High density lipoprotein and its apolipoprotein-defined subspecies and risk of dementia

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Abstract **Whether HDL is associated with dementia risk is unclear. In addition to apoA1, other apolipoproteins are found in HDL, creating subspecies of HDL that may have distinct metabolic properties. We measured apoA1, apoC3, and apoJ levels in plasma and apoA1 levels in HDL that contains or lacks apoE, apoJ, or apoC3 using a modified sandwich ELISA in a case-cohort study nested within the Ginkgo Evaluation of Memory Study. We included 995 randomly selected participants and 521 participants who developed dementia during a mean of 5.1 years of follow-up. The level of total apoA1 was not significantly related to dementia risk, regardless of the coexistence of apoC3, apoJ, or apoE. Higher levels of total plasma apoC3 were associated with better cognitive function at baseline (difference in Modified Mini-Mental State Examination scores tertile 3 vs. tertile 1: 0.60; 95% CI: 0.23, 0.98) and a lower dementia risk (adjusted hazard ratio tertile 3 vs. tertile 1: 0.73; 95% CI: 0.55, 0.96). Plasma concentrations of apoA1 in HDL and its apolipoprotein-defined subspecies were not associated with cognitive function at baseline or with the risk of dementia during follow-up. Similar studies in other populations are required to better understand the association between apoC3 and Alzheimer's disease pathology.**—Koch, M., S. T. DeKosky, M. Goodman, J. Sun, J. D. Furtado, A. L. Fitzpatrick, R. H. Mackey, T. Cai, O. L. Lopez, L. H. Kuller, K. J. Mukamal, and M. K. Jensen. **High density lipoprotein and its apolipoprotein-defined subspecies and risk of dementia. *J. Lipid Res*. 2020.** 61: **445–454.**

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Dementia and related neurologic conditions are one of the leading causes of long-term disability and mortality in the United States (1). Despite reductions in dementia risk factors over the last decades, the prevalence of dementia is increasing dramatically in aging societies (2). One of the key obstacles to developing disease-modifying therapies for dementia is the lack of biomarkers that can identify high-risk individuals before clinical disease manifestation and irreversible injury has occurred (3). So far, most studies have focused on imaging and biomarkers in cerebrospinal fluid as diagnostic tools to define the presence or absence of Alzheimer's disease (AD) and related dementia (4). An urgent need remains for effective biomarkers that are less expensive and less invasive than imaging and cerebrospinal fluid biomarkers (5).

Metabolic risk factors related to cholesterol metabolism are of particular interest given the preeminence of apolipoprotein loci among the genetic contributors to AD (6–9). A recent analysis of 11 cohort studies identified a panel of six plasma metabolites associated with cognitive function and dementia, four of which were subfractions of HDL (10). Even though higher plasma concentration of HDL cholesterol has been linked to lower dementia risk in some studies (10, 11), the overall evidence is inconclusive (12, 13).

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Abbreviations: AD, Alzheimer's disease; ADAS-cog, cognitive subscale of the Alzheimer Disease Assessment Scale; CHD, coronary heart disease; GEMS, Ginkgo Evaluation of Memory Study; HR, hazard ratio; MCI, mild cognitive impairment. 3MSE, Modified Mini-Mental State Examination.

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To date, little attention has been paid to the structural and functional heterogeneity of HDL when assessing the relationship of HDL with dementia (10, 11). In addition to triglycerides, cholesteryl esters, cholesterol, and phospholipids, HDL can carry various combinations of more than 100 different proteins (14, 15). Of these, apoA1 is the main structural component of circulatory HDL, whereas apoE, apoJ, and apoC3 are minor HDL apolipoprotein components present in less than 10% of HDL particles (16). Accordingly, HDL particles can be separated into subfractions that contain various combinations of apolipoproteins with differential risks on chronic disease (17). For instance, higher concentrations of HDL that contains apoC3 is associated with a higher risk of coronary heart disease (CHD), whereas higher concentrations of HDL that lacks apoC3 is associated with a lower risk (18). Similarly, the presence of apoC3 in HDL particles impairs the inverse association of HDL with diabetes (19). Based on these previous findings on CHD and diabetes, two strong risk factors for dementia (20, 21), we examined the association of HDL and its apolipoprotein-defined subspecies with cognitive function and the incidence of all-cause dementia and AD in a large, community-dwelling population of older adults.

MATERIALS AND METHODS

Study population and design

The Ginkgo Evaluation of Memory Study (GEMS) was a randomized, double-blind, placebo-controlled clinical trial (NCT00010803) investigating the hypothesis that an intervention of 240 mg *Ginkgo biloba* daily reduces the incidence of all-cause dementia in subjects with normal cognition or mild cognitive impairment (MCI) (22–24). The trial identified no association between *G. biloba* and dementia but provides an extraordinary resource for investigating biomarkers and dementia risk because of its dedication of resources to neurologist-adjudicated risk of all-cause dementia and AD and low loss to follow-up of 1.1% of participants per year due to deaths and other losses to follow-up (23). From October 2000 to May 2002, 3,069 elderly community-dwelling volunteers were enrolled at four field centers in the United States. An institutional review board at each investigational center approved this study, and participants provided written informed consent. For the current analysis, we used a case-cohort design. We included 1,000 individuals at risk for dementia at baseline drawn randomly from all 3,069 GEMS participants, of whom 166 developed dementia during follow-up (2000–2008) and 357 participants from outside the random subcohort who developed dementia during follow-up. After excluding participants without a plasma sample from the screening visit (n = 2) or missing information on HDL subspecies (n = 4), the analysis included 1,351 participants aged 74–96 years at study entry.

Biochemical measurements

The lipid laboratory at the Harvard T.H. Chan School of Public Health (Boston, MA) quantified plasma apolipoproteins in different lipoprotein subspecies in all case-cohort participants at study entry (2000–2002) and in a subset of participants at a 3-year (n = 806) or 4-year (n = 103) follow-up. To minimize plate-to-plate variation, plasma samples collected from the subset of participants at baseline and follow-up were incubated separately but on the same plates. A total of 23% of participants reported fasting for ≥4 h at blood draw.

