Serum cholesterol concentrations are associated with visuomotor speed in men: findings from the third National Health and Nutrition Examination Survey, 1988–1994[1–3]

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ABSTRACT

Background: Current international recommendations advise aggressive treatment of relative hypercholesterolemia despite an incomplete understanding of any neurobehavioral effects of low or lowered serum cholesterol.

Objective: The objective was to examine the relation between serum cholesterol concentrations and performance in immediate memory, visuomotor speed, and coding speed tests.

Design: The participants were 4110 adults aged 20–59 y who completed a set of neurobehavioral tests and had blood specimens collected as a part of the third National Health and Nutrition Examination Survey, 1988–1994.

Results: After adjustment for sociodemographic variables, serum trace elements and vitamins, dietary energy intake, and risk factors for cardiovascular disease, we found inverse linear associations of serum total cholesterol and non-HDL cholesterol with visuomotor speed in men. The least-squares mean (± SE) visuomotor speeds were 231.6 ± 2.6, 224.0 ± 2.2, and 218.9 ± 2.5 ms, respectively, for men with serum total cholesterol concentrations below the 25th, between the 25th and the 75th, and at or above the 75th percentile (*P* for trend < 0.001) and were 231.7 ± 2.7, 225.8 ± 2.4, and 214.1 ± 2.3 ms, respectively, for men with a non-HDL-cholesterol concentration below the 25th, between the 25th and the 75th, and at or above the 75th percentile (*P* for trend < 0.001). No significant associations were observed between memory or coding speed and the selected serum cholesterol measures in men, and the scores of the 3 neurobehavioral tests were unrelated to serum cholesterol in women.

Conclusion: Low serum total cholesterol and non-HDL cholesterol are associated with slow visuomotor speed in young and middle-aged men. *Am J Clin Nutr* 2004;80:291–8.

KEY WORDS Serum cholesterol, HDL cholesterol, LDL cholesterol, visuomotor speed, coding speed, memory, third National Health and Nutrition Examination Survey, NHANES III, cognitive function

INTRODUCTION

Cholesterol management is central to the prevention of coronary artery disease. However, published recommendations concerning both the treatment of high serum cholesterol and public health advice affect many millions of people and could have unintended psychological, neurologic, or behavioral effects (1). Increasing evidence from laboratory (2, 3) and animal (4, 5) studies suggests that circulating lipids can influence neurochemistry, neurophysiology, learning, and other aspects of cognitive function, leading to speculation about a relation between serum lipid concentrations and psychological well-being and behaviors in humans (6, 7). Three studies in humans that assessed the cross-sectional association between cholesterol and cognitive function found some evidence that high serum cholesterol concentrations or high consumption of cholesterol and other lipids was associated with better cognitive function (8–10). Similarly, low serum cholesterol concentrations were found to predict cognitive decline in prospective studies of aging American twins (11) and elderly Finns (12). These observations were reinforced by the findings of some (13, 14) but not all (15) clinical trials that studied the effects of cholesterol-lowering interventions on cognitive function. We sought to expand the literature on cholesterol and cognitive function by examining the associations between serum cholesterol and scores on neurobehavioral tests in young and middle-aged adults from a representative US population survey.

SUBJECTS AND METHODS

Study population

We analyzed the data from the third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional national survey of US civilians living in households conducted from 1988 to 1994. The sampling scheme was a stratified, multistage probability design with oversampling of African Americans and Mexican Americans to allow more precise estimates. Detailed descriptions of the survey were published elsewhere (16–19).

