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Comorbidity in knee osteoarthritis

de Rooij, M.

2017

document version
Publisher's PDF, also known as Version of record

Link to publication in VU Research Portal

citation for published version (APA)
de Rooij, M. (2017). *Comorbidity in knee osteoarthritis: Development and evaluation of tailored exercise therapy*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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Chapter 2

Prognosis of Pain and Physical Functioning in Patients With Knee Osteoarthritis: *A Systematic Review and Meta-Analysis*

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Published in:
Arthritis Care & Research (Hoboken) 2016;68(4):481-92

Abstract

Objective. To systematically summarize the literature on the course of pain in patients with knee osteoarthritis (OA), prognostic factors that predict deterioration of pain, the course of physical functioning, and prognostic factors that predict deterioration of physical functioning in persons with knee OA.
Methods. A search was conducted in PubMed, CINAHL, Embase, Psych-INFO, and SPORTDiscus up to January 2014. A meta-analysis and a qualitative data synthesis were performed.
Results. Of the 58 studies included, 39 were of high quality. High heterogeneity across studies (I^2 >90%) and within study populations (reflected by large SDs of change scores) was found. Therefore, the course of pain and physical functioning was interpreted to be indistinct. We found strong evidence for a number of prognostic factors predicting deterioration in pain (e.g., higher knee pain at baseline, bilateral knee symptoms, and depressive symptoms). We also found strong evidence for a number of prognostic factors predicting deterioration in physical functioning (e.g., worsening in radiographic OA, worsening of knee pain, lower knee extension muscle strength, lower walking speed, and higher comorbidity count).
Conclusion. Because of high heterogeneity across studies and within study populations, no conclusions can be drawn with regard to the course of pain and physical functioning. These findings support current research efforts to define subgroups or phenotypes within knee OA populations. Strong evidence was found for knee characteristics, clinical factors, and psychosocial factors as prognostics of deterioration of pain and physical functioning.

Introduction

Osteoarthritis (OA) of the knee is a major cause of joint pain and problems in daily functioning, such as difficulty with walking, climbing stairs, and sitting and rising from a chair. In Europe, OA is among the 10 most disabling conditions[1]. The development of difficulties in performing daily activities is more progressive in persons with OA than in persons without this disease. Persons with OA at middle age are more likely to develop persistent problems in daily functioning during the following 10 years[2].

The natural course of pain and physical functioning in OA of the knee is highly individual and variable. Some patients have been found to remain stable, while others will worsen or even improve[3–6]. Because of this variability, identification of risk factors for functional decline is important. Knowledge of risk factors can be used to inform patients of the likely course of their condition and to adapt treatment according to the prognosis.

In a previous systematic review by van Dijk et al.[7], the course of pain and physical functioning in knee OA during the first 3 years of follow up was found to be variable between studies; limited evidence was found for worsening of pain and physical functioning after 3 years of followup. A number of prognostic factors were identified: increased laxity, proprioceptive inaccuracy, age, a higher body mass index (BMI), knee pain intensity, and increased knee pain were found to predict a deterioration in physical functioning. However, the evidence for these conclusions was provided by only 1 high-quality cohort study with a follow up of 3 years[8]. No evidence was provided for predictors of deterioration in pain[7].

Since the previous systematic review, published in 2006[7], quite a number of longitudinal studies have been published on the course and prognosis of pain and physical functioning in persons with knee OA. The purpose of the present review is 4-fold. We systematically summarize the literature on the course of pain in patients with knee OA, prognostic factors that predict deterioration of pain, the course of physical functioning, and prognostic factors that predict deterioration of physical functioning in persons with knee OA.

Materials and Methods

A protocol for conducting this review was developed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[9]. The literature was systematically searched from inception up to January 7, 2014, using the following databases: PubMed, CINAHL, Embase, Psych-INFO, and SPORTDiscus. The search strategy was formulated in PubMed and, after consultation with an experienced medical librarian, adapted for use in other databases. We also included hip OA patients in the search strategy, but due to the large number of studies (see Results), we only present

the results for knee OA in the present study. Details on the Medline search strategy are presented in Supplementary Table 1 (available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract). The reference lists of all retrieved prognostic studies were also searched.

Inclusion criteria for the present study were the following: 1) the study population consisted of patients with radiographically and/or clinically diagnosed knee OA as defined by the American College of Rheumatology criteria[10], or according to Kellgren and Lawrence grades[11], or as diagnosed by a physician, or of patients who had knee pain for more than 1 month and were at high risk for developing knee OA (ages <35 years and/or with a high BMI and/or a history of knee injury)[12]; 2) the study used at least 1 measure evaluating pain or physical functioning; 3) the study was a prospective cohort study (or was analyzed as a prospective cohort study when the data were obtained from a clinical trial); 4) the study addressed changes in pain or physical functioning outcome over a period of more than 6 months; 5) the study sample consisted of at least 100 participants; 6) separate analyses were presented for knee OA in cases where a knee and hip OA population was included in the study; 7) the study was reported in the format of a full-text article; and 8) the study was published in English, Dutch, or German.

