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Clinical Research Article

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Long-term Change in Physiological Markers and Cognitive Performance in Type 2 Diabetes: The Look AHEAD Study

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Abstract

Context: The effects of physiological improvements on cognitive function among persons with type 2 diabetes mellitus (T2DM) are not fully understood.
Objective: To determine whether improvements in physiological markers (body weight, blood sugar control, and physical activity) during intensive lifestyle intervention (ILI) are associated with enhancements in cognitive function in older adults with T2DM.
Design: Multisite randomized controlled trial.
Setting: Academic research centers.
Patients or Other Participants: Participants were aged 45–76 years, with T2DM.
Intervention: The Action for Health in Diabetes (Look AHEAD) study, a randomized, controlled clinical trial of ILI.
Main Outcome Measure: Two to 3 cognitive assessments were collected from 1089 participants, the first and last occurring a mean (standard deviation) of 8.6 (1.0) and 11.5 (0.7) years after enrollment.
Results: Greater improvement in blood sugar control was associated with better cognitive scores (fasting glucose and Rey Auditory Verbal Learning Test [AVLT]: $P = 0.0148$; fasting glucose and Digit Symbol Coding (DSC): $P = 0.0360$; HbA1C and DSC: $P = 0.0477$); but

weight loss had mixed associations with cognitive scores (greater body mass index [BMI] reduction and worse AVLT overall: $P = 0.0053$; and greater BMI reduction and better DSC scores among those overweight but not obese at baseline: $P = 0.010$). Associations were strongest among those who were overweight (not obese) at baseline, and among those with a history of cardiovascular disease (CVD) at baseline.

Conclusions: Improvements in glycemic control, but not necessarily weight status, during ILI may be associated with better subsequent cognitive performance. These associations may differ by adiposity and CVD history.

Freeform/Key Words: lifestyle intervention, cognitive function, weight loss, glycemic control, type 2 diabetes, physical activity

Type 2 diabetes mellitus (T2DM) is present in over 25% of US adults aged 65 or older (1, 2). Type 2 diabetes mellitus doubles the risk of cognitive impairment and dementia (including Alzheimer's disease) and greatly increases health care needs and costs (3). A large body of evidence has established that improvement in glycemic control is attainable in T2DM (4–9), as is significant weight loss (10–12). Such improvements in physiological markers are associated with a reduced risk of several long-term adverse outcomes, including cardiovascular events, retinopathy, nephropathy, and neuropathy (13–15). These data have led many to hope that the effective treatment of T2DM could reduce the elevated risk of cognitive impairment associated with T2DM back down to levels typical of individuals free of T2DM. Such risk reduction could have a major impact on the global case burden of dementia, which is high and expected to rise steadily over the coming decades (16, 17).

But there is limited evidence that effectively treating T2DM reduces the risk of cognitive impairment. Evidence from shorter-term T2DM or pre-T2DM interventions (eg, roughly 9 months or less) targeting diet, physical activity (PA), or glycemic control largely supports the notion that cognitive functioning benefits over the course of such interventions (18–25), with few exceptions (26). But evidence from longer-term interventions (eg, greater than 1 year) and longer postintervention follow-up intervals is mixed. A small number of well-designed, effective, long-term interventions have noted cognitive benefits within the active treatment group over the course of the intervention (27), but several have also shown a lack of such benefit (28–31). Indeed, recent definitive systematic reviews have cited the lack of clarity about long-term cognitive effects of T2DM interventions as a major unmet need (32). This lack of clear cognitive benefit has prevented a clear understanding of the ultimate impact of long-term, effective T2DM treatment on dementia prevalence.

The gap in knowledge about the long-term cognitive impact of T2DM treatment arises from an incomplete understanding of the complex biological processes that connect T2DM to cognitive decline (33–38). Adverse health behaviors (eg, poor diet consumption) induce adverse peripheral changes (eg, fat accumulation, chronic hyperglycemia) as well as adverse changes to the brain (eg, cerebrovascular dysfunction). Peripheral and brain changes exacerbate each other in complex ways that to date are not fully understood. Brain changes may culminate in declines in basic cognitive skills and disruption of affective processes, which in turn may promote the adverse health behaviors. Whether adverse brain changes are driven primarily by mechanisms related to excess fat carriage, glycemic control, PA, or common pathways is not well understood, and it is unclear what specific effects modifying each peripheral factor might have in reducing the risk of adverse brain changes. It is further unclear whether adverse brain changes advance to a "point of no return" after which modification is no longer possible. These complex interactions may be why reports of associations between physiological markers and markers of brain health have been inconsistent (39–46).

This study sought to address this knowledge gap using data from the Action For Health In Diabetes (Look AHEAD) study. The Look AHEAD study tested the relative effectiveness of an intensive lifestyle intervention (ILI) to promote and maintain weight loss and increase PA compared to a diabetes support and education (DSE) control condition (47, 48). Prior analyses have reported that ILI–DSE differences in cognitive measures after 8 to 11 years of follow-up, as well as prevalence of mild cognitive impairment (MCI) and dementia, differed significantly by baseline body mass index (BMI) status and clinical history of cardiovascular disease (CVD) (47–50), with hints that ILI might be beneficial or harmful depending on these baseline variables. This study was designed to determine whether greater improvements in glycemic control, weight, and PA over follow-up were associated with greater cognitive benefits. Our hypothesis was that greater improvements in indicators of blood sugar control, greater increases in PA, and

greater weight loss would lead to better subsequent measures of cognitive functioning.

