A systematic review of the relationship between subchondral bone features, pain and structural pathology in peripheral joint osteoarthritis

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Abstract

Introduction: Bone is an integral part of the osteoarthritis (OA) process. We conducted a systematic literature review in order to understand the relationship between non-conventional radiographic imaging of subchondral bone, pain, structural pathology and joint replacement in peripheral joint OA.

Methods: A search of the Medline, EMBASE and Cochrane library databases was performed for original articles reporting association between non-conventional radiographic imaging-assessed subchondral bone pathologies and joint replacement, pain or structural progression in knee, hip, hand, ankle and foot OA. Each association was qualitatively characterised by a synthesis of the data from each analysis based upon study design, adequacy of covariate adjustment and quality scoring.

Results: In total 2456 abstracts were screened and 139 papers were included (70 cross-sectional, 71 longitudinal analyses; 116 knee, 15 hip, six hand, two ankle and involved 113 MRI, eight DXA, four CT, eight scintigraphic and eight 2D shape analyses). BMLs, osteophytes and bone shape were independently associated with structural progression or joint replacement. BMLs and bone shape were independently associated with longitudinal change in pain and incident frequent knee pain respectively.

Conclusion: Subchondral bone features have independent associations with structural progression, pain and joint replacement in peripheral OA in the hip and hand but especially in the knee. For peripheral OA sites other than the knee, there are fewer associations and independent associations of bone pathologies with these important OA outcomes which may reflect fewer studies; for example the foot and ankle were poorly studied. Subchondral OA bone appears to be a relevant therapeutic target.

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Introduction

Osteoarthritis (OA), the most common form of arthritis, is a major cause of chronic pain and disability. OA confers a huge burden on both individuals and health economies [1, 2]. There are currently no licensed disease-modifying osteoarthritis drugs (DMOADs) but ideally these should both inhibit structural progression and improve symptoms and/or function [3, 4]. While hyaline cartilage loss is the hallmark pathology, clinical OA usually involves multiple tissues. Describing the relationships of these tissues with structural progression and symptoms may identify potential tissue targets.

The subchondral bone in particular is intimately associated with hyaline cartilage and therefore a tissue of great potential interest. Conventional radiographs are known to be relatively insensitive to the structural features of OA [5], in part because they do not assess three-dimensional...
(3D) bone structure [6]. A number of non-conventional radiographic imaging modalities accurately demonstrate in vivo subchondral bone pathological changes, including magnetic resonance imaging (MRI), computed tomography (CT), dual-energy x-ray absorptiometry (DXA), scintigraphy and positron emission tomography (PET) [5, 7–13]. Hunter and colleagues found a moderate association between bone marrow lesions (BMLs), structural progression and longitudinal change in pain in a systematic review focused on MRI biomarkers and knee OA [7]. In another systematic review Kloppenburg and colleagues examined associations between MRI features and knee pain, but not structural pathology [14].

We therefore wished to comprehensively review the literature on subchondral bone structure assessed with all non-conventional radiographic imaging modalities, examining the common sites of peripheral OA and describing the relationships between imaging-detected subchondral bone features and joint replacement, structural progression and pain.

**Methods**

**Systematic literature search**

A systematic literature search of Medline (from 1950), EMBASE (from 1980) and the Cochrane library databases until September 2014 was performed. A full description of the search terms used is recorded in Additional file 1: Table S1. An abbreviation of the full search terms used was ‘knee, hip, hand, foot and ankle’ and ‘osteoarthritis’ and ‘subchondral bone’ manifestations of OA (‘bone marrow lesion,’ ‘osteophyte,’ ‘bone cyst,’ ‘bone area,’ ‘bone shape,’ ‘bone attrition,’ bone morphometry and mineral density) and ‘MRI’ or ‘CT’ or ‘DXA’ or ‘scintigraphy’ or ‘PET’. The search term ‘bone shape’ was not restricted to non-conventional radiographic imaging. The final search was restricted to humans. There was no language restriction and abstracts were not excluded. Exclusion criteria are listed in Fig. 1. Any analysis of fewer than 20 patients with confirmed OA was excluded to remove papers at risk of study imprecision. The inclusion criteria were in vivo observational studies of a human population with clinical

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**Fig. 1** Search strategy results and article exclusion. *Two articles included both cross-sectional and longitudinal data. Longitudinal data included 16 case–control studies and 55 cohort studies.*
and/or radiographic OA, which included an imaging description of the adjacent subchondral bone pathology to the osteoarthritic joint and the relationship of this with pain, structural progression or joint replacement. Analyses describing the relationship between OA bone manifestations and structural severity (cross-sectional) or progression (prospective cohorts) in populations without clinical and radiographic OA were included to incorporate early structural features of joint degeneration. The outcome measures of structural severity or progression included cartilage defects, cartilage thickness, cartilage volume, denuded subchondral bone, Kellgren-Lawrence (KL) grade, joint space width and joint space narrowing. Other outcome measures included joint replacement and any pain measures.

The articles identified by the preliminary search were screened by two reviewers (DH, AB) for relevance and for references not identified by the preliminary search, although no additional citations were found. Discordance in opinion was resolved by a third reviewer (SK). We applied the methods for reporting meta-analyses of observational studies in epidemiology that are recommended by the Cochrane collaboration [15, 16].

Data extraction
Data extraction was performed by two reviewers (DH, AB) as described in the Supplementary methods ‘data extraction’ (see Additional file 1).

Quality assessment
The quality of each observational study was independently assessed by two reviewers (TC, AB), as described in Supplementary methods ‘Quality assessment’ (see Additional file 1).

Best evidence synthesis
Statistical pooling of the data was considered inappropriate in light of the heterogeneous study populations, methodological quality and bone feature or outcome measurements for OA. Therefore a qualitative summary of the evidence for each bone feature (e.g., BML) and its association with pain or structural progression and joint replacement was provided based on the study design, adequacy of adjustment for confounders (age, body mass index and gender) and quality score as described in the Supplementary methods ‘Best evidence synthesis’ (see Additional file 1).

Studies that investigated the association between multiple bone features and OA pain or structural progression outcomes were considered as a single study for each bone feature. Included studies that established significant correlation between bone and pain, structural progression or joint replacement were described as positive (+) or negative (−) accordingly. If no association or inconclusive findings were described this was reported as no association (NA) or no conclusion (NC) respectively.

Results
Systematic literature search and selection
The Preferred reporting items for systematic reviews and meta-analyses (PRISMA) diagram in Fig. 1 describes the literature flow. Following exclusion of duplicates and triplicates, 2,456 articles met the search criteria. After applying inclusion/exclusion criteria, 139 articles were included for data extraction and quality scoring. In total, 71 papers provided longitudinal data (55 cohorts, 16 case–controls), 70 provided cross-sectional data, and two papers provided both.

Data extraction from selected studies
In only 12 studies did the mean age fall below 50 years [17–29]. Most (n = 93) described both genders; 2 studies included men only [27, 30], 14 studies included female individuals only [22, 28, 29, 31–41] and there was an undisclosed gender ratio in 6 [42–50]. Knee OA was defined using clinical and radiographic criteria and is described in Additional file 1: Table S6. Radiographic OA was invariably defined as KL grade ≥2 or any radiographic OA abnormality from the Altman atlas [51]. Individual pain or structural progression measures were examined in 88 studies; 52 studies examined multiple features. Subchondral bone was analyzed with MRI in 113 articles, DXA in 8 [30–32, 42, 52–55], CT in 4 [33, 40, 56, 57], and scintigraphy in 8 [24, 37, 38, 58–62], and no articles using PET met the inclusion criteria. Included articles described 116 knee, 15 hip, 6 hand and 2 ankle studies. Of these studies 13 described structural associations without clinical or radiographic OA [18, 19, 23, 25, 26, 35, 63–69]. There were no articles on studies of the foot that met the inclusion criteria.

Quality assessment of studies
Concordance of opinion in quality scoring was observed in 2,040 (89 %) of the 2,242 scoring items assessed, which are recorded in Additional file 1: Tables S3-S5. The majority of discordant scoring was for study design (criteria 17) and data presentation (criteria 18). Quality scores were converted to percentages of the maximum scores for each class of paper. The mean (range) quality score was 59 % (29–79), 54 % (22–83) and 59 % (47–76) for cross-sectional, cohort and case–control studies, respectively.

Relationship between knee bone feature and structural progression
The association of bone features with structural progression and joint replacement are described in Tables 1 and 5.
| Author | Feature (method) | Structural progression outcome | Adjustment for confounders | Association (magnitude) crude | Association (magnitude) adjusted | Association Quality (score %) |
|--------|------------------|-------------------------------|----------------------------|-------------------------------|---------------------------------|-----------------------------|
| Felson 2003 [70] | Baseline presence of BML in medial or lateral TFJ (C) | OARSI JSN grade progression of TFJ (L) | Age, sex, and BMI | OR 6.5, 95% CI 3.0 to 14.0 | + | High (83) |
| Dore 2010 [124] | Baseline semi-quantitative MRI BML size (C) TFJ | Incident TKR over 5 years (L) | Age, sex, BMI, knee baseline pain, leg strength, cartilage defects, tibial bone area, ROA | OR (95% CI) 2.04 (1.55 to 2.69) | OR (95% CI) 2.10 (1.13 to 3.90) | p = 0.019 |
| Driban 2013 [72] | Knee baseline BML volume (C) | 48-month change in OARSI JSN grade (L) | Age, sex, BMI | OR (95% CI) 1.27, 95% CI 1.11 to 1.46 | OR (95% CI) 3.36, 95% CI 1.55 to 7.28 | + | High (61) |
| Davies-Tuck 2010 [67] | Incident BML (new BML after 2 years with no BMLs at baseline) MRI TFJ (L) | Progression in semi-quantitative MRI cartilage defects score after 2 years. TFJ (L) | Age, gender, BMI, baseline cartilage volume | OR (95% CI) Medial TFJ 1.86 (0.70 to 4.93) p = 0.21 | Medial TFJ 2.63 (0.93 to 7.44) p = 0.07 | + | High (61) |
| Hochberg 2014 [44] | Semi-quantitative MRI baseline femoral condyle BML size (C) | Incident TKR over 6 years (L) | Age, gender, BMI, race, marital status, depressive symptoms, quality of life, mechanical pain, KL grade, clinical effusion. | Medial TFJ p < 0.0001 | Medial TFJ p = 0.02 | + | High (61) |
| Raynauld 2011 [75] | Baseline semi-quantitative BML score (C) TFJ | Incidence of TKR over 3 years (L) | Age, sex, BMI, JSW, WOMAC, | OR (95% CI) Medial TFJ 1.81 (1.08 to 2.03) p = 0.025 | BML medial plateau + | High (61) |
| Raynauld 2013 [74] | Baseline semi-quantitative BML WORMS score (C) medial TFJ | Incident TKR (L) 4 year follow up Time to TKR (L) | Age, BMI, gender WOMAC, CRP | OR (95% CI) 2.107 (1.26 to 3.54) p = 0.005 | Time to TKR incidence hazard ratio (95% CI) 2.13 (1.38 to 3.30) p = 0.001 | + | High (61) |
| Study Year | Study Details | Feature Measurements | Quality Grade | Effect Size | p Value | Notes |
|------------|---------------|----------------------|---------------|-------------|---------|-------|
| Crema 2014 [71] | MRI BML (semi-quantitative) (C) all regions (L) (all regions) | Cartilage loss (semi-quantitative) | Age, gender, BMI | NR | $\beta = 0.37$ to $0.64$ | + | High (56) |
| Guermazi 2014 Abstract [73] | Baseline semi-quantitative BML score WORMS (C) | Cartilage thickness loss over 30 months (L) | Age, sex, body mass index, and anatomical alignment axis (degrees) | NR | Combined BML score in the medial and lateral TFJ compartment OR 1.9, 95% CI 1.1 to 3.3 | + | High (56) |
| Scher 2008 [87] | Presence of any baseline semi-quantitative MRI BMLs (C) | Incident TKR (L) over 3 years | Age | NR | OR (95% CI) | + | High (56) |
| Sowers 2011 [28] | Semi-quantitative MRI BML size in TFJ (C) | Progression in KL grade (11-year follow up) (L) | Nil | R (95% CI) medial tibia $\sim 0.46$ (0.35 to 0.55) Lateral tibia $\sim 0.23$ (0.13 to 0.33) | NR | + | Low (53) |
| Kothari 2010 [82] | Semi-quantitative baseline MRI BML (WORMS) (C) TFJ | Semi-quantitative cartilage defect score change over 2 years (WORMS) (L) TFJ. | Age, sex, BMI, other bone lesions | OR 4.04, 95% CI 2.25 to 7.26 | OR 3.75, 95% CI 1.59 to 8.82 | + | Low (50) |
| Raynauld 2008 [85] | Change in BML size (mm) at 24 months in medial TFJ (L) | Medial cartilage volume (L) at 24 months in medial TFJ. | Age, gender, BMI, meniscal extrusion and tear, pain and bone lesions at baseline | NR | Change in BML size with femoral cartilage volume loss $\beta = -0.31$ standard error (0.08) $p = 0.0004$ | - | Larger medial BML size means more cartilage loss in medial compartment | Low (50) |
| Roemer 2009 [90] | Change in MRI semi-quantitative BML size (WORMS) (L) TFJ and PFJ | Progression in semi-quantitative cartilage defects in (WORMS) over 30 months (L) TFJ and PFJ | Age, sex, BMI, baseline KL grade | NR | OR (95% CI) | + | Low (50) |
| Dore 2010 [76] | Baseline semi-quantitative BML severity (C) (medial and lateral TFJ) | Ipsi-compartmental annual Cartilage volume loss (L) | Age, sex, BMI, meniscal damage | NR | Baseline BML severity $\beta = -22.1$ to $-42.0$, for all regions (p <0.05) | - | Bigger BML means bigger volume loss | Low (50) |
Table 1  Knee structural associations by feature and quality grade (Continued)

