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## Associations of dietary cholesterol and fat, blood lipids, and risk for dementia in older women vary by *APOE* genotype

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### Conflicts of Interest

All authors have no disclosures to report related to this work.

### Consent Statement

Written informed consent was provided by all participants prior to study participation, and approval was obtained from the Institutional Review Board at each participating site.

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## Abstract

**INTRODUCTION:** Whether *APOE*'s involvement in lipid metabolism contributes to Alzheimer's disease (AD) risk remains unknown.

**METHODS:** Incident probable dementia and cognitive impairment (probable dementia+mild cognitive impairment) were analyzed in relation to baseline serum lipids (total, LDL, HDL, and non-HDL cholesterol, total-to-HDL, LDL-to-HDL, remnant cholesterol, and triglycerides) using Mendelian randomization in 5,358 postmenopausal women from the Women's Health Initiative Memory Study. We also examined associations of baseline dietary cholesterol and fat with lipids based on *APOE* status.

**RESULTS:** After an average of 11.13 years, less favorable lipid levels related to greater dementia and cognitive impairment risk. Dementia (odds ratio[OR]=3.13; 95% confidence interval[CI]:2.31–4.24) and cognitive impairment (OR=2.38; 95% CI:1.85–3.06) risk were greatest in relation to higher remnant cholesterol levels. Greater cholesterol consumption related to poorer lipids in *APOE4*+ compared to *APOE3* carriers.

**DISCUSSION:** *APOE4*+ carriers consuming more cholesterol had less favorable lipids, which were associated with greater dementia and cognitive impairment risk.

## Keywords

Alzheimer's disease; mild cognitive impairment; dementia; cholesterol; Apolipoprotein E; diet; Mendelian randomization; Women's Health Initiative Memory Study

## 1 | Background

The Apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for Alzheimer's disease (AD),<sup>1,2</sup> which accounts for 60–80% of all dementia cases.<sup>3</sup> The *APOE* ε4 (*APOE4*) allele confers increased risk compared to ε3 (*APOE3*) homozygotes, while ε2 (*APOE2*) is protective.<sup>1,2</sup> However, specific mechanisms and neuropathological processes underlying *APOE4*-associated dementia risk remain elusive.<sup>2</sup> The increasing prevalence of dementia poses a substantial burden to the healthcare system, underscoring the need for preventive efforts.<sup>3,4</sup> Clarifying *APOE*'s role in dementia risk and its interactions with modifiable lifestyle factors may provide important insights into prevention strategies.

*APOE* plays a major role in lipid transport and metabolism,<sup>2,5</sup> accounting for an estimated 7% of phenotypic variance and 14% of polygenic variance in total serum cholesterol.<sup>6</sup> *APOE* also contributes an estimated 1–8.3% of phenotypic variance and 16% of genetic variance in LDL cholesterol.<sup>5,6</sup> *APOE4* carriers tend to have higher total and LDL cholesterol and lower HDL cholesterol levels compared to non-carriers.<sup>2,5,7,8</sup> *APOE4* carriers consuming diets high in saturated fat, total fat, and cholesterol have the least favorable lipid profiles, and conversely greatest lipid improvements when they decrease intake of the same compared to non-carriers.<sup>5,9,10</sup> Higher total cholesterol levels are associated with an increased risk of developing AD.<sup>11,12</sup> AD patients also tend to have higher total and LDL and lower HDL cholesterol levels compared to controls.<sup>13–16</sup> Additionally, higher total and LDL cholesterol levels are associated with greater deposition of AD neuropathological hallmarks in the brain.<sup>16,17</sup> Given that *APOE4* carriers' lipids are most responsive to diet,<sup>5,9,10</sup> these findings suggest that lipid management through dietary modification could potentially reduce AD risk.

The literature, however, does not consistently report greater dementia risk in relation to poorer blood lipid levels.<sup>18,19</sup> Few studies have assessed for causality between unfavorable lipid profiles and dementia risk. Additionally, associations between diet and *APOE* genotype in relation to blood lipids have been studied primarily in relatively small clinical samples. To address these shortcomings in the literature, we investigated relationships between dietary cholesterol and fat intake, blood lipids, *APOE* status, and dementia incidence in the Women's Health Initiative (WHI) Memory Study (WHIMS).<sup>20,21</sup> WHIMS, a randomized controlled clinical trial of hormone therapy, offers a well-screened sample of postmenopausal women with documented dementia incidence which is larger than those used in many published studies examining the aforementioned relationships. We first aimed to determine whether *APOE* moderates relationships between dietary cholesterol and fat consumption and blood lipid levels, and second, whether lipid levels are associated with dementia risk. Lastly, we performed Mendelian randomization to evaluate potential causality between blood lipids and dementia incidence, with *APOE* as a genetic instrument for lipid levels. Given *APOE*'s largely established associations with blood lipids and dementia, using *APOE* as a genetic instrument in Mendelian randomization minimizes issues of confounding and reverse causation. This analysis is therefore uniquely positioned to indicate whether blood lipids may have a causal influence on dementia risk.

## 2 | Methods

### 2.1 | Participants

WHIMS,<sup>20,21</sup> an ancillary study to the WHI hormone therapy clinical trial,<sup>22</sup> was designed to investigate effects of hormone therapy on incident cognitive impairment in women 65 years of age or older.<sup>20,21</sup> The present sample consisted of WHIMS participants who provided baseline dietary information and serum lipid profiles, were genotyped for *APOE*, and had follow-up adjudicated diagnosis of probable dementia, mild cognitive impairment (MCI), or no impairment (N=5,358). All women were initially free of cognitive impairment based on Modified Mini Mental State Exam (3MS) scores at baseline.<sup>20,21</sup> Written informed

consent was provided by all participants, and approval was obtained from the Institutional Review Board at each clinic site.

## 2.2 | Measures

Dietary information was obtained from a validated, self-administered, 145-item Food Frequency Questionnaire (FFQ) at baseline.<sup>23</sup> Average consumption of cholesterol (milligrams/day), saturated fat (grams/day), trans fat (grams/day), polyunsaturated fat (grams/day), monounsaturated fat (grams/day), protein (grams/day), carbohydrates (grams/day), and total calories (kcal/day) was estimated from participants' responses by the Fred Hutchinson Cancer Research Center Nutrition Assessment Shared Resource (NASR). Dietary estimates were conducted using the Nutrition Data System for Research (NDSR) software developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN. Validation information of dietary estimates has previously been published for all dietary variables included in this study, with the exception of trans fat.<sup>23</sup> Energy-adjusted correlation coefficients of dietary cholesterol (0.49), saturated fat (0.56), polyunsaturated fat (0.44), monounsaturated fat (0.57), protein (0.41), and carbohydrate (0.63) estimates from the FFQ in relation to average intake from four 24-hour recalls and a four-day food record were very similar to coefficients from the Willett 18, Willett 19, and Block/NCI FFQs.<sup>23</sup>

