largest of these studies has fewer than 80 incident cases and less than 65 progressors. Second, OA may be heterogeneous in its structural pathology (eg, bony proliferation versus cartilage loss); the biology of these features may differ, with risk factors for bone proliferation differing from risk factors for cartilage loss. Studies have suggested differential effects on osteophytes and narrowing [26,27]. Third, incidence and progression may be different in stages of disease that have different biology/pathogenesis. Risk factors may affect disease differently at different disease stages. For example, an increased rate of cartilage repair may make prevalent disease more sensitive to relative deficiencies of required nutrients (eg, vitamins C and D) than new disease; subchondral bone changes may become critical only when disease has reached a certain point. Fourth, limitations of imaging may result in different sensitivities to structural features and give rise to apparent differences in incidence versus progression risk factors that are not biologically meaningful. Without a single study that is large enough to yield multiple cases of incident and progressive disease, identifying which factors operate at different disease stages is impossible. Studies that combine investigation of incident and progressive disease are needed to ensure that risk factor differences by stage of disease are not due to different subject selection, measurement methods, or outcome ascertainments.

Preparing for studies that are oriented toward persons who are at high risk and persons who have pre-existing disease

Defining those who are at high risk of developing symptomatic knee osteoarthritis for studies of disease onset

Many epidemiologic studies of OA, including the Framingham Study, have documented that persons who are overweight and those who have a history of knee injury or operation are at high risk of later knee OA [28]. To incorporate this information into the design and planning of large cohort studies of incident knee OA, we derived a specific level of risk associated with these factors and the risk of disease in different gender and age subgroups using data from the Framingham Osteoarthritis Study along with data on the incidence of symptomatic knee OA from the Fallon Community Health Plan [29]. There were two different study groups at Framingham; the original cohort, studied for knee OA in 1983–1985 and again in 1992–1993 (8-year interval) and the Framingham Offspring (the sons and daughters of the original cohort plus their spouses). The latter subjects have been studied for OA only once. We used longitudinal data on knee OA from the Framingham Cohort Study to define incidence rates. For women, the per person incidence of symptomatic knee OA was 1% per year; it was 2% per year for symptomatic knee OA and was 4% per year for progressive radiographic disease [9]. Rates were slightly lower for men. High weight and body mass index (BMI) increased the risk of incident and progressive OA in women, but not in all men [30]. All of these rates are slight underestimates because only anteroposterior (AP) views of both knees were obtained; thus, there were no longitudinal data on the patellofemoral joint. Incorporation of views of the patellofemoral joint increases prevalence by at least 10% [31,32] and probably has a similar effect on incidence.

Although longitudinal data from the Framingham cohort study provided information on overall expected incidence rates, the cohort started off at a mean age 70, had small numbers of subjects in different risk subgroups, and a small number of incident cases. In addition, there were no subjects who were in their 50s. Therefore, to estimate the absolute risk of disease in those who were at high risk, we turned to the Framingham Offspring Osteoarthritis Study. Subjects spanned a wide range of age, AP and lateral views of the knees were acquired, and questions on knee symptoms were asked. We combined data on the offspring and cohort to create a large group of subjects (aged 50 to 80 years) to evaluate the prevalence of radiographic knee OA. We made the assumption that a 10-year prevalence difference of 10% between deciles of age would translate into a 1% incidence rate per person per year.

To identify persons who were at increased risk of developing incident OA, we used known risk factors—age, gender, weight, and history of knee injury or operation. We created a ‘‘high risk’’ group that was characterized as having a weight that was greater than the median or a history of knee injury or operation.

To define the median of weight, we used the Framingham population and chose sex- and age-decile–specific cut-points (eg, for women aged 51 to 60 years, the median weight was 142 pounds, whereas it was 138 pounds for women aged 61 to 70 years and 134 pounds for women aged 71 to 80 pounds). Lastly, because the apparent relative risk of knee OA in men who were at high risk was not that much greater than the risk in all men, we also created a ''very high risk'' group of men who were defined as having weights in the upper tertile or a history of knee injury or operation.

