Weight Loss, Exercise, or Both and Cardiometabolic Risk Factors in Obese Older Adults: Results of a Randomized Controlled Trial

Matthew Bouchonville, MD¹, Reina Armamento-Villareal, MD¹,², Krupa Shah, MD, MPH³, Nicola Napoli, MD, PhD⁴, David R. Sinacore, PT, PhD⁵,⁶, Clifford Qualls, PhD⁷, and Dennis T. Villareal, MD⁵,⁸,⁹

¹Division of Endocrinology, Diabetes, and Metabolism, University of New Mexico School of Medicine, Albuquerque, NM
²Section of Endocrinology, New Mexico Veterans Affairs Health Care System, Albuquerque, NM
³Division of Geriatrics and Aging, University of Rochester School of Medicine, Rochester, NY
⁴Division of Endocrinology, University Campus Bio-Medico Di Roma, Rome, Italy
⁵Division of Geriatrics and Nutritional Science, Washington University School of Medicine, St Louis, MO
⁶Program in Physical Therapy, Washington University School of Medicine, St Louis, MO
⁷Department of Mathematics and Statistics, University of New Mexico School of Medicine, Albuquerque, NM
⁸Division of Geriatrics, University of New Mexico School of Medicine, Albuquerque, NM
⁹Section of Geriatrics, New Mexico School of Medicine, Albuquerque, NM

Abstract

Background—Obesity exacerbates the age-related decline in insulin sensitivity and is associated with risk for cardiometabolic syndrome in older adults; however, the appropriate treatment for obese older adults is controversial.

Objective—To determine the independent and combined effects of weight loss and exercise on cardiometabolic risk factors in obese older adults.

Design—One-hundred-seven obese (BMI ≥30 kg/m²) older (≥65 yrs) adults with physical frailty were randomized to control group, diet group, exercise group, and diet-exercise group for 1 year.
Outcomes for this study included change in insulin sensitivity index (ISI), glucose tolerance, central obesity, adipocytokines, and cardiometabolic syndrome.

**Results**—Although similar increases in ISI occurred in the diet-exercise and diet groups at 6 months, the ISI improved more in the diet-exercise than in the diet group at 12 months (2.4 vs. 1.2; between-group difference, 1.2; 95% CI, 0.2-2.1); no changes in ISI occurred in both exercise and control groups. The diet-exercise and diet groups had similar improvements in insulin area under the curve (AUC) (−2.9 and −2.9 ×10³ mg.min/dl), glucose AUC (−1.4 and −2.2×10³ mg.min/dl), visceral fat (−787 and −561 cm³), tumor-necrosis factor (−17.0 and −12.8 pg/mL), adiponectin (5.0 and 4.0 ng/mL), waist circumference (−8.2 and −8.4 cm), triglyceride (−30.7 and −24.3 g/dL), and systolic/diastolic BP (−15.9 and −13.1/−4.9 and −6.7 mmHg), while no changes in these parameters occurred in both exercise and control groups. The cardiometabolic syndrome prevalence decreased by 40% in the diet-exercise and by 15% in the diet group. Body weight decreased similarly in the diet-exercise and diet groups (−8.6 and −9.7kg) but not in the exercise and control groups.

**Conclusions**—In frail, obese older adults, lifestyle interventions associated with weight loss improve insulin sensitivity and other cardiometabolic risk factors, but continued improvement in insulin sensitivity is only achieved when exercise training is added to weight loss.

**Keywords**
Aging; Obesity; Cardiometabolic Risks

**Introduction**

Obesity is increasingly prevalent and is expected to become an even greater public health concern in coming years (1:2). Current trends in the US suggest that older adults, defined as age ≥65 years, will represent 20% of the population by 2030, half of whom will be obese (3). This expanding population is particularly vulnerable as obesity in older adults is associated with loss of functional independence and diminished quality of life (1). Moreover, obese older adults are at increased risk for the cardiometabolic syndrome, a cluster of metabolic abnormalities predictive of cardiovascular disease and mortality (1:4). However, the clinical approach to obesity in older adults is controversial because of the reduction in relative health risks associated with increasing body mass index (BMI) in this group (5), and the concerns regarding the difficulty of behavioral change with advancing age, exacerbation of age-related loss of lean tissues, and feasibility of long-term weight loss and associated health consequences (1:6;7). Accordingly, the combination of weight loss and exercise is recommended as part of standard care for obese patients in general, but this recommendation is not universally accepted by geriatricians in elderly subjects. It is the prevailing concept that an extra weight may be protective against health risks (8;9). However, the absolute risk of death attributed to obesity in older adults increases with age up to 75 years (5). Moreover, lifestyle interventions directed at weight loss in obese adults are associated with reduced mortality in all age groups, regardless of successful weight loss (10). The mechanism for this observation has not been determined. Further, it is unclear from existing studies whether the beneficial effects of diet and regular exercise are distinct from one another or whether they have additive effects.
We recently reported that the combination of weight loss and exercise provides greater improvement in physical function than either intervention alone (11). We now report the results of the independent and combined effects of weight loss and exercise on insulin sensitivity and other cardiometabolic risk factors in this population of frail, obese older adults.

**Methods**

The principal aim of the parent randomized controlled trial (RCT) was to determine the independent and combined effects of weight loss and exercise on physical performance in obese older adults. The primary results showed that weight loss alone or exercise alone improves physical function and ameliorates frailty; however, a combination of weight loss and exercise provide greater improvement in physical function and amelioration of frailty than either intervention alone (11). The current study reports the secondary analyses of the RCT examining changes in insulin sensitivity and other cardiometabolic risk factors, which was pre-specified in the protocol.

**Study Population**

This monocentric RCT was followed in accordance with the ethical standards of the Washington University School of Medicine (WUSM) and was approved by the WUSM institutional review board. The study was conducted from April 2005 through August 2009 and was monitored by an independent data and safety monitoring board.

The participants of this trial have been described previously (11). Volunteers were recruited from the community through advertisements and provided written informed consent for participation. Eligible subjects were age ≥65 year with BMI ≥30 kg/m², stability of body weight within 2 kilograms over the preceding year, sedentary lifestyle (regular exercise of <1 hour/week), and on a stable medications for at least 6 months prior to enrollment. Additionally, all participants were required to have mild-to-moderate frailty determined by meeting at least two operational criteria: modified physical performance test score of 18-32, VO2peak of 11-18 ml/kg/min, or difficulty in performing two instrumental activities of daily living (ADL) or one basic ADL (11). Exclusion criteria included severe cardiopulmonary disease, musculoskeletal/neuromuscular impairments that precluded exercise training, significant cognitive impairment, a history of malignancy, and current smoking. Candidates were also excluded if they had a history of diabetes or fasting glucose of ≥126 mg/dl.

**Study Design**

In this 1-year RCT, 107 participants were randomly assigned to one of four groups stratified for sex: 1) control group, 2) 10% diet-induced weight loss group (diet group), 3) exercise training without weight loss (exercise group) and 4) 10% diet-induced weight loss and exercise training (diet-exercise group). The randomization algorithm was generated by the WUSM Biostatistics Division and maintained by a member of the research team who did not interact with the participants.
As previously described (11), participants in the control group received general information regarding a healthy diet at monthly visits with the staff, and prohibited from participating in diet or exercise programs.

Participants in the diet group were prescribed a balanced diet that provided a deficit of 500-750 kcal/day from daily energy requirement and consisted of 1 g/kg body weight of high-quality protein (1). Dietary compliance was reinforced during weekly visits with a dietitian. Standard behavioral strategies were used to modify eating habits. Goals for weight loss included a reduction of 10% from baseline at 6 months, followed by maintenance of this weight for the remaining 6 months of the study.

