CHECKing activity limitations in persons with early osteoarthritis of the knee or hip

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PART I

COURSE AND PROGNOSIS OF ACTIVITY LIMITATIONS

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Chapter 2

Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee

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Abstract

Objective. To predict the 2-year course of activity limitations in patients with early knee and/or hip osteoarthritis (OA).

Methods. The Cohort Hip & Cohort Knee (CHECK) study is a prospective follow-up study. The CHECK cohort, comprising participants (n = 1,002) with early OA-related knee and/or hip symptoms, was followed for 2 years. Participants completed questionnaires and underwent physical, laboratory and radiographic examination. Regression models were used to examine whether baseline variables predicted the course of activity limitations as measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Analyses were performed separately for participants with knee symptoms and participants with hip symptoms.

Results. After 2 years of follow-up activity limitations slightly decreased. Large between subject variation was observed in WOMAC change scores. In participants with knee symptoms, young age, non-western ethnicity, bilateral hip pain, morning stiffness in the knee, high comorbidity count, high body-mass index, high bodily pain, poor general health perception, and pain coping strategy were associated with a poor 2-year outcome on activity limitations. In participants with hip symptoms, few activity limitations at baseline, bilateral hip pain, morning stiffness in the knee, high comorbidity count, low active hip flexion, poor general health perception, and pain coping strategy were associated with a poor 2-year outcome on activity limitations.

Conclusion. After 2 years of follow-up, large between-subject variation was observed in the course of activity limitations. The course of activity limitations is to some extent predictable already at an early stage of knee and hip OA.

Introduction

Osteoarthritis (OA) of the knee and/or hip is a leading cause of activity limitations (e.g. stair-climbing, walking) in Western countries.[1-3] Activity limitations are defined as difficulties an individual may have in executing activities in the International Classification of Functioning, Disability and Health.[4] The course of activity limitations differs considerably between patients; some patients seem to be stable or to even improve, whereas others deteriorate.[5-7] Several socio-demographic factors, comorbidities, physical impairments, psychological factors, social factors and health behaviours have been linked to an increase in activity limitations in patients with OA.[8] However, these factors have been found in populations with established OA. Less research is directed at early OA. Therefore, in early OA, less is known about factors affecting activity limitations. This makes it difficult for physicians to distinguish between patients with poor and good prognoses at an early stage of the disease. As a result many patients with early OA are not sufficiently informed about their likely course of activity limitations, and are not referred for appropriate treatment.[9,10] This is unfortunate, because developing activity limitations is one of the main fears of patients with OA.[9]

To reduce this uncertainty about the course of activity limitations for both physicians and patients, identification of factors affecting activity limitations is needed. This enables physicians to identify patients at risk for developing activity limitations and to select patients eligible for treatment. The most efficient prevention efforts in OA may well target patients with early disease.[11] Therefore, it is important to investigate whether, already at an early stage of knee and hip OA, predictors for the course of activity limitations can be identified.

The purpose of the present study was to predict the 2-year course of activity limitations in patients with early knee and/or hip OA. To enhance the pragmatic applicability of the study results, the focus was on predictors that are routinely measured or easily implemented by physicians at an early stage of the disease.

Patients and methods

Study design and population

The Cohort Hip & Cohort Knee (CHECK) study is a prospective follow-up study of 1,002 individuals with early symptoms of the knee and/or hip.[12] The CHECK cohort was formed from October 2002 till September 2005. At baseline, the majority of participants (83%) reported knee symptoms,[12] of whom 76% fulfilled the American College of Rheumatology (ACR) criteria for the classification of knee OA.[13] Hip symptoms were reported by 59% of participants,[12] of whom 24% fulfilled the ACR criteria for the classification of hip OA.[14]

Two-year follow-up data show an increase in these percentages, as well as an increase in radiological signs (Wesseling J, et al: unpublished observations). Therefore the CHECK cohort can be considered as an early OA cohort, but definite description can only be made at a later stage. Nationwide in the Netherlands, 10 general and academic hospitals located in urbanized and semi-urbanized regions are participating. Participants were referred by general practitioners, referred from the outpatient clinics of the participating centres, or recruited through advertisements in the local newspapers and on the Web site of the Dutch Arthritis Association. During the baseline measurements, the physicians in the participating centres checked whether each patient fulfilled the inclusion criteria. Individuals were eligible for inclusion if they had pain and/or stiffness in the knee and/or hip (**Figure 1**), were ages 45-65 years, and had never or ≤ 6 months ago visited the general practitioner for these symptoms for the first time.

Exclusion criteria were any other pathologic condition that could explain the symptoms, comorbidity that did not allow physical evaluation and/or follow-up of ≥ 10 years, malignancy in the last five years, and inability to understand the Dutch language. Based on symptoms, a knee stratum ($n = 832$) and a hip stratum ($n = 588$) were defined. Participants with both knee and hip symptoms were included in both strata. The study was approved by the medical ethics committees of all participating centres, and all participants gave their written informed consent before entering the study.

