Stark - AD biomarkers, health, and cognition in MCI

Partial Least Squares analysis of Alzheimer's disease biomarkers, modifiable health variables,
and cognition in older adults with Mild Cognitive Impairment

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Jessica Stark¹, Daniela J. Palombo³, Jasmeet P. Hayes^{1,2}, Kelly J. Hiersche¹, Alexander N.
Hasselbach¹, Scott M. Hayes^{1,2} for the Alzheimer's Disease Neuroimaging Initiative*

¹Department of Psychology, The Ohio State University, 225 Psychology Building, 1835 Neil
Avenue, Columbus, OH, 43210 United States

²Chronic Brain Injury Initiative, The Ohio State University, 203 Bricker Hall, 190 North Oval
Mall, Columbus, OH, 43210 United States

³Department of Psychology, University of British Columbia, Vancouver, BC Canada
V6T 1Z4

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Correspondence to:

Scott M. Hayes, Ph.D.

Psychology Building

1835 Neil Ave.

Columbus, OH 43210

Email: hayes.1074@osu.edu

ABSTRACT

Objective: To identify novel associations between modifiable physical and health variables, Alzheimer's disease (AD) biomarkers, and cognitive function in a cohort of older adults with Mild Cognitive Impairment (MCI).

Method: Metrics of cardiometabolic risk, stress, inflammation, neurotrophic/growth factors, AD, and cognition were assessed in 155 MCI participants (Mean age = 74.2 years) from the Alzheimer's Disease Neuroimaging Initiative. Partial Least Squares analysis was employed to examine associations among these physiological variables and cognition.

Results: Latent variable 1 revealed a unique combination of AD biomarkers, neurotrophic/growth factors, including brain-derived neurotrophic factor, and education that were significantly associated with specific domains of cognitive function, including episodic memory, executive function, and processing speed, representing 47.9% of the covariance in the data. Age, BMI, and metrics tapping working memory, language or premorbid IQ were not significant.

Conclusions: Our data-driven analysis highlights the significant relationships between metrics associated with AD-pathology, neuroprotection, and neuroplasticity with tasks requiring fluid (episodic memory and executive function) rather than crystallized (premorbid IQ and language) ability. These data also indicate that biological metrics are more strongly associated with episodic memory, executive function, and processing speed than chronological age in older adults with MCI.

Keywords: Healthy Aging, Neuropsychology, Neuroprotection, Neuroplasticity, Memory, Executive Function

Age and Alzheimer's disease (AD)-related neural decline negatively affect multiple aspects of cognition, such as episodic memory (memory for specific personal past events), executive function (ability to plan, inhibit responses, and sustain attention), and processing speed (Buckner, 2004; Salthouse, 2010; Tromp, Dufour, Lithfous, Pebayle, & Després, 2015). Yet, there is substantial variability in aging and multiple factors have been shown to accelerate or mitigate cognitive decline. For instance, studies have shown that cardiometabolic variables such as body mass index (BMI; Farooqui, Farooqui, Panza, & Frisardi, 2012; Yaffe et al., 2004), inflammatory indicators such as c-reactive protein (CRP; Yaffe et al., 2004), neurotrophic/growth factors such as brain-derived neurotrophic factor (BDNF; Lista & Sorrentino, 2010; Miranda, Morici, Zanoni, & Bekinschtein, 2019), and blood and cerebrospinal fluid (CSF) biomarkers such as plasma tau and CSF A β ₁₋₄₂ are associated with cognition and AD risk (Chiu et al., 2014; Diniz, Pinto, & Forlenza, 2008; Matura et al., 2019).

