Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial1–3


ABSTRACT

Background: Persistent, low-grade inflammation is an independent predictor of several chronic diseases and all-cause mortality.

Objective: The intention of this study was to determine the independent and combined effects of diet-induced weight loss and exercise on markers of chronic inflammation.

Design: Three hundred sixteen community-dwelling, older (≥ 60 y), overweight or obese [body mass index (in kg/m²) ≥ 28], sedentary men and women with radiographic evidence of knee osteoarthritis were randomly assigned to four 18-mo treatments: healthy lifestyle control, diet-induced weight loss, exercise, and diet plus exercise. The exercise intervention consisted of combined weight training and walking for 1 h 3 times/wk. The weight-loss intervention consisted of a weekly session with a registered dietitian to provide education and support for lowering energy intake.

Results: The diet-induced weight-loss intervention resulted in significantly greater reductions in concentrations of C-reactive protein (P = 0.01), interleukin 6 (P = 0.009), and soluble tumor necrosis factor α receptor 1 (P = 0.007) than did no weight-loss treatment. Changes in soluble tumor necrosis factor α receptor 1 but not in C-reactive protein or interleukin 6 correlated with changes in body weight. Exercise training did not have a significant effect on these inflammatory biomarkers, and there was no significant interaction between weight loss and exercise training.

Conclusions: These findings provide evidence from a randomized controlled trial that a dietary intervention designed to elicit weight loss reduces overall inflammation in older, obese persons. Additional studies are needed to assess the effects of different modes and intensities of exercise on inflammation. Am J Clin Nutr 2004; 79:544–51.

KEY WORDS Weight loss, exercise, inflammation, obesity, elderly men and women

INTRODUCTION

An increasing amount of epidemiologic data show that persistent, low-grade inflammation is an independent predictor of ischemic heart disease (1, 2), stroke (3, 4), diabetes (5, 6), and all-cause mortality (7, 8). In addition to these epidemiologic findings, experimental evidence shows that markers of chronic inflammation, such as proinflammatory cytokines [interleukin 6 (IL–6) and tumor necrosis factor α (TNF-α)] and the acute-phase reactant C-reactive protein (CRP), play a direct role in the etiology of atherosclerosis and insulin resistance (9, 10). Given these widespread deleterious health effects of an augmented inflammatory state, identification of therapies that reduce chronic inflammation is critical.

Prospective clinical trial data suggest that a few pharmacologic interventions (such as statin use) decrease inflammation, as evidenced by lowered CRP concentrations (11). Other promising data suggest that decreasing energy intake and increasing physical activity could be effective in reducing overall inflammation. In observational studies, persons who are more physically active have lower concentrations of IL–6 and CRP and other markers of inflammation (fibrinogen and white blood cells) (12, 13). Moreover, chronic exercise training may attenuate the inflammatory process, thereby reducing circulating concentrations of proinflammatory cytokines (14, 15). Likewise, obese persons are characterized by having higher concentrations of inflammatory markers than do lean persons (16, 17), and studies are beginning to show that diet-induced weight loss decreases concentrations of CRP, IL–6, and TNF-α (16–21).

All of these previous studies of the effects of diet-induced weight loss and exercise training on inflammatory markers were limited by small sample sizes, by lack of randomization to treatments, or by lack of a control group. In addition, no prior study compared diet and exercise interventions alone with a combination of these treatments. Thus, the intention of the present study

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was to determine the independent and combined effects of diet-induced weight loss and exercise on markers of chronic inflammation by using a randomized controlled intervention trial in older, overweight and obese men and women with knee osteoarthritis.

**SUBJECTS AND METHODS**

**Study population**

Older (aged ≥ 60 y), overweight and obese [body mass index (BMI; in kg/m²) ≥ 28], sedentary (< 20 min of formal exercise/wk for past 6 mo) men and women were recruited for the present study from the community surrounding Winston-Salem through mass mailings and media advertisements. The subjects were initially screened by telephone for major eligibility criteria before progressing to 2 screening visits in the Geriatric Research Clinic. During their first visit, the participants provided written informed consent to participate in the study according to the Wake Forest University School of Medicine’s Institutional Review Board. The screening visits included a medical history review, physical examination, fasting blood profile, and 12-lead resting electrocardiogram to exclude subjects who 1) did not have radiographic evidence of tibiofemoral osteoarthritis; 2) did not have knee pain; 3) had contraindications for participation in an exercise program, severe hypertension, recent stroke, chronic obstructive pulmonary disease, type 1 diabetes, psychiatric disease, renal disease, liver disease, active cancer other than skin cancer, or anemia; 4) had cognitive impairment (Mini Mental State Examination score < 24); or 5) consumed ≥ 14 alcoholic drinks/wk.

