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Complete List of Authors:	Arumugam, Ashokan; College of Health Sciences University of Sharjah, Department of Physiotherapy Björklund, Martin; Umeå University, Department of Community Medicine and Rehabilitation – Physiotherapy Section; Centre for Musculoskeletal Research University of Gävle, Department of Occupational Health Sciences and Psychology, Centre for Musculoskeletal Research Mikko, Sanna; Umeå University, Department of Community Medicine and Rehabilitation – Physiotherapy Section Häger, Charlotte ; Umeå University, 1Department of Community Medicine and Rehabilitation – Physiotherapy Section

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Effects of neuromuscular training on knee proprioception in individuals with anterior cruciate ligament injury - A systematic review and GRADE evidence synthesis

Authors: Ashokan Arumugam (M.P.T., Ph.D.)[1], Martin Björklund (R.P.T., Ph.D.)[2, 3], Sanna Mikko (B.Sc.) [2], Charlotte K. Häger (R.P.T., Ph.D.)[2]

Author Affiliations:

[1]Department of Physiotherapy, College of Health Sciences, University of Sharjah, P.O. Box: 27272, Sharjah, United Arab Emirates;
[2]Department of Community Medicine and Rehabilitation – Physiotherapy Section, Umeå, University, SE-901 87, Umeå, Sweden;
[3]Department of Occupational Health Sciences and Psychology, Centre for Musculoskeletal Research, University of Gävle, Gävle, Sweden.

Corresponding author: Charlotte K. Häger

Address for Correspondence:

Name	Charlotte K. Häger
Designation	Professor
Department	Community Medicine & Rehabilitation – Physiotherapy Section
Institution	Umeå, University
Country	Sweden
Phone	+971 503193843
Email	charlotte.hager@umu.se

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Abstract

Objective

To systematically review and summarize the evidence for the effects of neuromuscular training on knee proprioception following ACL injury.

Design

Systematic Review

Methods

PubMed, CINAHL, SPORTDiscus, AMED, Scopus, and Physical Education Index were searched from inception to February 2020. Controlled or randomized clinical trials (RCTs) investigating the effects of neuromuscular training on knee-specific proprioception tests in individuals with a unilateral ACL injury were included. Two reviewers independently screened and extracted data and assessed risk of bias of the eligible RCTs using the Cochrane risk of bias 2 tool. Overall certainty in evidence was determined using the GRADE tool.

Results

Of 2706 articles retrieved, only nine RCTs, comprising in total 327 individuals with an ACL reconstruction (ACLR), met the inclusion criteria. Neuromuscular training interventions varied across studies: whole body vibration therapy, Nintendo-Wii-Fit training, balance training, sport-specific exercises, backward walking, etc. Outcome measures included joint position sense (JPS; n=7), thresholds to detect passive motion (TTDPM; n=3), or quadriceps force control (QFC; n=1). Overall, there were conflicting findings for reduced errors associated with JPS (one or more target angles), TTDPM or QFC of ACLR knee following neuromuscular training. Owing to serious concerns with three or more GRADE domains (risk of bias, inconsistency, indirectness, or imprecision associated with the findings) for each outcome of interest across studies, the certainty of evidence was very low.

Conclusions

The heterogeneity of interventions, methodological limitations, inconsistency of effects (on JPS/TTDPM/QFC) preclude recommendation of one optimal neuromuscular training intervention for improving proprioception following ACL injury in clinical practice. The low evidence thus questions common clinical neuromuscular training programs in practice. Our review highlights the urgent need for methodologically-robust RCTs with homogenous populations with ACL injury (managed conservatively or with reconstruction), novel/well-designed neuromuscular training interventions, and valid proprioception assessments, which also seem to be lacking.

PROSPERO registration number

CRD42018107349

Key words: Joint position sense, threshold to detect passive motion, ACL, sensorimotor training, literature review, neuroplasticity

Strengths and limitations of the study

- A systematic review of neuromuscular training on knee proprioception following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, using a broad search in six electronic databases.
- The risk of bias associated with the outcomes of interest (knee proprioception measures) in the included RCTs were assessed using the updated Cochrane risk of bias 2 tool.
- The overall certainty of evidence for the effects of neuromuscular training on knee joint position sense, threshold to detect passive motion, and quadriceps force control following ACL injury/reconstruction was ascertained using the GRADE tool.
- Only RCTs published in English were included.
- A meta-analysis was precluded because of clinical heterogeneity of interventions and outcome measures.

Introduction

Anterior cruciate ligament (ACL) injury is a common musculoskeletal injury[1, 2] accounting for an annual incidence rate of 68.6/100,000 person-years in the United States.[3] ACL injury is most prevalent in young athletes.[3] The injury occurs more often during competition rather than training, with ~70% or more of the injuries representing noncontact mechanisms[4, 5] such as landing from a jump, sudden deceleration and/or while cutting.[6] Thus, the injury mechanisms are related to neuromotor control, amongst other factors, of the individual. ACL injury is followed by a long period of rehabilitation and yet many individuals do not return to pre-injury levels of activity[7] which challenges the efficacy of existing preventative and rehabilitative strategies.

Individuals with an ACL injury present with a decreased number of proprioceptive mechanoreceptors (Pacinian capsules, Ruffini nerve endings and Golgi tendon organs)[8, 9] in the knee which might alter the somatosensory input to the central nervous system (CNS)[9] leading to decreased knee proprioception. Disturbed proprioception might also be caused by acute inflammation and pain, and the capsule and surrounding ligaments getting affected following instability.[10, 11] Although there has been a debate regarding the effects of ACL injury on different knee proprioception tests,[2, 12] our recent systematic review[13] suggests that knee JPS tests have sufficient validity in discriminating ACL-injured knees from asymptomatic knees (under review following revision). When compared to non-injured controls, individuals with ACL injury demonstrate altered movement strategies,[4, 14] quadriceps muscle weakness,[15] and onset and progression of osteoarthrosis.[6, 16] Due to the potential serious consequences of the injury, much attention and clinical efforts have been dedicated to preventative and rehabilitative strategies for ACL injury[11], including various neuromuscular training (NT) methods believed to improve the proprioceptive ability.

Even if proprioceptive deficits may negatively affect the neuromotor control, the rationale, mechanisms, and plausibility for improving proprioception by training need to be verified. In the context of neuroplasticity, functional magnetic resonance imaging (fMRI) has revealed that individuals with ACL-deficient knees demonstrate less activation in several sensorimotor cortical areas and increased activation in pre-supplementary motor areas, posterior secondary somatosensory area, and posterior inferior temporal gyrus compared to controls with asymptomatic knees during a knee flexion-extension task.[1] It seems individuals with ACLR adapt a visual-sensory-motor strategy instead of a normal sensory-motor strategy owing to aberrant sensory feedback following ACL injury.[17] Nevertheless, neuroplastic reorganization ensues where other potential sensory sources are used to organize the movement or regulate neuromotor control, particularly in (sporting) tasks with higher complexity. Therefore, ACL injuries might be regarded as a neuromotor control dysfunction rather than a simple peripheral musculoskeletal injury.[11, 18] It remains unclear though whether NT can improve proprioception after an ACL injury[11, 19] and the neurophysiological mechanisms underpinning such interventions need further substantiation.

To date, there is no consensus on the most effective rehabilitation programs for ACL injury, and the prevalence of reinjury after returning to sport is ~30%.[18] Owing to the neuroplastic changes and possibly altered proprioception following an ACL injury, NT has received much attention to enhance dynamic joint stability and relearn movement patterns and skills.[20] In this context, both NT and sensorimotor training terms have been used in the literature to describe the same phenomenon. NT for e.g., is defined as "…training enhancing unconscious motor responses by stimulating both afferent signals and central mechanisms responsible for dynamic joint control" [20] and sensorimotor training has been described as aiming to improve "…function of the CNS in

100 regulating movement in order to reach proper firing patterns for maintaining joint stability…”.[21]

101 Active knee motion will in any case stimulate proprioceptors, which in turn would alter the

102 demands on the CNS.[10, 19] Henceforth we will use the term NT in this review.

103 There are different ways to challenge proprioception, for example: vibration may be used to alter

104 afferent input from muscle spindles; an unstable surface can challenge input from the ankle;

105 vision can be occluded or head position can be changed to disturb visual- and vestibular

106 information,[10] or focus can be shifted to influence cognitive processing sources.[18] Due to a

107 putative visual-sensory-motor strategy following ACL injury, a modified visual feedback

108 training might decrease visual reliance and improve sensory-motor function.[18] Most studies

109 exploring the effects of NT on proprioception combine different exercises and various outcome

110 measures which precludes isolating the effects of a proprioception-specific exercise.[22] Therefore,

111 this study aimed at systematically reviewing and summarizing the evidence for the effects of NT

112 compared to comparator/control interventions on proprioception measured by knee-specific

113 proprioception tests in individuals with ACL injury or reconstruction.

114 Methods

115 We adhered to Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)

116 checklist.[23] The protocol was registered in PROSPERO (CRD42018107349).

117 Eligibility criteria

118 The structure of PICOS[24] was used to frame the following criteria:

119 1. **Participants:** Individuals over 15 years of age (both sexes) with a history of a unilateral

120 ACL rupture, managed conservatively or surgically reconstructed, with or without

concomitant meniscus and/or collateral ligament injuries, without any other lower extremity injuries/surgeries that would confound the outcomes of rehabilitation training;

2. **Intervention:** Specific NT, closed/open kinetic chain exercises, balance training, joint repositioning training, joint force sense training, co-ordination training, plyometric training, whole body vibration, virtual gaming training, an accelerated rehabilitation protocol or any other training programs focusing on improving the lower limb neuromuscular control and knee proprioception;
3. **Comparator:** Any other therapy, conventional training, usual care, placebo or sham therapy;
4. **Outcome measures:** Knee-specific proprioception tests targeting joint position sense (JPS), kinesthesia (threshold to detect passive motion [TTDPM]), force sense/perception, active movement extent discrimination, velocity sense, or psychophysical threshold methods;[13] they can be performed actively and/or passively with or without visual input in weight bearing or non-weight bearing positions;[10]
5. **Study design:** controlled or randomized clinical trials (RCTs).

Data Sources and Searches

Database-specific search terms (e.g. MeSH) were combined using Boolean operators ("AND" and "OR") under three conceptual domains: participants, interventions and outcomes. Six electronic databases were searched from their inception to 12 February 2020: PubMed, Cumulative Index to Nursing & Allied Health Literature (CINAHL), SPORTDiscus, the Allied and Complementary Medicine Database (AMED), Scopus, and Physical Education Index (via Proquest) (Online supplemental file 1).

Study Selection

One reviewer (SM) imported all titles and abstracts retrieved from the databases into EndNote X8. Two reviewers (AA and SM) independently checked titles, abstracts, and/or full text by following a screening questionnaire (online supplemental file 2). Any disagreements in inclusion of articles were adjudicated by two other reviewers (CH and MB) until consensus was reached. A manual search of the reference lists of included articles was performed.

Data Extraction

Data were extracted by one reviewer (SM) and verified by another reviewer (AA) using a customized data extraction sheet (online supplemental file 3). If any data were missing, the corresponding authors were contacted via email.

Quality Assessment

The risk of bias for each outcome of interest in the included studies was evaluated using the Cochrane ROB 2.[25] The tool has five domains: 1) randomization (number of signalling questions [n=3]), 2) deviations from intended interventions (n=7), 3) missing outcome data (n=5), 4) measurement of the outcomes (n=5), and 5) selection of the reported results (n=3). Each signalling question can be answered as 1) yes, 2) probably yes, 3) probably no, 4) no, and 5) no information. Responses to the questions provide the basis for judgement of the risk of bias at each domain level using a tool-specific algorithm resulting in one out of three possible judgements: 1) low risk of bias, 2) some concerns, or 3) high risk of bias. An overall risk of bias score for each outcome in a study can be low (with a low risk of bias for all domains), some concerns (if some concerns prevail in at least one domain without a high risk of bias for any domain) or high (if a high risk of bias underpins at least one domain or some concerns remain in multiple domains, defining multiple as more than two).

Evidence Synthesis

We determined the overall evidence level in this review using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) recommendations considering risk of bias, inconsistency (heterogeneity) in results, indirectness of evidence, imprecision of results, and other domains (e.g. publication bias if applicable).[26] The overall evidence was rated as very low, low, moderate or high. A meta-analysis was precluded owing to clinical heterogeneity of interventions and outcome measurements.

Patient and public involvement

Neither patients nor public were involved.

Results

Search Results

Electronic databases search identified a total of 2706 articles (excluding duplicates: 2162). Following title and abstract screening, 22 articles were shortlisted for full-text screening and subsequently nine articles were found to meet the inclusion criteria (Figure 1). The other thirteen articles were excluded for the following reasons: not an RCT (n=1),[27] no knee-specific proprioception tests (n=6),[28-33] participants did not have an ACL injury (n=1),[34] knee proprioception data were missing and the corresponding author did not respond to our emails (n=1),[35] a comparison between different surgical intervention groups with the same identical rehabilitation program (n=2),[36, 37] and finally, lack of a NT program (n=2).[38, 39] No additional relevant studies were identified through manual search of bibliographic references.

Study Design and Participants

All the nine studies included were RCTs with a total of 386 participants (only 327 were included in analysis), and two studies had their trial pre-registered.[40, 41] All participants had undergone a unilateral ACLR with either a bone-patellar-tendon-bone or a hamstring graft (Table 1).

Quality Assessment

The agreement (Cohen's kappa) of responses to the signalling questions between the two reviewers (AA and MB) was substantial (0.69 ± 0.047, $p < 0.001$). Disagreements were discussed and resolved by the two reviewers. Online supplemental figure 1 shows the percentage of studies judged as low risk, some concerns and high risk of bias in the five domains, and Table 2 shows domain judgements of each study. The overall risk of bias judgement showed that four of the included studies had a high risk of bias,[42-45] four had some concerns,[41, 46-48] and one study[40] had a high risk of bias for JPS and some concerns for quadriceps force control (QFC). The domain that most consistently showed risk of bias across studies was bias in selection of the reported results (Online supplemental figure 1 and Table 2). The most common reason was the absence of information regarding pre-specified plan of analyses. None of the included studies reported trial protocol publication and only two[40, 41] reported trial registration. Furthermore, two studies were judged to perform inappropriate multiple analyses.[42, 43] Judgement of bias in measurement of the outcome (domain 4, Table 2) showed most scattered results across studies (Online supplemental figure 1). A high risk of bias was found in three studies of which one had no information on measurements[45] and two showed inappropriate measurement methods of the outcome of interest.[40, 43] In the study by Zult et al., only one trial per target was performed to estimate JPS,[40] while Baltaci et al. used a test with presumably a high demand on motor and memory components,[43] without reporting its reliability or validity. The domain with least risk of bias was missing outcome data where all studies, except one,[44] had low risk of bias.

Rehabilitation Programs

The studies included a spectrum of rehabilitation programs employed to influence knee proprioception (Table 1). Two studies[42, 47] explored the effects of whole-body vibration therapy (WBVT) combined with or without conventional rehabilitation compared to conventional rehabilitation alone. Cho et al. compared closed kinetic chain exercises on a balance pad versus on a stable floor.[45] Risberg et al. compared the effects of a NT compared to strength training. In their NT program, the first half of the rehabilitation focused on exercises on a wobble board or trampoline and exercises to increase the range of motion, while the end of the program focused on specific training of plyometric, agility and sport-specific skills.[46] Baltaci et al. investigated the effects of Nintendo-Wii-Fit compared to conventional rehabilitation.[43] Beynnon et al. evaluated the effects of accelerated (19 weeks) vs. non-accelerated (32 weeks) programs of conventional training.[48] The timeframe and exercises in their experimental program ranged from 1-7 weeks for range of motion and muscle activation, 8-11 weeks for dynamic functional activities such as biking and jogging, and finally, 12-19 weeks for plyometric and agility drill exercises.[48] Kaya et al. studied the effects of neuromuscular (motor control) exercises for the lower limbs combined with standard rehabilitation compared with standard rehabilitation alone.[44] Shen et al. examined the outcome of standard rehabilitation combined with backward walking at 1.3 km/h on a treadmill for four groups (at four inclination angles 0°, 5°, 10°, and 15°, respectively) compared to standard rehabilitation in a comparator group.[41] Nevertheless, Zult et al. examined the effects of cross-education of strength training of the non-injured leg along with standard rehabilitation compared to standard rehabilitation alone.[40]

Knee-specific Proprioceptive Measures

Seven studies used active or passive JPS and all but one used (absolute) angular error as a variable to evaluate the outcome.[40-45, 47] Conversely, one study used monitored-rehab-system-software to define a virtual line/route to allow joint repositioning within 30-70% knee range of motion with and without visual feedback.[43] The differences between visual and blinded trails (2 each) based on the deviations from the computer-generated line (in mm) were used to measure proprioception.[43] All these studies used sitting or supine test position for assessing JPS. There were two to four predetermined target knee flexion angles across studies ranging from 15°-80°.[40-42, 44, 45, 47] Moreover, two studies[42, 43] used active knee motion and four used passive knee motion[40, 41, 44, 47] to set the target angle. Whether Cho et al. used active or passive knee motion to set/reproduce the target angle seems ambiguous. [45 45] Four studies[40, 42-45] used active knee motion and two[41, 47] used passive knee motion to reproduce the target angle. The JPS method used by Zult et al. was presumed based on their reference to Hortobagyi et al.[49]

The angular error was measured with 1-6 trials per each angle and one study[40] randomized the order of the joint angles used. Eyes were blinded during the test in six studies[40-42, 44, 45, 47] while one study used visual feedback when the individual was placing the knee in the target angle but no such feedback was given during reproduction of the target angle.[43] The difference between visual and non-visual trials was calculated in mm by the device as a measure of JPS.[43] A Biodex dynamometer (Biodex Medical Systems, Shirly, NY, USA) was used in five studies[40, 42, 44, 45, 47] to test JPS. Even so, one study used a continuous passive motion equipment[41] while another[43]

251 employed a functional squat system (Monitored Rehab System, Haarlem, and the Netherlands)
252 with a leg press machine and an associated computer program for assessing JPS.

253 Three studies[41, 46, 48] evaluated knee kinaesthesia with TTDPM using a bespoke device,[46, 48] or a
254 continuous passive motion equipment.[41] The knee was moved in flexion or extension at a
255 constant angular velocity of 0.5°/s [46] or 0.1°/s.[41, 48] While the participants were blindfolded in
256 two studies,[41, 48] the other study did not mention about visual feedback.[46] In all three studies, the
257 tests were performed thrice in each direction (flexion and/or extension) for both legs but whether
258 the order of direction or leg was randomized is not reported. In the study by Risberg et al.,[46]
259 TTDPM data were missing for 27 out of 74 participants because of device failure, which might
260 lower the power of the study.

