Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults[1–4]

Nicola Napoli, Krupa Shah, Debra L Waters, David R Sinacore, Clifford Qualls, and Dennis T Villareal

ABSTRACT

Background: Obesity impairs cognition and health-related quality of life (HRQOL) in older adults; however, the appropriate treatment of obese older adults remains controversial.

Objective: The objective was to determine the independent and combined effects of weight loss and exercise on cognition, mood, and HRQOL in obese older adults.

Design: One hundred seven frail, obese older adults were randomly assigned to a control, weight-management (diet), exercise, or weight-management-plus-exercise (diet-exercise) group for 1 y. In this secondary analysis, main outcomes were Modified Mini-Mental State Examination (3MS) and total Impact of Weight on Quality of Life-Lite (IWQOL) scores. Other outcomes included Word Fluency Test, Trail Making Test Parts A and B, and Geriatric Depression Scale (GDS) scores.

Results: Scores on the 3MS improved more in the diet (mean ± SE: 1.7 ± 0.4), exercise (2.8 ± 0.4), and diet-exercise (2.9 ± 0.4) groups than in the control group (0.1 ± 0.4) (between-group P = 0.0001–0.04); scores in the diet-exercise group improved more than in the diet group but not more than in the exercise group. Scores on the Word Fluency Test improved more in the exercise (4.1 ± 0.8) and diet-exercise (4.2 ± 0.7) groups than in the control group (−0.8 ± 0.8; both P = 0.001). For the Trail Making Test Part A, scores in the diet-exercise group (−11.8 ± 1.9) improved more than in the control group (−0.8 ± 1.9) (P = 0.001); a similar finding was observed for the Trail Making Test Part B. Scores on the IWQOL improved more in the diet (7.6 ± 1.6), exercise (10.1 ± 1.6), and diet-exercise (14.0 ± 1.4) groups than in the control group (0.3 ± 1.6) (P = 0.0001–0.03); scores in the diet-exercise group improved more than in the diet group but not more than in the exercise group. In the diet-exercise group, peak oxygen consumption and strength changes were independent predictors of 3MS changes; weight and strength changes were independent predictors of IWQOL changes. GDS scores did not change.

Conclusions: Weight loss and exercise each improve cognition and HRQOL, but their combination may provide benefits similar to exercise alone. These findings could inform practice guidelines with regard to optimal treatment strategies for obese older adults. This trial was registered at clinicaltrials.gov as NCT00146107. *Am J Clin Nutr* 2014;100:189–98.

INTRODUCTION

Obesity in the older population is an urgent public health problem, with more than one-third of adults aged ≥65 y in the United States now classified as obese (1). This increasing population is at risk of adverse outcomes because obesity in older adults is associated with physical and metabolic complications that impair health-related quality of life (HRQOL)[5] (2). Moreover, obese older adults may be at increased risk of dementia, given convergent metabolic mechanisms such as insulin resistance and chronic inflammation (3). Indeed, midlife obesity has been consistently associated with dementia risk (4–6); however, obesity in older adults has been associated with both increased (7, 8) and decreased (9, 10) dementia risk. Possible explanations for the paradoxical findings include confounding because of birth cohort effects (11) and weight loss preceding dementia diagnosis (12). Conversely, limited data from small, mostly short-term clinical trials suggest that weight loss and/or exercise may improve cognition, although other studies showed no effects (13–17). Importantly, most previous intervention studies included participants with wide ranges in age and BMI and thus did not focus on the

[1] From the Division of Endocrinology, University Campus Bio-Medico Di Roma, Rome, Italy (NN); the Division of Geriatrics and Aging, University of Rochester School of Medicine, Rochester, NY (KS); the Department of Preventive and Social Medicine, University of Otago, Dunedin School of Medicine, Dunedin, New Zealand (DLW); the Division of Geriatrics and Nutritional Science (DRS and DTV) and the Program in Physical Therapy (DRS), Washington University School of Medicine, St Louis, MO; the Department of Mathematics and Statistics (CQ) and the Division of Geriatrics (DTV), University of New Mexico School of Medicine, Albuquerque, NM; and the Section of Geriatrics, New Mexico VA Health Care System, Albuquerque, NM (DTV).

[2] Supported by grants RO1-AG025501, AG031176, and P30-DK56341 (Clinical Nutrition Research Unit); UL1-RR024992 (a Clinical and Translational Science Award); and DK20579 (Diabetes Research and Training Center) from the NIH and by resources at the New Mexico VA Health Care System.

[3] The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Aging or the NIH.

[4] Address correspondence to DT Villareal, New Mexico VA Health Care System, Geriatrics (111K), 1501 San Pedro Drive, Albuquerque, NM 87108. E-mail: dennis.villareal@va.gov.

[5] Abbreviations used: ET, exercise training; GDS, Geriatric Depression Scale; HRQOL, health-related quality of life; hs-CRP, high-sensitivity C-reactive protein; IGF-I, insulin-like growth factor I; ISI, insulin sensitivity index; IWQOL, Impact of Weight on Quality of Life–Lite; LE, lower extremity; RCT, randomized controlled trial; VO_{2peak}, peak oxygen consumption; WUSM, Washington University School of Medicine; 1-RM, one-repetition maximum; 3MS, Modified Mini-Mental State Examination.

Received December 30, 2013. Accepted for publication April 9, 2014.

First published online April 30, 2014; doi: 10.3945/ajcn.113.082883.

vulnerable population of obese older adults (2, 16, 17). Furthermore, the potential mediators of the effects of weight loss and/or exercise on cognition and HRQOL still need to be elucidated (16, 18).

Lifestyle intervention (weight loss and exercise) is recommended as the cornerstone of obesity treatment at all ages (19, 20). However, this recommendation remains controversial in obese older adults because of the reduction in relative health risks with increasing BMI in this group and the concerns around the difficulty of behavioral change with advancing age, exacerbation of age-related lean tissue losses, and feasibility of long-term weight loss and other related health consequences (1). Thus, although weight loss and exercise are recommended as standard care for obese patients in general, this recommendation is not universally accepted by geriatricians for older adults. It is the common perception that extra weight may be protective against health risks in older adults (21, 22). Nevertheless, we recently reported that the combination of weight loss and exercise provides greater improvement in physical function and cardiometabolic health than either intervention alone (23, 24). Accordingly, we now report the results of the effects of weight loss alone, exercise alone, or combined weight loss and exercise on cognition, mood, and HRQOL in this population of frail, obese older adults.

