possible OA disease pathways. With the creation of our large dataset and CC BOB-grading scale we present a step towards further understanding of the possible role of CC in knee OA and Knee pain, which will need future investigation.

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PREDICTORS OF LONGITUDINAL MRI-BASED CARTILAGE THICKNESS CHANGE IN THE OBSERVATIONAL MULTICENTER APPROACH COHORT

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Purpose: APPROACH (Applied public-private research enabling osteoarthritis clinical headway) is an exploratory, European, 5-centre, 2-year prospective follow-up cohort project. It was designed for identifying outcome measures that can identify patients with different OA phenotypes who may benefit form specific therapies and collected clinical, imaging, biomechanical and biochemical parameters for this purpose. The patients were selected by the rankings produced by machine learning models trained to estimate a high likelihood of joint space width loss and/or increased or sustained knee pain over the course of the study from demographic data, pain scores, and radiographic features. Current clinical trials rely on established criteria such as semi-quantitative Kellgren & Lawrence grades (KLG) and joint space narrowing (JSN) grades for enriching the cohort with knees likely to show structural progression. In addition to these, the APPROACH project included innovative potential predictors such as six-month change in laminar cartilage composition (based on cartilage T2 relaxometry), the machine-learning-predicted structural progression scores used for enrollment, and MOAKS cartilage damage extent and full thickness cartilage damage extent scores. The objective of this work was to investigate the association of these established and innovative predictors with longitudinal cartilage thickness change.

		N	Mean	SD	95% CI		% Progressors
MFTC	M000→M006	264	-0.040	0.108	-0.053	-0.026	18.2
	M000→M012	248	-0.062	0.128	-0.078	-0.046	24.6
	M000→M024	226	-0.104	0.152	-0.124	-0.084	35.0
LFTC	**M000→M006**	264	-0.010	0.095	-0.021	0.002	11.7
	M000→M012	248	-0.029	0.102	-0.042	-0.017	14.5
	M000→M024	226	-0.072	0.152	-0.092	-0.052	23.5

MFTC/LFTC: medial/lateral femorotibial compartment; SD: standard deviation; 95% CI: 95% confidence intervals; knees with progression exceeded the respective smallest detectable change (SDC) threshold (MFTC: -0.132mm, LFTC: -0.120mm). Number of knees included in analysis depended on availability and quality of MRIs and loss to follow-up

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Table 1 Change in MFTC and LFTC cartilage thickness and % of progressor knees

	MFTC			LFTC		
	OR	95% CI		OR	95% CI	
Kellgren & Lawrence grade (KLG)	1.67	1.27	2.19	2.06	1.50	2.83
Medial/lateral joint space narrowing (JSN)	1.60	1.16	2.22	4.43	2.43	8.05
Predicted structural progression probability	0.94	0.72	1.22	1.15	0.83	1.61
6 month change in deep layer T2 time	0.57	0.37	0.89	1.43	0.97	2.09
6 month change in superficial layer T2 time	0.76	0.52	1.11	1.44	0.82	2.52
Baseline MOAKS cartilage defects	2.49	1.17	5.29	3.31	1.56	7.03
Baseline MOAKS full thickness cartilage defects	5.18	2.70	9.95	6.54	3.10	13.81

OR: odds ratio; MFTC/LFTC: medial/lateral femorotibial compartment progression, defined as cartilage thickness loss exceeding the threshold of -0.132mm (MFTC) or -0.120mm (LFTC)

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Table 2 Association of predictors with 24 month cartilage thickness progression

Methods: 297 people with knee OA were included in the APPROACH cohort (age: 66.5±7.1 years, BMI: 28.1±5.3 kg/m^2, 77.5% women, Clinicaltrials.gov: NCT03883568). The study has been approved by the Ethical committees of the participating countries. KLG (KLG 0/1/2/3/4: n=54/79/67/87/11) and JSN (medial JSN 0/1/2/3: n=249/25/18/3, lateral JSN: n=157/76/42/20) were assessed on semi-flexed weight bearing knee radiographs. Weight-bearing medial (MFTC) and lateral (LFTC) compartment cartilage thickness was measured from 3D SPGR MRI at month 0, 6, 12, and 24 using manual, quality-controlled segmentations. Knees were classified as having progression in the MFTC and/or LFTC when the change exceeded the respective smallest detectable change (SDC) thresholds (MFTC: -0.132mm, LFTC: -0.120mm). Superficial and deep layer T2 times in the MFTC and LFTC were measured at 4 of the 5 centers for month 0 and 6 (one center: month 6 and 12) from manual, quality-controlled segmentations of the central 3 slices in both compartments. Six-month change in cartilage T2 was available for 212 knees and was used instead of site- and equipment-specific single-visit cartilage T2 times. Semi-quantitative MOAKS-atlas cartilage damage scores were assessed for the MFTC and the LFTC at baseline by an experienced radiologist. The association between the predictors (KLG, JSN, T2 change, MOAKS cartilage damage and full thickness damage extent, and machine-learning-predicted structural progression probability) and MFTC/LFTC progression exceeding the SDC threshold were analyzed using binary logistic regression with adjustment for site, age, sex, and BMI. For quantitative predictors, results were presented as odds ratios (OR) per SD.