A total of 316 subjects met the study criteria and were assigned to 1 of 4 treatments (exercise, diet-induced weight loss, exercise and diet-induced weight loss, or control) by using a stratified (by race: non-Hispanic white or African American), variable block randomization method. The participants were instructed to continue all of their medications and other treatments as prescribed by their personal physicians.

**Design**

The main purpose of this single-blind randomized controlled clinical trial was to determine the effects of 18 mo of exercise (EX) and diet-induced weight loss (WL) alone and in combination (WL + EX) on self-reported physical function and disability. The primary results showed a significant main effect of diet in improving physical function, stiffness, and pain and a significant main effect of exercise in improving mobility. The current study reports the effects of the interventions on serum concentrations of inflammatory biomarkers.

**Interventions**

The goal of the dietary weight-loss intervention was to produce and maintain an average weight loss of 5% of baseline body weight for the duration of the 18-mo intervention. The subjects were initially counseled to decrease their energy intake by 500 kcal/d, thus allowing for a loss of 0.5 kg body weight/wk. The intervention was divided into 3 phases: intensive (months 1–4), transition (months 5–6), and maintenance (months 7–18).

The major emphasis of the intensive phase was to heighten awareness of the need to change eating habits to lower energy intake. One introductory individual session was followed by 16 sessions (3 group sessions and 1 individual session per month). Each group session included problem solving, the review of a specific topic, and food-tasting of several well-balanced, low-fat, nutritious foods prepared with widely available ingredients. The individual sessions were used to review individual progress, solve problems, answer questions, and set goals. Body weight was measured weekly for both the WL and WL + EX groups and was recorded to the nearest 0.05 kg.

The transition phase included 8 wk of biweekly contacts (3 group and 1 individual session). The goals for this phase included assisting the participants who had not reached their weight goals to reestablish new goals and maintaining and preventing relapse in the participants who had reached their weight-loss goals.

The maintenance phase included monthly meetings and phone contacts every 2 wk. Additionally, newsletters were mailed regularly that provided pertinent nutritional information and notice of upcoming meetings. The goals of the maintenance phase included assisting participants who had reached their weight-loss goals to maintain their weight loss and providing counsel for participants who had a difficult time losing weight and adhering to the intervention. Adherence to the intervention was based on attendance at scheduled sessions and monthly weight assessments.

The 3 d/wk exercise program consisted of an aerobic phase (15 min), a resistance-training phase (15 min), and a cool-down phase (15 min). The first 4 mo of the 18-mo intervention was facility-based. After the first 4 mo, participants who wished to exercise at home underwent a 2-mo transition phase in which they alternated between the facility and the home. After the first 4 mo of facility-based exercise, 64% of the subjects in the 2 exercise groups remained in the facility-based program, 24% opted for the home-based program, and 12% of the subjects chose a combined facility-home-based program.

The participants were provided with an aerobic exercise prescription that included walking within a heart rate range of 50–75% of heart rate reserve. The resistance training portion of the program consisted of 2 sets of 12 repetitions of the following exercises: leg extension, leg curl, heel raise, and step up. Cuff weights and weighted vests were used to provide resistance. A 1-1.5 min rest interval separated each exercise. After 2 orientation sessions, the participants began with the lowest possible resistance. Weight was increased after the participant performed 2 sets of 12 repetitions for 2 consecutive days.

For the participants in the home-based program, weights were exchanged at the participant’s request or after a determination was made to increase weight during face-to-face or telephone contact. Telephone contacts were made biweekly during the first 2 mo of home-based exercise, triweekly during the following 2 mo, and monthly thereafter. Exercise and attendance logs were used to gather data and monitor progress. Exercise compliance was defined as the number of exercise sessions completed divided by the total number of prescribed sessions.

