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

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Chapter 6

The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence

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Abstract

Objective. The avoidance model in patients with knee and hip osteoarthritis (OA) hypothesizes that pain and psychological distress lead to avoidance of activities, and thereby to muscle weakness and activity limitations. This paper systematically reviews the scientific evidence for the validity of this avoidance model.

Methods. A qualitative data synthesis was used to identify levels of evidence.

Results. Sixty studies were included. In knee OA, strong evidence was found that avoidance of activities is associated with activity limitations via muscle weakness (mediation by muscle weakness), strong evidence was found for an association between muscle weakness and activity limitations, and weak evidence was found that pain and psychological distress are associated with muscle weakness via avoidance of activities (mediation by avoidance). In hip OA, weak evidence was found for mediation by muscle weakness; and strong evidence was found for an association between muscle weakness and activity limitations.

Conclusions. More research is needed on the consecutive associations between pain or psychological distress, avoidance of activities and muscle weakness, and to confirm causal relationships.

Introduction

Osteoarthritis (OA) of the knee and hip are leading causes of activity limitations worldwide.[1] Activity limitations are defined as difficulties an individual may have in executing activities (e.g. walking, stair climbing, rising up).[2] During the past decades several risk factors for the development of activity limitations have been identified, among which pain, psychological distress, avoidance of activities, and muscle weakness.[3-10] To be clinically useful, it should be known by means of which mechanisms these risk factors cause activity limitations in people with OA.

Theoretical models have been developed to examine the mechanisms underlying the associations between risk factors and activity limitations. A well-known model in chronic musculoskeletal pain is the fear-avoidance model[11] which has been extensively reviewed by Vlaeyen & Linton[12] and Leeuw et al.[13] Based upon previous work,[11,14-17] Dekker et al.[18] proposed the avoidance model in persons with OA, which is a theoretical model that explains how behavioural mechanisms may cause activity limitations in people with OA of the knee or hip. Different from the fear-avoidance model in which avoidance of activities is assumed to be caused by pain-related fear,[11-13] in the avoidance model in OA pain-related avoidance of activities is assumed to be caused by expectations[19] and to be strengthened by psychological distress (i.e., anxiety, depressed mood, low vitality, and fatigue).[18,20-22]

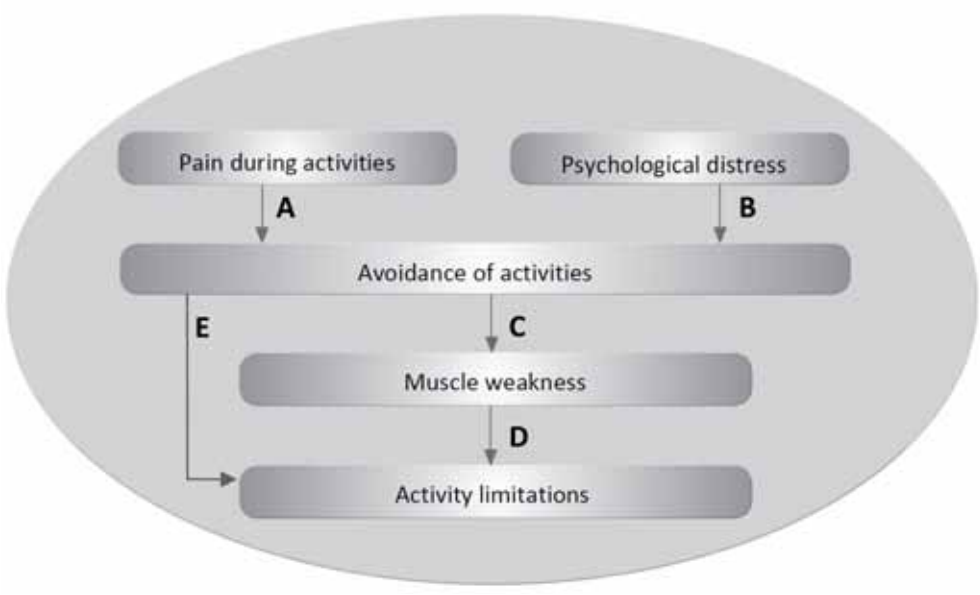

Figure 1. The avoidance model in knee and hip osteoarthritis.

According to the avoidance model in OA (**Figure 1**), the patient with OA experiences pain during activities. This leads to the expectation that renewed activity will cause greater pain, resulting in avoidance of activities. At first, avoidance of activities leads to less pain, due to the decreased load on the symptomatic joint. However, in the longer term, inactivity results in physical decline, most notably muscle weakness. Muscle weakness leads to an increase in activity limitations. In addition, it is hypothesized that psychological distress, which has been associated with pain in patients with OA,[23-25] enhances the tendency to avoid activities, leading to muscle weakness and activity limitations.[18,20-22]

Since the introduction of the avoidance model, seven studies have been performed that were primarily aimed at examining the validity of the model.[21,22,26-30] Although not explicitly testing the avoidance model, several other studies evaluated relationships between components of the model. The aim of the present study was to systematically review the scientific evidence for the validity of the avoidance model in patients with knee and hip OA.

