Title

Predictors of the outcome of physiotherapy following a meniscus tear: a systematic review.

Authors

Andrew Kemp (a), Ben Hodgson (a) Lee Barnes (b) Toby O Smith (c)

(a) HERE, Sussex MSK Partnership, 5th Floor, 177 Preston Rd, Brighton, UK BN1 6AG,
(b) Musculoskeletal Assessment and Rehabilitation Service, Red Wing, Crawley, Hospital, West Green Drive, Crawley, UK, RH11 7DH.
(c) School of Health Sciences, University of East Anglia, Queen's Building, Norwich Research Park, Norwich, UK, NR4 7TJ,

Corresponding Author: Andrew Kemp

Email address: andrew.kemp7@nhs.net

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Highlights

1. There is low/moderate quality evidence for predictors of the outcome of physiotherapy following a meniscal tear.
2. No or minimal association exists between gender, mechanical symptoms, BMI or age and the outcome of physiotherapy or exercise rehabilitation following a meniscus tear.
3. A worse baseline pain score is associated with a cross-over to surgery and less improvement with physiotherapy.

ABSTRACT

Background

Physiotherapy is indicated for treatment of a painful degenerative knee meniscus tear. Predicting the outcome remains uncertain.

Objective

The purpose of this systematic review was to identify which predictive factors are associated with the outcome of physiotherapy for degenerative knee meniscus tear.

Methods

A systematic electronic literature search was undertaken of PubMed, CINAHL, Medline with AMED and EMBASE via Ovid from inception to July 2021. Studies of adults receiving physiotherapy which presented data on the association of baseline variables and the treatment outcome were included. Study quality was assessed using CASP (Critical Appraisal Skills Programme) tools. Data were narratively analysed.

Results

1051 titles were retrieved and screened for eligibility. fifteen studies met the inclusion criteria. Nine studies investigated degenerative tears. The evidence-base was of low/moderate quality. Seven studies and five studies (100%) reported no association between mechanical symptoms and gender respectively ($p \geq 0.05$). There was no association with osteoarthritis in 80% of studies, age in 71% of studies, or body mass index in 60% of studies ($p \geq 0.05$). Three studies (75%) reported that higher baseline pain was associated with cross-over to surgery, worse pain or greater improvement with surgery ($p \geq 0.05$).

Conclusion

Patient demographic characteristics provide minimal association with outcome following physiotherapy for degenerative meniscus tear. The evidence-base is limited in size and quality. A large adequately powered prospective cohort study investigating a broad range of predictive factors is warranted to develop a predictive model to better stratify those most likely to benefit from physiotherapy.

Keywords: meniscus, physiotherapy, predictive factors

1.1 BACKGROUND

Meniscus tears are a common cause of knee pain with the estimated mean annual prevalence of these reported as 66 cases per 100,000 [1][2]. They can occur through injury but also through degenerative processes and may be classified accordingly. Meniscal tears can also be classified according to the pattern, depth of the tear and the location. Traumatic tears generally occur in younger, active individuals, whilst non-traumatic, degenerative tears are more common in the middle-aged and older populations and considered to represent cumulative stress [3].

Meniscus tears are not always associated with pain. In the Framingham study of 991 randomly assigned middle-aged and older adults, 61% percent of people with meniscal tears were asymptomatic [4]. The presence of meniscus tears on magnetic resonance imaging (MRI) ranged from 19% in women aged 50-59 years of age, to 56% of men aged between 70 to 90 years [4].

Treatment of a painful meniscus tear may include watchful waiting, analgesia, physiotherapy, corticosteroid injection and surgery. A meniscus tear causing a locked knee requires surgery and meniscus repair surgery may be suitable in adults with a recent tear and without significant degenerative cartilage changes [5]. However, for people unsuitable for meniscus repair and those without considerable mechanical symptoms, physiotherapy is recommended as a first-line treatment. Recent systematic reviews and meta-analysis in middle-aged and older adults show improvement with non-surgical management including physiotherapy [6][7][8][9][10]. However, up to 38% of study participants with a degenerative meniscus tear undertaking physiotherapy fail to improve sufficiently [11]. For those where physiotherapy does not provide sufficient improvement, surgery such as arthroscopic partial meniscectomy (APM), is frequently indicated.

Stratified medicine targets interventions according to the biological or risk characteristics shared by subgroups of people with the particular condition. It is considered central for progress in healthcare [12]. Prognosis research in terms of the identification of factors that predict an individual treatment response is a cornerstone of stratified medicine [12] and greater knowledge of who, with a meniscus tear is likely to respond to physiotherapy and who will not, is vital to ensure effective and efficient use of limited resources. It also follows the 'getting it right first time (GIRFT)' principles [13]. Referral of those that will respond favourable to physiotherapy will be of considerable benefit alongside commissioning effective and timely intervention for those who will not, reducing the overall economic burden. The PROGnosis RESearch Strategy (PROGRESS) includes recommendations for the conducting and reporting of prognosis research [14].

The objective of this systematic review is to identify the predictive factors that are associated with the outcomes for physiotherapy treatment of a degenerative knee meniscal tear and knee meniscus tear generally.

2.1 Methods

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: Registration no CRD42018110153). This paper has been reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines [15].

2.2 Search Strategy

A search of the databases: CINAHL, Medline, AMED and EMBASE via OVID was performed using the NICE Healthcare Databases Advanced Search (HDAS) from inception to July 2021. A search of PubMed was also completed. Medical subject headings (MeSH) text terms and Boolean operators were used. Search terms were adapted where necessary for each database. The search strategy for AMED database is found in **Supplementary File 1** as an example. There were no language limits. Reference lists of relevant publications were also searched along with a search of relevant articles via Google Scholar.

2.3 Study selection

The reviewers (AK, BH) independently screened the titles and abstracts of all retrieved publications. All potentially eligible publications were retrieved in full-text and independently assessed for eligibility by the two reviewers (AK, BH).

To be eligible, studies had to be prospective studies of adults diagnosed with a meniscus tear of any duration and had to have undertaken at least one session of physiotherapy treatment; needed to present an analysis of predictive factors for the outcome of physiotherapy; and use a standardised measure to evaluate the outcome of physiotherapy. This could include scores of pain, symptoms, or function using a validated self-reported measure or a quality-of-life score. Cross-over from physiotherapy to surgery was also considered an acceptable outcome. Whilst it may be regarded as a clinical decision, it is also an indication of failure to manage the condition non-operatively and therefore an important health outcome for patients and from a health utilisation perspective. Papers that were a secondary analysis of predictive factors from a prospective primary research article were permitted. Studies in which participants undertaking physiotherapy progressed to surgery due to insufficient improvement were eligible if there was an analysis of predictive factors for the physiotherapy treatment in isolation or if the effect of surgery was statistically excluded. There were no restrictions placed on the follow-up time frames. Abstract publications were included if the same data was not subsequently published. Studies investigating predictive factors for the outcome of physiotherapy following surgery were excluded.

