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Running Head: Knee extensor strength and risk of deterioration in knee OA

Title: Knee extensor strength and risk of structural, symptomatic and functional decline in knee osteoarthritis: A systematic review and meta-analysis

Adam G Culvenor, PT, PhD[1, 2], Anja Ruhdorfer, MD[1], Carsten Juhl, PhD[3, 4], Felix Eckstein, MD[1], Britt Elin Øiestad, PT, PhD[5]

[1] Institute of Anatomy, Paracelsus Medical University Salzburg & Nuremberg, Salzburg, AUSTRIA
[2] School of Allied Health, La Trobe University, Bundoora, AUSTRALIA
[3] Research Unit for Musculoskeletal Function and Physiotherapy, Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, DENMARK
[4] Department of Rehabilitation, University Hospital of Copenhagen, Herlev and Gentofte, DENMARK
[5] Department of Physiotherapy, Oslo and Akershus University College of Applied Sciences, Oslo, NORWAY

Address for correspondence:
Dr Adam G Culvenor
Institute of Anatomy, Paracelsus Medical University,
Strubergasse 21, A5020 Salzburg, AUSTRIA
Tel: +43662242080417; Fax: +436624420021249; Email: adam.culvenor@pmu.ac.at

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Potential conflict of interest:
Felix Eckstein is CEO of Chondrometrics GmbH, a company providing MR image analysis services to academic researchers and to industry. He has provided consulting services to Merck Serono, Bioclinica/Synarc and Samumed, has prepared educational sessions for Medtronic, and has received research support from Merck Serono, Abbvie, Kolon, Synarc, Ampio, BICL and Orthotrophix. No other authors declare a conflict of interest.

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ABSTRACT

Objective. To perform a systematic review and meta-analysis on the association between knee extensor strength and the risk of structural, symptomatic, or functional deterioration in individuals with or at risk of knee osteoarthritis (KOA).

Methods. We systematically identified and methodologically appraised all longitudinal studies (≥1-year follow-up) reporting an association between knee extensor strength and structural (tibiofemoral, patellofemoral), symptomatic (self-reported, knee replacement), or functional (subjective, objective) decline in individuals with or at risk of radiographic or symptomatic KOA. Results were pooled for each of the above associations using meta-analysis, or if necessary, summarized according to a best-evidence synthesis.

Results. Fifteen studies were included, evaluating >8,000 participants (51% female), with a follow-up time between 1.5 and 8 years. Meta-analysis revealed that lower knee extensor strength was associated with an increased risk of symptomatic (WOMAC-Pain: odds ratio [OR] 1.35, 95% confidence interval [CI] 1.10, 1.67) and functional decline (WOMAC-Function: OR 1.38, 95%CI 1.00, 1.89; chair-stand task: OR 1.03, 95%CI 1.03, 1.04), but not increased risk of radiographic tibiofemoral joint space narrowing (JSN) (OR 1.15, 95%CI 0.84, 1.56). No trend in risk was observed for KOA status (present vs. absent). Best-evidence synthesis showed inconclusive evidence for lower knee extensor strength being associated with increased risk of patellofemoral deterioration.

Conclusion. Meta-analysis showed that lower knee extensor strength is associated with an increased risk of symptomatic and functional deterioration, but not tibiofemoral JSN. The risk of patellofemoral deterioration in the presence of knee extensor strength deficits is inconclusive.

Keywords: muscle strength, osteoarthritis, progression, risk factor, symptoms

SIGNIFICANCE AND INNOVATIONS

1. The first meta-analysis evaluating whether lower knee extensor strength is associated with an increased risk of knee osteoarthritis deterioration/progression.
2. Individuals with lower knee extensor strength suffer from an increased risk of symptomatic and functional deterioration ranging from 1.5 to 8 years follow-up.
3. Lower knee extensor strength does not increase the risk of tibiofemoral joint space narrowing; the risk of patellofemoral deterioration in the presence of knee extensor strength deficits is inconclusive.

Knee osteoarthritis (KOA) is a leading cause of pain and disability among older adults (1). Despite its alarming prevalence, regulatory approved therapies that modify the onset or progression of structural damage in KOA have remained elusive. Treatment for KOA is restricted to managing symptoms and functional decline (2). However, even these therapeutic paradigms are largely limited to palliative measures, and surgical knee replacement remains the inevitable fate for many individuals with KOA (3). The identification of modifiable risk factors for KOA structural, symptomatic and functional decline is therefore a priority.

Knee extensor (KE) muscle strength is thought to be a modifiable risk factor of KOA, as low KE strength is commonly observed in individuals with KOA. A previous systematic review and meta-analysis has revealed that low KE strength predicts incident radiographic disease (4). However, whether low KE strength is associated with the progression of KOA, once present, is less clear. Although this question has been evaluated in several systematic reviews, these have broadly included a plethora of potential prognostic factors for radiographic (5, 6) or symptomatic (7, 8) progression, or specific patient characteristics (9) associated with progression without performing meta-analysis. Further, conclusions from these reviews are limited due to a maximum of three studies included, and the relationship between low KE strength and progression of patellofemoral OA has not been considered. Yet patellofemoral pathology represents an important and often unrecognized source of knee pain and disability (10-12).

The fact that earlier systematic reviews have included few studies evaluating low KE strength, likely reflects their focus on KOA *progression* (5-9), which, by definition, requires

participants to have KOA at study inclusion (i.e., individuals with pre-radiographic KOA were excluded). However, potential therapies aimed at modifying KOA progression may be better placed to target early stages of disease (i.e., pre-radiographic) when management strategies may be more efficacious (13). Therefore, the objective of this study was to perform a systematic review and meta-analysis to specifically investigate if low KE strength was associated with an increased risk of structural, symptomatic or functional deterioration in men and women with, or at risk of, KOA.

MATERIALS AND METHODS

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14) for conducting and reporting this systematic review. The protocol was registered on PROSPERO International prospective register (CRD42015026986).

