Knee extensor muscle weakness is a risk factor for the development of knee osteoarthritis. An updated systematic review and meta-analysis including 46,819 men and women In British Journal of Sports Medicine, 2021.

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Abstract

Objective: To update a systematic review on the association between knee extensor muscle weakness and the risk of incident knee osteoarthritis in women and men.
Design: Systematic review and meta-analysis
Data sources: Systematic searches in PubMed, EMBASE, SPORTDiscus, CINAHL, AMED, and CENTRAL in May 2021.

Eligible criteria for selecting studies: Longitudinal studies with at least two years follow-up including baseline measure of knee extensor muscle strength, and follow-up measure of symptomatic or radiographic knee osteoarthritis. Studies including participants with known knee osteoarthritis at baseline were excluded. Risk of bias assessment was conducted using six criteria for study validity and bias. Grading of Recommendations Assessments, Development and Evaluation (GRADE) assessed overall quality of evidence. Meta-analysis estimated the odds ratio (OR) for the association between knee extensor muscle weakness and incident knee osteoarthritis.

Results: We included 11 studies with 46,819 participants. Low quality evidence indicated that knee extensor muscle weakness increased the odds of symptomatic knee osteoarthritis in women (OR 1.85, 95% CI 1.29 to 2.64) and in adult men (OR 1.43, 95% CI 1.14 to 1.78), and for radiographic knee osteoarthritis in women: OR 1.43 (95% CI 1.19 to 1.71) and in men: OR 1.39 (95% CI 1.07 to 1.82). No associations were identified for knee injured populations except for radiographic osteoarthritis in men.

Discussion: There is low quality evidence that knee extensor muscle weakness is associated with incident symptomatic and radiographic knee osteoarthritis in women and men. Optimising knee extensor muscle strength may help to prevent knee osteoarthritis.

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What is already known

- Knee osteoarthritis is a leading cause of global disability and occurs at an alarming rate in young adults who suffer a traumatic knee injury
- Knee extensor muscle weakness may increase the risk for incident knee osteoarthritis

What are the new findings

- Low quality evidence indicates that individuals with knee extensor muscle weakness have higher odds for both symptomatic and radiographic knee osteoarthritis
- Low quality evidence indicates that no association exists between knee extensor muscle weakness and symptomatic and radiographic tibiofemoral osteoarthritis in women with a previous knee injury
- In men with a previous knee injury, low quality evidence indicates that knee extensor muscle weakness is associated with higher odds of radiographic (but not symptomatic) osteoarthritis

Introduction

Knee osteoarthritis is a leading cause of pain and disability in older adults[1, 2] and is associated with large healthcare and personal costs[3]. With no cure, treatment for knee osteoarthritis consists of weight control, physical activity, structured exercise, and analgesics[4]. Joint replacement is recommended for severe disease when non-pharmacological approaches have proven unsuccessful[2]. Due to the individual and societal burden of knee osteoarthritis, there is an urgent need for more knowledge on preventive strategies, particularly low-cost interventions targeting modifiable risk factors.

A possible modifiable risk factor is knee extensor muscle weakness[5]. Increasing knee extensor strength has for many years been an important treatment target in patients with knee osteoarthritis. The simplified theory underpinning the association between knee extensor muscle weakness and osteoarthritis is that muscles regulate joint loading and motion; and with optimal joint loads critical to maintenance of cartilage homeostasis weak muscles can increase susceptibility to degenerative joint pathology and negatively influence knee health[6].

In 2015, we published a systematic review and meta-analysis of longitudinal studies investigating the association between knee extensor muscle weakness and incident knee osteoarthritis[5]. Five studies with 5707 participants indicated increased odds of tibiofemoral osteoarthritis after 2.5 to 14-year follow-up in participants with knee extensor muscle weakness (OR 1.65, 95 % confidence interval (CI) 1.23 to 2.21). That analysis of only five studies, did not differentiate between symptomatic and radiographic osteoarthritis, and did not include studies on patellofemoral osteoarthritis, an emerging source of knee symptoms and disability. Further, there exists little knowledge on the contribution of knee extensor muscle weakness in subgroups at high risk for developing knee osteoarthritis, such as those following traumatic knee injury[7].

