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The Influence of Joint Loading on Bone Marrow Lesions in the Knee

A Systematic Review With Meta-analysis

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Background: Bone marrow lesions (BMLs) are considered as predictors of pain, disability, and structural progression of knee osteoarthritis. The relationship between knee loading and BMLs is not yet completely understood.

Purpose: To summarize the available evidence regarding the relationship between joint loading and the prevalence and progression of BMLs in the tibiofemoral joint.

Study Design: Meta-analysis.

Methods: Three databases (PubMed, Web of Science, and The Cochrane Library) were systematically screened for studies encompassing BMLs and changes in knee loading. A methodological quality assessment was conducted, and a meta-analysis computing overall odds ratios (ORs) was performed where possible.

Results: A total of 29 studies involving 7641 participants were included. Mechanical loading was categorized as body weight and composition, compartmental load, structural lesion, and physical activity. High compartmental loads and structural lesions increased the risk for BMLs (overall ORs ranging from 1.56 [95% CI, 1.13-2.15] to 8.2 [95% CI, 4.4-15.1]; $P = .006$). Body weight increased the risk for BMLs to a lesser extent (overall OR, 1.03; 95% CI, 1.01-1.05; $P = .007$). Contradictory results for the effect of physical activity on BMLs were found.

Conclusion: Augmented compartmental loads and structural lesions increased the risk of the presence or progression of BMLs. Body weight increased the risk for BMLs to a lesser extent. Contradictory results for the effect of physical activity on BMLs may be explained by a dose-response relationship, knee alignment, and structural lesions.

Clinical Relevance: It has been shown that unloading the knee temporarily may induce beneficial effects on osteoarthritis-related structural changes. Therefore, an early recognition of BMLs in the aging athlete's knee may provide information to counter the onset and aggravation of symptomatic knee osteoarthritis by reducing the knee load.

Keywords: knee; aging athlete; magnetic resonance imaging; biology of bone

Knee osteoarthritis (OA) is usually diagnosed and assessed by radiographic imaging using the Kellgren-Lawrence

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grading system.² However, not all radiographic OA is accompanied with symptoms, which is reflected by a much lower prevalence of symptomatic OA.⁴⁸ During the past decade, magnetic resonance imaging (MRI) has been used more frequently to visualize the structural changes associated with OA. Bone marrow lesions (BMLs) can be observed on MRI already before symptoms appear in people who are at risk for developing knee OA, such as patients undergoing meniscectomy.²³

A BML is generally defined as an area of either a hyperintense or hypointense signal in the trabecular subchondral bone on T2-weighted fat-suppressed or T1 MRI scans, respectively.^{59,71} Their volumes can be measured quantitatively (expressed in mm³) or semiquantitatively by using scales such as the Whole-Organ Magnetic Resonance Imaging Score (WORMS) and the Boston Leeds Osteoarthritis Knee Score (BLOKS).³⁹ Quantitative methods are more time consuming but provide a continuous

TABLE 1
Keywords Used for Search Strategy

PECO Dimension ^a	Population: Persons With or at Risk of Developing Knee Osteoarthritis	Exposure/Comparator: Mechanical Loading/Unloading	Outcome: Bone Marrow Lesion
Search terms	Osteoarthritis, knee (MeSH) OR "osteoarthritis, knee"	Motor activity (MeSH) OR resistance training (MeSH) OR exercise therapy (MeSH) OR sports (MeSH) OR walking (MeSH) OR running (MeSH) OR weightbearing (MeSH) OR stress, mechanical (MeSH) OR genu varum (MeSH) OR genu valgum (MeSH) OR jumping OR jump OR steps OR loading OR load OR unloading OR unload OR body weight (MeSH) OR weight gain (MeSH) OR weight loss (MeSH) OR body mass index (MeSH) OR "joint load" OR exercise (MeSH) OR "mechanical load" OR mechanical load OR joint load	Magnetic resonance imaging (MeSH) OR "bone marrow lesion" OR "bone marrow edema" OR BML OR BME OR bone marrow (MeSH)

^aPECO, patient, exposure, control, outcome.

score with a higher sensitivity and responsiveness for longitudinal change compared with semiquantitative measurements.⁵⁸ The exact pathophysiology of BMLs is still under debate. Histologically, a BML is characterized by bone marrow necrosis, trabecular abnormalities, bone marrow fibrosis and edema, and hyperplasia of blood vessel walls.³⁸ The destruction of adipose cells and fibrovascular regeneration have also been described in these regions.⁷¹ Larger BMLs were found in patients with OA with pain compared with patients with OA without pain.¹⁶ The resolution of BMLs has been related to a decrease in pain and a reduced loss of cartilage volume.^{16,74} This suggests that BMLs might be a modifiable feature for knee pain and knee OA as their development and regression seems to be a dynamic process.⁴⁴ Therefore, BMLs are of particular interest as targets for preventive and therapeutic interventions to counter knee OA.^{66,74} Subchondral BMLs may be observed in conjunction with several other conditions such as spontaneous osteonecrosis of the knee (SONK) and stress fractures.⁵⁹ However, they can be differentiated from OA-related BMLs, as shown by Roemer et al.⁵⁹ Indeed, SONK is characterized by an acute onset of severe medial joint pain and may lead to rapid joint destruction. The SONK-related BMLs are large and appear around a subchondral thickened area of necrosis and may rapidly progress to subchondral collapse.⁵⁹ The BMLs that are seen in relation to stress fractures are mostly seen in the osteoporotic elderly and can be differentiated from OA-related BMLs as they accompany a subchondral fracture line.⁵⁹

Essentially, BMLs are important predictors of compartment-specific increases in pain, disability, and structural progression of knee OA.^{24,31} Such lesions may result from traumas associated with excessive loads between the femoral condyle and the tibial plateau.²⁷ In previous studies, the prevalence of BMLs has been associated with anthropometric measures, such as body mass index (BMI),³¹ and biomechanical measures, such as knee malalignment⁷ and knee adduction moment (KAM).⁴³

Recently, Lim et al⁴⁷ systematically reviewed the literature for biomechanical factors, meniscal lesions, and

physical activity as risk factors for BMLs. Their data suggested an association between BMLs, meniscal lesions, and varus-valgus angles of the knee. However, this review did not take into account other aspects that can be attributed to knee loading, such as body weight and cartilage loss. Body weight has previously been associated with knee loading in overweight and obese older adults with knee OA^{52,53}; each pound of weight loss resulted in a 4-fold reduction in the load exerted on the knee per step during daily activities. Also, BMLs have been proposed as biomarkers of increased knee loading,⁸ and therefore, altered mechanical loads of the knee may be expressed as changes in the presence, number, or volume of BMLs. Several structural changes in the knee may influence its loading. For example, it has been shown that hyaline cartilage serves as a better shock absorber than fibrous menisci.²⁸ This finding suggests that a loss of cartilage may induce a reduced shock absorption capacity of the joint, increasing loads on the subchondral bone. Moreover, anterior cruciate ligament (ACL) lesions have been shown to alter knee kinematics.⁵⁴ These lesions might cause a shift of mechanical loads to joint regions that are not adapted to frequent load bearing.³

The involvement of the above-mentioned aspects of joint loading on BMLs has not yet been systematically appraised or quantified. Therefore, this systematic review aims to summarize the available evidence regarding the relationship between joint loading, as interpreted above, and the prevalence and progression of BMLs in the tibiofemoral joint.

MATERIALS AND METHODS

Protocol and Eligibility Criteria

As a general protocol for this review, the PRISMA guidelines⁴⁶ were followed. As shown in Table 1, keywords were determined based on PECO dimensions: knee OA (patient), loading (exposure), unloading (control), and BML (outcome). Similar search strategies were performed in 3 databases: PubMed, Web of Science, and The Cochrane Library. Because we focused on literature

regarding OA-related BMLs, we did not include “SONK” or “stress fracture” as keywords. No limits were used in the databases. Studies were eligible for this review if they reported relationships between tibiofemoral BMLs and joint loading. Studies were included if they were written in English, French, or Dutch. Studies were excluded if they only focused on the patellofemoral joint. No limit was set on the publication date.

