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High-Intensity Physical Activity Modulates Diet Effects on Cerebrospinal β -Amyloid Levels in Normal Aging and Mild Cognitive Impairment

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Abstract

We previously showed that amyloid- β 1-42 (A β 42) levels in cerebrospinal fluid (CSF) were markedly altered in response to a 4-wk dietary intervention in normal aging and mild cognitive impairment (MCI). Here, we re-examined the data to assess whether diet-induced effects on CSF A β 42 were modulated by high intensity physical activity (hi-PA). Normal older adults (n=18, mean age=68.6 $\pm$ 7.4yrs) and adults with amnesic MCI (n=23, mean age=68.0 $\pm$ 6.5yrs) received a low saturated fat/low glycemic index (LOW) diet or a high saturated fat/high glycemic index (HIGH) diet, and CSF levels of A β 42, tau, and IL-8 were measured at baseline and week 4. Pre-study activity levels were assessed using a 7-d questionnaire, and weekly duration of hi-PA was quantified. At baseline, increased hi-PA in normals predicted lower CSF levels of tau (r=-0.54, p=0.020) and IL-8 (r=-0.70, p=0.025). Diet-induced effects on CSF A β 42 during the intervention study were modulated by hi-PA, and the nature of this effect differed for normals and MCI (ANOVA, p=0.039). That is, for normal adults, increased hi-PA attenuated the effects of the HIGH diet on CSF A β 42 whereas in MCI, increased hi-PA potentiated the effects of the LOW diet. Our results suggest that normal adults who engage in hi-PA are less vulnerable to the pathological effects of an unhealthy diet, while in MCI, the benefit of a healthy diet on A β

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modulation is greatest when paired with hi-PA. Exercise may thus interact with diet to alter pathological processes that ultimately modify AD risk.

Keywords

exercise; diet; biomarker; amyloid; brain; Alzheimer; mild cognitive impairment; aging; tau; interleukin

Introduction

Efficiency of operation for man or machine is compromised with age. Under conditions of optimal care and maintenance however, age-related wear and tear can often be reduced. In humans, age is a risk factor for many conditions that compromise body and brain integrity including coronary and vascular disease, diabetes, and dementia. Regular physical activity and a healthy diet are well-established cornerstones of healthy aging, with consequences not only for mortality rate but also cognitive vitality due in part to their favorable effects on adiposity, cardiovascular and cerebrovascular health, immune and stress response, and efficiency of glucose regulation [1, 2].

Exercise, independent of diet, is neuroprotective [3] and has favorable effects on cognition, brain volume, and neuronal network activity in controlled trials of older cognitively healthy and memory-impaired adults [4–11]. Increased physical activity (PA) is also associated with reduced risk of cognitive impairment and incident dementia [12, 13], potentially through its effects on the Alzheimer disease (AD) biomarker amyloid- β ($A\beta$) in the brain [14–16].

Dietary composition also impacts body and brain integrity. Diets heavy in saturated fats and refined carbohydrates, such as the Western diet, increase risk of aging-related conditions including obesity, insulin resistance, type 2 diabetes, cardiovascular disease [17–19], and cognitive impairment and AD [20–22]. Conversely, Mediterranean-type diets low in saturated fats but rich in monounsaturated fats, omega 3 fatty acids, and unrefined sources of carbohydrates are protective [23–25]. One mechanism through which diet might affect AD risk is through its modulation of $A\beta$ 1-42 ($A\beta$ 42) in the CNS. Animal models demonstrate that high saturated fat or sucrose diets modify processing of amyloid precursor protein from which the toxic $A\beta$ peptide is produced [26]. In humans, diet can also have dramatic effects on $A\beta$ levels in the brain [27].

Diet and exercise thus represent two lifestyle interventions with demonstrable effects on longevity and age-related changes in brain structure and function [28]. Common and separate mechanisms of action have been described, promoting the idea that optimum benefits of these interventions in brain might best be observed when paired together [28, 29]. Indeed, the results of a well-controlled large prospective cohort study conducted from 1992 to 2006 documented the important finding that a healthy Mediterranean-type diet and physical activity have both independent and additive effects on AD risk [30].