Review articles were excluded. If studies on the same cohort presented different information, or reported on different prognostic factors, or presented results after different follow up periods, all studies were included (see Data analysis below). The selection was performed independently by 2 reviewers (MR and ML), using the criteria described above. If agreement was not achieved, a third reviewer (JH) was consulted, who made the final decision.

Data extraction

Two reviewers (MdR and MvdL) systematically extracted the following information from the included studies: authors, year of publication, setting, study population, study design, timing of outcome assessment, outcome measures, mean ± SD or the percentage of change in pain and physical functioning (pre and post values), and prognostic factors (univariate and multivariate associations, odds ratio [OR], risk ratio, and B coefficient) with outcome. The threshold level of significance of a predictor was set at $P \leq 0.05$. A nonsignificant association between a baseline characteristic and the outcome was regarded as an indication that this characteristic did not predict the outcome.

Methodologic quality

The methodologic quality of the selected articles was assessed independently by 2 reviewers (MdR and MvdL). A standard checklist of predefined criteria was used to assess the quality of the included studies, based on the Hayden criteria[13] (available from the corresponding author). The Hayden criteria are appropriate to assess the methodologic quality of studies on prognosis and prognostic factors and pertain to 6 areas of potential bias related to 1) participation (e.g., adequacy of the description of the target population, sampling frame, recruitment, inclusion and exclusion criteria, baseline study sample, and participation

rate), 2) study attrition (e.g., adequacy of the response rate, dropout rate, and loss to follow up), 3) measurement of prognostic factors (e.g., clarity of description of the independent variables measured, use of reliable measurement instruments, and proportion of the study sample that completed data for all independent variables), 4) outcome measurement (e.g., clarity of the definitions and descriptions of the variables measured and use of reliable and valid measurement instruments and cutoff points), 5) confounding, and 6) analysis (e.g., adequacy of the statistical analyses and presentation of the data, analyses, and results). We did not rate the risk of bias of confounding, because the aim of a prognostic model is to estimate the probability of a particular outcome and not to explore the causality of the association between a specific factor and the outcome. Thus we used a slightly modified Hayden score, by scoring 5 areas of potential bias, excluding confounding. The risk of bias of all 5 areas was rated as low, moderate, or high. As recommended by Hayden et al.[13], the studies were classified as high quality if in all 5 areas there was a low or a moderate risk of bias. Studies with a high risk for at least 1 area of bias were defined as low-quality studies. In case of disagreement between both reviewers, a third reviewer (JFMH) was consulted in order to achieve a final judgment.

Statistical analysis

Quantitative data analysis (meta-analyses) was performed if a minimum of 3 studies with eligible data were available. Data of the course were regarded as eligible for pooling if sufficient data (means ± SDs of the baseline and follow up measurement or change scores between baseline and follow up with SD) were presented in each individual study.

Table 1. Levels of evidence for predictors for pain and physical functioning outcome in persons with knee OA

Statistically significant	Level of evidence
Significant	
Strong	Consistent significant associations found in at least 2 high-quality studies
Moderate	Consistent significant associations found in 1 high-quality study and at least 1 low-quality study
Weak	Significant association found in 1 high-quality study or consistent significant associations found in at least 3 low-quality studies
Inconclusive	Significant association found in less than 3 low-quality studies
Inconsistent	Inconsistent significant findings irrespective of study quality
Nonsignificant	
Strong	Consistent non-significant associations found in at least 2 high-quality studies
Moderate	Consistent non-significant associations found in 1 high-quality study and at least in 1 low-quality study
Weak	Non-significant association found in 1 high-quality study or consistent non-significant associations found in at least 3 low-quality studies
Inconclusive	Non-significant associations found in less than 3 low-quality studies
Inconsistent	Inconsistent non-significant findings irrespective of study quality

Subsequently, these data were converted to standardized mean change (SMC) scores. Data of predictors were regarded as eligible for pooling if predictors were measured in a uniform way (i.e., using the same metric). To pool predictor effects for increase in pain and deterioration of physical functioning, estimates (and SEs) in individual studies were first converted to equal-effect sizes (and variance components). Log ORs were converted to log risk ratios using the prevalence, and regression coefficients were converted into standardized coefficients using the SD of the outcome and predictor variables. When univariable results were available, these were used for pooling; otherwise the multivariable estimates were used.

Pooling of effect sizes across studies was done using the SMC, log ORs, risk ratios, or standardized coefficients in a random effects model, weighted by the inverse variance[14]. Heterogeneity among studies was tested using the I^2 statistic[15]. The literature suggests 25% as low heterogeneity, 50% as moderate, and 75% as high[15].

