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Better memory functioning associated with higher total and LDL cholesterol levels in very elderly subjects without the APOE4 allele

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Abstract

Objective—To examine the association of cholesterol with cognitive functioning in oldest old community dwelling individuals with and without the APOE4 allele.

Method—185 non-demented community dwelling individuals (≥ 85) were assessed with a broad neuropsychological battery. Bloods were drawn to assess total, LDL, and HDL cholesterol, as well as for APOE genotyping.

Results—In contrast to our expectations, high total cholesterol and high LDL cholesterol were associated with higher memory scores for non-carriers of the APOE4 allele. No significant associations between cognitive performance and lipid profile were found for carriers of the APOE4 allele.

Conclusions—In oldest old non-demented non-carriers of the APOE4 allele, high cholesterol is associated with better memory function. Further examination of the role of APOE genotype on the association between cholesterol and cognitive performance, especially in the oldest old, is warranted.

Keywords

dementia; cognitive performance; apolipoprotein E; cholesterol

INTRODUCTION

The apolipoprotein e4 (APOE4) allele and high total cholesterol have both been associated with increased risk of dementia (1,2), specifically Alzheimer's Disease (1,3), however, the interaction of these two risk factors has not been clarified (2). Furthermore, APOE4 and high cholesterol may not be risk factors for dementia at all in the oldest old (4,5), despite the elevated risk of Alzheimer's Disease above the age of 85. High cholesterol in individuals above the age of 79 has actually been found to be associated with reduced risk of dementia (3), and APOE4 has not been found to have a significant relationship with memory or learning in non-demented individuals above the age of 85 (5). In this interim analysis, we examined associations *with cognitive function of* total cholesterol, LDL cholesterol, HDL cholesterol, and APOE4 status,

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in non-demented community dwelling individuals, all 85 years and above participating in an ongoing longitudinal study on risk and protective factors for dementia.

METHODS

We assessed cognitive function and lipid profile levels in 185 participants between the ages of 85 and 101. These participants were recruited from the New York City area. All participants were well-functioning and non-demented, based on a Clinical Dementia Rating (CDR) score of zero (no dementia) and Mini Mental State Examination appropriate for age and education norms (6,7). They reported no memory complaints and were able to provide detailed information regarding their own and their families' histories. Socio-demographic characteristics (e.g. age, sex, years of education) were recorded as well as medical conditions. Medication use was collected from all participants, including type of medication and dosage, and in order to control for cholesterol-lowering medication, two dichotomous variables were formed: current use of cholesterol-lowering medication, and past use of cholesterol-lowering medication. Participants also provided a blood sample after fasting for four hours. All protocols were reviewed and approved by the Mount Sinai Institutional Review Board and the Bronx VAMC Institutional Review Board.

To reduce the number of correlations between the three lipid measures and the eleven neuropsychological measures, factor analysis summarized them into memory (immediate recall, delayed recall, recognition, and Savings), executive functions (Trails A and Trails B), attention (diamond cancellation and letter cancellation), and language factors (animal fluency, Shipley vocabulary, and Boston naming test) factors.

Partial correlation analyses between lipid measures and the neuropsychological factors controlled for age, sex, years of education, current and past use of cholesterol medications, and APOE4 status. Separate partial correlations were also calculated by APOE4 status. Fisher's r-to-z transformation was used to compare the correlations of the APOE4 and non APOE4 groups.

RESULTS

The sample consisted of 102 males and 83 females, with a mean age of 88.8 (SD=3.1) and mean years of education of 14.8 (SD=3.3). Sixty-two reported current or past use of cholesterol-reducing medications. They had a mean total cholesterol level of 189.3 mg/dL (SD= 39.4), a mean LDL cholesterol level of 113.7 mg/dL (SD=33.6), and a mean HDL cholesterol level of 53.8 mg/dL (SD=17.9).

APOE4 carriers and non-carriers did not differ significantly in age, years of education, or cholesterol profiles. The means and standard deviations of these characteristics can be found in Table 1.

