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

Holla, J.F.M.

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Chapter 5

Risk factors and outcome of pain-related avoidance of activities in persons with early symptomatic knee osteoarthritis: a 5-year follow-up study

Jasmijn F.M. Holla

Marike van der Leeden

Dirk L. Knol

Leo D. Roorda

Wim K.H.A. Hilberdink

Willem F. Lems

Martijn P.M. Steultjens

Joost Dekker

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Abstract

Objective. It has been hypothesized (1) that pain and low vitality lead to an increase in avoidance of activities in persons with early symptomatic knee osteoarthritis (OA), and (2) that avoidance of activities leads to an increase in activity limitations. The present study aimed to evaluate these hypotheses.

Methods. Baseline, 2-year and 5-year follow-up data of 828 participants from the Cohort Hip and Cohort Knee (CHECK) study with early symptomatic knee OA were used. Autoregressive generalized estimating equations (GEE) and linear regression models were used to analyse the longitudinal and cross-sectional associations between self-reported knee pain, vitality, pain-related avoidance of activities and activity limitations. The models were adjusted for the covariates age, gender, education level, body-mass index, comorbidity, radiographic severity, and hip pain.

Results. (1) In longitudinal analyses, knee pain and vitality predicted a subsequent increase in avoidance of activities. (2) Pain-related avoidance of activities predicted a subsequent increase in activity limitations, however this relationship lost statistical significance ($p = 0.089$) after adjustment for covariates. Cross-sectional analyses showed strong relationships between knee pain, low vitality, pain-related avoidance of activities and activity limitations at all time-points.

Conclusions. In persons with early symptomatic knee OA, knee pain and low vitality lead to a subsequent increase in avoidance of activities. Pain-related avoidance of activities is related to activity limitations at inception of symptoms but also years later. Therefore, it can be recommended to monitor and target avoidance of activities at various stages of the disease.

Introduction

Osteoarthritis (OA) of the knee is an important cause of limitations in activities such as walking and lifting objects in older adults.[1] Activity limitations, defined by the World Health Organization as difficulties in executing activities,[2] generally develop slowly over time. However, there is a considerable inter-individual variation: some persons gradually worsen, others remain stable, and still others improve.[3,4] Inter-individual variation in activity limitations is predicted by differences in pain levels and pain coping strategies.[3,4] Several studies have demonstrated that the pain coping strategy 'avoidance of activities' is associated with activity limitations in persons with knee OA.[4-8] Pain-related avoidance of activities refers to avoidance of physical activities to prevent pain from occurring.[9,10]

The 'avoidance model' explains how pain-related avoidance of activities may lead to activity limitations in persons with knee OA.[5,8,11] According to this model, at an early-stage of the disease one experiences knee pain during activities. This leads to the expectation that renewed activity will cause greater pain. In the short term, avoidance may lead to less pain, due to the decreased load on the affected joint. However, in the longer term, inactivity results in physical deconditioning, most notably muscle weakness.[5,8,9,11] Muscle weakness leads to an increase in activity limitations.[7,9,12-13] In addition, psychological distress, especially low vitality, is hypothesized to strengthen the tendency to avoid activities, and thereby to lead to activity limitations.[5,14]

Little is known about the course of avoidance of activities in persons with OA of the knee. Dunlop et al.[15] used data from the Osteoarthritis Initiative (OAI) to study the one-year course of self-reported physical activity in 2301 persons with radiographic knee OA. They found that over one year, 48% of participants stayed as active as one year before, 23% showed an increase in physical activity, and 29% showed a decrease in physical activity. Studies with a longer follow-up period are lacking. The long-term course of avoidance of activities can best be examined in early disease, because in this stage most can be done to prevent progression.[16]

Predictors of avoidance of activities in persons with knee OA have been examined in several cross-sectional studies. Older age, female gender, lower education level, higher body-mass index (BMI), comorbidity, pain, depressed mood, and low vitality have been associated with avoidance of activities or physical inactivity in persons with knee OA.[5,17] However, the evidence for these associations is conflicting due to differences in methodological design.[17] Furthermore, most studies on this relationship addressed persons with established OA. Longitudinal studies on predictors of avoidance of activities are lacking.[17] According to the avoidance model, activity limitation is an important adverse outcome of pain-related avoidance of activities.[5,8,9,11] Cross-sectional studies provide convincing evidence for a relationship between avoidance of activities and activity limitations in persons with established knee OA[6,18-20] and early symptomatic knee OA.[5] Due to differences in methodological design, longitudinal studies on this relationship provide conflicting evidence:

four studies did find a significant relationship,[7,21-23] whereas five others did not.[12,13,24-26] The aim of the present study was to examine predictors and the outcome of avoidance of activities in persons with early symptomatic knee OA, using the avoidance model as theoretical framework. We hypothesize (1) that knee pain and low vitality lead to an increase in pain-related avoidance of activities in persons with early symptomatic knee OA, and (2) that pain-related avoidance of activities leads to an increase in activity limitations. These hypotheses were tested in a longitudinal and cross-sectional design.

