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Metabolic and Neurocognitive Changes Following Lifestyle Modification: Examination of Biomarkers from the ENLIGHTEN Randomized Clinical Trial

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Abstract

Background: Previous studies have demonstrated that aerobic exercise (AE) and the Dietary Approaches to Stop Hypertension (DASH) diet can improve neurocognition. However, the mechanisms by which lifestyle improves neurocognition have not been widely studied. We examined the associations between changes in metabolic, neurotrophic, and inflammatory biomarkers with executive functioning among participants from the Exercise and Nutritional Interventions for Neurocognitive Health Enhancement (ENLIGHTEN) trial.

Objective: To examine the association between changes in metabolic function and neurocognition among older adults with cognitive impairment, but without dementia (CIND) participating in a comprehensive lifestyle intervention.

Methods: ENLIGHTEN participants were randomized using a 2 × 2 factorial design to receive AE, DASH, both AE+DASH, or a health education control condition (HE) for six months. Metabolic biomarkers included insulin resistance (homeostatic model assessment [HOMA-IR]), leptin, and insulin-like growth factor (IGF-1); neurotrophic biomarkers included brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF); and inflammatory biomarkers included interleukin-6 (IL-6) and C-Reactive Protein (CRP).

Results: Participants included 132 sedentary older adults (mean age = 65 [SD = 7]) with CIND. Results demonstrated that both AE ($d = 0.48$, $p = 0.015$) and DASH improved metabolic function ($d = 0.37$, $p = 0.039$), without comparable improvements in neurotrophic or inflammatory biomarkers. Greater improvements in metabolic function, including reduced HOMA-IR (B = −2.3

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[−4.3, −0.2], $p = 0.033$) and increased IGF-1 (B = 3.4 [1.2, 5.7], $p = 0.004$), associated with increases in Executive Function.

Conclusion: Changes in neurocognition after lifestyle modification are associated with improved metabolic function.

Keywords

Aerobic exercise; CIND; DASH diet; executive function; lifestyle modification; metabolic function; vascular risk factors

INTRODUCTION

Emerging evidence suggests that lifestyle modification including aerobic exercise and dietary modification may improve neurocognition among individuals at risk for cognitive decline and Alzheimer's disease and related dementias (ADRD) [1–8]. Studies examining multicomponent interventions, including the FINGER trial, have demonstrated that interventions combining exercise and dietary modification can improve executive functions among older adults with vascular risk factors [9, 10], independent of age, education, or severity of cardiovascular disease (CVD) risk [11]. CVD risk factors may impair neurocognition through their impact on vascular function and cardiometabolic function, which is worsened by CVD risk factors and may be improved through lifestyle modification. Indeed, evidence increasingly suggests that lifestyle modification may improve neurocognition, both directly through vascular risk reduction [12] and indirectly through overlapping improvements in inflammatory [13], metabolic [14, 15], and neurotrophic pathways [16–20].

In the recently completed ENLIGHTEN (Exercise and NutritionaL Interventions for neurocoGnitive HealTh EnhaNcement) randomized clinical trial, we demonstrated that a 6-month intervention for older adults with CIND and CVD risk factors utilizing aerobic exercise and the Dietary Approaches to Stop Hypertension (DASH) diet showed that executive function was better among exercisers compared to non-exercisers, with improved aerobic fitness, reduced CVD risk, and reduced salt intake associated with changes in neurocognition [21]. Further, results showed that combining exercise with the DASH diet produced better performance compared to education controls [21]. In addition to changes in neurocognitive performance, results also demonstrated that individuals in the aerobic exercise groups demonstrated improvements in aerobic fitness, walk distance, and actigraphy-assessed physical activity. Similarly, individuals in the DASH diet groups demonstrated improvements in overall DASH diet pattern, as well as dietary potassium, magnesium, calcium, and sodium. In addition, both aerobic exercise and the DASH diet intervention groups demonstrated improvements in CVD risk factors [21]. The present secondary analyses studied metabolic, inflammatory, and neurotrophic biomarkers among ENLIGHTEN participants in order to better understand possible mechanistic pathways by which exercise and the DASH diet may affect neurocognition in older sedentary adults with CIND and CVD risk factors. We therefore examined 1) intervention-related changes in metabolic, inflammatory, and neurotrophic biomarkers, and 2) the associations between changes in biomarkers and changes in neurocognition.

