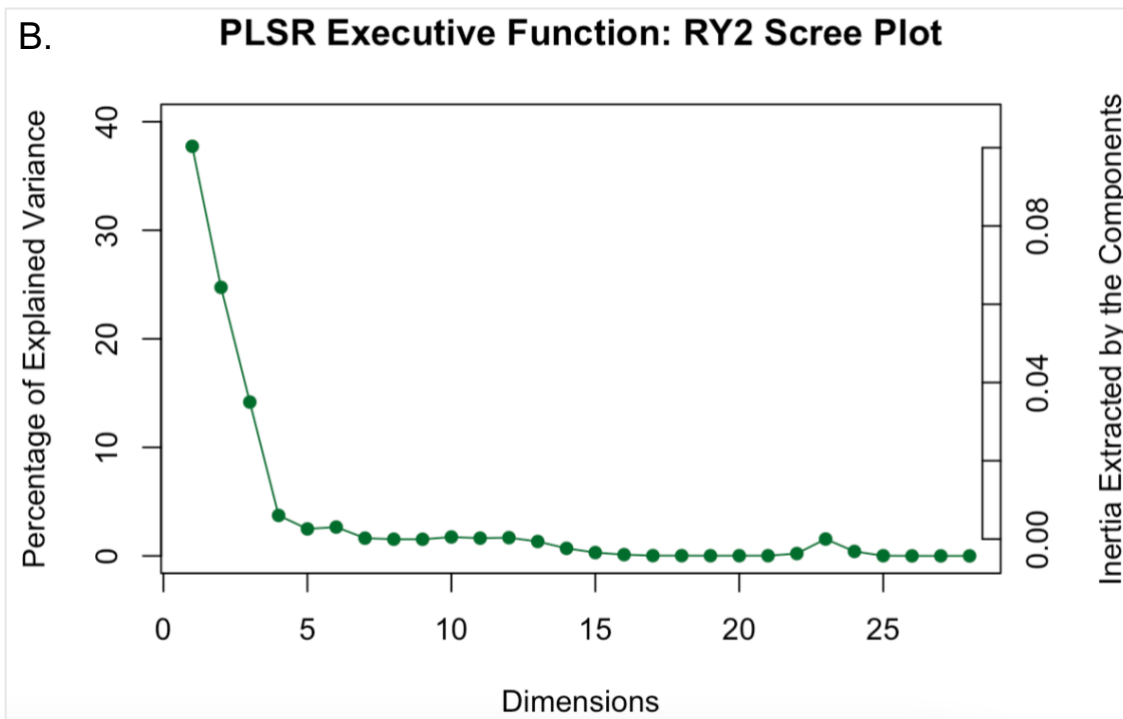
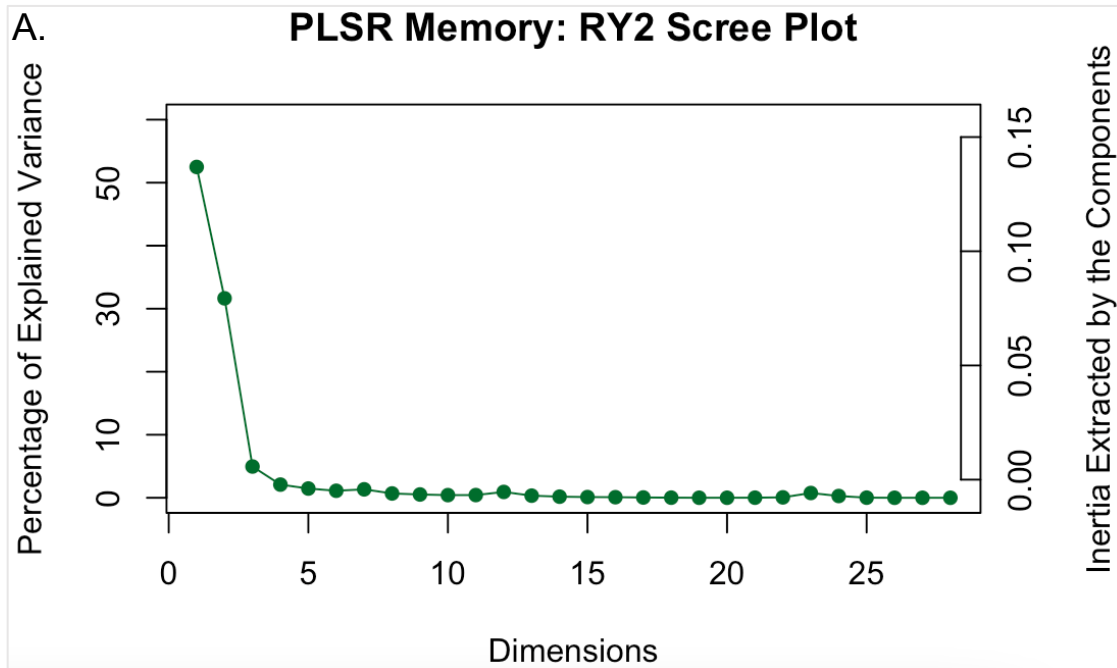


