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Association between cholesterol exposure and neuropathological findings: The ACT Study

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Abstract

We characterized the relationship between late life cholesterol exposure and neuropathological outcomes in a community-based, older adult cohort. Adult Changes in Thought is a cohort study that enrolls consenting randomly selected non-demented people aged ≥65 from a healthcare delivery system. We used late life HDL and total cholesterol lab values from Group Health computerized records, and calculated HDL and non-HDL levels. We evaluated neuropathological outcomes of Alzheimer's Disease, cerebral amyloid angiopathy, vascular brain injury, and Lewy body disease. Using linear mixed models with age and antilipemic medication as predictors, we obtained predicted cholesterol values at age 70 and 10 years prior to death for individuals with available cholesterol data in 10-year exposure windows. We used logistic regression to determine whether predicted late life cholesterol levels were associated with neuropathological outcomes controlling for age at death, *APOE* genotype, sex, and their interactions with cholesterol levels. 525 decedents came to autopsy by 08/2014. Of these, plasma cholesterol concentration was available for 318 (age 70, model 1) and 396 (10 years prior to death, model 2) participants. We did not find associations between late life cholesterol and Alzheimer's Disease neuropathological changes, and there were no associations between cholesterol levels and amyloid angiopathy or vascular brain injury. We observed an association between predicted non-HDL cholesterol at age 70 and Lewy body disease. Our study suggests an association between late life non-HDL

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cholesterol exposure and Lewy body disease. We did not observe associations between late life cholesterol levels and Braak stage or CERAD score.

Keywords

vascular; epidemiology; neuropathology; lipids; lewy body; alzheimer's

1. Introduction

Cholesterol plays a fundamental role in the organization of cell membranes and is critical to multiple facets of brain functioning, including synaptic transmission and growth factor signaling[1]. Although cholesterol has a central role in maintaining optimal brain health, alterations in lipid processing may have deleterious effects on aging processes. Accumulating evidence implicates central nervous system (CNS) lipids in the synthesis, deposition and clearance of amyloid β-peptides (Aβ) in animal models[2, 3], with higher central high-density lipoprotein (HDL) levels conferring protection against amyloid protein aggregation through ApoE-induced cholesterol efflux mechanisms[4]. Despite the compelling link between dysregulated CNS cholesterol metabolism and Alzheimer's disease (AD) in animals, a mechanistic association between peripheral cholesterol levels and AD neuropathology in humans remains inconclusive.

Research efforts to elucidate the association between blood levels of cholesterol and clinical AD suggest that peripheral levels of cholesterol may confer different risk profiles depending on age of exposure (i.e. mid-life versus late-life). Whereas higher levels of blood total cholesterol (TC) in *mid-life*[5–9] have been associated with increased risk of developing clinical AD or dementia more broadly[10], studies examining the association between blood TC in *late life* and clinical AD have frequently found no effect[6, 11] or in some cases a reduced risk of clinical AD in individuals with higher levels of blood TC[12]. One study also suggested conflicting associations between late life cholesterol exposure and subsequent clinical AD diagnoses, such that higher levels of not only HDL, but also TC and LDL [13] in late life have yielded decreased risk of AD.

The few studies that have considered autopsy outcomes have generated mixed results, particularly in relation to associations between late life cholesterol exposure and AD neuropathology. A seminal epidemiological study of cholesterol exposure and AD neuropathology suggested that only mid-life TC exposure was associated with amyloid deposition on autopsy (Odds Ratio [OR]= 1.039), whereas no increased risk was observed for late life TC and amyloid deposition[14]. Other investigations have suggested positive associations of late life TC and LDL with AD neuritic plaques [15–17], whereas others have noted significant associations between higher late life blood HDL, *but not TC or LDL*, and higher numbers of neuritic plaques [18]. Overall, the literature linking late life cholesterol exposure and AD pathology suggests that there may be a positive association, but the specific lipoproteins that confer risk and the timing of exposure in late life remains unclear.

The goal of this study was to characterize the relationship between blood cholesterol exposure in late life and neuropathologic outcomes from a community-based study.

