Using Neurodegenerative Disorder Biomarkers to Predict Neurocognitive Impairment in Older Adults

Abstract

Background: Neurodegenerative diseases are characterized by abnormal levels of beta-amyloid and neurofibrillary tangles composed of hyperphosphorylated tau, implicated in synapse loss and neuronal death. As this pathology accumulates, cognitive deficits manifest into a diagnosis of Mild Cognitive Impairment (MCI) or Prodromal Alzheimer's Disease (AD), with certain biomarkers tied with the onset of these symptoms.

Objective: To explore how different AD biomarkers (Ptau, AB42 and APOE ε4) are implicated in Mild Cognitive Impairment and Alzheimer's Disease.

Methods: This is a longitudinal observational study comprising baseline and two yearly follow up visits, collected from 2015 to 2023. 197 older adults (60-90 years old) were enrolled at the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). Cerebral Spinal Fluid (CSF) AD biomarker data (Ptau, AB42, and APOE ε4 allele presence) were collected at baseline, with neurocognitive assessments done at each follow-up visit to measure cognitive decline. Patients were stratified as 1 of 3 groups: Cognitively Normal (CN; n=150); Mild Cognitive Impairment (MCI; n =19); AD dementia (AD; n = 15). We aimed to accurately classify individuals into these groups based on their biomarker levels, with secondary analyses on the impact of age, sex, and education. We did an exploratory data analysis on group biomarker and demographic differences at baseline. We used multinomial logistic regression with LASSO and a confusion matrix to determine the best predictive variable for each group, using CN as the reference group. We used a random forest model regression with class weights, variable importance measures, and a confusion matrix to evaluate which of the two models had the strongest predictive performance.

Results: For the primary analysis, Ptau levels were positively associated with increased log-odds of categorization into the MCI and AD groups by 7.5e-04 and 4.8e-03, respectively. AB42 levels were highest in the CN group, with a negative association of -1.2e-04 and -3.5e-05 log-odds for MCI and AD groups. The presence of the APOE ε4 allele and education level were not

significant predictors of categorization across either group. Older age was a positive predictor for the MCI group, while education and sex were not associated with classification. However, using the random forest model, female sex had high importance for classification as cognitively normal. For the comparative random forests analysis, Ptau was the most important biomarker predictor across all groups and had the highest impact on model accuracy of all variables, followed by AB42.

Conclusions: This study demonstrates that Ptau is a significant predictor of MCI and clinically diagnosed AD, while AB42 may be implicated in predicting cognitive normality. Female sex may be protective against neurocognitive disorders, while older age was a predictor of neurocognitive decline. Future studies should have more balanced group sizes for the predictive model and could benefit from using longitudinal data to better understand the progression of MCI and AD through biomarkers.

Background

Neurodegenerative disease is characterized by abnormal accumulation of the protein fragment beta-amyloid ($A\beta_{1-42}$), and neurofibrillary tangles composed of hyperphosphorylated tau (p-tau), primarily in the medial temporal lobe and neocortical brain regions. Plaque and tangle pathology in these regions is accompanied by synapse loss and neuronal death (i.e., neurodegeneration) (Sharma et al., 2020). Neuropathologic changes begin well before the gradual emergence of obvious cognitive deficits that lead to a diagnosis of dementia (Bateman et al., 2012; Fagan et al., 2007; Price et al., 2009). As AD pathology accumulates, cognitive deficits become apparent on formal testing and subjective complaints increase, but do not necessarily affect daily activities and these conditions are known as mild cognitive impairment and prodromal AD. Increased Aβ and tau on PET imaging is indicative of Alzheimer's disease and predicts the development of dementia. The picture is slightly more complicated in CSF but it is evident that high ratio of CSF tau/$A\beta_{1-42}$ is a good predictor of the development of dementia (Braak et al., 1991; Salmon, 2000). Additionally, Thai et al., 2015 showed a subtle decline over two years in Aβ+ individuals who also carry the ApoE e4 allele and Insel et al., 2019 showed decline in Aβ+ individuals only after four to five years