Recently we examined the effects of a dietary intervention on AD biomarkers in cerebrospinal fluid (CSF) in healthy older adults and in individuals with amnesic mild cognitive impairment (MCI), a condition presumed to reflect the earliest stages of AD pathology [31]. A 4-wk high fat, high glycemic index diet (HIGH) vs. a low fat, low glycemic index diet (LOW) had dramatic effects on CSF $A\beta$ 42; the HIGH diet moved levels in a direction consistent with amplified AD-related pathology, whereas the LOW diet moved levels in the opposite direction. Importantly, diet effects on this AD biomarker differed for normal and MCI groups. For normals, CSF $A\beta$ 42 levels were reduced with the LOW diet

but increased with the HIGH diet. In MCI, the reverse pattern was observed. We speculated that the difference across groups reflected disease stage-dependent differences in CSF A β 42 concentrations, and, consistent with predictions based on observations in other animal and human studies [32–37], proposed a model to describe this relationship [27]. According to this model (see Figure 1), CSF and brain levels of A β 42 rise with age up to the point of fibrillar A β (plaque) deposition (pre-symptomatic disease). As AD pathology progresses, manifested by increased amyloid plaque deposition in the brain, CSF levels gradually decline.

Here, we assessed whether self-reported high-intensity PA (hi-PA) modulated the diet effects we previously observed on CSF levels of A β 42 and other biomarkers of AD pathology including tau protein (total and hyperphosphorylated tau), and interleukin-8 (IL-8) in normal aging and MCI. In light of clear neuroprotective effects of exercise [3], we predicted that hi-PA would potentiate the effect of the LOW diet on the primary outcome measure CSF A β 42 yet attenuate the effect of the HIGH diet. We also examined cross-sectional associations of hi-PA (min/wk) with AD biomarker concentrations in CSF and with peripheral metabolic markers of insulin sensitivity and adiposity to explore potential differences in the nature of these relationships for normal and MCI groups at baseline.

Materials and Methods

Subjects

The study was approved by the Institutional Review Board and the Research and Development Committee of the Veterans Affairs Puget Sound Health Care System, and all subjects provided written informed consent prior to enrollment. As part of the screening process, a comprehensive neuropsychological test battery was administered to all prospective subjects, and those whose delayed memory scores fell at least 1.5 SD below an estimate of premorbid ability (age- and education-adjusted Shipley Vocabulary test score) were considered for a diagnosis of amnesic MCI by expert consensus using all available cognitive data, demographics, and medical information in accordance with published criteria [38]. Given that the aim was to examine the acute effects of diet on normal aging and on early AD pathology, MCI with amnesic features was the targeted MCI subgroup in this study [31].

Baseline demographic, PA, and diet composition information by diagnosis (normal, MCI) and diet (LOW, HIGH) are provided in Table 1. CSF concentrations of A β 42 before and after the 4-wk diet intervention were available for 41 of the 49 participants enrolled in the parent study, including 18 normal older adults (mean age=68.6 $\pm$ 7.4 yrs) and 23 adults with amnesic MCI (mean age=68.0 $\pm$ 6.5 yrs). As expected, the normals outperformed adults with MCI on the Modified Mini-Mental State Examination (3MSE, $p=0.0001$), however there were no baseline differences between the LOW and HIGH groups within diagnostic group. The four groups were comparable in age and body mass index (BMI), and education level achieved was lower for normals randomized to the LOW relative to the HIGH diet ($p=0.023$). All subjects were free of major psychiatric disorders, alcoholism, neurologic disorders other than MCI, renal or hepatic disease, type 2 diabetes, chronic obstructive pulmonary disease, or unstable cardiac disease. Use of anti-hypertensives was permitted while use of cholesterol-lowering or diabetes medications was not.

Procedure

Participants were randomly assigned to receive a high saturated fat/high glycemic index diet (HIGH) or a low saturated fat/low glycemic index diet (LOW) for 4 weeks, as previously described [27]. Pre-study min/wk hi-PA were quantified, and oral glucose tolerance testing

(OGTT), dual energy X-ray absorptiometry (DEXA), blood collection, lumbar puncture (LP) for CSF collection, and cognitive testing occurred prior to and in the final week of the diet intervention.