Considering the putative mechanistic role of CNS HDL in protecting against amyloid aggregation in animal models[4], we hypothesized that higher blood HDL cholesterol exposure in late life might be associated with lower levels of neuritic plaques and neurofibrillary tangles; however, considering that higher levels of HDL in late life have not consistently shown the same protective effects as mid-life exposure, we also acknowledged that these associations might be reversed (i.e. higher blood HDL associated with higher AD pathology). In addition, given that higher non-HDL levels in late life have been linked with higher levels of AD neuropathology outcomes, we also examined these associations. To examine the specificity of these associations, we examined associations between blood cholesterol (HDL and non-HDL) and multiple neuropathology outcomes in addition to neuritic plaques and neurofibrillary tangles.

Since participants died at different ages, we faced a challenge in modeling exposure. We selected two approaches a priori: 1. Predicted cholesterol at age 70, and 2. Predicted cholesterol 10 years prior to death. Our rationale for these choices was that the first would provide potentially clinically relevant information regarding associations between cholesterol levels at age 70 and neuropathological findings at autopsy and thus may speak to late life risk factors for late onset AD (LOAD); we anticipated that the second approach would provide insights into the underlying biology, since we thought neuropathological lesions associated with cholesterol would take years to develop. Clinically, of course, one never knows if the person in front of you is 10 years prior to death. Our strategy enabled us to consider both ways of modeling exposure, providing complementary insights into associations between cholesterol exposures in late life and neuropathology outcomes.

2. Methods

2.1 Participants

The source of the study sample was The Adult Changes in Thought (ACT) study, a population-based prospective cohort study focused on brain aging and risk factors for dementia[19]. ACT is based within Group Health (GH), an integrated health care delivery system in Washington state. The ACT study recruits community-dwelling, nondemented adults aged 65 and older from among GH members living across the Seattle, WA area. The original ACT Study cohort included 2,581 randomly selected dementia-free older adults enrolled between 1994 and 1996, and an expansion cohort (n=811) was added between 2000 and 2002. In 2005, the study began ongoing enrollment to replace people who die, develop dementia, or drop out. The method of random sample selection was identical in all phases. Cognitive screening, physical function, medical history review, and functional status assessments are administered to ACT participants at study entry and subsequently every two years until a diagnosis of dementia is made.

Study analyses include people who died and came to autopsy (n=525 as of August, 2014) for whom medical record review has been completed. We required at least one measurement of HDL or non-HDL in the specified age window. Of 525 participants, 446 (85%) had available cholesterol data from at least one occasion during life. All autopsied participants provided written informed consent prior to death. As required by Washington state law, next-of-kin

also provided informed postmortem consent prior to autopsy. This study was approved by the GH and University of Washington Human Subjects Review Committees.

2.2 Health Factors Assessed

Cholesterol—Clinical data were captured as computerized laboratory data from 1988 onward. Plasma total cholesterol and HDL levels were determined using standard techniques. Non-HDL levels were calculated using the formula: Non-HDL=Total Cholesterol – HDL. We chose to use HDL and non-HDL values as primary predictors in our analyses[20].

Antilipemic Medication—We considered the possibility that whether an individual was 'on' or 'off' antilipemic medications during the time periods in which we were estimating cholesterol exposure (i.e. age 70; 10 years prior to death) might have an impact on blood cholesterol levels and their frequency of assessment. Three classes of antilipemic medications were used, including HMG-CoA reductase inhibitors, Clofibrate, and exchange resins. A dichotomous variable ('on' or 'off') was used to denote medication use, with start date defined as the initial prescription date +30 days. End date was defined as the date at which a prescription was scheduled to run out +30 days. In cases where data on medication supply was missing, these values were inferred based on review of each patient's prescription history.

Additional Health History Variables and Covariates (see Table 1)—Participants provided blood samples for *APOE* genotyping, and *APOE* was dichotomized (presence vs. absence of ε4 alleles) in analyses. Additional health covariates included age, sex, age at death and time to death. In terms of health history, medical records provided information about diabetes mellitus, hypertension, coronary artery bypass grafting (CABG), coronary angioplasty, myocardial infarction, and angina. These health variables are provided in Table 1 to provide an overview of vascular risk factors in the participant sample.