SUBJECTS AND METHODS

The parent randomized controlled trial (RCT) evaluated the independent and combined effects of weight loss and exercise on physical function in obese older adults. The principal results showed that a combination of weight loss and exercise provides greater improvement in physical function than either intervention alone (23). The present study reports secondary analyses of the RCT examining changes in cognition, mood, and HRQOL as prespecified in the protocol.

Study population

This study was conducted at Washington University School of Medicine (WUSM) and approved by the university's institutional review board. Study oversight was provided by a data and safety monitoring board. Volunteers were recruited through advertisements, and informed consent was obtained from each participant. Details of the inclusion and exclusion criteria have been described (23). Briefly, eligible participants had to be older (aged $\geq$65 y), obese [BMI (in kg/m^2) $\geq$30], sedentary (regular exercise $<$1 h/wk), and with stable body weight ($\pm$2 kg in the preceding year) and on stable medications ($\geq$6 mo) before enrollment. Participants were required to meet 2 of the following 3 operational criteria for mild-moderate frailty: physical performance test score of 18–32, peak oxygen consumption (VO_{2peak}) of 11–18 mL $\cdot$ kg^{-1} $\cdot$ min^{-1}, and difficulty in 2 instrumental activities of daily living or 1 basic activity of daily living (23, 25). Exclusion criteria included severe cardiopulmonary disease, musculoskeletal or neuromuscular impairments that precluded exercise training (ET), known diagnosis of dementia or positive screening with the Mini-Mental State Examination (score $<$24) (26), history of malignant neoplasm, and current smoking.

Study design

In this 52-wk RCT, participants were randomly assigned to 1 of the following 4 groups stratified by sex: *1*) control group, *2*) group who participated in a weight-management program (diet group), *3*) group who received ET (exercise group), and *4*) group who received both weight-management and ET (diet-exercise group). The randomization algorithm was generated by the WUSM Biostatistics Division and maintained by a research team member who did not interact with the participants.

As previously described (23), participants in the control group received general information about a healthy diet at regular visits with the staff and were prohibited from participating in any weight-loss or exercise program.

Participants in the diet group were prescribed a diet that provided an energy deficit of 500–750 kcal/d from daily requirements (2). Groups met with dietitians for food diary review, caloric intake adjustments, and behavioral therapy. They were instructed to set weekly behavioral goals and to attend weekly weigh-in sessions. The goal was to achieve $\sim$10% weight loss for 6 mo and to maintain this weight for the remaining 6 mo of the study. Participants in the exercise group were counseled on maintaining a weight-stable diet. They participated in a supervised progressive multicomponent ET program. Exercise sessions were $\sim$90 min ($\sim$15 min flexibility, 30 min aerobic, 30 min resistance training, and 15 min balance exercises) 3 times weekly at a WUSM exercise facility. The participants exercised so that their heart rate was $\sim$65% of their peak heart rate and gradually increased the intensity of exercise so that their heart rate was between 70% and 85% of their peak heart rate. The progressive resistance training included 9 upper-extremity and lower-extremity exercises with the use of weight-lifting machines. Participants performed 1–2 sets at a resistance of $\sim$65% of their one-repetition maximum (1-RM), with 8–12 repetitions of each exercise; they gradually increased the intensity to 2–3 sets at a resistance of $\sim$80% of their 1-RM, with 6–8 repetitions of each exercise (23). Participants who were randomly assigned to the diet-exercise group participated in both weight-management and ET programs described above, conducted separately from the other groups.

Outcome assessments

Main outcomes for this report were changes in the Modified Mini-Mental State Examination (3MS) and the total Impact of Weight on Quality of Life–Lite (IWQOL) at 12 mo. Other outcomes included the Word List Fluency Test, Trail Making Tests Parts A and B, and Geriatric Depression Scale (GDS)–Short Form. Outcomes were assessed at baseline, 6 mo, and 12 mo. Trained personnel who were blinded to group assignments conducted the assessments.

Cognitive measures

The 3MS is a test of global cognition with components for orientation, registration, attention, language, praxis, and immediate and delayed memory (27). Scores range from 0 to 100, with higher scores indicating better performance. The 3MS is more sensitive for mild cognitive impairment than the traditional 30-point Mini-Mental State Examination (27).

The Word List Fluency Test measures verbal production, semantic memory, and language. Participants were asked to name as many animals as possible in a 1-min period (28). Higher scores indicate better performance.

The Trail Making Test Parts A and B (Trails A and B) provides information on visuospatial scanning, speed of processing, mental flexibility, and executive function (29, 30). The tasks involve connecting 25 consecutively numbered circles (Trail A, greater focus on attention) or an alternating sequence of numbered and lettered circles (Trail B, greater focus on executive function). Shorter times to completion indicate better performance.

Mood

The GDS is a 15-item version of the 30-item form that assesses depressive symptoms during the past week (31). The scores range from 0 to 15, with higher scores indicating greater depression.

IWQOL

The IWQOL is a validated 31-item self-report measure of obesity-specific quality of life (32, 33). In addition to a total score, there are scores on 5 domains: physical function, self-esteem, sexual life, public distress, and work. Scores are transformed to a 0–100 scale, with 100 representing the best HRQOL.

Potential mediators or confounders of weight loss and exercise on outcomes grouped in blocks

Body weight and visceral fat

Body weight was measured in the morning after a 12-h fast. Visceral abdominal tissue volume was measured by MRI (Siemens), as previously described (34, 35). Briefly, 10 serial 10-mm axial images were acquired, beginning at L1 (identified by the origin of the psoas muscle) and moving downward (35). Baseline and 1-y images were batch-analyzed with the use of Hippo software (36).

Insulin sensitivity, inflammation, and insulin-like growth factor I

A standard 75-g oral-glucose-tolerance test was performed after an overnight fast and the insulin sensitivity index (ISI) was calculated by using the formula ISI = 10,000/square root of [(fasting glucose × fasting insulin) × (mean glucose × mean insulin)], as previously described (24, 37). As a marker of chronic inflammation, high-sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric assay (Hitachi 917; Roche). Insulin-like growth factor I (IGF-I) was measured by radioimmunoassay (Diagnostic Products).