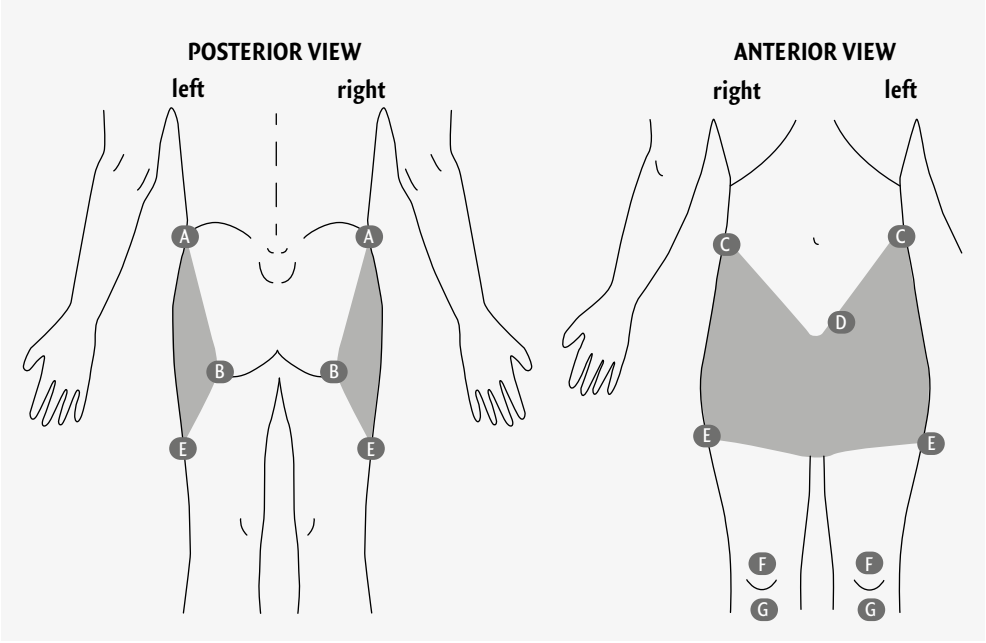

Figure 1. Participants were excluded if they only experienced pain in ≥ 1 of the marked areas in the left pain drawing. For inclusion, participants had to experience pain in ≥ 1 of the marked areas in the right pain drawing. A = iliac crest; B =ischial tuberosity; C = anterior superior iliac spine; D = pubic tubercle; E = one-third of the way down the spine; F = cranial border of the patella; G = tibial tuberosity.

Outcome measurement

Activity limitations were assessed with the physical functioning (PF) scale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[15] The WOMAC-PF is a disease-specific, self-administered instrument consisting of 17 items. Scores range from 0 to 68, with higher scores indicating more activity limitations. The WOMAC-PF is widely used in clinical research and has been shown to be reliable, valid, and responsive for use in patients with OA.[15-17]

The primary outcome, a dichotomous measure of activity limitations, was constructed according to Sharma et al.[7] Baseline and 2-year WOMAC-PF scores were categorized into quintile groups (knee stratum: 0-5, 6-11, 12-18, 19-26 and 27-68, hip stratum: 0-6, 7-12, 13-19, 20-27 and 28-68). For each participant, a poor outcome on activity limitations was defined as moving into a higher group or remaining within the 3 highest groups after 2 years. A good outcome on activity limitations was defined as moving into a lower group or remaining in one of the 2 lowest groups after 2 years. In addition, a continuous outcome measure of activity limitations was calculated by subtracting the baseline WOMAC-PF scores from the 2-year scores.

Potential prognostic factors measured at baseline

Based on clinical applicability, biological plausibility, expert opinions (physiatrists, rheumatologists, a general practitioner and expert researchers in the field were consulted), and the literature, the prognostic value of 47 variables for activity limitations in knee symptoms and 41 variables for activity limitations in hip symptoms was studied. Baseline characteristics were categorized into 7 groups: demographics, symptoms, comorbidity and interventions, participation and lifestyle, physical examination, laboratory/radiographic examination, and self-report questionnaires. The order in which these 7 groups of variables were studied was based on the usual clinical routine of the physician. According to this routine, information about demographics, symptoms, comorbidity, interventions, and participation and lifestyle were obtained from patient history. Therefore, the prognostic value of these factors was examined first. After anamnesis a physical examination is performed, followed by laboratory and radiographic examination. Because questionnaires are not routinely assessed in clinical practice, the prognostic value of variables measured with questionnaires was examined last. All variables assessed are listed in **Tables 1** and **2**.

Categorical variables were coded as dummy variables. Combinations of categories were based on frequency distributions (if categories were relatively small, they were combined)[18] or on combinations used in comparable studies.

For the physical and radiographic examination variables, we used the clinical signs and symptoms relating to the index knee or index hip (i.e. most affected knee or hip) in the analyses. Of the 832 and 588 participants with knee and hip symptoms, 44.5% and 64.6% reported unilateral symptoms, respectively. For participants with bilateral symptoms, we defined an index joint based on the following decision tree: 1) highest Kellgren/Lawrence score,[19] 2) lowest degree of active knee flexion (index knee) or active hip internal rotation (index hip), 3) highest pain during knee flexion (index knee) or highest pain during hip internal rotation (index hip), and 4) crepitus during knee flexion (index knee) or highest pain during hip flexion (index hip). In participants for whom we could not define an index knee or hip based on these signs, we randomly assigned an index joint.

Table 1. Baseline characteristics of the knee stratum (n = 832), and results of the prognostic factor selection steps 1 and 2 to select potential prognostic factors for a poor 2-year outcome on activity limitations*

