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Weight Cycling and Knee Joint Degeneration in Individuals with Overweight or Obesity: Four-Year Magnetic Resonance Imaging Data from the Osteoarthritis Initiative

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Objective: The aim of this study was to investigate the associations between weight cycling and knee joint degeneration in individuals with overweight or obesity with different patterns of weight change over 4 years.
Methods: A total of 2,271 individuals from the Osteoarthritis Initiative database were assessed (case-control study). Linear regression models using annual BMI measurements over 4 years were used to classify participants as weight cyclers or noncyclers. 3-T magnetic resonance imaging was used to quantify knee cartilage transverse relaxation time (T2) and cartilage thickness annually over 4 years in all subjects. Whole-Organ Magnetic Resonance Imaging Scores (WORMS) were obtained for cartilage, meniscus, and bone-marrow abnormalities in 958 subjects at baseline and at the 4-year follow-up. The longitudinal differences in cartilage T2 and thickness between weight cyclers and noncyclers were assessed using general estimating equations, whereas the differences in WORMS outcomes were compared using general linear models.
Results: No significant differences in the rate of change of cartilage thickness or T2 were found between weight cyclers and noncyclers. However, increases in maximum cartilage WORMS ($P = 0.0025$) and bone-marrow abnormalities ($P = 0.04$) were significantly greater in weight cyclers than in noncyclers.
Conclusions: Although participants' intent for weight cycling in this study was unknown, weight cyclers had significantly greater increases in cartilage and bone-marrow abnormalities over 4 years than noncyclers, independent of weight gain and loss.

Obesity (2021) **29**, 909-918.

Study Importance

What is already known?

- Although the effects of weight cycling on obesity-related outcomes, including mortality, cardiovascular disease, type 2 diabetes, body composition, and cancer, have been explored, with some studies reporting no effects and others citing increased risks, the effects of weight cycling on osteoarthritis have not been thoroughly investigated.

What does this study add?

- Weight cyclers had significantly greater increases in cartilage and bone-marrow abnormalities over 4 years than noncyclers, independent of weight gain and weight loss.

How might these results change the focus of clinical practice?

- Understanding the relationship between weight cycling and joint degeneration will guide clinicians on patient-specific, informed recommendations that may depend on whether individuals are able to sustain long-term weight loss or whether they are prone to weight fluctuation.

Introduction

Obesity, prevalent in approximately 39.8% of US adults (data from 2015/2016 (1)), is a risk factor for cardiovascular disease, hypertension, type 2 diabetes, and osteoarthritis (OA) (2). Weight loss is frequently recommended for individuals with obesity to reduce the risk of obesity-related diseases, and protective effects have been shown (3-5). However, sustained weight loss is often difficult to maintain, and an estimated 20% to 30% of individuals attempting weight loss experience episodic variation in body weight (6). This repetitive pattern of weight loss and regain has been termed weight cycling (7).

Although the effects of weight cycling on obesity-related diseases, including mortality, cardiovascular disease, type 2 diabetes, body composition, and cancer, have been explored, with some studies reporting no effects and others citing increased risks (8,9), the

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effects of weight cycling on OA have not been thoroughly investigated. However, the effects of weight loss and obesity on OA are well studied, and it has been shown that weight loss can prevent the onset of OA, improve symptoms and function, and increase quality of life (5). It has also been demonstrated that obesity is a strong risk factor for OA, with every 5 kg of weight gain increasing the risk for OA by 26% (10). Nonetheless, there is a knowledge gap on the impact of weight cycling on OA. Understanding this relationship between weight cycling and joint degeneration will guide clinicians on patient-specific, informed recommendations that may depend on whether individuals are able to sustain long-term weight loss or whether they are prone to weight fluctuation.

This study analyzed data from the OA Initiative (OAI), a longitudinal, multicenter study in 4,796 individuals with clinical and imaging data, including data from magnetic resonance (MR) imaging (MRI) of the knee joint. MRI can depict subtle knee morphologic changes, including cartilage defects and meniscus tears (11) that are not shown on radiographs, and thus it is a useful imaging modality to assess knee soft-tissue degeneration as well as bone changes related to OA, such as bone-marrow abnormalities. In addition, MRI cartilage transverse relaxation time (T2) is sensitive to tissue hydration and biochemical composition. In early cartilage degeneration, changes in the extracellular matrix (e.g., disorganization and breakdown of the collagen network) increase the mobility of water, thus increasing T2. The availability of clinical data in the OAI database (including annual BMI measurements and knee pain questionnaires) coupled with longitudinal MRI facilitates analysis of weight change fluctuations in conjunction with knee joint health.

The purpose of this study was to investigate the associations between weight cycling and the progression of structural knee joint degeneration, compositional cartilage degeneration, and cartilage thickness loss among individuals with overweight or obesity and to investigate whether these associations are independent of weight gain and weight loss.

Methods

Subject selection

This study analyzed data from the OAI (http://www.oai.ucsf.edu/) (12), a multicenter, longitudinal study of individuals aged 45 to 79 years at enrollment. The OAI data set includes MRI and radiographic knee images of individuals scanned over 8 years. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards of all participating centers.

The present study analyzed a sample of individuals enrolled in the OAI using the following inclusion criteria: (1) at least three (of five) annual BMI measurements available, (2) a baseline Kellgren-Lawrence score (KL) ≤ 3 in the right knee, (3) available semiquantitative joint morphologic measures at baseline and 4 years previously obtained from other analyses (13-17), and (4) BMI > 25 kg/m^2 at baseline. The OAI exclusion criteria were (1) inflammatory arthropathies (including rheumatoid arthritis) and severe disease that may impact weight change (i.e., cardiac failure, cancer), (2) MRI contraindications, and (3) use of ambulatory aids and the presence of comorbid conditions that may have affected the ability to participate in the study. For this analysis, we further excluded knees with (1) posttraumatic osseous deformities demonstrated on knee radiographs, (2) total joint replacements at the lower extremities, and (3) MRI evidence of fractures or abnormalities unrelated to OA that may have indicated a severe disease, such as tumors or inflammation. On the basis of these criteria, a total of 2,271 individuals were included in this study (Figure 1).

