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Original Contribution

The Relation between Apolipoprotein A-I and Dementia

The Honolulu-Asia Aging Study

Jane S. Saczynski[1], Lon White[2,3], Rita L. Peila[1], Beatriz L. Rodriguez[2,3], and Lenore J. Launer[1]

[1] Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, Bethesda, MD.
[2] Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, HI.
[3] Pacific Health Research Institute, Honolulu, HI.

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The association between apolipoproteins and neurodegeneration is unclear. The authors examined the association of dementia with serum levels of apolipoprotein A-I (ApoA-I) alone and in combination with the apolipoprotein E genotype (*ApoE*). Subjects were Japanese-American men in Hawaii followed since 1965 in the Honolulu Heart Program cohort and the Honolulu-Asia Aging Study. Lipid levels were assessed in 1980–1982. Dementia was diagnosed in 1991–1993, 1994–1996, and 1997–1999 by using a multistep procedure and international guidelines. The sample consisted of 929 men (107 dementia cases). The relation between ApoA-I and dementia was examined by using Cox proportional hazards models adjusted for age, education, and cardiovascular risk factors. Compared with men in the lowest quartile, men in the highest quartile of ApoA-I concentration had a significantly lower risk of dementia (hazard ratio = 0.25, 95% confidence interval: 0.08, 0.78). Compared with men with both risk factors, those with a high ApoA-I concentration and no *ApoE ε4* had a significantly lower risk of dementia (hazard ratio = 0.21, 95% confidence interval: 0.08, 0.52). Previous work has demonstrated an inverse relation between ApoA-I and cardiovascular disease, and the authors extended these findings to the risk of dementia. These results raise the possibility that different lipoprotein components of cholesterol may be differentially associated with dementia.

apolipoproteins; apolipoproteins E; dementia; lipids

Abbreviations: ApoA-I, apolipoprotein A-I; ApoE, apolipoprotein E; CI, confidence interval; HDL, high density lipoprotein; HR, hazard ratio.

Editor's note: *An invited commentary on this article is published on page 993.*

Evidence is increasing for an association between Alzheimer's disease and lipids (1, 2). Lipids may influence neurodegeneration through direct effects on the neurons or vessels (3), through atherosclerosis (4), or by chronic inflammation of the brain (5–7). High density lipoprotein (HDL)–like particles traffic cholesterol in the brain and are related to cholesterol metabolism, which may play an important role in amyloid β metabolism and deposition in the brain (8).

HDL particles are heterogeneous in size and apolipoprotein composition. It has been suggested that variability in these aspects of the HDL molecule may affect the antiatherogenic properties of the lipoprotein. Apolipoprotein

Correspondence to Dr. Jane S. Saczynski, Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Gateway Building, Room 3C-309, 7201 Wisconsin Avenue, Bethesda, MD 20892 (e-mail: saczynsj@mail.nih.gov).

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A-I (ApoA-I) is the major protein component of HDL and plays an important role in reverse cholesterol transfer (9). Evidence from studies of cardiovascular disease suggests that ApoA-I may be associated with lowered risk, independent of HDL cholesterol. For example, investigations of the roles of ApoA-I and HDL cholesterol in the risk of coronary heart disease found that although both ApoA-I and HDL cholesterol were significantly inversely associated with coronary heart disease, when examined in a multivariate model, ApoA-I, not HDL cholesterol, was significantly associated with heart disease (10, 11). Furthermore, examination of ApoA-I and coronary heart disease found that the apolipoprotein was associated with lower risk even at low concentrations of HDL cholesterol (12).

HDL cholesterol and ApoA-I reduce the risk of heart disease, but the relation with dementia is unclear. Case-control study reports indicate that ApoA-I levels are lower in subjects with dementia compared with controls (13–15), but, in these studies, lipids were measured after dementia was diagnosed, and levels may be influenced by the dementing process. Studies have also looked at the association between HDL cholesterol and dementia, but results are conflicting. In a case-control study, lower HDL cholesterol levels were reported in demented subjects (13), while prospective studies find weak (16) or no association between serum HDL cholesterol levels and the risk of dementia (17, 18). Discrepancy in the current literature with respect to the role of HDL cholesterol in neurodegeneration could be in part due to the role of specific apolipoprotein components of HDL not previously accounted for. Prospective studies of the associations between apolipoproteins and dementia risk are needed to more fully understand the relation between cholesterol and dementia.

