



Background

Alzheimer's disease (AD)

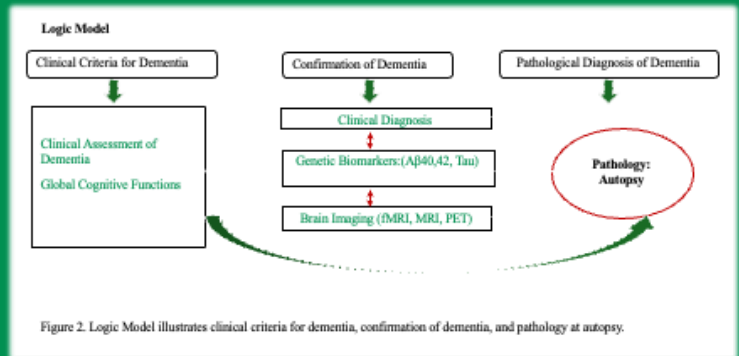
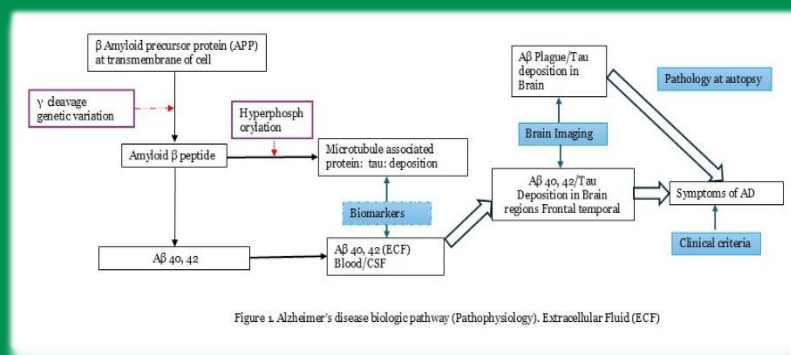
- 10.9% of 6.9 million Americans
- age > 65 years in the United States.
- Heritable (genetic) factors.
- Non-heritable (environment and lifestyle behaviors)
- Amyloid beta is a precursor of AD progression.
- Confirmed by biomarkers (A β 40,42, tau, TOMM40)
- Clinical criteria for the assessment of dementia
- Goldstandard - neuropathology for AD.

