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Chapter 3

Three trajectories of activity limitations in early symptomatic knee osteoarthritis: a 5-year follow-up study

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Abstract

Objectives. Knee osteoarthritis (OA) is a leading cause of activity limitations. The knee OA population is likely to consist of subgroups. The aim of the present study was to identify homogeneous subgroups with distinct trajectories of activity limitations in patients with early symptomatic knee OA, and to describe characteristics of these subgroups.

Methods. Follow-up data over a period of 5 years of 697 participants with early symptomatic knee OA from the Cohort Hip and Cohort Knee (CHECK) were used. Activity limitations were measured yearly with the Western Ontario and McMaster Universities Osteoarthritis Index. Latent class growth analyses identified homogeneous subgroups with distinct trajectories of activity limitations. Multivariable regression analyses examined differences in characteristics between the subgroups.

Results. Three subgroups were identified. Participants in Subgroup 1 ('good outcome'; $n = 330$) developed or displayed slight activity limitations over time. Participants in Subgroup 2 ('moderate outcome'; $n = 257$) developed or displayed moderate activity limitations over time. Participants in subgroup 3 ('poor outcome'; $n = 110$) developed or displayed severe activity limitations over time. Compared to the 'good outcome' subgroup, the 'moderate outcome' and 'poor outcome' subgroups were characterized by: younger age, higher body-mass index, greater pain, bony tenderness, reduced knee flexion, hip pain, osteophytosis, ≥ 3 comorbidities, lower vitality, or avoidance of activities.

Conclusions. Based on the 5-year course of activity limitations, we identified homogeneous subgroups of knee OA patients with good, moderate or poor outcome. Characteristics of these subgroups were consistent with existing knowledge on prognostic factors regarding activity limitations, which supports the validity of this classification.

Introduction

Knee osteoarthritis (OA) is a leading cause of activity limitations among older adults.¹ In the OA population, activity limitations increase slowly over time,² while the individual course is highly variable: some patients seem to be stable or even improve, whereas others deteriorate.³⁻⁵

The most common approach in describing the course of activity limitations in knee OA patients is to report a single longitudinal trajectory for the entire study population. Usually, the change score on activity limitations between two time points is presented, averaged over all patients. Because the population of knee OA patients is heterogeneous and consists of different phenotypes or subgroups,⁶⁻⁸ it is suboptimal to describe the course of activity limitations using the average of the population.⁹ Latent class modelling has been suggested as the most appropriate technique for examining inter-individual differences in intra-individual change.⁹ This technique takes into account heterogeneity between subgroups.

The aim of the present study was to identify homogeneous subgroups with distinct trajectories of activity limitations in patients with early symptomatic knee OA, and to describe characteristics of these subgroups.

Methods

Study design

A 5-year follow-up study of a sample of 701 individuals from the Cohort Hip and Cohort Knee (CHECK) study with early symptomatic OA of the knee was undertaken.¹⁰ Measurements were performed every year, resulting in six measurements over time.

Parent study

The CHECK cohort was formed between October 2002 and September 2005. It consists of 1,002 individuals with early symptomatic knee and/or hip OA.¹⁰ Ten general and academic hospitals in the Netherlands participated. Participants were recruited via general practitioners in the surroundings of the participating centres, through announcements in local newspapers and on the Dutch Arthritis Association website. The physicians in the participating centres checked whether participants fulfilled the inclusion criteria. The study was approved by the medical ethics committees of the participating centres. All participants gave their written informed consent before entering the study.

Study population

Inclusion criteria of the CHECK study are: (1) being aged between 45-65 years; (2) pain and/or stiffness in the knee and/or hip; (3) having at least two of the following clinical criteria for knee OA of the American College of Rheumatology (ACR): knee pain, morning stiffness < 30 minutes, crepitus or bony tenderness (participants who met this criterion were followed annually);¹¹ and (4) having had no consultation with a physician for these symptoms (or first consultation was within the 6 months immediately preceding inclusion). Exclusion criteria were: having any other pathological condition that could explain the knee and hip symptoms; having a comorbidity that would not allow physical evaluation and/or follow-up of at least 10 years duration; malignancy in the last 5 years; and inability to understand the Dutch language.¹⁰ For the present study we selected participants with knee pain, who had at least one follow-up measurement of activity limitations.

Measurements

Activity limitations were measured annually with the physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC-PF).^{12,13} Scores range from 0 to 68, with higher scores indicating greater activity limitations.

