

UC Davis

UC Davis Previously Published Works

Title

Effusion-synovitis worsening mediates the association between body mass index and Kellgren-Lawrence progression in obese individuals: data from the Osteoarthritis Initiative.

Permalink

<https://escholarship.org/uc/item/1x33c1x7>

Journal

Osteoarthritis and cartilage, 30(9)

ISSN

1063-4584

Authors

Bañuls-Mirete, M
Lombardi, AF
Posis, AIB
[et al.](#)

Publication Date

2022-09-01

DOI

10.1016/j.joca.2022.05.011

Peer reviewed

Osteoarthritis and Cartilage



Effusion-synovitis worsening mediates the association between body mass index and Kellgren-Lawrence progression in obese individuals: data from the Osteoarthritis Initiative

M. Bañuls-Mirete [†], A.F. Lombardi [‡], A.I.B. Posis [§] ||, A.H. Shadyab [§], E.Y. Chang [¶], N.E. Lane [#], M. Guma ^{†*}

[†] Department of Medicine, University of California, San Diego, La Jolla, CA, USA

[‡] Department of Radiology, University of California, San Diego, La Jolla, CA, USA

[§] Herbert Wertheim, School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA, USA

^{||} School of Public Health, San Diego State University, San Diego, CA, USA

[¶] Radiology Service, VA San Diego Healthcare System, USA

[#] Department of Medicine, University of California, Davis, Sacramento, CA, USA

ARTICLE INFO

Article history:

Received 3 January 2022

Accepted 31 May 2022

Keywords:

Synovitis

BMI

OAI

Knee OA radiographic progression

Mediation analysis

SUMMARY

Objective: Both obesity and synovitis are independently associated with knee osteoarthritis (KOA) progression. We examined whether synovitis mediates the relationship between body mass index (BMI) and KOA radiographic progression in the Osteoarthritis Initiative (OAI) cohort.

Design: We conducted a case-control study within the OAI. Cases ($n = 315$) were right knees with an increase of ≥ 1 Kellgren-Lawrence from baseline to 48 months of follow-up. Controls ($n = 315$) were right knees with no KL change. Cases and controls were matched by age, sex, race, and baseline KL. MRI Osteoarthritis Knee Score (MOAKS) at baseline and at 2 years was used for a semi-quantitative scoring (0–3) of effusion-synovitis and Hoffa-synovitis. Conditional logistic regression estimated associations between BMI and synovitis with KOA progression. Mediation analysis was used to assess the mediating effects of synovitis.

Results: The mean age of participants was 61 years, 70.8% were women, and 87% were White. KOA progression was associated with higher BMI (adjusted OR 1.05; 95%CI 1.01–1.09) and effusion-synovitis relative to no effusion-synovitis (adjusted OR 2.2; 95%CI 1.6–3.1). Associations between effusion-synovitis worsening and KOA progression were more pronounced among obese individuals (OR 34.1; 95%CI 4.2–274.8; $P = 0.001$) compared to normal weight (OR 3.2; 95%CI 0.8–12.8, $P = 0.096$) individuals. Effusion-synovitis at 2 years, but not at baseline, mediated the relationship between BMI and KOA progression over a 4-year period.

Conclusions: We found that effusion-synovitis worsening mediated the association between BMI and KOA progression and was associated with increased risk of KOA progression, particularly among obese individuals.

© 2022 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Introduction

Osteoarthritis (OA) is the most common rheumatic musculoskeletal disease, and affected 303 million people globally in 2017¹. It is a chronic disease that can affect any joint, but usually affects the knee, hands, hip and spine. Its growing prevalence is attributed to the aging population as well as an increase in risk factors leading to OA². Its variable clinical outcomes have a significant impact on the individual patient, including pain and disability³. OA is responsible for activity restrictions, especially walking, and leads to poor

* Address correspondence and reprint requests to: M. Guma, Department of Medicine, University of California, 9500 Gilman Drive, San Diego, La Jolla, CA, MC 0663, USA. Tel: 92093-0663; Fax: 858-822-6523.

E-mail addresses: marina.banyuls@gmail.com (M. Bañuls-Mirete), allombardi@health.ucsd.edu (A.F. Lombardi), aposis@health.ucsd.edu (A.I.B. Posis), ahshadya@health.ucsd.edu (A.H. Shadyab), e8chang@health.ucsd.edu (E.Y. Chang), nelane@ucdavis.edu (N.E. Lane), mguma@health.ucsd.edu (M. Guma).

quality of life³. The economic burden of OA on patients and society is considerable. In 2015 in the United States (US), annual total healthcare costs and lost wages among adults with OA relative to those without OA were \$1778 and \$189 per person, respectively, resulting in estimated national excess costs of \$45 billion and \$1.7 billion, respectively⁴. There is a lack of treatments that can prevent or slow the progression of OA.

Risk factors of OA can be separated into general health (age, gender, genetics, metabolic syndrome, obesity, diet), and joint-related (history of injury or surgery, malalignment, abnormal loading of the joints, synovial inflammation)³. Body mass index (BMI) is a risk factor for knee OA (KOA)⁵. Obese individuals have 1.5–2 times greater risk of developing knee OA and of KOA progression than individuals with normal BMI^{6,7}. Obesity is also associated with rapid KOA progression (total knee replacement over a 2-year follow-up)⁸. Variations in weight also affect KOA progression, as weight gain is strongly associated with increased progression of cartilage degeneration in individuals with risk factors for OA⁹, and weight loss in obese and overweight people have reduced cartilage degeneration¹⁰.

Although OA was believed to be a wear and tear disease with cartilage destruction increasing evidence indicates that low-grade synovial inflammation (synovitis), contributes to OA progression^{11,12}. Synovial inflammation or effusion was present in 46% of people with symptomatic KOA¹³. Synovitis can occur prior to incident radiographic OA¹⁴, and effusion-synovitis 1–2 years prior to diagnosis is significantly associated with 1.8–2.5 times risk of subsequent OA development^{15,16} and accelerated KOA^{17–19}. Synovial inflammation in OA is also associated with more severe pain and joint dysfunction¹⁶.