Search Strategy

We performed systematic searches in six electronic databases in October 2015 (and repeated in February 2016): Medline, EMBASE, SPORTDiscus, CINAHL, Scopus and Web of Science. The search strategy contained related terms within the four key themes of knee, osteoarthritis, risk factor and muscle strength, and was adjusted to each database's specifications (Appendix 1). No restrictions were placed on language or publication year. The search was undertaken independently by two authors (AGC, AR), who screened titles and abstracts for eligibility, and recursively reviewed the reference lists of all relevant articles for additional publications. When eligibility could not be confirmed from title and abstract, full-texts were reviewed. Disagreements were resolved by discussion and, if required, taken to an independent researcher (BEØ) for consensus.

Selection criteria

To be eligible for inclusion, studies had to include assessment of maximal KE strength (e.g., Newtons [N], Newton-metres [Nm], pound-feet [Lb-ft], or as a limb symmetry index [LSI]) in subjects with, or at risk of, radiographic or symptomatic KOA. Radiographic KOA could be defined using an established radiographic classification system, or as the presence of osteophytes and/or joint space narrowing (JSN). Symptomatic KOA could be defined using the American College of Rheumatology criteria (definite osteophyte and knee pain) (15) or other methods such as radiographic atlases and knee pain. Populations "at risk" included those aged >50 years with one or more established risk factor(s) for KOA including: knee symptoms, overweight, history of knee trauma, or family history of KOA. Additionally, studies had to be prospective (follow-up ≥1 year), and include a specific measure of structural, symptomatic or functional decline (i.e. outcome compared from baseline to follow-up). If multiple publications featuring data from the same study cohort on the same outcome measure were retrieved, the article reporting outcomes of interest for the greater number of eligible participants was included, or in cases where females and males could be evaluated separately with meta-analyses, studies reporting sex-specific outcomes were included.

Data extraction

The following data was extracted from the included studies independently by two authors (AGC, AR): number of subjects, sex, age, body mass index (BMI), prevalence of radiographic KOA, KE strength and follow-up years. The definition of structural (tibiofemoral or patellofemoral), symptomatic or functional deterioration assessed and the association with

baseline KE strength (separate for those with vs. those without [but at risk of] KOA where possible) was also extracted. Structural decline included increased JSN, worsening score on a radiographic atlas (e.g., Kellgren Lawrence grade [KLG]) and worsening MRI assessed structure (e.g., cartilage loss, increase in cartilage lesion scores). Symptomatic deterioration included worsening symptoms (e.g., WOMAC-pain) or total knee replacement (TKR), for which worsening knee symptoms not amenable to non-surgical management is a primary indication (16). Functional decline included worsening self-reported (e.g., WOMAC-function, SF-12 function) or performance-based measures (e.g., sit-to-stand, walking or stair-climbing tasks). When relevant studies did not report odds ratios (ORs) and 95% confidence intervals (CIs), or did not report adequate data for these to be computed, or were inadequate for comparing associations in males and females, we contacted the corresponding author for additional data to complete meta-analysis.

Risk of bias

Study quality was assessed by two reviewers (AGC, BEØ) using guidelines from the Centre for Reviews and Dissemination (CRD) (17). These guidelines are made up of 10 items assessing different domains of study quality. One item from the Downs and Black's checklist [Was the main outcome measure used accurate (i.e., valid and reliable)?] was additionally included to cover a lack of assessment of outcome measure accuracy in the CRD guidelines (18) to provide 11 items in total (Table 3). Each component of methodological quality was rated as 'Adequate', 'Unclear', or 'Inadequate'. Studies were classified as high-quality when they had a quality score ≥7 (>60% of the maximal attainable score) (6).

Evidence Synthesis

When more than one study evaluated the risk of the same outcome decline in the presence of KE strength deficits, meta-analysis was performed wherever possible, if the OR and 95%CI could be calculated. Meta-analysis was applied on the basis of the OR of outcome deterioration in subjects with lower KE strength. We used random-effects models as differences in population and outcomes were expected (Stata v14.0; StataCorp, Texas, USA). When ORs were not presented in the included studies, or could not be calculated based on the number of case knees in the exposed and unexposed groups, the estimate was transformed to OR from the standard mean difference of muscle strength between participants with and without outcome decline; this was done using the method described in the Cochrane Handbook (19). When associations were reported based on tertiles or quartiles of KE strength (20-23), the lowest strength group (exposed group) was compared to all other groups combined (non-exposed group). Data from adjusted analyses were extracted wherever possible. An OR>1 indicates lower KE strength being associated with outcome deterioration. Heterogeneity between studies was evaluated for each outcome measure using standard Q-tests, and was calculated as I^2 statistics, describing the percentage of the variability in effect estimates that is due to heterogeneity rather than chance. An I^2 value of 0% indicates that no inconsistency was seen between the results of individual studies, and an I^2 value of 100% indicates maximal inconsistency. When study results were reported based on the number of knees, we recalculated the result based on the number of study participants (20, 21, 24). Where sufficient data permitted, stratified analyses were performed for those with vs. without (but at risk of) KOA, males vs. females, and for the specific knee compartment affected (i.e., tibiofemoral/patellofemoral).

Data that could not be included in meta-analyses were summarized using best-evidence synthesis. The level of evidence was based on updated guidelines (25) and was divided into the following levels: i) strong evidence (consistent [>75%] findings among multiple [≥2] high-quality studies); ii) moderate evidence (findings in one high-quality study and consistent [75%] findings in ≥2 low-quality studies); iii) limited evidence (findings in one high-quality study or consistent findings in ≥3 low-quality studies); and iv) conflicting or inconclusive evidence (<75% of the studies reported consistent findings, or the results were from only one study).

RESULTS

Study Selection

The systematic search yielded a total of 2651 studies, with the last search conducted on 22 February 2016: Medline=312, EMBASE=1128, SportsDiscus=128, CINAHL=138, Scopus=879, and Web of Science=36. After removal of 985 duplicates, a further 1599 papers were excluded through screening of titles and abstracts, resulting in the full-text retrieval of 40 studies. These included two additional studies identified from reference screening of key papers (23, 24), and one additional study published online ahead-of-print (26). Fifteen studies were included in the final review (Figure 1). Reasons for exclusion of the other 25 studies, for which full-text review was completed, are detailed in Appendix 2. Additional data was provided by Thomas et al. (23), Zeni et al. (27) (unadjusted ORs separately for males and females) and Glass et al. (21) (adjusted ORs for males and females separately).

