ORIGINAL CONTRIBUTION

Association of Higher Levels of High-Density Lipoprotein Cholesterol in Elderly Individuals and Lower Risk of Late-Onset Alzheimer Disease

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Objective: To reexamine the association of lipid levels with Alzheimer disease (AD) using Cox proportional hazards models.

Design: Prospective cohort study.

Setting: Northern Manhattan, New York.

Participants: One thousand one hundred thirty elderly individuals free of cognitive impairment at baseline.

Main Outcome Measure: High-density lipoprotein cholesterol (HDL-C) levels.

Results: Higher levels of HDL-C (>55 mg/dL) were associated with a decreased risk of both probable and possible AD and probable AD compared with lower HDL-C levels (hazard ratio, 0.4; 95% confidence interval, 0.2-0.9; $P=.03$ and hazard ratio, 0.4; 95% confidence interval, 0.2-0.9; $P=.03$). In addition, higher levels of total and non–HDL-C were associated with a decreased risk of AD in analyses adjusting for age, sex, education, ethnic group, and *APOE*e4 genotype.

Conclusion: High HDL-C levels in elderly individuals may be associated with a decreased risk of AD.

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Dyslipidemia and late-onset Alzheimer disease (AD) are highly frequent in western societies. More than 50% of the US adult population has high cholesterol.[1] About 1% of people aged 65 to 69 years develop AD, and the prevalence increases to more than 60% for people older than 95 years.[2] Dyslipidemia is an established vascular risk factor, and vascular disease seems to have an important role in AD.[3] It remains unclear whether dyslipidemia increases the risk of AD. There is evidence that cholesterol alters the degradation of the amyloid precursor protein and shows an effect on amyloid fibril formation, which play a major role in the pathogenesis of AD.[4,5] However, other reports indicate that cholesterol depletion induces AD-type injuries in cultured hippocampal slices[5] and that plasma cholesterol levels have no effect on brain HMG-CoA reductase activity.[6] Observational studies relating plasma lipid levels or lipid-lowering treatment with the risk of dementia have also been inconsistent.[6-31] We previously reported associations between high levels of low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C) and vascular dementia,[32] as well as low levels of total cholesterol and risk of AD,[32] but no association of HDL-C, triglyceride, or LDL-C levels with AD,[32] amnestic or nonamnestic mild cognitive impairment (MCI),[33] or cognitive test performance over time.[34] These prospective analyses were from a cohort recruited in 1992 through 1994. Our objective in the present study was to reexamine the associations of lipids with dementia in a cohort recruited in 1999 through 2001, after the start of the widespread use of lipid-lowering treatment in the 1990s following the results of a landmark clinical trial of lipid lowering.[35]

METHODS

SUBJECTS AND SETTING

Participants were enrolled in a longitudinal cohort study by a random sampling of Medicare recipients 65 years or older residing in northern Manhattan, New York.[36] Each participant underwent an interview of general health and function, medical history, a neurological examination, and a neuropsychological battery.[37] Baseline data were collected from 1999

through 2001. Follow-up data were collected at sequential intervals of 18 months.

The current sample included participants without baseline dementia or MCI with information on plasma lipid levels and lipid-lowering treatment. Of the 2190 who were initially recruited, 146 (6.7%) were excluded because of prevalent dementia; 350 (16.1%), because of loss to follow-up; and 547 (25.2%), because of lack of data on lipid levels. The final analytic sample included 1130 individuals. The final sample was younger than those excluded (eTable 1; http://www.archneurol.com) and had more women than those lost to follow-up but fewer women than those with no lipid level data, fewer Hispanic individuals than those with prevalent dementia, and more white individuals than all excluded groups.

CLINICAL ASSESSMENTS

Data were available from medical, neurological, and neuropsychological evaluations.[37] All participants underwent a standardized neuropsychological test battery examining multiple domains at all assessments using the Mini-Mental State Examination, the Boston Naming Test, the Controlled Word Association Test, category naming, the complex ideational material and phrase repetition subtests from the Boston Diagnostic Aphasia Evaluation, the Wechsler Adult Intelligence Scale–Revised similarities subtest, the Mattis Dementia Rating Scale, the Rosen Drawing Test, the Benton Visual Retention Test, the multiple-choice version of the Benton Visual Retention Test, and the Buschke Selective Reminding Test.[37]

