Long Term Effect of Intensive Lifestyle Intervention on Cerebral Blood Flow

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OBJECTIVES: To determine whether long-term behavioral intervention targeting weight loss through increased physical activity and reduced caloric intake would alter cerebral blood flow (CBF) in individuals with type 2 diabetes mellitus.

DESIGN: Postrandomization assessment of CBF.

SETTING: Action for Health in Diabetes multicenter randomized controlled clinical trial.

PARTICIPANTS: Individuals with type 2 diabetes mellitus who were overweight or obese and aged 45 to 76 (N = 310).

INTERVENTIONS: A multidomain intensive lifestyle intervention (ILI) to induce weight loss and increase physical activity for 8 to 11 years or diabetes support and education (DSE), a control condition.

MEASUREMENTS: Participants underwent cognitive assessment and standardized brain magnetic resonance imaging (MRI) (3.0 Tesla) to assess CBF an average of 10.4 years after randomization.

RESULTS: Weight changes from baseline to time of MRI averaged −6.2% for ILI and −2.8% for DSE ($P < .001$), and increases in self-reported moderate or intense physical activity averaged 444.3 kcal/wk for ILI and 114.8 kcal/wk for DSE ($P = .03$). Overall mean CBF was 6% greater for ILI than DSE ($P = .04$), with the largest mean differences between ILI and DSE in the limbic region (3.39 mL/100 g per minute, 95% confidence interval (CI) = 0.07–6.70 mL/100 g per minute) and occipital lobes (3.52 mL/100 g per minute, 95% CI = 0.20–6.84 mL/100 g per minute). In ILI, greater CBF was associated with greater decreases in weight and greater increases in physical activity. The relationship between CBF and scores on a composite measure of cognitive function varied between intervention groups ($P = .02$).

CONCLUSIONS: Long-term weight loss intervention in overweight and obese adults with type 2 diabetes mellitus is associated with greater CBF. **J Am Geriatr Soc 66:120–126, 2018.**

Key words: type 2 diabetes mellitus; intensive lifestyle intervention; obesity; cerebral blood flow

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Type 2 diabetes mellitus may impair cerebral blood flow (CBF) through mechanisms related to vessel stiffness, poor vascular function, and lumen narrowing.[1] Obesity is also associated with low CBF.[2,3] Impaired CBF is linked to poor cognitive function and cognitive decline in individuals with insulin resistance and diabetes mellitus.[1,4] It is also a marker for microvascular disease in the brain and other vascular beds.[5,6]

Because of its relationship with obesity and evidence that it may be greater with greater levels of physical activity,[7] it is reasonable to hypothesize that a behavioral intervention targeting weight loss by increasing physical activity and reducing caloric intake may enhance CBF. The Action for Health in Diabetes (Look AHEAD) was a multicenter randomized controlled clinical trial that featured 10 years of such a multidomain intervention, which successfully induced long-term behavioral changes.[8,9] The

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Look AHEAD Brain MRI Study leveraged this resource and included the goal of assessing whether random assignment to long-term behavioral intervention had a legacy of greater CBF in older adults with type 2 diabetes mellitus.

Look AHEAD has previously reported that its intensive lifestyle intervention (ILI) improved markers of cerebrovascular disease and brain atrophy.[10] Findings have been mixed for cognitive function, with evidence that the intervention benefited cognitive function for participants whose BMI was initially 25.0 to 29.9 kg/m^2 but lowered cognitive function in heavier participants.[11,12] We examined CBF data to gain a deeper understanding of the effects of the ILI on brain health.

METHODS

The Look AHEAD design, methods, and CONSORT diagram have been published previously.[8,13] It was a single-blind randomized controlled trial that recruited 5,145 individuals from 2001 to 2004 who were overweight or obese and had type 2 diabetes mellitus. At enrollment, participants were aged 45 to 76 and had a body mass index (BMI) greater than 25.0 kg/m^2 (>27 kg/m^2 if taking insulin), glycated hemoglobin (HbA1c) of less than 11%, systolic blood pressure of less than 160 mmHg, diastolic blood pressure of less than 100 mmHg, and triglycerides of less than 600 mg/dL.

