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____Yue Zhang_____May 12, 2024_____

The Influence of Hypercholesterolemia on Cognitive Impairment in Age 65-74: A NACC Cross-Sectional Study

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Epidemiology

_____ Ambar Kulshreshtha, MD, PhD _____

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An abstract of
A thesis submitted to the Faculty of the
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Abstract

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By Yue Zhang

Cognitive impairment is a progressive neurodegenerative disorder characterized by significant cognitive decline. Some research suggests that cholesterol plays a role in cognitive impairment pathogenesis. This study investigates the relationship between hypercholesterolemia and cognitive impairment among individuals aged 65 to 74. We used logistic regression to evaluate the impact of hypercholesterolemia and cognitive impairment, adjusted for some confounders, including race, sex, education, diabetes, hypertension, smoking, and BMI, and stratified by age categories. The association is robust after adjusting for confounders, suggesting that hypercholesterolemia is a significant risk factor for cognitive impairment. These findings support cholesterol management as a potential strategy to modify cognitive impairment risk.

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Ambar Kulshreshtha, MD, PhD

Declaration

I declare that this thesis has been composed by myself and has not been submitted, in whole or in part, in any previous application for a degree. The work presented is entirely my own except where stated by reference and acknowledgment.

Table of Contents

1. Abstract

Cognitive impairment is a progressive neurodegenerative disorder characterized by significant cognitive decline. Some research suggests that cholesterol plays a role in cognitive impairment pathogenesis. This study investigates the relationship between hypercholesterolemia and cognitive impairment among individuals aged 65 to 74. We used logistic regression to evaluate the impact of hypercholesterolemia and cognitive impairment, adjusted for some confounders, including race, sex, education, diabetes, hypertension, smoking, and BMI, and stratified by age categories. The association is robust after adjusting for confounders, suggesting that hypercholesterolemia is a significant risk factor for cognitive impairment. These findings support cholesterol management as a potential strategy to modify cognitive impairment risk.

2. Acknowledgments

I want to express my deepest appreciation to my committee for providing guidance and feedback throughout this thesis. I would also like to extend gratitude to the people associated with the NACC database for their help in conducting this study. Also, I would like to express my heartfelt gratitude to my family for their unwavering support and encouragement throughout this journey. I am also deeply thankful to my friend JR, for the companionship and steadfast support.

3. Introduction

Cognitive Impairment is difficulties with thinking, learning, remembering, using judgment, and making decisions. Its symptoms includes memory deterioration, problems with concentration, task completion, comprehension, retention, following directions, and problem-solving.[1] The worldwide prevalence of cognitive impairment increases between 5.1% and 41% and the median is 19.0%. Additionally, the incidence is between 22 and 76.8 per 1000 person-years and median is 53.97 per 1000 person-years. [2] Cognitive impairments can be assessed by Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Mini-Cog. [3] The risk factors of cognitive impairment include age, genetic, educational attainment, traumatic brain injuries, and some chronic illnesses like Parkinson's disease, cardiovascular diseases, stroke, and diabetes.[4] No effective intervention to be confirmed across many studies. [5]

To explore the relationship between risk factors and cognitive impairment is important to understand the etiological factors of cognitive impairment. It's useful for early diagnosis, prevention, and the design of therapeutic strategies. This study aims to explore the association between high cholesterol and cognitive impairment, hypothesizing that high cholesterol may increase the risk of cognitive impairment-associated cognitive decline. To test this hypothesis, the study examines the relationship between hypercholesterolemia and cognitive impairment measured by the Montreal Cognitive Assessment (MoCA).

4. Literature review

4.1. Cognitive Impairment

Cognitive impairment involves problems with perception, focus, recollection, and problem-solving abilities. [6]It is not considered a disease but a symptom resulting from various conditions.[7] Two-thirds of Americans face some form of cognitive impairment. [8] The progression from normal to dementia sometimes includes four stages. No Cognitive Impairment (NCI) represents individuals with no cognitive decline. Subjective Cognitive Impairment (SCI) involves a perceived decline in cognitive abilities but is able for normal complex activities. [910]Mild Cognitive Impairment (MCI) means an obvious deterioration in cognitive functions such as memory and reasoning, distinct from normal aging. [1112] Finally, dementia significantly impairs both instrumental and daily activities, which means severe damage to cognitive and physical functions. [1314]

4.1.1. Montreal Cognitive Assessment (MoCA) in the Detection of cognitive impairments

The Montreal Cognitive Assessment (MoCA) is an accurate cognitive screening tool for detecting cognitive impairments, including Alzheimer's Disease. [15] It has excellent reliability and predictive values for Mild Cognitive Impairment (MCI), a clinical condition frequently leading to dementia. It's ideal for clinical settings. The MoCA can detect MCI patients and differentiate them from healthy older adults. [161718]

