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CLINICAL SCIENCE

Machine-learning, MRI bone shape and important clinical outcomes in osteoarthritis: data from the Osteoarthritis Initiative

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ABSTRACT

Objectives Osteoarthritis (OA) structural status is imperfectly classified using radiographic assessment. Statistical shape modelling (SSM), a form of machine-learning, provides precise quantification of a characteristic 3D OA bone shape. We aimed to determine the benefits of this novel measure of OA status for assessing risks of clinically important outcomes.

Methods The study used 4796 individuals from the Osteoarthritis Initiative cohort. SSM-derived femur bone shape (B-score) was measured from all 9433 baseline knee MRIs. We examined the relationship between B-score, radiographic Kellgren-Lawrence grade (KLG) and current and future pain and function as well as total knee replacement (TKR) up to 8 years.

Results B-score repeatability supported 40 discrete grades. KLG and B-score were both associated with risk of current and future pain, functional limitation and TKR; logistic regression curves were similar. However, each KLG included a wide range of B-scores. For example, for KLG3, risk of pain was 34.4 (95% CI 31.7 to 37.0)%, but B-scores within KLG3 knees ranged from 0 to 6; for B-score 0, risk was 17.0 (16.1 to 17.9)% while for B-score 6, it was 52.1 (48.8 to 55.4)%. For TKR, KLG3 risk was 15.3 (13.3 to 17.3)%; while B-score 0 had negligible risk, B-score 6 risk was 35.6 (31.8 to 39.6)%. Age, sex and body mass index had negligible effects on association between B-score and symptoms.

Conclusions B-score provides reader-independent quantification using a single time-point, providing unambiguous OA status with defined clinical risks across the whole range of disease including pre-radiographic OA. B-score heralds a step-change in OA stratification for interventions and improved personalised assessment, analogous to the T-score in osteoporosis.

Key messages

What is already known about this subject?

- There is a huge unmet need for accurate and reliable assessment of osteoarthritis (OA) status.
- MRI has demonstrated much more pathology but has been largely constrained to reader-dependent semiquantitative assessment.
- Machine-learning enables accurate, reader-independent quantification and we have previously demonstrated it can measure a characteristic OA three-dimensional bone shape with good precision.

What does this study add?

- Through application of machine learning, this study has provided a new highly reliable and precise measure of OA status, a quantified 3D femur bone shape termed the B-score.

How might this impact on clinical practice or future developments?

- B-score should enable improved stratification for interventions, accurate classification across the range of OA severity and improved personalised assessment, analogous to the role of the T-score in osteoporosis.

INTRODUCTION

Osteoarthritis (OA) is a serious disease resulting in pain, loss of function and reduced quality of life and represents a major public health problem.[1] The pathophysiology of OA involves multiple tissues, with deterioration of both cartilage and bone considered integral to the OA process.[2] End-stage disease can be successfully treated with joint replacement, but there has been limited progress with interventions that address earlier OA stages.

OA structural pathology has conventionally been assessed using X-rays. Radiographic determination of OA structural status is imprecise due to its dependence on acquisition method and reader reliability.[3] The most common scoring system, the semiquantitative Kellgren-Lawrence grade (KLG, scored 0–4), assesses cartilage and bone as well as (indirectly) meniscal changes.[4] Semiquantitative radiographic assessment has driven our understanding of structure-symptom relationships,[5] demonstrating associations at group, but not at individual patient level.

MRI has enabled detailed understanding of three-dimensional OA structural pathology and revealed multiple pathologies not evident on X-rays. MRI provides direct quantitative assessment of cartilage and bone[6 7] and the most responsive imaging biomarkers. However, there remains a strong need for validated surrogate measures of clinically important outcomes, which provide OA status from a single time point, without longitudinal evaluation.

In areas such as hypertension and diabetes, the provision of a single, quantitative measurement has provided breakthroughs in clinical management and drug discovery. In the management of osteoporosis, the dual-energy absorptiometry-based T-score

replaced imprecise and insensitive measures based on radiographic bone assessment and photon absorptiometry, creating a single standard measure.

In the field of clinical imaging, the appearance of a tissue can be learnt and then applied to automatically find and delineate that tissue in new, unseen images.[8] Importantly, this approach is agnostic, being independent of prior expert opinion. Statistical shape modelling (SSM), a type of supervised machine-learning, employs principal component analysis to reduce complex 3D geometric shapes to a single metric value.[9] Using SSM, we have identified a characteristic OA 3D bone shape, incorporating osteophyte ridge formation and widening and flattening of the articular surfaces. This bone shape predicts radiographic onset of OA,[10] is associated with radiographic structural progression[11] and discriminates knees with OA from non-OA.[12] In each of these studies, the femur had the greatest discrimination and responsiveness, and we have focused this study on femur shape, here termed 'B-score'. To determine the value of B-score as a measure of OA status, we examined its precision, relationship with the existing radiographic standard (KLG) and explored the relationships of both B-score and KLG with clinically important outcomes: pain, function and total knee replacement (TKR) surgery.

METHODS

Quantifying tissue shape

Patient image data

Data were obtained from the Osteoarthritis Initiative (OAI), a multicentre, longitudinal, prospective observational study of knee OA; bilateral knee MR images were collected in a standardised way together with clinical data from 4796 individuals with, or at risk of developing knee OA.[13] Data are publicly available at https://data-archive.nimh.nih.gov/oai/.

High-resolution sagittal 3D dual-echo at steady-state water-excitation (DESS-we) knee MRI images were acquired on recruitment into the OAI and at 1, 2 and 4 year timepoints, using a 3T MRI system (MAGNETOM Trio, Siemens Healthcare, Erlangen, Germany). Image acquisition parameters have been published in detail.[14]

Statistical shape modelling

Femur bones were automatically segmented from DESS-we images using active appearance models (AAMs), a type of SSM trained to search images, provided by Imorphics (Manchester, UK). AAMs are proven technology that can segment knee bone surfaces with submillimetre accuracy.[12 15] AAMs were constructed using a training set, from DESS-we images, selected to provide examples of all stages of OA.[16]

We constructed an 'OA vector', defined as the line passing through the mean shape of a population with OA (OA Group, defined as all knees with KLG ≥2 at all four time points of 0, 1, 2 and 4 years) and a population without OA (Non-OA Group, defined as those with KLG of 0 at each of the same time points).

B-score

Distances along the OA vector are termed 'B-score', with the origin (B-score 0) defined as the mean shape of the Non-OA Group for each gender. 1 unit is defined as 1 SD of the Non-OA Group along the OA vector (positive values towards the OA Group). Representative examples of differences in femur bone shape at various B-scores, and a heat map of the areas which change most with increasing B-score are shown in figure 1. The range of B-scores in the Non-OA Group was defined as the 95% confidence limits of B-scores in this group, being ±1.96; this enabled delineation of the Non-OA range of B-scores in figures and analysis. Expanded details of the methods for AAM search and construction of B-score are provided in online supplemental methods.

