Osteoarthritis and Cartilage 21 (2013) 1865–1875

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Is increased joint loading detrimental to obese patients with knee osteoarthritis? A secondary data analysis from a randomized trial

M. Henriksen †*, D.J. Hunter ‡, E.B. Dam §, S.P. Messier ‖, T.P. Andriacchi ¶#, L.S. Lohmander ††§§, J. Aaboe †, M. Boesen †‡‡, H. Gudbergsen †, H. Bliddal †, R. Christensen †§§

† *The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Frederiksberg, Copenhagen F, Denmark*
‡ *Rheumatology Department, Royal North Shore Hospital and Northern Clinical School, University of Sydney, NSW, Australia*
§ *Biomediq A/S, Copenhagen, Denmark*
‖ *Wake Forest University, Winston-Salem, NC, USA*
¶ *Stanford University, Stanford, CA, USA*
# *Palo Alto Veterans Administration, USA*
†† *Department of Orthopedics, Clinical Sciences Lund, Lund University, Sweden*
‡‡ *Department of Radiology, Copenhagen University Hospital, Frederiksberg, Copenhagen F, Denmark*
§§ *Institute of Sports Science and Clinical Biomechanics, Faculty of Health Sciences, University of Southern Denmark, Denmark*

ARTICLE INFO

Article history:
Received 4 February 2013
Accepted 4 October 2013

Keywords:
Osteoarthritis
Gait
Joint loading
Weight loss
Cartilage

SUMMARY

Objective: To investigate whether increased knee joint loading due to improved ambulatory function and walking speed following weight loss achieved over 16 weeks accelerates symptomatic and structural disease progression over a subsequent 1 year weight maintenance period in an obese population with knee osteoarthritis (OA).
Methods: Data from a prospective study of weight loss in obese patients with knee OA (the CARtilage in obese knee OsteoarThritis (CAROT) study) were used to determine changes in knee joint compressive loadings (model estimated) during walking after a successful 16 week weight loss intervention. The participants were divided into 'Unloaders' (participants that reduced joint loads) and 'Loaders' (participants that increased joint loads). The primary symptomatic outcome was changes in knee symptoms, measured with the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire, during a subsequent 52 weeks weight maintenance period. The primary structural outcome was changes in tibiofemoral cartilage loss assessed semi-quantitatively (Boston Leeds Knee Osteoarthritis Score (BLOKS) from MRI after the 52 weight maintenance period.
Results: 157 participants (82% of the CAROT cohort) with medial and/or lateral knee OA were classified as Unloaders ($n = 100$) or Loaders ($n = 57$). The groups showed similar significant changes in symptoms (group difference: −2.4 KOOS points [95% CI −6.8:1.9]) and cartilage loss (group difference: −0.06 BLOKS points [95% CI −0.22:0.11) after 1 year, with no statistically significant differences between Loaders and Unloaders.
Conclusion: For obese patients undergoing a significant weight loss, increased knee joint loading for 1 year was not associated with accelerated symptomatic and structural disease progression compared to a similar weight loss group that had reduced ambulatory compressive knee joint loads.
Clinicaltrials.gov: NCT00655941.

Introduction

Knee joint loading is believed to be implicated in the pathogenesis of knee osteoarthritis (OA)[1]. Dynamic loading of the knee during walking depends primarily on acceleration and deceleration of the body mass, muscle contractions, walking speed resulting in tibiofemoral compression forces. Cross-sectional studies associate

* Address correspondence and reprint requests to: M. Henriksen, The Parker Institute, Copenhagen University Hospital, Frederiksberg, Ndr. Fasanvej 57, DK-2000 F, Denmark.

1063-4584/$ – see front matter
http://dx.doi.org/10.1016/j.joca.2013.10.003

dynamic loading with presence and severity of radiographic tibiofemoral OA[2–4], subchondral bone density[5], presence of bone marrow lesions (BML)[6], meniscal extrusion[7], and cartilage defects[8], and more importantly, indicated that higher dynamic loading during walking predicts radiographic disease progression[9,10]. These studies underlie the rationale for reducing dynamic knee loads during walking to potentially delay or stop structural deterioration.

Obesity is a major risk factor for development and progression of knee OA[11,12], and is believed to act mainly through high mechanical loads[13], although systemic effects are also involved[14]. Accordingly, weight loss – a treatment designed to reduce loading – is advocated in obese and overweight persons with knee OA[15,16]. A recent study of weight loss in patients with knee OA showed that an average of 13 % weight loss over 16 weeks was associated with a 7% reduction in tibiofemoral compression forces during walking[17]. This has also been shown in long-term (18 months) studies[18,19], and 1 kg weight loss is on average associated with 2–4 kg reduction in tibiofemoral joint compression forces during walking[17,18].

Weight loss yields positive outcomes on pain, disability, walking speed, and ambulatory knee function[15,17,20]. Yet, reduced pain, higher walking speed, and improved ambulatory knee function are associated with increased joint loads[21–26]. Thus, while successful weight loss on average may reduce joint compression, it also raises concern of increased loading through improved function. Although increased joint loads are thought to be detrimental and accelerate structural changes, no data exist on such potentially undesirable effects of successful treatments. The results of our recent weight loss study in knee OA[17] offered the opportunity to address this concern, since approximately 1/3 of the participants responded to a significant weight loss by increasing walking speed and improving ambulatory knee function in a manner that increased knee joint loading during walking. Our previous cohort study[17] reported immediate biomechanical changes over the 16 week weight loss program, whereas the present study focus on changes during the subsequent 1 year period.

The objective of this study was to investigate whether increased loading of the knee joint (following successful weight loss) caused accelerated symptomatic and structural disease progression over 1 year compared to a group that reduced loading. We hypothesized that increased tibiofemoral joint compression forces during walking accelerate structural and symptomatic disease progression.

Patients & methods

Participants and weight loss program

We used data from the weight loss study in knee OA - the "CAROT study" (influence of weight loss or exercise on CARtilage in obese knee OsteoarThritis patients). Eligibility criteria for the CAROT study were age above 50 years, clinical knee OA confirmed by radiography (osteophytes and/or joint space narrowing assessed by a radiologist), and a BMI>30 kg/m^2. 192 knee OA patients were included and given an initial 16 week intensive diet intervention, aiming at weight loss>10%[17,20,27]. The dietary program consisted of a low-energy-diet plus meal replacements (Cambridge Weight Plan UK) and nutritional education as described elsewhere[20,27].

Following the weight loss program the participants were enrolled in a 1-year maintenance program with random assignment to (1) dietary consultancy, (2) exercise therapy, or (3) a no intervention control group. Thus the total study duration was 68 weeks (16 weeks weight loss + 52 weeks maintenance). The participant's most symptomatic knee at inclusion was designated as target knee for assessments throughout the study. The CAROT study was approved by the local ethical committee and written informed consent was obtained from each participant.

Study design overview

In the present study data from the biomechanics sub-cohort (82% of the CAROT cohort) were analyzed, consisting of participants eligible for gait analysis at inclusion (palpation of anatomical landmarks possible and able to walk independently without walking aid) with completed recordings of three-dimensional gait analysis before and after the weight loss program[17]. The change in peak knee compression forces after the 16 week weight loss intervention was used for group allocation of the participants into two exposure categories – 'Unloaders' and 'Loaders': Unloaders were defined as participants that decreased the peak compression force after the weight loss; Loaders were participants that increased the peak compression force. Any change, disregarding magnitude, resulted in 'group allocation'. We compared the changes in symptomatic, structural, and biomechanical variables (see below) from week 16–68 (maintenance period).