First, we determined the concentrations of apoC3, apoE, apoJ, and HDL based on apoA1 in whole plasma using sandwich ELISA. Plasma samples were diluted (1:40,000 for apoC3, 1:4,000 for apoE, 1:5,000 for apoJ, and 1:40,000 for apoA1) in Tween-containing diluent (1× PBS/2% BSA/0.05% Tween 20) and loaded in triplicate onto 96-well plates coated with antibody [anti-apoC3 at 0.5 mcg/well, anti-apoE at 0.5 mcg/well, and anti-apoA1 at 0.5 mcg/well (Academy Bio-Medical Co., Houston, TX) and anti-apoJ at 0.3 mcg/well (R&D Systems, Minneapolis, MN)]. Plates were incubated for 1 h at 37°C and washed three times with 1× PBS with 0.1% Tween 20. Detection antibodies conjugated to horseradish peroxidase or biotin were added [anti-apoC3-HRP at 0.1 mcg/well, anti-apoE-HRP at 0.1 mcg/well, and anti-apoA1-HRP at 1 mcg/well (Academy Bio-Medical Co.) and anti-apoJ-biotin at 0.1 mcg/well (R&D Systems)], and plates were incubated for 1 h at 37°C followed by three washes with 1× PBS with 0.1% Tween 20. For plates measuring apoJ, streptavidin peroxidase was added to conjugate to biotin. For all plates, color was developed by incubation with *o*-phenylenediamine solution (Sigma-Aldrich, St. Louis, MO), and absorbance of each well was determined at 450 nm using a 96-well plate reader. Each plate contained a calibration curve and two control samples to allow quality-control assessments. Replicates with a coefficient of variation >15% were repeated.

We then measured the following HDL subspecies: apoA1 levels in HDL that contains or lacks apoE, apoJ, or apoC3 using a patented modified sandwich ELISA protocol previously described in detail (25) following the removal of apoB-containing lipoproteins through dextran sulfate and magnesium chloride precipitation. Thus, these assays provide the concentration of HDL based on apoA1 in the HDL subspecies that contains a defining protein of interest, as well as the concentration of the defining protein in HDL. Briefly, the measurement of apoA1 levels in HDL that contains apoC3 was performed in 96-well plates coated with anti-apoC3 antibody (Academy Bio-Medical Co.). Diluted samples were added, and plates were incubated to bind the intact lipoproteins that contain apoC3. Plates were washed to remove the unbound components, and then a Tween-containing diluent (1× PBS/2% BSA/0.05% Tween 20) was added to dissociate the lipoprotein complex. After dissociation, the released components of the previously bound lipoproteins were transferred to a second 96-well plate coated with anti-apoA1 antibody (Academy Bio-Medical Co.) to measure the apoA1 levels in HDL that contains apoC3. The plate coated with anti-apoC3 was incubated with a detection antibody conjugated to horseradish peroxidase (anti-apoC3-HRP at 0.1 mcg/well; Academy Bio-Medical Co.) and processed as described earlier. apoA1 levels in HDL that lacks apoC3 was calculated as the difference of the measured total apoA1 concentration minus the measured apoA1 levels in HDL that contains apoC3. apoA1 levels in HDL that contains or lacks apoJ or apoE were quantified using the same approach applying apoJ at 0.3 mcg/well (R&D Systems) or apoE at 0.5 mcg/well (Academy Bio-Medical Co.) antibodies. In addition, we determined the concentration of apoC3 in HDL and whole plasma apoC3 and apoJ using sandwich ELISA. Total plasma cholesterol, HDL cholesterol, and plasma triglycerides were measured by an enzymatic assay (Thermo Fisher Scientific, Waltham MA). LDL cholesterol was calculated using the Friedewald formula (26).

Diagnosis of dementia and cognitive assessment

Our primary outcome was all-cause dementia. Participants underwent cognitive and functional assessments through the end of follow-up, death, or dementia diagnosis and were assessed

semiannually for incident all-cause dementia using criteria from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (27). Each participant underwent a detailed neuropsychological battery of 10 cognitive tests at study entry covering memory, construction, language, attention/psychomotor speed, executive function, and premorbid intellectual functioning. From 2000 to 2008, the Modified Mini-Mental State Examination (3MSE) and the Clinical Dementia Rating were administered semiannually. Participants completed the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-cog) semiannually until August 2004 and annually thereafter. If scores on the 3MSE, Clinical Dementia Rating, or ADAS-cog declined by a predefined threshold, the neuropsychological battery was readministered (22). Between 2004 and 2008, the neuropsychological battery was administered annually to all participants (28).

Participants classified as having potential cognitive dysfunction based on an algorithm of the neuropsychological battery and all clinical assessments then underwent a neurological exam by site neurologists and magnetic resonance imaging. Potential dementia cases were subsequently referred to a panel that reviewed all data and used a validated process to diagnose dementia (using criteria from the National Institute of Neurological and Communication Disorders and Stroke, Alzheimer's Disease and Related Disorders Association, the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences, and the Alzheimer's Disease Diagnostic and Treatment Centers) (27, 29, 30). Using these criteria, cases were classified as Alzheimer's dementia, vascular dementia, mixed dementia, or other dementia (23). Criteria for the classification of MCI were based on the consensus guidelines from the International Working Group on Cognitive Impairment (31). MCI was diagnosed when participants scored ⩽10th percentile for age and education on at least two tests of the neuropsychological battery (the Cardiovascular Health Study population used as a reference population) and a Clinical Dementia Rating global score of 0.5 (32).

Because ADAS-cog scores declined in the first half of follow-up (suggesting learning effects and the cessation of testing when dementia was diagnosed; **Fig. 1**), we did not examine cognitive decline as a supplemental outcome to dementia. Instead, we assessed the cross-sectional association of HDL and its apolipoprotein-defined subspecies at study screening with cognitive function.