2.3 Neuropathologic Evaluation and Outcomes

Seven neuropathologic outcomes were evaluated. We staged neurofibrillary degeneration by characterizing neurofibrillary tangle distribution across medial temporal, isocortical, and primary sensory and/or motor cortex by the method of Braak and Braak[21, 22], scored neuritic plaque density in isocortex by the method of the Consortium to Establish a Registry for Alzheimer's Disease staging [CERAD])[23, 24], and ranked severity of cerebral amyloid angiopathy (CAA) on a four point scale using Congo red histochemical stains to assess degree of leptomeningeal and penetrating arteriole involvement [25]. We characterized vascular brain injury by focusing on parenchymal injury through comprehensive examination for gross and microscopic infarcts. Specifically, for macrovascular brain injury, every brain (including bilateral cerebrum, cerebellum, and brainstem) underwent a detailed gross neuropathological analysis. Any suspected chronic (cystic) territorial and lacunar infarcts were recorded, measured, and sampled for histopathological examination. For microvascular brain injury, samples of bilateral middle frontal gyrus, inferior parietal lobule, super/middle temporal gyrus, and medial occipital lobe including calcarine cortex, as well as bilateral neostriatum (at the level of the anterior commissure) and thalamus, were routinely

obtained in alignment with the latest diagnostic guidelines and processed for histologic analysis using routine stains, and the number of cerebral microinfarcts was assessed in standardized screening sections of brain according to consensus protocols [26, 27]. Finally, we characterized Lewy body disease using routine and immunohistochemical stains in the brainstem [substantia nigra (SN); locus ceruleus (LC)], amygdala, and frontal or temporal cortex according to the latest guidelines [28].

For statistical analyses, we dichotomized outcomes using cutpoints associated with a clinical diagnosis of dementia. For Braak stage, we selected stage V and VI as index of high level neurofibrillary degeneration, thus compared stages V–VI to 0–IV[1]. For neuritic plaques, we compared moderate or frequent versus none or sparse, and for CAA, grades 1–4 versus none[25]. For cystic infarcts, we compared 1 or more versus none; for cerebral microinfarcts, we compared individuals with three or more to those with zero to two microinfarcts, because this cut point has been used in prior studies by our group, which found higher dementia risk in people with three or more infarcts [29]. We routinely evaluated atherosclerosis involving Circle of Willis and cerebral arteriolosclerosis on standard four point scales, but chose to focus our analyses on parenchymal injury (infarcts) rather than vascular pathology to emphasize the correlation with *injury* (in aligment with our other outcomes). For Lewy bodies, we compared the presence or absence.

2.4 Analyses

Primary Exposures and Analysis—To characterize blood cholesterol exposure, we predicted cholesterol levels at age 70 as well as 10 years prior to death. We used linear mixed models with age and antilipemic medication as predictors to obtain person-specific predicted cholesterol values at age 70 for individuals with available cholesterol data (i.e. ≥1 datapoint) between ages 65–75 years (n=318, n=283 with *APOE* genotype data), all of whom died after the age of 70. These criteria ensured that people had at least 1 data point within 5 years of the target age, and that we were estimating cholesterol levels at a time point when the person was alive. This approach uses all available data for each individual to estimate his/her cholesterol level at age 70. We then evaluated whether the predicted cholesterol level at age 70 was associated with neuropathologic outcomes using a logistic regression model, controlling for age at death (range: 71–99), sex, and the interaction between sex and age of death.

We used similar models to predict cholesterol levels 10 years prior to death for individuals with at least 1 data point between 5 and 15 years prior to death, using linear mixed models with time-to-death and antilipemic medications as predictors (n=396; n=348 with *APOE* genotype data). We then evaluated whether the predicted cholesterol level 10 years prior to death was associated with neuropathologic outcomes using logistic regression models, controlling for covariates.

Secondary Analyses—We carried out secondary analyses on the subset of ACT participants who had undergone *APOE* genotyping to determine whether the presence of at

[1]Note that when analyses were repeated combining levels III to VI (i.e. intermediate to high neuropathological changes), no substantive differences were observed in the results.

least one ε4 allele modified the relationship between cholesterol exposure and neuropathology. We restricted the analyses to neuropathologic outcomes that were deemed significant in the primary analyses. We used R for all statistical analyses.

