

Preliminary Communication

Effects of Intensive Diet and Exercise on Knee Joint Loads, Inflammation, and Clinical Outcomes Among Overweight and Obese Adults With Knee Osteoarthritis

The IDEA Randomized Clinical Trial

Stephen P. Messier, PhD; Shannon L. Mihalko, PhD; Claudine Legault, PhD; Gary D. Miller, PhD; Barbara J. Nicklas, PhD; Paul DeVita, PhD; Daniel P. Beavers, PhD; David J. Hunter, MBBS, PhD; Mary F. Lyles, MD; Felix Eckstein, MD; Jeff D. Williamson, MD; J. Jeffery Carr, MD; Ali Guermazi, MD, PhD; Richard F. Loeser, MD

 Supplemental content at jama.com

IMPORTANCE Knee osteoarthritis (OA), a common cause of chronic pain and disability, has biomechanical and inflammatory origins and is exacerbated by obesity.

OBJECTIVE To determine whether a $\geq 10\%$ reduction in body weight induced by diet, with or without exercise, would improve mechanistic and clinical outcomes more than exercise alone.

DESIGN, SETTING, AND PARTICIPANTS Single-blind, 18-month, randomized clinical trial at Wake Forest University between July 2006 and April 2011. The diet and exercise interventions were center-based with options for the exercise groups to transition to a home-based program. Participants were 454 overweight and obese older community-dwelling adults (age ≥ 55 years with body mass index of 27-41) with pain and radiographic knee OA.

INTERVENTIONS Intensive diet-induced weight loss plus exercise, intensive diet-induced weight loss, or exercise.

MAIN OUTCOMES AND MEASURES Mechanistic primary outcomes: knee joint compressive force and plasma IL-6 levels; secondary clinical outcomes: self-reported pain (range, 0-20), function (range, 0-68), mobility, and health-related quality of life (range, 0-100).

RESULTS At 18 months, 399 participants (88%) completed the study. Compared with exercise participants, knee compressive forces were lower in diet participants and IL-6 levels were lower in diet and diet + exercise participants.

	18-mo Outcomes, Mean (95% CI)			Difference, E vs D	Difference, E vs D+E
	Exercise (E)	Diet (D)	D + E		
Weight loss, kg	-1.8 (-5.7 to 1.8)	-8.9 (-12.4 to -5.3)	-10.6 (-14.1 to -7.1)		
Knee compressive forces, N	2687 (2590 to 2784)	2487 (2393 to 2581)	2543 (2448 to 2637)	200 (55 to 345) ^a	144 (1 to 287)
IL-6, pg/mL	3.1 (2.9 to 3.4)	2.7 (2.4 to 3.0)	2.7 (2.5 to 3.0)	0.43 (0.01 to 0.85) ^a	0.39 (-0.03 to 0.81) ^a
Pain	4.7 (4.2 to 5.1)	4.8 (4.3 to 5.2)	3.6 (3.2 to 4.1)	-0.11 (-0.81 to 0.59)	1.02 (0.33 to 1.71) ^a
Function	18.4 (16.9 to 19.9)	17.4 (15.9 to 18.9)	14.1 (12.6 to 15.6)	0.98 (-1.24 to 3.20)	4.29 (2.07 to 6.50) ^a
SF-36 physical	41.9 (40.5 to 43.2)	42.4 (41.1 to 43.7)	44.7 (43.4 to 46.0)	-0.55 (-2.53 to 1.43)	-2.81 (-4.76 to -0.86) ^a

^aDifferences were significant.

CONCLUSIONS AND RELEVANCE Among overweight and obese adults with knee OA, after 18 months, participants in the diet + exercise and diet groups had more weight loss and greater reductions in IL-6 levels than those in the exercise group; those in the diet group had greater reductions in knee compressive force than those in the exercise group.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00381290

JAMA. 2013;310(12):1263-1273. doi:10.1001/jama.2013.277669

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Stephen P. Messier, PhD, J. B. Snow Biomechanics Laboratory, Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC 27109 (messier@wfu.edu).

Osteoarthritis (OA) is the leading cause of chronic disability among older adults. Knee OA is the most frequent cause of mobility dependency and diminished quality of life,¹ and obesity is a major risk factor for knee OA.² Current treatments for knee OA are inadequate; of patients treated pharmacologically, only about half experience a 30% pain reduction, usually without improved function.³ The few studies of long-term weight loss in obese adults with knee OA showed equally modest improvements.^{4,5}

Knee OA is considered an active disease process with joint destruction driven by both biomechanical and proinflammatory factors.⁶ *In vitro*⁷ and *in vivo*⁸ animal models elucidate specific mechanical and biological factors that affect cartilage degradation and tissue changes associated with cartilage growth and remodeling. However, clinical studies are the best vehicle for determining the physiological basis of the biomechanical factors that affect OA pathogenesis and treatment.^{6,9}

Considering the adverse effects of drug therapy, the limited efficacy of surgical intervention in mild-to-moderate cases,¹⁰ and the long-term public health benefits of an effective treatment for OA and obesity-related complications,¹¹ we tested the hypothesis that achieving sustained, significant weight loss, with or without increased exercise, would reduce joint loading and inflammation and improve clinical outcomes more than increased exercise alone. This translational study compared the effects of diet-induced weight loss plus exercise (D+E), diet-induced weight loss only (D), and exercise-only (E) interventions on mechanistic outcomes (knee-joint compressive force, IL-6 levels) and clinical outcomes (pain, function, mobility, health-related quality of life [HRQL]) in overweight and obese adults with knee OA.

Methods

Study Design

Intensive Diet and Exercise for Arthritis (IDEA) was a single-blind, single-center, 18-month, randomized controlled trial. Participants were randomized into 1 of 3 groups: D+E, D, or E. We designated E as the comparison group because our work¹² indicated that aerobic walking or resistance training should be part of the standard of care for knee OA patients. Interventionists' responsibilities were limited to exercise and dietary therapy interactions with patients (no data collection). Personnel responsible for data collection without intervention responsibilities were blinded to group assignment. Trial design and rationale are detailed elsewhere.¹³

IDEA was conducted at Wake Forest University and Wake Forest School of Medicine between July 2006 and April 2011. The study was approved by the human subjects committee of Wake Forest Health Sciences. Informed consent was obtained in writing from all participants.

The sample consisted of ambulatory, community-dwelling persons age 55 years or older with the following: Kellgren-Lawrence¹⁴ grade 2 or 3 (mild or moderate) radiographic tibiofemoral OA or tibiofemoral plus patellofemoral OA of one or both knees, pain on most days due to knee OA, a body

mass index (BMI) from 27 through 41 (calculated as weight in kilograms divided by height in meters squared), and a sedentary lifestyle (<30 minutes per week of formal exercise for the past 6 months). Participants maintained and adjusted their usual medications as needed with their physicians' consent. Eligibility, sample size calculations, and screening measurements are detailed elsewhere.¹³ Race/ethnicity was determined by self-report. Participants chose between white/Caucasian (not Hispanic), black or African American (not Hispanic), Hispanic, Asian or Pacific Islander, American Indian, or Alaskan native. Effort was made to recruit a sample population that was representative of the racial/ethnic demographics of the local area.

