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Total Cholesterol and *APOE*-Related Risk for Alzheimer's Disease in the Alzheimer's Disease Neuroimaging Initiative

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Abstract.
Background: *APOE* ε4 allele confers greatest genetic risk for Alzheimer's disease (AD), yet mechanisms underlying this risk remain elusive. *APOE* is involved in lipid metabolism, and literature suggest relationships between high total cholesterol, *APOE*, and AD. Further investigation is needed to elucidate the potential role of total cholesterol in AD risk.
Objective: To investigate the relationship between total cholesterol and *APOE*-related AD risk in the Alzheimer's Disease Neuroimaging Initiative.
Methods: Participants ($N = 1{,}534$) were classified as controls (cognitively normal; $N = 404$), early mild cognitive impairment (MCI; $N = 294$), late MCI ($N = 539$), or AD ($N = 297$). Total cholesterol levels were compared across *APOE* genotype and diagnosis. Mendelian randomization was performed to examine causality between total cholesterol and AD risk using *APOE* as a genetic instrument.
Results: Total cholesterol was higher in *APOE4*+ compared to *APOE3* and *APOE2*+ ($ps < 0.04$) carriers. Those with AD and late MCI ($ps < 0.001$) had higher total cholesterol than the control group. Comparing *APOE4*+ to *APOE3* carriers, the predicted odds ratios per mg/dL greater total cholesterol were 1.11 for MCI (95% confidence interval, 1.04–7.32), 1.05 for early MCI (1.01–3.22), 1.13 for late MCI (1.05–11.70), 1.21 for AD (1.09–54.05), and 1.13 for composite dementia (MCI or AD; 1.06–11.59) ($ps < 0.05$, F-statistics > 10).
Conclusion: Higher total cholesterol may be a significant contributor to AD risk, particularly in *APOE4* carriers who, based on existing literature, tend to have impaired cholesterol metabolism. Our findings highlight a possible mechanism by which *APOE* confers AD risk and indicate potential for AD risk modification through maintenance of healthy total cholesterol levels.

Keywords: Alzheimer's disease, apolipoprotein E4, cholesterol, dementia, lipid metabolism

INTRODUCTION

Alzheimer's disease (AD), the most common cause of dementia [1], is the sixth leading cause of death in the United States [1, 2]. Despite decades of research, treatments currently available primarily offer symptom management rather than significant disease modification or reversal [3, 4]. A shift in focus from AD reversal to prevention may prove more successful in lowering AD incidence. Literature suggests that vascular risk factors, some of which are modifiable, may be important contributors to AD

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_ Acknowledgement_List.pdf

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[5–8]. Given that AD pathology begins years prior to symptom presentation [3, 4], further research into relationships between modifiable vascular biomarkers and AD is critical to progress in AD risk reduction and disease prevention.

The Apolipoprotein E (*APOE*) gene is the best-known genetic risk factor for AD [4, 9]. Mechanisms underlying this genetic risk, however, remain poorly understood. Structural differences between apolipoprotein E (ApoE) isoforms coded by *APOE* ε2, ε3, and ε4 alleles correspond to different binding affinities of ApoE to lipoprotein receptors and amyloid-β (Aβ) [9–11]. The E4 isoform has a higher binding affinity to larger lipoprotein receptors and a lower binding affinity to Aβ than E2 and E3 isoforms, contributing to altered lipid metabolism and impaired Aβ clearance in *APOE* ε4 carriers [9–15]. Aβ and tau accumulations are the neuropathological hallmarks of AD [3, 4, 9, 16–18]. Aβ first aggregates between neurons, which in turn facilitates deposition of hyperphosphorylated tau protein in the form of neurofibrillary tangles within neurons [9, 17, 18].

In addition to the impaired ability of *APOE* ε4 carriers to clear Aβ buildup, the role of *APOE* in cholesterol metabolism may relate to AD risk. *APOE*-related differences in cholesterol metabolism have been linked to differences in blood lipids—ε4 carriers tend to have the highest LDL and total blood cholesterol levels, while ε2 carriers have the lowest [11–13, 19, 20]. Higher total and LDL cholesterol both in midlife [21–26] and late life [24, 27–29] have been associated with mild cognitive impairment (MCI) and AD. Literature also suggest that AD patients have higher LDL and total cholesterol, and lower HDL cholesterol compared to controls [13, 28–32]. High LDL and total cholesterol have also been associated with impaired global cognition [33–35] and greater Aβ pathology [30,36]. However, literature on blood cholesterol and AD is equivocal [26, 37–39] and the mechanisms underlying this relationship remain elusive.