Other covariates

Trained technicians obtained information on age, sex, education, race/ethnicity, alcohol intake, smoking status, and medical history in interviews at study entry and then obtained measures of body weight, height, and blood pressure. Participants brought prescribed medicine and over-the-counter drugs to the clinic visit for transcription. The Center for Epidemiologic Studies Depression Scale was administered to assess depressive symptoms.

Statistical analysis

One missing value on the Center for Epidemiologic Studies Depression Scale was replaced with the median value observed in the GEMS population. We recalibrated concentrations of apolipoproteins and HDL subspecies according to methods outlined by Rosner et al. to account for batch effects (33). In brief, we regressed log2-transformed apolipoprotein concentrations separately on batch, age, sex, race/ethnicity, clinic site, education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale score, treatment assignment, and *APOE* ε4 carrier status, stroke, and dementia. Within each batch, biomarkers were recalibrated by adding the resulting value for the batch indicator minus the average of the combined batch coefficient (33).

We evaluated the baseline characteristics of participants who developed dementia during follow-up and who were selected into the random subcohort separately. We assessed partial correlations of concentrations of HDL and its apolipoprotein-defined subspecies assessed at study entry and follow-up controlling for age at randomization and sex. *P* values for tests of the equality of biomarkers assessed at study entry and follow-up were derived using the Wilcoxon signed-rank test. We used weighted linear regression models to assess the association of apolipoprotein concentrations and the ADAS-cog. To account for the oversampling of dementia cases, noncases in the subcohort were given a weight inversely proportional to the sampling fraction (3,069/1,000). We used Cox proportional hazards models with standard inverse probability weights and robust estimates of variance to assess the risk of dementia and AD according to apolipoprotein concentration, with study time as the underlying time axis. We tested the proportional-hazards assumption on the basis of Schoenfeld residuals.

Concentrations of apolipoproteins and HDL subspecies were modeled continuously and as sex-specific tertiles based on the distribution of the random subcohort. We first adjusted for age, sex, race/ethnicity, clinic site, and fasting status. In subsequent models, we additionally adjusted for education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale score, treatment assignment from the original trial, and *APOE* ε4 carrier status. We performed sensitivity analyses without adjusting for *APOE* ε4 carrier status, excluding

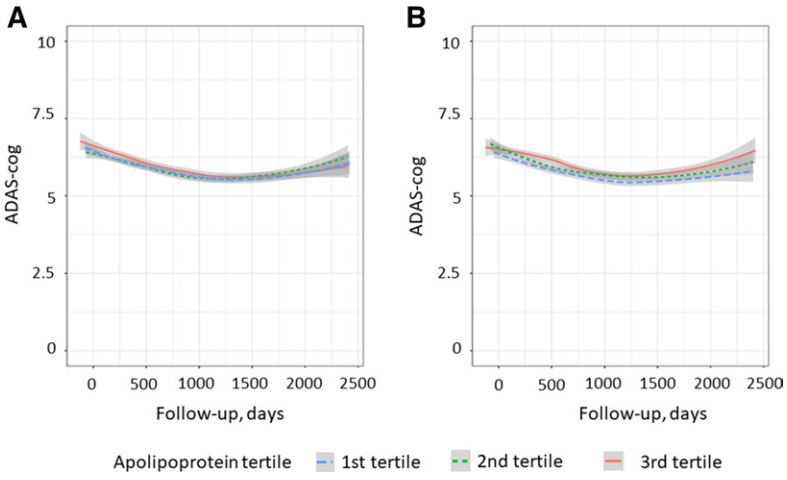

Fig. 1. Smoothed means of ADAS-cog scores not censored by death, dropout, or dementia, stratified by tertiles of apoA1 (A) and whole plasma apoC3 (B) concentrations measured at study entry, in the GEMS cohort.

the *APOE* ε4 carrier. The concentration of complementary HDL subspecies (e.g., apoA1 levels in HDL that contains or lacks apoC3) were modeled simultaneously, and likelihood ratio tests were used to assess slope heterogeneity of the two complementary subspecies. Wald tests for trend were performed with apolipoprotein concentrations modeled as the sex-specific median of each tertile. To test whether observed associations between the concentration of apolipoproteins and dementia varied by sex, we included their separate interaction terms. Given that a previous report suggested that associations of the apoJ concentration with dementia risk are modified by age (34), we tested for interaction by including an interaction term of apoJ and age. Further, we conducted sensitivity analyses of the concentration of apoC3 and dementia risk, excluding the first 2 years of follow-up and additionally adjusting for triglyceride concentration. Statistical analyses were performed using Stata version 12.1 (StataCorp, College Station, TX).

Data availability statement

The data that support the findings of this study are available at the University of Washington Collaborative Health Studies Coordinating Center at https://www.uwchscc.org.

RESULTS

Baseline characteristics of the random subcohort of the GEMS and participants with incident dementia during follow-up are shown in **Table 1**. Participants who subsequently

TABLE 1. Baseline characteristics of the random subcohort of the GEMS and dementia cases that developed during follow-up (n = 1,351)

