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SYSTEMATIC REVIEW

# Lower Limb Muscle Size after Anterior Cruciate Ligament Injury: A Systematic Review and Meta-Analysis

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## Abstract
**Background** Anterior cruciate ligament (ACL) injury is known to have a number of deleterious effects on lower limb muscle function. Alterations in muscle size are one such effect that have implications towards reductions in strength and functioning of the lower limbs. However, a comprehensive analysis of alterations in muscle size has yet to be undertaken.
**Objective** To systematically review the evidence investigating lower limb muscle size in ACL injured limbs.
**Design** Systematic review
**Data Sources** Database searches of Medline, SPORTDiscus, Embase, Cinahl and Web of Science as well as citation tracking and manual reference list searching.
**Eligibility Criteria for Selecting Studies** Individuals with ACL deficient or reconstructed limbs with an assessment of lower limb muscle size and control limb data (contralateral or uninjured control group)
**Methods** Risk of bias assessment was completed on included studies. Data were extracted and where possible meta-analyses performed. Best evidence synthesis was also undertaken.
**Results** 49 articles were included in this review, with 37 articles included in the meta-analyses. 66 separate meta-analyses were performed using various measures of lower limb muscle size. Across all measures, ACL deficient limbs showed lesser quadriceps femoris muscle size ($d$ range = − 0.35 to − 0.40), whereas ACL reconstructed limbs showed lesser muscle size in the quadriceps femoris ($d$ range = − 0.41 to − 0.69), vastus medialis ($d$ = − 0.25), vastus lateralis ($d$ = − 0.31), hamstrings ($d$ = − 0.28), semitendinosus ($d$ range = − 1.02 to − 1.14) and gracilis ($d$ range = − 0.78 to − 0.99) when compared to uninjured limbs.
**Conclusion** This review highlights the effect ACL injury has on lower limb muscle size. Regardless of whether an individual chooses a conservative or surgical approach, the quadriceps of the injured limb appear to have lesser muscle size compared to an uninjured limb. When undertaking reconstructive surgery with a semitendinosus/gracilis tendon graft, the harvested muscle shows lesser muscle size compared to the uninjured limb.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s40279-020-01419-0.

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**Key Points**

Anterior cruciate ligament (ACL) deficient limbs possess lower quadriceps femoris cross-sectional area and muscle volume than the contralateral uninjured limb.

Limbs with a prior ACL reconstruction have evidence of reduced muscle size in the quadriceps femoris, vastus medialis, vastus lateralis, the hamstrings, semitendinosus and gracilis compared to the contralateral uninjured limb.

In the prior ACL reconstructed limbs, the evidence of reduced muscle size in the quadriceps femoris is greatest within the first 30 weeks post-surgery.

In the prior ACL reconstructed limbs with semitendinosus or semitendinosus-gracilis grafts, there is a large effect and evidence of reduced muscle size in the semitendinosus up to 348 weeks post-surgery.

## 1 Introduction

Anterior cruciate ligament (ACL) rupture, a debilitating injury typically treated with surgical reconstruction to re-establish structural integrity of the knee, is characterised by a lengthy rehabilitation period [1, 2]. Rates of ACL reconstructions are increasing in the USA, Australia, England and New Zealand [3–7], suggesting an increase worldwide. For example, in Australia the rates of ACL reconstruction have risen in the last 15 years and are now the highest in the world per capita at 77.4 per 100 000 persons [6, 7]. The estimated annual cost of ACL surgery to the Australian economy is over $72 million (AUD) [7], not including rehabilitation, income replacement, societal costs and long-term disability associated with the injury. Recent work has shown 55–83% of people return to pre-injury levels of sport [1, 8] and 23% of patients passing return to play criteria [9]. While it is unknown whether the primary injury, surgery, or a combination of both are responsible, an estimated 50% of ACL reconstructed individuals present with radiographic evidence of knee joint osteoarthritis within 10 years following surgery [10, 11].

The long-term negative impacts of ACL injury and reconstructive surgery on knee function are multifactorial. Prior work has identified persistent deficits in objective markers of lower limb muscle function following rehabilitation, including reduced muscle strength [12, 13], muscle activation [14–17], muscle fibre force production [18] and muscle cross-sectional area (CSA) [19–21]. Reductions in quadriceps muscle volume are also noted in both ACL deficient [22, 23] and reconstructed [24–26] individuals. Additionally, reduced semitendinosus and gracilis volume [19, 27] is seen following harvesting of the respective tendons for reconstructive surgery. The reductions in lower limb muscle size seen after ACL injury and surgery may be linked to the decreased levels of strength in ACL injured limbs [19, 28, 29].

Reductions in quadriceps strength is one factor that could lead to alterations in biomechanics and consequently knee joint loading seen following ACL injury. These factors may subsequently influence the development of knee joint osteoarthritis [30–33] and risk of secondary injury [17, 34]. Recent work has also highlighted the influence of other knee and non-knee spanning muscles in contributing to knee joint loading [35–37]. Alterations in the size and strength of other lower limb muscles may contribute to the development of knee joint osteoarthritis and secondary ACL rupture following ACL injury. Combined, these maladaptations suggest that adequate and timely recovery of lower limb muscle size is imperative in restoring health, function and performance in ACL injured individuals.

While a number of systematic reviews have investigated reductions in muscle strength [12, 38], only one has investigated changes in muscle size following ACL injury [39], which focused solely on the quadriceps, without a meta-analysis. Therefore, we aimed to review and meta-analyse the evidence base related to changes in the size of all lower limb muscles in ACL injured populations to better understand the effect of injury and surgery on these individuals, and guide clinical prognoses.

## 2 Methods

### 2.1 Study Design

This review was registered on PROSPERO (ID: CRD42019129262) to reduce the risk of reporting bias and minimise research wastage.

This review is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [40]. A comprehensive systematic literature search of Medline, SPORTDiscus, Embase, Cinahl and Web of Science was conducted. The search terms (Table 1) were chosen to identify original research articles that fit the aims of the review. Where possible relevant MeSH and subject headings were included in the search strategies. The search captured all studies from inception to 17/03/2020 with retrieved references being imported into EndNote X8 (Thomson Reuters, New York City, NY, USA) and all subsequent screening following the PRISMA guidelines [40].

**Table 1** Key search terms. Boolean term OR was used within categories, AND was used between categories

| Body part | Descriptor of injury | Outcome measure |
|---|---|---|
| 'anterior cruciate ligament' | reconstruct* | morpho* |
| acl* | surg* | 'cross sectional area' |
| | injur* | csa |
| | rupture* | volume* |
| | deficien* | size |
| | tear* | thick* |
| | torn | length |

## 2.2 Study Selection

A pre-determined set of inclusion and exclusion criteria were used to screen retrieved articles (Table 2). The lead author (BD) screened the titles and abstracts for relevance. Articles deemed appropriate underwent full text review which was conducted by two authors (BD and JTH) for inclusion in the review. Any disputes were discussed and resolved through consultation with a third author (RGT).

## 2.3 Study Quality Assessment

Methodological quality assessment of included articles was performed using a modified version of the Downs and Black Checklist [41] by two authors (BD and RGT). The original checklist contains 27 items; however, a number of these are only relevant to intervention studies and as this review included mainly retrospective studies, items 4, 8, 13, 14, 15, 19, 20, 22, 23 and 24 were deemed inappropriate to assess study quality and were therefore removed. An additional item (28) was added to assess whether rehabilitation among participants was controlled for and reported in each study [42] (see Electronic Supplementary Material Table S1).

## 2.4 Data Extraction and Analysis

Data extraction included the population (ACL deficient or reconstructed), sample size, control comparisons (whether the uninjured contralateral limb and/or a healthy control group), time since injury or surgery, graft type used in reconstruction, imaging method used (magnetic resonance imaging, computed tomography or ultrasound), size measurement (e.g., muscle CSA, volume or thickness) and site of measurement (if relevant). For all extracted data, group mean and standard deviations (SD) for all reported muscle(s) and muscle groups were collated. Where articles reported standard error (SE), SD was calculated using; $SD = SE \times \sqrt{N}$ due to the statistical analysis applied (SD = standard deviation, SE = standard error, N = sample size).

For articles that reported measures at multiple time points, data from each point were extracted to allow for subgroup and regression analysis. However, articles that reported pre-surgical measures were not included in the ACL deficient analysis [20, 25, 43–46], as clear time points were not given as to when the pre-surgical measure was taken, and thus may have contaminated the results. Where data were not available or reported as median rather than mean, corresponding authors were contacted for the mean and standard deviation.

