Higher Total Cholesterol in *APOE*4 Carriers Contributes to Alzheimer's Disease Risk: Findings from the Alzheimer's Disease Neuroimaging Initiative

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INTRODUCTION

- *APOE* is the greatest genetic risk factor for Alzheimer's disease (AD),[1] with highest risk observed in ε4 allele carriers.[2]
- *APOE* contributes to blood cholesterol metabolism, and literature suggests associations between high total blood cholesterol, *APOE* ε4 allele, and AD.[3-10]
- However, mechanisms underlying *APOE*'s conferral of AD risk are poorly understood.[2]
- **AIMS: 1)** To examine whether total cholesterol levels differed between *APOE* genotypes.
  2) To determine whether total cholesterol levels differed between cognitively normal individuals and those with mild cognitive impairment or AD.
  3) To investigate potential causality between total cholesterol levels and AD using Mendelian randomization, with *APOE* as a genetic instrumental variable.

METHODS

Participants

- N = 1,534 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Data collected 2004-2017 from 55 sites across US and Canada[11-13]

Materials

- Measurement of total blood cholesterol levels
- Baseline diagnosis of cognitively normal (CN), mild cognitive impairment (MCI) due to Alzheimer's disease, or Alzheimer's disease (AD)
- *APOE* genotyping and classification:

***APOE* Groups**	***APOE* Genotypes**
*APOE*2+	ε2/ε2, ε2/ε3
*APOE*3	ε3/ε3
*APOE*4+	ε4/ε4, ε4/ε3

Sample Characteristics

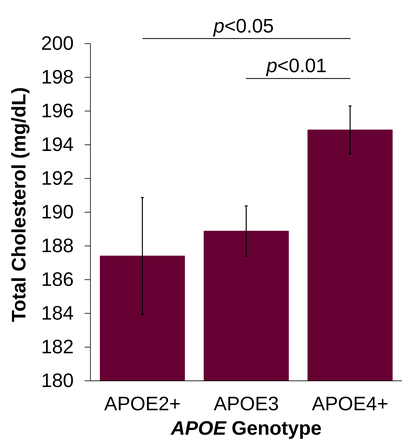
	Diagnostic Group		
	CN (N=404)	MCI (N=833)	AD (N=297)
Age, years (M±SD)	74.79 ± 5.73	72.97 ± 7.55	75.01 ± 7.71
Sex, male (N|%)	203 | 50.25	493 | 59.18	165.00 | 55.56
Education, years (M±SD)	16.30 ± 2.73	15.91 ± 2.85	15.08 ± 3.01
APOE Genotype (N|%)			
*APOE*2+	54 | 13.37	51 | 6.12	10 | 3.37
*APOE*3	241 | 59.65	373 | 44.78	85 | 28.62
*APOE*4+	109 | 26.98	409 | 49.10	202 | 68.01

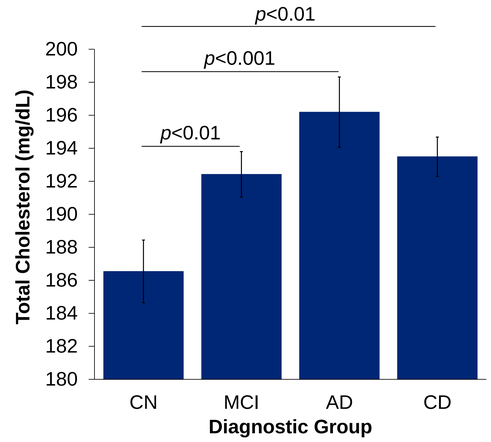
Statistical Analysis

- Generalized linear modeling of 1) total cholesterol across *APOE* groups and 2) total cholesterol across diagnostic groups
- Mendelian randomization (Wald Ratio Method):[14]
  1) Linear regression of lipids on *APOE* (*bx*)
  2) Logistic regression of diagnosis on *APOE* (*by*)
  3) Ratio of *by/bx* for each *APOE* group comparison

RESULTS

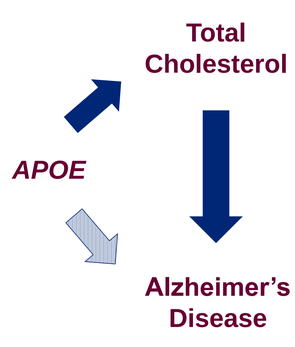
Total Cholesterol Across *APOE* and Diagnostic Groups



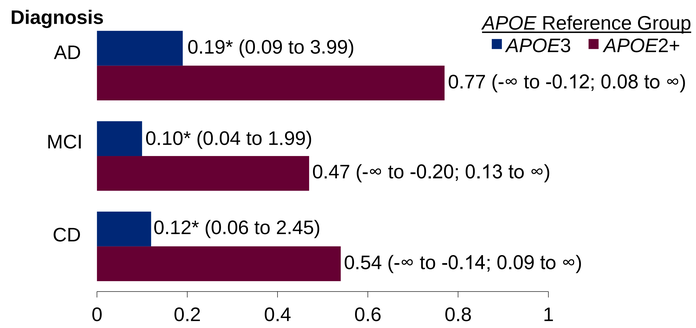


Regression models were adjusted for sex, age, and use of cholesterol-lowering medication.

Mendelian Randomization: Investigating Causality



An indirect association between *APOE* and AD, represented by the dotted arrow, is predicted to be mediated through total cholesterol[14,15]



OR = odds ratio, CI = confidence interval
*Statistically significant coefficients ($p < 0.05$) for regression of both total cholesterol on *APOE* and diagnosis on *APOE*, as well as F-statistic > 10[16]

DISCUSSION

- *APOE*4+ carriers had higher total cholesterol levels than both *APOE*2+ and *APOE*3 carriers.
- Total cholesterol levels were higher in AD and MCI groups compared to CN.
- Higher total cholesterol was associated with higher log odds ratios for MCI and AD in *APOE*4+ compared to *APOE*3 carriers.
- These findings suggest that dyslipidemia may be involved in *APOE*'s conferral of Alzheimer's risk.
- Maintenance of healthy total cholesterol levels may help reduce AD risk, particularly for *APOE*4+ carriers.

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