The assessment typically lasts about 10 minutes and covers a range of tasks, including Alternating Trail Making, Vasoconstriction Skills, Naming, Memory, Attention, Sentence Repetition, Verbal Fluency, Abstraction, Delayed Recall, and Orientation.[19] Each task aims for specific cognitive functions such as memory, language, visuo-constructional skills, and executive functions. MoCA scores range up to 30 points, with 26 or higher generally indicating normal cognitive function. Scores are based on the accuracy and completeness of responses. An educational adjustment grants an extra point to individuals with less than 12 years of formal education to offset educational impacts on performance. This tool is widely valued in clinical and research for its thorough approach to assessing cognitive function.[15]

4.2 Hypercholesterolemia

4. 2. 1. Hypercholesterolemia

Hypercholesterolemia is a common medical condition with higher blood cholesterol levels than general population.[2012] It has too much cholesterol leads to form the fatty deposits in the blood vessels, therefore, increases the risk of heart disease, stroke, and peripheral artery disease.[20]A blood cholesterol level more than 200 mg/dl is referred to as hypercholesterolemia.[2122]

There was a 17.6% rise in the prevalence of hypercholesterolemia between the periods 1999–2002 (25%) and 2013–2016 (29.4%). After declining at an average yearly rate of 0.3% since 2010, the prevalence of hypercholesterolemia was 12.2% in the years 2015–2016. [23] Common risk factors of hypercholesterolemia are high-fat and cholesterol diets, obesity, lack of exercise, smoking, and genetic predisposition. Age and other health conditions such as diabetes can also lead to hypercholesterolemia.[222425]

4. 2. 2. Cholesterol, hypercholesterolemia, and cognitive impairments

Research suggests an association between family hypercholesterolemia and mild cognitive impairment,[26] and the connection between cholesterol levels and cognitive function in the elderly.[27] Increasing cholesterol levels in neurons lead to stress in the endoplasmic reticulum and trigger apoptosis in neuronal cells within the hippocampus, which leads to cognitive decline and brain shrinkage.[2829]

5. Aims

This study aims to assess how hypercholesterolemia influences cognitive impairment risk in the 65-74 age group and the potential benefits of cholesterol management for cognitive impairment prevention and treatment.

6. Materials and Methods

6.1Data Collection

This study used a subset of data from the Uniform Data Set (UDS) that the National Institute on Aging's Alzheimer's Disease Research Centers (ADRC). [30]UDS data are collected annually during an in-person office visit, home visit, or telephone call by a clinical assessment. [3031]

This study only includes every participant's latest visit. We selected race， sex, education, diabetes, hypertension, smoking, and BMI variables and stratified them by three age categories: <65, 65-74, and >74. According to cognitive impairment standards， participants were divided into two groups based on clinically established thresholds. [15] Cognitive impairment status was added as a new variable and stratified into with and without cognitive impairment based on MoCA scores. MoCA scores between 0 and 25 are cognitive impairment, and 26 to 30 no cognitive impairment.[15]

6.2 Data analysis

We use logistic regression to examine the impact of hypercholesterolemia interacting with 65-74 age categories on the risk of cognitive impairment. Data analysis was conducted by R studio (Version 3.6.1). Descriptive statistics are about the demographics and characteristics of the study. According to cognitive impairment standards, participants were divided into two groups, following clinically established thresholds. [15] The multivariate logistic regression model (m2) assessed the relationship between hypercholesterolemia and cognitive impairment, adjusting for other confounders, while the simple logistic regression model (m1) assessed without controlling other confounders. The significance level was set as 0.05.

7. Results

We analyzed the characteristics of 6205 participants and stratified them by cognitive impairment (N=3773) and no cognitive impairment (N=2432). The univariate analysis showed statistical significance between hypercholesterolemia and cognitive impairment. There are also some statistical differences in the following groups between the cognitive impairment groups and non-cognitive impairment groups: cognitive impairment patients were older on average (70.72 ± 9.42 years) and had higher rates of hypertension (45.2%) and diabetes (14.7%). Education is also significant, with more cognitive impairment patients holding master's degrees (20.4%). In the cognitive impairment group, more males (48.8%), white (79.2%) and individuals preferred at home (25.2%). So, we need to adjust some variables because of the imbalance. (Table 1)