2.4 Data Extraction

Data were extracted from one reviewer (AK) and verified by a second (BH). Data on potential predictive factors had to be collected at baseline and included: participant characteristics such as age, gender, and BMI (body mass index), lifestyle factors, psychological factors, symptoms, imaging findings such as the type of meniscal tear and degree of osteoarthritis (OA), physical examination findings such as range of movement and joint effusion and physical performance measures. Blood test results and surgical findings were not included as possible predictive variables as surgery is not routinely performed before physiotherapy. The details included study design, author and study location, participant details, type of meniscus tear and degree of OA if relevant, outcome measures used, follow-up period and loss to follow up, details on the physiotherapy treatment including exercises, number of sessions and compliance and any other treatment permitted.

2.5 Quality Assessment

As there is no recommended validated tool for the assessment of quality in reviews of predictive factors incorporating multiple study designs, the quality of the papers was assessed using the appropriate CASP (Critical Appraisal Skills Programme) checklist [16][17]. Each item was independently

assessed by the two reviewers (AK, BH) and results for each study recorded on to a tailored data extraction form. The reviewers pooled the extracted data. Any difference of opinion or any items requiring further evaluation were resolved through discussion with author (TS).

2.6 Data Analysis

Data were narratively analysed to look at the factors that predict the outcome of physiotherapy such as baseline pain and body mass index (BMI). The results of studies including only those participants with a confirmed degenerative meniscus tear are presented separately from studies including participants with meniscal symptoms and those studies including younger participants with likely acute or traumatic meniscus tears to respect the differences in the nature and prognosis of these injuries. Meta-analysis was not undertaken due to study heterogeneity in relation to subject characteristics and study design.

3.0 Results

3.1 Study selection

The study search results are presented in **Figure 1.** Of 1051 citations screened, 80 studies were deemed as potentially eligible and reviewed as full-text papers. Fifteen studies met the inclusion/exclusion criteria and were therefore included [11][18][19][20][21][22][23][24][25][26][27][28][29][30][31]. The most frequent reason that studies were excluded at this stage was that there was no analysis of predictive variables. The 15 research articles arose from seven separate research studies [11][18][19][20][21][22][30]. Eight studies were secondary exploratory analyses [23][24][25][26][27][28][29][31].

3.2 Study characteristics

The study design, participant and physiotherapy treatment characteristics are outlined for each study in **Table 1**. Of the seven primary research studies [11][18][19][20][21][22][30], four were randomised controlled trials (RCTs) [11][18][19][30] and three were cohort studies [20][21][22]. The secondary exploratory analysis of outcome predictors were from the four separate RCT's [23][24][25][26][27][28][29][31]. The three cohort studies followed subjects with a meniscus tear undertaking a course of physiotherapy [19] and subsequent APM if required [20][21]

Of the seven primary research studies, two RCTs [11][19] and one cohort study [22] only included subjects with a non-traumatic degenerative meniscus tear. One RCT and the secondary exploratory analysis included middle-aged and older adults with either traumatic or non-traumatic meniscus tears, justified in that traumatic tears in older adults may be a consequence of degenerative changes. One RCT (and two secondary analysis studies) investigated middle-aged adults with a clinical examination consistent with a meniscus tear [18][27][28]. Two cohort studies [20][21] included subjects over the age of 18 years. Whilst the mean age of participants was 46 and 40 years respectively these studies included younger subjects with sub-acute/traumatic meniscus tears along with non-traumatic/degenerative meniscus tears.

The number of participants receiving physiotherapy intervention ranged between 33 [22] and 185 [20]. Overall, 764 participants were randomised to physiotherapy or received physiotherapy within a cohort study. In the studies including those with a confirmed non-traumatic degenerative meniscus tear [11][19][22], 272 participants undertook physiotherapy. Physiotherapy intervention included exercise rehabilitation (n=7), electrotherapy (n=2) and manual therapy (n=1). Participants in the

published series of studies from the MeTeOR trial were permitted intra-articular steroid injections [11] and two studies report permitting use of analgesics and non-steroidal anti-inflammatory drugs (NSAID's)[20][22]. The mean age in each study ranged from 45 to 59 years. The diagnosis of a painful meniscus tear was made following a clinical examination, x-ray, and MRI except in the series of studies by Gauffin et al [18][27][28]. Kise et al [19] included those with only a degenerative medial meniscus tear. Neogi et al [22] included only those with a degenerative medial meniscus posterior root tear and El Ghazaly et al [21] included those considered to have an unstable meniscus tear.

3.3 Predictive factors and outcomes

Analysis of predictive factors was determined from outcomes measured from six months [11] up to five years [28]. The predictive factors and outcomes varied across the studies and included baseline pain, age, gender, duration of symptoms, BMI, mechanical symptoms, imaging measures of osteoarthritis. Physical examination findings including range of movement (ROM), muscle strength, static knee alignment, swelling, foot planus and validated physical performance measures were assessed in two studies [18][20].

Predictive factors were most frequently determined using self-reported outcome measures. These included the Knee Injury and Osteoarthritis Score (KOOS n= 7), Lysholm scale (n=2), Western Ontario and McMaster Osteoarthritis Index (WOMAC n= 2), International Knee Documentation Committee (IKDC=1), and Global Rating of Change (GRC n=1). Appointment attendance and exercise compliance was recorded where possible for each study. Table 2 shows the outcomes from RCTs showing differential effects of physiotherapy and exercise rehabilitation versus APM.

3.4 Quality assessment and risk of bias within studies

A summary of the critical appraisal is presented in Tables 3 and 4. Overall, the quality of the evidence was low/moderate. All studies reported baseline predictive factors and predetermined outcomes using standardised measures. Methods for randomisation and allocation sequence generation was appropriate. Loss to follow-up was reported in six studies and reported as either a percentage or the actual number of participants was given [11][18][19][20][22][30]. All the studies report upon the number of subjects that were eligible for inclusion, however only the original RCTs study by Katz et al [11] and Kise et al [19] reported numbers of participants that were assessed for eligibility. No studies measured baseline characteristics of those who were unwilling to participate. No studies reported that outcome assessors and participants completing questionnaires or outcomes measures were blinded to the measurement of predictive variables. Five studies report upon compliance with the physiotherapy and home exercise programme [11][18][19][22][30]. Whilst a prospective power analysis was performed for determining outcomes of the RCT's [11][18][19][30], no studies performed a power calculation for the evaluation of predictive factors. Therefore, all studies are likely to be underpowered to determine predictive factors. Furthermore, only five papers [18][23][24][25][30] provide data for the non-statistically significant predictive factors.

3.5.0 Summary of Outcomes

Predictive factors that were found to have a significant association with the outcome from physiotherapy treatment (on multiple regression analysis or equivalent) in the studies described above have been synthesised and summarised below. Furthermore factors, that have been shown to have no predictive value in more than one study are also summarised. The outcomes from studies

including only middle-aged adults and those with a confirmed degenerative meniscus tear (traumatic or non-traumatic) are presented separately.

