A TWELVE YEAR FOLLOW-UP STUDY ON OSTEOARTHRITIS OF THE KNEE IN THE GENERAL POPULATION

An epidemiological study of classification criteria,
risk factors and prognostic factors

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Printing: Offsetdrukkerij Haveka B.V., Alblasserdam

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An epidemiological study of classification criteria,
risk factors and prognostic factors

EEN TWAALFJARIG VERVOLGONDERZOEK VAN KNIE ARTROSE IN DE ALGEMENE BEVOLKING

Een epidemiologisch onderzoek van classificatie criteria,
risico factoren en prognostische factoren

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. Dr C.J. Rijnvos
en volgens besluit van het College van Dekanen.

De openbare verdediging zal plaatsvinden op
woensdag 23 oktober 1991 om 13.45 uur

door

JOHANNES SIMON ANTONIUS GIJSBERTUS SCHOUTEN

geboren te Nijmegen

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...we should remain critical and watchful, but not in terms of a priori convictions, however logical they might seem to the believer.
Anonymous. Should we case-control? Lancet 1990;335:1127-8.

Voor Maria
Voor mijn moeder
Als herinnering aan mijn vader en Peter

The Epoz study has been financed in part by the Netherlands Prevention Fund and the follow-up study has been financed by the "Stimuleringsprogramma Gezondheids-onderzoek (SGO)", an incentive program for medical research financed jointly by the Dutch ministry of Education and Science and the ministry of Welfare, Public Health and Culture.

Financial support for the publication of this thesis from "Het Nationaal Reumafonds" and The Rotterdam Medical Research Foundation is gratefully acknowledged.

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CHAPTER 1

INTRODUCTION

Chapter 1

INTRODUCTION

Osteoarthritis (OA) is a well known cause of joint complaints and disability in the elderly. Pain is the most frequent joint complaint and the ability to cope with the demands of daily life can be substantially reduced as a result of OA. Population based studies have shown that people with radiographic osteoarthritis more often have pain in the affected joint (1,2,3) and difficulties in performing normal daily activities like walking, arising from a chair, getting in and out of bed, climbing a staircase, and housekeeping, even when frequent pain is absent (3,4). People with osteoarthritis are handicapped also in performing household chores, shopping and leisure activities (5). Moreover, work disability and losses in earnings are major problems for persons with osteoarthritis (6,7,8).

OA has a tremendous impact not only on an individual but also on society as a whole. The costs for society are due to costs of medical care, costs due to loss of working days (9) and the costs of the Social Security Disability Insurance. The large number of people suffering from osteoarthritis implies that these costs are considerable. Hardly anyone can escape from getting osteoarthritis although its consequences may vary from individual to individual.

In sheer contrast to the impact OA has on individual well-being and on society, is our lack of knowledge about the causes and prognostic factors of this disease (10,11). The possibilities to prevent OA and to influence the course of this condition are therefore limited. Therapies are basically symptomatic and consist of pharmacotherapy, physical therapy, physical rehabilitation and surgical interventions like joint replacement.

Obviously, there is a need to study OA. An epidemiological approach is of value since (clinical) epidemiology is concerned with the study of diagnosis, etiology and prognosis of disease in humans. In epidemiological research the occurrence of disease or the occurrence of outcome of disease are studied in relation to putative risk factors or putative prognostic factors respectively.

In this thesis studies on classification criteria, risk factors and prognostic factors of knee osteoarthritis in the general population are presented. From 1975 to 1978 a population survey was conducted in Zoetermeer, The Netherlands (The EPOZ-

study), to investigate the prevalence and risk factors of several chronic diseases. The rheumatic diseases were studied in particular. This survey gave the opportunity to evaluate the value of classification criteria for epidemiological research in the general population, developed by the American College of Rheumatology (ACR) (chapter 4). Furthermore, a follow-up study was conducted of the participants aged 46 to 66 years without radiographic osteoarthritis of the knee to investigate the incidence and risk factors of knee OA (chapter 5). A follow-up of all the participants aged 46 to 68 years with radiographic OA of the knee was performed to study the course and prognostic factors of knee OA (chapter 6). These follow-up studies took place in 1988 and 1989, 12 years after the initial population survey. Finally, the collected evidence is reconsidered and suggestions for future research are presented (chapter 7).

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CHAPTER 2

AIM OF THE STUDY

Chapter 2

AIM OF THE STUDY

CLASSIFICATION CRITERIA

Criteria to diagnose the disease or assess the outcome need to be considered in every epidemiological study . The criteria are needed to classify participants as those having the disease or outcome and those who have not. Classification criteria are not always uniformly accepted and commonly more than one combination of criteria is used.

The use of different classification criteria can lead to different study results and makes the comparison of different studies more difficult. Moreover, if non-differential misclassification occurs, the strength of an association between a putative risk factor and a disease is reduced as well as the power to detect an association. This methodological issue is discussed in more detail in this thesis with the aim of highlighting the consequences of this misclassification.

Classification criteria of knee osteoarthritis used in epidemiological research have almost always been based on radiographs. The criteria described by Kellgren and Lawrence have been used most commonly and were recommended for epidemiological studies at two international conferences (1,2,3). However, it was realized that these criteria should be validated and related to physical signs and symptoms (2).

In this thesis the results of a study on the relationship of findings from the medical history, physical examination and serum analysis with radiographic osteoarthritis are presented. The aim of this study was to assess whether it was necessary to take a radiograph to diagnose radiographic osteoarthritis or whether it could be predicted reliably from the medical history, physical examination and serum analysis.

Recently, the American College of Rheumatology (ACR, formerly the American Rheumatism Association - ARA) has developed new criteria for the classification and reporting of knee osteoarthritis (4). These criteria were based on a thorough examination of a group of patients attending a clinic with complaints of pain in the knee joint. The investigators have recommended criteria to be used in epidemiological research.

It is, however, unknown how these newly recommended ACR criteria will stand in a situation which is altogether different from the situation in a hospital where a selection of patients with joint complaints are seen. One aim of the study presented in this thesis is to investigate the agreement and validity of the ACR criteria for the classification of knee OA for epidemiological research in the general population.

RISK FACTORS

Risk factors are studied in epidemiological research with the aim of discovering the etiology of disease. The study of risk factors of knee osteoarthritis is no exception. Until now most studies on the risk factors for knee osteoarthritis have been cross-sectional.

A cross-sectional study has the disadvantage that uncertainty can exist about the question of whether the risk factor preceded the disease or vice versa. Furthermore, in a cross-sectional study, the effect of changes in the risk factor over time is more difficult to assess and for some diseases it is not possible to distinguish with certainty between a risk factor and a prognostic factor. Therefore, there are advantages in studying risk factors in a follow-up study.

The EPOZ-study, conducted between 1975 and 1978, gave the opportunity to conduct a follow-up study of risk factors of knee osteoarthritis among participants known to have no radiographic OA of the knee in 1975-78. As part of the studies included in this thesis a follow-up study on the incidence and risk factors of knee OA was conducted with the aim of contributing to the clarification of the etiology of knee OA.

PROGNOSTIC FACTORS

If more is known about the prognosis and prognostic factors of a disease, it may lead to the prevention of certain outcomes of the disease. For knee osteoarthritis this implies that prevention of severe disability could be possible. Furthermore, if the prognosis is known and can be predicted, patients can be informed more accurately about the outcome of their illness.

However, very little is known about the prognosis and prognostic factors of knee osteoarthritis. This makes the need to study the prognosis and prognostic factors of knee osteoarthritis obvious. Therefore, a further aim of this study is to investigate the course and prognostic factors of knee OA.

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CHAPTER 3

THE EPIDEMIOLOGY OF OSTEOARTHRITIS

A review with special emphasis on knee osteoarthritis

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3.1 INTRODUCTION

In medicine, scientific research is concerned with the etiology, diagnosis, prognosis and therapy of disease. Research questions concerning any of these four aspects of diseases serve as the starting-point for epidemiological research. In (clinical) epidemiology the occurrence of disease or the occurrence of outcome of illness is studied in relation to putative risk factors or prognostic factors.

In this review an overview of the epidemiological studies is given on the classification criteria, risk factors, and prognostic factors of osteoarthritis (OA), especially osteoarthritis of the knee. Therapy and intervention in relation to OA are not discussed because these subjects have not been studied as part of this thesis.

A number of good reviews on the epidemiology of OA have already been written by Peyron, Felson and Davis (1,2,3) However, none has focused exclusively on knee OA, although Felson reported on OA of the hip and knee.

In paragraph 3.2.1 on classification criteria a short outline is presented of the relevance of classification criteria for epidemiological research, followed by a historical overview and recommendations for future research. A recurrent point of discussion about the classification is the imperfect correlation between signs, symptoms, and radiological abnormalities and this is discussed in paragraph 3.2.2. Subsets of OA are described in paragraph 3.2.3 because subsets may have a different etiology or prognosis and for the research on etiology or prognosis it may be relevant to consider which subset is to be studied. In paragraph 3.3, risk factors for the occurrence of knee OA are reviewed. The one but last paragraph about prognostic factors of knee OA is short because little has been published on this subject. Concluding remarks in paragraph 3.5 form the last part of this review.

The articles used for this review are selected with the support of MEDLINE from the literature published between 1981 and 1990. In addition, references from articles on (knee) OA were selected.

3.2 CLASSIFICATION CRITERIA

3.2.1 Classification criteria in epidemiological research

3.2.1.1 Introduction

It is important to study the classification criteria for OA used in epidemiologic research. Perfect criteria of OA would classify subjects in distinct categories of diseased and non-diseased. Imperfect criteria introduce the problem of non-differential misclassification when subjects with OA are wrongly classified as having no OA and vice versa. Misclassification influences the estimate of the measure of the occurrence relation (e.g. the relative risk). If the misclassification is present to the same extent in the group with the risk factor as in the group without the risk factor, thus when non-differential misclassification occurs, then the true value is underestimated. Moreover, the sample size must be increased to reach sufficient power to detect weak associations. The imperfect diagnosis of OA also hampers the comparison of the results with other studies. Theory and consequences of non-differential misclassification are discussed in more detail in chapter four.

For the classification of OA two broad categories are sometimes distinguished, primary and secondary OA. The difference is that for primary OA the cause is not known while for secondary OA it is. For example, some forms of inborn errors of metabolism predispose to the early development of OA and OA occurring as a result of this genetic abnormality is called secondary. Most individuals, however, have primary OA because the cause is mostly unknown.

3.2.1.2 Historical overview

In the beginning of this century an article was devoted to the differential diagnosis of the "so-called rheumatoid diseases" (4). In this article several categories of rheumatic diseases were described and a difference was made between atrophic arthritis (rheumatoid arthritis) and hypertrophic arthritis (OA). Radiographs were used for the first time to differentiate these two forms from each other. In 1961, during the Symposium on Population Studies in relation to Chronic Rheumatic Diseases in Rome, criteria for diagnosing OA in epidemiological research were introduced. These criteria, developed by Kellgren and Lawrence, were based solely on radiographs. The criteria were published in the Atlas of Standard Radiographs of

Arthritis (5). According to these criteria, radiologic OA is scored on a five-point scale from 0 to 4. Where: 0 = absence of any signs of radiological osteoarthritis (ROA); 1 = doubtful narrowing of joint space and possible osteophytic lipping; 2 = definite osteophytes and possible narrowing of joint space; 3 = moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends; and 4 = large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

In 1966, during the Third International Symposium on Rheumatic Diseases in New York, criteria for diagnosing OA were discussed again. The subcommittee on classification criteria for osteoarthrosis reported: "All agreed that the most important single criterion was the radiologic one. There was no real consensus of opinion as to the importance of any of the other criteria.". They advised to study the association of symptoms, signs and laboratory measurements with radiological changes in order to get some idea of the value of these variables in diagnosing OA. The radiological criteria of Kellgren were again advised to be used in epidemiologic research (6,7).

In 1986 the Subcommittee on Classification Criteria of OA of the American College of Rheumatology (ACR) developed several sets of classification criteria for OA of the knee (8). This committee not only took radiological findings into account but also symptoms, physical signs and laboratory measurements. These ACR-criteria were developed in a clinical setting based on a thorough examination of patients with knee pain. The clinical diagnosis, based on symptoms, physical signs, radiographs and laboratory measures, served as the gold standard.

Although several criteria have been developed, none has been without critique. The radiological criteria of Kellgren have been criticized because, as was argued, osteophytes without jointspace narrowing are merely an age related phenomenon (9). Ahlback proposed other criteria which were also based on radiographs only but attached more importance to the joint space narrowing, and no value was given to the presence of osteophytes (10). The idea was that cartilage loss, reflected by loss of joint space on the radiograph, was the most important pathological defect in OA.

The radiological criteria in general have been criticized because not everyone with radiological abnormalities has complaints or other symptoms of OA (11,12,13). Physical signs, symptoms and ROA do not correlate perfectly. This will be discussed in section 3.2.2. In the study of the ACR-subcommittee the clinical diagnosis of OA was made in 94% of the cases with kneepain when osteophytes on the radiograph were present (8), supporting the importance of radiographs. According to the ACR-subcommittee, however, the presence of kneepain is obligatory for the diagnosis of knee OA.

Recently the criteria of the ACR-subcommittee have been criticized also (14). To the opinion of McAlindon et al, the ACR-criteria "have only been shown to perform well in differentiating OA from younger people with rheumatoid arthritis (RA).". They thought that the subjects had to be matched for age and gender before the criteria could be developed to exclude the influence of age and gender in differentiating patients with OA from those without. It was recommended that more research needed to be done before the criteria were to be applied.

In their comment on this editorial the ACR-subcommittee put forward that leaving out the patients with RA in the control group did not change the criteria substantially (15). They also stated that age was not selected as one of the first and most important variables and that the variable gender was not selected at all.

The question remains how well radiological criteria are associated with pathological abnormalities seen during autopsy or arthroscopy of the knee. The relation between radiological OA and pathological signs of OA seen on skeletal remnants, where only osteophytes and subchondral sclerosis can be seen but not cartilage changes, have been studied in a small study of 24 knees (16). The specificity and sensitivity of radiological OA were 100% and 12.5% respectively when pathological OA changes of the joint were taken as the gold standard.

In another study the cartilage thickness measured on standard antero-posterior radiographs was compared to actual cartilage thickness measured during pathological examination in seven knees (17). These were found to correlate well, correlation coefficient=0.88. However, more cartilage damage could be detected during pathological examination. In a small study of 10 patients with knee OA according to the ACR-criteria, of whom only 5 had radiological abnormalities, all had pathological signs of OA assessed by arthroscopy like fibrillation, deep fissures and erosions (18). On the other hand, cartilage thickness was found to correlate imperfectly with cartilage defects assessed during arthroscopy (19). For example, the specificity of medial joint space narrowing for the presence of medial compartment articular cartilage degeneration was 61% and the sensitivity was 71%.

The problems of diagnosing OA in general have been discussed again in a comment in the British Medical Journal (20). However, new methods of evaluating OA, like magnetic resonance imaging (MRI), are now being developed and seem to be promising in detecting osteoarthritic changes (21).

It can be concluded that the discussion about the diagnosis of OA has not stopped since the beginning of this century. There are no criteria that have not been criticized or have been accepted unanimously. Probably there are no perfect criteria but there is a need to have some generally accepted criteria and a need to

state the classification criteria clearly in every study.

Moreover, if certain radiological abnormalities, regarded as part of OA, are indeed causally related to complaints of joint pain, impairment and disability, it is worthwhile to study etiological factors of these radiological abnormalities. It is also of value to study how criteria are related to other criteria to improve the comparison of different studies.

3.2.1.3 Conclusions and recommendations for future research

The ACR-subcommittee suggested to use a subset of clinical variables, without radiographs and laboratory measurements, to diagnose OA of the knee in epidemiological research. The value of these criteria in epidemiological research in the general poulation is, however, not known.

It can be expected that the sensitivity and specificity are different in the general population as compared to a clinical population. In the general population, people with OA have to be distinguished mainly from people without rheumatic complaints or with rheumatic conditions different from those in a clinic. In the clinical situation the differential diagnosis is concerned with two or more possible diseases from which a patient might be suffering. Moreover, patients with OA from a clinic generally have more severe disease, rendering a diagnosis of OA on clinical grounds easier.

More research is therefore needed to investigate the validity and amount of agreement of the several sets of criteria in the general population. More needs to be known about the influence of the use of these criteria on the measure of the occurrence relation in epidemiologic research since misclassification might be considerable.

3.2.2 Symptoms, physical signs and radiography in osteoarthritis

For some investigators only criteria that also take into account symptoms and physical signs, other than radiological abnormalities, are acceptable as classification criteria. It is suggested that such criteria are of more clinical relevance. However, as stated in the previous section, ROA and symptoms do not correlate perfectly. On the other hand, it is relevant to study risk factors of radiological abnormalities per se if these abnormalities are causally related to pain and disability.

Epidemiological studies that have taken place in the general population indeed

have shown that not everyone with ROA suffers from pain in the affected joint. Even when severe ROA is present, some persons have not experienced pain in the affected knee and about 50% of those with grade 2 ROA have suffered or are still suffering from pain in the knee (11).

Cobb et al published the results of the population studies in Pittsburgh in 1957 (13). In their study "30% of those with marked osteoarthritic changes on X-ray have had pain at the relevant sites in the past five years.".

In the HANES study, 39% of those with grade 2 ROA of the knee replied to have had knee pain on most days for at least one month, for grade 3 or more this was 61% (12).

In the Framingham OA Study 19.2% with grade 2 and 40.0% with grade 3 or 4 reported to have had pain on most days for at least a month. Although the questions were the same, the figures are lower than the figures of the HANES study. At least in all these reports pain is more often present when severe ROA is observed compared to grade 2 ROA.

Other physical signs and symptoms, like morning stiffness or crepitus, are more often present in patients with ROA and kneepain as compared to those with ROA but without kneepain (12,13).

Obesity and some psychological or behavioural characteristics are possible risk factors of pain in subjects with ROA of the knee (11,12,22). However, obesity was not found to be related to pain in another study (23). No differences were found for gender, age or race between subjects having knee ROA with or without pain (12).

Further studies on the factors that lead to disability and pain among subjects with (radiological) signs of OA are certainly indicated. If the occurrence of OA itself can not be influenced, maybe the factors can be influenced that cause OA to become symptomatic or more severe. Obesity could be such a factor.

3.2.3 Subsets of osteoarthritis

3.2.3.1 Introduction

Distinguishing various subsets of OA is useful when it is likely that these subsets have a different etiology, prognosis, or prognostic factors. The distinction between subsets is to some extent arbitrary. It may be observed that certain characteristics are present or cluster in some patients, thus leading to defining another subset. This

new subset can than be studied in more detail and more differences, for example in etiology, with other subsets may be revealed. The subsets discussed in the following paragraph are based solely on radiological signs.

3.2.3.2 **Generalized osteoarthritis**

In 1952 Kellgren et al described patients with polyarthritic OA (24). He argued that "... in clinics dealing largely with rheumatic disease one often sees polyarthritic patients in whom the joint changes in the later stages resemble those of degenerative arthritis, though they differ somewhat in that they often have a rather acute spontaneous onset. Furthermore, these patients tend to present a definite pattern of joint involvement characterized by affection of the distal interphalangeal joints of the fingers, and the first carpo-metacarpal joints in the hand, the great toes and first tarso-metatarsal joints in the feet, the interfacetal joints of the spine, the knees, hips, and other limb joints. These patients also present certain characteristic clinical and radiological features which differ from those found in classical degenerative joint disease on the one hand and polyarthritis of the rheumatoid type on the other, and we have come to classify these cases under the heading of primary generalized OA, which we consider to be a distinct clinical entity.". The authors further described 120 cases selected from a rheumatology department because they had Heberden's nodes or arthritis of the first CMC joint or both. Only 10 men were included in this group. Knees were affected in 64 cases, most often bilaterally. This joint was most often affected after the DIP and CMC-1 joints. After a period of pain in the DIP joints during which the joints are warm, red and tender a chronic phase follows with formation of "bony outgrowths around the joint margins". Radiographs of the knees showed narrowing of the joint space "combined with rounded 'molten wax' bony outgrowths at the articular margins and a marked absence of the sharp-pointed osteophytes so commonly seen in the degenerative arthritis which follows injury".

After this description of primary generalized OA in patients attending a rheumatology clinic, this subset of OA was studied in the general population (25). Heberden's nodes were more often present when multiple joints showed definite radiological signs of OA. This phenomenon occurred in women especially. ROA of the DIP joint was also associated with ROA in other joints, also the knee. These findings suggest that some factors which are of influence on the occurrence of OA in one joint are also of importance in other joints. However, although the study was

limited to those aged 55 to 65, confounding by age may explain these findings. Multiple joint involvement may be just an age related phenomenon instead of a subset of OA.

This controversy, with on the one hand the idea of multiple joint involvement being a chance phenomenon where older peolpe have more joints involved because they are older and on the other hand the idea that some common etiologic factor causes OA in several joints, was studied by Ettinger et al who used the data of the Baltimore Longitudinal Study of Aging (26). They showed that age could not explain the association between ROA in one joint group like the knees, DIP or PIP joints and ROA in the other joint group completely. Therefore, an association, not explained by the age difference, exists between OA in one joint group and OA in another. This raises the question of what the common cause of OA in these joints is.

Non-nodal (without Heberden's nodes) and nodal generalized OA were distinguished and studied further in the general population (27). Nodal generalized OA occurred more frequently among women in every age-group and the non-nodal type was slightly more frequently seen in men. In either group pain was most often present in the knees.

The predisposition to generalized OA is thought to influence the development of secondary OA after meniscectomy (28).

A genetic predisposition (29), joint hypermobility (30,31), uric acid level (27), sex-hormones (32) and chondrocalcinosis (33,34,35) have all been suggested as etiologic factors in the occurrence of generalized OA. Obesity could also be a factor of importance because obesity is associated with several joint groups, not only the knee (25,36,37).

3.2.3.3 **Erosive osteoarthritis**

Although the name osteoarthritis suggests that inflammation is a general aspect of OA a separate subset is distinguished where inflammation is pronounced. This subset was described in 1961 by Crain (38) and followed by several other studies (39,40,41). It is characterized by the presence of signs and symptoms of inflammation like pain, redness, swelling, warmth and functional impairment of the joints. The DIP- and PIP-joints of the hands are mainly affected and occasionally the CMC-1 joints. Inflammatory OA typically occurs most often in middle aged women. The sedimentation rate can be slightly elevated and rheumatoid factor tests are negative. Radiographs of the joints show loss of cartilage, erosions and

osteophytes. The course is characterized by a period with episodes of inflammation followed by subsidence of the symptoms. Ultimately severe, nodal deformities of the joints result, resembling Heberden's nodes in the DIP-joints and Bouchard nodes in the PIP-joints.

A high incidence of RA in this group of patients has been reported (42). A family history of OA of the hands was reported by several patients but researchers made no comparison with patients without this syndrome in any study. An influence of the natural or artificial menopause has been suggested by Ehrlich. In one article he stated: "We also have seen accelerated onset after artificial menopause and have noted exacerbations when hormone therapy given postmenopausally is discontinued.", but he did not give any details to substantiate this observation (43).

An interesting study on erosive OA was published recently (44). In this study 24 patients with OA and radiological erosions of the interphalangeal joints were compared with age-sex matched patients with OA in the same joints. The erosive group had more severe and extensive OA in the hand joints. There were no significant differences in the prevalence of OA in other joints. After a follow-up of three years new erosions had developed in some patients and some patients showed resolution of erosions. The authors concluded that erosions are of a transient nature in interphalangeal OA and that erosive OA is not a specific disease. But still, inflammation was probably more pronounced in these joints with erosions and the OA was more severe. One could question why the OA was more severe and why inflammation was so pronounced.

3.2.3.4 **Chondrocalcinosis**

Several types of crystals have been found in joints affected by OA (45). Calcium-pyrophosphate-dihydrate (CPPD) and apatite crystals are two common types of crystals. The crystals can occur as calcifications in the articular cartilage of the joint or in menisci and can as such be identified on radiographs. This phenomenon is called chondrocalcinosis. When chondrocalcinosis is seen on a radiograph this most often is due to CPPD crystals (46). The discovery of CPPD crystals has led to the description of a new syndrome, calcium pyrophosphate deposition disease (CPDD) (46).

Chondrocalcinosis can be found on radiographs with OA. This raises the question of how these two phenomena are related. It could mean that they occur together just by chance with no consequences for the prognosis or etiological considerations, but it may also be a subset with other features that distinguishes it

from OA without CPPD. Several studies have shown an association between OA and chondrocalcinosis (33,34,35,47,48), thereby excluding that CPPD and OA occur together by chance only.

Two explanations have been suggested to explain this association. One explanation could be that CPPD leads to OA. The other that OA or damaged cartilage in general causes chondrocalcinosis to occur in the affected joint.

This last hypothesis was investigated in a study among subjects who had had a meniscectomy of a kneejoint (49). Chondrocalcinosis occurred more often in the post-meniscectomy knee (20%) as compared to the unoperated knee (4%). Therefore, chondrocalcinosis occurres more often in damaged joints.

Crystals or chondrocalcinosis in joints affected by OA also seem to be associated with more severe OA (33,46,50,51,52). Although this was not found in every study (34). This association with the severity of OA could not be confirmed in a population based study (47). A Berkson fallacy may explain this difference between studies when subjects with the simultaneous presence of chondrocalcinosis and severe OA are selected towards outpatient's clinics. This could be the case if the presence of crystals in the joints leads to more inflammation and in combination with severe OA results in more difficult to manage symptoms.

The finding of an association between chondrocalcinosis and severity of OA, the occurrence of chondrocalcinosis in damaged joints and the inflammatory effect of crystals in joints has led investigators to formulate the so called "loop-hypothesis" (49). In joints affected by OA chondrocalcinosis can occur as a result of the damaged cartilage. Subsequently the OA progresses more rapidly because of an inflammatory reaction, ultimately leading to more severe OA. This again leads to more chondrocalcinosis and more progression and a repetition of the vicious circle. In one autopsy study, however, both calcification and synovitis were independently associated with OA but were unrelated to each other (53).

Therefore, there is some evidence that chondrocalcinosis in a joint with OA forms a subset with more rapid progression of the joint damage, although this is not confirmed in a population based study.

Chondrocalcinosis is also associated with OA in joints that are normally not affected by OA (46,52) and this also makes chondrocalcinosis and OA a special subset. It also suggests that CPPD is a cause of OA, CPPD appearing first in joints were OA normally is not present and afterwards causing OA to occur.

Because CPPD is now regarded a distinct crystal deposition disease and a separate clinical entity (46), it is presented in this review under the heading of subsets of OA, although it could also have been discussed under the risk factors or

prognostic factors.

The loop hypothesis is an interesting one but *longitudinal* studies should be performed to substantiate this hypothesis. In such a study subjects with and without CPDD can be followed over time and the incidence OA in these two groups compared. In order to study whether CPDD influences the course of OA, subjects with similar degrees of OA with and without CPPD should be selected and the difference in outcome assessed.

3.3 RISK FACTORS

3.3.1 **Introduction**

The study of risk factors of knee OA is undertaken to clarify the etiology of disease. The conclusion as to whether a risk factor is causally related to knee OA should, however, be drawn with great care. In this paragraph risk factors of OA will be discussed with a special emphasis on knee OA. Conclusions and recommendations for future research are given.

3.3.2 **Genetics**

In two articles a good review of the literature on genetic factors in OA has been presented (54,55). In this section a few principal findings of interest will be mentioned in short and several approaches of studying the influence of a genetic predisposition on the occurrence of OA will be discussed.

3.3.2.1 **Inborn errors of metabolism**

The first possibility is the study of diseases which are known to be genetically determined. For example, disorders with a specific inborn error of metabolism like alkaptonuria (ochronosis) can lead to the early occurrence of OA. The study of such disorders has the advantage that one specific genetic abnormality can be studied in relation to the occurrence of OA (54). This may give insight in the several pathways by which OA can be caused since OA is considered to be a final common phenomenon resulting from several pathogenetic mechanisms. More examples of specific genetic diseases leading to OA are mentioned in two review articles (54,55).

3.3.2.2 **Family studies**

The second possibility is to investigate whether OA is more often present in the relatives of subjects who have OA. In considering such a study one must realize that it is still possible that certain environmental factors may cluster in families. When these factors are related to OA, it may erroneously be concluded that genetic influences are at work.

Such a family study has been conducted by Kellgren in the fifties (29). He hypothesized that if a genetic influence was of importance, it would especially come to expression at an early age in persons with generalized OA. He therefore selected subjects with generalized OA between 45 and 65 years of age. These subjects had to have ROA in at least 6 groups of joints, a group of joints being all the joints with the same name. Kellgren compared the prevalence of ROA in the first-degree relatives of these probands with the prevalence in a random sample from the general population. It turned out that ROA in at least one group of joints was not more common in the relatives. However, when polyarticular ROA (5 or more groups of joints involved) was studied, the frequency in the relatives was about twice as high both for women and men. He concluded: "It is clear that it is the multiple joint involvement which is familial and not the osteo-arthrosis as such.". The presence of Heberden's nodes was higher than expected among the female relatives when the proband had Heberden's nodes. Also, the frequency of moderate or severe ROA in at least 3 groups of joints was higher when Heberden's nodes were present in the proband. In another study it was shown that generalized ROA was *less* frequent among the relatives of probands aged 55 or over who had *no* ROA in their hands, feet, knees, spine or hips (56). Heberden's nodes were just as common in the relatives of probands without OA as in the general population. It remains to be seen whether familial clustering of OA is the reflection of a similarity in body mass index between family members since obesity is to a certain extent genetically determined (57,58) and obesity is related to OA in several joint groups (25,36,37).

3.3.2.3 Twin studies

A third approach to the study of a genetic influence on OA are twin studies. In one study monozygotic twins had a concordance for generalized ROA (ROA in 3 or more groups of joints) of 43% compared to 28% in dizygous twins (59). This difference between mono- and dizygous twins was greater when 5 or more groups of joint were involved. In the latter case the concordance was 57% in monozygous and 19% in dizygous female twins. With age correction this last figure was 33%. None of the monozygous co-twins of probands without osteoartrhitis had generalized OA against 14% in the dizygous twins. When the proband had Heberden's nodes the other twin had a chance of 60% of having Heberden's nodes when they where monozygous and 39% when dizygous. For the probands without Heberden's nodes these figures where 13% and 18% respectively. Because few details were presented in this publication the results are difficult to interpret but suggest that there is a genetic influence om some aspects of OA.

3.3.2.4 Race

Among black women the prevalence of ROA of the knee is higher compared to white women, even after adjusting for obesity, income and educational level (60). In the same study there was no increased prevalence of knee ROA among black men. Racial differences possibly reflect another genetic make-up.

3.3.2.5 Linkage analysis

A modern approach to the study of the familial occurrence of OA is chromosome linkage analysis. This approach may reveal whether OA is related to certain chromosomal markers within families. Recently, Patoli et al showed a linkage between type II collagen gene on chromosome 12 and primary OA (61). They defined OA as bilateral OA in weight-bearing joints (knee and hip). The presence of OA was confirmed radiolographically. In the family studied the condition of OA was inherited as an autosomal dominant trait. The mean age of onset was 38 years. In responding to this study Dieppe argued that these families were not representative of most subjects with OA (62). He concluded that the results suggested that "... an inherited abnormality in the collagen framework of articular cartilage can predispose to premature joint failure and that the outcome is indistinguishable from OA.".

In addition to this family study, a case-referent study was performed to study the frequency of certain collagen type II haplotypes (63). The cases consisted of 86 females, aged 60 or less, with early onset OA in more than one joint. Controls came from a hospital or from the community. One collagen type II haplotype was shown to cluster in the patients with OA (odds ratio = 2.3). These results only suggest but do not prove that alterations in collagen type II predispose to OA.

Recently, another linkage study was published which showed a linkage between one allele of the gene for type II procollagen and OA (64). Later it was found that this was due to a single base mutation in the gene for type II procollagen (65).

3.3.2.6 Conclusion

It seems that genetic influences are of some importance in OA. OA, especially generalized OA and Heberden's nodes, show a tendency to familial clustering. Twin studies suggest a slightly higher concordance among monozygous twins. Racial differences in OA prevalence for women may be due to genetic differences. Chromosomal differences in the gene for type II collagen with OA might be present

in some patients. Since obesity is partly genetically determined and related to OA, this could explain the familial clustering of OA and the difference in concordance between mono- and dizygous twins.

3.3.3 Prevalence by gender, age and country

It is well known from paleopathological studies that OA has occurred as long as several thousands of years ago (66,67). Epidemiologic research of the past few decades in several countries has shown that radiological OA of the knee is consistently present among the elderly with higher prevalences in females as compared to men.

The higher prevalence of knee OA in women compared to men is partly due to a difference in the number of obese subjects between men and women (68).

Differences in prevalence are present between countries and studies, but all studies show an increase with age (figures 3.1 and 3.2) (11,69,70,71,72,73,74,75,76). Even in the very old, up to the age of 90 years, the prevalence increases, at least in females (73). However, in one study the prevalence was lower at a higher age (71) and in the EPOZ-study the prevalence decreased at a very high age in men but not in women (72). This last finding might be due to a lower response rate among men with OA in the highest age group. It seems that hardly any one can escape from getting OA of the knee or some other joint, although it may take quite a few years in some persons. Clearly, OA is age related but the question still remains why some people get OA at an earlier age than others.

The reported differences between countries might be attributed to differences in classification criteria and to interobserver variability in diagnosing OA. However, in the studies presented in figures 3.1 and 3.2 the diagnosis was based on radiological criteria, most often those described by Kellgren (5). To reduce the interobserver differences Lawrence reread the radiographs from *three* countries. There were still some small differences (77). Moreover, racial differences could explain the difference in prevalence between certain countries for women (60).

In conclusion, gender and age are risk factors of knee ROA. The difference in prevalence between men and women is partly due to obesity. The difference between countries is at least partly due to interobserver variability. Possibly part of the difference in prevalence between countries for women is also due to a racial difference.

3.3.4 Obesity

Obesity is an important risk factor of knee OA and has been studied by several investigators (23,25,36,60,68,78,79,80). The risk of knee OA is about 2 to 5 times higher among the obese subjects. The exact value depends on the degree of obesity compared to the reference group, the gender, the severity of radiological OA and the presence of OA in one or in both knees. Body fat distribution, measured as triceps skinfold or subscapular skinfold, is not an independent risk factor for knee OA after adjusting for body mass index, age and race except in men for unilateral knee ROA (81).

The interpretation of the results from the cross-sectional studies, on the association between body mass index and knee OA, is hampered by a major

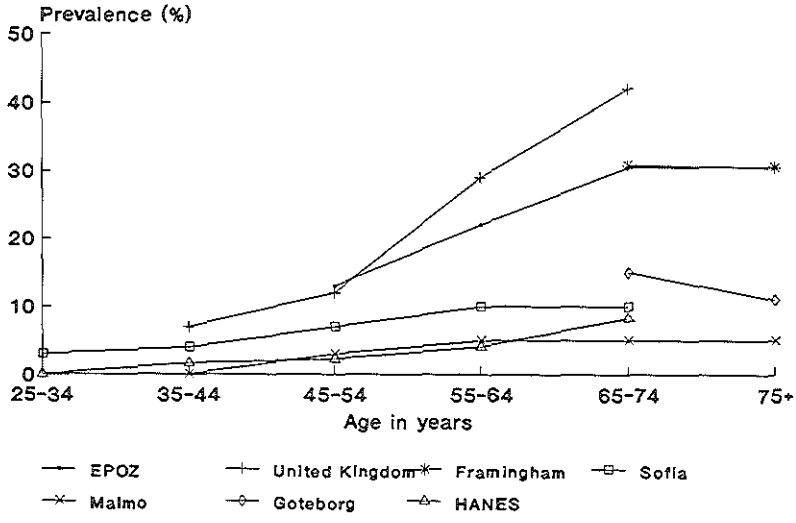

Figure 3.1. Prevalence of osteoarthritis of the knee in men by age in several studies.

problem. An etiological relation requires that the risk factor precedes disease occurrence. In the case of knee OA it may be that obesity is not a risk factor preceding OA but the result of knee OA. The latter hypothesis assumes that patients tend to be less active due to the pain and disability of OA and as a result gain weight.

Several approaches have been used to overcome this problem. One approach has been to use a longitudinal study design, such as in the Framingham Osteoarthritis Study. In this study body weight and height were measured 36 years before the presence of knee OA was assessed (23). The results from this study confirmed the findings of a relationship between obesity and knee OA from the cross-sectional studies for men as well as for women.

Another design has been to study the subjects without kneepain separately

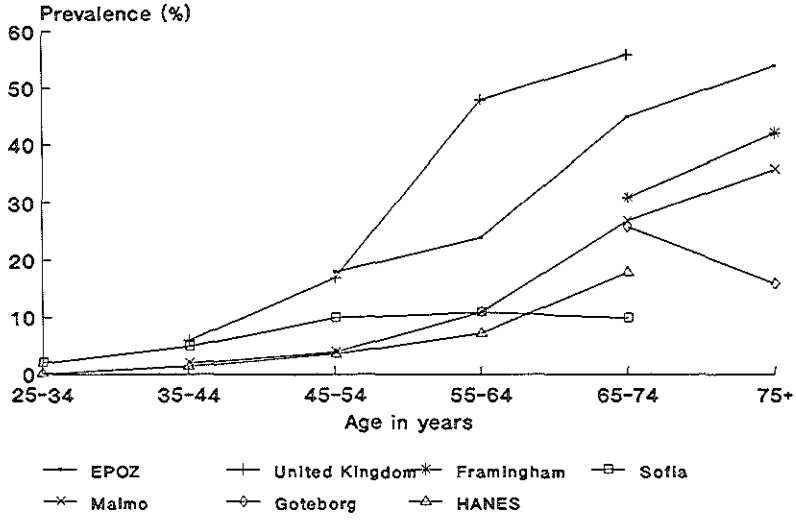

Figure 3.2. Prevalence of osteoarthritis of the knee in women by age in several studies.

from those with kneepain. In the former group the obesity can not occur as a result of painful knees. Since a relation was found between OA and obesity in the subjects without kneepain, the evidence is in favour of an effect of obesity on the occurrence of knee OA (60,68).

The third possibility has been to get an estimate of the body weight years before the cross-sectional study was undertaken, and preferably before onset of symptoms, instead of measuring the bodyweight at the time of the study. This also confirmed the relation of obesity with knee OA (60). In conclusion, there seems to be little doubt that obesity is a risk factor for knee OA.

How can this association be explained? Two hypothesis have been brought forward to explain the effect of obesity on the occurrence of knee OA. One possibility is an increase in wear and tear of the cartilage due to the high mechanical stress placed upon the knee by the heavy body weight. Thus, cartilage failure and ultimately OA will occur earlier in life when the functional demands of the joint and cartilage are high.

Another possible explanation might be a metabolic effect. This hypothesis stems from the finding that obesity is not only related to knee OA but also related to OA of non-weight bearing joints like the DIP-joints of the hand (25,36,37). This association is hard to explain by an increase in wear and tear since these joints do not bear any weight. The metabolic hypothesis is supported to some extent by the lack of convincing evidence that ROA of another weight bearing joint, the hip joint, is related to obesity (2,36,82). But this finding also pleads against a mechanical effect.

Possibly the obesity itself is not the cause of knee OA but merely related to another factor that causes knee OA. Uric acid, serum cholesterol and blood pressure are all related to obesity and have been studied to explain the association between obesity and knee OA but none of these could explain the relationship between OA and obesity (80). More interesting is the possiblity of an influence of Insulin-like growth factor-1 (IGF-1) on cartilage synthesis by the chondrocytes (83,84,85). It has been shown that the concentration of IGF-1 is inversely related to the level of obesity (86) and also to be lower among patients with OA (87).

More research is needed to explain the relationship between obesity and OA. Especially the effect of IGF-1 and the inverse relationship between OA and osteoporosis should be studied because there is also a low prevalence of osteoporosis among obese women. This inverse relationship is discussed in paragraph 3.6. Although patients with knee OA are advised to reduce weight, we do not know whether this influences the course of the disease nor do we know whether

body weight reduction prevents knee OA from occurring. Future research should also focus on this. Prevention of obesity is, at this moment, possibly one of the few ways to prevent knee OA.

3.3.5 Mechanical factors

3.3.5.1 Introduction

Impact loading has a detrimental effect on cartilage in animal studies of OA, and leads to degenerative changes (88). On the other hand, repetitive impulse loading stimulates chondrocytes to increase the production of proteoglycans (89,90,91,92). Impact loading may lead to degenerative changes but on the other hand may stimulate the synthetic activity of chondrocytes. In humans *reduced* joint use may give less OA. This is supported by the observation that joints in limbs affected by poliomyelitis have less often OA (93). However, splinting of a joint in animals leads to cartilage changes which resemble cartilage changes in OA (94). The effect of impact loading seems to be complex. Probably, a wide range of joint use stays within normal physiological range and only extremes to one side or the other lead to OA, or degenerative changes of cartilage.

3.3.5.2 Sport

Impact loading on the knee joint cartilage is increased in running. It is therefore of interest to study the effect of running on the occurrence of OA in humans.

In a retrospective follow-up study, with a mean follow-up of 25 years, former university cross-country runners were compared with former university swimmers for differences in pain in the hip or knee and for surgical procedures for OA (95). Neither pain nor surgical procedures were more often present in the former runners. In another study, radiographs of the knees of female long distance runners aged 50 or above showed more sclerosis and spur formation compared to female controls matched for age, occupation and years of schooling (96). In the same study, there were no differences in radiological signs of OA in male runners but the number was small and some of the controls were also runners or had been runners at some level.

