

# Serum Lipids Are Related to Alzheimer's Pathology in Nursing Home Residents

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## Key Words

Lipids and dementia · Alzheimer's disease ·  
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Cholesterol · Serum lipids

## Abstract

**Background:** Studies of associations between serum lipids and Alzheimer's disease (AD) or other dementias in the elderly show conflicting results, perhaps due to misclassification of the various dementias. **Methods:** For 358 nursing home residents, serum lipids were studied at admission and diagnoses established at autopsy. We used defined neuropathological criteria to distinguish the presence of AD and to avoid errors of clinical dementia assessment. **Results:** Residents with any AD pathology, as compared to those without AD pathology, had higher mean serum total cholesterol (TC; 200.4 vs. 185.9 mg/dl;  $p = 0.02$ ) and higher mean low-density lipoprotein cholesterol (LDL; 124.5 vs. 111.5 mg/dl;  $p = 0.03$ ). Further, mean TC, LDL and high-density lipoprotein cholesterol levels all increased progressively with increasing pathological certainty of AD ( $p$  for trend = 0.001, 0.02 and 0.02). **Conclusions:** TC and LDL were significantly related to pathologically defined AD. If serum lipids have a role in the pathogenesis of AD, interventions may modify the course of disease.

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## Introduction

Several studies [1–4], including one from our group [5], show that elderly people with Alzheimer's disease (AD) or with dementia or cognitive deficits have higher serum total cholesterol (TC) or higher low-density lipoprotein cholesterol (LDL) than sex- and age-matched nondemented peers. Others fail to find such differences [6–11], and still others find negative correlations of serum lipid values with AD (or with all dementias) [12–14]. Several reviewers advance limited explanations for these varying results [15–17]. As Kivipelto and Solomon [15] point out, the preponderance of prior reports is clinically based and lacks the postmortem neuropathology critical to establishing a trustworthy identification of dementing processes and distinction among dementia types.

We report on lipid-AD associations for those residents in a large nursing home who came to autopsy over a 20-year period, using defined neuropathological methods to identify the presence/absence of a dementing process and to distinguish AD. An estimated 4.5 million people in the USA have chronic dementia, some 30% of whom reside in a nursing home and comprise the frailest, most cognitively impaired and costliest segment of the geriatric population.

## Methods

### *Subjects and Procedures*

Our study involved residents of the Jewish Home and Hospital, a large nursing home affiliated with the Mount Sinai School of Medicine; it was approved by their respective Institutional Review Boards. From July 1, 1986, to June 6, 2006, permission was granted for autopsy of 456 residents. Personal and demographic information and pertinent medical data were abstracted from medical records. Fasting TC or a more extensive serum lipid profile was sampled at admission; as high-density lipoprotein (HDL) and triglyceride analyses were not carried out in the first years of the study, the earliest subjects have only TC values. Methods for the lipid analyses were stable throughout the study and have been previously described [18–20]. Admission TC values were available for 367 autopsied residents, and fuller admission lipid panel values (including HDL and derived LDL) were available for 299 of these residents. Three residents were autopsied elsewhere than at our pathology laboratory, and for 6 additional residents other information used in the analyses for tables 1 and 2 was not found. The remaining 358 residents with full information as to apolipoprotein E (ApoE) genotyping, TC values, age at admission, age at death, race, sex and neuropathological data were the subjects of our analyses; 292 of these 358 residents also had information on LDL and HDL values.

