Investigating the Association Between Cognitive Impairment or Dementia and Self-reported Depression

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1 Introduction

Dementia is a severe neurodegenerative disease that can lead to memory loss, cognitive disorder and disorientation. According to the World Health Organization 2020, dementia is the seventh leading cause of death in the world, with more than 55 million people currently diagnosed worldwide and the number is expected to triple by 2050[1].

Depression and dementia often coexist in later life. Epidemiological studies have shown that depression in early life is an important risk factor of dementia, and depressive symptoms later in life appear to be a prodromal symptom of dementia[2, 3, 4]. This association can also be explained in molecular biology, as depression can lead to dementia by damaging brain regions through various mechanisms, such as increased vascular disease and inflammation[5].

Here we used the retroactively retrieved data of about 899 patients followed by National Alzheimer's Consulting Center to investigate the association between self-reported depression and cognitive impairment or dementia, with consideration of the roles of other potential confounding factors.

2 Methods

2.1 Variables

Predictor of Interest

Each study participant self-reported depression or not. The predictor is a binary factor, which was coded as 1 if individual reported depression and 0 otherwise.

Outcome

Clinical dementia rating(CDR) measures the level of cognitive impairment of each study participant. It is a score valued 0, 0.5, or 1, which means individuals with no cognitive impairment, mild-cognitive impairment, and dementia, respectively.

Covariates

Covariates include participants' age at which the CDR score was taken, sex, race, residence, marital status, education level and whether a participant has relatives with dementia. Research has indicated different age-specific, gender-specific, and race-specific risks of dementia[6, 7, 8]. In addition, previous research supports that having relatives with dementia is a determinant of dementia[9]. Residence refers to the type of residence at time of evaluation and we regrouped this variable into three categories based on care levels. Marital status may also be a risk factor for dementia. Studies show that all unmarried participants, including those who are widowed, divorced, separated, and never married, have significantly higher likelihood of developing dementia than married participants[10, 11]. Thus, we regrouped marital status as having a marital partner currently and others. A cohort study conducted in Sweden shows that low level of education is related to an increased incidence of clinical Alzheimer Disease or dementia[12]. Therefore, we included education years in the current study and recoded it into two groups by year 15.

Interaction

Interaction between depression and familial heredity on dementia was reported in previous studies. In East Asian origin populations, the APOE $\epsilon 4$ allele is a stronger predictor of incident dementia in the presence of depressive syndrome and particular depressive symptoms[13].

2.2 Statistical Analysis

In univariate analysis, we used Pearson's χ^2 test or one-way ANOVA to compare the distribution of outcome among predictor groups. Similarly, Pearson's χ^2 test or two-sample t-test were used to explore

associations between depression and other covariates.

We started by fitting the marginal effect model to find the marginal relationship between depression and cognitive impairment. Then, we fitted the cumulative logits model and the proportional odds model adjusted for confounders, and conducted test of proportionality. Finally, we included interaction term between depression and relative with dementia, as we have found evidence during literature review.

3 Results

3.1 Exploratory Analysis

Among the study population, 349(38.8%) participants had no cognitive impairment, while 180(20.0%) had mild cognitive impairment and 370(41.2%) had dementia. Bi-variate exploratory analysis showed significant differences in the distribution of sex, race, education, marital status, type of residence and depression among groups with different levels of cognitive impairment (Table 1). Bar charts or box-plots also showed differences in the distribution of outcome among different predictor groups (Figure 1 - 8). Stratifying the study population by depressive status revealed that patients with depression were more likely to be white and male, with lower education level, have marriage partner and relatives with dementia, and live in a private residence (Table 2).

3.2 Model Fitting

General logistic model was not within our consideration since our outcome is a three-level ordinal category variable. We fitted two separate logistic regression models, one for whether a participant has cognitive impairment or not, and the other for whether a participant has dementia or not.

Marginal Effect Model

We first fitted a marginal effect model with depression, the predictor of interest, as the follows,

$$log\{\frac{Pr(CDR_i \geq j/2)}{Pr(CDR_i < j/2)}\} = \beta_{0j} + \beta_{1j} \times DEP_i, \text{ where } j = \{1, 2\}.$$

Results showed that the marginal effect of depression is significant on both cognitive impairment and dementia (Table 3 & Table 4).

