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Classification of tendon matrix change using ultrasound imaging: A systematic review and meta-analysis

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Abstract

Ultrasound imaging (US) is an accurate and reliable method used to diagnose tendinopathy. This systematic review aimed to identify common criteria and parameters used to diagnose tendinopathy, the methodological quality of studies, and the predictive value of US. Nineteen studies met the inclusion criteria, with the Achilles, quadriceps and patella tendons being investigated. Overall, there was significant heterogeneity between the criteria used to diagnose tendinopathy utilising US. The methodological quality of included studies was "good". Additionally, meta-analysis showed that US identified abnormalities were predictive of future symptoms, and classification of tendinopathy using three US defined parameters demonstrated a higher relative risk of developing clinical tendinopathy when compared to using two US defined parameters. Further research into the development of a standardised US criterion that incorporates both clinical and US findings is required to allow for greater consistency in the diagnosis of tendinopathy.

Keywords

Ultrasound imaging, tendinopathy, diagnosis, classification

Introduction

Tendinopathy is an umbrella term for the clinical presentation of tendon pain and dysfunction with accompanying presumed pathological structural change to the internal tendon matrix (Maffulli, et al. 1998, Plinsinga, et al. 2015, Rees, et al. 2009). It is frequently seen in clinical practice, with the most commonly affected tendons being the Achilles, patellar, rotator cuff and elbow extensors (McCreesh and Lewis 2013, Rees, et al. 2009). Overuse tendon injuries account for 30-50% of all sports injuries (Scott and Ashe 2006). The catalyst for the onset of tendinopathy can be due to both an increase (Ackermann and Renström 2012, Lewis 2009, Maffulli, et al. 1998, Rio, et al. 2014, Scott, et al. 2015) and a decrease (Arnoczky, et al. 2007, Reeves, et al. 2005) in mechanical loading of the tendon. It is chronic in nature, with recovery ranging from 3-14 months (Bonde, et al. 2003, Khan, et al. 2000). Similarly, studies have shown that a minimum of 6-months is required to see significant structural change on imaging (de Vos, et al. 2011, Ryan, et al. 2010, Ryan, et al. 2011). Although, there is some evidence that structural changes can be seen on imaging in a shorter time-frame (Docking, et al. 2016).

There have been alternate models to describe the pathogenesis of tendinopathy (Abate, et al. 2009, Arnoczky, et al. 2007, Cook and Purdam 2009, Fu, et al. 2010). Of these models, the continuum model of tendinopathy, as originally proposed by Cook and Purdam (Cook and Purdam 2009), has become a widely accepted theoretical base and method to stage tendinopathy (Cook and Purdam 2009, Cook, et al. 2016, McCreesh and Lewis 2013, Rees, et al. 2014). The stages

identified within this model are distinguished by specific clinical and imaging features (Cook, et al. 2016).

There are two primary methods for the diagnosis of tendinopathy (Scott, et al. 2013). Clinically, the diagnosis of tendinopathy is predominantly centred on the patient history and clinical examination (Coombes, et al. 2015, Lewis 2016, Lewis, et al. 2015, Malliaras, et al. 2015, Scase, et al. 2011, Scott, et al. 2013). In regard to specific tests that have been reported to aid the diagnosis of tendinopathy, two out of ten commonly used tests (pain on palpation and location of pain) were found to be sufficiently reliable and accurate when compared to ultrasound imaging (Hutchison, et al. 2013). While pain on palpation has been shown to be sensitive (56-84%) for reproducing clinical symptoms, it is not specific (47-73%) in identifying pathological structural change when compared to medical imaging (Cook, et al. 2001, Grimaldi, et al. 2017, Hutchison, et al. 2013). Furthermore, clinical tests alone do not allow clinician the ability to determine where their patient may be on the tendinopathy continuum as stages are primarily based off structural changes (Cook, et al. 2016).

Imaging presents a method where structural changes within the tendon matrix can be identified. Both ultrasound imaging (US) and magnetic resonance imaging (MRI) are used to confirm the presence of structural tendon change in the clinical setting, with the choice of which technique to use based on clinician preference (Scott, et al. 2013). Furthermore, US has demonstrated better accuracy (Khan, et al. 2003, Warden, et al. 2007), and sensitivity (Westacott, et al. 2011) when compared to MRI for assessing tendinopathy. Additionally, US has been shown to have good reliability (Ingwersen, et al. 2016) and is considered more patient-friendly and cost

effective than MRI for the assessment of musculoskeletal conditions, with the ability for dynamic assessment and the measurement of neovascularisation (Lento and Primack 2008, Mapes-Gonnella 2013).

Although numerous studies have examined the sensitivity and accuracy of imaging in identifying tendinopathy (Docking, et al. 2015, Scott, et al. 2013), research utilising US has been limited to classifying tendon structural change with the use of subjective grading scores established on a multitude of pathological features (Docking, et al. 2015, Ellis and Manuel 2015). In a recent literature review (Ellis and Manuel 2015), the most commonly reported abnormal tendon matrix features, as seen with US, included echogenicity, fusiform swelling, tendon thickness, neovascularisation, fibrillation, calcification and intra-substance tears.

It has been proposed that abnormalities identified on US may be considered as a risk factor for the development of future symptoms (Cook, et al. 2016, McAuliffe, et al. 2016). However, due to the cross-sectional design of many imaging studies (McAuliffe, et al. 2016) and the variability in features measured (Ellis and Manuel 2015), uncertainty remains as to the relevance of identified tendon structural abnormalities and their impact on the management of tendinopathy in populations where there is a high prevalence of tendon related pain (McAuliffe, et al. 2016). Although it is accepted that US identified tendon abnormalities can be considered a risk factor (Cook, et al. 2016, McAuliffe, et al. 2016), no study has investigated the predictability of varying classification systems utilising different US based parameters.

The lack of a homogenous and standardised US criterion for assessing tendon matrix change makes determining the clinical utility of US in the diagnosis and management of tendinopathy difficult. Identification of commonly used US parameters and classification systems, along with assessing the predictability of varying parameters, may aid in determining the clinical utility of US and lead to greater homogeneity within this topic area. Thus, the primary aim of this systematic review was to identify the US based tendinopathy classifications that are reported, including specific tendon matrix features measured. Following this review, the secondary aim was to appraise the methodological quality of the included studies. The final aim was to utilise meta-analysis to assess the predictive value of the different classification systems that were identified.

Methods

Study Design

The study followed the methodology proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher, et al. 2009). Following the PRISMA guidelines, a detailed search strategy was developed and implemented up to August 2017.

Eligibility Criteria

Studies were included if they met the following criteria:

- Published full-length research articles in English with the full text available

- Human participants (male or female) of any age, from any athletic or community background
- Longitudinal (randomised or non-randomised) or observational (retrospective or prospective) study design
- Minimum clinical follow-up over 24 hours as tendons demonstrate an immediate response to load on imaging (Koenig, et al. 2010, Rosengarten, et al. 2015)
- Tendinopathy in any location
- US as an outcome measure to assess tendon matrix changes (e.g. tendon thickness, echogenicity, collagen organisation, fibrillar pattern, vascularisation, etc.)
- Graded or classified tendinopathy stage using either a nominal or ordinal scale

Studies were excluded if they met the following criteria:

- Patients who had other medical conditions that may affect outcome measures (e.g. Rheumatoid arthritis, diabetes mellitus)
- Cross-sectional studies
- Focused on tendon tear or rupture
- Surgical interventions or injection therapies (corticosteroid or platelet rich plasma) as part of the treatment protocol

Search Methods

A detailed, multi-step search strategy using PRISMA guidelines, was conducted up to August 2017 to identify relevant studies regardless of publication date. The search was conducted in the following databases: Embase; PubMed; SPORTDiscus; EBSCOhost; CINAHL; ProQuest. In addition to the electronic database search, included articles reference lists were searched for additional articles. To ensure a wider search strategy of relevant articles, keywords were truncated to allow for variations in spelling, and combined using Boolean operators as outlined in Table 1. MeSH terms were also used to ensure review of relevant articles. Search strategies for databases were equivalent with the same keywords and Boolean operators, however slight adaptations were made depending on each databases' respective characteristics.

Study Selection

Search results were imported to EndNote reference management software (EndNote X8.0.1, Clarivate Analytics, 22 Thomson Place, 36T3 Boston, MA 02210). Duplicate records were removed. Titles and abstracts of retrieved articles were screened for eligibility. After the initial screening, the full-text of relevant studies were retrieved for further analysis.

Data Extraction

Data extracted included specific details regarding the study design, authors, year of publication, population, intervention methodology, tendon location and length

of follow-up. Specific data related to outcome measures included parameters measured and grading or classification system used.

Assessment of Methodological Quality

The Critical Appraisal Skills Programme (CASP) tool was used to assess methodological quality of included studies (Critical Appraisal Skills Programme 2017, Critical Appraisal Skills Programme 2017). Studies were assessed using the CASP toolkit independently by two researchers (WM and JF). The CASP toolkit is comprised of eight separate checklists to be used depending on study design and enables researchers to critically assess the validity and relevance of published articles. The included articles were assessed for quality using the CASP Cohort Study Checklist (Critical Appraisal Skills Programme 2017) and the CASP Randomised Controlled Trial Checklist (Critical Appraisal Skills Programme 2017). The CASP Cohort Study Checklist (Critical Appraisal Skills Programme 2017) provides 12 questions to assess study quality. The first two questions are screening questions, while the next ten provide a framework to assess the results of the study, the study validity and relevance. Similarly, the CASP Randomised Controlled Trial Checklist (Critical Appraisal Skills Programme 2017) uses 11 questions to assess validity, results and applicability of studies, with the first two questions being screening questions.

As was the method of a recent systematic review (McAuliffe, et al. 2016), questions seven, eight and nine in the CASP Cohort Study Checklist (Critical Appraisal Skills Programme 2017) and questions seven and eight in the CASP

Randomised Controlled Trial Checklist (Critical Appraisal Skills Programme 2017) were combined into one question, as they were deemed to investigate similar areas. Most questions are answered with 'yes', 'no' or 'can't tell'. The CASP checklists do not provide a scoring system to appraise the quality of evidence (Critical Appraisal Skills Programme 2017, Critical Appraisal Skills Programme 2017). However, although there is a lack of consensus as to what criteria to appraise in quantitative research, it is recognised that quality issues should be highlighted by reviewers (Goldsmith, et al. 2007). For the purpose of this systematic review, a scoring system was developed where '1' point was awarded for a 'yes' and '0' points for a 'no', with the maximum score being 12 for the CASP Cohort Study Checklist (Critical Appraisal Skills Programme 2017) and 10 for the CASP Randomised Controlled Trial Checklist (Critical Appraisal Skills Programme 2017).