Where sufficient data were available, meta-analyses were conducted using the 'metafor' [47] and 'meta' [48] packages in R (R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2019). Due to the differing methods and techniques used to calculate the obtained measures of muscle size, standardised mean differences (Cohen's $d$) and 95% confidence intervals were used to facilitate comparisons of studies. A random-effects model with a restricted maximum likelihood (REML) method was used to estimate the overall effect within each measure and subgroup, with the p value set at 0.05. The size of the effect was interpreted as small ($d = 0.20$ to 0.49), moderate ($d = 0.50$ to 0.79) or large ($d \geq 0.8$) [49]. Where a statistically significant overall effect size was seen within a measure, pooled time-point subgroups and meta-regressions were used to estimate the effect of time since surgery within the reconstructed limbs. Where the meta-regression relationship was logarithmic rather than linear, analyses were run with log transformed 'time since surgery' data. Due to the lack of reporting in articles investigating ACL deficient limbs, similar subgroup analyses and meta-regressions were not able to be run in this population.

**Table 2** Inclusion and exclusion criteria applied to retrieved articles

| Inclusion | Exclusion |
|---|---|
| English language | Cadaver studies |
| Full-text original article | Any secondary anterior cruciate ligament injury; revision or contralateral |
| Human subjects | Non-radiological-based measurements |
| Anterior cruciate ligament deficient or reconstructed individuals | Reviews, clinical commentary, conferences papers, case studies |
| Minimum of one morphological muscle measurement, obtained via radiological imaging | Allograft and synthetic graft reconstructions |
| Control data from uninjured limb or healthy control group | |

In some cases multiple groups from the same article appeared within a single meta-analysis. This was due to the reporting style and data in these articles being different populations (e.g., male or female, experiment or control). The decision was made to preserve the original mean and SD values and include them in the meta-analysis as separate cohorts. Where this occurs, article names in the forest plots are followed by brackets indicating the subgroup from the article.

Where a meta-analysis was unable to be run due to the inability to obtain data from the corresponding author, a best evidence synthesis was employed [50]. The level of evidence was ranked according to the following criteria;

- Strong: two or more studies of a high quality and generally consistent findings (≥ 75% of studies showing consistent results).
- Moderate: one high-quality study and/or two or more low quality studies and generally consistent findings (≥ 75% of studies showing consistent results).
- Limited: one low-quality study.
- Conflicting: inconsistent findings (< 75% of studies showing consistent results).
- None: no supportive findings in the literature.

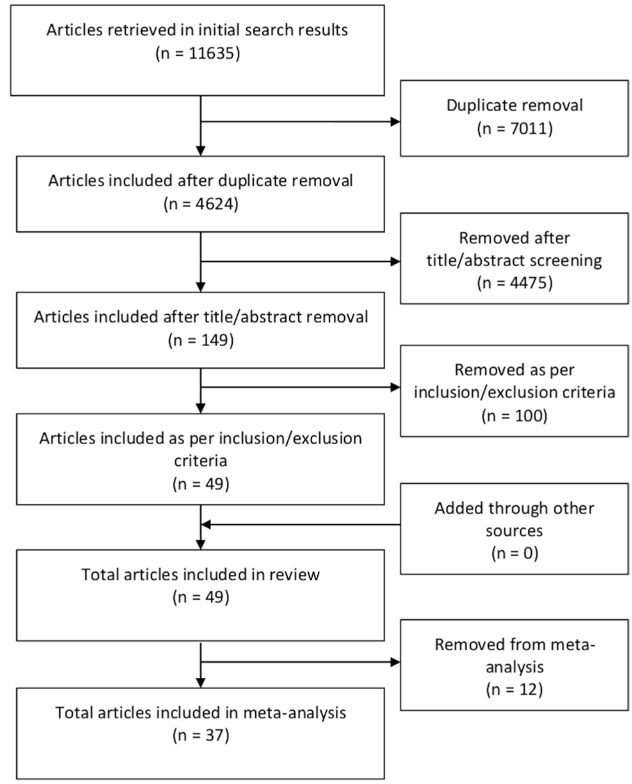



**Fig. 1** Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flowchart outlining study selection process

## 3 Results

### 3.1 Search Results

The initial search yielded 11,635 articles (Cinahl = 1187, Embase = 2693, Medline = 3129, SPORTDiscus = 1079 and Web of Science = 3547). After duplicate removal, title/abstract screening and full text review, a total of 49 articles were deemed eligible for inclusion in this review (Fig. 1).

### 3.2 Study Quality Assessment

Electronic Supplementary Material Table S2 shows the results of the quality assessment. Study quality ranged from 7 to 20 out of 20, with 27 articles (55%) deemed high quality.

### 3.3 Meta-analysis

Of the 49 articles included in this review, 37 [19–23, 25–27, 29, 43–46, 51–74] were included in the meta-analyses. The data have been grouped into five main comparisons:

1. Muscle CSA of ACL deficient limbs compared to the contralateral uninjured limb (Table 3);
2. Muscle volume of ACL deficient limbs compared to the contralateral uninjured limb (Table 4);
3. Muscle CSA of ACL reconstructed limbs compared to the contralateral uninjured limb (Table 5);
4. Muscle volume of ACL reconstructed limbs compared to the contralateral uninjured limb (Table 6) and
5. Muscle volume of ACL reconstructed limbs compared to a healthy control group (Electronic Supplementary Material Table S3).

Overall, there were 66 meta-analyses run, with 11 showing statistically significant effects. These 11 indicated reduced muscle size in specific muscles and muscle groups within the ACL deficient or reconstructed limbs when compared to the contralateral uninjured limbs. No statistically significant effects were found when comparing the ACL reconstructed limb to a healthy control group.

### 3.4 ACL Deficient Populations

Summaries of the results of the meta-analyses comparing the muscle CSA and volume of ACL deficient limbs to the contralateral uninjured limbs are found in Tables 3 and 4, respectively. Of these results, 12 measures of muscle CSA and 11 measures of muscle volume were analysed, with 2 showing statistically significant effect sizes.

**Table 3** Meta-analysis results for muscle cross-sectional area of the ACL deficient limb compared to the contralateral uninjured limb

| Muscle | Number of studies | Number of participants | Results |
|---|---|---|---|
| Biceps femoris—long head | 2 [22, 23] | 37 | X |
| Biceps femoris—short head | 2 [22, 23] | 37 | X |
| Gracilis | 2 [23, 72] | 79 | X |
| Hamstrings | 4 [22, 23, 59, 65] | 76 | X |
| Quadriceps | 5 [22, 23, 59, 65, 72] | 138 | ↓ |
| Rectus femoris | 2 [22, 23] | 37 | X |
| Sartorius | 2 [23, 72] | 79 | X |
| Semimembranosus | 3 [22, 23, 72] | 99 | X |
| Semitendinosus | 3 [22, 23, 72] | 99 | X |
| Vastus intermedius | 2 [22, 23] | 37 | X |
| Vastus lateralis | 2 [22, 23] | 37 | X |
| Vastus medialis | 2 [22, 23] | 37 | X |

↓ = significantly reduced cross-sectional area in the ACL deficient limb compared to the contralateral uninjured limb

X = no significant difference between limbs

**Table 4** Meta-analysis results for muscle volume of the ACL deficient limb compared to the contralateral uninjured limb

| Muscle | Number of studies | Number of participants | Results |
|---|---|---|---|
| Biceps femoris—long head | 2 [22, 23] | 37 | X |
| Biceps femoris – short head | 2 [22, 23] | 37 | X |
| Gracilis | 2 [23, 62] | 39 | X |
| Hamstrings | 4 [22, 23, 62, 74] | 77 | X |
| Quadriceps | 3 [22, 23, 74] | 55 | ↓ |
| Rectus femoris | 2 [22, 23] | 37 | X |
| Semimembranosus | 2 [22, 23] | 37 | X |
| Semitendinosus | 2 [22, 23] | 37 | X |
| Vastus intermedius | 2 [22, 23] | 37 | X |
| Vastus lateralis | 2 [22, 23] | 37 | X |
| Vastus medialis | 2 [22, 23] | 37 | X |

↓ = significantly reduced muscle volume in the ACL deficient limb compared to the contralateral uninjured limb

X = no significant difference between limbs

#### 3.4.1 Quadriceps Femoris

When comparing the ACL deficient limbs to the contralateral uninjured limbs, there was a moderate effect for both quadriceps femoris muscle CSA ($d = -0.35$; 95% CI $-0.59$ to $-0.11$; $I^2 = 0\%$, Fig. 2a) and volume ($d = -0.40$; 95% CI $-0.78$ to $-0.02$; $I^2 = 18\%$, Fig. 2b) indicating reduced muscle size in the deficient limb. All other muscles and groups showed no statistically significant effects (Table 3 and 4).