These variables and their link to cognition are typically examined in isolation, rather than simultaneously within the same study. Therefore, there is limited knowledge of the relative strength of associations between cognition and cardiometabolic, inflammation, neurotrophic/growth factors, and AD biomarkers. One exception is a study conducted by Meyer and colleagues (2019), which assessed neurotrophic/growth factors, inflammatory indicators, and AD biomarkers in cognitively normal, Mild Cognitive Impairment (MCI), and AD participants. Machine learning techniques were used to create predictor weights for both CSF proteins and AD biomarkers, which were subsequently used in three separate regression models predicting general cognitive function. They found that CSF protein and AD biomarkers accounted for 31% and 26% of the variance in cognitive scores respectively (P.-F. Meyer, Savard, Poirier, Morgan, & Breitner, 2019). However, this study did not examine metrics associated with cardiometabolic

risk, which are linked to cognition and dementia risk, and did not assess specific domains of cognitive function, which are known to be differentially impacted by aging and AD.

The goal of the current study was to address a gap in the literature by using a multivariate analysis to map associations between domain-specific cognitive function and multiple AD biomarkers, neurotrophic/growth factors, inflammatory markers, and cardiometabolic metrics in older adults with MCI. The Alzheimer's Disease Neuroimaging Initiative Phase 1 (ADNI1) was used to obtain data on modifiable health factors (such as those associated with cardiometabolic health: BMI, cholesterol), stress (e.g., cortisol), inflammation (e.g., CRP), neuroprotection (e.g., BDNF) and AD biomarkers (e.g., CSF A β ₁₋₄₂, plasma tau) in a cohort of older adults diagnosed with MCI. We implemented a Partial Least Squares (PLS) analysis, an unbiased and flexible multivariate technique for defining latent variables in a dataset, that does not require assigned predictor and outcome variables, but rather maps shared covariance between two sets of data (Abdi & Williams, 2013). PLS analysis was preferred to other multivariate or data-driven statistical approaches because it does not attempt to predict an outcome, making it an ideal fit for this cross-sectional data and the exploratory nature of our research question. Additionally, unlike multiple linear regression and principle components analysis, PLS analysis is well equipped to deal with a large number of variables (number of independent variables can be larger than the number of observations), or with multiple collinear variables (Van Roon, Zakizadeh, & Chartier, 2014). Data can have any distribution, such that they do not need to be normalized or on the same scale (Van Roon et al., 2014). Thus, PLS analysis was employed to identify and parse novel relationships across these identified physiological domains and cognition in a cohort of older adults with MCI.

Methods

Participants:

Participants with a diagnosis of MCI from the ADNI1 cohort were included in the current study. Full participant inclusion/exclusion criteria are available in the ADNI Procedures Manual, 2010, and are summarized here: 6th grade or higher education, fluent in English or Spanish, Mini Mental State Examination (MMSE) ≥ 24 , Clinical Dementia Rating of 0.5, subjective memory complaint by subject or study partner, impaired episodic memory, and sufficiently preserved general cognition and functional performance not meeting criteria for AD. Participants with missing data for any variables of interest were excluded, as complete data were necessary for PLS correlational analysis. One participant classified as MCI with an MMSE score of 23 was excluded. The final analysis sample included 155 MCI participants (age: 54.4 – 88.3 years; Mean = 74.2 years; SD = 7.6 years; education: 6 – 20 years; Mean = 16.0 years; SD = 2.9 years; 52 females; 151 White, 2 Asian, 2 Black; 68 *APOE* $\epsilon 4$ negative). Other ADNI cohorts (ADNIGO, ADNI2, and ADNI3) were excluded from the analysis as these cohorts did not assess neurotrophic and growth factors. Study procedures were approved by site-specific Institutional Review Boards and all participants and/or authorized representatives provided written informed consent consistent with the Declaration of Helsinki.

Neuropsychological Assessment

Neuropsychological data were obtained from screening (WMS-R Logical Memory and MMSE) and baseline visits (all other tests). Average time between appointments was 41.4 days. Nineteen raw scores from the assessment were included in the PLS analysis (see **Table 1**).

Episodic Memory – WMS-R Logical Memory I (immediate recall; number of story details correctly recalled), WMS-R Logical Memory II (delayed recall; number of story details correctly recalled), Rey Auditory Verbal Learning Test List 1 (RAVLT; number of words

correctly recalled), RAVLT List B (number of words correctly recalled on the interference list); RAVLT List 6 (number of words correctly recalled on the original list after interference); and RAVLT 30-minute delay recall (number of words correctly recalled on the original list).