In cases where studies were based on the same data (e.g., data from the progression cohort of the Osteoarthritis Initiative), we used results of the study of the highest quality and reported univariate instead of multivariate associations, with the longest follow up period, and with the largest sample size.

Sensitivity metaregression analyses of the course of pain and physical functioning were conducted using a random-effects model to examine the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), and quality of studies (high versus moderate/low quality) on the outcome. Finally, data from included studies were entered into a funnel graph (a scatterplot of study effects against a measure of study sizes) to investigate the likelihood of publication bias[16]. In the absence of bias, the plot should resemble a symmetrical inverted funnel.

A qualitative data analysis (best-evidence synthesis) was performed for all studies reporting on predictors of deterioration in pain and physical functioning. Five levels of evidence (strong, moderate, weak, inconclusive, and inconsistent) were defined to summarize the available evidence for the course and the predictive value of identified predictors[17] (Table 1). In order to establish the level of evidence, we took into account the number of studies, the methodologic quality of the studies, and the consistency of a predictor for the outcome. Findings were deemed to be consistent if, in more than 75% of the studies reporting on a predictor, the direction of the association was the same[18]. In describing the results, a distinction was made between self-reported and performance-based outcome measurements.

Results

The combined knee and hip OA literature search resulted in a total of 16,066 hits (Figure 1). After duplicate removal, 9,702 hits were screened on title and abstract. This screening resulted in 209 full-text articles that were studied for eligibility, and 62 articles were considered for inclusion, of which 58 were included in the present study on knee OA.

Study characteristics

Fifty-seven of the 58 included studies were prospective cohort studies, and 1 study was a clinical trial that was analyzed as prospective cohort study[19]. Participants were recruited from community settings, general practices, rheumatology clinics, and orthopedic clinics. The mean follow up period ranged from 0.5 to 8 years, of which 12 studies had a follow up duration longer than 3 years. Twenty-seven studies included patients with radiographically and/or clinically diagnosed knee OA[8,19–44], and 31 studies included patients who were at high risk of developing knee OA[4–6,12,45–71]. Thirty-four studies reported results on pain[5,12,19–22,24–26,29–33,36,38,43–47,50–53,55–58,62,63,65,66,71], and 45 studies reported results on physical functioning[4–6,8,12,19,20,22,23,25,27–31,33–42,44,45,48–50,52,54–56,58–61,64–70]. (For details of the included studies, see Supplementary Table 2, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

