Association of Bone Marrow Lesion Localisation with Weight Bearing Pain in People with Knee Osteoarthritis: Data From The Osteoarthritis Initiative

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Abstract

**Background:** Subchondral bone marrow lesions (BMLs) detected on MRI in knee osteoarthritis (OA) are associated with knee pain. The prevalence and progression of BMLs are increased by mechanical knee load. However, associations of BML location with weight-bearing knee pain are currently unknown. In this study, we aim to demonstrate associations of BML location with weight-bearing knee pain in knee OA.

**Methods:** We analyzed 1412 and 582 varus knees from cross-sectional and longitudinal Osteoarthritis Initiative datasets, respectively. BML scores were analysed for 5 anatomical regions (median and lateral femorotibial, medial and lateral patellofemoral, and subspinous). Weight-bearing and non-weight-bearing pain scores were derived from WOMAC pain items. Correlation and negative binomial regression models were used for analysis of associations between the BML scores and pain at baseline, and changes in the BML scores and changes in pain after 24-month follow up.

**Results:** Greater BML scores at medial femorotibial and lateral patellofemoral compartments were associated with total and weight-bearing pain scores, and statistical significance was retained after adjusting for BML scores at the other 4 joint compartments and other OA features, as well as for non-weight-bearing pain, age, sex and Body Mass Index (BMI) (femorotibial; B=0.08 (95%CI, 0.01-0.09) p=0.02, patellofemoral; B=0.13 (95%CI, 0.03-0.23) p=0.01). BML scores were not significantly associated with non-weight-bearing pain after adjustment for weightbearing pain and other demographic and OA features. Change over 24 months in BML score in the medial femorotibial compartment was significantly associated with change in weight-bearing pain after adjusting for non-weight-bearing pain, age, sex, baseline weight-bearing pain, BMI, and BML at the other 4 joint compartments (B=0.10 (95%CI, 0.02-0.18) p=0.01).

**Conclusions:** BML size at the medial femorotibial joint compartment was specifically associated with the severity and the change in weight-bearing pain, independent of non-weight-bearing pain, in knee OA. Specific associations of weight-bearing pain with BMLs in weight-bearing compartments of the knee indicate that BMLs in subchondral bone contribute to biomechanically-induced OA pain.

**Background**

Knee pain is the major source of disability and reason for hospital visits in patients with knee osteoarthritis (OA). OA knee pain is characteristically experienced during weight bearing activity, but might also occur at rest on an unloaded joint. Weight-bearing pain indicates biomechanical mechanisms, whereas chemical or neuroplastic mechanisms might dominate in non-weight-bearing pain. Recent accumulating clinical evidence [1-3] indicates that subchondral bone plays a role in generating joint pain in OA. Subchondral bone marrow lesions (BMLs) detected on MRI in knee OA are increased in people with knee OA compared to non-arthritic controls [1], and are strongly associated with pain. A previous study demonstrated that larger baseline BMLs were associated with greater baseline knee pain, and increases
in total knee BML volume were associated with increased knee pain severity [3]. Greater BML scores were associated with weight-bearing pain and less so with non-weight-bearing pain [2].

The exact pathophysiology of BMLs is still under debate. Histologically, BMLs are characterized by bone marrow necrosis, trabecular abnormalities, bone marrow fibrosis, edema, cellular infiltration and vascular proliferation [4,5]. Microarray analysis of subchondral BMLs in OA demonstrated upregulation of genes implicated in neurogenesis, osteochondral turnover and inflammation [5]. BMLs might contribute to OA pain by this generation of chemical factors, sensitising nerves within the subchondral bone. Sensitised subchondral nerves might be activated by biomechanical forces, for example while standing, walking or climbing stairs. If so, then BMLs in weight-bearing rather than non-weight-bearing regions would be expected to specifically associate with weight-bearing pain. However, associations of BML location with weight-bearing knee pain are currently unknown.