Study population and methods

Study design and population

We used 5-year follow-up data from a sample of the Cohort Hip and Cohort Knee (CHECK) cohort with early symptomatic knee OA.[27] Measurements were performed at baseline, after two years, and after five years, resulting in three measurements over time.

The CHECK cohort was formed between October 2002 and September 2005, and consists of 1002 individuals with early symptomatic knee and/or hip OA.[27] Ten academic and general hospitals in the Netherlands participated. Participants were recruited via general practitioners in the surroundings of the participating centres, and through announcements in local newspapers and on the website of the Dutch Arthritis Association. 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.

Inclusion criteria of the CHECK study were: being aged between 45 and 65 years; pain and/or stiffness in the knee and/or hip; having had no consultation with a physician for these symptoms (or first consultation was within the 6 months 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.[27] For the present study we used data of all participants who reported knee pain at baseline (n = 832) and provided sufficient data to be included in at least one analysis (n = 828 out of 832).

Measurements

Pain-related avoidance of activities was assessed with the resting subscale of the Pain Coping Inventory (PCI).[28] The PCI is a self-administered questionnaire that measures cognitive and behavioural pain coping strategies. The resting subscale consists of five items, which assess the level to which persons avoid activities when experiencing pain. Items are answered on a 4-point scale, ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which the strategy (e.g. stopping activities or taking rest by sitting or lying down) is applied when dealing with pain. The subscale scores range from 5 to 20, with higher scores indicating a more frequent use of avoidance of activities as a pain coping strategy. The PCI has been shown to be a valid measure of pain coping in persons with several chronic pain conditions[28] and also in patients with OA.[6]

Knee pain intensity was assessed with an 11-point numeric rating scale (NRS) for knee pain during the last week. The NRS has been shown to be a reliable and valid measure of pain, and is widely used in OA research.[29]

Vitality was assessed with the vitality subscale of the Short-Form 36 Health Survey (SF-36).[30] The SF-36 is a generic self-administered questionnaire. The vitality subscale consists of four items, which assess feelings of energy and fatigue. Items are answered on a 6-point scale, ranging from 1 (all of the time) to 6 (none of the time) in terms of how much of the time during the past 4 weeks one had been feeling full of pep and energy, worn out or tired. The subscale scores are linearly converted to a 0 to 100 scale, with higher scores indicating more feelings of energy and less feelings of fatigue. The SF-36 has been shown to be a reliable and valid measure of health-related quality of life in persons with OA.[30,31]

Activity limitations were assessed with the physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[32] Most items of this scale can be linked very precisely to the International Classification of Functioning, Disability, and Health (ICF) component "Activities".[33] The WOMAC is a disease specific self-administered questionnaire. The physical function subscale consists of 17 items, which assess the degree of difficulties one has in executing activities (e.g. walking or stair climbing). Items are answered on a 5-point scale, ranging from 0 (none) to 4 (extreme). The subscale scores range from 0 to 68, with higher scores indicating greater activity limitations. The WOMAC has been shown to be a reliable and valid measure of activity limitations in persons with OA.[32,34]

Additional data recorded were age, gender, education level, self-reported comorbidity count, BMI, the clinical criteria for knee OA of the American College of Rheumatology (ACR),[35] the Kellgren and Lawrence grade (KL-grade) for radiographic knee OA,[36] the clinical criteria for hip OA of the ACR,[37] and the presence of hip pain.

Statistical analysis

Descriptive statistics were used to analyse the baseline characteristics of the study population. The mean scores for the NRS for knee pain, the SF- 36 vitality subscale, PCI resting subscale, and WOMAC function subscale were calculated at baseline, 2-year, and 5-year follow-up. We used generalized estimating equations (GEE) to examine the development in these variables over time.[38]