3. Results

3.1 Primary Analysis 1 (Predicted Cholesterol Values at Age 70)

In the subsample of individuals with cholesterol levels measured between ages 65 and 75 (see Table 1), the average number of cholesterol observations in the exposure window was 4.3 (SD=4.5). Mean predicted blood HDL levels at age 70 were 55.2 mg/dL (SD: 15.2) and predicted Non-HDL levels were 171.3 mg/dL (SD: 36.1).

We observed an association between predicted blood non-HDL cholesterol at age 70 and Lewy body disease, both independent of location and specifically in the SN or LC (see Table 2). We noted trends (p<.10) for an association between non-HDL levels and Lewy body disease in frontal or temporal cortex and in the amygdala. There were no associations between non-HDL levels at age 70 and AD neuropathologic change or measures of vascular brain injury, nor were there significant associations between predicted HDL levels and neuropathologic outcome measures.

3.2 Primary Analysis 2 (Predicted Cholesterol Values 10 Years Prior to Death)

In the subsample of individuals with cholesterol levels between 5 and 15 years prior to death (see Table 1), the average number of cholesterol observations in the exposure window was 4.5 (SD=4.6). Mean predicted HDL levels 10 years prior to death were 55.6 mg/dL (SD: 15.1) and predicted Non-HDL levels were 169.6 mg/dL (SD: 35.7). We observed no significant associations between peripheral cholesterol levels and neuropathologic outcomes in the 10 years prior to death analysis (See Supplementary Table, S1).

Sensitivity Analysis—Cholesterol exposures at age 70 were predictive of Lewy body disease in primary analyses, but levels 10 years before death were not related. One hypothesis to explain this discrepancy is that cholesterol effects on Lewy body neuropathology accumulate over decades, which would be consistent with recent evidence that neurodegenerative diseases develop over decades[30]. Age 70 was about 16 years prior to death on average; 10 years prior to death may have been after the critical period for cholesterol effects. We conducted an additional sensitivity analysis of predicted cholesterol values 20 years prior to death. Results from this analysis (see Supplementary Table, S2) suggest a stronger relationship between Lewy body disease and cholesterol levels 20 years (mean associated age window = 69.3 ±5 years; n =295) relative to 10 years (mean associated age window = 77.4 ±5 years) prior to death. While post hoc and exploratory, these results support the hypothesis that cholesterol exposures decades earlier in life may be important for the development of Lewy body disease.

3.3 Secondary Analysis (*APOE* genotype)

Main effects of *APOE* genotype on pathology outcomes were consistent with the literature, with the presence of an *ε4* allele predicting any Lewy body disease (OR: 2.01, p<0.05),

Braak stage for neurofibrillary degeneration (OR: 3.01, $p<0.001$), CERAD score for neuritic plaques (OR: 3.06, $p<0.001$) and CAA (OR: 2.38, $p<0.005$).

Given that our significant findings in the primary analyses were restricted to predicted blood non-HDL cholesterol levels at age 70 and Lewy body disease, we focused our secondary analysis on this subset. Controlling for *APOE* genotype did not substantively impact the associations between blood non-HDL cholesterol and Lewy bodies (p<.1 for SN or LC, and frontal or temporal cortex), although the effect size for *any* Lewy body outcome (*OR*=1.25, $p<0.15$) was attenuated. We also examined interactions between *APOE* genotype and blood non-HDL cholesterol levels for Lewy body disease, but did not note any other significant modifying effects for *APOE* genotype.

4. Discussion

In this population-based autopsy series, we found that higher levels of blood non-HDL cholesterol estimated at age 70 were associated with Lewy body disease, and this relationship was not substantively impacted by *APOE* genotype or age of death. Contrary to our hypotheses, we did not find associations between HDL or non-HDL cholesterol and AD neuropathology (neuritic plaques or neurofibrillary degeneration). To our knowledge, this is the first epidemiological study to examine the role of peripheral blood cholesterol exposure in late life on neuropathologic outcomes at both a specified age and years prior to death.