Serum lipids (total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol [mg/dL] and triglycerides [mg/dL]) were measured from fasting blood samples obtained at baseline. Analysis of lipid levels was performed at the University of Minnesota Medical Center Advanced Research and Diagnostics Lab. Total cholesterol levels were determined using the Roche Modular P Chemistry analyzer (Roche Diagnostics Corporation, Indianapolis, IN 46250). Standardization was performed using a serum standard prepared in the laboratory and frozen at  $-70^{\circ}\text{C}$ . Inter-assay coefficients of variation (CVs) of total cholesterol were 3.8% at 205.5 mg/dL and 5.1% at 252.0 mg/dL. HDL cholesterol levels were determined using the HDL-C plus third generation direct method on the Roche Modular P Chemistry analyzer. Inter-assay CVs of HDL cholesterol were 3.4% at 29.2 mg/dL and 2.3% at 57.6 mg/dL. LDL cholesterol levels were calculated using the Friedewald formula.<sup>24</sup> Triglyceride levels were measured on the Roche Modular P Chemistry analyzer, which was calibrated with a serum standard frozen at  $-70^{\circ}\text{C}$ . Inter-assay CVs of triglycerides were 2.0% at 85 mg/dL and 1.8% at 183 mg/dL. *APOE* genotyping was also performed using baseline blood draw. SNPs rs429358 and rs7412 were used to classify participants into *APOE* genotypes ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 3$ ,  $\epsilon 2/\epsilon 4$ ,  $\epsilon 3/\epsilon 3$ ,  $\epsilon 3/\epsilon 4$ ,  $\epsilon 4/\epsilon 4$ ).

Demographic information and possible confounders were recorded at WHI enrollment, including participants' age, highest level of education, smoking status, weekly alcohol consumption, body mass index (BMI), medical history (including hypertension, cardiovascular disease, type 2 diabetes, and stroke), use of cholesterol-lowering medication, and assignment in WHI hormone replacement therapy and dietary modification clinical trials.<sup>22</sup> Cholesterol-lowering medications comprised all antihyperlipidemic drugs, including bile sequestrants, fibric acid derivatives, intestinal cholesterol absorption

inhibitors, HMG CoA reductase inhibitors, nicotinic acid derivatives, and miscellaneous antihyperlipidemics.<sup>22</sup>

### 2.3 | Cognitive Assessment

The 3MS was administered annually to assess participants' global cognitive function.<sup>20,21</sup> Additional cognitive testing was administered to women who scored below pre-determined cut points based on age and education level.<sup>20,21</sup> Testing included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery,<sup>25</sup> clinical evaluation, and proxy interviews.<sup>20,21</sup> Annual face-to-face assessment was performed between 1995 and 2007.<sup>20,21</sup> From 2008 through 2020, a validated, telephone-administered cognitive battery was administered as part of the WHIMS Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) study.<sup>26</sup> All collected information was submitted to a centralized panel of experts for adjudication of no cognitive impairment, MCI, or probable dementia following standardized diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MCI criteria defined by Peterson et al.).<sup>20,21,27</sup> For those who were classified as MCI before progressing to probable dementia, their first classification of probable dementia was used as the outcome.

### 2.4 | Statistical Analysis

We calculated total-to-HDL and LDL-to-HDL cholesterol ratios, non-HDL cholesterol (total cholesterol minus HDL cholesterol) and remnant cholesterol (total cholesterol minus LDL and HDL cholesterol; a measure of very low-density lipoprotein [VLDL] and intermediate-density lipoprotein [IDL] in the fasting state<sup>28</sup>). Participants were categorized into three groups based on *APOE* genotype: *APOE2+* ( $\epsilon 2/\epsilon 2$ ,  $\epsilon 2/\epsilon 3$ ), *APOE3* ( $\epsilon 3/\epsilon 3$ ), or *APOE4+* ( $\epsilon 4/\epsilon 4$ ,  $\epsilon 3/\epsilon 4$ ) carriers. Those with  $\epsilon 2/\epsilon 4$  genotype (N=129) were excluded given that  $\epsilon 2$  and  $\epsilon 4$  exert opposing effects on lipid metabolism and dementia risk, making it unclear to which group they best belong.<sup>2,5</sup>

Interactions between *APOE* status and dietary components (dietary cholesterol, saturated fat, trans fat, polyunsaturated fat, and monounsaturated fat) were examined in relation to blood lipids (LDL, HDL, non-HDL, and total cholesterol, LDL-to-HDL and total-to-HDL ratios, remnant cholesterol, and triglycerides) using multiple linear regression. *APOE3* carriers were treated as the reference group. Each model was adjusted for all dietary components of interest as well as total protein, carbohydrate, and calorie intake, WHI hormone therapy trial assignment (estrogen intervention, estrogen plus progestin intervention, estrogen control, or estrogen plus progestin control), WHI dietary modification trial assignment (low-fat intervention or control), use of lipid-lowering medication (HMG CoA reductase inhibitor, bile sequestrant, fibric acid derivative, unspecified antihyperlipidemic, combination of antihyperlipidemic medication, or none), smoking status (never, former, or current), alcohol consumption (servings per week), BMI, and age at baseline. Least squares means of lipids by *APOE* status were calculated from these regression models. A sensitivity analysis examining these same relationships was performed excluding those who reported <600 or >5,000 kcal/day (N=157; among those excluded, 23 were *APOE2+*, 88 were *APOE3*, and 43 were *APOE4+*). Supplementary analyses were additionally performed investigating blood lipid differences and diet-*APOE*-lipid associations across all 6 genotypes, using  $\epsilon 3/\epsilon 3$

genotype as reference and excluding those reporting <600 or >5,000 kcal/day (N=160; among those excluded, 23 were  $\epsilon 2/\epsilon 3$ , 3 were  $\epsilon 2/\epsilon 4$ , 88 were  $\epsilon 3/\epsilon 3$ , 43 were  $\epsilon 3/\epsilon 4$  and 3 were  $\epsilon 4/\epsilon 4$ ).

Relationships between blood lipids and cognitive outcomes were examined using multiple logistic regression and Mendelian randomization. Logistic regression was used instead of Cox regression due to violation of the proportional hazards assumption by lipid levels. Lipids in those with incident probable dementia were compared to those without impairment, and the analyses were repeated for cognitive impairment (probable dementia+MCI). Lipid levels were defined using tertiles in logistic regression models (Table S1 in Supplement). The models were initially adjusted for age, hormone therapy trial assignment, education, use of lipid-lowering medication, and year of diagnosis. Secondary analyses were performed with additional adjustment for factors related to blood lipids or cognitive impairment (smoking status, alcohol consumption, hypertension, BMI, cardiovascular disease, stroke, and diabetes). These models were also performed separately for each *APOE* group as a supplementary analysis.