DIAGNOSIS OF DEMENTIA AND MCI

The diagnosis of dementia was established on the basis of all available information gathered from the initial and follow-up assessments and medical records. Dementia was diagnosed by consensus of neurologists, psychiatrists, and neuropsychologists based on *DSM-IV* criteria.[38] The diagnosis of AD was based on the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[39] A diagnosis of probable AD was made when the dementia could not be explained by any other disorder. A diagnosis of possible AD was made when the most likely cause of dementia was AD, but there were other disorders that could contribute to the dementia such as stroke and Parkinson disease. Consistent with standard criteria[40] for all subtypes of MCI, those considered for MCI were required to have (1) memory complaint, (2) objective impairment in at least 1 cognitive domain based on the average of the scores on the neuropsychological measures within that domain and a 1.5-SD cutoff using normative corrections for age, years of education, ethnicity, and sex, (3) essentially preserved activities of daily living, and (4) no dementia. Our primary outcome was possible and probable AD. Given that lipids are known cerebrovascular risk factors, we conducted secondary analyses with probable AD as the outcome to try to separate cases of AD with a vascular component. Persons with MCI were excluded from the analyses.

LIPID LEVELS AND LIPID-LOWERING TREATMENT

At baseline, fasting plasma total cholesterol and triglyceride levels were determined using standard techniques. The HDL-C levels were determined after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid. The LDL-C levels were recalculated using the formula of Friedewald et al.[41] Non–HDL-C levels were calculated using the formula Non–HDL-C Level = Total Cholesterol Level – HDL-C Level. We report both LDL-C and non–HDL-C levels because recent studies suggest that the latter is a better predictor of outcomes.[42] Use of lipid-lowering treatment was ascertained by self-report.

OTHER COVARIATES

APOE genotypes were determined as described by Hixson and Vernier[43] with slight modification. We classified persons as being homozygous or heterozygous for the *APOEe4* allele or not having any *e4* allele. Type 2 diabetes mellitus and hypertension were defined by self-report at baseline and at each follow-up interval or by the use of disease-specific medications. Blood pressure measurements were also considered in the definition of hypertension. Hypertension was defined as a systolic blood pressure higher than 140 mm Hg or a diastolic blood pressure higher than 90 mm Hg.[44] Heart disease was defined as a history of arrhythmia, myocardial infarction, congestive heart failure, or angina pectoris at any time during life. The body mass index was calculated as weight in kilograms divided by height in meters squared.

STATISTICAL METHODS

First, we evaluated plasma lipid levels, demographic distributions, and clinical characteristics at baseline. Then we used Cox proportional hazard models to estimate the association of lipids with incident probable and possible AD and probable AD only. Plasma lipid levels were analyzed as a logarithmic-transformed continuous variable and grouped into quartiles. The time-to-event variable was duration of observation from baseline to dementia or last evaluation. Data from individuals in whom dementia or AD did not develop, who died, or who were lost to follow-up owing to relocation before development of dementia were censored at the time of their last evaluation.

After adjusting for sex and age, we additionally adjusted for ethnic group, education, *APOE* genotype, diabetes, heart disease, body mass index, hypertension, and lipid-lowering treatment.

RESULTS

During 4469 person-years of follow-up, there were 101 cases of incident AD of which 89 cases were diagnosed as having probable AD and 12 cases were diagnosed as having possible AD. The general characteristics of the sample are shown in **Table 1**. Compared with persons who did not develop incident AD during follow-up, persons who developed dementia were more often Hispanic and had a higher prevalence of diabetes at baseline (**Table 2**).

The mean (SD) age at onset of probable and possible AD was 82.9 (7.1) years and of probable AD, 83.1 (7.0) years. Higher plasma levels of HDL-C were associated with a decreased risk of both probable and possible AD and probable AD in models adjusting for age, sex, education, ethnic group, and *APOEe4* genotype but also in models additionally adjusting for vascular risk factors and lipid-lowering treatment (**Table 3**). This association was driven by the highest HDL-C level quartile, suggesting a threshold association.

Higher plasma total cholesterol, non–HDL-C, and LDL-C levels were associated with decreased risks of probable and possible AD and probable AD in models adjusting for age, sex, education, ethnic group, and *APOEe4* genotype. However, these associations were slightly attenuated and became nonsignificant after adjusting for vascular risk factors or lipid-lowering treatment.

Simultaneous inclusion of HDL-C and non–HDL-C levels in the models, restriction of the analyses to persons with longer follow-up time (observation time ≥ the median follow-up time of 4.2 years), or stratification by median of age, ethnicity, or diabetes did not change these relations.

