Brain and White Matter Hyperintensity Volumes After 10 Years of Random Assignment to Lifestyle Intervention

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OBJECTIVE

Type 2 diabetes increases the accumulation of brain white matter hyperintensities and loss of brain tissue. Behavioral interventions to promote weight loss through dietary changes and increased physical activity may delay these adverse consequences. We assessed whether participation in a successful 10-year lifestyle intervention was associated with better profiles of brain structure.

RESEARCH DESIGN AND METHODS

At enrollment in the Action for Health in Diabetes clinical trial, participants had type 2 diabetes, were overweight or obese, and were aged 45–76 years. They were randomly assigned to receive 10 years of lifestyle intervention, which included group and individual counseling, or to a control group receiving diabetes support and education through group sessions on diet, physical activity, and social support. Following this intervention, 319 participants from three sites underwent standardized structural brain magnetic resonance imaging and tests of cognitive function 10–12 years after randomization.

RESULTS

Total brain and hippocampus volumes were similar between intervention groups. The mean (SE) white matter hyperintensity volume was 28% lower among lifestyle intervention participants compared with those receiving diabetes support and education: 1.59 (1.11) vs. 2.21 (1.11) cc (P = 0.02). The mean ventricle volume was 9% lower: 28.93 (1.03) vs. 31.72 (1.03) cc (P = 0.04). Assignment to lifestyle intervention was not associated with consistent differences in cognitive function compared with diabetes support and education.

CONCLUSIONS

Long-term weight loss intervention may reduce the adverse impact of diabetes on brain structure. Determining whether this eventually delays cognitive decline and impairment requires further research.

Adults with type 2 diabetes are at increased risk for brain atrophy and cerebrovascular disease, which may lead to cognitive deficits, cognitive impairment, and dementia (1,2). Type 2 diabetes has a direct effect on brain health through impaired glucose and insulin transfer, brain insulin resistance, hypoglycemia, and hyperglycemia (3,4). It is also associated with many conditions that further increase risk of poor brain health; these conditions include hypertension, dyslipidemia, and

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**A complete list of the Action for Health in Diabetes Brain Magnetic Resonance Imaging (Look AHEAD Brain) Ancillary Study Research Group can be found in the APPENDIX.*

depression (3,4). Poorer brain health and cognition adversely affect metabolic processes, lifestyle, and type 2 diabetes management (5,6), which may spiral into additional declines. Identifying effective prevention strategies for these individuals is critical, since it is estimated that 1 of every 15 cases of dementia is attributable to diabetes (7).

Intentional weight loss may mitigate the adverse effects of diabetes on brain structure. While unproven, there is growing evidence it may provide long-term neuroprotection (8). To assess this, we describe the primary results of brain MRI among overweight and obese adults with type 2 diabetes following 10 years of random assignment to an effective behavioral intervention to promote and maintain weight loss through reduced caloric intake and increased physical activity compared with a control condition of support and education. Our primary hypothesis was that 10 years of lifestyle intervention would be associated with larger brain volumes and less white matter disease. We tested this by comparing standardized MRI measures from volunteers from the two intervention groups. We also examined the consistency of differences between intervention conditions among subgroups based on age, duration of diabetes, and history of cardiovascular disease. To our knowledge, this is the first description of whether differences in brain structure between treatment groups occur over the long term in the context of a randomized controlled clinical trial of lifestyle intervention.

RESEARCH DESIGN AND METHODS

The design and methods of the Action for Health in Diabetes (Look AHEAD) trial have been published previously (9). In brief, Look AHEAD recruited individuals with type 2 diabetes who were 45–76 years old and had a BMI $\geq$25 kg/m^2 ($\geq$27 kg/m^2 if taking insulin), HbA_{1c} $<$11% (97 mmol/mol), systolic blood pressure $<$160 mmHg, diastolic blood pressure $<$100 mmHg, and triglycerides $<$600 mg/dL. These individuals underwent a maximal graded exercise test to ensure that exercise could be safely prescribed, completed 2 weeks of self-monitoring, and attended a diabetes education session before randomization.