The relation between cholesterol and dementia may also be modified by genetic susceptibility. The apolipoprotein E gene (*ApoE*), particularly the *ε4* allelic variant, is currently the only accepted genetic risk factor associated with Alzheimer's disease; it is involved in lipid trafficking and is also related to increased risk of cardiovascular disease (19–21). Here, we examine the association of clinical dementia with ApoA-I serum levels alone and in combination with the *ApoE* (*ε4*) gene. The study is based on a sample of Japanese-American men in Hawaii, born between 1900 and 1919, who were part of the Honolulu Heart Program cohort established in 1965.

MATERIALS AND METHODS

The Honolulu Heart Program cohort included all Japanese-American men living on the island of Oahu and registered with the Selective Service at the start of the study. As part of the Honolulu Heart Program, men were examined in 1965, 1968, and 1971. In 1970, a 30 percent random sample of Honolulu Heart Program participants was asked to participate in the Cooperative Lipoprotein Study (22). Two additional examinations of the lipoprotein subsample were conducted in 1975–1978 and 1980–1982 (23). In the third follow-up of the Cooperative Lipoprotein Study (1980–1982; $n = 1{,}379$), ApoA-I was measured; this sample serves as the sampling frame for this analysis.

In 1991, the Honolulu Heart Program continued as the Honolulu-Asia Aging Study, which was designed to examine diseases of old age. Of the 1,379 men who participated in the 1980 lipoprotein examination, 929 took part in the 1991–1993 Honolulu-Asia Aging Study examination; this is the sample for our analysis. Of the 450 men who participated in the 1980 lipoprotein examination and did not participate in the Honolulu-Asia Aging Study examinations, 77 percent died before the 1991 examination, 4 percent refused to participate, and 19 percent received abbreviated telephone interviews. Follow-up examinations within the Honolulu-Asia Aging Study occurred in 1994–1996 and 1997–1999. The study was approved by the institutional review board of Kuakini Hospital. Informed consent was obtained from the study participants.

Dementia diagnosis

Case finding for dementia was conducted by using a multistep process that has been described in detail elsewhere (24, 25). Briefly, all participants were administered the 100-point Cognitive Abilities Screening Instrument (CASI) (26). At the 1991 examination, CASI score and age identified a subgroup for dementia evaluation. At the 1994 and 1997 examinations, an education-adjusted cutpoint (77 for participants with a low educational level and 79 for those with a high educational level) or absolute drop ($\geq$9 points) identified a subgroup for dementia examination. The clinical dementia evaluation included a proxy interview, neurological examination, neuropsychological test battery, and neuroimaging. Dementia diagnoses were made by a consensus committee according to *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised criteria (27); Alzheimer's disease diagnoses according to National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Dementias Association criteria (28); and vascular dementia diagnoses according to California Alzheimer's Disease Diagnostic and Treatment Centers criteria (29). The current sample included 107 dementia cases, of whom 61 were diagnosed as having probable or possible Alzheimer's disease, 28 with vascular dementia, and 18 with other dementias. For the 46 dementia cases identified at the 1991 examination, age at diagnosis was estimated from the proxy interview and neurological examination. For the 61 cases identified at the 1994 and 1997 examinations, age at diagnosis was calculated individually as the midpoint between the last interview and the interview at which the subject was diagnosed with dementia.

Lipid measurement

In 1980–1982, blood was drawn, and HDL cholesterol and serum triglyceride levels were measured. HDL cholesterol was measured in the supernatant fraction of plasma after heparin-manganese chloride precipitation (30). Plasma samples were frozen (−70°C), and, in 1996, ApoA-I was measured by using a Behring Nephelometer Analyzer (Behring Diagnostics Inc., Newark, New Jersey) calibrated with World Health Organization international reference material for standardization of ApoA-I (31). Quality control specimens consisted of three fresh-frozen serum pools with

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low, medium, and high concentrations of ApoA-I. The within- and between-assay coefficients of variability were consistently less than 2 percent and less than 2.5 percent, respectively. There was an average of 15 years between the blood draw and dementia diagnoses.

ApoE measurement

Blood samples were drawn at the 1991 Honolulu-Asia Aging Study examination, and *ApoE* genotyping was performed by polymerase chain reaction amplification followed by restriction enzyme digestion (32) at the Bryan Alzheimer's Disease Research Center at Duke University (Durham, North Carolina). Participants were categorized as *ApoE ε4* positive if they carried at least one copy of the *ε4* allele and as *ε4* negative otherwise.

