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Cognitive effects of adding caloric restriction to aerobic exercise training in older adults with obesity

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Abstract

Objective—This study examined the short and long-term effects of adding caloric restriction to five months of aerobic exercise training on executive function in sedentary older adults with obesity.

Methods—Sedentary years adults with obesity aged 65–79 completed a randomized trial investigating the cardiorespiratory benefits of adding moderate (~250kcal) or high (~600kcal) caloric restriction to a 20-week aerobic exercise program. Approximately half (n=88) completed a cognitive assessment battery at baseline, post-intervention, and 18–24 months after intervention completion. The primary outcome was an executive function composite score.

Results—In the overall sample, the executive function composite increased 0.114 from baseline to post-intervention (p=0.01). Randomization to caloric restriction did not significantly alter executive function over aerobic exercise alone, nor were there between-group differences on any individual executive function test at post-intervention or long-term follow-up. Adding caloric restriction to exercise was associated with a modest increase in MMSE score (p=0.04). In the overall sample, increases from baseline at long-term follow-up were noted in digit symbol and word list recall performance as well.

Conclusions—Adding caloric restriction to a 20-week aerobic exercise program does not worsen or improve executive function more than exercise alone assessed up to 24 months post-randomization.

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Introduction

Strong evidence is emerging that midlife obesity (body mass index (BMI) ≥30 kg/m^2) is a risk factor for dementia later in life. However, the interplay of obesity and weight loss on cognition after the age of 65 is not as well understood. Epidemiological studies indicate weight loss in older age is associated with poorer cognition (for review see[1–3]). However, it is difficult to disentangle whether unintentional weight loss in older age is a risk factor for, or marker of, dementia.[2]

Recommendations to achieve weight loss emphasize increasing physical activity and reducing caloric intake.[4] Evidence is strong that regular aerobic exercise benefits cognition in older adults, particularly executive function (EF).[5–8] Since work showing aerobic exercise enhanced synaptic plasticity in an adult rodent model,[9] human studies have shown that aerobic exercise enhances or maintains cognition,[6, 10, 11] cortical volume,[8] and cerebral blood flow.[12, 13] However, little work has addressed the cognitive effects of exercise in older adults with obesity, and obesity affects more than 35% of the older adult population[14] and may blunt the cardiorespiratory benefits of aerobic exercise.[15–17]

Adding caloric restriction (CR) to aerobic exercise can potentiate the benefits of exercise on cardiorespiratory fitness in older adults with obesity.[15, 18] CR literature in aging suggests intentional weight loss should promote neurocognitive health by improving insulin sensitivity and reducing fat mass, blood lipids, and inflammatory markers, all of which are negatively associated with brain health in human studies (for review see[19]). In addition, rodent (e.g.[20]) and non-human primate studies (e.g.[21]) show direct benefits of CR on the brain, including preservation of synaptic plasticity and brain volumes.

In spite of this compelling evidence, few well-controlled studies of exercise and CR in obese older adults have been published. One well-controlled study indicates that combined exercise and CR over 6–12 months may benefit cognition more than CR alone, but not more than exercise alone.[22] In contrast, results from the less well-controlled but better powered Action for Health in Diabetes (Look AHEAD) trial suggest that intensive lifestyle interventions combining weight loss and exercise in older adults with obesity and type 2 diabetes may be detrimental to cognition long-term.[23]

We tested the effects of adding CR to aerobic exercise on EF by including EF tests in a trial investigating whether adding CR to a 20-week aerobic exercise intervention[15] could potentiate benefits of aerobic exercise on cardiorespiratory fitness (peak VO_2) in sedentary older adults with obesity. We hypothesized that adding CR to aerobic exercise would enhance the benefits of aerobic exercise on EF in older adults with obesity.

Methods

Overall study design.

This study was ancillary to the Investigating Fitness Interventions in the Elderly (INFINITE) trial (NCT01048736), a 20-week, 3-group single-blind, randomized controlled trial in 180 men and women aged 65–79 years old from Forsyth County, NC and surrounding regions.[15] Participants were randomized to exercise only (Ex Only), exercise plus moderate CR (EX +Mod-CR), or exercise plus high CR (Ex+High-CR). As part of the ancillary study, the last 88 participants randomized into the parent study completed a cognitive assessment battery focused primarily on EF before and after the intervention. Of these 88, 70 participants completed a long-term follow-up visit that occurred 18–24 months after intervention completion. During this visit, participants repeated the cognitive assessment battery, blood was drawn to assess serum lipids and glucose, and anthropometric measurements were obtained. The study was approved by the Wake Forest School of Medicine IRB and was completed in accordance with the Declaration of Helsinki. All participants provided written, informed consent prior to study participation.

Participants.

The sample in this analysis is 88 participants who completed the baseline and post-intervention EF battery. All participants randomized after 1½8/2011 were included in the ancillary. Participants were 65–79 years old (mean=69.0 ± 3.5), had a BMI of 30–45 kg/m^2 (mean=35.3 ± 3.9), were weight stable (<5% weight change in past 6 months) and sedentary (self-reporting <20 minutes of exercise 3 times/week, including walking, in the past 6 months). Exclusion criteria included a Mini-Mental State Exam (MMSE) score < 24, osteoporosis, smoking within the past year, insulin-dependent diabetes, hip fracture, hip or knee replacement, or spinal surgery in the past 6 months, or clinical evidence of depression, heart disease, cancer, liver disease, renal disease, chronic pulmonary disease, uncontrolled hypertension, major physical impairment or contraindication for exercise or weight loss upon exam. All participants were approved for study participation by the study physician (ML). Participant characteristics are provided in Table 1. Comparison of characteristics in this sample with the full study cohort is presented in Supplementary Table 1.

Interventions

Aerobic training.—All participants completed the same aerobic exercise intervention, designed in accordance with the American Heart Association and American College of Sports Medicine physical activity recommendation for optimizing cardiovascular fitness in older adults.[24] Participants walked on treadmills 4 days/week for 5 months at the research facility under the supervision of 2 exercise interventionists to minimize individual variability in compliance and progression and to ensure a similar exercise stimulus across study groups.

