

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049226
Article Type:	Original research
Date Submitted by the Author:	19-Jan-2021
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
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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:

¹Department of Physiotherapy, College of Health Sciences, University of Sharjah, P.O. Box: 27272, Sharjah, United Arab Emirates;

²Department of Community Medicine and Rehabilitation – Physiotherapy Section, Umeå, University, SE-901 87, Umeå, Sweden;

³Department 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

Manuscript Type: A systematic review

Word count: 4517 (excluding abstract, tables, contributions, funding acknowledgements and references)

Ethical approval: Not required.

Funding sources: The Swedish Research Council (2017-00892); Region Västerbotten (ALF 7003575; Strategic funding VLL-358901; Project.No 7002795); The Swedish Research Council for Sports Science (CIF P2019 0068); and King Gustaf V and Queen Victoria's Foundation of Freemasons 2019 (Häger).

Conflicts of interest: None declared.

Ethical approval: Not required.

Competing interests: None declared.

1 **Effects of neuromuscular training on knee proprioception in individuals with anterior** 2 **cruciate ligament injury - A systematic review and GRADE evidence synthesis**

3 **Abstract**

4 **Objective**

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

7 **Design**

8 Systematic Review

9 **Methods**

10 PubMed, CINAHL, SPORTDiscus, AMED, Scopus, and Physical Education Index were
11 searched from inception to February 2020. Controlled or randomized clinical trials (RCTs)
12 investigating the effects of neuromuscular training on knee-specific proprioception tests in
13 individuals with a unilateral ACL injury were included. Two reviewers independently screened
14 and extracted data and assessed risk of bias of the eligible RCTs using the Cochrane risk of bias
15 2 tool. Overall certainty in evidence was determined using the GRADE tool.

16 **Results**

17 Of 2706 articles retrieved, only nine RCTs, comprising in total 327 individuals with an ACL
18 reconstruction (ACLR), met the inclusion criteria. Neuromuscular training interventions varied
19 across studies: whole body vibration therapy, Nintendo-Wii-Fit training, balance training, sport-
20 specific exercises, backward walking, etc. Outcome measures included joint position sense (JPS;
21 n=7), thresholds to detect passive motion (TTDPM; n=3), or quadriceps force control (QFC;
22 n=1). Overall, there were conflicting findings for reduced errors associated with JPS (one or
23 more target angles), TTDPM or QFC of ACLR knee following neuromuscular training. Owing to

1
2
3 24 serious concerns with three or more GRADE domains (risk of bias, inconsistency, indirectness,
4
5 25 or imprecision associated with the findings) for each outcome of interest across studies, the
6
7
8 26 certainty of evidence was very low.
9

10 27 **Conclusions**

11
12 28 The heterogeneity of interventions, methodological limitations, inconsistency of effects (on
13
14 29 JPS/TTDPM/QFC) preclude recommendation of one optimal neuromuscular training
15
16
17 30 intervention for improving proprioception following ACL injury in clinical practice. The low
18
19 31 evidence thus questions common clinical neuromuscular training programs in practice. Our
20
21 32 review highlights the urgent need for methodologically-robust RCTs with homogenous
22
23
24 33 populations with ACL injury (managed conservatively or with reconstruction), novel/well-
25
26 34 designed neuromuscular training interventions, and valid proprioception assessments, which also
27
28
29 35 seem to be lacking.

30 36 **PROSPERO registration number**

31
32
33 37 CRD42018107349
34

35 38 **Key words:** Joint position sense, threshold to detect passive motion, ACL, sensorimotor training,
36
37
38 39 literature review, neuroplasticity
39

40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

41 Strengths and limitations of the study

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

53

54 Introduction

55 Anterior cruciate ligament (ACL) injury is a common musculoskeletal injury^{1, 2} accounting for
56 an annual incidence rate of 68.6/100,000 person-years in the United States.³ ACL injury is most
57 prevalent in young athletes.³ The injury occurs more often during competition rather than
58 training, with ~70% or more of the injuries representing noncontact mechanisms^{4, 5} such as
59 landing from a jump, sudden deceleration and/or while cutting.⁶ Thus, the injury mechanisms are
60 related to neuromotor control, amongst other factors, of the individual. ACL injury is followed
61 by a long period of rehabilitation and yet many individuals do not return to pre-injury levels of
62 activity⁷ which challenges the efficacy of existing preventative and rehabilitative strategies.

63 Individuals with an ACL injury present with a decreased number of proprioceptive
64 mechanoreceptors (Pacinian capsules, Ruffini nerve endings and Golgi tendon organs)^{8, 9} in the
65 knee which might alter the somatosensory input to the central nervous system (CNS)⁹ leading to
66 decreased knee proprioception. Disturbed proprioception might also be caused by acute
67 inflammation and pain, and the capsule and surrounding ligaments getting affected following
68 instability.^{10, 11} Although there has been a debate regarding the effects of ACL injury on different
69 knee proprioception tests,^{2, 12} our recent systematic review¹³ suggests that knee JPS tests have
70 sufficient validity in discriminating ACL-injured knees from asymptomatic knees (under review
71 following revision). When compared to non-injured controls, individuals with ACL injury
72 demonstrate altered movement strategies,^{4, 14} quadriceps muscle weakness,¹⁵ and onset and
73 progression of osteoarthritis.^{6, 16} Due to the potential serious consequences of the injury, much
74 attention and clinical efforts have been dedicated to preventative and rehabilitative strategies for
75 ACL injury¹¹, including various neuromuscular training (NT) methods believed to improve the
76 proprioceptive ability.

1
2
3 77 Even if proprioceptive deficits may negatively affect the neuromotor control, the rationale,
4
5 78 mechanisms, and plausibility for improving proprioception by training need to be verified. In the
6
7 79 context of neuroplasticity, functional magnetic resonance imaging (fMRI) has revealed that
8
9 80 individuals with ACL-deficient knees demonstrate less activation in several sensorimotor cortical
10
11 81 areas and increased activation in pre-supplementary motor areas, posterior secondary
12
13 82 somatosensory area, and posterior inferior temporal gyrus compared to controls with
14
15 83 asymptomatic knees during a knee flexion-extension task.¹ It seems individuals with ACLR
16
17 84 adapt a visual-sensory-motor strategy instead of a normal sensory-motor strategy owing to
18
19 85 aberrant sensory feedback following ACL injury.¹⁷ Nevertheless, neuroplastic reorganization
20
21 86 ensues where other potential sensory sources are used to organize the movement or regulate
22
23 87 neuromotor control, particularly in (sporting) tasks with higher complexity. Therefore, ACL
24
25 88 injuries might be regarded as a neuromotor control dysfunction rather than a simple peripheral
26
27 89 musculoskeletal injury.^{11, 18} It remains unclear though whether NT can improve proprioception
28
29 90 after an ACL injury^{11, 19} and the neurophysiological mechanisms underpinning such interventions
30
31 91 need further substantiation.

32
33 92 To date, there is no consensus on the most effective rehabilitation programs for ACL injury, and
34
35 93 the prevalence of reinjury after returning to sport is ~30%.¹⁸ Owing to the neuroplastic changes
36
37 94 and possibly altered proprioception following an ACL injury, NT has received much attention to
38
39 95 enhance dynamic joint stability and relearn movement patterns and skills.²⁰ In this context, both
40
41 96 NT and sensorimotor training terms have been used in the literature to describe the same
42
43 97 phenomenon. NT for e.g., is defined as "...training enhancing unconscious motor responses by
44
45 98 stimulating both afferent signals and central mechanisms responsible for dynamic joint control"
46
47 99 ²⁰ and sensorimotor training has been described as aiming to improve "...function of the CNS in
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 100 regulating movement in order to reach proper firing patterns for maintaining joint stability...”.²¹

4
5 101 Active knee motion will in any case stimulate proprioceptors, which in turn would alter the
6
7 102 demands on the CNS.^{10, 19} Henceforth we will use the term NT in this review.
8
9

10
11 103 There are different ways to challenge proprioception, for example: vibration may be used to alter
12
13 104 afferent input from muscle spindles; an unstable surface can challenge input from the ankle;
14
15 105 vision can be occluded or head position can be changed to disturb visual- and vestibular
16
17 106 information,¹⁰ or focus can be shifted to influence cognitive processing sources.¹⁸ Due to a
18
19 107 putative visual-sensory-motor strategy following ACL injury, a modified visual feedback
20
21 108 training might decrease visual reliance and improve sensory-motor function.¹⁸ Most studies
22
23 109 exploring the effects of NT on proprioception combine different exercises and various outcome
24
25 110 measures which precludes isolating the effects of a proprioception-specific exercise.²² Therefore,
26
27 111 this study aimed at systematically reviewing and summarizing the evidence for the effects of NT
28
29 112 compared to comparator/control interventions on proprioception measured by knee-specific
30
31 113 proprioception tests in individuals with ACL injury or reconstruction.
32
33
34
35
36

37 114 **Methods**

38
39
40
41 115 We adhered to Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA)
42
43 116 checklist.²³ The protocol was registered in PROSPERO (CRD42018107349).
44
45

46 117 **Eligibility criteria**

47
48
49 118 The structure of PICOS²⁴ was used to frame the following criteria:

- 50
51
52 119 1. **Participants:** Individuals over 15 years of age (both sexes) with a history of a unilateral
53
54 120 ACL rupture, managed conservatively or surgically reconstructed, with or without
55
56
57
58
59
60

- 1
2
3 121 concomitant meniscus and/or collateral ligament injuries, without any other lower
4
5 122 extremity injuries/surgeries that would confound the outcomes of rehabilitation training;
6
7
8 123 2. **Intervention:** Specific NT, closed/open kinetic chain exercises, balance training, joint
9
10 124 repositioning training, joint force sense training, co-ordination training, plyometric
11
12 125 training, whole body vibration, virtual gaming training, an accelerated rehabilitation
13
14 126 protocol or any other training programs focusing on improving the lower limb
15
16 127 neuromuscular control and knee proprioception;
17
18
19 128 3. **Comparator:** Any other therapy, conventional training, usual care, placebo or sham
20
21 129 therapy;
22
23
24 130 4. **Outcome measures:** Knee-specific proprioception tests targeting joint position sense
25
26 131 (JPS), kinesthesia (threshold to detect passive motion [TTDPM]), force sense/perception,
27
28 132 active movement extent discrimination, velocity sense, or psychophysical threshold
29
30 133 methods;¹³ they can be performed actively and/or passively with or without visual input
31
32 134 in weight bearing or non-weight bearing positions;¹⁰
33
34
35 135 5. **Study design:** controlled or randomized clinical trials (RCTs).
36
37

38 136 **Data Sources and Searches**

39
40
41
42 137 Database-specific search terms (e.g. MeSH) were combined using Boolean operators (“AND”
43
44 138 and “OR”) under three conceptual domains: participants, interventions and outcomes. Six
45
46 139 electronic databases were searched from their inception to 12 February 2020: PubMed,
47
48 140 Cumulative Index to Nursing & Allied Health Literature (CINAHL), SPORTDiscus, the Allied
49
50 141 and Complementary Medicine Database (AMED), Scopus, and Physical Education Index (via
51
52 142 Proquest) (Online supplemental file 1).
53
54
55
56
57
58
59

143 Study Selection

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

149 Data Extraction

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

153 Quality Assessment

154 The risk of bias for each outcome of interest in the included studies was evaluated using the
155 Cochrane ROB 2.²⁵ The tool has five domains: 1) randomization (number of signalling questions
156 [n=3]), 2) deviations from intended interventions (n=7), 3) missing outcome data (n=5), 4)
157 measurement of the outcomes (n=5), and 5) selection of the reported results (n=3). Each
158 signalling question can be answered as 1) yes, 2) probably yes, 3) probably no, 4) no, and 5) no
159 information. Responses to the questions provide the basis for judgement of the risk of bias at
160 each domain level using a tool-specific algorithm resulting in one out of three possible
161 judgements: 1) low risk of bias, 2) some concerns, or 3) high risk of bias. An overall risk of bias
162 score for each outcome in a study can be low (with a low risk of bias for all domains), some
163 concerns (if some concerns prevail in at least one domain without a high risk of bias for any

1
2
3 164 domain) or high (if a high risk of bias underpins at least one domain or some concerns remain in
4
5 165 multiple domains, defining multiple as more than two).
6
7

8 9 166 **Evidence Synthesis**

10
11
12 167 We determined the overall evidence level in this review using the Grading of Recommendations,
13
14 168 Assessment, Development and Evaluation (GRADE) recommendations considering risk of bias,
15
16 169 inconsistency (heterogeneity) in results, indirectness of evidence, imprecision of results, and
17
18 170 other domains (e.g. publication bias if applicable).²⁶ The overall evidence was rated as very low,
19
20 171 low, moderate or high. A meta-analysis was precluded owing to clinical heterogeneity of
21
22 172 interventions and outcome measurements.
23
24
25

26 27 173 **Patient and public involvement**

28
29
30 174 Neither patients nor public were involved.
31
32

33 34 175 **Results**

35 36 37 176 **Search Results**

38
39
40 177 Electronic databases search identified a total of 2706 articles (excluding duplicates: 2162).
41
42 178 Following title and abstract screening, 22 articles were shortlisted for full-text screening and
43
44 179 subsequently nine articles were found to meet the inclusion criteria (Figure 1). The other thirteen
45
46 180 articles were excluded for the following reasons: not an RCT (n=1),²⁷ no knee-specific
47
48 181 proprioception tests (n=6),²⁸⁻³³ participants did not have an ACL injury (n=1),³⁴ knee
49
50 182 proprioception data were missing and the corresponding author did not respond to our emails
51
52
53 183 (n=1),³⁵ a comparison between different surgical intervention groups with the same identical
54
55
56
57
58
59
60

184 rehabilitation program (n=2),^{36, 37} and finally, lack of a NT program (n=2).^{38, 39} No additional
185 relevant studies were identified through manual search of bibliographic references.

186 **Study Design and Participants**

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

190 **Quality Assessment**

191 The agreement (Cohen's kappa) of responses to the signalling questions between the two
192 reviewers (AA and MB) was substantial (0.69 ± 0.047 , $p < 0.001$). Disagreements were
193 discussed and resolved by the two reviewers. Online supplemental figure 1 shows the percentage
194 of studies judged as low risk, some concerns and high risk of bias in the five domains, and Table
195 2 shows domain judgements of each study. The overall risk of bias judgement showed that four
196 of the included studies had a high risk of bias,⁴²⁻⁴⁵ four had some concerns,^{41, 46-48} and one study⁴⁰
197 had a high risk of bias for JPS and some concerns for quadriceps force control (QFC). The
198 domain that most consistently showed risk of bias across studies was bias in selection of the
199 reported results (Online supplemental figure 1 and Table 2). The most common reason was the
200 absence of information regarding pre-specified plan of analyses. None of the included studies
201 reported trial protocol publication and only two^{40, 41} reported trial registration. Furthermore, two
202 studies were judged to perform inappropriate multiple analyses.^{42, 43} Judgement of bias in
203 measurement of the outcome (domain 4, Table 2) showed most scattered results across studies
204 (Online supplemental figure 1). A high risk of bias was found in three studies of which one had
205 no information on measurements⁴⁵ and two showed inappropriate measurement methods of the

206 outcome of interest.^{40, 43} In the study by Zult et al., only one trial per target was performed to
207 estimate JPS,⁴⁰ while Baltaci et al. used a test with presumably a high demand on motor and
208 memory components,⁴³ without reporting its reliability or validity. The domain with least risk of
209 bias was missing outcome data where all studies, except one,⁴⁴ had low risk of bias.

210 **Rehabilitation Programs**

211 The studies included a spectrum of rehabilitation programs employed to influence knee
212 proprioception (Table 1). Two studies^{42, 47} explored the effects of whole-body vibration therapy
213 (WBVT) combined with or without conventional rehabilitation compared to conventional
214 rehabilitation alone. Cho et al. compared closed kinetic chain exercises on a balance pad versus
215 on a stable floor.⁴⁵ Risberg et al. compared the effects of a NT compared to strength training. In
216 their NT program, the first half of the rehabilitation focused on exercises on a wobble board or
217 trampoline and exercises to increase the range of motion, while the end of the program focused
218 on specific training of plyometric, agility and sport-specific skills.⁴⁶ Baltaci et al. investigated
219 the effects of Nintendo-Wii-Fit compared to conventional rehabilitation.⁴³ Beynnon et al.
220 evaluated the effects of accelerated (19 weeks) vs. non-accelerated (32 weeks) programs of
221 conventional training.⁴⁸ The timeframe and exercises in their experimental program ranged from
222 1-7 weeks for range of motion and muscle activation, 8-11 weeks for dynamic functional
223 activities such as biking and jogging, and finally, 12-19 weeks for plyometric and agility drill
224 exercises.⁴⁸ Kaya et al. studied the effects of neuromuscular (motor control) exercises for the
225 lower limbs combined with standard rehabilitation compared with standard rehabilitation alone.⁴⁴
226 Shen et al. examined the outcome of standard rehabilitation combined with backward walking at
227 1.3 km/h on a treadmill for four groups (at four inclination angles 0°, 5°, 10°, and 15°,
228 respectively) compared to standard rehabilitation in a comparator group.⁴¹ Nevertheless, Zult et

1
2
3 229 al. examined the effects of cross-education of strength training of the non-injured leg along with
4
5 230 standard rehabilitation compared to standard rehabilitation alone.⁴⁰
6
7

8 9 231 **Knee-specific Proprioceptive Measures**

10
11
12 232 Seven studies used active or passive JPS and all but one used (absolute) angular error as a
13
14 233 variable to evaluate the outcome.^{40-45, 47} Conversely, one study used monitored-rehab-system-
15
16 234 software to define a virtual line/route to allow joint repositioning within 30-70% knee range of
17
18 235 motion with and without visual feedback.⁴³ The differences between visual and blinded trails (2
19
20 236 each) based on the deviations from the computer-generated line (in mm) were used to measure
21
22 237 proprioception.⁴³ All these studies used sitting or supine test position for assessing JPS. There
23
24 238 were two to four predetermined target knee flexion angles across studies ranging from 15°-
25
26 239 80°. ^{40-42, 44, 45, 47} Moreover, two studies^{42, 43} used active knee motion and four used passive knee
27
28 240 motion^{40, 41, 44, 47} to set the target angle. Whether Cho et al. used active or passive knee motion to
29
30 241 set/reproduce the target angle seems ambiguous. ^{45 45} Four studies^{40, 42-45} used active knee motion
31
32 242 and two^{41, 47} used passive knee motion to reproduce the target angle. The JPS method used by
33
34 243 Zult et al. was presumed based on their reference to Hortobagyi et al.⁴⁹
35
36
37
38
39
40

41 244 The angular error was measured with 1-6 trials per each angle and one study⁴⁰ randomized the
42
43 245 order of the joint angles used. Eyes were blinded during the test in six studies^{40-42, 44, 45, 47} while
44
45 246 one study used visual feedback when the individual was placing the knee in the target angle but
46
47 247 no such feedback was given during reproduction of the target angle.⁴³ The difference between
48
49 248 visual and non-visual trials was calculated in mm by the device as a measure of JPS.⁴³ A Biodex
50
51 249 dynamometer (Biodex Medical Systems, Shirley, NY, USA) was used in five studies^{40, 42, 44, 45, 47}
52
53 250 to test JPS. Even so, one study used a continuous passive motion equipment⁴¹ while another⁴³
54
55
56
57
58
59
60

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°/s⁴⁶ 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

273 which reflect serious concerns. However, the participants with ACLR, intervention (cross-
274 education of the quadriceps with standard rehabilitation), and QFC⁴⁰ are directly related to our
275 research question. The certainty of evidence found was very low for improving QFC in
276 individuals with ACLR following NT because only one relevant study was found.