Confounders and mediators

A number of demographic and health factors were examined as potential confounders or mediators of the relation between ApoA-I and dementia. HDL cholesterol and triglycerides were included in the models to examine the contribution of ApoA-I to dementia risk independent of other lipids. ApoA-I has been shown to mediate the relation between HDL cholesterol and cardiovascular disease (10, 11), and HDL cholesterol has been found to moderate the effect of ApoA-I on coronary heart disease (12), suggesting that ApoA-I and HDL cholesterol may each have a unique contribution to atherosclerosis and dementia risk. Triglycerides may affect the relation between ApoA-I and dementia through cholesteryl ester transfer protein. For these reasons, we controlled for both lipids. Age, education, physical activity (self-reported time per week of moderate and strenuous activity categorized into tertiles of the sample distribution; the lowest tertile was the reference group), diabetes (self-report of diabetes diagnosis, use of oral hypoglycemic agents or insulin, fasting blood glucose $\geq$7.0 mmol/liter, or 2-hour postload glucose level $\geq$11.1 mmol/liter), use of antihypertensive medication, body mass index, smoking status, *ApoE* (*ε4*), and blood pressure were also included as potential confounders.

Statistical analysis

Baseline characteristics of participants were compared across ApoA-I quartiles by using age-adjusted analysis of variance for continuous variables and χ^2 statistics for categorical variables. The association of ApoA-I level with dementia was estimated with Cox proportional hazards models. The lowest quartile of ApoA-I was the reference group. Lipids, body mass index, and physical activity were measured in the lipoprotein study in 1980–1982, and smoking and blood pressure were measured at midlife at the second Honolulu Heart Program examination (1968).

Previous work has reported that higher levels of ApoA-I may lower the risk of dementia (13) whereas the *ApoE ε4* allele increases the risk, suggesting there may be a joint effect of ApoA-I and *ApoE ε4* on the risk of dementia. On the basis of this information, we classified participants into four categories: 1) low ApoA-I (defined as the bottom three quartiles of the sample distribution)/*ε4*; 2) high ApoA-I/*ε4*; 3) low ApoA-I/no *ε4*; and 4) high ApoA-I/no *ε4*. The low ApoA-I/*ε4* group served as the reference since these participants would be at the highest risk. We hypothesized that although the risk in all other groups would be lower than that in the reference group, the risk in the high ApoA-I/no *ε4* group would be lowest.

Three hazard models were estimated for ApoA-I. The first model adjusted for age (as the time scale); the second model adjusted for age, education, glucose (mmol/liter), body mass index, *ApoE ε4* zygosity, physical activity, smoking (packs smoked per year), and systolic blood pressure; and the third model additionally adjusted for HDL cholesterol (mmol/liter) and total plasma triglyceride (mmol/liter).

In the proportional hazards models, age at the lipid examination was defined as entry time, and participants were followed until age at dementia diagnosis, age at last observation, or age at death. When we removed from the analysis the 46 cases identified at the 1991 Honolulu-Asia Aging Study examination, the results were the same. Analyses were performed by using Statistical Analysis System version 8.0 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Compared with persons in the lipid sample who were lost to follow-up before the first phase of the Honolulu-Asia Aging Study ($n = 450$), the Honolulu-Asia Aging Study lipoprotein sample ($n = 929$) was younger, had a higher average body mass index, and had lower average glucose levels (table 1) but was otherwise similar. As expected, men with higher ApoA-I levels, on average, had higher HDL cholesterol and total cholesterol levels and a lower mean triglyceride concentration, glucose level, and body mass index (table 2). Other baseline characteristics were not significantly different across the quartiles of ApoA-I.

In the initial models (1 and 2), there were only marginal trends for higher concentrations of ApoA-I associated with lower risk of dementia (table 3). Compared with men in the lowest ApoA-I quartile, those in the highest quartile had a lower risk of dementia. In the fully adjusted model, men in the highest quartile of ApoA-I concentration had a significantly lower risk of dementia compared with those in the lowest quartile. In the fully adjusted model, *ApoE ε4* status was associated with a significantly higher risk of dementia (hazard ratio (HR) = 2.0, 95 percent confidence interval (CI): 1.2, 3.2).

Dementia subtype models showed results similar to those for the overall dementia models, although hazard ratios were not statistically significant, most likely because of small sample size. In the fully adjusted models for both Alzheimer's disease and vascular dementia, those men in the highest quartile of ApoA-I had the lowest risk of Alzheimer's disease (HR = 0.26, 95 percent CI: 0.05, 1.22) and vascular dementia (HR = 0.13, 95 percent CI: 0.01, 1.13).