The Look AHEAD Brain Magnetic Resonance Imaging study (Look AHEAD Brain) enrolled a subset of Look AHEAD participants at three clinical centers to participate in an ancillary study to assess brain structure and function at their year 10, 11, or 12 anniversary after Look AHEAD enrollment. Only those who were currently active in the trial (i.e., had not been lost to follow-up or did not refuse further Look AHEAD follow-up) at the Philadelphia, Pittsburgh, and Providence clinics; for whom MRI was safe; and who provided separate informed consent were eligible. The Look AHEAD Brain protocol and consent forms were approved by local institutional review boards before use. Participants and their health care providers were notified of significant incidental findings identified on the MRI scans.

Recruitment into the Look AHEAD Brain ancillary study occurred from October 2011 through October 2014. The three clinics had originally enrolled 1,008 participants into the Look AHEAD trial. When Look AHEAD Brain enrollment began, 5 of these participants had withdrawn from Look AHEAD, 89 had died, 20 had refused further follow-up, and 19 were lost to follow-up, leaving a potential of 875 recruits. Of these, 321 (37%) agreed to participate, were eligible for the study, and completed the MRI; 319 images (99%) met quality control standards and form the basis of this article. Compared with the remaining 554 of the 875 potential recruits (i.e., active Look AHEAD participants at these sites who were not included in our analysis), the MRI sample was slightly younger, had lower BMI, had better baseline cardiorespiratory fitness, was more likely to be female, and was less likely to be white (see Supplementary Material A). There was no difference in the participation rates between intervention and control groups: 37.1% and 36.3%, respectively (P = 0.81). The distribution of participants between the two groups did not vary among sites (P = 0.52, χ^2 test).

Interventions

At enrollment into the Look AHEAD trial, participants were randomly assigned by center, with equal probability, to an intensive lifestyle intervention (ILI) or a diabetes support and education (DSE) control condition. The ILI included diet modification and physical activity; it was designed to induce at least an average 7% weight loss at year 1 and to maintain this weight loss in subsequent years (10). 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 $\geq$175 min of physical activity per week through activities with an intensity similar to that of brisk walking.

Participants in ILI were seen weekly for the first 6 months and three times per month for the next 6 months, with a combination of group and individual contacts. During years 2–4, participants were seen individually at least once a month, contacted another time each month by phone or e-mail, and offered a variety of centrally approved group classes. After this, ILI participants were encouraged to continue individual monthly sessions, and annual campaigns were used to promote adherence. A tool kit of strategies was available for ILI participants having difficulty achieving the weight loss goals.

DSE participants were invited to three group sessions each year, which featured standardized protocols with a focus on diet, physical activity, and social support (11). Information on behavioral strategies was not presented, and participants were not weighed.

Participants' personal physicians provided all medical care and made changes in medications, with the exception of temporary changes in diabetes medication during periods of intensive weight loss in ILI to avoid and treat hypoglycemia.

Structural Brain MRI

Before the MRI, participants were screened for contraindications and instructed to remove all metal objects that they were wearing. Structural brain MRIs were obtained according to protocols that have been successful in previous studies (12) and provided standardized measures of validated overall and region-specific brain volumes and white matter hyperintensity volumes. The standardized MRI protocol was conducted on 3.0T scanners (Siemens, Phillips, GE). Structural scans used for this analysis included sagittal 3D fluid-attenuated inversion recovery imaging and T2- and T1-weighted sequences with whole-brain coverage. All scanners ran similar pulse sequences. Additional details are provided in Supplementary Material B.

T1-weighted scans from each subject were preprocessed to correct intensity

inhomogeneities and for brain extraction (13). A multiatlas label fusion method (14) was used to partition the brain into 154 anatomic regions of interest, which were organized within a hierarchical structure to allow volumetric measurements to be derived at various resolutions. This segmentation procedure was used to compute volumes for the whole brain, gray matter, white matter, ventricles, and the hippocampus for each study participant. Intracranial volumes were also computed to control for each participant's head size. White matter hyperintensities were segmented using a supervised learning–based multimodal segmentation method (15). The resulting white matter hyperintensity volumes include what has been called leukoaraiosis, ischemic white matter disease, and/or small vessel ischemia. These hyperintensities are the result of a nonnecrotic, ischemic effect on myelin that is secondary to the effects of aging, hypertension, and other small-vessel pathologic processes of the brain. Further details regarding image analysis are provided in Supplementary Material B.