Participants warmed up by walking for 3–5 minutes at a slow pace. The duration of exercise progressed to 30 minutes at 65–75% HRR by the end of the 6th week and thereafter. Each walking session ended with a 3–5 minute cool-down followed by large muscle flexibility exercises. A minimum of 2 heart rate readings were taken during the exercise session using

Polar heart rate monitors to monitor compliance to the prescribed intensity. Treadmill speed and grade were adjusted individually by study staff based on these HR values.

Caloric Restriction.—Participants randomized to the EX only group (n=28) were asked to maintain their regular dietary intake. Those assigned to either the EX+Mod-CR (−250 kcal/d deficit, n=30) or the EX+High-CR (−600 kcal/d deficit, n=30) groups were provided with a controlled diet consisting of lunch and dinner prepared by the Wake Forest School of Medicine Clinical Research Metabolic kitchen under the direction of a Registered Dietitian (RD). Participants picked up their food 3 times/week and were asked to keep a log of everything they consumed. The logs were reviewed and body weight was measured weekly by the study RD to verify diet compliance. Brief individual counseling sessions with the study RD were held weekly to facilitate motivation and compliance.

The individual calorie level assigned for each participant was derived by subtracting 250 kcals (Mod-CR) or 600 kcals (High-CR) from his/her estimated daily energy needs for weight maintenance. Individual daily energy need was calculated from the direct measurement of resting metabolic rate (RMR), applying an activity factor based on each participant's reported daily activities. RMR was measured after an overnight fast by indirect calorimetry (MGC Diagostics).[25] At the end of the intervention, RMR was measured again and participants were provided with a 7-day diet for weight maintenance, during which post-intervention follow-up testing occurred, as described previously.[15]

Outcomes

All assessments took place in the Geriatric Research Center of the WFSM Sticht Center on Aging by examiners blinded to treatment assignment. Baseline assessments took place within 3 weeks prior to starting the interventions. Post-intervention follow-up assessments took place during the 2 weeks after the intervention. Long-term follow-up assessments occurred 18–24 months after intervention completion.

Cognitive Outcomes.—Cognitive outcomes were measured at baseline, post-intervention follow-up and long-term follow-up. Cognitive tests were administered by a trained study coordinator in a quiet testing room. Prior to completing the cognitive assessment battery, participants were asked whether they had followed their normal daily eating and medication regimens and completed a finger stick glucose test to confirm blood glucose levels were >60 mg/dl. All participants presented with glucose levels higher than the cutoff.

The cognitive testing battery included: the Digit Symbol Coding task (DSC), the Trail Making Test (TMT) parts A and B, the Stroop task, phonemic fluency, semantic fluency, and the Rey Auditory Verbal Learning Task (RAVLT). The 90-second version of the DSC was administered; the outcome was the number of correct responses.[26–28] The TMT outcome was difference in time in parts A and B in seconds.[29] The interference score (interference score = [(time(s) needed for subtask3)−(time(s) needed for subtasks1+2)]/2) from the 40-item version of the Stroop task was used.[30,31] For phonemic fluency, participants verbally generated in one minute as many words as possible beginning with the letter F, and then did likewise for the letters A and S.[29] The sum of all 3 trials was used for analysis. For semantic fluency, participants verbally listed as many animals as possible within 1 minute and then

did likewise for kitchen items. The sum of both trials was used for analysis. The RAVLT is a word list memory task[29] and the sum of correctly recalled words across the first 5 trials was used. Global cognition was tested with the MMSE (30-point scale).[32]

A composite score of EF was calculated by summing the z-scores of DSC score, TMT B-A time, Stroop interference score, phonemic fluency, and semantic fluency. The sign of the z-score was reversed prior to summing when necessary so that larger z-scores indicate better performance.

Cardiometabolic outcomes—The primary outcome of the parent study was peak aerobic capacity (VO_{2peak}) determined on a motorized treadmill during a graded exercise test to exhaustion using a Ramp protocol.[15] Fasting and 2-hour postprandial glucose and insulin were measured in blood samples drawn before (0 min) and after (120 min) a 75g glucose ingestion. An estimate of insulin resistance by the homeostasis model of assessment (HOMA2-IR) was calculated using the fasting plasma insulin and glucose values as described.[33]

Statistical Methods—This analysis included the 88 participants who had EF composite scores at baseline and from at least one of the two follow-up visits. Baseline characteristics of the participants (Table 1) are described as mean/standard deviation (SD) or median (inter-quarter range) for continuous variables and count/percentage for categorical variables. Unadjusted mean scores for cognitive measures at each visit were calculated for each treatment group (Table 2).

The primary analysis for the ancillary study was to compare the EF z-score between treatment groups at post-intervention and long-term follow-up after adjusting for baseline measures using analysis of covariance (ANCOVA) with repeated measures. Similarly, ANCOVA with repeated measures was also used to compare the individual cognitive measures between groups at post-intervention and long-term follow-up. Adjusted mean scores and their 95% confidence intervals at post-intervention and long-term follow-up were estimated from the ANCOVA model. Two models were fitted for each cognitive outcome (including the primary outcome of the EF z-score): Model 1 adjusted for baseline task performance, age, sex, race, and education. Model 2 additionally adjusted for self-reported hypertension status, self-reported type 2 diabetes status, and BMI. Results for Model 2 were not meaningfully different from Model 1 for any outcome; therefore, results from Model 2 are shown for simplicity (Table 3). We also examined the interaction between group and visit.

In addition, we used ANCOVA with repeated measurements to evaluate the overall intervention effect (combining all groups) with changes in cognitive scores at post-intervention follow-up and long-term follow-up as the dependent variable, adjusted for the covariates in Model 2 (Table S2). An analysis using change in cognitive scores rather than adjusting for baseline is included as Table S3. All analyses were done using SAS v. 9.4 (Cary, NC). Significance was determined using a p-value < 0.05.