Overall scores were calculated as a percentage and quality was rated according to the methods reported by Kennelly (2011) where grades were categorized as 'poor', 'fair' or 'good'. Studies that scored ≥60% were considered as 'good' quality, while studies that scored between 45%-59% were 'fair' and studies that scored <45% were considered 'poor', as has been reported in previous studies (Adhia, et al. 2013, Barrett, et al. 2014, May, et al. 2010, May, et al. 2006). To ensure consistency of critical appraisal, the criteria used for each question in the CASP checklist was agreed upon between the two reviewers (WM and JF) prior to commencement of the appraisal process. Inter-rater agreement for each question and overall was calculated using Cohen's Kappa coefficient.

Synthesis and Analysis

To determine agreement between raters following the critical appraisal process, a Cohen's Kappa was calculated using SPSS software package (IBM SPSS Statistics for Macintosh, Version 24.0. Armonk, NY: IBM Corp.). Where quantitative methods were appropriate to statistically pool data, a meta-analysis was performed using Review Manager software (Review Manger (RevMan) for Macintosh, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A random effects models using the Mantel-Haenszel method was used to determine pooled relative risk (RR) of developing symptomatic tendinopathy with 95% confidence intervals (CI). Studies were included in the meta-analysis if they used similar methodology, reported on asymptomatic tendons that became symptomatic, and provided data on asymptomatic baseline structural changes and development of symptoms at follow-up. Studies were excluded from the meta-analysis if they included symptomatic tendons from baseline, used specific interventions as part of the rehabilitation process, or provided insufficient data on baseline or follow-up structural changes. RR was calculated for three subgroups; 1) tendon site (Achilles or patellar), 2) number of parameters used in classifications (3 parameters or 2 parameters), and 3) number of parameters used for specific tendon location.

The heterogeneity between studies was assessed using the I^2 statistic. The I^2 value describes the percentage of variation across the studies that is due to heterogeneity rather than chance, ranging from 0-100%, where 0% shows no heterogeneity and increasing values show increasing heterogeneity (Higgins, et al. 2003). I^2 values of 25% indicate low, 50% moderate and 75% high heterogeneity

(Higgins, et al. 2003). Similar to a previous systematic review (Smidt, et al. 2003), a RR >1.5 was considered clinically significant for the predictability of US identified abnormalities in asymptomatic tendons becoming symptomatic. RR was summarised using forest plots, while study and publication bias was assessed using funnel plots.

Where meta-analysis was not appropriate due to the heterogeneity of articles and criterion used to assess tendon matrix change on US, a qualitative approach was utilized. Results were synthesised to analyse tendon parameters measured, quality of evidence, predictive value of criteria and relationship to the continuum model of tendinopathy. This data synthesis was then used to inform and guide the development of the proposed criteria, with a greater weighting being placed on articles of 'good' quality and parameters that were predictive of tendinopathy.

Results

Search Results

The search results are shown in the PRISMA Flow Diagram (Figure 1). After the removal of duplicates and screening of titles and abstracts against the inclusion criteria, the full-text of 68 articles was retrieved and assessed for inclusion in the systematic review. Of these, nineteen articles (Archambault, et al. 1998, Boesen, et al. 2012, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, de Jonge, et al. 2010, de Vos, et al. 2007, Fredberg and Bolvig 2002, Fredberg, et al. 2008, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al.

2010, Ooi, et al. 2015, Visnes, et al. 2015) met the inclusion criteria and were included in the systematic review.

Characteristics of Included Studies

A detailed description of the included studies is provided in Table 2. Of the nineteen included studies, seventeen were cohort studies (Archambault, et al. 1998, Boesen, et al. 2012, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, de Vos, et al. 2007, Fredberg and Bolvig 2002, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015) and two were randomised controlled trials (de Jonge, et al. 2010, Fredberg, et al. 2008). While no limitations were placed on tendon location, all nineteen included studies investigated tendons in the lower limb, with the Achilles, patellar and quadriceps tendons assessed (Archambault, et al. 1998, Boesen, et al. 2012, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, de Jonge, et al. 2010, de Vos, et al. 2007, Fredberg and Bolvig 2002, Fredberg, et al. 2008, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015). Tendon matrix change was classified using either a nominal or ordinal scale. In a nominal scale, labels are descriptive, allowing for the counting but not ordering of data, while an ordinal scale allows for data to be ranked (Stevens 1946).

A nominal grading scale was used in twelve of the included studies (Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, Fredberg and Bolvig 2002, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Malliaras, et al. 2010, Visnes, et al. 2015), while an ordinal scale was used in the remaining seven studies (Archambault, et al. 1998, Boesen, et al. 2012, de Jonge, et al. 2010, de Vos, et al. 2007, Fredberg, et al. 2008, Khan, et al. 2003, Ooi, et al. 2015). The studies that used nominal scales classified tendon structural change as either 'normal' or 'abnormal' (Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, Fredberg and Bolvig 2002, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Malliaras, et al. 2010, Visnes, et al. 2015). Three studies that used an ordinal scale graded tendinopathy as 'Grade 1', 'Grade 2, or 'Grade 3' (Archambault, et al. 1998, Khan, et al. 2003, Ooi, et al. 2015), while one classified change as 'normal', 'slightly abnormal' or 'severely abnormal' (Fredberg, et al. 2008). Two studies used a 5-point scale (de Jonge, et al. 2010, de Vos, et al. 2007) and one used a 6-point scale (Boesen, et al. 2012).

Study Scoring and Quality

Overall CASP results are summarised in Table 3. Inter-rater agreement was calculated for each question using Cohen's Kappa. Overall, based on previously published guidelines (Fleiss 1981), Cohen's Kappa was excellent at 0.93 for the seventeen cohort studies and perfect at 1.00 for the two randomised controlled trials. Disagreements were discussed, and a consensus drawn between the two raters. The quality of all studies was rated as 'good' according to the categories proposed

by Kennelly (Kennelly 2011) and the criteria used in previous studies (Adhia, et al. 2013, Barrett, et al. 2014, May, et al. 2010, May, et al. 2006).

Synthesis of Evidence

A synthesis of evidence is provided in Table 4. Overall, there was significant heterogeneity between the parameters used to assess tendon matrix change and the ability to predict outcomes. Three studies (Boesen, et al. 2012, de Jonge, et al. 2010, de Vos, et al. 2007) measured only one parameter when assessing tendon matrix change, while six studies (Archambault, et al. 1998, Cook, et al. 2001, Cook, et al. 2000, Fredberg and Bolvig 2002, Fredberg, et al. 2008, Khan, et al. 1997) used two parameters and the remaining ten studies (Comin, et al. 2013, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015) used three parameters. No study included fibrillar pattern as a parameter to assess tendon matrix change. All studies were of good quality according to the previously stated scoring system. Additionally, no criteria were related to the stages of tendinopathy as proposed in the Cook and Purdam (Cook and Purdam 2009) continuum model. There were mixed results when looking at the predictive value of the individual criterion, with nine studies (Boesen, et al. 2012, Comin, et al. 2013, Cook, et al. 2001, de Jonge, et al. 2010, de Vos, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 2003, Ooi, et al. 2015) indicating abnormalities measured on US are unable to predict of clinical outcome, while the remaining ten studies (Archambault, et al. 1998, Cook, et al. 2000, Fredberg and Bolvig 2002, Fredberg, et al. 2008, Giombini, et al. 2013, Gisslén and Alfredson

2005, Gisslén, et al. 2007, Khan, et al. 1997, Malliaras, et al. 2010, Visnes, et al. 2015) showed US can be a predictor of clinical outcome.

Echogenicity

Echogenicity was the equal most commonly measured structural change on US with results summarised in Table 5. Of the included studies, sixteen measured echogenicity as a variable for structural change (Archambault, et al. 1998, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, Fredberg and Bolvig 2002, Fredberg, et al. 2008, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015). Overall, abnormal echogenicity was not defined in thirteen studies (Archambault, et al. 1998, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015). Two studies (Fredberg and Bolvig 2002, Jhingan, et al. 2011), defined abnormal echogenicity as the presence of a hypoechoic region larger than 1mm in size, with the remaining study (Fredberg, et al. 2008) using different values for the Achilles tendon (0.5mm) and patellar tendon (1mm).

Thickness

All studies that measured echogenicity also measured tendon thickness (Archambault, et al. 1998, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000,

Fredberg and Bolvig 2002, Fredberg, et al. 2008, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015), with results presented in Table 6. Similarly, thirteen studies (Archambault, et al. 1998, Comin, et al. 2013, Cook, et al. 2001, Cook, et al. 2000, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Khan, et al. 1997, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015) determined the presence of increased thickness as 'abnormal', however, cut-off values were not defined. Two studies (Fredberg and Bolvig 2002, Jhingan, et al. 2011) used a defined thickness as an increase of 1mm when related to the normal distal part of the tendon, while one study (Fredberg, et al. 2008) classified tendon thickening >0.5mm in the Achilles tendon and thickening >1mm in the patellar tendon as 'abnormal'.

Vascularity

Vascularity was measured in thirteen of the included studies (Boesen, et al. 2012, Comin, et al. 2013, de Jonge, et al. 2010, de Vos, et al. 2007, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Jhingan, et al. 2011, Khan, et al. 2003, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015). An outline of the criteria used to assess vascularity is provided in Table 7. As outlined in Table 7, ten studies (Boesen, et al. 2012, de Jonge, et al. 2010, de Vos, et al. 2007, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Hirschmüller, et al. 2012, Malliaras, et al. 2010, Ooi, et al. 2015, Visnes, et al. 2015) used varying scales to define 'abnormal' vascularity. The

remaining three studies (Comin, et al. 2013, Jhingan, et al. 2011, Khan, et al. 2003) used the presence of vascularity, with undefined parameters, to determine whether a tendon was classified as 'abnormal'.

Meta-analysis

Nine of the nineteen included studies were eligible for meta-analysis due to similarities in characteristics (Cook, et al. 2001, Cook, et al. 2000, Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Jhingan, et al. 2011, Khan, et al. 1997, Khan, et al. 2003, Ooi, et al. 2015). The remaining ten studies could not be included due to insufficient data on the development of symptoms, significant differences in study design and methodology, or the inclusion of symptomatic tendons at baseline. Overall, Figure 2 demonstrates that tendon abnormalities on US may be predictive of the development of future symptoms in both the patellar and Achilles tendons (RR=4.78, 95% CI 2.49-9.15) with low heterogeneity between studies (I^2=0%).