OA structural change particularly affects weight-bearing components of the joint and mechanical knee load increases the prevalence and progression of BMLs [6]. Knee OA is most commonly associated with varus angulation, with increased force and OA structural change affecting the medial femorotibial compartment. BMLs present predominantly medially in varus and laterally in valgus lower limbs [7]. BMLs typically occur in regions of the joint with the most severe structural change, for example, full-thickness cartilage lesions, and associations between BML scores and cartilage volume were reported [8]. A previous systematic review [6] suggested that a greater medial or lateral load was related to compartment-specific BMLs. Associations between BMLs, cartilage damage and varus angulation, and between weight-bearing and non-weight-bearing pain, necessitate careful phenotyping of large numbers of individuals in order to explore specific associations between subchondral BMLs in weight-bearing components of the knee and weight-bearing pain. Longitudinal cohorts can help indicate whether specifically localized BMLs might mediate weight-bearing pain, and support the development of BML scores for the stratification of treatments aiming to improve weight-bearing pain.

The purpose of this study was to assess the association between BML location and weight-bearing knee pain using the Osteoarthritis Initiative (OAI) dataset. We hypothesized that BML size at the medial femorotibial joint compartment in people with varus angulation is associated with severity of weight-bearing pain, independent of non-weight-bearing pain and the other OA related MRI features, and that increasing BML size over time is associated with increased weight-bearing pain severity.

**Patients And Methods**

**Study design and subjects**

Subjects were selected from the OAI, a publicly available multi-center, longitudinal, prospective observational study of knee OA. The OAI dataset includes data of MRI and radiographic images, and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaires [9]. Figure 1 shows a flowchart of participant selection. Of the 4796 participants enrolled in the OAI study, varus knee OA with BML score information of the MRI Osteoarthritis Knee Score (MOAKS) [10], WOMAC
questionnaires, femoro-tibial angle (FTA) and body mass index (BMI) were selected. For subjects with bilateral symptomatic knee OA, one knee was randomly selected using random number generator. We analyzed data from 1412 and 582 knees in the cross-sectional and longitudinal OAI datasets, respectively.

**Knee MRI grading**

We used data from MRI Osteoarthritis Knee Score (MOAKS) at baseline and 24-month follow up as knee MRI grading. In BML scoring, the knee was divided into 5 regions (median and lateral femorotibial, and medial and lateral patellofemoral joint, and subspinous region (Figure 2) [5]. Articular cartilage, osteophytes, Hoffa's synovitis, effusion, medial meniscus extrusion and anterior cruciate ligament tears were scored based on MOAKS [5] (supplemental text). We used the BML scores in the 5 anatomical regions, total cartilage score (0-42), total osteophyte score (0-32), Hoffa's synovitis score (0-3), effusion-synovitis score (0-3), medial meniscus extrusion (0-3), and anterior cruciate ligament tears (absent or present).

**Knee pain assessment**

Knee pain was assessed at baseline and 24-month follow up using the WOMAC questionnaires. A recent factor analysis of the five WOMAC pain questions suggested that there are two constructs within the five questions [11]. Based on the result, we defined weight-bearing pain as the sum of three WOMAC questions (pain on climbing stairs, on walking, and on standing) and non-weight-bearing pain as the sum of two WOMAC questions (pain in bed and when sitting or lying). The time points of interest for cross-sectional and longitudinal study were the baseline visit, and baseline and 24-month follow up visits.

**Statistical analysis**

Statistical analyses were performed with SPSS version 26 software. Spearman's correlation coefficients were used for correlations between BML score and weight-bearing pain. Pearson's correlation coefficients were used correlations for between changes in BML scores and changes in weight-bearing pain. Negative binomial regression was performed for analysis of associations between weight-bearing or no-weight-bearing pain or total WOMAC score and scores of BML, articular cartilage, osteophytes, Hoffa's synovitis, effusion and medial meniscus extrusion. P<0.05 indicated statistical significance.