Table 1. Characteristics of Participants with and without cognitive impairment

Characteristic	No Cognitive Impairment (n=2432)	Cognitive Impairment (n=3773)	P-value
Age (mean ± SD)	67.47 ± 10.06	70.72 ± 9.42	<0.001
BMI (mean ± SD)	27.17 ± 5.48	27.16 ± 5.42	0.952
Smoking Years (mean ± SD)	6.20 ± 11.28	7.63 ± 13.74	<0.001
Education(%)			<0.001
Bachelor	959 (39.4%)	1691 (44.8%)	
Doctorate	359 (14.8%)	410 (10.9%)	
High_GRE	199 (8.2%)	769 (20.4%)	
Master	915 (37.6%)	903 (23.9%)	
Race (%)			<0.001
Asian	90 (3.7%)	202 (5.4%)	
Black	214 (8.8%)	431 (11.4%)	
Hawaiian/Pacific	2 (0.1%)	9 (0.2%)	
Other	24 (1.0%)	33 (0.9%)	
USIndians/Alaska	15 (0.6%)	50 (1.3%)	
White	2072 (85.2%)	2988 (79.2%)	
NA	15 (0.6%)	60 (1.6%)	
Sex - Male (%)	894 (36.8%)	1843 (48.8%)	<0.001
Stay-home Status (%)			<0.001
No	1807 (74.3%)	2604 (69.0%)	
Yes	577 (23.7%)	949 (25.2%)	
NA	48 (2.0%)	220 (5.8%)	
Hypercholesterolemia (%)			<0.001
Absent	1294 (53.2%)	1757 (46.6%)	
Active	1064 (43.8%)	1883 (49.9%)	
Inactive	74 (3.0%)	133 (3.5%)	
Hypertension (%)			<0.001
Absent	1518 (62.4%)	1954 (51.8%)	
Active	863 (35.5%)	1705 (45.2%)	
Inactive	44 (1.8%)	107	
Diabetes (%)			<0.001
Absent	2191 (90.1%)	3177 (84.2%)	
Active	229 (9.4%)	554 (14.7%)	
Inactive	12 (0.5%)	32 (0.8%)	
NA	0 (0.0%)	10 (0.3%)	

We conduct two logistic regressions:
M1: Cognitive Impairment = HYPERCHO* AGE_CAT
M2: Cognitive impairment = Hypercholesterolemia *age_categries+race+
hypercholesterolemia *sex+diabetes+
hypercholesterolemia*eduction+BMI+Hypertention+smoking years.
In the unadjusted model, hypercholesterolemia did not significantly predict cognitive impairment(p=0.17). However, active hypercholesterolemia significantly increases 14% of cognitive impairment odds among individuals aged 65 to 74 when adjusting race, sex, education level, diabetes, BMI, hypertension, and smoking history (p=0.05, 95%CI [1.05,1.71]). We also examined the interactions between hypercholesterolemia and sex(p=0.74), and educational level. The interaction about sex and educational level are not significant. (Table 2)

Table 2: Summary of Active Hypercholesterolemia and Age Category in Logistic Regression Models

Unadjusted	**Odds Ratio (OR)**	**95% CI**	**P-value**
Hypercholesterolemia Active: Age 65-74	1.2	0.96 to 1.48	0.17
Hypercholesterolemia Active: Age >74	0.96	0.76 to 1.23	0.8
Adjusted			
Hypercholesterolemia Active: Age 65-74	1.34	1.05 to 1.71	0.05
Hypercholesterolemia Active: Age >74	1.13	0.86 to 1.48	0.45
Hypercholesterolemia Active: Sex	\	\	0.74
Hypercholesterolemia Active: Doctorate	\	\	0.36
Hypercholesterolemia Active: High_GRE	\	\	0.72
Hypercholesterolemia Active: Master	\	\	0.83

The model (M2) shows a good ability to distinguish between cognitively impaired patients and non-cognitive impaired individuals. Its performance stability in different samples is notable. This model is reliable in identifying individuals at risk of cognitive impairment for clinical and research use. (Figure 1a)