Method

Literature search and study selection

A review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[31] The PRISMA statement consists of a checklist and flow diagram that ensure the transparent and complete reporting of systematic reviews.[31] OVID/Embase, OVID/PsycInfo, PubMed and Ebsco/Cinahl were searched from inception. OVID/Embase up to 18 June 2013, OVID/PsycInfo up to 20 June 2013 and Pubmed and Ebsco/Cinahl up to 26 June 2013. A search specialist (JCFK) was consulted for developing an adequate search strategy. This search strategy included two searches. The first search aimed at identifying studies that examined the association between avoidance of activities and pain, psychological distress or muscle weakness. This search

Table 1. Levels of evidence for associations between components of the avoidance model in patients with knee and/or hip OA

Level of evidence	
Strong	Consistent* significant or non-significant associations found in at least two high-quality studies
Moderate	Consistent significant or non-significant associations found in one high-quality study and at least one low-quality study
Weak	Significant or non-significant association found in one high-quality study, or consistent significant or non-significant associations found in at least three low-quality studies
Inconclusive	Significant or non-significant association found in less than three low-quality studies (no further studies available)
Inconsistent	Inconsistent findings irrespective of study quality

* Findings were considered consistent if the results of at least 75% of the studies analysing a certain association pointed in the same direction.

included terms for knee or hip OA and avoidance of activities. The second search aimed at identifying studies that examined the association between muscle weakness and activity limitations. This search included terms for knee or hip OA, muscle weakness, and activity limitations. Together, these two separate searches comprehensively cover the entire model. Combining the two searches into one single search resulted in an unnecessary lengthy and complex search strategy and an unwieldy number of references. The full search strategy for PubMed is presented in **Appendix 1**. In addition, the reference lists of all selected studies and the private databases of the first and last author were checked to retrieve relevant publications which had not been found with the computerized search.

The publications had to meet the following selection criteria: 1) the study was aimed at patients suffering from symptomatic or radiographic knee or hip OA or pain; 2) the association (correlation coefficient, regression coefficient, odds ratio, risk ratio, coefficient of determination or difference in means, with corresponding p-value or 95% confidence interval) between at least two consecutive components of the avoidance model was presented; 3) the design was a cross-sectional or longitudinal observational study; and 4) the publication was a full research report. Studies on patients with knee or hip OA after total joint replacement were excluded.

The selection of relevant publications was made by two independent reviewers (JFMH and DCSR). The first selection was based on title and abstract, using the criteria described above. The final selection was based on full text. Disagreements between the two reviewers were discussed with a third reviewer (MvdL) until consensus was reached.

Assessment of methodological quality

The methodological quality of each of the selected studies was assessed independently by two reviewers (JFMH and DCSR). A standardized checklist of predefined criteria was used, which is a slightly modified version of the checklist by Hayden et al.[32] (available from the first author). This checklist was developed to assess the quality of prognostic studies in systematic reviews. The checklist includes judgments about six areas of potential study bias: 1) participation, e.g. judgments about the adequacy of the description of the source population, sampling frame, recruitment, inclusion criteria, exclusion criteria, baseline study sample, and participation rate; 2) attrition, e.g. judgments about the adequacy of the response rate, reasons for loss to follow-up, and differences in characteristics and outcomes between persons who completed the study and those who did not; 3) measurement of independent variables; 4) measurement of dependent or outcome variables, e.g. judgments about the clarity of the definitions and descriptions of the variables measured, and the use of reliable and valid measurement instruments and cut-off points; 5) confounding measurement and account, e.g. judgments about the valid and reliable measurement of all important confounders and the appropriateness of the methods used to account for confounders in the study design (e.g. matching for key variables, stratification) and statistical analyses (i.e. appropriate adjustment); and 6) analysis, e.g. judgments about the adequacy of the statistical analyses, and the presentation of the data, analyses and results. In accordance with Hayden et al.,[32] we did not use cut-offs to assess the risk of bias associated with participation and attrition. The judgments about the risks of participation and attrition bias were based on the presence of systematic differences between participants and eligible non-participants or completing and non-completing participants respectively. For longitudinal studies the

risk of bias for all six areas was rated as low, moderate or high. For cross-sectional studies attrition is not applicable, therefore the risk of bias for the five remaining areas was rated. Because there is no consensus based strategy available for the adjustment of potentially confounding factors in mediation analysis,[33] confounding was not scored in studies examining mediation effects. As recommended by Hayden et al.,[32] studies were classified as being of high-quality if in all areas the rating was a low or moderate risk of bias. Studies with a high risk for at least one area of bias were defined as low-quality studies. Conflicting scores for the areas of bias were discussed with a third reviewer (MvdL) until consensus was reached.

