Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals With Mild Cognitive Impairment

Nidia Celeste Horie, Valeria T. Serrao, Sharon Sanz Simon, Maria Rita Polo Gascon, Alessandra Xavier dos Santos, Maria Aquimara Zambone, Marta Merenciana del Bigio de Freitas, Edecio Cunha-Neto, Emerson Leonildo Marques, Alfredo Halpern, Maria Edna de Melo, Marcio C. Mancini, and Cintia Cercato*

Context: Obesity in midlife is a risk factor for dementia, but it is unknown if caloric restriction-induced weight loss could prevent cognitive decline and therefore dementia in elderly patients with cognitive impairment.

Objective: To evaluate the cognitive effect of intentional weight loss in obese elderly patients with mild cognitive impairment (MCI), considering the influence of age, apolipoprotein E (APOE) genotype, physical activity, biochemical markers, and diet.

Design: Single-center, prospective controlled trial.

Setting: Academic medical center.

Participants: Eighty obese patients with MCI, aged 60 or older (68.1 ± 4.9 y, body mass index [BMI] 35.5 ± 4.4 kg/m^2, 83.7% women, 26.3% APOE allele ϵ4 carriers).

Intervention: Random allocation to conventional medical care alone (n = 40) or together with nutritional counselling (n = 40) in group meetings aiming to promote weight loss through caloric restriction for 12 months.

Outcome Measurements: clinical data, body composition, neuropsychological tests (main outcome), serum biomarkers, APOE genotype, physical performance, dietary recalls.

Results: Seventy-five patients completed the follow-up. BMI, on average, decreased 1.7 ± 1.8 kg/m^2 (P = .021), and most of the cognitive tests improved, without difference between the groups. In analysis with linear generalized models, the BMI decrease was associated with improvements in verbal memory, verbal fluency, executive function, and global cognition, after adjustment for education, gender, physical activity, and baseline tests. This association was strongest in younger seniors (for memory and fluency) and in APOE allele ϵ4 carriers (for executive function). Changes in homeostasis model assessment-estimated insulin resistance, C-reactive protein, leptin and intake of energy, carbohydrates, and fats were associated with improvement in cognitive tests.

Conclusions: Intentional weight loss through diet was associated with cognitive improvement in patients with MCI. (***J Clin Endocrinol Metab*** **101: 1104–1112, 2016)**

Dementia is a syndrome characterized mainly by deterioration in cognitive function and is one of the major causes of disability and dependency among older people. Nearly 50 million people worldwide have dementia, and it is caused by a variety of conditions that affect the brain, of which the most common is Alzheimer's disease

* Author Affiliations are shown at the bottom of the next page.

Abbreviations: APOE4, apolipoprotein E allele ϵ4; BMI, body mass index; CAMcog, cognitive session of CAMDEX; CI95, 95% confidence interval; CRP, C-reactive protein; DB, digit span backwards; DF, digit span forward; HOMA-IR, homeostasis model assessment-estimated insulin resistance; IPAQ, International Physical Activity Questionnaire; IQ, intelligence quotient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test; RAVLTΣA1A5, RAVLT total learning; RAVLT-A6, RAVLT recall; RAVLT-A7, RAVLT delayed recall; SPPB, Short Physical Performance Battery; TMA, Trail Making Test part A; TMB, Trail Making Test part B.

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(1). Studies of secondary prevention have been performed with subjects with mild cognitive impairment (MCI), who have increased risk of dementia, but few strategies, such as physical activity, have been shown to reduce cognitive decline in prospective studies (2).

According to several epidemiological studies, obesity in midlife increases the risk of dementia later in life (3, 4), and insulin resistance, dyslipidemia, hypertension, low grade inflammation, and leptin resistance are associated with both obesity and cognitive decline. Caloric restriction is one of the mainstays of obesity treatment, and its neuroprotective effect has largely been demonstrated in both animal models (5) and also in cognitively normal humans (6, 7). In patients with cognitive impairment, however, its effects have not yet been tested. Research on the effects of a hypocaloric diet in the elderly faces major obstacles: late-life obesity has been associated with decreased dementia risk (8), and many studies show that weight loss is associated with increased mortality and disability, especially in subjects over 70 years of age (9). These risks, however, seem to be more important in underweight or normal-weight subjects than in obese (10) ones.