Participants were recruited between November 2006 and December 2009. Eligibility was determined by initial phone screen and 2 in-person screening visits.¹³ A stratified-block randomization method was used to assign all eligible persons to 1 of the 3 intervention groups, stratified by BMI and sex.

Interventions

The D group received the weight loss intervention, the E group received the exercise intervention, and the D+E group received both.

Intensive Weight Loss Intervention

The goal of this intervention was a mean group loss of at least 10% of baseline weight, with a desired range between 10% and 15%. The diet was based on partial meal replacements, including up to 2 meal-replacement shakes per day (Lean Shake; General Nutrition Centers). For the third meal, participants followed a weekly menu plan and recipes that were 500 to 750 kcal, low in fat, and high in vegetables. Daily caloric intake was adjusted according to the rate of weight change between intervention visits.

The initial diet plan provided an energy-intake deficit of 800 to 1000 kcal/day as predicted by energy expenditure (estimated resting metabolism \times 1.2 activity factor) with at least 1100 kcal for women and 1200 kcal for men. The calorie distribution goal was 15% to 20% from protein, less than 30% from fat, and 45% to 60% from carbohydrates, consistent with the Dietary Reference Intakes for Energy and Macronutrients¹⁵ and successful weight loss programs.¹⁶ As follow-up progressed, fewer meal replacements were consumed. Body weight was monitored weekly or biweekly during nutrition education and behavioral sessions: from months 1 through 6, 1 individual session and 3 group sessions per month, and from months 7 through 18, biweekly group sessions and an individual session every 2 months.

Exercise Intervention

The exercise intervention was conducted for 1 hour on 3 days/week for 18 months. During the first 6 months, participation was center-based. After 6-month follow-up testing and a 2-week transition phase, participants could remain in the facility program, opt for a home-based program, or combine the two. The program consisted of aerobic walking (15 minutes), strength training (20 minutes), a second aerobic phase (15 minutes), and cool-down (10 minutes).

Techniques to Improve Adherence

Diet and exercise interventionists were trained in behavioral techniques based on social cognitive theory and group dynamics.^{17,18} Adherence data were reviewed regularly to identify participants who needed additional counseling. Participants in both the D and E interventions monitored themselves by completing daily logs. A behavioral “toolbox” for participants in the D+E and D groups who had difficulty achieving the weight loss goal included additional individual and group counseling, social support, and incentives.

Measurements and Procedures

All participants were tested at baseline, 6 months, and 18 months. An initial symptom-limited, maximum exercise stress test excluded anyone with severe manifestations of coronary heart disease. The Modified Mini-Mental State Exam screened for cognitive deficiencies,¹⁹ and persons scoring less than 70 at baseline were ineligible.

Bone-on-bone peak tibiofemoral (knee) compressive force was the primary measure of knee joint loading. Instruments and knee joint compressive force calculations are described in the eMethods in the Supplement and elsewhere.²⁰

Blood samples were collected in the early morning after a 10-hour fast at baseline, 6 months, and 18 months. The 6- and 18-month samples were collected at least 24 hours after the last acute bout of exercise training (D+E and E groups) and sampling was postponed (1-2 weeks after recovery from symptoms) in the event of an acute respiratory, urinary tract, or other infection. All blood was collected, processed, divided into aliquots, and stored at -80°C until analysis.

The inflammation measure was plasma IL-6 in pg/mL. This cytokine is implicated in OA pathogenesis and showed significant improvement with weight loss in the Arthritis Diet and Activity Promotion Trial (ADAPT).²¹ All samples were measured in duplicate using enzyme-linked immunosorbent assays (Quantikine ELISA kits; R&D Systems) with the average used for data analyses.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale was used to measure self-reported pain.²² Participants indicated on a scale from 0 (none) to 4 (extreme) the degree of pain experienced while performing daily living activities in the last 48 hours due to knee OA. Total scores for the 5 items range from 0 to 20; higher scores indicate greater pain.^{22,23} Individual scores on the 17 items of the WOMAC self-reported function subscale were added to generate a summary score ranging from 0 to 68; higher scores indicate poorer function. A minimally clinically important difference of at least 20% improvement from baseline is required for both pain and function.²⁴ We used the 36-item short-form (SF-36)²⁵ to measure HRQL using 2 broad summary scores: physical and mental health, scaled from 0 (worst) to 100 (best).

We measured gait speed (m/s) and 6-minute walk distance (m).²⁶ Weight, height, and BMI were obtained at baseline, 6 months, and 18 months using standard techniques. D+E and D participants were weighed at each scheduled nutrition education and behavioral session. Whole body lean mass and fat mass were measured at baseline and 18 months by dual x-ray absorptiometry using a fan-beam scanner (Delphi A; Hologic)

and the manufacturer’s recommendations for patient positioning, scanning, and analysis. We used bilateral, posterior-anterior, weight-bearing knee x-rays to identify tibiofemoral OA and sunrise views to identify patellofemoral OA. To visualize the tibiofemoral joint, we used a positioning device to flex knees 15° , with the beam centered on the joint space.

Statistical Analysis

Primary outcomes for IDEA were IL-6 level and knee compressive force. Values for IL-6 were log-transformed for sample size calculations and analyses. Standard deviations were obtained from the ADAPT⁴ study, which measured the same outcomes in a similar population. The sample size of 150 participants per group was calculated based on both primary outcomes to obtain 80% power to detect a 20% difference in IL-6 group mean ratios at month 18 and a 15% between-group mean difference in knee compressive force at the .008 significance level adjusted for 2 outcomes, 3 treatment groups, and 80% retention. This sample size also provided 80% power for mean differences in secondary outcomes of 2.9 for WOMAC function and 1.0 in WOMAC pain at the .0167 (3 treatment groups) significance level.

Intention-to-treat analyses were conducted with SAS version 9.2 (SAS Institute). Two-sided nominal *P* values are reported. One-way analyses of variance and χ^2 tests addressed differences in baseline characteristics among groups. The effect of the intervention on knee compressive forces, IL-6 levels, WOMAC pain and function, walk speed, 6-minute walk distance, and SF-36 score were determined using mixed model regression analyses adjusted for IDEA stratification factors (BMI, sex, and baseline values). Analyses included all follow-up data, and intervention effects were estimated at each follow-up visit. A contrast for the intervention effect at 18 months was tested in each model, using the E group as the reference group. Effect sizes were calculated by subtracting the E mean from the D+E and D least-squared means and dividing by their pooled standard deviations. Unadjusted percent change at 18 months for each group was obtained by subtracting the baseline mean from the 18-month mean and dividing by the baseline mean. When the overall 18-month *P* value was $\leq .025$ for the primary outcomes, specific pairwise differences were noted, with the significance level adjusted for 6 comparisons ($P \leq .008$). For the secondary outcomes, the significance levels were .05 and .0167 (3 treatment groups).