Figure 1a: ROC Curve Analysis for Cognitive Impairment Status Prediction Model

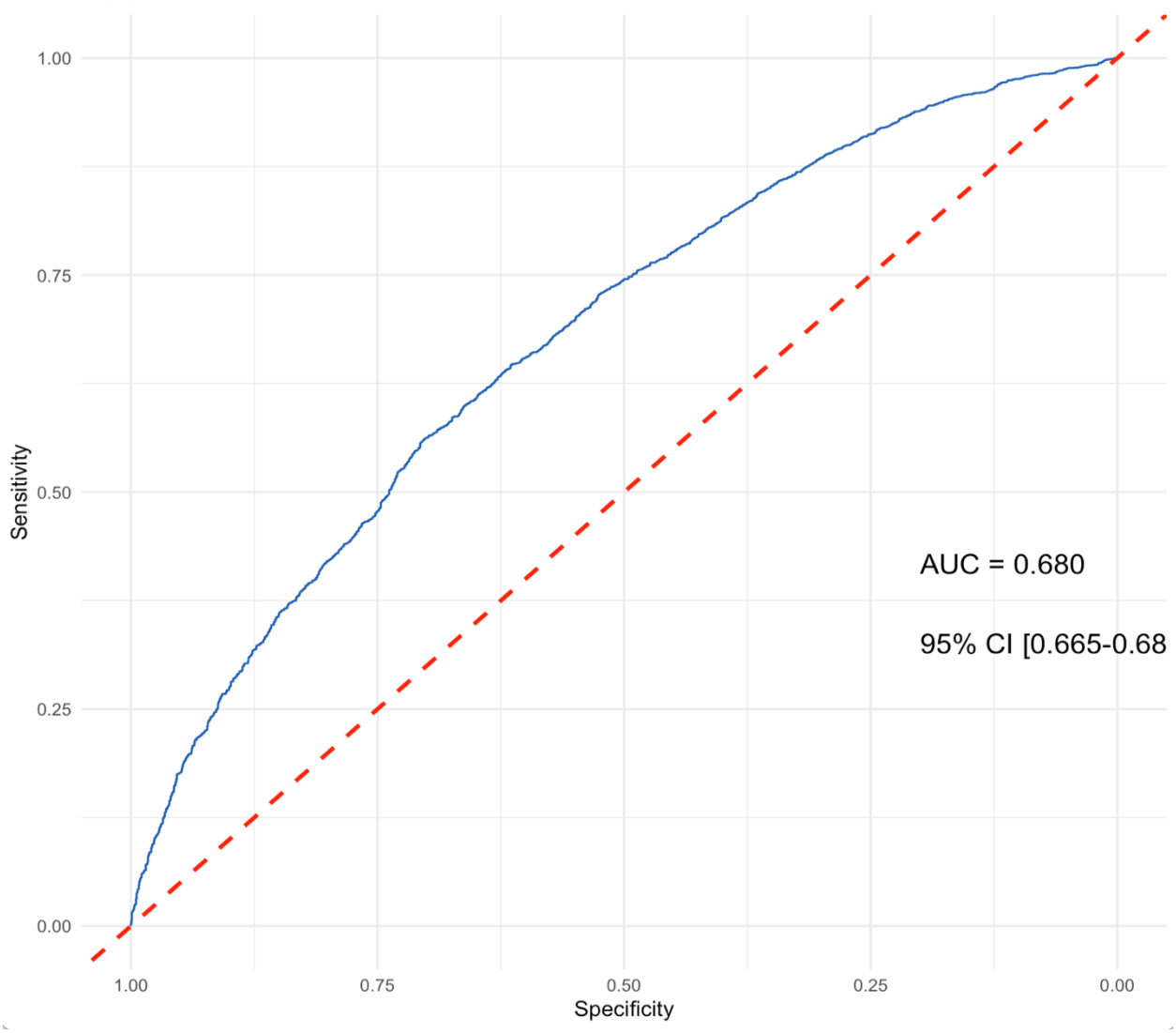
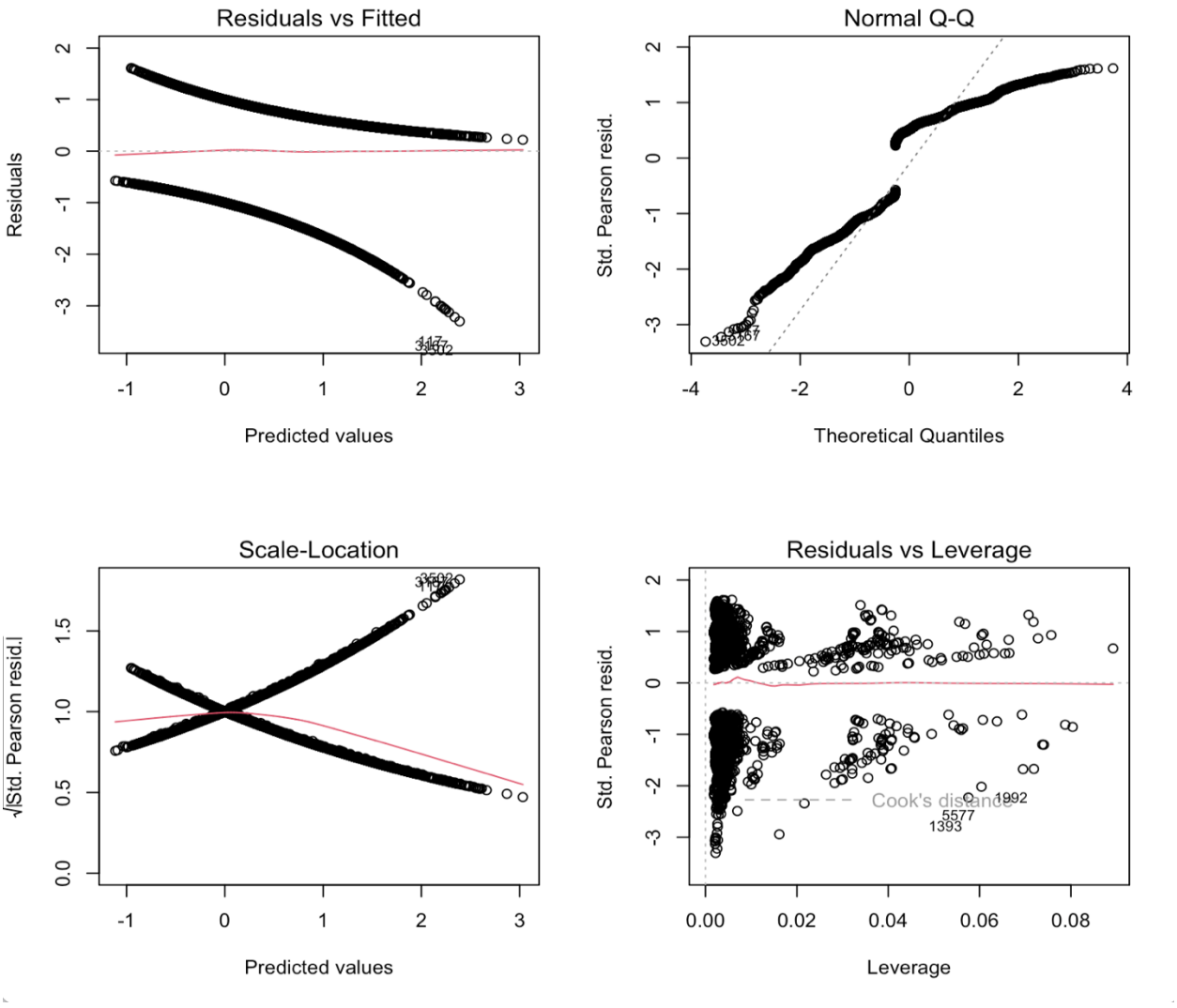


