Effect of a long-term intensive lifestyle intervention on prevalence of cognitive impairment

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ABSTRACT

Objective: To assess whether an average of 10 years of lifestyle intervention designed to reduce weight and increase physical activity lowers the prevalence of cognitive impairment among adults at increased risk due to type 2 diabetes and obesity or overweight.

Methods: Central adjudication of mild cognitive impairment and probable dementia was based on standardized cognitive test battery scores administered to 3,802 individuals who had been randomly assigned, with equal probability, to either the lifestyle intervention or the diabetes support and education control. When scores fell below a prespecified threshold, functional information was obtained through proxy interview.

Results: Compared with control, the intensive lifestyle intervention induced and maintained marked differences in weight loss and self-reported physical activity throughout follow-up. At an average (range) of 11.4 (9.5–13.5) years after enrollment, when participants' mean age was 69.6 (54.9–87.2) years, the prevalence of mild cognitive impairment and probable dementia was 6.4% and 1.8%, respectively, in the intervention group, compared with 6.6% and 1.8%, respectively, in the control group ($p = 0.93$). The lack of an intervention effect on the prevalence of cognitive impairment was consistent among individuals grouped by cardiovascular disease history, diabetes duration, sex, and *APOE* ε4 allele status (all $p \geq 0.50$). However, there was evidence ($p = 0.03$) that the intervention effect ranged from benefit to harm across participants ordered from lowest to highest baseline BMI.

Conclusions: Ten years of behavioral weight loss intervention did not result in an overall difference in the prevalence of cognitive impairment among overweight or obese adults with type 2 diabetes.

Clinicaltrials.gov identifier: NCT00017953 (Action for Health in Diabetes).

Level of evidence: This study provides Class II evidence that for overweight adults with type 2 diabetes, a lifestyle intervention designed to reduce weight and increase physical activity does not lower the risk of cognitive impairment. *Neurology*® 2017;88:2026–2035

GLOSSARY

3MSE = Modified Mini-Mental State Examination; **BMI** = body mass index; **DSE** = diabetes support and education; **FAQ** = Functional Assessment Questionnaire; **HbA1c** = glycated hemoglobin; **ILI** = intensive lifestyle intervention; **MCI** = mild cognitive impairment; **OR** = odds ratio.

Midlife obesity increases one's risk for dementia and cognitive decline in later life[1]; however, physical activity may reduce risks.[2] Behavioral interventions targeting weight loss and increased physical activity hold promise as strategies to reduce the risk of cognitive impairment[3,4]; however, evidence that weight loss is an effective strategy to prevent cognitive decline has not been consistent.[5] Weight loss can signal an increased risk for dementia[6] and midlife weight change in either direction may be associated with greater risk for dementia later in life.[7]

Type 2 diabetes mellitus increases the risk of dementia by 60%.[8] Many pathways may lead to this association, including reduced vascular function, increased inflammation, impaired glucose metabolism, and concomitant disorders, such as hypertension and depression. Weight loss

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Supplemental data at Neurology.org

through reduced caloric intake and increased physical activity has potential to provide benefits along each of these.[9–14] Adults with type 2 diabetes present many targets through which behavioral intervention for weight loss may benefit cognition.

The Look AHEAD (Action for Health in Diabetes) study was a randomized, controlled clinical trial that compared 10 years of intensive lifestyle intervention targeting weight loss and increased physical activity to a control condition.[15] Its lifestyle intervention did not improve overall cognitive function over 8 years of follow-up.[16] However, an ancillary study found that the intervention was associated with better measures of brain structure (i.e., less evidence of cerebrovascular disease and brain atrophy).[17] Here we report findings from a standardized assessment of mild cognitive impairment (MCI) and probable dementia after 10–13 years of follow-up.

METHODS Look AHEAD recruited 5,145 overweight or obese volunteers with type 2 diabetes.[15,18] These individuals were 45–76 years of age and had body mass index (BMI) >25 kg/m^2 (>27 kg/m^2 if on insulin), glycated hemoglobin (HbA1c) <11%, systolic/diastolic blood pressure <160/<100 mm Hg, and triglycerides <600 mg/dL.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all volunteers. The study protocol was approved by institutional review boards at all sites. Look AHEAD is registered at ClinicalTrials.gov (NCT00017953).