Interventions

Participants were randomly assigned with equal probability to a multidomain ILI or a diabetes support and education (DSE) control condition. Interventions were terminated in September 2012.[13]

The ILI included diet modification and physical activity designed to induce and maintain an average weight loss of 7% or greater.[14] ILI participants were assigned a daily calorie goal (1,200–1,800 based on initial weight), with fewer than 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 more than 175 minutes of physical activity per week in activities similar in intensity to brisk walking. Participants were seen weekly for the first 6 months and 3 times per month for the next 6 months, with a combination of group and individual contacts. During Years 2 to 4, they were seen individually at least once a month, contacted another time each month by telephone 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 run to promote maintenance of weight loss.

Participants in DSE were invited to attend 3 group sessions each year that featured standardized protocols with focus on diet, physical activity, and social support. They did not receive specific diet, activity, or weight goals.

Brain Magnetic Resonance Imaging

The Look AHEAD Brain MRI study enrolled Look AHEAD participants at 3 clinics to assess brain structure and function at their 10-, 11-, or 12-year anniversary of Look AHEAD enrollment. Only those for whom magnetic resonance imaging (MRI) was safe and who provided separate informed consent were eligible. Local institutional review boards approved the protocol and consent forms.

The 3 clinics had originally enrolled 1,008 participants in Look AHEAD. When the MRI study began, 5 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 underwent MRI; 310 (97%) images met CBF quality control standards.

Before MRI, participants were screened for contraindications and instructed to remove all metal objects. Measures of brain structure (overall and region-specific total and white matter hyperintensity volumes) were obtained according to standard protocols following training and quality control measures that the MRI Reading Center at the University of Pennsylvania administered.[10] CBF was assessed using multiphase pseudo continuous arterial spin labeling (pCASL) with background suppression for labeling the endogenous blood water.[15,16] Multiphase pCASL is a 50% improvement over pulsed ASL methods, does not require special radiofrequency coils and amplifiers, and is less susceptible to magnetic field inhomogeneity at the labeling plane. Parameters for the multiphase pCASL were tag duration of 1,600 ms, postlabeling delay of 1,000 ms, tag repetition time of 1.2ms, and phases of –90, 0, 90, and 180 degrees. Background suppression was achieved using selective saturation pulses immediately before the pCASL preparation sequence, followed by adiabatic inversion pulses.[17] Images were acquired using single-shot 3-dimensional gradient- and spin-echo, which has been shown to improve the signal-to-noise ratio by 300% over images acquired using 2-dimensional echo-planar imaging. We analyzed CBF totals[17] (white and gray matter) from 5 nonoverlapping regions of interest (frontal, occipital, parietal, temporal lobes; limbic region).

Cognitive Function

Centrally trained and certified staff masked to intervention assignment performed standardized cognitive function assessments.[11] Verbal learning and memory were assessed using the Rey Auditory Verbal Learning Test, speed of processing and working memory were assessed using the Digit Symbol Coding test, executive functions were assessed using the Modified Stroop Color and Word Test and the Trail-Making Test Part B, and global cognitive functioning was assessed using the Modified Mini-Mental State Exam. Tests were administered an average of 19 days from the date of MRI.

Other Measures

At Look AHEAD enrollment, self-reported characteristics and conditions were assessed using standardized questionnaires. Prescription medications were brought to clinics for verification. Blood pressure was measured in duplicate using an automated device (Dinamap Monitor Pro 100, GE Medical Systems, Sykesville, MD, USA). Hypertension was defined as measured blood pressure greater than 140/

90 mmHg or current pharmacological treatment. Blood specimens were collected after at least a 12-hour fast and analyzed centrally. History of cardiovascular disease was defined according to self-report of prior myocardial infarction, stroke, coronary or lower extremity angioplasty, carotid endarterectomy, or coronary bypass surgery.