Joint space was slightly wider in runners. This could suggest a stimulatory influence on chondrocytes but this finding was not statistically significant. There were no differences in clinical signs of knee OA like crepitation and instability. The

investigators also did an additional data analysis because former runners might have stopped running because of symptoms related to OA. If this phenomenon does occur, no difference can be found when former runners are included in the control group. In this additional analysis all the runners, including former runners from the control group were included in the "runners" group and were compared with the controls who had never run. No differences were observed in radiological signs of OA. However, the number of subjects was small. In yet another study, by Panush et al, seventeen male runners, who ran a minimum of 32 kilometres weekly for at least the past five consecutive years, had no more radiological OA (6%) than 18 sedentary non-runners (17%). Although the runners had a lower age (mean 56 years) than the non-runners (mean 61 years), this age difference was not statistically significant (97).

The last two studies were criticized because of the possibility of a "healthy runner effect"; people who take up running may be less susceptible to the development of OA (98,99). It is also possible that runners who have symptoms due to OA stop running, making a cross-sectional study less valuable (98,99). However, the first study was a retrospective follow-up study and did not show an effect of running on the occurrence of joint pain or surgical procedures for OA. The second study included former runners in the group of "runners" which was compared with the non-runners group who had never run. Again no difference was found.

Burry, in his comment on the relation between sport and OA, concluded: "Distance running, even over long periods of time, is not associated with any excess incidence of OA." (100). In women, however, more spur formation and sclerosis of the knee joint was observed, as discussed above.

In planning future research, one should consider that these studies were mostly cross-sectional and that the number of subjects was small. A large, prospective, follow-up study applying good classification criteria for OA is required to give a more definite answer. A large study has more statistical power to exclude an association with more certainty, the amount of joint use can be measured better and follow-up can be more complete. Also, the registration of traumatic events, joint complaints and reasons for stopping running, as well as the measurement of possible confounders like body weight and changes in these confounders can be done more trustworthy. However, this will not exclude the possible "healthy runner" effect.

A prospective follow-up study is now being conducted (101). The preliminary results show no major effect of running upon radiographic signs of knee OA after two years of follow-up, except for a possible small effect on spur formation in females.

Running is not the only activity that could be a risk factor but other sports, like soccer and american football, could also predispose to the development of knee OA. OA was studied among 81 former soccer players (102). Forty-one percent of the knees without and 100% of the knees with meniscectomy showed radiological signs of OA. Moreover, 32% of the knees of those aged 40-49 years showed signs of ROA. This seems to be higher than expected in a normal population (see figure 3.1). Subjects with knee trauma not due to soccer as well as those with anterior cruciate ligament insufficiency had been excluded. Klünder et al compared 57 former soccer players with 57 men admitted to the local hospital for complaints other than neurological and not for problems in the lower extremities who had never been active soccer players (103). Matching was done for bodyweight and age. Osteophytes alone were not regarded as a sign of OA. Eight previous soccer players and seven controls had signs of ROA in the knee joint. In another study twenty-three former american-football players were studied after a follow-up of 20 years and compared with 11 controls with about the same age (104). The football players who had had an injury of the knee had a higher prevalence of ROA (66%) compared to the controls (10%). The uninjured football players (n=14) had a prevalence of 36% but not statistically different from the controls.

It is possible that the contact sports, like soccer and american-football, lead to an increased risk of OA due to the traumatic events occurring during the participation in these sports.

Studies in parachutists (105) and physical education teachers (106) revealed no increased prevalence of OA of the knee. However, in the first study no controls were examined and the latter study the radiographs from the controlgroup had been read by another observer.

We still do not know with certainty the types of sport with the highest risk of causing OA of the knee. When further research on sports and OA is considered a larger number of subjects should be included. A prospective study is recommended in order to record all the minor and major traumatic events, including meniscectomy, and to measure confounding factors like body weight properly since these may explain the association or lack of an association between OA and sports. In future research the types of sport with a high risk of trauma's should be studied. Insight into the possible risk factors for these trauma's like training activities, field condition, sporting rules and sports material can give an opportunity to prevent OA in the long run. Treatment and rehabilitation programs for sportspeople who have sustained an injury should also be evaluated. Sport and OA is discussed in more detail in another review (107).

3.3.5.3 **Occupation**

High levels of mechanical forces acting on a joint or jointcartilage can be recognized in several specific occupations. These forces may exist for many years and sometimes almost a life time. This may result in an early wear of the joints and ultimately result in symptomatic OA. A study of the association of mechanical forces and OA can therefore be conducted by studying the association between some occupations and OA. In this section a few studies on knee OA and occupation will be discussed.

Kellgren reported in 1952 upon a study of ROA among miners. In this study ROA of the kneejoint was more common in miners compared to manual workers and office workers (108). In another study by Schlomka et al from 1955, the prevalence of OA of the knee joint in manual labors was found to be 32% compared to 13% among porters and clerks (109). Lindberg et al showed that heavy labour for more than 30 years in a shipyard was related to ROA of the knees (110). In their study an equal proportion of the people working in a shipyard had had a knee radiograph taken in a hospital compared to white collar workers and teachers. Although ROA was more often present on the radiographs of the men working on the shipyard, the results may have been invalidated by a selection bias; workers from the shipyard may have attended a hospital only when pain was severe enough to impair working activities. This might especially be the case when heavy work causes more severe pain to occur in paople with pre-existing OA. According to Anderson, miners have a higher prevalence of clinical OA in several joints compared to general labourers in a dockyard (111). In one study in the general population no relation between occupation and knee OA in elderly was reported (71).

Anderson hypothesized that the higher prevalence of knee OA among miners was due to postural requirements of the coalface (111). The results from the HANES-study and the Framingham Osteoarthritis Study support this hypothesis. Knee-bending requirement as well as strength demand for the job were related to ROA (60,112). Also, occupations requiring kneeling, like carpet layers, tile setters or floor layers have a higher rate of worker's compensation claims for knee morbidity (not necessarily OA) than occupations requiring no or less kneeling (113,114). However, this may not be so much due to the fact that this type of work causes musculoskeletal diseases but more that the pain as a result of a joint disease can not be combined with this type of work.

In conclusion, for some heavy labour jobs there seems to be an increased risk

of knee OA. Postural requirements may be related to this. Stress on the knee joint for years or traumatic events may explain the association between occupation and OA. Any new research on OA and occupation should be directed to the assessment of the risk in other jobs e.g. construction workers to identify the occupations with the greatest risk. Hardly anything is known about the factors related to these occupations that are possibly important risk factors for knee OA. Postural requirements are a possibility. Little is also known about the consequences of continuing certain types of work after an injury of the knee has taken place. More research on OA and occupations can certainly be done.

3.3.5.4 **Trauma**

Injuries to a joint are regarded as strong risk factors for the occurrence of OA (115). Injuries to the kneejoint are common and they are often due to sporting activities as was shown in a Dutch population survey where questions were asked about injuries to the kneejoint (116). In this survey the injuries were divided in three categories: traffic, sport, and home and leisure injuries. It was estimated that about 2000 knee injuries require admission to a hospital and about 50,000 require outpatient treatment per year in the Netherlands (116,117). Half of the admissions and half of the outpatient treatments for this condition were related to home and leisure activities (sporting activities excluded). The other half was related to sporting activities and traffic accidents.

Two population based studies have investigated injuries in relation to OA. Kellgren in 1957 reported that in men aged 55-64 years 41% of those with knee ROA grade 2 or more had either a history of previous trauma or had radiological evidence of an injury (25). For knee ROA grade 3 or more this was 68%. For women the percentages were 22 and 27 respectively. However, the prevalence of previous injury in the group without ROA was not reported. In the other population based study, the HANES study, questions were asked about knee injuries to all those who had reported kneepain (79). Subjects were 45 to 74 years of age. A strong association between knee injury and knee ROA was reported after analysing the data of the whole study-population. The association was stronger for ipsilateral than for bilateral ROA. However, there is a problem in interpreting these results because the questions about knee injury were only asked to those with kneepain. This may result in a bias because kneepain is associated with ROA. Nevertheless, the association between injury and ROA was quite strong while the association between ROA and pain was of a moderate degree. But even so, it would have been more informative when an analysis was performed limited to the group with

kneepain.

It is also of interest to know more about the type and severity of the injury in relation to OA. Several types of injury have been studied in relation to their effect on the occurrence of OA. For example, meniscectomy can be regarded as a traumatic event to the kneejoint and it is one of the most frequently performed orthopaedic operations. This operation is even done in animals to induce degenerative changes in order to study OA (118).

In humans the late results after meniscectomy, especially OA, have been studied by several researchers. Jackson reported on 577 cases comparing the incidence of ROA in the operated knee with the contralateral knee after a follow-up of at least 5 years (119). Those who had sustained an injury in the unoperated knee were excluded. In the operated knee 21% had developed ROA compared to 5% in the contralateral knee. These results are confirmed by the study of Allen et al who studied patients with meniscectomy in one knee from a total of 428 patients who had been operated between 1958 and 1970 (120). The follow-up took place after a mean of 17 years and 180 patients were still alive and could be traced. At follow-up 18.3% had ROA in the operated knee compared to 5.3% in the unoperated knee. Confirmation of the detrimental effect of meniscectomy comes further from another study (28). In this study a higher incidence of OA in the operated knee (92%) was found compared to the contralateral knee (52%) after a follow-up of at least 19 years. Definite narrowing of the joint space was present in 53% of the operated knees and 13% of the unoperated knees. Another study has again shown that patients with meniscectomy have an increased risk of developing OA (121).

In explaining these results one must consider the possibility that trauma preceding the operation is the actual cause of OA. However, removal of a meniscus in normal joints in animals leads to OA. Therefore, the results from animal studies confirm the findings from studies in humans.

Not only meniscectomy but also injuries to the ligaments of the knee joints like the anterior cruciate ligament (122,123) and collateral ligaments (124,125) lead to OA. These results are confirmed by animal studies in which rupture of the anterior cruciate ligament is done to study OA (126).

Since (severe) injuries are an established risk factor for OA, future research should be directed to the investigation of the effectiveness of prevention of trauma. People participating in sports seem to be especially at risk. Furthermore, research should be directed to investigate the effect of the type of treatment and rehabilitation on the outcome. It would also be of interest to know more about the

type and severity of the trauma that lead to OA of the knee.

3.3.6 Osteoporosis

Radin brought forward that the first change which leads to the degeneration of cartilage is an increase in bone-density of the underlying bone of the joint (88). The hypothesis is that changes in bone-density alter the forces that are placed upon the cartilage because the forces are less well transmitted to the underlying bone. This makes it of interest to study the relationship of OA and a condition with a lowered bone density like osteoporosis.

One of the early studies on the inverse relationship between OA and osteoporosis was published in 1972 (127). In this study, Foss et al reported the prevalence of OA in 140 patients with an upper femoral fracture. The patients were between 50 and 102 years old (mean 81 years). The diagnosis of OA was based on radiographs and 64 femoral heads were examined pathologically. Only three patients were regarded as having OA of which two also had Paget's disease. They also examined 100 patients with total hip replacement for OA. These patients were between 50 and 83 years (mean 63 years). In both groups an antero-posterior radiograph of the right hand was taken for measurement of the bone density of the second metacarpal. Patients with OA of the hip had higher bone densities compared to those with upper femoral fracture, even when taking age differences into account. They also had higher bone densities compared to the measurements from a normal population of 964 persons. In another study it appeared that women with primary OA of the hip had higher levels of bone mass than expected for this age group (128,129). Bone mineral content was measured by means of single photon-absorptiometry of the radius. Women with vertebral collapse or femoral neck fracture also had a lower grading for ROA of the distal interphalangeal joints (128). On the other hand, in women with nodal primary generalized osteoarthritis the total body calcium or cortical area measurement, as measures of bone mass, do not seem to be higher compared to healthy women (130). Recently it was shown in a follow-up study that women who develop OA of the hand joints have higher baseline bone mass and a greater likelihood of bone loss over time, even after adjusting for baseline body mass index and age (131).

There are other differences between women with osteoporosis and women with OA besides differences in bone mass. Women with OA have more body fat, a higher body weight, a greater muscle girth and higher muscle strength (132). These differences may explain the difference in bone mass between the two disease entities

since obesity is related to OA and inversely related to osteoporosis. This hypothesis is confirmed to some extent by the study of Price et al who showed that differences in trabecular bone density of the radius between women with generalized OA and normal controls disappeared when height and weight were taken into account (133). On the other hand, in a follow-up study adjusting for age and body mass index gave similar results, and the relation between bone mass and the occurrence of OA of the handjoints still existed (131).

Although evidence for an inverse relationship between OA and osteoporosis was presented, its explanation is complicated. Differences in the amount of obesity could eventually explain this, although results until now are equivocal. Surprisingly, the woman who developed OA also had more bone loss. Further research is certainly indicated to explain the inverse relation.

3.3.7 Smoking

Smoking was found to be a possible protective factor for OA of the knee. People who smoked had a lower risk of developing OA of the knee compared to non-smokers in a retrospective follow-up study (134). This was also apparent after adjusting for age, gender, weight, weight^2, weight change, knee injury, sports and physical activity level. The adjusted odds ratio was 0.76 per 20 cigarettes with a 95% confidence limit of 0.60-0.97. In another, cross-sectional, study this inverse association was present for men and women after adjusting for age (60). The age adjusted odds ratio for men was 0.79 (0.62-0.98) per 20 cigarettes and after adjusting for more variables, like obesity, the odds ratio still was 0.79 (0.61-1.02). For women these values were 0.74 (0.55-0.98) and 0.85 (0.62-1.59) respectively. More research is needed to determine whether the inverse relationship between smoking and OA is consistent.

3.3.8 Menopause, hysterectomy and oral contraceptives

An effect of hormonal influences or the menopause on OA occurrence has been hypothesized and some evidence for this was found (32,135). Spector et al reported a higher frequency of hysterectomy prior to the onset of OA (not necessarily in the knee) compared to controls of which one group of controls originated from the general population. However, an association between early menopause and knee OA

could not be shown in the HANES study (60). Possibly joint hypermobility could explain the findings of Spector et al. Joint hypermobility may be related to OA (30,31). Joint hypermobility is also related to prolapse of the uterus and this may have been an indication for surgical removal of the uterus (136). An additional analysis of the data of Spector et al may reveal whether this hypothesis is correct. It must be said, however, that the main reasons for the operation were dysfunctional bleedings and fibroma's. In another study knee joint tenderness or pain on movement of the knee was more often present among women with previous hysterectomy (137). In this abstract no results were discussed after adjusting for possible confounders.

In the Framingham OA Study no association was found between hysterectomy and knee OA (138). In the same study no effect of postmenopausal estrogen use was found (adjusted odds ratio and 95% confidence interval 0.71 (0.42-1.20)). A small positive effect of oral contraceptive use on OA (not specifically knee OA) has been described but this needs to be confirmed (139).

3.3.9 Other risk factors

Bloodpressure was related to OA of the knee according to a study of Lawrence, even after taking into account differences in age and body mass (140). These findings were not confirmed by another population based study (NHANES I) (80). In this study no statistically significant association resulted after adjusting for obesity.

Uric acid could also be a possible risk factor of OA in general (141,27). Other studies did not confirm this relationship (23,60). Joint hypermobility has also been related to the presence of OA (30,31).

3.4 PROGNOSTIC FACTORS

Papers on the natural course of knee OA are scarce. One of the few published and the most often cited article on this subject was written by Hernborg et al (142).

This paper presents the results of a study on 2195 subjects who were classified as having OA by a radiologist between 1950 and 1958. Radiographs were taken with the patients in supine position. This precludes reliable assessment of joint space narrowing. Patients with sclerosis of the femoro-tibial joint but without history of trauma, infection, rheumatoid arthritis or congenital deformity were selected for follow-up. Osteophytes were not used to select subjects with ROA. A total of 244 patients were selected and 71 could be re-examined in 1968. These subjects were 63 $\pm$ 8 years at baseline. In most cases there was a marked radiological deterioration, more frequently so in women. At baseline 71% of the knees showed no attrition of the underlying bone and 29% showed attrition of less than 5 mm. At follow-up 15% showed no attrition, 49% showed less than 5 mm and 36% more than 5 mm attrition.

Probably from the same group of 2195 subjects, who had been diagnosed as having radiological OA of the knee between 1950 and 1954 (?) another group was reexamined in 1968 (143). This group consisted of the subjects with osteophytes of the femoro-tibial joint. There were no structural changes in the femoro-tibial joint. It was not stated what was meant by "structural changes", but probably included sclerosis of the underlying bone and attrition of the bone surface. Those with the largest osteophytes were selected for follow-up and comprised 64 subjects (87 knees). At follow-up 61% of the knees showed no structural changes but the osteophytes had increased in size, the other 39% did show structural changes. The increase in size in osteophytes was slightly more in the group with structural changes.

Another small follow-up study of 35 patients with OA of the knee but without surgical interventions was done to study, among others, the changes over time of the radiological abnormalities (144). Follow-up was done after a mean of 6.9 years. Radiographs at baseline were not taken in weight-bearing position. At follow-up examination, the radiographs were taken in weight-bearing position. About 50% of the knees with varus angulation (at follow-up) showed increase of joint space narrowing. About 50 to 80 percent, depending on the side of the jointmargin, showed an increase in osteophytes.

Massardo et al did an eight year follow-up of patients with knee OA who had

participated in a short clinical trial on the effect of a NSAID or intra-articular corticosteroids (145), and 62% showed an increase in radiological signs of OA.

Prognostic factors have been studied to a very limited extent. It was suggested that weight was unrelated to radiological changes (143,144). But one study suggested the opposite (146). There have been discussions about the possible beneficial or harmful effects of NSAID's on the course of OA (147,148). But the idea that NSAID's could be harmful or beneficial stems largly from findings in in-vitro and animal studies (149). Only few studies in humans have been conducted and these show a possible harmful effect of indomethacine on the joints with OA (150,151).

Another prognostic factor could be the presence of chondrocalcinosis. This has been discussed in paragraph 3.2.3.4 of this review.

More research is needed to study the course of knee OA and the factors that influence the course of this disease to find possibilities for secondary prevention. The study of the course of ROA and prognostic factors is part of this thesis and will be discussed in more detail in chapter six.

3.5 CONCLUDING REMARKS

Today, there is no consensus about classification criteria for OA of the knees, although several sets have been developed. Little is known about the value of these criteria with respect to epidemiological research in the general population.

Age, gender, obesity and trauma are the most important risk factors known at this moment, but the etiology of knee OA is unknown in most cases. Certain jobs and sports also seem to increase the risk of knee OA. There is a possible genetic influence in some cases, especially when generalized OA or Heberden's nodes are present. A genetic difference for type II collagen plays a role in the minority of patients with OA. Osteoporosis is inversely related to OA and this needs further research, as well as the inverse relation with smoking. Little is known about the prognosis of OA and more research is needed to study possible prognostic factors.

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CHAPTER 4

CLASSIFICATION CRITERIA

Chapter 4.1

MISCLASSIFICATION OF DISEASE STATUS AND ITS CONSEQUENCES FOR THE STUDY OF RHEUMATIC DISEASES

ABSTRACT

The development and validation of diagnostic and classification criteria have a long history. In the study of rheumatic diseases these criteria have an important place in correctly classifying subjects participating in clinical and epidemiological studies. If imperfect criteria are used the classification of subjects can result in non-differential misclassification. This misclassification will lead to an underestimation of the strength of the true relation between a rheumatic disease and a putative risk factor. Spurious heterogeneity of the measure of effect, e.g. relative risk or odds ratio, between subgroups or studies can also only be the result of misclassification. Moreover, the power of a study will be reduced. In this chapter the effects of non-differential misclassification are discussed. In addition, numerical examples illustrate the consequences of non-differential misclassification and considerations for the design and interpretation of clinical and epidemiological studies are discussed.

INTRODUCTION

The study of diagnostic and classification criteria for rheumatic diseases has an important place in the research of rheumatic diseases. The development of diagnostic criteria has a long history and began in 1956 with the publication of the ARA-criteria for rheumatoid arthritis (1). Criteria have now been developed for several rheumatic diseases (2,3,4,5,6,7) and almost a complete issue of Arthritis and Rheumatism has recently been devoted to the diagnostic criteria of several types of vasculitis (8). Not only diagnostic criteria, but also criteria for the classification of disease progression (9), the assessment of disease activity (10) or health status (11) have been developed for the study of rheumatic diseases. A diagrammatic presentation of the several steps involved in developing classification criteria is given in figure 4.1.1. After the selection of relevant variables, patients are examined and

Consultation of experts (Delphi procedure)
Selection of relevant variables

Development of study protocol
Description of selected variables, methods and procedures for examining patients

Examination of patients
According to study protocol

Data check, check of diagnosis
Consensus on diagnosis between several physicians gives gold standard

Data analysis to select the best variables to predict diagnosis of interest
According to the statistical procedures described by Bloch et al (12)

Reporting of classification criteria

Validating criteria and assessing test-retest and interobserver variability
eg criterion and construct validity

Use of classification criteria in medical research

Adapting the criteria
Based on its use in practice and changing medical knowledge

Figure 4.1.1. A diagrammatic presentation of procedures involved in developing classification criteria.

the best variables related to the gold standard are selected. Validation should follow the reporting of the classification criteria and interobserver variability as well as test-

retest variability should be assessed. After some time, criteria will be adapted and changed as a result of new techniques and changing medical knowledge.

Although intuitively it seems obvious to aim at developing perfect criteria for the classification of diseases and outcome of illness, the consequences of imperfect criteria for the design of clinical and epidemiological research and for the interpretation of the results are less well known. As an example, Guccione et al have shown that different definitions of knee osteoarthritis (OA) lead to alterations in the strength of the association of knee OA with disability and an underestimation of the effect of knee OA on disability may thus occur, sometimes leading to a statistically non-significant result (13). Clearly, the use of imperfect diagnostic criteria leads to misclassification of subjects with the disease as not having the disease and vice versa.

This misclassification in diagnosis has been studied from a theoretical and methodological point of view. The results of these studies have mainly been published in epidemiological and statistical journals. The theoretical approach to misclassification highlights the importance of considering its implications for both the design and interpretation of clinical and epidemiological studies concerning rheumatic diseases. It makes clear why it is important to develop criteria for the diagnosis and outcome assessment of rheumatic diseases.

The methodology of the development of these criteria, especially the statistical aspects, has been described very clearly by Bloch et al (12). They discussed the methodology of *how* to develop criteria but the theoretical and methodological background of the reasons to develop criteria have not been given special emphasis. The reasons to develop criteria have only been stated in general terms like "The aim of this project was to develop classification criteria that would promote the more uniform description of the patients when various research endeavours are reported." (14). As will be shown in this article, additional reasons can be thought of.

In this chapter the theoretical and methodological aspects of *why* to develop the criteria are discussed. The influence of disease misclassification on the measure of effect, e.g. relative risk or odds ratio in etiological research, on the heterogeneity of the measure of effect, on the occurrence of confounding and the influence on statistical power is described. In addition, considerations and recommendations for the design and conduct of a study, and the interpretation of the results are discussed.

Table 4.1.1. Follow-up study on the occurrence of a rheumatic disease among HLA type positives and negatives.

A. Diagnosis established with a set of criteria with a sensitivity of 100% and a specificity of 100%.

	Total number	Rheumatic disease present	Rheumatic disease absent	10-year cumulative incidence
HLA-pos	900	36	864	36/900
HLA-neg	2100	24	2076	24/2100

Relative risk = (36/900) / (24/2100) = 3.50

B. Diagnosis established with a set of criteria with a sensitivity of 90% and a specificity of 90%.

HLA-pos	900	119	781	119/900
HLA-neg	2100	229	1871	230/2100

Relative risk = (119/900) / (229/2100) = 1.21

EFFECTS OF NON-DIFFERENTIAL MISCLASSIFICATION

Introduction

One of the objectives of research in medicine is to elucidate the etiology of disease. In epidemiological research, where the relation between putative risk factors and a disease are studied, serves the same objective.

For example, an investigator may be interested in the relation between a HLA-type and the occurrence of a rheumatic disease. A follow-up design is chosen and subjects with and without a special HLA-type are followed for 10 years and the occurrence of the rheumatic disease is assessed at several follow-up examinations. Table 4.1.1.A presents a fictional number of subjects at baseline and a fictional number of subjects who develop the rheumatic disease. The overall 10 year

cumulative incidence, 20/1000, is in the order of what can be expected for the study of rheumatic diseases. The relative risk, which is the cumulative incidence in subjects with the HLA-type divided by the cumulative incidence in the group without, is 3.50.

If the misclassification in diagnosing the rheumatic disease is independent of the HLA-type, the misclassification is non-differential (15,16). In this chapter we limit ourselves to the discussion of non-differential misclassification.

Misclassification can be characterized by the sensitivity and specificity of the classification criteria. Sensitivity stands for the proportion of the diseased subjects who fulfil the criteria while the complement of sensitivity is the proportion of false negative subjects. Specificity is the proportion of the non-diseased subjects who do not fulfil the criteria; its complement is the proportion of false positive subjects.

Let us assume that the investigator applies a set of criteria for the rheumatic disease reaching a sensitivity of 90% and a specificity of 90% in comparison with a gold diagnostic standard. Table 4.1.1.B gives the expected number of subjects with the rheumatic disease that will than be diagnosed among the subjects with or without the HLA-type. The relative risk is reduced to 1.21 compared to the true value of 3.50.

Underestimation of the true effect

From the example described above a general rule can be inferred. If non-differential misclassification occurs, the relative risk is changed towards the value of no effect (15,16) and for the relative risk this value is 1.

This example can be extended to several values of the incidence of the rheumatic disease, sensitivity and specificity (figures 4.1.2 and 4.1.3). Similar figures have been published by Copeland et al (17). As can be seen in figure 4.1.2, both the reduction of sensitivity and specificity, leading to more false negatives and false positives respectively, go with an increasing reduction of the relative risk. Moreover, the reduction is considerable for values of the sensitivity and specificity that show small departures from the perfect value of 100% as will be the case for the classification criteria of rheumatic diseases, where the sensitivity and specificity are usually about 90%.

The reduction also depends on the incidence of the rheumatic disease. The same sensitivity and specificity applied in a situation of a low incidence, comparable to that of most rheumatic diseases, will underestimate the true relative risk to an even larger extend. Figure 4.1.3 shows this for several values of the incidence and

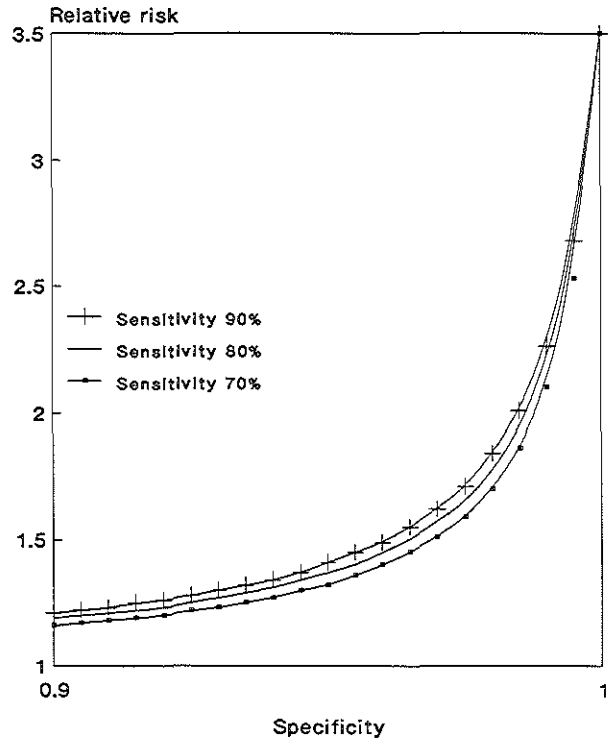

Figure 4.1.2. Relative risk by specificity and sensitivity in a follow-up study with an overall 10-year cumulative incidence of 20/1000.

specificity and a sensitivity of 90%. One could question whether an equal reduction of either the sensitivity or specificity would underestimate the true relative risk to the same extent. This is not the case as it depends on the incidence of the disease. When the incidence is low, the effect of a specificity of 90% on the underestimation of the true relative risk is more pronounced than of a sensitivity of 90%.

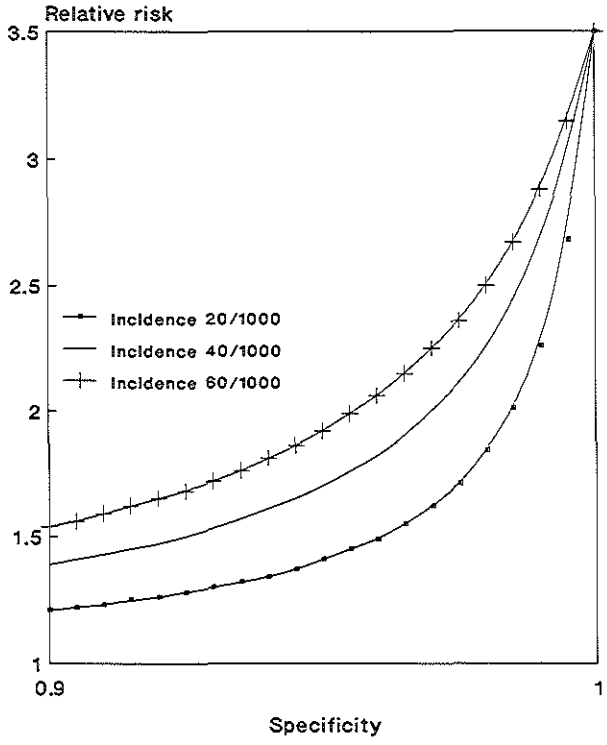

Figure 4.1.3. Relative risk by specificity in a follow-up study with several 10-year cumulative incidences and a sensitivity of the classification criteria of 90%.

Power and number of subjects

The power of a study is the chance of finding a statistically significant result if a true effect exists. The power is reduced when imperfect criteria for the diagnosis are used (18,19). This implies in practice that the number of subjects needed to detect a relation between a putative risk factor and a disease has to be increased. The costs of a study may therefore increase.

It can be calculated that for a follow-up study the power is reduced due to misclassification. From table 4.1.2, applying the same figures as shown in table 4.1.1,

Table 4.1.2. Relative risk, standard deviation, 95% confidence interval and study power for a follow-up study on the relation between HLA and a rheumatic disease. Results for several values of sensitivity and specificity of diagnostic criteria for the rheumatic disease.

Sensitivity	100%	90%	100%	90%
Specificity	100%	100%	90%	90%
Total HLA positive	900	900	900	900
HLA-positive cases	36	32	122	119
Total HLA negative	2100	2100	2100	2100
HLA-negative cases	24	22	232	229
True relative risk	3.50	3.50	3.50	3.50
Observed relative risk	3.50	3.50	1.23	1.21
Standard deviation +	0.260	0.275	0.104	0.106
95% confidence interval ∓	2.10-5.83	2.04-6.00	1.00-1.51	0.98-1.49
Power (%) *	99.8	99.6	46.8	39.4

* Power calculated with a personally written software program based on the formula in reference 20.
+ Of the log odds ratio
∓ Of the odds ratio

it can be seen that imperfect sensitivity and perfect specificity increase the standard deviation and thereby reduces the precision leading to a wider confidence interval. In this situation the power is reduced. Perfect sensitivity and imperfect specificity give a reduction of the standard deviation and thereby an increase in precision leading to a narrower confidence interval. However, the power is again markedly reduced. The combination of imperfect sensitivity and specificity yields an even lower power. The effect on the range of the confidence interval is less predictable because the imperfect specificity tends to decrease the range of the confidence interval and the imperfect sensitivity tends to increase the range of the confidence interval.

Spurious heterogeneity

A study could be envisaged to investigate whether the effect of the HLA status on

the occurrence of a rheumatic disease is different between young people and the elderly. This would imply the finding of different relative risks in the young and in the elderly; this is called heterogeneity of the relative risk.

Imperfect assessment of the diagnosis may introduce spurious differences between the effect estimates of the young and the elderly where, in reality, none exists (21). Table 4.1.3 gives a numerical example for a follow-up study with the same total numbers as in table 4.1.1. There is no true difference between the relative risk in the young and the elderly but when imperfect criteria with a sensitivity and specificity of 90% are used a spurious difference is introduced. The relative risk is 1.07 in the young but 1.48 in the elderly. Both are an underestimation of the true relative risk but to a different extent. From figure 4.1.3 it can be seen that this is due to the difference in incidence among the HLA-nega-

Table 4.1.3. Follow-up study on the occurrence of a rheumatic disease among HLA positives and negatives, stratified for age. Diagnostic criteria with a sensitivity of 100% and a specificity of 100%.

	Total number	Rheumatic disease present	Rheumatic disease absent	10-year cumulative incidence
Young				
HLA-pos	630	9	621	9/630
HLA-neg	1470	6	1464	6/1470

Relative risk = (9/630) / (6/1470) = 3.50.
With diagnostic criteria with a sensitivity of 90% and a specificity of 90% the relative risk is (70/630) / (152/1470) = 1.07.

Elderly				
HLA-pos	270	27	243	27/270
HLA-neg	630	18	612	18/630

Relative risk = (27/270) / (18/630) = 3.50.
With diagnostic criteria with a sensitivity of 90% and a specificity of 90% the relative risk is (49/270) / (77/630) = 1.48.

tives between the two age groups. A variant of this spurious heterogeneityoccurs when two studies with the same objective are compared. It is more common than an exception that different studies show different results; the relative risk can be higher in one study compared to the other. When identical but imperfect diagnostic criteria are applied a difference in relative risk or odds ratio will emerge even when no true difference exists when the incidence of the rheumatic disease in the reference group is different between the two studies. This phenomenon is illustrated in figure 4.1.3.

CHOICE OF CUT-OFF POINT

Occasionally a researcher can choose between various sets of criteria to diagnose a rheumatic condition. These criteria may have different combinations of sensitivity and specificity. Although the advice is to use the criteria with the highest sensitivity

Table 4.1.4. Sensitivity, specificity, relative risk (RR), risk difference (RD), likelihood ratio (LR) and the sum of sensitivity and specificity for diagnostic criteria of giant cell (temporal) arteritis when different rules for selecting N or more criteria out of 8 should be present to classify as positive. Incidences, true relative risk and risk difference are fictional.

Number of criteria $\geq$ N	Sens* (%)	Spec* (%)	RR	RD x 10^{-3}	LR+	Sens + Spec (%)
0	100.0	0.0	1.00	0.0	1	100.0
1	100.0	24.3	1.00	2.43	1.3	124.3
2	99.5	57.3	1.01	5.68	2.3	156.8
3	96.7	83.5	1.05	8.02	5.9	180.2
4	89.7	96.0	1.19	8.57	22.4	185.7
5	70.6	98.3	1.34	6.89	41.5	168.9
6	44.9	99.5	1.61	4.44	89.8	144.4
7	22.4	99.5	1.36	2.19	44.8	121.9
8	6.1	100.0	3.00	0.61	∞	106.1

Incidence in reference group is 5/1000.
True RR is 3.00 and true RD is 10/1000.
* Sensitivity and specificity are adapted from reference 12.
+ LR = sensitivity / (1 - specificity).

and specificity this is not sufficient to make a proper choice because one set of diagnostic criteria may have a high sensitivity with a low specificity and vice versa for the other.

Bloch et al have given a good example of this phenomenon for the diagnostic criteria of giant cell (temporal) arteritis (GCA) (12). Traditionally diagnostic criteria are presented in the form of a list of variables: symptoms, physical signs, radiological findings and laboratory measures. For GCA Bloch et al give a list of 8 variables and a patient would classify as having GCA if, for example, 4 or more variables are present. This cut-off point has a sensitivity of 89.7% and a specificity of 96.0% (table 4.1.4). But one could also have taken as a cut-off point that 3 or more variables have to be present to score as positive for the diagnosis of GCA. This cut-off point has a sensitivity of 96.7% and a specificity of 83.5%. More cases are identified but at the cost of including more false-positives. For every cut-off point the sensitivity and specificity can be calculated like Bloch et al have shown.

In table 4.1.4 the second and third column present the list of sensitivity and specificity as given in the article of Bloch et al. The other columns show the effect on the relative risk and risk difference in a fictional follow-up study of a risk factor and GCA. The risk difference is the difference in the risk in the group with the risk factor minus the risk in the group without the risk factor.

As can be seen, the relative risk and risk difference depend on the sensitivity and specificity. The change in specificity has a greater impact on the relative risk than the sensitivity. The maximum relative risk, closest to the true value, is reached when the likelihood ratio (sensitivity / (1 - specificity)) is maximal or when the specificity is 100%. However, the best estimate of the risk difference is reached when the sum of sensitivity and specificity is maximal (in the example at four criteria present). These results should, however, be interpreted with caution because it is assumed that *non-differential* misclassification is present.

The choice of the cut-off point will also be determined by medical reasons. For example, if a disease with a potentially fatal outcome that can be prevented is missed, one would choose to have a high sensitivity in order to diagnose all the cases and prevent the fatal outcome. If on the other hand the treatment is harmful itself one would tend to choose criteria with a high specificity.

In addition to the medical reasons and the considerations concerning the choice of the cut-off point given in the article by Bloch et al (12), the above mentioned consequences of choosing the cut-off-point based on the measures of effect, should also guide this choice.

THE EFFECT IN CASE-CONTROL STUDIES

In the above the emphasis was on follow-up studies but similar phenomena related to non-differential misclassification occur in case-control studies. The odds ratio will change towards 1 if this misclassification occurs, except when the specificity is 100%, and the power will be reduced. The theoretical aspects of misclassification due to imperfect diagnostic criteria in case-control studies have been described extensively by Brenner et al (19). It must, however, be realized here that the sensitivity and specificity of diagnostic criteria are different for (potential) cases and controls, because controls are often patients with another disease.

IMPERFECT ASSESSMENT OF A RISK FACTOR OR A CONFOUNDER

Until now the effect of imperfect diagnostic criteria on the estimated relative risk or odds ratio and power were discussed. Also of interest is the effect of misclassification of the risk factors themselves and of confounding variables. The misclassification of the risk factor status, in the example the assessment of the HLA markers, also leads to underestimation of the effect and reduced power and, therefore, more subjects are needed to detect a statistically significant result (21,22,23,24,25). Other (confounding) variables or covariates, can also be measured with imperfect sensitivity and specificity. For the theoretical aspects of misclassification of the confounders the reader is referred to other articles (18,21,25,26).

CONSIDERATIONS

It is important to realize that an imperfect diagnosis or classification can unintentionally severely affect the estimate of the relative risk or odds ratio. It highlights the importance of developing optimal criteria for the diagnosis and classification of rheumatic diseases. The development and validation of classification criteria should be undertaken as has been done already for several rheumatic diseases. The results from these studies show that the classification criteria have a sensitivity and specificity of about 90%, sometimes more. This could imply that observed relative risks from studies based on these criteria are an underestimation of the true effect, assuming that *non-differential* misclassification is present. Moreover, in studies where no statistically significant relationship was found this

might have been due to imperfect criteria. Not only because the observed relative risk is reduced but also because the power is reduced as a result of misclassification. Numerically small studies applying imperfect criteria can therefore hardly be conclusive in rejecting the existence of an assumed effect.

On the other hand, different classification criteria might result in different risk estimates as a result of another mechanism. Some classification criteria might be more relevant for the relation studied because they comprise a variable which can, on *a priori* knowledge, be expected to have a strong association with the putative risk factor or which turns out to be associated with the risk factor. A good example of this is presented in the article of Guccione et al (13). They studied the association between several criteria for knee OA and physical disability. One of these was the relation between knee OA and walking. One of their classification criteria was radiological OA grade 2 or more (Kellgren score) regardless the presence of knee pain and another was radiological OA grade 2 or more in combination with knee pain. In comparison with subjects without radiological OA and without pain, the odds ratio was 1.71 for people with radiological OA irrespective the presence of knee pain, while the odds ratio was 2.90 for the group with radiological OA combined with knee pain. Based on our prior knowledge this is to be expected as it is very likely that the pain itself has a major influence on the ability to walk.

Moreover, when another definition of physical disability was used, such as "dependence on others in housekeeping", the odds ratios were considerably reduced as compared to the odds ratios observed when walking was used as the measure of disability. This can be explained by the fact that for housekeeping not only knee OA is of influence but other factors are contributory. The relation is more circumstantial than it is for walking. Or to cite Noel Weiss: "It is particular when variation in the size of the exposure-disease association accords with knowledge of the relevant biology that the case for cause and effect is strengthened." (27).

Classification of disease can therefore not be separated completely from the risk factor studied. In some instances the use of other classification criteria does not lead to non-differential misclassification because the other criteria indeed have a specific (eg stronger) relation with the putative risk factor. For the study of a specific causal hypothesis it could then be advocated to study a subgroup of the disease of interest particularly if it can be expected that this subgroup has a stronger relation with the putative risk factor. Moreover, it should be realized that classification criteria are not constant over time but will change when our knowledge increases.

Criteria that have been developed need to be validated. Traditionally, in validation studies, the criteria are compared with a gold standard, usually the consensus of several rheumatologists about a clinical diagnosis based on extensive examinations of the patient. The traditional method of comparing criteria with a gold standard is called the study of criterion validity (28).

Criterion validity can be subdivided in concurrent validity and predictive validity. The simultaneous comparison with a gold standard is a form of concurrent validity. If, however, the comparison is made with a criterion measure that has not yet been certified this is called predictive validity. One could think of the predictive value of solitary osteophytes on radiographs for the development of full blown OA. Recently, the occurrence of hand OA was studied in a follow-up study and it was shown that doubtful osteophytes at baseline predicted the occurrence of other signs of OA at follow-up (29). Such a predictive validation study is hardly ever done but is valuable and has obvious clinical relevance. This is the more so when decisions concerning treatment are based on our perception of disease severity while little is known about the relation of the present disease status and the outcome of the disease in future (10).

Another type of validity is construct validity. Here, several criteria are compared and they are studied with regard to their influence on the magnitude of the measure of effect. The interest is in the ability of detecting relationships based on a theoretical construct, hypotheses or presumed causal mechanisms, with the disease according to these criteria. One could for example question the value of classification criteria for knee OA which bear no relation with obesity.