Physical Activity Assessment—During the screening visit, PA was assessed by self-report using a 7-d questionnaire. Trained medical personnel completed a structured interview with participants to obtain detailed descriptions of typical physical activities completed each day of the week. For each activity, participants were asked to provide the duration of the activity, to indicate whether heart rate increased, and if breathing was light, moderate, or heavy. Activities were categorized as *low intensity* if heart rate did not increase and breathing was light, including activities such as leisurely walking, stretching, and light gardening. Activities were categorized as *high intensity* if heart rate increased and breathing was moderate or heavy, including activities such as jogging, biking, or participation in structured classes of aerobic exercise. For each participant, only weekly duration of *high intensity* PA was quantified given that validity and reliability of vigorous activity by self-report is typically higher than that for lower intensity physical activity [39]. Quantification of min/wk hi-PA excluded activities of daily living (e.g., light house chores, grocery shopping and other errands).

Diet Intervention—Details of the diet intervention have been previously reported [27]. Briefly, participants were provided with all meals and snacks for a 4-wk period. In addition, participants were permitted to consume one 100 calorie nonfat beverage per day and one ‘free’ meal per week that was not on the diet plan. The HIGH diet consisted of 45% fat (25% from saturated fat), 35–40% carbohydrate (glycemic index >70), and 15–20% protein. The LOW diet consisted of 25% fat (<7% from saturated fat), 55–60% carbohydrate (glycemic index <55) and 15–20% protein. Caloric needs to maintain pre-study weight were calculated using well-established guidelines in dietetics by averaging the Mifflin-St. Jeor and Harris-Benedict equations, adjusted for PA, and rounding up to the nearest 200 calorie diet level [40, 41]. Participants and all study personnel involved in data collection were blinded to treatment assignment.

Lumbar Puncture and Biomarkers in CSF—Following a 12-h fast, an intravenous (IV) catheter was inserted and the lumbar 4–5 interspace was infiltrated with 1% lidocaine for local anesthesia. Using a 24-gauge Sprotte spinal needle, 30 ml of CSF was withdrawn into sterile syringes, aliquoted into pre-chilled polyethylene tubes, frozen immediately on dry ice, and stored at -70°C until assay. AD biomarkers of A β 42, total tau protein, and hyperphosphorylated tau at threonine 181 (p181-tau) were measured in CSF with the immunoassay INNO-BIA AlzBio3 (Innogenetics); detection limit was 15 pg/ml. IL-8 was measured by ultrasensitive ELISA (Invitrogen).

Glucose Tolerance, Insulin Sensitivity, and Adiposity—Following a 12-h fast and fasting blood collection via an indwelling IV catheter, participants ingested a 75 g glucose solution, and blood samples were collected 15, 60, and 120 minutes later to measure glucose and insulin using a previously described protocol [42, 43]. Glucose tolerance (insulin sensitivity) was estimated from insulin levels achieved during the 2-h OGTT reflected as integrated area under the curve (AUC). Total fat mass was quantified using DEXA.

Cognitive Testing—In light of our previously reported finding of a diet-induced effect on visual memory [27], we examined whether delayed recall scores on the Brief Visuospatial Memory Test (BVMT) [44] were modulated by hi-PA. Different but comparable versions of the BVMT were administered before and after the 4-week dietary intervention.

Statistical Analysis

As a follow-up to our previous findings [27] and consistent with predictions from animal work showing synergistic effects of diet and exercise on A β burden, our primary aim was to examine whether hi-PA modulated diet-induced changes in CSF A β 42. Regression analyses were first performed to residualize the data collected at week 4 from baseline to create change scores that reflect response to diet, corrected for inter-subject baseline differences. Residualized data were then subjected to an omnibus analysis of variance (ANOVA). The independent variables for this analysis included diet (LOW, HIGH), diagnosis (normal, MCI), min/wk hi-PA (continuous variable), and the interaction terms of diet by diagnosis and diet by diagnosis by hi-PA. Significant 3-way interactions were subsequently examined using separate one-way ANOVAs for each group defined by diet and diagnosis (i.e., normal-LOW, normal-HIGH, MCI-LOW, MCI-HIGH).

Secondary analyses were performed using a similar strategy to explore potential synergistic relationships between diet and hi-PA for other outcomes of interest including CSF biomarkers of tau and IL-8, peripheral metabolic indices including insulin sensitivity and adiposity (fat mass), and visual memory. Cross-sectional analyses at baseline were performed using ANOVA to examine interactions between PA and diagnosis, and multiple regression and correlation procedures when appropriate. For all analyses, age, gender, and education were entered as covariates but dropped if noncontributory. Skewed distributions were normalized using log transformation when appropriate, and missing data were handled using case-wise deletion. For secondary analyses, Bonferroni correction was used to adjust threshold of statistical significance to $\alpha=0.025$ for the two CSF biomarkers (tau, IL-8) and for the two peripheral measures of metabolic function (insulin AUC, total fat mass).