### *Neuropathological Assessment*

Neuropathological studies were carried out for the extent of AD-related lesions and diagnosis of AD at the neuropathology laboratory serving the Mount Sinai Alzheimer's Disease Brain Bank. They were performed in all cases by two neuropathologists (D.P.P. and Dr. Daniel Perl) who were blinded to clinical information and ApoE genotype status. The neuropathological examination has been previously described [21] and was in accordance with the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol [22]. Briefly, histological evaluation was performed for senile plaques on postmortem brain tissue blocks from 5 areas of the neocortex (middle frontal gyrus, orbital frontal cortex, superior temporal gyrus, inferior parietal lobule and calcarine cortex) and from additional areas of the hippocampus and adjacent entorhinal cortex, amygdala and brain stem. (Neurofibrillary tangles and vascular amyloid deposits were also assessed following the CERAD protocol but were not considered in the determination of diagnoses, and those data are not presented here.) The plaque densities were graded as absent, sparse, moderate and frequent (severe). Diagnoses of AD and related diseases were made according to the CERAD diagnostic criteria. The CERAD-based grouping for certainty of AD was made according to age-weighted density of neocortical plaques as: absence of any pathological dementing process (normal brain), possible AD, probable AD and definite AD. For the correlative assessment of dementing processes with lipid profiles, we grouped diagnoses as: normal brain; absence of AD but presence of pathological criteria for any other dementing process (dementia/non-AD); presence of AD diagnosis only, and presence of AD with additional pathological diagnosis of any other dementing process (AD plus). For example, cases with documented AD pathology that also showed more than rare, incidental neocortical Lewy bodies or that exhibited vascular lesions noted to contribute to dementia [23] were included in the AD plus group. We employed CERAD-recom-

mended histological stains: hematoxylin and eosin; modified Bielschowsky's, and thioflavin-S for plaques, neurofibrillary tangles and vascular amyloid deposits.

### *ApoE Genotyping*

Frozen brain specimens from each resident were studied for ApoE genotype [24]. Those conducting the neuropathological examinations, those conducting the ApoE genotyping and those collecting premortem clinical data were blinded to each others' information.

### *Statistical Analyses*

Serum lipid values and age at admission had approximately normal distributions. Although length of stay was skewed, it was not transformed since it was not included as a covariate. Group differences for demographic variables based upon presence or absence of AD neuropathology and presence or absence of non-AD dementing neuropathology were assessed by two-way analysis of variance. For serum lipid measures, similar 2-way analysis of covariance (ANCOVA) was performed controlling, a priori, for age at admission, race, sex, current use of a cholesterol-modifying agent at admission and presence of an ApoE  $\epsilon$ 4 allele. The lipid means noted in tables 1 and 2 were adjusted for these same covariates. One-way ANCOVA was performed separately for those with and without non-AD dementing pathology, using the same covariates. We also compared lipid variables for the 4 levels of diagnostic certainty for AD, as defined by CERAD criteria: normal brain, possible AD, probable AD and definite AD. The linearity of the association with diagnostic certainty was tested by stepwise linear regression, entering the covariates and then the diagnostic certainty. For each ANCOVA, we tested whether the groups differed in their relationships of each covariate with the lipid variable. Race was not used as a covariate in the 2-way ANCOVA for LDL since there was significant heterogeneity. In all other cases, the interaction of the covariate was not significant. Absence of an interaction also implies that associations of the independent and dependent variables were similar across the levels of the covariate.

## Results

Of the 358 residents for whom all of the information in tables 1 and 2 was available, 55 had normal brain at autopsy, 64 evidenced pathology of one or more dementia-related conditions but no evidence for AD (dementia/non-AD), and 239 met CERAD criteria for diagnosis of AD: 105 for definite AD, 92 for probable AD and 42 for possible AD. Similar to most large studies, an important proportion (here about half) of the 239 residents with a diagnosis of AD also had pathology of one or more additional dementing conditions (AD plus; table 1). The extent to which the additional neuropathology contributed to clinical manifestations in individual subjects is not known.