Cumulative Logits Model

The test of proportionality showed that the parallel assumption is violated ($p = 0.0014$), so we fitted cumulative logits model adjusting for confounders, as the follows,

$$\begin{aligned} log\{\frac{Pr(CDR_i \geq j/2)}{Pr(CDR_i < j/2)}\} &= \beta_{0j} + \beta_{1j} \times DEP_i + \beta_{2j} \times EDUC_i + \beta_{3j} \times MARI_i + \beta_{4j} \times RACE_i \\ &+\beta_{5j} \times RESID_i + \beta_{6j} \times RLDEM_i + \beta_{7j} \times SEX_i + \beta_{8j} \times FLAGE_i, \text{ where } j = \{1, 2\}. \end{aligned}$$

According to the result of cumulative logits model (Table 3 & Table 4), the odds of cognitive impairment for those with depression is significantly 3.532 (95%CI: (2.158, 5.783), $p < 0.001$) times that for those without depression, adjusting for other confounders. Meanwhile, the odds of dementia for those with depression is significantly 3.123 (95%CI: (1.973, 4.943), $p < 0.001$) times that for those without depression, adjusting for other confounders.

Hosmer-Lemeshow test showed the current model fitted data well ($H = 9.844$, $p = 0.910$). For other criteria of model performance, we have $AIC = 1397.04$, Cox-Snell pseudo $R^2 = 0.4031$, and Max-adjusted $R^2 = 0.4644$ (Table 5).

Adding Interaction between Depression and Relative with Dementia

Similarly, the test of proportionality showed that the parallel assumption is also violated ($p = 0.0018$).

Then we fitted the following model,

$$\begin{aligned} log\{\frac{Pr(CDR_i \geq j/2)}{Pr(CDR_i < j/2)}\} &= \beta_{0j} + \beta_{1j} \times DEP_i + \beta_{2j} \times EDUC_i + \beta_{3j} \times MARI_i + \beta_{4j} \times RACE_i + \beta_{5j} \times RESID_i \\ &+\beta_{6j} \times RLDEM_i + \beta_{7j} \times SEX_i + \beta_{8j} \times FLAGE_i + \beta_9 \times DEP_i \times RLDEM_i, \text{ where } j = \{1, 2\} \end{aligned}$$

Results from our model showed that (Table 3 & Table 4),

Given no relative with dementia, patients with depression have 2.232 (95%CI: (1.104, 4.511), p = 0.025) higher odds of cognitive impairment and 1.834 (95%CI: (0.913, 3.685), p = 0.089) higher odds of dementia compared to those without depression, adjusting for other confounders.

Given relative with dementia, the odds ratio of cognitive impairment is 5.263 (95%CI: (2.631, 10.527), $p < 0.001$) and the odds ratio of dementia is 4.694 (95%CI: (2.535, 8.692), $p < 0.001$), comparing patients with depression to those without depression, adjusting for other confounders.

When it comes to the interaction term, the odds ratio of cognitive impairment for those with depression compared with those without depression for patients having relative with dementia is insignificantly 2.358 (95%CI: (0.885, 6.284), p = 0.086) times that for patients without relative with dementia, adjusting for other confounders. For demantia, the odds ratio considering an interaction between depression and relative with dementia is significantly 2.560 (95%CI: (1.012, 6.473) , p = 0.047) times that without interaction.

Hosmer-Lemeshow test also showed the current model fitted data well (H = 16.942, p = 0.458). In addition, we have AIC = 1395.85, Cox-Snell pseudo R^2 = 0.407, and Max-adjusted R^2 = 0.468 (Table 5).

3.3 Model Diagnosis

Assumptions of our model were assessed for violations. We tested independence of observations by plotting quantile residuals in order and detected no violations because the plot is random pattern (Figure 9). We used the VIF test to check the multicollinearity, and the VIF values of all the predictors are less than 5 (Table 6 & Table 7), indicates there's no serious multicollinearity problem among the covariates. For influential cases, even though we found some leverage points, these points are all within the defined range of covariates and there is no need to remove them (Figure 10 & Figure 11).

4 Conclusion and Discussion

Our study explored the association between self-reported depression and cognitive impairment. Consistent with existing studies, we found that depression is strongly associated with the cognitive impairment. Specifically, among patients with no relatives with dementia, self-reported depression is significantly associated with increased cognitive impairment, but not significantly associated with dementia. However, for patients with relatives with dementia, self-reported depression is both significantly associated with cognitive impairment and dementia.