We conducted additional analyses relating lipid levels to vascular dementia (eTable 2). We used a definition of vascular dementia that included persons with possible AD with stroke. These analyses were limited by a small number of cases of vascular dementia (n=16). The results were not statistically significant. However, the hazard ratio for the fourth quartile of HDL-C level suggested that higher HDL-C level is also associated with a lower risk of vascular dementia (hazard ratio, 0.4; 95% confidence interval, 0.1-2.3) as expected, given the known association between high HDL-C levels and a lower risk of stroke.[45]

COMMENT

In this study, higher levels of HDL-C were associated with a decreased risk of both probable and possible AD. These results did not change when only probable AD was considered. In addition, higher levels of total cholesterol, non–HDL-C, and LDL-C were associated with a decreased risk of AD in analyses adjusting for age, sex, education, ethnic group, and *APOEe4* genotype. However, when the models were adjusted for vascular risk factors or lipid-lowering treatment, these associations were slightly attenuated and became nonsignificant.

Dyslipidemia, and particularly low HDL-C level,[45] is a known risk factor for cerebrovascular disease, and treatment with lipid-lowering medications can prevent stroke.[46] Stroke is associated with higher AD risk.[38] Stroke may interact with amyloid pathology in an additive way and lower the amyloid burden necessary to precipitate dementia.[47] Low concentrations of HDL-C are known to be independent risk factors for carotid artery atherosclerosis,[48] which in turn may lead to cognitive impairment through cerebral hypoperfusion, embolism, or disruption of white matter.[49] High-density lipoprotein cholesterol might also be linked with small-vessel disease by playing a role in the removal of excess cholesterol from the brain by interaction with *APOE* and heparan sulfate proteoglycans in the subendothelian space of cerebral microvessels.[31] Thus, a low HDL-C level could precipitate AD through a cerebrovascular pathway.

However, it is possible that dyslipidemia affects AD through noncerebrovascular mechanisms. Levels of brain cholesterol influence the clearance of amyloid and the formation of neurofibrillary tangles through alteration of the degradation of amyloid precursor protein.[4] Brain cholesterol influences the clearance of amyloid and the formation of neurofibrillary tangles through action at the lipid rafts located in neuronal membranes.[50] However, these notions seem to contradict studies demonstrating that brain cholesterol is almost entirely synthesized in situ and not transferred from the plasma into the brain.[51] Dyslipidemia could also be a marker for other AD risk factors. Low HDL-C levels accompany hyperinsulinemia,[52,53] which in turn was a strong risk factor for AD in our cohort,[54] and may affect amyloid clearance in the brain.[55]

Table 1. Demographic and Clinical Characteristics of the 1130 Individuals in the Study Population

Characteristic	No. (%)[a]
Female	742 (65.7)
Age, y, mean (SD)	75.7 (6.3)
Education, y, mean (SD)	10.9 (4.7)
Ethnic group[b]	
White/non-Hispanic	379 (33.5)
Black/non-Hispanic	346 (30.6)
Hispanic	385 (34.1)
APOE genotype *e4*/- or *e4*/*e4*	289 (25.6)
Total cholesterol level, mg/dL, mean (SD)	199.2 (38.2)
HDL-C level, mg/dL, mean (SD)	48.3 (14.6)
Non–HDL-C level, mg/dL, mean (SD)	150.9 (37.0)
Diabetes mellitus	185 (16.4)
Hypertension	672 (59.5)
Heart disease	213 (18.8)
Current smoking	106 (9.4)
Treatment with statins	264 (23.4)

Abbreviation: HDL-C, high-density lipoprotein cholesterol.
SI conversion factors: To convert total cholesterol and HDL-C to millimoles per liter, multiply by 0.0259.
[a] Some percentages are based on an incomplete sample because of small amounts of missing data.
[b] Classified by self-report using the format of the 1990 US census.[30]

Table 2. Comparison of Characteristics Among Persons With and Without Incident Late-Onset AD

Characteristic	No. (%)[a]	
	Persons Without AD (n=1029)	Persons With AD (n=101)
Female	676 (65.7)	66 (65.3)
Age, y, mean (SD)	75.3 (6.1)	79.7 (6.9)
Education, y, mean (SD)	11.3 (4.5)	7.6 (4.9)
Ethnic group[b]		
White/non-Hispanic	364 (35.4)	15 (14.0)[c]
Black/non-Hispanic	316 (30.7)	30 (29.7)
Hispanic	331 (32.2)	54 (53.5)[c]
APOE genotype *e4*/- or *e4*/*e4*	261 (25.4)	28 (27.7)
Total cholesterol level, mg/dL, mean (SD)	200.5 (38.2)	185.9 (36.1)
HDL-C level, mg/dL, mean (SD)	48.6 (14.6)	45.7 (13.5)
Non–HDL-C level, mg/dL, mean (SD)	151.9 (36.9)	140.2 (36.7)
Diabetes mellitus	161 (15.6)	24 (23.8)[c]
Hypertension	608 (59.1)	64 (63.4)
Heart disease	193 (18.8)	20 (19.8)
Current smoking	97 (9.4)	9 (8.9)
Treatment with statins	246 (23.9)	18 (17.8)