The objective of this study was therefore to update our systematic review and meta-analysis of the association between knee extensor muscle weakness and the risk of incident symptomatic or radiographic patellofemoral or tibiofemoral osteoarthritis in women and men. The secondary objective was to review the evidence of knee extensor muscle weakness as a risk factor for incident symptomatic or radiographic patellofemoral or tibiofemoral osteoarthritis in subgroups with high risk of knee osteoarthritis, such as following knee injury.

Methods

This systematic review was designed and conducted according to the Cochrane Handbook[8]. The reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline[9] (Appendix I) and was prospectively registered (PROSPERO ID: CRD42020214976).

Literature search and study selection

The search strategy for the current updated review was developed in 2015 for our original systematic review[5]. At that time in 2015 we consulted a librarian scientist and adapted the search strategy based on her feedback. Systematic searches with no constraints on date of publication or language were conducted in December 2020 in SPORTDiscus and CENTRAL, and in January 2021 in EMBASE, CINAHL, AMED, and PubMed by two authors (CBJ and BEØ). Searches were updated in May 2021 (search strategy in Appendix II). Two authors (BEØ and BB) independently screened all publications by title and abstract, and full-text as required, using the Rayyan application[10] and disagreements were resolved by consensus. Reference lists of included articles were reviewed and checked for potentially eligible studies. Citation tracking on included studies was performed in Web of Science by one author (CBJ).

Eligibility criteria

Prospective and retrospective cohort studies and randomized controlled trials with at least 2 years follow-up were eligible for inclusion. To be included, studies had to: i) assess knee extensor muscle strength at baseline; and ii) assess structural (e.g., tibiofemoral or patellofemoral joint with X-rays or magnetic resonance imaging) or symptomatic knee osteoarthritis (e.g., self-reported knee osteoarthritis defined by a health care provider or by using a self-reported score) at follow-up. Exclusion criteria were studies including participants with known symptomatic or radiographic knee osteoarthritis at baseline, studies of rheumatological diseases other than knee osteoarthritis and studies not reported in English or Scandinavian languages.

Risk of bias

Risk of bias was assessed using the questions adapted from Quality In Prognosis Studies (QUIPS) tool by Hayden et al.[11] covering six criteria for study validity and bias: study participation, study attrition, risk factor measurement, outcome measurement, confounding measurement and analysis. We modified the wording of the questions to "risk factor" instead of "prognostic factor". Two authors independently reviewed risk of bias of each study (BEO and AGC or JBT, and AGC and JBT for one paper[12]). Discrepancies between the two reviewers were resolved by consensus. The operationalization of the tool is shown in Appendix III.

Quality of evidence

We used the Grading of Recommendations Assessments, Development and Evaluation (GRADE) to assess the overall quality of the evidence[13]. The GRADE approach was adapted to prognostic research according to Huguet et al.[14]. GRADE rates the quality of evidence as high, moderate, low, or very low. The overall evidence is downgraded based on the following domain: early phase of investigation, study limitations, inconsistency, indirectness, imprecision, and publication bias. Two authors independently assessed the quality of evidence before consensus was reached (BEO and CBJ).

Data extraction and synthesis

The following data were extracted from each of the studies: number of participants at baseline and follow-up, participant characteristics (sex and age), sample characteristics (population source, country of origin), definition of knee osteoarthritis, and follow-up years. Data from analyses of the association between knee extensor muscle strength (in this paper referred to as knee extensor muscle weakness) and symptomatic and/or radiographic tibiofemoral and/or patellofemoral osteoarthritis was extracted from each study and for women and men separately wherever possible, by one author (CBJ). In studies with data from the same cohorts, data were extracted from the study with the largest sample. Most studies presented their results in Odds ratios (ORs), however, some presented the reduced OR of osteoarthritis in participants with high muscle strength compared to the ones with weak and these estimates were then reversed. Two studies[15, 16] presented the muscle strength for the group developing osteoarthritis and group not developing osteoarthritis. Based on these results the standardized mean differences (SMD) and standard error (SE) were estimated and later transformed to lnOR and SE LnOR using the formula from Chinn presented in the Cochrane Handbook.