Muscle strength and VO_{2peak}

The 1-RM (maximal weight a person can lift at one repetition) for biceps curl, bench press, and seated row was summed to calculate upper extremity 1-RM strength; the 1-RM for knee extension, knee flexion, and leg press was summed to calculate lower extremity (LE) 1-RM strength (23, 38). VO_{2peak} was assessed during graded treadmill walking by indirect calorimetry (True Max 2400; ParvoMedics), as previously described (25, 39). Briefly, the incremental test started at a speed determined during a warm-period to elicit ~70% of age-predicted maximum heart rate and remained constant throughout the test, and grade was increased by 2% every 2 min. The test continued until the subject could no longer exercise because of exhaustion or until other conditions, such as electrocardiogram changes or development of symptoms, made it unsafe to continue (25, 39).

Statistical analyses

The same statistical methodologies used in the parent RCT were applied (23). Briefly, intention-to-treat analyses were performed by including all available observations (3 visits) in the analysis. Baseline characteristics were compared by using ANOVAs or Fisher's exact test. Longitudinal changes between groups were tested by using mixed-model repeated-measures ANOVA. Change from baseline was used as the dependent variable with group, visit, and group × visit as independent effects and baseline values and education (for cognition) as covariates. The primary focus of the analyses for the main outcomes (3MS and total IWQOL) was the contrast emphasizing the 12-mo change in outcome in the 4 groups. In the mixed model, when the group × visit P value was <0.05, prespecified contrast statements were used to test the following 4 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, changes in the diet-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 by using mixed-model repeated-measures ANOVA. Pearson's correlation was used to examine relations among changes in variables, and 3MS and total IWQOL followed by stepwise multiple linear regression were used to identify which variables were independent contributors to the changes in the 3MS and total IWQOL in each intervention group. Baseline characteristics are presented as means ±SDs and changes in outcome variables are presented as least-squares adjusted means ± SEs unless otherwise indicated. Statistical tests were 2-tailed, and $P < 0.05$ was considered significant. Data analysis was generated by using SAS version 9.3 (SAS Institute).

RESULTS

The CONSORT (Consolidated Standards of Reporting Trials) diagram summarizing recruitment, randomization, and follow-up has been reported (23). Briefly, 107 participants were randomly assigned and 93 (87%) completed the study. Fourteen participants (4 in the control, 3 in the diet, 4 in the exercise, and 3 in the diet-exercise group) discontinued the intervention but were included in the intention-to-treat analyses. Baseline characteristics were not different between the groups (**Table 1**). Diet compliance was 83% (IQR: 79–89%) in the diet group and 82% (IQR: 76–89%) in the diet-exercise group. Exercise compliance was 88% (IQR: 85–92%) in the exercise group and 83% (IQR: 80–88%) in the diet-exercise group.

Scores on the 3MS improved more in the diet group (1.7 ± 0.4), exercise group (2.8 ± 0.4), and diet-exercise group (2.9 ± 0.4) than in the control group (0.1 ± 0.4). Scores improved more in the diet-exercise group than in the diet group but not more than in the exercise group (**Table 2**). Scores on the Word Fluency Test improved more in the exercise group (4.1 ± 0.8) and diet-exercise group (4.2 ± 0.7) than in the control group (−0.8 ± 0.8). The Word Fluency Test score tended to improve more in the

TABLE 1
Baseline characteristics of participants[1]

	Group				
	Control (n = 27)	Diet (n = 26)	Exercise (n = 26)	Diet-exercise (n = 28)	P[2]
Age (y)	69 ± 4[3]	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 (cm)	165.8 ± 9.7	169.2 ± 9.5	168.1 ± 10.1	165.4 ± 8.7	0.38
Weight (kg)	101.0 ± 16.3	104.1 ± 15.3	99.2 ± 17.4	99.1 ± 16.8	0.66
BMI (kg/m^2)	37.3 ± 4.7	37.2 ± 4.5	36.9 ± 5.4	37.2 ± 5.4	0.93
Visceral fat (cm^3)	2591 ± 1539	2175 ± 1082	2231 ± 1183	2086 ± 1337	0.58
Years of education	16.9 ± 3.0	15.3 ± 3.7	16.7 ± 4.2	16.3 ± 3.8	0.53
Physical performance test score	26.8 ± 4.5	28.6 ± 1.9	27.1 ± 3.1	28.0 ± 2.9	0.17
VO_{2peak} (L/min)	1.69 ± 0.49	1.84 ± 0.41	1.76 ± 0.51	1.73 ± 0.38	0.66
UE 1-RM strength (kg)	83.8 ± 34.4	106.5 ± 45.3	90.5 ± 45.5	90.1 ± 41.7	0.24
LE 1-RM strength (kg)	145.5 ± 42.9	169.5 ± 54.7	144.6 ± 45.6	154.6 ± 61.7	0.30
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)	1 (39)	0.82
Use of CNS-affecting drugs [n (%)]					
Antidepressant	3 (1)	2 1)	2 (1)	3 (1)	0.95
Anticholinergic	0 (0)	2 (1)	1 (0)	1 (0)	0.54
Sedative-hypnotic	1 (0)	1 (0)	1 (0)	1 (0)	1.00

[1] CNS, central nervous system; LE, lower extremity; UE, upper extremity; VO_{2peak}, peak oxygen consumption; 1-RM, 1-repetition maximum.
[2] P values were calculated with the use of ANOVA for quantitative data and Fisher's exact test for counts.
[3] Mean ± SD (all such values).

diet-exercise group than in the diet group. In both the Trails A and B tests, the scores in the diet-exercise group (−11.8 ± 1.9 and −21.8 ± 5.1, respectively) but not the diet group or exercise group improved more than in the control group (−0.8 ± 1.9 and −1.8 ± 4.9, respectively). GDS scores did not change in any group.

The total IWQOL scores improved more in the diet group (7.6 ± 1.6), exercise group (10.1 ± 1.6), and diet-exercise group (14.0 ± 1.4) than in the control group (0.3 ± 1.6). Scores in the diet-exercise group improved more than in the diet group but not more than in the exercise group (**Table 3**). All domains of the IWQOL (physical function, self-esteem, sexual life, public distress, work) followed the same pattern of improvement as the total IWQOL score, with the most consistent improvement occurring in physical function across the intervention groups.