Supplementary Material

Partial Least Squares Regression Analysis of Alzheimer's Disease Biomarkers, Modifiable Health Variables, and Cognitive Change in Older Adults with Mild Cognitive Impairment

Supplementary Figure 1. Pseudo-scrree plots per model.



Supplementary Table 1. Variable Importance on Projection (VIP) Scores and B_{PLS} Values with 95% Confidence Intervals Per Model for all input variables. VIP Scores represent whether a given input variable is an important predictor in the PLSR model (across all components). Variables with a VIP score > 1 (highlighted in yellow) are considered important to the PLS model's prediction. B_{PLS} values are conceptually equivalent to regression coefficients in multiple linear regression and indicate the strength and directionality for each X-matrix variable in relation to the Y-outcome. B_{PLS} values are significant if their 95% confidence interval does not cross zero (highlighted in blue).

Variable Name	Episodic Memory Model		Executive Function Model	
	VIP Score	BPLS Value [95% CI]	VIP Score	BPLS Value [95% CI]
Body Mass Index	0.56	0.08 [-0.10 – 0.25]	0.70	0.09 [-0.10 – 0.28]
Seated Systolic Blood Pressure	0.15	<0.01 [-0.14 – 0.15]	1.16	-0.15 [-0.33 – 0.04]
Seated Diastolic Blood Pressure	0.58	-0.04 [-0.16 – 0.09]	1.28	0.10 [-0.07 – 0.27]
Seated Pulse Rate	0.48	-0.05 [-0.19 – 0.09]	0.47	0.01 [-0.16 – 0.18]
Serum Glucose	0.94	-0.09 [-0.28 – 0.10]	0.89	0.04 [-0.09 – 0.18]
Triglycerides	0.33	0.02 [-0.11 – 0.16]	0.92	-0.11 [-0.29 – 0.07]
Cholesterol	0.49	-0.05 [-0.23 – 0.12]	1.57	-0.17 [-0.35 – 0.01]
Insulin* ⁺	0.66	0.09 [-0.07 – 0.25]	0.98	0.08 [-0.11 – 0.26]
C-reactive Protein* ⁺	0.53	-0.01 [-0.19 – 0.18]	0.77	-0.07 [-0.24 – 0.10]
Cortisol* ⁺	0.29	-0.01 [-0.15 – 0.13]	0.48	-0.04 [-0.21 – 0.13]
Interleukin-6 Receptor* ⁺	1.43	0.15 [-0.07 – 0.38]	0.92	0.11 [-0.08 – 0.29]
Insulin-like Growth Factor Binding Protein* ⁺	0.51	-0.07 [-0.25 – 0.11]	0.56	0.01 [-0.17 – 0.18]
Brain-derived Neurotrophic Factor* ⁺	1.03	-0.10 [-0.23 – 0.04]	0.64	-0.06 [-0.19 – 0.08]
Vascular Endothelial Growth Factor* ⁺	1.25	-0.13 [-0.32 – 0.06]	0.71	-0.08 [-0.25 – 0.09]
Epidermal Growth Factor* ⁺	0.62	-0.04 [-0.15 – 0.08]	0.57	0.03 [-0.11 – 0.18]
Heparin-binding Epidermal- Growth-Factor-like Growth Factor* ⁺	0.80	0.11 [-0.01 – 0.23]	1.01	0.11 [-0.04 – 0.27]