The purpose of the current study is to investigate total cholesterol as a potential mediator underlying *APOE* AD risk in a large sample of adults who participated in the Alzheimer's Disease Neuroimaging Initiative. First, we aim to determine whether *APOE* ε4 carriers in our sample have higher total cholesterol compared to non-ε4 carriers, as should be the case based on the existent literature. We then examine whether total cholesterol is higher among those diagnosed with AD or MCI compared to controls. Finally, we investigate potential causality between total cholesterol and AD employing Mendelian randomization, using *APOE* as a genetic instrument.

MATERIALS AND METHODS

Participants

We analyzed data collected at 55 sites from across the United States and Canada from 1,534 individuals who participated in the Alzheimer's Disease Neuroimaging Initiative (ADNI) between 2004 and 2017 [40–42]. Participants were aged 54 to 91 at baseline. All participants provided written informed consent, and study protocols were approved by institutional review boards of participating institutions [40–42]. Full inclusion and exclusion criteria are detailed in ADNI's General Procedures Manuals [40–42].

Materials

APOE genotype and non-fasting serum total cholesterol levels were obtained from blood samples [40–43]. The Concurrent Medications Log provided information on the use of statins or other cholesterol-lowering medication [40–42]. Physical and neurological examinations of all participants were completed by physicians to assess for neurological symptoms and changes in health status [40–42]. Details of all tests and procedures are available online and in ADNI's procedures manuals [40–43].

Procedure

At baseline, participants provided demographic and medication information and underwent vital sign assessment, neurological examination, cognitive assessment, and blood sample collection [40–43]. A diagnostic summary for each participant was completed based on cognitive function and health status criteria established and previously documented by ADNI [40–42]. Participants were classified as either cognitively normal (controls), MCI, or AD [40–43]. Those diagnosed with MCI were further classified as either early or late MCI based on the stage of clinical symptom presentation [41–44]. Those with early MCI exhibited milder cognitive and functional impairment as well as slower rate of progression than those with late MCI [44].

Statistical analysis

For analysis purposes, participants were grouped based on their *APOE* genotype as ε2 carriers

(*APOE*2+; ε2/ε2 or ε2/ε3), ε3 carriers (*APOE*3; ε3/ε3), or ε4 carriers (*APOE*4+; ε3/ε4 or ε4/ε4). No *APOE* ε2/ε4 carriers were included in the sample due to opposing effects of the ε2 and ε4 alleles on lipids and small sample sizes typically associated with the low frequency (4%) of this genotype in the population [45]. Generalized linear modeling was used to analyze total cholesterol levels by *APOE* genotype to confirm that *APOE* ε4 carriers had higher total cholesterol levels. Generalized linear modeling was also used to investigate differences in total cholesterol between diagnostic groups using three models: 1) controls compared to composite dementia (MCI+AD), 2) controls compared to MCI and AD groups separately, and 3) controls compared to early MCI, late MCI, and AD.

Mendelian randomization (MR) analysis was performed to investigate potential causality between total cholesterol and AD using the Wald ratio of coefficients method [46]. MR provides an alternative to randomized controlled trials due to its ability to investigate causality between a modifiable exposure and a disease in observational data by using a genetic instrumental variable [47–53]. MR relies on the assumptions that the genetic instrument is reliably associated with the exposure variable and is independent of confounding factors as well as the disease [47–53]. Given *APOE*'s established role in cholesterol metabolism [9–14, 19, 20] and AD risk [4, 9], we used *APOE* as a genetic instrument in MR to examine whether total cholesterol underlies or contributes to *APOE*-related AD risk. Based on Mendel's Law of Independent Assortment, risk for confounding is minimized in MR because the inheritance of one trait is independent of the inheritance of other traits [47–53]. The possibility of reverse causation between total cholesterol levels and AD is also minimized because the effect of *APOE* on total cholesterol levels begins before AD development [47–51].