Planned secondary comparisons examined the role of insulin resistance and cardiorespiratory fitness by adding change between baseline and post-intervention follow-up in either HOMA2-IR (Model 3) or peak VO_2 (Model 4) to Model 2 to test whether differences in group mean cognitive performance were associated with changes in cardiorespiratory fitness or insulin resistance, after adjusting for group assignment. Because individual weight loss and decreases in caloric intake varied, sensitivity analyses were performed to test whether changes in weight loss or decreased calorie consumption were associated with cognitive performance, regardless of group assignment.

Results

Adherence and compliance in the parent study were excellent (87% retention, >85% exercise attendance, >95% diet compliance).[15] No participant dropped out due to an intervention-related adverse event and baseline characteristics of those who dropped out were not different from those who completed the study. As in the parent study,[15] participants in the EX+Mod-CR (−9.45±4.50%) and EX+High-CR (−10.45±3.97%) both lost more body mass than EX only (−1.13±3.44%), and differences in body mass lost between CR groups did not reach statistical significance.

Overall effects of intervention on cognitive outcomes

Raw cognitive scores at baseline, post-intervention, and long-term follow-up are shown in Table 2. There were no between-group differences in cognitive performance at baseline (all p-values >0.10). No interactions between group and visit were statistically significant (all $p > 0.05$) for Models 1 and 2.

In the overall sample, performance improved by 0.114 on the EF composite between baseline and post-intervention follow-up (p=0.01, 95% CI (0.028, 0.200). The 0.074 improvement in EF between baseline and long-term follow-up was not significant (p=0.10, 95% CI (−0.14, 0.162)); however, the difference between post-intervention and long-term follow-up EF was not statistically different (p>0.10). Table S2 shows overall differences at post-intervention and long-term follow-up in the overall sample for all cognitive tests.

Effect of randomization to caloric restriction on cognitive outcomes

In both the minimally adjusted model (Model 1) and fully adjusted model (Model 2), randomization to EX+Mod-CR or EX+High-CR compared to EX only did not result in significant differences in the EF composite score, nor were there any between group differences on any individual EF test. (Table 3, Figure 1). In both Model 1 and Model 2, there was a modest association ($p = 0.04$) between group assignment and MMSE score, with those randomized to EX+High-CR having slightly higher global cognition scores compared to EX only.

Effect of visit time point on cognitive outcomes

There was not a significant effect of visit time point (post intervention vs. long term) for the EF composite score. This reflects the result reported above that the EF composite score increased post-intervention in all 3 groups and was not statistically different between post-

intervention and long-term follow-up. There were statistically significant effects of time point for both the DSC (p=0.0008) and RAVLT (p=0.0101) using Model 1 that were maintained or strengthened using Model 2 (DSC: p=0.0008, RAVLT: p=0.0095). This reflects that in the overall sample, the DSC showed a non-significant increase of 1.1 (p>0.10, 95% CI (−0.45, 2.65)) between baseline and post-intervention follow-up and an increase of 3.3 (p<0.001, 95% CI (1.73, 4.87) between baseline and long-term follow-up. RAVLT showed a non-significant increase of 1.9 (p<0.10, 95% CI (−0.32, 4.13)) between baseline and post-intervention follow-up and an increase of 4.15 (p<0.001, 95% CI (1.87, 6.43) between baseline and long-term follow-up. Semantic fluency also showed a time effect (p=0.02 in Models 1 and 2) reflecting that a slight increase in score of 0.33 (p>0.4, 95% CI (−0.58, 1.24)) between baseline and post-intervention changed to a trend for a decrease of −0.82 (p<0.10, 95% CI (−1.76, 0.13) in words listed between baseline and long-term follow-up. These effects of time occurred in the absence of a group effect, meaning the effects over time followed a similar trajectory in all 3 groups for each test.

Secondary Analyses

Previous research shows that insulin resistance is associated with poorer cognitive outcomes and brain health[34–37]. Insulin resistance was significantly improved in the CR groups in this study.[15] Inclusion of change in HOMA-IR did not significantly alter the main effect of group, but strengthened the effect of visit time point on the EF composite score (p=0.0435, Table 4).

Because peak VO_2 improved in all groups, we tested whether improved VO_2 was associated with improved cognitive performance. Cognitive outcomes were tested using Model 2 adding change in peak VO_2. No statistically significant associations were observed between change in peak VO_2 and any cognitive outcomes (Table 4).

Sensitivity Analyses

Although intervention compliance was excellent, individual variation existed in the amount of weight lost. Therefore, we tested whether the amount of weight lost (rather than randomized group assignment) predicted cognitive outcomes. Percent weight loss following the intervention was added to Model 2 in place of group assignment. No statistically significant associations between percent weight loss and difference in group mean in any EF outcomes were observed. It appeared from the overall effect from mixed effect models that weight loss was associated with a small improvement in MMSE score (β= −0.06, p=0.02).

Achieving the same weight loss target (e.g., 5%) required a different absolute reduction in caloric intake in each person. In order to explore the possibility that the absolute amount of calorie reduction influenced cognition, the caloric reduction for each individual was used in Model 2 instead of group assignment. No statistically significant associations between calorie reduction and any EF outcome were observed. However, cutting more calories was associated with a slightly better MMSE score (β=0.002, p=0.001).

Discussion

Establishing the risks and benefits of intentional weight loss for adults over the age of 65 is currently an important research topic given the rapid aging of the population, increasing prevalence of obesity, and equipoise in the field. We tested whether addition of CR to a 20-week aerobic exercise intervention potentiated the short-and long-term benefits of exercise on EF. EF improved in the overall sample immediately post-intervention; however, we did not observe statistically significant differences between groups in post-intervention EF immediately or 18–24 months post-intervention. Sensitivity analyses to test for effects of weight loss and absolute amount of calorie reduction independent of group did not alter outcomes.

