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Cover letter

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Wednesday 6th March 2013

Dr Michele Harms,
St George's,
University of London and Kingston University,
London, UK

Dear Dr Harms,

Please find enclosed our article entitled "*The effect of ACL injury on knee proprioception: A Meta-Analysis*". This paper is a meta-analysis considering current studies on knee proprioception following ACL injuries. We think the paper meets Physiotherapy's scope and aims to provide information on the advances of clinically relevant characteristics of the knee joint following injury. I can confirm this article is of original material, i.e. has not been submitted elsewhere for publication or has been published elsewhere.

Yours sincerely,

Nicola Relph. MSc.

Enclosure: Article.

***Title Page (with authors and addresses)**

The Effects of ACL Injury on Knee Proprioception: A Meta-Analysis

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KEY WORDS: Anterior Cruciate Ligament (ACL), Knee proprioception, Joint position sense, Threshold to detect passive motion.

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***Abstract**

Background It is suggested the anterior cruciate ligament (ACL) plays a significant role in knee proprioception, however, the effect of ACL injury on knee proprioception is unclear. Studies utilising the two most common measurement techniques, joint position sense and threshold to detect passive motion, have provided evidence both for and against a proprioceptive deficient following ACL injury.

Objective The objective of the study was to undertake a meta-analysis investigating the effects of ACL injury, treated conservatively or by reconstruction, on proprioception of the knee, measured using joint position sense and/or threshold to detect passive movement techniques.

Data Sources Seven databases were searched from their inception to December 2011 using the subject headings 'anterior cruciate ligament, proprioception, postural sway, joint position sense, balance, equilibrium or posture' to identify relevant studies.

Eligibility criteria PRISMA guidelines were followed. Studies that investigated the effect of ACL injury on either knee joint kinaesthesia or position sense were included in this review.

Data extraction and synthesis Two reviewers independently extracted data using a standardised assessment form. Comparisons were made using a fixed effect model with an inverse variance method using Review Manager Software (V5.1).

Results Patients with ACL injury have poorer proprioception than people without such injuries (SMD = 0.35°; P= 0.001 and SMD = 0.38°; P=0.03) when measured using joint position sense and threshold to detect passive motion techniques respectively. Patients had poorer proprioception in the injured than uninjured leg (SMD = 0.52°; P<0.001) and the proprioception of people whose ACL was repaired was better than those whose ligament was left unrepaired (SMD = -0.62°; P<0.001).

Limitations Heterogeneity of measurement techniques and lack of psychometric details.

Conclusion ACL injuries may cause knee proprioception deficits compared to uninjured knees and control groups. Although differences were statistically significant, the clinical significance of findings can be questioned.

The Effects of ACL Injury on Knee Proprioception: A Meta-Analysis

Introduction

The anterior cruciate ligament (ACL) controls knee movements in six directions; three rotations and three translations and thus is critical for stable lower extremity movement [1]. The ligament's main role in knee joint stability is to prevent excessive anterior translation (forward movement) of the tibia in relation to the femur and help direct the 'screw-home' mechanism which occurs during femoral and tibial rotation into full knee extension [2]. The ACL is also thought to play a significant role in knee proprioception [2]. Proprioception is a component of the somatosensory system which plays a critical role in normal human performance [2-4]. Its main role is to provide afferent information on the position and movements of a joint. In the ACL, 1% of its total area [5] is made up of three types of proprioceptive receptors; pacinian capsules, ruffini nerve endings and golgi tendon organs [6] and each has specific role. The pacinian capsules adapt rapidly to low degrees of joint stress, are sensitive to rapid changes in accelerations, and are therefore classified as dynamic receptors [7]. Whereas, ruffini nerve endings and golgi tendon organs are slow adapting with a high threshold to stress and are believed to provide information on the position of the knee joint [7].

Injuries to the ACL are career threatening for sports professionals and even when rehabilitation is completed, secondary injury problems, such as osteoarthritis are common [8,9]. It has long been thought that such ACL injuries can be detrimental to proprioception of the knee which may lead to abnormal movement patterns which are a mechanism for further injuries and long-term secondary problems [9]. However, research in to the effects of ACL injury on knee proprioception has yielded conflicting results [10]. Therefore, our aim was to undertake a systematic review to investigate the effects of ACL injury, whether treated conservatively or by reconstruction, on proprioception of the knee. The two most common proprioception measurement techniques [11]; joint kinaesthesia (threshold to detect passive motion (TTDPM)) and joint position sense (JPS) were considered. Joint position sense (JPS) involves passively moving a joint to a target angle, then the patient actively reproduces this angle [11]. Joint kinaesthesia traditionally measures the passive movement of a joint before movement is detected, called a threshold to detect passive motion (TTDPM). This involves asking the patient to indicate the first instance they perceive motion of the joint [11].

The aim of this review was to assess knee proprioception deficits following ACL injury whether treated conservatively or by reconstruction using JPS and TTDPM measurement techniques. The following null hypotheses were formulated.

- there are no difference in proprioception between ACL injured legs and the contra-lateral uninjured leg;
- there are no difference in proprioception between ACL injured legs and the leg of an external control participant;
- there are no difference in the proprioception of people with a reconstructed ACL injury (ACL-R) and those whose ACL has not been reconstructed; so-called ACL-deficient (ACL-D)

Methods

Protocol

No review protocol exists for a descriptive data meta-analysis. The PRISMA guidelines on meta-analysis were followed (http://www.prisma-statement.org/statement.htm).

Eligibility Criteria

Observational studies testing proprioception of the knee following ACL injury (conservatively managed or reconstructed). Adults (over 16 years) with an ACL injury confirmed by arthroscopy and/ or MRI and/ or clinical test (Lachman’s test, the pivot shift test or measurement using a knee arthrometer), including participants with ACL injuries combined with meniscus and/ or collateral ligament damage. The primary outcome measure was proprioception measured by mean angle of error in degrees. This took two forms. Studies measuring knee kinaesthesia used the TTDPM method where the mean angle of error was defined as *the difference in degrees from initiation of motion and the participant's perception of motion*. Studies measuring JPS utilised an index angle matching method in which the mean angle of error was defined *as the difference in degrees between the target angle and the angle reproduced by the participant*. The type of control measure (the participant's contra-lateral leg or the leg of an external matched control) was also collected.