Group definitions

BMI measurements were used to determine the annual rate of change in BMI over 4 years in each individual. The slope of the regression line was multiplied by 4 to determine the overall magnitude of BMI change, and the percentage of change over 4 years was defined as the magnitude of the BMI change divided by the baseline BMI. In addition to the magnitude of weight change, the trajectory of weight change may have affected longitudinal changes in joint structure and clinical symptoms. We devised a method to classify individuals into those with "steady" weight change and into those with "cyclic" weight change, which was based on the root mean square error (RMSE) of the regression line. We obtained RMSE measurements from each individual's regression model, and weight fluctuation was determined on the basis of the RMSE. We defined a subject with BMI variability, termed a *weight cycler* in this study, as an individual with an RMSE value (as previously described (18)) in the top 10% of all RMSE values. The remaining 90% of individuals were termed *noncyclers*. In addition, individuals were classified into three groups on the basis of their annual changes in BMI over 4 years: those with weight loss (>−5% change), those with weight gain (>5% change), and control subjects without weight change (−3% to 3% change). Clinically significant weight loss of 5% was defined on the basis of a previous study by Williamson et al. (19), and a threshold of 5% weight gain was chosen as previously defined (20). Figure 2 illustrates representative regression lines from individuals from the control and weight loss groups.

MRI

WORMS scoring. MR images of the right knee obtained at the baseline and 4-year follow-up visits were reviewed on picture archiving communication system workstations (Agfa, Ridgefield Park, New Jersey). Three radiologists with 7, 5, and 2 years of experience graded knee abnormalities using modified semiquantitative Whole-Organ MRI Scores (WORMS) (21,22). In equivocal cases, a consensus reading was performed with a musculoskeletal radiologist with 24 years of experience. Cartilage and bone-marrow lesions were assessed in six regions (patella, trochlea, medial femur [MF], medial tibia [MT], lateral femur [LF], and lateral tibia [LT]). The highest score of any lesion was recorded for each region. A subchondral bone-marrow edema pattern (BMEP) was defined as poorly marginated areas of increased T2 signal intensity and graded using a modified 4-point WORMS scale (23). Meniscal lesions were graded separately in six regions (medial/lateral and anterior/body/posterior) using the following 4-point scale: 0 = normal, 1 = intrasubstance signal, 2 = nondisplaced tear, 3 = displaced or complex tear, and 4 = complete destruction/maceration. The maximum cartilage, meniscus, or BMEP scores were defined as the maximum score in any region. WORMS were obtained in all knee images from among those in the weight cycler group who had baseline and 4-year follow-up data available (n = 189).

The reproducibility results for WORMS reading have been previously published (4). The intraclass correlation coefficients for

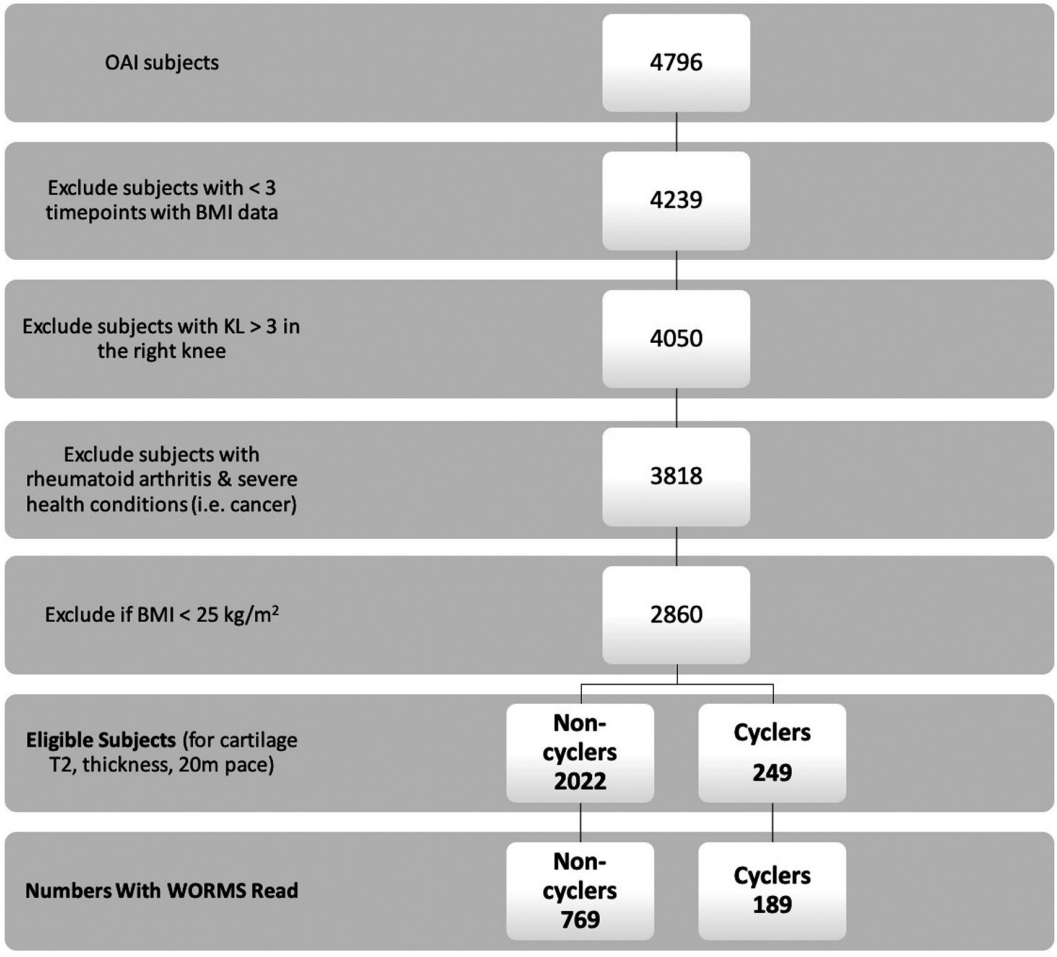

Figure 1 Subject selection. KL, Kellgren-Lawrence score; OAI, Osteoarthritis Initiative; WORMS, Whole-Organ Magnetic Resonance Imaging Scores.

intraobserver agreement were 0.85 (95% CI: 0.79-0.93) and 0.87 (95% CI: 0.81-0.94) for meniscus WORMS, 0.87 (95% CI: 0.81-0.92) and 0.84 (95% CI: 0.78-0.95) for cartilage WORMS, and 0.89 (95% CI: 0.85-0.91) and 0.86 (95% CI: 0.80-0.95) for BMEP scores. The intraclass correlation coefficients for interobserver agreement were 0.83 (95% CI: 0.76-0.91) for meniscus WORMS, 0.80 (95% CI: 0.74-0.87) for cartilage WORMS, and 0.88 (95% CI: 0.81-0.94) for BMEP scores.

