Journal of Gerontology: MEDICAL SCIENCES
2008, Vol. 63A, No. 6, 619–624

Baseline Serum Cholesterol Is Selectively Associated With Motor Speed and Not Rates of Cognitive Decline: The Women's Health and Aging Study II

Michelle M. Mielke,[1,2] Qian-Li Xue,[2,3] Jing Zhou,[2] Paulo H. M. Chaves,[2,3] Linda P. Fried,[2,3] and Michelle C. Carlson[2,4]

[1]Department of Psychiatry, Division of Geriatric Psychiatry and Neuropsychiatry,
[2]Center on Aging and Health, and
[3]Division of Geriatric Medicine and Gerontology, Johns Hopkins University School of Medicine, Baltimore, Maryland.
[4]Department of Mental Health, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland.

Background. Although several studies have investigated the association between cholesterol and dementia, few have examined cholesterol and decline across cognitive domains. We examined serum total and high-density lipoprotein (HDL) cholesterol, total-to-HDL ratio, and trajectories across cognitive domains.

Methods. Participants were 436 community-residing women (70–79 years old) in the Women's Health and Aging Study II; they were screened to be physically high-functioning and cognitively intact at baseline. Cognition and other health-related variables were assessed at five intervals spanning 9 years. Cognitive assessments included Trail Making Test Parts A (TMT-A) and B (TMT-B), Hopkins Verbal Learning Test-Revised, Purdue Pegboard, and Mini-Mental State Examination (MMSE). The association between baseline levels of serum lipids and cognitive trajectories were evaluated using Generalized Estimating Equations (GEE). Covariates included age, education, race, vascular disease, serum creatinine, depression, and lipid-lowering medications.

Results. In multivariate analyses, baseline higher total ($p = .02$) and HDL ($p = .03$) cholesterol were associated with better performance on the Purdue Pegboard. Using clinical cholesterol cutoffs, baseline serum total cholesterol levels >240 mg/dL were associated with the best performance ($p = .02$). Baseline lipids were not associated with any other cognitive tests; there were no Lipid × Time interactions.

Conclusion. Higher baseline serum lipid levels predicted better performance over time on a measure of motor speed, but not memory or psychomotor or executive functioning in this population of elderly women. This association suggests that peripheral cholesterol levels, measured in late-life, may not be a good predictor of subsequent cognitive decline. Future research examining peripheral cholesterol over the life span and its relationship with cognition is needed.

***Key Words*:** Cholesterol—Cognition—Motor speed—Biological aging.

MIDLIFE hypercholesterolemia is a recognized risk factor for cardiovascular disease, cerebrovascular disease, and mortality. Although this risk relationship has been extended to late life, research indicates that this may not be warranted. For example, several studies have suggested that high cholesterol in midlife (1,2), but not late life (3,4), is a risk factor for cardiovascular disease. This conflicting research on mid- versus late life hypercholesterolemia also extends to dementia, such that hypercholesterolemia in midlife (5–7), but not late life (8,9), has been a suggested risk factor for subsequent dementia. In fact, recent research raises the question as to whether high cholesterol in late life might even be protective (10,11). Given the high percentage of elderly persons taking lipid-lowering drugs, additional research into the possible benefits or risk of higher cholesterol in late life is clearly warranted.

An extension of this research is to examine cholesterol in relation to cognition in healthy, nondemented individuals. This is important because examining domain-specific declines in cognition, rather than dementia, may be more sensitive and may help to elucidate the effects of cholesterol on brain integrity and function. Thus far, few longitudinal studies have assessed the relationship between cholesterol and cognition in the elderly population. One study reported that high total and low-density lipoprotein (LDL) cholesterol were associated with poorer cognitive functioning (12), whereas another did not find an association (13). In contrast, two studies reported that high total and non-high-density lipoprotein (HDL) cholesterol were associated with better overall cognitive performance (14) and performance in specific cognitive abilities, including attention and word fluency (15). Importantly, some of these studies assessed cognition at follow-up in the absence of baseline values (12,15), so it is difficult to discern the temporality of the cholesterol–cognition relationship. Other studies have been restricted to the assessment of global cognition, or have focused on one or two cognitive abilities (12,14).