Baseline data were collected on participant characteristics (i.e. age, gender and body-mass index (BMI)), signs and symptoms (i.e. numeric rating scale (NRS) for pain during the last week (0-10), presence of bilateral knee pain, fulfilling the clinical criteria for knee OA of the ACR,¹¹ morning stiffness, bony tenderness, crepitus, hip pain, and total knee or hip replacement), radiographic features (i.e. osteophytosis, joint space narrowing, Kellgren and Lawrence grade¹⁴), comorbidity count, and psychological factors (i.e. vitality measured with the Short Form 36 Health Survey (SF-36)¹⁵ and avoidance of activities measured with the resting subscale of the Pain Coping Inventory^{16,17}). Details on the study protocol have been published elsewhere.¹⁰

Statistical analyses

To identify homogeneous subgroups of patients with distinct trajectories of activity limitations as measured by the WOMAC-PF, we conducted latent class growth analysis (LCGA). In LCGA latent trajectory classes (i.e. categorical latent variables) are used to allow homogeneous groups of individual longitudinal trajectories to vary around different means.^{9,18,19} The variance and covariance estimates of the growth factors (i.e. rate of change or slope of the longitudinal trajectories) within each class or subgroup are assumed to be fixed to zero.^{9,19} As a result, all individual longitudinal trajectories within a subgroup are homogeneous.⁹

The latent class growth models were estimated using full information maximum likelihood. Linear, quadratic and cubic trajectories were modelled. The course of activity limitations was best described by linear trajectories. The fit of four models with two to five linear trajectories were tested. The most appropriate model was determined based on fit indices, the entropy statistic, classification reliability, and considerations of parsimony and clinical relevance.⁹ The fit indices used were the Bayesian information criterion (BIC), the Vuong-Lo-Mendell-Rubin likelihood ratio test (LMR-LRT), and the bootstrap likelihood ratio test (BLRT).^{19,20} The BIC, LMR-LRT and BLRT are used for comparison across several plausible models.²⁰ The lowest value of BIC indicates the best fitting model.²⁰ Significant p values

($p < 0.05$) for the LMR-LRT and BLRT indicate that a model with a k number of trajectory subgroups has a better fit than a model with a $k-1$ number of trajectory subgroups.^{9,20} The entropy statistic and posterior probabilities of group membership were used as measures for the reliability of the trajectory subgroups. The entropy statistic and posterior probabilities of group membership range from 0 to 1 and have to be reasonably high: values close to 1 indicate good classification.⁹

To improve our understanding of the trajectory subgroups resulting from the LCGA, a linear mixed model with random effects calculated individual trajectories (slopes) of the 5-year course of activity limitations. For each subgroup, the individual slopes were plotted against the individual baseline WOMAC-PF scores.

Univariable and multivariable logistic regression analyses examined differences in demographic, clinical and psychological characteristics between the trajectory subgroups. One trajectory subgroup was chosen as a reference; the other trajectory subgroups were compared to that reference. For calculation of the mean WOMAC-PF change score and the regression analyses, a Multivariate Imputation by Chained Equation (MICE) procedure generated 10 multiple imputed datasets to estimate missing values.²¹ In the multivariable analyses we used a backward selection method (p -removal 0.05) taking into account the imputed datasets by using Rubin's pooling rules.²² The ORs and 95% CIs of the final regression models were estimated over the 10 imputed data sets. Furthermore, the area under the receiver operating characteristic curve (AUC), Hosmer-Lemeshow goodness-of-fit test,²³ and Nagelkerke's R^2 statistic²⁴ were calculated. Bootstrapping techniques (250 replications) adjusted the estimated ORs for overfitting and the model performance for overoptimism.²⁵ The shrinkage factor, a result of the bootstrap analyses, is a measure of overfitting. ORs can be corrected for overfitting by taking the exponent of the regression coefficient multiplied by the shrinkage factor.

Mplus V. 6.12 was used for LCGA; SAS V. 9.2 to calculate the individual slopes; SPSS V. 18 to generate descriptive statistics of the study population; and R software V. 2.14.1 for the MICE procedure and the regression analyses on the imputed data sets.

Results

Study population

Of 701 participants included, 14 (2%) and 12 (1.7%) participants underwent total knee and total hip replacement during the 5-year follow-up, respectively. The post-surgery WOMAC-PF data of these participants were coded as missing. As a result, four participants were excluded from the analyses. The baseline characteristics of the study population ($n = 697$) are presented in **Table 1**.

