Nontraumatic Knee Complaints in Adults in General Practice

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Niet-traumatische knieklachten bij volwassenen in de huisartsenpraktijk

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Chapter 1

General Introduction

INTRODUCTION

Musculoskeletal diseases are one of the major causes of disability worldwide and were a major reason to initiate the Bone and Joint Decade [1]. For this particular decade (i.e. the first 10 years of the 21st century) the World Health Organization outlined the aim to improve the health-related quality of life of people with bone and joint diseases and injuries worldwide, by raising awareness and understanding of the importance of these severe conditions and by increasing the amount of research funding [2].

Although musculoskeletal pain, injury, and dysfunction affect all ages, the elderly are particularly susceptible [3]. The clinical syndrome of joint pain and stiffness in older persons is the most common cause of disability and health care consultation in this age group [4].

In Dutch general practice, knee symptoms (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (19/1,000 patients per year), mostly presenting as knee pain or functional loss of the knee joint [5, 6]. Approximately 60% of patients with nontraumatic knee symptoms are >25 years old and disorders most diagnosed within this group are bursitis, tendinitis, and osteoarthritis (OA) [5].

To gain insight and to improve the management of nontraumatic knee symptoms, more knowledge is needed on the predictors of good or bad prognosis, clinical classification criteria of knee symptoms, measurement instruments to assess knee function, and current medical consumption. Establishing which patients are at higher risk for progression or persisting knee complaints would be useful in the selection of patients for future studies evaluating the effect of therapies.

Since data on the topics mentioned above are scarce, especially in primary care, we performed a prospective cohort study in general practice to study the course and to assess prognostic factors of persisting knee complaints.

HONEUR KNEE COHORT

A subgroup of the HONEUR knee cohort was used to assess prognostic factors of persisting knee complaints, the prognostic value of the clinical American College of Rheumatism (ACR) criteria for knee OA, the validity of the DynaPort® Knee Test, and to describe medical consumption.

The HONEUR knee cohort is an observational prospective cohort study with one-year follow-up, with the aim to collect knowledge on prognosis and prognostic factors of knee complaints in a primary care setting [7]. In this study, 40 general practitioners (GPs) from 5 municipalities in the southwest of the Netherlands participated; all are connected

to the ErasmusMC GP Research Network HONEUR and represent a total population of about 84,000 persons. Recruitment began in October 2001 in 1 municipality and a new municipality was added approximately every 3 months thereafter. All GPs recruited up to October 2003 [7].

In total, 1068 consecutive patients visiting their GP with a new episode of knee symptoms were enrolled in the study and followed for 1 year. New symptoms were defined as symptoms presented to the GP for the first time; recurrent symptoms for which the GP was not consulted within the past 3 months were also considered to be new symptoms.

For the work in this thesis, all patients aged >35 years with nontraumatic knee complaints (n = 549) were used. Disability and pain were assessed every 3 months by means of self-reported questionnaires. To assess persisting knee complaints at 1-year follow-up, an additional question addressing experienced recovery or worsening was added to the last questionnaire. At baseline and at 1-year follow-up, patients underwent a standardized physical examination of their knee by a trained physiotherapist. The baseline physical examination was planned to take place as close as possible to the date of the consultation with the GP.

OSTEOARTHRITIS

Osteoarthritis (OA), a degenerative joint disease, is a disease affecting all joint structures, not just hyaline articular cartilage [8]. Radiographic OA of the knee affects more than 33% of persons aged 60 years and older, whereas 10-15% of persons aged 60 years and older have symptomatic knee OA in which symptoms are defined as knee pain on most days [8]. With the aging of the Western population the prevalence of OA in the coming 20 years is expected to increase by about 40%, making OA the fourth leading cause of disability [9, 10].

To standardize the clinical definition of OA, the ACR developed classification criteria with the aim to create standardized definitions for inclusion in trials and cohort studies [11]. For knee OA, Altman et al. developed these criteria to classify clinical OA, clinical and radiographic OA, and clinical and laboratory OA [12].

In the clinical setting, OA is primarily a clinical diagnosis and radiological investigations are not useful in establishing the degree of OA. This is due to the absence of a clear connection between the severity of symptoms and limitations, and the extent of radiological abnormalities [13-16]. In clinical OA research, however, objective signs of the presence of OA (e.g. radiographic OA in combination with symptoms, or alternatively the ACR criteria) are often used as inclusion criteria.

To optimize the management of OA, it is important to increase our knowledge on the predictors of progression of OA. If certain prognostic factors are shown to be modifiable they may indicate which tools are needed to intervene in the progression of OA; this may, in turn, enhance our ability to prevent or slow down OA progression. Even if these prognostic factors are not modifiable they can still be used to identify high-risk groups, which may have implications for patient information and management [17]. Knowledge about modifiable factors and high-risk groups is also relevant for clinical research, e.g. for identifying patients for studies that evaluate therapeutic interventions, including disease-modifying therapies.

In this thesis, we provide an overview of the available evidence from the literature on prognostic factors of knee OA progression.

Further, it is of interest to assess the prognostic value of the clinical ACR criteria (i.e. combined sets) for knee OA, rather than the prognostic value of the individual characteristics separately. A combined set of characteristics developed to classify knee OA might have a higher prognostic value than the individual characteristics. Therefore, in patients visiting the GP with nontraumatic knee complaints we assessed the prognostic value of fulfilling the clinical ACR criteria on persisting or worsening knee complaints, and an increase in disability at 1-year follow-up.

CONTENTS OF THIS THESIS

Chapter 2 assesses the longitudinal and cross-sectional validity of the DynaPort® Knee Test (DPKT) in adults with nontraumatic knee complaints in general practice. In addition, our primary care population is compared to a secondary care population in which the DPKT was previously shown to be valid.

In **Chapter 3** evidence is presented from the literature on prognostic factors of knee OA progression. The available studies were systematically reviewed using modern methods of identifying, assessing, and summarizing the evidence.

Chapter 4 describes which signs and symptoms, based on clinical history and physical examination taken at baseline, are predictive for persisting symptoms at 1-year follow-up in adults with nontraumatic knee symptoms in general practice.

In **Chapter 5** the prognostic value of fulfilling the clinical ACR criteria on persisting or worsening knee complaints, and an increase of disability at 1-year follow-up is assessed in patients visiting the GP with nontraumatic knee complaints. The distribution of the clinical ACR criteria in this primary care population is also described.

Chapter 6 presents the self-reported medical treatment at baseline and medical consumption during 1-year follow-up, and describes whether the medical policy of the

GP is in accordance with the current clinical guideline on nontraumatic knee problems issued by the Dutch College of General Practitioners.

Chapter 7 addresses the Practice Guideline of the Dutch College of General Practitioners for Nontraumatic Knee Problems in Adults. This guideline is developed based on the available evidence in medical literature and recommendations for daily practice are provided.

Chapter 8 reflects on the main findings of the previous chapters, as well as the study limitations and their implications.

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Chapter 2

Longitudinal and cross-sectional validity of the DynaPort® Knee Test in adults with nontraumatic knee complaints in general practice

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ABSTRACT

Objective: The aim of the study was to determine the cross-sectional and longitudinal validity of a performance-based assessment of knee function, DynaPort® KneeTest (DPKT), in first-time consulters with nontraumatic knee complaints in general practice.
Methods: Patients consulting for nontraumatic knee pain in general practice aged >18 years were enrolled in the study. At baseline and 6-months follow-up knee function was assessed by questionnaires and the DPKT; a physical examination was also performed at baseline.
Hypothesis testing assessed the cross-sectional and longitudinal validity of the DPKT.
Results: Eighty-seven patients were included for the DPKT, 86 were available for analysis. The studied population included 44 women (51.2%), the median age was 54 (range 18-81) years. At follow-up, 77 patients (89.5%) were available for the DPKT. Only 3 out of 11 (27%) predetermined hypotheses concerning the cross-sectional and longitudinal validity were confirmed. Comparison of the general practice and secondary care population showed a major difference in baseline characteristics, DynaPort Knee Score, internal consistency, and hypotheses confirmation concerning the construct validity.
Conclusion: The validity of the DPKT could not be demonstrated for first-time consulters with nontraumatic knee complaints in general practice. Measurement instruments developed and validated in secondary care are therefore not automatically also valid in primary care setting.

Keywords: Knee function; Cross-sectional validity; Longitudinal validity; DynaPort® Knee Test; General practice; nontraumatic knee complaints

INTRODUCTION

Musculoskeletal conditions are a major burden on individuals, health systems, and social care systems, with indirect costs due to disability being predominant [1]. Although musculoskeletal pain, injury, and dysfunction affect all ages, the elderly are particularly targeted [2]. In general practice, knee complaints take second place after back pain in the prevalence of musculoskeletal disorders (48 per 1,000 patients per year), most presented as knee pain or function loss of the knee joint [3]. Pain and function are also important clinical outcomes in research projects and both can be measured subjectively or objectively. A Visual Analog Scale or a Likert scale can be used to measure pain subjectively. Function can be measured both subjectively and objectively on "impairment" and "disability" level.

Several tests are available to measure the function of the knee joint on the "disability level," including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [4, 5], the Medical Outcomes Study Short Form-36 (SF-36) [6, 7], and the Knee Society Score (KSS) [8]. The WOMAC and the SF-36 are self-report questionnaires whereas the KSS is a clinical rating scale. The KSS is subdivided in the KSS knee assessment score (built by ratings of pain, range of motion, and stability of the knee) and KSS function score (built by walking, climbing stairs, and use of walking aids).

In view of the risk of inter and intraobserver bias and the length of time needed for the more objective knee function measurement (like the KSS), most investigators prefer to use the patient-based assessment scales like the WOMAC and the SF-36 [9-11]. Because various studies report a moderate correlation between self-reports and performance-based tests and it is assumed that they measure different aspects of knee function [12-17], it seems useful to deploy them next to each other.

The DynaPort® KneeTest (DPKT), an accelerometerbased system, was developed to objectively assess knee-related functional abilities in an unobtrusive, userfriendly way [18]. This test has proved to be a useful performance-based instrument for use in patients with knee osteoarthritis undergoing a total knee replacement, showing good reliability and validity [19, 20]. However, the validity of the DPKT for patients with knee complaints in general practice is not yet known. It remains to be tested to what extent such instruments validated in secondary care can be applied in the primary care setting.

Therefore, this study assessed the cross-sectional and longitudinal (= responsiveness) validity of the DPKT in adults with nontraumatic knee complaints in general practice.

METHODS

Study design and study population

A subgroup of patients of the prospective HONEUR knee cohort was enrolled for this DPKT study. A detailed description of the HONEUR knee cohort had been published previously [21]. In brief, consecutive patients visiting their general practitioner with a first episode of knee complaints were enrolled in the study and followed for 1 year. New complaints were defined as complaints that were presented to the GP for the first time. Recurrent complaints for which the GP was not consulted within the last 3 months were also considered new complaints. Exclusion criteria were knee complaints that required urgent medical attention (fractures, infection), patients with malignancies, neurological disorders or systemic musculoskeletal diseases (e.g., Parkinson's disease, Rheumatoid Arthritis, Amyotrophic Lateral Sclerosis), as well as patients that were incapable of understanding the ramifications of participation. At baseline and 1-year follow up, they underwent a physical examination of both knees. Disability and pain were assessed every three months by self-reporting questionnaires.

For the DPKT study, patients of two out of five participating communities of the HONEUR knee cohort with nontraumatic knee complaints and aged >18 years were enrolled and followed for 6 months. For this validation study, we had equipment and personal for maximal 150 patients, but at least 80 patients were considered to be sufficient [22, 23]. At baseline, information about the knee complaints (duration, intensity), daily activities and social setting was collected and a physical examination of the knee was performed to assess knee function and disability. Functional disability and pain were assessed at baseline and at 6 months follow up by self-reported questionnaires containing the WOMAC [4, 5], the SF-36 [6, 7], the KSS function questions [8], Coop Wonca (consists of charts which comprise six scales designed to measure functional health status in primary) [24], and questions about experienced recovery or worsening. The DPKT was also assessed at baseline and at 6-month follow up.

Dynaport® Knee Test

A detailed description of the DPKT has been published previously [18]. In brief, test persons wore belts around the chest, waist and legs containing accelerometers while performing 29 activities that were closely related to daily life activities and that are problematic for patients with knee complaints. The activities were categorized into four clusters: locomotion (walking), rising and descending (stairs, slopes, and wooden blocks), lifting and moving objects (carrying a tray or a bag, picking up a weight, and walking with a shopping trolley), and transfers (going to sit or lie down and then standing up again, as

well as bending forward to pick up a weight and returning to the upright position) [18]. Custom-made software (DynaScope) extracted the relevant features from the signals of the accelerometers in the belt (in terms of acceleration, movement time, range of motion, frequency, or specific ratios) [18]. The values of all parameters were transformed into a score for each cluster and into a total score (KneeScore).

A modified score (KneeScore2) was recently developed and presented by Mokkink et al. [19]. In this score, based on internal consistency analysis, the test was reduced to 23 activities and provided a more precise estimate of the knee function. Therefore, for our analysis we used the KneeScore2 instead of the conventional KneeScore.

Statistical analyses

Hypothesis testing

In the absence of a gold standard to measure knee function, hypothesis testing was used to assess the cross-sectional and longitudinal validity. In accordance with guidelines for psychometric evaluation of self-report questionnaires [25], we formulated in advance 12 specific hypotheses about the expected associations between the KneeScore2 and other measures of the knee function (e.g., KSS knee function score, experienced change of knee function). The formulated predetermined hypotheses (Table 1) were based on the results of previous studies of the DPKT [12, 18, 20, 26] as well as on common sense (i.e., requirements the DPKT had at least to comply with, e.g., a difference between DynaPort cluster scores "rise and descent" when dichotomized on experienced discomfort in walking stairs). Of these hypotheses, at least nine (75%) had to be confirmed to support validity [25].

For the associations between KneeScore2 and other measures of knee function, mean scores were used and tested for significance with independent t-tests. In the absence of normally distributed outcome measures, we decided to use the median score and nonparametric tests for statistical significance (Wilcoxon) for all analyses. Based on the defined hypotheses, variables were dichotomized and the difference in KneeScore2 was tested for significance. In addition, correlations (Spearman) between continuous variables and KneeScore2 were calculated.

A p-value <0.05 was considered statistically significant. SPSS software version 11 was used to analyze the data.

Comparison between the validity of the DPKT in a primary care and secondary care population

If the DPKT was found not to be valid, we would then compare our primary care population with a secondary care population in which the DPKT was previously shown to be valid [19].

Table 1: Hypotheses to assess the cross-sectional and longitudinal validity

Hypothesis	Hypothesis confirmed
Statistically significant difference between DynaPort total scores in women when dichotomized on experienced bother in domestic work.	No
Statistically significant difference between DynaPort total score when dichotomized on age (cutoff point 60 years)	No
Statistically significant difference between DynaPort total scores when dichotomized on Coop-Wonca‡ physical health	No
Statistically significant difference between Dynaport cluster score 'rise & descent' when dichotomized on experienced discomfort when walking stairs (Lysholm#)	No
Statistically significant difference between DynaPort cluster scores 'rise & descent' and 'transfers' when dichotomized on range of motion (KSS*)	Yes
Statistically significant difference between DynaPort cluster scores 'transfers' when dichotomized on squatting (Lysholm#)	No
Higher correlation between DynaPort cluster score 'rise & descent' and KSS-function score than correlations between the other DynaPort scores and KSS-function (difference > 0.10)	Yes
Higher correlation (> 0.10) between DynaPort total score and SF-36 physical function than correlation between Dynaport total score and SF-36 bodily pain	Yes
High correlation (> 0.75) between passive flexion and DynaPort total score	No
Statistically significant difference between DynaPort total score when dichotomized on experienced change (worsening/recovery) in health (SF-36)	No
High correlation (> 0.75) between change in DynaPort total score and change in SF-36 score (follow up versus baseline)	No
High correlation (> 0.75) between change in DynaPort total score and change in SF-36 physical functioning score (follow up versus baseline)	No

‡ Coop-Wonca: measure experienced health by charts which comprise six scales designed to measure functional health status in primary care; # Lysholm questions: dichotomized on discomfort vs. no discomfort when walking stairs or squatting; * KSS: KSS knee function, scale 0 – 100, cut off point 50

Baseline characteristics (gender, age, body mass index [BMI]) and function scores (KSS, WOMAC, SF-36, KneeScore2) of the two study populations would be compared and, in addition, the hypotheses used in the study of Mokkink et al.[19] would also be applied in our population.

Internal consistency

To assess the internal consistency of the activities within the clusters of the DPKT the Cronbach's alpha was calculated and subsequently compared to the internal consistency of the clusters in the study of Mokkink et al. [19].

RESULTS

Study population

For the DPKT there were 330 eligible patients of which 87 participated. Reasons for nonparticipating were unwillingness or inability to match a date or hour for the extra visits required for the measurements [21].

Of these 87 patients, the data of 86 persons were available for analysis and data of one person were lost due to technical problems. The study population included 44 women (51.2%) and the median age was 54 (range 18 - 81) years; additional baseline characteristics are given in Table 2. There was no statistical significant difference in age, gender, BMI, or severity between patients included in the study and patients who were unable to attend the measurements.

At follow up, 77 persons (89.5%) were available for a second DPKT assessment. Comparison of persons available for analysis at follow up and those lost to follow up (n = 9, 10.5%) showed no significant differences with respect to age, gender, BMI, KSS knee score, KSS function score, and KneeScore2 at baseline. A significant difference (p = 0.02) between those lost to follow up and persons available for follow up was found for the SF-36 total score (median SF-36 score 55.8 vs. 73.2, respectively).

Hypothesis testing

Difference between KneeScore2 when dichotomized on experienced bother in domestic work (women), age, and experienced physical health (Table 1, hypothesis 1-3)

For experienced bother in domestic work, no significant difference for KneeScore2 was found (p = 0.09) (no bother vs. bother in domestic work, n = 13, median 41.2 [31.7 - 49.8] and n = 31, median 37.7 [18.1 - 51.9], respectively).

For age, there was no significant difference (p = 0.27) in KneeScore2 between persons aged < 60 years (n = 55, median 40.7 [4.7 - 89.6]) and those aged 60 years and older (n = 31, median 37.6 [10.2 - 51.8]).

Table 2: Baseline characteristics of the study population (n = 86)

Characteristics	
Age; median (range) in years	54 (18 – 81)
Women; n (%)	44 (51.2%)
Duration of complaints; n (%)	
< 1 week	10 (11.6%)
1 – 3 weeks	22 (25.6%)
3 weeks – 3 months	24 (27.9%)
3 months – 1 year	20 (23.3%)
> 1 year	10 (11.6%)
Bilateral complaints; n (%)	34 (39.5 %)
Left worse than right knee	8 (9.3%)
Right worse than left knee	19 (22.1%)
Left as much as right knee	7 (8.1%)
BMI; median (range)	25.5 (18.8 – 41.1)
KSS knee assessment score; median (range)*	67.0 (26.0 – 98.0)
KSS knee function score; median (range)*	90.0 (10.0 – 100.0)
SF-36 total score; median (range)#	71.7 (30.1 – 89.0)
SF-36 physical functioning score, median (range)#	75.0 (5.0 – 100.0)
KneeScore 1; median (range)◊	54.2 (11.4 – 73.9)
KneeScore 2; median (range)◊	41.0 (4.7 – 89.6)

For all scores: higher score represents a better knee function
KSS: Knee Society Score, scale 0-100; # SF-36: Medical Outcome Study Short Form-36, scale 0-100; ◊ DynaPort KneeScore1, scale 0-100; DynaPort KneeScore 2, expressed in Z-scores, no minimum and maximum

Also, for good vs. poor experienced physical health, no significant difference (p = 0.07) was found for KneeScore2 (n = 42, median 43.0 [4.7 - 89.6] and n = 44, median 37.9 [10.2 - 54.2], respectively).

Difference between DynaPort cluster scores "rise and descent" when dichotomized on experienced discomfort in walking stairs and KSS knee assessment score (Table 1, hypothesis 4-5)

Because the DynaPort cluster score "rise and descent" aims to measure problems in, for example, walking stairs, we expected to find a significant difference in this cluster when dichotomized on experienced discomfort in walking stairs. However, no significant difference (p = 0.08) in cluster score "rise and descent" was found (discomfort vs. no discomfort, n = 18, median 38.1 [15.5 - 54.0] and n = 68, median 44.2 [16.4 - 50.2], respectively).

For the KSS knee assessment score (scale 0 - 100), we found a significant difference

($p < 0.01$) in cluster score "rise and descent" between persons with a KSS knee assessment score ≤ 50 (n = 21, median 34.3 [15.5 - 48.3]) and those with a KSS knee assessment score > 50 (n = 63, median 40.9 [16.4 - 54.0]).

Difference between DynaPort cluster scores "transfers" when dichotomized on KSS knee assessment score and experienced discomfort in squatting (Table 1, hypothesis 5-6)

A significant difference ($p = 0.01$) was found for the DynaPort cluster score "transfers" between persons with a KSS knee assessment score ≤50 (n = 21, median 32.3 [3.6 - 45.8]) and those with a KSS knee assessment score > 50 (n = 63, median 38.2 [16.4 - 54.0]).

For experienced discomfort when squatting, no significant difference ($p = 0.40$) in DynaPort cluster score "transfers" was found (discomfort vs. no discomfort, n = 69, median 36.7 [3.6 - 55.7] and n = 17, median 38.2 [10.9 - 70.3], respectively).

Correlations between KneeScore2 and DynaPort cluster scores and KSS function score, range of motion, and SF-36 scores (Table 1, hypothesis 7-9)

Data on the correlations between the KneeScore2 and DynaPort cluster scores and the different function scores (KSS function and knee assessment score, SF-36) are given in Table 3.

We expected and found a higher (> 0.10) correlation between the KSS knee function score and DynaPort cluster score "rise and descent" than between the correlations between the KSS knee function score and the other cluster scores and KneeScore2. Also a higher correlation (> 0.10) was expected and found for the correlation between the KSS knee assessment score and the DynaPort cluster score "rise and descent" compared to the other DynaPort cluster scores and KneeScore2.

Because the angle of passive flexion (degrees) of the knee, assessed at physical examination, could represent the severity of complaints, we expected a high correlation (> 0.75) between the angle of passive flexion and KneeScore2, but found a low correlation ($r = 0.14$).

Hypotheses concerning longitudinal validity (Table 1, hypothesis 10-12)

We expected to find a significant difference for the change in KneeScore2 (baseline to follow up) when dichotomized on experienced recovery, but only a borderline significance was reached ($p = 0.08$, experienced recovery vs. no change or worsening, n = 12, median 4.7 [-2.7 - 27.9] and n = 43, median 2.1 [-51.4 - 26.4], respectively).

Further, we expected a high correlation between the change in KneeScore2 and the change in SF-36 total score, but this was not found ($r = 0.22$). The correlation between the change in KneeScore2 and the change in SF-36 physical functioning score was also moderate ($r = 0.36$).

Table 3: Correlations between KneeScore2 and KSS knee assessment and function score, SF-36 and passive flexion

	Spearman's rho
KSS function score and:	
'Rise & descent'	0.36
'Locomotion'	0.14
'Transfers'	0.12
'Lift & move'	0.20
KneeScore2	0.21
Range of motion (KSS knee assessment) and	
'Rise & descent'	0.34
'Locomotion'	0.32
'Transfers'	0.19
'Lift & move'	0.23
KneeScore2	0.25
SF-36 physical functioning and KneeScore2	0.27
SF-36 pain and KneeScore2	0.10
SF-36 total score and KneeScore2	0.12
Passive flexion# – KneeScore2	0.14

in degrees

Comparison with the validity of the DPKT in a secondary care population

Appendix presents a comparison of the characteristics of our primary care population and a secondary care population in which the DPKT had shown to be valid [19].

The baseline characteristics of the two populations differed considerably. Compared with the secondary care population [19], our population was younger (mean age 52.0 ± 13.5 vs. 66.7 ± 9.7 years), included less women (51.2% vs. 73.2%), and had a lower BMI (mean BMI 26.1 ± 4.1 vs. 31.4 ± 6.2).

Also, all knee function scores (baseline/follow up vs. pre- and postoperative) were higher in our population. For example, the KneeScore2 at baseline was 39.6 ± 10.9 in our population compared to 25.3 ± 11.9 in the preoperative secondary care population. Thus, knee function in our population was better than the knee function in the secondary care population.

In addition to our formulated hypotheses, we also tested the hypotheses used in the study by Mokkink et al. [19] to assess the construct validity. Table 4 presents a comparison between the two populations. In the secondary care population, 8 of the 10 hypotheses were confirmed, whereas in our primary care population only 1 of the 10 hypotheses was confirmed.

Table 4: Comparison between the primary care and secondary care of the construct validity of the KneeScore as assessed in secondary care, based on their prior hypotheses about the expected correlations

	Prior hypotheses in the study by Mokkink et al. [26]		Results primary care (current study)		Results secondary care (Mokking et al. [26])	
	r_s direction	r_s magnitude #	r_s	Hypothesis confirmed	r_s	Hypothesis confirmed
Range of motion	Positive	Low - Moderate	0.13	Yes	0.06	Yes
KSS functioning	Positive	High	0.21	No	0.64	Yes
WOMAC physical functioning	Positive	High	0.22	No	0.55	Yes
SF-36 physical functioning	Positive	High	0.27	No	0.62	Yes
QOM physical therapist	Positive	High	NA	-	0.68	Yes
QOM patient	Positive	Moderate	NA	-	0.32	No
Mean duration of activities	Positive	High	-0.41	No	0.93	Yes
KSS pain	Negative	Low	0.13	No	-0.47	No
SF-36 pain	Negative	Low	0.10	No	-0.32	Yes
WOMAC pain	Negative	Low	0.22	No	-0.35	Yes

Abbreviations: KSS, Knee Society Score; WOMAC, Western Ontario and McMaster University Osteoarthritis Index; SF-36, Medical Outcome Study Short Form-36; QOM, quality of movement (scored on 5-point scale by the physical therapist after the first test and by the patient in the questionnaire); range of motion: angle of active flexion (primary care) or active range of the operated leg (secondary care); NA: not assessed.
Spearman correlation magnitude high = r > 0.50, moderate r 0.35 – 0.50, low = r < 0.35

Internal consistency (Cronbach's alpha)

All clusters of the DPKT had a lower internal consistency compared with the study of Mokkink et al. [19]. We found a Cronbach's alpha of 0.67 for the cluster Locomotion, for Rise and Descent 0.85, for Transfers 0.65, and for Lift and Move 0.82. In the study by Mokkink et al. [26], a Cronbach's alpha of 0.95 was found for Locomotion, for Rise and Descent 0.91, for Transfers 0.73, and for Lift and Move 0.93.

DISCUSSION

Cross-sectional and longitudinal validity

The present study was performed to assess the crosssectional and longitudinal validity of the DPKT in patients visiting their general practitioner with nontraumatic knee complaints.

To assess the cross-sectional and longitudinal validity, 12 hypotheses were tested (Table 1). Of the nine hypotheses concerning the cross-sectional validity, only three were confirmed, all of which concerned the DynaPort cluster score "rise and descent." The remaining hypotheses concerning the KneeScore2 and the other cluster scores were not confirmed. Of the three hypotheses concerning the longitudinal validity, none was confirmed.

To determine the validity of the DPKT, nine hypotheses (75%) had to be confirmed. Thus, based on our findings, the cross-sectional and longitudinal validity of the DPKT could not be demonstrated for patients with nontraumatic knee complaints presenting in general practice.

Comparison with the validity in a secondary care population

Our findings are in contrast with the results of Mokkink et al. who confirmed the validity of the DPKT for a hospital-based population [19]. Our population consisted of first-time consulters with knee complaints (i.e., patients with a first or new episode of knee complaints) in general practice, whereas the secondary care population consisted of patients before or after a total knee replacement.

The difference between the two populations was considerable. All baseline characteristics and knee function scores differed between the two populations. Our population had less severe complaints and knee function was better.

For the hypotheses tested in both populations, a major difference was also found. In the secondary care population, hypothesis testing supported the construct validity. Even when we tested the validity of the DPKT based on these hypotheses, the validity was not supported.

Moreover, in our population the internal consistency of the clusters proved to be lower than the internal consistency reported by Mokkink et al. [19]. However, reliability, as assessed by internal consistency, is a measure of the extent to which the same or similar values are assigned to a static phenomenon. Cronbach values at or above 0.80 are generally accepted as indicative of adequate reliability [27].

In conclusion, substantial differences were found between a primary and secondary care population for baseline characteristics (e.g., age, gender, severity) as well as for the different knee function scores (e.g., KSS, KneeScore2). These differences had a strong influence on the construct validity and the internal consistency of the DPKT in these populations.

These data illustrate the need for validation in primary care of a measurement instrument that has been developed and validated in a secondary care setting.

KneeScore

In the present study we used the modified KneeScore2 for the analyses as presented by Mokkink et al.[19]. This KneeScore2 was developed based on internal consistency analysis and provides a more precise estimate of the knee function. We also analyzed the conventional KneeScore, but these scores provided even less confirmation of the hypotheses (two of the 12 hypotheses were confirmed). Thus, the KneeScore used could not explain the absence of validity of the DPKT in a community-based population.