Results

High Intensity Physical Activity Modulated Diet-Induced Changes in CSF A β 42

Pre-study levels of high intensity PA modulated the diet-induced effects on CSF A β 42 (ANOVA, diet by diagnosis by hi-PA interaction, $F_{3,33}=3.13$, $p=0.039$). The results of subsequent analyses indicated that with increasing min/wk hi-PA, the presumed beneficial effect of the LOW diet was significantly enhanced in MCI ($r=0.64$, $p=0.034$) whereas the presumed negative effect of the HIGH diet tended to be attenuated for normals ($r=-0.61$, $p=0.11$). Gender was not contributory in the analysis when included as a covariate. Figure 2 depicts this finding, with min/wk hi-PA represented as categorical variable (median split) for the purpose of illustration. There were no baseline differences across groups in CSF levels of A β , and no interactive effects involving diet and hi-PA were observed for other CSF biomarkers or for peripheral measures of metabolic function (insulin AUC, total fat mass). In normals, diet-induced changes in CSF A β 42 were negatively correlated with delayed recall on the BVMT ($r=-0.51$, $p=0.03$), particularly for those who reported fewer min/wk hi-PA ($r=-0.71$, $p=0.009$). That is, for these adults, a LOW diet-induced decrease in CSF A β 42 was associated with improved visual memory whereas a HIGH diet-induced increase in the peptide predicted poorer memory performance.

Cross-Sectional Associations at Baseline Involving High Intensity Physical Activity

Diet, Adiposity, and Insulin Sensitivity—At baseline, although daily caloric intake was positively correlated with min/wk hi-PA for the entire sample, diet composition (% protein, % carbohydrate, % cholesterol including saturated fats) was not. Importantly, there were no baseline differences across the four groups in min/wk hi-PA, total calories consumed, or dietary composition (all p -values >0.30). Lower insulin AUC (indicating higher glucose tolerance and insulin sensitivity) tended to predict more min/wk hi-PA in

MCI but not for normal older adults (ANOVA, diagnosis by hi-PA interaction, $F_{3,35}=4.11$, $p=0.05$; MCI alone, $p=0.036$; normals alone, $p=0.18$).

CSF Biomarkers—For the normal adults, more min/wk hi-PA was associated with lower CSF levels of tau (Figure 3A: $r=-0.54$, $p=0.020$) and IL-8 (Figure 3B: $r=-0.70$, $p=0.025$, data available for $n=10$), which were positively correlated with each other (Figure 3C: $r=0.87$, $p=0.001$). Associations involving p181-tau were similar to those involving total tau (p181-tau and hi-PA: $r=-0.44$, $p=0.07$; p181-tau and IL-8: $r=0.87$, $p=0.001$). For adults with MCI, min/wk hi-PA was not associated with either total tau ($p=0.60$) or IL-8 ($p=0.98$). Although baseline levels of A β 42 and total tau were highly correlated for normals ($r=0.61$, $p=0.007$) and for adults with MCI ($r=0.58$, $p=0.006$), baseline A β 42 was not associated with min/wk hi-PA for either group (normal: $r=-0.25$, $p=0.3$; MCI: $r=-0.01$, $p=0.9$).

Validity of Physical Activity Self-Report

Over the course of the 4-wk study, subjects did not gain or lose weight on the isocaloric LOW or HIGH diets. The meal plans for each arm of the study took into account basal caloric requirements adjusted for self-reported PA levels (from the 7-d questionnaire). If the PA reports were incorrect, subjects would not have remained weight-stable during the diet-intervention study. Objective evidence validating the self-report PA data in our study is provided by the observed negative correlation at baseline between min/wk hi-PA and pulse pressure (systolic BP minus diastolic BP; $r=-0.35$, $p=0.023$), an index of arterial stiffness linked to vascular aging [45]. That is, increasing amounts of high intensity PA by self-report predicted improved vascular health. Although β -blocker use was considered as a covariate for this analysis of pulse pressure, it was not contributory ($p=0.98$). Neither age nor education correlated with min/wk hi-PA ($p>0.20$).