The delay in the onset of clinical symptoms might be explained by the brain's capacity to compensate for the spreading accumulation of beta-amyloid (Aβ), neurofilament light chain (NfL), apolipoprotein E (*APOE*) and total tau (t-tau) (Twamley et al., 2006, Blennow K (2021). As a result, subtle alterations in cognition occurring in a preclinical stage of the disease may not be captured to assess dementia risk. Beginning in this preclinical stage, elevated levels of tau and low levels of Aβ42 in cerebrospinal fluid reflect the accumulation of AD pathology in the brain (Galasko et al., 1998). Nevertheless, levels of AD pathology alone cannot predict when, or whether, an individual will develop dementia. Several studies have reported an increase in plasma Aβ, t-tau, and NfL with aging (de Wolf F, Ghanbari M 2020, Syrjanen JA 2022). An increase in NfL might be attributed to cerebrovascular lesions and neuro injuries (Dong Y, 2023). CSF biomarkers vary demographically and underscore the clinical spectrum of memory decline. Identifying additional preclinical and prodromal markers of cognitive decline is a crucial step in affording clinical therapies for individuals in the earliest stages of the disease. Therefore, our study explores whether certain AD biomarker levels may predict the onset of mild cognitive impaired or preclinical AD.

In this study, we aim to predict based on Alzheimer's Disease (AD) biomarker levels whether people are more likely to become mildly cognitively impaired or diagnosed with clinical AD.

Methods

Study Design and Data Collection:

The data for this observational study with predictive modeling was collected from 2015 to 2023. 197 older adults (60-90 years old) were enrolled in a longitudinal observational study at the UCSD Shiley-Marcos Alzheimer's Disease Research Center (ADRC). Individuals were characterized into 1 of 3 groups at baseline: Cognitively Normal (CN; $n = 150$); Mild Cognitive Impairment (MCI; $n = 19$); or AD dementia (AD; $n = 15$). Biomarker sample data were collected once per patient at baseline, and two follow up visits were conducted a year apart to determine cognitive decline via neuropsychological testing.

Inclusion: Adult patients at 60 years or older. Diagnoses were made based on clinical interviews and neuropsychological test scores, blind to CSF AD biomarker data. Diagnoses were based on

the NIA-Alzheimer's Association 2011 guidelines and cerebrospinal fluid (CSF) AD biomarker data collection was done blind.

Exclusion: History or evidence of neurological and/or psychiatric conditions that might interfere with cognitive abilities (including depression); uncompensated systemic diseases; use of medications at doses that might interfere with cognitive performance, and that had been introduced or whose dose had been modified in the past two weeks; history of language deficit due to brain injury (stroke, head trauma, tumors, or other neurological diseases); history of learning disabilities (dyslexia, dysgraphia, or successive grade repetition).

Outcomes:

The primary endpoint of this study is to accurately predict whether participants will classify as: Cognitively Normal (Group 1: CN); diagnosed with Mild Cognitive Impairment (Group 2: MCI); and diagnosed with Alzheimer's Disease (Group 3: AD).

The covariates of interest are AD biomarker levels (APOE, AB42 and Ptau), with secondary analyses that adjust for age, sex, and education.

Statistical analysis

The statistical analysis for this study consisted of three main parts: exploratory data analysis, multinomial logistic regression with LASSO, and random forest modeling. We began our analysis by investigating the distribution and relationship of the key variables in our study: APOE allele presence, Ptau levels, AB42 levels, education, age, and sex. This stage of analysis utilized graphical representations to understand the data structure and identify patterns for further analysis. We then applied a multinomial logistic regression model that included LASSO for feature selection and regularization. This model was trained using 10 fold cross validation at set seed 858 for reproducibility. In this stage, we evaluated how each variable influenced the probability of a patient's classification into one of the four cognitive groups. The performance of this model was assessed using a confusion matrix which shows a detailed view of the factors that go into model validation. The final step of our analysis includes applying the random forest modeling algorithm as a comparison model to understand which of the two models have better predictive performance. In this model we have used 500 trees to capture the interaction between

the variables. To handle the disbalance in testing data group sizes we have set the class weight parameters. Similarly to the logistic regression stage we evaluated this model using a confusion matrix to analyze the overall performance of the model. The usage of the random forest model allowed us to additionally rank the variables based on their impact on the predictive power of the model by interpreting important plots.