Limitations of the study include the causal inference problem, highly unbalanced data, study design, self-reporting of Depression, and infeasible R^2 value. Firstly, the data has some sign of causal inference problem, so the model can only be used to analyze association. Taking RESIDENC for example. During literature review, we find that better care can improve mental health. However, within those living in skilled nursing facilities or assisted livings, who are supposed to have the best care, 95.5 % of them have dementia actually. This is counterfactual but it is not difficult to be interpreted because those who have dementia tend to live in these places to get better care. Therefore, RESIDENC might be influenced by dementia and it may not be seen as a confounder such that it may cause causal inference problems in our study. Secondly, the data is highly unbalanced, which may weaken the effectiveness of the tests. These imbalance may make the χ^2 tests less convincing. Thirdly, the current study uses retroactively retrieved data. Thus, there might be selection bias and inverse probability weighting will be needed to balance the importance of samples. For example, there are more male than female in the data, but according to the prior knowledge we know that there should be more female at this age range. Finally, the interested variable, depression, is self-reported. Thus, our result may not be generalized to the association between clinical depression and dementia.

Overall, the results provided by our study deserve further investigation. To improve the study analysis, we can add more confounders and use longitudinal data to obtain higher R^2 and enhance the test. A larger sample size and more accurate diagnosis of depression would help improve the accuracy and extrapolation of our conclusions. In addition, it is important to delve into the social, cultural and molecular biological mechanisms underlying the factors that influence dementia.

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Contributions

- **Study Design**: Junyan Dong; Wenchu Pan; Xuheng Qiang; Yubo Shao
- **Literature Review**: Junyan Dong; Xuheng Qiang
- **Exploratory Analysis**: Yubo Shao
- **Statistical Analysis**: Wenchu Pan
- **Model Diagnostics**: Junyan Dong
- **Tables & Figures**: Yubo Shao
- **Report writing & Editing**: Junyan Dong; Wenchu Pan; Xuheng Qiang; Yubo Shao
- **Presentation Slides**: Xuheng Qiang

Appendix

Table 1. Clinical Dementia Rating of Patients, Stratified by Characteristics

Characteristic	**Overall,** *N = 899*[1]	**No Cognitive Impairment,** *N = 349*[1]	**Mild Cognitive Impairment,** *N = 180*[1]	**Dementia,** *N = 370*[1]	***P* value**[2]
First Evaluation Age	74.37 (9.45)	70.32 (8.49)	75.13 (9.96)	77.82 (8.57)	**< 0.001**
Sex					**< 0.001**
Female	436 (48.50%)	235 (67.34%)	100 (55.56%)	101 (27.30%)	
Male	463 (51.50%)	114 (32.66%)	80 (44.44%)	269 (72.70%)	
Race					**< 0.001**
White	709 (78.87%)	262 (75.07%)	117 (65.00%)	330 (89.19%)	
Non-white	190 (21.13%)	87 (24.93%)	63 (35.00%)	40 (10.81%)	
Education					**< 0.001**
Elementary or High School	485 (53.95%)	141 (40.40%)	104 (57.78%)	240 (64.86%)	
College or above	414 (46.05%)	208 (59.60%)	76 (42.22%)	130 (35.14%)	
Marital Status					**< 0.001**
Married	518 (57.12%)	175 (50.14%)	84 (46.67%)	259 (70.00%)	
Others	381 (42.38%)	174 (49.86%)	96 (53.33%)	111 (30.00%)	
Depression					**< 0.001**
Yes	192 (21.36%)	33 (9.46%)	29 (16.11%)	130 (35.14%)	
No	707 (78.64%)	316 (90.54%)	151 (83.89%)	240 (64.86%)	
Relative with Dementia					0.87
Yes	454 (50.50%)	179 (51.29%)	88 (48.89%)	187 (50.54%)	
No	445 (49.50%)	170 (48.71%)	92 (51.11%)	183 (50.54%)	
Type of Residence					**< 0.001**
Retirement Community or Others	61 (6.79%)	16 (4.58%)	13 (7.22%)	32 (8.65%)	
Private Residence	659 (73.30%)	330 (94.56%)	162 (90.00%)	167 (45.14%)	
Professional Care	179 (19.91%)	3 (0.86%)	5 (2.78%)	171 (46.22%)	

