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Weight loss regimen in obese and overweight individuals is associated with reduced cartilage degeneration: 96-month data from the Osteoarthritis Initiative

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SUMMARY

Purpose: To investigate change in knee cartilage composition over 96 months in overweight and obese participants with constant weight compared to those with weight loss (WL), and to assess how different WL regimens are associated with these changes.

Methods: We studied right knees of 760 participants (age 62.6 ± 9.0y; 465 females) with a baseline body mass index (BMI) >25 kg/m2 from the Osteoarthritis Initiative with mild to moderate or with risk factors for knee osteoarthritis. Participants losing weight (>5% of baseline BMI over 72 months; $N = 380$) were compared to controls with stable weight (SW, $N = 380$). Participants losing weight were categorized based on WL method (diet and exercise, diet only, exercise only) and compared to those with stable weight. Magnetic resonance imaging (MRI) at 3T was performed at baseline, 48- and 96-months. The association of WL and WL method with change in cartilage composition, measured with T2 mapping, was analyzed using mixed random effects models.

Results: Compared to SW, WL was associated with a significantly slower increase in global (averaged over all compartments) cartilage T2 (adjusted mean difference of change in T2 ms/year [95% CI] between the groups: 0.24 [0.20, 0.41] ms/year; $P < 0.001$) and global deep layer cartilage T2 0.35 [0.20, 0.42] ms/year; $P < 0.001$), suggesting slower cartilage deterioration. Compared to the SW group, slower increases in global T2 were observed in the diet and diet and exercise groups, but not in the exercise only group ($P = 0.042$, $P = 0.003$ and $P = 0.85$, respectively).

Conclusion: Our results suggest that WL may slow knee cartilage degeneration over 96 months, and that these potential benefits may differ by method of WL.

Introduction

Obesity is one of the most common modifiable risk factors for osteoarthritis (OA)[1–3]. Increased loading forces have previously been shown to cause increased cartilage degradation and previous studies have shown that metabolic factors may be associated with obesity and OA[4–8]. For the detection of very early and potentially reversible cartilage changes, MRI-based compositional imaging, such as T2 relaxation time measurements, has previously shown to be useful due to its ability to quantify increases in water content of cartilage and abnormalities in collagen structure[9,10].

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A previous study found that knee cartilage T2 values increased significantly less over 48 months in participants losing a substantial amount of weight (>10% BMI loss) compared to those with moderate (5–10%) or no weight loss (<3%), suggesting that a protective effect of weight loss (WL) on knee cartilage in obese and overweight participants may depend on the amount of WL[11]. Moreover, in a WL intervention trial it was shown that when comparing participants losing weight with diet and exercise, or diet or exercise only over 18 months, participants in the diet only group showed a greater reduction in knee compressive force and greater improvement in knee pain and function compared to participants in the exercise only group[12].

However, to the best of our knowledge, the association of weight change and different WL regimens with changes in knee cartilage biochemical composition along with structural integrity has never been analyzed over an observational period longer than 48 months.

The objectives of this longitudinal study were therefore: (i) to analyze the association of moderate or greater weight loss (>5% of baseline BMI) over 72 months with concurrent 96 months biochemical cartilage deterioration, as measured by T2 relaxation time magnetic resonance (MR) imaging, and progression of structural changes of the knee joint, as assessed by the semi-quantitative WORMS score; and (ii) to explore how different WL regimens in obese and overweight participants impact cartilage T2 values, in comparison to participants without weight change.

Method

Participants

The Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu) is a prospective multi-center cohort study from which participants were selected for this analysis. The participants of the OAI are either healthy participants with risk factors for knee OA (incidence cohort) or with symptomatic knee OA with radiographic evidence of tibiofemoral OA (progression cohort). At all participating centers, this HIPAA-compliant study was approved by the local institutional review board and informed consent of each participant was obtained.

We studied OAI participants who were overweight or obese (BMI $\geq$ 25) with complete BMI information at baseline, 12-, 24-, 48- and 72-months. Those with end-stage OA (Kellgren Lawrence grade (KL) > 3) and with rheumatoid arthritis that developed during the study follow-up were excluded (Participant selection is illustrated in Fig. 1).