Results

Demographics

The average number of years of education was 17, equivalent to a Bachelor's degree, which remained relatively stable across all four groups. The average age at baseline was around 74 years old, with the age distribution approximately normal across all three groups (CN, MCI, AD). The distribution of males and females across all three groups were relatively even, although there were more females than males in the cognitive normal (CN) group (**Figure 1, Table 1**).

Biomarker Measures of Alzheimer's Disease

Biomarkers for Alzheimer's Disease measured at baseline included APOE genotype, Ptau, and AB42. In the CN group (Group 1), a greater proportion of the patients do not have the APOE allele. In the MCI and AD groups (Groups 2 and 3), a slightly higher proportion of patients have the APOE allele (**Figure 2**). For Ptau, both MCI and AD participants have similarly higher levels compared to CN patients, however, AD diagnosed patients have the highest levels of Ptau. AB42 levels are highest in patients categorized as cognitively normal (CN), with MCI and AD groups demonstrating similarly low levels of AB42 compared to the CN group (**Figure 2**).

Multinomial Logistic Regression + Confusion Matrix

Using multinomial logistic regression with LASSO to train the model to classify a patient into one of the groups based on their AD biomarker levels, education, age, and sex, a set of coefficients best fit for each group was generated with Group 1 (CN) as the reference group (**Figure 3, Table 2**).

For Group 2 (MCI), there was a -0.54 log-odds chance of categorization, with older age at baseline and higher Ptau levels positively associated with increases in log-odds chance of being

categorized by 2.22e-05 and 7.55e-04, respectively. Higher AB42 levels were associated with decreases in log-odds chance of categorization by -1.16e-04.

For Group 3 (AD), there was a -1.14 log-odds chance of categorization. Higher Ptau levels were associated with a 4.85e-03 log-odds increase in categorization as diagnosed with Alzheimer's Disease. Higher AB42 levels were negatively associated with chances of categorization by a log-odds of -3.47e-05.

A confusion matrix gave overall 82% accuracy to the multinomial regression prediction model (**Table 3**). Group 1 had a sensitivity of 1.0 and specificity of 0.029, with a balanced accuracy of 51%. Group 2 had a sensitivity of 0.0 and specificity of 1.0, with a balanced accuracy of 50%. Group 3 had a sensitivity of 0.067 and specificity of 1.0, with a balanced accuracy of 53%.

Random Forest + Confusion Matrix

Using Random Forest as a comparative model to classify a patient into one of the groups based on their AD biomarker levels, education, age, and sex, with coefficients indicating importance of each variable for predicting group categorization. (**Figure 4, Table 4**).

Of the biomarkers, Ptau has extremely high values across all groups (CN: 13.6, MCI: 7.9, AD: 11.0), indicating highest predictive importance of all variables, particularly for Group 1. AB42 has the highest importance in Group 3 (AD: 2.8), followed by Group 2 (2.3), then Group 1 (CN: 1.7). APOE ε4 carrier status had positive importance for CN (0.78) and MCI (1.4) groups, but strong negative importance for the AD group (-3.1).

Of the demographic variables, age has high positive values for the AD and CN groups by 2.9 and 2.7, respectively, with a slight positive value for the MCI group of 0.5. Sex has a slightly high predictive value for Group 1 (CN: 1.1), a minor negative value for Group 2 (-0.9), and slight positive impact on Group 3 (AD: 0.3). Education is slightly important for Group 1 (CN: 1.5), but negatively impacts prediction for Groups 2 and 3 by -2.5 and -1.2, respectively.

Mean Decrease Accuracy (MDA) demonstrates how much a model's accuracy decreases when a variable is removed, with higher values indicating more importance. Ptau levels have the highest MDA (17.2), followed by age at baseline (3.64), and AB42 levels (3.60), indicating they are the most critical variables to the model.