Search and Screening

First, 2 reviewers identified search terms using MeSH vocabulary and text word searching. Second, both reviewers pilot tested appropriate search strategies independently from each other. Both steps were discussed with a third reviewer until a consensus was reached. The last search was performed on June 30, 2014. The screening process was performed by 2 reviewers independently and blinded to each other’s results. Studies were first screened for the title, then the abstract, and finally the full text. After the screening process, both reviewers discussed all disagreements. If disagreements were not resolved by a consensus, a third reviewer was consulted.

Data Extraction and Risk of Bias

Data extraction was performed using a data extraction sheet based on a template provided by the Cochrane Collaboration.¹⁵ Two assessors performed data extraction independently for study design, study population, sample size, sex, age, loading outcome, BML outcome, association measures, or odds ratios (ORs). If the latter were not reported and if frequencies were provided, ORs were calculated based on the frequencies of the group of patients with the lowest knee load (eg, lowest quartile of body weight) and the group with the highest knee load (eg, highest quartile). No assumptions were made on missing or unclear information, and data extraction was based on the original reports. Different tools for the assessment of the risk of bias were used depending on the study design. The 6-item Cochrane risk of bias assessment tool was used to assess randomized controlled trials (RCTs).¹⁴ Other designs were assessed using tools provided by the Dutch Cochrane Collaboration for cohort and cross-sectional studies²¹ and for case-control studies.²² The risk of bias assessment was performed by 2 blinded reviewers. The interrater reliability was calculated using the Cohen κ . A third reviewer was consulted in case of disagreements and if no consensus was reached.

Meta-analysis

Meta-analyses were conducted with OpenMeta software (Analyst) for advanced meta-analyses from the Brown University Evidence-based Practice Center⁶⁸ using the random-effects method and heterogeneity (τ^2) calculation according to DerSimonian and Laird.¹⁸ Subgroup analyses were performed based on (1) study design (cross-sectional and prospective) and/or (2) knee compartment (medial and lateral). I^2 values with a significance level ($P < .01$) are reported as a measure of the degree of inconsistency

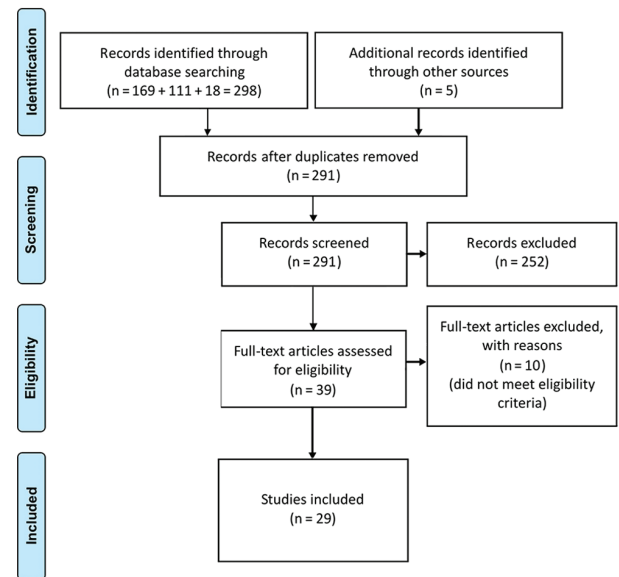


Figure 1. PRISMA flowchart.

in the studies’ results.³³ The I^2 values may range from 0% (no observed heterogeneity) to 100%, and values of 25%, 50%, and 75% can be considered as low, moderate, and high, respectively.³³

RESULTS

Study Selection

Complete search strategies for each database are presented in the Appendix (available in the online version of this article at <http://ajsm.sagepub.com/supplemental>). After the removal of duplicates, the screening process resulted in 286 articles. Twenty-nine studies met the eligibility criteria and were included in this review. Five of them were retrieved by screening the reference lists of the included articles (Figure 1).

Study Characteristics

The 29 included studies involved 7641 participants with or at risk of knee OA. Four different designs were included: 1 RCT,⁶ 1 case-control study,⁶³ 15 cohort studies,¹¹ and 12 cross-sectional studies.⁴

All studies investigated BMLs in the tibiofemoral joint in relation to joint loading as primary, secondary, or explanatory outcome measures. A BML was defined by most studies as a hypointense signal on T1-weighted and a hyperintense signal on T2-weighted MRI scans adjacent to the subchondral bone. Most studies ($n = 23$) obtained the BML scores from quantitative or semiquantitative methods. Consequently, these scores were dichotomized for

¹¹References 7, 10, 19, 20, 23, 29, 32, 35, 37, 40, 44, 45, 57, 64, 69.

⁴References 4, 8, 9, 30, 31, 36, 41, 43, 49, 62, 65, 73.

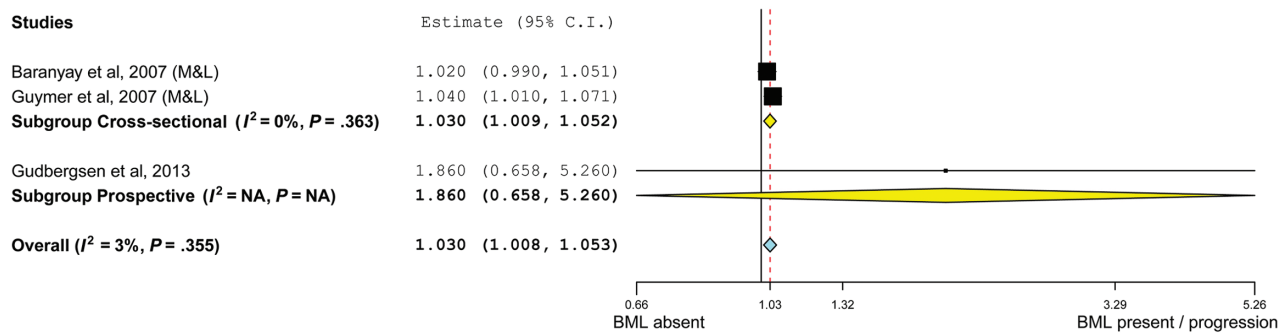


Figure 2. Forest plot for body weight as a risk factor for bone marrow lesions (BMLs). Overall odds ratio (OR) ($P = .007$) for body weight: higher body weight reflecting higher joint loading. Overall OR: $P = .007$. BML, bone marrow lesion; C.I., confidence interval; I^2 , heterogeneity; L, lateral compartment; M, medial compartment; M&M, medial and lateral; NA, not available.

the presence and/or progression of BMLs (prospective longitudinal design).[#] Five studies defined the presence of a BML if it appeared on ≥ 2 adjacent slices.^{4,9,10,31,57} One study did not provide information on how progression was determined.⁴⁴

Quality of Evidence. The risk of bias varied between the different studies. A complete quality assessment of the studies can be found in the Appendix (available online). Interrater reliability, calculated by the Cohen κ , was high for cross-sectional studies ($\kappa = 0.96$) and moderate for cohort studies ($\kappa = 0.53$) and case-control studies ($\kappa = 0.50$). One RCT was assessed with perfect agreement.⁶

Results of Individual Studies

Joint loading was approached differently in the included studies. For the readability of this review, we grouped the studies into 4 categories according to the approach used: (1) body weight and body composition (higher body weight or BMI reflecting higher joint load), (2) knee compartmental load (abduction or adduction stress in the knee joint), (3) knee structural lesion (higher joint load due to ligamentous or cartilage defects), and (4) physical activity (higher levels of physical activity associated with higher joint load).

Body Weight and Body Composition. This category encompasses 10 studies (Table 2).^{4,9,10,19,29-31,43,45,73} Four studies reported on body weight.^{4,29,31,43} Combined data from 3 of them showed a significantly increased risk for BMLs with a higher body weight (overall OR, 1.03; 95% confidence interval [CI], 1.01-1.05; $P = .007$) (Figure 2). No significant heterogeneity was observed ($I^2 = 3\%$, $P > .01$). One study that found no difference in body weight between people with and without BMLs was not included in the meta-analysis because no OR could be extracted from the article.⁴³

Eight studies reported on BMI.^{4,9,10,19,30,31,45,73} One study reported a significant correlation between BMI and the presence of BMLs ($r = 0.19$, $P = .04$), but no ORs were provided.⁷³ Therefore, data from 7 studies were

combined, which showed a significantly higher risk for BMLs in patients with a higher BMI (overall OR, 1.087; 95% CI, 1.036-1.41; $P < .001$) (Figure 3). No significant heterogeneity was observed ($I^2 = 47\%$, $P > .01$).