A meta-analysis was applied based on the lnORs of the association between knee extensor muscle weakness and symptomatic and radiographic knee osteoarthritis in women and men and the results were transformed to OR. A random effect model (restricted maximum likelihood method, REML) was applied due to expected heterogeneity based on difference in assessment of knee extensor muscle weakness and symptomatic and radiographic knee osteoarthritis. Heterogeneity was assessed with a standard Q-test and calculated as the I^2 statistic[17] measuring the proportion of variation (i.e., inconsistency) in the combined estimates due to between-study heterogeneity[18]. The between study variance tau-square was estimated. Subgroup analyses were performed for knee injured populations. Finally, because one of the eligible studies included a large homogenous population that was very different to all other studies (i.e., 18 year-old healthy male conscripts)[19] we treated this study separately in meta-analyses.

Results

The searches yielded a total of 1101 studies (after removing duplicates). After full-text review of 16 studies, 10 were identified as being eligible. The six studies excluded at full-text review investigated osteoarthritis progression (i.e., participants with osteoarthritis included at baseline)[20] [21, 22] examined the same study sample as another included study[23, 24], or defined osteoarthritis arthroscopically[25] (Figure 1). With the addition of one extra study identified from reference list screening[16], the final number of included studies was 11[5, 15, 19, 26-32], consisting of a total of 46,819 participants. Two studies included participants from the Multicenter Osteoarthritis (MOST) study[30, 32], one assessed participants with meniscal pathology only, and was thus included in the subgroup analysis of knee injured populations only[32]. Study characteristics are presented in Table 1.

Risk of bias and overall evidence

Most studies (8/11) were judged to have high risk of attrition bias, whereas most studies had low risk of bias related to analyses, risk factor measurement, outcome measurement and confounding factor measurement (Appendix IV). The overall quality of evidence of the estimates was rated as low. Evidence was downgraded based on study limitations, phase of investigation (observational studies), and indirectness (Appendix V). The quality of evidence of the estimates from the studies of knee injured was downgraded due to imprecision (small sample sizes with few cases of knee osteoarthritis) and thus rated as very low-quality evidence.

The association between knee extensor muscle weakness and knee osteoarthritis

Low quality evidence based on three studies indicated that knee extensor muscle weakness was associated with incident symptomatic osteoarthritis for both women (OR 1.85, 95% CI 1.29, 2.64) and men (OR 1.43, 95% CI 1.14, 1.78) (Figure 2). All three studies adjusted for age and BMI and other potential confounding factors. One study included 18 years old male conscripts with 23 years of follow-up[19], and showed that knee extensor weakness was inversely associated with symptomatic osteoarthritis: unadjusted OR 0.66 (95% CI 0.59, 0.74).Low quality of evidence based on seven studies revealed an association between knee extensor muscle weakness and radiographic tibiofemoral osteoarthritis in both women: OR 1.43 (95% CI 1.19, 1.71) and men: OR 1.39 (95% CI 1.07, 1.82) (Figure 3). Six of these seven studies adjusted for possible confounding factors (e.g. age, BMI, activity level). One study assessed radiographic patellofemoral osteoarthritis[29] and reported no association between musculoskeletal factors (of which knee extensor muscle weakness was one) and patellofemoral radiographic osteoarthritis, however, no data specifically related to knee extensor weakness was provided.