The control group served as a comparison group and was designed to provide attention, social interaction, and health education. The group met monthly for 1 h for the first 3 mo and discussed topics concerning osteoarthritis, obesity, and exercise. Question and answer sessions followed each presentation. Monthly phone contact was maintained during months 4–6 and bimonthly contact was maintained during months 7–18. During
each phone contact, information on pain, medications, illnesses, and hospitalization was obtained.

**Procedures**

Body weight was measured and blood was collected in the morning (between 0700 and 0900) via venipuncture after the participants had fasted overnight both at baseline and after 6 and 18 mo of intervention. Information concerning comorbid conditions was obtained from a medical history, information on medication use was collected, and a physical examination was performed. All staff involved in data collection were blinded to the treatment assignment of the participants.

Fasting serum concentrations of IL-6, TNF-α, soluble IL-6 receptor (IL-6sR), soluble TNF-α receptor 1 (sTNFR1), soluble TNF-α receptor 2 (sTNFR2), and CRP were measured by enzyme-linked immunosorbent assays. All samples were measured in duplicate, and the average of the 2 values was used for data analyses. Duplicate samples that did not provide a CV < 15% were reanalyzed, and all values were averaged for data analyses. All cytokines were measured by using Quantikine immunoassay kits (high-sensitivity for IL-6 and TNF-α) from R&D Systems (Minneapolis). In our laboratory, the inter- and intraassay CVs for IL-6 were 7.3% and 3.5%, respectively; those for TNF-α were 11.8% and 6.2%, respectively; and those for the soluble receptor assays were < 5%. The inter- and intraassay CVs for the CRP assay (ALPCO, Windham, NH) were 8% and 6.7%, respectively.

**Statistical analyses**

Statistical analyses were performed by using SAS software, version 8 (SAS Institute, Cary, NC). Descriptive statistics were calculated for each treatment group (WL, EX, WL+EX, and control) for each assessment (baseline, 6 mo, and 18 mo). Raw values are reported as means ± SDs unless otherwise indicated. We used the logarithmic transformation of CRP, IL-6, TNF-α, sTNFR1, and sTNFR2 to satisfy the model assumptions (normally distributed errors and linear relations). The only cytokine not transformed was IL-6sR. We used repeated-measures analysis of covariance to model each outcome variable separately by using the SAS mixed procedure. Because our primary focus was on change, the outcome used was the change from baseline. We included a random effect of subject that accounted for the within-subject correlation at the repeated measurements. The baseline value of the outcome variable, diet-induced weight loss (yes or no), exercise (yes or no), sex, race (white versus nonwhite), follow-up assessment (6 versus 18 mo), and baseline BMI were included as fixed effects in the model. There was no evidence of a weight loss × exercise interaction (P > 0.19 in all cases); thus, no interaction term was included. In a supplementary analysis, we also included 6- and 18-mo BMI in the model to assess whether the treatments had an effect above and beyond that explained by a change in BMI. To describe the models, adjusted means are reported as means ± SEs for categorical predictors, and slopes are reported for continuous predictors. Spearman’s rank correlation coefficient was used to examine the relations between change from baseline in cytokines and changes from baseline in BMI at 6 and 18 mo. No adjustment for multiple comparisons or for number of variables was made.

**RESULTS**

**Retention, adherence, and baseline characteristics**

Of the 316 randomly assigned participants, 252 (80%) completed the study (ie, returned for the final data collection visit). Blood was available for analysis from 272 subjects at baseline, 242 subjects at 6 mo, and 219 subjects at 18 mo. Analyses were conducted on data from subjects with a baseline blood sample and at least one follow-up sample. Retention of participants was not significantly different between the 4 groups (Table 1). Overall adherence to each of the 4 treatments was also not significantly different between the groups: control, 73%; WL, 72%; EX, 60%; and WL+EX, 64%. Subjects in the WL group lost 5.7% of their baseline body weight and reduced their BMI by 2.0 during the 18-mo intervention, whereas subjects in the WL+EX group lost 4.4% of their baseline body weight and reduced their BMI by 1.48 (P < 0.0001 relative to the control group). Body weight did not change significantly in the EX group (−2.6%) relative to the control group (−1.3%).