| Study Year | Study Details | Feature of Interest | Study Outcome | Covariates | Effect Size | Quality Grade |
|------------|---------------|---------------------|---------------|------------|-------------|---------------|
| Parsons 2014 | Baseline semi-quantitative BML score (C) | Annual TFJ JSN (L) | Age, sex, baseline KL grade | NR | $\beta = -0.10, 95\% \text{ CI } -0.18 \text{ to } -0.02$ | + Low (S0) |
| Wildi 2010 [95] | 24-month regional change in TFJ BML score WORMS (L) | 24-month regional change in cartilage volume (L) | nil | R correlation coefficients all <0.07, $p > 0.367$ for all three compartments at 24 months | NR NC Low (S0) |
| Pelletier 2007 [84] | Regional Semi-quantitative baseline BML score (medial or lateral TFJ) (C) | Regional cartilage volume over 24 months (medial or lateral TFJ) (L) | NR | Lateral compartment BML score $\beta = -0.31, p = 0.001$ | NR |
| Driban 2011 [79] | Baseline BML volume (C) and 24 month change in BML volume (L) in TFJ compartments | 24-month change in full thickness cartilage lesion area (L) | Age, sex, body mass index | NR | Baseline BML volume $r = 0.48, 95\% \text{ CI } 0.20 \text{ to } 0.69, p < 0.002$ | + Baseline femur BML volume with loss in ipsicompartmental full thickness cartilage lesion area. Low (S0) |
| Tanamas 2010 [89] | Baseline semi-quantitative MRI BML size (C) TFJ | Cartilage volume change over 2 years (L) TFJ Incident TKR over 4 years | Age, sex, BMI, baseline tibial cartilage volume and bone area | $R (95\% \text{ CI):}$ Total cartilage loss $0.61 (-0.11 \text{ to } 1.33)$ OR (95\% CI) Incident TKR $1.55 (1.04 \text{ to } 2.29), p = 0.03$ | Baseline BML volume $r = 0.48, 95\% \text{ CI } 0.20 \text{ to } 0.69, p < 0.002$ | + Baseline femur BML volume with loss in ipsicompartmental full thickness cartilage lesion area. Low (S0) |
| Madan-Sharma 2008 [93] | Baseline MRI semi-quantitative BML (C) TFJ | OARSI medial TFJ JSN grade progression over 2 years (L) TFJ | Age, sex, BMI, family effect | NR | 0.9 RR, 95\% CI 0.18 to 3.0 | NA Low (47) |
| Tanamas 2010 [88] | Semi-quantitative change in MRI BML severity (C) | Incident TKR over 4 years (L) | Age, gender, KL grade | OR (95\% CI) Medial TFJ 1.72 (0.93 to 3.18), $p = 0.08$ Lateral TFJ 0.95 (0.48 to 1.88), $p = 0.89$ | OR (95\% CI) Medial TFJ 1.99 (1.01 to 3.90), $p = 0.05$ Lateral TFJ 0.96 (0.48 to 1.94), $p = 0.91$ | + Association in the medial TFJ but not in the lateral TFJ Low (47) |
| Roemer 2012 [86] | Semi-quantitative BML (WORMS) TFJ and PFJ (C) | Semi-quantitative cartilage score | Age, sex, treatment, and BMI | NR | BML TFJ OR 4.74, 95\% CI 1.14 to 19.5 | + Low (44) |
| Study            | Feature                        | Quality Grade | Associations                                                                 |
|------------------|--------------------------------|---------------|------------------------------------------------------------------------------|
| Crema 2013 [78]  | MRI incident BML (WORMS) TFJ (L) | Progressive (30 month) semi-quantitative cartilage defect (WORMS) TFJ (L) | 6-month progression TFJ and PFJ (L) Age, sex, BMI, malalignment, meniscal disease |
|                  |                                |               | OR (95 % CI) 1.63 (0.67 to 3.92) + BMLs and cartilage score correlate         |
| Hernandez-Molina  | Crude presence of central BMLs on MRI (C) TFJ | Semi-quantitative cartilage defect (WORMS) (L) TFJ | Alignment, BMI, KL grade, sex, and age. |
| 2008 [81]        |                                |               | Medial TFJ cartilage loss OR 6.1, 95 % CI 1.0, 35.2 + Low (44)               |
| Koster 2011 [25] | Baseline BML presence (C) TFJ | Any progression in KL grade over 1 year (L) TFJ | Age, BMI |
|                  |                                |               | OR (95 % CI) 6.01 (1.92 to 18.8) p = 0.002 OR 5.29 (1.64 to 17.1) p = 0.005 |
| Hunter 2006 [91] | Change in MRI semi-quantitative BML score (L) TFJ | Change in semi-quantitative cartilage defect score (WORMS) (L) medial or lateral TFJ | Limb alignment |
|                  |                                |               | Ipsilateral cartilage loss β = 0.65 p = 0.003 Contralateral cartilage loss β = -0.27 p = 0.22 |
|                  |                                |               | Ipsilateral cartilage loss β = 0.26 p = 0.16 Contralateral cartilage loss β = -0.16 p = 0.52 |
| Roemer 2009 [94] | Baseline MRI BML crude presence or absence (WORMS) (L) TFJ | Semi-quantitative cartilage defect progression over 30 months (WORMS) (L) TFJ | Age, sex, race, BMI, alignment |
|                  |                                |               | OR (95 % CI) 1.74 (0.85 to 3.55) OR 1.79 (0.83 to 3.87) NA after adjustment |
| Kubota 2010 [92] | MRI BML semi-quantitative volume score change over 6 months (L) TFJ | KL grade progression over 6 months (L) TFJ | Nil |
|                  |                                |               | BML score higher in KL progression group p = 0.044 NA                        |
| Driban 2012      | MRI BML volume change (L) TFJ over 24 months | Change in cartilage thickness and denuded area of bone (L) TFJ over 24 months | Nil |
| abstract [80]    |                                |               | Cartilage thickness r = -0.34, p = 0.04 denuded bone r = 0.42, p = 0.01 Low (28) |
| Study              | Feature and Quality Grade Description                                                                 | Femoral Cartilage Indices | OR (95% CI) | p        | Effect Size | Quality Grade |
|--------------------|--------------------------------------------------------------------------------------------------------|---------------------------|-------------|----------|-------------|---------------|
| Carrino 2006 [77]  | Crude presence of MRI BML, TFJ (C) and (L)                                                           | Any grade of cartilage defect TFJ (C) and (L) | Nil         | p > 0.05  | NR          | +            | Low (22)     |
| MRI bone marrow lesion - cross-sectional studies               |                                                                                                       |                           | OR (95% CI) |          | +           | High (71%)    |
| Baranyay 2007 [63]| MRI BML defined as large or not large/absent in the medial and lateral compartments of TFJ (C)       | MRI semi-quantitative cartilage defects of medial and lateral compartments of TFJ (C) | Age, gender, BMI, cartilage volume or bone area | 1.81 (1.26 to 2.59) | p = 0.005 |                         |
|                    |                                                                                                       | Quantitative cartilage volume medial and lateral TFJ (C) |                         | 1.52 (1.14 to 2.04) | p = 0.005 |                         |
|                    |                                                                                                       |                           | OR (95% CI) |          | NA          | Nil NR       |
| Guymer 2007 [35]   | Presence or absence of MRI BMLs (C) TFJ                                                               | Presence or absence of semi-quantitative cartilage defects (C) TFJ | Age, height, weight, and tibial cartilage volume | 6.46 (1.04 to 38.39) | p = 0.04 |                         |
|                    |                                                                                                       |                           | OR (95% CI) |          | 3.51 (1.08 to 11.42) | Age, gender and BMI, KL score, knee injury or knee surgery, family history of TKR and Heberden's nodes |
|                    |                                                                                                       |                           |             |         |                         | Nil          | p < 0.001 | +            | High (71)     |
| Stehling 2010 [65]| Presence of any MRI semi-quantitative BMLs (C)                                                        | Presence of any WORMS MRI cartilage defects (C) | Age, gender and BMI, KL score | R = 0.56   | NR          | +            | High (71)     |
| Torres 2006 [103]  | MRI BML (WORMS) (C) TFJ and PFJ                                                                    | Semi-quantitative cartilage (WORMS) (C) | Nil | p = 0.005 | NR          | +            | High (68)     |
| Ip 2011 [99]       | Semi-quantitative MRI BML (C)                                                                        | KL grade (C)              | Age, sex, BMI, OA stage, joint effusion, and meniscal damage |                 | Highest BML score | p < 0.001 | +            | High (68)     |
| Hayes 2005 [22]    | Semi-quantitative MRI BML (C)                                                                        | KL grade (C)              | Nil | p = 0.005 | NR          | +            | High (61)     |
| Study                        | Method                        | Feature & Quality Grade | OR (95% CI) | p Value | Change in Cartilage Defects |
|-----------------------------|-------------------------------|-------------------------|-------------|---------|-----------------------------|
| Kornaat 2005 [100]          | Semi-quantitative MRI BMLs   | TFJ and PFJ (C)         | Nil         | 17 (3.8 to 72) | + Low (57)                 |
| Gudbergsen 2013 [98]        | Semi-quantitative MRI BMLs   | KL grade (C)            | Nil         | p < 0.001 | + Low (57)                 |
| Link 2003 [101]             | Semi-quantitative MRI BMLs   | KL grade (C)            | Nil         | p < 0.05   | + Low (54)                 |
| Felson 2001 [96]            | Semi-quantitative MRI BMLs   | KL grade (C)            | Nil         | p < 0.0001 | + Low (54)                 |
| Lo 2005 [102]               | Semi-quantitative MRI BMLs   | KL grade ≥ 2 (C)        | Nil         | p < 0.0003 | + Low (50)                 |
| Meredith 2009 [64]          | Sum of semi-quantitative MRI | Cartilage defect scores in the TFJ and PFJ (C) | Nil         | p < 0.001   | + Low (46)                 |
| Fernandez-Madrid 1994 [97]  | Crude presence of MRI BMLs   | KL grade (C)            | Nil         | p = 0.012  | + Low (43)                 |
| Scher 2008 [87]             | Semi-quantitative MRI BMLs   | Semi-quantitative cartilage defect (modified Noyes) (C) | Nil         | 1.68 (1.33 to 2.13) | True of TFJ but not PFJ |
| Zhao 2010 [105]             | Baseline crude presence of MRI BMLs at (C) TFJ | Overlying cartilage defect progression after 1 year (WORMS) (L) TFJ | Nil         | 1.23 (1.03 to 1.46) | + Low (56) |
Table 1  Knee structural associations by feature and quality grade (Continued)

| Study                        | Feature                          | Outcome                        | Age, sex, BMI | OR (95% CI) | p for trend |
|------------------------------|----------------------------------|---------------------------------|---------------|-------------|-------------|
| Aitken 2013                  | Semi-quantitative BMLs tibia, femur and patella | Cartilage volume and defect score tibia and femur | NR            | 1.8 (1.1 to 3.1) | < 0.01       |
| Stahl 2011 [41]              | Semi-quantitative MRI BML size (WORMS) (L) TFJ | Semi-quantitative cartilage defect size (L) TFJ | Nil           | 1.8 (1.1 to 3.1) | < 0.01       |
| MRI osteophyte - cohort studies | De-Lange 2014 abstract [106]     | Radiographic progression of JSN of TFJ (L) | Age, gender, BMI and baseline JSN | NR | High (61) |
| Liu 2014 Abstract [45]      | Baseline semi-quantitative osteophyte score (WORMS) (C) TFJ | Incident TKR at 6-months follow up (L) | Activity of daily living disability score | RR (95% CI) 3.01 (1.39 to 6.52) | + |
| Sowers 2011 [28]            | Semi-quantitative MRI osteophyte size in TFJ (C) | Progression in KL grade (11-year follow up) (L) | Nil           | R (95% CI) medial tibia ~0.65 (0.59 to 0.71) | + |
| MRI osteophyte - cross-sectional studies | Stehling 2010 [65] | Presence of any MRI semi-quantitative osteophytes (C) | Presence of any WORMS MRI cartilage defects (C) | Age, gender and BMI, KL score, knee injury or knee surgery, family history of TKR and Heberden's nodes | NR | High (71) |
| Torres 2006 [103]           | MRI osteophyte, (WORMS) TFJ and PFJ (C) | Semi-quantitative cartilage (WORMS) TFJ and PFJ (C) | Nil           | R = 0.73 | + |
| Hayes 2005 [22]             | Semi-quantitative MRI osteophyte (C) | KL grade (C) | Nil | p < 0.001 | + |
| Meredith 2009 [64]          | Sum of semi-quantitative MRI osteophytes in the TFJ and PFJ (C) | Sum of semi-quantitative MRI cartilage defect scores in the TFJ and PFJ (C) | Nil | p < 0.0001 | + |
| McCauley 2001 [26]          | MRI central osteophyte presence (C) TFJ | MRI cartilage lesion presence (C) TFJ | Crude association of 32 of 35 central osteophytes having adjacent cartilage lesions | NR | Low (29) |
| Roemer 2012 [108]           | MRI osteophyte (WORMS) (C) | Cartilage defect (WORMS) (C) | Age, sex, BMI, race, TFJ radiographic OA | OR 2378.1, 95% CI 249.8 to 22643.4 | + |