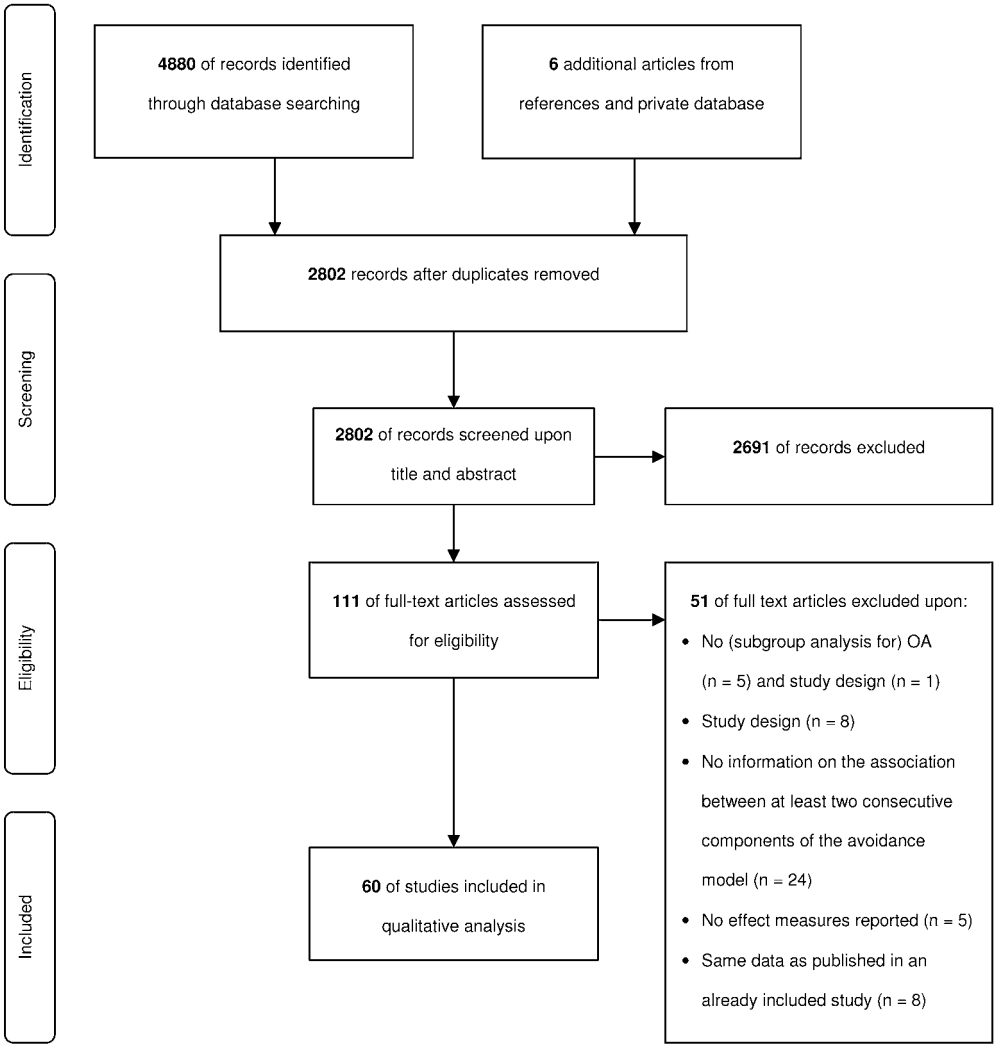

Figure 2. Flow chart of study inclusion process

Data extraction and synthesis

Two reviewers (JFMH and DCSR) systematically extracted data from the included studies regarding: authors, year of publication, study design, study population, part(s) of the avoidance model assessed, independent variables, dependent variables, adjustment for covariates, statistical analyses, and results. These data were recorded on a standardized score sheet.

Data were synthesized separately for: 1) patients with knee OA; 2) patients with hip OA; 3) combined populations of patients with either knee or hip OA; 4) studies examining mediation; 5) cross-sectional studies; and 6) longitudinal studies. The included studies were heterogeneous with regard to study design, study population, part(s) of the avoidance model assessed, independent variables, dependent variables, and covariate adjustment. Therefore, we considered meta-analysis inappropriate and performed a qualitative data analysis (i.e. best evidence synthesis).[34,35] Levels of evidence (i.e. strong, moderate, weak, inconclusive, inconsistent) were assigned based on Kuijpers et al.[36] and de Rooij et al.[37] (**Table 1**). To facilitate readability of the manuscript the results are categorized per inter-relationship between two or three components of the avoidance model.

Table 2. Characteristics of the included studies

	Knee OA (n = 45*)	**Hip OA (n = 8*)**	**Combined population (n = 12)**
Design			
Cross-sectional, n	36	6	11
Longitudinal, n	7	2	
Combined cross-sectional and longitudinal, n	2		1
Median follow-up period (range)	30 (18 to 60) months	48 (36 to 60) months	12 weeks
Population			
Number of included patients (range)	21 to 3975	26 to 427	40 to 4719
Clinical OA according to the ACR criteria, n	10	3	3
Radiographic OA, n	9	2	1
Clinical symptoms or radiographic OA, n	8	2	
Clinical symptoms and radiographic OA, n	8	1	2
Pain or early symptomatic OA, n	5		2
Patients waiting for TJR, n	5		2
No information on diagnostic criteria, n			2

OA = osteoarthritis.

Combined population = population consisting of patients with either knee or hip OA.

ACR = American College of Rheumatology. TJR = total joint replacement.

*5 studies involved both patients with knee OA and patients with hip OA but performed separate analyses for patients with knee OA and patients with hip OA. The characteristics of these studies are described in both column 2 and column 3.