Characteristics	Random Subcohort (n = 995)	Dementia Cases during Follow-Up (n = 521)
Males	534 (54)	265 (51)
Age (years)	78 (75, 85)	79 (75, 87)
APOE ε4 allele carrier[a]	180 (18)	144 (28)
Whites	951 (96)	489 (94)
Education (years)	14 (10, 20)	14 (8, 20)
Current alcohol drinker[b]	257 (50)	528 (54)
Current smoking[c]	40 (4)	20 (4)
BMI,[d] kg/m^2	27 (21, 35)	26 (21, 34)
Lipid-lowering medication use	267 (27)	160 (31)
History of cardiovascular disease	334 (34)	197 (38)
History of diabetes	87 (9)	49 (9)
MCI	154 (15)	198 (38)
3MSE at screening visit	94 (85, 99)	91 (81, 98)
ADAS-cog	6 (3, 11)	8 (4, 14)
Center for Epidemiologic Studies Depression Scale Depression Scale	3 (0, 10)	4 (0, 12)
G. biloba assignment	496 (50)	276 (53)
Apolipoproteins and HDL subspecies, mg/dl		
apoA1 in whole plasma	153 (100, 254)	153 (96, 253)
apoA1 in HDL that contains apoC3	11.2 (5.9, 20.7)	11.4 (5.8, 21.9)
apoA1 in HDL that lacks apoC3	141 (93, 238)	141 (84, 236)
apoA1 in HDL that contains apoJ[e]	2.2 (1.2, 3.8)	2.1 (1.2, 3.7)
apoA1 in HDL that lacks apoJ[e]	151 (98, 252)	151 (95, 251)
apoA1 in HDL that contains apoE[e]	11.3 (5.1, 27.5)	11.2 (4.8, 27.3)
apoA1 in HDL that lacks apoE[e]	141 (92, 237)	141 (87, 239)
apoC3 in HDL	10.0 (5.4, 17.9)	9.5 (5.0, 18.5)
apoC3 in whole plasma	15.0 (8.1, 27.0)	13.9 (8.0, 25.8)
apoJ in whole plasma	5.9 (4.0, 8.4)	5.9 (3.8, 8.4)
Triglycerides (mg/dl)[f]	121 (55, 281)	111 (52, 251)
Total cholesterol (mg/dl)[g]	189 (131, 260)	183 (125, 256)
HDL cholesterol (mg/dl)[h]	53 (38, 79)	53 (36, 81)
LDL cholesterol (mg/dl)[i]	107 (58, 167)	104 (54, 167)
All-cause dementia[j]	165 (17)	521 (100)
AD	112 (11)	352 (68)
Vascular dementia	9 (1)	24 (5)
Mixed dementia	39 (4)	123 (24)
Other dementia	5 (1)	22 (4)

Values are medians (95% CIs) or n (%). Percentages were calculated with missing data. MCI was diagnosed if participants scored ⩽10th percentile for age and education on at least two tests of the neuropsychological battery using the Cardiovascular Health Study population as a reference population and while also having a Clinical Dementia Rating global score of 0.5 (33). LDL cholesterol was calculated using the Friedewald formula (27).

[a] n = 288 missing.
[b] n = 21 missing.
[c] n = 24 missing.
[d] n = 7 missing.
[e] n = 1 missing.
[f] n = 6 missing.
[g] n = 4 missing.
[h] n = 2 missing.
[i] n = 8 missing.
[j] Per the case-cohort study design, the 165 cases that occurred within the random subcohort were included in both the case count and the subcohort count.

developed dementia during follow-up (mean follow-up time: 5.1 years; SD: 1.8 years; range: 10 days to 7.3 years) were more likely to be carriers of an *APOE ε4* allele and to have lower 3MSE scores at baseline than the random subcohort. Apolipoprotein concentrations assessed at study entry and at the 3-year follow-up were highly correlated ($r \geqslant 0.5$ for all partial correlation coefficients; data not shown).

In basic and fully adjusted models, including the *APOE* genotype, the concentration of HDL and its apolipoprotein-defined subspecies were unrelated to the risk of all-cause dementia or AD. These moieties were also unrelated to cognitive scores at baseline, with two possible exceptions (**Table 2**). Higher apoA1 levels in HDL that contains apoE were related to higher 3MSE scores in basic and fully adjusted models (indicating better cognitive function), while higher apoA1 levels in HDL that contains apoJ were associated with higher ADAS-cog scores (indicating worse cognitive function) in fully adjusted models. Higher apoA1 levels in HDL that lacks apoC3 or apoJ were associated with lower ADAS-cog scores in basic adjusted models, but associations were not robust to multivariable adjustment.

Higher concentrations of apoC3 in HDL and higher concentrations of apoC3 in whole plasma were associated with a lower risk of dementia and AD in basic adjusted models (**Table 3**). In models additionally adjusted for education, lifestyle factors, clinical characteristics, and *APOE ε4* carrier status, the inverse association remained statistically significant, except for apoC3 in HDL and dementia. Sensitivity analyses without adjusting for the *APOE* genotype and analyses restricted to the *APOE ε4* noncarrier yielded similar results as the overall analysis (**Table 4**). In sensitivity analyses excluding the first 2 years of follow-up, the results were not materially different. The hazard ratio (HR) for dementia was 0.91 (95% CI: 0.77, 1.09) per 1 SD higher concentration of apoC3 in HDL and 0.86 (95% CI: 0.74, 1.01) per 1 SD higher concentration of apoC3 in whole plasma in fully adjusted models. Higher concentrations of apoC3 in whole plasma were also associated with better baseline cognitive function in basic and fully adjusted models, as assessed by 3MSE **(Table 5)**. Compared with participants in the first tertile of apoC3 concentrations, participants in the third tertile had statistically significantly higher (better) 3MSE scores (difference: 0.54; 95% CI: 0.16, 0.93) in basic adjusted models. Higher concentrations of apoC3 in whole plasma and higher concentrations of apoC3 in HDL were also related to better cognitive performance on the basis of ADAS-cog scores in basic and fully adjusted models. The concentration of triglycerides was

TABLE 2. HRs for risk of dementia and AD, difference in cognitive scores at baseline, and 95% CIs according to plasma concentrations of HDL and its apolipoprotein-defined subspecies in the GEMS case cohort ($n = 1,351$)

