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

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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, and Web of Science (1990–February 2020), was conducted. Studies that 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 ORs with corresponding 95% CIs 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 Grading of Reccomendation, Assessment, Development and Evaluation (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 to 2.81; p<0.01), increasing age (MD: 1.46, 95% CI 0.26 to 2.66; p=0.02) and whole-organ MRI scoring method (WORMS) knee effusion score ≥1 (OR: 1.35, 95% CI 0.99 to 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 (BML; 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.

INTRODUCTION

Disability worldwide caused by OA increased from 10.5 million to 17.1 million, an increase of 62.9%. Current OA treatment lacks any disease-modifying treatments with a predominance of targeting symptoms rather than modify underlying disease. The clinical symptoms of OA can be assessed using several questionnaires, the most common of which is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Although pain is recognised as an important outcome measure in OA, it is not clear what the optimal assessment tool is 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 presymptomatic interventions. Several methods are used to define, diagnose and measure OA progression, including imaging techniques (eg, plain radiography, CT and MRI). Plain radiography provides high contrast and high-resolution images for cortical and trabecular bone, but not for non-ossified structures (eg, synovial...
METHODS

This systematic review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.

Search strategy

A systematic search of the literature was undertaken from 1 January 1990 to 1 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 online 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. One hundred 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 JSN, 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.
7. Minimum 6-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 (TOS). Any disagreements were addressed through discussion and adjudicated by a third reviewer (NS or FH). All studies that 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 while the 18-item non-RCT version was used for non-RCT designs (online 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 (TOS). In previous literature, D&B score ranges were given corresponding quality: excellent (scored 26–28); good (scored 20–25); fair (scored 15–19); and poor (scored <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 related to baseline and change in pain, function and structural scores for each study. No data were 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 ORs 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-effect 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% CIs and forest plots.

Due to the presentation of the data, there were minimal data to permit meta-analyses. Where there were 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 (ie, difference between hip OA and knee OA); (2) geographical region. Analyses were undertaken on STATA V.14.0 (Stata Corp) with forest plots constructed using RevMan Review Manager (RevMan; Computer program; V.5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.)

**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 the cohort characteristics (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%).

**RESULTS**

**Search strategy**

The results of the search strategy are presented in figure 1. In total, 11010 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.\(^{17-98}\)

**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, 45767 knees were included in the analysis. This consisted of 13870 men and 23497 women; 4 studies did not report the gender of their cohorts.\(^{17-20}\) Thirty-six studies were undertaken in the USA; 30 were undertaken in Europe; 9 were conducted in Australasia and 7 in Asia. Mean age of the cohorts was 61.7 years (SD: 7.56); 36 studies did not report age.\(^{17-21,34}\) 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 (online supplementary file 2). Based on the results of the D&B non-RCT tool (31 studies; online 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 6 studies (19%) basing their sample sizes on an a priori power calculation.