We sought to build on this literature by examining the association between baseline levels of serum total, HDL, total-to-HDL cholesterol ratio, and change in multiple cognitive domains in the Women's Health and Aging Study II (WHAS II), a population-based study of high-functioning older women. Participants were followed-up six times over 9 years and were administered a neuropsychological test

battery at each follow-up, allowing for better assessment of the longitudinal relationship between baseline cholesterol and specific cognitive abilities. We hypothesized a priori that low, not high, baseline cholesterol would be associated with worse performance, particularly on speed of processing measures. Cholesterol is a key component of myelin, which is essential for speeded transmission in neurons, and degrades with age.

Methods

Characteristics and Sampling of Population/Participants

The WHAS II is a prospective study of physical functioning among the two-thirds least disabled 70- to 79-year-old community-dwelling women in east Baltimore, Maryland. The sampling and recruitment of this cohort have been previously described (16,17). Briefly, trained interviewers determined eligibility according to whether the women: (i) were 70–79 years old, (ii) had sufficient hearing and proficiency in English to be interviewed, (iii) could be contacted by telephone, (iv) had a Mini-Mental State Examination (MMSE) (18) score of $\geq$24 or greater at the screening visit, and (v) reported no difficulty or difficulty in only one of the following four domains: mobility and exercise tolerance, upper extremity function, high functioning tasks (e.g., shopping), and basic self-care (16,17). Of 880 women screened eligible, 436 participated in the baseline examination.

Follow-ups were conducted roughly 1.5, 3, 6, 7.5, and 9 years later. Each examination consisted of a comprehensive medical history, medication inventory, physical and neurological examination, neuropsychological battery, and blood draw. Ten women (2.3%) had missing baseline cholesterol measurements and were excluded from the present analyses. There were no differences between women with missing and available cholesterol measurements with regard to age, race, education, and vascular disease. All women provided written informed consent, and the study was approved by the Johns Hopkins Institutional Review Board.

Cognitive Assessments

Cognitive testing was conducted by a trained technician. The MMSE measures global cognition, and the Trail Making Test (19) is made up of two parts to evaluate psychomotor and visual search speed (Part A: TMT-A) and set-shifting and attention (Part B: TMT-B). Hopkins Verbal Learning Test-Revised (HVLT-R) (20) assessed verbal learning of 12 words over three successive learning trials and a 20-minute delayed recall. Purdue Pegboard (21) measured fine motor speed by evaluating the time to place 10 pegs in holes for the dominant and nondominant hands.

Measurement of Lipids

Nonfasting blood was drawn at the baseline visit, and serum was extracted and frozen at –80°C until processing. Total and HDL cholesterol levels were determined using standard enzymatic techniques. As samples were nonfasting, we examined the total-to-HDL cholesterol ratio rather than calculating LDL levels using the Friedewald equation (22). Lipids are expressed in milligrams per deciliter (mg/dL).

Statistical Methods

The relationship between baseline cholesterol and cognition was examined longitudinally using Generalized Estimating Equations (GEE) (23). The GEE model is advantageous over other longitudinal methods because it does not assume a normal distribution of the cognitive outcome and accounts for the within-person correlation when examining multiple observations per participant. We used LOGLINK to ensure that predictions from the model take positive values, and chose a gamma distribution to more flexibly account for right-skewed outcomes. Dependent variables were the individual cognitive test scores; independent variables were baseline total cholesterol, HDL cholesterol, total-to-HDL cholesterol ratio, follow-up time, and the interactions of lipids and time. Cholesterol measures were centered at the mean. Due to the correlation between the three lipid variables, each lipid was analyzed separately. To standardize the interpretability across outcomes, and to incorporate a gamma distribution, the MMSE and HVLT-R–delayed and immediate scores were inverted (for example, 30 – MMSE) so that a lower score, or negative coefficient, meant better performance, similar to the other outcomes.

A previous study from our group characterized individual trajectories of cognitive decline over the 9-year follow-up (24). In these analyses, nonlinear rates of change were observed for TMT-B, HVLT-R–immediate, and HVLT-R–delayed recall. Thus a two-piece linear spline of time (25) was used to model the different rate of decline before and after examination 3 (0–3 and 3–9 years). In the current study, we also included the spline term for TMT-A for uniformity. The Purdue Pegboard was only available at examinations 1–3, so only one constant time slope was included.