Figure 1b also shows an adequate fit. The Residuals vs. Fitted plot illustrates evenly distributed residuals across predicted values without discernible patterns or outliers, indicating consistent model predictions across different response variable levels. As expected, Q-Q plot shows some deviations from normality, especially in the tails. But it did not compromise model validity. Outliers may not capture all the variability in Residual vs. Leverage Plot data, and a few points may significantly impact the model estimation. The Scale-Location plot suggests stable error variance about predictions and it supports homoscedasticity.

Figure 1b: Residual Diagnostics for Logistic Regression Model in Cognitive Impairment Status Study



8. Discussion

After adjusting race, sex, education level, diabetes, BMI, hypertension, and smoking history, the adjusted model shows a better fit. It is critical to consider these factors when exploring potential risk factors in cognitive impairment and hypercholesterolemia. This study also emphasizes the importance of comprehensive modeling in research.

This research aligns with previous findings about hypercholesterolemia's impact on cognitive impairment. One study found family hypercholesterolemia is associated with an increased risk of cognitive impairment. [32] A study also indicated early exposure to high cholesterol levels could be a risk factor for mild cognitive impairment.[26] But also contributes to some different findings. A study found high total cholesterol may be a protective factor for cognitive performance. [33] Research including participants between the ages of 70 and 90 showed that lower total cholesterol levels were linked to worse cognitive function. [34] Another follow-up research also revealed that among individuals aged 70, greater total cholesterol was linked to better cognitive scores. [35]

This study has some strengths. First, a large data source provided enough samples. Second, adjusting for confounders and robust analysis within a well-characterized cohort helps identify potential risk factors of cognitive impairment. However, there are also some limitations. The cross-sectional design is unable to draw causal inferences. Although the model discriminates between cognitive impairment status, the AUC value suggests improving if we want to know clinical utility. Furthermore, residual diagnostics confirmed the assumptions, although some outliers indicated extreme values may affect robustness. Meticulous data quality control and additional data transformations may need to be considered in future studies.

The significance of this study and its findings show potential to help future clinical and research strategies. By identifying hypercholesterolemia as one of the potential risk factors, this study could guide further research about cognitive impairment pathogenesis, prevention, and treatment. Hypercholesterolemia management may be a potential intervention to modify cognitive impairment risk.

9. Conclusion

In summary, this study found that active hypercholesterolemia is associated with a significantly higher risk of cognitive impairment. These results emphasize the importance of hypercholesterolemia. Recognizing hypercholesterolemia as a risk factor enhances understanding of cognitive impairment pathogenesis and could help prevent and treat strategies. This research highlights metabolic health as a key factor in reducing the burden of neurodegenerative diseases.