METHODS

Trial overview and primary results

The ENLIGHTEN trial was a randomized clinical trial of sedentary older adults at risk for dementia. Specific inclusion criteria included age ≥55 years, subjective cognitive complaints as indicated by a score of ≥0.5 on the Mail-In Cognitive Function Screening Instrument, sedentary lifestyle, at least one CVD risk factor (in addition to being sedentary), and objective evidence of cognitive impairment as indicated by a score of 19–25 on the Montreal Cognitive Assessment (MoCA) or a score of 12 on letter fluency or ≤15 on Animal fluency. Details of the study protocol and principal findings have been previously reported and included [21–23]. Briefly, a 2 × 2 factorial design was employed in which participants were randomized to one of 4 groups: Aerobic Exercise alone (AE), DASH diet alone (DASH), a combination of Aerobic Exercise and the DASH diet (AE+DASH), or Health Education (HE).

As previously reported, 160 participants completed a comprehensive neurocognitive test battery [24] as well as measures of aerobic fitness, dietary intake, and biomarker data at baseline and again following intervention. Participants in both AE conditions demonstrated changes in Executive Function ($p = 0.046$) with similar, albeit weaker, changes in both DASH conditions ($p = 0.059$), that persisted 1 year after completion of the intervention [23]. Further, changes in Executive Function were associated with changes in improved aerobic fitness, reduced CVD risk, and reduced dietary salt intake [21].

Assessment of biomarkers

Metabolic biomarkers

Insulin resistance: Insulin resistance was defined using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [25–27].

Leptin: Plasma leptin levels were analyzed from EDTA plasma samples, assayed using solid phase quantitative ELISA according to a standard protocol [28–30]. Leptin is an adipocyte-secreted hormone thought to be involved in both regulation of appetite and cognitive function [31, 32].

Insulin like Growth Factor (IGF-1): IGF-1 is an essential neurotrophic factor that is produced both peripherally and in the brain. Peripheral levels of IGF-1 have previously been associated with neurocognition [33–35], with lower IGF-1 levels associating with worse neurocognition and a greater likelihood of cognitive decline.

Neurotrophic biomarkers

Brain derived neurotrophic factor (BDNF): Total and free plasma BDNF levels were assayed. BDNF regulates neuronal development and function in both the central and peripheral nervous system and may mediate the improvements in cognition associated with exercise [36]. Total BDNF included both bound and unbound BDNF levels, whereas free BDNF assessed BDNF protein levels that were not bound to other proteins or receptors. In the present analyses, we focused on total BDNF as our primary outcome metric of interest.

Vascular endothelial growth factor (VEGF): VEGF induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces permeabilization of blood vessels [36].

Inflammatory biomarkers

Interleukin-6 (IL-6) and High-Sensitivity C-Reactive Protein (hsCRP): Both IL-6 and hsCRP were quantified by Lab Corp using commercial enzyme-linked immunosorbent assay kits (R&D Systems). Values exceeding 10 mg/dL were truncated, consistent with current guidelines for the analysis of inflammatory markers [37]. In addition, a small number of individuals had inflammation levels measured below the conventional lower levels of detection at either baseline (≤5%) or after treatment (≤11%).

Assessment of neurocognitive functioning

Neurocognitive functioning was assessed using a modified test battery recommended by the Neuropsy-chological Working Group for vascular cognitive disorders [24] designed to tap, *a priori*, 3 key domains of cognitive functioning: Executive Function, Memory, and Language/Verbal Fluency. Our primary outcome was the Executive Function, assessed by the Trail Making Test, the Stroop Test, Digit Span Forward and Backwards subtest from the Wechsler Adult Intelligence Scale (WAIS), the Digit Symbol Substitution Test from the WAIS, the Ruff 2 & 7 Test, and the Animal Naming Test [22].

Assessment of aerobic capacity and dietary habits

Aerobic fitness—Participants underwent a maximal graded exercise treadmill test in which workloads were increased at a rate of one metabolic equivalent per minute [38]. Expired air was collected by mouthpiece for quantification of minute ventilation, oxygen consumption, and carbon dioxide production with the Parvo Medics TrueOne measurement system (model 2400; Parvo Medics, Sandy, Utah).

Dietary habits—Diet was assessed by the Block Food Frequency questionnaire (FFQ) and a 4-day food diary. We quantified adherence to the DASH eating pattern, using a modified DASH scoring algorithm adopted from Folsom and colleagues [39, 40]. Dietary intake from a 4-day diary was utilized for all dietary components for which a score could be derived (fruits, vegetables, dairy, grains, fat calories, saturated fat calories, and sodium), with only those categories that could not be quantified by the diary being generated from the FFQ (meats, nuts/seeds/legumes, and sweets).