Predictive value of parameters

Six studies (Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Jhingan, et al. 2011, Khan, et al. 2003, Ooi, et al. 2015) used three parameters (echogenicity, thickness, vascularisation), while three studies (Cook, et al. 2001, Cook, et al. 2000, Khan, et al. 1997) used two parameters (echogenicity and thickness) when assessing structural change in patellar and Achilles tendons on US. Three parameters were found to have an increased risk of developing symptoms

(RR=6.49, 95% CI 2.49-16.94) when compared to those studies using two parameters (RR=3.66, 95% CI 1.15-11.62). I^2 values demonstrated low heterogeneity across subgroups (3 parameters I^2=7%, 2 parameters I^2=6%). This data is displayed in Figure 3.

In the patellar tendon, three studies (Giombini, et al. 2013, Gisslén and Alfredson 2005, Gisslén, et al. 2007) used three parameters to assess structural change, while three studies (Cook, et al. 2001, Cook, et al. 2000, Khan, et al. 1997) assessed change using two parameters. Figure 4 demonstrates that three parameters (RR=10.42, 95% CI 2.34-46.37) may indicate an increased risk of future symptoms when compared to the use of two parameters (RR=3.03, 95% CI 1.15-7.97). I^2 analysis showed low heterogeneity across both subgroups (3 parameters I^2=20%, 2 parameters I^2=0%). All four studies (Giombini, et al. 2013, Jhingan, et al. 2011, Khan, et al. 2003, Ooi, et al. 2015) assessing the Achilles tendon used three parameters and found an increased risk for developing symptoms (RR=5.45, 95% CI 1.62-18.37). Heterogeneity was low between the studies (I^2=0%).

Statistical significance was found for the predictive value of US assessment of the tendon matrix for both the Achilles (p=0.006) and patellar (p=0.0001) tendons. There was no statistical difference between the two groups (p=0.80). Similarly, both 3 parameters (p=0.0001) and 2 parameters (p=0.03) were determined to be statistically significant for predicting symptom development without a statistical difference between the two groups (p=0.45). In the patellar tendon, there was a statistical significance for the predictive value of both 3 parameters (p=0.002) and 2 parameters (0.02), with no statistical difference between groups (p=0.17). Funnel

plot analysis demonstrated no publication bias for all subgroup analysis (Figures 5, 6 and 7).

Discussion

There is considerable debate regarding the clinical utility of imaging in tendinopathy (Docking, et al. 2015). There are two important issues to consider which have led to this debate. The first issue is that in some studies abnormal structural tendon changes, as seen with US, have been reported in up to 59% of asymptomatic individuals (Brasseur, et al. 2004, Cook, et al. 1998, Fredberg and Bolvig 2002, Giombini, et al. 2013, Hirschmüller, et al. 2012, Khan, et al. 1997, Leung and Griffith 2008). It is therefore apparent that there is a disparity that can be seen between the findings of imaging versus the clinical presentation (Fredberg, et al. 2004). Secondly, although numerous studies have examined the sensitivity and accuracy of imaging in identifying tendinopathy (Docking, et al. 2015, Scott, et al. 2013), there is a lack of a valid clinical gold standard for diagnosing tendinopathy with which to reliably compare findings (Docking, et al. 2015). Additionally, with such a wide variety of classification systems and different imaging features reported, there appears to be a lack of agreement of an acceptable criterion or classification to match structural changes seen on US with the clinical stages of tendinopathy (Ellis and Manuel 2015). Furthermore, in the clinical setting, sonographers do not appear to use or refer to the continuum model of tendinopathy when diagnosing tendon disorders. Classifying patients according to structural changes, in addition to clinical symptoms, may allow the clinician to direct treatment to the key limiting factors (pain, function or load capacity) (Cook, et al. 2016, Scase, et al. 2011).

Classification of tendinopathy

The primary aim of this systematic review was to identify the current methods used to classify tendinopathy using US. To the authors' knowledge, this is the first systematic review and meta-analysis to focus specifically on current US parameters used to measure structural change in tendinopathy and the methods of classifying tendinopathy according to these parameters. We found that there is a distinct lack of homogeneity in the criteria used when assessing tendinopathy using US. While there is significant inconsistency in the currently used US tendinopathy classification methods, common US parameters used to measure structural change can be identified. These results align with those of Ellis and Manuel (Ellis and Manuel 2015), which demonstrated significant variability in both the overall classification scales used, and individual parameters measured from studies that examined tendinopathy with US. Additionally, this review demonstrated that there is a lack of a relationship between the classification systems employed clinically, and the widely accepted continuum model (Cook and Purdam 2009) of tendinopathy.

Quality of Included Studies

One of the secondary aims of this literature review was to assess the methodological quality of the literature. According to the previously described quality scoring system and, as presented in Table 3, all included studies were determined to be of good methodological quality. The main areas of concern within the methodological quality of included studies was in the minimisation of bias (Comin, et

al. 2013, Jhingan, et al. 2011, Khan, et al. 2003, Malliaras, et al. 2010), control of confounding factors (Archambault, et al. 1998, Comin, et al. 2013, Cook, et al. 2001, de Vos, et al. 2007, Fredberg and Bolvig 2002, Gisslén and Alfredson 2005, Gisslén, et al. 2007, Jhingan, et al. 2011, Khan, et al. 2003, Malliaras, et al. 2010), adequate follow-up (Archambault, et al. 1998, Hirschmüller, et al. 2012) and the presentation of results (Gisslén and Alfredson 2005, Gisslén, et al. 2007). Additionally, the main weaknesses of the included randomised controlled trials were concerned with recording of drop-outs (Fredberg, et al. 2008), blinding (de Jonge, et al. 2010, Fredberg, et al. 2008), and the similarity of treatment and control groups (Fredberg, et al. 2008). These results align with those of other systematic reviews (McAuliffe, et al. 2016) and provide a methodologically sound base for future research.

Predictive value of US based classification systems

A secondary aim of this review was to assess the predictive value of different US classification methods for the development of future symptoms. Overall, meta-analysis demonstrated that US identified tendon abnormalities may present an increased risk (RR=4.78) for the development of future symptoms in Achilles and patellar tendinopathy. This aligns with the systematic review by McAuliffe et al. (2016), who demonstrated US identified abnormalities were predictive (RR=4.97) for the development of symptomatic lower limb tendinopathy. However, further sub-group analysis according to parameters measured, showed significant differences to the predictive value of US. Notably, when measuring tendon matrix changes using US, the number of parameters measured may influence the predictive value of US in asymptomatic patients.

Meta-analysis demonstrated that including three parameters (echogenicity, thickness and vascularity; RR=6.49) was more predictive than those using two parameters (echogenicity and thickness; RR=3.66) for the development of future symptoms in the lower limb. This was highlighted further when looking at the patellar tendon where RR was considerably higher when using three parameters (RR=10.49) compared to two parameters (RR=3.03). These results differ to those of McAuliffe et al. (2016) in that McAuliffe et al. (2016) demonstrated US identified abnormalities were a risk factor for the development of tendinopathy in both the Achilles and patella tendons. However, these results indicated that by utilising more parameters to define tendon abnormalities using US, the RR of developing future clinical tendinopathy may be increased. To the authors knowledge, this is the first research to investigate the impact of individual US parameters on the predictive value of tendinopathy.

The synthesis of evidence illustrates that there is still debate as to the predictive value of US, with 53% of included studies determining US findings were predictive of future symptoms. Hirschmüller et al. (2012) found that neovascularisation Grade 1 may be predictive (odds ratio(OR) 6.9, 95% CI 2.6-18.8, p=0.0001) of future symptoms, however, hypoechogenicity, spindle-shaped thickening, and neovascularisation Grade 2-3 were not predictive (p>0.05). Whereas, Comin et al. (2013) reported moderate to severe hypoechoic regions may be predictive of symptoms in both the patellar and Achilles tendons (Fisher's exact p=0.038). However, intratendon defects (patellar p=0.166, Achilles p=0.403) and neovascularisation (patellar p=0.342, Achilles 0.089) were not statistically significant

for predicting symptoms. Additionally, Boesen et al. (2012) found no association between pain and abnormal neovascularisation at the end of a volleyball season with 35% of painful tendons demonstrating abnormal flow. Similarly, de Jonge et al. (2010) demonstrated no significant difference in VISA-A scores between patients with and without neovascularisation at baseline (p=0.71), while de Vos et al. (2007), reported no statistical difference in the predictive value of neovascularisation when compared to both the VAS (p=0.053) and VISA-A (p=0.147).

Conversely, Fredberg and Bolvig (2002) reported abnormal US had a 17% risk of developing symptomatic jumper's knee and 45% risk of developing symptomatic Achilles tendinopathy. Similarly, Fredberg et al. (2008) demonstrated an abnormal US had a RR of 2.8 (95% CI, 1.6-4.9; p=0.002) in the Achilles tendon and RR of 2.2 (95% CI, 0.9-5.7; p=0.09) for the patellar tendon. Additionally, Malliaras et al. (2010) determined there was an increased probability of pain in tendons with both hypoechoic regions (59%) and diffuse thickening (43%). This is supported by Visnes et al. (2015) with both hypoechogenicity (OR 3.3, 95% CI 1.1-9.2) and neovascularisation (OR 2.7, 95% CI 1.1-6.5) increasing the risk of developing symptomatic jumper's knee.

This variability in the reported results may be explained by two important factors. Firstly, research utilising US has been limited to classifying tendon structural change with the use of subjective grading scores established on a multitude of pathological features (Docking, et al. 2015, Ellis and Manuel 2015). Objective measurement of tendon structural change, seen with US, has been restricted to measuring dimensions such as tendon diameter, cross-sectional area of the tendon

and number or size of hypoechoic regions (Docking, et al. 2015). Secondly, although numerous studies have examined the sensitivity and accuracy of US in identifying tendinopathy (Docking, et al. 2015, Scott, et al. 2013), there is a lack of a valid clinical gold standard for diagnosing tendinopathy, making assessing the clinical utility of US difficult (Docking, et al. 2015, McAuliffe, et al. 2016).

Limitations

The exclusion of grey literature may increase the risk of publication bias (Conn, et al. 2003). It is also possible that non-English articles that may have met the inclusion criteria were missed. However, there is no evidence of systematic review bias form language restrictions (Morrison, et al. 2012). The exclusion of promising methods of US, such as elastography, may have an effect on publication bias. However, although early research shows promise as an adjunct to standard US (Ooi, et al. 2014), evidence is limited to smaller cross-sectional studies and there are some technical challenges to producing high-quality, reproducible elastograms (Domenichini, et al. 2017, Ooi, et al. 2014, Ryu and Jeong 2017). Moreover, as elastography is a recent development, many commercial US units lack the ability to assess this feature. A better understanding of fundamental properties of elastography (Ryu and Jeong 2017) and standardisation of imaging protocols (Ooi, et al. 2014) may allow future research to incorporate this technique into the US assessment of tendon matrix change. Additionally, study quality was assessed using the CASP tool (Critical Appraisal Skills Programme 2017, Critical Appraisal Skills Programme 2017), which does not utilise a scoring system to grade study quality, thus one was developed for the purpose of the review. The selection of quality

appraisal tool may impact review conclusions (Voss and Rehfuess 2013), however, this was addressed by using two independent reviewers and determining inter-rater agreement for each question on the checklist.