		Poor outcome on activity limitations	
	Value	Prognostic factor selection step 1, OR (95% CI)	Prognostic factor selection step 2, OR (95% CI)
Block 0: WOMAC function[15] (range 0–68)	14 (7–23)	1.03 (1.02, 1.05)†	
Block 1: demographics			
Age, mean ± SD years	56.0 ± 5.1	0.97 (0.96, 0.98)†	0.97 (0.94, 1.00)†
Women, no. (%)	663 (79.7)	1.14 (0.80, 1.62)	
Ethnicity, no. (%)‡			
Native or immigrant of western origin	775 (93.1)	reference	reference
Immigrant of non-western origin	16 (1.9)	4.21 (1.18, 14.98)†	3.77 (1.05, 13.54)†
Western immigrant of Indonesian origin	20 (2.4)	1.59 (0.65, 3.94)	1.80 (0.71, 4.54)
Household composition > 1, no. (%)	706 (84.9)	0.83 (0.54, 1.28)	
Educational level, no. (%)			
Primary school	23 (2.8)	reference	reference
Secondary school	571 (68.6)	0.49 (0.20, 1.19)†	0.46 (0.19, 1.14)†
Higher professional education/university	214 (25.7)	0.32 (0.13, 0.81)†	0.29 (0.11, 0.75)†
Block 2: symptoms			
Knee pain, no. (%)			
Unilateral	370 (44.5)	reference	
Bilateral with index knee	344 (41.3)	1.17 (0.86, 1.59)	
Bilateral with equal symptoms	118 (14.2)	1.32 (0.85, 2.04)	
Hip pain, no. (%)			
No pain	414 (49.8)	reference	reference
Unilateral	260 (31.3)	1.38 (1.00, 1.90)†	1.34 (0.92, 1.95)†
Bilateral with index hip	113 (13.6)	1.80 (1.14, 2.84)†	1.74 (1.05, 2.89)†
Bilateral with equal symptoms	45 (5.4)	3.16 (1.59, 6.31)†	2.89 (1.40, 5.97)†
NRS for pain intensity (range 0–10)	3 (2–5)	1.15 (1.07, 1.23)†	1.11 (1.03, 1.21)†
Pain during sitting/lying (WOMAC item),[15] no. (%)			
None/slight	603 (72.5)	reference	reference
Moderate	162 (19.5)	1.40 (0.98, 2.01)†	1.02 (0.69, 1.52)
Severe/extreme	44 (5.3)	1.68 (0.89, 3.16)†	1.06 (0.52, 2.13)
Morning stiffness knee < 30 minutes,[13] no. (%)	518 (62.3)	1.69 (1.26, 2.27)†	1.57 (1.14, 2.16)†
Morning stiffness hip ≤ 60 minutes,[14] no. (%)	247 (29.7)	1.51 (1.11, 2.05)†	0.99 (0.67, 1.47)
Block 3: comorbidity and interventions			
Comorbidity count, no. (%)			
0	210 (25.2)	reference	reference
1	251 (30.2)	1.18 (0.81, 1.71)	1.14 (0.78, 1.67)
2	177 (21.3)	1.54 (1.02, 2.31)†	1.49 (0.98, 2.26)†
≥ 3	177 (21.3)	2.63 (1.71, 4.03)†	2.28 (1.45, 3.58)†
Body-mass index, kg/m²	25.6 (23.6–28.4)	1.08 (1.04, 1.12)†	1.07 (1.03, 1.11)†
Use of pain medication, no. (%)	309 (37.1)	1.51 (1.13, 2.02)†	1.24 (0.91, 1.70)†
Knee or hip surgery during past year, no. (%)	6 (0.7)	0.65 (0.10, 3.99)	
Block 4: participation and lifestyle			
Paid employment, no. (%)	419 (50.4)	0.79 (0.59, 1.04)†	0.77 (0.58, 1.02)†
Demanding physical work, often/always, no. (%)	64 (7.7)	1.30 (0.76, 2.20)	
Physical activity during leisure, no. (%)			
0-2 days per week	381 (45.8)	reference	reference
3-5 days per week	315 (37.9)	0.81 (0.60, 1.11)†	0.80 (0.59, 1.10)†
6-7 days per week	106 (12.7)	0.75 (0.48, 1.16)†	0.74 (0.47, 1.15)†

Table 1. (continued)	**Value**	**Poor outcome on activity limitations**	
		Selection step 1, OR (95% CI)	**Selection step 2, OR (95% CI)**
Weekday alcohol consumption, no. (%)			
0 glasses	244 (29.3)	reference	
1-3 glasses	543 (65.3)	0.82 (0.60, 1.12)	
≥ 4 glasses	22 (2.6)	0.68 (0.28, 1.69)	
Tobacco use, no. (%)	119 (14.3)	1.33 (0.88, 1.99)†	1.30 (0.86, 1.96)
Block 5: physical examination			
Knee flexion, degrees	135 (130–140)	0.99 (0.97, 1.00)†	0.99 (0.98, 1.01)
Pain during knee flexion, no. (%)			
None/slight	744 (89.4)	reference	reference
Severe/extreme	81 (9.7)	1.55 (0.95, 2.53)†	1.43 (0.86, 2.38)†
Knee extension, degrees	2 (0–5)	1.00 (0.95, 1.04)	
Pain during knee extension, no. (%)			
None/slight	781 (93.3)	reference	
Severe/extreme	44 (5.3)	1.42 (0.74, 2.73)	
Palpable warmth, no. (%)	46 (5.5)	0.78 (0.42, 1.45)	
Crepitus during knee flexion, no. (%)	392 (47.1)	0.96 (0.73, 1.27)	
Pain on palpation of the joint line, no. (%)	374 (45.0)	1.52 (1.16, 2.01)†	1.47 (1.10, 1.95)†
Bony enlargement, no. (%)	36 (4.3)	1.41 (0.70, 2.84)	
Positive refill-test, no. (%)	61 (7.3)	0.53 (0.31, 0.93)†	0.45 (0.25, 0.78)†
Pain on patella femoral joint compression, no. (%)	235 (28.2)	1.39 (1.02, 1.90)†	1.32 (0.96, 1.81)†
Presence of Heberden's nodes, no. (%)	409 (49.2)	1.10 (0.83, 1.45)	
Block 6: laboratory/radiographic examination			
ESR, mm/hour	8 (5–14)	1.01 (0.99, 1.03)	
K/L knee score,[19] no. (%)			
0	566 (68.0)	reference	reference
1	200 (24.0)	1.14 (0.82, 1.59)	1.14 (0.82, 1.59)
2 or 3	59 (7.1)	1.53 (0.87, 2.68)†	1.53 (0.87, 2.68)†
Block 7: self-report questionnaires			
SF-36 scores,[27,28] mean ± SD (range 0–100)			
Bodily pain	67.3 ± 17.7	0.97 (0.97, 0.98)†	0.98 (0.97, 0.99)†
Vitality	63.9 ± 16.8	0.98 (0.97, 0.99)†	1.00 (0.99, 1.01)
Mental health	76.5 ± 14.7	0.99 (0.98, 1.00)†	0.99 (0.98, 1.01)
General health	53.3 ± 18.3	0.98 (0.97, 0.99)†	0.99 (0.98, 1.00)†
EQ-5D[29,30]			
Item on anxiety/depression, no. (%)			
Not anxious/depressed	658 (79.1)	reference	reference
Anxious/depressed	153 (18.4)	1.37 (0.94, 1.99)†	0.97 (0.58, 1.62)
VAS for health (range 0–100)	78.0 (70.0–85.0)	0.97 (0.96, 0.99)†	1.00 (0.98, 1.01)
Social Support[31] (range 12–60)	15 (12–22)	1.03 (1.01, 1.04)†	1.01 (0.99, 1.03)
Pain Coping Inventory[32]			
Distraction (range 5–20)	11 (9–13)	1.07 (1.03, 1.12)†	1.04 (0.98, 1.10)†
Transformation (range 4–16)	8 (7–10)	1.09 (1.03, 1.15)†	1.05 (0.99, 1.12)†
Reducing demands (range 3–12)	6 (5–7)	1.05 (0.97, 1.14)	
Resting (range 5–20)	9 (7–11)	1.10 (1.04, 1.16)†	1.05 (0.97, 1.13)
Retreating (range 7–28)	10 (8–13)	1.03 (0.99, 1.07)†	0.98 (0.93, 1.03)
Worrying (range 9–36)	13 (11–16)	1.03 (1.00, 1.07)†	0.95 (0.90, 1.00)†