One study found a significantly increased risk for the presence of BMLs with an increased total body fat mass in 153 asymptomatic patients (16% radiographic knee OA), even after adjusting for BMI (OR, 1.09; 95% CI, 1.01-1.18; $P = .03$).⁹ Skeletal muscle mass was not a significant risk factor for the presence of BMLs (OR, 1.11; 95% CI, 0.92-1.34; $P = .26$).⁹

Knee Compartmental Load. The effect of loading on the medial and/or lateral knee compartment was reported in 10 articles (Table 3).^{6-8,23,32,40,41,43,63,73} Moreover, KAM was used in 3 studies as a biomechanical measure of knee loading in the medial compartment during gait.^{7,8,43} In 1 cross-sectional study, significantly higher peak KAM (3.95%BW*Ht vs 3.47%BW*Ht, respectively; $P < .01$) and KAM impulses (1.35%BW*Ht*s vs 1.15%BW*Ht*s, respectively; $P < .01$) were measured in symptomatic OA knees with BMLs compared with knees without BMLs, but no ORs were reported.⁴³ Therefore, the meta-analysis was based on 1 cross-sectional study⁸ and 1 prospective study.⁷ Both KAM impulses and peak KAM increased the risk for the presence of BMLs in the medial compartment of the knee (overall OR_{KAMimpulse}, 5.26; 95% CI, 1.30-21.22; $P = .02$ [$I^2 = 59\%$, $P = .09$] and overall OR_{peakKAM}, 1.56; 95% CI, 1.13-2.15; $P = .006$ [$I^2 = 0\%$, $P = .40$]) (Figures 4 and 5). However, neither KAM nor peak KAM increased the risk for BML progression after 1 year.⁷

One study found that increased articular contact stresses in the tibiofemoral joint predicted BML worsening 30 months later (OR, 6.6; 95% CI, 2.7-16.5).⁶³ One RCT studied the effect of lateral wedge insoles on BML progression in the medial knee compartment.⁶ Previously, these insoles have been linked to decreased knee loads, and therefore, the researchers expected a decrease of BMLs in the medial knee compartment compared with sham insoles. However, changes in the size of BMLs were the same in both groups after 1 year (sham and real insoles).

Five studies investigated BMLs in relation to knee alignment.^{23,32,40,41,73} One study with a cross-sectional

[#]References 6-8, 23, 29, 30, 32, 35-37, 40, 41, 43, 45, 49, 62-65, 69, 73.

TABLE 2
Studies Reporting on Body Weight and Body Composition^a

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
<i>Cross-sectional studies</i>							
Baranyay et al ⁴ (2007)	No Sx (MCCS); N = 297 (63%)	58.0 ± 5.5	BMI, weight	Presence (Y/N)	—	BMI: total knee: OR, 1.03 (0.95-1.13) [P = .49]; medial: OR, 1.010 (0.900- 1.133); lateral: OR, 1.090 (0.980- 1.212) Weight: total knee: OR, 1.02 (0.99- 1.05) [P = .30]; medial: OR, 1.01 (0.970-1.052); lateral: OR, 1.04 (1.001-1.080)	5/6
Berry et al ⁹ (2010)	No Sx (community); N = 153 (81%)	47 ± 9	BMI, body composition	Presence (Y/N)	—	BMI: OR, 1.02 (0.96-1.07) [P = .60] Skeletal muscle mass: OR, 1.11 (0.92-1.34) [P = .26] Total body fat mass: OR, 1.09 (1.01- 1.18) [P = .03]	5/6
Doré et al ¹⁹ (2010)	TASOAC; N = 395 (51%)	63.2 ± 7.2	BMI	Presence (Y/N)	—	OR, 1.34 (1.09-1.65) [P = .005]	6/8
Guermazi et al ³⁰ (2012)	No Sx (Framingham community cohort); N = 710 (55%)	62.3 ± 8.4	BMI	Presence (Y/N)	—	117 (53%) vs 149 (54%) vs 103 (51%) [P = .79]; OR*, 0.915 (0.626-1.339)	5/6
Guymer et al ³¹ (2007)	No Sx (community); N = 176 (100%)	52.3 ± 6.6	BMI, weight	Presence (Y/N)	—	BMI: 30 ± 7 vs 27 ± 5 kg/m ² [P = .04]; total knee: OR, 1.10 (0.86- 1.19); medial: OR, 1.14 (1.04-1.25); lateral: OR, 0.990 (0.626-1.339) Weight: 81 ± 18 vs 71 ± 13 kg [P = .003]; total knee: OR, 1.04 (1.01- 1.08); medial: OR, 1.05 (1.02-1.09); lateral: OR, 1.01 (0.96-1.07)	5/6
Kean et al ⁴³ (2012)	Sx medial OAK; N = 169 (nk)	>50	Body weight	Presence (Y/N)	—	77.3 (SD, 14.5) vs 81.7 (SD, 16.4) [P > .05]	6/6
Zhai et al ⁷³ (2006)	Adult children of patients undergoing knee replacement for OAK; N = 115 (52%)	47 ± 7	BMI	Presence (Y/N)	—	BMI: r = 0.19, P = .04	3/6
<i>Prospective studies</i>							
Brennan et al ¹⁰ (2010)	No Sx; N = 142 (100%)	41.7 ± 5.3	BMI	Presence (Y/N)	10 y	OR, 1.13 (1.04-1.23) [P = .005] BMI evolution over 10 y: OR, 1.14 (1.03-1.26) [P = .01]	8/8
Doré et al ¹⁹ (2010)	TASOAC; N = 395 (51%)	63.2 ± 7.2	BMI	Progression after 2.7 y (Y/N)	2.7 y	BML increase after 2.7 y (n = 25%): OR, 1.23 (0.97-1.58) [P = .093]	6/8
Gudbergson et al ²⁹ (2013)	Obese OAK (CAROT); N = 192 (80%)	62.7 ± 6.3	Weight loss	Decrease (Y/N)	16 wk	Weight loss category: OR, 1.86 (0.66- 5.26) [P = .24] Weight loss (cont): OR, 1.13 (0.39- 3.28) [P = .81]	5/8
Laberge et al ⁴⁵ (2012)	No Sx (OAI incidence); N = 137 (41%)	50.9 ± 2.8	BMI	Presence (Y/N)	36 mo	8 (21%) vs 10 (27%) vs 17 (27%) [P = .279]; OR*, 3.182 (1.343-7.536)	6/8

^aBMI, body mass index; BML, bone marrow lesion; CAROT, Influence of Weight Loss or Exercise on Cartilage in Obese Knee Osteoarthritis Patients study; cont, continuous outcome; MCCS, Melbourne Collaborative Cohort Study; N, no; nk, not known; OAI, Osteoarthritis Initiative; OAK, knee Osteoarthritis; OR, odds ratio; OR*, calculated OR from the reported data; Sx, Symptomatic; TASOAC, Tasmanian Older Adult Cohort study; Y, yes.