To assess whether our results were biased because of missing data, we performed a sensitivity analysis using multiple imputation for all 454 randomized individuals. We imputed 50 fully observed data sets with complete data at 6- and 18-month visits, analyzed each data set using our previously stated analytic protocol, and aggregated the results. The imputation and aggregation were performed using PROC MI and PROC MIANALYZE, respectively, in SAS version 9.3. Data from the multiple imputation analyses are presented in the “Results” section and the intention-to-treat completers-only analyses are shown in the Supplement.

The dose-response relationship between each outcome variable and continuous and categorical weight change (<5%, 5%-9.9%, $\geq 10\%$) was assessed using mixed model regression

analyses, controlling for BMI, sex, baseline values, and group assignment. The weight loss categories reflect the weight loss goals of 5% or more for ADAPT and 10% or more for IDEA.^{4,13}

Results

Retention and Adherence

Figure 1 and Table 1 show eligibility criteria, characteristics, and progress of the randomized cohort. Of the 454 participants, 399 (88%) completed the study (returned for 18-month follow-up). Retention did not differ significantly among the groups (E, 89%; D, 85%; D+E, 89%), and noncompleters did not differ significantly from completers in terms of age, sex, race, number of comorbidities, initial radiographic score, knee pain, or physical function.

Adherence to exercise (number of sessions completed/number scheduled) for the E group was 66% for the first 6 months and 54% for 18 months; for the D+E group, it was 70% and 58%, respectively. Adherence to the diet intervention (number of individual and class sessions attended/number scheduled) was 61% for the D group and 63% for the D+E group. Three nonserious adverse events related to the trial included a muscle strain and 2 trips/falls during exercise sessions that resulted in soreness and bruising. The external safety monitor determined that 10 serious adverse events were unrelated to the study (eTable 1 in the Supplement). Seven participants underwent surgery during the study: E group participants had 1 knee surgery and 3 knee replacements; the D+E group had 1 foot surgery, 1 gallbladder surgery, and 1 hip replacement. All but the patient who had knee surgery returned to the study after surgery.

Weight Loss and Body Composition

Both diet groups (D and D+E) lost significantly ($P < .001$) more weight than the E group (Table 2). The D group lost 8.9 kg (9.5%) over 18 months; the mean loss in the D+E group was 10.6 kg (11.4%). Neither group regressed toward baseline values (eFigure in the Supplement). The E group lost 1.8 kg, or 2.0% of baseline body weight. At baseline, 79.3% of all participants had a BMI of 30 or greater. At 18 months, this was reduced to 55.5%, including 69.0% in the E group, 54.6% in the D group, and 43.3% D+E participants.

Total fat mass was significantly less in both diet groups relative to the E group after 18 months ($P < .001$). Fat mass remained essentially unchanged (-0.4 kg) in the E group, while decreasing 6.5 kg (18%) and 4.8 kg (13%) at 18 months in the D+E and D groups, respectively. The D+E and D groups lost significantly more lean mass than the E group ($P < .001$), but the percentage of lean mass at 18 months did not differ among the 3 groups.

Knee Joint Load and Inflammation

Evaluation of peak knee compressive force (the biomechanical outcome measure of joint loading) at 18 months demonstrated that the E group had decreased joint loading by 148 N (5%), the D group by 265 N (10%), and D+E by 230 N (9%) (Table 3 and Table 4). Of the pairwise between-group com-

parisons, the E vs D comparison had the greatest difference in compressive force of 200 N (95% CI, 55-345; $P = .007$). The differences between the E vs D+E groups and the D vs D+E groups were not significant (Table 5).

Plasma IL-6 level also differed significantly among the groups ($P = .008$); pairwise between-group comparisons revealed that the differences in the D+E and D groups relative to E were 0.39 pg/mL (95% CI, -0.03 to 0.81; $P = .007$) and 0.43 pg/mL (95% CI, 0.01 to 0.85; $P = .006$), respectively (Table 3, Table 4, and Table 5).

Pain and Function

Pairwise between-group comparisons of WOMAC pain and function at 18 months revealed that the D+E group had less pain relative to the E (mean score, 1.02; 95% CI, 0.33-1.71; $P = .004$) and D (1.13; 95% CI, 0.44-1.82; $P = .001$) groups (Table 5, Figure 2). Post hoc analysis revealed that 38% of the D+E group reported little or no pain after 18 months with scores of 0 or 1 compared with 20% and 22% of the participants in the D and E groups, respectively.

Pairwise between-group comparisons revealed that WOMAC function score was significantly better in the D+E group relative to the E group (mean, 4.29; 95% CI, 2.07-6.50; $P < .001$). Similarly, D+E participants had better function than D participants (3.30; 95% CI, 1.09-5.51, $P = .003$). The E vs D comparison showed no significant difference (Table 5).

Mobility and HRQL

At 18 months, the D+E group walked 0.04 m/s faster relative to the E group (95% CI, -0.07 to -0.02 ; $P = .003$). The differences between E vs D and D vs D+E comparisons were not significant. The 6-minute walk distance was 21.3 m farther in the D+E group relative to the E group (95% CI, -36.3 to -6.4 ; $P = .005$). The D+E group also walked 41.5 m farther than the D group (95% CI, -56.4 to -26.6 ; $P < .001$), and E participants walked further than D participants (20.2 m; 95% CI, 5.0 to 35.4; $P = .009$). The difference in the SF-36 physical subscale was 2.81 units in D+E relative to the E group (95% CI, -4.76 to -0.86 ; $P = .005$). Changes in the SF-36 mental subscale did not reach significance between any groups (Table 5).

Sensitivity Analysis

Results from the intention-to-treat completers-only analyses that did not use multiple imputations are shown in eTables 2 and 3 in the Supplement. Pairwise comparisons for knee joint compressive load, IL-6 level, pain, and function were statistically unchanged between the intention-to-treat and multiple imputation analyses. Comparisons between D+E and E for 6-minute walk distance and SF-36 physical subscale reached statistical significance only in the multiple imputation analysis (D+E was better than E; $P = .005$).

Dose Response to Weight Loss

We examined the relationship of percent weight change to 18-month mean (SE) mechanistic and clinical outcomes adjusted for intervention, BMI, sex, and baseline values. Independent of group assignment, the cohort was divided into 3 categories based on 18-month weight loss: high, -32.5% to

–10.1%; medium, –9.9% to –5.0%, and low, –4.9% to +9.9%. We found significant weight change dose-response effects in knee compressive force, IL-6 level, pain, and function; par-

ticipants in the high category had significantly lower joint loads, less systemic inflammation and pain, and better function at 18 months (eTable 4 in the Supplement).