Interventions. Participants were randomly assigned to intensive lifestyle intervention (ILI) or diabetes support and education (DSE).[19] ILI participants targeted daily calorie goals of 1,200–1,800 according to initial weight and ≥175 min/wk of physical activities such as brisk walking.

The goal was weight loss of 7%. Intervention sessions occurred weekly at months 1–6 and then tapered to 3 per month for the remainder of the first year, 6 months, and monthly thereafter, with additional support with monthly phone or e-mail contacts.

The DSE intervention involved 3 group sessions per year on diet, physical activity, and social support.[20]

Interventions began at enrollment (2001–2004) and ended in 2012.[18] The mean (range) lengths of intervention for ILI and DSE participants included in the analyses for this article were both 9.8 (8.4–11.1) years.

Weight, cardiorespiratory fitness, and baseline risk factors. Data were collected by trained and masked staff.[15] The Paffenbarger Physical Activity Questionnaire was administered in a subset of participants at baseline and years 1, 4, and 8. Fitness was determined with maximal graded exercise (baseline) and submaximal tests (years 1 and 4). Medication use was recorded annually. The Beck Depression Inventory queried depression symptoms. Fasting HbA1c levels were assayed centrally. *APOE* ε4 allele carrier status was determined for participants who provided consent.[21]

Cognitive function. Centrally trained, certified, and masked staff conducted standardized assessments of cognitive function between August 2013 and December 2014 during a postintervention continuation of Look AHEAD follow-up. These took place 10–13 years after enrollment. A subset of individuals had 1 or 2 earlier assessments as participants 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). The cognitive battery (supplemental data at Neurology.org) measured attention, concentration, verbal learning and memory, working memory, other executive function abilities, and processing speed.[16] We used the 100-point Modified Mini-Mental State Examination (3MSE) to assess global cognitive functioning, with higher scores reflecting better performance.[22]

Adjudication of cognitive impairment. A masked panel of experts adjudicated cognitive status to identify cognitive impairment and dementia using all available data. Potential cases included participants whose 3MSE test scores fell below prespecified age- and education-specific cutpoints for their cognitive assessment between August 2013 and December 2014. This simultaneously triggered the telephone administration of the Functional Assessment Questionnaire (FAQ) to a friend or family member identified by the participant to query functional status in instrumental activities of daily living.[23]

Two adjudicators independently reviewed all cognitive test scores, the FAQ, depression scores, and medical and health information to make their primary classification (no impairment, MCI, probable dementia). When they identified MCI, they also made a secondary classification of subtype: amnestic single domain, amnestic multiple domain, nonamnestic single domain, or nonamnestic multiple domain.[24] Adjudicators used a separate classification of "Cannot classify" if they could not make a confident classification due to a variety of reasons (e.g., depression, illness, incomplete data).

When both adjudicators agreed on the primary classification, it was recorded as final. If they disagreed, the case was referred to the full 5-member committee for discussion until consensus was reached. If the 2 adjudicators agreed on MCI but disagreed on subtype, they discussed the case to find consensus. If unable to agree, the case was referred to the full committee for discussion and final classification.

A gold standard for a diagnosis of dementia includes a clinical interview, a standardized neuropsychological assessment of major cognitive domains, assessment of the individual's functional abilities with a knowledgeable proxy, and assessments of other covariables such as depression or major medical illnesses. Look AHEAD employed all these components, except for the clinical interview due to its prohibitive cost. Its protocol exceeded the gold standard by having 2 expert adjudicators independently review clinical and neuropsychological data before classifying each case. Similar diagnostic protocols to ours are currently used in other large multicenter studies. Look AHEAD made no attempt to subtype dementia cases because it lacked the necessary tests to do so (e.g., imaging, amyloid imaging, tau).