Discussion

We assessed the potential synergistic effects of diet and exercise on a well-characterized biomarker of AD pathology in a 4-wk diet intervention study in older adults with normal cognitive status or amnesic MCI. For normals, the presumed deleterious effect of the HIGH diet on CSF A β 42 was attenuated with increasing amounts of engagement in hi-PA whereas in MCI, hi-PA potentiated the beneficial effect of the LOW diet on this biomarker. Of note, synergistic diet and exercise effects were not observed at the extremes representing best case (normal cognitive status, LOW diet) and worst case (early AD pathology, HIGH diet) health scenarios in our study. These findings provide new evidence that exercise and diet may interact to modify AD pathophysiology. In addition, the results of our cross-sectional analyses examining baseline correlations between hi-PA, and CSF levels of total tau, p181-tau, and IL-8 suggest that exercise may play a role in the modulation of aging- or disease-related processes in normal asymptomatic adults.

Previously we reported marked diet-induced changes in CSF concentrations of A β 42, and the nature of this effect across a continuum from lower to higher AD pathology was described by an inverted u-shaped function [27]. For normals, CSF A β 42 levels decreased in response to the 4-wk LOW diet and increased in response to the HIGH diet. That is, for cognitively healthy adults who fall on the left side of the apex (see Figure 1), the HIGH diet moved A β 42 levels rightward toward the ‘tipping point’ when A β deposition begins (presymptomatic disease). For adults on the right side of the tipping point who already have AD pathology (amnesic MCI), the LOW diet had a pathology-decelerating effect, now moving A β 42 leftward on the continuum in a direction consistent with an earlier stage of disease. CSF levels of A β 42 were unaffected by the HIGH diet for adults with MCI,

potentially because a more severe intervention is needed to modulate extant neuropathological processes.

In our study, more min/wk hi-PA was protective against the presumed pathological effects of the HIGH diet on CSF A β 42 in normal adults. This presumption that increased peptide levels reflects relatively more pathology was supported by our finding that higher CSF A β 42 levels in response to the HIGH diet predicted poorer visual memory, particularly for normals reporting fewer min/wk hi-PA. In animals, exercise has favorable effects on A β processing in transgenic mouse models of AD, reducing extracellular A β burden [14], even after the onset of pathology [46]. Exercise also overrides deleterious effects of excessive energy intake or high fat diets on neurogenesis and neurotrophin expression [47–49], and on aging-accelerating oxidative stress with favorable consequences for synaptic plasticity and cognition [50]. Independent and additive effects of exercise and dietary composition on neuropathological processes in animals [51] and incident AD in humans [30] implies that the relative benefit of one may also neutralize the deleterious effect of the other, at least in the absence of AD pathology.

In our adults with MCI, hi-PA potentiated the beneficial effect of the LOW diet. That is, the combination of increased amounts of high-intensity PA *plus* a healthy diet were needed to move A β 42 levels in a direction consistent with less pathology, thus highlighting the potential role of lifestyle intervention *potency* in the modulation of AD pathophysiological processes once initiated. Notably, in MCI, LOW diet-induced elevations in CSF A β 42 were not correlated with visual memory scores on the BVMT in our study, thus failing to provide immediate behavioral confirmation of the presumed salutary biomarker response. The results of a recent report, however, indicate that at least for adults with early AD pathology, changes in CSF concentrations of A β 42 are not necessarily coincident with changes in cognitive performance [52]. Although large prospective cohort studies report additive effects of healthy diet and exercise on AD risk [30], the preponderance of support for synergistic effects stems from animal work. In these studies, the combined regimen of exercise plus a healthy diet (i.e., low saturated fat, increased omega-3 fatty acids, or caloric restriction) with marked benefits on hippocampal function and neurotrophic factor expression, often exceeds that of either intervention alone [49, 53].

Our previous findings implicate a role of diet on A β processing in brain; the results of a recent cross-sectional study suggest that exercise can have a similar effect [15]. In this study, older adults with increased fibrillar A β deposition in brain, as measured by positron emission tomography – Pittsburgh compound-B, and reduced CSF A β 42 concentration consistently exercised less than older adults without this at-risk phenotype. Furthermore, older adults who met or exceeded the minimum American Heart Association exercise guidelines had higher levels of A β 42 in CSF relative to levels for non-exercisers. These findings indicate not only that exercise likely has a favorable effect on A β processing in brain, but also that an exercise- and diet-related increase in CSF A β 42 for at-risk older adults is likely a pathology-decelerating response.