Hepatocyte Growth Factor* ⁺	0.25	-0.02 [-0.18 – 0.16]	0.30	0.02 [-0.17 – 0.20]
Platelet-derived Growth Factor BB* ⁺	0.37	0.01 [-0.09 – 0.10]	0.50	<0.01 [-0.10 – 0.10]
Apolipoprotein E* ⁺	0.16	0.03 [-0.14 – 0.20]	0.93	0.02 [-0.15 – 0.18]
Tau ⁺	0.78	0.06 [-0.18 – 0.30]	1.40	0.16 [-0.08 – 0.39]
Aβ ₁₋₄₂ (CSF)	1.70	0.15 [0.01 – 0.29]	1.27	0.07 [-0.13 – 0.27]
Total tau (CSF)	1.46	<0.01 [-0.13 – 0.13]	1.25	<0.01 [-0.11 – 0.12]
P-tau ₁₈₁ (CSF)	1.55	0.03 [-0.06 – 0.12]	1.42	0.04 [-0.06 – 0.15]
P-tau ₁₈₁ /Aβ ₁₋₄₂	1.73	-0.08 [-0.16 – 0.01]	1.53	-0.09 [-0.20 – 0.02]
Total tau/Aβ ₁₋₄₂	1.83	-0.11 [-0.19 – -0.03]	1.70	-0.14 [-0.25 – -0.03]
Is APOE ε4 Positive	1.21	-0.05 [-0.14 – 0.06]	1.03	0.04 [-0.08 – 0.15]
Is APOE ε4 Negative	1.21	0.05 [-0.06 – 0.14]	1.03	-0.04 [-0.15 – 0.08]
Age	0.45	-0.05 [-0.19 – 0.10]	0.44	0.03 [-0.13 – 0.19]
Education	1.54	0.17 [0.01 – 0.34]	0.30	-0.03 [-0.20 – 0.14]

*these values are normalized; +plasma levels

VIP scores > 1 are **bold and highlighted in yellow**

BPLS values with 95% CIs that do not cross 0 are **bold and highlighted in blue**

Supplementary Table 2. Descriptive statistics for physiological and demographic predictor variables by gender.

Descriptive Statistics for Physiological and Demographic Variables Per Gender			
	Female (n=42)	Male (n=81)	Overall (N=123)
BMI (kg/m²)			
Mean (SD)	25.4 (4.4)	26.4 (3.4)	26.1 (3.8)
Systolic BP (mmHg)			
Mean (SD)	138 (19.5)	133 (17.6)	134 (18.3)
Diastolic BP (mmHg)			
Mean (SD)	73.2 (9.5)	73.6 (9.3)	73.4 (9.4)
Resting Pulse (Per Minute)			
Mean (SD)	65.8 (6.8)	64.0 (1.3)	64.6 (9.2)
Serum Glucose (mg/dL)			
Mean (SD)	98.1 (18.1)	104 (38.8)	102 (33.3)
Triglycerides (mg/dL)			
Mean (SD)	147 (72.7)	163 (122)	157 (107)
Cholesterol (mg/dL)			
Mean (SD)	212 (41.4)	191 (35.9)	198 (38.9)
Insulin (uIU/mL)			
Mean (SD)	0.31 (0.31)	0.30 (0.32)	0.30 (0.31)
C-reactive Protein (µg/mL)			
Mean (SD)	0.055 (0.48)	0.051 (0.45)	0.052 (0.46)
Cortisol (ng/mL)			
Mean (SD)	2.16 (0.10)	2.16 (0.13)	2.16 (0.12)
IL-6 Receptor (ng/mL)			
Mean (SD)	1.46 (0.19)	1.45 (0.13)	1.45 (0.15)
IGF Binding Protein (ng/mL)			
Mean (SD)	2.01 (0.21)	1.99 (0.22)	2.00 (0.22)
BDNF (ng/mL)			
Mean (SD)	0.36 (0.37)	0.25 (0.36)	0.28 (0.36)
VEGF (pg/mL)			
Mean (SD)	2.81 (0.18)	2.80 (0.10)	2.80 (0.13)
Epidermal Growth Factor (pg/mL)			
Mean (SD)	1.61 (0.55)	1.51 (0.59)	1.54 (0.58)