Cartilage T2. Cartilage T2 values were quantified at baseline and annually over 4 years in six regions (MT, LT, MF, LF, trochlea, and patella) using a machine learning–based algorithm as previously described (24,25). The following sequence of steps was performed: (1) reference identification, (2) deep learning–based cartilage segmentation for the entire data set, (3) nonrigid morphing driven by the cartilage mask extracted in step 2, and (4) voxel-by-voxel fitting of morphed T2 images (24). Using the segmentations obtained by the deep learning model to drive the voxel-based registration process helped solve the imbalance in tissue image occupancy. For the image registration, five-level recursive pyramidal multiresolution with a random-sampler approach served to estimate the nonrigid transformation between the fixed and moving image. The nonrigid registration technique was applied between the reference and each case using the T2 image with an echo time (TE) of 10 milliseconds. The best reference was chosen as the sample that minimized the average deformation of the overall data set: the minimal-deformation template. The transformation field obtained was applied to all of the T2-weighted images. T2 maps were obtained by fitting the morphed T2-weighted images obtained with different spin-lock times using a Levenberg-Marquardt mono-exponential value at each voxel. Although the OAI data set provided images with seven echoes (TE = 10, 20, 30, 40, 50, 60, and 70 milliseconds) for T2 calculation, the first echo (TE = 10 milliseconds) was not included in the T2-fitting procedure in order to reduce potential errors resulting from stimulated echoes, and a noise-corrected algorithm was implemented (26,27).

Cartilage thickness. A fully automatic method was developed and validated by our group for reliable cartilage segmentation and thickness measurement of knee MRI volumes as previously described (28). Three identical three-dimensional VNet architectures and three two-dimensional UNet-like architectures were trained to segment dual echo in the steady

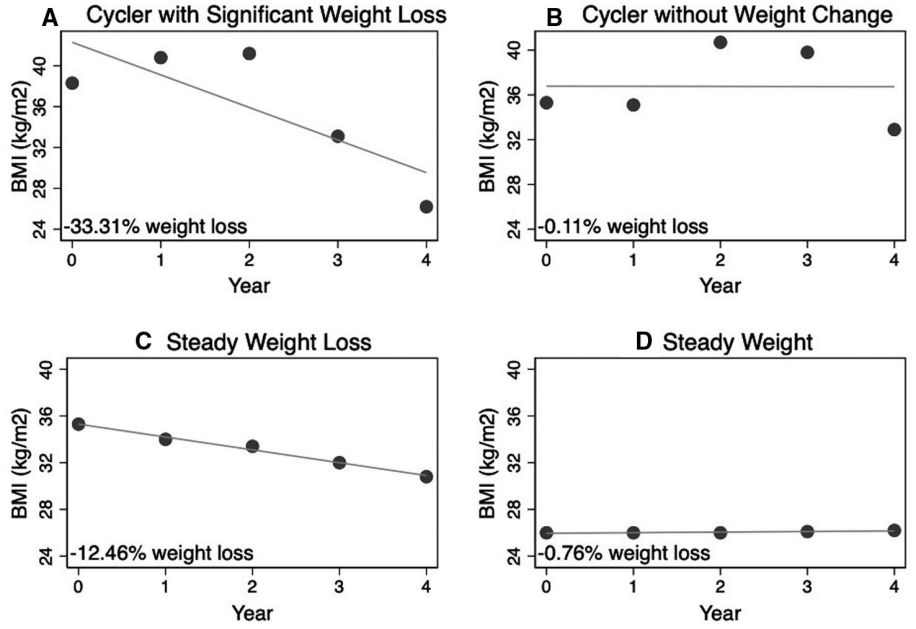

Figure 2 Regression models from representative individuals. (**A**) A 48-year-old female weight cycler with significant weight loss over 4 years (>5%), (**B**) a 51-year-old female weight cycler without weight change defined by –3% to 3% weight change over 4 years, (**C**) a 62-year-old female with steady weight loss over 4 years (>5%), and (**D**) a 55-year-old male with steady weight over 4 years (–3% to 3%).

state sequence volumes. Networks were implemented in TensorFlow version 1.10 (https://www.tensorflow.org/) and trained on a Nvidia (Santa Clara, California) TitanX (12,196 MiB) or Nvidia V100 (32,480 MiB) graphics processing unit. Cartilage segmentation was subsegmented into the LT, MT, patella, central weight–bearing LF, and central weight–bearing MF compartments. For each compartment and for each sagittal slice, a Euclidean distance transformation and skeletonization were performed. The value of the distance map was sampled at each skeleton point, and all points across all slices were averaged to calculate the mean thickness. Lateral and medial femoral compartments underwent Euclidean distance transformation and skeletonization before subsegmentation. Only the weight-bearing region was included in the mean thickness calculation for the LF and MF (28).

Twenty-meter walking speed

The 20-m walk assessment was used to assess walking speed annually at baseline and the 4-year follow-up. Participants were instructed to walk at their usual walking speed from the start to finish points of a marked 20-m distance (29); there were two trials (29), and the mean of those trials was used as an outcome measure in this study. This functional outcome was included to understand whether weight cycling had an effect on walking speed.

Questionnaires

Knee pain was assessed using the Western Ontario and McMaster Universities OA Index (WOMAC), a well-established questionnaire used to evaluate potential symptoms related to knee OA. This questionnaire has been used in previous OA studies (11,30).

Statistical analysis

Statistical analysis was performed using SAS Studio version 3.8 (SAS Institute, Inc., Cary, North Carolina). Descriptive statistics were performed using a SAS macro program called TABLEN (31). Differences in continuous parameters between groups (i.e., age and BMI) were assessed using Kruskal-Wallis tests, and differences in categorical parameters between groups (i.e., sex and race) were assessed using χ^2 tests.