Annual measures of weight were obtained throughout follow-up, and physical activity was reported at baseline and Years 1, 4, and 8 using the Paffenbarger questionnaire to estimate kilocalories per week of moderate or intense physical activity.[8]

Statistical Analysis

Baseline characteristics of participants included in our analyses were compared with those of others and between intervention groups using chi-square and t-tests. The primary outcome was mean CBF across the five brain regions. Mixed-effects models were used to compare this mean between intervention groups while controlling for interregional correlations. Covariate adjustment was made for current age, sex, education, race and ethnicity, clinic, and systolic and diastolic blood pressure. Because blood pressure was not measured at the time of MRI, we used values from the most recent prior examination and the examination after the MRI. These did not vary significantly between intervention groups. Cognitive function test scores were standardized by subtracting the overall mean and dividing this difference by its standard deviation to allow for comparisons between different tests and ordered so that positive scores reflected better performance.[11] A composite score was formed by averaging the individual standardized scores and renormalizing it to have standard deviation of 1.

RESULTS

Table 1 describes participants at Look AHEAD enrollment. The balance from the original randomization was largely preserved in this subset of participants, with slightly greater prevalence of greater BMI in DSE than ILI participants (P = .03).

The average time between randomization and MRI was 10.4 ± 0.5 years for ILI and DSE participants (P = .87). The average time between the end of the intervention and MRI was 0.6 ± 0.7 years for ILI participants and 0.5 ± 0.8 years for DSE participants (P = .19). MRI was achieved in 27% of ILI participants and 34% of DSE participants before the end of the intervention (P = .20), with the remainder achieved after the end.

Supplemental Table S1 shows BMI and physical activity levels over time. Mean levels at Look AHEAD baseline, mean changes from baseline averaged across all follow-up

Table 1. Characteristics at Enrollment in Action for Health in Diabetes

Characteristic	Diabetes Support and Education, n = 153	Intensive Lifestyle Intervention, n = 157	P-Value
Age, mean ± SD	57.5 ± 6.3	58.5 ± 6.6	.18
Sex, n (%)			
Female	112 (73.2)	104 (66.2)	.18
Male	41 (26.8)	53 (33.8)	
Race and ethnicity, n (%)			
African-American	36 (23.5)	31 (19.8)	.71
Non-Hispanic white	109 (71.2)	118 (75.2)	
Other, multiple	8 (5.2)	8 (5.1)	
Education, n (%)			
High school	23 (15.0)	29 (18.5)	.65
College graduate	58 (37.9)	53 (33.1)	
Post college	66 (43.1)	72 (45.9)	
Other	6 (2.9)	4 (2.6)	
Body mass index, kg/m^2, n (%)			
25.0–29.9	18 (11.8)	32 (20.4)	.03
30.0–39.9	99 (64.7)	102 (65.0)	
≥40.0	36 (23.5)	23 (14.6)	
Smoker, n (%)			
Never	75 (49.0)	81 (51.6)	.90
Former	72 (47.1)	70 (44.6)	
Current	6 (3.9)	6 (3.8)	
Hypertension, n (%)	128 (83.7%)	129 (82.2%)	.73
Blood pressure, mmHg, mean ± SD			
Systolic	130.4 ± 17.1	127.7 ± 16.4	.16
Diastolic	69.9 ± 9.6	70.0 ± 10.2	.89
Insulin use, n (%)	20 (13.1)	16 (10.2)	.43
Diabetes mellitus duration, years (missing, n = 6)			
<5	72 (47.7)	74 (48.4)	.73
≥5	79 (52.3)	79 (51.6)	
Glycosylated hemoglobin, %, mean ± SD	7.39 ± 1.36	7.27 ± 1.09	.38
History of cardiovascular disease, n (%)	13 (8.5)	13 (8.3)	.95