Four GEE models were used to examine the longitudinal associations between knee pain, vitality, pain-related avoidance of activities and activity limitations. GEE is a longitudinal regression technique that accounts for the dependency of observations within individuals over time, by choosing a 'working' correlation structure.[38] In all analyses we used an exchangeable working correlation structure, which implies that within-person correlations between all measurements are equal. GEE provides a regression coefficient for each independent variable that has a combined between-participants (i.e. cross-sectional) and within-participant (i.e. longitudinal) interpretation.[38] Because we were particularly interested in longitudinal relationships, we used autoregressive models which is a way to 'remove' the cross-sectional interpretation of the regression coefficients.[38] In an autoregressive model the value of the outcome variable at time-point t is related to both the value of the independent variable and the value of the outcome variable at time-point t – 1.[38] Because of this adjustment for the value of the outcome variable at time-point t – 1, autoregressive analysis can be interpreted as modelling change in the outcome variable. In model 1, we examined whether a higher score on the NRS for knee pain and a lower score on the SF-36 vitality subscale (independent variables) were associated with a subsequent increase in avoidance of activities as measured with the PCI resting subscale (dependent variable [**Table 2**]), or whether a higher score on the PCI resting subscale (independent variable) was associated with a subsequent increase in activity limitations as measured with the WOMAC function subscale (dependent variable [**Table 4**]). In model 2, we adjusted for the covariates age, gender (i.e. female vs. male), education level (higher professional education or university vs. primary or secondary education), BMI, comorbidity count (≥3 vs. <3), KL-grade (≥2 vs. <2) and hip pain (yes vs. no). In model 2 with the WOMAC function score as dependent variable (**Table 4**) we additionally adjusted for the NRS knee pain and SF-36 vitality score. Age, gender and education level were treated as time independent variables, and the NRS for knee pain, the SF-36 vitality score, BMI, comorbidity count, KL-grade and hip pain were treated as time dependent variables. Time

Table 1. Characteristics of the study population (n = 828)

	Baseline		2-year follow-up		5-year follow-up	
Characteristic	**Value**	**Missing, *n* (%)**	**Value**	**Missing, *n* (%)**	**Value**	**Missing, *n* (%)**
Age, years	55.9 ± 5.1					
Female, n (%)	659 (79.6)					
HPE / university, n (%)	214 (25.8)	20 (2.4)				
Body-mass index, kg/m²	26.3 ± 4.1	17 (2.1)	26.2 ± 4.1	65 (7.9)	26.4 ± 4.2	72 (8.7)
Comorbidity count ≥ 3, n (%)	177 (21.4)	14 (1.7)	187 (22.6)	54 (6.5)	188 (22.7)	72 (8.7)
Clinical knee OA*, n (%)	674 (81.4)					
Radiographic severity						
KL grade = 0, n (%)	357 (43.1)	96 (11.6)	284 (34.3)	91 (11.0)	233 (28.1)	107 (12.9)
KL grade = 1, n (%)	375 (45.3)		299 (36.1)		287 (34.7)	
KL grade = 2, n (%)	0		132 (15.9)		155 (18.7)	
KL grade = 3, n (%)	0		21 (2.5)		40 (4.8)	
KL grade = 4, n (%)	0		1 (0.1)		6 (0.7)	
Hip pain, n (%)	418 (50.5)		356 (43.0)	52 (6.3)	318 (38.4)	90 (10.9)
Clinical hip OA*, n (%)	111 (13.4)					
NRS for knee pain (range 0-10)	3.6 ± 2.1	18 (2.2)	3.4 ± 2.3	64 (7.7)	3.6 ± 2.4	101 (12.2)
SF-36 vitality (range 0-100)	63.9 ± 16.8	15 (1.8)	63.7 ± 17.9	61 (7.4)	64.4 ± 17.4	103 (12.4)
PCI resting (range 5-20)	9.2 ± 2.6	18 (2.2)	9.1 ± 2.5	78 (9.4)	9.3 ± 2.6	117 (14.1)
WOMAC function (range 0-68)	16.3 ± 11.8	17 (2.1)	15.5 ± 12.1	64 (7.7)	16.6 ± 13.0	102 (12.3)

Values are presented as mean ± SD unless otherwise indicated. * Clinical OA according to the criteria of the American College of Rheumatology. HPE = higher professional education. KL grade = Kellgren and Lawrence grade of the most affected knee. NRS = Numeric Rating Scale. SF-36 = Short Form 36 health survey. PCI = Pain Coping Inventory. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

was included as a dichotomous variable in all models. The time variable indicates the average change in the outcome variable between 2 and 5 years of follow-up.

Linear regression models were used to examine the cross-sectional associations between: 1) the NRS for knee pain, SF-36 vitality subscale (independent variables) and PCI resting subscale (dependent variable); and 2) the PCI resting subscale (independent variable) and WOMAC function subscale (dependent variable). Similar to the longitudinal models, for both associations we used an unadjusted model (model 1) and a model in which we adjusted for all covariates (model 2).

The regression coefficients (B), 95% confidence intervals (95% CI), standardized regression coefficients (β), and coefficients of determination (R^2) were calculated and presented. All analyses were performed using SPSS version 18.0.