**Table 1.** Relationships of admission characteristics with dementing neuropathologies

Risk factor	Normal brain	Dementia/non-AD	AD plus	AD only	p <sup>1</sup>	p <sup>2</sup>	p <sup>3</sup>
Age at admission, years	78.5 (1.1)	79.4 (1.0)	84.6 (0.7)	85.2 (0.7)	<0.000	0.88	0.39
Age at death, years	82.2 (1.1)	82.8 (1.0)	88.2 (0.7)	89.7 (0.7)	<0.000	0.64	0.25
Length of stay, years	3.69 (0.52)	3.40 (0.48)	3.49 (0.35)	4.45 (0.35)	0.32	0.15	0.43
Caucasian, %	76.4	75.0	83.6	87.2	0.08	0.86	0.71
Female, %	60.0	64.1	79.5	79.5	0.008	0.65	0.73
ApoE ε4, % <sup>4</sup>	16.4	12.5	35.2	37.6	0.006	0.55	0.72
TC <sup>5</sup> , mg/dl	180.4 (7.2)	190.6 (6.7)	196.5 (4.7)	204.4 (4.9)	0.02	0.84	0.12
Number	55	64	122	117			
LDL cholesterol <sup>5</sup> , mg/dl	108.6 (6.7)	114.2 (6.2)	122.5 (4.4)	126.8 (4.7)	0.03	0.90	0.36
Number	48	52	102	90			
HDL cholesterol <sup>5</sup> , mg/dl	42.3 (2.1)	43.5 (1.9)	44.5 (1.4)	46.9 (1.5)	0.14	0.73	0.29
Number	48	52	102	90			
TC/HDL <sup>6</sup>	4.46 (0.27)	4.56 (0.25)	4.70 (0.18)	4.44 (0.19)	0.81	0.42	0.72

Normal brain = At autopsy, no pathological evidence for any dementing process; dementia/non-AD = at autopsy, pathological evidence for some dementing process, but absent CERAD criteria for AD; AD plus = at autopsy, pathological evidence for AD plus a coexisting dementing process; AD only = at autopsy, pathological evidence for AD (CERAD criteria), without a coexisting dementing process; CERAD = Consortium to Establish a Registry for Alzheimer's Disease. All demographic values are means, with standard errors of the mean in parentheses. Number for each subgroup is the number for those individuals with TC values available.

<sup>1</sup> p for presence of AD neuropathology.

<sup>2</sup> p for presence of a dementing neuropathological process other than AD.

<sup>3</sup> p for interaction of AD neuropathology with a dementing neuropathological process other than AD.

<sup>4</sup> Percent of residents in subgroup with at least 1 ApoE ε4 allele.

<sup>5</sup> All lipid values adjusted for age at admission, race, sex, use of a cholesterol-modifying agent at admission and presence of an ApoE ε4 allele; for LDL only, not adjusted for race.

<sup>6</sup> Total cholesterol/HDL cholesterol. Subject numbers are the same as for HDL cholesterol.

**Table 2.** Association of neuropathological certainty of AD with serum lipids

Risk factor	Normal brain	Possible AD only	Probable AD only	Definite AD only	p <sup>1</sup>
Total cholesterol <sup>2</sup> , mg/dl	179.2 (7.2)	184.3 (12.5)	201.4 (8.2)	212.0 (6.4)	0.001
Number	55	16	39	62	
LDL cholesterol <sup>2</sup> , mg/dl	107.5 (6.8)	114.7 (12.1)	126.9 (7.5)	129.8 (6.9)	0.02
Number	48	13	36	41	
HDL cholesterol <sup>2</sup> , mg/dl	41.6 (2.1)	43.6 (3.6)	46.7 (2.3)	48.3 (2.1)	0.02
Number	48	13	36	41	
TC/HDL <sup>3</sup>	4.50 (0.22)	4.29 (0.39)	4.48 (0.24)	4.43 (0.22)	0.90
ApoE ε4, % <sup>4</sup>	16.4	25.0	35.9	41.9	0.002
Age at admission, years	78.5 (1.1)	84.2 (2.0)	87.0 (1.3)	84.4 (1.0)	<0.001
Age at death, years	82.2 (1.1)	88.0 (2.1)	91.3 (1.4)	89.1 (1.1)	<0.001

Each category defines those residents who, at autopsy, had CERAD criteria for possible, probable or definite AD, respectively, but without any coexisting dementing process. All demographic values are means, with standard errors of the mean in parentheses. Number for each subgroup is the number for those individuals with TC values available.

<sup>1</sup> p is for linear relationship to increasing certainty of AD neuropathology.