The participants selected for the neurobehavioral tests were a systematically selected half-sample of persons aged 20–59 y who were tested at a mobile examination center. Those with

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odd-numbered survey identification numbers participated in neurobehavioral tests, and those with even numbers participated in an allergy test. Persons who could speak neither English nor Spanish or who were legally blind were not given the test. Of those participating in the neurobehavioral tests, 534 did not complete the SRT (the simplest test) or completed the test but had an outlier, and 417 had no hematologic information. A total of 470 participants were excluded from the current analysis because they were pregnant ($n = 113$), had a history of cancer (including skin cancer, $n = 144$), or were participating in a cholesterol-lowering intervention ($n = 473$). An additional 30 participants were excluded because they had a history of a stroke or experienced a recent stroke that could compromise cognitive performance. Data from the remaining 2152 women and 1958 men were used for the current study.

Cognitive function assessment

NHANES III involved 3 neurobehavioral tests selected from a computerized test battery called the Neurobehavioral Evaluation System (17, 20, 21), which was designed to measure neurobehavioral performance in populations occupationally or environmentally exposed to chemicals. This system has been used to investigate the neurotoxic effects of organic solvents, organophosphate pesticides, nitrous oxide, lead, and mercury (19). The neurobehavioral tests administered in NHANES III were simple reaction time (SRT), symbol-digit substitution (SDS), and serial digit learning (SDL) test.

Visuomotor speed

Visuomotor speed was measured by the SRT test. The participant rested an index finger on a push button and pressed the button as quickly as possible whenever a solid square (4×4 cm) was displayed in the center of a blank computer screen. The square remained on the screen until the participant pressed the button, after which it was cleared from the screen. If there was no response, the square was cleared from the screen after an elapsed time of 1000 ms. The measured response was the latency (in ms) between the time of appearance of the square on the screen and the time when the participant pressed the button. Therefore, a better performance was associated with a shorter latency. A total of 50 trials were administered to each participant. The interval between trials varied randomly according to a uniform distribution ranging from 2.5 to 5.0 s to limit anticipatory responses. The mean reaction time of trials 11–50 was calculated. Values $\leq$50 or $\geq$750 ms were considered outliers and were not included in the calculation (19).

Coding speed

Coding speed was measured by the SDS test. On the upper half of the computer screen, the subject was presented with a grid that paired 1 of 9 different symbols with 1 of the digits from 1 to 9. A similar grid was displayed on the bottom half of the screen with the same symbols presented in a scrambled order and the spaces for the corresponding digits left blank. The participant was asked to enter, as quickly as possible, the matching digit for each symbol. A total of 5 trials were conducted with a different pairing of digits and symbols on each trial. The amount of time (in s) required to enter each digit was recorded, and the total latency of the last 4 trials was calculated. A quick coding speed was associated with a shorter latency. The SDS test score was modestly correlated with that of the SRT test (Pearson $r = 0.35$).

Learning and immediate memory

Learning and immediate memory were measured by the SDL test. The participant was presented with a series of digits displayed one at a time on the computer screen. Each digit was displayed on the screen for 0.6 s with intervals of 0.6 s between digits. After all the digits were displayed, the participant was asked to press the numeric keys to enter the entire sequence of numbers in the order in which they were presented. All the trials contained the same 8-digit sequence. Testing continued until the subject responded correctly on 2 consecutive trials or until the subject attempted 8 trials. For each trial, 2 points were credited when $<$6 of the 8 digits were in the correct position, 1 point when either 6 or 7 digits were in the correct position, and 0 points when all 8 digits were reported correctly. The score used in the current study represents the sum of the error scores for each trial. A lower score reflects better learning and immediate memory. The SDL test score was modestly correlated with the SDS score (Pearson $r = 0.49$) and was weakly correlated with the SRT score (Pearson $r = 0.27$).

