

The relationship between clinical characteristics, radiographic osteoarthritis and 3D bone area: data from the Osteoarthritis Initiative



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SUMMARY

Background: Radiographic measures of osteoarthritis (OA) are based upon two dimensional projection images. Active appearance modelling (AAM) of knee magnetic resonance imaging (MRI) enables accurate, 3D quantification of joint structures in large cohorts. This cross-sectional study explored the relationship between clinical characteristics, radiographic measures of OA and 3D bone area (tAB).

Methods: Clinical data and baseline paired radiographic and MRI data, from the medial compartment of one knee of 2588 participants were obtained from the NIH Osteoarthritis Initiative (OAI). The medial femur (MF) and tibia (MT) tAB were calculated using AAM. 'OA-attributable' tAB (OA-tAB) was calculated using data from regression models of tAB of knees without OA. Associations between OA-tAB and radiographic measures of OA were investigated using linear regression.

Results: In univariable analyses, height, weight, and age in female knees without OA explained 43.1%, 32.1% and 0.1% of the MF tAB variance individually and 54.4% when included simultaneously in a multivariable model. Joint space width (JSW), osteophytes and sclerosis explained just 5.3%, 14.9% and 10.1% of the variance of MF OA-tAB individually and 17.4% when combined. Kellgren Lawrence (KL) grade explained approximately 20% of MF OA-tAB individually. Similar results were seen for MT OA-tAB.

Conclusion: Height explained the majority of variance in tAB, confirming an allometric relationship between body and joint size. Radiographic measures of OA, derived from a single radiographic projection, accounted for only a small amount of variation in 3D knee OA-tAB. The additional structural information provided by 3D bone area may explain the lack of a substantive relationship with these radiographic OA measures.

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Introduction

Osteoarthritis (OA) causes pain and disability and has a profound impact on individuals and health economies alike. This impact is destined to increase in our ageing and increasingly obese population^{1–3}. Until recently, structural modification trials have depended on conventional radiography to define both the OA phenotype for participant inclusion and for assessing structural progression. Conventional radiography is less sensitive and specific

in detecting structural pathology and structural progression than magnetic resonance imaging (MRI)^{4,5}. MRI is therefore increasingly used to provide assessment of OA pathology. Another advantage of MRI is that its three dimensional data can be harnessed to provide quantification of important tissues using manual segmentation^{6–9}, or automated analysis techniques such as active appearance modelling (AAM) that enables relatively rapid, accurate quantification of large datasets^{10–12}.

Modern imaging approaches recognise that OA is a whole joint disease which may involve multiple tissues which confer different phenotypes¹³; subchondral bone in particular is integral to the pathogenesis and progression of OA^{13,14}. In particular, the area of subchondral bone at the femorotibial articulation is larger in OA knees than healthy controls and correlates with knee joint space narrowing, osteophytes and Kellgren Lawrence (KL) grade after

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adjusting for appropriate confounders in cross-sectional studies^{7–9}. While the severity of conventional radiographic OA may correlate with 3D subchondral bone area expansion, the additional value of bone area expansion of OA and the extent to which radiographic measures explain variation in this is unknown. Height, weight, gender and age are determinants of bone area in healthy knees^{12,15,16}. Therefore the objective of this study was to determine the bone area expansion attributable to OA and then establish what proportion of the variation of this is explained by radiographic measures of knee OA (metric joint space width, osteophyte grade, subchondral sclerosis grade).

Methods

Data used in the preparation of this cross-sectional analysis were obtained from the NIH Osteoarthritis Initiative (OAI) database, which is available for public access at <http://www.oai.ucsf.edu/>. This is a database of a multi-centre, prospective, longitudinal observational study of knee OA including approximately 4796 participants¹⁷. Knee radiographs and knee MRI scans were performed at baseline for all participants.

Our main subsample of knees was selected from those with available KL and other radiographic OA measure scoring from the central Boston University reads of plain films in the OAI. The availability of osteophyte and subchondral sclerosis scores was limited to knees of individuals who have had confirmed presence of radiographic OA (KL grade ≥ 2) in either knee at any time point. Participants without available KL, osteophyte and subchondral sclerosis grade data were excluded and the knee with the highest KL grade for each participant was selected. When the grades for both knees were the same, the right knee was chosen. Baseline MRI, radiographic and clinical data were included. A second subsample of 'normal' knees was selected in order to establish a formula for predicting 'normal' bone area based upon height, weight, age and gender. From the whole OAI cohort only knees were included with KL and WOMAC scores of zero at baseline, 1, 2 and 4 year time points and the absence of any historic OA knee symptoms prior to baseline.