It would be of great interest to know how the gold standard, used in the development of classification criteria, is related to a number of putative risk factors and how this relation changes when the classification criteria, derived from the gold standard, are applied. This could give us a more balanced view of the classification criteria and contribute to our understanding of the intrinsic value of the proposed criteria.

Validated criteria are preferred when a new study is undertaken. However, the best approach may be impractical or too expensive to be used for the total study population. It can then be useful to apply the "perfect method" in a sample of this study population. This gives the opportunity to adjust for misclassification in the analysis in order to obtain better estimates. It could also be possible to use the results from other validation studies to obtain better estimates.

When sensitivity and specificity are known for several sets of criteria, one could consider to choose those criteria with the highest specificity because in a

follow-up study the specificity has a larger impact on the relative risk as compared to the sensitivity when the incidence of the disease is low. A similar reasoning can be applied to case-control studies.

On the other hand, when the sensitivity is very low, or the incidence is fairly high, the sensitivity can also have a great influence. To get the best estimate of the relative risk in a follow-up study the likelihood ratio must be as large as possible or the specificity should be 100%. For the risk difference, however, the sum of sensitivity and specificity should be as large as possible. Furthermore, it is worth considering how the power and precision alter as a result of the application of different sets of criteria.

Occasionally, misclassification can be reduced by repeated measurements. This solution, however, will be more applicable for measurements of the risk factors and confounding variables.

Once again it must be emphasised that only the effects of *non-differential* misclassification were discussed in this chapter.

CONCLUSIONS

The importance of near to perfect diagnostic criteria for the study of rheumatic diseases has been demonstrated. It stresses the very reason why criteria should be developed and validated. Spurious findings may be the result of imperfect criteria used for the diagnosis of the disease. If non-differential misclassification occurs the effect of a risk factor is underestimated. Moreover, a greater number of subjects are needed to discover an effect and the cost of study may increase as a result of loss of statistical power. Spurious heterogeneity of the relative risk between subgroups can occur or real heterogeneity may be obscured. Results from different studies can differ just because of misclassification. It is worthwhile to consider validation of the criteria as part of the main study. In designing a study as well as in interpreting the results the possibility and extent of non-differential misclassification should be kept in mind.

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Chapter 4.2

DO CLINICAL FINDINGS ASSOCIATE WITH RADIOGRAPHIC OSTEOARTHRITIS OF THE KNEE ? [1]

ABSTRACT

From a population survey of 2865 subjects, test characteristics of a number of clinical findings relating to knee osteoarthritis were calculated against the standard of radiographic diagnosis. The clinical findings included from the history were age, gender, current pain in the knee, swollen knee, pain in both hands, morning stiffness, osteoarthritis in any joint, pain or stiffness, or both, in knees or hips when rising from seated position, and pain in knees or hips while climbing stairs; from the physical examination: Quetelet's index, Heberden's nodes, bony enlargement, palpable effusion, soft tissue swelling, limitation of knee function, pain with knee flexion and bony tenderness and, finally, the latex fixation test.

Of 18 clinical variables, all but Heberden's nodes, palpable knee effusion, pain in both hands and latex fixation test showed a significant association after adjustment for age. Neither one single variable nor a combination could predict radiographic osteoarthritis of the knee with reasonable accuracy and thus be applicable in clinical practice. The X-ray film, therefore, keeps its place in the diagnosis of knee osteoarthritis in general practice as well as in epidemiological research.

INTRODUCTION

In epidemiological research, diagnosis of osteoarthritis of the knee is based traditionally on the radiographic appearance of the joint. Osteoarthritis (OA) is judged according to Kellgren's criteria, described in the Atlas of Standard Radiographs of Arthritis (1). In 1986, the Subcommittee on Classification Criteria of

[1] An article based on this chapter was published as: Claessens AAMC, Schouten JSAG, Ouweland van den FA, Valkenburg HA. Do clinical findings associate with radiographic osteoarthritis of the knee? Ann Rheum Dis 1990;49:771-774.

Osteoarthritis of the American Rheumatism Association (ARA) prepared criteria for the classification and reporting of OA of the knee. The proposed criteria were developed by a Delphi procedure (2) and subsequently tested in a group of patients with knee pain referred to a rheumatological clinic (3). Variables to construct criteria were obtained from medical history, physical examination and laboratory tests. The subcommittee presented several sets of criteria and inferred that one of these, a combination of findings merely from medical history and physical examination could be applied in epidemiological research. Substitution of the X-ray film by a small number of clinical findings might be helpful indeed in future surveys.

Apart from the problem of precision or reproducibility of the clinical diagnosis OA (4,5), little is known about the association of clinical findings with radiographic OA. To test the value of single clinical and laboratory variables for the prediction of radiographic diagnosis, we studied a population based data set covering the relevant variables from medical history, physical and laboratory examinations, and radiography. By stepwise logistic regression analysis we investigated which combination of variables was most predictive regarding the radiographic diagnosis of knee OA.

METHODS

The study data are derived from a population survey conducted in the Dutch town of Zoetermeer between 1975 and 1978. The prevalence of rheumatic diseases and other chronic conditions was investigated (6). A total of 13,614 inhabitants aged 5 years and older, dwellers of two town districts, were invited to participate. The overall response rate was 78.2%. Standard anteroposterior weight bearing knee radiographs were taken from those aged 45 and older, irrespective of complaints. The study group thus comprised 2865 subjects (1320 men (46.1%) and 1545 women (53.9%)). The results are presented for the right knee only. Clinical and radiographic findings therefore refer to the same joint. A preliminary analysis on both joints showed no significant differences between the knees. From the data set all the variables relevant to the diagnosis of knee OA were selected. The variables included all those finally present in the ARA subcommittee's study, except crepitus and palpable warmth. The former was not investigated and the latter was found in only four knees.

Variables from the history included age, gender, current pain in the knee, swollen knee joint, pain in both hands, morning stiffness of less then 30 minutes in

arms or legs, or both, previous medical treatment for OA in any joint, pain in knees or hips, or both, when rising from a seated position, stiffness in knees or hips, or both, when rising from a seated position and pain in knees or hips, or both, while climbing stairs. Subjects with no pain in any joint, including the spine, were not questioned specifically about the last 3 variables, as we assumed that they would have given negative answers there.

Variables from the physical examination included the Quetelet's index (in kg/m^2), clinical Heberden's nodes at the right or left distal interphalangeal joints, bony enlargement, palpable effusion, soft tissue swelling, limitation of knee function, pain with knee flexion during examination, and bony tenderness. Function of the knee was scored on a scale ranging from 0 to 4. Grade 1 or more was regarded as limited function (grade 1 is minimal limitation of extension or flexion at physical examination). The clinical observations were made by six doctors; interobserver variability was reduced by combined three month training sessions.

From the laboratory tests available the latex fixation test was selected. A normal test result was defined as one with a titre $< 1/20$. The cut-off is lower than that applied for clinical use (1/640) in our laboratory.

Radiographs of the knees were studied without knowledge of the clinical findings. Radiographic OA was expressed on a five point scale (1). In this study, the diagnosis radiographic OA refers to grade 2 or more on the X-ray film of the right knee (grade 2 = definite osteophytes, and possible narrowing of joint space).
Prevalence, sensitivity, specificity, predictive value of a positive finding, likelihood ratio of a positive finding and odds ratio are defined as follows. The prevalence figure indicates the percentage of persons with a positive finding at the time of the examination. Sensitivity is the percentage of persons with a positive finding among all those who have ROA; likewise, specificity is expressed by the percentage of persons with a negative finding conditional on the absence of radiographic OA. The predictive value is the proportion of subjects with radiographic OA from among all those with a positive finding. The likelihood ratio of a positive finding expresses the chance that a positive finding is expected in a person with radiographic OA, over that in one without radiographic OA (7). The odds ratio gives the ratio of the odds for a positive finding in persons with radiographic OA, over the odds for a positive finding in persons without radiographic OA. Odds ratios are also given after adjustment for age, as the prevalence of radiographic OA is strongly associated with age.

Combinations of variables may show a stronger association with radiographic OA than any single variable. To determine the best predictive combination of

variables an initial choice was made out of all available clinical findings on the basis of their relevance by significance and by reported data. Then, for the total population, as well as for those with pain in the right knee at the time of study entry, the optimal combination of clinical findings was selected by a stepwise logistic regression analysis. The combination of variables selected by this procedure included for the population: age, gender, Quetelet's index, pain in knee or hips, or both, while rising from a seated position, bony enlargement, soft tissue swelling, and limitation of function; and for the group with knee pain: age, gender, Quetelet's index, pain in knee or hips, or both, while rising from a seated position and bony enlargement. To test the value of these two most predictive combinations sensitivity and specificity were determined as follows. Each subject's individual variables were applied to the risk-function (see Addendum) to calculate the predicted risk, or predicted probability of having radiographic OA. For each decile cut off point in the two distributions of risk-function outcomes sensitivity and specificity for either the whole population or the group with knee pain were calculated. These points are presented in a so called receiver-operator-characteristic curve (ROC-curve) (7) for both the population and the group with knee pain. Also, as radiographic OA is strongly associated with age, risk-functions including only age as continuous variable were developed, again for both the whole population and the group with knee pain. The BMDP statistical software package was used (8).

RESULTS

Right knee radiographic OA was detected on the films of 564/2865 (19.7%) of the population; in 191/1320 (14.5%) men and in 373/1545 (24.1%) women. Three hundred and seventy one subjects (12.9%) in the population had pain in the right knee at the time of study: 100/1320 (7.6%) men and 271/1545 (17.5%) women. One hundred and thirty five subjects (4.7%) had both radiographic OA and current knee pain: 37/1320 (2.8%) men and 98/1545 (6.3%) women. Table 4.2.1 lists the sensitivity, specificity, predictive value of a positive finding, and the likelihood ratio of a positive finding for the population and for the group with knee pain separately. Prevalences of age over 50 years and a normal latex test were more than 70% in the population. Some variables had a prevalence of less then 5%: swelling of the right knee, previous medical treatment for OA in any joint, palpable effusion, swelling of soft tissue, pain with movement of the knee at examination, and bony tenderness. The prevalences of other variables, except gender, varied between 6 and

22% of the population. Overall, high specificities were accompanied by low sensitivities. The predictive values of positive findings varied between 22 and 65% and showed no obvious improvement in the group with knee pain. Almost all likelihood-ratios in the group with kneepain were lower than the corresponding values in the total population. The best single variables were pain during flexion, limitation of function, history of swelling, swelling of soft tissue, bony enlargement and bony tenderness.

Table 4.2.2 lists the adjusted and unadjusted odds ratios with their 95% confidence intervals. The rank order by magnitude of the odds ratio is essentially unchanged after adjustment for age. Exceptions for the total population (column A) are the variables swelling of soft tissue (up by five places), pain climbing stairs (up by three places), Heberden's nodes (down by four places), bony tenderness (down by three places); and for the group with knee pain (column B) the variables swelling of soft tissue (up by five places), history of swelling (up by four places), pain on rising from a chair (up by three places), history of OA (down by six places), female gender (down by four places), and Heberden's nodes (down by three places). Most variables when adjusted for age showed a small decrease in odds ratio. When the odds ratios were adjusted for age all were significant in the total population except the variables pain in right and left hand, palpable effusion, Heberden's nodes, and a normal latex test.

The ROC curve shows the test characteristics of the best combinations of clinical findings that were most predictive in the population against the standard of radiographic knee OA (figure 4.2.1). The best combination of clinical variables performed somewhat better in the group with knee pain: the ROC curve ascends towards the upper left corner of the plot. In a separate ROC curve, the result when age alone was applied as a continuous variable in the risk function is shown in comparison with the combination of variables for the whole population.

DISCUSSION

The answer to the question "Do clinical findings associate with radiographic osteoarthritis of the knee?" is "yes". There is a significant association between radiographic OA and 14 of the 18 clinical findings studied. Also there is consistency in the rank order of variables according to the magnitude of likelihood ratios (table 4.2.1) and odds ratios (table 4.2.2) for the population as well as the group with knee pain. The strength of the associations of the different variables with radiographic

Table 4.2.1. Prevalence of several variables, and sensitivity, specificity, predictive value, and likelihood-ratio for clinical variables against the standard of radiographic knee osteoarthritis.

		Prevalence (%)		Sensitivity (%)		Specificity (%)		Predictive value* (%)		Likelihood ratio*	
Variable		A †	B	A	B	A	B	A	B	A	B
Pain during flexion	E ‡	2	13	6	22	99	92	56	60	5.3	2.7
Function limitation	E	6	22	17	38	96	88	52	64	4.4	3.1
History of swelling	H	2	16	6	23	99	88	49	52	4.0	1.9
Swelling soft tissue	E	0,5	3	1	3	100	97	43	36	3.7	1.0
Bony enlargement	E	11	28	26	50	93	85	47	65	3.6	3.2
Bony tenderness	E	3	15	7	22	98	89	44	53	3.2	1.9
Quetelet $>30\ kg/m^2$	E	10	17	20	28	93	90	42	62	2.8	2.8
Previous OA	H	2	6	4	10	99	96	40	58	2.7	2.5
History of pain	H	13	-	24	-	90	-	36	-	2.3	-
Pain rising chair	H	18	65	29	73	85	40	33	41	2.0	1.2
Heberden's nodes	E	12	17	17	24	90	88	29	53	1.7	2.0
Stiff rising chair	H	22	68	32	72	81	34	29	38	1.7	1.1
Pain climbing stairs	H	13	54	19	46	88	42	28	31	1.6	0.8
Morning stiffness	H	13	31	17	30	88	68	26	34	1.5	0.9
Palpable effusion	E	2	6	2	5	99	93	27	30	1.5	0.8
Pain in both hands	H	7	21	9	21	94	79	26	36	1.4	1.0
Female gender	H	54	73	66	73	49	27	24	36	1.3	1.0
Age > 50 years	H	79	80	90	92	23	26	22	42	1.2	1.2
Latex test negative	L	73	72	73	72	27	28	20	37	1.0	1.0

* Of a positive finding. † A: total population, B: group with knee pain. ‡ E: Physical examination, H: History, L: Laboratory test

OA is somewhat disappointing as no single clinical finding can accurately predict radiographic OA by means of its sensitivity and specificity, likelihood-ratio, or adjusted odds ratio. Interestingly, when the odds ratios are arranged in order of magnitude after adjustment for age the variables Heberden's nodes and bony

Table 4.2.2. Unadjusted and adjusted odds ratios of several clinical variables for radiographic knee osteoarthritis in the general population.

		Odds ratio		Adjusted Odds ratio	
Variable		A †	B	A	B
Pain during flexion	E ‡	5.5	3.1	4.3 (2.5-7.4)*	2.1 (1.1-4.2)
Function limitation	E	5.1	4.3	3.1 (2.2-4.4)	2.3 (1.3-4.1)
History of swelling	H	4.2	2.1	4.0 (2.4-6.8)	2.2 (1.2-4.0)
Swelling soft tissue	E	3.1	1.0	4.2 (1.3-13.8)	1.7 (0.5-6.5)
Bony enlargement	E	4.5	5.5	2.8 (2.1-3.6)	3.2 (1.9-5.6)
Bony tenderness	E	3.4	2.2	2.5 (1.6-4.0)	1.7 (0.9-3.1)
Quetelet > 30 kg/m²	E	3.3	3.6	2.6 (1.9-3.8)	2.4 (1.3-4.4)
Previous OA	H	2.8	2.6	1.9 (1.1-3.5)	1.7 (0.7-4.5)
History of pain	H	2.8	-	2.6 (2.0-3.3)	-
Pain rising chair	H	2.4	1.8	2.2 (1.7-2.7)	2.0 (1.2-3.3)
Heberden's nodes	E	1.8	2.3	1.2 (0.9-1.6)	1.6 (0.9-3.0)
Stiff rising chair	H	2.0	1.3	1.7 (1.4-2.1)	1.2 (0.8-2.1)
Pain climbing stairs	H	1.7	0.6	1.9 (1.4-2.4)	0.8 (0.5-1.3)
Morning stiffness	H	1.6	0.9	1.5 (1.1-1.9)	1.0 (0.6-1.6)
Palpable effusion	E	1.5	0.8	1.4 (0.7-2.8)	0.7 (0.3-1.8)
Pain both hands	H	1.4	1.0	1.3 (0.9-1.9)	1.0 (0.6-1.8)
Female gender	H	1.9	1.0	1.7 (1.4-2.1)	0.7 (0.4-1.2)
Age > 50 years	H	2.7	4.0	-	-
Latex test normal	L	1.0	1.0	1.0 (0.8-1.3)	1.0 (0.6-1.6)

* 95% confidence intervals for the odds ratio adjusted for age. † A: total population, B: group with knee pain. ‡ E: Physical examination, H: History, L: Laboratory test

tenderness in the population column and Heberden's nodes, female gender, and previous OA in the knee pain column decrease in rank order. These parameters being apparently related to age lose significance after adjustment for age.

In the analysis of variables, age is used in two different ways: firstly, as in the study of the ARA subcommittee (3) by dividing subjects into those above and below 50 years and, secondly, as a continuous variable in the risk function expression. The

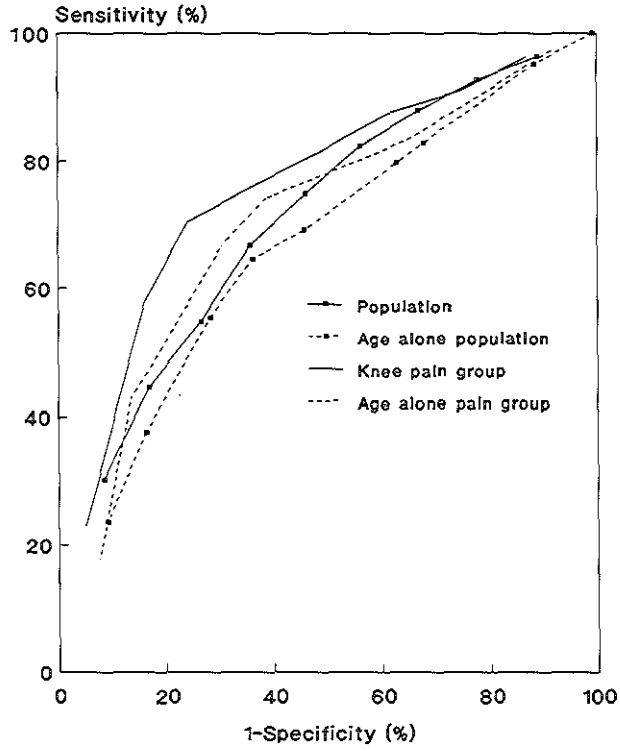

Figure 4.2.1. Receiver-operator-characteristic (ROC) curves showing the characteristics of the combinations of clinical findings that are most predictive for the population, as well as for the group with knee pain at study entry, against the standard of radiographic osteoarthritis of the right knee. The ROC-curves constructed by applying age alone in the risk function for the population as well as in the knee pain group are included in the plot. The lines connect nine points in the distribution of risk-function outcomes, for which sensitivity and specificity were calculated.

variable age over 50 years shows a high sensitivity, the highest of all, and a low specificity. This can be explained by the fact that our study is population based and includes only persons of over 45 years. Age is strongly associated with radiographic

OA and, therefore, age alone was applied as continuous variable in the risk function, separately from the calculation of the combination of clinical findings, to show the eventual gain in predictive value by the clinical findings.

The combination of variables, judged by the position of its ROC-curve (figure 4.2.1), is a better predictor of radiographic OA than is age alone. The ROC-curve of the combination of variables in the group with knee pain also performs better than age alone in that group. The difference, however, is marginal in both groups and it implies that there is little gain when a composite of clinical findings is used to predict radiographic OA. Overall, the ROC curves are far from ideal: a clinically useful test characteristic should include at least one point in the extreme upper left corner of the ROC plot.

The most authoritative paper with which to compare our work with is one published by the ARA subcommittee on classification criteria of osteoarthritis (3). The set of clinical criteria for knee OA in the ARA classification tree reached a sensitivity of 89% and a specificity of 88% against expert opinion as the standard. Consequently, the subcommittee concluded that clinical examination alone was a useful classification tool in epidemiological studies. If crepitus had been one of the variables in our analysis, this index, eventually, might have improved the characteristics of the most optimal combination. It is very unlikely, however, that this would have led to a comparably good result for sensitivity and specificity. On the other hand, the Quetelet's index, a strong predictor of knee OA (9,10,11) was included in our analysis, but not in the ARA subcommittee's classification tree. Our results confirm those of a preliminary report by Spector et al, who calculated a sensitivity of 59% and a specificity of 72% for two clinical signs of OA against X-ray diagnosis (4). The figures were obtained in a sample of 41 women drawn from the general population. These characteristics match well with the ROC curve for the total population presented here. We differ from Spector, however, as we believe that radiographs are still necessary for ascertaining OA in epidemiological studies. Moreover, our study shows that even in the group with knee pain at the time of the survey (subjects more likely to be general practitioners' patients) clinical findings are a poor classification tool. In general practice also, an X-ray examination will be necessary to diagnose knee OA. We conclude that a number of findings from medical history, physical examination and laboratory tests are associated with radiographic knee OA; nevertheless, the strength of association is insufficient to predict radiographic OA. In fact, the best combination of variables proves to be only slightly better than age alone to predict radiographic OA in the population. Clinical findings, either separately or in combination, cannot suffice as a diagnostic

tool for knee OA and can not be an alternative to X-ray examination.

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ADDENDUM

The most predictive variables for radiographic OA in both the whole population and the group with knee pain were selected by a stepwise logistic regression analysis. These variables define the risk-function (1). The risk function can be expressed as follows:

$$Y = \frac{\exp(\alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n)}{1 + \exp(\alpha + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_n X_n)}$$

Y = predicted probability of having radiographic OA
α = constant
β_n = coefficient for variable n
X_n = independent variable n (binary for all except Quetelet's index and age, which are continuous variables)

The selected clinical findings represent the independent X variables in the risk function. For every subject, each clinical variable, either binary or continuous, has an individual value. The outcome of the risk function or the dependent Y value ranges from 0 to 1 for each respondent. To calculate the sensitivity and the specificity, a certain Y value has to be chosen as a cut off point. Above this Y value the diagnosis radiographic OA is assumed to be present and below it absent. The series of 2865 Y values was split in deciles by defining nine cut off points: decile 1 counts the 10 % lowest Y values and thus subjects with the smallest chance of showing radiographic OA, and so on for each decile. For each cut off point sensitivity and specificity were calculated.

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Chapter 4.3

THE VALIDITY OF RADIOGRAPHIC CRITERIA AND THE CRITERIA OF THE AMERICAN COLLEGE OF RHEUMATOLOGY FOR OSTEOARTHRITIS OF THE KNEE IN EPIDEMIOLOGICAL RESEARCH

ABSTRACT

The objective of this study was to investigate the amount of agreement and construct validity of the criteria of the American College of Rheumatology (ACR), Kellgren's criteria and Ahlbäck's criteria for knee osteoarthritis in epidemiological research.

For the study of the agreement between sets of criteria, all the subjects with knee pain in 1988-89 and a random sample of the subjects without knee pain from a cohort studied during a population survey in 1975-78 were examined.

All the participants filled in a questionnaire about joint complaints. Physical signs were scored in duplicate and independently by two physicians in 431/508 (85%) of the subjects. All the antero-posterior weight bearing radiographs were judged independently by two physicians who were blinded for any other information.

The sets of criteria showed reasonable to good agreement when compared with each other but agreement was better 1) between the clinical criteria and clinical plus laboratory criteria based on the ACR decision trees; 2) between the sets of criteria with radiographic signs, except Ahlbäck's criteria; 3) and between the clinical criteria and clinical plus laboratory criteria from the ACR traditional formats. Ahlbäck's criteria and the clinical criteria with or without laboratory measurements from the traditional format were in bad agreement with all other criteria. When the agreement was studied in the 181 subjects with knee pain, percentage agreement and kappa were considerably less but again the same combinations came out better than the others as described above.

The construct validity was investigated in 2530 subjects from the same cohort by studying the relation of osteoarthritis with several putative risk factors and symptoms, physical signs and radiographic signs indicating an increased risk of having osteoarthritis in future.

For almost all of these baseline variables a relationship with osteoarthritis could be shown with all the sets of criteria. Ahlbäck's criteria and the clinical criteria based on the decision tree gave slightly better results than the others as judged by the magnitude of the odds ratio and the ROC-curve, which reflects the combined association with all baseline variables. Ahlbäck's criteria, however, gave much wider confidence intervals than the other sets of criteria. The clinical criteria with or without laboratory measurements based on the traditional format were hardly any better than knee pain as the only criterium.

Baseline radiographic osteoarthritis grade 2 or more according to Kellgren was related to future osteoarthritis as defined by several sets of criteria and this relation was stronger when knee pain at baseline was taken into account or when grade 3-4 radiographic osteoarthritis at baseline was used.

We conclude that the ACR-criteria based on the decision trees can be used in epidemiological research and that the traditional criteria format or decision lists should not be used except when the radiographic criteria are included. Kellgren's radiographic criteria grade 2 or more can also be used, especially when pain is taken into account or when grade 3 or 4 radiographic osteoarthritis is studied.

Ahlbäck's criteria yielded a low prevalence of OA, showed poor agreement with the other sets of criteria, but on the other hand did show a relatively strong relationship with several baseline variables, as judged by the magnitude of the odds ratio and the ROC-curve. Although several sets of criteria can be used in epidemiological research, study results can still vary since overlap between sets of criteria is not perfect.

INTRODUCTION

The radiographic criteria for osteoarthritis (OA) described in The Atlas of Standard Radiographs of Arthritis were developed by J.H. Kellgren and J.S. Lawrence (1,2) and were recommended at two international meetings for the use in epidemiological research (1,3,4). Other radiographic criteria have been developed by Ahlbäck, based exclusively on joint space narrowing (5) and have also been used in epidemiological research (6).

It was, however, noticed that radiographic criteria did not fully correspond with the criteria used for the diagnosis of OA in clinical practice and it was recommended to investigate the relationship between symptoms, physical signs and radiographic abnormalities (3,4).

It lasted, however, until 1986 before new criteria for knee OA were developed by the ACR Subcommittee on Classification Criteria of Osteoarthritis (7). In contrast with the previous radiographic criteria, these criteria were developed and evaluated in a clinical setting among patients with knee pain and included also findings from the medical history, physical examination and laboratory measurements besides radiographic signs.

The subcommittee developed several sets of criteria, and one set of criteria based only on the clinical examination and medical history was thought to be useful for population surveys and other epidemiological studies. However, the usefulness of the ACR-criteria for knee OA in epidemiological studies was not evaluated and more research to validate the criteria was recommended (7,8).

To investigate the agreement and validity of the ACR-criteria and the radiographic criteria for knee OA, we studied a sample from the general population including all those reporting knee pain. All the subjects had participated in a population survey on rheumatic diseases in 1975-78. The sets of ACR-criteria, the criteria of Kellgren and Lawrence (the Atlas of Standard Radiographs of Arthritis) and those of Ahlbäck were compared by calculating the percentage agreement and the kappa.

In addition, we investigated whether the choice of the criteria influenced the observed prevalence. The construct validity (9) was investigated by studying whether the criteria could show an increased risk of knee OA for putative risk factors or determinants assessed in 1975-78, such as gender, age, body mass index, meniscectomy, joint symptoms, physical signs and pre-existent radiographic OA according to Kellgren.

POPULATION AND METHODS

Baseline survey in 1975-78

A population study was conducted in 1975-78 in the Dutch town Zoetermeer to investigate the prevalence and determinants of rheumatic conditions and several other chronic diseases. During this study questions were asked about joint complaints. A physical examination was performed at the research centre, and antero-posterior weight bearing radiographs of the knee joint were taken.

The questionnaire comprised questions about age, gender, current knee pain, morning stiffness in arms or legs, or both, pain in knees or hips, or both, when rising from a seated position, stiffness in knees or hips, or both, when rising from a

seated position, and pain in knees or hips, or both, while climbing stairs. Subjects without pain in any joint, including the spine, were not questioned specifically about the last three variables as it was assumed that they would have given negative answers here.

The physical examination included, among others, measurements of body weight and length, without shoes but with indoor clothing, clinical Heberden's nodes at the right or left distal interphalangeal joints, and specifically for the knee joint: bony enlargement, limitation of knee function, pain with knee flexion during examination, and bony tenderness. Function of the knee was scored on a scale ranging from 0 to 4. Grade 1 or more was regarded as limited function (grade 1 is minimal limitation of extension or flexion at physical examination). The clinical observations were made by one of six doctors; interobserver variability was reduced by combined three-monthly training sessions.

The antero-posterior weight bearing radiograph was taken of both knees and judged by two physicians independently of each other and without any knowledge of the other data. A score was given according to the Atlas of Standard Radiographs of Arthritis on a five point scale (0-4) where a score of grade 2 (definite osteophytes and possible narrowing of joint space) or more was considered to indicate radiographic osteoarthritis of the knee (ROA) (1). If the difference in score between the two observers was two or more or if one had scored 2 and the other had scored 1, consensus was reached in a combined reading session. The highest score of either observer or the consensus result was used for the analysis. In the second half of the study the films were read by one observer (H.A. Valkenburg).

Follow-up in 1988-89

In 1988-89 a follow-up study was undertaken of the respondents born between 1909 and 1959. They were sent a two page questionnaire about the occurrence of several conditions, medication use and pain of the knee. The questions concerning pain of the knee were: 1. Did you ever had pain of the knee of at least one week duration?; 2. Did you have pain of the knee of at least one week duration in the past 12 months?; 3. Do you currently have pain of the knee of at least one week duration?. In the analysis pain was assumed to be present when the second and/or third question was answered in the affirmative.

All those, born between 1909 and 1939, who had pain of the knee of at least one week duration in the past 12 months and/or currently were invited for a follow-up examination (n=308). A random sample of subjects who had not given a positive answer to any of these two questions and matched for gender were also invited to

come to the research centre (n=362).

The follow-up examination included an extensive self-administered questionnaire about rheumatic and knee joint complaints. Among these was a question about the presence of morning stiffness in one or both knees (yes/no) and the duration of this stiffness (0-15, 15-30 and more than 30 minutes).

The physical examination was performed in duplicate by two out of five participating doctors who had no knowledge of the answers to the questionnaire or other data like radiology or laboratory results. They therefore were not informed about the participant's knee joint complaints. In case of a discrepancy between the two physicians for any physical sign the respondent was reexamined by the two physicians together to reach a consensus opinion.

The physical examination of the knee joint included the assessment of bony enlargement and bony tenderness at the joint margins, palpable warmth and crepitus. Bony enlargement, bony tenderness and palpable warmth were scored as present or absent.

Since there is no good description of how to assess crepitus this was evaluated in two ways: 1) with the whole hand encompassing the patello-femoral region and part of the lateral/medial side and 2) with the thumb and indexfinger placed on the lateral and medial tibio-femoral joint space. For both methods crepitus was assessed during active as well as passive movement of the joint. It was also noted whether the crepitus was more likely to be bony or synovial crepitus (sudden snaps). During the examination of crepitus the respondent was seated at the edge of the examination coach with the legs hanging over one side of the coach. An overall score was given for (bony) crepitus on a five point scale where 0 = absent; 1 = doubtful; 2 = present but slight; 3 = moderate; and 4 = severe crepitus. For all physical signs the consensus score was used in the analysis.

An antero-posterior weight bearing radiograph of the knees was taken and scored according to the same methods and procedures as described above for the baseline radiograph. Osteophytes at four joint margins, lateral and medial tibia and femur were also scored on a four point scale (0-3) where 0 = absent; 1 = small; 2 = moderate; and 3 = large. When both observers had given a score of 1 or more for the same and at least one place of the joint margins, osteophytes were considered to be present. The medial and lateral joint space was measured in millimetres for Ahlbäck's criteria. The mean of the two observers was used in the analysis. The laboratory measures included the erythrocyte sedimentation rate (ESR) according to Westergren and the latex fixation test, considered positive for titers > 1/80.

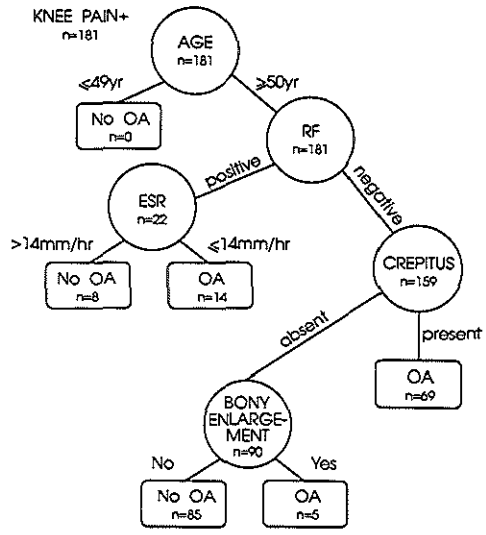

Figure 4.3.1. The clinical and laboratory criteria (CLAT) presented in a decision tree derived from reference 7 but with the criteria and numbers from the present study.

Classification criteria

Eight sets of criteria were studied and six of these are ACR criteria (7). Three sets of criteria are given as decision trees and figures 4.3.1 to 4.3.3 present them with the results from our study. The decision trees are a clinical and laboratory decision tree (CLAT, figure 4.3.1), a clinical and radiographic decision tree (CRAT, figure 4.3.2), and a clinical decision tree (CLIT, figure 4.3.3). Three other sets of criteria are of the traditional format (a list of criteria), in that an individual has to fulfil a certain number of criteria to classify as OA, (table 4.3.1); a clinical and laboratory list (CLAL, column 1), a clinical and radiographic list (CRAL, column 2), and a clinical list (CLIL, column 3). Other sets included in this study were the presence of knee pain together with radiographic OA grade 2 or more according to Kellgren (1) (KELPAIN) and knee pain with Ahlbäck's criteria based on joint space narrowing (5) (AHLPAIN) (table 4.3.2).

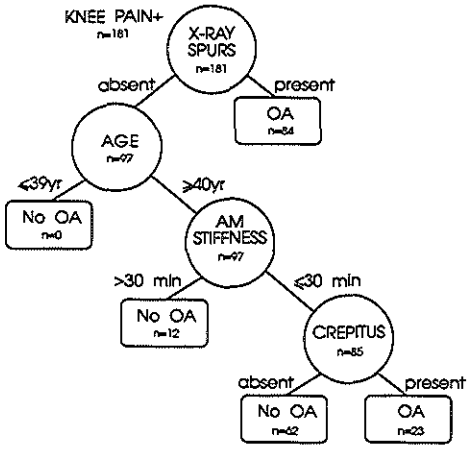

Figure 4.3.2. The clinical and radiographic criteria (CRAT) presented in a decision tree derived from reference 7 but with the criteria and numbers from the present study.

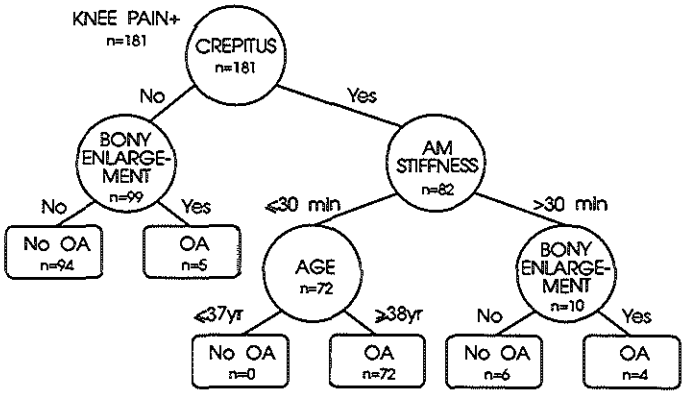

Figure 4.3.3. The clinical criteria (CLIT) presented in a decision tree derived from reference 7 but with the criteria and numbers from the present study.

Table 4.3.1. ACR-criteria of the traditional format.

Clinical and laboratory (CLAL)	Clinical and radiographic (CRAL)	Clinical (CLIL)
Knee pain +	Knee pain +	Knee pain +
at least 5 of 9:	Osteophytes +	at least 3 of 6:
Age ≥ 50 yrs	at least 1 of 3:	Age ≥ 50 yrs
Stiffness ≤ 30 minutes	Age ≥ 50 yrs	Stiffness ≤ 30 minutes
Crepitus	Stiffness ≤ 30 minutes	Crepitus
Bony tenderness	Crepitus	Bony tenderness
Bony enlargement		Bony enlargement
No palpable warmth		No palpable warmth
ESR < 40 mm/hour		
RF ≤ 1:80		
(SF OA)*		

Criteria are adapted from reference 7 as described in the text.
* Synovial fluid not included in this study.

STATISTICAL ANALYSIS

All the analyses were limited to one knee, the right knee. The assessment of OA was restricted to people with complete data sets and 29/537 subjects (5.4%) were therefore excluded because no blood or radiograph was available at follow-up.

Firstly, the prevalence of variables used for the classification criteria were calculated and the number of subjects fulfilling the various sets of criteria.

Secondly, the percentage agreement and kappa were calculated for all possible combinations of sets of criteria both for the total group of 508 subjects and separately for those with pain of the right knee. The kappa is the amount of actual agreement defined as the percentage of the total agreement that occurs beyond the proportion contributed by chance (10).

Thirdly, a number of baseline characteristics considered to show an increased risk of having OA in future were associated with the presence of OA, defined by the different sets of criteria, in the total group of 2530 people who responded to the

Table 4.3.2. Kellgren's criteria from the Atlas of Standard Radiographs of Arthritis and the criteria of Ahlbäck.

KELLGREN

Grade 1: Doubtful narrowing of joint space and possible osteophytic lipping.

Grade 2: Definite osteophytes and possible narrowing of joint space.

Grade 3: Moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends.

Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

AHLBÄCK

The articular space was classified as narrowed:
1. when it was narrower than half the width of the articular space in a) the other articulation of the same knee or b) the same articulation of the other knee, and/or
2. when it was narrower than 3 mm, and/or
3. when it decreased in a weightbearing as compared to non-weightbearing position*

The criteria are adapted from reference 1 (Atlas) and 5 (Ahlbäck)
* The third criterion of Ahlbäck was not used in this study

questionnaire in 1988-89. Twenty subjects who had no baseline measurement of the body weight were excluded for this part of the analysis.
The prevalence of OA at follow-up was calculated for the several sets of criteria. The relation of OA at follow-up with several putative risk factors, findings from the medical history, and findings from the physical examination assessed at baseline was expressed as the odds ratio and as the risk difference. In order to have a measure of precision the 95% confidence interval of the odds ratio, the standard error of the log odds ratio, and the chi-square value were calculated.

To study which set of criteria gave the strongest relationship with the combination of these variables a logistic regression model was used with the

Table 4.3.3. Baseline characteristics of the subjects examined during the baseline study in 1975-78 who responded to the questionnaire in 1988-89.

Number	2530 *
Gender M/F	1202/1328 (47.5/52.5)
Age at baseline (yrs)	49.3 ± 7.6
Age range at baseline (yrs)	36 - 68
Body mass index (kg/m^2)	24.8 ± 3.1
Meniscectomy +	91 (3.6)
Knee pain right knee	248 (9.8)
Pain walking stairs	249 (9.8)
Pain rising chair	283 (11.2)
Stiffness arm/leg	424 (16.8)
Stiffness rising chair	364 (14.4)
Bony enlargement	79 (3.1)
Function limitation	57 (2.3)
Bony tenderness	39 (1.5)
Pain on motion	29 (1.1)
Heberden's nodes	159 (6.3)
Radiographic OA (Kellgren score grade 2 or more)	239 (15.9) ∓

Figures are means ± standard deviation or numbers with percentage between parentheses
* Twenty subjects without a measurement of body weight at baseline excluded
+ Before follow-up in 1988-89
∓ n = 1504, who had a knee radiograph at baseline

diagnosis of OA as the dependent variable and all the baseline variables included in the model as the independent variables. After the coefficients of the independent variables were calculated for a given set of criteria these were used to calculate the risk of every subject to have OA at follow-up. The distribution of these risk scores was then used to assess ten different cut off points above which OA was assumed to be present and below it to be absent. In this way it is possible to calculate the sensitivity and specificity for every cut off point. The combinations of sensitivity and

specificity for every cut-off point are presented as a ROC-curve (receiver operator characteristic) with (1 - specificity) on the X-axis and the sensitivity on the Y-axis (10). The more this curve ascends towards the upper left corner the better is the association of this set of criteria with the combination of several variables in a logistic regression model.

To investigate the validity of pre-existent radiological abnormalities the association between Kellgren ROA at baseline and the presence of OA according to the several sets of criteria at follow-up was calculated and expressed as odds ratios in 1504/1543 respondents from the cohort aged 45 and older. The odds ratios were calculated for grade 2-4, grade 2-4 with pain as well as grade 3-4, with grade 0-1 as the reference group. A ROC-curve based on the data of this sample including the Kellgren score of the baseline radiograph as an independent variable was constructed.

Table 4.3.4. Characteristics of subjects with and without knee pain examined at follow-up in 1988-89.

Number	508 *
Age at follow-up (yrs)	61.0 ± 7.6
Age range at follow-up (yrs)	50 - 79
Gender M/F	181/327 (35.6/64.4)
Knee pain in any knee (at follow-up)	250 (49.2)
≥ one week in past 12 months	236 (94.4)
≥ one week duration, currently	148 (59.2)
Knee pain right knee	181 (35.6)
≥ one week in past 12 months	172 (95.0)
≥ one week duration, currently	105 (58.0)

Figures are means ± standard deviation or numbers with percentage between parentheses
* 29/537 subjects excluded because radiographs or blood sample was missing

RESULTS

In 1975-78 3541 people born between 1909 and 1939 had participated in the population study. During follow-up 333 had died and 139 were lost to follow-up.

The response rate for the questionnaire was 2550/3069 (83%). Twelve percent (308/2550) reported to have had knee pain of at least one week duration either in the past 12 months and/or currently. Baseline characteristics of the subjects who responded to the questionnaire are given in table 4.3.3. Differences between responders, non-responders and individuals lost to follow-up are shown in appendix A. Of those with knee pain one had died before the follow-up examination and 263/307 (86%) participated. Two people of those randomly selected and without knee pain had died, leaving 274/362 (76%).