We first assessed for possible confounding by dementia risk factors available in this sample prior to MR by performing analysis of variance (ANOVA) in the control group to check for differences in age, sex, education, body mass index (BMI), hypertension, and smoking history across *APOE* genotype [51]. MR analysis was then performed to estimate the causal effect of total cholesterol on dementia by the ratio of coefficients from logistic regression of dementia on *APOE* genotype and linear regression of total cholesterol on *APOE* genotype [46, 51–54]. Regression of dementia based on *APOE* genotype was modeled using five binary disease outcomes: controls versus AD, controls versus MCI, controls versus composite dementia, controls versus early MCI, and finally controls versus late MCI. This approach allowed for estimation of *APOE*'s influence on dementia via total cholesterol based on the different possible diagnostic categories available in this sample. Regression of total cholesterol by *APOE* genotype was performed by comparing two of the three *APOE* groups at a time (*APOE2*+ versus *APOE3*, *APOE3* versus *APOE4*+, and *APOE2*+ versus *APOE4*+). Additionally, given that this sample consists of case-control data, regression of total cholesterol by *APOE* status was modeled using only the control group, as is typically recommended for case-control studies in MR analysis [46]. Fieller's theorem was used to calculate 95% confidence intervals for each ratio estimate [46].

Sex, age, and use of cholesterol-lowering medication were included as covariates in analyses. BMI was also used in MR regression to control for possible confounding due to differences in BMI across *APOE* groups. Generalized linear models were performed using SAS University Edition 2.8.1 in SAS Studio platform version 3.8, ©2012–2018, SAS Institute Inc. MR analysis was performed using R (version 4.0.2 – ©2020 The R Foundation for Statistical Computing) within RStudio software (version 1.1.463 – ©2009–2018 RStudio, Inc.). Given the *a priori* hypotheses, significance was reported at $p < 0.05$.

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org.

RESULTS

Demographics

Sample demographics at baseline by diagnostic group are provided in Table 1. Mean baseline age of participants was 73.85 (SD = 7.21), and the sample was 56% male. A total of 26% of participants were considered cognitively normal, 54% were diagnosed with MCI (19% early MCI, 35% late MCI), and 20% were diagnosed with AD. A majority of participants had cardiovascular disease (1,048; 68%), and

Table 1
Sample characteristics in cases and controls

Variable	Diagnostic Group			
	Controls N = 404	Early MCI N = 294	Late MCI N = 539	AD N = 297
Age** (y), $M \pm SD$	74.79 ± 5.73	71.08 ± 7.35	74.0 ± 7.47	75.01 ± 7.71
Male* sex, n (%)	203 (50.25)	164 (55.78)	329 (61.04)	165 (55.56)
Education** (y), $M \pm SD$	16.3 ± 2.73	16.01 ± 2.66	15.86 ± 2.95	15.08 ± 3.01
Race, n (%)				
American Indian/Alaskan Native	1 (0.25)	1 (0.34)	1 (0.18)	0 (0)
Asian	7 (1.73)	4 (1.36)	10 (1.86)	6 (2.02)
Black or African American	27 (6.68)	6 (2.04)	21 (3.90)	12 (4.04)
Hawaiian or Other Pacific Islander	0 (0)	1 (0.34)	1 (0.19)	0 (0)
White	367 (90.84)	273 (92.86)	505 (93.69)	275 (92.59)
More than one race	2 (0.50)	6 (2.04)	1 (0.19)	4 (1.35)
Unknown	0 (0)	3 (1.02)	0 (0)	0 (0)
Ethnicity, n (%)				
Hispanic or Latino	13 (3.22)	13 (4.42)	15 (2.78)	8 (2.69)
Not Hispanic or Latino	389 (96.29)	280 (95.24)	521 (96.66)	287 (96.63)
Total Cholesterol (mg/dL), $M \pm SD$	191.9 ± 38.78	193.4 ± 39.80	196.3 ± 40.16	197 ± 41.39
CM Use**, n (%)	84 (20.79)	57 (19.39)	152 (28.20)	105 (35.35)
APOE Genotype**, n (%)				
APOE2+(ε2/2, ε2/3)	54 (13.37)	23 (7.82)	28 (5.19)	10 (3.37)
APOE3 (ε3/3)	241 (59.65)	149 (50.68)	224 (41.56)	85 (28.62)
APOE4+(ε3/4, ε4/4)	109 (26.98)	122 (41.50)	287 (53.25)	202 (68.01)
Body Mass Index**, $M \pm SD$	26.96 ± 4.39	27.99 ± 5.15	26.49 ± 4.29	25.67 ± 4.26
Smoking, n (%)	154 (38.12)	116 (39.46)	212 (39.33)	108 (36.36)
CVD, n (%)	271 (67.08)	198 (67.35)	373 (69.20)	206 (69.36)
Alcohol Abuse, n (%)	14 (3.46)	14 (4.76)	19 (3.53)	18 (6.06)

MCI, mild cognitive impairment; AD, Alzheimer's disease; M, mean; SD, standard deviation; CM, cholesterol-lowering medication; CVD, cardiovascular disease. *$p < 0.05$; **$p < 0.001$.