MRI sequences collected in the OAI are described in detail by Peterfy and colleagues¹⁸. The current study utilised the double-echo-in-steady-state sequence (DESS-we) of the Siemens 3T trio systems¹⁸. A training set of 96 knee MRIs, using the DESS-we sequence, were used to build active appearance models for the tibia and femur¹². This training set was selected to contain examples of each stage of OA with approximately equal numbers of knees fulfilling each KL grade. The mean bone shape had anatomical regions outlined as described previously (Fig. 1)¹⁹. We used a definition of the area of subchondral bone or 'tAB' similar to that designated by a nomenclature committee²⁰. However this definition was modified to include bone ('peripheral osteophytes') from around the cartilage plate. The boundary between the medial femur (MF)/medial trochlear femur and the lateral femur/lateral trochlear femur boundary in the femur was defined as a line on the bone corresponding to the anterior edge of the medial or lateral meniscus, and extended smoothly to the edge of the tAB. Active appearance models were used for the calculation of tAB from knee MRIs which measured the undulating 3D surface of bone. The surface area of the 3D subchondral bone (tAB) was measured in mm².

The medial compartment of the tibiofemoral joint was selected to compare medial MF tAB and medial tibia (MT) tAB with medial joint radiographic measures on the basis that this compartment is more frequently affected.

The following baseline radiographic OA measures were selected and divided into three non-KL (OARSI and metric) measures and KL

grade: metric minimum joint space width (mJSW) of the medial compartment on continuous scale, subchondral sclerosis score of the MF or MT (OARSI categorical scale 0–3), osteophyte score of the MF or MT (OARSI categorical scale 0–3), KL grade (categorical scale 0–4). These assessments were provided by the OAI. A semi-automated tool, shown to be as sensitive as manual measures, was used to measure mJSW^{21,22}. Further details of the methodology for these assessments is available²³.

Clinical baseline characteristics, provided by the OAI, included the known important clinical risk factors for knee OA: age, gender, weight, height and ethnicity and goniometer-measured knee alignment^{3,24,25}. It was this existing clinical knowledge, not a data-driven strategy, that guided the selection of covariates for statistical modelling.

Statistical analysis

Statistical analysis was conducted using STATA software, version 12 (College Station, TX, 2009). For categorical socio-demographic variables, chi-square tests were performed comparing participants with radiographic OA and those without radiographic OA. Alignment was trichotomised into extreme valgus ($< -6^\circ$) intermediate alignment (-6° to 6° ; reference category) and extreme varus ($> 6^\circ$).

To establish which covariates might operate as potential confounders, mediators or competing exposures in the multivariable regression analyses exploring the amount of variation explained by radiographic measures, a causal path diagram was constructed in the form a Directed Acyclic Graph (DAG)²⁶. This was drawn from established and hypothesized functional relationships between bone area and each covariate. No non-causal structural association between the radiographic exposure and the bone area outcome was identified (Appendix Fig. 4). The benefit of this approach is that it provides an explicit *a priori* model of the postulated relationships between the exposure, outcome variables and each of the available