In total, 3,244 participants met the inclusion/exclusion criteria and were categorized according to weight change between baseline and 72-months. Those with weight gain ($\geq$3% of baseline BMI) and with WL between 3 and 5% were excluded, to better define groups with WL and stable weight ($N = 1115$). Also, those with 'irregular' weight change, cycling through weight gain and WL between the follow-up time points were excluded ($N = 84$). For this determination, a linear regression model of the annual rate of change in BMI over 72 months was calculated and participants with a root mean square error of their weight change above the 95th percentile were categorized as participants with 'irregular' weight change, whereas participants with a root mean square error of their weight change below the 95th percentile were categorized as participants with 'steady' weight change[11]. In the OAI, T2 maps were only obtained from the right knee. Therefore, participants with missing right knee MRI at baseline were excluded ($N = 24$). This left 380 participants with WL >5% (WL group). From the remaining 1601 individuals with stable weight (stable weight group), 380 were randomly selected and frequency matched to the WL group in strata defined by baseline age (10 year strata from 45 to 65 and one 14 year strata from 65 to 79), sex (male/female), BMI (BMI in 2.5 kg/m^2 intervals) and KL grade (KL grade strata 0/1 and 2/3). MRI analysis was performed on all baseline MRIs of these matched 760 subjects, and on all available MRIs at 48-month and at 96-month follow-up for these subjects. The number of subjects with data for MRI analysis available for each follow-up time point were as follows: WL group: 48-month follow-up, $N = 269$; 96-month follow-up, $N = 217$; stable weight group: 48-month follow-up, $N = 266$; 96-month follow-up, $N = 169$. There was no significant difference found regarding the baseline subject characteristics age, BMI and KL grade as well as sex distribution between the participants that dropped out due to missing follow-up MRI scans at the 48-month ($P \geq 0.34$) and 96-month follow up ($P \geq 0.27$) as well as the participants that remained in the study until the end.

Weight loss questionnaire administered at 96-month follow-up

A WL questionnaire was administered to the participants at the 96-month follow-up. The questionnaire investigated how WL was achieved (i.e., increased physical activity, changes in diet, or a combination). Using the data from the questionnaire, we assessed the effect of the three different methods used for weight loss (diet only group (D group); exercise only group (E group); combination of diet and exercise group (D+E group)) on cartilage degeneration. Using the Katz comorbidity questionnaire, participants with cancer (e.g., throat, stomach, prostate cancer or leukemia), cardiac failure and/or other severe diseases (e.g., stroke, spine or hip fracture, severe infection) causing hospitalization that developed during the time period of the study, were excluded from these analyses[14].

MR Imaging

MR images were acquired using four identical 3.0T scanners (Siemens Magnetom Trio; Siemens Healthcare, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA). T2 relaxation time values were obtained using a sagittal two-dimensional (2D) multislice, multiecho (MSME) sequence with seven echo times (TEs; 10 ms–70 ms) and a repetition time (TR) of 2700 ms. The following four sequences were obtained for the morphological analysis: (i) 2D intermediate-weighted fast spin echo (FSE) sequences with fat suppression in the sagittal plane; (ii) 2D proton density-weighted FSE sequences in the sagittal plane; (iii) 3D T1-weighted fast low-angle shot gradient-echo sequences and (iv) 3D dual echo steady-state gradient-echo obtained in the sagittal plane, as described in the OAI MR protocol[15].

Image analysis

For the T2 analysis of the MR images an in-house, spline-based algorithm written in MATLAB (the Mathworks, Natick, Massachusetts) was used as previously described[16,17]. The cartilage of five compartments (patella (PAT), medial femoral condyle (MF), lateral femoral condyle (LF), medial tibia (MT), and lateral tibia (LT)) was semi-automatically segmented by two trained researchers (J.Z. and G.F.) using the first echo of the sagittal 2D MSME sequence and manually correcting the position of the points, in consensus and under supervision of an experienced radiologist (T.M.L.). The trochlea (TRO) was not segmented due to flow artifacts caused by the popliteal artery. T2 values of each compartment were calculated by using a mono-exponential decay model as the fitting function for the signal intensity using 6 echoes (TE 20–70 ms) after excluding the first echo in order to minimize errors and improve signal-to-noise ratio[16,18]. Mean T2 values were computed for each cartilage compartment, and the global T2 value for the overall knee joint was calculated from the mean of all compartments.