Interventions

Following baseline assessments, participants were randomized into one of four groups using a 2 × 2 factorial design. Participants were assigned equally between two intervention factors: 1) aerobic exercise and 2) the DASH diet, creating four separate groups:

1. *Aerobic Exercise (AE) alone*: Participants performed Aerobic Exercise for 6 months. For the initial 3 months, participants exercised 3 times a week at a level of 70–85% of their initial peak heart rate reserve (HRR) under supervision at a cardiac rehabilitation facility in central North Carolina. During months 4–6,

participants exercised 3 times per week on their own at home at 70–85% HRR, which they documented in weekly exercise logs. Participants did not receive any DASH or dietary counseling.

2. *DASH Diet (DASH):* Education on the DASH diet and feedback on participants' adherence were provided by a nutritionist in a series of half-hour sessions conducted weekly for the initial 12 weeks and then bi-weekly for weeks 13–24. Participants in the DASH condition were asked to maintain their current exercise habits for the 6-month trial duration.

3. *Combined Exercise and DASH diet (AE+DASH)*: Participants in the AE+DASH condition received both the Aerobic exercise and DASH interventions as described above.

4. *Health Education Control Group (HE)*: The HE control group received weekly 30 min educational phone calls for 3 months and then bi-weekly for 3 months and were asked to maintain their lifestyle habits. Phone calls were conducted by a health educator (a physician's assistant) on relevant, health-related topics.

Data analysis

Analyses were conducted using general linear models within SAS 9.4. Due to strong correlations among biologically-related biomarkers, we combined outcomes within domains in order to focus on three sets of outcomes: neurotrophins (BDNF and VEGF), metabolic function (HOMA-IR, Leptin, and IGF-1), and inflammation (IL-6 and CRP). Within each set of analyses, pre- and post-treatment biomarker levels were combined using a within-sample, mean z-score; [41], for neurocognition we used a 'gatekeeper' analytic approach, which we have used in other studies including our primary publication [42–44]. This latter approach has been advocated for its parsimonious approach to minimizing type-I error without substantial loss of power [45, 46]. Analyses of intervention-related biomarker changes were conducted using pre-planned factorial comparisons of DASH factor groups (AE + DASH and DASH-A) versus non-DASH groups (AE and HE), and Aerobic Exercise factor groups (AE + DASH and AE) versus non-AE groups (DASH-A and HE). Consistent with our primary analyses [21], neurocognitive function was indexed *a priori* in domains of interest, which were examined using separate rank-based composite scores within each domain of function. Because Executive Function was the only neurocognitive domain improved in the primary trial, changes in Language and Memory performance were not examined in the present analyses. In order to improve the robustness of model estimates, overlapping covariates were clustered where possible [47]. All analyses controlled for age, education, MoCA score, sex, race, cardiometabolic risk factor severity (CRF) [48], cardiovascular/inflammatory medications [21], genetic/familiar risk of ADRD (*APOE* genotype [21] and family history of dementia) [21, 49], and baseline level (T1) of the respective outcome. Analyses of changes in biomarkers examined the composite outcome score (T2 – T1) within each domain (neurotrophins, inflammation, and metabolic function) separately with the two treatment factors as the predictors of interest (AE and DASH): $\text{Biomarkers}_{T2-T1} = \text{Biomarkers}_{T1}$ + Age + Education +MoCA + Sex + Race + CRF + Medications + ADRD Risk + AE + DASH. Within each domain, scores were combined such that the direction of

change was consistent across markers. For example, for metabolic function, change values represented reductions in HOMA-IR, reductions in leptin, and increases in IGF-1.

In order to examine the association between changes in biomarkers and neurocognition, we conducted a secondary analysis in which changes in biomarkers served as the predictor of interest with Executive Function as the outcome: Executive Function_{T2-T1} = Executive Function_{T1} + Age + Education + MoCA + Sex + Race,+ CRF + Medicatio ns + ADRD Risk + Biomarkers_{T1} + $\text{Biomarkers}_{T2-T1}$. Because changes in our composite marker of Executive Function were based on mean-ranks and therefore cannot be interpreted as 'improvements', we hereafter refer to favorable changes in Executive Function as 'increases'. Assumptions regarding linearity, independence and distribution of residuals were assessed in all analyses, with log-transformation of highly skewed outcome variables (BDNF, VEGF, and leptin). Multiple imputation using PROC MI was used to handle missing data. Continuous predictors were scaled using the interquartile range, which can be interpreted as showing differences in the outcome variable between individuals at a high (75th percentile) and low (25th percentile) level of the predictor. Because results did not differ substantively between analyses using the full cohort (n = 160) and the substudy with complete biomarker data (n = 132), we have restricted our analyses to the sub-sample only.