Participants in the exercise group were counseled on maintaining a weight-stable diet. The multicomponent exercise sessions were of ~90 minutes duration (~15- min flexibility exercise, 30-min aerobic exercise, 30-min progressive resistance training, and 15-min balance exercises) conducted three times weekly at our exercise facility. All sessions were led by a physical therapist. Aerobic exercises consisted of treadmill, stationary cycling, and stair climbing. An initial goal of 65% of peak heart rate was achieved, followed by an increase in intensity to 70-85% of peak heart rate. Resistance training was performed using weight-lifting machines and consisted of nine upper and lower extremity exercises. Participants initially performed 1-2 sets of 8-12 repetitions at 65% of one-repetition maximum. The number of repetitions was then decreased to 6-8 repetitions/set and resistance was increased to approximately 70-85% of the one-repetition maximum (11).

Participants in the diet-exercise group participated in both weight management and exercise programs described above.

Additional details about the interventions including compliance data and exercise adaptations (e.g. improvements in strength, VO$_{2peak}$) have been reported (11).

**Outcome Measures**

The outcome in this secondary analyses was change in insulin sensitivity index (ISI) (12) at 12 months. Other outcomes included oral glucose tolerance test (OGTT) variables, abdominal adiposity, blood pressure (BP), lipids, adipocytokines, and cardiometabolic syndrome. Outcomes were assessed at baseline, 6 months, and 12 months, except MRI which was repeated only at 12-months. Personnel who conducted the assessments were not aware of group assignments.

**Oral glucose tolerance test**

A standard 75-g oral glucose tolerance test (OGTT) was performed after an overnight fast. Venous blood samples were obtained in fasted state, 30, 60, 90, and 120 min after glucose ingestion for the measurement of glucose and insulin using glucose oxidase method (YSI Inc., Yellow Springs) and radioimmunoassay. Areas under the curve (AUC) were calculated using the trapezoid method (13). ISI (12) was calculated using the formula: ISI=10000/\(\sqrt{(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin during OGTT})}\). This index correlated (r=0.73) with the rate of whole-body glucose disposal during
a euglycemic insulin clamp study (12). HOMA-IR was also calculated (14). OGTT was performed ~72 hours after the last exercise to minimize acute effects on insulin sensitivity.

**Waist circumference**
Waist circumference was measured horizontally at the midpoint between the highest point of the iliac crest and the lowest portion of the 12th rib in the standing position (15;16).

**Blood pressure**
Blood pressure was measured with a sphygmomanometer cuff of the appropriate size after participants remained in the supine position for 15 min.

**Fasting blood analyses**
Lipoprotein levels were measured using automated enzymatic/colorimetric assays (Roche/Hitachi System). High-sensitive C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay (Hitachi 917). Soluble tumor necrosis factor receptor 1 (sTNF R1) (R&D, Minneapolis) and adiponectin (Linco., St Louis) were measured using ELISA.

**Body composition**
Body fat mass, percent fat, and trunk fat were measured by dual X-ray absorptiometry (Hologic, Waltham MA) as described previously (17). Visceral and subcutaneous abdominal adipose tissue volumes were measured by MRI (Siemens), as described previously (18).

**Cardiometabolic syndrome**
Subjects who met ≥3 of the following criteria (19) were defined as having the cardiometabolic syndrome: waist circumference ≥102 cm in men and ≥88 cm in women, fasting glucose ≥100 mg/dL, triglyceride ≥50 mg/dL or drug treatment for elevated triglycerides, HDL-cholesterol <40 mg/dL in men and <50 mg/dL in women or drug treatment for low HDL-cholesterol, and systolic BP ≥130 or diastolic BP ≥85 mm Hg or on antihypertensive treatment with a history of hypertension.

**Statistical Analysis**
The sample size calculated for the main outcome of this study was sufficient to detect a clinically meaningful difference of 1.2±1.6 in the change in ISI among the groups, at an alpha level of 5%. Intention-to-treat analyses were performed using SAS version 9.2 (SAS Cary, NC). Baseline characteristics were compared using analyses of variance (ANOVAs) or chi-square tests. Longitudinal changes between groups were tested with the use of mixed-model repeated-measures ANOVA, adjusting for baseline values and sex. The primary focus of the analyses was the 12-month change in outcome in the four groups. In the mixed model, when the group-visit p value was <0.05, prespecified contrast statements were used to test three hypotheses: changes in the diet group were different from those in the control group; changes in the exercise group were different from those in the control group; and changes in the diet-exercise group were different from those in the diet group and exercise group. Analyses for within-group changes were performed using mixed-model repeated-measures ANOVA. Subjects were classified as having 3, 4, or 5 components of the cardiometabolic syndrome.
syndrome; chi-square test was used to compare proportions with the cardiometabolic syndrome before and after treatment. Pearson's correlation was used to examine relationships among changes in variables and ISI, followed by stepwise multiple linear regression analyses to identify which variables were independent contributors to the changes in ISI. Data are presented as mean±SD unless otherwise stated. Statistical tests were two-tailed, and p<0.05 was considered significant.

Results

Study population

The results of recruitment, randomization, and follow up have been reported. Briefly, 107 volunteers were randomized and 93 (87%) completed the study. Fourteen participants (4 in the control group, 3 in the diet group, 4 in the exercise group, and 3 in the diet-exercise group) discontinued the intervention due to personal or medical reasons but were included in the intention-to-treat analyses. Baseline characteristics were not significantly different (Table 1).

Attendance at group diet-behavioral therapy sessions was 82±8% in the diet-exercise group and 83±9% in the diet group. Attendance at exercise sessions was 82±10% (2.5±0.3 d/wk) in the diet-exercise group and 88±16% (2.5±0.3 d/wk) in the exercise group. Body weight decreased similarly in the diet-exercise (−8.6±3.8 kg [9% decrease]) and diet (−9.7±5.4 kg [10% decrease]) groups, while weight was constant in the exercise and control groups (Figure 1 A, Table 2). VO$_{2\text{peak}}$ relative to body weight (ml/kg/min) improved more (p<.001) in the diet-exercise group (3.2±2.4 ml/kg/min) than in the exercise group (1.4±1.0 ml/kg/min) or diet group (1.7±2.3 ml/kg/min) as previously reported (11). Absolute VO$_{2\text{peak}}$ (L/min) improved similarly (p=.92) in the diet-exercise group (0.15±0.12 L/min) and exercise group (0.14±0.15 L/min) and did not change in the diet group (−0.03±0.19 L/min) or control group (−0.09±0.15 L/min).

Insulin sensitivity index

Although similar increases in ISI occurred in the diet-exercise group and diet group at 6 months, the ISI increased more (p<.001) in the diet-exercise group than in the diet group at 12 months: an increase of 2.4±2.3 points in the diet-exercise group (71% increase), compared with an increase of 1.2±1.6 points in the diet group (44% increase) (Figure 1B, Table 2). No significant changes in ISI occurred in both exercise and control groups.

Other OGTT variables

Insulin AUC (−2.9±3.9 and −2.9±6.1 × 10$^3$ mg.min/dL), glucose AUC (−1.4±2.8 and −2.2±2.7 × 10$^3$ mg.min/dL), fasting insulin (−6.2±7.1 vs. −4.5±7.3 μU/mL), and HOMA-IR (−1.7±1.9 vs. −1.4±1.8) decreased similarly in the diet-exercise group and diet group, respectively (Table 2). No significant changes occurred in these variables in both exercise and control groups.
Central obesity

Trunk fat (−3.3±1.9 and −3.4±2.4 kg), visceral fat (−787±896 and −561±454 cm³) and subcutaneous fat (−464±475 and −457±326 cm³) decreased similarly in the diet-exercise group and diet group, respectively (Table 2). Trunk fat (−0.8±1.3 kg) and visceral fat (−115±244 cm³) decreased modestly in the exercise group.