The longitudinal differences in outcomes with annual measurements (cartilage T2, cartilage thickness, 20-m walking speed, and WOMAC pain) between weight cyclers and noncyclers were assessed using general estimating equations, whereas the differences in WORMS outcomes (available at baseline and 4 years) were compared using general linear models. An interaction between time and weight cycling group (weight cyclers vs. noncyclers) was included in the model. The outcome variables were designated as primary or secondary to address potential issues stemming from multiple comparisons. For cartilage thickness, the primary regions were the average, central MF, and MT. For T2, the primary regions were the average of all regions and the MF and MT. The medial side of the joint was the focus of this study because medial OA occurs more frequently than lateral OA (32,33), data from the OAI show that decreases in cartilage thickness over 1 year were greater in the medial compartment than in the lateral compartment (34), meniscus and cartilage lesions are more prevalent on the medial side of the joint (33), and the MF is a concentrated region of weight bearing (33). The remaining regions were designated as secondary outcomes. For WORMS, the primary outcome variables were 4-year changes in maximum WORMS of the cartilage, meniscus, and bone-marrow edema. Maximum scores

were chosen as the primary outcome because they are more sensitive to change than summation WORMS. The secondary outcome variables were 4-year region-specific changes in WORMS of the cartilage, meniscus, and bone-marrow edema. An interaction between weight cycling group and weight change group was included to determine whether the relationship between weight cycling and knee joint outcomes was modified by weight change. If the results of the interaction were significant, post hoc tests analyzing the effects of weight cycling on knee joint degeneration would be subdivided by the weight change group. As a sensitivity analysis to assess whether the effects of weight cycling on joint degeneration differed by sex, an interaction between weight cycling group and sex was added to each model. As an exploratory analysis, the models were examined to assess the relationship between weight change and imaging outcomes, adjusted for weight cycling group. All analyses were adjusted for age, sex, baseline BMI, and weight change group.

Results

Subject characteristics

A total of 2,271 participants were included in this study; of those, 249 were categorized as weight cyclers with BMI variability and 2,022 were categorized as noncyclers. The subject characteristics are listed in Table 1. The weight cyclers had a significantly ($P < 0.0001$) greater BMI at baseline (32.6 ± 4.25 kg/m^2) than noncyclers (30.1 ± 3.77 kg/m^2), and a significantly ($P < 0.0001$) higher percentage of females were categorized into the weight cycler group (n = 176, 70.7%) than into the noncycler group (n = 1,089, 53.9%). There were no significant differences in the distribution of race ($P = 0.25$) or KL grade between groups ($P = 0.13$).

Cartilage T2 measurements

The rate of change in mean cartilage T2 over 4 years was not significantly different between weight cyclers and noncyclers in any joint region ($P > 0.05$). The interaction between weight cycling group and weight change group was not significant ($P > 0.05$) in any analysis. The mean cartilage T2 increased in both weight cyclers and noncyclers over 4 years (Figure 3); however, over all time points and in all regions, cartilage T2 in weight cyclers was not significantly different from that in noncyclers ($P > 0.05$). Over all time points, there were no significant differences in mean cartilage T2 between the weight loss group and the control group ($P > 0.05$) in any region; however, the weight gain group had a significantly greater mean T2 (coefficient $_{[\text{weight gain group vs. control group}]}$ = 0.23, 95% CI: 0.07-0.39, $P = 0.004$) and MT T2 (coefficient = 0.25, 95% CI: 0.08-0.42, $P = 0.003$) than the control group.

TABLE 1 Subject characteristics

	Noncyclers (N = 2,022)	Weight cyclers (N = 249)	Total (N = 2,271)	P value
Age (y)				<0.00011
N	2,022	249	2,271	
Mean (SD)	61.4 (9.14)	58.8 (8.42)	61.1 (9.10)	
BMI (kg/m^2)				<0.00011
N	2,022	249	2,271	
Mean (SD)	30.1 (3.77)	32.6 (4.25)	30.4 (3.91)	
Sex, *n* (%)				<0.00012
Male	933 (46.1%)	73 (29.3%)	1,006 (44.3%)	
Female	1,089 (53.9%)	176 (70.7%)	1,265 (55.7%)	
Race, *n* (%)				0.250
Other non-White	34 (1.7%)	3 (1.2%)	37 (1.6%)	
White or Caucasian	1,611 (79.8%)	187 (75.1%)	1,798 (79.2%)	
Black or African American	366 (18.1%)	58 (23.3%)	424 (18.7%)	
Asian	9 (0.4%)	1 (0.4%)	10 (0.4%)	
Missing	2	0	2	
KL grade, *n* (%)				0.132
0	685 (33.9%)	69 (27.7%)	754 (33.2%)	
1	387 (19.1%)	53 (21.3%)	440 (19.4%)	
2	626 (31.0%)	91 (36.5%)	717 (31.6%)	
3	324 (16.0%)	36 (14.5%)	360 (15.9%)	
Weight change, *n* (%)				<0.00012
Control group	1,118 (55.3%)	77 (30.9%)	1,195 (52.6%)	
Weight gain	530 (26.2%)	62 (24.9%)	592 (26.1%)	
Weight loss	374 (18.5%)	110 (44.2%)	484 (21.3%)	
WOMAC pain score (right knee)				0.015
N	2,022	249	2,271	
Mean (SD)	2.3 (3.07)	2.9 (3.49)	2.4 (3.13)	

Differences in continuous parameters between groups (i.e., age and BMI) were assessed using Kruskal-Wallis tests, and differences in categorical parameters between groups (i.e., sex and race) were assessed using χ^2 tests.
KL, Kellgren-Lawrence score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