Hypothesis testing

In the absence of a gold standard to measure knee function, we tested predefined hypotheses to assess the validity of the DPKT. In these hypotheses, we did not include the WOMAC function questionnaire because of the increasing uncertainty about the validity of this questionnaire[28, 29]. However, even if we had included hypotheses related to comparison of the KneeScore2 and the WOMAC function score, it would not support the validity of the DPKT. Despite the fact that a significant association was found for the KneeScore2 when dichotomized on a high vs. a low WOMAC function score, the correlation between the KneeScore2 and the WOMAC function score was also low ($r = 0.15$). Because the requisite for validity was a confirmation of at least 75% of the hypotheses, this would not be improved by the extra hypotheses including the WOMAC score.

With regard to generic and disease specific questionnaires, age, gender, and comorbidity is known to influence the outcome[30]. For KneeScore 2, there was no statistical significant difference in patients with or without comorbidity ($p = 0.41$). This could influence our findings. However, the DPKT was found to be valid in a secondary care population[19] in which you may assume a higher prevalence of comorbidity. Therefore, we think the presence of comorbidity would not provide other findings with regard to the validity of the DPKT.

In our hypotheses, we expected a high correlation between the difference in the KneeScore2 and the difference in the SF-36 total and physical functioning score. It is debatable whether these expected correlations are too high. One can argue that the correlation between two instruments measuring knee function has to be moderate or low considering different aims of the instruments. A high correlation between the tests implies that they measure the same thing and this would not provide extra information. The DPKT aims to provide a more objective function score than the self-assessed SF-36 questionnaire. Many validation studies consider a correlation of ≥ 0.5 satisfactory to establish construct validity[13]. Even if we had included hypotheses assuming a lower correlation (e.g., 0.5) it would still not provide validity because 9 of the 12 hypotheses had to be confirmed. Besides, a correlation of 0.27 between KneeScore2 and the SF-36

physical functioning score is very low compared with correlations between performance based measures and self-report measures of function in other studies [13, 31].

Using hypothesis testing with predefined hypotheses to evaluate the validity of the DPKT is not often applied in assessing the cross-sectional and longitudinal validity of a measuring instrument [25, 32]. In the absence of a gold standard, most studies base the validity on the correlation between the measuring instrument and other specific measures. An example is the validation of the WOMAC in an Italian population [33]. Disadvantage of this method is that it provides less information about whether the instrument is able to measure what it is supposed to measure. Using hypothesis testing allows inclusion of hypotheses about specific test requirements the test has to comply with. Another advantage of predefined hypotheses is that it may reduce bias due to interpretation of the analyses. Therefore, this method provides more information about the instrument's ability to serve its purpose [32].

We choose to dichotomize most variables. Reason for this is that the findings are easier to interpret in clinical practice. However, consequences of dichotomizing are overall reduced statistical power, loss of information and an increased probability of a type II error [34, 35].

Sample size

Because our sample size is relatively small (n = 86) it might be harder to find a significant association between KneeScore 2 and the other parameters. However, the validity of the DPKT has previously been shown in a secondary population with a smaller sample size (n = 41 preoperative, n = 51 postoperative) [18, 20, 26]. Besides, for all measurement properties a sample size of at least 50 patients is considered necessary to receive a positive rating [22]. Also, other validation studies of performance based tests showed smaller sample sizes to be sufficient to validate the measure instrument [36 - 41].

In summary, we could not demonstrate the crosssectional and longitudinal validity of the DPKT in a primary care setting. This emphasizes the need to validate measurement instruments in a primary care setting.

Appendix: Comparison between our primary population and the secondary care population of Mokkink et al. [26*]

	Primary care (baseline) (n = 86)	Primary care (follow-up) (n = 76)	Secondary care (pre-operative) (n = 41)	Secondary care (post-operative) (n = 51)
Age (years)	52.0 ± 13.5	52.0 ± 13.5	66.7 ± 9.7	67.7 ± 10.1
Female gender (percentage)	44 (51.2%)	37 (48.1%)	30 (73.2%)	37 (72.5%)
BMI	26.1 ± 4.1	26.1 ± 4.1	31.4 ± 6.2	29.3 ± 4.8
KSS knee assessment score	64.6 ± 17.2	NA	NA	NA
KSS function score	85.1 ± 15.9	89.6 ± 10.9	52.6 ± 18.4	73.2 ± 20.0
KSS pain score	25.8 ± 14.0	35.1 ± 13.6	13.4 ± 12.7	40.8 ± 14.6
WOMAC total score	73.9 ± 18.3	86.9 ± 15.8	NA	NA
WOMAC physical functioning score	74.6 ± 19.4	87.6 ± 16.1	53.3 ± 15.2	59.5 ± 23.6
WOMAC pain score	72.9 ± 18.0	85.7 ± 16.4	46.4 ± 21.7	15.6 ± 17.0
WOMAC stiffness score	71.2 ± 24.0	84.2 ± 19.4	54.5 ± 20.2	28.7 ± 17.0
SF-36 total score	69.9 ± 11.2	74.5 ± 8.7	NA	NA
SF-36 physical functioning score	69.7 ± 20.6	84.0 ± 15.0	34.8 ± 14.5	59.5 ± 23.6
KneeScore2	39.6 ± 10.9	43.7 ± 8.9	25.3 ± 11.9	35.9 ± 12.8
DynaPort cluster scores:				
Locomotion	42.6 ± 11.9	46.3 ± 10.3	25.2 ± 14.5	39.2 ± 14.0
Rise and descent	40.2 ± 18.8	43.2 ± 10.1	20.4 ± 13.6	31.1 ± 15.0
Transfers	36.1 ± 10.4	41.2 ± 12.1	28.0 ± 12.7	35.1 ± 14.0
Lift and move objects	39.7 ± 12.8	44.2 ± 11.1	27.6 ± 13.3	38.4 ± 12.9

* Values are mean ± SD; NA: Not Assessed; Follow up primary care population: 6 months

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Chapter 3

Prognostic factors of progression of osteoarthritis of the knee: a systematic review of observational studies

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ABSTRACT

Objective: To provide an overview of prognostic factors of knee osteoarthritis (OA) progression.

Methods: We searched Medline and Embase up to December 2003 according to a specified search strategy (keywords for disease, location, and study design). Studies that fulfilled predefined criteria were assessed for methodologic quality. Study characteristics and associations were extracted and the results were summarized according to a best evidence synthesis.

Results: Of the 1,004 studies found, 37 met the inclusion criteria. Methodologic quality was assessed and only high-quality studies were included (n = 36). The best evidence synthesis yielded strong evidence that hyaluronic acid serum levels and generalized OA are predictive for progression of knee OA. Sex, knee pain, radiologic severity, knee injury, quadriceps strength, and regular sport activities were not predictive. Conflicting evidence for associations was found for several factors including body mass index and age. Limited evidence for an association with progression of knee OA was found for several factors, including the alignment (varus/valgus) of the joint. Limited evidence for no association with progression of OA was also found for several factors, including meniscectomy, several markers of bone or cartilage turnover, and the clinical diagnosis of localized OA.

Conclusion: Generalized OA and level of hyaluronic acid seem to be associated with the radiologic progression of knee OA. Knee pain, radiologic severity at baseline, sex, quadriceps strength, knee injury, and regular sport activities seem not to be related. For other factors, the evidence was limited or conflicting.

Keywords: Osteoarthritis; Knee; Progression; Prognostic factors; Systematic review

INTRODUCTION

Radiographic osteoarthritis (OA) of the knee affects more than 33% of persons age 60 years and older, whereas 10–15% of persons age 60 years and older have symptomatic knee OA in which symptoms are defined as knee pain on most days [1]. Because of aging of the population, the prevalence of OA is expected to increase in the next decades [2]; in western countries, the increase in prevalence in the next 20 years is expected to be around 40%, making OA the fourth leading cause of disability [2,3].

To optimize the management of OA, it is important to increase our knowledge regarding the predictors of progression of OA. If certain prognostic factors are modifiable, they may enhance our ability to reduce OA progression. Even if these prognostic factors are not modifiable, they can still be used to identify high-risk groups, which may have implications for patient information and the perspective of medical treatment [4]. Knowledge about modifiable factors and high-risk groups is also relevant for clinical research, such as for evaluating therapeutic interventions including disease-modifying therapies.

Several original studies have reported on prognostic factors of knee OA progression. Until now, however, a systematic overview of the determinants of progression of knee OA has not been available. To gain insight into the prognostic factors of progression of knee OA, we systematically reviewed the available studies on this topic using modern methods of identifying, assessing, and summarizing the available evidence.

MATERIALS AND METHODS

Identification of studies

To identify the observational studies on this subject, a search for relevant studies published up to December 2003 was performed in Medline and Embase. Key words used were knee, osteoarthritis (or arthritis, or arthrosis), prognostic (or progressive, or predictive, or precipitate), and case-control (or cohort, or retrospective, or prospective, or longitudinal, or follow-up). Screening the list of references of all identified relevant articles extended the search. A study was included when it fulfilled all of the following criteria: patients in the study had clinical or radiographic evidence of knee OA; the study investigated factors associated with the radiologic and/or clinical progression of knee OA; the follow up period was at least 1 year; the study design was a prospective cohort or a nested case-control study; the article was written in English, Dutch, German, or French; full text was available for the article; and the study population had no underlying pathology (e.g., rheumatoid arthritis, bacterial infection) of the joint.

Methodologic quality

To assess the methodologic quality of the included articles, a scoring list was used (Table 1) based on the scoring lists used by Lievense et al [5] and Scholten-Peeters et al [6] and on the framework for assessing internal validity of articles dealing with prognosis as described by Altman [7]. All studies were scored independently by 2 of the reviewers (JNB and MYB or MR). For each study, a total quality score was computed by counting all positively rated items (maximum score 13 points). In case of disagreement, both reviewers tried to achieve consensus. When consensus was not achieved, a third reviewer (BWK) was asked to give a final judgment.

Data extraction

Study characteristics (follow-up duration, study population characteristics) were extracted and, when possible, the odds ratio (OR) or relative risk was provided or calculated. Otherwise, other measures of associations (hazard ratio, correlations) or values for statistical significance (p-value) of the reported association were given.

Table 1. Criteria list for the methodological assessment of study quality

Study population
Description of source population
Valid inclusion criteria
Sufficient description of the baseline characteristics
Follow-up
Follow-up at least 12 months
Prospective data collection
Loss to follow-up ≤ 20%
Information about loss to follow-up
Exposure
Exposure assessment blinded for the outcome
Exposure measured identically in the studied population at baseline and/or follow-up
Outcome
Outcome assessment blinded for exposure
Outcome measured identically in the studied population at baseline and follow-up
Analysis
Measure of association and measures of variance given
Adjusted for age, sex or severity

Evidence synthesis

ORs or relative risks were statistically pooled when clinical and statistical homogeneity in several studies was assumed. In the absence of homogeneity, a best evidence synthesis was used to summarize the data.

The level of evidence was based on the guidelines of van Tulder et al [8] and was divided into the following levels: 1) strong evidence (consistent [>75%] findings among multiple [≥ 2] high-quality studies); 2) moderate evidence (findings in 1 high-quality study and consistent findings in multiple low-quality studies); 3) limited evidence (findings in 1 high-quality study or consistent findings in multiple low-quality studies); and 4) conflicting evidence (provided by conflicting findings [< 75% of the studies reported consistent findings]). When strong evidence was provided only by studies with a small sample size, we decided to judge those studies as not strongly associated. Articles were judged as high quality when they had a quality score >8 (> 60% of the maximal attainable score). Only statistically significant associations were considered as associated prognostic factors in the best evidence synthesis.

When several radiologic outcomes for the progression of OA were provided, the best evidence synthesis was based on the increase in the Kellgren and Lawrence (K/L) score or the decrease in joint space width (JSW).

RESULTS

Studies included

Of the 1,004 articles identified using our search strategy, 37 articles met the criteria for inclusion. In the methodologic quality assessment, the 3 reviewers scored 520 items in total and agreed on 402 items (77%; kappa 0.40). The 118 disagreements were resolved in a single consensus meeting. Almost all studies were of high quality and scored in the range of 9 to 12 (maximum score 13). One study (Sahlström et al. [9]) scored 6 (< 50%); because this was the only study of low quality, we excluded it from the analysis. An overview of the characteristics of the included studies (n = 36) is presented in Table 2.

All studies had a prospective research design. The studied populations were either population or hospital based. For the definition of OA, most studies used the Kellgren and Lawrence criteria or JSW. One study [12] used the Osteoarthritis Research Society International Atlas for the definition of OA, and another study [19] used the presence of clinical and radiologic OA. All studied populations, except 2 [12,34], contained more women than men. Progression was defined as radiologic progression in almost all studies. Only 4 studies [11,19,23,24,45] (15%) also reported on a clinical outcome (total knee replacement).

Table 2: Study characteristics of the reviewed manuscripts*

Author	Additional study information	Follow-up (months)	Definition osteoarthritis for inclusion	Study population	Mean age (years)	Percentage women	No. of patients	Quality score
Cerejo (2002) [10]	Subgroup of the MAK study	18	K/L	Elderly of the community	64 (sd 10,8)	73	230	12
Dieppe (1997) [11]	The Bristol 'OA 500' study	37.6	K/L	500 consecutive people seen at a rheumatology clinic with peripheral joint symptoms attributable to radiographic evidence of OA at that joint site	65.3	68	415	12
Felson (2003) [12]		15 and 30	Osteoarthritis Research Society International Atlas	Persons aged 45 years and older with symptomatic knee OA in the Veterans Administration hospital in Boston	66.2 (sd 9.4)	42	223	12
McAlindon (1996-a) [13]	Framingham Osteoarthritis Study	120	K/L	Population-based group followed for more than 40 years	70,3	63	556	12
Sharma (2001) [14]	MAK (Mechanical Factors in Arthritis of the Knee) study	18	K/L, JSW	Participants in MAK recruited: community-based study with senior citizens	64,0 (sd 11,1)	75	230	12
Spector (1994) [15]	Chingford study (subsample)	24	K/L	Women with unilateral knee OA, population based-cohort	56,8 (sd 5,9)	100	58	12
Vilim (2002) [16]	Subset of trial of glucosamine (Pavelka)	36	K/L, JSW	Patients with symptomatic primary knee OA, part of a placebo-arm of a 3-year trial	62.8 (range 48 - 74)	71	48	12
Bagge (1992) [17]	Subsample of cohort	48	K/L	Population-based study of the elderly (75-year old) in Göteborg	-	57	74	11
Brandt (1999) [18]		31.5 (range 23.0-6.2)	K/L	Independent community-based individuals, at least 65 years old, recruited from central Indiana bij random digit dialing	nonprogr: women 71.6, men 72.4; progr: women 70.1, men 72.7	70	82	11

Dieppe (1993) [19]		60	Clinical and radiological OA	Patients referred to a hospital based rheumatology unit	62.2 (sd 1.5)	65	60	11
Dieppe (2000) [20]	The Bristol 'OA 500' study	96	K/L	500 consecutive people seen at a rheumatology clinic with peripheral joint symptoms attributable to radiographic evidence of OA at that joint site	65,3	68	349	11
Ledingham (1995) [21]		24 (range 12 - 60)	K/L	Consecutive patients attending a general rheumatologic clinic with symptomatic knee OA	71 (range 34 -91)	63	188	11
Miyazaki (2002) [22]		72	K/L	Patients aged over 50 years with primary knee OA , and knee pain in daily activities managed at an orthopedic unit	69.9 (sd 7.8)	81	74	11
Sharif (1995-a) [23]		60	K/L	Patients referred to the Bristol Royal Infirmary Rheumatology	64.2 (sd 11.6)	69	75	11
Sharif (1995-b) [24]		60	JSW	Hospital out-patients with clinical knee OA	Not provided	Not provided	57	11
Sharif (2000) [25]		60	K/L	Hospital out-patients with clinical knee OA	65.2 (sd 9.9)	61	40	11
Zhang (1998) [26]	Framingham Osteoarthritis Study	96	K/L	Population-based group of women followed for more than 40 years	71 (range 63 -91)	100	551	11
Zhang (2000) [27]	Framingham Osteoarthritis Study	96	K/L	Population-based group of women followed for more than 40 years	71 (range 63 - 91)	100	473	11
Bettica (2002) [28]	Chingford study	48	Osteophytes and JSW	1003 women, aged 45-64 years	Not provided	100	216	10
Cooper (2000) [29]	Study based on population cohort	61.2	K/L	Men and women aged > 55 yr with knee pain, registered at a large general practice in Bristol	71.3	72	354	10
Doherty (1996) [30]		30	K/L	135 consecutive patients referred to hospital with knee OA	71 (range 41-88)	56	134	10
Felson (1995) [31]	Framingham Osteoarthritis Study	97.2 (sd 3.6)	K/L	Population based group followed for more than 40 years	70.8 (sd 5.0)	64	869	10

Table 2 continued

Author	Additional study information	Follow-up (months)	Definition osteoarthritis for inclusion	Study population	Mean age (years)	Percentage women	No. of patients	Quality score
Fraenkel (1998) [32]	Framingham Osteoarthritis Study, nested case-control	48	K/L	Population based group followed for more than 40 years	Not provided	67	423	10
Hart (2002) [33]	Chingford study	48	Osteophytes and JSW	1003 women, aged 45-64 years	54,1 (sd 5,9)	100	830	10
Lane (1998) [34]		108	Osteophytes and JSW	Members of the 50-plus runners association of the United States and a sample of the Stanford University Community	66	33	55	10
McAlindon (1996-b) [35]	Framingham Osteoarthritis Study	120	K/L	Population-based group followed for more than 40 years	70,3	64	640	10
Pavelka (2000) [36]		60	K/L	Patients with primary OA undergoing evaluation for their arthritis at the Prague Institute of Rheumatology, aged over 40 years	59.1 (sd 8.0)	76	139	10
Schouten (1992) [37]		146.4 (sd 10.8)	K/L	Population survey, study of several chronic diseases, especially rheumatic diseases, in Zoetermeer,The Netherlands, in subjects aged 20 years and older	57.2 (sd 6.1)	59	239	10
Sharma (2003) [38]	MAK	18	K/L	Community-based study with senior citizens	64,0 (sd 11,1)	74	171	10
Spector (1992) [39]		132 (range 108 - 180)	K/L	Group 1: consecutive patients attending a rheumatology clinic with OA of the hand or knee; group 2: symptomatic patients with OA of the hand or knee enrolled in a short-term drug study	group 1: 60, group 2: 61	Overall: 72	63	10

Spector (1997) [40]	Chingford study	48	K/L	Women with unilateral knee OA, population-based cohort	Not provided	100	845	10
Sugiyama (2003) [41]		48	JSW	Population-based survey, women aged 40-59 years with knee pain and early primary OA of the tibiofemoral joint	50.2 (sd 6.0)	100	110	10
Bruyere (2003-a) [42]	Subjects part of a double-blind placebo-controlled study evaluating the effect of glucosamine sulfate	36	ACR criteria	Patients from the outpatient clinic of the Bone and Cartilage Metabolism Research Unit of the University Hospital Centre in Liege, Belgium.	66.0 (sd 7.3)	76	157	9
Bruyere (2003-b) [43]	Subjects part of a double-blind placebo-controlled study evaluating the effect of glucosamine sulfate	36	ACR criteria	Patients from the outpatient clinic of the Bone and Cartilage Metabolism Research Unit of the University Hospital Centre in Liege, Belgium.	66.0 (sd 7.3)	76	157	9
Schouten (1993) [44]		146.4 (sd 10.8)	K/L	Population survey, study of several chronic diseases, especially rheumatic diseases, in Zoetermeer,The Netherlands, in subjects aged 20 years and older	57.4 (sd 6.34)	59	239	9
Wolfe (2002) [45]		31.2 (sd 48) and 102 (sd 99.6)	ACR criteria	Consecutive patients with OA of the knee of hip seen for clinical care at the Arthritis Center, Kansas, USA	63.41 (sd 11.77)	77	583	9

* OA: Osteoarthritis; MAK: Mechanical Factors in Arthritis of the Knee; K/L = Kellgren and Lawrence;
JSW: Joint Space Width; ACR-criteria: American College of Rheumatology criteria

Study results

An overview of the potential prognostic factors and their relationship to the progression of radiologic OA is presented in Tables 3, 4, 5, and 6 and is summarized below.

Systemic factors (Table 3)

Schouten et al [37] found a significant association between age and progression of knee OA only for the comparison of the fourth quartile (higher age) versus the first quartile (lower age). In their study, there was no significant association reported for the second and third quartile versus the first quartile. Miyazaki et al [22] also found a significant association between age and progression of knee OA. Bagge et al [17], Dieppe et al [19], and Felson et al [31] reported no significant association, but an OR or p-value was not provided. Wolfe and Lane [45] also found no significant association.

Although no ORs or p-values were given, Dieppe et al [19] and Felson et al [31] reported no significant association between sex and progression of knee OA. Ledingham et al [21] reported an association between sex and the change in cyst number but not between sex and change in K/L grade or joint space narrowing (JSN). Miyazaki et al [22], Schouten et al [37], Spector et al [39], and Wolfe and Lane [45] found no significant association between sex and progression of knee OA.

Hart et al [33] reported no statistically significant difference in bone density between the nonprogressive group and the progressive group (OR or p-value not provided). In contrast, Zhang et al [27] found an association between high versus low bone density and progression of knee OA (fourth versus first quartile OR 0.1, 95% confidence interval [95% CI] 0.03–0.3). The difference in progression of knee OA for the change in bone density of the lowest versus the second lowest group was not significant.

For insulin-like growth factor 1 (IGF-1), Schouten et al [37] found a significant association between progression of knee OA in the third versus the first tertile only. No significant association was found for the second versus the first tertile. Fraenkel et al [32] found no association between IGF-1 and progression of knee OA in the comparison of the third tertile versus the first; they also found no significant association for the comparison between men and women of the second tertile versus the first tertile.

Zhang et al [26] investigated the relationship between estrogen use and radiologic progression of knee OA. No significant association was found between current use, past use, or never use of estrogen and progression of knee OA. Schouten et al [37] found no association between uric acid concentration and progression of knee OA.

Disease characteristics (Table 4)

Only the study by Wolfe and Lane [45] found a significant relationship between knee pain at baseline and progression of knee OA. Dieppe et al [19] also investigated the relationship

Table 3: Systemic factors discussed in the reviewed studies*

Determinant	Author	Instrument of measurement	Definition of progression of osteoarthritis	Outcome (95% CI)#
Age	Bagge (1992) [17]	Dichotomous	Increase K&L grade ≥ 1	Not associated‡
	Dieppe (1993) [19]		JSN ≥ 2 mm	Not associated‡
	Felson (1995) [31]		Increase in K&L grade 2 to ≥ 3	Not associated‡
	Miyazaki (2002) [22]	Continuous in years	JSN > 1 grade on a four grade scale	OR = 1.22 (1.05 - 1.41)
	Schouten (1992) [37]	Fourth quartile vs first	Change in JSW ≤ -1 on a 9-point scale –4 to +4	OR = 3.84 (1.10 - 13.4)
	Wolfe (2002) [45]	Continuous in years	JSN score = 3 (maximal score on a four-point scale)	HR = 1.00 (0.98 - 1.02)
Female gender	Dieppe (1993) [19]		JSN ≥ 2 mm	Not associated‡
	Felson (1995) [31]		Increase in K&L grade 2 to ≥ 3	RR = 1.43 (0.80 – 2.58)
	Ledingham (1995) [21]		Increase in K&L grade, change in JSW, osteophytes, sclerosis, attrition, cut-off points not provided	Not associated‡
			Change in cyst size/number	OR = 2.17 (1.13 - 4.15)
	Miyazaki (2002) [22]		JSN > 1 grade on a four grade scale	OR = 2.14 (0.34 - 13.50)
	Schouten (1992) [37]		Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 0.50 (0.22 - 1.11)
	Spector (1992) [39]		Change of ≥ 1 grade JSN on a four-point scale or ≥ 10% reduction in JSW	p = 0.3
	Wolfe (2002) [45]		JSN score = 3 (maximal score on a four grade scale)	HR = 0.73 (0.44 - 1.19)
Low bone density	Hart (2002) [33]	Low vs high	Change of ≥ 1 grade of JSN on a four-point scale	Not associated‡
	Zhang (2000) [27]	BMD changes -0.04-0 vs < -0.04 g/cm^2	Increase of ≥ 1 grade in K&L score (baseline K&L ≥ 2)	OR = 0.4 (0.1 - 1.2)
		BMD changes >0 vs <-0.04 g/cm^2		OR = 0.3 (0.1 - 0.8)
		Second quartile vs first		OR = 0.3 (0.1 - 0.9)
		Third quartile vs first		OR = 0.2 (0.1 - 0.6)
		Fourth quartile vs first		OR = 0.1 (0.03 - 0.3)

Table 3 continued

Determinant	Author	Instrument of measurement	Definition of progression of osteoarthritis	Outcome (95% CI)#
IGF-1	Fraenkel (1998) [32]	Third tertile vs first in women	Increase of ≥ 1 grade on K&L score (baseline K&L≥ 2)	OR = 0.9 (0.5 - 1.6)
		Third tertile vs first in men		OR = 0.9 (0.3 - 3.0)
	Schouten (1993) [44]	Third tertile vs first	Change ≥ 2 overall score of changes of radiographic signs of OA on a five-point scale	OR = 2.58 (1.01 - 6.60)
Estrogen	Zhang (1998) [26]	Past estrogen use vs never use	Increase of ≥ 1 grade on K&L score (baseline K&L ≥ 2)	OR = 0.9 (0.6 - 1.4)
		Current estrogen use vs never use		OR = 0.4 (0.1 - 1.5)
Uric acid concentration	Schouten (1992) [37]	Highest vs lowest tertile	Change in JSW ≤ -1 on a 9-point scale –4 to +4	OR = 1.36 (0.46 – 4.02
		Middle vs lowest tertile		OR = 1.05 (0.36 - 3.00)

* OA = osteoarthritis; 95% CI = 95% confidence interval; K/L = Kellgren and Lawrence; JSN = joint space narrowing; OR = odds ratio; JSW = joint space width; HR = hazard ratio; RR = relative risk; BMD = bone mass density; IGF-1 = insulin-like growth factor 1.
#All outcomes were adjusted for age and sex (if applicable).
‡ No OR with 95% CI or p value provided.

between knee pain at baseline and a subsequent operation of the knee, and found a significant association ($p \leq 0.001$).

For markers of bone or cartilage turnover, Bettica et al [28] found a relationship between the level of type I collagen telopeptides in urine and progression of knee OA (p-value not provided). One study by Bruyere et al [42] and 2 studies by Sharif et al [23,25] found a significant association between the level of hyaluronic acid in serum and progression of knee OA. Conflicting associations were found for the level of keratan sulfate and the level of cartilage oligomeric matrix protein (COMP). With regard to COMP, Bruyere et al [42] found no significant association (OR or p-value not provided) in contrast to Sharif et al [24] and Vilim et al [16]. Bruyere et al [42] found no significant associations between osteocalcin, pyridinoline, or deoxypyridinoline and progression of knee OA (OR or p-values not provided). Doherty et al [30] found a statistically significant association for the level of inorganic pyrophosphate in the synovial fluid (OR 0.97, 95% CI 0.95–0.99). Ledingham et al [21] found a significant association between the presence of calcium pyrophosphate crystals and change in attrition of the knee joint (OR 2.41, 95% CI 1.33–4.39); the relationship of this determinant to progression in the K/L score or JSN was not provided. Sugiyama et

al [41] found a significant association between the level of type II procollagen propeptide and progression of knee OA ($p \leq 0.001$).

Concerning severity of OA, only Wolfe and Lane [45] found a significant association between the initial JSW score and progression. Ledingham et al [21] found a significant association with the change in attrition; in their study, no association was found between radiologic severity and change in the K/L score or JSN. Contradictory associations were found in the relationship between clinical severity and progression of knee OA [11,45].

Whereas Schouten et al [37] reported a significant association with Heberden's nodes, Cooper et al [29] found no significant association.

Ledingham et al [21] and Schouten et al [37] both reported a significant positive association between the presence of generalized OA (radiologically and/or clinically determined) and progression of knee OA. The clinical diagnosis of local OA made by a physical examination was not related to radiologic progression of knee OA in the study by Schouten et al [37].

Dieppe et al [19] found no association with duration of symptoms (OR or p-value not provided) and Wolfe and Lane [45] found a borderline significant association. In contrast to the significant relationship between C-reactive protein level (CRP) and progression of knee OA found by Spector et al [40], Sharif et al [25] did not find a significant association.

Ledingham et al [21] described synovial fluid volume and nodal warmth in relation to progression of knee OA. For synovial fluid volume as a continuous variable, a significant relationship was found (change in K/L score OR 1.03, 95% CI 1.01–1.05; change in attrition OR 1.80, 95% CI 1.00–1.05). With regard to nodal warmth in relation to change in K/L score, a significant relationship was found (OR 1.80, 95% CI 1.02–3.17).

