Title: Risk factors for pain and functional impairment in people with knee and hip osteoarthritis: a systematic review and meta-analysis

Concise Title: Factors associated with pain and impaired function in OA

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Work done on behalf of the OA Tech working research group.

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ABSTRACT

Objective: To identify risk factors for pain and functional deterioration in people with knee and hip osteoarthritis (OA) to form the basis of a future 'stratification tool' for OA development or progression.

Design: Systematic review and meta-analysis

Methods: An electronic search of the literature databases: MEDLINE, EMBASE, CINAHL, MEDLINE and Web of Science (1990-February 2020) was conducted. Studies which identified risk factors for pain and functional deterioration to knee and hip OA were included. Where data and study heterogeneity permitted, meta-analyses presenting mean difference (MD) and odd ratios (OR) with corresponding 95% confidence intervals (CI) were undertaken. Where this was not possible, a narrative analysis was undertaken. The Downs & Black tool assessed methodological quality of selected studies before data extraction. Pooled analysis outcomes were assessed and reported using the GRADE approach.

Results: 82 studies (41,810 participants) were included. On meta-analysis: there was moderate quality evidence that knee OA pain was associated with factors including: Kellgren and Lawrence≥ 2 (MD: 2.04, 95% CI:1.48,2.81; p<0.01), increasing age (MD: 1.46, 95% CI:0.26,2.66; p=0.02) and whole-organ MRI scoring method Knee effusion score ≥1 (OR: 1.35, 95% CI: 0.99,1.83; p=0.05). On narrative analysis: knee OA pain was associated with factors including WORMS meniscal damage≥1 (OR: 1.83). Predictors of joint pain in hip OA were large acetabular bone marrow lesions (OR: 5.23), chronic widespread pain (OR: 5.02) and large hip BMLs (OR: 4.43).

Conclusions: Our study identified risk factors for clinical pain in OA by imaging measures that can assist in predicting and stratifying people with knee/hip OA. A 'stratification tool' combining verified risk factors that we have identified, would allow selective stratification based on pain and structural outcomes in OA.

PROSPERO Registration: CRD42018117643

ARTICLE SUMMARY: strengths and limitations of this study

- This study has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist.
- Analyses have been undertaken respecting potential sources of know statistical heterogeneity.
- Searches included both published and unpublished sources of literature to reduce the risk of omitting potentially eligible data.
- There was a paucity of available data to permit meta-analyses of risk factors for pain and functional impairment.
- The variability in methods of assessing risk and reporting of frequency of risk characteristics limited analyses

INTRODUCTION

It has been reported that over 30.8 million US adults suffer from osteoarthritis (OA) (1). Between 1990-2010, the years lived with disability worldwide caused by OA increased from 10.5 million to 17.1 million, an increase of 62.9% (2). Current OA treatment lacks any disease-modifying treatments with a predominance to manage symptoms rather than modify underlying disease (3). The clinical symptoms of OA can be assessed using several questionnaires, the most common of which is the Western Ontario McMaster Arthritic Index (WOMAC) (4,5,6). Although pain is recognised as an important outcome measure in OA, it is not clear what the optimal assessment tools are in OA and how they relate to other risk factors.

OA has various subtypes and since current therapies cannot prevent OA progression, early detection and stratification of those at risk may enable effective pre-symptomatic interventions (7,8). Several methods are used to define, diagnose and measure OA progression, including imaging techniques [e.g. plain radiography, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)]. Plain radiography provides high contrast and high resolution images for cortical and trabecular bone, but not for non-ossified structures (e.g. synovial fluid) (9). The most recognised radiographic measure classifying OA severity is Kellgren and Lawrence (KL) grading which assesses osteophytes, joint space narrowing (JSN), sclerosis and bone deformity (10,11). However, it has been argued that MRI may be more suitable for imaging arthritic joints, providing a whole organ image of the joint (12). Whole-organ MRI scoring method (WORMS) is used in MRI for OA assessing damage, providing a detailed analysis of the joint.

Recently, OMERACT-OARSI (Outcome Measures in Rheumatology-Osteoarthritis Research Society International) have published a core domain set for clinical trials in hip and/or knee OA (13). Six domains were assessed as mandatory in the assessment of OA, including pain, physical function,

quality of life, patient's global assessment of the target joint, and adverse events including mortality and/or joint structure, depending on the intervention tested. However, there remains a need to identify risk factors for pain and structural damage in OA so that potential interventions can be studied in a timely manner. The purpose of this systematic review was therefore to identify risk factors for pain, worsening function and structural damage that can predict knee/hip OA development and progression. By identifying risk factors for OA pain and structural damage, tools for stratifying specific disease groups could be developed in the future.

METHODS

This systematic review has been reported in accordance with the PRISMA reporting guidelines. The review protocol was registered *a priori* through PROSPERO (Registration: CRD42018117643).

Search Strategy

A systematic search of the literature was undertaken from 1st January 1990 to 1st February 2020 using electronic databases: MEDLINE (Ovid), EMBASE (Ovid), MEDLINE, Web of Science and CINAHL (EBSCO). An example of the EMBASE search strategy of included search terms and Boolean operators is presented in **Supplementary File 1**. Unpublished literature databases including Clinicaltrials.gov, the WHO International Registry of Clinical Trials and OpenGrey were also searched.

Study Identification

Studies were eligible for inclusion if they were a full-text article that satisfied all of the following:

1) 100 or more participants analysed in the study (to increase power for comparisons);
2) convincing definition of OA using American College of Rheumatology criteria (14), based on symptoms of sustained pain and stiffness in the affected joint, radiographic changes

including osteophytes, cartilage loss, bone cysts/sclerosis and joint space narrowing, with normal inflammatory markers;

3) abstract/title that must refer to pain and/or structure in relation to OA as a primary disease;
4) Knee or hip OA;
5) pain and/or function scores;
6) joint imaged and
7) minimum six-month follow-up of pain/function outcome measures.

Non-English studies, letters, conference articles and reviews were excluded.

The titles and abstracts were reviewed by one reviewer (SS). The full-text for each paper was assessed for eligibility by one reviewer (SS) and double-checked by a second (TS). Any disagreements were addressed through discussion and adjudicated by a third reviewer (NS or FH). All studies which satisfied the criteria were included in the review.

Quality Assessment

To assess the risk of bias and the power of the methodology, the Downs & Black (D&B) tool was applied (15). These tools assessed the following aspects of each study: reporting quality, external validity, internal validity- bias, selection bias and power. The modified D&B tool was used. Accordingly, the 27-item randomised controlled trial (RCT) version was used for RCTs whilst the 18-item non-RCT version was used for non-RCT designs (**Supplementary File 2**). Both 18-item and 27-item tools have been demonstrated to be valid and reliable tools to assess RCT and non-RCT papers (14). Critical appraisal was performed by one reviewer (SS) and verified by a second (KT). Any disagreements were dealt with by discussion and adjudicated through a third reviewer (TS). In previous literature D&B score ranges were given corresponding quality: excellent (26-28); good (20-25); fair (15-19); and poor (<14) (14). Item 4 on the non-RCT and Item 5 from the RCT tool are scored

two points, hence the total scores equate to 19 and 28 points respectively. The D&B tool was used to exclude poor quality studies with a score 15/28 or lower in RCTs and 10/19 or lower in non-RCTs.

