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Review

Neuromuscular joint function in knee osteoarthritis: A systematic review and meta-analysis

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ABSTRACT

Background: Neuromuscular alterations are common in people with knee osteoarthritis (KOA). A comprehensive understanding of these alterations is important to enable targeted rehabilitation strategies.
Objectives: This systematic review and meta-analysis aimed to comprehensively understand the neuromuscular alterations around the knee joint in people with KOA.
Methods: Moderate- and high-quality studies based on a modified version of the Downs and Black checklist, comparing neuromuscular function of peri-articular muscles between people with KOA and controls were retrieved from five databases from inception to October 2020. Outcomes included normalized isokinetic strength, muscle size, voluntary activation, cortical and spinal-reflex excitability, and torque-related outcomes. Data were pooled according to structural KOA severity with sensitivity analysis based on sex. Evidence levels are presented in evidence gap maps.
Results: A total of 7 high-quality and 22 moderate-quality studies were retained (1146 people with KOA and 1353 age- and sex-matched controls). Studies demonstrated quadriceps and hamstring strength deficits and increased hamstring-to-quadriceps strength ratios across KOA severities. Women presented lower quadriceps strength at early KOA (very limited evidence) and lower voluntary activation at end stage KOA (very limited evidence) as compared with controls, whereas men did not (moderate evidence). People with KOA also demonstrated lower quadriceps force control ability with no change in rapid force production (very limited evidence). Voluntary activation deficits for quadriceps were evident (moderate evidence), with no change in quadriceps cortical excitability (very limited evidence) or soleus spinal reflexes (very limited evidence). No muscle size change was demonstrated except for the vastus medialis (limited evidence). Evidence gaps were found for neural and torque-related measures and differences in hamstring, gastrocnemius, soleus, and popliteus.
Conclusions: Neuromuscular deficits are evident across different structural KOA severities and are seen in muscle strength, voluntary activation, muscle size, and force control ability. Women may exhibit these alterations to a greater extent than men.
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Introduction

Knee extensor muscle weakness is a risk factor for knee osteoarthritis (KOA) [1] and is commonly observed in people with KOA [2,3]. Therefore, exercise is recommended as first-line treatment for KOA [4], with structured land-based exercises [4,5], knee extensor strengthening exercises [6], and aerobic exercises [6] forming the core of treatment programs. Strengthening of the knee extensors is effective in reducing pain and increasing both quality of life and functional capacity in people with KOA [5].

Although the importance of the knee extensors has been widely studied, less is known about differences from normal in the other muscles controlling the knee joint in people with KOA. It is important to comprehensively understand these neuromuscular alterations to provide targeted exercise strategies, as has been shown in a previous systematic review of hip strength deficits in people with KOA, showing that hip strengthening should be considered in the design of rehabilitation programmes [7]. Specifically for the knee, previous studies have shown strength deficits in quadriceps [2,3], hamstring [3], and gastrocnemius [8] muscles in people with KOA. Alterations are also seen in voluntary activation [9], spinal reflexes [10] and

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muscle sizes [11], which are likely contributors to the observed strength deficits. Although these alterations suggest the complexity of the neuromuscular alterations in people with KOA, the available evidence needs to be synthesized to comprehensively document these possible changes. Identification of these factors could inform the detail of exercise and treatment prescription in order to focus on parameters such as voluntary activation capacity, rapidity of force production and force control ability rather than only focusing on maximum muscle strength.

Therefore, the aim of the study was to identify neuromuscular alterations in the muscles controlling the knee joint (quadriceps, hamstring, gastrocnemius, soleus, and popliteus) in people with KOA as compared with age- and sex-matched healthy controls. Furthermore, because of sex-related differences in KOA in terms of severity and risks [12] and neuromuscular alterations [13], we aimed to understand whether there are neuromuscular differences between men and women with KOA. The findings will constitute a comprehensive review of neuromuscular alterations around the knee joint, which should inform exercise selection in people with KOA when designing rehabilitation strategies.

Methods

The updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for this systematic review and meta-analysis [14]. The study protocol was registered at PROSPERO (International Prospective Register of Systematic Reviews) (CRD42019160845, December 10, 2019).

Search strategy

The following electronic databases were systematically searched with no date restrictions until October 2020: PubMed, Embase, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL). MeSH terms and text words were included in the search terms. The search strategy was modified for each specific database, with keywords and concepts remaining identical. The main concepts were knee osteoarthritis AND neuromuscular (strength, reflex, activation, electromyography, size) AND lower limb muscles (quadriceps, hamstring, gastrocnemius, soleus, popliteus). Search strategies for all databases are available in Supplementary Material S1. Two reviewers (BT and CC) independently conducted the searches, removed duplicates, screened all abstracts for eligibility and retrieved full-text versions of eligible articles. Disagreements were resolved by a third reviewer (SCM). The reference lists of the included articles and related systematic reviews were searched for additional studies.

Selection criteria

Studies were eligible if they compared the neuromuscular function of the knee joint in participants with KOA to an age- and sex-matched control group. There were no age limitations for inclusion. Studies were included only if participants had KOA with radiographic confirmation, ideally described with Kellgren-Lawrence (KL) grades [15], with all stages of KOA (i.e., early, established and end stage). We excluded studies of people with a history of surgery for KOA (i.e., knee replacement). However, if the study reported data before participants underwent surgery, we included the study and used the baseline pre-surgical data. Data from these studies were pooled in the "end stage KOA" group. We had no restrictions on symptoms; studies of people with or without any knee symptoms/pain were included. We had no restrictions on the cause of KOA (i.e., idiopathic vs post-traumatic). We excluded studies without a control group or comparing the involved limb to the uninvolved limb of participants because of evidence of bilateral neuromuscular changes in unilateral KOA [16]. Radiographic confirmation of not having KOA for the control group was not a requirement for inclusion. If studies reported radiographic KOA for the control group, it is reported in the characteristics of the included studies. We included cross-sectional or prospective observational studies and interventional studies. Only baseline data from interventional studies were used. We included only studies published in English.

Outcome measures

The neuromuscular outcomes of interest were as follows: body-mass normalized muscle strength as measured by an isokinetic dynamometer or fixed force transducer; torque-related outcomes such as rate of torque development, torque variability or electromechanical delay; muscle size (thickness [cm] or area [cm^2]); voluntary activation deficits as measured by central activation ratio or twitch interpolation technique; and spinal reflex excitability or corticomotor excitability as measured by active motor threshold. These outcomes were identified from preliminary literature searches to include all relevant neuromuscular measures.

Data extraction

The study design, participant characteristics (number of participants, age, sex, structural severity, symptoms) and outcome measures (measured muscle groups and outcome) were extracted by 2 reviewers (BT and CC) independently in a Microsoft Excel spreadsheet. Discrepancies were resolved by consultation and checked with a third reviewer (SCM). Group means and standard deviations were extracted for main outcome measures. Corresponding authors were contacted by e-mail to request unreported data or additional details, if the reported data were incomplete.

Methodological quality assessment

A modified version of the Downs and Black checklist [7,17] was used to assess the risk of bias of included studies (Supplementary Material S2). The Downs and Black checklist is a methodological quality assessment tool for both randomised and non-randomised interventional studies with high internal consistency and inter-rater reliability [17]. The modified version contains 15 questions, excluding the questions about randomisation and interventions from the original version. The highest score of the modified version is 16, and thresholds for low, moderate and high quality were accepted as <60% (≤9), 60–74% (10–11), and >75% (≥12), respectively, guided by previous studies [18,19]. Low-quality studies were then excluded because they may cause over- or under-estimation of effect sizes and may distort results, thus leading to incorrect conclusions [20,21]. Two independent reviewers (BT and CC) assessed methodological quality, and disagreements were resolved by discussion and checked with a third reviewer (SCM).

Statistical analysis

Meta-analysis was performed when data from 2 or more studies were suitable to pool based on methodological homogeneity and similarly reported data. Data were pooled as the KOA versus control group and also based on the reported structural severity of KOA as follows: early KOA (KL grade 0–1), established KOA (KL grade 2–3), or end stage KOA (KL grade 4). In the literature, typically, a KL grade of 4 is clustered within the established KOA (KL grade ≥2) group. As such, in our analysis, we placed people with a KL grade of 4 in the end stage classification only when they were reported separately in the paper. Also, studies reporting data obtained before total knee replacement surgery were included in the end stage KL grade 4 group. A few studies reported a mix of KL levels (i.e., KL grade 1 or 2), which we included in the early KOA group. For studies sub-grouping

people with KOA (i.e., younger vs older) and reporting the data separately, we combined the data for all KOA groups by using Cochrane Review Manager v5.3 (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). To achieve the second aim of understanding potential sex-related differences, sensitivity analyses were based on sex when available, by pooling the data for women and men separately and comparing the results. Two further post-hoc sensitivity analyses based on pain and presence of patellofemoral damage were also performed.