Lean body mass

Lean body mass decreased less in the diet-exercise group (−1.8±1.7 kg) than in the diet group (−3.2±2.0 kg), while it increased in the exercise group (1.3±1.6 kg) as previously reported (11).

Adipocytokines

Serum hsCRP (−1.8±3.4 and −1.1±1.4 mg/L) and sTNF R1 (−17.0±29.2 and −12.8±21.7 pg/mL) decreased in the diet-exercise group and diet group, respectively, while sTNF R1 (12.3±20.6 pg/mL) increased in the control group (Table 2). Serum adiponectin (5.0±8.4 ng/mL and 4.0±5.5 ng/mL) increased in the diet-exercise group and diet group, respectively, but not in the exercise group and control group.

Cardiometabolic syndrome components

Fasting glucose (−5.4±9.0 and −3.7±11.5 mg/dL), waist (−8.2±10.3 and −8.4±8.6 cm), triglyceride (−30.7±40.0 and −24.3±33.1 mg/dl), systolic (−15.9±18.9 and −13.1±15.1 mmHg), and diastolic (−4.9±9.5 and −6.7±10.3 mmHg) BP decreased similarly in the diet-exercise group and diet group, respectively (Table 2). Waist (−4.0±9.1 cm) decreased modestly in the exercise group but otherwise no changes occurred in both exercise and control groups.

Prevalence of the cardiometabolic syndrome

The prevalence of the cardiometabolic syndrome (from 22/28 to 11/28 [−40% from baseline] and from 19/26 to 15/26 [−15% from baseline]) decreased in the diet-exercise group and diet group, respectively (Table 3). No changes in the prevalence occurred in the exercise and control groups.

Variables associated with ISI

Changes in body weight (r=−0.44; p<.001), trunk fat (r=−0.37; p<.001), visceral fat (r=−0.35; p<.01), sTNF R1 (r=−0.32; p<.01), and absolute VO2peak (r=.27; p=.02) correlated with changes in ISI. In the stepwise multiple regression analyses, only changes in body weight (β=−0.42) remained significant in the final model, explaining 18% of the variance in ISI changes (r=−0.42; P<.001).

Discussion

In this one-year RCT, diet-induced weight loss alone but not exercise training alone improved insulin sensitivity and other cardiometabolic risk factors in obese older adults. Importantly, the combination of these two interventions resulted in an even greater
improvement in insulin sensitivity at 12 months, a novel finding in this population, suggesting a distinct complementary effect of exercise training added to weight loss.

The cardiometabolic syndrome is a cluster of metabolic derangements predictive of cardiovascular disease (19) which increases with age (20). Likewise, increased intraabdominal fat typical of aging (21) is independently associated with cardiometabolic syndrome (22). Notably, the risk of cardiovascular disease is 3-fold higher in adults with cardiometabolic syndrome (23;24). The observation of improved insulin sensitivity in the current study is of particular significance as insulin resistance has been implicated as the principal mediator of cardiometabolic syndrome (25). Indeed, insulin resistance, as estimated by the ISI, has been associated with an increased risk of death in older adults (26). Accordingly, an intervention directed at improving insulin sensitivity may reduce the incidence of cardiometabolic syndrome and perhaps improve mortality in this population.

Existing data pertaining to the effects of weight loss and exercise training on insulin sensitivity have been conflicting. While it is widely accepted that weight loss is associated with improvements in insulin sensitivity, the independent effects of exercise are less clear. Several studies support the notion that exercise training per se is not associated with chronic effects on insulin sensitivity (27-29). Conversely, other studies showing positive effects of exercise were confounded by lack of control for weight loss (30-35) or assessment of insulin sensitivity in proximity to the exercise (36-39), introducing acute effects which are transient in nature (40). Similarly, previous data on the effect of lifestyle interventions on inflammation have been inconsistent. Studies associating inflammation with inactivity have suggested a role for exercise (41); however, while exercise and weight loss have been shown to reduce subclinical inflammation, the role of exercise in the absence of weight loss has been less apparent (42). Studies have demonstrated that diet-induced weight loss, but not exercise alone, is associated with increased adiponectin levels (43) and decreased markers of inflammation (44).

The design of the current study allowed for the effects of diet-induced weight loss and exercise training on cardiometabolic risk factors to be investigated independently and in combination. Weight loss of ~10 percent was achieved at 6 months, followed by a 6-month weight-maintenance in both, the weight loss (diet group) and the weight loss and exercise (diet-exercise group) interventions. In contrast, weight remained unchanged in the exercise intervention (exercise group) and control group. Lifestyle interventions associated with weight loss, but not exercise training alone, resulted in favorable changes in cardiometabolic risk factors including waist, BP, triglycerides, and glucose metabolism, which translated into reduced prevalence of cardiometabolic syndrome. Additionally, visceral adiposity and adipocytokines were positively affected by weight-loss interventions, but not by exercise training alone. These findings highlight the importance of weight loss-based lifestyle interventions for reducing multiple cardiometabolic risk factors in obese older adults.

A novel finding in this obese older cohort with frailty syndrome was that of improved insulin sensitivity at 12 months in the diet-exercise group beyond which was observed in the diet group achieving similar weight loss without exercise. Our findings suggest a beneficial effect of exercise on insulin sensitivity which is not apparent without a significant
prerequisite weight loss. At 6 months, we found no differences in improvement in insulin sensitivity between the diet group and diet-exercise group, suggesting that the changes in insulin sensitivity were entirely due to weight loss. However, while there were no differences in insulin sensitivity initially between the diet group and diet-exercise group, there was continued improvement in insulin sensitivity during the weight-stable half of the trial observed only in the diet-exercise group. No further improvement in insulin sensitivity occurred in the diet group during this phase of the trial. Because weight was stable during the second half of the trial, the continued improvement in insulin sensitivity in the diet-exercise group could only be attributed to the exercise. Conversely, exercise without prerequisite weight loss (and similar fitness improvement) was not associated with improvement in insulin sensitivity, ruling out an effect of exercise that might have been overshadowed by weight loss during the first 6 months in the diet-exercise group. Rather, this novel finding suggest a threshold effect by which the deleterious effect of excess adiposity on insulin sensitivity precluded any benefit of exercise until a significant amount of weight loss was achieved. Interestingly, variables which correlated with improved insulin sensitivity consisted mainly of weight- and fat-associated changes (e.g. trunk fat, visceral fat, S-TNF R1), which did not differ between the diet and the diet-exercise groups, suggesting a distinct complementary mechanism by which exercise potentiated insulin sensitivity. It is possible that the beneficial effect of exercise following a prerequisite weight loss may be related to improvement in peripheral insulin sensitivity, as exercise training has been shown to enhance responsiveness of muscles to insulin with increased activity of proteins involved in insulin signaling (45;46). Further, there is a growing literature describing beneficial effect of exercise but not weight loss on the muscle fatty acid oxidation capacity of obese individuals (47;48). The present study provides the first evidence that this independent effect of exercise may be contingent upon preceding weight loss in this older population.