Data Extraction

Data were extracted including: subject demographic data, study design, pain and function outcome measures, imaging used, OA severity scores, change in pain and function outcomes and change in OA severity scores. After all relevant data had been extracted, authors of these papers were approached to try and attain individual patient data (IPD) related to baseline and change in pain, function and structural scores for each study. No data was received from authors to inform this analysis.

Outcomes

The primary outcome was to determine the development of pain and functional impairment for those with knee and hip OA. The secondary outcome was to determine which factors are associated with structural changes in knee and hip OA.

Data Analysis

All data were assessed for study heterogeneity through scrutiny of the data extraction tables. These identified that there was minimum study-based heterogeneity based on: population, study design and interventions-exposure variabilities for given outcomes. Where there was study heterogeneity, a narrative analysis was undertaken. In this instance, the odds ratio (OR) of all predictor variables were tabulated with a range of OR presented. Where there was sufficient data to pool (two or more studies with data available to analyse) and study homogeneity evident, a pooled meta-analysis was deemed appropriate. As interpreted by the Cochrane Collaboration (16), when I^2 was 50% or greater representing high-statistical heterogeneity, a random-effects model meta-analysis was undertaken. When I^2 was less than this figure, a fixed effects model approach was adopted. Continuous

outcomes were assessed using mean difference (MD) scores of measures for developing severe OA, whereas dichotomous variables were assessed through OR data. All data were presented with 95% confidence intervals (CI) and forest-plots.

Due to the presentation of the data, there were minimal data to permit meta-analyses. Where there was insufficient data to pool the analysis (data only available from one study), a narrative analysis was undertaken to assess risk factors for the development of increased pain and functional impairment. Planned subgroup analyses included determine whether there was a difference in risk factors based on: (1) anatomical regions (i.e. difference between hip OA and knee OA); (2) geographical region. Analyses were undertaken on STATA version 14.0 (Stata Corp, Texas, USA) with forest plots constructed using RevMan Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.)

RESULTS

Search Strategy

The results of the search strategy are presented in **Figure 1**. In total, 11,010 citations were identified. Of these, 141 papers were deemed potentially eligible and screened at full-text level. Of these, 82 met the selected criteria and were included.

Characteristics of Included Studies

A summary of the included studies is presented as **Table 1**. This consisted of 31 non-RCTs (27 observational cohort studies/four case-control studies) and 51 RCTs.

In total, 45,767 knees were included in the analysis. This consisted of 13,870 males and 23,497 females; four studies did not report the gender of their cohorts (17,18,19,20). Thirty-six studies were

undertaken in the USA; 30 were undertaken in Europe; nine were conducted in Australasia and seven in Asia. Mean age of the cohorts was 61.7 years (standard deviation (SD): 7.56); 36 studies did not report age (17,21,22-54). Mean follow-up period was 35.4 months (SD: 33.6). The most common measures of pain were WOMAC pain (n=55; 50%) and Visual Analogue Scale (VAS) Pain (n=21; 19%). The most frequently used measures of function were WOMAC function (n=52; 44%), physical tests (n=16; 14%) and SF-36 (n=10; 9%).

Methodological Quality Assessment

The methodological quality of the evidence was moderate (**Supplementary File 2; Supplementary File 3**). Based on the results of the D&B non-RCT tool (31 studies; **Supplementary File 2**), recurrent strengths of the evidence were clear description of the participants recruited (29 studies; 94%), the representative nature that participants were to the population (31 studies; 100%), and variability in data presented for the main outcomes (31 studies; 100%). Furthermore the main outcome measures were deemed reliable and valid in all studies (31 studies; 100%) with 89% (27 studies; 87%) studies adopting appropriate statistical analyses for their datasets. Recurrent limitations were not clearly reporting the main findings (20 studies; 65%), issues regarding the representation of the cohort from the wider public (18 studies; 58%) and only six studies (19%) basing their sample sizes on an *a prior* power calculation.

The results from the D&B RCT checklist (51 studies; **Supplementary File 3**) similarly reported findings with strength of the evidence around clear reporting of the cohort characteristics (49 studies; 96%) and interventions (50 studies; 98%), adoption of reliable/valid outcome measures (51 studies; 100%) and reported high compliance to study processes (37 studies; 73%). Recurrent weaknesses included recruiting cohorts which may not have been reflective of the wider population (19 studies; 37%), in clinic settings which may not have represented typical clinical practice (21 studies; 41%) and poorly adjusting for potential confounders in analyses (26 studies; 51%).

Knee OA

Narrative Review

Findings from the narrative analysis found the following were predictors for worsening joint pain: KL3 or 4 in women (OR: 11.3; 95% CI: 6.2 to 20.4), a WORMS lateral meniscal cyst (MC) score of 1 (OR: 4.3; 95% CI: 1.2 to 15.4), presence of chronic widespread pain (CWP) (OR: 3.2; 95% CI: 1.9 to 5.3), increase of ≥2 in WORMS BML score after 15 months (OR: 3.2; 95% CI: 1.5 to 6.8), meniscal maceration (OR: 2.8; 95% CI: 1.8 to 4.4) or damage ≥2 in WORMS (OR: 1.8; 95% CI: 0.9 to 3.6). We also found the following were the highest predictors of worsening function in people with knee OA: KL of <3 (OR: 3.3; 95% CI: 0.7 to 15.9), modified KL 3a (OR: 1.7; 95% CI: 0.7 to 3.8), modified KL 4a (OR: 1.5; 95% CI: 0.7 to 3.0), presence of osteophytes (OR: 1.3; 95% CI: 0.7 to 2.4), female gender (OR: 1.8 (95% CI: 1.1 to 3.0) to OR: 2.1 (95% CI: 1.2 to 3.5)), ethnicity (OR: 1.03; 95% CI 0.59 to 1.83) and synovitis ≥1 (OR: 1.3; 95% CI: 0.8 to 1.9).

Meta-Analysis

Two studies were identified where data could be evaluated for OA risk factors by meta-analysis (41,67). Three variables significantly associated with the development of knee OA. As illustrated in **Table 2** and **Figures 2a-d**, age (MD: 1.46, 95% CI: 0.26 to 2.66; p=0.02; N=823), KL of ≥ 2(MD: 2.04, 95% CI: 1.48 to 2.81; p<0.01; N=823) and knee effusion score ≥1 (OR: 1.35, 95% CI: 0.99 to 1.83: p=0.05; N=823) were all associated with the development of knee OA based on moderate quality evidence. The variables of gender and BMI were not shown to be significantly associated with the knee OA development (**Table 2**).

Due to the limited availability of data it was not possible to conduct the planned subgroup analyses to determine whether there was a difference in risk factors based on anatomical or geographical regions.

Hip OA

Narrative Analysis

This was based on low-quality evidence. There was no association between the development of hip BML and BMI or age. Predictors for worsening joint pain for people with hip OA included a large acetabular BML (OR: 5.2; 95% CI: 1.2 to 22.9), a large femoral head BML (OR: 4.4; 95% 1.4 to 19.7) with any large hip BML (OR: 4.4; 95% CI: 1.5 to 13.2), CWP (OR: 5.0; 95% CI: 2.8 to 9.1) and depression (OR: 1.9; 95% CI: 1.2 to 2.9). Baseline knee pain score (MD:-1.4; 95% CI: -1.6 to -1.2) and baseline hip pain score (MD:-0.7; 95% CI: -1.0 to -0.5) were significantly associated with the development of hip BMLs and pain.

Meta-Analysis

There were insufficient data to permit meta-analysis for the hip OA dataset.