A recent study found that overweight or obese BMI status was significantly associated with a greater prevalence and severity of synovial inflammation imaging biomarkers (e.g., effusion-synovitis, size and intensity of infrapatellar fat pad signal abnormality, and synovial proliferation score)²⁰; however, whether synovitis mediates the association of BMI and OA is unclear. The aim of this study was to examine the extent to which synovitis may mediate the radiographic progression of knee OA observed among those with higher body weight to provide a better understanding of pathways explaining the relationship between BMI and KOA.

Material and methods

Database and subject selection

The study utilized data from the Osteoarthritis Initiative (OAI) cohort (<https://oai.nih.gov>), which is sponsored by the US National Institutes of Health (NIH) and fully available in (<https://oai.nih.gov>), and details have been published elsewhere²¹. Briefly, the OAI is a longitudinal, multicenter study of 4,796 participants with or at risk for symptomatic knee OA, aged 45–79 years at enrollment. It aimed at identifying biomarkers of development and progression of symptomatic knee OA. Approximately 24% of the OAI participants were normal weight, 39% were overweight, and 37% were obese. Approximately 29% of participants with normal BMI, 49% of overweight, and 62% of obese had Kellgren–Lawrence (KL) >1 at baseline.

We conducted a case-control study to control for known risk factors for knee OA radiographic progression (age, sex, race, and baseline KL score). The primary outcome was knee OA radiographic progression, defined by an increase in the knee X-ray of ≥ 1 KL score from baseline to 48 months follow-up. There were 3,284 subjects with right knee radiographic data available at baseline and at 48 months follow-up were selected. We excluded subjects with KL score 4 at baseline. Participants with total knee replacement were

included as OA progressors if their KL was <4 at baseline and they had an increase of ≥ 1 KL score before surgery. From 3,105 subjects, 315 right knees had an increase of ≥ 1 KL score from baseline to 48 months follow-up. Control right knees were randomly selected by individually matching for age, sex, race, and baseline KL score. A total of 630 right knees were included in our study: cases ($n = 315$) had KOA radiographic progression, and controls ($n = 315$) did not have radiographic progression (Supplementary Fig. 1).

Weight was measured in kilograms, using a calibrated balance beam scale, with participants without shoes. Height was measured in millimeters, using a stadiometer, with participants without shoes. Body mass index (BMI; kg/m^2) was calculated as weight in kilograms divided by the square of the height in meters. BMI was entered in the models as a continuous variable or as a categorical variable as follows: normal weight, $\text{BMI} < 24.9 \text{ kg}/\text{m}^2$; overweight, $\text{BMI} 25\text{--}29.9 \text{ kg}/\text{m}^2$; and obese, $\text{BMI} \geq 30 \text{ kg}/\text{m}^2$. Waist circumference, a measure of central adiposity, was assessed using a tape measure over bare skin, with the participant standing.

Imaging and image analysis of the knee

Radiographic progression

Fixed flexion knee radiographs and radiographic KL grades²² were provided in the OAI database. Subjects with baseline KL grades of 4 were excluded. Knee osteoarthritis radiographic progression was defined by an increase in the knee X-ray of ≥ 1 KL score from baseline to 48 months follow-up.

Knee MRI

The OAI 3 Tesla MRI knee protocol includes the following sequences: coronal intermediate-weighted²³ 2D turbo spin-echo (TSE), sagittal 3D dual-echo in steady state (DESS) with water excitation that can be reformatted on the coronal and axial planes, coronal T1-weighted 3D fast low-angle shot (FLASH), sagittal IW 2D TSE fat-saturated, and sagittal 2D multi-echo spin-echo (MESE). Sagittal intermediate-weighted fat-suppressed turbo spin echo (TR/TE, 3200/30 ms; FA = 180°) and axial reformatted water-excitation dual-echo in steady state (TR/TE, 16.3/4.7 ms; FA = 25°) sequences were also used in this study.

Effusion-synovitis and Hoffa-synovitis at baseline and 2 years follow-up were graded by a fellowship-trained musculoskeletal radiologist with seven years of experience, blinded to the subject's clinical information, according to the MRI Osteoarthritis Knee Score (MOAKS)²⁴. Effusion-synovitis was reported as high signal intensity (fluid-equivalent) within the joint cavity on the axial reformatted 3D DESS WE MR sequence excluding periarticular cysts and ganglia: Grade 0 = none (physiological), grade 1 = small (fluid continuous in the retropatellar space), grade 2 = medium (slight convexity of the suprapatellar bursa) and grade 3 = large (evidence of capsular distension). Hoffa-synovitis was reported as diffuse high-signal intensity within the fat pad on the mid-slices of the sagittal IW 2D TSE fat-saturated MR sequence. The score was based on size: 0 = normal, 1 = mild, 2 = moderate, 3 = severe. All images were analyzed using Osirix DICOM Viewer²⁵.

To assess for both intra- and interobserver variability, twenty cases were randomly selected and after more than six months had passed, effusion-synovitis and Hoffa's fat pad synovitis was independently scored by a second musculoskeletal radiologist (11 years of experience) and again by the initial musculoskeletal radiologist. We obtained an interobserver agreement of 100% ($P < 0.001$) for effusion-synovitis and 94% ($P < 0.001$) for Hoffa synovitis. The intra-observer agreement was 93% (Cohen's Kappa = 0.93, $P < 0.001$) for effusion-synovitis and 94% for Hoffa synovitis (Cohen's Kappa = 0.94, $P < 0.001$).

The corresponding radiographic osteoarthritis knee scores (Kellgren-Lawrence) previously available in the OAI study were used for group stratification according to the following grade scale: grade 0 = none (absence of osteoarthritis), grade 1 = doubtful (doubtful joint space narrowing), grade 2 = minimal (definite osteophytes and possible joint space narrowing), grade 3 = moderate (multiple osteophytes, definite joint space narrowing and slight sclerosis), and grade 4 = severe (large osteophytes, marked narrowing of joint space, severe sclerosis, deformity of bone ends)^{24,25}.

Statistical analysis

The SPSS Statistics version 26 software was used to perform the statistical analyses. We obtained *p*-values with 95% confidence intervals. Descriptive statistics are given as means and standard deviation (SD) or percentages. Differences between case and control baseline characteristics were assessed with Student's *t*-test continuous variables and chi-square tests for categorical variables. Paired *t*-test and McNemar's chi-square were used to assess the differences between continuous and categorical characteristics, respectively, at baseline and after 2 years. Conditional logistic regression analysis was performed to analyze the association of BMI, synovitis, and synovitis progression with KOA radiographic progression, controlling for prior knee injury.