Felson et al [12] found an association between medial bone marrow edema lesions versus no medial lesions in relation to progression of knee OA (OR 5.6, 95% CI 2.1–14.8). No association was found between lateral bone marrow edema lesions versus no lateral lesions in relation to progression.

Intrinsic factors (Table 5)

Three studies [10,14,22] reported a statistically significant association between varus alignment and progression of OA measured by a decrease in JSW. A nonsignificant relationship between the varus alignment and progression of OA was only found in the analysis of the K/L grade 0–1 group in the study by Cerejo et al [10]. In the study by Miyazaki et al [22], a statistically significant OR was found for the univariate analysis of varus alignment and progression of knee OA (OR 3.10, 95% CI 1.07–9.12), but not in the multivariate analysis. Cerejo et al [10] and Sharma et al [14] also investigated the relationship between valgus alignment and progression of lateral knee OA. Both studies found a statistically significant relationship with progression of OA (valgus versus nonvalgus OR 10.44 and 4.89, respectively). Sharma et al [14] also compared varus with neutral/mild valgus and

Table 4: Disease characteristics discussed in the reviewed studies*

Determinant	Author	Instrument of measurement	Definition of progression of OA	Outcome (95% CI)#
Knee pain	Cooper (2000) [29]	Present vs absent	Increase in ≥ 1 grade K&L score (baseline K&L ≥ 1)	OR = 0.8 (0.4 - 1.7)
			Increase in ≥ 1 grade K&L score (baseline K&L ≥ 2)	OR = 2.4 (0.7 - 8.0)
	Dieppe (1993) [19]	Present vs absent	JSN ≥ 2 mm	Not associated‡
	Miyazaki (2002) [22]	Present vs absent	JSN ≥ 1 grade on a four grade scale	OR = 0.93 (0.78 - 1.11)
	Spector (1992) [39]	Present vs absent	Change of ≥ 1 grade JSN on a four-point scale or 10% reduction in JSN	p = 0.2
	Wolfe (2002) [45]	Present vs absent	JSN score = 3 (maximal score on a four grade scale)	HR = 1.55 (1.07 - 2.24)
Markers bone / cartilage turnover				
Hyaluronic acid (serum)	Bruyere (2003-a) [42]	High serum level vs low	Change in mean JSW, cut-off point not provided	p = 0.02
	Sharif (1995-a) [23]	High serum level vs low	JSN ≥ 2 mm or knee joint surgery	p = 0.007
	Sharif (2000) [25]	High serum level vs low	JSN ≥ 2 mm or knee joint surgery	OR = 2.32 (1.16 - 4.66)
Keratan sulfate (serum)	Bruyere (2003-a) [42]	High serum level vs low	Change in mean JSW, cut-off point not provided	p = 0.02
	Sharif (1995-a) [23]	High serum level vs low	JSN ≥ 2 mm or knee joint surgery	p = 0.539
COMP (serum) #	Bruyere (2003-a) [42]	High serum level vs low	Change in mean JSW, cut-off point not provided	Not associated‡
	Sharif (1995-b) [24]	High serum level vs low	JSN ≥ 2 mm or knee joint surgery	p < 0.001
	Vilim (2002) [16]	High serum level vs low	JSN > 0.5 mm	p < 0.05
Severity				
Radiologic severity	Bruyere (2003-b) [43]	Radiographic severity, high vs low	JSN ≥ 0.5 mm	RR = 2.39 (0.99 - 5.79)
	Miyazaki (2002) [22]	JSW, >3 mm vs < 3 mm	JSN ≥ 1 grade on a four-point scale	OR = 0.74 (0.25 - 2.19)
	Ledingham (1995) [21]	Change in ≥ 1 radiographic feature vs no change	Change in attrition, cut-off point not provided	OR = 1.72 (1.36 - 2.19)
			Increase in K&L score or change in JSW, cut-off points not provided	Not associated‡
	Pavelka (2000) [36]	Joint space narrowing, continuous variable	Change in K&L grade ≥ 1	Not associated‡

	Wolfe (2002)[45]	Initial JSN score, high vs low	JSN score = 3 (maximal score on a four-point scale)	HR 2.62 (2.03 - 3.40)
Clinical severity	Dieppe (1997)[11]	Change in Steinbrocker grade (functional status)	Change ≥ 2 mm joint space and change in grade of sclerosis or osteophytes	p = 1.0
	Wolfe (2002)[45]	Global severity, continuous variable	JSN score = 3 (maximal score on a four-point scale)	HR = 1.02 (1.01 - 1.03)
		HAQ# disability, high vs low		HR = 1.34 (0.93 - 1.93)
Heberden's nodes	Cooper (2000)[29]		Increase of ≥ 1 grade on K&L score (baseline K&L ≥ 1)	OR = 0.7 (0.4 - 1.6)
			Increase of ≥ 1 grade on K&L score (baseline K&L ≥ 2)	OR = 2.0 (0.7 - 5.7)
	Schouten (1992)[37]	Presence of Heberden's nodes at baseline	Change in JSW ≤ -1 on a 9-point scale –4 to +4	OR = 5.97 (1.54 - 23.1)
Osteoarthritis	Ledingham (1995)[21]	Multiple joint OA vs local joint OA	Increase in K&L grade, cut-off point not provided	OR = 2.39 (1.16 - 4.93)
			Change in attrition	OR = 2.42 (1.02 – 5.77)
			Change in JSW, osteophytes, cyst, sclerosis, cut-off points not provided	Not associated‡
	Schouten (1992)[37]	Clinical diagnosis of generalized OA by physical examination	Change in JSW ≤ -1 on a 9-point scale –4 to +4	OR = 3.28 (1.30 - 8.27)
		Clinical diagnosis of localized OA by physical examination		OR = 1.17 (0.51 - 2.72)
Duration of symptoms	Dieppe (1993)[19]		JSN ≥ 2 mm	Not associated‡
	Wolfe (2002)[45]	Continuous in years	JSN score = 3 (maximal score on a four-point scale)	HR = 1.03 (1.00 - 1.05)
CRP#	Sharif (2000)[25]	Continuous variable	JSN ≥ 2 mm or knee joint surgery	OR = 1.12 (0.81 - 1.55)
	Spector (1997)[40]	Continuous variable	Increase K&L grade ≥ 1	p = 0.006

* COMP = cartilage oligomeric matrix protein; HAQ = Stanford Health Assessment Questionnaire; CRP = C-reactive protein; see Table 3 for additional definitions.

All outcomes were adjusted for age and sex (if applicable).

‡ No OR and 95% CI or p value provided.

Table 5: Intrinsic factors discussed in the reviewed studies*

Determinant	Author	Analysis of determinant	Definition of progression of osteoarthritis	Outcome (95% CI)#
Alignment	Cerejo (2000) [10]	Varus vs non-varus in K/L grade 0-1	Increase > 1 grade JSN on a 4-point scale	OR = 2.50 (0.67 - 9.39)
		Varus vs non-varus in K/L grade 2		OR = 4.12 (1.92 - 8.82)
		Varus vs non-varus in K/L grade 3		OR = 10.96 (3.10 - 37.77)
		Valgus vs non-valgus in K/L grade 2		OR = 2.46 (0.95 - 6.34)
		Valgus vs non-valgus in K/L grade 3		OR = 10.44 (2.76 - 39.49)
	Miyazaki (2002) [22]	Varus vs non-varus	Increase ≥ 1 grade JSN on a four-point scale	OR = 0.90 (0.66 - 1.23)‡
	Sharma (2001) [14]	Varus vs non-varus	Increase ≥ 1 grade in JSN on a four-point scale	OR = 4.09 (2.20 - 7.62)
		Varus vs neutral/mild valgus		OR = 2.98 (1.51 - 5.89)
		Valgus vs non-valgus		OR = 4.89 (2.13 - 11.20)
		Valgus vs neutral/ mild varus		OR = 3.42 (1.31 - 8.96)
Adduction moment	Miyazaki (2002) [22]	≥ 5 vs < 5	Increase ≥ 1 grade JSN on a four-point scale	OR = 6.46 (2.40 - 17.45)
Knee injury	Cooper (2000) [29]	Yes vs no	Increase of ≥ 1 grade K&L score (baseline K&L ≥1)	OR = 1.2 (0.5 - 3.0)
			Increase of ≥ 1 grade K&L score (baseline K&L ≥2)	OR = 1.1 (0.3 - 4.4)
	Schouten (1992) [37]	Injury knee joint, yes vs no	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 2.62 (0.93 - 7.36)
		Sport injury, yes vs no		OR = 0.62 (0.17 - 2.19)
Meniscectomy	Schouten (1992) [37]	Yes vs no	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 2.28 (0.57 - 9.03)
Chondrocalcinosis	Schouten (1992) [37]	Yes vs no	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 2.01 (0.55 - 7.42)

* See Table 3 for definitions.

All outcomes were adjusted for age and sex (if applicable).

‡ Univariate analysis OR = 3.10 (95% CI 1.07–9.12).

valgus with neutral/mild varus. In both comparisons, a statistically significant association was found (OR 2.98 and 3.42, respectively).

Miyazaki et al [22] also investigated the association between the adduction moment and progression of OA. For the adduction moment, a statistically significant association was reported.

Two studies reported the relationship between injury of the knee joint and progression of OA. Both studies found no statistically significant relationship. In the study by Cooper et al [29], the relationship between previous knee injury and progression of OA was investigated. In the study by Schouten et al [37], knee injury was assessed at follow-up. Schouten et al [37] also investigated the relationship between sport injury and progression of OA, but no statistically significant association was found.

For the relationship between meniscectomy and progression of OA, Schouten et al [37] found no statistically significant association. In the same study, the evaluated relationship between chondrocalcinosis and progression of knee OA was not statistically significant. Hart et al [33] investigated the relationship between the history of a fracture and the progression of OA, but no statistically significant relationship was found (OR or p-value not provided).

Extrinsic factors (Table 6)

In the study by Cooper et al [29], a significant relationship with body mass index (BMI) was only found in the comparison of the highest tertile versus the lowest tertile in the group with baseline K/L grade 2 or higher. No statistically significant relationship was found in the comparison of the middle tertile versus the lowest tertile in the group with baseline K/L grade 1 or higher or grade 2 or higher (OR 2.3, 95% CI 0.8–6.4 and OR 1.8, 95% CI 0.4–8.2, respectively) and in the comparison of the highest versus the lowest tertile in the group with baseline K/L grade 1 or higher. The studies by Dieppe et al [19], Miyazaki et al [22], and Spector et al [15] found no statistically significant relationship between BMI and the progression of OA. Schouten et al [37] found a significant association in the 2 highest quartiles versus the lowest quartile. In the comparison of the second quartile versus the first quartile, no statistically significant association was found. Ledingham et al [21] only found a significant association for the relationship of BMI with JSN. In that study, a borderline significant association was found for the relationship with the change in osteophytes and no statistical association was found in the relationship between change in K/L grade. Wolfe and Lane [45] also found a borderline significant relationship between BMI and progression of OA. Spector et al [15] also investigated the relationship between change in BMI and progression of OA, but no statistically significant association was found (OR or p-value not provided).

Two studies [18,38] investigated the relationship between quadriceps strength at baseline and progression of OA. Both studies found no statistically significant association.

Table 6: Extrinsic factors discussed in the reviewed studies*

Determinant	Author	Analysis of determinant	Definition of progression of osteoarthritis	Outcome (95% CI)#
BMI	Cooper (2000) [29]	Highest tertile vs lowest	Increase of ≥ 1 grade K&L score (baseline K&L ≥ 1)	OR = 2.6 (1.0 - 6.8)
		Highest tertile vs lowest	Increase of ≥ 1 grade K&L score (baseline K&L ≥ 2)	OR = 1.3 (0.3 - 5.0)
	Dieppe (1993) [19]	Continuous variable		Not associated‡
	Ledingham (1995) [21]	Continuous variable	Change in joint space, cut-off point not provided	OR = 1.07 (1.02 - 1.14)
			Change in osteophytes, cut-off point not provided	OR = 1.06 (1.00 - 1.12)
			Change in K&L grade, cyst, attrition, cut-off points not provided	Not associated‡
	Miyazaki (2002) [22]	Continuous variable		OR = 1.21 (0.91 - 1.61)
	Schouten (1992) [37]	Second quartile vs first	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 1.77 (0.48 - 6.50)
		Third quartile vs first		OR = 5.28 (1.54 - 18.1)
		Fourth quartile vs first		OR = 11.1 (3.28 - 37.3)
	Spector (1994) [15]	Third vs first tertile	Increase in K&L score or JSN, cut-off point not provided	RR = 4.69 (0.63 - 34.75)
	Wolfe (2002) [45]	Continuous variable	JSN score = 3	HR = 1.03 (1.00 - 1.06)
Quadriceps strength	Brandt (1999) [18]	Progressive vs non-progressive group§	Increase ≥ 1 grade K&L score	Not associated‡
	Sharma (2003) [38]	Higher vs lower quadriceps strength§	Increase ≥ 1 grade JSN	p = 0.09
Running	Lane (1998) [34]	Dichotomous¶	Increase ≥ 1 grade of score based on JSW, osteophyte formation and subchondral sclerosis	Not associated‡
	Schouten (1992) [37]	Dichotomous§	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 0.53 (0.17 - 1.68)
Regular sport	Cooper (2000) [29]	Dichotomous§	Increase of ≥ 1 grade K&L score (baseline K&L ≥ 1)	OR = 0.7 (0.4 - 1.6)
			Increase of ≥ 1 grade K&L score (baseline K&L ≥ 2)	OR = 0.9 (0.3 - 2.5)
	Schouten (1992) [37]	Physical activity: highest vs lowest level¶	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 0.43 (0.11 - 1.76)

		Walking: highest vs lowest level¶		OR = 1.47 (0.36 - 6.03)
		Standing: medium vs lowest level¶		OR = 3.80 (1.03 - 13.96)
		Standing: highest vs lowest level¶		OR = 2.09 (0.43 - 10.31)
Nutrition variables	McAlindon (1996-a) [13]	Vitamin D (dietary intake): middle tertile vs highest	Increase of ≥ 1 grade JSN score	OR = 2.99 (1.06 - 8.49)
		Vitamin D (serum levels): middle tertile vs highest		OR = 2.83 (1.02 - 7.85)
	McAlindon (1996-b) [35]	Vitamin C intake: middle tertile vs lowest	Increase of ≥ 1 grade K&L score	OR = 0.32 (0.14 - 0.77)
		Beta carotene intake: highest tertile vs lowest		OR = 0.42 (0.19 - 0.94)
		Vitamin E intake: middle tertile vs lowest		OR = 0.44 (0.19 - 1.00)
		Vitamin E intake: highest tertile vs lowest		OR = 0.68 (0.28 - 1.64)
Smoking	Schouten (1992) [37]	Smoked in past vs never smoked	Change in joint space ≤ -1 on a 9-point scale –4 to +4	OR = 1.07 (0.38 - 3.04)
		Current smoker vs never smoked		OR = 0.96 (0.34 - 2.75)
Depression / Anxiety	Wolfe (2002) [45]	Depression, yes vs no	JSN score = 3	HR = 1.09 (0.93 - 1.28)
		Anxiety, yes vs no		HR = 0.95 (0.84 - 1.08)

* See Table 3 for definitions.

All outcomes were adjusted for age and sex (if applicable); ‡ No OR with 95% CI or p value provided; § Assessed at baseline; ¶ Assessed at followup

Lane et al [34] and Schouten et al [37] investigated the relationship between running and progression of OA. In both studies, no statistically significant association was reported. In the study by Lane et al [34], running activities occurred during the follow-up period. In the study by Schouten et al [37], running was only assessed at baseline and no information about running during the follow-up period was presented.

Cooper et al [29] found no statistically significant association between regular sport activities assessed during follow-up and progression of OA (OR 0.7, 95% CI 0.4 –1.6). Schouten et al [37] analyzed different types of activities. All of these activities were assessed at follow-up. For physical activity in general, no statistical association was found. For walking, squatting/kneeling/crawling, knee knocking, and lifting heavy objects, no statistically significant association was found. For standing, a significant association was only found in the comparison of the medium versus the lowest level. A statistically significant association was also found between bowing legs or knocking knees and the progression of OA.

McAlindon et al [13,35] investigated the relationship between nutrition variables and progression of OA. For vitamin D, a low dietary intake and low serum level were statistically and significantly associated with progression of knee OA (OR 4.05, 95% CI 1.40–11.6 and OR 2.89, 95% CI 1.01–8.25 for lowest versus highest tertile of dietary intake and serum levels, respectively). Also for vitamin C intake, a significant association was found (highest versus lowest tertile OR 0.26, 95% CI 0.11–0.61). A significant association was reported for β-carotene intake only in the comparison of the highest versus the lowest tertile (middle versus lowest OR 1.42, 95% CI 0.68–3.00). For vitamin E intake, a borderline significant association was found in the comparison of the middle versus the lowest tertile, but no statistically significant association was found for the highest versus the lowest tertile. For the relationship between progression of OA and the intake of vitamin B1, vitamin B6, niacin, and folate, no statistically significant relationship was found.

Schouten et al [37] reported no statistical association between smoking and progression of OA. Wolfe and Lane [45] investigated the relationship between depression and anxiety and progression of knee OA. For both factors, no statistically significant association was found. The same study also investigated the relationship between being a high school graduate and progression of knee OA, but no statistically significant association was found. In another study, Dieppe et al [20] reported a statistically significant relationship between the use of drugs (nonsteroidal anti-inflammatory drugs [NSAIDs]) and the overall measure of change of OA (i.e., clinical improvement or worsening; $p = 0.017$ for improvement among users versus nonusers). Dieppe et al [11] also reported a statistically significant association between the use of walking aids and the clinical improvement of OA ($p < 0.001$).

Best evidence synthesis

Because of the heterogeneity of the reviewed studies, statistical pooling of the extracted data was not feasible. Therefore, we applied a best evidence synthesis. The best evidence synthesis demonstrated that, based on multiple high-quality studies, there seems to be strong evidence that the level of hyaluronic acid in serum and generalized OA are associated with radiologic progression of knee OA. Also based on multiple high-quality studies, there seems to be strong evidence that sex, knee injury, quadriceps strength, and regular sport activities are not associated, and that knee pain at baseline and radiologic severity of OA at baseline are not strongly associated with the radiologic progression of knee OA.

There is, as yet, limited evidence that there is a relationship between progression of knee OA and synovial fluid volume, nodal warmth, medial bone marrow edema lesions, adduction moment, alignment of the joint (varus/valgus), low serum levels and dietary intake of vitamin D, low intake of vitamin C, use of walking aids, and the use of drugs (NSAIDs). There also is limited evidence that there is no strong association between progression of knee OA and estrogen, uric acid concentration, clinical diagnosis of localized OA, the other markers of bone or cartilage turnover, lateral bone marrow edema lesions, meniscectomy, chondrocalcinosis, running, niacin, folate, smoking, depression or anxiety, being a high school graduate, and low intake of β-carotene, vitamin E, vitamin B1, and vitamin B6. Conflicting evidence is found in the relationship between progression of knee OA and age, bone density, IGF-1, Heberden's nodes, keratan sulfate, COMP, duration of symptoms, clinical severity, CRP level at baseline, and BMI.

DISCUSSION

There seems to be strong evidence that the presence of generalized OA and the level of hyaluronic acid in serum are predictors for radiologic progression of knee OA. There also seems to be strong evidence that sex, knee pain, radiologic severity at baseline, quadriceps strength, knee injury, and regular sport activities are not predictive. For the other studied factors, the evidence is limited or conflicting.

In this review, only significant associations were considered as associated prognostic factors in the best evidence synthesis. Several studies included small sample sizes, which implied low statistical power. For the factors with strong evidence for not being a predictor of OA progression, no associations were found in studies with both small and large sample sizes. For age, IGF-1, COMP, bone density, Heberden's nodes, and BMI, the conflicting associations could not be explained by the difference in sample size; how-

ever, the sample size might be an explanation for the conflicting findings for keratan sulfate, duration of symptoms, and the level of CRP.

Especially for the studies with small sample sizes, pooling of the data would have provided a more precise estimate of the association with the outcome. However, because of the heterogeneity of the setting of the studied populations and the differences in disease definition of the included studies, pooling of the data was not possible. Because of small sample sizes, we report instead that there seems to be strong evidence for no association rather than stating that there is no such association at all.

In the presented studies, OA at baseline was defined in different ways, including using the K/L scale, JSW, or radiologic and clinical characteristics of OA. In all determinants (except knee pain at baseline and the duration of symptoms) the conflicting findings are not likely to be explained by the difference in the definition of OA used.

In contrast to the review on prognostic factors of progression of hip OA by Lievense et al [5], we found only 4 studies (15%) that also used a clinical outcome for progression of knee OA [11,19,23,24,45]. The study by Dieppe et al [11] did not include persons with a total knee replacement in the analysis; the other 4 studies used either a radiologic change or a total knee replacement in their definition for progression of knee OA [19,23,24,45]. The numbers of patients with a total knee replacement in another study by Dieppe et al [11] (n = 415) and 2 studies by Sharif et al [23,24] (n = 75) were 12 and 14, respectively. In the study by Wolfe and Lane [45], the number of persons with a total knee replacement was not provided. Therefore, the present review mainly dealt with radiologic progression of knee OA and the conclusions cannot directly be applied to clinical progression of knee OA, whereas for clinical use it is of major interest to know the relationship between these factors and clinical progression of knee OA.

In contrast to the findings of radiologic severity as a predictor for progression of hip OA [5], we found evidence that radiologic severity hardly has predictive value for radiologic progression of knee OA. The reason for this difference may simply be that in the present review none of the studies reporting the relationship between radiologic severity and progression of knee OA used total knee replacement as an outcome measure, whereas in the review by Lievense et al [5] a total hip replacement was often used as an outcome, and radiologic severity was one of the indicators for a subsequent total hip or knee replacement [46].

Future research on the potential relationship between prognostic factors of radiologic progression of knee OA is needed. The factors where conflicting associations were found (e.g., BMI, age) especially need to be clarified. Furthermore, several factors were investigated in a single study only and provided limited evidence; replicated studies of these factors are needed.

Future study on clinical progression of knee OA is of major importance because of its implications for patient information and appropriate medical treatment. In the best

evidence synthesis, in case of strong evidence for either the presence or the absence of an association, future scientific consensus is needed on how to summarize the evidence provided by studies with a small sample size. In summary, this review provides the currently available evidence, but also identifies the lack of data with respect to prognostic factors of progression of knee OA.

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Chapter 4

Prognostic Factors in Adults With Knee Pain in General Practice

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ABSTRACT

Objective: To predict the 1-year outcome of incident nontraumatic knee symptoms in adults presenting in general practice.

Methods: Adults age >35 years with nontraumatic knee symptoms (n = 480) were followed for 1 year. At baseline, data on knee symptoms and demographics were collected and a physical examination performed. Knee symptoms were assessed by self-report questionnaires at 3-month intervals. After 1 year the physical examination was repeated. Multivariate prognostic regression models of patient characteristics, symptom characteristics, and physical examination were used to predict persisting knee symptoms after 1 year. Areas under receiving operating characteristic curves (AUC) were used to determine the predictive value of the model. To assess the added predictive value of symptom characteristics and physical examination, these models were added to the model of patient characteristics. The improvement was expressed as the difference between the 2 AUCs.

Results: In the multivariate prognostic model of patient characteristics, age >60 years, educational level, kinesophobia, and comorbidity of the skeletal system were associated with persistent knee symptoms after 1 year (AUC 0.67). Of the symptom characteristics, history of nontraumatic knee symptoms, bilateral symptoms, and duration of symptoms >3 months were associated (AUC 0.73). For determinants of physical examination, crepitus of passive extension was associated (AUC 0.55). The added value of the symptom characteristics model to the patient characteristics model was 0.09 (AUC 0.76). Physical examination added no further value.

Conclusion: Symptom characteristics are the strongest predictors of persisting knee symptoms at 1-year follow-up. Physical examination has no added value in predicting persistent knee symptoms in general practice.

INTRODUCTION

Musculoskeletal conditions are a major burden on individuals, health systems, and social care systems, with indirect costs due to disability being predominant [1]. Although musculoskeletal pain, injury, and dysfunction affect all ages, the elderly are particularly susceptible [2]. The clinical syndrome of joint pain and stiffness in older people is the most common cause of disability and health care consultation in this age group [3].

In general practice, knee symptoms (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (48/1,000 patients per year), mostly presenting as knee pain or functional loss of the knee joint [4,5]. Of these symptoms, ~20% are traumatic [5].

Approximately 60% of patients with nontraumatic knee symptoms are >25 years old. Disorders most diagnosed within this group are bursitis, tendinitis, and osteoarthritis (OA) [4]. In the elderly, the most common cause of knee symptoms is the presence of OA. In general practice, knee OA is common, and diagnosed patients often have a long history of knee symptoms prior to the diagnosis [6].

In spite of the high prevalence of knee symptoms in general practice, few studies to our knowledge have assessed the signs, symptoms, and prognosis of nontraumatic knee symptoms in general practice [7–9]. Until now, only a few studies on prognostic factors of knee OA used a clinical outcome to assess progression of knee OA [10,11].

To improve the management of nontraumatic knee symptoms, more knowledge is needed on the predictors of persisting or worsening knee symptoms, and on the predictors of good or bad prognosis. Moreover, establishing which patients are at higher risk for progression or persisting knee symptoms would be useful in studying the effect of disease-modifying therapies and in elucidating the disease process. Therefore, we performed a prospective cohort study in general practice to assess which signs and symptoms, based on clinical history and physical examination taken at baseline, are predictive for persisting symptoms at 1-year follow-up in patients with nontraumatic knee symptoms.

PATIENTS AND METHODS

Study design and population

For this study, a subgroup of the prospective HONEUR knee cohort was used; details on this cohort have been reported earlier [12]. In brief, consecutive patients visiting their general practitioner with a new episode of knee symptoms were enrolled in the study and followed for 1 year. In this prospective cohort study, 40 general practitioners from 5

municipalities in the southwest region of The Netherlands participated, connected to the Erasmus MC GP Research Network HONEUR and representing a total patient population of ~84,000. Recruitment began in October 2001 in 1 municipality and a new municipality was added approximately every 3 months. All general practitioners recruited up to October 2003 [12].

New symptoms were defined as symptoms presented to the general practitioner for the first time. Recurrent symptoms for which the general practitioner was not consulted within the past 3 months were also considered to be new symptoms. Exclusion criteria were knee symptoms that required urgent medical attention (fractures, infection), patients with malignancies, neurologic disorders, or systemic musculoskeletal diseases (e.g., Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients being incapable of understanding the ramifications of participation.

At baseline and at 1-year follow-up, patients underwent a standardized physical examination of their knee by trained physiotherapists. The physical examination at baseline was planned as close to the date of consultation of the general practitioner as possible. Disability and pain were assessed every 3 months by means of self-reported questionnaires.

For this study, all patients age >35 years with nontraumatic knee symptoms were included. At baseline and at follow-up, data on knee symptoms (duration, intensity), daily activities, and social circumstances were collected and a physical examination of the knee was performed.

Functional disability and pain were assessed both at baseline and at follow-up by self-report questionnaires containing the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index [13,14], the Medical Outcomes Study Short Form 36 Health Survey (SF-36) [15,16], the Knee Society Score (KSS) function questions [17,18], the Lysholm Knee Scoring Scale [19–21], the Tampa Scale for Kinesophobia (assessed at baseline) [22,23], and questions about experience of recovery or worsening (assessed at 1-year follow-up).

The physical examination assessed signs (e.g., swelling, temperature) and symptoms (e.g., function, pain) of the knee and hip. Further details about the physical signs and how they were elicited and scored are available from the corresponding author. For the outcome of persisting knee symptoms at 1-year follow-up, an additional question addressing experienced recovery or worsening, scored on a 7-point Likert scale, was added to the last questionnaire.

Statistical analysis

For the missing data, a multiple imputation strategy (multiple imputation by chained equations) was used [24]. First, to assess which factors of the medical history and physical examination reported at baseline were associated with persisting knee symptoms

(i.e., persisting or worsening knee symptoms) at 1-year follow-up, a univariate analysis was performed. The baseline factors that were analyzed were based on the literature [5,10] and on experienced clinical relevance. The determinants were divided in 3 subgroups: patient characteristics, symptom characteristics, and physical examination findings.

Patients with persisting knee symptoms were defined as patients who, after 1 year of follow-up, experienced knee symptoms (somewhat better, no recovery, worse, much worse, or worse than ever) versus recovered patients who experienced knee symptoms (much better or no symptoms).

In the multivariate backward logistic regression analysis, factors with $p < 0.2$ in the univariate analysis were included (p entry 0.05, p removal 0.10). To assess the prognostic value of determinants with persisting knee symptoms, a prognostic model was built by backward logistic regression and the area under the receiver operating characteristic curve (AUC) was estimated. Three models were built: the patient characteristics model, the selfreported symptom characteristics model, and the physical examination findings model.