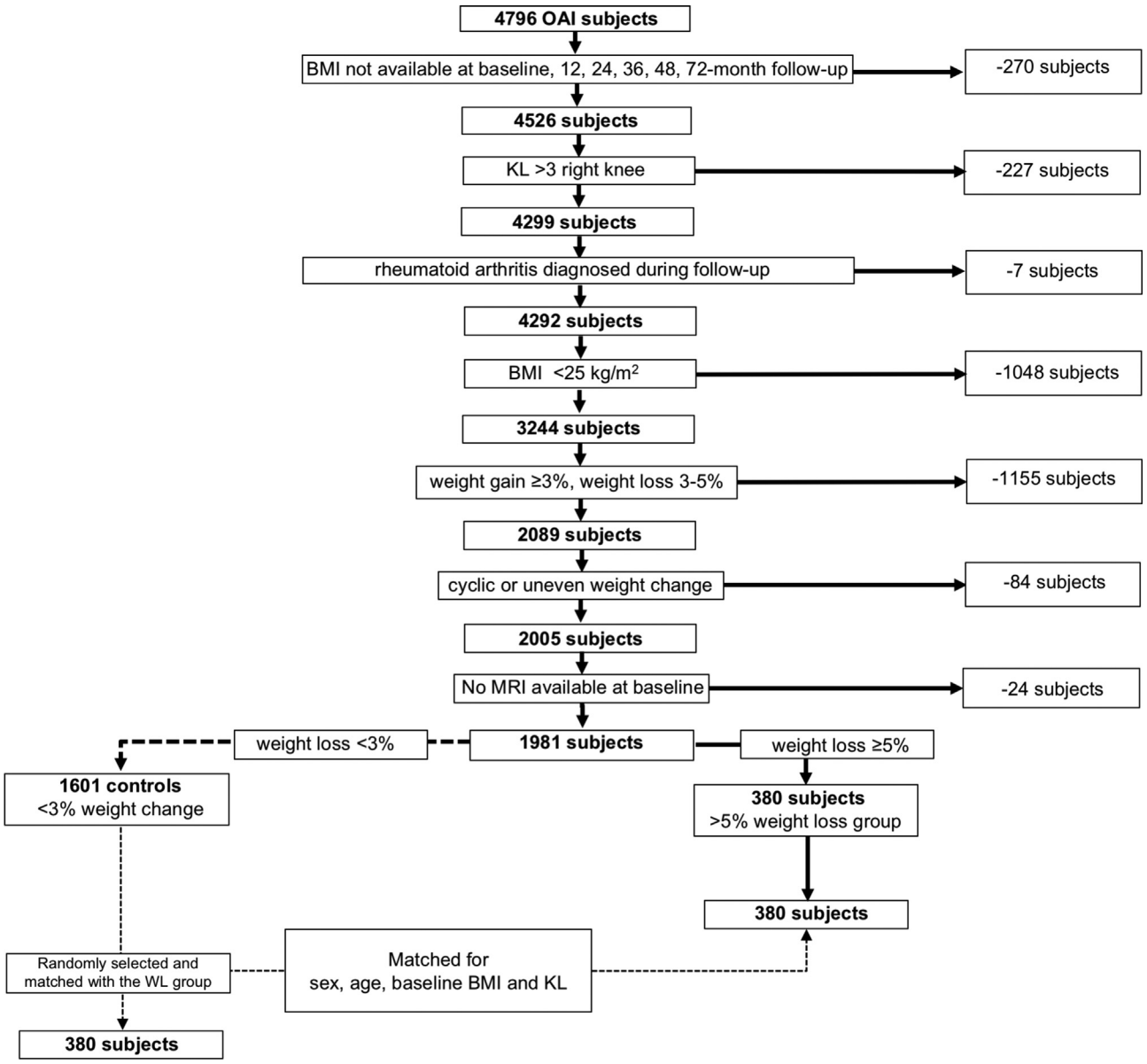

Fig. 1. Patient selection from OAI database for the weight loss (WL) group.

Laminar analysis algorithms automatically subdivided the cartilage of each compartment into a superficial layer (articular surface) and a deep layer (bone interface) of equal thickness[19]. In addition, cartilage gray-level co-occurrence matrix (GLCM) texture analysis was performed to evaluate the spatial distribution of cartilage T2 values within each cartilage compartment, as previously described[11,20–23]. Based on our previous work, two GLCM texture parameters were included in the analysis: contrast (contrast group) and variance (statistics group)[11,21,24].

Morphological MR sequences from both groups were reviewed on a picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA) by two radiologists (B.J.S. and A.S.G. with both 5 years of experience, respectively), blinded to patient information, using the semi-quantitative modified WORMS grading system, as previously described[25,26]. In cases of disagreement, a consensus reading was performed with a third more experienced musculoskeletal radiologist (T.M.L. with 23 years of experience).

Statistical analysis

Statistical analysis was performed with Stata/IC Version 13.1 software (StataCorp, College Station, TX) using a two-sided 0.05 level of significance. Analysis of variance (ANOVA) was used to test mean differences for continuous measures and chi-square tests were used to test ~~for~~ binary variables. Differences between the groups (WL group vs stable weight group; stable weight group vs D, D+E and E group) for baseline T2 and WORMS were calculated using a multivariable regression model, adjusting for age, sex, baseline BMI and KL score. Mixed-effects regression models adjusting for age, sex, baseline BMI, KL score were used to assess the differences in the annual rates of change of cartilage T2 and WORMS scores between participants with WL, and those with different WL methods, compared to the stable weight group. For all regression models the following assumptions were checked (with selected values

provided for the dependent variable of baseline, overall T2): We tested for non-linearity and if nonlinearity was detected we used the non-linear models. We tested for non-linearity by using an interaction between a quadratic term for time and the exposure variable (WL vs stable weight). If the quadratic term for time was significant, then we interpreted this as a quadratic relationship and a quadratic model was used. If the quadratic term was not significant, we used an interaction between time (linear) and the exposure group. Post estimation, the mixed models were used to quantify the differences in rates of change between groups. Normality of the dependent variables and the residuals (Shapiro–Wilk test, $P > 0.05$ for all), homogeneity of variances (Levene's test statistic = 1.49, $P = 0.16$), absence of influential outliers in the data (max observed: Cook's distance is 0.033 and leverage is 0.051), and absence of multicollinearity (none of predictor variable pairs have correlations above 0.2) were checked. We controlled for multiple measurements per participants by including the subject identification number as a random effect. The same mixed-effects regression models were repeated for the laminar as well as the exploratory texture analyses. For whole-joint analyses, average T2 values over all compartments (global knee cartilage T2) were used and therefore, no correction for multiple testing across the compartments had to be performed. The T2 analyses were repeated for the stable weight group in comparison to the D, D+E and E group, adjusting for age, sex, baseline BMI and baseline KL score.