RESULTS

Intervention

One hundred sixty individuals were randomized to the trial, all of whom completed the program. Of these, 132 (83% of randomized participants from the full cohort) consented to provide biomarker specimens at both pre- and post-intervention samples for analysis (Table 1). Participants who did not agree to participate in the biomarker ancillary study had better baseline Memory performance (p = 0.002), had a lower CVD medication burden (p = 0.014), and were more likely to be male (p = 0.050) compared to those who agreed to participate. The cohort providing biomarker data was comparable in distribution to the primary trial cohort regarding intervention group assignment: 35 participants in AE + DASH (27%), 34 in DASH-A (26%), 32 in AE (24%), and 31 in HE (23%).

Intervention-related changes in biomarkers

Intervention-related changes in biomarkers were examined in three separate domains: Metabolic (leptin, HOMA-IR, and IGF-1), Neurotrophic (BDNF and VEGF), and Inflammatory (IL-6 and CRP).Examination of intervention-related changes in metabolic biomarkers revealed that the AE groups showed improvements in metabolic function compared to the non-AE groups (AE: −0.11 [−0.26, 0.03] versus 0.17 [−0.03, 0.32]; p = 0.015). A similar effect was observed in the comparison of DASH factor groups to non-DASH groups (DASH: −0.08 [−0.22, 0.07] versus 0.13 [−0.28, 0.01]; p = 0.039) (Fig. 1). Changes in metabolic function corresponded to small-to-moderate effect size changes for both AE (d = 0.48) and DASH (d = 0.37). Follow-up characterization of group differences revealed that the AE + DASH group showed the largest metabolic function improvements (z-score change −0.26 [−0.5, −0.1]), followed by the DASH (z-score change −0.1 [−0.3,

0.1]), AE (z-score change −0.04 [−0.3, 0.2]), and HE demonstrating the worst metabolic changes (z-score change 0.23 [0.02, 0.40]) (Fig. 1).

In contrast, no consistent intervention factor differences were noted for any of our inflammation (AE: −0.01 [−0.16, 0.14] versus 0.00 [−0.16, 0.15], $p = 0.508$; DASH: −0.03 [−0.18, 0.12] versus 0.02 [−0.13, 0.17], $p = 0.689$) or neurotrophins (AE: −0.02 [−0.23, 0.18] versus 0.03 [−0.18, 0.23], $p = 0.501$; DASH: 0.01[−0.19, 0.20] versus −0.01 [−0.21, 0.20], $p = 0.448$).

Associations with neurocognitive change

In order to further characterize the relationships between biomarkers and Executive Function, we examined the associations between changes in individual metabolic biomarkers and Executive Function. Both reductions in HOMA-IR (B = −2.3 [−4.3, −0.2], $p = 0.033$) and increases in IGF-1 (B = 3.4 [1.2, 5.7], $p = 0.004$) associated with increases in Executive Function, whereas leptin changes were not associated.

DISCUSSION

Results from the present analyses suggest that changes in neurocognitive function following lifestyle modification may be partially attributable to improved metabolic function and insulin sensitivity, in particular. In explanatory analyses of individual metabolic biomarkers, changes in insulin sensitivity showed the strongest association with changes in neurocognition after carefully controlling for known confounders. In contrast, we did not observe any consistent associations between neurotrophic or inflammatory biomarkers and neurocognitive function.