277 Discussion

278 This review is the first, as far as we are aware, to systematically review the level of evidence for
279 effects of NT on knee proprioception in individuals with ACL injury. A previous review,
280 however, summarized the effects of proprioceptive and balance exercises following ACL
281 injury/reconstruction on certain outcome measures (muscle strength, hop test, etc.) but other than
282 knee-specific proprioception tests.⁵⁰ Another similar review published in 2003 did not find any
283 RCTs at all in this area.⁵¹ As of today, we identified nine studies employing a range of NT
284 methods, of which all but one⁴⁶ were published within the past decade. Nevertheless, there were
285 serious concerns with two or more GRADE domains (risk of bias, inconsistency, indirectness, or
286 imprecision associated with the findings) across studies implying a very low certainty of
287 evidence for improving JPS, TTDP, and QFC of ACLR knee following NT.

288 *Effects of NT on Knee Proprioception in Individuals with ACLR*

289 Most of the employed NT programs did not influence proprioception compared to comparator
290 interventions. Of the nine included articles, four studies reported reduction in JPS angular errors
291 of ACLR knee at one or more target angles (JPS at 45° but not 15°;⁴⁵ JPS at 60° but not 30°;⁴²
292 JPS at 15°, 45°, 75°;⁴⁴ JPS 20°, 50°, 80°⁴¹) and/or contralateral non-injured knee (JPS at 30° and
293 60°⁴²) favouring the NT group (exercises on a balance pad,⁴⁵ whole-body vibration therapy,⁴²
294 neuromotor control exercises⁴⁴ or backward treadmill walking⁴¹). Shen et al. also reported

1
2
3 295 improved TTDPM following backward treadmill walking.⁴¹ When we calculated mean
4
5 296 differences for author-reported post-operative^{42, 44} or change (pre- vs. post-intervention) scores⁴⁵
6
7 297 between groups for the ACLR leg with the Review Manager 5.3 software (the Cochrane
8
9 298 Collaboration), their 95% confidence intervals revealed no effects (see Table 1 and
10
11 299 supplementary files). Moreover, the remaining five studies did not report significant differences
12
13 300 in proprioception between groups.^{40, 43, 46-48}
14
15
16
17

18 301 Potential reasons for insignificant between-group differences include: 1) experimental and
19
20 302 comparator programs (with exercises that are wholly or partly similar) which potentially might
21
22 303 stimulate similar effects on proprioception in both programs;⁴³⁻⁴⁸ 2) the exercises did not
23
24 304 adequately stimulate proprioception sense;⁴⁰ 3) a lack of proprioception deficit following ACL
25
26 305 injury (TTDPM similar between ACL-injured and contralateral uninjured knee⁴⁸); 4) a lack of
27
28 306 valid, sensitive and responsive knee-specific proprioception test methods; 5) a short follow-up
29
30 307 period (a follow-up at least 18 months post-ACLR might be needed to regain proprioceptive
31
32 308 function⁵²) in most studies except two studies;^{44, 48} 6) type II errors arising from low sample sizes
33
34 309 in most studies (with missing power or sample size calculations); and 7) adherence rates of
35
36 310 participants to the prescribed program (only three studies have explicitly reported adherence
37
38 311 rates to training sessions/exercises [Table 1]).⁴⁶⁻⁴⁸ The heterogeneity of interventions,
39
40 312 methodological limitations, inconsistency in the magnitude and direction of effects, and
41
42 313 imprecision of effect estimates, found in this review, preclude recommendation of one optimal
43
44 314 NT intervention for improving proprioception following ACL injury in clinical practice.
45
46
47
48
49
50

51 315 ***Risk of Bias in the Included Studies***

52
53
54
55
56
57
58
59
60

1
2
3 316 Bias in selection of the reported variables/results due to absence of a pre-specified plan of
4
5 317 analyses applied to all but one study,⁴⁰ and none had published a trial protocol in a scientific
6
7 318 journal although two studies were registered in a trial registry.^{40, 41} A possible reason for the
8
9 319 absence of registration for most studies in this review may be that all but three studies were older
10
11 320 than five years. Yet, for example, the latest published study did not report trial registration.⁴⁴
12
13

14
15 321 Another concern was the method used to measure JPS. For instance, estimates of JPS based on 3-
16
17 322 5 repetitions may be insufficient in clinical trials.⁵³ Similarly, according to Selfe et al., five
18
19 323 repetitions in active knee JPS test, and six when performed passively, are necessary to ensure a
20
21 324 consistent proprioception score.⁵⁴ However, this was only met in two included studies.^{42, 44}
22
23

24
25 325 Almost all studies used AE for measuring JPS acuity which represents a task-oriented approach
26
27 326 to studying performance skill, in contrast to a process-orientation in which underlying processes
28
29 327 are in focus. The inconsistency in performance, i.e., response variability (variable error), may
30
31 328 reflect noise in sensory signal and its processing⁵⁵ and thus be a more process-oriented outcome
32
33 329 than AE. To understand possible underlying mechanisms, it would be advantageous to combine
34
35 330 task- and process-oriented measures.
36
37

38
39 331 In general, method descriptions of proprioception tests were short and, in some studies, deficient,
40
41 332 lacking information about factors that could influence the results. One such factor was
42
43 333 randomization of the order of target positions (cf. Zult et al.),⁴⁰ which is required to minimize the
44
45 334 effect of memory and reduce motor elements of the test. This is particularly applicable in tests
46
47 335 with active positioning, which was the case for most studies, enabling central motor programs.⁵⁶
48
49 336 Inadequate reporting of the proprioception tests would hinder their replication and raise risk of
50
51 337 bias rating. Moreover, Kaya et al. reported only post-intervention JPS scores, precluding
52
53 338 baseline scores, despite claiming their study to be an RCT.⁴⁴
54
55
56
57
58
59
60

339 *Mechanisms Underpinning NT Following ACLR*

340 Two of the included studies evaluated the effects of WBVT;^{42, 47} however, only one found a
341 favourable effect on proprioception.⁴² Two factors may contribute to the different findings
342 between these studies. First, time point: Fu et al. evaluated JPS 3 months after the intervention,
343 while Moezy et al. did it directly after the intervention period. Second, the use of active⁴² or
344 passive⁴⁷ knee movement when testing JPS. Active tests stimulate both joint and muscle-tendon
345 mechanoreceptors and induce alpha-gamma co-activation while passive tests assess joint
346 receptors to a higher degree^{10, 57} which potentially could mean a higher sensitivity of the active
347 test.

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

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

1
2
3 362 Review-Manager 5.3 software (the Cochrane Collaboration) (see Table 1 and supplementary
4
5 363 files). Different designs and levels of difficulty of the execution were found (e.g. a simple static
6
7 364 balance task [with and without visual input], dynamic exercises performed on the balance board,
8
9 365 backward walking on a treadmill, etc.).

10
11
12
13 366 There is a challenge to transfer the rehabilitation in the clinic to automatic movements required
14
15 367 for athletic activities.^{18, 62} Wii Fit or similar games have the potential to combine feedback with
16
17 368 an external focus in a sport-specific environment,⁴³ supporting the use of such training tools.
18
19 369 However, a study on Nintendo Wii Fit training did not support its use for improving knee
20
21 370 proprioception following ACLR.⁴³ Newer technology with stroboscopic-eyewear might have the
22
23 371 potential to decrease visual input without fully occluding it, making it possible to use them in
24
25 372 sport specific rehabilitation. To prepare the individual for complex athletic environments and
26
27 373 reduce re-injury risk, rehabilitation might focus on NT with reduced demands on visual inputs
28
29 374 and enhance automatic movement control with cognitive demands included.¹⁸ Whether such NT
30
31 375 training improves knee proprioception and, how this should be assessed in the best way,¹³ are yet
32
33 376 to be determined.

377 *The Ability of Tests to Discern Changes in Proprioception Following NT*

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

1
2
3 384 detect a greater difference in knee proprioception than TTDPMP following an ACL injury.²
4
5 385 However, our findings remain equivocal regarding the outcomes of JPS or TTDPMP following
6
7
8 386 NT.

9
10
11 387 Knee-specific proprioception tests provide an indirect measure of proprioception involving the
12
13 388 process of the CNS.¹⁰ Psychosocial factors,⁶⁴ pain and preinjury motor skills may influence the
14
15 389 central mechanisms and the outcome of such tests following NT. Knee-specific proprioception
16
17 390 tests are designed to exclude motor skills, but how successful that exclusion works, remains
18
19
20 391 unclear.

21 22 23 392 ***Limitations and Future Recommendations***

24
25
26
27 393 The nine included studies examined only individuals with ACLR but not those managed
28
29 394 conservatively following ACL injury. Owing to clinical heterogeneity of interventions and
30
31 395 outcomes, meta-analyses were precluded from the GRADE synthesis. The included studies had
32
33 396 methodological limitations (high risk of bias or some concerns) and only two studies^{40, 41} had
34
35 397 pre-registered their protocol. There is a need for high quality RCTs with low risk of bias in this
36
37
38 398 area.

39
40
41
42 399 The most common reason for exclusion of clinical trials in this review was that they did not
43
44 400 evaluate the effects of NT following ACLR with a knee-specific proprioception test. Perhaps, the
45
46 401 lack of consensus regarding the most appropriate, valid, reliable and responsive proprioception
47
48 402 tests, number of target angles or most responsive target angles (low vs. high) precluded such
49
50 403 outcomes in these studies. Therefore, psychometric properties of such tests must be established.¹³
51
52
53
54
55
56
57
58
59
60

1
2
3 404 When designing rehabilitation programs with long-term follow-up, aberrations in neuromotor
4
5 405 control and neuroplastic changes should preferably be addressed. To reflect a wide spectrum of
6
7 406 individual impairments, further research should investigate differences in individuals with ACL
8
9 407 injuries managed with surgical (graft types) or conservative treatment, both sexes, athletes and
10
11 408 non-athletes of different ages. Future studies might assess neuromotor control in functional tasks
12
13 409 rather than relying on knee-specific proprioception tests, given the challenges of isolating the
14
15 410 proprioceptive ability.
16
17
18
19

20 411 **Conclusion**

21
22
23 412 The existing nine studies on individuals with ACLR using heterogeneous interventions and knee-
24
25 413 specific proprioception measures revealed a very low certainty in current evidence for employing
26
27 414 NT programs to improve knee proprioception. The GRADE evidence synthesis revealed a high
28
29 415 risk of bias or some concerns, indirect evidence, conflicting findings, and imprecision of effect
30
31 416 estimates in the included studies. Methodologically-robust RCTs with homogenous populations
32
33 417 (having ACL injury managed with/without reconstruction), novel/well-designed NT
34
35 418 interventions, and valid proprioception measures are warranted to substantiate conclusive
36
37 419 evidence in this area.
38
39
40
41
42

43 420 **Contributors**

44
45 421 AA and CKH conceived the idea of the project. AA, MB, SM and CKH were responsible for
46
47 422 designing the review and conceptualising the initial review protocol. AA led the writing
48
49 423 of the manuscript. MB, SM and CKH contributed to writing the manuscript. AA, MB and CKH
50
51 424 have reviewed and revised the manuscript for intellectual content. All authors approved the final
52
53 425 version of the manuscript. AA is the guarantor of this work.
54
55
56
57
58
59
60

1
2
3 **426 Funding**
4

5 427 The work was supported by the Swedish Research Council (2017-00892); Region Västerbotten
6
7 428 (ALF 7003575; Strategic funding VLL-358901; Project. No. 7002795); the Swedish Research
8
9
10 429 Council for Sports Science (CIF P2019 0068); and King Gustaf V and Queen Victoria's
11
12 430 Foundation of Freemasons 2019 (Häger). The funders were not involved in the conception,
13
14
15 431 design, execution and writing of the review.
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

432 **References**

433

- 434 1. Kapreli E, Athanasopoulos S, Gliatis J, et al. Anterior Cruciate Ligament Deficiency
435 Causes Brain Plasticity: A Functional MRI Study. *Am J Sports Med.* 2009;37:2419-26.
- 436 2. Relph N, Herrington L, Tyson S. The effects of ACL injury on knee proprioception: a
437 meta-analysis. *Physiotherapy.* 2014;100:187-95.
- 438 3. Sanders TL, Maradit Kremers H, Bryan AJ, et al. Incidence of anterior cruciate ligament
439 tears and reconstruction: a 21-year population-based study. *Am J Sports Med.* 2016;44:1502-7.
- 440 4. Kobayashi H, Kanamura T, Koshida S, et al. Mechanisms of the anterior cruciate
441 ligament injury in sports activities: a twenty-year clinical research of 1,700 athletes. *J Sports Sci*
442 *Med.* 2010;9:669-75.
- 443 5. Johnston JT, Mandelbaum BR, Schub D, et al. Video analysis of anterior cruciate
444 ligament tears in professional American football athletes. *Am J Sports Med.* 2018;46:862-8.
- 445 6. Acevedo RJ, Rivera-Vega A, Miranda G, Micheo W. Anterior cruciate ligament injury:
446 identification of risk factors and prevention strategies. *Curr Sports Med Rep.* 2014;13:186-91.
- 447 7. Ardern CL, Taylor NF, Feller JA, Whitehead TS, Webster KE. Sports participation 2
448 years after anterior cruciate ligament reconstruction in athletes who had not returned to sport at 1
449 year: a prospective follow-up of physical function and psychological factors in 122 athletes. *Am*
450 *J Sports Med.* 2015;43:848-56.
- 451 8. Gao F, Zhou J, He C, et al. A Morphologic and Quantitative Study of Mechanoreceptors
452 in the Remnant Stump of the Human Anterior Cruciate Ligament. *Arthroscopy.* 2016;32:273-80.

- 1
2
3 453 9. Dhillon MS, Bali K, Prabhakar S. Differences among mechanoreceptors in healthy and
4
5 454 injured anterior cruciate ligaments and their clinical importance. *Muscles Ligaments Tendons J.*
6
7 455 2012;2:38-43.
8
9
10 456 10. Røijezon U, Clark NC, Treleaven J. Proprioception in musculoskeletal rehabilitation. Part
11
12 457 1: Basic science and principles of assessment and clinical interventions. *Man Ther.* 2015;20:368-
13
14 458 77.
15
16 459 11. Kapreli E, Athanasopoulos S. The anterior cruciate ligament deficiency as a model of
17
18 460 brain plasticity. *Med Hypotheses.* 2006;67:645-50.
19
20 461 12. Nakamae A, Adachi N, Ishikawa M, Nakasa T, Ochi M. No evidence of impaired
21
22 462 proprioceptive function in subjects with anterior cruciate ligament reconstruction: a systematic
23
24 463 review. *J ISAKOS.* 2017;2:191.
25
26 464 13. Arumugam A, Strong A, Tengman E, Røijezon U, Häger CK. Psychometric properties of
27
28 465 knee proprioception tests targeting healthy individuals and those with anterior cruciate ligament
29
30 466 injury managed with or without reconstruction: a systematic review protocol. *BMJ Open.*
31
32 467 2019;9:e027241.
33
34 468 14. Stensdotter AK, Tengman E, Olofsson LB, Häger C. Deficits in single-limb stance more
35
36 469 than 20 years after ACL injury. *European Journal of Physiotherapy.* 2013;15:78-85.
37
38 470 15. Fukunaga T, Johnson CD, Nicholas SJ, McHugh MP. Muscle hypotrophy, not inhibition,
39
40 471 is responsible for quadriceps weakness during rehabilitation after anterior cruciate ligament
41
42 472 reconstruction. *Knee Surgery, Sports Traumatology, Arthroscopy.* 2019;27:573-9.
43
44 473 16. Zebis MK, Andersen LL, Bencke J, Kjaer M, Aagaard P. Identification of athletes at
45
46 474 future risk of anterior cruciate ligament ruptures by neuromuscular screening. *Am J Sports Med.*
47
48 475 2009;37:1967-73.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 476 17. Grooms DR, Page SJ, Nichols-Larsen DS, Chaudhari AM, White SE, Onate JA.
4
5 477 Neuroplasticity Associated With Anterior Cruciate Ligament Reconstruction. *J Orthop Sports*
6
7 478 *Phys Ther.* 2017;47:180-9.
- 8
9
10 479 18. Grooms D, Appelbaum G, Onate J. Neuroplasticity Following Anterior Cruciate
11
12 480 Ligament Injury: A Framework for Visual-Motor Training Approaches in Rehabilitation. *J*
13
14 481 *Orthop Sports Phys Ther.* 2015;45:381-93.
- 15
16
17 482 19. Clark NC, Røijezon U, Treleaven J. Proprioception in musculoskeletal rehabilitation. Part
18
19 483 2: clinical assessment and intervention. *Man Ther.* 2015;20:378-87.
- 20
21 484 20. Risberg MA, Mork M, Jenssen HK, Holm I. Design and implementation of a
22
23 485 neuromuscular training program following anterior cruciate ligament reconstruction. *J Orthop*
24
25 486 *Sports Phys Ther.* 2001;31:620-31.
- 26
27
28 487 21. Moutzouri M, Gleeson N, Billis E, Panoutsopoulou I, Gliatis J. What is the effect of
29
30 488 sensori-motor training on functional outcome and balance performance of patients' undergoing
31
32 489 TKR? A systematic review. *Physiotherapy.* 2016;102:136-44.
- 33
34
35 490 22. Ordahan B, Kucuksen S, Tuncay I, Salli A, Ugurlu H. The effect of proprioception
36
37 491 exercises on functional status in patients with anterior cruciate ligament reconstruction. *J Back*
38
39 492 *Musculoskelet Rehabil.* 2015;28:531-7.
- 40
41
42 493 23. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred
43
44 494 reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med.*
45
46 495 2009;6:e1000097.
- 47
48
49 496 24. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS
50
51 497 and SPIDER: a comparison study of specificity and sensitivity in three search tools for
52
53 498 qualitative systematic reviews. *BMC Health Serv Res.* 2014;14:579.