Working Memory – Digit Span Forward (length of the longest digit span correctly recalled).

Executive Function – Digit Span Backward (length of the longest digit span correctly recalled), Trail Making Test (Trail B; number of seconds to correctly complete the trail).

Processing Speed – Trail Making Test (Trail A; number of seconds to correctly complete the trail), Digit Symbol Substitution Test (number of correctly drawn symbols).

Visuospatial Ability – Clock Drawing Test (number of clock details correctly drawn).

Language – Category Fluency (number of words produced in the correct category for Animals and Vegetables), The Boston Naming Test (number of drawings correctly named).

Premorbid IQ – American National Adult Reading Test (number of words incorrectly pronounced).

Global Cognition – MMSE (total score), Alzheimer's disease Assessment Scale (ADAS-COG; total score).

Cardiometabolic, Stress, and Inflammation Variables

BMI (kg/m²), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), pulse rate (per minute), cholesterol (mg/dL), triglycerides (mg/dL), and serum glucose (mg/dL) data were obtained. Insulin (uIU/mL), cortisol (ng/mL), CRP (ug/mL), and interleukin-6 receptor

(ng/mL) data were assessed from fasting plasma blood samples; these data were normalized and checked for the defined least detectable dose during the quality control process.

Growth Factors and Neurotrophic Factors

Insulin-like growth factor binding protein (ng/mL), epidermal growth factor (pg/mL), heparin-binding epidermal-growth-factor-like growth factor (HB-EGF-like-GF; pg/mL), hepatocyte growth factor (ng/mL), platelet-derived growth factor BB (PDGF; pg/mL), BDNF (ng/mL), and vascular-endothelial growth factor (pg/mL) were analyzed. Data were normalized and checked for the defined least detectable dose during the quality control process.

AD Biomarkers

Plasma Apolipoprotein E (apoE; ug/mL), plasma tau (pg/mL), CSF total tau (t-tau; pg/mL), CSF Phospho-tau (181; p-tau₁₈₁; pg/mL), and CSF A β ₁₋₄₂ (pg/mL) were also examined. Only values within the given ranges were included for analyses: A β ₁₋₄₂ 200 pg/mL – 1700 pg/mL, p-tau₁₈₁ 8 pg/mL – 120 pg/mL, and t-tau 80 pg/mL – 1300 pg/mL, as these are the reported technical limits.

Data Processing and Analysis

ADNI1 data were scrubbed using RStudio. Raw data files for all blood- and CSF-based biomarkers were checked for imputed values. To ensure data integrity, all analytes with >10% imputed values were removed. Participants who had missing data or invalid data as indicated by the ADNI manual were excluded.

The PLS Command line package (Version 6, 2013) was downloaded from the open source PLS User Guide: <http://pls.rotman-baycrest.on.ca/source/> and run in MATLAB (Version 2019b). A cross-covariance matrix between demographic (age, education), physical, health, and AD data (matrix 1) and cognitive data (matrix 2) was created and factorized using singular value

decomposition into mutually orthogonal singular vectors, otherwise called latent variables (Abdi & Williams, 2013). Latent variables describe the pattern of covariance between physical, health, and AD variables (matrix 1) and cognitive function (matrix 2). Latent variables were identified as statistically significant if the latent variable had a p -value of < 0.05 after 1500 permutations of the data, a process where behavioral observations are randomly shuffled within participants (Abdi & Williams, 2013). Reliability of a latent variable was assessed through split-half resampling, a procedure that determines the reliability of the associations described between the two matrices of data (physical, health, AD and cognitive) within a given latent variable (Kovacevic, Abdi, Beaton, & McIntosh, 2013). Latent variables are considered reliable if both sides of the data meet criteria for significance ($p < 0.05$; Kovacevic et al., 2013). Physical, health, and AD variables with a bootstrap ratio (BSR) with an absolute value greater than or equal to 1.96 (corresponding to $p \leq 0.05$), determined by 1000 resamplings with replacement of the data, were considered reliable contributors to the latent variables. Cognitive measures were considered to significantly contribute to the latent variable if their correlation with the latent variable was significantly different than zero ($p < 0.05$). Using these cutoffs, patterns of physical, health, AD variables, and cognitive scores that account for significant amounts of covariance in the data were determined (see **Table 1** for variables included in the analysis).