Previous studies have linked metabolic risk factors, including obesity and diabetes, to a greater risk of cognitive impairment [50, 51], Alzheimer's disease [52–54], and dementia [55–58]. There are several plausible mechanistic pathways linking changes in peripheral metabolic function to neurocognition. Impaired peripheral metabolism is thought to dysregulate CNS metabolic function [59], with numerous studies demonstrating that metabolic risk factors associated with CNS hypometabolism [60, 61]. Changes in peripheral markers of metabolism have been hypothesized to improve neurocognition by augmenting 'cross talk' between peripheral and central metabolic function, in which improved peripheral metabolism increases the efficiency and recruitment of central glucose resources and transport across the blood-brain barrier [62]. Because metabolic dys-function impairs both glucose and lipid homeostasis, causing central glucotoxicity and impaired brain insulin signaling, it has been suggested that exercise and diet may 'recalibrate' central homeostatic function by altering brain metabolic function [63, 64]. It has also been suggested that improved metabolic function may reduce microvascular burden [65] and stabilize cortical atrophy [15, 58], slowing the progression of neurocognitive impairment.

Several studies have shown that changes in metabolic risk factors are associated with improved cognitive outcomes, including the FINGER [66], Pre-DIVA [67], LOOK-AHEAD [68], and PREDIMED trials [69], among others [70, 71]. For example, the FINGER trial [66] recently demonstrated that a combined lifestyle and cognitive intervention focusing on

vascular risk reduction may confer cognitive benefits among older adults with vascular risk factors in processing speed, executive functions, and on a composite measure of neuropsychological functioning comprised of 14 subtests. While ENLIGHTEN differs from previously published trials in several important ways (e.g., lack of cognitive training and vascular risk reduction), the present findings nevertheless support the potential utility of reducing metabolic risk factors as a potential means of reducing the risk of late-life neurocognitive impairment. In addition, examination of individual components demonstrates that greater dietary changes conferred larger cognitive benefits [10], even among individuals with varying degrees of neuropathological burden [72]. Alternative intervention strategies to augment metabolic function, including weight loss and intranasal insulin administration, also suggest a potential role for targeted metabolic interventions to improve neurocognition. Intentional weight loss, which has robust effects on metabolic function [73], also has been suggested to improve neurocognition across varying intervention modalities [74]. Similarly, increasing evidence suggests that intranasal insulin administration may improve neurocognition [75, 76] and brain biomarkers [77–79] in both healthy and clinical samples. Additional studies should examine alterations in CNS metabolic function among individuals with metabolic risk factors to further delineate possible benefits of improved systemic metabolism on neurocognition.

Limitations

The present study has several limitations. First, the ENLIGHTEN trial examined changes over a 6-month time period, whereas many of the putative mechanisms of change may require a longer period of exposure to result in changes in behavioral markers of brain function or conversion to dementia. Future studies should attempt to integrate biomarker assessments over a longer period of time in order to better delineate the unique and overlapping influences of these important mechanistic pathways. In addition, some of our methodological approaches may have been limited by the short time period of intervention and follow-up, such as our assessments of dietary intake that used both diary measures and the FFQ. Second, our study was relatively small and the present findings must therefore be replicated in order to ensure the observed associations are robust. Specifically, we collected numerous neurocognitive outcomes and biomarkers of interest, increasing the possibility of type-I error. Although we attempted to mitigate this by carefully aggregating both neurocognitive outcome data and our biomarkers within biologically-related domains, it is possible the present findings were influenced by our small sample size and replication is therefore critical. Third, we did not collect neuroimaging markers of brain health in the present study and it is therefore possible that additional, subtle changes in brain function occurred that could only be detected using more sensitive neuroimaging modalities (e.g., functional connectivity or magnetic resonance spectroscopy) [80–82]. Finally, future studies would benefit from more careful collection of other metabolic biomarkers to more comprehensively examine the relationship between augmented metabolic function and changes inneurocognition. Collection of cerebrospinal biomarkers may also be considered in order to increase the specificity of biomarker data for CNS markers such as BDNF.

Conclusions

In the present study, lifestyle modification through aerobic exercise and the DASH diet resulted in small changes in insulin sensitivity, which were associated with changes in Executive Function. Future studies should examine changes in both peripheral and central markers of metabolic function in order to better delineate mechanisms linking improved peripheral metabolism to neurocognitive outcomes. Findings could provide important insight to guide prevention strategies among individuals at risk for neurocognitive decline and ADRD.