Measurement repeatability

All visually acceptable DESS-we images from the OAI retaken on the same day were assessed; a test-retest set (1 week apart) of those with definite OA were also analysed.[12 16] Repeatability

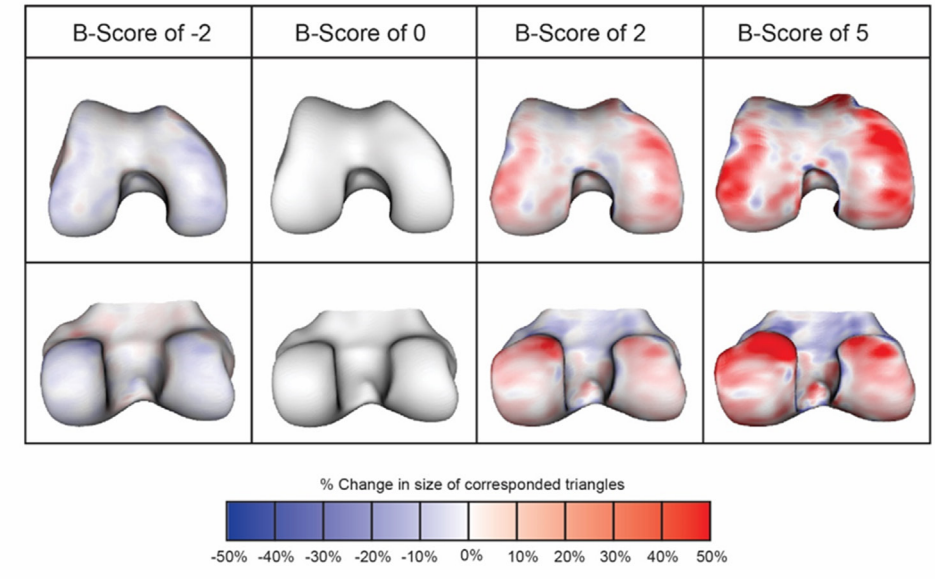

Figure 1 Figure shows change in shape for the anterior femur (top row) and posterior femur (bottom row), for various B-scores. Red indicates where there is an increase in size (locally calculated, based on anatomically corresponded triangles from the shape model), and blue indicates decrease in size (locally); scale shows percentage in area size change of each triangle. Change tends to be greatest around the edge of the cartilage plate (osteophyte region), but it also occurs in central subchondral regions where the bone flattens out.

(smallest detectable difference, SDD) was calculated as the 95% limits of agreement between the two image measurements, using the Bland-Altman method.

KLG reading was performed in the OAI using carefully acquired radiographs, with the knee positioned using a custom-designed frame allowing for a standard knee flexion angle and reporting position of the X-ray source.[17] Two expert readers independently assessed each radiograph; differences were adjudicated by a group including a more senior reader.

STATISTICAL ANALYSIS

All analyses were conducted using SAS V.9.4 (Cary, North Carolina, USA). Values for the associations with clinical outcomes are presented as proportion of the relevant population; referred to throughout as risk of a clinical outcome.

Pain by B-score and KL grade

Pain was assessed using the 7-day pain severity numeric rating scale (NRS, 0–10). Current pain was defined as NRS score at baseline, future pain as the median value of all later timepoints (up to 8 years, average follow-up 5 years). Knees were categorised as moderate pain (score ≥4) and severe pain (score ≥8).[18 19] As a sensitivity analysis, we assessed WOMAC-A pain (0–20 scale, moderate ≥4 and severe ≥8). Logistic regression analyses were performed for current and future pain as defined above against either KLG or baseline B-score, with no additional covariates.

Function by B-score and KL grade

Function was assessed using WOMAC function score (0–68), for the knee with the highest B-score per person. Current function was defined at baseline, future function as the median value at all later timepoints (follow-up as for pain). Moderate functional limitation was defined as ≥20 and severe as ≥35.[20 21] Logistic regression analyses were performed for current and future function as defined above against either KLG or baseline B-score, with no additional covariates.

Total knee replacement by B-score and KL grade

KL grade and B-score were independently assessed to determine predictors of TKR at any point during the follow-up period for an individual knee, defined as having an adjudicated TKR within a follow-up period of up to 8 years. This was assessed by modelling TKR as outcome against B-score and KLG separately using logistic regression models.

Logistic regression of KLG by B-score quartiles

To assess whether B-score provided additional information over KLG, two modelling approaches were considered. In the first, individual KLG groups were subdivided into quartiles based on B-score and assessed for the five clinical outcomes of current and future pain and function, and TKR, using logistic regression. The second approach involved initially modelling each outcome as described previously with KLG, then adding B-score to each model and assessing whether the regression coefficient for B-score was statistically significant and then calculating the resulting area under the curve (AUCs) for the combined models.

Confounders of B-score and risks of clinical outcomes

Potential confounders of the relationship between B-score and the risks of current pain, function and TKR were investigated by adjusting the models for age, sex, ethnicity, body mass index (BMI), alignment, previous knee surgery, non-steroidal anti-inflammatory drugs (NSAIDs) use and smoking status. A description of these variables is shown in the online supplemental methods section.

Table 1 Demographic and baseline characteristics

Parameter	Males N=1992	Females N=2799	Combined N=4791
Knee MRIs in the OAI dataset at baseline	n=1992	n=2799	n=4791
Both right and left	1929 (97)	2713 (97)	4642 (97)
Right only	37 (2)	49 (2)	86 (2)
Left only	26 (1)	37 (1)	63 (1)
Age (y)	n=1992	n=2799	n=4791
Mean (SD)	60.9 (9.5)	61.3 (9.0)	61.2 (9.2)
Median percentile (25th, 75th)	59 (53 to 70)	61 (54 to 69)	61 (53 to 69)
Min, Max	45 to 79	45 to 79	45 to 79
Race	n=1989	n=2797	n=4786
White	1666 (84)	2122 (76)	3788 (79)
Black or African American	276 (14)	595 (21)	871 (18)
Asian	13 (1)	32 (1)	45 (1)
Other non-white	34 (1)	48 (2)	82 (2)
Current cigarette smoker	n=1964	n=2766	n=4730
No	987 (50)	1513 (55)	2500 (53)
Yes	977 (50)	1253 (45)	2230 (47)
Use of NSAIDs at Baseline	n=1983	n=2796	n=4779
Yes	463 (23)	720 (26)	1183 (25)
No	1520 (77)	2076 (74)	3596 (75)
BMI (m/kg^2)	n=1990	n=2797	n=4787
Mean (SD)	28.8 (4.15)	28.5 (5.27)	28.6 (4.84)
Median percentile (25th, 75th)	28.5 (25.7 to 31.5)	28.1 (24.4 to 32.0)	28.2 (25.1 to 31.7)
Min, Max	18.3 to 44.6	16.9 to 48.7	16.9 to 48.7

All values are n (%) unless stated.
*BMI denotes body mass index, MRI magnetic resonance imaging, NSAIDS nonsteroidal anti-inflammatory drugs, and OAI Osteoarthritis Initiative.

RESULTS

Participant characteristics

Table 1 provides demographic and baseline characteristics. More than 96% of OAI participants had both knees assessed (total knees n=9433). Age ranged from 45 to 79 years. Median BMI was 28 kg/m^2 (range, 16.9–48.7).

Repeatability

A total of 139 knees were imaged twice on the same day within the OAI: the repeatability (SDD) of B-score in this group was 0.251 (B-score units). This group was representative of the whole OAI dataset (86 female, KLG 0, 1, 2, 3, 4 as fraction: 33%, 20%, 31%, 12%, 4%, BMI mean (SD) 30.3 (5.23); mean age (SD) 62.7 (9.45). A total of 35 knees were imaged in the test-retest set, at baseline and 1 week: SDD of B-score in these images was 0.254. This represents 2.5% of the likely range of B-scores (−3 to +7 in this study).