A striking negative finding from our study centers on the lack of association between blood cholesterol exposure in late life and AD neuropathology, as defined by neuritic plaque and neurofibrillary degeneration, in an adequately powered investigation. This finding is consistent with the lack of association between blood cholesterol and clinical diagnosis of AD from this cohort[11]. Prior literature has been mixed in terms of direction and degree of these associations in late life, with isolated studies suggesting no relationship between late-life cholesterol and AD neuropathology[14], while other indicating positive or mixed effects[15, 17, 18]. Our study differs from prior epidemiological studies in several important ways, including the timing (age 70 and 10 years prior to death) and statistical modeling (predicted values based on an exposure window) of cholesterol exposure; comparisons between investigations may be limited by these methodological differences. Nevertheless, the lack of association between cholesterol exposure in late life and AD neuropathology is remarkable given the mechanistic roles brain cholesterol has been reported to play in Aβ aggregation and clearance in animal models. In vitro studies have demonstrated that low brain cholesterol levels differentially inhibit β-cleavage and increase α-cleavage of amyloid precursor protein, resulting in more non-toxic APP degradation products and less Aβ production[31]. It's notable, however, that the brain is entirely devoid of LDL, and produces HDL independently of the peripheral cholesterol pool.[32] As such, relationships observed between peripheral cholesterol in late life and autopsy-confirmed AD reported in past studies may have been driven by other upstream or downstream factors. Alternatively, our results may also provide additional evidence for a different risk profile for cholesterol exposure in mid-life versus late life. Given the age range of individuals entering this study (>65), we cannot address the role of mid-life cholesterol; nonetheless, increasing evidence points to mid-life as a critical period for several vascular risk factors, including cholesterol,

in conferring risk for negative outcomes[9, 33]. For example, a recent epidemiological study noted that higher numbers of midlife vascular risk factors were associated with elevated amyloid deposition in late life (i.e. as indexed by amyloid PET imaging); in contrast, late life vascular risk factors did not confer risk for late-life amyloid deposition[34]. Taken together, it is possible and likely that cholesterol exposure has a distinct pathogenic role at earlier ages.

An additional finding in this study was the association between blood non-HDL levels at age 70 and Lewy body disease, specifically in brainstem structures, the substantia nigra or locus ceruleus. We further explored this finding in a sensitivity analysis, which showed that as we shifted the exposure window further away from death, cholesterol levels became more predictive of Lewy Body disease. A burgeoning literature on the potential role of lipid processing and Lewy body disease, and the major constituent protein α-synuclein, has developed in the past several years[35]. A recent study reported that rabbits fed a 2% cholesterol-enriched diet for 12 weeks displayed increased immunoreactivity for α-synuclein in the subthalamic nucleus[36]. Although peripheral cholesterol does not cross the blood-brain barrier (BBB), recent studies suggest that cholesterol metabolites (oxysterols), which more easily pass through the BBB, may be responsible for the higher α-synuclein levels in the brain[37]. Given the small, but notable effect of blood non-HDL cholesterol levels on Lewy body disease in our sample, additional research is needed to clarify the strength of the association and potential underlying mechanisms.

We also evaluated the association between predicted cholesterol values 10 years prior to death and neuropathology outcomes, which we thought might give us insights into biologically relevant associations between blood cholesterol levels and neuropathological findings at autopsy. We did not find significant associations between peripheral cholesterol levels 10 years prior to death and any neuropathologic outcome. The reason for the discordance of results across the two methods cannot be fully addressed in the current study, but it remains possible and likely that risk factors earlier in life (i.e. mid-life) play a disproportionate role in the development of pathology compared to the years immediately preceding death (supported in part by our sensitivity analysis for Lewy Body disease, examining 20 years prior to death). Of note, the average age of death in our sample was 86 years, so the age 70 window of cholesterol exposure represented more than 15 years prior to death. Given the age range of participants upon entry into the study, we were not able to examine exposures *more* than 20 years prior to death, thus we cannot adequately address or resolve the question of mid-life cholesterol exposure in either AD or Lewy Body pathology outcomes.