Cochrane Review Manager v5.3 was used for the meta-analyses. Standardised mean differences (SMDs; Hedges' adjusted *g*) with 95% confidence intervals (CIs) were calculated for variables of interest as the difference between the injured leg (KOA group) and healthy control leg (control group). The criteria for pooling the data for the meta-analysis were strict in terms of clinical tests (i.e., only fixed force transducer or isokinetic dynamometer strength tests that were body-mass normalized were included and only similar testing velocities and same contraction types [fast vs slow, eccentric vs concentric vs isometric] were pooled). The clinical population were also carefully selected (i.e., the same KOA structural severities). Therefore, data from different studies were pooled only if they met the pooling criteria. However, because this is a clinical population, there may always be other contributors to the outcome (i.e., pain or other factors that have not been measured). Therefore, random effects models were used for each meta-analysis when data were pooled. Single study results were also reported in forest plots to present data. The magnitude of the pooled SMD was interpreted based on Cohen's criteria, where SMD ≥0.8 indicated large, 0.5–0.8 moderate, and 0.2–0.5 small effect sizes [22]. Potential publication biases were examined by funnel plots for meta-analyses when ≥ 10 studies were included [21]. Heterogeneity of the pooled data was analysed with I^2. I^2 values were interpreted as no heterogeneity (≤25%), low heterogeneity (>25%), moderate heterogeneity (>50%), and high heterogeneity (>75%) [23].

Level of evidence

Level of evidence was reported according to the following criteria: strong evidence (multiple high-quality studies that were statistically homogenous); moderate evidence (multiple studies including at least one high-quality study regardless of heterogeneity or from multiple moderate-quality studies that are statistically homogenous); limited evidence (one high-quality study or multiple moderate-quality studies that are statistically heterogeneous); and very limited evidence (one moderate quality) [24].

Evidence gap maps

An evidence gap map was created to summarise the findings and show the level of evidence related to findings arranged by muscle group, measure and stage of KOA. This has the additional benefit of potentially avoiding research waste in areas with strong evidence and guiding future studies to fill the research gaps.

Results

Study selection

The search strategy yielded 14,295 papers after the removal of duplications (Fig. 1). After title and abstract screening, 277 articles were assessed in full text and 74 studies were eligible for quality assessment. After quality assessment, 45 low-quality studies were excluded, which left 7 high-quality [2,3,11,25–28] and 22 moderate-quality [8-10,13,29–46] studies for final inclusion. Details of methodological quality assessment of included studies are in Table 1 and excluded studies are in Supplementary Appendix S3.

Study characteristics

The characteristics and outcome measures of each included study are in Table 2. Study findings were all suitable for meta-analysis or presentation in forest plots and were therefore reported in Figs. 4, 5, 6 or Supplementary Appendix S4. Overall, the included 29 studies comprised measures of 1146 people with KOA and 1353 age- and sex-matched controls. Average participant ages ranged from 45 tp 74 years. Definitions of KOA and control group inclusion criteria were heterogeneous across studies in terms of structural changes within the joint and symptoms. Most studies reported quadriceps muscle strength, and other muscles or other neuromuscular outcomes were measured in only a few studies.

Findings

The overall comparison of the KOA group to controls showed deficits in quadriceps strength (isometric SMD [95% CI] −0.84 [−1.05; −0.62], concentric slow SMD [95% CI] −0.66 [−0.95; −0.38], concentric fast SMD [95% CI] −0.92 [−2.01; 0.16], eccentric slow SMD [95% CI] −0.82 [−1.27; −0.36], eccentric fast SMD [95% CI] −0.64 [−1.28; 0.00]) and quadriceps voluntary activation (SMD [95% CI] −0.65 [−1.12; −0.18]). The KOA and control groups did not differ in quadriceps cortical excitability (SMD [95% CI] 0.02 [−0.62; 0.67]), but torque variability for quadriceps was higher in the KOA than control group (SMD [95% CI] 0.98 [0.32; 1.64]). The 2 groups did not differ in quadriceps rate of torque development (SMD [95% CI] −0.09 [−0.65; 0.48]). The KOA group showed hamstring isometric strength deficits (SMD [95% CI] −0.54 [−0.83; −0.26]), but the KOA and control groups did not differ in hamstring concentric slow strength (SMD [95% CI] −0.45 [−0.96; 0.07]). The KOA group commonly showed gastro-soleus (i.e., plantar flexion) strength deficits for isotonic contractions but no difference from controls in isometrics (isometric SMD [95% CI] −0.51 [−1.11; 0.09], concentric slow SMD [95% CI] −2.05 [−2.69; −1.41], eccentric slow SMD [95% CI] −2.15 [−2.78; −1.52]) or soleus spinal excitability (SMD [95% CI] = 0.72 [−0.15; 1.59]). Muscle thickness was smaller in the KOA than control groups for vastus medialis (SMD [95% CI] −0.96 [−1.80; −0.11]) and vastus lateralis (SMD [95% CI] −0.32 [−0.58; −0.06]), with no difference in rectus femoris (SMD [95% CI] −0.13 [−0.61; 0.36]) or vastus intermedius (SMD [95% CI] −0.16 [−0.46; 0.14]). The 2 groups did not differ in muscle thickness of biceps femoris (SMD [95% CI] −0.14 [−0.94; 0.67]), gastrocnemius (SMD [95% CI] −0.40 [−1.21; 0.41]) or soleus (SMD [95% CI] 0.15 [−0.66; 0.95]). Quadriceps muscle area (cm^2) was similar between KOA and control groups (SMD [95% CI] 0.11 [−0.05; 0.27]).

The overall findings (direction, effect size and level of evidence) of all meta-analyses based on structural KOA severities for each outcome measure are summarised in the evidence gap maps (Figs. 2 and 3). We could not identify any publication bias for eligible outcomes (i.e., with > 10 studies in the meta-analysis; quadriceps isometric strength) as measured by funnel plots. All meta-analyses and funnel plots are in Supplementary Appendix S4.

Quadriceps and hamstring strength deficits were common at all structural KOA severities (early, established and end stage), but the magnitude of the effect depended on the contraction type (i.e., isometric, concentric, or eccentric) (Figs. 2, 4 and 5, Supplementary Appendix S4). Effect sizes were higher but not significantly for isometric and concentric quadriceps strength with increasing structural severity (Figs. 2 and 4, Supplementary Appendix S4). People with established KOA exhibited an increased ratio of hamstring to quadriceps strength, with a large effect size (very limited evidence), which suggests that quadriceps strength may be affected more than hamstring strength (Fig. 2).

In addition to reduced peak strength, people with established KOA exhibited higher quadriceps torque variability (expressed as the standard deviation from the target forces during an isometric quadriceps

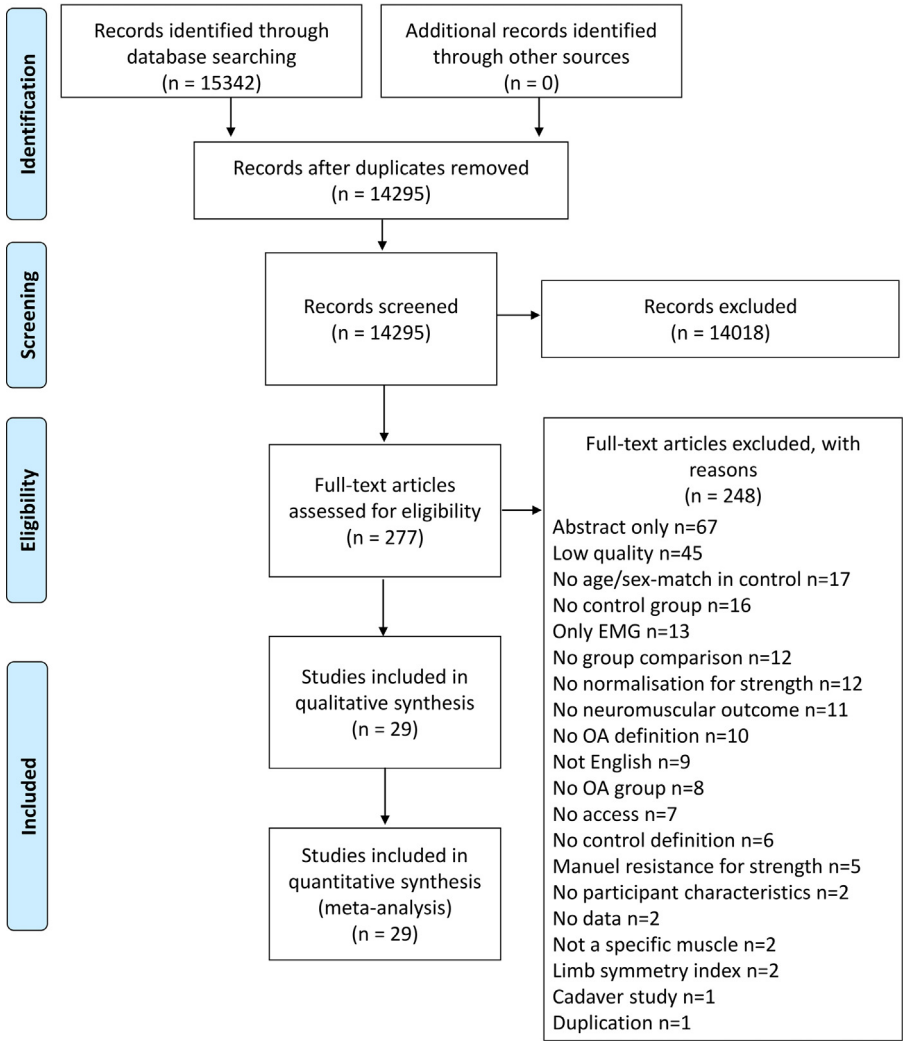

Fig. 1. Flow diagram of the study selection process. OA, osteoarthritis.