The results from the D&B RCT checklist (51 studies; online 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 \( \geq 2 \) in WORMS (OR: 1.8; 95% CI 0.9 to 3.6). We also found that the following were the highest predictors of worsening function in people with knee OA: KL of \( \leq 3 \) (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 \( \geq 1 \) (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 figure 2A–D, age (MD: 1.46, 95% CI 0.26 to 2.66; p=0.02; n=823), KL of \( \geq 2 \) (MD: 2.04, 95% CI 1.48 to 2.81; p<0.01; n=823) and knee effusion score \( \geq 1 \) (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.
| 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 et al.  | Observational cohort      | 198 hips             | 111:87         | Australia        | UTD                       | 132                                    | WOMAC Pain                            |
| Akelman et al.| RCT                       | 107 knee              | UTD            | USA              | 23.5                      | 84                                     | KOOS pain; SF-36 Physical; AP laxity; IKDC2000 |
| Amin et al.   | Observational cohort      | 265 knees             | 152:113        | USA              | 67                        | 30                                     | VAS Pain                              |
| Antony et al. | Observational cohort      | 463 knees             | 245:218        | USA              | 63                        | 24                                     | WOMAC Pain                            |
| Arden et al.  | RCT                       | 474 knees             | 185:289        | UK               | 64                        | 36                                     | WOMAC Pain; WOMAC Function            |
| Ayral et al.  | RCT                       | 665 knees             | 259:406        | Australia, Belgium, Canada, Denmark, Finland, France, Hungary, Norway, Spain, UK, USA | 61.3 | 12 | WOMAC Pain | WOMAC Function |
| Baselga Garcia-Escudero and Miguel Hernández Trillos | Observational cohort | 118 knees             | 43:75           | Spain             | 59.1                      | 24                                     | NRS; WOMAC Pain; WOMAC Function        |
| Bevers et al. | Observational cohort      | 125 knees             | 57:68          | The Netherlands   | 57                        | 24                                     | WOMAC Pain; WOMAC Function            |
| Bingham et al.| RCT                       | 2483 knees            | 735:1748       | USA              | UTD                       | 24                                     | WOMAC Pain; LEFS                       |
| Birmingham et al. | Observational cohort | 126 knees             | 100:26         | Canada            | 47.5                      | 24                                     | KOOS Function; SF-36 Physical; SF-36 Function |
| Bisicchia et al.| RCT                      | 150 knees             | 47:103         | Italy             | UTD                       | 12                                     | VAS Pain; SF-36                         |
| Brandt et al. | RCT                       | 431 knees             | 0:431          | USA              | 54.9                      | 30                                     | WOMAC Pain; VAS Pain                   |
| Brown et al.  | RCT                       | 690 knees             | 270:420        | USA              | UTD                       | 32 weeks                               | WOMAC Pain; NRS weekly pain            |
| Brown et al.  | RCT                       | 621 hips              | 237:384        | USA              | UTD                       | 32 weeks                               | WOMAC Pain; WOMAC Function            |

Continued
| Study design | Number joints (hip/knee) | Gender (male:female) | Country origin | Mean age (years) | Follow-up duration (months) | Pain outcome measures | Functional outcome measures |
|--------------|--------------------------|----------------------|----------------|-----------------|--------------------------|----------------------|--------------------------|
| RCT          | 319 knee                 | 0:319                | Belgium       | 64              | 36                       | WOMAC Pain           | WOAC Function           |
| RCT          | 100 knees                | 28:72                | Australia     | 26              | 120                      | American Knee Society; WOMAC Pain | WOAC Function           |
| Study design | Number joints (hip/knee) | Gender (male:female) | Country origin | Mean age (years) | Follow-up duration (months) | Pain outcome measures | Functional outcome measures |
| RCT          | 111 hips                | 96:90                | USA           | UTD             | UTD                      | WOMAC Pain           | WOAC Function           |
| Case control | 186 hips                | 88:117               | France        | 65              | 48                       | WOMAC Pain; NRS walking pain; KOOS Pain | WOAC Function |
| Case control | 3132 knees              | UTD                  | USA           | UTD             | UTD                      | WOMAC Pain           | WOAC Function           |
| Case control | 507 hips                | 202:305              | France        | UTD             | UTD                      |İKSS Pain             | Lequesne Index          |
| Observational cohort | 478 knees | 147:331               | Australia     | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 1412 knees | 611:801               | Austria       | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 439 knees              | 131:208              | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 3489 knees             | 867:1206             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 330 knees              | 111:2111             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 183 knees              | 112:71               | Italy         | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 4648 knees             | 918:1486             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 483 knees              | 185:2888             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 805 knees              | 416:289              | UK            | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| RCT          | 112:71                  | 112:71               | Italy         | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Case control | 183 knees               | 112:71               | Italy         | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 4648 knees             | 918:1486             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 483 knees              | 185:2888             | USA           | UTD             | UTD                      |IWOMAC Pain           | NA                       |
| Observational cohort | 805 knees              | 416:289              | UK            | UTD             | UTD                      |IWOMAC Pain           | NA                       |