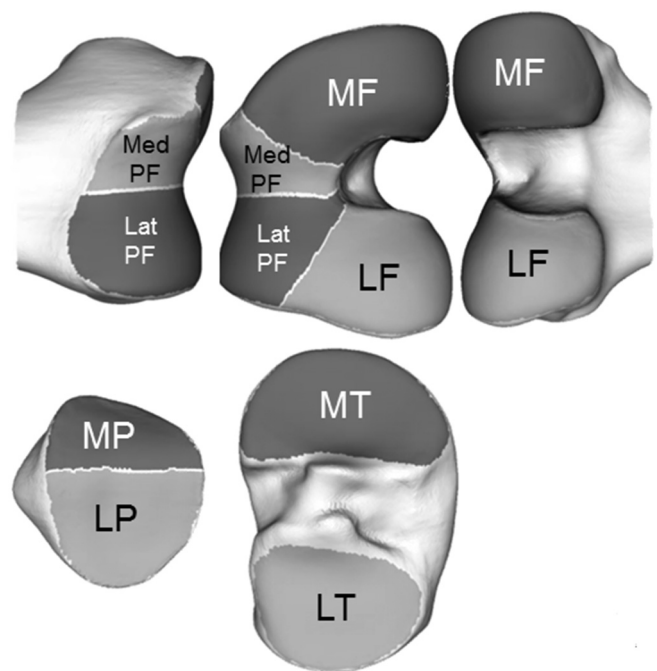


Fig. 1. Anatomical Bone areas: LF (lateral femur), MF (medial femur), MT (medial tibia), LT (lateral tibia), MP (medial patella), LP (lateral patella), LatPF (lateral trochlear), MedPF (medial trochlear).

covariates. Such models are invaluable for the specification and verification of the statistical analyses and results in appropriate adjustment and the most parsimonious model being chosen without the risk of over adjustment and thus reduction of statistical power which would otherwise occur.

The first analyses used the ‘normal’ subsample to obtain estimates of what normal bone area should be in the normal population. These estimates were obtained by modelling bone area with height, weight and age, stratified by sex thereby producing estimates that accounted for the sex differences in bone area. Having obtained the estimates, predicted bone area could be calculated for each of the 2588 knees in the main subsample.

$$\text{Bone area (MF)} = \text{intercept} + (A)(\text{HEIGHT}) + (B)(\text{WEIGHT}) + (C)(\text{AGE}) + \varepsilon$$

This was subtracted from the measured bone area (tAB) in each of the 2588 knees to provide the area of bone attributable to OA (OA-tAB).

Multivariable linear regression models were then constructed to determine the proportion of OA-tAB for MF and MT that could be explained by either non-KL measures of radiographic damage (joint space width (JSW), sclerosis, osteophytes) or KL grade. Although the methods of scoring non-KL measures of damage are different to that included in the KL scoring system, they measure similar pathology therefore models did not include both to avoid multicollinearity. These models were adjusted for alignment and ethnicity in different combinations and at each stage.

For univariable analyses two-tailed *P*-values have been presented ($P < 0.05$ was considered evidence of association without adjustment for multiplicity); for multivariable analyses 95% confidence intervals have been provided to give an indication of significance at the 5% level. However due to the large sample size we have considered both statistical significance and the associated improvement in R-squared when reporting which variables were associated with tAB to a substantive extent. Normality of residuals and homoscedasticity of errors was assessed using residual diagnostic plots as well as formal tests of heteroscedasticity (White's test and Breusch–Pagan test) and underlying assumptions of a Gaussian distribution and homoscedasticity were met.

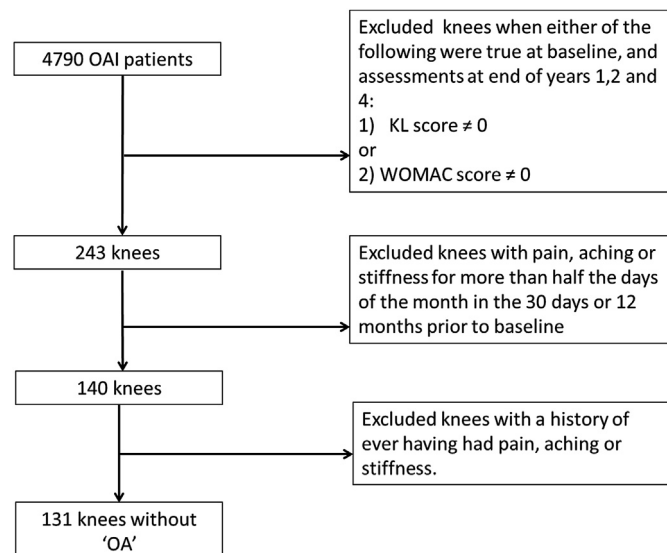


Fig. 2. Participant flow diagram for the ‘normal’ knee subsample.