Information Sources, Search Strategy

One researcher completed the search. The following electronic databases were accessed from their inception to December 2011: AMED, CINAHL, PubMed, Medline, PeDro, Sports Discus and the Cochrane Library. Primary journals; The Knee, American Journal of Sports Medicine and the British Journal of Sports Medicine were also manually searched, as were the reference lists of all selected studies. Key terms were: anterior cruciate ligament, proprioception, postural sway, joint position sense, balance, equilibrium or posture. Limits of the search were: English language studies (none of the researchers spoke foreign languages), human studies, adult participants and peer reviewed published full access articles. Unpublished literature and trial registries of current studies were not included in the search.

Study selection

The search results were merged using reference management software (Endnote 9.0) and duplicates removed. The titles and abstracts were screened and articles which obviously did not meet the selection criteria removed. The full text of the remaining studies was then checked against the selection criteria. Studies with missing outcome measure data were excluded at this stage.

Risk of Bias in individual Studies

The methodological quality of the studies that met the selection criteria was appraised by two of the research team independently to identify studies that had a low risk of bias. The quality assessment tool was based on that previously developed and used by the authors [12] but adapted to evaluate the factors that would introduce bias into this analysis (Appendix 1). The factors were: confirmation of the ACL injury (up to three points), population representation including classification of injury group and details of previous and/or concurrent injury (up to 19 points), representation of the sample (up to five points), homogeneity of participants (up to 13 points), sample size (up to 25 points), study design (up to four points), assessor blinding (up to five points) and statistical analysis (up to 14 points). 'Description of the sample' assessed whether details of age, gender, pre-injury levels of activity, previous injury to damaged knee, concurrent damage to injured knee, concurrent damage to ankle and/ or hip joint on the injured side, injury to the contra-lateral side and participation in a rehabilitation programme were noted. 'Statistical analysis' included whether details of the reliability and sensitivity of the measurement tools were noted. This gave a total of 88 points. The methodological quality scores were arbitrarily grouped as 'poor' (a score of less than 29/88), 'moderate' (a score of 30-58/88) or 'good' (a score of 59+/88). Studies of moderate to good quality (that is, 30–88/88) were selected as providing data of sufficient low risk of bias to enter in to the meta-analysis. Two reviewers appraised the literature. For the selected studies, the following data were extracted by one reviewer: the number of participants, mean angle of error measured using TTDPM and/ or JPS methods and accompanying standard deviation values to include in the meta-analysis and the following comparisons were made:

For joint position sense data:

- ACL injured leg versus contra-lateral leg control
- ACL injured leg versus external control leg

- Patients with a reconstructed ACL versus patients with a deficient ACL

For data on the threshold to detect passive motion:

- ACL injured leg versus contra-lateral leg control
- ACL injured leg versus external control leg

The comparisons were made using a fixed effect model with an inverse variance method and presented as forest plots using Review Manager Software (version 5.1). Standard mean difference between groups measured the effect size. Heterogeneity between comparable trials was tested using the chi squared test (level of significance = $p < 0.10$ Higgins & Green, 2008). Heterogeneity was further tested using I^2 percentages to consider the impact potential heterogeneity would have on the meta-analysis.

Results

Study Selection

The initial search strategy yielded 3076 articles, 2737 of which did not relate to the research question. Screening of the titles and abstracts of the remaining 339 articles revealed that 290 did not fully meet the inclusion criteria; the main exclusion factor was the use of techniques to measure proprioception other than TTDPM and/or JPS. A further 43 articles were excluded following the evaluation of methodological quality as they provided 'poor' quality data with a high risk of bias and/or had missing or inadequate outcome data. The main reasons for missing data were that median data were presented instead of mean data [13,14,15] or measures of the variability of the data (standard deviation) were missing [16]. This left six studies which were selected for inclusion in the meta-analysis. The flow chart detailing the selection process is shown in Figure 1.

Study Characteristics

Six studies involving 191 ACL injured patients were selected (Table 1). Sixty-one participants were ACL deficient and 130 had had an ACL reconstruction. There were 82 healthy controls from five studies [17-21]. The participants' contralateral leg was used as the control in four studies [18,19, 21,22]. Confirmation of ACL injury was provided by arthroscopy or MRI in five studies [17-20, 21]. Only Barrack *et al*.,[17] stated a Lachman's Test and Pivot Shift test had been used in addition to the arthroscopy. Mir *et al*., [21] did not report how the ACL injury had been confirmed. An autograft using the patella tendon was the most common surgery used to reconstruct the ACL [18-20] but, none of the included studies assessed laxity before and after surgery. Angoules *et al.,* [22] was the only study to use the same surgeon for every reconstruction to minimise surgical skill as a confounder. Mir *et al.* [21] and Anguoles *at al.,* [22] stated the type and number of surgical complications. None of the patients in the included studies had previous ACL injury to the injured knee. One [19], stated ACL patients had concurrent damage to other structures in the knee during the ACL injury. A rehabilitation programme had been completed by patients in four studies [17, 19, 21,22].

All six selected studies were of moderate quality (Table 2). Most recruited a convenience sample [17, 19, 20, 22] or did not state how their participants were recruited [18, 21]. Five studies matched the injured patients to controls by age [17-21] and four matched by gender [18-21]. None justified the sample size with a power calculation or the minimal detectable difference of the measurement tool. Two studies [17, 22] blinded assessors to the type of participant.

Generally the statistical analysis in the selected studies lacked important (Table 2). Only two [21,22] reported whether the data was normally distributed and hence justified the use of parametric statistical testing. Most used 'home-made' measurement devices prepared specifically for the study but the reliability and sensitivity were infrequently reported.

During analysis, data from the external control subjects and ACL patients in some studies were used in several comparisons, for example if a control group was compared to ACL-D and ACL-R patients or if the same ACL patients were measured from two different starting positions [18, 21]. Unfortunately the RevMan software did not allow us to stipulate the actual control and patient number values. However this number is clearly noted as a footnote to the affected figures and should be considered when analysing the comparison data.