We then tested for a joint effect of ApoA-I and *ApoE ε4* status by combining the two risk factors (table 4). In all models, compared with that for men in the low ApoA-I/*ApoE ε4* group (hypothesized to be the group at highest

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TABLE 1. Comparison of the current ApoA-I* lipid sample with the 1980 Honolulu Heart Program and 1991 Honolulu-Asia Aging Study sample (1965–1997), Hawaii†

Parameter	Lipid sample ($n = 929$)	Lipid sample without a 1991 examination (lost to follow-up) ($n = 450$)	1991 examination without a lipid examination ($n = 2,805$)
Age at lipid examination (years)	67.5 (4.5)	69.3 (5.6)	
Age at 1991 examination (years)	77.3 (4.5)		78.0 (4.7)
Education (no. of years)	10.4 (3.1)	10.2 (2.6)	10.5 (3.2)
Lipid examination total cholesterol (mmol/liter)	5.51 (0.87)	5.44 (1.17)	
Lipid examination HDL* cholesterol (mmol/liter)	1.22 (0.32)	1.25 (0.37)	
Lipid examination (g/liter)	1.42 (0.23)	1.43 (0.26)	
Lipid examination triglyceride (mmol/liter)	1.91 (1.43)	2.00 (2.99)	
Lipid examination glucose (mmol/liter)	6.19 (1.32)	6.59 (2.12)	
Lipid examination body mass index‡	23.7 (2.75)	23.3 (3.3)	
Systolic blood pressure (mmHg)	132.2 (16.7)		131.74 (17.1)
Dementia	11.5		13.1
Total Alzheimer's disease	6.6		7.5
Total vascular dementia	3.0		3.4
*ApoE** $\varepsilon 4$ zygosity	19.3		18.3

* ApoA-I, apolipoprotein A-I; HDL, high density lipoprotein; *ApoE*, apolipoprotein E gene.
† Values are expressed as mean (standard deviation) or percentage.
‡ Weight (kg)/height $(m)^2$.

TABLE 2. Comparison of ApoA-I† quartiles ($n = 929$) of Japanese-American men in the Honolulu-Asia Aging Study cohort, Hawaii, 1965–1997‡,§

Parameter	Serum ApoA-I quartile (g/liter)			
	1 ($\leq$1.26; $n = 230$)	2 (1.27–1.39; $n = 217$)	3 (1.40–1.56; $n = 262$)	4 ($\geq$1.57; $n = 220$)
Age at lipid examination (years)	67.8 (4.7)	67.9 (4.6)	67.4 (4.5)	67.1 (4.2)
Education (no. of years)	10.3 (3.0)	10.5 (3.3)	10.5 (3.0)	10.4 (3.0)
Lipid examination total cholesterol (mmol/liter)	5.17 (0.9)	5.46 (0.8)	5.67 (1.18)	5.63 (32.6)*
Lipid examination HDL† cholesterol (mmol/liter)	0.92 (0.1)	1.10 (0.2)	1.27 (0.2)	1.61 (0.3)*
Lipid examination ApoA-I (g/liter)	1.15 (0.1)	1.32 (0.1)	1.47 (0.1)	1.74 (0.2)*
Lipid examination triglyceride (mmol/liter)	2.05 (1.2)	1.96 (1.4)	2.04 (3.2)	1.60 (1.1)**
Lipid examination glucose (mmol/liter)	6.50 (1.8)	6.42 (1.7)	6.28 (1.7)	6.00 (1.2)**
Lipid examination body mass index¶	24.2 (2.8)	24.0 (2.9)	23.5 (3.0)	22.5 (2.9)*
ApoE†$\varepsilon 4$ zygosity	23.1	20.2	16.3	18.2
Dementia	13.5	10.1	13.7	8.2
Alzheimer's disease	7.4	5.3	8.8	4.1
Vascular dementia	4.4	1.8	3.1	2.7

* $p < 0.001$; ** $p < 0.01$. Analysis of variance was used for continuous variables and χ^2 analyses for categorical variables.
† ApoA-I, apolipoprotein A-I; HDL, high density lipoprotein; *ApoE*, apolipoprotein E gene.
‡ Values are expressed as mean (standard deviation) or percentage.
§ All analyses were adjusted for age.
¶ Weight (kg)/height $(m)^2$.