contraction) than controls (very limited evidence). In one study including all KOA severities, quadriceps rate of torque development did not differ from controls (very limited evidence) (Fig. 2, Supplementary Appendix S4). Rate of torque development was measured as the first derivative of the "small, medium and large" force pulses normalized to the maximum voluntary isometric contraction (%MVIC). The highest peak rate of torque development value of these force pulses was used.

For plantar flexion strength (gastrocnemius and soleus), people with early and established KOA exhibited lower strength than controls (very limited evidence), with no difference for people with end stage KOA (limited evidence) (Figs. 3 and 5).

Muscle size was not affected in quadriceps, hamstring, gastrocnemius or soleus muscles (limited to strong evidence), except for vastus medialis (limited evidence), which was lower in people with established KOA (large effect size, limited evidence) than controls (Figs. 2, 3, Supplementary Appendix S4). Muscle thickness was used as a measure of muscle size and measured using 2D B-mode ultrasonography in 3 studies [3,11,47]. Muscle area (cm^2) was also used to measure muscle size with a Dual Energy X-ray Absorptiometry scan and CT scan in one study [2].

Neural function was assessed for quadriceps femoris and soleus muscles only. For quadriceps femoris, people with end stage KOA did not differ from controls in cortical excitability (very limited evidence) and those with established and end stage KOA exhibited lower voluntary activation (moderate evidence) (Figs. 2, 3 and 4, Supplementary Appendix S4). Cortical excitability was assessed by measuring resting motor threshold using transcranial magnetic stimulation of the quadriceps representation at the primary motor cortex in one study [46]. Voluntary activation was measured in 6 studies, using twitch interpolation [9,28,45,46] or central activation ratio [13,34] calculations. The stimulus parameters also differed across these 6 studies. Methodological details can be found in Supplementary Appendix S5. The effects of the measurement method was checked with a sensitivity analysis. Studies using central activation ratio tended to report higher values for the KOA than control group and showed no difference between groups in pooled SMD (−0.22 [−0.58; 0.14]). Conversely, the twitch interpolation method showed a large effect size toward lower voluntary activation levels in the KOA than control group (SMD [95% CI] −0.88 [−1.40; −0.37]).

For soleus, people with KOA showed no difference from controls in spinal excitability (very limited evidence) during walking as measured by the Hoffman reflex/Muscle wave ratio (Fig. 3, Supplementary Appendix S4).

Evidence gaps were notable for most outcomes, with strong evidence for only 2: quadriceps muscle area and isometric hamstring strength in established KOA. Mostly, neural changes and torque-related outcomes (timing and control) were not investigated. Similarly, gastrocnemius and soleus muscles were measured in only 4 studies, and we found only very limited to limited evidence to make suggestions for these outcomes. Studies reporting hamstring muscle data were mainly limited to isometric strength. No studies were

Table 1
Methodological quality assessment of included studies. A modified Downs and Black scale [17] was used (header numbers refer to item number in the original scale).

Studies\Questions	1	2	3	5	6	7	10	11	12	15	18	20	21	22	25	Total Score	Quality Level
Aily et al. 2019 [25]	1	1	1	2	1	1	0	1	0	0	1	1	1	0	1	12	H
Alkjaer et al. 2015 [10]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Bade et al. 2010 [41]	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	10	M
Baert et al. 2013 [42]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Berger et al. 2011 [43]	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	10	M
Conroy et al. 2012 [2]	1	1	1	2	1	1	1	1	0	0	1	1	1	1	1	14	H
Goncalves et al. 2017 [8]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Hall et al. 2006 [26]	1	1	1	1	1	1	0	1	0	1	1	1	1	1	0	12	H
Hortobagyi et al. 2004 [44]	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	10	M
Hurley et al. 1997 [45]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	10	M
Kittelson et al. 2014 [46]	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	10	M
Kumar et al. 2013 [29]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	10	M
Kumar et al. 2014 [30]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Levinger et al. 2016 [31]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Liikavainio et al. 2008 [3]	1	1	1	2	1	1	1	1	0	0	1	1	1	0	0	12	H
Pap et al. 2004 [9]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	10	M
Patsika et al. 2014 [32]	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	10	M
Petrella et al. 2017 [33]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	10	M
Petterson et al. 2007 [13]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Ramsey et al. 2007 [34]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Ruhdorfer et al. 2020 [27]	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	12	H
Rutherford et al. 2011 [35]	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	11	M
Rutherford et al. 2013 [36]	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	11	M
Sanchez-Ramirez et al. 2016 [37]	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	11	M
Schmitt and Rudolph 2007 [38]	1	1	1	1	1	1	1	0	0	0	1	1	1	0	0	10	M
Serrao et al. 2015 [39]	1	1	1	1	1	1	0	1	0	0	1	1	1	0	0	10	M
Taniguchi et al. 2015 [11]	1	1	1	1	1	1	1	1	0	1	1	1	1	0	0	12	H
van Leeuwen et al. 2017 [28]	1	1	1	2	1	1	1	1	0	0	1	1	1	1	1	14	H
Winters and Rudolph 2014 [40]	1	1	1	1	1	1	1	1	0	0	1	1	0	0	0	10	M

H, high quality; M, moderate quality.

found for popliteus neuromuscular outcomes. Details of the evidence gaps are in Figs. 2 and 3.

Sensitivity analysis based on sex

Sensitivity analysis based on sex (women vs men) showed differences for several outcomes. Data were available for quadriceps voluntary activation, quadriceps isometric and concentric strength, hamstring isometric strength and quadriceps muscle (rectus femoris, vastus lateralis, vastus intermedius) thickness. Meta-analyses forest plots are in Fig. 6 and Supplementary Appendix S4.

For quadriceps isometric and concentric strength, we found an effect of sex in early KOA (Fig. 6, Supplementary Appendix S4). However, we found no effect of sex in established or end stage KOA for isometric strength; no data were available for concentric strength for comparison for established or end stage KOA. Women presented lower strength at early KOA (very limited evidence) than controls, whereas men showed no difference from controls (moderate evidence) (Fig. 6). The same analysis without any structural severity classifications (i.e., all KOA vs controls) supported these findings because women with KOA showed a greater reduction in strength (SMD [95% CI] −1.11 [−1.62; −0.61]) than men with KOA (SMD [95% CI] −0.74 [−1.18; −0.31]) as compared with age- and sex-matched controls. Quadriceps voluntary activation data were available for end stage KOA and showed that women with KOA had lower voluntary activation than controls (very limited evidence), whereas men did not (very limited evidence) (Fig. 6). We found no differences between the sexes for hamstring strength or quadriceps muscle thickness (Supplementary Appendix S4).

Post-hoc sensitivity analysis based on pain and presence of patellofemoral damage

For studies including both painful and pain-free KOA groups [2,26,27], using only painful KOA or all KOA group data did not change the results to a meaningful extent (Δ effect size <0.03). Five studies did not report pain levels for the included participants [13,32,38,41,46], and, again, excluding those studies from pooled data did not change the results meaningfully (Δ effect size <0.09). Pain and symptoms information from all included studies, and sensitivity analysis results can be found in Supplementary Appendix S6. Also, patellofemoral osteoarthritis involvement was reported in only 3 studies [8,38,40]. One study reported percentages and grades of patellofemoral OA [8] and 2 studies reported no patellofemoral involvement [38,40]. Sensitivity analysis excluding these studies did not change the results (Δ effect size =0.0).

Post-hoc sensitivity analysis based on study quality

The effect of study quality was checked for available outcomes, isometric quadriceps strength and slow concentric quadriceps strength. We found no differences in data between high-quality and moderate-quality studies when pooled. For isometric quadriceps strength, high-quality studies (SMD [95% CI] −0.94 [−1.34; −0.55]) and moderate-quality studies (SMD [95% CI] −0.77 [−1.03; −0.51]) yielded similar results. For slow concentric quadriceps strength, again, high-quality studies (SMD [95% CI] −0.67 [−1.16; −0.17]) and moderate-quality studies (SMD [95% CI] −0.68[−1.11; −0.26]) showed similar findings.