### 3.5 ACL Reconstructed Populations

Summaries of the results of the meta-analyses comparing muscle CSA and volume of the ACL reconstructed limbs to the contralateral uninjured limbs can be found in Tables 5 and 6, respectively. Of those included, 16 measures of muscle CSA and 12 measures of muscle volume were analysed, with 9 showing differences between limbs.

#### 3.5.1 Quadriceps Femoris

There was a moderate effect for both quadriceps femoris CSA and volume, indicating reduced muscle size in the reconstructed limbs when compared to the contralateral uninjured limb (Fig. 3). For quadriceps femoris CSA data, time subgrouping analysis showed large effects between limbs at 6 to 9 weeks and 26 to 30 weeks, whereas moderate effects were seen between limbs at both 52 to 86 weeks and 156 to 289 weeks (Fig. 3a). Studies included in the quadriceps femoris CSA meta-analysis had participants with a mix of harvest sites used for ACL reconstruction (patella tendon, iliotibial band and semitendinosus-gracilis tendon). For quadriceps femoris volume data, time subgrouping showed a large effect between limbs at 4 to 12 weeks (Fig. 3b). Studies included in the quadriceps femoris volume meta-analyses had participants with a mix of harvest sites used for ACL reconstruction (patella tendon, semitendinosus tendon and semitendinosus-gracilis tendon). Meta-regression analysis found no significant effect for time since surgery on quadriceps femoris CSA; however, a significant positive effect was seen for volume in the ACL-reconstructed limbs indicating differences between limbs decreased over time. (Electronic

**Table 5** Meta-analysis results for muscle cross-sectional area of the ACL reconstructed limb compared to the contralateral uninjured limb

| Muscle | Number of studies | Number of participants | Results |
|---|---|---|---|
| Biceps femoris | 4 [20, 45, 53, 71] | 135 | X |
| Biceps femoris – long head | 4 [19, 27, 66, 73] | 48 | X |
| Biceps femoris – short head | 4 [19, 27, 66, 73] | 48 | X |
| Gastrocnemius – lateral head | 2 [19, 73] | 28 | X |
| Gastrocnemius – medial head | 2 [19, 73] | 28 | X |
| Gracilis | 7 [19, 20, 45, 53, 58, 66, 73] | 182 | ↓ |
| Hamstrings | 6 [19, 27, 51, 52, 64, 73] | 102 | X |
| Quadriceps | 12 [19, 20, 29, 45, 46, 52, 53, 55, 64, 68, 70, 73] | 317 | ↓ |
| Rectus femoris | 3 [19, 57, 73] | 54 | X |
| Sartorius | 5 [19, 20, 66, 71, 73] | 80 | X |
| Semitendinosus | 10 [19, 20, 27, 45, 53, 54, 56, 58, 66, 73] | 293 | ↓ |
| Semimembranosus | 9 [19, 20, 27, 45, 53, 54, 66, 71, 73] | 199 | X |
| Thigh | 2 [54, 64] | 29 | X |
| Vastus intermedius | 2 [19, 73] | 28 | X |
| Vastus lateralis | 3 [19, 46, 73] | 47 | X |
| Vastus medialis | 2 [19, 73] | 28 | X |

↓ = significantly reduced muscle cross-sectional area in the ACL reconstructed limb compared to the contralateral uninjured limb

X = no significant difference between limbs

**Table 6** Meta-analysis results for muscle volume of the ACL reconstructed limb compared to the contralateral uninjured limb

| Muscle | Number of studies | Number of participants | Results |
|---|---|---|---|
| Biceps femoris – long head | 4 [19, 27, 66, 73] | 48 | X |
| Biceps femoris short head | 4 [19, 27, 66, 73] | 48 | X |
| Gracilis | 3 [19, 66, 73] | 34 | ↓ |
| Hamstrings | 4 [19, 27, 60, 73] | 114 | ↓ |
| Quadriceps | 7 [19, 25, 26, 61, 63, 68, 73] | 217 | ↓ |
| Rectus femoris | 6 [19, 26, 43, 61, 63, 73] | 173 | X |
| Sartorius | 3 [19, 66, 73] | 34 | X |
| Semitendinosus | 7 [19, 21, 27, 60, 66, 69, 73] | 165 | ↓ |
| Semimembranosus | 5 [19, 27, 60, 66, 73] | 118 | X |
| Vastus lateralis | 6 [19, 26, 44, 61, 63, 73] | 143 | ↓ |
| Vastus medialis | 6 [19, 26, 61, 63, 67, 73] | 166 | ↓ |
| Vastus intermedius | 5 [19, 61, 63, 64, 73] | 133 | X |

↓ = significantly reduced muscle volume in the ACL reconstructed limb compared to the contralateral uninjured limb

X = no significant difference between limbs

Supplementary Material Figure S1; intercept = 1.245, $p = 0.0002$; coefficient = 0.517, $p = 0.008$).

#### 3.5.2 Vastus Medialis

A small effect was found for vastus medialis volume, indicating reduced muscle size in the reconstructed limb when compared to the contralateral uninjured limb (Fig. 4a). Time subgrouping showed a moderate effect between limbs at 45 to 86 weeks (Fig. 4a). Studies included in the meta-analyses had participants with a mix of harvest sites used for ACL reconstruction (patella tendon, semitendinosus tendon and semitendinosus-gracilis tendon). Meta-regression analysis showed no significant effect for time since surgery on vastus medialis volume in the ACL reconstructed limb (Electronic Supplementary Material Table S4).

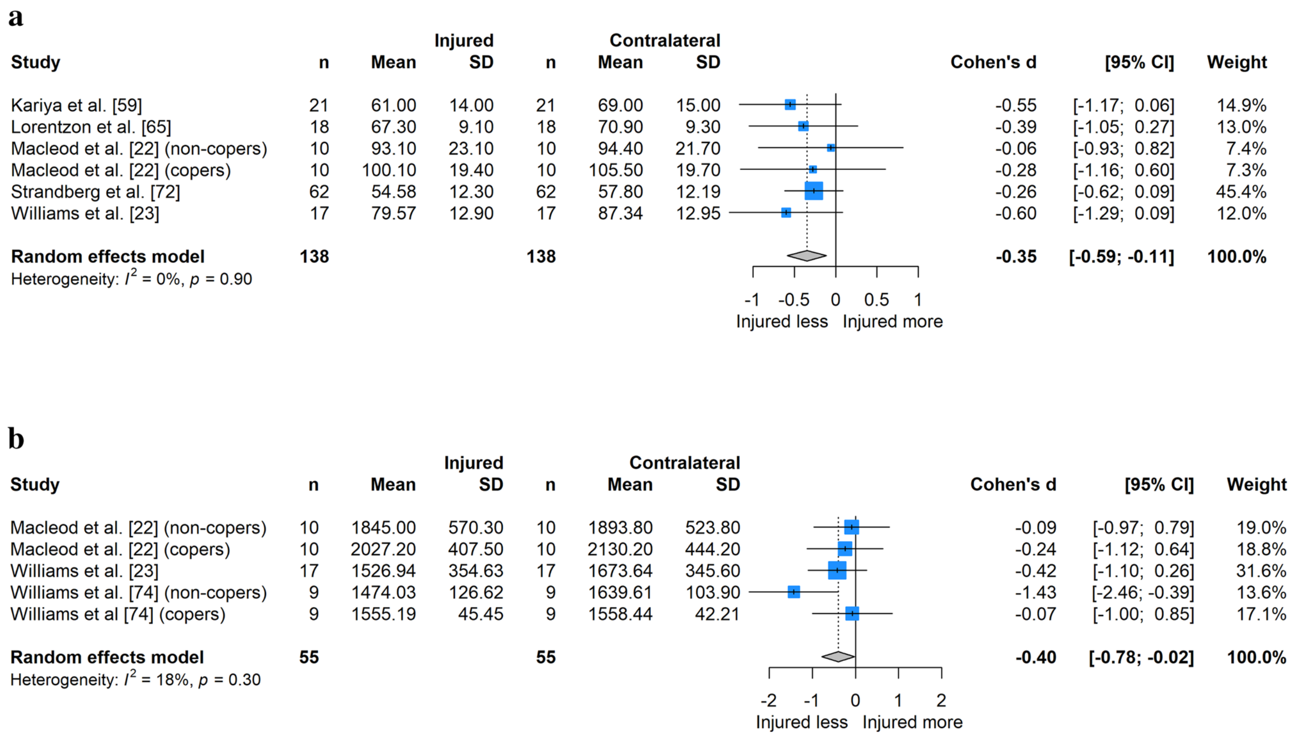



**Fig. 2** Results of the meta-analysis for **a** quadriceps femoris muscle cross-sectional area, and **b** quadriceps femoris muscle volume, in the ACL deficient limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