*APOE* was used as a genetic instrument in Mendelian randomization analysis given its role in lipid metabolism<sup>2,5-7</sup> and AD risk.<sup>1,2</sup> Mendelian randomization provides an alternative to randomized controlled trials for causal inference through the use of a genetic instrumental variable which is reliably associated with both the exposure variable and disease outcome.<sup>29</sup> A two-stage least squares (2SLS) method was used to estimate the causal effect of lipids (LDL, HDL, non-HDL, total, and remnant cholesterol and triglycerides) on the risk of probable dementia and cognitive impairment. Linear regression of each lipid on *APOE* status was first performed, followed by logistic regression of probable dementia or cognitive impairment on lipid levels from the first-stage regression. Adjustments were made for age given that among those who remained cognitively normal, *APOE4*+ carriers were significantly younger than both *APOE2*+ and *APOE3* carriers ( $p$ 's<0.05). To test the robustness of the Mendelian randomization results, we performed an additional 2SLS analysis using the *APOE4* risk allele on the rs429358 and rs7412 SNPs as the genetic instrument. A risk allele score was assigned to each *APOE* genotype group in the first-stage regression of this analysis ( $\epsilon 2/\epsilon 2=1$ ,  $\epsilon 2/\epsilon 3=2$ ,  $\epsilon 3/\epsilon 3=3$ ,  $\epsilon 3/\epsilon 4=4$ ,  $\epsilon 4/\epsilon 4=5$ ). All participants were white, which minimized issues related to population stratification.

Additional supplementary analyses were conducted to examine relationships between tertiles of dietary cholesterol and fat intake and cognitive outcomes within each *APOE* group, excluding those who reported <600 or >5,000 kcal/day. These models were initially adjusted for all dietary components of interest (dietary cholesterol, saturated fat, trans fat, monounsaturated fat, and polyunsaturated fat) as well as total protein, total carbohydrate, total energy intake, year of diagnosis, age at baseline, assignment in hormone therapy and dietary modification trials, education, and lipid-lowering medication. Further adjustment was also made for smoking, alcohol, BMI, hypertension, cardiovascular disease, stroke, and diabetes.

SAS University Edition 2.8.1 in SAS Studio, version 3.8, ©2012–2018, SAS Institute Inc. was used to perform multiple linear regression and multiple logistic regression analyses.

Mendelian randomization analysis was performed in R, version 4.0.3, ©2020, The R Foundation for Statistical Computing. Given the *a priori* hypotheses, significance was reported at  $p<0.05$ .

### 3 | Results

#### 3.1 | Sample Characteristics

Baseline sample characteristics are presented in Table 1. Participants (N=5,358) were followed for a median of 10 years (SD=6.34) between 1995 and 2020 until classification of MCI or probable dementia or until the final assessment for those who remained cognitively normal. In total, 588 (11%) participants received a classification of probable dementia, 347 (6%) were classified as MCI, and 4,423 (83%) remained cognitively normal. The mean age at WHI enrollment was 70.15 years (SD=3.84). Based on *APOE* status, 746 (14%) were classified as *APOE2+*, 3,379 (63%) as *APOE3*, and 1,233 (23%) as *APOE4+*. *APOE4+* carriers had higher levels of LDL, non-HDL, LDL-to-HDL, and total-to-HDL cholesterol compared to *APOE3* carriers, while *APOE2+* had lower levels of LDL, non-HDL, total, LDL-to-HDL, and total-to-HDL cholesterol compared to *APOE3* carriers ( $p$ 's<0.05; Table S2 in Supplement). Most participants had no history of cardiovascular disease (83%) or stroke (99%) and were not using lipid-lowering medications at baseline (88%). Cholesterol-lowering medication use was higher among *APOE4+* (15%) compared to *APOE2+* (8%) and *APOE3* (12%) carriers.

#### 3.2 | Relationships between dietary cholesterol and fat consumption and blood lipids

**3.2.1 | Primary analysis.**—Relationships between dietary cholesterol, trans fat, monounsaturated fat, and several blood lipids varied by *APOE* status (Table 2; Figure 1). Higher consumption of dietary cholesterol was associated with higher LDL (estimate=0.03 mg/dL, [95% CI (CI):0.002, 0.06],  $p=0.04$ ), non-HDL (estimate=0.04 mg/dL, [CI:0.01, 0.07],  $p=0.02$ ), LDL-to-HDL (estimate=0.001 mg/dL, [CI:0.0001, 0.002],  $p=0.03$ ), and total-to-HDL (estimate=0.001 mg/dL, [CI:0.0001, 0.002],  $p=0.03$ ) cholesterol levels in *APOE4+* compared to *APOE3* carriers. Higher monounsaturated fat intake was associated with higher levels of HDL cholesterol (estimate=0.50 mg/dL, [CI:0.17, 0.84],  $p=0.003$ ) in *APOE2+* compared to *APOE3* carriers. A stronger negative association between trans fat intake and HDL cholesterol was observed in *APOE2+* (estimate=-0.63 mg/dL, [CI:-1.20, -0.06],  $p=0.03$ ) compared to *APOE3* carriers, although *APOE3* carriers had lower HDL cholesterol levels overall in relation to higher trans fat consumption. (To convert LDL, HDL, and non-HDL cholesterol levels to mmol/L, multiply values by 0.0259). Relationships between blood lipids and saturated fat, monounsaturated fat, and polyunsaturated fat did not vary significantly by *APOE* status ( $p$ 's>0.05).

**3.2.2 | Sensitivity analysis.**—Sensitivity analysis excluding 157 participants with energy intake <600 or >5,000 kcal/day revealed similar results, though some associations were slightly attenuated (Table S3 in Supplement). Higher dietary cholesterol consumption among *APOE4+* carriers remained associated with higher non-HDL cholesterol levels (estimate=0.03, [CI:0.001, 0.07],  $p=0.04$ ) compared to *APOE3* carriers. *APOE2+* consuming more monounsaturated fat also still had higher levels of HDL cholesterol



(estimate=0.49, [CI:0.16, 0.83],  $p=0.004$ ) compared to *APOE3* carriers. However, associations between dietary cholesterol and LDL (estimate=0.03, [CI:–0.003, 0.06],  $p=0.07$ ), LDL-to-HDL (estimate=0.001, [CI:–0.0001, 0.002],  $p=0.07$ ), and total-to-HDL (estimate=0.001, [CI:–0.0001, 0.002],  $p=0.07$ ) cholesterol levels in *APOE4+* compared to *APOE3* carriers were no longer statistically significant. The association between trans fat and HDL cholesterol in *APOE2+* compared to *APOE3* carriers was also weakened (estimate=–0.57, [CI:–1.15, 0.003],  $p=0.05$ ).