Statistical analysis. We used χ^2 and t tests to determine between-group differences with respect to covariates for cognitive impairment. Changes over time in weight and physical activity between groups were plotted. Our primary research question was whether the prevalence of cognitive states (normal, MCI, dementia, and other) varied between intervention groups: we used logistic regression to compare groups with adjustment for

Table 1 Characteristics at the time of enrollment into the Look AHEAD (Action for Health in Diabetes) trial of participants who had cognitive function assessments

	Diabetes support and education (n = 1,884)	Intensive lifestyle intervention (n = 1,918)	*p* Value
Age, y, n (%)			
45–54	483 (25.6)	504 (26.3)	0.51
55–64	1,066 (56.6)	1,100 (57.4)	
65–76	335 (17.8)	314 (16.4)	
Female sex, n (%)	1,165 (61.8)	1,158 (60.4)	0.36
Race/ethnicity, n (%)			
African American	315 (16.7)	309 (16.1)	
American Indian	106 (5.6)	106 (5.5)	
Hispanic	248 (13.2)	263 (13.7)	0.97
Non-Hispanic white	1,157 (61.4)	1,177 (61.4)	
Other/multiple	58 (3.1)	63 (3.3)	
Education, n (%)			
High school or less	1,088 (59.5)	1,059 (56.4)	
College	392 (21.4)	450 (24.0)	0.12
Post college	350 (19.1)	369 (19.6)	
Body mass index, kg/m^2, n (%)			
25–29	274 (14.5)	317 (16.5)	
30–39	1,195 (63.4)	1,179 (61.5)	0.22
≥40	415 (22.0)	422 (22.0)	
HbA1c, %, n (%)			
<7.0	887 (47.1)	918 (47.9)	
7.0–8.9	818 (43.4)	847 (44.2)	0.25
≥9.0	179 (9.5)	153 (8.0)	
Diabetes duration, y, n (%)			
<5	866 (46.3)	904 (47.4)	0.48
≥5	1,004 (53.7)	1,001 (52.6)	
Insulin use, n (%)	275 (15.2)	285 (15.4)	0.88
Hypertension, n (%)	1,540 (81.7)	1,585 (82.6)	0.47
Prior cardiovascular disease, n (%)	206 (10.9)	235 (12.2)	0.20
Depressive symptoms, n (%)			
BDI <11	1,634 (87.2)	1,637 (85.4)	0.13
BDI ≥11	241 (12.8)	279 (14.6)	
Antidepressant use, n (%)	1,301 (70.7)	1,364 (72.0)	0.38
Alcohol intake, drinks/d, n (%)			
None	1,279 (67.9)	1,317 (68.7)	
<1	489 (26.0)	504 (26.3)	0.34
≥1	116 (6.2)	97 (5.1)	
Baseline smoking status, n (%)			
Never	992 (52.7)	984 (51.4)	
Past	817 (43.4)	846 (44.2)	0.52
Present	72 (3.8)	85 (4.4)	
Fitness, METS, mean (SD)	7.32 (2.01)	7.36 (1.96)	0.55

Continued

follow-up time. To adjust for potential learning effects, we also included a covariate (yes/no) to identify participants with prior cognitive assessments. We used tests of interaction to examine the consistency of differences between the intervention groups with respect to important clinical subgroups. Among these, interactions with baseline BMI and age were prespecified aims; other subgroup comparisons are exploratory. To portray the distribution of 3MSE scores by intervention assignment and baseline BMI, we performed percentile regression using SAS Proc QUANTREG (SAS Institute Inc., Cary, NC). In response to a reviewer's suggestion, we report supporting analyses of a composite outcome of death and cognitive impairment.

RESULTS Of the 5,145 participants who enrolled in the Look AHEAD trial, 539 (10.5%) had died and 804 (15.6%) others had refused further follow-up, had been lost to contact prior to the cognitive assessments, or otherwise did not provide cognitive assessments in years 10–13 (figure e-1). Adjudication of cause of death, based on medical records, took place separately from cognitive testing and adjudication of cognitive impairment, and thus did not contribute to the current analyses; among these 539 deaths, 15 (ILI) and 14 (DSE) were classified as having dementia as the cause or a contributing factor ($p = 0.85$).

