Research Article

Long-term Impact of Weight Loss Intervention on Changes in Cognitive Function: Exploratory Analyses from the Action for Health in Diabetes Randomized Controlled Clinical Trial

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Abstract

Background: Diabetes adversely impacts cognition. Lifestyle change can improve diabetes control and potentially improve cognition. We examined whether weight loss through reduced caloric intake and increased physical activity was associated with slower cognitive aging in older adults with type 2 diabetes mellitus.

Methods: The Look AHEAD randomized controlled clinical trial delivered 10 years of intensive lifestyle intervention (ILI) that yielded long-term weight losses. During 5 years spanning the end of intervention and postintervention follow-up, repeated cognitive assessments were obtained in 1,091 individuals who had been assigned to ILI or a control condition of diabetes support and education (DSE). We compared the means and slopes of scores on cognitive testing over these repeated assessments.

Results: Compared with DSE, assignment to ILI was associated with a -0.082 SD deficit in mean global cognitive function across repeated assessments ($p = .010$). However, overweight (body mass index [BMI] < 30 kg/m²) ILI participants had 0.099 (95% confidence interval [CI]: $-0.006, 0.259$) better mean global cognitive function compared with overweight DSE participants, while obese (BMI ≥ 30 kg/m²) ILI participants had -0.117 ($-0.185, -0.049$) SD worse mean composite cognitive function scores (interaction $p = .014$) compared to obese DSE participants. For both overweight and obese participants, cognitive decline was marginally (-0.014 SD/y overall) steeper for ILI participants ($p = .068$), with 95% CI for differences in slopes excluding 0 for measures of attention and memory.

Conclusions: The behavioral weight loss intervention was associated with small relative deficits in cognitive function among individuals who were obese and marginally greater cognitive decline overall compared to control.

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Keywords: Behavioral intervention, Intentional weight loss, Type 2 diabetes mellitus, Cognitive aging

Type 2 diabetes mellitus and mid-life obesity accelerate aging and the incidence of age-related conditions (1–3). There are many reasons that weight loss, through reduced caloric intake and increased physical activity might alter the rate these conditions accumulate. This was the premise of the Action for Health in Diabetes (Look AHEAD) randomized controlled clinical trial, which featured a 10-year intensive lifestyle intervention (ILI) delivered to adults with type 2 diabetes (4). During its intervention phase, the primary outcome was the incidence of major cardiovascular events, which was not significantly affected by the intervention. Important secondary outcomes included cancers, nephropathy, osteoporosis, sleep apnea, osteoarthritis, and mortality. During postintervention observation, the protocol was broadened to include mobility, falls, and late-life depression outcomes. To date, the intervention has been reported to benefit nephropathy, sleep apnea, mobility, and depression symptoms (5–9).

Among the age-related conditions adversely affected by diabetes is cognitive function. Affected adults have increased risks for cognitive deficits and dementia (10,11). Because obesity further increases risks in diabetes (12), weight loss might be expected to convey cognitive benefits. Look AHEAD has examined this with two cross-sectional analyses, the first near the end of its 10-year intervention in a subset of participants, the second 1–2 years after the intervention's end in the full cohort (13,14). Evidence for cognitive benefit was mixed for the primary cognitive outcome, a composite formed by averaging scores from five individual tests related to verbal learning and memory, speed of processing, working memory, executive function, and global cognitive functioning. Significant interactions between intervention assignment and baseline body mass index (BMI) were reported from cross-sectional testing of 987 participants tested during years 8–9 and cross-sectional testing of the full cohort ($N = 3,751$) during years 10–13. For participants who were initially overweight (BMI 25–29 kg/m²), composite cognitive function scores in the intervention group compared with the control group averaged (95% confidence interval [CI]) 0.276 (–0.033, 0.520) *SD* better at 8–9 years and 0.047 (–0.086, 0.179) *SD* better at 10–13 years (12,13). For participants who were initially obese (BMI ≥ 30 kg/m²), random assignment to the intervention compared the control was associated with –0.086 (–0.194, 0.021) *SD* worse scores at years 8–9 and –0.031 (–0.087, 0.026) *SD* worse scores at years 10–13. While CI for these cross-sectional comparisons included 0, interactions between intervention assignment and baseline BMI were statistically significant: $p = .008$ at 8–9 years and $p = .02$ at 10–13 years. Furthermore, there was a significant interaction between baseline BMI and the prevalence of cognitive impairment (centrally adjudicated mild cognitive impairment or dementia) at years 10–13 ($p = .03$), with odds ratio (OR) = 0.70 (0.40, 1.22) among those initially overweight and OR = 1.46 (0.83, 2.56) among those with BMI ≥ 40 kg/m² (15).