As reported (23), body weight decreased similarly in the diet-exercise and diet groups (−8.6 ± 3.8 and −9.7 ± 5.4 kg, respectively), whereas weight was constant in the exercise and control groups. Visceral fat decreased similarly in the diet-exercise and diet group (−787 ± 896 and −561 ± 454 cm^3, respectively), whereas it decreased modestly (−115 ± 244 cm^3) in the exercise group (24). The ISI increased more in the diet-exercise group (2.4 ± 2.3) than in the diet group (1.2 ± 1.6) but not more than in the exercise or control group (24). hs-CRP concentrations decreased similarly in the diet-exercise group and diet group (−1.8 ± 3.4 and 1.1 ± 1.4 mg/L) but not in the exercise or control group (24). IGF-I concentrations did not significantly change in any group (40). Upper extremity 1-RM strength increased similarly in the diet-exercise and exercise groups (18.5 ± 23.5 and 22.9 ± 25.4 kg) but not in the diet or control group (−5.6 ± 24.5 and −0.5 ± 13.1 kg) (between-group P = 0.0001). Likewise, LE 1-RM strength increased similarly in the diet-exercise and exercise groups (55.7 ± 37.3 and 64.0 ± 54.2 kg) but not in the diet or control group (6.1 ± 25.0 and −1.4 ± 41.5 kg) (between-group P = 0.0001). VO_{2peak} improved similarly in the diet-exercise group and exercise group (0.15 ± 0.12 and 0.14 ± 0.15 L/min) and did not change in the diet or control group (24).

Bivariate analyses showed that changes in several variables correlated with changes in 3MS and total IWQOL (Supplemental Table 1 under "Supplemental data" in the online issue). In addition, stepwise multiple regression showed that the following variables were independent predictors of changes in the 3MS: *1*) diet group: changes in ISI and hs-CRP (explaining 25% of the variance in changes in the 3MS); *2*) exercise group: changes in VO_{2peak} and LE 1-RM (explaining 24% of the variance in changes in the 3MS); and *3*) diet-exercise group: changes in LE 1-RM and VO_{2peak} (explaining 19% of the variance in changes in the 3MS) (**Table 4**). Moreover, stepwise multiple regression showed that the following variables were independent predictors of changes in the total IWQOL: *1*) diet group: changes in body weight (explaining 15% of the variance in changes in the IWQOL); *2*) exercise group: changes in LE 1-RM (explaining 17% of the variance in changes in the IWQOL); and *3*) diet-exercise group: changes in body weight and LE 1-RM (explaining 32% of the variance in changes in the IWQOL) (Table 4).

Supplementary analyses that evaluated the independent and interaction effects of weight-loss and exercise factors showed a significant interaction effect on our 2 main outcomes of 3MS and total IWQOL (Supplemental Table 2 under "Supplemental data" in the online issue), consistent with the main results.

DISCUSSION

In this 1-y RCT in frail, obese older adults, weight loss plus exercise and exercise alone equally improved scores in the global 3MS test and to a greater extent than weight loss alone. Similar positive results were observed on the Word Fluency and Trails A and B tests that assess cognitive domains such as language and

TABLE 2
Effects of diet, exercise, or a combination of both on cognition and mood in obese older adults[1]

	Baseline[2]	Change at 6 mo[3]	Change at 12 mo[3]	Difference in change from baseline to 12 mo (95% CI)	*P*[4]
Main outcome					
3MS					
Control group	96.3 ± 0.8	0.1 ± 0.4	0.1 ± 0.4	—	—
Diet group	96.0 ± 0.6	1.1 ± 0.4[5]	1.7 ± 0.4[5]	—	—
Exercise group	94.9 ± 0.9	1.9 ± 0.4[5]	2.8 ± 0.4[5]	—	—
Diet-exercise group	95.6 ± 0.8	1.8 ± 0.4[5]	2.9 ± 0.4[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	1.5 (0.1, 3.0)	0.04
Exercise vs control	—	—	—	3.0 (1.5, 4.5)	0.0001
Diet-exercise vs control	—	—	—	3.0 (1.5, 4.4)	0.0001
Diet-exercise vs diet	—	—	—	1.4 (0.0, 2.8)	0.04
Diet-exercise vs exercise	—	—	—	0.0 (−1.5, 1.4)	0.99
Other outcomes					
Word List Fluency					
Control group	17.9 ± 1.1	−0.4 ± 0.7	−0.8 ± 0.8	—	—
Diet group	17.3 ± 0.7	1.3 ± 0.7	1.4 ± 0.7	—	—
Exercise group	17.9 ± 0.8	2.3 ± 0.7[5]	4.1 ± 0.8[5]	—	—
Diet-exercise group	19.5 ± 0.8	2.2 ± 0.7[5]	4.2 ± 0.7[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	2.3 (−0.5, 5.0)	0.11
Exercise vs control	—	—	—	4.9 (2.1, 7.7)	0.001
Diet-exercise vs control	—	—	—	4.5 (1.8, 7.2)	0.001
Diet-exercise vs diet	—	—	—	2.3 (−0.3, 4.9)	0.08
Diet-exercise vs exercise	—	—	—	−0.3 (−3.0, 2.3)	0.80
Trail A					
Control group	42.9 ± 3.0	−1.6 ± 2.0	−0.8 ± 1.9	—	—
Diet group	41.8 ± 2.4	−6.1 ± 2.0[5]	−7.1 ± 2.0[5]	—	—
Exercise group	40.3 ± 2.3	−5.1 ± 2.0	−8.4 ± 2.1[5]	—	—
Diet-exercise group	47.7 ± 5.6	−7.4 ± 1.9[5]	−11.8 ± 1.9[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	−5.8 (−13.2, 1.5)	0.12
Exercise vs control	—	—	—	−6.6 (−14.1, 0.8)	0.08
Diet-exercise vs control	—	—	—	−12.9 (−20.1, −5.8)	0.001
Diet-exercise vs diet	—	—	—	−7.1 (−14.3, 0.2)	0.06
Diet-exercise vs exercise	—	—	—	−6.3 (−13.6, 1.1)	0.09
Trail B					
Control group	106.9 ± 7.8	−0.9 ± 4.8	−1.8 ± 4.9	—	—
Diet group	106.9 ± 9.3	−15.4 ± 5.0[5]	−20.7 ± 5.2[5]	—	—
Exercise group	102.5 ± 7.3	−8.9 ± 5.1[5]	−16.1 ± 5.5[5]	—	—
Diet-exercise group	102.2 ± 8.3	−14.7 ± 4.8[5]	−21.8 ± 5.1[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	−17.9 (−35.8, 0.3)	0.05
Exercise vs control	—	—	—	−12.6 (−31.2, 5.9)	0.18
Diet-exercise vs control	—	—	—	−18.1 (−36.1, 0.1)	0.049
Diet-exercise vs diet	—	—	—	−0.4 (−18.6, 18.3)	0.98
Diet-exercise vs exercise	—	—	—	−5.5 (−24.2, 13.3)	0.56
GDS					
Control group	1.9 ± 0.6	−0.7 ± 0.3	−0.1 ± 0.4	—	—
Diet group	1.4 ± 0.5	−0.6 ± 0.3	−0.2 ± 0.3	—	—
Exercise group	1.5 ± 0.4	−0.3 ± 0.3	−0.3 ± 0.3	—	—
Diet-exercise group	1.0 ± 0.2	0.1 ± 0.2	−0.4 ± 0.3	—	—
Intergroup comparisons					
Diet vs control	—	—	—	0.2 (−1.0, 1.3)	0.78
Exercise vs control	—	—	—	−0.1 (−1.2, 1.1)	0.92
Diet-exercise vs control	—	—	—	0.1 (−1.1, 1.2)	0.89