Figure 1. Participant Progress Through the Intensive Diet and Exercise for Arthritis (IDEA) Trial

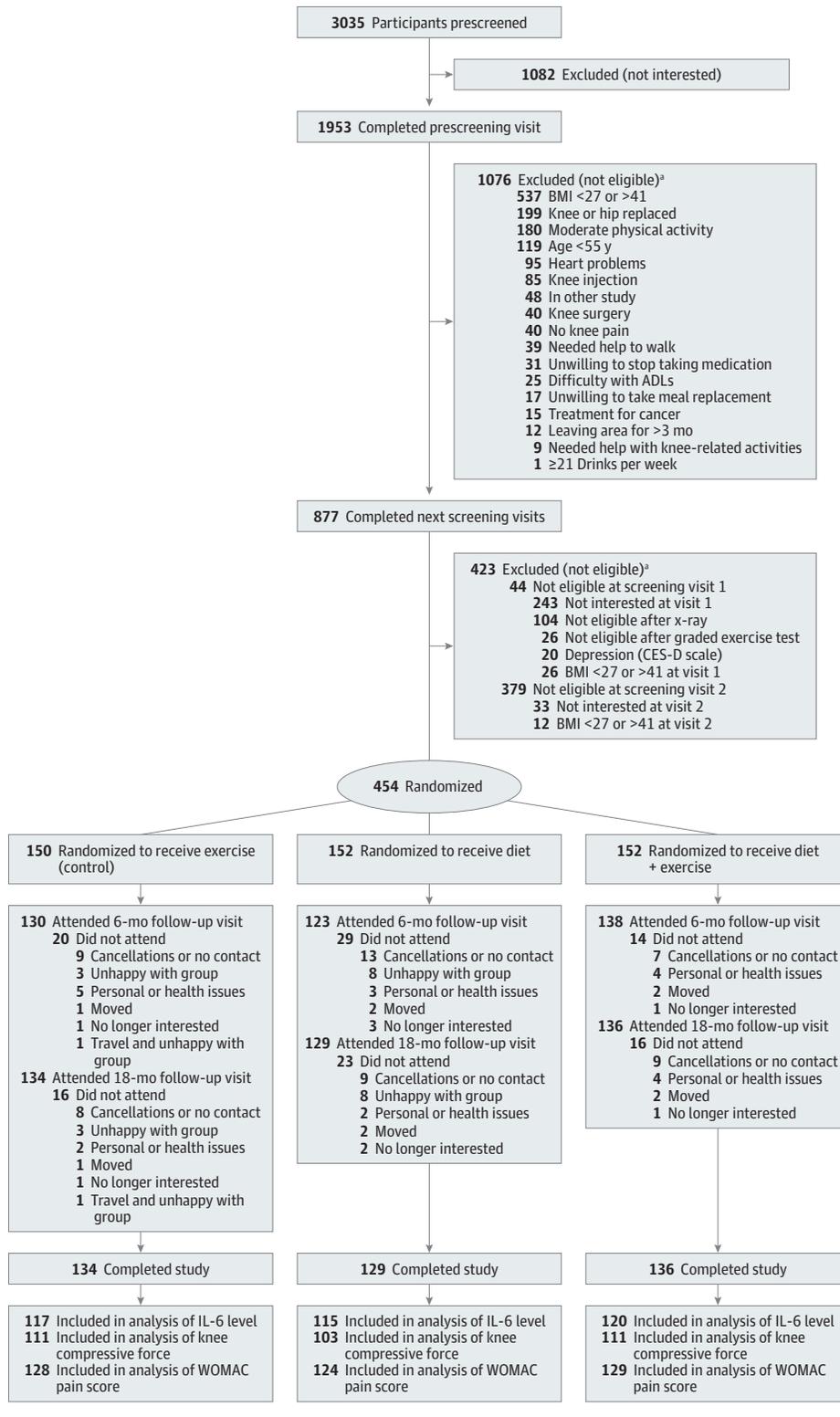


Table 1. Demographic and Clinical Characteristics of the Study Participants at Baseline

Baseline Characteristic	Overall (N = 454)	Exercise Group (Comparison) (n = 150)	Diet Group (n = 152)	Diet + Exercise Group (n = 152)	P Value
Age, mean (SD), y	66 (6)	66 (6)	66 (6)	65 (6)	.86
Female, No. (%)	325 (72)	108 (72)	108 (71)	109 (72)	.98
Nonwhite, No. (%)	85 (19)	30 (20)	25 (16)	30 (20)	.68
Weight, mean (SD), kg	93 (14.7)	92 (14.5)	93 (15.2)	93 (14.4)	.82
Height, mean (SD), m	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	1.66 (0.09)	.91
BMI, mean (SD) ^a	33.6 (3.7)	33.5 (3.7)	33.7 (3.8)	33.6 (3.7)	.90
Annual household income, No. (%), \$					
<20 000	40 (9)	14 (9)	15 (10)	11 (7)	.63
20 000-34 999	68 (15)	27 (18)	21 (14)	20 (14)	
35 000-49 999	86 (19)	32 (22)	25 (17)	29 (20)	
≥50 000	253 (57)	75 (60)	90 (51)	88 (59)	
Education, No. (%)					
≤High school	72 (16)	29 (19)	21 (14)	22 (14)	.35
>High school	380 (84)	120 (81)	130 (86)	130 (86)	
Comorbid illness, No. (%)					
Obesity (BMI ≥30)	360 (79)	118 (79)	121 (80)	121 (80)	.97
Arthritis in other joints	265 (61)	92 (63)	84 (57)	89 (62)	.59
Hypertension	273 (61)	89 (60)	93 (63)	91 (61)	.85
Cardiovascular heart disease	42 (10)	12 (8)	19 (13)	11 (8)	.22
Diabetes	59 (13)	18 (12)	18 (12)	23 (15)	.64
Kellgren-Lawrence grade, mean (SD)	2.56 (0.59)	2.53 (0.56)	2.58 (0.60)	2.59 (0.60)	.64
WOMAC function score (range, 0-68), mean (SD)	24.2 (10.9)	23.1 (10.3)	24.8 (10.4)	24.6 (11.7)	.33
WOMAC pain score (range, 0-20), mean (SD)	6.5 (3.1)	6.1 (2.9)	6.6 (3.0)	6.7 (3.4)	.24

Abbreviations: BMI, body mass index; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^a Calculated as weight in kilograms divided by height in meters squared.