[1] *n(%); Mean (SD)*
[2] *Pearson's χ^2 test; One-way ANOVA*

Table 2. Characteristics of Patients, Stratified by Depression Status

Characteristic	**No Depression,** *N = 707*[1]	**Depression,** *N = 192*[1]	***P* value**[2]
First Evaluation Age	74.14 (9.48)	75.22 (9.32)	0.16
Sex			**< 0.001**
Female	358 (50.64%)	78 (40.62%)	
Male	349 (49.36%)	114 (59.38%)	
Race			**< 0.001**
White	536 (75.81%)	173 (90.10%)	
Non-white	171 (24.19%)	19 (9.90%)	
Education			0.82
Elementary or High School	380 (53.75%)	105 (54.69%)	
College or above	327 (46.25%)	87 (45.31%)	
Marital Status			**0.028**
Married	394 (55.73%)	124 (64.58%)	
Others	313 (44.27%)	68 (35.42%)	
Relative with Dementia			0.25
Yes	350 (49.50%)	104 (54.17%)	
No	357 (50.50%)	88 (45.83%)	
Type of Residence			**< 0.001**
Retirement Community or Others	46 (6.51%)	15 (7.81%)	
Private Residence	558 (78.93%)	101 (52.60%)	
Professional Care	103 (14.57%)	76 (39.58%)	

[1] *n(%); Mean (SD)*
[2] *Pearson's χ^2 test; Two Sample t-test*

Table 3. Odds Ratio from Logistic Model (with Cognitive Impairment vs. without Cognitive Impairment)

Characteristic, *N = 899*	**Unadjusted Model**[1]	**Adjusted Model with Main Effects**[1]	**Adjusted Model with Interaction Term**[1]
Intercept	**1.237** (1.067, 1.435)	**0.008** (0.001, 0.044)	**0.008** (0.001, 0.045)
Depression			
Yes	**3.894** (2.602, 5.827)	**3.532** (2.158, 5.783)	**2.232** (1.104, 4.511)
Sex			
Male		**2.638** (1.828, 3.805)	**2.609** (1.806, 3.767)
Race			
Non-white		**1.794** (1.180, 2.726)	**1.803** (1.185, 2.742)
Marital Status			
Married		**1.615** (1.108, 2.353)	**1.636** (1.122, 2.387)
Education			
College or above		**0.422** (0.298, 0.596)	**0.427** (0.302, 0.603)
Relative with Dementia			
Yes		1.128 (0.81, 1.569)	1.007 (0.707, 1.436)
First Evaluation Age		**1.071** (1.050, 1.093)	**1.071** (1.050, 1.094)
Type of Residence			
Professional Care		**12.100** (3.202, 45.725)	**12.642** (3.342, 47.822)
Private Residence		**0.440** (0.228, 0.848)	**0.447** (0.232, 0.860)
Retirement Community or Others		*ref*	*ref*
Depression* RLDEM			
*Depression (Yes)** *Relative Dementia (Yes)*			2.358 (0.885, 6.284)
Deviance	1148.3	856.19	853.22
AIC	1152.3	876.19	875.22

[1] *OR with 95% confidence interval*

Table 4. Odds Ratio from Logistic Model (with Dementia vs. without Dementia)

Characteristic, *N = 899*	**Unadjusted Model**[1]	**Adjusted Model with Main Effects**[1]	**Adjusted Model with Interaction Term**[1]
Intercept	**0.514** (0.404, 0.600)	**0.014** (0.002, 0.084)	**0.014** (0.002, 0.089)
Depression			
Yes	**4.080** (2.903, 5.733)	**3.123** (1.973, 4.943)	1.834 (0.913, 3.685)
Sex			
Male		**2.482** (1.667, 3.695)	**2.437** (1.634, 3.635)
Race			
Non-white		0.921 (0.565, 1.502)	0.927 (0.567, 1.516)
Marital Status			
Married		**2.760** (1.783, 4.274)	**2.857** (1.838, 4.441)
Education			
College or above		**0.386** (0.264, 0.566)	**0.394** (0.268, 0.578)
Relative with Dementia			
Yes		1.099 (0.765, 1.579)	0.917 (0.612, 1.374)
First Evaluation Age		**1.048** (1.026, 1.070)	**1.048** (1.026, 1.070)
Type of Residence			
Professional Care		**11.941** (4.657, 30.614)	**12.673** (4.936, 32.537)
Private Residence		**0.325** (0.174, 0.608)	**0.327** (0.175, 0.611)
Retirement Community or Others		*ref*	*ref*
Depression* RLDEM			
*Depression (Yes)** *Relative Dementia (Yes)*			**2.560** (1.012, 6.473)
Deviance	1147.5	750.43	746.45
AIC	1151.5	770.43	768.45

[1] *OR with 95% confidence interval*

Table 5. Summary of Overall Model Performance

	Deviance	***AIC***	***H-L Test***	***Cox Snell R^2***	***Max Adjusted R^2***
Without Interaction Terms	1357.043	1397.043	$p = 0.910$	0.451	0.513
With Interaction Terms	1351.851	1395.851	$p = 0.458$	0.454	0.517