The 3,802 participants who contributed to this analysis differed from the 1,343 who had either died or were lost according to many baseline characteristics. For example, they were less likely to have hypertension (82% vs 86%, $p = 0.001$) or a history of cardiovascular disease (12% vs 20%, $p < 0.001$), to be from a minority racial/ethnic group (39% vs 32%, $p < 0.001$), and to be male (39% vs 45%, $p < 0.001$). On average, they were 2.3 years younger ($p < 0.001$) and had 0.18 units lower HbA1c ($p < 0.001$) and 0.39 kg/m^2 lower BMI. Importantly, there was no difference in intervention group membership ($p = 0.23$).

For ILI and DSE participants, central adjudication was based on cognitive assessments made at a mean (SD) of 11.4 (0.8) years postrandomization. The mean age (range) was 69.5 (55.2–87.2) and 69.7 (54.9–87.0) years for ILI and DSE participants, respectively ($p = 0.30$). Cognitive assessment rates in the originally enrolled cohorts were similar between the ILI (74.6%) and DSE groups (73.2%; $p = 0.23$).

The balance provided by the original randomization was preserved for baseline risk factors for cognitive impairment in this subset of participants (table 1). Throughout follow-up, ILI participants maintained greater median weight losses and mean self-reported levels of physical activity, although differences tended to attenuate over time (figure 1). Across follow-up, the mean (95% confidence interval) accrual of kilogram per person-year of measured weight loss (i.e., sum of weight losses from baseline

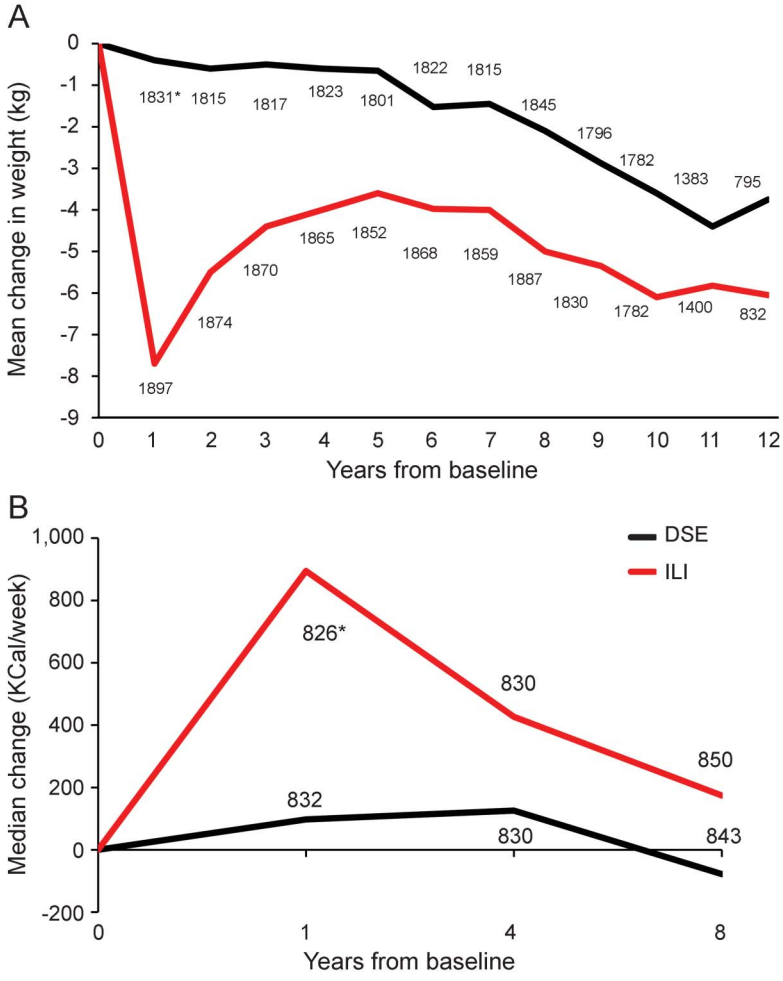
Table 1 Continued

	Diabetes support and education (n = 1,884)	Intensive lifestyle intervention (n = 1,918)	*p* Value
*APOE*4 alleles, n (%) (missing = 671)			
0	1,176 (77.1)	1,231 (76.7)	
1	323 (21.2)	344 (21.4)	0.96
2	27 (1.8)	30 (1.9)	