We hypothesized that intentional weight loss via caloric restriction in elderly obese subjects with MCI could slow the cognitive decline. We also evaluated the influence of other risk factors for dementia, such as age, presence of the apolipoprotein E allele ϵ4 (APOE4) (APOE4 carriers or APOE4 noncarriers), metabolic and inflammatory parameters, and diet. Considering the risks of lean mass and strength loss after weight loss, the safety of the intervention was verified by measuring changes in lean mass and physical functioning.

Materials and Methods

This study was approved by the ethics committee of the institution and was conducted in adherence with the Helsinki Declaration; the trial is registered with clinicaltrials.gov: NCT 01286389. Informed consent was obtained from all participants for being included in the study. A complete description of the inclusion and exclusion criteria, participants selection, measurements, and statistical analysis is in the Supplemental Material.

Trial design

This was a prospective, 1:1, randomized study to assess the cognitive effects of weight loss via caloric restriction in obese subjects with MCI according to the European Consortium on Alzheimer's disease (11), comparing groups who received conventional care with or without nutritional counseling for 12 months (Figure 1). It was performed from June 2011 to May 2013 at the outpatient clinic of the of Hospital das Clínicas, São Paulo University.

All patients were advised to engage in physical activity according to "The global recommendations on physical activity for health" from the World Health Organization (12); briefly, they should do at least 150 minutes of moderate-intensity aerobic physical activity or walking throughout the week, or if limited due to health conditions, they should be as physically active as their abilities and conditions allow. All patients received conventional medical care, which was provided through consultation with a geriatrician approximately every 2 months and which focused on control of comorbidities. Half of the patients received additionally nutritional counseling in groups conducted by nutritionists (26 to 28 1-hour meetings held over the course of 12 mo) that aimed to promote healthy eating habits and weight loss through caloric restriction. The group meetings included advice on eating a diet rich in fiber, fruits, vegetables, and whole grains and included at least 1 g/kg of weight of protein per day, with a recommended calorie deficit of approximately 500 kcal/d (or to a minimum of 1200 kcal/d), and the meetings also included lectures on food composition, meal preparation, eating habits, and self-monitoring techniques.

Participants and measurements

Eighty subjects with MCI (11), body mass index (BMI) more than or equal to 30 kg/m^2, age more than or equal to 60 years, without conditions that interfere with weight loss or cognition (eg, major depression [evaluated by the module Major Depressive Episode of Mini International Neuropsychiatric Interview (13)], hypothyroidism, heart failure, cancer, alcoholism, infectious diseases, and autoimmune activity; use of antiobesity drugs, benzodiazepines, neuroleptics, or estrogen replacement therapy in the past 2 mo) were selected.

Socio-demographic, anthropometric, and clinical data were recorded. Biochemical analysis included glucose, insulin, glycated hemoglobin (HbA1c), homeostasis model assessment-estimated insulin resistance (HOMA-IR), lipid profile, leptin, adiponectin, IL-6, TNFα, C-reactive protein (CRP), and APOE genotype. Because we had a small number of patients for some genotypes, the patients were classified as APOE4 carriers (homozygote or heterozygote for APOE4) or noncarriers. Physical performance was measured with the Short Physical Performance Battery (SPPB) (14). Food intake was estimated through 24-hour diet recall collected by trained nutritionists. The calculations for the energy and macronutrient intake were performed using the Avanutri 4.0 software (15). As a reference table for nutritional composition of foods was adopted the Brazilian Table of Food Composition (16), and when food was not listed in the table, it was used as a reference table of the United States Department of Agriculture (17). We recorded the level of physical activity using the International Physical Activity Questionnaire (IPAQ) (short version) (18) and classified the patients as active or sedentary

Obesity and Metabolic Syndrome Group (N.C.H., E.L.M., A.H., M.E.d.M., M.C.M., C.C.), São Paulo University, School of Medicine; Psychology Division (V.T.S., M.R.P.G.), Hospital das Clínicas, São Paulo University; Institute of Psychiatry (S.S.S.), São Paulo University, School of Medicine; Nutrition Division (A.X.d.S., M.A.Z.), Clinical Hospital, São Paulo University, School of Medicine; Discipline of Geriatrics (M.M.d.B.d.F.), São Paulo University, School of Medicine; and Division of Clinical Immunology and Allergy (E.C.-N.), São Paulo University, School of Medicine, São Paulo, Brazil 01246-903