10. References

1. Definition of cognitive impairment - NCI Dictionary of Cancer Terms - NCI. Published February 2, 2011. Accessed May 8, 2024. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cognitive-impairment
2. Pais R, Ruano L, P. Carvalho O, Barros H. Global Cognitive Impairment Prevalence and Incidence in Community Dwelling Older Adults—A Systematic Review. *Geriatrics*. 2020;5(4):84. doi:10.3390/geriatrics5040084
3. Hugo J, Ganguli M. Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. *Clin Geriatr Med*. 2014;30(3):421-442. doi:10.1016/j.cger.2014.04.001
4. Cognitive Impairment: A Call for Action, Now!
5. Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: Systematic review. *Br J Psychiatry J Ment Sci*. 2013;203:255-264. doi:10.1192/bjp.bp.113.127811
6. Trivedi JK. Cognitive deficits in psychiatric disorders: Current status. *Indian J Psychiatry*. 2006;48(1):10-20. doi:10.4103/0019-5545.31613
7. Australia H. Cognitive impairment – what it is and how to test for it. Published November 23, 2023. Accessed May 8, 2024. https://www.healthdirect.gov.au/cognitive-impairment
8. Hale JM, Schneider DC, Mehta NK, Myrskylä M. Cognitive impairment in the U.S.: Lifetime risk, age at onset, and years impaired. *SSM - Popul Health*. 2020;11:100577. doi:10.1016/j.ssmph.2020.100577
9. Hill NL, Mogle J, Wion R, et al. Subjective Cognitive Impairment and Affective Symptoms: A Systematic Review. *The Gerontologist*. 2016;56(6):e109-e127. doi:10.1093/geront/gnw091
10. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. *Alzheimers Dement*. 2014;10(6):844-852. doi:10.1016/j.jalz.2014.01.001
11. Eshkoor SA, Hamid TA, Mun CY, Ng CK. Mild cognitive impairment and its management in older people. *Clin Interv Aging*. 2015;10:687-693. doi:10.2147/CIA.S73922
12. Johnson M, Lin F. Communication Difficulty and Relevant Interventions in Mild Cognitive Impairment: Implications for Neuroplasticity. *Top Geriatr Rehabil*. 2014;30(1):18-34. doi:10.1097/TGR.0000000000000001
13. Aging Dementia - Pickup Family Neuroscience Institute. Hoag. Accessed May 8, 2024. https://www.hoag.org/specialties-services/neurosciences/programs/memory-cognitive-disorders/types-of-memory-cognitive-disorders/cognitive-severity-stages/
14. Grand JH, Caspar S, MacDonald SW. Clinical features and multidisciplinary approaches to dementia care. *J Multidiscip Healthc*. 2011;4:125-147. doi:10.2147/JMDH.S17773
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
16. Pinto TCC, Machado L, Bulgacov TM, et al. Is the Montreal Cognitive Assessment (MoCA) screening superior to the Mini-Mental State Examination (MMSE) in the detection of mild cognitive impairment (MCI) and Alzheimer's Disease (AD) in the elderly? *Int Psychogeriatr*. 2019;31(4):491-504. doi:10.1017/S1041610218001370
17. Lam B, Middleton LE, Masellis M, et al. Criterion and Convergent Validity of the Montreal Cognitive Assessment with Screening and Standardized Neuropsychological Testing. *J Am Geriatr Soc*. 2013;61(12):2181-2185. doi:10.1111/jgs.12541
18. Alzheimer's Disease Fact Sheet. National Institute on Aging. Published April 5, 2023. Accessed April 28, 2024. https://www.nia.nih.gov/health/alzheimers-and-dementia/alzheimers-disease-fact-sheet