SD = standard deviation.

assessments before MRI, and mean changes from baseline to the assessment preceding the MRI are shown. At baseline, DSE participants had slightly higher mean (standard error) BMI (36.4 (0.5) kg/m^2) than ILI participants (34.8 (0.4) kg/m^2) ($P = .01$). Baseline physical activity levels were similar between the groups ($P = .35$). Mean changes in BMI from baseline over time were −2.84 (0.57) kg/m^2 for DSE participants and −6.22 (0.52) kg/m^2 for ILI participants ($P < .001$). Mean changes in self-reported moderate or intensive physical activity over time were 114.8 (102.2) kcal/wk for DSE participants and 444.3 (108.0) kcal/wk for ILI participants ($P = .03$), although at the assessment before MRI, group differences in BMI and physical activity changes were no longer statistically significant.

Table 2 portrays covariate-adjusted mean CBF, overall (primary outcome) and for 5 brain regions. Total brain CBF levels were higher in ILI than DSE participants ($P = .04$). Across all regions, mean CBF levels were 6% to 7% greater in ILI than DSE participants; interregional differences between groups were minor (interaction $P = .95$).

Table 3 summarizes associations between changes in weight and physical activity levels over time and total brain CBF within intervention groups, using 95% confidence intervals (CIs) to assess within-group relationships and tests of interaction to assess whether relationships varied between intervention groups. To facilitate comparisons of measures, slopes were standardized to be reported as CBF per baseline standard deviation of the predictor measure. Average percentage weight change had little association with total brain CBF in DSE participants (the 95% CI for the slope squarely overlapped 0). For ILI participants, greater weight loss was related to greater CBF (95% CI excluded 0), but a test of interaction comparing slopes was not statistically significant ($P = .13$). A similar pattern was seen for physical activity, which was last assessed 2 to 4 years before MRI. In the DSE group, there was no association between changes in physical activity and CBF. Greater increases in physical activity were associated with greater CBF for ILI participants, but again, differences in slopes were not statistically significant ($P = .10$).

Associations between cognitive function scores and CBF are also summarized in Table 3. For DSE participants, poorer scores were associated with greater CBF consistently across tests. For ILI participants, there was not a significant association between test scores and CBF. Differences between intervention groups in the associations between scores and CBF were statistically significant ($P < .05$) for three tests (Digit Symbol Coding, Modified Stroop Color and Word Test, and Trail-Making Test Part B).

Greater CBF was associated with poorer composite cognitive function scores overall in DSE participants but not ILI participants (Figure 1A; $P = .02$). Similar patterns were seen in each of the 5 brain regions. We examined how CBF was associated with cognitive function in subgroups of participants based on BMI at Look AHEAD baseline (25.0–29.9 kg/m^2 (overweight participants, Figure 1B) and ≥30.0 kg/m^2 (obese participants, Figure 1C)). For participants who were initially overweight, CBF tended to be greater in those assigned to ILI than to DSE ($P = .04$). In this subgroup, the slopes from regressing CBF on cognitive function were similar in the ILI and DSE

Table 2. Cerebral Blood Flow According to Intervention Assignment

Region	Mean (SE) Cerebral Blood Flow (mL/100 g per Minute): DSE	ILI	Difference (ILI–DSE): Mean (Standard Error)	95% Confidence Interval
Overall	48.61 (1.54)	51.60 (1.50)	2.99 (1.43)	0.38–5.81
Frontal lobe	42.59 (3.21)	45.20 (3.22)	2.61 (1.69)	−0.71–5.92
Limbic region	54.65 (2.66)	58.04 (2.67)	3.39 (1.69)	0.07–6.70
Occipital lobe	53.54 (1.54)	57.06 (1.53)	3.52 (1.69)	0.20–6.84
Parietal lobe	47.91 (1.19)	50.71 (1.17)	2.80 (1.69)	−0.51–6.12
Temporal lobe	44.33 (1.26)	46.99 (1.25)	2.65 (1.69)	−0.66–5.97

Covariate adjustment for clinic, regional volume, age at magnetic resonance imaging, sex, race and ethnicity, baseline body mass index, and systolic and diastolic blood pressure. Comparison between intervention groups from mixed-effects model, $P = .04$; heterogeneity among regions, $P = .95$.