261 **Assessing Certainty in Evidence**

262 There were serious concerns with three GRADE domains (risk of bias, indirectness, and
263 imprecision associated with the findings) across the seven studies that measured JPS (Tables 3
264 and 4). The certainty of evidence found was very low for the effects of NT on improving JPS
265 following ACLR.

266 There were further serious concerns with all GRADE domains (risk of bias, inconsistency,
267 indirectness, and imprecision associated with the findings) across the three studies measuring
268 TTDPM (Tables 3 and 4). Therefore, the certainty of evidence found was very low for improving
269 TTDPM in individuals with ACLR following NT (Table 3).
270 An overall judgement of some concerns based on the Cochrane ROB 2 tool (Table 2) was found
271 for the study reporting changes in QFC following NT.[40] Available population, the magnitude and
272 direction of effect, and effect estimates of QFC (Tables 1 and 3) are derived from only one study

which reflect serious concerns. However, the participants with ACLR, intervention (cross-education of the quadriceps with standard rehabilitation), and QFC[40] are directly related to our research question. The certainty of evidence found was very low for improving QFC in individuals with ACLR following NT because only one relevant study was found.

Discussion

This review is the first, as far as we are aware, to systematically review the level of evidence for effects of NT on knee proprioception in individuals with ACL injury. A previous review, however, summarized the effects of proprioceptive and balance exercises following ACL injury/reconstruction on certain outcome measures (muscle strength, hop test, etc.) but other than knee-specific proprioception tests.[50] Another similar review published in 2003 did not find any RCTs at all in this area.[51] As of today, we identified nine studies employing a range of NT methods, of which all but one[46] were published within the past decade. Nevertheless, there were serious concerns with two or more GRADE domains (risk of bias, inconsistency, indirectness, or imprecision associated with the findings) across studies implying a very low certainty of evidence for improving JPS, TTDPM, and QFC of ACLR knee following NT.

Effects of NT on Knee Proprioception in Individuals with ACLR

Most of the employed NT programs did not influence proprioception compared to comparator interventions. Of the nine included articles, four studies reported reduction in JPS angular errors of ACLR knee at one or more target angles (JPS at 45° but not 15°;[45] JPS at 60° but not 30°;[42] JPS at 15°, 45°, 75°;[44] JPS 20°, 50°, 80°[41]) and/or contralateral non-injured knee (JPS at 30° and 60°[42]) favouring the NT group (exercises on a balance pad,[45] whole-body vibration therapy,[42] neuromotor control exercises [44] or backward treadmill walking[41]). Shen et al. also reported improved TTDPM following backward treadmill walking.[41] When we calculated mean differences for author-reported post-operative[42, 44] or change (pre- vs. post-intervention) scores[45] between groups for the ACLR leg with the Review Manager 5.3 software (the Cochrane Collaboration), their 95% confidence intervals revealed no effects (see Table 1 and supplementary files). Moreover, the remaining five studies did not report significant differences in proprioception between groups.[40, 43, 46-48]

Potential reasons for insignificant between-group differences include: 1) experimental and comparator programs (with exercises that are wholly or partly similar) which potentially might stimulate similar effects on proprioception in both programs;[43-48] 2) the exercises did not adequately stimulate proprioception sense;[40] 3) a lack of proprioception deficit following ACL injury (TTDPM similar between ACL-injured and contralateral uninjured knee[48]); 4) a lack of valid, sensitive and responsive knee-specific proprioception test methods; 5) a short follow-up period (a follow-up at least 18 months post-ACLR might be needed to regain proprioceptive function[52]) in most studies except two studies;[44, 48] 6) type II errors arising from low sample sizes in most studies (with missing power or sample size calculations); and 7) adherence rates of participants to the prescribed program (only three studies have explicitly reported adherence rates to training sessions/exercises [Table 1]).[46-48] The heterogeneity of interventions, methodological limitations, inconsistency in the magnitude and direction of effects, and imprecision of effect estimates, found in this review, preclude recommendation of one optimal NT intervention for improving proprioception following ACL injury in clinical practice.

Risk of Bias in the Included Studies

Bias in selection of the reported variables/results due to absence of a pre-specified plan of analyses applied to all but one study,[40] and none had published a trial protocol in a scientific journal although two studies were registered in a trial registry.[40, 41] A possible reason for the absence of registration for most studies in this review may be that all but three studies were older than five years. Yet, for example, the latest published study did not report trial registration.[44]

Another concern was the method used to measure JPS. For instance, estimates of JPS based on 3-5 repetitions may be insufficient in clinical trials.[53] Similarly, according to Selfe et al., five repetitions in active knee JPS test, and six when performed passively, are necessary to ensure a consistent proprioception score.[54] However, this was only met in two included studies.[42, 44]

Almost all studies used AE for measuring JPS acuity which represents a task-oriented approach to studying performance skill, in contrast to a process-orientation in which underlying processes are in focus. The inconsistency in performance, i.e., response variability (variable error), may reflect noise in sensory signal and its processing[55] and thus be a more process-oriented outcome than AE. To understand possible underlying mechanisms, it would be advantageous to combine task- and process-oriented measures.

In general, method descriptions of proprioception tests were short and, in some studies, deficient, lacking information about factors that could influence the results. One such factor was randomization of the order of target positions (cf. Zult et al.),[40] which is required to minimize the effect of memory and reduce motor elements of the test. This is particularly applicable in tests with active positioning, which was the case for most studies, enabling central motor programs.[56] Inadequate reporting of the proprioception tests would hinder their replication and raise risk of bias rating. Moreover, Kaya et al. reported only post-intervention JPS scores, precluding baseline scores, despite claiming their study to be an RCT.[44]

Mechanisms Underpinning NT Following ACLR

Two of the included studies evaluated the effects of WBVT;[42, 47] however, only one found a favourable effect on proprioception.[42] Two factors may contribute to the different findings between these studies. First, time point: Fu et al. evaluated JPS 3 months after the intervention, while Moezy et al. did it directly after the intervention period. Second, the use of active[42] or passive[47] knee movement when testing JPS. Active tests stimulate both joint and muscle-tendon mechanoreceptors and induce alpha-gamma co-activation while passive tests assess joint receptors to a higher degree[10, 57] which potentially could mean a higher sensitivity of the active test.

WBVT has shown effects on body posture, flexibility, proprioception (TTDPM in patients with osteoarthritis), coordination and muscle power.[58-60] It has been promoted as an effective method to induce a reflex muscle contraction in subjects with difficulties to evoke voluntary contractions.[61] The mechanism behind the improvements can be that the mechanical stimuli stimulate primary endings of muscle spindles, especially type II fibers, which activate a-motor neurons. This could potentially stimulate central motor command, which facilitates increased muscle activation and voluntary movements.[58]

Cho et al. showed a significant effect on knee proprioception (JPS and TTDPM) with closed kinetic chain exercises on a balance pad/board.[45] Exercises on a balance board are widely used to improve proprioception.[30, 50] In this review, a few NT programs included, amongst other exercises, balance training with or without a balance pad/board.[43-46, 48] Additionally, one study claimed backward walking to stimulate joint/muscle receptors and sensory afferents to the CNS and augment proprioceptive and balance training.[41] Among these studies, all but one,[41] did not show significant mean differences between groups in proprioception calculated using the

Review-Manager 5.3 software (the Cochrane Collaboration) (see Table 1 and supplementary files). Different designs and levels of difficulty of the execution were found (e.g. a simple static balance task [with and without visual input], dynamic exercises performed on the balance board, backward walking on a treadmill, etc.).

There is a challenge to transfer the rehabilitation in the clinic to automatic movements required for athletic activities.[18, 62] Wii Fit or similar games have the potential to combine feedback with an external focus in a sport-specific environment,[43] supporting the use of such training tools. However, a study on Nintendo Wii Fit training did not support its use for improving knee proprioception following ACLR.[43] Newer technology with stroboscopic-eyewear might have the potential to decrease visual input without fully occluding it, making it possible to use them in sport specific rehabilitation. To prepare the individual for complex athletic environments and reduce re-injury risk, rehabilitation might focuses on NT with reduced demands on visual inputs and enhance automatic movement control with cognitive demands included.[18] Whether such NT training improves knee proprioception and, how this should be assessed in the best way,[13] are yet to be determined.

The Ability of Tests to Discern Changes in Proprioception Following NT

There is neither a gold standard proprioception test (targeting JPS, kinaesthesia, force sense) nor a standard procedure with established psychometric properties to test each proprioception sense following ACL injury. In this review, JPS and TTDPM were commonly reported. The Ruffini and Golgi receptors are slow-adapting receptors, responding to a change in joint position. Nevertheless, the Pacinian receptors that respond to low degrees of joint stress are more sensitive to rapid changes in accelerations and contribute to a low TTDPM.[2, 63] JPS has been reported to

384 detect a greater difference in knee proprioception than TTDPM following an ACL injury.[2]
385 However, our findings remain equivocal regarding the outcomes of JPS or TTDPM following
386 NT.

387 Knee-specific proprioception tests provide an indirect measure of proprioception involving the
388 process of the CNS.[10] Psychosocial factors,[64] pain and preinjury motor skills may influence the
389 central mechanisms and the outcome of such tests following NT. Knee-specific proprioception
390 tests are designed to exclude motor skills, but how successful that exclusion works, remains
391 unclear.

392 ***Limitations and Future Recommendations***

393 The nine included studies examined only individuals with ACLR but not those managed
394 conservatively following ACL injury. Owing to clinical heterogeneity of interventions and
395 outcomes, meta-analyses were precluded from the GRADE synthesis. The included studies had
396 methodological limitations (high risk of bias or some concerns) and only two studies[40, 41] had
397 pre-registered their protocol. There is a need for high quality RCTs with low risk of bias in this
398 area.

399 The most common reason for exclusion of clinical trials in this review was that they did not
400 evaluate the effects of NT following ACLR with a knee-specific proprioception test. Perhaps, the
401 lack of consensus regarding the most appropriate, valid, reliable and responsive proprioception
402 tests, number of target angles or most responsive target angles (low vs. high) precluded such
403 outcomes in these studies. Therefore, psychometric properties of such tests must be established.[13]

When designing rehabilitation programs with long-term follow-up, aberrations in neuromotor control and neuroplastic changes should preferably be addressed. To reflect a wide spectrum of individual impairments, further research should investigate differences in individuals with ACL injuries managed with surgical (graft types) or conservative treatment, both sexes, athletes and non-athletes of different ages. Future studies might assess neuromotor control in functional tasks rather than relying on knee-specific proprioception tests, given the challenges of isolating the proprioceptive ability.

Conclusion

The existing nine studies on individuals with ACLR using heterogeneous interventions and knee-specific proprioception measures revealed a very low certainty in current evidence for employing NT programs to improve knee proprioception. The GRADE evidence synthesis revealed a high risk of bias or some concerns, indirect evidence, conflicting findings, and imprecision of effect estimates in the included studies. Methodologically-robust RCTs with homogenous populations (having ACL injury managed with/without reconstruction), novel/well-designed NT interventions, and valid proprioception measures are warranted to substantiate conclusive evidence in this area.

Contributors

AA and CKH conceived the idea of the project. AA, MB, SM and CKH were responsible for designing the review and conceptualising the initial review protocol. AA led the writing of the manuscript. MB, SM and CKH contributed to writing the manuscript. AA, MB and CKH have reviewed and revised the manuscript for intellectual content. All authors approved the final version of the manuscript. AA is the guarantor of this work.

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607 **Table 1. Summary of study characteristics**

Study citation	Sample size[a], age (mean ± SD), gender; ACLD/ACLR (Graft)	Intervention; Adherence to prescribed exercises/ training	Comparator; Adherence to prescribed exercises/ training	Knee-specific proprioception test; outcome	Between-group (experimental vs. control) comparisons of ACL-injured (reconstructed) limb - mean difference (95% confidence interval)[b]
Baltaci et al. (2013) [43]	Exp: n=15, 28.6±6.8 years, 15 men; Com: n=15, 29.3±5.7 years, 15 men; ACLR (hamstring tendon graft).	Nintendo Wii Fit training: 3 times/week; 60 min/session; from week 1-12 after ACLR. **Adherence:** NR	Conventional rehabilitation: Week 1-12 after ACLR; **Adherence:** NR	**Proprioception test:** JPS (ipsilateral replication method); **Body position:** NR; **Instrument:** Monitored Rehab System with a leg press machine and a computer game; **Procedure:** Active-active, with and without blindfolding of the eyes (2 trials each); **Starting angle (SA):** NR; **Target angle (TA):** NR; **Outcome measure:** absolute angular error (AAE; difference between visual and non-visual results for each leg)	**JPS (°)[c] at 12 weeks post-intervention:** 1.90 [-31.20, 35.00] 33.30 [-28.02, 94.62]

Beynnon et al. (2011) [48]	Int: n=19, 29.7±10.1 years, 13 males, 6 females; Com: n=17, 30.2±9.9 years, 9 males, 8 females; ACLR (patellar tendon graft)	Accelerated rehabilitation: daily exercises at home + 3 times/week exercises under supervision from week 1-19 after ACLR; **Adherence:** 94% (range, 25%-292%) over 19 weeks	Non-accelerated rehabilitation: daily exercises at home + 3 times/week exercises under supervision from Week 1-32 after ACLR; **Adherence:** 53% (range, 13%-108%) over 32 weeks	**Proprioception test:** TTDPM; **Body position:** Seated; **Instrument:** A customized joint motion detection system; **Procedure:** passive movement of the knee into flexion or extension (3 trials for both ACL-reconstructed and contralateral uninjured knees) with eyes blindfolded; **SA:** NR; **Angular velocity:** 0.1°/s; **Outcome measure:** Threshold angle (difference between the initial angle [SA] and the angle at which the test was stopped) to detect passive knee motion into flexion or extension (mean of the three trials in one direction).	**TTDPM (°)[c] at 24 months post-ACLR:** **SA (NR):** 0.09 [-0.42, 0.60]
Cho et al. (2013) [45]	Int: n=14, 29.92±5.46 years; 14 males; Com: n=14, 28.78±7.24 years; 14 males; ACLR (NR).	Unstable exercise group: exercises performed on a balance pad or balance board; 60 min/session; 3 times/week early after injury, for 6 weeks; **Adherence:** NR	Stable exercise group: exercises performed on a stable floor: 3 times/week Early after injury, for 6 weeks; **Adherence:** NR	**Proprioception test:** JPS; **Body position:** seated (?); **Instrument:** Biodex dynamometer; **Procedure:** NR-active, with eyes blindfolded; **SA:** 90°; **TA:** 15°, 45°; **Outcome measure:** AAE (mean of the three trials at each angle).	**JPS (°)[d] at 6 weeks post intervention:** TA 15°: 0.14 [-0.69, 0.97] TA 45°: -0.87 [-1.91, 0.17]

Fu et al. (2013) [47]	Int: n=24, 23.3±5.2 years; Com: n=24, 25.2±7.3 years; ACLR (hamstring graft).	Conventional rehabilitation program + Whole-body vibration therapy: 2 times/week from week 5-13 after ACLR; **Adherence:** 83.2% over 12 weeks	Conventional rehabilitation program: week 5-13 after ACLR; **Adherence:** 84.4% over 12 weeks	**Proprioception test:** JPS; **Body position:** seated; **Instrument:** Biodex dynamometer; **Procedure:** passive-passive, eyes blindfolded; **SA:** 90°; **TA:** 30°, 60°; **Outcome measure:** AAE (mean of the three trials at each angle)	**JPS (°)[c] at 6 months post-ACLR:** **TA 30°:** -0.82 [-2.69, 1.05] **TA 60°:** -0.70 [-2.31, 0.91]
Kaya et al. (2019) [44]	Int (Group 1): n=20; 29.35±9.71 years; 20 males; Com (Group 2): n=20; 31.60±8.45 years; 20 males; ACLR (tibialis anterior allograft).	Standard rehabilitation program (0-2 weeks) + neuromuscular control exercises (3-36 weeks); **Adherence:** NR	Standard rehabilitation program (0-36 weeks); **Adherence:** NR	**Proprioception test:** JPS; **Body position:** seated (?); **Instrument:** Biodex dynamometer; **Procedure:** passive-active, eyes blindfolded; **SA:** 90°; **TA:** 15°, 45°, 75°; **Outcome measure:** AAE (mean of six trials at each angle)	**JPS (°)[c] at 24 months post-ACLR:** **TA 15°:** -1.51 [-3.30, 0.28] **TA 45°:** -1.69 [-5.06, 1.68] **TA 75°:** -1.30 [-3.34, 0.74]
Moezy et al. (2008) [42]	Int: n=12, 24.51±3.38 years; Com: n=11, 22.70±3.77 years; ACLR (patellar tendon graft)	Whole-body vibration therapy: 3 times/week from week 12-16 after ACLR; **Adherence:**	Conventional strengthening exercises program: 3 sessions/week Week 12-16 after ACLR;	**Proprioception test:** JPS; **Body position:** seated; **Instrument:** Biodex dynamometer; **Procedure:** active-active, eyes blindfolded; **SA:** 90°; **TA:** 30°, 60°;	**JPS (°)[e,d] at 16 weeks post-ACLR:** **TA 30°:** 1.66 [-0.40, 3.72] **TA 60°:** 3.03 [1.54, 4.52]

		NR	**Adherence:** NR	**Outcome measure:** AAE (mean of five trials at each angle for both ACL-reconstructed and contralateral uninjured knees)	
Risberg et al. (2007) [46]	Int: n = 39; 3 females - 27.2 (range: 20.6-37.9) years and 26 males - 27.7 (16.7-39.6) years; Com: n=35, 14 females - 26.5 (19.8-38.0) years and 21 males - 31.2 (19.4-40.3) years; ACLR (patellar tendon graft)	Neuromuscular training program: 2-3 times/week from week 1-24 after ACLR; **Adherence:** 71% over ~20 weeks	Traditional strength training: 2-3 times/week from week 1-24 after ACLR; **Adherence:** 91% over ~20 weeks	**Proprioception test:** TTDPM; **Body position:** NR; **Instrument:** a customized TTDPM device; **Procedure:** passive movement of the knee into flexion and extension (three trials for each direction for both ACL-injured knees and contralateral uninjured knees); no information on blindfolding of eyes; **SA:** 15°; **Angular velocity:** 0.5°/s; **Outcome measure:** threshold angle to detect passive knee motion into flexion and extension (mean of three trials for each angle in each direction).	**TTDPM (°)[c] at 6 months post-ACLR:** **SA 15°:** -0.02 [-0.39, 0.35] (Note: TTDPM data were available only for the first 47 participants out of 74 in total).
Shen et al. (2019) [41]	Int (A): n=10; 36.6±12.1 years; 5 male, 5 females. Int (B): n=11; 37.5±9.39 years; 6 male, 5 females. Int (C): n=11; 34±10.29 years; 7 male, 4 females.	Standard rehabilitation + backward walking on the treadmill: Int. groups A, B, C, and D underwent backward walking	Standard rehabilitation with range of motion exercises, power exercises, walking, and cycling (duration and other	**Proprioception test 1:** JPS; **Body position:** supine lying; **Instrument:** continuous passive motion device; **Procedure:** passive-passive, eyes blindfolded; **SA:** 0°; **TA:** 20°, 50°, 80°, **Outcome measure:** AAE (mean of the three trials at each angle for ACL-injured knees?).	**Int (A) vs. Com group at 4 weeks post-intervention[d]:** **JPS (°)[c]:** **TA 20°:** -1.40 [-2.59, -0.21] **TA 50°:** -1.36 [-2.35, -0.37] **TA 80°:** -1.28 [-2.31, -0.25] **TTDPM (°)[c]:**