<sup>2</sup> All lipid values adjusted for age at admission, race, sex and presence of an ApoE ε4 allele.

<sup>3</sup> Total cholesterol/HDL cholesterol. Subject numbers are the same as for HDL cholesterol.

<sup>4</sup> Percent in subgroup with an ApoE ε4 allele.

Of these 358 residents, the average age at admission was  $82.9 \pm 8.8$  years, the median 83 years. The average age at death was  $86.8 \pm 9.2$  years, the median 87, with a range of 49–107 years (table 1). Twenty-one percent of subjects were <80 years of age at death.

The frequency of ApoE genotypes was:  $\epsilon 2/\epsilon 2$ , 1%;  $\epsilon 2/\epsilon 3$ , 12%;  $\epsilon 2/\epsilon 4$ , 2%;  $\epsilon 3/\epsilon 3$ , 57%;  $\epsilon 3/\epsilon 4$ , 25%, and  $\epsilon 4/\epsilon 4$ , 3%. This distribution of genotypes was quite similar to a large population-based sample of individuals >65 years old from two counties in Iowa [25]. For residents with any AD diagnosis, 36.4% had an  $\epsilon 4$  allele; for those with normal brains, the proportion was 16.4%. The presence of non-AD dementing pathology was not associated with an increased frequency of an  $\epsilon 4$  allele (table 1). The frequency of having an  $\epsilon 4$  allele increased progressively and significantly with increasing certainty of AD diagnosis (table 2). Twenty-two of the 358 residents were using a statin or other lipid-modifying agent at admission, and all admission serum lipid values were adjusted for such use. This adjustment led to only trivial changes of the results.

TC at admission (mean  $\pm$  SEM) for those residents with normal brain at autopsy was  $180.4 \pm 7.2$  mg/dl, for those with dementia/non-AD  $190.6 \pm 6.7$  mg/dl and for those with any diagnosis of AD  $200.4 \pm 3.4$  mg/dl (table 1). Analysis by 2-way ANCOVA showed a difference of TC for the presence of AD ( $p = 0.02$ ), but no significant difference for the presence of non-AD neuropathological lesions and no significant interaction of AD neuropathology with other than AD dementing neuropathology. All TC, LDL and HDL means were adjusted for covariates as noted.

Similarly, mean LDL at admission for those with normal brain, dementia/non-AD, AD plus and AD only showed the same group-related directional differences as those noted for TC. Again, there was a significant difference of LDL values for the presence of AD, but no significant differences for the presence of other than AD neuropathological lesions or for the interaction of AD with other than AD pathology (table 1). No significant differences of HDL were noted for these comparisons. Analyses of TC and LDL serum values by quartiles did not indicate threshold effects for any of the neuropathological categories.

To examine whether the level of pathological certainty of AD diagnoses was related to lipid values, residents with AD only (uncomplicated AD pathology) were further categorized, using CERAD criteria, as: possible AD only, probable AD only and definite AD only. Mean TC showed progressive increase as the extent of AD pathology increased from normal brain to possible AD only to probable

AD only to definite AD only, with  $p$  for trend = 0.001 (table 2). Similarly, mean group LDL values increased with pathological certainty of AD, with  $p$  for trend = 0.02. The group means for HDL also increased progressively with greater certainty of AD pathology, with  $p$  for trend = 0.02 (table 2). This significant trend of mean HDL – from normal brain to possible AD only to probable AD only to definite AD only – was the sole result that suggested an association of HDL with AD. Of interest, the clinically useful TC/HDL ratio showed almost no variation for any of the 4 neuropathological categories (table 1) or for the different levels of CERAD-based certainty of AD (table 2).