Synthesis of results

Effects of ACL injury on proprioception - Joint Position Sense Studies

Five studies compared the injured leg to the participant’s un-injured leg (n=170) as the control [18-22]. The pooled standard mean difference of mean angle of error was 0.52° (95% CI 0.41 to 0.63; P<0.001; I^2 = 63%) indicating that the un-injured leg had a lower mean angle of error (better joint position sense) compared to the injured leg (Figure 2). Four studies compared the injured legs (n=140) to an external control (n=104) [18-20, 22]. The pooled standard mean difference of the mean angle of error was 0.35° (95% CI 0.14 to 0.55; P= 0.001; I^2 = 78%) indicating that the control group had better joint position sense than ACL patients (figure 3). Three studies compared ACL reconstructed (n=116) and ACL deficient legs (n=100) [18, 20, 22]. The pooled standard mean difference of the mean angle error (°) was -0.62° (95% CI -0.76 to -0.48; P<0.001; I^2 = 42%) indicating that ACL reconstructed patients had significantly better joint position sense (figure 4).

Effects of ACL injury of proprioception - Threshold to Detect Passive Motion Studies

Two studies compared the injured leg (n=71) with the un-injured (n=71) leg in ACL patients [17,20]. The pooled standard mean difference of mean angle error was 0.02° (95% CI -0.32 to 0.35; P= 0.91; I^2 = 61%) indicating no difference. These studies also compared ACL injured legs (n=71) to external control legs (n=30) which showed a difference in mean angle error of 0.38° (95% CI 0.04 to 0.72; P= 0.03; I^2 = 73%) indicating that the external control group had a significantly lower mean angle of error than the injured leg group (figure 5).

Joint position sense studies and threshold to detect passive motion studies both indicated differences between injured leg and external controls. However, only data collected using the JPS method detected proprioception differences between injured and non-injured legs.

Discussion

This review examined the effect of ACL injury on proprioception, in terms of joint position sense and threshold to detect passive motion. The results indicate that there are statistically significant differences in the proprioception, in terms of JPS acuity and threshold to detection of movement, of patients with ACL injury in that they have poorer proprioception than people without such injuries and poorer proprioception in the injured than uninjured leg. The proprioception of people whose ACL was reconstructed was statistically significantly better than those whose ligament is left unreconstructed (ACL- deficient). These differences are seen whether the comparator group is a patient's uninjured leg, or a control group of people with no injuries; suggesting that either can be used as a control group in future research. The differences were seen most clearly when joint position sense was measured but was less consistent when threshold to detect passive motion measurement techniques were used.

It is thought that mechanoreceptors in the ACL provide afferent information on the relative position and movement of the knee joint [3, 7, 23, 24] and that ACL injury impairs proprioception through disruption to the transmission of this sensory information [5]. Our results give some support to this belief. However, although statistically significant, the differences found were very small (less than one degree) which is unlikely to be clinically or functionally important. A proprioceptive deficit of at least 5 degrees is thought be the minimum to indicate a clinically important difference [25] although there is little evidence to support, or refute, this value.

The discrepancy between the statistical and functional significance of the differences found may be because the proprioception measurement techniques used were insufficiently accurate to reliably detect clinically significant differences between groups [11]. None of the trials in the current analysis included information on the reliability, sensitivity, measurement error of the measurement techniques used. Hence it is possible that the differences found are due to measurement error and/or the measurement techniques were insufficiently sensitive to detect clinically significant differences. Another explanation is that the comparisons were under-powered because the sample was too small, (none of the included studies calculated sample size using power estimations). However our pooled analysis involved nearly 200 patients and the 95% confidence intervals of the comparisons made were small, indicating that a lack of power was not an issue. Further researcher is needed to evaluate the sensitivity and reliability of techniques to measure proprioception at the knee, before they can meaningfully be used as an evaluation tool.

A more likely, but controversial, explanation for our results is that ACL injury may not have a major impact on proprioception at the knee. This support's the view that muscle, rather than ligaments, provide the primary afferent information in the sensorimotor system [10] , which is not a surprise given that only 1% of the ACL total area is made up of proprioceptive receptors [5] and that receptors are often still deficient six months after reconstructive surgery [5]. It may, to some degree, also explain the inconclusive evidence for reconstructive surgery and conservative (non-surgical) rehabilitation [10,26,27] some patients 'cope' with an ACL-deficiency and have an apparently stable knee even after complete rupture, while others do not 'cope' despite reconstructive surgery and apparent stability [5,12,10,26]. Joint stability relies on synergy between muscles and ligaments [1, 2, 28, 29]. Once the ligament is damaged, patients may adapt by using proprioceptive information from the muscles to a great extent to compensate for the lack of information from the ligament. This may explain why some patients cope better with ACL injury (however it is managed) than others [12]; some may be more able to make that adaption than others. Rehabilitation can improve proprioception and joint stability in patients with and without reconstruction [19,27] the mechanism being an adaptation to use increased proprioceptive information from the muscles or other ligaments, rather than restoring proprioception through the ACL per se. Further research is needed to test this hypothesis further and to the clinical significance of knee proprioception deficits.

We found greater differences in joint position sense (JPS) than studies using TTDPM. TTDPM techniques may be insufficiently sensitive to detect the responses of rapid receptors such as the pacianian capsules in the ACL [5] as measurements incorporate the participants' reaction time, which is unrelated to their injury. JPS methods may be more sensitive by measuring the slower responses of the ruffini nerve endings and golgi tendon organs [24] as they allow the conscious perception of joint motion and position.

A limitation of this meta-analysis is that all data collection was retrospective, which inevitably means that pre-injury proprioception is unknown. It is possible that the patients who suffered injuries had poorer proprioception which predisposed them to injury. Large scale normative studies are needed to give insight into the distribution of proprioception abilities across the population and whether this predisposes people to ACL injury. Such studies should consider a measurement technique that explores the full range of knee motion and direction using large sample sizes that represents the complete ACL patient population and normative data on proprioception ability.