At baseline, age, sex, race, body weight, BMI, and concentrations of the inflammatory markers were not significantly different between treatment groups (Table 1). In addition, comorbid conditions and the severity of knee osteoarthritis were not significantly different between treatment groups (data not shown). Baseline inflammatory markers were not significantly different between subjects who dropped out or did not have a follow-up blood draw and those who completed the study and all assessments.

**Treatment effects on markers of inflammation**

**C-reactive protein**

CRP concentrations decreased more in subjects in the WL group than in subjects who did not undergo weight loss (ie, those in the EX and control groups); change in (Δ) log CRP = −0.26 ± 0.07 compared with 0.04 ± 0.07 μg/mL; P = 0.01 (see Figure 1 for adjusted means by treatment and visit); however, there was no significant main effect of exercise on changes in CRP concentrations (P = 0.57). Overall, there was a significant effect of sex, such that CRP decreased more in men than in women (Δ log CRP = −0.29 ± 0.09 compared with −0.02 ± 0.06 μg/mL; P = 0.0062), but there was no significant effect of race (P = 0.88).

**Interleukin 6 and soluble interleukin 6 receptor**

There was a significant main effect of WL (P = 0.009) but not EX (P = 0.86) on changes in IL-6 concentrations; IL-6 concentrations decreased more in subjects in the WL group than in subjects who did not undergo weight loss (Δ log IL-6 = −0.13 ± 0.04 compared with −0.01 ± 0.04 pg/mL; Figure 2). There was also an overall effect of race such that IL-6 concentrations decreased more in nonwhites than in whites (Δ log IL-6 = −0.13 ± 0.06 compared with −0.01 ± 0.03 pg/mL; P = 0.042). There was no significant effect of sex on IL-6 (P = 0.14).

There were no significant effects of WL (P = 0.81; Figure 2), EX (P = 0.44; Figure 2), or sex (P = 0.62) on changes in IL-6sR concentrations. There was a marginally significant racial difference, however, in which IL-6sR concentrations decreased more in nonwhites than in whites (Δ IL-6sR = −2205 ± 747 compared with −639 ± 367 pg/mL; P = 0.055).
There were no significant effects of WL ($P = 0.67$), EX ($P = 0.30$), or sex ($P = 0.84$) on changes in TNF-α concentrations (see Figure 3 for adjusted means by treatment and visit); however, TNF-α concentrations decreased more in nonwhites than in whites ($\Delta \log \text{TNF-α} = -0.20 \pm 0.08$ compared with $-0.01 \pm 0.04 \text{pg/mL}; P = 0.017$). Diet-induced WL resulted in a significant reduction in sTNFR1 concentrations compared with no WL ($\Delta \log \text{sTNFR1} = -0.070 \pm 0.017$ compared with $-0.013 \pm 0.017 \text{pg/mL}; P = 0.007$; Figure 3). In addition, sTNFR1 concentrations decreased more in nonwhites than in whites ($\Delta \log \text{sTNFR1} = -0.084 \pm 0.02$ compared with $0.002 \pm 0.01 \text{pg/mL}; P = 0.001$). There were no significant effects of EX ($P = 0.54$) or sex ($P = 0.84$).

There were no significant effects of WL ($P = 0.23$), EX ($P = 0.08$), or sex ($P = 0.62$) on changes in sTNFR2 concentrations (Figure 3). There was a marginally significant racial difference, in which sTNFR2 concentrations decreased more in nonwhites than in whites ($\Delta \log \text{sTNFR2} = -0.046 \pm 0.02$ compared with $0.001 \pm 0.01 \text{pg/mL}; P = 0.07$).

### Ratios of cytokines to cytokine receptors

We also calculated the ratios of IL-6 and TNF-α to their respective receptors and the ratio of TNF-α to the sum of both of its receptors. There were no significant effects of WL, EX, sex, or race on IL-6/IL-6R, TNF-α/sTNFR1, TNF-α/sTNFR2, or TNF-α/R1+R2, except that race was significant at 0.0494 as a
predictor of TNF-α/sTNFR2 (with whites having higher ratios). The log of the ratios was used in these analyses.