	Int (D): (n=10); 32.9±11.45 years; 6 male, 4 females. Com: n=10; 35.5±10.1 years; 7 male, 3 females; ACLR (patellar tendon graft, hamstring tendon graft, allograft)	training at 1.3 km/h at different inclination angles of the treadmill (0°, 5°, 10°, and 15°, respectively); 20 min/day, 5 days/week for 4 weeks; **Adherence:** NR	parameters: NR); **Adherence:** NR	**Proprioception test 2:** TTDPM; **Body position:** Supine lying; **Instrument:** continuous passive motion device; **Procedure:** passive movement of the knee into flexion (3 times for each angle for ACL-injured knees?) with eyes blindfolded; **SA:** 20°, 50°, 80°; **Angular velocity:** 1°/s; **Outcome measure:** Threshold angle to detect passive knee motion into flexion (mean of three trials for each angle in one direction).	**SA 20°:** -1.34 [-2.11, -0.57] **SA 50°:** -1.40 [-2.05, -0.75] **SA 80°:** -1.29 [-2.00, -0.58]
Zult et al. (2018) [40]	Int: n =29 (22), 28±9 years; Com: n = 26 (21), 28±10 years n=24 males n=20 females ACLR (patellar tendon graft/ hamstring tendon graft (SSG)/ Artificial)	Standard rehabilitation + Strength training of the quadriceps of the non-injured leg; 2 quadriceps exercises, 8–12 reps. maximum, 3 sets; 2 times/week from week 1-12 after ACLR; **Adherence:**	Standard rehabilitation: 2 times/week from week 1-12 after ACLR; **Adherence:** NR explicitly; however, two participants who performed <26 sessions were excluded from analysis	**Proprioception test 1:** JPS[g] **Body position:** seated (?); **Instrument:** Biodex dynamometer (?); **Procedure:** passive-active, eyes blindfolded (?); **SA:** 90° (?); **TA:** 15°, 30°, 45°, and 60°; **Outcome measure:** AAE (one trial at each angle). **Proprioception test 2:** Quadriceps force control (QFC); **Body position:** seated (?); **Instrument:** Biodex dynamometer (?); **Procedure:** A target force matching task with the target set at 20% MVC for	**JPS (°)[e] at 26 weeks post-ACLR:** **TA 15°:** 1.00 [-1.12, 3.12] **TA 30°:** 2.00 [-0.12, 4.12] **TA 45°:** -1.00 [-3.39, 1.39] **TA 60°:** -1.00 [-2.79, 0.79] **QFC (Nm)[e,f] at 26 weeks post-ACLR:** **Concentric 60°/s:** 6.00 [0.67, 11.33] **Eccentric 60°/s:**

	NR explicitly; however, one participant who performed <26 sessions was excluded from analysis after week 26	after week 26	three isometric trials (at 65° of knee flexion [5 s duration]) and 40 Nm for dynamic trials (four concentric and eccentric trials at 20°/s from 10°-90° knee flexion) (20°/s between 10° and 90° of knee flexion); **Outcome measure:** force accuracy (absolute error) determined over the terminal 3 s data for isometric trials (at 65° knee flexion) and over the middle 2 s data for concentric and eccentric trials.	-1.00 [-3.99, 1.99] **Isometric:** 1.00 [-0.76, 2.76]

[a]Included in ana
[b]Calculated with Review Manager (RevMan) 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark);
[c]Mean difference between groups were calculated based on post-intervention/final follow-up scores reported by the authors;
[d]Difference between four intervention groups and the comparator group were same and so only one comparison is presented.
[e]Mean difference between groups were calculated based on change scores from baseline (pre- vs. post-intervention) reported by the authors;
[f]Quadriceps force accuracy; both legs (within each group) showed improved force control (22–34%) at 26 weeks post-surgery ($p < 0.050$) according to the authors;
[g]JPS method has been presumed based on authors' reference to the method employed by Hortobagyi et al. [49];
ACLR - anterior cruciate ligament reconstruction, Int – intervention group; com – comparator group; JPS - joint position sense, NR- not reported, TTDPM - threshold to detection of passive motion, min. - minutes, reps – repetitions.

Table 2. Risk of bias assessment of included studies according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) - judgements in five domains and an overall judgement using the descriptors of low risk of bias (low), some concerns, and high risk of bias (High).

Included studies	Outcome variable	1. Bias from the randomization process	2. Bias due to deviations from intended interventions	3. Bias due to missing outcome data	4. Bias in measurement of the outcome	5. Bias in selection of the reported result	O ju
Baltaci et al. 2013 [43]	JPS	High	Some concerns	Low	High	High	H
Beynnon et al. 2011 [48]	TTDPM	Low	Low	Low	Low	Some concerns	So
Cho et al. 2013[45]	JPS	Some concerns	Some concerns	Low	High	Some concerns	H
Fu et al. 2013[47]	JPS	Low	Low	Low	Low	Some concerns	So
Kaya et al. 2019[44]	JPS	Some concerns	High	High	Low	Some concerns	H
Moezy et al. 2008[42]	JPS	Some concerns	Low	Low	Some concerns	High	H
Risberg et al. 2007 [46]	TTDPM	Low	Low	Low	Low	Some concerns	So
Shen et al. 2019[41]	JPS	Some concerns	Low	Low	Low	Some concerns	So
	TTDPM	Some concerns	Low	Low	Low	Some concerns	So
Zult et al. 2018[40]	JPS	Low	Some concerns	Low	High	Some concerns	H
	QFC	Low	Some concerns	Low	Low	Some concerns	So

JPS - joint position sense, TTDPM - threshold to detect passive motion, QFC - quadriceps force control.

Table 3. Applying the GRADE approach to rate the certainty in evidence found in the review

Certainty assessment							№ of patients		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neuromuscular Training	Comparator Intervention	
Knee joint position sense (JPS)									
7	Randomized trials	very serious[a]	serious[b]	serious[c]	serious[d]	none	139	105	⨁◯◯◯ VERY LOW
Knee joint threshold to detect passive motion (TTDPM)									
3	Randomized trials	serious[a]	serious[b]	serious[c]	serious[d]	none	84	51	⨁◯◯◯ VERY LOW
Quadriceps force control (QFC)									
1	Randomized trial	serious[a]	serious[e]	not serious	serious[e]	none	22	21	⨁◯◯◯ VERY LOW

Note: GRADE domains are explained further in Tables 5 and 6.

a. Included studies had a high risk of bias or some concerns based on the Cochrane ROB2 tool;
b. The direction and/or magnitude of effect was inconsistent across trials;
c. Clinical heterogeneity (of participants, interventions, and method of assessing outcome measures);
d. Number of participant <400 and/or wide 95% confidence intervals of effect size estimates;
e. Available population, the magnitude and direction of effect, and effect estimates come from only one study.

Table 4. GRADE evaluation of the certainty in evidence for knee joint position sense (JPS) and threshold to detect passive motion (TTDPM) following neuromuscular training in individuals with anterior cruciate ligament reconstruction

GRADE domain	Reviewer judgment	Concerns about GRADE domains
	Knee joint position sense (JPS)	
Risk of bias (methodological limitations)	Among seven RCTs[40-45, 47] reporting changes in JPS following neuromuscular training, five RCTs were found to have a high risk of bias while the remaining two studies have some concerns based on the Cochrane ROB 2 tool (see Table 4). Indeed, we judged that the included RCTs have very serious methodological limitations.	Very serious
Inconsistency	The direction and/or magnitude of effect on JPS was inconsistent across most of the included RCTs. In summary, the between-group comparisons of five RCTs showed borderline or no change in JPS angular errors of the ACLR knee for one or more target angles following interventions. We noted significant differences in reduction of JPS angular errors for all target angles favoring the intervention groups (backward treadmill walking or motor control exercises) in only two RCTs as reported by the authors.[41, 44] In fact, Kaya et al. (2019) had reported only post-intervention scores but they neither reported nor compared the baseline scores (post-operative scores).[44] Two other studies [42, 45] presented with insignificant effects at a low target angle (15° or 30°) and significant effects at a high target angle (45° or 60°) of JPS favoring the intervention group (whole-body vibration therapy[42] or exercises on a balance pad[45]). When we calculated mean differences for author-reported post-operative[44] or change (pre- vs. post-intervention) scores,[42, 45] between groups for the ACLR leg with the Review Manager 5.3 software (the Cochrane Collaboration), their 95% confidence intervals revealed no effects. Overall, we judged the evidence to have serious inconsistency in the direction and/or magnitude of effects.	Serious
Indirectness	The participants (with ACLR [different grafts]), different neuromuscular training and comparator interventions, and knee specific JPS measures in the included studies provide evidence to the research question. However, the heterogeneity of interventions precludes recommendation of one optimal neuromuscular training intervention for	Serious

	clinical practice. In addition, variations in the methods of JPS measurements (active vs. passive angle reproduction, low vs. high target angles, etc.) precluded a meta-analysis. However, forest plots have been presented for easy understanding of the confidence intervals and overall findings on JPS following neuromuscular rehabilitation training in individuals with ACLR (see appendices). We judged the evidence to have serious indirectness especially owing to variations in the interventions and outcome measures.	
Imprecision	A total of 244 patients was included from seven RCTs reporting changes in JPS following neuromuscular training (n = 139) or comparator interventions (n = 105). Most of the included trails reported non-significant results with wider 95% confidence intervals for one or more JPS (target) angles (see appendices). Therefore, we judged the evidence to have serious imprecision.	Serious
Publication bias	Since negative and positive findings have been published, and a comprehensive search for RCTs has been done, we did not suspect a publication bias.	None
	Knee joint threshold to detect passive motion (TTDPM)	
Risk of bias (methodological limitations)	Three RCTs[20, 41, 48] reporting changes in TTDPM following neuromuscular training were found to show some concerns in risk of bias based on the Cochrane ROB 2 tool (see Table 4). We judged the included RCTs to be of serious methodological limitations.	Serious
Inconsistency	The direction and/or magnitude of effect was conflicting between the three RCTs. As two trials reported insignificant effects and one[41] reported significant effects (see appendices), we judged the evidence to have serious inconsistency in the direction and/or magnitude of effects.	Serious
Indirectness	The participants (with ACLR [different grafts]), different neuromuscular training and comparator interventions, and knee specific TTDPM measures in the included studies provide some evidence to the research question in hand. However, the heterogeneity of interventions and TTDPM measurements (starting angles, angular velocity, etc.) precluded a meta-analysis. We judged the evidence to have serious indirectness especially owing to variations in the interventions and TTDPM methods.	Serious

Imprecision	A total of 135 patients was included in three RCTs reporting the effects of neuromuscular training (n = 84) or comparator interventions (n = 51) on TTDPM. Two trails[46, 48] reported non-significant results while another one[41] reported significant effects which is evident with their confidence intervals (see appendices). However, Shen et al. (2019) reporting significant effects on TTDPM included only 10 to 11 participants in each group while the other two studies with a relatively larger sample size declared no significant effects on TTDPM. Therefore, we judged the evidence to have serious imprecision.	Serious
Publication bias	As both negative and positive findings have been published, and a comprehensive search for RCTs has been done, we did not suspect a publication bias.	None

Note: Effect size estimates – a forest plot (see supplementary files) has been presented for easy understanding of the mean differences between groups and corresponding 95% confidence intervals related to outcome measures; however, a meta-analysis was not formally included in the review owing to heterogeneity of the interventions and JPS/TTDPM methods.

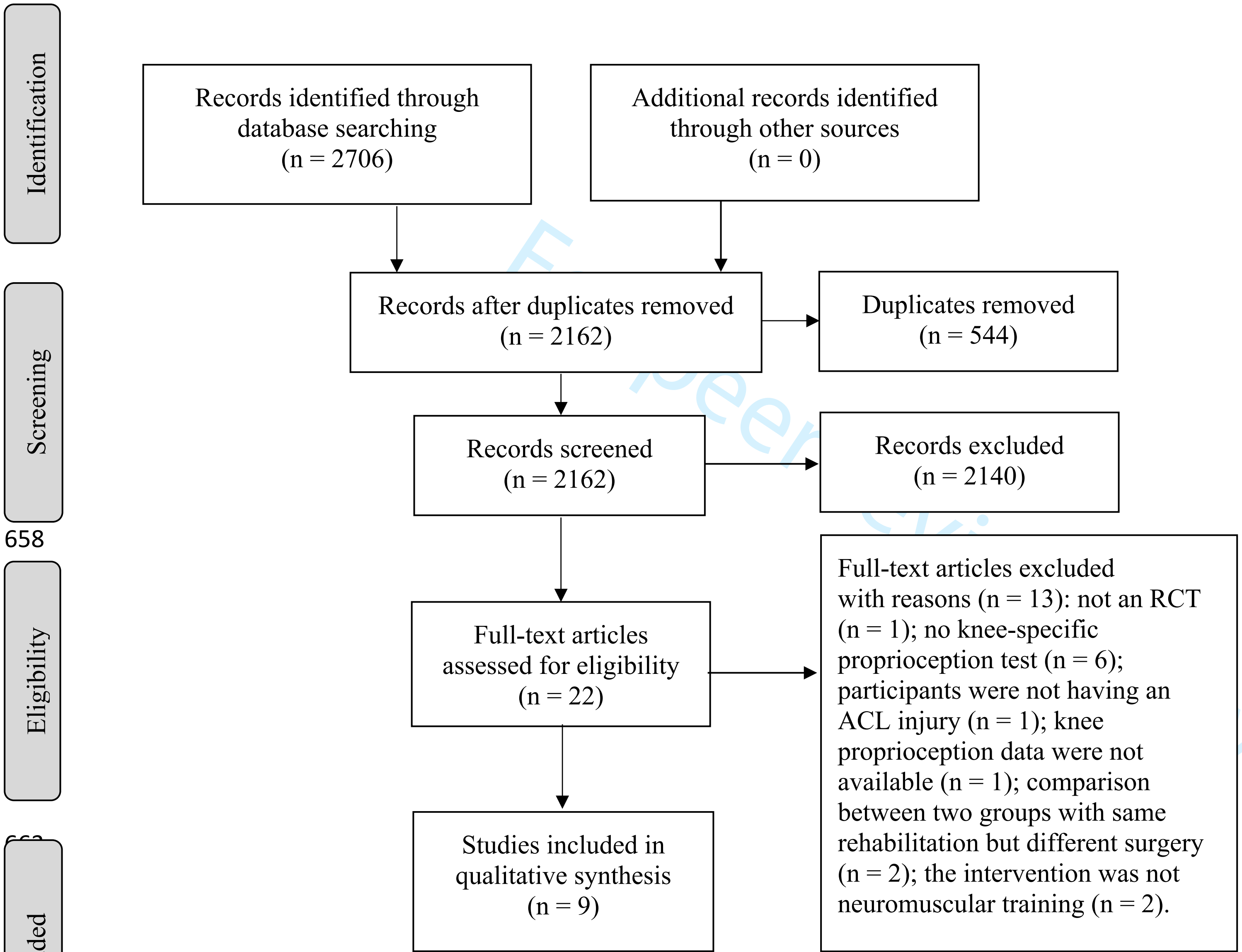


Figure 1. Flow diagram depicting the steps involved in screening and selection of eligible articles

Online supplemental file 1.