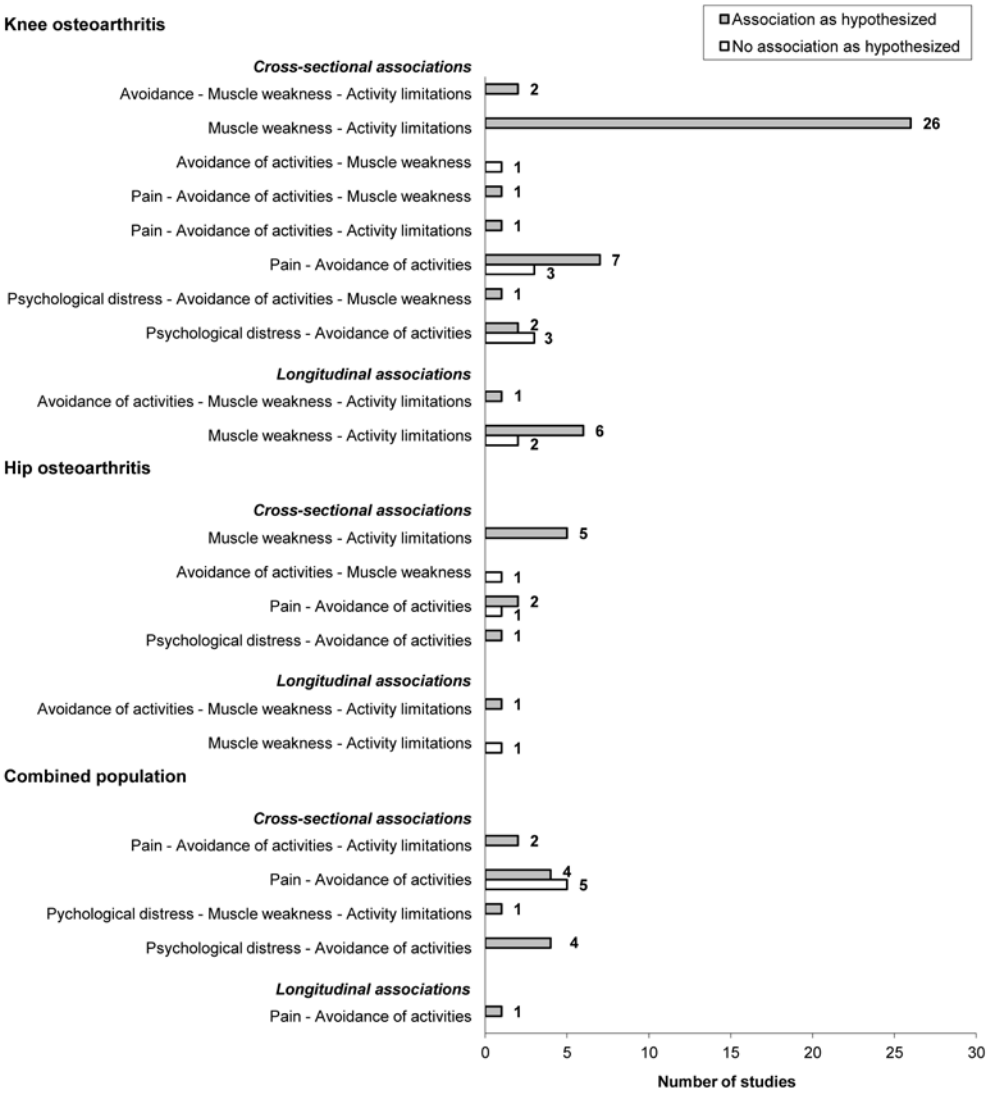

Figure 3. Overview of the number and results of included studies that examined associations between consecutive components of the avoidance model. Combined population = population consisting of patients with either knee or hip osteoarthritis.

Results

Selection of studies

In all, 60 studies were included in the qualitative analysis. The inclusion process is shown in **Figure 2**. If studies were based on the same study population and contained the same information with respect to the association at issue, the most recent publication,[38-41] the publication presenting mediation analyses,[5,21,28,42,43] the publication with the largest sample size,[44,45] or the publication presenting stratified analyses for patients with knee OA and patients with hip OA[46-48] was included in the review. If studies of the same study population presented different information with respect to the association at issue, both studies were included.

Study characteristics

In all, 40 of the 60 studies included involved patients with knee OA,[6,7,21,22,27,39,49-82] 3 studies involved patients with hip OA,[40,44,83] and 17 studies involved both patients with knee OA and patients with hip OA.[9,26,28-30,46,84-94] Five of these 17 studies performed separate analyses:[9,28,46,93,94] the results of these 5 studies are analysed separately for patients with knee OA and patients with hip OA. A summary of the characteristics of the included studies is presented in **Table 2**, and the number of studies that examined a particular association is presented in **Figure 3**. A detailed description of the included studies (**Appendix 2**) is available at: http://link.springer.com/content/esm/art:10.1007/s10865-014-9571-8/file/MediaObjects/10865_2014_9571_MOESM1_ESM.doc.

Methodological quality

Overall agreement on methodological quality of the included studies between the reviewers was 91.1%. Thirty seven studies were of high-quality and 23 studies were of low-quality (**Table 3**). The low-quality judgments were most often based on a high risk of bias in the areas confounding and/or analysis. The studies were judged on their quality of examining the associations hypothesized in the avoidance model. Because not all included studies were primarily aimed at examining these associations, some studies with a high-quality design for their own research purpose were judged as having a moderate or high risk of bias in the present review.

Knee osteoarthritis

Avoidance of activities – Muscle weakness – Activity limitations (paths C & D in Figure 1)

Strong evidence was found for the hypothesis that avoidance of activities is associated with activity limitations via muscle weakness (mediation by muscle weakness) in 2 cross-sectional studies.[21,22] In a high-quality study among 151 patients with early symptomatic knee OA, all associations hypothesized in the avoidance model were examined in one structural equation model.[21] Mediation was examined using a bootstrapping approach. The association between avoidance of activities and activity limitations was found to be partially (18.1%) mediated by muscle weakness. In a high-quality study among 107 patients