Table 1 Continued
| Study design       | Number joints (hip/knees) | Gender (male:female) | Country origin                                                                 | Mean age (years) | Follow-up duration (months) | Pain outcome measures                                      | Functional outcome measures                                      |
|--------------------|----------------------------|----------------------|-------------------------------------------------------------------------------|-----------------|-----------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| Hill et al^5       | 202 knees                  | 102:100              | Australia                                                                     | 61              | 12                          | KOOS Pain                                                  | KOOS Function and kinematic assessment                          |
| Hochberg et al^70  | 522 knees                  | 84:438               | France, Germany, Poland, Spain                                                | 62.7            | 24                          | WOMAC Pain                                                 | WOMAC Function                                                |
| Hoeksma et al^71   | 109 hips                   | 33:76                | The Netherlands                                                               | 72              | 6                           | WOMAC Pain; Huskisson's VAS; EQ-5D Pain                  | WOMAC Function; EQ-5D Function                                  |
| Housman et al^39   | 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 et al^72     | 264 knees                  | 39:93                | Taiwan                                                                        | 62              | 6                           | WOMAC Pain                                                 | NA                                                            |
| Huizinga et al^73  | Observational cohort       | 298 knees            | The Netherlands                                                               | 51              | 12                          | VAS Pain                                                    | Lequesne index; walking speed                                 |
| Jin et al^6        | 413 knees                  | 205:208              | Australia                                                                     | 63.2            | 24                          | WOMAC Pain; VAS Pain                                      | WOMAC Function                                                |
| Kahn et al^74      | Observational cohort       | 174 knees            | USA                                                                           | 67.0            | 6                           | WOMAC Pain                                                 | WOMAC Function                                                |
| Karsdal et al^38   | 2207 knees                 | 773:1424             | Denmark                                                                       | UTD             | 24                          | WOMAC Pain                                                 | WOMAC Function                                                |
| Katz et al^77      | RCT                        | 330 knees            | USA                                                                           | UTD             | 12                          | KOO Pain                                                    | WOMAC Function; SF-36 Function                                 |
| Kim et al^75       | RCT                        | 352 knees            | Republic of Korea                                                             | 68.1            | 144                         | WOMAC                                                        | Knee Society Knee Score Function; ROM; UCLA Activity           |
| Kinds et al^78     | RCT                        | 565 knees            | The Netherlands                                                               | UTD             | 60                          | WOMAC Pain                                                 | WOMAC Function                                                |