In table 4.3.4 some characteristics of the group examined at follow-up are presented. Table 4.3.5 shows that subjects with pain in the right knee more often had symptoms and signs that are included in the sets of ACR criteria for OA of the

Table 4.3.5. Number and percentage of several variables composing the classification criteria in subjects with knee pain of the right knee, knee pain in the left knee only and no knee pain.

	Knee pain in right knee	Knee pain left knee only	No knee pain
Number	181	69	258
Age (≥ 50 years)	181 (100)*	69 (100)	258 (100)
Rheumatoid factor negative (Latex fixation ≤ 1/80)	159 (87.8)	62 (89.9)	234 (90.7)
ESR (≤ 14 mm/hr)	122 (67.0)	50 (72.5)	196 (76.0)
ESR (< 40 mm/hr)	174 (96.1)	68 (98.6)	254 (98.4)
Morning stiffness in the knee(s) (≤ 30 min)	166 (91.7)	64 (92.8)	252 (97.7)
Bony enlargement +	34 (18.8)	8 (11.6)	23 (8.9)
Bony tenderness +	69 (38.1)	9 (13.0)	31 (12.0)
No palpable warmth +	175 (96.7)	69 (100)	256 (99.2)
Spurs on radiograph +	84 (46.4)	22 (31.9)	58 (22.5)
Crepitus +	82 (45.3)	25 (36.2)	69 (26.7)
Kellgren score (grade 2 or more) +	85 (47.0)	18 (26.1)	52 (20.2)
Ahlbäck +	19 (10.5)	5 (7.2)	3 (1.2)

* Percentage between parentheses

\+ Of the right knee

knee than the others. It is apparent that these signs and symptoms were quite common in the general population. Especially 1) absence of stiffness of more than 30 minutes, 2) negative rheumatoid factor, 3) low ESR, and 4) no palpable warmth all had a high prevalence in the group with knee pain as well as in those without (table 4.3.5).

In figures 4.3.1 to 4.3.3 and tables 4.3.6 and 4.3.7 the number of subjects fulfilling the several sets of criteria are presented. When the classification is based on the CLAL or CLIL criteria almost everyone with knee pain would classify as having OA (table 4.3.7). The classifications based on the CLAT, CRAT, CLIT, CRAL, or KELPAIN criteria yielded corresponding but lower prevalences and the AHLPAIN criteria resulted in a very low prevalence.

Table 4.3.6. Diagnosis of knee osteoarthritis in subjects with pain of the right knee according to several sets of criteria displayed in the three ACR decision trees.

Clinical and laboratory criteria (CLAT) †	88 (48.6)*
Age ≥ 50 yrs, RF pos, ESR ≤ 14	14
Age ≥ 50 yrs, RF neg, Crepitus	69
Age ≥ 50 yrs, RF neg, no crepitus, bony enlargement	5
Clinical and radiographic criteria (CRAT) ‡	107 (59.1)*
Spurs	84
No spurs, age ≥ 40, no stiffness, crepitus	23
Clinical criteria (CLIT) §	81 (44.8)*
No crepitus, bony enlargement	5
Crepitus, no stiffness, age ≥ 38 yrs	72
Crepitus, stiffness, bony enlargement	4

* Percentage of total number of 181 subjects with knee pain in the right knee between parentheses

† According to figure 4.3.1

‡ According to figure 4.3.2

§ According to figure 4.3.3.

Table 4.3.7. Diagnosis of knee osteoarthritis in subjects with pain of the right knee according to several sets of criteria presented by traditional ACR formats with clinical and laboratory criteria, only clinical criteria or with clinical, and radiographic criteria; the Kellgren score for radiographic osteoarthritis with knee pain; and the criteria of Ahlbäck with knee pain.

Clinical and laboratory criteria (CLAL) †	167 (92.2)*
Age ≥ 50, stiffness -, warmth -, ESR < 40, RF -	58
Age ≥ 50, stiffness -, crepitus, warmth -, ESR < 40, RF -	22
Age ≥ 50, stiffness -, tenderness, warmth -, ESR < 40, RF -	21
Age ≥ 50, stiffness -, crepitus, tenderness , enlargement, warmth -, ESR < 40, RF -	15
Age ≥ 50, stiffness -, crepitus, tenderness, warmth -, ESR < 40, RF -	14
Others (combinations of criteria with less than 6 subjects)	37
Clinical criteria (CLIL) ‡	175 (96.7)*
Age ≥ 50, stiffness -, warmth -	64
Age ≥ 50, stiffness -, crepitus, warmth -	28
Age ≥ 50, stiffness -, tenderness, warmth -	24
Age ≥ 50, stiffness -, crepitus, tenderness, enlargement, warmth -	18
Age ≥ 50, stiffness -, crepitus, tenderness, warmth -	17
Others (combinations of criteria with less than 4 subjects)	24
Clinical and radiographic criteria (CRAL) §	84 (46.4)*
Spurs, age ≥ 50 yrs, crepitus, stiffness ≤ 30 min	49
Spurs, age ≥ 50 yrs, stiffness ≤ 30 min	32
Spurs, age ≥ 50 yrs, crepitus	3
Kellgren grade 2+ with pain (KELPAIN) ‖	85 (47.0)*
Ahlbäck with pain (AHLPAIN) ‖	19 (10.5)*

* Percentage of total number of 181 subjects with knee pain in right knee between parentheses

† According to the first column in table 4.3.1

‡ According to the third column in table 4.3.1

§ According to the second column in table 4.3.1

‖ According to table 4.3.2

Agreement

The percentages agreement and kappas for the assessment of intercriteria variability are presented in table 4.3.8 for the total group of 508 people seen at the research centre. The three sets of criteria based on the decision trees revealed high percentages of agreement (91% to 97%) and good kappas (72% to 89%). Three sets of criteria which included radiographic criteria namely CRAT, CRAL and KELPAIN, also showed high percentages of agreement (94% to 95%) and good kappas (80% to 85%) when compared with each other. The interrelationship between the criteria derived from the traditional format, CLAL and CLIL criteria, was very good. However, comparison of the clinical and clinical plus laboratory criteria from the traditional format with the others, except AHLPAIN, yielded lower percentages agreement (81% to 87%) and lower kappas (53% to 67%). Three sets of criteria with radiographic criteria, namely CRAT, CRAL, and KELPAIN, compared to those without gave percentages agreement of 81% to 94% and kappas of 52% to 79%. Comparison of AHLPAIN with the others resulted in low percentages agreement and kappas throughout.

When the analysis was limited to the group with knee pain in the right knee the percentages agreement and kappas were lower (table 4.3.9). The CLAL and CLIL criteria showed very low kappas (-0.4% to 11%) and low percentages agreement (48% to 62%) with the other criteria, except AHLPAIN, but agreement was better between these two sets of criteria. Criteria from the three decision trees corresponded reasonably well with each other, percentages agreement ranged from 75% to 92% and kappas from 51% to 83% respectively. Criteria with radiographic signs had a good overlap with each other, except with AHLPAIN. Comparing the CLAT and CLIT criteria from the decision trees with three sets with radiographic criteria namely CRAT, CRAL and KELPAIN revealed a moderate agreement for the CRAT criteria, as stated above, but lower for the CLAT with the CRAL and the KELPAIN criteria. Again AHLPAIN associated poorly.

Construct validity

The eight tables which show the details about the analysis of the construct validity are presented as an addendum to this chapter. This paragraph is only a broad outline of the results concerning the construct validity.

The baseline characteristics presented in table 4.3.3 were all studied in relation to the presence of knee OA at follow-up as defined by several sets of criteria described above. Implicitly, it is assumed that these variables indicate an increased risk of having OA of the knee in future. If the sets of criteria indeed are valid

Table 4.3.8. Percentage agreement (Ag) and kappa in percentage (Ka) for several classification criteria of knee osteoarthritis.

	Decision tree				*Traditional format*				Kellgren	
	Clin, lab		Clin, X-ray		Clin		Clin, lab		Clin, X-ray		Clin		with pain	
	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka
Decision tree														
Clin, lab	-	-												
Clin, X-ray	91	72	-	-										
Clin	97	89	94	79	-	-								
Traditional format														
Clin, lab	82	53	87	67	83	55	-	-						
Clin, X-ray	87	52	95	85	89	60	82	55	-	-				
Clin	82	56	86	66	81	53	98	97	82	54	-	-		
Kellgren with pain	87	53	94	80	89	61	82	54	95	84	81	53	-	-
Ahlbäck with pain	84	17	82	24	86	23	70	12	86	29	69	13	86	28

Table 4.3.9. Percentage agreement (Ag) and kappa in percentage (Ka) for several classification criteria of knee osteoarthritis in 181 subjects with knee pain in the right knee.

	Decision tree						*Traditional format*				Kellgren	
	Clin, lab		Clin, X-ray		Clin		Clin, lab		Clin, X-ray		Clin		with pain	
	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka	Ag	Ka
Decision tree														
Clin, lab	-	-												
Clin, X-ray	75	51	-	-										
Clin	92	83	82	65	-	-								
Traditional format														
Clin, lab	49	-0.4	62	11	51	11	-	-						
Clin, X-ray	62	25	87	75	70	39	51	7.3	-	-				
Clin	51	4	61	7	48	5.4	96	58	49	3.7	-	-		
Kellgren with pain	63	26	82	65	70	40	50	5.4	87	75	48	1.7	-	-
Ahlbäck with pain	54	6	50	13	60	13	16	-0.007	62	19	13	-0.005	61	19

criteria for knee OA, these sets should show an association between knee OA and these variables.

A first indication of whether the measures of association will be equivalent can be gained form the calculation of the prevalences of knee OA at follow-up. These ranged from 8 per 1000 to 69 per 1000. Ahlbäck's criteria yielded the lowest prevalence and the clinical criteria of the traditional format the highest. Both the clinical criteria and the clinical criteria plus laboratory criteria of the traditional format had a prevalence that was almost equal to the prevalence of knee pain. The other sets, except Ahlbäck's criteria, showed prevalences close to each other, ranging from 32 per 1000 to 42 per 1000 (table 4.3.A.1).

As expected, all sets of criteria associated statistically significant with various baseline variables. However, the strength of the association, expressed as the odds ratio, fluctuated considerably. For example, for age 60 and above compared to below 50 the odds ratio with Ahlbäck's criteria was 8.2 (95% CI: 2.7-25.1) while with the clinical criteria from the traditional format the odds ratio was 1.4 (95% CI: 0.9-2.2). For meniscectomy the odds ratio was 7.4 (95% CI: 4.1-13.4) with the set that includes radiographic criteria from the traditional format but 3.9 (95% CI: 2.3-6.6) with the set of clinical criteria from the traditional format.

The clinical with or without laboratory criteria from the traditional format which classified almost all subjects with knee pain as having OA, showed hardly any associations with age and body mass index. In contrast to the others the criteria of Ahlbäck and the clinical criteria from the decision tree in general yielded high odds ratios. The ROC-curves of these latter sets of criteria perform better as they ascend more towards the upper left corner, contrary to the sets of criteria from the traditional format that classified almost everyone with knee pain as having OA (fig. 4.3.4 and 4.3.5).

Although the magnitude of the odds ratio can be used to express the strength of an association, the value of the risk difference may point in another direction (see chapter 4.1). For example, the sets of criteria of the traditional format that classified almost everyone with knee pain as having OA, tended to give higher risk differences but lower odds ratios. On the other hand, for age and body mass index both the odds ratios and the risk differences were lower compared to, for example, the sets of the three decision tree.

Another aspect worth studying when comparing sets of criteria is the estimate of the precision, given as the standard error. The standard errors varied little except in the case of the criteria of Ahlbäck where higher values were observed. Generally speaking, the rank order of the standard errors corresponded inversely with the rank

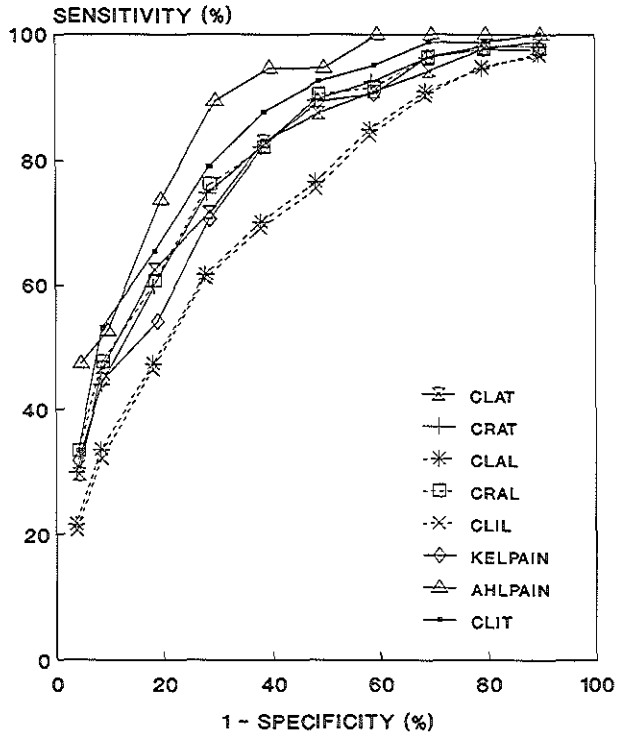

Figure 4.3.4. ROC-curves reflecting the combined association of several putative risk factors, findings from medical history and physical examination at baseline with the presence of knee osteoarthritis at follow-up according to several classification criteria in 2530 subjects.

order of the prevalences.

As Kellgren's criteria have been used in epidemiological research for a long time they were studied in more detail. Grade 2 or more ROA at baseline was related to future OA, especially when criteria were used that took radiographic signs into account. The odds ratios were much higher when baseline ROA grade 2 or more with pain or grade 3 or more were analyzed (table 4.3.A.8).

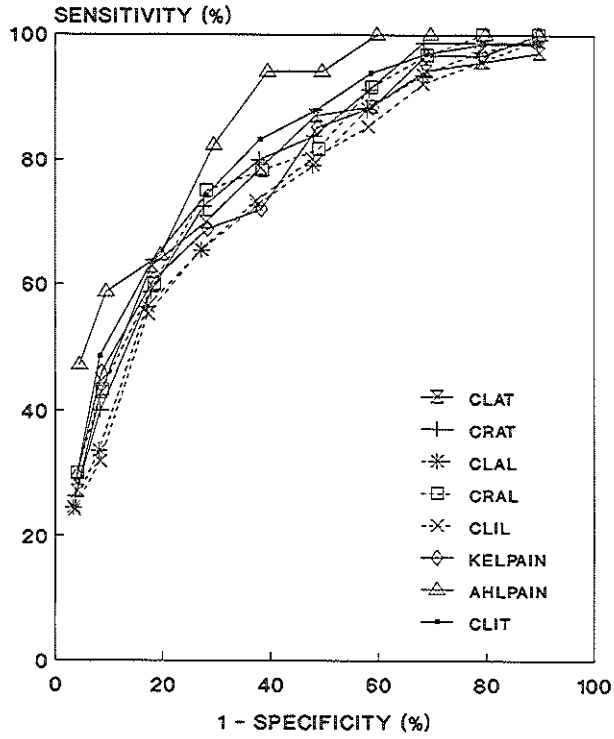

Figure 4.3.5. ROC-curves reflecting the combined association of several putative risk factors, findings from medical history and physical examination and radiographic OA at baseline with the presence of knee osteoarthritis at follow-up according to several classification criteria in 1487 subjects.

In the ROC-curves of figure 4.3.5, ROA at baseline was included as an independent variable, together with the other variables used for the ROC-curves of figure 4.3.4. The curves come closer to each other but essentially the same pattern is presented as in figure 4.3.4.

DISCUSSION

In this study the validity of several sets of classification criteria for knee osteoarthritis was investigated in a general population setting. The objective was not only to compare the criteria with each other but also to study whether the use of different criteria leads to varying results in the assessment of the association with several putative risk factors, symptoms, and signs that point to an increased risk of having OA in the future.

The study population comprised subjects who had participated in a population survey in 1975-78. In 1988-89 all the subjects with knee pain of at least one week duration in the past 12 months or with current knee pain of such a duration were invited for a follow-up examination. The duration of knee pain was arbitrarily taken as one week to include subjects with knee pain of some severity and to exclude subjects with a short and non-significant period of knee pain or knee pain more than 12 months ago. As no description of the frequency, severity or quality of the knee pain was given for the ACR-criteria, we could not base our selection on that study (7). The same questions about knee pain were asked again when the participant came to the research centre and 199/250 (80%) of the knee pain group again answered affirmative on these questions. Medication for knee pain was used by 50/250 (20%) in this group.

In article of Altman et al (7), the description of some of the ACR-criteria in the traditional format was different from the notation of the same variable applied in the decision tree. For example, in the decision tree rheumatoid factor (RF) was positive when the value was more than 1:40 but in the traditional format rheumatoid factor was positive when the value was more than or equal to 1:40. These inaccuracies led us to take age in the list as 50 years or more, stiffness as less than or equal to 30 minutes and the latex fixation test for rheumatoid factor as positive when the value was more than 1:80.

The cut off point for rheumatoid factor was set higher as the latex fixation test has large interlaboratory variability (11) and came closer to the one used in clinical practice at the Department of Rheumatology, University Hospital Groningen, The Netherlands, where the samples were analyzed. Moreover, at a titer of more than 1:80 the prevalence of positive values is 10 percent, which is to be expected in a group of elderly subjects from the general population.

We have not analyzed the effects of the interobserver variability and the change of cut off points of the individual criteria composing the sets of criteria on the agreement and validity but this certainly needs to be investigated. Standardisation

procedures and protocols for the assessment of physical signs like crepitus are also desired as has been suggested by others (12).

Agreement

The control subjects were matched for gender since we also intended to study risk factors for knee pain but these results will not be presented in this thesis. This approach may have led to an increase in the prevalence of osteoarthritis, because more subjects with pain are included compared to a random sample from the general population. Selecting more subjects with OA may increase the kappa (13). However, the same population was studied for every set of criteria and therefore still renders a comparison of kappa values possible. Moreover, we also calculated the percentage agreement and kappa for the group with knee pain in the right knee exclusively.

Almost all subjects with knee pain were classified as having OA according to the ACR-sets of clinical with or without laboratory criteria presented in a traditional format. This is due to the fact that subjects with knee pain from the general population often have no morning stiffness, no palpable warmth, a low ESR and no rheumatoid factor. Therefore, only one additional criterium is needed for an individual to be classified as having OA. This situation is clearly different from the way the criteria were developed by the ACR subcommittee where clinic patients were studied and more than fifty percent of the control subjects had rheumatoid arthritis and for this mere reason were often positive for stiffness, palpable warmth, a raised ESR and rheumatoid factor. In this regard McAlindon et al are correct when they state that "the criteria have only been shown to perform well in the differentiation of OA from younger people with RA." (8).

Fewer subjects with knee pain are classified as having OA when the ACR-decision trees are applied. In the tree for clinical criteria, for example, the subjects who are negative for crepitus can only be classified as having OA when bony enlargement is present, whereas in this population of people aged 50 and above, the traditional format with clinical criteria alone would classify subjects who are negative for crepitus if they are positive for at least two other common criteria, e.g. no palpable warmth and no stiffness of more than 30 minutes. This discrepancy between the decision trees and traditional format is also reflected by the lower percentage agreement and kappa when the criteria from trees are compared with those of the traditional format.

An exception to this are the sets of criteria which comprise radiographic signs. These sets, except Ahlbäck's criteria, give good agreement and high kappas when

they are compared with each other. The sets of clinical with or without laboratory criteria derived from the decision tree are in good agreement with each other as are the corresponding sets of the traditional format. Ahlbäck's criteria reveal a very poor agreement when compared to the other sets, even with the sets comprising radiographic criteria.

In conclusion, although most of the sets of criteria show reasonable to good agreement, they do not completely overlap. Ahlbäck's criteria and the sets of clinical criteria with or without laboratory measurements based on the traditional format are poor classification tools. For the sets of criteria of the traditional format this is due to the fact that almost all individuals with knee pain classify as having OA. For Ahlbäck's criteria the suggestion emerges that this definition of radiographic OA selects a different set of subjects with more severe OA.

Construct validity

When the criteria are used to asses the prevalence of knee OA at follow-up in this cohort, the prevalence can differ more than nine fold and subsequently the relation with several putative risk factors may also vary. For example, a weak relation with age was found when the clinical with or without laboratory criteria of the traditional format were used, while the other sets of criteria distinctly showed a relationship between age and OA. On the other hand, all the sets of criteria provide a statistically significant association with almost all other putative risk factors, symptoms and signs assessed at baseline. In general the clinical criteria derived from the decision tree and Ahlbäck's criteria yielded somewhat higher and the criteria of the traditional format without radiographs somewhat lower odds ratios.

There is, however, a limitation in using the odds ratio alone to express the strength of the association, as the criteria of the traditional format resulted in greater risk differences, another measure to express the strength of an association, for some variables. Notable exceptions are the associations of these criteria with age, body mass index, bony enlargement, function limitation, bony tenderness and pain on motion, where both the risk difference and the odds ratio are lower compared to the clinical criteria derived from the decision tree. This suggests that the decision tree is at the advantage in selecting subjects with OA, as this set shows a stronger relationship with factors assumed to indicate an increased risk of having OA in future. This is confirmed when the ROC-curves are compared. The ROC-curve of the CLIT criteria ascends more towards the extreme upper left corner.

The clinical criteria based on the decision tree show a relation with gender, age and body mass index but one could argue that this is a biased result. The physician

may have judged, for example, crepitus to be more often present in obese subjects, women, elderly, or in subjects with knee pain, assuming that OA occurs more often among such individuals.

There are a few arguments against this possibility. First of all, the physician did not know whether pain was present, although during the examination this may have become apparent. Secondly, crepitus was the first sign to be examined, before the physician knew the results of the other parts of the examination. Thirdly, the odds ratio and the risk difference were lower for gender with the CLIT criteria in the analysis compared to knee pain with Kellgren ROA, the latter criterion being assessed independently of the other data, and hence this is a counter argument against a bias.

A cautious remark is necessary for the clinical criteria form the decision tree in which crepitus is the most important variable. It needs to be investigated whether the observed crepitus is related to OA of the patello-femoral or the femoro-tibial joint. This differentiation could in part explain discrepancies between certain sets of criteria, as in the case of Kellgren's criteria, that focus exclusively on the femoro-tibial joint.

In the general population, the clinical with or without laboratory criteria of the traditional format classify almost everyone with knee pain as having OA. One could of course reason that all subjects with knee pain have early OA, be it that this concept of OA shows a weak relationship with body mass index a variable assumed to play a role in the etiology of knee OA. We would therefore postulate that it is unlikely that everyone with knee pain of one week duration from the general population has OA, other causes of pain are likely to be present. Moreover, there is a need for criteria which distinguish subgroups or subsets from people who complain of knee pain. Studying such subgroups should be stimulated since more specific hypotheses for the causes of knee OA and ultimately knee pain can be developed.

Changing the cut off point to higher levels for the criteria of the traditional format would select smaller numbers of people classifying as having OA and hence decrease the prevalence. This might result in an improvement of the traditional format criteria in terms of better agreement with other sets and stronger associations with putative risk factors.

The combination of pain and the radiographic criteria of Kellgren seems to be a valid classification tool, comparable to the other sets of criteria which include radiographic signs. The presence of grade 2 or more radiographic osteoarthritis at baseline according to Kellgren's criteria relates to an increased risk of having OA in future as defined by several sets of criteria. This risk is further increased for ROA

grade 2 or more when pain is present or when grade 3 or more is used as the criterion for ROA. This supports the finding that pain with grade 2 or more according to Kellgren shows reasonable agreement with the ACR-criteria and has construct validity comparable to the ACR-criteria.

Although not everyone with grade 2 or more ROA develops OA according to the other criteria, Kellgren's criteria could effectively be used as an indication for future OA. This line of thinking is also applied in the study of causes of hypertension which is a well known risk factor for cardiovascular disease or in the study of bone density where the primary interest is in bone-fractures. Moreover, subjects with OA according to the various (ACR) criteria should still be evaluated over time to see if all individuals indeed develop more severe OA and whether the signs and symptoms persist or subside.

The criteria of Ahlbäck related with higher odds ratios to several baseline variables but its agreement with other sets of criteria was poor. The standard errors were large because few individuals were classified as having OA. This leads to a reduced power in epidemiologic research in the general population when the study population is small and only few will be classified as having OA. In a clinic situation these individuals can be readily identified but more patients need to be screened than for selection by other sets of criteria.

Our study supports the suggestion of Altman et al that "the clinical examination alone may be useful for population surveys and other epidemiological studies" (7). In their study the emphasis was on the decision trees which had better sensitivity and specificity in comparison with the criteria from the traditional format. Our study confirms their preference for the criteria derived from the decision tree, be it that the criteria based on the traditional format including radiographic signs operated equally well.

It should be realised that our clinical data were the result of a consensus between two doctors in 152/181 (84%) of the subjects with knee pain in the right knee. The others were seen by only one physician due to organisational difficulties. This procedure reduces interobserver variability, which can be substantial for crepitus, bony enlargement and tenderness (12,14), although it was found that for these physical signs the interobserver variability was better than for some others used in the clinical assessment of knee OA (12).

The ACR-criteria are based on the diagnosis of a physician confirmed by the study coordinators (7), and it has been suggested that they do not give an impression of the cartilage degeneration that is regarded as the most important abnormality in OA (8).

A small study indicated that patients with OA according to the ACR-criteria all have signs of cartilage degeneration seen during arthroscopy (15). Another study showed a poor relation between cartilage thickness assessed on standard radiographs and arthroscopic cartilage defects (16), but a good correlation was observed between the radiographic cartilage thickness and thickness measured during histologic examination (17). More research is needed to investigate in more detail the relationship between the ACR-criteria and cartilage degeneration. Moreover, one could question whether the cartilage defects seen during arthroscopy are related to joint complaints and inevitably lead to more severe defects, more pain and disability.

Although arthroscopy could be a gold standard, in epidemiological research arthroscopy will hardly be feasible. New imaging techniques like MRI as well as markers of OA, measurable in serum or urine could be of use in future epidemiological research as a more direct assessment of cartilage degeneration.

More research is needed to determine how the criteria developed for knee OA are related to future outcomes like disability or recurrent episodes of knee pain and how the criteria evolve over time. Better criteria could emerge when subgroups can be distinguished that have a high probability of becoming disabled.

Altman et al suggested that radiographs are not needed in epidemiological research. Based on the results of our comparative study we could support this opinion. It should be realized, however, that radiographs have the advantage that they can be judged without any knowledge of other data, by more than one observer, are useful in the assessment of disease progression (18) and may show the anatomic location of the abnormalities in the joint.

In conclusion, the ACR criteria show reasonable to good agreement in the general population but the overlap is far from perfect. The clinical criteria with or without laboratory measurements stemming from the traditional format and Ahlbäck's criteria, however, showed poor agreement with the other criteria. Kellgren's criteria with concomitant pain are comparable to the ACR-criteria, and especially to the ones comprising radiographic criteria. Grade 2 or more ROA according to Kellgren relates to an increased risk of having OA in the future based on the ACR-criteria, and this is the more so for grade 2-4 with simultaneous pain or the severe forms of ROA, grades 3-4.

With all sets of criteria statistically significant associations with several variables could be found, ascertaining construct validity. As a result of the incomplete overlap, the odds ratios varies and this certainly will occur again in future epidemiologic research in the general population.

Since almost all subjects with knee pain are classified as having OA when the

clinical criteria with or without laboratory measurements of the traditional format are applied, we would advice these criteria not to be used in epidemiologic research in the general population.

Ahlbäck's criteria are poorly related to the others, select a low number of cases with possibly severe OA, are likely to be more closely related to cartilage loss, and could constitute an interesting set to study as they showed a relatively strong relationship with factors assumed to point to an increased risk for knee OA. The low prevalence is however a disadvantage.

Future research is needed to gain more insight into the interobserver variability of the criteria, to develop protocols for the assessment of physical signs, and to assess the relationship between cartilage abnormalities and the (ACR) criteria. It is also of value to follow the subgroups of subjects with OA defined by the several sets of criteria over time to determine whether they harbour a different risk of developing more severe OA, pain and disability.

For future epidemiologic research on knee OA it is recommended to obtain, when feasible, a radiograph which can be analyzed independently or as part of the ACR-sets of criteria which contain this parameter. This does not exclude studies using only clinical classification criteria. These are certainly not uninformative.

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ADDENDUM

Table 4.3.A.1. The prevalence of osteoarthritis in the right knee at follow-up in 1988-89 according to several sets of criteria among 2530 subjects examined at baseline during a population study in 1975-78. *

	Number	Prevalence per 1000
Decision tree		
Clinical and laboratory criteria	88	35
Clinical and radiographic criteria	107	42
Clinical criteria	81	32
Traditional format		
Clinical and laboratory criteria	167	66
Clinical and radiographic criteria	84	33
Clinical criteria	175	69
Kellgren with pain	85	34
Ahlbäck with pain	19	8
Pain right knee	181	72

* Twenty subjects without baseline measurement of body mass index excluded

Table 4.3.A.2. The relationship of putative risk factors for knee osteoarthritis with knee osteoarthritis defined by several classification criteria.

	Gender (M=0,F=1)	Age † (50-59 yrs)	Age † (≥ 60 yrs)	BMI ‡ (medium)	BMI ‡ (high)	Meniscectomy
Decision tree						
Clin, lab	2.8 (1.7-4.6)*	1.7 (1.1-2.9)	3.6 (2.1-6.2)	1.1 (0.6-2.0)	2.3 (1.4-4.0)	4.7 (2.5-9.0)
Clin, X-ray	3.7 (2.3-5.9)	1.5 (1.0-2.4)	2.7 (1.6-4.6)	1.0 (0.6-1.8)	2.7 (1.6-4.4)	6.0 (3.4-10.6)
Clin	3.5 (2.1-6.1)	1.8 (1.0-3.0)	4.6 (2.7-8.0)	1.3 (0.7-2.7)	3.5 (1.9-6.4)	6.4 (3.5-12.0)
Traditional format						
Clin, lab	2.4 (1.7-3.5)	1.1 (0.8-1.5)	1.5 (0.9-2.3)	0.9 (0.6-1.4)	1.7 (1.1-2.4)	4.1 (2.4-7.0)
Clin, X-ray	4.3 (2.5-7.6)	1.5 (1.0-2.5)	2.4 (1.3-4.3)	1.0 (0.5-2.0)	2.7 (1.5-4.6)	7.4 (4.1-13.4)
Clin	2.3 (1.7-3.3)	1.1 (0.8-1.5)	1.4 (0.9-2.2)	0.9 (0.6-1.3)	1.6 (1.1-2.3)	3.9 (2.3-6.6)
Kellgren with pain	4.1 (2.3-7.0)	1.6 (1.0-2.6)	2.4 (1.3-4.3)	1.0 (0.5-1.8)	2.3 (1.3-3.9)	6.7 (3.7-12.2)
Ahlbäck with pain	4.9 (1.4-16.8)	2.3 (0.7-7.4)	8.2 (2.7-25.1)	0.5 (0.1-5.4)	8.0 (1.8-35.0)	5.2 (1.5-18.0)

* Odds ratio and 95% confidence interval between parentheses

† Age at baseline with age group < 50 years as reference

‡ Body mass index measured at baseline with lowest tertile of body mass index as reference.

Table 4.3.A.3. The relationship of findings from the baseline medical history with knee osteoarthritis at follow-up defined by several classification criteria.

	Pain knee	Pain walking stairs	Pain rising chair	Stiffness arm/leg	Stiffness rising chair
Decision tree					
Clin, lab	3.7 (2.3-6.1)*	5.9 (3.7-9.2)	6.2 (3.9-9.6)	2.8 (1.8-4.4)	5.7 (3.7-8.8)
Clin, X-ray	3.5 (2.3-5.6)	6.0 (4.0-9.2)	4.9 (3.2-7.4)	3.2 (2.1-4.8)	5.2 (3.5-7.8)
Clin	3.9 (2.4-6.5)	7.1 (4.5-11.3)	6.0 (3.8-9.6)	3.2 (2.0-5.1)	6.4 (4.1-10.0)
Traditional format					
Clin, lab	3.0 (2.1-4.5)	4.3 (3.0-6.3)	4.2 (2.9-5.9)	2.7 (1.9-3.7)	3.8 (2.7-5.3)
Clin, X-ray	3.7 (2.3-6.1)	5.3 (3.3-8.5)	4.8 (3.0-7.7)	3.2 (2.1-5.1)	5.7 (3.6-8.8)
Clin	3.1 (2.1-4.5)	4.2 (2.9-6.0)	4.0 (2.8-5.7)	2.5 (1.8-3.6)	3.6 (2.6-5.1)
Kellgren with pain	3.9 (2.4-6.4)	4.4 (2.7-7.1)	4.2 (2.6-6.8)	3.2 (2.0-5.0)	4.5 (2.9-7.0)
Ahlbäck with pain	4.3 (1.6-11.5)	5.5 (2.1-14.0)	2.9 (1.0-8.0)	3.7 (1.5-9.2)	3.5 (1.4-9.0)

* Odds ratio with 95% confidence interval

Table 4.3.A.4. The relationship of findings from the baseline physical examination with knee osteoarthritis at follow-up defined by several classification criteria.

	Bony enlargement	Function limitation	Bony tenderness	Pain on motion	Heberden's nodes
Decision tree					
Clin, lab	3.3 (1.6-7.2)*	4.1 (1.8-9.4)	7.8 (3.5-17.5)	3.3 (1.0-11.0)	2.2 (1.2-4.3)
Clin, X-ray	3.5 (1.8-7.0)	3.3 (1.5-7.5)	7.3 (3.4-15.9)	3.7 (1.3-10.9)	2.4 (1.3-4.3)
Clin	4.2 (2.0-8.8)	5.4 (2.5-11.7)	10.0 (4.6-22.0)	5.0 (1.7-14.8)	2.7 (1.4-5.1)
Traditional format					
Clin, lab	2.4 (1.2-4.6)	2.4 (1.1-5.1)	5.1 (2.5-10.7)	2.3 (0.8-6.7)	1.9 (1.1-3.2)
Clin, X-ray	4.1 (2.0-8.5)	3.6 (1.5-8.7)	5.6 (2.3-13.8)	4.8 (1.7-14.2)	2.1 (1.1-4.1)
Clin	2.3 (1.2-4.3)	2.3 (1.1-4.8)	4.9 (2.3-10.1)	2.2 (0.8-6.3)	1.9 (1.2-3.2)
Kellgren with pain	4.6 (2.3-9.3)	3.6 (1.5-8.6)	6.8 (2.9-15.8)	4.8 (1.6-14.1)	1.6 (0.8-3.3)
Ahlbäck with pain	6.0 (1.7-21.1)	8.5 (2.4-30.2)	12.9 (3.6-46.2)	10.8 (2.4-49.2)	7.1 (2.7-19.0)

* Odds ratio with 95% confidence interval

Table 4.3.A.5. The relation of putative risk factors for knee osteoarthritis with knee osteoarthritis defined by several classification criteria.

	Gender (M=0,F=1)				Age ┼ (50-59 yrs)				Age ┼ (≥ 60 yrs)			BMI ╪ (medium)				BMI ╪ (high)			Meniscectomy			
	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	OR	SE	RD	X^2	OR	SE	RD	OR	SE	RD	X^2
Decision tree																						
Clin, lab	2.8	0.25	3.2	19	1.7	0.25	1.7	23	3.6	0.28	5.5	1.1	0.31	0.2	15	2.3	0.27	3.1	4.7	0.33	10.1	27
Clin, X-ray	3.7	0.24	4.6	33	1.5	0.23	1.6	16	2.7	0.26	5.0	1.0	0.30	0	26	2.7	0.25	4.3	6.0	0.29	15.0	49
Clin	3.5	0.28	3.4	24	1.8	0.27	1.5	34	4.6	0.28	6.5	1.3	0.36	0.5	26	3.5	0.31	4.0	6.4	0.32	12.7	45
Traditional format																						
Clin, lab	2.4	0.18	5.1	27	1.1	0.18	0.4	2.9	1.5	0.23	2.7	0.9	0.22	-0.4	12	1.7	0.19	3.4	4.1	0.27	14.8	31
Clin, X-ray	4.3	0.29	4.0	30	1.5	0.25	1.4	9	2.4	0.30	1.9	1.0	0.33	0	19	2.7	0.28	3.4	7.4	0.30	14.8	60
Clin	2.3	0.17	5.1	25	1.1	0.18	0.4	2	1.4	0.23	2.4	0.9	0.21	-0.6	12	1.6	0.19	3.4	3.9	0.27	14.5	29
Kellgren with pain	4.1	0.28	3.9	29	1.6	0.25	1.5	9	2.4	0.30	3.3	1.0	0.32	-0.1	15	2.3	0.27	2.9	6.7	0.31	13.6	50
Ahlbäck with pain	4.9	0.63	1.0	8	2.3	0.61	0.5	19	8.2	0.57	2.4	0.5	1.23	-0.1	22	8.0	0.75	1.7	5.2	0.64	2.6	8

OR: odds ratio

SE: standard error of the log odds ratio, lower means smaller confidence interval

RD: risk difference

X^2: Chi-square value, higher means lower p-value

┼ Age at baseline with age group < 50 years as reference, Chi-square value combined for all age strata

╪ Body mass index measured at baseline with the lowest tertile of body mass index as reference, Chi-square value combined for all BMI strata

Table 4.3.A.6. The relation of findings from the baseline medical history with knee osteoarthritis at follow-up defined by to several classification criteria.

	Pain knee				Pain walking stairs				Pain rising chair				Stiffness arm/leg				Stiffness rising chair			
	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2
Decision tree																				
Clin, lab	3.7	0.25	6.9	31	5.9	0.23	10.4	72	6.2	0.23	10.4	81	2.8	0.23	4.6	22	5.7	0.22	9.1	77
Clin, X-ray	3.5	0.23	7.8	34	6.0	0.21	12.7	67	4.9	0.21	10.3	89	3.2	0.21	6.2	34	5.2	0.20	10.1	79
Clin	3.9	0.26	6.8	33	7.1	0.24	11.2	90	6.0	0.24	9.6	74	3.2	0.24	4.9	28	6.4	0.23	9.1	83
Traditional format																				
Clin, lab	3.0	0.20	9.6	34	4.3	0.19	14.1	71	4.2	0.18	13.3	71	2.7	0.17	7.7	34	3.8	0.17	11.6	67
Clin, X-ray	3.7	0.25	6.6	30	5.3	0.24	9.2	60	4.8	0.24	8.2	53	3.2	0.23	5.0	28	5.7	0.23	8.6	72
Clin	3.1	0.19	10.2	36	4.2	0.18	14.2	69	4.0	0.18	13.3	69	2.5	0.17	7.5	31	3.6	0.17	13.3	64
Kellgren with pain	3.9	0.25	7.0	34	4.4	0.25	7.8	43	4.2	0.24	7.4	42	3.2	0.23	5.0	28	4.5	0.23	7.3	51
Ahlbäck with pain	4.3	0.50	1.8	10	5.5	0.48	2.3	16	2.9	0.53	1.2	4	3.7	0.47	1.4	9	3.5	0.48	1.3	8

OR: odds ratio

SE: standard error of the log odds ratio, lower means smaller confidence interval

RD: risk difference

X^2: Chi-square value, higher means lower p-value

Table 4.3.A.7. The relation of findings from the baseline physical examination with knee osteoarthritis at follow-up defined by several classification criteria.

	Bony enlargement				Function limitation				Bony tenderness				Pain on motion				Heberden's nodes			
	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2	OR	SE	RD	X^2
Decision tree																				
Clin, lab	3.3	0.39	6.8	11	4.1	0.42	9.0	13	7.8	0.41	17.3	34	3.3	0.62	6.9	4	2.2	0.33	3.7	6
Clin, X-ray	3.5	0.35	8.7	14	3.3	0.42	8.3	9	7.3	0.39	19.2	35	3.7	0.55	9.7	7	2.4	0.30	4.9	9
Clin	4.2	0.37	8.5	18	5.4	0.40	11.0	22	10.0	0.40	20.2	50	5.0	0.55	10.7	11	2.7	0.32	4.6	10
Traditional format																				
Clin, lab	2.4	0.34	7.5	7	2.4	0.39	7.6	5	5.1	0.38	19.3	23	2.3	0.55	7.3	2	1.9	0.26	5.0	6
Clin, X-ray	4.1	0.37	8.3	17	3.6	0.45	7.3	9	5.6	0.46	12.3	18	4.8	0.55	10.6	10	2.1	0.35	3.2	5
Clin	2.3	0.34	7.2	6	2.3	0.39	7.2	5	4.9	0.38	19.0	22	2.2	0.54	7.0	2	1.9	0.26	5.3	7
Kellgren with pain	4.6	0.36	9.6	22	3.6	0.45	7.3	9	6.8	0.43	14.8	26	4.8	0.55	10.6	10	1.6	0.38	1.8	1
Ahlbäck with pain	6.0	0.64	3.1	10	8.5	0.64	4.7	16	12.9	0.65	7.1	25	10.8	0.77	6.2	15	7.1	0.50	3.3	21

OR: odds ratio

SE: standard error of the log odds ratio, lower means smaller confidence interval

RD: risk difference

X^2: Chi-square value, higher means lower p-value

Table 4.3.A.8. The relationship of radiographic osteoarthritis according to Kellgren grade at baseline with knee osteoarthritis at follow-up defined by several classification criteria.