#### 3.5.3 Vastus Lateralis

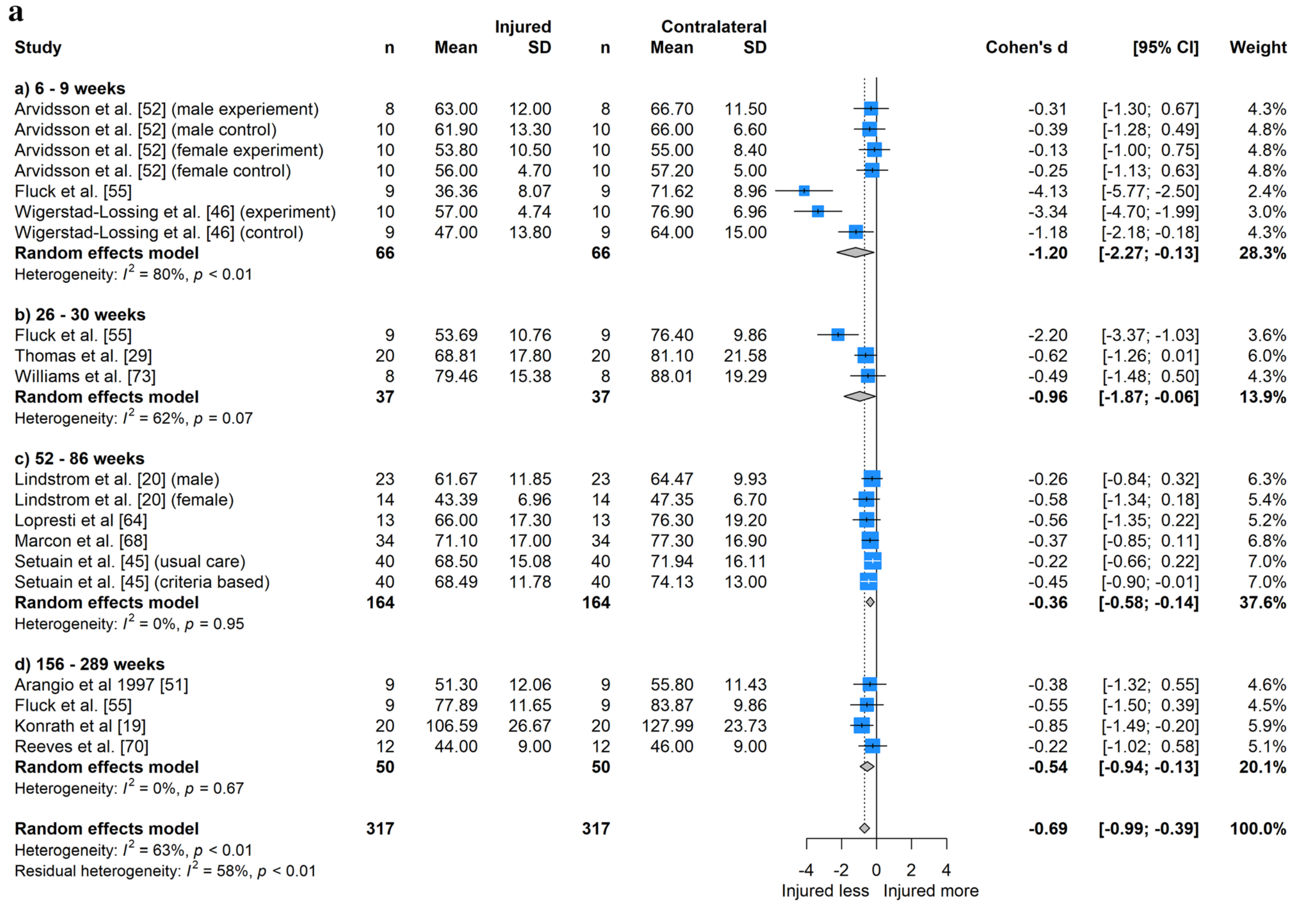
Similar to the vastus medialis, a small effect was found for vastus lateralis volume, indicating reduced muscle size in the reconstructed limb when compared to the contralateral uninjured limb (Fig. 4b). Time subgrouping showed no effects between limbs at any subgroup (Fig. 4b). Studies included in the meta-analyses had participants with a mix of harvest sites used for ACL reconstruction (patella tendon, semitendinosus tendon and semitendinosus-gracilis tendon). Meta-regression analysis showed no significant effect for time since surgery on vastus lateralis volume in the ACL reconstructed limb (Electronic Supplementary Material Table S4).

#### 3.5.4 Hamstrings

A small effect was found for total hamstring muscle volume indicating reduced muscle size in the reconstructed limb when compared to the contralateral uninjured limb (Fig. 5). Time subgrouping analysis showed no significant effects between limbs for any time subgroup (Fig. 5). Studies included in the hamstring meta-analysis had participants with either semitendinosus or semitendinosus-gracilis harvested for ACL reconstruction. Meta-regression analysis also showed no significant effect for time since surgery on total hamstring muscle volume in the ACL reconstructed limbs (Electronic Supplementary Material Table S4).

#### 3.5.5 Semitendinosus

A large effect was found for semitendinosus muscle CSA and volume, indicating reduced muscle size in the reconstructed limb when compared to the contralateral uninjured limb (Fig. 6). For semitendinosus CSA, time subgrouping analysis showed a large effect at both 52 to 53 weeks and 156 to 348 weeks post-surgery, whilst a moderate effect between limbs was seen at 26 to 30 weeks (Fig. 6a). For semitendinosus muscle volume, time subgrouping showed a large effect between limbs at 26 weeks, 100 to 156 and 212 to 348 weeks post-surgery (Fig. 6b). All studies included in the meta-analyses for semitendinosus CSA and volume had participants with semitendinosus tendon harvested for ACL reconstruction. Meta-regression analysis showed no effect for time since surgery on semitendinosus muscle CSA or volume in the ACL reconstructed limbs (Electronic Supplementary Material Table S4).



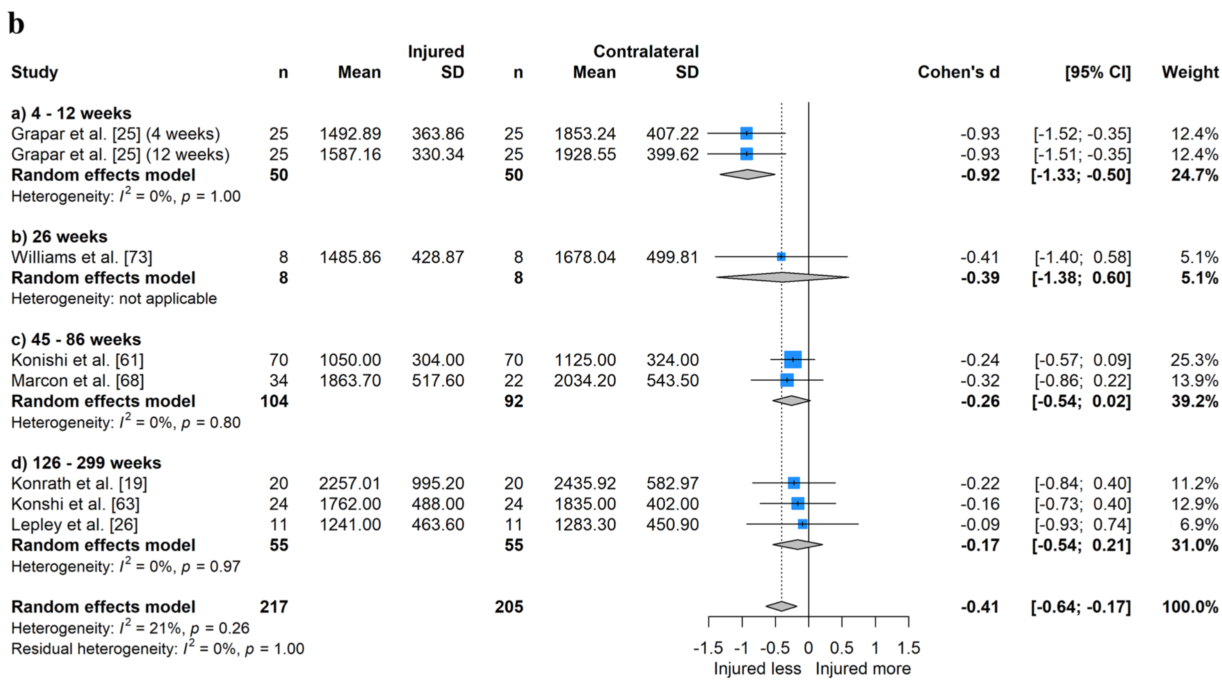




**Fig. 3** Results of the meta-analysis for **a** quadriceps femoris cross-sectional area, and **b** quadriceps femoris muscle volume, in the ACL reconstructed limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

#### 3.5.6 Gracilis

Large and moderate effects for gracilis muscle CSA and volume were found, indicating reduced muscle size in the reconstructed limb when compared to the contralateral uninjured limb (Fig. 7). For gracilis CSA data, time subgrouping showed large effects between limbs at 52 to 53 weeks and 104 to 348 weeks post-surgery (Fig. 7a). For gracilis muscle volume data, time subgrouping analysis showed a moderate effect at 156 to 348 weeks post-surgery (Fig. 7b). All studies included in the meta-analysis for gracilis CSA and volume had participants with gracilis tendon harvested for ACL reconstruction. Meta-regression analysis showed no effect for time since surgery on gracilis CSA or volume in the ACL reconstructed limbs (Electronic Supplementary Material Table S4).