Missing data

For the WOMAC-PF, the number (percentage) of participants with missing data was 15 (2.2%) at baseline (T₀), 32 (4.6%) at T₁, 36 (5.2%) at T₂, 38 (5.5%) at T₃, 57 (8.2%) at T₄, and 74 (10.6%) at T₅. In all, 140 participants had data missing at more than one time point

Table 1. Baseline characteristics of the study population

Baseline characteristics	Total (n = 697)	Subgroup 1 (n = 330) 'good outcome'	Subgroup 2 (n = 257) 'moderate outcome'	Subgroup 3 (n = 110) 'poor outcome'
<i>Demographics</i>				
Age (years)	56.0 ± 5.1	56.2 ± 5.2	55.8 ± 5.2	55.6 ± 4.8
Female, no. (%)	567 (81.3)	262 (79.4)	213 (82.9)	92 (83.6)
Body-mass index (kg/m ²)	26.6 ± 4.3	25.5 ± 3.6	27.4 ± 4.4	28.0 ± 4.9
<i>Clinical signs and symptoms</i>				
NRS for knee pain (range 0-10)	3.7 ± 2.1	2.9 ± 1.9	4.0 ± 1.8	5.4 ± 1.8
Bilateral knee pain, no. (%)	399 (57.2)	184 (55.8)	141 (54.9)	74 (67.3)
Clinical knee OA, no. (%)	606 (86.9)	279 (84.5)	223 (86.8)	104 (94.5)
Morning stiffness knee, no. (%)	497 (71.3)	218 (66.1)	187 (72.8)	92 (83.6)
Bony tenderness, no. (%)	365 (52.4)	145 (43.9)	146 (56.8)	74 (67.3)
Crepitus, no. (%)	367 (52.7)	178 (53.9)	126 (49.0)	63 (57.3)
Active knee flexion range (degrees)	133.3 ± 10.0	135.2 ± 9.0	132.4 ± 9.7	130.0 ± 12.3
Total knee replacement after 5-year follow-up, no. (%)	12 (1.7)	2 (0.6)	5 (1.9)	5 (4.5)
Hip pain, no. (%)	348 (49.9)	133 (40.3)	144 (56.0)	71 (64.5)
Total hip replacement after 5-year follow-up, no. (%)	10 (1.4)	1 (0.3)	4 (1.6)	5 (4.5)
<i>Radiographic features</i>				
KL-grade = 0, no. (%)	295 (42.3)	155 (47.0)	94 (36.6)	46 (41.8)
KL-grade = 1, no. (%)	321 (46.1)	150 (45.5)	117 (45.5)	54 (49.1)
Osteophytosis, no. (%)	122 (17.5)	51 (15.5)	44 (17.1)	27 (24.5)
Joint space narrowing, no. (%)	107 (15.4)	40 (12.1)	42 (16.3)	25 (22.7)
<i>Comorbidity count</i>				
0, no. (%)	166 (23.8)	100 (30.3)	52 (20.2)	14 (12.7)
1, no. (%)	205 (29.4)	107 (32.4)	73 (28.4)	25 (22.7)
2, no. (%)	151 (21.7)	76 (23.0)	57 (22.2)	18 (16.4)
≥ 3, no. (%)	162 (23.2)	44 (13.3)	70 (27.2)	48 (43.6)
<i>WOMAC data</i>				
WOMAC pain (range 0-20)	5.3 ± 3.4	3.5 ± 2.7	6.0 ± 2.7	9.0 ± 2.9
WOMAC stiffness (range 0-8)	2.8 ± 1.6	2.1 ± 1.4	3.1 ± 1.4	4.4 ± 1.5
WOMAC function (range 0-68)	16.8 ± 11.6	9.8 ± 7.4	19.5 ± 8.5	32.7 ± 10.2
<i>Psychological factors</i>				
SF-36 vitality (range 0-100)	63.4 ± 16.8	68.5 ± 14.5	61.6 ± 16.5	51.9 ± 17.3
PCI resting (range 5-20)	9.3 ± 2.5	8.7 ± 2.4	9.4 ± 2.4	10.9 ± 2.7

Values are presented as mean ± SD unless otherwise indicated. KL-grade = Kellgren and Lawrence grade; NRS = numeric rating scale; OA = osteoarthritis; PCI = Pain Coping Inventory; SF-36 = Short Form 36 Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

(mean 1.8 time points). The mean number of missing values per independent variable was 19.9 (2.9%) (median: 13 (1.9%), range: 0-78 (0-11.2%)).

Five-year course of activity limitations

The mean (SD) baseline WOMAC-PF score was 16.8 (11.6). In the study population as a whole, little change in activity limitations was observed between baseline and 5-year follow-up: the mean WOMAC-PF score increased with 1.1 points (SD change = 11.5).

Subgroups based on trajectories

A linear, three-class model was identified as most appropriate, based on fit indices, entropy statistic, classification reliability, considerations of parsimony and interpretability (Table 2). Although the fit indices seemed to favour a four-class model, the three-class model showed a better entropy value and better internal reliability for each trajectory (i.e. better average posterior probabilities of group membership). In addition, Subgroups 1 and 2 in the four-class model had similar (1 and 1.2 respectively) estimated slopes, with only 45 patients assigned to the additional subgroup. Because the additional subgroup had marginal added value, we deemed the three-class model as the most appropriate.