19. Julayanont P, Nasreddine ZS. Montreal Cognitive Assessment (MoCA): Concept and Clinical Review. In: Larner AJ, ed. *Cognitive Screening Instruments: A Practical Approach*. Springer International Publishing; 2017:139-195. doi:10.1007/978-3-319-44775-9_7
20. Ibrahim MA, Asuka E, Jialal I. Hypercholesterolemia. In: *StatPearls*. StatPearls Publishing; 2024. Accessed April 29, 2024. http://www.ncbi.nlm.nih.gov/books/NBK459188/
21. Hypercholesterolemia - an overview | ScienceDirect Topics. Accessed April 28, 2024. https://www.sciencedirect.com/topics/medicine-and-dentistry/hypercholesterolemia
22. CDC. About High Cholesterol | cdc.gov. Centers for Disease Control and Prevention. Published March 20, 2023. Accessed April 29, 2024. https://www.cdc.gov/cholesterol/about.htm
23. York SP BS (Pharm), MBA, PhD Professor of Pharmacy Administration College of Pharmacy & Health Sciences, St John's University Jamaica, New. Hypercholesterolemia Trends. Accessed April 28, 2024. https://www.uspharmacist.com/article/hypercholesterolemia-trends
24. Blood Cholesterol - Causes and Risk Factors | NHLBI, NIH. Published April 19, 2024. Accessed April 29, 2024. https://www.nhlbi.nih.gov/health/blood-cholesterol/causes
25. CDC. Know Your Risk for High Cholesterol | cdc.gov. Centers for Disease Control and Prevention. Published May 15, 2023. Accessed April 29, 2024. https://www.cdc.gov/cholesterol/risk_factors.htm
26. Zambón D, Quintana M, Mata P, et al. Higher Incidence of Mild Cognitive Impairment in Familial Hypercholesterolemia. *Am J Med*. 2010;123(3):267-274. doi:10.1016/j.amjmed.2009.08.015
27. Cheng Y, Jin Y, Unverzagt FW, et al. The relationship between cholesterol and cognitive function is homocysteine-dependent. *Clin Interv Aging*. 2014;9:1823-1829. doi:10.2147/CIA.S64766
28. Wang HL, Wang YY, Liu XG, et al. Cholesterol, 24-Hydroxycholesterol, and 27-Hydroxycholesterol as Surrogate Biomarkers in Cerebrospinal Fluid in Mild Cognitive Impairment and Alzheimer's Disease: A Meta-Analysis. *J Alzheimers Dis JAD*. 2016;51(1):45-55. doi:10.3233/JAD-150734
29. Cheon SY. Impaired Cholesterol Metabolism, Neurons, and Neuropsychiatric Disorders. *Exp Neurobiol*. 2023;32(2):57-67. doi:10.5607/en23010
30. About NACC data | National Alzheimer's Coordinating Center. Accessed April 29, 2024. https://naccdata.org/requesting-data/nacc-data
31. Uniform Data Set version 3 | National Alzheimer's Coordinating Center. Accessed April 29, 2024. https://naccdata.org/data-collection/forms-documentation/uds-3
32. de Oliveira J, Moreira ELG, de Bem AF. Beyond cardiovascular risk: Implications of Familial hypercholesterolemia on cognition and brain function. *Ageing Res Rev*. 2024;93:102149. doi:10.1016/j.arr.2023.102149
33. Pang K, Liu C, Tong J, Ouyang W, Hu S, Tang Y. Higher Total Cholesterol Concentration May Be Associated with Better Cognitive Performance among Elderly Females. *Nutrients*. 2022;14(19):4198. doi:10.3390/nu14194198
34. Thorvaldsson V, Skoog I, Johansson B. Cholesterol and cognitive aging: Between-person and within-person associations in a population-based representative sample not on lipid-lowering medication. *Psychol Aging*. 2020;35(4):508-516. doi:10.1037/pag0000449
35. Corley J, Starr JM, Deary IJ. Serum cholesterol and cognitive functions: the Lothian Birth Cohort 1936. *Int Psychogeriatr*. 2015;27(3):439-453. doi:10.1017/S1041610214001197