Database-specific search strategies

AMED

(Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)

S1: "Anterior Cruciate Ligament" OR (ZU "anterior cruciate ligament") OR "Knee joint" OR (ZU "knee joint)

S2: Injur* OR (ZU "injuries") OR (ZU "anterior cruciate ligament injuries") OR Reconstruction OR (ZU "anterior cruciate ligament reconstruction") OR

S3: Propriocep* OR (ZU "proprioception") OR Neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR (ZU "kinetics") OR Coordination OR Balance OR (ZU "balance") OR Plyometric (ZU "plyometric exercise") OR Vibration OR (ZU "vibration") OR Exercise* OR (ZU "exercise") OR Intervention OR Training OR Rehabilitation OR (ZU "rehabilitation") OR Therap* OR (ZU "therapy") OR Treatment

S4: Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination"

Limiters - Language: English, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - AMED - The Allied and Complementary Medicine Database

CINAHL

Limiters - Peer Reviewed; Human; Language: English, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - CINAHL with Full Text

(Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "Active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense") AND (S6 AND S7 AND S8 AND S9)

S6: “Anterior Cruciate Ligament” OR (MH "Anterior Cruciate Ligament") “Knee joint” OR (MH "Knee Joint+")

S7: Injur* OR (MH "Anterior Cruciate Ligament Injuries") OR Reconstruction OR (MH "Anterior Cruciate Ligament Reconstruction") OR Rupture OR Tear OR (MH "Rupture+") OR Conservative OR Deficiency OR “Joint instability” OR (MH "Joint Instability+"

S8: Propriocep* OR (MH "Proprioception+") OR Neuromuscular OR (MH "Neuromuscular Control") OR sensorimotor OR "sensory-motor" OR "Kinetic chain" OR (MH "Closed Kinetic Chain Exercises") OR (MH "Open Kinetic Chain Exercises") OR Coordination OR Balance OR (MH "Balance Training, Physical") OR (MH "Balance, Postural") OR Plyometric OR Vibration OR (MH "Vibration" OR Exercise* OR (MH "Exercise+") OR Intervention OR Training OR Rehabilitation OR Therapy OR (MH "Physical Therapy+") OR Treatment

S9: Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "Active movement extent discrimination"

Physical Education Index (ProQuest)

((("Anterior Cruciate Ligament" OR "Knee joint") AND (Injur* OR Trauma OR Reconstruct* OR Ruptur* OR Tear OR Conservative OR Deficienc* OR "Joint instabilit*") AND (Propriocep* OR Kinesthes* OR neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR Coordination OR Balance OR Plyometric OR Vibration OR Exercise* OR Intervention OR Training OR Rehabilitation OR Therap* OR Treatment) AND (Propriocep* OR Kinesthes* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense"))) AND at.exact("Article") AND la.exact("ENG") AND PEER(yes)

PubMed

(((((Anterior Cruciate Ligament[Text Word] OR "Anterior Cruciate Ligament"[Mesh] OR Knee joint[Text Word] OR "knee joint"[MeSH Terms]) AND "loattrfull text"[sb]) AND (((injury[All Fields]) OR Reconstruction[Text Word] OR "Anterior Cruciate Ligament Reconstruction"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh] OR Rupture[Text Word] OR Tear[Text Word] OR "Rupture"[Mesh] OR Conservative[Text Word] OR "Conservative Treatment"[Mesh] OR Deficiency[Text Word] OR Joint instability[Text Word] OR "Joint Instability"[Mesh]))) AND (((proprioception[All Fields]) OR "Proprioception"[Mesh] OR Neuromuscular[Text Word] OR sensorimotor[Text Word] OR sensory-motor[Text Word] OR Kinetic chain[Text Word] OR Coordination[Text Word] OR "Psychomotor Performance"[Mesh] OR Balance[Text Word] OR "Postural Balance"[Mesh] OR Plyometric[Text Word] OR "Plyometric

Exercise"[Mesh] OR ("exercise"[MeSH Terms] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms]) OR "Exercise Therapy"[Mesh] OR Intervention[Text Word] OR Training[Text Word] OR "Resistance Training"[Mesh] OR Rehabilitation[Text Word] OR "Rehabilitation"[Mesh] OR Therapy[Text Word] OR Treatment[Text Word] OR "Treatment Outcome"[Mesh]))) AND (((proprioception[All Fields]) OR "Proprioception"[Mesh] OR ("kinesthesis"[MeSH Terms] OR "kinesthesis"[All Fields]) OR "Kinesthesis"[Mesh] OR joint position sense[Text Word] OR (("joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND position detection[Text Word]) OR threshold to detect passive motion[Text Word] OR (passive[All Fields] AND motion direction discrimination[Text Word]) OR (passive[All Fields] AND motion detection threshold[Text Word]) OR (threshold[All Fields] AND motion detection[Text Word]) OR threshold hunting[Text Word] OR detection threshold[Text Word] OR discrimination threshold[Text Word] OR (ipsilateral[All Fields] AND matching[Text Word]) OR contralateral matching[Text Word] OR joint angle error[Text Word] OR distance estimation error[Text Word] OR passive recognition[Text Word] OR direction accuracy[Text Word] OR active reproduction[Text Word] OR Joint reposition[Text Word] OR force sense[Text Word] OR force perception[Text Word] OR velocity sense[Text Word] OR (active[All Fields] AND ("movement"[MeSH Terms] OR "movement"[All Fields]) AND extent[All Fields] AND ("discrimination (psychology)"[MeSH Terms] OR ("discrimination"[All Fields] AND "(psychology)"[All Fields]) OR "discrimination (psychology)"[All Fields] OR "discrimination"[All Fields])) OR sensorimotor[Text Word] OR sensory-motor[Text Word]) AND "loattrfull text"[sb])) AND "loattrfull text"[sb] AND ("loattrfull text"[sb] AND English[lang]) AND English[lang]

Scopus

("Anterior Cruciate Ligament" OR "Knee joint") AND (injur* OR trauma OR reconstruct* OR ruptur* OR tear OR conservative OR deficienc* OR "Joint instabilit*") AND (propriocep* OR kinesthes* OR neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR coordination OR balance OR plyometric OR vibration OR exercise* OR intervention OR training OR rehabilitation OR therap* OR treatment) AND (propriocep* OR kinesthes* OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense" OR sensorimotor OR sensory-motor) AND NOT INDEX (medline) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "NEUR")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Article") OR LIMIT-TO (EXACTKEYWORD , "Male") OR LIMIT-TO (EXACTKEYWORD , "Female") OR LIMIT-TO (EXACTKEYWORD , "Controlled Study") OR LIMIT-TO (EXACTKEYWORD , "Proprioception"))

SPORTDiscus

Limiters - Peer Reviewed; Language: English; Publication Type: Academic Journal; Document Type: Article, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - SPORTDiscus

(Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)

S1: Anterior Cruciate Ligament OR (DE "CRUCIATE ligaments") OR (DE "ANTERIOR cruciate ligament") “Knee joint” OR (DE "KNEE"

S2: Injur* OR (DE "ANTERIOR cruciate ligament injuries") OR (DE "CRUCIATE ligament injuries) OR Reconstruction OR Rupture OR Tear OR Conservative OR Deficiency OR “Joint instabilit*”

S3: Propriocep* OR (DE "PROPRIOCEPTION") OR Neuromuscular OR sensorimotor OR sensory-motor OR Kinetic chain OR Coordination OR (DE "MOTOR ability") OR Balance OR Plyometric OR (DE "PLYOMETRICS) OR Vibration OR Exercise* OR Intervention OR Training OR Rehabilitation OR (DE "TREATMENT programs") OR (DE "REHABILITATION") OR Therap* OR Treatment OR (DE "KNEE injuries -- Treatment")

S4: Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination"

Online supplemental file 2.

Screening protocol – to screen eligible studies at the title, abstract, and full-text screening stages

Questions for all stages: title, abstract and full-text screening (follow stages 1-9):

1) Is the study published in a scientific journal or published as a dissertation/thesis?
   a. No - exclude
   b. Yes or uncertain - go to step 2
2) Is the study written in English?
   a. No - exclude
   b. Yes or uncertain - go to step 3
3) Does the study deal with individuals who are 15 years of age and above?
   a. No - exclude
   b. Yes or uncertain - go to step 4
4) Does this study investigate individuals with an anterior cruciate ligament injury managed with conservative treatment or surgical reconstruction?
   a. No - exclude
   b. Yes or uncertain - go to step 5
5) Is the study a primary study (i.e. no letter to the editor, book reviews, published study designs/trial protocols, commentaries, editorials, interviews, newspaper articles, patient education handouts, consensus statements or clinical practice guidelines)?
   a. No - exclude
   b. Yes or uncertain - go to step 6
6) Does the intervention group in the study undergo neuromuscular training rehabilitation?
   a. No - exclude
   b. Yes or uncertain - go to step 7
7) Is the comparator/control group in the study include any of the following: any other therapy, conventional training, usual care, placebo or sham therapy?
   a. No - exclude
   b. Yes or uncertain - go to step 8
8) Does the study evaluate knee proprioception using a specific test (joint position sense, joint position detection, threshold to detect passive motion, passive motion direction discrimination, passive motion detection threshold, threshold for motion detection, threshold hunting, detection threshold, discrimination threshold, ipsilateral matching, contralateral matching, joint angle error, distance estimation error, passive recognition, direction accuracy, active reproduction, active movement extent discrimination, force sense, force perception, velocity sense or any other related tests)- before and after the intervention?
   a. No - exclude
   b. Yes or uncertain - go to step 9
9) Does the study report (objective) focal measures of knee proprioception for any of the specific tests mentioned in point 8?
   a. No - exclude
   b. Yes or uncertain - choose one of the following options:
      i. Title and abstract screening stage - include
      ii. Full-text screening stage - follow step 10-11

Additional questions for full-text stage only:

10) Does the study use at least one (appropriate) statistical test to compare the intervention and comparator/control groups for knee proprioception?

- a. No - exclude
- b. Yes or uncertain - go to step 11

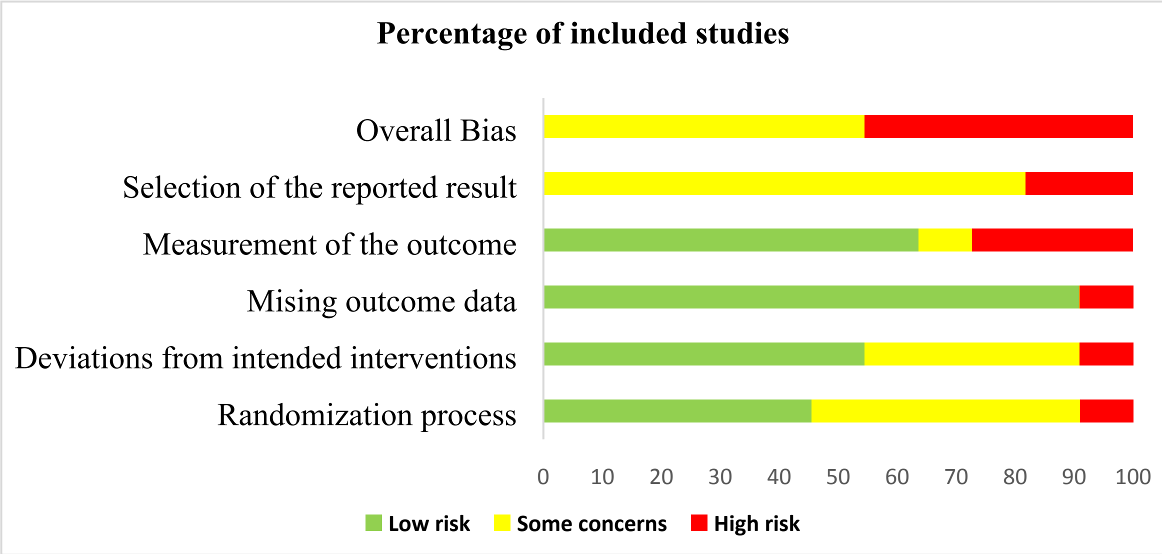
11) Are the points 1-10 scored as “yes or uncertain”

- a. If all “yes” - include
- b. If any “uncertain” - discuss with another reviewer to come to an agreement whether to include the study or not

Online supplemental file 3.

Data extraction template

Publication details	Study citation, clinical trial registration, and published study protocol if available
Aim of the study	Primary and/or secondary aims relevant for the review.
Eligibility criteria	Inclusion and exclusion criteria for participants
Randomized/controlled clinical trial	Randomization method?
Participant allocation	Concealed or not?
Number of participants identified	Identified, included and excluded?
All participants accounted for entire study	Yes or no?
Experimental group	Experimental intervention (type of neuromuscular rehabilitation training) given.
Comparator group	Comparator intervention given.
Assessment method, equipment used, and outcome measure(s) of interest	Those related to knee-specific proprioception senses.
Method(s) used for measuring the outcome(s) appropriate?	Authors quoted any data on reliability and validity based on the previous literature or their own data?
Multiple measurements of the same outcome measure within the outcome domain?	Different methods measuring same proprioception sense and different time points?
Participant characteristics	Anthropometric, demographic, physical activity and function levels, and any other relevant information to ACL injury and/or surgery.
Groups were similar at baseline	Anthropometrics, demographics, outcome measure(s) of interest, and any other prognostic indicators.
Blinding	Participants, investigators, therapists/clinicians/those delivering the interventions, and outcome assessors.
The outcome measure of interest was obtained from more than 85% of the participants initially allocated to groups	For continuous outcomes, availability of data from 95% (or possibly 90%) of the participants would often be sufficient.
If data were missing, how they were handled	'Last observation carried forward', 'baseline observation carried forward' or any other method?
Analyses preplanned	Information available from Registered trial protocol or any other relevant information available?
Between-group statistical comparisons	Statistical analysis for measurement of proprioception was done by "intention to treat" or "per-protocol" analysis? Multiple analysis of data? Corrected for multiple analysis of data? Selective reporting of analysis?
Results	Selective reporting of a particular outcome measurement?
Conclusion	Authors' conclusions

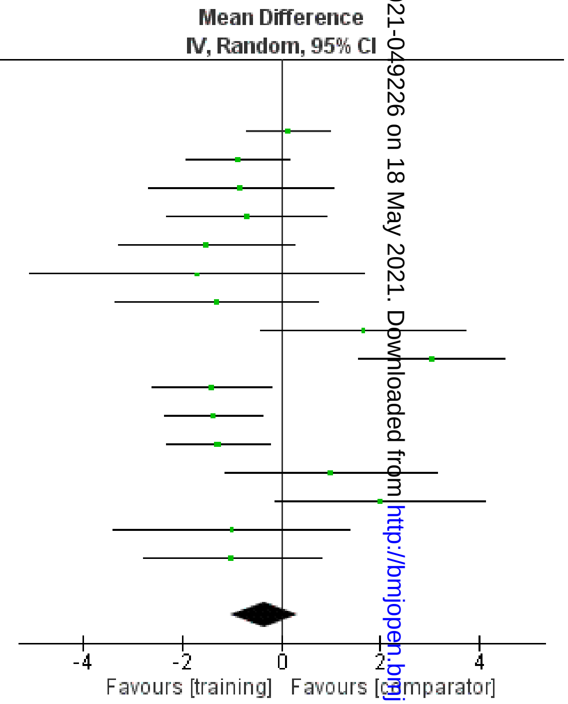


Online supplemental figure 1. Risk of bias assessment in each of the five domains and overall bias. Percentage of studies showing low risk of bias, some concerns and high risk of bias.

Note: For studies having more than one relevant outcome, each outcome is considered separately for risk of bias assessment.

Study or Subgroup	Neuromuscular training Mean	SD	Total	Comparator Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Baltaci JPS 1	2.4	61	15	0.5	23.6	15		Not estimable
Baltaci JPS 2	47	114.9	15	13.7	38.5	15		Not estimable
Cho JPS 15	1.95	1.04	14	1.81	1.2	14	8.9%	0.14 [-0.69, 0.97]
Cho JPS 45	0.64	1.71	14	1.51	1.01	14	8.2%	-0.87 [-1.91, 0.17]
Fu JPS 30	4.43	3.09	19	5.25	2.84	20	5.7%	-0.82 [-2.69, 1.05]
Fu JPS 60	4.07	2.17	19	4.77	2.93	20	6.4%	-0.70 [-2.31, 0.91]
Kaya JPS 15	15.44	1.74	17	16.95	3.13	15	5.9%	-1.51 [-3.30, 0.28]
Kaya JPS 45	45.63	2.94	17	47.32	6.05	15	2.8%	-1.69 [-5.06, 1.68]
Kaya JPS 75	74.55	1.54	17	75.85	3.77	15	5.2%	-1.30 [-3.34, 0.74]
Moezy JPS 30	1.93	2.93	10	0.27	1.58	10	5.2%	1.66 [-0.40, 3.72]
Moezy JPS 60	3.47	1.88	10	0.44	1.49	10	6.8%	3.03 [1.54, 4.52]
Shen JPS 20	4.47	1.22	10	5.87	1.48	10	7.8%	-1.40 [-2.59, -0.21]
Shen JPS 50	4.37	1.07	10	5.73	1.18	10	8.4%	-1.36 [-2.35, -0.37]
Shen JPS 80	4.49	0.92	10	5.77	1.39	10	8.2%	-1.28 [-2.31, -0.25]
Zult JPS 15	0	3	22	-1	4	21	5.0%	1.00 [-1.12, 3.12]
Zult JPS 30	2	3	22	0	4	21	5.0%	2.00 [-0.12, 4.12]
Zult JPS 45	-2	4	22	-1	4	21	4.4%	-1.00 [-3.39, 1.39]
Zult JPS 60	0	3	22	1	3	21	5.9%	-1.00 [-2.79, 0.79]
Total (95% CI)			**255**			**247**	**100.0%**	**-0.34 [-1.01, 0.32]**

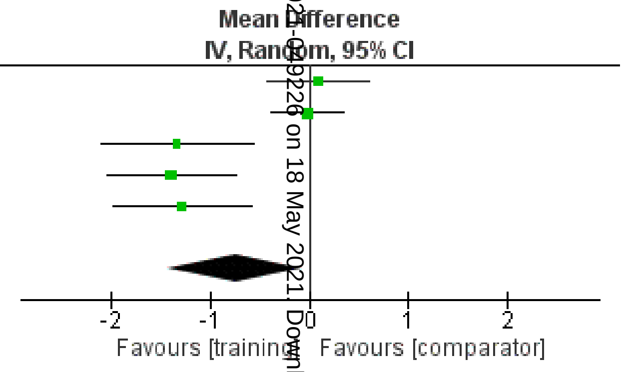
Heterogeneity: Tau² = 1.13; Chi² = 46.08, df = 15 (P < 0.0001); I² = 67%
Test for overall effect: Z = 1.01 (P = 0.31)



Online supplementary figure 2. A meta-analysis comparing mean differences between the neuromuscular training and comparator groups for knee joint position sense.

Study or Subgroup	Neuromuscular training Mean	SD	Total	Comparator Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Beynnon TTDPM	1.35	0.87	19	1.26	0.7	17	21.0%	0.09 [-0.42, 0.60]
Risberg TTDPM 15	1.2	0.76	23	1.22	0.52	24	22.2%	-0.02 [-0.39, 0.35]
Shen TTDPM 20	2.26	0.89	10	3.6	0.87	10	18.2%	-1.34 [-2.11, -0.57]
Shen TTDPM 50	2.07	0.75	10	3.47	0.74	10	19.5%	-1.40 [-2.05, -0.75]
Shen TTDPM 80	2.27	0.7	10	3.56	0.9	10	19.0%	-1.29 [-2.00, -0.58]
Total (95% CI)			**72**			**71**	**100.0%**	**-0.75 [-1.43, -0.07]**

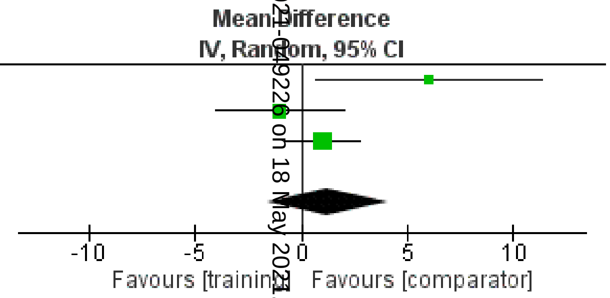
Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 27.98$, df = 4 ($P < 0.0001$); $I^2 = 86\%$
Test for overall effect: Z = 2.16 (P = 0.03)



Online supplementary figure 3. A meta-analysis comparing mean differences between the neuromuscular training and comparator groups for knee joint threshold to detect passive motion.