Implications for future research

Given the complexity of the relationship between structure, dysfunction and pain in tendinopathy, there is scope to develop a standardised method to assess tendon structural change on US, incorporating a number of parameters, and allowing for greater consistency in the diagnosis of tendinopathy. Based on the results of this systematic review and meta-analysis, future criteria for diagnosing tendinopathy using US should include measures of all three parameters (tendon thickness, echogenicity and vascularity) when assessing tendon structural change. Furthermore, there is a need for further studies to assess the validity of developing a clinical gold standard for the diagnosis of tendinopathy that incorporates both clinical and US findings to formulate a diagnosis of tendinopathy. Additionally, in order to better integrate clinical and US findings, there is an opportunity to develop a method that merges the continuum model with US parameters to form an overall criteria that allows for greater consistency in the diagnosis of tendinopathy. Using the results of this literature review, an ordinal scale may be developed to diagnose tendinopathy using US as ‘normal’, ‘reactive/early dysrepair’ or ‘late dysrepair/degenerative’ to better align with the continuum model (Ellis and Manuel, 2015, Scase, et al. 2011). However, cut-off values would need to be determined to distinguish between the different stages within the continuum.

Conclusions

This review demonstrates that there is significant variability in the US based criteria used to diagnose tendinopathy. Notably, US is predictive of the development of future clinical symptoms. Furthermore, the assessment of tendon structural change using three parameters revealed a higher RR when compared to using two parameters, indicating the predictive value of using three parameters. Furthermore, as imaging is one component of the clinical picture, there is scope to for future research to develop a standardised criterion that incorporates both clinical and US features to diagnose tendinopathy. This has the potential to improve the monitoring and clinical management of tendinopathies.

Table 1: Search strategy used for database search

Database	Search Strategy
ProQuest	((mesh(tendinopathy) OR all(tendinopath* OR tendonopath* OR tendinitis OR tendinosis)) AND ((mesh(ultrasonography) OR all(ultrasonograph* OR ultrasound OR sonograph*)) AND all(classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)
PubMed	((((("Tendinopathy"[Mesh]) AND (tendinopath* OR tendonopath* OR tendinitis OR tendinosis)) AND "Ultrasonography"[Mesh]) AND (ultrasonograph* OR ultrasound OR sonograph*)) AND (classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)
Embase	('tendinitis'/exp OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND ('echography'/exp OR ultrasonograph* OR ultrasound OR sonograph*) AND classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*
CINAHL	(MH "Tendinopathy+" OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND (MH "Ultrasonography+" OR ultrasonograph* OR ultrasound OR sonograph*) AND classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*
SPORTDiscus	(DE "TENDINITIS" OR DE "ACHILLES tendinitis" OR DE "CALCIFIC tendinitis" OR tendinopath* OR tendonopath* OR tendinitis OR tendinosis) AND (DE "ULTRASONIC imaging" OR DE "DIAGNOSTIC ultrasonic imaging" OR ultrasonograph* OR ultrasound OR sonograph*) AND (classification OR classify* OR grade OR grading OR stage OR staging OR characteris* OR characteriz*)

Table 2: Characteristics of included studies

Author	Study Design	Demographics	Population	Tendon	US Structural Changes	Classification	Ultrasound Imaging & Follow Up
Archambault, et al. (1998)	Cohort Study	N = 33 (M - 20, F - 13) Mean Age - 35.8 (range 18-59)	Sports Medicine Clinic	Achilles	Echogenicity Thickness	***1***: Normal (parallel margins, homogeneous) ***2***: Enlarged tendon (bowed margins, homogeneous) ***3***: Hypoechoic (with or without enlargement)	*US:* Initial visit *Follow Up:* 24.3 months
Boesen, et al. (2012)	Cohort Study	N = 86 (M - 56, F - 30) Mean Age - 21.7 (range N/A)	Badminton	Achilles Patellar Quadriceps	Vascularity	***0***: no Doppler ***1:*** 1 or 2 tiny foci ***2:*** <5% colour ROI ***3:*** 5-24% colour ROI ***4:*** 25-49% colour ROI ***5:*** >50% colour ROI	*US:* Initial & Follow Up *Follow-up:* 8 months
Comin, et al. (2013)	Cohort Study	N = 79 (M - 35, F - 44) Mean Age - 27.6 (range 18-40)	Ballet Dancers	Achilles Patellar	Echogenicity Thickness Vascularity Calcification	***Normal*** ***Abnormal:*** presence of (1) hypoechogenicity (undefined), or (2) incr. thickness (undefined), or (3) vascularity (undefined), or (4) intratendon calcification (undefined)	*US:* Initial visit *Follow Up:* 24 months
Cook, et al. (2000)	Cohort Study	N = 26 (M - 8, F - 18) Mean Age - N/A (range 14-18)	Junior Basketball	Patellar	Echogenicity Thickness	***Normal*** ***Abnormal:*** presence of (1) hypoechoic region, or (2) fusiform swelling (all undefined)	*US:* Initial & Follow Up *Follow Up:* 16 months (12-24 months)
Cook, et al. (2001)	Cohort Study	N = 24 (M -24) Mean Age - 29.8 (at follow-up)	Football, Basketball, Cricket	Patellar	Echogenicity Thickness	***Normal*** ***Abnormal:*** presence of (1) hypoechoic region, or (2) fusiform swelling (all undefined)	*US:* Initial & Follow Up *Follow Up*: 47.1 months (32-80 months)

de Jonge, et al. (2010)	RCT	N = 50 (63 tendons - M - 26, F -37) Mean Age - 44.6 (range 26-59)	Sports Medicine Clinic	Achilles	Vascularity	***0:*** no vessels ***1:*** one vessel mostly in anterior part ***2:*** one/two vessels throughout tendon ***3:*** three vessels throughout tendon ***4:*** >3 large vessels throughout tendon	*US:* Initial & Follow Up *Follow Up:* 12 months
de Vos, et al. (2007)	Cohort Study	N = 52 (63 tendons - M - 26, F -37) Mean Age - 44.6 (range 26-59)	Sports Medicine Clinic	Achilles	Vascularity	***0:*** no vessels ***1+:*** one vessel mostly in anterior part ***2+:*** one/two vessels throughout tendon ***3+:*** three vessels throughout tendon ***4+:*** >3 large vessels throughout tendon	*US:* Initial & Follow Up *Follow Up:* 12 weeks
Fredberg and Bolvig (2002)	Cohort Study	N = 54 (M - 54) Mean Age - N/A (range 18-35)	Soccer	Achilles Patellar	Echogenicity Thickness	***Normal*** ***Abnormal:*** presence of (1) >1mm thickening (2) > 1mm hypoechoic region	*US:* Initial & Follow Up *Follow Up:* 12 months
Fredberg, et al. (2008)	RCT	N = 207 (M - 207) Mean Age - 25.0 (range 17-37)	Soccer	Achilles Patellar	Echogenicity Thickness	***Normal*** ***Slightly Abnormal:*** (1) Thickening 0.5-1mm (2) Hypoechoic region 1-2mm ***Severely Abnormal:*** (1) Thickening >1mm (2) Hypoechoic region >2mm	*US:* Initial & Follow Up *Follow Up:* 12 months
Giombini, et al. (2013)	Cohort Study	N = 37 (M - 15, F - 22) Mean Age - 27 (range 16-36)	Fencers	Achilles Patellar Quadriceps	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) Focal/Diffuse thickening (undefined) (2) Focal/Diffuse hypoechogenicity (undefined) (3) Vascularity >2 (0- no flow, 1- flow outside tendon, 2- 1 or 2 vessels inside tendon, 3- multiple vessels inside tendon)	*US:* Initial & Follow Up *Follow Up:* Avg. 3 years

Gisslén and Alfredson (2005)	Cohort Study	N = 60 (M - 29, F - 31) Mean Age - 17.2 (range 15-19)	Junior Volleyball	Patellar	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) Increased thickness (undefined) (2) Hypoechogenicity (undefined) (3) Vascularity >2 (0- no flow, 1- flow outside tendon, 2- 1 or 2 vessels inside tendon, 3- multiple vessels inside tendon)	*US:* Initial & Follow Up *Follow Up:* 7 months
Gisslén, et al. (2007)	Cohort Study	N = 22 (M - 11, F - 11) Mean Age - 16.3 (range 15-16 at start)	Junior Volleyball	Patellar	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) Increased thickness (undefined) (2) Hypoechogenicity (undefined) (3) Vascularity >2 (0- no flow, 1- flow outside tendon, 2- 1 or 2 vessels inside tendon, 3- multiple vessels inside tendon)	*US:* Initial, Regular intervals & Follow Up (6 total) *Follow Up:* 3 years
Hirschmüller, et al. (2012)	Cohort Study	N = 634 (M - 425, F - 209) Mean Age - 41.2 (range 17-73)	Long Distance Runners	Achilles	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) Tendon thickening (undefined) (2) Hypo/hyper echogenicity (undefined) (3) Vascularity (0 – no Doppler, 1 – 1 or 2 tiny foci, 2 – <5% colour ROI, 3 – 5-24% colour ROI, 4 – 25-49% colour ROI, 5 – 50% colour ROI)	*US:* Initial visit *Follow Up:* 12 months
Jhingan, et al. (2011)	Cohort Study	N = 18 (M -18) Mean Age - 23.5 (range 22-27.5)	Soccer	Achilles	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) Thickening (> 1mm) (2) Hypoechogenicity (> 1mm) (3) Paratendon Blurring (4) Vascularity (undefined)	*US:* Initial visit *Follow Up:* 12 months
Khan, et al. (1997)	Cohort Study	N = 30 (F - 30) Mean Age – 24 (range N/A)	Basketball	Patellar	Echogenicity Thickness	***Normal*** ***Abnormal:*** presence of (1) Increased thickness (undefined) (2) Hypoechogenicity (undefined)	*US:* Initial & Follow Up *Follow Up*: 18.3 months (range 12-34 months)