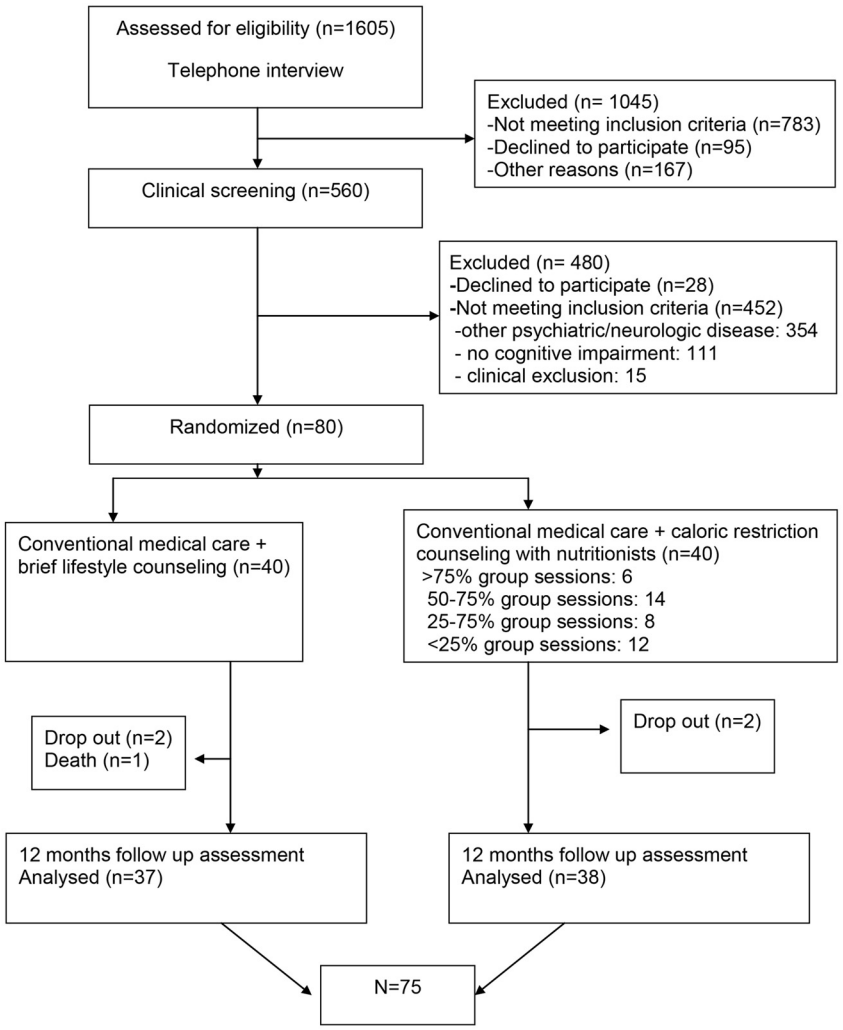

Figure 1. Study flow chart from recruitment until 12-month follow-up.

(active ≥150 min of physical activity/wk). All these measures, except genotyping, were repeated after 12 months.

The neuropsychological battery included measures of premorbid intelligence quotient (IQ) (estimated by vocabulary and matrix reasoning [19] tests), verbal memory Rey Auditory Verbal Learning Test (RAVLT) (20) (RAVLT delayed recall [RAVLT-A7], RAVLT total learning [RAVLTΣA1A5], RAVLT recall [RAVLT-A6] recognition), attention (digit span forward [DF] and digit span backwards [DB] [21], Trail Making Test part A [TMA]), working memory (DB and Trail Making Test part B [TMB]), psychomotor processing speed (TMA and TMB) (22), executive function (Modified Wisconsin Card Sorting Test, 48 cards version [23], TMB, and verbal fluency), language (phonemic verbal fluency [24], measured with words starting with F, A, or S, and semantic verbal fluency, measured with number of animals), and cognitive complaints (Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]) (25). Two tests of global cognition were used at the screening, Montreal Cognitive Assessment (MoCA) (26, 27) and cognitive session of Cambridge Examination for Mental Disorders of the Elderly (CAMcog) (28). All of these tests, except MoCA and IQ, were repeated after 12 months.