(Continued)

TABLE 2 (*Continued*)

	Baseline[2]	Change at 6 mo[3]	Change at 12 mo[3]	Difference in change from baseline to 12 mo (95% CI)	*P*[4]
Diet-exercise vs diet	—	—	—	−0.1 (−1.0, 0.9)	0.87
Diet-exercise vs exercise	—	—	—	0.1 (−0.9, 1.2)	0.77

[1] The samples for analysis were $n = 27$ for the control group, $n = 26$ for the diet group, $n = 26$ for the exercise group, and $n = 28$ for the diet-exercise group. GDS, Geriatric Depression Scale; 3MS, Modified Mini-Mental State Examination; —, not applicable.

[2] Values are observed means ± SEs.

[3] Values are least-squares adjusted means ± SEs from the repeated-measures analysis.

[4] *P* values for comparisons between groups for changes from baseline to 12 mo were calculated with the use of mixed-model repeated-measures ANOVA contrasts (with baseline values and education as covariates in analyses of cognitive tests and with baseline values as covariates in analyses of mood). The *P* value for the group × visit interaction for the main outcome of 3MS was 0.001. *P* values for the group × visit interaction for the other outcomes were 0.01 for Word Fluency, 0.04 for Trail A, 0.38 for Trail B, and 0.36 for the GDS.

[5] $P < 0.05$ for the comparison of the value at the follow-up time with the within-group baseline value, as calculated with the use of mixed-model repeated-measures ANOVA.

attention/executive function. Moreover, weight loss plus exercise and exercise alone equally improved scores in the IWQOL and to a greater extent than weight loss alone.

To our knowledge, the current study is the first RCT to directly compare the independent and combined effects of weight loss and exercise on cognition in obese older adults. Although weight loss is the primary treatment of obesity, whether weight-loss therapy is net beneficial or harmful in older adults is unclear (1). For example, in contrast to the consistent association between midlife obesity and dementia risk (4–6), observational studies have shown a paradoxical relation between BMI and cognition in older adults (9, 41, 42). A few interventional studies examined the effect of weight loss on cognition and reported positive and negative results, but these lacked a rigorous RCT design and focused on middle-aged, not older, adults (16). The current RCT, therefore, clearly shows for the first time that weight loss improves cognition in frail, obese older adults. However, we also found that the positive effects of weight loss on cognition were not additive to ET.

Our results, which showed positive effects of ET on cognition in obese older adults, are in general agreement with most previous RCTs of exercise training in nonobese middle-aged and older adults (17, 18). However, an important addition is the use of combined aerobic and resistance ET in obese older adults, whereas most previous studies in other populations used aerobic training alone. Although aerobic training studies usually showed positive effects on cognition (17), the few resistance training studies yielded equivocal results (43–45). Characteristics of studies showing cognitive benefits from resistance training were of longer duration using high-intensity protocols (46, 47). In the current 1-y RCT, we used moderate- to high-intensity aerobic and resistance training to improve VO_{2peak} and 1-RM strength in obese older adults. Therefore, the current RCT provides novel data on the effects of combined aerobic and resistance training on cognition in this high-risk older population.

The stepwise multiple regression supported our findings that weight loss and exercise had independent effects on cognition. In final models, changes in ISI and hs-CRP predicted changes in the 3MS in the diet group, whereas changes in VO_{2peak} and LE 1-RM strength predicted changes in the 3MS in the exercise group. Thus, the positive effects of weight loss on cognition may be mediated through weight-loss–induced improvement in insulin sensitivity and decreased inflammation (14). Our findings are consistent with animal models that suggest that improved insulin signaling and reduced inflammation induce higher brain synaptic plasticity and stimulation of neurofacilatory pathways in the brain, resulting in improved cognition (48, 49). In addition, the positive effects of exercise may be mediated through training-induced improvement in aerobic fitness and muscle strength (18). Our findings are also consistent with animal models that suggest that ET results in neurogenesis and angiogenesis, which are linked to improved memory and learning (50, 51). IGF-I has been shown to be an upregulated neurotrophic factor in both aerobic and resistance exercise (18). We found that IGF-I concentrations did not change in response to ET, possibly because of diminished growth hormone/IGF-I axis response with aging (52). Interestingly, changes in VO_{2peak} and LE 1-RM were the independent predictors of change in the 3MS in both the exercise group and diet-exercise group. These findings are consistent with a ceiling effect of ET on cognition vis-à-vis weight loss, such that we observed no further effect of diet when added to exercise in the diet-exercise group.

HRQOL reflects an individual's subjective evaluation of and reaction to health. Indeed, obesity impairs important aspects of HRQOL (19) and by using an obesity-specific quality of life instrument, IWQOL (32), we found that weight loss improved HRQOL specifically in obese older adults. This finding was further supported in our stepwise multiple regression, where change in body weight was the lone predictor of change in total IWQOL in the diet group. Interestingly, although exercise was not associated with weight loss, exercise also improved HRQOL as assessed by the IWQOL. In fact, change in LE 1-RM was the lone predictor of change in IWQOL score in the exercise group, suggesting the importance of better physical function in improving a sense of well-being (53). Accordingly, among the 5 IWQOL domains, physical function showed the most consistent improvement across all groups. Importantly, change in body weight and change in LE 1-RM were both independent predictors of change in total IWQOL in the diet-exercise group, suggesting that weight loss and exercise might have additive effects on HRQOL. Indeed, the score in the total IWQOL increased more in the diet-exercise group than in the diet group, although it did not increase more than in the exercise group.