	SD *mg/dl*	HR for Dementia per SD	HR for AD per SD	Difference in 3MSE per SD	Difference in ADAS-cog per SD
apoA1 in whole plasma	51				
Basic		0.98 (0.86, 1.11)	1.03 (0.90, 1.18)	0.03 (0.15, 0.21)	−0.10 (−0.20, 0.01)
Multivariable + *APOE*		1.01 (0.89, 1.14)	1.04 (0.91, 1.20)	−0.08 (−0.26, 0.09)	−0.02 (−0.12, 0.08)
apoA1 in HDL that contains apoC3	4.6				
Basic		1.01 (0.90, 1.14)	1.02 (0.89, 1.17)	0.04 (−0.14, 0.22)	0.04 (−0.07, 0.14)
Multivariable + *APOE*		1.03 (0.91, 1.17)[a]	1.04 (0.90, 1.20)[b]	0.002 (−0.17, 0.18)[c]	0.06 (−0.04, 0.16)[d]
apoA1 in HDL that lacks apoC3	48				
Basic		0.97 (0.85, 1.11)	1.02 (0.88, 1.19)	0.01 (−0.19, 0.20)	−0.11 (−0.22, −0.01)
Multivariable + *APOE*		0.99 (0.87, 1.13)	1.03 (0.88, 1.20)	−0.09 (−0.27, 0.10)	−0.05 (−0.15, 0.06)
apoA1 in HDL that contains apoJ	0.8				
Basic[e]		0.90 (0.78, 1.03)	0.90 (0.77, 1.06)	−0.02 (−0.22, 0.17)	0.09 (−0.02, 0.20)
Multivariable + *APOE*		0.91 (0.79, 1.06)	0.91 (0.76, 1.08)	−0.09 (−0.28, 0.09)	0.13 (0.02, 0.23)
apoA1 in HDL that lacks apoJ	50				
Basic[e]		1.01 (0.89, 1.15)	1.07 (0.93, 1.23)	0.04 (−0.15, 0.23)	−0.13 (−0.24, −0.02)
Multivariable + *APOE*		1.04 (0.91, 1.18)	1.07 (0.93, 1.25)	−0.05 (−0.24, 0.14)	−0.07 (−0.17, 0.04)
apoA1 in HDL that contains apoE	7.8				
Basic[e]		0.94 (0.83, 1.06)	0.92 (0.80, 1.07)	0.31 (0.15, 0.48)	−0.05 (−0.14, 0.04)
Multivariable + *APOE*		0.93 (0.83, 1.05)	0.91 (0.78, 1.05)	0.18 (0.02, 0.34)	0.04 (−0.05, 0.13)
apoA1 in HDL that lacks apoE	48				
Basic[e]		1.00 (0.89, 1.13)	1.06 (0.92, 1.21)	−0.08 (−0.25, 0.10)	−0.08 (−0.18, 0.02)
Multivariable + *APOE*		1.00 (0.89, 1.13)	1.04 (0.90, 1.20)	−0.14 (−0.31, 0.04)	−0.03 (−0.13, 0.07)

HRs were obtained from weighted Cox proportional hazard regression models, and differences in the cognitive scores were obtained from weighted linear regression models adjusted for age, sex, race/ethnicity, clinic site, and fasting status. Values in parentheses are 95% CIs. Each lipoprotein was modeled separately except for complementary subspecies (apoA1 in HDL containing or lacking apoC3), which were included simultaneously in models. Multivariable analyses were adjusted for age, sex, race/ethnicity, clinic site, fasting status, education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale score, treatment assignment, and *APOE ε4* carrier status.

[a] *P*-hetereogeneity apoA1 levels in HDL containing or lacking apoC3 = 0.71; *P*-heterogeneity apoA1 levels in HDL containing or lacking apoJ = 0.27; and *P*-heterogeneity apoA1 levels in HDL containing or lacking apoE = 0.44.

[b] *P*-hetereogeneity apoA1 levels in HDL containing or lacking apoC3 = 0.92; *P*-heterogeneity apoA1 levels in HDL containing or lacking apoJ = 0.23; and *P*-heterogeneity apoA1 levels in HDL containing or lacking apoE = 0.22.

[c] *P*-hetereogeneity apoA1 levels in HDL containing or lacking apoC3 = 0.57; *P*-heterogeneity apoA1 levels in HDL containing or lacking apoJ = 0.79; and *P*-heterogeneity apoA1 levels in HDL containing or lacking apoE = 0.01.

[d] *P*-hetereogeneity apoA1 levels in HDL containing or lacking apoC3 = 0.24; *P*-heterogeneity apoA1 levels in HDL containing or lacking apoJ = 0.03; and *P*-heterogeneity apoA1 levels in HDL containing or lacking apoE = 0.34.

[e] $n = 1,350$.

TABLE 3. HRs for risk of dementia and AD, difference in cognitive scores at baseline, and 95% CIs according to plasma concentrations of apoC3 and apoJ in the GEMS case cohort (n = 1,351)

	SD *mg/dl*	HR for Dementia per SD	HR for AD per SD	Difference in 3MSE Scores per SD	Difference in ADAS-cog Scores per SD
apoC3 in HDL	4.1				
Basic		0.86 (0.75, 0.99)	0.81 (0.68, 0.95)	0.17 (−0.01, 0.34)	−0.16 (−0.26, −0.06)
Multivariable + *APOE*		0.89 (0.76, 1.03)	0.82 (0.69, 0.99)	0.09 (−0.09, 0.26)	−0.10 (−0.20, 0.0003)
Multivariable + *APOE* + triglycerides		0.95 (0.81, 1.12)	0.89 (0.73, 1.08)	0.02 (−0.20, 0.24)	−0.03 (−0.15, 0.08)
apoC3 in whole plasma	6.1				
Basic		0.82 (0.72, 0.94)	0.79 (0.67, 0.92)	0.16 (−0.01, 0.32)	−0.17 (−0.26, −0.08)
Multivariable + *APOE*		0.86 (0.75, 0.99)	0.88 (0.69, 0.98)	0.12 (−0.03, 0.28)	−0.15 (−0.24, −0.06)
Multivariable + *APOE* + triglycerides		0.91 (0.75, 1.10)	0.88 (0.71, 1.11)	0.15 (−0.10, 0.40)	−0.10 (−0.23, 0.03)
apoJ in whole plasma	1.4				
Basic		0.92 (0.78, 1.07)	0.87 (0.72, 1.06)	0.04 (−0.17, 0.25)	−0.07 (−0.19, 0.05)
Multivariable + *APOE*		0.92 (0.79, 1.08)	0.87 (0.72, 1.05)	0.04 (−0.16, 0.24)	−0.07 (−0.19, 0.04)

HRs were obtained from weighted Cox proportional hazard regression models, and differences in the cognitive scores were obtained from weighted linear regression models adjusted for age, sex, race/ethnicity, clinic site, and fasting status. Values in parentheses are 95% CIs. Multivariable analyses were adjusted for age, sex, race/ethnicity, clinic site, fasting status, education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale score, treatment assignment, and *APOE* ε4 carrier status.