A confusion matrix using the Random Forest model gave an overall accuracy of 73% to the categorical prediction model. Group 1 (CN) had a sensitivity of 0.75 and specificity of 1.0, with a balanced accuracy of 88%. Group 2 (MCI) had a sensitivity of 0.0 and specificity of 0.83, with a balanced accuracy of 42%. Group 3 (AD) had no value for sensitivity, but a specificity of 0.89.

Discussion

Higher AB42 levels in CSF were visually associated with cognitive normality (Group 1, CN) and negatively associated with MCI and AD, based on the multinomial regression model (Figure 2, Table 2). AB is a main component that contributes to amyloid plaque formation. Previous evidence revealed that lower levels of AB42 in cerebrospinal fluid and increased uptake of AB accumulation in the brain is implicated in risk for AD pathology (Cao et al., 2010). Therefore it is important to detect the AB accumulation in the brain at an early stage. The importance of AB42 in predicting groups was demonstrated in the Random Forests model, as well, particularly for patients categorized in the AD group. With a strong positive MDA and large positive coefficient values across all three groups, AB42 seems to be a critical biomarker for protection against and prediction of cognitive decline.

The presence of the APOE ε4 carrier gene was visually seen in both MCI (Group 2) and AD (Group 3) patients at baseline; however, APOE ε4 carrier status was not a significant predictor of categorization in either group using multinomial regression. Nevertheless, several studies revealed that presence of APOE ε4 may increase the risk of Alzheimer's disease (Bryant, 2021). In addition, Luke et al., revealed APOE ε4 carrier status has age dependent effects that can be the strongest predictor to detect the MCI and AD progression in longitudinal study (Luke et al., 2016). In the Random Forests model, APOE ε4 carrier status had a slightly positive importance for predicting the MCI group, however, its negative MDA indicates that removing APOE actually increases the accuracy of the model and thus might not be a great predictor of cognitive decline. Thus, both models suggest that APOE ε4 carrier status may not be a significant predictor

of MCI or AD, however, the lack of predictive value in these models may be due to the small sample sizes in the neurodegenerative disorder groups (MCI, AD).

Higher Ptau levels were visually associated with both MCI and AD diagnosis. Several studies revealed that people with MCI and AD have overexpression of tau protein in CSF leads to destabilization of protein levels in the brain. Identifying tau protein level in CSF in the early stage, could be helpful in differentiating MCI and AD people (Shekhar et al., 2016). This was statistically supported with increased chances of classification in MCI and AD groups. For the neurocognitive impairment groups, Ptau seems more important in predicting AD over MCI, based on the Random Forest Analysis, and is associated with slightly higher odds of classification in the AD group over the MCI group. The Random Forest model demonstrated the extreme predictive power of Ptau on both the accuracy of the model, with the highest MDA of 17.2, and on the importance of the variable in categorization of all three groups, with the highest importance values of all variables. This suggests that Ptau is the most important predictor for all groups.

Education was not a significant predictor of categorization for any of the groups in the multinomial regression analyses, and was not important in the Random Forests model for accuracy or predictive power. Female sex had the most importance for predicting group 1 in the random forest model, indicating a trend toward better cognitive outcomes in females. Older age was a slight negative predictor of cognitive normality and positive predictor of MCI diagnosis using multinomial regression, as well as an important predictor for both groups in the random forest model, which follows considering older age is associated with more cognitive dysfunction.

Overall, this study confirmed that certain AD biomarkers (AB42 and ptau) are significant predictors of Mild Cognitive Impairment and clinically diagnosed Alzheimer's Disease.

The multinomial regression predictive model performed relatively poorly for all three groups, which could be due to the relatively small populations in groups 2 and 3, leading to less accurate predictions. However, the multinomial regression model still seems to perform better than the random forest model, which has slightly lower overall accuracy and very little to no sensitivity

for both MCI and AD groups. Nevertheless, both models seem to point to Ptau as a significant predictor for cognitive decline and AB42 for cognitive normality.