To estimate the proportion of the total effect of BMI on KOA radiographic progression mediated by synovitis, a mediation analysis was conducted via the PROCESS macro for SPSS using 5,000 bootstrap samples (SPSS, Inc., Chicago, IL, USA)²⁶. Logistic regression models were fit to estimate the total effect, direct effect, and indirect effect, controlling for prior knee injury²⁷. The underlying model of our analyses is illustrated in [Supplementary Fig. 2](#). In this framework, the total effect represents the effect of the exposure (BMI) on the outcome (KOA radiographic progression) controlling for knee injury. The direct effect is the effect of BMI on KOA radiographic progression, controlling for synovitis and knee injury (pathway C). The indirect effect is the effect of synovitis on KOA radiographic progression in response to one unit increase of BMI, controlling for knee injury (through pathway A and B). Using these estimates, we calculated the estimated proportion mediated of the total effect of BMI on KOA radiographic progression through synovitis when natural direct effect and natural indirect effect were in the same direction.

In sensitivity analyses, we performed sex stratified analyses to examine differences between men and women. We also performed stratified analyses for KOA radiographic progression by synovitis worsening and BMI category. To assess whether results differed among those with advanced KL, we repeated analyses among those with KL 0/1 and 2/3, separately. To account for potentially non-linear associations of BMI with synovitis and KOA, we repeated

	All	Cases N = 315	Controls N = 315	P
Age (years)	60.9 ± 8.3	60.9 ± 8.3	60.9 ± 8.3	0.99
Sex women (%)	70.8	70.8	70.8	0.99
Race (%)				
White/Caucasian	87	87	87	0.99
Black/African American	12.7	12.7	12.7	
Others	0.3	0.3	0.3	
Education				
High school graduate (%)	11.5	12.2	11	0.50
Some college (%)	23.3	25.6	20.8	
College graduate (%)	22.3	20.2	24.4	
Some graduate school (%)	8.8	9.1	8.4	
Graduate degree (%)	34.1	33	35.4	
Income				
Less than \$10 K (%)	2.4	2.3	2.4	0.97
\$10 K to > \$25 K (%)	8.3	9	7.6	
\$25 K to < \$50 K (%)	25.3	25.4	25.1	
\$50 K to < \$100 K (%)	40.0	39.8	40.2	
\$100 K or greater (%)	24.1	23.5	24.7	
Injury in right knee (%)	25.2	27.9	22.5	0.14
BMI (kg/m ²)	28.63 ± 4.8	29.1 ± 4.7	28.2 ± 4.9	0.014
BMI				
Normal weight (%)	24.9	21	28.9	0.045
Overweight (%)	37.1	37.5	36.8	
Obesity (%)	37.9	41.5	34.3	
Abdominal circumference (cm)	102.43 ± 12.80	103.91 ± 12.83	100.95 ± 12.62	0.004
Diabetes Mellitus (%)	5.1	4.4	5.7	0.59
Kellgren-Lawrence				
KL 0 (%)	36.8	36.8	36.8	0.99
KL 1 (%)	30.2	30.2	30.2	
KL 2 (%)	25.1	25.1	25.1	
KL 3 (%)	7.9	7.9	7.9	

Table 1

Osteoarthritis and Cartilage

Baseline characteristics of the study participants

	All	Cases (N = 315)	Controls (N = 315)	P
Effusion-synovitis				
Presence (%)	49.8	59.6	40.1	<0.001
Score 0	50.2	40.4	59.9	<0.001
Score 1	43.9	48.7	39.2	
Score 2	5.6	10.3	1	
Score 3	0.3	0.3	0	
Hoffa-synovitis				
Presence (%)	51.9	61.9	42	<0.001
Score 0	48.1	38.1	58	<0.001
Score 1	43.9	48.1	39.8	
Score 2	7	11.9	2.2	
Score 3	1	1.9	0	

Table II

Osteoarthritis and Cartilage

MRI characteristics of the study participants

mediation analyses using a categorical indicator of BMI (normal weight vs overweight or obese).

Results

Demographics of the control and case groups

Of the 630 individuals in our sample, there were $n = 315$ cases with KOA radiographic progression, and $n = 315$ controls that did not have KOA radiographic progression. The mean age (SD) of participants was 61 ± 8 years, 70.8% were women, and 87% were White (Table I). Baseline knee KL score was as follows: 36.8% grade 0, 30.2% grade 1, 25.1% grade 2% and 7.9% grade 3. There were no statistically significant differences in age, sex, race, or baseline history KL scores between cases and controls. There were no

statistically significant differences in education, income, or diabetes between groups. Medical history of injury in the right knee was slightly more frequent in cases (27.9% vs 22.5%; $P = 0.14$) and a greater proportion of controls were diabetic (5.7% vs 4.4%), although not statistically significant.

BMI was obtained at the baseline visit. One-fourth (24.9%) of individuals were normal weight (BMI <24.9 kg/m²), 37.1% were overweight (BMI 25–29.9 kg/m²) and 37.0% were obese (BMI ≥ 30 kg/m²). Average BMI was 28.63 ± 4.8 kg/m². Compared with controls, cases had higher BMI (29.1 ± 4.7 vs 28.2 ± 4.9 , $P < 0.05$), and were more likely to be obese (41.5% vs 34.3%) than controls ($P < 0.05$). Abdominal circumference (102.43 ± 12.80) was higher in cases than in controls (103.91 ± 12.83 vs 100.05 ± 12.62 , $P < 0.05$). Of interest, differences in BMI category were apparent in women (45% obese cases vs 34% obese controls), but not in men (34% obese cases vs 35% obese controls) (Supplementary Tables 1 and 2).

Effusion-synovitis and Hoffa-synovitis in cases and controls

Effusion-synovitis was present in 49.8% of our sample, with a mean (SD) score of 0.56 ± 0.6 , (range 0–3) and 51.9% had Hoffa synovitis with a score of 0.61 ± 0.66 (range 0–3). At baseline, cases had a higher prevalence of both effusion-synovitis and Hoffa-synovitis than controls (59.6% vs 40.1%, $P < 0.01$, for effusion-synovitis and 61.9% vs 42%, $P < 0.01$, for Hoffa-synovitis respectively: Table II). When stratified by sex, cases had a greater prevalence of synovitis effusion compared to controls in men, whereas both effusion-synovitis and Hoffa-synovitis were different in women (Supplementary Table 3). The prevalence of synovitis did not vary by baseline KL score (Supplementary Table 4).