The prevalence of radiographic knee OA in each subgroup of age and gender is shown in Table 1. Sample size is greater than 200 for each gender and decile group. Analyses in which cut-points of BMI were used, instead of weight, yielded similar estimates. The analyses are restricted to those who did not have frequent knee symptoms; it is likely that in a study of persons who have disease or who are at high risk, all persons who had frequent knee symptoms would have been included. We were interested in persons who, even without frequent knee symptoms, would be at high risk of disease.

Among men, the prevalence of radiographic OA increased from 10.3% to 20.3% over a 10-year period from age 51 to 60 years through age 61 to 70 years. It increased to 33.6% in persons who were aged 71 to 80 years. The number of subjects who was older than age 80 was small; therefore, these figures are not depicted. In all men, the decile differences in prevalence translate into incidence rates of 1% to 1.2% per person per year. If only men who are at high risk are considered, the expected incidence, based on these prevalence data, still would be approximately 1.2% per year. It is only among men who are at very high risk that there is an increase in the prevalence of disease (17.2% at ages 51 to 60 years; 30% at ages 61 to 70 years, and 50% at ages 71 to 80 years). This

Table 1
Prevalence of asymptomatic radiographic knee osteoarthritis (anteroposterior or lateral) in Framingham Study men and women by age and risk group

Gender	51–60 y	61–70 y	71–80 y
Men			
All	10.3%	20.3%	33.6%
High risk[a]	15.1%	23.9%	39.0%
Very high risk[b]	17.2%	30.0%	50.0%
Women			
All	4.3%	20.7%	31.5%
High risk[a]	8.7%	28.6%	38.2%

[a] High-risk persons are those who have a history of knee injury or operation or who weigh more than the Framingham Study median weight for their age and gender-specific group. Weight cutoffs for women: for 51–60 years, 142 pounds; for 61–70 years, 138 pounds; and for 71–80 years, 134 pounds. No persons who had knee symptoms are included.

[b] Very high-risk persons are those who have a history of knee injury or operation or whose weight places them in the upper third of the age- and gender-specific Framingham subjects' weight distribution. No person who had knee symptoms is included. Weight cutoffs for men: for 51–60 years, 194 pounds; for 61–70 years, 187 pounds; and for 71–80 years, 182 pounds.

averages to approximately 1.6% per year. Among women, although the increase in prevalence is substantial, especially in the 50s and 60s, the difference is not much greater among those who are in the high risk compared with all women. Numerous studies showed an increased risk of prevalent and incident disease among women who are overweight [3]. An estimate of incidence that was similar to Framingham data was obtained in a large health maintenance organization–based study that used clinical OA as the outcome.

Added to these should be subjects who have frequent knee pain. Based on Framingham Study findings, 50% of these will not have knee OA by radiograph. This group is believed to be at high risk of OA; in the Framingham Study, these subjects developed radiographic OA at a rate of 5% per year (40% followed 8 years).

Identifying a threshold of pain to define symptomatic disease

To study symptomatic OA, it needs to be defined. The American College of Rheumatology and National Data Workgroup have defined symptomatic OA for all joints as the presence of joint pain plus evidence of radiographic disease in the symptomatic joint. OA pain varies in its severity and frequency from person to person. What level or frequency of pain should be used to define the presence of disease?

Health ABC is a longitudinal study of body composition changes and disability in a community-based sample of 3075 white and black men and women, aged 70 to 79 years, who were selected so as not to have major mobility disability at baseline. Subjects have been surveyed for knee symptoms using a variety of questions, including that of the Western Ontario and McMaster Universities (WOMAC; a valid survey used to assess the severity and impact of knee symptoms).