Reproducibility

To calculate both of the intra- and inter-reader reproducibility for T2 measurements acquired for the present study, the reproducibility error was assessed by calculating the root mean square average of the single coefficients of variation (CV) on a percentage basis, as previously reported[27]. Inter-reader reproducibility was assessed in 10 randomly selected participants between the two readers (J.Z. and G.F.) overall and for each of the five compartments segmented (PAT, MF, LF, MT, and LT). Averaged over all compartments, the inter-reader reproducibility for T2 measurements was 1.93%. The CVs for each compartment were 2.26% (range 1.12–2.52%) for PAT, 1.63% (range 1.48–1.94%) for MF, 1.59% (range 1.24–2.14%) for LF, 2.36% (range 2.01–2.63%) for MT, and 1.83% (range 1.56–2.32%) for LT. For intra-reader reproducibility, both readers repeated the T2 segmentations in the same 10 randomly selected participants with at least 14 days separating the readings. The intra-reader reproducibility for overall mean T2 measurements of J.S. and G.F. were 1.12% (range 0.93–2.28%) and 2.06% (range 1.05–2.31%), respectively.

In order to calculate the intra- and inter-reader reproducibility of the WORMS grading for the present study, each of the two readers (B.J.S. and A.S.G.) performed WORMS grading twice independently for 10 randomly selected participants, the two readings of each reader were at least 14 days apart. Intra-class correlation coefficients (ICCs) were calculated in order to compare the WORMS overall and to compare each WORMS subscore (meniscus, cartilage, bone marrow edema pattern (BMEP)) separately. The 95% confidence interval (CI) of the intra-reader agreement for overall WORMS grading as well as for the subscores meniscus, cartilage and BMEP ranged from 0.74 to 0.95. ICCs for inter-reader agreement were 0.83 (95% CI: 0.74–0.95) for overall WORMS. The 95% CI ranged from 0.74 to 0.94 for the subscores meniscus, cartilage and BMEP. Similar intra-reader and inter-reader agreements of WORMS gradings by our group have been published in previous studies[17,26,28].

Table I
Subject demographics

	Stable overweight*	>5% weight loss*
	$N = 380$	$N = 380$
Baseline		
Age [years ± SD]	62.1 ± 8.6	63.0 ± 9.4
Females [n (%)]	233 (61.3%)	232 (61.1%)
BMI [kg/m^2 ± SD]	29.9 ± 3.5	29.8 ± 3.6
KL scores		
K/L score 0 [n (%)]	113 (29.7%)	116 (30.5%)
K/L score 1 [n (%)]	74 (19.5%)	69 (18.2%)
K/L score 2 [n (%)]	120 (31.6%)	121 (31.8%)
K/L score 3 [n (%)]	73 (19.2%)	74 (19.5%)

* Participants in the two different groups are matched in terms of age, sex, baseline BMI and baseline KL score.

Results

Subject characteristics

Subject characteristics are presented in Table I. When comparing participants with WL to those with stable weight, there were no differences found between the groups in mean baseline age and BMI as well as sex and KL distribution ($P > 0.18$, respectively), as both cohorts were frequency matched for these variables. After 96 months, WL participants had lost 3.52 ± 1.83 kg/m^2 on average, while the BMI change of the group with stable weight was 0.03 ± 0.86 kg/m^2. When participants were distributed into categories of method of WL, participants in the D+E group ($N = 101$, 58.8 ± 7.7 years) were significantly younger than participants in the E or D group (E group: $N = 33$, 62.2 ± 8.9 years, $P = 0.005$; D group: $N = 41$, 62.7 ± 8.2 years, $P = 0.045$). Weight change trajectories are presented in Fig. 2. However, there were no significant differences found between the WL method groups at baseline in the D+E, D or E group regarding the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain (D+E = 2.3 ± 2.6; D = 2.1 ± 3.1; E = 2.0 ± 2.8; $P = 0.52$), WOMAC stiffness (D+E = 1.4 ± 1.5; D = 1.6 ± 1.4; E = 1.3 ± 1.5; $P = 0.77$), WOMAC disability (D+E = 7.7 ± 10.6; D = 7.5 ± 10.4; E = 6.7 ± 9.0; P = 0.60) and the SF-12 Mental Health (D+E = 54.6 ± 7.0; D = 53.8 ± 8.5; E = 53.6 ± 7.5; $P = 0.63$). In total, 11 participants that were free of OA at baseline (KL = 0 or 1) progressed to KL 2 or higher over 96 months, these participants were all in the stable weight group.