highly correlated with the concentration of apoC3 in HDL (r = 0.50; P = < 0.00001) and apoC3 in whole plasma (r = 0.50; P = < 0.00001) in age- and sex-adjusted analyses. In analyses additionally adjusted for triglyceride concentration, the observed inverse associations between the concentration of apoC3 in HDL and in whole plasma with the risk of dementia and AD were not statistically significant (Table 3). Plasma concentrations of apoJ were unrelated to cognitive function, all-cause dementia, or AD in basic or fully adjusted models (Table 3). No statistically significant interaction was found between sex and apolipoprotein concentrations on the risk of

TABLE 4. HRs and 95% CIs for risk of dementia or AD according to plasma concentrations of apoC3 and apoJ in the GEMS case cohort (n = 1,351)

	Apolipoprotein Tertile				
	1st	2nd	3rd	*P*- Linear Trend	HR per SD
Dementia					
apoC3 in HDL					
Basic	1 (ref)	0.84 (0.65, 1.08)	0.67 (0.51, 0.88)	0.003	0.86 (0.75, 0.99)
Multivariable	1 (ref)	0.82 (0.64, 1.05)	0.64 (0.48, 0.85)	0.002	0.86 (0.74, 1.00)
Multivariable + *APOE*	1 (ref)	0.86 (0.67, 1.11)	0.66 (0.50, 0.88)	0.005	0.89 (0.76, 1.03)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.82 (0.61, 1.09)	0.66 (0.47, 0.91)	0.02	0.83 (0.69, 1.00)
apoC3 in whole plasma					
Basic	1 (ref)	0.73 (0.56, 0.94)	0.67 (0.52, 0.86)	0.002	0.82 (0.72, 0.94)
Multivariable	1 (ref)	0.76 (0.59, 0.98)	0.67 (0.52, 0.88)	0.005	0.83 (0.72, 0.95)
Multivariable + *APOE*	1 (ref)	0.80 (0.62, 1.04)	0.73 (0.55, 0.96)	0.03	0.86 (0.75, 0.99)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.72 (0.53, 0.98)	0.66 (0.48, 0.90)	0.01	0.79 (0.66, 0.93)
apoJ in whole plasma					
Basic	1 (ref)	0.86 (0.64, 1.16)	0.82 (0.58, 1.17)	0.29	0.92 (0.78, 1.07)
Multivariable	1 (ref)	0.86 (0.64, 1.16)	0.84 (0.59, 1.20)	0.35	0.91 (0.78, 1.07)
Multivariable + *APOE*	1 (ref)	0.92 (0.68, 1.24)	0.87 (0.61, 1.24)	0.45	0.92 (0.79, 1.08)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.79 (0.55, 1.11)	0.86 (0.57, 1.30)	0.50	0.93 (0.77, 1.12)
AD					
apoC3 in HDL					
Basic	1 (ref)	0.80 (0.60, 1.06)	0.56 (0.41, 0.77)	<0.001	0.81 (0.68, 0.95)
Multivariable	1 (ref)	0.76 (0.57, 1.02)	0.53 (0.38, 0.73)	<0.001	0.79 (0.66, 0.95)
Multivariable + *APOE*	1 (ref)	0.81 (0.61, 1.10)	0.55 (0.39, 0.77)	0.001	0.82 (0.69, 0.99)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.82 (0.60, 1.16)	0.59 (0.40, 0.87)	0.01	0.82 (0.66, 1.03)
apoC3 in whole plasma					
Basic	1 (ref)	0.73 (0.54, 0.97)	0.59 (0.44, 0.80)	0.001	0.79 (0.67, 0.92)
Multivariable	1 (ref)	0.75 (0.56, 1.01)	0.60 (0.44, 0.83)	0.002	0.79 (0.67, 0.93)
Multivariable + *APOE*	1 (ref)	0.80 (0.59, 1.08)	0.65 (0.47, 0.92)	0.01	0.88 (0.69, 0.98)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.75 (0.52, 1.08)	0.61 (0.42, 0.89)	0.009	0.78 (0.64, 0.96)
apoJ in whole plasma					
Basic	1 (ref)	0.79 (0.56, 1.10)	0.75 (0.50, 1.12)	0.17	0.87 (0.72, 1.06)
Multivariable	1 (ref)	0.76 (0.54, 1.07)	0.76 (0.50, 1.15)	0.19	0.87 (0.72, 1.05)
Multivariable + *APOE*	1 (ref)	0.83 (0.58, 1.17)	0.79 (0.52, 1.19)	0.25	0.87 (0.72, 1.05)
Multivariable excluding *APOE* ε4 carrier[a]	1 (ref)	0.68 (0.45, 1.01)	0.79 (0.49, 1.27)	0.33	0.91 (0.72, 1.14)

HRs were obtained from weighted Cox proportional hazard regression models adjusted for age, sex, race/ethnicity, clinic site, and fasting status. Multivariable analyses were adjusted for age, sex, race/ethnicity, clinic site, fasting status, education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale score, treatment assignment, and *APOE* ε4 carrier status.

[a] n = 1,070.