DSE = diabetes support and education; ILI = intensive lifestyle intervention

Table 3. Relationships Between Total Brain Cerebral Blood Flow and Changes in Weight and Physical Activity and Cognitive Function

Intervention Assignment	Relationship with Total Brain Cerebral Blood Flow, Slope (Standard Error) (mL/100 g per Minute)/(Standard Deviation)	95% Confidence Interval	Interaction P-Value
Average change from baseline			
Percentage change in weight			
DSE	−0.259 (0.781)	−2.315–1.398	.13
ILI	−2.525 (1.097)	−4.686 to −0.364	
Physical activity (kcal/wk)			
DSE	0.502 (1.218)	−1.903–2.904	.10
ILI	3.288 (1.171)	0.978–5.597	
Cognitive function			
Modified Mini-Mental State Examination			
DSE	−1.805 (1.207)	−4.180–0.157	.16
ILI	0.472 (1.166)	−1.824–2.767	
Digit Symbol Coding Test			
DSE	−1.669 (1.075)	−3.785–0.446	.04
ILI	1.362 (1.153)	−0.098–3.623	
Modified Stroop Color and Word Test			
DSE	−2.091 (1.110)	−4.275–0.094	.01
ILI	1.474 (0.993)	−0.480–3.429	
Trail-Making Test Part B			
DSE	−2.757 (1.039)	−4.801 to −0.713	.04
ILI	0.120 (1.100)	−2.044–2.285	
Rey Auditory Verbal Learning			
DSE	−0.476 (1.057)	−2.557–1.604	.32
ILI	0.949 (1.052)	−1.121–3.019	
Composite			
DSE	−2.256 (1.076)	−4.375 to −0.137	.02
ILI	1.188 (1.142)	−1.059–3.435	

Covariate adjustment for age, sex, education, race and ethnicity, clinic, blood pressure, baseline value, and total brain volume.

Positive scores reflect better performance.

DSE = diabetes support and education; ILI = intensive lifestyle intervention.