Measurements of serum cholesterol

NHANES III participants were randomly assigned to a morning or a nonmorning group. Most participants from the nonmorning group did not fast 12 h before a blood sample was collected. During the health examination, blood samples were collected from examinees across a range of fasting statuses and were processed according to a standard protocol (16). We selected 3 cholesterol measures: serum total cholesterol (TC), HDL cholesterol, and non-HDL cholesterol (NHDLC). LDL cholesterol was calculated by using the Friedewald equation, and a substantial percentage of participants had missing LDL-cholesterol values because of limitations with the Friedewald equation (22) or participants' fasting status. Therefore, the current study used NHDLC (TC $-$ HDL cholesterol) rather than LDL cholesterol. All cholesterol measures were categorized into 3 sex-specific levels: high, at or above the 75th percentile (men: TC $\geq$224 mg/dL, HDL cholesterol $\geq$52 mg/dL, and NHDLC $\geq$178 mg/dL; woman: TC $\geq$215 mg/dL, HDL cholesterol $\geq$63 mg/dL, and NHDLC $\geq$166 mg/dL); low, below the 25th percentile (men: TC $<$169 mg/dL, HDL cholesterol $<$36 mg/dL, and NHDLC $<$120 mg/dL; woman: TC $<$169 mg/dL, HDL cholesterol $<$44 mg/dL, and NHDLC $<$111 mg/dL); and intermediate (the remaining subjects).

Definition of covariates

Covariates were selected from the literature(19, 23–25) and included demographic variables (eg, age, income, and education), questionnaire variables [eg, previous night's night sleep (more than usual, not more than usual); energy level (tired, not tired); consumption of coffee, tea, or cola in the past 3 h (yes, no); and consumption of alcohol in the past 3 h (yes, no)]. The risk factors for cardiovascular diseases included current cigarette smoker (yes, no), current alcohol drinker (yes, no), high blood pressure (yes, no), waist-to-hip ratio [high ($>$1.00 for men and $>$0.80 for women) and low], and leisure-time physical activity. Smokers were defined as those who had smoked cigarettes in the past 5 d, and drinkers were those who had consumed $\geq$12 drinks

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in the previous 12 mo. Hypertension was defined in 2 ways: uncontrolled hypertension (a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg) and hypertension that necessitated medication. Serum trace elements; vitamins C, E, and A; carotenoids (α-carotene, β-carotene); calcium; iron; and lead were measured. Vitamin E and β-carotene are fat-soluble and correlated with TC; these variables are reported per unit of cholesterol. We also measured serum total protein and serum albumin concentrations and determined daily dietary energy intakes from a 24-h dietary recall as indicators of malnutrition or energy deprivation. Serum glucose was used to control for acute effects of low energy intake. For the women, we were concerned about possible confounding from menopausal status and created an indicator variable for menopausal status by dichotomizing the continuous age variable by using 51 y (the average age when menopause starts) as the cutoff. Depression has been identified as a risk factor for poor cognitive performance (26, 27) and has been linked with low serum cholesterol concentrations as well. Because a diagnosis of depression was available only for adults aged 19–39 y in NHANES III, we controlled for depression in the secondary analysis.

Statistical methods

As recommended by the National Center of Health Statistics, we used SUDAAN software (28) (SAS-callable version 7.5; SAS Institute, Research Triangle Park, NC) with appropriate weighting and nesting variables (16–19). In all analyses that related cognitive function to serum cholesterol or covariates, we controlled for age (continuous). No data transformation was performed. Because this study evaluated results from 3 neurobehavioral tests, a Bonferroni adjustment of the α level to $P < 0.017$ (0.05/3) was considered when examining the association between any domain of cognitive function and serum cholesterol.