Analysis

The statistical analyses were performed using the Statistical Package for Social Science software version 20.0 (SPSS). $P \leq .05$ was considered significant, and all tests were 2-sided. Bivariate analysis was performed with 2-sample t tests or Mann-Whitney test for continuous variables and χ^2 test or Fisher's test for categorical variables. The generalized estimating equation was used in the longitudinal analysis. The independent variable group shows the main effect of intervention group, the time variable shows the effect of time between pretest and follow-up, whereas the interaction term group × time can be interpreted as the effect of the intervention (Table 1 and Supplemental Material). Because both groups lost similar amounts of weight after the intervention period (mean ΔBMI intensive group = −2.1 [−4.8; 0.7] kg/m^2, conventional group = −1.3 [−4.1; 1.4] kg/m^2, P = .428) (Table 1 and Supplemental Material), we decided to a posteriori pool the longitudinal analysis between groups and to test for the effects of change of BMI as a continuous variable.

To evaluate the relationship between BMI change and variation in cognitive domains, considering the effect of covariates, the regression with the generalized linear model with normal distribution and identity link function was used. Cognitive tests were grouped according to the next domains on the basis of a generally accepted description: global cognition (CAMcog and IQCODE), verbal memory (RAVLTΣA1A5, RAVLT-A6, and RAVLT-A7 recognition), executive ability (TMA, TMB, Modified Wisconsin Card Sorting Test, and DB), language/fluency (phonemic verbal fluency and semantic verbal fluency), and attention (DF and DB). With scores from 2 time points, principal-components analysis with varimax rotation and Kaiser normalization was performed on these domain-specific test groups to generate single components for each domain. Standardized regression factor scores were then generated from these components by Bartlett´s method. The difference (Δ) between the cognitive tests results at 12-month follow-up, subtracted from the baseline score, was considered the dependent variable. The variables ΔBMI, gender, APOE4, physical activity at 12 months, age, education, and baseline test score were all considered predictors of change in cognitive status. Age and APOE4 genotype (carrier) are 2 important risk factors for dementia and had been described as influence for weight loss; therefore, the interaction between weight loss and cognitive change was also verified. The result was presented with tests of the main effects for age, APOE4, and ΔBMI and the interaction between a risk factor and ΔBMI, with values of β (indicating the linear fit), SE, and significance.

Table 1. Baseline Characteristics by Intervention Group

Characteristics	Groups	Conventional; Mean (SD), n (%)	Intensive; Mean (SD), n (%)	*P*
Age (y)		68.3 (5.3)	67.9 (4.5)	.688
Gender (female)		34 (85%)	33 (82.5%)	.762
Education (y)		8.3 (4.3)	9.4 (4.8)	.277
IQ		97,6 (11)	98 (10.6)	.845
MoCA (0–30)		19.1 (3.5)	19.2 (3.1)	.920
IADL (9–27)		25.8 (2.1)	25.6 (1.6)	.156
BMI class				.280
BMI <35 (kg/m^2)		23 (57.5%)	24 (60%)	
BMI 35–39.9 (kg/m^2)		13 (32.5%)	8 (20%)	
BMI ≥40 (kg/m^2)		4 (10%)	8 (20%)	
Comorbidities				
Charlson comorbidity index		1.3 (1.1)	1.5 (1.4)	.538
Hypertension (%)		34 (85%)	28 (70%)	.108
Diabetes (%)		18 (45%)	15 (37,5%)	.496
Prediabetes (%)[a]		14 (35%)	16 (40%)	.644
Metabolic syndrome (%)		35 (87,5%)	32 (80%)	.546
Previous smoking (%)[b]		11 (27.5%)	16 (40%)	.237
Physical function				
Physically active (%)		23 (57.5%)	27 (67.5%)	.356
SPPB (0–12)		10.5 (1.8)	10.5 (1.5)	.694
Balance (0–4)		3.8 (0.6)	3.8 (0.7)	.748
4-m walk (s)		4.7 (1.0)	4.8 (0.9)	.644
Sit/get up (sec)		12.3 (5.0)	11.4 (2.7)	.298
Genotype				.834
$\epsilon4\epsilon4$ n (%)		0	1 (2.5%)	
$\epsilon3\epsilon4$ n (%)		7 (17.5%)	7 (17.5%)	
$\epsilon2\epsilon4$ n (%)		3 (7.5%)	3 (7.5%)	
$\epsilon3\epsilon3$ n (%)		27 (67.5%)	26 (65%)	
$\epsilon2\epsilon3$ n (%)		3 (7.5%)	3 (7.5%)	
APOE4 carriers (%)		10 (25%)	11 (27.5%)	
MCI type				.993
Amnestic multiple domain		18 (45%)	19 (47.5%)	
Amnestic single domain		8 (20%)	7 (17.5%)	
Nonamnestic multiple domain		2 (5%)	2 (5%)	
Nonamnestic single domain		12 (30%)	12 (30%)	

Abbreviations: IADL, instrumental activities of daily life; IPAQ, international physical activity questionnaire.