Heterogeneity of variance was greater than the recommended level of 50% [30] in all but one comparison; this may be due to variability in the recruitment strategies across studies. The time since injury when proprioception was measured ranged from 12 days [19] to over two years [20] and the use of rehabilitation programmes was not consistent. The high I^2 levels may indicate that ACL injury had effects other than proprioception deficits [30] such as kinematic adaptations [31] and movement variability [32]. Highly varied measurement techniques were also evident, which is a limitation that hampers further analysis [10]. In this analysis, three different pieces of measuring equipment and varied knee movements, in terms of direction and speed of motion, were used. Proprioception increases towards the extremes of range of movement to protect the joint from injury [5, 33], thus studies that do not include measurements across the whole range of movement may either under- or over-estimate knee proprioception. These inconsistent methods of measuring proprioception could have contributed to the high levels of heterogeneity in the current analysis.

Conclusions

This review examined the effect of ACL injury on proprioception, in terms of joint position sense and threshold to detect passive motion. The results indicate that patients with ACL injury may have poorer proprioception than people without such injuries and poorer proprioception in the injured than uninjured leg. The proprioception of people whose ACL is reconstructed may be better than those whose ligament is left unreconstructed (ACL-deficient). These differences are seen whether the comparator group is a patient's uninjured leg, or a control group of people with no injuries; suggesting that either can be used as a control group in future research.

There are no conflicts of interest.

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Appendix 1 – Scoring System

Authors	
Article Title	
Source	
Years/Volume/Pages	
Institute affiliation & Contact address	

Do not proceed if one of the following six categories is not adhered to:-

	Yes
Human Study	
English Language	
All participants adults / teenagers	
Were all subjects ACL deficient and/or reconstructed or acting as a healthy control group?	
Were ACL participants categorised into ACL-D, ACL-R or ACL-R pre and post op?	
Was at least one OM a direct measure of proprioception, either TTDPM or JPS?	

POPULATION

A. Confirmation of ACL Deficiency

Was ACL deficiency confirmed by:

	Score
Not stated	0
Arthroscopy or MRI OR clinical examination using Lachmans, pivot shift test or knee arthrometer	1
Arthroscopy or MRI AND clinical examination using Lachmans, pivot shift test or knee arthrometer	3

B. Representation of Population

Were the ACL participants classified into -

	Score
A sub-group of deficient or reconstructed patients recruited (e.g. those who are undergoing or have completed rehab or copers/ non-copers/ adapters, or limited by age, sex, activity)	1
ACL deficient or ACL reconstructed groups only	3
People with all types of ACL problem (deficient and reconstructed)	5

Were ACL-R classified according to:

	Yes	No
Type of surgery stated	1	
Type and number of complications stated	1	
Same surgeon for every ACL-R participant	1	
Assessment of laxity pre and post surgery	1	

Did any ACL participant (ACL-D or ACL-R) have any of the following:- If authors do not mention a previously reconstructed ACL assume the answer is ‘no’.

	Yes	No
Previous Injury to ACL Knee		2
Concurrent damage to ACL knee during ACL injury		2
Injury to the ankle or hip on ACL injury side		2
Injury to contralateral leg		2
Rehabilitation prior to the point of assessment		2

C. Representation of Sample

Was the recruitment strategy -

	Score
Not stated in the text	0
Stated in the text	1

Based on convenience sampling (e.g. physio department, surgical list, sports club)	3
Based on comprehensive sampling (e.g. recruitment of ACL-D and ACL-R across different populations)	5

D. Homogeneity of Participants

Was a control comparison used?

	Score
No	0
Contra-lateral leg	1
Separate control group (true control)	3

Were the following factors *similar or comparable* between the controls and ACL injury group?

	True Control	Contra-lateral Knee
Age	2	1
Sex	2	1
Pre-injury levels of activity	2	1

E. Sample Size

Was a justification of sample size given (power calculation or accuracy/minimal detectable difference of the measurement tool)?

Yes	No
10	0

Were the numbers of participants between:-

Number of participants in each group	Control Group	ACL injury group 1	ACL injury group 2	Score
0-5				0
6-10				1
11-15				2
16-20				3
21-25				4
>26				5
TOTAL				

METHODOLOGICAL QUALITY

F. Study Design

Was the study design clearly described?

Yes	No
1	0

Was the data collection -?

	Yes
Retrospective	0
Prospective	3

G. Assessor Blinding / Bias

Were the outcome assessors blind to the type of participants?

Yes	No
5	0

H. Statistical Analysis

Were the correct statistics used for data analysis in accordance to the type of data collected (i.e. parametric/ non-parametric)? NOTE: if parametric tests were used, was normality of the data assessed?

Yes	No / no statistics used
5	0

Was the level of significance appropriate and analysis correctly interpreted? -

No	0
Level was appropriate only	1
Level was appropriate and correct interpretation was made	3

Were the OMs tested for inter-tester and test-retest reliability?

