American Journal of Epidemiology

Vol. 187, No. 4
DOI: 10.1093/aje/kwx329
Advance Access publication: October 19, 2017

Original Contribution

Relationship of Lipids and Lipid-Lowering Medications With Cognitive Function

The Multi-Ethnic Study of Atherosclerosis

Kwok Leung Ong*, Margaret J. Morris, Robyn L. McClelland, Timothy M. Hughes, Jayanthi Maniam, Annette L. Fitzpatrick, Seth S. Martin, José A. Luchsinger, Stephen R. Rapp, Kathleen M. Hayden, Veit Sandfort, Matthew A. Allison, and Kerry-Anne Rye

* Correspondence to Dr. Kwok-Leung Ong, School of Medical Sciences, University of New South Wales, Level 4E, Wallace Wurth Building, Gate 9 High Street, Sydney, NSW 2052, Australia (e-mail: oklws@yahoo.com.hk).

Initially submitted April 13, 2017; accepted for publication October 3, 2017.

Studies on the relationship of cholesterol concentrations and lipid-lowering medications with dementia risk have yielded inconsistent findings. Therefore, we investigated the association of lipid concentrations and lipid-lowering medications with cognitive function in the Multi-Ethnic Study of Atherosclerosis across 3 different cognitive domains assessed by means of the Cognitive Abilities Screening Instrument (CASI; version 2), the Digit Symbol Coding (DSC) Test, and the Digit Span (DS) Test in 2010–2012. After adjustment for sociodemographic and confounding factors, including concentrations of other lipids and use of lipid-lowering medication, higher total cholesterol, low-density lipoprotein cholesterol, and non–high-density-lipoprotein cholesterol concentrations were modestly associated with higher DS Test scores. None of the lipid parameters were associated with CASI or DSC Test scores. Similarly, changes in lipid concentrations were not associated with any cognitive function test score. Using treatment effects model analysis and after adjusting for confounding factors, including lipid concentrations, the use of any lipid-lowering medication, especially statins, was associated with higher scores on the CASI and backward DS tests but not on the DSC and forward DS tests. Our study does not support a robust association between lipid concentrations and cognitive function or between the use of lipid-lowering medication, especially statins, and worse cognitive function.

cholesterol; cognitive decline; cognitive function; lipid-lowering medications; lipids; statins

Abbreviations: *APOE*, apolipoprotein E gene; CVD, cardiovascular disease; DS, Digit Span; DSC, Digit Symbol Coding; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; SD, standard deviation; TC, total cholesterol.

Hypercholesterolemia has been suggested as a risk factor for both dementia and Alzheimer disease (1, 2). Animal studies have shown an association between high cholesterol concentrations and impaired cognitive function (3–7). Conversely, studies of the association between plasma cholesterol concentrations and risk of dementia in human populations have yielded inconsistent findings, with some studies suggesting an association of high midlife cholesterol concentrations with increased dementia risk (8, 9) and others not finding such an association (10–12). Moreover, studies of cholesterol concentrations measured in later life usually do not demonstrate a significant association with cognitive function or even show an inverse relationship (12, 13).

The most commonly used lipid-lowering medications are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors ("statins"). In 2012, the Food and Drug Administration issued a warning on postmarketing reports of cognitive impairment (such as memory loss, forgetfulness, amnesia, memory impairment, and confusion) associated with statin use (14). Since then, the authors of several review articles have concluded that there is no strong evidence that statins have adverse cognitive effects (15–19).

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of participants who were free of clinically apparent cardiovascular disease (CVD) at baseline (examination 1) (20). Using existing data collected on this cohort, we

investigated the relationships of concentrations of different lipids, their ratios, and use of lipid-lowering medications with cognitive function. We hypothesized that this would provide more supporting evidence on whether the use of lipid-lowering medications might be associated with worse cognitive function.

METHODS

Participants

The MESA study consists of 6,814 men and women from 4 major ethnic groups (non-Hispanic white, African American, Hispanic American, and Chinese American) who, at baseline, were aged 45–84 years and free of clinically apparent CVD (20). None of the participants had physician-diagnosed CVD or current atrial fibrillation or had undergone procedures related to CVD at or before baseline. Between July 2000 and August 2002, participants from 6 US communities were recruited and enrolled in MESA at a baseline visit. Investigators at each field site recruited participants from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges. In the last few months of the recruitment period, supplemental sources (lists of Medicare beneficiaries from the Centers for Medicare and Medicaid Services and referrals by participants) were used to ensure inclusion of adequate numbers of minority and elderly subjects. Approximately equal numbers of men and women were recruited at each site, according to prespecified age and race/ethnicity proportions.

Over a follow-up period of 8.0–11.4 years (mean = 9.5 years), participants made up to 4 in-person clinic visits that were approximately 2 years apart. A total of 581, 867, 996, and 2,098 participants did not attended examinations 2, 3, 4, and 5, respectively. The study was approved by the institutional review boards at all participating centers, and informed written consent was obtained from all participants. The study was performed in compliance with the principles of the Declaration of Helsinki. The study objectives, design, and protocol have been described in detail previously (20).

Among 6,814 participants at baseline (2000–2002), 4,716 participated in examination 5 (2010–2012). Of these, 4,591 participants had available data on global cognitive function, and among these, 4,150 also had data on processing speed and working memory recorded at examination 5. Additionally, 4,076 had available data on lipid concentrations (total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides) and use of lipid-lowering medications from examination 5. After exclusion of participants with invalid tests of global cognitive function or extremely low test scores (described below), dementia (based on *International Classification of Diseases, Ninth Revision*, codes), or use of dementia medications at examinations 1–5, a total of 3,926 participants were eligible for inclusion in this analysis.