To assess the added predictive value of self-reported symptom characteristics, these factors were added to the model of patient characteristics; improvement was expressed as the difference between the AUCs. Adding the physical findings model to the model of patient and symptom characteristics assessed the added predictive value of determinants of physical examination. For this model, the AUC was also estimated. In addition, based on the age groups used in the American College of Rheumatology clinical classification criteria of knee OA [25], we also performed these analyses separately for the patient age subgroups 35–49 years and ≥ 50 years.

We chose to dichotomize most variables because this allows estimation of odds ratio parameters through a logistic regression analysis [26], which are easier to interpret in clinical practice. However, the consequences of dichotomizing are an overall reduced statistical power, loss of information, and an increased probability of a Type II error [27,28]. SPSS software, version 11 (SPSS, Chicago, IL) was used to analyze the data.

RESULTS

Study population

A total of 549 patients were included. Their mean ± SD age was 53.8 ± 11.4 years, their mean ± SD body mass index (BMI) was 27.1 ± 4.3, and 269 (49%) were women. Details on the baseline characteristics of the study group are presented in Table 1.

At 1-year follow-up, 480 (87.4%) persons were still available for the study; of these, 236 (49.2%) reported persisting knee symptoms. The 69 (12.6%) patients lost to follow-up

Table 1: Baseline characteristics (n = 549 and n = 480*) and univariate analysis of the association between factors and persisting knee complaints for the total group[1] (n = 480) and subgroups aged 36-49 years[2] (n = 185) and 50 years and older[3] (n = 295)

			Total population	Age 36-49 year	Age > 50 years
Characteristic	**n = 549**	**n = 480**	**OR (95% CI)[1]**	**OR (95% CI)[2]**	**OR (95% CI)[3]**
Patient characteristic					
Age; mean (sd)	53.8 (11.4)	53.6 (11.2)			
Age > 60 year; n (%)	147 (26.8)	129 (26.9)	**2.16 (1.42, 3.28)**		**2.06 (1.28, 3.31)**
Female gender; n (%)	269 (49.0)	239 (49.8)	**1.56 (1.08, 2.24)**	1.29 (0.71, 2.34)	**1.66 (1.04, 2.64)**
BMI; mean (sd)	27.1 (4.3)	27.1 (4.2)			
BMI > 25; n (%)	362 (65.9)	328 (68.3)	1.12 (0.76, 1.66)	0.94 (0.50, 1.74)	1.24 (0.76, 2.05)
Low/moderate educational level; n (%)	363 (66.1)	322 (67.1)	**2.02 (1.36, 2.99)**	**2.29 (1.23, 4.28)**	**1.74 (1.04, 2.91)**
Private insurance; n (%)	253 (46.1)	228 (47.5)	0.83 (0.58, 1.19)	0.96 (0.53, 1.75)	0.76 (0.48, 1.20)
Presence comorbidity skeletal system; n (%)	299 (54.5)	264 (55.0)	**1.80 (1.25, 2.60)**	**1.82 (1.00, 3.31)**	**1.67 (1.04, 2.68)**
Presence other comorbidity; n (%)	117 (21.3)	97 (20.2)	1.20 (0.77, 1.89)	1.03 (0.49, 2.15)	1.33 (0.74, 2.37)
Kinesiophobia (Tampa total score); mean (sd)	25.7 (6.2)	25.5 (6.0)			
Kinesiophobia (Tampa > 25); n (%)	253 (46.1)	219 (45.6)	**1.99 (1.37, 2.89)**	1.07 (0.58, 1.95)	**2.85 (1.76, 4.62)**
Payed employment (>8 hours/wk); n (%)	325 (59.2)	288 (60.0)	**0.49 (0.33, 0.71)**	**0.54 (0.21, 1.35)**	**0.51 (0.32, 0.81)**
Sport; n (%)	326 (59.4)	300 (62.5)	**0.78 (0.54, 1.13)**	1.18 (0.63, 2.19)	**0.62 (0.39, 1.00)**
Complaint characteristic					
Duration of complaints > 3 months; n (%)	155 (28.2)	134 (27.9)	**3.04 (1.98, 4.65)**	**2.76 (1.36, 5.60)**	**3.11 (0.82, 5.32)**
Signs/symptoms knee; n (%)					
warm	205 (37.4)	191 (39.8)	**1.67 (1.15, 2.42)**	**2.09 (1.13, 3.85)**	**1.44 (0.90, 2.30)**
swollen	217 (39.5)	197 (41.0)	**1.28 (0.88, 1.86)**	1.04 (0.55, 1.94)	1.35 (0.85, 2.16)
crepitus	338 (61.6)	300 (62.5)	**1.85 (1.26, 2.70)**	1.50 (0.79, 2.86)	**2.23 (1.38, 3.59)**
Presence history nontraumatic knee complaints; n (%)	81 (14.8)	66 (13.8)	**5.12 (2.97, 8.81)**	**1.87 (0.57, 6.12)**	**6.27 (3.31, 11.86)**
Presence history traumatic knee complaints; n (%)	307 (55.9)	265 (55.2)	**2.26 (1.47, 3.46)**	1.72 (0.88, 3.36)	**2.64 (1.51, 4.61)**
Presence locked knee; n (%)	64 (11.7)	57 (11.9)	1.10 (0.63, 1.91)	0.74 (0.85, 2.20)	1.24 (0.61, 2.52)
Bilateral complaints; n (%)	172 (31.3)	142 (29.6)	**3.74 (2.33, 6.00)**	**2.47 (1.19, 5.13)**	**4.99 (2.62, 9.50)**
Recurrent complaints; n (%)	231 (42.1)	205 (42.7)	**1.75 (1.21, 2.53)**	1.11 (0.61, 2.01)	**2.34 (1.45, 3.78)**
Feeling of giving way; n (%)	202 (36.8)	178 (37.1)	**1.46 (1.00, 2.13)**	1.10 (0.57, 2.11)	**1.58 (0.99, 2.54)**
Limited when walking stairs; n (%)	439 (80.0)	383 (79.8)	**1.45 (0.91, 2.30)**	1.16 (0.60, 2.27)	1.56 (0.81, 2.99)
Cause of complaints overburden; n (%)	168 (30.6)	139 (29.0)	0.93 (0.62, 1.38)	1.04 (0.56, 2.27)	0.92 (0.54, 1.57)
Pain (11-point scale); mean (sd)	4.3 (2.1)	4.3 (2.1)	1.02 (0.93, 1.11)	1.03 (0.90, 1.20)	**1.00 (0.89, 1.12)**

SF-36; mean (sd)	67.8 (11.2)	68.2 (11.0)	**0.98 (0.97, 1.00)**	1.00 (0.97, 1.02)	**0.98 (0.96, 1.00)**
Physical functioning (SF-36)	65.1 (23.4)	65.2 (23.1)	**1.00 (0.99, 1.00)**	1.01 (0.99, 1.02)	0.99 (0.98, 1.00)
Mental health (SF-36)	80.5 (16.5)	81.0 (15.9)	1.00 (0.99, 1.00)	1.00 (0.98, 1.02)	0.99 (0.98, 1.01)
WOMAC score; mean (sd)					
Total score	29.3 (19.7)	28.9 (19.7)	1.00 (0.99, 1.00)	1.01 (0.99, 1.03)	0.99 (0.98, 1.01)
Physical functioning score	27.8 (21.1)	27.4 (21.1)	1.00 (0.99, 1.00)	1.01 (0.99, 1.02)	0.99 (0.98, 1.01)
Pain score	29.7 (18.7)	29.3 (18.7)	1.00 (0.99, 1.01)	1.00 (0.99, 1.02)	1.00 (0.99, 1.01)
Stiffness score	31.8 (24.6)	31.5 (24.4)	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)	1.00 (0.99, 1.01)
Lysholm total score; mean (sd)	67.5 (18.7)	69.1 (16.3)	1.00 (0.98, 1.01)	1.01 (0.99, 1.03)	0.99 (0.98, 1.01)
Physical examination					
Varus; n (%)	108 (19.6)	89 (18.5)	2.04 (0.60, 6.85)	NA	1.30 (0.36, 4.71)
Valgus; n (%)	159 (28.9)	145 (30.1)	1.49 (0.68, 3.28)	1.64 (0.43, 6.32)	1.38 (0.52, 3.66)
Swollen knee joint; n (%)	169 (30.8)	151 (31.5)	**1.29 (0.88, 1.91)**	1.33 (0.69, 2.56)	1.22 (0.75, 1.98)
Warm knee joint; n (%)	127 (23.1)	112 (23.3)	0.84 (0.25, 2.81)	0.42 (0.04, 4.07)	1.19 (0.26, 5.41)
Pain passive flexion; n (%)	273 (49.7)	237 (49.4)	1.25 (0.87, 1.80)	1.08 (0.59, 1.99)	1.25 (0.78, 2.00)
Pain passive extension; n (%)	163 (29.7)	138 (28.8)	1.11 (0.75, 1.66)	0.63 (0.31, 1.30)	**1.40 (0.85, 2.30)**
Pain active flexion; n (%)	209 (38.1)	180 (37.5)	1.18 (0.77, 1.83)	**1.82 (0.84, 3.92)**	0.98 (0.57, 1.68)
Pain active extension; n (%)	91 (16.6)	77 (16.0)	1.31 (0.77, 2.23)	**1.82 (0.74, 4.43)**	1.22 (0.62, 2.40)
Crepitus passive flexion; n (%)	193 (35.2)	165 (34.4)	1.24 (0.85, 1.81)	1.36 (0.70, 2.65)	1.10 (0.69, 1.77)
Crepitus passive extension; n (%)	119 (21.7)	102 (21.3)	**1.84 (1.18, 2.89)**	1.23 (0.57, 2.67)	1.40 (0.85, 2.30)
Crepitus active flexion; n (%)	223 (40.6)	194 (40.4)	1.12 (0.73, 1.74)	1.33 (0.63, 2.82)	**0.89 (0.51, 1.57)**
Crepitus active extension; n (%)	242 (44.1)	204 (42.5)	**1.53 (0.93, 2.52)**	1.32 (0.56, 3.13)	1.53 (0.82, 2.85)
Positive anterior drawer test; n (%)	100 (22.3)	90 (18.8)	0.92 (0.24, 3.49)	0.59 (0.04, 6.08)	1.25 (0.25, 6.14)
Floating patella; n (%)	146 (27.1)	125 (26.0)	0.97 (0.64, 1.47)	0.74 (0.35, 1.59)	1.01 (0.61, 1.68)
Bony swelling of the joint; n (%)	55 (10.1)	52 (10.8)	**1.92 (1.03, 3.59)**	0.84 (0.23, 3.08)	**2.32 (1.10, 4.91)**
Pain internal rotation hip; n (%)	91 (16.6)	72 (15.0)	**1.88 (1.11, 3.17)**	**1.97 (0.76, 5.09)**	**1.76 (0.94, 3.32)**
Restriction internal rotation hip; n (%)	134 (24.5)	111 (23.1)	**1.47 (0.95, 2.27)**	0.83 (0.35, 1.97)	**1.66 (0.99, 2.80)**
Presence Heberden's nodes; n (%)	107 (19.5)	94 (19.5)	**1.41 (0.86, 2.31)**	1.64 (0.62, 4.35)	1.20 (0.66, 2.17)
Bakers cyst; n (%)	14 (2.6)	14 (2.9)	0.98 (0.92, 1.04)	0.64 (0.11, 3.59)	1.25 (0.78, 1.98)
Bursitis prepatellaris; n (%)	77 (14.0)	66 (13.8)	1.00 (0.59, 1.68)	0.95 (0.38, 2.39)	0.98 (0.52, 1.85)
Pain iliotibial tract; n (%)	85 (15.5)	70 (14.6)	1.20 (0.72, 2.01)	0.85 (0.37, 1.95)	1.52 (0.78, 2.98)

* n = 549: total population at baseline, n = 480: baseline characteristics of the population available at follow-up. In bold: $p < 0.2$

BMI: Body Mass Index; Pain 11-point scale: scale 0-10 (0 represents no pain, 10 represents worst pain); SF-36: Medical Outcome Study Short Form-36 (scale 0 – 100); WOMAC: Western Ontario and McMasters University Osteoarthritis Index (scale 0 – 100); Lysholm: scale 0-100; Tampa: Tampa Scale of Kinesiophobia, scale 17-68, lower score represents less fear of movement; For all scores, except Lysholm and SF-36 score: lower score represents better function/outcome; NA: not available

showed no significant differences compared with those not lost to follow-up regarding baseline age, sex, BMI, KSS knee and function score, SF-36 score, comorbidity, and WOMAC scores. Of the persons lost to follow-up, reasons for no longer participating were lack of time/lack of interest (n = 36, 52.2%), severe comorbidity (n = 15, 21.7%), or treatment by an orthopedic surgeon (n = 4, 5.8%), and 14 (20.3%) patients provided no reason.

Multiple imputation was used to replace the missing values. There were 8 missing values for the dependent variable persistent knee symptoms. Of the patient characteristics, symptom characteristics, and characteristics of physical examination, the range of missing values was 3–20. An exception was the Heberden's nodes characteristic, for which there were 178 missing values. Further information about the proportion of missing data for each covariate is available from the corresponding author.

During 1-year follow-up, 43 (9.0%) patients underwent an operation for their knee. Of these, 18 (41.9%) reported persisting knee symptoms and 25 (58.1%) reported recovery ($p = 0.26$). Also during the 1-year follow-up, the WOMAC scores increased, with the largest increase at the 3-month follow-up measurement (Table 2).

Univariate analysis of the total group (n = 480)

The factors analyzed in the univariate analysis and their association with persisting knee symptoms are shown in Table 1. Of the patient characteristics, 7 variables were significant at $p < 0.2$: age >60 years, female sex, a low/moderate educational level, comorbidity of the skeletal system, kinesophobia (Tampa score >25), paid employment >8 hours per week, and sport participation.

Of the self-reported symptom characteristics, 12 variables were significant at $p < 0.2$: a warm knee, a swollen knee, crepitus of the knee, the presence of bilateral symptoms, duration of symptoms >3 months, feeling of giving way, limitation when walking stairs, recurrent symptoms, a history of nontraumatic knee symptoms, a history of traumatic knee symptoms, SF-36 physical component summary (PCS) score (continuous variable), and the SF-36 total score (continuous variable). The baseline WOMAC total score, WOMAC physical functioning score, WOMAC pain score, and WOMAC stiffness score were not associated with persisting knee symptoms.

Of the variables on physical examination, 7 variables were significant at $p < 0.2$: a swollen knee joint, crepitus with passive extension, crepitus with active extension, a bony swelling of the joint, pain of internal rotation of the hip, a restriction of internal rotation of the hip, and the presence of Heberden's nodes.

Table 2: WOMAC scores* during 1 year follow-up

Measurement during follow-up	Number of patients with available data	WOMAC total score; mean (sd)	WOMAC pain score; mean (sd)	WOMAC stiffness score; mean (sd)	WOMAC physical functioning score; mean (sd)
Baseline	549	29.3(19.7)	29.7 (18.7)	31.8 (24.6)	29.0 (21.0)
3 months	431	18.9 (18.0)	17.8 (17.3)	22.6 (22.1)	18.7 (18.9)
6 months	411	16.5 (18.1)	15.9 (17.6)	19.1 (21.9)	16.3 (18.9)
9 months#	75	14.4 (17.3)	14.1 (15.9)	15.7 (20.2)	14.3 (17.9)
1 year	480	14.3 (18.0)	13.7 (17.7)	16.6 (21.5)	14.2 (18.5)

* WOMAC: Western Ontario and McMasters University Osteoarthritis Index (scale 0 – 100), a lower score represents better function

Only available in an a-select part of the study population

Multivariate analysis of the total group (n = 480)

Of the patient characteristics, 4 variables remained in the multivariate prognostic model: age >60 years, a low/moderate educational level, presence of comorbidity of the skeletal system, and kinesophobia (AUC = 0.67, median predicted values 0.49, range 0.54, interquartile range [IQR] 0.28) (Table 3). Of the self-reported symptom characteristics, 4 variables remained in the model: the presence of bilateral symptoms, a history of knee symptoms (traumatic and nontraumatic), and duration of symptoms >3 months (AUC = 0.73, median predicted values 0.36, range 0.68, IQR 0.34). Of the variables on physical examination, only the crepitus of passive extension of the knee remained in the model (AUC = 0.55, median predicted values 0.47, range 0.16, IQR 0.0).

To assess the added value of self-reported symptom characteristics on the model of patient characteristics, we added the model of self-reported symptom characteristics to the model of patient characteristics and calculated the AUC (Table 3). The strongest predictors in this new model were the symptom characteristics variables. The AUC improved, with an increase of 0.09 to 0.76 (median predicted values 0.42, range 0.83, IQR 0.37). We then added the variable of crepitus of passive extension of the knee to assess the added value of this variable, but the model did not improve any further (AUC 0.76, median predicted values 0.45, range 0.83, IQR 0.36).

Univariate analysis of the age 35–49 years subgroup (n = 185)

For the age group 35–49 years, the factors analyzed in the univariate analysis and their association with persisting knee symptoms are shown in Table 1.

Table 3: Multivariate prognostic logistic regression models of patient characteristics, complaint characteristics and variables of physical examination (n = 480)

Model	OR (95% CI)
1. Patient characteristics (AUC = 0.67, Nagelkerke R square 0.12)	
Age > 60 years	2.02 (1.30, 3.13)
Low/moderate educational level	1.74 (1.16, 2.63)
Comorbidity of musculoskeletal system	1.70 (1.15, 2.50)
Kinesiophobia	1.85 (1.26, 2.72)
2. Complaint characteristics (AUC = 0.73, Nagelkerke R square 0.23)	
Bilateral complaints	2.96 (1.77, 4.97)
History of nontraumatic knee complaints	4.30 (2.38, 7.79)
History of traumatic knee complaints	1.56 (0.97, 2.49)
Duration > 3 months	2.18 (1.36, 3.48)
3. Physical Examination (AUC = 0.55, Nagelkerke R square 0.03)	
Crepitus passive extension	1.91 (1.01, 3.63)
4. Patient characteristics + complaint characteristics (AUC = 0.76, Nagelkerke R square 0.27)	
Age > 60 years	1.40 (0.86, 2.29)
Low/moderate educational level	1.84 (1.17, 2.87)
Comorbidity of musculoskeletal system	1.50 (0.99, 2.28)
Kinesiophobia	1.49 (0.98, 2.26)
Bilateral complaints	2.74 (1.62, 4.64)
History of nontraumatic knee complaints	3.45 (1.85, 6.44)
History of traumatic knee complaints	1.50 (0.93, 2.43)
Duration > 3 months	2.15 (1.32, 3.48)
5. Patient characteristics + complaint characteristics + physical examination (AUC = 0.76, Nagelkerke R square 0.27)	
Age > 60 years	1.35 (0.83, 2.22)
Low/moderate educational level	1.82 (1.16, 2.85)
Comorbidity of musculoskeletal system	1.47 (0.97, 2.24)
Kinesiophobia	1.48 (0.97, 2.25)
Bilateral complaints	2.74 (1.62, 4.63)
History of nontraumatic knee complaints	3.28 (1.75, 6.15)
History of traumatic knee complaints	1.49 (0.92, 2.42)
Duration > 3 months	2.13 (1.31; 3.45)
Crepitus passive extension	1.39 (0.83, 2.33)

Of the patient characteristics, 3 variables were significant at $p < 0.20$: low/moderate educational level, comorbidity of the musculoskeletal system, and paid employment >8 hours per week. Of the self-reported symptom characteristics, 4 variables were significant at $p < 0.20$: duration of symptoms >3 months, a warm knee, a history of nontraumatic knee symptoms, and the presence of bilateral symptoms. Of the characteristics on

Table 4: Multivariate prognostic logistic regression models of patient characteristics, complaint characteristics and variables of physical examination of patients aged 36-49 years (n = 185)

Model	OR (95% CI)
1. Patient characteristics (AUC = 0.63, Nagelkerke R square 0.07)	
Low/moderate educational level	2.09 (1.11, 3.96)
Comorbidity of the musculoskeletal system	1.73 (0.93, 3.19)
2. Complaint characteristics (AUC = 0.64, Nagelkerke R square 0.18)	
Duration > 3 months	3.05 (1.47, 6.33)
Warm knee	1.94 (1.02, 3.67)
3. Patient characteristics + complaint characteristics (AUC = 0.71, Nagelkerke R square 0.25)	
Low/moderate educational level	2.35 (1.21, 4.57)
Comorbidity of the musculoskeletal system	1.76 (0.93, 3.33)
Duration > 3 months	2.85 (1.35, 6.01)
Warm knee	2.48 (1.28, 4.80)

physical examination, 3 variables were significant at $p < 0.20$: pain with active flexion of the knee, pain with active extension of the knee, and pain of internal rotation of the hip.

Multivariate analysis of the age 35–49 years subgroup (n = 185)

Of the patient characteristics, 2 variables remained in the multivariate model: low/moderate educational level and presence of comorbidity of the musculoskeletal system (AUC = 0.63, median predicted values 0.42, range 0.30, IQR 0.30) (Table 4). Of the self-reported symptom characteristics, 2 variables remained in the multivariate model: duration of symptoms >3 months and a warm knee (AUC = 0.64, median predicted values 0.31, range 0.99, IQR 0.67). Of the characteristics on physical examination, no variables remained in the multivariate model.

To assess the added value of self-reported symptom characteristics on the model of patient characteristics, we added the model of self-reported symptom characteristics to the model of patient characteristics and calculated the AUC (Table 4). The strongest predictors in this new model were a low/moderate educational level, duration of symptoms >3 months, and a warm knee. The AUC improved, with an increase of 0.08 to 0.71 (median predicted values 0.31, range 0.99, IQR 0.68).

Univariate analysis of the age ≥50 years subgroup (n = 295)

In the age group ≥50 years, 7 patient characteristics variables were significant at $p < 0.20$: age >60 years, female sex, low/moderate educational level, comorbidity of the musculoskeletal system, kinesophobia, paid employment, and sport participation.

Of the self-reported symptom characteristics, 10 variables were significant at $p < 0.20$: duration of symptoms >3 months, a warm knee, crepitus of the knee, a history of nontraumatic knee symptoms, a history of traumatic knee symptoms, feeling of giving way, bilateral symptoms, SF-36 total score, SF-36 PCS score, and recurrent symptoms.

Of the characteristics of physical examination, 5 variables were significant at $p < 0.20$: crepitus of active flexion, pain when passive extension, a bony swelling of the joint, pain of internal rotation of the hip, and restriction of internal rotation of the hip.

Multivariate analysis of the age ≥50 years subgroup (n = 295)

Of the patient characteristics, 4 variables remained in the multivariate model: age >60 years, female sex, kinesophobia, and sport participation (AUC = 0.69, median predicted values 0.52, range 0.57, IQR 0.25) (Table 5). Of the self-reported symptom characteristics, 4 variables remained in the multivariate model: duration >3 months, a history of nontraumatic knee symptoms, recurrent symptoms, and bilateral symptoms (AUC = 0.76, median predicted values 0.42, range 0.85, IQR 0.64). Of the characteristics of physical examination, no variables remained in the multivariate model.

To assess the added value of symptom characteristics on the model of patient characteristics, we added the model of symptom characteristics to the model of patient characteristics and calculated the AUC (Table 5). In this new model, the strongest predictors were the variables of selfreported symptom characteristics. The AUC improved, with an increase of 0.11 to 0.80 (median predicted values 0.48, range 0.91, IQR 0.72).

DISCUSSION

The present study investigated the prognostic factors of patient characteristics, symptom characteristics, and findings from physical examination to predict persisting knee symptoms at 1-year follow-up in patients visiting their general practitioner with incident knee symptoms.

The following were associated with persisting knee symptoms: age >60 years, low/moderate education level, comorbidity of the skeletal system, kinesophobia, presence of bilateral symptoms, history of traumatic or nontraumatic knee symptoms, duration of symptoms >3 months, and crepitus of passive extension of the knee. The self-reported

Table 5: Multivariate prognostic logistic regression models of patient characteristics, complaint characteristics and variables of physical examination of patients aged 50 years and older (n = 295)

Model	OR (95% CI)
1. Patient characteristics (AUC = 0.69, Nagelkerke R square 0.15)	
Age > 60 years	2.00 (1.21, 3.31)
Female gender	1.64 (1.00, 2.69)
Kinesiophobia	2.77 (1.69, 4.56)
Sport	0.64 (0.39, 1.07)
2. Complaint characteristics (AUC = 0.76, Nagelkerke R square 0.30)	
Duration > 3 months	2.10 (1.14, 3.85)
History of nontraumatic knee complaints	5.03 (2.52, 10.07)
Recurrent complaints	1.79 (1.04, 3.10)
Bilateral complaints	3.54 (1.77, 7.09)
3. Patient characteristics + complaint characteristics (AUC = 0.80, Nagelkerke R square 0.35)	
Age > 60 years	1.69 (0.96, 2.98)
Female gender	1.45 (0.83, 2.52)
Kinesiophobia	2.21 (1.26, 3.85)
Sport	0.67 (0.38, 1.20)
Duration > 3 months	2.15 (1.14, 4.04)
History of nontraumatic knee complaints	3.57 (1.73, 7.36)
Recurrent complaints	1.78 (1.00, 3.14)
Bilateral complaints	3.43 (1.68, 7.00)

symptom characteristics variables were the strongest predictors of persisting knee symptoms, whereas the findings from physical examination showed no added prognostic value.

Similarly, in the subgroups based on age, self-reported symptom characteristics were the strongest predictors for persisting knee symptoms, and the determinants from the physical examination had no prognostic value. In the younger age group (36–49 years) duration of symptoms >3 months was a strong predictor for persisting knee symptoms. In the older age group (≥50 years), a history of nontraumatic knee symptoms was the strongest predictor.

Despite the high prevalence of knee symptoms in general practice [5], few studies have investigated prognostic factors of knee symptoms in a primary care setting [8,29].

Compared with a secondary care population, our population had less severe symptoms and better knee function [30]; this might lead to different prognostic factors for persisting knee symptoms compared with a secondary care population. The findings on prognostic factors emerging from this study could be used to better inform patients, and as a basis for management of clinical treatment.

Our study population was relatively heterogeneous. All patients with nontraumatic knee symptoms were included in the study, and the predictors were applied to all

patients in the study. However, compared with a nationwide registration study [31], our population differed not substantially from patients with knee symptoms in other Dutch general practices [12]. Therefore, we assume our population to be representative of a primary care population and we do not expect bias due to selective recruitment. Although one may assume that most patients >35 years of age will have knee symptoms indicative of OA, the results can not be directly interpreted as predictors of OA. The diagnosis of OA can be supported by radiologic criteria; however, in the present study we chose not to include radiographs of the knee because only a small proportion of patients in primary care are referred for radiographs [4]. Moreover, radiologic severity does not seem to be related to progression of knee OA [10]. Based on the age groups in the ACR classification criteria for knee OA [25], we performed subgroup analyses for the older and younger persons in our study group, which led to slight differences in the prognostic variables. However, the present results cannot be directly interpreted as predictors for OA in patients >50 years of age.

For the outcome, we used patients' self-reported recovery or persisting knee symptoms at 1 year of follow-up compared with those at baseline (thentest), and such selfreports may be susceptible to recall bias [32]. However, it is reported that recall bias does not invalidate the thentest results [33].

With regard to the self-reported symptom characteristics, it is debatable whether generic health measures such as the SF-36 should be included. However, in our univariate and multivariate analyses, these variables were not statistically significant and had no predictive value. Even if these variables were included in patient characteristics, they still had no prognostic value. Therefore we do not expect bias due to the choice to include generic health measures in the self-reported symptom characteristics.

At baseline, data about knee symptoms (duration, intensity), daily activities, and social setting were collected by self-report questionnaires so that self-reported symptom characteristics would not only be disease specific, but would also depend on the experience of the patient. However, in clinical practice,both symptom characteristics and the patient's experience play a role in the decision to visit a general practitioner. For example, pain could be experienced in different ways. In addition to the level of pain and the extent of limitations caused by pain, the patient's interpretation of their symptoms will influence their decision to visit a general practitioner.

Crepitus of passive extension of the knee was associated with persisting knee symptoms in the physical examination model, but this determinant had no added value in the prediction of persisting knee symptoms. In our study, the physical examination was performed by trained physiotherapists according to a standardized test protocol [12]. In clinical practice, due to lack of standardization of the examination of the knee joint, the physical examination may be even less predictive than it was found to be in the present

study. However, with respect to the diagnostic value, the general practitioner may still elect to perform the physical examination of the knee.

Although treatment could have effect on the prognosis, we decided to only assess baseline factors in this study. With regard to treatment, only a total knee replacement would provide total recovery from knee symptoms. In our cohort, 43 (9.0%) patients underwent an operation for their knee. Of these, 18 (41.9%) reported persisting knee symptoms and 25 (58.1%) reported a recovery. Therefore, we do not suspect bias due to treatment.