- 1
2
3 499 25. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in
4
5 500 randomised trials. *BMJ*. 2019;366.
- 6
7
8 501 26. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating
9
10 502 quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-6.
- 11
12 503 27. Laboute E, Verhaeghe E, Ucay O, Minden A. Evaluation kinaesthetic proprioceptive
13
14 504 deficit after knee anterior cruciate ligament (ACL) reconstruction in athletes. *J Exp Orthop*.
15
16 505 2019;6:1-7.
- 17
18
19 506 28. Feil S, Newell J, Minogue C, Paessler HH. The effectiveness of supplementing a standard
20
21 507 rehabilitation program with, superimposed neuromuscular electrical stimulation after anterior
22
23 508 cruciate ligament reconstruction. *Am J Sports Med*. 2011;39:1238-47.
- 24
25
26 509 29. Ihara H, Nakayama A. Dynamic joint control training for knee ligament injuries. *Am J*
27
28 510 *Sports Med*. 1986;14:309-15.
- 29
30
31 511 30. Vathrakokilis K, Malliou P, Gioftsidou A, Beneka A, Godolias G. Effects of a balance
32
33 512 training protocol on knee joint proprioception after anterior cruciate ligament reconstruction. *J*
34
35 513 *Back Musculoskelet Rehabil*. 2008;21:233-7.
- 36
37
38 514 31. Saha S, Adhya B, Dhillon MS, Saini A. A Study on the Role of Proprioceptive Training
39
40 515 in Non Operative ACL Injury Rehabilitation. *Indian J Physiother Occup Ther*. 2015;9:226-31.
- 41
42 516 32. Lim J-M, Cho J-J, Kim T-Y, Yoon B-C. Isokinetic knee strength and proprioception
43
44 517 before and after anterior cruciate ligament reconstruction: A comparison between home-based
45
46 518 and supervised rehabilitation. *J Back Musculoskelet Rehabil*. 2019;32:421-9.
- 47
48
49 519 33. Liu-Ambrose T, Taunton JE, MacIntyre D, McConkey P, Khan KM. The effects of
50
51 520 proprioceptive or strength training on the neuromuscular function of the ACL reconstructed
52
53 521 knee: a randomized clinical trial. *Scand J Med Sci Sports*. 2003;13:115-23.

- 1
2
3 522 34. Lee SJ, Ren Y, Chang AH-I, Geiger F, Zhang L-Q. Effects of pivoting neuromuscular
4
5 523 training on pivoting control and proprioception. *Med Sci Sports Exerc.* 2014;46:1400-9.
6
7 524 35. Peultier-Celli L, Mainard D, Wein F, et al. Comparison of an innovative rehabilitation,
8
9 525 combining reduced conventional rehabilitation with balneotherapy, and a conventional
10
11 526 rehabilitation after anterior cruciate ligament reconstruction in athletes. *Front Surg.* 2017;4:61.
12
13 527 36. Faggal MS, Abdelsalam MS, Adel Elhakk SM, Mahmoud NF. Proprioceptive training
14
15 528 after ACL reconstruction: Standard versus stump preservation technique. *Physiother Pract Res.*
16
17 529 2019;40:69-75.
18
19 530 37. San Martín-Mohr C, Cristi-Sánchez I, Pincheira PA, Reyes A, Berral FJ, Oyarzo C. Knee
20
21 531 sensorimotor control following anterior cruciate ligament reconstruction: A comparison between
22
23 532 reconstruction techniques. *PLoS One.* 2018;13:e0205658.
24
25 533 38. Büyükturan Ö, Büyükturan B, Kurt EE, Yetis M. Effects of Tai Chi on partial anterior
26
27 534 cruciate ligament injury: A single-blind, randomized-controlled trial. *Turk J Phys Med Rehabil.*
28
29 535 2019;65:160-8.
30
31 536 39. Wang L. Immediate effects of neuromuscular joint facilitation intervention after anterior
32
33 537 cruciate ligament reconstruction. *J Phys Ther Sci.* 2016;28:2084-7.
34
35 538 40. Zult T, Gokeler A, van Raay J, et al. Cross-education does not accelerate the
36
37 539 rehabilitation of neuromuscular functions after ACL reconstruction: a randomized controlled
38
39 540 clinical trial. *Eur J Appl Physiol.* 2018;118:1609-23.
40
41 541 41. Shen M, Che S, Ye D, Li Y, Lin F, Zhang Y. Effects of backward walking on knee
42
43 542 proprioception after ACL reconstruction. *Physiother Theory Pract.* 2019.
44
45 543 42. Moezy A, Olyaei G, Hadian M, Razi M, Faghihzadeh S. A comparative study of whole
46
47 544 body vibration training and conventional training on knee proprioception and postural stability
48
49
50
51
52
53
54
55
56
57
58
59

- 1
2
3 545 after anterior cruciate ligament reconstruction. *British journal of sports Medicine*. 2008;42:373-
4
5 546 85.
6
7
8 547 43. Baltaci G, Harput G, Haksever B, Ulusoy B, Ozer H. Comparison between Nintendo Wii
9
10 548 Fit and conventional rehabilitation on functional performance outcomes after hamstring anterior
11
12 549 cruciate ligament reconstruction: prospective, randomized, controlled, double-blind clinical trial.
13
14 550 *Knee Surg Sports Traumatol Arthrosc*. 2013;21:880-7.
15
16
17 551 44. Kaya D, Guney-Deniz H, Sayaca C, Calik M, Doral MN. Effects on Lower Extremity
18
19 552 Neuromuscular Control Exercises on Knee Proprioception, Muscle Strength, and Functional
20
21 553 Level in Patients with ACL Reconstruction. *Biomed Res Int*. 2019:1-7.
22
23
24 554 45. Cho SH, Bae CH, Gak HB. Effects of closed kinetic chain exercises on proprioception
25
26 555 and functional scores of the knee after anterior cruciate ligament reconstruction. *J Phys Ther Sci*.
27
28 556 2013;25:1239-41.
29
30
31 557 46. Risberg MA, Holm I, Myklebust G, Engebretsen L. Neuromuscular training versus
32
33 558 strength training during first 6 months after anterior cruciate ligament reconstruction: a
34
35 559 randomized clinical trial. *Phys Ther*. 2007;87:737-50.
36
37
38 560 47. Fu CLA, Yung SHP, Law KYB, et al. The effect of early whole-body vibration therapy
39
40 561 on neuromuscular control after anterior cruciate ligament reconstruction: a randomized
41
42 562 controlled trial. *Am J Sports Med*. 2013;41:804-14.
43
44
45 563 48. Beynnon BD, Johnson RJ, Naud S, et al. Accelerated versus nonaccelerated rehabilitation
46
47 564 after anterior cruciate, ligament reconstruction:A prospective, randomized, double-blind
48
49 565 investigation evaluating knee joint laxity using roentgen, stereophotogrammetric analysis. *Am J*
50
51 566 *Sports Med*. 2011;39:2536-48.
52
53
54
55
56
57
58
59

- 1
2
3 567 49. Hortobágyi T, Garry J, Holbert D, Devita P. Aberrations in the control of quadriceps
4
5 568 muscle force in patients with knee osteoarthritis. *Arthritis Care Res.* 2004;51:562-9.
6
7
8 569 50. Cooper RL, Taylor NF, Feller JA. A systematic review of the effect of proprioceptive and
9
10 570 balance exercises on people with an injured or reconstructed anterior cruciate ligament. *Res*
11
12 571 *Sports Med.* 2005;13:163-78.
13
14
15 572 51. Baltaci G, Kohl HW. Does proprioceptive training during knee and ankle rehabilitation
16
17 573 improve outcome? *Phys Ther Rev.* 2003;8:5-16.
18
19 574 52. Iwasa J, Ochi M, Adachi N, Tobita M, Katsube K, Uchio Y. Proprioceptive improvement
20
21 575 in knees with anterior cruciate ligament reconstruction. *Clin Orthop Relat Res.* 2000:168-76.
22
23
24 576 53. Han J, Waddington G, Adams R, Anson J, Liu Y. Assessing proprioception: A critical
25
26 577 review of methods. *J Sport Health Sci.* 2016;5:80-90.
27
28 578 54. Selfe J, Callaghan M, McHenry A, Richards J, Oldham J. An investigation into the effect
29
30 579 of number of trials during proprioceptive testing in patients with patellofemoral pain syndrome. *J*
31
32 580 *Orthop Res.* 2006;24:1218-24.
33
34
35 581 55. van Beers RJ, Sittig AC, van der Gon Denier JJ. How humans combine simultaneous
36
37 582 proprioceptive and visual position information. *Exp Brain Res.* 1996;111:253-61.
38
39
40 583 56. Gandevia SC, Burke D. Does the nervous system depend on kinesthetic information to
41
42 584 control natural limb movements? *Behav Brain Sci.* 1992;15:614-
43
44
45 585 57. Clark NC, Akins JS, Heebner NR, et al. Reliability and measurement precision of
46
47 586 concentric-to-isometric and eccentric-to-isometric knee active joint position sense tests in
48
49 587 uninjured physically active adults. *Phys Ther Sport.* 2016;18:38-45.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 588 58. Avelar NC, Costa SJ, da Fonseca SF, et al. The effects of passive warm-up vs. whole-
4
5 589 body vibration on high-intensity performance during sprint cycle exercise. *J Strength Cond Res*.
6
7 590 2012;26:2997-3003.
8
9
10 591 59. Chow DHK, Lee TY, Pope MH. Effects of whole body vibration on spinal proprioception
11
12 592 in healthy individuals. *Work*. 2018.
13
14 593 60. Trans T, Aaboe J, Henriksen M, Christensen R, Bliddal H, Lund H. Effect of whole body
15
16 594 vibration exercise on muscle strength and proprioception in females with knee osteoarthritis.
17
18 595 *Knee*. 2009;16:256-61.
19
20
21 596 61. Herrero AJ, Menendez H, Gil L, et al. Effects of whole-body vibration on blood flow and
22
23 597 neuromuscular activity in spinal cord injury. *Spinal Cord*. 2011;49:554-9.
24
25
26 598 62. Benjaminse A, Gokeler A, Dowling AV, et al. Optimization of the anterior cruciate
27
28 599 ligament injury prevention paradigm: novel feedback techniques to enhance motor learning and
29
30 600 reduce injury risk. *J Orthop Sports Phys Ther*. 2015;45:170-82.
31
32
33 601 63. Ochi M, Iwasa J, Uchio Y, Adachi N, Sumen Y. The regeneration of sensory neurones in
34
35 602 the reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Br*. 1999;81:902-6.
36
37
38 603 64. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience
39
40 604 education on musculoskeletal pain: A systematic review of the literature. *Physiother Theory*
41
42 605 *Pract*. 2016;32:332-55.
43
44
45 606

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

Study citation	Sample size ^a , age (mean ± SD), gender;	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:

6/bmjopen-2021-049226 on 18 May 2021. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

	<p>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;</p> <p>ACLR (patellar tendon graft, hamstring tendon graft, allograft)</p>	<p>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</p>	<p>parameters: NR); Adherence: NR</p>	<p>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).</p>	<p>SA 20°: -1.34 [-2.11, -0.57] SA 50°: -1.40 [-2.05, -0.75] SA 80°: -1.29 [-2.00, -0.58]</p>
<p>Zult et al. (2018) ⁴⁰</p>	<p>Int: n =29 (22), 28±9 years; Com: n = 26 (21), 28±10 years n=24 males n=20 females</p> <p>ACLR (patellar tendon graft/ hamstring tendon graft (SSG)/ Artificial)</p>	<p>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:</p>	<p>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</p>	<p>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).</p> <p>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</p>	<p>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]</p> <p>QFC (Nm)^{e,f} at 26 weeks post-ACLR: Concentric 60°/s: 6.00 [0.67, 11.33] Eccentric 60°/s:</p>

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]
---	---------------	--	--

^aIncluded in ana

^bCalculated with Review Manager (RevMan) 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre Copenhagen, Denmark);

^cMean difference between groups were calculated based on post-intervention/final follow-up scores reported by the authors;

^dDifference between four intervention groups and the comparator group were same and so only one comparison is presented.

^eMean difference between groups were calculated based on change scores from baseline (pre- vs. post-intervention) reported by the authors;

^fQuadriceps 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;

^gJPS 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	Overall judgement
Baltaci et al. 2013 ⁴³	JPS	High	Some concerns	Low	High	High	High
Beynnon et al. 2011 ⁴⁸	TTDPM	Low	Low	Low	Low	Some concerns	Some concerns
Cho et al. 2013 ⁴⁵	JPS	Some concerns	Some concerns	Low	High	Some concerns	High
Fu et al. 2013 ⁴⁷	JPS	Low	Low	Low	Low	Some concerns	Some concerns
Kaya et al. 2019 ⁴⁴	JPS	Some concerns	High	High	Low	Some concerns	High
Moezy et al. 2008 ⁴²	JPS	Some concerns	Low	Low	Some concerns	High	High
Risberg et al. 2007 ⁴⁶	TTDPM	Low	Low	Low	Low	Some concerns	Some concerns
Shen et al. 2019 ⁴¹	JPS	Some concerns	Low	Low	Low	Some concerns	Some concerns
	TTDPM	Some concerns	Low	Low	Low	Some concerns	Some concerns
Zult et al. 2018 ⁴⁰	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.

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.

- Included studies had a high risk of bias or some concerns based on the Cochrane ROB2 tool;
- The direction and/or magnitude of effect was inconsistent across trials;
- Clinical heterogeneity (of participants, interventions, and method of assessing outcome measures);
- Number of participant <400 and/or wide 95% confidence intervals of effect size estimates;
- 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

1		
2		
3		
4		clinical practice. In addition, variations in the methods of JPS measurements (active vs.
5		passive angle reproduction, low vs. high target angles, etc.) precluded a meta-analysis.
6		However, forest plots have been presented for easy understanding of the confidence
7		intervals and overall findings on JPS following neuromuscular rehabilitation training in
8		individuals with ACLR (see appendices). We judged the evidence to have serious
9		indirectness especially owing to variations in the interventions and outcome measures.
10		
11	Imprecision	A total of 244 patients was included from seven RCTs reporting changes in JPS
12		following neuromuscular training (n = 139) or comparator interventions (n = 105).
13		Most of the included trails reported non-significant results with wider 95% confidence
14		intervals for one or more JPS (target) angles (see appendices). Therefore, we judged
15		the evidence to have serious imprecision.
16		
17	Publication bias	Since negative and positive findings have been published, and a comprehensive search
18		for RCTs has been done, we did not suspect a publication bias.
19		
20		
21		Knee joint threshold to detect passive motion (TTDPM)
22		
23	Risk of bias	Three RCTs ^{20, 41, 48} reporting changes in TTDPM following neuromuscular training
24	(methodological	were found to show some concerns in risk of bias based on the Cochrane ROB 2 tool
25	limitations)	(see Table 4). We judged the included RCTs to be of serious methodological
26		limitations.
27		
28	Inconsistency	The direction and/or magnitude of effect was conflicting between the three RCTs. As
29		two trials reported insignificant effects and one ⁴¹ reported significant effects (see
30		appendices), we judged the evidence to have serious inconsistency in the direction
31		and/or magnitude of effects.
32		
33	Indirectness	The participants (with ACLR [different grafts]), different neuromuscular training and
34		comparator interventions, and knee specific TTDPM measures in the included studies
35		provide some evidence to the research question in hand. However, the heterogeneity of
36		interventions and TTDPM measurements (starting angles, angular velocity, etc.)
37		precluded a meta-analysis. We judged the evidence to have serious indirectness
38		especially owing to variations in the interventions and TTDPM methods.
39		
40		
41		
42		
43		
44		
45		
46		

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46

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 one⁴¹ 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.