Previous Studies

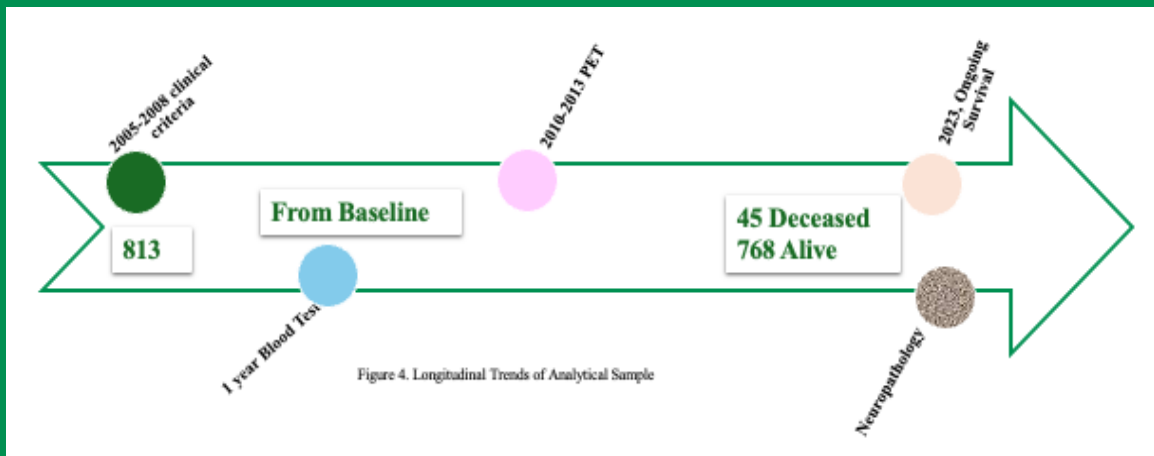
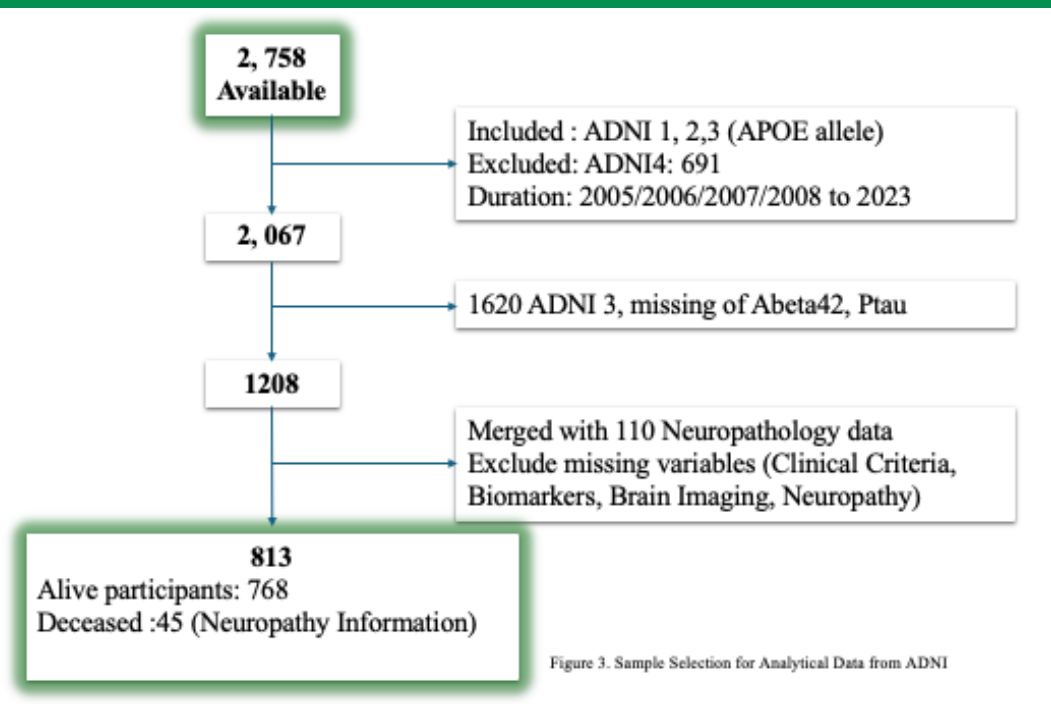
- Gaps: Inconsistency findings
- inconclusive methodology

Current Study: Aims/Hypothesis

- To evaluate the validity of composite clinical criteria for dementia and biomarkers for dementia with neuropathy at autopsy.
- Validates global cognitive scores by biomarkers and neuropathy for AD.



Methods



Population

Alzheimer's Disease Neuroimaging Initiative (ADNI) cross-sectional, prospective, retrospective study, ADNI 1, 2; Age > 60 years, n=813.

- Established analytical data set from raw data

- Predictor: Construct of global cognitive score (GBS): includes Mini-Mental State examination (MMSE), geriatric depression scale, AD assessment Scale Cognitive, Clinical Dementia Rating, Bunston Naming Test, Clocking Drawing Score, Copy Score, Auditory Verbal Learning Test, Logical Memory Delayed, and Immediate Recall.

Outcomes

- Construct A β 42 positivity, tau/A β 42, and ptau/A β 42, variables
- Prospective study: GBS validated in neuropathology at autopsy
- Cross-sectional study: GBS validated in genetic biomarkers (A β 42, tau, p-tau, tau/A β 42, and ptau/A β 42)
- Retrospective study: GBS validated with brain imaging (Amyloid PET)
- Neuropathology : Neurofibrillary Tangles (NFTs), Amyloid and neocortical neuritic plaque in brain autopsy.
- Covariates : Age, race, education, medical conditions, father/mother had AD.
- Medical Conditions: psychiatric, neurological, head injury, eyes, ears, nose and throat, cardiac, respiratory, hepatological, Gastroenterology, diabetes, allergy, and surgery.