Khan, et al. (2003)	Cohort Study	N = 45 (M - 27, F - 18) Mean Age - 42 (range 20-66)	Sports Medicine Centre	Achilles	Echogenicity Thickness Vascularity	***1:*** Normal ***2:*** Thickened (>6mm) homogenous echotexture ***3:*** Hypo/Hyperechoic areas with/without thickening (>6mm) Vascularity: normal or abnormal	*US:* Initial & 12 months *Follow Up:* 24 months
Malliaras, et al. (2010)	Cohort Study	N = 58 (M -36, F - 22) Mean Age - 37.3 (range N/A)	Volleyball	Patellar	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of Diffuse Thickening (undefined) Hypoechogenicity (undefined) Vascularity min 1 vessel >1mm in length in sagittal plane	*US:* Initial & Monthly *Follow Up:* 5 months
Ooi, et al. (2015)	Cohort Study	N = 41 (M - 25, F- 16) Mean Age - 37.3 (range N/A)	Runners	Achilles	Echogenicity Thickness Vascularity	***1:*** Normal ***2:*** heterogeneous echotexture (undefined), bowed tendon margins (undefined), mild neovascularisation (1 or 2 intratendinous vessels >1mm in length) ***3:*** marked thickening (undefined), discrete hypoechoic areas (undefined), moderate to severe neovascularisation (>2 vessels peripheral and internal)	*US:* Initial (Pre-race 1wk) & 3-days post-race *Follow Up:* 10 days
Visnes, et al. (2015)	Cohort Study	N = 158 (M - 74, F - 84) Mean Age - 16.8 (range N/A)	Junior Volleyball	Patellar Quadriceps	Echogenicity Thickness Vascularity	***Normal*** ***Abnormal:*** presence of (1) hypoechogenicity (undefined) or (2) thickness (undefined) (3) increased vascularity > stage 2 (0- no flow, 1- flow outside tendon, 2- 1 or 2 vessels inside tendon, 3- multiple vessels inside tendon)	*US:* Initial & 6-monthly *Follow Up* 4 years (average 1.7years)

Notes: N = number, M = male, F = female, US = ultrasound imaging, N/A = not available, incr. = increased, RCT = randomised controlled trial, mm = millimetres, wk = week

Table 3: Summary of CASP scores for included studies

Cohort Studies													
	1	***2***	***3***	***4***	***5a***	***5b***	***6a***	***6b***	***7***	***10***	***11***	***12***	***Score***
Archambault, et al. (1998)	✓	✓	✓	✓	✓	✗	✗	✗	✓	✓	✓	✓	75%
Boesen, et al. (2012)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Comin, et al. (2013)	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓	75%
Cook, et al. (2000)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Cook, et al. (2001)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	92%
de Vos, et al. (2007)	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✓	✓	83%
Fredberg and Bolvig (2002)	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	✓	✓	83%
Giombini, et al. (2013)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Gisslén and Alfredson (2005)	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	✓	83%
Gisslén, et al. (2007)	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	✓	83%
Hirschmüller, et al. (2012)	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	83%
Jhingan, et al. (2011)	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓	75%
Khan, et al. (1997)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Khan, et al. (2003)	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓	75%
Malliaras, et al. (2010)	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓	75%
Ooi, et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Visnes, et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%

Randomised Controlled Trials													
	1	***2***	***3***	***4***	***5***		***6***		***7***	***9***	***10***	***11***	
de Jonge, et al. (2010)	✓	✓	✓	✗	✓		✓		✓	✓	✓	✓	90%
Fredberg, et al. (2008)	✓	✓	✗	✗	✗		✗		✓	✓	✓	✓	60%

Notes: CASP = Critical Appraisal Skills Programme, ✓ = yes, ✗ = no

Table 4: Synthesis of Evidence

Author	US Parameter Assessed				Study Quality	Was the criteria able to predict outcomes?	Is the criteria based off the continuum model?
	Echogenicity	Thickness	Vascularisation	Fibrillar Pattern			
Archambault, et al. (1998)	✓	✓	✗	✗	Good	✓	✗
Boesen, et al. (2012)	✗	✗	✓	✗	Good	✗	✗
Comin, et al. (2013)	✓	✓	✓	✗	Good	✗	✗
Cook, et al. (2000)	✓	✓	✗	✗	Good	✓	✗
Cook, et al. (2001)	✓	✓	✗	✗	Good	✗	✗
de Jonge, et al. (2010)	✗	✗	✓	✗	Good	✗	✗
de Vos, et al. (2007)	✗	✗	✓	✗	Good	✗	✗
Fredberg and Bolvig (2002)	✓	✓	✗	✗	Good	✓	✗
Fredberg, et al. (2008)	✓	✓	✗	✗	Good	✓	✗
Giombini, et al. (2013)	✓	✓	✓	✗	Good	✓	✗
Gisslén and Alfredson (2005)	✓	✓	✓	✗	Good	✓	✗
Gisslén, et al. (2007)	✓	✓	✓	✗	Good	✓	✗
Hirschmüller, et al. (2012)	✓	✓	✓	✗	Good	✗	✗
Jhingan, et al. (2011)	✓	✓	✓	✗	Good	✗	✗
Khan, et al. (1997)	✓	✓	✗	✗	Good	✓	✗
Khan, et al. (2003)	✓	✓	✓	✗	Good	✗	✗
Malliaras, et al. (2010)	✓	✓	✓	✗	Good	✓	✗
Ooi, et al. (2015)	✓	✓	✓	✗	Good	✗	✗
Visnes, et al. (2015)	✓	✓	✓	✗	Good	✓	✗

Notes: US = ultrasound imaging, ✓ = yes, ✗ = no

Table 5: Classification of Echogenicity

Author	Grading/Classification	Abnormal Echogenicity
	Nominal Scale	
Comin, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] hypoechogenicity, or [2] increased thickness, or [3] vascularity, or [4] intratendon defect (all undefined)	Presence of hypoechoic regions (undefined)
Cook, et al. (2000)	***Normal*** ***Abnormal****:* presence of [1] hypoechoic region, or [2] fusiform swelling (both undefined)	Presence of hypoechoic regions (undefined)
Cook, et al. (2001)	***Normal*** ***Abnormal****:* presence of [1] hypoechoic region, or [2] fusiform swelling (both undefined)	Presence of hypoechoic regions (undefined)
Fredberg and Bolvig (2002)	***Normal*** ***Abnormal****:* presence of [1] thickening >1mm, or [2] hypoechoic region >1mm	Hypoechoic region >1mm
Giombini, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] focal/diffuse thickening, or [2] focal/diffuse hypoechogenicity, or [3] vascularity > grade 2	Focal/Diffuse hypoechogenicity (undefined)
Gisslén and Alfredson (2005)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Presence of hypoechoic regions (undefined)
Gisslén, et al. (2007)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Presence of hypoechoic regions (undefined)

Hirschmüller, et al. (2012)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypo/hyper echogenicity, or [3] vascularity > grade 1	Presence of hyper/hypo echoic regions (undefined)
Jhingan, et al. (2011)	***Normal*** ***Abnormal****:* presence of [1] thickening >1mm, or [2] hypoechogenicity >1mm, or [3] paratendon blurring, or [4] vascularity	Hypoechoic region >1mm
Khan, et al. (1997)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity (both undefined)	Presence of hypoechoic regions (undefined)
Malliaras, et al. (2010)	***Normal*** ***Abnormal****:* presence of [1] diffuse thickening, or [2] hypoechogenicity (both undefined), or [3] vascularity >1mm	Presence of hypoechoic regions (undefined)
Visnes, et al. (2015)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Presence of hypoechoic regions (undefined)
	Ordinal Scale	
Archambault, et al. (1998)	***Grade 1****:* Normal (parallel margins, homogeneous) ***Grade 2****:* Enlarged tendon (bowed margins, homogeneous) ***Grade 3***: Hypoechoic (with or without enlargement)	***Grade 3***: Presence of hypoechoic regions (undefined)
Fredberg, et al. (2008)	***Normal*** ***Slightly Abnormal****:* presence of [1] thickening or hypoechoic region 0.5-1mm in AT, and [2] thickening or hypoechoic region 1-2mm in PT ***Severely Abnormal****:* presence of [1] thickening or hypoechoic region >1mm AT, and thickening or hypoechoic region >2mm in PT	Hypoechoic region >0.5mm in AT Hypoechoic region >1mm in PT

Khan, et al. (2003)	***Grade 1****:* Normal ***Grade 2****:* Thickened (>6mm), homogenous echotexture ***Grade 3***: Hyper/hypo echoic areas with/without thickening ***Vascularity****:* normal or abnormal	***Grade 3***: Presence of hyper/hypo echoic regions (undefined)
Ooi, et al. (2015)	***Grade 1****:* Normal ***Grade 2****:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation ***Grade 3****:* discrete hypoechoic areas, marked thickening, moderate to severe neovascularisation	***Grades 2-3***: heterogeneous echotexture (undefined) or discrete hypoechoic regions (undefined)

Notes: mm = millimetres, AT = Achilles tendon, PT = patellar tendon

Table 6: Classification of Tendon Thickness

Author	Grading/Classification	Abnormal Thickness
	Nominal Scales	
Comin, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] hypoechogenicity, or [2] increased thickness, or [3] vascularity, or [4] intratendon defect (all undefined)	Increased thickness (undefined)
Cook, et al. (2000)	***Normal*** ***Abnormal****:* presence of [1] hypoechoic region, or [2] fusiform swelling (both undefined)	Fusiform swelling (undefined)
Cook, et al. (2001)	***Normal*** ***Abnormal****:* presence of [1] hypoechoic region, or [2] fusiform swelling (both undefined)	Fusiform swelling (undefined)
Fredberg and Bolvig (2002)	***Normal*** ***Abnormal****:* presence of [1] thickening >1mm, or [2] hypoechoic region >1mm	Thickening >1mm
Giombini, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] focal/diffuse thickening, or [2] focal/diffuse hypoechogenicity, or [3] vascularity > grade 2	Focal/Diffuse thickening (undefined)
Gisslén and Alfredson (2005)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Increased thickness (undefined)
Gisslén, et al. (2007)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Increased thickness (undefined)

Hirschmüller, et al. (2012)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypo/hyper echogenicity, or [3] vascularity > grade 1	Increased thickness (undefined)
Jhingan, et al. (2011)	***Normal*** ***Abnormal****:* presence of [1] thickening >1mm, or [2] hypoechogenicity >1mm, or [3] paratendon blurring, or [4] vascularity	Thickening >1mm
Khan, et al. (1997)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity (both undefined)	Increased thickness (undefined)
Malliaras, et al. (2010)	***Normal*** ***Abnormal****:* presence of [1] diffuse thickening, or [2] hypoechogenicity (both undefined), or [3] vascularity >1mm	Increased thickness (undefined)
Visnes, et al. (2015)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity > grade 2	Increased thickness (undefined)
	Ordinal Scales	
Archambault, et al. (1998)	***Grade 1****:* Normal (parallel margins, homogeneous) ***Grade 2****:* Enlarged tendon (bowed margins, homogeneous) ***Grade 3***: Hypoechoic (with or without enlargement)	***Grade 2-3***: Enlarged tendon with bowed margins (undefined)
Fredberg, et al. (2008)	***Normal*** ***Slightly Abnormal****:* presence of [1] thickening or hypoechoic region 0.5-1mm in AT, and [2] thickening or hypoechoic region 1-2mm in PT ***Severely Abnormal****:* presence of [1] thickening or hypoechoic region >1mm AT, and thickening or hypoechoic region >2mm in PT	Thickening >0.5mm in AT Thickening >1mm in PT