Descriptive Statistics for Physiological and Demographic Variables Per Gender

	Female (<i>n</i> =42)	Male (<i>n</i> =81)	Overall (<i>N</i> =123)
HB-EGF-like-GF (pg/mL)			
Mean (SD)	1.92 (0.29)	1.92 (0.39)	1.92 (0.36)
Hepatocyte Growth Factor (ng/mL)			
Mean (SD)	0.57 (0.10)	0.60 (0.09)	0.59 (0.10)
Platelet-Derived Growth Factor (pg/mL)			
Mean (SD)	3.21 (0.41)	3.16 (0.45)	3.18 (0.44)
Plasma apoE (μg/mL)			
Mean (SD)	1.72 (0.19)	1.66 (0.14)	1.68 (0.16)
Plasma Tau (pg/mL)			
Mean (SD)	2.79 (1.31)	2.88 (2.05)	2.85 (1.82)
CSF Aβ₁₋₄₂ (pg/mL)			
Mean (SD)	694 (280)	756 (368)	735 (340)
CSF t-tau (pg/mL)			
Mean (SD)	347 (120)	289 (117)	309 (121)
CSF p-tau (pg/mL)			
Mean (SD)	35.0 (14.1)	28.5 (13.1)	3.7 (13.7)
CSF p-tau/Aβ₁₋₄₂ (Ratio)			
Mean (SD)	0.06 (0.03)	0.05 (0.03)	0.05 (0.031)
CSF t-tau/Aβ₁₋₄₂ (Ratio)			
Mean (SD)	0.58 (0.29)	0.47 (0.26)	0.51 (0.28)
Age (y)			
Mean (SD)	71.5 (7.4)	75.1 (7.4)	73.9 (7.6)
Education (y)			
Mean (SD)	15.1 (3.0)	16.4 (2.9)	16.0 (3.0)

BDNF, brain-derived neurotrophic factor; BMI, body mass index; BP, blood pressure; CSF, cerebrospinal fluid; HB-EGF-like-GF, heparin-binding epidermal growth factor like-growth factor; IL6, interleukin-6; IGF, insulin-like growth factor; p-tau, phosphorylated tau₁₈₁; t-tau, total tau; VEGF, vascular endothelial growth factor.

Supplementary Table 3. Descriptive statistics for baseline physiological and demographic predictor variables by diagnostic status at two-year follow-up.