Preliminary analyses indicated that a sex difference was prominent; therefore, the formal analyses were performed separately by sex. Before multivariable modeling, we examined the association between each domain of cognitive function and each covariate. If a covariate in continuous form was shown to not be related with poor performance on the neurobehavioral tests, further examination was made by using percentiles or clinically recommended cutoffs, if available, to identify a possible nonlinear association. For illustration purposes only, all serum elements—including 3 cholesterol measures—were categorized into 3 sex-specific levels: at or above the 75th percentile, between the 25th and the 75th percentile, and below the 25th percentile. Daily dietary energy intake was categorized in the same way. However, in the multivariable regression, the continuous variables that were categorized for reporting remained in continuous form if the R^2 value of the regression model was better than that obtained with the use of categorized variables. Multivariable models were generated in a stepwise fashion for each neurobehavioral test. In the first step, the main effect and covariates, for which the overall P values of age-adjusted means were <0.20, were entered into the model. In the second step, the covariates with a P value > 0.10 were dropped, and the interactions between main effect and vitamins E and A per cholesterol unit, dichotomized age variables, and ethnicity were tested. We kept the covariates with P values of regression coefficients <0.05 in multivariable models. However, to avoid overadjustment and to increase the precision of estimates, we removed any covariate whose addition to the multivariable model resulted in a change of $<10\%$ in the mean score of cognitive measures. The main effects were always retained. The least-squares means of each test score were calculated for each level of main effects from the finalized regression models. Regression models with cholesterol in continuous form were also run to assess the linear relations. Finally, we conducted a secondary analysis of data on participants aged 19–39 y to examine whether the inclusion of depression altered the findings from the overall sample.

RESULTS

Selected characteristics of the men and women are provided and compared in **Table 1**. The average age of the subjects was ≈37 y, and 89% of the men and 87% of the women were non-African Americans. There were significant differences between men and women in most of the characteristics presented in this table. For example, compared with men, women had a more favorable serum cholesterol profile (ie, lower NHDLC and higher HDL-cholesterol concentrations) and they performed more slowly in the visuomotor speed test but more quickly in the coding speed test.

As shown in **Table 2**, the performances on the neurobehavioral tests were associated with many factors. The average scores for all 3 tests increased with age and decreased as the education level increased. Serum antioxidants (eg, vitamin E, β-carotene, and selenium) were associated with memory and coding speed in both sexes. The concentrations of serum albumin, total protein, and serum glucose were associated with performance on different tests at P values <0.017. The adults with regular leisure-time physical activity performed significantly better on all 3 tests than did the adults who had no leisure-time physical activity. Low dietary energy intake resulted in a poor immediate memory and slow coding speed for both men and women.

After adjustment for age only (data not shown), the difference in visuomotor speed between the men with high or low TC concentrations was 9.7 ms ($P < 0.017$); there was no significant difference in visuomotor speed in the women with different cholesterol concentrations. However, the women with high age-adjusted HDL-cholesterol concentrations performed significantly better on the immediate memory tests than did the women with low HDL-cholesterol concentrations ($P < 0.017$). High age-adjusted HDL-cholesterol concentrations were also associated with a quick coding speed in women. To address potential confounding by other factors known to affect cognitive function, we conducted multivariable regressions that included serum trace elements and vitamins, macronutrients, leisure-time physical activity, and daily dietary energy intake as covariates. All the associations diminished from the age-adjusted results in women, but the association between serum cholesterol and visuomotor speed in men strengthened somewhat after multivariable adjustment. The least-square mean visuomotor speed values were 231.6 ± 2.6 ms for men with a low TC concentration and 218.9 ± 2.5 ms for men with a high TC concentration (**Table 3**). The difference in visuomotor speed between subjects with high and low TC concentrations was 12.7 ms (231.6 − 218.9), and the difference in visuomotor speed between subjects with high and low NHDLC concentrations was as much as 17.5 ms (231.7 − 214.2). A series of multiple linear regression analyses with TC in continuous form showed a decrement of 5.0 ± 1.2 ms ($P < 0.001$) in visuomotor speed for each 1-mmol/L (39-mg/dL) increase in serum TC concentration. In the secondary analysis, in

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Table 1
Selected demographic characteristics and serum profiles for 4110 men and women aged 20–59 y: third National Health and Nutrition Examination Survey, 1988–1994