Table 3. Risk of bias and study quality of the included studies

Reference	Participation	Attrition	Independent variables	Outcome variable(s)	Confounding	Analysis	Quality score
Allen et al. 2010 [84]	moderate	n/a	low	high	moderate	moderate	low
Amin et al. 2009 [49]	low	low	moderate	low	low	low	high
Bennell et al. 2004 [50]	low	n/a	low	low	low	moderate	high
Brown et al. 2009 [51]	moderate	n/a	low	low	moderate	moderate	high
Chmelo et al. 2012 [52]	low	n/a	low	high	moderate	moderate	low
Chun et al. 2013 [53]	moderate	n/a	low	moderate	moderate	moderate	high
Colbert et al. 2012 [54]	moderate	low	high	low	low	low	low
de Groot et al. 2008 [85]	low	n/a	low	low	low	low	high
Dekker et al. 1993 [26]	moderate	n/a	high	low	n/a	high	low
Fiala et al. 2013 [86]	moderate	n/a	low	low	moderate	low	high
Figueiredo Neto et al. 2011 [55]	moderate	n/a	low	moderate	high	high	low
Fitzgerald et al. 2004 [56]	low	n/a	low	moderate	moderate	moderate	high
Goncalves et al. 2012 [57]	low	n/a	high	low	moderate	moderate	low
Hamilton et al. 2013 [27]	moderate	n/a	low	low	n/a	low	high
Holla et al. 2012 [21]	moderate	n/a	low	low	n/a	low	high
Hopman-Rock et al. 1996 [29]	moderate	n/a	high	low	n/a	high	low
Hopman-Rock et al. 1998 [30]	moderate	n/a	high	low	n/a	moderate	low
Hurley et al. 1997 [58]	low	n/a	high	low	moderate	moderate	low
Hutchings et al. 2007 [87]	low	moderate	low	high	low	low	low
Kauppila et al. 2009 [59]	low	n/a	low	low	low	low	high
Lee et al. 2012 [81]	low	n/a	moderate	low	low	low	high
Liikavainio et al. 2008 [60]	low	n/a	low	low	high	high	low
Maly et al. 2005 [61]	low	n/a	moderate	low	moderate	moderate	high
Maly et al. 2006 [62]	low	n/a	moderate	low	moderate	moderate	high
McAlindon et al. 1993 [63]	low	n/a	high	moderate	low	low	low
Miller et al. 2001 [64]	moderate	moderate	low	low	low	low	high
Murphy et al. 2008 [88]	low	n/a	low	low	low	moderate	high
Murphy et al. 2012 [89]	low	n/a	low	low	moderate	high	low
Murphy et al. 2013 [90]	moderate	n/a	low	low	low	low	high
O'Reilly et al. 1998 [65]	moderate	n/a	low	moderate	low	low	high
Perrot et al. 2008 [91]	low	n/a	low	low	high	high	low
Perrot et al. 2009 [92]	low	n/a	low	high	high	high	low

Table 3. (*continued*)

Reference	Participation	Attrition	Independent variables	Outcome variable(s)	Confounding	Analysis	Quality score
Pisters et al. 2014 [28]	low	low	low	low	n/a	low	high
Pua et al. 2009 [44]	low	n/a	low	low	low	low	high
Pua et al. 2009 [40]	low	n/a	low	low	low	low	high
Pua et al. 2011 [66]	low	n/a	low	low	low	low	high
Rejeski et al. 1996 [67]	low	n/a	moderate	low	high	moderate	low
Riddle et al. 2011 [68]	moderate	n/a	low	low	low	low	high
Rosemann et al. 2007 [46]	low	n/a	low	low	low	moderate	high
Rydevik et al. 2010 [83]	low	n/a	low	low	high	high	low
Saleh et al. 2005 [69]	moderate	n/a	low	low	high	moderate	low
Schmitt et al. 2008 [70]	low	n/a	low	low	high	moderate	low
Segal et al. 2009 [71]	low	n/a	moderate	low	high	high	low
Serrao et al. 2012 [72]	moderate	n/a	low	low	moderate	high	low
Sharma et al. 1999 [73]	low	n/a	low	low	low	low	high
Sharma et al. 2003 [6]	low	low	low	low	low	low	high
Steultjens et al. 2001 [93]	low	n/a	low	low	high	moderate	low
Steultjens et al. 2002 [22]	low	n/a	low	low	n/a	low	high
Thomas et al. 2008 [7]	moderate	moderate	moderate	low	low	low	high
Tonelli et al. 2011 [74]	low	n/a	low	low	low	moderate	high
Topp et al. 2000 [75]	low	n/a	low	low	moderate	moderate	high
van Baar et al. 1998 [94]	low	n/a	low	low	low	moderate	high
van der Esch et al. 2006 [76]	low	n/a	low	low	low	low	high
van der Esch et al. 2008 [39]	low	n/a	low	low	low	low	high
van Dijk et al. 2010 [9]	low	low	low	low	low	moderate	high
White et al. 2010 [77]	moderate	low	moderate	moderate	low	low	high
White et al. 2011 [78]	moderate	low	moderate	moderate	low	low	high
White et al. 2012 [82]	low	n/a	moderate	low	low	low	high
White et al. 2013 [79]	moderate	n/a	moderate	low	low	low	high
Wood et al. 2008 [80]	moderate	n/a	moderate	low	moderate	low	high

The risk of bias for the six areas (1) participation, (2) attrition, (3) measurement of independent variables, (4) measurement of outcome variables, (5) confounding measurement and account, and (6) analysis was rated as low, moderate or high. Attrition was not applicable (n/a) for cross-sectional studies. Confounding was not scored for studies examining mediation effects. Studies were classified as being of high-quality if in all areas the risk of bias was low or moderate. Studies with a high risk of bias for at least one area were defined as low-quality studies.

with clinical knee OA,[22] mediation was examined using the generally accepted approach of Baron and Kenny and the Sobel test.[95] The association between avoidance of activities and activity limitations was found to be partially (15.2%) mediated by muscle weakness.