Abbreviations: AD, Alzheimer disease; HDL-C, high-density lipoprotein cholesterol.
SI conversion factors: To convert total cholesterol and HDL-C to millimoles per liter, multiply by 0.0259.
[a] Some percentages are based on an incomplete sample because of small amounts of missing data.
[b] Classified by self-report using the format of the 1990 US census.[30]
[c] Statistically significant at a $P \leq .05$ level vs control group.

Observational studies that have examined the association of plasma lipid levels with cognitive function,[6,17,28,30,56] animal studies,[57,58] and studies relating

Table 3. HRs and 95% CIs Relating Quartiles of Plasma Lipid Levels With the Risk of Incident Probable and Possible AD and Probable AD

Lipid Level Quartile (Range, mg/dL)	No. (%)		Model 1[a]		Model 2[b]		Model 3[c]	
	At Risk	Incident Dementia	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Probable and possible AD								
Total cholesterol								
1 (≤173.00)	292 (25.8)	40 (13.7)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (173.01-197.00)	276 (24.4)	24 (8.7)	0.6 (0.4-1.0)	.05	0.8 (0.5-1.3)	.38	1.1 (0.6-1.9)	.80
3 (197.01-226.00)	290 (25.7)	23 (7.9)	0.6 (0.3-1.0)	.03	0.7 (0.4-1.2)	.16	0.8 (0.4-1.5)	.51
4 (>226.00)	272 (24.1)	14 (5.1)	0.4 (0.2-0.7)	.002	0.5 (0.3-1.0)	.05	0.8 (0.4-1.5)	.46
P value for trend				.001		.04		.33
HDL-C								
1 (≤38.00)	300 (26.5)	32 (31.7)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (38.01-46.00)	270 (23.9)	24 (23.8)	0.8 (0.4-1.3)	.34	0.8 (0.5-1.5)	.53	0.8 (0.4-1.5)	.52
3 (46.01-56.00)	284 (25.1)	29 (28.7)	0.8 (0.4-1.3)	.31	1.0 (0.6-1.8)	.94	1.1 (0.6-1.9)	.77
4 (>56.00)	276 (24.4)	16 (15.8)	0.4 (0.2-0.7)	.002	0.5 (0.3-0.9)	.04	0.4 (0.2-0.9)	.03
P value for trend				.004		.09		.10
Non–HDL-C								
1 (≤124.00)	289 (25.6)	40 (39.6)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (124.01-149.00)	281 (24.9)	24 (23.8)	0.7 (0.4-1.1)	.11	0.8 (0.5-1.3)	.30	0.8 (0.4-1.4)	.43
3 (149.01-175.00)	288 (25.5)	22 (21.8)	0.6 (0.4-1.0)	.06	0.8 (0.462-1.3)	.39	0.9 (0.5-1.7)	.90
4 (>175.00)	272 (24.1)	15 (14.9)	0.5 (0.2-0.8)	.009	0.6 (0.299-1.0)	.06	0.7 (0.4-1.3)	.27
P value for trend				.006		.07		.39
LDL-C								
1 (≤96.80)	285 (25.2)	36 (35.6)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (96.81-120.90)	280 (24.8)	26 (25.7)	0.8 (0.5-1.4)	.44	1.1 (0.6-1.8)	.79	1.2 (0.6-2.0)	.61
3 (120.91-143.05)	283 (25.0)	19 (18.8)	0.5 (0.3-0.8)	.009	0.6 (0.3-1.0)	.06	0.6 (0.3-1.1)	.09
4 (>143.06)	282 (25.0)	20 (19.8)	0.6 (0.3-0.9)	.04	0.8 (0.5-1.4)	.43	0.9 (0.5-1.7)	.85
P value for trend				.009		.13		.34
Probable AD								
Total cholesterol								
1 (≤173.00)	292 (25.8)	39 (13.4)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (173.01-197.00)	276 (24.4)	20 (7.2)	0.5 (0.3-0.9)	.02	0.7 (0.4-1.2)	.23	0.9 (0.5-1.8)	.91
3 (197.01-226.00)	290 (25.7)	18 (6.2)	0.5 (0.3-0.8)	.007	0.6 (0.3-0.9)	.05	0.6 (0.3-1.2)	.13
4 (>226.00)	272 (24.1)	12 (4.4)	0.3 (0.2-0.6)	.001	0.5 (0.2-0.9)	.04	0.7 (0.3-1.4)	.32
P value for trend				.001		.02		.13
HDL-C								
1 (≤38.00)	300 (26.5)	29 (32.6)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (38.01-46.00)	270 (23.9)	22 (24.7)	0.8 (0.4-1.4)	.35	0.9 (0.5-1.5)	.59	0.8 (0.4-1.6)	.51
3 (46.01-56.00)	284 (25.1)	24 (27.0)	0.7 (0.4-1.2)	.19	0.9 (0.5-1.7)	.82	0.9 (0.5-1.9)	.98
4 (>56.00)	276 (24.4)	14 (15.7)	0.3 (0.2-0.7)	.002	0.5 (0.2-0.9)	.04	0.4 (0.2-0.9)	.03
P value for trend				.002		.07		.06
Non–HDL-C								
1 (≤124.00)	289 (25.6)	37 (41.6)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (124.01-149.00)	281 (24.9)	23 (25.8)	0.7 (0.4-1.2)	.16	0.8 (0.5-1.4)	.44	0.8 (0.5-1.6)	.57
3 (149.01-175.00)	288 (25.5)	16 (18.0)	0.5 (0.3-0.9)	.01	0.7 (0.4-1.2)	.16	0.8 (0.4-1.5)	.43
4 (>175.00)	272 (24.1)	13 (14.6)	0.4 (0.2-0.8)	.008	0.5 (0.3-1.0)	.07	0.7 (0.3-1.4)	.26
P value for trend				.002		.04		.23
LDL-C								
1 (≤96.80)	285 (25.2)	33 (37.1)	1 [Reference]		1 [Reference]		1 [Reference]	
2 (96.81-120.90)	280 (24.8)	24 (27.0)	0.8 (0.5-1.4)	.53	1.2 (0.7-2.0)	.61	1.2 (0.7-2.2)	.49
3 (120.91-143.05)	283 (25.0)	15 (16.9)	0.4 (0.2-0.8)	.004	0.5 (0.3-0.9)	.034	0.5 (0.2-0.9)	.04
4 (>143.06)	282 (25.0)	17 (19.1)	0.5 (0.3-0.9)	.03	0.8 (0.4-1.5)	.44	0.9 (0.5-1.7)	.73
P value for trend				.005		.09		.20