Abbreviations: BDI = Beck Depression Inventory; HbA1c = glycated hemoglobin; METS = metabolic equivalents.
No participant had a history of stroke at Look AHEAD enrollment.

over examinations) among ILI participants was 38.3 (33.2–43.4) kg greater among ILI compared with DSE participants, i.e., approximately 3.8 kg/y. The mean accrual of kilocalories per week of moderate or vigorous physical activity across the 3 assessments was 1,308 (992–1,624) kcal/wk greater among ILI than

Figure 1 Median changes in weight and mean changes in physical activity from baseline by intervention assignment



(A) Median changes in weight from baseline by intervention assignment. (B) Mean changes from baseline in kilocalories per week expended in moderate or vigorous activities reported according to the Paffenbarger physical activity index by intervention assignment. DSE = diabetes support and education; ILI = intensive lifestyle intervention. *Number.

DSE participants. Our analysis set contained 95 ILI and 90 DSE participants who had undergone bariatric surgery during follow-up.

Table 2 presents the primary findings from the central adjudication of cognitive impairment. Within both intervention groups, 90.3% of the cohort met criteria for cognitively normal classification. The prevalence of MCI and probable dementia was similar between intervention groups, with no overall difference in the prevalence of the cognitive states, i.e., normal, MCI, dementia, and other ($p = 0.93$). Further, the distribution of MCI subtypes was similar between groups.

Table 3 shows that the prevalence of cognitive impairment (either MCI or probable dementia) was greater among older participants ($p < 0.001$), male participants ($p = 0.006$), those with a history of cardiovascular disease ($p < 0.001$), and those carrying an *APOE* ε4 allele ($p = 0.002$). Prevalence did not vary by baseline BMI ($p = 0.94$) or duration of diabetes ($p = 0.22$). There was some evidence that the relationship between intervention assignment with cognitive impairment varied by baseline BMI ($p = 0.03$). Among those with initial BMI <30 kg/m^2 (i.e., those who were overweight but not obese), the odds ratio (OR) for cognitive impairment was 0.70; however the 95% confidence interval (0.40–1.22) did not exclude 1. Among participants with initial BMI >40 kg/m^2, this OR was 1.46 (0.83–2.56). Within this heaviest group, baseline BMI ranged up to 63.5 kg/m^2, with mean 44.6 kg/m^2. The lowest estimated OR associated with assignment to lifestyle intervention was for the youngest participants (OR 0.52 [0.22–1.19]), but the youngest participants contributed relatively few cases overall (n = 25 total).

Among the full Look AHEAD cohort, there were 536 participants who died prior to completion of the cognitive assessments for cognitive impairment and were not assessed: 252 ILI and 287 DSE participants. We examined the prevalence of a composite outcome of cognitive impairment and death, which was available on 4,341 (84.4%) of the original 5,145 randomized participants. This composite was prevalent among 19.4% of the ILI participants and 21.1% of the DSE participants: OR 0.90 (0.77–1.04), $p = 0.16$.

To investigate further the potential interaction between intervention assignment and BMI, we performed analysis of covariance on 3MSE scores (the measure of global cognitive functioning used to trigger adjudication), with adjustment for age, sex, education, and race/ethnicity. There was a significant interaction between intervention assignment and baseline BMI ($p = 0.006$). Figure 2 shows the relationship with 25th, 50th, and 75th