[INSERT TABLE 1 HERE]

Results

Three significant latent variables (all values $p = 0$) were identified. Latent Variable 1 (LV1; **Figure 1**) accounted for 47.9% of the crossblock covariance. LV1 was considered reliable, as it met criteria for split-half reliability (all values $p < 0.05$; Kovacevic et al., 2013). For LV1, neurotrophic/growth factors, AD biomarkers, and education were significantly

associated with performance across multiple cognitive domains. Specifically, HB-EGF-like-GF, PDGF, BDNF, plasma tau, CSF t-tau, CSF p-tau₁₈₁, CSF A β ₁₋₄₂, and education were significantly associated with performance on measures of episodic memory (WMS-R Logical Memory immediate and delayed recall, RAVLT List B and delayed recall), processing speed (Trail A and Digit Symbol Substitution Test), executive function (Trail B), visuospatial ability (Clock Drawing), verbal fluency (Category Fluency Vegetables), and global cognition (MMSE, ADAS-COG). All significant cognitive tests had equal contributions to LV1, as they all had error bars (representing 95% confidence intervals) overlapping with one another (**Figure 1**). Better performance on this subset of cognitive measures was associated with increased neurotrophic/growth factor levels, less AD pathology and higher education (for individual BSRs, see **Figure 1**). Of these variables, CSF AD biomarkers and education had the highest BSRs, revealing that these variables had the strongest associations with cognition, followed by growth factors such as HB-EGF-like-GF, PDGF, and BDNF.

LV2 and LV3 were also significant, accounting for 16.6% and 12.0% of the crossblock covariance respectively. For LV2, insulin, hepatocyte growth factor, and AD biomarkers were significantly associated with performance in the same cognitive domains as LV1. Specifically, higher insulin, hepatocyte growth factor, and CSF A β ₁₋₄₂, and lower CSF t-tau and CSF p-tau₁₈₁ were associated with better performance on tasks tapping episodic memory, executive function, processing speed, visuospatial ability and global cognition, although performance on digit span backward was not in the expected direction (see **Supplemental Figure 1** for details). However, LV2 did not meet criteria for split-half reliability (matrix 2 had a value of $p > 0.05$), and many cognitive outcomes had correlations with 95% confidence intervals close to crossing the x-axis (0), and thus should be interpreted with caution. For LV3, lower levels of cardiometabolic

variables, higher levels of neurotrophic/growth factors (except for PDGF, which was lower), older age, and higher education were associated with better performance in executive function (longest digit span backward length), and premorbid IQ (ANART; see **Supplemental Figure 2** for details). LV3 met criteria for split-half reliability (all values $p < 0.05$). However, the two significant cognitive outcomes in LV3 have correlations with 95% confidence intervals close to crossing the x-axis (0), and LV3 accounts for a relatively low percentage of the overall crossblock covariance; thus, the relationships reported within LV3 should be interpreted with abundant caution.