DISCUSSION

Our systematic review and meta-analysis identified risk factors for knee and hip OA pain and structural damage based on evaluation of 82 studies. For the knee, increasing pain in knee OA was associated with KL grade 3 or 4 in women, WORMS lateral MC, presence of CWP, increase of ≥2 in WORMS BML score after 15 months and meniscal maceration. In addition, KL<3, KL 3a, KL 4a, osteophyte presence and female gender were associated with worsening function in people with knee OA. On meta-analysis, age, radiological features (KL score of 2 or more) and knee effusion were associated with development and/or progression of knee OA.

Our meta-analysis identified risk factors that are appreciated only when results were pooled together. These were namely WORMS-defined knee effusion score ≥1. To our knowledge, this is the

currently the largest and most up to date systematic review of its kind, reviewing 82 primary studies in 41,810 participants. Nonetheless, some risk factors from our meta-analysis have been recognised previously. For example, Silverwood *et al.* reported previous injuries are associated to developing knee OA, supporting the present analysis (95). Kingsbury *et al.* identified age and KL grade as predictive factors for developing knee OA, supporting the present findings (96). Therefore the meta-analyses provided both novel and supporting findings for risk factors associated with developing and progressing knee OA. A machine learning study assessed risk factors associated with pain and radiological progression in knee OA found that BMLs, osteophytes, medial meniscal extrusion, female gender and urine CTX-II contributed to progression (95). Nelson *et al's.* work is supported by other studies (95,96). Therefore the findings of this analysis support previous findings.

After plain radiography, MRI was the most used modality with WORMS as the commonest scoring reported for MRI. The MRI Osteoarthritis Knee Score (MOAKS) (98), expanded on WORMS by scoring entire sub-regions for BMLs rather than each BML, further division of cartilage regions and refined the features assessed in meniscal morphology**.** Due to this progression from WORMS, having no MOAKS studies included in our final selection was surprising. This could be due to the eligibility criteria being too restrictive. A future systematic review and meta-analysis focusing on the imaging aspect of evaluating OA will be important. In hip OA, the evaluation of BML size and location is essential in predicting pain progression and these can be assessed effectively using MRI. We recommend that all MRI studies for hip OA evaluate BML size and location.

Gait analysis is considered a risk factor for pain/function and was therefore included as a target outcome measure. However, few studies included gait analysis measures, which could not be included in the analysis, perhaps due to the minimum sample size (n=100) being too restrictive.

There were several limitations within our study. Firstly, despite identifying novel risk factors for exhibiting knee OA, a small dataset was pooled together for the meta-analysis (two studies) compared to Silverwood *et al.* (34 studies) (93). This was particularly apparent for hip OA where only 12 studies assessed this population (8,17,23,30,46,47,48,50,54,71,76,94). Consequently the small dataset influenced the GRADE assessment that determined the evidence as low to moderate, restricting the strength of the associations of risk factors with OA development and progression. Further work may impact our confidence in the estimated effect, for both studies recruiting participants with hip and knee OA. Secondly, the eligibility criteria may have been too restrictive, resulting in limited papers including gait analysis or MOAKS. Wet biomarkers were not included in our analyses. Finally, the inability to pool data was partly attributed to variability in methods to report data. Standardising data collection and reporting is important in conducting meta-analyses. We believe the following should be undertaken to improve data pooling in future work: ensuring group comparisons in studies are selected from the same population (people with confirmed OA) to improve internal validity, observational studies should conduct a power analysis to determine sample sizes and all studies should include absolute frequency of events data rather than summary odds ratios. Such considerations will improve future meta-analyses to identify OA risk factors.

To conclude, our work helps to develop steps towards building a stratification tool for risk factors for knee OA pain and structural damage development. We also highlight the need for collection of core datasets based on defined domains, that has recently also been highlighted by the OMERACT-OARSI core domain set for knee and hip OA (13). Collection of future datasets based on standardised core outcomes will assist in more robust identification of risk factors for large joint OA.

DECLARATIONS

Contributorship statement: SS, TS and KT conducted the information searches and primary data analysis for the study. FAH was involved in conception of the study, reviewing the results and assisting in writing the manuscript, NS conceived the study, contributed to data analysis, obtained funding and reviewed the manuscript.

Data sharing statement: Extra data sharing is available by emailing nsofat@sgul.ac.uk

Ethics: No Ethical Approval was required for this study

Patient and Public Involvement: The research team acknowledges the assistance of both the OA tech network and Engineering and Physical Sciences Research Council. The authors also acknowledge receiving assistance from a meeting that enabled a consensus to be met on the eligibility criteria to be used, and this meeting consisted of the following people: Dr Angela Kedgley, Mrs Abiola Harrison, Professor Alan Boyde, Professor Alan Silman, Dr Amara Ezeonyeji, Miss Caroline Hing, Professor Cathy Holt, Ms Debbie Rolfe, Dr Enrica Papi, Ms Freija Ter Heegde, Mr Jingsong Wang, Dr John Garcia, Dr Mark Elliott, Professor Mary Sheppard, Miss Natasha Kapella, Mr Richard Rendle, Dr Shafaq Sikandar, Dr Sherif Hosny, Miss Soraia Silva, Miss Soraya Koushesh, Miss Susanna Cooper and Dr Thomas Barrick. No writing assistance was used.

Role of Funding Source: This study was funded by the Engineering and Physical Sciences Research Council (EPSRC) under the reference code 'EP/N027264/1' and The Wellcome Trust ISSF award to NS [Grant number 204809/Z/16/Z]. The funder had no input on the study design, data collection and analysis, manuscript preparation or the choice to submit it for publication.

Competing interests: None of the authors had any relation or contact with companies whose products or services may be related to the topic of the article.

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Table 1: Characteristics of included studies

	Study Design	Number joints (hip/knees)	Gender (male:female)	Country origin	Mean age (years)	Follow-up duration (months)	Pain outcome measures	Functional outcome measures
Ahedi 2014 (54)	Observational cohort	198 hips	111:87	Australia	UTD	132	WOMAC Pain	NA
Akelman 2016 (20)	RCT	107 knee	UTD	USA	23.5	84	KOOS pain; SF-36 Body pain	SF-36 Physical; AP laxity; IKDC2000
Amin 2008 (55)	Observational cohort	265 knees	152:113	USA	67	30	VAS Pain	WOMAC Function
Antony 2017 (56)	Observational cohort	463 knees	245:218	USA	63	24	WOMAC Pain	NA
Arden 2016 (57)	RCT	474 knees	185:289	UK	64	36	WOMAC Pain	WOMAC Function
Ayral 2003 (58)	RCT	665 knees	259:406	Australia, Belgium, Canada, Denmark, Finland, France, Hungary, Norway, Spain, United Kingdom U.S.A.	61.3	12	WOMAC Pain	WOMAC Function
Baselga Garcia-Escudero 2015 (59)	Observational cohort	118 knees	43:75	Spain	59.1	24	NRS; WOMAC Pain	WOMAC Function
Bevers 2015 (60)	Observational cohort	125 knees	57:68	Netherlands	57	24	WOMAC Pain	WOMAC Function
Bingham 2006 (53)	RCT	2483 knees	735:1748	USA Canada Austria Czech Republic France Germany Hungary Ireland Italy Netherlands Poland Croatia	UTD	24	WOMAC Pain	WOMAC Function
Birmingham 2009 (61)	Observational cohort	126 knees	100:26	Canada	47.5	24	KOOS Pain	KOOS Function; SF-36