Khan, et al. (2003)	***Grade 1****:* Normal ***Grade 2****:* Thickened (>6mm), homogenous echotexture ***Grade 3***: Hyper/hypo echoic areas with/without thickening ***Vascularity****:* normal or abnormal	Tendon diameter >6mm
Ooi, et al. (2015)	***Grade 1****:* Normal ***Grade 2****:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation ***Grade 3****:* discrete hypoechoic areas, marked thickening, moderate to severe neovascularisation	***Grade 2-3***: Increased thickness (undefined)

Notes: mm = millimetres, AT = Achilles tendon, PT = patellar tendon

Table 7: Classification of Vascularity

Author	Grading/Classification	Abnormal Vascularity
	Nominal Scales	
Comin, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] hypoechogenicity, or [2] increased thickness, or [3] vascularity, or [4] intratendon defect (all undefined)	Presence of vascularity (undefined)
Giombini, et al. (2013)	***Normal*** ***Abnormal****:* presence of [1] focal/diffuse thickening, or [2] focal/diffuse hypoechogenicity, or [3] vascularity >2 (***0***- no flow, ***1***- flow outside tendon, ***2***- 1 or 2 vessels inside tendon, ***3***- multiple vessels inside tendon)	***Vascularity Grade 2-3***: >1 vessel inside tendon
Gisslén and Alfredson (2005)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity >2 (***0***- no flow, ***1***- flow outside tendon, ***2***- 1 or 2 vessels inside tendon, ***3***- multiple vessels inside tendon)	***Vascularity Grade 2-3***: >1 vessel inside tendon
Gisslén, et al. (2007)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity >2 (***0***- no flow, ***1***- flow outside tendon, ***2***- 1 or 2 vessels inside tendon, ***3***- multiple vessels inside tendon)	***Vascularity Grade 2-3***: >1 vessel inside tendon
Hirschmüller, et al. (2012)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypo/hyper echogenicity, or [3] vascularity >1 (***0*** – no Doppler, ***1*** – 1 or 2 tiny foci, ***2*** – <5% colour ROI, ***3*** – 5-24% colour ROI, ***4*** – 25-49% colour ROI, ***5*** – >50% colour ROI)	***Vascularity Grade 1-5***: >1 or 2 tiny foci

Jhingan, et al. (2011)	***Normal*** ***Abnormal****:* presence of [1] thickening >1mm, or [2] hypoechogenicity >1mm, or [3] paratendon blurring, or [4] vascularity	Presence of vascularity (undefined)
Malliaras, et al. (2010)	***Normal*** ***Abnormal****:* presence of [1] diffuse thickening, or [2] hypoechogenicity (both undefined), or [3] vascularity >1mm	Presence of >1 vessel >1mm in length
Visnes, et al. (2015)	***Normal*** ***Abnormal****:* presence of [1] increased thickness, or [2] hypoechogenicity, or [3] vascularity >2(***0***- no flow, ***1***- flow outside tendon, ***2***- 1 or 2 vessels inside tendon, ***3***- multiple vessels inside tendon)	***Vascularity Grade 2-3***: >1 vessel inside tendon
	Ordinal Scales	
Boesen, et al. (2012)	***0*** – no Doppler ***1*** – 1 or 2 tiny foci ***2*** – <5% colour ROI ***3*** – 5-24% colour ROI ***4*** – 25-49% colour ROI ***5*** – >50% colour ROI	***Grade 2-5***: > 1 or 2 tiny foci
de Jonge, et al. (2010)	***0*** – no vessels ***1*** – one vessel mostly in anterior part ***2*** – one/two vessels throughout tendon ***3*** – three vessels throughout tendon *4* – >3 large tendons throughout tendon	***Grade 1-4***: > 1 vessel in tendon
de Vos, et al. (2007)	***0*** – no vessels ***1+*** – one vessel mostly in anterior part ***2+*** – one/two vessels throughout tendon ***3+*** – three vessels throughout tendon ***4+*** – >3 large vessels throughout tendon	***Grade 1-4***: >1 vessel in tendon

Khan, et al. (2003)	***Grade 1****:* Normal ***Grade 2****:* Thickened (>6mm), homogenous echotexture ***Grade 3***: Hyper/hypo echoic areas with/without thickening ***Vascularity****:* normal or abnormal	Presence of vascularity (undefined)
Ooi, et al. (2015)	***Grade 1****:* Normal ***Grade 2****:* Heterogeneous echotexture, bowed tendon margins, mild neovascularisation (1 or 2 intratendinous vessels >1mm in length) ***Grade 3****:* discrete hypoechoic areas, marked thickening, moderate to severe neovascularisation (>2 vessels peripheral and internal)	***Grade 2-3***: >1 vessel >1mm in length

Notes: ROI = region of interest, mm = millimetre

Figure 1

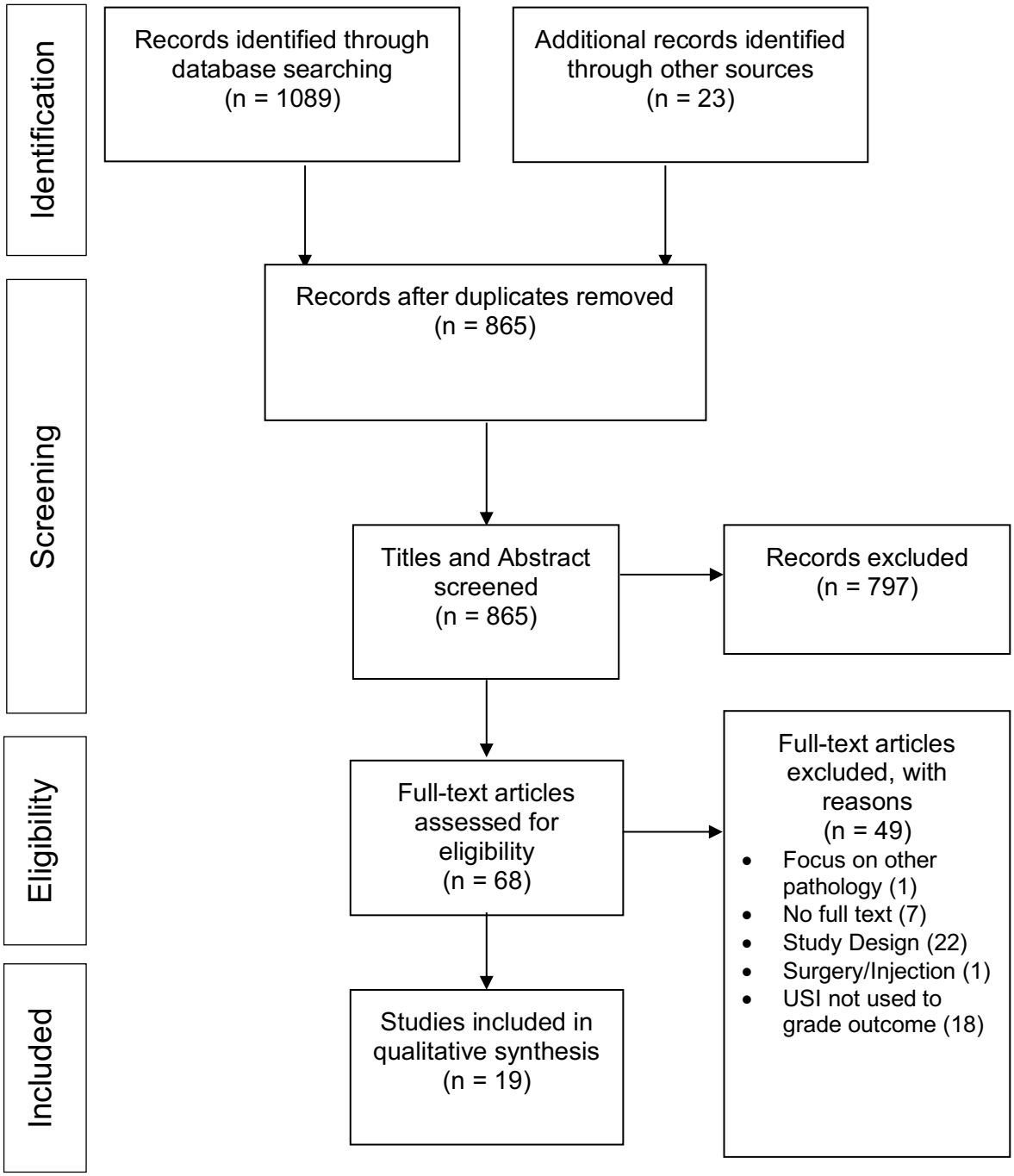

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1089)
Additional records identified through other sources (n = 23)
Records after duplicates removed (n = 865)
Titles and Abstract screened (n = 865)
Records excluded (n = 797)
Full-text articles assessed for eligibility (n = 68)
Full-text articles excluded, with reasons (n = 49)
Focus on other pathology (1)
No full text (7)
Study Design (22)
Surgery/Injection (1)
USI not used to grade outcome (18)
Studies included in qualitative synthesis (n = 19)