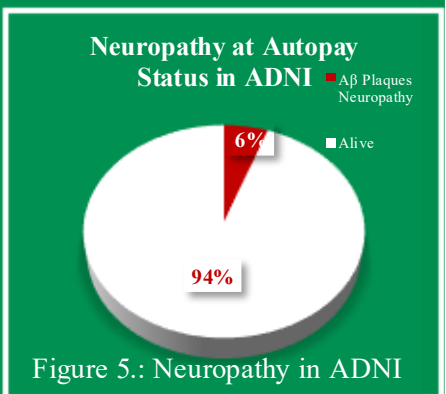


Figure 5: Neuropathy in ADNI

Results

- Education: No education and education
- Race: White and Non-White
- Statistical Analysis (STATA 19)
- Factor and principal component analysis, Cronbach's alpha
- Machine learning cross-validation (AUC & AUCPR) : h20 : train, valid models: Gbinclass/gbmclass/random forest fitting models
- LASSO regression, Multiple logistic; Cox proportional hazards
- Machine Learning cross-validation –GBS - 80 % reliability, Cronbach's alpha: 0.84.

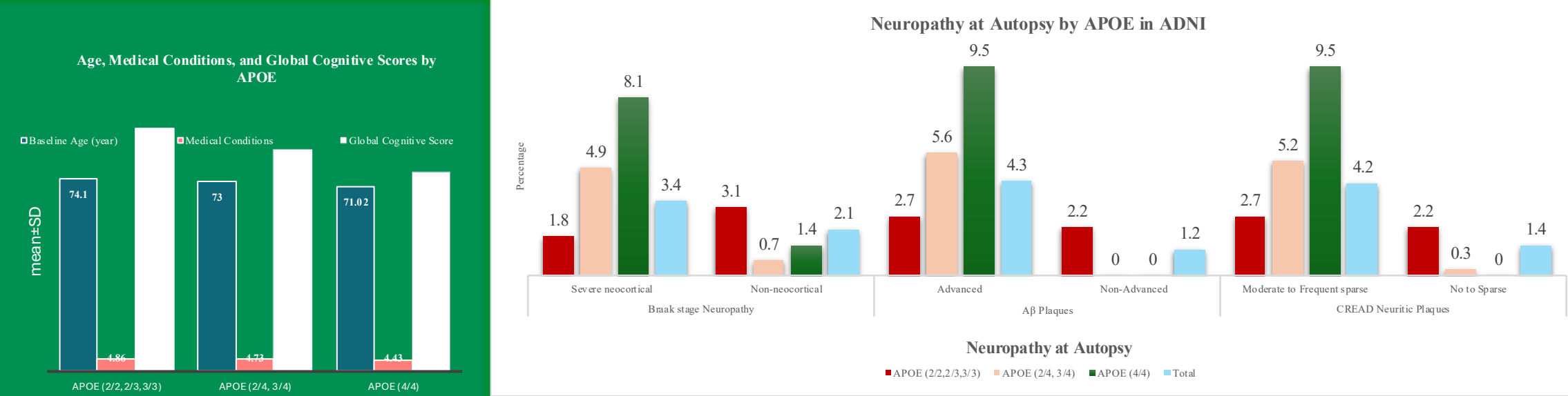
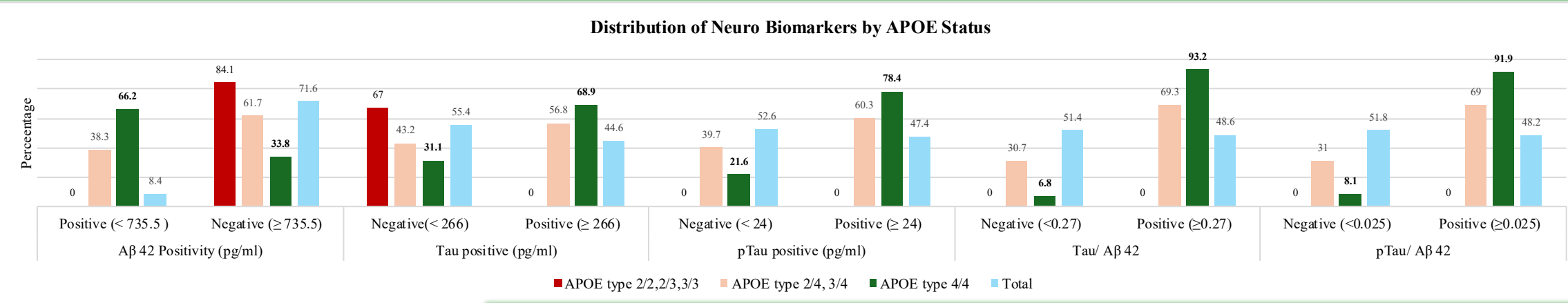
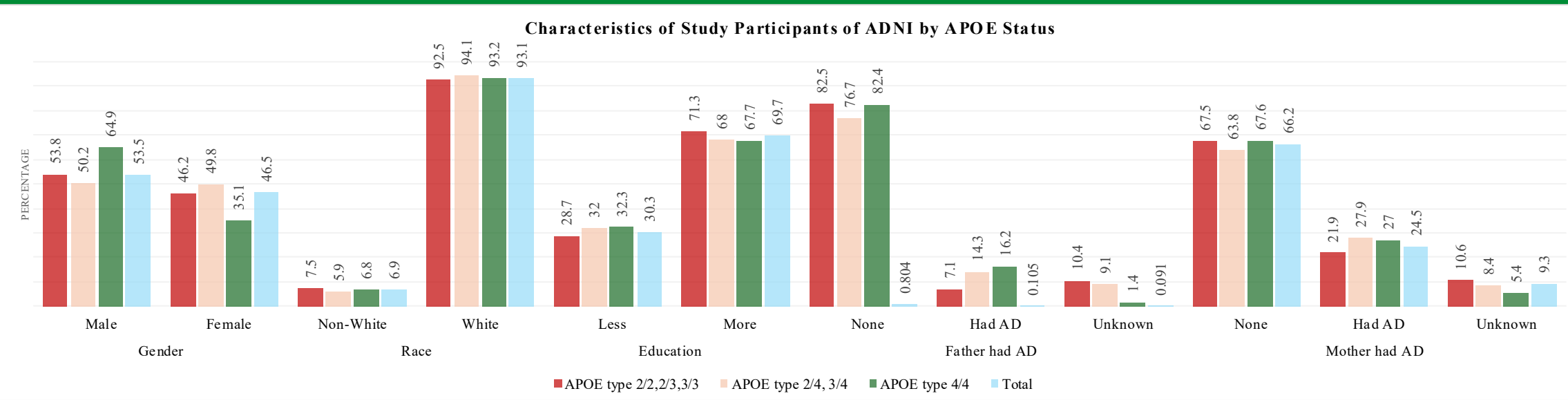