The 185 participants demonstrated a significant positive association of the memory factor with total cholesterol (r=.161, df=173, p=.033). No significant associations were found for LDL (r=.117, df=170, p=.127) or HDL (r=.031, df=174, p=.682) with memory, or for any of the cholesterol measures with the executive, attention, or language factors. Stratifying by whether or not subjects carried one or more APOE4 alleles indicated that the association between cholesterol and cognition was attributable to the APOE4 non-carriers only. The non-carriers demonstrated a significant association of memory with total cholesterol (r=.244, df=137, p=.004) and with LDL cholesterol (r=.208, df=133, p=.016) but not with HDL cholesterol (r=-.026, df=135, p=.765). Carriers of the APOE4 allele showed no significant correlations between memory and total cholesterol (r= -.058, df=30, p=.754), LDL cholesterol (r=-.148, df=30, p=.420), or HDL cholesterol (r=.144, df=32, p=.416).

Since a U-shaped association between cholesterol and cognition is biologically plausible, we repeated the analyses examining the quadratic associations. Quadratic associations were not significant in any cognitive function and APOE4 status. This suggests that individuals with the highest total and LDL cholesterol are those with the best memory scores.

Although the APOE4 non-carriers and carriers demonstrated differences in the significance level of the associations between total and LDL cholesterol and memory, Fisher's r to z test showed that the correlations did not differ significantly.

DISCUSSION

A positive association was observed between total cholesterol and memory function in this nondemented oldest old sample. The effect was evident specifically among those without an APOE4 allele. In this group, there was also an association between elevated LDL cholesterol and memory. In view of results from other studies showing a negative relationship between cholesterol and cognitive function in younger subjects (2), our results suggest that the association of cholesterol with memory may be age-dependent.

It is possible that individuals who survive beyond age of 85, especially those with high cholesterol, may be more robust and therefore less susceptible to the adverse effects of high cholesterol (4). This possibility is supported by the recent observation that—unlike in younger subjects—the metabolic syndrome (including high cholesterol but also hypertension and obesity) may be associated with a decreased risk of cognitive decline in individuals above age 70 (8).

Low levels of cholesterol have been associated with the onset of dementia (9), perhaps due to a decline in cholesterol levels after high cholesterol at middle age, a risk factor for dementia (10). Such declines have also been correlated with the onset of and death from noncardiovascular diseases (11,12,13). A decrease in cholesterol may be a symptom of the progression of dementia (10) or may indicate the approach of dementia (9). Some studies have demonstrated that a decrease in cholesterol even nine years prior to the onset of dementia is related to the diagnosis (4). The rate of decline may play a role; it has been demonstrated that total cholesterol may decrease over time for the general population, but may decline significantly faster in those who eventually experience cognitive impairment (14). Another explanation could be that changes in cholesterol, not a decline or low level, are associated with dementia (14).

High total cholesterol has been correlated with a lower risk of mortality in the elderly (13). It may be conjectured that high levels of cholesterol suggests better health than that of individuals with lower levels of cholesterol. Specifically, these individuals may be exhibiting greater liver functioning, as low total cholesterol levels may be a symptom of liver disease (13).

Cholesterol lowering medications could be an explanation for the better memory functioning; it has been found that cholesterol medication may be protective against dementia (10). *Medication use was controlled for*. Statins in particular have been associated with positive effects on cardiovascular risk factors which may be associated with impaired cognition, such reducing β-amyloid production (10). Simvastatin has been suggested as the most effective statin (15) When statins and specifically simvastatin were controlled for, the results were unchanged, since 98% of those currently taking cholesterol medications in our sample were taking statins.

The APOE4 allele has also been associated with risk factors for dementia including depression and high cholesterol at middle age (16). While the 39 APOE4 carriers may constitute a larger proportion of the sample than might be expected at this age range (21%, similar to what is seen

at younger ages (17), despite increased mortality due to cardiovascular diseases), the statistical power for this group is might have been too low. However, it should be noted that the size of the correlations in this group was smaller. Also, as this group tends to have higher levels of cholesterol (16) throughout life, the negative effects of midlife high cholesterol may negate any potential protective effects on memory in late life.