The models in this study could be overfitted and therefore over-optimized because we did not validate them by bootstrapping or external validation. However, our findings correspond with those of van der Waal et al [29]. In our study, we also investigated the determinants of physical examination on persisting knee symptoms, which, to our knowledge, no previous studies have investigated in a general practice population.

In contrast to our finding that self-reported symptom characteristics are the strongest predictors of persisting knee symptoms, Thomas et al found clinical history, physical examination, and severity of radiographic knee OA on plain radiograph to be of limited value over generic factors in predicting a poor outcome after 18 months of follow-up [34]. However, in their study patients were recruited by postal surveys addressing knee pain. This is a major difference from our study, in which patients visiting their general practitioner with incident nontraumatic knee pain were included.

Additionally, our findings correspond with the findings from other studies of prognostic indicators for patients with musculoskeletal pain in primary care, in which a longer history of pain, previous episodes of pain, and multiple-site pain were the strongest predictors of future pain status [7].

In conclusion, the present study shows that variables of symptom characteristics are the strongest predictors of persistent knee symptoms. Of the predictors found, most are not amenable to modification; this causes limitations with respect to the treatment of nontraumatic knee symptoms. However, in the case of kinesophobia, specific interventions (e.g., sport activities) can be considered. Perhaps intensive treatment (e.g., through education, medication, or physiotherapy) of patients with a higher risk of persisting knee symptoms might provide a better outcome. Therefore, further research on the treatment of knee symptoms is needed. Furthermore, for the individual prognosis of a patient, a prediction rule is needed to provide risk estimations of persisting knee symptoms. To develop a prediction rule, the prognostic models have to be internally and externally validated. Should a prediction rule be developed, we advise that it be based on data from more primary care knee cohorts with longer periods of follow-up. With regard to the major burden of knee symptoms, further research on prevention is also recommended.

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Chapter 5

The prognostic value of the clinical ACR classification criteria of knee osteoarthritis for persisting knee complaints and increase of disability in general practice

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Osteoarthritis and Cartilage; in press

ABSTRACT

Objective: To assess the prognostic value of the clinical American College of Rheumatism (ACR) classification criteria of knee osteoarthritis (OA) on persisting knee complaints and increase of disability in adult patients with knee pain in general practice after 1-year follow-up.

Methods: Patients (aged > 35 years) consulting for nontraumatic knee complaints in GP were enrolled in the study. At baseline and 1-year follow-up knee complaints and function were assessed by questionnaires and a physical examination was performed. The prognostic value of fulfilling the clinical ACR criteria of knee OA at baseline on the outcomes persisting knee complaints and increase of disability was determined.

Results: 549 patients were included in the study of which 480 (87.4%) were available for follow-up. The studied population consisted of 236 (49.2%) women with mean age 53.6 (sd 11.3), mean BMI 27.1 (sd 4.2), 288 (60.0%) patients had payed employment, and 292 (60.8%) patients fulfilled the ACR clinical criteria of knee OA. After one year follow-up, 236 (49.2%) patients reported persisting knee complaints, and 84 (17.5%) reported an increase of disability.

There was no association of fulfilling the ACR clinical criteria of knee OA at baseline with persisting knee complaints (OR 1.15; 95% CI 0.80, 1.67) or increase of disability (OR 1.05; 95% CI 0.43, 2.58) at follow-up.

Conclusion: The ACR clinical classification criteria of knee OA have no prognostic value for predicting persisting knee complaints or an increase of disability at one year of follow-up in adult patients with nontraumatic knee complaints in GP.

INTRODUCTION

Musculoskeletal diseases are one of the major causes of disability around the world and have important consequences to the individual and society. Within musculoskeletal diseases, rheumatoid arthritis, osteoarthritis (OA) and back pain are the most important causes of disability [1].

Although musculoskeletal pain and dysfunction affect all ages, the elderly are particularly targeted [2, 3]. The clinical syndrome of joint pain and stiffness in older people is the most common cause of disability and healthcare consultation in this age group [4].

In general practice, knee complaints (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (48/1000 patients per year), mostly presented as knee pain or functional loss of the knee joint [5, 6]. About 60% of patients with nontraumatic knee complaints is aged over 25 years. Disorders most diagnosed within this group in primary care are bursitis, tendonitis and OA [5]. In the elderly, the most common cause of knee complaints is the presence of OA [7].

In spite of the high prevalence of knee complaints in general practice, few studies have investigated the symptomatic course of nontraumatic knee complaints in general practice [8-10]. In a previous study we reported that almost 50% of patients visiting their general practitioner with incident knee complaints had persisting or worse knee complaints after 1-year follow-up [8]. In that study, especially complaint characteristics (e.g. bilateral symptoms, duration of symptoms) were the strongest predictors of persisting knee complaints at 1-year follow-up [8].

In clinical practice, it would be helpful to be able to distinguish between different groups of knee conditions with different effective treatment pathways, different courses and different prognoses, and subsequently inform the patient about the course of the disease.

To standardize the clinical definition of OA, the American College of Rheumatism (ACR) developed classification criteria especially with the aim to create standardized definitions for inclusion in trials and cohort studies [11]. For knee OA, Altman et al. developed these criteria to classify clinical OA, clinical and radiographic OA, and clinical and laboratory OA [12].

Considering the fact that knee OA is thought to be a chronic condition, it would be of interest to assess the prognostic value of clinical ACR criteria (combined sets) for knee OA instead of the prognostic value of individual characteristics separately. A combined set of characteristics developed to classify knee OA might have a higher prognostic value than individual characteristics.

Until now no studies investigating the prognostic value of fulfilling the ACR criteria on the prognosis of nontraumatic knee complaints in general practice are available.

Therefore, we performed a prospective cohort study in general practice to assess the prognostic value of fulfilling the ACR criteria on persisting or worsening knee complaints, and an increase of disability at 1-year follow-up in patients visiting the GP with

nontraumatic knee complaints. Additionally we will describe how the ACR criteria are distributed in a primary care population with new nontraumatic knee complaints.

METHODS

Study design and population

For this study, a subgroup of the prospective HONEUR knee cohort was used; details on this cohort have been reported earlier [13]. In brief, consecutive patients of age ≥ 12 years visiting their general practitioner (GP) with a new episode of knee complaints were enrolled in the study and followed for 1 year. In this prospective cohort study, 40 GPs from five municipalities in the southwest region of the Netherlands, connected to the ErasmusMC GP Research Network HONEUR and representing a total patient population of around 84.000 patients, participated. Recruitment was started in October 2001 in one municipality and a new municipality was added approximately every 3 months. All GPs recruited up to October 2003 [13]. New complaints were defined as complaints that were presented to the GP for the first time in a period of 3 months. Recurrent complaints for which the GP was not consulted within the last 3 months were also considered as new complaints. Exclusion criteria were knee complaints that required urgent medical attention (fractures, infection), patients with malignancies, neurological disorders or systemic musculoskeletal diseases (e.g. Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as incapability of understanding the implications of participation. At baseline and at 1-year follow-up, patients underwent a standardized physical examination of their knee by trained physiotherapists. The physical examination at baseline was planned as close to the date of consultation of the GP as possible.

For this study, all patients aged 35 years and older with nontraumatic knee complaints were included. At baseline and 12-months follow-up, information on knee complaints (duration, intensity), daily activities and social circumstances was collected and a physical examination of the knee was performed. In patients with bilateral complaints, both knees were examined. For the analysis, the self-nominated worst knee was used.

Functional disability and pain were assessed both at baseline and 12-months follow-up by self-reported questionnaires containing the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) [14, 15], the Medical Outcome Study Short Form-36 (SF-36) [16, 17], the Knee Society Score (KSS) function questions [18, 19], the Lysholm Knee Scoring Scale [20-22], the Tampa Scale for Kinesiophobia (assessed at baseline) [23, 24].

The physical examination included signs (e.g. swelling, temperature) and symptoms (e.g. function, pain) of the knee and hip. Further details about the physical signs and how they were elicited and scored are available from the corresponding author.

For the outcome persisting knee complaints at 1-year follow-up, a question addressing experienced recovery or worsening scored on a 7-point Likert scale was added to the last questionnaire.

Statistical analysis

First, we assessed which patients fulfilled the clinical ACR criteria of OA as described by Altman et al [12]. Clinical OA of the knee is defined as knee pain and at least three out of six of the following criteria: age > 50 years, morning stiffness < 30 minutes, crepitus, bony tenderness, bony enlargement, and no palpable warmth.

Differences between patients fulfilling the clinical ACR criteria and patients not fulfilling these criteria were assessed.

Hereafter, we univariately analyzed the association of fulfilling the clinical ACR criteria and age, gender, Body Mass Index (BMI), and disability (WOMAC function score) at baseline.

To assess the prognostic value of the clinical ACR criteria, we first univariately assessed the association with persisting knee complaints, and an increase of disability after 1-year follow-up. Additionally, the enter method of logistic regression or linear regression was used to adjust for differences in patient characteristics and baseline severity.

Persisting knee complaints were defined as patients who experienced knee complaints as somewhat better, no recovery, worse, much worse, or worse than ever, versus recovered patients who experienced knee complaints as much better and no complaints after 1-year follow-up. The increase of disability was assessed by the difference between WOMAC function score at baseline and 1-year follow-up.

SPSS software version 11 was used to analyze the data. For the missing data of participants available for follow-up at 1-year, a multiple imputation strategy (MICE) was used [25] for the 1-year outcome data or relevant baseline information (e.g. persistent knee complaints, WOMAC function score).

Table 1: Study population characteristics (n = 480)

Characteristic	Osteoarthritis (ACR criteria) (n = 292)	No osteoarthritis (n = 188)	OR (95% CI)	Total (n = 480)
Baseline				
Age; mean (sd)	57.2 (10.4)	47.9 (10.2)*	1.10 (1.07; 1.12)	53.6 (11.3)
Female gender; n (%)	158 (54.1)	78 (41.5)*	1.60 (1.10; 2.32)	236 (49.2)
BMI; mean (sd)#	27.6 (4.4)	26.3 (3.8)*	1.08 (1.03; 1.13)	27.1 (4.2)
Duration of complaints; n (%)				
< 3 weeks	124 (42.5)	83 (44.1)	1.00	207 (43.1)
3 weeks – 3 months	83 (28.4)	53 (28.2)	0.73 (0.40; 1.32)	136 (28.3)
3 months – 1 year	42 (14.4)	28 (14.9)	0.77 (0.41; 1.43)	70 (14.6)
> 1 year	43 (14.7)	21 (11.2)	0.73 (0.36; 1.49)	64 (13.3)
WOMAC function score; mean (sd)#	30.8 (20.6)	21.8 (20.8)*	1.02 (1.01; 1.03)	27.4 (21.1)
WOMAC pain score; mean (sd)#	31.6 (18.8)	26.2 (18.1)*	1.02 (1.01; 1.03)	29.2 (18.7)
Knee complaints affects performance at work; n (%)	89 (30.5)	64 (34.0)	1.21 (0.82; 1.79)	153 (31.9)
ACR criteria; n (%)				
Knee pain	292 (100)	167 (88.8)	NA	459 (95.6)
Age > 50 years	220 (75.3)	54 (28.7)*	7.41 (4.90; 11.21)	273 (56.9)
Stiffness < 30 minutes	195 (66.8)	39 (20.7)*	7.36 (4.80; 11.57)	234 (48.8)
Crepitus	210 (71.9)	58 (30.9)*	4.24 (2.61; 6.89)	268 (55.8)
Bony tenderness	206 (70.5)	43 (22.9)*	8.08 (5.29; 12.33)	249 (51.9)
Bony enlargement	45 (15.4)	7 (3.7)*	4.74 (2.09; 10.76)	52 (10.8)
No palpable warmth	239 (81.8)	121 (64.4)*	2.36 (1.54; 3.64)	360 (75.0)

History of traumatic knee complaints in the past; n (%)	176 (60.3)	89 (47.3)*	1.68 (1.03; 2.76)	265 (55.2)
History of nontraumatic knee complaints in the past; n (%)	53 (18.2)	13 (6.9)*	3.25 (1.70; 6.19)	66 (13.8)
Limited when walking stairs; n (%)	254 (87.0)	129 (68.6)*	2.85 (1.79; 5.54)	383 (79.8)
Self reported swollen knee joint; n (%)	130 (44.6)	62 (33.0)*	1.61 (1.10; 2.36)	197 (39.5)
Other physical examination; n (%)				
Effusion knee joint (ballottement)	100 (34.2)	51 (27.1)	1.28 (0.83; 1.96)	151 (31.5)
Pain active extension	54 (18.5)	23 (12.2)	0.83 (0.47; 1.47)	180 (37.5)
Pain active flexion	121 (41.4)	59 (31.4)	0.81 (0.51; 1.30)	77 (16.0)
Pain internal rotation hip	54 (18.5)	18 (9.6)*	2.15 (1.22; 3.81)	72 (15.0)
Restriction internal rotation hip	77 (26.4)	34 (18.1)*	1.62 (1.03; 2.55)	111 (23.1)
Patellofemoral apprehension test	57 (19.5)	11 (5.9)*	3.89 (1.98; 7.65)	68 (14.2)
Bursitis prepatellaris; n (%)	44 (15.1)	22 (11.7)	1.34 (0.77; 2.32)	66 (13.8)
Pain iliotibial tract; n (%)	50 (7.1)	20 (10.6)	1.71 (0.98; 2.98)	70 (14.6)
Pain ligamentum patellae; n (%)	32 (11.0)	17 (9.0)	1.30 (0.77; 2.18)	49 (10.2)
Pain borders patella; n (%)	145 (49.6)	64 (34.0)*	2.00 (1.37; 2.93)	281 (43.5)
Pain tuberositas tibiae; n (%)	30 (10.3)	6 (3.2)*	3.41 (1.39; 8.38)	36 (7.5)
After 1 year follow-up				
Persistent knee complaints; n (%)	148 (50.7)	88 (46.8)	1.15 (0.80; 1.67)	236 (49.2)
WOMAC function score; mean (sd)#	16.3 (19.7)	9.0 (14.7)*	1.02 (1.01; 1.04)	13.3 (18.3)
WOMAC pain score; mean (sd)#	15.6 (18.9)	9.9 (14.8)*	1.02 (1.01; 1.03)	13.7 (17.7)
Increase in disability; n (%)	54 (18.5)	30 (16.0)	1.20 (0.73; 1.95)	84 (17.5)
Knee complaints affects performance at work; n (%)	36 (12.3)	27 (14.4)	0.86 (0.50; 1.47)	63 (13.1)

* Statistical significant difference ($p < 0.05$) compared to presence of osteoarthritis (ACR criteria)

BMI: Body Mass Index; WOMAC: Western Ontario and McMasters University Osteoarthritis Index (scale 0 – 100), a lower score represents better function/outcome

OR: Odds Ratio, sd: standard deviation

RESULTS

Study population

A total of 549 patients aged ≥ 35 years with nontraumatic knee complaints were included, of which 480 were available for follow-up. Persons lost to follow-up (n=69; 12.6%) showed no significant differences compared with those not lost to follow-up regarding baseline age, gender, BMI, KSS knee and function score, SF-36 score, co-morbidity, WOMAC scores, Lysholm scores, Tampa scores, and knee OA according the clinical ACR criteria.

Of the persons lost to follow-up, reasons for not participating any more were lack of time/lack of interest (n=36, 52.2%), severe co-morbidity like cancer or cerebrovascular accident (n=15, 21.7%), treatment by an orthopedic surgeon (n=4, 5.8%). Further, 14 patients (20.3%) provided no reason.

The mean age was 53.6 (sd 11.3) years, mean BMI was 27.1 (sd 4.2), and 236 (49%) were women. Table 1 presents details on the characteristics of the study group. Detailed information about baseline characteristics (e.g. KSS knee and function scores, Tampa scale for kinesiophobia) is reported earlier [8].

After 1-year follow-up, 236 (49.2%) patients reported persisting knee complaints, and 84 (17.5%) reported an increase of disability (mean difference 13.9, sd 20.3).

With regard to the missing values, multiple imputation was used to replace the missings. There were both eight missing values of the dependent variable 'persistent knee complaints' and 'increase of disability'. Of the patient characteristics, complaint characteristics, and the characteristics of physical examination, the range of missing values was 3 – 20.

Clinical ACR criteria

Of the 480 included patients, 292 (61 %) fulfilled the clinical ACR criteria of osteoarthritis. Of these, besides knee pain, 123 (26%) fulfilled three out of six, 109 (23%) fulfilled four out of six, 50 (10%) fulfilled five out of six, and 10 (2%) fulfilled all clinical ACR criteria.

One of the six ACR criteria is age >50 years. But also in the patients aged ≤ 50 years, 72 of 232 patients (31%) fulfilled the (other) clinical ACR criteria. Of these, 59 (81%) had a traumatic history of the knee in the past. With increase in age, also the percentage of patients who fulfilled the ACR clinical criteria increased (Table 2).

Table 2: Osteoarthritis (ACR) in 10-year age groups (n = 480)

Age (years)	Osteoarthritis; n (%)	No Osteoarthritis; n (%)	Total; n
35 – 45	41 (29.7)	97 (70.3)	138
46 – 55	99 (65.1)	53 (34.9)	152
56 – 65	82 (78.1)	23 (21.9)	105
66 – 75	57 (83.8)	11 (16.2)	68
76 – 85	13 (76.5)	4 (23.4)	17
Total	292 (60.8)	188 (39.2)	480

Comparison with patients without OA (Table 1)

In the univariate analysis, fulfilling the ACR criteria at baseline was associated with increasing age, female gender, increasing BMI , and more disability (increase of WOMAC function score) at baseline.

Also, patients fulfilling the ACR criteria differed statistically significant from patients not fulfilling these criteria on a history of (non)traumatic knee complaints, limited when walking stairs, self-reported swollen knee joint, pain of internal rotation of the hip, restriction of internal rotation of the hip, and WOMAC function score at follow-up.

Further, patient fulfilling the clinical ACR criteria had more serious complaints and co-morbidity, and differed statistically significant on pain of the borders of the patella, and pain of the tuberositas tibiae.

As a result of the classification, all separate ACR criteria were more often present in patients fulfilling the clinical ACR criteria.

Prognostic value of the clinical ACR criteria

For the prognostic value of fulfilling the ACR criteria, there was univariately no association with persisting knee complaints (OR 1.15, 95% CI 0.80; 1.67) or an increase of disability (Beta 0.03 [95% CI –0.05; 0.10]) after 1 year follow-up. Adjustment for age, gender, BMI, and baseline severity (WOMAC function and pain) did not change the found association.

DISCUSSION

In the present study the ACR clinical classification criteria of knee OA had no prognostic value for predicting persisting or worsening knee complaints or an increase of disability

in adult patients with nontraumatic knee complaints in general practice after 1-year follow-up.

This study also showed that patients fulfilling the ACR criteria of clinical knee OA had more serious complaints (lower WOMAC function and pain score) and co-morbidity at baseline and after 1-year follow-up.

Despite the high prevalence of knee complaints in general practice [6], the prognostic value of the ACR clinical classification criteria of knee OA has received little attention.

We found that the clinical ACR criteria of knee OA have no prognostic value. A plausible reason for the absence of the prognostic value of the ACR clinical classification criteria may be that the follow-up of 1-year is too short to show a difference between both groups. One-year follow-up could be too short to discriminate between the knee OA and the other diagnoses in primary care and more pronounced differences might show up after a longer period of follow-up (e.g., > 5 years). A follow-up after 7 years is planned for the HONEUR knee cohort.

Also, the fluctuating course of symptoms of knee OA [5] might provide noice and regression to the mean.

Compared to a secondary care population, our population had less severe complaints and knee function was better [26]; this might lead to less pronounced findings than in a secondary care population. Also in secondary care, patients with knee complaints based on OA have to be distinguished from among other things rheumatoid arthritis, arthralgia or fibromyalgia, osteonecrosis, meniscal or ligamentous or cruciate abnormalities, osteonecrosis, and septic arthritis [12]. This in contrast with patients in primary care where besides knee OA the differential diagnosis of nontraumatic knee complaints mainly consists of a bursitis prepatellaris, iliotibial tract syndrome, and soft tissue disorders [5] because of the low incidence of rheumatoid arthritis, septic arthritis, and osteonecrosis (e.g. considerable effusion will appear less often due to the low percentage of rheumatoid arthritis). Also, exclusion criteria of our study were among others infection of the knee joint or the presence of rheumatoid arthritis. Therefore, the criterion 'no palpable warmth' might discriminate in secondary care but probably not or even the other way around in primary care. However, even if we did not include the ACR criterion 'no palpable warmth' the clinical ACR criteria still had no prognostic value on persisting knee complaints or an increase of disability in adult patients with nontraumatic knee complaints in general practice after 1-year follow-up.

Further, in our study, recurrent complaints for which the GP was not consulted within the last 3 months were also considered as new complaints. We also performed the analysis for the subgroup of patients who never consulted for knee pain before, but we did not find other results for this group. Therefore, we do not expect bias due to the inclusion criteria used.

Patients classified with clinical OA had statistically significant more serious complaints at baseline and follow-up and showed more co-morbidity of the knee (lower WOMAC pain and function scores, higher prevalence of pain of the iliotibial tract, pain of the borders of the patella, and pain of the tuberositas tibiae). This might indicate that besides knee OA also other disorders contribute to the knee complaints making it more difficult to distinguish the specific signs and symptoms of knee OA.

For the outcome we used patients' self-reported recovery or persisting knee complaints at 1-year follow-up compared with those at baseline. Such self-reports may be susceptible to recall bias [27]. However, response shifts in different directions may have a similar meaning when comparing patient groups who deteriorated or improved [27].

In our study the physical examination was performed by trained physiotherapists according to a standardized test protocol [13]. Standardization of the examinations among researchers was accomplished by a series of training sessions before starting the inclusion of patients and these sessions were repeated regularly over the course of the inclusion period [13]. In our study, we don't have information about the reliability of the physical examination.

But, a study about the reliability of physical examination in knee OA reported that, with exception of physical examination for instability, a comprehensive knee examination can be performed with adequately reliability and that standardization further improves the reliability for some physical signs and techniques (e.g., alignment, bony swelling) [28].

In clinical practice, however, due to lack of standardization of the examination of the knee joint, the ACR criteria obtained by the physical examination, e.g., bony enlargement in overweight people, might be less reproducible and valid to assess.

In our study, 61% of the patients fulfilled the clinical ACR criteria of knee OA. This is in contrast with the study by Peat et al. where 30% of the participants fulfilled the clinical ACR criteria of knee OA [29]. A reason for this difference might be that in the study by Peat et al. patients were recruited by postal surveys in the open population addressing knee pain in the last 12 months. This is a major difference with our study in which patients visiting their GP with incident nontraumatic knee pain were included.

Another reason for the high percentage of patients fulfilling the clinical ACR criteria could be that the criterium 'no palpable warmth' would more often be fulfilled because we did not include patients with an infection of the knee joint or rheumatoid arthritis. But even if we did not include this criterium, there still was a higher percentage of patients fulfilling the clinical ACR criteria (42%).

With regard to the clinical ACR criteria of knee OA, doubts have been expressed about the validity of these criteria in primary care or the general population [29, 30].

Peat et al. report the ACR criteria seem to reflect later signs in advanced disease [29]. In their study the combination of frequent knee symptoms and radiographic evidence of definite OA was used to assess the performance of the ACR criteria of knee OA in the

general population. Also, in our study, especially specific later signs of knee OA like bony enlargement are more prevalent in patients fulfilling the clinical ACR. Another striking observation is that most patients ≤ 50 years fulfilling the clinical ACR criteria report a history of traumatic knee complaints. This is in accordance with previous studies who reported knee trauma to be a risk factor for incident knee OA [31, 32], especially for knee OA at younger age.

Also, with respect to the WOMAC scores in primary care, there is increasing uncertainty about the validity and reliability of this questionnaire [33, 34]. One can suppose that some patients were considered wrongly as suffering from an increased disability, while the increase in WOMAC score was due to the reliability of measurement. However, we do not expect bias due to the reliability of the measurement. Because, it is also possible that some patients were considered wrongly as decreased disability due to the reliability of the measurement.

In conclusion, this study shows the absence of the prognostic value of the ACR clinical classification criteria of knee OA for predicting persisting knee complaints and an increase of disability after 1-year follow-up in adult patients consulting their GP with incident knee complaints. Further studies should establish whether the present clinical ACR criteria do have prognostic value at longer follow-up or whether ACR criteria are valid for use in primary care.

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Chapter 6

Medical treatment and medical consumption in adults with nontraumatic knee complaints in general practice

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Submitted

ABSTRACT

Objective: To assess the medical treatment of the general practitioner (GP) at baseline and medical consumption during 1-year follow-up in adult patients visiting the GP with nontraumatic knee complaints.

Methods: Patients (aged > 35 years) consulting for nontraumatic knee complaints in general practice were enrolled in the study. At baseline, knee complaints, knee function, and medical treatment were assessed. During 1-year follow-up, medical consumption was assessed with 3-monthly questionnaires. In addition, factors associated with baseline referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee were determined.

Results: Of the 549 patients included in the study, 480 (87.4%) were available for follow-up. The study population consisted of 236 (49.2%) women, mean age 53.6 (sd 11.3) years, and mean BMI 27.1 (sd 4.2). At baseline, 193 (35.2%) patients were advised by the GP to avoid heavy loading of the knee, and 150 (27.3%) received a prescription for pain medication. Of all patients, 311 (56.6%) received a referral to either a physiotherapist or orthopedic surgeon, or for X-ray of the knee. During 1-year follow-up, 182 (37.9%) patients revisited the GP, 180 (37.5%) visited a physiotherapist, and 114 (23.8%) an orthopedic surgeon.

Patient characteristics associated with referral to a physiotherapist were female gender, younger age, and crepitus of active extension of the knee. Associated with a referral to an orthopedic surgeon were no paid employment, feeling of giving way, and pain on passive flexion of the knee. Referral for X-ray of the knee was associated with female gender, older age, and a bony swelling of the joint.

Conclusion: Medical treatment at baseline partly corresponds with recommendations given in the Guideline of the Dutch College of General Practitioners for nontraumatic knee complaints in adults. In this study group, medical consumption is relatively high during 1-year follow-up.

INTRODUCTION

Musculoskeletal conditions are a major burden on individuals, health systems, and social care systems, with indirect costs due to disability being predominant [1]. Although musculoskeletal pain, injury, and dysfunction affect all ages, the elderly are particularly targeted [2, 3]. In general practice, knee complaints (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (19/1000 patients per year), mostly presented as knee pain or functional loss of the knee joint [4, 5]. About 60% of patients with nontraumatic knee complaints are aged > 25 years. Disorders most diagnosed within this group in primary care are bursitis, tendonitis and osteoarthritis (OA)

The Dutch College of General Practitioners (NHG) developed a clinical guideline for nontraumatic knee complaints in adults which includes recommendations with regard to diagnostic and therapeutic policies [6]. In this guideline, X-ray for the knee is not recommended because the absence of an abnormality on X-ray can not exclude the presence of a disease. In addition, several studies have reported the absence of a clear correlation between radiological knee OA and clinical knee OA [4, 6-10].

With regard to treatment, several policies are advised. For knee pain, pain medication (acetominophen, NSAIDs) is advised. For a bursitis prepatellaris, avoidance of burden and friction of the joint is recommended, while for an iliotibial tract syndrome a decrease of sport activities which cause complaints, or exercises, are advised. For knee OA, besides pain medication, active physical exercise (e.g., walking, swimming) is advised. If this advice is insufficient, a referral to a physiotherapist could be considered. A referral to an orthopedic surgeon is advised for severe (recurrent) knee complaints in spite of adequate conservative therapy [6]. A revised guideline for nontraumatic knee complaints has recently been published in which an active policy (e.g., referral to physiotherapist for exercise therapy) by the general practitioner (GP) is recommended [4].

Despite the major burden on health systems, until now no studies have investigated the medical treatment and medical consumption of nontraumatic knee complaints in general practice. Furthermore, we were interested to explore whether there is a difference in medical policy when complaints are classified according to specific classification criteria, e.g. the clinical ACR criteria for knee OA.

Therefore, we performed a prospective cohort study in general practice to assess the medical policy of the GP at baseline, and medical consumption during 1-year follow-up in patients visiting the GP with nontraumatic knee complaints. Additionally, we assessed which signs and symptoms of clinical history and physical examination at baseline are associated with a baseline referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee.

METHODS

Study design and population

For this study, a subgroup of the prospective HONEUR knee cohort was used; details of this cohort have been reported earlier [11]. In brief, consecutive patients of age ≥ 12 years visiting their GP with a new episode of knee complaints were enrolled in the study and followed for 1 year. This prospective cohort study involved the participation of 40 GPs from 5 municipalities in the southwest region of the Netherlands; all were connected to the ErasmusMC GP Research Network HONEUR and together represented a total patient population of around 84,000 patients. Recruitment was started in October 2001 in 1 municipality and a new municipality was added approximately every 3 months thereafter. All GPs recruited patients up to October 2003 [11]. New complaints were defined as complaints that were presented to the GP for the first time. Recurrent complaints for which the GP was not consulted within the last 3 months were also considered as new complaints. Exclusion criteria were knee complaints that required urgent medical attention (e.g., fractures, infection), patients with malignancies, neurological disorders or systemic musculoskeletal diseases (e.g., Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients that were incapable of understanding the ramifications of study participation.