TABLE 5. Differences (95% CIs) in 3MSE at study screening or ADAS-cog scores at baseline according to plasma concentrations of apoC3 and apoJ in the GEMS case cohort (n = 1,351)

	Apolipoprotein Tertile, Difference (95% CI)				
	1st	2nd	3rd	*P*-Trend	Difference (95% CI) per SD
3MSE scores					
apoC3 in HDL					
Basic	0 (ref)	0.02 (−0.37, 0.41)	0.41 (0.01, 0.81)	0.05	0.17 (−0.01, 0.34)
Multivariable	0 (ref)	−0.03 (−0.40, 0.34)	0.29 (−0.10, 0.67)	0.19	0.09 (−0.08, 0.26)
Multivariable + *APOE*	0 (ref)	−0.02 (−0.40, 0.35)	0.28 (−0.10, 0.67)	0.20	0.09 (−0.09, 0.26)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	−0.11 (−0.52, 0.29)	0.08 (−0.35, 0.50)	0.98	−0.001 (−0.19, 0.19)
apoC3 in whole plasma					
Basic	0 (ref)	0.40 (0.02, 0.79)	0.54 (0.16, 0.93)	0.005	0.16 (−0.01, 0.32)
Multivariable	0 (ref)	0.48 (0.11, 0.85)	0.60 (0.23, 0.98)	0.002	0.13 (−0.03, 0.28)
Multivariable + *APOE*	0 (ref)	0.48 (0.11, 0.85)	0.60 (0.23, 0.98)	0.002	0.12 (−0.03, 0.28)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	0.39 (−0.02, 0.80)	0.39 (−0.02, 0.80)	0.09	0.05 (−0.12, 0.22)
apoJ in whole plasma					
Basic	0 (ref)	0.09 (−0.34, 0.53)	−0.19 (−0.72, 0.34)	0.49	0.04 (−0.17, 0.25)
Multivariable	0 (ref)	0.11 (−0.30, 0.52)	−0.14 (−0.64, 0.36)	0.58	0.04 (−0.16, 0.24)
Multivariable + *APOE*	0 (ref)	0.09 (−0.33, 0.50)	−0.15 (−0.65, 0.35)	0.56	0.04 (−0.16, 0.24)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	0.39 (−0.02, 0.80)	0.39 (−0.02, 0.80)	0.82	0.05 (−0.12, 0.22)
ADAS-cog scores					
apoC3 in HDL					
Basic	0 (ref)	−0.38 (−0.59, −0.16)	−0.39 (−0.61, −0.17)	0.001	−0.16 (−0.26, −0.06)
Multivariable	0 (ref)	−0.31 (−0.52, −0.09)	−0.30 (−0.53, −0.08)	0.009	−0.11 (−0.21, −0.01)
Multivariable + *APOE*	0 (ref)	−0.29 (−0.51, −0.08)	−0.28 (−0.51, −0.06)	0.02	−0.10 (−0.20, 0.0003)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	−0.14 (−0.37, 0.09)	−0.14 (−0.38, 0.10)	0.37	−0.05 (−0.16, 0.05)
apoC3 in whole plasma					
Basic	0 (ref)	−0.27 (−0.49, −0.05)	−0.45 (−0.67, −0.23)	<0.001	−0.17 (−0.26, −0.08)
Multivariable	0 (ref)	−0.24 (−0.45, −0.03)	−0.47 (−0.68, −0.25)	<0.001	−0.16 (−0.25, −0.07)
Multivariable + *APOE*	0 (ref)	−0.23 (−0.44, −0.02)	−0.44 (−0.65, −0.22)	<0.001	−0.15 (−0.24, −0.06)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	−0.13 (−0.36, 0.10)	−0.26 (−0.49, −0.03)	0.04	−0.10 (−0.20, −0.004)
apoJ in whole plasma					
Basic	0 (ref)	−0.06 (−0.31, 0.18)	0.03 (−0.26, 0.33)	0.87	−0.07 (−0.19, 0.05)
Multivariable	0 (ref)	−0.08 (−0.31, 0.16)	0.02 (−0.27, 0.31)	0.92	−0.08 (−0.19, 0.04)
Multivariable + *APOE*	0 (ref)	−0.05 (−0.29, 0.18)	0.03 (−0.25, 0.32)	0.86	−0.07 (−0.19, 0.04)
Multivariable excluding *APOE* ε4 carrier[a]	0 (ref)	−0.06 (−0.31, 0.20)	0.27 (−0.04, 0.58)	0.09	−0.02 (−0.14, 0.11)

Differences in 3MSE scores or ADAS-cog scores obtained from weighted linear regression models adjusted for age, sex, race/ethnicity, clinic site, and fasting status. Multivariable analyses were adjusted for age, sex, race/ethnicity, clinic site, fasting status, education, alcohol consumption, smoking status, BMI, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, Center for Epidemiologic Studies Depression Scale, treatment assignment, and *APOE* ε4 carrier status.

[a] n = 1,070.

dementia (all $P > 0.05$), and apolipoprotein concentrations were similar in *APOE* ε4 carriers and noncarriers (**Table 6**).

DISCUSSION

In this observational study of 1,351 elderly men and women, concentrations of total apoA1, HDL subspecies, and apoJ were unrelated to cognitive function, risk of all-cause dementia, and AD. Higher apoC3 levels in HDL and higher apoC3 levels in whole plasma were associated with better cognitive function and a lower risk of all-cause dementia and AD. These observations do not support the use of HDL subspecies defined by its apolipoprotein content as biomarkers for the risk of dementia in elderly populations.

Basic studies tend to suggest a potential benefit of circulating apoA1 in cognition, as circulating apoA1 appears to enter the central nervous system (35), where it binds

TABLE 6. Concentration of plasma HDL (mg/dl) and its apolipoprotein-defined subspecies, apoC3, and apoJ at screening visit by *APOE* ε4 carrier status in GEMS case cohort (n = 995)

	APOE ε4 Carrier (n = 615)	*APOE* ε4 Noncarrier (n = 182)	*APOE* Genotype Missing (n = 200)
apoA1 in whole plasma	152 (96, 253)	152 (98, 254)	157 (105, 254)
apoA1 in HDL that contains apoC3	11.1 (5.8, 21.2)	11.1 (5.9, 20.3)	11.6 (6.1, 20.0)
apoA1 in HDL that lacks apoC3	140 (89, 241)	141 (92, 238)	145 (97, 238)
apoA1 in HDL that contains apoJ	2.3 (1.1, 3.9)	2.2 (1.2, 3.7)	2.2 (1.2, 3.9)
apoA1 in HDL that lacks apoJ	150 (95, 251)	151 (96, 252)	156 (103, 252)
apoA1 in HDL that contains apoE	9.3 (4.2, 21.7)	11.8 (5.5, 26.2)	12.1 (5.2, 21.2)
apoA1 in HDL that lacks apoE	141 (92, 238)	140 (89, 237)	143 (94, 234)
apoC3 in HDL	10.0 (4.9, 17.3)	10.1 (5.5, 18.4)	9.7 (5.1, 16.0)
apoC3 in whole plasma	14.7 (8.2, 25.6)	15.4 (8.5, 27.6)	14.2 (7.6, 25.4)
apoJ in whole plasma	5.9 (4.0, 8.9)	5.9 (4.0, 8.2)	6.1 (3.9, 9.2)