Discussion

In this systematic review, we aimed to identify neuromuscular alterations in the muscles controlling the knee joint in people with KOA as compared with age- and sex-matched controls. We provide a synthesis of all neuromuscular alterations with evidence levels, juxtaposed with gaps in evidence for which further research is likely required. Studies showed lower quadriceps, hamstring, gastrocnemius and soleus muscle strength (very limited to moderate evidence) in the KOA than control group, which shows the need to target these muscle groups while designing exercise protocols for people with KOA. Voluntary activation deficits were evident for quadriceps femoris muscle (moderate evidence), which suggests neural contribution to muscle weakness in people with KOA. However, we found no

Table 2
Characteristics of the included studies and outcome measures reported in each study.

Author/year (study design)	Sample size (men/women)	Age (mean [SD] or median [range])	Structural severity and symptoms	Outcome measures
Aily et al. 2019 [25] Cross-sectional	KOA middle-aged: 20 (10/10) KOA older: 20 (10/10) Control middle-aged: 20 (10/10) Control older: 20 (10/10)	KOA middle-aged: 45.3 (2.7) KOA older: 74.3 (2.8) Control middle-aged: 45.2 (3.7) Control older: 74.6 (3.1)	KOA: KL grade 2 and 3, Clinical signs, ACR criteria*, persistent knee pain Control: KL grade 0 and 1, asymptomatic, no previous knee injury	Quadriceps muscle thickness, Quadriceps concentric and isometric strength
Alkjaer et al. 2015 [10] Cross-sectional	KOA: 11 (0/11) Control: 11 (0/11)	KOA: 69.0 (6.6) Control: 66.1 (4.5)	KOA: KL grade 1−4, Clinical diagnosis Control: Healthy	Soleus Hoffmann reflex
Bade et al. 2010 [41] Intervention	KOA: 24 (12/12) Control: 17 (9/8)	KOA: 65.0 (9.4) Control: 66.8 (6.5)	KOA: End stage KOA Control: No knee pain	Quadriceps isometric strength
Baert et al. 2013 [42] Cross-sectional	Early KOA: 14 (0/14) Established KOA: 12 (0/12) Control: 14 (0/14)	Early KOA: 65.4 (8.9) Established KOA: 68.3 (6.8) Control: 65.8 (9.9)	Early KOA: Knee pain, KL grade 0, 1 or 2− (osteophytes only) Established KOA: KL grade ≥2, Clinical signs, ACR criteria* Control: Asymptomatic, had no history of KOA or other pathology involving any lower extremity joints. KL grade 0 and 1	Quadriceps concentric and isometric strength, Hamstring isometric strength
Berger et al. 2011 [43] Cross-sectional	KOA: 8 (4/4) Control: 8 (4/4)	KOA: 61.3 (3.8) Control: 61.8 (5.9)	KOA: Clinical signs, ACR criteria*, persistent pain and diagnosis by radiographs and symptoms Control: No self-reported history of knee pain	Quadriceps isometric strength
Conroy et al. 2012 [2] Cross-sectional	KOA pain: 170 (69/101) KOA no pain: 91 (38/53) Control: 334 (140/194)	KOA pain: 74.1 (3.1) KOA no pain: 73.7 (2.9) Control: 73.3 (2.7)	KOA: KL grade ≥2 and knee pain or no knee pain Control: No knee pain, no radiographic KOA	Quadriceps muscle area (cm^2), Quadriceps concentric strength
Goncalves et al. 2017 [8] Cross-sectional	Mild KOA: 22 (12/10) Moderate KOA: 15 (8/7) Control: 15 (8/7)	Mild KOA: 55.9 (6.62) Moderate KOA: 57.6 (6.31) Control: 54.20 (6.30)	KOA: Clinical signs, ACR criteria*, Mild: KL grade 2, Moderate KL grade 3 Control: Asymptomatic individuals with no radiographic signs of KOA	Gastrocnemius isometric, concentric, eccentric strength
Hall et al. 2006 [26] Cross-sectional	Painful KOA: 36 (14/22) No-pain KOA: 23 (7/16) Control: 55 (17/38)	Painful KOA: 68.78 (7.80) No-pain KOA: 69.22 (5.78) Control: 67.49 (8.45)	KOA: KL>2, pain Control: KL grade <2, no pain	Quadriceps isometric strength
Hortobagyi et al. 2004 [44] Cross-sectional	KOA: 20 (5/15) Control: 20 (5/15)	KOA: 57.5 (7.3) Control: 56.8 (5.0)	KOA: KL grade ≥2 and knee pain Control: No pain	Quadriceps torque variability
Hurley et al. 1997 [45] Cross-sectional	KOA: 103 (38/65) Control: 25 (7/18)	Mean (95%CI); KOA: 60.73 (58.7, 62.73) Control: 65.6 (61.66, 69.54)	KOA: ACR criteria*, knee pain Control: No history of recurrent knee pain, no episode of knee pain in the last 12 months	Quadriceps voluntary activation
Kittelson et al. 2014 [46] Cross-sectional	KOA: 17 (8/9) Control: 20 (10/10)	KOA: 63.9 (1.8) Control: 58.3 (2.5)	KOA: Waiting for knee arthroplasty Control: No current knee pain or history of knee trauma	Quadriceps voluntary activation, corticospinal excitability
Kumar et al. 2013 [29] Cross-sectional	KOA: 16 (8/8) Control: 12 (6/6)	KOA: 65.2 (9.5) Control: 59.5 (10.4)	KOA: KL grade ≥2, ACR criteria* Control: KL grade ≤1, healthy	Quadriceps isometric strength
Kumar et al. 2014[30] Cross-sectional	KOA: 37 (16/21) Control: 23 (12/11)	KOA: 66.6 (8.4) Control: 62.0 (10.5)	KOA: KL grade ≥2 Control: No history of lower extremity injuries, KOOS pain 99.5 (1.8)	Quadriceps isometric strength
Levinger et al. 2016 [31] Cross-sectional	KOA: 19 (9/10) Control: 10 (3/7)	KOA: 66.1 (1.2) Control: 67.4 (2.4)	KOA: Waiting for knee replacement surgery Control: Asymptomatic with no signs of KOA or history of knee pain or injury	Quadriceps isometric strength
Liikavainio et al. 2008 [3] Cross-sectional	KOA: 54 (54/0) Control: 53 (53/0)	KOA: 59.0 (5.3) Control: 59.2 (4.7)	KOA: KL grade 1 to 4, ACR criteria* Control: KL grade 0, no KOA according to ACR criteria*	Quadriceps and hamstring isometric strength, Muscle thickness and area (cm^2) (RF, VL, VI)
Pap et al. 2004 [9] Cross-sectional	KOA: 68 (27/41) Control: 85 (30/55)	KOA: 56.7 (9.5) Control: 58.1 (8.7)	KOA: ACR criteria* Control: No signs of clinical KOA, no history of knee trauma	Quadriceps voluntary activation
Patsika et al. 2014 [32] Cross-sectional	KOA: 12 (0/12) Control: 11 (0/11)	KOA: 60.33 (6.66) Control: 56.54 (5.46)	KOA: KL grade 2 or 3 Control: No pain or injury to the knee or hip	Quadriceps and hamstring concentric and eccentric strength
Petrella et al. 2017 [33] Cross-sectional	KOA: 20 (20/0) Control: 20 (20/0)	KOA: 52.35 (5.00) Control: 51.40 (8.07)	KOA: KL grade 1 or 2, ACR criteria*	Quadriceps isometric, concentric and eccentric strength

(*continued*)

Table 2 (*Continued*)