The current study displays numerous strengths, including the use of a large, population-based sample with multiple cholesterol ascertainments. The longitudinal, observational design permitted statistical modeling of blood cholesterol exposure windows in the context of an adequately powered study. Given those strengths, the lack of association between peripheral cholesterol levels and AD neuropathology is particularly notable, as we had ample power to detect an association if it has been present. Further, Lewy body disease is less prevalent than advanced Braak stage or CERAD score, thus we had *greater* power to

find associations with AD neuropathologic outcomes than Lewy body disease, and yet the study yielded a negative finding with respect to AD-related neuropathology.

In terms of limitations, although we incorporated antilipemic medications into our statistical models of cholesterol exposure, we did not analyze antilipemic type or dose. Given the scope and the complexity of the exposure models we used, we elected not to incorporate additional vascular risk factors into our analyses. Although this allowed us to focus on specific associations between blood cholesterol levels and neuropathology, this choice limits our ability to address the *independent* role of cholesterol against the backdrop of comorbid risk factors or disentangle the relative contribution of cholesterol versus other vascular risk factors to neuropathological outcomes. In addition, our study focused on cholesterol exposure in late life; as such, we cannot address the role of mid-life cholesterol exposure on AD pathology, nor can our data speak to risk factors for early onset AD. Moreover, amyloid plaque distribution (Thal phase) data using β amyloid immunohistochemical assessments was not available for the entire autopsy cohort (the NIA-AA Guidelines were released in 2012)[26, 27]; thus, we could not test whether blood cholesterol levels are associated with brain β amyloid distribution. Finally, selection bias remains a relevant concern when interpreting the results of autopsy studies; as such, we cannot comprehensively address whether neuropathologic outcomes are representative of aging adults who die but do not go on to autopsy.

In terms of future studies, increasing evidence suggests that advanced age is typified by co-morbid changes rather than single disease processes. To elucidate the selective effects of blood cholesterol levels on Lewy body disease, it will be important for future studies to disentangle associations with multiple neuropathologic changes. Given the limited literature on cholesterol and Lewy body disease, further examination of possible mechanisms of action as well as timing of effects will be critical to understanding which pathways may be responsible for the relationships we observed. Finally, increasing evidence points to disparate risk profiles conferred by cholesterol exposure in mid-life versus late life; in order to elucidate the role of cholesterol exposure, including the identification of critical epochs of exposure, future studies that span both mid- and late life ages will be critical.

In summary, we found an association between blood non-HDL cholesterol levels estimated at age 70 and Lewy body disease in a longitudinal population-based study. We did not observe any primary associations between HDL or non-HDL cholesterol in late life and AD neuropathology. Although these findings suggest that peripheral cholesterol in late life may not serve as a direct risk factor for AD, indirect mechanisms of peripheral cholesterol in late life on AD neuropathologic outcomes remain an understudied possibility. Moreover, the role of *brain* cholesterol levels was not addressed in this study and may play an integral role in AD neuropathologic outcomes. This study adds to the body of literature on long-term outcomes of lipid exposure and highlights the complex associations between late life cardiovascular risk factors and pathological outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Vance JE. Dysregulation of cholesterol balance in the brain: contribution to neurodegenerative diseases. Dis Model Mech. 2012; 5:746–755. [PubMed: 23065638]
2. Sparks DL, Kuo YM, Roher A, Martin T, Lukas RJ. Alterations of Alzheimer's disease in the cholesterol-fed rabbit, including vascular inflammation. Preliminary observations. Annals of the New York Academy of Sciences. 2000; 903:335–344. [PubMed: 10818523]
3. Sparks DL, Scheff SW, Hunsaker JC 3rd, Liu H, Landers T, Gross DR. Induction of Alzheimer-like beta-amyloid immunoreactivity in the brains of rabbits with dietary cholesterol. Experimental neurology. 1994; 126:88–94. [PubMed: 8157129]
4. Lee CY, Tse W, Smith JD, Landreth GE. Apolipoprotein E promotes beta-amyloid trafficking and degradation by modulating microglial cholesterol levels. The Journal of biological chemistry. 2012; 287:2032–2044. [PubMed: 22130662]
5. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Iivonen S, Mannermaa A, Tuomilehto J, Nissinen A, Soininen H. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002; 137:149–155. [PubMed: 12160362]
6. 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. The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry. 2008; 16:343–354. [PubMed: 18448847]
7. Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA. Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord. 2009; 28:75–80. [PubMed: 19648749]
8. Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J, Nissinen A. Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. Neuroepidemiology. 1998; 17:14–20. [PubMed: 9549720]
9. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001; 322:1447–1451. [PubMed: 11408299]
10. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005; 64:277–281. [PubMed: 15668425]
11. Li G, Shofer JB, Kukull WA, Peskind ER, Tsuang DW, Breitner JC, McCormick W, Bowen JD, Teri L, Schellenberg GD, Larson EB. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology. 2005; 65:1045–1050. [PubMed: 16217057]
12. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005; 64:1689–1695. [PubMed: 15911792]
13. Reitz C, Tang MX, Schupf N, Manly JJ, Mayeux R, Luchsinger JA. Association of higher levels of high-density lipoprotein cholesterol in elderly individuals and lower risk of late-onset Alzheimer disease. Archives of Neurology. 2010; 67:1491–1497. [PubMed: 21149810]
14. Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, Wolozin B, Sano M, Cruz-Sanchez FF, Thal LJ, Petanceska