The MRI Reading Center at the University of Pennsylvania administered quality control based on the Alzheimer's Disease Neuroimaging Initiative and Function Bioinformatics Research Network quality control programs and corresponding phantoms. This featured quarterly scans of both phantoms. Specific tests included signal-to-noise ratio, maximum spatial distortion, signal–to–fluctuation noise ratio, and radius of decorrelation. Each clinical center sent digital images of their phantom quality control data to the reading center for in-house review and was responsible for keeping MRI scanners within the study specifications. A standard image-processing quality control procedure, which consisted of visual inspection of final segmentations for a randomly selected subset of subjects and automated outlier detection on quantitative results, was applied to ensure the quality of the final data.

Weight, Cardiorespiratory Fitness, and Baseline Risk Factors

Certified clinic staff masked to intervention assignment performed all data collection. Annual measures of weight were obtained using digital scales throughout follow-up (9). A maximal graded exercise test was administered at baseline and a submaximal exercise test at years 1 and 4. Changes in cardiorespiratory fitness were computed as the difference between estimated metabolic equivalents (METs) when the participants achieved or exceeded 80% of age-predicted maximal heart rate (or Borg rating of perceived exertion $\geq$16 if the participant was using β-blocking medication) at baseline and at the subsequent assessment. One MET is approximate resting metabolism; 4 METs approximate walking on flat ground at just under 4 miles/hour. Self-reported physical activity was measured in a subset of participants at baseline and during the assessment visits at years 1, 4, and 8 using the Paffenbarger Physical Activity Questionnaire to estimate weekly calorie expenditure from moderate to vigorous physical activity.

Risk factor measurements were also obtained at the Look AHEAD baseline. Self-reported characteristics and conditions were assessed using standardized questionnaires. Participants brought current prescription medications to update medication records. The Beck Depression Inventory provided a measure of depression symptoms. Height was measured in duplicate using a stadiometer. Blood pressure was measured in duplicate using a Dinamap Monitor Pro 100 automated device. Blood specimens were collected after at least a 12-h fast and were analyzed by the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA) using standardized laboratory procedures for measuring HbA_{1c}. For participants who provided consent, TaqMan genotyping for the rs7412 and rs429358 single nucleotide polymorphisms was used to assign apolipoprotein E (apoE) allele carrier status (16).

Cognitive Function

Standardized assessments of cognitive function were performed by centrally trained and certified staff who were masked to intervention assignment. The cognitive test battery consisted of the following assessments (17): Global cognitive functioning was assessed by the Modified Mini-Mental Status Exam. Attention and concentration were measured with the Trail Making Test-Part A (TMT-A). Immediate and delayed verbal memory was assessed with the Rey Auditory Verbal Learning Test. Processing speed/attention was assessed with the Digit Symbol Coding Test. Processing speed/cognitive flexibility was assessed by the Modified Stroop Color and Word Test (Stroop). Executive function (set shifting) was assessed with the Trail Making Test-Part B (TMT-B) and the difference between TMT-B and TMT-A scores. The mean (SD) time between the tests and the MRI was 19 (65) days.

Statistical Analysis

We examined whether there was evidence for differential enrollment between intervention groups with respect to baseline risk factors for atrophy and white matter hyperintensity volumes. Mean changes from baseline in BMI, cardiorespiratory fitness, and self-reported physical activity were compared between groups after adjusting for baseline measurements using analyses of covariance. Our analyses follow the intention-to-treat approach in which participants are grouped by original intervention assignment, regardless of adherence. Total brain volume was the primary outcome; white matter hyperintensity volume and hippocampal volumes were secondary outcomes. We also report total white matter, gray matter, and ventricle volumes as supporting measures. Comparisons were based on analyses of covariance with adjustments for age, clinic site, and intracranial volume, as specified in the study protocol. Log transformations were applied to the white matter hyperintensity and ventricle volumes because of their skewed distribution. In supporting analyses we added baseline covariates that were unbalanced between intervention groups. Three subgroup analyses were prespecified to assess the consistency of any intervention effects across participants grouped by age, duration of diabetes, and history of cardiovascular disease. Differences in cognitive test scores between intervention groups were assessed using analyses of covariance. To limit the effect of extreme cognitive function scores, 1% winsorization was used: scores below the 1st percentile and above the 99th percentile were replaced by the values of these percentiles for the Modified Mini-Mental Status Exam, Stroop, and Trail Making Test difference scores. Log transformations were also applied to TMT-A, TMT-B, and Stroop scores.

RESULTS

Table 1 portrays the characteristics of the MRI cohort by intervention assignment.