Demographic characteristic and serum indicator	Men ($n = 1958$)	Women ($n = 2152$)
Sociodemographic variables		
Ethnicity, non-African American (%)[1]	88.9 ± 0.9	87.3 ± 1.1
Education, above high school (%)[1]	78.5 ± 1.7	81.6 ± 1.5[2]
Age (y)[3]	36.6 ± 0.3	36.84 ± 0.4
Family income index[3,4]	3.1 ± 0.1	2.99 ± 0.10
Health risk factors		
Physical activity, inactive (%)[1]	14.5 ± 1.4	22.5 ± 1.5[5]
Hypertension, yes (%)[1]	12.7 ± 1.0	5.8 ± 0.8[5]
Total serum cholesterol (mg/dL)[3]	193.5 ± 1.4	191.2 ± 1.3
HDL cholesterol (mg/dL)[3]	46.6 ± 0.7	54.7 ± 0.6[6]
Non-HDL cholesterol (mg/dL)[3]	146.9 ± 1.7	136.5 ± 1.6[6]
Other serum indicators[3]		
Total protein (g/dL)	7.4 ± 0.03	7.26 ± 0.02[6]
Albumin (mg/dL)	4.4 ± 0.03	4.13 ± 0.02[6]
Cotinine (ng/mL)	107.9 ± 6.2	71.52 ± 6.0[6]
Lead (μg/dL)	4.2 ± 0.1	2.34 ± 0.1[6]
Vitamin E/total cholesterol (mg/mg)	5.3 ± 0.1	5.32 ± 0.1
Vitamin A/total cholesterol (μg/mg)	0.3 ± 0.01	0.28 ± 0.01
Cognitive function[3]		
Visuomotor speed (ms)	224.9 ± 1.8	239.64 ± 1.8[6]
Immediate memory scores	4.3 ± 0.2	4.39 ± 0.2
Coding speed (s)	93.4 ± 1.1	87.37 ± 1.0[6]

[1] Percentage ± SEM.
[2] Significantly different from men, $P < 0.05$ (Cochran-Mantel-Haenszel test).
[3] $\bar{x}$ ± SEM.
[4] Calculated on the basis of family income and family size. An index <1 is normally categorized as below the poverty line.
[5] Significantly different from men, $P < 0.01$ (Cochran-Mantel-Haenszel test).
[6] Significantly different from men, $P < 0.01$ (*t* test)

which a history of depression was an additional covariate, all of the estimates remained unchanged relative to the overall sample (data not shown).

DISCUSSION

Using a nationally representative sample, we documented that low serum TC and low serum NHDLC concentrations are significantly associated with slow visuomotor speed in young and middle-aged men. All of these associations are independent of sociodemographic factors, daily dietary energy intake, leisure-time physical activity, and serum trace elements, vitamins, and macronutrients. We did not observe an association between serum cholesterol and the performance on neurobehavioral tests in women.

The main findings of the current study are consistent with those of previous studies. In a naturalistic cross-sectional study of 177 healthy adults aged 25–60 y of both sexes, Muldoon et al (9) observed an association between poor performance on the Block Design Test and low serum TC. Similarly, Benton (10) reported a relation between low TC and slow mental speed from the results of a choice reaction time test in college students. These observations from cross-sectional studies were reinforced by findings from a clinical trial (13), which found decreased cognitive performance on tests for attention and psychomotor speed in hypercholesterolemic persons after treatment with lovastatin, and by findings from a twin study, which found that low serum TC concentrations predicted a decline in SDS performance (11). The principal similarity in cognitive demand between the Block Design, Choice Reaction Time, and SDS tests and the SRT in the current study is the speed of information processing. All of these tests require visuoconstructional abilities and rapid manipulation of information. A sex difference was salient in the current study, which may have been due to sex hormones or to other unmeasured sex-related factors. We observed that men were quicker than were women on the visuomotor speed test; the effect of low serum cholesterol on visuomotor speed might be more salient in a population with a rapid basal speed.