Research Design and Methods

Look AHEAD study design

The design and methods of Look AHEAD have been published previously (51), as have its CONSORT diagram and primary results (12). It was a single-masked randomized, controlled trial that recruited 5145 individuals during 2001 to 2004 with a BMI > 25 kg/m^2 (>27 kg/m^2 if on insulin), glycated hemoglobin A1c (HbA1c) < 11%, systolic/diastolic blood pressure < 160/100 mmHg, and triglycerides < 600 mg/dl. During the screening process, each prospective participant was required to complete a 2-week run-in, during which they were asked to successfully record information each day about diet and PA. In addition, each participant met with a behavioral psychologist or interventionist to confirm that they understood intervention requirements and to exclude any participant with significant competing life stressors or other issues (depression, alcohol abuse) likely to impair adherence. Participants provided written informed consent. Local Institutional Review Boards approved the protocols.

Look AHEAD intervention

Participants were randomly assigned with equal probability to the ILI or DSE groups. The multidomain ILI included diet modification and PA designed to induce weight loss to an average > 7% at 1 year and maintain this over time (52). Intensive lifestyle intervention participants were assigned a daily calorie goal (1200–1800 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 PA goal was > 175 minutes per week through activities similar in intensity to brisk walking.

Diabetes support and education participants were invited (but not required) to attend 3 group sessions each year, which focused on diet, PA, and social support (53). These individuals did not receive specific diet, activity, or weight goals—or information on behavioral change strategies.

Interventions were terminated in September 2012. The mean (range) length of intervention for both ILI and DSE participants reported in this manuscript were both 9.9 (8.4–11.0) years.

Subsamples provide cognitive measurements

The Look AHEAD Movement and Memory study invited 1232 Look AHEAD participants at 4 of its 16 centers to participate in an ancillary study to assess cognitive function at follow-up years 8 or 9. Only those who were currently active (ie, had not been lost to follow-up or refused further involvement) and who provided separate informed consent were eligible. A total of 978 individuals enrolled in that ancillary study and provided the cognitive measurements listed below. In addition, the Look AHEAD Brain MRI study invited 875 Look AHEAD participants at 3 of its 16 centers to assess brain structure and function at either follow-up years 10, 11, or 12. A total of 321 individuals enrolled in that study and provided cognitive measurements. Finally, the Look AHEAD Continuation study was offered to all Look AHEAD participants at all 16 centers who were still active at follow-up years 10 through 13. A total of 3751 participants provided cognitive assessments as part of that study. Of the 5145 individuals who were originally randomized by the Look AHEAD study, 3920 participants provided at least 1 cognitive assessment through the 3 ancillary studies. Of those, 2831 provided 1 cognitive test, 774 provided 2 cognitive assessments, and 315 provided 3 cognitive assessments. The current analysis includes only the 1089 individuals who provided 2 or 3 cognitive assessments. Participants at sites that conducted multiple substudies were allowed to be enrolled in more than 1 substudy, but no participant completed cognitive testing more than once per 12-month period.

Assessment of physiological markers

Certified clinic staff, masked to intervention assignment, collected data (51). Digital scales were used throughout follow-up to obtain annual measures of weight. The Paffenbarger Physical Activity Questionnaire was used to estimate weekly minutes of moderate to vigorous PA at enrollment and 4 and 8 years later in a subset of participants (54). The subset came from selected clinical sites that included this questionnaire as part of their assessments. Data collected on the flights of stairs climbed, distance walked, and other fitness, sport, and recreational activities performed during the week prior to the assessment visit were used to compute kcal/week of leisure-time PA. Blood specimens were collected after a > 12-hour fast and analyzed centrally for HbA1c and fasting glucose.

Assessment of cognitive function

Centrally trained, certified, and masked staff conducted standardized assessments of cognitive function across years 8 to 13 of follow-up (55). All cognitive tests were performed after the participant had provided a fasting blood draw and subsequently had a snack; cognitive testing was performed prior to procedures that required physical exertion. Verbal learning and memory were evaluated with the Rey Auditory Verbal Learning Test (AVLT). Speed of

processing and working memory were evaluated with the Digit Symbol Coding (DSC) test. Executive function was evaluated with the Modified Stroop Color and Word Test and the Trail Making Test-Part B. Global cognitive functioning was evaluated with the Modified Mini-Mental Status Exam. Test scores were standardized, using z-scores, by subtracting the overall cohort-wide mean of the initial assessments from the individual test score and dividing this by the standard deviation. Scores were ordered so that higher scores reflected better performance (49). The primary cognitive measure for the Look AHEAD trial was an average of these z-scores (composite cognitive function). Among individuals analyzed in this study, the first and last cognitive assessments occurred a mean (standard deviation [SD]) of 8.6 (1.0) and 11.5 (0.7) years after enrollment.