The association between muscle weakness and knee osteoarthritis following knee injury

Very low quality evidence based on results from two studies of knee injured populations showed no association between knee extensor muscle weakness and incident symptomatic osteoarthritis (OR 1.20, 95% CI 0.85, 1.71) (Figure 4)[12, 32]. Correspondingly, very low quality evidence based on three studies showed no association between knee extensor muscle weakness and radiographic osteoarthritis (OR 1.08, 95% CI 0.87, 1.33)[16, 27, 29]. An association between knee extensor muscle weakness and incident radiographic osteoarthritis was observed in men (OR 1.42, 95% CI 1.01, 2.00), but not in women (OR 0.72, 95% CI 0.25, 2.06) (Figure 5). Two of the studies were adjusted for possible confounding factors (i.e. age, previous injury or surgery). Correspondingly, very low quality evidence based on three studies showed no association between knee extensor muscle weakness and radiographic osteoarthritis (OR 1.08, 95% CI 0.87, 1.33).

Discussion

In this update of our systematic review, we included six new studies in addition to the five studies included in our previous review[5]. The findings highlight that there is low quality evidence that knee extensor muscle weakness increases the odds of both symptomatic and radiographic knee osteoarthritis by around 30%. This relationship appears to be more pronounced in women than men. These findings extend our previous systematic review and meta-analysis published in 2015[5], where we reported a somewhat stronger association between knee extensor muscle weakness and incident knee osteoarthritis (OR 1.65, 95% CI 1.23 to 2.21), however those results included a mix of symptomatic and radiographic osteoarthritis. The inclusion of additional studies published since 2015 continues to support the importance of knee extensor muscle weakness as a potential risk factor for incident knee osteoarthritis.

The current meta-analysis showed an association between knee extensor muscle weakness and risk of incident symptomatic and radiographic knee osteoarthritis for both women and men. Despite the growing awareness of the importance of muscle strength in preventing osteoarthritis, relatively few new studies assessed the relationship between knee extensor muscle weakness and knee osteoarthritis since 2015, likely owing to the challenges of lengthy follow-ups required for monitoring radiographic knee osteoarthritis development. One new study we included assessed more than 40,000 male conscripts aged 18 years[19], which showed a protective effect of low quadriceps strength for incident knee osteoarthritis (OR 0.66, 95% CI 0.59, 0.74), and due to its size, it had considerable influence on the overall pooled result. This study differed from the remaining studies in several ways, which are important to highlight. Firstly, participants were much younger than any other included sample. Secondly, the follow-up time was 23 years – more than 8 years longer than any other study. Thirdly, participants had on average high baseline muscle strength – men in the lowest strength quartile had a mean strength of 177 Nm (SD 21). This is much higher than normative data for young men aged 20-29 years (estimated at approximately 107 Nm after converting from Newtons using the formula: *Strength in N*(shank length*body length*)[33]. They reported a mean isometric knee extensor strength of 242 N, and applying the formula used in Turkiewicz[19] to calculate Nm, this would for a male of 1.80 m tall correspond to a mean of 107 Nm (e.g. 242 N*(0.246*1,80m) = 107 Nm). Consequently, the study sample of young men may have been too strong to detect a relationship with knee osteoarthritis. Given that some authors have speculated that a certain threshold of strength is required to maintain knee joint health[26], it is plausible that all young male conscripts surpass such a threshold. Conscripts undergo a selection process and are likely healthier and more active than population-based cohorts, or those with a history of knee injury or other risk factors, such as those included in the OAI and MOST cohorts.

Five of the 11 studies investigated individuals with either ACL injury or meniscal pathology. No elevated overall odds of developing symptomatic or radiographic osteoarthritis was found, but men with knee extensor muscle weakness had higher odds of developing radiographic osteoarthritis. In general, the individual studies showed wide CIs, indicating imprecise estimates. Furthermore, the case numbers were low both in the study including meniscal pathology[32] and the studies of ACL injured participants[16, 29]. Consequently, we need high quality studies assessing knee extensor strength over several years after injury to increase the knowledge on a possible protective effect of quadriceps strength.

A challenge of combining the included studies is the different methods used to define knee osteoarthritis. Five studies included symptomatic knee osteoarthritis, and five included radiographic knee osteoarthritis. Moderate inter-rater reliability results have been found for the Kellgren and Lawrence classification system[34, 35], increasing the risk of misclassifications when defining participants with or without osteoarthritis, in particularly for cases in the transition between early (grade 1) and definite (grade 2) osteoarthritis.