Table 6. Test of Multicollinearity (with Cognitive Impairment vs. without Cognitive Impairment)

Characteristic	$\boldsymbol{GVIF^{1/(2*DF)}}$
Depression	1.419
Sex	1.114
Race	1.131
Marital Status	1.148
Education	1.060
Relative with Dementia	1.083
First Evaluation Age	1.036
Type of Residence	1.009
*DEP * RLDEM*	1.457

Table 7. Test of Multicollinearity (without Dementia vs. with Dementia)

Characteristic	$\boldsymbol{GVIF^{1/(2*DF)}}$
Depression	1.356
Sex	1.106
Race	1.094
Marital Status	1.170
Education	1.058
Relative with Dementia	1.128
First Evaluation Age	1.042
Type of Residence	1.022
*DEP * RLDEM*	1.408

Figure 1: DEP vs. CDR

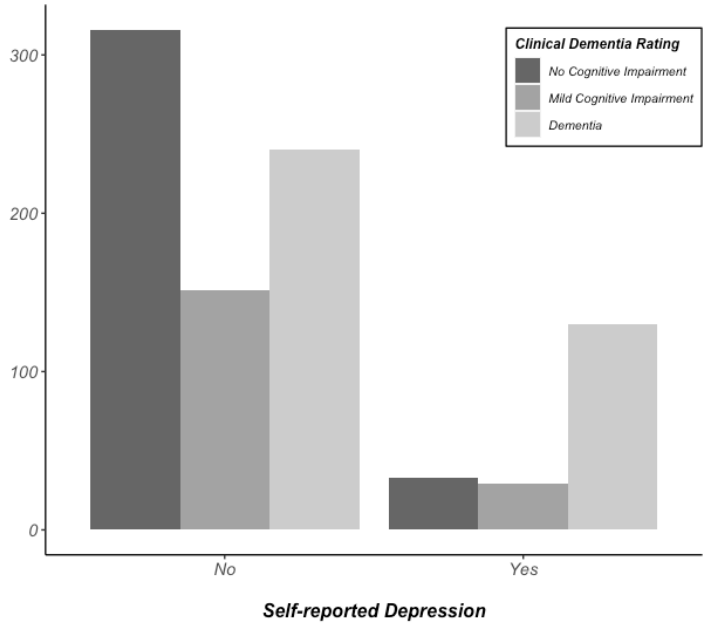

Figure 2: EDUC vs. CDR