								Physical; LEFS
Bisicchia 2016 (52)	RCT	150 knees	47:103	Italy	UTD	12	VAS Pain; SF-36	SF-36
Brandt 2005 (62)	RCT	431 knees	0:431	USA	54.9	30	WOMAC Pain; VAS Pain	WOMAC Function
Brown 2012 (51)	RCT	690 knees	270:420	USA	UTD	32 weeks	WOMAC Pain; NRS weekly pain	WOMAC Function; SF-36 Function
Brown 2013 (50)	RCT	621 hips	237:384	USA	UTD	32 weeks	WOMAC Pain	WOMAC Function
Bruyere 2004 (63)	RCT	319 knee	0:319	Belgium	64.0	36	WOMAC Pain	WOMAC Function
Campbell 2006 (49)	RCT	100 knees	28:72	Australia	UTD	120	American Knee Society Score; WOMAC Pain	American Knee Society Score (function); WOMAC Function
Chandrasekaran 2016A (48)	Case-Control	111 hips	66:45	USA	UTD	24	Modified Harris Hip Score; Nonarthritic hip score; VAS Pin	Modified Harris Hip Score; Nonarthritic hip score; Hip Outcome Score; Sports & ADLs
Chandrasekaran 2016B (47)	Case-Control	186 hips	96:90	USA	UTD	24	Modified Harris Hip Score; Nonarthritic hip score; VAS Pin	Modified Harris Hip Score; Nonarthritic hip score; Hip Outcome Score; Sports & ADLs
Conrozier 2016 (64)	RCT	205 knees	88:117	France	65	26	WOMAC Pain; NRS walking pain	WOMAC Function
Davis 2017 (19)	Case-control	3132 knees	UTD	USA	UTD	48	WOMAC Pain; KOOS Pain	WOMAC Function

Dougados 2001 (46)	RCT	507 hips	202:305	France	UTD	36	VAS Pain	Lequesne Index
Dowsey 2012 (65)	Observational cohort	478 knees	147:331	Australia	70.8	24	IKSS Pain	IKSS Function
Eckstein 2013 (45)	RCT	1412 knees	611:801	Austria	UTD	48	WOMAC Pain	NA
Ettinger 1997 (44)	RCT	439 knees	131:308	USA	UTD	18	Pain intensity score	Physical Test
Felson 2013 (66)	Observational cohort	3498 knees	867:1206	USA	61.2	30	WOMAC Pain	PASE
Felson 2007 (67)	Observational cohort	330 knees	111:2111	USA	62.1	15	NA	Quadriceps strength (N)
Filardo 2015 (43)	RCT	183 knees	112:71	Italy	UTD	48	KOOS Pain; IKDC	KOOS Function; Tegner; IKDC
Glass 2013 (42)	Observational cohort	4648 knees	918:1486	USA	UTD	24	WOMAC Pain; NRS Pain	WOMAC Function
Guermazi 2010 (41)	Case-control	493 knees	185:308	USA	UTD	60	WOMAC Pain	PASE
Hamilton 2017 (68)	Observational cohort	805 knees	416:289	UK	66	30	WOMAC Pain	WOMAC Function
Hellio le Graverand 2013 (69)	RCT	1457 knees	343:1114	USA Canada Australia, Belgium, Czech Republic, Germany, Hungary, Italy, Poland, Russian Federation, Slovakia, Spain, Argentina Peru	61.0	180	Oxford Knee Score	Oxford Knee Score; American Knee Society Score; Tegner
Henriksen 2013 (40)	RCT	157 knees	28:129	Denmark	UTD	24	WOMAC Pain	WOMAC Function
Hill 2016 (5)	RCT	202 knees	102:100	Australia	61	12	KOO Pain	KOOS Function and kinematic assessment
Hochberg 2016 (70)	RCT	522 knees	84:438	France Germany	62.7	24	WOMAC Pain	WOMAC Function

				Poland Spain				
Hoeksma 2004 (71)	RCT	109 hips	33:76	Netherlands	72	6	WOMAC Pain; Huskisson's VAS; EQ-5D Pain	WOMAC Function; EQ-5D Function
Housman 2014 (39)	RCT	391 knees	130:261	USA Canada France UK Germany	UTD	6	SF-36 Body Pain; Harris Hip Score; VAS Pain	SF-36 Function; Harris Hip Score; ROM
Huang 2003 (72)	RCT	264 knees	39:93	Taiwan	62	6	WOMAC Pain	NA
Huizinga 2017 (73)	Observational cohort	298 knees	201:97	Netherlands	51	12	VAS Pain	Lequesne index; Walking speed
Jin 2016 (6)	RCT	413 knees	205:208	Australia	63.2	24	WOMAC Pain; VAS Pain	WOMAC Function
Kahn 2013 (74)	Observational cohort	174 knees	70:102	USA	67.0	6	WOMAC Pain	WOMAC Function
Karsdal 2015 (38)	RCT	2207 knees	773:1424	Denmark	UTD	24	WOMAC Pain	WOMAC Function
Katz 2013 (37)	RCT	330 knees	143:187	USA	UTD	12	KOO Pain	WOMAC Function; SF-36 Function
Kim 2017 (75)	RCT	352 knees	9:153	Republic of Korea	68.1	144	WOMAC	Knee Society Knee Score Function; ROM; UCLA Activity
Kinds 2012 (18)	RCT	565 knees	UTD	Netherlands	UTD	60	WOMAC Pain	WOMAC Function
Kongtharvonskul 2016 (36)	RCT	148 knees	25:123	Thailand	UTD	6	WOMAC Pain; VAS Pain	WOMAC Function
Lequesne 2002 (76)	RCT	163 hips	102:61	France	63.2	24	VAS Pain	Lequesne Index
Lohmander 2014 (35)	RCT	170 knees	52:116	Bulgaria Canada Croatia Finland Germany Poland Serbia Africa Sweden	UTD	12	WOMAC Pain	WOMAC Function

				USA				
Maheu 2014 (8)	RCT	345 hips	159:186	France	62.2	36	WOMAC Pain; Global Hip Pain	Lequesne Index; WOMAC Function; Global handicap NRS
Marsh 2016 (34)	RCT	168 knees	57:112	Canada	UTD	24	WOMAC	WOMAC
McAlindion 2013 (33)	RCT	146 knees	57:89	USA	UTD	24	WOMAC Pain	WOMAC Function; Physical Test
Messier 2004 (32)	RCT	316 knees	89:227	USA	UTD	18	WOMAC Pain	WOMAC Function; Physical Test
Messier 2005 (77)	RCT	142 knees	37:105	USA	68.5	18	WOMAC Pain	WOMAC Function; Physical Test
Messier 2013 (78)	RCT	454 knees	128:325	USA	66	18	WOMAC Pain	WOMAC Function; Physical Test; SF-36 Physical
Michel 2005 (31)	RCT	300 knees	146:154	Switzerland	UTD	24	WOMAC Pain	WOMAC Function; Physical Test
Muraki 2014 (79)	Observational cohort	1558 knees	553:1005	Japan	67.0	40	WOMAC Pain	WOMAC Function;
Muraki 2015 (80)	Observational cohort	1525 knees	546:979	Japan	67.0	40	WOMAC Pain	WOMAC Function
Pavelka 2000 (30)	RCT	277 knees; 117 hips	109:285	Czech Republic	58	60	NA	Lequesne Index
Pavelka 2002 (81)	RCT	202 knees	45:157	Czech Republic	UTD	36	WOMAC Pain	WOMAC Function; Lequesne Index
Pham 2004 (29)	Observational cohort	301 knees	97:204	France	UTD	12	VAS Pain	Lequesne Index
Podsiadlo 2014 (28)	Observational cohort	114 knees	49:65	Australia	UTD	72	WOMAC Pain	WOMAC Function
Rat 2011 (82)	RCT	300 knees	118:182	France	67	6	SF-36 Body Pain; OAKHQOL Pain; VAS Pain	Lequense Index; SF-36 Physical; OAKHQOL Physical Activity