^bValues in parentheses are 95% CIs unless otherwise indicated.

design reported different knee angles between OA knees with BMLs and knees without BMLs, but no ORs were provided.⁴¹ Four studies prospectively investigated the association between varus and valgus of the knee and the progression of BMLs.^{23,32,40,41} One study did not find an association between knee alignment and the presence of BMLs 2 years later, but the authors did not provide any data.⁷³ In contrast, all other included studies reported

positive associations between knee malalignment and BML progression. Hunter et al⁴⁰ found a significant association between knee malalignment and the progression of BMLs after 15 months ($\beta = .6$, $P = .008$ for the lateral compartment; $\beta = .8$, $P = .003$ for the medial compartment), but no ORs were reported. This study also provided cross-sectional data from which we were able to calculate the OR. Hayashi et al³² found an increased relative risk (RR) for

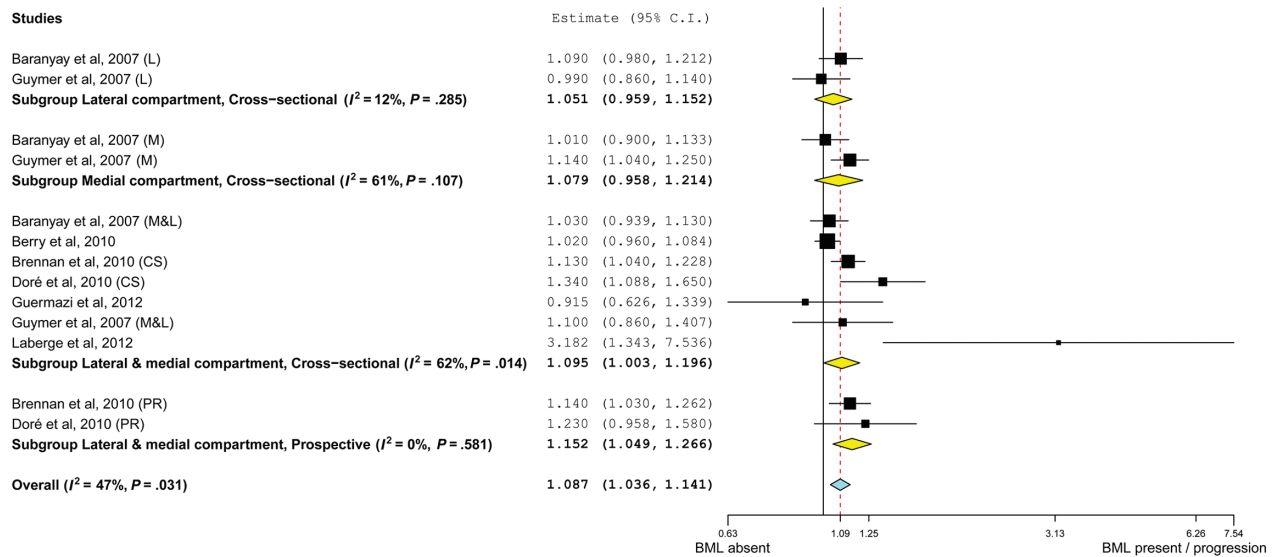


Figure 3. Forest plot for body mass index (BMI) as a risk factor for bone marrow lesions. Overall odds ratio (OR) ($P = .005$) for BMI: higher BMI reflecting higher joint loading. Overall OR: $P < .001$. BML, bone marrow lesion; CS, cross-sectional; L, lateral; M, medial; M&L, medial and lateral; PR, prospective.

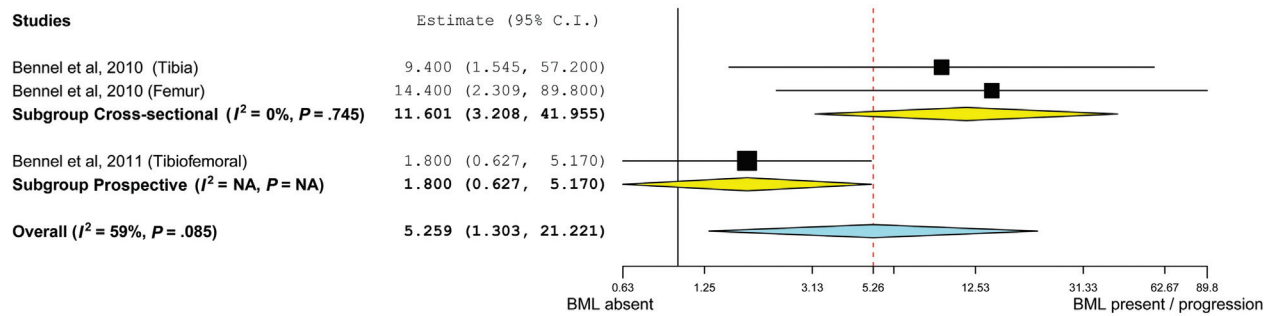


Figure 4. Forest plot for knee adduction moment (KAM) impulse as a risk factor for bone marrow lesions. Overall odds ratio ($P = .02$) for KAM impulse: higher KAM impulse reflecting higher joint loading in the medial compartment. BML, bone marrow lesion.

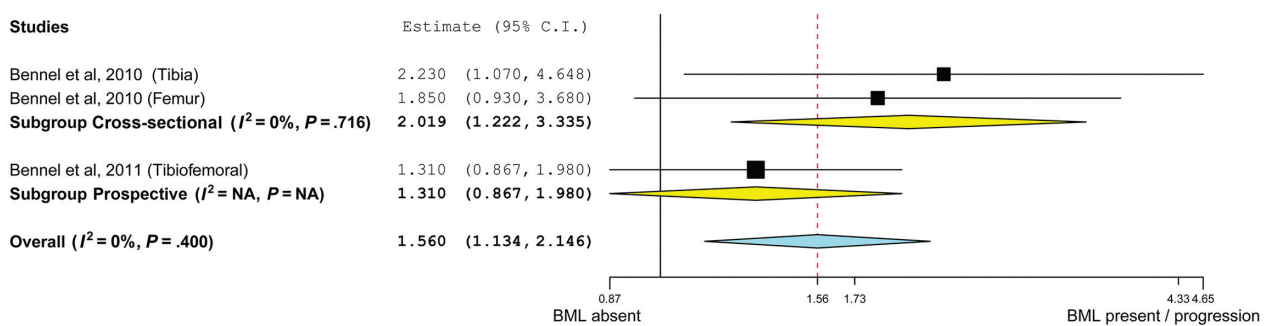


Figure 5. Forest plot for peak knee adduction moment (KAM) as a risk factor for bone marrow lesions. Overall odds ratio ($P = .006$) for peak KAM: higher peak KAM reflecting higher joint loading in the medial compartment. BML, bone marrow lesion; NA, not available.

BML progression after 30 months with knee alignment (RR, 1.7; 95% CI, 1.4-2.0), but no ORs were provided. We calculated ORs for enlarging BMLs in baseline valgus

knees versus neutral and varus versus neutral. Consequently, data from 3 studies resulted in an overall OR of 3.22 (95% CI, 1.91-5.44; $P < .001$) but with a high