Results

Of the 4796 participants in the OAI database 131 met our criteria for ‘normal’ knees (Fig. 2). Mean age was 60 years and 58% were female with 12% being obese (BMI greater than 30 kg/m²). Of the 4796 participants in the OAI database, 4490 had KL data available. After applying the inclusion criteria for selection of our main subsample, 2588 (57%) knees had radiographic and clinical data available for analysis (Fig. 3). Mean age was 61 years and 58% were female with 37% being obese.

Models of the ‘normal’ knee subsample with clinical data

When considering the clinical covariates stratified by sex, height, weight, and age in males explained 22.5%, 21.6%, and 3.5% of the MF tAB variance respectively in univariable analyses (results not shown). In females these clinical covariates explained 43.1%, 32.1% and 0.1% of the MF tAB. Similar values were identified for MT tAB. The greatest variance in tAB was explained by height in both medial compartment models in both sexes. When all the clinical covariates were entered in the model they explained 26.6% and 28.9% variance in MF and MT tAB respectively for males (Tables I and II), while in females they accounted for 54.4% and 53.7% in MF and MT tAB respectively (Tables I and II).

In general, taller and heavier individuals had greater tAB. Females were more likely to have smaller tAB having adjusted for height and weight compared to males and evidence of a linear relationship between age and tAB was observed.

Models with OA-attributable bone area

In univariable analysis both varus and valgus alignment tended to be associated with larger bone area, and explained 2% and 1.2% of the variation in MF OA-tAB and MT OA-tAB respectively (Model 2: Tables III and IV). Having adjusted for radiographic measures (Models 7 & 8: Tables III and IV) extreme valgus alignment was not consistently associated with differences in bone area to a significant degree.

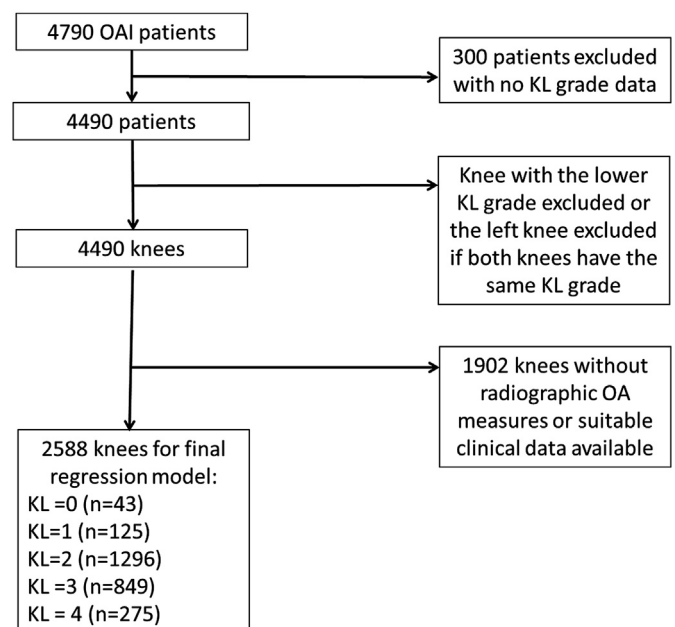


Fig. 3. Participant flow diagram for the main subsample.

Table I
Associations between MF bone area and selected clinical variables in non-exposed group

MF	Male model		Female model	
	Coefficient (95% CI), significance	R-squared	Coefficient (95% CI), significance	R-squared
Clinical characteristic				
Height	1.01 (0.14, 1.89) $P = 0.023$	0.266	1.79 (1.21, 2.38) $P < 0.001$	0.544
Weight	4.27 (0.45, 8.10) $P = 0.029$		6.47 (3.38, 9.58) $P < 0.001$	
Age	0.84 (−4.55, 6.24) $P = 0.755$		2.24 (−1.46, 5.95) $P = 0.231$	

Table II
Associations between MT bone area and selected clinical variables in non-exposed group

MT	Male model		Female model	
	Coefficient (95% CI), significance	R-squared	Coefficient (95% CI), significance	R-squared
Clinical characteristic				
Height	0.50 (0.03, 0.98) $P = 0.039$	0.289	0.83 (0.55, 1.10) $P < 0.001$	0.537
Weight	2.79 (0.71, 4.87) $P = 0.010$		3.14 (1.67, 4.61) $P < 0.001$	
Age	0.44 (−2.50, 3.38) $P = 0.767$		1.19 (−0.57, 2.95) $P = 0.182$	

When using the non-KL radiographic variables on a univariable basis, JSW, osteophytes and sclerosis were each significantly associated with MF OA-tAB, however each explained just 5.3%, 14.9% and 10.1% of the variance of MF OA-tAB (results not shown). Higher grades for osteophytes and sclerosis were associated with larger bone areas, whilst wider joint spaces were associated with smaller bone areas. In the univariable MT OA-tAB models, the variance explained by JSW, osteophytes and sclerosis was 6.0%, 10.1% and 8.3% respectively.

