

Original Investigation

Associations Between Serum Cholesterol Levels and Cerebral Amyloidosis

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IMPORTANCE Because deposition of cerebral β -amyloid ($A\beta$) seems to be a key initiating event in Alzheimer disease (AD), factors associated with increased deposition are of great interest. Whether elevated serum cholesterol levels act as such a factor is unknown.

OBJECTIVE To investigate the association between serum cholesterol levels and cerebral $A\beta$ during life early in the AD process.

DESIGN, SETTING, AND PARTICIPANTS A multisite, university medical center-based, cross-sectional analysis of potential associations between contemporaneously assayed total serum cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and cerebral $A\beta$, measured with carbon C11-labeled Pittsburgh Compound B (PIB) positron emission tomography. Seventy-four persons (mean age, 78 years) were recruited via direct outreach in stroke clinics and community senior facilities following a protocol designed to obtain a cohort enriched for cerebrovascular disease and elevated vascular risk. Three patients had mild dementia. All others were clinically normal ($n = 33$) or had mild cognitive impairment ($n = 38$).

RESULTS Cerebral $A\beta$ was quantified using a Global PIB Index, which averages PIB retention in cortical areas prone to amyloidosis. Statistical models that controlled for age and the apolipoprotein E $\epsilon 4$ allele revealed independent associations among the levels of LDL-C, HDL-C, and PIB index. Higher LDL-C and lower HDL-C levels were both associated with a higher PIB index. No association was found between the total cholesterol level and PIB index. No association was found between statin use and PIB index, and controlling for cholesterol treatment in the statistical models did not alter the basic findings.

CONCLUSIONS AND RELEVANCE Elevated cerebral $A\beta$ level was associated with cholesterol fractions in a pattern analogous to that found in coronary artery disease. This finding, in living humans, is consistent with prior autopsy reports, epidemiologic findings, and animal and in vitro work, suggesting an important role for cholesterol in $A\beta$ processing. Because cholesterol levels are modifiable, understanding their link to $A\beta$ deposition could potentially and eventually have an effect on retarding the pathologic cascade of AD. These findings suggest that understanding the mechanisms through which serum lipids modulate $A\beta$ could offer new approaches to slowing $A\beta$ deposition and thus to reducing the incidence of AD.

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Cholesterol, vital to neuronal structure and function, has important roles in the synthesis, deposition, and clearance of β -amyloid ($A\beta$)¹⁻³ and may have a pathogenic role in Alzheimer disease (AD). Interest in the potential role of cholesterol is heightened by a series of epidemiologic reports⁴⁻⁶ that generally demonstrate a correspondence between the atherogenic risk factors for cardiovascular disease and clinically diagnosed AD. In addition, observational studies⁷ have found that statin use is associated with reduced odds of AD. There are also important connections among apolipoprotein E (APOE), $A\beta$,⁸ and cholesterol. A strong genetic risk factor for AD, the *APOE* $\epsilon 4$ allele is associated with earlier and higher deposition of $A\beta$. APOE is the primary transporter of cholesterol in the brain, and its isoforms differentially modulate brain cholesterol levels.⁸ Thus, the potential role of peripheral cholesterol in cerebral $A\beta$ deposition is of interest.

The epidemiological evidence on serum cholesterol and AD is, however, complex. Higher midlife total cholesterol has been associated with elevated risk of AD in late life,^{5,6} and higher late-life high density lipoprotein cholesterol (HDL-C) levels associated with a reduced risk of AD.⁹ The findings of another study¹⁰ have shown no association, and still others^{11,12} have reported higher total cholesterol levels (typically measured in late life) to be associated with reduced risk of AD. In

contrast to the observational studies about statin use and AD, randomized controlled treatment trials of statins in AD have been uniformly negative.^{13,14}

It is also possible that any association between cholesterol and AD reflects processes that have nothing to do with $A\beta$. For example, community-based autopsy studies¹⁵ have demonstrated an important role for cerebrovascular lesions in the mix of conditions that generally underlie clinical AD. The association between lipids and AD may therefore alternatively reflect the role of dyslipidemia as a risk factor for cerebral ischemia. We investigated whether there is an in vivo association between serum lipids and cerebral $A\beta$ deposition.