Table 2 Cognitive status by intervention assignment

Cognitive status	Diabetes support and education (n = 1,884), n (%)	Intensive lifestyle intervention (n = 1,918), n (%)	*p* Value
Normal	1,701 (90.3)	1,732 (90.3)	
Mild cognitive impairment			
Amnestic single domain	28 (1.5)	31 (1.6)	
Amnestic multiple domain	50 (2.6)	52 (2.7)	
Nonamnestic single domain	40 (2.1)	35 (1.8)	
Nonamnestic multiple domain	6 (2.1)	4 (0.2)	
Total mild cognitive impairment	124 (6.6)	122 (6.4)	
Probable dementia	34 (1.8)	34 (1.8)	
Other			0.93[a]
Unable to classify	13 (0.7)	16 (0.8)	
Cognitive impairment unable to classify	8 (0.4)	11 (0.6)	
Cognitive and functional impairment unable to classify	4 (0.2)	1 (0.1)	
Functional impairment unable to classify	0 (0.0)	2 (0.1)	
Total other	25 (1.3)	30 (1.6)	

[a] Comparison of distributions of normal, total mild cognitive impairment, probable dementia, and total other between intervention groups.

percentile regression and linear regression curves across the full range of baseline BMIs. Qualitatively, at the lowest BMI levels, participants in the lifestyle intervention had slightly better 25th and 50th percentiles of 3MSE scores. However, for individuals with the highest BMIs, this ordering was reversed, so that participants in the lifestyle intervention tended to have lower scores.

DISCUSSION Our analyses showed that random assignment to an average of 10 years of a lifestyle intervention that produced sustained relative weight losses and increases in physical activity did not alter the subsequent prevalence of cognitive impairment. However, a prespecified subgroup analysis revealed a statistically significant interaction with baseline BMI that suggested potential benefit from lifestyle intervention for the least heavy participants and potential harm in the heaviest participants. Among this large cohort of aging individuals with type 2 diabetes, those who were oldest, had a history of cardiovascular disease, were male, and were *APOE* ε4 carriers had increased odds of cognitive impairment.

Evidence from clinical trials for the beneficial effects of intentional weight loss on cognition in cohorts of adults without cognitive impairment is mixed; however, a meta-analysis supports a modest effect on executive function and memory.[25] Small nonrandomized studies[26,27] report that bariatric surgery improves cognitive function through 2 years. No prior studies had the sufficient size and length of follow-up to establish whether these short-term alterations in cognitive function translate to reduced rates of cognitive impairment in the future.

Outcomes from this study are consistent with those in our earlier report based on cognitive assessments of 978 participants from 4 Look AHEAD sites, 8–9 years after randomization.[16] We found no significant differences between intervention groups on measures of global cognitive function, verbal memory, attention, executive function, or processing speed.

These null results occurred despite the Look AHEAD intervention producing long-term improvements in diabetes control[18] and, in a subset of 319 participants undergoing brain MRI, evidence of less subclinical cerebrovascular disease and atrophy.[17] The intervention also improved measures of depression, sleep apnea, lipids, blood pressure control, and inflammation as measured over shorter time frames.[9,10,14,28,29] Additional details on measures of intervention adherence such as session attendance, diet, and physical activity appear elsewhere.[30] It is possible that dose of physical activity, although sufficient to improve several measures of overall health, was not sufficient to improve cognitive function. The relatively low prevalence of MCI and probable dementia seen in the Look AHEAD cohort likely limited power. It may be that the legacy of the adverse cognitive effects conveyed by diabetes endures for some time, so that any intervention effects may only be expressed after a long latency period. Cognitive deficits appear early in the development in diabetes[31]; it may be that Look AHEAD missed a window of opportunity for prevention. Whether our null findings are limited to individuals with diabetes, or extend more generally to other cohorts, is unknown.

Lower relative rates of cognitive impairment among overweight (BMI of 25–29 kg/m^2) participants assigned to ILI compared with controls is consistent with better performance on cognitive function tests administered earlier in a subset of Look AHEAD participants.[16] In that prior report, tests of interaction to compare the relative intervention effects among overweight and heavier participants at enrollment reached nominal levels of statistical significance for processing speed ($p = 0.03$) and a composite formed by averaging scores across the cognitive battery ($p = 0.05$). The associations for 3MSE we now describe in the full Look AHEAD cohort are consistent with this interaction.