Relationship of B-score with KL grade

Distribution of B-score by KLG is shown in figure 2. There was a large range of B scores for each KLG, reflecting the increased measurement sensitivity of the measure, with B-score range increasing with KLG. Mean B-score had a non-linear association with KLG, increasing more rapidly at grades 3 and 4; CIs were wider with increased KLG. For example, the 95% confidence limits of B-score for a KLG3 knee (n=1237) were –0.2 and +6.0. 3.4% of KLG0 knees had B-scores greater than the non-OA range, KLG1:7.9%, KLG2:33.1% KLG3:57.6%,

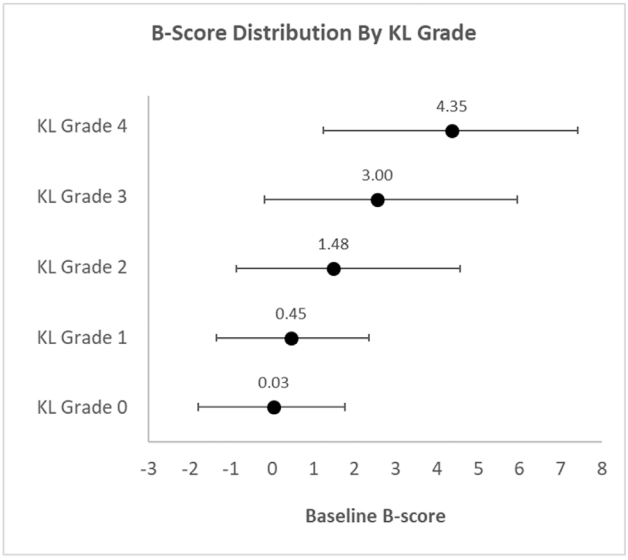

Figure 2 Distribution of B scores by KL grade are displayed for males and females (mean and 95% CIs for each grade). Mean B score for each KL grade is noted above each line.

KLG4:89.3%. Proportions of B-score bins classified by KLG are shown in online supplemental table S4 and online supplemental figure S3.

KLG and clinically important outcomes

The risk of moderate knee pain or limitation of function increased across the range of KLG from around 10% to around 60%; this was not linear, and risk increased more rapidly between KLG 3 and 4 (figure 3). Risks of severe knee pain or severe limitation of function also increased from 2% to 15% and 8% to 35%, respectively. Risk of TKR increased in a curvilinear manner, with risk increasing approximately 2.5-fold for each increase in KLG. Risk of future pain and function are shown in online supplemental figure S1.

B-score and clinically important outcomes

The risks of moderate knee pain or loss of function increased across the range of B-score from around 10% to around 60% and are curvilinear (figure 4 and online supplemental table S1). Risks of severe knee pain or severe function limitation increased similarly. Risk of TKR also increased similarly. Risks of future pain and function are shown in online supplemental figure S1. The distribution of pain, function and other OA-related factors at baseline is shown in online supplemental table S2. AUCs for the relationship of B-score and all five outcomes were comparable with those found for KLG and those outcomes (online supplemental table S3).

Additional information provided by B-score

Within KLG2-4, ORs for all clinical outcomes varied significantly between lowest and highest B-score quartiles ($p<0.001$) (for KLG3 knees, see table 2). No statistically significant differences were found between lowest and highest quartiles in KLG 0 and 1 knees. In terms of discrimination, addition of B-score resulted in improvement in the AUCs in all models, although of small magnitudes (online supplemental table S3), while the regression coefficient for B-score was statistically significant ($p<0.05$) in all models.

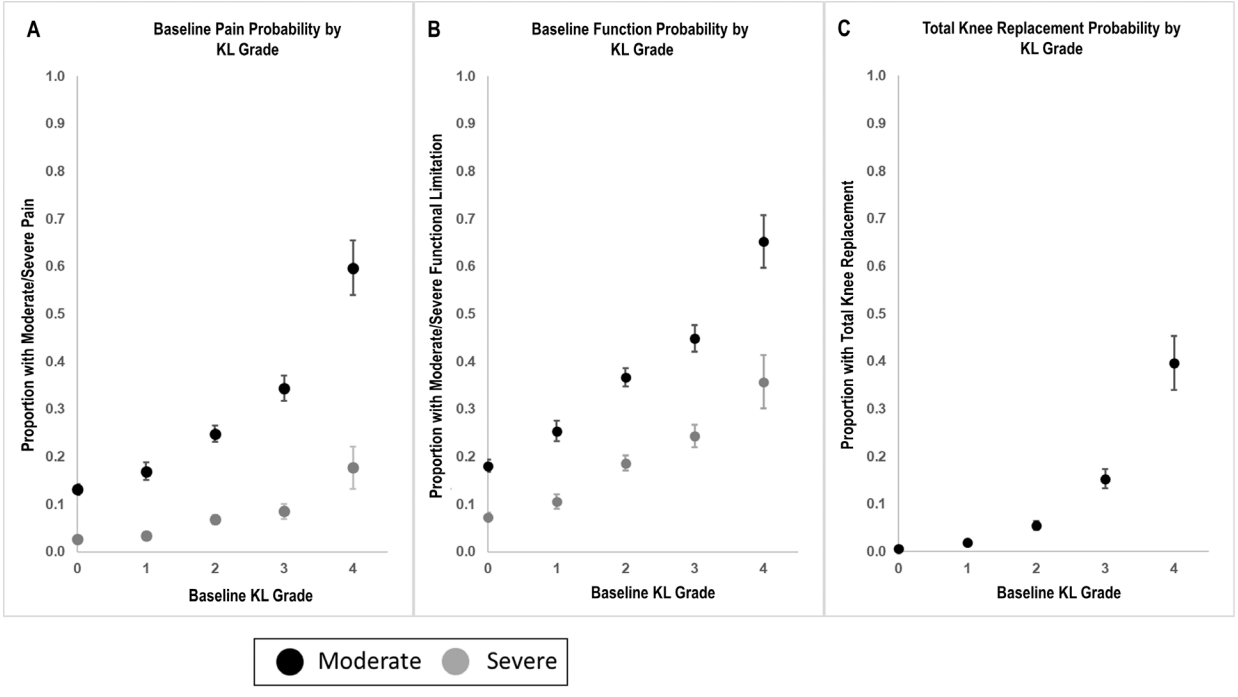

Figure 3 Error bars show 95% confidence limits for each measure. Pain: moderate or greater pain was defined as NRS pain ≥4 on the 10-unit scale (black points); severe pain as NRS pain ≥8 (grey points). Function: moderate or greater limitation of function was defined as function ≥20 on the 68-point WOMAC function scale (black points); severe loss of function was defined as ≥36 (grey points). TKR—risk of total knee replacement over follow-up period (up to 8 years, average follow up 5 years).

