Detecting Early Alzheimer's Using Longitudinal Data

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Outline

- Introduction
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- Objectives
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- Conclusion

Introduction

- Dementia
  - Decline in memory, reasoning or other thinking skills.
- Alzheimer's
  - Specific brain disease.
  - Affects memory, thinking and behavior.
  - Symptoms eventually grow severe enough to interfere with daily tasks.

Introduction

- While treatments are available to lessen the symptoms, there is no cure currently available.
- Brain Imaging via magnetic resonance imaging (MRI), is used for evaluation of patients with suspected AD.

Dataset Description

- 150 randomly selected subjects aged 60 to 96.

Response Variable

Clinical Dementia Rating

- 0 – No Dementia
- 1 – Very Mild Dementia
- 2 – Mild Dementia
- 3 – Moderate Dementia
- 4 – Severe Dementia

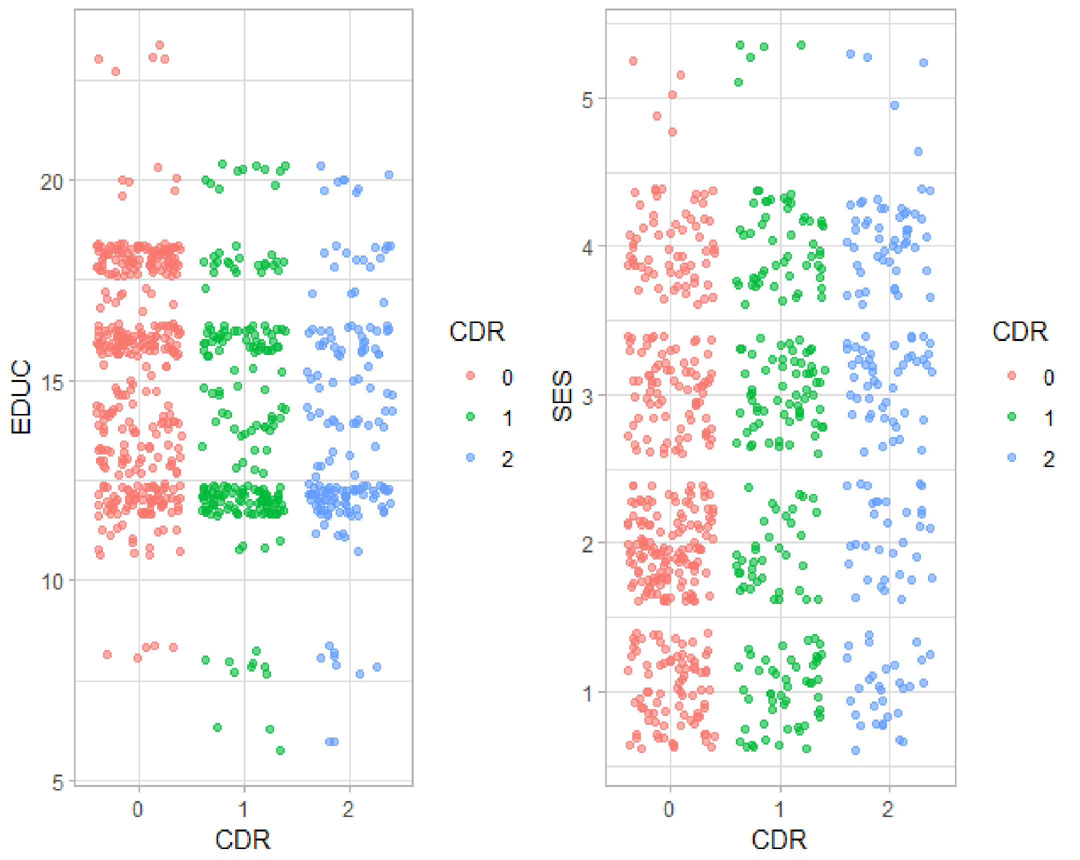
Dataset Description

- **Covariates**
  - Time
  - Gender
  - Age
  - Years of Education
  - Socioeconomic Status
  - Mini Mental State Examination (MMSE)
  - Estimated Total Intracranial Volume (eTIV)
  - Normalize Whole Brain Volume (nWBV)