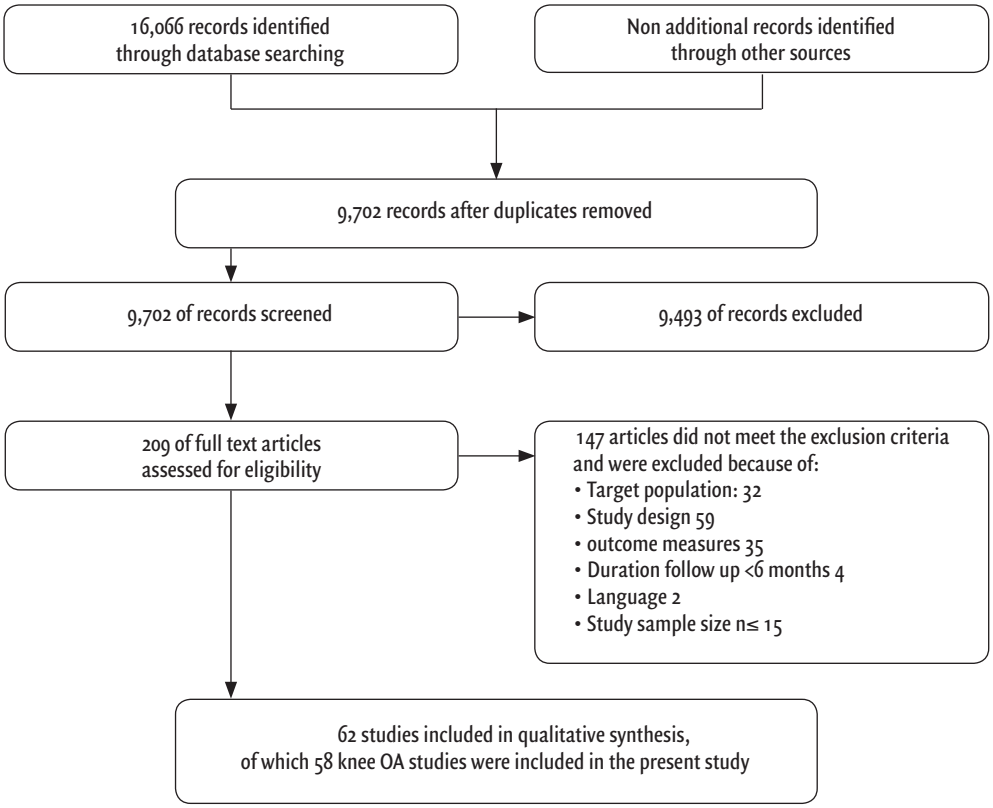

Figure 1. Screening for eligibility. OA = osteoarthritis

Methodologic quality scores

Overall agreement on methodologic quality scores between reviewers was 87.4%, while discussion was necessary in 12.6% of the cases to reach consensus. In 2 of 58 cases, the third reviewer made the final decision. Thirty-nine studies were of high quality (see Supplementary Table 3, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

Course of knee pain

Twenty-one studies reported on the course of pain[5,12,20,24,25,29,31,36,38,43–45,47,51,52,55,56,58,63,65,66]. Because of overlapping data from cohorts and inappropriateness of reported data, only 9 studies were included in the meta-analysis on the course of pain[12,25,31,36,38,44,47,52,58] (Figure 2). There was evidence of high statistical heterogeneity across studies (I^2 = 90.47%, P < 0.01). Sensitivity analysis showed that the course of OA did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee-pain population), or quality of studies (high versus moderate/low quality) (data not shown). Furthermore, large SDs of change scores were seen within studies. For example in the study of Riddle and Dumenci[38], the mean change ± SD of knee pain was 4.3 ± 16.59. If one neglects the heterogeneity, the results

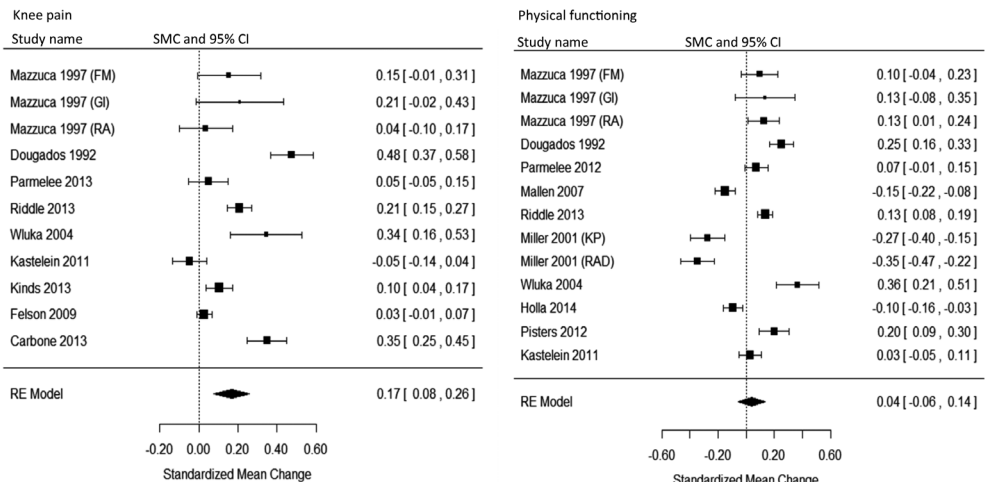

Figure 2. Standardized mean change (SMC) of the overall course of knee pain and physical functioning in patients with knee osteoarthritis. A positive mean change score indicates improvement in pain or physical functioning and a negative mean change score indicates deterioration in pain or physical functioning. Data from subgroup populations within a single study. 95% CI = 95% confidence interval; FM = referred from family medicine specialist; GI = referred from general internist; RA = referred from rheumatologist; KP = knee pain population; RAD = radiologic knee osteoarthritis; RE = random effects.

suggest a small, statistically significant improvement in pain over time (SMC = 0.17 [95% confidence interval (95% CI) 0.08, 0.26]). Egger's test provided evidence for no significant publication bias in the course of pain (data not shown).

Prognostic factors of deterioration in knee pain

Twenty-eight studies assessed a total of 80 prognostic factors of deterioration in pain[5,19–22,25,26,29–33,36,37,39,43–46,52,53,55,57,58,62,63,65,71]. A meta-analysis could be performed for only 2 prognostic factors (higher knee pain intensity at baseline and female sex). Of 6 studies evaluating baseline pain as a prognostic factor[19,33,37,46,58,63], 3 studies could be included in the meta-analysis[19,33,37]. The results indicate that a higher level of knee pain at baseline

Table 2. Summary of qualitative data analysis: studies describing prognostic factors of deterioration in pain in knee osteoarthritis for which strong evidence was found