In our study, more min/wk hi-PA predicted lower baseline CSF levels of total tau (and p181-tau) for cognitively normal older adults, consistent with reports of others [15]. Here, we also report an association between min/wk hi-PA and CSF levels of the inflammatory marker IL-8, which in turn predicts CSF levels of tau in these adults. Inflammation is a key process in the pathogenesis of many neurodegenerative disorders and has received much attention as it relates to AD [54]. In transgenic mouse models of AD, chronic exercise markedly decreases brain levels of total and p181-tau protein in a dose-dependent manner [55, 56], and reduces tau-related neuroinflammation [57]. In a large cohort of older adults from the MacArthur Studies of Successful Aging, higher PA levels were associated with

lower levels of inflammatory markers in the periphery [58]. Although synergistic effects of diet and exercise on the regulation of tau and cellular antioxidant systems have been documented in animal studies, associations of tau, p181-tau, and IL-8 to min/wk hi-PA at baseline were not perturbed by the HIGH or LOW diets in our 4-wk diet intervention study, implying that synergistic effects on these AD biomarkers likely require a longer period of dietary modification. Nonetheless, our cross-sectional data supplement the evolving extant literature and provide further evidence that increasing dose of exercise, at least in the absence of AD pathology, may predict a more favorable AD biomarker profile.

Our study has a number of limitations. Sample size was small necessitating replication in a larger cohort. The small sample also precluded an examination of other potential moderator variables such as gender or apolipoprotein E genotype, and increased risk of over-interpretation of the data. At baseline, total caloric intake for the diet intervention was adjusted for PA to ensure no weight change over the 4-wk period. As a consequence, greater amounts of hi-PA were always paired with higher daily caloric intake. Thus, effects linked to hi-PA in our study may also be related to total calories consumed. Another limitation relates to the reliance on self-report to quantify PA. Self-report measures of PA are notoriously variable with respect to validity. Variables that typically compromise validity include timing of record keeping relative to when activities occurred (e.g., activities in the last 7 days vs. activities in the last 12 months), and expectations regarding social customs (e.g., should be more active), self-perceptions (e.g., exercise perceived as more intense or longer in duration than actual episode), or demand characteristics of the study (e.g., expectations about what should be recorded) [59]. In our study, 7-d physical activity information was collected during an in-person structured interview by medical personnel with extensive experience collecting sensitive medical and personal information from older adults. During the screening visit, the physical activity data was collected together with other health-related information, and the subject was not lead to believe that the physical activity report in any way affected eligibility for participation in the study. The validity of self-report is supported by the success with which we were able keep participants weight-stable over the 4-wk diet intervention period given that the daily caloric requirements took into account 7-d physical activity information. If the reports were inaccurate, pre-study estimates of calorie intake would have also been inaccurate, and subjects would have gained or lost weight while in the 4-wk trial. Objective criterion-based validity of self-report in our study is supported by a significant negative correlation between min/wk hi-PA and baseline pulse pressure, indicating that increased amounts of exercise are associated a reduction in age-related arterial stiffness. Finally, our interpretation of the data is based on CSF levels of amyloid as a surrogate marker of brain amyloid burden rather than other more direct measurements such as PET imaging with Pittsburgh Compound-B or potentially more sensitive markers such as soluble amyloid precursor proteins [60]. Thus it is possible that asymptomatic subjects in our study, presumed to be free of AD pathology given the results of cognitive testing, were misclassified with potential consequences for data interpretation.

Lifestyle factors such as diet and exercise can have a daily cumulating impact on the state of the organism, for better or worse, and may interact to override or potentiate the effects of the other. Our results suggest that in normal aging, exercise may offset the potential pathological effects of a Western-type diet on AD biomarkers in brain; whereas for adults with amnesic MCI, the maximum pathology-decelerating effect may only be obtained through a lifestyle regimen that includes exercise *plus* a healthy diet low in saturated fats and refined carbohydrates. These findings provide new evidence to support potential synergistic effects of diet and exercise on AD biomarkers in humans, and set the stage for larger controlled trials to further examine the independent and combined effects of these lifestyle interventions on age- and disease-related neuropathological processes.

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Figure 1.
Model of hypothetical trajectory of brain and CSF A β 42 with increasing AD symptoms and pathology [27].

Figure 2.