Values are medians (95% CIs).

amyloid β and exerts neuroprotective effects (36). Nonetheless, prospective studies on plasma apoA1 concentrations and the risk of dementia, AD, or cognitive decline are sparse and provide inconsistent results. Higher concentrations of plasma apoA1 was associated with a lower risk of dementia in the Honolulu-Asia Aging Study (37). Consistent with our own findings, the plasma concentration of apoA1 was unrelated to cognitive decline in the Swedish Adoption Twin Study of Aging (38) and the risk of dementia or AD in the National Finnish population study (12). Similarly, in participants with subjective cognitive decline or MCI from the Amsterdam Dementia Cohort, the plasma concentration of apoA1 was unrelated to the clinical progression to MCI or AD (39). However, in a subgroup analysis, a higher plasma concentration of apoA1 was associated with a lower risk of progression to MCI or AD in E4 carriers with subjective cognitive decline (39). There is strong prior evidence that inverse associations between HDL or apoA1 and dementia outcomes would reflect protective properties of HDL on cerebral vessels (40). The lack of an association in the current study might be attributable to the advanced age of the study population, as HDL-cholesterol concentrations are more strongly related to dementia in previous studies when assessed at midlife compared with late life (41, 42). In previous studies, plasma concentrations of apoC-III were lower and concentrations of apoJ were higher in middle-aged populations, while apoA-I levels were similar to concentrations in the current study (43–46). Further, HDL function might be differentially related to specific subtypes of dementia pathology, which should be explored in future studies.

In the current analysis, the majority of HDL particles in plasma lacked apoC3, apoJ, or apoE and were unrelated to cognitive function, all-cause dementia, and AD. A couple of HDL subtypes were associated with cognitive function, but results were specific for only one cognitive measure. If these associations are specific for the domains the cognitive function tests address or if findings are due to chance needs to be evaluated in further studies. In an imaging substudy nested in GEMS, apoA1 levels in HDL that contained or lacked apoC3 or apoJ were differentially associated with hippocampal volume (47). Higher apoA1 levels in HDL that contained apoC3 or apoJ were associated with lower hippocampal volume, whereas apoA1 levels in HDL that lacked apoC3 or apoJ were associated with higher hippocampal volume. The latter findings suggest that plasma HDL subspecies might be more closely related to brain pathology than to clinical outcomes. However, these subspecies were not statistically significantly related to β-amyloid deposition or white-matter lesion volume in the GEMS imaging substudy (47). Further studies should clarify the role of HDL and its apolipoprotein-defined subspecies in the disease processes underlying AD, especially in younger populations.

ApoC3 is a small protein that is primarily synthesized in the liver (48), but is also found in the brain. Based on the direct association of apoC3 with CVD (49) and type 2 diabetes (50), major risk factors for dementia, the inverse associations of apoC3 with cognitive function and dementia were unanticipated. However, our findings are in line with previous studies that found lower apoC3 concentrations in participants with AD compared with participants without AD (51, 52).

Several explanations may exist for the inverse association between concentration of apoC3 and cognitive function and dementia. First, weight loss has been shown to lower plasma apoC3 levels (53), and unintended weight loss has been described as a common finding in the preclinical stage of dementia (54), suggesting the possibility of reverse causality. Therefore, studies that address midlife apoC3 in relation to dementia risk are critical. An alternative explanation for our findings is that apoC3 may cross the blood-brain barrier and bind β-amyloid (52). Hence, higher apoC3 levels in plasma might possibly reflect greater β-amyloid efflux capacity, which could translate to a lower risk of dementia. Long-term prospective cohort studies in younger populations with brain amyloid imaging are required to better understand the association between apoC3 and AD pathology. We cannot easily disentangle the separate concentrations of apoC3 and triglycerides with dementia risk, as the two are highly correlated and, accounting for the concentration of triglycerides, attenuated the risk of dementia and AD attributed to apoC3.

Genome-wide association studies and cross-sectional epidemiologic analyses have suggested that variants of the apoJ encoding gene and higher plasma concentrations of apoJ (also known as clusterin) are associated with a higher prevalence of AD (7, 55). Despite higher apoJ levels in prevalent AD cases, apoJ concentrations at baseline were not associated with a subsequent risk of dementia over a 7-year follow-up period in the Rotterdam study (55). Our finding of a lack of association between the concentration of apoJ and cognitive function, incident dementia, and AD is consistent with other large-scale prospective studies (55, 56) and underscores the importance of prospective analyses when identifying biomarkers involved in AD pathology.

Weaknesses and strengths of our study bear mention. The GEMS population was limited to elderly participants aged 75 years or older, and therefore the underlying biological processes leading to dementia were already underway, making generalizations to younger populations difficult. In sensitivity analyses of apoC3 we excluded individuals at immediate dementia risk. However, we cannot exclude reverse causality given the long preclinical phase of dementia. We focused on selected apolipoproteins in the pathophysiology of AD from previous studies. However, other proteins have been identified in HDL particles that might be relevant to AD (57). *APOE* genotype information was not available for all participants. The major strength of this study included the repeated assessment of novel HDL subspecies defined by apolipoprotein content, detailed and frequent evaluation of neurological status, and the comprehensive adjustment for potential confounders.

In conclusion, higher concentrations of apoC3 were associated with better cognitive function and a lower risk of dementia and AD, but apoA1, regardless of the presence of apoC3, apoJ, or apoE, and total apoJ were not consistently associated with cognitive function, risk of dementia, or AD

in this elderly population. Long-term prospective cohort studies in younger populations with brain imaging are required to further elucidate the association between apoC3 concentration and AD pathology.

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