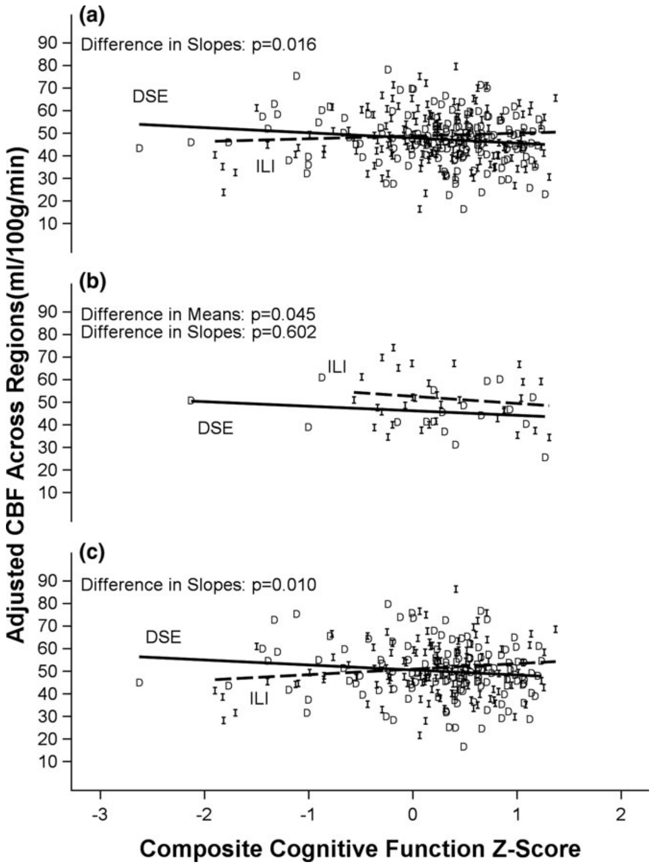

Figure 1. Relationships between composite cognitive function and average cerebral blood flow in 5 brain regions (adjusted for current age, sex, education, race and ethnicity, clinic, blood pressure, and average regional volume): (A) overall; (B) baseline body mass index (BMI) <30.0 kg/m^2; (C) baseline BMI ≥30.0 kg/m^2.

groups (P = .60). For participants who were obese initially, the slopes linking CBF to cognitive function differed significantly between the ILI and DSE groups (P = .01); there was a trend for a negative association in the DSE group and a positive association in ILI participants.

DISCUSSION

Maintaining appropriate CBF is necessary for normal brain functioning. This involves a complex interplay of systems for vascular responses (vasodilation and vasoconstriction) that are necessary to avoid hypo- and hyperperfusion.[18] It also involves angiogenesis, in which the vascular network is extended in response to injury and increases in metabolic requirements.[19,20] Although lower CBF may reflect poorer circulation due to cerebrovascular disease, higher CBF may be a response to greater metabolic demands,[6] perhaps resulting from less efficient cognitive function. This complex relationship may explain why some studies have found no relationship between CBF and cognitive function in individuals with diabetes mellitus.[21]

Our analyses of CBF collected at visits spanning the termination of the Look AHEAD interventions yield three principal findings. First, there was evidence that the 10-year ILI led to approximately 6% greater CBF across brain regions than the control condition. In the intervention group, CBF was correlated with changes in weight and physical activity over time; these relationships were not evident in the control group. Second, in the control group, there was an inverse association between cognitive function test scores and CBF; higher CBF was found in those with poorer performance. Third, in the intervention group, there appeared to be little or no association between cognitive performance and CBF, although there was some evidence that this finding varied depending on a participant's initial weight status.

Lifestyle Intervention and CBF

Observational and limited clinical trial data link greater levels of physical activity to greater CBF, although this association may wane with age.[22,23] Although obesity is associated with lower CBF in individuals with diabetes mellitus,[24] there is little evidence linking weight loss through behavioral intervention to changes in CBF. Ours is the first report that, overall, a long-term lifestyle intervention is associated with greater CBF. We see this as a benefit, which is consistent with earlier reports from Look AHEAD that its intervention was associated with less cerebrovascular disease (white matter hyperintensity volume) and better profiles of nephropathy and neuropathy (both associated with fewer microvascular complications).[10,25,26] It is also consistent with beneficial effects that Look AHEAD has reported on risk factors for vascular disease, including blood pressure, high-density lipoprotein cholesterol, and markers of inflammation.[9,27]

CBF and Cognitive Function in the Control Group

Overall, DSE participants had lower CBF than ILI participants, but in this control group, greater CBF was associated with poorer cognitive performance. This may appear counterintuitive. One possible explanation is that this reflects an adaptive response to greater metabolic requirements related to poorer cognitive efficiency through vascular dilation or angiogenesis,[18,28] although we have no data to support this speculation.

CBF and Cognitive Function in the Intervention Group

In contrast to DSE participants, there appeared to be no overall association between CBF and cognitive function in ILI participants. It is possible that this is linked to a blunted neurovascular response to decreases in cognitive efficiency and neurodegeneration. Possible explanations include weight loss–induced alterations in apelin and leptin levels,[29,30] hormones that may promote angiogenesis and vasodilation,[31–34] or decreases in cardiac output, which may lead to lower CBF independent of blood pressure.[35]

Differences in Relationships Depending on Baseline BMI

As noted in the Introduction, there were significant interactions between the ILI effects on cognitive function and cognitive impairment depending on initial obesity status. When delivered to individuals with a BMI less than 30.0 kg/m^2, ILI was associated with better cognitive function and less cognitive impairment; when delivered to heavier individuals, ILI was associated with poorer cognitive function.