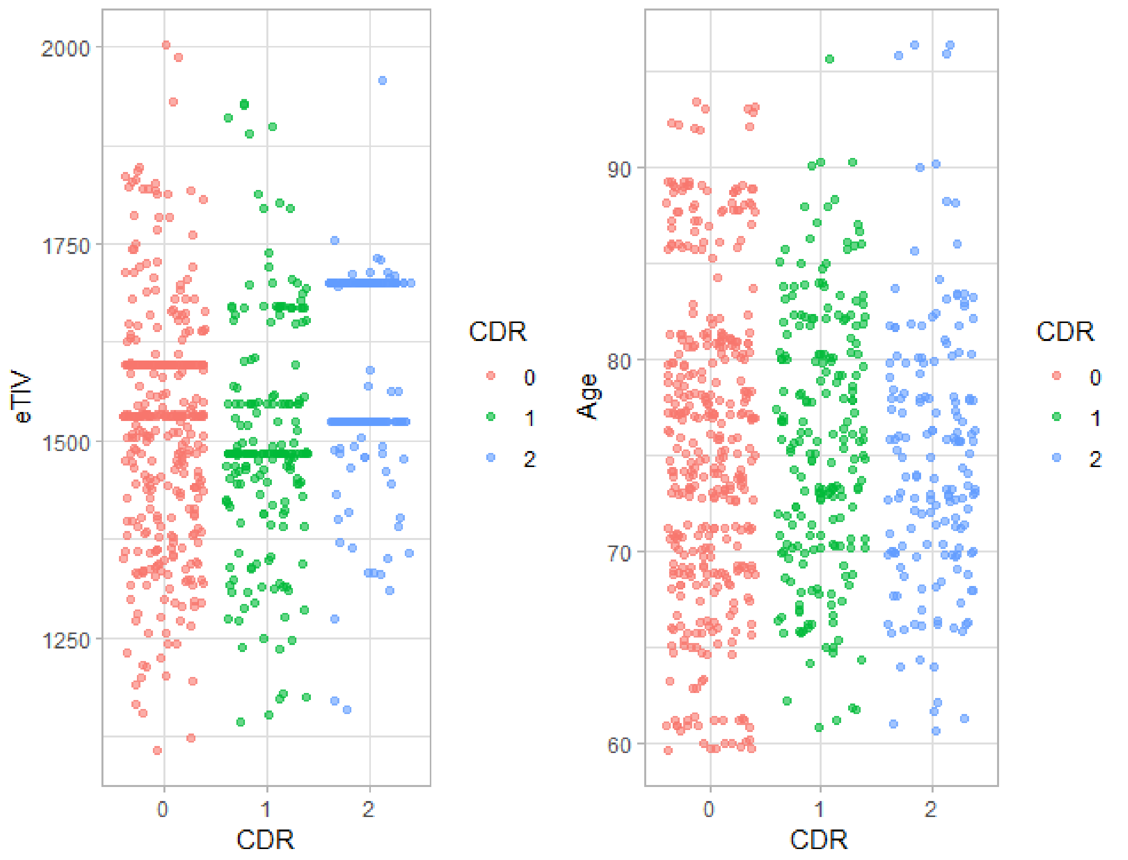
Objective of the Study

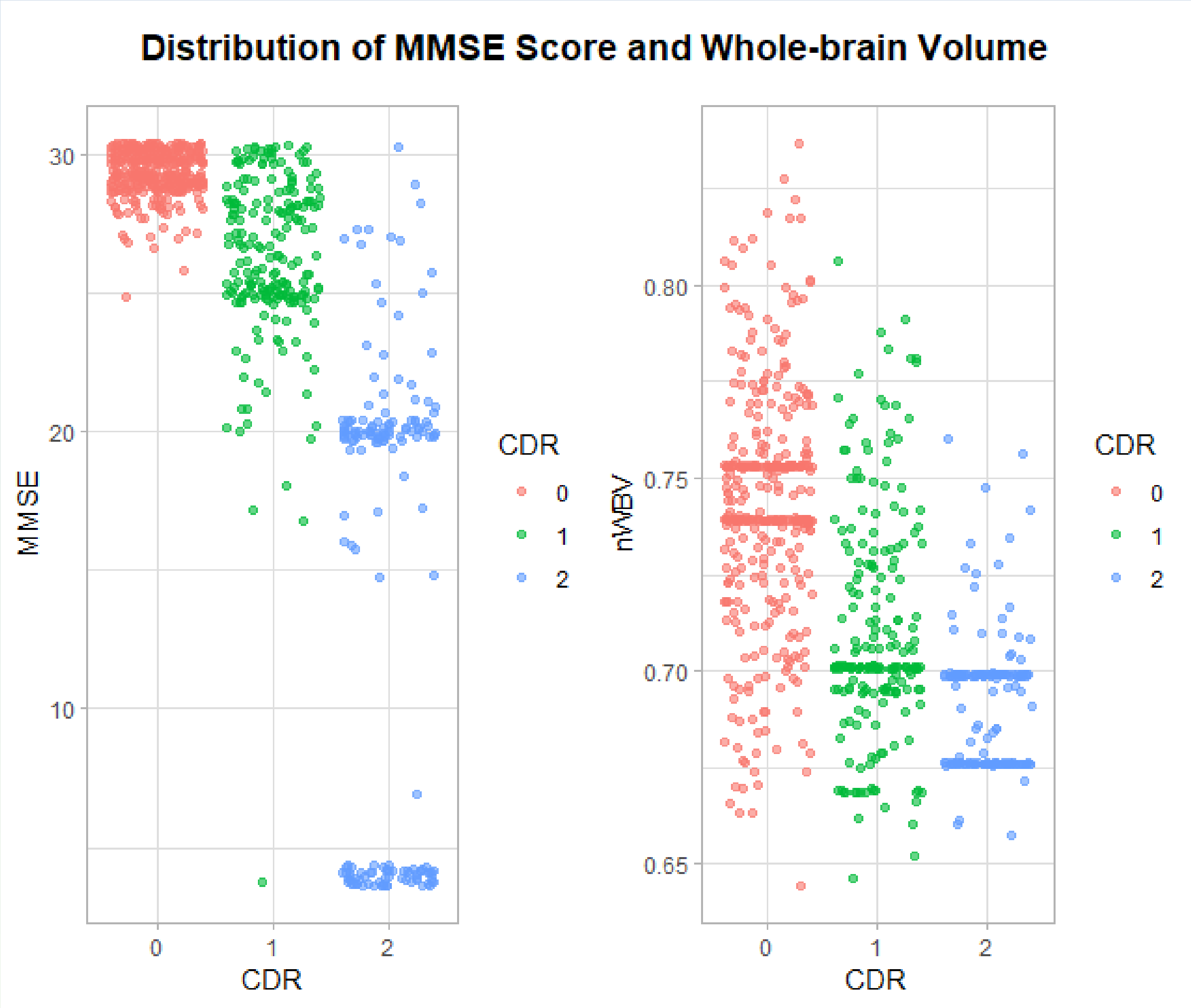
- Implementing a Marginal Ordinal Regression Model
- Implementing a Generalized Linear Mixed Effect Model for an Ordinal Response
- Assess changes in the odds of a more favorable response over the duration of the study
- Determining which covariates have a significant effect on CDR

Distribution of Education and Social Economic Status



Distribution of Total Intracranial Volume and Age




Distribution of MMSE Score and Whole-brain Volume
MMSE
30
20
10
0
1
2
CDR
CDR
0
1
2
nWBV
0.80
0.75
0.70
0.65
0
1
2
CDR
CDR
0
1
2