The origins of these relations between TC, NHDLC, and measures of visuomotor speed are not clear. The current study provides additional evidence to rule out some proposed explanations. Muldoon et al (13) speculated that lovastatin penetrates the central nervous system and, conceivably, cognitive effects may be the result of neuropharmacologic actions that are independent of cholesterol lowering. Statin drugs lower circulating concentrations of vitamin E and ubiquinone and may affect the synthesis of polyunsaturated fatty acids, which are integral to neuronal membranes (27). The association we observed may be independent of any neuropharmacologic actions because, in the current study, the participants were not taking any cholesterol-lowering medications. Cholesterol is a component of circulating complex lipoprotein particles that carry phospholipids, triacylglycerol, and many micronutrients such as β-carotene and vitamin E (9). Vitamin E has been shown to be related to cognitive function

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Table 2
Age-adjusted cognitive function scores by level of covariate for 4110 men and women aged 20–59 y: third National Health and Nutrition Examination Survey, 1988–1994

	Median		Visuomotor speed		Coding speed		Immediate memory	
Covariate	Men	Women	Men	Women	Men	Women	Men	Women
Age group (y)			*ms*		*s*			
20–29, reference			223.7 ± 2.7[1]	234.4 ± 1.9	84.9 ± 1.8	77.9 ± 1.1	3.7 ± 0.3	3.4 ± 0.2
30–39			223.4 ± 2.8	238.7 ± 2.4	88.0 ± 1.2	81.9 ± 1.2[2]	4.0 ± 0.3	4.2 ± 0.3
40–49			226.9 ± 4.0	241.4 ± 3.8	100.5 ± 2.2[2]	93.9 ± 1.8[2]	4.3 ± 0.3	5.1 ± 0.3[2]
≥50			228.2 ± 4.3	250.5 ± 4.3[2]	116.2 ± 2.9[2]	110.7 ± 3.0[2]	6.4 ± 0.5[2]	6.0 ± 0.5[2]
P for trend			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Education (y)								
≥12, reference			220.9 ± 1.7	235.6 ± 2.0	87.3 ± 0.7	82.1 ± 0.8	3.6 ± 0.1	3.7 ± 0.2
6–11			237.5 ± 4.8[2]	255.8 ± 3.9[2]	111.2 ± 2.2[2]	108.4 ± 2.0[2]	6.7 ± 0.4[2]	7.2 ± 0.4[2]
<6			251.5 ± 6.8[2]	273.0 ± 12.1[2]	144.6 ± 6.8[2]	138.4 ± 9.5[2]	10.6 ± 0.8[2]	11.5 ± 1.2[2]
P for trend			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Vitamin E/cholesterol (μg/mg)[3]								
High, reference	6.6 ± 0.12	6.6 ± 0.1	228.4 ± 3.7	236.5 ± 3.6	93.0 ± 2.6	85.5 ± 1.8	4.0 ± 0.3	3.7 ± 0.3
Intermediate	5.0 ± 0.03	5.1 ± 0.03	221.1 ± 2.0	238.9 ± 2.2	91.6 ± 1.2	85.8 ± 1.2	4.1 ± 0.2	4.2 ± 0.3
Low	4.1 ± 0.03	4.1 ± 0.03	230.1 ± 3.3	243.9 ± 3.8	97.5 ± 1.3	92.1 ± 1.4[2]	4.8 ± 0.3	5.2 ± 0.3[2]
P for trend			0.14	0.34	0.01	0.01	0.04	<0.001
β-Carotene/cholesterol (μg/mg)[3]								
High, reference	0.13 ± 0.01	0.18 ± 0.004	222.7 ± 3.0	235.3 ± 2.7	92.5 ± 2.0	81.5 ± 1.3	4.3 ± 0.2	3.6 ± 0.3
Intermediate	0.06 ± 0.001	0.08 ± 0.001	225.4 ± 2.4	237.0 ± 2.3	92.3 ± 1.3	88.6 ± 1.1[2]	3.9 ± 0.2	4.5 ± 0.2[2]