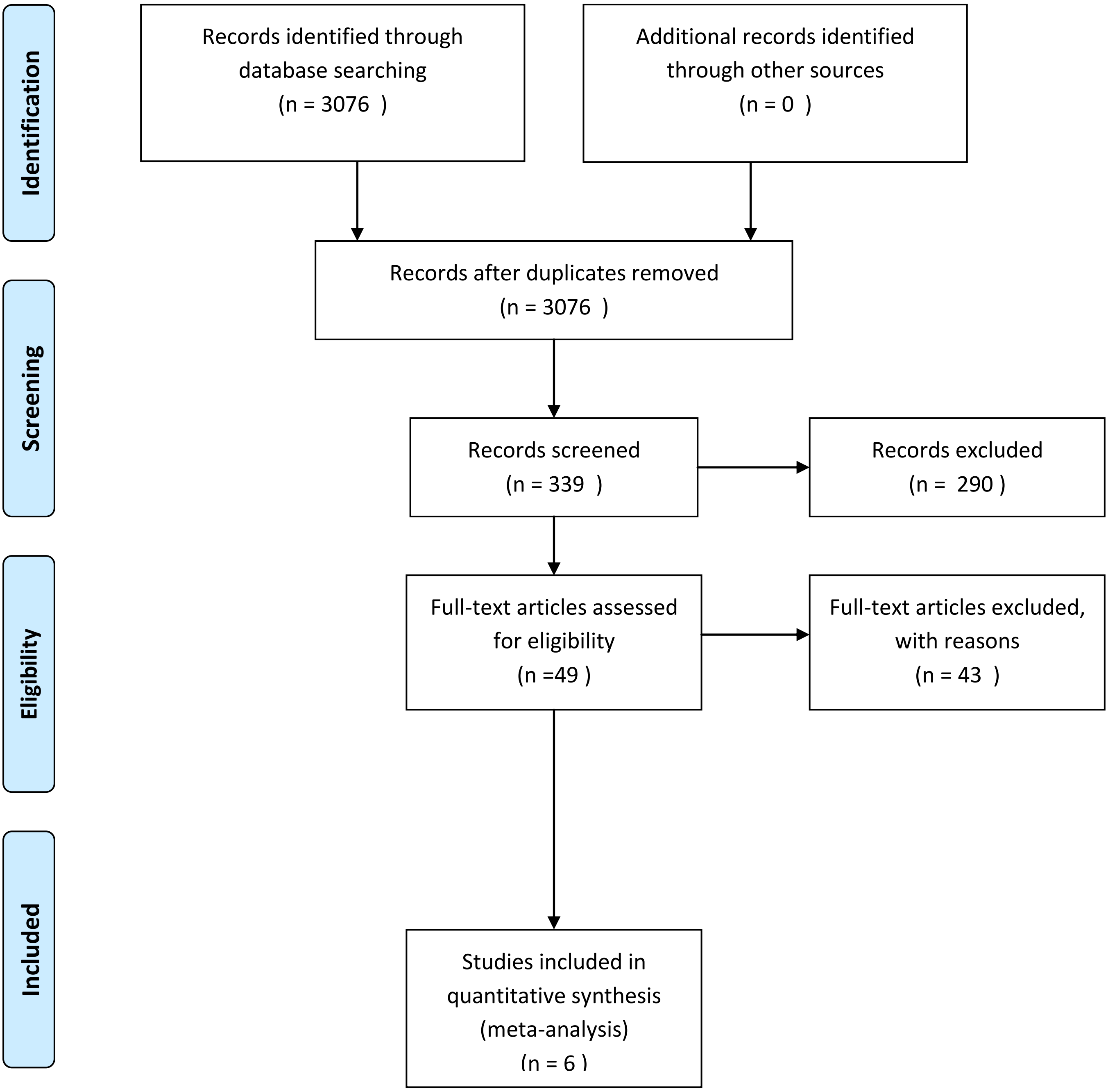
	Score
No evidence of reliability testing	0
Reliability was reported using results from external studies	1
Yes, reliability tested within the study and ICC / Kappa yielded good results (>.07)	3

Were the OMs tested for sensitivity to change?

	Score
No evidence of sensitivity to change testing	0
Sensitivity to change was reported using results from external studies	1
Yes, effect size / MDC yielded good results (>.07)	3

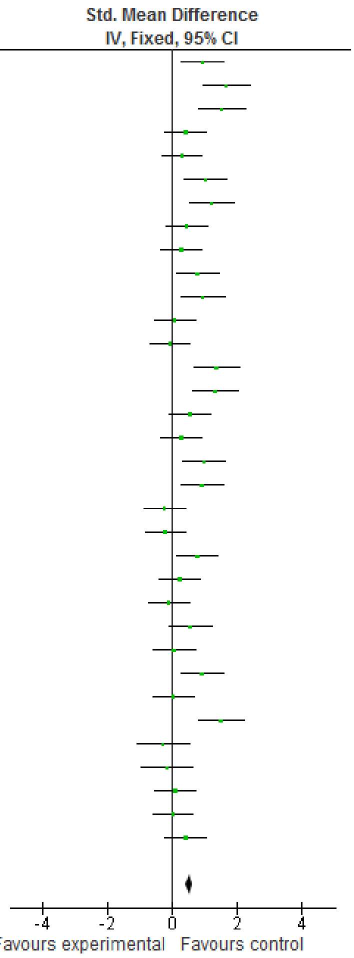
TOTAL SCORE: /87

Figure(s)


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 3076)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 3076)
Records screened (n = 339)
Records excluded (n = 290)
Full-text articles assessed for eligibility (n =49)
Full-text articles excluded, with reasons (n = 43)
Studies included in quantitative synthesis (meta-analysis) (n = 6)