**Results**

The participant characteristics in this cross-sectional and longitudinal study are shown in Table 1.
### Table 1
Participant characteristics at baseline in cross sectional and longitudinal study

|                        | Cross sectional study | Longitudinal study |
|------------------------|-----------------------|--------------------|
| Included participants  | 1412                  | 582                |
| Male (%)               | 38.9                  | 42.8               |
| Age (years)            | 61.7 (8.8)            | 61.4 (8.8)         |
| BMI (kg/m²)            | 29.6 (4.9)            | 30.7 (4.8)         |
| Total BML score, 0–45  | 4.2 (3.7)             | 3.7 (2.8)          |
| BML score at medial FT joint, 0–15 | 1.2 (2.0) | 1.2 (1.7) |
| BML score at lateral FT joint, 0–15 | 0.6 (1.4) | 0.2 (0.6) |
| BML score at medial PF joint, 0–6 | 0.8 (1.0) | 0.8 (1.0) |
| BML score at lateral PF joint, 0–6 | 0.9 (1.2) | 1.1 (1.5) |
| BML score at subspinous region, 0–3 | 0.5 (0.8) | 0.4 (0.7) |
| Articular cartilage score, 0–42 | 9.0 (5.6) | 9.0 (4.7) |
| Osteophyte score, 0–32 | 8.8 (6.5)            | 8.7 (6.4)          |
| Hoffa’s synovitis score, 0–3 | 0.7 (0.7) | 0.7 (0.7) |
| Effusion-synovitis score, 0–3 | 0.8 (0.9) | 0.8 (0.8) |
| Medial meniscus extrusion score, 0–3 | 0.9 (1.0) | 1.1 (1.0) |
| Anterior cruciate ligament tears (%) | 9.4                  | 6.2                |
| FTA (degree)           | 185.9 (2.6)           | 186.1 (2.0)        |
| Weight bearing pain, 0–15 | 2.3 (2.4)          | 1.7 (2.1)          |
| Non-weight bearing pain, 0–10 | 0.9 (1.5) | 0.7 (1.3) |

Data of at baseline in cross sectional and longitudinal study are displayed as mean (SD).

BMI; Body Mass Index, BML; bone marrow lesion, FTA; femoro-tibial angle, FT; femorotibial, PF; patellofemoral.

Greater BML, cartilage, osteophyte, Hoffa’s synovitis or effusion-synovitis scores were each associated with total pain scores adjusted for age, sex and BMI (Table 2). Associations between BML, osteophyte and effusion-synovitis scores and total pain scores remained significant after also adjusting for the other OA related MRI features and anterior cruciate ligament tears (Table 2).
### Table 2
Cross-sectional associations between OA related MRI features and total pain score

|                          | Spearman's r | P       | B₁ (95% CI) | P       | B₂ (95% CI) | P       |
|--------------------------|--------------|---------|-------------|---------|-------------|---------|
| Total BML score          | 0.33         | <0.001**| 0.09 (0.06–0.13) | <0.001**| 0.05 (0.01–0.09) | 0.02*   |
| Medial FT joint          | 0.29         | <0.001**| 0.05 (0.03–0.08) | 0.001**| 0.08 (0.02–0.16) | 0.02*   |
| Lateral FT joint         | 0.09         | 0.003**| -0.01 (-0.18–0.15) | 0.87    | -0.03 (-0.19–0.14) | 0.74    |
| Medial PF joint          | 0.02         | 0.44    | 0.06 (-0.06–0.17) | 0.32    | 0.06 (-0.06–0.18) | 0.31    |
| Lateral PF joint         | 0.12         | <0.001**| 0.14 (0.05–0.23) | 0.003**| 0.13 (0.03–0.23) | 0.01*   |
| Subspinous region        | 0.18         | <0.001**| -0.04 (-0.21–0.14) | 0.69    | -0.06 (-0.24–0.12) | 0.53    |
| Articular cartilage score| 0.32         | <0.001**| 0.05 (0.03–0.08) | <0.001**| 0.003 (-0.03–0.04) | 0.86    |
| Osteophytes score        | 0.26         | <0.001**| 0.04 (0.02–0.06) | <0.001**| 0.02 (0.002–0.04) | 0.04*   |
| Hoffa's synovitis score  | 0.17         | <0.001**| 0.29 (0.14–0.45) | <0.001**| 0.08 (-0.09–0.26) | 0.35    |
| Effusion score           | 0.24         | <0.001**| 0.28 (0.16–0.40) | <0.001**| 0.15 (0.02–0.29) | 0.03*   |
| Medial meniscus extrusion score | 0.20   | <0.001**| 0.19 (0.08–0.29) | 0.001**| 0.06 (-0.06–0.18) | 0.36    |