Cognitive assessment instruments used at examination 5

Three standardized and validated tests were used to assess the cognitive domains of global cognitive function, processing speed, and memory (21). These tests have been described in detail elsewhere (21). Briefly, global cognitive function was assessed by means of the Cognitive Abilities Screening Instrument (CASI; version 2) (22). The CASI measures attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, verbal fluency, abstraction, and judgment. Scores for individual items were summed to obtain an overall cognitive function score ranging from 0 to 100. The CASI was completed by 4,591 participants across the 6 MESA study centers, resulting in a completion rate of 97.4% among those returning for examination 5. Removal of extremely low scores due to incomplete examinations and clinically recognized dementia resulted in the elimination of 199 (4%) participants: 125 participants with invalid CASI scores and 74 persons with an *International Classification of Diseases, Ninth Revision*, code documenting a history of dementia or use of dementia medication at the time of or prior to cognitive testing. The remaining 4,392 participants (96%) were judged to be free of dementia and to have valid and complete cognitive testing data.

Processing speed and visuomotor ability were assessed by means of the Digit Symbol Coding (DSC) Test (23). This test measures how quickly simple perceptual or mental operations can be performed, which, along with working memory (see the next test below), account for a large proportion of age-related variance in memory, reasoning, and other cognitive abilities (24). The DSC scores ranged from 0 to 133.

Working memory and attention were assessed by means of the Digit Span (DS) Test (23). The test was administered in 2 parts and required the participant to repeat spans of numbers that increased in length, first forwards and then backwards. Total scores ranged from 0 to 28. Forward (range, 0–14) and backward (range, 0–14) DS scores were analyzed separately because they assessed somewhat different aspects of memory. The forward DS Test mainly assesses attention and short-term auditory memory, while the backward DS Test measures working memory—the ability to manipulate verbal information while it is in temporary storage.

Because there were no well-validated clinical cutoff points for these tests and because the scores differed significantly across racial/ethnic groups, participants with scores in the lowest 10% within each racial/ethnic group were defined as having abnormally low scores. Web Table 1 (available at https://academic.oup.com/aje) shows the cutoff points of these test scores in each racial/ethnic group.

Laboratory measurement

At all clinic visits, venous blood samples were collected after a 12-hour fast by certified technicians using standardized venipuncture procedures. HDL-C was measured using the cholesterol oxidase method (Roche Diagnostics, Indianapolis, Indiana) after precipitation of non-HDL cholesterol (non-HDL-C) with magnesium/dextran sulfate. Triglyceride concentrations were measured using a glycerol-blanked enzymatic method with the Triglyceride GB reagent (Roche Diagnostics) on the Roche COBAS FARA centrifugal analyzer (Roche Diagnostics). In plasma samples that had a triglyceride value less than 400 mg/dL, LDL-C was calculated using the Friedewald formula. The 3 most commonly used indices of atherogenesis—TC:HDL-C ratio, LDL-C:HDL-C ratio, and triglyceride:HDL-C ratio—were also calculated.

High-sensitivity C-reactive protein, fibrinogen, and interleukin-6 concentrations were measured in all participants at the baseline examination as described previously (25). Apolipoprotein E gene (*APOE*) isoforms were estimated from the single nucleotide polymorphisms rs429358 and rs7412 as described previously (21).

Other variables of interest

Information on demographic and socioeconomic factors was obtained using standardized questionnaires at all visits. Information on medication use was obtained by asking the participant to bring to the clinic containers for all medications used during the previous 2 weeks. The name of each medication, the prescribed dose, and the frequency of administration from the containers was recorded. Low-, moderate-, and high-intensity statin therapy was defined according to the 2013 American College of Cardiology/American Heart Association guidelines on the treatment of blood cholesterol to reduce atherosclerotic CVD risk in adults (26). Elevated levels of depressive symptoms were defined as Center for Epidemiologic Studies Depression Scale score ≥16 and/or use of antidepressant medication, as described previously (27). Physical activity was measured as the self-reported total number of minutes of moderate and vigorous activity per week, multiplied by metabolic equivalent level (28). Hypertension was defined as blood pressure ≥140/90 mm Hg or use of antihypertensive medication. Diabetes was defined as fasting glucose concentration ≥126 mg/dL or use of glucose-lowering medication. Ten-year CVD risk was estimated using Framingham risk scores as described previously (29).

Statistical analysis

For this analysis, we utilized data on lipid values from examinations 1 and 5 and data on cognitive function from visit 5. Data are presented as mean values (with standard deviations) or percentages. For variables with a skewed distribution, data are presented as median values (with interquartile ranges) and were log-transformed before analysis. Comparison of baseline clinical characteristics between 2 groups of participants was performed by independent *t* test for continuous variables and χ^2 test for categorical variables. Those variables with *P* values less than 0.1 were used as covariates in subsequent regression analysis.

Multivariable linear regression analysis with robust standard error estimation was used to assess the association of different measures of lipid concentrations and their ratios with cognitive scores after adjusting for covariates. Because lipid-lowering medications (statins, fibrates, niacin, and/or bile-acid sequestrants) and *APOE* genotype can affect lipid concentrations, we adjusted for use of lipid-lowering medication and *APOE* genotype as covariates in all subsequent regression analyses. To avoid the confounding effect of frailty, we also adjusted the data for absolute change in body weight between the 2 most recent examinations and the number of days between these 2 examinations. Similar results were obtained when absolute change in body weight was replaced by relative change in body weight in all analyses (data not shown). No multicollinearity was detected (variance inflation factors <5.5 in all analyses). In a separate analysis, we also assessed the associations of absolute and relative changes in each lipid concentration measure and their ratios from examination 1 to examination 5 with cognitive scores at examination 5 using multivariable linear regression analysis with robust standard error estimation, after adjusting for the covariates, including history of lipid medication use.