Overall balance between intervention groups afforded by the original randomization of the full Look AHEAD cohort was maintained, except for a modest imbalance in the distributions of baseline BMI and apoE4 alleles.

The intervention phase of Look AHEAD ended in September 2012. The average (± SD) duration that Look AHEAD Brain participants were followed during this phase was 9.8 ± 0.7 years for ILI participants and 9.9 ± 0.7 years for DSE participants (P = 0.13). The average time participants spent in the postintervention phase of Look AHEAD until their MRI was 0.6 ± 0.7 years for ILI participants and 0.5 ± 0.8 years for DSE (P = 0.19).

The ILI, compared with the DSE condition, produced substantial differences in BMI, cardiorespiratory fitness, and self-reported physical activity among participants included in our analyses. At year 1, the mean (SD) percentage weight change from baseline for these ILI participants was −12.3% (9.2%), compared with −0.9% (5.1%) for DSE participants. At year 8, mean changes were −7.1% (9.0%) for ILI participants compared with –5.7% (12.2%) for DSE participants. (Supplementary Material C presents annual median percentage weight changes before the MRI for the ILI and DSE participants.) At year 1, the ILI increases in cardiorespiratory fitness averaged 26.3% (27.8%) compared with 6.9% (26.8%) for DSE participants. At year 4, increases were 8.0% (31.4%) for ILI participants compared with 1.2% (32.0%) for DSE participants. Mean increases in self-reported physical activity at year 1 were 853 (1,465) kcal/week for ILI participants compared with 7 (1,007) kcal/week for DSE participants. At year 8, these were 154 (1,939) kcal/week for ILI participants compared with 13 (1,332) kcal/week for DSE participants.

Table 2 presents the main findings for brain volumes. Total brain and hippocampus volumes were similar between intervention groups (P = 0.44 and P = 0.78, respectively). The mean (SE) white matter hyperintensity volume was 28% smaller among ILI participants compared with DSE participants (P = 0.02): 1.59 (1.11) vs. 2.21 (1.11) cc. The mean ventricle volume was 9% smaller among ILI participants compared with DSE participants (P = 0.04): 28.93 (1.03) vs. 31.72 (1.03) cc. Additional covariate adjustment for baseline BMI (Table 2) and apoE4 genotype did not materially alter these results, which remained statistically significant (i.e., both remained $P < 0.05$).

Table 1—Characteristics at the time of enrollment into the Look AHEAD trial of participants who had successful MRI scans in the Look AHEAD Brain study, by intervention assignment

	DSE (n = 155)	ILI (n = 164)	P value
Age, years			0.50
45–54	44 (28.4)	40 (24.4)	
55–64	91 (58.7)	96 (58.5)	
65–76	20 (12.9)	28 (17.1)	
Female sex	114 (73.5)	110 (67.1)	0.21
Race/ethnicity			0.70
African American	37 (23.9)	33 (20.1)	
Non-Hispanic white	110 (71.0)	123 (75.0)	
Other/multiple	8 (5.2)	8 (4.9)	
Education, years			0.61
<13	24 (16.1)	30 (18.8)	
13–16	58 (38.9)	54 (33.8)	
>16	67 (45.0)	76 (47.5)	
BMI, kg/m^2			0.046
25–29	18 (11.6)	32 (19.5)	
30–39	99 (63.9)	106 (64.6)	
≥40	38 (24.5)	26 (15.9)	
HbA_{1c}, % (mmol/mol)			0.58
<7.0 (53)	65 (42.5)	73 (44.8)	
7.0–8.9 (53–74)	75 (49.0)	81 (49.7)	
≥9.0 (75)	13 (8.5)	9 (5.5)	
Diabetes duration, years			0.97
<5	73 (47.7)	76 (47.5)	
≥5	80 (52.3)	84 (52.5)	
Insulin use	20 (13.6)	18 (11.5)	0.57
Hypertension	129 (83.2)	135 (82.3)	0.83
Prior cardiovascular disease	13 (8.4)	13 (7.9)	0.88
Depressive symptoms			0.77
BDI score <11	135 (87.7)	142 (86.6)	
BDI score ≥11	19 (12.3)	22 (13.4)	
Antidepressant use	28 (19.0)	32 (20.4)	0.77
Alcohol intake, drinks/day			0.56
<1	143 (92.3)	154 (93.9)	
≥1	12 (7.7)	10 (6.1)	
Baseline smoking status			0.97
Never	77 (49.7)	83 (50.9)	
Past	72 (46.5)	74 (45.4)	
Current	6 (3.9)	6 (3.7)	
Fitness, METs			0.07
<7.1	84 (54.2)	72 (43.9)	
≥7.1	71 (45.8)	92 (56.1)	
Paffenbarger activity questionnaire score			0.72
<1,060	73 (47.1)	70 (42.7)	
≥1,060	35 (22.6)	41 (25.0)	
Not collected	47 (30.3)	53 (32.3)	
ApoE4 alleles, n			0.008
0	110 (71.0)	100 (61.0)	
1	22 (14.2)	47 (28.7)	
2	2 (1.3)	0 (0.0)	
Not collected	21 (13.6)	17 (10.4)	