Study or Subgroup	Neuromuscular training Mean	SD	Total	Comparator Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Zult QFC Con 60 deg/s	-1	6	22	-7	11	21	18.8%	6.00 [0.67, 11.33]
Zult QFC Ecc 60 deg/s	-5	5	22	-4	5	21	34.7%	-1.00 [-3.99, 1.99]
Zult QFC Isometric	0	1	22	-1	4	21	46.5%	1.00 [-0.76, 2.76]
Total (95% CI)			**66**			**63**	**100.0%**	**1.25 [-1.58, 4.07]**

Heterogeneity: Tau² = 3.66; Chi² = 5.08, df = 2 (P = 0.08); I² = 61%
Test for overall effect: Z = 0.86 (P = 0.39)



Online supplementary figure 4. A meta-analysis comparing mean differences between the neuromuscular training and comparator groups for knee joint quadriceps force control.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 5-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO registration number CRD42018107349
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pages 7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplemental file 1 (pages 43-46)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 9-10, online supplemental file 2 (page 47-48)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 9, Online supplemental file 3. Data extraction template

PRISMA 2009 Checklist

			(page 49)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Online supplemental file 3 (page 49)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pages 9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Pages 9-10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Pages 9-10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pages 9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1 (page 42)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pages 10-11, Table 1 (pages 31-36)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 11-12, Table 2 (page 37)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 (pages 31-36), online

PRISMA 2009 Checklist

			supplemental figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	online supplemental figures 2-4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pages 11-12, Table 2 (page 37), Table 3 (page 38), Table 4 (pages 39-41)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17, Pages 20-21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 22

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Effects of neuromuscular training on knee proprioception in individuals with anterior cruciate ligament injury - A systematic review and GRADE evidence synthesis

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Effects of neuromuscular training on knee proprioception in individuals with anterior cruciate ligament injury - A systematic review and GRADE evidence synthesis

Authors: Ashokan Arumugam (M.P.T., Ph.D.)[1], Martin Björklund (R.P.T., Ph.D.)[2, 3], Sanna Mikko (B.Sc.)[2], Charlotte K. Häger (R.P.T., Ph.D.)[2]

Author Affiliations:

[1]Department of Physiotherapy, College of Health Sciences, University of Sharjah, P.O. Box: 27272, Sharjah, United Arab Emirates;
[2]Department of Community Medicine and Rehabilitation – Physiotherapy Section, Umeå, University, SE-901 87, Umeå, Sweden;
[3]Department of Occupational Health Sciences and Psychology, Centre for Musculoskeletal Research, University of Gävle, Gävle, Sweden.

Corresponding author: Charlotte K. Häger

Address for Correspondence:

Name	Charlotte K. Häger, R.P.T., Ph.D.
Designation	Professor
Department	Community Medicine and Rehabilitation – Physiotherapy Section
Institution	Umeå University
Country	Sweden
Mobile	+46 90 786 9275
Email	charlotte.hager@umu.se

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Effects of neuromuscular training on knee proprioception in individuals with anterior cruciate ligament injury - A systematic review and GRADE evidence synthesis

Abstract

Objective

To systematically review and summarize the evidence for the effects of neuromuscular training compared to any other therapy (conventional training/sham) on knee proprioception following anterior cruciate ligament (ACL) injury.

Design Systematic Review

Data Sources

PubMed, CINAHL, SPORTDiscus, AMED, Scopus, and Physical Education Index were searched from inception to February 2020.

Eligibility Criteria

Randomized controlled trials (RCTs) and controlled clinical trials investigating the effects of neuromuscular training on knee-specific proprioception tests following a unilateral ACL injury were included.

Data extraction and synthesis

Two reviewers independently screened and extracted data and assessed risk of bias of the eligible studies using the Cochrane risk of bias 2 tool. Overall certainty in evidence was determined using the GRADE tool.

Results Of 2706 articles retrieved, only nine RCTs, comprising 327 individuals with an ACL reconstruction (ACLR), met the inclusion criteria. Neuromuscular training interventions varied across studies: whole body vibration therapy, Nintendo-Wii-Fit training, balance training, sport-specific exercises, backward walking, etc. Outcome measures included joint position sense (JPS; n=7), thresholds to detect passive motion (TTDPM; n=3), or quadriceps force control (QFC; n=1). Overall, between-group mean differences indicated inconsistent

findings with an increase or decrease of errors associated with JPS by ≤2º, TTDPM by ≤1.5º, and QFC by ≤6 Nm in the ACLR knee following neuromuscular training. Owing to serious concerns with three or more GRADE domains (risk of bias, inconsistency, indirectness, or imprecision associated with the findings) for each outcome of interest across studies, the certainty of evidence was very low.

Conclusions The heterogeneity of interventions, methodological limitations, inconsistency of effects (on JPS/TTDPM/QFC) preclude recommendation of one optimal neuromuscular training intervention for improving proprioception following ACL injury in clinical practice. There is a need for methodologically-robust RCTs with homogenous populations with ACL injury (managed conservatively or with reconstruction), novel/well-designed neuromuscular training, and valid proprioception assessments, which also seem to be lacking.

PROSPERO registration number

CRD42018107349

Key words: Joint position sense, threshold to detect passive motion, ACL, sensorimotor training, literature review, neuroplasticity

Strengths and limitations of the study

- A systematic review of neuromuscular training on knee proprioception following the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, using a broad search in six electronic databases.
- The risk of bias associated with the outcomes of interest (knee proprioception measures) in the included RCTs were assessed using the updated Cochrane risk of bias 2 tool.
- The overall certainty of evidence for the effects of neuromuscular training on knee joint position sense, threshold to detect passive motion, and quadriceps force control following ACL injury/reconstruction was ascertained using the GRADE tool.
- Only RCTs published in English were included.
- A meta-analysis was precluded because of clinical heterogeneity of interventions and outcome measures.

Introduction

Anterior cruciate ligament (ACL) injury is a common musculoskeletal injury [1,2] accounting for an annual incidence rate of 68.6/100,000 person-years in the United States.[3] ACL injury is most prevalent in young athletes (14-18 years for females and 19-25 years for males).[3] The injury occurs more often during competition rather than training, with ~70% or more of the injuries representing noncontact mechanisms[4,5] such as landing from a jump, sudden deceleration and/or while cutting.[6] Thus, the injury mechanisms are related to neuromotor control, amongst other factors, of the individual. ACL injury is predominantly treated by surgical reconstruction,[3] and followed by a long period of rehabilitation and yet many individuals do not return to pre-injury levels of activity[7] which challenges the efficacy of existing preventative and rehabilitative strategies.

Individuals with an ACL injury present with a decreased number of proprioceptive mechanoreceptors (Pacinian capsules, Ruffini nerve endings and Golgi tendon organs)[8,9] which might alter somatosensory input to the central nervous system (CNS)[9] leading to decreased knee proprioception. Disturbed proprioception might also be caused by acute inflammation and pain, and the capsule and surrounding ligaments getting affected following instability.[10,11] Although there has been a debate regarding the effects of ACL injury on different knee proprioception tests,[2,12] our recent systematic review[13] suggests that knee JPS tests have sufficient validity in discriminating ACL-injured knees from asymptomatic knees (accepted). When compared to non-injured controls, individuals with ACL injury demonstrate altered movement strategies,[4,14] quadriceps muscle weakness,[15] and onset and progression of osteoarthrosis.[6,16] Due to the potential serious consequences of the injury, much attention and clinical efforts have been dedicated to preventative and rehabilitative strategies for ACL injury,[11] including various neuromuscular training (NT) methods believed to improve the proprioceptive ability.

Even if proprioceptive deficits could affect neuromotor control, the rationale, mechanisms, and plausibility for improving proprioception by training need to be verified. In the context of neuroplasticity, functional magnetic resonance imaging has revealed that individuals with ACL-deficient knees demonstrate less activation in several sensorimotor cortical areas and increased activation in pre-supplementary motor areas, posterior secondary somatosensory area, and posterior inferior temporal gyrus compared to controls with asymptomatic knees during a knee flexion-extension task.[1] It seems individuals with ACL reconstruction adapt a visual-sensory-motor strategy instead of a normal sensory-motor strategy owing to aberrant sensory feedback following ACL injury.[17] Nevertheless, neuroplastic reorganization ensues where other potential sensory sources are used to organize the movement or regulate neuromotor control, particularly in (sporting) tasks with higher complexity. Therefore, ACL injuries might be regarded as a neuromotor control dysfunction rather than a simple peripheral musculoskeletal injury.[11,18] It is yet unclear though whether neuromuscular training (NT) can improve proprioception after an ACL injury[11,19] and the neurophysiological mechanisms underpinning such interventions need further substantiation.

To date, there is no consensus on the most effective rehabilitation programs for ACL injury, and the prevalence of reinjury after returning to sport is up to 30%.[18] Owing to the neuroplastic changes and possibly altered proprioception following an ACL injury, NT has received much attention to enhance dynamic joint stability and relearn movement patterns and skills.[20] In this context, both NT and sensorimotor training terms have been used. NT is defined as "…training enhancing unconscious motor responses by stimulating both afferent signals and central mechanisms responsible for dynamic joint control" [20] and sensorimotor training aims to improve "…function of the CNS in regulating movement in order to reach proper firing patterns for maintaining joint stability…".[21] Active knee motion will in any case stimulate proprioceptors, which in turn would alter the demands on the CNS,[10,19]. Henceforth we will use the term NT in this review.

There are different ways to challenge proprioception, for example: vibration may be used to alter afferent input from muscle spindles; an unstable surface can challenge input from the ankle; vision can be occluded or head position can be changed to disturb visual- and vestibular information,[10] or focus can be shifted to influence cognitive processing sources.[18] Due to a putative visual-sensory-motor strategy following ACL injury, a modified visual feedback training might decrease visual reliance and improve sensory-motor function.[18] Most studies exploring the effects of NT on proprioception combine different exercises and various outcome measures which precludes isolating the effects of a proprioception-specific exercise.[22] Therefore, this study aimed at systematically reviewing and summarizing the evidence for the effects of NT compared to comparator/control interventions on proprioception measured by knee-specific proprioception tests in individuals with anterior cruciate ligament injury or reconstruction.

Methods

We adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) checklist[23] and the reporting guidelines for Synthesis Without Meta-analysis (SWiM) in systematic reviews.[24] The protocol was registered in PROSPERO (CRD42018107349). A list of acronyms used in the review is summarized in Box 1.

Eligibility criteria

The structure of PICOS[25] was used to frame the following criteria:

1. **Participants:** Individuals aged over 15 years of age (both sexes) with a history of a unilateral ACL rupture, managed conservatively or surgically reconstructed, with or

without concomitant meniscus and/or collateral ligament injuries on the injured leg, without any other lower extremity injuries/surgeries that would confound the outcomes of rehabilitation training;

2. **Intervention:** Specific neuromuscular training, closed or open kinetic chain exercises, balance training, joint repositioning training, joint force sense training, co-ordination training, plyometric training, whole body vibration, virtual gaming training, an accelerated rehabilitation protocol or any other training programs focusing on improving the lower limb neuromuscular control and knee proprioception;
3. **Comparator:** Any other therapy, conventional training, usual care, placebo or sham therapy;
4. **Outcome measures:** Knee-specific proprioception tests targeting joint position sense (JPS), kinesthesia (threshold to detect passive motion [TTDPM]), force sense/perception, active movement extent discrimination, velocity sense, or psychophysical threshold methods;[13] they can be performed actively and/or passively with or without visual input in weight bearing or non-weight bearing positions;[10]
5. **Study design:** randomized controlled trials (RCTs) or controlled clinical trials.

Data Sources and Searches

Database-specific search terms (e.g. MeSH) were combined using Boolean operators ("AND" and "OR") under three conceptual domains: participants, interventions and outcomes. Six electronic databases were searched from their inception to 12 February 2020: PubMed, Cumulative Index to Nursing & Allied Health Literature (CINAHL via EBSCOhost), SPORTDiscus (via EBSCOhost), the Allied and Complementary Medicine

Database (AMED via EBSCOhost), Scopus, and Physical Education Index (via Proquest) (Online supplemental file 1).

Study Selection

One reviewer (SM) imported all titles and abstracts retrieved from the databases into EndNote X8. Two reviewers (AA and SM) independently checked titles, abstracts, and/or full text by following a screening questionnaire (online supplemental file 2). Any disagreements in inclusion of articles were adjudicated by two other reviewers (CH and MB) until consensus was reached. A manual search of the reference lists of included articles was performed.

Data Extraction

Data were extracted by one reviewer (SM) and verified by another reviewer (AA) using a customized data extraction sheet (online supplemental file 3). If any data were missing, the corresponding authors were contacted via email.

Quality Assessment

The risk of bias for each outcome of interest in the included studies was evaluated using the Cochrane ROB 2.[26] The tool has five domains: 1) randomization (number of signaling questions (n=3), 2) deviations from intended interventions (n=7), 3) missing outcome data (n=5), 4) measurement of the outcomes (n=5), and 5) selection of the reported results (n=3). Each signaling question can be answered as 1) yes, 2) probably yes, 3) probably no, 4) no, and 5) no information. Responses to the questions provide the basis for judgement of the risk of bias at each domain level using a tool-specific algorithm resulting in one out of three possible judgements: 1) low risk of bias, 2) some concerns, or 3) high risk of bias. An overall risk of bias score for each outcome in a study can be low (with a low risk of bias for all

173 domains), some concerns (if some concerns prevail in at least one domain without a high risk of bias for any domain) or high (if a high risk of bias underpins at least one domain or some concerns remain in multiple domains, defining multiple as more than two).

176 **Evidence Synthesis**

177 The overall evidence level in this review was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool considering the following five domains: 1. risk of bias: high risk, some concerns, or low risk associated with knee proprioception measures based on the Cochrane ROB 2 tool; 2. Inconsistency of findings: similar or conflicting direction of effect, effect estimates and overlap of confidence intervals for knee proprioception measures from different studies; 3. indirectness of evidence: appropriateness of participants, interventions, and outcomes used to answer the review question; 4. imprecision of results: the length of 95% confidence intervals of effect estimates and overall sample (number of participants) from which effect estimates are derived; and other domains: e.g. publication bias if applicable.[27] The overall evidence was rated as very low, low, moderate or high.

188 A meta-analysis was precluded owing to clinical heterogeneity of interventions and outcome measurements (JPS, TTDPM and QFC). For instance, despite seven studies targeting JPS, a meta-analysis was not appropriate because at most two studies used the same method (active-active,[28,29] passive-passive[30,31] or passive-active[32,33]) but the starting and target angles and the number of trials per each angle varied between these proprioception tests in the included studies. Further, the neuromuscular training interventions, targeting JPS, widely varied between studies[28-34]: closed kinetic chain exercises on a balance pad,[34] whole-body vibration therapy (WBVT),[29,30] motor control exercises for the lower limbs,[32] backward walking on a treadmill,[31] Nintendo Wii Fit training,[28] and cross-education of strength training of the non-

injured leg along with standard rehabilitation.[33] Further, in addition to inconsistent findings among the studies, a significant statistical heterogeneity (I^2>60%) in a random-effects meta-analysis was evident. Although meta-analyses were excluded, the Review Manager 5.3 software (the Cochrane Collaboration) was used to calculate between-group mean differences (effect sizes) and their 95% confidence intervals for summarizing the findings for each outcome of interest in Table 1.

Patient and public involvement

Neither patients nor public were involved.

Results

Search Results

Electronic databases search led to a total of 2706 articles (excluding duplicates: 2162). After title and abstract screening, 22 articles were shortlisted for full-text screening and subsequently nine articles met the inclusion criteria (Figure 1). Thirteen articles were excluded owing to the following reasons: not an RCT (n= 1),[35] no knee-specific proprioception tests (n= 6),[36-41] participants were without an ACL injury (n = 1),[42] knee proprioception data were missing and the corresponding author did not respond to our emails (n = 1),[43] a comparison between different surgical intervention groups with same rehabilitation program (n = 2),[44,45] and lack of a neuromuscular rehabilitation training program (n = 2).[46,47] No additional relevant studies were identified through manual search of bibliographic references.

Study Design and Participants

All the nine studies included were RCTs with a total of 386 participants and two studies had their trial pre-registered in a clinical trial registry.[31,33] All participants had undergone an ACL reconstruction with a bone-patellar-tendon-bone or a hamstring graft (Table 1).

Quality Assessment

The agreement (Cohen's kappa) of responses to the signaling questions between the two reviewers (AA and MB) was substantial (0.69 ± 0.047, $p < 0.001$). Disagreements were discussed and resolved by the two reviewers. Online supplemental figure 1 shows the percentage of studies judged as low risk, some concerns and high risk of bias in the five domains, and Table 2 shows domain judgements of each study. The overall risk of bias judgement showed that four of the included studies had a high risk of bias,[28,29,32,34] four had some concerns,[30,31,48,49] and one study[33] had a high risk of bias for JPS and some concerns for quadriceps force control (QFC). The domain that most consistently showed risk of bias across studies was bias in selection of the reported results (Online supplemental figure 1 and Table 2). The most common reason was the absence of information regarding pre-specified plan of analyses. None of the included studies reported trial protocol publication and only two[31,33] reported trial registration. Furthermore, two studies were judged to perform inappropriate multiple analyses.[28,29] Judgement of bias in measurement of the outcome (domain 4, Table 2) showed most scattered results across studies (Online supplemental figure 1). A high risk of bias was found in three studies of which one had no information on measurements[34] and two showed inappropriate measurement methods of the outcome of interest.[28,33] In the study by Zult et al., only one trial per target was performed to estimate JPS,[33] while Baltaci et al. used a test with presumably a high demand on motor and memory components,[28] without reporting its reliability or validity. The domain with least risk of bias was missing outcome data where all studies, except one,[32] had low risk of bias.