The strengths of our study include the degree of adherence to the 1-year interventions which allowed for assessment of the distinct effects of weight loss versus exercise without weight loss on multiple cardiometabolic risk factors. The similar degree of weight loss in the diet and diet-exercise groups allowed for unbiased comparison of the two interventions. The 6-month weight loss followed by 6-month weight maintenance phase±exercise training allowed for examination of the temporal pattern of changes over time. Our study was designed to examine the chronic rather than acute effects of exercise; therefore, we performed the metabolic tests several hours (~72 hours) after the last bout of exercise. Potential limitations include that we assessed insulin sensitivity using OGTT rather than the gold standard of glucose clamp technique. However, the ISI has been validated against the clamp (12) and found to be similar in its relationship with cardiovascular risk factors (49). We did not have muscle biopsy samples to directly assess metabolic outcomes within skeletal muscles in response to lifestyle interventions, which should be considered in future investigations in this population. We selected participants who volunteered for the study so our results may not necessarily apply to the general obese older population. Another potential limitation is that many statistical tests have been performed without rigorous correction for the multiplicity of tests. Our approach to minimize the risk for type 1 error included: 1) using pre-specified contrast statements to test three specific hypotheses and 2)
performing these focused tests only after achieving a significant omnibus F test (p<0.05) (see *Statistical Analysis*).

In conclusion, lifestyle interventions associated with weight loss result in clinically important improvements in insulin sensitivity and multiple other cardiometabolic risk factors in obese older adults. Importantly, exercise training in combination with diet-induced weight loss results in an even greater improvement in insulin sensitivity when continued for a prolonged period. Therefore, a lifestyle intervention strategy incorporating weight loss and regular exercise may best reduce the risk for cardiometabolic syndrome in obese older adults. Moreover, optimal treatment strategy in obese older adults should consider the positive effects of exercise on lean tissues and its additive effect on improving physical function when combined with weight loss (11).

**Acknowledgments**

We thank the participants for their cooperation and the staff of the Clinical and Translational Sciences for their skilled assistance in the performance of this study. This study was supported by grants RO1-AG025501, RO1-AG031176, and P30-DK56341 (Clinical Nutrition Research Unit), UL1-RR024992 (Clinical and Translational Science Award), DK20579 (Diabetes Research and Training Center) from the National Institutes of Health and resources at the New Mexico VA Health Care System.

**Authors’ roles:** Study design: DTV, DRS. Acquisition of data: KS, NN, RA, DRS, DTV. Study conduct: DTV, KS, RA, NN, DRS. Data analysis and interpretation: DTV, MB, KS, RA, NN, DRS, CQ. Drafting of the manuscript: DTV, MB, RA, CQ. Critical revision of the manuscript for important intellectual content: DTV, MB, RA, NN, DRS, KS, CQ. Statistical analysis: CQ. Primary responsibility for final content: DTV and CQ

**Reference List**

1. Villareal DT, Apovian CM, Kushner RF, Klein S. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. Am J Clin Nutr. 2005; 82/5:923–934. [PubMed: 16280421] [also published in: Obes Res. 2005; 13:1849-1863].

2. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med. 2012; 42/6:563–570. [PubMed: 22608371]

3. Sommers, Andrew R. Text in: CRS Report for Congress: Accessed: December 5 2. U.S. Congressional Research Service: Obesity Among Older Americans (RL34358, Feb. 20, 2009). 2011.

4. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. Circulation. 2004; 110/18:2952–2967. [PubMed: 15509809]

5. Stevens J, Cai J, Pamuk ER, Williamson DF, Thun MJ, Wood JL. The effect of age on the association between body-mass index and mortality. N Engl J Med. 1998; 338/1:1–7. [PubMed: 9414324]

6. Waters DL, Ward AL, Villareal DT. Weight loss in obese adults 65years and older: A review of the controversy. Exp Gerontol. 2013

7. Bales CW, Buhr G. Is obesity bad for older persons? A systematic review of the pros and cons of weight reduction in later life. J Am Med Dir Assoc. 2008; 9/5:302–312. [PubMed: 18519110]

8. Miller SL, Wolfe RR. The danger of weight loss in the elderly. J Nutr Health Aging. 2008; 12/7:487–491. [PubMed: 18615231]

9. Rolland Y, Kim MJ, Gammmack JK, Wilson MM, Thomas DR, Morley JE. Office management of weight loss in older persons. Am J Med. 2006; 119/12:1019–1026. [PubMed: 17145241]
10. Gregg EW, Gerzoff RB, Thompson TJ, Williamson DF. Intentional weight loss and death in overweight and obese U.S. adults 35 years of age and older. Ann Intern Med. 2003; 138/5:383–389. [PubMed: 12614090]

11. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med. 2011; 364/13:1218–1229. [PubMed: 21449785]

12. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care. 1999; 22/9:1462–1470. [PubMed: 10480510]

13. Allison DB, Paultre F, Maggio C, Mezzitis N, Pi-Sunyer FX. The use of areas under curves in diabetes research. Diabetes Care. 1995; 18/2:245–250. [PubMed: 7729306]

14. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28/7:412–419. [PubMed: 3899825]

15. Villareal DT, Miller BV III, Banks M, Fontana L, Sinacore DR, Klein S. Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. Am J Clin Nutr. 2006; 84/6:1317–1323. [PubMed: 17158411]

16. WHO STEPwise approach to surveillance (STEPS). World Health Organization (WHO); Generva: 2008. 2013.

17. Villareal DT, Banks M, Sinacore DR, Siener C, Klein S. Effect of weight loss and exercise on frailty in obese older adults. Arch Intern Med. 2006; 166/8:860–866. [PubMed: 16636211]

18. Arif H, Racette SB, Villareal DT, Holloszy JO, Weiss EP. Comparison of methods for assessing abdominal adipose tissue from magnetic resonance images. Obesity (Silver Spring). 2007; 15/9:2240–2244. [PubMed: 17890492]

19. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JJ, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009; 120/16:1640–1645. [PubMed: 19805654]

20. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the Third National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2003; 163/4:427–436. [PubMed: 12588201]

21. Beaufrebre B, Morio B. Fat and protein redistribution with aging: metabolic considerations. Eur J Clin Nutr. 2000; 54(Suppl 3):S48–S53. [PubMed: 11041075]

22. Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, et al. Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch Intern Med. 2005; 165/7:777–783. [PubMed: 15824927]

23. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes. 2001; 24/4:683–689. [PubMed: 11315831]

24. Alexander CM, Landsman PB, Deutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes. 2003; 52/5:1210–1214. [PubMed: 12716754]

25. Kirk EP, Klein S. Pathogenesis and pathophysiology of the cardiometabolic syndrome. J Clin Hypertens (Greenwich ). 2009; 11/12:761–765. [PubMed: 20021538]

26. de Boer IH, Katz R, Chonchol MB, Fried LF, Ix JH, Kestenbaum B, et al. Insulin resistance, cystatin C, and mortality among older adults. Diabetes Care. 2012; 35/6:1355–1360. [PubMed: 22432118]

27. Segal KR, Edano A, Abalos A, Albu J, Blando L, Tomas MB, et al. Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. J Appl Physiol. 1991; 71/6:2402–2411. [PubMed: 1778939]
28. Ross R, Dagone D, Jones PJ, Smith H, Paddags A, Hudson R, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: A randomized, controlled trial. Ann Intern Med. 2000; 133/2:92–103. [PubMed: 10896648]

29. Brochu M, Malita MF, Messier V, Doucet E, Strychar I, Lavoie JM, et al. Resistance training does not contribute to improving the metabolic profile after a 6-month weight loss program in overweight and obese postmenopausal women. J Clin Endocrinol Metab. 2009; 94/9:3226–3233. [PubMed: 19567540]