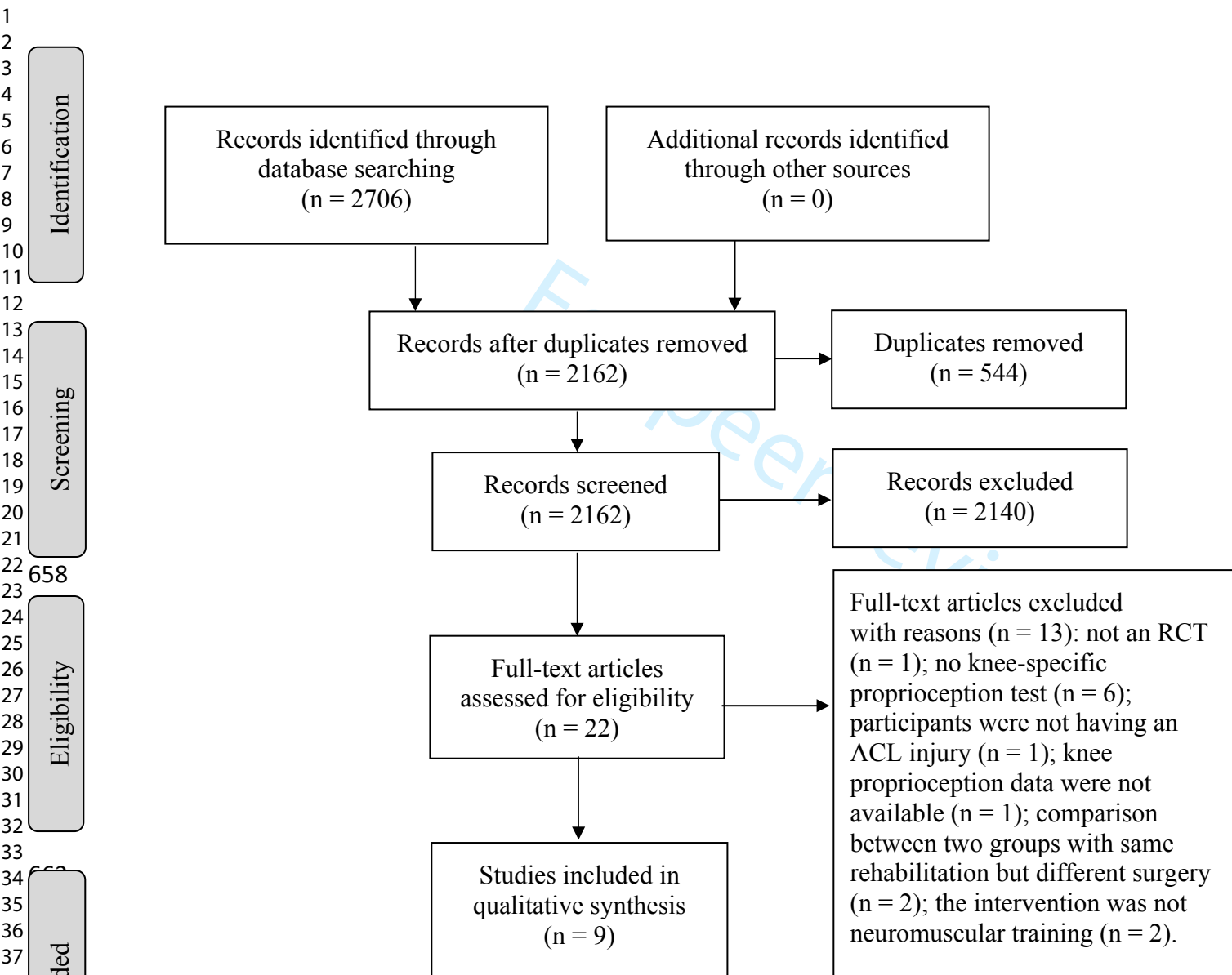


Figure 1. Flow diagram depicting the steps involved in screening and selection of eligible articles

1
2 666 **Online supplemental file 1.**

3
4 667 **Database-specific search strategies**

5
6 668 **AMED**

7
8 669 (Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesia") OR
9 670 sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection"
10 671 OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR
11 672 "passive motion detection threshold" OR "threshold for motion detection" OR "threshold
12 673 hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral
13 674 matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation
14 675 error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR
15 676 "joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active
16 677 movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)

17 678 S1: "Anterior Cruciate Ligament" OR (ZU "anterior cruciate ligament") OR "Knee joint"
18 679 OR (ZU "knee joint")

19 680 S2: Injur* OR (ZU "injuries") OR (ZU "anterior cruciate ligament injuries") OR

20 681 Reconstruction OR (ZU "anterior cruciate ligament reconstruction") OR

21 682 S3: Propriocep* OR (ZU "proprioception") OR Neuromuscular OR sensorimotor OR
22 683 sensory-motor OR "Kinetic chain" OR (ZU "kinetics") OR Coordination OR Balance OR

23 684 (ZU "balance") OR Plyometric (ZU "plyometric exercise") OR Vibration OR (ZU

24 685 "vibration") OR Exercise* OR (ZU "exercise") OR Intervention OR Training OR

25 686 Rehabilitation OR (ZU "rehabilitation") OR Therap* OR (ZU "therapy") OR Treatment

26 687 S4: Propriocep* OR (ZU "proprioception") OR Kinesthe* OR (ZU "kinesthesia") OR

27 688 sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection"

28 689 OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR

29 690 "passive motion detection threshold" OR "threshold for motion detection" OR "threshold

30 691 hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral

31 692 matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation

32 693 error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR

33 694 "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR

34 695 "active movement extent discrimination"

35 696 Limiters - Language: English, Expanders - Apply related words, Search modes - Find any

36 697 of my search terms, Interface - EBSCOhost Research Databases, Search Screen -

37 698 Advanced Search, Database - AMED - The Allied and Complementary Medicine

38 699 Database

39 700

40 701 **CINAHL**

41 702 Limiters - Peer Reviewed; Human; Language: English, Expanders - Apply related words,

42 703 Search modes - Find any of my search terms, Interface - EBSCOhost Research Databases,

43 704 Search Screen - Advanced Search, Database - CINAHL with Full Text

44 705 (Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesia") OR

45 706 sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection"

46 707 OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR

47 708 "passive motion detection threshold" OR "threshold for motion detection" OR "threshold

48 709 hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral

49 710 matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation

50 711 error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR

51 712 "Joint reposition" OR "Active movement extent discrimination" OR "force sense" OR

52 713 "force perception" OR "velocity sense") AND (S6 AND S7 AND S8 AND S9)

1
2 714 S6: "Anterior Cruciate Ligament" OR (MH "Anterior Cruciate Ligament") "Knee joint"
3 715 OR (MH "Knee Joint+")
4 716 S7: Injur* OR (MH "Anterior Cruciate Ligament Injuries") OR Reconstruction OR (MH
5 717 "Anterior Cruciate Ligament Reconstruction") OR Rupture OR Tear OR (MH
6 718 "Rupture+") OR Conservative OR Deficiency OR "Joint instability" OR (MH "Joint
7 719 Instability+")
8 720 S8: Propriocep* OR (MH "Proprioception+") OR Neuromuscular OR (MH
9 721 "Neuromuscular Control") OR sensorimotor OR "sensory-motor" OR "Kinetic chain" OR
10 722 (MH "Closed Kinetic Chain Exercises") OR (MH "Open Kinetic Chain Exercises") OR
11 723 Coordination OR Balance OR (MH "Balance Training, Physical") OR (MH "Balance,
12 724 Postural") OR Plyometric OR Vibration OR (MH "Vibration" OR Exercise* OR (MH
13 725 "Exercise+") OR Intervention OR Training OR Rehabilitation OR Therapy OR (MH
14 726 "Physical Therapy+") OR Treatment
15 727 S9: Propriocep* OR (MH "Proprioception+") OR Kinesthe* OR (MH "Kinesthesia") OR
16 728 sensorimotor OR sensory-motor OR "joint position sense" OR "joint position detection"
17 729 OR "threshold to detect passive motion" OR "passive motion direction discrimination" OR
18 730 "passive motion detection threshold" OR "threshold for motion detection" OR "threshold
19 731 hunting" OR "detection threshold" OR "discrimination threshold" OR "ipsilateral
20 732 matching" OR "contralateral matching" OR "joint angle error" OR "distance estimation
21 733 error" OR "passive recognition" OR "direction accuracy" OR "active reproduction" OR
22 734 "Joint reposition" OR "force sense" OR "force perception" OR "velocity sense" OR
23 735 "Active movement extent discrimination"

24 736

25 737 **Physical Education Index (ProQuest)**

26 738 (((("Anterior Cruciate Ligament" OR "Knee joint") AND (Injur* OR Trauma OR
27 739 Reconstruct* OR Ruptur* OR Tear OR Conservative OR Deficienc* OR "Joint
28 740 instabilit*")) AND (Propriocep* OR Kinesthes* OR neuromuscular OR sensorimotor OR
29 741 sensory-motor OR "Kinetic chain" OR Coordination OR Balance OR Plyometric OR
30 742 Vibration OR Exercise* OR Intervention OR Training OR Rehabilitation OR Therap* OR
31 743 Treatment) AND (Propriocep* OR Kinesthes* OR sensorimotor OR sensory-motor OR
32 744 "joint position sense" OR "joint position detection" OR "threshold to detect passive
33 745 motion" OR "passive motion direction discrimination" OR "passive motion detection
34 746 threshold" OR "threshold for motion detection" OR "threshold hunting" OR "detection
35 747 threshold" OR "discrimination threshold" OR "ipsilateral matching" OR "contralateral
36 748 matching" OR "joint angle error" OR "distance estimation error" OR "passive recognition"
37 749 OR "direction accuracy" OR "active reproduction" OR "Joint reposition" OR "active
38 750 movement extent discrimination" OR "force sense" OR "force perception" OR "velocity
39 751 sense")))) AND at.exact("Article") AND la.exact("ENG") AND PEER(yes)

40 752

41 753 **PubMed**

42 754 ((((((Anterior Cruciate Ligament[Text Word] OR "Anterior Cruciate Ligament"[Mesh] OR
43 755 Knee joint[Text Word] OR "knee joint"[MeSH Terms]) AND "loattrfull text"[sb]) AND
44 756 (((injury[All Fields]) OR Reconstruction[Text Word] OR "Anterior Cruciate Ligament
45 757 Reconstruction"[Mesh] OR "Anterior Cruciate Ligament Injuries"[Mesh] OR
46 758 Rupture[Text Word] OR Tear[Text Word] OR "Rupture"[Mesh] OR Conservative[Text
47 759 Word] OR "Conservative Treatment"[Mesh] OR Deficiency[Text Word] OR Joint
48 760 instability[Text Word] OR "Joint Instability"[Mesh]))) AND (((proprioception[All
49 761 Fields]) OR "Proprioception"[Mesh] OR Neuromuscular[Text Word] OR
50 762 sensorimotor[Text Word] OR sensory-motor[Text Word] OR Kinetic chain[Text Word]
51 763 OR Coordination[Text Word] OR "Psychomotor Performance"[Mesh] OR Balance[Text
52 764 Word] OR "Postural Balance"[Mesh] OR Plyometric[Text Word] OR "Plyometric

765 Exercise"[Mesh] OR ("exercise"[MeSH Terms] OR "exercises"[All Fields] OR "exercise
 766 therapy"[MeSH Terms]) OR "Exercise Therapy"[Mesh] OR Intervention[Text Word] OR
 767 Training[Text Word] OR "Resistance Training"[Mesh] OR Rehabilitation[Text Word] OR
 768 "Rehabilitation"[Mesh] OR Therapy[Text Word] OR Treatment[Text Word] OR
 769 "Treatment Outcome"[Mesh])) AND (((proprioception[All Fields]) OR
 770 "Proprioception"[Mesh] OR ("kinesthesia"[MeSH Terms] OR "kinesthesia"[All Fields])
 771 OR "Kinesthesia"[Mesh] OR joint position sense[Text Word] OR ("joints"[MeSH Terms]
 772 OR "joints"[All Fields] OR "joint"[All Fields]) AND position detection[Text Word]) OR
 773 threshold to detect passive motion[Text Word] OR (passive[All Fields] AND motion
 774 direction discrimination[Text Word]) OR (passive[All Fields] AND motion detection
 775 threshold[Text Word]) OR (threshold[All Fields] AND motion detection[Text Word]) OR
 776 threshold hunting[Text Word] OR detection threshold[Text Word] OR discrimination
 777 threshold[Text Word] OR (ipsilateral[All Fields] AND matching[Text Word]) OR
 778 contralateral matching[Text Word] OR joint angle error[Text Word] OR distance
 779 estimation error[Text Word] OR passive recognition[Text Word] OR direction
 780 accuracy[Text Word] OR active reproduction[Text Word] OR Joint reposition[Text Word]
 781 OR force sense[Text Word] OR force perception[Text Word] OR velocity sense[Text
 782 Word] OR (active[All Fields] AND ("movement"[MeSH Terms] OR "movement"[All
 783 Fields]) AND extent[All Fields] AND ("discrimination (psychology)"[MeSH Terms] OR
 784 ("discrimination"[All Fields] AND ("psychology")[All Fields]) OR "discrimination
 785 (psychology)"[All Fields] OR "discrimination"[All Fields])) OR sensorimotor[Text Word]
 786 OR sensory-motor[Text Word] AND "loattrfull text"[sb])) AND "loattrfull text"[sb]
 787 AND ("loattrfull text"[sb] AND English[lang]) AND English[lang]

788 789 Scopus

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

811 812 SPORTDiscus

813 Limiters - Peer Reviewed; Language: English; Publication Type: Academic Journal;
 814 Document Type: Article, Expanders - Apply related words, Search modes - Find any of

1
2 815 my search terms, Interface - EBSCOhost Research Databases, Search Screen - Advanced
3 816 Search, Database - SPORTDiscus
4 817 (Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR
5 818 sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to
6 819 detect passive motion" OR "passive motion direction discrimination" OR "passive motion
7 820 detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR
8 821 "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR
9 822 "contralateral matching" OR "joint angle error" OR "distance estimation error" OR
10 823 "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint
11 824 reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active
12 825 movement extent discrimination") AND (S1 AND S2 AND S3 AND S4)
13 826 S1: Anterior Cruciate Ligament OR (DE "CRUCIATE ligaments") OR (DE "ANTERIOR
14 827 cruciate ligament") "Knee joint" OR (DE "KNEE"
15 828 S2: Injur* OR (DE "ANTERIOR cruciate ligament injuries") OR (DE "CRUCIATE
16 829 ligament injuries) OR Reconstruction OR Rupture OR Tear OR Conservative OR
17 830 Deficiency OR "Joint instabilit*"
18 831 S3: Propriocep* OR (DE "PROPRIOCEPTION") OR Neuromuscular OR sensorimotor
19 832 OR sensory-motor OR Kinetic chain OR Coordination OR (DE "MOTOR ability") OR
20 833 Balance OR Plyometric OR (DE "PLYOMETRICS) OR Vibration OR Exercise* OR
21 834 Intervention OR Training OR Rehabilitation OR (DE "TREATMENT programs") OR
22 835 (DE "REHABILITATION") OR Therap* OR Treatment OR (DE "KNEE injuries --
23 836 Treatment")
24 837 S4: Propriocep* OR (DE "PROPRIOCEPTION") OR Kinesthe* OR sensorimotor OR
25 838 sensory-motor OR "joint position sense" OR "joint position detection" OR "threshold to
26 839 detect passive motion" OR "passive motion direction discrimination" OR "passive motion
27 840 detection threshold" OR "threshold for motion detection" OR "threshold hunting" OR
28 841 "detection threshold" OR "discrimination threshold" OR "ipsilateral matching" OR
29 842 "contralateral matching" OR "joint angle error" OR "distance estimation error" OR
30 843 "passive recognition" OR "direction accuracy" OR "active reproduction" OR "Joint
31 844 reposition" OR "force sense" OR "force perception" OR "velocity sense" OR "active
32 845 movement extent discrimination"
33 846
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

847 **Online supplemental file 2.**848 **Screening protocol – to screen eligible studies at the title, abstract, and full-text**
849 **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?

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 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

850

851

For peer review only

852 **Online supplemental file 3.**853 **Data extraction template**

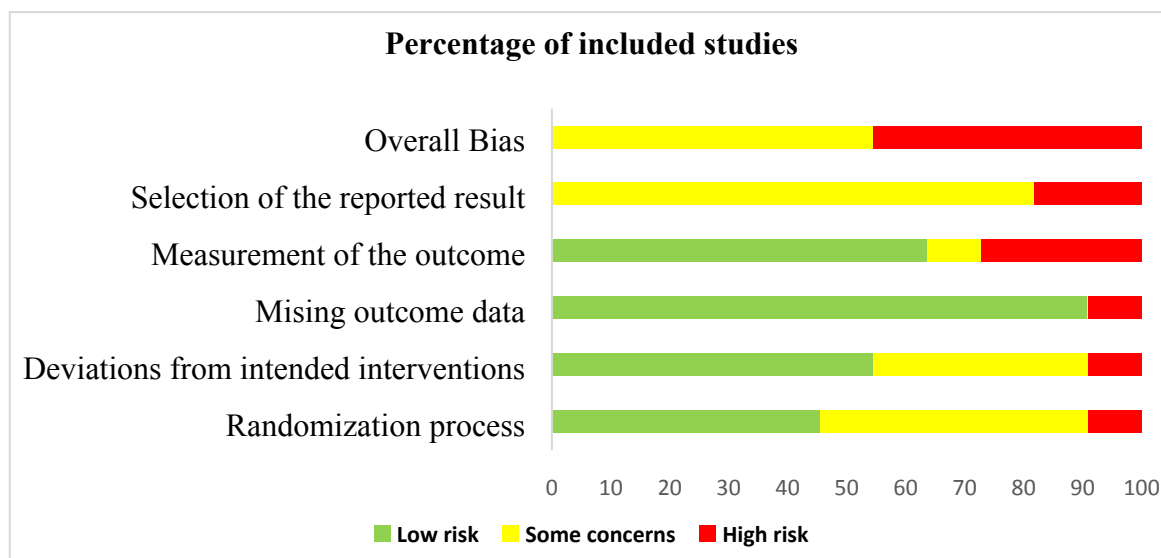
Publication details	Study citation, clinical trial registration, and published study protocol if available
Aim of the study	Primary and/or secondary aims relevant for the review.
Eligibility criteria	Inclusion and exclusion criteria for participants
Randomized/controlled clinical trial	Randomization 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