Methods

Standard Protocol Approvals

All study activities were conducted under protocols approved by the institutional review boards at University of California, Berkeley, University of California, Davis, University of California, San Francisco, and University of Southern California, Los Angeles. All participants provided written informed consent.

Participants were 74 elderly persons (mean age, 78 years) from the Aging Brain study.¹⁶ Participants were recruited from stroke clinics, support groups, community senior facilities, and a university memory clinic using criteria designed to obtain a cohort with cognitive function between normal and mildly impaired and representing a wide range of atherosclerotic disease and vascular risk. Inclusion criteria included age of 60 years or older with cognitive function in the normal to mild dementia range; recruitment emphasized persons older than 70 years without dementia. Exclusion criteria were severe or unstable medical illness, Axis I psychopathologic condition other than depression, head injury with significant loss of consciousness and/or cognitive sequelae, sensory or physical limitations that would preclude cognitive testing, diagnosis of dementia due to causes other than AD or vascular disease or the combination thereof, use of medications likely to impair cognitive function (antidementia medications accepted), excessive alcohol use, and history of drug or alcohol abuse within the past 5 years. Data from 43 of these participants were included in our prior article on cardiovascular risk and $A\beta$.¹⁷ Clinical diagnostic evaluations appropriate for memory disorders and dementia were performed using uniform diagnostic criteria and clinical protocols. Three patients had mild dementia, 33 were cognitively normal, and 38 had mild cognitive impairment. Participant characteristics are given in Table 1.

Although cholesterol levels were heterogeneous, the distributions seem to reflect the effects of treatment because means of total cholesterol and low-density lipoprotein cholesterol (LDL-C) were within the current optimal levels established by the American Heart Association. The mean fasting total cholesterol level for the group was 171 mg/dL, and mean levels for the LDL-C and HDL-C were 92 and 54 mg/dL, respectively (to convert cholesterol values to millimoles per liter, multiply by 0.0259) (Figure 1).

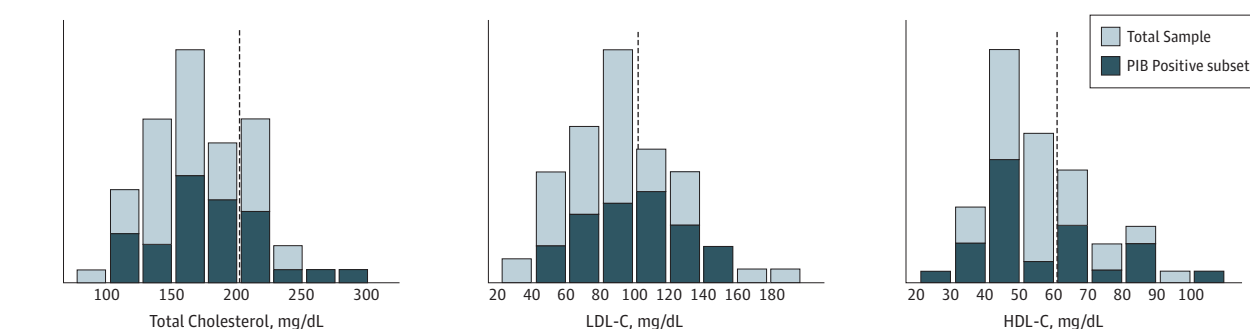
Table 1. Characteristics of the 74 Study Participants