In GEE models, there were three main coefficients of interest. The first coefficient was time (in years from the baseline examination), which indicated log mean change in cognitive test performance per year for someone whose cholesterol level was at the mean. As mentioned above, two time variables modeled the nonlinear changes in the cognitive tests. Performance on all tests declined over time (24). The second coefficient was baseline lipid level, which indicated the baseline difference (in log units) in cognitive test performance per standard deviation (*SD*) increase in lipids. The third coefficient represented the interaction between lipid levels and time. A significant value indicated that the rate of decline varied by baseline lipid level for examinations 1–3 and/or 3–6.

Lipids were first examined as continuous variables, per *SD* unit increase. We then examined total cholesterol by established, clinically relevant cutoffs that corresponded to normal, moderate, and high cholesterol based on National Cholesterol Education Program (NCEP) guidelines: $<$200, 200–239, and $\geq$240. For multivariate analyses, covariates were included depending on their association to the outcomes in univariate analyses ($p < .05$) and their importance based on the literature. Covariates were assessed at baseline and included age, race (white v non-white), education (continuous), serum creatinine levels, lipid-lowering medication

use, depressive symptoms as assessed by the Geriatric Depression Scale (GDS) (26), and vascular disease. The latter was composed of a continuous composite variable ranging from 0 to 7 based on adjudicated myocardial infarction (MI), diabetes, peripheral arterial disease, heart failure, and angina, and self-reported hypertension and ever smoking. TMT-B comprises two cognitive abilities: executive function and psychomotor speed. To isolate the executive function component, we controlled for TMT-A by adding the variable to the TMT-B model as a covariate.

To account for missing data in the outcomes, we implemented a multiple imputation procedure that replaced each missing value with a set of plausible values simulated from the observed data that were highly predictive of missingness, including baseline age, education, body mass index, and other observed values of the same outcome. The imputation was carried out via a Monte Carlo Markov Chain (27) under the assumption of multivariate normality for all missing variables and data missing at random (28). Based on the fraction of missing information, 20 imputed data sets were sufficient to provide stable estimates. Each imputed data set was then analyzed using GEE, and the resulting parameter estimates were appropriately combined across data sets to yield final estimates. Analyses were conducted using Stata Version 9 (StataCorp, College Station, TX).

Results

Baseline demographic and health characteristics are summarized in Table 1. Mean age was 74.5 years, and mean education 12.5 years; 81% were white. Forty-one percent had total cholesterol levels higher than 240 mg/dL. Fifty-four women (12.7%) reported taking lipid-lowering medications, the majority being statins. Almost half of the participants had been diagnosed with hypertension, 8% had a prior MI, and 5.4% had a prior stroke. Mean cognitive performances were within normal range using established norms. Participants had an average follow-up of 3.2 (SD = 1.7) visits, corresponding to 4.2 years (SD = 3.4). Of the 426 participants with available baseline cholesterol, 281 (66.1%) participated at examination 6 (9 years). Women lost to follow-up had lower baseline MMSE scores (27.6 vs 28.4, $p < .001$), lower education (11.7 vs 13.0 years, $p < .01$), and higher GDS scores (4.9 vs 3.7, $p < .01$) than did participants who remained in the study. There were no differences ($p > .1$) between the two groups with regard to baseline cholesterol levels.

We next examined the association between each individual baseline lipid level and cognitive decline using multivariate analyses (Table 2). Each SD unit increase in total (b = –0.019, $p = .015$), and HDL cholesterol (b = –0.018, $p = .025$) was associated with better baseline performance on the Purdue Pegboard. There was no Lipid × Time interaction, suggesting that rates of decline did not differ by baseline cholesterol levels. There was no baseline association between cholesterol and any other cognitive test.