Figure 2

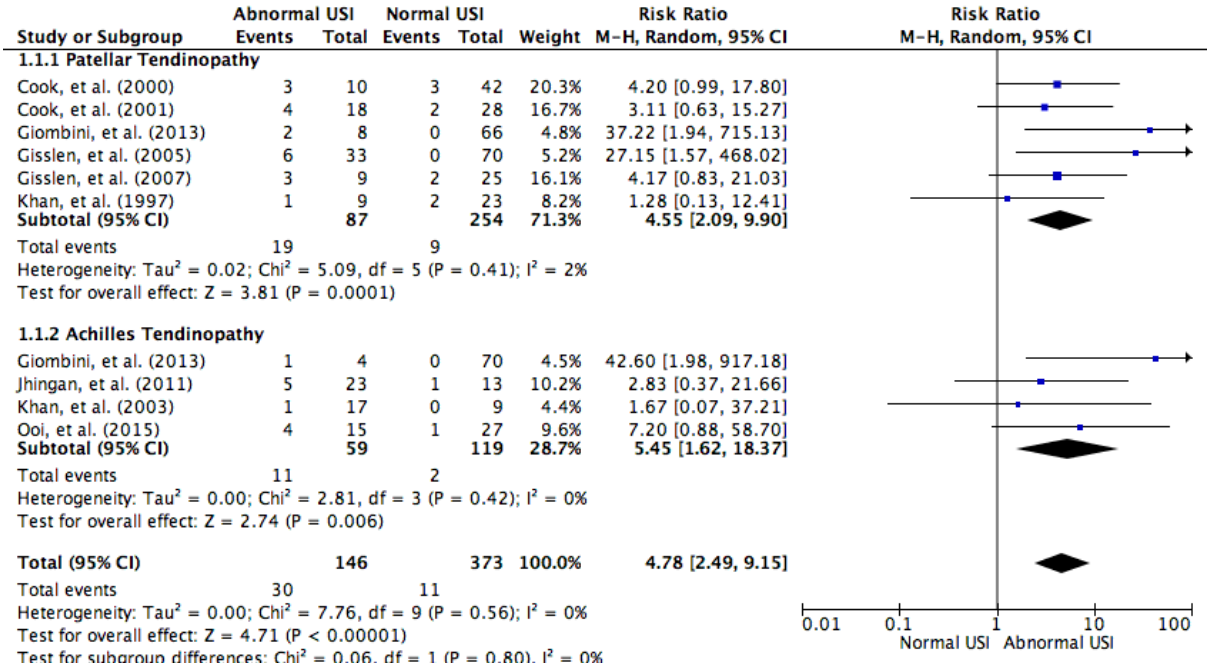

Abnormal USI
Normal USI
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.1.1 Patellar Tendinopathy
Cook, et al. (2000) 3 10 3 42 20.3% 4.20 [0.99, 17.80]
Cook, et al. (2001) 4 18 2 28 16.7% 3.11 [0.63, 15.27]
Giombini, et al. (2013) 2 8 0 66 4.8% 37.22 [1.94, 715.13]
Gisslen, et al. (2005) 6 33 0 70 5.2% 27.15 [1.57, 468.02]
Gisslen, et al. (2007) 3 9 2 25 16.1% 4.17 [0.83, 21.03]
Khan, et al. (1997) 1 9 2 23 8.2% 1.28 [0.13, 12.41]
Subtotal (95% CI) 87 254 71.3% 4.55 [2.09, 9.90]
Total events 19 9
Heterogeneity: Tau² = 0.02; Chi² = 5.09, df = 5 (P = 0.41); I² = 2%
Test for overall effect: Z = 3.81 (P = 0.0001)
1.1.2 Achilles Tendinopathy
Giombini, et al. (2013) 1 4 0 70 4.5% 42.60 [1.98, 917.18]
Jhingan, et al. (2011) 5 23 1 13 10.2% 2.83 [0.37, 21.66]
Khan, et al. (2003) 1 17 0 9 4.4% 1.67 [0.07, 37.21]
Ooi, et al. (2015) 4 15 1 27 9.6% 7.20 [0.88, 58.70]
Subtotal (95% CI) 59 119 28.7% 5.45 [1.62, 18.37]
Total events 11 2
Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
Total (95% CI) 146 373 100.0% 4.78 [2.49, 9.15]
Total events 30 11
Heterogeneity: Tau² = 0.00; Chi² = 7.76, df = 9 (P = 0.56); I² = 0%
Test for overall effect: Z = 4.71 (P < 0.00001)
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.80), I² = 0%
0.01 0.1 1 10 100
Normal USI Abnormal USI

Figure 3

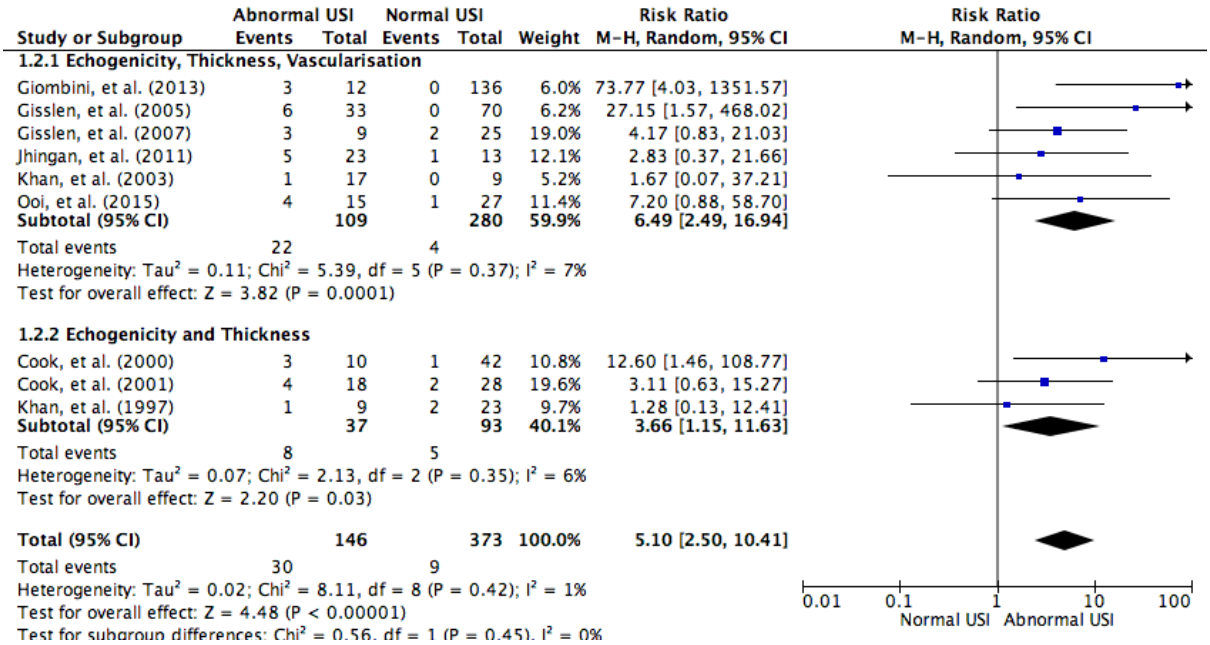

Abnormal USI
Normal USI
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.2.1 Echogenicity, Thickness, Vascularisation
Giombini, et al. (2013) 3 12 0 136 6.0% 73.77 [4.03, 1351.57]
Gisslen, et al. (2005) 6 33 0 70 6.2% 27.15 [1.57, 468.02]
Gisslen, et al. (2007) 3 9 2 25 19.0% 4.17 [0.83, 21.03]
Jhingan, et al. (2011) 5 23 1 13 12.1% 2.83 [0.37, 21.66]
Khan, et al. (2003) 1 17 0 9 5.2% 1.67 [0.07, 37.21]
Ooi, et al. (2015) 4 15 1 27 11.4% 7.20 [0.88, 58.70]
Subtotal (95% CI) 109 280 59.9% 6.49 [2.49, 16.94]
Total events 22 4
Heterogeneity: Tau² = 0.11; Chi² = 5.39, df = 5 (P = 0.37); I² = 7%
Test for overall effect: Z = 3.82 (P = 0.0001)
1.2.2 Echogenicity and Thickness
Cook, et al. (2000) 3 10 1 42 10.8% 12.60 [1.46, 108.77]
Cook, et al. (2001) 4 18 2 28 19.6% 3.11 [0.63, 15.27]
Khan, et al. (1997) 1 9 2 23 9.7% 1.28 [0.13, 12.41]
Subtotal (95% CI) 37 93 40.1% 3.66 [1.15, 11.63]
Total events 8 5
Heterogeneity: Tau² = 0.07; Chi² = 2.13, df = 2 (P = 0.35); I² = 6%
Test for overall effect: Z = 2.20 (P = 0.03)
Total (95% CI) 146 373 100.0% 5.10 [2.50, 10.41]
Total events 30 9
Heterogeneity: Tau² = 0.02; Chi² = 8.11, df = 8 (P = 0.42); I² = 1%
Test for overall effect: Z = 4.48 (P < 0.00001)
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%
0.01
0.1
1
10
100
Normal USI
Abnormal USI

Figure 4

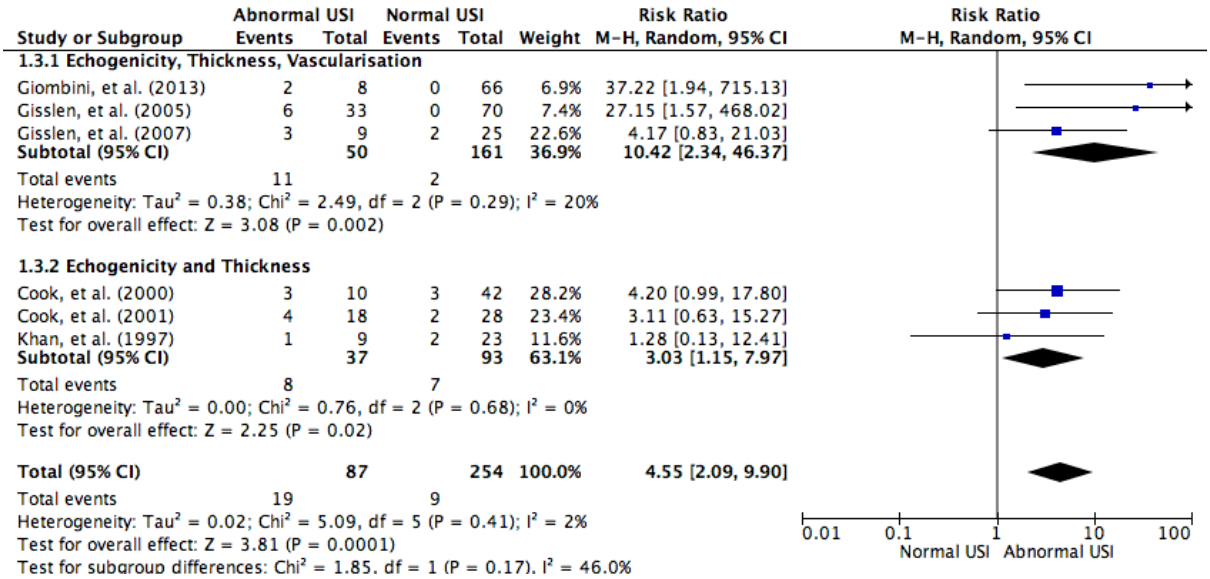

Abnormal USI
Normal USI
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.3.1 Echogenicity, Thickness, Vascularisation
Giombini, et al. (2013) 2 8 0 66 6.9% 37.22 [1.94, 715.13]
Gisslen, et al. (2005) 6 33 0 70 7.4% 27.15 [1.57, 468.02]
Gisslen, et al. (2007) 3 9 2 25 22.6% 4.17 [0.83, 21.03]
Subtotal (95% CI) 50 161 36.9% 10.42 [2.34, 46.37]
Total events 11 2
Heterogeneity: Tau² = 0.38; Chi² = 2.49, df = 2 (P = 0.29); I² = 20%
Test for overall effect: Z = 3.08 (P = 0.002)
1.3.2 Echogenicity and Thickness
Cook, et al. (2000) 3 10 3 42 28.2% 4.20 [0.99, 17.80]
Cook, et al. (2001) 4 18 2 28 23.4% 3.11 [0.63, 15.27]
Khan, et al. (1997) 1 9 2 23 11.6% 1.28 [0.13, 12.41]
Subtotal (95% CI) 37 93 63.1% 3.03 [1.15, 7.97]
Total events 8 7
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.25 (P = 0.02)
Total (95% CI) 87 254 100.0% 4.55 [2.09, 9.90]
Total events 19 9
Heterogeneity: Tau² = 0.02; Chi² = 5.09, df = 5 (P = 0.41); I² = 2%
Test for overall effect: Z = 3.81 (P = 0.0001)
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.0%
0.01
0.1
1
10
100
Normal USI
Abnormal USI