To investigate interactions with sex and race/ethnicity, we estimated *P* values for interaction by including each additive interaction term in the regression models in the full sample after adjusting for the main effects of the covariates and the categorical subgroup variable.

The relationships between use of lipid-lowering medication and cognitive scores were analyzed using the multivariable linear regression models with endogenous treatment effects and robust standard error estimation in STATA ("etregress" command; StataCorp LP, College Station, Texas). We believed that this method could help us better assess the causal effect of a treatment on an outcome (cognitive function) based on observational data (30–32). The outcome model was the same as the one used for the multivariable linear regression analysis described above. The treatment model included age, sex, race/ethnicity, waist:hip ratio, height, education, smoking status (current, former, or never smoker), pack-years of smoking, current alcohol drinking, total gross family income, marital status, employment status, health insurance, diabetes, hypertension, physical activity, HDL-C, LDL-C, and log-transformed triglyceride level at examination 5. For participants taking lipid-lowering medication, the last untreated lipid concentrations at examination 4 or earlier were used, if available, in the treatment model. Finally, we conducted a sensitivity analysis to account for potential language and reporting biases, to determine whether the exclusion of participants who did not speak English at home would influence the results.

In all of the analyses, a 2-tailed *P* value less than 0.05 was considered statistically significant. The analyses were performed using SPSS 22 (SPSS Inc., Chicago, Illinois) and STATA 14.0.

RESULTS

Participant characteristics

Web Table 2 shows the clinical characteristics of the 3,926 participants at examination 5. In general, and compared with those with corresponding normal scores (i.e., scores falling in the top 90%), participants with low CASI, DSC, forward DS, or backward DS test scores were more likely to be older, less educated, retired, non-English-speaking, foreign-born, and less physically active than those with normal test scores. Participants with low test scores also tended to report no alcohol intake; to have a lower family income; to be widowed, divorced, or separated; to have a higher waist:hip ratio; to be shorter; to more often have diabetes or hypertension; and to have elevated depressive symptoms compared with those with normal test scores. For circulating concentrations of inflammatory markers such as C-reactive protein and interleukin-6, levels were higher in participants with low scores on the CASI and DSC tests but lower in participants with low forward and backward DS test scores.

Table 1. Lipid Concentrations According to Cognitive Function Test Scores at Examination 5, Multi-Ethnic Study of Atherosclerosis, 2010–2012[a]

Cognitive Function Test and Lipid Measure	Level of Cognitive Function[b]			
	Normal		Low	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Cognitive Abilities Screening Instrument				
TC, mg/dL	184 (37)		180 (37)	
LDL-C, mg/dL	106 (32)		101 (32)[c]	
HDL-C, mg/dL	56 (17)		57 (18)	
Non-HDL-C, mg/dL	128 (35)		124 (34)[d]	
Triglycerides, mg/dL[e]		95 (70–131)		96 (70–134)
TC:HDL-C ratio	3.49 (1.03)		3.41 (1.03)	
LDL-C:HDL-C ratio	2.05 (0.84)		1.95 (0.82)[d]	
Triglyceride:HDL-C ratio[e]		1.79 (1.15–2.76)		1.77 (1.14–2.86)
Digit Symbol Coding Test				
TC, mg/dL	184 (37)		177 (39)[f]	
LDL-C, mg/dL	106 (32)		100 (34)[f]	
HDL-C, mg/dL	56 (17)		55 (16)	
Non-HDL-C, mg/dL	128 (35)		122 (38)[c]	
Triglycerides, mg/dL[e]		95 (70–130)		95 (69–138)
TC:HDL-C ratio	3.49 (1.03)		3.40 (1.04)	
LDL-C:HDL-C ratio	2.05 (0.84)		1.94 (0.82)[d]	
Triglyceride:HDL-C ratio[e]		1.80 (1.14–2.76)		1.72 (1.18–2.86)
Forward Digit Span Test				
TC, mg/dL	184 (37)		181 (36)	
LDL-C, mg/dL	106 (32)		102 (31)[d]	
HDL-C, mg/dL	56 (17)		55 (16)	
Non-HDL-C, mg/dL	128 (35)		125 (35)	
Triglycerides, mg/dL[e]		94 (70–130)		101 (71–140)[d]
TC:HDL-C ratio	3.48 (1.03)		3.46 (1.02)	
LDL-C:HDL-C ratio	2.05 (0.84)		1.99 (0.80)	
Triglyceride:HDL-C ratio[e]		1.78 (1.13–2.76)		1.89 (1.26–2.91)
Backward Digit Span Test				
TC, mg/dL	184 (37)		178 (37)[c]	
LDL-C, mg/dL	106 (32)		101 (32)[c]	
HDL-C, mg/dL	56 (17)		54 (17)	
Non-HDL-C, mg/dL	128 (35)		124 (35)	
Triglycerides, mg/dL[e]		94 (70–130)		101 (75–139)[c]
TC:HDL-C ratio	3.48 (1.03)		3.50 (1.02)	
LDL-C:HDL-C ratio	2.04 (0.84)		2.00 (0.79)	
Triglyceride:HDL-C ratio[e]		1.78 (1.13–2.75)		1.89 (1.25–3.13)[c]

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol.