Table 1 Continued

| Study design       | Number joints (hip/knees) | Gender (male:female) | Country origin                                                                 | Mean age (years) | Follow-up duration (months) | Pain outcome measures                                      | Functional outcome measures                                      |
|--------------------|----------------------------|----------------------|-------------------------------------------------------------------------------|-----------------|-----------------------------|------------------------------------------------------------|---------------------------------------------------------------|
| Hellio le Graverand et al^9 | 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; American Knee Society Score; Tegner | Oxford Knee Score; American Knee Society Score; Tegner |
| Henriksen et al^40 | RCT                        | 157 knees            | Denmark                                                                       | UTD             | 24                          | WOMAC Pain                                                 | WOMAC Function                                                |
| Hill et al^5       | RCT                        | 202 knees            | Australia                                                                     | 61              | 12                          | KOO Pain                                                    | KOOS Function and kinematic assessment                          |
| Hochberg et al^70  | RCT                        | 522 knees            | France, Germany, Poland, Spain                                                | 62.7            | 24                          | WOMAC Pain                                                 | WOMAC Function                                                |
| Hoeksma et al^71   | RCT                        | 109 hips             | The Netherlands                                                               | 72              | 6                           | WOMAC Pain; Huskisson's VAS; EQ-5D Pain                  | WOMAC Function; EQ-5D Function                                  |
| Housman et al^39   | RCT                        | 391 knees            | USA, Canada, France, UK, Germany                                              | UTD             | 6                           | SF-36 Body Pain; Harris Hip Score; VAS Pain              | SF-36 Function; Harris Hip Score; ROM                           |
| Huang et al^72     | RCT                        | 264 knees            | Taiwan                                                                        | 62              | 6                           | WOMAC Pain                                                 | NA                                                            |
| Huizinga et al^73  | Observational cohort       | 298 knees            | The Netherlands                                                               | 51              | 12                          | VAS Pain                                                    | Lequesne index; walking speed                                 |
| Jin et al^6        | RCT                        | 413 knees            | Australia                                                                     | 63.2            | 24                          | WOMAC Pain; VAS Pain                                      | WOMAC Function                                                |
| Kahn et al^74      | Observational cohort       | 174 knees            | USA                                                                           | 67.0            | 6                           | WOMAC Pain                                                 | WOMAC Function                                                |
| Karsdal et al^38   | RCT                        | 2207 knees           | Denmark                                                                       | UTD             | 24                          | WOMAC Pain                                                 | WOMAC Function                                                |
| Katz et al^77      | RCT                        | 330 knees            | USA                                                                           | UTD             | 12                          | KOO Pain                                                    | WOMAC Function; SF-36 Function                                 |
| Kim et al^75       | RCT                        | 352 knees            | Republic of Korea                                                             | 68.1            | 144                         | WOMAC                                                        | Knee Society Knee Score Function; ROM; UCLA Activity           |
| Kinds et al^78     | RCT                        | 565 knees            | The Netherlands                                                               | UTD             | 60                          | WOMAC Pain                                                 | WOMAC Function                                                |

Continued
| Study design | Number of joints (hip/knees) | Gender (male:female) | Country origin | Mean age (years) | Follow-up duration (months) | Pain outcome measures | Functional outcome measures |
|--------------|-----------------------------|---------------------|----------------|-----------------|--------------------------|----------------------|---------------------------|
| Kongtharvonskul et al\(^{36}\) | RCT | 148 knees | 25:123 | Thailand | UTD | 6 | WOMAC Pain; VAS Pain |
| Lequesne et al\(^{76}\) | RCT | 163 hips | 102:61 | France | 63.2 | 24 | VAS Pain; Lequesne Index |
| Lohmander et al\(^{35}\) | RCT | 170 knees | 52:116 | Bulgaria Canada Croatia Finland Germany Poland Serbia Africa Sweden USA | UTD | 12 | WOMAC Pain; WOMAC Function |
| Maheu et al\(^{8}\) | RCT | 345 hips | 159:186 | France | 62.2 | 36 | WOMAC Pain; Global Hip Pain; WOMAC Function; Lequesne Index; Global handicap NRS |
| Marsh et al\(^{34}\) | RCT | 168 knees | 57:112 | Canada | UTD | 24 | WOMAC | WOMAC |
| McAlindion et al\(^{33}\) | RCT | 146 knees | 57:89 | USA | UTD | 24 | WOMAC | WOMAC Function; Physical Test |
| Messier et al\(^{32}\) | RCT | 316 knees | 89:227 | USA | UTD | 18 | WOMAC | WOMAC Function; Physical Test |
| Messier et al\(^{77}\) | RCT | 142 knees | 37:105 | USA | 68.5 | 18 | WOMAC | WOMAC Function; Physical Test |
| Messier et al\(^{78}\) | RCT | 454 knees | 128:325 | USA | 66 | 18 | WOMAC | WOMAC Function; Physical Test; SF-36 Physical |
| Michel et al\(^{31}\) | RCT | 300 knees | 146:154 | Switzerland | UTD | 24 | WOMAC | WOMAC Function; Physical Test |
| Muraki et al\(^{79}\) | Observational cohort | 1558 knees | 553:1005 | Japan | 67.0 | 40 | WOMAC | WOMAC Function |
| Muraki et al\(^{80}\) | Observational cohort | 1525 knees | 546:979 | Japan | 67.0 | 40 | WOMAC | WOMAC Function |
| Pavelka et al\(^{30}\) | RCT | 277 knees; 117 hips | 109:285 | Czech Republic | 58 | 60 | NA | Lequesne Index |
| Pavelka et al\(^{81}\) | RCT | 202 knees | 45:157 | Czech Republic | UTD | 36 | WOMAC | WOMAC Function; Lequesne Index |
| Pham et al\(^{29}\) | Observational cohort | 301 knees | 97:204 | France | UTD | 12 | VAS Pain | Lequesne Index |