A modest association was noted between group randomization and better global cognition measured with the MMSE based on Model 2 (Table 3). The estimated magnitude of improvement in MMSE score conferred by adding weight loss was less than half a point and therefore likely not of clinical significance. The effect was supported by sensitivity analyses showing modest benefit on MMSE score associated with greater weight loss and greater calorie deficits, but reduced to non-statistical significance by adjustment for insulin resistance and cardiorespiratory fitness (Table 4). These findings suggest that intentional weight loss combined with exercise for a short period (20 weeks) does not negatively alter cognition in sedentary older adults with obesity, but provides little additional cognitive benefit over aerobic exercise alone.

These data contribute to evidence suggesting that adding weight loss to exercise in older adults with obesity is safe, although it may not specifically benefit cognition. Napoli and colleagues[22] completed a year-long 4-arm randomized controlled trial comparing exercise, moderate CR, CR and exercise together, or control. Participant selection largely matched the current study (sedentary, aged ≥ 65, BMI ≥ 30 kg/m^2, MMSE ≥ 24). Weight loss was comparable to this study; participants in the CR only condition achieved ~10% weight loss, exercise + CR ~9% weight loss, and exercise only had no significant weight loss. They examined change in cognitive score at baseline, 6 months, and 12 months. After 12 months, both the exercise and exercise+CR groups showed cognitive benefit compared to control. As here, they saw no significant differences between exercise and exercise+CR. Thus, it may be that exercise is the more potent intervention for cognitive benefit, and CR does not enhance or mitigate these effects. It is interesting that CR potentiated the benefits of exercise on insulin resistance and cardiorespiratory fitness both in this study and the Napoli study, yet did not significantly enhance cognition over exercise alone.

The relatively short duration of interventions and duration of follow-up for these studies raises important points about how long an exercise intervention should last. In the current study, the EF composite score did not improve between short- and long-term follow-up. However, the DSC and RAVLT showed continued improvements in score at long-term follow-up. In the Napoli study, most cognitive outcomes improved between 6-and 12-month time points. This suggests that benefits to the brain from lifestyle interventions may peak later or require longer intervention than benefits in measures like muscle strength, cardiorespiratory fitness, or body weight.

The Look AHEAD study supports the idea that a longer lifestyle modification period may benefit cognition.[23] This large RCT randomly assigned participants aged 42–76 with type 2 diabetes to receive a support and education group or a lifestyle intervention that aimed to achieve 10% weight loss at one year through regular meetings that supported adhering to caloric intake and exercise goals. While the intervention was less tightly controlled than this study or the Napoli study, lifestyle changes were maintained > 1 year, and modest cognitive benefits were observed at the 8-year follow-up in people without obesity.

The Look AHEAD study observed a significant interaction between baseline BMI and long-term cognitive outcomes such that in participants with type 2 diabetes who also had obesity at baseline (BMI≥30), the lifestyle intervention led to poorer cognitive outcomes than the support and education group. Even after losing significant amounts of weight, two-thirds of participants in the INFINITE study were still had obesity at study conclusion. This raises the possibility that obesity may alter the response of the brain to weight loss in older adults, or that more weight loss may be necessary in order for benefit to occur.

Finally, the current study used aerobic exercise alone while the Napoli study combined aerobic and strength training. The preponderance of research on the effects of exercise on cognition in aging has used aerobic exercise. However, strength training may provide separate or additional benefit to the brain.[38, 39] Even less research has been conducted on the effects of non-exercise movement that reduces sedentary time, which may be an important part of an exercise prescription for maintaining cognition.

Strengths of this study include the well-monitored intervention, detailed physiological outcomes, and good representation of measures of EF. One important limitation in interpreting improvements that occurred in the overall sample is the lack of a weight loss only or no-contact control group. While overall improvements in EF are expected based on many previous observations of the effects of exercise on cognition in aging, this study design cannot definitively attribute improvements in EF to exercise. Other limitations include limited testing of memory domains and relatively short duration of the intervention. In addition, the study included a greater proportion of women than men. While this accurately reflects the population, it limits the ability to test whether there are sex differences in response to exercise and weight loss in this trial. Although the sample size of this trial is comparable to many other exercise intervention trials focused on cognitive outcomes, the small sample size is a significant limitation. Future studies that are fully powered and have longer intervention durations are needed for more definitive understanding of the effects of intentional weight loss on cognition. Finally, future studies will ideally include gold-standard methods such as doubly-labeled water to assess CR fidelity.

Ideally, research on lifestyle interventions in aging will result in personalized ‘prescriptions’ that optimize quality of life physically and mentally. The subtle differences in results in our study, the study by Napoli et al., and the Look AHEAD trial highlight some important gaps in knowledge to be filled in order to tailor lifestyle interventions to benefit cognition in older adults.

Conclusions

This study adds to accumulating evidence that adding intentional weight loss to exercise does not positively or negatively influence cognition. Further investigation is needed to determine how to best tailor lifestyle interventions to benefit cognition in sedentary older adults with obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Emmerzaal TL, Kiliaan AJ, and Gustafson DR, 2003–2013: a decade of body mass index, Alzheimer's disease, and dementia. J Alzheimers Dis, 2015 43(3): p. 739–55. [PubMed: 25147111]
2. Ishii M and Iadecola C, Metabolic and Non-Cognitive Manifestations of Alzheimer's Disease: The Hypothalamus as Both Culprit and Target of Pathology. Cell Metab, 2015 22(5): p. 761–76. [PubMed: 26365177]
3. Pedditizi E, Peters R, and Beckett N, The risk of overweight/obesity in mid-life and late life for the development of dementia: a systematic review and meta-analysis of longitudinal studies. Age Ageing, 2016 45(1): p. 14–21. [PubMed: 26764391]
4. Jensen MD, et al., 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation, 2014 129(25 Suppl 2): p. S102–38. [PubMed: 24222017]
5. Baker LD, et al., Effects of aerobic exercise on mild cognitive impairment: a controlled trial. Arch Neurol, 2010 67(1): p. 71–9. [PubMed: 20065132]
6. Colcombe S and Kramer AF, Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci, 2003 14(2): p. 125–30. [PubMed: 12661673]
7. Erickson KI and Kramer AF, Aerobic exercise effects on cognitive and neural plasticity in older adults. Br J Sports Med, 2009 43(1): p. 22–4. [PubMed: 18927158]
8. Erickson KI, et al., Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A, 2011 108(7): p. 3017–22. [PubMed: 21282661]
9. van Praag H, Kempermann G, and Gage FH, Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat Neurosci, 1999 2(3): p. 266–70. [PubMed: 10195220]
10. Baker LD, et al., Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. J Alzheimers Dis, 2010 22(2): p. 569–79. [PubMed: 20847403]