When entered simultaneously into a model that did not adjust for alignment, the non-KL radiographic variables were associated

with OA-tAB independently of each other, but accounted for just 17.4% and 12.9% of the variance in MF and MT OA-tAB respectively (Model 3: Tables III and IV). In the MF OA-tAB model some counter-intuitive trends were observed such as a wider JSW being associated with a larger bone area.

Adjusting for alignment, when entered individually JSW, osteophytes and sclerosis were still independently associated with OA-tAB in the expected direction, and explained an additional 6.7%, 17.2% and 11.5% of MF OA-tAB variance (Models 4, 5 & 6: Table III). When entered simultaneously the radiographic variables explained 18.7% of MF OA-tAB variance having adjusted for alignment (Model

Table III
Multivariable associations between OA-attributable MF area and radiographic variables

MF	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Clinical alignment							
Less than -6°	39.58 (6.44, 72.73)		71.59 (30.84, 112.33)	8.09 (−30.87, 47.05)	53.37 (13.06, 93.68)	17.21 (−22.44, 56.87)	−3.04 (−32.91, 26.84)
Greater than 6°	146.53 (111.49, 181.58)		131.78 (89.61, 173.96)	158.18 (116.53, 199.84)	124.89 (81.09, 168.70)	131.39 (88.97, 173.81)	82.54 (50.79, 114.29)
Radiographic variables							
JSW		2.92 (−5.21, 11.06)	−33.17 (−38.69, −27.64)			3.91 (−4.24, 12.05)	
Osteophytes							
Grade 1		12.58 (−8.55, 33.70)		23.98 (3.90, 44.06)		13.52 (−7.53, 34.57)	
Grade 2		58.89 (29.75, 88.02)		90.39 (63.44, 117.35)		59.56 (30.44, 88.68)	
Grade 3		193.38 (166.87, 219.90)		240.28 (217.65, 262.92)		195.92 (169.36, 222.49)	
Sclerosis							
Grade 1		−0.17 (−24.72, 24.38)			24.55 (3.12, 45.99)	−0.23 (−24.66, 24.20)	
Grade 2		89.53 (55.95, 123.11)			157.30 (134.30, 180.30)	83.74 (50.32, 117.18)	
Grade 3		171.52 (109.59, 233.44)			276.89 (225.62, 328.15)	147.19 (85.14, 209.25)	
KL grade							
Grade 1							32.20 (13.52, 50.88)
Grade 2							66.42 (50.91, 81.93)
Grade 3							170.33 (153.03, 187.63)
Grade 4							375.86 (349.88, 401.74)
R-squared	0.02	0.174	0.067	0.172	0.115	0.187	0.209
Model F ($P=$)	36 ($P < 0.001$)	70 ($P < 0.001$)	52 ($P < 0.001$)	93 ($P < 0.001$)	58 ($P < 0.001$)	60 ($P < 0.001$)	161 ($P < 0.001$)

Table IV
Multivariable associations between OA-attributable MT area and radiographic variables