* Values are the median (interquartile range) unless otherwise indicated. Prognostic factor selection steps 1 and 2 are described in the Statistical analysis section. References for the measurement instruments are indicated in the first column. OR = odds ratio; 95% CI = 95% confidence interval; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; NRS = numeric rating scale; ESR = erythrocyte sedimentation rate; K/L = Kellgren/Lawrence; SF-36 = Short Form 36 Health Survey; EQ-5D = EuroQol 5 domains; VAS = visual analogue scale. † P < 0.2. ‡ Categories are based on the definition of ethnic minorities of Statistics Netherlands, whereby Western immigrants of Indonesian and Japanese origin are analysed as a separate group.

Table 2. Baseline characteristics of the hip stratum (n = 588), and results of the prognostic factor selection steps 1 and 2 to select potential prognostic factors for a poor two-year outcome on activity limitations*

		Poor outcome on activity limitations	
	Value	Prognostic factor selection step 1, OR (95% CI)	Prognostic factor selection step 2, OR (95% CI)
Block 0: WOMAC function[15] (range 0–68)	16 (8–25)	1.01 (1.00, 1.03)†	
Block 1: demographics			
Age, mean ± SD years	55.8 ± 5.3	0.98 (0.95, 1.01)†	0.98 (0.95, 1.01)†
Women, no. (%)	475 (80.8)	1.00 (0.65, 1.53)	
Ethnicity, no. (%)‡			
Native or immigrant of western origin	557 (94.7)	reference	reference
Immigrant of non-western origin	5 (0.9)	0.95 (0.12, 7.76)	0.97 (0.11, 8.22)
Western immigrant of Indonesian origin	12 (2.0)	2.81 (0.75, 10.62)†	2.86 (0.75, 10.95)†
Household composition > 1, no. (%)	499 (84.9)	0.97 (0.59, 1.61)	
Educational level, no. (%)			
Primary school	11 (1.9)	reference	reference
Secondary school	407 (69.2)	0.52 (0.13, 2.06)	0.47 (0.12, 1.88)
Higher professional education/university	155 (26.4)	0.38 (0.09, 1.55)†	0.33 (0.08, 1.38)†
Block 2: symptoms			
Knee pain, no. (%)			
No pain	170 (28.9)	reference	reference
Unilateral	182 (31.0)	1.32 (0.86, 2.03)	1.03 (0.63, 1.66)
Bilateral with index knee	178 (30.3)	1.57 (1.01, 2.44)†	1.00 (0.59, 1.69)
Bilateral with equal symptoms	58 (9.9)	1.36 (0.74, 2.49)	0.76 (0.38, 1.51)
Hip pain, no. (%)			
Unilateral	380 (64.6)	reference	reference
Bilateral with index hip	159 (27.0)	1.21 (0.82, 1.78)	1.23 (0.82, 1.86)
Bilateral with equal symptoms	49 (8.3)	2.32 (1.21, 4.43)†	2.31 (1.16, 4.61)†
NRS for pain intensity (range 0-10)	4 (2–5)	1.05 (0.97, 1.14)	
Pain during sitting/lying (WOMAC item),[15] no. (%)			
None/slight	387 (65.8)	reference	
Moderate	147 (25.0)	0.93 (0.63, 1.37)	
Severe/extreme	38 (6.5)	1.15 (0.57, 2.31)	
Morning stiffness knee < 30 minutes,[13] no. (%)	274 (46.6)	2.02 (1.43, 2.84)†	1.89 (1.24, 2.90)†
Morning stiffness hip ≤ 60 minutes,[14] no. (%)	326 (55.4)	1.42 (1.02, 1.98)†	1.22 (0.85, 1.76)
Block 3: comorbidity and interventions			
Comorbidity count, no. (%)			
0	142 (24.1)	reference	reference
1	170 (28.9)	1.29 (0.81, 2.04)	1.24 (0.78, 1.98)
2	113 (19.2)	1.59 (0.95, 2.66)†	1.46 (0.86, 2.46)†
≥ 3	152 (25.9)	2.85 (1.75, 4.63)†	2.51 (1.52, 4.13)†
Body-mass index, kg/m²	25.4 (23.2–28.2)	1.07 (1.02, 1.12)†	1.06 (1.01, 1.10)†
Use of pain medication, no. (%)	250 (42.5)	1.54 (1.09, 2.16)†	1.29 (0.90, 1.85)†
Knee or hip surgery during past year, no. (%)	7 (1.2)	1.54 (0.30, 7.84)	
Block 4: participation and lifestyle			
Paid employment, no. (%)	296 (50.3)	0.74 (0.53, 1.04)†	0.71 (0.50, 1.00)†
Demanding physical work, often/always, no. (%)	54 (9.2)	0.88 (0.49, 1.58)	
Physical activity during leisure, no. (%)			
0-2 days per week	254 (43.2)	reference	reference
3-5 days per week	233 (39.6)	0.70 (0.48, 1.01)†	0.67 (0.45, 0.98)†
6-7 days per week	83 (14.1)	0.72 (0.43, 1.19)†	0.68 (0.41, 1.14)†