Table 2. Body Composition Values Across the 18-Month Intervention Period by Study Group^a

	Exercise Group (Comparison)				Diet Group				Diet + Exercise Group			
	0	6 mo	18 mo	Δ	0	6 mo	18 mo	Δ	0	6 mo	18 mo	Δ
Weight, mean, kg	92.3	92.4	90.5	-1.8	93.4	85.5	84.5	-8.9	93.0	84.3	82.4	-10.6
95% CI	89.9 to 94.6	89.7 to 95.2	87.7 to 93.2	-5.7 to 1.8	91.0 to 95.8	82.8 to 88.1	81.8 to 87.1	-12.4 to -5.3	90.6 to 95.3	81.8 to 86.8	79.7 to 85.1	-14.1 to -7.1
No. of patients	150	122	115		152	115	120		152	133	121	
Fat mass, mean, kg	37.0		36.7	-0.4	36.3		31.5	-4.8	36.8		30.3	-6.5
95% CI	35.7 to 38.4		34.9 to 38.4	-2.5 to 1.8	34.9 to 37.6		29.7 to 33.3	-7.0 to -2.6	35.5 to 38.1		28.6 to 32.0	-8.6 to -4.4
% Fat mass	40		41	1	40		38	-2	40		37	-3
Lean mass, mean, kg	56.1		53.5	-2.6	55.3		51.1	-4.2	55.6		50.8	-4.7
95% CI	54.0 to 58.1		51.2 to 55.7	-5.7 to 0.5	53.2 to 57.6		48.8 to 53.4	-7.4 to -1.1	53.6 to 57.6		48.7 to 53.0	-7.7 to -1.8
% Lean mass	60		59	-1	60		62	2	60		63	3
No. of patients	131		94		128		88		136		102	

Abbreviations: 0, baseline; Δ, change from baseline within group.

^a All P < .001 comparing the Diet + Exercise and Diet groups vs the Exercise (comparison) group.

Discussion

In this translational study of weight loss and exercise among overweight and obese adults with knee OA, we found that after 18 months, mean weight loss was greater in the D+E group and the D group compared with the E group. In addition, when

compared with the E group, the D+E group had less inflammation, less pain, better function, faster walking speed, and better physical HRQL.

Primary Outcomes

Peak knee compressive forces decreased and walking speeds increased in all 3 groups after the 18-month intervention pe-

riod. In pairwise between-group comparisons, peak knee compressive forces were 200 N per step less in the D group than in the E comparator group (Table 5). The clinical importance of

this difference is unknown, although it appears that weight loss reduces knee-joint loading even as preferred walking speed increases.

Table 3. IDEA Outcomes From Multiple Imputation-Based Model That Used 50 Multiply Imputed Data Sets per Variable: Exercise (Comparison) Group and Diet Group

	Exercise Group					Diet Group				
	0	6 mo	18 mo	Δ (%)	Month 18 Adjusted ^a	0	6 mo	18 mo	Δ (%)	Month 18 Adjusted ^a
Knee compressive force, N	2768	2877	2620	-148 (-5)	2687	2626	2466	2361	-265 (-10)	2487
95% CI	2612-2925	2720-3034	2475-2765		2590-2784	2480-2773	2333-2598	2242-2481		2393-2581
IL-6, pg/mL	3.0	2.9	3.0	0.1 (0)	3.1	3.2	2.7	2.7	-0.5 (16)	2.7
95% CI	2.6-3.3	2.6-3.3	2.7-3.3		2.9-3.4	2.8-3.6	2.4-3.1	2.3-3.0		2.4-3.0
WOMAC pain score	6.1	4.5	4.4	-1.7 (-28)	4.7	6.6	4.9	4.8	-1.8 (-27)	4.8
95% CI	5.6-6.6	4.0-5.1	3.9-4.9		4.2-5.1	6.1-7.1	4.4-5.3	4.2-5.3		4.3-5.2
WOMAC function score	23.1	17.7	17.6	-5.5 (-24)	18.4	24.8	18.3	17.7	-7.1 (-29)	17.4
95% CI	21.4-24.8	15.9-19.5	15.8-19.4		16.9-19.9	23.2-26.5	16.6-20.0	15.7-19.8		15.9-18.9
Walk speed, m/s	1.23	1.32	1.30	0.07 (6)	1.29	1.18	1.25	1.27	0.09 (8)	1.29
95% CI	1.20-1.26	1.29-1.35	1.27-1.33		1.27-1.31	1.15-1.21	1.22-1.28	1.25-1.30		1.27-1.31
6-min walk, m	480	533	525	45 (9)	525	475	505	502	26 (6)	505
95% CI	466-495	518-547	511-540		515-535	462-488	492-518	488-515		495-515
SF-36 physical	36.8	41.5	42.0	5 (14)	41.9	36.0	41.8	42.0	6 (17)	42.4
95% CI	35.3-38.2	39.9-43.1	40.3-43.6		40.5-43.2	34.5-37.4	40.2-43.4	40.3-43.7		41.1-43.7
SF-36 mental	56.5	56.1	55.4	-1.0 (-2)	55.6	55.9	55.0	54.9	-1.0 (-2)	55.3
95% CI	55.1-57.8	54.8-57.5	54.0-56.8		54.4-56.7	54.5-57.2	53.6-56.4	53.6-56.1		54.2-56.5

Abbreviations: O, baseline; Δ, change from baseline within group; SF-36, 36-item short form; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^a Mixed-effects model was adjusted for baseline body mass index, sex, and baseline values. Knee compressive force and IL-6 significance levels were set at .025; for secondary outcomes, the significance level was .05.

Table 4. IDEA Outcomes From Multiple Imputation-Based Model That Used 50 Multiply Imputed Data Sets per Variable: Diet + Exercise Group

	Diet + Exercise Group					P Value
	0	6 mo	18 mo	Δ (%)	Month 18 Adjusted ^a	
Knee compressive force, N	2655	2593	2425	-230 (-9)	2543	.02 ^b
95% CI	2506-2804	2460-2725	2306-2544		2448-2637	
IL-6, pg/mL	3.2	2.8	2.7	-0.5 (-15)	2.7	.008 ^b
95% CI	2.9-3.6	2.5-3.2	2.4-3.1		2.5-3.0	
WOMAC pain score	6.7	4.6	3.7	-3.0 (-45)	3.6	.002 ^c
95% CI	6.1-7.2	4.1-5.1	3.1-4.2		3.2-4.1	
WOMAC function score	24.6	16.5	14.2	-10.3 (-42)	14.1	<.001 ^c
95% CI	22.7-26.5	14.7-18.3	12.4-16.1		12.6-15.6	
Walk speed, m/s	1.20	1.32	1.33	0.12 (10)	1.33	.008 ^d
95% CI	1.17-1.23	1.28-1.35	1.29-1.36		1.31-1.35	
6-min walk, m	467	537	537	70 (15)	546	<.001 ^e
95% CI	453-481	522-552	520-553		536-556	
SF-36 physical	36.6	43.5	44.7	8 (23)	44.7	.01 ^f
95% CI	35.1-38.1	41.9-45.0	43.1-46.2		43.4-46.0	
SF-36 mental	57.2	56.9	56.1	-1.1 (-2)	55.8	.85
95% CI	56.2-58.3	55.7-58.2	54.9-57.2		54.7-57.0	

Abbreviations: O, baseline; Δ, change from baseline within group; SF-36, 36-item short form; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^a Mixed-effects model was adjusted for baseline body mass index, sex, and baseline values. Knee compressive force and IL-6 significance levels were set at .025; for secondary outcomes, the significance level was .05.

^b Diet + Exercise and Diet groups less than Exercise group (refer to Table 3).