**3.2.3 | Supplementary analysis.**—Supplementary analysis using all 6 *APOE* genotypes revealed significant blood lipid differences in  $\epsilon 2/\epsilon 3$  and  $\epsilon 3/\epsilon 4$  compared to  $\epsilon 3/\epsilon 3$  carriers (Table S4 in Supplement), as well as several interactions between dietary components and *APOE* genotype in relation to lipids (Table S5 in Supplement). Higher dietary cholesterol intake in *APOE*  $\epsilon 3/\epsilon 4$  was associated with higher non-HDL (estimate=0.03 mg/dL, [CI:0.001, 0.07],  $p=0.04$ ) and lower HDL (estimate=–0.01, [CI:–0.02, –0.0003],  $p=0.04$ ) cholesterol levels compared to  $\epsilon 3/\epsilon 3$  carriers. Higher trans fat consumption in *APOE*  $\epsilon 2/\epsilon 4$  was associated with lower LDL (estimate=–5.80, [CI:–10.20, –1.40],  $p=0.0098$ ) and LDL-to-HDL (estimate=–0.15, [CI:–0.27, –0.04],  $p=0.009$ ) cholesterol levels compared to  $\epsilon 3/\epsilon 3$  carriers. Higher saturated fat consumption in  $\epsilon 2/\epsilon 4$  was associated with higher triglyceride (estimate=4.32, [CI:1.74, 6.90],  $p=0.001$ ) and remnant cholesterol (estimate=0.88, [CI:0.36, 1.39],  $p=0.0008$ ) levels compared to  $\epsilon 3/\epsilon 3$  carriers. Higher monounsaturated fat consumption in  $\epsilon 2/\epsilon 4$  was associated with higher LDL (estimate=2.85, [CI:0.55, 5.16],  $p=0.02$ ) and LDL-to-HDL (estimate=0.06, [CI:0.0002, 0.12],  $p=0.049$ ) cholesterol levels, and lower triglyceride levels (estimate=–4.26, [CI:–8.48, –0.05],  $p=0.048$ ) compared to  $\epsilon 3/\epsilon 3$  carriers. Higher polyunsaturated fat consumption in  $\epsilon 2/\epsilon 4$  was associated with lower LDL cholesterol levels (estimate=–2.38, [CI:–4.66, –0.11],  $p=0.04$ ) compared to  $\epsilon 3/\epsilon 3$  carriers. Higher trans fat intake in  $\epsilon 2/\epsilon 3$  was associated with lower HDL cholesterol (estimate=–0.65, [CI:–1.23, –0.06],  $p=0.03$ ) compared to  $\epsilon 3/\epsilon 3$ , while higher monounsaturated fat intake in  $\epsilon 2/\epsilon 3$  was associated with higher HDL cholesterol levels (estimate=0.51, [CI:0.17, 0.85],  $p=0.003$ ) compared to  $\epsilon 3/\epsilon 3$  carriers. However, the considerable imbalance in sample sizes across *APOE* genotypes (i.e. 3,291  $\epsilon 3/\epsilon 3$  compared to 35  $\epsilon 2/\epsilon 2$  and 90  $\epsilon 4/\epsilon 4$  carriers) warrants caution when interpreting results from this supplementary analysis.

### 3.3 | Relationships between blood lipids and dementia risk

**3.3.1 | Logistic regression.**—Results from logistic regression examining probable dementia and cognitive impairment in relation to blood lipid tertiles are shown in Table 3. Higher total blood cholesterol levels were associated with greater risk for probable dementia (odds ratio [OR]=1.14, [CI:1.02, 1.28],  $p$  for trend=0.02), with ORs of 1.19 (CI:0.95, 1.50) and 1.31 (CI:1.05, 1.65) for the top second and third tertiles, respectively, compared to the bottom first tertile after full covariate adjustment. Higher total cholesterol levels were not significantly associated with risk for cognitive impairment (OR=1.09, [CI:0.99, 1.20],  $p$  for trend=0.06), with ORs of 1.08 (CI:0.90, 1.30) and 1.19 (CI:0.99, 1.43) for the top second and third tertiles, respectively. LDL, HDL, non-HDL, LDL-to-HDL, total-to-HDL, and remnant cholesterol and triglycerides were not significantly associated with risk for probable dementia or cognitive impairment ( $p$ 's>0.05).

**3.3.2 | Mendelian randomization.**—Mendelian randomization comparing *APOE* groups revealed significantly greater risk for probable dementia per mg/dL increase in LDL cholesterol (OR=1.43, [CI:1.28, 1.59]), non-HDL cholesterol (OR=1.27, [CI:1.18, 1.37]), total cholesterol (OR=1.47, [CI:1.31, 1.65]), remnant cholesterol (OR=2.08, [CI:1.66, 2.59]), and triglycerides (OR=1.16, [CI:1.11, 1.21]) and per mg/dL decrease in HDL cholesterol (OR=0.53, [CI:0.43, 0.64]) ( $p$ 's<0.001; Table 4). Cognitive impairment risk was also higher with each increasing mg/dL of LDL cholesterol (OR=1.32, [CI:1.21, 1.45]), non-HDL cholesterol (OR=1.21, [CI:1.14, 1.28]), total cholesterol (OR=1.35, [CI:1.23, 1.49]), remnant cholesterol (OR=1.78; [CI:1.47, 2.14]), and triglycerides (OR=1.12; [CI:1.08, 1.17]), and per mg/dL decrease in HDL cholesterol (OR=0.60, [CI:0.51, 0.71]) ( $p$ 's<0.001).

Mendelian randomization using the *APOE4* risk allele as the genetic instrument revealed similar results (Table 5). Probable dementia risk was greater per mg/dL increase in LDL cholesterol (OR=1.05, [CI:1.04, 1.06]), non-HDL cholesterol (OR=1.05, [CI:1.03, 1.06]), total cholesterol (OR=1.05, [CI:1.04, 1.07]), remnant cholesterol (OR=3.13, [2.31, 4.24]), and triglycerides (OR=1.25, [CI:1.18, 1.33]), and per mg/dL decrease in HDL cholesterol (OR=0.70, [CI:0.63, 0.77]) ( $p$ 's<0.001). Additionally, risk for cognitive impairment was greater per mg/dL increase in LDL cholesterol (OR=1.04, [CI:1.03, 1.05]), non-HDL cholesterol (OR=1.03, [CI:1.02, 1.05]), total cholesterol (OR=1.04, [CI:1.03, 1.05]), remnant cholesterol (OR=2.38, [CI:1.85, 3.06]), and triglycerides (OR=1.19, [CI:1.13, 1.25]), and per mg/dL decrease in HDL cholesterol (OR=0.76, [CI:0.70, 0.82]) ( $p$ 's<0.001).

**3.3.3 | Supplementary analysis.**—Supplementary logistic regression models examining cognitive outcomes in relation to blood lipid tertiles within *APOE* status groups are presented in Table S6 in Supplement. Moderately higher total cholesterol levels in the second tertile were associated with greater dementia risk in *APOE3* carriers after full adjustment (OR=1.52, [CI:1.12, 2.06],  $p$ =0.01). The second tertile of total-to-HDL levels was also associated with lower dementia (OR=0.67, [CI:0.49, 0.91],  $p$ =0.01) and cognitive impairment (OR=0.77, [CI:0.60, 0.99],  $p$ =0.045) risk after full adjustment in *APOE3* carriers. Higher total-to-HDL levels were associated with lower cognitive impairment risk in *APOE4+* after full adjustment (OR=0.81, [CI:0.67, 0.97],  $p$  for trend=0.02), with ORs of 0.86 (CI:0.61, 1.21) and 0.65 (CI:0.45, 0.93) for the top second and third tertiles, respectively. Higher HDL cholesterol levels were associated with greater cognitive impairment risk in *APOE4+* carriers after full covariate adjustment (OR=1.28, [CI:1.06, 1.54],  $p$  for trend=0.01), with ORs of 1.56 (CI:1.09, 2.22) and 1.64 (CI:1.12, 2.40) for the second and third tertiles, respectively. However, it should be noted that these models are unlikely to appropriately reflect lipid-dementia relationships due to low statistical power from a small proportion of dementia and cognitive impairment cases and small sample sizes. The models for *APOE2+* and *APOE3* groups were unable to converge, presumably related to these reasons.