Approximately a quarter of Look AHEAD participants enrolled in one or two ancillary studies that provided repeat cognitive assessments over several years. We hypothesized that, within this subset of over 1,000 individuals, random assignment to the intervention would result in differences in the rates of decline in cognitive function across the up to five years spanning the termination of the

intervention. We also examined whether any differences in intervention groups varied depending on individual's initial weight status.

Methods

The design and methods of Look AHEAD have been published previously (4), as have its CONSORT diagram and primary results (16). It was a single-masked randomized controlled trial that recruited 5,145 individuals (during 2001–2004) who were overweight or obese and had type 2 diabetes. At enrollment, participants were ages 45–76 years and had BMI > 25 kg/m² (>27 kg/m² if on insulin), glycated hemoglobin (HbA1c) $<11\%$, systolic/diastolic blood pressure $<160/100$ mmHg, and triglycerides <600 mg/dL. Participants provided informed consent. Local Institutional Review Boards approved protocols.

Interventions

Participants were randomly assigned with equal probability to ILI or Diabetes Support and Education (DSE). ILI included diet modification and physical activity designed to induce an average weight loss $\geq 7\%$ at year 1 and maintain this over time (17). ILI participants were assigned a daily calorie goal (1,200–1,800 based on initial weight), with $<30\%$ of total calories from fat ($<10\%$ from saturated fat) and a minimum of 15% of total calories from protein. The physical activity goal was ≥ 175 minutes per week through activities similar in intensity to brisk walking.

DSE participants were invited to attend three group sessions each year, which focused on diet, physical activity, and social support (18). They did not receive specific diet, activity, or weight goals or information on behavior change strategies.

Interventions were terminated September, 2012 (16). The mean (range) length of intervention for ILI and DSE participants in this manuscript were both 9.8 (8.4, 11.1) years.

Cognitive Function

Cognitive assessment was performed among those enrolled in the postintervention observation study between August 2013 and December 2014, 10–13 years after their enrollment. A subset had one or two earlier assessments in the Look AHEAD Movement and Memory Study (4 clinics: years 8–11) and the Look AHEAD Brain MRI study (3 clinics: years 10–12) (13,19). These individuals provide longitudinal data for this manuscript. Overall, 38% of these cognitive assessments occurred during the intervention phase, up to 3.0 years prior to its termination. The remainder was collected up to 2.3 years after intervention termination. The time between the first and last (ie, second or third) cognitive assessment ranged from 1 to 5 years (average 2.8 years). Supplementary Table 1 provides additional detail on the temporal pattern of assessments.

Assessments were performed by centrally trained and certified masked staff (13). Verbal learning and memory were evaluated with the Rey Auditory Verbal Learning Test (AVLT). Speed of processing and working memory was evaluated with the Digit Symbol Coding test (DSC). Executive function was evaluated with the Modified

Stroop Color and Word Test (MSCWT) and the Trail Making Test-Part B (TMT-B). Global cognitive functioning was evaluated with the Modified Mini-Mental Status Exam (3MSE).

Baseline Assessment of Risk Factors for Cognitive Decline

Decline

Self-reported characteristics and conditions were assessed using standardized questionnaires. The Beck Depression Inventory provided a measure of depression symptoms. Blood pressure was measured in duplicate using a Dinamap Monitor Pro 100 automated device. Blood specimens were collected after a 12-hour fast and analyzed using standardized laboratory procedures for measuring HbA_{1c}. For participants who provided consent, genotyping for APOE ε4 genotype was performed using two TaqMan assays on a 7900 HT (Applied Biosystems, Waltham, MA) using master mix and probes purchased from Life Sciences (assay C_3084793_20 for rs429358 (R130C) and assay C_904973_10 for rs7412 (R176C)). Annual measures of weight were obtained using digital scales throughout follow-up.

Statistical Analysis

Comparisons of baseline characteristics between participants included in our analyses with those of other Look AHEAD participants, and between intervention groups, were based on chi-squared and *t* tests. Cognitive function test scores were standardized (z-scores) by subtracting the overall cohort-wide mean of the initial assessments and dividing this by their standard deviation (SD). The primary cognitive measure for the Look AHEAD program was a composite: the average of these scores (13). We adopt this as the primary measure in our analyses, with the domain-specific scores being supportive measures. General linear models were fitted using restricted maximum likelihood (20) to longitudinal scores. Inferences and CI were based on the average scores over repeat assessments, and separately on their slope over time, with covariate adjustment for baseline age, sex, education, race/ethnicity, clinic site, and repetition (ie, whether the first, second, or third test administration). Inverse probability weighting was used to assess the sensitivity of findings to missing data (21).