Deterioration of knee pain predictors	Association*	Reference	Study quality
Predictors			
Clinical factors			
Higher knee pain intensity	Univariate	Blagojevic 2008[46]	High
	Univariate	Peat 2009[63]	Low
	Multivariate (?)	Kinds 2013[58]	High
	Multivariate (9)	Oak 2013[33]	High
	Multivariate (5)	Riddle 2013[37]	Low
	Multivariate (4)	Riddle 2013[38]	High
	Multivariate (5)	Steultjens 2001[19]	High
Bilateral knee symptoms	Univariate	Blagojevic 2008[46]	High
	Univariate	Jinks 2008[57]	High
Psycho social factors			
More depressive symptoms	Univariate	Blagojevic 2008[46]	High
	Univariate	Jinks 2008[57]	High
	Univariate, mulitvariate	Peat 2009[63]	Low
	Univariate, mulitvariate (15)	Riddle 2011[65]	High
	Multivariate (10)†	Parmelee 2013[36]	Low
Nonpredictors of deterioration knee pain			
Demographics			
Sex	Univariate†	Blagojevic 2008[46]	High
	Univariate†	Jinks 2008[57]	High
	Multivariate (?)†	Kinds 2013[58]	High
	Multivariate (?)†	Kinds 2013[58]	High
	Multivariate (4)†	Miranda 2002[62]	Low
	Multivariate (9)†	Oak 2013[33]	High
	Multivariate (10)†	Parmelee 2013[36]	Low
	Multivariate (5)†	Riddle 2013[37]	Low
	Multivariate (5)†	Steultjens 2001[19]	High

* Number of variables in multivariate model shown in parentheses. (?) = unkown.

† Nonsignificant

is a prognostic factor for higher levels of pain in the future (B = -0.48 [95% CI -0.52, -0.44]). Heterogeneity across studies was low to moderate (I^2 = 29.88%, P = 0.24) (see Supplementary Figure 1, available on the Arthritis Care & Research website at http://onlinelibrary.wiley.com/doi /10.1002/acr.22693/abstract). Of 8 studies evaluating sex as a prognostic factor[19,33,36,38,46,57,58,62], 3 studies could be included in the meta-analysis[46,58,62]. The results indicate that female sex is a prognostic factor for higher levels of pain in the future (OR 0.76 [95% CI 0.63, 0.92]). Heterogeneity across studies was low (I^2 = 0.0%, P = 0.38) (Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693-/abstract).

In the qualitative data synthesis, strong evidence was found for the following prognostic factors as predictors for deterioration of pain: higher knee pain at baseline, presence of bilateral knee symptoms, and more depressive symptoms (Table 2). Sex was found to be a nonpredictor of deterioration of pain (strong evidence). For other variables, weak, inconclusive, or inconsistent evidence was found (see Supplementary Table 4, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693/abstract).

Course of physical functioning

Thirty-one studies reported on the course of self-reported physical functioning [4–6,8,12,20,25,27,28,31,35, 36,38,41,44,45,48–50,54–56,59,60,61,64–66,68–70]. Because of overlapping data from cohorts and inappropriateness of reported data, only 10 studies were included in the meta-analysis of the course of physical functioning[4,12,25,31,35,36,38,44,59,61] (Figure 2). There was evidence of high statistical heterogeneity across studies (I^2 = 92.93%, P < 0.01). Sensitivity analysis showed that the course of OA did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), or quality of studies (high versus moderate/low quality) (data not shown). Large standard deviations of change scores were seen within studies. For example, in the study of Holla et al.[54], the mean ± SD change of knee pain was -0.7 ± 9.8[54]. If one neglects the heterogeneity, the results suggest that the average course of physical functioning is stable over time (SMC = 0.04 [95% CI -0.06, 0.14]). Egger's test provided evidence for no significant publication bias in the course of physical functioning (data not shown).

Prognostic factors of deterioration of physical functioning

Thirty-eight studies assessed a total of 148 prognostic factors of deterioration in physical functioning[5,6,8,19,20,22,23,25,27–31,33–37,39–42,44,45,48,49,52,54,58–61,64,65,67–70]. A meta-analysis could be performed for only 2 prognostic factors. The results of the meta-analyses of 3 studies[54,67,69] indicate that the presence of bilateral knee pain is of predictive value for deterioration in physical functioning (risk ratio 0.79 [95% CI 0.63, 0.98]). Heterogeneity across studies was moderate (I^2 = 59.45%, P = 0.08) (see Supplementary Figure 2, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/ 10.1002/acr.22693/abstract). Of 5 studies evaluating knee pain intensity as a prognostic factor[8,

[35,48,54,59], 3 studies could be included in the meta-analysis[8,48,54]. The results suggest that higher knee pain at baseline is of prognostic value for deterioration in physical functioning (OR 0.90 [95% CI 0.83, 0.99]). Heterogeneity across studies was high (I^2 = 78.05%, P = 0.05) (Supplementary Figure 2, available at http://online-library.wiley.com/doi/10.1002/acr.22693/abstract).