11. Lautenschlager NT, et al., Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. Jama, 2008 300(9): p. 1027–37. [PubMed: 18768414]
12. Burdette JH, et al., Using network science to evaluate exercise-associated brain changes in older adults. Front Aging Neurosci, 2010 2: p. 23. [PubMed: 20589103]
13. Pereira AC, et al., An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A, 2007 104(13): p. 5638–43. [PubMed: 17374720]
14. Bugg JM, et al., Cognitive and neural correlates of aerobic fitness in obese older adults. Exp Aging Res, 2012 38(2): p. 131–45. [PubMed: 22404537]
15. Nicklas BJ, et al., Effects of caloric restriction on cardiorespiratory fitness, fatigue, and disability responses to aerobic exercise in older adults with obesity: A randomized controlled trial. J Gerontol A Biol Sci Med Sci, 2018.
16. Lynch NA, et al., Reductions in visceral fat during weight loss and walking are associated with improvements in VO(2 max). J Appl Physiol (1985), 2001 90(1): p. 99–104. [PubMed: 11133898]
17. Manini TM, et al., Effects of exercise on mobility in obese and nonobese older adults. Obesity (Silver Spring), 2010 18(6): p. 1168–75. [PubMed: 19834467]
18. Villareal DT, et al., Weight loss, exercise, or both and physical function in obese older adults. N Engl J Med, 2011 364(13): p. 1218–29. [PubMed: 21449785]
19. Mattson MP, Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab, 2012 16(6): p. 706–22. [PubMed: 23168220]
20. Spolidoro M, et al., Food restriction enhances visual cortex plasticity in adulthood. Nat Commun, 2011 2: p. 320. [PubMed: 21587237]
21. Willette AA, et al., Calorie restriction reduces the influence of glucoregulatory dysfunction on regional brain volume in aged rhesus monkeys. Diabetes, 2012 61(5): p. 1036–42. [PubMed: 22415875]
22. Napoli N, et al., Effect of weight loss, exercise, or both on cognition and quality of life in obese older adults. American Journal of Clinical Nutrition, 2014 100(1): p. 189–198. [PubMed: 24787497]
23. Espeland MA, et al., Long-term Impact of Behavioral Weight Loss Intervention on Cognitive Function. Journals of Gerontology Series a-Biological Sciences and Medical Sciences, 2014 69(9): p. 1101–1108.
24. Nelson ME, et al., Physical Activity and Public Health in Older Adults: Recommendation from the American College of Sports Medicine and the American Heart Association. Medicine and Science in Sports and Exercise, 2007 39(8): p. 1435–1445. [PubMed: 17762378]
25. De Weir J, New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol London, 1949 109: p. 1–9. [PubMed: 15394301]
26. Yordanova J, et al., Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. Brain, 2004 127(Pt 2): p. 351–62. [PubMed: 14607784]
27. Salthouse TA, What do adult age differences in the Digit Symbol Substitution Test reflect? J Gerontol, 1992 47(3): p. P121–8. [PubMed: 1573192]
28. Salthouse TA, Influence of processing speed on adult age differences in working memory. Acta Psychol (Amst), 1992 79(2): p. 155–70. [PubMed: 1598844]
29. Strauss E, Sherman EMS, and Spreen O, A compendium of neuropsychological tests: administration, norms, and commentary. Third Edition ed. 2006, New York: Oxford University Press.
30. Houx PJ, Jolles J, and Vreeling FW, Stroop interference: aging effects assessed with the Stroop Color-Word Test. Exp Aging Res, 1993 19(3): p. 209–24. [PubMed: 8223823]
31. Van der Elst W, et al., Establishing normative data for repeated cognitive assessment: a comparison of different statistical methods. Behav Res Methods, 2013 45(4): p. 1073–86. [PubMed: 23344738]
32. Folstein MF, Folstein SE, and McHugh PR, “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 1975 12(3): p. 189–198. [PubMed: 1202204]

33. Levy JC, Matthews DR, and Hermans MP, Correct homeostasis model assessment (HOMA) evaluation uses the computer program. Diabetes Care, 1998 21(12): p. 2191–2192. [PubMed: 9839117]

34. Benedict C, et al., Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care, 2012 35(3): p. 488–94. [PubMed: 22301128]

35. Bruehl H, et al., Cognitive impairment in nondiabetic middle-aged and older adults is associated with insulin resistance. J Clin Exp Neuropsychol, 2010 32(5): p. 487–93. [PubMed: 20524222]

36. Craft S, Insulin resistance and cognitive impairment: a view through the prism of epidemiology. Arch Neurol, 2005 62(7): p. 1043–4. [PubMed: 16009754]

37. Matsuzaki T, et al., Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. Neurology, 2010 75(9): p. 764–70. [PubMed: 20739649]

38. Mavros Y, et al., Mediation of Cognitive Function Improvements by Strength Gains After Resistance Training in Older Adults with Mild Cognitive Impairment: Outcomes of the Study of Mental and Resistance Training. J Am Geriatr Soc, 2017 65(3): p. 550–559. [PubMed: 28304092]

39. Best JR, et al., Long-Term Effects of Resistance Exercise Training on Cognition and Brain Volume in Older Women: Results from a Randomized Controlled Trial. J Int Neuropsychol Soc, 2015 21(10): p. 745–56. [PubMed: 26581787]

What is known about this subject:

- It is well-accepted that aerobic exercise is beneficial for the brain in older adults.
- Obesity is known to blunt the cardiovascular benefits of exercise. Adding caloric restriction to exercise appears to potentiate the cardiovascular benefits of exercise in people with obesity.
- There is currently limited evidence about the effects of adding caloric restriction to aerobic exercise on cognition and the brain. One well-controlled study suggested that adding caloric restriction did not add additional cognitive benefit.