Effusion-synovitis and Hoffa-synovitis scores are not associated with BMI

Recent work showed that being overweight or obese was significantly associated with a greater prevalence and severity of synovial inflammation imaging biomarkers²⁰. Therefore, we

Measure of synovitis	Indirect effect Coefficient (95%CI)	Direct effect Coefficient (95%CI)	Mediation %
All individuals (N = 619)			
Effusion-synovitis	0.0004 (–0.0082, 0.0095)	0.0453 (0.0106, 0.0801)	1
Hoffa-synovitis	0.0013 (–0.0075, 0.0106)	0.0448 (0.0102, 0.0794)	2
Women (N = 446)			
Effusion-synovitis	0.0005 (–0.0083, 0.0097)	0.0486 (0.0104, 0.0867)	1
Hoffa-synovitis	–0.0013 (–0.0134, 0.0112)	0.0526 (0.0139, 0.0913)	
B. Direct and indirect effects of BMI on KOA radiographic progression through synovitis by KL			
Measure of synovitis	Indirect effect Coefficient (95%CI)	Direct effect Coefficient (95%CI)	Mediation %
KL 0–1 (N = 413)			
Effusion-synovitis	–0.0013 (–0.0119, 0.0078)	0.0475 (0.0052, 0.0897)	
Hoffa-synovitis	0.0034 (–0.0049, 0.137)	0.0432 (0.0011, 0.0853)	7
KL 2–3 (N = 206)			
Effusion-synovitis	–0.0090 (–0.034, 0.0132)	0.057 (–0.0069, 0.1207)	
Hoffa-synovitis	–0.0208 (–0.0503, 0.006)	0.0711 (0.0061, 0.136)	

Coefficients and 95% CIs for product-of-coefficients mediation analysis for the association of BMI on KOA radiographic progression by effusion- or Hoffa-synovitis with knee injury as a covariate. The SPSS PROCESS macro was used to test the mediating effects. * $P < 0.05$.

Table III

Osteoarthritis and Cartilage

A. Direct and indirect effects of BMI on KOA radiographic progression through synovitis

determined the synovitis scores per BMI category. As shown in [Supplementary Table 5](#), there were no statistically significant differences between BMI categories with respect to the prevalence or severity of synovial inflammation. Of interest, the overweight group was the category with higher presence of synovitis compared to normal and obese weight. These results were obtained in both men and women groups and baseline KL score (data not shown). Also, there were no statistically significant correlations between BMI and abdominal circumference and synovitis scores (data not shown).

Mediation of the association of BMI with KOA radiographic progression by synovitis

We first performed conditional logistic regression to determine the associations of BMI and baseline synovitis with KOA radiographic progression. The odds of KOA radiographic progression was higher for every kg/m^2 increase in BMI (adjusted OR 1.05; 95% CI 1.01–1.09, $P = 0.006$), controlling for prior knee injury, similar among those with KLO-1 (adjusted OR 1.052; 95% CI 1.052–1.101, $P = 0.03$) and KL2-3 at baseline (adjusted OR 1.057; 95% CI 0.98–1.13, $P = 0.112$). Moreover, the odds of KOA radiographic progression was higher among those with effusion-synovitis relative to no effusion-synovitis (adjusted OR 2.2; 95% CI 1.5–3.1, $P < 0.001$) and Hoffa-synovitis relative to no Hoffa-synovitis (adjusted OR 2.2; 95% CI 1.6–3, $P < 0.001$), controlling for prior knee injury. Findings were similar when stratifying according to KL at baseline (effusion-synovitis relative to no effusion-synovitis in KLO-1 [adjusted OR 2.01; 95% CI 1.35–3.1, $P = 0.001$] vs KL2-3 [adjusted OR 2.57; 95% CI 1.38–4.77, $P = 0.003$], and Hoffa-synovitis relative to no Hoffa-synovitis in KL2-3 [adjusted OR 1.9; 95% CI 1.35–2.9, $P = 0.001$] vs KL2-3 [adjusted OR 2.67; 95% CI 1.47–4.95, $P = 0.001$]).

In the mediation analysis, effusion-synovitis or Hoffa synovitis at baseline did not mediate the relationship between BMI and KOA radiographic progression ([Table III](#)). Similar results were observed when we repeated the analyses in women and stratified by KL score at baseline ([Table IIIB](#)).

Effusion-synovitis and Hoffa-synovitis changes between baseline and 2 years

We then measured the effusion-synovitis and Hoffa-synovitis at 2 years to determine whether the synovitis worsening was associated with radiographic progression at 4 years and if it mediated the relationship between BMI and KOA radiographic progression. Of the 630 participants at baseline, 568 had MRI available at 2 years since recruitment ([Table IV](#)). The MRIs showed effusion-synovitis in 64.1% of our sample, with a score of 0.88 ± 0.81 (range 0–3), and 60% had Hoffa synovitis with a score of 0.79 ± 0.76 (range 0–3). After 2 years, 91.55% of cases (increased from 59.5% at baseline) had effusion-synovitis, while effusion-synovitis prevalence did not change in controls (around 40% in both baseline and at 2 years). Similar worsening was observed in Hoffa synovitis.

Worsening of the synovial inflammation at 2 years was significantly more pronounced in cases than controls ([Table V](#)), and when stratified by KL score at baseline ([Supplementary Table 6](#)). When stratified by sex, both women and men had similar worsening, although the worsening of Hoffa-synovitis was more evident in men ([Supplementary Table 7](#)).