The trajectories of the three classes or subgroups are presented in Figure 1. The three subgroups differed both in slope and baseline value of the WOMAC-PF score. To facilitate

Table 2. Fit indices, entropy and average posterior probabilities across models with different numbers of subgroups

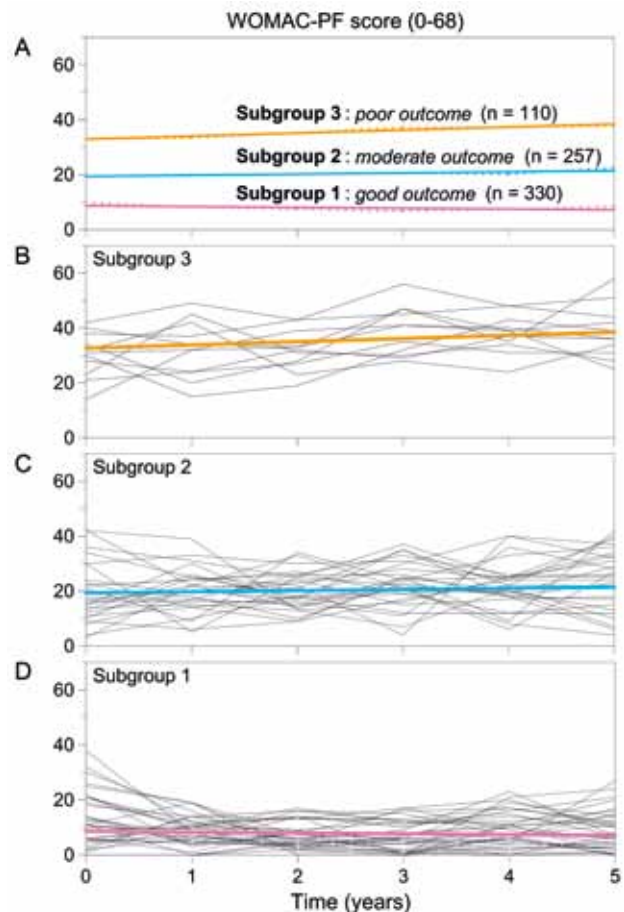
No. of subgroups	BIC	LMR-LRT p value	BLRT p value	Entropy	Posterior probabilities
2	29007.29	<0.0001	<0.0001	0.899	Subgroup 1 (n = 474): 0.98 Subgroup 2 (n = 223): 0.96
3	28299.85	0.0003	<0.0001	0.887	Subgroup 1 (n = 330): 0.97 Subgroup 2 (n = 257): 0.92 Subgroup 3 (n = 110): 0.96
4	28058.11	0.01	<0.0001	0.868	Subgroup 1 (n = 280): 0.95 Subgroup 2 (n = 236): 0.90 Subgroup 3 (n = 136): 0.89 Subgroup 4 (n = 45): 0.97
5	27969.60	0.12	<0.0001	0.817	Subgroup 1 (n = 195): 0.91 Subgroup 2 (n = 184): 0.83 Subgroup 3 (n = 176): 0.87 Subgroup 4 (n = 109): 0.88 Subgroup 5 (n = 33): 0.97

The lowest value of BIC indicates the best fitting model. Significant p-values ($p < 0.05$) for the LMR-LRT and BLRT indicate that a model with a k number of latent trajectory subgroups has a better fit than a model with a k-1 number of subgroups. Entropy and posterior probability values close to 1 indicate good classification. BIC = Bayesian information criterion; BLRT = bootstrap likelihood ratio test. LMR-LRT = Vuong-Lo-Mendell-Rubin likelihood ratio test.

interpretation of the trajectories in the subgroups, we plotted the individual slopes against the individual baseline levels of activity limitations (**Figure 2**). Subgroup 1 consisted of 330 participants (47.3%). The intercept of the trajectory of Subgroup 1 was 8.7 (95% CI: 7.8 to 9.5) and the slope was -0.3 (95% CI: -0.5 to -0.1). These participants moved from moderate or high levels of activity limitations at baseline to low levels over 5 years, or reported permanent low levels of activity limitations. For example, in **Figure 2**, the participant indicated with no. 1 reported a moderate outcome of activity limitations at T₀ and improved over 5 years of follow-up: she had a WOMAC-PF T₀ score of 19 and a slope of -2, leading to a WOMAC-PF T₅ score of 9. The participant indicated with no. 2, reported a permanent good outcome of activity limitations: he had a WOMAC-PF T₀ score of 7 and a slope of 0, leading to a WOMAC-PF T₅ score of 7. Participants in Subgroup 1 were defined as having a 'good outcome' on activity limitations.