Data are n (%) unless otherwise indicated. No participants had a history of stroke at enrollment in the Look AHEAD trial. BDI, Beck Depression Inventory.

The Look AHEAD Brain protocol specified three subgroup comparisons based on age, duration of diabetes, and history of cardiovascular disease. As seen in Table 3, there was little evidence that the intervention effect varied by age (all

Table 2—Brain volumes by intervention assignment

Brain volumes	DSE	ILI	*P* value
Adjusted for intracranial volume, age, and clinical site			
Gray matter	601.39 (2.25)	604.59 (2.16)	0.31
White matter	497.82 (1.40)	498.35 (1.35)	0.78
Total brain	1,104.10 (2.02)	1,106.25 (1.94)	0.44
Hippocampus	7.70 (0.05)	7.67 (0.05)	0.78
Total white matter hyperintensity*	2.21 (1.11)	1.59 (1.11)	0.02
Ventricle*	31.72 (1.03)	28.93 (1.03)	0.04
Additionally adjusted for baseline BMI			
Gray matter	601.29 (2.26)	604.71 (2.17)	0.28
White matter	497.62 (1.40)	498.57 (1.35)	0.63
Total brain	1,103.73 (2.02)	1,106.68 (1.94)	0.29
Hippocampus	7.69 (0.05)	7.68 (0.05)	0.87
Total white matter hyperintensity*	2.20 (1.11)	1.59 (1.11)	0.03
Ventricle*	31.82 (1.03)	28.82 (1.03)	0.03

Data are mean (SE) (cubic centimeters) unless otherwise indicated. The prespecified primary outcome was total brain volume. Volumes of total white matter hyperintensities and the hippocampus were prespecified as secondary outcomes. The additional MRI outcomes are presented as supporting data. *Log-transformed volumes are presented as back-transformed mean (SE).

$P > 0.40$). There was some evidence that intervention effects varied depending on duration of diabetes: participants with ≥5 years' duration when enrolled in Look AHEAD tended to have larger estimates of intervention effects for white matter hyperintensity volumes (interaction $P = 0.03$) and ventricle volume (interaction $P = 0.08$) than those with shorter durations (for which no intervention effects on these outcomes were apparent). Intervention effects on MRI outcomes were only apparent for participants free of cardiovascular disease at enrollment; however, interactions were not statistically significant ($P > 0.10$). We also examined whether there were differences in intervention effects by apoE4 genotype, but found no evidence for this (interaction $P > 0.50$).

Table 4 summarizes results from cognitive function tests. For only one of these did the mean difference between intervention groups reach statistical significance: ILI participants performed better on the TMT-A test of attention and processing speed ($P = 0.0007$). Brain volumes had modest relationships with performance on cognitive function tests in the expected direction. For example, after adjustment for age, intracranial volume, and time between the cognitive testing and the MRI, the digit symbol substitution test scores had partial correlations of 0.12 ($P = 0.03$) with gray matter volume and −0.14 ($P = 0.01$) with ventricle volumes. Thus, better digit symbol coding performance (higher scores) was associated with larger gray matter volumes and smaller ventricle volumes. Stroop scores had a partial correlation of 0.14 ($P = 0.01$) with hippocampus volume and −0.14 ($P = 0.01$) with white matter hyperintensity volumes. TMT-A scores had a partial correlation of −0.13 ($P = 0.01$) with gray matter volumes and 0.16 ($P = 0.003$) with ventricle volumes. Rey delayed learning scores had a partial correlation of −0.24 ($P < 0.001$) with white matter hyperintensity volumes. Note that the *P* values for the correlations listed above are not corrected for multiple comparisons.