Table 2
Results from generalized linear modeling comparing total cholesterol levels between *APOE* genotypes

Variable	LSM (SE) (mg/dL)	Estimate	95% CI	χ^2	p
APOE Genotype					
APOE2+	187.40 (3.47)	–7.48	–14.65, –0.31	4.18	< 0.05
APOE3	188.88 (1.49)	–6.00	–9.80, –2.20	9.58	< 0.01
APOE4+	194.88 (1.42)	0.00			
CM Use		–19.94	–24.10, –15.78	88.31	< 0.0001
Sex (F)		27.14	23.47, 30.81	210.20	< 0.0001
Age		–0.44	–0.69, –0.18	11.36	< 0.001

LSM, least square mean of total cholesterol; SE, standard error; CI, confidence interval; CM, cholesterol-lowering medication.

398 (26%) reported using cholesterol-lowering medication (333 of whom had cardiovascular disease).

Total cholesterol and APOE genotype

APOE4+ had significantly higher total cholesterol compared to both *APOE3* (95% CI [–9.80, –2.20], $p < 0.01$) and *APOE2*+(95% CI [–14.65, –0.31], $p = 0.04$). Least square means of each *APOE* group's total cholesterol level are presented in Supplementary Figure 1, and full results from this generalized linear model are presented in Table 2.

Total cholesterol and diagnosis

Total cholesterol was significantly higher in the composite dementia group compared to controls (95% CI [2.74, 11.03], $p < 0.01$). When comparing AD and MCI separately to the control group, both those diagnosed with AD (95% CI [4.20, 12.10], $p < 0.001$) and MCI had significantly higher total cholesterol (95% CI [1.54, 10.21], $p < 0.01$).

A generalized linear model including early and late MCI diagnostic groups revealed further significant differences in total cholesterol, which was higher in those with late (95% CI [3.86, 13.22], $p < 0.001$)

Table 3
Results from generalized linear modeling comparing total cholesterol levels between diagnostic groups

Model	Variable	LSM (SE) (mg/dL)	Estimate	95% CI	χ^2	p
Model 1	Diagnosis					
	CN	186.61 (1.91)	0.00			
	MCI/AD	193.49 (1.19)	6.88	2.74, 11.03	10.61	<0.01
	CM Use		–19.66	–23.80, –15.52	86.58	<0.0001
	Sex (F)		27.47	23.79, 31.15	214.10	<0.0001
	Age		–0.45	–0.70, –0.20	12.21	<0.001
Model 2	Diagnosis					
	CN	186.54 (1.90)	0.00			
	MCI	192.42 (1.38)	5.87	1.54, 10.21	7.04	<0.01
	AD	196.19 (2.13)	9.65	4.20, 15.10	12.05	<0.001
	CM Use		–19.95	–24.10, –15.80	88.58	<0.0001
	Sex (F)		27.35	23.67, 31.03	212.08	<0.0001
	Age		–0.47	–0.73, –0.22	13.28	<0.001
Model 3	Diagnosis					
	CN	186.46 (1.90)	0.00			
	EMCI	187.25 (2.24)	0.79	–4.71, 6.29	0.08	0.79
	LMCI	195.00 (1.63)	8.54	3.86, 13.22	12.79	<0.001
	AD	196.20 (2.12)	9.73	4.30, 15.17	12.32	<0.001
	CM Use		–20.39	–24.54, –16.24	92.59	<0.0001
	Sex (F)		27.45	23.78, 31.12	214.78	<0.0001
	Age		–0.53	–0.78, –0.27	16.25	<0.0001

Model 1 compared those with MCI or AD to the CN (control) group. Model 2 compared AD and MCI groups separately to the CN group. Model 3 compared AD, late MCI, and early MCI groups separately to the CN group. LSM, least square mean of total cholesterol; SE, standard error; CI, confidence interval; CM, cholesterol-lowering medication; CN, cognitively normal controls; MCI, mild cognitive impairment; AD, Alzheimer's disease; EMCI, early MCI; LMCI, late MCI.