30. Bouchonville et al. Page 12

31. Balducci S, Zanuso S, Nicolucci A, De FP, Cavallo S, Cardelli P, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: a randomized controlled trial: the Italian Diabetes and Exercise Study (IDES). Arch Intern Med. 2010; 170/20:1794–1803. [PubMed: 21059972]

32. Solomon TP, Haus JM, Kelly KR, Rocco M, Kashyap SR, Kirwan JP. Improved pancreatic beta-cell function in type 2 diabetic patients after lifestyle-induced weight loss is related to glucose-dependent insulinotropic polypeptide. Diabetes Care. 2010; 33/7:1561–1566. [PubMed: 20200305]

33. Yassine HN, Marchetti CM, Krishnan RK, Vrobel TR, Gonzalez F, Kirwan JP. Effects of exercise and caloric restriction on insulin resistance and cardiometabolic risk factors in older obese adults--a randomized clinical trial. J Gerontol A Biol Sci Med Sci. 2009; 64/1:90–95. [PubMed: 19164269]

34. Villareal DT, Banks MR, Patterson BW, Polonsky KS, Klein S. Weight Loss Therapy Improves Pancreatic Endocrine Function in Obese Older Adults. Obesity (Silver Spring). 2008; 16/6:1349–1354. [PubMed: 18388888]

35. Kahn SE, Larson VG, Beard JC, Cain KC, Fellingham GW, Schwartz RS, et al. Effect of exercise on insulin action, glucose tolerance, and insulin secretion in aging. Am J Physiol. 1990; 258/6(Pt 1):E937–E943. [PubMed: 12972442]

36. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. Diabetes Care. 2003; 26/3:557–562. [PubMed: 12610001]

37. Cox JH, Cortright RN, Dohm GL, Houmard JA. Effect of aging on response to exercise training in humans: skeletal muscle GLUT-4 and insulin sensitivity. J Appl Physiol. 1999; 86/6:1999–2025. [PubMed: 10368369]

38. Dengel DR, Pratley RE, Hagberg JM, Rogus EM, Goldberg AP. Distinct effects of aerobic exercise training and weight loss on glucose homeostasis in obese sedentary men. J Appl Physiol. 1996; 81/1:318–325. [PubMed: 8828680]

39. Ross R. Does exercise without weight loss improve insulin sensitivity? Diabetes Care. 2003; 26/3:944–945. [PubMed: 12610063]

40. Hojbjerre L, Sonne MP, Alibegovic AC, Nielsen NB, Dela F, Vaag A, et al. Impact of physical inactivity on adipose tissue low-grade inflammation in first-degree relatives of type 2 diabetic patients. Diabetes Care. 2011; 34/10:2265–2272. [PubMed: 21836102]

41. Christiansen T, Poulsen SK, Bruun JM, Ploug T, Pedersen SB, Richtelsen B. Diet-induced weight loss and exercise alone and in combination enhance the expression of adiponectin receptors in adipose tissue and skeletal muscle, but only diet-induced weight loss enhanced circulating adiponectin. J Clin Endocrinol Metab. 2010; 95/2:911–919. [PubMed: 19996310]

42. Nicklas BJ, Ambrosius W, Messier SP, Miller GD, Penninx BW, Looser RF, 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. [PubMed: 15051595]
45. O’Gorman DJ, Karlsson HK, McQuaid S, Yousif O, Rahman Y, Gasparro D, et al. Exercise training increases insulin-stimulated glucose disposal and GLUT4 (SLC2A4) protein content in patients with type 2 diabetes. Diabetologia. 2006; 49/12:2983–2992. [PubMed: 17019595]

46. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JF, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin signaling in skeletal muscle in patients with type 2 diabetes. Diabetes. 2004; 53/2:294–305. [PubMed: 14747278]

47. Goodpaster BH, Katsiaras A, Kelley DE. Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity. Diabetes. 2003; 52/9:2191–2197. [PubMed: 12941756]

48. Berggren JR, Boyle KE, Chapman WH, Houmard JA. Skeletal muscle lipid oxidation and obesity: influence of weight loss and exercise. Am J Physiol Endocrinol Metab. 2008; 294/4:E726–E732. [PubMed: 18252891]

49. Lorenzo C, Haffner SM, Stancakova A, Laakso M. Relation of direct and surrogate measures of insulin resistance to cardiovascular risk factors in nondiabetic finnish offspring of type 2 diabetic individuals. J Clin Endocrinol Metab. 2010; 95/11:5082–5090. [PubMed: 20702522]
Figure 1.
Mean percent changes in body weight (Panel A) and insulin sensitivity (Panel B) during the 1-year interventions. In Panel A, the changes in body weight in the diet-exercise group and the diet group differed significantly from the changes in body weight in the exercise group and control group. In Panel B, the change in insulin sensitivity in the diet-exercise group differed significantly from the changes in insulin sensitivity in the diet group, exercise group, and control group. Values are mean ± standard error.
## Table 1
Baseline Characteristics of Participants

|                  | Control (n = 27) | Diet (n = 26) | Exercise (n = 26) | Diet-Exercise (n = 28) | P Value * |
|------------------|-----------------|---------------|------------------|------------------------|-----------|
| Age, mean (SD), y| 69 (4)          | 70 (4)        | 70 (4)           | 70 (4)                 | 0.85      |
| Female, n (%)    | 18 (67)         | 17 (65)       | 16 (61)          | 16 (57)                | 0.89      |
| White, n (%)     | 22 (81)         | 23 (88)       | 21 (81)          | 25 (89)                | 0.78      |
| Height, mean (SD), cm | 165.8 (9.7) | 169.2 (9.5)  | 168.1 (1.1)      | 165.4 (8.7)            | 0.38      |
| Weight, mean (SD), kg | 101.0 (16.3) | 104.1 (15.3) | 99.2 (17.4)      | 99.1 (16.8)            | 0.66      |
| Body mass index, mean (SD), kg/m² | 37.3 (4.7) | 37.2 (4.5)  | 36.9 (5.4)       | 37.2 (5.4)             | 0.93      |
| Total fat mass (kg) | 43.8 (9.9) | 42.8 (6.6)  | 41.6 (9.4)       | 41.9 (11.5)            | 0.67      |
| Body fat percent, mean (SD) | 43.4 (6.7) | 41.6 (5.8)  | 40.2 (10.5)      | 42.1 (7.1)             | 0.53      |
| Modified Physical Performance Test, mean (SD) | 26.8 (4.5) | 28.6 (1.9)  | 27.1 (3.1)       | 28.0 (2.9)             | 0.17      |
| VO₂peak relative to body weight, mean (SD), ml/kg/min | 16.3 (3.8) | 17.6 (2.2)  | 17.4 (3.5)       | 17.3 (3.5)             | 0.55      |
| Absolute VO₂peak, mean (SD), L/min | 1.69 (0.49) | 1.84 (0.41) | 1.76 (0.51)      | 1.73 (0.38)            | 0.66      |
| History of cardiovascular disease, n (%) | 8 (30)       | 8 (31)       | 7 (27)           | 9 (31)                 | 0.98      |
| Previous cigarette use, n (%) | 9 (33)       | 7 (26)       | 9 (34)           | 11 (39)                | 0.82      |
| Antihypertensive | 16 (59)         | 15 (57)       | 18 (69)          | 18 (64)                | 0.82      |
| Antidyslipidemic | 8 (29)          | 8 (30)        | 10 (26)          | 8 (25)                 | 0.86      |