TABLE 3
Effects of diet, exercise, or a combination of both on the IWQOL in obese older adults[1]

	Baseline[2]	Change at 6 mo[3]	Change at 12 mo[3]	Difference in change from baseline to 12 mo (95% CI)	*P*[4]
Main outcome					
Total IWQOL					
Control group	75.4 ± 3.7	−2.4 ± 1.4	0.3 ± 1.6	—	—
Diet group	82.8 ± 1.8	8.5 ± 1.5[5]	7.6 ± 1.6[5]	—	—
Exercise group	77.2 ± 3.5	7.1 ± 1.6[5]	10.1 ± 1.6[5]	—	—
Diet-exercise group	76.5 ± 3.0	10.2 ± 1.4[5]	14.0 ± 1.4[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	6.1 (0.6, 11.7)	0.03
Exercise vs control	—	—	—	9.5 (3.9, 15.1)	0.001
Diet-exercise vs control	—	—	—	13.6 (8.2, 18.9)	0.0001
Diet-exercise vs diet	—	—	—	7.4 (2.1, 12.8)	0.007
Diet-exercise vs exercise	—	—	—	4.1 (−1.4, 9.5)	0.15
Other outcomes					
Physical function					
Control group	62.5 ± 4.1	−0.6 ± 1.9	−0.3 ± 2.1	—	—
Diet group	73.4 ± 2.1	11.5 ± 1.9[5]	9.9 ± 2.0[5]	—	—
Exercise group	67.4 ± 4.2	8.7 ± 2.0[5]	10.4 ± 2.1[5]	—	—
Diet-exercise group	67.7 ± 4.0	15.7 ± 1.8[5]	16.3 ± 1.9[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	8.3 (0.9, 15.7)	0.03
Exercise vs control	—	—	—	9.8 (2.3, 17.3)	0.001
Diet-exercise vs control	—	—	—	15.7 (8.4, 23.0)	0.0001
Diet-exercise vs diet	—	—	—	7.4 (0.2, 14.6)	0.007
Diet-exercise vs exercise	—	—	—	5.9 (−1.4, 13.2)	0.14
Self-esteem					
Control group	71.3 ± 4.3	−3.5 ± 2.5	2.2 ± 2.8	—	—
Diet group	74.7 ± 3.6	14.7 ± 2.6[5]	9.7 ± 2.6[5]	—	—
Exercise group	71.7 ± 4.8	5.0 ± 2.7	10.3 ± 2.8[5]	—	—
Diet-exercise group	71.7 ± 4.1	9.7 ± 2.5[5]	14.7 ± 2.6[5]	—	—
Intergroup comparisons					
Diet vs. control	—	—	—	6.7 (−3.3, 16.7)	0.19
Exercise vs. control	—	—	—	8.0 (−2.2, 18.1)	0.12
Diet-exercise vs control	—	—	—	12.5 (2.6, 22.3)	0.01
Diet-exercise vs diet	—	—	—	5.7 (−4.0, 15.4)	0.24
Diet-exercise vs exercise	—	—	—	4.5 (−5.4, 14.4)	0.37
Sexual life					
Control group	77.0 ± 7.1	−3.3 ± 3.0	1.6 ± 3.3	—	—
Diet group	86.2 ± 3.8	1.0 ± 3.2	4.0 ± 3.4	—	—
Exercise group	74.4 ± 5.3	9.1 ± 3.4[5]	14.4 ± 3.3[5]	—	—
Diet-exercise group	74.7 ± 5.0	13.4 ± 3.0[5]	17.3 ± 3.0[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	0.2 (−12.3, 12.7)	0.97
Exercise vs control	—	—	—	13.4 (1.2, 25.7)	0.03
Diet-exercise vs control	—	—	—	16.3 (4.6, 28.0)	0.007
Diet-exercise vs diet	—	—	—	16.1 (4.0, 28.2)	0.009
Diet-exercise vs exercise	—	—	—	2.9 (−8.9, 14.7)	0.63
Public distress					
Control group	83.9 ± 3.9	−1.3 ± 1.7	−3.9 ± 1.9	—	—
Diet group	91.0 ± 2.4	5.5 ± 1.8[5]	5.0.2 ± 1.9[5]	—	—
Exercise group	89.2 ± 3.4	3.9 ± 1.9[5]	4.1 ± 2.0[5]	—	—
Diet-exercise group	86.1 ± 3.6	5.2 ± 1.7[5]	9.2 ± 1.7[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	7.5 (0.4, 14.7)	0.04
Exercise vs control	—	—	—	6.9 (−0.4, 14.1)	0.06
Diet-exercise vs control	—	—	—	12.6 (5.8, 19.5)	0.0004
Diet-exercise vs diet	—	—	—	5.1 (−1.8, 12.0)	0.15
Diet-exercise vs exercise	—	—	—	5.8 (−1.2, 12.8)	0.11

(Continued)

TABLE 3 (*Continued*)

	Baseline[2]	Change at 6 mo[3]	Change at 12 mo[3]	Difference in change from baseline to 12 mo (95% CI)	P[4]
Work					
Control group	85.0 ± 3.3	−5.0 ± 2.2	−4.0 ± 2.4	—	—
Diet group	89.0 ± 2.1	4.1 ± 2.2[5]	3.3 ± 2.3[5]	—	—
Exercise group	84.0 ± 4.1	5.1 ± 2.5	8.0 ± 2.6[5]	—	—
Diet-exercise group	85.5 ± 3.2	5.9 ± 2.2[5]	9.3 ± 2.2[5]	—	—
Intergroup comparisons					
Diet vs control	—	—	—	6.5 (−2.0, 15.0)	0.13
Exercise vs control	—	—	—	12.2 (3.4, 20.9)	0.006
Diet-exercise vs control	—	—	—	13.2 (4.9, 21.4)	0.002
Diet-exercise vs diet	—	—	—	6.7 (−1.6, 14.9)	0.11
Diet-exercise vs exercise	—	—	—	1.0 (−7.5, 9.5)	0.82

[1] The samples for analysis were $n = 27$ for the control group, $n = 26$ for the diet group, $n = 26$ for the exercise group, and $n = 28$ for the diet-exercise group. IWQOL, Impact of Weight on Quality of Life–Lite; —, not applicable.