Limitations:

The number of MCI and AD participants is relatively small, observational study design, limiting the number of predictors, and thus the predictive power, of both models.

Conclusions/Implications:

The predictive models we have used are relatively weak for predicting whether patients will fall into cognitively normal or impaired groups based on AD biomarker data. This model may benefit in the future from more balanced group sizes to improve predictions for MCI and AD categories. However, the findings still align with scientific understanding around the importance of AD biomarkers in clinical diagnosis of Mild Cognitive Impairment and Alzheimer's Disease. Ptau seems to be the most relevant biomarker for the successful identification of patients with MCI or AD, while AB42 shows a more protective effect against cognitive decline and is a relevant predictor of cognitive normality. Given its strong predictive value implicated in both models, Ptau should be a focal point in predictive modeling and risk assessment for AD and MCI in future studies.

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Tables and Figures

Figure 1: **Sex, Age, and Education Distributions by Group at baseline**

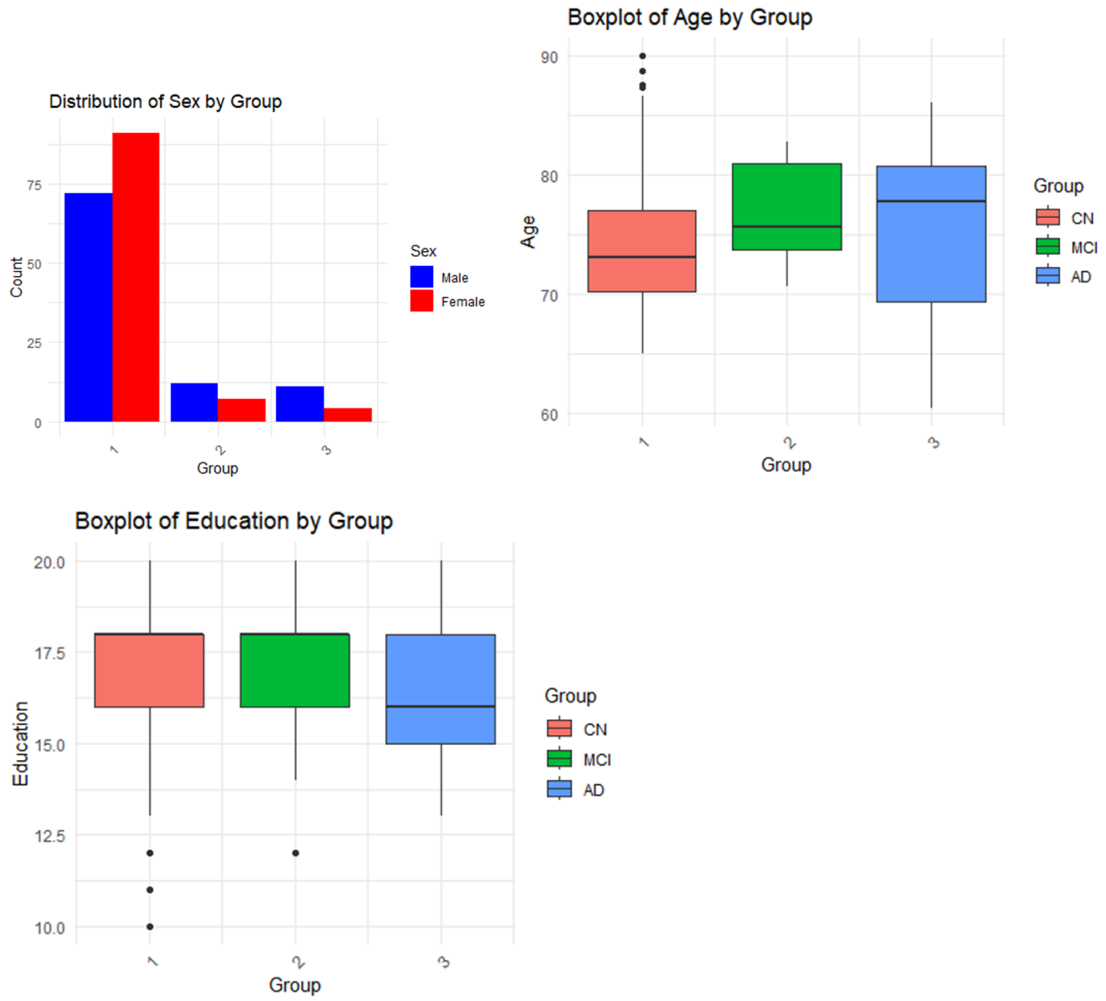


Figure 2: **AD Biomarker levels across groups at baseline**

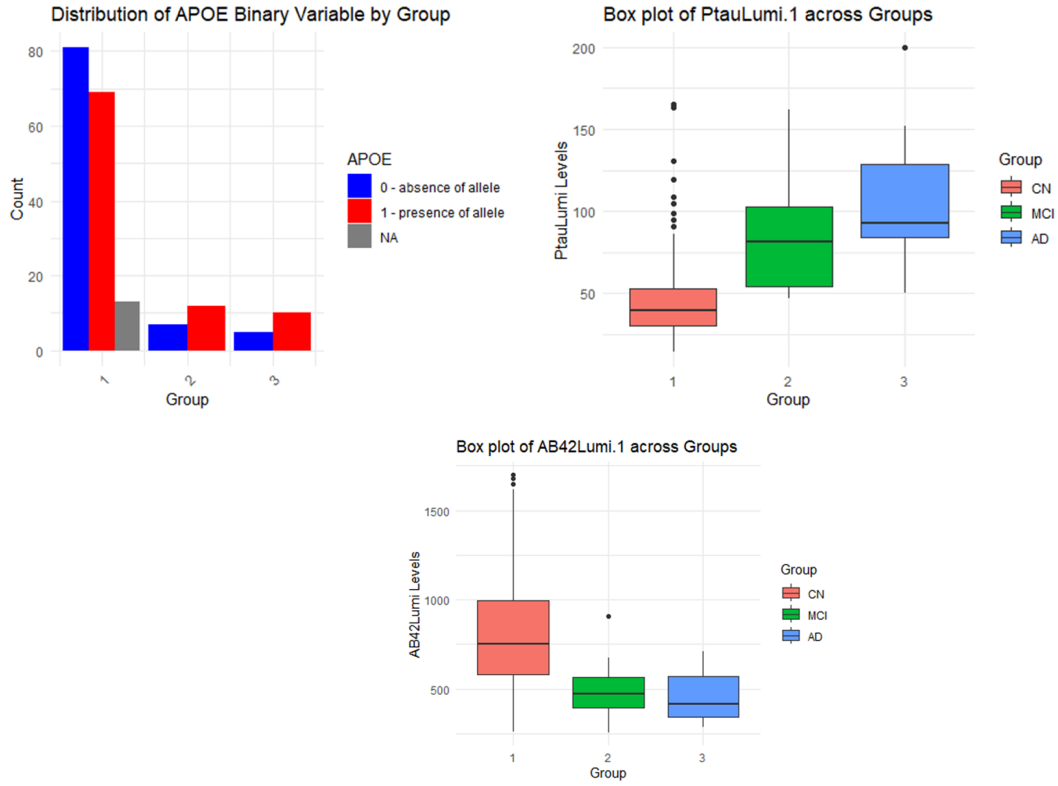
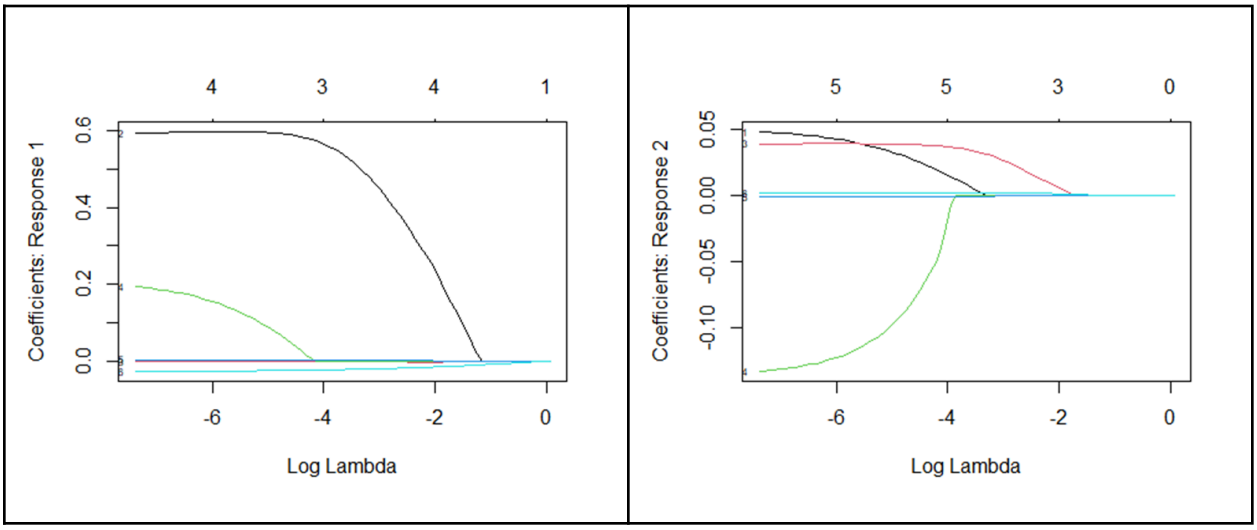