To estimate what level and frequency of knee pain to use in defining symptomatic knee OA, we used surveys that were administered during Health ABC. Health ABC is unique in that all subjects were asked a large battery of questions about knee pain, including its frequency, activities that brought it on, and its impact. To choose the measure of knee pain, we used the following validation criteria: (1) the number of days of activity limitation that was due to knee pain in a recent month, (2) WOMAC activity-related pain score, and (3) correlation with the presence of radiographic OA. Twenty-six percent of subjects reported current frequent knee symptoms (“pain, aching or stiffness in or around the knees on most days”) in the past month (Table 2, category e). These subjects had the highest WOMAC activity-related pain scores, the most days of knee-related activity limitation, and most had radiograph knee OA. Those who had occasional activity-related pain, but not current frequent pain in the past 30 days (4% of the cohort; group d in Table 2), had high average WOMAC pain levels but few days with limited activity that was due to pain. Those who had frequent symptoms in the past year but not in the past month (4%; group c in Table 2) had intermedi-

Table 2
Evaluation of a proposed knee pain classification using Health ABC data

Category	Any WOMAC activity pain	Mean WOMAC pain score (of 25)[a]	Days in past month with knee-related activity limitation[b]
a. No symptoms in past 12 months	0%	0.0 (±0.0)	0.0 (±0.0)
b. Infrequent symptoms (yes to "any pain, aching or stiffness" in the past 12 months, but not c–e)	39%	1.0 (±1.5)	0.1 (±1.5)
c. Past frequent symptoms (yes to "pain, aching or stiffness on most days of a month" in past 12 months, but not d–e)	54%	3.5 (±4.2)	2.7 (±7.7)
d. Activity pain (moderate or worse pain with activity in past 30 days (from WOMAC), but not e	100% (by definition)	6.4 (±2.9)	1.4 (±5.4)
e. Current frequent knee symptoms ("pain aching or stiffness on most days" in past 30 days)	96%	7.7 (±4.6)	5.7 (±10.4)

[a] Values are the percent or mean (± SD) for knees in each pain category.
[b] Values are mean (± SD) for subjects in each pain category.

ate levels of activity-related pain and activity limitation, whereas those who had infrequent symptoms or only mild activity-related pain (17%; group b in Table 2) had the lowest values for these validation criteria. Therefore, based on activity limitation, WOMAC scores, and the correlation with radiograph OA, ''frequent pain'' is likely to be the best threshold to define symptoms. Other estimates of the prevalence of frequent knee pain in the community yield similar estimates of 25% to 30%; in the Framingham Study, 34.4% of those who were aged 60 and older reported pain, aching, or stiffness on most days.

Frequent knee symptoms do not always last forever. Although the proportion of subjects who experience an improvement or even remission in symptoms is not known, symptom improvement is not rare. For example, in a review of natural history studies, Felson [33] found that approximately one third of patients who had clinical knee OA had some improvement in symptoms over time. A 1-month follow-up of Framingham subjects suggested that 10% who had frequent symptoms did not report frequent symptoms when requestioned. Thus, in population studies of OA, it may be useful to evaluate symptoms repeatedly to identify those who have persistent symptoms.

The Multicenter Osteoarthritis Study and the Osteoarthritis Initiative

Two large, prospective cohort studies that focus on the risk factors for knee OA recently were undertaken with funding from the National Institutes

of Health and other sources. The Multicenter Osteoarthritis Study (MOST) began in 2001 and the Osteoarthritis Initiative (OAI) started in 2002. Both are in the process of recruiting and studying subjects. The two studies share several important design strategies, but they also differ in important details. MOST and OAI address the limitations of traditional epidemiologic designs as follows:

- The studies focus on symptomatic knee OA. Similar definitions of frequent symptoms and radiograph changes are used to define symptomatic knee OA. The primary incidence outcome is new symptomatic OA of the knee.
- Inclusion of subjects who do and do not have symptomatic OA at baseline, with the former to be studied for disease progression. The enrichment with subjects who have prevalent symptomatic OA at baseline (ie, recruited in greater proportion than their representation in the population) permits a definitive assessment of risk factors for progression and whether risk factors for incidence and progression are, in fact, different.
- Adequate power to evaluate risk factors for incident symptomatic disease onset by enrichment of the cohort with subjects who do not have disease at baseline but who have risk factors for knee OA. Selecting those who have risk factors increases the likelihood of incidence by 1.5-fold to 1.67-fold over other subjects of the same age and gender (ie, older adults who are at high risk of knee OA anyway). Both studies include obesity, previous knee injury and knee surgery, and knee symptoms without existing radiographic disease as risk factors to enrich the cohort.
- Inclusion of the assessment of modifiable risk factors, such as physical activity, quadriceps strength, and dietary measures.
- Knee radiographs that are to be acquired serially will be used to define the presence of disease and its incidence and progression. Symptomatic OA will be defined as the presence of frequent knee pain and radiographic OA (definite osteophyte) in the symptomatic knee.
- MR imaging will be obtained repeatedly in both studies on most subjects. The availability of MR images will allow investigation of the effect of MR image findings on the development and progression of knee OA and correlation of MR imaging features with symptoms and radiographic abnormalities. MR imaging provides a wonderfully rich set of information; however, it will not be used to evaluate the presence of disease because it has not been validated adequately for this purpose, whereas radiographs serve as an accepted standard for end point definitions in OA.
- Use of case-cohort design to increase efficiency of investigations of expensive assessments, including MR image readings and biochemical measurements.

Although there are great similarities between these two studies, there also are important differences in their structure, size, and follow-up (Table 3). Some of the risk factors to be assessed will differ. Also, although the focus of MOST is the incidence of symptomatic OA—also an element of OAI—OAI's goals are

Table 3
Differences between Multicenter Osteoarthritis Study and Osteoarthritis Initiative

Category	MOST	OAI
Funding	NIH Grant (data available through study investigators)	NIH contract (data to become a public access database) jointly funded with private (pharmaceutical company) contributions
Clinical centers	University of Alabama, Birmingham University of Iowa	University of Pittsburgh Ohio State University University of Maryland/ Johns Hopkins Memorial Hospital Rhode Island
Number of subjects	3000	5000
Frequency of follow-up	Every 15 mo	Every 12 mo
Length of follow-up	30 mo	48 mo
Age of eligibility	50–79 y	45–79 y
Knee pain eligibility	Frequent knee pain in the past 30 d	Frequent knee pain in a 30-day period in the past 12 mo
Eligibility for persons who do not have frequent knee pain	Overweight Knee injury/operation	Overweight Knee injury/operation Parents/siblings with total knee replacement Frequent knee-bending activities that increase risk Hand OA
MR imaging	1.0 Tesla (some get 1.5 Tesla also)	3.0 Tesla

broader with a charge to evaluate biomarkers that might identify persons whose disease is likely to progress.

Summary

MOST and OAI will be the first large-scale epidemiologic studies to focus on OA among those who have symptomatic disease and those who are at high risk of symptomatic disease. Targeting these subjects is practical (they will provide sufficient cases of disease to perform an efficient longitudinal study) and relevant; they are the subjects who will be targeted by any preventative interventions. These are the individuals who are interested in preventing disease. Direct clinical and public health impacts will emanate from the focus on symptomatic knee OA in these projects. This is in contrast to other epidemiologic studies of OA that focused principally on radiographic outcomes. For completeness sake and to evaluate the effects of risk factors on structural outcomes, MOST and OAI also will study radiographic outcomes. Inclusion of symptom and structural outcomes will permit a differentiation between factors that affect structural changes and those that affect symptoms. Both studies are timely in incorporating a new set of

measurement tools, such as MR imaging and clinical instruments that assess symptoms and disability accurately.

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