For clinical purposes, we also examined cholesterol using standardized clinical cutoffs (<200, 200–239, ≥240 mg/dL). Forty-one percent ($n = 174$) of women had borderline high and 41% ($n = 172$) had high total cholesterol. There were no differences between the cholesterol groups, with regard to age, education, lipid-lowering medication use, stroke, or MI. In multivariate analyses (Table 3), there was a dose-response association between baseline total cholesterol and time on the Purdue Pegboard such that participants with total cholesterol ≥240 mg/dL (b = –1.960, $p = .023$) had the best performance, followed by participants with total cholesterol 200–239 mg/dL (b = –1.260, $p = .146$) relative to the <200 mg/dL reference group. The Lipid × Time interaction term was again not significant, and there was no association between these clinical cholesterol cutoffs and performance on any other cognitive test.

Lipid-lowering medication use was not associated with cognitive performance cross-sectionally or longitudinally, and excluding women taking lipid-lowering medications did not change the results (data not shown). There were also no interactions between lipid-lowering drug use and cholesterol or depression and cholesterol in relation to cognitive trajectories. In other analyses, we examined the effect of health on the cholesterol–cognition relationship separately by: (i) excluding participants with poor ($n = 5$) or fair ($n = 40$) self-reported health status at baseline and (ii) excluding

Table 1. Baseline Demographic and Health Characteristics in Participants With Baseline Cholesterol Levels ($N = 426$): Women's Health and Aging Study II

Variable	Mean (SD) or %
Age, y	74.5 (2.8)
Education, y	12.5 (3.3)
African American	19.0%
BMI, kg/m^2	26.7 (5.2)
Geriatric Depression Scale 30-item, cont.	4.1 (3.8)
Geriatric Depression Scale >10	6.8%
Total cholesterol, mg/dL	233.6 (38.7)
HDL cholesterol, mg/dL	56.7 (16.6)
Ever smoke	45.1%
Minutes moderate exercise per week	69.1 (61.2)
Systolic blood pressure	152.6 (21.7)
Diastolic blood pressure	76.9 (16.2)
Lipid-lowering medication use	12.7%
Ever diagnosed with:	
Stroke	5.4%
Diabetes	7.6%
Myocardial infarction	8.0%
Angina	9.9%
Hypertension	48.6%
Peripheral arterial disease	3.3%
Heart failure	1.4%
Cognitive tests*	
Trail Making Test, Part A (TMT-A)	46.4 (20.3)
Trail Making Test, Part B (TMT-B)	133.3 (75.9)
MMSE	28.1 (1.8)
HVLT-R, Immediate recall	22.7 (4.9)
HVLT-R, Delayed recall	8.1 (2.7)
Purdue Pegboard	26.0 (4.5)

Notes: *Values for the TMT-A, TMT-B, and Purdue Pegboard are the mean time to completion in seconds; those for the MMSE and HVLT are the mean total score.

SD = standard deviation; BMI = body mass index; HDL = high-density lipoprotein; MMSE = Mini-Mental State Examination; HVLT-R = Hopkins Verbal Learning Test-Revised.

Table 2. Longitudinal Multivariate Association Between Individual Baseline Serum Lipids and Cognition Over 9 Years

Blood Cholesterol (mg/dL) per *SD* Increase	Cholesterol Coefficient		Cholesterol × Time Examinations 1–3		Cholesterol × Time Examinations 4–6	
	B	*p* Value	*B*	*p* Value	*B*	*p* Value
TMT-A						
Total cholesterol	−0.009	.678	−0.006	.523	0.003	.528
HDL cholesterol	0.011	.647	0.005	.586	−0.003	.530
Total/HDL cholesterol ratio	−0.013	.569	−0.006	.520	0.003	.509
TMT-B						
Total cholesterol	−0.023	.336	0.005	.527	0.001	.846
HDL cholesterol	0.002	.945	−0.001	.979	−0.002	.589
Total/HDL cholesterol ratio	−0.018	.445	0.002	.796	0.004	.427
Pegboard*						
Total cholesterol	−0.019	.015	0.001	.683		
HDL cholesterol	−0.018	.025	0.003	.161		
Total/HDL cholesterol ratio	0.005	.568	−0.002	.526		
HVLT-R, Immediate Recall						
Total cholesterol	−0.003	.802	0.002	.707	0.001	.619
HDL cholesterol	0.014	.269	−0.003	.543	0.001	.680
Total/HDL cholesterol ratio	−0.013	.317	0.003	.446	−0.001	.850
HVLT-R, Delayed Recall						
Total cholesterol	−0.009	.642	−0.002	.719	0.002	.479
HDL cholesterol	0.010	.642	−0.007	.290	0.002	.523
Total/HDL cholesterol ratio	−0.011	.610	0.006	.344	−0.001	.670
MMSE						
Total cholesterol	0.024	.613	−0.003	.851	−0.010	.172
HDL cholesterol	−0.045	.333	0.003	.848	0.004	.610
Total/HDL cholesterol ratio	0.025	.584	0.005	.768	−0.009	.259