SS, Refolo LM. Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurology. 2003; 61:199–205. [PubMed: 12874399]

15. Lesser GT, Beeri MS, Schmeidler J, Purohit DP, Haroutunian V. Cholesterol and LDL relate to neuritic plaques and to APOE4 presence but not to neurofibrillary tangles. Curr Alzheimer Res. 2011; 8:303–312. [PubMed: 21244352]
16. Lesser GT, Haroutunian V, Purohit DP, Schnaider Beeri M, Schmeidler J, Honkanen L, Neufeld R, Libow LS. Serum lipids are related to Alzheimer's pathology in nursing home residents. Dement Geriatr Cogn Disord. 2009; 27:42–49. [PubMed: 19129700]
17. Matsuzaki T, Sasaki K, Hata J, Hirakawa Y, Fujimi K, Ninomiya T, Suzuki SO, Kanba S, Kiyohara Y, Iwaki T. Association of Alzheimer disease pathology with abnormal lipid metabolism: the Hisayama Study. Neurology. 2011; 77:1068–1075. [PubMed: 21911734]
18. Launer LJ, White LR, Petrovitch H, Ross GW, Curb JD. Cholesterol and neuropathologic markers of AD: a population-based autopsy study. Neurology. 2001; 57:1447–1452. [PubMed: 11673587]
19. Kukull WA, Higdon R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, van Belle G, Jolley L, Larson EB. Dementia and Alzheimer disease incidence: a prospective cohort study. Archives of Neurology. 2002; 59:1737–1746. [PubMed: 12433261]
20. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, Deedwania P, Olsson AG, Boekholdt SM, Demicco DA, Szarek M, LaRosa JC, Pedersen TR, Grundy SM, Group TNTS, Group IS. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation. 2008; 117:3002–3009. [PubMed: 18519851]
21. Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? European archives of psychiatry and clinical neuroscience. 1999; 249(Suppl 3):14–22.
22. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica. 1991; 82:239–259. [PubMed: 1759558]
23. Mirra SS. The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary. Neurobiology of aging. 1997; 18:S91–94. [PubMed: 9330994]
24. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology. 1991; 41:479–486. [PubMed: 2011243]
25. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke; a journal of cerebral circulation. 1997; 28:1418–1422.
26. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012; 8:1–13. [PubMed: 22265587]
27. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Trojanowski JQ, Vinters HV, Hyman BT, National Institute on A, Alzheimer's A. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. Acta Neuropathol. 2012; 123:1–11. [PubMed: 22101365]
28. Dickson DW, Braak H, Duda JE, Duyckaerts C, Gasser T, Halliday GM, Hardy J, Leverenz JB, Del Tredici K, Wszolek ZK, Litvan I. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. The Lancet Neurology. 2009; 8:1150–1157. [PubMed: 19909913]
29. Sonnen JA, Larson EB, Crane PK, Haneuse S, Li G, Schellenberg GD, Craft S, Leverenz JB, Montine TJ. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Annals of Neurology. 2007; 62:406–413. [PubMed: 17879383]
30. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. Neuron. 2014; 84:608–622. [PubMed: 25442939]