Table 2. (continued)

	Value	Poor outcome on activity limitations	
		Prognostic factor selection step 1, OR (95% CI)	Prognostic factor selection step 2, OR (95% CI)
Weekday alcohol consumption, no. (%)			
0 glasses	157 (26.7)	reference	reference
1-3 glasses	399 (67.9)	0.75 (0.51, 1.10)†	0.77 (0.52, 1.14)†
≥ 4 glasses	18 (3.1)	1.13 (0.41, 3.12)	1.11 (0.40, 3.09)
Tobacco use, no. (%)	80 (13.6)	1.25 (0.77, 2.03)	
Block 5: physical examination			
Hip internal rotation, degrees	30 (23–35)	0.99 (0.98, 1.01)	
Pain during hip internal rotation, no. (%)			
None/slight	460 (78.2)	reference	
Severe/extreme	125 (21.3)	1.15 (0.76, 1.76)	
Hip flexion, degrees	118 (110–125)	0.98 (0.96, 0.99)†	0.98 (0.96, 0.99)†
Pain during hip flexion, no. (%)			
None/slight	468 (79.6)	reference	reference
Severe/extreme	113 (19.2)	1.36 (0.89, 2.07)†	1.15 (0.74, 1.78)
Presence of Heberden's nodes, no. (%)	296 (50.3)	0.94 (0.68, 1.32)	
Block 6: laboratory/radiographic examination			
ESR, mm/hour	8 (5–13)	1.00 (0.98, 1.02)	
K/L hip score[19] no. (%)			
0	454 (77.2)	reference	
1	87 (14.8)	1.23 (0.74, 2.02)	
2 or 3	44 (7.5)	0.92 (0.48, 1.76)	
Block 7: self-report questionnaires			
SF-36 scores,[27,28] mean ± SD (range 0–100)			
Bodily pain	67.2 ± 17.6	0.98 (0.97, 0.99)†	0.99 (0.98, 1.01)
Vitality	63.0 ± 16.8	0.99 (0.98, 0.99)†	1.00 (0.98, 1.01)
Mental health	76.3 ± 14.0	0.99 (0.98, 1.00)†	1.01 (0.99, 1.02)
General health	53.2 ± 18.0	0.97 (0.96, 0.98)†	0.98 (0.97, 0.99)†
EQ-5D[29,30]			
Item on anxiety/depression, no. (%)			
Not anxious/depressed	470 (79.9)	reference	
Anxious/depressed	107 (18.2)	1.28 (0.82, 2.01)	
VAS for health (range 0–100)	76.5 (70.0–85.0)	0.97 (0.96, 0.99)†	0.99 (0.97, 1.01)
Social Support[31] (range 12–60)	16 (12–22)	1.02 (1.00, 1.04)†	1.01 (0.99, 1.03)
Pain Coping Inventory[32]			
Distraction (range 5–20)	11 (9–13)	1.05 (1.00, 1.11)†	1.02 (0.95, 1.09)
Transformation (range 4–16)	8 (7–10)	1.08 (1.02, 1.15)†	1.05 (0.97, 1.13)†
Reducing demands (range 3–12)	6 (5–7)	1.05 (0.95, 1.15)	
Resting (range 5–20)	9 (8–11)	1.08 (1.01, 1.16)†	0.99 (0.91, 1.08)
Retreating (range 7–28)	10 (8–13)	1.01 (0.96, 1.06)	
Worrying (range 9–36)	14 (11–16)	1.03 (0.98, 1.07)	

* Values are the median (interquartile range) unless otherwise indicated. Prognostic factor selection steps 1 and 2 are described in the Statistical analysis section. References for the measurement instruments are indicated in the first column. See Table 1 for definitions. † $P < 0.2$. ‡ Categories are based on the definition of ethnic minorities of Statistics Netherlands, whereby Western immigrants of Indonesian and Japanese origin are analysed as a separate group.

Statistical analysis

Changes in activity limitations between baseline and 2-year follow-up measurements were analysed using paired-samples *t*-tests. Logistic and linear regression models were built to predict the 2-year course of activity limitations. Dependent variables were the dichotomous and continuous outcome measures of activity limitations.

Independent variables (the prognostic factors described in the previous paragraph) were selected in 4 steps. First, the individual relationship of each prognostic factor with the outcome was studied. Second, after controlling for collinearity, the prognostic factors identified at step 1 with a value of $P < 0.20$ were entered into a multivariable regression model. This was done separately for each of the 7 groups of related factors (see previous paragraph). Third, the prognostic factors identified at step 2 (the multivariable regression analyses per group) with a value of $P < 0.20$ were entered into a backward stepwise regression model (*P* removal 0.10). Variables were entered in seven consecutive blocks (**Tables 1** and **2**). Adding a next block of prognostic factors to the model may cause loss of significance of prognostic factors added in a previous block. Therefore, to remove all prognostic factors with a value of $P > 0.10$ from the final model, at step 4 the prognostic factors identified in step 3 were entered in 1 block into a backward stepwise regression model (*P* removal 0.10).