FIGURE ONE HERE

Study Characteristics

The 15 studies included had a follow-up time ranging from 1.5 to 8 years (Table 1). Ten studies were classified as high-quality. Participant numbers varied between 82 and 3,975 (overall 51% female). The study samples consisted of elderly people (mean age ≥60 years), who were generally overweight (BMI ≥25kg/m^2) with radiographic KOA (Table 1). Study populations included those with radiographic KOA (22, 24, 27-30), those with, or at high risk of, radiographic KOA (20, 21, 26, 31-33), and those with knee symptoms (23), knee symptoms and functional limitations (34), or knee symptoms and KLG≥1 (35). Structural decline was assessed by a longitudinal increase in the KLG>1 (24); an increase in Osteoarthritis Research society International (OARSI) JSN grade ≥1 (29) or ≥0.5 (20); reduction in quantitative measures of the radiographic joint space width ≥328μm (32) or >0.2mm annually (35); and increased cartilage lesion Whole Organ MRI Score (WORMS) ≥1 (22). Two studies reported results for patellofemoral structural deterioration using increase in JSN OARSI grade ≥0.5 (20) and increase in MRI cartilage lesion WORMS≥1 (22). Symptomatic decline was assessed by an increase in the WOMAC-pain score >3 (on the 20-point scale) (21) or ≥15% of baseline score (24), by total knee replacement (26, 27), or by an increase in pain on visual analogue scale (VAS). However, pain data were eventually excluded because the authors did not report muscle strength for specific pain change groups (22). Functional decline was assessed with increased WOMAC-function score using Sharma et al.'s quintile method' (23, 28, 31), any increase in WOMAC-function score (22, 30), or an improvement by <3.6 points on the 68-point WOMAC function scale (33). Other measures of functional decline were a reduction in the SF-12 score using the quintile method (31), any increase in the Functional Performance Inventory (FPI) score (34), a reduction in the ability to perform a chair-stand task using the quintile method (28, 31), any decrease in walking

speed (30), or a "poor walking speed" outcome using the quintile method (31), any decrease in car-transfer speed (34), or any decrease in stair-climbing speed (34). Similar to VAS pain, the WOMAC-function data from Amin et al. was excluded because muscle strength was not reported for specific WOMAC-function change groups (22).

TABLE ONE HERE

Synthesis of results and subgroup analysis

Meta-analysis could be performed on five outcomes with ≥2 studies included (Figures 2 & 3). Only one study reported data separately for those at risk of (but without) KOA (KLG 0-1) (32); others reported data for the entire cohort (i.e., radiographic KOA only, or those with and without KOA combined) (Figure 3). We did not perform subgroup analysis based on KOA status (presence vs. absence) separately for men and women, as only two studies were included in each of these meta-analyses (Figure 3).

FIGURE TWO HERE

FIGURE THREE HERE

Structural deterioration

Meta-analysis showed no increased risk of tibiofemoral JSN (OR 1.11, 95%CI 0.81, 1.53; I^2=75.2%) in individuals with lower KE strength (Figure 2). Stratified analysis for KOA status showed no trend in risk of tibiofemoral JSN for individuals with lower KE strength based on the presence or absence of KOA (Figure 3). Stratified analysis for sex showed similar results for men and women (Figure 3). In best-evidence synthesis, there was inconclusive evidence

for lower KE strength increasing the risk of tibiofemoral KLG and cartilage lesion deterioration, and patellofemoral JSN and cartilage lesion deterioration (Table 2), due to only one study evaluating each outcome.

Symptomatic deterioration

Pooling of WOMAC-pain and TKR data revealed that baseline KE strength deficits significantly increased the risk of worsening WOMAC-pain (OR 1.35, 95% CI 1.10, 1.67; I^2=0.0%), but not TKR (OR 1.69, 95% CI 0.80, 3.57; I^2=74.2%) (Figure 2). Knee OA subgroup analysis showed that lower KE strength was associated with an increased risk of WOMAC-pain and TKR in only the mixed group and the isolated KOA group, respectively (Figure 3). Stratified analyses for sex showed an increased risk of WOMAC-pain decline and TKR in women, which was not found in men (Figure 3).

Functional deterioration

Meta-analysis showed an increased risk of WOMAC-function decline (OR 1.38, 95% CI 1.00, 1.89; I^2=88.4%) and chair-stand performance deterioration (OR 1.03, 95% CI 1.03, 1.04; I^2=0.0%) with lower KE strength (Figure 2). There was no trend for risk based on KOA status (Figure 3). Stratified analysis for sex was not possible due to limited data. Data from six other subjective and objective functional outcomes could not be pooled due to only a single study evaluating one particular outcome (31, 34), or a lack of data, precluding conversion to an OR (30, 31). Best-evidence synthesis of three high-quality studies showed conflicting evidence for the relationship between lower KE strength and both self-reported and objective outcomes (Table 2).

TABLE TWO HERE

Risk of bias

Study quality is presented in Table 3. Assessment of prognostic factors, length of follow-up and assessment of main outcome measures were adequate for all selected studies. Two thirds (67%) of the studies included followed up a sufficient portion (i.e., ≥80%) of the cohort, and the majority (87%) sufficiently described the exposed (low muscle strength) and unexposed (normal/high muscle strength) groups. No study clearly demonstrated a dose-response relationship between KE muscle strength and outcome decline.

TABLE THREE HERE

DISCUSSION

This systematic review included 15 studies with more than 8,000 study participants with, or at risk of, KOA. The results of the meta-analysis showed that individuals with lower KE strength suffer from an increased risk of symptomatic (WOMAC-pain) and functional (WOMAC-function and chair-stand task performance) deterioration, but not tibiofemoral structural deterioration; however, the effect size was relatively small in most analyses. There was inconclusive and conflicting evidence in the best-evidence synthesis for lower KE strength increasing the risk of patellofemoral structural deterioration and other measures of functional decline (self-reported and objectively measured), respectively. Few differences in deterioration risk were identified between those with and without KOA, but only one of the studies included separate groups of people with and without KOA. When stratified by sex,

meta-analysis revealed an increased risk of symptomatic decline (WOMAC-pain, TKR) was present in women, but not in men.