B₁: OA related MRI features adjusted for age, sex and BMI. BML subscores in addition adjusted for BML at the other four joint compartments. B₂: OA related MRI features adjusted for age, sex, BMI, the other OA related MRI features and anterior cruciate ligament tears. *p < 0.05, ** p < 0.01

Greater BML, cartilage, osteophyte, Hoffa's synovitis or effusion-synovitis scores were each associated with weight bearing pain adjusted for non-weight bearing pain, age, sex, BMI (Table 3). Only association between BML and weight-bearing pain remained significant after adjusting for the other OA related MRI features and anterior cruciate ligament tears (Table 3). Separate models explored association of BML localization with weight-bearing pain. Greater BML scores at medial femorotibial and lateral patellofemoral compartments were significantly associated with greater weight-bearing pain, and these associations retained significance after adjustment for BML scores at the other 4 joint compartments (Table 3).
|                          | Spearman's $r$ | P        | $B_1$ (95% CI)       | P        | $B_2$ (95% CI)       | P        |
|--------------------------|---------------|----------|----------------------|----------|----------------------|----------|
| Total BML score          | 0.34          | < 0.001**| 0.08 (0.04–0.11)     | < 0.001**| 0.07 (0.02–0.11)     | 0.005**  |
| Medial FT joint          | 0.29          | < 0.001**| 0.10 (0.04–0.16)     | 0.001**  | 0.08 (0.02–0.16)     | 0.02*    |
| Lateral FT joint         | 0.09          | 0.003**  | -0.01 (-0.18-0.15)   | 0.87     | -0.03 (-0.19-0.14)   | 0.74     |
| Medial PF joint          | 0.03          | 0.35     | 0.06 (-0.06-0.17)    | 0.32     | 0.06 (-0.06-0.18)    | 0.31     |
| Lateral PF joint         | 0.13          | < 0.001**| 0.14 (0.05–0.23)     | 0.003**  | 0.13 (0.03–0.23)     | 0.01*    |
| Subspinous region        | 0.18          | < 0.001**| -0.04 (-0.21-0.14)   | 0.69     | -0.06 (-0.24-0.12)   | 0.53     |
| Articular cartilage score| 0.32          | < 0.001**| 0.05 (0.01–0.1)      | 0.03*    | 0.02 (-0.01-0.05)    | 0.25     |
| Osteophytes score        | 0.26          | < 0.001**| 0.04 (0.01–0.07)     | 0.01*    | 0.01 (-0.01-0.03)    | 0.46     |
| Hoffa's synovitis score  | 0.18          | < 0.001**| 0.3 (0.03–0.60)      | 0.03*    | -0.03 (-0.21-0.15)   | 0.72     |
| Effusion score           | 0.24          | < 0.001**| 0.4 (0.13–0.59)      | 0.002**  | 0.08 (-0.06-0.22)    | 0.26     |
| Medial meniscus extrusion score | 0.22          | < 0.001**| 0.15 (-0.05–0.36)    | 0.14     | 0.03 (-0.12-0.13)    | 0.96     |

$B_1$: OA related MRI features adjusted for non-weight-bearing pain, age, sex and BMI. BML subscores were in addition adjusted for BML at the other four joint compartments. $B_2$: OA related MRI features adjusted for non-weight-bearing pain, age, sex, BMI, the other OA related MRI features and anterior cruciate ligament tears. BML subscores were in addition adjusted for BML at the other four joint compartments. *p < 0.05, ** p < 0.01

BML; bone marrow lesion, FT; femorotibial, PF; patellofemoral.
Greater BML, cartilage, osteophyte, Hoffa’s synovitis or effusion-synovitis scores were each also associated with non-weight-bearing pain adjusted for weight-bearing pain, age, sex, BMI (Table 4). However, only medial meniscus extrusion score remained significantly associated with non-weightbearing pain after adjusting for the other OA-related MRI features and anterior cruciate ligament tears (Table 4).