Results

The 1,091 Look AHEAD participants with repeat cognitive assessments differed from the 912 other Look AHEAD participants enrolled at their clinical sites with respect to many baseline characteristics (Supplementary Table 2), including younger age, lower HbA_{1c} levels, lower rates of insulin use, shorter durations of diabetes, less hypertension, less history of cardiovascular disease, better self-reported general health, fewer symptoms of depression, less history of smoking, and greater levels of fitness (all $p \leq .05$). Table 1 describes these 1,091 participants at their Look AHEAD enrollment. The balance from randomization was largely preserved, with slightly greater prevalence of history of cardiovascular disease among ILI participants (15.0% vs 10.8%), $p = .04$.

Mean baseline BMI was similar for the intervention groups (Table 2; $p = .36$). However, within the overweight stratum (but not the obese stratum), mean BMI was slightly greater among the DSE than ILI participants ($p = .03$). There were substantially greater weight losses during the intervention in ILI participants, averaging between 5% and 7% of initial body weight across follow-up in both the overweight and obese strata. At the conclusion of the cognitive

Table 1. Characteristics at the Time of Look AHEAD Enrollment of Participants Who had Repeated Cognitive Assessments: Mean (SD) or *N* (%)

	DSE <i>N</i> = 537	ILI <i>N</i> = 554	<i>p</i> Value
Age, years	58.17 (6.61)	58.47 (6.79)	.47
Sex			
Female	315 (58.7)	326 (58.8)	.95
Male	222 (41.3)	228 (41.2)	
Race/Ethnicity			
African-American	111 (20.7)	113 (20.4)	.65
American Indian	2 (0.4)	5 (0.9)	
Hispanic	23 (4.3)	18 (3.2)	
Non-Hispanic White	384 (71.5)	404 (72.9)	
Other, Multiple	17 (3.2)	14 (2.5)	
Education			
High School	280 (52.1)	281 (50.7)	.05
College Graduate	113 (21.0)	133 (24.0)	
Post College	110 (20.5)	123 (22.2)	
Other	34 (6.3)	17 (3.1)	
BMI, kg/m ²			
25–29	70 (13.0)	99 (17.9)	.08
30–39	350 (65.2)	346 (62.4)	
≥40	117 (21.8)	109 (19.7)	
Smoking, Missing = 2			
Never	284 (53.0)	276 (49.9)	.60
Former	230 (42.9)	253 (45.8)	
Current	22 (4.10)	24 (4.3)	
HbA _{1c} , %	7.20 (1.13)	7.19 (1.11)	.81
Insulin use, Missing = 39	60 (5.70)	79 (7.5)	.14
Diabetes Duration, Missing = 9			
<5 years	252 (47.1)	271 (49.3)	.53
≥5 years	280 (52.6)	279 (50.7)	
Hypertension	441 (81.1)	461 (83.2)	.63
History of CVD	58 (10.8)	83 (15.0)	.04
APOE ε4 alleles, Missing = 118			
0	371 (77.8)	381 (76.8)	.63
1	94 (19.7)	106 (21.4)	
2	12 (2.5)	9 (1.8)	

Note: BMI = Body mass index; CVD = ; DSE = Diabetes support and education; ILI = Intensive lifestyle intervention. CVD: Self-report of prior myocardial infarction, coronary artery bypass, angioplasty/stent procedures, peripheral vascular disease, stroke, stable angina, and class I/II heart failure.

testing, differences in weight losses between intervention groups were no longer statistically significant in the overweight stratum (about a 1% mean difference), but remained significant in the obese stratum (about a 2% mean difference).

Table 3 summarizes standardized mean cognitive function scores. Across repeated exams, mean (95% CI) performance on the composite measure was -0.082 ($-0.144, -0.020$) SD lower among ILI compared with DSE for the composite cognitive function score ($p = .010$) and 95% CI for mean differences for three of the five individual tests excluded 0. Composite cognitive function declined in both intervention groups, with marginally greater mean declines in the ILI than DSE participants: by -0.014 ($-0.029, 0.001$) SD/y ($p = .068$). CI for slopes excluded 0 in two of the five individual tests. Additional covariate adjustment for history of cardiovascular disease, due to its slight imbalance in Table 2, had essentially no impact on any results (data not shown).