Previous reviews have suggested that lower KE strength is not a risk factor for structural progression of KOA (5, 6, 9) or that there is limited/conflicting evidence for symptomatic progression (7, 8), but these studies did not synthesize results in a meta-analysis. Our current analyses extend findings from these previous reviews by reporting a pooled OR that shows lower KE strength is not associated with an increased risk of structural tibiofemoral OA deterioration, neither in men nor women. In contrast to the conflicting evidence for symptomatic progression reported previously, our meta-analysis demonstrates that lower KE strength is associated with increased risk of worsening symptoms (WOMAC-pain and TKR), particularly in women. The current review further extends previous reviews by demonstrating that lower KE strength is associated with functional decline, both subjectively and objectively, which has not been reported previously. The inclusion of individuals with, or at risk of, KOA, ensured we were able to capture deterioration throughout a wider spectrum of disease than when only studying patients with established radiographic KOA, and enabled some stratified analyses for KOA status to be performed.

The large variety of outcome measures used to assess deterioration in KOA limited our ability to pool all data and was responsible for only two studies being pooled for most outcomes. These results reflect the lack of universally accepted outcome measures in KOA. The pooled data from this low number of studies thus needs to be interpreted with some caution given the considerable influence that one study can have on the pooled results (and the low-quality of some studies). Other potential limitations of this review include the

pooling of studies that used different approaches to assess the same outcome. For example, pooled tibiofemoral JSN data included quantitative joint space width measures (assessed in mm) as well as semi-quantitative JSN (assessed in grades of severity). These differences in criteria likely were responsible for some inconsistency in the analyses (I^2 ranging from 0 to 88%), but studies assessing the same outcome measure were considered sufficiently homogenous in population and outcome to pool. Given that our review included patients with, or at risk of, KOA, the proportion of participants with radiographic KOA varied between studies. The stratified analysis based on KOA status was limited by only one study reporting results separately for those with vs. without KOA (32). The distinct lack of data for the group without, but at risk of, KOA should be a focus of future research as the potential to modify disease progression may be greatest prior to the development of radiographic disease (13).

Even though the included studies were all prospective cohort studies, methodological weaknesses were revealed through risk of bias assessment, with one-third of included studies being deemed low-quality (Table 3). Important confounding factors, such as age, sex and BMI were not always well matched between groups. The relationship between KE strength and risk of structural, symptomatic and functional decline is difficult to isolate from these potential confounding factors.

Our results differ from a recent meta-analysis that found low KE strength to increase the risk of incident tibiofemoral radiographic KOA (4). Different mechanisms are likely to play a role between muscle strength and incident and progressive KOA. Muscle strength is generally lower in those with established KOA than those without (36), thus the variation in strength in those with pre-existing KOA may be too little to observe an association with future

structural deterioration. However, in our stratified analysis for KOA status, we observed no trend in risk between those with and without KOA. In predicting deterioration of knee structure, muscle strength may not serve as the best surrogate measure of muscle function. Other measures, such as endurance or activation, may be independently related to disease. Unlike isolated KE measures of muscle strength, physical performance measures, such as the one-leg-rise task, account for functional (weight-bearing) lower-limb (KE) endurance, and have been shown to be predictive of incident tibiofemoral OA (37) and future function/quality of life (38).

Although the risk of patellofemoral deterioration (JSN/worsening cartilage) in the presence of lower KE strength was inconclusive, of note was the significant associations observed between lower KE strength and both lateral patellofemoral cartilage deterioration (22) and patellofemoral JSN in women (20). Although these may be chance findings, there may potentially be a stronger association between low KE strength and patellofemoral deterioration (compared with tibiofemoral deterioration), which warrants further investigation.

Our pooled results, demonstrating that lower KE strength is associated with an increased risk of symptomatic and functional decline, particularly in women, underpin the importance of optimizing KE strength. Poor KE strength may lead to symptoms via abnormal loading and structural (patellofemoral) pathology, particularly as patellofemoral pathology has been reported to be a potent source of symptoms, more so than tibiofemoral pathology (10, 11). The fact that women, and not men, with KE strength deficits were at increased risk of TKR likely reflects the interaction of other factors, such as willingness to consider surgery, that

contribute to the complex decision to undergo TKR (39). There may be a larger risk of TKR in the presence of lower KE strength in individuals with established KOA compared to those without KOA (Figure 3), but because significant associations were observed in the combined KOA group more so than the isolated KOA group in other variables, there appears to be a limited trend in risk based on KOA status.

The different patient-reported and objectively measured functional outcomes included in this review all assess slightly different aspects of self-reported function and physical performance, yet meta-analysis of both aspects of function (WOMAC-function and chair-stand performance) resulted in significant associations with lower KE strength. Conflicting evidence existed for the association between lower KE strength and other measures of function. Even though the assessment of KE strength was conducted with a similar laboratory based set-up (i.e., seated KE), the type of strength assessed (isokinetic/isometric, speed) and the reporting of measurement units was divergent (Table 1). This inconsistency reflects a lack of recommended gold standard for both the units of force measurement and method of normalization to body size.

The finding that lower KE strength is associated with an increased risk of symptomatic and functional decline suggests that interventions aimed at increasing KE strength may effectively minimize this risk. A large systematic review found an average 17% gain in strength following 1-6 months of resistance training in patients with KOA, and that this increase in KE strength improved self-reported pain and function in over 50-70% of the cohort (40). Also in line with our findings, the limited number of clinical trials evaluating the effect of KE strengthening on KOA progression fail to show a significant effect on disease

progression (41-43). Given that knees in the earliest stages of disease may be more responsive to targeted interventions, future research focusing on early KOA MRI changes may reveal a promising capacity of strengthening interventions to alter structural disease processes prior to established disease.

In conclusion, this systematic review and meta-analysis showed that lower KE strength was associated with an increased risk of symptomatic (women only) and functional deterioration (men and women) in individuals with, or at risk of, KOA. There was no evidence of KE strength deficits being associated with an increased risk of tibiofemoral structural deterioration. No trend in risk was observed for KOA status (present vs. at risk). Best-evidence synthesis showed inconclusive evidence for lower KE strength being associated with increased risk of patellofemoral deterioration. Although a maximum of four studies were pooled for each outcome and a risk of bias existed for most studies, KE weakness appears to be an attractive target for minimizing symptomatic and functional decline, particularly in women.