Statistical analysis

Analyses were limited to the 1089 participants who had repeat (ie, 2 or 3) cognitive assessments (which were only done at 6 of the 16 Look AHEAD clinical sites) (55). Demographic characteristics of the sample with repeated cognitive tests are reported by mean (SD) and tested for difference using the Student's *t*-test for continuous and frequency (%) and chi-square tests for categorical measures. Mean (SD) and median (interquartile range) are presented for first, second, and third cognitive scores. We examined the association between the change over follow-up in physiological markers (BMI, self-reported leisure-time PA, HbA1c, and fasting plasma glucose) and standardized cognitive scores in mixed effect models adjusted for baseline level of the T2DM marker, randomization arm, age, sex, race/ethnicity, education, clinical site, years from randomization, number of prior cognitive assessments, and the correlation between repeated measurements of the cognitive score. In this analysis, only those measurements of physiological markers collected at clinical evaluations between the baseline evaluation and the clinical evaluation prior to commencement of cognitive testing were utilized. The last analyzed physiological measurements occurred approximately 1.6 to 1.7 years on average prior to the first analyzed cognitive test (see Table 1). Each participant was clinically evaluated approximately once per year over the entire duration of follow-up. Interaction analyses assessed differences in these relationships by randomization arm, obesity category at enrollment (overweight vs obese) and preintervention history of CVD. All associations with a *P*-value less than 0.05 were considered statistically significant. For each physiological marker and cognitive score, values that were greater than 3 times the interquartile range below or above the first or third quartile were defined as outliers. After fitting our primary models, we removed all such outliers from the data set, refitted all statistical models, and evaluated the effect of outlier removal on findings reported by the models. We also refitted all models that used change in BMI, fasting glucose, and HbA1C as the primary predictor of interest, within the subsample of individuals that provided PA data via the Paffenbarger Physical Activity Questionnaire. We evaluated differences in model coefficients between the full sample and the PA subsample.

Results

Characteristics of individuals who received multiple cognitive assessments are shown in Table 1. This sample was fairly well matched across intervention arms (51% ILI, 49% DSE), and there were no statistically significant differences between treatment groups in demographic variables, including age, sex, and race. Within this sample, ILI had slightly higher level of educational attainment ($P = 0.048$), were less likely to be obese at baseline (ILI: 82%, DSE: 87%; $P = 0.028$), and were more likely to have a clinical history of CVD (ILI: 15%, DSE: 11%; $P = 0.032$). Compared to other Look AHEAD participants, those who underwent multiple cognitive assessments (which were only performed in 6 of the 16 Look AHEAD clinical sites among participants with sufficiently long follow-up) were on average 6 months younger, were less likely to be Hispanic and more likely to be African American or Caucasian, were more likely to have completed postcollege education and less likely to have completed other education, and had lower HbA1c and fasting plasma glucose (Table 2).

Raw cognitive test scores at the first cognitive test and cognitive change are shown in Table 3. Mean performance in each test was typical of cognitively normal older adults. Cognitive tests scores were largely stable over time in this cohort. Therefore, we analyzed standardized cognitive test scores adjusting for the order of test across test administrations as our primary outcome of interest.

Baseline BMI, glycemic status, and PA are listed in Table 4, as are summaries of change between randomization and the clinical visit preceding the first cognitive assessment. Mean BMI at baseline was in the range of Class II obesity, mean fasting glucose and HbA1C were above diagnostic thresholds for T2DM, and mean level of PA was below current consensus recommendations for PA attainment. On average, BMI, fasting glucose, and HbA1C decreased over follow-up, while PA increased. However, variability in changes over follow-up were substantial, with both increases and decreases in each of these variables observed. Body mass index change and glycemic change

Table 1. Participant characteristics at the time of randomization, broken out by randomization group

	Intensive Lifestyle Intervention (N = 554)	Diabetes Support and Education (N = 536)	*P*-value
Age, mean ± SD, years	58.5 ± 6.8	58.2 ± 6.6	0.4583
Gender, No. (%)			0.9796
Male	228 (41.2%)	221 (41.2%)	
Female	326 (58.8%)	315 (58.8%)	
Race, No. (%)			0.6505
African American	113 (20.4%)	111 (20.7%)	
American Indian	5 (0.9%)	2 (0.4%)	
Hispanic	18 (3.2%)	23 (4.3%)	
Non-Hispanic White	404 (72.9%)	383 (71.5%)	
Other	14 (2.5%)	17 (3.2%)	
Education, No. (%)			0.0482
High school	281 (50.7%)	280 (52.2%)	
College graduate	133 (24.0%)	112 (20.9%)	
Postcollege	123 (22.2%)	110 (20.5%)	
Other[a]	17 (3.1%)	34 (6.3%)	
BMI, mean ± SD, kg/m^2	35.6 ± 5.9	35.9 ± 5.7	0.3515
Obesity group (kg/m^2), No. (%)			0.0283
BMI < 30kg/m^2	99 (17.9%)	70 (13.1%)	
BMI ≥ 30kg/m^2	455 (82.1%)	466 (86.9%)	
Paffenbarger, mean ± SD, kcal/week	780.5 ± 958.8	853.1 ± 1070	0.3325
HbA1c, mean ± SD, %	7.2 ± 1.1	7.2 ± 1.1	0.8112
Glucose, mean ± SD, mg/dL	150.1 ± 45.8	149.5 ± 42.1	0.8098
Prior CVD, No. (%)			0.0320
No	471 (85.0%)	479 (89.4%)	
Yes	83 (15.0%)	57 (10.6%)	
Time from randomization to first cognitive test	8.6 ± 1.0	8.6 ± 1.0	0.7968
Time between last analyzed physiological measurement and first cognitive test	1.6 ± 1.1	1.7 ± 1.1	0.3363