Figure 3: Multinomial Logistic Regression w/ LASSO Coefficient Outputs



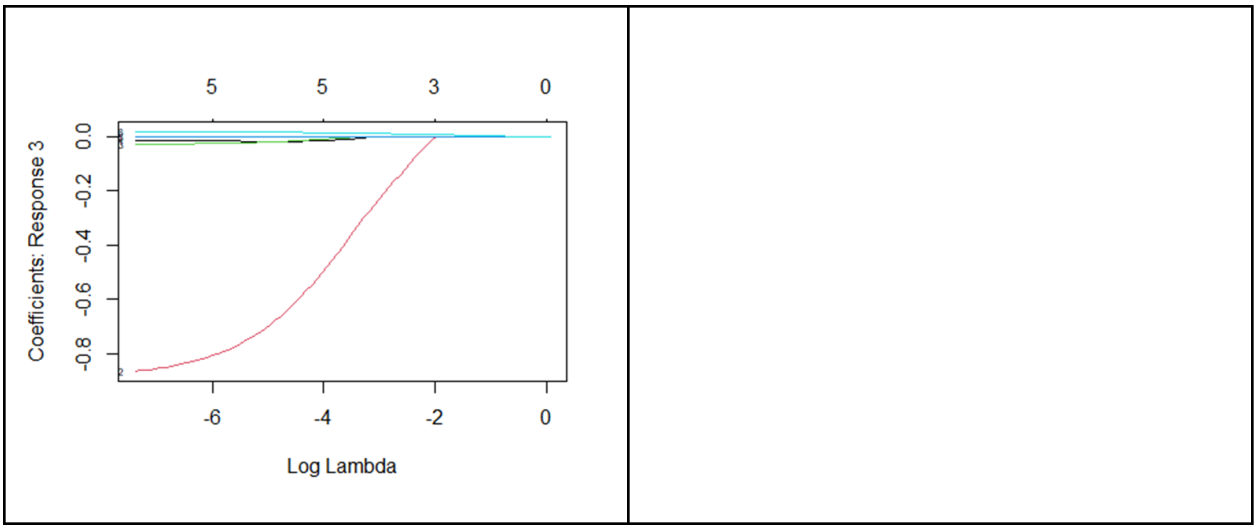


Figure 4: Random Forest MDA and MDG

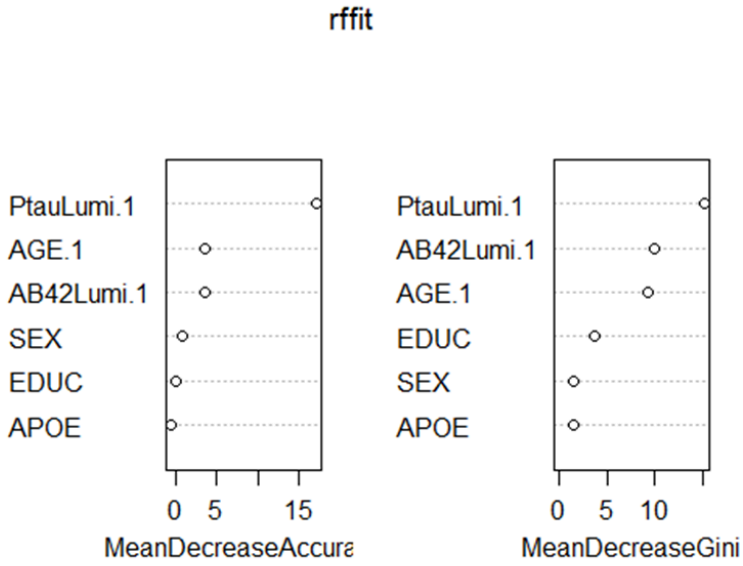


Table 1: Demographics

Characteristic	**1**, N = 150[1]	**2**, N = 19[1]	**3**, N = 15[1]
AGE.1			
<60	0 (0%)	0 (0%)	0 (0%)
60-65	1 (0.7%)	0 (0%)	3 (20%)
66-70	36 (24%)	0 (0%)	1 (6.7%)
71-75	60 (40%)	7 (37%)	2 (13%)
76+	53 (35%)	12 (63%)	9 (60%)
EDUC			
10	1 (0.7%)	0 (0%)	0 (0%)
11	1 (0.7%)	0 (0%)	0 (0%)
12	8 (5.3%)	1 (5.3%)	0 (0%)
13	5 (3.3%)	0 (0%)	2 (13%)
14	5 (3.3%)	2 (11%)	2 (13%)
15	4 (2.7%)	1 (5.3%)	0 (0%)
16	37 (25%)	3 (16%)	5 (33%)
17	6 (4.0%)	1 (5.3%)	0 (0%)
18	52 (35%)	7 (37%)	3 (20%)
19	2 (1.3%)	1 (5.3%)	0 (0%)
20	29 (19%)	3 (16%)	3 (20%)
SEX			
Male	67 (45%)	12 (63%)	11 (73%)
Female	83 (55%)	7 (37%)	4 (27%)

[1] n (%)