### 3.4 | Supplementary analysis examining relationships between diet and dementia risk within *APOE* groups

Logistic regression models examining probable dementia and cognitive impairment risk in relation to dietary cholesterol and fat within each *APOE* group are presented in Table S7 in

Supplement. Higher saturated fat intake was associated with lower cognitive impairment risk in *APOE3* carriers after full adjustment ( $p$  for trend=0.04), with ORs of 0.75 (CI:0.52, 1.09) and 0.58 (CI:0.34, 0.98) for the second and third tertiles, respectively. However, *APOE2+* and *APOE3* models did not converge, likely due to low power related to small sample sizes and a low proportion of dementia and cognitive impairment cases.

## 4 | Discussion

Our findings in this sample of older, postmenopausal women of: (1) less favorable blood lipid profiles in relation to higher dietary cholesterol intake in *APOE4+* compared to *APOE3* carriers, and (2) greater dementia and cognitive impairment risk in relation to unfavorable lipid levels are largely consistent with the existing literature.<sup>5,9,10–12</sup>

*APOE4+* carriers consuming diets higher in cholesterol had higher LDL, non-HDL, LDL-to-HDL, and total-to-HDL cholesterol levels compared to *APOE3* carriers. While the associations of dietary cholesterol with LDL, LDL-to-HDL, and total-to-HDL levels were attenuated in sensitivity analyses, non-significant trends in the same direction remained.

Analyses including all 6 genotypes indicated higher non-HDL and lower HDL levels in relation to greater dietary cholesterol intake in  $\epsilon 3/\epsilon 4$  compared to  $\epsilon 3/\epsilon 3$  carriers. There were no significant differences between  $\epsilon 4/\epsilon 4$  and  $\epsilon 3/\epsilon 3$  carriers, which is likely related to low statistical power due to a substantial difference in group size, with 3,291  $\epsilon 3/\epsilon 3$  but only 90  $\epsilon 4/\epsilon 4$  carriers.

The opposing effects of *APOE*  $\epsilon 2$  and  $\epsilon 4$  alleles on lipid metabolism seem to be reflected in our results. For instance,  $\epsilon 2/\epsilon 4$  carriers had higher triglyceride and remnant cholesterol levels in relation to higher saturated fat intake, as well as lower LDL levels in relation to higher polyunsaturated fat intake compared to  $\epsilon 3/\epsilon 3$  carriers, which appears consistent with previous reports of  $\epsilon 4$  carriers' lipids being more responsive to dietary components which may be harmful (saturated fat) or beneficial (polyunsaturated fat).<sup>9,10</sup> *APOE*  $\epsilon 2/\epsilon 4$  carriers also had lower LDL and LDL-to-HDL levels in relation to higher trans fat intake, which might reflect a protective effect of  $\epsilon 2$  allele in the context of trans fat intake. Nevertheless, results from analyses including all 6 genotypes should be interpreted with caution, as they may be biased from low statistical power due to the comparison of small and unequal sample sizes. Overall, the interactions between diet, *APOE*, and blood lipids suggest that *APOE* may act as an effect modifier of lipid levels in response to cholesterol and fat consumption and support the possibility that *APOE4+* carriers' lipid profiles may benefit most from reduced dietary cholesterol intake.

Greater dementia risk in relation to unfavorable blood lipid levels in this cohort was confirmed by multiple logistic regression and Mendelian randomization, with the latter providing support for possible causality. Mendelian randomization additionally indicated greater cognitive impairment risk in relation to unfavorable blood lipids. Associations between all lipids with greater dementia and cognitive impairment risk may reflect one mechanism underlying *APOE4*-related AD risk. Interestingly, odds ratios for dementia and cognitive impairment were highest for remnant cholesterol from both Mendelian

randomization analyses, suggesting that elevated remnant cholesterol levels have a potentially stronger role in *APOE4*-related dementia risk compared to more commonly investigated lipids, such as total and LDL cholesterol. It should be noted that WHIMS assessed for all-cause dementia, although AD accounts for most dementia cases<sup>3</sup> and was the most common classification of dementia cases in WHIMS.<sup>20</sup> Still, we cannot rule out that the current sample may include a few vascular dementia cases, for which hypercholesterolemia and *APOE4* are also risk factors.<sup>30,31</sup> These findings should also be considered within the unique context of the present study, namely the fact that this sample consists exclusively of postmenopausal women. Menopause in its own right is associated with less favorable lipid profiles compared to pre-menopause,<sup>32</sup> particularly for *APOE3* and *APOE4* carriers.<sup>33</sup> Additionally, *APOE4*-associated AD risk is stronger in women than men.<sup>34</sup> If dyslipidemia is causally involved in dementia development, a notion that seems to be supported by our Mendelian randomization results, sex differences in dementia risk may relate to the additional influence of menopause on blood lipids in women in combination with *APOE*, dietary cholesterol and fat, and other contributing factors.

Based on statin literature, the possibility of dementia risk reduction via lipid-lowering therapy remains inconclusive.<sup>35,36</sup> Given that the hallmark neuropathology begins decades prior to symptom presentation,<sup>3</sup> statin use alone may be insufficient to substantially alter the course of the disease. Promoting healthy lipid profiles earlier in life prior to pathological onset could be a more effective strategy for reducing dementia risk. Population studies indicate the potential for diet to reduce dementia risk. For example, AD prevalence has historically been higher in Western countries,<sup>4,7,37</sup> which have higher consumption of saturated fat, trans fat, and cholesterol from red and processed meat, high-fat dairy, and fried and processed foods compared to less-developed, non-Western regions.<sup>4,7,38</sup> Dementia rates in non-Westernized regions are projected to rise along with increasing consumption of a Western diet.<sup>37,38</sup> Evidence-based dietary approaches to promote healthy blood lipid profiles include Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and plant-based diets.<sup>39–41</sup> These dietary patterns, along with the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, may aid in reducing dementia risk – especially in *APOE4* carriers – by emphasizing consumption of unprocessed plant foods and reducing intake of saturated fat, trans fat, and cholesterol.<sup>4,7,38,42–44</sup>

Research in mice further supports the possibility of AD risk reduction through dietary modification. For instance, mice fed a diet high in cholesterol subsequently developed higher levels of total cholesterol in plasma and  $\beta$ -amyloid ( $A\beta$ , a neuropathological hallmark of AD) in the brain compared to controls.<sup>45</sup> Similarly, a high-fat diet resulted in greater  $A\beta$  deposition and neuroinflammation, impaired sensory-motor function and social interaction, and a nonsignificant trend of poorer short-term memory in APP/PS1 mice compared to those fed a control diet.<sup>46</sup>

Female mice with human *APOE4* targeted replacement exhibited greater deficits in hippocampal-dependent learning and memory from insulin resistance induced from six months of a high-fat diet compared to *APOE3* mice.<sup>47</sup> The cognitive impairments in the *APOE4* mice were accompanied by unique epigenetic and metabolomic changes in hippocampus compared to *APOE3* mice.<sup>47</sup> A subsample of *APOE4* mice who were then

fed a low-fat diet for one month showed a complete rescue of cognitive function along with a reversal of the changes in the hippocampal epigenome and metabolome which had been induced by the high-fat diet.<sup>47</sup> These reports corroborate epidemiological observations linking diet with blood lipids, and *APOE*-related AD, further supporting the possibility that *APOE4* AD risk may be modifiable through dietary intervention.