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TABLE 3. Hazard ratios (with corresponding 95% confidence intervals) for the association of ApoA-I* quartiles with the risk of dementia in the Honolulu-Asia Aging Study cohort (1965–1997) ($n = 929$), Hawaii

ApoA-I quartile (g/liter)	No.	Model 1†		Model 2‡		Model 3§	
		HR*	95% CI*	HR	95% CI	HR	95% CI
≤1.26	230	1.00	Reference	1.00	Reference	1.00	Reference
1.27–1.39	217	0.98	0.44, 2.20	0.70	0.38, 1.28	0.57	0.30, 1.01
1.40–1.56	262	1.40	0.66, 3.10	1.22	0.71, 2.09	0.79	0.39, 1.58
≥1.57	220	0.72	0.28, 1.80	0.61	0.31, 1.20	0.25	0.08, 0.78
p_{trend}		NS*		NS		0.12	

* ApoA-I, apolipoprotein A-I; HR, hazard ratio; CI, confidence interval; NS, not significant.
† Adjusted for age.
‡ Additionally adjusted for education, alcohol intake, physical activity, body mass index, systolic blood pressure, glucose (mg/dl), diabetes status, hypertensive medication, apolipoprotein E *ε4* gene, and weight loss.
§ Additionally adjusted for high density lipoprotein cholesterol (mmol/liter) and total plasma triglyceride (mg%).

risk), the risk of dementia was lower for those in the high ApoA-I/*ApoE ε4* group (fully adjusted HR = 0.34, 95 percent CI: 0.10, 1.13) and the low ApoA-I/no *ApoE ε4* group (fully adjusted HR = 0.54, 95 percent CI: 0.32, 0.91) and, as hypothesized, was lowest in the high ApoA-I/no *ApoE ε4* group (fully adjusted HR = 0.21, 95 percent CI: 0.08, 0.52). The risk for the high ApoA-I/no *ApoE ε4* group was lower than the risk for either of the two risk factors alone. However, the formal tests of statistical interaction between ApoA-I quartiles and *ApoE ε4* status were not significant (age-, sex-, and education-adjusted model: quartile 2 HR = 0.90, $p = 0.85$; quartile 3 HR = 1.09, $p = 0.96$; quartile 4 HR = 0.72, $p = 0.86$).

DISCUSSION

This study examined the association of lipoprotein levels with risk of dementia in older Japanese-American men. We found a decreasing risk of dementia with increasing ApoA-I concentrations independent of a number of lifestyle, demographic, and biologic covariates, including HDL cholesterol and triglycerides. There was also a joint effect of ApoA-I and the *ApoE* (*ε4*) gene on the risk of dementia.

The association between ApoA-I and the risk of dementia has mostly been studied in case-control samples whose lipids were measured after the diagnosis of dementia (13–15). Results from prospective population-based studies are mixed (33, 34). However, these studies had a relatively short period between lipid measurement and dementia diagnosis, so it is possible that the dementing process could have already altered lipid levels. Longer follow-up periods may show a different relation between lipids and the risk of dementia. Our study was based on a prospective design, with lipid concentrations measured an average of 15 years prior to dementia diagnoses.

TABLE 4. Hazard ratios (with corresponding 95% confidence intervals) for the joint effect of ApoA-I* and *ApoE *ε4* with the risk of dementia in the Honolulu-Asia Aging Study cohort (1965–1997) ($n = 900$), Hawaii**

ApoA-I/*ApoE* group	No.	Model 1†		Model 2‡		Model 3§	
		HR*	95% CI*	HR	95% CI	HR	95% CI
Low ApoA, *ε4* positive	135	1.00	Reference	1.00	Reference	1.00	Reference
Low ApoA, *ε4* negative	551	0.68	0.42, 1.11	0.54	0.32, 0.91	0.54	0.32, 0.91
High ApoA, *ε4* positive	39	0.80	0.30, 2.12	0.58	0.19, 1.72	0.34	0.10, 1.13
High ApoA, *ε4* negative	175	0.47	0.23, 0.95	0.35	0.16, 0.76	0.21	0.08, 0.52

* ApoA-I, apolipoprotein A-I; *ApoE*, apolipoprotein E gene; HR, hazard ratio; CI, confidence interval.
† Adjusted for age.
‡ Additionally adjusted for education, alcohol intake, physical activity, body mass index, systolic blood pressure, glucose (mg/dl), diabetes status, hypertensive medication, *ApoE ε4* gene, and weight loss.
§ Additionally adjusted for high density lipoprotein cholesterol (mmol/liter) and total plasma triglyceride (mg%).