In the qualitative data synthesis, strong evidence was found for the following prognostic factors for deterioration of self-reported physical functioning: worsening in radiographic OA, higher knee pain at baseline, worsening of knee pain, pain on patellofemoral joint compression, lower knee extension muscle strength, more disability, higher comorbidity count, poor general health, lower vitality, poor mental health, and more depressive symptoms. Lower walking speed at baseline and higher comorbidity count was found to be a prognostic factor for deterioration in physical functioning in performance-based outcome (strong evidence) (Table 3).

Sex, smoking, alcohol consumption, living with others, radiographic OA of the knee at baseline, decreased knee flexion, decreased hip internal/external rotation, and a specific coping strategy (retreating) were found to be non-predictors of self-reported physical functioning (strong evidence). For performance-based physical functioning, sex, radiographic OA of the knee at baseline, duration of knee symptoms, and specific coping strategies (reducing demands and transformation) were found to be nonpredictors of physical functioning (strong evidence) (Table 3).

Discussion

The aim of the present study was to describe the course of pain and physical functioning in patients with knee OA, and to identify prognostic factors for the course of OA through a systematic review of the literature. Quantitative and qualitative data analyses were used to summarize the results. A summary of predictors and nonpredictors of deterioration in pain and physical functioning for which strong evidence was found is presented in Table 4.

Because of high heterogeneity across studies, the course of pain and physical functioning in knee OA was found to be indistinct. Sensitivity analysis showed that these findings did not depend on the effects of follow up length (<3 years versus >3 years), study population (radiographically or clinically diagnosed knee OA versus knee pain population), or quality of studies (high versus moderate/low quality). However, within study populations, high heterogeneity was also present. Looking closely at the data, large SDs of change scores were seen, indicating that there are considerable within-patient differences in the course of pain and physical functioning; some patients deteriorate, some patients remain stable, and others improve. Calculating an average score neglects these between-patient differences. Our results strongly support current attempts to identify subgroups or phenotypes within OA populations. For example, in a 5-year follow up study, Holla et al.[4] identified 3 subgroups with distinct trajectories of

Table 3. Summary of qualitative data analysis: studies describing prognostic factors of deterioration in physical functioning in knee osteoarthritis for which strong evidence was found

Deterioration in physical functioning predictors	Outcome measurement	Association*	Reference	Study quality
Predictors				
Knee characteristics				
Worsening of ROA of the knee	Self-reported	Univariate	Wluka 2004[44]	High
	Self-reported	Multivariate (?)†	Ledingham 1995[29]	Low
	Self-reported	Multivariate (8)	Wesseling 2015[5]	High
	Self-reported	Multivariate (7)	White 2010[68]	High
Higher knee pain intensity at baseline	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (?)	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)†	Sharma 2003[8]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (6)	Pisters 2012[35]	High
Worsening of knee pain	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Univariate, multivariate (10)	Sharma 2003[8]	High
Pain on patella-femoral joint compression	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate	Thomas 2008[67]	High
Lower knee extension muscle strength	Self-reported	Univariate, multivariate (4)	Miller 2001[61]	High
	Self-reported	Univariate	Thomas 2008[67]	High
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (6)	Amin 2009[22]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
	Self-reported	Multivariate (4)	Rejeski 2001[64]	Low
Clinical Factors				
Lower walking speed	Performance-based	Univariate, multivariate (3)	van Dijk 2010[41]	High
	Performance-based	Multivariate (9)	Oak 2013[33]	High
More disability	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Multivariate (?)†	Kinds 2013[58]	High
	Self-reported	Multivariate (9)	Oak 2013[33]	High
	Self-reported	Multivariate (4)	Riddle 2013[37]	Low
Higher comorbidity count	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (4)	van Dijk 2010[41]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (10)	Parmelee 2013[36]	Low
	Self-reported	Multivariate (6)	Pisters 2012[35]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	Low
Higher comorbidity count	Performance-based	Univariate, multivariate (3)	Van Dijk 2010[41]	High
	Performance-based	Multivariate (19)	Colbert 2013[49]	High
	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
Poor general health	Self-reported	Univariate, multivariate (10)	Holla 2010[54]	High
	Self-reported	Univariate	Mallen 2007[59]	High
Psycho social factors				
Lower vitality	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (5)	van Dijk 2011[42]	High
Poor mental health	Self-reported	Univariate	Holla 2010[54]	High
	Self-reported	Univariate, multivariate (15)	Riddle 2011[65]	High
	Self-reported	Univariate, multivariate (10)	Sharma 2003[8]	High
	Self-reported	Univariate	van Dijk 2011[42]	High
More depressive symptoms	Self-reported	Univariate	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)	Parmelee 2013[36]	Low
	Self-reported	Univariate, multivariate (15)	Riddle 2011[65]	High
	Self-reported	Multivariate (19)	Colbert 2012[48]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	High