TABLE 3
Studies Reporting on Knee Compartmental Loads and BMLs^a

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
<i>Cross-sectional studies</i>							
Bennell et al ⁸ (2010)	Sx medial OAK; N = 91 (51%)	64.5 ± 1.6	Peak KAM, KAM impulse	Presence (Y/N)	—	Medial tibia: peak KAM: OR, 2.23 (1.07-4.7) [P = .017]; KAM impulse: OR, 9.4 (1.53-57.2) [P = .01] Medial femur: peak KAM: OR, 1.85 (0.93-3.7) [P = .0440]; KAM impulse: OR, 14.4 (2.3-89.8) [P = .01]	4/6
Hunter et al ⁴⁰ (2006)	BOKS; N = 217 (44%)	66.4 ± 9.4	Knee alignment	Presence (Y/N)	—	MC (most varus quartile vs valgus): tibia: OR*, 8.492 (3.589-20.094); femur: OR*, 15.789 (5.740-43.432) LC (valgus vs most varus quartile): tibia: OR*, 3.310 (1.403-7.808); femur: OR*, 5.744 (1.520-21.707)	6/8
Issa et al ⁴¹ (2007)	OAK; N = 146 (75%)	70 ± 11	Knee alignment	WORMS	—	MC: difference in WORMS 1 and 0: 5.1 (2.6-7.6) [P < .05]; difference in WORMS 2-3 vs 0: 7.4 (5.2-9.5) [P < .05] LC: difference in WORMS 1 and 0: -0.1 (-2.5 to 2.3) [P > .05]; difference in WORMS 2-3 vs 0: -2.6 (-7.1 to -1.8) [P < .05]	4/6
Kean et al ⁴³ (2012)	Sx medial OAK; N = 169 (nk)	>50	Peak KAM, KAM impulse	Presence (Y/N)	—	Presence vs absence: peak KAM (M): 3.95 (3.76-4.13) vs 3.47 (3.23-3.71) [P < .01]; KAM impulse (mean): 1.35 (1.28-1.42) vs 1.15 (1.07-1.24) [P < .01]	6/6
Zhai et al ⁷³ (2006)	Adult children of patients undergoing knee replacement for OAK; N = 115 (52%)	47 ± 7	Knee alignment	Presence (Y/N)	—	"No association" (P > .05)	3/6
<i>Prospective studies</i>							
Bennell et al ⁷ (2011)	Sx medial OAK; N = 144 (56%)	64.4 ± 8.0	Peak KAM, KAM impulse	Progression after 1 y (Y/N)	1 y	Peak KAM: OR, 1.31 (0.86-1.98) [P = .21] KAM impulse: OR, 1.80 (0.63-5.17) [P = .28]	6/8
Bennell et al ⁶ (2011)	Sx medial OAK; N = 200 (59%)	63.3 ± 8.1	Lateral wedged insoles	Progression after 1 y (Y/N)	1 y	Difference (pre – post) in median BML changes after 1 y between real and sham insoles: 0 (-0.31 to 0.31)	6/6
Englund et al ²³ (2010)	MOST; N = 1204 (61%)	62.2 ± 7.9	Knee alignment	Progression after 30 mo (Y/N)	30 mo	MC: varus vs valgus: OR*, 3.226 (2.103-4.948) LC: valgus vs varus: OR*, 2.913 (1.871-4.535)	7/8
Hayashi et al ³² (2012)	With or at high risk of OAK (MOST); N = 1422 (61%)	62.1 ± 7.9	Knee alignment	Progression after 30 mo (Y/N)	30 mo	MC: varus: RR, 1.5 (1.2-1.9) LC: valgus: RR, 1.4 (1.0-2.1) More loaded compartments: RR, 1.7 (1.4-2.0) MC and LC: varus vs valgus: OR*, 1.597 (1.257-2.028)	6/8
Hunter et al ⁴⁰ (2006)	BOKS; N = 217 (44%)	66.4 ± 9.4	Knee alignment	Progression after 15/30 mo (Y/N)	15 and 30 mo	Progression: β = .8, P = .003 (medial compartment of femur and tibia) β = .6, P = .008 (lateral compartment of femur and tibia)	6/8

(continued)

TABLE 3
(continued)

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
Segal et al ⁶³ (2012)	MOST; N = 38 (61%)	63.5 ± 8.4	Articular surface contact stress: case region: mean, 3.59 ± 1.09 MPa and peak, 8.64 ± 2.91 MPa; control region: mean, 1.13 ± 1.70 MPa and peak, 2.78 ± 4.31 MPa	Progression after 30 mo (Y/N)	30 mo	Mean contact stress: OR, 6.6 (2.7- 16.5) [<i>P</i> < .0001] Peak contact stress: OR, 2.3 (1.5-3.6) [<i>P</i> < .0001]	4/6

^aBML, bone marrow lesion; BOKS, Boston Osteoarthritis of the Knee Study; KAM, knee adduction moment; LC, lateral compartment; MC, medial compartment; MOST, Multicenter Osteoarthritis Study; N, no; nk, not known; OAK, knee Osteoarthritis; OR, odds ratio; OR*, calculated OR from the reported data; RR, relative risk; Sx, Symptomatic; WORMS, Whole-Organ Magnetic Resonance Imaging Score; Y, yes.
^bValues in parentheses are 95% CIs unless otherwise indicated.

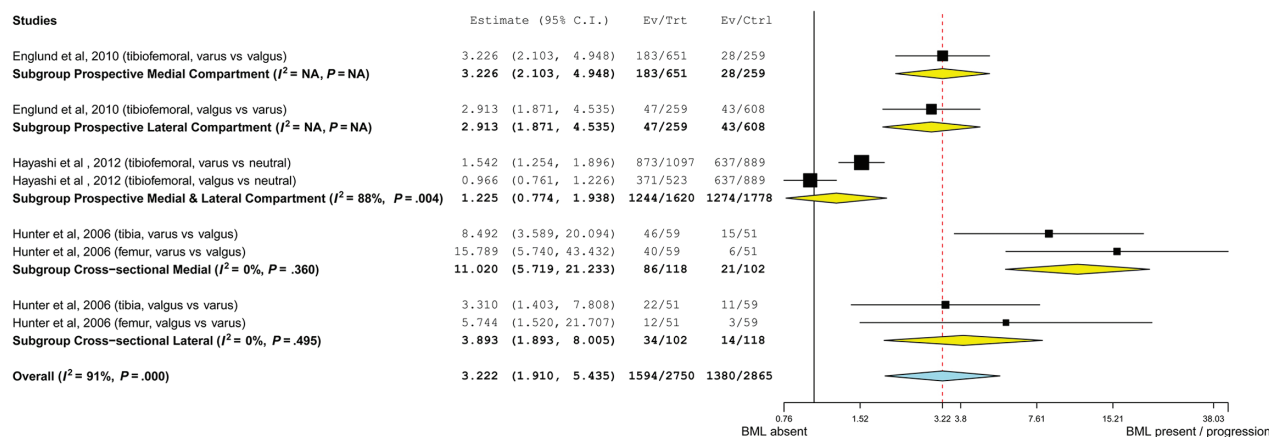


Figure 6. Forest plot for knee alignment as a risk factor for bone marrow lesions. Overall odds ratio (*P* < .001) for knee alignment: higher varus/valgus reflecting higher joint loading in the medial/lateral compartment. BML, bone marrow lesion.

heterogeneity of the study results (*I*² = 91%, *P* = .000). Subgroup analyses show that this heterogeneity is caused by a significant *I*² value (*I*² = 88%, *P* = .004) in 1 subgroup. This was the only subgroup in which the presence of BMLs in both medial and lateral compartments was evaluated for both varus loads as well as for valgus loads (Figure 6). All other subgroups evaluated varus loads in the medial knee compartment and valgus loads in the lateral knee compartment.

Knee Structural Lesions. Knee structural lesions were investigated in relation to BMLs in 9 studies (Table 4).^{4,23,31,36,37,40,49,69,73} Four studies found that meniscal lesions increased the risk for BML presence and progression (overall OR, 4.06; 95% CI, 2.73-6.04; *P* < .001 [*I*² = 56%, *P* > .01]) (Figure 7).^{23,37,49,69} Meniscal lesions increased the risk of BML progression after 30 months, 2 years, and 10 years (overall OR, 3.2; 95% CI, 2.1-4.8; *I*² =

53%, *P* = .048).^{23,37,69} Two studies with a cross-sectional design also found an increased risk for the presence of BMLs when meniscal lesions were present (overall OR, 8.2; 95% CI, 4.4-15.1; *I*² = 0%, *P* = .417).^{49,69}

Two studies found positive associations between ACL lesions (degeneration, tears) and BMLs.^{36,37} Hovis et al³⁶ found that knees with ACL lesions had significantly more BMLs than normal knees, and Huetink et al³⁷ found that ACL ruptures increased the risk of BML progression after 10 years (OR ranging from 2.4 [95% CI, 0.9-6.5] in the medial femur to 5.5 [95% CI, 1.3-23.7] in the lateral femur). However, BML scores did not differ between knees with complete and incomplete ACL tears.³⁶

Five studies showed a positive association between cartilage lesions and BMLs.^{4,23,31,40,73} Data from 1 longitudinal study indicated that cartilage lesions predict BML progression after 30 months in the medial and lateral