These outcomes suggest that weight loss may benefit cognitive function in overweight (but not obese) individuals with diabetes. However, there

Table 3 Consistency of intervention effects on cognitive impairment (mild cognitive impairment or dementia) across subgroups, with covariate adjustment for time from randomization

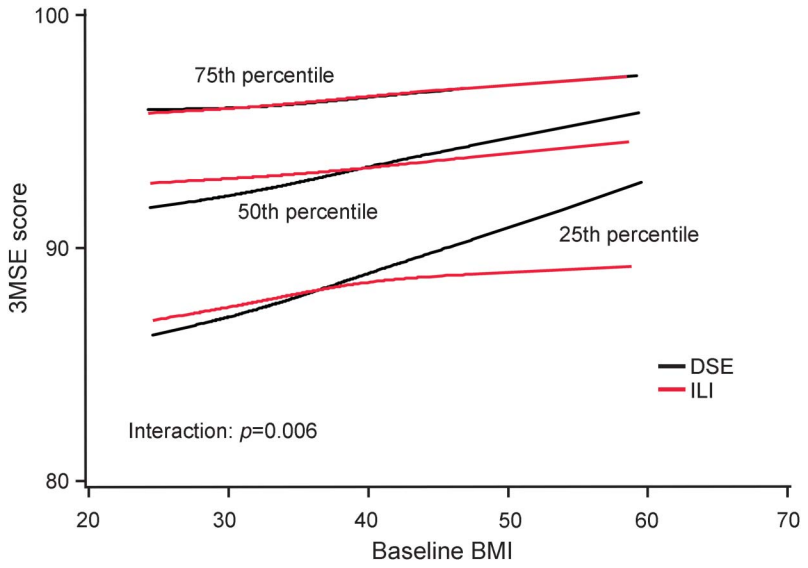
Subgroup based on baseline characteristics	Cases/total n (%)		OR (95% CI) for cognitive impairment	Relative intervention effect: ILI vs DSE OR (95% CI)	Interaction *p* value
	Diabetes support and education	Intensive lifestyle intervention			
Age, y					
45–54	16/482 (3.3)	9/502 (1.8)	Reference	0.52 (0.22–1.19)	
55–64	91/1,059 (8.6)	96/1,089 (8.8)	5.99 (3.88–9.23)	1.08 (0.80–1.47)	
65–76	63/330 (19.1)	63/309 (20.4)	16.45 (10.42–25.96)	1.10 (0.74–1.65)	0.10[a]
			$p < 0.001$		
BMI[b]					
25–29	33/273 (12.1)	27/315 (8.6)	Reference	0.70 (0.40–1.22)	
30–39	110/1,184 (9.3)	106/1,170 (9.1)	1.07 (0.72–1.59)	1.04 (0.77–1.39)	
40+	27/414 (6.5)	35/415 (8.4)	1.03 (0.75–1.42)	1.46 (0.83–2.56)	0.03[c]
			$p = 0.94$		
CVD history[b]					
No	134/1,666 (8.0)	126/1,666 (7.6)	Reference	0.98 (0.75–1.28)	
Yes	36/205 (17.6)	42/234 (18.0)	2.04 (1.51–2.75)	1.11 (0.65–1.87)	0.61
			$p < 0.001$		
Diabetes duration, y[b]					
<5	69/860 (8.0)	67/898 (7.5)	Reference	0.96 (0.67–1.38)	
≥5	99/997 (9.9)	101/989 (10.2)	1.16 (0.91–1.48)	1.13 (0.83–1.55)	0.53
			$p = 0.22$		
Sex[b]					
Female	81/1,160 (7.0)	78/1,151 (6.8)	Reference	1.02 (0.73–1.42)	
Male	89/711 (12.5)	90/749 (12.0)	1.41 (1.11–1.79)	1.02 (0.73–1.42)	0.98
			$p = 0.006$		
***APOE*4 alleles**[b]					
None	99/1,168 (8.5)	101/1,217 (8.3)	Reference	1.02 (0.75–1.38)	
1 or 2	43/348 (12.4)	39/371 (10.5)	1.56 (1.17–2.07)	0.84 (0.52–1.36)	0.50
			$p = 0.002$		