	Grade 0-1 (n=1265)*			Grade 2-4 (n=239)			Grade 2-4 with pain (n=45)			Grade 3-4 (n=34)		
	n	%	OR	n	%	OR	n	%	OR	n	%	OR
Decision tree												
Clin, lab	56	4.4	1	14	5.9	1.3 (0.7-2.5)+	7	15.6	4.0 (1.7-9.3)	4	11.8	2.9 (1.0-8.5)
Clin, X-ray	60	4.7	1	20	8.4	1.8 (1.1-3.1)	8	17.8	4.3 (1.9-9.7)	7	20.6	5.2 (2.2-12.4)
Clin	49	3.9	1	17	7.1	1.9 (1.1-3.4)	8	17.8	5.4 (2.4-12.1)	6	17.6	5.3 (2.1-13.4)
Traditional format												
Clin, lab	85	6.7	1	25	10.5	1.6 (1.0-2.6)	10	22.2	4.0 (1.9-8.3)	6	17.6	3.0 (1.2-7.4)
Clin, X-ray	41	3.2	1	19	7.9	2.6 (1.5-4.5)	7	15.6	5.5 (2.3-13.1)	7	20.6	7.7 (3.2-18.8)
Clin	90	7.1	1	26	10.9	1.6 (1.0-2.5)	10	22.2	3.7 (1.8-7.8)	7	20.6	3.4 (1.4-8.0)
Kellgren with pain	42	3.3	1	19	7.9	2.5 (1.4-4.4)	8	17.8	6.3 (2.8-14.4)	7	20.6	7.6 (3.1-18.3)
Ahlbäck with pain	8	0.6	1	9	3.8	6.1 (2.4-16.1)	5	11.1	19.6 (4.4-53)	6	17.6	33.7 (11.0-103)

* Reference category for every other category

+ Odds ratio with 95% confidence interval between parentheses

CHAPTER 5

RISK FACTORS

Chapter 5

THE INCIDENCE AND RISK FACTORS OF RADIOGRAPHIC OSTEOARTHRITIS OF THE KNEE IN THE GENERAL POPULATION

ABSTRACT

The incidence and putative risk factors for radiographic OA of the knee were investigated in a 12 year follow-up study of 123 men and 135 women, aged 46 to 66 at baseline. They had participated in a population survey on rheumatic diseases in 1975-78. None of them had a Kellgren score for ROA grade 2 or more for the baseline weight bearing antero-posterior radiographs.

The occurrence of ROA grade 2 or more at follow-up was assessed independently by two observers, without knowledge of any other data.

The incidence of knee ROA was not increased among the older compared to the younger persons. Women had a higher incidence compared to men and this was not due to a difference in body mass index at baseline or age. Body mass index at baseline was related to the occurrence of knee ROA in women but not in men. Other factors like injury of the knee joint; jogging or being a member of a sporting club, previous, early varus or valgus angulations, Heberden's nodes, a clinical diagnosis of generalized OA, and smoking were unrelated to knee OA occurrence. The prevalence of meniscectomy (n=3) and chondrocalcinosis at baseline (n=3) was low and too small to study these putative risk factors fruitfully. Occupation related knee loading or knee damage were not risk factors for knee ROA, with the exception of standing in men where standing was inversely related with knee ROA.

We concluded that gender, and body mass index in women are risk factors of knee ROA and that the increased incidence of knee ROA in women is not the result of a difference in body mass index between men and women.

INTRODUCTION

In the past decades several studies on osteoarthritis of the knee have been conducted in the general population (1,2,3,4,5,6,7). These studies have almost all

been cross-sectional in design. One study was a retrospective follow-up study, but those with osteoarthritis of the knee at baseline were not excluded from the study of putative risk factors of knee OA (7). No follow-up studies have been undertaken on the occurrence and risk factors of OA of the knee in the general population, where subjects free of OA at baseline were followed over time. The advantage of follow-up studies of subjects free of OA over cross-sectional studies is that in the latter it is difficult to be certain whether the risk factor preceded the occurrence of the disease. If this can be ascertained, an important requirement to assess cause and effect is fulfilled. Moreover, sometimes one can not distinguish between a risk factor which influences the occurrence of a disease and a prognostic factor that influences the duration of a disease. A population survey of rheumatic diseases conducted between 1975 and 1978 gave the opportunity to study the incidence and risk factors of radiographic knee OA in a follow-up study.

METHODS

Population survey in 1975-78

Between 1975 and 1978 a population survey was undertaken in the Dutch town Zoetermeer. The aim of this survey was to study the prevalence and risk factors of several chronic diseases, especially rheumatic diseases in the persons of 20 years and older. Data were collected by a self-administered questionnaire, physical examination, radiographs and serum analyses.

With the questionnaire information was obtained about gender, age, current physical activities (jogging), membership of a sporting club and smoking.

Physical examination comprised the measurement of body weight, body length, triceps skinfold thickness, the assessment of Heberden's nodes and a diagnosis of generalized or localized OA. Body weight and length were measured with indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Triceps skinfolds were measured at the left and right arm and the mean of these two measurements was used. The skinfolds were measured in the part of the study and abandoned later because of large interobserver variability. The presence in at least one joint was considered to be positive for Heberden's nodes. A trained physician diagnosed localized or generalized OA based on his physical examination without knowledge of the radiographic findings. A diagnosis of localized OA was made when clinical OA was considered to be present in 1 or 2 joint groups, a diagnosis of generalized OA when 3 or more joint groups were

involved.

Radiographs of the knees were taken in people aged 45 years and over as weight bearing antero-posterior radiographs. These were scored on a five point scale (0-4) in 1975-78 according to the Atlas of Standard Radiographs of Arthritis (8). Two observers scored the first half of the radiographs. Because one observer left the department during the survey, the second part of the radiographs were scored by a single observer (H.A. Valkenburg). If the difference in score between the two observers was two or more or if one had scored 1 (doubtful) and the other had scored 2 (definite, but mild), the radiographs were reviewed by the two observers together during a consensus meeting. A score of grade 2 or more was considered to be positive for radiographic osteoarthritis. The highest score of the two observers was used in the analysis if no consensus reading was needed.

Serum analysis comprised, among others, the assessment of serum uric acid levels.

Follow-up in 1988-89

In 1988-89 a follow-up took place of a random sample of all the subjects born after 1909 who had a radiograph of the knee with ROA grade 0 or 1 in both knee joints and who also had responded to a questionnaire with, among others, questions about knee pain in 1988-89. The selection was based on the score for ROA given by the observers in 1975-78.

The selected subjects were requested to fill in a second self administered questionnaire. This questionnaire included questions about trauma to the knee joint, sporting injuries to the knee joint, meniscectomy and previous, early presence of bow-legs or knock-knees. An occupational history was included with detailed questions about the type of occupation, the number of years of employment in the various jobs, lifting heavy objects, knocking one's knee and other questions about knee loading: hours of walking, standing, squatting, kneeling and crawling. These last three aspects were combined in one question. A score was given for the level of physical activity in the job, based on a scoring list developed by another institution (9).

The radiographs taken at baseline were reevaluated in 1989, independently by two observers according to the same procedures and criteria as in 1975-78. If the score for knee ROA on the radiograph were confirmed to be 0 or 1 the subject was included in the analysis. Only one knee was studied, the knee with the lowest score or one randomly selected if both had the same score. As a result of this procedure the knees with the lowest score were included for the analysis, thereby excluding

doubtful ROA as much as possible.

During the second evaluation in 1989, chondrocalcinosis was scored on a four point scale (0-3), separately for the medial and lateral joint space. The medial and lateral scores were added, because of the small numbers, and the mean score of the two observers combined. A mean score of 0.5 or more was regarded as positive for chondrocalcinosis.

In 1988-89 the radiographs of the knees were taken in the same way and scored according to the same procedures by two physicians as this was done at baseline in 1975-78. A grade 2 or more was considered to indicate the presence of ROA of the knee according to the Atlas of Standard radiographs of Arthritis (8).

STATISTICAL ANALYSIS

The data analysis was performed for men and women separately and limited to those with a measurement for body mass index at baseline. As a result, two subjects were excluded. The characteristics of the men and women were calculated as means with standard deviations or numbers with percentage. To assess the relation with the occurrence of knee ROA, the cumulative incidence and the odds ratio with 95 percent confidence intervals were calculated for several putative risk factors. The cut off point were based on tertiles of the distribution. The answers given by the respondents for occupation-related factors were multiplied with the years of employment in that job and the values for all the jobs a respondent had had were added to form a sum-score. In the analysis cut off points were based on these sum-scores and tertiles were chosen as cut off point. When, however, more than one third had a score of 0, the cut off point was set at 0 and the other cut off point divided the rest in two groups of equal size.

To investigate whether the difference in incidence between men and women was due to a difference in body mass index or age, the odds ratio for gender was calculated after stratification for body mass index at baseline and age. Also, the Mantel Haenszel odds ratio was calculated. BMDP statistical software was used for the calculations (10).

Table 5.1. Characteristics of subjects without radiographic osteoarthritis of the knee at baseline in 1975-78.

	Men	Women
Number	123	135
Duration of follow-up (yrs)	12.6 ± 0.8	12.6 ± 1.1
Age at baseline (yrs)	52.6 ± 5.1	52.8 ± 4.8
Age range at baseline (yrs)	46 - 66	46 - 64
Age at follow-up (yrs)	64.6 ± 5.3	64.9 ± 4.9
Age range at follow-up (yrs)	57 - 79	57 - 76
Body mass index at baseline (kg/m^2)	24.8 ± 2.9	25.3 ± 3.5
Body weight at baseline (kg)	77.3 ± 10.0	67.3 ± 10.1
Uric acid at baseline (mg/100 ml)*	5.4 ± 1.0	4.5 ± 1.1
Triceps skinfold thickness (mm)+	10.3 ± 4.9	21.2 ± 7.3
Meniscectomy	2 (1.6)	1 (0.7)
Injury to the knee joint	6 (4.9)	10 (7.4)
Injury to the knee joint during sport	14 (11.4)	3 (2.2)
Jogging or member of sporting club	15 (12.2)	29 (21.5)
Bow legs or knock-knees	4 (3.3)	8 (5.9)
Chondrocalcinosis	3 (2.4)	0 (0.0)
Heberden's nodes	6 (4.9)	17 (12.6)
Diagnosis of generalized OA	14 (11.4)	27 (20.0)
Diagnosis of localized OA	31 (25.2)	30 (22.2)
Smoking		
Never	15 (12.2)	56 (41.5)
Ex	53 (43.1)	28 (20.7)
Current	55 (44.7)	51 (37.8)
ROA grade 2 or more at follow-up	13 (10.6)	36 (26.7)

Figures are means ± standard deviation or numbers with percentage between parentheses
* n=122 for men and n= 134 for women
+ n=88 for men and n=93 for women

RESULTS

In 1975-78, 2166/2227 persons (97.3%) had a radiograph of the knee taken and 1744/2166 subjects (80.5%) had a grade 0 or 1 in both knees. In the 12 year follow-up period 223/1744 persons (12.8%) had died and 62/1521 (4.0%) of the remaining group was lost to follow-up. The response rate to the questionnaire was 82.1% (1198/1459). Only a random sample of 398 subjects was selected for follow-up examination and 293/398 (73.6%) came for follow-up examination. Details about the differences between responders, non-responders and individuals lost to follow-up are given in appendix A. In 260/293 participants (88.7%) the grade 0 or 1 was confirmed. Of these, 258 who had a measurement of their body weight were included in the analysis.

Characteristics of the study group are presented in table 5.1. As can be seen in this table, the prevalence of meniscectomy and chondrocalcinosis is very low. For the other variables the prevalence ranged from 2.2 to 44.7 percent. The age range at follow-up was 57 to 79 years. After more than 12 years, ROA had occurred in 49 subjects (19.0%): 13 men and 36 women.

In men, as shown in table 5.2, age and anthropometric variables were unrelated to the occurrence of ROA of the knee. The other variables presented in table 5.3 are neither associated with ROA occurrence, although the incidence tended to be increased for meniscectomy, injury to the knee joint, a diagnosis of generalized OA and smoking in the past.

In contrast to the results in men, the occurrence of ROA of the knee was increased in women for higher levels of body mass index at baseline but not significantly so for higher levels of body weight or triceps skinfold thickness (table 5.4). Also in women the incidence of knee ROA was unrelated to age (table 5.4). Table 5.5 shows that the occurrence of knee ROA tended to be increased for injury to the knee joint during sports, but this was not statistically significant.

For the occupation related factors, only standing showed an inverse relation with knee ROA in men but not in women (table 5.6). Women have a higher incidence of knee ROA, compared to men and this is not explained by the influence of body mass index or age (table 5.7). All the occupational scores derived from the answers on questionnaire given by the participants correlated with the score for physical activity independently developed by others (9).

Table 5.2. Numbers and percentages of subjects with radiographic osteoarthritis of the knee and the odds ratios for several categories of age, body mass index, body weight, triceps skinfold thickness and uric acid in a 12 year follow-up study of 123 men from the general population.

	ROA/ total	Percentage	Odds ratio (95% CI)*
Age at baseline (yrs)			
45-49	4/53	7.5	1
50-54	4/29	13.8	1.96 (0.45-8.50)
55-59	3/26	11.5	1.60 (0.33-7.77)
≥ 60	2/15	13.3	1.89 (0.31-11.5)
Body mass index (kg/m^2)			
< 23.63	5/39	12.8	1
23.63-25.83	4/43	9.3	0.70 (0.17-2.81)
> 25.83	4/41	9.8	0.74 (0.18-2.97)
Body weight (kg)			
< 72	5/40	12.5	1
73-81	3/41	7.3	0.55 (0.12-2.49)
> 81	5/42	11.9	0.95 (0.25-3.55)
Skinfold thickness (mm)			
< 7.8	5/29	17.2	1
7.8-11.4	2/28	7.1	0.37 (0.07-2.09)
> 11.4	3/31	9.7	0.51 (0.11-2.38)
Uric acid (mg/100 ml)			
< 5.1	5/40	12.5	1
5.1-5.8	4/42	9.5	0.74 (0.18-2.97)
> 5.8	4/40	10.0	0.78 (0.19-3.14)

* 95% confidence interval

DISCUSSION

In the study presented in this chapter only subjects without radiographic OA of the knee at baseline were selected for follow-up to study the incidence and risk factors of radiographic OA of the knee. The assessment of radiographic OA was based on the grading according to Kellgren, as described in the Atlas of Standard Radiographs of Arthritis, since these were advised to be used for epidemiologic research in the general population (8,11,12). Moreover, in this way the comparability with other large scale population studies on OA and the baseline survey on which this follow-up is based, is maintained (1,2,3,4,5,7).

Population studies on knee OA have shown an increase of the prevalence with

Table 5.3. The cumulative risk for osteoarthritis of the knee and the odds ratios for several variables in a 12 year follow-up study of 123 men from the general population.

	Cumulative incidence (%)		Odds ratio (95% CI) *
	Risk factor		
	Absent	Present	
Meniscectomy	9.9	50.0	9.08 (0.53-154)
Injury to the knee joint	9.4	33.3	4.82 (0.79-29.4)
Sport injury to the knee joint	10.1	14.3	1.49 (0.29-7.52)
Jogging/member sporting club	11.1	6.7	0.57 (0.07-4.74)
Bow legs or knock-knees	10.9	0	§
Chondrocalcinosis	10.8	0	§
Heberden's nodes	11.1	0	§
Diagnosis of generalized OA	9.2	21.4	2.70 (0.64-11.3)
Diagnosis of localized OA	10.9	9.7	0.88 (0.23-3.42)
Smoking			
Never	6.7		
Ex		17.0	2.86 (0.33-24.6)
Current (at baseline)		5.5	0.81 (0.08-8.38)

* 95% confidence interval between parentheses

§ Not statistically significant

age (1,2,5,7). Although in some studies a further increase was not observed in elderly men (1,3,7), in women aged 45 and over (3), and sometimes even a decrease in men and women aged 70-79 was observed (6). But in the last mentioned study other criteria than Kellgren's were used. In our study the age range was 57 to 79 years at follow-up and no statistically significant increase in the incidence of knee ROA with age was seen, neither in men nor in women. The incidence tended to increase in men and to decrease in women, the trend was not statistically significant ($p=0.5$ for men and $p=0.3$ for women). In the original EPOZ-study no increase in the prevalence of knee OA at baseline was observed in the men and this phenomenon repeats itself in this follow-up study since the incidence was not age-related. This could imply that age in the elderly is less relevant as a risk factor for knee OA. This result can also be explained by a cohort effect in that certain birth cohorts are at higher risk for developing OA than others.

Another explanation could be a selection bias, when elderly subjects with OA of the knee tend to come less often to the research centre. This can not be excluded since a complete response was not attained. However, when the relation between pain on the first questionnaire and age ($\geq$ 55 vs $<$ 55 yrs) was studied in the 293 subjects who came for follow-up, the odds ratios were 3.2 (95% CI:1.0-9.9) and 1.0 (95% CI: 0.4-2.3) for men and women respectively. When the analysis was based on the group of 398 subjects invited for follow-up the odds ratios were 2.9 (95% CI: 1.0-8.2) and 1.3 (95% CI:0.5-2.3), respectively. As these odds ratios are virtually the same, this suggests that probably no selection bias has occurred through a mechanism where elderly persons with knee pain tended to come for the follow-up examination more or less often.

Another suggestion to explain the lack of a relation between higher age and knee OA could be selection by mortality of those with knee OA. This has been observed for women in one study (13). This increased mortality was not related to the presence of pain, and therefore assumed not to be related to the side effects of medication like NSAID use. In yet another study the excess mortality was present among patients with OA aged 55 and above and was due to an excess mortality related to gastrointestinal and respiratory diseases (14). The increase in mortality in these studies was however small and in our study the 12 year mortality was 12.8% in those with grade 0-1 (see results section of this chapter) and 13.7% in those with grade 2-4 (table 6.1.1), both figures without adjustments for age or gender.

Further research is needed to determine whether indeed the incidence of knee ROA does not increase at higher age and whether this could be due to changes in (putative) risk factors with age, e.g. joint use and traumatic events.

Table 5.4. Numbers and percentages of subjects with radiographic osteoarthritis of the knee and the unadjusted odds ratio for several categories of age, body mass index, body weight, triceps skinfold thickness and uric acid in a 12 year follow-up study of 135 women from the general population.

	ROA/ total	Percentage	Odds ratio (95% CI)*
Age at baseline (yrs)			
45-49	18/51	35.3	1
50-54	7/35	20.0	0.46 (0.17-1.26)
55-59	7/36	19.4	0.44 (0.16-1.21)
≥ 60	4/13	30.8	0.82 (0.22-3.02)
Body mass index (kg/m^2)			
< 23.32	6/44	13.6	1
23.32-26.37	12/45	26.7	2.30 (0.78-6.82)
> 26.37	18/46	39.1	4.07 (1.43-11.6)
Body weight (kg)			
< 64	8/47	17.0	1
64-70	13/44	29.5	2.04 (0.75-5.55)
> 70	15/44	34.1	2.52 (0.94-6.74)
Triceps skinfold thickness (mm)			
< 17.6	8/30	26.7	1
17.6-23.0	12/32	37.5	1.65 (0.56-4.86)
> 23.0	9/31	29.0	1.13 (0.37-3.45)
Uric acid (mg/100 ml)			
< 4.1	11/41	26.8	1
4.1-4.8	16/52	30.8	1.21 (0.49-3.01)
> 4.8	9/41	22.0	0.77 (0.28-2.11)

* 95% confidence interval

In this study we observed a relation between body mass index at baseline and the occurrence of knee ROA in women but not in men. For women this confirms other

Table 5.5. The cumulative risk for osteoarthritis of the knee and the unadjusted odds ratio for several variables in a 12 year follow-up study of 135 women from the general population.

	Cumulative risk in percentage		Odds ratio (95% CI)*
	Risk factor Absent	Present	
Meniscectomy	26.9	0	§
Injury to the knee joint	27.2	20.0	0.67 (0.14-3.31)
Sport injury to the knee joint	25.8	66.7	5.77 (0.51-65.6)
Jogging/member sporting club	29.2	17.2	0.50 (0.18-1.44)
Bow legs or knock-knees	26.8	25.0	0.91 (0.18-4.74)
Chondrocalcinosis	-┼		
Heberden's nodes	26.3	29.4	1.17 (0.38-3.59)
Diagnosis of generalized OA	27.8	22.2	0.74 (0.27-2.02)
Diagnosis of localized OA	25.7	30.0	1.24 (0.51-3.03)
Smoking			
Never	25.0		
Ex		32.1	1.42 (0.52-3.85)
Current (at baseline)		25.5	1.03 (0.43-2.46)

* 95% confidence interval

┼ No woman with chondrocalcinosis

§ Not statistically significant

studies (6,15,16). In the same studies the relation was less strong for men. In the retrospective follow-up study (15), the study with a design closest to ours, the odds ratio was 1.51 (95% CI: 1.14-1.98) in men for the highest quintile of body mass index compared to the three lowest quintiles, a rather moderate increased risk. Triceps skinfold thickness was related to knee ROA in women but not in men (17), but not after adjusting for age, race, body mass index and subscapular skinfold and inversely related to unilateral knee OA in men after adjusting for the same variables (18). We observed no statistically significant relationship for triceps skinfold.Gender was a strong risk factor for knee ROA in our study, women had a higher incidence

compared to men, confirming the findings from other studies(1,2,5,7). The difference between men and women was not due to a difference in body mass index at baseline or age. This is in contrast with the results of the HANES-study where the higher prevalence of knee ROA in women was partly due to a difference in body mass index and also to triceps skinfold thickness (17).

In the discussion of the other variables it is important to realise that the low

Table 5.6. The relation of several occupation related factors with the occurrence of radiographic knee osteoarthritis in 123 men and 87 women from the general population

	Men	Women
Physical activity		
Medium +	1.86 (0.41-8.38)*	1.75 (0.55-5.51)
High	1.67 (0.37-7.47)	0.96 (0.29-3.18)
Walking		
Medium	0.44 (0.10-1.88)	1.83 (0.56-5.96)
High	0.61 (0.16-2.36)	1.40 (0.41-4.71)
Standing		
Medium	0.17 (0.04-0.86)	2.71 (0.85-8.66)
High	0.18 (0.04-0.88)	1.00 (0.28-3.56)
Squatting, kneeling, crawling		
Medium	1.00 (0.23-4.30)	1.76 (0.54-5.72)
High	1.44 (0.37-5.53)	0.98 (0.27-3.53)
Knee knocking		
Medium	0.99 (0.27-3.66)	2.07 (0.68-6.27)
High	0.46 (0.09-2.36)	0.57 (0.14-2.29)
Lifting heavy objects		
Medium	0.63 (0.16-2.43)	0.77 (0.23-2.59)
High	0.46 (0.11-1.98)	0.62 (0.20-1.89)

* Odds ratio with 95% confidence interval between parentheses

+ Lowest level as reference for every variable

prevalence and the small numbers developing knee OA, especially in men, hampers the interpretation of the results.

For example, we observed no relation with meniscectomy because only a small number had had a meniscectomy. Other factors related to trauma, like injury or injury during sports, were also unrelated to knee OA occurrence although an indication in the direction of a positive association was observed, except for injury in women. Although injury to a joint is generally an accepted risk factor for OA, the reported association between knee OA and injury in the HANES study may have been biased to some extent. In this study the questions about joint trauma were only asked to people with joint complaints, implicitly assuming that those who had no joint complaints also had not sustained an injury. Since more people with OA are included in the group with joint complaints, more people with OA are given the opportunity to give a positive answer on the question about joint trauma and for more subjects without OA, who had no joint complaints, it is assumed that they had not sustained a joint injury. More positive answers about joint about joint trauma in subjects with OA compared to those without therefore results at least partly from the opportunity given to more subjects with OA to give a positive answer.

The occurrence of knee OA could be increased in subjects with Heberden's nodes or a clinical diagnosis of generalized OA since this may reflect a generalized susceptibility, possibly of a genetic origin (19,20). It has also been observed that primary generalized OA influences the development of OA after meniscectomy (21). In chapter 6.1 we report on the prognostic factors of knee ROA. Heberden's nodes or generalized OA were found to be related to cartilage loss. Possibly these factors are not involved in the occurrence of OA but when other factors have caused OA they influence its course resulting from an increase in cartilage loss.

Knee bending on the job and physical demands for the job have been related to knee OA in two studies (16,22) and an increased prevalence has been observed for distinct occupations like mining (23), but no relation between previous strenuous professional work and knee OA was observed in another study (6).

In the two studies which did report a relationship, the knee bending and physical demands were assessed with a independent scoring list, the Dictionary of Occupational Titles, where the physical demand was scored on a five point scale and knee bending as present or absent. In our study we were also able to assess physical demands with a independent scoring list (9).

In contrast with the other studies we observed no relation between physical demands on the job and knee OA occurrence, the positive association observed for

Table 5.7. The relation of gender with the occurrence of radiographic OA in a 12 year follow-up study of 258 men and women from the general population, unadjusted and stratified for body mass index (BMI) at baseline and age.

	Cumulative incidence (%)		Odds ratio (95% CI)
	Men	Women	
Unadjusted	13/123 (10.6)	36/135 (26.7)	3.08 (1.54-6.13)
Stratified for BMI			
Low	5/37 (13.5)	6/47 (12.8)	0.94 (0.26-3.35)
Medium	4/48 (8.3)	11/40 (27.5)	4.17 (1.21-14.4)
High	4/38 (10.5)	19/48 (39.6)	5.57 (1.70-18.2)
MH odds ratio*			2.91 (1.41-6.00)
Stratified for age			
< 55 years	8/82 (9.8)	25/86 (29.1)	3.79 (1.60-9.01)
≥ 55 years	5/41 (12.2)	11/49 (22.4)	2.08 (0.66-6.59)
MH odds ratio*			3.05 (1.51-6.19)

* Mantel-Haenszel odds ratio: the odds ratio adjusted for BMI or age.

men was not statistically significant. The score given to each job was multiplied with the number of employment years in this job. This could have given lower scores for workers with OA if people quit the job early because they had knee joint complaints as a result of OA. However, only one participant had changed his job because of knee joint complaints and none received social security payments because of losing their job as a result of knee pain.

The other occupation related factors were based on a score derived from the answers to the questionnaire. This score revealed no associations or merely associations that pointed in a direction opposite to what was expected. Surprisingly, men who had employed in jobs with increased standing less often developed knee OA but no relation with other, more demanding occupational activities or stress on

the knee joint was observed. This could be due to a healthy worker effect.

The discrepancies between the studies could be due to methodological differences and to overcome part of the differences the scoring methods used in the other studies could be applied to this studies.

In this study no suggested protective effect of smoking could be observed contrary to others (16,24).

In conclusion, in this 12 year follow-up study no relation between age and the occurrence of knee OA was observed. Gender and obesity in women were the strongest risk factors for knee OA. No increased risk was observed for Heberden's nodes, generalized OA, traumas or other increased stress on the knee joint. Smoking was not observed to be protective for knee OA.

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CHAPTER 6

PROGNOSTIC FACTORS

Chapter 6.1

PROGNOSTIC FACTORS OF CARTILAGE LOSS IN OSTEOARTHRITIS OF THE KNEE

ABSTRACT

The natural history and prognostic factors of cartilage loss in knee OA were studied in subjects from a general population survey on rheumatic diseases in 1975-78. Baseline data were collected by questionnaire, physical examination and weight-bearing antero-posterior knee X-rays. Follow-up of the subjects aged 46-68 with radiological OA grade 2-4 (Kellgren) took place in 1988-89. Cartilage loss was assessed by two observers who scored the change in joint space width between two X-rays.

Thirty-four percent had cartilage loss. Prognostic factors and adjusted odds ratios with 95% confidence intervals were: body mass index (BMI) OR=11.1 (3.3-37.3) 4-th vs 1-st quartile; body weight OR=7.9 (2.6-24.0) 3-rd vs 1-st tertile; triceps skinfold OR=32.4 (2.2-475) 3-rd vs 1-st tertile; age OR=3.8 (1.1-13.4) > 60 vs ≤ 49 yrs; Heberden's nodes OR=6.0 (1.5-23.1), generalized OA OR=3.3 (1.3-8.3), and previous bow legs or knock knees OR=5.1 (1.1-23.1). There was no statistically significant relation for gender, meniscectomy, injury, uric acid, chondrocalcinosis, smoking and occupation related factors, except possibly standing.

INTRODUCTION

Insight into the natural history and prognostic factors of a disease is needed to influence the course of the disease. For such a common condition as osteoarthritis (OA) of the knee, however, surprisingly little is known about the natural history and prognostic factors (1,2,3). The few longitudinal studies on the natural history (4,5,6,7) showed that the outcome based on symptoms, signs and radiological changes varied greatly between subjects. However, these studies concerned only few persons, were retrospective in design and most often based on selected patients from a hospital. Moreover, few prognostic factors were studied. Therefore, they were of limited value for the study of prognostic factors to explain the variability in

outcome. In a large longitudinal, population based study, the National Health and Nutrition Examination Survey-I Epidemiologic Follow-up Study, the natural history of radiological OA of the knee was studied with mortality, symptoms and functional limitations as outcome (8). Changes in radiological signs of OA, however, were not investigated. Only pain and swelling at baseline were evaluated as prognostic factors for pain and functional ability as outcome, but others were not.

Several prognostic factors could possibly explain the variability in outcome of knee OA. Obesity is believed to be a prognostic factor since patients with knee OA are advised to reduce their weight (9). Although plausible in relation to cartilage damage due to increased loading, little evidence exists whether weight reduction prevents progression. In one study it was reported that obesity was a prognostic factor (10), but no relationship was found in two other studies (5,7). Chondrocalcinosis could also be a prognostic factor because a relation with the severity of OA has been observed (11,12), although this could not be confirmed in a population based study (13). Generalized OA may reflect a genetic predisposition to the development of OA in several joints (14), sometimes due to an abnormality of type II collagen gene (15,16,17). Mechanical influences, increased joint use and traumatic events like a meniscectomy have been suggested as prognostic factors for cartilage defects (18).

There is a need to elucidate factors that can prevent progression of knee OA, and for which longitudinal studies are preferred. In a general population survey for the study of rheumatic diseases, that took place in the general population between 1975 and 1978, data were collected to study the natural history and prognostic factors of cartilage loss in knee OA. The results of this study are presented in this chapter.

METHODS

Population survey in 1975-78

From 1975 to 1978 a population survey was undertaken in the Dutch town Zoetermeer. The aim of this survey was to study the prevalence and risk factors of several chronic diseases, especially rheumatic diseases in the persons of 20 years and older. Data were collected by a self-administered questionnaire, physical examination, radiographs and serum analyses.

In the questionnaire information was obtained about gender, age, current physical activities, membership of a sporting club and smoking.

Physical examination comprised the measurement of body weight, body length, triceps skinfold thickness, the assessment of Heberden's nodes and a diagnosis of generalized or localized OA. Body weight and length were measured with indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Triceps skinfolds were measured at the left and right arm and the mean of these two measurements was used. The skinfolds were measured only during the first part of the study and abandoned later because of large interobserver variability. The presence in at least one joint was considered to be positive for Heberden's nodes. A physician diagnosed localized OA or generalized OA based on his physical examination without knowledge of the radiographic findings. A diagnosis of localized OA was made when clinical OA was considered to be present in 1 or 2 joint groups, a diagnosis of generalized OA when 3 or more joint groups were involved.

Radiographs of the knees were taken in people aged 45 years and over as weight bearing antero-posterior radiographs. These were scored on a five point scale (0-4) in 1975-78 according to the Atlas of Standard Radiographs (19). Two observers scored the first half of the radiographs. Because one observer left the department during the survey, the second part of the radiographs were scored by a single observer (Prof. Dr H.A. Valkenburg). If the difference in score between the two observers was two or more or if one had scored 1 (doubtful) and the other had scored 2 (definite, but mild), the radiographs were reviewed by the two observers together during a consensus meeting. A score of grade 2 or more was considered to be positive for radiological osteoarthritis. In the case no consensus reading was necessary the highest score of the two observers was used in the analysis.

Serum analysis comprised, among others, the assessment of serum uric acid levels.

Follow-up in 1988-89

In 1988-89 a follow-up took place of all the subjects born after 1909 who had a radiograph taken of the knees and also had ROA grade 2 or more in at least one knee joint. The selection was based on the score given by the observers in 1975-78.

The subjects with ROA grade 2 or more at baseline were requested to fill in a self administered questionnaire. This questionnaire included questions about trauma to the knee joint, sporting injuries to the knee joint, meniscectomy and previous, early presence of bow-legs or knock-knees. An occupational history was also included with detailed questions about the type of the occupation, the number of years of employment in these jobs, lifting heavy objects, knocking one's knee and

other questions about knee loading: hours of walking, standing, squatting, kneeling and crawling. These last three aspects were combined in one question. A score based on a scoring system developed by another institution was given for physical demands of the jobs (20).

The radiographs taken at baseline were reevaluated in 1989 independently by two observers according to the same procedures and criteria as in 1975-78. If the score for knee ROA on the radiograph was confirmed to be 2 or more then the subject was included in the analysis. For those who had bilateral ROA only one randomly assigned knee was used in the analysis. During the second reading in 1989, chondrocalcinosis was scored on a four point scale (0-3), separately for the medial and lateral joint space. The medial and lateral scores were added, because of the small numbers, and the mean score of the two observers combined. A mean score of 0.5 or more was regarded as positive for chondrocalcinosis.

In 1988-89 the radiographs of the knee joint were taken in the same way as was done at baseline in 1975-78. The progression of cartilage loss was assessed independently by two observers without any knowledge of other data. The observers scored the change in jointspace width between the radiograph taken at baseline and the radiograph taken at follow-up with the two radiographs placed side by side on the screen. The score, on a nine-point scale, ranged from -4 to +4 depending on whether there was a decrease or increase in joint space width. Change in joint space width was scored for the medial and lateral side separately. The mean of the scores of the two observers was calculated and used in the analysis except when the difference was 3 or more or if one had scored -2 and the other 0 or -1 and +1. These radiographs were judged again during a consensus meeting of the two observers. With this procedure coding errors were corrected and discrepancies around the point of yes or no change were critically reviewed. When in the lateral and medial compartment the joint space width had decreased, the side with the largest mean decrease was used in the analysis. When on both sides the joint space width had increased the compartment with the smallest increase was used in the analysis. When the joint space had increased on one side but had decreased on the other the side with the decrease was used in the analysis. A (mean) score of -1 or lower was considered to indicate progression of cartilage loss.

STATISTICAL ANALYSIS

Firstly, the (baseline) characteristics for the total group were calculated and cutoff-

points determined for several continuous variables. Age was categorized in five-years age intervals. Cutoff-points for body mass index were quartiles and cutoff-points for body weight, skin fold thickness and uric acid were tertiles. The scores based on the answers to the questionnaire for occupation-related factors or the score for physical activity during work were multiplied with the years of employment in that job and all these values were added for all the jobs a respondent had had to form one sum-score. In the analysis cutoff-points were based on these sum-scores and tertiles were chosen as cutoff-point. When, however, more than one third had a score of 0, the cutoff-point was set at 0 and the other cutoff-point divided the group with a score

Table 6.1.1. Response, radiological diagnoses and cartilage loss in subjects with radiological osteoarthritis of the knee.

	Number (%)
ROA grade 2 or more at baseline	422
Died	58 (13.7)
Lost to follow-up	36 (8.5)
Eligible for follow-up	328 (77.7)
Response	239 (72.9)
Radiographs judged in 1989	233
ROA grade 2 after reevaluation	142 (100)
Bilateral OA	51 (35.9)
Right knee	95 (66.9)
Left knee	98 (69.0)
Radiographs from 1975-78	
Grade 2 (1989 score)	121 (85.2)
Grade 3 or 4 (1989 score)	21 (14.8)
Radiographs from 1988-89	
Grade 0 or 1	15 (10.6)
Grade 2	58 (40.8)
Grade 3 or 4	69 (48.6)
Cartilage loss	48 (33.8)

of more than 0 in two groups of equal size.

Secondly, the percentage of subjects with cartilage loss was calculated for several prognostic factors. The odds ratios and 95% confidence intervals were calculated as the measure of effect and precision, respectively. Thirdly, a logistic regression model was used to adjust for possible confounders. Every variable was adjusted for age, gender and body mass index.

Table 6.1.2. Characteristics of subjects with radiological osteoarthritis of the knee.

Duration of follow-up (yrs)	12.2 ± 0.9
Age at baseline (yrs)	57.2 ± 6.1
Age range at baseline (yrs)	46 - 68
Age at follow-up (yrs)	68.8 ± 6.1
Age range at follow-up (yrs)	58 - 79
Body mass index (kg/m^2)	26.4 ± 3.0
Body weight (kg)	73.9 ± 10.5
Skin fold thickness (mm)†	17.3 ± 8.4
Uric acid (mg/100 ml)‡	5.1 ± 1.4
Gender (M/F)	58/84 (40.8/59.2)
Meniscectomy	13 (9.2)
Injury to the knee joint	27 (19.0)
Injury to the knee joint during sport	19 (13.4)
Jogging or member of sporting club	25 (17.6)
Bow legs or knock-knees	10 (7.0)
Chondrocalcinosis	13 (9.2)
Heberden's nodes	15 (10.6)
Diagnosis of generalized OA	38 (26.8)
Diagnosis of localized OA	47 (33.1)
Smoking	
Never	53 (37.3)
Ex	44 (31.0)
Current	45 (31.7)

Figures are means ± standard deviation or number with percentage between parentheses
† n=80
‡ n=141

RESULTS

Table 6.1.1 gives the response and radiographic findings in 1975-78 and 1988-89. In 1975-78 422 subjects were judged to have ROA in at least one knee joint. Fifty-eight subjects had died and 36 were lost to follow-up. In 1988-89, after a mean duration of follow-up of 12.2 years, 239 subjects came to the research centre for follow-up examination. This gave a response rate of 72.9 per cent. Details about differences between responders and non-responders are given in appendix A. After reevaluation of the baseline radiographs, the presence of ROA grade 2 or more was confirmed in 142 persons. Thirty-four per cent had cartilage loss in the affected joint over a 12 years time period. Characteristics of the subjects are given in table 6.1.2.

In tables 6.1.3 and 6.1.4 the percentage of subjects with cartilage loss and the unadjusted odds ratios with 95 per cent confidence intervals are shown for several prognostic factors. Body mass index, body weight, uric acid, and chondrocalcinosis, Heberden's nodes and a diagnosis of generalized OA were all significantly related to cartilage loss. Age, triceps skinfold thickness, gender, meniscectomy, (sport) injury to the knee joint, bow legs or knock-knees, jogging or member of a sporting club, diagnosis of localized OA, and smoking did not show a relation with cartilage loss.

Tables 6.1.3 and 6.1.4 also show the results after adjusting for the potential confounders age, gender and BMI. Age, BMI, weight, triceps skinfold thickness, bow legs or knock knees, Heberden's nodes and generalized OA were significantly related to cartilage loss. However, adding Heberden's nodes or generalised OA to the model with gender, BMI and age reduced the odds ratios for the age strata and they lost statistical significance (OR (95% CI): 2.05 (0.54-7.94), $\geq$ 60 yrs vs. 45-49 yrs). The relation between chondrocalcinosis and cartilage loss was confounded as was shown by the reduction of the odds ratio after adjusting for age, gender and BMI. This relationship was confounded most by BMI, after adjusting for age and gender alone the OR (95% CI) was 3.12 (0.92-10.5). Of the occupation related factors only standing (medium versus lowest tertile) was statistically related to cartilage loss (table 6.1.5).

DISCUSSION

In this study OA of the knee was assessed in the general population according to the methods described by Kellgren (19). These criteria are used most often in epidemiological research and were recommended at two international congresses as

Table 6.1.3. Cumulative risks, unadjusted and adjusted odds ratios of categorized continuously distributed prognostic factors for cartilage loss in 142 subjects with radiological osteoarthritis of the knee from the general population.

	progression/ total	(%)	Odds Ratio (95% CI)*	Adjusted odds ratio (95% CI)*
Age (yrs) ┼				
45-49	5/22	(22.7)	1	1
50-54	10/36	(27.8)	1.31 (0.38-4.50)	2.21 (0.57-8.66)
55-59	9/31	(29.0)	1.39 (0.39-4.92)	1.94 (0.49-7.61)
> 60	24/53	(45.3)	2.82 (0.90-8.76)	3.84 (1.10-13.4)
Body mass index (kg/m^2) ╪				
< 24.35	5/35	(14.3)	1	1
24.35-25.96	7/34	(20.6)	1.56 (0.44-5.49)	1.77 (0.48-6.50)
25.97-27.73	14/36	(38.9)	3.82 (1.20-12.2)	5.28 (1.54-18.1)
> 27.73	22/37	(59.5)	8.80 (2.78-27.9)	11.1 (3.28-37.3)
Weight (kg) ╪				
< 69	7/45	(15.6)	1	1
69-78	16/51	(31.4)	2.48 (0.91-6.74)	2.95 (1.03-8.46)
> 78	25/46	(54.3)	6.46 (2.39-17.46)	7.94 (2.62-24.0)
Skin fold thickness (mm) ╪ §				
< 12.0	9/27	(33.3)	1	1
12.0-19.8	12/26	(46.2)	1.71 (0.56-5.21)	28.3 (2.49-321)
> 19.8	9/27	(33.3)	1.00 (0.32-3.10)	32.4 (2.21-474)
Uric acid (mg/100 ml) ‖				
< 4.3	10/45	(22.2)	1	1
4.3-5.4	17/48	(35.4)	1.92 (0.77-4.81)	1.05 (0.36-3.00)
> 5.4	21/48	(43.8)	2.72 (1.10-6.73)	1.36 (0.46-4.02)

* 95% confidence interval

┼ Adjusted for gender and body mass index

╪ Adjusted for gender and age

§ n=80

‖ Adjusted for age, gender, body mass index; n=141

Table 6.1.4. Cumulative incidence, unadjusted and adjusted odds ratios of categorized prognostic factors for cartilage loss in 142 subjects with radiological osteoarthritis of the knee from the general population.