Low	0.03 ± 0.001	0.04 ± 0.001	226.6 ± 2.6	249.5 ± 3.3[2]	96.9 ± 1.4	91.1 ± 1.6[2]	5.3 ± 0.3	5.0 ± 0.3[2]
P for trend			0.59	0.01	0.02	<0.001	0.01	0.01
Serum selenium (ng/mL)[3]								
High, reference	142.5 ± 1.0	140.7 ± 0.8	225.9 ± 3.0	237.7 ± 2.0	91.3 ± 1.7	85.3 ± 1.3	4.0 ± 0.3	3.8 ± 0.2
Intermediate	125.0 ± 0.1	120.5 ± 0.6	222.2 ± 2.4	240.3 ± 2.6	91.5 ± 1.3	87.0 ± 1.3	4.1 ± 0.2	4.5 ± 0.2
Low	108.5 ± 0.1	104.9 ± 0.7	229.9 ± 3.5	239.2 ± 2.3	100.0 ± 2.1[2]	90.2 ± 1.5[2]	5.1 ± 0.3[2]	4.8 ± 0.3[2]
P for trend			0.19	0.59	0.01	0.02	0.03	0.01
Serum albumin (g/dL)[3]								
High, reference	4.7 ± 0.02	4.4 ± 0.01	217.8 ± 2.4	240.5 ± 2.7	89.8 ± 1.5	85.2 ± 1.3	3.4 ± 0.3	4.1 ± 0.3
Intermediate	4.3 ± 0.01	4.1 ± 0.02	224.9 ± 2.6	236.2 ± 2.0	93.7 ± 1.1[2]	86.1 ± 1.2	4.3 ± 0.2	4.1 ± 0.2
Low	3.9 ± 0.01	3.7 ± 0.01	234.0 ± 2.9[2]	247.1 ± 4.0	97.4 ± 2.0[2]	93.3 ± 2.4[2]	5.0 ± 0.4	5.5 ± 0.4[2]
P for trend			<0.001	0.01	<0.01	0.01	0.05	0.01
Serum total protein (g/dL)[3]								
High, reference	7.80 ± 0.01	7.64 ± 0.01	226.5 ± 2.9	244.6 ± 2.3	95.8 ± 1.8	90.8 ± 1.4	4.6 ± 0.3	5.0 ± 0.3
Intermediate	7.32 ± 0.01	7.15 ± 0.01	226.0 ± 2.4	238.2 ± 3.0	93.8 ± 1.5	87.2 ± 1.5	4.4 ± 0.3	4.2 ± 0.2
Low	6.83 ± 0.02	6.72 ± 0.02	220.8 ± 2.1	234.5 ± 3.0[2]	89.4 ± 1.4	82.5 ± 1.2[2]	3.7 ± 0.4	3.7 ± 0.3[2]
P for trend			0.11	0.02	0.13	<0.001	0.03	0.01
Serum glucose (mg/dL)[3]								
High, reference	100.8 ± 0.7	98.7 ± 0.7	227.6 ± 3.0	248.0 ± 2.6	93.9 ± 1.6	90.3 ± 1.7	4.9 ± 0.3	4.7 ± 0.3
Intermediate	89.3 ± 0.3	86.5 ± 0.3	224.6 ± 2.1	236.6 ± 1.9	92.7 ± 1.1	85.7 ± 1.2	4.1 ± 0.2	4.3 ± 0.2
Low	77.5 ± 0.5	77.1 ± 0.3	219.9 ± 3.0	236.1 ± 2.6	94.4 ± 2.1	87.2 ± 1.8	3.6 ± 0.3	4.0 ± 0.3
P for trend			0.13	0.01	0.59	0.03	0.001	0.24
Daily dietary energy intake (kcal/d)[3]								
High, reference	4,181.6 ± 72.5	2,753.4 ± 52.9	224.2 ± 2.3	237.5 ± 2.5	91.4 ± 1.2	85.8 ± 1.4	3.6 ± 0.2	3.9 ± 0.2
Intermediate	2,691.7 ± 37.6	1,799.4 ± 23.5	224.4 ± 2.2	237.0 ± 2.3	91.8 ± 1.2	84.7 ± 1.2	4.2 ± 0.2	4.3 ± 0.3
Low	1,642.7 ± 24.9	1,078.3 ± 28.0	227.1 ± 4.1	247.0 ± 3.7	99.3 ± 2.3[2]	94.4 ± 1.7[2]	5.3 ± 0.4[2]	5.2 ± 0.3[2]
P for trend			0.81	0.03	0.01	0.01	<0.001	<0.001
Physical activity								
Regular, reference			217.1 ± 1.7	230.8 ± 2.5	87.8 ± 1.2	81.8 ± 1.2	3.6 ± 0.2	3.4 ± 0.2
Irregular			227.3 ± 2.4[2]	238.7 ± 1.8[2]	95.1 ± 1.1[2]	86.5 ± 1.1[2]	4.4 ± 0.2[2]	4.3 ± 0.2[2]
None			237.4 ± 6.1[2]	253.1 ± 3.2[2]	102.0 ± 2.4[2]	96.6 ± 1.9[2]	5.8 ± 0.4[2]	6.0 ± 0.4[2]
P for trend			<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[1] $\bar{x}$ ± SEM (all such values).
[2] Significantly different from the reference group, $P < 0.05$ (Bonferroni adjustment).
[3] Sex-specific distribution: high, at or above the 75th percentile; intermediate, between the 25th and 75th percentiles; low, below the 25th percentile.