Notes: Each lipid was analyzed in a separate model controlling for age, race, education, serum creatinine levels, lipid-lowering drug use, depression, and vascular disease. For all cognitive tests, a negative number means better performance.

*The Purdue Pegboard was only available at examinations 1–3.

SD = standard deviation; TMT-A = Trail Making Test, Part A; HDL = high-density lipoprotein; TMT-B = Trail Making Test, Part B; HVLT-R = Hopkins Verbal Learning Test-Revised; MMSE = Mini-Mental State Examination.

participants with known stroke, diabetes, MI, or angina at baseline. The results remained unchanged (data not shown).

Discussion

In this population-based, longitudinal study of high-functioning older women, high baseline total cholesterol was selectively associated with a measure of motor speed, but not with cognitive abilities including memory, executive functioning, attention, and global cognition. Women with higher baseline total and HDL cholesterol performed faster at baseline on the Purdue Pegboard, whereas rates of decline were independent of cholesterol levels. Interestingly, this finding was not replicated with TMT-A, a measure of psychomotor speed.

Previous results have reported that high cholesterol was associated with better visuomotor (29) and psychomotor speed (30,31), attention, and concentration (15). One randomized controlled trial also found that lowering cholesterol levels using simvastatin, led to worse performance on psychomotor and attentional tests (32). Although our results suggest that high baseline cholesterol was associated with better performance on a measure of motor speed, we did not replicate this finding with psychomotor (TMT-A) and attentional tasks (TMT-B). One possible explanation for this potential contradiction is that peripheral cholesterol does not pass the blood–brain barrier (BBB) into the brain and, therefore, may be a better measure of peripheral versus cognitive processes. A more specific measure of brain cholesterol metabolism is 24S-hydroxycholesterol (24S-OHC), which is only formed in the brain but able to cross the BBB and be measured in peripheral blood. If cholesterol is associated with cognitive functioning, 24S-OHC may be a more precise measure.

It is biologically plausible that high cholesterol could be related to better motor speed, especially in later life. Cholesterol has many important functions, such as maintaining cell membranes, which is of particular importance to aging cells (33). Furthermore, a recent study reported that cholesterol availability is the critical prerequisite, and a rate-limiting step, of myelin growth (34). Myelin is fundamental in increasing the speed of neurotransmission, and therefore, motor responses. As normal processes slow with age, higher cholesterol levels may help counteract the effects of myelin deterioration. Future research should pursue the association between serum cholesterol and other peripheral measures of speed and efficiency, such as walking speed and frailty.

From the standpoint of biological aging, speed is often identified as one of the most robust observed metrics (35). MacDonald and colleagues (36) suggested that, instead of chronological aging, cognitive decline may be more influenced by biological aging and disease processes, such as

Table 3. Longitudinal Association Between Baseline Clinical Cholesterol Cutoffs and Cognition

Blood Cholesterol (mg/dL) per *SD* Increase	Cholesterol Coefficient		Cholesterol × Time Examinations 1–3		Cholesterol × Time Examinations 4–6	
	B	*p* Value	*B*	*p* Value	*B*	*p* Value
TMT-A						
Total cholesterol						
200–239 vs <200	−1.037	.674	0.808	.373	−0.382	.470
>240 vs <200	−0.475	.848	0.234	.805	−0.046	.925
TMT-B						
Total cholesterol						
200–239 vs <200	−1.910	.480	1.192	.305	0.444	.756
>240 vs <200	−2.017	.448	0.661	.473	0.062	.928
Pegboard						
Total cholesterol						
200–239 vs <200	−1.260	.146	0.273	.340		
>240 vs <200	−1.960	.023	0.081	.774		
HVLT-R, Immediate Recall						
Total cholesterol						
200–239 vs <200	−0.161	.910	0.475	.308	0.096	.698
>240 vs <200	−0.305	.827	0.295	.532	0.147	.544
HVLT-R, Delayed Recall						
Total cholesterol						
200–239 vs <200	0.216	.924	−0.017	.982	0.470	.231
>240 vs <200	−0.850	.703	0.006	.994	0.379	.272
MMSE						
Total cholesterol						
200–239 vs <200	−0.280	.955	−1.331	.460	−0.271	.755
>240 vs <200	4.875	.331	−0.257	.887	−1.291	.133