CBF data may contribute to our understanding of the interaction. For individuals with an initial BMI less than 30.0 kg/m^2, associations between CBF and cognitive function were different from those for heavier participants. For nonobese ILI participants and for both nonobese and obese DSE participants, associations were consistent with a neurovascular response related to cognitive deficits. For obese ILI participants, who achieved greater overall weight losses than nonobese participants,[36] CBF data provide no evidence of such a neurovascular response.

Limitations

The original randomization, standardization, long-term adherence, and rich characterization are strengths of our study, but no assessments of brain MRI or cognitive function were obtained at baseline and, being composed of volunteers for a clinical trial, the cohort may not resemble general clinic populations. Although there is no available evidence that enrollment in the MRI study was differential according to intervention,[10] unmeasured confounders may have influenced findings. It follows that our findings should be viewed as exploratory and hypothesis generating.

Summary

A long-term behavioral intervention for weight loss in type 2 diabetes mellitus may result in an increase in overall CBF, but in obese individuals with poor cognitive function, weight loss may impair neurovascular responses to increases in CBF. This finding is consistent with data from Look AHEAD that, although a behavioral intervention for overweight individuals may improve cognitive function, it results in relative decrements in cognitive function and greater prevalence of cognitive impairment in obese individuals with type 2 diabetes mellitus.