	Cumulative incidence (%)		Odds Ratio (95% CI) ┼	Adjusted OR* (95% CI) ┼
	Prognostic factor Absent	Present		
Gender (M=0, F=1) ╪	39.7	29.8	0.65 (0.32-1.30)	0.50 (0.22-1.11)
Meniscectomy	32.6	46.2	1.78 (0.56-5.61)	2.28 (0.57-9.03)
Injury to the knee joint	30.4	48.1	2.12 (0.90-4.98)	2.62 (0.93-7.36)
Sport injury to the knee joint	35.0	26.3	0.66 (0.22-1.97)	0.62 (0.17-2.19)
Jogging/member sporting club	35.9	24.0	0.56 (0.21-1.52)	0.53 (0.17-1.68)
Bow legs or knock knees	31.8	60.0	3.21 (0.86-12.0)	5.13 (1.14-23.1)
Chondrocalcinosis	31.0	61.5	3.56 (1.10-11.6)	2.01 (0.55-7.42)
Heberden's nodes	29.9	66.7	4.68 (1.50-14.6)	5.97 (1.54-23.1)
Diagnosis of generalized OA	25.0	57.9	4.13 (1.89-9.02)	3.28 (1.30-8.27)
Diagnosis of localized OA	32.6	36.2	1.17 (0.56-2.43)	1.17 (0.51-2.72)
Smoking				
Never	32.1		1	1
Ex		38.6	1.33 (0.58-3.08)	1.07 (0.38-3.04)
Current (at baseline)		31.1	0.96 (0.41-2.25)	0.96 (0.34-2.75)

* Odds ratio adjusted for age, gender and body mass index
┼ 95% confidence interval
╪ Adjusted for age and body mass index

the best classification method available for epidemiologic research (19,21,22). To improve the diagnosis of knee ROA, the radiographs were reevaluated and only the radiographs with a grade 2 or more ROA on two separate readings, in 1975-78 and 1988-89, were included in the analysis. This reevaluation enhances the specificity by excluding false positive radiographs. Of the 233 radiographs scored in 1989, 142 (61%) were judged again to have ROA grade 2. The large number excluded was partly due to the fact that half of the 233 films were read by a single observer

Table 6.1.5. Unadjusted and adjusted odds ratios of several occupation related prognostic factors for cartilage loss in 105 subjects with radiological osteoarthritis of the knee from the general population who had been or still are employed.

	Unadjusted odds ratio † (95% CI) ‡	Adjusted odds ratio * † (95% CI) ‡
Physical activity		
Medium	1.28 (0.48-3.38)	1.50 (0.48-4.69)
High	1.00 (0.37-2.69)	0.43 (0.11-1.76)
Walking		
Medium	1.85 (0.67-5.13)	2.09 (0.61-7.20)
High	1.98 (0.72-5.44)	1.47 (0.36-6.03)
Standing		
Medium	3.45 (1.20-9.95)	3.80 (1.03-13.96)
High	2.57 (0.87-7.61)	2.09 (0.43-10.31)
Squatting, kneeling, crawling		
Medium	0.67 (0.25-1.81)	1.18 (0.36-3.89)
High	0.42 (0.15-1.22)	0.31 (0.09-1.04)
Knee knocking		
Medium	0.51 (0.19-1.35)	0.71 (0.22-2.24)
High	0.56 (0.21-1.50)	0.36 (0.11-1.15)
Lifting heavy objects		
Medium	0.92 (0.35-2.46)	1.00 (0.33-3.02)
High	0.96 (0.36-2.51)	0.65 (0.19-2.28)

* Adjusted for age, gender and BMI
† Lowest level as reference for every prognostic factor
‡ 95% confidence interval

(Prof. Dr. H.A. Valkenburg) in 1975-78. Of these radiographs only 55% were considered to have ROA when reevaluated in 1989 compared to 80% of the radiographs read by two observers in 1975-78. Most likely, this one observer preferred to score with a high sensitivity but with a concomitant low specificity, in the case of doubtful radiographs, in order not to loose information.
Cartilage loss is regarded as the central pathological feature of osteoarthritis and was therefore used as the outcome for disease progression. Cartilage loss could be

assessed by joint space difference between two radiographs taken more than 12 years apart. Joint space narrowing is, according to the participants in a validation study of radiographic OA progression, the most important variable to assess progression of knee osteoarthritis (10). The same study showed that joint space narrowing has good inter-reader agreement, test retest correlation and construct validity in the identification of the correct time sequence of two radiographs. Moreover, judging the change in joint space width was found to be superior compared to measuring the joint space in detecting the correct time sequence of two consecutive radiographs (10).

On the other hand, cartilage thickness measured on antero-posterior radiographs was correlated with actual cartilage thickness during pathological examination of seven knees (correlation coefficient: 0.88) (23). However, more cartilage damage could be detected during pathological examination and this is in accordance with another study which showed that cartilage thickness on radiographs was found to correlate imperfectly with cartilage defects seen during arthroscopy (24). How these results can be applied to the detection of cartilage loss by judging change in joint space width remains to be a subject for further study. For the time being no other method is available for the study of progression of osteoarthritic abnormalities in epidemiological research. Moreover, if non-differential misclassification can be assumed to be present, the observed relations would be stronger.

In our study the radiographs were read as pairs to detect even small changes. For the assessment of radiographic changes of rheumatoid arthritis it has been shown that reading films in pairs increases accuracy in detecting changes and reduces variability compared to two separate readings (25). The readings of change in joint space width was done without any knowledge of the other data except, of course, the presence of chondrocalcinosis on the first radiograph, excluding the possibility of information bias.

In this study, there was a relationship between age and cartilage loss after adjusting for BMI and gender but this relationship became less strong and non-significant after adjusting for Heberden's nodes or generalized OA. Although women, compared to men tended to have cartilage loss less often, women had more often severe progression when progression of cartilage loss had occurred.

Body mass index, body weight and triceps skinfolds were found to be related to cartilage loss in subjects with knee ROA (table 6.1.3). These results confirm the observation of Altman et al that obesity was related to OA progression (10). Moreover, this result supports the advice given to patients with knee OA to reduce weight.

Interleukin-1 could play a role in the pathogenesis of OA. It reduces the production of proteoglycanes by the chondrocytes and stimulates the formation of metallo-proteinases which reduces cartilage matrix (26). Interleukin-1 could result from joint inflammation, for example in gout and pseudogout. It may therefore be hypothesised that progression of cartilage loss is more severe when high levels of uric acid are present or when chondrocalcinosis is present in the joint. Moreover, more severe OA occurs in patients with chondrocalcinosis (11,12). In this study there was a relationship of cartilage loss with chondrocalcinosis and uric acid but this was reduced after adjusting for age, gender and BMI.

The relationship of cartilage loss with Heberden's nodes and a clinical diagnosis of generalized OA suggests some systemic influence on cartilage or a cartilage abnormality that is present in all the joints. It is known that Heberden's nodes and generalized OA cluster in families (14). Recent research has shown that coinheritance of generalized OA with specific alleles of the gene for type II collagen may occur in these families (15,16) and in some families a single base mutation in the type II procollagen gene is present (17). This finding is also in accordance with the observation of Doherty et al who showed that primary generalized OA predisposes to the development of secondary OA in the knee after meniscectomy (27), confirming that generalized OA reflects some general influence on cartilage or a cartilage abnormality that is present in all the joints.

Injury to the knee joint and especially meniscectomy are unrelated to cartilage loss in persons with knee ROA, although the odds ratios were above 1 and almost statistically significant for injury after adjusting for potential confounders. An effect of meniscectomy on cartilage loss can not be excluded because of the small number of subjects with a meniscectomy in this study.

Bow legs or knock knees were also related to cartilage loss. Valgus or varus deformity induces cartilage and bone changes similar to those found in OA in animal experiments (28). Moreover, the results support the idea that tibial osteotomy could be beneficial in knee OA (29). However, since the question about bow legs or knock knees was asked in 1988-89 a recall bias can not be excluded completely.

Repetitive impulse loading may lead to progressive cartilage loss (18). In certain occupations the stress on the joint may be increased and kneebending requirement on the job is related to knee OA occurrence (30,31). This makes it of interest to study the relationship between cartilage loss and several occupational factors related to knee loading and trauma. A relationship is found in this study between occupation-related standing and cartilage loss. Moreover, when walking and

standing were included together in one model the odds ratios for standing were slightly increased but for walking they were reduced considerably, suggesting a harmful effect of standing. Possibly, a lack of cyclic loading or continued pressure associated with standing influences cartilage metabolism and results in cartilage loss (32,33). Moreover, Anderson found a low frequency of localized OA in a group who had to walk 0.25 miles or more at work (34). It must be realized, however, that a selection of those with a predisposition to develop progressive OA for jobs with activities where knee loading is reduced might have occurred (healthy worker effect). This could also explain why no effect of other, more traumatic, occupation related factors was found.

Jogging or being a member of a sporting club and sporting injury were unrelated to cartilage loss. Possibly, this also reflects a kind of "healthy worker effect". For sporting injury it may also be that the question was not accurate enough because it was not asked which knee had sustained the injury. On the other hand it may be that these activities were all within a physiological range since the cartilage will adapt to its requirements. Immobilization leads to thinning of the cartilage and reduced proteoglycan production in animals (35) and repetitive loading leads to increased production of cartilage matrix components (36,37). The lack of repetitive impulse loading in people standing at their work could also explain the relation of standing with cartilage loss.

In addition to the above analysis of the data, a stratified analysis was performed to gain an impression of whether an alteration of the selection criterium for the presence of knee OA would lead to different results. As was pointed out in chapter 4, the choice of classification criteria can influence the association between a putative risk factor and the occurrence of knee OA. We therefore did an analysis for the group with knee pain and ROA at baseline in contrast to the group with ROA but without knee pain. Furthermore, the group of 142 subjects was divided based on the grade of severity of radiographic OA at baseline. The results are presented in appendix B. They will not be discussed in detail but it is worth mentioning that for age, body mass index, weight, Heberden's nodes and a diagnosis of generalized OA the odds ratios were higher both in the group with knee pain at baseline compared to the one without and in the group with more severe ROA contrasted to the one with mild ROA, suggesting that corresponding results will be found in groups of people in whom knee OA is diagnosed applying other sets of criteria. More research in larger groups of subjects with knee OA is, however, needed to confirm our findings. For the other variables there was seldom significant heterogeneity between the odds ratios of the two strata but for some the impression

emerged that the odds ratios indeed were different. For more details the reader is referred to tables B.1 to B.6 of appendix B.

In conclusion, this study shows that cartilage loss is not always progressive in subjects with knee ROA. Obesity, weight, triceps skinfold thickness, Heberden's nodes and a diagnosis of generalized OA were all related to cartilage loss over a 12 years time period. No effect could be shown of chondrocalcinosis or uric acid after adjusting for age, gender and BMI. Traumatic events tended to be related to cartilage loss but sporting injuries and sporting activities or high stresses to the joint during work, except standing, were unrelated to cartilage loss in subjects with knee ROA.

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Chapter 6.2

THE EFFECT OF BODY MASS INDEX AND CHANGE IN BODY WEIGHT ON THE PROGRESSION OF KNEE OSTEOARTHRITIS AND KNEE PAIN

ABSTRACT

The objective of this study was to investigate the effect of body mass index and change in body weight on progression of knee osteoarthritis and future knee pain. A 12 year follow-up study was conducted in 142 subjects with radiographic osteoarthritis of the knee identified during a population survey on rheumatic diseases in two districts in the Dutch town Zoetermeer. The main outcome measures were the presence of knee pain at follow-up, change in joint space width (cartilage loss), growth of osteophytes, and overall progression based on the comparison of two antero-posterior weight bearing radiographs. Body mass index at baseline was related to cartilage loss, growth of osteophyte and overall progression even after adjusting for age and gender. Change in body weight over time in either direction was unrelated to any of the measures of OA progression. Baseline body mass index was related to knee pain at follow-up even after adjusting for age and gender. This relation was much weaker after adjustments were made for progression of knee OA. Body weight change was unrelated to knee pain at follow-up. We concluded that a high body mass index, but not a change in body weight, has an adverse effect on the progression of knee OA. A high body mass index also has an adverse effect on future knee pain, probably by affecting progression of knee OA.

INTRODUCTION

The possibilities to influence the course of osteoarthritis (OA) are limited. One of the few advices generally given to patients with knee OA is to reduce their weight (1). Whether weight reduction influences the course of knee OA or the presence of future pain is, however, unknown. Moreover, although an effect of obesity on the occurrence of knee OA has been shown (2,3,4), the effect on the course of knee

OA has not extensively been studied and small studies have lead to equivocal results (5,6,7). A follow-up study was therefore conducted of all the subjects with radiographic knee OA who had been identified during a population survey in 1975-78 and prognostic factors of knee OA were evaluated. The primary aim of this study was to investigate the effect of body mass index (BMI) and a change in body weight on the progression of knee OA and the presence of future pain. In addition, it was studied whether the effect on the presence of future knee pain was due to the effect on the progression of OA.

METHODS

Baseline survey in 1975-78

From 1975 to 1978 a population survey was conducted in two districts of the Dutch town Zoetermeer (n=10,646, response 78%). The aim of this survey was to study several chronic diseases, especially rheumatic diseases. Data were collected by a self-administered questionnaire, physical examination, and joint radiology. Body weight and body length were measured without shoes but with indoor clothing. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Antero-posterior weight bearing radiographs of the knees were made in people 45 years and older. These were scored on a five point scale (0-4) in 1975-1978 according to the Atlas of Standard Radiographs (8) without knowledge of any other data. Two observers scored the first half of the radiographs and the second half was scored by one observer (Prof. H.A. Valkenburg, originally trained by J.H. Kellgren and J.S. Lawrence and standardized against the latter where population survey films are concerned). When the difference in score between the two observers was two or more or if one had scored 1 (doubtful) and the other had scored 2 (definite), the radiographs were judged again by the two observers together during a consensus meeting. A score of grade 2 or more was considered to be definite radiographic osteoarthritis (ROA).

Follow-up in 1988-89

In 1988 a questionnaire about knee pain was sent to all the participants in 1975-78 born between 1909 and 1959. They were asked whether they had had knee pain of at least one week duration in the preceding year and/or currently had this pain.

In 1988-89 a follow-up examination took place of all the subjects born after 1909 who had a radiograph of the knees taken at baseline and had a score for

ROA of grade 2 or more. The same questions about knee pain were asked as in the first follow-up questionnaire, an antero-posterior weight bearing radiograph of the knee joints was taken, and body weight and length measured according to the same methods as in 1975-78. The radiographs taken at baseline in 1975-78 and at follow-up were judged (again) in 1989 independently by two observers according to the same criteria and procedures as described above. If the score for knee ROA given in 1975-78 was confirmed to be 2 or more the subject was included in the analysis. For those who had bilateral ROA one randomly assigned knee was used in the analysis. Subjects were considered to have knee pain at follow-up if they had given a positive answer to any of the two questions on both questionnaires and if the knee pain was related to the affected knee used in the analysis.

At the time of the follow-up examination the radiographs of the knee joint were taken the same way as in 1975-78. Overall progression, cartilage loss and osteophyte growth were assessed independently by two observers who had no knowledge of the other data. These outcome variables were scored with the two radiographs placed side by side. For cartilage loss the change in jointspace width between the two radiographs was scored on a nine-point scale, ranging from -4 to +4 depending on whether their was a decrease or increase in joint space width respectively. This change was scored for the medial and lateral side separately. The mean of the scores of the two observers was calculated. However, if the difference between the observers was 3 or more or when one had scored +1 and the other -1 or one had scored -2 and the other 0 the radiographs were judged again to reach consensus. When the change was different for the two knee compartments, lateral and medial, the side with the severest loss of cartilage or the smallest increase in joint space width was used in the analysis. A mean score of -1 or lower, was considered to indicate cartilage loss. Osteophyte growth was scored on four joint margins, lateral and medial tibia and femur. For every joint margin a score was given on a five point scale (0-4) and the four scores were summed. The sum scores of the observers were combined to calculate the mean which could range from 0-16. A score of 5 or more was considered to indicate osteophyte growth. The overall progression was based on an overall score for changes of radiographic signs of OA on a five point scale (0-4). A score of 2 or more for the mean of the two observers was considered to indicate overall progression. The cut off points for the outcome variables were assessed before the analysis of any association was undertaken.

STATISTICAL ANALYSIS

Firstly, the means of several anthropometric variables were calculated as well as the mean change in these variables over time.

Secondly, the number and percentage with cartilage loss, osteophyte growth, overall progression, and knee pain for three categories of baseline BMI and body weight change were calculated. The categories were based on the tertiles of the distributions of these variables. After this, the unadjusted and gender and age adjusted odds ratios with 95% confidence intervals of the second and third category compared to the lowest category were calculated by using a logistic regression model. For change in body weight adjustments were also made for body weight at baseline.

Thirdly, the relation of baseline BMI with future pain was investigated further by introducing the variables for progression of OA in the model. If baseline BMI is related to future knee pain because it causes more progression of OA, the odds ratio's of BMI for knee pain will be reduced after introducing the variables for progression in the model. The putative confounding factors age, baseline body weight and BMI were put in the model as continuous variables. All the confidence

Table 6.2.1. Characteristics of the subjects with radiographic osteoarthritis OA of the knee.

Number	142
Number of women	84 (59.2)
Age at baseline (yrs)	57.2 ± 6.05
Body mass index at baseline (kg/m^2)	26.4 ± 2.96
Body mass index at follow-up (kg/m^2)	26.8 ± 3.77
Change in body mass index (kg/m^2)	0.42 ± 2.52
Body weight at baseline (kg)	73.9 ± 10.47
Body weight at follow-up (kg)	73.8 ± 11.45
Change in body weight in (kg)	-0.004 ± 6.50
Knee pain at follow-up	27 (19.0)
Changes in ROA in 12 years :	
Cartilage loss	48 (33.8)
Growth of osteophytes	58 (40.8)
Overall progression	85 (59.9)

Figures are means ± standard deviation or number with percentage between parentheses

intervals are 95% confidence intervals. The analyses were done with BMDP statistical software (9).

RESULTS

In 1975-78 422 out of 2227 respondents had ROA grade 2 or more. In the 12 years between baseline survey and follow-up 58 persons had died and 36 were lost to follow-up. The response rate of those eligible was 72.9 percent, 239 of 328. Differences between responders and non-responders are presented in appendix A. All baseline radiographs except 6 could be scored again and 142 were confirmed to

Table 6.2.2. Numbers, percentages, unadjusted and adjusted odds ratios for cartilage loss, osteophyte growth and overall progression index in subjects with radiographic OA of the knee for tertiles of baseline body mass.

	Baseline body mass index (kg/m^2)		
	≤ 24.91 (n=46)	24.92-26.95 (n=46)	≥ 26.96 (n=50)
Cartilage loss :			
Number (%)	7 (15.2)	13 (28.3)	28 (56.0)
Unadjusted odds ratio	1	2.19 (0.78-6.14)*	7.09 (2.66-18.9)
Adjusted for age, gender	1	2.71 (0.92-7.95)	8.47 (3.00-24.0)
Osteophyte growth :			
Number (%)	12 (26.1)	17 (37.0)	29 (58.0)
Unadjusted odds ratio	1	1.66 (0.68-4.04)	3.91 (1.65-9.28)
Adjusted for age, gender	1	1.68 (0.68-4.15)	3.71 (1.55-8.92)
Overall progression :			
Number (%)	18 (39.1)	27 (58.7)	40 (80.0)
Unadjusted odds ratio	1	2.21 (0.96-5.08)	6.22 (2.50-15.5)
Adjusted for age, gender	1	2.42 (1.02-5.73)	5.97 (2.36-15.1)

* 95% confidence interval within parentheses

Table 6.2.3. Numbers, percentages, unadjusted and adjusted odds ratios for knee pain at follow-up in subjects with radiographic OA of the knee for tertiles of body mass index at baseline.

	Body mass index at baseline (kg/m^2)		
	≤ 24.91 (n=46)	24.92-26.95 (n=46)	≥ 26.96 (n=50)
Number (%)	3 (6.5)	6 (13.0)	18 (36.0)
Unadjusted odds ratio	1	2.15 (0.50-9.17)*	8.06 (2.19-29.7)
Adjusted for:			
Age	1	2.37 (0.55-10.3)	7.89 (2.13-29.3)
Gender	1	2.15 (0.49-9.40)	7.79 (2.05-29.5)
Age, gender	1	2.31 (0.52-10.2)	7.43 (1.95-28.4)
Cartilage loss	1	1.84 (0.42-8.03)	5.35 (1.37-20.8)
Osteophyte growth	1	1.98 (0.46-8.54)	6.50 (1.72-24.6)
Overall progression	1	1.59 (0.36-7.13)	4.75 (1.22-18.5)
Cartilage loss, osteophyte growth, and overall progression	1	1.43 (0.31-6.52)	3.85 (0.94-15.8)
All variables	1	1.47 (0.30-7.27)	3.85 (0.87-17.1)

* 95% confidence interval within parentheses

have ROA grade 2 or more.

In this group 36/142 (25%) had knee pain of at least one week duration currently or in the past 12 months in *either* knee on the first questionnaire, which was confirmed in 33/36 (92%) on the second questionnaire. Twenty-nine out of thirty-six (81%) had at least one day of knee pain in the previous month and 25/36 (69%) more than 14 days. In those who confirmed the answers these figures were 27/33 (82%) and 24/33 (73%) respectively, and in those who had not answered positive to any of these questions on the first questionnaire these figures were 2/106 (2%) and 0/106 respectively. Medication for knee pain was used by 15/36 (42%) of the subjects who answered positive on the first questionnaire, and 14/33 (42%)

among those who confirmed the presence of pain on the second, compared to 1/106 (0.9%) among those without knee pain on the first questionnaire. On the second questionnaire 53/142 (37%) answered positive on one or both questions, and 33/53 (62%) had already answered this on the first questionnaire.

Table 6.2.1 presents some characteristics of the participants. The mean change in BMI was small (0.42 kg/m^2) as well as the mean change in body weight (-0.004 kg) although the variability in change was considerable. Table 6.2.2 shows that baseline BMI is a strong prognostic factor for cartilage loss, osteophyte growth as well as for overall progression of knee OA. Baseline BMI was related to future knee pain, also after adjusting for age and gender (table 6.2.3). After introducing the variables for OA progression in the model, the odds ratios reduced considerably (table 6.2.3). There was no effect of change in body weight on progression of OA or pain as is shown in tables 6.2.4 and 6.2.5. Similarly, change in BMI was not associated with knee OA progression or future pain while the relation of baseline body weight with OA progression was comparable to baseline BMI, where the adjusted odds ratios were related to future knee pain and decreased after

Table 6.2.4. Number, mean changes of body weight and body mass index, baseline body weight and body mass index, and cumulative incidence for cartilage loss, osteophyte growth and overall progression in subjects with radiographic OA of the knee in three tertiles of body weight change.

	Body weight change (kg)			
	≤ -3.0 (n=49)	-2.0-2.0 (n=50)	≥ 3.0 (n=43)	p-value
Body weight change (kg)	-6.5	0.1	7.3	< 0.0001
BMI change (kg/m^2)	-1.9	0.5	3.0	< 0.0001
Baseline body weight (kg)	76.4	72.7	72.2	0.1
Baseline BMI (kg/m^2)	26.7	26.1	26.3	0.6
Cartilage loss	18 (36.7)	14 (28.0)	16 (37.2)	0.6
Osteophyte growth	18 (36.7)	18 (36.0)	22 (51.2)	0.3
Overall progression	29 (59.2)	28 (56.0)	28 (65.1)	0.7
Knee pain at follow-up	9 (18.4)	9 (18.0)	9 (20.9)	0.9

Figures are means or numbers with percentage between parentheses

introducing the parameters for progression of OA in the model (data not shown).

DISCUSSION

Persons with radiographic knee OA were identified from the general population according to the criteria described by Kellgren (8). This diagnosis was confirmed by two independent observers who reevaluated the radiographs. The assessment of cartilage loss, osteophyte growth and overall progression was done with the

Table 6.2.5. Unadjusted and adjusted odds ratio for cartilage loss, osteophyte growth and overall progression in subjects with radiographic OA of the knee for tertiles of baseline body weight change.

	Body weight change (kg)		
	≤ -3.0 (n=49)	-2.0-2.0 (n=50)	≥ 3.0 (n=43)
Cartilage loss :			
Unadjusted odds ratio	1	0.67 (0.29-1.56)*	1.02 (0.44-2.38)
Adjusted for age, gender	1	0.84 (0.34-2.06)	1.43 (0.57-3.60)
Adjusted for baseline body weight	1	0.85 (0.34-2.11)	1.45 (0.58-3.62)
Adjusted for all	1	0.91 (0.34-2.42)	1.81 (0.67-4.86)
Osteophyte growth :			
Unadjusted odds ratio	1	0.97 (0.43-2.20)	1.80 (0.78-4.15)
Adjusted for age, gender	1	0.82 (0.34-1.93)	1.53 (0.63-3.72)
Adjusted for baseline body weight	1	1.13 (0.48-2.64)	2.21 (0.92-5.27)
Adjusted for all	1	0.90 (0.36-2.22)	1.84 (0.72-4.67)
Overall progression:			
Unadjusted odds ratio	1	0.88 (0.40-1.95)	1.29 (0.55-3.00)
Adjusted for age, gender	1	0.74 (0.31-1.73)	1.11 (0.44-2.75)
Adjusted for baseline body weight	1	1.00 (0.44-2.29)	1.50 (0.63-3.59)
Adjusted for all	1	0.80 (0.32-1.98)	1.26 (0.49-3.25)

* 95% confidence interval within parentheses

radiographs placed side by side to discover even small changes. Change in jointspace width (cartilage loss) and change in osteophyte size were judged to be valid phenomena to assess progression which also had reasonable test-retest and interobserver variability, and to be the two most important variables seen on radiographs to score progression of OA of the knee (5).

BMI at baseline had a strong effect on every variable for OA progression. These results confirm the suggestion of Altman et al of an effect of obesity on knee OA progression (5) and could explain why obesity is related to physical disability like walking difficulties in patients with arthritis (10). Patients with obesity were found to be more often disabled compared to patients with normal BMI. This could partly be due to an effect of obesity on the progression of knee OA which ultimately leads to more severe knee joint abnormalities as seen on radiographs. Further support for such a mechanism is found in our study. The effect of BMI on knee pain also seems (partly) be due to an effect of BMI on progression of osteoarthritic abnormalities (table 6.2.3).

The presence of pain in 19% of this group with radiographic OA is low. From cross-sectional studies it is known that ROA is poorly related to pain (11,12,13,14). Our prevalence of pain is lower compared to others but may be the result of the different questions concerning knee pain. For example, in two studies the respondents were asked "Have you had pain in or around the knee (including the back of the knee) on most days for at least one month ?" (13,14). Such a question can be answered positive even if this period has occurred many years ago. Moreover, even in these two studies where the same question was asked the prevalences differed greatly. In one study the overall prevalence of pain was 19.2% and 40.0% for grade 2 and grade 3-4 ROA respectively (13), and in the other study 39% and 61% for grade 2 and grade 3-4 respectively (14). Moreover, in some publications it is not clear whether the presence of pain was assessed in the affected OA knee. When the occurrence of pain is assessed as being present in either knee, an increase in the prevalence of knee pain will be the result.

In our study, of those who answered positive on the first questionnaire, 92% confirmed the questions, 82% had knee pain of one day or more in the previous month compared to 2% in those with negative answers and 42% used medication for knee pain. We have excluded those who had knee pain more than 12 months ago and selected a group with more recent knee pain of some chronicity for which medication was used in a considerable number of people. The lack of pain is not the result of the use of medication since only one subject without knee pain according to our definition used medication for knee pain. Moreover, it was indeed

possible to find an association between progression of knee OA and our definition of knee pain. It also shows that when radiographic OA is studied the occurrence of future knee pain is low and therefore the presence of knee ROA does not inevitably lead to pain.

Surprisingly, we observed no effect of body weight change on knee OA progression or future knee pain. One could question whether the contrast in change between the three categories is large enough to show a difference in progression or future presence of knee pain. We believe the contrast in the two extremes of body weight change (mean: -6.5 and +7.3 kg; median: -6.0 and +6.0 kg respectively) to be large enough to expect some effect and such a difference in change is also within a range that can be realized in clinical practice since attaining and keeping a lower weight over longer periods of time is difficult. For example, in several trials on the effect of weight reduction on blood pressure change, the weight reduction ranged from -2.0 to -7.4 kg (15). However, it could be that weight reduction should be more extreme to be effective. This is suggested by a study in grossly obese subjects who underwent gastroplasty and where an extreme reduction of weight (mean 44 kg) occurred concurrently with a reduction of joint complaints (16). This study lacked, however, a control group.

It is also possible that those with painful knees related to more progression may have followed the advice to reduce their body weight which masked the relation between the change in body weight and progression. On the other hand OA progression could go with an increase in body weight when more progression leads to more pain and less physical activity. However, if the analysis was limited to those with or without pain at baseline no relation between change and future knee pain or progression could be observed. Moreover, it is unlikely that a change in physical activity in such an elderly population will be dramatic, since their level of physical activity is already at a low range.

Furthermore, the body weight change could have occurred recently and therefore does not reflect a sustained change. One would hardly expect an effect of recent changes present for a short period of time. However, in 1985-86, 69 women from this study had participated in an earlier study on osteoporotic fractures (17). In 1988-89 their mean change in body weight was -6.2, -0.2, and 7.8 kg for the lowest (n=15), middle (n=27), and highest (n=27) tertile of change in body weight respectively. In 1985-86, the corresponding mean changes were -2.3, -0.3, and 6.7 kg respectively. This suggests that the observed changes are not recent but reflect a sustained change over longer periods of time.

As described in chapter 6.1 an additional analysis was performed to determine

whether the results would stand when the analysis was repeated in a group with another definition of knee OA. The group was therefore stratified for pain at baseline and severity of radiographic OA. These results are presented in appendix B, tables B.7 and B.8. These additional analyses tend to support our findings described above but for osteophyte growth no effect of baseline body mass index was seen in the group with severe radiographic knee OA. For knee pain in future the odds ratios were higher for the group with knee pain at baseline compared to those without and for those with severe radiographic knee OA compared to those with mild ROA, again for baseline body mass index. For the change in body mass index the additional analysis gave similar results Some odds ratios were higher in the group with knee pain compared to the one without and for the group with severe ROA compared to the one with mild ROA, but no statistically significant heterogeneity was apparent.

More research, in larger groups of patients with knee OA is certainly indicated to investigate whether these results can be confirmed. More statistical power is needed to exclude with more certainty that no effect of change in body weight on progression of knee OA exists.

We conclude that in this observational study no clear evidence exists for an effect of body weight change on the progression of knee OA, although BMI at baseline is highly related to progression of knee OA as well as the presence of future pain. But pain likely results in part from the effect of BMI on progression of OA. More research is indicated and a trial directed towards sustained weight reduction could be highly informative but will be difficult to execute. The short term effect of weight reduction on pain has not been studied, as far as we know, but could be worth trying.

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Chapter 6.3

INSULIN-LIKE GROWTH FACTOR-1: A PROGNOSTIC FACTOR OF KNEE OSTEOARTHRITIS

ABSTRACT

During a population survey in 1975-78, persons with radiographic osteoarthritis (ROA) of the knee were identified. After 12 years a follow-up study was conducted to study the effect of circulating insulin-like growth factor-1 (IGF-1) on cartilage loss, osteophyte growth and overall progression in 141 persons with confirmed ROA of the knee. The outcome measures were scored by comparing the radiographs taken at baseline and at follow-up. Insulin-like growth factor-1 was measured by radioimmunoassay in serum taken at follow-up and in 79% of the baseline sera. After adjusting for age, gender and body mass index at baseline, IGF-1 concentration at follow-up was related to osteophyte growth and overall progression. The adjusted odds ratio of the highest versus the lowest tertile was 2.96 (95% CI: 1.15-7.60) for osteophyte growth and 2.58 (1.01-6.60) for overall progression. No relationship was found with cartilage loss. These results were confirmed when baseline IGF-1 was studied. We conclude that the circulating IGF-1 concentration has an effect on the course of knee OA by influencing osteophyte formation but not by preventing cartilage loss.

INTRODUCTION

Despite its high prevalence (1), very little is known about the natural history of osteoarthritis. Although originally the view was held that in osteoarthritis only cartilage loss occurs, it has been shown that cartilage metabolism is enhanced, leading to an increased synthesis of proteoglycanes and collagen (2,3,4). This increased anabolic activity is seen as an attempt of repair of the cartilage damage (5) and might slow net cartilage loss. It is therefore of interest to study the factors that stimulate cartilage synthesis.

One of these could be insulin-like growth factor-1 (IGF-1). IGF-1 stimulates chondrocytes to synthesise proteoglycanes and collagen in in-vitro experiments

(6,7,8). Moreover, in patients with OA the anabolic activity of synovial fluid from OA joints is partly due to IGF-1 (9). Further evidence for an anabolic effect of IGF-1 on cartilage in adults comes from studies in acromegalic patients where joint spaces are wide (10,11). In men as well as women with OA it was found that IGF-1 levels were lower compared to controls with a similar age and weight distribution (12). No difference in IGF-1 levels was found in female patients with OA (13).

These equivocal results are difficult to explain but it might be that IGF-1 could not only have an anabolic effect on cartilage, leading to less or less severe OA, but also have an effect on juxta-articular bone formation and osteophyte growth, leading to more or more severe signs of OA, larger osteophytes and more sclerosis, as seen on radiographs. This hypothesis is supported by the findings that in acromegaly increased bone formation occurs (14). Also, skeletal mass seems to increase after administering growth hormone in normal elderly men and in animal experiments (15,16).

The studies on IGF-1 mentioned above have all been cross-sectional and no longitudinal study has been published to investigate the effect of IGF-1 on the course of OA in humans. A follow-up study was therefore undertaken of all the persons with radiographic knee OA from a population survey among 10646 persons in 1975-78. The aim of the study was to investigate, among others, the effect of IGF-1 on the course of OA by focusing on the effect on cartilage formation and growth of osteophytes separately.

METHODS

Population survey in 1975-78

Between 1975 and 1978 a population survey was conducted in the Dutch town Zoetermeer (response 78%) to study several chronic diseases and, especially, rheumatic diseases in the persons of 20 years and older. Data were collected by a self-administered questionnaire, physical examination, joint radiology and serum analyses.

Body weight and length were measured without shoes but with indoor clothing. Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2).

Radiographs of the knees were taken in people 45 years and older as weight bearing antero-posterior radiographs. These were scored on a five point scale (0-4) in 1975-1978 according to the Atlas of Standard Radiographs of Arthritis (17). Two observers scored the first half of the radiographs and the second half was scored by

one observer (H.A. Valkenburg). If the difference in scores between the two observers was two points or more or if one had scored 1 (doubtful) and the other had scored 2 (definite), the radiographs were judged again by the observers together during a consensus meeting. A score of 2 or more was considered to be definite radiographic osteoarthritis (ROA). In 1975-78 422 out of 2227 respondents born after 1909 had ROA grade 2 or more in at least one knee.

Serum was stored at -20° C.

Follow-up study in 1988-89

In 1988-1989 a follow-up took place of all the subjects aged 46-68 years in 1975-78 with ROA grade 2 or more in at least one knee joint. The selection was based on the score given by the observers in 1975-78. The subjects with ROA grade 2 or more at baseline were invited for a follow-up examination which included a weight-bearing antero-posterior radiograph of the knee joints and blood sampling. In the 12 years between baseline survey and follow-up 58 persons had died and 36 were lost to follow-up. The response rate of those eligible for the follow-up study was 72.9 percent, 239 of 328.

The radiographs taken at baseline were judged again in 1989 independently by two observers (JSAG and HAV) according to the same criteria and procedures as described above. If the score for knee ROA on the radiograph taken in 1975-78 was confirmed to be 2 or more the subject was included in the analysis. For those who had bilateral ROA one randomly assigned knee was used in the analysis. All radiographs except 6 could be reevaluated and in 142 of the 233 subjects (61%) the diagnosis of ROA grade 2 or more was confirmed. The number excluded was partly due to the fact that the second half of the films was read by a single observer (HAV) in 1975-78. Of these radiographs only 55% were considered to have ROA when reevaluated in 1989 compared to 80% of the radiographs read by two observers in 1975-78. This one observer preferred to score with a high sensitivity but with a concomitant low specificity in order not to loose information. Blood could be taken from 141 participants and these were included in the analysis.

At the time of the follow-up the radiographs of the knee joint were taken the same way as it was done at baseline in 1975-78 and scored for ROA (Kellgren score) according to the same methods and procedures as described above. Joint space width was measured and rounded to the nearest millimetre by two observers on all the radiographs. The mean of the two observers was calculated separately for the lateral and medial joint space. The size of the osteophytes was scored on four joint margins, lateral and medial tibia, and femur. Each joint margin was scored on

a four-point scale (0-3) and the four scores were summed to arrive at one sum score. These observer sum scores were combined to calculate the mean, which could range from 0 to 12. Each observer scored these radiographic signs of OA independently and without knowledge of any other data, including the scores for the other radiograph.

The overall progression, cartilage loss and osteophyte growth were also assessed independently by these two observers who had no knowledge of the other data. These outcome variables were scored with the two radiographs placed side by side. For cartilage loss the observers scored the change in joint space width between the two radiographs on a nine-point scale, ranging from -4 to +4, depending on whether there was a decrease in joint space width or an increase respectively. Change in joint space width was scored for the medial and lateral side separately and the mean of the two observers was calculated. If, however the difference between the observers was 3 or more or when one had scored +1 and the other -1 or one had scored -2 and the other 0 the radiographs were judged again during a meeting of the two observers to reach a consensus score for change in joint space. When there was a difference in change between the two knee compartments, lateral and medial, the compartment with the severest loss of cartilage or the smallest increase in joint space width was used in the analysis. Osteophyte growth was scored on four joint margins, lateral and medial tibia, and femur. For every joint margin a score was given on a five point scale (0-4) and the scores were summed for all the joint margins. The sum scores of the observers were combined to calculate the mean which could range from 0 to 16. A score of more than 4.0 was considered to indicate osteophyte growth. The overall progression was based on an overall score for changes of radiographic signs of OA on a five point scale (0-4). A score of 2 or more for the mean of the two observers was considered to indicate overall progression. The cutoff-points for the outcome variables were determined before the analysis of any association was undertaken. At the follow-up serum was sampled and stored at -20° C.

The IGF-1 concentration was measured by radioimmunoassay using commercially available kits (Medgenix Diagnostics, Fleurus, Belgium) (18). The intra-assay variation of IGF-1 measurement amounted 5.6% and the inter-assay variation was 11.6%. Although the IGF-1 levels were measured in serum taken at baseline and serum at follow-up the values for the IGF-1 concentration at follow-up were used in the analysis and presented in this article since baseline serum was only available in 112/141 respondents (79.4%).

STATISTICAL ANALYSIS

The analysis consisted of several parts. The associations of gender, age and BMI measured at baseline with IGF-1 were assessed with linear regression analysis and p-values calculated. The same calculations were made for joint space width, osteophyte size, Kellgren score at baseline and at follow-up; and for overall progression, cartilage loss and osteophyte growth. IGF-1 was the dependent variable and the residuals were normally distributed even conditionally on all the independent variables.

Table 6.3.1. Characteristics of the subjects with radiographic osteoarthritis of the knee.

Number of subjects	141
Number of women	83 (58.9)
Age at baseline (yrs)	57.4 ± 6.34
Body mass index at baseline (kg/m^2)	26.3 ± 2.87
IGF-1 at follow-up (nmol/l)	16.6 ± 5.66
IGF-1 at baseline (nmol/l) +	19.6 ± 6.65
Changes over 12 years:	
Number with cartilage loss	47 (33.3)
Number with growth of osteophytes	58 (41.1)
Number with overall progression	84 (59.6)

Figures are means ± standard deviation or numbers with percentage within parentheses
+ n = 112

Secondly, the relationship between gender, age and baseline BMI with overall progression, cartilage loss and osteophyte growth was assessed with logistic regression analysis. Furthermore, the study population was categorised in three groups based on the tertiles of the distribution of the IGF-1 concentration at follow-up. The number and percentage showing overall progression, cartilage loss and osteophyte growth were calculated for every category of IGF-1 concentration. Unadjusted odds ratios were calculated with the group with the lowest level of IGF-1 as the reference. In addition, odds ratios were calculated adjusted for the

confounders age, gender and BMI. For this last part of the analysis a logistic regression model was used. The confidence intervals are 95% confidence intervals with the Z-value of 1.96 used for calculating the confidence intervals. All the analyses were done with BMDP statistical software (19).

RESULTS

Baseline characteristics, mean IGF-1 concentrations and overall changes in radiographic signs of OA are shown in table 6.3.1. Differences between responders and non-responders are described in appendix A. Table 6.3.2 shows the regression coefficients of several variables with IGF-1 as the dependent variable. IGF-1 concentration decreases with age and tends to increase with body mass index at

Table 6.3.2. The regression coefficients of age, gender, baseline body mass index, baseline IGF-1 and several radiographic signs of osteoarthritis with IGF-1 concentration (nmol/l) as the dependent variable in subjects with osteoarthritis of the knee.

Variable	Regression Coefficient	Standard error	P-value (2-sided)
Age (years)	-0.170	0.078	0.03
Gender (male as reference)	-1.249	0.966	0.20
Body mass index (kg/m^2)	0.073	0.167	0.66
IGF-1 at baseline (nmol/l)*	0.583	0.063	< 0.0001
Joint space at baseline (mm)	0.196	0.392	0.6
Joint space at follow-up (mm)	0.453	0.298	0.13
Score for cartilage loss	0.400+	0.412	0.33
Size of osteophytes at baseline	0.305	0.226	0.18
Size of osteophytes at follow-up	0.488	0.169	0.005
Score for growth of osteophytes	0.291	0.145	0.046
Kellgren score at baseline	0.853	1.175	0.47
Kellgren score at follow-up	0.672	0.557	0.23
Score for overall progression	0.734	0.417	0.08

* n = 112

\+ positive means less loss with increasing concentration of IGF-1

baseline. Joint space width tends to increase and cartilage loss tends to decrease with increasing levels of IGF-1 but there was no statistical significance. Osteophyte size and growth were both positively associated with IGF-1. This association remained statistically significant after adding age, gender and baseline BMI as independent variables to the model (data not shown). IGF-1 concentrations did not increase for higher Kellgren scores. However, overall progression tended to be higher when IGF-1 was high. This association became statistically significant after

Table 6.3.3. The odds ratio of the possible confounders age, gender and baseline body mass index (BMI) for cartilage loss, osteophyte growth and overall progression in subjects with osteoarthritis of the knee.