Note: p = 0.00003
β = -433 mm³ per unit increase in BML
p < 0.01
| Reference | Study Design | Imaging Method | Feature | Quality Grade | Effect Size | p-Value | Association |
|-----------|--------------|----------------|---------|---------------|-------------|---------|-------------|
| Link 2003 [101] | Semi-quantitative MRI osteophytes (C) | KL grade (C) | Nil | p <0.01 | NR | + | Low (54) |
| Fernandez-Madrid 1994 [97] | Crude presence of MRI osteophytes (C) | KL grade (C) | Nil | p <0.001 | NR | + | Low (46) |
| MRI bone attrition - cohort studies | | | | | | | |
| Kothari 2010 [82] | Semi-quantitative baseline MRI attrition (WORMS) (C) | Semi-quantitative cartilage defect score change over 2 years (WORMS) (L) TFJ | Age, sex, BMI, other bone lesions | OR 3.17, 95% CI 1.64 to 6.16 | OR 1.85, 95% CI 0.71 to 4.82 | NR | + | Low (50) |
| MRI bone attrition - cross-sectional studies | | | | | | | |
| Torres 2006 [103] | MRI attrition (WORMS) TFJ and PFJ (C) | Semi-quantitative cartilage (WORMS) TFJ and PFJ (C) | Nil | R = 0.75 | NR | + | High (68) |
| MRI bone attrition - case control studies | | | | | | | |
| Reichenbach 2008 [110] | Semi-quantitative MRI bone attrition (WORMS) (C) | KL grade and semi-quantitative cartilage defects (WORMS) (C) | Nil | NR | NR | + | Low (43) |
| MRI bone Shape/dimension – cohort studies | | | | | | | |
| Neogi 2009 [109] | Baseline semi-quantitative MRI bone attrition size (WORMS) (C) TFJ | Cartilage defects progression (WORMS) after 30 months TFJ | Age, sex, BMI | OR 5.5, 95% CI 3.0 to 10.0 | OR 3.0, 95% CI 2.2 to 4.2 | NR | + | Low (59) |
| MRI bone Shape/dimension – cohort studies | | | | | | | |
| Cicuttini 2004 [111] | Baseline quantitative MRI tibial bone area (C) | TKR incidence (L) over 4 years | Age, sex, height, weight, BMI, WOMAC, ROA severity | NR | OR (95% CI) 1.2 (1.0 to 1.4) | + | High (78) |
| Ding 2008 [20] | Baseline MRI tibial bone area (C) TFJ | Progressive cartilage volume loss (L) TFJ | Age, sex, BMI, OA family history, muscle strength and ROA. | \( \beta \) (95% CI) \( \beta \) (95% CI) - Medial femoral cartilage | \( \beta \) (95% CI) Medial femoral cartilage \( \beta \) = 0.35 (0.14 to 0.56) Total femoral cartilage \( \beta \) = 0.13 (0.02 to 0.25) | Medial femoral cartilage \( \beta \) = 0.17 (0.04 to 0.29) Total femoral cartilage \( \beta \) = 0.07 (0.003 to 0.14) | High (72) |
| Ding 2006 [18] | Baseline MRI tibial bone area (C) TFJ | Change in semi-quantitative MRI cartilage defect scores over 2.3 years (L) TFJ | Age, sex, BMI, radiographic OA Features | NA | OR (95%CI) Medial TFJ 1.24 (1.01 to 1.51) | - | High (61) |
| Study | Baseline tibial bone area (C) | Progressive semi-quantitative cartilage defect score (L) | Age, sex, BMI, baseline cartilage defects, BML | Lateral tibial bone area OR (95 % CI) | Bone area size is associated with increasing cartilage defect scores |
|-------|-----------------------------|--------------------------------------------------------|-----------------------------------------------|-------------------------------------|------------------------------------------------------------------|
| Dore 2010 [68] | Baseline tibial bone area MRI (C) | Increase or no increase in semi-quantitative MRI tibial cartilage defects over 2.7 years (L) | Age, sex, body mass index, baseline cartilage defects, and subchondral bone mineral density | OR (95 % CI) medial tibia 1.6 (1.0 to 2.6) p = 0.04 lateral tibia 2.4 (1.4 to 4.0) p <0.01 | Low (50) |
| Hudelmaier 2013 [180] Abstract | Annual change in segmented MRI knee bone area (L) | Baseline KL grade (C) | Nil | Medial tibia p <0.05 | Low (50) |
| Kalichman 2007 [165] | MRI patellar length ratio, trochlea sulcus angle (C) | JSN grade (C) | Age, sex, BMI | NR | NC |
| Kalichman 2007 [115] | MRI patellar length ratio, trochlea sulcus angle (C) | Cartilage defect (WORMS) (C) | Age, sex, BMI | NR | Low (57) |
| Study          | MRI/CT technique                     | Feature/Quality grade | Age, Sex, BMI (C) | Effect Size (95% CI) | p Value | Summary |
|---------------|-------------------------------------|-----------------------|------------------|----------------------|---------|---------|
| Stefanik 2012 | MRI lateral trochlear inclination and trochlear angle (C) | Semi-quantitative cartilage defect (WORMS) (C) | Age, sex, BMI | Lateral trochlear inclination OR 2, 95% CI 1.9 to 3.7, p < 0.0001, trochlear angle OR 2.0, 95% CI 1.2 to 3.5, p < 0.0001 | + | Low (57) |
| Frobell 2010  | MRI bone area - manual segmentation (C) | KL grade, OARSI JSN grade (C) | Age and BMI | Medial tibia JSN and KL OR 2, 95% CI 1.9 to 3.7, p < 0.0001, trochlear angle OR 2.0, 95% CI 1.2 to 3.5, p < 0.0001 | + | Low (57) |
| Wang 2005     | Annual % change in tibial bone area (L) 2 years follow up | Baseline JSN (C) | Age, sex, BMI, WOMAC score, SF-36 score, physical activity, radiographic OA features, baseline tibial plateau bone area. | Medial tibia JSN and KL OR 3.0 (1.1 to 8.9) p = 0.03, lateral tibia OR 1.9 (1.0 to 3.8) p = 0.04 | + Association with medial tibia but not in the lateral tibia | Low (57) |
| Jones 2004    | Tibial bone area (MRI) (C) | Radiographic JSN (C) | Age, sex, height, weight | Medial tibia JSN and knee OR 3.0 (1.1 to 8.9) p = 0.03, lateral tibia OR 1.9 (1.0 to 3.8) p = 0.04 | + | Low (50) |
| Eckstein 2010 | MRI tibial bone area (segmented) (C) | OARSI JSN grade (C) | Nil | Medial tibia JSN and knee OR 3.0 (1.1 to 8.9) p = 0.03, lateral tibia OR 1.9 (1.0 to 3.8) p = 0.04 | + | Low (43) |
| Bowes 2013    | Change in segmented MRI 3D bone area over 4 years (L) | KL grade defined ROA knee (C) and (L) | Nil | Medial tibia JSN and knee OR 3.0 (1.1 to 8.9) p = 0.03, lateral tibia OR 1.9 (1.0 to 3.8) p = 0.04 | + Higher KL grades had greater increase in bone area, | High (71) |
| Neogi 2013    | MRI 3D bone shape (tibia, femur and patella) (C) | Incident TFJ ROA KL grade ≥2 (L) | Age, sex, BMI | OR 3.0, 95% CI 1.8 to 5.0 | + Developing 3D OA knee shape is associated with increasing ROA knee | High (65) |
| Hunter 2013   | Change in MRI knee bone area over 24 months (L) | Incident TFJ ROA (KL grade ≥2) (L) | Nil | NR | + for all bone regions Enlarging bone area associated with increasing ROA knee | Low (59) |
| Wluka 2005    | Change in MRI tibial bone area (L) | Baseline radiographic JSN (C) | Age, BMI, pain, physical activity | Medial tibial bone area R = 160, 95% CI 120 to 201, p < 0.0001, lateral tibia R = 145, 95% CI 103 to 186, p < 0.0001 | + | Low (47) |
| Kotharii 2010 | Semi-quantitative baseline MRI bone cyst (WORMS) (C) TFJ | Semi-quantitative cartilage defect score change over 2 years (WORMS) (L) TFJ. | Age, sex BMI, other bone lesions | OR 1.66, 95% CI 0.55 to 4.99, OR 0.47, 95% CI 0.11 to 2.03 | NA | Low (50) |
| Tanamas 2010  | Semi-quantitative change in MRI bone cyst size (L) | Knee Cartilage volume loss over 2 years (L) TFJ | Nil | NR | + | Low (47) |
### Table 1 Knee structural associations by feature and quality grade (Continued)

| Study                  | Feature and Quality Description                                                                 | Baseline MRI semi-quantitative bone cyst (C) | OARSI medial TFJ JSN grade progression over 2 years (L) TFJ | Age, sex, BMI and family effect | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (47) |
|------------------------|------------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------|--------------------------------|--------------------------------|----|----------|
| Madan-Sharma 2008 [93] | Baseline MRI semi-quantitative bone cyst (C) TFJ                                           | OARSI medial TFJ JSN grade progression over 2 years (L) TFJ | Age, sex, BMI and family effect | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (47) |
| Carrino 2006 [77]      | Crude presence of MRI bone cyst TFJ (C) and (L)                                           | Any grade of cartilage defect TFJ (C) and (L) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (22) |
| MRI bone cyst — cross-sectional studies |                                                                                          | Semi-quantitative cartilage (WORMS) TFJ and PFJ (C) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (22) |
| Stehling 2010 [65]     | Presence of any MRI semi-quantitative cyst (C)                                           | Presence of any WORMS MRI cartilage defects (C) | Age, gender and BMI, KL score, knee injury or knee surgery, family history of TKR and Heberden's nodes | Beta = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Torres 2006 [103]      | MRI bone cyst (WORMS) TFJ and PFJ (C)                                                     | Semi-quantitative cartilage (WORMS) TFJ and PFJ (C) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Hayes 2005 [22]        | Semi-quantitative MRI bone cyst (C)                                                        | KL grade (C)                                 | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Link 2003 [101]        | Crude presence of MRI bone cyst (C)                                                        | KL grade (C)                                 | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Crema 2010 [122]       | MRI Bone cysts (WORMS) (C)                                                                | Cartilage defect (WORMS) (C)                 | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| CT bone cyst — cross-sectional studies |                                                                                          | Semi-quantitative cartilage (WORMS) TFJ and PFJ (C) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Okazaki 2014 [40]      | Number of CT bone cysts (medial femur and tibia) (C)                                       | Knee KL grade (C)                           | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| MRI subchondral bone morphometry - cohort studies |                                                                                          | MRI BVF, trabecular number, thickness and spacing (C) | OARSI medial TFJ JSN progression between 24 and 48 months (L) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Lo 2012 Abstract [53]  | MRI BVF, trabecular number, thickness and spacing (C)                                       | OARSI medial TFJ JSN progression between 24 and 48 months (L) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| MRI subchondral bone morphometry - cross-sectional studies |                                                                                          | MRI bone volume fraction, trabecular number, spacing & thickness of medial tibia (C) | The presence of any grade of radiographic medial & lateral JSN (C) | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |
| Driban 2011 [49]       | MRI bone volume fraction (C)                                                               | Radiographic JSN (C)                         | Nil  | β = −11.81 (−16.64 to −6.98) | RR 1.6, 95 % CI 0.5 to 4.0 | NA | Low (71) |