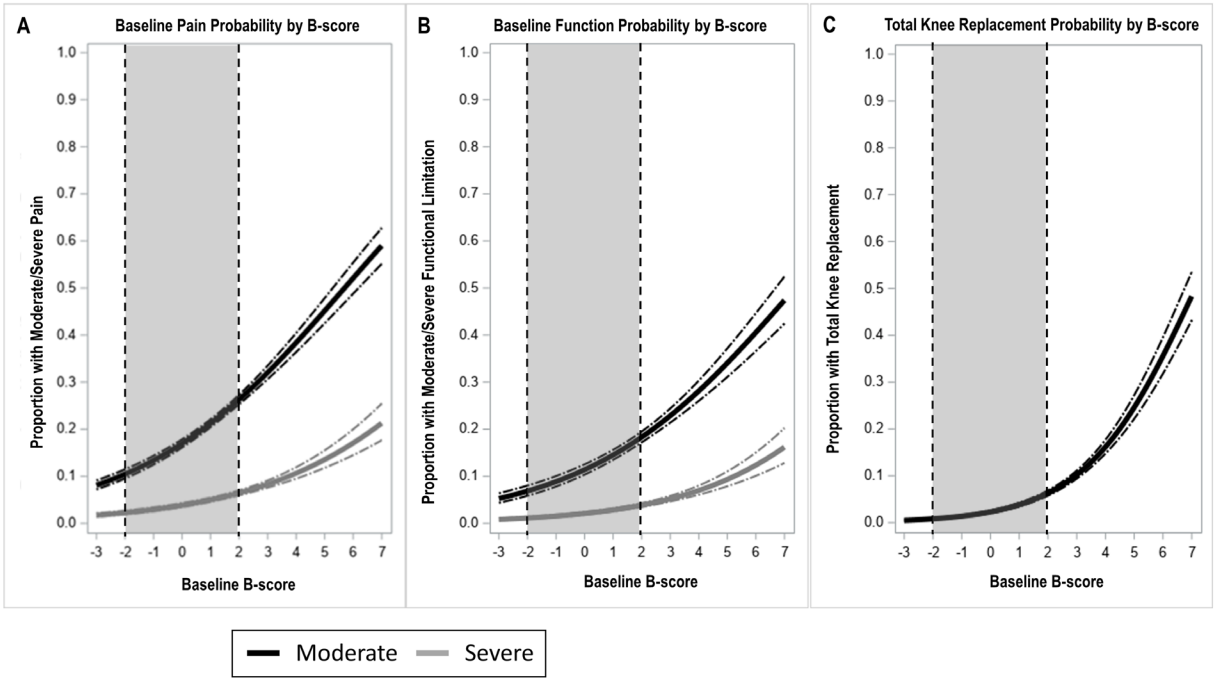

Figure 4 Error bars show 95% CIs for each measure. Moderate or greater pain was defined as NRS pain ≥4 on the 10-unit scale (black lines); severe pain as NRS pain ≥8 (grey lines). Moderate or greater limitation of function was defined as function ≥20 on the 68-point WOMAC function scale (black lines); severe limitation of function was defined as ≥36 (grey lines). TKR—risk of total knee replacement over follow-up period (up to 8 years, average follow-up 5 years). Limits of non-OA group B-scores are provided using a dotted line and greyed area.

Increased discrimination of all risks, using B-score at individual patient level

The increased utility of B-score is demonstrated by considering a KLG3 knee. The mean(CI) risk of a moderately painful knee based on this KLG was 34.4 (31.7 to 37.0)%. B-score within KLG3 knees ranged (95% CI) from 0 to 6; if the knee had a B-score of 0 the risk of a moderately painful knee was 17.0 (16.1 to 17.9)% while for a B-score of 6 it was 52.1 (48.8 to 55.4)%. The risk of a moderate limitation of function for a KLG3 was 20.6 (18.2 to 22.9)% if the knee had a B-score of 0 the risk of moderate function limitation was 11.4 (10.4 to 12.5)% while for a B-score of 6 it was 40.6 (36.6 to 44.6)%. For TKR, KLG3 knee had risks of 15.3 (13.3 to 17.3)%, whereas B-score 0 had negligible risk of TKR 2.3 (2.0 to 2.6)% and B-score six had a risk of 35.6 (31.8 to 39.6)%.

Confounders of, and additional information provided by, B-score

After adjustment for covariates the effect sizes from regression were still classified as 'small' for the risk of pain, function or TKR (online supplemental table S1).

DISCUSSION

Machine-learning has made possible the development of a quantitative measure of OA status; we have termed this the B-score. In this large observational cohort, B-score produced logistic regression models for clinically important outcomes, which were very similar in terms of predictive validity to those of the existing radiographic standard, providing construct validity for this new measure. However, by providing a scalar measure enabling

Table 2 ORs and 95% CIs for B score quartiles among KLG 3 & 4 knees, compared with the lowest B score quartile, for all current and future clinical outcomes

Outcome	B- Score Quartile 2	B-ScoreQuartile 3	B-scoreQuartile 4
Pain moderate - current	1.36 (0.95,1.94)	1.76 (1.24,2.49)***	2.4 (1.69,3.4)***
Pain severe - current	1.43 (0.67,3.05)	3.13 (1.59,6.16)**	3.54 (1.8,6.93)***
Function loss moderate - current	1.67 (1.12,2.51)*	1.91 (1.28,2.86)**	2.35 (1.58,3.49)***
Function loss severe - current	1.22 (0.5,2.99)	2.66 (1.21,5.84)*	2.03 (0.89,4.63)
Pain moderate - future	1.95 (1.33,2.86)***	2.54 (1.74,3.69)***	3.18 (2.18,4.62)***
Pain severe - future	1.25 (0.49,3.21)	3.28 (1.46,7.4)**	3.62 (1.61,8.14)**
Function loss moderate - future	1.61 (0.99,2.62)	2.83 (1.79,4.48)***	3.52 (2.23,5.55)***
Function loss severe - future	1.23 (0.37,4.06)	2.95 (1.05,8.29)*	2.16 (0.73,6.41)
Total knee replacement	1.21 (0.73,2.01)	1.51 (0.93,2.47)	2.58 (1.62,4.09)***

*P<0.05, **p<0.01, ***p<0.001.

at least 40 measurable subdivisions for OA structural change, B-score provides increased discrimination of risk over KLG for all clinically important outcomes. As a fully automated (reader-independent) measurement, B-score allows for rapid analysis of large datasets; and in both clinical trials and routine practice, provides a consistent measurement metric. As a scalar measure (compared with the categorical KLG), B-score permits the use of more powerful statistical methods for analysis.

The primary utility afforded by the precision of B-score is demonstrated by comparison with KLG. We have presented an example for KLG3 in the Results section, demonstrating the benefits conferred by having a range of B-scores within a single KLG. This applies for all KLG, even for a KLG0 knee, (often considered to be normal), for which the mean risk of moderate pain was 12%, while B-score risk range (−2 to +2) was 10%–27%. In day-to-day clinical use, it is unlikely that KLGs can be as consistent and repeatable as those in the OAI, where images are carefully acquired and read. Several studies estimated inter-reader agreement of KLG and found a 'moderate' intraclass coefficient of around 0.5–0.7.[22–24] In practice, this means that a KLG3 knee has an equal chance of being scored as KLG2, 3 or 4. This misclassification profoundly affects the risks exemplified above: a KLG3 knee had a risk of between 13.3% and 17.3% of TKR within 8 years. If the knee is equally likely to be scored as KLG2 or KLG4, then this becomes 4.5%–45.5%, a 10-fold increase in CI.

B-score provides a measure of OA status across the whole range of OA structural severity, including early disease. This is often conceptualised as KLG2, but the findings of the current study show that 31% of those categorised as KLG2 had a B-score within the non-OA range, and KLG0-1 knees included 8% with B-scores above the non-OA range. There is currently no consensus on a definition of 'early' OA, and B-score can provide a valuable measure. We have used the 95% CI of those who almost certainly do not have radiographic OA (B-score of ≤ 1.96), and this seems a well-validated basis for a cut-off point. In clinical trials, B-score would provide a reliable stratification tool and has already shown to be a sensitive outcome measure.[25] A number of therapies, including platelet-rich plasma and hyaluronic acid, are used in early OA,[26] and their effect on OA structural progression can now be meaningfully assessed. Implications for clinical practice require further consideration, and at present may improve assessment of prognosis more than selection of therapy (given our limited non-surgical therapeutic options). However, B-score may initially provide clinical usefulness in situations where MRI is already commonly performed (eg, sporting injuries or 'possible early OA').

It was not the intention of this study to suggest that bone shape pathology is causally related with the clinically important outcomes; bone shape is likely reflecting a broader OA construct. It is widely believed that the clinically important outcomes used in this study are related to age, sex, ethnicity, BMI and alignment, and these covariates are often used as inclusion criteria in OA clinical trials. In this study, these covariates had negligible effects on the ORs of the relationship between B-score, a measure of bone pathology, and clinically important outcomes.