Table 2: Multinomial Logistic Regression w/ LASSO

	Intercepts	Education	Sex	Age	APOE	AB42	Ptau
MCI	-0.54	.	.	2.22e-05	.	-1.16e-04	7.55e-04
AD	-1.14	.	.	.	.	-3.47e-05	4.85e-03

The reference category is: Group 1 CN

Table 3: Multinomial Confusion Matrix

	Group 1 (CN)	Group 2 (MCI)	Group 3 (AD)
Sensitivity	1.0	0.00	.066
Specificity	0.03	1.00	1.00
Balanced Accuracy	0.51	0.50	0.53

Table 4: Random Forest Variable Importance

	Group 1 (CN)	Group 2 (MCI)	Group 3 (AD)	Mean Decrease Accuracy
Education	1.466	-2.537	-1.171	-0.096
Sex2 (Female)	1.088	-0.938	0.288	0.711
Age	2.710	0.499	2.910	3.64
APOE	0.776	1.417	-3.100	-0.54
AB42	1.679	2.293	2.846	3.60
Ptau	13.555	7.950	10.973	17.17

Table 5: Random Forest Confusion Matrix

	Group 1 (CN)	**Group 2 (MCI)**	**Group 3 (AD)**
Sensitivity	0.75	0.00	NA
Specificity	1.00	0.83	0.89
Balanced Accuracy	.875	0.42	NA