Author/year (study design)	Sample size (men/women)	Age (mean [SD] or median [range])	Structural severity and symptoms	Outcome measures
			Control: KL grade 0, no signs or symptoms of KOA, no history of knee pain or trauma to lower limbs	
Petterson et al. 2007 [13] Cross-sectional	KOA: 44 (19/25) Control: 44 (19/25)	KOA: 62.3 (6.8) Control: 61.3 (7.7)	KOA: Waiting for knee arthroplasty Control: Healthy with no history of diagnosed knee abnormality	Quadriceps voluntary activation and isometric strength
Ramsey et al. 2007 [34] Intervention	KOA: 15 (9/6) Control: 15 (9/6)	KOA Men: 51.3 (6.4) KOA Women: 49.3 (7.9) Control Men: 52.0 (5.2) Control Women: 47.5 (5.6)	KOA: KL grade ≥2, ACR criteria* Control: No knee pain or radiographic KOA	Quadriceps voluntary activation and isometric strength
Ruhdorfer et al. 2020 [27] Prospective cohort	KOA: 81 (44/37) Control: 337 (180/157)	KOA Men: 61.8 (7.3) KOA Women: 65.5 (7.8) Control Men: 62.4 (9.4) Control Women: 62.9 (8.7)	KOA: KL grade ≥2, no pain at baseline, 1- and 2-year follow-ups and pain at 3- and 4-year follow-ups Control: KL grade <2, no pain at baseline and 1,2,3,4-year follow-ups	Quadriceps and hamstring isometric strength
Rutherford et al. 2011 [35] Cross-sectional	KOA: 15 (10/5) Control: 16 (8/8)	KOA: 61 (9) Control: 56 (6)	KOA: Waiting for knee arthroplasty Control: Asymptomatic	Quadriceps, hamstring and gastrocnemius isometric strength
Rutherford et al. 2013 [36] Cross-sectional	KOA: 11 (6/5) Control: 35 (16/19)	KOA: 59 (8) Control: 56 (6)	KOA: ACR criteria*, KL grade 4 Control: Asymptomatic	Quadriceps, hamstring and gastrocnemius isometric strength
Sanchez-Ramirez et al. 2016 [37] Cross-sectional	Early KOA: 14 (0/14) Established KOA: 19 (0/19) Control: 14 (0/14)	Early KOA: 70.4 (4.6) Established KOA: 68.37 (6.7) Control: 68.0 (3.9)	Early KOA: KL grade 0 or 1 on radiography Established KOA: KL grade ≥2, ACR criteria* Control: No history of knee symptoms, KL 0	Quadriceps and hamstring isometric and concentric strength
Schmitt and Rudolph 2007 [38] Cross-sectional	KOA: 28 (14/14) Control: 26 (13/13)	KOA: 60.4 (39–78) Control: 58.5 (38–76)	KOA: KL grade ≥2 Control: No history of knee pain or lower limb injury, KL 0 or 1	Quadriceps isometric strength
Serrao et al. 2015 [39] Cross-sectional	KOA: 22 (22/0) Control: 18 (18/0)	KOA: 52 (8.1) Control: 51.86 (6.47)	KOA: ACR criteria*, KL grade 1 or 2 Control: No history of knee pain or lower limb injury, KL grade 0	Quadriceps concentric and eccentric strength
Taniguchi et al. 2015 [11] Cross-sectional	KOA: 8 (0/8) Control: 23 (0/23)	KOA: 62.3 (6.5) Control: 60.7 (7.9)	KOA: KL grade 2 Control: No history of knee pain	Quadriceps isometric strength, muscle thickness (RF, VM, VL, VI, BF, GAST, SOL)
van Leeuwen et al. 2017 [28] Cross-sectional	KOA: 31 (17/14) Control: 29 (14/15)	KOA: 70.0 (5.8) Control: 69.1 (4.6)	KOA: KL grade ≥2, No pain/symptoms Control: KL grade 0 or 1, No pain/symptoms	Quadriceps voluntary activation
Winters and Rudolph 2014 [40] Cross-sectional	KOA: 26 (14/12) Control: 23 (12/11)	KOA: 65.3 (7.8) Control: 63.09 (7.66)	KOA: KL grade ≥2, or KL grade 1 and knee pain Control: Healthy	Quadriceps rate of torque development

ACR, American College of Rheumatology; BF, biceps femoris; GAST, gastrocnemius; KL, Kellgren-Lawrence; KOA, knee osteoarthritis; KOOS, Knee Injury and Osteoarthritis Outcome Score; RF, rectus femoris; SOL, soleus; VI, vastus intermedius; VL, vastus lateralis; VM, vastus medialis.

* ACR criteria: KL score≥2, pain, clinical features (e.g., crepitus, morning stiffness and bony enlargement of the knee) [74,75].

cortical or spinal excitability differences between KOA and control groups (very limited evidence) but rather selective atrophy of vastus medialis (limited evidence) and vastus lateralis (strong evidence), with no changes in muscle size (thickness or area) of other muscles (limited to moderate evidence). Finally, studies showed increased quadriceps torque variability, meaning less ability to control force production, in the KOA group. KOA and control groups did not differ in quadriceps rate of torque development.

Strength is important to maintain function, including daily life activities such as walking and stair climbing, and preventing injuries (i.e., falls). People with KOA commonly report deficits in these functional tasks [48,49]. Our results indicate that people with KOA experience muscle weakness around their knee joints, which effects multiple muscles at a range of structural KOA severity and may result in a vicious cycle of increasing pain and difficulty performing activities of daily living [50]. Although most strength tests included in this study were performed using isokinetic dynamometers, a simple, clinically applicable manual strength test has been shown to predict knee cartilage loss over 3 years [51]. Therefore, clinicians can easily include quantified strength tests in their clinical examination to better inform exercise selection. Exercise has been shown to improve pain and physical function in people with KOA [5,52], even in severe cases [53]. Hence, increased muscle strength may be the mechanism explaining the positive correlation between exercise and KOA symptom relief [54]. Exercise is also safe and low cost for people with KOA [55] and can therefore be implemented in treatment because most of these people have strength deficits in peri-articular muscles as compared with age- and sex-matched controls. Although recommended, exercise is still underutilized in this group [56]. Thus, referral to exercise therapy should be encouraged.

Women are at greater risk of KOA than men and experience greater severity [12]. Previous studies reported conflicting findings of the effect of sex on the relation between muscle function and KOA. Earlier studies suggested that reduced muscle strength may be a risk

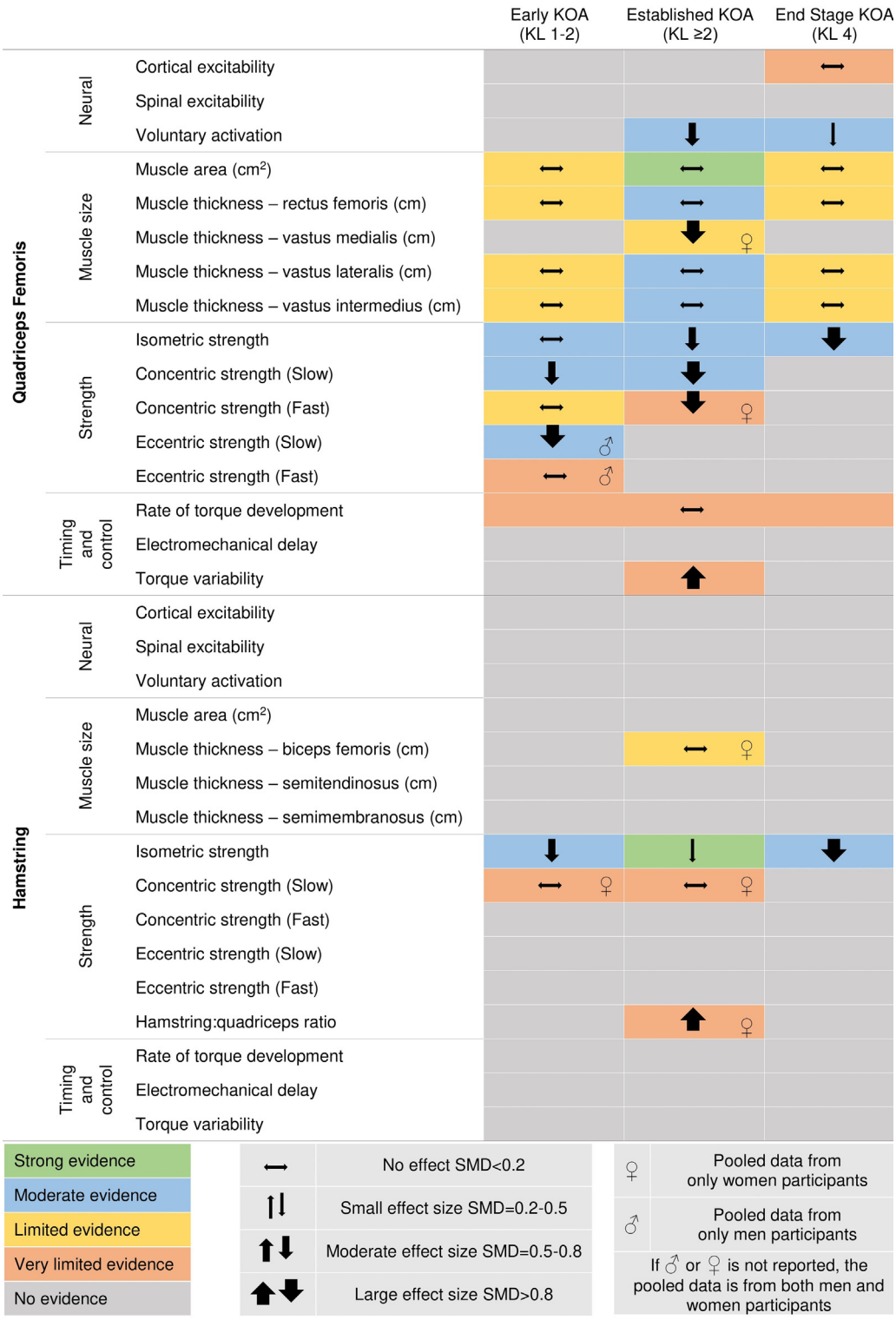

Fig. 2. Findings and literature gap map for quadriceps and hamstring neuromuscular outcomes ordered from central to peripheral. Data are pooled according to the structural severity as per Kellgren-Lawrence (KL) grades [15]. Colours represent the evidence level [24] and directions represent knee osteoarthritis (KOA) group data as compared with the control, with the effect size magnitude shown by the arrow thickness. SMD, standardised mean difference.