Association of BMI with worsening of synovitis and KOA radiographic progression

We then determined if worsening of synovitis at 2 years was associated with BMI. As shown in [Table VI](#), there were no statistically significant associations between BMI categories with

	Baseline (N = 568)	2 Years (N = 568)	P
Effusion-synovitis			
Presence (%)	49.8	64.1	<0.001
Score 0	50.2	35.9	<0.001
Score 1	43.9	43.5	
Score 2	5.6	17.1	
Score 3	0.3	3.5	
Hoffa-synovitis			
Presence (%)	51.9	60	<0.001
Score 0	48.1	40	<0.001
Score 1	43.9	44	
Score 2	7	13.6	
Score 3	1	2.5	
BMI	28.58 ± 4.8	28.7 ± 5	0.016
Abdominal circ (cm)	102.32 ± 12.80	103.7 ± 12.9	<0.001

Table IV

Osteoarthritis and Cartilage

MRI characteristics between baseline and at 2 years

prevalence and severity of synovial inflammation at 2 years. Similar results were obtained in both men and women groups (data not shown). A greater proportion of overweight and obese developed worsening synovitis compared to normal weight, but this was not statistically significant ([Table VI](#)).

The odds of KOA radiographic progression was higher among those with effusion-synovitis worsening relative to no effusion-synovitis worsening (adjusted OR 9.9; 95% CI 5.6–17.5, $P < 0.001$) and Hoffa-synovitis relative to no Hoffa-synovitis (adjusted OR 17.8; 95% CI 7.8–40.6, $P < 0.001$), controlling for prior knee injury. We then stratified KOA radiographic progression by synovitis worsening and BMI category. The association between effusion-synovitis and Hoffa-synovitis worsening and KOA radiographic progression was more pronounced among obese individuals

	Cases (N = 284)	Controls (N = 284)	P
Effusion-synovitis			
Presence (%)	91.5	37.6	<0.001
Score 0	8.5	63.4	<0.001
Score 1	50.7	36.3	
Score 2	33.8	0.4	
Score 3	7	0	
Hoffa-synovitis			
Presence (%)	89.7	31.3%	<0.001
Score 0	11.3	68.7	<0.001
Score 1	57	31	
Score 2	26.8	0.4	
Score 3	4.9	9	
Worsening of effusion-synovitis (%)	57.4	10.6	<0.001
Worsening of Hoffa-synovitis (%)	46.1	5.6	<0.001
BMI (kg/m^2) at 24 m	29.3 ± 5.1	28.2 ± 4.9	0.015
Abdominal circ (cm) at 24 m	105.2 ± 13.4	102.1 ± 13.4	0.004

Table V

Osteoarthritis and Cartilage

MRI characteristics of the study participants after 2 years

	Normal weight n = 145	Overweight N = 213	Obese N = 210	P
Effusion-synovitis at 2y				
Presence (%)	64.3	67.9	69.5	0.561
Score 0	38.6	35.2	34.8	0.459
Score 1	46.2	43.2	41.9	
Score 2	13.8	18.3	18.1	
Score 3	1.4	3.3	5.2	
Hoffa synovitis at 2y				
Presence (%)	58.6	67.5	64.0	0.197
Score 0	44.8	35.7	41.0	0.137
Score 1	42.8	47.9	41.0	
Score 2	12.4	14.1	13.8	
Score 3	0	2.3	4.2	
Worsening effusion-synovitis	29.7%	33%	37.8%	0.265
Worsening Hoffa synovitis	23.4%	24.1%	29.2%	0.366

Table VI

Osteoarthritis and Cartilage

MRI characteristics of the study participants after 2 years (2y) by BMI category

(adjusted OR 34.1; 95% CI 4.2–274.8; $P = 0.001$ and adjusted OR 65.3; 95% CI 1.9–2181.2; $P = 0.001$ respectively), while it was not significant in the normal weight category (Table VII). Approximately 93% of the individuals who were obese and had effusion-synovitis of Hoffa-synovitis progression at 2 years, developed KOA radiographic progression at 4 years (Supplementary Table 8).

Mediation of the association of BMI with KOA radiographic progression by synovitis progression

Finally, we determined whether synovitis progression mediated the association between BMI and KOA radiographic progression. Mediation analysis showed that effusion-synovitis worsening at 2 years mediated the relationship between BMI and KOA radiographic progression among all participants. Effusion synovitis worsening mediated approximately 51% of the relationship between BMI and KOA radiographic progression. Of interest, there were greater magnitudes of effect with more advanced disease (i.e., higher KL), and synovitis-effusion worsening mediated 72% in the group with knee KL2-3 at baseline (Table VIII). Hoffa synovitis worsening at 2 years mediated 27% of the relationship, however the indirect effect was not statistically significant (Table VIII). When stratifying by sex and BMI category, the mediation of effusion-synovitis worsening was significant in women and obese individuals (Table VIII and Supplementary Fig. 9).

Discussion

This study examined the mediating effect of synovial inflammation with the association between BMI and KOA radiographic progression. Effusion-synovitis or Hoffa synovitis at baseline did not mediate the relationship between BMI and KOA radiographic progression. However, effusion-synovitis worsening at 2 year-follow-up mediated the relationship between BMI and KOA radiographic progression over a 4-year period. A mediation model seeks to identify and explain the mechanism or process that underlies an observed relationship. Our mediation model suggests that the BMI influences the synovitis, which in turn influences knee OA progression.

BMI is a well-known risk factor for radiographic KOA⁵. Our findings of associations between BMI and radiographic KOA are consistent with prior reports. Although in our study, only women and not men with KOA radiographic progression had higher BMI and abdominal circumference compared to controls. Prior studies have reported that overweight and obesity are essential in OA pathogenesis and progression^{6,28}, and the association of BMI with progression was stronger in women²⁹. Women are more seriously impacted by KOA³⁰ due to differences in knee anatomy, previous knee injury, hormonal influences³¹, and differences in cartilage health even before the onset of clinical knee disease³².

Our study also confirmed that subjects with KOA radiographic progression were more likely to have effusion-synovitis or Hoffa synovitis¹⁵. Both effusion-synovitis and Hoffa synovitis were shown to be associated with KL grade, joint space width, joint space narrowing, and total subchondral bone marrow lesion volume³³. Of interest, the prevalence of Hoffa-synovitis prevalence was similar between participants with or without knee injury³⁴. After stratification by sex, effusion-synovitis differed between cases and controls in both women and men, whereas Hoffa-synovitis differed only in women. In prior studies, the association with KOA radiographic progression was stronger for effusion-synovitis than for Hoffa-synovitis¹⁵. This could be explained by the reduced sensitivity of Hoffa-synovitis as a measure of synovial inflammation³⁵.