CONCLUSIONS

Obesity, sedentary lifestyles, and lower physical activity have been associated with smaller brain volumes and increased cerebrovascular disease in many cohorts (18–20). The Look AHEAD intervention was designed to reduce caloric intake and increase physical activity. We are aware of no clinical trials that have assessed the effects of reduced caloric intake on brain structure among individuals with diabetes, for whom the blood-brain barrier may be compromised and energy metabolism in the brain altered (21). Two small, nonrandomized studies reported that caloric restriction does not affect brain volumes over 6–12 weeks in individuals without diabetes (22,23). A number of clinical trials showed that physical activity interventions produce short-term (i.e., <2 years) benefits for brain volumes (24). While physical activity interventions may prevent the occurrence of cerebrovascular events after stroke and are recommended to reduce risks (25,26), there is only limited evidence from randomized clinical trials that behavioral intervention is successful in preventing subclinical cerebrovascular disease (27).

Based on the existing literature, the Look AHEAD study is the first randomized clinical trial to demonstrate that randomization to a behavioral intervention is associated with better long-term structural markers of brain health. While statistical significance was not reached for the primary MRI outcome of total brain volume ($P = 0.44$), random assignment to the 10-year behavioral intervention was associated with significantly smaller white matter hyperintensity volumes and ventricle volumes. Ventricle volume may be a more sensitive measure of atrophy than total brain volume (28). The Women's Health Initiative, using a similar MRI protocol, found that white matter hyperintensity volumes increased by 0.3 cc/year and ventricle volumes increased 1.5 cc/year in women with diabetes (29). The mean intervention effects we report for these outcomes—0.6 and 2.8 cc, respectively—correspond roughly to 2 years of aging in the Women's Health Initiative cohort (mean age 78 years).

The benefit for cerebrovascular disease is consistent with a report that weight loss through bariatric surgery reduces the risk of composite microvascular complications (including retinopathy, renal disease, and neuropathy) (30). The benefit for ventricular volume is consistent with animal models in which caloric restriction reduces atrophy (31) and with results from trials of physical activity interventions in which activity preserves and increases brain volumes (24).

The Look AHEAD intervention resulted in better long-term diabetes control and some remission of diabetes (32,33). Intensive pharmacological control of diabetes was associated with larger brain volume in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (however, also slightly greater volumes of abnormal white matter) (12). The Look AHEAD intervention

Table 3—Consistency of intervention group differences among prespecified subgroups: age, history of cardiovascular disease, and duration of type 2 diabetes

	Intervention (DSE/ILI) effect or percentage difference		Interaction
	Mean (SE)	95% CI	*P* value
Gray matter volume, cc			
Age at baseline, years			0.78
45–54	−5.93 (6.49)	−18.70 to 6.84	
55–64	−1.48 (4.35)	−10.05 to 7.08	
65–76	1.12 (8.76)	−16.11 to 18.36	
Diabetes duration, years			0.97
<5	0.13 (5.45)	−10.61 to 10.86	
≥5	0.44 (5.20)	−9.79 to 10.66	
History of cardiovascular disease			0.61
No	−0.66 (3.86)	−8.25 to 6.93	
Yes	6.26 (12.96)	−19.24 to 31.75	
White matter volume, cc			
Age at baseline, years			0.68
45–54	0.48 (3.79)	−6.98 to 7.94	
55–64	−2.09 (5.54)	−7.09 to 2.92	
65–76	2.39 (5.12)	−7.68 to 12.46	
Diabetes duration, years			0.16
<5	1.40 (2.83)	−4.17 to 6.97	
≥5	−4.06 (2.70)	−9.36 to 1.25	
History of cardiovascular disease			0.44
No	−0.44 (2.03)	−4.44 to 3.55	
Yes	−5.94 (6.83)	−19.37 to 7.49	
Total brain volume, cc			
Age at baseline, years			0.56
45–54	−4.31 (5.70)	−15.52 to 6.90	
55–64	−2.12 (3.82)	−9.64 to 5.40	
65–76	5.72 (7.69)	−9.40 to 20.84	
Diabetes duration, years			0.73
<5	1.41 (4.80)	−8.03 to 10.86	
≥5	−0.89 (4.57)	−9.89 to 8.11	
History of cardiovascular disease			0.76
No	0.68 (3.39)	−6.00 to 7.36	
Yes	−2.94 (11.41)	−25.39 to 19.50	
White matter hyperintensity volume,* % cc			
Age at baseline, years			0.72
45–54	−35 (18)	−63 to 13	
55–64	−19 (16)	−37 to −13	
65–76	−33 (24)	−70 to 34	
Diabetes duration, years			0.03
<5	7 (23)	−30 to 64	
≥5	−44 (12)	−63 to −16	
History of cardiovascular disease			0.12
No	−29 (11)	−47 to −4	
Yes	66 (86)	−60 to 359	
Ventricle volume,* % cc			
Age at baseline, years			0.42
45–54	−16 (7)	−30 to −1	
55–64	−5 (6)	−15 to 7	
65–76	−5 (11)	−24 to 20	
Diabetes duration, years			0.08
<5	1 (7)	−12 to 16	
≥5	−14 (6)	−25 to −3	
History of cardiovascular disease			0.16
No	−8 (4)	−17 to 1	
Yes	17 (19)	−15 to 62	