Rehabilitation Programs

The studies included a spectrum of rehabilitation programs employed to influence knee proprioception (Table 1). Only one study by Baltaci et al. investigated the effects of using feedback with an external focus in a simulated sport-specific gaming environment with Nintendo Wii Fit compared to conventional rehabilitation.[28] On the contrary, the remaining eight studies focused on having an internal focus (mainly related to the position of specific body parts) for neuromuscular training. Two studies[29,30] explored the effects of whole-body vibration therapy (WBVT) combined with or without conventional rehabilitation compared to conventional rehabilitation alone. Cho et al. compared closed kinetic chain exercises on a balance pad versus on a stable floor.[34] Risberg et al. compared the effects of a NT compared to strength training. In their neuromuscular program, the first half of the rehabilitation focused on exercises on a wobble board or trampoline and exercises to increase the range of motion, while the end of the program focused on specific training of plyometric, agility and sport-specific skills.[48] Beynnon et al. evaluated the effects of accelerated (19 weeks) vs. non-accelerated (32 weeks) programs of conventional training.[49] The timeframe and exercises in their experimental program ranged from 1-7 weeks for range of motion and muscle activation, 8-11 weeks for dynamic functional activities such as biking and jogging, and finally, 12-19 weeks for plyometric and agility drill exercises.[49] Kaya et al. studied the effects of neuromuscular (motor control) exercises for the lower limbs combined with standard rehabilitation compared with standard rehabilitation alone.[32] Shen et al. examined the outcome of standard rehabilitation combined with backward walking at 1.3 km/h on a treadmill for four groups (at four inclination angles 0°, 5°, 10°, and 15°, respectively) compared to standard rehabilitation in a comparator group.[31] Nevertheless, Zult et al. examined the effects of cross-education of strength training of the non-injured leg along with standard rehabilitation compared to standard rehabilitation alone.[33]

267 **Knee-specific Proprioceptive Measures**

268 Seven studies used active or passive JPS and all but one used (absolute) angular error as a variable to evaluate the outcome.[28-34] Conversely, one study used a computer program (monitored-rehab-system-software) to define a virtual line/route to allow joint repositioning within 30-70% knee range of motion with and without visual feedback.[28] The differences between visual and blinded trials (2 each) based on the deviations from the computer-generated line (in mm) were used to give information about the sense of proprioception.[28] All these studies used sitting or supine test position for assessing JPS. There were two to four predetermined target knee flexion angles across studies ranging from 15°-80°.[29-34] Moreover, two studies[28,29] used active knee motion and four used passive knee motion[30-33] to set the target angle. Whether Cho et al. used active or passive knee motion to set/reproduce the target angle seems ambiguous.[34] Four studies[28,29,32-34] used active knee motion and two[30,31] used passive knee motion to reproduce the target angle. The JPS method used by Zult et al. was presumed based on their reference to Hortobagyi et al.[50]

281 The angular error was measured with 1-6 trials per each angle and one study[33] randomized the order of the joint angles used. Eyes were blinded during the test in six studies[29-34] while one study used visual feedback when the individual was placing the knee joint in the target angle but no such feedback was given during reproduction of the target angle.[28] The difference between visual and non-visual trials was calculated in mm by the device as a measure of JPS.[28] A Biodex dynamometer (Biodex Medical Systems, Shirly, NY, USA) was used in five studies[29,30,32-34] to test JPS. Even so, one study used a continuous passive motion equipment[31] while another[28] employed a functional squat system (Monitored Rehab System, Haarlem, and the Netherlands) with a leg press machine and an associated computer program for assessing JPS.

Three studies[31,48,49] evaluated knee kinesthesia with the threshold to detect passive motion (TTDPM) using a bespoke device,[48,49] or a continuous passive motion equipment.[31] The knee joint was moved in flexion or extension at a constant angular velocity of 0.5°/s [48] or 0.1°/s.[31,49] While the participants were blindfolded in two studies,[31,49] the other study did not mention about visual feedback.[48] In all three studies, the tests were performed three times in each direction (flexion and/or extension) for both legs but whether the order of direction or leg was randomized is not reported. In the study by Risberg et al.,[48] TTDPM data were missing for 27 out of 74 participants because of device failure, which might lower the power of the study.

Effects of NT on Knee Proprioception in Individuals with ACLR

There were conflicting findings among the included studies for the effects of NT on improving JPS, TTDPM and QFC. Overall, mean differences between groups indicated inconsistent findings with an increase or decrease of JPS angular errors (one or more target angles) by ≤2º, TTDPM by ≤1.5º, and QFC (concentric/eccentric/isometric contractions) by ≤6 Nm following neuromuscular training.

Of the nine included articles, four reported reduction in JPS angular errors of ACLR knee at one or more target angles (JPS at 45° but not 15° [34]; JPS at 60° but not 30° [29]; JPS at 15°, 45°, 75° [32]; JPS 20°, 50°, 80° [31]) and/or contralateral non-injured knee (JPS at 30° and 60° [29]) favoring the NT group (exercises on a balance pad [34], whole-body vibration therapy [29], neuromotor control exercises [32] or backward treadmill walking [31]). Shen et al. also reported improved TTDPM following backward treadmill walking.[31] When we calculated mean differences for author-reported post-operative [29,32] or change (pre- vs. post-intervention) scores [34] between groups for the ACLR leg with the Review Manager 5.3 software (the Cochrane Collaboration), their 95% confidence intervals revealed no effects (see Table 1).

Moreover, the remaining five studies did not report significant differences in proprioception between groups.[28,30,33,48,49]

Assessing Certainty in Evidence

There were serious concerns with three GRADE domains (risk of bias, indirectness, and imprecision associated with the findings) across the seven studies that measured JPS (Tables 3 and 4). The certainty of evidence found was very low for the effects of NT on improving JPS following ACLR.

There were further serious concerns with all GRADE domains (risk of bias, inconsistency, indirectness, and imprecision associated with the findings) across the three studies measuring TTDPM (Tables 3 and 4). Therefore, the certainty of evidence found was very low for improving TTDPM in individuals with ACLR following NT (Table 3).
An overall judgement of some concerns based on the Cochrane ROB 2 tool (Table 2) was found for the study reporting changes in QFC following NT.[33] Available population, the magnitude and direction of effect, and effect estimates of QFC (Tables 1 and 3) are derived from only one study which reflect serious concerns. However, the participants with ACLR, intervention (cross-education of the quadriceps with standard rehabilitation), and QFC[33] are directly related to our research question. The certainty of evidence found was very low for improving QFC in individuals with ACLR following NT because only one relevant study was found.

Discussion

This review is the first, as far as we are aware, to address effects of neuromuscular rehabilitation training on knee proprioception in individuals with ACL injury. A previous review, however, summarized the effects of proprioceptive and balance exercises following

ACL injury/reconstruction on certain outcome measures (muscle strength, hop test, etc.) but other than knee-specific proprioception tests.[51] Another similar review did not find any RCTs in this area.[52] We identified nine studies employing a range of NT methods, of which all but one[48] were published within the past decade. Nevertheless, there were serious concerns with two or more GRADE domains (risk of bias, inconsistency, indirectness, or imprecision associated with the findings) across studies implying a very low certainty of evidence for improving JPS, TTDPM, and QFC of ACLR knee following NT.

Effects of NT on Knee Proprioception in Individuals with ACLR

Most of the employed NT programs did not influence proprioception compared to comparator interventions. Potential reasons for insignificant between-group differences include: 1) experimental and comparator programs (with exercises that are wholly or partly similar) which potentially might stimulate similar effects on proprioception in both programs;[28,30,32,34,48,49] 2) the exercises did not adequately stimulate proprioception sense;[33] 3) a lack of proprioception deficit following ACL injury (TTDPM similar between ACL-injured and contralateral uninjured knee[49]); 4) a lack of valid, sensitive and responsive knee-specific proprioception test methods; 5) a short follow-up period (a follow-up at least 18 months post-ACLR might be needed to regain proprioceptive function[53]) in most studies except two studies;[32,49] 6) type II errors arising from low sample sizes in most studies (with missing power or sample size calculations); and 7) adherence rates of participants to the prescribed program (only three studies have explicitly reported adherence rates to training sessions/exercises [Table 1]).[30,48,49] The heterogeneity of interventions, methodological limitations, inconsistency in the magnitude and direction of effects, and imprecision of effect estimates, found in this review, preclude recommendation of one optimal NT intervention for improving proprioception following ACL injury in clinical practice.

Risk of Bias in the Included Studies

Bias in selection of the reported variables/results due to absence of a pre-specified plan of analyses applied to all but one study,[33] and none had published a trial protocol in a scientific journal although two studies were registered in a trial registry.[31,33] A possible reason for the absence of registration for most studies in this review may be that all but three studies were older than five years. Yet, one latest published study did not report trial registration.[32]

Another concern was the method used to measure JPS. For instance, estimates of JPS based on 3-5 repetitions, in clinical trials, may be insufficient.[54] According to Selfe et al. five repetitions in active knee JPS test, and six when performed passively, are necessary to ensure a consistent proprioception score.[55] However, this was only met in two included studies.[29,32]

All studies used absolute angular error (AAE) for measuring JPS acuity which represents a task-oriented approach to studying performance skill, in contrast to a process-orientation in which underlying processes are in focus. The inconsistency in performance, i.e., response variability (variable error), may reflect noise in sensory signal and its processing[56] and thus be a more process-oriented outcome than AAE. To understand possible underlying mechanisms, it would be advantageous to combine task- and process-oriented measures.
In general, method descriptions of proprioception tests were short and, in some studies, deficient, lacking information about factors that could influence the results. One such factor was randomization of the order of target positions (cf. Zult et al.),[33] which is required to minimize the effect of memory and reduce motor elements of the test. This is particularly applicable in tests with active positioning, which was the case for most studies, enabling central motor programs.[57] Inadequate reporting of the proprioception tests would hinder their replication and raise risk of bias rating. Moreover, Kaya et al. reported only post-intervention JPS scores, precluding baseline scores, despite claiming their study to be an RCT.[32]

Among seven RCTs[28-34] investigating changes in JPS following NT, five RCTs were found to have a high risk of bias while the remaining two studies have some concerns based on the Cochrane ROB 2 tool (Table 2). Therefore, included RCTs have been judged to have very serious methodological limitations in the GRADE evidence synthesis.

Mechanisms Underpinning NT Following ACLR

Two of the included studies evaluated the effects of WBVT;[29,30] however, only one found a favorable effect on proprioception (JPS – target angle 60°).[29] Two factors may contribute to the different findings between these studies. First, time point at which WBVT was given: Fu et al. employed WBVT at one-month post-ACLR for 2 months and evaluated JPS at 3 and 6 months after the surgery (Table 2). [30] On the other hand, Moezy et al. gave WBVT at 3 months post-ACLR for one-month and assessed JPS at 4 months after the surgery.[29] It seems starting WBVT at 3 months, rather than at one-month, post-ACLR might have better on improving knee JPS. Second, the use of active[29] or passive[30] knee movement when testing JPS. Active tests stimulate both joint and muscle-tendon mechanoreceptors and induce alpha-gamma co-activation while passive tests assess joint receptors to a higher degree[10,58] which potentially could mean a higher sensitivity of the active test.

WBVT has shown effects on body posture, flexibility, proprioception (TTDPM in patients with osteoarthritis), coordination and muscle power.[59-61] It has been promoted as an effective method to induce a reflex muscle contraction in subjects with difficulties to evoke voluntary contractions.[62] The mechanism behind the improvements can be that the mechanical stimuli stimulate primary endings of muscle spindles, especially type II fibers, which activate a-motor neurons. This could potentially stimulate central motor command, which facilitates increased muscle activation and voluntary movements.[59]

Cho et al. showed a significant effect on knee proprioception (JPS and TTDPM) with closed kinetic chain exercises on a balance pad/board.[34] Exercises on a balance board are widely used to improve proprioception.[38,51] In this review, a few NT programs included, amongst other exercises, balance training with or without a balance pad/board.[28,32,34,48,49] Additionally, one study claimed backward walking, a closed kinematic chain exercise, to stimulate joint/muscle receptors and sensory afferents to the CNS and augment proprioceptive and balance training.[31] Among these studies, all but one,[31] did not show significant mean differences between groups in proprioception calculated using the Review Manager 5.3 software (the Cochrane Collaboration) (see Table 1 and supplementary files). Different designs and levels of difficulty of the execution were found (e.g. a simple static balance task [with and without visual input], dynamic exercises performed on the balance board, backward walking on a treadmill, etc.).

There is a challenge to transfer the rehabilitation in the clinic to automatic movements required for athletic activities.[18,63] Wii Fit or similar games have the potential to combine feedback with an external focus in a sport-specific environment,[28] supporting the use of such training tools. However, a study on Nintendo Wii Fit training did not support its use for improving knee proprioception following ACLR.[28] Newer technology with stroboscopic eyewear might have the potential to decrease visual input without fully occluding it, making it possible to use them in sport specific rehabilitation. To prepare the individual for complex athletic environments and reduce re-injury risk, rehabilitation might focus on NT with reduced demands on visual inputs and enhance automatic movement control with cognitive demands included.[18] Whether such NT training improves knee proprioception and, how this should be assessed in the best way,[13] are yet to be determined.

The Ability of Tests to Discern Changes in Proprioception Following NT

There is neither a gold standard proprioception test (targeting JPS, kinesthesia, force sense) nor a standard procedure with established psychometric properties to test each proprioception sense following ACL injury. In this review, JPS and TTDPM were commonly reported. The Ruffini and Golgi receptors are slow-adapting receptors, responding to a change in joint position. Nevertheless, the Pacinian receptors that respond to low degrees of joint stress are more sensitive to rapid changes in accelerations and contribute to a low TTDPM.[2,64] JPS has been reported to detect a greater difference in knee proprioception than TTDPM following an ACL injury.[2] However, our findings remain equivocal regarding the outcomes of JPS or TTDPM following NT.

Knee-specific proprioception tests provide an indirect measure of proprioception involving the process of the CNS.[10] Psychosocial factors,[65] pain and preinjury motor skills may influence the central mechanisms and the outcome of such tests following NT. Knee-specific proprioception tests are designed to exclude motor skills, but how successful that exclusion works, remains unclear.

Limitations and Future Recommendations

The nine included studies looked at only individuals with ACLR but not those managed conservatively following ACL injury. Owing to clinical heterogeneity of interventions and outcome measurements, meta-analyses were precluded from the GRADE evidence synthesis. The included studies had methodological limitations (high risk of bias or some concerns) and all, but two studies,[31,33] had not pre-registered/published their protocol. There is a need for high quality RCTs with low risk of bias in this area.

Grey literature was not included in the current review which could be seen as a limitation. The most common reason for exclusion of clinical trials in this review was that they did not evaluate the effects of NT following ACLR with a knee-specific proprioception test. Perhaps, the lack of consensus regarding the most appropriate, valid, reliable and responsive proprioception tests, number of target angles or most responsive target angles (low vs. high) might have precluded such outcomes in these studies. Therefore, psychometric properties of such tests must be established.[13]

When designing rehabilitation programs with long-term follow-up, aberrations in neuromotor control as well as neuroplastic changes should preferably be addressed. To reflect a wide spectrum of individual impairments, further research should investigate differences in individuals with ACL injuries managed with surgical (graft types) or conservative treatment, both sexes, athletes and non-athletes of different ages. Future studies might assess neuromotor control in functional tasks rather than relying on knee-specific proprioception tests, given the challenges of isolating the proprioceptive ability.

Conclusion

The existing nine studies on individuals with an ACL reconstruction using heterogeneous interventions and knee-specific proprioception measures revealed a very low certainty in current evidence for employing NT programs to improve knee proprioception. The GRADE evidence synthesis revealed a high risk of bias or some concerns, indirect evidence, conflicting findings, and imprecision of effect estimates in the included studies. Well-designed RCTs with homogenous populations (having ACL injury managed with or without reconstruction), novel/well-designed NT interventions, and valid proprioception measures are warranted to substantiate conclusive evidence in this area.

Contributors

AA and CKH conceived the idea of the project. AA, MB, SM and CKH were responsible for designing the review and conceptualising the initial review protocol. AA led the writing of the manuscript. MB, SM and CKH contributed to writing the manuscript. AA, MB and CKH have reviewed and revised the manuscript for intellectual content. All authors approved the final version of the manuscript. AA is the guarantor of this work.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. A detailed protocol of the review has been registered in PROSPERO (CRD42018107349).

Competing interests

None declared.

Patient consent for publication

Not required.

Figure caption

Figure 1. Flow diagram depicting the steps involved in screening and selection of eligible articles

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Table 1. Summary of study characteristics

Study citation	Sample size[a], age (mean ± SD), gender; ACLR (Graft)	Intervention; Adherence to prescribed exercises/ training	Comparator; Adherence to prescribed exercises/ training	Knee-specific proprioception test; outcome	Between-group (experimental vs. control) comparisons of ACL-injured (reconstructed) limb - mean difference (95% confidence interval)[b]
Baltaci et al. (2013) [28]	Exp: n=15, 28.6±6.8 years, 15 men; Com: n=15, 29.3±5.7 years, 15 men; ACLR (hamstring tendon graft).	Nintendo Wii Fit training: 3 times/week; 60 min/session; from week 1-12 after ACLR. **Adherence:** NR	Conventional rehabilitation: Week 1-12 after ACLR; **Adherence:** NR	**Proprioception test:** JPS (ipsilateral replication method); **Body position:** NR; **Instrument:** Monitored Rehab System with a leg press machine and a computer game; **Procedure:** Active-active, with and without blindfolding of the eyes (2 trials each); **Starting angle (SA):** NR; **Target angle (TA):** NR; **Outcome measure:** absolute angular error (AAE; difference between visual and non-visual results for each leg)	**JPS[c] at 12 weeks post-intervention:** 1.90 [-31.20, 35.00] 33.30 [-28.02, 94.62]

Beynnon et al. (2011) [49]	Int: n=19, 29.7±10.1 years, 13 males, 6 females; Com: n=17, 30.2±9.9 years, 9 males, 8 females; ACLR (patellar tendon graft)	Accelerated rehabilitation: daily exercises at home + 3 times/week exercises under supervision from week 1-19 after ACLR; **Adherence:** 94% (range, 25%-292%) over 19 weeks	Non-accelerated rehabilitation: daily exercises at home + 3 times/week exercises under supervision from Week 1-32 after ACLR; **Adherence:** 53% (range, 13%-108%) over 32 weeks	**Proprioception test:** TTDPM; **Body position:** Seated; **Instrument:** A customized joint motion detection system; **Procedure:** passive movement of the knee into flexion or extension (3 trials for both ACL-reconstructed and contralateral uninjured knees) with eyes blindfolded; **SA:** NR; **Angular velocity:** 0.1°/s; **Outcome measure:** Threshold angle (difference between the initial angle [SA] and the angle at which the test was stopped) to detect passive knee motion into flexion or extension (mean of the three trials in one direction).	**TTDPM (°)[c] at 24 months post-ACLR:** **SA (NR):** 0.09 [-0.42, 0.60]
Cho et al. (2013) [34]	Int: n=14, 29.92±5.46 years; 14 males; Com: n=14, 28.78±7.24 years; 14 males; ACLR (NR).	Unstable exercise group: exercises performed on a balance pad or balance board; 60 min/session; 3 times/week early after injury, for 6 weeks; **Adherence:** NR	Stable exercise group: exercises performed on a stable floor: 3 times/week Early after injury, for 6 weeks; **Adherence:** NR	**Proprioception test:** JPS; **Body position:** seated (?); **Instrument:** Biodex dynamometer; **Procedure:** NR-active, with eyes blindfolded; **SA:** 90°; **TA:** 15°, 45°; **Outcome measure:** AAE (mean of the three trials at each angle).	**JPS (°)[d] at 6 weeks post intervention:** TA 15°: 0.14 [-0.69, 0.97] TA 45°: -0.87 [-1.91, 0.17]