Abbreviations: AD, Alzheimer disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259.

[a]Model 1: adjusted for age and sex.

[b]Model 2: adjusted for age, sex, education, ethnic group, and *APOEe4* genotype.

[c]Model 3: adjusted for age, sex, education, ethnic group, *APOEe4* genotype, diabetes mellitus, hypertension, heart disease, body mass index, and lipid-lowering treatment.

plasma lipid-lowering treatment to cognitive functioning[6,11,30,59,60] have also been conflicting. We previously reported associations between high levels of LDL-C and decreased levels of HDL-C and vascular dementia,[32] and low levels of total cholesterol and risk of AD,[32] but no association of HDL-C, triglyceride, or LDL-C levels with AD,[32] amnestic or nonamnestic MCI,[33] or cognitive test performance over time.[34] In the present study, higher levels

of HDL-C were associated with a decreased risk of AD. This association was characterized by a threshold effect with a clear reduction in disease risk in persons in the highest HDL-C level quartile (>56 mg/dL [to convert to millimoles per liter, multiply by 0.0259]) even after adjusting for vascular risk factors and lipid-lowering treatment. As mentioned earlier, in a previous study among 1168 participants who were recruited from the same community between 1992 and 1994, we observed no association between HDL-C level and AD.[32] The current report is the first to report prospective analyses from the cohort recruited in 1999 through 2001. The analyses by Moroney et al[22] and Reitz et al,[32] which focused on dementia, the same outcome we focus on in the current article, both reported a modest inverse relationship between HDL-C level and AD risk in the 1992-1994 cohort, although not statistically significant. The 7-year difference between the 1992-1994 cohort and the 1999-2001 cohort is important because period effects were likely to influence the latter cohort. One significant period effect is the widespread use of lipid-lowering medications in the 1990s following the reporting of the landmark Scandinavian Simvastatin Survival Study (4S) in 1994.[35] This study sparked the widespread use of HMG-COA inhibitors. The introduction of HMG-COA inhibitors and other therapies is known to have influenced trends in cardiovascular morbidity and mortality in developed countries.[61] We do not have data to directly address how secular trends in the 1990s affected differences between the 1992-1994 and 1999-2001 cohorts. However, it seems reasonable to speculate that persons in their 60s who survived to 1992 were different compared with the same demographic group in the 1990s. Compared with the 1992-1994 cohort,[33] the 1999-2001 cohort had a similar mean age (75.5 vs 75.9 years), higher mean years of education (10.9 vs 8.8), a lower proportion of Hispanic (34.1% vs 45.1%) and black (30.6% vs 32.9%) individuals, a higher proportion of non-Hispanic white individuals (33.5% vs 21.5%), higher mean HDL-C level (48.3 mg/dL vs 47.2 mg/dL), lower prevalence of current smoking (9.4% vs 10.6%) and heart disease (18.8% vs 34.1%), and a higher proportion of persons treated with lipid-lowering treatment (23.4% vs 14.5%). With the exception of the ethnic differences, the differences in characteristics are in line with the secular trends in better cardiovascular health and use of lipid-lowering treatment mentioned previously. We believe that that this is why the inverse relation of HDL-C level with AD risk was not statistically significant in the 1992-1994 cohort and is significant in the 1999-2001 cohort.