Table 2. The longitudinal association of knee pain and vitality with pain-related avoidance of activities in persons with early symptomatic knee osteoarthritis

Model	Independent variable	B (95% CI)	β	R^2
0	Time (5-year vs. 2-year follow-up)	0.23 (-0.03, 0.49)	0.05	0.27
	Previous PCI resting score (5-20)	0.64 (0.60, 0.69)	0.65‡	
1	Time (5-year vs. 2-year follow-up)	0.25 (-0.00, 0.51)	0.05	0.29
	Previous PCI resting score (5-20)	0.60 (0.55, 0.65)	0.60‡	
	NRS knee pain score (0-10)	0.08 (0.03, 0.13)	0.07*	
	SF-36 vitality score (0-100)	-0.02 (-0.02, -0.01)	-0.10‡	
2	Time (5-year vs. 2-year follow-up)	0.14 (-0.14, 0.42)	0.03	0.31
	Previous PCI resting score (5-20)	0.62 (0.57, 0.67)	0.62‡	
	NRS knee pain score (0-10)	0.08 (0.02, 0.13)	0.06*	
	SF-36 vitality score (0-100)	-0.01 (-0.02, -0.01)	-0.09‡	
	Age, years	0.01 (-0.01, 0.03)	0.03	
	Female	0.07 (-0.18, 0.32)	0.01	
	Higher professional education/university	0.22 (-0.01, 0.44)	0.04	
	Body-mass index, kg/m²	0.00 (-0.03, 0.02)	0.00	
	Comorbidity count ≥ 3	0.26 (0.00, 0.53)	0.04	
	Kellgren and Lawrence grade ≥ 2	0.39 (-0.02, 0.80)	0.05	
	Hip pain	-0.15 (-0.37, 0.06)	-0.03	

The dependent variable, pain-related avoidance of activities, was measured with the resting subscale of the Pain Coping Inventory (PCI). Autoregressive generalized estimating equations were used (i.e. the value of the outcome variable is related to the value of the independent variables and the outcome variable one time-point earlier). In model 0, a total of 1411 (85.2%) PCI resting scores from 746 participants were used for analysis. In model 1, a total of 1405 (84.8%) PCI resting scores from 745 participants were used for analysis. In model 2, a total of 1289 (77.8%) PCI resting scores from 681 participants were used for analysis. B (95% CI) = regression coefficient (95% confidence interval). β = standardized regression coefficient. R^2 = coefficient of determination. NRS = Numeric Rating Scale. SF-36 = Short Form 36 health survey. * $p < 0.05$. ‡ $p < 0.001$.

Results

Study population

Of the 828 participants included, 14 (1.7%) and 15 (1.8%) participants underwent total knee and total hip replacement during the 5-year follow-up, respectively. The post-surgery data of these participants were coded as missing. The baseline characteristics of the study population and the number of missing values per variable are presented in **Table 1**.

Course of pain-related avoidance of activities, knee pain, vitality and activity limitations

The average course of pain-related avoidance of activities was relatively stable during the 5-year follow-up (**Table 1**). GEE analysis showed a small increase on the PCI resting subscale (B = 0.20, p = 0.032) between 2 and 5 years of follow-up indicating a small increase in pain-related avoidance of activities.

Table 3. The cross-sectional association of knee pain and vitality with pain-related avoidance of activities in persons with early symptomatic knee osteoarthritis

	Baseline		2-year follow-up		5-year follow-up	
Independent variable	**B (95% CI)**	**β**	**B (95% CI)**	**β**	**B (95% CI)**	**β**
Model 1	n = 807		n = 746		n = 710	
NRS knee pain score (0-10)	0.17 (0.08, 0.25)	0.14‡	0.20 (0.12, 0.28)	0.18‡	0.16 (0.08, 0.24)	0.15‡
SF-36 vitality score (0-100)	-0.04(-0.05, -0.03)	-0.27‡	-0.04(-0.05, -0.03)	-0.30‡	-0.04 (-0.06, -0.03)	-0.30‡
	R^2 = 0.11		R^2 = 0.15		R^2 = 0.14	
Model 2	n = 800		n = 664		n = 656	
NRS knee pain score (0-10)	0.14 (0.06, 0.23)	0.12‡	0.18 (0.09, 0.27)	0.15‡	0.12 (0.03, 0.21)	0.11*
SF-36 vitality score (0-100)	-0.03 (-0.05, -0.02)	-0.23‡	-0.04(-0.05, -0.03)	-0.26‡	-0.04 (-0.05, -0.03)	-0.27‡
Age, years	0.01 (-0.03, 0.04)	0.01	0.03(-0.01, 0.06)	0.05	0.02 (-0.02, 0.06)	0.04
Female	0.26 (-0.16, 0.68)	0.04	0.10(-0.36, 0.56)	0.02	0.36 (-0.11, 0.82)	0.06
HPE / university	0.21 (-0.18, 0.59)	0.04	0.36(-0.05, 0.78)	0.06	0.22 (-0.20, 0.64)	0.04
Body-mass index, kg/m²	0.07 (0.03, 0.12)	0.12‡	0.04(-0.01, 0.08)	0.06	0.03 (-0.02, 0.08)	0.05
Comorbidity count ≥ 3	0.72 (0.30, 1.15)	0.12‡	0.91 (0.45, 1.36)	0.15‡	0.44 (-0.01, 0.89)	0.07
KL-grade ≥ 2	n/a		0.08(-0.37, 0.54)	0.01	0.26 (-0.16, 0.68)	0.05
Hip pain	0.05 (-0.29, 0.39)	0.01	-0.09(-0.47, 0.29)	-0.02	0.42 (0.02, 0.82)	0.08*
	R^2 = 0.14		R^2 = 0.17		R^2=0.16	