### 3.6 Best Evidence Synthesis

Of the 49 articles included in this review, 12 were not in the above meta-analyses for the following reasons:

- Data not able to be obtained ($n=8$) [24, 75–81]
- Unique measures of ultrasound muscle size that were not grouped for meta-analysis ($n=4$) [82–85].

For these articles a best evidence synthesis (BES) was undertaken (Table 7). Due to the low number of studies, all of the muscle size measures were combined to obtain a single outcome for each muscle and group.

#### 3.6.1 Quadriceps—ACL Reconstructed Limb Compared to Contralateral Uninjured Limb

When comparing the ACL reconstructed limbs to the contralateral uninjured limbs there was strong evidence to suggest reduced muscle size in the reconstructed limbs quadriceps femoris, vastus lateralis and rectus femoris (Table 7). There was also moderate evidence to suggest reduced muscle size in the vastus medialis and vastus intermedius. Similar to the meta-analyses for these muscles, studies included participants with mixed graft types (patella tendon, quadriceps tendon, iliotibial tract, semitendinosus tendon and semitendinosus-gracilis tendon).

#### 3.6.2 Knee Flexors—ACL Reconstructed Limb Compared to Contralateral Uninjured Limb

There was moderate and strong evidence to suggest reduced muscle size in the reconstructed limbs semitendinosus and gracilis muscles of the ACL reconstructed limbs, respectively, when compared to the contralateral uninjured limbs. There was also limited and strong evidence to suggest no difference in semimembranosus and biceps femoris ultrasound-derived muscle size, respectively (Table 7). Similar to the meta-analysis on these measures, studies included (or provided subgroup results for) participants with the semitendinosus and/or gracilis tendon harvested for reconstruction.

#### 3.6.3 Gluteus maximus—ACL Reconstructed Limb Compared to Contralateral Uninjured Limb

When comparing the ACL reconstructed limbs to the contralateral uninjured limbs there was moderate evidence to suggest reduced muscle size in the gluteus maximus of the reconstructed limb (Table 7). The single study that presented these data included participants with mixed graft types (patella tendon and semitendinosus-gracilis tendon).

#### 3.6.4 Hamstrings—ACL Reconstructed Limb Compared to Healthy Control Group

When comparing the ACL reconstructed limb to a healthy control group, there was strong evidence to suggest an increase in semitendinosus size in the reconstructed limb (Table 7); however, studies included participants with mixed graft types (patella tendon and semitendinosus tendon). There was also moderate evidence to suggest reduced muscle size in the biceps femoris of the reconstructed limb from a single study that included participants with patella tendon grafts. Finally, there is moderate evidence to suggest there is no difference in semimembranosus size between the groups with the one study using this measure including participants with patella tendon grafts.

## 4 Discussion

### 4.1 Statement of Main Findings

The main findings of this systematic review and meta-analyses are:

1. ACL deficient limbs (without subsequent surgical repair) have lower quadriceps femoris CSA and volume than the contralateral uninjured limb.
2. Regardless of graft site, ACL reconstructed limbs have lower quadriceps femoris CSA and deficits in quadriceps femoris, vastus medialis and vastus lateralis volume compared to the contralateral uninjured limb.
3. ACL reconstructed limbs have lower semitendinosus and gracilis CSA and muscle volume as well as lower total hamstring muscle volume compared to the contralateral uninjured limbs, when the respective tendons are harvested for reconstruction.

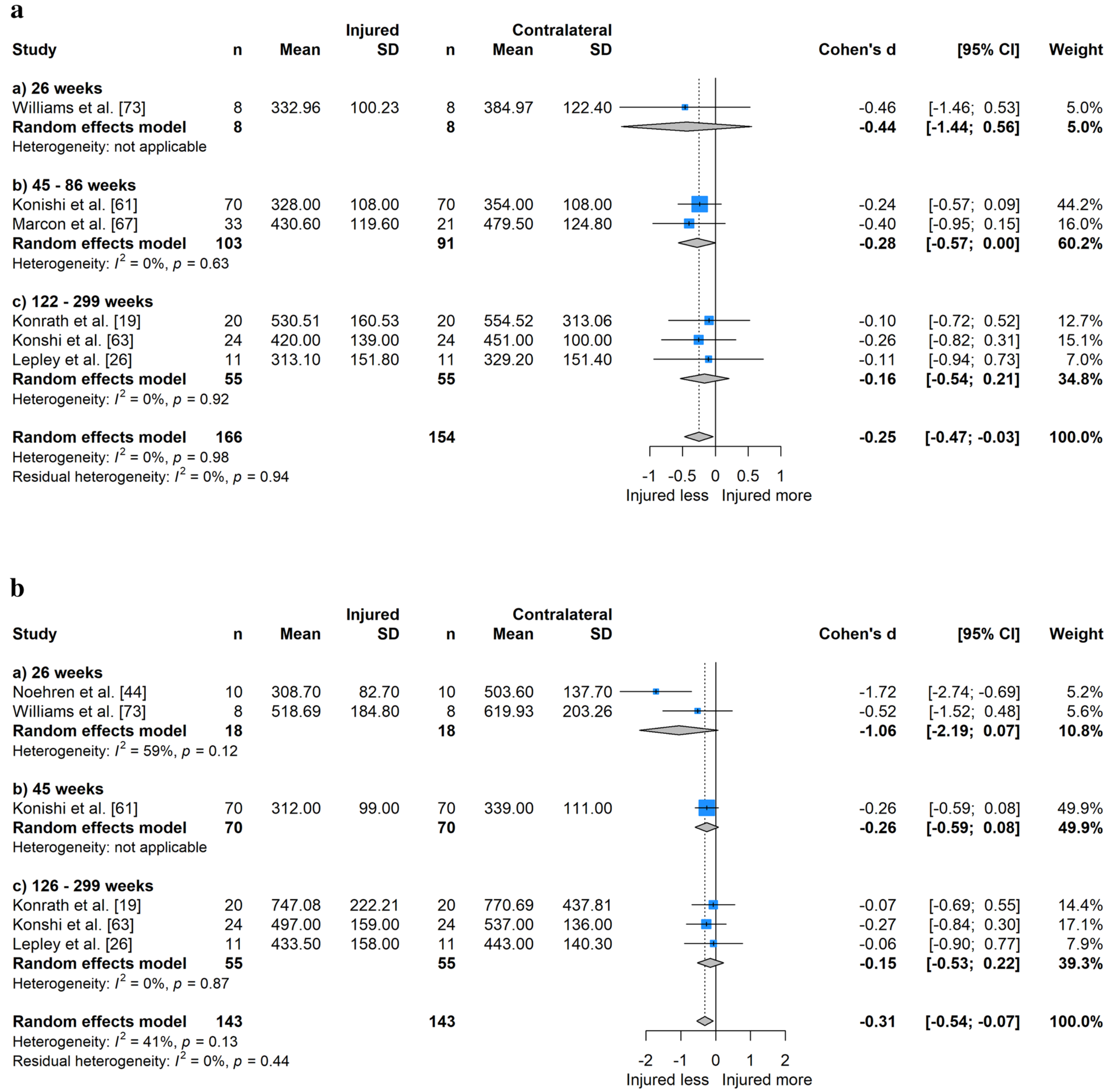



**Fig. 4** Results of the meta-analysis for **a** vastus medialis, and **b** vastus lateralis muscle volume, in the ACL reconstructed limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

## 4.2 ACL Deficient Limbs

Suffering an ACL rupture causes knee joint instability, which is commonly treated with a surgical reconstruction. However, there is evidence to suggest approximately 25% of ACL injured individuals have successful 2-year outcomes and comparable knee function to non-injured individuals, without reconstructive surgery [86]. Conservative management of ACL injury carries some benefits over a surgical approach, namely avoiding the trauma and extensive healing time-frame associated with reconstructive surgery, as well as graft site morbidity. However, the results of the current meta-analysis highlight the atrophic effects the initial injury has on selected lower limb muscles. In ACL deficient limbs, quadriceps femoris muscle size appears significantly impacted by injury, showing reductions in both CSA and volume compared to the contralateral uninjured limb. It remains unclear if this reduction in quadriceps femoris size influences an individual's ability to successfully undergo conservative management.