The importance of knee extensor strength for osteoarthritis outcomes identified in the current review is supported by our other recent systematic review evaluating knee osteoarthritis progression and functional decline[36]. From the 15 included studies in that review an association between knee extensor weakness and symptomatic and functional decline was identified, particularly in women, whereas no relationship was observed between knee extensor muscle weakness and radiographic tibiofemoral joint space narrowing. Furthermore, we found inconclusive and conflicting evidence for knee extensor muscle weakness increasing the risk of patellofemoral structural deterioration and functional decline. Symptoms and functional decline are important consequences of knee osteoarthritis, yet they are not always closely related to structural changes[37]. The best available evidence suggests that knee extensor strengthening exercises should be implemented in patients with early signs of functional decline, which may be most important in women. Although we did not grade the level of evidence in our previous review, and the current review showed low and very low quality of evidence, results of these reviews together indicate that women with weak knee extensors are likely most at risk of symptomatic knee osteoarthritis, and for functional deterioration over time. Although we found an association between knee extensor muscle weakness and incident symptomatic and radiographic knee osteoarthritis, the therapeutic benefit and preventive effect of strengthening knee extensor muscles to prevent osteoarthritis has not yet been established. No clinical trial has been able to determine that an intervention for muscle strengthening can prevent symptomatic and/or radiographic knee osteoarthritis. Nevertheless, current best available evidence indicates that achieving and maintaining optimal knee extensor muscle strength is likely to be important for longer-term knee joint health and symptoms.

Strengths and Limitations

There are several limitations that need to be acknowledged. Firstly, there was considerable heterogeneity in the included studies. For example, there were differences in study populations, knee osteoarthritis definitions, knee extensor muscle weakness assessment methods and reporting of results. Although the study populations varied, our results likely apply across different populations as different population-based samples from various parts of the world were included (i.e., five studies included population-based participants, five studies involved previously knee injured participants, one study included male military participants). The risk of bias assessment showed that most studies had high risk of bias for study attrition. Consequently, data from participants that remained in the study may not accurately represent data from the total sample. Furthermore, the GRADE approach showed low and very low quality of evidence for these results. This indicates that even though the analyses revealed associations between knee extensor weakness and incident knee osteoarthritis, there is uncertainty in the results.

This study has some deviations from the PROSPERO protocol: We were able to perform *a priori* defined sub-group analyses for populations with knee injury. However, due to few studies and lack of data, sub-group analyses could not be performed for overweight or obese, malalignment and activity level. We changed from the ROBINS-I tool as developed by COCHRANE for non-randomized intervention studies, to the QUIPS tool because that tool was developed for assessing methodological quality of cohort studies.

Implications

Despite only low quality evidence linking knee extensor muscle weakness and incident knee osteoarthritis, knee extensor strengthening exercises should be highlighted in public recommendations for physical activity and health across the world, not only as a self-management target for people with knee pain (well-established effect size for lower-limb strengthening intervention on reducing pain is 0.5[38]), but also because of the potential protective effect on knee osteoarthritis development. This recommendation should be seen in the light of the fact that exercise is a low-cost intervention, especially if implemented as part of self-management, and exercise has a low risk of adverse events[39]. Future clinical trials need to confirm the protective effect of strengthening exercises on development of knee osteoarthritis.

Conclusion

In this updated systematic review and meta-analysis including 11 studies with 46,819 individuals we found low level evidence that knee extensor muscle weakness was associated with symptomatic and radiographic knee osteoarthritis at least two years later in both women and men. More studies are needed to provide valid estimates for specific subgroups, such as patients with previous knee injury or obesity. Best-evidence suggest that strengthening knee extensor muscles will help reduce the risk of developing knee osteoarthritis, but clinical trial evidence is required to confirm this.