Covariate adjustment was made for intracranial volume and clinic site. *Log-transformed volumes are presented as back-transformed mean (SE).

also resulted in lower concentrations of inflammation markers, improvements in blood pressure control, less sleep apnea, and fewer symptoms of depression (33–36), all of which may be hypothesized to result in better brain health. Of particular relevance to the benefits we report for white matter hyperintensities, the Look AHEAD intervention has also been shown to reduce the incidence of a measure of chronic kidney disease throughout 10 years, thus slowing the progression of microvascular disease outside the brain (37).

Type 2 diabetes is associated with an accelerated accrual of age-related diseases, collectively known as the "geriatric syndrome" (3,38). This syndrome, which includes structural changes in the brain, is multifactorial and linked to many interrelated risk factors. Weight reduction and increased physical activity have been recommended as potential strategies to slow the progression of the geriatric syndrome (38); thus, it is possible that the benefits of the Look AHEAD weight loss intervention on brain structure resonate more broadly with a generalized slowing of this syndrome. Additional evidence for this comes from the Look AHEAD finding that its intervention resulted in substantial savings in overall health care costs that were greater among older participants (>$800/participant/year for those ≥65 years old at enrollment) and cut across a range of age-related conditions (39). Similar to the intervention effects we report for brain structure, an overall benefit on health care utilization was not evident for participants with a history of cardiovascular disease.

We did not see consistent evidence for cognitive function benefits from the lifestyle intervention. This agrees with an earlier report on 978 Look AHEAD participants who were assessed with the same battery 8 or 9 years after randomization (17): no differences were seen between intervention groups for any cognitive function test (all $P > 0.30$), and cognitive function scores were not correlated with weight loss. It also agrees with findings from the ACCORD trial that its benefits on brain atrophy did not affect cognitive function (12). It may be that there are different time scales for effects, with the emergence of intervention effects on brain

Table 4—Mean cognitive function test scores by intervention assignment, with adjustment for age and clinical site

Cognitive function test	DSE	ILI	*P* value for difference
Modified Mini-Mental Status Exam	93.61 (0.51)	92.55 (0.51)	0.14
Trail Making Test, seconds*			
Part A	32.83 (1.03)	28.72 (1.03)	0.0007
Part B	83.77 (1.04)	82.61 (1.04)	0.82
Difference (part B – part A)	46.83 (1.06)	50.12 (1.06)	0.43
Rey Auditory Verbal Learning Test, *n* correct			
Immediate	8.40 (0.16)	8.21 (7.90)	0.40
Delayed	8.17 (0.26)	7.80 (0.27)	0.30
Digit Symbol Coding Test, *n* correct	43.96 (0.82)	45.06 (0.83)	0.35
Modified Stroop Color and Word Test, seconds*	26.26 (1.04)	27.07 (1.04)	0.59

Data are mean (SE) unless otherwise indicated. *Higher scores reflect poorer performance.

structure occurring earlier than for cognitive function; changes in cognitive function may lag substantially behind changes in brain structure (40). This issue may be resolved with longer follow-up. It may also be that competing mechanisms are involved, so that any benefits conveyed through improvements in brain structure are counterbalanced by other unknown factors. Thus, while the correlations we report between MRI outcomes and cognitive function scores are modest, these are within the ranges that have been reported for individuals with diabetes (1). We note that in many reports all-cause weight loss is associated with cognitive decline in later life.