What does this study add:

- This study is a well-controlled trial adding caloric restriction to aerobic exercise.
- It demonstrates no harm to adding caloric restriction to aerobic exercise in sedentary older adults with obesity.
- It is important corroboration of the one previously published well-controlled trial on this topic that also includes a longer follow-up period.

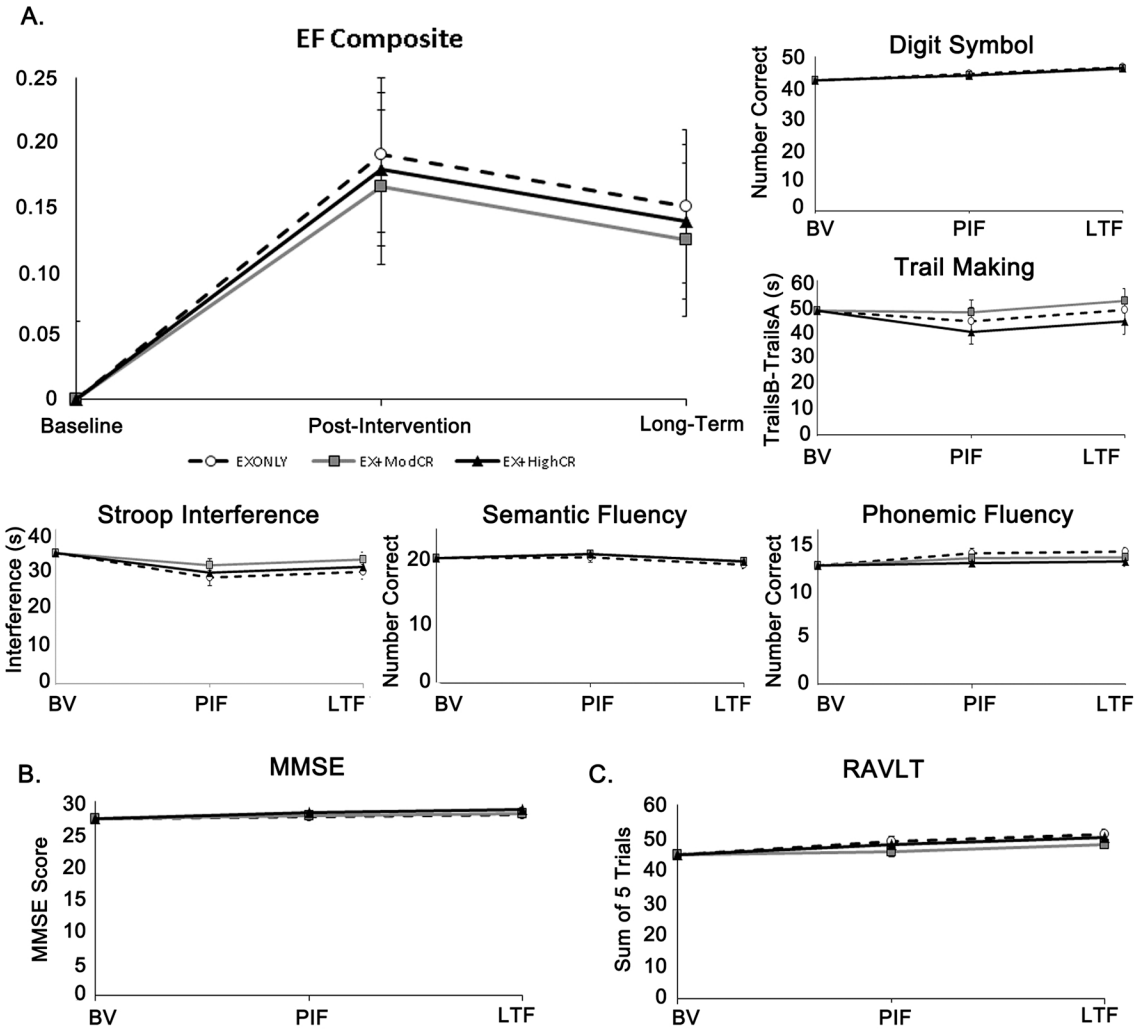

Figure 1. Adjusted cognitive scores at post-intervention and long-term follow-up.

Scores are adjusted for age, sex, race, education, BMI, hypertension, diabetes status, and baseline values. A) The EF composite z-score is shown in the main panel with the five cognitive tests used to calculate the z-score around it. B) Adjusted MMSE scores at and C) Adjusted RAVLT scores calculated as the sum of responses for the first five trials at all three time points. EX Only is shown in dashed line/white circles, EX+ModCR is grey line/grey squares, EX+HighCR is black line/black triangle.

Table 1.