854

855

856

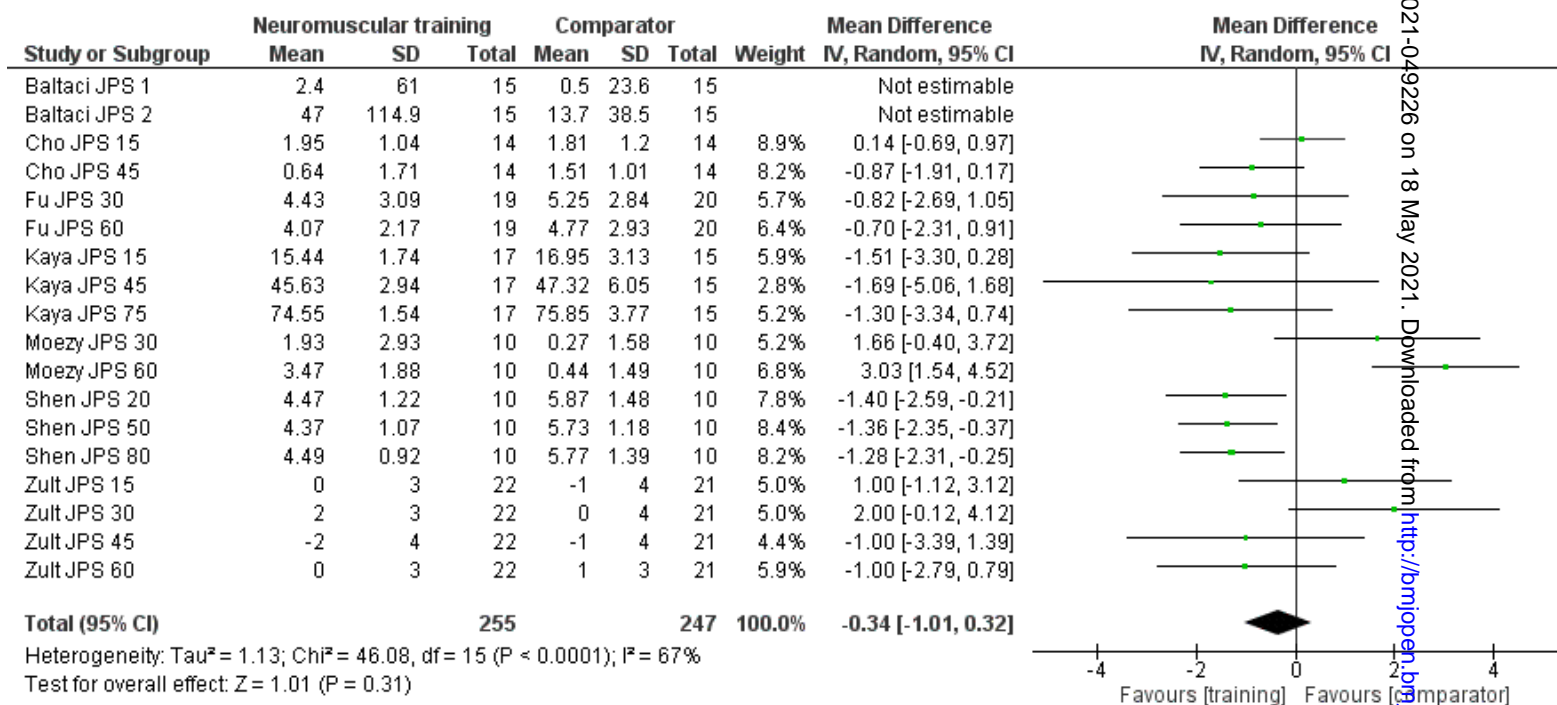
857



858

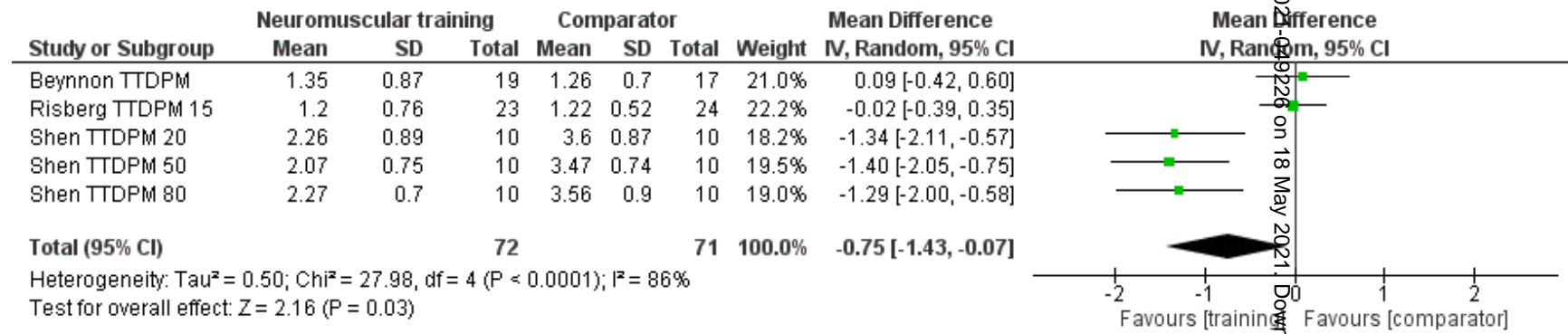
859 **Online supplemental figure 1.** Risk of bias assessment in each of the five domains and
 860 overall bias. Percentage of studies showing low risk of bias, some concerns and high risk
 861 of bias.

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

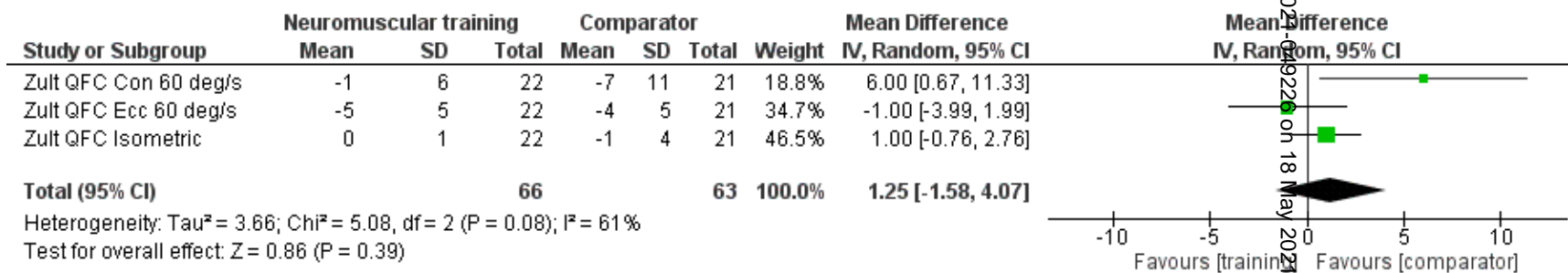


Online supplementary figure 2. A meta-analysis comparing mean differences between the neuromuscular training and comparator groups for knee joint position sense.

1136/bmjopen-2024-019226 on 18 May 2021. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.



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.



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

1136/bmjopen-2024-019229 on 18 May 2024. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.



PRISMA 2009 Checklist

 1136/bmjopen-2021-049226 on 18 May 2022. Downloaded from <http://bmjopen.bmj.com/> by guest. Protected by copyright.

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

Page 1 of 2

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

			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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-049226.R1
Article Type:	Original research
Date Submitted by the Author:	25-Mar-2021
Complete List of Authors:	Arumugam, Ashokan; University of Sharjah College of Health Sciences, Department of Physiotherapy Björklund, Martin; Umea University, Department of Community Medicine and Rehabilitation – Physiotherapy Section; University of Gavle Department of Occupational Health and Psychology, Department of Occupational Health Sciences and Psychology, Centre for Musculoskeletal Research Mikko, Sanna; Umea University, Department of Community Medicine and Rehabilitation – Physiotherapy Section Häger, Charlotte ; Umea University, 1Department of Community Medicine and Rehabilitation – Physiotherapy Section
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Knee < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

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:

¹Department of Physiotherapy, College of Health Sciences, University of Sharjah, P.O. Box: 27272, Sharjah, United Arab Emirates;

²Department of Community Medicine and Rehabilitation – Physiotherapy Section, Umeå, University, SE-901 87, Umeå, Sweden;

³Department 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

Manuscript Type: A systematic review

Word count: 5135 (excluding abstract, tables, contributions, funding acknowledgements and references)

Ethical approval: Not required.

Funding sources: The Swedish Research Council (2017-00892); Region Västerbotten (ALF 7003575; Strategic funding VLL-358901; Project.No 7002795); The Swedish Research Council for Sports Science (CIF P2019 0068); and King Gustaf V and Queen Victoria's Foundation of Freemasons 2019 (Häger).

Conflicts of interest: None declared.

Ethical approval: Not required.

Competing interests: None declared.

1
2
3 1 **Effects of neuromuscular training on knee proprioception in individuals with anterior**
4
5 2 **cruciate ligament injury - A systematic review and GRADE evidence synthesis**
6
7

8
9 3 **Abstract**

10
11 4 **Objective**

12
13 5 To systematically review and summarize the evidence for the effects of neuromuscular
14
15 6 training compared to any other therapy (conventional training/sham) on knee proprioception
16
17 7 following anterior cruciate ligament (ACL) injury.

18
19
20 8 **Design** Systematic Review

21
22 9 **Data Sources**

23
24 10 PubMed, CINAHL, SPORTDiscus, AMED, Scopus, and Physical Education Index were
25
26 11 searched from inception to February 2020.

27
28 12 **Eligibility Criteria**

29
30 13 Randomized controlled trials (RCTs) and controlled clinical trials investigating the effects of
31
32 14 neuromuscular training on knee-specific proprioception tests following a unilateral ACL
33
34 15 injury were included.

35
36 16 **Data extraction and synthesis**

37
38 17 Two reviewers independently screened and extracted data and assessed risk of bias of the
39
40 18 eligible studies using the Cochrane risk of bias 2 tool. Overall certainty in evidence was
41
42 19 determined using the GRADE tool.

43
44 20 **Results** Of 2706 articles retrieved, only nine RCTs, comprising 327 individuals with an ACL
45
46 21 reconstruction (ACLR), met the inclusion criteria. Neuromuscular training interventions
47
48 22 varied across studies: whole body vibration therapy, Nintendo-Wii-Fit training, balance
49
50 23 training, sport-specific exercises, backward walking, etc. Outcome measures included joint
51
52 24 position sense (JPS; n=7), thresholds to detect passive motion (TTDPM; n=3), or quadriceps
53
54 25 force control (QFC; n=1). Overall, between-group mean differences indicated inconsistent

1
2
3 26 findings with an increase or decrease of errors associated with JPS by $\leq 2^\circ$, TTDPM by $\leq 1.5^\circ$,
4
5 27 and QFC by ≤ 6 Nm in the ACLR knee following neuromuscular training. Owing to serious
6
7
8 28 concerns with three or more GRADE domains (risk of bias, inconsistency, indirectness, or
9
10 29 imprecision associated with the findings) for each outcome of interest across studies, the
11
12 30 certainty of evidence was very low.

13
14 31 **Conclusions** The heterogeneity of interventions, methodological limitations, inconsistency of
15
16 32 effects (on JPS/TTDPM/QFC) preclude recommendation of one optimal neuromuscular
17
18 33 training intervention for improving proprioception following ACL injury in clinical practice.
19
20 34 There is a need for methodologically-robust RCTs with homogenous populations with ACL
21
22 35 injury (managed conservatively or with reconstruction), novel/well-designed neuromuscular
23
24 36 training, and valid proprioception assessments, which also seem to be lacking.

25
26
27
28 37 **PROSPERO registration number**

29
30 38 CRD42018107349

31
32
33 39 **Key words:** Joint position sense, threshold to detect passive motion, ACL, sensorimotor
34
35 40 training, literature review, neuroplasticity
36
37

38 41
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **42 Strengths and limitations of the study**
4

- 5
6 43 • A systematic review of neuromuscular training on knee proprioception following the
7
8 44 Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines, using a
9
10 45 broad search in six electronic databases.
11
12 46 • The risk of bias associated with the outcomes of interest (knee proprioception measures)
13
14 47 in the included RCTs were assessed using the updated Cochrane risk of bias 2 tool.
15
16
17 48 • The overall certainty of evidence for the effects of neuromuscular training on knee joint
18
19 49 position sense, threshold to detect passive motion, and quadriceps force control
20
21 50 following ACL injury/reconstruction was ascertained using the GRADE tool.
22
23
24 51 • Only RCTs published in English were included.
25
26 52 • A meta-analysis was precluded because of clinical heterogeneity of interventions and
27
28 53 outcome measures.
29
30
31
32 54

55 Introduction

56 Anterior cruciate ligament (ACL) injury is a common musculoskeletal injury^{1,2} accounting
57 for an annual incidence rate of 68.6/100,000 person-years in the United States.³ ACL injury is
58 most prevalent in young athletes (14-18 years for females and 19-25 years for males).³ The
59 injury occurs more often during competition rather than training, with ~70% or more of the
60 injuries representing noncontact mechanisms^{4,5} such as landing from a jump, sudden
61 deceleration and/or while cutting.⁶ Thus, the injury mechanisms are related to neuromotor
62 control, amongst other factors, of the individual. ACL injury is predominantly treated by
63 surgical reconstruction,³ and followed by a long period of rehabilitation and yet many
64 individuals do not return to pre-injury levels of activity⁷ which challenges the efficacy of
65 existing preventative and rehabilitative strategies.

66 Individuals with an ACL injury present with a decreased number of proprioceptive
67 mechanoreceptors (Pacinian capsules, Ruffini nerve endings and Golgi tendon organs)^{8,9}
68 which might alter somatosensory input to the central nervous system (CNS)⁹ leading to
69 decreased knee proprioception. Disturbed proprioception might also be caused by acute
70 inflammation and pain, and the capsule and surrounding ligaments getting affected following
71 instability.^{10,11} Although there has been a debate regarding the effects of ACL injury on
72 different knee proprioception tests,^{2,12} our recent systematic review¹³ suggests that knee JPS
73 tests have sufficient validity in discriminating ACL-injured knees from asymptomatic knees
74 (accepted). When compared to non-injured controls, individuals with ACL injury
75 demonstrate altered movement strategies,^{4,14} quadriceps muscle weakness,¹⁵ and onset and
76 progression of osteoarthritis.^{6,16} Due to the potential serious consequences of the injury,
77 much attention and clinical efforts have been dedicated to preventative and rehabilitative
78 strategies for ACL injury,¹¹ including various neuromuscular training (NT) methods believed
79 to improve the proprioceptive ability.

1
2
3 80 Even if proprioceptive deficits could affect neuromotor control, the rationale, mechanisms,
4
5 81 and plausibility for improving proprioception by training need to be verified. In the context of
6
7 82 neuroplasticity, functional magnetic resonance imaging has revealed that individuals with
8
9 83 ACL-deficient knees demonstrate less activation in several sensorimotor cortical areas and
10
11 84 increased activation in pre-supplementary motor areas, posterior secondary somatosensory
12
13 85 area, and posterior inferior temporal gyrus compared to controls with asymptomatic
14
15 86 knees during a knee flexion-extension task.¹ It seems individuals with ACL reconstruction
16
17 87 adapt a visual-sensory-motor strategy instead of a normal sensory-motor strategy owing to
18
19 88 aberrant sensory feedback following ACL injury.¹⁷ Nevertheless, neuroplastic reorganization
20
21 89 ensues where other potential sensory sources are used to organize the movement or regulate
22
23 90 neuromotor control, particularly in (sporting) tasks with higher complexity. Therefore, ACL
24
25 91 injuries might be regarded as a neuromotor control dysfunction rather than a simple
26
27 92 peripheral musculoskeletal injury.^{11,18} It is yet unclear though whether neuromuscular
28
29 93 training (NT) can improve proprioception after an ACL injury^{11,19} and the neurophysiological
30
31 94 mechanisms underpinning such interventions need further substantiation.
32
33
34
35
36
37
38
39 95 To date, there is no consensus on the most effective rehabilitation programs for ACL injury,
40
41 96 and the prevalence of reinjury after returning to sport is up to 30%.¹⁸ Owing to the
42
43 97 neuroplastic changes and possibly altered proprioception following an ACL injury, NT has
44
45 98 received much attention to enhance dynamic joint stability and relearn movement patterns
46
47 99 and skills.²⁰ In this context, both NT and sensorimotor training terms have been used. NT is
48
49 100 defined as "...training enhancing unconscious motor responses by stimulating both afferent
50
51 101 signals and central mechanisms responsible for dynamic joint control"²⁰ and sensorimotor
52
53 102 training aims to improve "...function of the CNS in regulating movement in order to reach
54
55 103 proper firing patterns for maintaining joint stability...".²¹ Active knee motion will in any case
56
57
58
59
60

1
2
3 104 stimulate proprioceptors, which in turn would alter the demands on the CNS,^{10,19}. Henceforth
4
5 105 we will use the term NT in this review.
6
7
8

9 106 There are different ways to challenge proprioception, for example: vibration may be used to
10
11 107 alter afferent input from muscle spindles; an unstable surface can challenge input from the
12
13 108 ankle; vision can be occluded or head position can be changed to disturb visual- and
14
15 109 vestibular information,¹⁰ or focus can be shifted to influence cognitive processing sources.¹⁸
16
17 110 Due to a putative visual-sensory-motor strategy following ACL injury, a modified visual
18
19 111 feedback training might decrease visual reliance and improve sensory-motor function.¹⁸ Most
20
21 112 studies exploring the effects of NT on proprioception combine different exercises and various
22
23 113 outcome measures which precludes isolating the effects of a proprioception-specific
24
25 114 exercise.²² Therefore, this study aimed at systematically reviewing and summarizing the
26
27 115 evidence for the effects of NT compared to comparator/control interventions on
28
29 116 proprioception measured by knee-specific proprioception tests in individuals with anterior
30
31 117 cruciate ligament injury or reconstruction.
32
33
34
35
36

37 118 **Methods**

38
39
40 119 We adhered to the Preferred Reporting Items for Systematic review and Meta-Analysis
41
42 120 (PRISMA) checklist²³ and the reporting guidelines for Synthesis Without Meta-analysis
43
44 121 (SWiM) in systematic reviews.²⁴ The protocol was registered in PROSPERO
45
46 122 (CRD42018107349). A list of acronyms used in the review is summarized in Box 1.
47
48
49

50 123 **Eligibility criteria**

51
52
53 124 The structure of PICOS²⁵ was used to frame the following criteria:

- 54 125 1. **Participants:** Individuals aged over 15 years of age (both sexes) with a history of a
55
56 126 unilateral ACL rupture, managed conservatively or surgically reconstructed, with or
57
58
59
60

- 1
2
3 127 without concomitant meniscus and/or collateral ligament injuries on the injured leg,
4
5 128 without any other lower extremity injuries/surgeries that would confound the
6
7
8 129 outcomes of rehabilitation training;
9
10 130 2. **Intervention:** Specific neuromuscular training, closed or open kinetic chain
11
12 131 exercises, balance training, joint repositioning training, joint force sense training, co-
13
14 132 ordination training, plyometric training, whole body vibration, virtual gaming
15
16 133 training, an accelerated rehabilitation protocol or any other training programs
17
18 134 focusing on improving the lower limb neuromuscular control and knee
19
20 135 proprioception;
21
22 136 3. **Comparator:** Any other therapy, conventional training, usual care, placebo or sham
23
24 137 therapy;
25
26 138 4. **Outcome measures:** Knee-specific proprioception tests targeting joint position sense
27
28 139 (JPS), kinesthesia (threshold to detect passive motion [TTDPM]), force
29
30 140 sense/perception, active movement extent discrimination, velocity sense, or
31
32 141 psychophysical threshold methods;¹³ they can be performed actively and/or passively
33
34 142 with or without visual input in weight bearing or non-weight bearing positions;¹⁰
35
36 143 5. **Study design:** randomized controlled trials (RCTs) or controlled clinical trials.
37
38
39
40
41
42