Fu et al. (2013) [30]	Int: n=24, 23.3±5.2 years; Com: n=24, 25.2±7.3 years; ACLR (hamstring graft).	Conventional rehabilitation program + Whole-body vibration therapy: 2 times/week from week 5-13 after ACLR; **Adherence:** 83.2% over 12 weeks	Conventional rehabilitation program: week 5-13 after ACLR; **Adherence:** 84.4% over 12 weeks	**Proprioception test:** JPS; **Body position:** seated; **Instrument:** Biodex dynamometer; **Procedure:** passive-passive, eyes blindfolded; **SA:** 90°; **TA:** 30°, 60°; **Outcome measure:** AAE (mean of the three trials at each angle)	**JPS (°)[c] at 6 months post-ACLR:** **TA 30°:** -0.82 [-2.69, 1.05] **TA 60°:** -0.70 [-2.31, 0.91]
Kaya et al. (2019) [32]	Int (Group 1): n=20; 29.35±9.71 years; 20 males; Com (Group 2): n=20; 31.60±8.45 years; 20 males; ACLR (tibialis anterior allograft).	Standard rehabilitation program (0-2 weeks) + neuromuscular control exercises (3-36 weeks); **Adherence:** NR	Standard rehabilitation program (0-36 weeks); **Adherence:** NR	**Proprioception test:** JPS; **Body position:** seated (?); **Instrument:** Biodex dynamometer; **Procedure:** passive-active, eyes blindfolded; **SA:** 90°; **TA:** 15°, 45°, 75°; **Outcome measure:** AAE (mean of six trials at each angle)	**JPS (°)[c] at 24 months post-ACLR:** **TA 15°:** -1.51 [-3.30, 0.28] **TA 45°:** -1.69 [-5.06, 1.68] **TA 75°:** -1.30 [-3.34, 0.74]
Moezy et al. (2008) [29]	Int: n=12, 24.51±3.38 years; Com: n=11, 22.70±3.77 years; ACLR (patellar tendon graft)	Whole-body vibration therapy: 3 times/week from week 12-16 after ACLR; **Adherence:** NR	Conventional strengthening exercises program: 3 sessions/week Week 12-16 after ACLR; **Adherence:** NR	**Proprioception test:** JPS; **Body position:** seated; **Instrument:** Biodex dynamometer; **Procedure:** active-active, eyes blindfolded; **SA:** 90°; **TA:** 30°, 60°; **Outcome measure:** AAE (mean of five trials at each angle for both ACL-	**JPS (°)[e,d] at 4 months post-ACLR:** **TA 30°:** 1.66 [-0.40, 3.72] **TA 60°:** 3.03 [1.54, 4.52]

				reconstructed and contralateral uninjured knees)	
Risberg et al. (2007) [48]	Int: n = 39; 3 females - 27.2 (range: 20.6-37.9) years and 26 males - 27.7 (16.7-39.6) years; Com: n=35, 14 females - 26.5 (19.8-38.0) years and 21 males - 31.2 (19.4-40.3) years; ACLR (patellar tendon graft)	Neuromuscular training program: 2-3 times/week from week 1-24 after ACLR; **Adherence:** 71% over ~20 weeks	Traditional strength training: 2-3 times/week from week 1-24 after ACLR; **Adherence:** 91% over ~20 weeks	**Proprioception test:** TTDPM; **Body position:** NR; **Instrument:** a customized TTDPM device; **Procedure:** passive movement of the knee into flexion and extension (three trials for each direction for both ACL-injured knees and contralateral uninjured knees); no information on blindfolding of eyes; **SA:** 15°; **Angular velocity:** 0.5°/s; **Outcome measure:** Threshold angle (difference between the SA and the angle at which the test was stopped) to detect passive knee motion into flexion or extension mean of the three trials in one direction (mean of three trials for each angle in each direction).	**TTDPM (°)[c] at 6 months post-ACLR:** **SA 15°:** -0.02 [-0.39, 0.35] (Note: TTDPM data were available only for the first 47 participants out of 74 in total).
Shen et al. (2019) [31]	Int (A): n=10; 36.6±12.1 years; 5 male, 5 females. Int (B): n=11; 37.5±9.39 years; 6 male, 5 females. Int (C): n=11; 34±10.29 years; 7 male, 4 females.	Standard rehabilitation + backward walking on the treadmill: Int. groups A, B, C, and D underwent backward walking	Standard rehabilitation with range of motion exercises, power exercises, walking, and cycling (duration and other	**Proprioception test 1:** JPS; **Body position:** supine lying; **Instrument:** continuous passive motion device; **Procedure:** passive-passive, eyes blindfolded; **SA:** 0°; **TA:** 20°, 50°, 80°, **Outcome measure:** AAE (mean of the three trials at each angle for ACL-injured knees?).	**Int (A) vs. Com group at 1 month post-intervention[d]:** **JPS (°)[c]:** **TA 20°:** -1.40 [-2.59, -0.21] **TA 50°:** -1.36 [-2.35, -0.37] **TA 80°:** -1.28 [-2.31, -0.25] **TTDPM (°)[c]:**

	Int (D): (n=10); 32.9±11.45 years; 6 male, 4 females. Com: n=10; 35.5±10.1 years; 7 male, 3 females; ACLR (patellar tendon graft, hamstring tendon graft, allograft)	training at 1.3 km/h at different inclination angles of the treadmill (0°, 5°, 10°, and 15°, respectively); 20 min/day, 5 days/week for 4 weeks; **Adherence:** NR	parameters: NR); **Adherence:** NR	**Proprioception test 2:** TTDPM; **Body position:** Supine lying; **Instrument:** continuous passive motion device; **Procedure:** passive movement of the knee into flexion (3 times for each angle for ACL-injured knees?) with eyes blindfolded; **SA:** 20°, 50°, 80°; **Angular velocity:** 1°/s; **Outcome measure:** Threshold angle to detect passive knee motion into flexion (mean of three trials for each angle in one direction).	**SA 20°:** -1.34 [-2.11, -0.57] **SA 50°:** -1.40 [-2.05, -0.75] **SA 80°:** -1.29 [-2.00, -0.58]
Zult et al. (2018) [33]	Int: n =29 (22), 28±9 years; Com: n = 26 (21), 28±10 years n=24 males n=20 females ACLR (patellar tendon graft/ hamstring tendon graft (SSG)/ Artificial)	Standard rehabilitation + Strength training of the quadriceps of the non-injured leg; 2 quadriceps exercises, 8–12 reps. maximum, 3 sets; 2 times/week from week 1-12 after ACLR; **Adherence:** NR explicitly;	Standard rehabilitation: 2 times/week from week 1-12 after ACLR; **Adherence:** NR explicitly; however, two participants who performed <26 sessions was excluded from analysis after week 26	**Proprioception test 1:** JPS[g] **Body position:** seated (?); **Instrument:** Biodex dynamometer (?); **Procedure:** passive-active, eyes blindfolded (?); **SA:** 90° (?); **TA:** 15°, 30°, 45°, and 60°; **Outcome measure:** AAE (one trial at each angle). **Proprioception test 2:** Quadriceps force control (QFC); **Body position:** seated (?); **Instrument:** Biodex dynamometer (?); **Procedure:** A target force matching task with the target set at 20% MVC for	**JPS (°)[e] at 26 weeks post-ACLR:** **TA 15°:** 1.00 [-1.12, 3.12] **TA 30°:** 2.00 [-0.12, 4.12] **TA 45°:** -1.00 [-3.39, 1.39] **TA 60°:** -1.00 [-2.79, 0.79] **QFC (Nm)[e,f] at 6 months (26 weeks) post-ACLR:** **Concentric 60°/s:** 6.00 [0.67, 11.33] **Eccentric 60°/s:** -1.00 [-3.99, 1.99]

	however, one participant who performed <26 sessions was excluded from analysis after week 26	three isometric trials (at 65° of knee flexion [5 s duration]) and 40 Nm for dynamic trials (four concentric and eccentric trials at 20°/s from 10°-90° knee flexion) (20°/s between 10° and 90° of knee flexion); **Outcome measure:** force accuracy (absolute error) determined over the terminal 3 s data for isometric trials (at 65° knee flexion) and over the middle 2 s data for concentric and eccentric trials.	**Isometric:** 1.00 [-0.76, 2.76]

[a]Included in analysis;
[b]Calculated with Review Manager (RevMan) 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark);
[c]Mean difference between groups were calculated based on post-intervention/final follow-up scores reported by the authors;
[d]Difference between four intervention groups and the comparator group were same and so only one comparison is presented.
[e]Mean difference between groups were calculated based on change scores from baseline (pre- vs. post-intervention) reported by the authors;
[f]Quadriceps force accuracy; both legs (within each group) showed improved force control (22–34%) at 26 weeks post-surgery ($p < 0.050$) according to the authors;
[g]JPS method has been presumed based on authors' reference to the method employed by Hortobagyi et al.[50];
ACLR - anterior cruciate ligament reconstruction, Int – intervention group; com – comparator group; JPS - joint position sense, NR- not reported, TTDPM - threshold to detection of passive motion, min. - minutes, reps – repetitions.

Table 2. Risk of bias assessment of included studies according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) - judgements in five domains and an overall judgement using the descriptors of low risk of bias (low), some concerns, and high risk of bias (High).

Included studies	Outcome variable	1. Bias from the randomization process	2. Bias due to deviations from intended interventions	3. Bias due to missing outcome data	4. Bias in measurement of the outcome	5. Bias in selection of the reported result	Overall judgement
Baltaci et al. 2013 [28]	JPS	High	Some concerns	Low	High	High	High
Beynnon et al. 2011 [49]	TTDPM	Low	Low	Low	Low	Some concerns	Some concerns
Cho et al. 2013[34]	JPS	Some concerns	Some concerns	Low	High	Some concerns	High
Fu et al. 2013[30]	JPS	Low	Low	Low	Low	Some concerns	Some concerns
Kaya et al. 2019[32]	JPS	Some concerns	High	High	Low	Some concerns	High
Moezy et al. 2008[29]	JPS	Some concerns	Low	Low	Some concerns	High	High
Risberg et al. 2007 [48]	TTDPM	Low	Low	Low	Low	Some concerns	Some concerns
Shen et al. 2019[31]	JPS	Some concerns	Low	Low	Low	Some concerns	Some concerns
	TTDPM	Some concerns	Low	Low	Low	Some concerns	Some concerns
Zult et al. 2018[33]	JPS	Low	Some concerns	Low	High	Some concerns	High
	QFC	Low	Some concerns	Low	Low	Some concerns	Some concerns

JPS - joint position sense, TTDPM - threshold to detect passive motion, QFC - quadriceps force control.

716 **Table 3. Applying the GRADE approach to rate the certainty in evidence found in the review**

Certainty assessment							№ of patients		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neuromuscular Training	Comparator Intervention	
Knee joint position sense (JPS)									
7	Randomized trials	very serious[a]	serious[b]	serious[c]	serious[d]	none	139	105	⨁◯◯◯ VERY LOW
Knee joint threshold to detect passive motion (TTDPM)									
3	Randomized trials	serious[a]	serious[b]	serious[c]	serious[d]	none	84	51	⨁◯◯◯ VERY LOW
Quadriceps force control (QFC)									
1	Randomized trial	serious[a]	serious[e]	not serious	serious[e]	none	22	21	⨁◯◯◯ VERY LOW

717 Note: GRADE domains are explained further in Table 4.

718 a. Included studies had a high risk of bias or some concerns based on the Cochrane ROB2 tool;

719 b. The direction and/or magnitude of effect was inconsistent across trials;

720 c. Clinical heterogeneity (of participants, interventions, and method of assessing outcome measures);

721 d. Number of participant <400 and/or wide 95% confidence intervals of effect size estimates;

722 e. Available population, the magnitude and direction of effect, and effect estimates come from only one study.

723

Table 4. GRADE evaluation of the certainty in evidence for knee joint position sense (JPS)

GRADE domain	Reviewer judgment	Concerns about GRADE domains
	Knee joint position sense (JPS)	
Risk of bias (methodological limitations)	Among seven RCTs[28-34] reporting changes in JPS following neuromuscular training, five RCTs were found to have a high risk of bias while the remaining two studies have some concerns based on the Cochrane ROB 2 tool (see Table 2). Indeed, we judged that the included RCTs have very serious methodological limitations.	Very serious
Inconsistency	The direction and/or magnitude of effect on JPS was inconsistent across most of the included RCTs. In summary, the between-group comparisons of five RCTs showed borderline or no change in JPS angular errors of the ACLR knee for one or more target angles following interventions. We noted significant differences in reduction of JPS angular errors for all target angles favoring the intervention groups (backward treadmill walking or motor control exercises) in only two RCTs as reported by the authors.[31,32] In fact, Kaya et al. had reported only post-intervention scores but they neither reported nor compared the baseline scores (post-operative scores).[32] Two other studies [29,34] presented with insignificant effects at a low target angle (15° or 30°) and significant effects at a high target angle (45° or 60°) of JPS favoring the intervention group (whole-body vibration therapy[29] or exercises on a balance pad[34]). When we calculated mean differences for author-reported post-operative[32] or change (pre- vs. post-intervention) scores,[29,34] between groups for the ACLR leg with the Review Manager 5.3 software (the Cochrane Collaboration), their 95% confidence intervals revealed no effects. Overall, we judged the evidence to have serious inconsistency in the direction and/or magnitude of effects.	Serious
Indirectness	The participants (with ACLR [different grafts]), different neuromuscular training and comparator interventions, and knee specific JPS measures in the included studies provide evidence to the research question. However, the heterogeneity of interventions precludes recommendation of one optimal neuromuscular training intervention for clinical practice. In addition, variations in the methods of JPS measurements (active vs passive angle reproduction, low vs. high target angles, etc.) precluded a meta-analysis. We judged the evidence to have serious indirectness especially owing to variations in	Serious

	the interventions and outcome measures.	
Imprecision	A total of 244 patients was included from seven RCTs reporting changes in JPS following neuromuscular training (n = 139) or comparator interventions (n = 105). Most of the included trials reported non-significant results with wider 95% confidence intervals for one or more JPS (target) angles (see Table 1). Therefore, we judged the evidence to have serious imprecision.	Serious
Other considerations	Since negative and positive findings have been published, and a comprehensive search for RCTs has been done, we did not suspect a publication bias.	None
	Knee joint threshold to detect passive motion (TTDPM)	
Risk of bias (methodological limitations)	Three RCTs[31, 48, 49] reporting changes in TTDPM following neuromuscular training were found to show some concerns in risk of bias based on the Cochrane ROB 2 tool (see Table 2). We judged the included RCTs to be of serious methodological limitations.	Serious
Inconsistency	The direction and/or magnitude of effect was conflicting between the three RCTs. As two trials reported insignificant effects and one[41] reported significant effects (see Table 1), we judged the evidence to have serious inconsistency in the direction and/or magnitude of effects.	Serious
Indirectness	The participants (with ACLR [different grafts]), different neuromuscular training and comparator interventions, and knee specific TTDPM measures in the included studies provide some evidence to the research question in hand. However, the heterogeneity of interventions and TTDPM measurements (starting angles, angular velocity, etc.) precluded a meta-analysis. We judged the evidence to have serious indirectness especially owing to variations in the interventions and TTDPM methods.	Serious
Imprecision	A total of 135 patients was included in three RCTs reporting the effects of neuromuscular training (n = 84) or comparator interventions (n = 51) on TTDPM. Two trials[48,49] reported non-significant results while another one[31] reported significant effects which is evident with their confidence intervals (see Table 1). However, Shen et al. (2019) reporting significant effects on TTDPM included only 10 to 11 participants in each group while the other two studies with a relatively larger sample size declared	Serious

	no significant effects on TTDPM. Therefore, we judged the evidence to have serious imprecision.	
Other considerations	As both negative and positive findings have been published, and a comprehensive search for RCTs has been done, we did not suspect a publication bias.	None

ACLR - anterior cruciate ligament reconstruction, RCTs – randomized controlled trials, ROB – risk of bias

Box 1. A list of acronyms used in the review

Acronym	**Definition**
ACL	Anterior cruciate ligament
ACLR	Anterior cruciate ligament reconstruction
AAE	Absolute angular error
CNS	Central nervous system
CT	Controlled Clinical trial
GRADE	Grading of recommendations, assessment, development and evaluation
JPS	Joint position sense
NT	Neuromuscular training
PRISMA	Preferred reporting items for systematic review and meta-analysis
PICOS	Participants, intervention, comparator, outcome measures, study design
QFC	Quadriceps force control
RCT	Randomized controlled trial
ROB	Risk of bias
TTDPM	Thresholds to detect passive motion
WBVT	Whole-body vibration therapy