A plausible mechanism through which diet and blood lipids could contribute to dementia pathology is through altered levels of oxysterols, which are oxidized products of cholesterol.<sup>48</sup> Dyslipidemia and dietary cholesterol intake may lead to imbalanced oxysterol levels, which appear to promote dementia pathology.<sup>48,49</sup> While further research is needed, existing literature suggests that dietary and blood lipid management may help lower dementia risk through maintenance of optimal oxysterol levels.<sup>48,49</sup>

Our study is not without limitations. Analyses were adjusted for hormone use during WHIMS participation, but prior history of hormone use could have influenced blood lipid levels and dementia or MCI risk. Although generalizability is limited due to the entirely female sample, our results are largely consistent with previous reports of variation in diet-blood lipid associations by *APOE* and relations between lipids and AD risk in samples of both men and women.<sup>5,9–13</sup> Dietary habits were assessed using a self-administered FFQ, hence possible inaccuracies related to self-reporting remain. Dietary estimates did not account for changes in food supply following national regulations of trans fats in 2018.<sup>50</sup> The attenuation of some diet-*APOE*-lipid relationships in sensitivity analyses and the inconsistent results in supplementary analyses among all 6 *APOE* genotypes and within *APOE* groups are likely influenced by a loss of statistical power. These preliminary findings nonetheless provide a novel contribution to the literature and provide motivation for future research in larger samples. Finally, given the heterogeneity of dementia and MCI cases in WHIMS, our findings should be interpreted with caution. These limitations should not undermine the unique aspects of our study; these include a large, well-screened, prospectively followed sample, examination of a large lipid panel, and Mendelian randomization analysis to investigate causality.

Overall, we report that *APOE4* carriers consuming higher amounts of dietary cholesterol and trans fat had less favorable blood lipid profiles, which were in turn associated with greater risk for dementia and cognitive impairment. Unfavorable lipid profiles might be important clinical indicators of risk for dementia and cognitive impairment in middle-aged and older individuals. Uncovering and correcting dyslipidemia early may therefore be a critical component of dementia risk management, especially for *APOE4* carriers. Further investigations of dementia risk in relation to dietary or pharmacologic modifications of blood lipids are needed and could have important implications for the prevention and treatment of dementia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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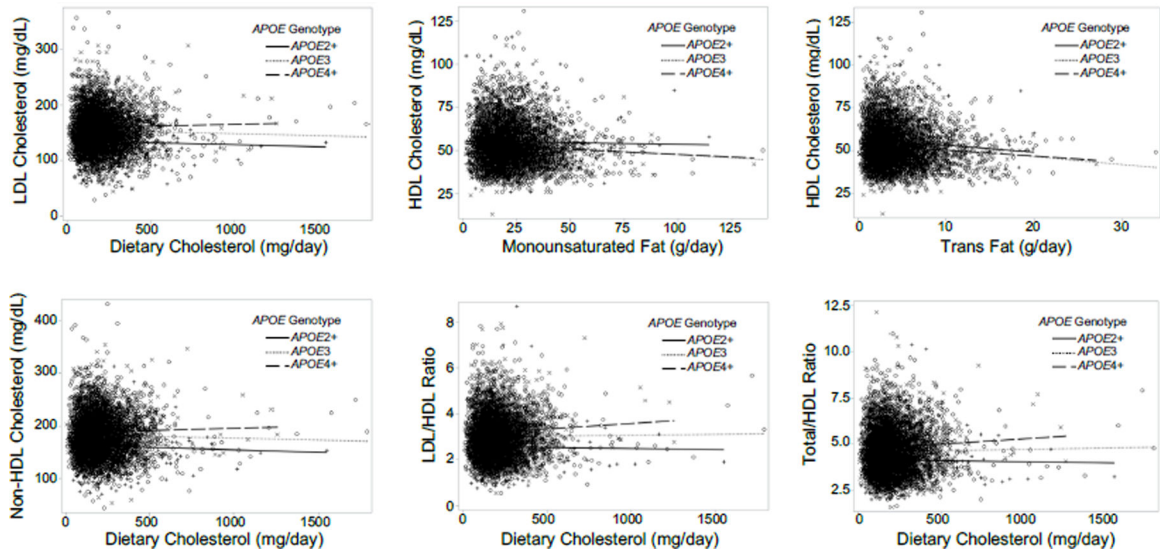
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### Highlights

- Less favorable serum lipids were associated with higher dementia incidence.
- Mendelian randomization findings suggest causality between lipids and dementia.
- Lipid levels in older women may be clinical indicators of dementia risk.
- *APOE4* carriers had poorest lipid profiles in relation to cholesterol consumption.
- *APOE* risk for dementia may be modifiable through lipid management.



**Figure 1. APOE Significantly Modifies the Relationships Between Diet and Lipids.**

Greater consumption of dietary cholesterol was associated with greater higher LDL, non-HDL, LDL-to-HDL, and total-to-HDL cholesterol levels in *APOE4+* compared to *APOE3* carriers. Greater consumption of monounsaturated fat and trans fat were associated with higher and lower HDL cholesterol levels, respectively, in *APOE2+* compared to *APOE3* carriers.

*SI conversion factor:* To convert cholesterol levels to mmol/L, multiply values by 0.0259. To convert triglyceride levels to mmol/L, multiply values by 0.0113.

*Abbreviations:* HDL = high-density lipoprotein; LDL = low-density lipoprotein.