Participant characteristics at baseline (n=88)

	Overall (N = 88)	EX only (N = 28)	EX+Mod CR (N = 30)	EX+High CR (N = 30)	P-value
	Mean(±SD)	Mean(±SD)	Mean(±SD)	Mean(±SD)	
Age (years)	69.0 (3.5)	69.0 (3.7)	68.9 (3.3)	69.0 (3.5)	0.96
Female, N (%)	68 (77.3)	22 (78.6)	23 (76.7)	23 (76.7)	0.98
White, N (%)	56 (63.6)	18 (64.3)	18 (60.0)	20 (66.7)	0.86
Education, N (%)					0.80
< High School	21 (23.9)	8 (28.6)	7 (23.3)	6 (20.0)	
High School	46 (52.3)	15 (53.6)	14 (46.7)	17 (56.7)	
> High School	21 (23.9)	5 (17.9)	9 (30.0)	7 (23.3)	
Weight (kg)	95.3(13.7)	96.6(13.9)	93.9(13.7)	95.7(13.8)	0.81
BMI (kg/m^2)	35.3(3.9)	35.2(3.2)	35.7(4.4)	35.0(3.9)	0.87
Percent Body Fat (%)	44.9(5.8)	45.0(5.5)	45.5(6.2)	44.2(5.9)	0.61
Resting Seated Blood Pressure					
SBP (mmHg)	134.0(16.4)	133.3(12.8)	134.5(18.8)	134.2(17.4)	0.85
DBP (mmHg)	73.6(10.2)	74.8(11.1)	73.1(8.9)	72.9(10.6)	0.49
HDL cholesterol (mg/dl)	59.3(15.7)	57.3(13.4)	57.9(13.8)	62.6(19.2)	0.20
LDL cholesterol (mg/dl)	110.1(36.0)	115.6(37.4)	115.0(37.7)	100.0(31.7)	0.09
Triglycerides (mg/dl)	120.2(58.6)	122.7(50.6)	129.3(58.0)	108.9(65.7)	0.36
Fasting Glucose (mg/dl)	102.7(15.3)	104.4(14.9)	100.2(16.6)	103.6(14.5)	0.85
HOMA2-IR	2.1(1.1)	1.9(0.8)	2.3(1.4)	2.1(1.1)	0.66
Self-reported comorbidities, N (%)					
Hypertension	57 (64.8)	19 (67.9)	19 (63.3)	19 (63.3)	0.92
Non-insulin treated diabetes	14 (15.9)	6 (21.4)	2 (6.7)	6 (20.0)	0.23
Medication Use, N (%)					
Antihypertensive	60 (68.2)	19 (67.9)	22 (73.3)	19 (63.3)	0.71
Antidiabetic	13 (14.8)	5 (17.9)	2 (6.7)	6 (20.0)	0.30
Cholesterol-lowering	38 (43.2)	12 (42.9)	10 (33.3)	16 (53.3)	0.29
Antidepressant/Mood	30 (34.1)	12 (42.9)	9 (30.0)	9 (30.0)	0.50
Peak VO2 (ml/kg/min)	17.6(3.6)	17.7(3.8)	18.0(3.9)	17.2(3.2)	0.62

Table 2.

Unadjusted mean scores for cognitive measures at baseline, post-intervention and long-term follow-up.

	Baseline Unadjusted Mean (±SD)			Post-intervention Unadjusted Mean (±SD)			Long-term follow-up Unadjusted Mean (±SD)		
	EX Only n = 28	**EX+Mod-CR n = 30**	**EX+High-CR n = 30**	**EX Only n = 21**	**EX+Mod-CR n = 28**	**EX+High-CR n = 27**	**EX Only n = 20**	**EX+Mod-CR n = 21**	**EX+High-CR n = 21**
EF Composite	−0.1(0.8)	0.0(0.6)	0.1(0.6)	0.2(0.8)	0.2(0.6)	0.2(0.5)	0.1(0.7)	0.1(0.8)	0.1(0.5)
DSC	40.8(9.0)	42.8(9.9)	43.0(8.0)	43.1(9.6)	44.4(8.8)	43.8(8.8)	43.9(9.1)	47.5(10.9)	46.8(7.6)
Trails B-A	48.4(39.2)	47.6(38.2)	48.7(38.4)	47.0(30.0)	46.2(28.1)	39.7(23.1)	46.7(34.3)	55.8(47.9)	45.2(22.1)
Stroop Interference	40.1(33.0)	31.3(11.9)	30.3(8.9)	31.0(15.6)	29.3(11.0)	29.3(8.8)	29.4(14.8)	35.2(15.4)	30.2(8.8)
Semantic Fluency	20.1(5.6)	20.0(3.9)	20.8(3.9)	20.9(5.6)	20.8(5.0)	21.4(4.3)	19.0(4.1)	20.1(5.5)	20.4(3.4)
Phonemic Fluency	12.6(4.9)	12.2(4.0)	12.1(4.5)	14.1(5.0)	13.0(4.0)	12.9(3.6)	13.9(4.3)	13.4(4.2)	11.8(3.7)
MMSE	27.5(2.5)	27.2(2.1)	27.5(2.3)	27.9(2.3)	27.5(2.2)	28.6(2.0)	28.0(1.3)	28.6(2.0)	28.4(1.3)
RAVLT	45.6(10.0)	45.3(8.1)	42.9(9.5)	50.2(8.4)	46.1(9.5)	47.6(10.2)	52.8(10.3)	49.6(9.2)	47.8(10.4)

No significant differences were noted at baseline (all p-values > 0.10)

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Table 3.

Adjusted mean scores show effects of randomization on cognitive outcomes at post-intervention and long-term follow-up based on mixed-effect models.

Values show adjusted mean scores for cognitive variables at post-intervention and long-term follow-up time points with 95% confidence intervals shown in parentheses. Columns on the right show p-values reflecting the main effect of time (was there a significant difference in group mean over follow-up visits) and the main effect of group randomization for each variable.