^c Diet + Exercise group less than Exercise and Diet groups (refer to Table 3).

^d Diet + Exercise group greater than Exercise and Diet groups (refer to Table 3).

^e Diet + Exercise group greater than Exercise and Diet groups; Exercise group greater than Diet group (refer to Table 3).

^f Diet + Exercise group greater than Exercise group (refer to Table 3).

Table 5. Pairwise Between-Group Differences at 18-Month Follow-Up for Primary and Secondary Outcomes Using Multiple Imputation Adjusted for Baseline Body Mass Index, Sex, and Baseline Values

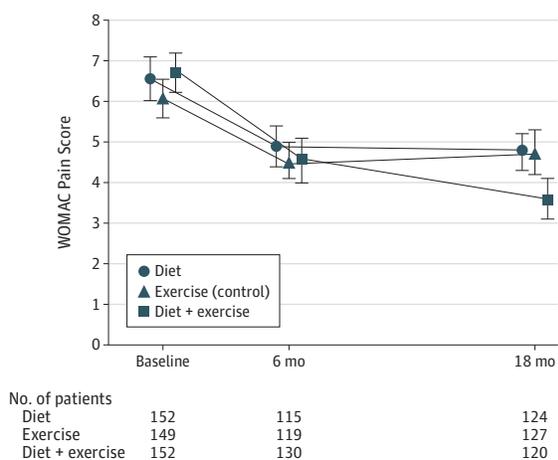
	Exercise vs Diet	P Value ^a	Exercise vs Diet + Exercise	P Value ^a	Diet vs Diet + Exercise	P Value ^a
Knee compressive force, N	200 (55 to 345)	.007	144 (1 to 287)	.05	-56 (-199 to 88)	.45
IL-6, pg/mL	0.43 (0.01 to 0.85)	.006 ^b	0.39 (-0.03 to 0.81)	.007 ^b	-0.04 (-0.47 to 0.40)	.98 ^b
WOMAC pain score	-0.11 (-0.81 to 0.59)	.76	1.02 (0.33 to 1.71)	.004	1.13 (0.44 to 1.82)	.001
WOMAC function score	0.98 (-1.24 to 3.20)	.38	4.29 (2.07 to 6.50)	<.001	3.30 (1.09 to 5.51)	.003
Walk speed, m/s	-0.01 (-0.04 to 0.02)	.59	-0.04 (-0.07 to -0.02)	.003	-0.04 (-0.07 to -0.01)	.02
6-min walk, m	20.2 (5.0 to 35.4)	.009	-21.3 (-36.3 to -6.4)	.005	-41.5 (-56.4 to -26.6)	<.001
SF-36 physical score	-0.55 (-2.53 to 1.43)	.59	-2.81 (-4.76 to -0.86)	.005	-2.26 (-4.30 to -0.23)	.03
SF-36 mental score	0.23 (-1.47 to 1.93)	.79	-0.26 (-1.95 to 1.43)	.76	-0.49 (-2.25 to 1.26)	.85

Abbreviations: SF-36, 36-item short form; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^a Knee compressive force and IL-6, significance levels were set at .008; for secondary outcomes the significance level was .0167.

^b P value from the log-adjusted variable comparisons.

Figure 2. Mean WOMAC Pain Scores Across the 18-Month Intervention Period



The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale was used to measure self-reported pain while performing daily living activities in the last 48 hours due to knee osteoarthritis. Total scores range from 0 to 20; higher scores indicate greater pain. The estimates are based on the previously stated number of observations and multiply imputed values for the missing observations within each group adjusted for baseline body mass index, sex, and baseline values. *P* = .002 comparing the diet + exercise group with the diet group and exercise group. Error bars indicate 95% CIs.

Whether inflammation constitutes a separate OA disease pathway or instead is the downstream result of chronic excessive biomechanical stress is debated.^{6,27} Systemic inflammation markers, including IL-6, distinguished patients with knee or hip OA from controls,²⁸ and higher systemic levels of IL-6 have been associated with increased odds of developing knee OA.²⁹ Diffusion of such cytokines from the synovial fluid into the cartilage could contribute to cartilage matrix loss by stimulating chondrocyte catabolic activity and inhibiting anabolic activity.^{6,30} In addition to these direct effects on the joint, inflammatory mediators can affect muscle function and lower the pain threshold.³¹ IL-6 concentrations less than 2.5 pg/mL have been shown to reduce the risk of mobility disability and

improve markers of metabolic syndrome.³² Participants in all 3 groups exceeded this level (mean, 3.1 pg/mL) at baseline, with significant improvements in D+E and D relative to E at 18-month follow-up. Our study was powered to detect a 15% and 20% difference in knee compressive force and IL-6 level but found differences of approximately 8% and 14%, respectively. Results need to be interpreted with this in mind.

Secondary Outcomes

With regard to pain, between-group differences in WOMAC score were 1.02 and 1.13 units in the D+E vs E and the D+E vs D groups, with D+E having less pain. Hence, the clinical significance of 1.02-point and 1.13-point between-group differences in the WOMAC pain scale remains uncertain.³³

Post hoc analysis revealed that nearly 40% of D+E participants had WOMAC pain scores of 0 or 1 (no or little pain) at 18-month follow-up compared with 20% of the D group and 22% of the E group; pain worsened from baseline in 10% of the D+E group compared with 22% in the D group and 28% in the E group. The D group, which had similar decreases in joint loads and inflammation, experienced only half the D+E pain reduction. Reasons for this finding are unclear. The pain reduction in the E group, despite increased joint loads, inflammation, and walk speed, may indicate psycho-physiological effects of exercise on the central³⁴ and peripheral nervous systems.³⁵

Patients in our cohort reported relatively mild pain at baseline (averaging 6.5 on a 0-20 scale), similar to participants in previous long-term OA clinical trials.^{4,5,36} This entry level may have been an advantage because lack of adherence due to extreme pain was uncommon, but it left little room for improvement.

Despite use of an active comparison group with level 1 evidence of efficacy,³⁷ the D+E group had better clinical outcomes (ie, pain, function, and mobility). Adherence to exercise for the D+E and E groups was 70% and 66%, respectively, during the first 6 months of center-based activity. As participants incorporated home-based exercise after month 6, adherence decreased to 58% and 54% at 18 months. The D+E group improvement in function and mobility was modest but significantly greater than either the D or E group and greater than that achieved by the ADAPT D+E group.⁴ Improvements

also exceeded those observed in a randomized controlled trial that compared a very low-energy diet with an attention control group⁵ in which function improved in the diet group at 3-month follow-up but regressed toward baseline values by 12 months. We attribute these results to challenging yet attainable weight loss and exercise goals with a social cognitive behavioral framework.