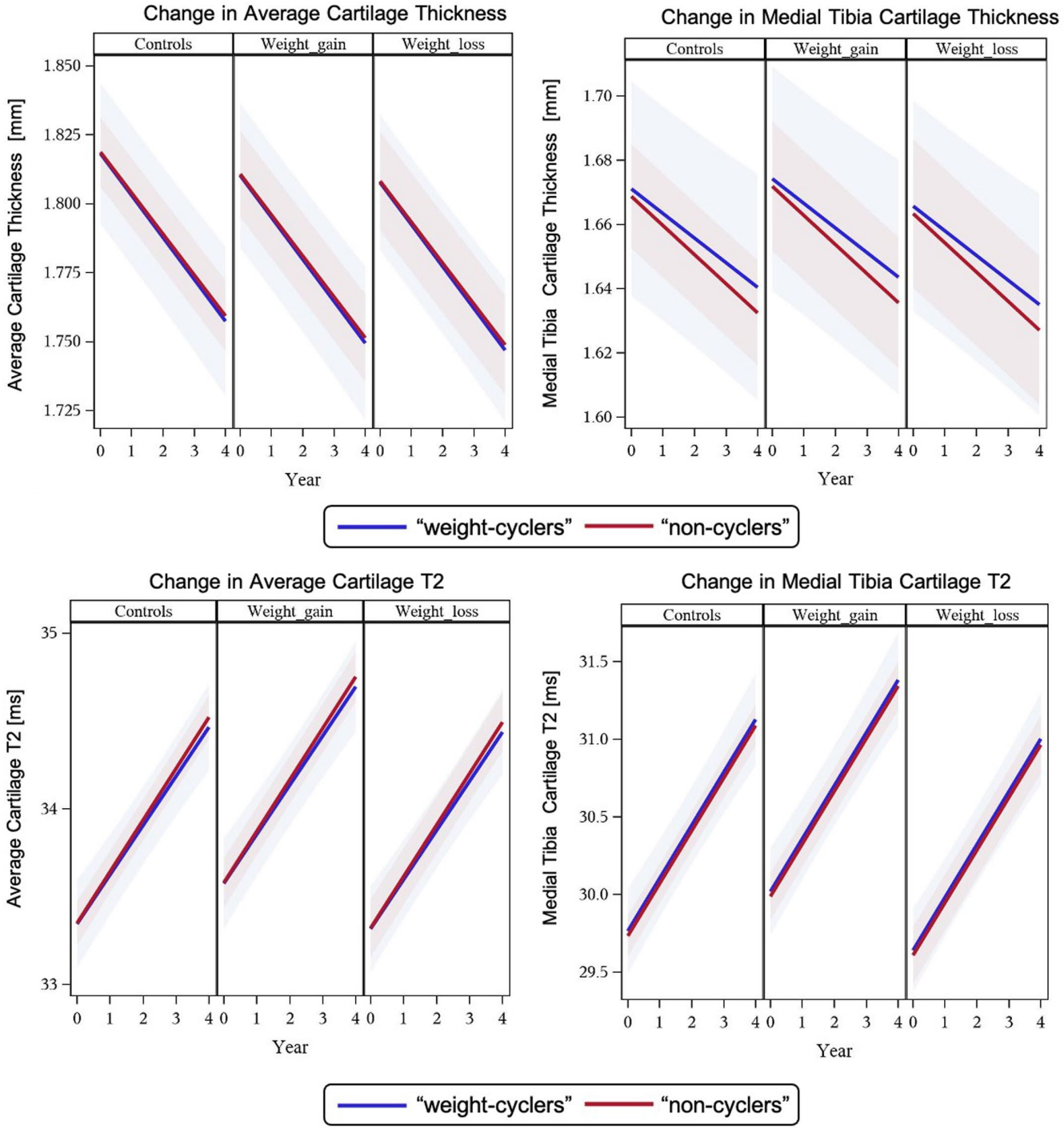

Figure 3 The rates of change in both cartilage thickness and cartilage T2 were not significantly different between weight cyclers with BMI variability and noncyclers without BMI variability (modeled results adjusted for age, gender, baseline BMI, and weight change group are shown). The interaction between weight cycling group and the weight change group was not significant. The shaded areas represent 95% CIs. [Color figure can be viewed at wileyonlinelibrary.com]

Cartilage thickness

The rate of change in cartilage thickness over 4 years was not significantly different between weight cyclers and noncyclers in any joint region ($P > 0.05$). The interaction between weight cycling group and weight change group was not significant ($P > 0.05$) in any analysis. Cartilage thickness decreased in both weight cyclers and noncyclers over 4 years (Figure 3); however, over all time points and in all regions, cartilage thickness in weight cyclers was not significantly different

from that in noncyclers ($P > 0.05$). Adjusting for weight cycling group (BMI variation), there were no significant differences in cartilage thickness among the weight gain, weight loss, and control groups in any region or at any time point.

WORMS

Over 4 years, increases in maximum cartilage WORMS (coefficient $_{[\text{weight cyclers vs. noncyclers}]}$ = 0.27, 95% CI: 0.09-0.45, P = 0.002) and bone-marrow abnormalities (coefficient = 0.14, 95% CI: 0.006-0.28, P = 0.04) were significantly greater in weight cycling than in noncyclers (Figure 4, Table 2). Longitudinal changes in meniscus scores were not significantly different (P = 0.89) between weight cyclers and noncyclers. The interaction between weight cycling group and weight change group was not significant ($P > 0.05$) in any analysis. Adjusting for weight cycling group (BMI variation), the weight loss group had significantly smaller changes in the maximum cartilage scores (coefficient $_{[\text{weight loss group vs. control group}]}$ = −0.22, 95% CI: −0.38 to −0.06, P = 0.004) and maximum meniscus scores than the control group (coefficient = −0.15, 95% CI: −0.28 to −0.01, P = 0.02), whereas there were no significant differences in the weight gain group compared with the control group ($P > 0.05$, Table 2).

WOMAC pain and 20-m walking speed

Over all time points, weight cyclers had a significantly slower walking speed than noncyclers (coefficient $_{[\text{weight cyclers vs. noncyclers}]}$ = −0.03, 95% CI: −0.05 to −0.002, P = 0.03). Adjusting for weight cycling group (BMI variation), over all time points, the weight gain group had a significantly slower 20-m walking speed than the control group (coefficient $_{[\text{weight gain group vs. control group}]}$ = −0.02, 95% CI: =−0.04 to −0.01, P = 0.001), whereas there were no significant differences in the weight loss group (P = 0.72).

There were no significant differences in the rate of change in WOMAC pain or 20-m walking speed between weight cyclers and noncyclers over 4 years (P = 0.19). Adjusting for weight cycling group (BMI variation), there were no significant differences in the WOMAC pain score among the weight change groups (P = 0.57).

In the sensitivity analyses for all outcomes, the interaction between weight cycling group and sex was not significant ($P > 0.05$); thus, the relationship between weight cycling and joint degeneration did not vary by sex.