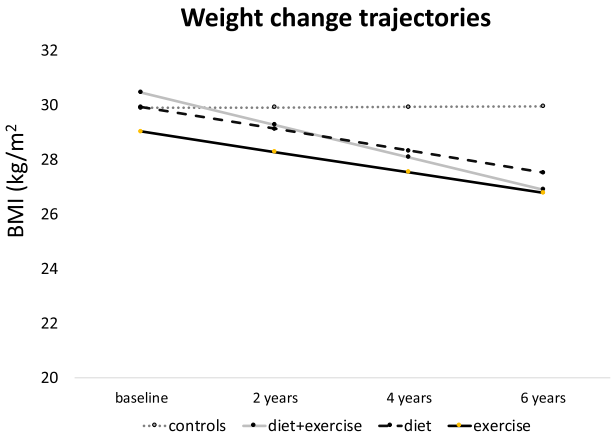

Fig. 2. Trajectories of BMI for the control group as well as the different WL regimen groups (diet&exercise; diet only; exercise only).

Comparison of baseline and rates of change of cartilage T2 over 96 months between WL and stable weight groups

There were no significant differences at baseline in global cartilage T2 as well as in each compartment separately between participants with WL and those with stable weight (adjusted mean differences in baseline T2 between stable overweight group and 5% WL group [95% confidence interval (CI)]: global knee, 0.34 [−0.29, 0.37], $P = 0.13$; patella, 0.16 [−0.16, 0.18], $P = 0.65$; medial tibia, 0.55 [0.18, 0.61], $P = 0.19$; lateral tibia, 0.50 [−0.37, 0.63], $P = 0.11$; medial femur, 0.03 [−0.03, 0.05], $P = 0.76$; lateral femur, 0.39 [−0.38, 0.57], $P = 0.17$; Table II). The rate of increase over 96 months of global T2 was significantly smaller in the WL group compared to the stable weight group, suggesting less cartilage degeneration over 96 months (adjusted mean difference of change in T2 ms/year [95% CI] between the stable overweight and the >5% WL group: 0.24 [0.20, 0.41] ms/year; $P < 0.001$; Table III). In the deep layer this effect was found for the global cartilage (Adjusted mean differences of change in T2 [95% CI]: global knee T2, 0.35 [0.20, 0.42], $P < 0.001$) and in all compartments (patella: 0.15 [0.06, 0.19], $P_{patella} = 0.03$; medial femur, 0.33 [0.17, 0.40], $P_{medial\ femur} < 0.001$; lateral femur, 0.56 [0.42, 0.61], $P_{lateral\ femur} < 0.001$; medial tibia, 0.42 [0.31, 0.48], $P_{medial\ tibia} < 0.001$; lateral tibia, 0.24 [0.14, 0.42], $P_{lateral\ tibia} < 0.001$), whereas in the superficial layer the medial femur (0.21 [0.04, 0.45], $P = 0.01$) and the medial tibia (0.48 [0.39, 0.75], $P < 0.001$) showed a significantly lower rate of change in the WL group compared to the stable weight group. These results were supported by the texture analyses, which showed significantly less increase in contrast and variance averaged over all compartments ($P < 0.001$; supplemental data).

Table II
Baseline T2 parameters*

T2 Parameters baseline	Stable overweight group vs >5% weight loss group ($N = 380$)	*P*-value
Cartilage T2		
Global knee	0.34 [−0.29, 0.37]	0.13
PAT	0.16 [−0.16, 0.18]	0.65
MT	0.55 [0.18, 0.61]	0.19
LT	0.50 [−0.37, 0.63]	0.11
MF	0.03 [−0.03, 0.05]	0.76
LF	0.39 [−0.38, 0.57]	0.17
Deep layer T2		
Global knee	0.36 [−0.06, 0.46]	0.09
PAT	0.06 [−0.10, 0.11]	0.91
MT	0.13 [−0.13, 037]	0.15
LT	0.45 [−0.03, 0.59]	0.051
MF	0.04 [−0.38, 0.12]	0.93
LF	0.33 [−0.22, 0.43]	0.35
Superficial layer T2		
Global knee	0.28 [0.21, 0.36]	0.37
PAT	−0.04 [−0.10, 0.01]	0.79
MT	0.21 [0.11, 0.30]	0.63
LT	0.27 [0.19, 0.35]	0.55
MF	0.25 [0.15, 0.33]	0.50
LF	0.68 [0.59, 0.78]	0.40

PAT, patella; MT, medial tibia; LT, lateral tibia; MF, medial femur; LF, lateral femur.
* Multivariable linear regression models adjusting for age, sex, baseline BMI and KL score. Adjusted mean differences [95% confidence interval] (ms).