**Association between changes in BMI and changes in markers of inflammation**

The Spearman rank correlation coefficients for the relation between changes in inflammation markers and changes in BMI in the entire cohort are shown in **Table 2**. Changes in the soluble TNF-α receptors but not in CRP or other cytokines correlated directly with changes in BMI. To assess the contribution of changes in adiposity to changes in CRP and cytokines, we performed a secondary analysis to examine whether the treatment effect of diet-induced WL on the reductions in CRP, IL-6, and sTNFR1 concentrations was independent of the loss in body weight. We added BMI as an intervening variable to the model. BMI was marginally significant ($\beta = 0.029, P = 0.057$) as a predictor of CRP concentrations, but there was still a significant...
effect of WL on changes in CRP (P = 0.020). BMI was not a significant predictor of IL-6 concentrations (β = −0.004, P = 0.60), and there was still a significant effect of WL (P = 0.008). BMI was a strong predictor of sTNFR1 concentrations (β = 0.0092, P = 0.007), but there was still a significant effect of WL (P = 0.019).

DISCUSSION

The findings of the present study provide randomized controlled trial evidence that a diet-induced weight-loss intervention reduces chronic inflammation in older, obese men and women, which was discernible by lowered circulating concentrations of CRP, IL-6, and sTNFR1. However, we did not find a statistically significant effect of exercise training on these inflammatory biomarkers, nor was there an interaction between weight loss and exercise training. Moreover, although our study was not powered to detect whether there were sex or racial differences in the inflammatory responses to the weight-loss and exercise treatments, our data suggest that this may be the case. Reductions in CRP were greater in men than in women, and IL-6, TNF-α, and their soluble receptors decreased more in African Americans than in whites. Because these effects were independent of treatment assignment, additional studies are required to determine whether the magnitude of a weight-loss-induced reduction in chronic inflammation differs by sex or race.

The results of the present study are consistent with previous studies that showed that weight loss through energy restriction reduces concentrations of inflammatory biomarkers in obese women (16–21). Additionally, our findings extend those of previous studies in several ways. First, our data provide evidence from a randomized controlled design that causally links the observed decreases in CRP, IL-6, and sTNFR1 to the weight-loss intervention. Second, unlike previous studies in which diet and exercise were studied in isolation, our study design allowed us to investigate the combined effects of diet and exercise on changes in inflammation. Finally, we measured circulating concentrations of the IL-6 and TNF-α soluble receptors, which, because of the short half-life of these cytokines, may be more representative of the inflammatory response (22, 23). In this regard, the lack of a decrease in TNF-α concentrations may be a result of its transient production and short half-life (24), whereas the soluble TNF receptors are more stable in the circulation and are thought to reflect previous biological effects of TNF-α (22–25).

Although changes in sTNFR1 were mostly accounted for by changes in body weight, the effects of the weight-loss intervention on CRP and IL-6 were not related to the amount of body weight lost, nor was BMI a strong predictor of 6- and 18-mo CRP and IL-6 concentrations. This suggests that the ability of this treatment to lower CRP and IL-6 was not solely due to a resultant reduction in body weight. It may be that BMI, not being a measure of body composition, is an inadequate indicator of changes in adiposity affecting inflammation. Alternatively, there may be an effect of some underlying physiologic mechanism triggered by the general reduction in energy intake. In this regard, studies in animal models indicate that attenuation of inflammation through energy restriction may be one mechanism by which energy restriction extends the life span (26, 27). Because concentrations of cytokines and their soluble receptors are often interrelated (21), the mechanism by which weight loss lowers these concentrations likely involves a common regulatory pathway that controls overall cytokine production. Studies in humans involving tight control of the degree of energy restriction are necessary to determine the mechanisms by which weight loss lowers chronic inflammation.

In our study, the average decrease in CRP, the best overall marker of underlying chronic inflammation, in the subjects who underwent diet-induced weight loss was 1.54 μg/mL, or 5.8%. In 2 previous studies in which the degree of energy restriction was more severe (ie, total intake of 1200 kcal/d), CRP decreased 26% (19) and 32% (28). This suggests that there is likely a dose-response effect of energy restriction in its capacity to attenuate chronic inflammation. Unfortunately, no data are available regarding the clinical manifestations of this decline in CRP, although an ≈15% reduction in CRP after 1 y of statin use is associated with a lowered risk of coronary events (29). Thus, longitudinal studies are needed to determine whether there is a reduction in the incidence of cardiovascular disease and diabetes associated with the decline in CRP seen with weight loss.