We did perform a number of sensitivity analyses on the choice of symptom cut-points, in the absence of widespread consensus on what constitutes moderate and severe symptoms. As well as using a second tool, (WOMAC pain, see online supplemental figure S2) which showed a similar symptom-structure relationship to the NRS score used in the main paper, we also performed sensitivity testing using values of 7, 8 or 9 as cut-off for 'severe' pain, and 32, 34 or 36 as cut-off points for function loss and found that the choice of any of these cut-off points was not an important effect (data not shown).

The strength of this work includes very large patient numbers, but there are limitations. We have not attempted to explore longitudinal change or relationship to cartilage as we focused on the benefits of this new measure at a single time point, and its clear relationships with clinically important outcomes. Our non-OA group, used to set the scale of B-score, was drawn from the OAI with a population aged 45–80, in contrast to the osteoporosis T-score which uses a reference population of healthy young adults. Although we used the DESS-we MR images in this study and have previously demonstrated that the method is applicable to similar MRI sequences,[27] the method would need validation for other MRI sequences. We used a regression analysis for the risk of TKR, rather than hazard or incident rate analysis, as TKR was a 'rare' outcome in our data set, and also to allow the reader to compare estimates in our study (figures 3 and 4). The machine-learning technology can almost certainly be applied to cheaper imaging methods such as CT. Although the method for B-score determination used in this study is proprietary, several methods for bone shape measurement have been published, and the measurement of bone shape is actively being pursued by multiple groups. The bone shape vector revealed here may not hold for very late stages of the disease, where fewer patient numbers were available in this study. When osteophytes begin to carry load directly, they are likely to remodel and may produce shape changes that are less systematic than those reported here.

In conclusion, machine learning has enabled the development of a new objective, precise single time-point measure, B-score, representing OA status. B-score demonstrated similar relationships to clinically important outcomes as the current radiographic standard, but with the increased precision of B-score (providing approximately 10 times more detail on OA structural status), enabling better risk discrimination for clinically important outcomes. B-score should enable improved stratification for interventions and improved personalised assessment, in the same way that bone mineral density and more specifically, the T-score, has done historically for osteoporosis.

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Competing interests MAB and AB are employees of Imorphics, a wholly owned subsidiary of Stryker Corporation. KK is a consultant for Flexion Therapeutics Inc. OA and BD have no conflicts of interest to disclose. NB is an employee of Flexion Therapeutics. PGC has done consultancies or speakers bureaus for AbbVie, Bristol Myers Squibb, Eli Lilly, EMD Serono, Flexion Therapeutics, Galapagos, GlaxoSmithKline, Novartis, Pfizer, Roche, Samumed and Stryker.

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Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Material: Machine-learning, MRI bone shape and important clinical outcomes in osteoarthritis: data from the Osteoarthritis Initiative

SUPPLEMENTARY RESULTS

Supplementary Table S1. Effect of correcting for covariates (Age, Sex, Race, BMI, Alignment, Previous Knee Surgery, Use of NSAIDS, Smoking Status) on risks of clinically important outcomes

Outcome Variable	Unadjusted Odds Ratio B-score [95% CI] (p-value)	Adjusted Odds Ratio B-score [95% CI] (p-value)
Current NRS Pain		
Moderate Pain	1.322 [1.288,1.358] (<0.0001)	1.153 [1.084,1.227] (<0.0001)
Severe Pain	1.314 [1.260,1.370] (<0.0001)	1.184 [1.079,1.300] (0.0004)
Current WOMAC Pain		
Moderate Pain	1.322 [1.289,1.357] (<0.0001)	1.204 [1.131,1.281] (<0.0001)
Severe Pain	1.345 [1.300,1.391] (<0.0001)	1.146 [1.060.1.239] (0.0006)
Current Function (worst knee)		
Moderate limitation of function	1.334 [1.300,1.368] (<0.0001)	1.108 [1.033,1.188] (0.0039)
Severe limitation of function	1.333 [1.295,1.373] (<0.0001)	1.257 [1.100,1.436] (0.0008)
Total Knee Replacement	1.694 [1.624,1.767] (<0.0001)	1.653 [1.508,1.811] (<0.0001)

Potential confounders of the relationship between B-score and the risks of current pain, function and TKR were investigated by adjusting the models for age, sex, ethnicity BMI, alignment, previous knee surgery, NSAID use and smoking status. A description of these variables is shown in the Supplementary Methods section below.

Supplementary Table S2. Osteoarthritis Indicators at Baseline

Parameter	Males n = 3921 knees	Females n = 5512 knees	Combined n = 9433 knees
WOMAC-A (pain) at baseline, n (%)	n=3921	n=5512	n=9433
0 to <4: No pain to low pain	2983 (76.1)	3942 (71.5)	6925 (73.4)
4 to <8: Moderate pain	644 (16.4)	956 (17.3)	1600 (17.0)
8 or more: Severe pain	294 (7.5)	614 (11.1)	908 (9.6)
NRS (pain) at baseline, n (%)			
0 to <4: No pain to low pain	3146 (80.2)	4188 (76.0)	7334 (77.8)
4 to <8: Moderate pain	600 (15.3)	975 (17.7)	1575 (16.7)
8 or more: Severe pain	175 (4.5)	349 (6.3)	524 (5.55)
Function limitation, n (%)	n=3921	n=5512	n=9233
0 to <20: No or low limitation	3480 (88.9)	4547 (82.5)	8027 (85.1)
20 to <36: Moderate limitation	356 (9.1)	735 (13.3)	1091 (11.6)
36 or more: Severe limitation	85 (2.2)	230 (4.2)	315 (3.3)
Alignment (degrees)	n=3861	n=5393	n=9254
Mean (SD)	0.81 (2.98)	-1.07 (2.76)	-0.28 (3.00)
Median percentile (25th, 75th)	0.50 (-1, 3)	-1 (-3, 0)	-1 (-2, 1.5)
Min, Max	-11,15	-20, 11	-20, 15
Previous knee surgery, n (%)	n=3921	n=5512	n=9433
Yes	693 (17.7)	447 (8.1)	1140 (12.1)
Kellgren-Lawrence Grade at baseline, n (%)	n=3705	n=5129	n=8834
0	1496 (40.0)	1927 (37.6)	3423 (38.8)
1	653 (17.6)	924 (18.0)	1577 (17.9)
2	824 (22.2)	1506 (29.4)	2330 (26.4)
3	560 (15.1)	656 (12.8)	1216 (13.8)
4	172 (4.6)	116 (2.3)	288 (3.3)
B-score at baseline	n=3921	n=5512	n=9433
Mean (SD)	0.90 (1.77)	1.05 (1.78)	0.99 (1.78)
Median percentile (25th, 75th)	0.61 (–0.23, 1.68)	0.77 (–0.18, 1.93)	0.71 (–0.20, 1.84)
Min, Max	–3.41, 8.69	–3.46, 9.97	–3.46, 9.97

WOMAC denotes Western Ontario and McMaster Universities Osteoarthritis Index.

Supplementary Table S3. Area under the curve for logistic regression models of B-score and KL grade vs current clinical outcomes.