A potential nonlinear behaviour of continuous factors with the outcome was examined by using restricted cubic spline functions and spline plots.[18] Multicategory dummy variables went to the next step of the model building process when ≥ 1 of the set of dummy variables was significantly related to the outcome.

For the paired-samples *t*-tests, we used data from the complete cases only. For the regression analyses, missing values were estimated using the Multiple Imputation by Chained Equation (MICE) procedure.[20,21] Before missing values were imputed, we studied the missing data mechanisms.[18] Missing values were at least partly missing at random; therefore, imputation of the missing values may reduce bias.[22] Missing values were imputed in 4 groups of related variables, whereby 10 multiple imputed datasets were

Table 3. Mean WOMAC-PF two-year change scores of participants with knee symptoms and participants with hip symptoms, grouped by the dichotomous outcome definition: poor versus good outcome on activity limitations*

	Stratum knee (n = 832)				Stratum hip (n = 588)			
	WOMAC-PF				WOMAC-PF			
	No. (%)		change		No. (%)		change	
Poor outcome	405	(48.7)	5.45	± 6.38	292	(49.7)	5.89	± 6.15
Stayed in low function score group	188	(22.6)	0.21	± 5.87	127	(21.6)	0.85	± 5.04
Moved to worse group	217	(26.1)	9.99	± 6.82	165	(28.1)	9.77	± 7.00
Good outcome	427	(51.3)	-6.57	± 5.10	296	(50.3)	-7.43	± 5.69
Stayed in high function score group	163	(19.6)	-0.11	± 2.14	108	(18.4)	-0.02	± 2.45
Moved to better group	264	(31.7)	-10.56	± 6.93	188	(32.0)	-11.68	± 7.55
Total	832	(100.0)	-0.72	± 9.84	588	(100.0)	-0.82	± 10.41

* Values are the mean ± SD unless otherwise indicated. Mean values were calculated over the 10 imputed data sets. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; PF = physical function scale.

generated. The outcome variable was included in all the imputation models.[23]

The regression coefficients (B) and 95% confidence intervals (95% CIs) of the final regression models were estimated over the 10 imputed datasets according to Rubin's rules.[24] Furthermore, for the logistic regression models, the odds ratios (ORs), area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow goodness-of-fit test,[25] and Nagelkerke's R^2 statistic were calculated,[26] and for the linear regression models the R^2 was calculated.

Paired-samples t-tests were performed with SPSS, version 15.0 (SPSS). The MICE procedure and regression analyses on the imputed data sets were performed with R software, version 2.8.1 (R foundation for Statistical Computing).

Results

Study population

Of the 1,002 participants included at baseline, 926 (92.4%) completed the WOMAC-PF after 2 years. The knee and hip strata consisted of 832 and 588 participants, respectively. The baseline characteristics of the study population are presented in **Tables 1** and **2**.

In the knee and hip strata, missing outcome values were imputed for 77 (9.3%) and 57 (9.7%) participants, respectively. The mean number of missing values per independent variable was 21 (median 21 [2.5%], range: 0-105 [0-12.6%]) for the knee stratum, and 11 (median 12 [2.0%], range 0-31 [0-5.3%]) for the hip stratum.

Two-year course of activity limitations

Using the dichotomous outcome measure of activity limitations, 405 (48.7%) of the participants with knee symptoms were classified as experiencing a poor 2-year outcome. In participants with hip symptoms, 292 (49.7%) were classified as experiencing a poor 2-year outcome.

The median baseline WOMAC-PF scores for the knee and hip strata were 14 (interquartile range [IQR] 7-23) and 16 (IQR 8-25), respectively. In both participants with knee symptoms (mean ± SD WOMAC-PF change score -0.7 ± 9.8; $P = 0.05$) and participants with hip symptoms (-0.8 ± 10.4; $P = 0.09$), a small overall improvement in activities was observed between baseline and 2-year follow-up. The correlation between activity limitations at baseline and after 2 years was 0.65 ($P = 0.00$) for participants with knee symptoms and 0.62 ($P = 0.00$) for participants with hip symptoms. An overview of the mean WOMAC-PF change scores grouped by the dichotomous outcome subgroups is given in **Table 3**.

Prognostic factors in participants with knee symptoms

Examination of a potential nonlinear behaviour of continuous factors with each outcome measure showed that for all factors, a linear fit was appropriate. The prognostic factors, analysed in the univariable and multivariable regression analyses per group, and their association with the dichotomous outcome measure of activity limitations in participants with knee symptoms are given in **Table 1**.

The final multivariable logistic regression model identified the following 10 baseline prognostic factors for a poor 2-year outcome on activity limitations: young age, non-Western ethnicity, bilateral hip pain, morning stiffness in the knee, high comorbidity count, high body-mass index (BMI), high bodily pain, poor general health perception, frequent use of the pain coping strategy distraction, and infrequent use of the pain coping strategy

Table 4. Multivariable logistic regression models of prognostic factors associated with a poor 2-year outcome on activity limitations in patients with knee symptoms and patients with hip symptoms*