Walk speed and 6-minute walk distance, measures of mobility, were below normative values for healthy older adults at baseline.^{38,39} At follow-up at 18 months, the D+E group demonstrated significant pairwise differences relative to the E and D groups (Table 5). Himann et al³⁸ found that walking speed decreased 1% to 2% per decade of adult life until age 62 years, when the decline was 12% to 16% per decade. The cohort in our study reversed this trend by increasing their walking speed and 6-minute walk distance, D+E participants significantly more than the E and D groups. These improvements, in part, may have been due to the significant reduction in knee pain. The D+E group significantly improved the physical health dimension of HRQL relative to the E group with a pairwise difference of 2.81 and an improvement from baseline of 8 units. A minimally important improvement from baseline of 4.11 in the physical subscale has been reported for patients with psoriatic arthritis.⁴⁰ There were no between-group differences in mental health subscale scores.

A multiple imputation analysis revealed minimal differences from our original intention-to-treat analysis, indicating the strength of the primary analysis. This was due to the low drop-out rate relative to similar studies.^{12,41} Drop-out did not occur differentially with respect to randomization group, sex, or baseline BMI ($P > .05$).

Independent of group assignment, participants who lost 10% or more of body weight improved function and reduced knee compressive force, systemic IL-6 concentrations, and pain more than those who lost 5% to 9.9% or less than 5% of their baseline weight. These data are consistent with the National Institutes of Health recommendation for overweight and obese adults to lose 10% of baseline weight as an initial goal.¹¹ Weight loss programs for older adults are not without risks. In addition to fat mass, weight loss reduces lean mass, which is associated in older adults with muscle weakness, greater risk of falls and injury, and loss of independence and mobility, although exercise can attenuate it.⁴² The D+E and D groups lost substantial fat mass (D+E, -10.6 kg [-18%]; D, -8.9 kg [-13%])

and -4.7 kg (-9%) and -4.2 kg (-8%), respectively, of lean mass. However, relative to total body weight at 18 months, lean mass actually increased 3% in the D+E group and 2% in the D group.

This study has several limitations. Patients in this study had mild-to-moderate radiographic knee OA at baseline (Kellgren-Lawrence scores of 2-3) and similar levels of knee pain. Whether patients with more severe knee OA (Kellgren-Lawrence score of 4) and higher levels of pain would benefit from this long-term intervention is unknown. The musculoskeletal model used to calculate knee compressive forces has several limitations. Several knee ligaments are not included, it assumes that the hip flexors and hip abductors do not co-contract during stance, and its grouped muscle model design cannot distinguish between smaller muscle anatomical units. Nonetheless, we have used this model previously,^{20,43-45} and as we recently demonstrated,²⁰ our muscle and joint force predictions are in agreement with those based on a variety of other models^{46,47} and from measured forces from instrumented knee joint prostheses.^{48,49} The IDEA trial also benefited from its single-site design, as single-site studies tend to have larger treatment effects than multicenter trials.⁵⁰

Osteoarthritis and other obesity-related diseases place an enormous physical and financial burden on the US health care system.⁵¹ The estimated 97 million overweight and obese Americans are at substantially higher risk for many life-threatening and disabling diseases, including OA.¹¹ The findings from the IDEA trial data suggest that intensive weight loss may have both anti-inflammatory and biomechanical benefits; when combining weight loss with exercise, patients can safely achieve a mean long-term weight loss of more than 10%, with an associated improvement in symptoms greater than with either intervention alone.

Conclusion

Among overweight and obese adults with knee OA, after 18 months, participants in the D+E and D groups had more weight loss and greater reductions in IL-6 levels than those in the E group, those in the D group had greater reductions in knee compressive force than those in the E group, and those in the D+E group had less knee pain and better function than those in the D and E groups and improved physical HRQL than those in the E group.

ARTICLE INFORMATION

Author Affiliations: Department of Health and Exercise Science, Wake Forest University, Winston-Salem, North Carolina (Messier, Mihalko, Miller, Nicklas, Loeser); Division of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina (Legault, Beavers); Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Messier, Nicklas, Lyles, Williamson); Department of Kinesiology, East Carolina University, Greenville, North Carolina (DeVita); Rheumatology Department, Northern Clinical School, University of Sydney, Sydney, Australia (Hunter); Institute of Anatomy and Musculoskeletal

Research, Paracelsus Medical University, Salzburg, Austria (Eckstein); Chondrometrics, Ainning, Germany (Eckstein); Department of Radiology, Wake Forest School of Medicine, Winston-Salem, North Carolina (Carr); Department of Radiology, Boston University School of Medicine, Boston, Massachusetts (Guermazi); Section on Molecular Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina (Loeser).

Author Contributions: Dr Messier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Messier, Mihalko,

Legault, Miller, Nicklas, DeVita, Williamson, Carr, Loeser.

Acquisition of data: Messier, Legault, Nicklas, Williamson, Carr, Guermazi, Loeser.

Analysis and interpretation of data: Messier, Legault, Miller, Nicklas, DeVita, Beavers, Hunter, Lyles, Eckstein, Williamson, Carr, Guermazi, Loeser.

Drafting of the manuscript: Messier, Mihalko, Legault, Nicklas, DeVita, Hunter, Lyles, Williamson, Loeser.

Critical revision of the manuscript for important intellectual content: Messier, Mihalko, Legault, Miller, Nicklas, DeVita, Beavers, Hunter, Lyles, Eckstein, Williamson, Carr, Guermazi, Loeser.

Statistical analysis: Messier, Legault, Beavers.

Obtained funding: Messier, Mihalko, Legault, Miller, DeVita, Williamson, Carr, Loeser.

Administrative, technical, or material support:

Messier, Legault, DeVita, Beavers, Hunter, Lyles, Eckstein, Williamson.

Study supervision: Messier, Mihalko, Legault, Miller, Nicklas, Lyles, Williamson, Carr, Guermazi, Loeser.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Messier reported receiving grants from the US Army, giving expert testimony for Anspach Meeks Ellenberger, receiving payments for lectures from the Michigan Arthritis Collaboration and Boston University, and receiving travel expenses from the Hospital for Special Surgery Osteoarthritis Summit. Dr Legault reported receiving payment for lectures from Charité University in Berlin. Dr DeVita reported consulting with Wake Forest personnel on knee biomechanics and receiving grants from the Department of Defense and the National Institutes of Health (NIH). Dr Beavers reported receiving grants from the NIH. Dr Hunter reported serving on the board of the Osteoarthritis Research Society International; receiving grants from the National Health and Medical Research Council, Australian Research Council, and the NIH; and receiving royalties from DonJoy. Dr Lyles reported receiving a grant from the NIH. Dr Eckstein reported receiving a grant from the NIH; consulting fees from MerckSerono, Novartis, Abbott, Perceptive, Bioclinica; serving on a speakers' bureau for Synthes and Medtronic; owning stock from Chondrometrics; and receiving travel expenses from MerckSerono. Dr Guermazi reported serving as a consultant for Genzyme, Astra-Zeneca, Novartis, MerckSerono, TissueGene, and sanofi-aventis and owning stock from Boston Imaging Core Lab. No other disclosures were reported.