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; SD, standard deviation.
[a] "Other" educational attainment referred to a highest level of educational attainment that was less than a high school diploma or general education development (GED), or did not fit into any of the following categories: high school diploma or equivalency (GED), some vocational school, some college, associate degree (junior college), Bachelor's degree, some graduate school, Master's degree, doctorate, professional (MD, JD, DDS, etc.).

over follow-up were only modestly correlated (Pearson's rho = 0.18).

Associations between cognitive measures and change in the physiological markers over follow-up are presented in Table 5. Greater BMI reduction over follow-up was associated with a poorer mean score over follow-up on the AVLT. There was a trend toward greater weight loss being associated with a poorer mean Modified Mini-Mental Status Exam scores as well. Greater reduction in fasting glucose over follow-up was associated with a better mean AVLT score and a better mean DSC score. There was a trend toward greater reduction in fasting glucose over follow-up being associated with a better mean composite cognitive score as well. Greater reduction in HbA1C over follow-up was associated with a better mean DSC score as well. All other associations between cognitive measures and changes over follow-up in BMI, fasting glucose, and HbA1C were not statistically significant. In addition, associations between changes in PA over follow-up and cognitive measures were not significant. Intervention group assignment was not a statistically significant modifier of the relationship between cognitive function and physiological markers (data not shown). These results were not materially modified by adding smoking status, systolic blood pressure, or diastolic blood pressure at the time of randomization as additional covariates. The results were also not substantially modified by removing outliers from the data set (data not shown). The results for BMI, HbA1C, and fasting glucose were highly similar in the full sample and the subsample that provided Paffenbarger Physical Activity Questionnaire data (data not shown).

Certain associations between cognitive function and change in physiological markers differed significantly by baseline history of CVD and by baseline BMI category. In particular, greater increase in PA over follow-up was associated with better composite cognitive scores among

Table 2. Comparison of the characteristics at the time of randomization of all randomized Look AHEAD participants and the subset that had more than one cognitive assessment

	Included (N = 1089)	Excluded (N = 4055)	*P*-value
Age, mean ± SD, years	58.3 ± 6.7	58.8 ± 6.9	0.0269
Gender, No. (%)			0.5822
Male	449 (41.2%)	1633 (40.3%)	
Female	641 (58.8%)	2422 (59.7%)	
Race, No. (%)			<0.0001
African American	224 (20.6%)	580 (14.3%)	
American Indian	7 (0.6%)	251 (6.2%)	
Hispanic	41 (3.8%)	639 (15.8%)	
Non-Hispanic White	787 (72.2%)	2465 (60.8%)	
Other	31 (2.8%)	120 (3.0%)	
Education, No. (%)			<0.0001
High school	561 (51.5%)	2033 (50.1%)	
College graduate	245 (22.5%)	873 (21.5%)	
Postcollege	233 (21.4%)	743 (18.3%)	
Other [a]	51 (4.7%)	406 (10.0%)	
BMI, mean ± SD, kg/m^2	35.8 ± 5.8	36.0 ± 5.9	0.2380
Obesity Group (kg/m^2), No. (%)			0.5063
BMI < $30kg/m^2$	169 (15.5%)	596 (14.7%)	
BMI ≥ $30kg/m^2$	921 (84.5%)	3459 (85.3%)	
Paffenbarger, mean ± SD, %	816.7 ± 1016	875.6 ± 1190	0.2144
HbA1c, mean ± SD, %	7.2 ± 1.1	7.3 ± 1.2	0.0066
Glucose, mean ± SD, mgdL	149.8 ± 44.0	153.9 ± 46.0	0.0083
Prior CVD, No. (%)			0.2841
No	950 (87.2%)	3483 (85.9%)	
Yes	140 (12.8%)	572 (14.1%)	

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; SD, standard deviation.
[a] "Other" educational attainment referred to a highest level of educational attainment that was less than a high school diploma or general education development (GED), or did not fit into any of the following categories: high school diploma or equivalency (GED), some vocational school, some college, associate degree (junior college), Bachelor's degree, some graduate school, Master's degree, doctorate, professional (MD, JD, DDS, etc.).