Table 4
Odds ratios of cases per mg/dL increase in total cholesterol from Mendelian randomization analysis

APOE Group Comparison	Early MCI OR (95% CI)	Late MCI OR (95% CI)	MCI (Early & Late) OR (95% CI)	AD OR (95% CI)	MCI & AD OR (95% CI)
APOE2+^{R} versus *APOE3*	0.90^{N}	0.90 (0, 1.00; 1.05, ∞)	0.90 (0, 0.99; 1.06, ∞)	0.89^{N}	0.90 (0, 0.99; 1.06, ∞)
APOE3^{R} versus *APOE4*+	1.05* (1.01, 3.22)	1.13* (1.05, 11.70)	1.11* (1.04, 7.32)	1.21* (1.09, 54.05)	1.13* (1.06, 11.59)
APOE2+^{R} versus *APOE4*+	1.51 (0, 0.90; 1.06, ∞)	1.70 (0, 0.87; 1.09, ∞)	1.60 (0, 0.87; 1.08, ∞)	2.16 (0, 0.82; 1.14, ∞)	1.72 (0, 0.87; 1.09, ∞)

*APOE*4 + carriers had significantly higher odds ratios of early MCI, late MCI, combined early and late MCI, AD, and combined MCI or AD. MCI, mild cognitive impairment; AD, Alzheimer's disease; OR, odds ratio, CI, confidence interval; ^{N}, no finite confidence interval exists other than the entire real line; ∞, infinity; ^{R}, reference group. *Statistically significant coefficients ($p < 0.05$) for regression of both total cholesterol on *APOE* and diagnosis on *APOE*, as well as F-statistic > 10 [43].

but not early MCI ($p = 0.79$) compared to the control group. Results from all generalized linear models are presented in Table 3 and Supplementary Figure 2.

Mendelian randomization analysis

Mendelian randomization relies on the assumption that there are no unmeasured confounders of the relationship between the genetic instrumental variable and the outcome [47, 51–53]. This assumption was assessed by checking for differences in the distribution of available risk factors for AD across *APOE* genotypes among controls (Supplementary Table 1). There were significant differences in BMI ($p = 0.04$) but not age, sex, education, hypertension, or smoking history across *APOE* genotypes; BMI was therefore included as a covariate in subsequent analyses.

MR analysis predicted significant odds ratios of diagnosis per mg/dL greater total cholesterol for *APOE4*+ compared to *APOE3*, but not *APOE3* compared to *APOE2*+ or *APOE4*+ compared to *APOE2*+. In *APOE4*+ compared to *APOE3*, odds ratios per mg/dL greater total cholesterol were 1.11, 95% CI [1.04, 7.32] for MCI, 1.05 [1.01, 3.22] for early MCI, 1.13 [1.05, 11.70] for late MCI, 1.21 [1.09, 54.05] for AD, and 1.13 [1.06, 11.59] for composite dementia (ps < 0.05 and F-statistics > 10). Full MR results are shown in Table 4.

DISCUSSION

In agreement with the literature, we report significantly higher total cholesterol in *APOE* ε4 allele carriers compared to non-carriers [11–13, 19, 45], and in those with AD and MCI diagnosis compared to the control group [27–29, 31, 33]. Additionally, those with late, but not early, MCI had significantly higher total cholesterol compared to the non-demented control group. Further research is necessary to determine whether increasing total cholesterol values we observed across progression stages toward AD might contribute to the development of AD, or whether advancing AD pathology is causative of higher cholesterol, although the results of MR analysis suggest it may be the former. Mendelian randomization revealed higher risk for AD, late MCI, and early MCI in relation to higher total cholesterol levels in *APOE4+* compared to *APOE3*. Collectively, our results suggest that high total cholesterol levels may contribute to AD risk and, furthermore, may be one mechanism through which *APOE* influences AD risk.

Traditionally, it was believed that cholesterol in the brain is produced locally and does not seem to relate directly to peripheral cholesterol levels [17, 18, 55–58]. However, recent evidence suggests that cholesterol in the periphery may influence brain cholesterol levels through conversion into 27-hydroxycholesterol (27-OH), an oxysterol which can cross the blood-brain barrier and enter the brain from the periphery [17, 18, 55–57]. Once in the brain, 27-OH promotes Aβ production and accumulation [17, 18, 56] and may act as a critical link between unhealthy blood lipid profiles and AD. Production of 27-OH appears to increase in states of high blood cholesterol and following consumption of cholesterol-containing foods in which the cholesterol has already been oxidized [55, 56]. Cholesterol also accumulates in Aβ plaques and brain cholesterol levels positively correlate with AD severity, both of which may occur in part due to AD-related impairments in blood-brain barrier integrity [17, 58–60]. The modifiable nature of blood lipids through pharmaceutical and lifestyle approaches may therefore present an important opportunity to affect AD risk.