31. Ehehalt R, Keller P, Haass C, Thiele C, Simons K. Amyloidogenic processing of the Alzheimer beta-amyloid precursor protein depends on lipid rafts. J Cell Biol. 2003; 160:113–123. [PubMed: 12515826]

32. Poirier J, Miron J, Picard C, Gormley P, Theroux L, Breitner J, Dea D. Apolipoprotein E and lipid homeostasis in the etiology and treatment of sporadic Alzheimer's disease. Neurobiology of aging. 2014; 35(Suppl 2):S3–10. [PubMed: 24973118]

33. Kivipelto M, Solomon A. Cholesterol as a risk factor for Alzheimer's disease - epidemiological evidence. Acta Neurol Scand Suppl. 2006; 185:50–57. [PubMed: 16866911]

34. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Sharrett AR, Wagenknecht LE, Wong DF, Mosley TH. Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition. JAMA. 2017; 317:1443–1450. [PubMed: 28399252]

35. Hu G. Total cholesterol and the risk of Parkinson's disease: a review for some new findings. Parkinson's disease. 2010; 2010:836962.

36. Marwarha G, Ghribi O. Does the oxysterol 27-hydroxycholesterol underlie Alzheimer's disease-Parkinson's disease overlap? Experimental gerontology. 2014

37. Rantham Prabhakara JP, Feist G, Thomasson S, Thompson A, Schommer E, Ghribi O. Differential effects of 24-hydroxycholesterol and 27-hydroxycholesterol on tyrosine hydroxylase and alpha-synuclein in human neuroblastoma SH-SY5Y cells. Journal of neurochemistry. 2008; 107:1722–1729. [PubMed: 19014385]

Table 1

Characteristics of Participant Sample

Characteristics	Predicted Cholesterol at Age 70 Total (N=318) Mean (SD) or n(%)	Predicted Cholesterol 10 Years Prior to Death Total (N=396) Mean (SD) or n(%)
Age at Death	85.9 (5.7)	87.4 (6.6)
Female (%)	166 (52.2)	212 (53.54%)
White Race (%)	304 (95.6)	384 (96.97%)
Education (Years)	14.4 (3.0)	14.3 (3.1)
APOE ε4 Allele Present	96 (33.9% of observed) n=283	107 (30.8% of observed) n=348
Hypertension Medication Use (% Ever)	207 (65.3)	261 (66.2)
Diabetes (%)	63 (19.8)	72 (18.2)
Coronary Artery Disease (%) *	103 (32.4)	135 (34.2)

* Coronary artery disease was defined as any history of myocardial infarction, CABG, coronary angioplasty, or angina.

Table 2

Odds Ratios of Neuropathology Outcomes for Predicted HDL and Non-HDL Levels at Age 70

		Odds Ratio (95% CI) for a 1 SD Difference	
Outcome	**Freq (N)**	**HDL**	**Non-HDL**
Braak Stage 5 or 6	89 (314)	0.97 (0.74, 1.28)	1.04 (0.80, 1.35)
CERAD Intermediate or Frequent	149 (314)	0.83 (0.65, 1.06)	0.99 (0.78, 1.24)
Any Cerebral Amyloid Angiopathy	92 (312)	1.20 (0.92, 1.56)	1.02 (0.79, 1.31)
Presence of Cystic Infarcts	97 (311)	0.90 (0.69, 1.17)	1.13 (0.89, 1.43)
Presence of Microinfarcts			
Any	106 (313)	0.86 (0.66, 1.12)	1.00 (0.79,1.28)
Any cerebral	35 (313)	1.04 (0.80, 1.34)	1.03 (0.81, 1.30)
Any deep	97 (311)	0.81 (0.61, 1.06)	1.02 (0.79, 1.31)
Lewy Body Disease			
Any	54 (314)	1.00 (0.72, 1.39)	1.35 (1.02, 1.79) *
SN or LC	42 (314)	0.73 (0.50, 1.09)	1.45 (1.07, 1.96) *
Amygdala	53 (299)	1.18 (0.83, 1.69)	1.29 (0.95, 1.74)
Frontal or temporal cortex	18 (313)	1.10 (0.65, 1.86)	1.45 (0.99, 2.13)

* $p<.05$