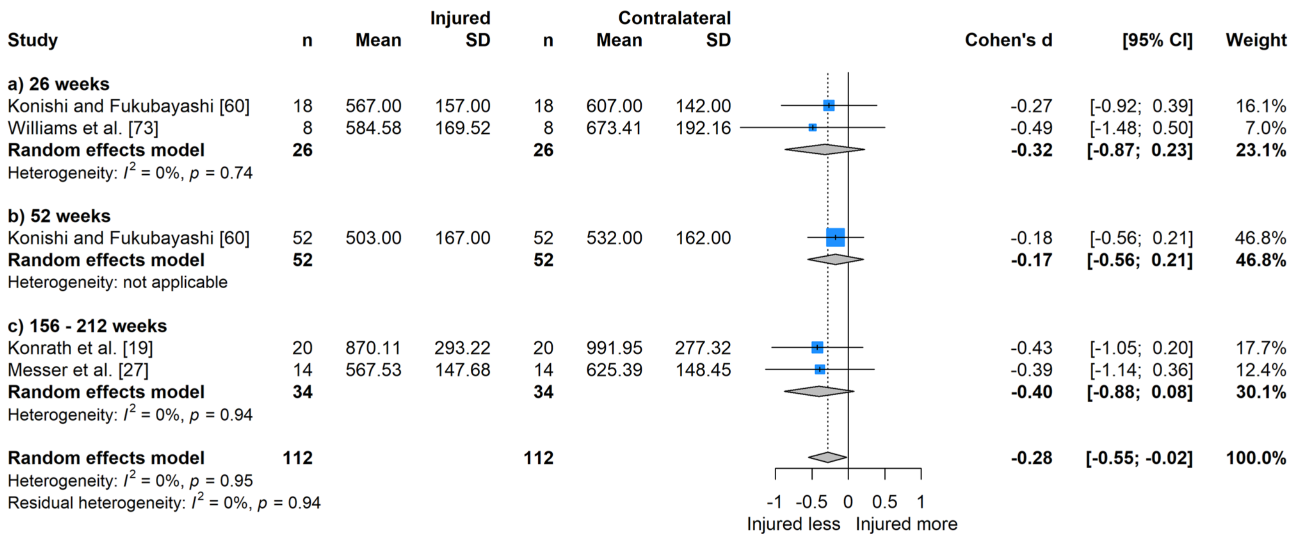



**Fig. 5** Results of the meta-analysis for total hamstring muscle volume in the ACL reconstructed limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

## 4.3 ACL Reconstructed Populations

Similar to the ACL deficient limbs, reconstructed limbs showed significantly reduced quadriceps femoris muscle size. This is in agreement with the results of a recent meta-analysis that investigated changes in quadriceps CSA and volume following ACL reconstruction [39]. It is beyond the scope of this meta-analysis to assess any differences between graft types, but it appears all grafts (semitendinosus/gracilis and patella tendon) result in significantly reduced quadriceps size. The meta-regression results suggested that quadriceps femoris CSA did not change as a function of time, but volume did appear to improve showing a reduction in effect size between limbs. This finding combined with the results from post-operative subgrouping in CSA and volume suggests that this reduction in muscle size may be most pronounced during early recovery, slowly returning to near that of the uninjured limb over the first 2 years following surgery.

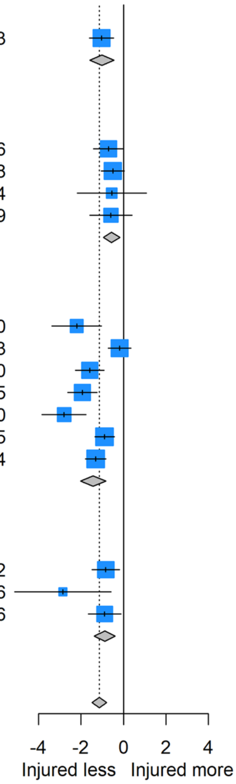
Further breakdown of the individual muscles within the quadriceps group showed that reduced muscle size is most likely concentrated in the vasti muscles, in particular vastus medialis and vastus lateralis which showed significantly reduced volume compared to the uninjured limb. Rectus femoris CSA and volume data showed no significant differences within the meta-analyses. However, the best evidence synthesis suggested strong evidence towards reduced rectus femoris muscle size in the ACL reconstructed limb when compared to the uninjured limb. These findings suggest that a percentage of ACL reconstructed individuals present with reduced rectus femoris size, although this may not present as commonly as reductions in the vasti muscles. The reason for this remains unclear; however, it may be in part due to the differing action of the rectus femoris. Unlike the vasti muscles, the rectus femoris is a hip flexor, potentially exposing it to a unique stimulus (relative to the vasti) in the post-operative period and thus protecting it against atrophy.

In the ACL reconstructed limbs there was evidence of reduced total hamstring muscle volume when compared to the contralateral uninjured limb. This seems to be solely attributed to a large reduction in the semitendinosus muscle size, when its tendon is harvested for reconstruction. Similar to the quadriceps femoris CSA findings, semitendinosus meta-regression analysis showed no significant impact of time since surgery on semitendinosus CSA and volume. However, subgrouping for time suggests that reductions in semitendinosus muscle size occur within the first few months following surgery but, unlike the quadriceps femoris findings, do not recover, with the latest available data (348 weeks post-surgery) showing large deficits in the reconstructed limb [27, 66].

Similarly, the gracilis of the ACL reconstructed limbs have significantly reduced CSA and volume when compared to the contralateral uninjured limb when the gracilis tendon is harvested for reconstruction. This is also strongly supported within the best evidence synthesis. Whilst the meta-regression-analyses showed no significant impact of time since surgery on gracilis CSA and volume, when subgrouping for time, the findings suggest that a reduction in muscle size is apparent within the first few months following surgery and does not recover up to 348 weeks later.

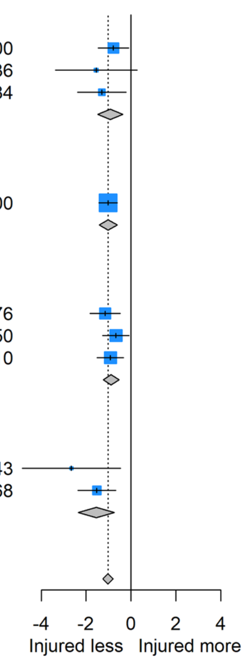
**a**

| Study | Injured n | Injured Mean | Injured SD | Contralateral n | Contralateral Mean | Contralateral SD | Cohen's d | [95% CI] | Weight |
|---|---|---|---|---|---|---|---|---|---|
| **a) 13 weeks** | | | | | | | | | |
| Gandolfi et al. [56] | 27 | 7.81 | 1.13 | 27 | 9.14 | 1.43 | -1.03 | [-1.60; -0.46] | 8.2% |
| **Random effects model** | **27** | | | **27** | | | **-1.02** | **[-1.59; -0.45]** | **8.2%** |
| Heterogeneity: not applicable | | | | | | | | | |
| **b) 26 - 30 weeks** | | | | | | | | | |
| Eriksson et al. [54] | 16 | 10.64 | 2.98 | 16 | 12.67 | 2.76 | -0.71 | [-1.42; 0.01] | 7.3% |
| Gandolfi et al. [56] | 27 | 8.06 | 1.41 | 27 | 8.87 | 1.78 | -0.50 | [-1.05; 0.04] | 8.3% |
| Macleod et al. [66] | 3 | 9.15 | 2.50 | 3 | 11.12 | 4.34 | -0.55 | [-2.18; 1.08] | 3.2% |
| Williams et al [73] | 8 | 7.90 | 2.53 | 8 | 9.71 | 3.49 | -0.59 | [-1.60; 0.41] | 5.6% |
| **Random effects model** | **54** | | | **54** | | | **-0.56** | **[-0.95; -0.17]** | **24.4%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.98$ | | | | | | | | | |
| **c) 52 - 53 weeks** | | | | | | | | | |
| Burks et al. [53] | 9 | 2.10 | 1.60 | 9 | 6.60 | 2.40 | -2.21 | [-3.38; -1.03] | 4.8% |
| Gandolfi et al. [56] | 27 | 9.42 | 1.37 | 27 | 9.68 | 1.43 | -0.19 | [-0.72; 0.35] | 8.4% |
| Janssen et al. [58] | 22 | 8.30 | 3.00 | 22 | 14.00 | 4.10 | -1.59 | [-2.26; -0.91] | 7.5% |
| Lindstrom et al. [20] (male) | 23 | 1.80 | 2.30 | 23 | 6.40 | 2.45 | -1.94 | [-2.64; -1.24] | 7.3% |
| Lindstrom et al. [20] (female) | 14 | 1.42 | 1.42 | 14 | 5.51 | 1.50 | -2.80 | [-3.84; -1.76] | 5.4% |
| Setuain et al. [45] (usual care) | 40 | 6.26 | 2.08 | 40 | 8.58 | 3.05 | -0.89 | [-1.35; -0.43] | 8.8% |
| Setuain et al. [45] (criteria based) | 40 | 6.31 | 1.58 | 40 | 8.79 | 2.14 | -1.32 | [-1.80; -0.83] | 8.7% |
| **Random effects model** | **175** | | | **175** | | | **-1.43** | **[-2.03; -0.83]** | **50.9%** |
| Heterogeneity: $I^2 = 80\%$, $p < 0.01$ | | | | | | | | | |
| **d) 156 - 348 weeks** | | | | | | | | | |
| Konrath et al. [19] | 20 | 9.25 | 3.89 | 20 | 12.16 | 3.02 | -0.84 | [-1.48; -0.19] | 7.7% |
| Macleod et al. [66] | 3 | 6.24 | 1.21 | 3 | 11.95 | 2.56 | -2.85 | [-5.12; -0.58] | 1.9% |
| Messer et al. [27] | 14 | 8.95 | 4.03 | 14 | 12.42 | 3.76 | -0.89 | [-1.67; -0.11] | 6.9% |
| **Random effects model** | **37** | | | **37** | | | **-0.89** | **[-1.38; -0.40]** | **16.5%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.59$ | | | | | | | | | |
| **Random effects model** | **293** | | | **293** | | | **-1.14** | **[-1.48; -0.79]** | **100.0%** |
| Heterogeneity: $I^2 = 68\%$, $p < 0.01$ | | | | | | | | | |
| Residual heterogeneity: $I^2 = 66\%$, $p < 0.01$ | | | | | | | | | |