3.5.1 Pain

Five studies (621 participants) have examined the association of baseline pain levels with the outcome of physiotherapy treatment [20][24][29][30][31]. One RCT [30], two RCT secondary analysis [24] and one cohort study [20] report an association between baseline pain and the outcome of physiotherapy. One secondary analysis reports an association on univariate regression analysis but has not been included on the multivariate analysis [31] and one secondary exploratory analysis shows no association [29]. In the ESCAPE RCT [30] post hoc analysis of outcomes showed that for every millimetre increase in reported baseline pain during weight bearing (VAS 0-100) the effect of APM provided 0.14 greater IKDC score than physiotherapy (regression coefficient 0.14 [95%CI 0.01 to 0.27, *p*=0.03). In the secondary exploratory analysis of those participants randomised to physiotherapywho crossed over to APM, pain during activities was found to be a predictor of cross-over to surgery on univariate analysis (p<0.01) however pain was not included in the multivariate regression analysis. In a similar study from the MeTeOR trial comparing physiotherapy to APM and post-operative physiotherapy, the multivariate regression analysis shows that in those participants who crossed over from physiotherapy to APM within the first 140 days after randomisation, scoring over 40 on the WOMAC pain score (higher level of pain) compared to those scoring under 40 was predictive of cross-over from physiotherapy to APM [24].

In the cohort study of Rathleff et al [20], a higher baseline pain score measured using the KOOS pain subscale was the most significant factor to predict a worse outcome with physiotherapy treatment measured using the KOOS pain subscale between 12-24 months following treatment (*P*=<0.0001, 95% CI -0.8 -0.4) [20].

In the secondary analysis of the RCT of Kise et al [29] comparing exercise therapy to APM, there was no association between the baseline KOOS pain score and the outcome of either physiotherapy or APM (102 participants) measured using the KOOS pain sub-score at 2 years. The authors did not provide numerical data for non-significant results.

Degenerative tear

There is inconsistency in the data from 3 RCTs, including only participants with a degenerative meniscus tear (471 participants). Scoring over 40 on the WOMAC pain score was predictive of cross-over to surgery (Relative Risk (RR)=1.90, 95% CI 1.05 3.42) [24]. For every millimetre increase in baseline weight bearing pain (VAS 0-100), outcomes on IKDC score were 0.14 points better with APM than physiotherapy indicating that a greater baseline pain is associated with better outcomes with APM than physiotherapy [30]. There was no association of baseline KOOS pain with the KOOS pain at two-year follow-up in the other study [29].

3.5.2 Mechanical/meniscal symptoms

Seven separate papers (822 participants) investigate potential associations between the presence of mechanical and meniscal symptoms and the outcome of physiotherapy and exercise rehabilitation. Five of these are secondary analyses [23][24][25][27][28] from RCTs studies [11][18][30] comparing outcomes against those of APM.

Baseline presence of mechanical symptoms categorised as daily joint catching (p=0.216) or joint locking for less than two seconds (p=0.964) within the last month did not have a significant main or interaction effect with the improvement in KOOS pain score following exercise or surgery [18]. This was a consistent finding also when outcomes were assessed at both 3 [27] and 5 years (p=0.279)[28].

In the participants who crossed-over from physiotherapy to surgery (n=48), mechanical symptoms (locking or catching) measured using a 5-item inventory, ranging on a scale 0-100 with a score of 100 representing the greatest severity of mechanical symptoms and 0 representing no mechanical symptoms, neither the aggregated score or separated individual mechanical symptoms of locking or catching (none vs any) were associated with cross-over (RR=1.20 95% CI 0.72 1.99) [24].

The secondary analysis [23] of the RCT by Katz et al [11] included participants that underwent physiotherapy versus those randomised to APM *and* those that crossed over from physiotherapy to APM. Overall, mechanical symptoms (clicking, catching, locking, popping, and giving way) improved more in those treated with APM than those treated only with physiotherapy. When mechanical symptoms were summed to create an overall mechanical symptoms score, results showed no association between the baseline mechanical symptom score and the improvement in WOMAC pain score at six months in either those treated with physiotherapy or APM. Furthermore, the association between the baseline mechanical symptoms score and change in WOMAC pain score was not significantly different between physiotherapy and APM treatment groups (p =0.44) [23].

A further secondary analysis reports the potential interaction of the presence of individual 'meniscal symptoms' (clicking, catching, locking, popping, giving way, and swelling) at baseline on the outcomes of participants randomised to physiotherapy versus those randomised to APM (excluding participants that crossed-over) and measured using the KOOS pain score at six months following treatment. Despite the results showing that participants *without* clicking, catching, popping, or locking and *with* giving way and swelling having a small but greater improvement in KOOS pain score after APM than after physiotherapy, overall, there was no significant differences in KOOS pain score between those participants treated with either physiotherapy or APM with or without each meniscal symptom (p>0.05) [25].

In the post hoc analysis of outcomes from the ESCAPE RCT, there was no statistically significant interaction effect for mechanical symptoms between the outcomes of physiotherapy compared to APM (*p*=0.81)[30].

Degenerative tear

In the four studies involving those with a degenerative meniscus tear, three secondary analysis studies all from the MeTeOR trial [23][24][25] report no statistically significant association between mechanical/meniscal symptoms and the outcome of physiotherapy. There was also no statistically significant interaction effect for mechanical symptoms between the outcomes of physiotherapy compared to APM within the ESCAPE trial (*p*=0.81)[30].

3.5.3 Age

Seven studies (881 participants) [18][20][21][24][27][29][30] including 3 secondary analysis studies have investigated the association of age with the outcome of physiotherapy and exercise rehabilitation. Five studies (679 participants) reported no association of age on the outcome of physiotherapy [20][21][24][27][30]. Katz et al [24] show no difference in the univariate risk ratio for cross-over to surgery from physiotherapy for those under 60 years compared to those 60 and over (OR: 1.18 95% CI 0.73, 1.91). The was no interaction effect of age with the outcomes of physiotherapy

verses APM(*p*=0.53) [30]. Numerical data is not provided for non-statistically significant results in the two cohort studies [20][21] and the secondary analysis of predictive factors from the RCT of exercise therapy versus APM by Kise et al [27].

Gauffin et al [14][22] reports an association between age and outcomes of both physiotherapy rehabilitation and surgery measured using the KOOS pain scale at six months, one year and three years. Those subjects randomised to physiotherapy rehabilitation and those randomised to surgery aged '55 and over' both had better KOOS pain score at one-year (p=0.037) and three years (p=0.011) compared to the group '55 and under'. There was no significant between treatment group difference.

Degenerative tear

In the three studies of those with a degenerative meniscus tear (471 participants) no association between age and outcome of physiotherapy was reported and there was no interaction effect with on the outcome of physiotherapy compared to surgery [24]29][30].