At baseline and at 1-year follow-up, patients underwent a standardized physical examination of their knee by trained physiotherapists. The physical examination at baseline was planned as close to the date of consultation of the GP as possible. Disability, pain, and medical consumption (e.g. visit of the GP or physiotherapist) were assessed every 3 months by self-reported questionnaires.

For the present study, all patients aged 35 years and older with nontraumatic knee complaints were included. At baseline and at follow-up, information on knee complaints (duration, intensity), daily activities, social circumstances, and medical treatment by the GP was collected with a structured questionnaire and a physical examination of the knee was performed. Functional disability and pain were assessed both at baseline and at follow-up by self-reported questionnaires containing the Western Ontario and McMasters University Osteoarthritis Index (WOMAC) [12, 13], the Medical Outcome Study Short Form-36 (SF-36) [14, 15], the Knee Society Score (KSS) function questions [16, 17], the Lysholm Knee Scoring Scale [18-20], and the Tampa Scale for Kinesiophobia (assessed at baseline) [21, 22]. During follow-up, medical consumption was assessed every 3 months by asking which of the following medical professionals was visited during the previous 3 months: GP, physiotherapist, occupational therapist, rheumatologist, orthopedic surgeon, occupational physician, alternative therapist.

For the outcome 'medical consumption during follow-up', we assessed whether a patient had visited a medical professional during the 1-year follow-up. To avoid bias due to repeated measurements, patients visiting a medical professional more than once were counted one time.

The physical examination assessed signs (e.g., swelling, temperature) and symptoms (e.g., function, pain) of the knee and hip.

Statistical analysis

First, self-reported medical treatment at baseline and medical consumption during 1-year follow-up are presented using descriptive statistics. Because there are no other specific classification criteria, only initial treatment of patients with or without clinical knee OA according to the clinical ACR criteria will be compared [23].

Thereafter, univariate analyses were performed to assess which factors of the patient's characteristics, clinical history, and physical examination at baseline were associated with a baseline referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee. The baseline factors analyzed were based on the literature [4-6, 24] and on experienced clinical relevance.

In the multivariate backward logistic regression analyses, factors with a p-value <0.2 in the univariate analysis were included (p-value entry 0.05, p-value removal 0.10). To assess the association of determinants with a referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee, a multivariate model was built by backward logistic regression and the area under the ROC curve (AUC) was estimated. Three models were built, i.e. a model of associated factors of a baseline referral to a physiotherapist, a model of associated factors or a baseline referral to an orthopedic surgeon, and a model of associated factors of a referral for X-ray of the knee.

SPSS software version 11 was used to analyze the data. For the missing data, a multiple imputation strategy (MICE) was used [25].

RESULTS

Study population

A total of 549 patients aged ≥ 35 years with nontraumatic knee complaints were included of which 480 were available for follow-up. Persons lost to follow-up (n=69; 12.6%) showed no significant differences compared with those not lost to follow-up regarding age, gender, BMI, KSS knee and function score, SF-36 score, co-morbidity, WOMAC scores,

referral for X-ray, and referral to an orthopedic surgeon. However, a significant difference was found for referral to a physiotherapist, i.e. 26 of 140 patients (18.6%; p = 0.004).

Of the persons lost to follow-up, reasons for no longer participating were lack of time/lack of interest (n=36, 52.2%), severe co-morbidity such as cancer or a cerebrovascular accident (n=15, 21.7%), treatment by an orthopedic surgeon (n=4, 5.8%), and 14 patients (20.3%) provided no reason.

The mean age was 53.6 ± 11.3 years, mean body mass index (BMI) was 27.1 ± 4.2, 236 (49%) were women, and 348 (63.4%) were labelled as having clinical knee OA according to the clinical ACR criteria. Table 1 presents details on the characteristics of the study group.

At 1-year follow-up, 236 (49.2%) patients reported persisting knee complaints.

Medical treatment (Table 1 and 2)

At baseline, 193 (35.2%) patients were advised to avoid heavy loading of the knee, 150 (27.3%) received a prescription for medication of which 15 (2.7%) acetaminophen and 137 (25.0%) NSAIDs. Of all patients, 311 (56.6%) received a referral of which 140 (25.4%) to a physiotherapist, 59 (10.7%) to an orthopedic surgeon, and 112 (20.4%) were sent for an X-ray of the knee (Table 1).

During 1-year follow-up, 182 (37.9%) patients revisited their GP, 180 (37.5%) consulted a physiotherapist, and 114 (23.8%) visited an orthopedic surgeon (Table 2).

There was no clear difference in medical consumption between patients with or without knee OA according to the clinical ACR criteria for knee OA. Also, no difference was found between people with or without overweight, and between patients with or without a duration of knee complaints > 1 year at baseline. Patients with a history of (non)traumatic knee complaints in the past more often visited a physiotherapist compared to patients without a history of (non)traumatic knee complaints. Patients using pain medication at baseline visited their GP more often compared to patients without pain medication (Table 2).

Univariate analysis baseline referral to physiotherapist, orthopedic surgeon, or X-ray (Table 3)

Referral to physiotherapist

In the univariate analysis of factors associated with a referral to a physiotherapist, only female gender showed a significant association (OR 1.74, 95% CI 1.17; 2.57). Four characteristics had a p-value < 0.20; these were age (continuous in years), pain at active flexion of the knee, pain of active extension of the knee, and crepitus during active extension of the knee.

Table 1: Baseline characteristics of the study population (n = 549)

Characteristic	Osteoarthritis (n = 348)#	No osteoarthritis (n = 201)#	Total (n = 549)
Age in years; mean (sd)	57.4 (10.6)	47.5 (9.7)*	53.8 (11.4)
Female gender; n (%)	190 (54.6)	82 (40.8)*	272 (49.5)
BMI; mean (sd)	27.5 (4.4)	26.3 (3.9)*	27.1 (4.3)
WOMAC; mean (sd)			
total score	68.1 (19.2)	75.3 (19.7)*	72.2 (21.1)
function score	69.6 (20.7)	76.9 (20.9)*	70.7 (19.7)
Duration of knee complaints; n (%)			
< 3 weeks	142 (40.8)	89 (44.3)	231 (42.1)
3 weeks – 3 months	98 (28.2)	57 (28.4)	155 (28.2)
3 months – 1 year	54 (15.5)	30 (14.9)	84 (15.3)
> 1 year	50 (14.4)	21 (10.4)	71 (12.9)
Presence history of traumatic knee complaints; n (%)	210 (60.3)	97 (48.3)*	307 (55.9)
Presence history of nontraumatic knee complaints; n (%)	68 (19.5)	13 (6.5)*	81 (14.8)
Co-morbidity skeletal system; n (%)	207 (59.5)	92 (45.8)*	299 (54.5)
Policy of general practitioner; n (%)			
Wait and see	57 (16.4)	33 (16.4)	90 (16.4)
Rest	50 (14.4)	30 (14.9)	80 (14.6)
To avoid heavy loading of the knee	125 (35.9)	68 (33.8)	193 (35.2)
Cold compresses	32 (9.2)	11 (5.5)	43 (7.8)
Knee exercises	59 (17.0)	40 (19.9)	99 (18.0)
To lose weight	27 (7.8)	5 (2.5)*	32 (5.8)
Medical therapy			
Medication	106 (30.5)	46 (22.9)	150 (27.3)
Analgetics	12 (3.4)	3 (1.5)	15 (2.7)
NSAIDs	94 (27.0)	43 (21.4)	137 (25.0)
Injection in the knee joint	2 (0.6)	1 (0.5)	3 (0.5)
X-ray of the knee	81 (23.3)	20 (10.0)*	112 (20.4)
Referral to physiotherapist	88 (25.3)	52 (25.9)	140 (25.4)
Referral to orthopedic surgeon	37 (10.6)	22 (10.9)	59 (10.7)

Presence/absence of clinical osteoarthritis according to the clinical ACR criteria for osteoarthritis of the knee
* Significant difference ($p < 0.05$) between presence and absence of osteoarthritis

Referral to orthopedic surgeon

In the univariate analysis of factors associated with a referral to an orthopedic surgeon, 7 factors showed a significant association. These were no paid employment (OR 3.84, 95%

Table 2: Medical consumption during follow-up (n = 480)

	Osteoarthritis#		Overweight persons#		Duration > 1 year#		History (non)traumatic knee complaints#		Use of painkillers at baseline#		Total population
Referral (n; %)	OA+ (n = 304)	OA- (n = 176)	BMI < 27.5 (n = 284)	BMI ≥ 27.5 (n = 192)	D- (n = 343)	D+ (n = 134)	H- (n = 201)	H+ (n = 279)	No use (n = 352)	Use (n = 128)	**n = 480**
General practitioner	115 (37.8)	67 (38.1)	100 (35.2)	82 (42.7)	123 (35.9)	58 (43.3)	66 (32.8)	116 (41.6)	121 (34.4)	*61 (47.7)**	**182 (37.9)**
Physiotherapist	115 (37.8)	65 (36.9)	105 (37.0)	72 (37.5)	125 (36.4)	54 (40.3)	65 (32.3)	*115 (41.2)**	137 (38.9)	43 (33.6)	**180 (37.5)**
Rehabilitation specialist	1 (0.3)	1 (0.6)	1 (0.4)	1 (0.5)	1 (0.3)	1 (0.7)	0	2 (0.7)	2 (0.6)	0	**2 (0.4)**
Rheumatologist	3 (1.0)	1 (0.6)	3 (1.1)	1 (0.5)	2 (0.6)	2 (1.5)	1 (0.5)	3 (1.1)	3 (0.9)	1 (0.8)	**4 (0.8)**
Orthopedic surgeon	67 (22.0)	47 (26.7)	67 (23.6)	45 (23.4)	76 (22.2)	37 (27.6)	42 (20.9)	72 (25.8)	90 (25.6)	24 (18.8)	**114 (23.8)**

Osteoarthritis: knee OA assessed by clinical ACR criteria for knee OA, OA+: presence of knee OA, OA-: no knee OA; Overweight people: assessed by Body Mass Index (BMI); Duration: duration of complaints, D-: duration < 1 year, D+: duration > 1 year; H-: no history of (non)traumatic knee complaints in the past, H+: history of (non)traumatic knee complaints in the past; Use of painkillers at baseline: use of acetaminophen or NSAIDs at baseline

* Significant difference ($p < 0.05$); in italic: significant difference ($p < 0.05$) with total population

Table 3: Univariate analyses of baseline referral to physiotherapist, orthopedic surgeon, or X-ray (n = 549)

	Referral to physiotherapist (n = 140)	Referral to orthopedic surgeon (n = 59)	Referral for X-ray (n = 112)
Characteristic	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Patient characteristic			
Female gender	***1.74 (1.17; 2.57)****	1.17 (0.68; 2.02)	***1.94 (1.26; 2.97)****
Age (continuous in years)	***0.98 (0.97; 1.00)***	0.82 (0.40; 1.69)	***1.05 (1.03; 1.07)****
BMI (continuous)	0.99 (0.95; 1.04)	0.96 (0.90; 1.03)	1.03 (0.98; 1.08)
BMI > 27.5	0.89 (0.60; 1.33)	0.73 (0.41; 1.29)	0.90 (0.59; 1.39)
No paid employment	1.19 (0.44; 3.22)	***3.84 (1.26; 11.1)****	1.59 (0.51; 5.00)
Low/moderate educational level	1.25 (0.82; 1.90)	***1.85 (0.97; 3.52)***	1.07 (0.69; 1.69)
Clinical history			
Warm knee	0.93 (0.62; 1.38)	0.84 (0.47; 1.49)	***1.50 (0.98; 2.30)***
Swollen knee	0.92 (0.62; 1.37)	***1.71 (0.99; 2.95)***	1.24 (0.82; 1.90)
Crepitus knee	1.06 (0.71; 1.59)	***2.03 (1.08; 3.80)****	1.25 (0.81; 1.95)
Pain (11-point scale)	1.04 (0.95; 1.14)	1.04 (0.91; 1.19)	1.02 (0.93; 1.13)
Duration of complaints > 1 year	1.03 (0.59; 1.82)	1.53 (0.75; 3.11)	***1.87 (1.07; 3.26)****
Presence of locked knee	0.91 (0.49; 1.69)	***1.68 (0.80; 3.53)***	***1.51 (0.83; 2.76)***
Feeling of giving way	0.94 (0.63; 1.41)	***2.98 (1.71; 5.21)****	***1.58 (1.04; 2.41)****
WOMAC physical functioning score	1.00 (0.99; 1.01)	1.00 (0.98; 1.01)	***1.01 (1.00; 1.02)***
WOMAC pain score	1.00 (0.99; 1.01)	1.00 (0.99; 1.02)	1.00 (0.99; 1.01)
WOMAC stiffness score	1.00 (0.99; 1.01)	***1.01 (1.00; 1.02)***	***1.01 (1.00; 1.02)***
WOMAC total score	1.00 (0.99; 1.01)	1.00 (0.99; 1.02)	1.01 (1.00; 1.02)
SF-36 physical functioning score	1.00 (0.99; 1.01)	0.99 (0.98; 1.00)	***0.99 (0.98; 1.00)****
SF-36 total score	1.01 (0.99; 1.02)	0.99 (0.97; 1.02)	***0.98 (0.96; 1.00)****
Co-morbidity of the musculoskeletal system	1.02 (0.69; 1.51)	0.77 (0.45; 1.33)	1.28 (0.84; 1.96)
History of nontraumatic knee complaints in the past	1.31 (0.78; 2.20)	***2.07 (1.09; 3.94)****	***1.98 (1.17; 3.34)****
History of traumatic knee complaints in the past	0.92 (0.62; 1.36)	***2.66 (1.42; 4.98)****	***1.55 (1.00; 2.39)****
Bother from paid employment	1.15 (0.76; 1.74)	1.05 (0.60; 1.80)	***0.47 (0.29; 0.78)****
Physical examination			
Swollen knee joint	1.02 (0.67;1.55)	***1.62 (0.93; 2.82)***	***1.67 (1.08; 2.58)****
Warm knee joint	1.24 (0.79; 1.95)	1.20 (0.64; 2.24)	***1.48 (0.92; 2.38)***
Floating patella	1.19 (0.76; 1.88)	0.86 (0.44; 1.69)	1.04 (0.63; 1.92)
Pain on passive flexion	1.26 (0.86; 1.86)	***2.43 (1.36; 4.36)****	***1.63 (1.07; 2.49)****
Pain on passive extension	1.06 (0.70; 1.62)	1.27 (0.72; 2.27)	0.87 (0.54; 1.39)
Pain on active flexion	***1.32 (0.89;1.95)***	***1.55 (0.90; 2.67)***	***1.64 (1.07; 2.50)****
Pain on active extension	***1.57 (0.96; 2.58)***	***2.04 (1.09; 3.82)****	0.82 (0.46; 1.48)
Crepitus on passive flexion	0.98 (0.90; 1.07)	0.99 (0.90; 1.09)	0.99 (0.92; 1.06)
Crepitus on passive extension	0.85 (0.52; 1.37)	1.44 (0.78; 2.67)	1.33 (0.82; 2.18)
Crepitus on active flexion	1.18 (0.80; 1.74)	1.07 (0.62; 1.85)	***1.54 (1.01; 2.34)****
Crepitus on active extension	***1.41 (0.96; 2.08)***	1.18 (0.69; 2.04)	***1.34 (0.88; 2.03)***
Pain palpation joint cleft	1.08 (0.73; 1.59)	1.16 (0.67; 2.00)	1.02 (0.67; 1.55)
Bony swelling of the joint	0.88 (0.45; 1.69)	1.41 (0.63; 3.14)	***1.93 (1.04; 3.58)****
Pain on internal rotation hip	1.30 (0.78; 2.15)	***1.62 (0.83; 3.13)***	***2.20 (1.31; 3.71)****
Restriction internal rotation hip	0.91 (0.56; 1.49)	1.31 (0.69; 2.50)	***1.68 (1.02; 2.77)****
Presence of Heberden's nodes	1.04 (0.64; 1.69)	0.94 (0.47; 1.89)	1.25 (0.75; 2.08)
Pain iliotibial tract	0.95 (0.66; 1.35)	0.98 (0.85; 1.13)	0.99 (0.91; 1.07)
Jumpers knee	0.69 (0.37; 1.29)	0.94 (0.41; 2.14)	1.03 (0.56; 1.87)
Prepatellar bursitis	0.95 (0.48; 1.87)	1.42 (0.63; 3.21)	1.13 (0.57; 2.24)

BMI: Body Mass Index, Pain on 11-point scale (scale 0-10), WOMAC: Western Ontario and McMasters University Osteoarthritis Index (scale 0-100), SF-36: Medical Outcome Study Short Form-36 (scale 0-100); For all scores (except SF-36 score): lower score represents better function/outcome; * Significant ($p < 0.05$); in italic and bold: $p < 0.20$

CI 1.26; 11.1), self-reported crepitus of the knee (OR 2.03, 95% CI 1.08; 3.80), feeling of giving way (OR 2.98, 95% CI 1.71; 5.21), a history of nontraumatic knee complaints in the past (OR 2.07, 95% CI 1.09; 3.94), a history of traumatic knee complaints in the past (OR 2.66, 95% CI 1.42; 4.98), pain on passive flexion of the knee (OR 2.43, 95% CI 1.36; 4.36), and pain on active extension of the knee (OR 2.04, 95% CI 1.09; 3.82).

Besides these, 7 characteristics had a p-value < 0.20. These were a low/moderate educational level, self-reported swollen knee, self-reported presence of a locked knee, the WOMAC stiffness score, a swollen knee joint at physical examination, pain on active flexion of the knee, and pain on internal rotation of the hip.

Referral for X-ray

In the univariate analysis of prognostic factors of a referral for X-ray, 16 characteristics showed a significant association. These were female gender (OR 1.94, 95% CI 1.26; 2.97), age (continuous in years, OR 1.05, 95% CI 1.03; 1.07), duration of complaints > 1 year (OR 1.87, 95% CI 1.07; 3.26), feeling of giving way (OR 1.58, 95% CI 1.04; 2.41), SF-36 physical functioning score (OR 0.99, 95% CI 0.98; 1.00), SF-36 total score (OR 0.98, 95% CI 0.96; 1.00), history of nontraumatic knee complaints in the past (OR 1.98, 95% CI 1.17; 3.34), history of traumatic knee complaints in the past (OR 1.55, 95% CI 1.00; 2.39), bother at work (OR 0.47, 95% CI 0.29; 0.78), swollen knee at physical examination (OR 1.67, 95% CI 1.08; 2.58), pain on passive flexion of the knee (OR 1.63, 95% CI 1.07; 2.49), pain on active flexion of the knee (OR 1.64, 95% CI 1.07; 2.50), crepitus of active flexion of the knee (OR 1.54, 95% CI 1.01; 2.34), bony swelling of the joint (OR 1.93, 95% CI 1.04; 3.58), pain on internal rotation of the hip (OR 2.20, 95% CI 1.31; 3.71), and a restriction of internal rotation of the hip (OR 1.68, 95% CI 1.02; 2.77).

Besides these, 6 characteristics had a p-value < 0.20. These were a self-reported warm knee, self-reported presence of a locked knee, WOMAC physical functioning score, WOMAC stiffness score, a warm knee at physical examination, and crepitus of active extension of the knee.

Multivariate analysis baseline referral to physiotherapist, orthopedic surgeon, or X-ray (Table 4)

Referral to physiotherapist

Of the variables analyzed, 3 remained in the multivariate model. These were female gender, younger age (continuous variable), and crepitus of active extension of the knee (AUC 0.61).

Table 4: Multivariate analyses of referral to physiotherapist or orthopedic surgeon, or for X-ray

Model	OR (95% CI)
Referral to physiotherapist (AUC 0.61)	
Female gender	1.87 (1.25; 2.79)
Age (continuous variable)	0.97 (0.96; 0.99)
Crepitus on active extension	1.54 (1.03; 2.31)
Referral to orthopedic surgeon (AUC 0.67)	
No paid employment	3.58 (0.94; 13.5)
Feeling of giving way	2.68 (1.25; 5.72)
Pain on passive flexion knee	2.22 (1.03; 4.75)
Referral for X-ray (AUC 0.69)	
Female gender	1.68 (0.96; 2.94)
Age (continuous variable)	1.05 (1.03; 1.08)
Bony swelling of the joint	2.20 (1.02; 4.78)

Referral to orthopedic surgeon

Also in this model, 3 of the variables analyzed remained in the multivariate model, i.e. no paid employment, feeling of giving way, and pain on passive flexion of the knee (AUC 0.67). Adjustment for age and gender did not change the associations found.

Referral for X-ray

Of the variables analyzed, 3 remained in the multivariate model. These were female gender, age (continuous variable), and a bony swelling of the joint (AUC 0.69).

DISCUSSION

The present study assessed initial medical treatment by the GP, and medical consumption of patients with nontraumatic knee complaints during 1-year follow-up. At baseline, 193 (35.2%) patients were advised to avoid heavy loading of the knee and 150 (27.3%) received a prescription for medication. Of all patients, 311 (56.6%) were referred to a physiotherapist (140, 25.4%), an orthopedic surgeon (59, 10.7%), or for X-ray of the knee (112, 20.4%).

During 1-year follow-up, 182 (37.9%) patients revisited their GP, 180 (37.5) visited a physiotherapist, and 114 (23.8%) visited an orthopedic surgeon.

Factors related to a referral to a physiotherapist were female gender, younger age (continuous variable), and crepitus of active extension of the knee. Referral to an orthopedic surgeon was associated with no paid employment, feeling of giving way, and pain

of passive flexion of the knee. Associated with a referral for X-ray of the knee were female gender, higher age (continuous variable), and a bony swelling of the joint.

Concerning the initial treatment by GPs, our findings show that this treatment was only partly in accordance with the Dutch College of General Practitioners Guideline for nontraumatic knee complaints in adults [4].

In the revised guideline, there are no crucial differences with respect to the initial guideline. One exception is that physical activities (e.g., walking, cycling) are strongly recommended; in addition, in case of inactivity a referral to a physiotherapist is advised.

With regard to X-ray of the knee, the guideline indicates that an X-ray has less additive value for the diagnosis because the absence of a visible abnormality on X-ray cannot exclude the presence of a disease [4, 6-10]. It is noteworthy that a bony swelling of the joint is predictive for a referral for X-ray, whilst a bony swelling of the joint indicates OA of the knee [4, 23, 26, 27]. A possible explanation for this could be that the patient asked for an X-ray, or that the GP still had doubts about the diagnosis.

Concerning a referral to an orthopedic surgeon, the guideline recommends a referral in case of a relapsing bursitis prepatellaris, a persisting Baker's cyst, or severe knee OA in which conservative treatment (analgetics, physiotherapy) has insufficient effect. However, in our study, severity of knee complaints was not directly associated with referral to an orthopedic surgeon whilst the absence of paid employment, feeling of giving way, and pain of passive flexion of the knee were associated. Feeling of giving way and pain of passive flexion could emerge from the degree of severity. In the present study, because no information is available about the effect of conservative treatment on the complaints, we cannot explore this aspect.

Suprisingly, the absence of paid employment is associated with a referral to an orthopedic surgeon. We expected to find the opposite, because people who work generally need a quick recovery to reduce work absence and may more often ask for an early referral [28, 29].

With regard to the prescription of analgetics, the guideline's advice regarding prescription of medication (acetominophen, NSAIDs) is only partly in accordance with the WHO pain relief ladder [4, 30].

In the present study, more than 25% of the population received a prescription for analgetics, especially NSAIDs. The reason for the high percentage of NSAIDS compared to the low prescription of acetaminophen could be that, during the study period, only acetaminophen was also sold over-the-counter and therefore patients might already have used acetaminophen before consulting their GP. However, we have no information on which medication was used before visiting the GP for the knee complaints. Nevertheless, it seems there is an overconsumption of NSAIDs compared with acetaminophen. At present, also NSAIDs (in a low dosage) are sold over-the-counter.

During 1-year follow-up we saw a relatively high amount of medical consumption; almost half of our population re-visited their GP or a physiotherapist and almost a quarter visited an orthopedic surgeon. We expected this to be the case due to a high percentage of OA patients. Knowing that older people more often suffer from osteoarthritis than younger people, we re-analysed the medical consumption in people younger than 60 versus people older than 60. We saw, however similar consumption in both groups. The same was true for the group of patients that fulfilled the clinical ACR criteria for knee OA [31] versus those who did not. The only difference we found between people fulfilling the clinical ACR criteria and those who did not was the advice 'to lose weight' and the referral for X-ray during initial management by the GP.

Patients with a history of (non)traumatic knee complaints more often visited a physiotherapist. Their former experience and the effect of physiotherapy could have influenced the decision for referral to a physiotherapist; however, we have no information about (para)medical treatment in the past. Also, a recurrent visit to the GP could influence the decision to consult a physiotherapist.

Patients who received pain medication at baseline more often visited their GP during follow-up. Reasons for this could be that the analgetics were insufficient, or that the GP asked the patients to return to evaluate the effect of the analgetics.

Our findings with regard to baseline treatment correspond reasonably well with the report of Glazier et al. [32] who investigated primary care physicians' management of 3 common musculoskeletal problems, including knee OA. In their study, the initial treatment of the GPs was compared with the opinion of a multidisciplinary expert panel; they found that primary care physicians' management of 3 common musculoskeletal problems was largely in accordance with the recommendations by the panel [32].

In Italy, treatment of OA of the knee in general and specialty practice was compared to proposed treatment guidelines for OA (ACR 2000; EULAR 2000; APS 2002) [33]. It was found that the published guidelines were properly applied by most physicians in terms of the pharmacological approach. However, it is difficult to compare those results with ours because of the heterogeneity of the practices (primary and secondary care), absence of a primary care guideline, and their focus on OA of several joints (besides the knee, also hip and hands) as opposed to nontraumatic knee complaints in adults in our study.

Compared to a nationwide registration study [34], our population did not differ substantially from patients with knee complaints in other Dutch general practices [11]. Therefore, we assume that our population is representative for a primary care population and that no bias is likely due to selective recruitment.

A limitation of our study is that we investigated initial treatment and medical consumption during follow-up assessed by the self-reported questionnaires of the patients. We did not obtain information directly from the GP. Another limitation is that we have no information about the diagnosis of the GP. Especially when comparing the initial

management with the recommendations of the Dutch College of General Practitioners Guideline for nontraumatic knee complaints in adults, this information would have been of additional value.

Another limitation of our study is that we analyzed many variables, which increases the possibility of chance findings. This could explain the moderate AUC found for the multivariate models. Therefore, the models need to be further validated (internally and externally), which emphasizes the need to investigate medical treatment and medical consumption also based on additional primary care populations.

In conclusion, the present study describes medical management at baseline, factors associated with a referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee, and the medical consumption during 1-year follow-up. The medical treatment at baseline partly corresponds with the guidelines Dutch College of General Practitioners for nontraumatic knee complaints in adults; moreover, during the 1-year follow-up, the medical consumption is relatively high.

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Chapter 7

Dutch College of General Practitioners (NHG) Practice Guideline – Nontraumatic Knee Problems In Adults (first revision)

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INTRODUCTION

The NHG practice guidelines on nontraumatic knee problems in adults provide recommendations on the diagnosis and treatment of knee problems that are not the result of trauma. Together with two other sets of practice guidelines, this document is the third in a series on knee problems in general practice (see Table 1). Knee problems at an early age are dealt with by the NHG practice guideline 'Nontraumatic Knee Problems in Children and Adolescents', and knee problems as the result of trauma are dealt with in the NHG Practice Guideline on Traumatic Knee Problems [1, 2]. There is some overlap between these three sets of guidelines. Some conditions of the knee are seen in both young people and adults: this is particularly true of disorders of the meniscus which are not always caused by trauma but can occur spontaneously. These guidelines will deal with the following conditions: prepatellar bursitis, iliotibial band syndrome, Baker's cyst and osteoarthritis. Arthritis of the knee caused by gout, reactive arthritis and rheumatoid arthritis will not be discussed [3, 4], neither will knee complaints resulting from referred pain or those caused by a disorder of the hip such as osteoarthritis. The plica syndrome, the clinical significance of which is controversial, will not be discussed here [5, 6].