[a] Data are expressed as mean (SD). For variables with a skewed distribution, data are expressed as median (IQR). *P* values were calculated in a multivariable linear regression model with continuous measures of lipid concentrations as the dependent variable after adjustment for age, sex, and race/ethnicity.

[b] Participants with scores in the bottom tertile (lowest 10%) within each racial/ethnic group were defined as having abnormally low scores (see Web Table 1 for the cutoff points of these test scores in each racial/ethnic group).

[c] $P < 0.01$.

[d] $P < 0.05$.

[e] *P* values were calculated using log-transformed data.

[f] $P < 0.001$.

Table 2. Cross-Sectional Associations Between Lipid Concentrations and Cognitive Function Test Scores at Examination 5 (Multivariable Regression Analysis), Multi-Ethnic Study of Atherosclerosis, 2010–2012

Cognitive Function Test and Lipid Measure	1-SD Increment	Change in Cognitive Test Score (β)[a]			
		Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Cognitive Abilities Screening Instrument	8.1				
TC, mg/dL	37.0	0.001	−0.015	−0.017	−0.018
LDL-C, mg/dL	32.3	0.000	−0.008	−0.014	−0.015
HDL-C, mg/dL	16.9	0.016	−0.029	−0.025	−0.026
Non-HDL-C, mg/dL	35.4	−0.006	−0.002	−0.016	−0.017
Triglycerides, mg/dL[f]	0.45	−0.015	0.019	0.011	0.013
TC:HDL-C ratio	1.03	−0.021	0.010	−0.004	−0.004
LDL-C:HDL-C ratio	0.83	−0.017	0.005	−0.005	−0.005
Triglyceride:HDL-C ratio[f]	0.64	−0.020	0.024	0.027	0.021
Digit Symbol Coding Test	18.3				
TC, mg/dL	37.0	0.027[g]	0.001	−0.013	−0.015
LDL-C, mg/dL	32.3	0.013	−0.004	−0.010	−0.012
HDL-C, mg/dL	16.9	0.058[h]	−0.009	0.004	0.004
Non-HDL-C, mg/dL	35.4	0.002	0.005	−0.012	−0.014
Triglycerides, mg/dL[f]	0.45	−0.026	0.026[g]	0.030[g]	0.030
TC:HDL-C ratio	1.03	−0.042[i]	−0.001	−0.030	−0.031
LDL-C:HDL-C ratio	0.83	−0.033[g]	−0.006	−0.023	−0.024
Triglyceride:HDL-C ratio[f]	0.64	−0.046[i]	0.021	0.022	0.012
Forward Digit Span Test	2.7				
TC, mg/dL	37.0	0.030[g]	0.023	0.050[i]	0.050[i]
LDL-C, mg/dL	32.3	0.033[g]	0.036[g]	0.043[i]	0.043[i]
HDL-C, mg/dL	16.9	0.032[g]	−0.007	−0.019	−0.019
Non-HDL-C, mg/dL	35.4	0.016	0.025	0.047[i]	0.048[i]
Triglycerides, mg/dL[f]	0.45	−0.047[i]	−0.020	−0.037[g]	−0.039[g]
TC:HDL-C ratio	1.03	−0.009	0.013	0.045[g]	0.044[g]
LDL-C:HDL-C ratio	0.83	0.006	0.024	0.042[g]	0.042[g]
Triglyceride:HDL-C ratio[f]	0.64	−0.048[i]	−0.015	−0.023	−0.025

Table continues

Association of lipid concentrations with cognitive function test scores

Multivariable linear regression showed that, compared with persons with normal test scores, participants with lower CASI scores had lower LDL-C, lower non-HDL-C, and a lower LDL-C:HDL-C ratio at examination 5 (Table 1). However, no significant association was found between any lipid measure and CASI score after adjusting for confounding factors (Table 2). Similarly, participants with lower DSC Test scores had lower TC, LDL-C, non-HDL-C, and LDL-C:HDL-C ratio at examination 5 (Table 1), but there were no significant associations for these variables after adjustment for confounding factors (Table 2).

Participants with lower forward and backward DS Test scores had lower LDL-C but higher triglyceride concentrations at examination 5 (Table 1). Moreover, participants with a lower backward DS Test score also had lower TC and triglyceride:HDL-C ratio at examination 5 (Table 1). In multivariable regression analysis, after adjustment for confounding factors (Table 2), higher TC, LDL-C, and non-HDL-C at examination 5 were associated with higher scores on both the forward and backward DS tests. Additionally, at examination 5, higher TC:HDL-C and LDL-C:HDL-C ratios, but lower triglyceride concentrations, were associated with a higher forward DS score (Table 2). All of these associations were very modest, although they reached statistical significance. No significant interactions were found with sex or race/ethnicity.

In a separate analysis, we analyzed the change in lipid measures from baseline (examination 1) to examination 5. As Table 3 shows, absolute change or relative change in lipid concentrations and their ratios were not significantly associated with any cognitive function test score at examination 5.

Table 2. Continued

Cognitive Function Test and Lipid Measure	1-SD Increment	Change in Cognitive Test Score (β)[a]			
		Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
Backward Digit Span Test	2.4				
TC, mg/dL	37.0	0.043[i]	0.033	0.045[g]	0.045[g]
LDL-C, mg/dL	32.3	0.039[i]	0.036[g]	0.040[g]	0.039[g]
HDL-C, mg/dL	16.9	0.051[i]	0.009	0.007	0.007
Non-HDL-C, mg/dL	35.4	0.021	0.028	0.043[g]	0.043[g]
Triglycerides, mg/dL[f]	0.45	−0.047[i]	−0.007	−0.013	−0.012
TC:HDL-C ratio	1.03	−0.016	0.014	0.031	0.031
LDL-C:HDL-C ratio	0.83	0.001	0.022	0.032	0.032
Triglyceride:HDL-C ratio[f]	0.64	−0.055[h]	−0.008	−0.015	−0.017

Abbreviations: *APOE*, apolipoprotein E gene; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol.