Raynauld 2011 (27)	RCT	123 knees	44:79	Canada	UTD	24	WOMAC Pain	WOMAC Function
Reginster 2001 (26)	RCT	212 knees	50:162	Belgium	UTD	36	WOMAC Pain	WOMAC Function
Reginster 2013 (83)	RCT	1371 knees	425:946	Australia Austria Belgium Canada Czech Republic Denmark Estonia France Germany Italy Lithuania Netherlands Poland Portugal Romania Russian Federation Spain United Kingdom	62.9	36	WOMAC Pain; VAS Pain	WOMAC Function
Riddle 2015 (25)	Observational cohort	467 knees	209:258	USA	UTD	24	KOOS Pain	WOMAC Function
Romagnoli 2017 (84)	Observational cohort	105 knees	16:69	Italy	67.7	66	Knee Society Score Clinical; VAS Pain	Knee Society Score Function; ROM
Roman-Blas 2017 (24)	RCT	158 knees	26:132	Spain	UTD	6	WOMAC Pain; VAS Pain	WOMAC Function
Rozendaal 2008 (31)	RCT	222 hips	68:154	Netherlands	UTD	24	WOMAC Pain; VAS Pain	WOMAC Function
Sanchez-Ramirez 2015 (85)	Observational cohort	186 knees	59:127	Canada	61	24	WOAMC Pain	WOMAC Function; Physical Test
Sawitzke 2010 (86)	RCT	662 knees	215:447	USA	57	24	WOMAC Pain	WOMAC Function
Skou 2016 (87)	Observational cohort	1682 knees	434:818	Denmark	62.2	84	WOMAC Pain	PASE; Physical Test
Sowers 2011 (88)	Observational cohort	724 knees	0:363	USA	56	132	NA	WOMAC Function; Physical Test
Spector 2005 (89)	RCT	284 knees	115:169	UK	63.3	12	WOMAC Pain	WOMAC Function

Sun 2017 (90)	RCT	121 knees	31:90	Taiwan	63	6	WOMAC Pain; VAS Pain	WOMAC Function; Lequesne Index; Physical Test
Urish 2013 (22)	RCT	336 knees	96:67	USA	UTD	36	WOMAC	WOMAC
Valdes 2012 (17)	Observational cohort	860 knees; 928 hips	UTD	UK	UTD	38	WOMAC Pain	NA
Van der Esch 2016 (99)	Observational cohort	402 knees	64:137	Netherlands	61.2	24	NRS Pain	WOMAC Function; Physical Test
Weng 2009 (91)	RCT	264 knees	26:106	Taiwan	64	12	VAS Pain	Lequesne Index; ROM; Physical Test
White 2016 (92)	Observational cohort	2110 knees	992:118	USA	61.0	84	VAS Pain	WOMAC Function
Witt 2005 (93)	RCT	294 knees	70:154	Germany	64.0	12	WOMAC Pain; SF-36 Body Pain; VAS Pain	WOMAC Function; SF-36 Function
Yu 2016 (21)	Observational cohort	204 knees	74:130	Australia	UTD	12	KOOS Pain; VAS Pain	KOOS ADL; Physical Function
Yusuf 2011 (94)	Observational cohort	74 knees; 31 hips; 11 hip and knees	19:98	Netherlands	60	72	WOMAC Pain; SF-36 Body Pain; Pain on movement	WOMAC Function; SF-36 Function; Physical Test

ADLs – Activities of Daily Living; IKDC - International Knee Documentation Committee; KOOS - Knee Injury and Osteoarthritis Outcome Score; LEFS – Lower Extremity Functional Scale; NA – not applicable; NRS – numerical rating scale; PASE – Physical Activity Scale for the Elderly; RCT – randomised controlled trial; ROM – range of motion; OAKHQOL - osteoarthritis knee and hip quality of life questionnaire; SF-36 – Short Form-36; UCLA Activity - UK – United Kingdom; USA - United States of America; UTD – unable to determine; VAS – visual analogue scale; WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index

Table 2. Meta-Analysis Results: Exhibit Knee OA

Variable	N	Effect Estimate	P-Value	Statistical Heterogeneity (I^2%)	GRADE Assessment
Gender	823	0.91 (0.48 to 1.72)*	0.78	87	Low quality evidence[1]
Age	823	1.46 (0.26 to 2.66)	0.02	0	Moderate quality evidence[2]
KL ≥2	823	2.04 (1.48 to 2.81)	<0.01	35	Moderate quality evidence[2]
Knee effusion score ≥1	823	1.35 (0.99 to 1.83)	0.05	0	Moderate quality evidence[2]
BMI	823	-0.08 (-0.75 to 0.58)	0.81	0	Moderate quality evidence[2]

BMI – body mass index; KL – Kellgren Lawrence scale; I2 – inconsistency-squared; N- number of participants in analysis; NE – not estimable

* - random effects model analysis

[1]GRADE – Outcomes downgraded one level due to risk of bias, two level due to imprecision and inconsistency; [2]GRADE – Outcomes downgraded one level due to risk of bias

Figure and Table Legends

Figure 1: PRISMA flow-chart

Figure 2a: Forest-plot to present the association between gender and presentation of knee OA.
Figure 2b: Forest-plot to present the association between age and presentation of knee OA.
Figure 2c: Forest-plot to present the association between knee effusion score greater or equal to 1 and presentation of knee OA.
Figure 2d: Forest-plot to present the association between BMI and presentation of knee OA.

Table 1: Characteristics of included studies

Supplementary File 1: Search strategy adopted for the EMBASE database search.

Supplementary File 2: Methodological appraisal results based on the Downs and Black non-RCT Checklist

Supplementary File 3: Methodological appraisal results based on the Downs and Black RCT Checklist