	Cartilage loss	Osteophyte growth	Overall progression
Gender	0.62 (0.31-1.26)*	2.07 (1.02-4.18)	1.96 (0.99-3.91)
Age (per 5 years)	1.47 (1.09-1.99)	1.09 (0.83-1.44)	1.24 (0.93-1.64)
BMI (per 5 kg/m^2)	3.57 (1.80-7.06)	3.53 (1.80-6.94)	4.58 (2.13-9.82)

* 95% confidence interval within parentheses

adding age, gender and baseline BMI as independent variables to the model (data not shown).

Table 6.3.3 gives the relationship of the confounders age, gender and baseline BMI with three outcome variables. Women have more often growth of osteophytes and possibly more overall progression. In the elderly cartilage loss was increased. BMI is related to cartilage loss, osteophyte growth and overall progression.

Tables 6.3.4 to 6.3.6 give the results of the analysis of the association between IGF-1 and several variables of radiographic OA progression. In table 6.3.4 it is shown that cartilage loss was unrelated to IGF-1 levels although cartilage loss tended to be higher in the middle tertile compared to the lowest especially after adjusting for age, the most important confounder. Adjusting for several confounders did not result in an association between IGF-1 and cartilage loss. IGF-1 was related to osteophyte growth and this relationship was even stronger after adjusting for several confounders (table 6.3.5). The overall progression was increased in the group

with the highest level of IGF-1 after adjusting for several confounders (table 6.3.6). A logistic regression analysis with the baseline IGF-1 concentration as independent variable instead of IGF-1 at follow-up confirmed the findings presented in this article.

Table 6.3.4. Number with cartilage loss, cumulative incidence and unadjusted and adjusted odds ratio for several levels of IGF-1 in subjects with radiographic osteoarthritis of the knee.

	Concentration of IGF-1 (nmol/l)		
	≤ 13.7 (n=47)	13.8-18.3 (n=45)	≥ 18.4 (n=49)
Number with progression	12	19	16
Cumulative incidence (%)	25.5	42.2	32.7
Unadjusted odds ratio	1	2.13 (0.88-5.16)*	1.41 (0.58-3.43)
Odds ratio adjusted for:			
Age	1	2.44 (0.98-6.07)	1.80 (0.71-4.56)
Gender	1	2.11 (0.87-5.13)	1.30 (0.53-3.21)
Body mass index	1	2.15 (0.84-5.50)	1.43 (0.56-3.68)
Age, gender, body mass index	1	2.33 (0.88-6.21)	1.54 (0.56-4.21)

* 95% confidence interval within parentheses

DISCUSSION

The subjects with radiographic osteoarthritis were identified first during a population survey in 1975-78 according to the methods described by Kellgren (17). The presence of ROA was confirmed by two observers before the subjects were included in the analysis. Radiographs were judged side by side for progression to have the greatest sensitivity of detecting changes. It has been shown that this method is the most sensitive for detecting changes in rheumatoid arthritis progression compared to reading the radiographs separately (20). Moreover, judging joint space narrowing was found to be superior to measuring the joint space in detecting the correct time sequence of two consecutive radiographs (21).

Cartilage loss and growth of osteophytes were studied separately because, based

Table 6.3.5. Number with osteophyte growth, cumulative incidence and unadjusted and adjusted odds ratio for several levels of IGF-1 in subjects with radiographic osteoarthritis of the knee.

	Concentration of IGF-1 (nmol/l)		
	≤ 13.7 (n=47)	13.8-18.3 (n=45)	≥ 18.4 (n=49)
Number with progression	15	18	25
Cumulative incidence (%)	31.9	40.0	51.0
Unadjusted odds ratio	1	1.42 (0.61-3.34)*	2.22 (0.97-5.10)
Odds ratio adjusted for:			
Age	1	1.47 (0.62-3.49)	2.42 (1.03-5.68)
Gender	1	1.49 (0.62-3.56)	2.68 (1.12-6.37)
Body mass index	1	1.35 (0.54-3.36)	2.33 (0.96-5.64)
Age, gender, body mass index	1	1.46 (0.57-3.73)	2.96 (1.15-7.60)

* 95% confidence interval within parentheses

on the literature, one could hypothesize that high IGF-1 levels prevented cartilage loss but stimulated osteophyte growth. The IGF-1 concentrations used in the analysisand used to present the results in this article were those measured at follow-up because only 112 subjects had serum left from the baseline survey. These subjects are a selected group because they were less often female and had less often osteophyte growth when compared to those of whom no serum was left. On the other hand, the levels of IGF-1 at follow-up correlated well with IGF-1 at baseline (table 6.3.2) and the main findings were confirmed if these baseline IGF-1 concentrations were used in the logistic regression analyses (data not shown).

One of the main findings of this study is a relation of IGF-1 with osteophyte growth especially after adjusting for age, gender and baseline BMI (tables 6.3.2 and 6.3.5). The adjustments were made for age, gender and BMI at baseline as it is known that these factors are related to IGF-1 concentrations (22). In the present study they are also related to several outcome variables (table 6.3.3). The BMI at baseline was chosen to adjust and not the BMI at follow-up because one can not exclude that the level of BMI at follow-up is (partly) the result of inactivity due to

Table 6.3.6. Number with overall progression, cumulative incidence and unadjusted and adjusted odds ratio for several levels of IGF-1 in subjects with radiographic osteoarthritis of the knee.

	Concentration of IGF-1 (nmol/l)		
	≤ 13.7 (n=47)	13.8-18.3 (n=45)	≥ 18.4 (n=49)
Number with progression	24	27	33
Cumulative incidence (%)	51.1	60.0	67.3
Unadjusted odds ratio	1	1.44 (0.63-3.29)*	1.98 (0.86-4.52)
Odds ratio adjusted for:			
Age	1	1.55 (0.67-3.58)	2.34 (0.99-5.53)
Gender	1	1.50 (0.65-3.49)	2.33 (0.99-5.51)
Body mass index	1	1.29 (0.53-3.14)	1.96 (0.81-4.77)
Age, gender, body mass index	1	1.43 (0.57-3.60)	2.58 (1.01-6.60)

* 95% confidence interval within parentheses

pain resulting from OA of the knee. From an etiological point of view it is preferable to measure the determinant and confounders before the outcome occurs. Moreover, including body weight at baseline instead of or in addition to BMI led to similar results (data not shown).

This finding of an association between osteophyte growth and IGF-1 was confirmed by a linear regression analysis of the size of the osteophyte at follow-up on IGF-1 levels (table 6.3.2). Even after adjusting for age, gender and baseline BMI the relation between IGF-1 and osteophyte size at follow-up was still present in the linear regression analysis (data not shown). High levels of IGF-1 within a physiological range for the elderly therefore probably stimulate osteophyte growth and confirms the finding that growth hormone, probably via IGF-1, stimulates bone formation (14,16,15). In another, small study of women a clear relationship between IGF-1 and bone density was, however, confounded by age (23). Furthermore, these results of our study might explain the inverse relation found between osteoporosis and osteoarthritis (24).

As described in chapter 6.1 a stratified analysis was done, with the stratification

based on the presence or absence of knee pain at baseline or based on the severity of the radiographic OA at baseline. These analyses showed higher odds ratios for osteophyte growth and overall progression in the group with knee pain at baseline compared to those without and for the group with severe ROA compared to the group with mild ROA. In appendix B the details are presented.

No influence on cartilage loss could be detected in our study. The relationship between IGF-1 and joint space width at follow-up tended to be positively correlated in the linear regression analysis but the logistic regression analysis pointed in another direction but neither analysis was statistically significant. Finding no association is unexpected because in-vitro research has shown a clear effect of IGF-1 on proteoglycan and collagen formation (6,7,8). Moreover, joint space width tends to be wider in acromegaly (10,11). Higher levels are possibly needed to affect cartilage formation in vivo. One could also argue that the increased formation of cartilage is counteracted by an increased cartilage loss resulting from the increased stresses on the cartilage due to increased stiffness of juxta-articular bone as a result of increased bone formation. According to Radin this might play a role in the pathogenesis of OA (25). The stratified analyses showed no indication for a harmful effect of IGF-1 on cartilage in the group with knee pain at baseline or the group with severe ROA. For the middle tertile of IGF-1 concentrations, however, there was more often cartilage loss compared to the lowest, in the group with knee pain or mild ROA.

It is also of interest to speculate that the responsiveness of chondrocytes to IGF-1 in in-vitro experiments, the presence of IGF-1 receptors and the presence of IGF-1 in synovial fluid are of importance for an autocrine function of IGF-1 in cartilage metabolism (18,26). This idea is strengthened by the observation that chondrocytes can produce IGF-1. In addition, we recently reported evidence for a contrasting modulation by transforming growth factor-ß of IGF-1 production by chondrocytes and osteoblasts (27). Circulating levels of IGF-1, therefore, do not necessarily reflect the local IGF-1 production in chondrocytes.

One other study has shown lower levels of IGF-1 in OA compared to controls (12). Based on our findings one would have expected higher levels. This difference might be due to patient selection, because these patients were not a general population sample. Moreover, equal levels of IGF-1 have been described in one other study (13), although the limited information written in this abstract makes it difficult to interpret these findings. In two studies slightly higher levels of growth-hormone were found in OA patients (12,28). This observation might corroborate our findings. Growth hormone levels can not be assessed reliably when patients are not

fasting and are not stress free; we therefore did not measure growth hormone. It should, however, be realized that we have studied the influence on progression of OA and not on the occurrence of OA. The other studies were in fact case-control studies conducted with an etiological question.

Recently, studies have been conducted to investigate the beneficial effects of growth hormone in normal elderly men with physiologically low levels of IGF-1 (15). A beneficial effect in OA has been suggested before, when it was shown that growth hormone could heal cartilage defects in animal experiments (29). In another tissue a role for IGF-1 in regeneration has been suggested, when an increase in IGF-1 was observed in regenerating muscle cells (30). In thinking about the usefulness of IGF-1 to prevent progression of OA, our data show that one should be careful in providing growth hormone to patients with OA. It may not only be beneficial, but potentially worsen OA, a common condition in the elderly.

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CHAPTER 7

GENERAL DISCUSSION
AND
SUGGESTIONS FOR FUTURE RESEARCH

Chapter 7

GENERAL DISCUSSION AND SUGGESTIONS FOR FUTURE RESEARCH

Six years ago, in 1985, leading scientists in the field of research on osteoarthritis met to discuss the state of the art concerning OA and to recommend future lines of research (1). At first, steps were taken to define OA and a definition was given in which several aspects, ranging from pathological abnormalities to clinical signs and symptoms were combined. It was however recognised that "... this challenge to the definition of OA is a symptom of the need for further research that may clarify conceptions of the nature of the disorders.".

New taxonomic classification systems for osteoarthritis, especially for epidemiologic studies needed to be developed. Until now the diagnosis of OA in epidemiologic research was based on the Atlas of Standard Radiographs of Arthritis (2) but even at the time of the development of this atlas (1963) it was recognised that more research was needed to clarify the relation between radiographic abnormalities and physical signs and symptoms. It took, however, nearly 25 years, until 1986, before the ACR criteria on knee OA were published. Criteria for OA of the hand and hip followed in the years thereafter, reflecting not only the need for criteria but also a renewed interest in OA, stimulated by an enhanced emphasis on diseases affecting quality of life in the steadily growing number of elderly.

Criteria can be helpful in improving the research and comparability of studies in this field. In chapter 4.1, for example, it is shown that, from a theoretical point of view, the use of different criteria may lead to varying results as a consequence of non-differential misclassification. Associations with e.g. putative risk factors are much weaker when this type of misclassification occurs.

The use of different criteria may indeed lead to varying results, even when the sets developed by the ACR are applied, which all showed good comparability with the "gold" standard of the clinical diagnosis. Different clusters of people or patients with knee OA are identified, however, in the general population. For example, as discussed in chapter 4.3, virtually all subjects with knee pain would have knee OA when some of the ACR criteria were applied. This is the direct result from the

manner the criteria were developed. As no real or absolute gold standard exists, the diagnosis of the clinician, checked by the investigators, is taken as the gold standard when criteria are developed. Moreover, criteria are derived from patients attending a clinic, who generally will suffer from the more severe form of the disease. In the case of knee OA many control patients were included who had rheumatoid arthritis. This led to the selection of criteria very common in the general population like the absence of palpable warmth or rheumatoid factor.

The use of the physician's diagnosis as the gold standard is a reasonable option. It reflects the experience and knowledge gathered from similar patients encountered before. The primary choice of patients with knee pain can also be regarded as an appropriate choice. In medicine the concern is with the cure, the alleviation of complaints, or the prevention of disease.

On the other hand the ACR criteria are largely clinical and lack the feature of cartilage degeneration which is regarded as the central pathognomonic phenomenon of OA. In a small study it was shown that patients with knee OA according to the ACR criteria all had cartilage degenerations observed by arthroscopy (3) but cartilage thickness as measured on standard radiographs does not correlate perfectly with cartilage defects seen during arthroscopy (4). When cartilage defects are considered as the gold standard, it would enhance our knowledge when the comparison of the ACR criteria with arthroscopic findings would be repeated in a larger study. In epidemiological research an invasive method as arthroscopy is not feasible and in the general population the diagnosis rests on the use of non-invasive criteria.

The radiographic criteria with knee pain and the ACR criteria yield different results although they overlap to a certain extend. Some sets of criteria, however, should not be used since these would classify almost everyone with knee pain as having OA.

It could be true that everyone with knee pain in the general population should be considered as having OA but this would hardly be in accordance with our concept of joint degeneration. In this concept the people selected by classification criteria for OA should generally be older, have a higher body mass index and be more often female compared to those who do not fulfil the criteria. Moreover, they should have more often complaints and abnormalities found during physical examination 12 years earlier, assumed to be related to the presence of OA in future.

In addition, when the criteria also identify subjects with knee pain who share other variables or parameters than those contained in the sets of criteria, subgroups

of subjects with knee pain can be distinguished. Although the data were not presented in this thesis, the several sets of criteria select subjects with knee pain which differ from others with knee pain in the general population in such a way that these were older and had a higher body mass index in the past.

Future research will eventually show whether and to what extend these subgroups of subjects with knee pain differ in causal pathways, prognosis and response to treatment. A new research project could be undertaken to investigate whether all the different clusters of people with OA identified by the different sets of criteria have, for example, a different risk of developing disability, sustained periods of knee pain or response to treatment.

In this way the relevance from another point of view (the relation with future disability etc.), of one or the other sets of criteria applied to diagnose OA can be evaluated. Studying who is at risk for such an outcome, leads to the description of better criteria and the separation of subgroups with OA when disability is taken as the gold standard of outcome. Simultaneously, in such a study the changes over time of the various individual criteria can be studied.

New imaging techniques and methods to study cartilage in vivo are now being developed. Magnetic Resonance Imaging and measurements of markers of cartilage degeneration may be new methods to be used in epidemiological research, but their merits have yet to be assessed. These new methods could especially be valuable to investigate the properties of cartilage and its degenerative changes.

In the same workshop mentioned above, a special place was reserved for the epidemiology of OA. Until that time epidemiologic research on knee OA in the general population had revealed the ubiquitous nature of the condition with little differences between countries and an increased prevalence in the elderly, women, obese subjects, and certain occupations like mining (5,6,7,8). Furthermore, knee OA as part of generalized OA was described and the familial clustering of generalized OA was observed (9). The discrepancy between joint complaints and radiographic knee OA was recognised (5,10), and an inverse relationship of OA with osteoporosis was noted (11).

The need was felt to analyze further the existing data sets, and several large population based studies were mentioned. Furthermore, longitudinal studies and studies on the course of OA were recommended.

In the six years following these recommendations, the existing data sets of several population based studies on OA have been studied in more detail or have been used as a starting point for follow-up studies. The data of the EPOZ study,

the HANES study, the Framingham study, the Tecumseh Community Health Study, and the Baltimore Longitudinal Study of Aging were analyzed and additional interesting observations were made.

Obesity was repeatedly seen to be related to knee OA and it was observed that the relationship was stronger in women and for bilateral knee OA (12,13,14,15). It was also made likely that obesity was not the result of knee OA (12,15) and the relationship was unexplained by systemic factors like blood pressure, uric acid levels or related to serum cholesterol (16). Several indices of obesity, besides body mass index, like skinfold measurements were associated with an increased prevalence of knee OA (17), although the body fat distribution did not seem to be a determinant independent of body mass index (18). The higher prevalence in women was observed to be partly due to a difference in body mass index between men and women (17). However, in the study on the incidence of radiographic knee OA in men and women without knee ROA at baseline, presented in this thesis, the relation with obesity was only observed in women and the difference between men and women in the occurrence of knee OA could not be explained by a difference in obesity or age.

In an American study, black women had a higher prevalence of knee ROA than white women and this was not the result of black women being more obese or a difference in income or educational level (15).

An association with occupation related physical activities and knee bending was observed in two studies (15,19) but not confirmed by the studies in this thesis and in another (20). Injury to the knee joint, assumed to be a cause of knee OA, proved to be so in the HANES study, although a bias can not be excluded completely (14). Our study did not confirm this relation.

Coincidentally, the prevalence of knee OA was observed to be lower among smokers (15,21), again not confirmed by the results of our study. Postmenopausal estrogen use was unrelated to knee OA in the Framingham study (22) but a relation was observed between OA and hysterectomy (23) but not confirmed by another study (22).

One of the recommendations resulting from the above mentioned workshop was to focus on (repetitive) trauma as a causal factor for knee OA and the response of cartilage to injury.

Epidemiological research has not been extensive on this subject although some studies have indicated that traumatic events are of importance although the extend of the trauma or joint use that causes OA is unclear. The effect of joint injury and joint use should be investigated in more detail.

It seems that a certain range of joint use does not lead to OA but very low use, like immobilisation, or overuse could. More research is needed to clarify the normal range of joint use which is not harmful and especially the circumstances in which this range is reduced and hence normal use may be detrimental. Detailed assessment of joint use is necessary, and better methods than questionnaires should preferably be used.

Conflicting evidence now exists between our study and two others on the relation between occupation and the occurrence of knee OA (15,19). This could be due to differences in methodology, range of knee loading during work, or populations, but also to the selection of workers for certain jobs, or random variability. An approach to solve this discrepancy could be to use the job coding method applied in the other studies to the population from our study.

We also mentioned a healthy worker effect as an explanation why no relationship between occupation and knee OA was observed. But this raises the question what the characteristics are of workers who do not seem to be at risk of developing OA while exposed to increased knee loading during work. Are there any protective factors and how are these related to the selection of workers for certain jobs? By virtue of intake selection procedures, there merely could be an absence of known risk factors although in our study adjustments were made for age and obesity. Trauma antecedent to the job could be another factor of importance.

In relation to joint use and traumatic events it is also of interest to study the response of cartilage to changes in joint use and injury. Joint research efforts of epidemiologists, clinicians and basic scientists are needed to study these interactions.

Follow-up studies are still scarce but one such study (on hip OA) was conducted by van Saase et al in the EPOZ-cohort. Obesity was not related to the occurrence of hip OA, as had been suggested, but could be related to the progression of hip OA (24).

A follow-up of the participants in the Tecumseh Community Health Study, examined for the first time in 1962-65, was conducted in 1985 and revealed a higher incidence of OA of the hand joints in women with a higher metacarpal bone mass at baseline and in those with more bone loss (25). The Baltimore Longitudinal study of Aging, in a 20 year follow-up study in men, showed an increase of the incidence of osteoarthritis of the handjoints with age and also showed that isolated joint space narrowing as well as isolated doubtful osteophytes predicted the development of definite radiographic features of OA (26). The HANES study is now used to examine the relationship of baseline knee OA with future disability (27). These data

still need to be analyzed in more detail.

The follow-up study on knee OA presented in this thesis has its place in this list of new and old undertakings. It is one of the first and few follow-up studies in the general population on OA.

The observed relation between the presence of Heberden's nodes and future cartilage loss is of interest and needs further investigation to show if generalized OA reflects some general influence on cartilage or whether an abnormality of cartilage in all joints is responsible for this. A genetic predisposition can be thought of and the developments in genetic research could be of value in epidemiologic research. The observation that people with Heberden's nodes also have an increased risk of developing OA as a result of other causes (meniscectomy (28)) supports the need for further research to identify the underlying cause for this susceptibility.

One of the most important observations in osteoarthritic research is the recognition that not only cartilage breakdown occurs but also repair. This has stimulated thoughts about repair mechanisms and holds a promise for the future in developing drugs that can be regarded as a "healing agent" for cartilage degeneration.

It was shown that Insulin-like Growth Factor-1 could stimulate chondrocytes to form cartilage and collagen and could also influence bone metabolism. We therefore focused on Insulin-like Growth Factor-1 as a hormone of importance in the repair process of OA. Unfortunately, it could not be shown to prevent cartilage loss. This should not be regarded as proof that there is no place for IGF-1 in cartilage formation in vivo. Moreover, we observed an effect on the growth of osteophytes suggesting a role in the progression of knee OA. It needs to be assessed whether this reflects a response to cartilage damage or is harmful because osteophytes lead to complaints.

We observed a relation of baseline obesity with future knee pain, possibly through a mechanism were obesity affects the joint degeneration as seen on radiograph. Although this suggests that weight reduction could be beneficial, it was disappointing and cause for concern that no effect of weight change could be shown. Since weight reduction is one of the few prognostic factors that can be influenced, more research is needed to determine whether these initial observations can be confirmed. A trial on the effect of weight reduction on knee joint complaints and progression of OA would be informative.

In general more research on the prognosis and prognostic factors of OA is needed. For example, some NSAID's have been suggested to be chondroprotective while others have been regarded as damaging for cartilage (29,30,31). Evidence of a

harmful effect on cartilage in patients is, however, limited. More research is certainly needed to indicate if treatment with certain NSAID's is to be preferred because of their chondroprotective effect. The first steps to study this in patients have now been taken (32).

Finally, to establish a link between the studies on classification criteria described in chapter 4 and the study on prognostic factors described in chapter 6, the prognostic factors were studied after stratification of the group according to the presence or absence of pain at baseline in the affected joint and according to the severity of the radiographic abnormalities.

These results are presented in appendix B. No adjustments were made for confounding factors. In general, the results supported the findings in the total group with radiographic OA. There were sometimes differences in odds ratios between two strata. Statistically significant heterogeneity between odds ratios or large non-significant differences were, however, observed for only a few prognostic factors.

Moreover, the odds ratios tended to be higher for some important prognostic factors in the group with knee pain at baseline compared to the group without and for the group with severe ROA compared to the group with mild ROA. This was the case for age, body mass index, body weight, Heberden's nodes, a diagnosis of generalized OA and Insulin-like growth factor-1. This suggest that the reported prognostic factors are also of importance for groups with OA based on other classification criteria but a larger study is needed to confirm whether the described relations between the prognostic factors and knee OA are consistent when other classification criteria are used or when patients seen at a clinic are studied.

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SAMENVATTING

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In dit proefschrift komen drie verschillende onderwerpen over knie artrose aan de orde. Vanuit een epidemiologische context wordt aandacht besteed aan classificatie criteria, risico factoren en prognostische factoren.

In een korte introductie in **hoofdstuk 1** wordt de relevantie van onderzoek naar artrose toegelicht. Onderzoek naar artrose is belangrijk vanwege de gevolgen van deze aandoening voor de patiënt, in de zin van pijnklachten en moeilijkheden bij het dagelijks functioneren, vanwege de maatschappelijke gevolgen in termen van financiële belasting, en vanwege het ontbreken van kennis ten aanzien van de oorzaken, het beloop en mogelijkheden om deze aandoening te voorkomen of te genezen.

In **hoofdstuk 2** worden de doelstellingen van de verschillende studies uit dit proefschrift besproken. Zo werden classificatie criteria bestudeerd om inzicht te krijgen in de validiteit en overeenstemming van diverse soorten classificatie criteria die gebruikt (kunnen) worden in epidemiologisch onderzoek. Een studie naar risico factoren van knie artrose kan bijdragen aan het opsporen van de oorzaken van deze aandoening. Prognostische factoren werden bestudeerd om de variabiliteit in het beloop van knie artrose te verklaren en nieuwe mogelijkheden om het beloop te beïnvloeden op het spoor te komen.

Hoofdstuk 3 is een literatuur overzicht over de epidemiologie van knie artrose. De classificatie criteria van Kellgren, Ahlbäck en de American College of Rheumatology (ACR) worden in het kader van de ontwikkeling van classificatie criteria voor wetenschappelijk onderzoek beschreven. Eveneens komt het onvolledige verband tussen klachten en verschijnselen aan de orde; niet iedereen met (radiologische) verschijnselen van knie artrose heeft hier klachten van. In het kader van de classificatie criteria worden tot slot enkele subgroepen van artrose besproken zoals de gegeneraliseerde artrose, erosieve (inflammatoire) artrose, en artrose in combinatie met chondrocalcinose.

Vervolgens worden risico factoren die beschreven zijn in andere studies kort aan de orde gesteld, zoals genetische aspecten, leeftijd, geslacht, ras, obesitas, mechanische belasting en trauma, ontbreken van osteoporose, roken, hysterectomie, urinezuur, bloeddruk en gewrichtslaxiteit.

Tot slot worden enkele studies genoemd waarin het beloop en prognostische factoren bestudeerd zijn. Opvallend hierbij is het geringe aantal studies naar het beloop en de prognostische factoren van knie artrose.

Hoofdstuk 4, inzake classificatie criteria, is onderverdeeld in drie delen. In

hoofdstuk 4.1 wordt de theoretische achtergrond van de effecten van non-differentiële misclassificatie ten aanzien van de aan- of afwezigheid van de te bestuderen ziekte uiteengezet. Als er geen perfecte criteria worden gebruikt, dan kan de classificatie van personen resulteren in non-differentiële misclassificatie. Door deze misclassificatie wordt het verband tussen een reumatische aandoening en een mogelijk risico factor onderschat. De misclassificatie kan ook resulteren in een verschil in de effectmaat (het relatieve risico, odds ratio of risico verschil) tussen twee groepen of studies, terwijl er geen werkelijk verschil is. Bovendien wordt de "power" van een studie verminderd. In dit hoofdstuk worden deze effecten van non-differentiële misclassificatie bovendien geïllustreerd aan de hand van een aantal voorbeelden en worden overwegingen gegeven van belang bij de opzet en interpretatie van epidemiologische studies.

De **hoofdstukken 4.2 en 4.3** zijn gebaseerd op een bevolkingsonderzoek uitgevoerd van 1975 tot 1978 in Zoetermeer, de EPOZ-studie (Epidemiologische Preventief Onderzoek Zoetermeer). Alle 13.614 inwoners van 5 jaar en ouder uit twee wijken, een met een plattelandsachtergrond en een ander met een stads-achtergrond, werden gevraagd hieraan deel te nemen en uiteindelijk deed 78 procent mee. Bij iedereen van 20 jaar en ouder werd onderzoek gedaan naar de prevalentie en risico factoren van reumatische aandoeningen zoals artrose, rugklachten en verschillende vormen van artritis zoals reumatoïde artritis en spondylitis ankylopoetica. Voor dit onderzoek werden gegevens verzameld door middel van een vragenlijst met onder andere vragen over gewrichtsklachten en -aandoeningen, een lichamelijk onderzoek met onder andere een gewrichts-onderzoek van de knie, en röntgenfoto's van verschillende gewrichten zoals een voor-achterwaartse röntgenfoto van de knieën bij de staande respondent. Deze röntgenfoto werd beoordeeld op de aanwezigheid van radiologische artrose volgens de Atlas of Standard Radiographs of Arthritis (Kellgren score).

Het doel van de studie weergegeven in **hoofdstuk 4.2** was na te gaan of de aanwezigheid van radiologische knie artrose nauwkeurig voorspeld kon worden op basis van anamnestische gegevens, een lichamelijk onderzoek en laboratorium bevindingen. De gegevens van 2865 respondenten van 45 jaar en ouder, bij wie een röntgenfoto genomen was, werden hiervoor geanalyseerd. De sensitiviteit, specificiteit, likelihood ratio en de voorspellende waarde van een positieve test van een aantal relevante variabelen werden berekend met de radiologische artrose graad 2 of meer volgens Kellgren als standaard.

De anamnestische gegevens, afkomstig van de vragenlijst, waren leeftijd, geslacht, pijn van de knie, zwelling van de knie, pijn in beide handen,

ochtendstijfheid, artrose in een of meerdere gewrichten, pijn en/of stijfheid in knieën of heupen tijdens overeind komen uit een stoel, pijn in knieën en/of heupen tijdens trap lopen; van het algemeen lichamelijke onderzoek: Quetelet index (kg/m^2) en noduli van Heberden; en van het lichamelijke onderzoek van de knie: benige zwelling, vocht, weke delen zwelling (gewrichts kapsel), beperkte knie functie (flexie en/of extensie), pijn tijdens bewegen van de knie, drukpijn op de gewrichtsranden; en van het laboratorium onderzoek de latex-fixatie test.

Alle variabelen, behalve noduli van Heberden, vocht in de knie, pijn in beide handen en de latex-fixatie test waren statistisch significant gerelateerd aan radiologische knie artrose na adjusteren voor leeftijd. Geen enkele variabele, noch een combinatie van variabelen kon de aanwezigheid van radiologische knie artrose nauwkeurig voorspellen.

De conclusie was dat de röntgenfoto zijn plaats behoudt in de diagnose van knie artrose in klinisch en epidemiologisch onderzoek.

De validiteit en overeenstemming van diverse soorten classificatie criteria, namelijk de classificatie criteria van Kellgren, Ahlbäck en die van de American College of Rheumatology (ACR) werden bestudeerd en de resultaten staan beschreven in **hoofdstuk 4.3.**

Voor deze studie werden alle respondenten uit het EPOZ onderzoek geboren tussen 1909 en 1938 die door middel van een vragenlijst aangaven kniepijn te hebben in 1988-89 opnieuw onderzocht, evenals een aselecte steekproef gematched voor geslacht van degenen die geen kniepijn hadden. Tijdens het vervolg onderzoek werden aanvullende vragen gesteld over gewrichtsklachten en werd, in het merendeel van de gevallen door twee artsen onafhankelijk van elkaar, een lichamelijk onderzoek uitgevoerd waarbij met name afwijkingen aan de knie werden beoordeeld. Bovendien werd een voor-achterwaartse röntgenfoto gemaakt bij de staande respondent. Deze werd door twee artsen beoordeeld, wederom onafhankelijk van elkaar, waarbij de artsen geen kennis hadden van andere gegevens.

Over het algemeen vertoonden de verschillende soorten criteria redelijk tot goede overeenstemming met elkaar. De overeenstemming was beter 1) tussen de klinische en klinische plus laboratorium criteria gebaseerd op de ACR beslisboom, 2) tussen de sets van criteria die radiologische criteria bevatten, met uitzondering van de criteria van Ahlbäck, en 3) tussen de klinische en klinische plus laboratorium criteria gebaseerd op de ACR criteria die in de vorm van een lijst van criteria ("traditional format") gepresenteerd werden. De klinische en klinische plus laboratorium criteria gebaseerd op de lijst van criteria en de criteria van Ahlbäck

vertoonden een slechte overeenstemming met de andere criteria.

In hetzelfde EPOZ cohort werd de relatie bestudeerd tussen verschillende factoren, relevant voor de aanwezigheid van artrose, en artrose gedefinieerd volgens de verschillende soorten criteria. Deze factoren waren in 1975-78 bepaald en naar verwachting gaven zij een indicatie voor het hebben van knie artrose in de toekomst. Voorbeelden hiervan zijn leeftijd, Quetelet index, meniscectomie, en knieklachten en afwijkingen aan de knie tijdens het lichamelijk onderzoek. Indien de voorgestelde criteria inderdaad parameters zijn waarmee artrose kan worden vastgesteld, dan zou een relatie aan te tonen moeten zijn met deze factoren.

Over het algemeen kon met alle criteria met bijna alle variabelen een statistisch significante relatie worden aangetoond. De sterkte van dit verband uitgedrukt als odds ratio of risico verschil kon evenwel sterk verschillen. De klinische en klinische plus laboratorium criteria gebaseerd op de ACR criteria die in de vorm van een lijst van criteria werden gepresenteerd gaven nauwelijks een andere relatie te zien dan kniepijn als het enige criterium omdat volgens deze criteria vrijwel iedereen met kniepijn artrose zou hebben.

De criteria van Ahlbäck met kniepijn, lieten, ondanks het, volgens deze definitie, kleine aantal respondenten met artrose, ook een verband zien met meerdere variabelen maar de betrouwbaarheids-intervallen rond de odds ratio's waren veel breder. De odds ratio's waren hierbij over het algemeen groter dan voor de andere criteria. De criteria van Kellgren met kniepijn gaven resultaten die vergelijkbaar waren met de anderen. Hoewel over het algemeen de, sterk op de aanwezigheid van crepitus gebaseerde, klinische criteria volgens de ACR beslisboom betere associaties (grotere odds ratio's) te zien gaven kan niet worden uitgesloten dat dit is toe te schrijven aan artrose van het patello-femorale gewricht en niet aan artrose van het femoro-tibiale gewricht.

De aanwezigheid van radiologische artrose volgens Kellgren in 1975-78 betekende een groter risico op het hebben van artrose 12 jaar later bij gebruik van andere soorten criteria. Dit verband was duidelijker indien in 1975-78 kniepijn aanwezig was of naarmate de ernst van de radiologische artrose groter was.

Over het algemeen zijn alle verschillende voorgestelde combinaties van criteria dus bruikbaar voor epidemiologisch onderzoek maar verschillen kunnen optreden in de grootte van de risico-schatter van het verband met veronderstelde geassocieerde factoren of de breedte van het betrouwbaarheids interval rond de risico-schatter. De klinische en klinische plus laboratorium criteria gebaseerd op de ACR criteria die in de vorm van een lijst van criteria werden gepresenteerd kunnen beter niet worden gebruikt.

In **hoofdstuk 5** worden de resultaten van een studie naar de incidentie en risico factoren van radiologische knie artrose gepresenteerd. Voor deze studie werden 123 mannen en 135 vrouwen in de leeftijd van 46 tot 66 jaar die geen radiologische knie artrose (ROA) hadden tijdens het EPOZ-onderzoek in 1975-78 na 12 jaar opnieuw onderzocht.

De afwezigheid van radiologische knie artrose werd bevestigd door twee artsen na een onafhankelijke herbeoordeling van de röntgenfoto's. De aanwezigheid van ROA graad twee of meer tijdens het vervolgonderzoek werd vastgesteld op een voor-achterwaartse gewichtsdragende röntgenfoto die beoordeeld werd door dezelfde twee artsen onafhankelijk van elkaar en zonder kennis van andere gegevens.

De 12 jaars cumulatieve incidentie was 10,6 % voor mannen en 26,7 procent bij vrouwen. Deze hogere incidentie bij vrouwen kon niet worden verklaard door een verschil in overgewicht bij het begin van de studie of door leeftijds-effecten. De incidentie was opmerkelijk genoeg niet hoger bij ouderen.

De Quetelet index was een risico factor bij vrouwen maar niet bij mannen. Andere factoren vastgesteld in 1975-78 zoals trimmen of lid zijn van een sportclub, tricepshuidplooimeting, lichaamsgewicht, serum urinezuur, noduli van Heberden, een klinische diagnose van gegeneraliseerde artrose (diagnose van artose in 3 of meer gewrichtsgroepen zonder radiologische gegevens), en een klinische diagnose van gelokaliseerde artrose (artrose in 1 of 2 gewrichtsgroepen) en roken waren niet gerelateerd aan een verhoogd risico op het krijgen van radiologische knie artrose.

Factoren, gevraagd door middel van een vragenlijst tijdens het vervolg onderzoek in 1988-89, namelijk trauma of blessure van het knie gewricht en vroegere X- of O-benen bleken eveneens geen risico factor te zijn. Meniscectomie (n=3) en chondrocalcinose (n=3) kwamen te sporadisch voor om zinvol te kunnen bestuderen.

Aan het beroep gerelateerde knie belasting, geïnventariseerd gedurende het vervolg onderzoek, gaf geen verhoogd risico op radiologische knie artrose behalve staan tijdens het beroep dat een inverse relatie met het ontstaan van radiologische knie artrose liet zien voor mannen.

Hoofdstuk 6 bespreekt een vervolg-onderzoek naar de prognostische factoren van (radiologische) knie artrose. Respondenten van het EPOZ-onderzoek uit 1975-78 met radiologische knie artrose graad 2 of meer volgens Kellgren en geboren na 1909 (46-68 jaar) werden voor deze studie geselecteerd. De graad 2 of meer ROA werd bevestigd door twee beoordelaars, onafhankelijk van elkaar en zonder informatie te hebben van de beoordeling uit 1975-78 of van andere studie-variabelen, voordat de gegevens van deze respondent in de analyse werden

betrokken.

Prognostische factoren vastgelegd tijdens het bevolkings-onderzoek in 1975-78 waren: geslacht, leeftijd, lichaamsgewicht, Quetelet index (kg/m^2), triceps-huidplooimeting, serum urinezuur, trimmen of lid zijn van een sportclub, chondrocalcinose op de eerste röntgenfoto (beoordeeld in 1988), noduli van Heberden, een klinische diagnose van gegeneraliseerde artrose (diagnose van artose in 3 of meer gewrichtsgroepen zonder radiologische gegevens), en een klinische diagnose van gelokaliseerde artrose (artrose in 1 of 2 gewrichtsgroepen) en roken.

Bovendien werden mogelijke prognostische factoren vastgesteld door middel van een vragenlijst tijdens het vervolgonderzoek in 1988-89. Daarbij werden vragen gesteld over een meniscectomie, trauma en blessure van het kniegewricht, vroegere X- of O-benen en over de beroepsgeschiedenis met specifieke vragen over knie belastende activiteiten. Het lichaamsgewicht en de lengte werden gemeten en er werd een voor-achterwaartse röntgenfoto gemaakt bij de staande respondent.

De uitkomst maten waren gewrichtsspleet versmalling (kraakbeenverlies), groei van osteophyten en overall progressie. Deze werden gescoord door de röntgenfoto's uit 1975-78 en uit 1988-89 te vergelijken, waarvoor de twee röntgenfoto's naast elkaar werden geplaatst. De veranderingen werden beoordeeld door twee artsen, onafhankelijk van elkaar en zonder informatie over andere gegevens.

Pijn in de aangedane knie werd ook bestudeerd als uitkomstmaat. Op twee vragenlijsten werden vragen gesteld over pijn in de knie. Gevraagd werd "Heeft u in de afgelopen 12 maanden kniepijn gehad die langer dan één week duurde ?" en "Heeft u nu kniepijn die al langer dan één week duurt ?". Indien één van beide vragen op de eerste vragenlijst positief werd beantwoord en wederom tenminste een van beide vragen op de tweede vragenlijst, dan werd dit beschouwd als zijnde positief voor kniepijn in de analyse. Uiteindelijk konden de gegevens van 142 personen voor dit onderzoek worden gebruikt.

In **hoofdstuk 6.1** wordt de studie naar de prognostische factoren van kraakbeenverlies besproken. Overall had 34 procent kraakbeenverlies. Prognostische factoren gemeten in 1975-78 waren Quetelet index, lichaamsgewicht en tricepshuidplooimeting, ook na adjusteren voor geslacht en leeftijd. Bovendien waren noduli van Heberden en een diagnose van gegeneraliseerde artrose prognostische factoren voor kraakbeenverlies, ook na adjusteren voor geslacht, leeftijd en Quetelet index. Een hogere leeftijd predisponeerde ook tot meer kraakbeen verlies na adjusteren voor geslacht en Quetelet index maar dit werd deels verklaard door het confounding effect van de aanwezigheid van noduli van Heberden en de door de arts gestelde diagnose van gegeneraliseerde artrose. Chondrocalcinose was

gerelateerd aan kraakbeenverlies maar de leeftijd en met name de Quetelet index verstoorden in belangrijke mate deze relatie. Na adjusteren voor geslacht, leeftijd en Quetelet index was vroegere X- of O-benen, aangegeven op de follow-up vragenlijst, significant gerelateerd aan kraakbeenverlies. Van de variabelen die een indicatie vormden voor knie belasting tijdens het werk was staan mogelijk enigszins positief geassocieerd met kraakbeenverlies. De overige variabelen waren niet statistisch significant gerelateerd aan kraakbeenverlies maar bijvoorbeeld trauma van de knie en meniscectomie toonden een positieve tendens en trimmen of lid zijn van een sportclub een negatieve tendens met kraakbeenverlies.

In **hoofdstuk 6.2** wordt de studie beschreven die als doelstelling had het onderzoeken van het effect van Quetelet index en verandering in lichaamsgewicht op de progressie van knie artrose, beoordeeld aan de hand van veranderingen op de twee röntgenfoto's en kniepijn. De Quetelet index gemeten in 1975-78 was een prognostische factor voor kraakbeenverlies, groei van osteophyten en overall progressie. Gewichtsverandering, al dan niet na adjusteren voor geslacht, leeftijd en lichaamsgewicht gemeten in 1975-78, was niet gerelateerd aan progressie van knie artrose. Kniepijn na 12 jaar follow-up kwam vaker voor bij respondenten met een hoge Quetelet index in 1975-78. Het toevoegen van de maten voor progressie van artrose aan het logistische regressie model zwakte het verband tussen Quetelet index en kniepijn af. Dit suggereert dat de invloed van de Quetelet index op de aanwezigheid van kniepijn in de toekomst deels verloopt via een effect op de progressie van de artrose. Verandering in lichaamsgewicht was niet gerelateerd aan kniepijn.