[a] Results are expressed as the standardized regression coefficient (β) per 1-SD increase in each lipid measure, as estimated in multivariable linear regression with each cognitive function test score as the dependent variable.

[b] Results were adjusted for age, sex, and race/ethnicity.

[c] Results were further adjusted for education, smoking status, pack-years of smoking, current alcohol drinking, total gross family income, marital status, employment status, language spoken at home, health insurance, foreign-born status, physical activity, use of lipid-lowering medication (yes or no), waist:hip ratio, height, diabetes, hypertension, log-transformed C-reactive protein level, fibrinogen level, log-transformed interleukin-6 level, *APOE* genotype, and presence of elevated depressive symptoms.

[d] Results were further adjusted for HDL-C concentration (except for TC:HDL-C ratio, LDL-C:HDL-C ratio, and triglyceride:HDL-C ratio), LDL-C concentration (except for TC, non-HDL-C, TC:HDL-C ratio, and LDL-C:HDL-C ratio), and log-transformed triglyceride concentration (except triglyceride:HDL-C ratio), where appropriate.

[e] Results were further adjusted for absolute change in body weight between the 2 most recent examinations and number of days between the 2 examinations.

[f] Data were log-transformed before analysis.

[g] $P < 0.05$.

[h] $P < 0.001$.

[i] $P < 0.01$.

Association of lipid-lowering medications with cognitive function test scores

As Table 4 shows, participants with a low CASI score were more likely to use lipid-lowering medications, especially statins, at examination 5. Although the use of fibrates was significantly higher among participants with a lower forward DS Test score at examination 5 than among those with a higher forward DS Test score (Table 4), this result should be interpreted with caution, as the number of participants taking fibrates was small.

In a treatment effects model, the use of any lipid-lowering medication, especially statins, at examination 5 was significantly associated with higher CASI score (Table 5). Use of any lipid-lowering medication was also significantly associated with higher backward DS Test score. This association was similar for statins and nonstatin drugs. The use of any lipid-lowering medication was not associated with DSC Test score or forward DS Test score at examination 5, despite the fact that use of other nonstatin medications tended to be associated with lower forward DS Test score. No significant interaction was found with sex or race/ethnicity.

The associations of any lipid-lowering medication use and statin use with CASI and backward DS Test scores did not differ significantly across participants with low, intermediate, and high 10-year CVD risks (Web Table 3). In a separate analysis, the associations with CASI and backward DS Test scores were similar between statins with low blood-brain barrier permeability and statins with high permeability (Web Table 4). The associations with backward DS Test scores were similar among participants receiving low-, moderate-, and high-intensity statin therapy, although the association with CASI score tended to be smaller with statin therapy of lower intensity (Web Table 4). Over 9.5 years of follow-up, an increase in the intensity of statin therapy was associated with higher CASI and backward DS Test scores (Web Table 5). All of these associations were also very modest, though they reached statistical significance.

In the sensitivity analysis excluding 779 participants who primarily spoke a non-English language at home at baseline (examination 1), use of any lipid-lowering medication was still significantly associated with higher CASI and backward DS Test scores, although the association of statins with higher CASI score did not reach statistical significance (Web Table 6). The associations of statins and other nonstatin drugs with backward DS Test score still remained significant (Web Table 6).

DISCUSSION

In this study, we found that higher TC, LDL-C, and non-HDL-C at examination 5 were associated with better working

Table 3. Associations Between Change in Lipid Concentrations From Baseline (Examination 1) to Examination 5 and Cognitive Function Test Scores at Examination 5, Multi-Ethnic Study of Atherosclerosis, 2000–2012

Measure of Change in Lipid Concentration	1-SD Increment	Change in Cognitive Test Score (β)[a,b,c]			
		CASI	DSC Test	Forward DS Test	Backward DS Test
Absolute change					
TC, mg/dL	39.6	−0.017	0.008	0.022	0.033
LDL-C, mg/dL	35.1	−0.013	0.001	0.031	0.037
HDL-C, mg/dL	10.6	−0.023	−0.006	−0.012	0.003
Non-HDL-C, mg/dL	39.5	−0.006	0.011	0.029	0.032
Triglycerides, mg/dL	68.1	0.015	0.026	0.001	−0.004
TC:HDL-C ratio	1.05	0.007	0.008	0.019	0.006
LDL-C:HDL-C ratio	0.86	−0.002	−0.002	0.021	0.011
Triglyceride:HDL-C ratio	2.09	0.019	0.024	0.003	−0.008
Relative change					
TC, mg/dL	19.7	−0.027	0.007	0.018	0.023
LDL-C, mg/dL	30.9	−0.018	−0.004	0.020	0.026
HDL-C, mg/dL	20.6	−0.020	−0.001	−0.003	0.007
Non-HDL-C, mg/dL	26.9	−0.017	0.009	0.020	0.027
Triglycerides, mg/dL	41.1	0.008	0.025	−0.025	0.005
TC:HDL-C ratio	22.9	0.000	0.007	0.024	0.023
LDL-C:HDL-C ratio	34.7	−0.001	−0.001	0.024	0.030
Triglyceride:HDL-C ratio	47.6	0.010	0.018	−0.011	0.007

Abbreviations: *APOE*, apolipoprotein E gene; CASI, Cognitive Abilities Screening Instrument; DS, Digit Span; DSC, Digit Symbol Coding; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol.