[2] Values are observed means ± SEs.

[3] Values are least-squares adjusted means ± SEs from the repeated-measures analysis.

[4] P values for comparison between groups for changes from baseline to 12 mo were calculated with the use of mixed-model repeated-measures ANOVA contrasts (with baseline values as covariates). The P value for the group × visit interaction for the main outcome of total IWQOL was 0.0001. The P value for the group × visit interaction for the other outcomes were 0.0001 for physical function, 0.001 for self-esteem, 0.04 for public distress, 0.01 for sexual life, 0.02 for work, and 0.04 for public distress.

[5] $P < 0.05$ for the comparison of the value at the follow-up time with the within-group baseline value, as calculated with the use of mixed-model repeated-measures ANOVA.

The strengths of our study include the RCT design, comprehensive lifestyle programs, and the degree of adherence to the 1-y intervention, which allowed for assessment of the distinct effects of weight loss, exercise, or a combination of both on cognition and HRQOL. A limitation is that we were unable to include neuroimaging studies to examine brain structure and

TABLE 4
Final models in the stepwise multiple regression analyses identifying predictors of changes in the 3MS and total IWQOL among the intervention groups[1]

	β	P
Final model of variables affecting change in 3MS		
Diet group (multiple $R = 0.503$, $P = 0.0003$)		
Change in ISI	0.468 ± 0.119	0.0001
Change in hs-CRP	−0.309 ± 0.119	0.01
Exercise group (multiple $R = 0.489$, $P = 0.001$)		
Change in VO_{2peak}	0.319 ± 0.121	0.01
Change in LE 1-RM strength	0.314 ± 0.131	0.01
Diet-exercise group (multiple $R = 0.436$, $P = 0.002$)		
Change in LE 1-RM strength	0.272 ± 0.136	0.03
Change in VO_{2peak}	0.257 ± 0.124	0.04
Final model of variables affecting change in total IWQOL		
Diet group ($R = 0.383$, $P = 0.002$)		
Change in body weight	−0.383 ± 0.123	0.002
Exercise group strength ($R = 0.406$, $P = 0.002$)		
Change in LE 1-RM	0.406 ± 0.149	0.002
Diet-exercise group (multiple $R = 0.564$, $P = 0.0001$)		
Change in body weight	−0.365 ± 0.128	0.004
Change in LE 1-RM strength	0.293 ± 0.116	0.01

[1] Values are βs ± SEs. The samples for analysis were $n = 23$ for the control group, $n = 23$ for the diet group, $n = 22$ for the exercise group, and $n = 25$ for the diet-exercise group. Stepwise multiple linear regression analysis was used to identify which variables were independent contributors to the changes in the 3MS and total IWQOL in each intervention group. Variables entered into the model were as follows: change in body weight, change in visceral fat, change in ISI, change in hs-CRP, change in insulin-like growth factor I, change in VO_{2peak}, change in upper extremity 1-RM strength, change in LE 1-RM strength, and years of education (for 3MS only). hs-CRP, high-sensitivity C-reactive protein; ISI, insulin sensitivity index; IWQOL, Impact of Weight on Quality of Life–Lite; LE, lower extremity; VO_{2peak}, peak oxygen consumption; 1-RM, one-repetition maximum; 3MS, Modified Mini-Mental State Examination.

function because of the participant burden from the other tests as part of the parent RCT (23). We were unable to detect an effect of our interventions on mood, probably because of the low baseline GDS scores. Participants who volunteered may be different from the general population so our results may not necessarily generalize to the obese older population. Another potential limitation is that many statistical tests were performed without rigorous correction for the multiplicity of tests. Our approach to minimize type 1 error for our main outcomes (3MS and total IWQOL) included the following: *1*) the use of prespecified contrast statements to test 4 specific hypothesis and *2*) performing these focused tests only after achieving a significant overall F test ($P < 0.05$).

Obesity in older adults challenges our health care professionals and health delivery systems (54–56). We previously showed that weight loss and exercise each ameliorate frailty and decrease cardiometabolic risk factors, but the combination of both provides the greatest benefits. Optimal treatment strategies in obese older adults should consider the relative positive effects and risks of weight loss, exercise, or both in improving multiple health outcomes in this growing segment of the older population (1, 2, 23, 24).

The authors' responsibilities were as follows—DTV: had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; DRS and DTV: conceived of and designed the study and obtained funding; NN, KS, DRS, and DTV: acquired the data; NN, KS, DLW, DRS, CQ, and DTV: analyzed and interpreted the data, drafted the manuscript, and critically revised the manuscript for important intellectual content; CQ: performed statistical analysis; and NN, KS, and DTV: supervised the study. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The authors did not declare any conflicts of interest.