Table 3. Cognitive scores at the times of the first, second, and third cognitive assessment among the six tests in the cognitive battery, along with the timepoint at which those scores were collected

Cognitive Test		First Cognitive Score N = 1089	Second Cognitive Score N = 1089	Third Cognitive Score N = 315
Modified Mini-Mental State Exam	Mean (95% CI)	92.6 (92.3, 93.0)	92.7 (92.4, 93.1)	93.5 (92.9, 94.2)
	Median (IQR)	94 (90, 97)	94 (90, 97)	95 (91, 98)
Rey Auditory Verbal Learning Test	Mean (95% CI)	7.4 (7.3, 7.6)	7.9 (7.6, 8.1)	8.6 (8.2, 8.9)
	Median (IQR)	7 (5, 10)	8 (5, 10)	9 (6, 11)
Digit Symbol Coding	Mean (95% CI)	43.0 (42.3, 43.7)	41.4 (40.8, 42.1)	42.5 (41.3, 43.8)
	Median (IQR)	43 (36, 50)	42 (34, 49)	42 (35, 50)
Trail Making Test – Part B	Mean (95% CI)	99.5 (96.0, 103.0)	103.5 (99.8, 107.3)	100.1 (93.3, 106.8)
	Median (IQR)	83 (63, 114)	84 (63, 116)	82 (63, 110)
Stroop	Mean (95% CI)	31.0 (30.1, 32.0)	32.0 (31.0, 33.0)	31.8 (29.9, 33.7)
	Median (IQR)	28 (21, 37)	28 (21, 39)	28 (21, 38)
Cognitive Composite Score	Mean (95% CI)	0.2 (0.1, 0.2)	0.2 (0.1, 0.2)	0.3 (0.2, 0.4)
	Median (IQR)	0.3 (-0.1, 0.7)	0.3 (-0.2, 0.7)	0.4 (-0.1, 0.8)

The larger positive numbers correspond to better performance on all tests, except for the Trail Making Test – Part B. The median (IQR) number of years between randomization and the first, second, and third cognitive tests was 8.1 (8.0, 8.5), 11.1 (10.3, 12.0), and 12.0 (11.1, 12.1).
Abbreviations: CI, confidence interval; IQR, interquartile range.

Table 4. Levels of physiological markers at the time of randomization, and change in those markers between randomization and the visit prior to the first cognitive assessment, among participants who received 2 or 3 cognitive assessments

Diabetes Marker		Baseline			Change Over Follow-up		
		Overall	DSE	ILI	Overall	DSE	ILI
BMI (kg/m^2)[a]	Mean (95% CI)	35.75 (35.41, 36.10)	35.92 (35.44, 36.40)	35.59 (35.10, 36.09)	-4.69 (-5.14, -4.24)	-2.20 (-2.79, -1.60)	-7.10 (-7.72, -6.49)
	Median (IQR)	34.87 (31.44, 39.10)	35.05 (31.66, 39.14)	34.75 (31.14, 39.06)	-3.85 (-8.59, 0.17)	-1.48 (-5.78, 2.03)	-6.33 (-11.07, -2.27)
Paffenbarger (kcal/week)[b]	Mean (95% CI)	816.68 (743.2, 890.2)	853.10 (743.3, 962.9)	780.47 (682.3, 878.6)	252.51 (190.1, 314.9)	83.09 (-0.47, 166.7)	421.00 (331.4, 510.7)
	Median (IQR)	448 (84, 1177)	504 (112, 1183.5)	420 (56, 1148)	179.2 (-95.7, 591.4)	78.6 (-206.4, 378.1)	296.8 (18.67, 819.2)
Glucose (mg/dL)	Mean (95% CI)	149.81 (147.2, 152.4)	149.49 (145.9, 153.1)	150.13 (146.3, 154.0)	-9.04 (-10.9, -7.14)	-5.44 (-8.06, -2.82)	-12.53 (-15.3, -9.80)
	Median (IQR)	140 (120, 170)	142 (121, 169)	138.5 (120, 172)	-7.4 (-22.6, 7.6)	-4.1 (-17.2, 10.4)	-11.3 (-25.8, 3.8)
HbA1c, %	Mean (95% CI)	7.20 (7.13, 7.26)	7.20 (7.11, 7.30)	7.19 (7.10, 7.28)	-0.15 (-0.21, -0.10)	-0.07 (-0.14, 0.00)	-0.24 (-0.31, -0.17)
	Median (IQR)	7 (6.5, 7.7)	7 (6.5, 7.7)	7 (6.4, 7.7)	-0.15 (-0.6, 0.27)	-0.04 (-0.5, 0.37)	-0.21 (-0.69, 0.19)

Abbreviations: CI, confidence interval; DSE, Diabetes support and education; HbA1c, hemoglobin A1c; ILI, Intensive lifestyle intervention; IQR, interquartile range.
[a]BMI change is presented in this table only as percent change in BMI.
[b]Paffenbarger leisure time physical activity was collected on a subset of individuals.

those who reported a history of CVD at baseline, but among those who did not report a history of CVD, this association was not statistically significant (interaction *P*-value, 0.0170; Fig. 1). Similarly, greater reduction in HbA1c over follow-up was associated with a better AVLT score among participants who reported a history of CVD at baseline, and the association was not statistically significant among those who did not report a history of CVD at baseline (interaction *P*-value, 0.0336; Fig. 1). Among those who were overweight at baseline, greater weight loss and HbA1C reduction over follow-up were associated with better DSC scores, while these associations were not statistically significant among individuals who were obese at baseline (interaction *P*-values, 0.010 and 0.023; Fig. 2). Similarly, among those overweight at baseline, greater increases in PA over follow-up were associated with better cognitive composite scores, but among those obese at baseline this association was not statistically significant (interaction *P*-value, 0.031; Fig. 2). These interaction effects were not substantially modified by outlier removal (data not shown).