[INSERT FIGURES 1 AND 2 HERE]

Discussion

To summarize, we identified a latent variable (LV1) that accounted for a large amount of crossblock covariance, revealing a pattern in the data suggesting that increased neurotrophic/growth factor levels, less AD pathology, and higher education are associated with better performance on tasks often associated with fluid intelligence (episodic memory, executive function, processing speed, visuospatial ability, verbal fluency) as well as metrics of global cognition (**Figure 1**). Direct measures of working memory (e.g., longest sequence recalled for digit span forward) and tasks associated with crystallized intelligence (confrontational naming, premorbid IQ), were not significantly associated with this pattern. This pattern suggests that markers of neuroprotection, neuroplasticity, and AD pathology may hold relatively less importance for cognitive metrics associated with crystallized intelligence. Interestingly, modifiable cardiometabolic risk factors (such as BMI, cholesterol, etc.), which are often associated with cognition in older adults (Farooqui et al., 2012; Yaffe et al., 2004), did not contribute to the pattern described. Chronological age also did not significantly contribute to the

pattern described for LV1. The general discussion mainly focuses on LV1, which accounted for the most cross-block variance and met criteria for split-half reliability.

Our results extend the literature by showing a novel association between HB-EGF-like-GF and cognition. Specifically, better cognitive performance was associated with higher levels of plasma HB-EGF-like-GF in LV1. Previous research has shown that this growth factor may have neuroprotective properties, as infusions of HB-EGF-like-GF in rats one day post-stroke were associated with neuroprotection against cell death (Shim & Madsen, 2018). Moreover, in rats with cypermethrin exposure (a pesticide associated with AD neuropathology), exogenous administration of HB-EGF-like-GF inhibited cypermethrin-induced accumulation of $A\beta_{1-42}$ and p-tau in the frontal cortex and hippocampus, and led to decreases in learning and memory deficits caused by cypermethrin exposure (Maurya, Mishra, Abbas, & Bandyopadhyay, 2016). Our finding is consistent with animal models demonstrating HB-EGF-like-GF's potential neuroprotective role (Maurya et al., 2016; Shim & Madsen, 2018). To our knowledge, a link between HB-EGF-like-GF and human cognition has not been reported. However, in one study exploring older adults who were cognitively normal or had MCI, higher levels of CSF HB-EGF-like-GF were associated with decreased levels of CSF $A\beta_{1-42}$ and increased levels of CSF t-tau, which is contrary to our finding (P. F. Meyer et al., 2018), as our results suggest that HB-EGF-like-GF may be associated with potential cognitive benefits. This unique finding necessitates additional research in order to clarify the role of HB-EGF-like-GF in human cognition.

Our LV1 findings for two other neurotrophic/growth factors, BDNF and PDGF, support previous research showing positive associations between these two neurotrophic/growth factors and cognition. Higher levels of BDNF were associated with better cognitive performance (on WMS-R Logical Memory immediate and delayed recall, RAVLT List B and delayed recall, Trail

A and Digit Symbol Substitution Test, Trail B, Clock Drawing, Category Fluency Vegetables, MMSE, and ADAS-COG), consistent with the putative role of BDNF in neuroprotection (Lista & Sorrentino, 2010; Miranda et al., 2019). For LV1, higher PDGF was also related to better cognitive performance, which is consistent with studies showing higher levels of PDGF were associated with reduced cognitive decline (Taipa et al., 2019). However, it should be noted that the relationship between PDGF and cognition was not entirely consistent. For LV3, lower levels of PDGF were associated with higher premorbid IQ and digit span (backward) performance (although LV3 should be interpreted with caution).

AD biomarkers exhibited some of the strongest associations with cognition in LV1. Lower levels of plasma tau were associated with higher cognitive performance, supporting previous research demonstrating that plasma tau levels in those with MCI were negatively associated with episodic memory and verbal fluency performance (Chiu et al., 2014). Lower levels of CSF t-tau and CSF p-tau₁₈₁ were associated with better cognitive performance, consistent with recent work (Nathan et al., 2017). Lower levels of CSF A β ₁₋₄₂ were correlated with lower cognitive scores, a pattern similar to recent findings revealing that low CSF A β ₁₋₄₂ levels were associated with cognitive impairment in participants with MCI (Matura et al., 2019). Increased levels of CSF t-tau, CSF p-tau₁₈₁, and CSF A β ₁₋₄₂ in those with MCI are all associated with increased risk of converting to dementia (Diniz et al., 2008). These associations between AD biomarkers and cognition contribute to our understanding of cognitive decline in MCI, demonstrating that AD biomarkers are associated with a broad range of cognitive domains (see **Figure 1**).