TABLE 4
Studies Reporting on Knee Structural Lesions and BMLs^a

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
<i>Cross-sectional studies</i>							
Baranyay et al ⁴ (2007)	No Sx (MCCS); N = 297 (63%)	58.0 ± 5.5	Cartilage lesion	Presence (Y/N)	—	MC tibiofemoral: OR, 1.80 (1.21-2.69) [<i>P</i> = .004] LC tibiofemoral: OR, 1.45 (1.02-2.07) [<i>P</i> = .04] Total knee: OR, 1.21 (1.02-1.47) [<i>P</i> = .03]	5/6
Guymer et al ³¹ (2007)	No Sx (community); N = 176 (100%)	52.3 ± 6.6	Cartilage lesion	Presence (Y/N)	—	MC tibiofemoral: OR, 3.51 (1.08-11.42) [<i>P</i> = .04] LC tibiofemoral: OR, 1.02 (0.17-6.12) [<i>P</i> = .98] Total knee: OR, 2.12 (0.83-5.45) [<i>P</i> = .12]	5/6
Hovis et al ³⁶ (2012)	Sx OAk (OAI progression); N = 105 (e: 56%; c: 79%)	64.5 ± 9.6	ACL lesion	WORMS	—	Normal vs abnormal ACL: 1.83 ± 2.06 vs 4.35 ± 3.03 [<i>P</i> < .0001] Complete vs incomplete ACL tear: 4.40 ± 3.22 vs 4.17 ± 2.44 [<i>P</i> > .05]	1/6
Lo et al ⁴⁹ (2009)	Sx OAk (OAI progression); N = 160 (50%)	61 ± 10	Meniscal lesion	Presence of large BMLs (Y/N)	—	Medial meniscal lesion: no lesion vs lesion: 0% vs 35% [<i>P</i> < .0001] (MC); OR*, 37.218 (2.228-621.613) Lateral meniscal lesion: no lesion vs lesion: 6% vs 23% [<i>P</i> < .0022] (LC); OR*, 4.472 (1.616-12.378)	3/6
Wang et al ⁶⁹ (2010)	Sx OAk; N = 100 (54%)	63.3 ± 10.4	Meniscal lesion	Presence (Y/N)	—	Medial meniscal lesion: OR, 10.41 (3.9-27.8) [<i>P</i> < .001] Lateral meniscal lesion: OR, 10.66 (2.7-42.2) [<i>P</i> = .001] (LM extrusion)	7/8
Zhai et al ⁷³ (2006)	Adult children of patients undergoing knee replacement for OAk; N = 115 (52%)	47 ± 7	Cartilage lesion	BML size (ordinal)	—	MC: Spearman ρ = 0.26, <i>P</i> < .01 LC: Spearman ρ = 0.26, <i>P</i> < .01	3/6
<i>Prospective studies</i>							
Englund et al ²³ (2010)	MOST; N = 1204 (61%)	62.2 ± 7.9	Meniscal lesion, cartilage lesion	Progression after 30 mo (Y/N)	30 mo	Medial meniscal lesion: OR*, 2.922 (2.176-3.923) (MC); minor lesion: RR, 1.8 (1.3-2.3) [<i>P</i> ≤ .05] (MC); major lesion: RR, 2.4 (1.8-3.2) [<i>P</i> ≤ .05] (MC) Lateral meniscal lesion: OR*, 5.440 (3.689-3.923) (LC); minor lesion: RR, 4.0 (2.7-5.9) [<i>P</i> ≤ .05] (LC); major lesion: RR, 5.0 (3.2-7.7) [<i>P</i> ≤ .05] (LC) MC tibiofemoral: OR*, 3.400 (2.387-4.845) LC tibiofemoral: OR*, 5.150 (3.275-8.099)	7/8
Huetink et al ³⁷ (2010)	Subacute knee problems; N = 326 (33%)	42 ± 8	ACL lesion, meniscal lesion	Progression after 10 y (Y/N)	10 y	ACL lesion: femur: OR, 5.5 (1.3-23.7) [<i>P</i> = .22 (LC) and OR, 2.4 (0.9-6.5) [<i>P</i> = .078] (MC); tibia: OR, 1.1 (0.2-5.6) [<i>P</i> = .938] (LC) and OR, 4.0 (0.9-18.4) [<i>P</i> = .078] (MC) Medial meniscal lesion: tibia: OR, 4.1 (1.1-15.9) [<i>P</i> = .04] (MC); femur: OR, 1.7 (0.7-3.9) [<i>P</i> = .248] (MC) Lateral meniscal lesion: tibia: OR, 4.4 (1.1-17.3) [<i>P</i> = .034] (LC); femur: OR, 0.7 (0.1-4.0) [<i>P</i> = .732] (LC)	5/8

(continued)

TABLE 4
(continued)

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
Hunter et al ⁴⁰ (2006)	BOKS; N = 217 (44%)	66.4 ± 9.4	Cartilage lesion: loss over 15 or 30 mo	WORMS (baseline); change in WORMS after 15 or 30 mo	15 and 30 mo	Cartilage loss in ipsilateral compartment per 1-unit difference in baseline BML at 30 mo: $\beta = 1.58$, $P < .0001$ (MC tibiofemoral); $\beta =$ 1.88 , $P < .0001$ (LC tibiofemoral) Cartilage loss in contralateral compartment per 1-unit difference in baseline BML at 30 mo: $\beta = -.74$, $P < .0001$ (MC tibiofemoral); $\beta = -$ $.21$, $P = .09$ (LC tibiofemoral) Cartilage loss in ipsilateral compartment per 1-unit increase in BML score at 30 mo: $\beta = .26$, $P =$ $.16$ (MC tibiofemoral); $\beta = .45$, $P =$ $.10$ (LC tibiofemoral) Cartilage loss in contralateral compartment per 1-unit increase in BML score at 30 mo: $\beta = -.16$, $P = .52$ (MC tibiofemoral); $\beta = -.08$, $P = .059$ (LC tibiofemoral)	6/8
Wang et al ⁶⁹ (2010)	Sx OAK; N = 100 (54%)	63.3 ± 10.4	Meniscal lesion	Progression after 2 y (Y/N)	2 y	Medial meniscal lesion: OR, 3.3 (1.2- 9.1) [$P = .02$] Lateral meniscal lesion: not analyzed because of small sample size	7/8

^aACL, anterior cruciate ligament; BML, bone marrow lesion; BOKS, Boston Osteoarthritis of the Knee Study; c, control group; e, experimental group; LC, lateral compartment; LM, lateral meniscus; MC, medial compartment; MCCS, Melbourne Collaborative Cohort Study; MOST, Multicenter Osteoarthritis Study; N, no; OAI, Osteoarthritis Initiative; OAK, knee Osteoarthritis; OR, odds ratio; OR*, calculated OR from the reported data; RR, relative risk; Sx, Symptomatic; WORMS Whole-Organ Magnetic Resonance Imaging Score; Y, yes.

^bValues in parentheses are 95% CIs unless otherwise indicated.

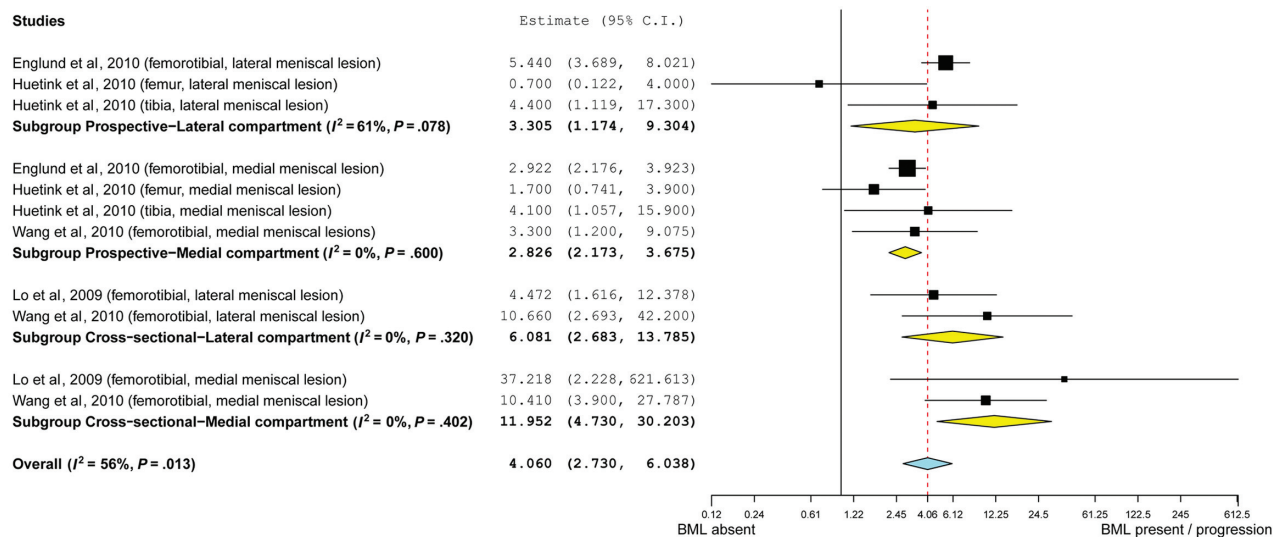


Figure 7. Forest plot for meniscal lesions as a risk factor for bone marrow lesions. Overall odds ratio ($P < .001$) for meniscal lesion: higher meniscal lesions reflecting higher joint loading in the medial compartment. BML, bone marrow lesion.