Outcome measures

Major outcomes

The co-primary outcomes of this secondary analysis were changes in patient-reported symptoms and tibiofemoral cartilage loss assessed from magnetic resonance imaging (MRI) using the cartilage1 score of the Boston Leeds Knee Osteoarthritis Score (BLOKS)[28]. Changes were calculated by subtracting the week 68 value (1 year follow-up) from the week 16 value (post weight loss). All assessors were blinded to the case status.

Symptomatic assessment. Symptoms were assessed using the Knee Osteoarthritis Outcome Score (KOOS)[29] – quantified as the average of four of the five KOOS subscales (Pain; Symptoms; Function in daily living; and Knee related quality of life) named KOOS4. The scores range from 0 (worst) to 100 (best).

MRI acquisition and reading. On a 1.5 T whole body scanner (Philips Intera, software release 12.1.5.0) all participants had MRI of their target knee using a flex coil. The entire protocol is described elsewhere[30] and included sagittal 3D FLASH gradient-echo (reconstructed to 3 mm slices, TR 21 ms, TE 8.4 ms, FA 20°, FOV 160 × 160 mm, matrix 512 × 512), sagittal non fat sat DUAL turbo spin echo proton density and T2-weighted sequence (4 mm slices, TR 2531.3 ms, TE 15/100, FOV 170 × 170 matrix 256 × 256), coronal T1 turbo spin echo (3 mm slices, TR 500 ms, TE 17 ms, FOV 150 × 150 mm, matrix 512 × 512) and STIR (3 mm slice, TR 1797, TI 9 ms, TE 55 ms, FOV 150 × 150 mm, matrix 512 × 512). We used the sagittal FLASH and proton/T2-weighted DUAL echo sequences for cartilage loss scoring. Because is difficult to separate fluid and cartilage on the FLASH sequence, minor cartilage losses are difficult to detect reliably. We partly compensated for this by using the corresponding sagittal dual spin echo sequence to verify the score and to adjust for potential joint fluid between the cartilage layers. We used the coronal T1 and STIR images for BML scoring.

Cartilage loss was assessed in the medial and lateral weight bearing femoral and tibial regions according to the cartilage1 score in BLOKS[28] and graded semi-quantitatively on a 0–3 scale based on regional involvement of any cartilage loss (including partial and full thickness loss): 0: None; 1: <10%; 2: 10–75%; 3: >75% of region cartilage surface area. The maximum score across all four regions defined the global tibiofemoral value used as primary outcome. The maximum score across the medial tibial and medial femoral regions defined the medial score, and likewise for the lateral regions. HG performed all BLOKS assessments; intra- and inter-reader reliability were assessed by HG and MB (Kappa coefficients: cartilage: inter-reader: 0.59; intra-reader: 0.81. BML: inter-reader: 0.65;

intra-reader: 0.66, similar to previous studies[28,31]). Representative images are given in Fig. 1.

Minor outcomes

Secondary symptomatic outcomes were changes from week 16–68 in each of the five KOOS subscales.

Secondary structural outcome was changes from week 16–68 in BMLs. BMLs appear as ill-defined signal intensity changes in the subchondral bone. BMLs were assessed semi-quantitatively in the medial and lateral weight bearing femoral and tibial regions according to the BLOKS[28]. They were graded on a 0–3 scale based on the regional involvement: 0: None; 1: <10%; 2: 10–25%; 3: >25% of the region. The maximum score across all four regions defined the global maximal tibiofemoral value. The maximum score across the medial tibial and medial femoral regions defined the medial BML score, and likewise for the lateral regions.

Objective physical function. Six-minute walking distance was measured using the 6-min walk test[32], performed in-doors on a pre-defined 100 m route. The participants walked the route as many times as possible in 6 min at maximum speed. Distance covered in meters was the result of the test.

Explanatory variables

Walking biomechanics. Walking biomechanics were acquired at week 0, 16, and 68 by three-dimensional gait analysis using a six camera 100 Hz motion analysis system (MX13, Vicon, Oxford, UK) synchronized with two force platforms operating at 1000 Hz (AMTI, Watertown, MA, USA). The details of the gait analysis protocol are described elsewhere[17]. The participants walked unshod on a 10 m walkway at self-selected walking speeds determined during practice walks. Once self-selected walking speed was determined, six acceptable walking trials were recorded, defined as ±0.1 km/h of the self-selected walking speed.

The analyses focused on the stance phase of the gait cycle. Internal inter-segmental net resultant forces and moments were calculated using the Plug-In-Gait (Vicon, Oxford, UK). Peaks in the knee joint moments were extracted, averaged across the six trials, and reported in Newton-meters (Nm). Peak knee joint compressive forces (reported in Newtons (N)) were estimated using a statically determinate muscle model[33]. In brief, the knee compression force was estimated as the vector sum of (1) the inter-segmental reaction forces resolved along the long axis of the tibia, (2) the compression components of the assumed active muscle group forces and (3) the axial component of the cruciate ligament forces. The included muscles were the hamstrings, gastrocnemius and quadriceps muscles. The muscle forces were estimated by dividing the net sagittal plane joint moments with the muscle moment arms derived from third-order polynomials based on the sagittal knee joint angle[34]. The axial cruciate ligament forces were estimated assuming that the cruciates only resist antero-posterior shear calculated as the sum of the antero-posterior knee joint reaction force and the antero-posterior component of the muscle forces acting over the knee. Based on 30 individuals assessed twice separated by one week done prior to the study, intra-class correlation coefficient for the estimation of peak compression force in our lab is 0.91 (95% CI: 0.83–0.96), similar to previous reports on obese knee OA patients[35].

Ambulatory knee function assessment. Changes from week 0 (pre-weight loss) to week 16 in self-selected walking speed (during gait analyses) and internal knee extensor moments were used as indicators of changes in ambulatory knee function, with increases indicating improvement[36].

Statistical methods

To explore what factors that explain the changes in compression forces in each group, group-wise multiple regression analyses were done with weight loss, changes in internal knee extensor moment, and walking speed as predictors.

From an epidemiological perspective this study was designed as a nested prospective cohort with biomechanically 'Exposed' and 'Unexposed' individuals[37]. The groups can differ in measured or unmeasured characteristics because of group assignment (Unloaders vs Loaders)[38].

For the purpose of transparent reporting, we present estimates from both basic and adjusted statistical models for the primary outcomes[37]. Basic analyses: General linear models were used to compare changes from week 16 to week 68 between groups with a factor for group (Unloaders vs Loaders) including