Ordinal Model Without Covariates

- Analysis of Maximum Likelihood Estimates

Analysis of Maximum Likelihood Estimates						
Parameter		**DF**	**Estimate**	**Standard Error**	**Wald Chi-Square**	**Pr > ChiSq**
Intercept	**2**	1	-1.2579	0.0880	204.5319	<.0001
Intercept	**1**	1	-0.00533	0.0730	0.0053	0.9418

- Intercept 2 = -1.2579 = logit of response in category 2
- Intercept 1 = -0.0053 = logit of response in category 1 & 2

Probability of Responses

- Probability of response in category 2 (CDR = 2):

$$\frac{1}{\left[1+\exp\left(-(-1.2579)\right)\right]} = 0.2213$$

- Probability of response in category 1 & 2 (CDR = 1 & 2):

$$\frac{1}{\left[1+\exp\left(-(-0.0053)\right)\right]} = 0.4987$$

- Probability (CDR = 0): 376/750
- Probability (CDR = 1): 208/750
- Probability (CDR = 2): 166/750

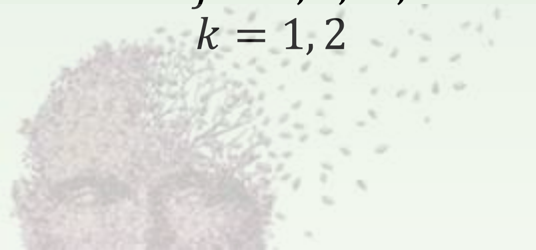
Marginal Ordinal Regression Model

Analyzes the relationship between the response variable and covariates without taking into account the between subject heterogeneity.

Let Y_{ij} denote the ordinal response for the i^{th} subject at the j^{th} occasion with K categories

$$log\left\{\frac{P(Y_{ij} \leq k)}{P(Y_{ij} > k)}\right\}$$
$$= \alpha_k + \beta_1(time)_{ij} + \beta_2(Age)_i + \beta_3(Gender)_i + \beta_4(MMSE)_{ij} + \beta_5(eTIV)_{ij} + \beta_6(nWBV)_{ij}$$
$$+ \beta_7(time)_{ij} * (MMSE)_{ij} + \beta_8(time)_{ij} * (nWBV)_{ij}$$

$i = 1, 2, \dots, 150$
$j = 1, 2, \dots, 5$
$k = 1, 2$



Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept1		-27.2082	5.4584	-37.9064	-16.5099	-4.98	<.0001
Intercept2		-22.4017	5.3760	-32.9385	-11.8649	-4.17	<.0001
time		-14.5014	2.2537	-18.9186	-10.0842	-6.43	<.0001
Age		0.0385	0.0202	-0.0012	0.0781	1.90	0.0574
Gender	F	0.5647	0.2923	-0.0082	1.1375	1.93	0.0534
Gender	M	0.0000	0.0000	0.0000	0.0000	.	.
MMSE		0.7087	0.1068	0.4994	0.9181	6.63	<.0001
eTIV		0.0014	0.0011	-0.0008	0.0035	1.23	0.2176
nWBV		3.1034	5.4013	-7.4829	13.6897	0.57	0.5656
time*MMSE		0.0232	0.0570	-0.0885	0.1349	0.41	0.6840
time*nWBV		19.2936	2.0004	15.3728	23.2143	9.64	<.0001

$$log\left\{\frac{P(Y_{ij} \leq k)}{P(Y_{ij} > k)}\right\} = -27.2082 - 14.5014time_{ij} + 0.0385Age_i + 0.5647Gender_i + 07087MMSE_{ij} + 0.0014eTIV_{ij} + 3.1034nWBV_{ij} + 0.0232time_{ij} * MMSE_{ij} + 19.2936time_{ij} * nWBV_{ij}$$

$$log\left\{\frac{P(Y_{ij} \leq k)}{P(Y_{ij} > k)}\right\} = -22.4017 - 14.5014time_{ij} + 0.0385Age_i + 0.5647Gender_i + 07087MMSE_{ij} + 0.0014eTIV_{ij} + 3.1034nWBV_{ij} + 0.0232time_{ij} * MMSE_{ij} + 19.2936time_{ij} * nWBV_{ij}$$