Regarding demographic variables, higher education was associated with superior cognitive performance in LV1, consistent with the well-documented role of education as a source

of cognitive reserve (Stern, 2013). Surprisingly, chronological age did not significantly contribute to the pattern of covariance in LV1. This null finding was unexpected as multiple episodic memory and executive function tasks significantly contributed to LV1, and these cognitive domains typically decline with age (Buckner, 2004; Tromp et al., 2015). However, cognitive aging studies often do not include any array of physiological and health metrics. These data suggest neurotrophic/growth factors, AD biomarkers, and education may better predict performance on tasks of episodic memory, executive function, processing speed, visuospatial ability, verbal fluency, and global cognition than chronological age.

The current study had limitations. Some variables such as Insulin-like Growth Factor 1 and Interleukin-6 did not pass ADNI's internal quality control processes, precluding inclusion in our analysis. Other variables, such as sex or *APOE* ϵ 4 status, were not included in the analysis because it is generally not recommended to include binarized variables (sex) or those with limited variability (*APOE* ϵ 4 genotype: only 3 possible values: 0, 1, or 2 alleles) in a PLS analysis (a variable with low variance is problematic for the calculation of correlation coefficients and can lead to faulty bootstrap resampling).

Overall, these findings emphasize that markers of neuroprotection, neuroplasticity, and AD significantly contribute to episodic memory, executive function, and processing speed in older adults with MCI. Our results suggest that modifiable variables, such as BDNF, which research has shown can be upregulated with physical exercise, may serve as potential targets for future interventions to slow cognitive impairment and progression to dementia (Lista & Sorrentino, 2010).

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Table 1. Participant Demographic, Neuropsychological, Physical, Health, and AD Biomarker Data Entered into the PLS Analysis. KEY = ADAS-COG = Alzheimer’s disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Exam; CSF = Cerebrospinal Fluid; RAVLT = Rey Auditory Verbal Learning Test; WMS-R = Weschler Memory Scale – Revised

Demographic Variables			Physical, Health, and AD Variables		
	Unit	Mean (SD)		Unit	Mean (SD)
Age	Years	74.2 (7.6)	Body Mass Index	kg/m ²	25.8 (3.7)
Education	Years	16.0 (2.9)	Seated Systolic Blood Pressure	mmHg	134.4 (18.0)
Neuropsychological Variables			Seated Diastolic Blood Pressure	mmHg	74.3 (9.7)
WMS-R Logical Memory Immediate Recall	Number of story details correctly recalled	6.9 (3.2)	Seated Pulse Rate	Per minute	64.3 (9.7)
WMS-R Logical Memory Delay Recall	Number of story details correctly recalled	3.7 (2.7)	Serum Glucose	mg/dL	101.8 (31.6)
RAVLT List 1	Number of words correctly recalled	4.0 (1.4)	Triglycerides	mg/dL	163.4 (185.9)
RAVLT List 6	Number of words correctly recalled	3.5 (3.0)	Cholesterol	mg/dL	200.5 (45.5)
RAVLT List B	Number of words correctly recalled	3.5 (1.4)	Insulin* ⁺	uIU/mL	0.3 (0.3)
RAVLT Delay Recall	Number of words correctly recalled	2.5 (3.0)	C-reactive Protein**	ug/mL	0.1 (0.5)
Longest Digit Span Forward	Length of longest digit span correctly recalled	6.5 (1.1)	Cortisol**	ng/mL	2.2 (0.1)
Longest Digit Span Backward	Length of longest digit span correctly recalled	4.6 (1.1)	Interleukin-6 Receptor* ⁺	ng/mL	1.5 (0.1)
Trail Making Test, Trail B Score**	Seconds to correctly complete the trail	135.7 (73.3)	Insulin-like Growth Factor Binding Protein* ⁺	ng/mL	2.0 (0.2)
Trail Making Test, Trail A Score**	Seconds to correctly complete the trail	46.4 (24.6)	Brain-derived Neurotrophic Factor* ⁺	ng/mL	0.3 (0.4)
Digit Symbol Substitution Score	Number of correctly drawn symbols	36.6 (10.9)	Vascular Endothelial Growth Factor* ⁺	pg/mL	2.8 (0.1)
Clock Drawing Score	Number of clock details correctly drawn	4.1 (1.1)	Epidermal Growth Factor* ⁺	pg/mL	1.6 (0.6)
Clock Copy Score	Number of clock details correctly drawn	4.6 (0.8)	Heparin-binding Epidermal- Growth-Factor-like Growth Factor * ⁺	pg/mL	1.9 (0.4)