*P values, as calculated with the use of analyses of variance for quantitative data and chi-square tests for counts.
|                          | Mean (SD) Value       | Difference in Change from Baseline to 12 mo (95% CI) | *P* Value |
|--------------------------|-----------------------|-----------------------------------------------------|-----------|
|                          | Baseline | Change at 6 mo | Change at 12 mo |                                      |
| **Insulin sensitivity index** |          |               |               |                                      |
| Control group            | 3.3 (2.0) | −0.1 (0.8)     | 0.2 (1.4)     | −                                   |
| Diet group               | 2.7 (1.6) | 1.1 (1.2)      | 1.2 (1.6)     | −                                   |
| Exercise group           | 3.5 (2.6) | 0.1 (1.4)      | 0.1 (1.9)     | −                                   |
| Diet-exercise group      | 3.4 (2.4) | 1.2 (1.6)      | 2.4 (2.3)     | −                                   |
| **Intergroup comparisons** |          |               |               |                                      |
| Diet vs. control         | −         | −             | −             | 1.0 (0.0 to 1.8)                     | 0.05     |
| Exercise vs. control     | −         | −             | −             | −0.1 (−1.2 to 0.8)                   | 0.66     |
| Diet-exercise vs. diet   | −         | −             | −             | 1.2 (0.2 to 2.1)                     | 0.02     |
| Diet-exercise vs. exercise | −       | −            | −             | 2.3 (1.4 to 3.4)                     | <0.001   |
| **Other OGTT variables** |          |               |               |                                      |
| Insulin AUC (× 10^3 mg.min/dL) |          |               |               |                                      |
| Control group            | 9.1 (5.1) | 0.9 (3.3)      | 0.6 (4.0)     | −                                   |
| Diet group               | 12.9 (7.5)| −3.1 (−5.9)    | −2.9 (6.1)    | −                                   |
| Exercise group           | 10.7 (6.8)| 0.1 (3.6)      | −0.1 (3.6)    | −                                   |
| Diet-exercise group      | 10.8 (5.5)| −2.9 (4.1)     | −2.9 (3.9)    | −                                   |
| **Intergroup comparisons** |          |               |               |                                      |
| Diet vs. control         | −         | −             | −             | −3.5 (−6.3 to −1.4)                  | <0.01    |
| Exercise vs. control     | −         | −             | −             | −0.5 (−3.0 to 1.9)                   | 0.78     |
| Diet-exercise vs. diet   | −         | −             | −             | 0.0 (−1.8 to 2.9)                    | 0.67     |
| Diet-exercise vs. exercise | −       | −            | −             | −3.0 (−5.2 to 0.4)                   | 0.02     |
| Glucose AUC (× 10^3 mg.min/dL) |          |               |               |                                      |
| Control group            | 19.0 (2.8)| 0.2 (3.2)      | −0.3 (1.9)    | −                                   |
| Diet group               | 18.6 (3.5)| −1.8 (2.3)     | −2.2 (2.7)    | −                                   |
| Exercise group           | 18.1 (2.8)| 0.3 (2.2)      | −0.3 (2.7)    | −                                   |
| Diet-exercise group      | 18.1 (3.6)| −0.9 (2.9)     | −1.4 (2.8)    | −                                   |
| **Intergroup comparisons** |          |               |               |                                      |
| Diet vs. control         | −         | −             | −             | −2.5 (−3.8 to −0.8)                  | <0.01    |
| Exercise vs. control     | −         | −             | −             | 0.0 (−1.8 to 1.4)                    | 0.80     |
| Diet-exercise vs. diet   | −         | −             | −             | 0.8 (−0.8 to 2.2)                    | 0.35     |
| Diet-exercise vs. exercise | −       | −            | −             | −1.7 (−2.9 to 0.2)                   | 0.08     |
| Fasting insulin (μU/mL)  |          |               |               |                                      |
| Control group            | 16.0 (9.9)| 0.1 (7.1)      | −2.0 (9.5)    | −                                   |
| Diet group               | 17.5 (9.9)| −5.0 (6.8)     | −4.5 (7.3)    | −                                   |
| Exercise group           | 16.0 (10.2)| −1.1 (6.3)     | −2.1 (6.4)    | −                                   |
|                                      | Mean (SD) Value | Difference in Change from Baseline to 12 mo (95% CI) | P Value * |
|--------------------------------------|-----------------|------------------------------------------------------|----------|
|                                      | Baseline        | Change at 6 mo                                      | Change at 12 mo |
| **Diet-exercise group**              | 17.0 (12.0)     | −3.3 (6.3)†                                         | −6.2 (7.1)†  |        |
|                                      |                 |                                                     |            |        |
| **Intergroup comparisons**           |                 |                                                     |            |        |
| Diet vs. control                     | −                  | −                                                   | −2.5 (−6.7 to 1.2) | 0.12   |
| Exercise vs. control                 | −                  | −                                                   | 0.1 (−4.4 to 3.3) | 0.88   |
| Diet-exercise vs. diet               | −                  | −                                                   | −1.7 (−5.4 to 2.4) | 0.45   |
| Diet-exercise vs. exercise           | −                  | −                                                   | −4.1 (−8.4 to −0.6) | 0.02   |
| **HOMA-IR**                          |                 |                                                     |            |        |
| Control group                        | 4.1 (2.9)        | 0.3 (2.6)                                           | −0.3 (2.9)   |        |
| Diet group                           | 4.2 (2.8)        | −1.3 (1.7)†                                         | −1.4 (1.8)†  |        |
| Exercise group                       | 4.0 (2.7)        | −0.3 (1.7)†                                         | −0.7 (1.8)   |        |
| Diet-exercise group                  | 4.4 (3.6)        | −1.1 (1.4)†                                         | −1.7 (1.9)†  |        |
|                                      |                 |                                                     |            |        |
| **Intergroup comparisons**           |                 |                                                     |            |        |
| Diet vs. control                     | −                  | −                                                   | −1.1 (−2.0 to 0.2) | 0.12   |
| Exercise vs. control                 | −                  | −                                                   | −0.4 (−1.3 to 1.0) | 0.78   |
| Diet-exercise vs. diet               | −                  | −                                                   | −0.3 (−1.5 to 0.6) | 0.43   |
| Diet-exercise vs. exercise           | −                  | −                                                   | −1.0 (−2.3 to −0.1) | 0.04   |
| **Body weight and central obesity**  |                 |                                                     |            |        |
| **Body weight (kg)**                 |                 |                                                     |            |        |
| Control group                        | 101.0 (16.3)     | 0.9 (2.8)                                           | −0.1 (3.5)   |        |
| Diet group                           | 104.1 (15.3)     | −9.0 (5.4)†                                         | −9.7 (5.4)†  |        |
| Exercise group                       | 99.2 (17.4)      | −0.3 (2.3)†                                         | −0.5 (3.6)   |        |
| Diet-exercise group                  | 99.1 (16.8)      | −7.7 (4.2)†                                         | −8.6 (3.8)†  |        |
|                                      |                 |                                                     |            |        |
| **Intergroup comparisons**           |                 |                                                     |            |        |
| Diet vs. control                     | −                  | −                                                   | −9.0 (−1.1 to −6.7) | <0.001 |
| Exercise vs. control                 | −                  | −                                                   | −0.4 (−2.7 to 1.8) | 0.72   |
| Diet-exercise vs. diet               | −                  | −                                                   | 0.3 (−1.9 to 2.6) | 0.78   |
| Trunk fat (kg)                       |                 |                                                     |            |        |
| Control group                        | 22.4 (5.6)       | −0.3 (1.4)†                                         | 0.5 (2.9)    |        |
| Diet group                           | 21.8 (4.1)       | −3.2 (2.7)†                                         | −3.4 (2.4)†  |        |
| Exercise group                       | 21.2 (4.1)       | −0.6 (1.1)†                                         | −0.8 (1.3)†  |        |
| Diet-exercise group                  | 20.9 (4.8)       | −3.4 (1.8)†                                         | −3.3 (1.9)†  |        |
|                                      |                 |                                                     |            |        |
| **Intergroup comparisons**           |                 |                                                     |            |        |
| Diet vs. control                     | −                  | −                                                   | −3.9 (−5.2 to −2.9) | <0.001 |
| Exercise vs. control                 | −                  | −                                                   | −1.3 (−2.4 to −0.8) | 0.04   |
| Diet-exercise vs. diet               | −                  | −                                                   | 0.1 (−0.9 to 1.3) | 0.74   |
| Diet-exercise vs. exercise           | −                  | −                                                   | −2.5 (−3.8 to −1.5) | <0.001 |
| **Visceral fat (cm³)**               |                 |                                                     |            |        |
| Control group                        | 2591 (1539)      | −                                                   | 15 (589)     |        |
|                          | Mean (SD) Value | Difference in Change from Baseline to 12 mo (95% CI) | P Value * |
|--------------------------|-----------------|------------------------------------------------------|-----------|
|                          | Baseline        | Change at 6 mo | Change at 12 mo                                    |           |
| **Diet group**           | 2175 (1087)     | -            | −561 (454)†                                         |           |
| **Exercise group**       | 2231 (1183)     | -            | −115 (244)†                                         |           |
| **Diet-exercise group**  | 2086 (1337)     | -            | −787 (896)†                                         |           |
| **Intergroup comparisons** |                  |              |                                                     |           |
| Diet vs. control         | -               | -            | −576 (−866 to −285)                                 | <0.001    |
| Exercise vs. control     | -               | -            | −130 (−380 to 120)                                  | 0.39      |
| Diet-exercise vs. diet   | -               | -            | −226 (−615 to 163)                                  | 0.19      |
| Diet-exercise vs. exercise | -           | -            | −672 (−1031 to −312)                                | <0.001    |
| **Subcutaneous fat (cm³)** |                |              |                                                     |           |
| Control group            | 3805 (1036)     | -            | 305 (889)                                           |           |
| Diet group               | 3558 (958)      | -            | −457 (326)†                                         |           |
| Exercise group           | 3256 (978)      | -            | −83 (326)                                           |           |
| Diet-exercise group      | 3600 (1389)     | -            | −464 (475)†                                         |           |
| **Intergroup comparisons** |                  |              |                                                     |           |
| Diet vs. control         | -               | -            | −762 (−1134 to −389)                                | <0.001    |
| Exercise vs. control     | -               | -            | −388 (−760 to −16)                                  | 0.02      |
| Diet-exercise vs. diet   | -               | -            | −7 (−231 to 217)                                    | 0.96      |
| Diet-exercise vs. exercise | -          | -            | −381 (−605 to −156)                                 | 0.03      |
| **Lean body mass (kg)**  |                |              |                                                     |           |
| Control group            | 57.3 (11.5)     | −0.7 (2.3)   | −0.8 (2.5)                                          |           |
| Diet group               | 61.4 (13.0)     | −3.5 (2.7)† | −3.2 (2.0)†                                         |           |
| Exercise group           | 57.6 (13.7)     | 1.1 (2.1)†  | 1.3 (1.6)†                                          |           |
| Diet-exercise group      | 57.2 (10.3)     | −1.7 (1.6)† | −1.8 (1.7)†                                         |           |
| **Intergroup comparisons** |                  |              |                                                     |           |
| Diet vs. control         | -               | -            | −2.4 (−3.6 to 1.2)                                  | <0.001    |
| Exercise vs. control     | -               | -            | 2.1 (0.9 to 3.3)                                    | <0.001    |
| Diet-exercise vs. diet   | -               | -            | 1.2 (0.3 to 2.3)                                    | 0.04      |
| Diet-exercise vs. exercise | -          | -            | −3.1 (−4 to −2.2)                                   | <0.001    |
| **hs-CRP and adipocytokines** |            |              |                                                     |           |
| **hs-CRP (mg/L)**        |                |              |                                                     |           |
| Control group            | 3.8 (3.9)       | 0.7 (3.2)   | 2.2 (5.0)                                           |           |
| Diet group               | 3.5 (3.0)       | −1.0 (1.4)† | −1.1 (1.4)†                                         |           |
| Exercise group           | 4.0 (4.0)       | −0.2 (1.7)  | 0.7 (2.8)                                           |           |
| Diet-exercise group      | 4.8 (6.3)       | −1.8 (3.7)† | −1.8 (3.4)†                                         |           |
| **Intergroup comparisons** |                  |              |                                                     |           |
| Diet vs. control         | -               | -            | −3.3 (−5.2 to −1.6)                                 | <0.001    |
| Exercise vs. control     | -               | -            | −2.9 (−4.7 to −1.1)                                 | <0.01     |
|                          | Mean (SD) Value | Difference in Change from Baseline to 12 mo (95% CI) | P Value * |
|--------------------------|----------------|-----------------------------------------------------|-----------|
|                          | Baseline | Change at 6 mo | Change at 12 mo |                                      |
| Diet-exercise vs. diet   | -        | -              | -              | −0.7 (−2.2 to 1.2) | 0.56 |
| Diet-exercise vs. exercise | -        | -              | -              | −1.1 (−2.7 to 0.7) | 0.23 |