Conclusions

In this study, cognitive function was measured 2 to 3 times in a large subgroup of middle-aged persons with T2DM between 8 and 11 years after their randomization to an ILI or DSE program in the Look AHEAD clinical study. There were 3 key findings. First, greater improvements in glycemic control over follow-up were associated with better cognitive performance in the overall sample. Second, associations between weight loss over follow-up and subsequent cognitive function were mixed, with suggestions that greater weight loss may be associated with either cognitive benefit or harm, depending on the cognitive test. Finally, associations between improvements in glycemic control, PA, and weight over follow-up and cognitive test score differed by baseline adiposity and CVD history, such that benefits were especially evident among those with a history of CVD and those with baseline overweight rather than obesity. Overall, the findings suggest that in overweight or obese individuals with T2DM enrolled in an intervention study, long-term improvements in differing physiological markers may have differing consequences for cognitive functioning, and those consequences may differ based on baseline health factors.

The most consistent finding of this study was that greater improvements in glycemic control over the course of 8 to 11 years of follow-up were associated with better scores on cognitive tests. This finding was observed in the overall sample as well as in subsamples defined by a clinical history of CVD or baseline BMI in the overweight (not

Table 5. Associations between improvement in physiological markers between randomization and the visit prior to cognitive testing and mean standardized cognitive test score

Cognitive Score	BMI[a]		Paffenbarger per 1000 kcal/wk Change	
	Decrease over follow-up		Change over follow-up	
	ß (95% CI)	*P*-value	ß (95% CI)	*P*-value
Modified Mini-Mental State Exam	-0.015 (-0.032, 0.002)	0.0853	-0.028 (-0.096, 0.039)	0.4098
Rey Auditory Verbal Learning Test	-0.028 (-0.048, -0.008)	0.0053	0.003 (-0.074, 0.081)	0.9325
Digit Symbol Coding	0.015 (-0.005, 0.034)	0.1358	0.051 (-0.025, 0.127)	0.1909
Trail Making Test – Part B	-0.009 (-0.026, 0.007)	0.2693	-0.041 (-0.105, 0.024)	0.2139
Stroop	0.008 (-0.011, 0.027)	0.4086	0.054 (-0.022, 0.130)	0.1612
Cognitive Composite Score	-0.006 (-0.019, 0.007)	0.3933	0.007 (-0.044, 0.059)	0.7882
Cognitive score	Glucose[a] per 10 mg/dl change		HbA1c	
	Decrease over follow-up		Decrease over follow-up	
	ß (95% CI)	*P*-value	ß (95% CI)	*P*-value
Modified Mini-Mental State Exam	0.005 (-0.013, 0.023)	0.5678	-0.018 (-0.077, 0.040)	0.5381
Rey Auditory Verbal Learning Test	0.026 (0.005, 0.046)	0.0148	0.043 (-0.025, 0.111)	0.2172
Digit Symbol Coding	0.022 (0.001, 0.042)	0.0360	0.067 (0.001, 0.134)	0.0477
Trail Making Test – Part B	0.004 (-0.013, 0.021)	0.6287	-0.012 (-0.068, 0.044)	0.6748
Stroop	0.004 (-0.016, 0.024)	0.6885	0.028 (-0.036, 0.093)	0.3891
Cognitive Composite Score	0.012 (-0.002, 0.026)	0.0869	0.021 (-0.024, 0.066)	0.3600

All variables are coded such that positive beta values reflect an association between an improvement in the physiological marker and greater performance on the cognitive test. Models adjusted for randomization arm, race, sex, clinical site, education group, years from randomization, order of cognitive test (first, second, or third), level of the physiological marker as randomization, and repeated measures.

Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin A1c; wk, week.

[a]BMI and glucose were reverse-coded such that increases infer improvement.

obese) range. This finding adds to a mix of literature in which, on one hand, poorer glycemic control in middle age is associated with an increased risk of cognitive decline in old age (3), and short-term (eg, less than 9 months) enhancement of glycemic control is associated with similarly short-term improvement in cognitive function (18–25), but the association between glycemic control and concurrent cognitive function is weak (32), and the ability of long-term glycemic control improvement to improve long-term cognitive function is unclear (27–31). Recent review articles have articulated 1 possible reason for these mixed results: the high complexity and interconnectedness of biological mechanisms that link T2DM to cognitive decline (33–38). Our data adds to this literature by showing that individuals with T2DM who were enrolled in either an ILI or DSE program and showed greater improvements in glycemic control over 8 to 11 years of follow-up also showed greater cognitive performance at follow-up. We speculate that our large sample size, long follow-up duration, and wide distribution of glycemic change values contributed to our ability to detect this association.