Table 3. (cont'd)

Deterioration in physical functioning predictors	Outcome measurement	Association	Reference	Study quality
Nonpredictors Demographics				
Sex				
	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
	Self-reported	Univariate, multivariate (10)†	Parmelee 2013[36]	Low
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (19)†	Colbert 2012[48]	High
	Self-reported	Multivariate (?)†	Kinds 2013[58]	High
	Self-reported	Multivariate (9) †	Oak 2013[33]	High
	Self-reported	Multivariate (6) †	Pisters 2012[35]	High
	Self-reported	Multivariate (5)	Riddle 2013[37]	Low
	Performance-based	Univariate†	van Dijk 2010[41]	High
	Performance-based	Multivariate (19)	Colbert 2012[48]	High
	Performance-based	Multivariate (19)†	Colbert 2012[48]	High
	Performance-based	Multivariate (9)†	Oak 2013[33]	High
	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
	Performance-based	Multivariate (5) †	Steultjens 2001[19]	High
Other patient characteristics				
Smoking				
	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
Alcohol consumption	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Mallen 2007[59]	High
	Self-reported	Multivariate (19)†	Colbert 2012[48]	High
Living with others	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	van Dijk 2011[42]	High
Characteristics of the knee				
Radiographic OA of the knee at baseline	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Miller 2001[61]	High
	Self-reported	Univariate	Thomas 2008[67]	High
	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Univariate, multivariate (9)†	White 2010[68]	High
Radiographic OA of the knee at baseline	Performance-based	Univariate†	Miller 2001[61]	High
	Performance-based	Univariate†	Miller 2001[61]	High
	Performance-based	Univariate†	van Dijk 2010[41]	High
	Performance-based	Multivariate (5)†	Steultjens 2001[19]	High
Range of knee flexion at baseline	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	Thomas 2008[67]	High
	Self-reported	Univariate†	Van Dijk 2010[41]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
Duration of knee symptoms	Performance-based	Multivariate (5)†	Pisters 2012[35]	High
	Performance-based	Multivariate (5)†	Steultjens 2001[19]	High
Decreased Range of motion internal/external rotation hip	Self-reported	Univariate†	van Dijk 2010[41]	High
	Self-reported	Multivariate (6)†	Pisters 2012[35]	High
	Self-reported	Univariate†	Thomas 2008[67]	High
Psycho social factors				
Retreating	Self-reported	Univariate†	Holla 2010[54]	High
	Self-reported	Univariate†	van Dijk 2011[42]	High
Reducing demands	Performance-based	Univariate†	Steultjens 2001[19]	High
	Performance-based	Univariate†	van Dijk 2011[42]	High
Transformation	Performance-based	Univariate†	Steultjens 2001[19]	High
	Performance-based	Univariate†	van Dijk 2011[42]	High

* Number of variables in multivariate model shown in paratheses. (?) unknown.† Nonsignificant
For other variables, weak, inconclusive, or inconsistent evidence was found (see Supplementary Table 5, available on the Arthritis Care & Research website at http://onlinelibrary-.wiley.com/doi/10.1002/acr. 22693/abstract).

functioning, patients with a good, moderate, or poor outcome of physical functioning. Moreover, recently, 5 homogeneous clinical phenotypes were identified (minimal joint disease phenotype, strong muscle strength phenotype, severe radiographic OA phenotype, obese phenotype, and depressive mood phenotype), based on 4 clinical characteristics in knee OA patients[72]. Future research of subgroups or phenotypes has high potential to advance our understanding of the disease and specifically to target treatment to these specific subgroups.

We identified a number of prognostic factors that predict the course of pain among patients with knee OA. The presence of higher knee pain intensity at baseline predicts deterioration of pain (as shown in the quantitative analysis). In addition, we found

Table 4. Summary of predictors and nonpredictors for deterioration in pain and physical functioning: strong evidence found in the quality synthesis*

	Deterioration of knee pain	Deterioration in physical functioning
Predictor		
Higher knee pain intensity at baseline	Yes	Yes
Presence of bilateral knee symptoms	Yes	_
More depressive symptoms	Yes	Yes
Worsening of radiographic OA in the knee	-	Yes
Worsening of knee pain	-	Yes
Pain on patella-femoral joint compression	-	Yes
Lower knee extension strength	-	Yes
Lower walking speed	-	Yes
More disability	-	Yes
Higher comorbidity count	-	Yes
Poor general health	-	Yes
Lower vitality	-	Yes
Poor mental health	-	Yes
More depressive symptoms	-	Yes
Nonpredictor		
Sex	Yes	Yes
Radiographic OA in the knee at baseline	-	Yes
Duration of knee symptoms	-	Yes
Decreased knee flexion	-	Yes
Decreased hip internal/external rotation	-	Yes
Smoking	-	Yes
Alcohol consumption	-	Yes
Living with others	-	Yes
Coping strategies (retreating, reducing demands and transformation)	-	Yes