The dependent variable, pain-related avoidance of activities, was measured with the Pain Coping Inventory (range: 5-20).
B (95% CI) = regression coefficient (95% confidence interval). β = standardized regression coefficient.
R^2 = coefficient of determination. NRS = Numeric Rating Scale. SF-36 = Short Form 36 health survey.
HPE = higher professional education. KL-grade = Kellgren and Lawrence grade for knee osteoarthritis.
n/a = not applicable because all participants had a KL-grade < 2. * p < 0.05. ‡ p < 0.001.

The average course of knee pain, vitality and activity limitations showed little change too. The average NRS knee pain score slightly increased between 2 and 5 years of follow-up (B = 0.20, p = 0.017). The average WOMAC function score slightly decreased (B = -0.70, p = 0.049) between baseline and 2 years of follow-up, and slightly increased (B = 1.43, p <0.001) between 2 and 5 years of follow-up, indicating a slight decrease followed by a small increase in activity limitations.

Predictors of pain-related avoidance: longitudinal and cross-sectional associations

The results of the GEE analyses showing the longitudinal association of knee pain and vitality with pain-related avoidance of activities are presented in **Table 2**. Model 1 describes the association of the NRS knee pain score and SF-36 vitality score with a subsequent change in PCI resting score. Model 2 describes the same association after adjustment for all covariates (i.e. age, gender, education level, BMI, comorbidity count, KL-grade, and hip pain). The positive B of the NRS knee pain score and negative B of the SF-36 vitality score indicate that greater knee pain and lower vitality were associated with a subsequent increase in PCI resting score (i.e. an increase in avoidance of activities). The adding of the NRS knee pain score and SF-36 vitality score to the basic model with as independent variables the previous PCI resting score and the time variable led to an additional explanation of variance in PCI resting scores of 2%. The previous PCI resting score and time contributed most to the explanation of variance in PCI resting scores (27%).

The results of the linear regression analyses showing the cross-sectional association of knee pain and vitality with pain-related avoidance of activities are presented in **Table 3**. The cross-sectional association of knee pain and low vitality with avoidance of activities was fairly stable over time. At all time-points (i.e. baseline, 2-year and 5-year follow-up), a higher NRS knee pain score and lower SF-36 vitality score were associated with a higher PCI resting score. In crude analyses, the NRS knee pain and SF-36 vitality scores explained 11%-15% of variance in PCI resting scores. In addition to a higher NRS knee pain score and lower SF-36 vitality score, higher BMI, comorbidity count ≥3 and hip pain were found to be associated with a higher PCI resting score. Adjustment for all covariates in model 2 led to an additional explanation of variance in PCI resting scores of 2%-3% (i.e. R^2 of model 2 - R^2 of model 1).

Outcome of pain-related avoidance: longitudinal and cross-sectional associations

The results of the GEE analyses showing the longitudinal association of avoidance of activities with activity limitations are presented in **Table 4**. Model 1 describes the association of the PCI resting score with a subsequent change in WOMAC physical function score. The positive B of the PCI resting score indicates that a higher level of avoidance of activities was associated with a subsequent increase in WOMAC function score (i.e. increase in activity limitations). The adding of the PCI resting score to the basic model with as independent variables the previous WOMAC function score and the time variable led to an additional explanation of variance in WOMAC function scores of 1%. The previous WOMAC function score and time contributed most to the explanation of variance in WOMAC function scores (47%). After adjustment for all covariates in model 2, the association between a higher PCI resting score and a subsequent increase in WOMAC function score lost statistical significance (p = 0.089). A higher NRS knee pain score, lower SF-36 vitality score, higher BMI, comorbidity count ≥3, and more severe radiographic knee OA were found to independently predict an increase in WOMAC function score (i.e. an increase in activity limitations).