**sTNF R1 (pg/mL)**

|                          |          | -2.2 (24.7) | 12.3 (20.6) | -          |
|--------------------------|----------|-------------|------------|------------|
| Control group            | 167.2 (34.7) | -          | -          |           |
| Diet group               | 155.8 (34.7) | -11.9 (−19.7) | −12.8 (21.7) | -          |
| Exercise group           | 166.6 (51.2) | −0.6 (22.4) | 9.6 (20.4) | -          |
| Diet-exercise group      | 177.5 (49.1) | −21.6 (26.4) | −17.0 (29.2) | -          |

**Intergroup comparisons**

|                          |          |          | -25.1 (−36.7 to −8.7) | <0.01 |
|--------------------------|----------|----------|----------------------|-------|
| Diet vs. control         | -        | -        | -                    | -     |
| Exercise vs. control     | -        | -        | -2.7 (−15.2 to 12.9) | 0.87  |
| Diet-exercise vs. diet   | -        | -        | -4.2 (−18.7 to 8.1)  | 0.44  |
| Diet-exercise vs. exercise | -        | -        | −26.6 (−40.3 to −13.5) | <0.001 |

**Adiponectin (ng/mL)**

|                          |          | -3.2 (10.8) | −4.9 (20.6) | -          |
|--------------------------|----------|-------------|------------|------------|
| Control group            | 31.9 (23.3) | -          | -          |           |
| Diet group               | 23.3 (12.1) | 2.8 (4.7)† | 4.0 (5.5)† | -          |
| Exercise group           | 20.8 (7.4) | 1.0 (5.9)† | 1.6 (5.1)† | -          |
| Diet-exercise group      | 24.4 (13.0) | 2.5 (5.7)† | 5.0 (8.4)† | -          |