[a] Results are expressed as the standardized regression coefficient (β) per SD increase in each lipid measure, as estimated in multivariable linear regression with each cognitive function test score as the dependent variable.

[b] Results were adjusted for examination 5 age, sex, race/ethnicity, education, smoking status, pack-years of smoking, current alcohol drinking, total gross family income, marital status, employment status, language spoken at home, health insurance, foreign-born status, physical activity, waist:hip ratio, height, diabetes, hypertension, log-transformed C-reactive protein level, fibrinogen level, log-transformed interleukin-6 level, *APOE* genotype, presence of elevated depressive symptoms, and history of lipid-lowering medication use at examinations 1 and 5 ("no use at both examinations," "use at examination 1 but no use at examination 5," "no use at examination 1 but use at examination 5," or "use at both examinations"), as well as baseline HDL-C, LDL-C, and triglyceride concentrations at examination 1 and change in body weight from examination 1 to examination 5.

[c] All *P* values were greater than 0.05.

memory at examination 5. Higher TC:HDL-C and LDL-C:HDL-C ratios, but lower triglyceride concentrations, were also modestly associated with better short-term memory. However, the associations were modest in magnitude, and none of the lipid parameters were associated with CASI and DSC Test scores. Moreover, we did not find any significant association between changes in lipid measures over the prior 9.5 years (from examination 1 to examination 5) and cognitive function test scores at examination 5. Therefore, our study did not support any consistent association between lipid profile and cognitive function.

There are reports showing an association of high midlife cholesterol concentrations with increased risk of Alzheimer disease (8, 9). Previous preclinical studies suggest that high cholesterol concentrations may cause neuropathological Alzheimer disease by increasing amyloid β-protein formation from amyloid precursor protein, decreasing the flux of amyloid precursor protein through the nonamyloidogenic α-secretase pathways, and affecting different nonamyloid factors such as local inflammation or tau metabolism (3–5, 33). Nevertheless, there are also some cross-sectional and longitudinal population studies in the literature showing that higher TC in late life may be associated with a lower dementia risk (34–36). Some of these findings may be confounded by frailty, since participants who are more frail may have lower cholesterol concentrations due to conditions such as poor nutritional status and thus have worse cognition. In this analysis, we tried to reduce this potential confounding effect by adjusting the data for recent change in body weight. However, we did not observe any robust association between lipid profile and cognitive function.

Analysis of the relationship between lipid-lowering medications and different cognitive scores using a treatment effects model identified a significant association of the use of any lipid-lowering medication, especially statins, with better global cognitive function and working memory at examination 5 as assessed by the CASI and backward DS Test, respectively, but not processing speed as assessed by the DSC Test. All of these associations remained significant after adjustment for lipid concentrations, suggesting a relationship that is independent of these concentrations. In fact, it has been suggested that statins can exert their

Table 4. Use of Lipid-Lowering Medications (%) at Examination 5 According to Cognitive Function Test Scores at Examination 5, Multi-Ethnic Study of Atherosclerosis, 2010–2012[a]

Lipid-Lowering Medication	Cognitive Test and Level of Cognitive Function[b]							
	CASI		DSC Test		Forward DS Test		Backward DS Test	
	Normal	Low	Normal	Low	Normal	Low	Normal	Low
Statins	36.3	44.0[c]	36.8	39.2	36.6	40.5	36.9	38.0
Fibrates	1.6	1.5	1.7	0.5	1.4	2.7[d]	1.5	1.6
Niacin	1.1	0.5	1.1	0.5	1.1	0.4	1.1	0.3
Bile-acid sequestrants	0.5	1.3	0.7	0.3	0.6	0.7	0.6	0.8
Other	1.6	1.5	1.5	2.3	1.6	1.6	1.6	1.1
Any of the above	38.0	45.7[c]	38.6	41.0	38.3	43.0	38.7	39.6

Abbreviations: CASI, Cognitive Abilities Screening Instrument; DS, Digit Span; DSC, Digit Symbol Coding.

[a] *P* values were calculated using a logistic regression model with binary measures of use of different lipid-lowering medications after adjustment for age, sex, and race/ethnicity.

[b] Participants with scores in the bottom tertile (lowest 10%) within each racial/ethnic group were defined as having abnormally low scores (see Web Table 1 for the cutoff points of these test scores in each racial/ethnic group).

[c] $P < 0.01$.

[d] $P < 0.05$.

cardioprotective effect beyond their lipid-lowering ability (37), although the clinical importance of the long-term pleiotropic effects of statins is unclear.

It has been suggested that some statins may have better blood-brain barrier permeability than other statins and that this difference may contribute to the beneficial effects of some statins, but not others, on dementia and Alzheimer disease (38, 39). However, in this analysis, we found that the associations with CASI and backward DS Test scores were similar between statins with low and high blood-brain barrier permeability (Web Table 4). It has also been suggested that short-term statin use does not adversely affect cognitive function, while long-term statin use may have a beneficial effect (18, 19, 38). Because MESA is a community-based cohort study, the number of participants taking nonstatin lipid-lowering medications and different types of statins was small. There was a lack of data on the duration of statin therapy. This limited further analysis by drug type and duration of therapy.