knee compartments (calculated OR_{medial} , 3.4 [95% CI, 2.4-4.8] and $OR_{lateral}$, 5.2 [95% CI, 3.3-8.1]).²³ Hunter et al⁴⁰ showed a longitudinal inverse association: knee compartments with higher BML scores increased the risk of

cartilage loss after 30 months ($\beta = 1.58-1.88$, $P < .0001$). Moreover, they found that an increase in BMLs was strongly associated with further worsening of cartilage lesions after 30 months, but after adjustment for limb

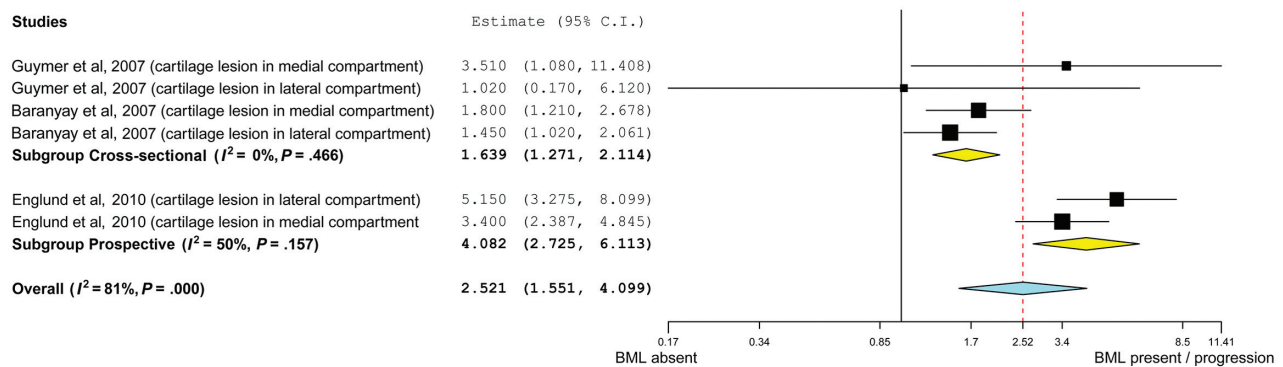


Figure 8. Forest plot for cartilage lesions as a risk factor for bone marrow lesions. Overall odds ratio ($P < .001$) for cartilage lesion: higher cartilage lesions reflecting higher joint loading in the medial compartment. BML, bone marrow lesion.

alignment, this association was not significant; no ORs were provided.⁴⁰ Worth mentioning, a BML in the lateral compartment seemed to be protective of cartilage loss in the medial compartment ($\beta = -.74$, $P < .0001$).⁴⁰ One study showed significant cross-sectional correlations between the presence of BMLs and cartilage lesions ($\rho = 0.26$, $P < .01$), but no ORs were reported.⁷³ A meta-analysis was performed based on 3 studies (overall OR, 2.52; 95% CI, 1.55-4.10; $P < .001$), with high heterogeneity ($I^2 = 81\%$, $P = .000$).^{4,23,31} This extreme inconsistency among studies is substantially reduced and became nonsignificant once differences in study design are accounted for (Figure 8).

Physical Activity. Eight studies investigated the effect of physical activity on BMLs (Table 5).^{4,20,35,44,57,62,64,65} Four of them investigated the effect of long-distance running on BMLs, but their methodological quality was rated very low.^{35,44,62,64} None of these studies showed any long-term effects of long-distance running on BMLs. One study showed a higher prevalence of BMLs in marathon runners ($n = 5/10$) compared with active controls ($n = 1/12$).⁶⁴

Two studies of good methodological quality found no association between physical activity scores and BMLs.^{4,57} Moreover, 1 of these studies showed that walking on a weekly basis was protective against the presence of tibiofemoral BMLs after 10 years.⁵⁷ On the contrary, 2 studies reported a higher risk of physical activity for the presence or progression (after 2.7 years) of BMLs.^{20,65} Doré et al²⁰ showed that walking more than 10,000 steps per day increases the risk of BML progression after 2.7 years (RR, 1.97; 95% CI, 1.19-3.27; $P = .009$). Stehling et al⁶⁵ reported that patients with high scores on the Physical Activity Scale for the Elderly (PASE) had significantly more BMLs than patients with low PASE scores (OR, 1.9; 95% CI, 0.8-4.3).

DISCUSSION

This systematic review summarizes the literature regarding the interaction between knee mechanical loading and BMLs. Therefore, we included 29 studies and categorized the reported loading variables into 4 categories. We found

that increased compartmental loads and structural lesions increased the risk of BML presence/progression tremendously (overall OR ranging from 1.56 [95% CI, 1.13-2.15] to 8.2 [95% CI, 4.4-15.1]; $P = .006$). Additionally, we discovered that body weight increased the risk for BMLs to a lesser extent (overall OR, 1.03; 95% CI, 1.01-1.05; $P = .007$). Also, we found contradictory results for the presence/progression of BMLs due to physical activity. This may be explained by the fact that the effect of physical activity may be different according to the context in which the physical activity is performed (knee alignment, presence of structural lesions, etc). Moreover, Doré et al²⁰ showed that the number of people with BML progression after 2.7 years was significantly higher in the group that walked more than 10,000 steps per day versus those who walked less than 10,000 steps per day, indicating a possible dose-response relationship.

Studies within the body weight and body composition category provided heterogeneous results with small combined ORs for weight and BMI. In this context, it should be noted that recently, different hypothetical phenotypes of OA were suggested, each with their respective key drivers of the disease.⁴² Two of these drivers (ie, mechanotransduction and metabolic drivers) can both be linked to body weight. Mechanotransduction has been interpreted as a “mechanical load that may drive a wear and tear effect,” and the metabolic driver was interpreted as “unhealthy phenotypes, such as obesity, that may drive OA through adipokines.”^{42(p11)} Thus, using body weight as an outcome for mechanical knee loading solely may be an underestimation of its contribution to OA. Findings of an association between BMI and the development of OA in nonweightbearing joints empower the hypothesis of adipose tissue being a driver of the disease.^{12,55} This may be explained by the possible role of adipose tissue in the pathogenesis of OA: proinflammatory cytokines (including tumor necrosis factor- α and interleukin-1 β) that are released by adipocytes may contribute to the development of OA and associated BMLs.⁵⁶ Interestingly, Berry et al⁹ showed that the prevalence of BMLs was higher with increasing total body fat mass but not with increasing BMI. This is in line with recent reports indicating that BMI is not an absolute surrogate marker for total fat