Note: BVF, trabecular number and thickness are positively associated with JSN progression but negatively associated with trabecular spacing.
| Study | BMD variable | BMD measurement | JSN variable | Age, sex, BMI | p-value | OR (CI) | Notes |
|-------|--------------|-----------------|-------------|-------------|---------|--------|-------|
| Lindsey 2004 [123] | MRI bone volume fraction, trabecular and trabecular number (TFJ) | Cartilage volume of tibia or femur in contralateral TFJ compartment (C) | Nil | Medical TFJ cartilage with lateral TFJ BVF and trabecular number. $\beta = 0.29$ to $0.36$, $p = 0.0020$ to $0.02$ | Nil | NR | + With contralateral BVF and trabecular number, but – with trabecular spacing |
| Lo 2012 [54] | MRI bone volume fraction, trabecular thickness, number, spacing and DXA BMD of (proximal medial tibia) | Radiographic medial JSN grade (C) | Nil | All $p < 0.0001$ | Nil | NR | + (BV/TV, thickness, number, BMD) (spacing) |
| Chiba 2012 [34] | MRI bone volume fraction and trabecular thickness of the medial & lateral femur & tibia. | Metric JSW (radiographic) of the medial and lateral TFJ (C) | Nil | Bone volume fraction $-0.48$ ($p < 0.001$) trabecular thickness $-0.51$ ($p < 0.001$) | Nil | NR | - |
| Dore 2010 [68] | Baseline proximal tibial BMD, DXA | Increase or no increase in semi-quantitative MRI tibial cartilage defects over 2.7 years (L) | Age, sex, BMI, baseline cartilage defects and subchondral tibial bone area | NR | OR (95 % CI) medial tibia 1.6 (1.2 to 2.1) $p < 0.01$ lateral tibia 1.2 (0.9, 1.6) $p = 0.19$ | + Association only observed in medial tibia |
| Lo 2012 Abstract [53] | DXA-measured medial/lateral periarticular BMD (paBMD) | OARSI medial TFJ JSN progression (L) | Nil | OR 8.4, 95 % CI 2.8 to 25.0, $p < 0.0001$ | nil | OR | + JSN association with baseline M.L paBMD |
| Bruyere 2003 [42] | Subchondral tibial bone BMD (DXA) | Minimum medial JSW TFJ after one year (L) | Age, sex, BMI, minimum JSW | NR | $R = -0.43$, $p = 0.02$ | Negative correlation i.e., lower BMD gives bigger JSW or less JSN |
| Dore 2009 [52] | DXA tibial subchondral BMD | Radiograph JSN grade and MRI cartilage defect and volume (C) | Age, sex BMI | NR | Medial tibial BMD vs JSN $R = 0.11$, $p < 0.01$, defect $R = 0.16$, $p < 0.01$, cartilage volume $R = 0.12$, $p = 0.01$ | + Higher the BMD the greater the JSN and cartilage defects, |
| Lo 2006 [55] | DXA medial/lateral BMD ratio at the tibial plateau (C) | Radiographic JSN grade (medial and lateral TFJ) (C) | Age, sex, BMI | $p < 0.0001$ | NR | OR | + With medial JSN, – with lateral JSN |
| Lo 2012 [54] | DXA BMD (proximal medial tibia) | Radiographic medial JSN grade (C) | Nil | $p < 0.0001$ | NR | + |
| Akamatsu 2014 [31] Abstract | BMD (DXA) (C) (medial tibia and femoral condyle) | Medical TFJ JSN (radiographic) (C) | Nil | Tibia $R = 0.571$, $p < 0.001$ femur $R = 0.550$, $p < 0.001$ | NR | OR | + Medial femoral and tibial condyle BMD correlated with medial JSN |
| Volumetric CT BMD - case control studies | | | | | | | |
| Bennell 2008 [56] | KL grade (C) | Age, sex, BMI | NR | $p < 0.05$ | NC BMD falls in posterior tibial | Low (59) |
### Table 1 Knee structural associations by feature and quality grade (Continued)

| Feature                                      | Association                                                                 | p-value | Grade |
|----------------------------------------------|-----------------------------------------------------------------------------|---------|-------|
| Volumetric BMD in tibial subchondral bone    | Coefficient 0.26 to 0.29 (p = 0.0005 to 0.001)                              | +       | High  |
| Progression of minimum JSN of the medial TFJ from baseline to 30 months (L) | Age, BMI, KL grade (NB all women)                                           | r = 0.22 to 0.30 (p < 0.05) | r = 0 to 0.08 (p < 0.05) | NA after adjustment for covariates | High (56) |
| Baseline JSW, treatment group                  | Nil                                                                         | p < 0.005 | NR    | +     | Low (50) |
| Progression of JSN by ≥2 mm or knee operation incidence after 5 years (L) | Nil                                                                         | p < 0.005 | NR    | +     | Low (50) |
| Ipsilateral OA scale of JSN (C)               | Coefficient 0.47 to 0.48 (p < 0.0001)                                      | +       | High  |
| Baseline late-phase subchondral bone scintigraphy (adjusted for healthy diaphysis uptake) of the medial tibia and whole knee (C) | Age, gender, BMI, osteophyte OARSI score, knee alignment knee symptoms | Coefficient 0.26 to 0.29 (p = 0.0005 to 0.001) | + | High (71) |
| Radiographic JSN presence (C)                | Nil                                                                         | p = 0.049 | NR    | +     | Low (50) |
| 1. Presence of diffuse cartilage defects semi-quantitative scoring (MRI). 2. Presence of ROA knee (KL ≥2) (C) | OR 1.94 (1.44 to 2.62) p < 0.001                                           | + Wider bones and elevated tibial plateau were associated with the presence of ROA knee. Cartilage defects were only associated with bone width | OR (95 % CI) knee ROA 1.94 (1.44 to 2.62) p < 0.001 | + Wider bones and elevated tibial plateau were associated with the presence of ROA knee. Cartilage defects were only associated with bone width | Low (46) |

Positive correlation reported between bone feature and outcome measure (+); negative correlation reported between bone feature and outcome measure (−). BMD bone mineral density, BMI body mass index, BML bone marrow lesion, BOKS Boston osteoarthritis of the knee study, BOKS Boston–Leeds osteoarthritis knee score, BVF bone volume fraction, C a feature or outcome described in cross-section, CT computed tomography, DXA dual-energy x-ray absorptiometry, GARP Genetics, osteoarthritis and progression study, JSN joint space narrowing, JSW joint space width, KL Kellgren-Lawrence, ROSS knee osteoarthritis scoring system, L a feature or outcome described longitudinally, MAK-2 mechanical factors in arthritis of the knee, NC no conclusion could be found for an association between bone feature and outcome measure, SWAN Michigan study of women’s health across the nation, MOST multicentre osteoarthritis study, MRI magnetic resonance imaging, NA no association, NR not reported, OA osteoarthritis, OAI Osteoarthritis Initiative, OR odds ratio, RR relative risk ratio, SSR subchondral surface ratio TASSOC Tasmanian older adult cohort, TFJ tibiofemoral joint, VAS visual analogue scale, WORMS whole-organ magnetic resonance imaging score, CRP C-reactive protein, TKR total knee replacement, OARSI Osteoarthritis Research Society International, PFJ patellofemoral joint, ROA radiographic osteoarthritis
Bone marrow lesions
MRI (31 cohort, 15 cross-sectional, 4 case–control studies): in prospective cohorts with high-quality, well-adjusted analyses the presence and increasing size of baseline BMLs and incidence of BMLs conferred greater odds of structural progression [67, 70–73]. Similarly increasing baseline BML size increased the risk of total knee replacement (TKR) and expedited the outcome of TKR [44, 74–76]. The association between BMLs and structural progression of OA was maintained in cohorts without clinical features of knee OA [67] and in analyses with poorer quality or statistical adjustment [25, 28, 76–90]. Only five low quality cohort analyses did not support these findings [91–95]. All cross-sectional analyses found positive correlation between BMLs and structural severity of OA [22, 29, 35, 63–65, 87, 96–103]. Three case–control analyses found similar associations [17, 104, 105]. In summary, BMLs are independently associated with structural progression of OA of the knee and incident TKR.

Osteophytes
MRI (three cohorts, eight cross-sectional studies): in one prospective cohort with high quality and well-adjusted analysis, the increasing size of osteophytes conferred greater odds of structural progression of OA [106]. In lower quality, inadequately adjusted, prospective cohorts, increasing osteophyte size increased the risk of incident TKR and structural progression of OA [28, 45]. The increasing size and presence of osteophytes was associated with greater structural progression or severity in all included analyses [22, 26, 28, 45, 64, 65, 97, 101, 103, 106–108]. In summary, osteophytes are independently associated with knee structural progression and are associated with TKR incidence.

Bone attrition
MRI (one cohort, two cross-sectional, one case–control study): one prospective, well-adjusted, but below-average-quality cohort analysis found an association with baseline attrition severity and structural progression that became insignificant after covariate adjustment [82]. The unadjusted cross-sectional analyses and case–control analysis found similar associations with structural severity [103, 109, 110]. In summary, bone attrition is associated, but not independently so, with structural progression.

Bone shape/dimension
MRI (eight cohort, seven cross-sectional, four case–control studies): in prospective cohorts with high quality well-adjusted analyses, greater baseline tibial plateau bone area conferred greater odds of structural progression of OA and incidence of TKR [18, 20, 111, 112]. The same association was observed in a lower quality, prospective-cohort, well-adjusted analysis [113] and in a study of the knee in patients who predominantly had no radiographic evidence of knee OA [18]. The mismatch ratio of the femoral and tibial OA [18]. The mismatch ratio of the femoral and tibial articulating areas was not associated with structural progression after adjustment [114], but the trochlear sulcus angle and shape was associated with cross-sectional patellofemoral structural severity demonstrated on MRI [115, 116]. All cross-sectional [23, 66, 107, 117] and case–control [118–121] analyses of tibial bone area or 3D knee bone shape found association with structural severity [23, 66, 107, 117–121]. In summary, tibial bone area is independently associated with structural progression of OA of the knee and incidence of TKR.

Bone cyst
MRI and CT (five cohort, five cross-sectional studies): two prospective cohorts with well-adjusted but below-average-quality analyses of cysts reported no association with structural progression of OA before or after adjustment [82, 93]. Two prospective cohorts with low quality unadjusted analyses of cysts found an association with structural progression of OA [77, 88]. Cross-sectional well-adjusted [65] and unadjusted [22, 40, 101, 122] cyst analyses found an association with structural severity. In summary, after covariate adjustment there is no independent association between cysts and structural progression of OA.

Trabecular bone morphometry
MRI (one cohort, five cross-sectional studies): one prospective cohort, unadjusted, below-average-quality analysis reported increasing bone volume fraction, trabecular number and thickness and decreasing trabecular spacing were associated with structural progression [53]. The same bone changes were associated with structural severity in cross-sectional unadjusted analyses [34, 49, 50, 54, 123]. In summary, increasing bone volume fraction, trabecular number, trabecular thickness, and decreasing trabecular spacing are associated with structural progression and severity of OA of the knee.

Peri-articular bone mineral density
DXA and CT (three cohort, four cross-sectional, one–case control study): two prospective cohorts with well-adjusted but below-average-quality analyses reported that increasing tibial subchondral BMD is associated with structural progression of OA [42, 68]. In one prospective cohort with an unadjusted below-average-quality analysis, the medial-to-lateral ratio of tibial peri-articular BMD was associated with structural progression [53]. All cross-sectional analyses [31, 52, 54, 55], including two that were well-adjusted [52, 55], reported increasing BMD with greater structural severity. One well-adjusted analysis using quantitative CT (qCT) reported higher and lower BMD in
the anterior and posterior tibial plateau, respectively, in knees of patients with moderate OA relative to asymptomatic controls. In summary, increasing peri-articular radiographic BMD is associated with structural progression and severity of OA.

### Scintigraphy

Scintigraphy (three cohort, two cross-sectional studies): prospective cohorts with high quality analyses found greater late-phase bone signal was associated with structural progression of OA, with no or inadequate covariate adjustment [37, 38], but not after adequate covariate adjustment [37]. A prospective cohort, with below-average-quality, unadjusted analysis found greater bone signal was associated with structural progression of OA [58]. Bone signal was associated with structural severity in well-adjusted and unadjusted cross-sectional analyses [59, 62]. In summary, bone scintigraphy signal is associated, but not independently so, with structural progression of OA.

### 2D Knee bone shape

One cross-sectional, well-adjusted analysis identified an association between greater femoral and tibial bone width and elevating tibial plateau, and greater structural severity [36]. In summary, 2D bone shape is associated with structural severity of OA.

### Relationship between knee bone feature and pain

The association between bone features and pain is described in Tables 2 and 5. In all types of study, bone features were compared with the presence, chronicity and severity of pain. In longitudinal studies, bone features were also compared with change in the presence or severity of pain (e.g., change in Western Ontario and McMaster Universities arthritis index (WOMAC) pain score). Change in the presence of pain included developing new frequent pain, [49], or the resolution of existing pain.

### Bone marrow lesions

MRI (9 cohort, 18 cross-sectional, 5 case–control studies): in 3 prospective cohort, well-adjusted, high quality analyses the baseline or longitudinal increase in size of BMLs was associated with longitudinally increasing knee WOMAC pain severity [21, 72, 124]. This association was observed in one [28] but not two [89, 95] similar prospective-cohort, unadjusted, lower quality analyses. Baseline BML size in the lateral but not the medial tibiofemoral joint was associated with incident frequent knee pain in a prospective-cohort, well-adjusted, high quality analysis [125]. Longitudinally increasing BML size was associated with incident frequent knee pain in a similar but inadequately adjusted analysis of below average quality [126]. In cross-sectional studies the size or presence of BMLs was inconsistently associated with the presence of a heterogenous range of pain measures, irrespective of adequate covariate adjustment [22, 29, 48, 96, 97, 99, 101, 103, 125, 127–135]. In summary, BMLs are independently associated with longitudinally increasing pain severity and are associated with incident frequent knee pain.