	ACL			Contra Lateral Leg				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Angolues (u)	4.13	1.51	20	2.63	1.64	20	2.9%	0.93 [0.28, 1.59]
Angoules (a)	3.98	1.38	20	1.98	0.92	20	2.4%	1.67 [0.94, 2.40]
Angoules (b)	3.9	1.48	20	1.98	0.92	20	2.5%	1.53 [0.81, 2.24]
Angoules (c)	2.43	1.19	20	1.98	0.92	20	3.2%	0.41 [-0.21, 1.04]
Angoules (d)	2.27	0.97	20	1.98	0.92	20	3.2%	0.30 [-0.32, 0.92]
Angoules (e)	3.95	2.2	20	2.2	0.85	20	2.8%	1.03 [0.36, 1.69]
Angoules (f)	3.72	1.5	20	2.2	0.85	20	2.7%	1.22 [0.54, 1.90]
Angoules (g)	2.73	1.4	20	2.2	0.85	20	3.2%	0.45 [-0.18, 1.08]
Angoules (h)	2.47	1.05	20	2.2	0.85	20	3.2%	0.28 [-0.35, 0.90]
Angoules (i)	3.8	1.96	20	2.52	1.1	20	3.0%	0.79 [0.14, 1.44]
Angoules (j)	3.65	1.23	20	2.52	1.1	20	2.9%	0.95 [0.29, 1.61]
Angoules (k)	2.63	1.37	20	2.52	1.1	20	3.3%	0.09 [-0.53, 0.71]
Angoules (l)	2.45	1.2	20	2.52	1.1	20	3.3%	-0.06 [-0.68, 0.56]
Angoules (m)	5.32	2.77	20	2.5	0.7	20	2.6%	1.37 [0.67, 2.06]
Angoules (n)	4.36	1.81	20	2.5	0.7	20	2.6%	1.33 [0.64, 2.02]
Angoules (o)	3.18	1.58	20	2.5	0.7	20	3.1%	0.55 [-0.09, 1.18]
Angoules (p)	2.78	1.23	20	2.5	0.7	20	3.2%	0.27 [-0.35, 0.90]
Angoules (q)	4.73	2.51	20	2.83	0.98	20	2.9%	0.98 [0.32, 1.64]
Angoules (r)	3.97	1.41	20	2.83	0.98	20	2.9%	0.92 [0.27, 1.58]
Angoules (s)	2.62	0.79	20	2.83	0.99	20	3.2%	-0.23 [-0.85, 0.39]
Angoules (t)	2.63	0.86	20	2.83	0.98	20	3.2%	-0.21 [-0.83, 0.41]
Angoules (v)	3.85	1.42	20	2.63	1.64	20	3.0%	0.78 [0.13, 1.42]
Angoules (w)	2.98	1.23	20	2.63	1.64	20	3.2%	0.24 [-0.39, 0.86]
Angoules (x)	2.5	1	20	2.63	1.64	20	3.3%	-0.09 [-0.71, 0.53]
Fischer Rasmussen (a)	3.5	1.37	18	2.7	1.42	18	2.8%	0.56 [-0.11, 1.23]
Fischer Rasmussen (b)	3.1	1.54	18	3.02	0.93	18	2.9%	0.06 [-0.59, 0.71]
Fischer Rasmussen (c)	4.06	1.21	20	3.1	0.79	20	2.9%	0.92 [0.27, 1.58]
Fischer Rasmussen (d)	3.14	1.03	20	3.1	0.9	20	3.3%	0.04 [-0.58, 0.66]
Fremery (a)	6.7	2.2	20	3.6	1.8	20	2.5%	1.51 [0.80, 2.22]
Mir (a)	3.65	2.39	12	4.28	2.08	12	1.9%	-0.27 [-1.08, 0.53]
Mir (b)	3.77	2.04	12	4.13	2.51	12	2.0%	-0.15 [-0.95, 0.65]
Ozenci (a)	4.75	2.15	20	4.54	1.98	20	3.3%	0.10 [-0.52, 0.72]
Ozenci (b)	4.58	1.87	20	4.52	1.55	20	3.3%	0.03 [-0.59, 0.65]
Ozenci (c)	5.3	1.74	20	4.64	1.37	20	3.2%	0.41 [-0.21, 1.04]
Total (95% CI)			**660**			**660**	**100.0%**	**0.52 [0.41, 0.63]**

Heterogeneity: Chi² = 88.54, df = 33 (P < 0.00001); I² = 63%
Test for overall effect: Z = 9.15 (P < 0.00001)

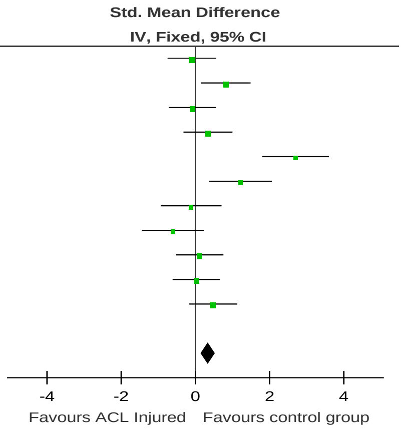


Note: The total number of patients was 170 not 660.

	ACL			Control				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Fischer Rasmussen (b)	3.1	1.54	18	3.22	0.96	20	10.5%	-0.09 [-0.73, 0.54]
Fischer Rasmussen (c)	4.06	1.21	20	3.06	1.18	20	10.2%	0.82 [0.17, 1.47]
Fischer Rasmussen (d)	3.14	1.03	20	3.22	0.96	20	11.1%	-0.08 [-0.70, 0.54]
Fischer-Rasmussen (a)	3.5	1.37	18	3.06	1.18	20	10.4%	0.34 [-0.30, 0.98]
Fremery (a)	6.7	2.2	20	2.2	0.7	20	5.5%	2.70 [1.82, 3.58]
Fremery (b)	3.6	1.7	10	2.2	0.7	20	6.2%	1.21 [0.39, 2.04]
Mir (a)	3.65	2.39	12	3.9	1.77	12	6.7%	-0.11 [-0.92, 0.69]
Mir (b)	3.77	2.04	12	5.49	3.31	12	6.3%	-0.60 [-1.43, 0.22]
Ozenci (a)	4.75	2.15	20	4.54	1.34	20	11.1%	0.11 [-0.51, 0.74]
Ozenci (b)	4.58	1.87	20	4.54	1.34	20	11.1%	0.02 [-0.60, 0.64]
Ozenci (c)	5.3	1.74	20	4.54	1.34	20	10.8%	0.48 [-0.15, 1.11]
Total (95% CI)			**190**			**204**	**100.0%**	**0.35 [0.14, 0.55]**

Heterogeneity: Chi² = 45.63, df = 10 (P < 0.00001); I² = 78%

Test for overall effect: Z = 3.28 (P = 0.001)

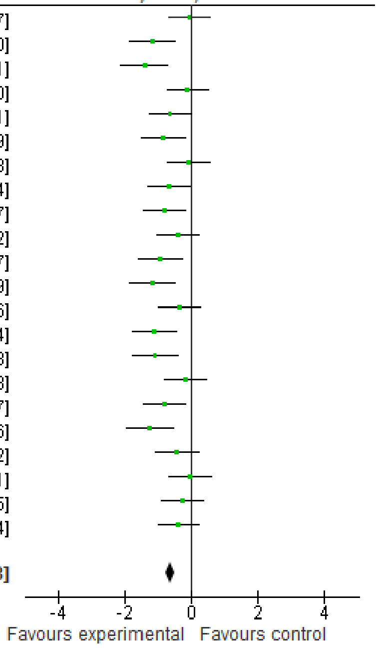


Note: The total number of patients was 140 not 190 and external controls was 104 not 204.