	Stratum knee (n = 832)		Stratum hip (n = 588)	
Variable	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Intercept	3.36 (0.32, 35.91)	0.32	18.10 (1.83, 179.11)	0.01
WOMAC function To			0.98 (0.97, 1.00)	0.07
Age, years	0.97 (0.94, 1.00)	0.05		
Ethnicity†				
Native or immigrant of western origin	Reference			
Immigrant of non-western origin	4.03 (1.06, 15.38)	0.04		
Immigrant of Indonesian origin	1.80 (0.68, 4.79)	0.24		
Hip pain				
No pain	Reference			
Unilateral	1.26 (0.90, 1.78)	0.18	Reference	
Bilateral with index hip	1.60 (0.98, 2.59)	0.06	1.16 (0.77, 1.75)	0.48
Bilateral with equal symptoms	2.76 (1.33, 5.74)	0.01	2.22 (1.11, 4.45)	0.02
Morning stiffness knee < 30 minutes	1.37 (0.99, 1.88)	0.05	1.73 (1.20, 2.50)	0.00
Comorbidity count				
0	Reference		Reference	
1	1.01 (0.67, 1.53)	0.95	1.04 (0.64, 1.70)	0.88
2	1.21 (0.77, 1.89)	0.41	1.10 (0.63, 1.93)	0.73
≥ 3	1.53 (0.93, 2.53)	0.09	1.82 (1.05, 3.14)	0.03
Body-mass Index, kg/m²	1.06 (1.02, 1.11)	0.00		
Hip flexion, degrees			0.98 (0.96, 0.99)	0.01
SF-36 subscale for bodily pain	0.98 (0.97, 1.00)	0.00		
SF-36 subscale for general health	0.99 (0.98, 1.00)	0.06	0.98 (0.97, 0.99)	0.00
PCI subscale for distraction	1.26 (0.98, 1.62)	0.07		
PCI subscale for transformation			1.07 (0.98, 1.14)	0.06
PCI subscale for worrying	0.63 (0.42, 0.95)	0.03		
AUC	0.69 (0.66, 0.73)		0.69 (0.64, 0.73)	
Nagelkerke's R^2	0.15		0.14	
Hosmer-Lemeshow statistic	13.49	0.14	10.18	0.34

* For the multivariable regression analyses, prognostic factors were selected according to variable selection steps 3 and 4 as described in the Statistical analysis section. To = baseline; PCI = Pain Coping Inventory, AUC = area under the receiver operating characteristic curve. See **Table 1** for additional definitions. † Categories are based on the definition of ethnic minorities of Statistics Netherlands, whereby Western immigrants of Indonesian and Japanese origin are analysed as a separate group.

worrying (AUC = 0.69 [95% CI 0.66, 0.73], Nagelkerke's R^2 = 0.15, Hosmer-Lemeshow statistic = 13.49; P = 0.14). ORs and 95% CIs are given in **Table 4**. The AUC of the univariable logistic regression model with only the baseline WOMAC-PF score as an independent variable was 0.61 (95% CI 0.57, 0.65).

The final multivariable linear regression model for participants with knee symptoms identified the following 5 baseline prognostic factors for 2-year worsening on the continuous outcome measure of activity limitations: low WOMAC-PF score (few activity limitations at baseline, B = -0.43; 95% CI -0.50, -0.36), non-Western ethnicity (B = 5.12 [95% CI 0.24, 10.01]) or Indonesian ethnicity (B = 4.42 [95% CI 0.46, 8.38]), pain on palpation of the joint line (B = 2.56 [95% CI 1.27, 3.86]), no intra-articular fluid (positive refill test: B = -2.20 [95% CI -4.58, 0.18]), and low Short Form 36 (SF-36) bodily pain score (higher pain at baseline, B = -0.10 [95% CI -0.15, -0.06]). The R^2 of the model was 0.20, which is an increase in explained variance of 6% compared to the univariable regression model with only the baseline WOMAC-PF score as an independent variable (R^2 = 0.14).

Prognostic factors in participants with hip symptoms

The prognostic factors analysed in the univariable and multivariable regression analyses per group, and their association with the dichotomous outcome measure of activity limitations in participants with hip symptoms are given in **Table 2**.

The final multivariable logistic regression model identified the following 7 baseline prognostic factors for a poor 2-year outcome on activity limitations: low WOMAC-PF score (few activity limitations at baseline), bilateral hip pain, morning stiffness in the knee, high comorbidity count, reduced active hip flexion, poor general health perception, and frequent use of the pain coping strategy transformation (AUC = 0.69 [95% CI 0.64, 0.73], Nagelkerke's R^2 = 0.14, Hosmer-Lemeshow statistic = 10.18; P = 0.34). ORs and 95% CIs are given in **Table 4**. The AUC of the univariable logistic regression model with only the baseline WOMAC-PF score as independent variable was 0.55 (95% CI 0.50, 0.60).

The final multivariable linear regression model for participants with hip symptoms identified the following 2 baseline prognostic factors for 2-year worsening on the continuous outcome measure of activity limitations: low WOMAC-PF score (few activity limitations at baseline, B = -0.46 [95% CI -0.55, -0.37]), and a low SF-36 bodily pain score (higher pain at baseline, B = -0.09 [95% CI -0.15, -0.04]). The R^2 of the model was 0.20, which is an increase in explained variation of 1% compared with the univariable regression model with only the baseline WOMAC-PF score as independent variable, for which the R^2 was 0.19.

Discussion

The present study investigated predictors of the 2-year course of activity limitations in 1,002 participants with early OA of the knee and/or hip. Overall, half of the participants were classified as experiencing a poor 2-year outcome on the dichotomous measure of activity limitations. On the continuous measure, a slight improvement in activities was observed after 2 years of follow-up. The correlation between activity limitations at baseline and after 2 years was moderate.

