Introduction

The primary aim of this project is to measure trajectories of memory and cognitive loss in individuals at risk for developing mild cognitive impairment (MCI) or dementia. Specifically, we want to see the how the trajectories differ for non-dementia individuals compared to individuals diagnosed with dementia or MCI. We also want to see if there is a period before diagnosis that the memory and cognitive loss trajectory changes in the dementia individuals.

For this study, 216 healthy, community dwelling, cognitively intact elders were enrolled and examined annually for an average of 15.7 years. Age, gender, and SES were recorded on each individual. The category fluency for animals test (Animal Score) was performed during each examination to measure memory and cognitive abilities. Individuals who had at least two consecutive clinical Dementia Ratings of 0.5 were categorized as having developed MCI.

Methods

RStudio version 3.4.2 was used for all statistical analysis.

Initially, 216 individuals were enrolled in the study. A priori, it was decided that only individuals that had 3 or more time points recorded would be involved in analysis. Therefore, only 187 individuals were included in the analysis.

Categorical data was presented using percents and group sizes. Numerical variables were presented using means and standard deviations.

Based on likelihood maximization over 0.1 day intervals across the period prior to dementia diagnosis, a change point of -3.9 was identified. This value represents a change in trajectory of the animal score over time. On average, at 3.9 years prior to dementia diagnosis, the relationship between animal score and time changed. In order to find a confidence interval around the change point, bootstrapping

randomly sampled the data 1000 times with replacement and found a change point associated with each sampling. Then, the 2.5 and 97.5 quantiles were calculated to get the 95% confidence interval around the change point estimate.

Age difference was calculated by subtracting age of onset from the age for each individual at each time point. If an individual didn't develop dementia, the age difference variable was zero. The variable involving the change point was added to the model by comparing the estimated change point to the age difference. If the age difference was greater than the change point value, than the value for the change point was age difference minus the change point. If the change point was greater than the age difference, than the value for the change point variable was zero.

A mixed model with a random intercept for each individual and an AR(1) covariance structure on time points was run with animal score as the outcome. Adjusted age, dementia status, the interaction between adjusted age and dementia status, SES, gender, and the change point variable. The age variable was adjusted by taking the original age and subtracting the minimum age of the study (59 years). This allowed for the intercept to have a more interpretable value. Gender and Dementia status were treated as categorical variables, with non-dementia men being the reference group.

Proper standard error estimates for each coefficient were generated from the same bootstrapping as mentioned above. The above mixed model was ran in the bootstrap, to get estimates for each coefficient. The standard deviations were then calculated across the 1000 estimates for each coefficient and used as their corresponding standard errors. These standard errors and the coefficient estimates from the original model were used to test the statistically significance of each coefficient.

Results

Table One shows the demographics for the entire cohort (column 1), those diagnosed with dementia (column 2), and those not diagnosed with dementia (column 3). There were on average about 16 years of observations for each individual. There were slightly more females involved in the study than males. Nearly two-thirds of individuals diagnosed with dementia were female. The average SES was

about 49 for demented and non-demented individuals. The average age for demented individuals was higher than that of non-demented individuals (84.8 vs. 77.72 year old respectively). The age of onset of dementia was 90.7.

The change point identified was 3.9 years prior to diagnosis, with a 95% confidence interval of -5.30 to -2.60 years.

Table Two shows the results of the mixed modelling. The intercept represents the predicted animal score for a male without dementia at age 59. There was not a significant difference in trajectories between men and women (p = 0.0916), when controlling for the other variables. There was also not a significant difference in average animal score for those with dementia and those without (p = 0.0916). Finally, there was not a significant difference in the relationship between age and animal score for those with dementia and those without (p = 0.9486) prior to the change point. SES had a statistically significant impact on animal score (p = 0.0314). For everyone 1 unit increase in SES, there was a 0.039 point increase in animal score on average (95% CI: 0.003 to 0.074). There was also a significant relationship between age and animal score (p < 0.0001). For everyone 1 year increase in age, there is on average a 0.183 point decrease in animal score (95% CI: -0.232 to -0.134). This is the estimated slope for all non-dementia patients and dementia patients approximately 4+ years prior to their diagnosis. Finally, the change point was also significant (p < 0.0001). This value shows how the relationship between age and animal score changes for those diagnosed with dementia less than 4 years prior to their diagnoses and onward (after the change point). For individuals diagnosed with dementia after four years prior to their diagnosis, a 1 year increase in age is now associated with a 1.112 point decrease on average in animal score.

Graph one visually shows the relationship between animal score and age for non-dementia individuals (blue lines) and those diagnosed with dementia (yellow lines). Each line represents a single individual's animal score as an individual ages.

Graph two visually shows the relationship between animal score and time before diagnosis for individuals diagnosed with dementia. The red line denotes when the dementia diagnoses was made. The blue dashed line denotes the change point estimate.

Conclusions

The cognitive loss trajectory was the same for dementia and non-dementia individuals up to four years prior to dementia diagnoses. At this point, dementia individuals developed a more negative relationship between age and animal score. A one year increase in age was associated with a great drop in animal score than those who have not been diagnosed with dementia (-1.112 vs. -0.183 respectively). It appears that four years before diagnosis is a critical time for those developing cognitive loss. Using these results, medical professionals may be able to be identified dementia in individuals sooner. An earlier diagnosis would allow for individuals to get treatment sooner and could possibly contribute to better long term outcomes.