Figure 6: Characteristics of Participants in ADNI

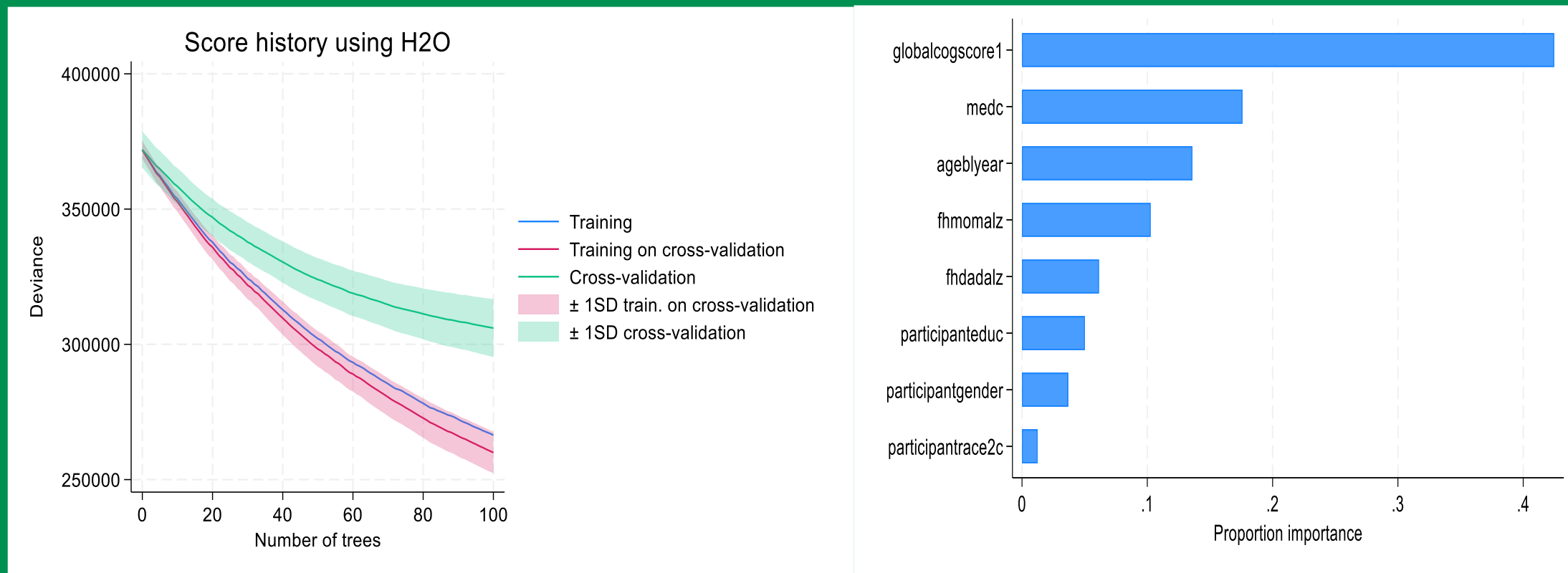


Figure 7: Machine Learning Training and Cross Validation in Neuropathy

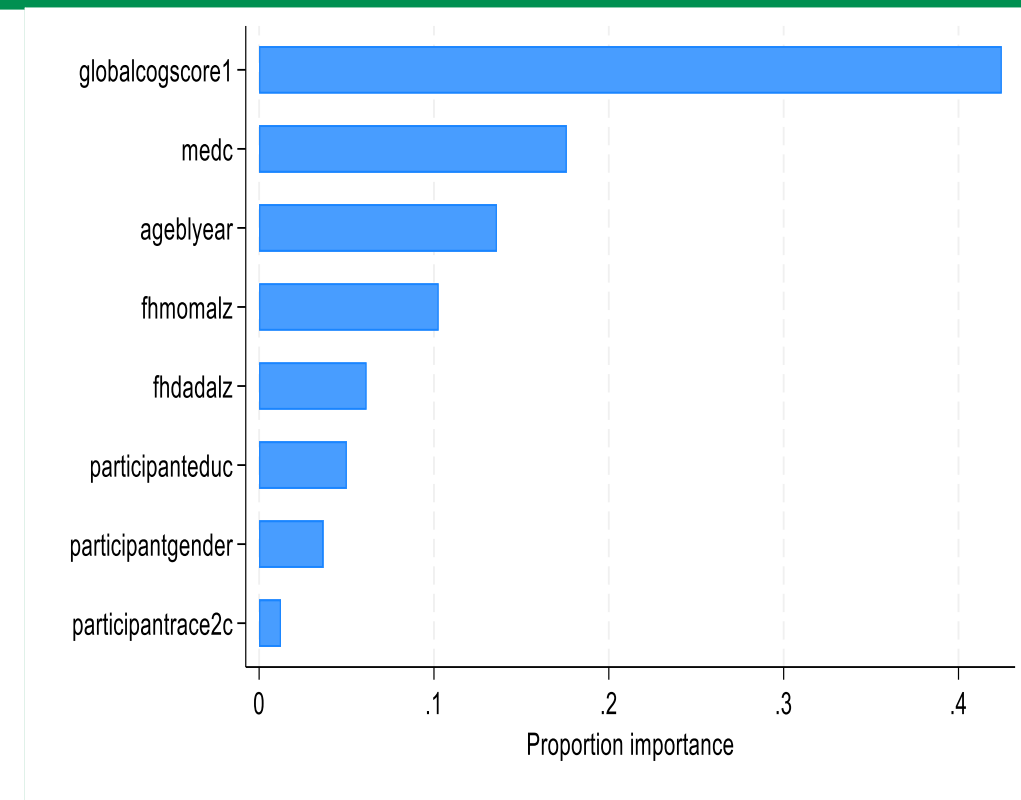


Figure 8: Proportion of Importance Factors for Neuropathy

Table 1. Machine Learning Model and Cox Proportional Hazard Models for Cross-Validation of global Cognitive Scores with AD Neuropathy at Autopsy, sequential, multistage