[a] Fasting glucose between 100 and 125 mg/dL or impaired glucose tolerance.

[b] Just 1 patient was a current smoker.

Partial linear correlation analysis between changes in cognitive tests and clinical and laboratory variables was performed (the adjustments are described at the Supplemental Material).

Results

Baseline characteristics of the study participants can be found in Table 1. There were 80 patients, mean age 68.1 ± 4.9 years, without premorbid IQ deficit, BMI between 30 and 49.5 kg/m^2. The estimated energy intake was 1517 ± 515 kcal/d (17.3 kcal/kg weight). The average diet composition was 50.2% carbohydrate, 29.1% lipid, and 20.7% protein. Twenty-one patients (26.3%) were APOE4 carriers. There were no significant differences between the groups at baseline for age, gender, education, comorbidities, genotype, measurements, or laboratory analysis.

Five women did not complete the follow-up: 4 dropped out and one died of pneumonia (Figure 1).

BMI decreased by an average of 1.7 ± 1.8 kg/m^2 (P = .021), without significant change of lean mass, and 35 (43.8%) patients had weight loss greater than 5% of initial body weight. The proportion of physically active patients did not change (initial 62.5%, final 70.7%; P = .282). The SPPB, gait speed, and time to sit/get up improved significantly. There was improvement on most of the cognitive tests (Table 2).

The generalized estimating equation was used for comparisons between groups in the longitudinal analysis. The complete results for body composition, biochemical markers, physical function, and diet can be found in the Supplemental Table 1 and for cognitive tests in the Supplemental Table 2. There was no significant time-group interaction for most of the tests after 12 months, except for

Table 2. Cognitive Evaluation at Baseline and Variation After 12 Months

	Baseline		Change		
	Mean	**CI95**	**Mean**	**CI95**	***P***
Global cognition					
CAMcog (0–107)	85.2	83.7, 86.8	2.7	1.7, 3.7	<.0001
IQCODE (1–5)	3.49	3.4, 3.56	−0.28	−0.38, −0.18	<.0001
Memory					
RAVLT-A7 (0–15)	6.6	6.0, 7.2	1.2	0.7, 1.8	<.0001
RAVLTΣA1A5 (0–75)	38.5	36.8, 40.2	2.6	0.9, 4.3	.002
Executive function/attention/ psychomotor speed					
Digits forward (0–16)	6.7	6.4, 7.1	−0.2	−0.6, 0.2	.357
Digits backward (0–14)	4.2	3.8, 4.5	0.1	−0.2, 0.5	.371
Phonemic fluency F,A,S	29.1	27.2, 30.9	0.9	−0.4, 2.3	.165
Semantic fluency	14.3	13.4, 15.2	1.5	0.5, 2.4	.002
Wisconsin categories	2.9	2.6, 3.3	0.5	0.1, 0.9	.017
TMA (s)	65.1	59.3, 71.5	−4.3	−9.8, 1.1	.119
TMB (s)	185.1	163.4, 209.8	−3.8	−23.4, 15.9	.709

CI95 −95% confidence interval; difference between time (initial vs final) tested by generalized estimation equation. Abbreviations: CAMcog, cognitive session of the Cambridge Examination for Mental Disorders of the Elderly; IQCODE, Informant Questionnaire on Cognitive Decline in Elderly; RAVLT-A7, Rey auditory verbal learning test − delayed recall; RAVLTΣA1A5, Rey auditory verbal learning test − total learning; TMA, trail making test part A; TMB, trail making test part B.

time to walk 4 m (conventional group, −0.2 s [95% confidence interval, CI95, −0.7; 0.3]; intensive group, −0.9 seconds [CI95, −1.4; −0.4]; $P = .012$).

Generalized linear models were used to analyze the relationship between BMI change and cognitive change (Table 3 and Figure 2). Improvements in global cognition, verbal memory, language, and executive function were correlated with a decrease in BMI. For verbal memory and language, there was interaction between BMI change and age, meaning that the effect of weight loss was more beneficial to younger patients. For executive function, age had an independent effect (the older the patient, the worse the performance), and there was interaction between APOE4 status and BMI change: among APOE4 carriers, a decrease in BMI was more beneficial. The change in attention did not correlate with BMI, age, or APOE4 status (data not shown). In Figure 2, the correlation between BMI and cognitive change (standardized scores) was illustrated, and for didactical purposes, the patients were separated in 2 age groups and 2 genotype groups.