It is important for investigators to question the clinical significance of the SES estimate. It is associated with a very small increase in animal score, and it is possible that this change is not clinically meaningful.

This study had several limitations. First, 29 individuals had to be dropped from analysis due to missingness, nearly 15% of the entire cohort. Second, the change point had a fairly large confidence interval. It could be that the change point occurred earlier or later than the value used in the model. Finally, data on more dementia patients should be included to see if this estimated change point and the relationship of age and animal score holds.

GitHub Link

Full Code to generate the above analysis can be found at:

https://github.com/BIOS6623-UCD/bios6623-elcotton

Tables and Graphs

Table One: Demographics

Variable	All Patients	Dementia Diagnosis	No Dementia Diagnosis
N	216	71	145
# Obs (mean ± sd)	15.67 ± 8.42	18.73 ± 6.18	14.17 ± 8.97
Sex (n (%))			
Male	42.13 (91)	33.8 (24)	46.21 (67)
Female	57.87 (125)	66.2 (47)	53.79 (78)
SES-Baseline (mean ± sd)	49.1 ± 11.54 (NA = 1)	49.01 ± 12.89	49.15 ± 10.86
Age-Baseline (mean ± sd)	80.05 ± 9.22	84.8 ± 6.07	77.72 ± 9.62
Age at onset (mean ± sd)	90.7 ± 4.93 (NA = 145)	90.7 ± 4.93	NA

Table Two: Model Results

Variable	Estimate	SE	95% CI	P-value
Intercept	24.59	1.3593	(21.926,27.255)	<0.0001
Age	-0.183	0.0251	(-0.232,-0.134)	<0.0001
Change Point	-0.929	0.1503	(-1.223,-0.634)	<0.0001
Gender	-0.562	0.4649	(-1.473,0.349)	0.2269
SES	0.039	0.0181	(0.003,0.074)	0.0314
Dementia	-4.348	2.5773	(-9.4,0.703)	0.0916
Interaction (Dementia and Age)	0.005	0.0816	(-0.155,0.165)	0.9486

Graph 1: Animal Score over time
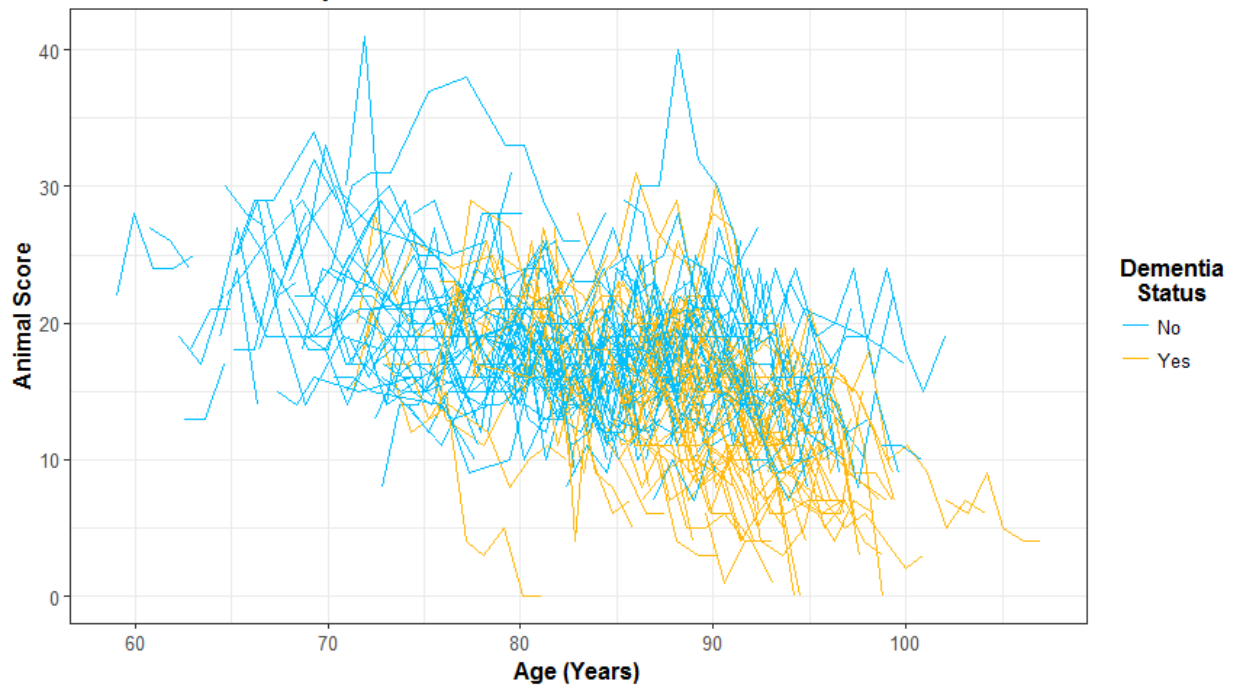
Graph 2: Animal Score over time for Dementia Patients