Our study had the advantage of making use of data with good quality control as part of a large, well-characterized sample of

Table 5. Associations Between Use of Lipid-Lowering Medications and Cognitive Function Test Scores at Examination 5 in a Multivariable Linear Regression Model With Endogenous Treatment Effects, Multi-Ethnic Study of Atherosclerosis, 2010–2012[a]

Lipid-Lowering Medication[b]	No. of Cases	Cognitive Function Test							
		CASI		DSC Test		Forward DS Test		Backward DS Test	
		RC (SE)	*P* Value	RC (SE)	*P* Value	RC (SE)	*P* Value	RC (SE)	*P* Value
Total	1,523	1.66 (0.51)	0.001	6.37 (4.76)	0.18	−0.07 (1.42)	0.96	2.16 (0.33)	<0.001
Medication type[c]									
Statins	1,358	1.46 (0.53)	0.005	7.51 (4.85)	0.12	−0.54 (1.55)	0.73	2.16 (0.33)	<0.001
Other (nonstatin) medications	69	1.25 (1.33)	0.35	9.60 (9.85)	0.33	−2.60 (0.94)	0.006	3.46 (0.39)	<0.001

Abbreviations: *APOE*, apolipoprotein E gene; CASI, Cognitive Abilities Screening Instrument; DS, Digit Span; DSC, Digit Symbol Coding; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, regression coefficient; SE, standard error.

[a] In this analysis, the covariates in the outcome model included age, sex, race/ethnicity, education, smoking status, pack-years of smoking, current alcohol drinking, total gross family income, marital status, employment status, language spoken at home, health insurance, foreign-born status, physical activity, waist:hip ratio, height, diabetes, hypertension, log-transformed C-reactive protein level, fibrinogen level, log-transformed interleukin-6 level, *APOE* genotype, presence of elevated depressive symptoms, HDL-C concentration, LDL-C concentration, and log-transformed triglyceride concentration. The covariates in the treatment model included age, sex, race/ethnicity, waist:hip ratio, height, education, smoking status, pack-years of smoking, current alcohol drinking, total gross family income, marital status, employment status, health insurance, diabetes, hypertension, physical activity, HDL-C concentration, LDL-C concentration, and log-transformed triglyceride concentration. For participants taking lipid-lowering medication, the last untreated lipid concentrations recorded at examination 4 or earlier were used, if available, in the treatment model.

[b] Data were compared with those of participants who were not taking any lipid-lowering medication at examination 5 ($n = 2,403$).

[c] Ninety-six participants were excluded from the analysis because they took both statins and nonstatin medications.

clinically apparently healthy participants. Other strengths of the study include the availability of data on 3 different cognitive function tests, as well as data on multiple socioeconomic factors for use in the adjustment models. The longitudinal study design of MESA also allowed the analysis of change in lipid concentrations.

However, there were several limitations of our study. Although the MESA cognitive assessment was designed to include tests that could be administered validly to the 4 different ethnic groups, the number and type of cognitive function tests performed at examination 5 were limited and were not likely to provide reliable individual domain scores. Another major limitation is that cognitive function is assessed at 1 time point only. Therefore, longitudinal analysis of the change in cognitive function and hence the temporal relationship between lipid concentrations and cognitive function was not possible. Although a treatment effects model was used to assess the relationship between the use of lipid-lowering medications and cognitive scores, our analysis was limited by the cross-sectional observational study design. We adjusted the data for multiple confounding factors but cannot exclude the possibility of residual bias due to unmeasured confounders (such as use of medications that induce cognitive decline). Because this was an observational study, our findings could have been confounded by indication bias, in which statins may be less often administered to participants with greater risk of cognitive decline due to the postmarketing reports of cognitive impairment associated with statin use. There could also have been many changes in the types of statins prescribed, drug doses, and drug combinations during the study period, and an increasing number of participants were lost to follow-up in subsequent examinations. Randomized controlled trials are needed to assess any causal relationship of lipid profile and lipid-lowering medications with cognitive function.

In conclusion, our study does not support a robust association between lipid concentrations and cognitive function or between the use of lipid-lowering medication, especially statins, and worse cognitive function.

ACKNOWLEDGMENTS

Author affiliations: Lipid Research Group, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia (Kwok Leung Ong, Kerry-Anne Rye); Department of Pharmacology, School of Medical Sciences, University of New South Wales, Sydney, New South Wales, Australia (Margaret J. Morris, Jayanthi Maniam); Department of Biostatistics, School of Public Health, University of Washington, Seattle, Washington (Robyn L. McClelland); Department of Internal Medicine, Division of Gerontology and Geriatric Medicine, School of Medicine, Wake Forest University, Winston-Salem, North Carolina (Timothy M. Hughes); Department of Family Medicine, School of Medicine, University of Washington, Seattle, Washington (Annette L. Fitzpatrick); Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington (Annette L. Fitzpatrick); Department of Global Health, Schools of Public Health and Medicine, University of Washington, Seattle, Washington (Annette L. Fitzpatrick); Ciccarone Center for the Prevention of Heart Disease, Division of Cardiology, Johns Hopkins Medical Institutions, Baltimore, Maryland (Seth S. Martin); Departments of Medicine and Epidemiology, Columbia University Medical Center, New York, New York (José A. Luchsinger); Department of Psychiatry and Behavioral Medicine, School of Medicine, Wake Forest University, Winston-Salem, North Carolina (Stephen R. Rapp); Department of Social Sciences and Health Policy, Division of Public Health Sciences, School of Medicine, Wake Forest University, Winston-Salem, North Carolina (Kathleen M. Hayden); Radiology and Imaging Sciences, NIH Clinical Center, Bethesda, Maryland (Veit Sandfort); and Department of Family Medicine and Public Health, School of Medicine, University of California, San Diego, La Jolla, California (Matthew A. Allison).