Increasing evidence indicates that OA involves all the joint tissues, including the synovial membrane^{16,36}. Synovial inflammation is present in the OA joint and has been associated with radiographic and pain progression^{16,37–39}. Of interest, several studies have shown that synovium of obese individuals have increased macrophage infiltration, marked fibrosis, and higher levels of TLR4 gene expression than non-obese individuals⁴⁰. The expression of inflammatory cytokines (IL-6) in serum, and adipocytokines (leptin) in the synovial fluid were also found to be positively correlated with BMI, and it differed significantly between obese and non-obese subjects⁴¹. Synovial fluid also has higher levels of β -tryptase produced by mast cells in obese individuals²³. In addition, studies performed in animal models with diet-induced obesity and

Worsening	BMI	OR	(95%CI)	P
Effusion-synovitis				
	All (N = 566)	9.9	5.6–17.5	<0.001
	Normal (N = 145)	3.2	0.8–12.8	0.096
	Overweight (N = 212)	11.3	2.6–48.58	0.001
	Obese (N = 209)	34.1	4.2–274.8	0.001
Hoffa-synovitis				
	All (N = 562)	17.8	7.8–40.6	<0.001
	Normal (N = 144)	65.2	0.21–19668	0.151
	Overweight (N = 212)	9.3	2.8–42.4	0.004
	Obese (N = 209)	65.2	1.9–2181.2	0.02

Table VII

Osteoarthritis and Cartilage

Risk of KOA radiographic progression in subjects with worsening synovitis relative to no worsening synovitis per BMI category

surgically induced OA also showed an increase of pro-inflammatory macrophages⁴² and proinflammatory mediators IL-1 β , IL-6 and TNF in the synovium⁴³, promoting OA.

Despite data on the synovial changes in obese individuals, only one study reported that overweight and obesity were associated with greater prevalence and severity of synovitis²⁰. In our study, though, there were no statistically significant associations between BMI categories with prevalence and severity of synovial inflammation at baseline or at 2-year follow-up. Differences in synovitis quantification could explain this discrepancy. The study by Kant-hawang *et al.*²⁰ also used MOAKS to evaluate effusion-synovitis in

the knee but the investigators added other grading systems (two for effusion-synovitis, two for Hoffa's fat pad synovitis, and two for synovial proliferation score) as independent markers of joint inflammation.

While we did not observe any mediation by baseline synovitis, there was evidence to suggest that effusion-synovitis worsening at 2 years mediated the relationship between BMI and KOA radiographic progression. As in previous studies^{44,45}, worsening in synovitis scores was associated with KOA radiographic progression. We observed that obesity dramatically increased the risk of KOA progression radiographic in patients with worsening synovitis. Approximately 93% of the individuals who were obese and had effusion-synovitis of Hoffa-synovitis progression at 2 years, developed KOA progression at 4 years. Our results are consistent with a recent report that showed that being overweight with Hoffa-synovitis or effusion-synovitis was associated with greater odds of incident radiographic KOA in women⁴⁶. In that study, the authors studied whether the relationship between BMI and KOA differed by effusion/synovitis status⁴⁶. We now describe additional information, and our mediation model proposes that BMI also influences worsening synovitis, which in turn influences knee OA progression. Of interest, a prior study described that progression of synovitis was 18% in the weight gain group vs 7% in the stable weight subgroup (OR 2.88; 95%CI 1.39–5.94)⁴⁷. Future research with larger sample size and longer follow-up should explore whether losing weight, specifically in obese OA individuals with synovitis, delays the KOA progression. Although some reports did not show significant improvement in synovitis score by MRI after weight loss⁴⁸, these studies did not evaluate changes in synovial composition or inflammation.

Notable strengths of this study include the size of the study population, and its population-based design from the OAI cohort, with has an extensive characterization of participants. However,

Measure of synovitis	Indirect effect Coefficient (95%CI)	Direct effect Coefficient (95%CI)	Mediation %
All individuals (N = 560)			
Effusion-synovitis	0.0308 (0.0076, 0.0585)	0.036 (-0.0031, 0.075)	51
Hoffa-synovitis	0.0206 (-0.0036, 0.0477)	0.0503 (0.0118, 0.089)	27
Women (N = 396)			
Effusion-synovitis	0.0293 (0.0041, 0.0584)	0.0365 (-0.0064, 0.794)	44
Hoffa-synovitis	0.0153 (-0.0087, 0.0430)	0.0534 (0.0116, 0.0952)	21
Men (N = 164)			
Effusion-synovitis	0.0380 (-0.0239, 0.1161)	0.0324 (-0.0624, 0.127)	54
Hoffa-synovitis	0.0527 (-0.0325, 0.1746)	0.0223 (-0.078, 0.122)	66
B. Direct and indirect effects of BMI on KOA radiographic progression through synovitis worsening by KL			
Measure of synovitis	Indirect effect Coefficient (95%CI)	Direct effect Coefficient (95%CI)	Mediation %
KL 0–1 (N = 372)			
Effusion-synovitis	0.029 (-0.02, 0.066)	0.055 (0.0023, 0.10)	35
Hoffa-synovitis	0.0238 (-0.007, 0.057)	0.0559 (0.0079, 0.104)	30
KL 2–3 (N = 190)			
Effusion-synovitis	0.0332 (0.0013, 0.081)	0.0114 (-0.0537, 0.076)	72
Hoffa-synovitis	0.015 (-0.025, 0.067)	0.0407 (-0.025, 0.106)	26

Coefficients and 95% CIs for product-of-coefficients mediation analysis for the association of BMI on KOA radiographic progression by effusion or Hoffa synovitis worsening with knee injury as a covariate. The SPSS PROCESS macro was used to test the mediating effects. * $P < 0.05$.