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TABLES

Table 1. Study characteristics

Study	Cohort	No. of subjects (% of cohort)	Men/ Women	Age ± SD, yrs*	BMI ± SD, kg/m^2*	Radiographic KOA (%)▪	Strength units	Strength assessed	Follow-up, yrs
Amin 2009[22]	BOKS	265/317 (84%)	154/111	67 ± 9	31.5 ± 5.8	100∑	Nm/BW	Conc: 60°/s	2.5Ω
Brandt 1999[24]	-	82/112 (73%)	25/57	72 ± 5	81.9 ± 16.5Δ	100	Lb-ft/BW	Conc: 60°/s	2.6
Colbert 2012[30]	OAI	3975/4796 (83%)∂	2317/1658	62 ± 9	28.6 ± 4.8	55€	N	Isom: 60° flexion	3
Culvenor 2016[25]	OAI	272/316 (86%)	110/162	65 ± 8	29.2 ± 4.2	91	N	Isom: 60° flexion	2
Eckstein 2013[31]	OAI	1412/3981 (35%)▪	611/801	62 ± 9	29.0 ± 4.6	71	N/BW	Isom: 60° flexion	2
Glass 2013[21]	MOST	2404/2946 (82%)	918/1486	62 ± 8	30.6 ± 5.8	36	Nm	Conc: 60°/s	5
Miller 2001[33]	OASIS	346/480 (72%)₳	235/245£	72 ± 5	29.6 ± 5.2	52	N/BW	Conc: 30°/s	2.5
Miyazaki 2012[34]	-	84/136 (62%)	6/78	72 ± 3	25.0 ± 2.9	81	Kgw	Isom: 90° flexion	8
Pisters 2012[29]	-	211/288 (73%)	56/155	66 ± 9	28.5 ± 4.5	100@	N/BW#	Isom: angle NR	5
Segal 2010[20]	MOST	2182/2697 (81%)▪	892/1290	62 ± 8	30.3 ± 5.6	NR	Nm	Conc: 60°/s	2.5
Sharma 2003[28]	MAK	171/178 (96%)	45/126	64 ± 11	30.0 ± 5.5	100	Lb-ft	Isok: 120°/s	1.5
Sharma 2003[27]	MAK	236/285 (83%)	64/172	69 ± 11	30.8 ± 6.0	100	Lb-ft	Isok: 120°/s	3
Thomas 2008[23]	CASK	621/757 (82%)	338/283	65 ± 8	NR	69&	mmHg	Isom: 90° flexion	1.5
White 2010[32]	MOST	1801/2244 (80%)	1135/666	63 ± 8	30.9 ± 6.0	59¶	Nm	Conc: 60°/s	2.5
Zeni 2010[26]	-	115/120 (96%)	59/61£	60 ± 10	32.2 ± 6.5	100	N/BW‡	Isom: 75° flexion	2

*at baseline quads assessment

▪ ≥Kellgren Lawrence grade 2 unless indicated

sum score for left and right side together

£ males and female numbers reported for total cohort, not number included in analyses

@ knee osteoarthritis defined according to American College of Rheumatology radiologic or clinical criteria

& knee osteoarthritis defined as presence of definite osteophyte

€ knee osteoarthritis defined as JSN ≥1 using OARSI atlas

¶ patellofemoral joint included in osteoarthritis definition – defined as patellofemoral osteophyte ≥grade 2, or patellofemoral JSN ≥grade 2 with an osteophyte, cyst or sclerosis score ≥grade 1

∑ tibiofemoral osteoarthritis (77%) defined as Kellgren Lawrence ≥grade 2; patellofemoral osteoarthritis (23%) defined as definite osteophyte

‡ N/BMI reported in paper, but N/BW provided by authors and presented in table for consistency

Ω 1.25 years follow-up used if 2.5 years unavailable

Δ body mass (kg)

ð WOMAC-Function: 3935/4796 (82%); SF-12: 3767/4796 (79%); Chair-stand task: 3597/4796 (75%); Walk task: 3605/4796 (75%)

▪ estimated from number of knees

₳ data are for functional performance inventory (for stair-climb task: 291/480 [61%], car-transfer task: 301/480 [63%])

BOKS, Boston Osteoarthritis of the Knee Study (symptomatic and radiographic knee OA); OAI, Osteoarthritis Initiative (with or at risk of symptomatic knee OA); MOST, Multicentre Osteoarthritis Study (with or at risk of radiographic knee OA); OASIS, Observational Arthritis Study in Seniors (self-reported knee pain and functional limitation); MAK, Mechanical Factors in Arthritis of the Knee (radiographic knee OA and functional limitations); CASK, Clinical Assessment Study of the Knee (knee symptoms); Lb-ft, pound-foot; BW, body weight, N, Newton; Nm, Newton-meters; NR, not reported. Conc, concentric; Ecc, eccentric; Isom, isometric; Isok, isokinetic; OA, osteoarthritis, Kgw, kilogram weight

Table 2. Data not included in meta-analysis

Decline	Study	No. with decline	Effect size*	Association $	Study quality
Structure					
Kellgren Lawrence grade	Brandt et al[24]	17/82 (21%)	Total: 1.04 (0.39, 2.74)	o	Low-quality
			Female: 1.00 (0.33, 2.99)	o	
			Male: 0.36 (0.04, 3.29)	o	
Patellofemoral JSN	Segal et al[20]	91/2182 (4%)§	Total: 1.38 (1.00, 1.91)	-	Low-quality
			Female: 1.59 (1.12, 2.26)	-	
			Male: 0.67 (0.30, 1.48)^	o	
TFJ and PFJ cartilage lesions	Amin et al[22]	TFJ: 118/265 (45%)	TFJ medial: 1.14 (0.77, 1.71)	o	High-quality
		PFJ: 58/265 (22%)	TFJ lateral: 0.83 (0.48, 1.44)	o	
			PFJ medial: 1.17 (0.73, 1.86)	o	
			PFJ lateral: 2.27 (1.29, 3.98)	-	
Function					
WOMAC-Function	Pisters et al[29]	NR	β 0.11 (0.01, 1.36) (p=0.08)	o	High-quality
SF-12 Function	Colbert et al[30]	1978/3767 (53%)	1.01 (1.00, 1.01)	o	High-quality
Functional Performance Inventory	Miller et al[33]	NR	Co-efficient 0.048 (p<0.05)	-	High-quality
Car-transfer task	Miller et al[33]	NR	Co-efficient -0.665 (p>0.05)	o	High-quality
Stair-climb task	Miller et al[33]	NR	Co-efficient 0.932 (p<0.001)	-	High-quality
Walk task	Colbert et al[30]	1682/3605 (47%)	1.02 (1.01, 1.02)	-	High-quality