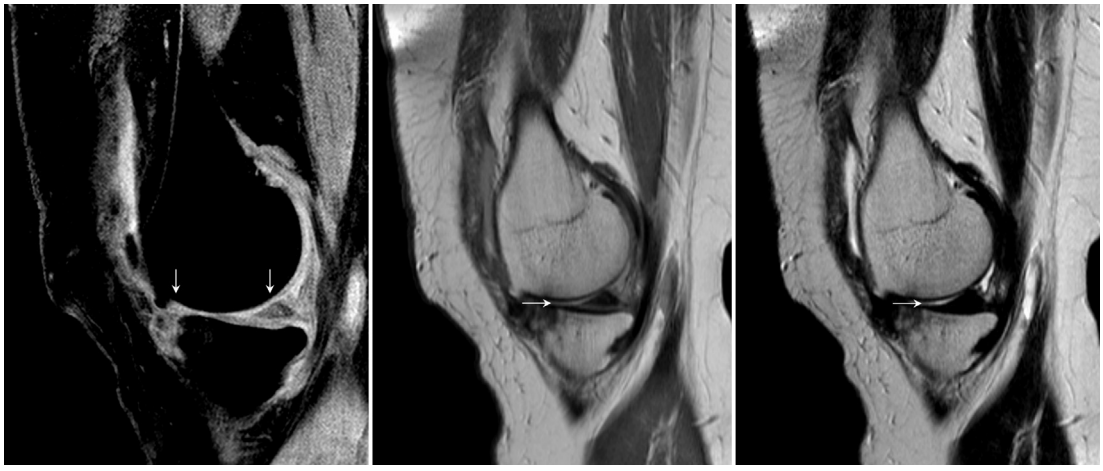

Fig. 1. Representative images from the 3D reconstructed 2 mm sagittal 3D FLASH gradient-echo (left), sagittal non fat sat DUAL turbo spin echo proton density weighted (middle) and T2-weighted (right) sequences in the medial part of the medial tibiofemoral joint. The FLASH image indicates reduced cartilage thickness (cartilage loss) in the anterior weight bearing region of the femur (between the vertical arrows) corresponding to a grade 2 cartilage loss (defined as any cartilage loss in 10–75% of region cartilage surface area). Because of the limited contrast between fluid and cartilage in the FLASH sequence image, the score was confirmed from the proton density weighted (middle) and T2-weighted (right) images indicating fluid between the femoral and tibial cartilage (horizontal arrows). Note the anterior osteophyte, bone marrow changes in the anterior tibia, and a moderate effusion in the medial recess and posterior to the meniscus.

the week 16 value, and the week 0 knee joint compressive forces as covariates. Adjusted analysis: We repeated the analysis further including age, sex, week 16 BMI, and the randomization code in the underlying RCT (Diet, Exercise and Control) as covariates. All minor and explanatory outcomes were analyzed according to the same algorithm, however only the adjusted results are presented.

To account for missing data we did multiple imputation of missing measurements, assuming data were missing at random and followed a multivariate normal distribution. As the results were unchanged we present the imputed case analyses. All analyses were done applying SAS software (v. 9.2; SAS Institute, NC, USA). Statistical significance was accepted at $P < 0.05$.

Sensitivity analyses were performed by cross-sectional correlations (Spearman) between knee compression force and the primary outcomes at week 16 and 68. Furthermore, we redefined Loaders and Unloaders based on the changes in knee compression force from week 16–68 ($Unloaders_{16-68}$ and $Loaders_{16-68}$) and comparing the changes in outcomes between those groups using the same statistical models as above.

Results

Of the 192 CAROT participants, 177 (92%) were eligible for the biomechanics sub-cohort (Fig. 2). Of those, 157 had complete walking biomechanics records at week 0 and 16 and constituted the current sample. Of these, 100 (64%) participants were defined as "Unloaders" and 57 (36%) as "Loaders". The group allocations in the underlying RCT (Diet, Exercise and Control) were equally distributed in the two groups ($\chi^2 = 3.22$; df = 2; $P = 0.89$).

One year after the weight loss (i.e., at week 68), there were 144 participants (92%) remaining in the biomechanics sub-cohort, i.e., 13 participants lost to follow-up (Fig. 2). These were distributed with 7 (7%) in the Unloader group and 6 (11%) in the Loader group. The characteristics of the lost participants were not different from those completing the study (data not shown).

Changes from week 0–16

At week 0 the Unloaders walked faster and with higher knee compression force than the Loaders (Appendix 1). After the weight loss the Unloaders on average reduced peak knee compression force by −509 N [95% CI: −588:−429] while it increased by 425 N [95% CI: 322:528] among Loaders.

Among the Unloaders the ambulatory knee function was not improved from week 0 to week 16, seen as no statistically significant change in walking speed and a reduction in the knee extensor moment (Appendix 1). The explanatory multiple regression showed that reduced compression force was predicted by reductions in the knee extensor moment and body mass ($R^2 = 0.46$). In contrast, the ambulatory knee function was improved among the Loaders, seen as increases in walking speed and internal knee extensor moment (Appendix 1). Explanatory multiple regression showed that only the increase in knee extensor moment predicted

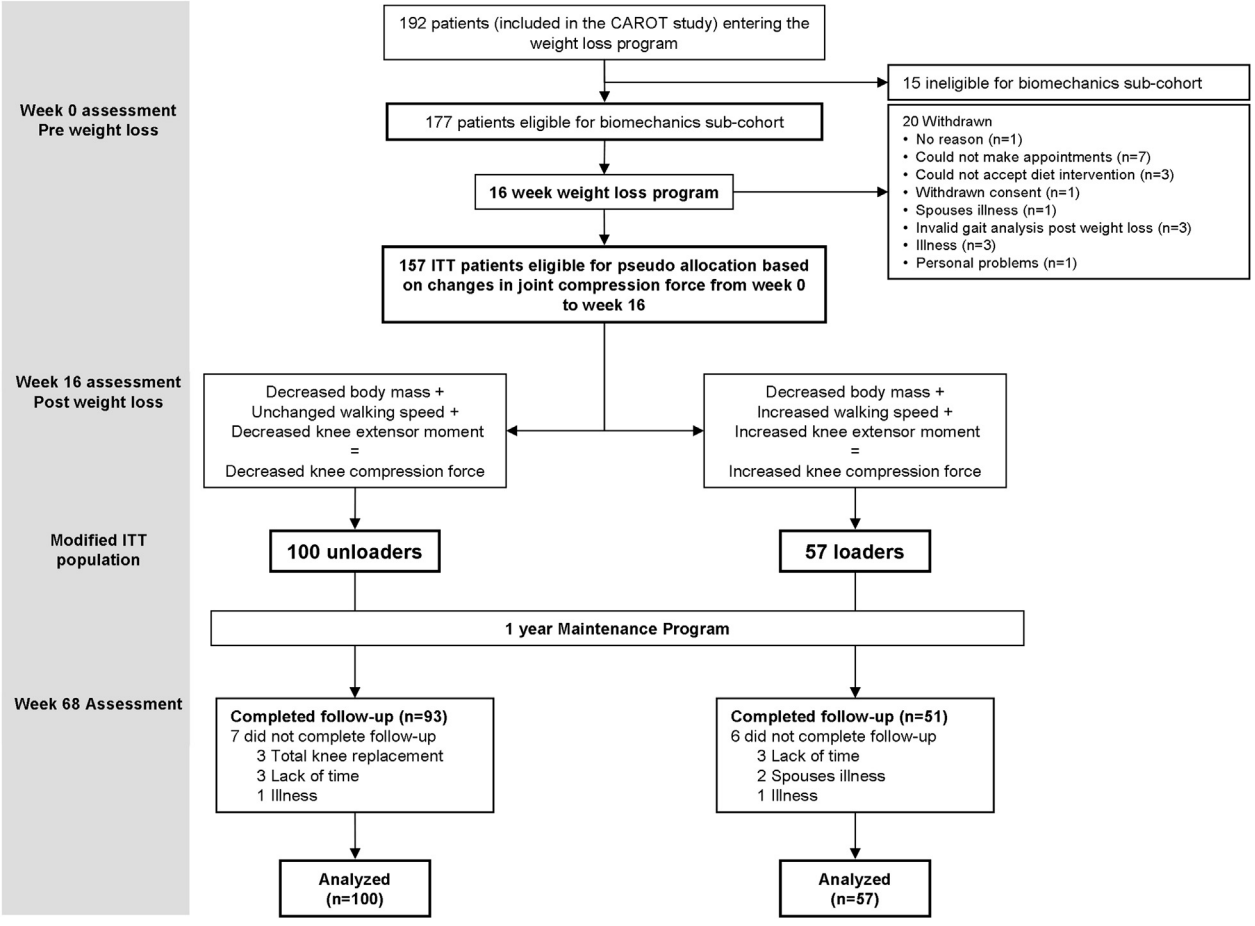

Fig. 2. Study profile illustrating the flow of patients through the study.

joint compression change ($R^2 = 0.74$). Cross-sectional summaries of the week 0, 16, and 68 data are available in Appendix 1.