**b**

| Study | Injured n | Injured Mean | Injured SD | Contralateral n | Contralateral Mean | Contralateral SD | Cohen's d | [95% CI] | Weight |
|---|---|---|---|---|---|---|---|---|---|
| **a) 26 week** | | | | | | | | | |
| Konishi and Fukubayashi [60] | 18 | 99.00 | 44.00 | 18 | 134.00 | 45.00 | -0.79 | [-1.46; -0.11] | 11.6% |
| Macleod et al. [66] | 3 | 102.67 | 16.51 | 3 | 199.27 | 86.36 | -1.55 | [-3.38; 0.27] | 1.6% |
| Williams et al. [73] | 8 | 95.19 | 36.36 | 8 | 168.54 | 70.84 | -1.30 | [-2.38; -0.22] | 4.6% |
| **Random effects model** | **29** | | | **29** | | | **-0.92** | **[-1.48; -0.37]** | **17.7%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.74$ | | | | | | | | | |
| **b) 52 weeks** | | | | | | | | | |
| Konishi and Fukubayashi [60] | 52 | 72.00 | 38.00 | 52 | 114.00 | 44.00 | -1.02 | [-1.43; -0.61] | 31.8% |
| **Random effects model** | **52** | | | **52** | | | **-1.01** | **[-1.42; -0.60]** | **31.8%** |
| Heterogeneity: not applicable | | | | | | | | | |
| **c) 100 - 156 weeks** | | | | | | | | | |
| Konrath et al. [19] | 20 | 123.85 | 75.14 | 20 | 234.44 | 112.76 | -1.15 | [-1.82; -0.48] | 11.9% |
| Nishino et al. [69] | 23 | 111.40 | 55.70 | 23 | 152.50 | 65.50 | -0.68 | [-1.27; -0.08] | 15.0% |
| Nomura et al. [21] | 24 | 132.80 | 44.30 | 24 | 178.90 | 55.10 | -0.92 | [-1.52; -0.33] | 15.0% |
| **Random effects model** | **67** | | | **67** | | | **-0.88** | **[-1.24; -0.53]** | **41.9%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.59$ | | | | | | | | | |
| **d) 212 - 348 weeks** | | | | | | | | | |
| Macleod et al. [66] | 3 | 78.20 | 36.24 | 3 | 223.69 | 68.43 | -2.66 | [-4.85; -0.46] | 1.1% |
| Messer et al. [27] | 14 | 98.48 | 54.38 | 14 | 179.40 | 51.68 | -1.53 | [-2.37; -0.68] | 7.5% |
| **Random effects model** | **17** | | | **17** | | | **-1.54** | **[-2.35; -0.73]** | **8.6%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.64$ | | | | | | | | | |
| **Random effects model** | **165** | | | **165** | | | **-1.02** | **[-1.25; -0.79]** | **100.0%** |
| Heterogeneity: $I^2 = 0\%$, $p = 0.63$ | | | | | | | | | |
| Residual heterogeneity: $I^2 = 0\%$, $p = 0.87$ | | | | | | | | | |



◂**Fig. 6** Results of the meta-analysis for, **a** semitendinosus muscle cross-sectional area, and **b** semitendinosus muscle volume, in the ACL reconstructed limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

### 4.4 Clinical Implications

Reductions in quadriceps muscle size are potentially impacted through two key mechanisms: (1) disuse atrophy associated with the period of unloading post-injury and surgery [87, 88]; (2) neuromuscular inhibition, which lowers neural drive and fibre recruitment, leading to a lessened stimulus for adaptation, which is shown to significantly impact the quadriceps post-injury and surgery [23, 26, 28]. The quadriceps contribute the majority of force to knee joint compressive loading [35], as well supporting, braking and redirecting the centre of mass during sports specific movements such as side step cutting [89]. Quadriceps dysfunction therefore may impact the development of both knee joint osteoarthritis, and the potential for secondary ACL injury. Addressing the atrophy of the quadriceps muscle group in ACL deficient and reconstructed limbs, through exercise-based interventions should be of high importance and started as early as possible. However, care needs to be taken when aiming to restore quadriceps muscle size following reconstruction as time is needed for biological healing post-surgery, as well as allowing for the incorporation of grafted tissue into the ACL. Eccentrically biased [75] and blood flow-restricted resistance training [90, 91] have been shown to be safe and effective approaches to improve muscle size in the early post-operative period. Consequently both of these approaches represent an opportunity to address the potential quadriceps atrophy in the early period post-surgery and prepare the individual for the higher resistance training loads in the later parts of the program which will also promote optimum muscle mass gains.

Restoration of semitendinosus and gracilis size following tendon harvest for ACL reconstruction may be limited, as the structural integrity of the muscle–tendon unit is severely disrupted due to the surgical intervention. This is supported by our results with the longest period post-surgery that was available (348 weeks) still showing significant deficits in the ACL reconstructed limb. The choice of graft remains a key consideration for surgeons to factor in when initially choosing a harvest site for reconstruction, as it is possible that the reduction in size and therefore the force producing capacity of the semitendinosus and gracilis may be permanent. Although work appears to be underway looking to address these deficits [92], to date, the authors are not aware of any published exercise interventions showing a restoration of semitendinosus and gracilis muscle size following tendon harvest for ACL reconstruction. Future research should continue to investigate if exercise-based interventions in these muscles might be a useful approach to offset the extent of what seems inevitable atrophy.

### 4.5 Quality Assessment

Overall, only 55% of articles included in this review were deemed to be of a high quality. There were two areas of poor performance in the quality assessment that may have the potential to significantly impact the findings of included articles. These were: (1) there was a lack of control in post-operative rehabilitation, with only 55% of all articles included in this review controlling for rehabilitation and (2) there were low percentages of external validity, with only 22% reporting the source of the population and how they were selected, and only 8% reporting the proportion of participants asked who agreed to participate. The low percentage scoring in these areas suggests that a number of articles included in this review may be unintentionally biasing their results by not controlling for these factors.

### 4.6 Limitations

One of the main limitations of this systematic review was an inability to split any meta-analyses based on the graft type of included participants. Advantageously, the studies included in the meta-analyses undertaken on hamstring volume, as well as semitendinosus and gracilis volume and CSA, were made up of studies which only included participants with semitendinosus/gracilis tendon harvests. The lack of data within the quadriceps-specific studies limited the ability to split by graft types, without large reductions in the power of the meta-analyses. Furthermore, some studies included mixed cohorts with multiple graft types. The lack of data within some meta-analyses was a further limitation, and certain results may therefore have suffered from sparse data bias. Additionally, visual inspection of funnels plots for meta-analyses with over ten included articles showed evidence of potential publication bias (Electronic Supplementary Material Figure S2). However, we reported all analyses to provide transparency of our methods and limit-biased reporting. Another limitation was the time-point subgrouping of data from individual studies. Grouping was done via the mean 'time since surgery' values reported; however, studies often included populations from a larger range (e.g., 6 to 12 months). Additionally, the vast majority of comparisons made were between the injured limb and the contralateral uninjured limb. As such, the true reduction in size of muscles may be masked, as changes in strength, activation and functional performance are known to occur bilaterally in ACL injured individuals [38, 93] and the same may be true of CSA and volume.