43 144 **Data Sources and Searches**

44
45
46 145 Database-specific search terms (e.g. MeSH) were combined using Boolean operators
47
48 146 (“AND” and “OR”) under three conceptual domains: participants, interventions and
49
50 147 outcomes. Six electronic databases were searched from their inception to 12 February 2020:
51
52 148 PubMed, Cumulative Index to Nursing & Allied Health Literature (CINAHL via
53
54 149 EBSCOhost), SPORTDiscus (via EBSCOhost), the Allied and Complementary Medicine
55
56
57
58
59
60

1
2
3 150 Database (AMED via EBSCOhost), Scopus, and Physical Education Index (via Proquest)
4
5 151 (Online supplemental file 1).
6
7
8

9 152 **Study Selection**

10
11
12 153 One reviewer (SM) imported all titles and abstracts retrieved from the databases into
13
14 154 EndNote X8. Two reviewers (AA and SM) independently checked titles, abstracts, and/or full
15
16 155 text by following a screening questionnaire (online supplemental file 2). Any disagreements
17
18 156 in inclusion of articles were adjudicated by two other reviewers (CH and MB) until
19
20 157 consensus was reached. A manual search of the reference lists of included articles was
21
22 158 performed.
23
24
25

26 159 **Data Extraction**

27
28
29
30 160 Data were extracted by one reviewer (SM) and verified by another reviewer (AA) using a
31
32 161 customized data extraction sheet (online supplemental file 3). If any data were missing, the
33
34 162 corresponding authors were contacted via email.
35
36
37

38 163 **Quality Assessment**

39
40
41 164 The risk of bias for each outcome of interest in the included studies was evaluated using the
42
43 165 Cochrane ROB 2.²⁶ The tool has five domains: 1) randomization (number of signaling
44
45 166 questions (n=3), 2) deviations from intended interventions (n=7), 3) missing outcome data
46
47 167 (n=5), 4) measurement of the outcomes (n=5), and 5) selection of the reported results (n=3).
48
49 168 Each signaling question can be answered as 1) yes, 2) probably yes, 3) probably no, 4) no,
50
51 169 and 5) no information. Responses to the questions provide the basis for judgement of the risk
52
53 170 of bias at each domain level using a tool-specific algorithm resulting in one out of three
54
55 171 possible judgements: 1) low risk of bias, 2) some concerns, or 3) high risk of bias. An overall
56
57 172 risk of bias score for each outcome in a study can be low (with a low risk of bias for all
58
59
60

1
2
3 173 domains), some concerns (if some concerns prevail in at least one domain without a high risk
4
5 174 of bias for any domain) or high (if a high risk of bias underpins at least one domain or some
6
7
8 175 concerns remain in multiple domains, defining multiple as more than two).
9

10 11 176 **Evidence Synthesis**

12
13
14 177 The overall evidence level in this review was determined using the Grading of
15
16 178 Recommendations, Assessment, Development and Evaluation (GRADE) tool considering the
17
18 179 following five domains: 1. risk of bias: high risk, some concerns, or low risk associated with
19
20 180 knee proprioception measures based on the Cochrane ROB 2 tool; 2. Inconsistency of
21
22 181 findings: similar or conflicting direction of effect, effect estimates and overlap of confidence
23
24 182 intervals for knee proprioception measures from different studies; 3. indirectness of evidence:
25
26 183 appropriateness of participants, interventions, and outcomes used to answer the review
27
28 184 question; 4. imprecision of results: the length of 95% confidence intervals of effect estimates
29
30 185 and overall sample (number of participants) from which effect estimates are derived; and
31
32 186 other domains: e.g. publication bias if applicable.²⁷ The overall evidence was rated as very
33
34 187 low, low, moderate or high.
35
36
37
38
39

40
41 188 A meta-analysis was precluded owing to clinical heterogeneity of interventions and outcome
42
43 189 measurements (JPS, TTDPm and QFC). For instance, despite seven studies targeting JPS, a
44
45 190 meta-analysis was not appropriate because at most two studies used the same method (active-
46
47 191 active,^{28,29} passive-passive^{30,31} or passive-active^{32,33}) but the starting and target angles and the
48
49 192 number of trials per each angle varied between these proprioception tests in the included
50
51 193 studies. Further, the neuromuscular training interventions, targeting JPS, widely varied
52
53 194 between studies²⁸⁻³⁴: closed kinetic chain exercises on a balance pad,³⁴ whole-body vibration
54
55 195 therapy (WBVT),^{29,30} motor control exercises for the lower limbs,³² backward walking on a
56
57 196 treadmill,³¹ Nintendo Wii Fit training,²⁸ and cross-education of strength training of the non-
58
59
60

1
2
3 197 injured leg along with standard rehabilitation.³³ Further, in addition to inconsistent findings
4
5 198 among the studies, a significant statistical heterogeneity ($I^2 > 60\%$) in a random-effects meta-
6
7 199 analysis was evident. Although meta-analyses were excluded, the Review Manager 5.3
8
9
10 200 software (the Cochrane Collaboration) was used to calculate between-group mean differences
11
12 201 (effect sizes) and their 95% confidence intervals for summarizing the findings for each
13
14 202 outcome of interest in Table 1.

17 18 203 **Patient and public involvement**

19
20
21 204 Neither patients nor public were involved.

23 24 205 **Results**

26 27 206 **Search Results**

28
29
30
31 207 Electronic databases search led to a total of 2706 articles (excluding duplicates: 2162). After
32
33 208 title and abstract screening, 22 articles were shortlisted for full-text screening and
34
35 209 subsequently nine articles met the inclusion criteria (Figure 1). Thirteen articles were
36
37 210 excluded owing to the following reasons: not an RCT ($n = 1$),³⁵ no knee-specific
38
39 211 proprioception tests ($n = 6$),³⁶⁻⁴¹ participants were without an ACL injury ($n = 1$),⁴² knee
40
41 212 proprioception data were missing and the corresponding author did not respond to our emails
42
43 213 ($n = 1$),⁴³ a comparison between different surgical intervention groups with same
44
45 214 rehabilitation program ($n = 2$),^{44,45} and lack of a neuromuscular rehabilitation training
46
47 215 program ($n = 2$).^{46,47} No additional relevant studies were identified through manual search of
48
49 216 bibliographic references.

50 51 52 53 54 55 217 **Study Design and Participants**

1
2
3 218 All the nine studies included were RCTs with a total of 386 participants and two studies had
4
5 219 their trial pre-registered in a clinical trial registry.^{31,33} All participants had undergone an ACL
6
7 220 reconstruction with a bone-patellar-tendon-bone or a hamstring graft (Table 1).
8
9

10 11 221 **Quality Assessment**

12
13
14 222 The agreement (Cohen's kappa) of responses to the signaling questions between the two
15
16 223 reviewers (AA and MB) was substantial (0.69 ± 0.047 , $p < 0.001$). Disagreements were
17
18 224 discussed and resolved by the two reviewers. Online supplemental figure 1 shows the
19
20 225 percentage of studies judged as low risk, some concerns and high risk of bias in the five
21
22 226 domains, and Table 2 shows domain judgements of each study. The overall risk of bias
23
24 227 judgement showed that four of the included studies had a high risk of bias,^{28,29,32,34} four had
25
26 228 some concerns,^{30,31,48,49} and one study³³ had a high risk of bias for JPS and some concerns for
27
28 229 quadriceps force control (QFC). The domain that most consistently showed risk of bias
29
30 230 across studies was bias in selection of the reported results (Online supplemental figure 1 and
31
32 231 Table 2). The most common reason was the absence of information regarding pre-specified
33
34 232 plan of analyses. None of the included studies reported trial protocol publication and only
35
36 233 two^{31,33} reported trial registration. Furthermore, two studies were judged to perform
37
38 234 inappropriate multiple analyses.^{28,29} Judgement of bias in measurement of the outcome
39
40 235 (domain 4, Table 2) showed most scattered results across studies (Online supplemental figure
41
42 236 1). A high risk of bias was found in three studies of which one had no information on
43
44 237 measurements³⁴ and two showed inappropriate measurement methods of the outcome of
45
46 238 interest.^{28,33} In the study by Zult et al., only one trial per target was performed to estimate
47
48 239 JPS,³³ while Baltaci et al. used a test with presumably a high demand on motor and memory
49
50 240 components,²⁸ without reporting its reliability or validity. The domain with least risk of bias
51
52 241 was missing outcome data where all studies, except one,³² had low risk of bias.
53
54
55
56
57
58
59
60

242 **Rehabilitation Programs**

243 The studies included a spectrum of rehabilitation programs employed to influence knee
244 proprioception (Table 1). Only one study by Baltaci et al. investigated the effects of using
245 feedback with an external focus in a simulated sport-specific gaming environment with
246 Nintendo Wii Fit compared to conventional rehabilitation.²⁸ On the contrary, the remaining
247 eight studies focused on having an internal focus (mainly related to the position of specific
248 body parts) for neuromuscular training. Two studies^{29,30} explored the effects of whole-body
249 vibration therapy (WBVT) combined with or without conventional rehabilitation compared to
250 conventional rehabilitation alone. Cho et al. compared closed kinetic chain exercises on a
251 balance pad versus on a stable floor.³⁴ Risberg et al. compared the effects of a NT compared
252 to strength training. In their neuromuscular program, the first half of the rehabilitation
253 focused on exercises on a wobble board or trampoline and exercises to increase the range of
254 motion, while the end of the program focused on specific training of plyometric, agility and
255 sport-specific skills.⁴⁸ Beynnon et al. evaluated the effects of accelerated (19 weeks) vs. non-
256 accelerated (32 weeks) programs of conventional training.⁴⁹ The timeframe and exercises in
257 their experimental program ranged from 1-7 weeks for range of motion and muscle
258 activation, 8-11 weeks for dynamic functional activities such as biking and jogging, and
259 finally, 12-19 weeks for plyometric and agility drill exercises.⁴⁹ Kaya et al. studied the effects
260 of neuromuscular (motor control) exercises for the lower limbs combined with standard
261 rehabilitation compared with standard rehabilitation alone.³² Shen et al. examined the
262 outcome of standard rehabilitation combined with backward walking at 1.3 km/h on a
263 treadmill for four groups (at four inclination angles 0°, 5°, 10°, and 15°, respectively)
264 compared to standard rehabilitation in a comparator group.³¹ Nevertheless, Zult et al.
265 examined the effects of cross-education of strength training of the non-injured leg along with
266 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
269 variable to evaluate the outcome.²⁸⁻³⁴ Conversely, one study used a computer program
270 (monitored-rehab-system-software) to define a virtual line/route to allow joint repositioning
271 within 30-70% knee range of motion with and without visual feedback.²⁸ The differences
272 between visual and blinded trials (2 each) based on the deviations from the computer-
273 generated line (in mm) were used to give information about the sense of proprioception.²⁸ All
274 these studies used sitting or supine test position for assessing JPS. There were two to four
275 predetermined target knee flexion angles across studies ranging from 15°-80°.²⁹⁻³⁴ Moreover,
276 two studies^{28,29} used active knee motion and four used passive knee motion³⁰⁻³³ to set the
277 target angle. Whether Cho et al. used active or passive knee motion to set/reproduce the
278 target angle seems ambiguous.³⁴ Four studies^{28,29,32-34} used active knee motion and two^{30,31}
279 used passive knee motion to reproduce the target angle. The JPS method used by Zult et al.
280 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 study³³ randomized
282 the order of the joint angles used. Eyes were blinded during the test in six studies²⁹⁻³⁴ while
283 one study used visual feedback when the individual was placing the knee joint in the target
284 angle but no such feedback was given during reproduction of the target angle.²⁸ The
285 difference between visual and non-visual trials was calculated in mm by the device as a
286 measure of JPS.²⁸ A Biodex dynamometer (Biodex Medical Systems, Shirley, NY, USA) was
287 used in five studies^{29,30,32-34} to test JPS. Even so, one study used a continuous passive motion
288 equipment³¹ while another²⁸ employed a functional squat system (Monitored Rehab System,
289 Haarlem, and the Netherlands) with a leg press machine and an associated computer program
290 for assessing JPS.

1
2
3 291 Three studies^{31,48,49} evaluated knee kinesthesia with the threshold to detect passive motion
4
5 292 (TTDPM) using a bespoke device,^{48,49} or a continuous passive motion equipment.³¹ The knee
6
7 293 joint was moved in flexion or extension at a constant angular velocity of 0.5°/s⁴⁸ or
8
9 294 0.1°/s.^{31,49} While the participants were blindfolded in two studies,^{31,49} the other study did not
10
11 295 mention about visual feedback.⁴⁸ In all three studies, the tests were performed three times in
12
13 296 each direction (flexion and/or extension) for both legs but whether the order of direction or
14
15 297 leg was randomized is not reported. In the study by Risberg et al.,⁴⁸ TTDPM data were
16
17 298 missing for 27 out of 74 participants because of device failure, which might lower the power
18
19 299 of the study.

300 *Effects of NT on Knee Proprioception in Individuals with ACLR*

301 There were conflicting findings among the included studies for the effects of NT on
302 improving JPS, TTDPM and QFC. Overall, mean differences between groups indicated
303 inconsistent findings with an increase or decrease of JPS angular errors (one or more target
304 angles) by $\leq 2^\circ$, TTDPM by $\leq 1.5^\circ$, and QFC (concentric/eccentric/isometric contractions) by
305 ≤ 6 Nm following neuromuscular training.

306 Of the nine included articles, four reported reduction in JPS angular errors of ACLR knee at
307 one or more target angles (JPS at 45° but not 15°³⁴; JPS at 60° but not 30°²⁹; JPS at 15°, 45°,
308 75°³²; JPS 20°, 50°, 80°³¹) and/or contralateral non-injured knee (JPS at 30° and 60°²⁹)
309 favoring the NT group (exercises on a balance pad³⁴, whole-body vibration therapy²⁹,
310 neuromotor control exercises³² or backward treadmill walking³¹). Shen et al. also reported
311 improved TTDPM following backward treadmill walking.³¹ When we calculated mean
312 differences for author-reported post-operative^{29,32} or change (pre- vs. post-intervention)
313 scores³⁴ between groups for the ACLR leg with the Review Manager 5.3 software (the
314 Cochrane Collaboration), their 95% confidence intervals revealed no effects (see Table 1).

1
2
3 315 Moreover, the remaining five studies did not report significant differences in proprioception
4
5 316 between groups.^{28,30,33,48,49}
6
7
8

9 317 **Assessing Certainty in Evidence**

10
11
12 318 There were serious concerns with three GRADE domains (risk of bias, indirectness, and
13
14 319 imprecision associated with the findings) across the seven studies that measured JPS (Tables
15
16 320 3 and 4). The certainty of evidence found was very low for the effects of NT on improving
17
18 321 JPS following ACLR.
19
20
21

22 322 There were further serious concerns with all GRADE domains (risk of bias, inconsistency,
23
24 323 indirectness, and imprecision associated with the findings) across the three studies measuring
25
26 324 TTDP (Tables 3 and 4). Therefore, the certainty of evidence found was very low for
27
28 325 improving TTDP in individuals with ACLR following NT (Table 3).
29
30
31

32 326 An overall judgement of some concerns based on the Cochrane ROB 2 tool (Table 2) was
33
34 327 found for the study reporting changes in QFC following NT.³³ Available population, the
35
36 328 magnitude and direction of effect, and effect estimates of QFC (Tables 1 and 3) are derived
37
38 329 from only one study which reflect serious concerns. However, the participants with ACLR,
39
40 330 intervention (cross-education of the quadriceps with standard rehabilitation), and QFC³³ are
41
42 331 directly related to our research question. The certainty of evidence found was very low for
43
44 332 improving QFC in individuals with ACLR following NT because only one relevant study was
45
46 333 found.
47
48
49
50

51 334 **Discussion**

52
53
54 335 This review is the first, as far as we are aware, to address effects of neuromuscular
55
56 336 rehabilitation training on knee proprioception in individuals with ACL injury. A previous
57
58 337 review, however, summarized the effects of proprioceptive and balance exercises following
59
60

1
2
3 338 ACL injury/reconstruction on certain outcome measures (muscle strength, hop test, etc.) but
4
5 339 other than knee-specific proprioception tests.⁵¹ Another similar review did not find any RCTs
6
7 340 in this area.⁵² We identified nine studies employing a range of NT methods, of which all but
8
9 341 one⁴⁸ were published within the past decade. Nevertheless, there were serious concerns with
10
11 342 two or more GRADE domains (risk of bias, inconsistency, indirectness, or imprecision
12
13 343 associated with the findings) across studies implying a very low certainty of evidence for
14
15 344 improving JPS, TTDPM, and QFC of ACLR knee following NT.
16
17
18
19

20 345 *Effects of NT on Knee Proprioception in Individuals with ACLR*

21
22
23 346 Most of the employed NT programs did not influence proprioception compared to
24
25 347 comparator interventions. Potential reasons for insignificant between-group differences
26
27 348 include: 1) experimental and comparator programs (with exercises that are wholly or partly
28
29 349 similar) which potentially might stimulate similar effects on proprioception in both
30
31 350 programs;^{28,30,32,34,48,49} 2) the exercises did not adequately stimulate proprioception sense;³³ 3)
32
33 351 a lack of proprioception deficit following ACL injury (TTDPM similar between ACL-injured
34
35 352 and contralateral uninjured knee⁴⁹); 4) a lack of valid, sensitive and responsive knee-specific
36
37 353 proprioception test methods; 5) a short follow-up period (a follow-up at least 18 months post-
38
39 354 ACLR might be needed to regain proprioceptive function⁵³) in most studies except two
40
41 355 studies;^{32,49} 6) type II errors arising from low sample sizes in most studies (with missing
42
43 356 power or sample size calculations); and 7) adherence rates of participants to the prescribed
44
45 357 program (only three studies have explicitly reported adherence rates to training
46
47 358 sessions/exercises [Table 1]).^{30,48,49} The heterogeneity of interventions, methodological
48
49 359 limitations, inconsistency in the magnitude and direction of effects, and imprecision of effect
50
51 360 estimates, found in this review, preclude recommendation of one optimal NT intervention for
52
53 361 improving proprioception following ACL injury in clinical practice.
54
55
56
57
58
59
60

362 ***Risk of Bias in the Included Studies***

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

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

372 All studies used absolute angular error (AAE) for measuring JPS acuity which represents a
373 task-oriented approach to studying performance skill, in contrast to a process-orientation in
374 which underlying processes are in focus. The inconsistency in performance, i.e., response
375 variability (variable error), may reflect noise in sensory signal and its processing⁵⁶ and thus
376 be a more process-oriented outcome than AAE. To understand possible underlying
377 mechanisms, it would be advantageous to combine task- and process-oriented measures.