Discussion

In this study, BMI variation (weight cycling) over 4 years was associated with increases in cartilage and bone-marrow abnormalities as well as slower walking speed. These relationships were independent of the amount of weight change that occurred. There were no associations between BMI variation over 4 years and changes in cartilage thickness or cartilage biochemical composition, measured using MRI cartilage T2 quantification. This study suggests that BMI variation may exacerbate the progression of degenerative changes of cartilage and bone marrow, regardless of the amount of overall weight change, but is not significantly associated with more subtle changes in quantitative cartilage outcomes such as thickness or collagen matrix organization and water content (MRI T2).

One of the challenges in quantifying weight cycling is the lack of a universal definition (9). Intentionality of weight loss or unexplained weight loss are factors that have been considered when defining weight cycling. Coupled with varied research designs (prospective studies vs. retrospective self-reporting), the amount of weight variation, and the net change in weight (whether there is a negative energy balance resulting in weight loss, a positive energy balance resulting in weight gain, or no change) (9), there is no standardized definition for weight cycling. In this study, we define weight cycling using RMSEs of a linear regression that models annual BMI data over 4 years (18). Because the OAI does not provide information on motives for weight change (i.e., intentional vs. unintentional), the term *BMI variation*, which was quantified from the RMSE value, may technically be a more accurate description of this study's intent than the term *weight cycling*. However, to simplify interpretation, in this study, we use the terms *weight cyclers* and *noncyclers* to describe the subject groups.

The mechanisms responsible for the associations between weight cycling and the progression of morphologic joint degeneration are unknown

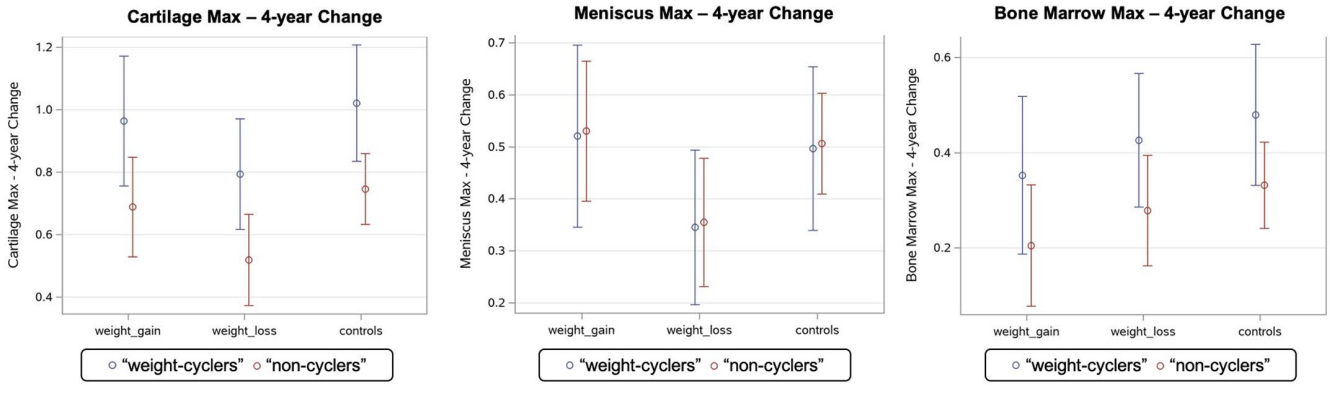

Figure 4 Over all time points, weight cyclers had a significantly slower walking speed than noncyclers without BMI variability (P = 0.04). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score was not significantly different at any time point (P = 0.25). The rates of change in both WOMAC pain and 20-m walking speed were not significantly different between weight cyclers with BMI variability and noncyclers (modeled results adjusted for age, gender, baseline BMI, and weight change group are shown). The interaction between weight cycling group and weight change group was not significant. The shaded areas represent 95% CIs. Max, maximum. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Associations between BMI variability (weight cycling) and changes in Max WORMS over 4 years

Dependent variable (WORMS)	Effect	Weight change	Coefficient	Lower 95% CI	Upper 95% CI	*P* value	Overall *P* value
Change in cartilage Max score	Weight cyclers	—	0.27	0.09	0.45	**0.002**	0.01
		Weight gain	−0.05	−0.23	0.11	0.51	
	Weight change	Weight loss	−0.22	−0.38	−0.06	**0.004**	
Change in meniscus Max score	Weight cyclers	—	−0.009	−0.15	0.13	0.89	**0.04**
		Weight gain	0.02	−0.12	0.17	0.74	
	Weight change	Weight loss	−0.15	−0.28	−0.01	**0.02**	
Change in bone–marrow Max score	Weight cyclers	—	0.14	0.006	0.28	**0.04**	0.19
		Weight gain	−0.12	−0.26	0.01	0.07	
	Weight change	Weight loss	−0.05	−0.17	0.07	0.40	

Bold represents $P < 0.05$.
Max, maximum; WORMS, Whole-Organ Magnetic Resonance Imaging Scores.

but may potentially be related to changes in mechanical unloading and loading patterns and changes in adipose tissue growth due to weight regain following weight loss coupled with increased inflammation (35). Studies have shown that weight gain during a relapse from weight loss causes rapid adipose tissue growth and metabolic shifts favoring lipid storage, suggesting the consequences of weight regain may differ from those of initial weight gain (35). Adipose tissue secretes many inflammatory mediators, including cytokines and adipokines, creating a systemic environment of increased inflammation that may lead to OA (36). It was also shown that subjects with weight variability have elevated C-reactive protein (CRP) levels (37), which is a nonspecific finding but may also be seen with local joint inflammation (38). Although inflammation may play a role in the relationship between weight cycling and knee degeneration, future studies are needed to examine the physiological mechanisms that occur during weight cycling.

The question of why weight cyclers show greater morphologic knee joint changes (as evidenced by progression of WORMS) but do not show significant changes in quantitative measures (i.e., cartilage thickness) is important to examine. Possible explanations include that WORMS of 2 and 3 represent localized areas of lesions or thinning, which may not be detected with quantitative measures of the *entire* cartilage region. In addition, cartilage swelling may *increase* cartilage WORMS (39), indicating progression of OA but, at the same time, may *increase* cartilage thickness. Generally, decreases in cartilage thickness indicate progression of OA. However, as individuals in this study had varied KL grades at baseline (signifying different stages of disease), both increases in thickness due to swelling and decreases due to cartilage thinning may have occurred depending on an individual's baseline disease severity. These contrasting changes in thickness may explain why cartilage thickness was not significantly different among groups even though WORMS were. The results from this study are consistent with another study reporting that WORMS were higher in subjects with mild OA (KL 2) than in control subjects without OA but that cartilage thickness and volume were not significantly different (39). Thus, cartilage WORMS may be well suited to assess the longitudinal changes in joint morphology with weight cycling, as these scores are more likely to detect localized features that may not be identified using average regional thickness measurements.