Subgroup 2 consisted of 257 participants (36.9%). The intercept of the trajectory of Subgroup 2 was 19.3 (95% CI: 17.7 to 20.9) and the slope was 0.4 (95% CI: 0.1 to 0.8). These participants moved from fairly low or fairly high levels of activity limitations to moderate

Figure 1. Trajectories of activity limitations measured by the physical function subscale of the Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC-PF). Higher scores indicate a worse outcome. A = Observed (dotted lines) and estimated (solid lines) mean scores of the three trajectory subgroups. B = Random 10% of observed individual scores and estimated mean score of participants in Subgroup 3 ('poor outcome'). C = Random 10% of observed individual scores and estimated mean score of participants in Subgroup 2 ('moderate outcome'). D = Random 10% of observed individual scores and estimated mean score of participants in Subgroup 1 ('good outcome').



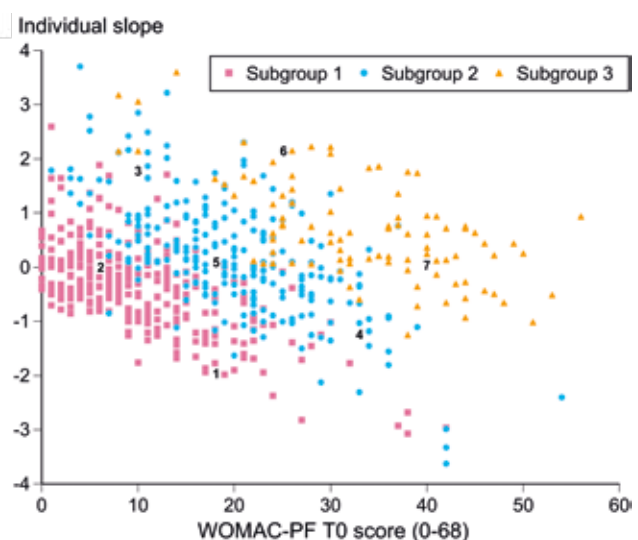
levels over 5 years (e.g. the participants indicated with no. 3 and 4 in **Figure 2**), or reported permanent moderate levels of activity limitations (e.g. the participant indicated with no. 5 in **Figure 2**). Participants in Subgroup 2 were defined as having a ‘moderate outcome’ on activity limitations.

Subgroup 3 consisted of 110 participants (15.8%). The intercept of the trajectory of Subgroup 3 was 32.7 (95% CI: 29.9 to 35.4) and the slope was 1.2 (95% CI: 0.6 to 1.7). These participants moved from low or moderate levels of activity limitations to high levels over 5 years (e.g. the participant indicated with no. 6 in **Figure 2**), or reported permanent high levels of activity limitations (e.g. the participant indicated with no. 7 in **Figure 2**). Participants in Subgroup 3 were defined as having a ‘poor outcome’ on activity limitations.

Characteristics of the subgroups

Results of univariable and multivariable logistic regression analyses comparing participants in the subgroups are shown in **Tables 3** and **4**. Multivariable regression analyses showed that, after adjustment for all other baseline characteristics, participants in Subgroup 2 (‘moderate outcome’), compared to participants in Subgroup 1 (‘good outcome’), were characterized by: a higher BMI, a higher score on the NRS for knee pain, hip pain, presence of ≥ 3 comorbidities, and a lower score on the SF-36 subscale for vitality (**Table 4**). Participants in Subgroup 3 (‘poor outcome’), compared to participants in Subgroup 1 (‘good outcome’), were characterized by: a younger age, a higher score on the NRS for knee pain, presence of bony tenderness, a lower range of active knee flexion, hip pain, presence of osteophytosis, presence of ≥ 3 comorbidities, a lower score on the SF-36 subscale for vitality, and a higher score on the resting subscale of the Pain Coping Inventory.

Figure 2. Plot of the individual slopes (y-axis) against the baseline scores (x-axis) on activity limitations. A slope of -1 indicates that the score on the physical function subscale of the Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC-PF) decreases on average with 1 point per year. Subgroup 1 = participants having a ‘good outcome’ on activity limitations over 5 years. Subgroup 2 = participants having a ‘moderate outcome’ on activity limitations over 5 years. Subgroup 3 = participants having a ‘poor outcome’ on activity limitations over 5 years. For explanation of the numbers 1–7 in the plot, refer the Results section of the manuscript.



Discussion

The present study used data from a 5-year follow-up period of 697 participants with early symptomatic knee OA to identify homogeneous subgroups of patients with distinct trajectories of activity limitations. Three subgroups were identified: (1) a 'good outcome', (2) a 'moderate outcome' and (3) a 'poor outcome' subgroup. The validity of this classification is supported by the demographic, clinical and psychological characteristics of these subgroups.

The 5-year change in activity limitations of the 'good outcome' and 'poor outcome' subgroup (17.2% and 18.3% of the WOMAC-PF baseline score, respectively) exceeded or almost exceeded the criterion for minimal clinically important change (i.e. 17% for improvement and 22% for worsening).²⁶ The estimated 5-year change on the WOMAC-PF was -1.5 points in the 'good outcome' subgroup, +2 points in the 'moderate outcome' subgroup, and +6 points in the 'poor outcome' subgroup. The average probability of subgroup membership for each estimated subgroup was 92% or higher, suggesting that most participants were correctly classified.