Table 4 summarizes analyses for participants grouped by original weight status. The treatment assignment by obesity interaction for mean composite cognitive score was statistically significant

Table 2. Mean (SD) BMI at Enrollment and Weight Loss Averaged Across Follow-up

	Mean (SD)		
	BMI At Baseline	Percent Change in Weight From Baseline Over Follow-up Prior to Cognitive Testing	Percent Change in Weight From Baseline At Conclusion of Cognitive Testing
Overall			
DSE, N = 536	35.92 (5.67)	-2.21 (7.01)	-4.60 (9.87)
ILI, N = 554	35.59 (5.94)	-7.10 (7.39)	-6.42 (9.06)
p value	.36	<.001	.002
Overweight (BMI 25–29 kg/m ²)			
DSE, N = 70	28.70 (1.08)	-0.60 (5.33)	-3.16 (9.23)
ILI, N = 99	28.27 (1.31)	-5.21 (6.12)	-4.20 (8.56)
p value	.03	<.001	.45
Obese (BMI ≥ 30 kg/m ²)			
DSE, N = 466	37.00 (5.27)	-2.45 (7.21)	-4.81 (9.96)
ILI, N = 445	37.19 (5.33)	-7.52 (7.58)	-6.90 (9.11)
p value	.59	<.001	.001

Note: BMI = Body mass index; DSE = Diabetes support and education; ILI = Intensive lifestyle intervention.

Table 3. Mean Levels and Changes OverTime (slopes) in Cognitive Function z-scores, With Covariate Adjustment for Age, Sex, Education, Race/Ethnicity, Clinical Site, Years From Randomization, and Number of Prior Cognitive Assessments

	Cognitive Function z-score Mean (SE) Over Follow-up Mean Difference: ILI-DSE (95% CI)		Change in Cognitive Function z-score Per Year Slope (SE) Mean Difference: ILI-DSE (95% CI)	
	DSE	ILI	DSE	ILI
Composite	0.234 (0.023)	0.152 (0.022)	-0.059 (0.011)	-0.073 (0.011)
	-0.082 (-0.144, -0.020), <i>p</i> = .010		-0.014 (-0.029, 0.001) <i>p</i> = .068	
Individual Tests 3MSE	0.277 (0.030)	0.177 (0.029)	-0.046 (0.020)	-0.044 (0.020)
	-0.100 (-0.182, -0.019)*		0.002 (-0.026, 0.030)	
MSCWT	0.245 (0.032)	0.122 (0.032)	-0.084 (0.022)	-0.072 (0.022)
	-0.124 (-0.213, -0.034)*		0.012 (-0.020, 0.043)	
DSC	0.287 (0.033)	0.202 (0.033)	-0.038 (0.016)	-0.061 (0.016)
	-0.086 (-0.177, 0.006)		-0.023 (-0.045, -0.001)*	
AVLT Delayed	0.176 (0.034)	0.153 (0.034)	-0.073 (0.022)	-0.107 (0.022)
	-0.023 (-0.117, 0.071)		-0.033 (-0.064, -0.003)*	
Trails-B	0.207 (0.028)	0.123 (0.028)	-0.053 (0.021)	-0.072 (0.021)
	-0.084 (-0.162, -0.006)*		-0.019 (-0.049, 0.010)	

Note: AVLT = Auditory Verbal Learning Test; CI = Confidence interval; DSC = Digit Symbol Coding test; DSE = Diabetes support and education; ILI = Intensive lifestyle intervention; MSCWT = Modified Stroop Color and Word Test; 3MSE = Modified Mini-Mental Status Exam.

*95% CI excludes 0.

(*p* = .014). Among overweight participants, the mean composite score across repeated assessments was slightly higher among ILI compared with DSE participants: 0.099 (-0.060, 0.259). Among obese participants, the mean composite score was -0.117 (-0.185, -0.040) *SD*/y lower among ILI compared with DSE participants.

Also in Table 4 are mean changes (slopes) for the composite cognitive function for participants grouped by weight status. Mean slopes were slightly steeper for ILI participants compared with DSE participants for both obesity groups, although 95% CI include 0. These differences were similar for both overweight and obese groups (interaction *p* = .795).