‘Health markers’ at admission were generally similar for residents without AD compared to those with AD. Body weights of all non-AD versus AD residents, respectively, averaged 57.47 versus 56.38 kg ( $p = 0.56$ ) and, 6 months after admission, 57.70 versus 57.33 kg ( $p = 0.85$ ). (Weights were corrected for age and sex; height is difficult to measure with accuracy in a nursing home population; and of note, BMI is untrustworthy in the elderly, as there are important and interindividually variable losses of both lean body mass and height [26].) Other admission health markers were: hematocrit, 35.0 versus 35.7% ( $p = 0.39$ ); serum albumin, 3.31 versus 3.50 g/dl ( $p = 0.02$ ), and serum creatinine, 1.16 versus 1.13 g/dl ( $p = 0.76$ ). Excluding all dementia diagnoses, the mean number of comorbidities at admission was 5.1 for non-AD versus 4.6 for all AD residents ( $p = 0.13$ ). There was a slightly longer but nonsignificant length of stay for the AD residents (table 1). To exclude residents who were particularly frail/sick at admission (and likely to have a shorter life expectancy), we repeated the statistical analyses presented in tables 1 and 2 excluding those who died within 1, 3, 6 or 12 months after admission. For each of these postadmission exclusion periods, there were only small differences from the results in these tables, and all significant findings remained significant.

## Discussion

Within a large cohort of nursing home residents, we found consistent relationships between TC and LDL at admission and CERAD-based findings of AD later at autopsy (tables 1, 2). No significant associations were found between serum lipids and non-AD dementing pathology. Also, there were no significant associations between HDL and AD, except for the single significant finding of progressively higher serum HDL with progressive pathological certainty of AD diagnosis (table 2). These lipid-AD

associations were independent of the presence of ApoE  $\epsilon$ 4 and of other known risk factors, and were strongest in those residents with 'pure', uncomplicated AD (AD only, table 1) and in those with the greatest pathologically based certainty of AD diagnosis (definite AD, table 2).

While several investigators similarly report that higher TC or LDL is associated with AD specifically (or with all dementias, or with cognitive decline) [1–5], our findings appear to be at odds with a number of other prior studies of lipid-AD (or lipid-dementia) associations in the elderly. Many report that older people with a clinical diagnosis of AD or dementia have similar [6–8, 11, 27, 28], or sometimes lower [12–14], mean TC or LDL compared with a matched, but nondemented, population. Several reviewers suggest that an observed acceleration of the age-associated fall of serum lipids in those who eventually develop dementia might explain some of the variation in results [15–17]. However, such a trend does not explain our observations that those with AD pathology had significantly higher TC and LDL values than the control population at very late ages.

Some variations of results might be anticipated due to population differences. Almost without exception, prior investigations compare community-based demented people with age-matched control populations, while the present cohort consisted solely of nursing home residents who were admitted for varying combinations of chronic disease or dementia and differed from those of most cited studies as to age, average serum lipid values, and prevalence and severity of cognitive impairment and frailty. Several of these differences could have altered expressions of disease, but it is not evident how such alterations might have affected the relationships we have noted for AD neuropathology specifically with TC and LDL.

The comparatively higher TC and LDL in those with AD pathology might be explained if those with normal brain and those with dementia/non-AD had entered with greater comorbidities and resulting hypolipidemia. However, in the present instance, there is little support for this hypothesis (see Results). The present findings are consistent with those of Buchman et al. [29], who note a clear association of several measures of physical frailty specifically with the neuropathology of AD, but not with that of other dementing conditions. In addition, greater comorbidities for those without AD could not explain the finding within the AD only cohort of significant, progressively higher TC, LDL and HDL with increasing neuropathological certainty of AD diagnosis (table 2).

Probably the most important methodological difference between the current and earlier studies was the abil-