Characteristic	No. of Patients ^a
Sex, No.	
Male	52
Female	22
Age, mean (SD) [range], y	77.8 (6.1) [68-91]
Educational level, mean (SD), y	14.5 (2.8)
Clinical status, No.	
CDR 0	33
CDR 0.5	38
CDR 1	3
APOE genotypes	
$\epsilon 3/\epsilon 3$	40
$\epsilon 2/\epsilon 3$	14
$\epsilon 3/\epsilon 4$	18
$\epsilon 2/\epsilon 4$	1
$\epsilon 4/\epsilon 4$	1
Vascular disease, No.	
Stroke or TIA	40
MI	15
CABG	21
≥ 1 of any of these diseases	48
Anticholesterol drugs	
Statins	48
Other agents	4

Abbreviations: APOE, apolipoprotein E; CABG, coronary artery bypass graft; CDR, Clinical Dementia Rating; MI, myocardial infarction; TIA, transient ischemic attack.

^a Data are presented as number of patients unless otherwise indicated.

Figure 1. Distributions of Cholesterol Values



Total sample and subset of sample who had Pittsburgh Compound B positron emission tomographic scans that were positive for β -amyloid deposition (PIB positive). Dashed vertical lines mark the target guideline values given by the

American Heart Association. LDL-C indicates low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. To convert cholesterol values to millimoles per liter, multiply by 0.0259.

PET Imaging

Cerebral A β was measured with positron emission tomography (PET) using the tracer carbon C11-labeled Pittsburgh Compound B (PIB), which specifically binds fibrillar A β plaques. The PIB radiotracer was synthesized at Lawrence Berkeley National Laboratory (Berkeley, California) using a previously published protocol.¹⁸ The PIB PET imaging was conducted using a Siemens ECAT HR scanner in 3-dimensional acquisition mode (Siemens AG). PIB (10–115 mCi [370–555 MBq]) was injected as a bolus into an antecubital vein after which dynamic acquisition frames were obtained for a total of 90 minutes during progressively longer intervals.¹⁹

Image Analysis

The PIB data were preprocessed using SPM8 statistical software (The Mathworks Inc). Frames 6 through 35, as well as the sum of frames 1 through 5, were realigned to frame 17. Realigned frames that reflected the first 20 minutes of acquisition (frames 1–23) were then averaged and used to guide coregistration with the T1-weighted magnetic resonance image. Distribution-volume ratio (DVR) images were generated from PIB frames corresponding to 35 to 90 minutes after injection and quantified using Logan graphical analysis and the participant's gray matter cerebellar reference region.

The DVR values were extracted from regions of interest (ROIs) vulnerable to early A β deposition, which include the frontal cortex (anterior to the precentral gyrus), lateral parietal cortex, lateral temporal cortex, posterior cingulate, and precuneus. The ROIs were defined using the Desikan-Killiany atlas and the semiautomated FreeSurfer processing stream.²⁰

A global measure of PIB uptake (Global PIB Index) was generated in each subject's native space by averaging the mean DVR value of these ROIs.²¹ The occipital cortex was also examined because of its susceptibility to cerebral amyloid angiopathy. This Global PIB Index served as the primary dependent variable. For purposes of describing the sample (but not for data analysis), PIB positivity was defined. Eleven young adults (mean [SD] age, 24.5 [3.4] years) underwent PIB PET using the same acquisition and processing procedures described above.

The PIB uptake was determined using DVR values from the Global PIB Index. Values 2 SDs above the young average for these 2 regions were established as defining values of PIB positivity. Therefore, participants with a Global PIB Index of 1.08 or higher were determined to be PIB positive (32 cases).

