Appendix 1

Determination of sample size by the FNIH

The dataset of the Foundation for the National Institutes of Health (FNIH) osteoarthritis (OA) Biomarkers Consortium (http://www.FNIH.org), consisting of 600 subjects, which is a case-control study nested within the OAI (Osteoarthritis Initiative, https:// nda.nih.gov/oai). The samples of FNIH constitute subjects with at least one knee with Kellgren-Lawrence grade (KLG) of 1–3 at baseline and complete data including knee radiographs, magnetic resonance imaging (MRI) and clinical data at the baseline and 24-month visits. Participants who underwent knee/hip replacement surgery from baseline to 24 months were excluded. For better covariate balance among the groups, and to the extent feasible, knees selected for the four groups were frequency matched for KLG and body mass index (BMI) (kg/m^2) categories (<25; 25 to <27.5; 27.5 to <30; 30 to <35; ≥35). MRIs of the selected index knees were reviewed for artifacts that would interfere with image analysis. If artifacts were present the knee and subject were excluded and a replacement selected. Radiographic progression was defined as a loss of minimum joint space width (minJSW) of ≥0.7 mm in the medial femorotibial compartment between baseline and follow-up assessments at 24, 36, or 48 months. This threshold was established based on the distribution of changes in minJSW observed over a 12-month period in normal knees from healthy reference participants in the OAI. It was estimated to correspond to a 10% probability of change attributable to measurement error. Symptomatic progression was characterized by a sustained increase in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, with scores ≥9 on a scale ranging from 0 to 100. This score is derived from the original Likert scale that ranges from 0 to 20 used within the OAI framework, reflecting the minimum clinically important difference (MCID) (45,46).

References

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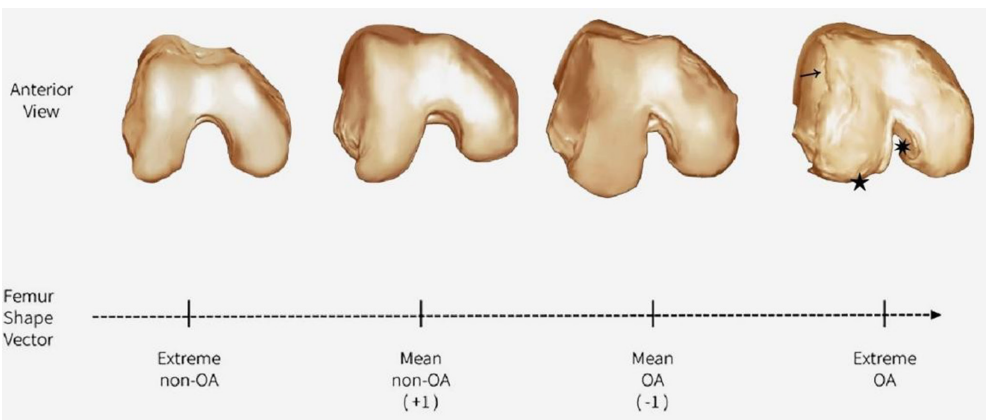

Figure S1 Schematic diagram of femur 3D bone shape vector. →: arrow pointing to increased ridge of osteogenic growth around the cartridge plate; ★: widening and flattening of the condyles; ✷: narrowing of the notch. 3D, three dimensional.

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Table S1 Baseline MOAKS of the case and the control group

Parameter	Control (n=321)	Case (n=216)	P value
Cartilage surface area			
No. of subregions with score Area	4.15 (2.09)	5.90 (2.22)	<0.001
Cartilage thickness			
No. of subregions with score Mm	1.39 (0.49)	1.58 (0.59)	<0.001
No. of subregions with any BMLs	2.53 (1.68)	3.89 (1.98)	<0.001
Medial meniscus score	4.23 (4.59)	9.76 (4.51)	<0.001
No. of subregions with osteophyte	5.88 (3.72)	7.72 (3.37)	<0.001
Synovitis score (intercondylar)	0.67 (0.64)	1.00 (0.72)	<0.001
0	156 (48.60)	67 (31.02)	
1	146 (45.48)	120 (55.56)	
2	15 (4.67)	28 (12.96)	
3	4 (1.25)	1 (0.46)	
Effusion score	0.71 (0.72)	1.03 (0.90)	<0.001
0	137 (42.68)	71 (32.87)	
1	143 (44.55)	82 (37.96)	
2	37 (11.53)	49 (22.69)	
3	4 (1.25)	14 (6.48)	

Data are presented as mean (standard deviation) or n (%). No. of subregions with score Area: the number of cartilage surface area subregion with scores >0; No. of subregions with score Mm: the number of cartilage thickness subregion with scores >0. BMLs, bone marrow lesions; MOAKS, MRI Osteoarthritis Knee Score; MRI, magnetic resonance imaging.