As an exploratory analysis, this study examined the relationship between weight change and imaging outcomes, adjusted for BMI variation. Overall, the weight loss group had significantly smaller changes in the cartilage and meniscus WORMS than the control group. The weight gain group had significantly lower walking speed and increased cartilage T2 over all time points. These results suggest that weight loss may slow the progression of joint degeneration as measured by cartilage WORMS and that weight gain may exacerbate early changes in cartilage biochemical composition as measured by T2 and may slow walking speed. Previous studies have examined the relationship between weight loss and knee joint degeneration, reporting that weight loss is associated with less progression of cartilage degeneration (4) and smaller increases in cartilage T2 (40). The results of our study concur with those of Gersing et al. (4); however, they are not consistent with those of Serebrakian et al. (40), possibly because of differences in study design, such as the group definitions (their study defined weight loss as >10% loss, whereas this study defined weight loss as >5% loss), sample size (n = 127 in their study vs. n = 2,271 in this study), time points studied (their study included baseline and 4-year follow-up T2, whereas this study included annual T2 from baseline to 4 years), and inclusion criteria (their study included all BMI at baseline, whereas this study

included BMI > 25 kg/m^2 at baseline). The results of this study also differ from previously reported associations between weight gain and progression of meniscus (41) and cartilage degeneration (20) WORMS, possibly because of varied definitions of weight gain and sample-size variations; however, our study still showed an association between weight gain and early cartilage degeneration, as evidenced by elevated cartilage T2, indicating disrupted collagen organization. Despite differences in study design, inclusion criteria, and outcome measures, we and others have shown that weight loss is associated with a slower progression of cartilage degeneration, whereas weight gain may be associated with increased progression of disease.

The primary limitations of this study are its retrospective nature and lack of information about reasons for weight cycling (as these data were not available in the OAI database). A future prospective study may be useful to track the causes for weight cycling (such as the interval of joint injury) and how they affect joint degeneration; this information may aid in identifying whether a specific reason for weight cycling may particularly impact joint degeneration. In addition, WORMS scoring was available in only a subset of subjects; thus, direct comparison with the full data set was not the primary analysis. However, as a sensitivity analysis, we analyzed cartilage T2, cartilage thickness, and clinical outcomes (WOMAC and walking speed) in the subset of subjects with WORMS available; the results were similar to those in the entire cohort. Severe illness, including cardiac failure, cancer, and/or other severe diseases, may affect weight change; thus, these were part of the exclusion criteria. BMI values were used to define weight cyclers versus noncyclers; however, it should be noted that this definition does not accurately account for muscle mass and body composition. Although analyzing cartilage T1ρ or other cartilage quantitative measures would be of interest, we were able to analyze only T2 measurements, as only these measurements were provided by the OAI. Voxel-based T2 analysis would also aid in understanding the local cartilage effects in response to weight cycling by providing insight on why significant associations were found for WORMS but not for average T2 values. To address missing data due to loss at follow-up, a sensitivity analysis using mixed models (which are robust to handling missing data) was performed; compared with the results from generalized estimating equations analysis, the results were similar, without significant changes. Multiple comparison may also be a limitation, but in order to address this issue, we preemptively designated primary and secondary analyses to limit the number of models run. Despite these limitations, our study also has pertinent strengths, particularly because of its large sample size and use of both semiquantitative and quantitative outcomes. Moreover, although the effects of weight cycling on a variety of outcomes, including cardiac disease and diabetes (8,9), have been studied, this is the first investigation, to our knowledge, of the effects of weight cycling on knee joint degeneration.

Overall, the results of this study suggest that individuals with BMI variability have significantly greater increases in cartilage and bone-marrow abnormalities over 4 years compared with those who do not have high BMI variability, and the relationship is independent of the amount of weight change. These results suggest that weight cycling may exacerbate the progression of degenerative changes of cartilage and bone marrow, regardless of the amount of overall weight change.O