Continued
| Study design          | Number joints (hip/knees) | Gender (male:female) | Country origin                                      | Mean age (years) | Follow-up duration (months) | Pain outcome measures                          | Functional outcome measures                      |
|-----------------------|---------------------------|----------------------|-----------------------------------------------------|------------------|----------------------------|-----------------------------------------------|--------------------------------------------------|
| **Podsiadlo et al**²⁸ | Observational cohort      | 114 knees            | 49:65 Australia                                     |                  |                           | WOMAC Pain                                    | WOMAC Function                                   |
| **Rat et al**²⁹       | RCT                       | 300 knees            | 118:182 France                                      |                  | 67                        | SF-36 Body Pain; OAKHQOL; VAS Pain             | Lequense Index; SF-36 Physical Activity           |
| **Raynauld et al**³⁰  | RCT                       | 123 knees            | 44:79 Canada                                        |                  | 24                        | WOMAC Pain                                    | WOMAC Function                                   |
| **Reginster et al**³¹ | RCT                       | 212 knees            | 50:162 Belgium                                      |                  | 36                        | WOMAC Pain                                    | WOMAC Function                                   |
| **Reginster et al**³² | RCT                       | 1371 knees           | 425:946 Australia Austria Belgium Czech Republic   | 62.9             | 36                        | WOMAC Pain; VAS Pain                           | WOMAC Function                                   |
| **Riddle and Jiranek**| Observational cohort      | 467 knees            | 209:258 USA                                         |                  | 24                        | KOOS Pain                                      | WOMAC Function                                   |
| **Romagnoli et al**³³ | Observational cohort      | 105 knees            | 16:69 Italy                                         |                  | 67.7                      | Knee Society Score Clinical; VAS Pain          | Knee Society Score Function; ROM                 |
| **Roman-Blas et al**³⁴ | RCT                       | 158 knees            | 26:132 Spain                                        |                  | 6                         | WOMAC Pain; VAS Pain                           | WOMAC Function                                   |
| **Rozendaal et al**³⁵ | RCT                       | 222 hips             | 68:154 The Netherlands                              |                  | 24                        | WOMAC Pain                                    | WOMAC Function                                   |
| **Sanchez-Ramirez et al**³⁶ | Observational cohort | 186 knees            | 59:127 Canada                                       |                  | 61                        | WOMAC Pain                                    | WOMAC Function                                   |
| **Sawitzke et al**³⁷  | RCT                       | 662 knees            | 215:447 USA                                         |                  | 57                        | WOMAC Pain                                    | WOMAC Function                                   |
### Table 1  Continued