We calculated the mean difference between the weight changes from baseline at the time of the last cognitive assessment and the

average weight changes during the follow-up that spanned the intervention, that is, difference between the two right-most columns of Table 2. These mean (*SE*) differences were -2.38 (0.31) percent for DSE and 0.69 (0.33) percent for ILI, *p* < .001. Overall weight gain (ie, a positive difference) was associated with slightly better composite cognitive function with a small, but statistically significant, fitted slope of 0.005 *SD* per percent weight change (*p* = .030). This relationship was independent of weight status (interaction *p* = .609), intervention assignment (*p* = .836), and the interaction between obesity and intervention assignment (three-way interaction *p* = .237). The interaction between weight status and intervention assignment on composite cognitive function remained statistically significant after covariate adjustment for these interactions (*p* = .021).

Table 4. Mean Levels of Cognitive Function z-scores for Participants Grouped by Intervention Assignment and Baseline Obesity, With Covariate Adjustment for Age, Sex, Education, Race/Ethnicity, Clinical Site, Years From Randomization, and Number of Prior Cognitive Assessments

	Intervention Assignment		
	DSE Mean (SE)	ILI Mean (SE)	Difference (95% CI) Interaction <i>p</i> Value
Composite Mean, SD			
Overweight	0.172 (0.062)	0.271 (0.053)	0.099 (−0.060, 0.259)
Obese	0.244 (0.024)	0.126 (0.025)	−0.117 (−0.185, −0.049)*
Difference (95% CI)	−0.072 (−0.203, 0.060)	0.145 (0.029, 0.260)*	0.216 (0.043, 0.389)*
Overweight—Obese	<i>p</i> = .286	<i>p</i> = .014	<i>p</i> = .014
Composite Slopes, SD/y			
Overweight	−0.057 (0.016)	−0.075 (0.015)	−0.018 (−0.054, 0.018)
Obese	−0.059 (0.011)	−0.072 (0.011)	−0.013 (−0.029, 0.004)
Difference (95% CI)	−0.003 (−0.032, 0.027)	0.003 (−0.024, 0.029)	0.005 (−0.034, 0.045)
Overweight—Obese	<i>p</i> = .858	<i>p</i> = .849	<i>p</i> = .795

Note: CI = Confidence interval; DSE = Diabetes support and education; ILI = Intensive lifestyle intervention.

*95% CI excludes 0.

Among the 1,091 individuals, there were 17 cases of adjudicated probable dementia (9 ILI and 8 DSE) and 60 cases of adjudicated mild cognitive impairment (31 ILI and 29 DSE).

There were many differences in the subset of participants included in our analyses compared to the original randomized participants from the six clinics that contributed one or no cognitive assessments (and therefore were excluded from our analyses due to lost follow-up or death, Supplementary Table 2). To assess the impact of this on results, we repeated the analyses in Tables 3 and 4 using inverse probability weighting. Weights (the estimated probability of inclusion) were generated by applying logistic regression to all baseline factors in Table 1 after imputing any missing predictors. Supplementary Tables 3 and 4 summarize the results. While means were altered by the weighting, inference results were consistent, and at least as strong as in unweighted analyses. In these analyses (Supplementary Table 3), the slope (SE) among ILI participants was −0.076 (0.011) SD/y compared to −0.061 (0.011) SD/y among DSE participants (*p* = .048). The interaction between intervention assignment and weight status on mean composite cognitive function (Supplementary Table 4) reached *p* = .017.

Discussion

Look AHEAD featured a well-designed long-term behavioral intervention that was effective in inducing and sustaining relative weight losses over 10 years. It benefited many important age-related outcomes, including physical function, mobility, health care costs, depression symptoms, microvascular disease, and sleep apnea (5–9,22). However, we saw no overall improvement in cognition in response to ILI, consistent with prior reports (13,14). While assignment to the Look AHEAD ILI appeared to leave a legacy of relatively better cognitive function among overweight participants, it resulted in small relative deficits in cognitive function in obese participants and slightly greater rates of cognitive decline overall. Our findings are exploratory and significance levels across some inferences are marginal, so that any interpretations must be cautious.

There were no cognitive assessments in Look AHEAD before Year 8, thus we can only speculate about earlier differences between intervention groups. As noted in the introduction, 8 or 9 years after interventions, began ILI participants who were initially overweight averaged 0.276 (−0.033, 0.520) SD better performance on

composite cognitive function than overweight DSE participants (13). If the average rate of decline in the DSE group as a measure of usual aging (−0.059 SD/y for composite cognitive function), the estimated differences are comparable to several years of cognitive aging and may have been greater earlier during follow-up in ILI if the slopes in Table 4 extend to early times. However, our finding that the rate of cognitive decline may be increased among ILI participants during later follow-up suggests that any benefits that may have accrued are shrinking at a rate of 0.017 SD/y. For participants who were initially obese, ILI compared with DSE was associated with a relative deficit of −0.086 (−0.194, 0.021) SD for composite cognitive function at years 8–9, which may be expanding at a rate of 0.013 SD/y, if the results in Table 4 hold.