Figure 1: PRISMA flow-chart

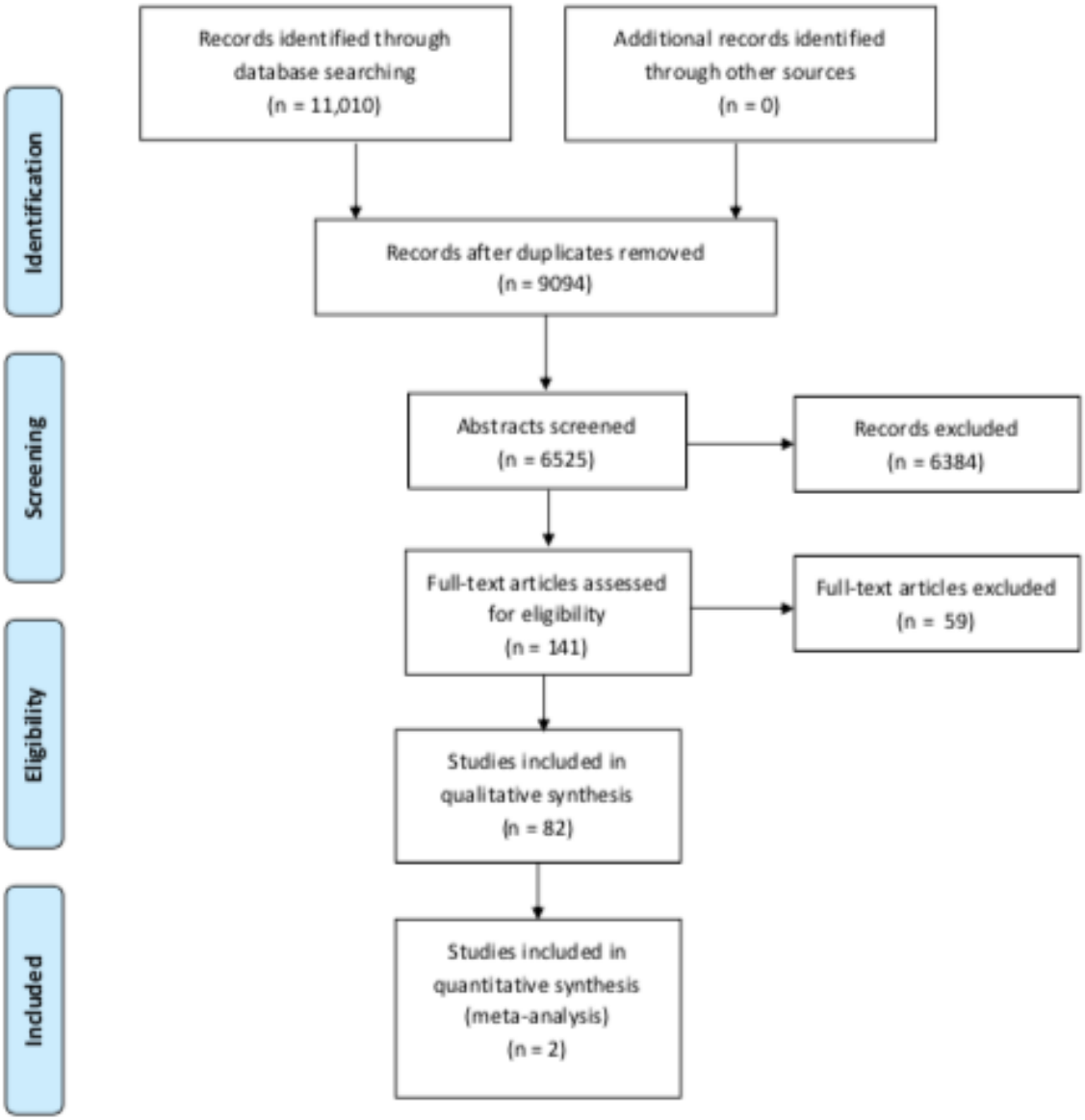


Figure 2a: Forest-plot to present the association between gender and presentation of knee OA.

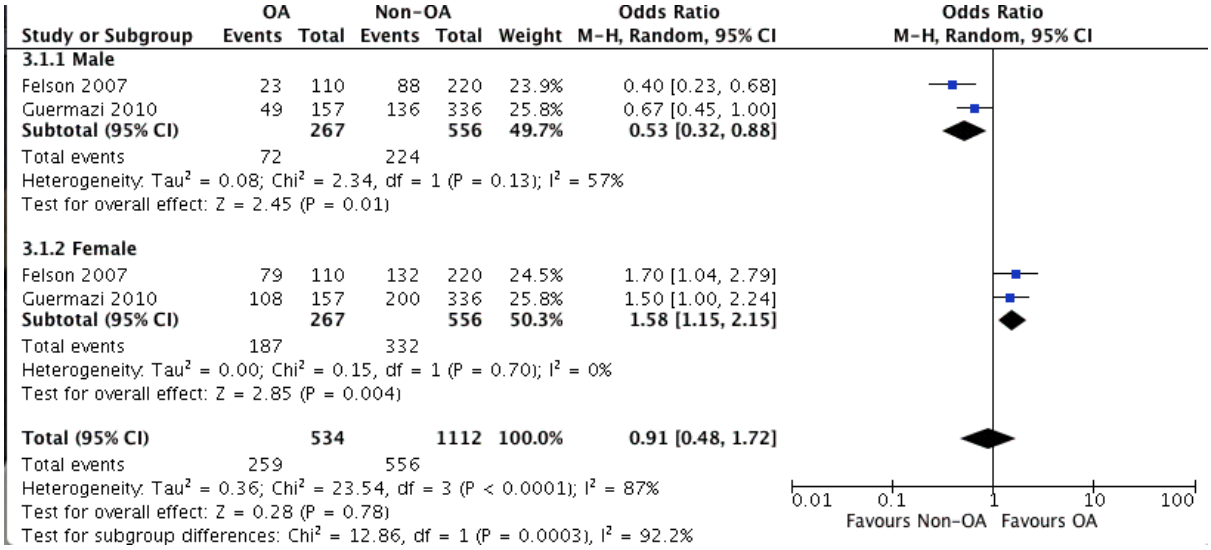


Figure 2b: Forest-plot to present the association between age and presentation of knee OA.

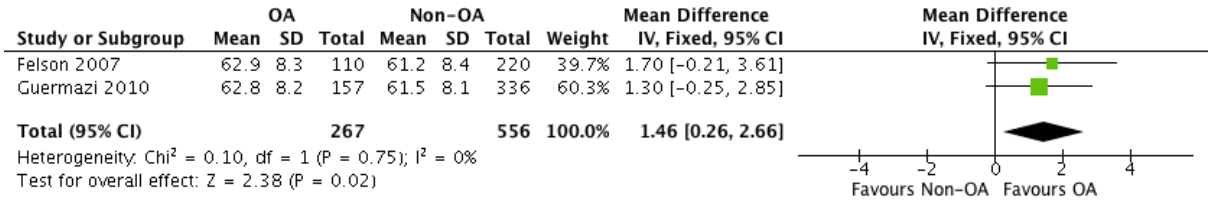


Figure 2c: Forest-plot to present the association between knee effusion score greater or equal to 1 and presentation of knee OA.

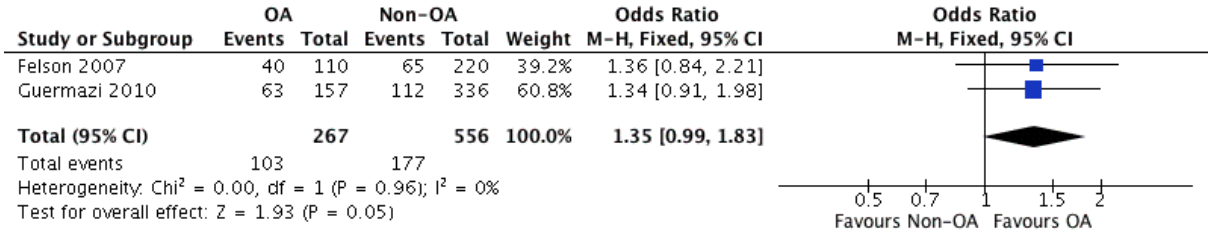
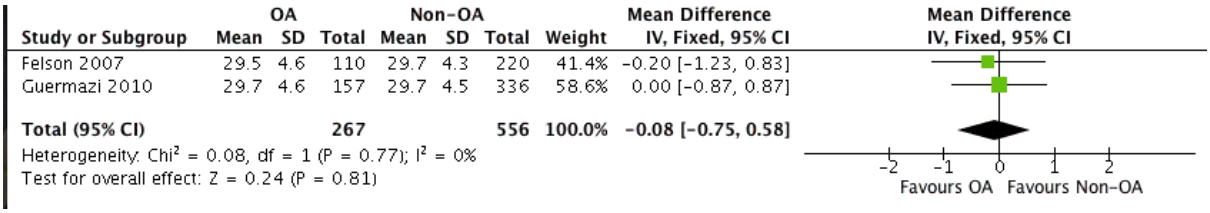


Figure 2d: Forest-plot to present the association between BMI and presentation of knee OA.