Table S2 Univariate logistic regression analysis for risk factors of KOA progression

Intercept and parameter	OR	95% CI	P value
Menicus extrusion	2.60	1.72–3.93	<0.001
No. of subregions with osteophyte	1.11	1.05–1.18	<0.001
Synovitis score	1.62	1.22–2.15	0.001
Effusion score	1.18	0.94–1.46	0.148
No. of subregions with score Area	1.25	1.16–1.64	<0.001
No. of subregions with score Mm	1.62	1.13–2.34	0.009
No. of subregions with any BMLs	1.34	1.19–1.51	<0.001

No. of subregions with score Area: the number of cartilage surface area subregion with scores >0; No. of subregions with score Mm: the number of cartilage thickness subregion with scores >0. OR adjusted for: age, sex, body mass index (BMI), history of injury, minJSW at the medial tibial-femoral joint, KL grade, WOMAC pain score and WOMAC disability Score. BMI, body mass index; BMLs, bone marrow lesions; CI, confidence interval; KL, Kellgren-Lawrence; KOA, knee osteoarthritis; minJSW, the minimum joint space width; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table S3 Multivariate logistic regression analysis for risk factors of KOA progression

Intercept and parameter	OR	95% CI	P value
Menicus extrusion	1.61	1.01–2.57	0.044
No. of subregions with osteophyte	1.04	0.97–1.12	0.260
Synovitis score	1.30	0.95–1.79	0.106
Effusion score	0.90	0.70–1.16	0.407
No. of subregions with score Area	1.08	0.96–1.23	0.201
No. of subregions with score Mm	0.90	0.56–1.44	0.657
No. of subregions with any BMLs	1.21	1.05–1.39	0.009
Medial meniscus score	1.38	1.16–1.64	<0.001

No. of subregions with score Area: the number of cartilage surface area subregion with scores >0; No. of subregions with score Mm: the number of cartilage thickness subregion with scores >0. OR adjusted for: age, sex, BMI, history of injury, minJSW at the medial tibial-femoral joint, KL grade, WOMAC pain score and WOMAC disability Score. BMI, body mass index; BMLs, bone marrow lesions; CI, confidence interval; KL, Kellgren-Lawrence; KOA, knee osteoarthritis; minJSW, the minimum joint space width; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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Table S4 Mediation analysis of bone morphology at baseline or the change of bone morphology at 24 months on the association between MME and KOA progression