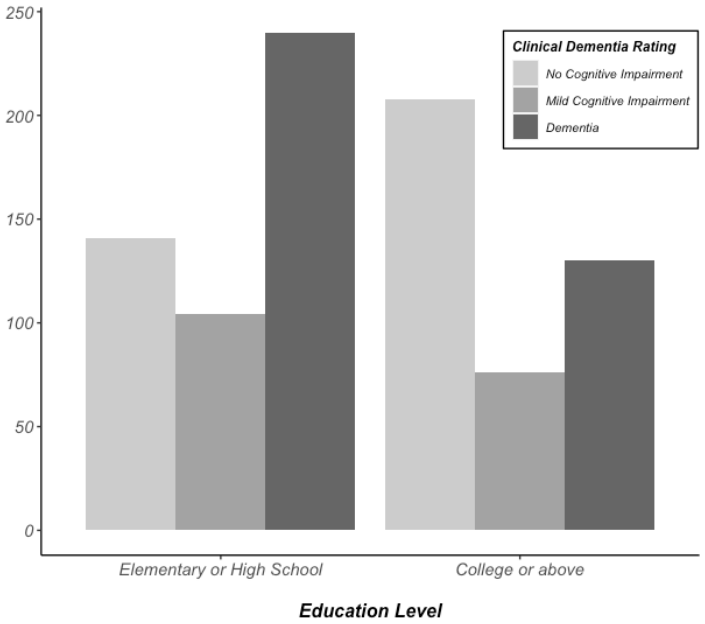

Figure 3: Race vs. CDR

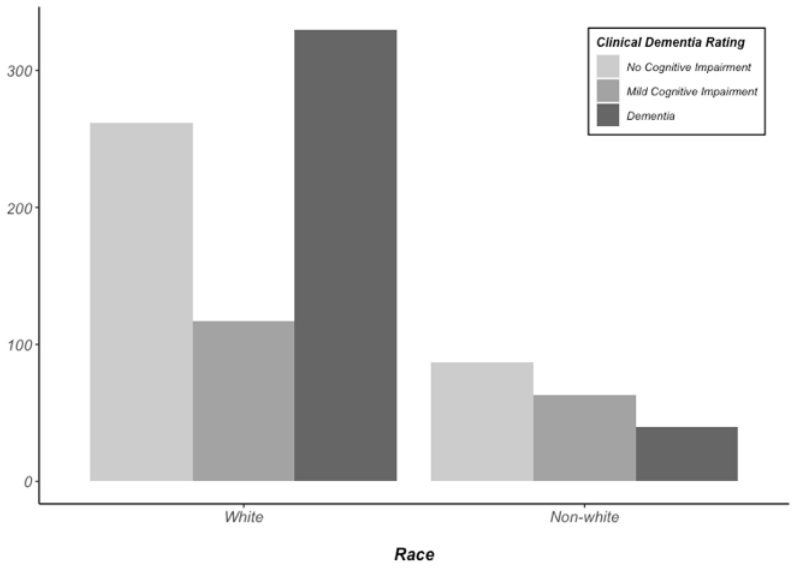

Figure 4: RLDEM vs. CDR

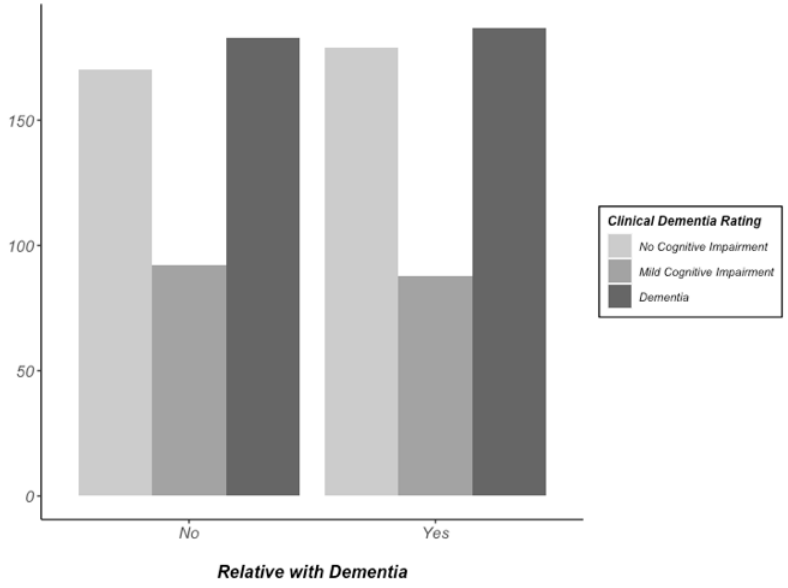

Figure 5: MARISTAT vs. CDR

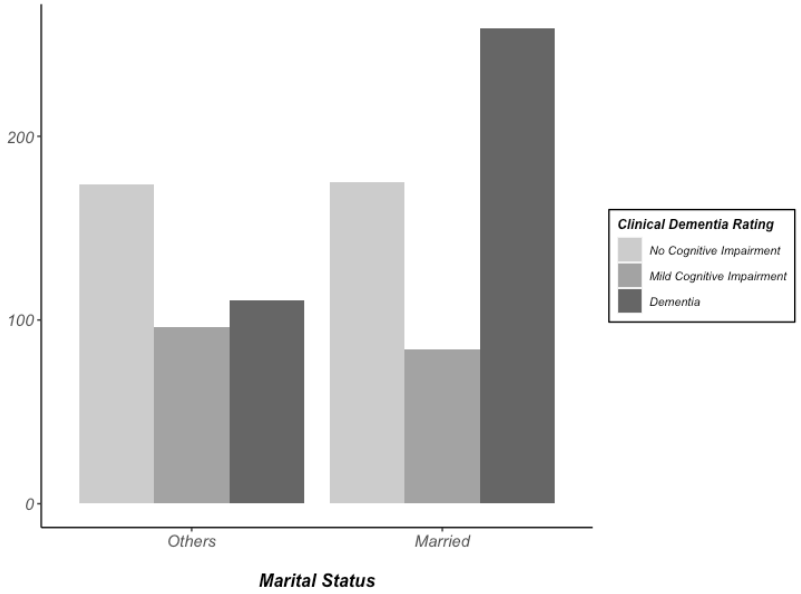

Figure 6: SEX vs. CDR

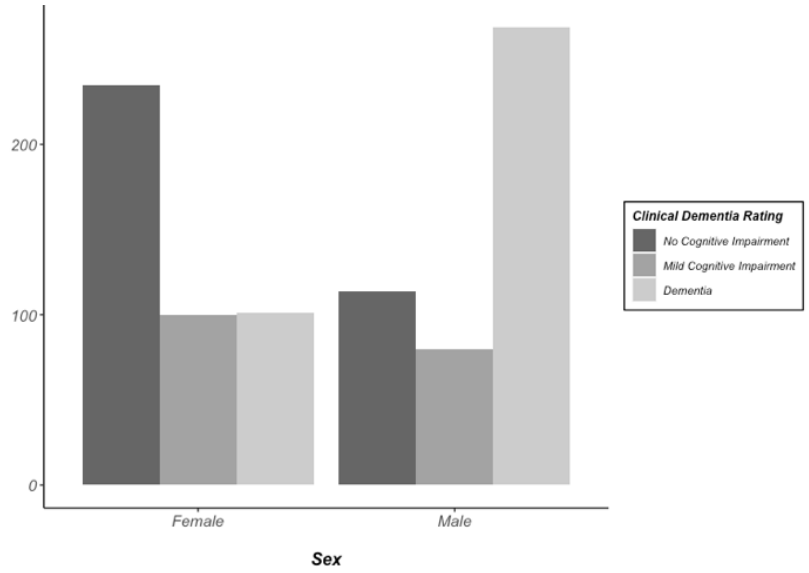

Figure 7: RESIDENC vs. CDR

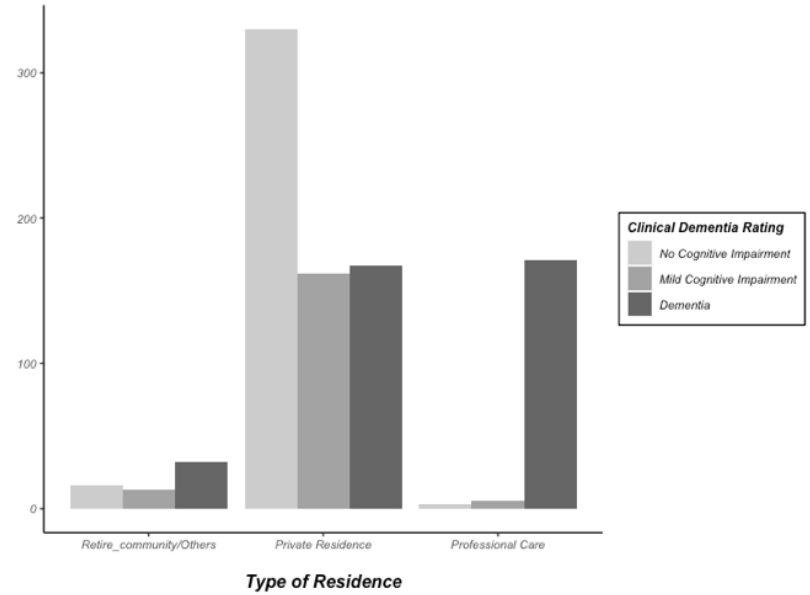