The results of the linear regression analyses showing the cross-sectional association of pain-related avoidance of activities with activity limitations are presented in **Table 5**. The cross-sectional association of pain-related avoidance of activities with activity limitations was fairly stable over time. At all time-points, a higher PCI resting score was associated with a higher WOMAC function score. In crude analyses, the PCI resting score explained 12%-15% of variance in WOMAC function scores. In addition to a higher PCI resting score, a higher NRS knee pain score, lower SF-36 vitality score, higher BMI, comorbidity

Table 4. The longitudinal association of pain-related avoidance of activities with activity limitations in persons with early symptomatic knee osteoarthritis

Model	Independent variable	B (95% CI)	β	R^2
0	Time (5-year vs. 2-year follow-up)	2.00 (1.01, 3.00)	0.08‡	0.47
	Previous WOMAC function score (0-68)	0.78 (0.74, 0.82)	0.73‡	
1	Time (5-year vs. 2-year follow-up)	2.00 (1.03, 2.97)	0.08‡	0.48
	Previous WOMAC function score (0-68)	0.75 (0.71, 0.79)	0.70‡	
	PCI resting score (5-20)	0.29 (0.10, 0.49)	0.06*	
2	Time (5-year vs. 2-year follow-up)	1.65 (0.63, 2.67)	0.07*	0.51
	Previous WOMAC function score (0-68)	0.63 (0.56, 0.69)	0.58‡	
	PCI resting score (5-20)	0.20 (-0.01, 0.41)	0.04	
	NRS knee pain score (0-10)	0.32 (0.02, 0.61)	0.05*	
	SF-36 vitality score (0-100)	-0.03 (-0.06, 0.00)	-0.05*	
	Age, years	0.03 (-0.06, 0.11)	0.01	
	Female	0.43 (-0.58, 1.44)	0.01	
	Higher professional education/university	-0.34 (-1.43, 0.75)	-0.01	
	Body-mass index, kg/m^2	0.23 (0.10, 0.36)	0.08‡	
	Comorbidity count ≥ 3	1.89 (0.63, 3.15)	0.06*	
	Kellgren and Lawrence grade ≥ 2	3.19 (1.43, 4.94)	0.08‡	
	Hip pain	0.84 (-0.13, 1.82)	0.03	

Pain-related avoidance of activities was measured with the resting subscale of the Pain Coping Inventory (PCI). Activity limitations (dependent variable) were measured with the physical function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Autoregressive generalized estimating equations were used (i.e. the value of the outcome variable is related to the value of the independent variables and the outcome variable one time-point earlier). In model 0, a total of 1451 (87.6%) WOMAC function scores from 760 participants were used for analysis. In model 1, a total of 1430 (86.4%) WOMAC function scores from 757 participants were used for analysis. In model 2, a total of 1309 (79.0%) WOMAC function scores from 693 participants were used for analysis.
B (95% CI) = regression coefficient (95% confidence interval). β = standardized regression coefficient. R^2 = coefficient of determination. NRS = Numeric Rating Scale. SF-36 = Short Form 36 health survey. * $p < 0.05$. ‡ $p < 0.001$.

count ≥3, and hip pain were found to be associated with a higher WOMAC function score. Adjustment for all covariates led to an additional explanation of variance in WOMAC function scores of 38%-50% (i.e. R^2 of model 2 - R^2 of model 1).

Discussion

The present study used data from a 5-year follow-up period of 828 participants with early symptomatic knee OA to examine predictors and the outcome of pain-related avoidance of activities. First, we found that the average 5-year course of pain-related avoidance of activities was fairly stable over time. It seems that once one has adopted avoidance behaviour, there is a high chance that this behaviour persists. Knee pain, vitality and activity limitations showed a similar stable course over the 5-year follow up, indicating that OA is – in general – a slowly progressive disease.