| Table 4 | Cross-sectional associations between OA related MRI features and non-weight-bearing pain |
|---------|-------------------------------------------------------------------------------------|
|         | Spearmans’ r | P       | B₁ (95% CI) | P       | B₂ (95% CI) | P       |
| Total BML score          | 0.19          | < 0.001** | -0.01 (-0.06-0.04) | 0.63   | -0.04 (-0.10-0.02) | 0.21   |
| Articular cartilage score | 0.22          | < 0.001** | 0.01 (-0.02-0.04) | 0.45   | -0.01 (-0.06-0.04) | 0.65   |
| Osteophytes score        | 0.20          | < 0.001** | 0.02 (-0.01-0.05) | 0.15   | 0.02 (-0.01-0.05) | 0.15   |
| Hoffa’s synovitis score  | 0.11          | < 0.001** | 0.08 (-0.16-0.32) | 0.52   | 0.06 (-0.20-0.31) | 0.68   |
| Effusion score           | 0.18          | < 0.001** | -0.02 (-0.18-0.18) | 0.99   | -0.01 (-0.004-0.36) | 0.90   |
| Medial meniscus extrusion score | 0.20          | < 0.001*  | 0.16 (0.01-0.32) | 0.04*  | 0.18 (-0.55-0.68) | 0.045* |

B₁: OA related MRI features adjusted for weight-bearing pain, age, sex and BMI. B₂: OA related MRI features adjusted for weight-bearing pain, age, sex, BMI, the other OA related MRI features and anterior cruciate ligament tears. *p < 0.05

BML; bone marrow lesion, FT; femorotibial, PF; patellofemoral.

Changes from baseline to 24-month follow up of variables in the longitudinal study are shown in Table 5. Changes in total and site-specific BML scores were associated with change in weight-bearing pain. Specifically, change in BML score at medial femorotibial compartments was significantly associated with change in weight-bearing pain after adjusting for sex, baseline weight-bearing pain, age, BMI, BML at the other four joint compartments and change in non-weight-bearing pain (Table 6). No significant association between change in medial meniscus extrusion score and change in non-weight-bearing pain was found after adjusting for sex, baseline non-weight-bearing pain, age, BMI and medial meniscus extrusion score, and change in weight-bearing pain (B = 0.15 (95%CI, -0.15-0.44) p = 0.33).
Table 5
Changes in MRI scores, femorotibial angle and pain between baseline and 24-month follow up (n = 582)

| Characteristic (units or possible range) | Mean change (range) |
|-----------------------------------------|---------------------|
| BMI (kg/m^2)                            | 0.02 (-10.5 to 13.1) |
| Total BML score, 0–45                    | 0.7 (-7 to 12)      |
| BML score at medial FT joint, 0–15       | 0.5 (-4 to 10)      |
| BML score at lateral FT joint, 0–15      | 0.1 (-2 to 5)       |
| BML score at medial PF joint, 0–6        | 0.03 (-5 to 3)      |
| BML score at lateral PF joint, 0–6       | 0.1 (-3 to 3)       |
| BML score at subspinous region, 0–3      | 0.07 (-3 to 3)      |
| Articular cartilage score, 0–42         | 0.8 (-10 to 9)      |
| Osteophyte score, 0–32                   | 0.4 (-12 to 14)     |
| Hoffa's synovitis score, 0–3             | 0.08 (-2 to 2)      |
| Effusion-synovitis score, 0–3            | 0.1 (-2 to 2)       |
| Medial meniscus extrusion score, 0–3     | 0.2 (-2 to 3)       |
| New anterior cruciate ligament tears (%) | 0.7                  |
| FTA (degree)                            | 0.4 (-3.9 to 2.0)   |
| Weight bearing pain, 0–15                | 0.5 (-10 to 10)     |
| Non-weight bearing pain, 0–10            | 0.02 (-11 to 13)    |