The fact the association was present in analyses for probable and possible AD and probable AD only support the notion that HDL-C levels are associated with AD independently of stroke. However, we lacked information on subclinical cerebrovascular disease in approximately 20% of persons without stroke. If plasma lipid levels are associated with dementia associated with subclinical cerebrovascular disease, our findings could underestimate the relation of HDL-C level with AD associated with stroke ("possible AD").

An interesting and seemingly paradoxical observation in our study is that both low non–HDL-C and HDL-C levels are associated with higher AD risk. Traditionally, high non–HDL-C and low HDL-C levels are considered vascular risk factors and simultaneous components of the metabolic syndrome in adults.[62] However, HDL-C level may be a stronger predictor of stroke[45] and vascular mortality[63] in elderly individuals compared with other lipid measures. In this study, we extend this observation to AD.

We previously observed that higher total cholesterol and non–HDL-C levels were related to a decreased risk of AD after adjusting for age and sex, education, ethnic group, and *APOEe4* genotype. This is consistent with our previous observations showing relations between high total cholesterol level and a lower AD risk[32] and consistent with other studies demonstrating a protective effect of late-life total cholesterol level on the risk of MCI or AD.[21,27] It is possible that low total cholesterol and LDL-C levels are part of a prodromal stage of AD. At this stage, patients show alterations in the energetic profile as weight loss, reduced caloric intake, and increased energy requirement,[64] and low total cholesterol levels might reflect malnutrition in subjects with prodromal AD. Also, lipid levels decrease with aging and may not have the same significance they have in middle age, implying the possibility that studies with shorter follow-up or higher baseline age lack the ability to detect a harmful effect. These notions are consistent with findings by the Honolulu-Asia Aging Study, which observed in a study with 26 years of follow-up that total cholesterol levels in men with dementia at the end of follow-up declined at least 15 years before the diagnosis and remained lower than total cholesterol levels in men without dementia.[65] We tried to eliminate these possibilities by repeating all analyses restricted to persons with longer follow-up but this did not change our results. Finally, it is possible that this association is due to survival bias.

This study has important strengths. It is a prospective cohort study designed for the diagnosis of cognitive decline that has complete clinical and neuropsychological evaluation at each interval. Our study has sensitive measures of cognitive change in several specific domains, including memory. In addition, we had the ability to diagnose dementia and cognitive impairment without dementia at baseline, thus allowing us to follow up an unbiased sample. A limitation of this study is that we used only one measurement of lipid levels, which could have led to measurement error due to intraperson variability. However, this would have led to an underestimation of the associations between lipid levels and AD. An important consideration in the interpretation of the results is that it was conducted in an urban multiethnic elderly community with a high prevalence of risk factors for mortality and dementia. Thus, our results may not be generalizeable to cohorts with younger individuals or to cohorts with participants with a lower morbidity burden.