Table III
Comparison of rate of change of global and laminar T2 over 96-months

T2 Parameters 96 months	Stable overweight vs >5% weight loss	*P*-value
	Adjusted mean difference of change in T2 ms/year [95% CI]	
Cartilage T2		
Global knee	0.24 [0.20, 0.41]	**<0.001**
PAT	0.12 [0.06, 0.26]	0.05
MT	0.45 [0.39, 0.59]	**<0.001**
LT	0.18 [0.13, 0.20]	**0.02**
MF	0.19 [0.15, 0.30]	**0.03**
LF	0.32 [0.24, 0.58]	**0.001**
Deep layer T2		
Global knee	0.35 [0.20, 0.42]	**<0.001**
PAT	0.15 [0.06, 0.19]	**0.03**
MT	0.42 [0.31, 0.48]	**<0.001**
LT	0.24 [0.14, 0.42]	**<0.001**
MF	0.33 [0.17, 0.40]	**<0.001**
LF	0.56 [0.42, 0.61]	**<0.001**
Superficial layer T2		
Global knee	0.04 [−0.13, 0.09]	0.50
PAT	0.08 [0.06, 0.22]	0.12
MT	0.48 [0.39, 0.75]	**<0.001**
LT	0.06 [0.02, 0.19]	0.40
MF	0.21 [0.04, 0.45]	**0.01**
LF	0.08 [0.05, 0.18]	0.25

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella.
*The adjusted mean differences of associations of T2 relaxation times between the weight loss group and stable weight group over 96 months were assessed using multivariable regression models adjusting for age, sex, baseline BMI and baseline KL score. Significant results ($P < 0.05$) are bolded.

Comparison of rates of change of WORMS cartilage, meniscal and BMEP lesions over 96 months between WL and stable weight groups

At baseline there were no significant differences found between the stable weight and WL groups in cartilage, meniscal and BMEP WORMS scores (all $P > 0.05$; supplemental data). Over 96 months, the WL group showed significantly lower rates of progression of the sum WORMS of both menisci together and the sum WORMS of the medial meniscus (Adjusted mean differences of rate of change/year [95% CI] between stable overweight and >5% WL group: WORMS meniscus lesions sum, 0.08 [0.02, 0.21], $P = 0.021$ and WORMS medial meniscus lesions sum, 0.06 [0.02, 0.09], $P = 0.005$; Table IV). There were no significant differences between WL and stable weight groups in the rate of change of the global knee BMEP score, the global knee cartilage score or the cartilage score for each compartment separately ($P > 0.05$ for each comparison).

Table IV
Comparison of rate of change of cartilage, meniscus and bone marrow edema pattern WORMS sum score over 96-months

Rate of change of WORMS over 96 months	Stable overweight vs >5% weight loss	*P*-value
	Adjusted mean difference of rate of change/year [95% CI]	
Cartilage lesions		
Global knee	0.10 [−0.06, 0.25]	0.34
PAT	0.02 [0.00, 0.04]	0.46
T	0.00 [−0.06, 0.05]	0.93
MT	0.02 [−0.3, 0.04]	0.42
LT	0.02 [−0.03, 0.04]	0.46
MF	0.03 [−0.03, 0.04]	0.28
LF	0.01 [−0.03, 0.04]	0.74
Meniscus lesions		
Meniscus lesions sum	0.08 [0.02, 0.21]	**0.021**
Medial meniscus lesions sum	0.06 [0.02, 0.09]	**0.005**
Lateral meniscus lesions sum	0.02 [0.00, 0.08]	0.86
BMEP lesions		
BMEP lesions sum	0.02 [0.00, 0.08]	0.85

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella.
*The adjusted mean differences of associations of the rate of change of WORMS between the weight loss group and stable weight group over 96 months were assessed using multivariable regression models adjusting for age, sex, baseline BMI and baseline KL score. Significant results (**$P < 0.05$**) are bolded.

Rates of change in participants with different WL methods and participants with stable weight

At baseline there were no significant differences found in cartilage T2 between the participants with stable weight and the participants with different methods of weight loss ($P > 0.05$, respectively; supplemental data). Over 96 months, the rates of increase in global cartilage T2 were lower in the D and D+E groups compared to the stable weight group (mean T2 (ms/year) [95% confidence interval (CI)]: stable weight group = 0.37 [0.26, 0.47] vs D+E group 0.14 [0.09, 0.18], $P = 0.003$; stable weight group vs D group 0.15 [0.03, 0.46], $P = 0.04$; Table V), indicating less progression of cartilage degeneration in the diet groups compared to the group with stable weight. On the other hand, the E group (exercise only) showed no significant difference in cartilage T2 averaged over all compartments compared to the stable weight group (mean T2 (ms) [95% CI]: stable weight group vs E group = 0.40 [0.24, 0.55], $P = 0.85$).