Funding/Support: Support for this study was provided by grants from the National Institutes of Health—R01 AR052528-01 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases, P30 AG21332 from the National Institute on Aging, M01-RR00211 from the National Center for Research Resources—and by General Nutrition Centers.

Role of the Sponsor: The sponsors had no role in the design and conduct of the study; collection, analysis, and interpretation of data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the IDEA research staff and the IDEA participants for their important contributions. The participants did not receive compensation for their contributions, and the staff were not compensated besides their salaries.

REFERENCES

- Lawrence RC, Felson DT, Helmick CG, et al; National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. *Arthritis Rheum*. 2008;58(1):26-35.
- Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis: the Framingham Study. *Ann Intern Med*. 1988;109(1):18-24.

- Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet*. 2011;377(9784):2226-2235.
- Messier SP, Loeser RF, Miller GD, 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;50(5):1501-1510.
- 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;70(10):1798-1803.
- Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. *Exerc Sport Sci Rev*. 2005;33(4):195-200.
- Guilak F, Sah RL, Setton LA. Physical regulation of cartilage metabolism. In: Mow VC, Hayes WC, eds. *Basic Orthopaedic Biomechanics*. Philadelphia, PA: Lippincott-Raven; 1997.
- Arokoski JP, Jurvelin JS, Väänänen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports*. 2000;10(4):186-198.
- Guilak F, Fermor B, Keefe FJ, et al. The role of biomechanics and inflammation in cartilage injury and repair. *Clin Orthop Relat Res*. 2004;(423):17-26.
- Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med*. 2002;347(2):81-88.
- Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults [report No. 98-4083]. National Heart, Lung, and Blood Institute. <http://www.ncbi.nlm.nih.gov/books/NBK2003/>. Accessed August 28, 2013.
- Ettinger WH Jr, Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the Fitness Arthritis and Seniors Trial (FAST). *JAMA*. 1997;277(1):25-31.
- Messier SP, Legault C, Mihalko S, et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: design and rationale. *BMC Musculoskelet Disord*. 2009;10:93.
- Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. *Ann Rheum Dis*. 1957;16(4):494-502.
- Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids (macronutrients). Institute of Medicine. <http://www.iom.edu/Reports/2002/Dietary-Reference-Intakes-for-Energy-Carbohydrate-Fiber-Fat-Fatty-Acids-Cholesterol-Protein-and-Amino-Acids.aspx>. Accessed August 29, 2013.
- Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA*. 2003;289(14):1799-1804.
- Bandura A. *Self-Efficacy: The Exercise of Control*. New York, NY: W.H. Freeman & Co; 1997.
- Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev*. 1977;84(2):191-215.

- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.
- Messier SP, Legault C, Loeser RF, 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;19(3):272-280.
- Nicklas BJ, Ambrosius W, Messier SP, et al. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. *Am J Clin Nutr*. 2004;79(4):544-551.
- Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-1840.
- Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes following total hip or knee arthroplasty in osteoarthritis. *J Orthop Rheumatol*. 1988;1:95-108.
- Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. *Osteoarthritis Cartilage*. 2000;8(6):395-403.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Med Care*. 1992;30(6):473-483.
- Penninx BW, Messier SP, Rejeski WJ, et al. Physical exercise and the prevention of disability in activities of daily living in older persons with osteoarthritis. *Arch Intern Med*. 2001;161(19):2309-2316.
- Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. In: Hunter DJ, ed. *Osteoarthritis*. 93 ed. Philadelphia, PA: W.B. Saunders Co; 2009:1-24.
- Otterness IG, Swindell AC, Zimmerer RO, Poole AR, Ionescu M, Weiner E. An analysis of 14 molecular markers for monitoring osteoarthritis: segregation of the markers into clusters and distinguishing osteoarthritis at baseline. *Osteoarthritis Cartilage*. 2000;8(3):180-185.
- Livshits G, Zhai G, Hart DJ, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford Study. *Arthritis Rheum*. 2009;60(7):2037-2045.
- Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum*. 2012;64(6):1697-1707.
- Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Med Clin North Am*. 2009;93(1):83-100.
- Esposito K, Marfella R, Ciotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. *JAMA*. 2004;292(12):1440-1446.

33. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88(3):287-294.
34. Dishman RK, Berthoud HR, Booth FW, et al. Neurobiology of exercise. *Obesity (Silver Spring)*. 2006;14(3):345-356.
35. Scheef L, Jankowski J, Daamen M, et al. An fMRI study on the acute effects of exercise on pain processing in trained athletes. *Pain*. 2012;153(8):1702-1714.
36. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA*. 2013;309(2):155-162.
37. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis: Part II, OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage*. 2008;16(2):137-162.
38. Himann JE, Cunningham DA, Rechnitzer PA, Paterson DH. Age-related changes in speed of walking. *Med Sci Sports Exerc*. 1988;20(2):161-166.
39. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158(5 pt 1):1384-1387.
40. Leung YY, Zhu TY, Tam LS, Kun EW, Li EK. Minimal important difference and responsiveness to change of the SF-36 in patients with psoriatic arthritis receiving tumor necrosis factor- α blockers. *J Rheumatol*. 2011;38(9):2077-2079.
41. Aaboe J, Bliddal H, Messier SP, Alkjær T, Henriksen M. Effects of an intensive weight loss program on knee joint loading in obese adults with knee osteoarthritis. *Osteoarthritis Cartilage*. 2011;19(7):822-828.
42. Chomentowski P, Dubé JJ, Amati F, et al. Moderate exercise attenuates the loss of skeletal muscle mass that occurs with intentional caloric restriction-induced weight loss in older, overweight to obese adults. *J Gerontol A Biol Sci Med Sci*. 2009;64(5):575-580.
43. 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;52(7):2026-2032.
44. Messier SP, Legault C, Schoenlank CR, Newman JJ, Martin DF, DeVita P. Risk factors and mechanisms of knee injury in runners. *Med Sci Sports Exerc*. 2008;40(11):1873-1879.
45. DeVita P, Hortobagyi T. Functional knee brace alters predicted muscle and joint forces in people with ACL reconstruction during walking. *J Appl Biomech*. 2001;17:297-311.
46. Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact loads during normal gait. *J Biomech*. 2009;42(14):2294-2300.
47. Lin YC, Walter JP, Banks SA, Pandy MG, Fregly BJ. Simultaneous prediction of muscle and contact forces in the knee during gait. *J Biomech*. 2010;43(5):945-952.
48. Messier SP, Mihalko SL, Beavers DP, et al. Strength Training for Arthritis Trial (START): design and rationale. *BMC Musculoskelet Disord*. 2013;14(1):208.
49. Fregly BJ, Besier TF, Lloyd DG, et al. Grand challenge competition to predict in vivo knee loads. *J Orthop Res*. 2012;30(4):503-513.
50. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. *Ann Intern Med*. 2011;155(1):39-51.
51. Centers for Disease Control and Prevention (CDC). Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation: United States, 2007-2009. *MMWR Morb Mortal Wkly Rep*. 2010;5(39):1261-1265.