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There are a number of potential limitations of this study. First, we had only a single measurement of ApoA-I, so we could not examine changes in ApoA-I and dementia risk. In addition, serum samples were frozen for an average of 15 years before ApoA-I was analyzed. While ApoA-I levels do decrease with age (35) and may degrade with long-term storage (36), the ApoA-I levels in our sample were comparable to age- and sex-specific population means reported in the Third National Health and Nutrition Examination Survey (37). It has been shown that ApoA-I samples are stable in storage for 1 year (38); however, in the absence of longer follow-up of stored samples, we cannot rule out the possibility that long-term frozen storage may result in measurement inaccuracies. Third, because we did not administer a complete neurological evaluation to all subjects, our dementia screening criteria may have missed incident cases. Finally, the generalizability of our results may be limited by the geographic, ethnic, and gender restrictions of our sample.

The heterogeneity of the size and apolipoprotein composition of HDL molecules may, in part, explain why high ApoA-I is associated with a significantly lower risk of dementia only after controlling for HDL cholesterol and triglycerides. The density of ApoA-I on the HDL molecule may be related to the composition of cholesterol or the homeostasis of the lipoprotein and may also alter reverse cholesterol transport and modulate the risk of vascular diseases (39, 40). The relation between ApoA-I and HDL cholesterol with respect to dementia risk may not be linear. Rather, the level of ApoA-I relative to the level of HDL cholesterol and other lipids may provide unique information about an association between lipoproteins and dementia above that of HDL cholesterol or ApoA-I level alone. This finding is consistent with those regarding the relation between ApoA-I and cardiovascular disease that report a lower risk of heart disease with increasing concentrations of ApoA-I, independent of HDL cholesterol (10, 11). In addition, ApoA-I has been associated with lowered risk of heart disease even when HDL cholesterol levels are low (12).

Lipoproteins may influence neurodegeneration as a carrier of cholesterol. There is evidence that brain cholesterol is related to amyloid metabolism in the brain and that disruption of cholesterol homeostasis in Alzheimer's disease is linked to amyloid β pathology (41). A recent study reported correlations between cerebrospinal fluid and serum levels of ApoA-I that were related to the amyloid β40/amyloid β42 ratio in the cerebrospinal fluid (42). These findings suggest that ApoA-I plasma levels, by regulating cholesterol levels in cerebrospinal fluid, may moderate the deposition of amyloid β. Lipoproteins may also influence the risk of dementia through antiinflammatory processes (43), inhibitory effects against oxidative stress (44, 45), and reduction of vascular injury (46).

Although the association of *ApoE ε4* with the risk of dementia is a robust finding, the relation between cholesterol and the risk of dementia in carriers of the *ApoE ε4* allele has not been fully examined (19). Repair of neuronal damage and antioxidant activity are reduced with the *ApoE ε4* allele (17, 47, 48). Several studies have shown that the ability of ApoE to generate HDL-like particles in the brain that transport cholesterol may be isoform dependent, with the amount of cholesterol released as HDL from *ApoE ε3*–expressing astrocytes being greater than that released from *ApoE ε4*–expressing astrocytes (49, 50). Because brain cholesterol homeostasis is maintained by the HDL cholesterol supply from astrocytes (51), *ApoE ε4* carriers may have a decreased cholesterol supply to the neurons and disrupted cholesterol homeostasis. Although the *ApoE ε4* allele is associated with lower levels of plasma HDL cholesterol, there is variability in the levels of HDL and ApoA-I in *ε4* carriers. We found that the combination of low ApoA-I/*ApoE ε4* was associated with a fivefold increase in risk compared with those with neither of the two risk factors. This risk is higher than that associated with either ApoA-I or *ApoE ε4* alone.

Other potential mechanisms such as dietary and lifestyle choices or genetic differences specific to Japanese-American men may also influence the relation between ApoA-I and dementia pathology. Mutations in the cholesteryl ester transfer protein gene have an approximately 6 percent prevalence (any mutation) in the Honolulu Heart Program cohort (52) and may influence the relation between ApoA-I and dementia in this sample. The size of the HDL particle and plasma levels are regulated by cholesteryl ester transfer protein, and mutations may alter the composition of HDL and its constituents (53). Perhaps there are also specific genetic mutations of the ApoA-I gene or interactions between diets high in fish oil and HDL cholesterol and its components that alter associations with neurodegeneration. The specific mechanism by which lipoprotein impacts cardiovascular disease is not fully understood, and there is even less work on the relation between lipoproteins, cholesterol, and dementia.

Inconsistent findings in the literature on the relation between lipids and dementia may reflect the fact that lipoprotein and apolipoprotein components of cholesterol are more informative than the total HDL measure. Mechanistic studies of cholesterol and the HDL molecule are needed to more fully understand the relation between cholesterol and dementia.