### Osteophytes

MRI (one cohort, eight cross-sectional, one case–control study): one prospective cohort, unadjusted, below-average-quality analysis reported increasing baseline osteophyte size was associated with increasing WOMAC pain severity score [28]. In well-adjusted cross-sectional analyses, osteophyte size was associated with the presence [130] but not severity of pain [136]. In unadjusted cross-sectional analyses osteophytes were inconsistently associated with a heterogenous range of pain measures [22, 97, 101, 103, 127, 137]. In summary, osteophytes are associated with longitudinally increasing pain severity and the cross-sectional presence of pain.

### Bone attrition

MRI (no cohort, two cross-sectional, one case–control study): cross-sectional analyses found greater attrition was associated with greater pain severity, without covariate adjustment [103, 138], but not after adequate covariate adjustment [138]. An unadjusted case–control analysis found an association between attrition and prevalent pain [139]. In summary, bone attrition is associated, but not independently so, with severity of pain.

### Bone shape/dimension

MRI (one cohort, one cross-sectional study): one prospective, well-adjusted, high quality analysis found the femorotibial articulating surface mismatch was associated with incident frequent knee pain [114]. One unadjusted cross-sectional analysis found the irregularity of the femoral condyle surface was associated with severity of knee pain [47]. In summary, specific features of bone shape are independently associated with incident frequent knee pain and severity of pain.

### Bone cyst

MRI (one cohort, five cross-sectional, two case–control studies): one prospective cohort, unadjusted, low quality analysis found no association between bone cyst size and increasing WOMAC pain score [28]. In mostly unadjusted cross-sectional [22, 101, 103, 130, 137] and case control analyses [139, 140] of heterogenous cyst measures and pain measures, an association between cysts and pain was inconsistently found. In summary, bone cysts may not be associated with longitudinal severity of pain and cross-sectional association with pain is uncertain.
| Author | Feature (method) | Knee pain outcome | Adjustment for confounders | Association (magnitude) crude | Association (magnitude) adjusted | Association | Quality score (%) |
|--------|------------------|-------------------|---------------------------|-------------------------------|--------------------------------|-------------|-------------------|
| MRI bone marrow lesion - cohort studies |
| Foong 2014 [21] | Change in BML size (L) and incident BMLs (L) in all three knee compartments | WOMAC Knee pain severity at 2-year and 10-year visits (L) | Age, sex, BMI leg strength, and the presence of ROA | Incident or change in total BML size $\beta = 1.53$ (95% CI 0.37 to 2.70). | Medial tibial change in BML size $\beta = 2.96$ (95% CI 0.59-5.34) | + | High (67) |
| Driban 2013 [72] | Knee baseline BML volume (C), BML volume change (L) (TFJ) | 48-month change in WOMAC pain (L) | Age, sex, BMI | $\beta = 0.21$ (standard error 0.07) $p = 0.004$ | Unused | Longitudinal (L) changes in BML correlated with (L) changes in pain severity | High (61) |
| Dore 2010 [124] | MRI BML size (L) regional or whole TFJ over 2.7 years | Change in WOMAC pain (L) over 2.7 years | Age, sex, BMI, quality of life, and baseline pain, function | $\beta$ (95% CI) Total BML size change = 1.06 (0.10 to 2.03) | $\beta$ (95% CI) total BML size change = 1.13 (0.28 to 1.98) | + | High (56) |
| Kornaat 2007 [173] | Semi-quantitative MRI BML change over 2 years (L) TFJ | Mean WOMAC pain over 2 years | Age, sex and BMI | $\beta$ (95% CI) = 2 (−8 to 11) | NA | NA | High (56) |
| Moisio 2009 [125] | Baseline MRI semi-quantitative BML score (C) TFJ and PFJ | Incident frequent knee pain 2 years after baseline (L) | Age, sex, BML score, % denuded bone | OR (95% CI) medial tibia and femur 1.41 (0.86 to 2.33), lateral tibia and femur 1.70 (1.07 to 2.69) | + Lateral TFJ BML score associated with incident frequent knee pain | High (56) |
| Sowers 2011 [28] | Semi-quantitative MRI BML size in TFJ (C) | Increasing WOMAC pain (L) | Nil | Medial and lateral TFJ BMLs both $p < 0.005$ | NR | + | Low (53) |
| Zhang 2011 [126] | Semi-quantitative change in MRI BML size (L) TFJ over 30 months | Incidence of frequent knee pain, and categorical severity (L) over 30 months | Synovitis and effusions | OR (95% CI) Severity of frequent knee pain OR 3.0 (1.2 to 6.0) | OR (95% CI) Incident frequent knee pain $p$ for trend = 0.005. Severity of frequent knee pain OR 2.2 (1.0 to 4.7) $p = 0.047$ | + Ipsilateral association | Low (50) |
| Wildi 2010 [95] | 24-month change in regional TFJ BML score WORMS (L) | 24-month change in WOMAC pain (L) | Nil | $R < 0.15$, $p > 0.067$ for all compartments | NR | NA, all compartments had no correlation | Low (50) |
| Tanamas 2010 [89] | Baseline semi-quantitative MRI BML size (C) | Annual change in WOMAC pain (L) | Nil | NR | NR | NA | Low (50) |
| MRI bone marrow lesion - cross-sectional studies |
| Zhai 2006 [135] | Semi-quantitative MRI BML (C) | WOMAC pain >1 (C) | Age, BML, sex, knee strength, chondral defects | OR 1.44, 95% CI 1.04, 2.00 | + | High (79) |
| Sharma 2014 [133] | Semi-quantitative BML score WORMS TFJ or PFJ (C) | Prevalent frequent knee symptoms (C) | Age, sex, body mass index (BMI), previous knee injury, and previous knee surgery | OR 1.96, 95% CI 1.38 to 2.77 | + BML association with prevalent knee symptoms | High (71) |
| Study | MRI Method | Feature | Quality Score | OR (95% CI) | p Value | Follow-up |
|-------|------------|---------|---------------|-------------|---------|-----------|
| Kornaat 2006 [130] | Semi-quantitative MRI BML (C) | Chronic pain presence (C) | Age, sex, and BMI | NR | OR 1.13, 95% CI 0.41, 3.11, p = 0.76 | NA | High (71) |
| Lo 2009 [131] | Semi-quantitative MRI BML (BLOKS) (C) | WOMAC pain (C) | Synovitis, effusion scores | p for trend = 0.0009 | p for trend = 0.006 | + | High (71) |
| Stefanik 2014 abstract [134] | BML (WORMS) (C) (patellofemoral joint) | Prevalent knee pain (any pain in last 30 days) and pain VAS (C) | Adjusted for age, sex, BMI, depressive symptoms and TFJ BMLs | NR | Isolated BML of the lateral PFJ, OR (95% CI) 1.4 (0.9 to 2.0), medial PFJ, OR (95% CI) 1.1 (0.8 to 1.5). Isolated lateral PFJ BMLs OR 6.6 (1.7 to 11.5) | NC | High (71) |
| Ratzlaff 2013 [132] | Total BML volume in the femur or tibia (C) | Weight-bearing knee pain WOMAC subscale (C) | Age, sex, BMI, race, and medial minimum joint space width | NR | Total BML volume femur p = 0.003, tibia p = 0.101 | + Femoral NA Tibial | High (71) |
| Ip 2011 [99] | Semi-quantitative MRI BML (C) | WOMAC pain (C) | Age, sex, BMI, OA stage, joint effusion, and meniscal damage | NR | Total WOMAC pain R = 0.05, 95% CI −0.04 to 0.14. Stair climbing pain R = 0.09 (0.00 to 0.18) | NC | High (68) |
| Torres 2006 [103] | MRI BML (WORMS) TFJ and PFJ (C) | Pain VAS (C) | Age, BMI | Coefficient 5.00, 95% CI 3.00 to 7.00 | Coefficient 3.72, 95% CI 1.76 to 5.68 | + | High (68) |
| Kim 2013 [129] | Summary score and severity of MRI BML (WORMS) (C) | WOMAC pain severity or presence of knee pain (C) | Age, sex, BMI, radiographic OA | NR | BML summary score medial TFJ OR 2.33, 95% CI 1.02 to 5.33, p <0.001 | + Severity of BML is proportional to WOMAC in medial compartment after adjustment | High (64) |
| Moisio 2009 [125] | Baseline MRI semi-quantitative BML score (C) TFJ and PFJ | Presence of baseline moderate to severe knee pain (C) | Percent denuded bone, age, sex, BMI | NR | Bone marrow lesion score, OR 0.95, 95% CI 0.63 to 1.44. Not significant in all compartments | NA found on cross-sectional analysis | High (64) |
| Ratzlaff 2014 [48] Abstract | Median BML volume (PFJ, TFJ) (C) | Stair-climbing knee pain WOMAC (C) | Nil | TFJ p = 0.01, patellofemoral p = 0.01, femur p = 0.02, tibia p = 0.03 | NR | + | High (64) |
| Hayes 2005 [22] | Semi-quantitative MRI BML (C) | Chronic pain presence (C) | Nil | p = 0.001 | NR | + | High (61) |
| Ai 2010 [127] | Semi-quantitative MRI BML (C) | Pain verbal rating scale (Likert) (C) | Nil | p = 0.33 | NR | NA | Low (57) |
| Bilgici 2010 [128] | MRI BML (WORMS) (C) | WOMAC pain, pain VAS (C) | Nil | WOMAC r = 0.508, p <0.01 Pain VAS r = 0.488, p <0.01 | NR | + | Low (57) |
| Sowers 2003 [29] | Semi-quantitative MRI BML (C) | Chronic pain presence (C) | Nil | OR 5.0, 95% CI 2.4 to 10.5 | NR | + | Low (54) |
| Link 2003 [101] | Semi-quantitative MRI BML (C) | WOMAC pain (C) | Nil | p >0.05 | NR | NA | Low (54) |
| Felson 2001 [96] | Semi-quantitative MRI BML (C) | Chronic pain presence (C) | Nil | p <0.001 | OR 3.31, 95% CI 1.54 to 7.41 | + | Low (54) |
| Study                      | Feature Description                                                                 | Chronic Pain Measure | Radiographic and Other Measures                                                                 | P-value or OR | Confidence Interval | Quality Score |
|----------------------------|-------------------------------------------------------------------------------------|----------------------|--------------------------------------------------------------------------------------------------|---------------|---------------------|---------------|
| Fernandez-Madrid 1994 [97]| Semi-quantitative MRI BML size (C)                                                  | Nil                  | Radiographic severity, age, sex, and effusion score                                              | Nil           | [2.8, 95% CI 1.2 to 6.5] | Low (46)      |
| Javaid 2010 [140]          | Baseline semi-quantitative MRI BML size (WORMS) (C) TFJ and PFJ                     | Incident frequent knee pain after 15 months (L)         | Age, sex, race, BMI                                                                             | Nil           | OR 2.8, 95% CI 1.2 to 6.5 | High (76)     |
| Felson 2007 [181]          | Semi-quantitative MRI osteophyte, size (WORMS) (L) TFJ and PFJ                     | Incident frequent knee pain at 15 months (L)            | Age, sex, race, BMI, quadriceps strength, KL score, malalignment, baseline BML score            | Nil           | OR 4.1, 95% CI 2.1 to 8.1 | High (71)     |
| Javaid 2012 [139]          | Baseline Semi-quantitative MRI osteophyte, size (WORMS) (C) TFJ and PFJ            | Presence of frequent knee pain (C) after 2 years         | Nil                                                                                             | Nil           | OR 1.70, 95% CI 1.08 to | Low (59)      |
| Zhao 2010 [105]            | Baseline crude presence of MRI BMLs at (C) TFJ                                     | Change in WOMAC Pain (L)                                 | Nil                                                                                             | Nil           | p = 0.60             | Low (56)      |
| Stahl 2011 [41]            | Semi-quantitative MRI osteophyte (WORMS) (L) TFJ                                 | Changes in WOMAC score (L)                               | Nil                                                                                             | Nil           | Data not shown        | Low (47)      |
| Sowers 2011 [28]           | Semi-quantitative MRI osteophyte, size in TFJ (C)                                  | Increasing WOMAC pain (L)                                | Nil                                                                                             | Nil           | Medial and lateral TFJ BMLs both p <0.001 | Low (53)      |
| Kornaat 2006 [130]         | Semi-quantitative MRI osteophyte (C)                                               | Chronic pain presence (C)                                | Nil                                                                                             | Nil           | Patellofemoral OR 2.25, 95% CI 1.06 to 4.77 | High (71)     |
| Sengupta 2006 [136]        | Semi-quantitative MRI osteophyte (WORMS) (C)                                      | Pain severity WOMAC, chronic pain (C)                    | Nil                                                                                             | Nil           | OR 0.97, 95% CI 0.86 to 1.10 | NA            |
| Torres 2006 [103]          | MRI osteophyte, (WORMS) TFJ and PFJ (C)                                            | Pain VAS (C)                                               | Nil                                                                                             | Nil           | Coefficient 1.18, 95% CI 0.63 to 1.72 | High (68)     |
| Hayes 2005 [22]            | Semi-quantitative MRI osteophyte (C)                                               | Chronic pain presence (C)                                | Nil                                                                                             | p <0.001      |                            | High (61)     |
| Ai 2010 [127]              | Semi-quantitative MRI osteophytes (C)                                              | Pain verbal rating scale (Likert) (C)                    | Nil                                                                                             | p = 0.166     |                            | Low (57)      |
| Hayashi 2012 [137]         | Crude presence of MRI osteophytes (C)                                              | Nil                                                        | OR 4.2 to 6.4, p = 0.001-0.011                                                                   | Nil           |                            | Low (57)      |
| Study                          | Feature & Quality Score                          | Association | p Value | CI      | Score |
|-------------------------------|------------------------------------------------|-------------|---------|---------|-------|
| Link 2003 [101]               | Semi-quantitative MRI osteophytes (C)           | WOMAC pain (C) Nil | p >0.05 | NR     | NA    | Low (54) |
| Fernandez-Madrid 1994 [97]    | Crude presence of MRI osteophytes (C)           | Crude pain presence (C) Nil | NR | NR | NA | Low (46) |
| MRI osteophyte - case-control studies |                                    | Whole knee severe osteophyte OR 4.7, 95 % CI 1.3 to 18 | + | High (76) |
| Javaid 2010 [140]             | Baseline semi-quantitative MRI osteophyte, size (WORMS) (C) TFJ and PFJ Incident frequent knee pain after 15 months (L) | Age, sex, race, BMI NR | OR (95 % CI) pain severity OR 1.6 (1.1 to 2.3), nocturnal pain OR 1.1 (0.5 to 2.1). | OR (95 % CI) pain severity OR 0.9 (0.6 to 1.4), nocturnal pain OR 1.0 (0.5 to 2.1). | NA | High (71) |
| MRI bone attrition - cross-sectional studies |                                    | Pain severity and nocturnal pain (WOMAC) (C) | Age, sex, BMI, BMLs, effusions and KL grade | COEFFICIENT 3.33, 95 % CI 1.79 to 4.87 | COEFFICIENT 1.91, 95 % CI 0.68 to 3.13 | + | High (68) |
| Hernandez-Molina 2008 [138]   | Semi-quantitative MRI bone attrition (WORMS) (C) Presence of frequent knee pain (C) after 2 years | Pain VAS (C) Nil | OR 2.40, 95 % CI 1.51 to 3.83 | OR 0.9 (0.6 to 1.4), nocturnal pain OR 1.0 (0.5 to 2.1). | NR | + | Low (59) |
| Torres 2006 [103]             | MRI attrition, (WORMS) TFJ and PFJ (C)          | Pain VAS (C) Nil | Coefficient 3.33, 95 % CI 1.79 to 4.87 | OR (95 % CI) pain severity OR 1.6 (1.1 to 2.3), nocturnal pain OR 1.1 (0.5 to 2.1). | OR (95 % CI) pain severity OR 0.9 (0.6 to 1.4), nocturnal pain OR 1.0 (0.5 to 2.1). | NA | High (71) |
| MRI bone attrition - case-control studies |                                    | Pain VAS (C) Nil | Coefficient 3.33, 95 % CI 1.79 to 4.87 | OR (95 % CI) pain severity OR 1.6 (1.1 to 2.3), nocturnal pain OR 1.1 (0.5 to 2.1). | OR (95 % CI) pain severity OR 0.9 (0.6 to 1.4), nocturnal pain OR 1.0 (0.5 to 2.1). | NA | High (71) |
| Javaid 2012 [139]             | Baseline semi-quantitative MRI attrition size (WORMS) (C) TFJ and PFJ Incident frequent knee pain at 48 months (L) | Sex, race, age, BMI, tobacco use, activity level, knee coronal alignment, baseline symptoms, injury history, surgical history, KL grade, and JSW | OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | - larger SSR gets less incident frequent knee pain | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | - larger SSR gets less incident frequent knee pain | High (61) |
| MRI bone shape/dimension - cohort studies |                                    | Knee pain VAS (C) Nil | Irregularity of femoral condyle contour r = 0.472, p = 0.0021 | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | + | Low (50) |
| MRI bone shape/dimension - cross-sectional studies |                                    | Knee pain VAS (C) Nil | Irregularity of femoral condyle contour r = 0.472, p = 0.0021 | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | + | Low (50) |
| Ochiai 2010 [47]              | MRI irregularity of femoral condyle contour (C)  | Knee pain VAS (C) Nil | Irregularity of femoral condyle contour r = 0.472, p = 0.0021 | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | + | Low (50) |
| MRI bone cyst - cohort studies |                                    | Knee pain VAS (C) Nil | Irregularity of femoral condyle contour r = 0.472, p = 0.0021 | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | + | Low (50) |
| Sowers 2011 [28]              | Semi-quantitative MRI bone cyst size in TFJ (C)  | Increasing WOMAC pain (L) Nil | NR | NR | NA | Low (53) |
| MRI bone cyst - cross-sectional studies |                                    | Knee pain VAS (C) Nil | Irregularity of femoral condyle contour r = 0.472, p = 0.0021 | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | Medial SSR OR 0.48, 95 % CI 0.30 to 0.75, p = 0.0009. | + | Low (50) |
| Study Year | Study Design | Bone Feature | Outcome Feature | Association | Association Type | Source Strength |
|------------|--------------|--------------|-----------------|-------------|-----------------|----------------|
| 2006       | MRI bone cyst (C) | Chronic pain presence (C) | Nil | NR | Patellofemoral OR 1.83, 95% CI (0.80 to 4.16) | High (71) |
| 2006       | MRI bone cyst (WORMS) TFJ and PFJ (C) | Pain VAS (C) | Age, BMI | Coefficient 2.50, 95% CI 0.38 to 5.38 | Coefficient 0.82, 95% CI 0.50 to 2.14 | NA |
| 2005       | Semi-quantitative MRI bone cyst (C) | Chronic pain presence (C) | Age, sex, and BMI | p < 0.001 | NR | + |
| 2012       | Crude presence of MRI bone cysts (C) | Presence of pain on WOMAC pain subscale (C) | Nil | OR 6.7 to 17.8, p = 0.004 to 0.03 | NR | + |
| 2003       | Crude presence of MRI bone cyst (C) | WOMAC pain (C) | Nil | p > 0.05 | NR | NA |
| 2010       | Baseline semi-quantitative MRI bone cyst size (WORMS) (C) TFJ and PFJ | Incident frequent knee pain after 15 months (L) | Nil | NR | NR p > 0.1 | NA |
| 2012       | Baseline semi-quantitative MRI bone cyst size (WORMS) (C) TFJ and PFJ | Presence of frequent knee pain (C) after 2 years | Nil | OR 1.61, 95% CI 1.03 to 2.52 | NR | + |
| 2012       | BMD of patellar lateral facet (qCT) (C) | WOMAC – knee pain at rest (C) | Nil | Total lateral patella facet p = 0.04, inferior lateral facet p = 0.005 | NR | Low (57) |