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References

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. *NCHS Data Brief*, no. 288. National Center for Health Statistics; 2017.
2. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol* 2018;71:69-84.
3. Vidal J. Updated review on the benefits of weight loss. *Int J Obes Relat Metab Disord* 2002;26(suppl 4):S25-S28.
4. Gersing AS, Schwaiger BJ, Nevitt MC, et al. Is weight loss associated with less progression of changes in knee articular cartilage among obese and overweight patients as assessed with MR imaging over 48 months? Data from the Osteoarthritis Initiative. *Radiology* 2017;284:508-520.
5. Bliddal H, Leeds AR, Christensen R. Osteoarthritis, obesity and weight loss: evidence, hypotheses and horizons—a scoping review. *Obes Rev* 2014;15:578-586.
6. Kakinami L, Knäuper B, Brunet J. Weight cycling is associated with adverse cardiometabolic markers in a cross-sectional representative US sample. *J Epidemiol Community Health* 2020;74:662-667.
7. Mackie GM, Samocha-Bonet D, Tam CS. Does weight cycling promote obesity and metabolic risk factors? *Obes Res Clin Pract* 2017;11:131-139.
8. Byun SS, Bello NA, Liao M, Makarem N, Aggarwal B. Associations of weight cycling with cardiovascular health using American Heart Association's Life's Simple 7 in a diverse sample of women. *Prev Med Rep* 2019;16:100991. doi:10.1016/j.pmedr.2019.100991
9. Mehta T, Smith DL Jr, Muhammad J, Casazza K. Impact of weight cycling on risk of morbidity and mortality. *Obes Rev* 2014;15:870-881.
10. Lementowski PW, Zelicof SB. Obesity and osteoarthritis. *Am J Orthop (Belle Mead NJ)* 2008;37:148-151.
11. Link TM, Steinbach LS, Ghosh S, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 2003;226:373-381.
12. Peterfy C, Schneider E, Nevitt M. The Osteoarthritis Initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. *Osteoarthritis Cartilage* 2008;16:1433-1441.
13. Baum T, Stehling C, Joseph GB, et al. Changes in knee cartilage T2 values over 24 months in subjects with and without risk factors for knee osteoarthritis and their association with focal knee lesions at baseline: data from the osteoarthritis initiative. *J Magn Reson Imaging* 2012;35:370-378.
14. Joseph GB, Baum T, Carballido-Gamio J, et al. Texture analysis of cartilage T2 maps: individuals with risk factors for OA have higher and more heterogeneous knee cartilage MR T2 compared to normal controls–data from the osteoarthritis initiative. *Arthritis Res Ther* 2011;13:R153. doi:10.1186/ar3469
15. Stehling C, Lane NE, Nevitt MC, Lynch J, McCulloch CE, Link TM. Subjects with higher physical activity levels have more severe focal knee lesions diagnosed with 3T MRI: analysis of a non-symptomatic cohort of the osteoarthritis initiative. *Osteoarthritis Cartilage* 2010;18:776-786.
16. Kretzschmar M, Lin W, Nardo L, et al. Association of physical activity measured by accelerometer, knee joint abnormalities, and cartilage T2 measurements obtained from 3T Magnetic resonance imaging: data from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2015;67:1272-1280.
17. Gersing AS, Solka M, Joseph GB, et al. Progression of cartilage degeneration and clinical symptoms in obese and overweight individuals is dependent on the amount of weight loss: 48-month data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2016;24:1126-1134.
18. Kataja-Tuomola M, Sundell J, Männistö S, et al. Short-term weight change and fluctuation as risk factors for type 2 diabetes in Finnish male smokers. *Eur J Epidemiol* 2010;25:333-339.
19. Williamson DA, Bray GA, Ryan DH. Is 5% weight loss a satisfactory criterion to define clinically significant weight loss? *Obesity (Silver Spring)* 2015;23:2319-2320.
20. Bucknor MD, Nardo L, Joseph GB, et al. Association of cartilage degeneration with four year weight gain–3T MRI data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage* 2015;23:525-531.
21. Alizai H, Virayavanich W, Joseph GB, et al. cartilage lesion score: comparison of a quantitative assessment score with established semiquantitative MR scoring systems. *Radiology* 2014;271:479-487.
22. Peterfy CG, Guermazi A, Zaim S, et al. Whole-organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. *Osteoarthritis Cartilage* 2004;12:177-190.
23. Stahl R, Jain SK, Lutz J, et al. Osteoarthritis of the knee at 3.0 T: comparison of a quantitative and a semi-quantitative score for the assessment of the extent of cartilage lesion and bone marrow edema pattern in a 24-month longitudinal study. *Skeletal Radiol* 2011;40:1315-1327.
24. Razmjoo A, Caliva F, Lee J, et al. T2 analysis of the entire osteoarthritis initiative dataset. *J Orthop Res* 2020;39:74-85.
25. Norman B, Pedoia V, Majumdar S. Use of 2D U-Net convolutional neural networks for automated cartilage and meniscus segmentation of knee MR imaging data to determine relaxometry and morphometry. *Radiology* 2018;288:177-185.

26. Miller AJ, Joseph PM. The use of power images to perform quantitative analysis on low SNR MR images. *Magn Reson Imaging* 1993;11:1051-1056.
27. Raya J, Dietrich O, Horng A, Weber J, Reiser M, Glaser C. T2 measurement in articular cartilage: Impact of the fitting method on accuracy and precision at low SNR. *Magn Reson Med* 2010;63:181-193.
28. Iriondo C, Liu F, Caliva F, Kamat S, Majumdar S, Pedoia V. Towards understanding mechanistic subgroups of osteoarthritis: 8 year cartilage thickness trajectory analysis [published online September 8, 2020]. *J Orthop Res*. doi:10.1002/jor.24849
29. Øiestad BE, White DK, Booton R, et al. Longitudinal course of physical function in people with symptomatic knee osteoarthritis: data from the Multicenter Osteoarthritis Study and the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken)* 2016;68:325-331.
30. Phan CM, Link TM, Blumenkrantz G, et al. MR imaging findings in the follow-up of patients with different stages of knee osteoarthritis and the correlation with clinical symptoms. *Eur Radiol* 2006;16:608-618.
31. Meyers J. Demographic table and subgroup summary macro %TABLEN. SAS Communities Library. Published March 22, 2020. Accessed March 11, 2021. https://communities.sas.com/t5/SAS-Communities-Library/Demographic-Table-and-Subgroup-Summary-Macro-TABLEN/ta-p/634030
32. Strover S. Understanding arthritis of the knee. KNEEguru. 2008. Accessed March 11, 2021. https://www.kneeguru.co.uk/
33. Takatalo J, Karppinen J, Niinimäki J, et al. Prevalence of degenerative imaging findings in lumbar magnetic resonance imaging among young adults. *Spine* 2009;34:1716-1721.
34. Eckstein F, Maschek S, Wirth W, et al. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. *Ann Rheum Dis* 2009;68:674-679.
35. Strohacker K, Carpenter KC, McFarlin BK. Consequences of weight cycling: an increase in disease risk? *Int J Exerc Sci* 2009;2:191-201.
36. Urban H, Little CB. The role of fat and inflammation in the pathogenesis and management of osteoarthritis. *Rheumatology (Oxford)* 2018;57(suppl 4):iv10-iv21.
37. Yatsuya H, Tamakoshi K, Yoshida T, et al. Association between weight fluctuation and fasting insulin concentration in Japanese men. *Int J Obes Relat Metab Disord* 2003;27:478-483.
38. Pearle AD, Scanzello CR, George S, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage* 2007;15:516-523.
39. Reichenbach S, Yang M, Eckstein F, et al. Does cartilage volume or thickness distinguish knees with and without mild radiographic osteoarthritis? The Framingham Study. *Ann Rheum Dis* 2010;69:143-149.
40. Serebrakian AT, Poulos T, Liebl H, et al. Weight loss over 48 months is associated with reduced progression of cartilage T2 relaxation time values: Data from the Osteoarthritis Initiative. *J Magn Reson Imaging* 2015;41:1272-1280.
41. Guimaraes JB, Nevitt MC, McCulloch CE, et al. Association of weight change with progression of meniscal intrasubstance degeneration over 48 months: data from the Osteoarthritis Initiative. *Eur Radiol* 2018;28:953-962.