Associations between weight loss and cognitive function were inconsistent in this study. In the overall sample, greater weight loss over follow-up was associated with poorer scores on a test of verbal learning and memory, but among those who were overweight (not obese) at baseline, greater weight loss over that period was associated with better scores on a test of processing speed and working memory. These mixed results add to the highly complex literature on weight change late in the lifespan. On one hand, overweight and obesity in middle age are associated with an increased risk of cognitive decline in old age (56, 57). On the other hand, substantial weight loss among cognitively healthy older adults is associated with increased risk of dementia years or even decades in the future (58, 59), and overweight and obesity among elderly individuals may even protect against cognitive decline (56, 60). Complicating this literature is that it is not always clear whether the weight loss is intentional, with intentional weight loss hypothesized to be beneficial and unintentional weight loss hypothesized to represent adverse processes (61, 62). In addition, most prior studies did not report whether weight loss represented primarily a loss of fat mass (which is hypothesized to be beneficial (63)) or lean mass (which represents aging-related sarcopenia, an adverse health condition (64, 65)). Mechanisms relating late-life weight loss to cognitive decline are complex; in particular it is unclear whether clinically-latent neurodegenerative disease

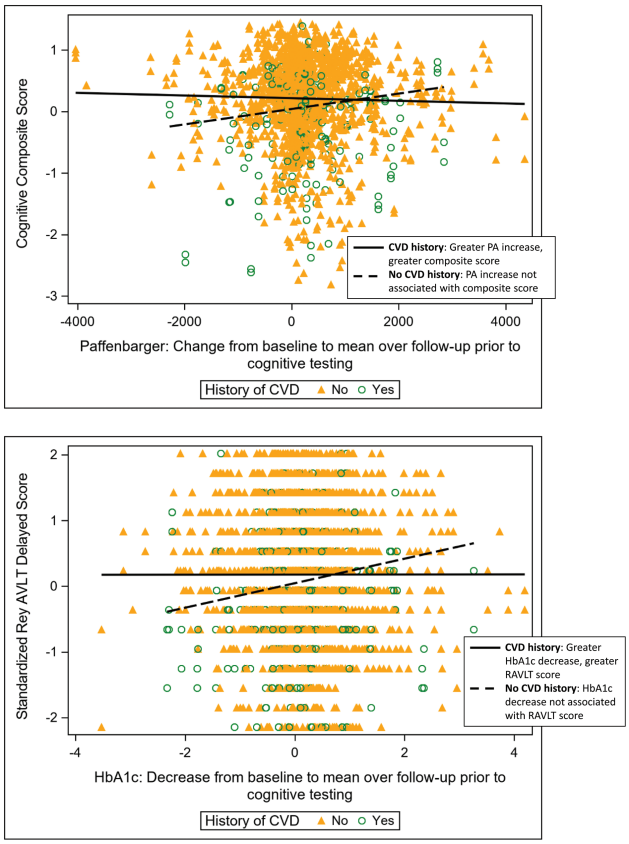

Figure 1. Top: Greater increase in physical activity (as measured by the Paffenbarger questionnaire) was associated with greater cognitive composite scores among those with a cardiovascular disease (CVD) clinical history prior to randomization but not among those without (interaction *P*-value = 0.0170). **Bottom:** Greater reduction in hemoglobin A1c (HbA1c) over follow-up was associated with better Rey Auditory Verbal Learning Test (RAVLT) scores among those with a CVD clinical history but not among those without (interaction *P*-value = 0.0336). Raw values are presented with unadjusted slopes for each group.