A correlation analysis between changes in cognitive test scores and clinical variables was performed (Table 4 and Supplemental Tables 3 and 4). Leptin increase was associated to attention improvement (DF). Reductions in HOMA-IR correlated with improvements in global cognition (CAMcog) and phonemic fluency. Decreased CRP correlated with an increase in delayed memory. The decrease in caloric intake correlated with improvement in verbal memory and executive function (TMB). The decrease in carbohydrate intake was associated with improvement in verbal memory, executive func-

Table 3. Adjusted Model for Change in Cognitive Domains Related to Variation in BMI, Age, APOE4 Genotype (Carrier or Not), and Interaction Between BMI Change and Age (for Language) or Between BMI Change and APOE4 Genotype (for Executive Function)

Domains	**ΔGlobal Cognition**				**ΔVerbal Memory**				**ΔLanguage/Fluency**				**ΔExecutive**			
Parameters	***β***	**SE**	χ^2	***P***	***β***	**SE**	χ^2	***P***	***β***	**SE**	χ^2	***P***	***β***	**SE**	χ^2	***P***
ΔBMI	−0.12	0.05	4.96	.026	−1.81	0.82	4.87	.027	−2.32	0.82	8.04	.005	−0.18	0.08	4.75	.029
Age (y)	0.00	0.02	0.00	.956	0.01	0.03	0.06	.811	0.01	0.02	0.09	.765	−0.04	0.02	4.11	.043
APOE4+	0.13	0.21	0.39	.533	−0.18	0.19	0.87	.352	−0.01	0.19	0.00	.951	−0.48	0.29	2.69	.101
ΔBMI* age					0.02	0.01	4.03	.045	0.03	0.01	8.17	.004				
ΔBMI*E4+													−0.20	0.10	3.88	.049

Model adjusted for age, the presence of APOE4, baseline testing, education (y), gender, and level of physical activity. APOE4+, carrier of APOE4 genotype; global cognition, CAMcog and IQCODE; Δ verbal memory, composite score of RAVLTΣA1A5, RAVLT-A6, and RAVLT-A7 recognition; Δexecutive, composite score of TMA, Wisconsin classification cards and DB; Δlanguage/fluency, composite score corresponding to phonemic and phonetic fluency; ΔBMI*E4+, parameter of interaction between ΔBMI and APOE4 genotype; ΔBMI* age, parameter of interaction between ΔBMI and age in years.