Descriptive Statistics for Physiological and Demographic Variables Per Diagnostic Status at 2-Year Follow-Up			
	Convert to AD (<i>n</i>=55)	Stay MCI (<i>n</i>=68)	Overall (<i>N</i>=123)
BMI (kg/m²)			
Mean (SD)	25.6 (3.5)	26.4 (4.0)	26.1 (3.8)
Systolic BP (mmHg)			
Mean (SD)	139 (19.1)	131 (16.9)	134 (18.3)
Diastolic BP (mmHg)			
Mean (SD)	74.0 (9.1)	72.9 (9.6)	73.4 (9.4)
Resting Pulse (Per Minute)			
Mean (SD)	65.2 (9.7)	64.1 (8.8)	64.6 (9.2)
Serum Glucose (mg/dL)			
Mean (SD)	106 (45.6)	98.2 (17.6)	102 (33.3)
Triglycerides (mg/dL)			
Mean (SD)	161 (97.6)	155 (115)	157 (107)
Cholesterol (mg/dL)			
Mean (SD)	201 (36.3)	196 (41.1)	198 (38.9)
Insulin (uIU/mL)			
Mean (SD)	0.28 (0.32)	.32 (.31)	0.30 (0.31)
C-reactive Protein (µg/mL)			
Mean (SD)	-0.03 (0.40)	.12 (.49)	0.05 (0.46)
Cortisol (ng/mL)			
Mean (SD)	2.19 (0.11)	2.13 (.13)	2.16 (0.12)
IL-6 Receptor (ng/mL)			
Mean (SD)	1.42 (0.16)	1.48 (.14)	1.45 (0.15)
IGF Binding Protein (ng/mL)			
Mean (SD)	2.00 (0.24)	2.00 (.20)	2.00 (0.22)
BDNF (ng/mL)			
Mean (SD)	0.25 (0.35)	.31 (.37)	0.28 (0.36)
VEGF (pg/mL)			
Mean (SD)	2.80 (0.12)	2.80 (.14)	2.80 (0.13)
Epidermal Growth Factor (pg/mL)			

**Descriptive Statistics for Physiological and Demographic Variables
Per Diagnostic Status at 2-Year Follow-Up**

	Convert to AD (n=55)	Stay MCI (n=68)	Overall (N=123)
Mean (SD)	1.49 (0.56)	1.59 (0.59)	1.54 (0.58)
HB-EGF-like-GF (pg/mL)			
Mean (SD)	1.91 (0.38)	1.93 (0.35)	1.92 (0.36)
Hepatocyte Growth Factor (ng/mL)			
Mean (SD)	0.59 (0.09)	0.60 (0.10)	0.59 (0.10)
Platelet-Derived Growth Factor (pg/mL)			
Mean (SD)	3.11 (0.43)	3.23 (0.44)	3.18 (0.44)
Plasma apoE (ug/mL)			
Mean (SD)	1.67 (0.17)	1.69 (0.15)	1.68 (0.16)
Plasma Tau (pg/mL)			
Mean (SD)	2.73 (1.19)	2.94 (2.21)	2.85 (1.82)
CSF Aβ₁₋₄₂ (pg/mL)*			
Mean (SD)	636 (240)	815 (387)	735 (340)
CSF t-tau (pg/mL)			
Mean (SD)	333 (104)	289 (130)	309 (121)
CSF p-tau (pg/mL)			
Mean (SD)	32.8 (11.3)	29.0 (15.3)	3.7 (13.7)
CSF p-tau/Aβ₁₋₄₂ (Ratio)			
Mean (SD)	0.06 (0.02)	0.05 (0.04)	0.051 (0.03)
CSF t-tau/Aβ₁₋₄₂ (Ratio)			
Mean (SD)	0.58 (0.22)	0.46 (0.31)	0.51 (0.28)
Age (y)			
Mean (SD)	74.3 (7.6)	73.5 (7.6)	73.9 (7.6)
Education (y)			
Mean (SD)	15.5 (3.2)	16.3 (2.7)	16.0 (3.0)
ADNI Memory Composite Score (z-score)*			
Mean (SD)	-0.37 (0.46)	0.07 (0.57)	-0.13 (0.56)
ADNI Executive Function Composite Score (z-score)*			
Mean (SD)	-0.34 (0.74)	0.17 (0.80)	-0.06 (0.81)

*significant difference between groups ($p < 0.05$)

BDNF, brain-derived neurotrophic factor; BMI, body mass index; BP, blood pressure; CSF, cerebrospinal fluid; HB-EGF-like-GF, heparin-binding epidermal growth factor like-growth factor; IL6, interleukin-6; IGF, insulin-like growth factor; p-tau, phosphorylated tau₁₈₁; t-tau, total tau; VEGF, vascular endothelial growth factor.