MT	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Clinical Alignment							
Less than -6°	4.25 (-11.07, 19.57)		20.46 (1.82, 39.09)	5.80 (-12.71, 24.30)	12.53 (-6.28, 31.35)	10.06 (-8.79, 28.91)	-10.66 (-24.96, 3.65)
Greater than 6°	60.72 (44.52, 76.91)		52.43 (33.14, 71.72)	52.00 (31.97, 72.05)	51.54 (30.95, 71.93)	44.82 (24.47, 65.17)	37.00 (21.80, 52.20)
Radiographic variables							
JSW		-2.93 (-6.80, 0.93)	-16.69 (-19.22, -14.16)			-2.87 (-6.76, 1.02)	
Osteophytes							
Grade 1		15.47 (5.37, 25.58)		22.56 (13.32, 31.81)		15.26 (5.16, 25.37)	
Grade 2		48.20 (32.61, 63.80)		67.91 (54.51, 81.32)		46.65 (31.04, 62.26)	
Grade 3		98.60 (78.49, 118.72)		128.28 (111.85, 144.72)		96.14 (76.02, 116.25)	
Sclerosis							
Grade 1		7.93 (-3.48, 19.35)			23.28 (13.42, 33.15)	8.54 (-2.87, 19.97)	
Grade 2		26.08 (10.32, 41.84)			63.20 (52.39, 74.01)	24.71 (8.96, 40.46)	
Grade 3		45.07 (15.95, 74.20)			113.66 (91.69, 135.63)	38.42 (9.15, 67.68)	
KL grade							
Grade 1							14.76 (5.82, 23.71)
Grade 2							15.56 (8.13, 22.99)
Grade 3							62.04 (53.76, 70.33)
Grade 4							138.47 (126.08, 150.87)
R-squared	0.012	0.129	0.083	0.128	0.104	0.135	0.147
Model F ($P=$)	27 ($P < 0.001$)	49 ($P < 0.001$)	66 ($P < 0.001$)	66 ($P < 0.001$)	53 ($P < 0.001$)	41 ($P < 0.001$)	106 ($P < 0.001$)

7: Table III). Comparing Models 4 and 7, after adjusting, alignment and the non-KL radiographic variables the association between JSW and OA-tAB was reduced in magnitude, to the extent that it did not differ significantly from zero. Similarly in Model 7 the differences in OA-tAB between knees with sclerosis grades 1–3 and those without sclerosis were reduced compared to Model 6, although grades 2 & 3 still differed from grade 0. The coefficients for osteophyte grades 1, 2 & 3 remained comparatively stable between Models 5 & 7.

Adjusting for alignment, JSW, osteophytes and sclerosis explained an 8.3%, 12.8% and 10.4% MT OA-tAB variance individually (Models 4, 5 & 6: Table IV); when entered simultaneously they explained approximately 13.5% of variance in MT OA-tAB (Model 7: Table IV). Similar trends to those found for MF OA-tAB were observed in the differences in the non-KL radiographic variable coefficients between Models 4–6 and Model 7.

When using the KL grade on a univariable basis, grades 1–4 were associated with greater OA-tAB compared to grade 0; the higher the grade, the greater the difference (results not shown). Having adjusted for alignment, (Model 8: Tables III and IV) the differences were slightly reduced in magnitude for KL3 and KL4, but KL remained independently associated with both MF and MT OA-tAB. Compared to the model in which the non-KL radiographic variables were entered simultaneously whilst adjusting for clinical variables (Model 7: Tables III and IV), the adjusted KL model explained slightly more variance for both MF OA-tAB (adjusted R^2 KL = 0.209 vs non-KL = 0.187) and MT OA-tAB (adjusted R^2 KL = 0.147 vs non-KL = 0.135) but the differences were not substantive.

Discussion

This cross-sectional analysis is the first to establish the proportion of OA-attributable tAB variance explained by a comprehensive set of traditional radiographic measures of OA using automated imaging analysis technology in a large OA cohort. The accuracy of the relationship between radiographic OA and tAB is uniquely described with the use of 3D images of knee bones and the

lowest coefficient of the variance of tAB measurement, in the published literature, of less than 1%¹².

When considering the regression models of 'normal' knees the largest proportion of variance in tAB in the current study was described by participant height for both MF and MT tAB. This allometric relationship has previously been described in young healthy individuals with normal knee joints using manual segmentation of knee MRIs and multi-linear regression modelling¹⁶. We similarly observed that this allometric relationship explained a greater proportion of variance in tAB in females.

Tibial tAB has been reported to significantly correlate with increasing age in healthy populations^{27,28}. A similar relationship has been described both in populations with knee OA and in healthy participants, although this correlation significantly reduced in magnitude after adjusting for the presence of radiographic OA, suggesting tAB enlargement is directly relevant to OA²⁹. In our analysis of a population with normal knees a linear relationship between tAB and age was also noted. However this association was not considered substantive; age explained only 0.1% of the variance in tAB and thus may only be a minor determinant of tAB.