| Study design            | Number of joints (hip/knees) | Gender (male:female) | Country origin | Mean age (years) | Follow-up duration (months) | Pain outcome measures | Functional outcome measures |
|-------------------------|------------------------------|----------------------|----------------|------------------|----------------------------|-----------------------|----------------------------|
| Skou et al\(^87\)        | 1682 knees                   | 434:818              | Denmark        | 62.2             | 84                         | WOMAC Pain            | PASE; Physical Test        |
| Sowers et al\(^88\)       | 724 knees                    | 0:363                | USA            | 56               | 132                        | NA                    | WOMAC Function; Physical Test |
| Spector et al\(^89\)      | 284 knees                    | 115:169              | UK             | 63.3             | 12                         | WOMAC Pain            | WOMAC Function             |
| Sun et al\(^90\)         | 121 knees                    | 31:90                | Taiwan         | 63               | 6                          | WOMAC Pain; VAS Pain  | WOMAC Function; Lequesne Index; Physical Test |
| Urish et al\(^92\)        | 336 knees                    | 96:67                | USA            | UTD              | 36                         | WOMAC Pain            | WOMAC Function             |
| Valdes et al\(^17\)       | 860 knees; 928 hips         | UTD                  | UK             | UTD              | 38                         | WOMAC Pain            | NA                         |
| Van der Esch et al\(^98\)| 402 knees                    | 64:137               | The Netherlands| 61.2             | 24                         | NRS Pain              | WOMAC Function; Physical Test |
| Weng et al\(^91\)         | 264 knees                    | 26:106               | Taiwan         | 64               | 12                         | VAS Pain              | Lequesne Index; ROM; Physical Test |
| White et al\(^92\)        | 2110 knees                   | 992:118              | USA            | 61.0             | 84                         | VAS Pain              | WOMAC Function             |
| Witt et al\(^93\)         | 294 knees                    | 70:154               | Germany        | 64.0             | 12                         | WOMAC Pain; SF-36 Body Pain; VAS Pain | WOMAC Function; SF-36 Function |
| Yu et al\(^21\)           | 204 knees                    | 74:130               | Australia      | UTD              | 12                         | KOOS Pain; VAS Pain   | KOOS ADL; Physical Function |
| Yusuf et al\(^94\)        | 74 knees; 31 hips; 11 hip and knees | 19:98              | The Netherlands| 60               | 72                         | WOMAC Pain; SF-36 Body Pain; Pain on movement | WOMAC Function; SF-36 Function |

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; OAKHQOL, Osteoarthritis Knee and Hip quality of Life Questionnaire; PASE, Physical Activity Scale for the Elderly; RCT, randomised controlled trial; ROM, range of motion; SF-36, Short Form-36; UTD, unable to determine; VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
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.

Table 2  Meta-analysis results: exhibit knee osteoarthritis

| Variable              | N   | Effect estimate | P value | Statistical heterogeneity (I² %) | GRADE assessment       |
|-----------------------|-----|-----------------|---------|---------------------------------|------------------------|
| Gender                | 823 | 0.91 (0.48 to 1.72)* | 0.78    | 87                              | Low-quality evidence†  |
| Age                   | 823 | 1.46 (0.26 to 2.66) | 0.02    | 0                               | Moderate-quality evidence‡ |
| KL ≥2                 | 823 | 2.04 (1.48 to 2.81) | <0.01   | 35                              | Moderate-quality evidence‡ |
| Knee effusion score ≥1| 823 | 1.35 (0.99 to 1.83) | 0.05    | 0                               | Moderate-quality evidence‡ |
| BMI                   | 823 | −0.08 (−0.75 to 0.58) | 0.81    | 0                               | Moderate-quality evidence‡ |

*Random effects model analysis.
†GRADE—outcomes downgraded one level due to risk of bias, two level due to imprecision and inconsistency.
‡GRADE—outcomes downgraded one level due to risk of bias.
BMI, body mass index; I², inconsistency squared; KL, Kellgren Lawrence Scale; N, number of participants in analysis; NE, not estimable.

Figure 2  (A) Forest plot to present the association between gender and presentation of knee osteoarthritis (OA). (B) Forest plot to present the association between age and presentation of knee OA. (C) Forest plot to present the association between knee effusion score greater or equal to 1 and presentation of knee OA. (D) Forest plot to present the association between body mass index and presentation of knee OA.
fied age and KL grade as predictive factors for developing hip OA. Our systematic review and meta-analysis identified risk factors 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 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, which could not be included in the analysis.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. Second, 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 are 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 ORs. 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, which 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.

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Contributors Conception and design; drafting of the article; critical revision of the article; final approval of the article: NS, FH, TOS and SS. Analysis and interpretation of the data; collection and assembly of data: TOS, SS and KT. Provision of study materials or patients: N/A. Statistical expertise: TOS. Obtaining of funding: administrative, technical, or logistic support: NS, TOS and FH.

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