Bone morphology	Baseline			Change of 24 months		
	Estimate	95% CI	P value		95% CI	P value
Medial area						
Femur						
ACME (average)	0.0011	−0.0087 to 0.0119	0.816	0.0510	0.0197 to 0.0885	<0.001
ADE (average)	0.2247	0.1190 to 0.3224	<0.001	0.1756	0.0803 to 0.2681	<0.001
Total effect	0.2258	0.12151 to 0.3227	<0.001	0.2267	0.1238 to 0.3234	0.002
Proportion mediated (%) (average)	4.98	−4.33 to 5.92	0.816	22.53	10.30 to 24.66	<0.001
Tibia						
ACME (average)	−0.000113	−0.009679 to 0.01	0.99	0.0029	0.010 to 0.0547	0.004
ADE (average)	0.2259	0.1201 to 0.3228	<0.001	01964	0.0934 to 0.2928	<0.001
Total effect	0.2259	0.1217 to 0.3228	<0.001	0.2258	0.1211 to 0.3235	<0.001
Proportion mediated (%) (average)	0	−4.36 to 4.59	0.99	13.02	4.39 to 28.67	0.004
Patella						
ACME (average)	0.0059	−0.0027 to 0.0186	0.186	0.0086	−0.0017 to 0.0255	0.126
ADE (average)	0.2191	0.1140 to 0.3164	<0.001	0.2172	0.1146 to 0.3139	<0.001
Total effect	0.23442	0.13193 to 0.33	<0.001	0.2258	0.1221 to 0.3215	<0.001
Proportion mediated (%) (average)	2.63	−1.32 to 9.57	0.186	3.81	−0.82 to 12.54	0.126
Trochlea						
ACME (average)	0.0004	−0.0080 to 0.009	0.938	0.0419	0.0165 to 0.0730	<0.001
ADE (average)	0.2255	0.1208 to 0.3227	<0.001	0.1839	0.0847 to 0.2748	<0.001
Total effect	0.2259	0.1217 to 0.3226	<0.001	0.2257	0.1220 to 0.3228	<0.001
Proportion mediated (%) (average)	0.16	−3.91 to 4.93	0.938	18.55	7.85 to 36.49	<0.001
Lateral area						
Femur						
ACME (average)	0.000424	−0.007319 to 0.01	0.846	0.040	−0.0024 to 0.0167	0.3180
ADE (average)	0.2251	0.1199 to 0.3219	<0.001	0.2219	0.1158 to 0.3173	<0.001
Total effect	0.2259	0.1216 to 0.3228	<0.001	0.2259	0.1217 to 0.3228	<0.001
Proportion mediated (%) (average)	0.32	−3.82 to 5.58	0.846	1.75	−1.23 to 8.18	0.3180
Tibia						
ACME (average)	0	−0.0092 to 0.0060	0.788	0.01443	−0.00663 to 0.04	0.1440
ADE (average)	0.2270	0.1222 to 0.3253	<0.001	0.2103	0.1120 to 0.3003	<0.001
Total effect	0.2260	0.1218 to 0.3228	<0.001	0.2250	0.1206 to 0.3216	<0.001
Proportion mediated (%) (average)	−0.42	−4.85 to 3.15	0.788	6.57	−2.75 to 16.87	0.1440
Patella						
ACME (average)	0.0051	−0.0027 to 0.0177	0.236	0.0088	−0.0033 to 0.0258	0.1720
ADE (average)	0.2201	0.1153 to 0.3179	<0.001	0.2167	0.1160 to 0.3110	0.1720
Total effect	0.2252	0.1214 to 0.3221	<0.001	0.2255	0.1223 to 0.3208	<0.001
Proportion mediated (%) (average)	2.25	−1.25 to 9.24	0.236	3.89	−1.54 to 13.16	0.1720
Trochlea						
ACME (average)	−0.0007	−0.0071 to 0.0052	0.820	0.0099	−0.0059 to 0.0299	0.270
ADE (average)	0.2267	0.1223 to 0.3235	<0.001	0.2163	0.1179 to 0.3061	<0.001
Total effect	0.2261	0.1218 to 0.3228	<0.001	0.2262	0.1211 to 0.3232	<0.001
Proportion mediated (%) (average)	−0.30	−3.67 to 2.32	0.820	4.37	−2.95 to 14.22	0.270
Notch						
ACME (average)	0	−0.0070 to 0.0071	0.964	0.0230	0.0044 to 0.0459	0.004
ADE (average)	0.2260	0.1183 to 0.3226	<0.001	0.2026	0.0992 to 0.2954	<0.001
Total effect	0.2260	0.1215 to 0.3227	<0.001	0.2256	0.1212 to 0.3232	<0.001
Proportion mediated (%) (average)	−0.02	−3.30 to 3.62	0.964	10.20	2.06 to 23.25	0.004
Shape (vector)						
Femur						
ACME (average)	0.0144	−0.0035 to 0.0358	0.1080	0.0523	0.0208 to 0.0896	<0.001
ADE (average)	0.2117	0.1106 to 0.3081	<0.001	0.1786	0.0815 to 0.2711	<0.001
Total effect	0.2261	0.13213 to 0.3220	<0.001	0.2310	0.1245 to 0.3242	<0.001
Proportion mediated (%) (average)	6.37	−1.70 to 1.79	0.1080	26.67	9.82 to 42.90	<0.001
Tibia						
ACME (average)	0.02078	−0.0058 to 0.0486	0.134	0.0195	0.0008 to 0.0434	0.054
ADE (average)	0.2057	0.1009 to 0.3040	<0.001	0.2078	0.1056 to 0.3043	<0.001
Total effect	0.2264	0.1215 to 0.3225	<0.001	0.2273	0.1196 to 0.3222	<0.001
Proportion mediated (%) (average)	9.17	−2.40 to 26.4	0.134	8.59	−0.0033 to 0.2137	0.054
Patella						
ACME (average)	0.0080	−0.0022 to 0.0237	0.156	0.0047	−0.0003 to 0.0206	0.260
ADE (average)	0.2184	0.1166 to 0.3117	<0.001	0.2214	0.1153 to 0.3173	<0.001
Total effect	0.2263	0.1209 to 0.3224	<0.001	0.2261	0.1208 to 0.3217	<0.001
Proportion mediated (%) (average)	3.51	−1.03 to 11.08	0.156	2.08	−1.23 to 9.36	0.260

Proportion mediated = ACME/ADE ×100%. ACME, average causal mediation effects (indirect effect); ADE, average direct effects; CI, confidence interval; KOA, knee osteoarthritis; MME, medial meniscal extrusion.

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