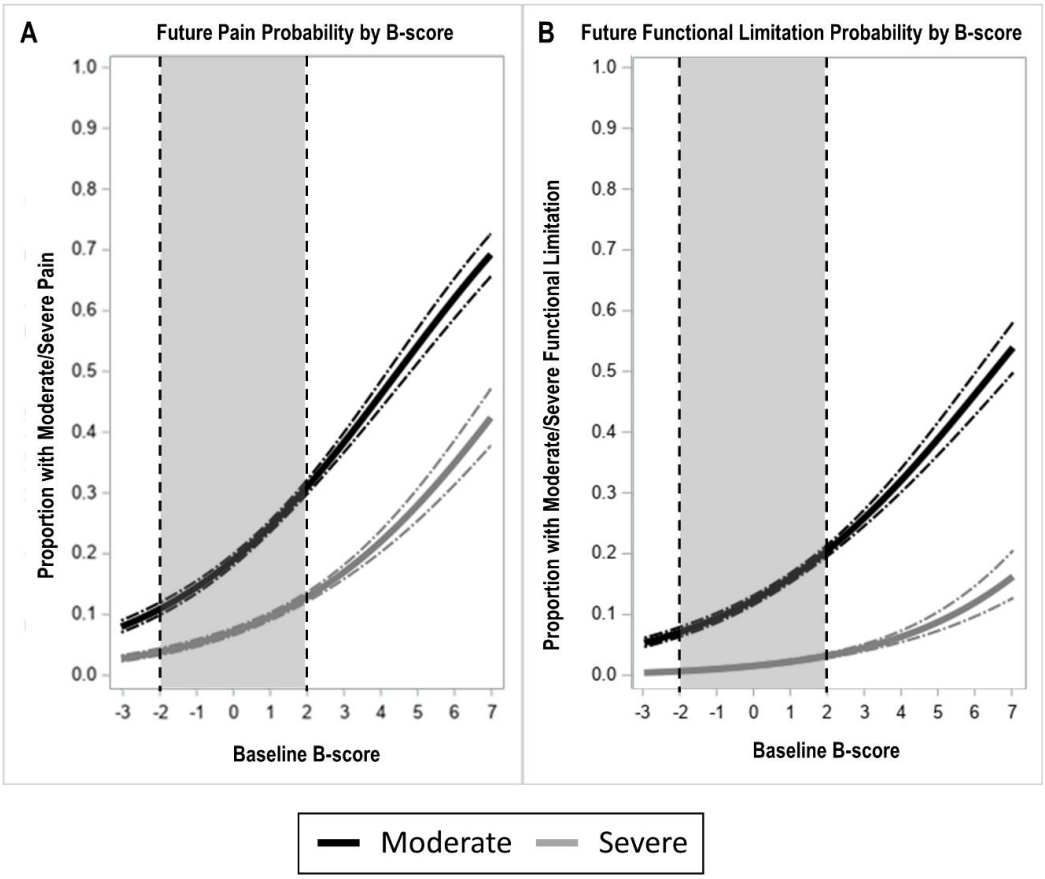
Outcome	KL grade	B-score and KL grade	B score
Moderate Pain	64.88%	66.41%	63.73%
Severe Pain	65.45%	68.14%	65.28%
Moderate Functional Limitation	66.1%	69.17%	65.0%
Severe Functional Limitation	67.26%	69.94%	67.67%
Total Knee Replacement	82.84%	85.02%	79.5%

Supplementary Table S4. Proportions of KL grades by B-score, and B-score by KL grade

		KL Grade				
B-score range	***n***	**0**	**1**	**2**	**3**	**4**
< -3 to -2·5	33	79%	15%	6%	0%	0%
< -2·5 to -2	112	77%	17%	4%	2%	0%
< -2 to -1·5	221	73%	14%	12%	1%	0%
< -1·5 to -1	449	63%	20%	14%	3%	0%
< -1 to -0·5	768	60%	22%	15%	3%	0%
< -0·5 to 0	1,098	58%	19%	19%	4%	0%
> 0 to 0·5	1,258	50%	23%	21%	6%	0%
> 0·5 to 1	1,230	44%	23%	25%	7%	1%
> 1 to 1·5	994	34%	23%	30%	12%	1%
> 1·5 to 2	729	23%	18%	37%	20%	2%
> 2 to 2·5	514	14%	13%	45%	26%	2%
> 2·5 to 3	371	9%	12%	40%	33%	6%
> 3 to 3·5	267	4%	4%	39%	38%	15%
> 3·5 to 4	202	0%	0%	50%	42%	8%
> 4 to 4·5	169	1%	1%	41%	40%	18%
> 4·5 to 5	148	0%	1%	36%	41%	22%
> 5 to 5·5	105	0%	0%	26%	47%	27%
> 5·5 to 6	71	0%	0%	38%	35%	27%
> 6 to 6·5	53	0%	0%	15%	43%	42%
> 6·5 to 7	34	0%	0%	15%	56%	29%

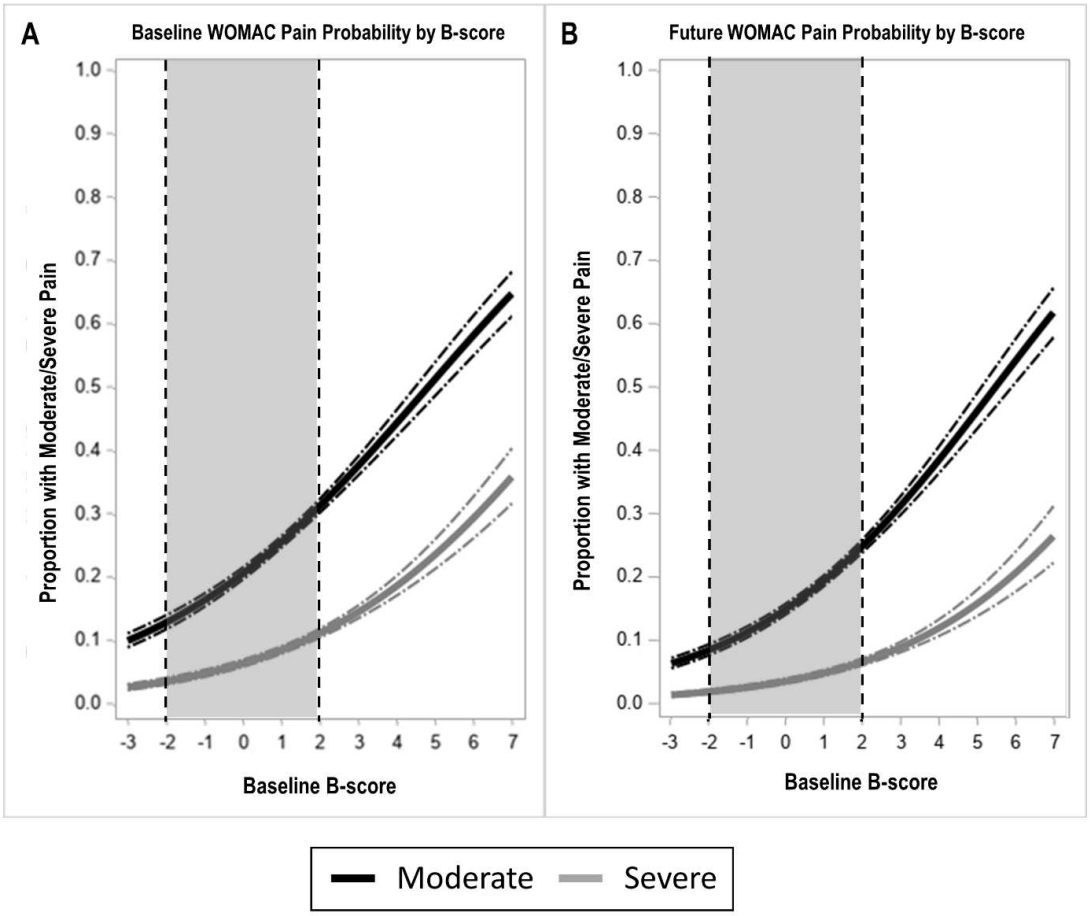
Proportions of knees recorded as KL grades 0, 1,2,3,4 for 20 bins of B-score. Note that measurement repeatability supports the use of 40 categories; we have used 20 here to ensure that outer bins contain sufficient numbers. Data are graphically represented in Supplementary Figure S3.