This is the first study in early symptomatic knee OA that used LCGA to examine inter-individual differences in intra-individual change in the course of activity limitations. Because LCGA uses a statistical procedure to test whether the hypothesized trajectory subgroups

Table 3. Results of univariable logistic regression analyses of baseline characteristics associated with subgroup membership (Subgroup 1 'good outcome' (n = 330) used as the reference group)

Characteristic	Subgroup 2 'moderate outcome' (n = 257)		Subgroup 3 'poor outcome' (n = 110)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, years	0.99 (0.95 to 1.02)	0.35	0.98 (0.94 to 1.02)	0.34
Female	1.26 (0.83 to 1.91)	0.29	1.33 (0.75 to 2.35)	0.33
Body-mass index, kg/m ²	1.13 (1.08 to 1.18)	<0.0001	1.16 (1.10 to 1.23)	<0.0001
NRS for knee pain (0-10)	1.40 (1.27 to 1.53)	<0.0001	1.90 (1.65 to 2.18)	<0.0001
Bilateral knee pain	0.96 (0.70 to 1.34)	0.83	1.63 (1.04 to 2.56)	0.03
Morning stiffness knee	1.37 (0.96 to 1.96)	0.08	2.62 (1.51 to 4.57)	0.0006
Bony tenderness	1.65 (1.18 to 2.29)	0.003	2.58 (1.64 to 4.05)	<0.0001
Crepitus	0.81 (0.59 to 1.13)	0.22	1.20 (0.77 to 1.86)	0.41
Active knee flexion range, degrees	0.97 (0.95 to 0.99)	0.0008	0.95 (0.93 to 0.97)	<0.0001
Hip pain	1.89 (1.36 to 2.62)	0.0002	2.70 (1.72 to 4.22)	<0.0001
Osteophytosis	1.26 (0.82 to 1.96)	0.30	1.77 (1.04 to 3.01)	0.03
Joint space narrowing	1.61 (1.00 to 2.59)	0.05	2.13 (1.21 to 3.74)	0.009
Comorbidity count ≥ 3	2.50 (1.64 to 3.80)	<0.0001	5.46 (3.32 to 8.97)	<0.0001
SF-36 vitality (0-100)	0.97 (0.96 to 0.98)	<0.0001	0.94 (0.92 to 0.95)	<0.0001
PCI resting (5-20)	1.13 (1.05 to 1.21)	0.0009	1.39 (1.26 to 1.52)	<0.0001

NRS = numeric rating scale; PCI = Pain Coping Inventory; SF-36 = Short Form 36 Health Survey.


emerge from the data, this method allows the discovery of unexpected yet potentially meaningful subgroups.²⁷ The identified subgroups remind us of the classification introduced by Sharma et al.⁵ in 2003. Based on clinical reasoning, Sharma et al.⁵ categorized their study population into good and poor outcome subgroups using a quintile grid of baseline and 3-year WOMAC-PF scores. The poor and good outcome subgroups of Sharma et al.⁵ resemble our ‘poor outcome’ and ‘good outcome’ subgroups, respectively. Our ‘moderate outcome’ subgroup is a novel finding. The classification by Sharma et al. has been used in several studies without being empirically validated. Although not specifically designed for this purpose, our study provides credence to the Sharma et al.⁵ classification, and refines it by adding the ‘moderate outcome’ subgroup. Studies in other samples are needed to externally validate our findings (i.e. replicate the three subgroups with the estimated intercepts and slopes).

In both our classification and the Sharma et al.⁵ classification, the change over time as well as the level of activity limitations at baseline define subgroups of participants with distinct trajectories of activity limitations. The ‘poor outcome’ subgroup showed more activity

Table 4. Multivariable logistic regression models of baseline characteristics associated with subgroup membership (Subgroup 1 ‘good outcome’ (n = 330) used as the reference group)