3.5.4 Degree of Osteoarthritis

Five studies (715 participants) have investigated the association of osteoarthritis with the outcome of physiotherapy [12][16][19][21]. In the cohort study of adults over the age of 18 years categorised as having an unstable meniscus tear (n=70), the presence of osteoarthritis was associated with a worse pain visual analogue score (VAS) and worse Lysholm score following physiotherapy compared to those without osteoarthritis (p=0.001) [16]. Interpretation of these results is difficult as there were significant differences in VAS and Lysholm score between groups at baseline.

Degenerative tear

In the RCT [11] (351 participants) and two further secondary analysis studies [24][26] including only those with a degenerative meniscus tear, no association between degree of osteoarthritis and the outcome of physiotherapy was found. When severity of OA measured using the Kellgren and Lawrence scale [25] and graded as 0-2 and compared to grade 3 osteoarthritis, there was no associated with the degree of change in WOMAC physical function score [11]. Furthermore, in the participants who crossed-over from physiotherapy to surgery, degree of osteoarthritis was not a significant predictor of cross-over (n=48) (RR 1.03 95%CI 0.55, 1.95) [24]. In the post hoc analysis of confounding variables in the RCT of van de Graaf and colleagues [30] comparing outcomes of physiotherapy and APM, there was no significant interaction effect for severity of osteoarthritis on xray (*p*=0.74*).*

Macfarlane et al [26] investigated MRI features of osteoarthritis and outcomes of physiotherapy (99 participants) showing that whilst those with least cartilage damage and no bone marrow lesions improve less with physiotherapy than those undergoing APM, the interaction between osteoarthritis, treatment, and outcome of the KOOS pain score was not statistically significant (p=0.13).

3.5.5 Meniscal tear type/ characteristics

Three studies (participants=310) have investigated the association of meniscal tear characteristics on the outcome physiotherapy [20][21][29]. In an arthroscopy restricted prospective cohort study of adults over the age of 18 years, multivariate analysis showed that bucket-handle type meniscus tears were associated with greater improvement in the KOOS pain score compared to flap lesions in subjects treated with either physiotherapy or APM (p=0.02) [20]. However, caution should be applied when interpreting these results as only 11/185 participants had bucket-handle tears. Also in their prospective cohort study, El Ghazaly et al [21] report a statistically significant improvement in pain

(VAS) following physiotherapy (p=0.001) in adults with an unstable meniscus tear. Improvement in pain (VAS) and Lysholm score was significantly greater in subjects treated with APM. Those participants with an unstable medial meniscus tear reported higher pain VAS scores than those with a lateral meniscus tear following the physiotherapy intervention (p=0.005). In the post hoc analysis of the ESCAPE RCT, there was no interaction effect for the location of the meniscus tear, whether it was located medially versus laterally or both [30].

Degenerative tear

The post hoc analysis of RCT data [30] showed no interaction effect for tear location and one secondary analysis of outcomes from an RCT comparing exercise therapy with APM investigated meniscus tear characteristics in those with a degenerative medial meniscus tear. No association was found between meniscal extrusion or meniscal degeneration and the outcome of exercise therapy or APM (107 participants) [29]. The authors did not provide numerical data for non-significant results.

3.5.6 BMI

Five studies (698 participants) have investigated the association of BMI on the outcomes of physiotherapy and exercise [20][22][24][29][30]. Three studies report no association between BMI and the outcome of physiotherapy (n=340) [20][24][29]. In RCT participants that crossed-over from physiotherapy to APM, BMI was not associated with cross-over (RR 1.16 95% CI 0.68, 1.96) [24]. Rathleff et al [20] and Kise et al [29] do not provide the numerical data for the non-significant findings. In the prospective cohort study of adults with a degenerative posterior root tear of the medial meniscus there was a moderate correlation between BMI and the outcomes of physiotherapy measured using the Lysholm score (n=37) with a (*r=0.47*)[22]. Post hoc analysis of the RCT data reporting non-inferiority of physiotherapy compared to APM also shows an interaction effect for BMI. Obese participants who were treated with APM scored on average 10.7 points higher on the IKDC outcome measure for increased function compared to those obese participants treated with physiotherapy (95% CI 4.7 to 16.8, *p*=0.001). There was no interaction effect for adults categorised as normal weight (*p*=0.57) or overweight (*p*=0.60)[30].

Degenerative tear

Three of the above studies investigated the predictive value of BMI on the outcome of physiotherapy in adults with a degenerative tear only [22][24][29]. Two secondary analyses of the outcomes of RCTs comparing physiotherapy and exercise to APM (both with and without post-operative exercise) (150 participants) report no association between BMI and the KOOS score and GRC for pain and function in those treated with either surgery or exercise rehabilitation [29] and no association with cross-over to surgery [24]. BMI was moderately correlated with the outcome measured using the Lysholm score in one study in those with a degenerative posterior root tear of the medial meniscus [22] and obese participants treated with APM reported on average 10.7 higher for function on the IKDC outcome measure compared to obese participants treated with physiotherapy [30].

3.5.7 Gender

There was evidence from five studies (761 participants) [20][21][24][29][30] that gender was not associated with the outcome of physiotherapy and exercise rehabilitation. No association was found between gender and cross-over from physiotherapy to surgery (RR 1.28 95%CI 0.78, 2.11) [24]. In an

arthroscopy restricted cohort, gender was not associated with the outcome of physiotherapy measured using the KOOS pain subscale ($p \geq 0.05$ 95% CI -2.6, 8.3) [20]. The numerical data was not provided from one RCT secondary analysis [29] and one cohort study [21]. There were no studies to report an association of gender with the outcome of physiotherapy. In the post hoc analysis of the ESCAPE RCT, there was no interaction effect of gender on the outcomes of those undertaking physiotherapy compared to those undertaking APM [30].

Degenerative tear

In the three studies including only those with a degenerative tear, there was no association between gender and the KOOS score or GRC for pain and function [29] and also cross-over from physiotherapy to surgery [24] and no effect on the IKDC score for function for those treated with physiotherapy compared to APM [30].

3.5.8 Duration of symptoms

Degenerative tear

One study investigated the association of duration of symptoms with cross-over from physiotherapy to APM [24]. A duration of symptoms lasting less than one year was associated with cross over to physiotherapy (n=48) (RR=1.74; 95% CI=O.98, 3.08) [24].