Abbreviations: BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; DSE = diabetes support and education; ILI = intensive lifestyle intervention; OR = odds ratio.
[a] With age as a continuous variable.
[b] Additional covariate adjustment for age.
[c] With BMI as a continuous variable.
ORs less than 1 occur when prevalence is less among ILI participants.

were relatively increased rates of cognitive impairment and lower global cognitive function scores among ILI participants with higher BMIs, who achieved weight losses and increases in physical activity at least as large as other participants during follow-up.[32] The epidemiologic evidence for the relation between obesity and cognitive impairment is mixed, with some studies showing a direct association, others an inverse association, and some a null association.[33] It is not clear whether these conflicting data are due to biases (e.g., survival bias, reverse causality). It is possible that there are neuroprotective factors associated with obesity. One possibility may be leptin, which is correlated with obesity and linked to neurogenesis and attenuated apoptosis in the brain.[33,34] Perhaps any benefits that weight loss may convey through vascular-related risk profiles in less heavy individuals are overridden by larger decreases in obesity-related neuroprotective factors, such as leptin, in heavier individuals.

Older age and history of cardiovascular disease are established independent risk factors for cognitive impairment among individuals with type 2 diabetes.[35] *APOE* ε4 alleles also increase risk.[36] The presence of these risk factor relationships within

Figure 2 Percentiles of Modified Mini-Mental State Examination (3MSE) scores by intervention assignment and baseline body mass index (BMI)



Percentile regression and linear regression were used to produce smoothed curves. The *p* value is from a test of an interaction between baseline BMI and intervention assignment from a linear regression model with adjustment for sex, race/ethnicity, education, and current age. DSE = diabetes support and education; ILI = intensive lifestyle intervention.

the Look AHEAD cohort provides evidence of internal validity and the generalizability of our findings to the larger population of adults with type 2 diabetes.

The increased risk of cognitive impairment conferred by diabetes is slightly lower among men than women.[8] Among individuals with diabetes, male sex may be associated with a slightly lower risk for dementia.[35] In contrast, the odds of cognitive impairment in Look AHEAD participants were 41% higher among men than women. In general populations, the incidence of cognitive impairment is greater among men than women at younger ages, but the rates appear to cross around the age of 80 years.[37] Thus, it is possible that the sex-related differences we see in Look AHEAD reflect the relatively younger age distribution of the cohort.

The lack of association between cognitive function and duration of diabetes is not consistent with reports that diabetes accelerates the rate of cognitive decline,[30] and that longer durations of diabetes are associated with increased prevalence of cognitive impairment.[38] The lack of association with baseline BMI is consistent with reports of the obesity paradox, which suggests that obesity may protect cognitive health later in life. Although this phenomenon is poorly understood, it may result from obesity-related alterations in hormones, angiogenesis, or perhaps reverse causation.[39]

Our study benefits from the initial randomization, high levels of retention, the success of the Look AHEAD intervention in producing long-term changes in weight and physical activity, the rich characterization of participants, and the central adjudication of MCI and probable dementia. Although roughly 10% of the cohort died prior to assessments of cognitive impairment, supporting analyses combining deaths with cognitive impairment yielded similar findings. No measures of cognitive function or impairment were obtained at enrollment into the Look AHEAD trial; however, risk factors were balanced in the initial randomization and in the subgroup examined in this study. The Look AHEAD cohort may not resemble more general cohorts of adults with type 2 diabetes. At enrollment, the study cohort had similar racial/ethnic distribution to the US population of individuals with type 2 diabetes, but its participants tended to be heavier, to be more highly educated, and to have better overall health profiles.[40] ILI outcomes may be impossible to replicate in other settings. If the DSE control reduced rates of cognitive impairment, this outcome may have blunted differences between intervention groups. The time frame of any intervention effect is unknown; it is possible that they may have occurred earlier and waned, or may appear with longer follow-up. The *p* values we present in table 3 are not adjusted for multiple comparisons and should be viewed as hypothesis-generating.

While intentional weight loss produces many health benefits among individuals with diabetes, it appears to have little overall effect on the odds of cognitive impairment among obese adults with type 2 diabetes.

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