factor specifically for women [57]; however, pooling data from different studies did not identify any difference between men and women and revealed that strength deficits are KOA development risk factors for both men and women [1]. Our sensitivity analysis showed that women exhibit quadriceps strength deficits at early stages of KOA, whereas men do not. Pooled data from all KOA severities also showed similar findings, with women exhibiting these deficits to a greater extent than men as compared with their sex-matched controls. Sex-specific associations between muscle weakness and KOA progression have been previously reported, with women experiencing muscle strength deficits showing increased risk of disease progression [58]. Previous studies also reported that knee extensor and knee flexor

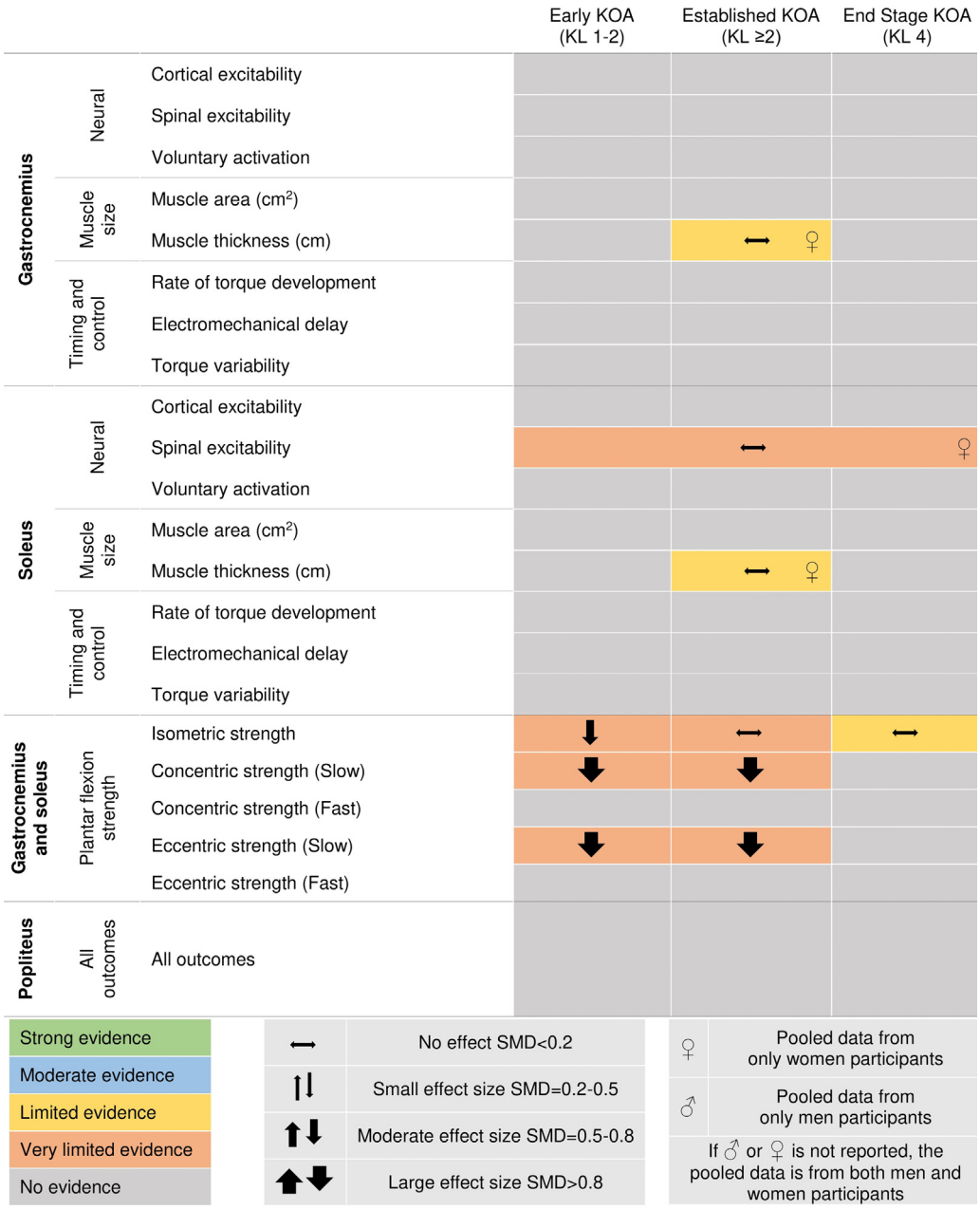

Fig. 3. Findings and literature gap map for gastrocnemius, soleus, and popliteus neuromuscular outcomes ordered from central to peripheral. Data are pooled according to the structural severity as per Kellgren-Lawrence (KL) grades [15]. Colours represent the evidence level [24] and directions represents knee osteoarthritis (KOA) group data as compared with the control, with the effect size magnitude shown by the arrow thickness. SMD, standardised mean difference.

strength deficits predict knee replacement in the subsequent 2 years in women but not men, independent of radiographic severity [59]. Overall, these findings suggest that muscle strength may play an important role in KOA, especially for women at earlier disease stages, and therefore potentially merit particular targeting strategies.

Muscle size is an important aspect of neuromuscular function, and previous studies of people with a knee injury history showed that muscle size may explain strength deficits [60]. Therefore, changes in muscle size in people with KOA can be expected because they also present muscle strength impairments around their knee joint. However, our results showed that overall quadriceps femoris muscle size either as muscle area (cm^2) or muscle thickness (cm) was no different from controls. Limited evidence showed vastus medialis atrophy in the KOA group (i.e., decreased muscle thickness as measured by ultrasonography) with a large effect size (SMD [95% CI] −0.96 [−1.80; −0.11]). Although vastus lateralis atrophy was not evident across different structural severities when all data were pooled as KOA versus controls, vastus lateralis atrophy was also seen, with a small effect size (SMD [95% CI] −0.32 [−0.58; −0.06]). This finding was in relation to the low number of studies for each structural severity. Different devices were used for measuring muscle thickness or area, mainly ultrasonography but also Dual Energy X-ray Absorptiometry scan and CT scan. Studies using different systems reported similar results, so the findings were not likely dependant on the measurement method. For calf and hamstring muscles, limited evidence showed no change in muscle size (measured as thickness [cm]).

The vastus medialis is seen as an important dynamic medial stabilizer of the patellofemoral joint, and its isolated atrophy is variably reported in other painful knee conditions such as patellofemoral pain syndrome [61]. The reason for muscle-specific greater atrophy in the