This work was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute, by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences, and by grant K24AG045334 from the National Institute on Aging. K.L.O. was supported by a Vice-Chancellor's Postdoctoral Fellowship from the University of New South Wales (grant RG134592) and a Career Development Fellowship from the Australian National Health and Medical Research Council (grant 1122854).

We thank the investigators, staff, and participants of the MESA study for their valuable contributions.

A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Conflict of interest: none declared.

REFERENCES

1. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry*. 2008;16(5):343–354.
2. Purnell C, Gao S, Callahan CM, et al. Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord*. 2009;23(1):1–10.
3. Thirumangalakudi L, Prakasam A, Zhang R, et al. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. *J Neurochem*. 2008;106(1):475–485.
4. Ullrich C, Pirchl M, Humpel C. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. *Mol Cell Neurosci*. 2010;45(4):408–417.
5. Ehrlich D, Humpel C. Chronic vascular risk factors (cholesterol, homocysteine, ethanol) impair spatial memory, decline cholinergic neurons and induce blood-brain barrier leakage in rats in vivo. *J Neurol Sci*. 2012; 322(1-2):92–95.
6. Ramírez C, Sierra S, Tercero I, et al. ApoB100/LDLR-/- hypercholesterolaemic mice as a model for mild cognitive

impairment and neuronal damage. *PLoS One*. 2011;6(7): e22712.
7. Kim B, Feldman EL. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. *Exp Mol Med*. 2015;47:e149.
8. Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med*. 2002;137(3): 149–155.
9. Evans RM, Emsley CL, Gao S, et al. Serum cholesterol, *APOE* genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. *Neurology*. 2000;54(1): 240–242.
10. Kalmijn S, Foley D, White L, et al. Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia Aging Study. *Arterioscler Thromb Vasc Biol*. 2000;20(10):2255–2260.
11. Tan ZS, Seshadri S, Beiser A, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. *Arch Intern Med*. 2003;163(9):1053–1057.
12. Mielke MM, Zandi PP, Shao H, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. *Neurology*. 2010;75(21):1888–1895.
13. van Vliet P. Cholesterol and late-life cognitive decline. *J Alzheimers Dis*. 2012;30(suppl 2):S147–S162.
14. Food and Drug Administration, US Department of Health and Human Services. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm#hcp. Published February 28, 2012. Updated January 19, 2016. Accessed August 30, 2017.
15. Bitzur R. Remembering statins: do statins have adverse cognitive effects? *Diabetes Care*. 2016;39(suppl 2): S253–S259.
16. Samaras K, Brodaty H, Sachdev PS. Does statin use cause memory decline in the elderly? *Trends Cardiovasc Med*. 2016; 26(6):550–565.
17. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med*. 2013;159(10): 688–697.
18. Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. *Mayo Clin Proc*. 2013;88(11): 1213–1221.
19. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532–2561.
20. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol*. 2002; 156(9):871–881.
21. Fitzpatrick AL, Rapp SR, Luchsinger J, et al. Sociodemographic correlates of cognition in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Geriatr Psychiatry*. 2015;23(7):684–697.
22. Teng EL, Hasegawa K, Homma A, et al. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr*. 1994;6(1):45–58.
23. Wechsler D. *Wechsler Adult Intelligence Scale-III (WAIS-III)*. New York, NY: Psychological Corporation; 1996.
24. Salthouse TA. Shared and unique influences on age-related cognitive change. *Neuropsychology*. 2017;31(1):11–19.
25. Veeranna V, Zalawadiya SK, Niraj A, et al. Association of novel biomarkers with future cardiovascular events is influenced by ethnicity: results from a multi-ethnic cohort. *Int J Cardiol*. 2013;166(2): 487–493.
26. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S1–S45.
27. Ong KL, Morris MJ, McClelland RL, et al. Lipids, lipoprotein distribution and depressive symptoms: the Multi-Ethnic Study of Atherosclerosis. *Transl Psychiatry*. 2016;6(11):e962.
28. Bertoni AG, Whitt-Glover MC, Chung H, et al. The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2009; 169(4):444–454.
29. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117(6):743–753.
30. Heckman JJ. Dummy endogenous variables in a simultaneous equation system. *Econometrica*. 1978;46(4):931–959.
31. Maddala GS. *Limited-Dependent and Qualitative Variables in Econometrics*. Cambridge, United Kingdom: Cambridge University Press; 1983.
32. Spieker AJ, Delaney JA, McClelland RL. Evaluating the treatment effects model for estimation of cross-sectional associations between risk factors and cardiovascular biomarkers influenced by medication use. *Pharmacoepidemiol Drug Saf*. 2015;24(12):1286–1296.
33. Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. *Arch Neurol*. 2011; 68(10):1239–1244.
34. Stewart R, White LR, Xue QL, et al. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol*. 2007;64(1):103–107.
35. Mielke MM, Zandi PP, Sjögren M, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology*. 2005;64(10):1689–1695.
36. Reitz C, Tang MX, Luchsinger J, et al. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol*. 2004;61(5):705–714.
37. Ludman A, Venugopal V, Yellon DM, et al. Statins and cardioprotection—more than just lipid lowering? *Pharmacol Ther*. 2009;122(1):30–43.
38. Shah NP, Swiger KJ, Martin SS. Impact on cognitive function—are all statins the same? *Curr Atheroscler Rep*. 2015;17(1):466.
39. Shepardson NE, Shankar GM, Selkoe DJ. Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations. *Arch Neurol*. 2011;68(11):1385–1392.