Positive correlation reported between bone feature and outcome measure (+); negative correlation reported between bone feature and outcome measure (−). BMI body mass index, BML bone marrow lesion, C a feature or outcome described in cross-section, knee pain on most days for at least the last month (chronic pain) confidence interval (CI), KL Kellgren-Lawrence, L a feature or outcome described longitudinally, NA no association, NC no conclusion could be found for an association between bone feature and outcome measure, NR not reported, OA osteoarthritis, OAI Osteoarthritis Initiative, OR odds ratio, PFJ patellofemoral joint, ROA radiographic osteoarthritis, SSR subchondral surface ratio VAS visual analogue scale, WOMAC Western Ontario and McMaster Universities arthritis index, qCT quantitative computed tomography.
**2D Knee bone shape**
One inadequately adjusted cross-sectional analysis found an association between the elevation of the lateral tibial plateau and severity of pain [36]. In summary, 2D lateral tibial bone shape is associated with cross-sectional severity of pain.

**Relationship between hand bone feature and structural progression**
The association between bone features and structural progression is described in Tables 3 and 5.

**Bone marrow lesions**
MRI (one case series, two cross-sectional studies): one well-adjusted, high quality analysis of a prospective OA case series, found that increasing BML number and size in the interphalangeal joints at baseline conferred greater odds of structural progression of OA [141]. Two adjusted cross-sectional analyses found increasing BML number and size scores were associated with increasing severity of structural progression [142, 143]. In summary, BMLs are independently associated with structural progression of hand OA.

**Osteophyte attrition and cysts**
One cross-sectional, adjusted analysis found greater MRI attrition or MRI osteophyte number and size was associated with greater structural severity [142]. However, greater presence of cysts observed on MRI was not associated with greater structural severity of OA [142]. In summary, osteophytes and attrition, but not cysts, are associated with structural severity of hand OA.

**Relationship between hand bone feature and pain**
The association between bone features and pain is described in Tables 4 and 5.

**Bone marrow lesions**
MRI (one case series, one cross-sectional study): one well-adjusted, high quality analysis of a prospective OA case series, found that increasing BML number and size at baseline was not associated with longitudinal change in hand pain [144]. One adjusted cross-sectional analysis found no association of BMLs with severity of pain [145]. In summary, BMLs are not independently associated with longitudinal or cross-sectional severity of pain.

**Osteophyte attrition and cysts**
One cross-sectional, adjusted analysis found no association between bone features, osteophytes, attrition or cysts observed on MRI, and pain severity [145]. In summary, osteophytes, attrition and cysts are not associated with severity of hand pain.

**2D and 3D hip bone shape**
Scintigraphy
Scintigraphy (one cross-sectional study): one cross-sectional unadjusted analysis found no significant association between bone signal in the hands and severity of pain. In summary, bone scintigraphy signal is not associated with severity of pain in hand OA.

**Peri-articular bone mineral density**
DXA (two cross-sectional studies): one well-adjusted [30] and one adjusted [32] cross-sectional analysis found greater BMD was associated with greater structural severity. In summary, BMD is associated with structural severity of hip OA.

**Relationship between hip bone feature and structural progression**
The association between bone features, and structural progression and joint replacement is described in Tables 3 and 5.

**Bone marrow lesions**
MRI (two cross-sectional studies): one well-adjusted [69] and one unadjusted [46] cross-sectional analysis both found that BMLs were associated with greater structural severity. In summary, BMLs are associated with structural severity of hip OA.

**Trabecular bone morphometry**
One unadjusted cross-sectional analysis found greater MRI bone volume fraction, trabecular thickening, trabecular number and lower trabecular spacing were associated with greater structural severity of OA [33]. In summary, bone volume fraction, trabecular thickening, number and spacing are associated with structural severity in hip OA.
| Author | Feature (method) | Structural severity or progression outcome | Adjustment for confounders | Association (magnitude) | Quality (score %) |
|--------|------------------|--------------------------------------------|-----------------------------|-------------------------|-----------------|
| **Hand MRI bone marrow lesion case series** | | | | | |
| Haugen 2014 [141] | BMLs - semi-quantitative at 2nd to 5th IPJs (C) | Progression of hand OA (JSN, KL grade or new erosion) (L) | Age, sex, BMI, | OR 2.73, 95 % CI 1.29 to 5.78 | High (61) |
| **Hand MRI bone marrow lesion cross-sectional studies** | | | | | |
| Haugen 2012 Abstract [143] 299 | BML (Oslo MRI hand score) (C) IPJs | Radiographic JSN grade IPJ (OARSI atlas) (C) | Age, sex, | OR 10.0, 95 % CI 4.2 to 23 | Low (43) |
| Haugen 2012 [142] | BML (Oslo MRI hand score) (C) IPJs | Hand KL grade of IPJs (C) | Age, sex | NR | High (64) |
| **Hand MRI osteophyte cross-sectional studies** | | | | | |
| Haugen 2012 [142] | Osteophyte (Oslo MRI hand score) (C) IPJs | Hand KL grade of IPJs (C) | Age, sex | NR | High (64) |
| **Hand MRI attrition cross-sectional studies** | | | | | |
| Haugen 2012 [142] | Attrition (Oslo MRI hand score) (C) IPJs | Hand KL grade of IPJs (C) | Age, sex | NR | High (64) |
| **Hand MRI bone cyst cross-sectional studies** | | | | | |
| Haugen 2012 [142] | Cyst (Oslo MRI hand score) (C) IPJs | Hand KL grade of IPJs (C) | Age, sex | NR | High (64) |
| **Hip MRI BML cross-sectional studies** | | | | | |
| Neumann 2007 [46] | Semi-quantitative BMLs (C) | Semi-quantitative cartilage lesions (C) | Nil | R = 0.44, p ≤0.001 | Low (43) |
| Dawson 2013 Abstract [69] | Femoral head BMLs (MRI) (C) | 1. Presence of hip OA. 2. Femoral head cartilage volume (MRI) (C) | Age, sex, BMI | NA | Low (14) |