Second, in longitudinal analyses we found that higher knee pain and lower vitality predict a subsequent increase in avoidance of activities. Our results strengthen the evidence for the

Table 5. The cross-sectional association of pain-related avoidance of activities with activity limitations in persons with early symptomatic knee osteoarthritis

	Baseline		2-year follow-up		5-year follow-up	
Independent variable	**B (95% CI)**	**β**	**B (95% CI)**	**β**	**B (95% CI)**	**β**
Model 1	*n* = 808		*n* = 746		*n* = 711	
PCI resting score (5-20)	1.56 (1.26, 1.85)	0.34	1.66 (1.34, 1.97)	0.35‡	1.92 (1.58, 2.26)	0.38‡
	R^2 = 0.12		R^2 =0.12		R^2 =0.15	
Model 2	*n* = 798		*n* = 662		*n* = 656	
PCI resting score (5-20)	0.75 (0.50, 0.99)	0.16‡	0.56 (0.30, 0.82)	0.12‡	0.75 (0.50, 1.01)	0.15‡
NRS knee pain score (0-10)	2.99 (2.70, 3.29)	0.54‡	3.05 (2.75, 3.35)	0.57‡	3.29 (3.01, 3.58)	0.61‡
SF-36 vitality score (0-100)	-0.06 (-0.10, -0.02)	-0.09*	-0.09 (-0.13, -0.06)	-0.14‡	-0.08 (-0.12, -0.04)	-0.11‡
Age, years	0.09 (-0.03, 0.20)	0.04	0.08 (-0.04, 0.20)	0.03	0.07 (-0.04, 0.19)	0.03
Female	0.47 (-1.00, 1.94)	0.02	-0.10 (-1.65, 1.44)	-0.00	0.16 (-1.36, 1.68)	0.00
HPE / university	-1.16 (-2.52, 0.20)	-0.04	-1.12 (-2.52, 0.28)	-0.04	-0.81 (-2.19, 0.57)	-0.03
Body-mass index, kg/m²	0.26 (0.11, 0.40)	0.09‡	0.36 (0.20, 0.51)	0.13‡	0.33 (0.18, 0.48)	0.11‡
Comorbidity count ≥ 3	3.13 (1.61, 4.64)	0.11‡	1.93 (0.38, 3.49)	0.07*	1.88 (0.40, 3.35)	0.06*
KL-grade ≥ 2	n/a		0.47 (-1.07, 2.00)	0.02	1.55 (0.17, 2.93)	0.05*
Hip pain	1.56 (0.36, 2.76)	0.07*	1.42 (0.15, 2.68)	0.06*	2.25 (0.95, 3.55)	0.09‡
	R^2 =0.50		R^2 =0.56		R^2 =0.65	

Pain-related avoidance of activities was measured with the resting subscale of the Pain Coping Inventory (PCI). Activity limitations (dependent variable) were measured with the Western Ontario and McMaster Universities Osteoarthritis Index (range: 0-68).
B (95% CI) = regression coefficient (95% confidence interval). β = standardized regression coefficient. R^2 = coefficient of determination. NRS = Numeric Rating Scale. SF-36 = Short Form 36 health survey. HPE = higher professional education. KL-grade = Kellgren and Lawrence grade for knee osteoarthritis. n/a = not applicable because all participants had a KL-grade < 2. * $p < 0.05$. ‡ $p < 0.001$.

validity of the avoidance model in persons with early symptomatic knee OA. According to this model, the initial experience of knee pain during physical activity leads to the expectation that renewed activity results in more pain. As a consequence the person with OA will avoid activities. Low vitality is thought to strengthen this avoidance behaviour.[5,9]

Third, in longitudinal analyses pain-related avoidance of activities was found to predict an increase in activity limitations in the crude model. It is hypothesized that avoidance leads to activity limitations via physical deconditioning.[5,8,9] Physical deconditioning, particularly muscle weakness, hampers the execution of daily activities.[39] In the adjusted model the longitudinal association between pain-related avoidance of activities and activity limitations lost statistical significance ($p = 0.089$). The course of both pain-related avoidance of activities and activity limitations was found to be stable, and also the cross-sectional association between pain-related avoidance of activities and activity limitations was fairly stable across time-points. This makes it difficult to demonstrate longitudinal associations. Nevertheless, we found a trend towards an association between pain-related avoidance of activities and a subsequent increase in activity limitations which suggests that pain-related avoidance of activities contributes to the development of activity limitations. Further research with a longer follow-up period is needed to demonstrate the longitudinal relationship between pain-related avoidance of activities and activity limitations.

Knee pain, low vitality, higher BMI, higher comorbidity count and radiographic severity were found to predict a subsequent increase in activity limitations. This finding confirms that multiple factors contribute to the development of activity limitations in knee OA, including disease at the level of the joint, pain, and low vitality, as well as comorbidity and overweight.[3,9]

In addition to the associations hypothesized in the avoidance model, we found a consistent association between higher comorbidity count and pain-related avoidance of activities in cross-sectional analyses. Comorbid diseases such as cardiac conditions and diabetes mellitus limit exercise tolerance,[40] which may induce patients to avoid activities. Alternatively, because of fear-avoidance beliefs[10,41] or negative outcome expectations, persons who react to knee pain with avoidance of activities may react in a similar way to comorbidity.