Pisters et al[29]	NR	β 0.60 (0.37, 1.03) (p=0.06)	o	High-quality

* data presented as odds ratio (95% confidence interval) unless indicated otherwise

^ For males, low vs middle tertile not reported, so data presented are low vs high knee extensor strength

§ number of participants estimated from number of knees

$ - lower strength predictive of deterioration; o no association observed

β, standardized regression co-efficient; SF-12, Short-Form-12; WOMAC, Western Ontario and MacMaster Universities Osteoarthritis Index; NR, not reported; JSN, joint space narrowing; TFJ, tibiofemoral joint; PFJ, patellofemoral joint;

Table 3. Risk of bias assessment using the Centre for Reviews and Dissemination and an additional item from the Downs and Black Scale

	Item number											
Study	1	2	3	4	5	6	7	8	9	10	11	Total
Amin et al.[22]	A	A	A	U	A	A	A	A	U	U	A	8
Brandt et al.[24]	U	A	A	U	I	U	A	I	U	U	A	4
Colbert et al.[30]	A	A	A	A	A	A	A	A	A	U	A	10
Culvenor et al.[25]	A	A	A	A	A	A	A	A	U	U	A	9
Eckstein et al.[31]	A	A	A	I	A	U	A	I	U	U	A	6
Glass et al.[21]	A	A	U	U	A	A	A	A	U	U	A	7
Miller et al.[33]	A	A	U	A	A	A	A	I	A	U	A	8
Miyazaki et al.[34]	A	A	A	I	A	A	A	I	U	U	A	7
Pisters et al.[29]	A	A	A	A	A	A	A	I	A	U	A	9
Segal et al.[20]	A	A	U	U	A	U	A	A	U	U	A	6
Sharma et al.[28]	I	A	A	U	A	U	A	A	U	U	A	6
Sharma et al.[27]	A	A	A	I	A	A	A	A	U	U	A	8
Thomas et al.[23]	A	A	U	U	I	A	A	A	U	U	A	6
White et al.[32]	A	A	U	I	A	A	A	A	U	U	A	7
Zeni et al.[26]	A	A	A	I	I	A	A	A	A	U	A	8

A, adequate; U, unclear; I, inadequate

Risk of bias item description:

1. Were there sufficient description of the groups and the distribution of prognostic factors?^
2. Were the prognostic factors accurately assessed?
3. Were the groups assembled at a similar point in disease progression?^
4. Were the groups comparable on all important compounding factors?^
5. Was there adequate adjustment for the effects of these confounding factors?
6. Was outcome assessment blind to exposure status?
7. Was follow-up long enough for the outcomes to occur?
8. Was a sufficient proportion of the cohort followed-up?
9. Were dropout rates and reasons for drop outs similar across exposed and unexposed groups?^
10. Was a dose-response relationship between intervention and outcome demonstrated?
11. Was the main outcome measure used accurate (valid and reliable)?

^ Studies that report knee extensor weakness as a continuous variable, where exposed and unexposed groups were not analyzed separately, were scored adequate.

FIGURE LEGENDS

Figure 1. Flow diagram of study selection

Figure 2. Results of meta-analyses on low knee extensor strength and the risk of structural (joint space narrowing), symptomatic (WOMAC-Pain, total knee replacement) and functional (WOMAC-Function, chair-stand task) deterioration. OR, odds ratio; CI, confidence interval; WOMAC, Western Ontario McMasters University Osteoarthritis Index.

Figure 3. Results of meta-analyses on: (A) sex-specific low knee extensor strength and the risk of structural (joint space narrowing) and symptomatic (WOMAC-Pain, total knee replacement) deterioration; and (B) low knee extensor strength and the risk of structural (joint space narrowing), symptomatic (WOMAC-Pain, total knee replacement), and function (WOMAC-Function, Chair-stand test) based on KOA subgroup status (radiographic KOA, mixed, no radiographic KOA). OR, odds ratio; CI, confidence interval; WOMAC, Western Ontario McMasters University Osteoarthritis Index; KOA, knee osteoarthritis.