Figure 5

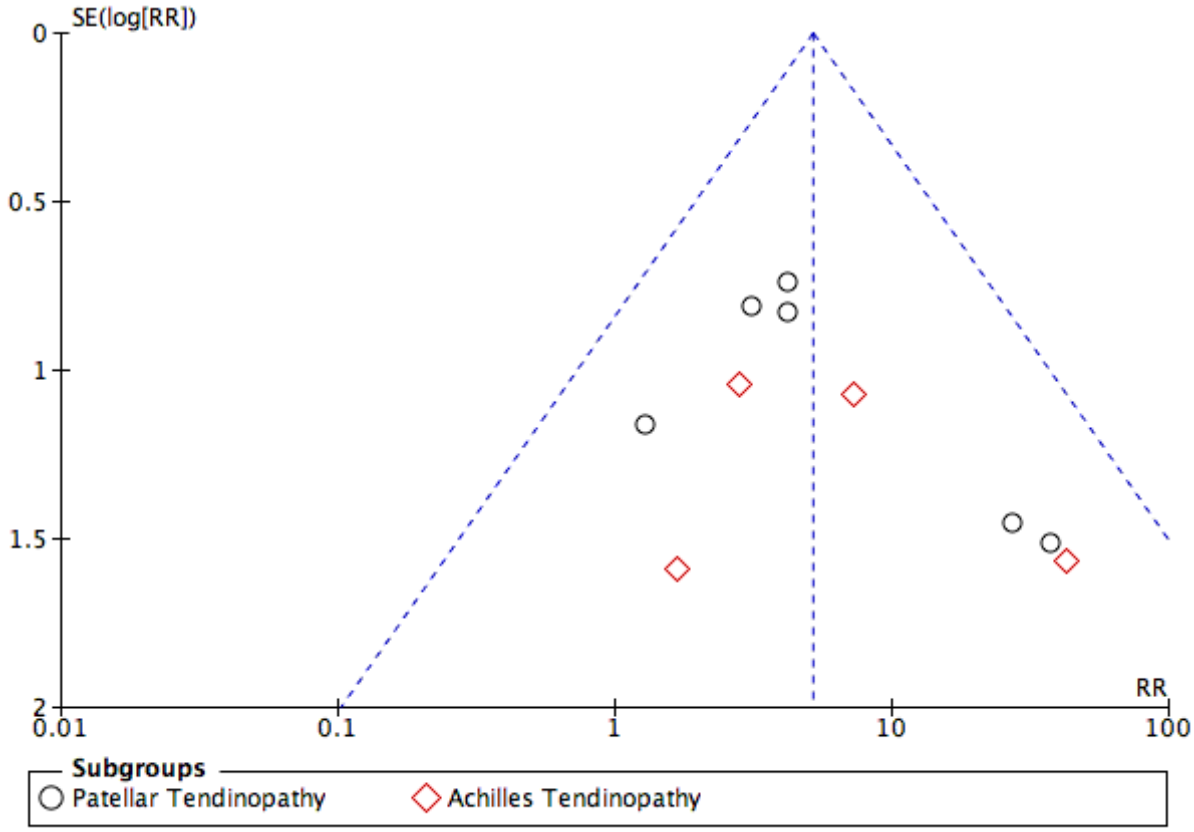

SE(log[RR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
RR
Subgroups
Patellar Tendinopathy
Achilles Tendinopathy

Figure 6

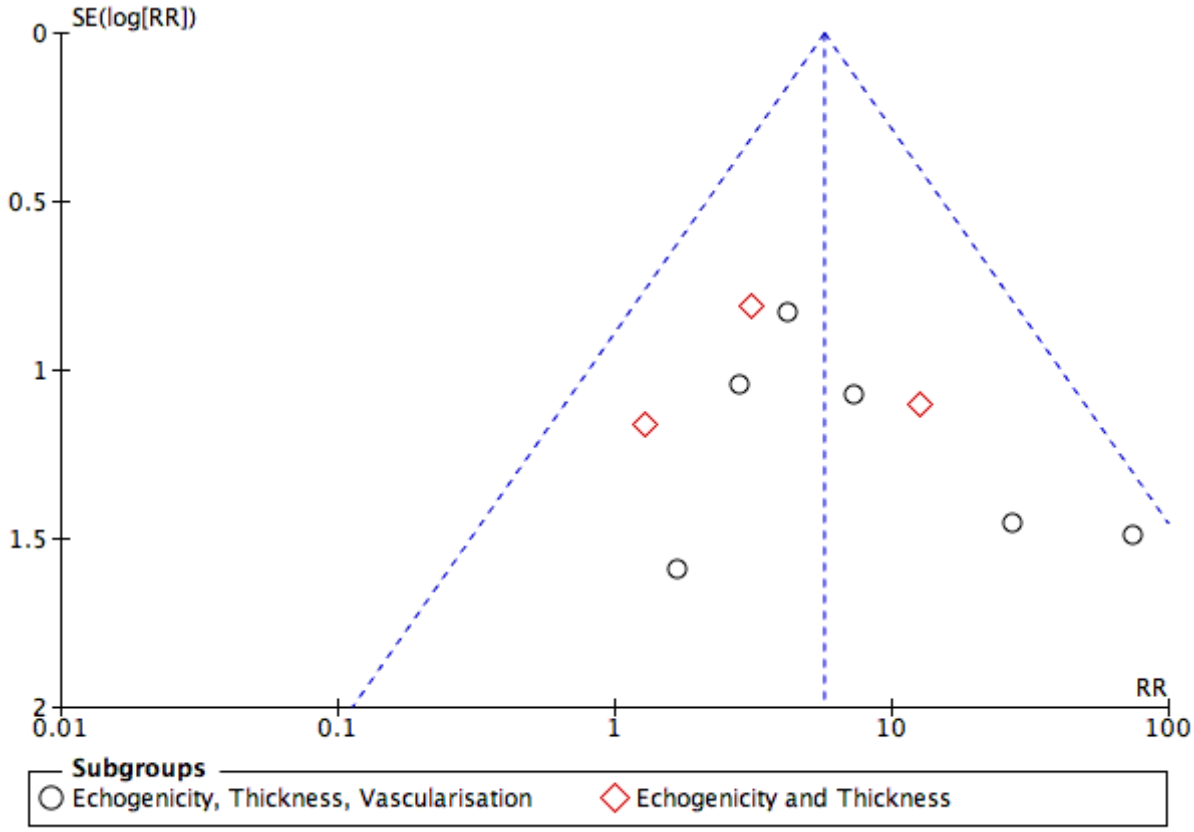
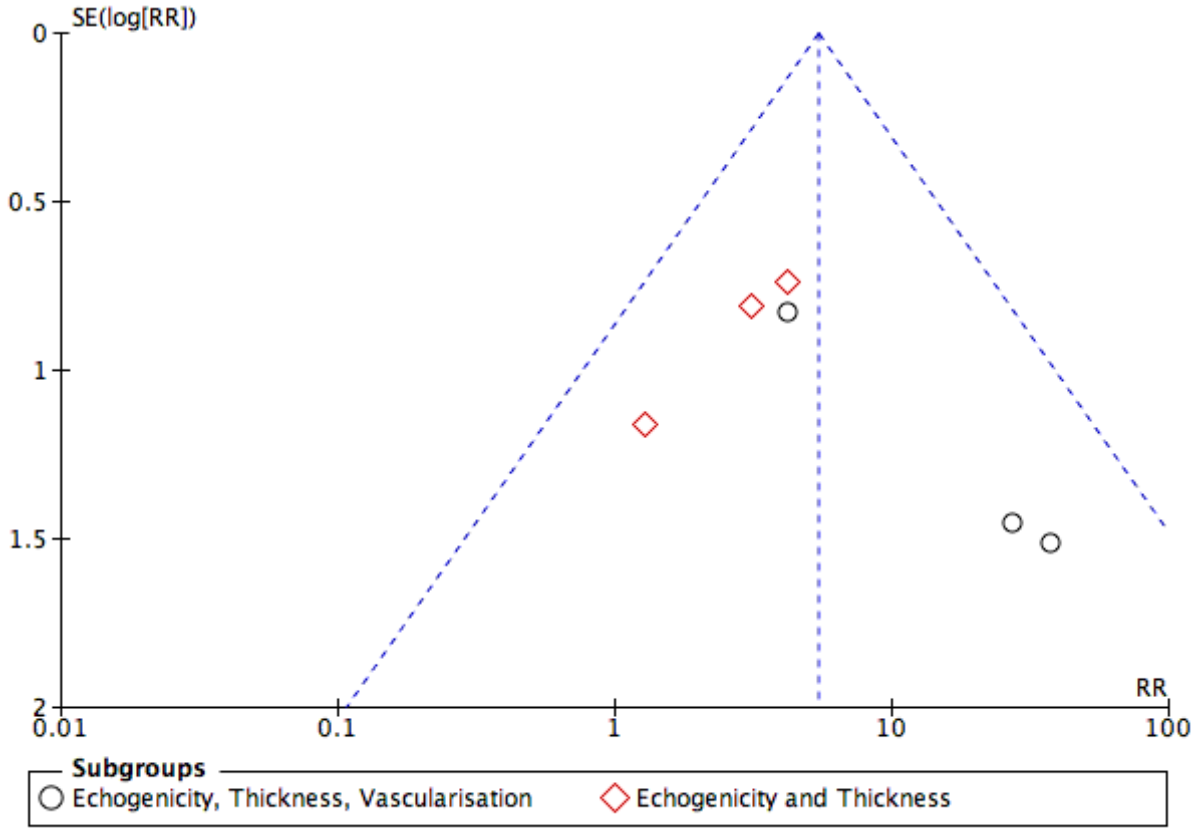

SE(log[RR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
RR
Subgroups
Echogenicity, Thickness, Vascularisation
Echogenicity and Thickness

Figure 7


SE(log[RR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
RR
Subgroups
Echogenicity, Thickness, Vascularisation
Echogenicity and Thickness

Acknowledgements

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Figure Captions List