378 In general, method descriptions of proprioception tests were short and, in some studies,
379 deficient, lacking information about factors that could influence the results. One such factor
380 was randomization of the order of target positions (cf. Zult et al.),³³ which is required to
381 minimize the effect of memory and reduce motor elements of the test. This is particularly
382 applicable in tests with active positioning, which was the case for most studies, enabling
383 central motor programs.⁵⁷ Inadequate reporting of the proprioception tests would hinder their
384 replication and raise risk of bias rating. Moreover, Kaya et al. reported only post-intervention
385 JPS scores, precluding baseline scores, despite claiming their study to be an RCT.³²

1
2
3 386 Among seven RCTs²⁸⁻³⁴ investigating changes in JPS following NT, five RCTs were found to
4
5 387 have a high risk of bias while the remaining two studies have some concerns based on the
6
7
8 388 Cochrane ROB 2 tool (Table 2). Therefore, included RCTs have been judged to have very
9
10 389 serious methodological limitations in the GRADE evidence synthesis.
11

13 390 *Mechanisms Underpinning NT Following ACLR*

16 391 Two of the included studies evaluated the effects of WBVT;^{29,30} however, only one found a
17
18 392 favorable effect on proprioception (JPS – target angle 60°).²⁹ Two factors may contribute to
19
20 393 the different findings between these studies. First, time point at which WBVT was given: Fu
21
22 394 et al. employed WBVT at one-month post-ACLR for 2 months and evaluated JPS at 3 and 6
23
24 395 months after the surgery (Table 2).³⁰ On the other hand, Moezy et al. gave WBVT at 3
25
26 396 months post-ACLR for one-month and assessed JPS at 4 months after the surgery.²⁹ It seems
27
28 397 starting WBVT at 3 months, rather than at one-month, post-ACLR might have better on
29
30 398 improving knee JPS. Second, the use of active²⁹ or passive³⁰ knee movement when testing
31
32 399 JPS. Active tests stimulate both joint and muscle-tendon mechanoreceptors and induce alpha-
33
34 400 gamma co-activation while passive tests assess joint receptors to a higher degree^{10,58} which
35
36 401 potentially could mean a higher sensitivity of the active test.
37
38 402 WBVT has shown effects on body posture, flexibility, proprioception (TTDPM in patients
39
40 403 with osteoarthritis), coordination and muscle power.⁵⁹⁻⁶¹ It has been promoted as an effective
41
42 404 method to induce a reflex muscle contraction in subjects with difficulties to evoke voluntary
43
44 405 contractions.⁶² The mechanism behind the improvements can be that the mechanical stimuli
45
46 406 stimulate primary endings of muscle spindles, especially type II fibers, which activate a-
47
48 407 motor neurons. This could potentially stimulate central motor command, which facilitates
49
50 408 increased muscle activation and voluntary movements.⁵⁹
51
52
53
54
55
56
57
58
59
60

1
2
3 409 Cho et al. showed a significant effect on knee proprioception (JPS and TTDPM) with closed
4
5 410 kinetic chain exercises on a balance pad/board.³⁴ Exercises on a balance board are widely
6
7 411 used to improve proprioception.^{38,51} In this review, a few NT programs included, amongst
8
9 412 other exercises, balance training with or without a balance pad/board.^{28,32,34,48,49} Additionally,
10
11 413 one study claimed backward walking, a closed kinematic chain exercise, to stimulate
12
13 414 joint/muscle receptors and sensory afferents to the CNS and augment proprioceptive and
14
15 415 balance training.³¹ Among these studies, all but one,³¹ did not show significant mean
16
17 416 differences between groups in proprioception calculated using the Review Manager 5.3
18
19 417 software (the Cochrane Collaboration) (see Table 1 and supplementary files). Different
20
21 418 designs and levels of difficulty of the execution were found (e.g. a simple static balance task
22
23 419 [with and without visual input], dynamic exercises performed on the balance board,
24
25 420 backward walking on a treadmill, etc.).
26
27
28
29
30
31 421 There is a challenge to transfer the rehabilitation in the clinic to automatic movements
32
33 422 required for athletic activities.^{18,63} Wii Fit or similar games have the potential to combine
34
35 423 feedback with an external focus in a sport-specific environment,²⁸ supporting the use of such
36
37 424 training tools. However, a study on Nintendo Wii Fit training did not support its use for
38
39 425 improving knee proprioception following ACLR.²⁸ Newer technology with stroboscopic
40
41 426 eyewear might have the potential to decrease visual input without fully occluding it, making
42
43 427 it possible to use them in sport specific rehabilitation. To prepare the individual for complex
44
45 428 athletic environments and reduce re-injury risk, rehabilitation might focus on NT with
46
47 429 reduced demands on visual inputs and enhance automatic movement control with cognitive
48
49 430 demands included.¹⁸ Whether such NT training improves knee proprioception and, how this
50
51 431 should be assessed in the best way,¹³ are yet to be determined.
52
53
54
55
56
57

58 432 ***The Ability of Tests to Discern Changes in Proprioception Following NT***
59
60

1
2
3 433 There is neither a gold standard proprioception test (targeting JPS, kinesthesia, force sense)
4
5 434 nor a standard procedure with established psychometric properties to test each proprioception
6
7 435 sense following ACL injury. In this review, JPS and TTDPM were commonly reported. The
8
9 436 Ruffini and Golgi receptors are slow-adapting receptors, responding to a change in joint
10
11 437 position. Nevertheless, the Pacinian receptors that respond to low degrees of joint stress are
12
13 438 more sensitive to rapid changes in accelerations and contribute to a low TTDPM.^{2,64} JPS has
14
15 439 been reported to detect a greater difference in knee proprioception than TTDPM following an
16
17 440 ACL injury.² However, our findings remain equivocal regarding the outcomes of JPS or
18
19 441 TTDPM following NT.

20
21
22
23
24 442 Knee-specific proprioception tests provide an indirect measure of proprioception involving
25
26 443 the process of the CNS.¹⁰ Psychosocial factors,⁶⁵ pain and preinjury motor skills may
27
28 444 influence the central mechanisms and the outcome of such tests following NT. Knee-specific
29
30 445 proprioception tests are designed to exclude motor skills, but how successful that exclusion
31
32 446 works, remains unclear.

33 34 35 36 37 447 ***Limitations and Future Recommendations***

38
39
40 448 The nine included studies looked at only individuals with ACLR but not those managed
41
42 449 conservatively following ACL injury. Owing to clinical heterogeneity of interventions and
43
44 450 outcome measurements, meta-analyses were precluded from the GRADE evidence synthesis.

45
46
47 451 The included studies had methodological limitations (high risk of bias or some concerns) and
48
49 452 all, but two studies,^{31,33} had not pre-registered/published their protocol. There is a need for
50
51 453 high quality RCTs with low risk of bias in this area.

52
53
54 454 Grey literature was not included in the current review which could be seen as a limitation.

55
56
57 455 The most common reason for exclusion of clinical trials in this review was that they did not
58
59 456 evaluate the effects of NT following ACLR with a knee-specific proprioception test. Perhaps,

1
2
3 457 the lack of consensus regarding the most appropriate, valid, reliable and responsive
4
5 458 proprioception tests, number of target angles or most responsive target angles (low vs. high)
6
7
8 459 might have precluded such outcomes in these studies. Therefore, psychometric properties of
9
10 460 such tests must be established.¹³
11
12

13 461 When designing rehabilitation programs with long-term follow-up, aberrations in neuromotor
14
15 462 control as well as neuroplastic changes should preferably be addressed. To reflect a wide
16
17 463 spectrum of individual impairments, further research should investigate differences in
18
19 464 individuals with ACL injuries managed with surgical (graft types) or conservative treatment,
20
21 465 both sexes, athletes and non-athletes of different ages. Future studies might assess
22
23 466 neuromotor control in functional tasks rather than relying on knee-specific proprioception
24
25 467 tests, given the challenges of isolating the proprioceptive ability.
26
27
28
29

30 468 **Conclusion**

31
32
33 469 The existing nine studies on individuals with an ACL reconstruction using heterogeneous
34
35 470 interventions and knee-specific proprioception measures revealed a very low certainty in
36
37 471 current evidence for employing NT programs to improve knee proprioception. The GRADE
38
39 472 evidence synthesis revealed a high risk of bias or some concerns, indirect evidence,
40
41 473 conflicting findings, and imprecision of effect estimates in the included studies. Well-
42
43 474 designed RCTs with homogenous populations (having ACL injury managed with or without
44
45 475 reconstruction), novel/well-designed NT interventions, and valid proprioception measures are
46
47 476 warranted to substantiate conclusive evidence in this area.
48
49
50

51 477 **Contributors**

52
53
54 478 AA and CKH conceived the idea of the project. AA, MB, SM and CKH were responsible for
55
56 479 designing the review and conceptualising the initial review protocol. AA led the writing
57
58
59
60

1
2
3 480 of the manuscript. MB, SM and CKH contributed to writing the manuscript. AA, MB and
4
5 481 CKH have reviewed and revised the manuscript for intellectual content. All authors approved
6
7 482 the final version of the manuscript. AA is the guarantor of this work.
8
9

10 483 **Funding**

11
12 484 The work was supported by the Swedish Research Council (2017-00892); Region
13
14 485 Västerbotten (ALF 7003575; Strategic funding VLL-358901; Project. No. 7002795); the
15
16 486 Swedish Research Council for Sports Science (CIF P2019 0068); and King Gustaf V and
17
18 487 Queen Victoria's Foundation of Freemasons 2019 (Häger). The funders were not involved in
19
20 488 the conception, design, execution and writing of the review.
21
22

23 489 **Data availability statement**

24
25 490 All data relevant to the study are included in the article or uploaded as supplementary
26
27 491 information. A detailed protocol of the review has been registered in PROSPERO
28
29 492 (CRD42018107349).
30
31

32 493 **Competing interests**

33
34 494 None declared.
35
36

37 495 **Patient consent for publication**

38
39 496 Not required.
40
41

42 497
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

498 **Figure caption**

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

501

For peer review only

502 **References**

503

- 504 1. Kapreli E, Athanasopoulos S, Gliatis J, et al. Anterior Cruciate Ligament Deficiency
505 Causes Brain Plasticity: A Functional MRI Study. *Am J Sports Med.*
506 2009;37(12):2419-2426.
- 507 2. Relph N, Herrington L, Tyson S. The effects of ACL injury on knee proprioception: a
508 meta-analysis. *Physiotherapy.* 2014;100(3):187-195.
- 509 3. Sanders TL, Maradit Kremers H, Bryan AJ, et al. Incidence of anterior cruciate
510 ligament tears and reconstruction: a 21-year population-based study. *Am J Sports*
511 *Med.* 2016;44(6):1502-1507.
- 512 4. Kobayashi H, Kanamura T, Koshida S, et al. Mechanisms of the anterior cruciate
513 ligament injury in sports activities: a twenty-year clinical research of 1,700 athletes. *J*
514 *Sports Sci Med.* 2010;9(4):669-675.
- 515 5. Johnston JT, Mandelbaum BR, Schub D, et al. Video analysis of anterior cruciate
516 ligament tears in professional American football athletes. *Am J Sports Med.*
517 2018;46(4):862-868.
- 518 6. Acevedo RJ, Rivera-Vega A, Miranda G, Micheo W. Anterior cruciate ligament
519 injury: identification of risk factors and prevention strategies. *Curr Sports Med Rep.*
520 2014;13(3):186-191.
- 521 7. Ardern CL, Taylor NF, Feller JA, Whitehead TS, Webster KE. Sports participation 2
522 years after anterior cruciate ligament reconstruction in athletes who had not returned
523 to sport at 1 year: a prospective follow-up of physical function and psychological
524 factors in 122 athletes. *Am J Sports Med.* 2015;43(4):848-856.
- 525 8. Gao F, Zhou J, He C, et al. A Morphologic and Quantitative Study of
526 Mechanoreceptors in the Remnant Stump of the Human Anterior Cruciate Ligament.
527 *Arthroscopy.* 2016;32(2):273-280.
- 528 9. Dhillon MS, Bali K, Prabhakar S. Differences among mechanoreceptors in healthy
529 and injured anterior cruciate ligaments and their clinical importance. *Muscles*
530 *Ligaments Tendons J.* 2012;2(1):38-43.
- 531 10. Røijezon U, Clark NC, Treleaven J. Proprioception in musculoskeletal rehabilitation.
532 Part 1: Basic science and principles of assessment and clinical interventions. *Man*
533 *Ther.* 2015;20(3):368-377.
- 534 11. Kapreli E, Athanasopoulos S. The anterior cruciate ligament deficiency as a model of
535 brain plasticity. *Med Hypotheses.* 2006;67(3):645-650.
- 536 12. Nakamae A, Adachi N, Ishikawa M, Nakasa T, Ochi M. No evidence of impaired
537 proprioceptive function in subjects with anterior cruciate ligament reconstruction: a
538 systematic review. *J ISAKOS.* 2017;2(4):191.

- 1
2
3 539 13. Arumugam A, Strong A, Tengman E, Røijezon U, Häger CK. Psychometric
4 540 properties of knee proprioception tests targeting healthy individuals and those with
5 541 anterior cruciate ligament injury managed with or without reconstruction: a
6 542 systematic review protocol. *BMJ Open*. 2019;9(4):e027241.
- 8
9 543 14. Stensdotter AK, Tengman E, Olofsson LB, Häger C. Deficits in single-limb stance
10 544 more than 20 years after ACL injury. *Europ J Physiother*. 2013;15(2):78-85.
- 12 545 15. Fukunaga T, Johnson CD, Nicholas SJ, McHugh MP. Muscle hypotrophy, not
13 546 inhibition, is responsible for quadriceps weakness during rehabilitation after anterior
14 547 cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*.
15 548 2019;27(2):573-579.
- 18 549 16. Zebis MK, Andersen LL, Bencke J, Kjaer M, Aagaard P. Identification of athletes at
19 550 future risk of anterior cruciate ligament ruptures by neuromuscular screening. *Am J*
20 551 *Sports Med*. 2009;37(10):1967-1973.
- 22 552 17. Grooms DR, Page SJ, Nichols-Larsen DS, Chaudhari AM, White SE, Onate JA.
23 553 Neuroplasticity Associated With Anterior Cruciate Ligament Reconstruction. *J*
24 554 *Orthop Sports Phys Ther*. 2017;47(3):180-189.
- 26 555 18. Grooms D, Appelbaum G, Onate J. Neuroplasticity Following Anterior Cruciate
27 556 Ligament Injury: A Framework for Visual-Motor Training Approaches in
28 557 Rehabilitation. *J Orthop Sports Phys Ther*. 2015;45(5):381-393.
- 31 558 19. Clark NC, Røijezon U, Treleaven J. Proprioception in musculoskeletal rehabilitation.
32 559 Part 2: clinical assessment and intervention. *Man Ther*. 2015;20(3):378-387.
- 34 560 20. Risberg MA, Mork M, Jenssen HK, Holm I. Design and implementation of a
35 561 neuromuscular training program following anterior cruciate ligament reconstruction. *J*
36 562 *Orthop Sports Phys Ther*. 2001;31(11):620-631.
- 38 563 21. Moutzouri M, Gleeson N, Billis E, Panoutsopoulou I, Gliatis J. What is the effect of
39 564 sensori-motor training on functional outcome and balance performance of patients'
40 565 undergoing TKR? A systematic review. *Physiotherapy*. 2016;102(2):136-144.
- 43 566 22. Ordahan B, Kucuksen S, Tuncay I, Salli A, Ugurlu H. The effect of proprioception
44 567 exercises on functional status in patients with anterior cruciate ligament
45 568 reconstruction. *J Back Musculoskelet Rehabil*. 2015;28(3):531-537.
- 47 569 23. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009).
49 570 Preferred reporting items for systematic reviews and meta-analyses: the PRISMA
50 571 statement. *PLoS med*. 2009;6:e1000097.
- 52 572 24. Campbell M, McKenzie JE, Sowden A, et al. Synthesis without meta-analysis
53 573 (SWiM) in systematic reviews: reporting guideline. *BMJ*. 2020;368.
- 55 574 25. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi SJBhsr.
56 575 PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three
57 576 search tools for qualitative systematic reviews. *BMC Health Serv Res*.
58 577 2014;14(1):579.
- 60

- 1
2
3 578 26. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias
4 579 in randomised trials. *BMJ*. 2019;366.
- 6 580 27. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating
7 581 quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
- 10 582 28. Baltaci G, Harput G, Haksever B, Ulusoy B, Ozer H. Comparison between Nintendo
11 583 Wii Fit and conventional rehabilitation on functional performance outcomes after
12 584 hamstring anterior cruciate ligament reconstruction: prospective, randomized,
13 585 controlled, double-blind clinical trial. *Knee Surg Sports Traumatol Arthrosc*.
14 586 2013;21(4):880-887.
- 16 587 29. Moezy A, Olyaei G, Hadian M, Razi M, Faghihzadeh S. A comparative study of
17 588 whole body vibration training and conventional training on knee proprioception and
18 589 postural stability after anterior cruciate ligament reconstruction. *Br J Sports Med*.
20 590 2008;42(5):373-385.
- 22 591 30. Fu CLA, Yung SHP, Law KYB, et al. The Effect of Early Whole-Body Vibration
23 592 Therapy on Neuromuscular Control After Anterior Cruciate Ligament
24 593 Reconstruction: A Randomized Controlled Trial. *Am J Sports Med*. 2013;41(4):804-
25 594 814.
- 28 595 31. Shen M, Che S, Ye D, Li Y, Lin F, Zhang Y. Effects of backward walking on knee
29 596 proprioception after ACL reconstruction. *Physiother Theory Pract*. 2019.
- 31 597 32. Kaya D, Guney-Deniz H, Sayaca C, Calik M, Doral MN. Effects on Lower Extremity
32 598 Neuromuscular Control Exercises on Knee Proprioception, Muscle Strength, and
33 599 Functional Level in Patients with ACL Reconstruction. *Biomed Res Int*. 2019:1-7.
- 35 600 33. Zult T, Gokeler A, van Raay J, et al. Cross-education does not accelerate the
36 601 rehabilitation of neuromuscular functions after ACL reconstruction: a randomized
37 602 controlled clinical trial. *Eur J Appl Physiol*. 2018;118(8):1609-1623.
- 40 603 34. Cho SH, Bae CH, Gak HB. Effects of closed kinetic chain exercises on
41 604 proprioception and functional scores of the knee after anterior cruciate ligament
42 605 reconstruction. *J Phys Ther Sci*. 2013;25(10):1239-1241.
- 44 606 35. Laboute E, Verhaeghe E, Ucay O, Minden A. Evaluation kinaesthetic proprioceptive
45 607 deficit after knee anterior cruciate ligament (ACL) reconstruction in athletes. *J Exp*
46 608 *Orthop*. 2019;6(1).
- 49 609 36. Feil S, Newell J, Minogue C, Paessler HH. The effectiveness of supplementing a
50 610 standard rehabilitation program with, superimposed neuromuscular electrical
51 611 stimulation after anterior cruciate ligament reconstruction. *Am J Sports Med*.
52 612 2011;39(6):1238-1247.
- 54 613 37. Ihara H, Nakayama A. Dynamic joint control training for knee ligament injuries. / L'
55 614 entrainement au controle dynamique de l' articulation dans le cas des traumatismes
56 615 ligamentaires du genou. *Am J Sports Med*. 1986;14(4):309-315.