Previous short-term studies of lifestyle interventions including physical activity in adults with diabetes have reported benefits (23,24). A meta-analysis of short-term (<2 years) studies of intentional weight loss interventions found modest cognitive benefits (mainly memory and executive function) for general cohorts of obese adults (25). The Finnish Diabetes Prevention study found that 4 years of a lifestyle intervention targeting weight loss among individuals with impaired glucose tolerance did not produce long-term effects on cognitive performance (26).

In contrast, a number of studies have reported that weight loss in older adults may be a signal of impending cognitive decline (27,28). Often this weight loss is interpreted as a consequence of neurodegeneration, which may alter dietary intake through changes in hormone levels, affect, and smell (28,29). In Look AHEAD, ILI weight loss was designed to be intentional, resulting from decreased caloric intake and increased physical activity. However, the longer-term weight losses may have included both an intentional and an unintentional component, and it is impossible to disentangle any separate contributions.

The ILI was associated with less microvascular disease in the brain (19) and in other vascular beds (5), and less brain atrophy (19). At various times during follow-up, ILI was also associated with better blood pressure control (30,31), better profiles of inflammatory markers (32), less sleep apnea (6), and lower rates of depressive symptoms (9), all of which may be expected to be neuroprotective effects. Across the course of ILI, there was little relative increase in the rate of serious hypoglycemic events and better overall diabetes control (16,33). Within the subgroup included in our analyses, rates of these

events were 0.31/100 person-years in the DSE group compared with 0.51/100 person-years in the ILI group ($p = .19$). Including these events as covariates and, separately, excluding participants with these events did not alter findings. We cannot rule out that ILI results in an increase in subclinical hypoglycemia, which may have resulted in cognitive impairment. However, there is not consistent evidence that hypoglycemia has long-term effects on the brain and some evidence that, at least in type 1 diabetes, the brain adapts to chronic hypoglycemia (34,35). Leptin may promote neurogenesis and attenuate apoptosis in the brain (36,37); ILI may have produced lower levels of leptin.

Another possibility is described in Look AHEAD's earlier cross-sectional papers on cognitive function (13,14). Both report significant interactions for intervention effects on cognitive function depending on participant's baseline history of cardiovascular disease: ILI was associated with marked deficits in cognitive function among participants with such a history. This interaction was independent of BMI and the interaction we report between BMI and intervention assignment. Thus, it is possible that the increased rate of cognitive aging we saw long-term among ILI participants is related to how the impact of weight loss on cognitive function is altered by the history and on-trial accumulation of cardiovascular disease.

DSE participants with obesity had better cognitive function than overweight participants and the obesity status did not affect their rate of cognitive decline. This may reflect some selection process during Look AHEAD recruitment or differential survival and retention, but is also consistent with reports of the "obesity paradox" for dementia risk in which it is increased among individuals with midlife obesity but decreased among individuals with late-life obesity (38).

Having no earlier cognitive assessments limits our ability to describe the time course of effects. Differential lost follow-up may have biased our results, but supporting analyses do not point to a large effect. Analyses were not prespecified. Effect sizes are not large and power is limited by the relatively short average follow-up time. As volunteers to a clinical trial, the Look AHEAD cohort may not represent more general clinical populations. The Look AHEAD ILI may not be duplicated elsewhere and it is not clear whether our findings may generalize to different approaches to behavioral weight loss intervention.

It is possible that the results we report as a legacy of the intervention are associated with differential postintervention changes in behavior between groups. There is some evidence that this occurred, in that mean weight had increased among ILI participants and decreased among DSE participants compared with their average weight at the end of the intervention. However, across the cohort these weight changes had a slight, but significant, positive relationship with composite cognitive function: following termination of the intervention, weight gain, not weight loss, was associated with slightly better cognitive function.

Summary

Ten years of lifestyle intervention to reduce weight was associated with small relative deficits in cognitive function among obese individuals. Intentional weight loss may leave a legacy of slightly greater rates of cognitive decline, however this requires further study.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Clinical Sites

University of Pennsylvania

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Conflict of Interest

None reported.

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