Study or Subgroup	ACL-R Mean	ACL-R SD	ACL-R Total	ACL-D Mean	ACL-D SD	ACL-D Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Angoules (b)	3.9	1.48	20	3.98	1.38	20	4.9%	-0.05 [-0.67, 0.57]
Angoules (c)	2.43	1.19	20	3.98	1.38	20	4.1%	-1.18 [-1.86, -0.50]
Angoules (d)	2.27	0.97	20	3.98	1.38	20	3.9%	-1.41 [-2.10, -0.71]
Angoules (f)	3.72	1.5	20	3.95	2.2	20	4.9%	-0.12 [-0.74, 0.50]
Angoules (g)	2.73	1.4	20	3.95	2.2	20	4.7%	-0.65 [-1.29, -0.01]
Angoules (h)	2.47	1.05	20	3.95	2.2	20	4.5%	-0.84 [-1.49, -0.19]
Angoules (j)	3.65	1.23	20	3.8	1.96	20	4.9%	-0.09 [-0.71, 0.53]
Angoules (k)	2.63	1.37	20	3.8	1.96	20	4.6%	-0.68 [-1.32, -0.04]
Angoules (l)	2.45	1.2	20	3.8	1.96	20	4.5%	-0.81 [-1.46, -0.17]
Angoules (n)	4.36	1.81	20	5.32	2.77	20	4.8%	-0.40 [-1.03, 0.22]
Angoules (o)	3.18	1.58	20	5.32	2.77	20	4.4%	-0.93 [-1.59, -0.27]
Angoules (p)	2.78	1.23	20	5.32	2.77	20	4.1%	-1.16 [-1.84, -0.49]
Angoules (r)	3.97	1.41	20	4.73	2.51	20	4.8%	-0.37 [-0.99, 0.26]
Angoules (s)	2.62	0.79	20	4.73	2.51	20	4.2%	-1.11 [-1.78, -0.44]
Angoules (t)	2.63	0.86	20	4.73	2.51	20	4.2%	-1.10 [-1.77, -0.43]
Angoules (v)	3.85	1.42	20	4.13	1.51	20	4.9%	-0.19 [-0.81, 0.43]
Angoules (w)	2.98	1.23	20	4.13	1.51	20	4.5%	-0.82 [-1.47, -0.17]
Angoules (x)	2.5	1	20	4.13	1.51	20	4.0%	-1.25 [-1.93, -0.56]
Fischer Rasmussen (a)	3.5	1.37	18	4.06	1.21	20	4.5%	-0.43 [-1.07, 0.22]
Fischer Rasmussen (b)	3.1	1.54	18	3.14	1.03	20	4.7%	-0.03 [-0.67, 0.61]
Ozenci (a)	4.75	2.15	20	5.3	1.74	20	4.9%	-0.28 [-0.90, 0.35]
Ozenci (b)	4.58	1.87	20	5.3	1.74	20	4.8%	-0.39 [-1.02, 0.24]
Total (95% CI)			**436**			**440**	**100.0%**	**-0.62 [-0.76, -0.48]**

Heterogeneity: Chi² = 36.03, df = 21 (P = 0.02); I² = 42%
Test for overall effect: Z = 8.85 (P < 0.00001)

Std. Mean Difference
IV, Fixed, 95% CI

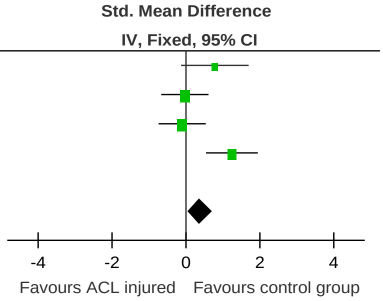


Note: The total number of ACL-R was 116 not 436 and ACL-D was 100 not 440.

	ACL			Control Group				Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Fixed, 95% CI**
Barrack	3.53	1.22	11	2.67	0.84	10	14.5%	0.78 [-0.11, 1.68]
Ozenci (a)	1.01	0.16	20	1.03	0.91	20	30.3%	-0.03 [-0.65, 0.59]
Ozenci (b)	0.96	0.27	20	1.03	0.91	20	30.3%	-0.10 [-0.72, 0.52]
Ozenci (c)	1.93	0.42	20	1.03	0.91	20	24.9%	1.24 [0.56, 1.93]
Total (95% CI)			**71**			**70**	**100.0%**	**0.38 [0.04, 0.72]**

Heterogeneity: Chi² = 10.93, df = 3 (P = 0.01); I² = 73%

Test for overall effect: Z = 2.20 (P = 0.03)



Note: The total number of external controls was 30 not 70.

Figures Labels

Figure 1: A PRISMA flow chart of article reduction.

Figure 2-4: Forest plots on the significant joint position sense comparisons. The letters in brackets following the first authors name refer to subgroups and/ or knee motion during proprioception measurement;

Angoules (a) = ACL-D (Pre Hamstring ACL-R) target angle 15°, Angoules (b) = ACL-R (Hamstring- 3months post op) target angle 15°,Angoules (c) = ACL-R (Hamstring- 6months post op) target angle 15°,Angoules (d) = ACL-R (Hamstring- 12 months post op) target angle 15°,Angoules (e) = ACL-D (Pre Hamstring ACL-R) target angle 45°,Angoules (f) = ACL-R (Hamstring- 3months post op) target angle 45°,Angoules (g) = ACL-R (Hamstring- 6months post op) target angle 45°,Angoules (h) = ACL-R (Hamstring- 12 months post op) target angle 45°,Angoules (i) = ACL-D (Pre Hamstring ACL-R) target angle 75°,Angoules (j) = ACL-R (Hamstring- 3months post op) target angle 75°,Angoules (k) = ACL-R (Hamstring- 6months post op) target angle 75°,Angoules (l) = ACL-R (Hamstring- 12months post op) target angle 75°,Angoules (m) = ACL-D (Pre Patella Tendon ACL-R) target angle 15°,Angoules (n) = ACL-R (Patella Tendon- 3months post op) target angle 15°,Angoules (o) = ACL-R (Patella Tendon- 6months post op) target angle 15°,Angoules (p) = ACL-R (Patella Tendon- 12months post op) target angle 15°,Angoules (q) = ACL-D (Pre Patella Tendon ACL-R) target angle 45°,Angoules (r) = ACL-R (Patella Tendon- 3months post op) target angle 45°,Angoules (s) = ACL-R (Patella Tendon- 6months post op) target angle 45°,Angoules (t) = ACL-R (Patella Tendon- 12months post op) target angle 45°Angoules (u) = ACL-D (Pre Patella Tendon ACL-R) target angle 75°,Angoules (v) = ACL-R (Patella Tendon- 3months post op) target angle 75°,Angoules (w) = ACL-R (Patella Tendon- 6months post op) target angle 75°,Angoules (x) = ACL-R (Patella Tendon- 12months post op) target angle 75°,