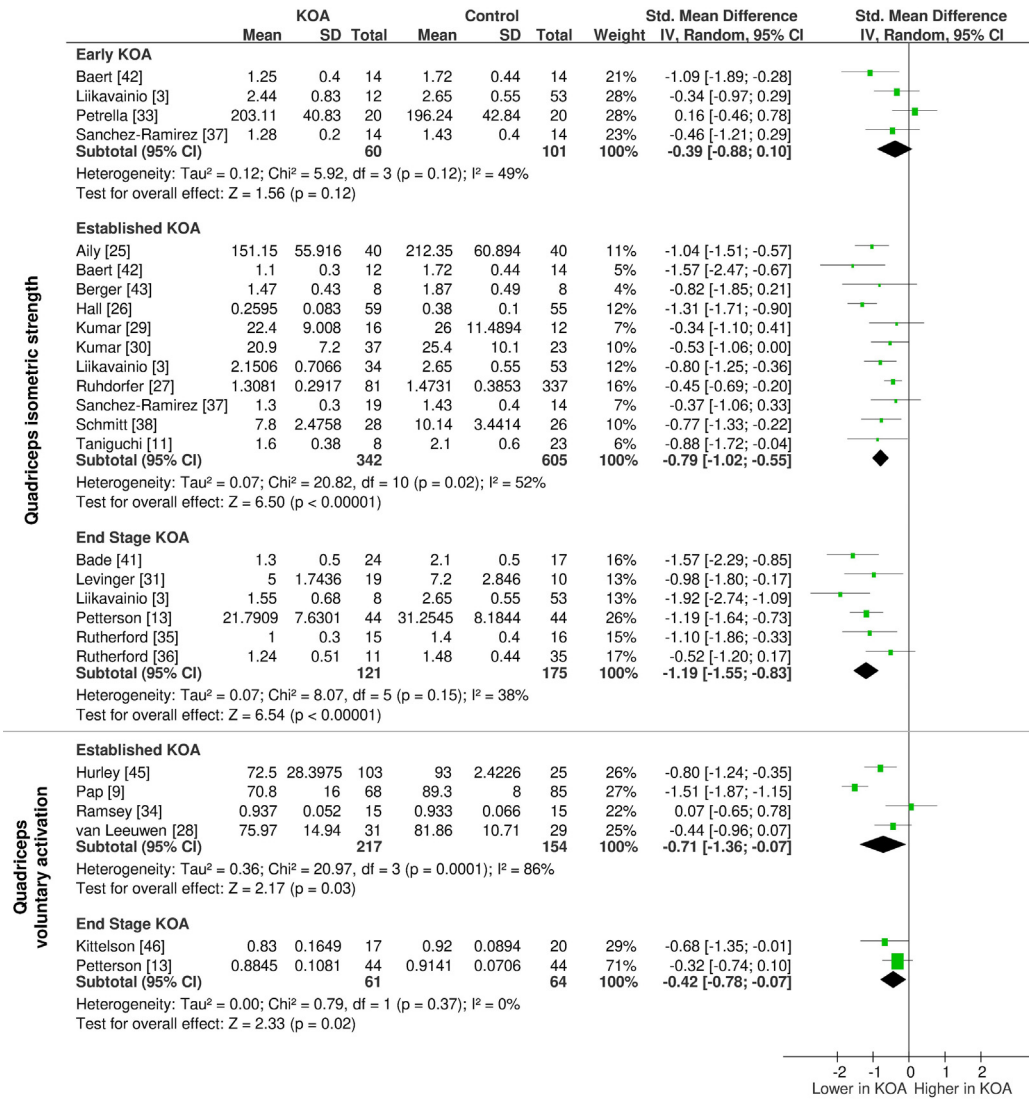

Fig. 4. Forest plots of quadriceps isometric strength and voluntary activation. KOA, knee osteoarthritis.

vastus medialis is currently unknown, with several suggestions in circulation. One is biomechanical factors such as varus or valgus malalignment affecting patellar movements in KOA [62]. Although the cause–effect direction is unknown, this change in patella mechanics may be associated with an imbalance of the vastus medialis and vastus lateralis [61]. Biomechanical measurements were not the focus in our study; therefore, we can only speculate about their effects on the outcomes we found. Future studies may investigate this specific vastus lateralis and greater vastus medialis atrophy and its relation to patellar movement and knee biomechanics. Another explanation could be reflex inhibition of vastus medialis due to pain, which was an outcome in our study, but no studies could be identified for the quadriceps femoris muscle. The vastus medialis cross-sectional area was also found associated with pain and protective of knee cartilage in the subsequent 2 years in people with KOA [63]. However, the findings of vastus medialis atrophy in our study was based on limited evidence; therefore, future studies are needed to substantiate these findings and hypotheses. Also, we did not include muscle quality measurements (i.e., intermuscular fat percentage) in our search strategy and therefore no results. Although muscle area is not different, fat content and therefore quality of the muscles might be affected in people with KOA [2]. Hence, future research in this area should consider including muscle quality measurements as well as muscle size measurements such as muscle thickness or area.

Understanding the mechanisms behind muscle weakness is important, so we explored possible alterations of cortical and spinal pathways. Mainly, voluntary activation deficits in quadriceps were present in established and end stage KOA, but we found no studies for early KOA or other muscles. Voluntary activation deficits, also known as arthrogenic muscle inhibition, are an inability to fully activate muscles, therefore limiting force production [64]. Our findings indicate these deficits contribute to the quadriceps-femoris muscle-strength deficits we identified in people with KOA. Different methodologies and variability in applied stimuli are a challenge when pooling data from different studies and understanding voluntary activation levels. The studies we included used 2 different calculation methods: twitch interpolation [9,28,45,46] or central activation ratio [13,34]. Of note, when checking for the effects of measurement method, we found that studies using a central activation ratio tended to report higher values for the KOA than control group and showed no difference between groups in pooled SMD (−0.22 [−0.58; 0.14]. Conversely, the twitch interpolation method conferred a large effect size toward lower voluntary activation levels in the KOA group (SMD [95% CI] −0.88 [−1.40; −0.37]). Therefore, the findings could be technique-dependant, and future research should aim to understand these differences between the 2 approaches.

Notably, sensitivity analysis showed that women present quadriceps voluntary activation deficits at end stage KOA, whereas men do

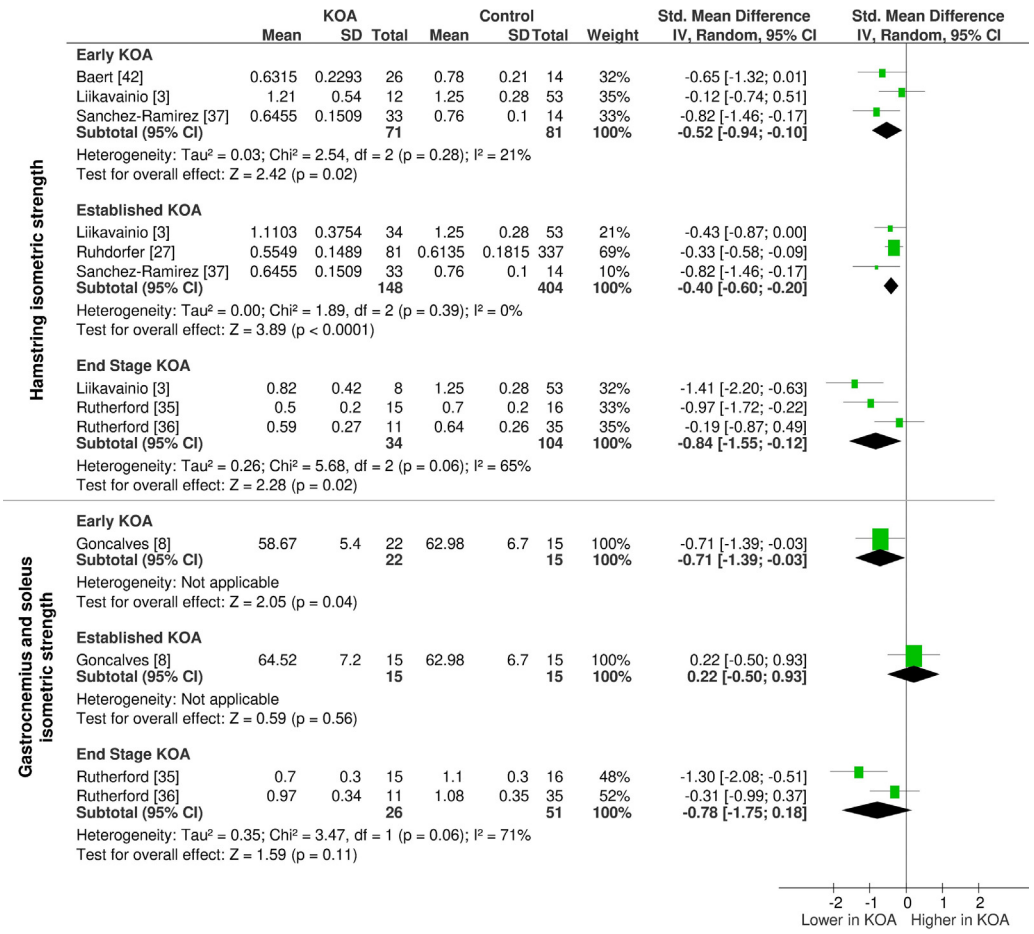

Fig. 5. Forest plots of hamstring and gastrocnemius-soleus isometric strength. KOA, knee osteoarthritis.

not, albeit with very limited evidence. This finding further suggests that women may be experiencing neuromuscular deficits to a greater degree than men, with involvement of corticospinal pathways; however, repeat studies are needed to increase the evidence level. Despite a marked evidence gap for cortical and spinal excitability outcomes, the very limited evidence available showed no change in quadriceps cortical excitability or soleus spinal reflexes. Because of methodological variation and dependency on high-cost devices, it is not easy to measure these outcomes in clinical practice. In the research context, more consistent and repeatable methodologies should be used for comparisons across studies. Recently, corticospinal adaptations have been found correlated with muscle strength and self-reported knee function satisfaction after anterior cruciate ligament reconstruction [65]. Also, spinal reflexes may increase as a compensatory mechanism to maintain muscle function when needed in sudden movements, such as protection against falls in people with KOA [10]. Hence, future high-quality studies investigating cortical and spinal excitability of peri-articular muscles are needed to confirm these findings.