	Machine Learning Regression Models			Cox Proportional Hazard Models			
	AUC	AUCP	Accur	Unadjusted	Adjusted	Full Ω	
	%	%	%	HR (95 % CI)]	C- Statistic (95 % CI)	C- Statistic	
Neuropathy at Autopsy- Prospective							
Braak Stage Advanced							
Random Forest Multiclass	78	79	81	95			
Global Cognitive Score				1.03(1.00, 1.06) ***	58	1.06(1.01,1.11) *	84
Aβ Plaques Advanced							
Random Forest Multiclass	87	88	90	95			
Global Cognitive Score				0.96(0.94,0.98) ***	77	0.96(0.94,0.98) ***	81
Global Cognitive Score							
Neuritic Plaques: Moderate to Frequent sparse							
Random Forest Multiclass	74	77	95				
Global Cognitive Score				1.0(0.99,1.0)	52	1.0(0.99,0.00)	28
Amyloid Positivity: Amyloid PET Brain Imaging- Retrospective							
Gradient Boosting Binary	72	73	74				
Global Cognitive Score				0.98(0.97,1.00) **	63	0.98(0.96,1.00) *	83

HR: Hazard Ratio; OR: odd ratio; Ω :adjusted Model; social demographic: baseline age, gender, race, education, family history of dementia" mother had AD, father had AD. Medical conditions. AUC: Area Under Curve, AUCPR: AUC precision.

Results

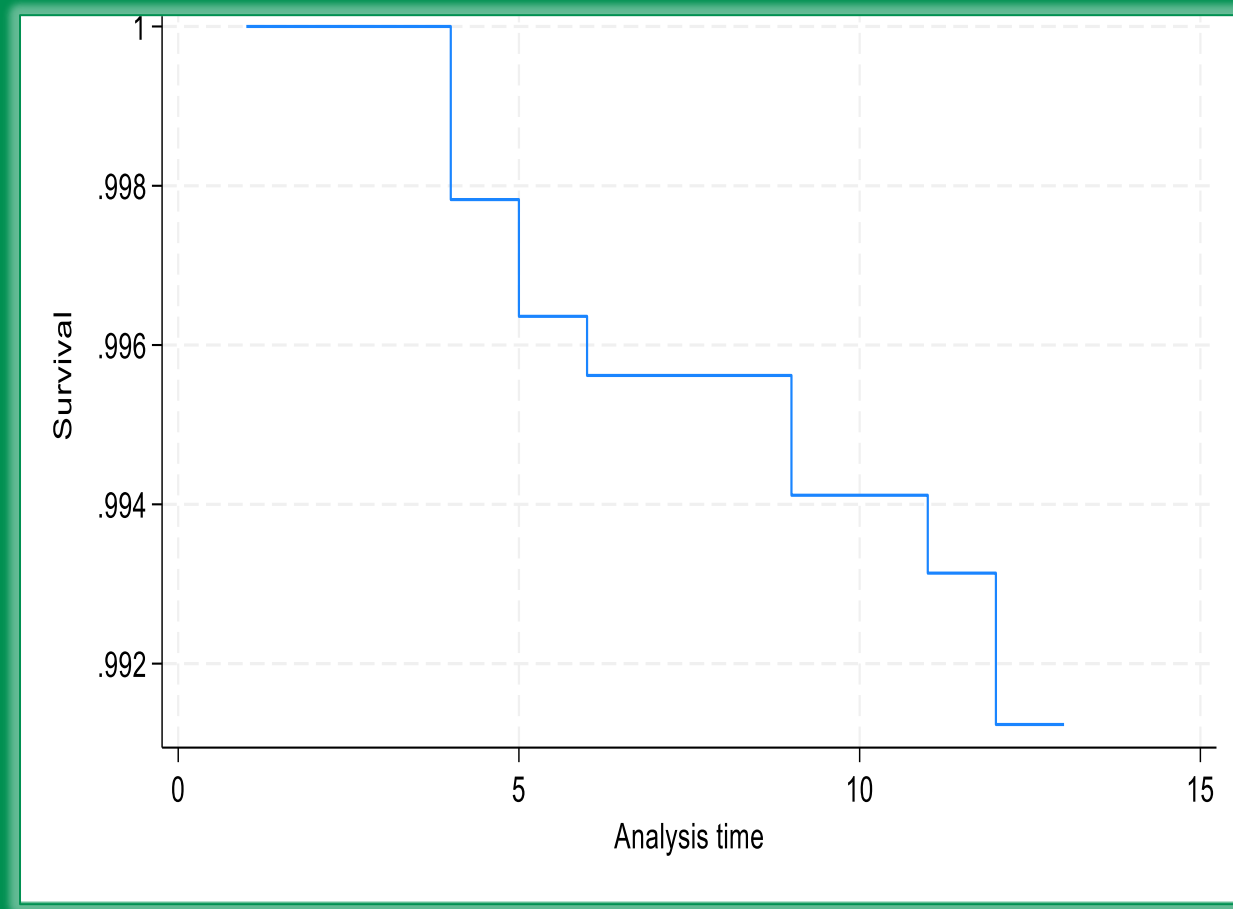


Figure 9: Survival Analysis of Participants at Baseline over time

Table 2. Cox Proportional Hazard and Logistic Regression Models for Cross-Validation of global Cognitive Scores with AD Neuropathy at Autopsy, sequential, multistage