Weak evidence was found for the hypothesis that avoidance of activities is associated with activity limitations via muscle weakness (mediation by muscle weakness) in 1 longitudinal study.[28] In this high-quality study among 216 patients with clinical and/or radiographic knee OA, the associations between avoidance of activities, knee extension strength and activity limitations measured after 1, 2, 3 and 5 years of follow-up were analysed using Generalized Estimating Equations (GEE) analyses.[28] Mediation was examined using the approach of Baron and Kenny and the Sobel test.[95] The association between avoidance of activities and self-reported and performance-based activity limitations over 5 years was found to be partially (9.1% and 11.6% respectively) mediated by muscle weakness.

Muscle weakness – Activity limitations (path D in Figure 1)

Strong evidence was found for the hypothesis that muscle weakness is associated with activity limitations. The association between muscle strength and activity limitations was examined in 26 cross-sectional studies,[39,49,51,53,56-68,70-73,75,76,80,93,94] 16 were high-quality (**Figure 3**). An association between muscle weakness and activity limitations was found in all studies.

The longitudinal association between muscle weakness and activity limitations was examined in 8 studies with follow-up periods ranging from 18 to 36 months,[6,7,9,49,54,64,77,78] 7 were high-quality. An association between muscle weakness and activity limitations was found in 6 (5 high-quality) studies.

Avoidance of activities – Muscle weakness (path C in Figure 1)

In addition to the 2 cross-sectional studies[21,22] and 1 longitudinal study[28] that did find mediation by muscle weakness, the association between avoidance of activities and knee extension strength was assessed in 1 low-quality study (**Figure 3**).[52] This study did not find a statistically significant association between avoidance of activities (physical activity) and muscle weakness.

Pain – Avoidance of activities – Muscle weakness (paths A & C in Figure 1)

Weak evidence was found for the hypothesis that pain is associated with muscle weakness via avoidance of activities (mediation by avoidance).[21] In this high-quality, cross-sectional study among 151 patients with early symptomatic knee OA, the association between pain and muscle weakness was found to be partially (15.3%) mediated by avoidance.

Pain – Avoidance of activities – Activity limitations (paths A & E in Figure 1)

Weak evidence was found for the hypothesis that pain is associated with activity limitations via avoidance of activities (mediation by avoidance).[27] In this high-quality, cross-sectional study among 105 patients with medial knee pain, mediation was examined using the approach of Baron and Kenny and the Sobel test.[95] The association between pain and activity limitations was found to be partially but substantially (30.9%) mediated by avoidance.

Pain – Avoidance of activities (path A in Figure 1)

Inconsistent evidence was found for the hypothesis that pain is associated with avoidance of activities. The association between pain and avoidance of activities was examined in

10 cross-sectional studies,[46,50,52,55,69,74,79,81,82,94] 7 were high-quality (**Figure 3**). An association between pain and avoidance of activities was found in 7 studies (5 high-quality).

Psychological distress – Avoidance of activities – Muscle weakness (paths B & C in Figure 1)
Weak evidence was found for the hypothesis that psychological distress is associated with muscle weakness via avoidance of activities (mediation by avoidance).[21] In this high-quality, cross-sectional study among 151 patients with early symptomatic knee OA, the association between psychological distress (i.e. low vitality and poor mental health) and muscle weakness was found to be substantially mediated by avoidance.

Psychological distress – Avoidance of activities (path B in Figure 1)
Inconsistent evidence was found for the hypothesis that psychological distress is associated with avoidance of activities. The association between psychological distress and avoidance of activities was examined in 5 cross-sectional studies,[46,55,74,81,82] 4 were high-quality (**Figure 3**). An association between psychological distress (i.e. depressed mood and negative affect) and avoidance of activities was found in 2 high-quality studies.

Hip osteoarthritis

Avoidance of activities – Muscle weakness – Activity limitations (paths C & D in Figure 1)
Weak evidence was found for the hypothesis that avoidance of activities is associated with activity limitations via muscle weakness (mediation by muscle weakness).[28] In this high-quality, longitudinal study among 149 patients with clinical and/or radiographic hip OA, the associations between avoidance of activities, hip abduction strength and activity limitations measured after 1, 2, 3 and 5 years of follow-up were analysed using GEE analyses. After adjustment for age, gender, duration of symptoms, body-mass index, educational level and comorbidity, the association between avoidance of activities and performance-based activity limitations over 5 years was found to be partially (8.9%) mediated by muscle weakness.

Muscle weakness – Activity limitations (path D in Figure 1)
Strong evidence was found for the hypothesis that muscle weakness is associated with activity limitations in cross-sectional studies. The cross-sectional association between muscle strength and activity limitations was examined in 5 studies,[40,44,83,93,94] 3 were high-quality (**Figure 3**). An association between muscle weakness and activity limitations was found in all studies.

In addition to the study that examined mediation by muscle weakness,[28] the longitudinal association between muscle strength and activity limitations was examined in 1 high-quality study (**Figure 3**) with a follow-up period of 36 months.[9] This study did not find a significant association between weakness of the knee extensors at baseline, weakness of the hip abductors at baseline, or a change in muscle strength between baseline and 12 months of follow-up, and activity limitations after 36 months.

Avoidance of activities – Muscle weakness (path C in Figure 1)
In addition to the longitudinal study that examined mediation by muscle weakness,[28] the association between avoidance of activities and muscle strength was assessed in 1 high-

quality cross-sectional study (**Figure 3**).[44] This study did not find a significant association between avoidance of activities and weakness of the knee extensors.

Pain – Avoidance of activities (path A in Figure 1)

Inconsistent evidence was found for the hypothesis that pain is associated with avoidance of activities. The association between pain and avoidance of activities was examined in 3 cross-sectional studies,[44,46,94] all were high-quality (Figure 3). An association between pain and avoidance of activities was found in 2 studies.