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REFERENCES

1. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004;363:1139–46.

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2. De la Torre JC. Vascular basis of Alzheimer's pathogenesis. Ann N Y Acad Sci 2002;977:196–215.
3. Moser DJ, Hoth KF, Robinson RG, et al. Blood vessel function and cognition in elderly patients with atherosclerosis. Stroke 2004;35:369–72.
4. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349:151–4.
5. McGeer EG, McGeer PL. The importance of inflammatory mechanisms in Alzheimer's disease. Exp Gerontol 1998;33:371–8.
6. Schmidt R, Schmidt H, Curb JD, et al. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol 2002;52:168–74.
7. Yanker BA. Mechanisms of neuronal degeneration in Alzheimer's disease. Neuron 1996;16:921–32.
8. Reiss AB, Siller KA, Rahman MM, et al. Cholesterol in neurologic disorders of the elderly: stroke and Alzheimer's disease. Neurobiol Aging 2004;25:977–89.
9. Leroy A, Dallongeville J, Fruchart JC. Apolipoprotein A-1 containing lipoproteins and atherosclerosis. Curr Opin Lipidol 1995;6:281–5.
10. von Eckardstein A, Fischer F, Schulte H, et al. Association of serum apolipoprotein A-1 (but not high-density lipoprotein cholesterol) with healed myocardial infarction in men independent of serum insulin and C-peptide. Am J Cardiol 2001;88:723–6.
11. Luc G, Bard JM, Ferrieres J, et al. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease. Arterioscler Thromb Vasc Biol 2002;22:1155–61.
12. Sharp DS, Burchfiel CM, Rodriguez BL, et al. Apolipoprotein A-1 predicts coronary heart disease only at low concentrations of high-density lipoprotein cholesterol: an epidemiological study of Japanese-Americans. Int J Clin Lab Res 2000;30:39–48.
13. Merchard A, Xia Y, Visvikis S, et al. Decreased high-density lipoprotein cholesterol and serum apolipoprotein A1 concentrations are highly correlated with the severity of Alzheimer's disease. Neurobiol Aging 2000;2:27–30.
14. Kawano M, Kawakami M, Otsuka M, et al. Marked decrease of plasma apolipoprotein AI and AII in Japanese patients with late-onset non-familial Alzheimer's disease. Clin Chim Acta 1995;239:209–11.
15. Kuriyama M, Takahashi K, Yamano T, et al. Low levels of serum apolipoprotein A I and A II in senile dementia. Jpn J Psychiatry Neurol 1994;48:589–93.
16. Reitz C, Tang MX, Luchsinger J, et al. Relation of plasma lipids to Alzheimer's disease and vascular dementia. Arch Neurol 2004;61:705–14.
17. Tan ZS, Seshadri S, Beiser A, et al. Plasma total cholesterol level as a risk factor for Alzheimer disease. Arch Intern Med 2003;163:1053–7.
18. Moroney J, Tang MX, Berglund L, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. JAMA 1999;282:254–60.
19. Eichner JE, Dunn ST, Perveen G, et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. Am J Epidemiol 2002;155:487–95.
20. Mahley RW, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet 2000;1:507–37.
21. Reiss AB. Cholesterol and apolipoprotein E in Alzheimer's disease. Am J Alzheimers Dis Other Demen 2005;20:91–6.
22. Castelli WP, Cooper GR, Doyle JT, et al. Distribution of triglyceride and total, LDL and HDL cholesterol in several populations: a cooperative lipoprotein phenotyping study. J Chronic Dis 1977;30:147–69.
23. Curb JD, Reed DM, Yano K, et al. Plasma lipids and lipoproteins in elderly Japanese-American men. J Am Geriatr Soc 1986;34:773–80.
24. White L, Petrovitch H, Ross GW, et al. Prevalence of dementia in older Japanese-American men in Hawaii. The Honolulu-Asia Aging Study. JAMA 1996;276:955–60.
25. Havlik RJ, Izmirlian G, Petrocitch H, et al. APOE-epsilon4 predicts incident AD in Japanese-American men: The Honolulu-Asia Aging Study. Neurology 2000;54:1526–9.
26. 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;6:45–58; discussion 62.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IIIR. 3rd ed, rev. Washington, DC: American Psychiatric Association, 1987.
28. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;43:939–44.
29. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology 1992;42:473–80.
30. Albers JJ, Warnick GR, Johnson N, et al. Quality control of plasma high-density lipoprotein cholesterol measurement methods. Circulation 1980;62(4 pt 2):IV9–18.
31. Marcovina SM, Albers JJ, Henderson LO, et al. International Federation of Clinical Chemistry standardization project for measurements of apolipoproteins A-1 and B. Clin Chem 1993;39:773–81.
32. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with Hhal. J Lipid Res 1990;31:545–8.
33. Reitz C, Tang MX, Luchsinger J, et al. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol 2004;61:705–14.
34. Li G, Shofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer disease. Neurology 2005;65:1045–50.
35. Lind L, Vessby B, Sundström J. The apolipoprotein B/AI ratio and the metabolic syndrome independently predict risk for myocardial infarction in middle-aged men. Arterioscler Thromb Vasc Biol 2006;26:406–10.
36. Hiura Y, Mahajan D, Steinbeck K, et al. Effect of long-term storage at −20°C and −80°C on apolipoprotein A1 and B in obese subjects. Br J Biomed Sci 2001;58:30–3.
37. Bachorik PS, Lovejoy KL, Carroll MD, et al. Apolipoprotein B and A1 distributions in the United States, 1988–1991: results of the National Health and Nutrition Examination Survey III (NHANES III). Clin Chem 1997;43:2364–78.
38. Imbert-Bismut F, Messous D, Thibaut V, et al. Intra-laboratory analytical variability of biochemical markers of fibrosis (Fibrotest) and activity (Actitest) and reference ranges in healthy blood donors. Clin Chem Lab Med 2440;42:323–33.
39. Schultz JR, Verstuyft JG, Gong EL, et al. Protein composition determines the anti-atherogenic properties of HDL in transgenic mice. Nature 1993;365:762–4.