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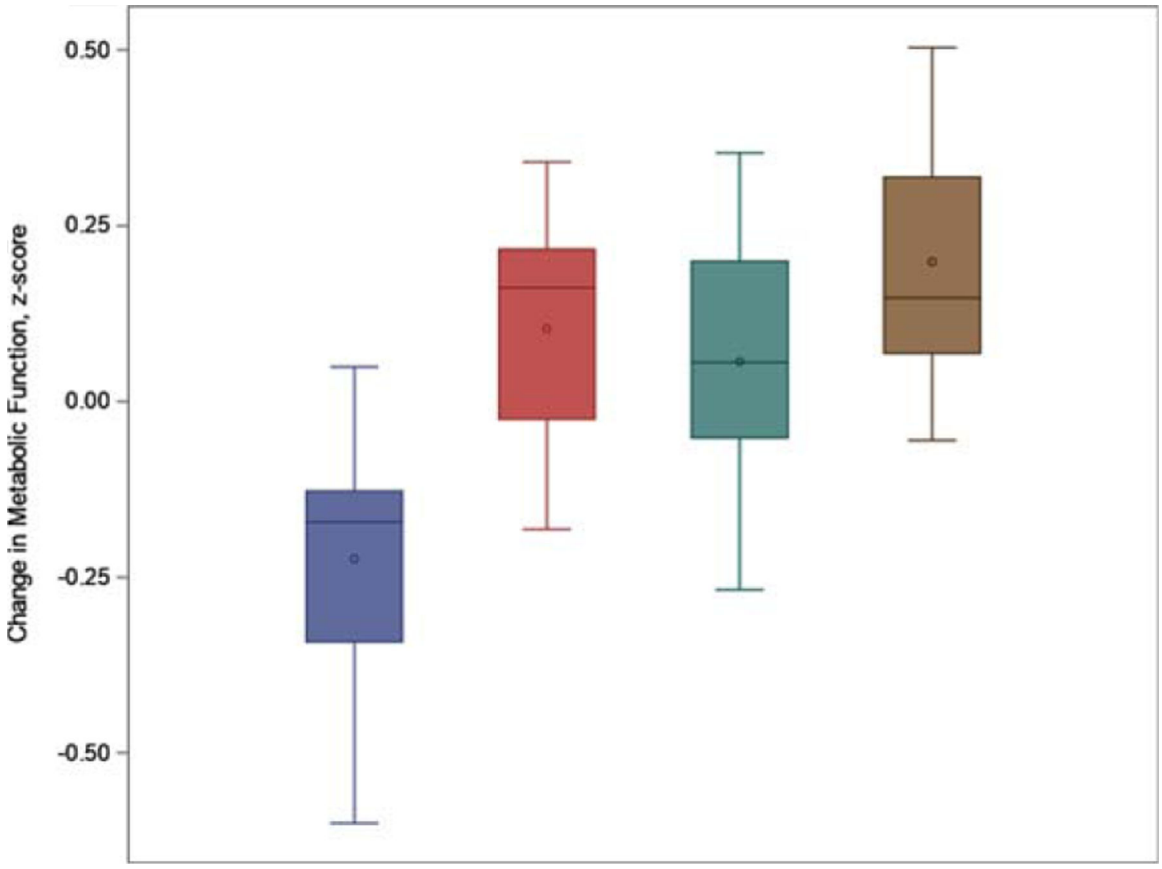

Fig. 1.

Pre-to-post intervention changes in metabolic biomarker levels (mean z-score change) across intervention groups. Values are adjusted for baseline metabolic function, age, education, sex, cardiometabolic risk factors, genetic risk, race, and MoCA score. Blue = AE + DASH, Red = DASH, Green = AE, Gold = HE. Changes following intervention were noted for both the AE factor groups (AE + DASH and AE; $d = 0.48$, $p = 0.015$) and the DASH groups (AE + DASH and DASH; $d = 0.37$, $p = 0.039$).

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Table 1:

Background and metabolic characteristics across the study sample. *P*-values represent omnibus tests for overall group differences using analysis of variance for continuous outcomes and chi-square for categorical outcomes