	Post-intervention Adjusted mean (95% CI)			Long-term Follow-up Adjusted mean (95% CI)			p-value	p-value
Outcomes	**ExOnly**	**Ex+Mod-CR**	**Ex+High-CR**	**ExOnly**	**Ex+Mod-CR**	**Ex+High-CR**	**visit**	**group**
Model 2								
EF Composite	0.190(0.062,0.319)	0.165(0.049,0.280)	0.179(0.059,0.298)	0.150(0.021,0.279)	0.124(0.006,0.243)	0.138(0.017,0.260)	0.1825	0.9430
DSC	44.52(42.22,46.82)	43.96(41.97,45.96)	44.07(41.98,46.16)	46.72(44.44,49.01)	46.17(44.12,48.21)	46.27(44.15,48.40)	0.0008	0.9028
Trials B-A	44.27(33.81,54.72)	47.78(38.54,57.02)	39.98(30.35,49.61)	48.49(38.14,58.83)	52.00(42.34,61.66)	44.20(34.23,54.17)	0.2945	0.3834
Stroop Interference	27.32(23.49,31.16)	30.54(27.14,33.94)	28.60(25.10,32.11)	28.94(25.12,32.76)	32.15(28.60,35.70)	30.22(26.59,33.84)	0.2085	0.3278
Semantic Fluency	20.36(19.03,21.69)	20.92(19.73,22.11)	20.88(19.65,22.11)	19.22(17.90,20.54)	19.78(18.54,21.01)	19.74(18.47,21.01)	0.0166	0.7124
Phonemic Fluency	13.59(12.49,14.68)	13.04(12.07,14.00)	12.58(11.58,13.58)	13.69(12.60,14.78)	13.14(12.16,14.13)	12.69(11.67,13.70)	0.6521	0.2915
RAVLT	48.80(45.54,52.06)	45.61(42.69,48.53)	47.65(44.55,50.75)	51.04(47.79,54.29)	47.86(44.87,50.85)	49.89(46.73,53.06)	0.0095	0.2345
MMSE	27.61(27.05,28.16)	27.80(27.29,28.30)	28.36(27.84,28.88)	28.00(27.45,28.55)	28.19(27.66,28.71)	28.75(28.21,29.30)	0.0881	0.0384

Model 2 adjusted for Model 1 variables (baseline task performance, age, sex, race, and education) + hypertension status, type 2 diabetes status, and BMI.

No interaction between group and visit was statistically significant.

Table 4.

Inclusion of insulin resistance (Model 3) and cardiorespiratory fitness (Model 4) on the effects of randomization on cognitive outcomes.

	Post-intervention Adjusted mean (95% CI)			Long-term Follow-up Adjusted mean (95% CI)			p-value	p-value
Outcomes	**ExOnly**	**Ex+Mod-CR**	**Ex+High-CR**	**ExOnly**	**Ex+Mod-CR**	**Ex+High-CR**	**visit**	**group**
Model 3								
EF Composite	0.178(0.038,0.318)	0.254(0.123,0.385)	0.251(0.124,0.378)	0.115(−.025,0.256)	0.192(0.059,0.325)	0.189(0.060,0.317)	0.0435	0.6445
DSC	44.29(41.84,46.75)	45.43(43.23,47.63)	45.26(43.06,47.46)	46.21(43.77,48.65)	47.35(45.10,49.59)	47.18(44.96,49.40)	0.0038	0.7269
Trials B-A	43.40(31.59,55.20)	46.33(35.78,56.88)	38.60(28.27,48.93)	49.01(37.32,60.70)	51.94(40.94,62.95)	44.22(33.55,54.88)	0.1847	0.4346
Stroop Interference	27.16(23.00,31.32)	30.16(26.35,33.97)	28.58(24.84,32.31)	28.47(24.31,32.63)	31.47(27.51,35.43)	29.89(26.05,33.73)	0.3338	0.5021
Semantic Fluency	20.59(19.13,22.05)	21.27(19.93,22.61)	21.27(19.97,22.57)	19.21(17.75,20.66)	19.89(18.50,21.27)	19.89(18.55,21.23)	0.0058	0.6852
Phonemic Fluency	13.99(12.81,15.17)	12.97(11.91,14.03)	12.53(11.49,13.58)	14.08(12.90,15.26)	13.06(11.98,14.14)	12.63(11.57,13.69)	0.7118	0.1260
RAVLT	49.11(45.58,52.64)	45.03(41.74,48.31)	46.94(43.67,50.22)	51.39(47.86,54.91)	47.30(43.95,50.65)	49.22(45.89,52.55)	0.0121	0.2014
MMSE	27.66(27.07,28.26)	27.65(27.08,28.22)	28.25(27.70,28.80)	28.04(27.45,28.64)	28.03(27.44,28.63)	28.63(28.06,29.20)	0.1093	0.0960
Model 4								
EF Composite	0.175(0.041,0.308)	0.119(−.003,0.242)	0.146(0.024,0.268)	0.134(0.001,0.267)	0.079(−.047,0.205)	0.105(−.018,0.229)	0.1884	0.7943
DSC	44.45(42.10,46.80)	43.58(41.48,45.69)	43.67(41.55,45.79)	46.54(44.21,48.87)	45.67(43.51,47.83)	45.76(43.60,47.91)	0.0021	0.7834
Trials B-A	43.70(32.67,54.74)	47.61(37.72,57.51)	40.16(30.18,50.14)	48.79(37.94,59.64)	52.70(42.29,63.11)	45.25(34.94,55.55)	0.2259	0.4650
Stroop Interference	27.33(23.37,31.28)	31.55(27.95,35.14)	28.63(25.06,32.20)	28.89(24.97,32.81)	33.11(29.34,36.88)	30.19(26.50,33.88)	0.2445	0.1801
Semantic Fluency	20.43(19.13,21.73)	20.49(19.31,21.68)	20.75(19.56,21.94)	19.36(18.07,20.64)	19.42(18.18,20.66)	19.68(18.45,20.90)	0.0241	0.8913
Phonemic Fluency	13.35(12.23,14.46)	12.69(11.69,13.69)	12.42(11.42,13.43)	13.48(12.37,14.59)	12.82(11.79,13.84)	12.55(11.53,13.57)	0.5991	0.3491
RAVLT	48.74(45.51,51.96)	44.11(41.16,47.06)	47.26(44.26,50.25)	50.86(47.66,54.07)	46.24(43.20,49.28)	49.39(46.32,52.45)	0.0177	0.0561
MMSE	27.64(27.06,28.23)	27.80(27.27,28.34)	28.38(27.84,28.92)	28.00(27.42,28.58)	28.16(27.59,28.73)	28.73(28.17,29.30)	0.1336	0.0533

Model 3 adjusted for Model 2 variables + HOMA2-IR change.

Model 4 Model 2 variables + peak VO2 change.