Supplementary File 1: Search strategy adopted for the EMBASE database search.

1 exp arthritis/
2 exp osteoarthritis/
3 exp joint diseases/
4 exp arthropathy/
5 exp arthralgia/
6 exp joint pain/
7 exp chronic pain/
8 exp gonarthrosis/
9 exp osteoarthrosis/
10 exp degenerative arthritis/
11 (degenerative adj2 arthritis).tw.
12 or/1-11
13 (Hip adj2 Joint).mp.
14 (Knee adj2 Joint).mp.
15 or/13-14
16 and/12,15
17 Imaging.tw.
18 Radiography.tw.
19 Radiology.tw.
20 Magnetic resonance imagining.tw.
21 MRI.tw.
22 Computed Tomography.tw.
23 CT.tw.
24 Ultrasound.tw.
25 US.tw.
26 USS.tw.
27 Sonography.tw.
28 X-ray.tw.
29 Radiograph.tw.
30 PET.tw.
31 Bone marrow lesions.tw.
32 BML.tw.
33 cytokines.tw.
34 extracellular matrix degradation.tw.
35 ECM degradation.tw.
36 GWAS.tw.
37 cartilage.tw.
38 serum.tw.
39 synovitis.tw.
40 or/17-39
41 exp pain/
42 exp peripheral nervous system disease/
43 exp somatosensory disorders/
44 ((pain* or discomfort*) adj10 (central or complex or nerv* or neuralg* or neuropath*)).mp.
45 ((neur* or nerv*) adj6 (compress* or damag*)).mp.
46 WOMAC.tw.
47 McGill.tw.
48 VAS.tw.
49 Visual analogue.tw.
50 NRS.tw.
51 Numerical rating scale.tw.
52 Analgesic.tw.
53 Analgesia.tw.
54 or/41-53
55 or/40,54
56 and/16,55
57 limit 56 to English language

Supplementary File 2: Methodological appraisal results based on the Downs and Black non-RCT Checklist

	Downs and Black Non-Randomised Controlled Trial Checklist Items																		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**Total**
Ahedi (54)	1	1	1	0	1	1	0	1	1	1	1	UC	1	1	1	UC	1	0	13
Amin (55)	1	1	0	1	1	1	1	0	0	UC	1	1	1	1	UC	1	1	0	12
Antony (560	1	1	1	2	1	1	1	0	1	0	UC	UC	1	1	1	UC	1	0	13
Baselga Garcia-Escudero (59)	1	1	1	0	1	1	1	1	UC	UC	1	1	1	1	UC	0	1	1	13
Bevers (60)	1	1	1	2	0	1	1	1	UC	0	1	1	1	1	1	1	1	0	15
Birmingham (61)	1	1	1	1	1	1	1	1	1	1	UC	1	1	UC	1	1	1	0	15
Chandrasekaran (48)	1	1	1	1	1	1	1	1	0	UC	1	1	1	1	UC	1	1	1	15
Chandrasekaran (47)	1	1	1	1	1	1	0	1	0	UC	1	1	1	1	UC	1	UC	1	13
Davis (19)	1	1	1	0	0	1	1	0	1	1	1	UC	1	1	1	UC	1	0	12
Dowsey (65)	1	1	1	1	1	1	1	1	1	1	1	UC	1	1	1	1	1	0	16
Felson (66)	1	1	1	1	0	1	1	1	0	UC	1	1	1	UC	1	1	1	0	13
Felson (67)	1	1	1	1	0	1	1	1	0	UC	1	1	1	UC	1	1	1	0	13
Glass (42)	1	1	1	2	0	1	1	1	1	1	1	1	1	1	1	1	1	0	17
Guermazin (41)	1	1	1	2	0	1	1	1	1	1	1	1	1	UC	1	1	1	0	16
Hamilton (68)	1	1	0	0	1	1	1	1	UC	UC	1	1	1	1	UC	UC	1	1	12
Huizinga (73)	1	1	1	0	1	1	1	0	UC	UC	1	1	1	1	UC	0	1	0	11
Khan (74)	1	1	1	1	0	1	1	1	1	1	0	1	1	UC	1	1	1	0	14
Muraki (79)	1	1	1	1	1	1	1	1	1	UC	1	1	1	1	0	1	1	0	15
Muraki (80)	1	1	1	2	1	1	1	1	1	UC	1	1	1	1	0	1	1	0	16
Pham (29)	1	1	1	1	1	1	1	1	UC	UC	1	1	1	0	1	1	1	0	14
Podsiadlo (28)	1	1	1	1	0	1	1	1	UC	UC	1	1	1	UC	UC	1	1	0	12
Riddle (25)	1	1	1	2	1	1	0	0	1	1	0	1	1	1	1	1	1	1	16
Romagnoli (84)	1	0	1	0	0	1	1	1	1	1	1	1	1	UC	1	UC	1	1	13
Sanchez-Ramirez (85)	1	1	1	2	1	1	1	1	1	1	1	1	1	UC	1	1	1	0	17
Skou (87)	1	1	1	2	0	1	1	1	1	1	1	1	1	UC	1	1	1	0	16
Sowers (88)	1	1	1	0	1	1	1	1	1	UC	1	1	1	UC	1	0	0	0	12
Valder (17)	1	1	1	1	1	1	0	1	UC	UC	1	1	1	0	1	1	0	0	12
Van der Esch (99)	1	1	1	1	1	1	1	1	1	1	1	1	1	UC	1	0	1	0	15
White (92)	1	1	1	2	0	1	1	0	1	1	1	1	1	1	0	1	1	0	15
Yu (21)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	17
Yusuf (94)	1	1	1	1	1	1	1	0	UC	UC	1	1	1	UC	1	1	1	0	13

UC: Unclear; 2: Yes; 1: Yes/partially; 0: No

Checklist items

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
5. Are the main findings of the study clearly described?
6. Does the study provide estimates of the random variability in the data for the main outcomes?
7. Have the characteristics of patients lost to follow-up been described?

8. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
9. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
10. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
11. If any of the results of the study were based on "data dredging", was this made clear?
12. Were the statistical tests used to assess the main outcomes appropriate?
13. Were the main outcome measures used accurate (valid and reliable)?
14. Were study participants in different groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
15. Were the participants in different groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
16. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
17. Were losses of patients to follow-up taken into account?
18. Did the study mention having conducted a power analysis to determine the sample size needed to detect a significant difference in effect size for one or more outcome measures?