3.5.9 Physical performance measures/examination findings

Degenerative tear

Two studies (150 participants) investigated a range of physical examination findings and physical performance measures. Katz et al [24] report that following multivariate analysis, no physical examination findings including ROM, muscle strength, static knee alignment or the timed 'up and go test' predicted cross-over from physiotherapy to surgery. Kise et al [29] reports the 6-meter hop test to be the only measure predictive of the outcome of both physiotherapy and surgery using the KOOS score and the Global rating of Change (GRC) for pain (102 participants). In participants after surgery a 1 second better hop test was associated with better scores for KOOS Pain, ADL, Sport/Rec and QoL (range: 7.6-11.0 points, 95% CI from 3.0 to 12.3 to 4.9-17.0 compared to the improvement after physiotherapy: 2.6-5.5 points, 95% CI from 0.2 to 4.9 to 2.1-9.0 points). After surgery a 1 second better hop showed a 65% (95% CI 32-108%) and 70% (95% CI 38-109%) higher odds for better or much better GRC Pain and Function scores at two years compared to physiotherapy where there was 17% higher odds for a better or much better GRC pain score. Following physiotherapy, a 2.09-3.60 second better hop test and following surgery a 0.63-1.99 second better hop test was associated with clinically meaningful differences in KOOS symptoms, sport, and recreation, QoL and GRC pain at two years [29].

3.5.10 Knee function

Degenerative tear

One secondary exploratory analysis study (43 participants) has investigated the predictive value of baseline knee function on cross-over from physiotherapy to surgery [31]. The authors report that worse knee function measured using the IKDC score at both six months (odds ratio 0.94 (95%CI 0.90 to 0.98)) and 24 months (odds ratio 0.97 (95% CI 0.94 to 1.0) had low predictive value, explaining (in combination with lower education level and better general health at 6 months) 16% and (in combination with lower education level at 24 months) 11% of the reason for progression to APM.

3.5.11 Education level

Degenerative tear

The same secondary analysis study (43 participants) [31] reports lower education level to have low predictive value (in combination with worse knee function and better general health) explaining 16% (6 months) and 11% (24 months) of the reason for cross -over from physiotherapy to APM.

3.5.12 General health

Degenerative tear

The same secondary analysis study (43 participants) from the ESCAPE trial [31] reports that a better general health (in combination with lower education and worse knee function) explained 16% in variance for cross-over from physiotherapy to surgery at 6 months. A better general health did not explain variance at 24 months.

4.0 Discussion

To our knowledge, this is first systematic review of factors associated to the outcome of physiotherapy following a meniscus tear. The evidence forming the basis of this review is however of low/moderate quality and the results of the review should be interpreted with due caution when applying clinically. Despite this, the results for the meniscus tear population generally show that across six studies, neither gender nor the presence of mechanical symptoms are associated with the outcome of physiotherapy. There was no association of OA and BMI in 75% of studies and no association of age with physiotherapy outcome in 67% of studies investigating these factors. A greater baseline pain score/level was associated with a poorer outcome of physiotherapy in 67% of the studies that investigated this. Individual studies show that better performance of the 6-meter timed hop test was associated with a better outcome of both physiotherapy and surgery. A less than one year duration of symptoms is associated with a greater risk of cross-over from physiotherapy to surgery. Worse knee function and lower educational or has low predictive value for cross-over from physiotherapy to surgery. Evidence suggesting greater improvement in pain in those with a bucket-handle meniscus tear compared to a flap tear is insufficient.

4.1 Clinical implications

The evidence from the included studies that no association exists between mechanical symptoms and measures of pain or cross-over to surgery following the course of physiotherapy is an important finding. Contrary to this, mechanical symptoms have generally been considered a pivotal indication for surgery [33]. Mechanical symptoms however may not be a specific symptom related to a meniscus tear as catching and locking have been shown to exist to an equal degree in those both with and without a meniscus tear when confirmed at arthroscopy [34]. This review's findings suggest that mechanical symptoms as an isolated finding may not be an adequate reason to reject physiotherapy intervention. It is important to note however that all studies excluded those with a locked knee and in Gauffin et al [18][27][28] those with joint locking for more than two seconds more than once weekly were excluded. These results do not challenge the rationale for surgery in the context of a locked knee

or significant mechanical symptoms. Neither do these findings challenge the rational for surgery in those with traumatic tears and mechanical symptoms that may be suitable for meniscal repair as preservation of the meniscus is considered optimal. Further studies investigating of the importance of mechanical symptoms remain indicated.

As expected, the findings from the review show no association of gender with outcome [20][21][24][29] and this is reflected in clinical practise. The evidence from two studies that a worse baseline pain score is a significant factor that is associated a poorer outcome from physiotherapy [20][24] is consistent finding in other studies including those with patellofemoral pain [35], shoulder pain [36], whiplash associated disorder [37], non-specific neck pain [38], and lateral epicondylitis [39]. This finding recommends that clinicians prioritise strategies to reduce pain intensity for those affected and may also support early identification and support for that those at risk of worse pain. The effectiveness and cost-effectiveness of stratified care against predictive variables has been shown in low back pain (LBP) [40] and may now be indicated for people with meniscus tears.

Whilst this review has highlighted conflicting evidence regarding BMI as being associated with of the outcome of physiotherapy [20][22][24][29][30], it remains a risk factors for the development of OA so should remain a target for intervention. The results of this review do not challenge the current recommendations of conservative treatment as first line management in those with osteoarthritis and a meniscus tear and those with an isolated degenerative meniscus tear. However, the small sample sizes and quality of evidence would not support translation of the findings related to the type of meniscus tear into clinical practise.

4.2 Research implications

The results suggest that further large scale, adequately powered prospective inception cohort studies should be performed to investigate the predictors of outcome in those with a meniscus tear. In all the included studies, the analysis of predictive variables was retrospective and determined from the outcomes of either an RCT investigating physiotherapy versus surgery or were taken following longitudinal observation of those undertaking physiotherapy and surgery if required. The included studies are limited by their small sample size, and they are inadequately powered to sufficiently determine predictive value. Rather than drawing clear conclusions from the included studies, the results should be viewed as hypothesis generating.

The importance of predictive and factors for the management of those with musculoskeletal pain has been demonstrated in those with LBP [40]. Many clinicians now base decision about initial management of LBP on prognostic factors rather than treatment decision made upon a structural diagnosis. Given the indication that some predictors may be important, but quality of evidence is low/moderate, exploring this with large, well designed inception cohorts is indicated. No studies to date have investigated psychosocial variables as predictors of the outcome from physiotherapy in the meniscus tear population. The predictive value of psychosocial variables has been shown in studies of shoulder pain [36] and LBP [41]. Exercise and treatment adherence should also be investigated as this has been shown to have a significant effect on treatment outcome [42]. Future studies should investigate whether predictive factors are different for subgroups of those with a meniscus tear. Studies should initially investigate predictive factors in the younger and older populations separately and potentially investigate those with a traumatic versus a non-traumatic tear separately.

4.3 Strengths and weaknesses of this review

This review used the CASP tools for randomised controlled trials and cohort studies as an assessment of study quality as no specific objective scoring or assessment tool exists to cover all the studies. The

CASP tools are designed as teaching aids to support the appraisal of different forms of research. The tool does not allow for scoring of individual research papers for quality. The assessment of study quality is formed from the assessment of the reviewers using the tool for guidance and therefore subject to the bias of the reviewers. To try and reduce bias as much as possible the included articles were assessed by two reviewers.