Although our findings indicate that dietary weight loss can be advocated as an effective therapy for reducing chronic inflammation, our study did not test whether this reduction is associated with an improvement in risk factors for diseases associated with inflammation. However, previous data do provide evidence that improvement in disease risk factors are related to reductions in inflammatory biomarkers. For example, relative changes in endothelium-dependent vasodilation were indirectly related to changes in CRP after 6 mo of statin treatment (30). Also, decreases in adhesion molecules and improvement in endothelial function with sustained weight loss were related to decreases in IL-6 and TNF-α, independent of change in adiposity and body fat distribution (16), and increases in HDL cholesterol with weight loss were associated with decreases in CRP concentrations (28). Finally, exercise-induced changes in serum TNF-α correlated with changes in glycated hemoglobin and fasting serum insulin

| TABLE 2 |
| Correlations between change (Δ) in BMI and change in CRP and cytokines |
| Δ CRP | n | Δ BMI (Spearman’s correlation coefficient) | P |
| 6 mo | 242 | 0.11 | 0.08 |
| 18 mo | 214 | 0.07 | 0.30 |
| Δ IL-6 | 6 mo | 229 | −0.06 | 0.36 |
| 18 mo | 208 | 0.00 | 0.95 |
| Δ IL-6sR | 6 mo | 231 | 0.04 | 0.59 |
| 18 mo | 210 | −0.12 | 0.09 |
| Δ TNF-α | 6 mo | 232 | 0.16 | 0.02 |
| 18 mo | 210 | −0.06 | 0.40 |
| Δ sTNFR1 | 6 mo | 240 | 0.25 | <0.0001 |
| 18 mo | 219 | 0.18 | 0.007 |
| Δ sTNFR2 | 6 mo | 240 | 0.18 | 0.006 |
| 18 mo | 219 | 0.11 | 0.10 |

1 IL-6, interleukin 6; IL-6sR, soluble IL-6 receptor; TNF-α, tumor necrosis factor α; sTNFR1 and sTNFR2, soluble TNF-α receptors 1 and 2, respectively.
Thus, it is likely that weight-loss-induced improvements in disease risk factors may be mediated, in part, through effects on inflammation, but additional studies are needed to confirm this.

It is well known that an acute bout of exercise increases concentrations of proinflammatory cytokines and acute phase reactants (32, 33). However, the long-term consequence of regular exercise training on these inflammatory markers is unclear. In contrast with our findings, the results of several previous smaller studies showed that exercise training decreases inflammation. For example, 12 wk of aerobic exercise in patients with stable congestive heart failure reduced TNF-α concentrations, and improvements in physical performance (6-min walk) correlated with the reductions in TNF-α (34). In addition, exercise training in patients with intermittent claudication reduced CRP after 3 mo (15), and CRP decreased after 9 mo of training for a marathon (35). In overweight women, exercise training for 5 mo decreased serum concentrations of TNF-α, sTNFR1, and sTNFR2 (31). The exercise dose in most of these prior studies was greater than in the current study [ie, cycling at 80% of peak heart rate 3 d/wk (36)]. However, the long-term consequence of regular exercise training decreases inflammation. In overweight women, exercise training for 5 mo decreased sTNFR1, the effect of the intervention was independent of differences in the response of these inflammatory biomarkers may be due to differences in study design (ie, nonrandomized or uncontrolled), differences in the type of subjects studied, or differences in the exercise training stimulus.

Because all of the subjects in our study had knee osteoarthritis, it is possible that our results are limited to persons with this condition. CRP and proinflammatory cytokines are higher in persons with osteoarthritis, and even modestly elevated CRP concentrations predict radiographic progression of knee osteoarthritis (36, 37). The average baseline CRP values observed in the present study are higher than the CRP values reported for similarly aged obese men and women (28, 38); however, they are similar to the CRP values reported in similarly aged men and women with knee osteoarthritis (36).

In summary, the results of the present randomized controlled trial in older, obese men and women with knee osteoarthritis showed that 18 mo of a dietary weight-loss intervention reduced circulating concentrations of CRP, IL-6, and sTNFR1. Except for sTNFR1, the effect of the intervention was independent of changes in body weight. Additional studies with larger sample sizes are needed to explore the possibility of sex and race differences in the response of these inflammatory biomarkers to weight loss. In addition, more trials are needed to assess the effects of different modes and intensities of exercise on inflammation.

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