Fischer-Rasmussen (a) = ACL-R group with a starting angle of 60°, Fischer-Rasmussen (b) = ACL-R group with a starting angle of 0°, Fischer-Rasmussen (c) = ACL-D group with a starting angle of 60°,Fischer-Rasmussen (d) = ACL-D group with a starting angle of 0°,

Fremerey (a) = ACL-R group, Fremerey (b) = ACL-D Group,

Mir (a) = ACL-R group with starting angle of 60°, Mir (b) = ACL-R group with a starting angle of 0°,

Ozenci (a) = ACL-R (autograft technique) group, Ozenci (b) = ACL-R (allo-graft technique) group and Ozenci (c) = ACL-D group.

Figure 5: Forest plot on the significant threshold to detect passive motion comparison. The letters in brackets following the first authors name refer to subgroups and/ or knee motion during proprioception measurement;

Ozenci (a) = ACL-R (autograft technique) group, Ozenci (b) = ACL-R (allo-graft technique) group and Ozenci (c) = ACL-D group.

Table(s)

Table 1: Characteristics of the articles included in the meta-analysis investigating the effects of ACL injuries on proprioception deficits.

Study	Participants	Age, mean (SD) and Gender ACL patients	Age, mean (SD) and Gender Controls	Equipment	Knee ROM	Method of measuring proprioception
Barrack *et al*.,[17]	11 ACL-D 10 Controls.	25 (NP) years 9 men, 2 women	25 (NP)years NP	Purpose built proprioception device.	From a starting angle of 40° at an angular velocity of 0.5°/s.	TTDPM - Mean angle of error in degrees from 10 trials randomly assigned to flexion or extension
Fischer-Rasmussen and Jensen[18]	20 ACL-D 18 ACL-R 20 Controls	ACL-D 27(5) years 11 men, 9 women ACL-R 27(5) years 9 men, 9 women	27(4) years 11 men, 9 women (Plus uninjured knees of patients)	Purpose built proprioception device.	From a starting angle of 25° flexion to 15, 20, 25, 30, 35 or 60° flexion to full extension.	JPS (passive positioning then active repositioning task) – Mean angle of error in degrees from 20 trials randomly assigned to target angles.
Fremerey *et al*.,[19]	10 ACL-D 20 ACL-R 20 Controls	ACL-D 22.7(3.2) years 7 men, 3 women ACL-R 28.4(4.4) years 13 men, 7 women	26.4(4.8) years 13 men, 7 women (Plus uninjured knees of patients)	Purpose built proprioception device.	From a starting angle of 0° to random target angles in 3 intervals; extension 0-20° , mid range 40-60° and flexion 80-100°. All passive motion was set at 0.5°/s.	JPS (passive positioning then passive repositioning task) – Mean angle of error in degrees from trials randomly assigned from the extension range, mid-range and flexion range.
Ozenci *et al*.,[20]	20 ACL-R (auto-graft) 20 ACL-R (allo-graft) 20 ACL-D 20 Controls	ACL-D 29.0(5.4) years 18 men, 2 women ACL-R Auto – 29.5(6.9) years 20 men Allo – 30.2(4.6) years 16 men, 4 women	27.6(2.6) years 17 men, 3 women (Plus uninjured knees of patients)	Cybex Dynamometer	JPS - From full extension to flexion (no further details given). TTDPM - From 15° flexion to either flexion or extension at an angular velocity of 1°/s.	JPS (passive positioning then active repositioning task) – Mean angle of error in degrees from 10 trials. TTDPM - Mean angle of error in degrees from 10 trials randomly assigned to either flexion or extension.
Anguoles *et al*.,[21]	20 ACL-R (hamstring) 20 ACL-R (patella tendon)	16 men, 4 women 18 men, 2 women	N/A	Con-Trex Dynamometer	JPS – From full extension (0°) to flexion angles of 15, 45 & 75°.	JPS (passive positioning then active repositioning task) – Mean angle of error in degrees from three trials.

Mir *et al*.,[22]	12 ACL-R 12 Controls	23(4.75)years 12 men	22(4.35) years 12 men (Plus uninjured knees of patients)	Digital camera, markers.	From a starting angle of 60° flexion to 30° flexion and from a starting angle of 0° flexion to 30° flexion. All motion was at an angular velocity of 10°/s.	JPS (active positioning then active repositioning task) - Mean error angle in degrees over 3 trials.

ACL-D: Patients with an ACL deficiency, ACL-R: Patients with a reconstructed ACL, TTDPM: Threshold to detect passive motion, JPS: Joint position sense.

NP: Not Provided, NA: Not applicable.

Table 2: Methodological quality score for each of the articles included in the meta-analysis

Scoring Section (maximum score)	Barrack *et al*.,[17]	Fischer-Rasmussen and Jensen[18]	Fremerey *et al*.,[19]	Ozenci *et al*.,[20]	Angoules *et al*.,[21]	Mir *et al*.,[22]
Confirmation of ACL Deficiency (3)	3	1	3	1	3	0
Representation of Population (19)	9	8	10	14	13	10
Representation of Sample (5)	3	0	3	3	3	0
Homogeneity of Participants (13)	5	11	11	7	4	11
Sample Size (25)	3	9	7	9	6	4
Study Design (4)	1	1	1	1	4	1
Assessor Blinding / Bias (5)	5	0	0	0	5	0
Statistical Analysis (14)	1	1	4	3	14	9
Total (88)	**30**	**31**	**39**	**38**	**52**	**35**
Quality Level	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

Note: Studies were grouped in to poor (a score of less than 29/88), moderate (a score of 30-58/88) or good (a score of 59+/88) studies based on their final methodological quality score.