Category Fluency: Animals	Number of words produced in the correct category	15.7 (4.7)	Hepatocyte Growth Factor**⁺	ng/mL	0.6 (0.1)
Category Fluency: Vegetables	Number of words produced in the correct category	10.7 (3.4)	Platelet-derived Growth Factor BB*⁺	pg/mL	3.2 (0.5)
Boston Naming Test Total Correct	Number of drawings correctly named	25.6 (4.1)	Apolipoprotein E*⁺	ug/mL	1.7 (0.2)
ANART Errors**	Number of words incorrectly pronounced	14.6 (10.0)	Tau⁺	pg/mL	2.8 (1.7)
MMSE	Total score	26.9 (1.8)	Aβ₁₋₄₂ (CSF)	pg/mL	741.9 (336.2)
ADAS-COG**	Total Score	11.7 (4.6)	Total tau (CSF)	pg/mL	312.9 (130.3)
			P-tau₁₈₁ (CSF)	pg/mL	31.3 (15.2)

*these values are normalized **higher scores = poorer performance ⁺plasma levels

Figure 1. Correlation profile and bootstrap ratios for Latent Variable 1. **A.** The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV1 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on logical memory immediate was positively correlated with levels of brain-derived neurotrophic factor, and had a negative correlation with CSF tau). Variables with bootstrap ratios $\geq |1.96|$ (equivalent to a p-value of ≤ 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's Disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).

Figure 2. For display purposes, scatterplots of each participant's Digit Symbol Substitution raw score (**Panel A**) and WMS-R Logical Memory Delayed Recall raw score (**Panel B**) are plotted against their individual physical/health/AD score (representing how well an individual's physical/health/AD variables contribute to the overall pattern in LV1).

Supplementary Figure 1. Correlation profile and bootstrap ratios for Latent Variable 2. A. The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV2 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on logical memory immediate was positively correlated with CSF A β ₁₋₄₂, and had a negative correlation with CSF tau). Variables with bootstrap ratios $\geq |1.96|$ (equivalent to a p-value of ≤ 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's Disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).

Supplementary Figure 2. Correlation profile and bootstrap ratios for Latent Variable 3. A. The correlation between each cognitive test variable to the identified physical, health, and AD variables listed in panel B. Significant variables have 95% confidence intervals (error bars) that do not cross the x-axis (0). **B.** Each Physical, Health, and AD Variable's contribution to LV3 represented by their bootstrap ratios, indicating directionality with significant cognitive tests represented in A (for instance, performance on digit span backward was positively correlated with education, and had a negative correlation with BMI). Variables with bootstrap ratios $\geq |1.96|$ (equivalent to a p-value of ≤ 0.05) are considered significant contributors to the LV and are indicated by *. (**KEY PANEL A:** ADAS-COG = Alzheimer's disease Assessment Scale, Cognitive Subsection; ANART = American National Adult Reading Test; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; **KEY PANEL B:** APOE = apolipoprotein E; BDNF = brain-derived neurotrophic factor; BMI = body mass index; CSF = cerebrospinal fluid; HB-EGF-like-GF = heparin-binding epidermal growth factor-like growth factor; IGF = insulin-like growth factor; P-tau = phospho-tau 181; VEGF = vascular endothelial growth factor).