Psychological distress – Avoidance of activities (path B in Figure 1)

Weak evidence was found for the hypothesis that psychological distress is associated with avoidance of activities. The cross-sectional association between psychological distress and avoidance of activities was assessed in 1 high-quality study (**Figure 3**).[46] This study found an association between depressed mood and avoidance of activities.

Combined populations consisting of patients with either knee or hip osteoarthritis

In addition to the studies discussed in the preceding paragraphs, 12 studies[26,29,30,84-92] examined parts of the avoidance model in a combined group of patients with either knee or hip OA (**Figure 3**). In these studies additional evidence was obtained for the hypothesis that psychological distress is associated with activity limitations via muscle weakness (mediation by muscle weakness: 1 low-quality study);[26] the hypothesis that pain is associated with activity limitations via avoidance of activities (mediation by avoidance: 2 low-quality studies);[29,30] and the hypothesis that psychological distress is associated with avoidance of activities (3 high-quality studies and 1 low-quality study).[85,88-90] The cross-sectional association between pain and avoidance of activities was examined in 9 cross-sectional studies,[84-92] 4 were high-quality. Taking these studies into account, the evidence from cross-sectional studies for the hypothesis that pain is associated with avoidance of activities was still inconsistent. The longitudinal association between pain and avoidance of activities was examined in 1 low-quality study with a follow-up period of 12 weeks.[87] This study did find a significant association between a decrease in pain and a decrease in avoidance of activities (inconclusive evidence).

Discussion

This is the first review that provides an overview of the evidence from observational studies for the validity of the avoidance model in OA: a theoretical model that explains how behavioural mechanisms may lead to activity limitations in patients with knee and hip OA.[18,20-22] Strong evidence was found for the hypothesis that avoidance of activities leads to muscle weakness and subsequently activity limitations (mediation by muscle weakness) in patients with knee OA (paths C & D in **Figure 1**).[21,22,28] In addition, strong evidence from 31 studies was found for an association between muscle weakness and activity limitations. [6,7,9,39,49,51,53,54,56-68,70-73,75-77,80,93,94]

The assumed mechanism underlying these associations is twofold. Enduring avoidance of activities results in physical deconditioning including muscle weakness. Subsequently,

muscle weakness may directly lead to activity limitations because muscle strength is needed for all activities of daily living;[96] and muscle weakness may indirectly lead to activity limitations via instability of the knee.[43,76] The strength of the association between muscle weakness and activity limitations may depend on the activity and the presence of other impairments such as proprioceptive inaccuracy and high laxity of the knee.[43,76,96] A substantial part (9.1 to 18.1%) of the association between avoidance and activity limitations was found to be mediated by muscle weakness. Besides this indirect association, a direct association between avoidance and activity limitations was found. This indicates that muscle weakness is not the only mechanism explaining the association between avoidance of activities and activity limitations.[21] Another mechanism may for example be low self-efficacy: patients who avoid activities may lose confidence in their capabilities, which will be expressed in activity limitations.[22]

In patients with hip OA, weak evidence was found for mediation by muscle weakness;[28] and strong evidence from 5 studies was found for an association between muscle weakness and activity limitations.[40,44,83,93,94] Because stabilization of the hip joint is particularly provided by its shape, in patients with hip OA muscle weakness is believed to be a manifestation of general physical deconditioning, and is therefore directly associated with activity limitations. The evidence for both an indirect (via muscle weakness) and direct association between avoidance of activities and activity limitations supports the assumption that specific subgroups of patients may benefit from behavioural exercise therapy in which special attention is given to the development of a more active lifestyle.[97]

One study provided weak evidence for the hypothesis that pain and psychological distress lead to avoidance of activities and subsequently muscle weakness (mediation by avoidance) in patients with knee OA (paths A, B & C in **Figure 1**). The assumed mechanism underlying these associations is that pain during activities leads to avoidance and subsequently muscle weakness through the expectation that renewed activity results in more pain.[21] A substantial part (≥ 15.3%) of the associations between pain or psychological distress and muscle weakness was found to be mediated by avoidance.

The results of studies that examined the consecutive associations between pain or psychological distress and avoidance of activities were inconsistent, which can be explained by differences in study populations, covariate adjustment, model building strategies, and measurement instruments. In all 4 studies that examined the association between psychological distress and avoidance of activities in a combined population of patients with either knee or hip OA an association between psychological distress and avoidance of activities was found.[85,88-90] This finding can be explained by uniformity in measurement instruments: all 4 studies used accelerometers to measure avoidance of activities and 3 of the 4 studies used the same measure for psychological distress, i.e. momentary fatigue.[88-90] Accelerometry is a reliable method to objectively measure avoidance of activities that is not susceptible to response and recall bias, in contrast to self-report questionnaires.[89] In the measurements of fatigue, recall bias was eliminated by using momentary assessments during the accelerometer measurements.[88-90] To improve the quality and comparability of results, the use of a smaller set of reliable and valid measurement instruments is recommended. Event monitoring and use of accelerometers have potential to provide better evidence for the validity of the avoidance model.

Especially fatigue was found to be associated with avoidance of activities.[88-90] This is in agreement with a study in early symptomatic knee OA in which a negative association

between vitality (i.e. the opposite of fatigue) and avoidance of activities was found.[21] Fatigue and low vitality seem to be particularly associated with avoidance of activities. It seems advisable to distinguish fatigue and low vitality from the other components of psychological distress, i.e. anxiety and depressed mood.