Table 1 Three-part NHG practice guidelines on the knee

NHG Practice Guideline – Nontraumatic Knee Problems in Adults
- prepatellar bursitis
- iliotibial band syndrome
- Baker's cyst
- osteoarthritis
NHG Practice Guideline – Nontraumatic Knee Problems in Children and Adolescents
- genua vara, genua valga
- Osgood-Schlatter disease
- jumpers' knee
- patellofemoral pain syndrome
NHG Practice Guideline Traumatic Knee Problems
- contusion, distortion
- collateral ligament injury
- cruciate ligament injury
- meniscus injury
- patellar dislocation

BACKGROUND

Definitions

Prepatellar bursitis: acute or chronic inflammation of the prepatellar bursa, characterized by a fluctuating and sometimes painful swelling over the patella.
Iliotibial band syndrome: an overuse injury of the distal part of the iliotibial tract which runs from the iliac crest to the lateral condyl of the tibia. It is characterized by pain at the level of the lateral femoral condyl which occurs on exercise and disappears at rest.
Baker's cyst: a usually non-painful, fluctuating swelling located at the back of the knee.
Osteoarthritis: osteoarthritis of the knee joint, characterized by pain both at the beginning of a movement ('start-up' pain) and on weightbearing, which may cause limitations of daily activity. Following a period of inactivity or a night's sleep, there is usually a short period of stiffness. Exacerbations of pain (also known as 'flares') often occur and may be accompanied by increased stiffness, warmth and hydrops. In osteoarthritis one or more compartments may be affected (patellofemoral and medial or lateral tibiofemoral). Osteoarthritis is primarily a clinical diagnosis.

Epidemiology

After neck and back problems, knee problems are the most commonly seen musculoskeletal problems in general practice. The incidence of all types of knee problem (both traumatic and nontraumatic) is 13.7 and the prevalence is 19.0 per 1000 people per year, equally distributed over both sexes [7].

It is estimated that 15% of adult patients who consult a general practitioner with nontraumatic knee problems have prepatellar bursitis, 15% have iliotibial ligament syndrome and 3% have a Baker's cyst [8, 9].

The incidence of osteoarthritis in general practice is 1.9 and the prevalence is 5.6 per 1000 people per year. After middle-age these figures rise steeply, particularly in women in whom osteoarthritis is the most frequently-occurring chronic joint disorder [7, 10, 11].

Etiology and natural history

Prepatellar bursitis often results from repeated impacts or from an occupation that requires excessive kneeling (e.g. carpet layer, upholsterer) or from sporting activities (judo, wrestling) [12-14]. It has an acute form and a chronic form. The acute form is characterized by inflammation that is usually aseptic. The chronic form involves swelling that can last for a number of weeks or recurs frequently. If the aggravating factor is removed, then the prognosis is usually good.

The *iliotibial band syndrome* is caused by recurrent friction between the iliotibial tract and the lateral femoral condyl [15, 16]. The iliotibial tract moves forwards over the condyl when the knee is stretched and backwards when the knee is bent. Friction becomes painful at the point when the knee is bent to just slightly below 30°. This condition occurs mainly in distance sports such as long-distance running and cycling. After modification of the loading activity and the correction of the statics that led to the syndrome, the prognosis in this condition is usually favorable.

A *Baker's cyst* probably comes about when the bursa at the back of the knee becomes filled with synovial fluid as a result of the overproduction of synovial fluid (hydrops). A valvular mechanism prevents the fluid from flowing back into the joint. Overproduction can be caused by a symptomatic or asymptomatic intra-articular abnormality such as osteoarthritis, rheumatoid arthritis or a meniscus lesion [17, 18]. If the underlying cause of the overproduction of synovial fluid is not removed, this condition will continue to be present in varying degrees of severity.

Osteoarthritis is the result of the interplay of several factors [19]. Both systemic factors (such as hereditary susceptibility [20], nutrition [21-23], and bone density [24-26] and local biomechanical factors (such as muscle weakness [27], overweight [28], work-related weight-bearing [29-32] and knee trauma [33-37]) influence the extent of osteoarthritis to some degree.

Osteoarthritis occurs more frequently in women, particularly postmenopausal women, than in men. However, the protective effect of estrogens in the development of this condition has not been proven [38-43].

The main change found in osteoarthritis is a reduction in thickness and quality of the cartilage. In reaction to this, the underlying subchondral bone becomes thickened and osteophytes form along the edges of the joint. The synovial tissue also becomes chronically inflamed. These processes result in an irregular joint surface, a bony swelling of the joint, possible thickening of the joint capsule and sometimes in the accumulation of synovial fluid (hydrops). Clinical manifestations are pain [44-46], limitation of movement and, over the course of time, loss of function. Osteoarthritis may occur throughout the entire knee or may be limited to the patellofemoral compartment or the medial or lateral tibiofemoral compartments. This situation can lead to genu varum or genu valgum depending on the compartment. Pre-existing varus of valgus deformity may contribute to the development or deterioration of the osteoarthritis. Osteoarthritis follows an intermittently progressive course. The severity of pain and of abnormalities seen on radiographic investigation is not related to the radiological progression of osteoarthritis [47]. Temporary exacerbations characterized by an increase in symptoms may occur regularly.

DIAGNOSTIC GUIDELINES

The patient usually complains of pain in or around the knee. The general practitioner should always bear in mind that the symptoms may be an expression of a condition of the hip, and that symptoms in the thigh or the hip may also indicate a knee condition [48]. If examination of the knee does not result in an adequate explanation of the patient's symptoms, the hip should also be examined. If there are alarm symptoms (such as fever) or if disease progression is abnormal, the general practitioner may depart from the diagnostic pathway laid down here [14].

History taking

The general practitioner should concentrate on:
- pain: location, duration and course;
- swelling;
- locking symptoms: 'locked knee' or no longer being able to straighten the knee (consistent with an intra-articular condition);
- morning stiffness and start-up pain (consistent with an intra-articular condition);
- circumstances under which symptoms worsen or decrease (rest, exercise, climbing stairs, playing sports);
- relationship with professional or other job-related activities;
- functional limitations and hindrances in daily life;
- knee complaints or previous knee trauma.

Physical examination

The GP asks the patient to uncover both legs; look for left-right differences and carry out the following examination:
- inspection (ventral):
  - o positional abnormalities: varus or valgus;
  - o atrophy of the quadriceps muscles;
  - o swelling: local or diffuse, ventral or dorsal;
  - o widening of the joint;
- inspection, palpation and range of movement examination (patient in supine position):
  - o local swelling: redness, fluctuation, pain;
  - o ballottement of the patella [14];
  - o redness and temperature of the knee;
  - o pain on pressure over the joint space;
  - o crepitation during range of movement examination;

- o active and passive flexion and extension: limited, painful;
- o hip rotation: limited endorotation (consistent with osteoarthritis).

Tests to reveal a meniscus injury are not advised due to the difficulty of carrying them out and also as they are of limited use to the general practitioner in making the correct diagnosis [49, 50].

Further investigations

If, after history taking and physical examination, there is still some doubt about the diagnosis, referral for radiographic investigation may be indicated. Radiographic investigations are of little use in general practice, as the absence of visible abnormalities does not exclude a condition such as osteoarthritis. Osteoarthritis is primarily a clinical diagnosis and radiological investigations are not useful in establishing the degree of osteoarthritis. This is due to the absence of a clear connection between the severity of symptoms and limitations and the extent of radiological abnormalities [16, 51-53]. This is also true of MRI investigation in osteoarthritis [54, 55]. Suspicion of a meniscus injury is the only indication for MRI investigation.

Evaluation

The GP should try to differentiate between an intra-articular and an extra-articular disorder.
The presence of hydrops, locking symptoms, crepitations and limitations in active and passive movement are indicative of an *intra-articular disorder*. Besides potential arthritis, diagnoses that can be made are:
- *meniscus injury*: recurrent hydrops with or without locking symptoms (see the NHG Guidelines on Traumatic Knee Problems);
- *osteoarthritis*: advancing age, short-lasting starting up and morning stiffness (< 30 minutes), bony widening of the joint, varus or valgus position, crepitation on range of movement investigation [56].

The absence of hydrops and locked knee are indicative of an *extra-articular disorder*, although they do not necessarily exclude an intra-articular disorder. Diagnoses that can be made are:
- *prepatellar bursitis*: fluctuating localized prepatellar swelling, sometimes red or painful;
- *iliotibial band syndrome*: pain at the level of the lateral femoral condyl during sporting activities;
- *Baker's cyst*: fluctuating swelling located at the back of the knee.

TREATMENT GUIDELINES

Information and advice

In *prepatellar bursitis* the patient should be advised to avoid pressure and friction (i.e. bending and stretching the knee) for a few days. If, due to sporting or professional activities, there are recurrences then the wearing of knee-protectors is advised.

In *iliotibial band syndrome*, the GP should advise a reduction in the sports activities that led to the complaints. If so desired, the patient can temporarily take up a different sport that exerts less pressure on their knees. The GP may also advise exercises to stretch the iliotibial tract [57]. These may be carried out independently or under the supervision of a physical therapist [58, 59], although research into the effectiveness of this has not been carried out. Once the symptoms have lessened or disappeared, the intensity of the sports activities can be gradually increased.

A *Baker's cyst* does not usually require any treatment. Its management depends on the underlying intra-articular condition and its accompanying symptoms. A Baker's cyst occasionally bursts and extensive leakage into the calf results in a clinical presentation of pseudothrombosis in the leg.

The general practitioner should be active in the management of patients with *osteoarthritis*. Interventions that have been advised should be specifically evaluated to see if they have had the desired effect, and, if necessary, other measures should be taken. By means of guidance, recommendations on physical exercise and the prescription of analgesics, it is possible for general practitioners themselves to care for the majority of patients with osteoarthritis. Explain that the course of the disease is changeable and that bad periods will be interspersed with good ones with fewer symptoms. There are indications that if overweight patients lose weight this will reduce their functional limitations. Help from a dietician is effective in achieving this [60-65]. Recommend regular and sufficiently intensive physical exercise, the form of which is dependent on the patient's preference (e.g. at least 30 minutes intensive exercise each day) [66]. It is to be expected that this will lead to an improvement in general functioning and a reduction in pain. Emphasize that if these activities are discontinued their positive effects may well disappear.

For more information on guidance, general practitioners can use the NHG patient letter which can be found on http://www.nhg.org.

Non-medicinal treatment

Refer patients with *osteoarthritis*, particularly those who are sedentary, to a physical therapist for exercise therapy. Exercise therapy includes exercises that are aimed at the

improvement of functions (such as muscle strength and range of motion), exercises and recommendations aimed at increasing activity levels (such as walking), and programs that promote an active lifestyle and integrate exercises into daily life [67-69]. If exercise therapy and medication do not provide enough relief, then transcutaneous electrical nerve stimulation (TENS) may be used [69, 70]. Ultrasound treatment has not proved to be effective in osteoarthritis [71]. Several studies have shown that acupuncture has equally little clinically-relevant effect [72, 73]. Cooling the knee and massages with ice do not relieve the patient's symptoms [74]. There are indications that a hard brace, an elastic brace and orthopedic insoles may relieve pain and improve function in osteoarthritis, but there is insufficient evidence to recommend these methods [75-79]. The beneficial effects on the symptoms and on disease progression of using a walking stick have equally little support, but, due to the simplicity of the measure, the use of a stick (on the 'good side') can be tried out. Special shoes are not recommended as their value has not been demonstrated.

Medicinal treatment

If in *prepatellar bursitis* there is increasing local redness and also general symptoms such as fever and malaise, the GP should consider the possibility of bacterial infection. In this event prescribe flucloxacillin 500 mg 4/D for 7 days [80, 81]. If the prepatellar bursa is inflamed but there is no bacterial infection and it is causing cosmetic or functional problems, its contents may be aspirated. It is possible that the bursitis will resolve more quickly, if, after intrabursal aspiration a corticosteroid is injected, (for example 20-40 mg methylprednisolone with or without a few ml local anesthetic) than if aspiration only is carried out [82]. Oral NSAIDs are of no additional value in this case [82].

For the relief of pain in *iliotibial band syndrome*, paracetamol is advised (see Farmacotherapeutische Richtlijn Pijnbestrijding, www.nhg.org). NSAIDs have not been shown to be of any extra benefit in this condition [83]. An injection of local anesthetic and a corticosteroid (e.g. 20-40 mg methylprednisolone) at the site of the pain may reduce the pain in the short-term [84]. The patient is advised to rest the knee for a few days directly after the injection in order to avoid overloading the knee. The results in the longer term are unknown.

In *osteoarthritis*, as well as more the general recommendations, an analgesic should also be advised. If required, recommend paracetamol for a period of two weeks. Due to its broad safety profile, paracetamol should be the drug of first choice [85-87]. As second choice, or if paracetamol does not give the required result, ibuprofen, diclophenac or naproxen should be given. If necessary, this treatment can be extended by one to two weeks. When choosing from this group of NSAIDs, any comorbidities (such as cardiovascular or gastrointestinal conditions), side effects and interactions (acetylsalicylic

acid), and any history of reactions to NSAIDs, should be taken into account. Due to their potential adverse effects, great caution is advised in prescribing NSAIDs to patients over the age of 70, patients with impaired renal function, hypertension, heart failure or atherosclerotic cardiovascular disease, as well as those who are taking anticoagulants. For more information and the circumstances in which gastric protective measures are advised, see Farmacotherapeutische Richtlijn Pijnbestrijding (www.nhg.org). Current scientific research in this field does not allow further discussion on the influence of NSAIDs on the progression of osteoarthritis for the time being [88-90].

As it has not yet been proven that NSAIDs are effective in osteoarthritis in the long-term, an 'on-demand' regime is advised: after a period of a maximum of a few weeks, in the event of worsening of symptoms NSAIDs should only be taken temporarily, at fixed times and only for a pre-arranged period [91-95]. Topical NSAIDs applied to the skin in the form of a cream or a gel, have fewer gastro-intestinal side effects but are probably only effective for a short time [96, 97].

The addition of an opiod, such as tramadol, gives extra pain relief and is a way of reducing the dosage of the NSAID whilst maintaining adequate pain relief [98-103]. However, due to their side effects (particularly nausea and dizziness), opioids should be introduced gradually so that their analgesic effect builds up slowly. The frequently-occurring side effects of opioids, as well as dependency and withdrawal symptoms impose limits on their long-term use. Long-term use of medication should be avoided. In addition, in the event of a flare, or if general measures and analgesics do not give sufficient pain relief, an intra-articular injection of a corticosteroid, e.g. triamcinolone or methylprednisolone, should be considered [104, 105]. Give 20 to 40 mg each time at intervals of 1 to 3 months. The effect on the pain can last for 1 to 4 weeks and is probably greater if the joint is rested temporarily. Intra-articular injections of hyaluronic acid may give some short-term reduction of the pain as well as some functional improvement. As their long-term effects have not be adequately investigated, as they need to be given several times at intervals of a few weeks, and as they are expensive, these injections are not advised for use in general practice [91, 104, 106-112]. The therapeutic effect of chondroitin and glucosamine in patients with osteoarthritis has not be adequately demonstrated [91, 113-117]. For this reason, the use of these products is not advised.

Follow-up and referral

The GP should actively manage patients with osteoarthritis and regularly evaluate the effects that recommendations are having. In the other conditions under discussion, regular follow up is not necessary. Tell the patient to come back only if the condition continues or symptoms return.

If *prepatellar bursitis* persists or recurs frequently, the patient may need to be referred to an orthopedic or general surgeon for removal of the bursa.

If a *Baker's cyst* continues to be problematic, referral to an orthopedic surgeon for further investigations into the underlying cause, or removal of the bursa, is indicated.

In cases of persisting *iliotibial band syndrome*, referral to a sports physician or sports physical therapist may be necessary.

Patients with *osteoarthritis* who, despite conservative therapy, continue to suffer severe symptoms and hindrances in their everyday functioning, or in whom hydrops persists, should be referred to an orthopedic surgeon. If hydrops persists and/or is a major problem, then referral to a rheumatologist may also be considered.

Secondary care is able to offer more in the way of conservative management (for example, in positional deformities a brace may be considered) [75-79]. In addition, surgical intervention may be considered in patients who have a reasonably good general condition and are motivated to undergo an operation and the subsequent period of rehabilitation [118-123].

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Chapter 8

General Discussion

NONTRAUMATIC KNEE COMPLAINTS IN GENERAL PRACTICE

In general practice, knee complaints (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (19/1000 patients per year), mostly presented as knee pain or functional loss of the knee joint [1, 2]. Of these complaints, approximately 20% are traumatic [2].

In spite of the high prevalence of knee complaints few studies have assessed the signs, symptoms and prognosis of nontraumatic knee complaints. Especially in general practice these data are scarcely available [3-5].

The aim of this thesis was to provide more knowledge about the course and prognosis of nontraumatic knee complaints in adults in general practice.

In this chapter, we summarize and discuss the most important results found, reflect on the implications for general practice, and provide recommendations for future research.

ADDITIVE VALUE OF THIS STUDY

The prospective HONEUR knee cohort is a unique and representative study for adult patients seen in general practice with nontraumatic knee complaints.

Van der Waal et al. investigated the determinants of the clinical course of musculoskeletal complaints in general practice [5]. In their cohort study, patients consulting their general practitioner (GP) with a new episode of a musculoskeletal complaint were included and followed for 18 months. However, in contrast to our study, they did not include physical examination and therefore could not study the determinants of physical examination on persisting knee complaints. To our knowledge, no previous studies have investigated predictors of physical examination on the prognosis of knee complaints in a general practice population.

Similar to our investigation, Peat et al. performed a prospective cohort study of knee pain and knee osteoarthritis (OA) in the general population aged 50 years and over [4]. In their study, however, patients were recruited by postal surveys addressing knee pain and had not necessarily consulted the GP for their complaints. This is a major difference compared with our study, which included patients visiting their GP with incident nontraumatic knee pain.

Wesseling et al. performed a prospective 10-year follow-up study initiated by the Dutch Arthritis Association (DAA) on participants with early OA-related complaints of hip and/or knee [6]. In their cohort, GPs were asked to refer eligible persons consulting with hip or knee complaints to the study; participants were also recruited at secondary

care clinics and via advertisements and articles in the local newspapers and on the DAA website [6]. Until now, no follow-up results of this cohort study have been published.

Most studies investigating knee symptoms are carried out in a hospital setting and only cover serious or persisting knee complaints. In this thesis, we show substantial differences between primary and secondary care populations for baseline characteristics as well as for the different knee function scores (Chapter 2). This emphasizes the need for primary care studies in patients with knee complaints.

Compared to a nationwide registration study [7] our population did not differ substantially from patients with knee complaints in other Dutch general practices regarding age, gender, and International Classification of Primary Care (ICPC) code of knee complaints [8]. Therefore we assume that our population is representative for a primary care population and do not expect bias due to selective recruitment.

Based on the above arguments, we believe that our findings provide new and relevant knowledge about nontraumatic knee complaints in adults in general practice.

MEASUREMENT INSTRUMENTS AND CLINICAL OUTCOME

In our studies we used several measurement instruments to assess knee pain and knee function, including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [9, 10], the Medical Outcomes Study Short Form-36 (SF-36) [11, 12], and the Knee Society Score (KSS) [13]. The WOMAC and SF-36 are self-report questionnaires whereas the KSS is a clinical rating scale. In a subgroup of our study we also applied the DynaPort® Knee Test (DPKT); this is a performance-based test to assess knee function.

In this thesis, we could not demonstrate the cross-sectional and longitudinal validity of the DPKT in primary care patients, whereas this test proved to be a useful performance-based instrument for use in secondary care, showing good reliability and validity [14, 15] (Chapter 2).

In primary care, due to less severe complaints than in secondary care, scores of measurement instruments and performance-based tests can be difficult to interpret, and there is a need to define which scores or changes in scores are important [16, 17]. In this thesis, substantial differences were found between a primary and secondary care population for baseline characteristics as well as for the different knee function scores, which had a strong influence on the construct validity and internal consistency of the DPKT in a primary compared to a secondary care population (Chapter 2).

For younger and/or more active patients with knee injury and knee OA, the Knee injury and Osteoarthritis Outcome Score (KOOS), an extension of the WOMAC, was developed [18]. The KOOS showed good reliability, content and construct validity, and

responsiveness [19]. However, this instrument was evaluated in an out-patient setting only and has not been evaluated for all types of knee problems [19].

With regard to other performance-based tests (e.g., walking tests, stair-climb tests) to assess knee function, a systematic review by Terwee et al. concluded that more and well-designed studies are needed to assess the measurement properties of performance-based methods in patients with knee or hip OA [20]. Many performance-based tests, especially the walking tests, represented minor variations on the same theme. However, no information could be given as to which of these tests might be the most useful; this was due to insufficient justification given for the choice of the activities included in the test, and for the functional items that were measured [20].

In this thesis, we used 'soft' outcome measures (self-reported recovery, increase of disability) which could be more susceptible for bias (Chapters 4 and 5). The reasons for this choice were the absence of X-rays, and the lack of validated outcome measures for use in primary care. However, an advantage of using these outcome measures is that they better resemble the use in clinical practice; especially because X-ray of the knee is not recommended in primary care because of the limited value for the diagnosis. Moreover, X-ray findings would change very little during a 1-year follow-up period (Chapter 7).

For the outcome of prognostic factors of knee complaints (Chapter 4), we used the patient's self-reported recovery or persisting knee complaints at 1-year follow-up compared with those at baseline (thentest). Although self-reports may be susceptible to recall bias [21], it is reported that recall bias does not invalidate thentest results [22]. Many studies use the difference between WOMAC score at baseline and at follow-up to assess recovery or worsening. However, doubts have been expressed about the content validity of the WOMAC score, because in patients with knee OA self-reported physical functioning as assessed by the WOMAC questionnaire was influenced more by pain than performance-based physical functioning [23]. As a result, due to the fluctuating course of knee symptoms in patients with knee OA, the WOMAC score might also fluctuate.

Moreover, a follow-up period of 1 year might be too short to measure a difference in knee function or progression of complaints. In addition to validity and reliability, for an evaluative instrument designed to measure longitudinal changes over time, sufficient 'responsiveness' or 'sensitivity to change' is a third requirement [17]. In most studies evaluating the responsiveness of a measurement instrument, the ability to detect clinically important differences is based on a comparison with a gold standard, such as global perceived effect [24-27]. However, the use of such external criteria as absolute measures of change may be debatable because the stability of the resulting estimates of instrument responsiveness has been questioned [28]. Especially for knee complaints or knee OA, no information is available about which period of follow-up is needed to assess a clinically important difference.

Further, in this thesis we chose to dichotomize most of the variables (Chapters 2, 4, 5). The rationale for this is that, in clinical practice, the findings are easier to interpret. However, the consequences of dichotomizing include a reduction in statistical power, loss of information, and an increased probability of a type II error [29, 30].

With respect to physical examination, it was performed by a trained physiotherapist according to a standardized test protocol. However, irrespective of the training and standard test protocol, inter-observer bias might still occur. In clinical practice, however, due to lack of standardization of the examination of the knee, physical examination may be even less predictive due to more 'noise' than in the present study.

In conclusion, the above points emphasize the need to validate (internal and external, cross-sectional and longitudinal) measurement instruments and performance-based tests for use in a primary care setting.

CLASSIFICATION CRITERIA

For the diagnosis 'OA of the knee' several classification tools are used, including the clinical American College of Rheumatology (ACR) classification criteria of knee OA. To standardize the clinical definition of OA, the ACR developed classification criteria with the specific aim to create standardized definitions for inclusion in trials and cohort studies [31], but not for diagnosing the individual patient. For knee OA, Altman et al. developed these criteria to classify clinical OA, clinical and radiographic OA, and clinical and laboratory OA [32].

In this thesis, we assessed the prognostic value of the clinical ACR criteria for knee OA and also described the distribution in a primary care population with new nontraumatic knee complaints (Chapter 5). We found that about 60% of these patients fulfilled the clinical ACR criteria, while a study in a general population found that only 30% of the patients fulfilled these criteria [33].

With regard to the clinical ACR criteria of knee OA, doubts have been expressed about the validity of these criteria in primary care or in the general population [33, 34]. This is because the clinical criteria sets (with or without laboratory criteria) did not provide results consistent with the other sets of the ACR criteria [34]. Also, much of what might be classified as symptomatic radiographic knee OA in the general population and primary care did not fulfill the ACR clinical criteria [33]. Further, also for hip OA, there was poor agreement between the set of clinical criteria and the sets in which radiological signs were included [35].

Most classification tools are mainly developed and validated in a secondary care population. However, as stated before, there is a major difference between a primary and secondary care setting (Chapter 2). Especially due to less severe complaints and bet-

ter knee function, primary care patients (as well as control persons] differ substantially from a secondary care population, which might lead to less pronounced findings.

Because of this, a classification tool for primary care needs to have a larger distinguishing power in order to discriminate between small differences in the population.

In our study, we also found that patients fulfilling the clinical ACR criteria had more co-morbidity of the knee, such as a prepatellar bursitis, pain of the iliotibial tract, pain of the borders of the patella, and pain of the tuberositas tibiae (Chapter 5). This might indicate that, besides knee OA, other disorders might also contribute to the same knee complaints or co-occur with knee OA, making it more difficult to distinguish the specific signs and symptoms of knee OA.

Therefore, classification criteria also need to differentiate between disease-specific signs and symptoms; the above emphasizes the need to validate classification criteria for use in a primary care setting.

INCIDENT KNEE COMPLAINTS VERSUS PROGRESSION OF KNEE COMPLAINTS

In our systematic review, we assessed prognostic factors of progression of knee OA (Chapter 3). In this systematic review, all studies reported on a radiological outcome measure and only one study also reported on a clinical outcome measure. For both a clinical outcome and a radiological outcome, progression was defined as an increase in complaints (pain, physical limitation), increase in the Kellgren and Lawrence score, or in joint space narrowing.

However, it is debatable whether the division between incident and progressive disease is really clear, because OA has a variable course and pathologic changes of OA generally remain stable or worsen [36]. This could make it difficult to distinguish between incident and progressive disease.

Even with stable pathology, patients may experience symptomatic improvement and some individuals have OA changes on radiography without consequences for symptoms [36, 37]. Therefore, if a patient presents for the first time with knee complaints, the question remains: are these complaints due to incident knee OA or progressive knee OA? Much effort has been devoted to developing a standard definition of OA in which symptoms, disability, and joint structural diseases are summarized [37]. However, one of the difficulties for a standard definition is the poor correlation between symptomatic knee OA and radiological knee OA [38-41]. Bearing in mind that it is already difficult to develop a standard definition for knee OA, it is even more difficult to assess whether a patient has incident or progressive knee OA.

Besides, it is noteworthy that most risk factors for OA also turn out to be a prognostic factor [42-44]. This supports the difficulty to assess whether a patient presents with incident

or progressive disease. One solution might be to ignore the distinction between incident and progressive disease and consider all symptoms (e.g., pain, decrease of knee function) as progressive disease.

Further, with regard to the length of follow-up of a study, no information is available about which follow-up period is needed to assess the clinical progression of knee OA. For radiological progression, most studies wait at least two years to determine radiological progression, because the change during one year may be small and of doubtful clinical significance [45]. For clinical OA, however, it is more difficult to assess which period of follow-up would provide clinical significance; especially because periods of 'flares' alternate with periods of recovery (Chapter 7) making it difficult for the individual patient to distinguish between a temporary exacerbation and progression.

In conclusion, we have outlined the difficulties related to the definitions 'incident' and 'progressive' knee OA. This emphasizes the need for more insight into the pathogenesis and natural course of knee OA.

MEDICAL TREATMENT AND CONSUMPTION

In this thesis, we assessed medical treatment at baseline and medical consumption during follow-up; it was found that medical treatment at baseline partly corresponded with the advice given in the Dutch College of General Practitioners Guideline for non-traumatic knee problems in adults (Chapters 6 and 7).

With regard to the burden and costs made in health care, the medical treatment and consumption is of interest. Particularly the indications for medical treatment and the reasons for medical consumption would provide useful information. To study medical consumption, a prospective cohort study (like our HONEUR knee cohort) is an ideal study design, because observational cohort studies are the best for exploring the natural course of a disease [46].

In this thesis, we found a difference in treatment between patients with or without knee OA according to the clinical ACR criteria for the advice 'to lose weight' and a referral for X-ray of the knee. This is in accordance with the non-medical advice for knee OA provided in the Dutch College of General Practitioners Guideline for nontraumatic knee problems in adults (Chapter 7).

With respect to medical consumption, over the 1-year follow-up we found no difference for patients with baseline OA according to the clinical ACR criteria of knee OA, overweight persons, and duration of OA >1 year. Patients with a history of (non)traumatic knee problems more often visited a physiotherapist, while patients using analgesics more often visited their GP. Overall, medical consumption was relatively high during the 1-year follow-up (Chapter 6).

Medical consumption could be determined by several factors, including the physician's opinion and the patient's expectations of the received treatment. For the GP, recurrent visits by patients for the same complaints could result in a referral to a physiotherapist or orthopedic surgeon. Therefore, also these aspects of medical consumption should be taken in account when investigating causes of medical consumption.

In conclusion, this thesis provides information about medical treatment at baseline and medical consumption during follow-up; however, we could not assess the exact indications for medical treatment.

DUTCH COLLEGE OF GENERAL PRACTITIONERS GUIDELINE FOR NONTRAUMATIC KNEE PROBLEMS IN ADULTS

In this thesis, the revised Dutch College of General Practitioners guideline for nontraumatic knee problems in adults is presented (Chapter 7). This guideline is developed based on the available evidence in the literature, and advice for daily practice is provided. Various other studies have explored the etiologic factors and prevention of knee OA, the course of nontraumatic knee complaints, and the treatment of knee complaints, e.g. the CHECK cohort, the CAS-K study, and the BOKS study[4, 6, 47]. Therefore, if the Dutch guideline would be revised 5 years from now, more evidence-based information should be available on the natural course of knee complaints in primary care or in the general population, and more insight should be available into the prognostic factors of knee complaints for short and longer periods of follow-up. Also, more data should be available about the indications and effects of treatment, which might lead to improved evidence-based advice regarding the prevention of knee OA.