Supplementary File 3: Methodological appraisal results based on the Downs and Black RCT Studies Checklist

	Downs and Black Randomised Controlled Trial Checklist Items																										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**Total**
Akelman (20)	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	UC	1	1	**26**
Arden (57)	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	UC	1	1	1	1	1	1	1	0	1	UC	**23**
Ayral (58)	1	1	1	1	1	1	1	1	1	1	0	UC	UC	1	1	1	1	1	1	1	0	1	1	UC	UC	1	0	**20**
Bingham (53)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	UC	1	1	1	1	1	0	1	0	UC	1	1	0	**22**
Bisicchia (52)	1	0	1	1	0	1	1	1	1	1	1	1	1	0	1	UC	1	1	1	1	1	1	1	0	0	1	0	**20**
Brandt (62)	1	1	1	1	1	0	1	1	1	1	UC	UC	UC	UC	1	1	1	1	1	1	UC	1	1	UC	0	1	0	**18**
Brown (50)	1	1	1	1	1	1	1	1	1	0	UC	UC	UC	1	1	1	1	1	1	1	UC	UC	1	UC	UC	UC	1	**18**
Brown (51)	1	1	1	1	1	1	1	1	1	0	UC	UC	UC	1	1	1	1	1	1	1	UC	UC	1	1	UC	1	1	**19**
Bruyere (63)	1	1	1	1	1	0	1	0	1	1	UC	UC	1	1	1	1	1	1	UC	1	UC	UC	1	UC	UC	1	1	**18**
Campbell (49)	1	1	1	1	0	0	0	1	1	0	1	UC	1	1	1	1	1	1	1	1	1	1	1	1	UC	1	0	**20**
Conrozier (64)	1	1	1	1	0	0	1	1	1	1	UC	UC	UC	1	1	1	1	0	1	1	0	1	1	1	0	1	UC	**18**
Dougados (46)	1	1	1	1	1	1	1	1	1	0	1	0	0	UC	UC	1	1	1	1	1	0	UC	1	UC	1	1	UC	**18**
Eckstein (45)	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	UC	1	1	1	1	1	0	**26**
Ettinger (44)	1	1	1	1	1	0	1	1	1	1	UC	UC	0	0	UC	1	1	1	UC	1	0	1	1	1	1	1	1	**19**
Filardo (43)	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	**25**
Hellio le Graverand (69)	1	1	1	1	1	0	1	1	1	1	UC	UC	UC	UC	1	1	UC	1	1	1	0	UC	1	1	UC	1	0	**17**
Henriksen (40)	1	1	1	1	2	1	1	1	0	1	UC	UC	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	**24**
Hill (5)	1	1	1	1	0	0	1	1	1	1	1	0	UC	1	1	1	1	1	1	1	0	1	1	1	0	1	1	**21**
Hochberg (70)	1	1	1	1	1	1	1	1	1	1	UC	UC	UC	1	UC	1	1	1	UC	1	0	UC	1	1	UC	1	0	**18**
Hoeksma (71)	1	1	1	1	0	1	1	1	1	0	1	1	0	0	1	1	1	1	0	1	1	1	1	1	UC	1	1	**21**
Housman (39)	1	1	1	1	0	0	1	1	1	0	0	UC	0	1	0	1	1	1	UC	1	0	1	1	UC	0	1	1	**16**
Huang (72)	1	1	1	1	0	1	1	0	1	0	UC	UC	UC	UC	1	1	UC	1	1	1	1	UC	1	UC	0	1	1	**16**
Jin (6)	1	1	1	1	0	1	1	1	0	1	UC	UC	0	1	1	1	1	1	UC	1	0	1	1	1	0	1	0	**18**
Karsdal (38)	1	1	1	1	1	0	1	1	1	0	UC	UC	UC	1	1	1	1	1	0	1	0	UC	1	1	1	1	UC	UC
Katz (37)	1	1	1	1	2	1	1	1	1	0	0	0	0	0	0	1	0	1	0	1	0	1	1	0	1	1	UC	**17**
Kim (75)	1	0	1	1	0	1	1	0	1	1	UC	UC	UC	1	1	1	0	1	1	1	UC	1	1	1	0	1	0	**17**

Kinds (18)	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	**25**
Kongtharvonskul (36)	1	1	1	1	2	1	1	1	0	1	1	UC	0	1	1	1	1	1	0	1	1	1	1	1	1	1	0	**23**
Lequesne (76)	1	1	1	1	1	1	1	1	1	1	UC	UC	0	1	1	1	1	1	1	1	0	UC	1	1	1	1	0	**21**
Lohmander (35)	1	1	1	1	0	1	1	1	1	1	UC	UC	0	1	1	0	1	1	1	1	0	1	1	1	0	1	1	**20**
Maheu (8)	1	1	1	1	0	1	0	1	0	1	UC	UC	0	1	1	1	1	UC	1	1	0	1	1	1	1	0	0	**17**
Marsh (34)	1	1	0	1	2	1	1	0	1	1	UC	UC	1	0	0	1	1	1	UC	1	UC	UC	UC	UC	1	1	0	**16**
McAlindion (33)	1	1	1	1	1	1	1	1	0	1	0	UC	0	1	1	1	1	1	1	1	0	1	1	1	UC	1	0	**20**
Messier (32)	1	1	1	1	1	0	1	1	0	0	0	UC	0	0	1	1	1	1	0	1	UC	1	1	1	1	0	1	**17**
Meissier (77)	1	1	0	1	2	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	**25**
Messier (78)	1	1	1	1	2	1	1	1	0	1	1	1	0	0	1	1	1	1	0	1	1	1	1	UC	1	1	1	**23**
Michel (31)	1	1	1	1	0	0	1	1	0	1	UC	UC	1	1	1	1	1	1	1	1	UC	1	1	1	0	0	1	**19**
Pavelka (30)	1	1	1	0	1	0	1	1	0	1	UC	UC	0	1	1	1	1	1	1	1	0	1	1	UC	1	1	0	**18**
Pavelka (81)	1	1	1	1	1	0	1	1	1	1	1	UC	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	**25**
Rat (82)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	UC	1	1	**25**
Raynauld (27)	1	1	1	1	2	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	**26**
Reginster (83)	1	1	1	1	1	1	1	1	0	1	UC	UC	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	**22**
Reginster (26)	1	1	1	1	1	0	1	1	0	1	0	UC	1	1	1	1	1	1	1	1	1	1	1	1	UC	1	1	**22**
Roman-Blas (24)	1	1	1	1	1	0	1	1	1	1	UC	UC	0	1	1	1	1	1	0	1	0	UC	1	1	1	1	0	**19**
Rozendaal (31)	1	1	1	1	2	1	1	1	1	0	UC	UC	0	1	1	0	1	1	1	1	UC	1	1	1	1	1	UC	**21**
Sawitzke (86)	1	0	1	1	2	0	1	1	0	1	1	UC	0	1	1	1	1	1	1	1	UC	UC	1	UC	1	UC	UC	UC
Spector (89)	1	1	1	1	2	0	1	1	1	1	UC	UC	0	UC	UC	1	1	1	0	1	0	UC	1	UC	1	1	0	**17**
Sun (90)	1	1	1	1	1	1	1	1	1	1	UC	UC	1	1	1	1	1	1	1	1	UC	1	1	1	1	1	1	**24**
Urish (22)	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	0	**24**
Weng (91)	1	1	1	1	0	1	1	0	1	0	UC	UC	1	0	UC	1	1	1	1	1	UC	UC	1	1	0	1	1	**17**
Witt (93)	1	1	1	1	1	1	1	1	1	1	UC	UC	1	0	0	1	1	1	1	1	UC	1	1	1	1	1	1	**22**

UC: Unclear; 2: Yes; 1: Yes/partially; 0: No

Checklist items

1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the Intervention?
16. If any of the results of the study were based on “data dredging”, was this made clear?
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcomes appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?
23. Were study subjects randomized to intervention groups?
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?
27. Was there sufficient power to detect treatment effect at significance level of 0.05?