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REFERENCES

1. Nealon RS, Howe PR, Jansen L et al. Impaired cerebrovascular responsiveness and cognitive performance in adults with type 2 diabetes. J Diab Complic 2017;31:462–467.
2. Willeumier KC, Taylor DV, Amen DG. Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity 2011;19:1095–1097.
3. Tucsek Z, Toth P, Tarantini S et al. Aging exacerbates obesity-induced cerebrovascular rarefaction, neurovascular uncoupling, and cognitive decline in mice. J Gerontol A Biol Sci Med Sci 2014;69A:1339–1352.
4. Birdsill AC, Carlsson CM, Willette AA et al. Lower cerebral blood flow is associated with lower memory function in metabolic syndrome. Obesity 2013;21:1313–1320.
5. Fazekas F, Niederkorn K, Schmidt R et al. White matter signal abnormalities in normal individuals: Correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. Stroke 1988;19:1285–1288.
6. Tamura MK, Pajewski NM, Bryan RN et al. Chronic kidney disease, cerebral blood flow, and white matter volume in hypertensive adults. Neurology 2016;86:1208–1216.
7. Barnes JN. Exercise, cognitive function, and aging. Adv Physiol Educ 2015;39:55–62.
8. The Look AHEAD Research Group. Design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials 2003;24:610–628.
9. The Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four year results of the Look AHEAD trial. Arch Intern Med 2010;170:1566–1575.
10. Espeland MA, Erickson K, Neiberg RH et al. Brain and white matter hyperintensity volumes after ten years of random assignment to lifestyle intervention. Diabetes Care 2016;39:764–771.
11. Espeland MA, Rapp SR, Bray GA et al. Long-term impact of behavioral weight loss intervention on cognitive function. J Gerontol A Biol Sci Med Sci 2014;69A:1101–1108.
12. Espeland MA, Luchsinger JA, Baker LD et al. Effect of a long-term intensive lifestyle intervention on prevalence of cognitive impairment. Neurology 2017;88:2026–2035.
13. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013;369:145–154.
14. The Look AHEAD Research Group. The Look AHEAD Study: A description of the lifestyle intervention and the evidence supporting it. Obesity 2006;14:737–752.
15. Jung Y, Wong EC, Liu TT. Multiphase pseudocontinuous arterial spin labeling (MP-PCASL) for robust quantification of cerebral blood flow. Magn Reson Med 2010;64:799–810.
16. Ye FQ, Frank JA, Weinberger DR et al. Noise reduction in 3D perfusion imaging by attenuating the static signal in arterial spin tagging. Magn Reson Med 2000;44:92–100.
17. Xu G, Rowley HA, Wu G et al. Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRII on 3.0 T and comparison with 150-water PET in elderly subjects at risk for Alzheimer's disease. NMR Biomed 2010;23:286–293.
18. Daulatzai MA. Cerebral hypoperfusion and glucose hypometabolism: Key pathophysiological modulators promote neurodegeneration, cognitive impairment, and Alzheimer's disease. J Neurosci Res 2017;95:943–972.
19. Lin TN, Sun SW, Cheung WM et al. Dynamic changes in cerebral blood flow and angiogenesis after transient cerebral ischemia in rats. Stroke 2002;33:2985–2991.
20. Perrey S. Promoting motor function by exercising the brain. Brain Sci 2013;3:101–122.
21. Brundel M, van den Berg E, Reijmer YD et al. Cerebral haemodynamics, cognition and brain volumes in patients with type 2 diabetes. J Diab Complic 2012;26:205–209.
22. Boraxbekk CJ, Salami A, Wahlin A et al. Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—a multimodal approach. NeuroImage 2016;131:133–141.
23. Maass A, Duzel S, Goerke M et al. Vascular hippocampal plasticity after aerobic exercise in older adults. Molecul Psych 2015;20:585–593.
24. Selim M, Jones R, Novak P et al. The effects of body mass index on cerebral blood flow. Clin Auton Res 2008;18:331–338.
25. The Look AHEAD Research Group. Effect of a long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes. Lancet Diabetes Endocrinol 2014;2:801–809.
26. Pownall HJ, Schwartz AV, Bray GA et al. Changes in regional body composition over 8 years in a randomized lifestyle trial. Obesity (Silver Spring) 2015;24:1899–1905.
27. Belalcazar LM, Reboussin DM, Haffner SM et al. A 1-year lifestyle intervention for weight loss in persons with type 2 diabetes reduces high C-reactive protein levels and identifies metabolic predictors of change. Diabetes Care 2010;33:2297–2303.
28. Loane DJ, Kumar A. Microglia in the TBI brain: The good, the bad, and the dysregulated. Exp Neurol 2016;275:316–327.
29. Abbenhardt C, McTiernan A, Alfano CM et al. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. J Intern Med 2013;274: 163–175.
30. Castan-Laurell I, Vitkova M, Daviaud D et al. Effect of hypocaloric diet-induced weight loss in obese women on plasma apelin and adipose tissue expression of apelin and APJ. Eur J Endocrinol 2008;158:905–910.
31. Castan-Laurell I, Dray C, Attane C et al. Apelin, diabetes, and obesity. Endocrine 2011;40:1–9.
32. Busch HJ, Schirmer SH, Jost M et al. Leptin augments cerebral hemodynamic reserve after three-vessel occlusion: Distinct effects on cerebrovascular tone and proliferation in a nonlethal model of hypoperfused rat brain. J Cerebral Blood Flow Metal 2011;31:1085–1092.
33. Tahergorabi Z, Khazaej M. Leptin and its cardiovascular effects: Focus on angiogenesis. Adv Biomed Res 2015;4:79.
34. Sawicka M, Janowska J, Chudek J et al. Potential beneficial effect of some adipokines positively correlated with the adipose tissue content on the cardiovascular system. Int J Cardiol 2016;222:581–589.
35. Meng L, Hou W, Chui J et al. Cardiac output and cerebral blood flow: The integrated regulation of brain perfusion in adult humans. Anesthesiology 2015;123:1198–1208.
36. Unick JL, Beavers D, Bond DS et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med 2013;126:236–242.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Body mass index and self-reported physical activity at baseline and changes from baseline.

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