**Table 1.**Sample Characteristics by *APOE* Status

	<i>APOE2+</i>	<i>APOE3</i>	<i>APOE4+</i>	<i>P</i> -value
N	746	3,379	1,233	
Age, M (SD)	70.33 (4.03)	70.17 (3.84)	69.98 (3.72)	0.12
Body Mass Index (kg/m <sup>2</sup> ), M (SD)	28.42 (5.69)	28.37 (5.43)	28.25 (6.10)	0.78
Education, N (%)				0.76
<High school	36 (4.8)	201 (5.9)	66 (5.4)	
High school	265 (35.5)	1,132 (33.5)	434 (35.2)	
College	282 (37.8)	1,266 (37.5)	454 (36.8)	
Postgraduate	163 (21.8)	780 (23.1)	279 (22.6)	
Smoking, N (%)				0.98
Never	403 (54.0)	1,822 (53.9)	654 (53.0)	
Former	296 (39.7)	1,336 (39.5)	496 (40.2)	
Current	47 (6.3)	221 (6.5)	83 (6.7)	
Alcohol servings per week, M (SD)	2.43 (5.20)	2.65 (5.50)	2.69 (5.40)	0.54
Serum blood lipids (mg/dL), M (SD)				
LDL cholesterol	134.34 (32.45)	154.31 (34.95)	159.74 (35.78)	<0.001
HDL cholesterol	55.25 (12.71)	53.67 (12.25)	52.30 (12.43)	<0.001
Non-HDL cholesterol	162.20 (37.95)	182.16 (39.07)	188.55 (38.83)	<0.001
Total cholesterol	217.45 (36.17)	235.83 (39.01)	240.86 (38.55)	<0.001
Remnant cholesterol	27.86 (12.63)	27.85 (13.39)	28.82 (13.36)	0.08
Triglycerides	139.71 (63.13)	139.79 (66.92)	144.59 (66.84)	0.08
LDL/HDL ratio	2.57 (0.93)	3.01 (0.92)	3.21 (1.00)	<0.001
Total/HDL ratio	4.14 (1.18)	4.59 (1.18)	4.83 (1.26)	<0.001
Total energy intake (kcal/day), M (SD)	1,611.09 (677.73)	1,582.89 (648.84)	1,583.64 (658.81)	0.56
Dietary carbohydrate (g/day), M (SD)	193.67 (79.18)	192.89 (78.63)	196.67 (81.84)	0.36
Dietary protein (g/day), M (SD)	67.36 (30.68)	66.37 (29.20)	66.23 (30.41)	0.67
Dietary total fat (g/day), M (SD)	62.27 (34.61)	59.55 (32.93)	58.12 (32.55)	0.03
Saturated fat	21.38 (12.50)	20.29 (12.00)	19.78 (12.01)	0.02
Monounsaturated fat	23.53 (13.36)	22.49 (12.68)	21.94 (12.40)	0.03
Polyunsaturated fat	12.51 (7.44)	12.12 (6.98)	11.85 (6.82)	0.13
Trans fat	4.47 (3.10)	4.28 (3.02)	4.26 (2.99)	0.27
Dietary cholesterol (g/day), M (SD)	227.49 (145.02)	214.49 (133.12)	204.65 (128.00)	0.001
Probable Dementia, N (%)	59 (7.9)	321 (9.5)	208 (16.9)	<0.001
Mild Cognitive Impairment, N (%)	49 (6.6)	211 (6.2)	87 (7.1)	0.21
Cholesterol-lowering medication, N (%)	61 (8.2)	418 (12.4)	186 (15.1)	0.003
HMG CoA reductase inhibitor	43 (5.8)	365 (10.8)	164 (13.3)	
Bile sequestrant	3 (0.4)	17 (0.5)	9 (0.7)	
Fibric acid derivative	14 (1.9)	22 (0.7)	12 (1.0)	
Unspecified antihyperlipidemic	0 (0)	1 (0.0)	0 (0)	
Combination antihyperlipidemic	1 (0.1)	13 (0.4)	1 (0.1)	

**SI conversion factor:** To convert cholesterol levels to mmol/L, multiply values by 0.0259. To convert triglyceride levels to mmol/L, multiply values by 0.0113.

**Abbreviations:** HDL = high-density lipoprotein; LDL = low-density lipoprotein.

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**Table 2.** Interactions of Dietary Cholesterol and Fat with *APOE* Status in Relation to Blood Lipids

Blood Lipid	<i>APOE</i> Group (ref= <i>APOE3</i> )	C x <i>APOE</i> Estimate (95% CI)	SF x <i>APOE</i> Estimate (95% CI)	TF x <i>APOE</i> Estimate (95% CI)	MF x <i>APOE</i> Estimate (95% CI)	PF x <i>APOE</i> Estimate (95% CI)
LDL Cholesterol	<i>APOE2+</i>	0.01 (-0.02, 0.04)	0.29 (-0.37, 0.95)	0.33 (-1.42, 2.09)	-0.33 (-1.35, 0.69)	-0.30 (-1.26, 0.66)
	<i>APOE4+</i>	0.03 (0.002, 0.06)*	0.23 (-0.40, 0.85)	-0.23 (-1.81, 1.34)	-0.55 (-1.53, 0.43)	0.25 (-0.63, 1.12)
	<i>APOE2+</i>	-0.01 (-0.02, 0.002)	-0.20 (-0.41, 0.02)	-0.63 (-1.20, -0.06)*	0.50 (0.17, 0.84) <sup>†</sup>	-0.19 (-0.50, 0.12)
HDL Cholesterol	<i>APOE4+</i>	-0.01 (-0.02, 0.0001)	-0.05 (-0.26, 0.15)	0.09 (-0.42, 0.60)	0.13 (-0.19, 0.45)	-0.01 (-0.29, 0.28)
	<i>APOE2+</i>	0.02 (-0.02, 0.05)	0.39 (-0.34, 1.13)	0.71 (-1.25, 2.67)	-0.62 (-1.76, 0.52)	-0.24 (-1.32, 0.84)
	<i>APOE4+</i>	0.04 (0.01, 0.07)*	0.33 (-0.37, 1.03)	-0.43 (-2.19, 1.33)	-0.72 (-1.81, 0.38)	0.27 (-0.71, 1.25)
Total Cholesterol	<i>APOE2+</i>	0.01 (-0.03, 0.04)	0.20 (-0.53, 0.93)	0.07 (-1.87, 2.02)	-0.12 (-1.24, 1.01)	-0.43 (-1.50, 0.64)
	<i>APOE4+</i>	0.03 (-0.003, 0.06)	0.28 (-0.42, 0.97)	-0.34 (-2.09, 1.41)	-0.59 (-1.68, 0.50)	0.27 (-0.71, 1.24)
	<i>APOE2+</i>	0.0004 (-0.0004, 0.001)	0.01 (-0.004, 0.03)	0.02 (-0.02, 0.07)	-0.02 (-0.05, 0.004)	-0.004 (-0.03, 0.02)
LDL/HDL Ratio	<i>APOE4+</i>	0.001 (0.0001, 0.002)*	0.01 (-0.01, 0.03)	-0.02 (-0.06, 0.03)	-0.01 (-0.04, 0.01)	0.001 (-0.02, 0.02)
	<i>APOE2+</i>	0.001 (-0.001, 0.002)	0.02 (-0.004, 0.04)	0.04 (-0.02, 0.10)	-0.03 (-0.07, 0.002)	-0.003 (-0.04, 0.03)
	<i>APOE4+</i>	0.001 (0.0001, 0.002)*	0.01 (-0.01, 0.03)	-0.02 (-0.07, 0.03)	-0.02 (-0.05, 0.01)	-0.001 (-0.03, 0.03)
Remnant Cholesterol	<i>APOE2+</i>	0.01 (-0.005, 0.02)	0.11 (-0.13, 0.35)	0.37 (-0.27, 1.01)	-0.29 (-0.66, 0.08)	0.06 (-0.29, 0.41)
	<i>APOE4+</i>	0.01 (-0.003, 0.02)	0.10 (-0.13, 0.33)	-0.20 (-0.77, 0.37)	-0.17 (-0.53, 0.19)	0.02 (-0.30, 0.34)
	<i>APOE2+</i>	0.03 (-0.03, 0.09)	0.52 (-0.68, 1.71)	1.83 (-1.37, 5.02)	-1.37 (-3.23, 0.48)	0.24 (-1.51, 2.00)
Triglycerides	<i>APOE4+</i>	0.04 (-0.01, 0.09)	0.49 (-0.65, 1.63)	-0.95 (-3.82, 1.92)	-0.82 (-2.61, 0.97)	0.10 (-1.50, 1.70)

\*  $p < 0.05$ ,  
<sup>†</sup>  $p < 0.01$ .