Week 16

At week 16 (after weight loss) the Loaders walked with significantly higher peak compression forces and peak internal knee extensor and flexor moments compared to the Loaders (Table I). There were no other statistically significant differences between the Unloaders and Loaders at week 16 (Table I).

Outcomes at week 68

The change over 1 year from week 16 in KOOS4 did not differ significantly between groups (Table II). Similarly, the group difference in the change in global tibiofemoral cartilage loss score was not statistically significant (Table II). The results did not change in the adjusted analyses.

The changes in secondary outcomes at the week 68 are presented in Table II. The results did not support statistically significant differences in the changes from week 16 between Unloaders and Loaders, except for the second peak abductor moment that increased more among the Loaders (Table II). Both groups increased the peak tibiofemoral compression force during the maintenance period; the Loaders more so than the Unloaders ($P = 0.06$; Table II).

Sensitivity analyses

The cross-sectional correlations between the peak compression force and cartilage loss scores at week 16 and 68 were not significant ($r = 0.03$; $P = 0.696$ and $r = -0.09$; $P = 0.277$, respectively). Similar results were found regarding the KOOS4 (week16:$r = 0.08$; $P = 0.35$; week 68:$r = 0.05$; $P = 0.53$). When creating and comparing groups based on changes in joint compression from week 16–68, there were no statistically significant group differences in the changes in the primary and secondary outcomes (Appendix 2).

Discussion

This study showed that improvements in ambulatory knee function yielding increased peak knee joint compression forces

Table I
Variables at week 16 according to categorized biomechanical response to a 16 week weight loss intervention

	Mean (SD)*		Mean* difference (95% CI) (Unloaders–Loaders)	*P*-value
	Unloaders ($n = 100$)	Loaders ($n = 57$)		
Demographics				
Body mass, kg	87.7 (12.6)	89.3 (14.3)	−1.6 (−6.0; 2.7)	0.46
Height, m	1.66 (0.08)	1.67 (0.08)	−0.00 (−0.03; 0.03)	0.88
BMI, kg/m^2	31.7 (3.9)	32.2 (4.3)	−0.04 (−1.8; 0.9)	0.51
Symptom duration, y	8.9 (9.1)	9.2 (8.7)	−0.2 (−3.1; 2.7)	0.89
Age, y	62.5 (6.3)	63.5 (6.5)	−1.1 (−3.1; 1.0)	0.32
Gender, number of females (%)	83 (83%)	46 (81%)	n/a	0.72†
Alignment, degrees	5.7 (4.9)	5.9 (4.5)	−0.2 (−1.8; 1.4)	0.79
Kellgren/Lawrence, 0–4				
0, *n*(%)	0 (0%)	0 (0%)	n/a	0.19†
1, *n*(%)	8 (8%)	8 (14%)	n/a	
2, *n*(%)	34 (34%)	25 (44%)	n/a	
3, *n*(%)	42 (42%)	15 (26%)	n/a	
4, *n*(%)	16 (16%)	9 (16%)	n/a	
Primary outcomes				
Global max tibiofemoral cartilage loss, 0–3	2.0 (0.9)	1.8 (0.9)	0.1 (−0.1; 0.4)	0.34
KOOS4, 0–100	66.6 (16.4)	64.3 (17.1)	2.3 (−3.2; 7.7)	0.41
Secondary outcomes				
MRI				
Medial max tibiofemoral cartilage loss, 0–3	1.8 (1.0)	1.6 (1.0)	0.2 (−0.1; 0.5)	0.19
Lateral max tibiofemoral cartilage loss, 0–3	1.3 (0.7)	1.2 (0.6)	0.1 (−0.1; 0.3)	0.32
Global max tibiofemoral BML, 0–3	1.5 (1.0)	1.4 (0.9)	0.2 (−0.1; 0.5)	0.26
Medial max tibiofemoral BML, 0–3	1.1 (1.0)	1.0 (0.9)	0.1 (−0.2; 0.4)	0.52
Lateral max tibiofemoral BML, 0–3	0.3 (0.6)	0.4 (0.6)	−0.0 (−0.2; 0.2)	0.71
Patient reported				
KOOS pain, 0–100	69.5 (18.4)	68.7 (19.3)	0.8 (−5.3; 7.0)	0.79
KOOS symptoms, 0–100	72.9 (18.2)	69.1 (20.0)	3.8 (−2.4; 9.9)	0.23
KOOS activities of daily living, 0–100	73.9 (17.3)	72.4 (19.0)	1.4 (−4.4; 7.3)	0.63
KOOS sports and recreation, 0–100	33.0 (26.4)	31.8 (24.3)	1.2 (−7.2; 9.7)	0.77
KOOS quality of life, 0–100	50.1 (19.0)	47.0 (16.8)	3.1 (−2.9; 9.1)	0.31
Walking biomechanics				
Peak joint compression, N	2,378 (741)	2,647 (602)	−269 (−484; −54)	0.02
Walking speed, m/s	1.21 (0.17)	1.23 (0.20)	−0.02 (−0.08; 0.04)	0.50
Peak knee extensor moment, Nm	46.8 (23.7)	54.6 (18.0)	−7.9 (−14.5; −1.2)	0.02
Peak knee flexor moment, Nm	−13.2 (17.0)	−7.9 (16.5)	−5.4 (−10.9; 0.1)	0.06
First peak knee abduction moment, Nm	43.0 (17.7)	39.5 (15.7)	3.6 (−2.0; 9.1)	0.21
Second peak knee abduction moment, Nm	40.0 (17.1)	39.2 (16.8)	0.8 (−4.8; 6.4)	0.77
First peak knee rotator moment, Nm	−0.6 (1.0)	−0.5 (1.0)	0.1 (−0.4; 0.3)	0.76
Second peak knee rotator moment, Nm	14.2 (5.5)	14.0 (5.7)	0.2 (−1.6; 2.1)	0.79
Objective physical function				
6 MWD, m	485.6 (74.5)	496.4 (70.6)	−10.7 (−34.7; 13.3)	0.38

* Arithmetic mean.
† Frequencies tested using chi squared.

Table II
Changes from week 16 to week 68 in primary and secondary outcomes (i.e., after the 1-year maintenance period). Data are presented for patients grouped according to their biomechanical response to the 16 week weight loss program (Unloaders vs Loaders)