Figure 8: FEVALAGE vs. CDR

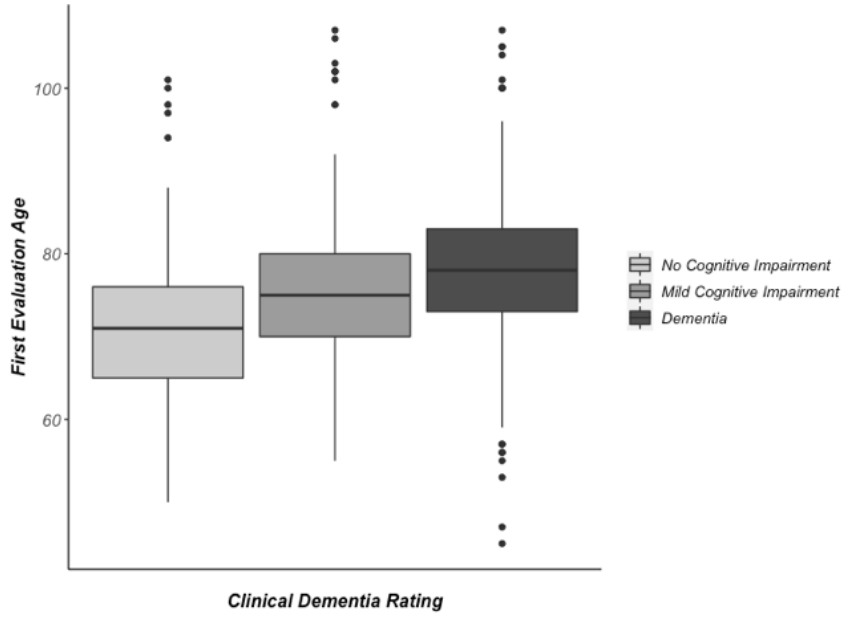

Figure 9: Independence of Observations

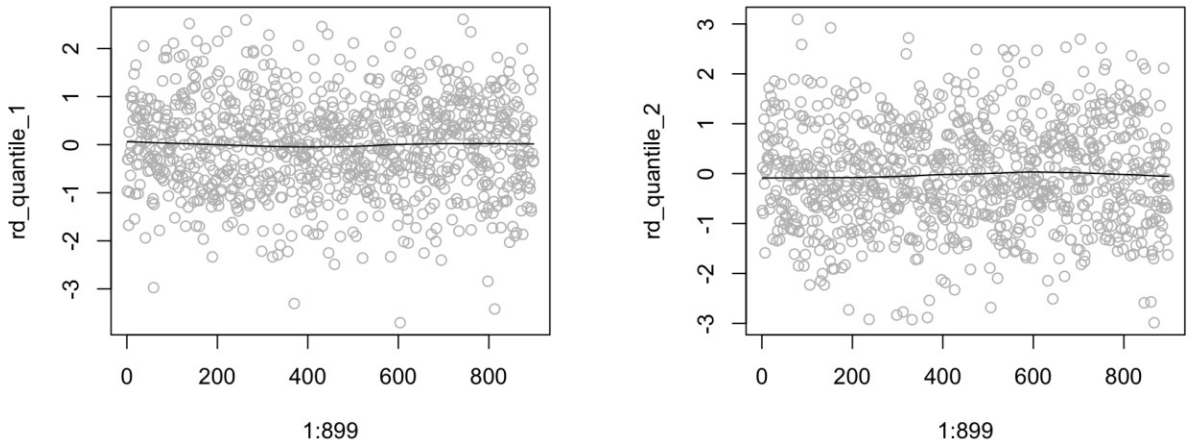

Figure 10: Influence Measure (with Cognitive Impairment vs. without Cognitive

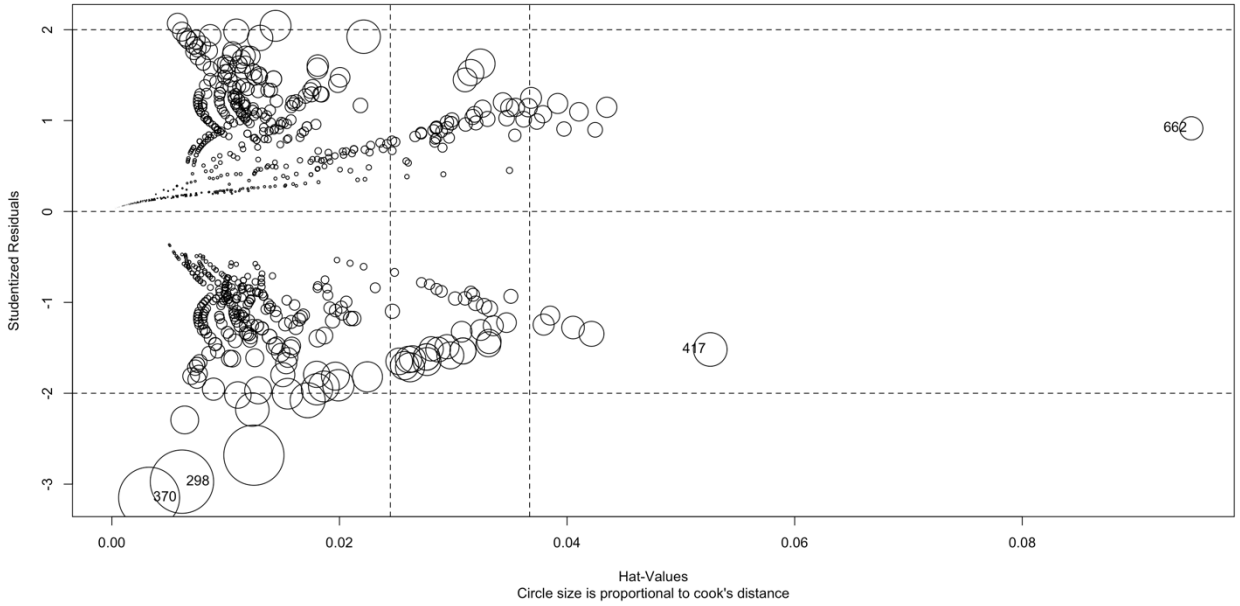

Figure 11: Influence Measure (with Dementia vs. without Dementia)