The searches were performed using five comprehensive databases along with a search of the reference lists and a search of google scholar. The authors have attempted to review and retrieve all relevant sources of data as generally, studies providing significant or interesting results are more likely to be published. However, it is conceivable the searches may not have included all possible sources of data suitable for inclusion. More specifically the searches did not include conference proceedings and databases of unpublished research in this area and therefore the data included in the review may be incomplete.

5.0 Conclusion

The association between predictive variables and physiotherapy treatment outcome appears to be inadequately investigated. On the limited data available, gender, mechanical symptoms and age have been shown to have either no or a small association with the outcome of physiotherapy. A worse baseline pain score appears associated with worse outcome of physiotherapy. There was either insufficient, no consistent result or conflicting evidence for BMI, the duration of symptoms, baseline physical performance of the 6m hop test, type or characteristics of the meniscus tear and degree of knee osteoarthritis. Worse knee function, lower education and better general health have low predictive value are predictors of progression from physiotherapy to surgery, but these have low predictive value. The studies to date are of a low/moderate quality and lack adequate power. A large, adequately powered inception cohort study is now required to investigate the predictive value of the type of meniscus tear including those with stable tears and degenerative type tears compared to those with potentially unstable configurations. Further evaluation of the predictive value of physical performance measures should also be investigated along with psychosocial variables which have not yet been investigated.

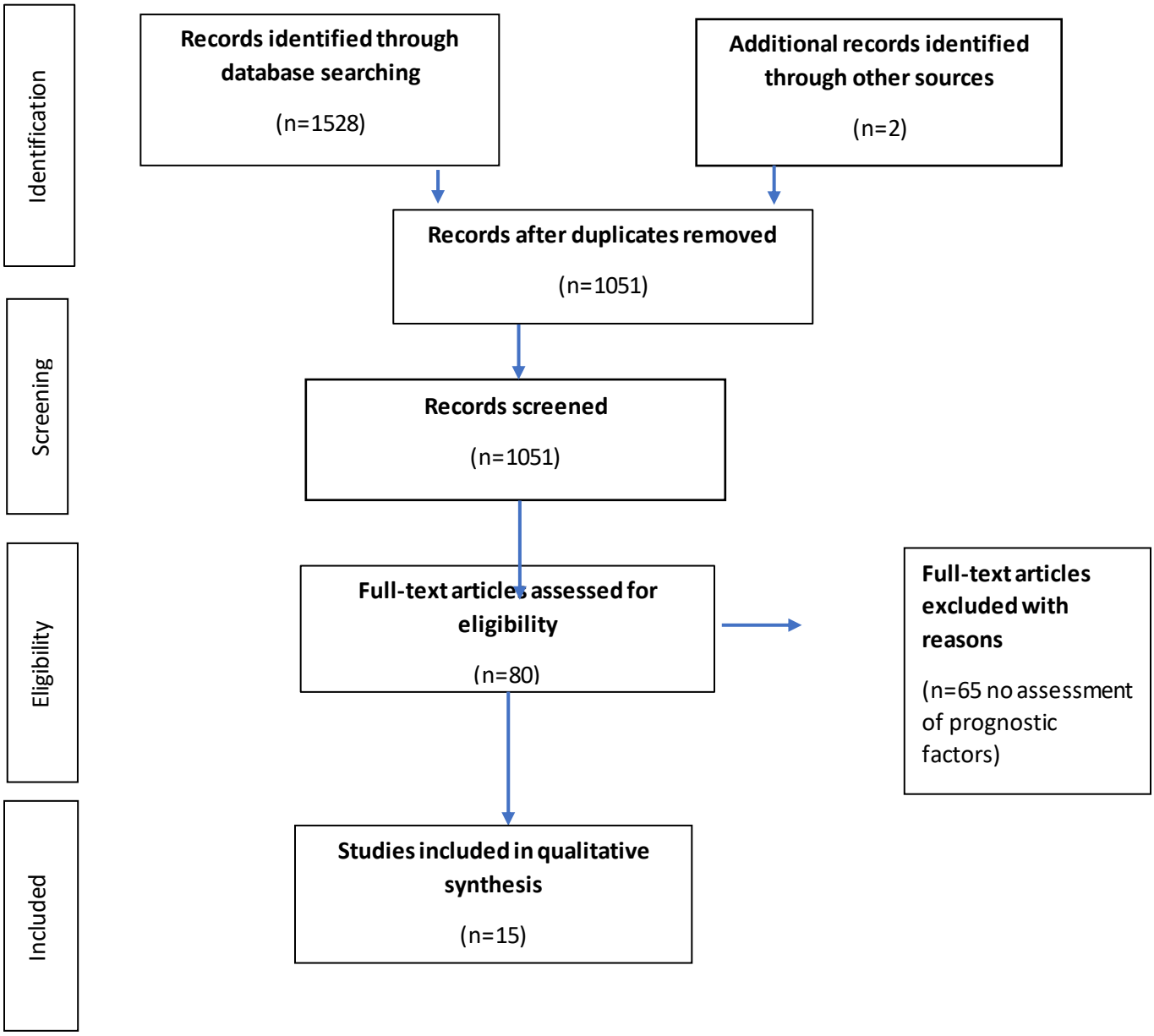

Fig 1. PRISMA (2009) flow chart outlining the literature search and study selection

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Table 1 Study Characteristics

Study Design	Author, Date and Country of clinical setting	Participants: start (S) n=, Finish (F) n=; Duration of symptoms (D)	Participant Mean age years (A), SD (range) years or equivalent	Meniscus pathology;	Primary Outcome Measure	Follow up period	Loss to follow up	PT treatment	Duration of PT treatment	No of PT appointments	Compliance with supervised of home exercise program	Other permitted intervention
(MeTeOR trial) RCT, 2 groups comparing PT to APM with post-op PT.	Katz et al (2013) USA	S:n=351 F:n=320 D>1m	A=58 yrs (SD 7)	Mild to moderate OA and degen MT	WOMAC pain	6 and 12m	31	Supervised and home exs. Massage and joint/soft tissue mobilization, NMES or IFC	6w	Ave 8.4 (scheduled 9.3)	UTD	Corticosteroid injection (12% of participants)
Secondary analysis of data assessing predictive value mechanical symptoms (MeTeOR trial) RCT, 2 groups comparing PT to APM with post-op PT.	Katz et al (2013) USA	S:n=351 F:n UTD D>1m	A= 58 yrs (SD=UTD)	Mild to moderate OA and degen MT	WOMAC pain	6m	0	Supervised and home exs. Massage and joint/soft tissue mobilization, NMES or IFC	6w	Ave 8.4 (scheduled 9.3)	UTD	Corticosteroid injection (12% of participants)
Secondary analysis of subjects who crossed over from PT to APM (MeTeOR trial). RCT, 2 groups comparing PT to APM with post-op PT.	Katz et al (2016) USA	S:n=48, F:n=48 D>1m	<60 yrs n=29 ≥60 yrs n=19	Mild to mod OA and degen MT	Cross-over pt>Surgery	6m	0	Supervised and home exs. Massage and joint/soft tissue mobilization, NMES or IFC	6w	Ave 8.4 (scheduled 9.3)	UTD	Corticosteroid injection (12% of participants)
Secondary analysis of data assessing predictive value meniscal symptoms (MeTeOR trial)	Macfarlane et al (2021) USA	S/Fn (PT and APM) =287 D>1m	A= 58.5 (SD=6-8)	Mild to mod OA and degen MT	KOOS pain	6m	0	Supervised and home exs. Massage and joint/soft tissue mobilization, NMES or IFC	6w	Ave 8.4 (scheduled 9.3)	UTD	Corticosteroid injection (12% of participants)