Another possible explanation is antagonistic pleiotropy, which suggests that successful aging may depend on a complex restructuring and adaptation of metabolism (18). Often antagonistic pleiotropy is discussed as a hypothesis that might explain why protective factors during early and middle ages may become detrimental in later life; Huntington's chorea, which significantly reduces life span, may also increase early fertility (18). However, this process may also perform in the opposite way: risk factors during middle age, like high cholesterol, may become protective in late life (10). Although counter-intuitive, this theory suggests that if individuals survive to a late age, it is likely that their metabolism is able to adapt to the challenges of aging. This robustness and the addition of the protection of high cholesterol may result in a healthier older person. As their metabolism adjusts, factors that previously increased the risk for poor aging, like high cholesterol, may become protective.

This study has several limitations. The cross-sectional sample does not allow us to examine causation. The sample represents a convenience sample, not an epidemiological sample; however, it is extremely difficult to compile an epidemiological sample of the oldest old. As this study examines the non-demented oldest old, these participants might represent a group of "survivors," for whom good mental health may be affected by many factors, including physical and social activity, nutrition, genetic prosperity, and general health. It must be noted that most assessments were done in the home of the participant, where the interviewer recorded information directly from the labels of participants' medications, providing good reliability for this data. However, data regarding medication use relies on the participants complying with their medication regimen. Additionally, the participants fasted for four hours prior to the blood draw. Had participants fasted for the typically required eight hours, the cholesterol profile might have been slightly different. Finally, the limited number of APOE4 individuals in our sample impaired our ability to establish the effect of the APOE genotype on the relationship between cholesterol and memory. The longitudinal component of the current study will further clarify the complex relationship among dementia, cholesterol, APOE genotype, age, and aging.

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Table 1

Means, standard deviations, and prevalences of the APOE genotypes and of APOE4 carriers and non-carriers

	Percent in sample	Age	Education	TC	HDL	LDL	Cholesterol medication use- current	Cholesterol medication use- ever	Prevalence*
APOE4 Non - carriers	79%	88.7 SD=3.1	14.7 SD=3.2	190.0 SD=37.9	53.4 SD=17.0	114.2 SD=32.1	35/146 24.0%	50/146 34.2%	75%
2/3	21.6%	88.11 SD=2.1	14.6 SD=3.0	187.6 SD=42.0	52.6 SD=15.1	111.2 SD=35.5	12/40 30%	14/40 35%	13.15%
3/3	57.3%	88.9 SD=3.3	14.8 SD=3.3	190.9 SD=36.4	53.7 SD=17.8	115.4 SD=30.7	26/106 24.5%	53/106 50%	62.79%
APOE4 carriers	21%	89.0 SD=3.3	14.9 SD=3.7	186.5 SD=45.2	55.1 SD=21.0	111.8 SD=39.4	6/39 15.4%	12/39 30.8%	25%
2/4	5.9%	90.0 SD=3.6	13.7 SD=3.5	179.0 SD=52.9	58.9 SD=19.4	102.5 SD=39.7	4/11 36.4%	6/11 54.5%	1.68%
3/4	13%	88.7 SD=3.2	15.5 SD=3.5	191.2 SD=36.4	55.5 SD=21.2	114.5 SD=36.4	9/24 37.5%	12/24 50%	18.78%
4/4	2.2%	87.3 SD=2.1	15.3 SD=5.6	179.8 SD=79.9	43.5 SD=25.3	119.9 SD=60.9	1/4 25%	1/4 25%	3.01%

*All values of prevalence are from the Framingham Offspring Study (Schaefer EF, Lamon-Fava S, Johnson S, Ordovas JM, Schaefer MM, Castelli WP, Wilson PW: Effects of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. Arteriosclerosis and Thrombosis 1994; 14: 1105-1113.)