- 1
2
3 616 38. Vathrakokilis K, Malliou P, Gioftsidou A, Beneka A, Godolias G. Effects of a
4 617 balance training protocol on knee joint proprioception after anterior cruciate ligament
5 618 reconstruction. *J Back Musculoskelet Rehabil.* 2008;21(4):233-237.
- 7 619 39. Saha S, Adhya B, Dhillon MS, Saini A. A Study on the Role of Proprioceptive
8 620 Training in Non Operative ACL Injury Rehabilitation. *Indian J Physiother Occup*
9 621 *Ther.* 2015;9(3):226-231.
- 12 622 40. Lim J-M, Cho J-J, Kim T-Y, Yoon B-C. Isokinetic knee strength and proprioception
13 623 before and after anterior cruciate ligament reconstruction: A comparison between
14 624 home-based and supervised rehabilitation. *J Back Musculoskelet Rehabil.*
15 625 2019;32(3):421-429.
- 18 626 41. Liu-Ambrose T, Taunton JE, MacIntyre D, McConkey P, Khan KM. The effects of
19 627 proprioceptive or strength training on the neuromuscular function of the ACL
20 628 reconstructed knee: a randomized clinical trial. *Scand J Med Sci Sports.*
21 629 2003;13(2):115-123.
- 23 630 42. Lee SJ, Ren Y, Chang AH-I, Geiger F, Zhang L-Q. Effects of pivoting neuromuscular
24 631 training on pivoting control and proprioception. *Med Sci Sports Exerc.*
25 632 2014;46(7):1400-1409.
- 28 633 43. Peultier-Celli L, Mainard D, Wein F, et al. Comparison of an innovative
29 634 rehabilitation, combining reduced conventional rehabilitation with balneotherapy, and
30 635 a conventional rehabilitation after anterior cruciate ligament reconstruction in
31 636 athletes. *Front Surg.* 2017;4:61.
- 33 637 44. Faggal MS, Abdelsalam MS, Adel Elhakk SM, Mahmoud NF. Proprioceptive training
34 638 after ACL reconstruction: Standard versus stump preservation technique. *Physiother*
35 639 *Pract Res.* 2019;40(1):69-75.
- 38 640 45. San Martín-Mohr C, Cristi-Sánchez I, Pincheira PA, Reyes A, Berral FJ, Oyarzo C.
39 641 Knee sensorimotor control following anterior cruciate ligament reconstruction: A
40 642 comparison between reconstruction techniques. *PLoS One.* 2018;13(11):e0205658.
- 42 643 46. Büyükturan Ö, Büyükturan B, Kurt EE, Yetis M. Effects of Tai Chi on partial anterior
43 644 cruciate ligament injury: A single-blind, randomized-controlled trial. *Turk J Phys*
44 645 *Med Rehabil.* 2019;65(2):160-168.
- 46 646 47. Wang L. Immediate effects of neuromuscular joint facilitation intervention after
47 647 anterior cruciate ligament reconstruction. *J Phys Ther Sci.* 2016;28(7):2084-2087.
- 50 648 48. Risberg MA, Holm I, Myklebust G, Engebretsen L. Neuromuscular training versus
51 649 strength training during first 6 months after anterior cruciate ligament reconstruction:
52 650 a randomized clinical trial. *Phys Ther.* 2007;87(6):737-750.
- 54 651 49. Beynnon BD, Johnson RJ, Naud S, et al. Accelerated versus nonaccelerated
55 652 rehabilitation after anterior cruciate, ligament reconstruction: A prospective,
56 653 randomized, double-blind investigation evaluating knee joint laxity using roentgen,
57 654 stereophotogrammetric analysis. *Am J Sports Med.* 2011;39(12):2536-2548.

- 1
2
3 655 50. Hortobágyi T, Garry J, Holbert D, Devita P. Aberrations in the control of quadriceps
4 656 muscle force in patients with knee osteoarthritis. *Arthritis Care Res.* 2004;51(4):562-
5 657 569.
- 7 658 51. Cooper RL, Taylor NF, Feller JA. A systematic review of the effect of proprioceptive
8 659 and balance exercises on people with an injured or reconstructed anterior cruciate
9 660 ligament. *Res Sports Med.* 2005;13(2):163-178.
- 11 661 52. Baltaci G, Kohl HW. Does proprioceptive training during knee and ankle
12 662 rehabilitation improve outcome? *Phys Ther Rev.* 2003;8(1):5-16.
- 14 663 53. Iwasa J, Ochi M, Adachi N, Tobita M, Katsube K, Uchio Y. Proprioceptive
15 664 improvement in knees with anterior cruciate ligament reconstruction. *Clin Orthop*
16 665 *Relat Res.* 2000(381):168-176.
- 18 666 54. Han J, Waddington G, Adams R, Anson J, Liu Y. Assessing proprioception: A critical
19 667 review of methods. *J Sport Health Sci.* 2016;5(1):80-90.
- 21 668 55. Selfe J, Callaghan M, McHenry A, Richards J, Oldham J. An investigation into the
22 669 effect of number of trials during proprioceptive testing in patients with patellofemoral
23 670 pain syndrome. *J Orthop Res.* 2006;24(6):1218-1224.
- 25 671 56. van Beers RJ, Sittig AC, van der Gon Denier JJ. How humans combine simultaneous
26 672 proprioceptive and visual position information. *Exp Brain Res.* 1996;111(2):253-261.
- 28 673 57. Gandevia SC, Burke D. Does the nervous system depend on kinesthetic information
29 674 to control natural limb movements? *Behav Brain Sci.* 1992;15:614-614.
- 31 675 58. Clark NC, Akins JS, Heebner NR, et al. Reliability and measurement precision of
32 676 concentric-to-isometric and eccentric-to-isometric knee active joint position sense
33 677 tests in uninjured physically active adults. *Phys Ther Sport.* 2016;18:38-45.
- 35 678 59. Avelar NC, Costa SJ, da Fonseca SF, et al. The effects of passive warm-up vs. whole-
36 679 body vibration on high-intensity performance during sprint cycle exercise. *J Strength*
37 680 *Cond Res.* 2012;26(11):2997-3003.
- 39 681 60. Chow DHK, Lee TY, Pope MH. Effects of whole body vibration on spinal
40 682 proprioception in healthy individuals. *Work.* 2018.
- 42 683 61. Trans T, Aaboe J, Henriksen M, Christensen R, Bliddal H, Lund H. Effect of whole
43 684 body vibration exercise on muscle strength and proprioception in females with knee
44 685 osteoarthritis. *Knee.* 2009;16(4):256-261.
- 46 686 62. Herrero AJ, Menendez H, Gil L, et al. Effects of whole-body vibration on blood flow
47 687 and neuromuscular activity in spinal cord injury. *Spinal cord.* 2011;49(4):554-559.
- 49 688 63. Benjaminse A, Gokeler A, Dowling AV, et al. Optimization of the anterior cruciate
50 689 ligament injury prevention paradigm: novel feedback techniques to enhance motor
51 690 learning and reduce injury risk. *J Orthop Sports Phys Ther.* 2015;45(3):170-182.
- 53
54
55
56
57
58
59
60

- 1
2
3 691 64. Ochi M, Iwasa J, Uchio Y, Adachi N, Sumen Y. The regeneration of sensory
4 692 neurones in the reconstruction of the anterior cruciate ligament. *J Bone Joint Surg Br.*
5 693 1999;81(5):902-906.
6
7
8 694 65. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience
9 695 education on musculoskeletal pain: A systematic review of the literature. *Physiother*
10 696 *Theory Pract.* 2016;32(5):332-355.
11
12 697
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

698 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]

Beynon 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:

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

6/bmjopen-2021-049226 on 18 May 2024. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16</p>	<p>however, one participant who performed <26 sessions was excluded from analysis after week 26</p>	<p>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° knee flexion); Outcome measure: force accuracy (absolute error) determined over the terminal 3 s data for isometric trials (65° knee flexion) and over the middle 2 s data for concentric and eccentric trials.</p>	<p>Isometric: 1.00 [-0.76, 2.76]</p>
---	--	--	---

17 699 ^aIncluded in analysis;

18 700 ^bCalculated with Review Manager (RevMan) 5.3 (The Cochrane Collaboration 2014, Nordic Cochrane Centre, Copenhagen, Denmark);

19 701 ^cMean difference between groups were calculated based on post-intervention/final follow-up scores reported by the authors;

20 702 ^dDifference between four intervention groups and the comparator group were same and so only one comparison is presented.

21 703 ^eMean difference between groups were calculated based on change scores from baseline (pre- vs. post-intervention) reported by the authors;

22 704 ^fQuadriceps force accuracy; both legs (within each group) showed improved force control (22–34%) at 26 weeks post-surgery ($p < 0.050$)
23 705 according to the authors;

24 706 ^gJPS method has been presumed based on authors' reference to the method employed by Hortobagyi et al.⁵⁰;

25 707 ACLR - anterior cruciate ligament reconstruction, Int – intervention group; com – comparator group; JPS - joint position sense, NR- not
26 708 reported, TTDPM - threshold to detection of passive motion, min. - minutes, reps – repetitions.
27 709

710 **Table 2. Risk of bias assessment of included studies according to the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) -**
 711 **judgements in five domains and an overall judgement using the descriptors of low risk of bias (low), some concerns, and high risk of bias**
 712 **(High).**
 713

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

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

715

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

Certainty assessment							N ^o of patients		Certainty
N ^o 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 ^c	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.

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 intervention 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 one⁴¹ 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 one³¹ reported significant effects which is evident with their confidence intervals (see Table 1). However, Shen 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

1
2
3 724 no significant effects on TTDPM. Therefore, we judged the evidence to have serious
4 725 imprecision.
5 726
6 **Other** 727 As both negative and positive findings have been published, and a comprehensive
7 **considerations** 728 search for RCTs has been done, we did not suspect a publication bias.
8
9 729
10 730
11 731

None

12 732 ACLR - anterior cruciate ligament reconstruction, RCTs – randomized controlled trials, ROB – risk of bias
13 733

For peer review only

6/bmjopen-2021-049226 on 18 May 2021. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

734 **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

735

1136/bmjopen-2021-049226 on 18 May 2021. Downloaded from <http://bmjopen.bmj.com/> by guest. Protected by copyright.

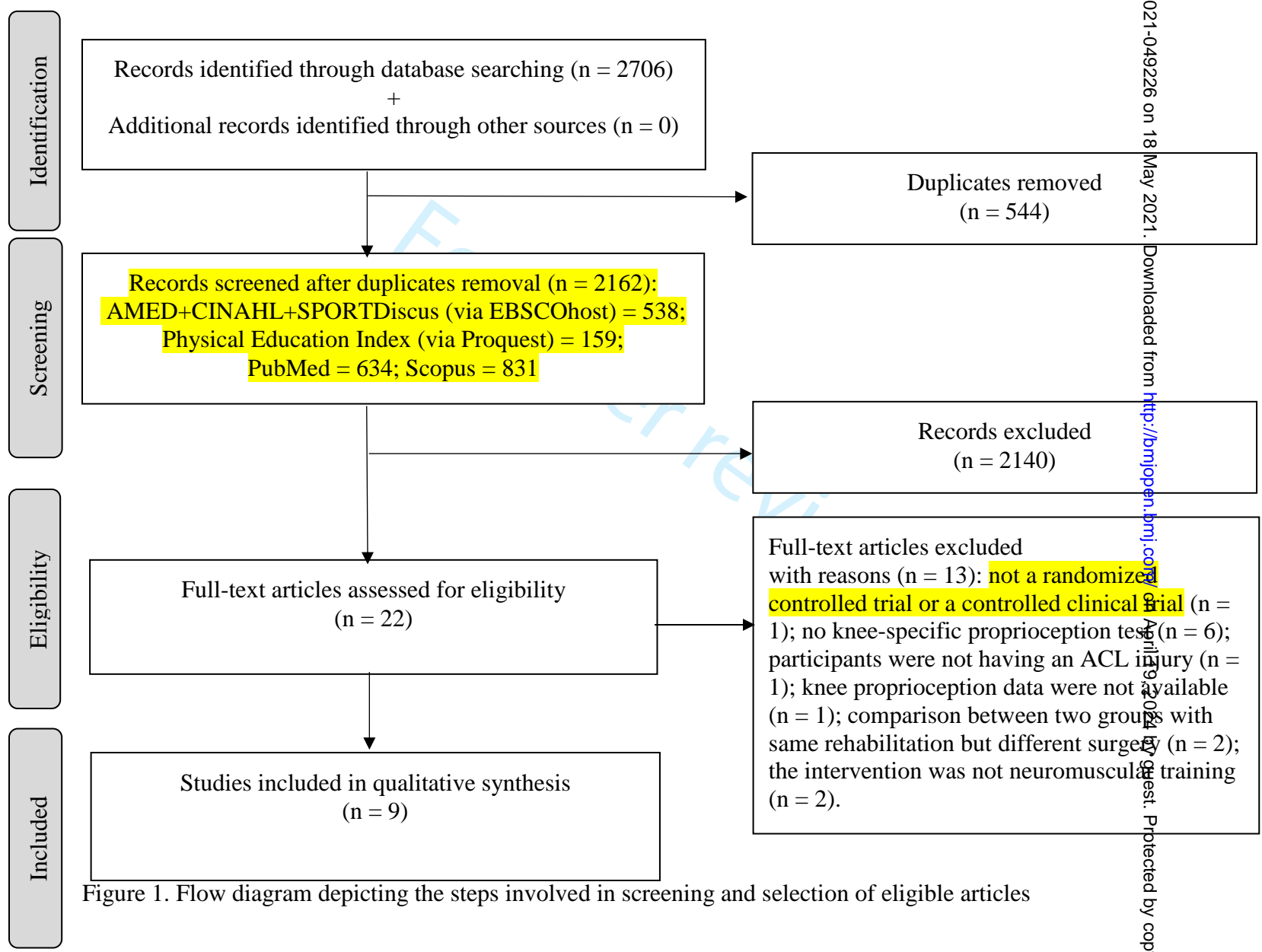
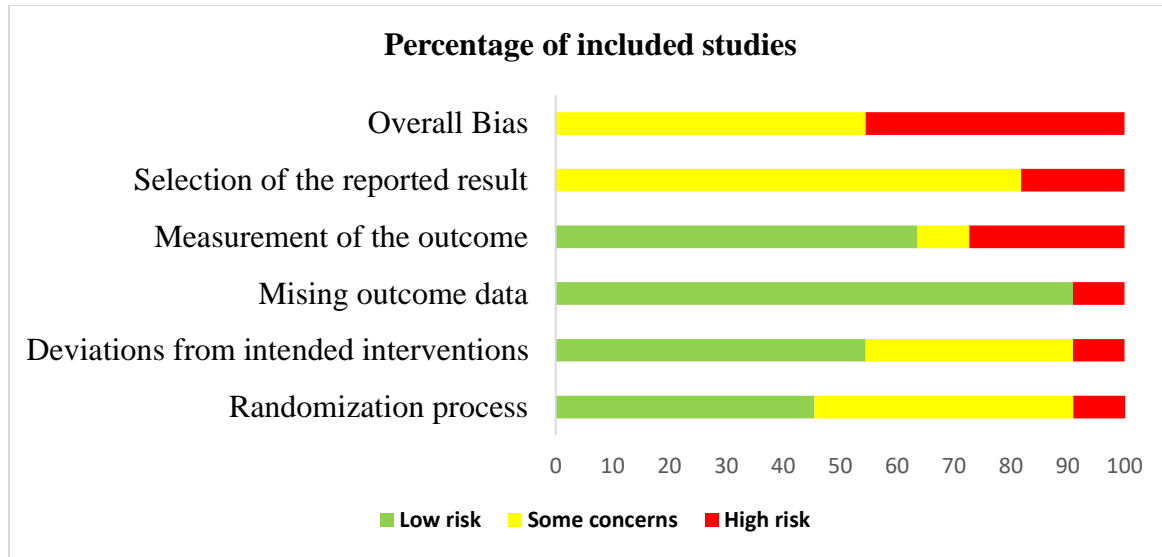


Figure 1. Flow diagram depicting the steps involved in screening and selection of eligible articles



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 "kinesthesia") 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 "kinesthesia") 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 "Kinesthesia") 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 "Kinesthesia") 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 ("kinesthesia"[MeSH Terms] OR "kinesthesia"[All Fields]) OR "Kinesthesia"[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 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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

1136/bmjopen-2021-049226 on 18 May 2022. Downloaded from <http://bmjopen.bmj.com/> by guest. Protected by copyright.



PRISMA 2009 Checklist

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

1136/bmjopen-2021-079226 on 18 March 2021. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

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

Page 1 of 2

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

			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.

1136/bmjopen-2021-049226 on 18 May 2021. Downloaded from <http://bmjopen.bmj.com/> on April 19, 2024 by guest. Protected by copyright.

Synthesis Without Meta-analysis (SWiM) reporting items

The citation for the Synthesis Without Meta-analysis explanation and elaboration article is: Campbell M, McKenzie JE, Powden 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*
<i>Methods</i>			
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
<i>Results</i>			

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
<i>Discussion</i>			
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)).