Bigger the BML, the more the JSN

BML score association with more JSN

BMLs inversely associated with cartilage volume

Correlation between BML and cartilage lesions
| Study                                                                 | Measurement                                                                 | Methods                                                                 | Results                                                                 | Notes/Comments                                                                 |
|----------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| **Hip CT bone morphometry cross-sectional studies**                   |                                                                              |                                                                         |                                                                        |                                                                                |
| Chiba 2011 [33]                                                       | Acetabular and femoral head subchondral trabecular morphometry: bone volume  | Hip joint space volume (CT) (C)                                         | Femoral head Bone volume fraction r = −0.691, p < 0.001                | NR                                                                             |
|                                                                      | fraction, trabecular thickness, number, separation (CT) (C)                  |                                                                         |                                                                        |                                                                                |
|                                                                      |                                                                              |                                                                         |                                                                        | Joint space narrowing is associated with increased bone volume fraction, trabecular thickening, trabecular number and spacing decrease |
| **Hip DXA BMD cross-sectional studies**                               |                                                                              |                                                                         |                                                                        |                                                                                |
| Chaganti 2010 [30]                                                    | Femoral neck BMD (C) DXA                                                      | Hip ROA Modified Croft score (Categorical 0–4) (C)                      | Age, BMI, height, activity level, race, 6-m walk pace, Nottingham muscle strength, inability to do chair stands, and clinic site, | p < 0.0001                                      |
|                                                                      |                                                                              |                                                                         |                                                                        |                                                                                |
|                                                                      |                                                                              |                                                                         |                                                                        | + Higher BMD for higher grade of OA of hip                                   |
| Antoniades 2000 [32]                                                 | DXA BMD of the femoral neck of left (nondominant) hip with ROA (C)          | Radiographic OA (Croft score) (C)                                       | BMI, lifetime physical activity, menopausal status, use of oestrogen, and smoking | OR 1.63, 95% CI 1.06 to 2.50 (C)                                             |
|                                                                      |                                                                              |                                                                         |                                                                        | OR 1.80, 95% CI 1.05 to 3.12 (C)                                           |
|                                                                      |                                                                              |                                                                         |                                                                        | + Association between BMD and hip ROA grade in the index hip               |
|                                                                      |                                                                              |                                                                         |                                                                        | Higher OA grade means higher BMD                                            |
| **2D Hip bone shape longitudinal studies**                           |                                                                              |                                                                         |                                                                        |                                                                                |
| Agricola 2013 [146]                                                   | Baseline 2D femoral and acetabular shape modes (segmented by statistical shape modelling) | THR at or within 5 years (L)                                           | 5 modes were associated with THR OR 1.71 to 2.01, p ≤ 0.001           | 3 modes were associated with THR OR 1.78 to 2.10, p ≤ 0.001                   |
|                                                                      |                                                                              |                                                                         |                                                                        | + Increasing femoral head asphericity is associated with THR               |
| Agricola 2013 [147]                                                   | Baseline alpha angle (2D femur shape) dichotomous abnormal > 60°, normal ≤ 60° (C) | Incident ROA hip (KL > 1), incident end-stage ROA hip (KL > 2 or THR) at or within 5 years (L) | OR (95% CI) Incident ROA hip 6.82 (3.55 to 13.10) p < 0.0001          | OR (95% CI) incident ROA hip 2.42 (1.15 to 5.06) p = 0.02, incident severe ROA or THR 3.67 (1.68 to 8.01) p < 0.0001 |
|                                                                      |                                                                              |                                                                         |                                                                        | + Elevated alpha angle is associated with incident end-stage OA hip       |
| Agricola 2013 [148]                                                   | Baseline 2D centre edge angle (acetabular shape): 25° < normal < 40°, undercoverage < 25°, overcoverage > 40° (C) | Incidence within 5 years of: 1. ROA hip (KL > 1), 2. end-stage OA (KL > 2 or THR) | OR (95% CI) overcoverage 0.52 (0.19 to 1.43) p = 0.21, undercoverage 3.64 (1.91 to 6.99) p = 0.00 | OR (95% CI) overcoverage 0.34 (0.13 to 0.87) p = 0.025, undercoverage 5.45 (2.40 to 12.34) p = 0.00 |
|                                                                      |                                                                              |                                                                         |                                                                        | + Overcoverage is protective against OA incidence (−), Undercoverage is associated with greater odds of OA incidence and end-stage OA (+) |
| **2D and 3D hip bone shape cross-sectional studies**                 |                                                                              |                                                                         |                                                                        |                                                                                |
| Gosvig 2010 [149]                                                     | Categorical hip 2D deformity: 1. normal, 2. ’pistol grip’, 3) deep acetabular socket (C) | Presence of radiographic hip OA (JSW ≤ 2 mm) (C)                      | Age, sex, BMI, other hip deformities                                     | RR (95% CI) pistol grip 2.2 (1.7 to 2.8) p < 0.001, deep acetabular socket |
|                                                                      |                                                                              |                                                                         |                                                                        | +                                                                             |

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- **Table 3** Hand, hip and ankle structural associations by feature and quality grade (Continued)
### Table 3 Hand, hip and ankle structural associations by feature and quality grade (Continued)

| Study/Type                  | Measurement/Findings                                                                 | Features/OA/Clinical             | Unadjusted Difference with CAM (mm) (95% CI) | Adjusted Difference with CAM (mm) (95% CI) | Conclusion |
|-----------------------------|-------------------------------------------------------------------------------------|----------------------------------|---------------------------------------------|-------------------------------------------|------------|
| Reichenbach 2011 [27]       | Combined femoral and acetabular cartilage thickness                                 | Age, BMI (NB all participants were young men) | 2.4 (2.0 to 2.9) | p <0.001, normal (p >0.05) | NC         |
|                             | **Reichenbach 2011 [27]**                                                          |                                  |                                             |                                           |            |
|                             | The presence or absence of any 3D semi-quantitative MRI-defined cam-deformity (C)   |                                  |                                             |                                           |            |
| Doherty 2008 [43]           | Presence of radiographic hip OA (JSW ≤2.5 mm) (C)                                  | Age, sex, BMI, BMD, physical activity, history of hip injury, type 3 hand (index finger shorter than ring finger), hand nodes, and center-edge angle | **OR (95% CI)** pistol grip deformity 5.75 (4.00 to 8.27). Femoral head-to-neck ratio 10.45 (7.16 to 15.24) |                                           | +          |
|                             | **Doherty 2008 [43]**                                                            |                                  |                                             |                                           | Low (53)   |
|                             | Non-spherical femoral head 2D shape assessment: 1. appearance of ‘pistol grip deformity’ (C), 2. maximum femoral head diameter ratio to minimum parallel femoral neck diameter (C) |                                  |                                             |                                           |            |
| Barr 2012 [150]             | 2D Shape measures of centre-edge angle (acetabular shape) (C)                      | Age, gender, BMI, KL grade, use of walking stick, WOMAC function, duration of pain | **OR (95% CI)** mode 2 0.74 (0.50 to 1.10) p >0.05 |                                           |           |
|                             | **Barr 2012 [150]**                                                             |                                  |                                             |                                           |            |
|                             | THR vs no radiographic progression over 5 years (L)                               |                                  |                                             |                                           |            |
| Nicholls 2011 [39]          | Total hip replacement (L)                                                         | BMI, age                         | **OR (p value)** Triangular index 1.131 (0.021). Alpha angle 1.056 (<0.0005). Centre edge angle 0.906 (0.004) |                                           | +          |
|                             | **Nicholls 2011 [39]**                                                           |                                  |                                             |                                           | High (71)  |
|                             | CAM deformity; mean modified triangular index height, alpha angle. 2D acetabular dysplasia; mean lateral center edge angle, (C) |                                  |                                             |                                           |            |
| Knupp 2009 [24]             | Late phase bone scintigraphy, semi-quantitative retention scoring of tibiotalar joint (C) | TIBIOTALAR ROA grade and JSN (C) | Nil 0.62 to 0.75 (p <0.01) |                                           | +          |
|                             | **Knupp 2009 [24]**                                                             |                                  |                                             |                                           | Low (57)   |
|                             | Ipsilateral late phase bone scintigraphy, retention presence in tibiotalar joint (C) | TIBIOTALAR ROA grade and JSN (C) | Nil 0.62 to 0.75 (p <0.01) |                                           | +          |
|                             | **Kraus 2013 [60]**                                                             |                                  |                                             |                                           |            |
|                             | Ipsilateral late phase bone scintigraphy, retention presence in tibiotalar joint (C) | TIBIOTALAR ROA grade and JSN (C) | Nil 0.62 to 0.75 (p <0.01) |                                           | +          |
|                             | **Kraus 2013 [60]**                                                             |                                  |                                             |                                           |            |
|                             | Ankle scintigraphic subchondral bone cross-sectional studies                      |                                  |                                             |                                           |            |
|                             | **Kraus 2013 [60]**                                                             |                                  |                                             |                                           |            |

**Positive correlation was reported between bone feature and outcome measure (+); negative correlation reported between bone feature and outcome measure (−).**

| Abbreviations | Definition                                                                 |
|---------------|----------------------------------------------------------------------------|
| BMD           | Bone mineral density                                                      |
| BML           | Bone marrow lesion                                                         |
| C             | A feature or outcome described in cross-section                           |
| CT            | Computed tomography                                                       |
| DXA           | Dual-energy x-ray absorptiometry                                           |
| HOAMS         | Hip Osteoarthritis MRI Scoring System                                      |
| IPJ           | Interphalangeal joint                                                     |
| KL            | Kellgren-Lawrence                                                         |
| L             | A feature or outcome described longitudinally                              |
| NA            | No association                                                             |
| NC            | No conclusion could be found for an association between bone feature and outcome measure |
| MRI           | Magnetic resonance imaging                                                |
| OA            | Osteoarthritis                                                             |
| OARSI         | Osteoarthritis Research Society International                             |
| OR            | Odds ratio                                                                 |
| RR            | Relative risk                                                              |
| TFJ           | Tibiofemoral joint                                                         |
| THR           | Total Hip Replacement                                                      |
| TKR           | Total Knee Replacement                                                     |
| VAS           | Visual Analogue Scale                                                      |
| WOMAC         | Western Ontario and McMaster Universities Arthritis Index                 |
| WORMS         | Whole-organ Magnetic Resonance Imaging Score                               |

Positive correlation was reported between bone feature and outcome measure (+); negative correlation reported between bone feature and outcome measure (−). BMD bone mineral density, BML bone marrow lesion, C a feature or outcome described in cross-section, CT computed tomography, DXA dual-energy x-ray absorptiometry, HOAMS Hip osteoarthritis MRI scoring system, IPJ interphalangeal joint, JSN joint space narrowing, JSW joint space width, KL Kellgren-Lawrence, L a feature or outcome described longitudinally, NA no association, NC no conclusion could be found for an association between bone feature and outcome measure, MRI magnetic resonance imaging, IPJ patellofemoral joint, ROA radiographic osteoarthritis, OA osteoarthritis, OARSI Osteoarthritis Research Society International, OR odds ratio, RR relative risk, TFJ tibiofemoral joint, THR total hip replacement, TKR total knee replacement, VAS visual analogue scale, WOMAC Western Ontario and McMaster Universities arthritis index, WORMS whole-organ magnetic resonance imaging score.
**Table 4** Hand and hip pain associations by feature and quality score

| Author | Feature (method) | Pain outcome | Adjustment for confounders | Association (magnitude) crude | Association (magnitude) adjusted | Association | Quality score (%) |
|--------|------------------|--------------|----------------------------|-------------------------------|---------------------------------|-------------|-------------------|
| Hand MRI bone marrow lesion case series | Haugen 2014 Abstract [144] | Sum scores (0–48) for BMLs (Oslo hand OA MRI score) (C) | AUSCAN pain scale (L) | Age, sex, BML, follow-up time | $\beta = -0.26$, 95 % CI $-0.55$ to $0.03$ | NA | High (61) |
| Hand MRI bone marrow lesion cross-sectional studies | Haugen 2012 [145] | BML (Oslo MRI hand score) (C) IPJs sum scores | AUSCAN pain scale (C) | Age, sex | OR (95 % CI) 0.96 (0.82 to 1.12) | NA | High (64) |
| Hand MRI osteophyte cross-sectional studies | Haugen 2012 [145] | Osteophyte (Oslo MRI hand score) (C) IPJs sum scores | AUSCAN pain scale (C) | Age, sex | OR (95 % CI) 1.04 (0.98 to 1.10) | NA | High (64) |
| Hand MRI attrition cross-sectional studies | Haugen 2012 [145] | Attrition (Oslo MRI hand score) (C) IPJs sum scores | AUSCAN pain scale (C) | Age, sex | OR (95 % CI) 1.15 (0.98 to 1.34) | NA | High (64) |
| Hand MRI subchondral cyst cross-sectional studies | Haugen 2012 [145] | Cyst (Oslo MRI hand score) (C) IPJs sum scores | AUSCAN pain scale (C) | Age, sex | OR (95 % CI) 0.93 (0.56 to 1.55) | NA | High (64) |
| Hand scintigraphy subchondral bone cross-sectional studies | Macfarlane 1993 [61] | Late phase isotope bone scan small joints of the hand (C) | Hand pain VAS (C) | Nil | Correlation coefficient $0.06$, $p = 0.304$ | NR | NA | Low (57) |
| Hip MRI bone marrow lesion cross-sectional studies | Kumar 2013 [151] | Total hip semi-quantitative BML score (C) | Self-reported hip pain HOOS score (C) | Nil | p correlation $-0.29$ ($p <0.01$) | A higher BML score means a lower or worse HOOS pain score | High (71) |
| | Maksymowych 2014 [152] | Semi-quantitative BML HIP (HOAMS) (C) | Baseline WOMAC pain (C) | Nil | $p <0.001$ | NR | + | High (64) |
| Hip MRI subchondral cyst cross-sectional studies | Kumar 2013 [151] | Total hip semi-quantitative subchondral cyst score (C) | Self-reported hip pain HOOS score (C) | Nil | p correlation $-0.37$ ($p <0.001$) | A higher cyst score means a lower or worse HOOS pain score | High (71) |

Positive correlation reported between bone feature and outcome measure (+); negative correlation reported between bone feature and outcome measure (−). AUSCAN Australian/Canadian Osteoarthritis hand index, BML bone marrow lesion, C a feature or outcome described in cross-section, chronic pain knee pain on most days for at least the last month, HOAMS Hip osteoarthritis MRI scoring system, HOOS Hip dysfunction and osteoarthritis outcome score, IPJ interphalangeal joint, L a feature or outcome described longitudinally, NA no association, NR not recorded, OA osteoarthritis, OR odds ratio, VAS visual analogue scale.
identified the same associations as the cohort analyses [39, 43, 150]. In summary, asphericity of the femoral head and acetabular undercoverage of the femoral head are independently associated with structural progression and THR.