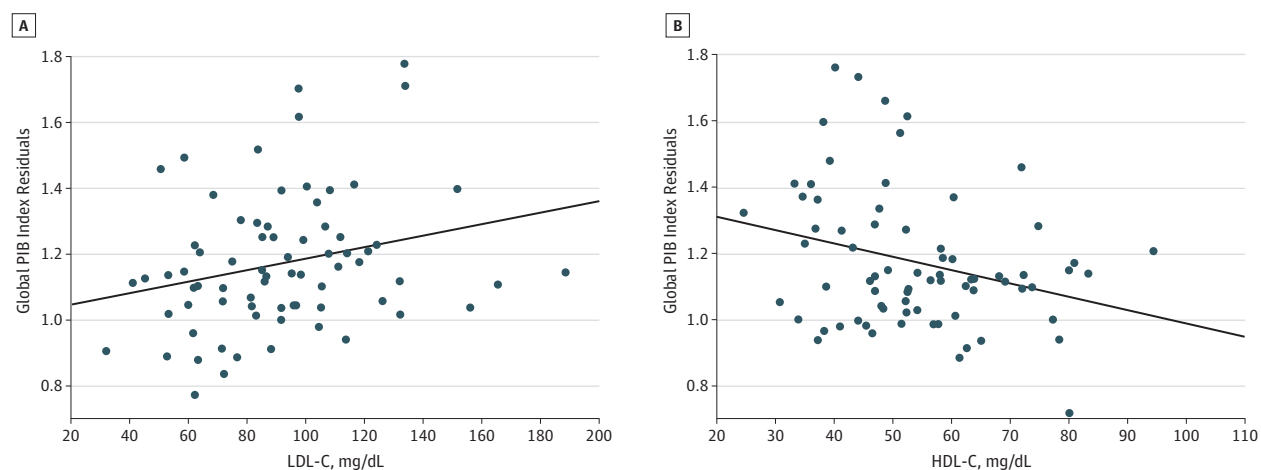
Other Measures

Fasting HDL-C, LDL-C, and triglyceride levels were assayed at a central laboratory under standardized research protocols from blood samples obtained at study enrollment. *APOE* genotyping was performed using TaqMan probes.²² Fluorescence was detected using an ABI 7900HT Sequence Detection System, and the alleles are scored using Sequence Detector Software (Applied Biosystems Inc). *APOE* 2 assays for single-nucleotide polymorphisms in exon 4 were run on each sample. These assays included a C/T single-nucleotide polymorphism at amino acid 112 and a C/T single-nucleotide polymorphism at amino acid 158. The *APOE* alleles (ϵ 2, ϵ 3, ϵ 4) were determined according to Yu et al.²³ Quantitative levels of apolipoprotein A (APOA1) and apolipoprotein B (APOB) were measured. Medications to treat cholesterol levels were recorded by a physician or nurse during a clinic visit and recorded using the National Alzheimer Coordinating Center Uniform Data Set (version 2.0) form A4.

Results

Associations between lipids and A β were tested in a series of multiple linear regression models that covaried age, sex, and *APOE* ϵ 4 status. In this data set, LDL-C is uncorrelated with HDL-C ($r = 0.06$, $P > .50$) and triglycerides ($r = 0.08$, $P > .50$); HDL-C and triglycerides were negatively correlated ($r = -0.24$, $P = .045$). Initial models evaluated total cholesterol, HDL-C, LDL-C, and triglycerides as individual predictors of A β . In those separate models, HDL-C was negatively associated ($P = .02$) and LDL-C was positively associated ($P = .052$) with the Global PIB Index, whereas total cholesterol and triglycerides had no association with the Global PIB Index ($P = .56$ and $.71$, respectively). Modeled jointly and covarying age, sex, and *APOE* ϵ 4,

Figure 2. Independent Effects of Low-density Lipoprotein Cholesterol (LDL-C) and High-density Lipoprotein Cholesterol (HDL-C) on Cerebral β -Amyloid ($A\beta$)



Individual data points and the slope of the regression of $A\beta$ on LDL-C (A) and HDL-C (B). The Global Pittsburgh Compound B (PIB) Index values are residual values from the model that evaluated HDL-C and LDL-C simultaneously while

covarying age, sex, and $APOE \epsilon 4$ status. To convert cholesterol values to millimoles per liter, multiply by 0.0259.