In addition to alterations in strength, we identified alterations in other torque-related outcomes. Overall, we found increased quadriceps torque variability and no change in quadriceps femoris rate of torque development. However, there was only very limited evidence to suggest these outcomes. No studies were found for electromechanical delay, which is an important indicator of the speed of force generation and transmission [66,67]. We found no studies that measured these torque-related outcomes in other muscles.

Torque variability of the quadriceps femoris was increased in people with KOA, with very limited evidence, which suggests that these people may have impairments in their ability to control the muscle force they are producing. Precise control of movement is important for knee function, and impairments may alter knee joint loading, suggested to be a contributing factor for cartilage degeneration [68]. Previous studies showed that a training protocol including controlled muscle contractions with low load may improve muscle force control in older adults [69]. Future studies may include torque variability measurements of the muscles controlling the knee joint in people with KOA to understand the changes better and also test its clinical relevance.

Rate of torque development is an important part of functionality because it represents how fast a person can generate muscle force [70]. Previous studies of knee-injured populations showed that even when muscle strength recovers, rate of torque development may still be reduced [71]. Importantly, rapid force production may be more relevant to daily life activities than maximum strength because most of these activities require a quick muscle response [70]. It is even more important for older adults because it is correlated with balance [72] and fall history [73]. We found no change in rate of torque development; however, this observation was based on very limited evidence, so future studies are needed on rate of torque development in people with KOA. Different methodological approaches to the calculation of rate of torque development have been reported, with different time points (early vs late) and processing methods (MVIC normalized vs not) used. Standardization of methods and reporting should inform synthesis of the changes observed in people with KOA.

There are several common limitations in the literature reviewed in our study. First, a high level of selection bias may be present in the included studies because the studies did not report participant selection procedures clearly (Table 1). Included participants are highly likely to have more symptoms; therefore, the results may be inflated

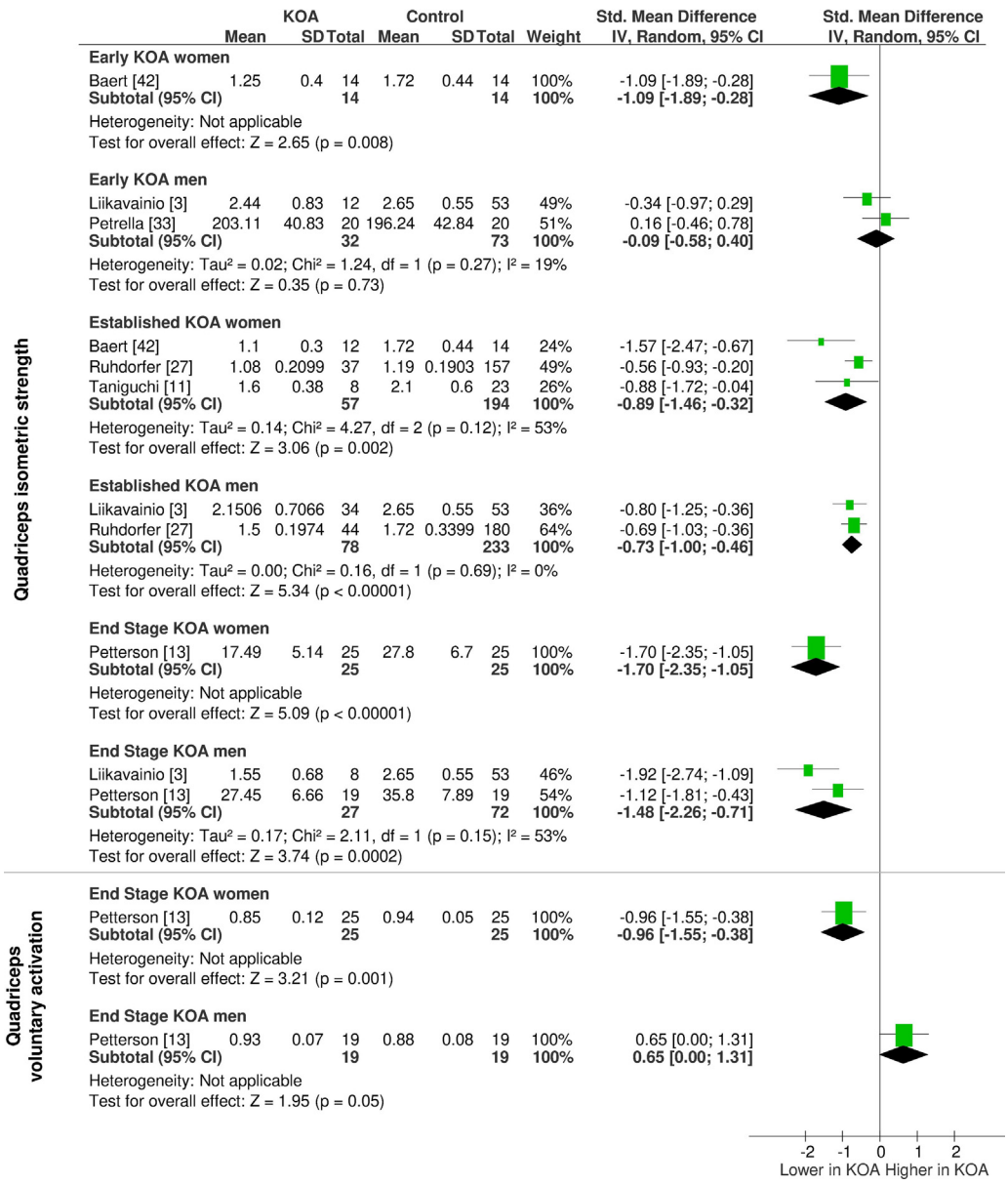

Fig. 6. Sensitivity analysis based on sex for quadriceps isometric strength and voluntary activation. KOA, knee osteoarthritis.

toward more alterations in the KOA than control group. However, because the target population is mainly symptomatic people, they may better represent the people who need optimized rehabilitation programmes. Future studies should better report the participant selection process. Second, we did not perform a separate analysis for the excluded studies, which were low quality according to our quality assessment. However, we know that low-quality studies may cause over- or underestimation of effect sizes and may distort results, thus leading to incorrect conclusions [20,21]. Hence, we believe that excluding low-quality studies actually improved the confidence level in our result (i.e., making suggestions with the evidence level or showing an evidence gap).

Structural severity and pain definitions differed greatly across studies, thus causing heterogeneity when grouping people. We pooled our data according to structural severity (KL grades); however, most of the studies defined KOA severities and control groups somewhat differently (Table 2). Therefore, it should be noted that these differences in definitions caused variability in the pooled data, thus leading to some uncertainty in the boundaries between the classifications of KOA severity. Pain or patellofemoral damage were not in the inclusion criteria for this review, so we performed a post-hoc sensitivity analysis to determine whether it had an effect on the outcome and could not identify any effects based on available evidence. However, future studies should include pain measurements because it may be a confounding factor in the measurement of muscle strength.

Although it was not possible to analyse the effect of age due to similar age groups across the included studies, one study investigating the effect of age [47] showed that people with KOA had similar changes (i.e., lower strength) as ageing. Therefore, future studies may consider including age as a confounding factor for neuromuscular function measurements.

Conclusions

Our study identified major neuromuscular alterations around the knee joint in people with KOA, including strength, muscle size, neural changes and other torque-related outcomes (i.e., rate of torque

development, torque variability), which facilitates the clinical recognition of these changes. We also provide an important evidence gap map, which will be a useful guide for future studies. Overall, we found deficits in maximum force capacity of muscles as well as force control. Most studies focused on the quadriceps femoris, with more evidence gaps remaining for other muscles (i.e., hamstring, gastrocnemii and soleus). Changes in muscle size were evidenced for only the vastus medialis and lateralis, with muscle size of the other quadriceps femoris heads, hamstrings or calf muscles remaining unaffected. Neural changes were poorly investigated, leaving a huge evidence gap and opportunity for future studies.

Enhancing functional outcome in people with KOA is important, so interventions that assess neuromuscular deficits in clinical examination and implement targeted individualised exercise programmes could be developed and tested for people with KOA. Implementing exercise with carefully chosen features (i.e., not only targeting improved maximum strength but also force control ability or rate of force development) may provide better outcomes, but further laboratory and interventional studies are needed to strengthen the evidence and inform robust clinical recommendations. Repeated measures of neuromuscular function would be a potential tool to understand intervention mechanisms together with the clinical effectiveness of interventions. The subsequent effects on outcomes for people with KOA would be the key impact markers that ultimately determine the value of neuromuscular measures in people with KOA.

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Availability of data and material

The data that support the findings of this study are available on request from the corresponding author (BT).

Authors' contributions

Conception and design of the study: BT, DM and SCM; screening of the articles, data extraction, methodological quality ratings and data analysis: BT and CC; first drafting of the manuscript: BT; critical revision of the manuscript: DM and SCM. BT: Conceptualization, Data curation, Formal analysis. All authors approved the version to be published.

Declaration of Competing Interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.rehab.2022.101662.

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