Blood lipids can be managed and are modifiable through pharmacological and lifestyle interventions [13, 61–82]. Aside from statins and other cholesterol-lowering medications, lifestyle interventions reported to be effective in maintaining optimal lipid profiles include minimal consumption of foods containing saturated fat, trans fat, and cholesterol, as well as exercise and stress management [13, 64–72]. Specific dietary approaches that may help establish healthy cholesterol levels and potentially also influence dementia risk include Dietary Approach to Stop Hypertension (DASH) [73], Mediterranean [74–76], Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND; a combination of Mediterranean and DASH diets) [77], Okinawan [78], and plant-based diets [68, 74, 79–82]. All of these diets involve lower consumption of cholesterol, saturated fat, and trans fat compared to Western diets given their emphasis on plant foods and healthy fats while reducing or avoiding intake of red meat, high-fat dairy products, and fried and processed foods [68, 73–82].

Greater AD risk in relation to consumption of saturated fat, trans fat, and cholesterol has been previously established [13, 83–89]. Population studies also report that developing, non-Western countries have very low rates of AD in *APOE* ε4 and non-ε4 carriers alike, but that these rates are expected to rise—possibly due to increasing incorporation of the Western diet which is rich in cholesterol, saturated fat, and trans fat [13, 19, 65, 87, 90–93]. Furthermore, blood cholesterol levels in *APOE* ε4 allele carriers appear to be more responsive to changes in cholesterol and fat consumption compared to non-carriers [71, 72], suggesting that AD risk conferred by *APOE* may be at least partially modifiable. While the literature on statin use and dementia risk is currently inconclusive [94–98], perhaps lifestyle interventions alone or in combination with pharmacological treatments may achieve greater success. It is exciting to think that such interventions could potentially positively affect AD risk in addition to beneficial consequences on health in general.

This study is not without limitations. A significantly greater proportion of participants in late MCI and AD groups were on cholesterol-lowering medication compared to controls (Table 1). Nevertheless, this would only have biased our results toward the null. Further, LDL levels tend to be higher in relation to both *APOE4* [11,13,19] and AD risk [13, 28, 30–32], which we could not investigate because LDL cholesterol is not measured in ADNI. An additional research question that we did not explore in the current study due to the lack of data is whether duration of elevated blood cholesterol levels is important. The sample is not representative of the general population considering that ADNI participants are highly educated and predominantly white, with a selection bias toward MCI and AD diagnoses (74%). The distribution of

APOE genotypes in this sample also differs from that found in the general population, although this is not entirely surprising given that the majority of participants have been selectively recruited for their MCI or AD diagnosis. The estimated global frequencies of the *APOE* ε2, ε3, and ε4 alleles are approximately 8%, 78%, and 14%, respectively [9]. Our sample includes fewer ε3 (45.47%) and more ε4 (46.94%) allele carriers in comparison. Finally, while our overall sample size is on the smaller end of the spectrum for MR analyses, all of our significant findings exceed an F-statistic of 10, indicating that *APOE* is a sufficiently strong genetic instrumental variable for use in MR [51]. Existing reports of associations and potential causality between *APOE*, total cholesterol, and AD further justify use of MR in our approach [9, 11–13, 19–36, 99].

This should not undermine the unique strengths of the current study, including a large sample of participants from across both the U.S. and Canada. Our sample also has additional diagnostic information regarding early versus late stage MCI, which is rarely available. Further, MR provides important information regarding potential causality of associations between total cholesterol, *APOE* genotype, and AD risk. Given the lack of understanding of mechanisms underlying *APOE*'s conferral of AD risk, a key contribution of our study is the exploration of this mechanistic link via Mendelian randomization.

Identification of exact processes by which *APOE* influences AD pathology and confers risk is critical for the development of successful prevention and treatment methods. Our findings add to the growing literature suggesting that lipid profiles may be a clinically meaningful feature of AD and provide support for a potential mechanism by which *APOE* gene confers AD risk. Maintaining low total cholesterol may therefore be a critical aspect of preventative care for AD, particularly for *APOE* ε4 allele carriers.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/21-5091r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-215091.

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