RCT, 2 groups comparing PT to APM with post-op PT.												
Secondary analysis of predictive value of MRI findings (MeTeOR trial) RCT, 2 groups comparing PT to APM with post-op PT.	Macfarlane et al (2019)	Total S:n=220,PT S:n=99 APM S:n=121 D>1m	A=59 SD=7	Mild to mod OA and degen MT	KOOS pain	6m	0	Supervised and home exs. Massage and joint/soft tissue mobilization, NMES or IFC	6w	Ave 8.4 (scheduled 9.3)	UTD	Corticosteroid injection (12% of participants)
RCT, APM and PT vs PT	Gauffin et al (2014) Sweden	S/F:n (APM)=75/70 S/F:n (PT)=75/60 (D) 7/12	A=54 PT SD=6 APM SD=5 A range=45-64 yrs	Symptoms of MT with Xray ≤50% reduction jt space	KOOS pain	1y	13%	Supervised and home exs, strengthening and balance/proprioception	3m	Ave 19/24 scheduled sessions	53% of participants completed exercise diary	UTD
RCT, APM and PT vs PT, *3 year analysis of outcomes*	Gauffin et al (2017) Sweden	S/F:n (APM)=75/86 S/F:n (PT)=75/64 (inc crossover subjects)	A=54 PT SD=6 APM SD=5 A range=45-64 yrs	Symptoms of MT with Xray ≤50% reduction jt space	KOOS	3y	21%	Supervised and home exs, strengthening and balance/proprioception	3m	Ave 19/24 scheduled sessions	53% of participants completed exercise diary	UTD
RCT, APM and PT vs PT, 5 *year analysis of outcomes*	Sonesson et al (2020) Sweden	S/F:n (APM)= 75/85 S/F:n=(PT) 75/61	(A)APM =55 SD=5 (A) PT=54 SD=6	Symptoms of MT with Xray ≤50% reduction jt space	KOOS	5y	32%	Supervised and home exs, strengthening and balance/proprioception	3m	Ave 19/24 scheduled sessions	53% of participants completed exercise diary	UTD
RCT, APM vs ET, *secondary analysis of predictive factors*	Kise et al (2016) Norway	S/F:n (ET) 70/55 S/F:n (APM) 70/52 (D) ET (17.3 m SD 21.5)	(A) (35-60) ET=50.2 (SD=6.2) APM=48.9 (SD=6.1)	Degen MMT and upto grade 2 KL OA	KOOS, GRC	2y	21%	Supervised exs, (strengthening and neuromuscular) 2-3 sessions per week	3m	24-36 sessions	Excellent compliance=37% Satisfactory compliance =24% Poor compliance=21%	UTD

		APM (12.0 SD 15.7)									Declined participation/lost data=17%^	
RCT, APM vs PT	Van de Graaf (2018) Netherlands	S/F: n (PT) 162/148 S/F:n (APM) 159/141 (D) UTD	(A)(45-70) APM=57.6 (SD=6.5) PT=57.3 (SD=6.8)	Non-obstructive MT and up to grade 3 KL OA	IKDC,RAND36 Tegner Activity Scale	2y	10%	CV, coordination/balance and closed kinetic chain Exs 2 sessions per week	8w	16	PT mean 17 sessions (range 0-40)	UTD
RCT, APM vs PT *Secondary analysis of predictive factors in participants who crossed-over from physiotherapy to surgery*	Noorduyn (2021) Netherlands	S/F:n 43 (D) UTD	(A) 56.4 (SD 7.0)	Non-obstructive MT and up to grade 3 KL OA	IKDC,RAND36 Tegner Activity Scale Cross-over to surgery	2y	10%	CV, coordination/balance and closed kinetic chain Exs 2 sessions per week	8w	16	PT mean 17 sessions (range 0-40)	UTD
Cohort	El Ghazaly et al (2015) Egypt	Sn=70 Fn=70 (D)=>4weeks	A=40 (18-67yrs)	Unstable meniscal tear Upto grade 2 KL OA	Lysholm knee score, VAS	Ave 12.5m (6-24m)	0	Faradic stim, Supervised exs (strengthening and neuromuscular) 3 sessions per week	8w	24	UTD	UTD
Cohort	Rathleff et al (2015) Denmark	Sn=185 Fn=156 D=UTD	A (>18 yrs) males (n=100) 45 SD 15, females (n=85) 46.5 SD 15	MT No OA	KOOS	12-24 m	16%	UTD	UTD	UTD	UTD	NSAID's
Cohort	Neogi et al (2013) India	Sn=37 Fn=33 (D) UTD	A=55.8yrs (50-62 range)	Post root degen MMT KL 0-2	Lysholm score	Ave 35m (range26-49)	6%	Supervised exs (strengthening and stretching)	12w	30 sessions ?no attended	UTD	NSAID's (Celecoxib 200mg or Ibuprofen

												1600mg) or Paracetamol and Tramadol (100mg nocte)

APM arthroscopic partial meniscectomy; Degen degenerative; Ex's exercises; ET Exercise therapy; GRC Global Rating of Change; IFC interferential current; KL Kellgren and Lawrence scale; KOOS Knee injury and Osteoarthritis Outcome Scale; MMT medial meniscus tear; MT Meniscsus tear; NMES Neuromuscular Electrical stimulation; NSAIDs Non-steroidal Anti-inflammatory Drugs; OA Osteoarthritis; PT Physiotherapy; Post-op PT Post-operative physiotherapy; RCT randomised controlled trial; SD standard deviation; UTD unreported; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2 Differential effects of physiotherapy and exercise rehabilitation versus APM