n=813	Unadjusted	Age	Adjusted Medical Conditions	Full Ω
Neuropathy (Prospective and Retrospective)				
Braak Neuropathy				
Advanced §§				
Global Cognitive Score [OR (95 % CI)]	0.95 (.93, .97) ***	0.95(0.93, 0.97) ***	0.95(0.93,0.97) ***	0.94(0.92,0.97) ***
AUC %	78	83	84	89
Cut-off Score	87	99	99	92.5
Aβ Plaques Advanced §§§				
Global Cognitive Score	0.96(0.94,0.98) ***	0.97(0.95,0.99) **	0.97(0.95,0.98) **	0.96 (0.94, 0.98) ***
[OR (95 % CI)]				
AUC %	72	75	77	0.82
Cut-off Score	85	91	85.5	58.5
Neuritic Plaques Moderate to Frequent sparse				
Global Cognitive Score	0.96 (0.95,0.98) ***	0.97 (0.95,0.99) **	0.96 (0.94,0.98) **	0.95 (0.94,0.98) ***
[OR (95 % CI)]				
AUC %	70	76	77	82
Cut-off Score	85	92.5	78.5	109
PET – Retrospective				
Amyloid Positivity PET Retro				
Global Cognitive Score	0.95 (0.94,0.96) ***	0.95 (0.94,0.96) ***	0.95 (0.94,0.96) ***	0.95 (0.93,0.96) ***
[OR (95 % CI)]				
AUC %	74	75	75	76
Cut-off Score	89	90.5	88.5	89
Biomarkers: Cross-sectional				
A β 42 (higher vs Lower) Cx	1.05	1.04	1.04	1.05
Global Cognitive Score	(1.04,1.06) ***	(1.03, 1.06) **	(1.03,1.06)**	(1.04,1.06)**
[OR (95 % CI)]				
AUC %	73	73	73	74
Cut-off Score	89	84.5	98	75.5
Tau				
Global Cognitive Score	0.96 (0.95,0.96) ***	0.96 (0.95,0.97) ***	0.96 (0.95,0.97) **	0.95
[OR (95 % CI)]				
AUC %	73	73	73	76
Cut-off Score	85	88.5	76.5	78.5
pTau				
Global Cognitive Score	0.95 (0.94,0.96)**	0.95 (0.94,0.96) ***	0.95 (0.94,0.96)**	0.95 (0.94,0.96) ***
[OR (95 % CI)]				
AUC %	72	75	75	77
Cut-off Score	87	83.5	88.5	91
Tau/ Aβ 42				
Global Cognitive Score	0.93 (0.92,0.94)**	0.93 (0.92,0.95) ***	0.94 (0.92,0.95) ***	0.93 (0.92,0.95) **
[OR (95 % CI)]				
AUC %	79(87)	80(86.5)	80(97)	80(101)
Cut-off Score	79(87)	80(86.5)	80(97)	80(101)
pTau/ Aβ 42				
Global Cognitive Score	0.95 (0.94,0.96) ***	0.95 (0.94,0.96) ***	0.95 (0.94,0.96) ***	95 (0.94, 0.96) ***
[OR (95 % CI)]				
AUC %	72	75	75	77
Cut-off Score	87	83.5	88.5	91

HR: Hazard Ratio; OR: odd ratio; Ω :adjusted Model; social demographic: baseline age, gender, race, education, family history of dementia" mother had AD, father had AD. Medical conditions. AUC: Area Under Curve, AUCPR: AUC precision.

Conclusion

The findings would provide public health implications of global composite criteria as comprehensive screening tools for assessment of AD and dementia espccially for individuals who were incompatible to proceed for MRI.

Acknowledgement: Thank to ADNI for providing data.