Strengths and Limitations

The validity of our findings is strengthened by the randomized controlled clinical trial design of Look AHEAD, its effective long-term interventions, and the standardized protocols of MRI and cognitive assessments we used. Outcomes and analytical approaches were prespecified. Our participants were chosen from among volunteers for a long-term trial of behavioral intervention and may have been healthier than the general population of overweight or obese adults with diabetes. Of those approached to participate in the brain MRI study, 63% did not consent or were ineligible. Thus the findings presented here may not represent other populations such as those without diabetes or who are not overweight. We lack baseline measures of brain structure, which prevents us from examining changes and whether any intervention effects differed by preintervention brain structure. We have not examined which factors may mediate intervention effects. These include changes in weight and physical activity, as well as markers of improved diabetes control, hypertension, blood pressure, sleep apnea, depression, medication use, and inflammation. The varying measurement schedules for and interrelationships between these markers require sophisticated analytical approaches that are outside the scope of this article.

Summary

Long-term intensive weight-loss intervention may delay increases in subclinical cerebrovascular disease and brain atrophy associated with type 2 diabetes. If so, this furthers the importance of implementing behavioral interventions in adults with this disease and may hold great public health significance as the number of older adults with diabetes continues to increase rapidly. However, it is unknown whether the beneficial effects on brain anatomy that we describe may ultimately lead to better cognitive functioning and lower risk for cognitive impairment.

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Author Contributions. M.A.E. led the writing group, performed the statistical analysis, and wrote the manuscript. K.E., P.J.L., and K.D.-M. wrote and critically revised the manuscript. R.H.N. performed the statistical analysis and wrote and revised the manuscript. J.M.J., T.A.W., R.R.W., and B.J.M.-C. enrolled participants, oversaw data collection, and wrote and revised the manuscript. L.D., G.E., M.-K.H., C.D., and R.N.B. oversaw the processing and central reading of the images and wrote and revised the manuscript. M.A.E. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

Clinical Sites. Members of the Look AHEAD Brain Ancillary Study Research Group are affiliated with various clinical sites, as follows: University of Pennsylvania: Thomas A. Wadden (principal investigator), Barbara J. Maschak-Carey (program coordinator), Robert I. Berkowitz (coinvestigator), Bernadette Bailey, Yuliis Bell, Norman Butler, Raymond Carvajal, Christos Davatzikos, Renee Davenport, Lisa Diewald, Mark Elliott, Lucy Faulconbridge, Barry Fields, Krista Huff, Mary Jones-Parker, Brendan Keenan, Sharon Leonard, Qing-Yun Li, Katelyn Reilly, Kelly Sexton, Bethany Staley, and Matthew Voluck; University of Pittsburgh: John M. Jakicic, PhD (principal investigator), Jacqueline Wesche-Thobaben (program coordinator), Kirk Erickson (coinvestigator), Andrea Hergenroeder (coinvestigator), Scott Kurdilla, Regina L. Leckie, Juliet Mancino, Meghan McGuire, Tracey Murray, Anna Peluso, Deborah Viszlay, and Jen C. Watt; Miriam Hospital/Alpert Medical School of Brown University, Providence, RI: Rena

R. Wing (principal investigator), Caitlin Egan (program coordinator), Kathryn Demos (coinvestigator), Kirsten Annis, Ryan Busha, Casie Damore, Causey Dunlap, Lynn Fanella, Lucas First, Michelle Fisher, Stephen Godbout, Anne Goldring, and Ariana LaBossiere; and the MRI Reading Center: Nick Bryan (principal investigator), Lisa Desiderio (program coordinator), Christos Davatzikos, Guray Erus, Meng-Kang Hsieh, and Ilya Nasrallah.

Coordinating Center. The coordinating center for the Look AHEAD Brain Ancillary Study Group was at the Wake Forest School of Medicine, with which the following members of the research group are affiliated: Mark A. Espeland (principal investigator), Judy Bahnson (program coordinator), Ramon Casanova (coinvestigator), Satoru Hayasaka (coinvestigator), Denise Houston (coinvestigator), Paul Laurienti (coinvestigator), Robert Lyday (coinvestigator), Jerry M. Barnes, Tara D. Beckner, Delilah Cook, Michelle Gordon, Debra Hege, Amelia Hodges, Patricia Hogan, Ashley Morgan, Rebecca H. Neiberg, Ginger Pate, and Jennifer Walker.

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