Supplementary Figure S1. Future (A) NRS pain and (B) functional limitation by B-score



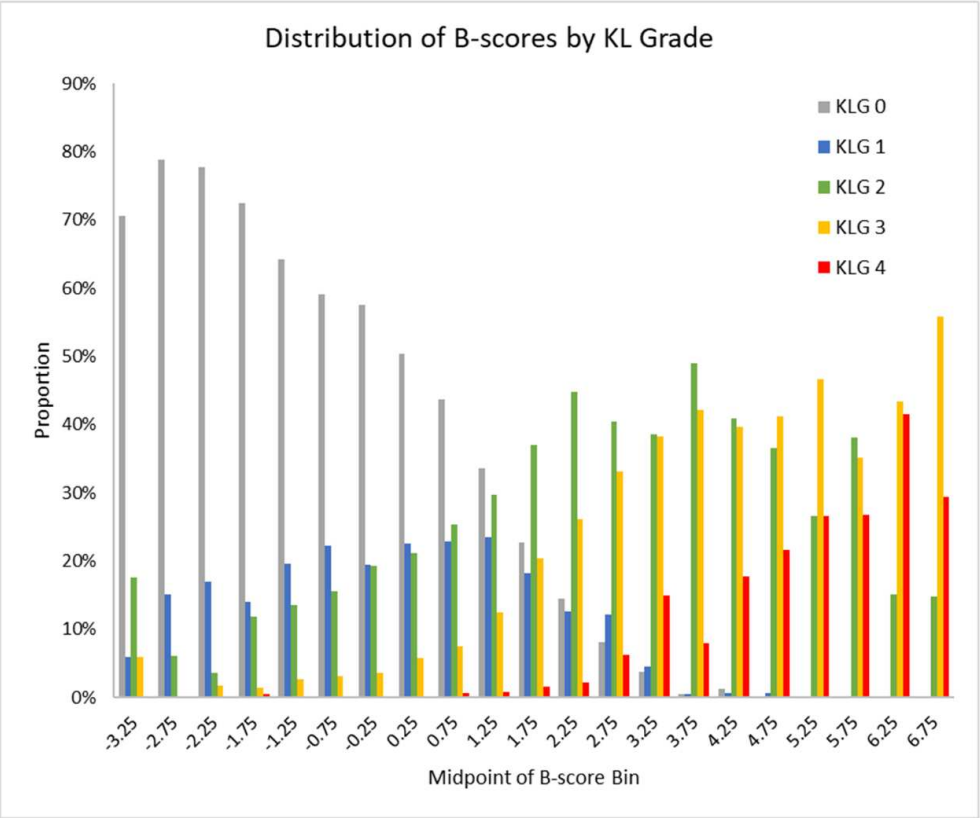
Error bars show 95% confidence intervals for each measure. Moderate or greater pain was defined as NRS pain ≥4 on the 10-unit scale (black lines); severe pain as NRS pain ≥8 (grey lines). Moderate or greater limitation of function was defined as function ≥10 on the 68-point WOMAC function scale (black lines); severe loss of function was defined as ≥20 (grey lines). Limits of Non-OA group B-scores are provided using a dotted line and greyed area. Future values were determined as the median value at all follow-up time points (excluding baseline, up to 8 years, average follow-up 5 years).

Supplementary Figure S2. Current (A) and future (B) WOMAC pain by B-score



Error bars show 95% confidence intervals for each measure. Moderate or greater pain was defined as WOMAC pain ≥4 on the 10-unit scale (black points); severe pain as WOMAC pain ≥8 (grey points). Limits of Non-OA group B-scores are provided using a dotted line and greyed area.

Supplementary Figure S3. Distribution of B-scores by KL Grade



Graphic representation of data in Supplementary Table S4

SUPPLEMENTARY METHODS

Definition of variables and assessment of confounders

All data from the Osteoarthritis Initiative (OAI) that were utilised in this study are publicly available at https://data-archive.nimh.nih.gov/oai.

For the different outcomes assessed, the influence of covariates (both confounders and competing exposures) chosen *a priori* from previously established clinical relationships was evaluated. Given the large sample size, both the statistical significance and the size of the estimates were considered. The covariates considered and adjusted for in the regression models were age, sex, BMI, ethnicity, previous knee surgery, alignment, NSAID use and smoking status described in more detail below.

Covariates were coded as recorded by the OAI. Age was modelled as a continuous variable in years, sex was binary (male or female), BMI as a continuous variable in kg/m^2. Ethnicity was categorised as White or Caucasian, Black or African-American, Asian, Other Non-white. Previous knee surgery was modelled as a binary variable coded as zero if participant had no history of previous surgery and one if they reported any previous knee surgery. In the OAI previous knee surgery was defined as “history of knee surgery (including arthroscopy, ligament repair, and meniscectomy)”. Alignment was measured using a goniometer and recorded in degrees which was modelled as a continuous variable in degrees. NSAID use was modelled as a binary variable (yes or no). The definition of NSAID use was any use of prescription or non-prescription NSAIDS (e.g., Ibuprofen, Diclofenac, Aspirin…) for joint pain or arthritis for more than half the days of the month in the past 30 days. Smoking status was modelled as a categorical variable with 3 levels (never, current and former).

The variables considered for the regression models were based on *a priori* relationships between the outcomes. For TKR for example, we considered clinically important risk factors such as age, gender, weight, and pain, which may influence the surgeon`s decision to

operate. We also considered whether health insurance could affect the outcome with participants potentially not offered a TKR for financial reasons; however, on exploration of the data we found that 98% of participants that had a TKR had some form of health insurance while 96% of those not having a TKR had insurance.

Tests for interactions

Interactions, including that for age were considered during an initial analysis, but as the differences between univariable and adjusted models showed that the odds ratios represented small effects after adjustment, a parsimonious model was chosen as the final model, excluding interactions.

Statistical Shape Modelling

Femur bones were automatically segmented from DESS-we images using active appearance models (AAMs), a type of SSM trained to search images, provided by Imorphics (Manchester, UK). AAMs are proven technology, which can segment knee bone surfaces with sub-millimetre accuracy [1, 2] [*references 15, 16 respectively in main paper*]. AAMs were constructed using a training set, consisting of expert manual segmentations of DESS-we images, selected to provide examples of all stages of OA. The training set was selected to contain examples of each stage of OA (43 KLG0 and KLG1, 7 KLG2, 28 KLG3, 18 KLG 4) [3] [*reference 17 in main paper*]. Accuracy of bone segmentation was excellent, with point-to-surface accuracy against careful manual segmentation of ± 0.49mm (95% confidence limits of error), and repeatability of all bone measurements was excellent with typical coefficient of variations of 0.4% to 0.6% [1]. Adding additional training examples to the model beyond the

96 examples, with differing degrees of osteoarthritis, did not increase segmentation accuracy.

The construction of an AAM parameterises femur bone shape using principal component analysis. Each time that a femur bone shape is identified within an image using an AAM, the femur bone shape is returned as a set of principal components.

OA Vector

Using the principal components from the AAM, we calculated the mean shape from two populations:

1. The “Non-OA group”, being the group of all knees with KLG0 radiograph reading at 0,1,2 and 4 years in the OAI (n=885), regardless of sex

2. The “OA group”, being the group of all knees with KLG ≥2 at 0, 1, 2 and 4 years (n = 1,713), regardless of sex.

There is no risk of over-training any subsequent models using 2,597 knees, as the only information taken from these populations of knees was the mean shape of the two groups. An “OA vector” was defined as the line passing through the mean shape of the Non-OA group shape, and the OA group (Supplementary Figure S4).

Supplementary Figure S4. Sammon plot illustrating the shape distributions of 600 femurs used in the training set and the OA vector.