With regard to other recent guidelines, the Osteoarthritis Research Society International (OARSI) developed recommendations based on a critical appraisal of existing guidelines, a systematic review of research evidence, and the consensus opinions of an international, multidisciplinary group of experts[48, 49]; they reported 25 recommendations about general aspects of OA, non-pharmacological modalities of treatment, pharmacological modalities of treatment, and surgical modalities of treatment. The recommendations in the Dutch guideline with regard to the treatment of knee OA largely corresponds with those of the OARSI guideline, but are described in less detail. For example, improvement of the patient's clinical status by regular telephone contacts or the recommendation to provide advice for appropriate footwear, are not (or are only partly) mentioned in the Dutch guideline because of the limited evidence to date.

Based on evidence and expert opinion, the European League Against Rheumatism (EULAR) developed 10 recommendations for the management of knee OA[50]; these are similar to those of the Dutch guideline for nontraumatic knee complaints in adults. One

important difference is the more explicit advice of the EULAR to tailor treatment of knee OA according to knee risk factors (obesity, physical activity), general risk factors (age, comorbidity), level of pain and disability, sign of inflammation (e.g. effusion), and location and degree of structural damage.

The ACR recommendations for the medical management of hip or knee OA include advice on non-pharmacological modalities and drug therapy[51]; this guideline emphasizes that these recommendations are not fixed, rigid mandates, and also recognizes that the final decision concerning the therapeutic regimen for an individual patients rests with the treating physician.

Compared to the Dutch College of General Practitioners guideline for nontraumatic knee problems, there is no difference in advice with regard to the treatment of knee OA.

The National Institute for Health and Clinical Excellence (NICE) formulated a guide for the care and management of OA (of all joints) in adults based on systematic reviews of best available evidence[52]; the latter recommendations mainly correspond with those of the Dutch guideline.

In the Netherlands, a national interdisciplinary guideline for the diagnosis and treatment of hip and knee OA was developed (CBO guideline)[53]; this guideline for the diagnosis of knee OA mentions X-ray. This in contrast to the Dutch guideline for nontraumatic knee problems in adults, which states that radiographic investigations are of little use in general practice because the absence of visible abnormalities does not exclude a condition such as OA (Chapter 7). Another difference is that the CBO guideline recommends to prescribe glucosamines for 3 months on trial, whereas the Dutch guideline advises against this because the therapeutic effect of glucosamine in patients with OA is not yet adequately demonstrated (Chapter 7). The remaining recommendations in the CBO guideline largely correspond with those in the Dutch guideline for nontraumatic knee problems in adults.

In addition, recommendations by the Institute for Clinical Systems Improvement[54] and the American Academy of Orthopaedic Surgeons[55] mainly concur with the Dutch College of General Practitioners guideline for nontraumatic knee problems.

A characteristic of most guidelines is that they only focus on knee OA rather than on nontraumatic knee problems. This makes the Dutch guideline unique and offers the possibility for use in a broader patient population.

In conclusion, there is general agreement between the various (international) guidelines of knee problems, and those of the Dutch College of General Practitioners Guideline for nontraumatic knee problems in adults. Because it offers advice for knee problems (including knee OA) the Dutch guideline is unique and can therefore be used for a broader-based population.

IMPLICATIONS FOR DAILY PRACTICE AND RESEARCH

This thesis may have implications for the GP. Some of the findings presented in this thesis (the systematic review, patient characteristics of the HONEUR knee cohort) have already been incorporated in the revised version of the Dutch General Practitioners (NHG) Practice Guideline for nontraumatic knee problems in adults (Chapter 7).

Our systematic review provides currently available evidence and also identifies the lack of data with respect to prognostic factors of progression of knee OA (Chapter 3). For the GP, the conclusion from this review - that generalized OA and the level of hyaluronic acid seems to be associated with radiological progression of knee OA - could be useful because, in daily practice, the presence of generalized OA might have implications for management and prognosis. However, due to the costs of the laboratory test, GPs do not frequently assess hyaluronic acid in serum.

At present, besides our study on prognostic factors of knee problems (Chapter 4), other studies evaluating the course and prognosis of knee OA are being performed using clinical outcome measures. Therefore, in the future, our review will need to be updated to provide the latest available evidence of studies on prognostic factors of progression of knee OA or knee complaints using a radiological as well as a clinical outcome measure.

For a clinician, subgroups based on age or severity could be preferable with respect to patient information and indications for treatment. However, analysis of subgroups in cohorts could cause a decrease of statistical power due to smaller population sizes, making it more difficult to develop a useful model for clinical practice. Therefore, to improve statistical power and enable subgroup analysis, future cohort studies with a large study size are required.

The recommendations in the Dutch guideline for nontraumatic knee problems in adults (Chapter 7) mainly correspond with those in other guidelines. The strength of the Dutch guideline is its usefulness for a broad-based population, such as a primary care population. Because of the large number of ongoing studies exploring etiologic factors, the prevention of knee OA, the course of nontraumatic knee complaints, and the treatment of knee complaints, an update of the Dutch guideline is recommended after 5 years.

Further, a 1-year follow-up period might be too short to discriminate between knee OA and the other diagnoses in primary care; a more effective distinction might be provided after a longer period of follow-up (e.g., >5 years). A follow-up after 7 years is planned for the HONEUR knee cohort (in 2009) together with an X-ray investigation. It would be interesting to assess prognostic factors for worsening knee complaints, the prognostic value of the ACR criteria, and medical consumption after 7 years follow-up. Alternatively, diagnostic criteria could be formulated based on their predictive value for a radiologically confirmed OA with persistent symptoms.

Concerning measurement instruments and clinical classification criteria, this thesis underlines the need for validation in a primary care setting (Chapters 2 and 5). In future, additional measurement instruments and classification criteria for use in primary care should be developed which would provide uniform measures and outcomes in primary care research, which might result in more accurate risk estimates.

Finally, this thesis emphasizes the need for more research, not only among patients with knee OA, but also for patients with other types of knee complaints in primary care.

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Summary

In general practice, knee complaints (traumatic and nontraumatic) take second place after back pain in the prevalence of musculoskeletal disorders (19/1000 patients per year), mostly presented as knee pain or functional loss of the knee joint. Of these complaints, approximately 20% are traumatic.

In spite of the high prevalence of knee complaints few studies have assessed the signs, symptoms and prognosis of nontraumatic knee complaints. Especially in general practice these data are scarcely available.

The aim of this thesis was to provide more knowledge about the course and prognosis of nontraumatic knee complaints in adults in general practice.

In **Chapter 2** we determined the cross-sectional and longitudinal validity of a performance-based assessment of knee function, the DynaPort® Knee Test (DPKT), in first-time consulters with nontraumatic knee complaints in general practice (GP).

Patients consulting for nontraumatic knee complaints in GP aged > 18 years were enrolled in the study. At baseline and 6-months follow-up knee function was assessed by questionnaires and the DPKT; a physical examination was also performed at baseline. Hypothesis testing assessed the cross-sectional and longitudinal validity of the DPKT.

Eighty-seven patients were included for the DPKT, 86 were available for analysis. The studied population included 44 women (51.2%), the median age was 54 (range 18-81) years. At follow up, 77 patients (89.5%) were available for the DPKT. Only 3 out of 11 (27%) predetermined hypotheses concerning the cross-sectional and longitudinal validity were confirmed. Comparison of the general practice and secondary care population showed a major difference in baseline characteristics, DynaPort Knee Score, internal consistency, and hypotheses confirmation concerning the construct validity.

Therefore, we could not demonstrate the validity of the DPKT for first-time consulters with nontraumatic knee complaints in GP. Further, measurement instruments developed and validated in secondary care are therefore not automatically also valid in primary care setting.

In **Chapter 3** a systematic review to prognostic factors of knee osteoarthritis (OA) is presented. We searched Medline and Embase according to a specified search strategy (keywords for disease, location, and study design). Studies that fulfilled predefined criteria were assessed for methodological quality. Study characteristics and associations were extracted and the results were summarized according to a best evidence synthesis.

Of the 1,004 studies found, 37 met the inclusion criteria. Methodological quality was assessed and only high-quality studies were included (n = 36). The best evidence synthesis yielded strong evidence that hyaluronic acid serum levels and generalized OA are predictive for progression of knee OA. Sex, knee pain, radiologic severity, knee injury, quadriceps strength, and regular sport activities were not predictive. Conflicting

evidence for associations was found for several factors including body mass index and age. Limited evidence for an association with progression of knee OA was found for several factors, including the alignment (varus/valgus) of the joint. Limited evidence for no association with progression of OA was also found for several factors, including meniscectomy, several markers of bone or cartilage turnover, and the clinical diagnosis of localized OA.

Consequently, we concluded that generalized OA and serum levels of hyaluronic acid seem to be associated with the radiologic progression of knee OA. Knee pain, radiologic severity at baseline, sex, quadriceps strength, knee injury, and regular sport activities seem not to be related. For other factors, the evidence was limited or conflicting.

In **chapter 4 – 6**, we investigated a subgroup of the prospective HONEUR knee cohort. Adults age >35 years with nontraumatic knee symptoms were followed for one year. At baseline, data on knee symptoms and demographics were collected and a physical examination performed. Knee symptoms and medical consumption were assessed by self-report questionnaires at 3-month intervals. After one year the physical examination was repeated. In total, 549 patients were included of which 480 (87.4%) were available for follow-up. The studied population consisted of 236 (49.2%) women, mean age 53.6 (sd 11.3), mean BMI 27.1 (sd 4.2), and 288 (60.0%) patients had payed employment. After 1-year follow-up, 236 (49.2%) patients reported persisting knee complaints.

Chapter 4 describes the course, prognosis and prognostic factors for persistence of nontraumatic knee complaints in adults in GP.

Multivariate prognostic regression models of patient characteristics, symptom characteristics, and physical examination were used to predict persisting knee symptoms after 1 year. Areas under receiving operating characteristic curves (AUC) were used to determine the predictive value of the model. To assess the added predictive value of symptom characteristics and physical examination, these models were added to the model of patient characteristics. The improvement was expressed as the difference between the 2 AUCs.

In the multivariate prognostic model of patient characteristics, age >60 years, educational level, kinesophobia, and comorbidity of the skeletal system were associated with persistent knee symptoms after 1 year (AUC 0.67). Of the symptom characteristics, history of nontraumatic knee symptoms, bilateral symptoms, and duration of symptoms >3 months were associated (AUC 0.73). For determinants of physical examination, crepitus of passive extension was associated (AUC 0.55). The added value of the symptom characteristics model to the patient characteristics model was 0.09 (AUC 0.76). Physical examination added no further value.

We concluded that symptom characteristics are the strongest predictors of persisting knee symptoms at 1-year follow-up. Physical examination has no added value in predicting persistent knee symptoms in general practice.

In **chapter 5** we assessed the prognostic value of the clinical ACR classification criteria of knee OA on persisting knee complaints and increase of disability in adult patients with knee pain in GP after 1-year follow-up.

In this study, 292 (60.8%) patients fulfilled the ACR clinical criteria of knee OA. After one year follow-up, 236 (49.2%) patients reported persisting knee complaints, and 84 (17.5%) reported an increase of disability.

There was no association of fulfilling the ACR clinical criteria of knee OA at baseline with persisting knee complaints (OR 1.15; 95% CI 0.80, 1.67) or increase of disability (OR 1.05; 95% CI 0.43, 2.58) at follow-up.

Therefore, we concluded that the ACR clinical classification criteria of knee OA have no prognostic value for predicting persisting knee complaints or an increase of disability at one year of follow-up in adult patients with nontraumatic knee complaints in GP.

Chapter 6 describes the medical treatment of the general practitioner (GP) at baseline and medical consumption during 1-year follow-up in adult patients visiting the GP with nontraumatic knee complaints. In addition, factors associated with baseline referral to a physiotherapist or orthopedic surgeon, or for X-ray of the knee were determined.

At baseline, 193 (35.2%) patients were advised by the GP to avoid heavy loading of the knee, and 150 (27.3%) received a prescription for pain medication. Of all patients, 311 (56.6%) received a referral to either a physiotherapist or orthopedic surgeon, or for X-ray of the knee. During 1-year follow-up, 182 (37.9%) patients revisited the GP, 180 (37.5%) visited a physiotherapist, and 114 (23.8%) an orthopedic surgeon.

Patient characteristics associated with referral to a physiotherapist were female gender, younger age, and crepitus of active extension of the knee. Associated with a referral to an orthopedic surgeon were no paid employment, feeling of giving way, and pain on passive flexion of the knee. Referral for X-ray of the knee was associated with female gender, older age, and a bony swelling of the joint.

We concluded that medical treatment at baseline partly corresponds with recommendations given in the Guideline of the Dutch College of General Practitioners for nontraumatic knee problems in adults. Further, in this study group, medical consumption is relatively high during 1-year follow-up.

In **Chapter 7**, the revised Dutch College of General Practitioners guideline for nontraumatic knee problems in adults is presented. This guideline is developed based on the

available evidence in medical literature and recommendations for daily practice are provided.

Chapter 8 reflects on the findings in this thesis and recommendations for clinical practice and future research are made.

Samenvatting

Knieklachten zijn, na rugklachten, in de huisartsenpraktijk de meest voorkomende klacht van het bewegingsapparaat (19/1000 patiënten per jaar). Patiënten presenteren zich doorgaans bij de huisarts met kniepijn of functieverlies van het kniegewricht. Van al deze knieklachten heeft ongeveer 20% een traumatische oorzaak.

Ondanks de hoge prevalentie van knieklachten zijn er weinig studies verricht naar de klachten, symptomen en prognose van niet-traumatische knieklachten. Met name voor de huisartsgeneeskunde zijn deze data nauwelijks beschikbaar.

Doel van dit proefschrift was om meer kennis over het beloop en de prognose van niet-traumatische knieklachten bij volwassenen in de huisartsenpraktijk te verschaffen.

In **Hoofdstuk 2** bepaalden we de cross-sectionele en longitudinale validiteit van een performance test van kniefunctie, de DynaPort® Knie Test (DPKT), bij patiënten met een eerste episode van niet-traumatische knieklachten in de huisartsenpraktijk.

Patiënten die de huisarts consulteerden voor niet-traumatische knieklachten (leeftijd > 18 jaar) werden geïncludeerd voor de studie. Bij het begin van de studie en na 6 maanden follow-up werd de kniefunctie bepaald met behulp van vragenlijsten en de DPKT. Ook werd aan het begin van de studie een lichamelijk onderzoek uitgevoerd. De cross-sectionele en longitudinale validiteit van de DPKT werd bepaald door het testen van hypotheses.

Zevenentachtig patiënten werden geïncludeerd voor de DPKT waarvan er 86 beschikbaar waren voor de analyses. De studiepopulatie bestond uit 44 vrouwen (51.2%), de mediane leeftijd was 54 (range 18-81 jaar). Bij follow-up waren 77 (89.5%) patiënten beschikbaar voor de DPKT. Slechts 3 van de 11 (27%) vooraf opgestelde hypotheses met betrekking tot de cross-sectionele en longitudinale validiteit werden bevestigd. De vergelijking tussen onze eerstelijns en een tweedelijns populatie liet een aanzienlijk verschil zien voor de baseline karakteristieken, DynaPort Knie Score, interne consistentie, en ook wat betreft het bevestigen van de hypotheses met betrekking tot de constructvaliditeit.

Op basis van onze bevindingen konden wij de validiteit van de DPKT niet aantonen voor patiënten die de huisarts voor de eerste keer consulteerden met niet-traumatische knieklachten. Verder zijn meetinstrumenten die in een tweedelijns setting zijn ontwikkeld en gevalideerd niet automatisch ook valide voor een eerstelijns setting.

Hoofdstuk 3 is een systematische review naar prognostische factoren van progressie van knie artrose. Met behulp van een specifieke zoekactie (zoektermen voor ziekte, locatie en studieopzet) doorzochten we Medline en Embase. Van studies die voldeden aan vooraf opgestelde criteria werd de methodologische kwaliteit bepaald. Studiekarakteristieken en associaties werden kort weergegeven en de resultaten samengevat overeenkomstig een 'best evidence synthese'.

Van de 1004 gevonden studies voldeden 37 aan de inclusie criteria. De methodologische kwaliteit werd bepaald en alleen studies van hoge kwaliteit (n = 36) werden geïncludeerd. De best evidence synthese gaf sterk bewijs dat serum concentraties van hyaluronzuur en de aanwezigheid van gegeneraliseerde artrose voorspellend zijn voor progressie van knieartrose. Geslacht, kniepijn, radiologische ernst, knietrauma, sterkte van de m.quadriceps, en regelmatige sportactiviteiten waren niet voorspellend. Tegengesteld bewijs voor een associatie met progressie van knieartrose werd gevonden voor verscheidene factoren, waaronder body mass index (BMI) en leeftijd. Beperkt bewijs voor een associatie met progressie van knieartrose werd gevonden voor verscheidene factoren, waaronder de stand van het gewricht (varus/valgus). Beperkt bewijs voor het ontbreken van een associatie met progressie van knieartrose werd voor verscheidene factoren gevonden, waaronder een meniscectomie, verscheidene markers van bot- of kraakbeenafbraak en de klinische diagnose van lokale artrose.

Daarom concludeerden we dat gegeneraliseerde artrose en de serum concentratie van hyaluronzuur geassocieerd lijken te zijn met radiologische progressie van knieartrose. Kniepijn, baseline radiologische ernst, geslacht, sterkte van de m.quadriceps, knietrauma en regelmatige sportactiviteiten lijken niet gerelateerd met progressie van knieartrose. Voor andere factoren was het bewijs beperkt of tegengesteld.

In **hoofdstuk 4 – 6** onderzochten we een subgroep van het prospectieve HONEUR knie cohort. Volwassenen (> 35 jaar) met niet-traumatische knieklachten werden gevolgd gedurende 1 jaar. Bij de start van de studie werden gegevens over kniesymptomen en demografische kenmerken verzameld en een lichamelijk onderzoek werd uitgevoerd. Gedurende de follow-up werden driemaandelijks gegevens verzameld over de knieklachten en medische consumptie door vragenlijsten die door de deelnemers zelf ingevuld werden. Na 1 jaar follow-up werd het lichamelijk onderzoek herhaald. In totaal werden 549 patiënten geïncludeerd waarvan 480 (87.4%) beschikbaar waren voor follow-up. De studiepopulatie bestond uit 236 (49.2%) vrouwen, gemiddelde leeftijd was 53.6 jaar (standaard deviatie (sd) 11.3), gemiddelde BMI was 27.1 (sd 4.2), en 288 patiënten (60%) hadden een betaalde baan. Na één jaar follow-up gaven 236 (49.2%) patiënten aan persisterende knieklachten te hebben.

Hoofdstuk 4 beschrijft het beloop, de prognose en prognostische factoren voor het persisteren van niet-traumatische knieklachten bij volwassenen in de huisartsenpraktijk.

Multivariate prognostische regressie modellen van patiëntkarakteristieken, klacht karakteristieken en lichamelijk onderzoek werden gebruikt om persisterende knieklachten na 1 jaar te voorspellen. De oppervlaktes onder de receiving operating characteristic curves (AUC) werden gebruikt om de voorspellende waarde van het model te bepalen.

Om de additieve voorspellende waarde van klachtkarakteristieken en lichamelijk onderzoek te bepalen, werden deze modellen toegevoegd aan het model van de patiënt karakteristieken. De verbetering werd uitgedrukt als het verschil tussen de 2 AUCs.

In het multivariate prognostische model van de patiëntkarakteristieken waren leeftijd >60 jaar, opleidingsniveau, bewegingsangst en comorbiditeit van het bewegingsapparaat geassocieerd met persisterende knieklachten na 1 jaar (AUC 0.67). Van de klacht karakteristieken waren een voorgeschiedenis van niet-traumatische knieklachten, bilaterale klachten en duur van de klachten (> 3 maanden) geassocieerd (AUC 0.73). Voor de determinanten van lichamelijk onderzoek was crepiteren bij passieve extensie van de knie geassocieerd (AUC 0.55). De toegevoegde waarde van het model van de klachtkarakteristieken op het model van de patiëntkarakteristieken was 0.09 (AUC 0.76). Lichamelijk onderzoek had geen toegevoegde waarde.

Wij concludeerden dat klacht karakteristieken de sterkste voorspellers zijn van persisterende knieklachten na 1 jaar follow-up. Lichamelijk onderzoek heeft geen toegevoegde waarde in het voorspellen van persisterende knieklachten in de huisartsenpraktijk.

In **hoofdstuk 5** bepaalden we de prognostische waarde van de American College of Rheumatology (ACR) klinische classificatie criteria van knieartrose op persisterende knieklachten en toename van verminderd functioneren na 1 jaar bij volwassen patiënten met kniepijn in de huisartspraktijk.

In deze studie voldeden 292 (60.8%) patiënten aan de klinische ACR criteria voor knieartrose. Na 1 jaar follow-up rapporteerden 236 (49.2%) patiënten persisterende knieklachten en 84 (17.5%) patiënten rapporteerden een toename van verminderd functioneren.

Er werd geen associatie gevonden tussen persisterende knieklachten en het op baseline voldoen aan de klinische ACR criteria voor knie artrose (OR 1.15; 95% BI 0.80, 1.67) of een toename van verminderd functioneren na 1 jaar follow-up (OR 1.05, 95% BI 0.43, 2.58).

Daarom concludeerden we dat de klinische ACR classificatie criteria voor knieartrose geen prognostische waarde hebben voor het voorspellen van persisterende knieklachten of een toename van verminderd functioneren in volwassenen patiënten in de huisartsenpraktijk na 1 jaar follow-up.

Hoofdstuk 6 beschrijft de medische behandeling door de huisarts bij baseline en de medische consumptie gedurende 1 jaar follow-up van volwassen patiënten die de huisarts bezochten met niet-traumatische knieklachten. Als toevoeging werden factoren bepaald die geassocieerd zijn met een baseline verwijzing naar een fysiotherapeut, orthopeed of voor een röntgenfoto van de knie.

Op baseline werd aan 193 (35.2%) patiënten geadviseerd de knie te ontzien en 150 (27.3%) patiënten kregen pijnmedicatie voorgeschreven. Van alle patiënten kregen 311 (56.6%) een verwijzing naar een fysiotherapeut, orthopeed of voor een röntgenfoto van de knie. Gedurende 1 jaar follow-up bezochten 182 (37.9%) patiënten opnieuw de huisarts, 180 (37.5%) bezochten een fysiotherapeut en 114 (23.8%) bezochten een orthopeed.

Patiëntkarakteristieken geassocieerd met een verwijzing naar een fysiotherapeut waren vrouwelijk geslacht, jongere leeftijd en crepiteren bij actieve extensie van de knie. Het ontbreken van een betaalde baan, gevoel door de knie te zakken en pijn bij passieve flexie van de knie waren geassocieerd met een verwijzing naar een orthopeed. Een verwijzing voor een röntgenfoto van de knie was geassocieerd met vrouwelijk geslacht, oudere leeftijd en een benige verbreding van het gewricht.

Wij concludeerden dat baseline medische behandeling gedeeltelijk overeenkomt met de aanbevelingen uit de standaard voor niet-traumatische knieproblemen bij volwassenen van het Nederlands Huisartsen Genootschap (NHG). Bovendien is voor deze studiegroep de medische consumptie gedurende 1 jaar follow-up relatief hoog.

In **hoofdstuk 7** wordt de herziene NHG standaard 'Niet-traumatische knieproblemen bij volwassenen' gepresenteerd.

Hoofdstuk 8 reflecteert op de bevindingen van dit proefschrift en aanbevelingen voor de klinische praktijk en toekomstig onderzoek worden gegeven.

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Curriculum Vitae

CURRICULUM VITAE

Janneke Belo werd op 29 augustus 1978 geboren te Rotterdam. Samen met haar 2 broers en zus groeide zij op in Capelle aan den IJssel. Na het behalen van haar VWO diploma aan het Driestar College te Gouda begon zij in 1996 met de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. Tijdens haar studie geneeskunde volgde zij keuzeonderwijs over de chronische patiënt bij de afdeling huisartsgeneeskunde. In 2000 deed zij bij de afdeling huisartsgeneeskunde haar afstudeeronderzoek naar de rol van de huisarts in de zorg voor terminaal zieke kinderen. Na het behalen van het artsexamen in 2002 werd zij september 2002 aangenomen bij de huisartsopleiding te Rotterdam als huisarts in opleiding. In het voorjaar van 2003 werd dit omgezet tot arts in opleiding tot huisarts en onderzoeker (aioto), een combinatietraject van de opleiding tot huisarts en wetenschappelijk onderzoeker. In augustus 2004 behaalde zij haar Master of Science in de klinische epidemiologie aan het Nederlands Instituut for Health Sciences (NIHES). Sinds 22 juni 2007 staat zij ingeschreven als huisarts in het huisartsenregister. Sinds 1 juli 2007 is zij werkzaam als huisarts in dienst bij een huisarts (Hidha) bij H.J. van Duijn, huisarts te Katwijk aan den Rijn. Daarnaast is zij sinds 1 augustus 2008 als staflid verbonden aan de huisartsopleiding te Rotterdam waar zij coördinator Wetenschappelijke Vorming en coördinator Vakinhoudelijk Onderwijs is.

Zij is gehuwd met Paul van Kruistum met wie zij in Katwijk aan Zee woont.

PhD Portfolio

PHD PORTFOLIO

Name PhD student:	Janneke N. Belo
ErasmusMC Department:	General Practice
PhD period:	2003-2009
Promotor:	Prof.dr. B.W. Koes
Copromotor:	Dr. S.M.A Bierma-Zeinstra

1.PHD TRAINING

Research Skills

MSc in Clinical Epidemiology, NIHES, Rotterdam, 2003 – 2004 (70 EC):

Various courses in research methodology, including: Principles of Research in Medicine and Epidemiology, Clinical Decision Analysis, Methods of Public Health Research, Topics in Evidence-Based Medicine, Methods of Health Services Research, Prevention Research, Study Design, Classical Methods for Data-analysis, Clinical Epidemiology, Methodological Topics in Epidemiologic Research, Modern Statistical Methods, Epidemiology of Infectious Diseases, Advanced Diagnostic Research, Prognostic Research.

Professional Education

Vocational training for general practitioner, ErasmusMC, Department of General Practice, 2002 – 2007

Presentations

Abstracts presented at the following national and international conferences:

- Annual Science Conference of the Dutch College of General Practitioners:
  - 2004, Leiden (poster presentation)
  - 2007, Amsterdam (oral presentation)
  - 2009, Utrecht (oral presentation)
- Annual Dutch Symposium of Epidemiology, 2005, Wageningen (2 poster presentations)
- Symposium of the Musculoskeletal Research Departments of Amsterdam, Keele, and Rotterdam, 2005, Keele, Great Britain (oral presentation)
- Annual European League Against Rheumatism (EULAR) conference:
  - 2005, Vienna, Austria (2 poster presentations)

2007, Barcelona, Spain (poster presentation)
2008, Paris, France (poster presentation)
2009, Copenhagen, Denmark (poster presentation)

- IEA EEF Europian Congress of Epidemiology, 2006, Utrecht (poster presentation)
- Symposium of the Musculoskeletal Research Departments of Keele, Aberdeen, Rotterdam, Manchester, and Amsterdam (KARMA), 2006, Amsterdam (oral presentation)
- Osteoarthritis Research Society International (OARSI) conference, 2008, Rome, Italy (poster presentation)

Presentations about knee osteoarthritis and knee complaints in General Practice

- Training for General Practitioners Katwijk, 2008, Katwijk (oral presentation)
- Arthron Conference, Research Centre for Rheumatic Diseases Amsterdam, 2008, Amsterdam (oral presentation)
- Training for General Practitioners, Post Academical Education for General Practitioners, 2009, Utrecht (oral presentation)

National and international conferences

- Symposium of the musculoskeletal research cluster of the ErasmusMC (MUSC), 2004, Rotterdam
- WONCA Europe – Junior Doctor Conference, 2004, Amsterdam
- WONCA Europe Conference, 2004, Amsterdam
- Annual Science Conference of the Dutch College of General Practitioners, 2008, Rotterdam

2. TEACHING ACTIVITIES

- Teaching 3rd year medical students, Clinical Reasoning, ErasmusMC, 2003, 2004, 2005, 2007, Rotterdam
- Teaching students of the Vocational Training for Physician of mentally disabled persons, Evidence Based Medicine, ErasmusMC, 2008, Rotterdam
- Teaching students of the Vocational Training for General Practitioners, Education in Science, ErasmusMC, 2008, 2009, Rotterdam
- Teaching 1st year medical students, Clinical Reasoning, ErasmusMC, 2009, Rotterdam