* For all other variables studied in this review, weak, inconclusive, or inconsistent evidence was found (see Supplementary Tables 4 and 5, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.22693 / abstract). OA = osteoarthritis

strong evidence that the presence of bilateral knee symptoms and depressive symptoms predict deterioration of pain (qualitative analysis). From quantitative analysis, female sex was found to be a predictor of deterioration of pain. Remarkably, when applying a qualitative evidence synthesis, evidence was found for female sex to be a nonpredictor. These opposite conclusions could be due to differences in the number of included studies in the quantitative analysis compared to the qualitative analysis. Only a limited number of studies investigating sex as a risk factor could be included in the meta-analysis, due to inappropriateness of reported data for pooling and a lack of sex- specific effect estimates (as sex was often used as an adjustment factor rather than as a risk factor).

For all other factors identified in our review, the evidence was found to be limited, inconsistent, or inconclusive. Unexpectedly, we found inconsistent evidence that BMI predicts deterioration of pain (4 of 6 studies reported a positive association between BMI and deterioration of pain, while 2 studies did not find an association). This inconsistency might be explained by differences in how BMI was categorized or analyzed between studies.

With respect to prognostic factors that predict the course of physical functioning, we found strong evidence that knee characteristics (worsening of radiographic OA, worsening of knee pain, pain on patellofemoral joint compression, lower knee extension strength), clinical variables (lower walking speed at baseline, more disability, higher comorbidity count, poor general health), and psychosocial factors (lower vitality, poor mental health, more depressive symptoms) all predict deterioration (qualitative analysis). For all other factors identified in our review, the evidence was found to be limited, inconsistent, or inconclusive. Remarkably, we found inconsistent evidence that age predicts deterioration in physical functioning. Despite the fact that 11 studies reported on the association between age and physical functioning, we could not pool these data to calculate a precise effect estimate for the association between age and physical functioning, since variations in measurement scale and statistical analysis existed.

In comparison to a previous review on this topic[7], a large number of high-quality studies were included (39 compared with 1 in the previous review). These studies provided strong evidence for a large number of predictors of deterioration in pain and physical functioning. Contrary to the previous review[7], we distinguished between self-reported and performance-based outcomes of physical functioning and we presented an overview of nonpredictors of deterioration of pain or physical functioning.

Some of the identified prognostic factors are modifiable and could therefore be targeted during treatment. For example, in case of muscle weakness of the lower extremity, the course of pain and physical functioning would improve with specific strengthening exercises[73]. Also, as depressive symptoms predict deterioration in pain and physical functioning, early identification and treatment of depressive symptoms may have a positive impact on the course of knee OA. Finally, because pain predicted deterioration of physical functioning, prescription of effective pain medication may be indicated[74].

Some methodologic issues should be considered. First, we included a high number of eligible studies. Due to pragmatic reasons, we decided to include only studies with a sample size of ≥100 participants. This size selection may have resulted in selection bias of included studies. Second, patients may have received effective treatment, which may be a source of variance in the course of pain and physical functioning. Insufficient information is provided in the included studies as to whether or not patients received treatment during the study period. Third, to our knowledge, this is the first meta-analysis (quantitative analysis) on the course and prognostic factors. Despite the high number of included studies (which could be included in the qualitative analysis), only a small number of studies could be included in the meta-analyses because different measurement scales and metrics were used to assess the outcome and predictor variables. More uniformity in the selection of potential predictor variables and in instruments to measure these variables will facilitate future meta-analyses, leading to stronger conclusions. Finally, we preferably used univariable estimates, due to the considerable diversity in statistical techniques and choice of covariates used in individual multivariate models. Where univariable effect estimates were not available, we used multivariable effect estimates, which may have influenced our results, because risk factors, if adjusted for potential confounders, have different effect estimates compared to the univariable effect estimates.

In conclusion, because of high heterogeneity across studies and within study populations, no conclusions can be drawn with regard to the course of pain and physical functioning. These findings support current research efforts to define subgroups or phenotypes within knee OA populations. Strong evidence was found for knee characteristics, clinical factors, and psychosocial factors as prognostics of deterioration in pain and physical functioning. Treatment of modifiable factors such as knee pain, upper leg muscle strength, comorbidity, and depressive symptoms may reduce the risk of deterioration of knee pain and physical functioning.

Acknowledgements

We thank D. G. de Rooij, PhD, for advice and critical reading of the manuscript, and Rene Otten and Remke Albers for their contribution as medical information specialists regarding the literature search.

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