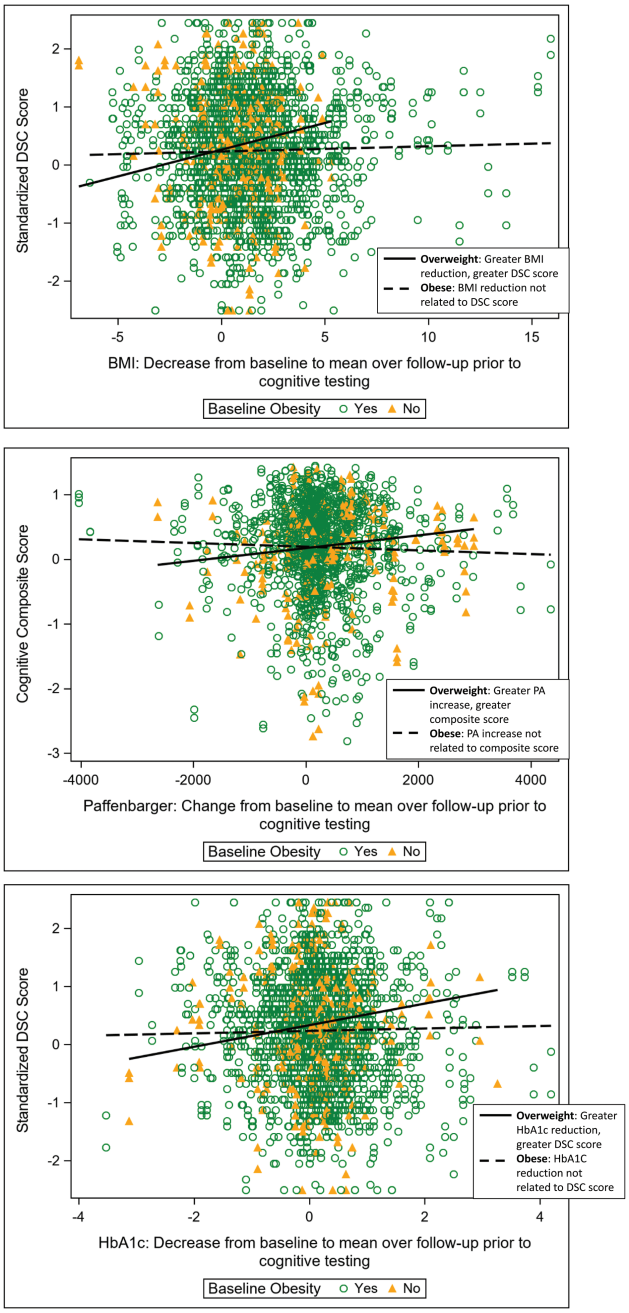

Figure 2. Among trial participants who were overweight at randomization, greater reductions in body mass index (BMI) and hemoglobin A1c (HbA1C) over follow-up were associated with better digit symbol coding (DSC) score at follow-up, and greater increase in physical activity (PA) over follow-up was associated with better cognitive composite score. However, these associations were not significant among participants who were obese at randomization (interaction *P*-values: 0.010, 0.023, 0.031). Raw values are presented with unadjusted slopes for each group.

modifies the brain circuitry governing energy homeostasis, thus giving rise to weight loss at the same time, as it promotes progressive cognitive decline, or whether aging-related changes to the skeletal muscle, adipose tissue, and gut could cause weight loss directly and thereby exacerbate neurodegenerative changes (66–68). Our data, in a weight loss clinical trial, suggests that weight loss in the context of T2DM can be associated with inconsistent cognitive outcomes. As greater numbers of adults enter their senior years with concurrent overweight and T2DM, future research that clarifies the cognitive impact of weight loss is especially urgent.

Our results regarding baseline health status as a modifier of the effect of improvements in physiological markers on cognitive function were mixed. On one hand, improvements in weight, glycemic control, and PA were primarily associated with better cognition among those who were relatively lighter (overweight but not obese) at baseline. This finding is consistent with a "too little, too late" scenario in which the injury processes associated with obesity may have had more deleterious effects on the brains of obese individuals relative to overweight individuals. In this scenario, neural plasticity

and repair mechanisms associated with the improvements in physiological markers may have been exhausted in obese individuals, thus leading to an apparent lack of brain benefit among obese persons. On the other hand, improvements in glycemic control and PA were associated with better cognition among Look AHEAD participants who had a clinical history of CVD, but not among those who did not. One possible explanation for this result is survivor bias (69), that is, the possibility that persons with the combination of T2DM and CVD are also the individuals more likely to have died during follow-up and, therefore, to have been censored from this study. In this scenario, those individuals with concurrent T2DM and CVD who were represented in the study may have been those whose CVD and T2DM cases were relatively mild, thus alleviating the "too little, too late" concern and making cognitive responses to physiological changes possible. Another possible explanation is that treatments for CVD cause their own improvements in cognitive function (70) or potentiate positive cognitive effects of weight loss, PA, and glucose control. In this scenario, it is not the cardiovascular event that makes enhanced cognition possible but rather the exposure to cardiovascular drugs. Overall, our data does not support a simplistic scenario in which the cognitive benefits of improvements in physiological markers are confined to those with better cardiometabolic health at baseline.

Key strengths of this study include its large, diverse, and richly phenotyped cohort, and its long duration of follow-up and repeated standardized assessment of cognitive function. An important limitation was a lack of cognitive assessment at enrollment; however, screening procedures (eg, successful record-keeping, behavioral interview) enhanced the likelihood that enrollees were free of cognitive impairment at baseline. Look AHEAD volunteers came from the subset of community-dwelling individuals for whom an ILI at an academic research center was feasible and safe; thus, the result might not generalize to a more general population of persons with diabetes. While we cannot rule out the potential that differential follow-up may have influenced our findings, covariate adjustment for factors potentially related to this may have limited any such affects. Heterogeneity in the number of cognitive tests per person is an additional limitation to consider when evaluating this work. Finally, cognitive testing occurred after an overnight fast followed by a snack, and the postsnack rise circulating glucose concentration could have varied between individuals. Therefore, we cannot rule out the possibility that interindividual variability in circulating glucose at the time of cognitive testing contributed to cognitive test scores.

In conclusion, in a large sample of older adults with T2DM enrolled in a behavioral clinical trial and greater improvements in glycemic control over 8 to 11 years of follow-up were associated with better cognitive functioning at follow-up, and associations between weight loss and cognitive functioning at follow-up were mixed. The influence of baseline health status on associations between improvements in physiological markers and cognitive function at follow-up were similarly mixed.

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A full listing of the LookAHEAD Research Group at the end of the Continuation phase of the study is provided below. Adam Spira received an honorarium from Springer Nature Switzerland AG for guest editing a special issue of *Current Sleep Medicine Reports*.

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