A strength of our study is that we longitudinally studied a large sample of persons with early symptomatic knee OA from onset of disease (an inception cohort). Nearly all studies that examined the validity of the avoidance model had a cross-sectional design.[5,8,11,42-44] The avoidance model is a causal model. Although no one observational study can prove causality, longitudinal studies enable the evaluation of the development of a variable over time in relation to the development of other variables (i.e. the temporal relationship between variables), which is a step towards demonstrating causality.[38] The relationships among the components of the avoidance model are likely to be dynamic. While we examined the associations between knee pain, low vitality, avoidance of activities and activity limitations in the sequence hypothesized by our theoretical model, it is possible that these relationships are characterized by constant feedback loops, such as those suggested by the fear-avoidance model.[10,45] Examination of the existence of these feedback loops is an interesting topic for future research.

Our study also has some limitations. First, after 5 years of follow-up 3.5% of our study population had undergone total joint replacement. At baseline none of these participants had a knee or hip with a KL-grade >1, which indicates the potential of rapid progression in some patients with OA. The post-surgery data of these participants were coded as missing which may have slightly biased our results. Second, we measured pain-related avoidance of activities with the resting subscale of the PCI which is a self-report questionnaire. This resting subscale has shown a very stable association with activity limitations, not only in the present study but also in previous studies in which self-report and performance-based measures of activity limitations were used.[5,7] Nevertheless, because self-report questionnaires are susceptible to response and recall bias, it is recommended to validate our findings using an objective measure of avoidance of activities such as accelerometry. Third, the use of pairwise deletion of cases allowed us to use as much data as possible, however hampered the comparison of results between models. Therefore, we also performed all analyses using listwise deletion of cases, which yielded comparable results (data not shown).

The results of the present study indicate that pain-related avoidance of activities is associated with activity limitations. Therefore, combined exercise and behavioural treatment interventions have been developed aiming at increasing the level of activities and thereby reducing activity limitations. Several studies have examined the effectiveness of such programs and reported beneficial effects on both avoidance of activities[46-48] and activity limitations.[48-50]

In summary, in persons with early symptomatic knee OA we found that the course of pain-related avoidance of activities is fairly stable over time. Knee pain and low vitality were found to predict a further increase in pain-related avoidance of activities. These results are illustrated in **Figure 1**, and support the hypothesis that, already at an early stage of knee OA, knee pain and low vitality lead to a subsequent increase in avoidance of activities. Longitudinal analyses showed a trend towards an association between pain-related avoidance of activities and a subsequent increase in activity limitations. Cross-sectional analyses showed that pain-related avoidance of activities is related to activity limitations at inception of symptoms and also years later. Therefore, it can be recommended to monitor and target avoidance of activities at various stages of the disease.

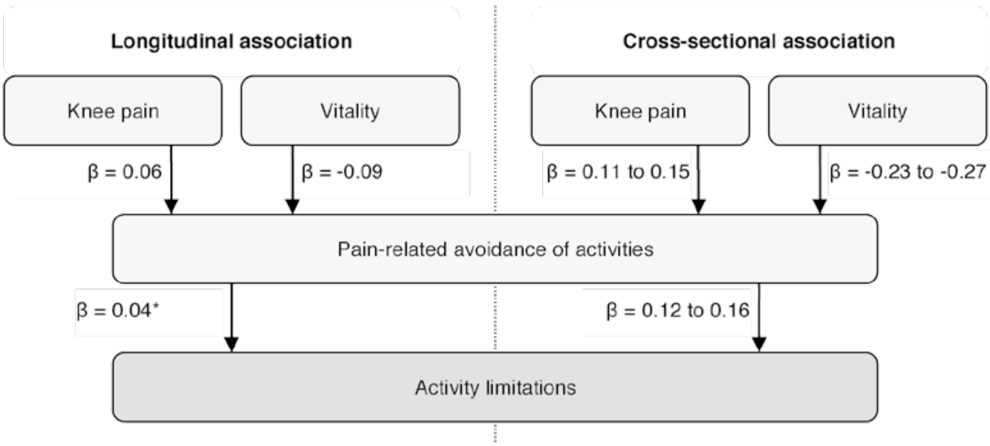

Figure 1. Schematic representation of the evidence from the present study for the validity of the avoidance model. β = standardized regression coefficient adjusted for the other variables in the model, i.e. age, gender, education level, BMI, comorbidity count, Kellgren and Lawrence grade for radiographic knee osteoarthritis and hip pain. All βs are statistically significant at the 0.05 level, except the β indicated with * $p = 0.089$. Cross-sectional analyses were performed at baseline, after 2 years, and 5 years of follow-up resulting in a range of βs.

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