11. Supplement:

```
 setwd("/Users/yue/Desktop/thesis")
library(tidyverse)
library(readxl)
library(tableone)
library(lme4)
library(lubridate)
library(pROC)
library(broom)
# Read the data
ftld <- read.table("data.txt", header = TRUE, sep = "\t", fill = TRUE)

# clean data
dt <- ftld %>%
 select(
  NACCID, CANCER, DIABETES, TOBAC30, EDUC, NACCFAM, TBI, NACCBMI, NACCMOCA,
  RACE, NACCAGE, PARK, SEX, SMOKYRS, STAYHOME, HYPCHOL, STROKDEC,
  VISITYR, DECAGE, CBSTROKE, HYPERCHO, HYPERTEN, VISITYR, VISITMO, VISITDAY
 ) %>%
 filter(
  !is.na(VISITMO),
  !is.na(NACCID),
  HYPERCHO %in% c(0, 1, 2),
  NACCMOCA %in% 0:30
 ) %>%
 mutate(
  CI = NACCMOCA < 26,
  TIME = make_date(VISITYR, VISITMO, VISITDAY)
 )

dt.2 <- dt %>%
 mutate(
  TOBA = case_when(
   TOBAC30 == 0 ~ "No",
   TOBAC30 == 1 ~ "Yes",
   TOBAC30 == 9 ~ NA
  ),
  EDUC = as.numeric(EDUC),
  BMI = NACCBMI,
  MOCA = NACCMOCA,
  HYPCHOL = case_when(
   HYPCHOL == 0 ~ "No",
   HYPCHOL == 1 ~ "Yes"
  ),
  EDUC = case_when(
   EDUC <= 12 ~ "High_GRE",
   EDUC > 12 & EDUC <= 16 ~ "Bachelor",
```

```
    EDUC > 16 & EDUC <= 19 ~ "Master",
    EDUC > 19 ~ "Doctorate"
  ),
  RACE = case_when(
    RACE == 1 ~ "White",
    RACE == 2 ~ "Black",
    RACE == 3 ~ "USIndians/Alaska",
    RACE == 4 ~ "Hawaiian/Pacific",
    RACE == 5 ~ "Asian",
    RACE == 50 ~ "Other",
    RACE == 99 ~ NA
  ),
  SEX = case_when(
    SEX == 1 ~ "Male",
    SEX == 2 ~ "Female"
  ),
  STAYHOME = case_when(
    STAYHOME == 1 ~ "Yes",
    STAYHOME == 0 ~ "No"
  ),
  HYPERCHO = case_when(
    HYPERCHO == 1 ~ "Active",
    HYPERCHO == 0 ~ "Absent",
    HYPERCHO == 2 ~ "Inactive"
  ),
  HYPERTEN = case_when(
    HYPERTEN == 0 ~ "Absent",
    HYPERTEN == 1 ~ "Active",
    HYPERTEN == 2 ~ "Inactive"
  ),
  DIABETES = case_when(
    DIABETES == 0 ~ "Absent",
    DIABETES == 1 ~ "Active",
    DIABETES == 2 ~ "Inactive"
  ),
  FAM = case_when(
    NACCFAM == 0 ~ "No",
    NACCFAM == 1 ~ "Yes",
    NACCFAM == 9 ~ NA
  ),
  TBI = case_when(
    TBI == 0 ~ "Absent",
    TBI == 1 ~ "Active",
    TBI == 2 ~ "Inactive"
  ),
  AGE = NACCAGE
) %>%
select(-NACCBMI, -NACCAGE)
```

```
dt.2 <- dt.2 %>%
 mutate(
  AGE = ifelse(AGE < 18 | AGE > 120, NA, AGE),
  BMI = ifelse(BMI < 10 | BMI > 100, NA, BMI),
  SMOKYRS = ifelse(SMOKYRS < 0 | SMOKYRS > 87, NA, SMOKYRS),
  DECAGE = ifelse(DECAGE < 15 | DECAGE > 110, NA, DECAGE)
 )

dt.2$DECAGE[dt.2$DECAGE %in% c(888, 999, -4)] <- NA
dt.2$CANCER[dt.2$CANCER == 8] <- NA
dt.2$DIABETES[dt.2$DIABETES == 9] <- NA
test.df <- data.frame(table(dt.2$NACCID))
test.df <- test.df[test.df$Freq > 1, ]
dt.3 <- dt.2[!dt.2$NACCID %in% test.df$Var1, ] %>% select(-VISITYR, -VISITDAY, -VISITMO, -NACCMOCA)

# Create age variable
dt.3$AGE_CAT <- cut(dt.3$AGE,
            breaks = c(18, 65, 74, 120),
            labels = c("<65", "65-74", ">74"))


# table1
CreateTableOne(vars = c("AGE","EDUC","BMI","MOCA","RACE","SEX","SMOKYRS","STAYHOME","FAM","HYPERCHO","HYPERTEN","DIABETES"),strata = "CI",data=dt.3,
        factorVars = c("EDUC","RACE","SEX","STAYHOME",
                "HYPERCHO","HYPERTEN","DIABETES"),includeNA =T)


# Logistic regression model
# unadjusted
m333 <- glm(CI ~ HYPERCHO* AGE_CAT,family="binomial",data = dt.3)
summary(m333)
exp(coef(m333))
exp(confint(m333, level = 0.90))

# adjusted
m40 <- glm(CI ~ HYPERCHO * AGE_CAT + HYPERCHO+ HYPERCHO* SEX+DIABETES+HYPERCHO*EDUC +BMI +  HYPERTEN + SMOKYRS, family="binomial", data=dt.3)
summary(m40)
exp(coef(m40))
exp(confint(m40, level = 0.90))

# fit
glance(m333)
glance(m40)
```

```
# Roc
# Preparing data
dt.4 <- dt.3 %>%
 select(CI, HYPERCHO, AGE_CAT, RACE, SEX, EDUC, DIABETES, BMI, HYPERTEN, SMOKYRS) %>%
 filter(complete.cases(.))

# Fitting the logistic regression model
m555 <- glm(CI ~ HYPERCHO * AGE_CAT + RACE + HYPERCHO * SEX + DIABETES + HYPERCHO *
EDUC + BMI + HYPERTEN + SMOKYRS,
        family = "binomial", data = dt.4)

# Conducting ROC analysis
roc_result <- roc(response = dt.4$CI, predictor = predict(m555, type = "response"))

# Calculating AUC and CI
auc_value <- auc(roc_result)
auc_ci_bounds <- ci(roc_result, of = "auc")

# Create AUC
ci_text <- sprintf("AUC = %.3f\n95%% CI [%0.3f-%0.3f]", auc_value, auc_ci_bounds[1],
auc_ci_bounds[2])
print(ci_text)

# data
roc_data <- data.frame(
 True_Positive_Rate = roc_result$sensitivities,
 False_Positive_Rate = 1 - roc_result$specificities,
 Thresholds = roc_result$thresholds
)

# ROC plot
roc_plot <- ggroc(roc1,color = "#1c61b6") +
 annotate("text", x = 0.2, y = 0.2, label = ci_text, hjust = 0, vjust = -1, color = "black", size = 5) +
 geom_abline(slope = 1, intercept = 1, linetype = "dashed", color = "red", size = 1) +
 labs(title = "ROC Curve for Model Validation", x = "Specificity", y = "Sensitivity") +
 theme_minimal()

# Print the plot
print(roc_plot)

# Checking the residuals
par(mfrow=c(2,2))
plot(m40)
```