Results: Cartilage thickness loss increased with time and was more pronounced for the MFTC than the LFTC (Table 1).

Knee-specific KLG and compartment-specific OARSI-atlas JSN scores at baseline were associated with both MFTC and LFTC progression for all observation periods (see Table 2 for 24 month associations). Six-month decrease in MFTC deep layer T2 times was associated with MFTC progression over 24 months (Table 2). No other associations were observed for change in deep or superficial layer T2 times. A lower machine-learning-predicted structural progression probability was associated with MFTC progression over the initial 6 months period (OR: 0.72, 95% CI: [0.53, 0.97]) but not with MFTC progression over 12 and 24 months or LFTC progression (Table 2). Presence of MOAKS cartilage damage at baseline was associated with progression in both the MFTC and LFTC, except for LFTC progression over 6 months (Table 2). Presence of MOAKS full thickness damage was also associated with both, MFTC and LFTC progression (Table 2).

Conclusions: Despite the inclusion of a large number of knees without

definite radiographic OA (KLG<2), cartilage thickness loss was commonly observed in the Approach cohort. Besides the established radiographic predictors, only semi-quantitatively assessed MOAKS cartilage damage and full-thickness cartilage damage were associated with quantitatively measured subsequent structural progression. Change in laminar cartilage T2 times or the predicted structural progression probability were, in contrast, not consistently associated with cartilage thickness loss and the few observed associations rather indicated a protective instead of a deleterious effect of these potential predictors. Training the machine learning model with a wider set of features than that available for screening of Approach participants is, however, likely to result in improved prediction of progression.This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (APPROACH grant n° 115770). This communication reflects the views of the authors and neither IMI nor the European Union and EFPIA are liable for any use that may be made of the information contained herein.

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EFFECTS OF WEIGHT CHANGE ON KNEE AND HIP RADIOGRAPHIC MEASUREMENTS AND PAIN OVER 4 YEARS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: Osteoarthritis (OA) is present in 10.5% of the US population, often affects large weight-bearing joints such as the hip and knee, and its prevalence increases with higher levels of BMI. Since obesity is a modifiable risk factor for OA, understanding the effects of weight gain and weight loss on hip and knee OA is critical for the development of effective, long-term therapeutic strategies for OA. While studies have shown beneficial effects of weight loss on knee OA including reduced symptomatic outcomes, slower progression of MRI structural outcomes, less inflammation, less knee joint mechanical loads, and reduced serum markers for cartilage degradation, fewer studies have investigated the effects of weight gain on knee OA. In addition, few studies have assessed the effects of both weight loss and weight gain on structural and symptomatic hip OA. The purpose of this study was to assess the effects of weight loss and weight gain on knee and hip radiographic changes and pain over 4 years.

Methods: This study utilized data from the Osteoarthritis Initiative (OAI), a multi-center, longitudinal study of individuals aged 45-79 years at enrollment, aimed at assessing biomarkers for OA development and progression. Participants from the Osteoarthritis Initiative with weight change and radiographic knee and hip OA data at baseline and year 4 exams (n=2752) were classified as those with weight gain (>5% gain), weight loss (>-5% loss), or as controls (-3 to 3% change) over four years. Standardized bilateral standing posterior-anterior fixed flexion knee radiographs were acquired in all subjects in the OAI. To investigate disease burden and progression of OA, Kellgren Lawrence (KL) gradings and joint space narrowing (JSN - medial and lateral knee joint sides) were assessed at baseline and 4-year follow-up. Knee radiographic progression (binary) was defined as positive if KL grade at 4-year follow-up was greater than KL grade at baseline. Progression of JSN was defined as positive if JSN grade at 4-year follow-up was greater than JSN grade at baseline. JSN progression was defined in the lateral and medial femoro-tibial joints, and also if either the lateral or medial joint had progression. Pelvis radiographs were assessed for hip OA using the OARSI atlas, and classified as “definite”, “possible”, or “none.” Hip radiographic worsening was defined as positive if a hip radiographic grading at 4 years was greater than that at baseline. A similar definition for binary progression of JSN was utilized.Right and left hip and knee pain were assessed at baseline and 4-years. Individuals were classified into those that *developed knee pain* (no pain at baseline and developed pain at 4-years), those whose *pain resolved* (pain at baseline and no pain at 4-year follow-up), and those who had no pain at baseline or follow-up. Subjects with pain at baseline and follow-up were excluded from the analysis with pain outcomes. General estimating equations with logistic regression (accounting for two knees or hips per person) were used to assess the relationship between weight change group and outcomes (binary 4-year radiographic progression, or binary 4-year pain progression). All analyses were adjusted for age, sex, and baseline BMI.