Table VIII

Osteoarthritis and Cartilage

A. Direct and indirect effects of BMI on KOA radiographic progression through synovitis worsening

there are a few limitations. While there is strong evidence to support a correlation between MRI assessed synovitis and histology⁴⁹, MOAKS grading system, a semi-quantitative MRI scoring tool, was used in non-contrast MRI to assess effusion-synovitis and Hoffa synovitis. Quantitative MRI grading of the synovitis of the entire 4 years of follow up would have been useful to better understand the relationship between BMI, synovitis, and OA progression. Although KL gradings are generally not a very sensitive measure of progression, the relationship between BMI and KOA by effusion/synovitis status was similar in knees with both baseline KLO-1 and KL2-3, although the mediation effect was more evident in KL2-3. The lower prevalence of OA in men may explain the lack of statistical significance of some analyses that showed clinically meaningful percentages of mediation. Additionally, in case-control studies, matching may contribute to selection bias, potentially biasing estimates towards the null⁵⁰. Given the observational nature of this study, residual confounding may be possible. However, we had a substantial number of participants with MRI at 2 years, and we were able to match on key confounders and control for prior knee injury.

In conclusion, our data show that effusion-synovitis worsening at 2 year-follow-up mediated the relationship between BMI and KOA radiographic progression over a 4-year period. Further studies are needed to determine whether synovitis mediates the relationship between BMI and KOA pain progression and to identify risk factors of synovitis progression in obese individuals.

Author contributions

Study design: AHS, NEL, MG; MRI imaging scoring: AFL, EYC; Data analysis and interpretation: MBM, AIBP, AHS, NEL, MG; Writing – original draft: MBM, AIBP, NEL, MG. Writing – comments and review: all authors.

Conflict of interest

There is no conflict of interest.

Funding information

This work was supported by the National Institute of Health (AR073324 to MG, T32 AG058529 to AIBP), and by the VA Merit Review Grants (I01CX001388 and I01RX002604 to EYC and AFL).

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.joca.2022.05.011>.

References

1. Disease GBD, Injury I, Prevalence C. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392(10159):1789–858.
2. Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. *Osteoarthritis Cartilage* 2020;28(3):242–8.
3. Palazzo C, Nguyen C, Lefevre-Colau MM, Rannou F, Poiraudou S. Risk factors and burden of osteoarthritis. *Ann Phys Rehabil Med* 2016;59(3):134–8.
4. Zhao X, Shah D, Gandhi K, Wei W, Dwibedi N, Webster L, et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. *Osteoarthritis Cartilage* 2019;27(11):1618–26.
5. Xu C, Marchand NE, Driban JB, McAlindon T, Eaton CB, Lu B. Dietary patterns and progression of knee osteoarthritis: data from the osteoarthritis initiative. *Am J Clin Nutr* 2020;111(3):667–76.
6. Pishgar F, Guermazi A, Ashraf-Ganjouei A, Haj-Mirzaian A, Roemer FW, Zikria B, et al. Association between Patellofemoral and medial Tibiofemoral compartment osteoarthritis progression: exploring the effect of body weight using longitudinal data from osteoarthritis initiative (OAI). *Skeletal Radiol* 2021;50(9):1845–54.
7. Jacobs CA, Vranceanu AM, Thompson KL, Lattermann C. Rapid progression of knee pain and osteoarthritis biomarkers greatest for patients with combined obesity and depression: data from the osteoarthritis initiative. *Cartilage* 2020;11(1):38–46.
8. Deveza LA, Downie A, Tamez-Pena JG, Eckstein F, Van Spil WE, Hunter DJ. Trajectories of femorotibial cartilage thickness among persons with or at risk of knee osteoarthritis: development of a prediction model to identify progressors. *Osteoarthritis Cartilage* 2019;27(2):257–65.
9. Bucknor MD, Nardo L, Joseph GB, Alizai H, Srikhun W, Nevitt MC, et al. Association of cartilage degeneration with four year weight gain—3T MRI data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2015;23(4):525–31.
10. Gersing AS, Schwaiger BJ, Nevitt MC, Zarnowski J, Joseph GB, Feuerriegel G, et al. Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2019;27(6):863–70.
11. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016;12(10):580–92.
12. Sanchez-Lopez E, Coras R, Torres A, Lane NE, Guma M. Synovial inflammation in osteoarthritis progression. *Nat Rev Rheumatol* 2022;18(5):258–75.
13. D'Agostino MA, Conaghan P, Le Bars M, Baron G, Grassi W, Martin-Mola E, et al. EULAR report on the use of ultrasonography in painful knee osteoarthritis. Part 1: prevalence of inflammation in osteoarthritis. *Ann Rheum Dis* 2005;64(12):1703–9.
14. Haywood L, McWilliams DF, Pearson CI, Gill SE, Ganesan A, Wilson D, et al. Inflammation and angiogenesis in osteoarthritis. *Arthritis Rheum* 2003;48(8):2173–7.
15. Atukorala I, Kwok CK, Guermazi A, Roemer FW, Boudreau RM, Hannon MJ, et al. Synovitis in knee osteoarthritis: a precursor of disease? *Ann Rheum Dis* 2016;75(2):390–5.
16. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone* 2012;51(2):249–57.
17. Davis JE, Ward RJ, MacKay JW, Lu B, Price LL, McAlindon TE, et al. Effusion-synovitis and infrapatellar fat pad signal intensity alteration differentiate accelerated knee osteoarthritis. *Rheumatology (Oxford)* 2019;58(3):418–26.
18. Harkey MS, Davis JE, Lu B, Price LL, Ward RJ, MacKay JW, et al. Early pre-radiographic structural pathology precedes the onset of accelerated knee osteoarthritis. *BMC Musculoskelet Disord* 2019;20(1):241.
19. Harkey MS, Davis JE, Price LL, Ward RJ, MacKay JW, Eaton CB, et al. Composite quantitative knee structure metrics predict the development of accelerated knee osteoarthritis: data from the osteoarthritis initiative. *BMC Musculoskelet Disord* 2020;21(1):299.
20. Kanthawang T, Bodden J, Joseph GB, Lane NE, Nevitt M, McCulloch CE, et al. Obese and overweight individuals have greater knee synovial inflammation and associated structural and cartilage compositional degeneration: data from the osteoarthritis initiative. *Skeletal Radiol* 2021;50(1):217–29.
21. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance

- imaging protocol for the knee. *Osteoarthritis Cartilage* 2008;16(12):1433–41.
22. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16(4):494–502.
 23. Takata K, Uchida K, Mukai M, Takano S, Aikawa J, Iwase D, et al. Increase in tryptase and its role in the synovial membrane of overweight and obese patients with osteoarthritis of the knee. *Diabetes Metab Syndr Obes* 2020;13:1491–7.
 24. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage* 2011;19(8):990–1002.
 25. Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging* 2004;17(3):205–16.
 26. Montoya AK, Hayes AF. Two-condition within-participant statistical mediation analysis: a path-analytic framework. *Psychol Methods* 2017;22(1):6–27.
 27. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. *Behav Res Ther* 2017;98:39–57.
 28. Belluzzi E, El Hadi H, Granzotto M, Rossato M, Ramonda R, Macchi V, et al. Systemic and local adipose tissue in knee osteoarthritis. *J Cell Physiol* 2017;232(8):1971–8.
 29. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. *Indian J Med Res* 2013;138:185–93.
 30. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13(9):769–81.
 31. Hame SL, Alexander RA. Knee osteoarthritis in women. *Curr Rev Musculoskelet Med* 2013;6(2):182–7.
 32. Hanna FS, Teichtahl AJ, Wluka AE, Wang Y, Urquhart DM, English DR, et al. Women have increased rates of cartilage loss and progression of cartilage defects at the knee than men: a gender study of adults without clinical knee osteoarthritis. *Menopause* 2009;16(4):666–70.
 33. Krasnokutsky S, Belitskaya-Levy I, Bencardino J, Samuels J, Attur M, Regatte R, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis Rheum* 2011;63(10):2983–91.
 34. Hart HF, Culvenor AG, Patterson BE, Doshi A, Vora A, Guermazi A, et al. Infrapatellar fat pad volume and Hoffa-synovitis after ACL reconstruction: association with early osteoarthritis features and pain over 5 years. *J Orthop Res* 2021;40(1):260–7.
 35. Roemer FW, Guermazi A, Zhang Y, Yang M, Hunter DJ, Crema MD, et al. Hoffa's fat pad: evaluation on unenhanced MR images as a measure of patellofemoral synovitis in osteoarthritis. *AJR Am J Roentgenol* 2009;192(6):1696–700.
 36. Ishibashi K, Sasaki E, Ota S, Chiba D, Yamamoto Y, Tsuda E, et al. Detection of synovitis in early knee osteoarthritis by MRI and serum biomarkers in Japanese general population. *Sci Rep* 2020;10(1):12310.
 37. Xie J, Huang Z, Yu X, Zhou L, Pei F. Clinical implications of macrophage dysfunction in the development of osteoarthritis of the knee. *Cytokine Growth Factor Rev* 2019;46:36–44.
 38. Ballegaard C, Riis RG, Bliddal H, Christensen R, Henriksen M, Bartels EM, et al. Knee pain and inflammation in the infrapatellar fat pad estimated by conventional and dynamic contrast-enhanced magnetic resonance imaging in obese patients with osteoarthritis: a cross-sectional study. *Osteoarthritis Cartilage* 2014;22(7):933–40.
 39. Belluzzi E, Stocco E, Pozzuoli A, Granzotto M, Porzionato A, Vettor R, et al. Contribution of infrapatellar fat pad and synovial membrane to knee osteoarthritis pain. *Biomed Res Int* 2019;2019, 6390182.
 40. Harasymowicz NS, Clement ND, Azfer A, Burnett R, Salter DM, Simpson A. Regional differences between perisynovial and infrapatellar adipose tissue depots and their response to class II and class III obesity in patients with osteoarthritis. *Arthritis Rheumatol* 2017;69(7):1396–406.
 41. Duan L, Ma Y, Wang Y, Liu J, Tan Z, Wu Q, et al. Infrapatellar fat pads participate in the development of knee osteoarthritis in obese patients via the activation of the NFkappaB signaling pathway. *Int J Mol Med* 2020;46(6):2260–70.
 42. Sun AR, Panchal SK, Friis T, Sekar S, Crawford R, Brown L, et al. Obesity-associated metabolic syndrome spontaneously induces infiltration of pro-inflammatory macrophage in synovium and promotes osteoarthritis. *PLoS One* 2017;12(8), e0183693.
 43. Larranaga-Vera A, Lamuedra A, Perez-Baos S, Prieto-Potin I, Pena L, Herrero-Beaumont G, et al. Increased synovial lipodystrophy induced by high fat diet aggravates synovitis in experimental osteoarthritis. *Arthritis Res Ther* 2017;19(1):264.
 44. Roemer FW, Guermazi A, Collins JE, Losina E, Nevitt MC, Lynch JA, et al. Semi-quantitative MRI biomarkers of knee osteoarthritis progression in the FNIH biomarkers consortium cohort - methodologic aspects and definition of change. *BMC Musculoskelet Disord* 2016;17(1):466.
 45. Wang Y, Teichtahl AJ, Pelletier JP, Abram F, Wluka AE, Hussain SM, et al. Knee effusion volume assessed by magnetic resonance imaging and progression of knee osteoarthritis: data from the Osteoarthritis Initiative. *Rheumatology (Oxford)* 2019;58(2):246–53.
 46. Roemer FW, Guermazi A, Hannon MJ, Fujii T, Omoumi P, Hunter DJ, et al. Presence of MRI-defined inflammation particularly in overweight and obese women increases risk of radiographic knee osteoarthritis: the POMA Study. *Arthritis Care Res (Hoboken)* 2021.
 47. Landsmeer MLA, de Vos BC, van der Plas P, van Middelkoop M, Vroegindeweyj D, Bindels PJE, et al. Effect of weight change on progression of knee OA structural features assessed by MRI in overweight and obese women. *Osteoarthritis Cartilage* 2018;26(12):1666–74.
 48. Dagaard CL, Henriksen M, Riis RGC, Bandak E, Nybing JD, Hangaard S, et al. The impact of a significant weight loss on inflammation assessed on DCE-MRI and static MRI in knee osteoarthritis: a prospective cohort study. *Osteoarthritis Cartilage* 2020;28(6):766–73.
 49. Loeuille D, Chary-Valckenaere I, Champigneulle J, Rat AC, Toussaint F, Pinzano-Watrin A, et al. Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: correlating magnetic resonance imaging findings with disease severity. *Arthritis Rheum* 2005;52(11):3492–501.
 50. Mansournia MA, Jewell NP, Greenland S. Case-control matching: effects, misconceptions, and recommendations. *Eur J Epidemiol* 2018;33(1):5–14.