Means and SEM representing change from baseline to week 4 for CSF levels of Aβ42, expressed as residual scores, for normal adults and adults with MCI by high-intensity physical activity (hi-PA) groups created using a median split on min/wk. In all analyses, min/wk hi-PA was entered as a continuous variable. Categorical hi-PA groups depicted in this figure were created solely for the purpose of illustration. A significant 3-way interaction involving diet, diagnosis, and hi-PA on CSF Aβ42 (ANOVA, $p=0.039$) and the results of follow-up analyses indicated that the HIGH diet-induced increase in CSF Aβ42 was attenuated for normal adults completing more min/wk hi-PA ($r=-0.61$, $p=0.11$), while in MCI, the LOW diet effect on CSF Aβ42 was potentiated by increasing amounts of hi-PA ($r=0.64$, $p=0.034$). There were no baseline differences between groups.

Figure 3. Scatter plots and least squares regression lines depicting baseline associations between, A) min/wk hi-PA and CSF concentration of total tau protein (pg/mL, log transformed, $n=18$), $r=-0.54$, $p=0.020$, B) min/wk hi-PA and CSF concentration of IL-8 (pg/mL, $n=10$), $r=-0.70$, $p=0.025$ and C) CSF concentrations of total tau protein (pg/mL, log transformed) and IL-8 (pg/mL), $r=0.87$, $p=0.001$.

Table 1

Demographics, pre-study physical activity and diet composition, and other baseline characteristics of normal and MCI groups in the LOW and HIGH diet conditions.

	NORMAL		MCI	
	LOW	HIGH	LOW	HIGH
N (males)	10 (4)	8 (3)	11 (5)	12 (9)
Age, yrs	68.9 (7.9)	68.3 (7.2)	67.8 (5.7)	68.2 (7.4)
Education, yrs*	13.4 (1.9)	15.9 (2.2)	15.3 (2.0)	15.1 (1.9)
MSE	96.6 (2.8)	97.9 (2.9)	94.9 (5.8)	93.4 (4.4)
High-intensity PA, min/wk	153 (162)	206 (302)	199 (258)	234 (220)
Pulse pressure, mmHg	53.8 (15.5)	52.9 (13.7)	49.0 (11.7)	46.3 (11.5)
BMI, kg/m²	26.8 (2.3)	30.1 (4.6)	26.4 (4.0)	28.3 (3.5)
Body fat, %	33.7 (7.7)	36.0 (7.6)	26.7 (8.0)	28.6 (9.1)
Fasting insulin, mU/mL	6.7 (3.9)	8.4 (2.6)	6.9 (4.7)	6.6 (5.3)
Insulin AUC, mU/mL	10251 (4119)	10023 (4628)	9146 (5841)	7093 (3661)
Calorie intake, kcal	2053 (772)	1971 (218)	2291 (954)	2131 (382)
Protein, %	15.3 (2.9)	17.1 (3.2)	16.7 (1.7)	16.3 (3.6)
Carbohydrate, %	47.6 (6.5)	48.0 (7.4)	45.8 (6.2)	50.3 (4.7)
Total fat, %	33.4 (6.8)	34.1 (8.0)	36.2 (5.9)	32.1 (4.6)
Saturated fat, %	10.3 (3.6)	12.5 (4.8)	13.4 (5.2)	11.5 (2.6)

Means (SD) are provided unless otherwise indicated. Abbreviations: LOW diet = low saturated fat/low glycemic index; HIGH diet = high saturated fat/high glycemic index; MSE = modified Mini-Mental Status Examination score (max = 100); High-intensity PA = minutes per week of high-intensity physical activity (includes activities such as jogging and biking); Pulse pressure = systolic – diastolic blood pressure; BMI = body mass index; Body fat = percent total body fat (excluding head) as measured by DEXA; Fasting insulin = plasma insulin levels following a 12-h fast; Insulin AUC = integrated area under the curve defined by plasma insulin values obtained during an oral glucose tolerance test at minutes 0, 15, 60, and 120; Calorie intake = average daily calorie intake as determined by a 3-d food diary; Protein = % daily calories from protein as per 3-d diary; Carbohydrate = % daily calories from carbohydrates as per 3-d diary; Total fat = % daily calories from fat as per 3-d diary; Saturated fat = % daily calories from saturated fat as per 3-d diary.

* Education level achieved was lower for normal adults assigned to the LOW vs. the HIGH diet, $p=0.023$.