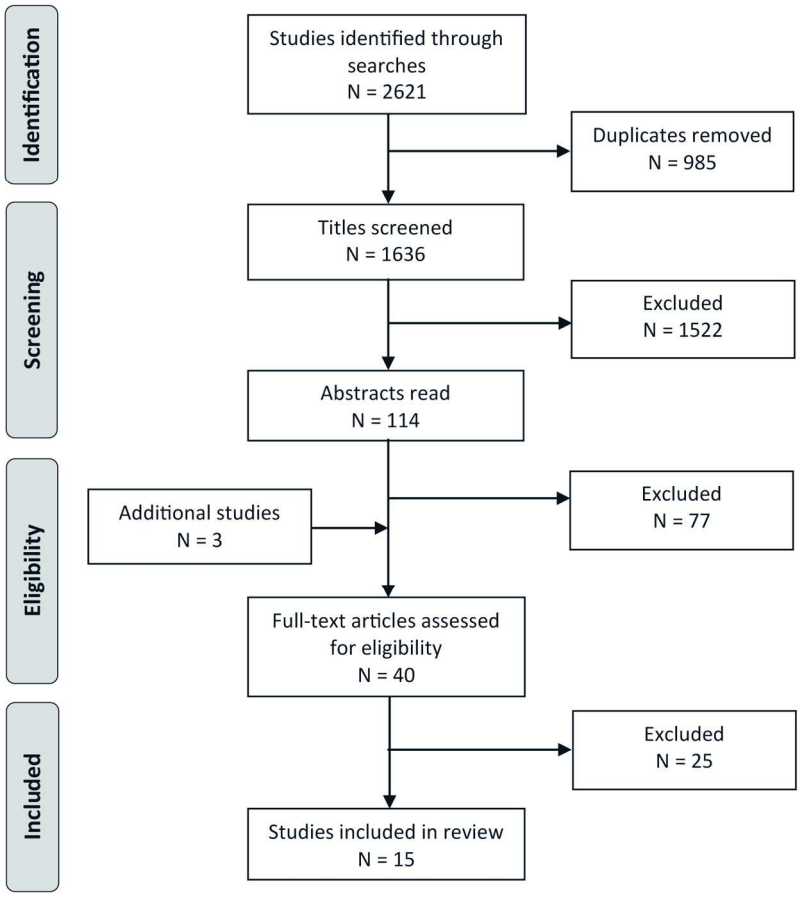

Figure 1. Flow diagram of study selection

159x145mm (300 x 300 DPI)

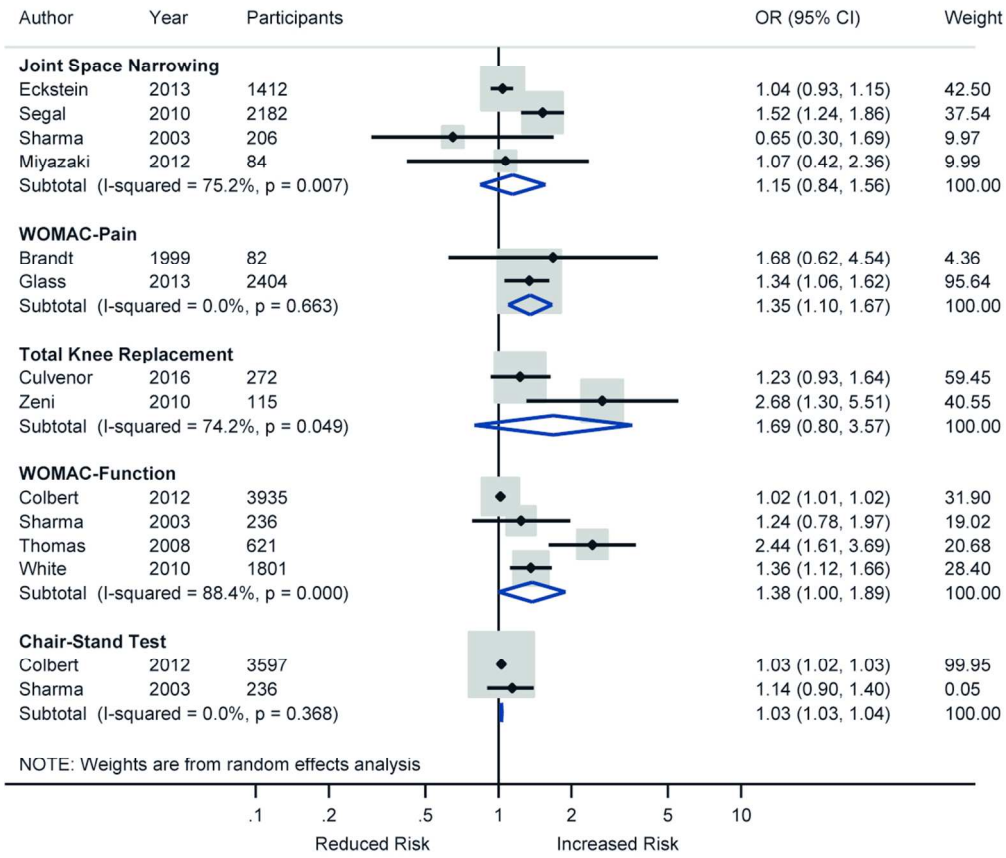

Figure 2. Results of meta-analyses on knee extensor weakness and the risk of structural (joint space narrowing), symptomatic (WOMAC-Pain, total knee replacement) and functional (WOMAC-Function, chair-stand task) deterioration. OR, odds ratio; CI, confidence interval; WOMAC, Western Ontario McMasters University Osteoarthritis Index.

205x182mm (150 x 150 DPI)

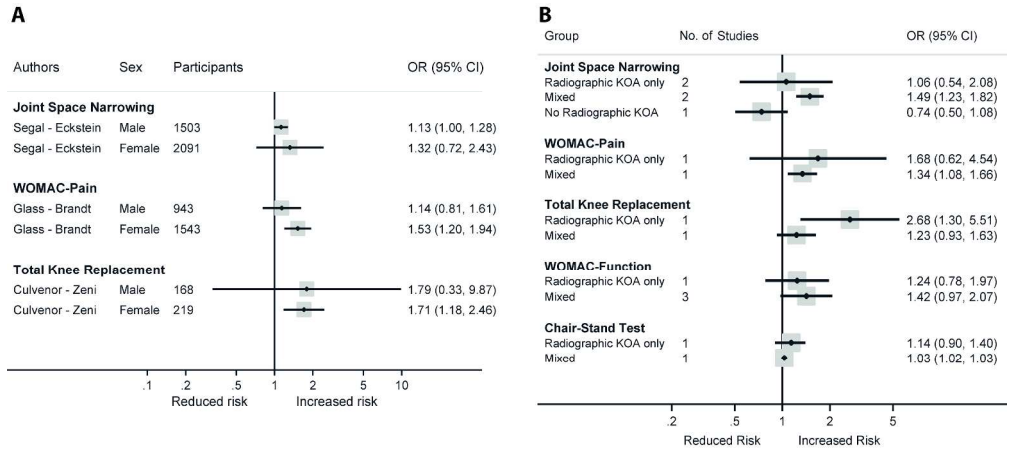

Figure 3. Results of meta-analyses on: (A) sex-specific low knee extensor strength and the risk of structural (joint space narrowing) and symptomatic (WOMAC-Pain, total knee replacement) deterioration; and (B) low knee extensor strength and the risk of structural (joint space narrowing), symptomatic (WOMAC-Pain, total knee replacement), and function (WOMAC-Function, Chair-stand test) based on KOA subgroup status (radiographic KOA, mixed, no radiographic KOA). OR, odds ratio; CI, confidence interval; WOMAC, Western Ontario McMasters University Osteoarthritis Index; KOA, knee osteoarthritis.