Evidence from longitudinal studies was only found for the association between muscle weakness and activity limitations in patients with knee OA. Most studies (all except 1) examined the association between baseline muscle strength and change in activity limitations or a poor outcome of activity limitations over time. Temporality (i.e. the hypothesized cause precedes the outcome in time) is one criterion for causality but does not prove causality. Therefore, from these studies no causal inferences can be drawn.[98] A stricter criterion for causality requires that a decrease in muscle strength precedes an increase in activity limitations.[98] One high-quality study examined the association between change in muscle strength at the first year of follow-up and change in activity limitations at three years of follow-up, and found an association.[9] However, studies on the effect of exercise therapy reported conflicting evidence for an association between change in muscle strength and treatment response.[99-102] Thus, evidence for associations between changes is inconsistent. There is a clear need for longitudinal research on associations between changes in all consecutive components of the avoidance model in both patients with knee OA and patients with hip OA.

In this review some methodological choices were made that need explanation. First, studies included were heterogeneous regarding study design, patient selection, measurements and data analysis. Also studies in knee and hip pain populations were included. Although, the diagnosis of OA is highly likely, it is possible that inclusion of patients with pain that was not caused by early OA has slightly biased the results. Second, the methodological quality of the included studies was assessed with a slightly modified version of the checklist by Hayden et al.[32] This checklist was originally designed to assess the quality of longitudinal studies on associations between risk factors and health outcomes. Because the risk of bias in the areas measurement, confounding and analysis does not largely differ between cross-sectional and longitudinal studies, we deemed the checklist also satisfactory for assessing the methodological quality of cross-sectional studies. Third, levels of evidence were assigned based on the consistency of statistically significant findings whereby the strength of the association was not taken into account.[36,37] Therefore, the level of evidence (i.e., strong, moderate or weak) for a certain association does not provide information regarding to its strength. Fourth, the results of multivariable analyses might have been influenced due to differences in the number and diversity of included covariates, and differences in model building strategies. Therefore, an additional analysis was performed in which only results of univariable analyses were synthesized. This additional analysis yielded comparable results (not shown). Relevant confounders should be identified and tested systematically using a theoretical framework.[103] Many of the included studies analysed the data using multivariable stepwise regression models. Multivariable regression is an appropriate method to adjust for confounding, however stepwise selection techniques do not allow specific testing of confounding and may lead to bias in studies aimed at examining causal relationships.[103] Therefore, to further validate the avoidance model in knee OA, more high quality studies are needed that are guided by the underlying theoretical framework. Finally, because our research group performs relatively many studies on avoidance of activities, muscle strength and activity limitations in patients with knee and hip OA, a considerable amount of included studies was performed by people of our own research group. This may have biased the quality judgments.

In conclusion, in patients with knee OA the association between avoidance of activities and activity limitations is for a substantial part explained by muscle weakness. In both knee OA and hip OA, muscle weakness is associated with activity limitations. These results emphasize the importance of muscle strength in maintenance of activities. More research is needed on the consecutive associations between pain or psychological distress, avoidance of activities and muscle weakness, and to confirm causal relationships.

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Appendix 1

PubMed 26 June 2013

[Mesh] = Medical Subject Headings

[tiab] = words only searched in title or abstract

#	Searches	Results
1	Search ("Osteoarthritis, Hip"[Mesh] OR "Osteoarthritis, Knee"[Mesh] OR gonarthr*[tiab] OR coxarthr*[tiab] OR ((knee[tiab] OR knees[tiab] OR hip[tiab] OR hips[tiab] OR lower limb*[tiab] OR lower extremit*[tiab]) AND (osteoarthr*[tiab] OR degenerative arthr*[tiab] OR arthrosis[tiab] OR arthroses[tiab] OR arthralgi*[tiab]))) AND ("Muscle Weakness"[Mesh] OR "Muscle Strength"[Mesh] OR "Muscular Atrophy"[Mesh] OR weakness*[tiab] OR strength*[tiab] OR atroph*[tiab]) AND ("Physical Fitness"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Mobility Limitation"[Mesh] OR disabilit*[tiab] OR ((physical*[tiab] OR walk*[tiab] OR activity[tiab] OR activities[tiab] OR mobilit*[tiab]) AND (limitation*[tiab] OR perform*[tiab] OR difficult*[tiab] OR abilit*[tiab] OR function[tiab] OR functions[tiab] OR functioning[tiab]))	**584**
2	Search ("Osteoarthritis, Hip"[Mesh] OR "Osteoarthritis, Knee"[Mesh] OR gonarthr*[tiab] OR coxarthr*[tiab] OR ((knee[tiab] OR knees[tiab] OR hip[tiab] OR hips[tiab] OR lower limb*[tiab] OR lower extremit*[tiab]) AND (osteoarthr*[tiab] OR degenerative arthr*[tiab] OR arthrosis[tiab] OR arthroses[tiab] OR arthralgi*[tiab]))) AND ("Rest"[Mesh] OR "Sedentary Lifestyle"[Mesh] OR "Repression-Sensitization"[Mesh] OR "Adaptation, Psychological"[Mesh:noexp] OR ((avoid*[tiab] OR adaptati*[tiab] OR interferenc*[tiab]) AND (activity[tiab] OR activities[tiab] OR movement*[tiab] OR moving[tiab] OR exercis*[tiab] OR "Exercise"[Mesh])) OR rest[tiab] OR resting[tiab] OR coping[tiab] OR cope[tiab] OR inactiv*[tiab] OR disus*[tiab] OR sedentar*[tiab] OR accelerometer*[tiab] OR activity monitor*[tiab] OR physical activit*[tiab])	**1226**
3	Search (#1) NOT (#2)	**490**