Notes: All models control for age, race, education, serum creatinine levels, lipid-lowering drug use, depression, and vascular disease. For all cognitive tests, a negative number means better performance.

SD = standard deviation; TMT-A = Trail Making Test, Part A; HDL = high-density lipoprotein; TMT-B = Trail Making Test, Part B; HVLT-R = Hopkins Verbal Learning Test-Revised; MMSE = Mini-Mental State Examination.

central nervous system integrity. Low lipid levels may contribute to an overall reduced neuronal functioning, and myelin integrity, thus globally affecting processing speed, but not other cognitive abilities. Additional research with longer follow-up is needed to determine whether lipid levels are a causal factor or a subsequent marker in the biological aging process.

High cholesterol levels measured in late life may not be as detrimental to cognitive processes as high levels in midlife. Persons who survive to old age with high cholesterol may be a more robust, and select, population and therefore not as susceptible to the adverse effects of high lipid levels in late life, in this case cognitive decline. Indeed, longitudinal studies of older adults have found no association between high cholesterol and all-cause mortality (37,38), and some even reported an association between hypercholesterolemia and reduced mortality (39,40). This interpretation suggests that it may not be possible to extrapolate findings from midlife to late life.

There are limitations that warrant future consideration. First, the study population consisted of high-functioning older women, and may not generalize to men or younger persons. Second, lipid levels were examined only at baseline; future investigations will need to examine the effects of time-dependent changes in lipid levels and changes in cognition. Third, blood samples were not fasting. Last, use of serum total cholesterol limits our ability to examine the specificity to which lipids are associated with cognition because cholesterol is not transported from the periphery through the BBB to brain; serum 24S-OHC may better reflect ongoing brain cholesterol metabolism.

Advantages of the WHAS II study design include the use of a representative cohort selected to be high-functioning at baseline and followed for 9 years, with repeated neuropsychological assessments extending beyond global cognition. Furthermore, loss to follow-up was minimal. Our ability to observe a significant and specific association in this initially high-functioning cohort may be magnified or extended to cognitive abilities with the progression of functional decline.

In this population-based study of older women, high baseline cholesterol was selectively associated with better motor speed, but not with cognitive abilities. Additional research is needed to determine whether high cholesterol is selectively associated with neural brain functioning or whether this association extends more broadly to other biological systems such as physical functioning and mobility. This finding adds to the current literature suggesting that high cholesterol levels in elderly women may not be associated with the same level of risk as high cholesterol levels in midlife, with regard to subsequent cognitive decline. We do not, however, currently advocate that cholesterol levels should be raised in elderly persons or that patients should be taken off statins for the purpose of regaining speed and enhanced neural transmission. Although high cholesterol

might be beneficial for faster processing speed, it is still a risk factor for cardiovascular disease. Concern about risk for the latter likely outweighs even a small benefit in processing speed, especially when high cholesterol does not appear to be associated with cognition in later life.

Acknowledgment

This research was supported in part by National Institute on Aging grants R37 AG19905 and R01 AG19825-01 and by the Johns Hopkins Older Americans Independence Center (1P50AG 021334-01).

Correspondence

Address correspondence to Michelle M. Mielke, PhD, Johns Hopkins University School of Medicine, Center on Aging and Health and Department of Psychiatry, Division of Geriatric Psychiatry and Behavioral Sciences, 550 N. Broadway, Suite 308, Baltimore, MD 21205. E-mail: mmielke1@jhmi.edu

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Received January 17, 2007
Accepted August 26, 2007
Decision Editor: Luigi Ferrucci, MD, PhD