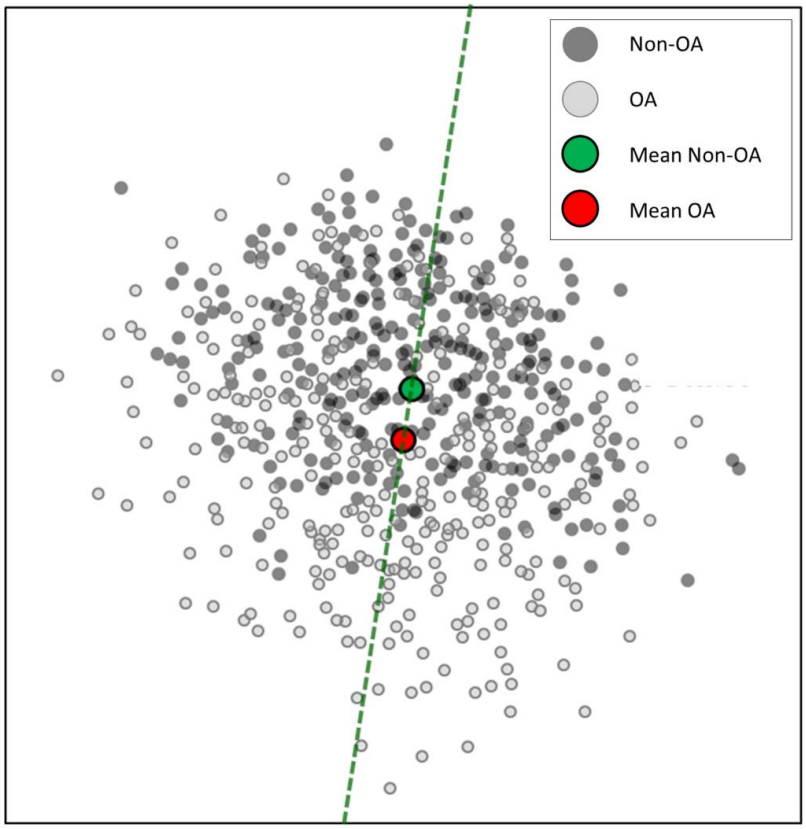


Figure shows the population of the training set, randomly sampled down to 600 points for legibility of figure. A Sammon plot reduces all of the principal component dimensions into 2 dimensions while preserving the distances between shapes as far as possible. Green circle shows the average shape of the Non-OA group (dark grey circles), and red circle the average shape of the OA group (light grey circles). Dotted green line is the OA vector, the line which passes through these two mean shapes. Histograms showing the projection of points from the Non-OA and OA groups onto the OA vector is shown in Supplementary Figure S5 below.

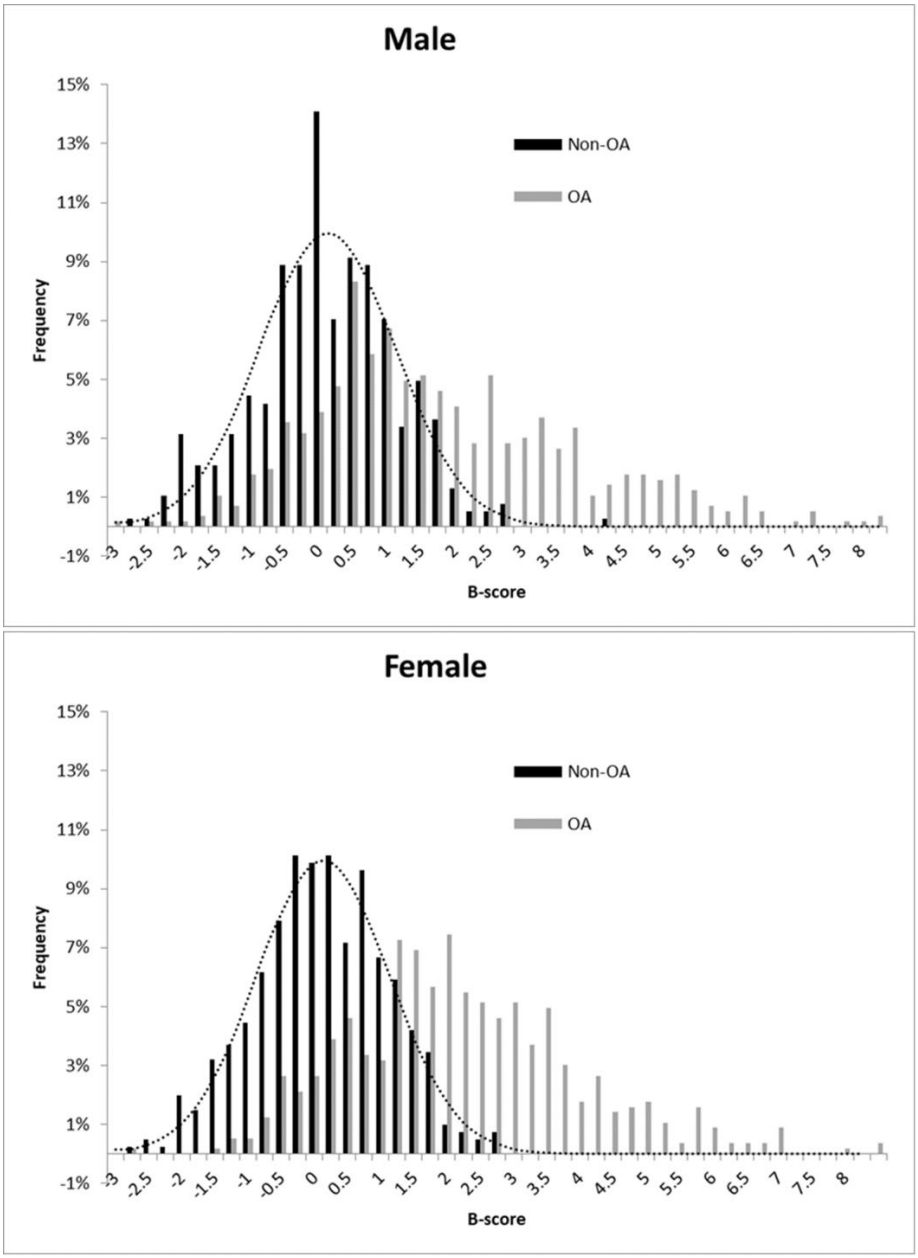
B-Score and sex

Each parameterized femur bone shape was projected orthogonally onto the OA vector to provide a distance along the OA vector. This distance was then normalised as follows: the origin (B-score of 0) was defined as the mean shape of the Non-OA Group for each sex. Means were determined separately for males and females (although the OA vector is constructed using both sexes). Males and females (with or without OA) have systematically different 3D bone shape [4] [*reference not cited in main text*], other than the OA shape

described here, resulting in a systematic difference along the OA vector for each sex. This is corrected, by calculating the means separately for each sex, but continuing to use the OA vector which contains both sexes. The distribution of male and female knees from the Non-OA or OA groups, after the correction are shown in Supplementary Figure S5.

Preparing entirely separate models for sex did not improve classification of OA vs Non-OA, sensitivity to change, and the logistic regression models for pain, function and TKA were indistinguishable from those using a vector containing all males and females (data not shown). As a result, a single vector combining the sexes was used for this study, with the origin corrected separately for males and females. Scale is defined as 1 standard deviation of the distribution of the Non-OA Group along the OA vector (with positive direction being toward the OA Group).

Supplementary Figure S5: Distribution of Non-OA and OA groups following correction of means.



A normal distribution of mean value 0 and a standard deviation of 1 is shown in each histogram using dotted line. Both males and females from the Non-OA group (confirmed KLG0 over 4-year period), are normally distributed along the OA vector, centered on 0 after correction for sex.

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