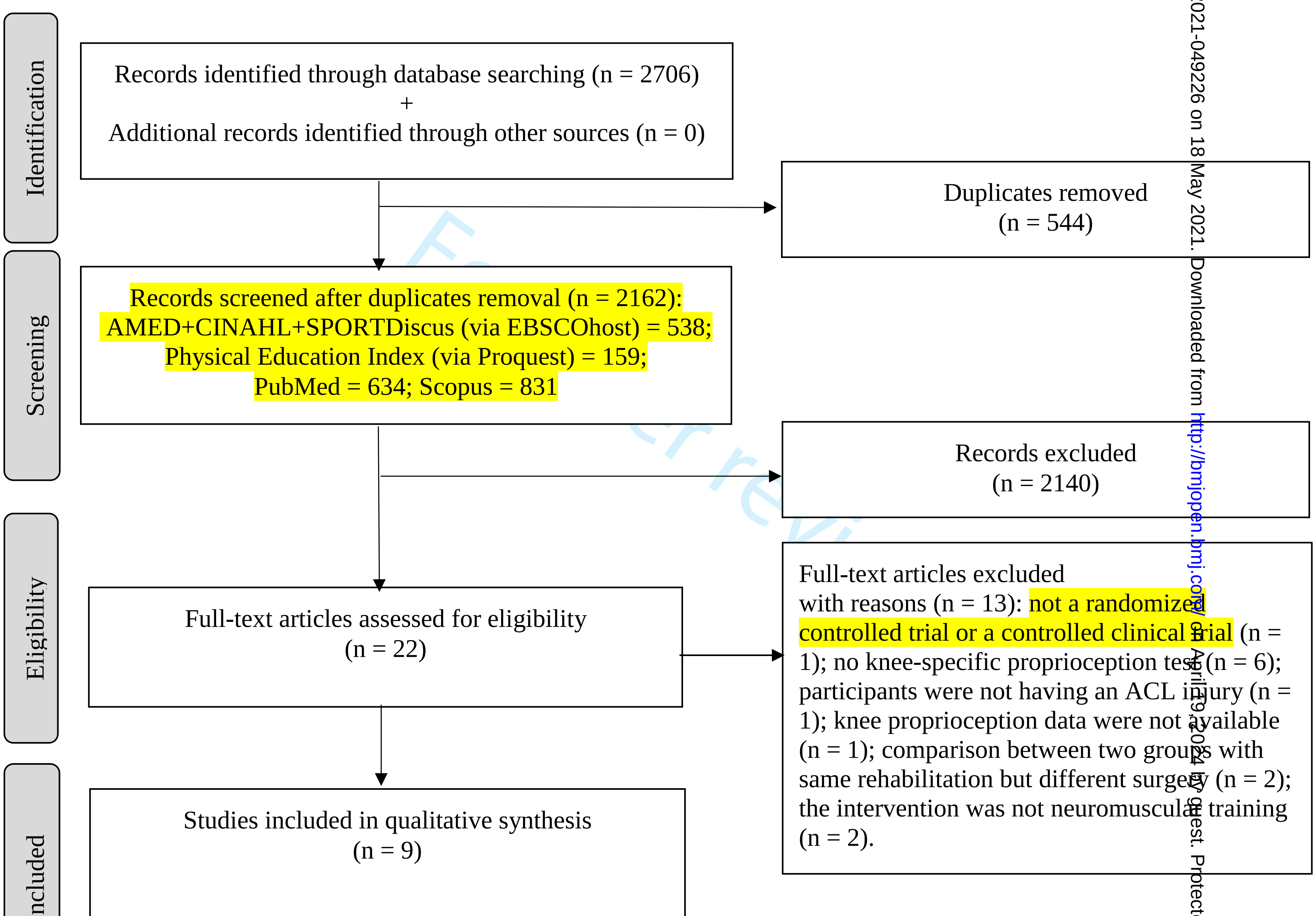
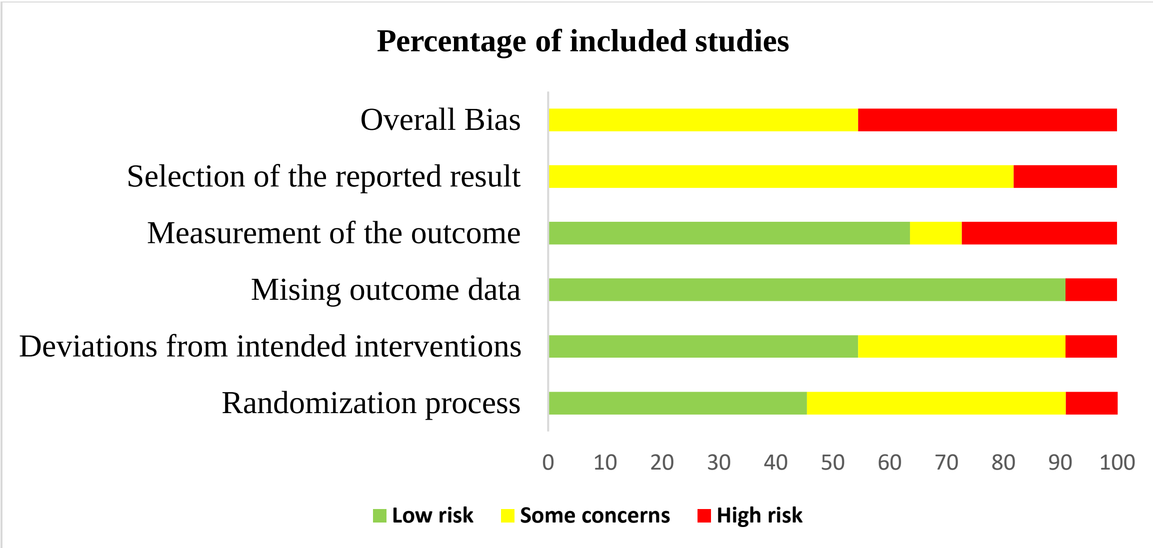


Figure 1. Flow diagram depicting the steps involved in screening and selection of eligible articles



Online supplemental figure 1. Risk of bias assessment in each of the five domains and overall bias. Percentage of studies showing low risk of bias, some concerns and high risk of bias.

Note: For studies having more than one relevant outcome, each outcome is considered separately for risk of bias assessment.

Online supplemental file 1.

Database-specific search strategies

AMED

(Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)
S1: “Anterior Cruciate Ligament” OR (ZU "anterior cruciate ligament") OR “Knee joint” OR (ZU "knee joint)
S2: Injur* OR (ZU "injuries") OR (ZU "anterior cruciate ligament injuries") OR Reconstruction OR (ZU "anterior cruciate ligament reconstruction") OR
S3: Propriocep* OR (ZU "proprioception") OR Neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR (ZU "kinetics") OR Coordination OR Balance OR (ZU "balance") OR Plyometric (ZU "plyometric exercise") OR Vibration OR (ZU "vibration") OR Exercise* OR (ZU "exercise") OR Intervention OR Training OR Rehabilitation OR (ZU "rehabilitation") OR Therap* OR (ZU "therapy") OR Treatment
S4: Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination"
Limiters - Language: English, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - AMED - The Allied and Complementary Medicine Database

CINAHL

Limiters - Peer Reviewed; Human; Language: English, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - CINAHL with Full Text
(Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR

"direction accuracy" OR "active reproduction" OR "Joint reposition" OR "Active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense") AND (S6 AND S7 AND S8 AND S9)
S6: “Anterior Cruciate Ligament” OR (MH "Anterior Cruciate Ligament") “Knee joint” OR (MH "Knee Joint+"
S7: Injur* OR (MH "Anterior Cruciate Ligament Injuries") OR Reconstruction OR (MH "Anterior Cruciate Ligament Reconstruction") OR Rupture OR Tear OR (MH "Rupture+") OR Conservative OR Deficiency OR “Joint instability” OR (MH "Joint Instability+"
S8: Propriocep* OR (MH "Proprioception+") OR Neuromuscular OR (MH "Neuromuscular Control") OR sensorimotor OR "sensory-motor" OR "Kinetic chain" OR (MH "Closed Kinetic Chain Exercises") OR (MH "Open Kinetic Chain Exercises") OR Coordination OR Balance OR (MH "Balance Training, Physical") OR (MH "Balance, Postural") OR Plyometric OR Vibration OR (MH "Vibration" OR Exercise* OR (MH "Exercise+") OR Intervention OR Training OR Rehabilitation OR Therapy OR (MH "Physical Therapy+") OR Treatment
S9: Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesis") OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "Active movement extent discrimination"

Physical Education Index (ProQuest)

((("Anterior Cruciate Ligament" OR "Knee joint") AND (Injur* OR Trauma OR Reconstruct* OR Ruptur* OR Tear OR Conservative OR Deficienc* OR "Joint instabilit*") AND (Propriocep* OR Kinesthes* OR neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR Coordination OR Balance OR Plyometric OR Vibration OR Exercise* OR Intervention OR Training OR Rehabilitation OR Therap* OR Treatment) AND (Propriocep* OR Kinesthes* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense"))) AND at.exact("Article") AND la.exact("ENG") AND PEER(yes)

PubMed

(((((Anterior Cruciate Ligament[Text Word] OR "Anterior Cruciate Ligament"[Mesh] OR Knee joint[Text Word] OR "knee joint"[MeSH Terms]) AND "loattrfull text"[sb]) AND (((injury[All Fields]) OR Reconstruction[Text Word] OR "Anterior Cruciate Ligament Reconstruction"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh] OR Rupture[Text Word] OR Tear[Text Word] OR "Rupture"[Mesh] OR Conservative[Text Word] OR

"Conservative Treatment"[Mesh] OR Deficiency[Text Word] OR Joint instability[Text Word] OR "Joint Instability"[Mesh]))) AND (((proprioception[All Fields]) OR "Proprioception"[Mesh] OR Neuromuscular[Text Word] OR sensorimotor[Text Word] OR sensory-motor[Text Word] OR Kinetic chain[Text Word] OR Coordination[Text Word] OR "Psychomotor Performance"[Mesh] OR Balance[Text Word] OR "Postural Balance"[Mesh] OR Plyometric[Text Word] OR "Plyometric Exercise"[Mesh] OR ("exercise"[MeSH Terms] OR "exercises"[All Fields] OR "exercise therapy"[MeSH Terms]) OR "Exercise Therapy"[Mesh] OR Intervention[Text Word] OR Training[Text Word] OR "Resistance Training"[Mesh] OR Rehabilitation[Text Word] OR "Rehabilitation"[Mesh] OR Therapy[Text Word] OR Treatment[Text Word] OR "Treatment Outcome"[Mesh]))) AND (((proprioception[All Fields]) OR "Proprioception"[Mesh] OR ("kinesthesis"[MeSH Terms] OR "kinesthesis"[All Fields]) OR "Kinesthesis"[Mesh] OR joint position sense[Text Word] OR (("joints"[MeSH Terms] OR "joints"[All Fields] OR "joint"[All Fields]) AND position detection[Text Word]) OR threshold to detect passive motion[Text Word] OR (passive[All Fields] AND motion direction discrimination[Text Word]) OR (passive[All Fields] AND motion detection threshold[Text Word]) OR (threshold[All Fields] AND motion detection[Text Word]) OR threshold hunting[Text Word] OR detection threshold[Text Word] OR discrimination threshold[Text Word] OR (ipsilateral[All Fields] AND matching[Text Word]) OR contralateral matching[Text Word] OR joint angle error[Text Word] OR distance estimation error[Text Word] OR passive recognition[Text Word] OR direction accuracy[Text Word] OR active reproduction[Text Word] OR Joint reposition[Text Word] OR force sense[Text Word] OR force perception[Text Word] OR velocity sense[Text Word] OR (active[All Fields] AND ("movement"[MeSH Terms] OR "movement"[All Fields]) AND extent[All Fields] AND ("discrimination (psychology)"[MeSH Terms] OR ("discrimination"[All Fields] AND "(psychology)"[All Fields]) OR "discrimination (psychology)"[All Fields] OR "discrimination"[All Fields])) OR sensorimotor[Text Word] OR sensory-motor[Text Word]) AND "loattrfull text"[sb])) AND "loattrfull text"[sb] AND ("loattrfull text"[sb] AND English[lang]) AND English[lang]

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("Anterior Cruciate Ligament" OR "Knee joint") AND (injur* OR trauma OR reconstruct* OR ruptur* OR tear OR conservative OR deficienc* OR "Joint instabilit*") AND (propriocep* OR kinesthes* OR neuromuscular OR sensorimotor OR sensory-motor OR "Kinetic chain" OR coordination OR balance OR plyometric OR vibration OR exercise* OR intervention OR training OR rehabilitation OR therap* OR treatment) AND (propriocep* OR kinesthes* OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "active movement extent discrimination" OR "force sense" OR "force perception" OR "velocity sense" OR sensorimotor OR sensory-motor) AND NOT INDEX (medline) AND (LIMIT-TO (SRCTYPE , "j")) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "NEUR")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Human") OR LIMIT-TO (EXACTKEYWORD , "Article") OR LIMIT-TO (EXACTKEYWORD , "Male") OR LIMIT-TO (EXACTKEYWORD , "Female") OR LIMIT-TO (EXACTKEYWORD , "Controlled Study") OR LIMIT-TO (EXACTKEYWORD , "Proprioception"))

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Limiters - Peer Reviewed; Language: English; Publication Type: Academic Journal; Document Type: Article, Expanders - Apply related words, Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced Search, Database - SPORTDiscus
(Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)
S1: Anterior Cruciate Ligament OR (DE "CRUCIATE ligaments") OR (DE "ANTERIOR cruciate ligament") "Knee joint" OR (DE "KNEE"
S2: Injur* OR (DE "ANTERIOR cruciate ligament injuries") OR (DE "CRUCIATE ligament injuries) OR Reconstruction OR Rupture OR Tear OR Conservative OR Deficiency OR "Joint instabilit*"
S3: Propriocep* OR (DE "PROPRIOCEPTION") OR Neuromuscular OR sensorimotor OR sensory-motor OR Kinetic chain OR Coordination OR (DE "MOTOR ability") OR Balance OR Plyometric OR (DE "PLYOMETRICS) OR Vibration OR Exercise* OR Intervention OR Training OR Rehabilitation OR (DE "TREATMENT programs") OR (DE "REHABILITATION") OR Therap* OR Treatment OR (DE "KNEE injuries -- Treatment")
S4: Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR "passive motion detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active movement extent discrimination"

Online supplemental file 2.

Screening protocol – to screen eligible studies at the title, abstract, and full-text screening stages

Questions for all stages: title, abstract and full-text screening (follow stages 1-9):

1) Is the study published in a scientific journal or published as a dissertation/thesis?
   a. No - exclude
   b. Yes or uncertain - go to step 2
2) Is the study written in English?
   a. No - exclude
   b. Yes or uncertain - go to step 3
3) Does the study deal with individuals who are 15 years of age and above?
   a. No - exclude
   b. Yes or uncertain - go to step 4
4) Does this study investigate individuals with an anterior cruciate ligament injury managed with conservative treatment or surgical reconstruction?
   a. No - exclude
   b. Yes or uncertain - go to step 5
5) Is the study a primary study (i.e. no letter to the editor, book reviews, published study designs/trial protocols, commentaries, editorials, interviews, newspaper articles, patient education handouts, consensus statements or clinical practice guidelines)?
   a. No - exclude
   b. Yes or uncertain - go to step 6
6) Does the intervention group in the study undergo neuromuscular training rehabilitation?
   a. No - exclude
   b. Yes or uncertain - go to step 7
7) Is the comparator/control group in the study include any of the following: any other therapy, conventional training, usual care, placebo or sham therapy?
   a. No - exclude
   b. Yes or uncertain - go to step 8
8) Does the study evaluate knee proprioception using a specific test (joint position sense, joint position detection, threshold to detect passive motion, passive motion direction discrimination, passive motion detection threshold, threshold for motion detection, threshold hunting, detection threshold, discrimination threshold, ipsilateral matching, contralateral matching, joint angle error, distance estimation error, passive recognition, direction accuracy, active reproduction, active movement extent discrimination, force sense, force perception, velocity sense or any other related tests)- before and after the intervention?
   a. No - exclude
   b. Yes or uncertain - go to step 9
9) Does the study report (objective) focal measures of knee proprioception for any of the specific tests mentioned in point 8?
   a. No - exclude
   b. Yes or uncertain - choose one of the following options:

i. Title and abstract screening stage - include
ii. Full-text screening stage - follow step 10-11

Additional questions for full-text stage only:

10) Does the study use at least one (appropriate) statistical test to compare the intervention and comparator/control groups for knee proprioception?
    a. No - exclude
    b. Yes or uncertain - go to step 11
11) Are the points 1-10 scored as "yes or uncertain"
    a. If all "yes" - include
    b. If any "uncertain" - discuss with another reviewer to come to an agreement whether to include the study or not

Online supplemental file 3.
Data extraction template

Publication details	Study citation, clinical trial registration, and published study protocol if available
Aim of the study	Primary and/or secondary aims relevant for the review.
Eligibility criteria	Inclusion and exclusion criteria for participants
Randomized controlled trial or controlled clinical trial	Randomization method?
Participant allocation	Concealed or not?
Number of participants identified	Identified, included and excluded?
All participants accounted for entire study	Yes or no?
Experimental group	Experimental intervention (type of neuromuscular rehabilitation training) given.
Comparator group	Comparator intervention given.
Assessment method, equipment used, and outcome measure(s) of interest	Those related to knee-specific proprioception senses.
Method(s) used for measuring the outcome(s) appropriate?	Authors quoted any data on reliability and validity based on the previous literature or their own data?
Multiple measurements of the same outcome measure within the outcome domain?	Different methods measuring same proprioception sense and different time points?
Participant characteristics	Anthropometric, demographic, physical activity and function levels, and any other relevant information to ACL injury and/or surgery.
Groups were similar at baseline	Anthropometrics, demographics, outcome measure(s) of interest, and any other prognostic indicators.
Blinding	Participants, investigators, therapists/clinicians/those delivering the interventions, and outcome assessors.
The outcome measure of interest was obtained from more than 85% of the participants initially allocated to groups	For continuous outcomes, availability of data from 95% (or possibly 90%) of the participants would often be sufficient.
If data were missing, how they were handled	'Last observation carried forward', 'baseline observation carried forward' or any other method?
Analyses preplanned	Information available from Registered trial protocol or any other relevant information available?
Between-group statistical comparisons	Statistical analysis for measurement of proprioception was done by "intention to treat" or "per-protocol" analysis? Multiple analysis of data? Corrected for multiple analysis of data? Selective reporting of analysis?
Results	Selective reporting of a particular outcome measurement?
Conclusion	Authors' conclusions

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	2
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	2
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	
4. Information sources:	Key databases searched and search dates.	2
5. Risk of bias:	Methods of assessing risk of bias.	
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	2
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	3
10. Interpretation:	General interpretation of the results and important implications	
OTHER		
11. Funding:	Primary source of funding for the review.	1
12. Registration:	Registration number and registry name.	3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Pages 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pages 5-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	PROSPERO registration number CRD42018107349
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pages 7-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Online supplemental file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pages 9-10, online supplemental file 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 9, Online supplemental file 3. Data extraction template

PRISMA 2009 Checklist

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Online supplemental file 3. Data extraction template
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pages 9-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Pages 9-11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Pages 9-11

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pages 9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pages 11-12, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 12, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pages 11-12, Table

PRISMA 2009 Checklist

			2, Table 3, Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 17-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, Hartmann-Boyce J, Ryan R, Shepperd S, Thomas J, Welch V, Thomson H. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline BMJ 2020;368:l6890 http://dx.doi.org/10.1136/bmj.l6890

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	Lines 95-117, 123-143; further groupings of populations, interventions, outcomes, study design are explained in pages 12-15.	NA
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	NA	NA
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	Line 200-202, 698-704; Table 1	NA
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	Lines 200-202	NA
4 Criteria used to prioritise results for	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	Lines 123-143, 176-187	NA

Synthesis Without Meta-analysis (SWiM) reporting items

summary and synthesis			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Heterogeneity was examined using GRADE domains (inconsistency and imprecision of findings and indirectness of evidence). Please see line 317–333. Tables 3 and 4.	NA
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	Lines 176-187	NA
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	Narrative summary on pages 11-16; Table 1 (study characteristics); Table 2 (risk of bias summary); Tables 3 and 4 (GRADE evidence synthesis); Figure 1 (screening of studies)	NA
Results			

Synthesis Without Meta-analysis (SWiM) reporting items

8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Lines 300-333; Tables 3 and 4 (GRADE evidence synthesis)	NA
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	Lines 188-202	NA

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
*If the information is not provided in the systematic review, give details of where this information is available (e.g., protocol, other published papers (provide citation details), or website (provide the URL)).