**Relationship between hip bone feature and pain**
The association between bone features and pain is described in Tables 4 and 5.

**Bone marrow lesions**
MRI (two cross-sectional studies): two cross-sectional, unadjusted analyses found that increasing semi-quantitative BML scores were associated with greater severity of pain [151, 152]. In summary, BMLs are associated with severity of pain in hip OA.

**Bone cyst**
One cross-sectional, unadjusted analysis found that increasing semi-quantitative cyst scores on MRI were associated with greater severity of pain [151]. In summary: cysts are associated with severity of pain in hip OA.

**Relationship between ankle bone features and structural progression**
The association between bone features and structure is described in Table 3 and 5.

### Table 5: The summary subchondral bone associations with joint replacement, structural progression and pain in peripheral OA

| Subchondral bone feature of OA | Pain and structural associations | Knee and structural associations | Hand structure | Hand pain | Hip structure | Hip pain | Ankle structure |
|--------------------------------|---------------------------------|---------------------------------|----------------|----------|--------------|---------|----------------|
| MRI bone marrow lesions        | Progression (i) LPS (i)         | Progression (i) LPS (i)         | No LPS (w)     | No severity (n) | THR (i)     | IFP (i) | TKR (n) |
| MRI osteophytes                | Progression (i) LPS (n)         | Severity (n)                    | No severity (n) | No severity (n) | TKR (n)     | IFP (i) | TKR (n) |
| MRI bone attrition             | No progression (0)              | LPS (n)                         | Severity (n)   | No severity (n) | TKR (n)     | IFP (i) | TKR (n) |
| MRI bone shape or dimensions   | Progression (i) LPS (n)         | Severity (n)                    | No severity (n) | No severity (n) | TKR (n)     | IFP (i) | TKR (n) |
| MRI bone cyst                  | No progression (0)              | LPS (n)                         | Severity (n)   | No severity (n) | TKR (n)     | IFP (i) | TKR (n) |
| MRI or CT trabecular morphology| Progression (n)                 | Severity (n)                    |                |           |              |         |         |
| DXA or CT Peri-articular BMD   | Progression (n)                 | Severity (n)                    |                |           |              |         |         |
| 2D Bone shape                  | Severity (w)                    | Severity (n)                    | Progression (i) | THR (i) |              |         |         |
| Scintigraphy                   | No Progression (0)              | No severity (n)                 | Severity (w)   |           |              |         |         |

*CT* computed tomography, *DXA* dual-energy x-ray absorptiometry, (i) independent association, *IFP* incident frequent pain, (n) association with no or inadequate covariate adjustment, *TKR* total knee replacement, *THR* total hip replacement, *LPS* mean change in longitudinal pain severity, (w) well-adjusted association, (0) association insignificant after covariate adjustment.

**Scintigraphy**
Scintigraphy (two cross-sectional studies): one well-adjusted [59] and one unadjusted [62] cross-sectional analysis found the presence or semi-quantitative scoring of late-phase bone signal in the tibiotalar joint was associated with greater structural severity. In summary, bone scintigraphy signal is associated with ankle structural severity.

**Discussion**
This systematic review is the first to have incorporated quality scoring alongside statistical adjustment in the comprehensive examination of the relationship of subchondral bone pathology with both structural progression of OA and pain for all non-conventional types of radiographic imaging of peripheral joints with OA. This systematic review has concluded that there are independent associations between imaging-assessed bone pathology and structural progression and pain in the knee, hand, and hip.

Subchondral bone pathology may lead to cartilage degeneration by altering the biomechanical force distribution across joint cartilage, or disruption of the osteochondral junction and release of soluble biomediators influencing the cartilage [153, 154]. In OA the homeostatic process of subchondral bone remodeling fails, leading to increased bone turnover, volume and change in stiffness and shock-absorbing capacity [155–157]. BMLs histologically represent increased bone turnover [158]. Cartilage overlying
altered bone has been observed to have greater damage than healthy bone in knees from human cadavers [159]. That study, and an excluded study [160], concur with the independent association between BMLs, and structural progression of OA in knees and hands and total knee replacement, as concluded by this analysis. Although randomised control trials were not excluded from this review, several such trials were excluded on the basis of failure to formally quantify any correlation between BMLs and structural progression outcomes. These include the strontium [161], intensive weight-loss therapy [162] and glucosamine [163] trials, and some of these describe a concordant reduction in BML size and cartilage volume loss.

Osteophytes represent subchondral bone hypertrophy typical of OA. They represent endochondral and direct bone formation and create a circumferential increase in bone area around each knee cartilage plate, particularly on the medial side in OA [118], which concurs with the independent association between osteophytes demonstrated on MRI and structural progression as observed in this analysis.

In terms of bone morphology, knee OA is associated with shallow trochlear patellar grooves in multiple epiphyseal dysplasia [164]. These findings concur with the findings of Stefanik and Kalichman, and colleagues in studies of knee OA in this review [115, 116, 165]. Anterior cruciate ligament (ACL) rupture represents a risk factor for developing knee OA. In cases of ACL tear in previously normal knees of young healthy adults, the 3D shape of the femur, tibia and patella expands more rapidly than in controls without radiographic evidence of knee OA in the subsequent 5 years [166]. The 3D shape of the same knee bones has also been associated with the outcome of joint replacement [167]. This highlights the importance of bone shape and concurs with our conclusion that 3D knee shape and 2D hip shape are independently associated with structural progression of OA and total joint replacement.

We found that bone attrition and cysts were associated with structural progression or severity, but not after co-variate adjustment, which included other OA subchondral bone features. This suggests these bone features are an epiphenomenon of the pathogenic process of structural progression rather than a primary cause. This hypothesis is supported by bone cysts and attrition frequently occurring synchronously with BMLs [88, 138] and incident bone attrition has been strongly associated with the presence of BMLs within the same compartment [168].

Increasing bone volume fraction, trabecular number and thickness, but decreasing trabecular spacing on CT and MRI studies were associated with structural progression. These specific associations concur with numerous histological analyses of peripheral joint OA [169–171].

Subchondral bone, particularly BMLs, have been found to be associated with pain in knee, hip and hand OA. However, some analyses, in which pain was measured using heterogenous pain outcomes, report an absence of longitudinal or cross-sectional association with BMLs [101, 172, 173]. Furthermore, previous systematic reviews have concluded moderate association at the most between BMLs and knee pain [7, 14]. With the benefit of incorporating more well-adjusted analyses in this systematic review, we have highlighted that BMLs are independently longitudinally associated with change in severity of pain, but are only associated with incident frequent knee pain. In analyses excluded from the current review, incident knee BMLs predicted incident knee pain in healthy community-based adults at risk of OA [174]. Concurrent trends in reduction of pain and BML size were observed in the zoledronic acid trial [175] and the intensive diet and exercise for arthritis trial [176]. These were not included because they did not make a formal comparison of pain and BMLs. The mechanism by which BMLs may cause pain is unknown but may include subchondral microfractures, angina from a decreased blood supply causing ischaemia, and raised intraosseous pressure [177–179].

The independent association between a mismatch of the femoral and tibial articulating surface areas and incident frequent knee symptoms indicates that bone shape may predict not only the incidence of radiographic knee OA [120], but also symptomatic OA.

In terms of limitations, stratifying observational studies by quality may artificially create relatively high quality studies from a collection of generally low quality studies. However the distribution and summary statistics of quality scores indicate a suitably broad range of quality, particularly in the influential cohort studies with a mean of 54 % and range of 22–83 %. The decision to exclude articles reporting analysis of association that included fewer than 20 patients with OA may seem arbitrary. However, several papers report associations with the presence or absence of pain or structural progression based upon small numbers of patients. Our threshold decision reflects the absence of specific guidelines on how to exclude such papers, with inherent risk of imprecision, in the context of heterogeneous populations and statistical analyses. Had these papers been included there would have been no change in any of the conclusions in Table 5 (data not shown). The use of joint replacement as an outcome measure has a number of limitations including the effect of patient willingness, variation in orthopaedic opinion, availability of health services and health insurance, and therefore may be influenced depending upon the country and context in which the study is performed.

Publication bias could not be assessed with a funnel plot as there were insufficient results for odds and relative risk ratios. The heterogenous nature of the measures
of bone features and structural or pain outcomes precluded a meta-analysis or calculation of an effect size. This was because there were insufficient analyses describing the same association between the same bone features and outcome measure pair.

Conclusions
In conclusion subchondral bone plays an integral role in the pathogenesis of OA. BMLs, osteophytes identified on MRI and tibial bone area are independently associated with structural progression of knee OA. BMLs and tibial bone area are independently associated with TKR. BMLs are independently associated with structural progression of hand OA and 2D hip bone shape is associated with progression of structural hip OA and THR. BMLs are independently associated with longitudinal change in severity of pain and femorotibial articulating area mis-match is independently associated with incident frequent knee pain. These bone features may be used in the future for targeting treatment, stratifying patients into those most in need of OA modification and measuring treatment response.

Additional file

Additional file 1: Supplementary material: supplementary methods and results. (DOC 1659 kb)

Abbreviations
2D: two-dimensional; 3D: three-dimensional; ACL: anterior cruciate ligament; BLOCKS: Boston–Leeds osteoarthritis knee score; BMD: bone mineral density; BML: bone marrow lesion; BOKS: Boston osteoarthritis of the knee study; BVF: bone volume fraction; Cam: a resemblance to a camshaft; CRP: C-reactive protein; CT: computed tomography; DMOAD: disease-modifying osteoarthritis drug; DXA: dual-energy x-ray absorptiometry, EMBASE: Excerpta Medica database; GARP: Genetics, osteoarthritis and progression study; HOAMS: Hip osteoarthritis MRI scoring system; IPJ: interphalangeal joint; JSN: joint space narrowing; JWJ: joint space width; KL: Kellgren-Lawrence; KOSS: knee osteoarthritis scoring system; MOST: multicentre osteoarthritis study; MRI: magnetic resonance imaging; NA: no association; NC: no conclusion; OA: osteoarthritis; OAIS: Osteoarthritis Initiative; OARSI: Osteoarthritis Research Society International; OR: odds ratio; PET: positron emission tomography; PFJ: patellofemoral joint; PRISMA: Preferred reporting items for systematic reviews and meta-analyses; qCT: quantitative computed tomography; ROA: radiographic osteoarthritis; RR: relative risk ratio; SSR: subchondral surface ratio; THR: total hip replacement; TFJ: tibiofemoral joint; TKR: total knee replacement; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities arthritis index; WORMS: whole-organ magnetic resonance imaging score.

Competing interests
Dr Bowes is an employee and shareholder of Imorphics Ltd. Professor Conaghan, Sarah Kingsbury, Andrew Barr, Devan Hopkinson and Thomas Mark Campbell have nothing to disclose.

Authors’ contributions
AB carried out conception and design, eligibility assessment, extraction of data, quality assessment, along with drafting and revising of the manuscript content. DH carried out design, eligibility assessment and extraction of data. TC carried out conception and design, quality assessment and revising the manuscript for content. MB carried out conception and design along with revising the manuscript for content. SK carried out conception and design, eligibility assessment and reviewing the manuscript for content. PC carried out conception and design, quality assessment and revising the manuscript for content. All authors read and approved the final manuscript version for publication.

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