	Least squares means (SE)		Least squares means difference (95% CI) (Unloaders–Loaders)	*P*
	Unloaders ($n = 100$)	Loaders ($n = 57$)		
Primary outcomes				
Patient reported				
ΔKOOS4, 0–100*	−3.6 (1.2)	−2.3 (1.7)	−1.3 (−5.6; 3.0)	0.55
ΔKOOS4, 0–100†	−3.8 (1.5)	−1.4 (1.8)	−2.4 (−6.8; 1.9)	0.27
MRI				
ΔGlobal max tibiofemoral cartilage loss, 0–3†	0.01 (0.01)	0.07 (0.01)	−0.06 (−0.22; 0.10)	0.47
ΔGlobal max tibiofemoral cartilage loss, 0–3*	−0.06 (0.06)	0.00 (0.07)	−0.06 (−0.22; 0.11)	0.49
Secondary outcomes†				
Demographics				
ΔBody mass, kg†	4.9 (0.9)	6.3 (1.2)	−1.4 (−3.9; 1.1)	0.28
ΔBMI, kg/m^2†	1.5 (0.3)	2.0 (0.4)	−0.5 (−1.4; 0.4)	0.28
Patient reported				
ΔKOOS pain, 0–100†	−3.4 (1.8)	−0.8 (2.2)	−2.5 (−7.8; 2.7)	0.34
ΔKOOS symptoms, 0–100†	−3.3 (1.7)	−0.9 (2.1)	−2.3 (−7.3; 2.7)	0.36
ΔKOOS activities of daily living, 0–100†	−3.3 (1.7)	−3.1 (2.1)	−0.2 (−5.3; 4.9)	0.95
ΔKOOS sports and recreation, 0–100†	−6.5 (2.5)	−3.8 (3.0)	−2.7 (−10.0; 4.6)	0.46
ΔKOOS quality of life, 0–100†	−5.6 (2.0)	−0.9 (2.4)	−4.7 (−10.4; 1.0)	0.11
MRI				
ΔMedial max tibiofemoral cartilage loss, 0–3†	0.02 (0.05)	0.12 (0.07)	−0.10 (−0.26; 0.06)	0.23
ΔLateral max tibiofemoral cartilage loss, 0–3†	−0.01 (0.05)	−0.05 (0.06)	0.04 (−0.10; 0.19)	0.56
ΔGlobal max tibiofemoral BML, 0–3†	−0.12 (0.08)	−0.06 (0.10)	−0.06 (−0.30; 0.19)	0.65
ΔMedial max tibiofemoral BML, 0–3†	0.04 (0.06)	0.00 (0.08)	0.04 (−0.14; 0.23)	0.66
ΔLateral max tibiofemoral BML, 0–3†	0.06 (0.05)	−0.06 (0.06)	0.12 (−0.04; 0.27)	0.14
Walking biomechanics				
ΔPeak joint compression, N†	175.1 (67.8)	415.4 (96.3)	−240.4 (−491.1; 10.3)	0.06
ΔWalking speed, m/s†	−0.01 (0.01)	0.00 (0.02)	−0.01 (−0.05; 0.03)	0.61
ΔPeak knee extensor moment, Nm†	4.3 (2.2)	10.5 (2.7)	−6.2 (−13.6; 1.1)	0.10
ΔPeak knee flexor moment, Nm†	7.3 (1.6)	2.3 (1.9)	5.0 (−0.4; 9.7)	0.03
ΔFirst peak KAM, Nm†	−0.1 (1.1)	0.2 (1.3)	−0.3 (−3.4; 2.8)	0.84
ΔSecond peak KAM, Nm†	4.3 (1.0)	7.6 (1.2)	−3.3 (−6.1; 0.4)	0.03
ΔFirst peak knee rotator moment, Nm†	−0.4 (0.2)	−0.5 (0.2)	0.0 (0.4; −0.5)	0.91
ΔSecond peak knee rotator moment, Nm†	1.1 (0.4)	1.3 (0.4)	−0.2 (−1.3; 0.9)	0.70
Objective physical function				
Δ6 MWD, m†	−4.0 (10.9)	20.1 (13.5)	−24.0 (−56.3; 8.2)	0.14

* Basic analysis: adjusted for week 16 value and pre-weight loss peak compression force.
† Adjusted analysis: adjusted for week 16 value, pre-weight loss peak compression force, age, gender, week 16 BMI, and randomization in the underlying RCT.

after a 16 week weight loss program provided neither detriment nor improvement to structural or symptomatic disease progression 1 year later compared to participants that decreased peak knee joint compression forces.

The Unloaders' reductions in joint compression force were related to the weight loss magnitude and reduction in knee extensor moments suggesting reduced demands to the quadriceps – linked to lower body mass. As muscles are significant contributors to joint compression forces[39], the biomechanical response to weight loss among the Unloaders corresponds with the hypothesis of a relationship between weight and joint loads. In contrast, the Loaders increased joint compression significantly - despite significant weight loss – mainly caused by increased knee extensor moments, representing improved ambulatory knee function with enhanced employment of the quadriceps. Increasing knee extensor moments and walking speed typically follow each other – as in the present study. This shows that opposite responses in ambulatory mechanics can emerge from a treatment with a hypothesized mono-directional mechanism of action: Reducing joint loads. These opposite responses could indicate regression to the mean. While this is a true concern, we adjusted our analyses for the pre-weight loss value, which is known to be an effective way of handling potential regression to the mean[40].

Our findings are unexpected, as the Loaders were hypothesized to have larger structural and symptomatic deterioration. The present study does not provide insights into the underlying biological mechanisms, but there are some indications from existing literature that may provide hypothetical explanations. In support of our results, an animal study indicated that increased joint loading insufficiently explain the obesity–OA relationship[41]. Knee joint compressive forces during running range between 8 and 14 times body weight[42], yet the relationship between running and OA is unclear. In fact, moderate running has been indicated as chondroprotective[43]. Furthermore, weight bearing exercises may be beneficial for cartilage quality in individuals at risk of knee OA[44].

The peak knee abductor moment (KAM) is often used as proxy for dynamic loading of the medial compartment. Yet medial loads are mediated or enhanced by the knee extensor moment, because the combination of the KAM and the extensor moment is a better predictor of peak medial loads than the KAM alone[45]. The overall compression force is a composite and generic measure for loading, yet relates not only to the medial compartment. Significant changes in overall compression force indicate increasing medial and lateral compartment loads thus making it applicable for all tibiofemoral OA.

While dynamic loading of the knee joint is widely accepted as a risk factor for structural disease progression[9,10] the current evidence does not support dynamic loading modifications as effective to prevent structural progression over a 1-year follow-up[46]. Our results showed that increased loading did not yield detectable structural disease progression when compared to a

group with reduced joint loading. Further, the Loaders had higher loadings at week 16 and 68 (Table I&II). This is in contrast to studies that indicate high dynamic loading as a risk factor for progression[9,10]. However, these studies are based on cross-sectional data, whereas the present study assessed longitudinal changes. Further, these studies had either a longer follow-up[9] or used a dynamic load measure that can increase with reduced walking speed (KAM impulse[25]) and it is uncertain if the results were related to increased load or reduced walking speed in patients with more severe OA[10]. Thus, the selection of the load measure and the length of follow-up are important in the interpretation of these data.

Many parameters in ambulatory biomechanics are intimately coupled and their role in knee OA may interact with other factors. It is very likely that the effects of joint compression modifications are confounded by other factors (including phenotypic, hormonal, biomechanical etc.) that are unaltered by load modifying interventions. The relevant modifiable factors associated with changes in knee biomechanics – and their interactions – are yet to be identified.

This is the first study to assess the effects of increased joint loads on symptomatic and structural disease progression in knee OA, and therefore we cannot compare our results directly to other studies. Pain relief has been shown to increase joint loadings during walking[21–23,47], leading to speculations about accelerated joint destruction. Also, exercise improves pain and physical disability[48]. According to the prevailing theory about increased joint loading, improvements in pain and function should lead to accelerated disease progression. However, no long-term follow-up studies on structural deterioration associated with pain relief exist in spite of extensive research on pharmacological pain relief and exercise for knee OA. In this study both groups had similar pain reductions and similar structural changes over 1 year in spite of substantial differences in the change in load from pre-weight loss to the final assessment.