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REFERENCES

1. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996;3(2):213-219.
2. Fratiglioni L, De Ronchi D, Agüero-Torres H. Worldwide prevalence and incidence of dementia. *Drugs Aging*. 1999;15(5):365-375.
3. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology*. 2005;65(4):545-551.
4. Burns M, Duff K. Cholesterol in Alzheimer's disease and tauopathy. *Ann N Y Acad Sci*. 2002;977:367-375.
5. Sponne I, Fifre A, Koziel V, Oster T, Olivier JL, Pillot T. Membrane cholesterol interferes with neuronal apoptosis induced by soluble oligomers but not fibrils of amyloid-beta peptide. *FASEB J*. 2004;18(7):836-838.
6. Michikawa M. Cholesterol paradox: is high total or low HDL cholesterol level a risk for Alzheimer's disease? *J Neurosci Res*. 2003;72(2):141-146.
7. 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.
8. Atzmon G, Gabriely I, Greiner W, Davidson D, Schechter C, Barzilai N. Plasma HDL levels highly correlate with cognitive function in exceptional longevity. *J Gerontol A Biol Sci Med Sci*. 2002;57(11):M712-M715.
9. Goldstein FC, Ashley AV, Endeshaw YW, Hanfelt J, Lah JJ, Levey AI. Effects of hypertension and hypercholesterolemia on cognitive functioning in patients with Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2008;22(4):336-342.
10. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM. Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity: the Rotterdam Study. *J Neurol Neurosurg Psychiatry*. 2009;80(1):13-17.
11. Hajjar I, Schumpert J, Hirth V, Wieland D, Eleazer GP. The impact of the use of statins on the prevalence of dementia and the progression of cognitive impairment. *J Gerontol A Biol Sci Med Sci*. 2002;57(7):M414-M418.
12. Helzner EP, Luchsinger JA, Scarmeas N, et al. Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol*. 2009;66(3):343-348.
13. Kivipelto M, Helkala EL, Hänninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study. *Neurology*. 2001;56(12):1683-1689.
14. Kivipelto M, Solomon A. Cholesterol as a risk factor for Alzheimer's disease: epidemiological evidence. *Acta Neurol Scand Suppl*. 2006;185:50-57.
15. Kontush A, Chapman MJ. HDL: close to our memories? *Arterioscler Thromb Vasc Biol*. 2008;28(8):1418-1420.
16. Kuo YM, Emmerling MR, Bisgaier CL, et al. Elevated low-density lipoprotein in Alzheimer's disease correlates with brain abeta 1-42 levels. *Biochem Biophys Res Commun*. 1998;252(3):711-715.
17. Kuriyama M, Hokezu Y, Togo S, et al. Serum lipids, lipoproteins and apolipoproteins in patients with senile dementia [in Japanese]. *Nippon Ronen Igakkai Zasshi*. 1992;29(7-8):559-564.
18. 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(3):589-593.
19. Lesser G, Kandiah K, Libow LS, et al. Elevated serum total and LDL cholesterol in very old patients with Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2001;12(2):138-145.
20. Li L, Cao D, Desmond R, et al. Cognitive performance and plasma levels of homocysteine, vitamin B12, folate and lipids in patients with Alzheimer disease. *Dement Geriatr Cogn Disord*. 2008;26(4):384-390.
21. 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.
22. Moroney JT, Tang MX, Berglund L, et al. Low-density lipoprotein cholesterol and the risk of dementia with stroke. *JAMA*. 1999;282(3):254-260.
23. Muckle TJ, Roy JR. High-density lipoprotein cholesterol in differential diagnosis of senile dementia. *Lancet*. 1985;1(8439):1191-1193.
24. Panza F, Capurso C, D'Introno A, et al. Total cholesterol levels and the risk of mild cognitive impairment and Alzheimer's disease. *J Am Geriatr Soc*. 2007;55(1):133-135.
25. Raffaitin C, Gin H, Empana JP, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study. *Diabetes Care*. 2009;32(1):169-174.
26. Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. *Lancet Neurol*. 2005;4(12):841-852.
27. Solfrizzi V, Panza F, Colacicco AM, et al; Italian Longitudinal Study on Aging Working Group. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology*. 2004;63(10):1882-1891.
28. Teunissen CE, De Vente J, von Bergmann K, et al. Serum cholesterol, precursors and metabolites and cognitive performance in an aging population. *Neurobiol Aging*. 2003;24(1):147-155.
29. van Exel E, de Craen AJ, Gussekloo J, et al. Association between high-density lipoprotein and cognitive impairment in the oldest old. *Ann Neurol*. 2002;51(6):716-721.
30. Yaffe K, Barrett-Connor E, Lin F, Grady D. Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol*. 2002;59(3):378-384.
31. Zuliani G, Ble' A, Zanca R, et al. Lipoprotein profile in older patients with vascular dementia and Alzheimer's disease. *BMC Geriatr*. 2001;1:5.
32. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol*. 2004;61(5):705-714.
33. Reitz C, Tang MX, Manly J, Schupf N, Mayeux R, Luchsinger JA. Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment. *Dement Geriatr Cogn Disord*. 2008;25(3):232-237.
34. Reitz C, Luchsinger J, Tang MX, Manly J, Mayeux R. Impact of plasma lipids and time on memory performance in healthy elderly without dementia. *Neurology*. 2005;64(8):1378-1383.
35. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344(8934):1383-1389.
36. Tang MX, Stern Y, Marder K, et al. The APOE-epsilon4 allele and the risk of Alzheimer disease among African Americans, whites, and Hispanics. *JAMA*. 1998;279(10):751-755.
37. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol*. 1992;49(5):453-460.
38. Honig LS, Tang MX, Albert S, et al. Stroke and the risk of Alzheimer disease. *Arch Neurol*. 2003;60(12):1707-1712.
39. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 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;34(7):939-944.
40. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 1999;56(3):303-308.
41. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499-502.
42. Kastelein JJ, van der Steeg WA, Holme I, et al; TNT Study Group; IDEAL Study Group. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117(23):3002-3009.
43. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res*. 1990;31(3):545-548.
44. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572.
45. Sacco RL, Benson RT, Kargman DE, et al. High-density lipoprotein cholesterol and ischemic stroke in the elderly: the Northern Manhattan Stroke Study. *JAMA*. 2001;285(21):2729-2735.
46. Sacco RL, Benjamin EJ, Broderick JP, et al. American Heart Association Prevention Conference, IV: prevention and rehabilitation of stroke. risk factors. *Stroke*. 1997;28(7):1507-1517.

47. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease: the Nun Study. *JAMA*. 1997;277(10):813-817.
48. Sharrett AR, Patsch W, Sorlie PD, Heiss G, Bond MG, Davis CE. Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb*. 1994;14(7):1098-1104.
49. Breteler MM, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and distribution of cognitive function in elderly people: the Rotterdam Study. *BMJ*. 1994; 308(6944):1604-1608.
50. Reid PC, Urano Y, Kodama T, Hamakubo T. Alzheimer's disease: cholesterol, membrane rafts, isoprenoids and statins. *J Cell Mol Med*. 2007;11(3):383-392.
51. Dietschy JM, Turley SD. Cholesterol metabolism in the brain. *Curr Opin Lipidol*. 2001;12(2):105-112.
52. Lewis GF, Steiner G. Hypertriglyceridemia and its metabolic consequences as a risk factor for atherosclerotic cardiovascular disease in non-insulin-dependent diabetes mellitus. *Diabetes Metab Rev*. 1996;12(1):37-56.
53. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab*. 2009;5(3):150-159.
54. Luchsinger JA, Tang M-X, Shea S, Mayeux R. Hyperinsulinemia and risk of Alzheimer disease. *Neurology*. 2004;63(7):1187-1192.
55. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res*. 2007;4(2):147-152.
56. Henderson VW, Guthrie JR, Dennerstein L. Serum lipids and memory in a population based cohort of middle age women. *J Neurol Neurosurg Psychiatry*. 2003; 74(11):1530-1535.
57. Sparks DL, Schreurs BG. Trace amounts of copper in water induce beta-amyloid plaques and learning deficits in a rabbit model of Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2003;100(19):11065-11069.
58. Schreurs BG, Smith-Bell CA, Lochhead J, Sparks DL. Cholesterol modifies classical conditioning of the rabbit (*Oryctolagus cuniculus*) nictitating membrane response. *Behav Neurosci*. 2003;117(6):1220-1232.
59. Gibellato MG, Moore JL, Selby K, Bower EA. Effects of lovastatin and pravastatin on cognitive function in military aircrew. *Aviat Space Environ Med*. 2001; 72(9):805-812.
60. Muldoon MF, Barger SD, Ryan CM, et al. Effects of lovastatin on cognitive function and psychological well-being. *Am J Med*. 2000;108(7):538-546.
61. Cooper R, Cutler J, Desvigne-Nickens P, et al. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. *Circulation*. 2000;102(25):3137-3147.
62. Grundy SM, Cleeman JI, Daniels SR, et al; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112(17):2735-2752.
63. Corti MC, Guralnik JM, Salive ME, et al. HDL cholesterol predicts coronary heart disease mortality in older persons. *JAMA*. 1995;274(7):539-544.
64. Scacchi R, De Bernardini L, Mantuano E, et al. DNA polymorphisms of apolipoprotein B and angiotensin I-converting enzyme genes and relationships with lipid levels in Italian patients with vascular dementia or Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1998;9(4):186-190.
65. Stewart R, White LR, Xue QL, Launer LJ. Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol*. 2007;64(1):103-107.

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