**SI conversion factor:** To convert cholesterol levels to mmol/L, multiply values by 0.0259. To convert triglyceride levels to mmol/L, multiply values by 0.0113.

**Abbreviations:** C = dietary cholesterol; CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MF = dietary monounsaturated fat; PF = dietary polyunsaturated fat; ref = reference group; SF = dietary saturated fat; TF = dietary trans fat; x = interaction between dietary variable and *APOE*.

**Table 3.**

Odds Ratios of Probable Dementia and Cognitive Impairment per Lipid Tertiles

Covariate Adjustment	Blood Lipid	Probable Dementia			Cognitive Impairment			P for trend
		1	2	3	1	2	3	
Limited Adjustment	LDL Cholesterol	1.00	1.10 (0.88, 1.37)	1.20 (0.96, 1.50)	1.00	1.04 (0.87, 1.24)	1.10 (0.92, 1.32)	0.28
	HDL Cholesterol	1.00	1.04 (0.83, 1.31)	1.14 (0.91, 1.43)	1.00	0.97 (0.81, 1.17)	1.02 (0.85, 1.23)	0.79
	Non-HDL Cholesterol	1.00	1.17 (0.94, 1.46)	1.17 (0.93, 1.46)	1.00	1.12 (0.93, 1.34)	1.10 (0.92, 1.32)	0.31
	Total Cholesterol	1.00	1.18 (0.94, 1.47)	1.28 (1.03, 1.60)	1.00	1.08 (0.90, 1.29)	1.17 (0.98, 1.40)	0.08
	LDL/HDL Ratio	1.00	0.94 (0.76, 1.17)	1.08 (0.87, 1.34)	1.00	0.98 (0.82, 1.18)	1.08 (0.90, 1.29)	0.40
	Total/HDL Ratio	1.00	0.83 (0.67, 1.03)	0.99 (0.80, 1.23)	1.00	0.90 (0.75, 1.07)	1.03 (0.86, 1.23)	0.79
	Remnant Cholesterol	1.00	0.90 (0.72, 1.12)	1.05 (0.84, 1.31)	1.00	0.89 (0.74, 1.07)	1.02 (0.85, 1.23)	0.76
	Triglycerides	1.00	0.91 (0.73, 1.13)	1.03 (0.83, 1.29)	1.00	0.92 (0.77, 1.10)	1.03 (0.86, 1.23)	0.79
	LDL Cholesterol	1.00	1.11 (0.88, 1.39)	1.22 (0.97, 1.52)	1.00	1.06 (0.88, 1.27)	1.12 (0.93, 1.35)	0.23
	HDL Cholesterol	1.00	1.04 (0.82, 1.32)	1.14 (0.89, 1.46)	1.00	0.97 (0.80, 1.17)	1.02 (0.84, 1.25)	0.80
Full Adjustment	Non-HDL Cholesterol	1.00	1.19 (0.95, 1.49)	1.19 (0.94, 1.49)	1.00	1.13 (0.94, 1.36)	1.12 (0.92, 1.35)	0.26
	Total Cholesterol	1.00	1.19 (0.95, 1.50)	1.31 (1.05, 1.65)	1.00	1.08 (0.90, 1.30)	1.19 (0.99, 1.43)	0.06
	LDL/HDL Ratio	1.00	0.95 (0.76, 1.19)	1.09 (0.87, 1.38)	1.00	0.99 (0.82, 1.20)	1.09 (0.91, 1.32)	0.35
	Total/HDL Ratio	1.00	0.84 (0.67, 1.05)	1.00 (0.79, 1.26)	1.00	0.90 (0.75, 1.09)	1.03 (0.85, 1.24)	0.78
	Remnant Cholesterol	1.00	0.91 (0.72, 1.15)	1.09 (0.86, 1.38)	1.00	0.91 (0.75, 1.10)	1.04 (0.86, 1.27)	0.63
	Triglycerides	1.00	0.91 (0.72, 1.14)	1.06 (0.84, 1.34)	1.00	0.92 (0.77, 1.12)	1.04 (0.86, 1.26)	0.68

**Abbreviations:** CI = confident interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio.

**Table 4.** Odds Ratios for Dementia per Unit (mg/dL) Increase in *APOE* Status-Predicted Levels of Blood Lipids

Blood Lipid	Probable Dementia		Cognitive Impairment	
	OR (95% CI)	P-value	OR (95% CI)	P-value
LDL Cholesterol	1.43 (1.28, 1.59)	<0.001	1.32 (1.21, 1.45)	<0.001
HDL Cholesterol	0.53 (0.43, 0.64)	<0.001	0.60 (0.51, 0.71)	<0.001
Non-HDL Cholesterol	1.27 (1.18, 1.37)	<0.001	1.21 (1.14, 1.28)	<0.001
Total Cholesterol	1.47 (1.31, 1.65)	<0.001	1.35 (1.23, 1.49)	<0.001
Remnant Cholesterol	2.08 (1.66, 2.59)	<0.001	1.78 (1.47, 2.14)	<0.001
Triglycerides	1.16 (1.11, 1.21)	<0.001	1.12 (1.08, 1.17)	<0.001

*Abbreviations:* CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio.

**Table 5.** Odds Ratios for Dementia per Unit (mg/dL) Increase in Blood Lipids using *APOE4* Risk Score-Predicted Levels of Blood Lipids

Blood Lipid	Probable Dementia		Cognitive Impairment	
	OR (95% CI)	P-value	OR (95% CI)	P-value
LDL Cholesterol	1.05 (1.04, 1.06)	<0.001	1.04 (1.03, 1.05)	<0.001
HDL Cholesterol	0.70 (0.63, 0.77)	<0.001	0.76 (0.70, 0.82)	<0.001
Non-HDL Cholesterol	1.05 (1.03, 1.06)	<0.001	1.03 (1.02, 1.05)	<0.001
Total Cholesterol	1.05 (1.04, 1.07)	<0.001	1.04 (1.03, 1.05)	<0.001
Remnant Cholesterol	3.13 (2.31, 4.24)	<0.001	2.38 (1.85, 3.06)	<0.001
Triglycerides	1.25 (1.18, 1.33)	<0.001	1.19 (1.13, 1.25)	<0.001

**Abbreviations:** CI = confidence interval; HDL = high-density lipoprotein; LDL = low-density lipoprotein; OR = odds ratio.