This study has strengths and limitations. An important strength is the blinded nature of our results. Both participants and study staff were blinded to the “group allocation” as they were not aware of the biomechanical response at anytime during the study. This is an advantage with respect to other studies of mechanical interventions that are very difficult to blind effectively. A further strength is the large change in joint loads in both groups (Unloaders: −18% and Loaders: +19%) although the within-group dispersions also were quite large. No data exist on the magnitude of clinically relevant load changes, and in spite of large changes, identification of magnitude and direction of joint load changes that yield clinically relevant changes in symptoms and structural disease parameters was not possible. The changes are larger than previous changes after weight loss[18,19], which might have been influenced by a similar Unloader/Loader response regressing the average change.

A limitation is the applied knee model that is subject to assumptions that might influence the results. Importantly, it does not allow co-activation between knee extensors and flexors, which may underestimate the magnitude of the knee compression force. Further, the patellofemoral joint is not included, but we did not assess structural changes in that region. Yet, it is likely that similar biomechanical responses would occur due to the close association between patellofemoral compression and knee extensor employment. There are many other ways to express joint loads and we cannot rule out that changes in other indices of joint loads may have pathomechanical significance in knee OA. It may even be speculated that there may be “good” and “bad” loading, but the characteristics and causal mechanisms behind such qualitative labels remain to be illuminated.

The lack of group differences could be a reflection that the study is underpowered. However, the group sizes and observed variations allow for detections of mean differences of eight KOOS4 points and 0.45 cartilage loss score points with a statistical power above 80%, corresponding to effect sizes of 0.48 and 0.50, respectively. These differences would be both clinically relevant and plausible.

Because of the limited contrast between fluid and cartilage using the Flash MRI sequence, smaller cartilage losses are easily missed, which is a limitation. In an attempt to partially compensate for this we compared the Flash and dual spin echo images to verify cartilage lesion scores. Also, the semi quantitative assessment (BLOKS) of structural changes might not be sensitive to changes over 1 year, as it has only been tested after 2 years follow-up[49]. Nor will detailed within-grade structural changes be detected using this method. Furthermore, fluctuations in walking biomechanics over 1 year may blur the effects on symptoms and structures. Moreover, changes in habitual physical activity may affect structural progression[50], but unfortunately we did not assess physical activity. However, our results are robust to different statistical models and sensitivity analyses.

This study was based on weight loss as a means to improve pain and disability with implications for knee biomechanics assuming that weight loss mainly works through mechanical unloading of the knee[13]. Our results suggest that the primary effects of weight loss are not through mechanical unloading, but are the result of interactive effects with other factors. It is important to stress that these data do not imply weight loss as ineffective in knee OA, because it has repeatedly been shown that weight loss causes symptomatic relief[14,20,51,52] with effect sizes comparable to other interventions[15]. Furthermore, weight loss is generally associated with desirable ‘side effects’ such as improved physical performance[53], and reductions in morbidity and mortality. Weight loss should therefore be advocated in persons with obesity/overweight and knee OA.

Importantly, our results suggest that care must be taken when developing a theoretical framework on which biomechanical interventions in knee OA are considered. Our results indicate that improvements in ambulatory knee function associated with increased joint loads are safe in terms of detectable symptomatic and structural progression of knee OA over 1 year in obese patients. However, generalization to all types of OA interventions or for longer term perspectives is premature.

In conclusion, our study showed that for obese patients with knee OA, improving ambulation (by weight loss) with concomitant increased knee joint loading (Loaders) produced no detectable difference in the rate of symptomatic and structural disease progression over 1 year relative to a similar weight loss group (Unloaders) that had reduced ambulatory load.

Author contributions

The authors have made the following contributions to this manuscript. Marius Henriksen is responsible for the integrity of the work.

Marius Henriksen: Conception, design, data acquisition, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

David Hunter: Analysis and interpretation, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Erik B Dam: Analysis and interpretation, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Stephen P Messier: Analysis and interpretation, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Thomas P Andriacchi: Analysis and interpretation, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

L Stefan Lohmander: Study conception and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Jens Aaboe: Conception, data acquisition, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Mikael Boesen: Conception, data acquisition, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Henrik Gudbergsen: Conception, data acquisition, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Henning Bliddal: Conception, design, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Robin Christensen. Conception, design, analysis and interpretation, manuscript drafting, critical revision of the manuscript for important intellectual content, final approval of the manuscript.

Role of the funding source

The sponsors did not play any role in the study, design, collection, analysis, or interpretation of data; nor in the writing of the manuscript or decision to submit the manuscript for publication.

Conflict of interest

No conflicts of interest are declared.

Acknowledgments

This study was supported by grants from the Oak Foundation, the Velux Foundation, the Cambridge Weight Plan, the Danish Rheumatism Association, the Augustinus Foundation, the A. P. Møller Foundation for the Advancement of Medical Science, the Hørslev Fonden, the Bjarne Jensens Fond, the Danish Research Foundation, and the Aase og Ejnar Danielsens Foundation.

Appendix 1

Cross-sectional data at week 0, 16 and 68 according to groups based on changes in joint loading from week 0 till 16 (Unloaders and Loaders).

	Unloaders ($n = 100$)			Loaders ($n = 57$)		
	Week 0	Week 16	Week 68	Week 0	Week 16	Week 68
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Body mass, kg	102.3 (1.4)	87.7 (12.6)	91.7 (15.7)	102.4 (1.9)	89.3 (14.3)	94.8 (15.3)
BMI, kg/m^2	36.9 (0.4)	31.7 (3.9)	33.1 (5.0)	36.9 (0.6)	32.2 (4.3)	34.2 (5.0)
Primary outcomes						
Global max tibiofemoral cartilage loss, 0–3	2.0 (0.8)	2.0 (0.9)	1.9 (0.9)	1.9 (0.9)	1.8 (0.9)	1.8 (0.9)
KOOS4, 0–100	56.1 (1.3)	66.6 (16.4)	62.8 (17.2)	52.2 (2.0)	64.3 (17.1)	62.4 (17.5)
Secondary and explanatory outcomes						
MRI						
Medial max tibiofemoral cartilage loss, 0–3	1.9 (0.9)	1.8 (1.0)	1.8 (1.0)	1.6 (1.1)	1.6 (1.0)	1.5 (1.1)
Lateral max tibiofemoral cartilage loss, 0–3	1.4 (0.6)	1.3 (0.7)	1.3 (0.7)	1.3 (0.6)	1.2 (0.6)	1.3 (0.6)
Global max tibiofemoral BML, 0–3	1.7 (1.0)	1.5 (1.0)	1.6 (1.0)	1.5 (1.0)	1.4 (0.9)	1.3 (0.8)
Medial max tibiofemoral BML, 0–3	1.2 (1.1)	1.1 (1.0)	1.1 (1.0)	1.1 (1.1)	1.0 (0.9)	1.0 (1.0)
Lateral max tibiofemoral BML, 0–3	0.4 (0.8)	0.3 (0.6)	0.3 (0.6)	0.5 (0.8)	0.4 (0.6)	0.5 (0.7)
Patient reported						
KOOS pain, 0–100	59.2 (1.5)	69.5 (18.4)	66.7(19.3)	56.0 (2.3)	68.7 (19.3)	67.0 (20.1)
KOOS symptoms, 0–100	63.0 (1.6)	72.9 (18.2)	68.0 (20.2)	58.1 (2.3)	69.1 (20.0)	67.6 (20.3)
KOOS activities of daily living, 0–100	62.6 (1.5)	73.9 (17.3)	70.7 (18.0)	57.9 (2.4)	72.4 (19.0)	68.8 (20.6)
KOOS sports and recreation, 0–100	23.2 (2.0)	33.0 (26.4)	29.6 (23.1)	20.4 (2.4)	31.8 (24.3)	28.7 (26.3)
KOOS quality of life, 0–100	39.6 (1.5)	50.1 (19.0)	45.8 (20.4)	36.6 (2.2)	47.0 (16.8)	46.1 (17.0)
Walking biomechanics						
Peak joint compression, N	2,886 (80.6)	2,378 (741)	2,728 (734)	2,222 (61.9)	2,647 (602)	2785 (702)
Walking speed, m/s	1.20 (0.02)	1.21 (0.17)	1.22 (0.16)	1.12 (0.02)	1.23 (0.20)	1.22 (0.18)
Peak knee extensor moment, Nm	57.0 (2.9)	46.8 (23.7)	57.4 (21.7)	39.4 (2.0)	54.6 (18.0)	57.1 (21.8)
Peak knee flexor moment, Nm	−8.3 (2.2)	−13.2 (17.0)	−5.1 (15.2)	−15.7 (2.0)	−7.9 (16.5)	−6.5 (17.0)
First peak knee abduction moment, Nm	48.6 (2.0)	43.0 (17.7)	41.7 (16.0)	46.9 (2.4)	39.5 (15.7)	40.1 (14.6)
Second peak knee abduction moment, Nm	44.5 (2.0)	40.0 (17.1)	43.1 (20.1)	42.6 (2.6)	39.2 (16.8)	44.9 (16.0)
First peak knee rotator moment, Nm	−0.7 (0.1)	−0.6 (1.0)	−1.0 (1.5)	−0.4 (0.1)	−0.5 (1.0)	−0.9 (1.1)
Second peak knee rotator moment, Nm	16.4 (0.7)	14.2 (5.5)	15.5 (6.1)	15.2 (0.8)	14.0 (5.7)	15.1 (5.5)
Objective physical function						
6 MWD, m	448.6 (72.3)	485.6 (74.5)	485.3 (84.1)	478.1 (74.6)	496.4 (70.6)	506.1 (85.3)