Table 2. Parameter Estimates and Significance Values for Multiple Regression of Global PIB Index on Sex, Age, $APOE \epsilon 4$, HDL-C, and LDL-C

Variable	Estimate (SE)	t Ratio	P Value
Sex	0.021 (0.028)	0.75	.45
Age	0.012 (0.004)	2.82	.006
$APOE \epsilon 4$ status ^a	-0.088 (0.027)	-3.23	.002
HDL-C	-0.004 (0.002)	-2.43	.02
LDL-C	0.002 (0.001)	2.17	.03

Abbreviations: APOE, apolipoprotein E; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PIB, Pittsburgh Compound B.

^a Reference value is no $\epsilon 4$.

lower HDL-C ($P = .02$) and higher LDL-C ($P = .03$) levels were both associated with a higher Global PIB Index. These associations were independent of $APOE \epsilon 4$, which was positively associated ($P = .002$) with the Global PIB Index (Figure 2). The increase in R^2 gives a measure of effect size. Compared with age and sex alone, the addition of $APOE \epsilon 4$ to the model explained an additional 11% of variance in the Global PIB Index, and adding HDL-C and LDL-C to the model explained an additional 11% beyond the effect of $APOE \epsilon 4$. Table 2 provides the parameter estimates for the joint HDL-C and LDL-C model. Models testing the effect of triglycerides in combination with HDL-C, LDL-C, or both found no significant effect of triglycerides on the Global PIB Index.

$APOA1$ is moderately strongly correlated with HDL-C, and $APOB$ is strongly correlated with LDL-C. When modeled jointly with the covariates age, sex, and $APOE \epsilon 4$, lower $APOA1$ ($P = .02$) and higher $APOB$ ($P = .047$) are both significant predictors of the Global PIB Index. However, neither has any effect on the Global PIB Index that is independent of HDL-C and LDL-C.

The role of current cholesterol treatment was investigated. We found little evidence of drug effects on the Global PIB Index in either simple or fully adjusted models regardless of how the treatment indicator was modeled (eg, any drug vs none, statins vs other vs none, or lipophilic statins vs hydro-

philic vs none). No treatment indicator was significantly associated with the Global PIB Index on a bivariate basis ($P = .41$ -.75) or in models controlling for age, sex, and $APOE \epsilon 4$. As expected, statin treatment was associated with lower LDL-C levels. Adding statin treatment as a covariate to either the unadjusted (bivariate) or fully adjusted models described above did not reduce the parameter estimates for either HDL-C or LDL-C, and the pattern of P values produced by the models remained the same.

Discussion

Higher fasting levels of LDL-C and lower levels of HDL-C were both associated with greater brain amyloid independently of $APOE$ genotype. To our knowledge, this is the first human experimental evidence of a direct relationship between cholesterol fractions in blood and amyloid deposition in the brain. Two prior reports^{24,25} have linked elevated LDL-C to $A\beta$ in patients with AD at autopsy, but to our knowledge, the present article is the first to find a correlation in vivo early in the disease process.

The brain is rich in cholesterol, accounting for nearly 25% of all cholesterol in the body.²⁶ Substantial in vitro and ani-

mal evidence indicates that cholesterol levels in the brain affect the synthesis, clearance, and toxicity of A β . The A β peptide results from the dual cleavage of amyloid precursor protein (APP), a transmembrane protein, by β -secretase 1 in extracellular space and by γ -secretase within the transmembrane domain. Thus, the characteristics of the cellular lipid bilayer may influence trafficking and proteolysis. Membrane-bound cholesterol is concentrated in lipid rafts, microdomains that also carry APP and β - and γ -secretases and in which most of the metabolism of APP occurs.²⁷ In vitro studies²⁸ report that lower cholesterol levels shift APP processing to nonraft regions of the membrane where the benign α -secretase cleavage pathway is favored. Additional in vitro work has demonstrated that modulation of local cholesterol levels modifies A β production. For example, adding cholesterol to cultured HEK 293 cells increased A β production 4-fold, whereas adding a statin to these cultures markedly reduced A β .²⁹ Similarly, reduction of cellular cholesterol inhibited the production of A β in hippocampal cells.³⁰