ity to distinguish AD from other dementing processes using standardized, defined neuropathological methods. Only very few prior lipid/AD studies use pathological information to identify the presence of AD and other dementing processes [4, 5, 30, 31]. The findings of Kuo et al. [4] and of our earlier study [5] are both similar to the present results, and Pappolla et al. [31] note an association of TC with brain amyloid in a very small AD cohort. Launer et al. [30] report significant relationships of cortical and hippocampal neuropathological markers of AD only with late-life serum HDL in community-based, Japanese-American men. In addition to the cohort characteristics and a much smaller proportion of demented subjects, there are other important differences in the study design, procedures and statistical methods of Launer et al. [30] that could result in outcomes different from ours. Aside from these few reports, the preponderance of studies utilizes clinical and psychometric instruments only. There is a known potential for appreciable variability in the clinical (intertest) estimation of dementia prevalence within a population [32–34] and also for discrepancy in the clinical-pathological correlation for the presence of a dementing process [35–38]. In addition, clinical observation and available clinical tools often fail to distinguish the various dementing processes from one another [35, 39–44]. If defined pathological criteria are accepted as the 'gold standard' for diagnosis, the clinical assignment of subjects as demented (vs. not demented), and of demented subjects as 'AD' or 'vascular dementia' or 'other dementia', has the potential for grouping errors. True differences of TC or LDL between designated subgroups could have been masked if the subgroups included subjects improperly defined as to dementia type or as to the presence/absence of dementia. The fidelity of the neuropathologically based diagnostic procedures employed in this study should have enabled a more accurate definition of the presence of a dementing process and a clearer distinction of AD from other dementing conditions, thus minimizing such misclassifications. The differences between our observations and those of clinically based lipid-dementia studies, as well as the variability among the clinically based studies, may be at least partially explained by the difficulties in defining accurately the 'dementia mix' within each cohort.

Several limitations of this study should be addressed. The time interval from lipid measurements at admission to the time of death varied widely within the cohort. However, the mean lengths of stay among the subgroups being compared in table 1 or table 2 did not differ significantly. Also, recalculation of results excluding those

who died before 1, 3, 6 or 12 months did not alter significances of the lipid-AD findings. Autopsy permission was routinely requested and was granted for about 10% of all deaths. Families of demented residents, compared to the nondemented, might have been more likely to consent to postmortem examination. However, this did probably not affect autopsy rates for those with AD compared to those with other dementias (dementia/non-AD) nor for the subgroup of those with normal brain who were nevertheless clinically demented. As with other neuropathologically based studies, it is not evident whether any such bias might have affected our analyses. Given the absence of preadmission measurements of serum lipids and the poor reliability of family/caretaker estimates of dementia duration, the temporal relationships of elevated TC and LDL levels with the onset or prior course of AD cannot be derived from the current information. The present findings should be generalized with caution, since nursing home populations differ in several respects from community-based populations of similar ages.

Our results document significant relationships of serum TC and LDL to AD as defined by neuropathological criteria, as well as direct, significant relationships of TC, LDL and HDL with increasing CERAD-defined pathological certainty of AD. However, relationships per se cannot establish a role of these serum lipoproteins in the pathogenesis of AD. There are many genes associated with AD that also relate to peripheral and brain cholesterol and to lipoprotein homeostasis [45]. A number of mechanisms have been proposed for the involvement of cholesterol homeostasis in the development of AD [45–51]. Although serum TC, LDL and HDL do not normally

cross the blood-brain barrier, they might participate in brain cholesterol homeostasis by acting upon substances that do cross the blood-brain barrier [46, 52] or by being able to cross if the blood-brain barrier is rendered abnormally ‘porous’ in various circumstances [46, 53, 54]. From another viewpoint, the role of TC and LDL in promoting disease within blood vessels is well established, and increasing evidence from epidemiological and other studies confirms vascular-related conditions as risk factors for AD [47, 55, 56]. More directly, large-vessel cerebrovascular disease [55] and atherosclerosis of the circle of Willis [57] are significantly associated with a higher frequency of neuritic plaques. Extracranial vascular disease and reduced cardiac output are likely factors in the significantly reduced cerebral blood flow of those with dementia as compared to nondemented peers [58, 59] and in the cerebral hypoperfusion that predicts AD/dementia [60]. Viewed in a broader perspective, AD and vascular disease share many common risk factors [46, 47, 53, 61] as well as certain etiopathogenic processes [47]. If our observations of significant serum lipid-AD relationships do, indeed, indicate a role of these lipids in the pathogenesis of AD, efforts to lower TC and LDL may prove effective in modifying the course of AD [48, 62, 63].

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