Appendix 2

Sensitivity analysis: changes in primary and secondary outcomes from week 16 to week 68 (i.e., after a 1-year maintenance period following a 16 week weight loss intervention). Data are presented for patients grouped according to their changes in peak compression forces from week 16 to week 68. The 'Unloaders$_{16-68}$' group represents participants that during the 52 weeks decreased their peak compression force during walking. The 'Loaders$_{16-68}$' group represents participants that during the 52 weeks increased their peak compression force during walking.

	Least squares means (SE)		Least squares means difference (95% CI) (Unloaders$_{16-68}$–Loaders$_{16-68}$)	*P*
	Unloaders$_{16-68}$ ($n = 45$)	Loaders$_{16-68}$ ($n = 112$)		
Primary outcomes				
ΔKOOS4, 0–100‡	−2.8 (1.9)	−2.8 (1.4)	−0.0 (−4.2:4.2)	0.99
ΔGlobal max tibiofemoral cartilage loss, 0–3‡	0.05 (0.07)	0.02 (0.05)	0.03 (−0.13:0.19)	0.69
Secondary outcomes‡				
Demographics				
ΔBody mass, kg	4.3 (1.1)	5.8 (0.9)	−1.4 (−3.8:0.9)	0.23
ΔBMI, kg/m^2	1.3 (0.4)	1.9 (0.3)	−0.5 (−1.4:0.3)	0.23
Patient reported				
ΔKOOS pain, 0–100	−1.5 (2.3)	−2.8 (1.7)	1.3 (−3.7:6.4)	0.60
ΔKOOS symptoms, 0–100	−0.8 (2.2)	−3.1 (1.6)	2.3 (−2.5:7.1)	0.35
ΔKOOS activities of daily living, 0–100	−2.6 (2.2)	−3.5 (1.6)	0.8 (−4.0:5.7)	0.73
ΔKOOS sports and recreation, 0–100	−7.9 (3.1)	−4.3 (2.3)	−3.6 (−10.6:3.3)	0.31
ΔKOOS quality of life, 0–100	−6.9 (2.5)	−2.3 (1.8)	−4.6 (−10.1:0.8)	0.10
MRI				
ΔMedial max tibiofemoral cartilage loss, 0–3	−0.02 (0.07)	−0.08 (0.05)	0.6 (−0.10:0.21)	0.45
ΔLateral max tibiofemoral cartilage loss, 0–3	−0.03 (0.06)	−0.02 (0.05)	0.01 (−0.13:0.15)	0.88
ΔGlobal max tibiofemoral BML, 0–3	−0.18 (0.11)	−0.06 (0.08)	0.12 (−0.11:0.36)	0.31
ΔMedial max tibiofemoral BML, 0–3	0.03 (0.08)	0.03 (0.06)	−0.0 (−0.18:0.17)	0.96
ΔLateral max tibiofemoral BML, 0–3	0.01 (0.07)	0.02 (0.05)	0.0 (−0.15:0.16)	0.93
Objective physical function				
Δ6 MWD, m	2.4 (13.8)	6.5 (10.3)	−4.1 (−34.7:26.6)	0.79
Explanatory variables‡				
Walking biomechanics				
ΔPeak joint compression, N	−322.5 (53.8)	519.7 (38.6)	−842.1 (−961.7:−722.6)	<0.0001
ΔWalking speed, m/s	−0.07 (0.01)	0.03 (0.01)	−0.10 (−0.13:−0.07)	<0.0001
ΔPeak knee extensor moment, Nm	−8.4 (1.9)	14.3 (1.4)	−22.7 (−27.0:−18.4)	<0.0001
ΔPeak knee flexor moment, Nm	1.3 (2.0)	7.3 (1.5)	−6.0 (−10.4:−1.6)	0.008
ΔFirst peak KAM, Nm	1.8 (1.3)	−0.9 (1.0)	2.7 (−0.2:5.6)	0.07
ΔSecond peak KAM, Nm	5.8 (1.3)	5.4 (1.0)	0.4 (−2.4:3.1)	0.80
ΔFirst peak knee rotator moment, Nm	−0.2 (0.2)	−0.5 (0.1)	0.3 (−0.1:0.7)	0.18
ΔSecond peak knee rotator moment, Nm	0.5 (0.5)	1.4 (0.3)	−0.9 (−1.9:0.1)	0.08

‡Adjusted analysis: adjusted for baseline value, pre-weight loss (week 0) peak compression force, age, gender, week 16 BMI, and randomization in the underlying RCT.

References

1. Andriacchi TP, Mündermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Curr Opin Rheumatol 2006 Sep;18(5):514–8.
2. Baliunas AJ, Hurwitz DE, Ryals AB, Karrar A, Case JP, Block JA, *et al*. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthritis Cartilage 2002 Jul;10(7):573–9.
3. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H. Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. Arthritis Care Res (Hoboken) 2010 Apr;62(4):501–9.
4. Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum 2005 Sep;52(9):2835–44.
5. Hurwitz DE, Sumner DR, Andriacchi TP, Sugar DA. Dynamic knee loads during gait predict proximal tibial bone distribution. J Biomech 1998 May;31(5):423–30.
6. Bennell KL, Creaby MW, Wrigley TV, Bowles KA, Hinman RS, Cicuttini F, *et al*. Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis. Ann Rheum Dis 2010 Jun;69(6):1151–4.
7. Vanwanseele B, Eckstein F, Smith RM, Lange AK, Foroughi N, Baker MK, *et al*. The relationship between knee adduction moment and cartilage and meniscus morphology in women with osteoarthritis. Osteoarthritis Cartilage 2010 Jul;18(7):894–901.
8. Creaby MW, Wang Y, Bennell KL, Hinman RS, Metcalf BR, Bowles KA, *et al*. Dynamic knee loading is related to cartilage defects and tibial plateau bone area in medial knee osteoarthritis. Osteoarthritis Cartilage 2010 Nov;18(11):1380–5.
9. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 2002 Jul;61(7):617–22.
10. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011 Oct;70(10):1770–4.
11. Lohmander LS, Gerhardsson d V, Rollof J, Nilsson PM, Engstrom G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann Rheum Dis 2009 Apr;68(4):490–6.
12. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord 2001 May;25(5):622–7.
13. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted!. Ann Rheum Dis 2006 Nov;65(11):1403–5.
14. Richette P, Poitou C, Garnero P, Vicaut E, Bouillot JL, Lacorte JM, *et al*. Benefits of massive weight loss on symptoms, systemic