Results: For radiographic *knee* OA, weight loss was associated with significantly lower odds of KL grade worsening over four years (OR=0.69, 95% CI= 0.53 - 0.91, p=0.009), and weight gain was significantly associated with higher odds of medial knee JSN (OR=1.29, 95% CI=1.01 - 1.64, p=0.038) compared to controls. Table 1 lists the associations between weight change and knee and hip radiographic outcomes. For *knee* pain, weight loss was significantly associated with knee pain resolution (pain at baseline that resolved at the 4-year follow-up) (OR=1.40, 95% CI=1.06-1.86, p=0.019), while weight gain was associated with incident knee pain (OR=1.34, 95% CI= 1.08-1.67, p=0.009) compared to controls. For all hip outcomes, no significant associations (p>0.05) were found with weight change group.

KNEE	KL worsening			Medial or lateral JSN			Medial JSN			Lateral JSN		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Controls		Reference			Reference			Reference			Controls	
Weight Gain	0.95	0.76 – 1.19	0.652	1.14	0.91 – 1.41	0.256	**1.29**	**1.01 – 1.64**	**0.038**	0.97	0.69 – 1.36	0.869
Weight Loss	**0.69**	**0.53 – 0.91**	**0.009**	0.88	0.68 – 1.13	0.318	0.85	0.63 – 1.13	0.263	1.01	0.69 – 1.47	0.956

HIP	Worsening of hip ROA			Superolateral or Superomedial JSN			Superomedial JSN			Superolateral JSN		
Controls		Reference			Reference			Reference			Reference	
Weight Gain	1.31	0.88 – 1.95	0.181	1.17	0.81 – 1.68	0.411	1.23	0.79 – 1.90	0.362	1.16	0.71 – 1.88	0.560
Weight Loss	1.02	0.64 – 1.63	0.925	1.07	0.73 – 1.57	0.739	1.22	0.78 – 1.90	0.380	0.96	0.58 – 1.62	0.891

Conclusions: In this study, weight loss (>-5% loss over 4 years) was associated with significantly less progression of *knee* radiographic OA KL grade) and less *knee* pain over 4 years. Weight gain (>5% over 4 years) was associated with greater medial *knee* radiographic progression and *knee* pain development. In contrast, no significant effects were observed between weight change (loss or gain) and *hip* OA. This large, longitudinal study (n=2752 with 4-year follow-up) suggests that weight loss may protect against, and weight gain may exacerbate radiographic knee OA and *knee pain*, while weight change (5% threshold) does not have significant effects on hip OA.

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A GENOME WIDE ASSOCIATION STUDY OF DXA-DERIVED MINIMUM JOINT SPACE WIDTH OF THE HIP PROVIDES FURTHER INSIGHTS INTO ITS GENETIC ARCHITECTURE: FINDINGS FROM UK BIOBANK

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Purpose: Cartilage is vital for joint health and function with its degeneration being a key feature of osteoarthritis (OA). Minimum joint space width measured on X-rays ($mJSW_{X\text{-}ray}$) or high-resolution dual-energy X-ray absorptiometry images ($mJSW_{DXA}$) can provide a proxy for cartilage thickness and pathological joint space narrowing (JSN). Defining the genetic architecture of mJSW provides a route to identify new biological pathways involved in JSN pathogenesis, some of which may represent future therapeutic targets. To date the largest genome-wide association study (GWAS) for $mJSW_{X\text{-}ray}$ encompassed 21,240 individuals, comprising meta-analysis of discovery (n=13,013 from 6 cohorts) and replication samples (n=8,227 from 7 cohorts). Five loci were detected, containing single nucleotide polymorphisms (SNPs) that were robustly associated with $mJSW_{X\text{-}ray}$ ($P < 5x10^{-8}$), of which four SNPs were also associated with hip OA (HOA). Recently the UK Biobank Study (UKB) released hip DXA images from more than 40,000 participants with genome-wide genotyping data. This resource provides an opportunity to (i) describe the genetic architecture of $mJSW_{DXA}$ for the first time, (ii) identify genes and biological pathways that influence mJSW, and (iii) determine whether genetic determinants of $mJSW_{DXA}$ are largely shared with those that influence $mJSW_{X\text{-}ray}$.

Methods: High-resolution left hip iDXA images were obtained in UKB. Eighty five outline points were automatically placed around the femoral head and acetabulum of each image by a machine learning-based algorithm before being manually checked and corrected if necessary