REFERENCES

1. Waters DL, Ward AL, Villareal DT. Weight loss in obese adults 65 years and older: a review of the controversy. Exp Gerontol 2013;48:1054–61.
2. 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;82:923–34.
3. Luchsinger JA, Gustafson DR. Adiposity, type 2 diabetes, and Alzheimer's disease. J Alzheimers Dis 2009;16:693–704.
4. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala E, Tuomelehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62:1556–60.
5. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330:1360.
6. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology 2008;71:1057–64.
7. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;163:1524–8.
8. Kanaya AM, Lindquist K, Harris TB, Launer L, Rosano C, Satterfield S, Yaffe K. Total and regional adiposity and cognitive change in older adults: the Health, Aging and Body Composition (ABC) Study. Arch Neurol 2009;66:329–35.
9. Atti AR, Palmer K, Volpato S, Winblad B, De RD, Fratiglioni L. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. J Am Geriatr Soc 2008;56:111–6.
10. Hughes TF, Borenstein AR, Schofield E, Wu Y, Larson EB. Association between late-life body mass index and dementia: the Kame Project. Neurology 2009;72:1741–6.
11. Gustafson D. A life course of adiposity and dementia. Eur J Pharmacol 2008;585:163–75.
12. Knopman DS, Edland SD, Cha RH, Petersen RC, Rocca WA. Incident dementia in women is preceded by weight loss by at least a decade. Neurology 2007;69:739–46.
13. Siervo M, Nasti G, Stephan BC, Papa A, Muscariello E, Wells JC, Prado CM, Colantuoni A. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. J Am Coll Nutr 2012;31:79–86.
14. Witte AV, Fobker M, Gellner R, Knecht S, Floel A. Caloric restriction improves memory in elderly humans. Proc Natl Acad Sci USA 2009;106:1255–60.
15. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300:1027–37.
16. Siervo M, Arnold R, Wells JC, Tagliabue A, Colantuoni A, Albanese E, Brayne C, Stephan BC. Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis. Obes Rev 2011;12:968–83.
17. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2008;3:CD005381.
18. Voss MW, Nagamatsu LS, Liu-Ambrose T, Kramer AF. Exercise, brain, and cognition across the life span. J Appl Physiol (1985) 2011;111:1505–13.
19. NIH. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults–the evidence report. Obes Res 1998;6(suppl 2):51S–209S.
20. Jakicic JM, Clark K, Coleman E, Donnelly JE, Foreyt J, Melanson E, Volek J, Volpe SL. American College of Sports Medicine position stand. Appropriate intervention strategies for weight loss and prevention of weight regain for adults. Med Sci Sports Exerc 2001;33:2145–56.
21. Miller SL, Wolfe RR. The danger of weight loss in the elderly. J Nutr Health Aging 2008;12:487–91.
22. Rolland Y, Kim MJ, Gammack JK, Wilson MM, Thomas DR, Morley JE. Office management of weight loss in older persons. Am J Med 2006;119:1019–26.
23. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, Napoli N, Qualls C, Shah K. Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med 2011;364:1218–29.
24. Bouchonville M, Armamento-Villareal R, Shah K, Napoli N, Sinacore DR, Qualls C, Villareal DT. Weight loss, exercise, or both and cardiometabolic risk factors in obese older adults: results of a randomized controlled trial. Int J Obes (Lond) 2014;38:423–31.
25. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women. Obes Res 2004;12:913–20.
26. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
27. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry 1987;48:314–8.
28. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. Br J Psychiatry 1973;123:467–70.
29. Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. J Clin Psychol 1987;43:402–9.
30. Lezak MD, Howeieson DB, Loring DW. Neuropsychological assessment. New York, NY: Oxford University Press, 2004.
31. Jl S, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence of a shorter version. Clin Gerontol 1986;5:165–73.
32. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. Obes Res 2001;9:102–11.
33. Kolotkin RL, Crosby RD, Williams GR, Hartley GG, Nicol S. The relationship between health-related quality of life and weight loss. Obes Res 2001;9:564–71.
34. 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;15:2240–4.

35. Racette SB, Weiss EP, Villareal DT, Arif H, Steger-May K, Schechtman KB, Fontana L, Klein S, Holloszy JO. One year of caloric restriction in humans: feasibility and effects on body composition and abdominal adipose tissue. J Gerontol A Biol Sci Med Sci 2006;61:943–50.
36. Lancaster JL, Ghiatas AA, Alyassin A, Kilcoyne RF, Bonora E, DeFronzo RA. Measurement of abdominal fat with T1-weighted MR images. J Magn Reson Imaging 1991;1:363–9.
37. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–70.
38. Villareal DT, Holloszy JO. DHEA enhances effects of weight training on muscle mass and strength in elderly women and men. Am J Physiol Endocrinol Metab 2006;291:E1003–8.
39. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Klein S, Ehsani AA, Holloszy JO. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. J Appl Physiol 2007;102:634–40.
40. Shah K, Armamento-Villareal R, Parimi N, Chode S, Sinacore DR, Hilton TN, Napoli N, Qualls C, Villareal DT. Exercise training in obese older adults prevents increase in bone turnover and attenuates decrease in hip bone mineral density induced by weight loss despite decline in bone-active hormones. J Bone Miner Res 2011;26:2851–9.
41. Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT Jr, Luchsinger JA. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol 2009;66:336–42.
42. Nourhashémi F, Deschamps V, Larrieu S, Letenneur L, Dartigues JF, Barberger-Gateau P. Body mass index and incidence of dementia: the PAQUID study. Neurology 2003;60:117–9.
43. Lachman ME, Neupert SD, Bertrand R, Jette AM. The effects of strength training on memory in older adults. J Aging Phys Act 2006;14: 59–73.
44. Kimura K, Obuchi S, Arai T, Nagasawa H, Shiba Y, Watanabe S, Kojima M. The influence of short-term strength training on health-related quality of life and executive cognitive function. J Physiol Anthropol 2010;29:95–101.
45. Tsutsumi T, Don BM, Zaichkowsky LD, Delizonna LL. Physical fitness and psychological benefits of strength training in community dwelling older adults. Appl Human Sci 1997;16:257–66.
46. Cassilhas RC, Viana VA, Grassmann V, Santos RT, Santos RF, Tufik S, Mello MT. The impact of resistance exercise on the cognitive function of the elderly. Med Sci Sports Exerc 2007;39:1401–7.
47. Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. Arch Intern Med 2010;170:170–8.
48. Zhao WQ, Chen H, Quon MJ, Alkon DL. Insulin and the insulin receptor in experimental models of learning and memory. Eur J Pharmacol 2004;490:71–81.
49. Morgan D, Gordon MN, Tan J, Wilcock D, Rojiani AM. Dynamic complexity of the microglial activation response in transgenic models of amyloid deposition: implications for Alzheimer therapeutics. J Neuropathol Exp Neurol 2005;64:743–53.
50. van Praag H, Shubert T, Zhao C, Gage FH. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005;25: 8680–5.
51. Pereira AC, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci USA 2007;104:5638–43.
52. Giannoulis MG, Martin FC, Nair KS, Umpleby AM, Sonksen P. Hormone replacement therapy and physical function in healthy older men: time to talk hormones? Endocr Rev 2012;33:314–77.
53. Fontaine KR, Bartlett SJ, Barofsky I. Health-related quality of life among obese persons seeking and not currently seeking treatment. Int J Eat Disord 2000;27:101–5.
54. van Baak MA, Visscher TL. Public health success in recent decades may be in danger if lifestyles of the elderly are neglected. Am J Clin Nutr 2006;84:1257–8.
55. Arterburn DE, Crane PK, Sullivan SD. The coming epidemic of obesity in elderly Americans. J Am Geriatr Soc 2004;52:1907–12.
56. Lapane KL, Resnik L. Obesity in nursing homes: an escalating problem. J Am Geriatr Soc 2005;53:1386–91.