		Improvement from baseline (SD)		
Author, date and country	Outcome measure	Physiotherapy	APM	Between group difference (SD) (*)
Katz et al 2013 US	WOMAC physical-function score 6 months (0-100 points)	18.5 (15.6 to 21.5)	20.9 (17.9 to 23.9)	2.4 (-1.8 to 6.5)
	WOMAC physical -fun∞ction score 12 months	22.8 (19.8 to 22.8)	23.5 (20.5 to 26.5)	0.7 (-3.5 to 4.9)
	KOOS pain score 6 months (0-100)	21.3 (18.4 to 24.2)	24.2 (21.3 to 27.1)	2.9 (-1.2 to 7.0)
	KOOS pain score 12 months (0-100)	27.3 (24.1 to 30.4)	26.8 (23.7 to 30.0)	-0.4 (-4.8 to 4.0)
	SF-36 physical activity score 6 months (0-100)	23.1 (19.2 to 27.0)	24.2 (20.3 to 28.0)	1.1 (-4.4 to 6.6)
	SF-36 physical activity score 12 months (0-100)	28.1 (24.0 to 32.1)	25.0 (20.9 to 29.1)	-3.0 (-8.8 to 2.7)
Gauffin et al 2014 Sweden	KOOS pain score 3 months	10.6 (5.9 to 15.4)	22.2 (17.3 to 27.2)	11.6 (4.7 to 18.5)*
	KOOS pain score 12 months	18.8 (12.9 to2 4.8)	29.4 (25.0 to 33.8)	10.6 (3.4 to 17.7)*
	KOOS symptoms 3 months	6.7 (2.5 to 10.8)	15.3 (11.4 to 19.2)	8.6 (2.9 to 14.3)*
	KOOS symptoms 12 months	17.3 (12.3 to 22.2)	23.2 (19.2 to 27.2)	5.9 (-0.3 to 12.2)
	KOOS ADL 3 months	8.0 (3.5 to 12.4)	15.8 (11.1 to 20.4)	7.8 (1.4 to 14.2)*
	KOOS ADL 12 months	14.2 (8.9 to 19.4)	21.0 (16.8 to 25.2)	6.8 (-3.3 to 15.9)
	KOOS sports 3 months	12.2 (6.5 to 17.9)	23.9 (17.7 to 30.2)	11.7 (3.2 to 20.2)*
	KOOS sports 12 months	22.9 (15.5 to 30.3)	29.2 (22.9 to 35.6)	6.3 (-3.3 to 15.9)
	KOOS QOL 3 months	10.8 (5.2 to 16.5)	22.4 (17.1 to 27.7)	11.6 (3.9 to 19.2)*
	KOOS QOL 12 months	23.8 (17.5 to 30.0)	31.4 (25.1 to 37.7)	7.6 (-1.2 to 16.5)
	EQ-5D (Index) 0-1.00 3 months	0.13 (0.07 to 0.20)	0.16 (0.09 to 0.22)	0.002(-0.07 to 0.12)
	EQ-5D (Index) 0-1.00 12 months	0.19 (0.12 to 0.26)	0.21 (0.15 to 0.26)	0.02 (-0.07 to 0.12)
	EQ-5D (VAS) 0-100 3 months	6.7 (1.2 to 12.2)	12.7 (7.5 to 17.9)	6.0 (-1.5 to 13.5)
	EQ-5D (VAS) 0-100 12 months	10.3 (5.2 to 15.5)	15.4 (10.9 to 19.9)	5.0 (-1.7 to 11.8)
Kise et al 2016 Norway	KOOS score 3 months			0.2 (-5.3 to 5.0)
	KOOS score 12 months			-4.6 (-9.8 to 0.5)
	KOOS score 2 years	25.3 (21.6 to 29.0)	24.4 (20.7 to 28.0)	0.9 (-4.3 to 6.1)
	KOOS pain 3 months			-1.8 (-7.01 to 3.5)
	KOOS pain 12 months			-4.2 (-9.5 to 1.1)
	KOOS symptoms 3 months			3.0 (-1.8 to 7.9)
	KOOS symptoms 12 months			3.1 (-1.8 to 7.9)
	KOOS ADL 3 months			1.4 (-3.0 to 5.9)
	KOOS ADL 12 months			1.1 (-3.4 to 5.6)
	KOOS sports 3 months			2.1 (-5.5 to 9.6)
	KOOS sports 12 months			-7.1 (-14.7 to 0.4)
	KOOS QOL 3 months			-4.0 (-10.3 to 2.2)
	KOOS QOL 12 months			-10.3 (-16.6 to 4.1)
van de Graaf et al 2018 Netherlands	IKDC function 3 months			1.1 (-∞ to 5.0)*
	IKDC function 6 months			4.2 (-∞ to 8.1)
	IKDC function 12 months			7.1 (-∞ to 11.1)
	IKDC function 24 months			5.3 (-∞ to 9.3)
	Pain (VAS) weight bearing 3 months			-3.3 (-9.3 to to 2.7)
	Pain (VAS) weight bearing 6 months			-9.1 (-15.2 to -3.0)
	Pain (VAS) weight bearing 12 months			-7.0 (-13.3 to -0.67)

	Pain (VAS) weight bearing 24 months			-8.3 (-14.9 to -1.7)

Table 3 Assessment of Study quality and Bias (Randomised controlled trials)

Author, Date and country.	trial addresses clearly focused issue	Was assignment randomised	Were all participants properly accounted for	Were participants and study personnel blinded	Were groups similar at the start of the trial	Aside for experimental intervention were groups treated equally	How large was treatment effect	How precise was estimate of treatment effect	Can results be applied locally or in context	Were clinically important outcomes considered	Are the benefit worth the harms and costs
Katz et al (2013) US							NA	NA			
Gauffin et al (2014) Sweden							NA	NA			
Kise (2016) Norway							NA	NA			
Van de Graaf (2018) Netherlands							NA	NA			

Table 4 CASP quality tool (Cohort study)

Author, year and country	Does study address a clearly focused issue	Was cohort recruited in an acceptable way	Was exposure accurately measured to minimise bias	Was outcome accurately measured to minimise bias	Have authors identified all important confounding factors	Have they taken account of the confounding factors in the design and/or analysis	Was the follow up of subjects complete enough	Was the follow up of subjects long enough	What are the results of this study	How precise are the results	Do you believe the results	Can the results be applied to the local population	Do the results fit with other available evidence	What are the implications for practise
El Ghazaly et al (2015) Egypt									NA					NA
Rathleff et al (2015) Denmark									NA					NA
Neogi et al (2013) India									NA					NA

Supplementary file 1: Search strategy used in AMED

1. Menisc* adj5 (pathology OR tear OR degenerate* OR lesion) ti.ab
2. (pathology OR tear OR degenerate* OR lesion).ti,ab
3. (menisc*).ti,ab
4. 2 AND 3
5. 1 OR 4
6. exp REHABILITATION/ OR exp THERAPY/
7. exp "PHYSICAL THERAPY MODALITIES"/
8. exp "MUSCULOSKELETAL MANIPULATIONS"/
9. exp ACUPUNCTURE/
10. (rehabilitation OR therapy OR "physical therapy modalities" OR "MUSCULOSKELETAL MANIPULATIONS" OR acupuncture).ti,ab
11. *(6 OR 7 OR 8 OR 9 OR 10)*
12. *(5 AND 11)*