In **hoofdstuk 6.3** wordt de studie beschreven naar het effect van serum Insulin-like growth factor-1 (IGF-1) op de progressie van knie artrose zoals kraakbeen verlies, groei van osteophyten en overall progressie. Serum IGF-1 werd hiervoor gemeten door middel van een radio-immuno essay tijdens het vervolg onderzoek en in 79% van de sera uit 1975-78. Hoge IGF-1 concentraties waren gerelateerd aan meer groei van osteophyten en overall progressie. De voor leeftijd, geslacht en Quetelet index geadjusteerde odds ratio's van de hoogste ten opzichte van de laagste tertiel was 2.96 (95% betrouwbaarheidsinterval: 1.15-7.60) voor groei van osteophyten en 2.58 (1.01-6.60) voor overall progressie. Er was geen duidelijk verband tussen IGF-1 concentraties en kraakbeenverlies. Deze gegevens suggereren een effect van IGF-1 op de progressie van knie artrose door de groei van osteophyten te stimuleren maar niet door het verlies aan kraakbeen te voorkomen.

In een algemene discussie, beschreven in **hoofdstuk 7**, worden de resultaten van de hiervoor beschreven onderzoeken besproken in het licht van recent

uitgevoerd artrose onderzoek elders en suggesties voor verder onderzoek gedaan.

In de appendix A worden verschillen gegeven tussen responders en non-responders.

In Appendix B worden de resultaten gegeven van de relaties tussen diverse variabelen en progressie van knie artrose na stratificatie voor de aan- of afwezigheid van kniepijn in 1975-78 en de ernst van de radiologische artrose in 1975-78 om een indruk te krijgen over de consistentie van de bevindingen als andere soorten criteria voor artrose wordt gebruikt om respondenten met artrose te selecteren. Over het algemeen waren deze resultaten in overeenstemming met de bevindingen beschreven in hoofdstuk 6, blijkend uit een grotere odds ratio voor de groep met kniepijn of de groep met ernstige radiologische artrose en/of uit het ontbreken van significante heterogeniteit van de odds ratio's tussen de twee strata.

APPENDICES

A. Differences between responders, non-responders and individuals lost to follow-up

B. Stratified analysis for the study of prognostic factors

Appendix A

Table A 1. Baseline characteristics of responders and non-responders to the first follow-up questionnaire in 1988. All born between 1909 and 1939. ╪

	Responders	Non-responders	p-value┼
Number	2550	519	
Age (yrs)	49.3 ± 7.6	50.0 ± 8.3	0.06
Body mass index (kg/m^2)	24.8 ± 3.1	25.3 ± 3.6	0.001
Body weight (kg)	71.3 ± 11.0	72.0 ± 11.9	0.2
Triceps skinfold thickness (mm)	15.5 ± 7.6	15.9 ± 8.4	0.3
Uric acid (mg/100 ml)	4.9 ± 1.2	5.0 ± 1.2	0.3
Number of women	1338 (52.5)	265 (51.1)	0.6
Radiographic knee OA* (≥ 45 yrs)			
Grade 0-1	1292 (80.6)	264 (81.2)	0.4
Grade 2	249 (15.5)	44 (13.5)	
Grade 3-4	62 (3.9)	17 (5.2)	
Questionnaire			
Knee pain*	339 (13.3)	81 (15.6)	0.2
Pain walking stairs	253 (9.9)	62 (11.9)	0.2
Pain rising from chair	287 (11.3)	86 (16.6)	< 0.001
Stiffness arm/leg	431 (16.9)	101 (19.5)	0.2
Stiffness rising chair	368 (14.4)	96 (18.5)	0.02
Jogging/member sporting club	522 (20.5)	87 (16.8)	0.05
Smoking			
Never	674 (26.5)	121 (23.3)	< 0.001
Ex	809 (31.8)	129 (24.9)	
Current	1065 (41.8)	269 (51.8)	
Physical examination			
Bony enlargement knee joint*	100 (3.9)	25 (4.8)	0.3
Function limitation knee joint*	83 (3.3)	17 (3.3)	0.9
Bony tenderness knee joint*	63 (2.5)	18 (3.5)	0.2
Pain on motion knee joint*	33 (1.3)	10 (1.9)	0.3
Heberden's nodes	159 (6.2)	30 (5.8)	0.7
Diagnosis of generalized OA	334 (13.1)	73 (14.1)	0.6
Diagnosis of localized OA	517 (20.3)	101 (19.5)	0.7

╪ See chapter 4.3 for further explanation
* Right and/or left knee
┼ Two sided p-value for a difference between responders and non-responders
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 2. Baseline characteristics of responders to the first follow-up questionnaire in 1988 and subjects lost to follow-up. All born between 1909 and 1939. ‡

	Responders	Lost to follow-up	p-value†
Number	2550	139	
Age (yrs)	49.3 ± 7.6	48.0 ± 6.8	0.04
Body mass index (kg/m^2)	24.8 ± 3.1	24.4.3 ± 3.0	0.2
Body weight (kg)	71.3 ± 11.0	71.3 ± 11.1	0.9
Triceps skinfold thickness (mm)	15.5 ± 7.6	17.0 ± 8.4	0.06
Uric acid (mg/100 ml)	4.9 ± 1.2	5.0 ± 1.3	0.3
Number of women	1338 (52.5)	69 (49.6)	0.5
Radiographic knee OA* (≥ 45 yrs)			
Grade 0-1	1292 (80.6)	68 (86.1)	0.5
Grade 2	249 (15.5)	9 (11.4)	
Grade 3-4	62 (3.9)	2 (2.5)	
Questionnaire			
Knee pain*	339 (13.3)	11 (7.9)	0.07
Pain walking stairs	253 (9.9)	10 (7.2)	0.3
Pain rising from chair	287 (11.3)	19 (13.7)	0.4
Stiffness arm/leg	431 (16.9)	14 (10.1)	0.04
Stiffness rising chair	368 (14.4)	13 (9.4)	0.09
Jogging/member sporting club	522 (20.5)	27 (19.4)	0.8
Smoking			
Never	674 (26.5)	21 (15.1)	< 0.01
Ex	809 (31.8)	56 (40.3)	
Current	1065 (41.8)	62 (44.6)	
Physical examination			
Bony enlargement knee joint*	100 (3.9)	1 (0.7)	0.05
Function limitation knee joint*	83 (3.3)	2 (1.4)	0.2
Bony tenderness knee joint*	63 (2.5)	1 (0.7)	0.2
Pain on motion knee joint*	33 (1.3)	0 (0.0)	0.2
Heberden's nodes	159 (6.2)	5 (3.6)	0.2
Diagnosis of generalized OA	334 (13.1)	24 (17.3)	0.2
Diagnosis of localized OA	517 (20.3)	22 (15.8)	0.2

‡ See chapter 4.3 for further explanation
* Right and/or left knee
† Two sided p-value for a difference between responders and subjects lost to follow-up
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 3. Baseline characteristics of responders and non-responders invited for the follow-up examination, who had knee pain at follow-up on the first questionnaire. ╪

	Responders	Non-responders	p-value┼
Number	263	44	
Age (yrs)	50.0 ± 7.9	52.6 ± 8.0	0.04
Body mass index (kg/m^2)	25.3 ± 3.1	26.8 ± 4.5	0.01
Body weight (kg)	71.3 ± 10.3	73.0 ± 13.7	0.4
Triceps skinfold thickness (mm)	17.5 ± 7.9	21.0 ± 7.8	0.03
Uric acid (mg/100 ml)	4.8 ± 1.3	4.8 ± 1.5	0.9
Number of women	171 (65.0)	34 (77.3)	0.1
Radiographic knee OA* (≥ 45 yrs)			
Grade 0-1	118 (67.8)	23 (67.1)	0.9
Grade 2	40 (23.0)	8 (23.5)	
Grade 3-4	16 (9.2)	3 (8.8)	
Questionnaire			
Knee pain*	81 (30.8)	15 (34.1)	0.7
Pain walking stairs	67 (25.5)	8 (18.2)	0.3
Pain rising from chair	73 (27.8)	11 (25.0)	0.7
Stiffness arm/leg	75 (28.5)	13 (29.5)	0.9
Stiffness rising chair	82 (31.2)	15 (34.1)	0.7
Jogging/member sporting club	54 (20.5)	5 (11.4)	0.2
Smoking			
Never	73 (27.9)	19 (43.2)	0.1
Ex	75 (28.6)	8 (18.2)	
Current	114 (43.5)	17 (38.6)	
Physical examination			
Bony enlargement knee joint*	27 (10.3)	4 (9.1)	0.8
Function limitation knee joint*	16 (6.1)	2 (4.5)	0.7
Bony tenderness knee joint*	17 (6.5)	4 (9.1)	0.5
Pain on motion knee joint*	8 (3.0)	4 (9.1)	0.06
Heberden's nodes	23 (8.7)	4 (9.1)	0.9
Diagnosis of generalized OA	52 (19.8)	10 (22.7)	0.7
Diagnosis of localized OA	66 (25.1)	12 (27.3)	0.8
First follow-up questionnaire			
Knee pain of > 1 week duration			
In past 12 months	248 (94.3)	41 (93.5)	0.8
Currently	156 (59.3)	30 (68.2)	0.3
Medication for knee pain	52 (20.1)	11 (25.6)	0.4
Meniscectomy	26 (9.9)	8 (18.2)	0.1

╪ See chapter 4.3 for further explanation
* Right and/or left knee
┼ Two sided p-value for a difference between responders and non-responders
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 4. Baseline characteristics of responders and non-responders invited for the follow-up examination, who had no knee pain at follow-up on the first questionnaire. ‡

	Responders	Non-responders	p-value†
Number	274	88	
Age (yrs)	48.9 ± 7.4	49.0 ± 8.2	0.9
Body mass index (kg/m^2)	24.8 ± 3.2	24.8 ± 3.4	0.9
Body weight (kg)	70.0 ± 10.7	72.7 ± 12.6	0.04
Triceps skinfold thickness (mm)	16.1 ± 7.7	14.9 ± 7.9	0.3
Uric acid (mg/100 ml)	4.7 ± 1.2	5.2 ± 1.3	0.005
Number of women	175 (63.9)	42 (47.7)	0.007
Radiographic knee OA* (≥ 45 yrs)			
Grade 0-1	134 (79.8)	43 (87.8)	0.3
Grade 2	29 (17.3)	4 (8.2)	
Grade 3-4	5 (3.0)	2 (4.1)	
Questionnaire			
Knee pain*	29 (10.6)	3 (3.4)	0.04
Pain walking stairs	26 (9.5)	0 (0)	0.003
Pain rising from chair	29 (10.6)	5 (5.7)	0.2
Stiffness arm/leg	47 (17.2)	6 (6.8)	0.02
Stiffness rising chair	37 (13.5)	6 (6.8)	0.09
Jogging/member sporting club	55 (20.1)	21 (23.9)	0.4
Smoking			
Never	77 (28.1)	21 (23.9)	0.7
Ex	78 (28.5)	28 (31.8)	
Current	119 (43.4)	39 (44.3)	
Physical examination			
Bony enlargement knee joint*	10 (3.6)	3 (3.4)	0.9
Function limitation knee joint*	10 (3.6)	1 (1.1)	0.2
Bony tenderness knee joint*	5 (1.8)	0 (0)	0.2
Pain on motion knee joint*	2 (0.7)	0 (0)	0.4
Heberden's nodes	13 (4.7)	10 (11.4)	0.03
Diagnosis of generalized OA	35 (12.8)	15 (17.0)	0.3
Diagnosis of localized OA	51 (18.6)	11 (12.5)	0.2
First follow-up questionnaire			
Knee pain of > 1 week duration			
In past 12 months	- §	-	
Currently	-	-	
Medication for knee pain	2 (0.7)	0 (0)	0.4
Meniscectomy	6 (2.2)	2 (2.3)	0.9

‡ See chapter 4.3 for further explanation
* Right and/or left knee
† Two sided p-value for a difference between responders and non-responders
§ Absent by definition
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 5. Baseline characteristics of responders and non-responders invited for follow-up examination, randomly selected of the responders to the first follow-up questionnaire who had no radiographic osteoarthritis in 1975-78. ǂ

	Responders	Non-responders	p-value†
Number	293	105	
Age (yrs)	52.7 ± 5.0	55.6 ± 6.3	< 0.001
Body mass index (kg/m^2)	25.2 ± 3.3	25.5 ± 3.2	0.3
Body weight (kg)	72.1 ± 11.3	73.4 ± 10.8	0.3
Triceps skinfold thickness (mm)	16.4 ± 8.6	16.0 ± 8.5	0.8
Uric acid (mg/100 ml)	4.9 ± 1.1	5.2 ± 1.4	0.02
Number of women	160 (54.6)	51 (48.6)	0.3
Radiographic knee OA* (≥ 45 yrs)			
Grade 0	194 (66.2)	68 (64.8)	0.8
Grade 1	99 (33.8)	37 (35.2)	
Questionnaire at baseline			
Knee pain*	46 (15.7)	9 (8.6)	0.07
Pain walking stairs	37 (12.6)	9 (8.6)	0.3
Pain rising from chair	44 (15.0)	9 (8.6)	0.1
Stiffness arm/leg	56 (19.1)	13 (12.4)	0.1
Stiffness rising chair			
Jogging/member sporting club	52 (17.7)	15 (14.3)	0.4
Smoking			
Never	84 (28.7)	31 (29.5)	0.8
Ex	90 (30.7)	29 (27.6)	
Current (at baseline)	119 (40.6)	45 (42.9)	
Physical examination at baseline			
Bony enlargement knee joint*	15 (5.1)	8 (7.6)	0.3
Function limitation knee joint*	13 (4.4)	3 (2.9)	0.5
Bony tenderness knee joint*	7 (2.4)	2 (1.9)	0.8
Pain on motion knee joint*	5 (1.7)	0 (0)	0.2
Heberden's nodes	26 (8.9)	10 (9.5)	0.8
Diagnosis of generalized OA	44 (15.0)	21 (20.0)	0.2
Diagnosis of localized OA	75 (25.6)	30 (28.6)	0.6
First follow-up questionnaire			
Knee pain of > 1 week duration			
In past 12 months	37 (12.6)	10 (9.5)	0.5
Currently	21 (7.2)	8 (7.6)	0.9
Medication for knee pain	11 (3.8)	4 (3.8)	0.9
Meniscectomy	7 (2.4)	1 (1.0)	0.4

ǂ See chapter 4.3 and chapter 5 for further explanation
* Right and/or left knee
† Two sided p-value for a difference between responders and non-responders
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 6. Baseline characteristics of responders and non-responders invited for follow-up examination, who had radiographic osteoarthritis grade 2 or more according to Kellgren in 1975-78. ╪

	Responders	Non-responders	p-value┼
Number §	239	89	
Age (yrs)	55.9 ± 6.0	56.8 ± 6.4	0.2
Body mass index (kg/m^2)	26.2 ± 2.9	27.0 ± 4.2	0.06
Body weight (kg)	73.7 ± 11.4	74.3 ± 12.3	0.6
Triceps skinfold thickness (mm)	16.7 ± 8.1	18.4 ± 7.3	0.2
Uric acid (mg/100 ml)	5.1 ± 1.4	4.8 ± 1.1	0.04
Number of women	137 (57.3)	57 (64.0)	0.3
Radiographic knee OA* (≥ 45 yrs)			
Grade 2	193 (80.8)	68 (76.4)	0.4
Grade 3-4	46 (19.2)	21 (23.6)	
Questionnaire			
Knee pain*	63 (26.4)	16 (18.0)	0.1
Pain walking stairs	52 (21.8)	10 (11.2)	0.03
Pain rising from chair	60 (25.1)	18 (20.2)	0.4
Stiffness arm/leg	73 (30.5)	17 (19.1)	0.04
Stiffness rising chair	67 (28.0)	21 (23.6)	0.4
Jogging/member sporting club	35 (14.6)	11 (12.4)	0.6
Smoking			
Never	88 (36.8)	34 (38.2)	0.8
Ex	68 (28.5)	23 (25.8)	
Current (at baseline)	83 (34.7)	32 (36.0)	
Physical examination			
Bony enlargement knee joint*	29 (12.1)	12 (13.5)	0.7
Function limitation knee joint*	22 (9.2)	10 (11.2)	0.6
Bony tenderness knee joint*	14 (5.9)	5 (5.6)	0.9
Pain on motion knee joint*	11 (4.6)	5 (5.6)	0.7
Heberden's nodes	22 (9.2)	12 (13.5)	0.3
Diagnosis of generalized OA	51 (21.3)	25 (28.1)	0.2
Diagnosis of localized OA	78 (32.6)	19 (21.3)	0.05

╪ See chapter 4.3 and chapter 6.1 for further explanation
§ 58/422 (13.7%) died, 36/364 (9.9%) lost to follow-up, and 328/364 (90.1%) eligible for follow-up
┼ Two sided p-value for a difference between responders and non-responders
* Right and/or left knee
Figures are means ± standard deviation or numbers with percentage between parentheses

Table A 7. Baseline characteristics of responders invited for follow-up examination and subjects lost to follow-up. All had radiographic osteoarthritis grade 2 or more according to Kellgren in 1975-78. ǂ

	Responders	Lost to follow-up	p-value†
Number*	239	36	
Age (yrs)	55.9 ± 6.0	56.2 ± 6.6	0.8
Body mass index (kg/m^2)	26.2 ± 2.9	25.6 ± 3.6	0.3
Body weight (kg)	73.7 ± 11.4	72.1 ± 12.9	0.4
Triceps skinfold thickness (mm)	16.7 ± 8.1	17.0 ± 7.9	0.9
Uric acid (mg/100 ml)	5.1 ± 1.4	5.0 ± 1.4	0.6
Number of women	137 (57.3)	23 (63.9)	0.5
Radiographic knee OA* (≥ 45 yrs)			
Grade 2	193 (80.8)	29 (80.6)	0.9
Grade 3-4	46 (19.2)	7 (19.4)	
Questionnaire			
Knee pain*	63 (26.4)	9 (25.0)	0.9
Pain walking stairs	52 (21.8)	6 (16.7)	0.5
Pain rising from chair	60 (25.1)	6 (16.7)	0.3
Stiffness arm/leg	73 (30.5)	11 (30.6)	0.9
Stiffness rising chair	67 (28.0)	7 (19.4)	0.3
Jogging/member sporting club	35 (14.6)	4 (11.1)	0.6
Smoking			
Never	88 (36.8)	10 (27.8)	0.5
Ex	68 (28.5)	13 (36.1)	
Current (at baseline)	83 (34.7)	13 (36.1)	
Physical examination			
Bony enlargement knee joint*	29 (12.1)	2 (5.6)	0.2
Function limitation knee joint*	22 (9.2)	2 (5.6)	0.5
Bony tenderness knee joint*	14 (5.9)	1 (2.8)	0.4
Pain on motion knee joint*	11 (4.6)	0 (0)	0.2
Heberden's nodes	22 (9.2)	5 (13.9)	0.4
Diagnosis of generalized OA	51 (21.3)	10 (27.8)	0.4
Diagnosis of localized OA	78 (32.6)	5 (13.9)	0.02

ǂ See chapter 4.3 and chapter 6.1 for further explanation

* 58/422 (13.7%) died, 36/364 (9.9%) lost to follow-up, and 328/364 (90.1%) eligible for follow-up

† Two sided p-value for a difference between responders and subjects lost to follow-up

* Right and/or left knee

Figures are means ± standard deviation or numbers with percentage between parentheses

Appendix B

Table B 1. Unadjusted odds ratios (OR) of several prognostic factors for cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according to knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR	p-value	OR	p-value	p-value
Age (years)					
45-49	1		1		
50-54	1.93	0.4	0.50	0.6	0.3
55-59	1.52	0.6	2.00	0.6	0.9
60-65	2.42	0.2	5.00	0.1	0.6
Body mass index (kg/m^2)					
< 24.35	1		1		
24.35-25.96	1.55	0.55	1.33	0.84	0.92
25.97-27.73	3.06	0.09	4.80	0.20	0.76
> 27.73	4.50	< 0.001	9.33	0.07	0.92
Weight (kg)					
< 69	1		1		
69-78	1.21	0.76	12.00	0.02	0.09
> 78	5.59	< 0.002	12.00	0.03	0.57
Skin fold thickness (mm)†					
< 12.0	1		1		
12.0-19.8	1.42	0.58	2.00	0.67	0.85
> 19.8	1.06	0.92	0.50	0.67	0.67
Uric acid (mg/100 ml)‡					
< 4.3	1		1		
4.3-5.4	1.19	0.76	6.67	0.03	0.11
> 5.4	2.38	0.10	5.56	0.07	0.45

§ See chapter 6.1 for further explanation
* Test for a difference between the odds ratios of the two strata
† n = 80
‡ n = 141

Table B 2. Unadjusted odds ratios (OR) of several prognostic factors for cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according to the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity*
	OR	p-value	OR	p-value	p-value
Age (years)					
45-49	1		1		
50-54	1.47	0.6	0.86	0.9	0.7
55-59	1.87	0.4	0.75	0.9	0.6
60-65	2.23	0.3	3.25	0.2	0.8
Body mass index (kg/m^2)					
< 24.35	1		1		
24.35-25.96	1.67	0.53	1.07	0.95	0.75
25.97-27.73	3.18	0.11	15.00	0.03	0.32
> 27.73	10.83	<0.001	4.50	0.12	0.48
Weight (kg)					
< 69	1		1		
69-78	1.50	0.53	5.14	0.07	0.28
> 78	5.33	0.003	12.00	0.01	0.50
Skin fold thickness (mm)†					
< 12.0	1		1		
12.0-19.8	1.59	0.50	1.67	0.64	0.97
> 19.8	1.07	0.92	0.75	0.80	0.79
Uric acid (mg/100 ml)‡					
< 4.3	1		1		
4.3-5.4	1.29	0.67	7.33	0.02	0.11
> 5.4	2.26	0.15	5.50	0.04	0.38

§ See chapter 6.1 for further explanation
* Test for a difference between the odds ratios of the two strata
† n = 80
‡ n = 141

Table B 3. Unadjusted odds ratios (OR) of categorized prognostic factors for cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according to knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR	p-value	OR	p-value	p-value
Gender (M=0, F=1)	0.64	0.29	0.33	0.17	0.48
Meniscectomy	0.78	0.76	5.68	0.11	0.17
Injury to the knee joint	0.99	0.98	8.00	0.01	0.05
Sport injury to the knee	0.76	0.66	0.53	0.61	0.80
Jogging or member of sporting club	0.64	0.43	0.53	0.62	0.89
Bow legs or knock knees	3.48	0.1	2.43	0.48	0.81
Chondrocalcinosis	2.57	0.19	5.67	0.11	0.57
Heberden's nodes	2.03	0.31	∞	0.004	0.15
Generalized OA	3.20	0.01	5.83	0.02	0.51
Localized OA	1.68	0.25	0.36	0.15	0.07
Smoking					
Never	1		1		
Ex	2.44	0.09	0.60	0.56	0.18
Current	1.76	0.31	0.40	0.28	0.15

§ See chapter 6.1 for further explanation

* Test for a difference between the odds ratios of the two strata

Table B 4. Unadjusted odds ratios (OR) of categorized prognostic factors for cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity *
	OR	p-value	OR	p-value	p-value
Gender (M=0, F=1)	0.69	0.40	0.35	0.14	0.42
Meniscectomy	2.92	0.19	0.62	0.57	0.19
Injury to the knee joint	1.61	0.39	2.69	0.20	0.60
Sport injury to the knee	0.71	0.62	0.56	0.54	0.84
Jogging or member of sporting club	0.81	0.73	0.22	0.08	0.24
Bow legs or knock knees	2.85	0.29	2.00	0.45	0.80
Chondrocalcinosis	3.00	0.13	4.25	0.19	0.80
Heberden's nodes	3.09	0.08	∞	0.02	0.38
Generalized OA	3.64	0.006	5.00	0.03	0.73
Localized OA	1.07	0.89	1.89	0.39	0.51
Smoking					
Never	1		1		
Ex	0.91	0.87	5.56	0.04	0.09
Current at baseline	1.69	0.32	0.19	0.12	0.09

§ See chapter 6.1 for further explanation
* Test for a difference between the odds ratios of the two strata

Table B 5. The relation of several occupation related factors with cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population, stratified according to knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR+	p-value	OR+	p-value	p-value
Physical activity					
Medium	1.85	0.3	0.67	0.7	0.4
High	1.59	0.4	0.50	0.6	0.4
Walking					
Medium	1.85	0.3	2.25	0.5	0.9
High	3.18	0.05	0.50	0.6	0.17
Standing					
Medium	4.96	0.02	3.00	0.3	0.7
High	4.84	0.02	1.00	1	0.3
Squatting, kneeling, crawling					
Medium	0.63	0.4	0.75	0.8	0.9
High	0.52	0.3	0.25	0.3	0.6
Knee knocking					
Medium	0.26	0.03	2.50	0.4	0.08
High	0.44	0.14	1.50	0.7	0.3
Lifting heavy objects					
Medium	0.91	0.9	2.4	0.5	0.5
High	1.25	0.7	0.45	0.4	0.4

§ See chapter 6.1 for further explanation
* Test for a difference between the odds ratios of the two strata
+ Odds ratio with lowest level as reference

Table B 6. The relation of several occupation related factors with cartilage loss in 142 subjects with radiographic osteoarthritis of the knee from the general population, stratified according to the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Physical activity					
Medium	1.48	0.6	0.78	0.8	0.5
High	1.43	0.6	0.67	0.7	0.5
Walking					
Medium	1.58	0.5	2.45	0.3	0.7
High	1.80	0.4	8.75	0.06	0.3
Standing					
Medium	3.54	0.06	2.67	0.3	0.8
High	2.75	0.1	2.78	0.3	0.9
Squatting, kneeling, crawling					
Medium	0.89	0.8	0.42	0.4	0.5
High	0.36	0.1	0.64	0.6	0.6
Knee knocking					
Medium	0.37	0.1	0.75	0.7	0.5
High	0.53	0.3	1.12	0.9	0.5
Lifting heavy objects					
Medium	0.97	0.9	0.71	0.7	0.8
High	0.99	0.9	3.33	0.3	0.4

§ See chapter 6.1 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio with lowest level as reference

Table B 7. The relation of body mass index (kg/m^2) at baseline with cartilage loss, osteophyte growth and overall progression in subjects with ROA of the knee with or without knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Cartilage loss					
Low ‡	1		1		
Medium	2.45	0.14	1.25	0.8	0.6
High	7.20	0.0003	5.00	0.09	0.8
Osteophyte growth					
low	1		1		
Medium	1.39	0.54	1.87	0.51	0.8
High	4.44	0.003	2.00	0.45	0.5
Overall progression					
Low	1		1		
Medium	2.01	0.14	2.25	0.42	0.9
High	7.14	0.0001	3.00	0.26	0.4
Knee pain at follow-up					
Low	1				
Medium	0.75	0.76	∞	0.09	0.2
High	4.15	0.04	∞	0.008	0.3

§ See chapter 6.2 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio
‡ Low is lowest level of body mass index

Table B 8. The relation of body mass index (kg/m^2) at baseline with cartilage loss, osteophyte growth and overall progression in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Cartilage loss					
Low ‡	1		1		
Medium	2.07	0.28	2.33	0.34	0.9
High	8.00	0.0004	5.13	0.05	0.7
Osteophyte growth					
Low	1		1		
Medium	2.58	0.11	0.60	0.54	0.2
High	6.98	0.0005	0.94	0.95	0.06
Overall progression					
Low	1		1		
Medium	2.56	0.06	1.28	0.8	0.5
High	7.39	0.0001	3.00	0.27	0.4
Knee pain at follow-up					
Low	1		1		
Medium	1.07	0.9	∞	0.09	0.3
High	3.96	0.04	∞	0.003	0.3

§ See chapter 6.2 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio
‡ Low is lowest level of body mass index

Table B 9. The relation of change in body weight with cartilage loss, osteophyte growth and overall progression in subjects with radiographic osteoarthritis of the knee with or without knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Cartilage loss					
Low ¶	1		1		
Medium	0.57	0.28	0.80	0.78	0.72
High	0.88	0.80	2.00	0.46	0.44
Osteophyte growth					
low	1		1		
Medium	0.77	0.60	1.37	0.69	0.54
High	1.62	0.32	3.60	0.20	0.48
Overall progression					
Low	1		1		
Medium	0.69	0.43	1.57	0.60	0.40
High	1.09	0.86	4.00	0.24	0.33
Knee pain at follow-up					
Low	1				
Medium	1.42	0.63	0.44	0.32	0.29
High	1.42	0.63	1.20	0.84	0.89

§ See chapter 6.2 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio
¶ Low means decrease in body weight, high is increase in body weight

Table B 10. The relation of change in body weight with cartilage loss, osteophyte growth and overall progression in 142 subjects with radiographic osteoarthritis of the knee from the general population stratified according the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Cartilage loss					
Low ¶	1		1		
Medium	0.65	0.42	0.64	0.57	0.99
High	0.89	0.83	1.50	0.63	0.60
Osteophyte growth					
Low	1		1		
Medium	0.76	0.60	1.54	0.58	0.45
High	1.56	0.39	3.86	0.15	0.40
Overall progression					
Low	1		1		
Medium	0.64	0.34	2.67	0.30	0.19
High	1.17	0.75	2.00	0.48	0.63
Knee pain at follow-up					
Low	1		1		
Medium	1.00	1	0.90	0.90	0.92
High	1.15	0.84	1.29	0.77	0.92

§ See chapter 6.2 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio
¶ Low is decrease in body weight, high is increase in body weight

Table B 11. The relation of Insulin-like growth factor-1 (nmol/l) with cartilage loss, osteophyte growth and overall progression in 141 subjects with radiographic osteoarthritis of the knee from the general population stratified according to knee pain at baseline. §

	Pain absent		Pain present		Heterogeneity*
	OR+	p-value	OR+	p-value	p-value
Cartilage loss					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	3.21	0.03	0.67	0.7	0.14
IGF-1 > 18.3	1.48	0.48	1.00	1	0.7
Osteophyte growth					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	1.23	0.67	2.33	0.4	0.5
IGF-1 > 18.3	1.39	0.50	8.56	0.02	0.09
Overall progression					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	1.58	0.33	1.00	1	0.7
IGF-1 > 18.3	1.41	0.47	8.67	0.05	0.17

§ See chapter 6.3 for further explanation
* Test for a difference between the odds ratios of the two strata
+ Odds ratio

Table B 12. The relation of Insulin-like growth factor-1 (nmol/l) with cartilage loss, osteophyte growth and overall progression in 141 subjects with radiographic osteoarthritis of the knee from the general population stratified according the grading of radiographic osteoarthritis (ROA) at baseline. §

	ROA grade 2		ROA grade 3-4		Heterogeneity*
	OR†	p-value	OR†	p-value	p-value
Cartilage loss					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	3.10	0.04	1.00	1	0.3
IGF-1 > 18.3	1.60	0.43	0.83	0.82	0.5
Osteophyte growth					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	1.24	0.68	2.10	0.4	0.6
IGF-1 > 18.3	1.49	0.44	5.20	0.05	0.2
Overall progression					
IGF-1 < 13.8	1		1		
IGF-1 13.8-18.3	1.42	0.47	1.52	0.65	0.9
IGF-1 > 18.3	1.34	0.61	8.57	0.04	0.15

§ See chapter 6.3 for further explanation
* Test for a difference between the odds ratios of the two strata
† Odds ratio

EEN WOORD VAN DANK EN HERINNERING

Na meer dan vier jaar intensief bezig te zijn geweest met dit promotie onderzoek is het goed eens stil te staan en terug te kijken over die vier jaar.

Beste Hans, we zijn vier jaar bezig geweest met dit onderzoek. Hoewel het oorspronkelijk in de bedoeling lag om de therapie van knieklachten in de huisartspraktijk te onderzoeken hebben we er goed aangedaan om het werk dat je zelf begonnen bent als het EPOZ-onderzoek af te maken. Verschillende follow-up studies zijn het resultaat geweest van jou initiatief. Voor wat betreft het onderzoek naar artrose is dit achteraf gezien uniek en op dit moment is er belangstelling voor het onderzoek naar artrose en follow-up studies in het bijzonder. Mocht het follow-up onderzoek naar knie artrose met enthousiasme ontvangen worden dan is dit voor het grootste deel te danken aan jouw initiatief en inzet. Naar het zich laat aanzien, maar nog niet geheel zeker, zal het niet meer gebeuren dat je nog als promotor op zult treden voor een promovendus die onderzoek heeft gedaan naar een aandoening van het bewegingsapparaat. Ik vind het bijzonder dat ik nog bij jou heb kunnen promoveren. Er zijn weinig onderzoekers met zo'n gevarieerd scala aan ervaringen, als clinicus, als epidemioloog en als iemand die letterlijk grensoverschrijdend onderzoek heeft gedaan door een warme belangstelling voor het werk in ontwikkelingslanden. Ik ben blij dat ik iets heb mogen leren van dat brede scala van jouw ervaringen. Wat ik heb geleerd laat zich het best omschrijven zoals je zelf de epidemiologie getypeerd hebt: "Met Ter Braak heeft het ons geleerd 'zindelijk te denken', en ziekte en gezondheid te plaatsen in de bredere context van de mens omringende wereld.". Maar ik heb meer van je geleerd dan het doen van onderzoek alleen. We hebben menige "boom" opgezet, hoewel, het zal niemand die jou kent verbazen, het van tijd tot tijd nodig was in deze bomen te snoeien. Niet duidelijk is wat de toekomst brengt maar bij mij blijft de herinnering "Het was een waardevolle ontmoeting".

Arno, beste kameraad, van jou had ik, tijdens mijn studietijd in Nijmegen, in alle toonaarden wel eens iets gehoord maar tot diepgaande gesprekken had dat nooit geleid. Op 1 april 1987 kwam hierin acuut een verandering toen wij samen begonnen aan onze opleiding tot epidemioloog. Al voor die datum hadden we in het enthousiasme om onderzoek te doen kunnen delen toen je na je sollicitatie belde om mijn indrukken te vernemen. Geen van beiden hebben we spijt gehad van onze keuze om epidemiologisch onderzoek te gaan doen, hoewel het salaris geregeld stof tot spreken gaf. In de jaren dat we samen een werkkamer deelden hebben we gedeeld in onze ervaringen, ideeën en gevoelens en tot op de dag van vandaag heeft dit voor mij een bijzondere betekenis. Ieder van ons gaat een eigen weg en gezien de drukke werkzaamheden is het niet uitgesloten dat we in de toekomst meer communiceren via "Letters to the editor" dan via brieven aan elkaar, desondanks verliezen we elkaar niet uit het oog en zullen we nog geregeld omzien in enthousiasme. Veel succes in je epidemiologische werk.

Beste Else en kamergenoot, samen hebben we onderzoek gedaan naar aandoeningen van het bewegingsapparaat, tegen weer en wil en ondanks en dankzij. Naar het zich laat aanzien gaan we hiermee door na ons vertrek van het instituut. Else, je bent een meid met karakter en je enthousiasme is aanstekelijk. Je directe

benadering is mij vreemd maar ik ben je in de loop van de tijd zeer gaan waarderen.

Beste Frank, we delen dezelfde universiteit als onze opleidingsplaats en we hadden elkaar als eens ontmoet toen ik mijn co-assistentschappen liep en jij je opleiding tot internist voltooide. Je hebt op vele manieren bijgedragen aan dit onderzoek, als een van de artsen die de respondenten onderzocht, door kritisch alle manuscripten door te lezen, suggesties te doen waardoor het onderzoek en de artikelen beter werden en door je betrokkenheid bij onderzoek van het bewegingsapparaat in het algemeen.

Beste Carlie, Marijke en Helen. Jullie zijn van alle medewerksters het meest bij dit project betrokken geweest. In het onderzoekcentrum hebben we als een hecht team samengewerkt. Eerlijk gezegd was het gezien jullie ervaring en inzet niet echt nodig dat ik ook nog meedeed, maar ja, een AIO moest ook wat. Het was mij een waar genoegen. Wat jammer Helen dat je eerder af moest haken. Marijke, in dit proefschrift staat de röntgenfoto centraal, de kwaliteit daarvan is dan ook cruciaal. Je hebt daar uitstekend voor gezorgd en bij het beoordelen van de foto's moest ik dan ook vaak denken: een echte "Ter Haar". Carlie, het is toch wel bijzonder om een medewerkster te hebben die in haar vrije tijd klassieke talen studeert. Je inbreng in dit onderzoek is vitaal gebleken. Je hebt je niet alleen tijdens kantooruren voor ingezet maar ook daarbuiten. Samen konden we de administratieve en organisatorische problemen uitstekend de baas. Dat jij en Helen zo makkelijk een andere baan konden vinden is, zo weet ik nu uit ervaring, niet alleen een kwestie van een schaarste op de arbeidsmarkt voor analisten. Veel succes in jullie nieuwe werk.

Beste Robert, je hebt de data-management zelfs tijdens drukke andere werkzaamheden voor andere projecten uitstekend verzorgd. Je zult goed slagen in je nieuwe werk.

Angela, met veel enthousiasme en inzet heb je tijdens je studie je wetenschappelijke stage op ons instituut gedaan. Je hebt meegedaan aan het onderzoek van de respondenten en de analyses gedaan voor hoofdstuk 4.2, hetgeen resulteerde in een publikatie. Ik heb op een heel plezierige wijze met je kunnen samenwerken.

Lilian, nog bedankt voor de data invoer van de eerste vragenlijst. Vele medewerkers en medewerksters hebben een steentje bijgedragen aan dit onderzoek maar speciaal wil ik toch Cilia noemen die altijd klaar stond om mee te helpen grote en kleine problemen op te lossen.

Van de statistici wil ik Theo en Dick bedanken voor het doorlezen van hoofdstuk 4.1 en het geven van waardevolle suggesties hierbij. Wim, beste buurman, ik ben blij dat ik bij jou te allen tijde aan kon kloppen voor statistisch advies.

Beste Stella, samen hebben we met veel plezier de cursus in Boston gedaan. Dat zou nog eens moeten gebeuren maar het is waarschijnlijker dat we op een andere manier contact houden. Op de afdeling hebben we elkaar de nodige support gegeven en ik vond het leuk om paranimf te zijn bij jouw promotie.

Met veel interesse en plezier hebben we voor het hoofdstuk over IGF-1 samengewerkt met Prof. Dr S.W.J. Lamberts (Afdeling Interne Geneeskunde III, Dijkzigt Ziekenhuis). Piet Uitterlinden van het laboratorium van Interne III van het

Dijkzigt Ziekenhuis heeft voor de bepaling van het IGF-1 gezorgd, waarvoor hartelijke dank.

Graag wil ik ook Miek van Leeuwen bedanken (Reumatologe van de afdeling Reumatologie, Academisch Ziekenhuis Groningen, hoofd Prof. Dr M. van Rijswijk) voor het bieden van de mogelijkheid om reumafactoren te bepalen die nodig waren voor hoofdstuk 4.3.

Antoon en Wim, jullie hebben vanuit een klinisch perspectief enkele hoofdstukken beoordeeld waardoor er een betere tekst tot stand kwam. Wie weet doet zich in de toekomst nog eens een gelegenheid voor artikelen te beoordelen of een onderzoeksproject te starten. Carin, ook jij hebt bijgedragen aan het tot stand komen van het proefschrift, het ga je goed.

Aan mijn vrienden van het Instituut Epidemiologie en Biostatistiek: zoals Wim Kan al zei: "Geen mens die dat proefschrift leest; nou ja, alleen je vrienden. Die lezen dat, die drinken je sherry op en zeggen: 'mooi proefschrift'.". Op 23 oktober denken we nog eens terug ...

Lieve Maria, veel is er te zeggen maar dit gedichtje voor jou, geschreven door iemand met een bijzondere gave, zegt genoeg.

WEES ER

Wees er
wie je bent
met gedachten
van nu van toen
Wees er
want jouw deel
een deel van het geheel
jouw zijn
betekent
Mens zijn
Voelen, kijken, de hand reiken
dat verstaan
en er niet aan voorbijgaan
Wees er
ook als de weg niet recht is
als ze je wegstrepen
als jouw deel niet telt
Wees er
want ik zal er zijn
ik zal de hand reiken
ik zal verstaan
Wees er
om dan verder te gaan

ABOUT THE AUTHOR

Jan Schouten was born on november 1-st 1958 in Nijmegen. He attended secondary school at "Nebo-Mariënbosch-Gabriël College" in Nijmegen and graduated in 1977 (Atheneum B). From 1977-1978 he studied chemistry at the catholic University Nijmegen.

In 1978 he started his medical study at the same university. During his study he participated in the IFMSA exchange program for medical students and spent 6 weeks at the University Hospital in Arhus, Denmark. He was a member of the Medical Working group for Developing Countries and in 1986 he worked for four months in the St. Anthony's Hospital, Dgodge in Ghana. In the same year he conducted a study on the cardiovascular and respiratory effects of adenosine in humans at the Department of Internal Medicine of the St Radboudhospital in Nijmegen (head: Prof. Dr A. van 't Laar) under the supervision of Dr P. Smits and Dr Th. Thien. In 1987 he obtained his medical degree.

In the same year the study, presented in this thesis, was started at the Department of Epidemiology and Biostatistics, Erasmus University Medical School (head: Prof. Dr H.A. Valkenburg, in 1988 succeeded by Prof. Dr A. Hofman). At this department he received his training as a researcher and epidemiologist. He followed several courses in (advanced) biostatistics, (advanced) epidemiology, clinical decision making and clinical trials at the Erasmus University Medical School, The New England Epidemiology Institute (K. Rothman, Boston) and the London School of Hygiene and Tropical Medicine.

He organized several educational programs and assisted in the education of medical students and participants of courses in epidemiology.