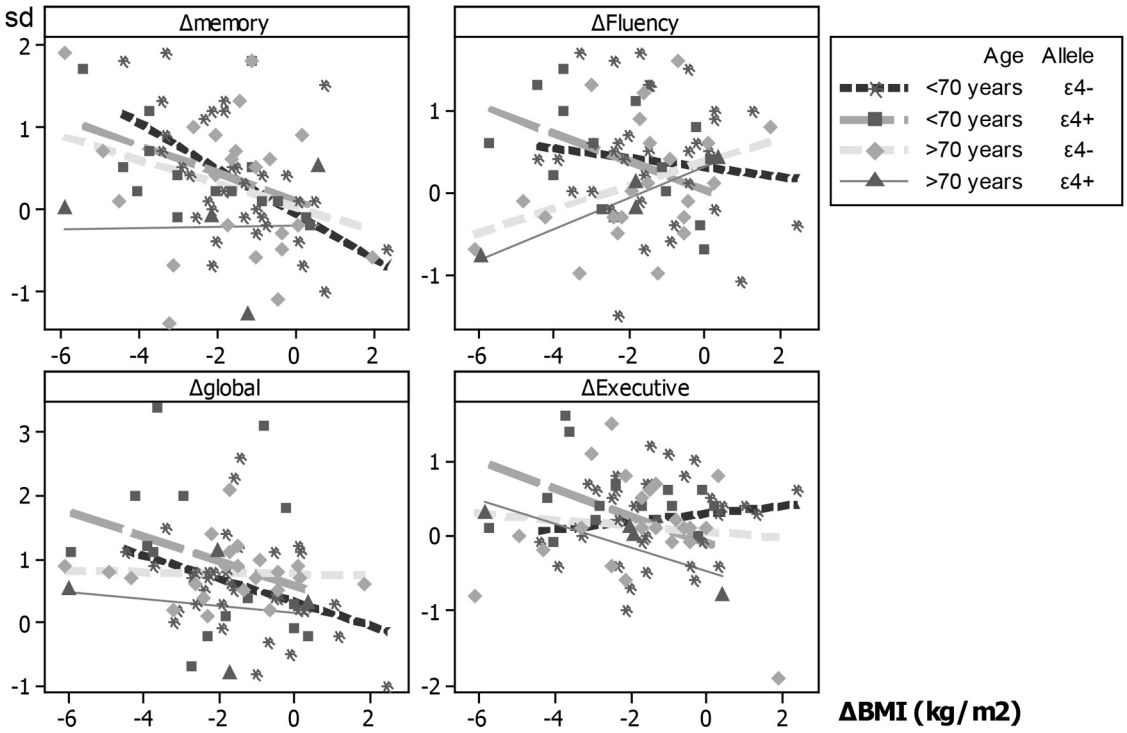

Figure 2. Adjusted scatter plot showing the relation between BMI (kg/m^2) change and cognitive change after 12 months of intervention, by group (aged below or above 70 y or APOE4 carrier or noncarrier Legend). APOE4+, carrier of APOE4 genotype. Global cognition, CAMcog and IQCODE; Δ verbal memory, composite score of RAVLTΣA1A5, RAVLT-A6, and RAVLT-A7 and recognition; Δexecutive, composite score of TMA; WI classification cards and DB; Δ language/fluency, composite score corresponding to phonemic and phonetic fluency. All the tests were adjusted to gender, education, baseline test, and physical activity.

tion (TMB), and subjective complaints (IQCODE). Decreases in fat intake were associated with improvements in verbal memory and TMB.

Discussion

As far as we know, this is the first clinical trial that investigated the effects of intentional weight loss via caloric restriction in patients with MCI. Cognitive tests have proven to be good predictors of the conversion of MCI to dementia and are suitable to evaluate treatment response (29); for this study we evaluated multiple cognitive domains. Delayed recall is considered one of the main tests for predicting the progression of cognitive impairment (30). Worsened performances on the TMB have already been associated with obesity (31), metabolic syndrome and type 2 diabetes (32), and it is considered useful for predicting dementia (33). One previous study has demonstrated its improvement associated with intentional

Table 4. Partial Linear Correlation Between Change in Cognitive Tests and Change in Leptin, HOMA-IR, CRP, and Diet, Adjusted to Age, Gender, Baseline Test, Education, Presence of Apolipoprotein ϵ2 or ϵ4 Allele, and Physical Activity Level

	Δleptin	ΔHOMAIR	ΔCRP	Δkcal	ΔCarbohydrate	ΔLipid
ΔCAMcog	−0.085	−0.393[c]	0.002	−0.154	−0.110	−0.113
ΔΣA1A5 (RAVLTA1A5)	−0.074	−0.212	0.049	−0.346[c]	−0.253[b]	−0.318[c]
ΔA7 (RAVLT-A7)	−0.151	−0.238[a]	−0.299[b]	−0.303[b]	−0.336[c]	−0.312[c]
ΔDigits forward	0.383[c]	−0.143	0.212[a]	−0.167	−0.137	−0.166
ΔPhonemic fluency	0.227[a]	−0.273[b]	−0.038	−0.184	0.027	−0.218[a]
ΔTMB[d]	0.176	0.090	0.047	0.267[b]	0.290[b]	0.241[b]
ΔIQCODE[d]	−0.004	−0.039	−0.056	0.216[a]	0.315[c]	0.139

Leptin and dietary parameters, adjusted also to initial BMI.

[a] $P < .1$.

[b] $P < .05$.

[c] $P < .01$.

[d] Greater the score, worse the performance, for the other tests, greater the score, better the performance.

weight loss in patients without cognitive impairment (34). In our study, for tests of verbal memory, language, executive function, and global cognition, improved scores were correlated with a decrease in BMI. Even considering that it is a secondary analysis, it is interesting that it endorses the main study´s hypothesis. For younger patients, the effect was more pronounced particularly to memory and language. The concept of a better therapeutic window for cognitive protection was already discussed at the context of hormone therapy (35): apparently, starting some hormone combinations nearby menopause is beneficial, but starting many years after menopause increases dementia risk. Other therapies, like monoclonal antibodies against B amyloid (36), also had shown mixed results, and one of the possible influences was considered the treatment window: maybe after the amyloid plaques are wide spread, treatments that target the amyloid are no longer enough to prevent the development of dementia. It is possible that older patients, having a more advanced neuropathology, were less responsive to metabolic changes and then less responsive to our intervention.