Discussion

In this study we analyzed the effects of WL on knee cartilage composition (T2 relaxation time) and structural deterioration of cartilage, menisci and bone marrow (WORMS) over 96 months. We found slower cartilage T2 increase in participants losing weight compared to those with stable weight, suggesting less progression of cartilage degeneration in participants losing weight, especially in the medial compartments. Moreover, we also found less progression of meniscal lesions, especially in the medial meniscus, over 96 months. This study also investigated the association of different WL regimens including diet, exercise and diet combined with exercise and knee joint cartilage composition and structural degeneration over 96 months. We found that individuals losing weight with diet and exercise as well as with diet only showed significantly less increase of cartilage T2 whereas those losing weight with exercise only showed no significant difference compared to those with stable weight in both layers over 96 months in the exercise only group.

Our findings of less cartilage degeneration, as measured with global T2 relaxation time, and T2 in the medial compartment of the knee cartilage, in individuals with WL compared to those without WL are in line with a previous study including participants with surgical and non-surgical WL, showing that reduced progression of cartilage thickness loss and quality deterioration in the medial compartment was associated with the amount of WL, measured using MR-based dGEMRIC measurements[29]. Moreover, another study found an inverse linear relationship between weight change and medial cartilage volume loss, indicating that the greater the WL, the less the cartilage volume of the medial tibia decreased in average over 2.7 years[30]. However, all these studies had a relatively limited follow-up period while our study has a follow-up period of 8 years and provides advanced MRI biomarkers including the assessment of compositional cartilage and structural knee joint degeneration.

Interestingly, we found that the evidence for a potential beneficial effect of WL on cartilage composition was seen in all knee compartments over 96 months. In the laminar analysis, the superficial layer showed less cartilage T2 increase in the medial femoral condyle and medial tibia in the WL group compared to those with stable weight. The lack of association of WL with morphological cartilage changes assessed using the subscore WORMS cartilage may be explained by the fact that differences in cartilage T2 relaxation time measurements may be detected before differences in morphological cartilage lesions may occur, as previous studies have shown that increased cartilage T2 values predicted longitudinal morphological degeneration in the cartilage, meniscus, and bone marrow in participants with risk factors for OA[16]. However, the present study assessed WORMS outcomes over 8 years and it seems likely that any effects of WL on morphological progression would be detected in this time frame.

Our study also evaluated differences in compositional cartilage changes among groups reporting different WL methods over a duration of 96 months. A previous study assessing the associations between different types of weight loss (exercise, diet, diet and exercise) and structural knee changes over 18 months found no

Table V
Comparison of rate of change of T2 parameters for each weight loss method group compared to the stable weight group over 96 months

T2 Parameters	Stable weight $N = 380$	Diet& Exercise $N = 101$	*P*-value	Diet $N = 41$	*P*-value	Exercise $N = 33$	*P*-value
	Change in T2 ms/year 95% CI		Diet& Exercise vs SW	Change in T2 ms/year 95% CI	Diet vs SW	Change in T2 ms/year 95% CI	Exercise vs SW
Cartilage T2							
Global knee	0.37 [0.26, 0.47]	0.14 [0.09, 0.18]	**0.003**	0.15 [0.03, 0.46]	**0.04**	0.40 [0.24, 0.55]	0.85
PAT	0.30 [0.21, 0.38]	0.26 [0.02, 0.53]	0.81	0.24 [0.18, 0.56]	0.40	0.44 [0.03, 0.86]	0.31
MT	0.55 [0.41, 0.69]	0.06 [0.02, 0.32]	**<0.001**	0.07 [0.02, 0.36]	**<0.001**	0.42 [0.31, 0.75]	0.13
LT	0.42 [0.29, 0.55]	0.34 [0.11, 0.57]	0.65	0.22 [−0.10, 0.53]	0.44	0.52 [0.18, 0.86]	0.12
MF	0.23 [0.17, 0.38]	0.04 [0.02, 0.21]	**0.02**	0.27 [0.05, 0.50]	0.53	0.29 [0.07, 0.52]	0.73
LF	0.53 [0.38, 0.69]	0.25 [0.21, 0.41]	**0.02**	0.51 [0.28, 0.73]	0.14	0.53 [0.30, 0.76]	0.78
Deep layer T2							
Global knee	0.40 [0.28, 0.52]	0.08 [0.04, 0.12]	**<0.001**	0.09 [0.00, 0.18]	**0.001**	0.34 [0.16, 0.53]	0.21
PAT	0.20 [0.12, 0.28]	0.13 [0.09, 0.39]	0.38	0.09 [0.02, 0.42]	0.22	0.24 [0.17, 0.64]	0.85
MT	0.49 [0.34, 0.64]	0.09 [0.02, 0.39]	**<0.001**	0.12 [0.05, 0.36]	**<0.001**	0.21 [0.07, 0.34]	**0.01**
LT	0.38 [0.25, 0.51]	0.33 [0.13, 0.52]	0.13	0.06 [0.03, 0.28]	0.01	0.33 [0.11, 0.55]	0.34
MF	0.37 [0.18, 0.56]	0.03 [0.01, 0.6]	**0.001**	0.28 [0.01, 0.57]	0.06	0.30 [0.02, 0.59]	0.44
LF	0.63 [0.47, 0.80]	0.16 [0.08, 0.31]	**<0.001**	0.13 [0.01, 0.34]	**0.002**	0.55 [0.28, 0.80]	0.18
Superficial layer T2							
Global knee	0.36 [0.29, 0.43]	0.34 [0.13, 0.58]	0.87	0.41 [0.10, 0.73]	0.53	0.67 [0.38, 1.02]	**0.013**
PAT	0.46 [0.35, 0.56]	0.28 [0.04, 0.56]	0.20	0.40 [0.08, 0.56]	0.79	0.26 [0.04, 0.40]	**0.026**
MT	0.61 [0.41, 0.80]	0.13 [0.08, 0.25]	**0.001**	0.17 [0.01, 0.72]	**0.02**	0.63 [0.43, 0.92]	0.96
LT	0.51 [0.41, 0.61]	0.56 [0.24, 0.88]	0.59	0.42 [0.02, 0.85]	0.59	0.77 [0.31, 1.24]	0.14
MF	0.18 [0.06, 0.63]	0.09 [0.18, 0.37]	0.27	0.12 [0.01, 0.41]	0.07	0.33 [0.12, 1.50]	**0.023**
LF	0.42 [0.34, 0.51]	0.49 [0.21, 0.78]	0.32	0.61 [0.22, 1.00]	0.15	0.69 [0.27, 1.11]	0.08