Positive values represent increases from baseline to follow up. BMI; Body Mass Index, BML; bone marrow lesion, FTA; femoro-tibial angle, FT; femorotibial, PF; patellofemoral.
Table 6

| BML score changes     | Pearson’s r | p       | B (95% CI)         | P     |
|-----------------------|-------------|---------|--------------------|-------|
| Total score           | 0.13        | 0.002*  | 0.07 (0.00-0.13)   | 0.04* |
| Medial FT joint       | 0.16        | <0.001**| 0.10 (0.02-0.18)   | 0.01* |
| Lateral FT joint      | -0.06       | 0.13    | -0.21 (-0.53-0.11) | 0.20  |
| Medial PF joint       | -0.01       | 0.73    | -0.10 (-0.31-0.11) | 0.34  |
| Lateral PF joint      | 0.02        | 0.58    | 0.10 (-0.09-0.30)  | 0.29  |
| Subspinous region     | 0.10        | 0.01    | 0.21 (-0.03-0.45)  | 0.09  |

B: Model for total BML score adjusted for sex, baseline weight-bearing pain, age, and BMI, total BML score, and change in non-weight-bearing pain. BML subscores in addition adjusted

Discussion

In cross-sectional analyses, we firstly demonstrated that BML size at the medial femorotibial joint compartment in varus knee OA participants was associated with weight-bearing pain severity, and that this association was not explained by non-weight-bearing pain, other OA related MRI features, age, sex or BMI. In longitudinal analyses, increasing BML size at the medial femorotibial joint compartment was associated with increased weight-bearing pain severity. Our findings support the hypothesis that BMLs increase OA knee pain due to biomechanical factors acting through the affected subchondral bone.

Greater BML scores at medial femorotibial compartments were significantly associated with greater total and weight-bearing pain, even after adjusting for non-weight-bearing pain and the other OA related MRI features. Change in BML score at the medial femorotibial compartment was significantly associated with change in weight-bearing pain. In contrast to these findings, BML scores were not significantly associated with non-weight-bearing pain in our fully adjusted models. Hence, we conclude that BMLs at weight-bearing components are specifically associated with weight-bearing pain. We previously demonstrated that subchondral bone histopathology characteristic of BMLs, occurring in middle third of medial tibial plateau (an important weight-bearing area), was associated with knee OA pain, not dependent on chondropathy and synovitis [12].

BMLs at the lateral patellofemoral joint compartment were also associated with weight-bearing pain. Patellar BMLs have been associated with any knee pain, and with pain when going up or down stairs [13]. The patellofemoral joint is one of the most commonly affected compartments in knee OA, and varus knee deformity has been associated with worsening of patellofemoral OA, especially in the lateral facet [14]. We extend these findings to identify that BMLs at the lateral, and not at medial patellofemoral joint compartments were significantly associated with the severity of weight-bearing pain in people with varus angulation. This again suggests a biomechanical explanation linking BMLs to OA pain. However,
patellofemoral BML score change was not associated with pain change, suggesting that BML changes at the patellofemoral joint has a smaller impact on changes in weight-bearing pain than does BML change at the femorotibial joint.

BMLs represent regions of subchondral bone histologically characterized as displaying increased bone turnover and expression of factors that can increase nerve sensitization [5]. We previously showed that nerve growth factor expression within osteochondral channels and subchondral osteoclast density each is associated with knee OA pain [12], and calcitonin gene-related peptide immunoreactive sensory nerves within osteochondral channels are associated with pain in human and rat knee OA [15]. Activation of sensory nerves in subchondral bone might contribute to weight-bearing pain in knee OA. BMLs might be an imaging biomarker for pathology which sensitisises subchondral nerves, and therefore increases weight-bearing pain in knee OA. Further investigation is needed to clarify the cellular and molecular factors which might mediate the observed association between BMLs and weight-bearing pain.

Our results suggested that BMLs might mediate mechanically-induced pain such as during weight-bearing. Biomechanical factors may reciprocally contribute to the pathogenesis of BMLs. Previous studies [6] reported that increased mechanical load due to malalignment of the knee joint is a risk factor for incident or enlarging BMLs in the femorotibial joint. Meniscus and cartilage can be shock absorbers that protect subchondral bone from overloading. Associations between meniscal pathology [16, 17] or cartilage loss [16, 18] and increasing BML size might be mediated by altered biomechanical forces through the subchondral bone. Patellofemoral bracing, which may reduce contact stress across patellofemoral joint, reduced BML volume at patellofemoral joint compartments in patients with painful patellofemoral OA [19]. BMLs therefore might result from increased mechanical load imposed on subchondral bone. However, lateral wedge insoles, which might reduce the load in the medial femorotibial joint compartment during walking [20], did not significantly changes in BMLs and pain in medial knee OA [21], and the extent of biomechanical unloading that is required to reverse BML pathology remains uncertain. Treatments with large effects on mechanical load such as high tibial osteotomy and valgus bracing might be needed to reduce BMLs at medial femorotibial joint compartments.