Among APOE4 carriers, a decrease in BMI was associated with executive improvements, showing greater benefits in patients with greater dementia risk. The effect of APOE polymorphism on treatment response has been demonstrated in other studies; APOE4 carriers with dementia appear to have a worse response to treatment than noncarriers (37); yet in patients with MCI or mild dementia, this effect varies: cognitive improvement with rosiglitazone was demonstrated only among APOE4 noncarriers (38), and carriers showed better response with bapineuzumabe (39) and donepezil (40). A former study (41) reported that APOE4 carriers who consumed a high-fat diet had a greater risk of developing Alzheimer's Dementia compared with noncarriers, effect probably linked with the function of APOE at the lipoprotein transport. In our study, APOE4 carriers showed a slight better cognitive response to caloric restriction; although this pattern did not repeated in all cognitive areas, this finding deserves attention in future research.

The value of plasma leptin for predicting cognitive change is uncertain, because a previous longitudinal study with a community-based sample found that higher leptin levels were associated with lower dementia risk (42); however, a study of elderly obese individuals found that higher leptin levels were associated with brain atrophy (43). The use of leptin in animal models has been associated with memory improvement (44). In our group, an increase in leptin was associated with greater improvement in attention (DF), and in executive function (phonemic fluency), there was the same trend. Analysis of the correlation between metabolic variables and changes in cognitive performance revealed associations between a decrease in insulin resistance and an improvement in cognition, and a decrease in CRP and improvement in memory. Insulin resistance is associated with increased risk of cognitive decline and the correlation between improvement in memory and a decrease in insulin resistance and CRP (6) has already been described.

In a previous study, we found that weight loss after bariatric surgery for severely obese women (mean age, 40.5; mean BMI, 51.1 kg/m^2) was associated with a reverse in hypermetabolism in the posterior cingulate gyrus and an improvement in executive function (7). A previous study with healthy subjects (mean age, 60.5) (6) also demonstrated an improvement in memory after a caloric restriction of only 11.6%. The decrease in reported caloric intake of the patients in our study was only 8.7% (−132 kcal/d, $P = .061$); even so, improvements in memory and executive function were correlated with decreased consumption of energy, carbohydrates, and fat.

Of note, most tests involving memory and executive function showed improvements. Because the interval between baseline and final evaluation was long (ie, 12 mo), it is unlikely that this improvement is attributable only to a learning effect, especially considering that patients with cognitive deficit suffer less effect learning (45), and cognitive change showed a dose-response relationship with the variation in BMI. Because variations in some tests were related to clinical and metabolic variables, it is possible that the clinical management of comorbidities contributed to this improvement. Even though loss of muscle mass, strength, and functional capacity are potential risks associated with of weight loss in the elderly (46), our results actually demonstrated a functional improvement and stability of lean mass.

Limitations

The weight loss difference between the groups was lower than expected, limiting the analyses by the initial study design. Thus, the initial goal, which depended on comparing cognition variations in groups with different degrees of weight loss, was not fully achieved. It is possible that the long period of intervention and the mobility difficulties of the elderly decreased adherence to group meetings, and the nutritional counseling was a mild intervention. Because the process of recruiting volunteers included information on the risks of obesity, it is also possible that this may have increased motivation to lose weight in both groups. We therefore considered it most useful to make an exploratory analysis considering the decrease of BMI as a continuous variable and to observe its influence on cognitive tests. Also, due to the exploratory nature of the

analyses and the relatively small sample, it was not possible to carry a multiple comparisons correction.

Our group was predominantly women, so the results may not be generalizable. The number of patients might have been too small for a detailed analysis by genotype.

Conclusions

Intentional weight loss through caloric restriction in obese subjects with MCI was safe and correlated with improvements in memory, executive function, global cognition and language, and this association was strongest in younger seniors and in APOE4 carriers. Changes in metabolic markers and diet were also associated with improvement in cognitive tests.

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Address all correspondence and requests for reprints to: Dr Nidia Celeste Horie, PhD, Faculdade de Medicina, Universidade de São Paulo, Rua Dr Enéas de Carvalho Aguiar, 155, 8o. Andar, Bloco 3 (Endocrinologia), São Paulo 05403-000, São Paulo, Brazil. E-mail: nidiachorie@yahoo.com.br.

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