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella.
*The associations between different weight loss methods and rate of change in cartilage T2 over 96 months were assessed using multivariable regression models adjusting for age, sex, baseline BMI and baseline KL score. Significant results (**$P < 0.05$**) are bolded.

significant differences between the different groups in cartilage volume, thickness and percentage of denuded bone area[13], which may have been caused by the fairly short follow-up time of this previous study in comparison to our study. Moreover a previous study found, that the WL interventions diet, exercise and diet plus exercise did not show consistent effects yet on serum levels of potential biomarkers of osteoarthritis, such as cartilage oligomeric matrix protein or transforming growth factor β1, after 18 months[31]. Also, cartilage and meniscal lesions were not assessed semi-quantitatively in the previous study evaluating structural knee changes[13]. In a further study, participants of both diet groups (diet and exercise group and diet only group) showed a significantly greater reduction of the inflammatory marker Interleukin (IL) 6 compared to the exercise group, suggesting less inflammation and therefore less OA progression in the dietary groups[12]. Moreover in the same study both dietary groups showed lower compressive forces compared to the exercise group — this comparison reached the level of significance in the diet group and showed a statistical trend in the diet and exercise group ($P = 0.05$)[12]. The reduction of inflammation and knee joint loading detected in the previous study in the dietary groups compared to the exercise group, may be consistent with our findings regarding the rate of progression of cartilage degeneration.

Our study has several limitations. Firstly, our study performed a retrospective analysis of WL in the OAI cohort, therefore several confounders could not be controlled for, e.g., exact amount of exercise or calorie uptake. Moreover, WL methods were self-reported only and no other data were available. Further investigations are needed of possible reasons for different effects of different WL methods, including different effects on lipids, blood sugar levels and metabolic status. Secondly, we can only speculate that any bias due to loss to follow-up will be similar in the two groups. The group sizes of participants with diet alone and exercise alone WL regimens were small in comparison to the diet plus exercise group and the amount of WL achieved was different between the groups. Although we adjusted for the amount of WL in total, this may be a potential confounder and needs to be considered when interpreting the data. A further limitation is that on a whole-joint level we worked with T2 values averaged over the whole knee. It needs to be noted, that differences in change of T2 and WORMS were assessed in these analyses. Due to the large number of participants in total and fairly wide ranges of baseline parameters, the assessment of the level of significance of associations alone may lack of information. However, when taking into account the baseline standard deviation in global knee T2 of 2.89 ms, a mean estimated difference of cartilage T2 of 1.92 ms over 96 months represents 2/3 of the baseline standard deviation and this represents a large difference for a clinically used biomarker.

In summary, our study showed that in individuals with risk factors or mild to moderate radiographic evidence for OA, moderate or greater weight loss (>5% of baseline BMI) was significantly associated with less progression over 96 months of compositional cartilage degeneration in all knee compartments as well as with less progression of meniscal lesions, compared to participants with stable weight. Our data suggests that participants who lost weight with diet and exercise and diet alone potentially showed less worsening of cartilage composition, while the participants in the exercise WL group did not demonstrate significant differences compared to the participants with stable weight over 96 months.

Author contributions

Alexandra Gersing, M.D (alexandra.gersing@ucsf.edu). and Thomas Link, Ph.D., M.D (thomas.link@ucsf.edu). take responsibility for the integrity of the work as a whole, from inception to finished article.

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Competing interest statement

None of the authors have any financial or other interests related to the manuscript submitted to Osteoarthritis and Cartilage that might constitute a potential conflict of interest.

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Supplementary data

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