**Intergroup comparisons**

|                          |          |          | 8.9 (3.5 to 14.8) | <0.01 |
|--------------------------|----------|----------|-------------------|-------|
| Diet vs. control         | -        | -        | -                 | -     |
| Exercise vs. control     | -        | -        | 6.5 (0.8 12.3)    | 0.02  |
| Diet-exercise vs. diet   | -        | -        | 1.0 (−4.5 to 6.2) | 0.74  |
| Diet-exercise vs. exercise | -        | -        | 3.4 (−1.9 to 9.0) | 0.21  |

**Metabolic syndrome components**

**Fasting glucose (mg/dL)**

|                          |          | 2.4 (9.4) | −0.6 (11.8) | -          |
|--------------------------|----------|----------|------------|------------|
| Control group            | 101.7 (10.1) | -        | -          |           |
| Diet group               | 96.2 (12.2) | −3.5 (8.7)† | −3.7 (11.5)† | -          |
| Exercise group           | 99.7 (8.4) | 0.9 (8.9) | −1.3 (8.3) | -          |
| Diet-exercise group      | 99.3 (11.3) | −2.4 (7.0)† | −5.4 (9.0)† | -          |

**Intergroup comparisons**

|                          |          |          | −3.1 (−8.3 to 2.3) | 0.27 |
|--------------------------|----------|----------|-------------------|------|
| Diet vs. control         | -        | -        | -                 | -    |
| Exercise vs. control     | -        | -        | −0.7 (−5.5 to 5.3) | 0.96 |
| Diet-exercise vs. diet   | -        | -        | −1.7 (−6.6 to 3.7) | 0.58 |
| Diet-exercise vs. exercise | -        | -        | −4.1 (−9.5 to 0.9) | 0.11 |

**Waist circumference (cm)**

|                          |          | 1.2 (7.2) | 1.0 (6.1)  | -          |
|--------------------------|----------|----------|------------|------------|
| Control group            | 117.5 (12.8) | -        | -          |           |
| Diet group               | 118.2 (11.5) | −8.5 (10.5)† | −8.4 (8.6)† | -          |
| Exercise group           | 114.9 (12.7) | −0.1 (8.0) | −4.0 (9.1)† | -          |
|                      | Mean (SD) Value | Difference in Change from Baseline to 12 mo (95% CI) | P Value * |
|----------------------|----------------|-----------------------------------------------------|-----------|
|                      | Baseline       | Change at 6 mo                                      | Change at 12 mo |
| Diet-exercise group  | 116.0 (14.8)   | −7.9 (10.0) †                                       | −8.2 (10.3) † |

**Intergroup comparisons**

- Diet vs. control
- Exercise vs. control
- Diet-exercise vs. diet
- Diet-exercise vs. exercise

**HDL cholesterol (mg/dL)**

- Control group 51.7 (13.4)
- Diet group 53.3 (12.9)
- Exercise group 53.7 (13.9)
- Diet-exercise group 55.2 (15.4)

**Intergroup comparisons**

- Diet vs. control
- Exercise vs. control
- Diet-exercise vs. diet
- Diet-exercise vs. exercise

**Triglyceride (mg/dL)**

- Control group 123.2 (50.4)
- Diet group 144.6 (60.1)
- Exercise group 158.4 (73.8)
- Diet-exercise group 134.7 (65.1)

**Intergroup comparisons**

- Diet vs. control
- Exercise vs. control
- Diet-exercise vs. diet
- Diet-exercise vs. exercise

**Systolic blood pressure (mm Hg)**

- Control group 133.3 (18.6)
- Diet group 135.3 (19.1)
- Exercise group 131.2 (11.7)
- Diet-exercise group 138.6 (23.6)

**Intergroup comparisons**

- Diet vs. control
- Exercise vs. control
- Diet-exercise vs. diet
- Diet-exercise vs. exercise

**Diastolic blood pressure (mm Hg)**

- Control group 71.5 (10.7)

*Int J Obes (Lond). Author manuscript; available in PMC 2014 September 01.*
| Group                  | Baseline (SD) | Change at 6 mo | Change at 12 mo | Difference in Change from Baseline to 12 mo (95% CI) | P Value |
|-----------------------|---------------|----------------|-----------------|------------------------------------------------------|---------|
| Diet group            | 75.7 (11.0)   | -6.0 (9.6)     | -6.7 (10.3)     | -5.5 (−11.1 to 0.8)                                   | 0.09    |
| Exercise group        | 70.9 (8.3)    | -1.4 (11.1)    | -2.1 (6.1)      | -1.0 (−7.6 to 4.4)                                   | 0.60    |
| Diet-exercise group   | 74.0 (10.1)   | -4.5 (10.6)‡   | -4.9 (9.5)‡     | -1.8 (−5.0 to 6.6)                                   | 0.77    |

**Intergroup comparisons**

| Comparison          | Difference (95% CI) | P Value |
|---------------------|----------------------|---------|
| Diet vs. control    | -5.5 (−11.1 to 0.8)  | 0.09    |
| Exercise vs. control| -1.0 (−7.6 to 4.4)   | 0.60    |
| Diet-exercise vs. diet | -1.8 (−5.0 to 6.6) | 0.77    |
| Diet-exercise vs. exercise | -2.8 (−8.6 to 3.2) | 0.36    |

*P values, as calculated with the use of mixed-model repeated-measures analyses of variance contrasts

‡*P < 0.05 for the comparison of the value from baseline, as calculated with the use of mixed-model repeated-measures analyses of variance

Abbreviations: CI, confidence interval; OGTT, oral glucose tolerance test; AUC, area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high sensitivity C-reactive protein; sTNF R1, soluble tumor necrosis factor receptor 1
Table 3

Effect of Diet, Exercise, or Combined on the Prevalence of the Cardiometabolic Syndrome in Obese Older Adults

| Participants with cardiometabolic syndrome, no. (%) | Control (n=27) | Diet (n=26) | Exercise (n=26) | Diet-Exercise (n=28) | P Value* |
|-----------------------------------------------------|---------------|-------------|----------------|---------------------|---------|
| **Baseline**                                        |               |             |                |                     |         |
| 3 criteria                                          | 9 (33)        | 8 (31)      | 7 (27)         | 11 (39)             |         |
| 4 criteria                                          | 8 (30)        | 7 (27)      | 12 (46)        | 9 (32)              |         |
| 5 criteria                                          | 3 (11)        | 4 (15)      | 2 (8)          | 2 (7)               |         |
| **Total**                                           | 20 (74)       | 19 (73)     | 21 (81)        | 22 (79)             | 0.90    |
| **Six months**                                      |               |             |                |                     |         |
| 3 criteria                                          | 8 (30)        | 7 (27)      | 6 (23)         | 6 (21)              |         |
| 4 criteria                                          | 13 (48)       | 4 (15)      | 11 (42)        | 8 (29)              |         |
| 5 criteria                                          | 1 (4)         | 2 (8)       | 3 (12)         | 2 (7)               |         |
| **Total**                                           | 22 (82)       | 13 (50)     | 20 (77)        | 16 (57)             | 0.04    |
| **1 year**                                          |               |             |                |                     |         |
| 3 criteria                                          | 7 (26)        | 10 (39)     | 9 (35)         | 4 (14)              |         |
| 4 criteria                                          | 9 (33)        | 4 (15)      | 9 (35)         | 5 (18)              |         |
| 5 criteria                                          | 4 (15)        | 1 (4)       | 2 (8)          | 2 (7)               |         |
| **Total**                                           | 20 (74)       | 15 (58)     | 20 (77)        | 11 (39)             | 0.02    |

* Between-group difference in the proportions of participants with the cardiometabolic syndrome at baseline, six months, and 1 year, as calculated with the use of Chi-square test.