Characteristic	Subgroup 2 ‘moderate outcome’ (n = 257)			Subgroup 3 ‘poor outcome’ (n = 110)		
	OR (95% CI)	p Value	OR shrunk	OR (95% CI)	p Value	OR shrunk
Age, years				0.94 (0.88 to 1.00)	0.04	0.94
Body-mass index, kg/m ²	1.12 (1.07 to 1.18)	<0.0001	1.12			
NRS for knee pain (0-10)	1.35 (1.22 to 1.49)	<0.0001	1.33	1.81 (1.51 to 2.16)	<0.0001	1.72
Bony tenderness				2.63 (1.38 to 5.02)	0.003	2.41
Active knee flexion range, degrees				0.96 (0.93 to 1.00)	0.03	0.97
Hip pain	1.54 (1.07 to 2.22)	0.02	1.51	2.34 (1.22 to 4.48)	0.01	2.17
Osteophytosis				5.68 (2.57 to 12.55)	<0.0001	4.85
Comorbidity count ≥ 3	1.76 (1.10 to 2.81)	0.02	1.72	3.28 (1.62 to 6.64)	0.001	2.95
SF-36 vitality (0-100)	0.98 (0.97 to 0.99)	0.002	0.98	0.96 (0.94 to 0.98)	0.0001	0.96
PCI resting (5-20)				1.16 (1.02 to 1.31)	0.02	1.14
<i>Model quality parameters</i>						
Slope	0.96			0.91		
AUCshrunk	0.74			0.90		
Nagelkerke’s R ² shrunk	0.22			0.55		
p-Value Hosmer-Lemeshow statistic	0.25			0.83		

AUCshrunk = area under the receiver operation characteristic curve after adjustment for overoptimism using bootstrapping techniques; Nagelkerke’s R²shrunk = Nagelkerke’s R squared after adjustment for overoptimism using bootstrapping techniques; NRS = numeric rating scale; ORshrunk = OR after adjustment for overfitting using bootstrapping techniques; PCI = Pain Coping Inventory; SF-36 = Short Form 36 Health Survey; Slope = shrinkage factor obtained after bootstrapping, well calibrated models have a slope of 1.



limitations at baseline and a greater worsening of activity limitations than the ‘moderate outcome’ and ‘good outcome’ subgroup. This can be explained by a “horse-racing effect” (i.e. a person whose level of activity limitations has been increasing faster than average previously – and who as a result of this has a higher than average level of activity limitations at baseline – will continue to increase in activity limitations faster than average in the future).²⁸ There were also participants who did not change in activity limitations. Apparently, although our study population was recruited at inception of symptoms, some participants have already deteriorated before inclusion and showed no or little additional change during the study. This emphasizes the need to consider both factors related to change and factors related to stable low function states in developing prevention programs, and is an interesting finding for further research.⁵

The characteristics of the subgroups are consistent with existing knowledge on prognostic factors regarding activity limitations in knee OA, which supports the validity of our classification. Compared to participants in the ‘good outcome’ subgroup, participants in the ‘moderate outcome’ and ‘poor outcome’ subgroups were characterized by: younger age, a higher BMI, more pain, bony tenderness, a reduced range of knee flexion, hip pain, osteophytosis, ≥ 3 comorbidities, lower vitality, or avoidance of activities. This is in accordance with other longitudinal studies that have identified higher BMI,^{2,4,5,29} greater knee pain,^{2,5,30} bony tenderness,²⁹ concomitant hip pain,⁴ severity of radiographic knee OA,²⁹ comorbidity,^{4,30,31} low vitality,³¹ and avoidance of physical activities³⁰ as risk factors for a poor outcome on activity limitations. Osteophytosis, comorbidities, bony tenderness, and concomitant hip pain were strongest associated with membership of the ‘poor outcome’ subgroup.

A major strength of our study is that the study population was assembled at inception of symptoms. This is important because if observation is begun at different points in the course of OA for the various participants, description of their prognosis will lack precision.³² Our study may be criticized for not studying participants meeting criteria for clinical OA or radiographic OA. The pathophysiology of OA is poorly understood; there is little relation between clinical features and structural tissue changes, and some OA phenotypes may develop radiographic signs only late in the disease process.⁸ We believe that the onset of symptoms is the best starting point to study the course of the disease, including the course of activity limitations. A sensitivity analysis in participants who fulfilled the ACR clinical criteria for knee OA ($n = 606$) yielded similar results (data not shown). Additional strengths are the longitudinal design with six measurements over a 5-year follow-up period; the use of LCGA taking into account heterogeneity in the course of activity limitations; the use of a plot of individual change against the baseline level of activity limitations, which facilitated interpretation of trajectories in the three identified subgroups; and the regression analyses to describe differences in characteristics between the subgroups. A final comment concerns LCGA: although LCGA is an attractive method to identify homogeneous subgroups, the choice of the most appropriate number of subgroups remains somewhat arbitrary, requiring clinical and statistical judgment.^{9,20} Based on strong arguments (see Results section), we judged the three-group model as most appropriate.

For clinicians it is important to be aware that the knee OA population consists of subgroups with differing prognoses regarding activity limitations. Furthermore, identification of homogeneous subgroups may contribute to the development of tailored preventive interventions in knee OA patients.^{5–8}

In conclusion, based on the 5-year course of activity limitations, three trajectory subgroups of knee OA patients were identified. The characteristics of these subgroups were consistent with existing knowledge on prognostic factors regarding activity limitations, which supports the validity of this classification.