- Relative to baseline, the odds of a more favorable response at the end of the study is approximately zero ($e^{-14.5014*5}$).
- The odds of clinical dementia rating is greater among the female subjects ($e^{0.5647} = 1.76$) compared the male subjects
- For each one unit increase in MMSE, cumulative log odds of clinical dementia rating change by 0.7087, while holding other variables constant

Generalized Linear Mixed Model for an Ordinal Response

- Let Y_{ij} denote the ordinal response for the i^{th} subject at the j^{th} occasion

$$log\left\{\frac{P(Y_{ij}\leq k|b_i)}{P(Y_{ij}>k|b_i)}\right\} = \alpha_k + \beta_1(time)_{ij} + \beta_2(Age)_i + \beta_3(Gender)_i + \beta_4(MMSE)_{ij} + \beta_5(eTIV)_{ij} + \beta_6(nWBV)_{ij} + \beta_7(time)_{ij} * (MMSE)_{ij} + \beta_8(time)_{ij} * (nWBV)_{ij} + b_{1i} + b_{2i}\,(time)_{ij}$$

$i = 1, 2, \dots, 150$
$j = 1, 2, \dots, 5$

b_{1i}- Random effect of intercept for subject i

b_{2i}- Random effect of slope of time for subject i

Random Intercept Model or Random Intercept-Slope Model

Random Intercept Model

Fit Statistics	
-2 Log Likelihood	554.77
AIC (smaller is better)	576.77
AICC (smaller is better)	577.13
BIC (smaller is better)	609.89
CAIC (smaller is better)	620.89
HQIC (smaller is better)	590.23

Random Intercept-Slope Model

Fit Statistics	
-2 Log Likelihood	553.53
AIC (smaller is better)	575.53
AICC (smaller is better)	575.88
BIC (smaller is better)	608.64
CAIC (smaller is better)	619.64
HQIC (smaller is better)	588.98

H_0: Random intercept model is adequate

H_1: Random intercept- slope model is adequate

-2 Log Likelihood for Random Intercept Model: 554.77

-2 Log Likelihood for Random Intercept-Slope Model: 553.53

Test value: 554.77 – 553.53 = 1.24

p-value > 0.05

At 95% confidence level, we can conclude that the random intercept-slope model is adequate.

Random Intercept-Slope Model

Solutions for Fixed Effects							
Effect	**CDR**	**Gender**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept	0		-26.6089	6.1611	149	-4.32	<.0001
Intercept	1		-20.8880	6.0566	149	-3.45	0.0007
time			-12.3192	2.3932	149	-5.15	<.0001
Age			0.01183	0.02520	442	0.47	0.6388
Gender		F	0.6314	0.3752	442	1.68	0.0931
Gender		M	0	.	.	.	.
MMSE			0.8404	0.08986	442	9.35	<.0001
eTIV			0.000137	0.001120	442	0.12	0.9026
nWBV			2.6129	6.6338	442	0.39	0.6939
time*MMSE			-0.02259	0.02998	442	-0.75	0.4514
time*nWBV			17.9713	3.4153	442	5.26	<.0001

- Intercept 1: Log of odds of clinical dementia rating 0 vs. 1.
- Intercept 2: Log of odds of clinical dementia rating (0,1) & 2.
- Conditioned on random effects, the odds of CDR decreasing is approximately zero ($e^{-12.3192} \approx 0$) for each year.
- Given two subjects have the same random effect, with one unit increase in MMSE, the log of odds of clinical dementia rating increases by 0.8404
- Given two subjects have the same random effect, the odds of clinical dementia rating is greater among female group ($e^{0.6314} = 1.88$) as compared to the male group.

Conclusions

- At the completion of the study, most of the subjects had the same clinical dementia rating they had at the beginning of the study.
- Mini-mental health examination score have a highly significant effect on clinical dementia rating. Higher values of MMSE indicates lower clinical dementia rating.

References

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THANK YOU!