Our observations are in line with recent studies in which the course of activity limitations in knee and hip OA was found to deteriorate slowly over time.[8] The slight decrease we observed in activity limitations might be explained by the natural course of OA. This course varies considerably over time, with fluctuating severity of symptoms.[2,8] CHECK is an inception cohort: participants were included based on knee and/or hip symptoms. Therefore, it is likely that there was a relatively high prevalence of exacerbation of symptoms at the time of inclusion. It is plausible that after 2 years, some of these symptoms had improved (regression towards the mean [RTM]). However, the alternative to an inception cohort is an open population study, which is less efficient due to the inclusion of non-symptomatic patients. Moreover, the observed decrease in activity limitations was very small and only statistically significant in participants with knee symptoms due to the large sample size.

In accordance with studies in established OA, large inter-individual differences in the course of activity limitations were observed.[8] Apparently, already at an early stage of the disease the course of activity limitations is variable. Identification of prognostic factors is therefore highly relevant. This enables physicians to identify patients at risk for development of activity limitations and to select patients eligible for treatment.

One of the strongest prognostic factors for a poor outcome on activity limitations in participants with knee symptoms was concomitant hip pain. In participants with hip symptoms, we found that morning stiffness of the knee was a prognostic factor for a poor outcome on activity limitations. Apparently, patients with both knee and hip symptoms have a relatively high risk at developing activity limitations. An explanation for this finding could be that having both early knee and hip symptoms is a sign of the development of generalized OA. Because generalized OA is characterized by involvement of ≥ 3 joints, it is likely that this subset of OA leads to more activity limitations. In addition, patients with both knee and hip symptoms are probably less able to compensate for limitations in their symptomatic knee or hip by using their ipsilateral hip or knee joint in comparison with patients with only knee or only hip symptoms.

Comorbidity count was identified as prognostic factor for a poor outcome on activity limitations in both participants with knee symptoms and participants with hip symptoms. OA is a disease with one of the highest rates of comorbidity,[33] and a relationship with activity limitations has frequently been shown.[8] Therefore, future research should address how comorbidity influences activity limitations, and how therapeutic interventions aimed at preventing activity limitations in OA can be adjusted/optimized for OA patients with comorbidities.

The predictors of activity limitations identified in the present study are similar to predictors found in studies in established OA. Associations between activity limitations in knee and/or hip OA and ethnicity,[11,34,35] multiple-site joint pain,[36,37] morning stiffness,[38] comorbidity count,[5,39] BMI,[8] impaired hip flexion,[33] bodily pain,[8] general health perception,[6] and the pain coping strategy transformation[40] have been identified previously in established OA. Furthermore, the results of the present study confirm earlier observations that radiographic status is not closely associated with physical function in patients with knee or hip OA.[41-43] Apparently in both early and established OA the same underlying processes of an increase in activity limitations are playing a role.

Few activity limitations at baseline was found to be a prognostic factor for an increase in activity limitations. This finding is contrary to expectation and previous observations.[5] The contrasting results might be explained by a floor effect of the WOMAC, which may

have caused RTM. In the present study, participants with few activity limitations at baseline (a WOMAC-PF baseline score of 0-5 in the knee stratum or of 0-6 in the hip stratum) had a relatively high risk of declining. They could only remain stable or increase in activity limitations over time, whereas participants with more activity limitations at baseline could both improve and deteriorate on the WOMAC-PF scale. Therefore, in future studies of activity limitations in patients with early OA, the use of an outcome instrument with an extended measurement range for few activity limitations is recommended.

In the multivariable logistic model for participants with knee symptoms, younger age was found to be a prognostic factor for an increase in activity limitations. This association is contrary to associations found in other longitudinal studies of activity limitations in patients with OA.[6,7] The contrasting observations might be explained by the fact that our study population was younger (mean ± SD age of 56 ± 5 years) than the other study populations (mean ± SD ages of 65 ± 9 and 69 ± 10 years, respectively).[6,7] OA related symptoms at a relatively young age might be indicative of a more severe and progressive course of the disease, with an associated poor functional prognosis.

In the present study, we investigated the predictive values of the candidate prognostic factors by means of logistic and linear regression analyses. The linear regression models identified fewer prognostic factors for the course of activity limitations than the logistic regression models, possibly because the results of the linear regression analyses were more influenced by a floor effect of the WOMAC-PF. Therefore, to avoid bias due to a possible floor effect, we conducted additional linear regression analyses in which we adjusted for the WOMAC-PF baseline score in all steps of the model building process. The additional linear regression analyses with WOMAC-PF baseline adjustment identified almost the same prognostic factors as the logistic regression models. In both participants with knee symptoms and participants with hip symptoms 6 prognostic factors identified in the logistic analyses were also identified in the linear analyses with WOMAC-PF baseline adjustment.

Some comments have to be made about the applicability of the present study's results in clinical practice. First, plotting the WOMAC-PF change score against the WOMAC-PF baseline score identified that a floor effect of the WOMAC-PF has caused RTM.[44] The degree in which participants could improve in activities was limited by this floor effect. Therefore, it is likely that the slight decrease in activity limitations we found was an underestimation of the true 2-year decrease in activity limitations.

Second, the discriminative ability and the variance in outcome accounted for by the presented regression models are relatively low. Because we did not correct for overfitting the presented regression coefficients, the explained variance and discriminative ability of the models may have been overoptimistic. Our models need validation and further evaluation before they can be used clinically in actual patient care.[45] It is expected that a longer follow-up time is necessary for constructing reliable prediction rules for use in clinical practice. Thus, further research on predictors for activity limitations using a longer follow-up time is recommended.

Finally, the overlap in predictors for a poor outcome on activity limitations in participants with knee symptoms and participants with hip symptoms was possibly caused by the overlap in data used in both the knee and hip analyses. Nevertheless, many older people with joint pain in the lower limb have more than one joint affected.[37] Therefore our results seem to be applicable to the typical knee and hip OA population.

In conclusion, participants overall reported little change in activity limitations after 2 years. However, large between-subject differences were observed in the course of activity limitations. The course of activity limitations is to some extent predictable already at an early stage of knee and hip OA.

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