Regarding pharmacotherapy to BMLs, a previous study reported that the bisphosphonate zoledronic acid reduced BML size and knee pain in people with OA [22]. However, recent meta-analysis [23] and randomized controlled trial [24] did not support analgesic effects of bisphosphonates in knee OA. These studies support that biomechanical unloading is more effective than current pharmacotherapy for BML associated pain. Knee OA pain has multiple sources, and targeting BMLs would be expected to have greatest benefit in those cases where BMLs are the predominant driver of weight-bearing pain.

In this study, medial meniscus extrusion score was significantly associated with non-weight-bearing pain severity after adjusting for weight-bearing pain and the other OA related MRI. A recent study reported that patients with medial submeniscal flap tear complained of pains during sleep, but not during daytime activities [25]. Pain associated with meniscal tears might be caused by increased mechanical load on meniscus not only during loaded knee but also during unloaded knee flexion-extension motion. However,
change in meniscus extrusion score was not associated with change in non-weight bearing pain, which suggests that meniscus extrusion may have a relative small impact on non-weight-bearing pain.

Not only BMLs, but also synovitis [26], effusion-synovitis [27], cartilage defects [28] and osteophytes [29] have previously been associated with knee OA pain. We also demonstrated that osteophyte and effusion scores were independently associated with total pain score, even after adjusting for the other OA related MRI features. Significant associations of cartilage and Hoffa’s synovitis scores did not retain statistical significance after adjusting for the other OA related MRI features including BML score, suggesting that some of these observed associations may be explained by other closely associated OA features.

Our study has several potential limitations. We investigated only 2 time points (baseline and 24 months). A previous study using OAI dataset demonstrated that changes in total knee BML volume after 24 months were positively associated with changes in knee pain severity [3]. However, multiple assessments with shorter intervals are needed to evaluate how fluctuations of BML size relate to changes in weight-bearing pain. BML size was assessed semi-quantitatively and, although our study had a large sample size, quantitative BML measurements might have provided additional information. Direct measurement of mechanical loading through joint compartments was not possible in the current study, and interventional studies would be required to confirm our conclusions that BMLs are biomarkers for pathology which causes biomechanically-induced nociceptive pain.

In conclusion, we demonstrated that BML size at medial femorotibial joint compartments in varus knee OA was associated with weight-bearing pain, that this association was specific for weight-bearing rather than non-weight bearing pain, and was over and above any effects of other OA-related MRI features, age, sex and BMI. Our findings suggest that specific association of weight-bearing pain with BMLs in weight-bearing compartments of the knee indicates that BMLs aggravate biomechanical factors leading to OA pain.

Declarations

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Competing interests

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F. McWilliams: grants from Pfizer Ltd.

The remaining authors have no conflicts of interest to declare.

Author Contributions
All authors approved the final version to be published. K.A. has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. K.A., M.S., D.M. and D.W. designed the study, analyzed and interpreted results. K.A., D.M. and D.W. wrote the manuscript.

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Ethics approval and consent to participate

The OAI study was approved by the Institutional Review Board of the University of California, San Francisco, and its affiliates. All participants gave written informed consent.

Availability of data and materials

The datasets analysed during this study are available from the Osteoarthritis Initiative website (https://nda.nih.gov/oai/).

Consent for publication

Not applicable

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**Figures**
Figure 1

Subject selection from OAI database n = number of participants included in the analysis.
Figure 2

Delineation of subregional divisions for BML scoring For BML scoring, the knee was divided into 4 articular sub-regions (medial and lateral femorotibial, and medial and lateral patellofemoral compartment) and subspinous region based on MOAKS; MFT, median femorotibial compartment; LFT, lateral femorotibial compartment; PF, patellofemoral compartment; S, subspinous region.

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