References

1. Michaud CM, McKenna MT, Begg S, Tomijima N, Majmudar M, Bulzacchelli MT et al. The burden of disease and injury in the United States 1996. *Popul Health Metr* 2006;**4**:11.
2. van Dijk GM, Dekker J, Veenhof C, van den Ende CH. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. *Arthritis Rheum* 2006;**55**:779-85.
3. Dekker J, van Dijk GM, Veenhof C. Risk factors for functional decline in osteoarthritis of the hip or knee. *Curr Opin Rheumatol* 2009;**21**:520-4.
4. Holla JF, Steultjens MP, Roorda LD, Heymans MW, Ten Wolde S, Dekker J. Prognostic factors for the two-year course of activity limitations in early osteoarthritis of the hip and/or knee. *Arthritis Care Res (Hoboken)* 2010;**62**:1415-25.
5. Sharma L, Cahue S, Song J, Hayes K, Pai YC, Dunlop D. Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. *Arthritis Rheum* 2003;**48**:3359-70.
6. Knoop J, van der Leeden M, Thorstensson CA, Roorda LD, Lems WF, Knol DL et al. Identification of phenotypes with different clinical outcomes in knee osteoarthritis: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2011;**63**:1535-42.
7. Felson DT. Identifying different osteoarthritis phenotypes through epidemiology. *Osteoarthritis Cartilage* 2010;**18**:601-4.
8. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet* 2011;**377**:2115-26.
9. Jung T, Wickrama KAS. An introduction to latent class growth analysis and growth mixture modeling. *Soc Pers Psychol Compass* 2008;**2**:302-17.
10. Wesseling J, Dekker J, van den Berg WB, Bierma-Zeinstra SM, Boers M, Cats HA et al. CHECK: Cohort Hip & Cohort Knee; similarities and differences with the Osteoarthritis Initiative. *Ann Rheum Dis* 2009;**68**:1413-9.
11. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;**29**:1039-49.
12. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;**15**:1833-40.
13. Roorda LD, Jones CA, Waltz M, Lankhorst GJ, Bouter LM, van der Eijken JW et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. *Ann Rheum Dis* 2004;**63**:36-42.
14. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;**16**:494-502.
15. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473-83.
16. Kraaimaat FW, Evers AW. Pain-coping strategies in chronic pain patients: psychometric characteristics of the pain-coping inventory (PCI). *Int J Behav Med* 2003;**10**:343-63.
17. Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF et al. Avoidance of activities in early symptomatic knee osteoarthritis: results from the CHECK cohort. *Ann Behav Med* 2012;**44**:33-42.

18. Verkleij SP, Hoekstra T, Rozendaal RM, Waarsing JH, Koes BW, Luijsterburg PA et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. *Ann Rheum Dis* 2012;**71**:1517-23.
19. Muthén LK, Muthén BO. *Mplus user's guide*. Sixth ed. Los Angeles, CA: Muthén & Muthén; 2010.
20. Nylund KL, Asparouhov T, Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a monte carlo simulation study. *Structural Equation Modeling* 2007;**14**:535-69.
21. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999;**18**:681-94.
22. Wood AM, White IR, Royston P. How should variable selection be performed with multiply imputed data? *Stat Med* 2008;**27**:3227-46.
23. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley & Sons; 1989.
24. Nagelkerke NJD. A note on a general definition of the coefficient of determination. *Biometrika* 1991;**78**:691-2.
25. Steyerberg EW. *Clinical prediction models: a practical approach to development, validation, and updating*. New York: Springer Science & Business Media; 2009.
26. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol* 2002;**29**:131-8.
27. Andruff H, Carraro N, Thompson A, Gaudreau P. Latent class growth modelling: a tutorial. *Tutor in Quant Methods Psychol* 2009;**5**:11-24.
28. Peto R. The horse-racing effect. *Lancet* 1981;**2**:467-8.
29. Thomas E, Peat G, Mallen C, Wood L, Lacey R, Duncan R et al. Predicting the course of functional limitation among older adults with knee pain: do local signs, symptoms and radiographs add anything to general indicators? *Ann Rheum Dis* 2008;**67**:1390-8.
30. Pisters MF, Veenhof C, van Dijk GM, Heymans MW, Twisk JW, Dekker J. The course of limitations in activities over 5 years in patients with knee and hip osteoarthritis with moderate functional limitations: risk factors for future functional decline. *Osteoarthritis Cartilage* 2012;**20**:503-10.
31. van Dijk GM, Veenhof C, Lankhorst GJ, van den Ende CH, Dekker J. Vitality and the course of limitations in activities in osteoarthritis of the hip or knee. *BMC Musculoskelet Disord* 2011;**12**:269.
32. Fletcher RH, Fletcher SW. *Clinical epidemiology: the essentials*. 4th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.