Gender appeared to explain a large amount of the variance of tAB in our analysis. However the magnitude decreased substantively when adjusted for height. Similar gender differences in height have been observed in patients with healthy knees which accounts for the large proportion of tAB variance explained by gender in unadjusted regression modelling¹⁵.

When considering radiographic data, osteophytes, joint space narrowing and KL grade correlated with tAB in previous cross-sectional analyses of OA knees^{7–9,30}. These analyses did not adjust for the tAB attributable to OA. Our study used OA-attributable tAB and demonstrated the same statistically significant associations, however they did not explain a substantive proportion of OA-attributable tAB variance in uni- and multi-variable models. This may reflect the lack of sensitivity of traditional radiographic measures in detecting structural progression and the additional structural information afforded by the 3D measure we employed. Indeed approximately 80% of the variance of OA-attributable tAB was not explained by radiographic covariates. The apparent lack of substantive association with the

radiographic measures may reflect the limitations of 2D radiographic imaging. Semi-quantitative MRI scores based on similar 3D imaging may prove to be more strongly associated with 3D bone area that is attributable to OA. Unfortunately only 115 OAI knee MRI scans have this scoring available in the public domain which currently precludes an analysis of significant size.

Of the three non-KL radiographic variables, osteophytes explained the largest variance in tAB. This may reflect the expansion of subchondral tAB in OA being largely a product of endochondral and direct bone formation in the medial and lateral peripheral articular cartilage plate^{12,31}.

There are limitations to this study. We have aimed to be cautious in only presenting substantive associations. The OAI is a large cohort and therefore we wanted to demonstrate whether significant statistical associations were substantiated by a significant proportion of tAB variance explained. Although JSW and KL grades were available for 4490 participants in the OAI database, we were limited to approximately 2588 participants by the availability of osteophyte and sclerosis variables.

Magnetic resonance cannot directly identify the presence of calcium. In the segmentation of knee DESS-we MRI sequence the material imaged is assumed to represent bone rather than another tissue type. Confirmation that these surfaces are actually bone requires further work. Finally the automated segmentation used here is both accurate and repeatable however all subtle details of particular diseases may not be identified^{32,33}. The majority of the cohort was Caucasian with smaller numbers of other ethnic groups. Therefore conclusions cannot be readily generalised to non-Caucasian groups.

In conclusion, radiographic measures, derived from a single radiographic projection, are only weakly associated with OA-attributable bone area measured in 3D. This may reflect the additional 3D MRI structural information, unaccounted for by these 2D radiographic measures. We also confirmed the substantive allometric relationship of bone area with body size. Future analyses of bone area as a measure of structural progression should adjust for OA-attributable bone area.

Author contributions

MB, BD, EH, PC, GP, SK and AB contributed to the planning and design of this analysis. AB & BD drafted the article and MB, PC, SK and EH revised the article. All authors approved the final version for publication.

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Conflict of interest

Dr Bowes is an employee and shareholder of Imorphics Ltd.

Professor Conaghan, Sarah Kingsbury, Bright Dube, Andrew Barr and Elizabeth Hensor and George Peat have nothing to disclose.

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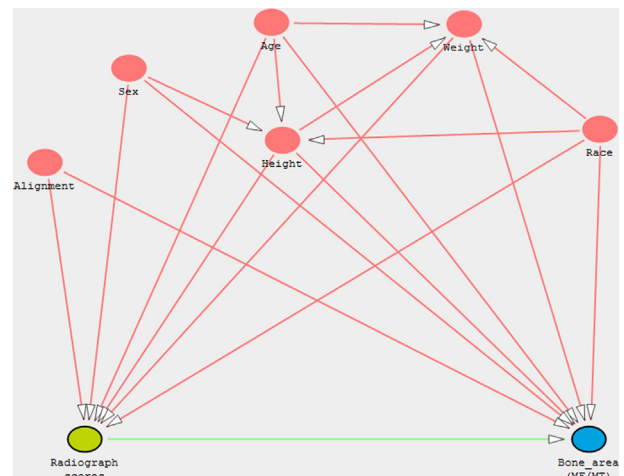
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Appendix



Appendix Fig. 4. Directed acyclic graph approach to confounding – a causal path diagram.

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