Variable	AE +DASH (*n* = 35)	DASH-A (*n* = 34)	AE (*n* = 32)	HE (*n* = 31)	Omnibus *p*
Age, y	64.4 (6.4)	66.1 (6.7)	65.9 (7.3)	65.2 (7.0)	0.715
Education, y	15.9 (2.1)	16.0 (2.0)	15.2 (2.4)	15.9 (2.7)	0.411
Gender, Male	13 (37%)	14 (41%)	10 (31%)	12 (39%)	0.862
Race/Ethnicity					
Caucasian, non-Hispanic	15 (43%)	21 (62%)	12 (38%)	17 (55%)	0.183
Caucasian, Hispanic	1 (3%)	0 (0%)	1 (3%)	0 (0%)	
African-American	17 (49%)	11 (32%)	16 (50%)	14 (45%)	
American Indian	0 (0%)	2 (6%)	0 (0%)	0 (0%)	
Other	2 (6%)	0 (0%)	3 (9%)	0 (0%)	
MoCA Score	24.9 (2.5)	24.6 (2.6)	24.4 (2.6)	24.5 (2.2)	0.819
ASCVD Risk Score	14.7 (9.4)	16.2 (12.6)	16.1 (9.8)	16.5 (13.2)	0.922
Body mass Index, kg/m^2	32.9 (3.6)	32.2 (4.7)	32.3 (5.8)	32.7 (5.8)	0.897
Diabetes, n (%)	9 (26%)	8 (24%)	9 (28%)	6 (19%)	0.869
Metabolic Risk Score, z-score	−2.15 (1.1)	−2.07 (1.1)	−2.2 (0.9)	−2.1 (1.0)	0.942
Systolic Blood Pressure, mm Hg	130 (15)	129 (15)	132 (14)	133 (12)	0.734
Diastolic Blood Pressure, mm Hg	76 (7)	75 (7)	76 (8)	77 (9)	0.599
Triglycerides	129 (53)	114 (41)	119 (50)	112 (49)	0.479
High Density Lipoprotein	56 (14)	59 (18)	61 (17)	60 (22)	0.624
Anti-Depressant Medication, n (%)	8 (23%)	7 (21%)	7 (22%)	8 (26%)	0.966
Biomarkers					
HOMA-IR, U (*n* = 132)	4.3 (3.1)	3.0 (2.1)	3.5 (2.1)	3.5 (2.2)	0.159
Leptin, pg/ml (*n* = 132)	44,123 (44,857)	39,474 (44,145)	51,082 (53,700)	43,022 (42,648)	0.893
IGF-1, pg/ml (*n* = 132)	64.1 (20.2)	60.0 (15.2)	63.1 (19.5)	59.2 (19.6)	0.633
Total BDNF, pg/ml (*n* = 132)	5454 (4780)	4708 (3051)	4500 (3266)	5595 (5154)	0.748
VEGF-A, pg/ml (*n* = 132)	51.5 (52.2)	55.5 (60.1)	48.2 (34.0)	48.6 (33.9)	0.857
IL-6, pg/ml (*n* = 132)	3.0 (1.9)	3.4 (2.4)	3.7 (2.1)	3.6 (2.8)	0.655
CRP, pg/ml (*n* = 132)	2.9 (2.9)	2.6 (2.9)	3.5 (3.3)	2.5 (2.9)	0.534

Table 2:

Biomarker changes from pre to post aerobic exercise (AE) and dietary approaches to stop hypertension (DASH) intervention factors

Biomarker Changes	**AE + DASH**	**DASH**	**AE**	**HE**	**AE *p***	**DASH *p***
			Neurotrophic Biomarkers			
Neurotrophins*(n* = 132), z-score	**−0.12 (−0.4, 0.16)**	**0.19 (−0.1, 0.5)**	**0.12 (−0.2, 0.4)**	**−0.03 (−0.3, 0.3)**	**0.763**	**0.843**
			Inflammatory Biomarkers			
Inflammation (*n* = 132), **z-score**	**−0.02 (−0.2, 0.2)**	**−0.05 (−0.3, 0.2)**	**−0.02 (−0.3, 0.2)**	**−0.04 (−0.3, 0.2)**	**0.820**	**0.891**
			Metabolic Biomarkers			
Metabolic Function (n - 132), z-score	**−0.26 (−0.5, −0.1)**	**−0.04 (−0.3, 0.2)**	**−0.11 (−0.3, 0.1)**	**0.23 (0.4, −0.02)**	**0.015**	**0.039**
IGF-1, pg/ml (*n* = 132)	0.5 (−2.9, 3.9)	1.1 (−2.3, 4.5)	2.2 (−1.4, 5.7)	1.1 (−2.5, 4.7)	0.763	0.555
Leptin, pg/ml (*n* = 132)	−10,633 (−15952, −5314)	−1,192 (−6579, 4194)	−3,245 (−8857, 2367)	−2133 (−7714, 3448)	0.062	0.246
HOMA-IR, U (*n* = 159)	−0.6 (−1.1, −0.1)	−0.1 (−0.6, 0.5)	−10.1 (−0.7, 0.5)	0.7 (0.2, 1.3)	0.018	0.018