TABLE 5
Studies Reporting on Physical Activity and BMLs^a

Study	Study Population; Sample Size (% Female)	Age, y	Loading Outcome	BML Outcome	Follow-up	Results ^b	Quality Score
<i>Cross-sectional studies</i>							
Baranyay et al ⁴ (2007)	No Sx (MCCS); N = 297 (63%)	58.0 ± 5.5	Physical activity score	Presence (Y/N)	—	“Not significantly associated”	5/6
Hohmann et al ³⁵ (2004)	Marathon runners; N = 8 (0%)	23-58	Marathon running	Narrative	—	BML noticed on before and after images in 1 ACL-reconstructed runner; “BML not noticed on any other images”	2/8
Schueler-Weidekamm et al ⁶² (2006)	Long-distance runners; N = 26 (73%)	33 ± 5	Training level (high vs low)	Presence (Y/N)	—	High vs low training level: n = 1 (4%) vs n = 1 (4%)	2/6
Stehling et al ⁶⁵ (2010)	No Sx (OAI incidence); N = 236 (58%)	50.6 ± 3.0	Physical activity	Presence (Y/N)	—	Low vs medium vs high physically active (PASE score tertiles): n = 19 (28%) vs n = 51 (42%) vs n = 25 (54%) [P = .0251] Low vs high physically active (extreme PASE tertiles): OR*, 1.880 (0.831-4.253)	4/6
<i>Prospective studies</i>							
Doré et al ²⁰ (2013)	TASOAC; N = 405 (51%)	51-81	Steps/d	Progression after 2.7 y (Y/N)	2.7 y	<10,000 vs ≥10,000 steps/d: 14% progressed vs 24% [P = .016] ≥10,000 steps/d: RR, 1.97 (1.19-3.27) [P = .009]	5/8
Krampla et al ⁴⁴ (2001)	Marathon runners; N = 8 (0%)	27-46	Marathon running	Presence (Y/N)	6 wk	Little change in signal alterations of bone marrow after marathon; 1 runner showed new cyst surrounded by bone marrow edema at 8 wk after marathon; in all other runners, signal alterations of bone marrow decreased after 8 wk	4/8
Racunica et al ⁵⁷ (2007)	No Sx (MCCS); N = 297 (63%)	58.0 ± 5.5	Physical activity	Presence (Y/N), presence after 10 y (Y/N)	10 y	Cross-sectional: vigorous weightbearing exercise: OR, 0.4 (0.1-1.5) [P = .19]; vigorous physical activity: OR, 0.7 (0.4-1.1) [P = .12] Longitudinal: vigorous physical activity: OR, 0.9 (0.6-1.2) [P = .4]; less vigorous physical activity: OR, 0.7 (0.4-1.3) [P = .3]; walking (weekly frequency): OR, 0.6 (0.3-0.98) [P = .04]	6/8
Stahl et al ⁶⁴ (2008)	Marathon runners; N = 22 (45%)	31 ± 5	Marathon running	WORMS, volume	5 d	Before marathon: runners vs control: n = 5 vs 1 [P < .05]; 752 vs 290 mm ³ [no P value provided]; mean WORMS of 1.8 vs 1 [no P value provided] After marathon: “no statistically significant changes”	4/8

^aACL, anterior cruciate ligament; BML, bone marrow lesion; MCCS, Melbourne Collaborative Cohort Study; N, no; OAI, Osteoarthritis Initiative; OR, odds ratio; OR*, calculated OR from the reported data; PASE, Physical Activity Scale for the Elderly; Sx, Symptomatic; TASOAC, Tasmanian Older Adult Cohort study; WORMS, Whole-Organ Magnetic Resonance Imaging Score; Y, yes.

^bValues in parentheses are 95% CIs unless otherwise indicated.

mass or adipose tissue mass in elderly persons.^{13,60,61} Therefore, we propose to take body composition into account when investigating body weight and physical activity as confounding parameters in OA in future studies.

Within the category of compartmental load, a strong equality exists across all included cross-sectional studies using different parameters (KAM, knee alignment, contact stress).^{8,32,40,41,43} The shown risks of all parameters measuring medial/lateral loads strongly suggest that compartment-specific BMLs are related to a greater medial or lateral load. Surprisingly, an RCT investigating the

effect of lateral wedge insoles worn for 12 months did not find significant changes in BMLs in patients with medial knee OA.⁶ The insoles were known to reduce the load in the medial compartment of the knee during walking.³⁴ Possible explanations for the absence of a statistical significance were a too short follow-up period, nonstandardized shoes, and a heterogeneous response due to different baseline severity grades.⁶

Several included studies showed an increased risk for the presence of BMLs with knee structural lesions. We were not able to differentiate between different kinds of meniscal lesions (subluxation, root tears, etc) because of

the low number of studies included and because of the different definitions used for meniscal lesions. For example, 1 study defined “meniscal derangement” as “disruption of the overall morphology of the meniscus and diffuse hyperintense signal in the body of the meniscus,”^{49(p744)} while another assessed the “extent of meniscal extrusion.”^{69(p998)} A third study defined a meniscal lesion as a “meniscal tear, maceration, and/or destruction or resection of the anterior horn, body segment, and the posterior horn of the medial and lateral menisci,”^{23(p1797)} and the last study defined “meniscal tears and subluxations.”^{37(p538)} Moreover, ACL ruptures and meniscal lesions (tear, extrusion) alter the biomechanics of the knee, which may result in an increased peak articular pressure.^{1,11} This could explain the association with BMLs because such a redistribution of loads may result in a higher susceptibility for BMLs in the more loaded compartments.¹¹ Hunter et al⁴⁰ showed that higher BML scores at baseline predicted significantly greater cartilage loss after 15 or 30 months, and therefore, BMLs were found to be predictors for cartilage lesions. This finding may be the reflection of an OA-induced altered bone structure, resulting in a decreased shock absorption capacity of the bone. Nevertheless, it is in contrast to our hypothesis of cartilage being the shock absorber and thus protecting subchondral bone from overloading. However, in favor of our hypothesis, another study found that the prevalence of cartilage lesions at baseline was associated with the incidence or enlarging of BMLs after 30 months.²³ Additionally, increased local bone density, which may reflect increased loading,⁶⁷ was shown to be related to the presence of BMLs.⁵⁰

One study found that the presence of BMLs in the lateral compartment was protective of cartilage loss in the medial compartment.⁴⁰ One possible explanation for this finding is that it represents pseudowidening (and thus decreased loading) of the medial compartment because of an increased valgus angle.⁴⁰

A higher physical activity level was found to be related to the progression or a higher occurrence of BMLs.^{20,65} It was unclear whether the association of BMLs with physical activity was independent of other structural changes (eg, cartilage and meniscal lesions) as they are usually interrelated. Moreover, none of the studies corrected their findings for knee alignment. The 4 studies investigating the effect of running were of low methodological quality because of the small sample sizes and the descriptive nature of the outcomes.^{35,44,62,64} In general, BMLs remained detectable immediately^{35,64} or 6 weeks⁴⁴ after a long-distance running race only in those knees with pre-existing structural changes (ligamentous and/or meniscal). Unfortunately, long-term follow-up data were not available, and it remains unclear whether this phenomenon is transient.

The results of this review may be of interest for clinical decision making. Already, BMLs have been significantly and independently associated with pain in knee OA,⁷² and changes in BMLs correlate with changes in pain.^{19,25} Treatment guidelines for knee OA generally recommend exercise therapy, with pain reduction as one of its main treatment goals.^{26,51} In our previously published

systematic literature review, we found that one of the proposed hypotheses for the explanation of the beneficial effect of exercise in knee OA is an exercise-induced reduction of the focal peak load in the tibiofemoral joint, but this hypothesis needs to be confirmed in clinical trials.⁵ However, the results of the present review suggest that BMLs may be associated with such focal loads. Interestingly, Wiegant et al⁷⁰ found beneficial effects of unloading the knee by means of joint distraction on OA-related structural changes; however, they did not report on BMLs.

This study is the first comprehensive review including a meta-analysis of the effect of knee loading on BMLs. Studies on patients with radiological knee OA and on patients at risk of developing knee OA were both included for this review, and a broad spectrum of types of loading was taken into account. We tried to combine the data as much as possible to avoid too much influence from separate study results and in an attempt to settle controversies arising from conflicting results.¹⁷ However, the results of our meta-analysis should be interpreted with caution for those analyses with significant heterogeneity. To reduce the influence of heterogeneity on our results, subgroup analyses for potentially important sources of heterogeneity including study design (cross-sectional vs prospective) and knee compartment (lateral vs medial) were performed. This approach has previously been used by others in meta-analyses to counter heterogeneity.³³ On the other hand, it is not uncommon that heterogeneity is present in meta-analyses: nearly 16% of 509 meta-analyses in the Cochrane Database of Systematic Reviews show I^2 values $\geq 70\%$.³³

CONCLUSION

This review included 29 studies investigating the effect of joint loading on tibiofemoral BMLs. Augmented compartmental loads and structural lesions increased the risk of the presence or progression of BMLs. Body weight increased the risk for BMLs to a lesser extent. Contradictory results for the effect of physical activity on BMLs were found but may be explained by a dose-response relationship and the fact that the effect of physical activity may be different according to the context (knee alignment, structural lesions, etc) in which the physical activity is performed.

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