282x125mm (300 x 300 DPI)

Appendix 1. **Systematic search strategy**

MEDLINE	Knee [MeSH] OR knee [tiab] OR Knee joint [MeSH] OR Knee joint [tiab] OR tibiofemoral [tiab] OR Patellofemoral joint [MeSH] OR Patellofemoral joint [tiab] **AND** Muscle strength [MeSH] OR muscle strength [tiab] OR muscle weakness [MeSH] OR muscle weakness [tiab] OR quadriceps strength [tiab] OR quadriceps weakness [tiab] OR knee extension strength [tiab] OR knee extension weakness [tiab] OR knee strength [tiab] OR knee power [tiab] OR muscle power [tiab] OR muscle performance [tiab] OR muscle function [tiab] OR lower limb strength [tiab] OR lower limb weakness [tiab] **AND** Risk factors [MeSH] OR risk factors [tiab] OR risk [MeSH] OR risk [tiab] OR causality [MeSH] OR causal* [tiab] OR prognos* [tiab] OR causation [tiab] OR predisposing [tiab] OR predict* [tiab] OR longitudinal [tiab] **AND** Osteoarthritis [MeSH] OR Osteoarthritis, Knee [MeSH] OR osteoarthr* [tiab] OR arthrosis* [tiab] OR degenerative arthritis [tiab] OR gonarthr* [tiab]
Embase	Knee [MeSH] OR knee [tiab] OR Knee joint [tiab] OR tibiofemoral [tiab] OR Patellofemoral joint [MeSH] OR Patellofemoral joint [tiab] **AND** Muscle strength [MeSH] OR muscle strength [tiab] OR muscle weakness [MeSH] OR muscle weakness [tiab] OR quadriceps strength [tiab] OR quadriceps weakness [tiab] OR knee extension strength [tiab] OR knee extension weakness [tiab] OR knee strength [tiab] OR knee power [tiab] OR muscle power [tiab] OR muscle performance [tiab] OR muscle function [MeSH] OR muscle function [tiab] OR lower limb strength [tiab] OR lower limb weakness [tiab] OR limb weakness [MeSH]OR knee function [MeSH] OR muscle isometric contraction [MeSH] **AND** Risk factors [MeSH] OR risk factors [tiab] OR risk [MeSH] OR risk [tiab] OR causal* [tiab] OR prognos* [tiab] OR prognosis [MeSH] OR causation [tiab] OR predisposing [tiab] OR predict* [tiab] OR prediction [MeSH] OR longitudinal [tiab] OR longitudinal study [MeSH] **AND** Osteoarthritis [MeSH] OR Osteoarthritis, Knee [MeSH] OR knee, arthritis [MeSH] OR osteoarthr* [tiab] OR arthrosis* [tiab] OR degenerative arthritis [tiab] OR gonarthr* [tiab]
SportDISCUS	Knee OR knee joint OR tibiofemoral OR patellofemoral **AND** Muscle strength OR muscle weakness OR quadriceps strength OR quadriceps weakness OR knee extension strength OR knee extension weakness OR knee strength OR knee power OR muscle power OR muscle performance OR muscle function OR lower limb strength OR lower limb weakness **AND** Risk factors OR risk OR causal* OR prognos* OR causation OR predisposing OR predict* OR longitudinal **AND** Osteoarthr* OR arthrosis* OR degenerative arthritis OR gonarthr*
CINAHL	Knee OR knee joint OR tibiofemoral OR patellofemoral **AND** Muscle strength OR muscle weakness OR quadriceps strength OR quadriceps weakness OR knee extension strength OR knee extension weakness OR knee strength OR knee power OR muscle power OR muscle performance OR muscle

	function OR lower limb strength OR lower limb weakness **AND** Risk factors OR risk OR causal* OR prognos* OR causation OR predisposing OR predict* OR longitudinal **AND** Osteoarthr* OR arthrosis* OR degenerative arthritis OR gonarthr*
Scopus	Knee OR knee joint OR tibiofemoral OR patellofemoral **AND** Muscle strength OR muscle weakness OR quadriceps strength OR quadriceps weakness OR knee extension strength OR knee extension weakness OR knee strength OR knee power OR muscle power OR muscle performance OR muscle function OR lower limb strength OR lower limb weakness **AND** Risk factors OR risk OR causal* OR prognos* OR causation OR predisposing OR predict* OR longitudinal **AND** Osteoarthr* OR arthrosis* OR degenerative arthritis OR gonarthr*
Web of Science	Knee OR knee joint OR tibiofemoral OR patellofemoral **AND** Muscle strength OR muscle weakness OR quadriceps strength OR quadriceps weakness OR knee extension strength OR knee extension weakness OR knee strength OR knee power OR muscle power OR muscle performance OR muscle function OR lower limb strength OR lower limb weakness **AND** Risk factors OR risk OR causal* OR prognos* OR causation OR predisposing OR predict* OR longitudinal **AND** Osteoarthr* OR arthrosis* OR degenerative arthritis OR gonarthr*

Appendix 2. Reasons for study exclusion after full-text review

The 25 studies that were excluded after full-text review had a cross-sectional study design (1-5); did not report data for knee extensor muscle weakness related to the deterioration of structure, symptoms or function (6-9); investigated participants <50 years of age (10, 11); evaluated quadriceps muscle mass (12), investigated incident structural or symptomatic disease, where other studies from the same cohort focus on structural and symptomatic decline (13-15), investigated concurrent change in knee extensor strength and not prognostic capacity (16), included strength measures at follow-up in evaluation of outcome decline (17), investigated the same outcome in the same study population as another included study (18-22); was a review (23); investigated balance, which we considered an impairment (not a functional outcome) (24), or investigated only those with symptomatic improvement – a different population from all other included studies (25).

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