inflammation and cartilage turnover in obese patients with knee osteoarthritis. Ann Rheum Dis 2011 Jan;70(1):139–44.
15. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007 Apr;66(4):433–9.
16. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage 2008 Feb;16(2):137–62.
17. Aaboe J, Bliddal H, Messier SP, Alkjaer T, Henriksen M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. Osteoarthritis Cartilage 2011 Jul;19(7):822–8.
18. Messier SP, Gutekunst DJ, Davis C, DeVita P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis Rheum 2005 Jul;52(7):2026–32.
19. Messier SP, Legault C, Loeser RF, Van Arsdale SJ, Davis C, Ettinger WH, *et al*. Does high weight loss in older adults with knee osteoarthritis affect bone-on-bone joint loads and muscle forces during walking? Osteoarthritis Cartilage 2011 Mar;19(3):272–80.
20. Riecke BF, Christensen R, Christensen P, Leeds AR, Boesen M, Lohmander LS, *et al*. Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial. Osteoarthritis Cartilage 2010 Jun;18(6):746–54.
21. Henriksen M, Simonsen EB, Alkjaer T, Lund H, Graven-Nielsen T, Danneskiold-Samsoe B, *et al*. Increased joint loads during walking - a consequence of pain relief in knee osteoarthritis. Knee 2006 Sep 28;13:445–50.
22. Schnitzer TJ, Popovich JM, Andersson GB, Andriacchi TP. Effect of piroxicam on gait in patients with osteoarthritis of the knee. Arthritis Rheum 1993 Sep;36(9):1207–13.
23. Hurwitz DE, Ryals AR, Block JA, Sharma L, Schnitzer TJ, Andriacchi TP. Knee pain and joint loading in subjects with osteoarthritis of the knee. J Orthop Res 2000 Jul;18(4):572–9.
24. Mündermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis Rheum 2004 Apr;50(4):1172–8.
25. Robbins SM, Maly MR. The effect of gait speed on the knee adduction moment depends on waveform summary measures. Gait Posture 2009 Nov;30(4):543–6.
26. Landry SC, McKean KA, Hubley-Kozey CL, Stanish WD, Deluzio KJ. Knee biomechanics of moderate OA patients measured during gait at a self-selected and fast walking speed. J Biomech 2007;40(8):1754–61.
27. Christensen P, Bliddal H, Riecke BF, Leeds AR, Astrup A, Christensen R. Comparison of a low-energy diet and a very low-energy diet in sedentary obese individuals: a pragmatic randomized controlled trial. Clin Obes 2011 Mar 21;1:31–40.
28. Hunter DJ, Lo GH, Gale D, Grainger AJ, Guermazi A, Conaghan PG. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). Ann Rheum Dis 2008 Feb;67(2):206–11.
29. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)–development of a self-administered outcome measure. J Orthop Sports Phys Ther 1998 Aug;28(2):88–96.
30. Gudbergsen H, Lohmander LS, Jones G, Christensen R, Bartels EM, Danneskiold-Samsoe B, *et al*. Correlations between radiographic assessments and MRI features of knee osteoarthritis – a cross-sectional study. Osteoarthritis Cartilage 2013 Apr;21(4):535–43.
31. 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 Aug;19(8):990–1002.
32. Enright PL, McBurnie MA, Bittner V, Tracy RP, McNamara R, Arnold A, *et al*. The 6-min walk test: a quick measure of functional status in elderly adults. Chest 2003 Feb;123(2):387–98.
33. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991 Jan;9(1):113–9.
34. Draganich LF, Andriacchi TP, Andersson GB. Interaction between intrinsic knee mechanics and the knee extensor mechanism. J Orthop Res 1987;5(4):539–47.
35. Messier SP, Legault C, Mihalko S, Miller GD, Loeser RF, DeVita P, *et al*. The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. BMC Musculoskelet Disord 2009;10:93.
36. Boyer KA, Angst MS, Asay J, Giori NJ, Andriacchi TP. Sensitivity of gait parameters to the effects of anti-inflammatory and opioid treatments in knee osteoarthritis patients. J Orthop Res 2012 Jul;30(7):1118–24.
37. Vandenbroucke JP, von EE, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 2007 Oct 16;147(8):W163–94.
38. Rochon PA, Gurwitz JH, Sykora K, Mamdani M, Streiner DL, Garfinkel S, *et al*. Reader's guide to critical appraisal of cohort studies: 1. Role and design. BMJ 2005 Apr 16;330(7496):895–7.
39. Pandy MG, Andriacchi TP. Muscle and joint function in human locomotion. Annu Rev Biomed Eng 2010 Aug 15;12:401–33.
40. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol 2005 Feb;34(1):215–20.
41. Griffin TM, Huebner JL, Kraus VB, Yan Z, Guilak F. Induction of osteoarthritis and metabolic inflammation by a very high-fat diet in mice: effects of short-term exercise. Arthritis Rheum 2012 Feb;64(2):443–53.
42. Scott SH, Winter DA. Internal forces of chronic running injury sites. Med Sci Sports Exerc 1990 Jun;22(3):357–69.
43. Van Ginckel A, Baelde N, Almqvist KF, Roosen P, McNair P, Witvrouw E. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC). Osteoarthritis Cartilage 2010 Dec;18(12):1564–9.
44. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum 2005 Nov;52(11):3507–14.
45. Walter JP, D'Lima DD, Colwell Jr CW, Fregly BJ. Decreased knee adduction moment does not guarantee decreased medial contact force during gait. J Orthop Res 2010 Oct;28(10):1348–54.
46. Bennell KL, Bowles KA, Payne C, Cicuttini FM, Williamson E, Forbes A, *et al*. Effects of lateral wedge insoles on symptoms and structural disease progression in medial knee

osteoarthritis: a 12-month randomised controlled trial. Osteoarthritis Cartilage 2010 Oct;18(Suppl 2):S11.
47. Shrader MW, Draganich LF, Pottenger LA, Piotrowski GA. Effects of knee pain relief in osteoarthritis on gait and stair-stepping. Clin Orthop 2004 Apr;421:188–93.
48. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010 Apr;18(4):476–99.
49. Felson DT, Lynch J, Guermazi A, Roemer FW, Niu J, McAlindon T, *et al*. Comparison of BLOKS and WORMS scoring systems part II. Longitudinal assessment of knee MRIs for osteoarthritis and suggested approach based on their performance: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2010 Nov;18(11):1402–7.
50. Dore DA, Winzenberg TM, Ding C, Otahal P, Pelletier JP, Martel-Pelletier J, *et al*. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis 2013 Jul;72(7):1170–5.
51. Messier SP, Loeser RF, Miller GD, Morgan TM, Rejeski WJ, Sevick MA, *et al*. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004 May;50(5):1501–10.
52. Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis 2011 Oct;70(10):1798–803.
53. Miller GD, Nicklas BJ, Davis C, Loeser RF, Lenchik L, Messier SP. Intensive weight loss program improves physical function in older obese adults with knee osteoarthritis. Obesity (Silver Spring) 2006 Jul;14(7):1219–30.