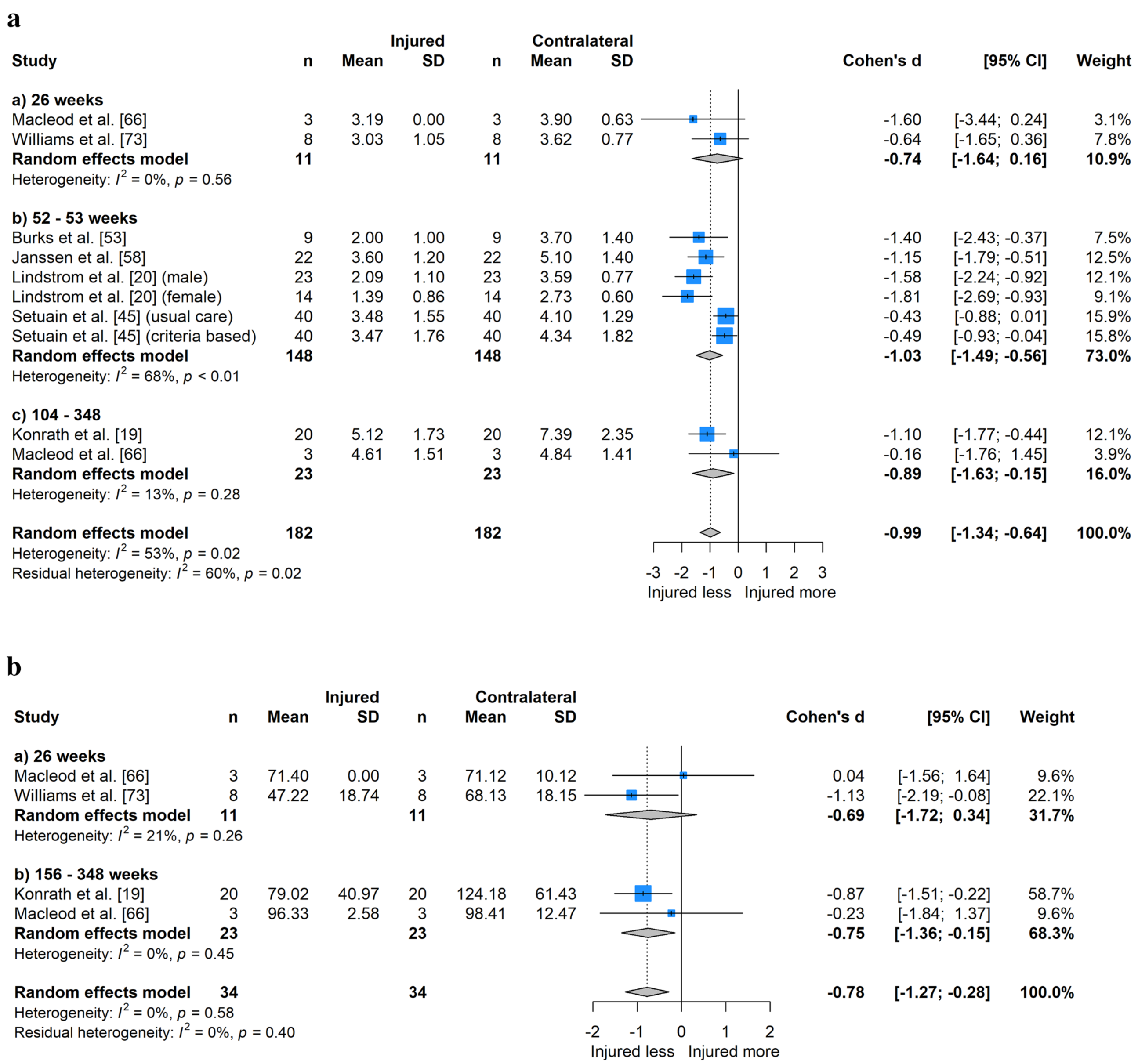



**Fig. 7** Results of the meta-analysis for, **a** gracilis muscle cross-sectional area, and **b** gracilis muscle volume in the ACL reconstructed limb compared to the contralateral uninjured limb. Negative effect size indicates the ACL injured limb measure is less than the contralateral uninjured limb

There was also a strong focus in the majority of articles on quadriceps, hamstrings and gracilis size. No included articles investigating ACL deficient populations included measures of muscle size from the lower leg or proximal hip. Only two articles investigating ACL reconstructed individuals included measures of gastrocnemius size, and only one article included measures of gluteus maximus size. Emerging research has highlighted the importance of the muscles of the shank and hip in opposing anterior shear and valgus knee forces [36, 37] as well as contributing to knee joint compressive loading [35]. If these muscle groups are shown to be reduced in size following ACL injury, this may pose serious implications for both the development of knee joint osteoarthritis and subsequent injury. Future work should investigate the effect of ACL injury and surgery on these muscles, specifically the gluteals, gastrocnemius and soleus.

**Table 7** Results of the best evidence synthesis for ACL reconstructed populations

| Measure | Number of studies | Number of participants | Lower (%) | No difference (%) | Higher (%) | Quality (Mean ± Sd) | Level of evidence |
|---|---|---|---|---|---|---|---|
| ACL reconstructed limb compared to contralateral uninjured limb | | | | | | | |
| Biceps femoris | 3 [78, 80, 85] | 38 | | 100 | | 70.0 ± 18.0 | Strong |
| Gluteus maximus | 1 [75] | 40 | 100 | | | 80 | Moderate |
| Gracilis | 3 [75, 78, 80] | 63 | 100 | | | 71.7 ± 18.9 | Strong |
| Quadriceps | 6 [24, 75, 78, 80, 81, 84] | 174 | 83.3 | 16.7 | | 72.5 ± 15.1 | Strong |
| Rectus femoris | 3 [76, 77, 83] | 69 | 100 | | | 70.0 ± 5.0 | Strong |
| Semimembranosus | 1 [78] | 13 | | 100 | | 50 | Limited |
| Semitendinosus | 2 [78, 80] | 23 | 100 | | | 67.5 ± 24.7 | Moderate |
| Vastus intermedius | 2 [76, 77] | 60 | 100 | | | 70.0 ± 7.1 | Moderate |
| Vastus lateralis | 3 [76, 77, 83] | 69 | 100 | | | 70.0 ± 5.0 | Strong |
| Vastus medialis | 2 [76, 77] | 60 | 100 | | | 70.0 ± 7.1 | Moderate |
| ACL reconstructed limb compared to a healthy control group | | | | | | | |
| Biceps femoris | 1 [79] | 10 | 100 | | | 80 | Moderate |
| Semimembranosus | 1 [79] | 10 | | 100 | | 80 | Moderate |
| Semitendinosus | 2 [79, 82] | 18 | | | 100 | 75 ± 7.1 | Strong |

Level of evidence is defined as follows:

Strong: two or more studies of a high quality and generally consistent findings (≥ 75% of studies showing consistent results)

Moderate: one high-quality study and/or two or more low quality studies and generally consistent findings (≥ 75% of studies showing consistent results)

Limited: one low-quality study

## 5 Conclusion

This review highlights the overall differences in lower limb muscle size when comparing the ACL injured limb to the uninjured contralateral limb, in ACL reconstructed and deficient populations. Regardless of whether an individual chooses a conservative or surgical rehabilitation approach, the quadriceps femoris of the injured limb appear to show significantly reduced muscle size in the short term, with the potential to recover to levels matching their contralateral limb in the long term. However, if an individual undergoes reconstructive surgery with a semitendinosus and/or gracilis tendon graft, the harvested muscle display long-term deficits in muscle size that may not be fully reversible. These findings suggest the need to focus the hypertrophic plans of rehabilitation around regaining quadriceps femoris muscle size, whilst considering the potential for possible permanent reductions in semitendinosus and gracilis muscle size if these tendons are harvested for reconstruction.

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## Declarations

**Conflict of interest** Benjamin Dutaillis, Nirav Maniar, David Opar, Jack Hickey and Ryan Timmins declare that they have no conflicts of interest relevant to the content of this review.

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**Author contributions** Concept and design (BD, NM, DAO and RGT), running of search strategy (BD), inclusion/exclusion criteria assessment (BD and JTH), quality assessment (BD and RGT), data extraction (BD), data analysis and interpretation (BD, NM, DAO, JTH and RGT), manuscript preparation (BD, NM, DAO, JTH and RGT).

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