Competing interests: We declare no competing interests by conducting this manuscript

Contributorship: All coauthors have read, commented, and reviewed at least three versions of the manuscript and the final draft. All coauthors have been involved in the quality assessments of the articles included in the systematic review. All coauthors agreed to update the systematic review with this design. Britt Elin Øiestad and Carsten B. Juhl performed the systematic searches, extracted data and selected articles for inclusion. Carsten B. Juhl conducted the meta-analyses. All authors critically reviewed the results and the certainty of evidence.

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Figure legends

Figure 1. Flow diagram of study selection.

Figure 2. Association between muscle weakness and symptomatic knee osteoarthritis.

Figure 3. Association between muscle weakness and radiographic knee osteoarthritis.

Figure 4. Association between muscle weakness and symptomatic knee osteoarthritis in knee injured individuals.

Figure 5. Association between muscle weakness and radiographic knee osteoarthritis in knee injured individuals.

542 Table 1. Characteristics of included studies (n=11)

First author	Number of subjects assessed and total cohort	Number (%) women	Age* (SD)	Sample characteristics	Definition of osteoarthritis	Definition of knee extensor strength**	Mean follow-up years
Culvenor et al. 2016	372/4796	208 (56)	61 (9)	Participants from OAI in USA	Radiographic (osteophyte + OARSI atlas JSN ≥1)	Isometric (N)	4
Ericsson et al. 2019	34/45	11 (32)	57 (range 50-61)	Participants from an exercise trial post-meniscectomy in Sweden	Radiographic (K&L ≥2)	Isokinetic concentric peak torque (Nm/kg*100)	11
Hootman et al. 2004	3081/5614	659 (21)	47 (10)	Population-based cohort with no previous knee injury in USA	Self-reported by physician	Isokinetic concentric peak torque ((kg/m)/BW)	14.4
Keays et al. 2010	56/113	17 (30)	27 (5)	ACL reconstructed in Australia	Radiographic (K&L ≥1)	Isokinetic strength index of contralateral knee	6
Øiestad et al. 2010	164/210	71 (43)	27 (9)	ACL reconstructed in Norway	Symptomatic radiographic (pain last month + K&L ≥2)	Isokinetic concentric total work (Joules)	12.1
Segal et al. 2009	1617/3026	937 (58)	61 (8)	Participants from MOST in USA	Symptomatic (pain, aching or stiffness last month + K&L ≥2)	Isokinetic concentric peak torque (Nm)	2.5
Slemenda et al. 1998	280/462	141 (20)	71 (5)	Community-dwelling elderly participants from USA	Radiographic (K&L ≥2)	Isokinetic concentric peak torque (Pound-foot)	2.5
Takagi et al. 2018	491/517	282 (57)	65 (10)	Participants from a population-based cohort Japan	Radiographic (K&L ≥2)	Isometric 20° flexion (kg-force)	6

Thorlund et al. 2016	531/3026	291 (55)	62 (7)	Participants with meniscal pathology from MOST in USA	Symptomatic (pain, aching or stiffness last month + K&L ≥2)	Isokinetic concentric peak torque ($Nm*kg^{-0.74}$)	7
Turkiewicz et al. 2017	40117/41886	0 (0)	18	Participants were men who underwent a mandatory military conscription examination in 1969-1970 from Sweden	First record of knee osteoarthritis registered in inpatient or specialist care between 1987-2010	Isometric (Newtons*shank length (m))	22.8
Wellsandt et al. 2020	76/142	27 (36)	29 (11)	ACL injured participants from USA	Radiographic (K&L ≥2)	Limb symmetry index of maximal voluntary isometric contraction	5

SD, standard deviation; OAI, Osteoarthritis Initiative; OARSI, Osteoarthritis Research Society International, K&L, Kellgren and Lawrence classification system; ACL, anterior cruciate ligament; MOST, Multicenter Osteoarthritis Study; N, Newton; Nm, newton meter; BW, body weight; kg, kilogram; m, meters; OA, osteoarthritis; JSN, joint space narrowing. *Mean age at baseline. **All studies tested knee extensor strength using isokinetic equipment.