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40. Barzilai N, Atzmon G, Schechter C, et al. Unique lipoprotein phenotype and genotype associated with exceptional longevity. JAMA 2003;290:2030–40.
41. Eckert G, Kirsch C, Leutz, et al. Cholesterol modulates amyloid beta-peptide's membrane interactions. Pharmacopsychiatry 2003;36:S136–43.
42. Fagan AM, Younkin LH, Morris JC, et al. Differences in the Abeta40/Abeta42 ratio associated with cerebrospinal fluid lipoproteins as a function of apolipoprotein E genotype. Ann Neurol 2000;48:201–10.
43. Navab M, Anantharamaiah GM, Fogelman AM. The role of high-density lipoprotein in inflammation. Trends Cardiovasc Med 2005;15:158–61.
44. Navab M, Hama SY, Cooke CJ, et al. Normal high density lipoprotein inhibits three steps in the formation of mildly oxidized low density lipoprotein. J Lipid Res 2000;41:1481–94.
45. Garner B, Waldeck AR, Witting PK, et al. Oxidation of high density lipoproteins. Evidence for direct reduction of lipid hydroperoxides by methionine residues of apolipoprotein A-I and A-II. J Biol Chem 1998;273:6088–95.
46. Kontush A, Chapman MJ. Antiatherogenic small, dense HDL—guardian angel of the arterial wall? Nat Clin Pract Cardiovasc Med 2006;3:144–53.
47. Ma J, Brewer B, Potter H. Alzheimer Aβ neurotoxicity: promotion by antichymotrypsin, ApoE4; inhibition by Aβ-related peptides. Neurobiol Aging 1996;17:773–80.
48. Herz J, Beffert U. Apolipoprotein E receptors: linking brain development and Alzheimer's disease. Nat Rev Neurosci 2000;1:51–8.
49. Gong JS, Kobayashi M, Hayashi H, et al. Apolipoprotein E (ApoE)-isoform-dependent lipid release from astrocytes prepared from human ApoE3- and ApoE4-knock-in mice. J Biol Chem 2002;277:29919–26.
50. Michikawa M, Fan QW, Isobe I, et al. Apolipoprotein E exhibits isoform-specific promotion of lipid efflux from astrocytes and neurons in culture. J Neurochem 2000;74:1008–16.
51. Michikawa M, Yanagisawa K. Apolipoprotein E4 isoform-specific actions on neuronal cells in culture. Mech Ageing Dev 1999;107:233–43.
52. Zhong S, Sharp DS, Grove JS, et al. Increased coronary heart disease in Japanese-American men with mutation on the cholesteryl ester transfer protein gene despite increased HDL levels. J Clin Invest 1996;97:2917–23.
53. Nagano M, Yamashita S, Hirano K, et al. Molecular mechanisms of cholesteryl ester transfer protein deficiency in Japanese. J Atheroscler Thromb 2004;11:110–21.

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