Consideration of possible mechanisms that link cholesterol fractions and A β must account for the fact that essentially all central nervous system cholesterol is locally synthesized and that there is minimal exchange of HDL-C particles and essentially no exchange of LDL-C and very low density lipoprotein cholesterol-C particles across the intact blood-brain barrier.³¹ At the same time, animal evidence demonstrates a potential role for serum cholesterol in A β deposition. For example, in transgenic APP mice, a high-cholesterol diet was reversibly associated with greater A β plaque formation.^{32,33} Similarly, feeding rabbits a high-cholesterol diet doubled the number of A β plaques.³⁴

Oxysterols, which do efficiently pass the blood-brain barrier, have gained considerable recent attention as a potential link among serum cholesterol, altered brain cholesterol metabolism, and A β .^{2,35} The oxysterol 24-hydroxycholesterol (24-OH, cerebrosterol) is produced almost entirely in the brain, where it plays an important role in cholesterol homeostasis.² The brain also synthesizes a small amount of 27-hydroxycholesterol (27-OH). However, most 27-OH is produced by peripheral tissues, and serum hypercholesterolemia is associated with increased brain levels of 27-OH.³⁶ Thus, the balance between 27-OH and 24-OH may affect amyloidosis³⁷ perhaps through cholesterol metabolism or perhaps by more directly affecting A β production.²

In addition, A β degradation is less efficient in a high cholesterol environment. Cholesterol efflux from brain and microglia is achieved by APOE-dependent mechanisms that involve HDL-C particles, and it may be that HDL-C function associated with apolipoproteins or other factors that affect cholesterol efflux are important.³⁸ Interestingly, it was recently reported that genetic variation in ABCA7—known to affect cellular cholesterol efflux—modifies the risk of AD in African Americans.³⁹

Alternatively, systemic hyperlipidemia may damage the blood-brain barrier via inflammatory and other mechanisms, with consequent leakage of serum cholesterol, inflammatory cytokines, and other amyloidogenic factors,⁴⁰ or it may be that HDL-C and LDL-C are themselves unimportant but correlate with some other factor(s) that is the mechanistic driver. Cholesterol fractions may reflect unmeasured genetic factors or dietary patterns.⁴¹ For example, evidence exists that a high-fat diet affects the conformational state of APOE,⁴² perhaps reducing its ability to clear A β .

These data do not convincingly exclude the possibility that statin treatment is associated with lowered A β production, which is an effect that has been observed in vitro.^{29,43} A larger sample and better treatment history would be needed to address this definitively.

In conclusion, in this small high-vascular-risk cohort, HDL-C and LDL-C levels had the same pattern of association with A β levels as they do with coronary artery disease. However, the mean lipid profile for this cohort falls within the range considered desirable from the standpoint of cardiac health. The regulation of cholesterol in the periphery and brain and the processing of APP are processes that change with age. Thus, a major limitation of our study is that the findings are cross-sectional and obtained late in life. Cholesterol levels were measured at a single time point, contemporaneously with the amyloid measure. Our cohort is small, and the findings need replication. An important factor in any replication effort may be the level of vascular risk in the study cohort. Our cohort was enriched for vascular risk, whereas many existing AD clinical trial cohorts use selection criteria that minimize cerebrovascular disease. Investigation of the potential modulatory role of serum cholesterol on amyloidosis is important because a substantial amount is known about manipulating lipid metabolism, and any factor that could reduce A β deposition could have a major effect on the incidence of AD.

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Study concept and design: Reed, Mack, DeCarli, Chui, Jagust.

Acquisition of data: Reed, Mack, DeCarli, Chui, Jagust.

Analysis and interpretation of data: Reed, Villeneuve, DeCarli, Chui, Jagust.

Drafting of the manuscript: Reed.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Reed, Villeneuve.

Obtained funding: Reed, DeCarli, Chui, Jagust.

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