because of its antioxidant properties (29). Researchers, therefore, speculate that low concentrations of one or more components of lipoprotein particles circulating in the bloodstream may produce subtle but measurable impairments of mental processes by influencing the supply of fat-soluble micronutrients, specifically, vitamin E, β-carotene, and vitamin A (9). This hypothesis was

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Table 3
Multivariable-adjusted cognitive function scores by level of selected serum cholesterol in 4110 men and women aged 20–59 y: third National Health and Nutrition Examination Survey, 1988–1994[1]

	Median		Visuomotor speed		Coding speed		Immediate memory	
Serum cholesterol	Men	Women	Men	Women	Men	Women	Men	Women
Total cholesterol[2]	*mg/dL*		*ms*		*s*			
High, reference	242.0 ± 1.6	237.8 ± 2.0	218.9 ± 2.5	237.7 ± 2.9	92.1 ± 1.4	85.8 ± 1.1	4.4 ± 0.3	4.3 ± 0.2
Intermediate	193.3 ± 1.4	189.7 ± 9.9	224.0 ± 2.2	240.6 ± 2.0	93.4 ± 1.0	85.4 ± 0.8	4.4 ± 0.3	4.5 ± 0.2
Low	152.3 ± 1.1	152.2 ± 1.0	231.6 ± 2.6[3]	238.8 ± 2.3	94.3 ± 1.3	87.8 ± 0.9	4.1 ± 0.2	4.1 ± 0.2
P for trend			0.001	0.58	0.62	0.12	0.60	0.15
HDL cholesterol[2]								
High, reference	60.1 ± 0.6	69.7 ± 0.7	220.7 ± 2.6	239.6 ± 2.4	94.7 ± 1.3	86.7 ± 0.8	4.2 ± 0.2	4.2 ± 0.2
Intermediate	43.4 ± 0.4	51.9 ± 0.5	225.5 ± 2.4	239.0 ± 1.9	94.1 ± 1.0	86.7 ± 0.8	4.2 ± 0.2	4.5 ± 0.2
Low	31.8 ± 0.7	38.4 ± 0.4	227.6 ± 2.3	240.7 ± 3.7	90.3 ± 1.3	84.2 ± 1.0	4.7 ± 0.2	4.2 ± 0.2
P for trend			0.33	0.86	0.11	0.89	0.07	0.06
Non-HDL cholesterol[2]								
High, reference	193.6 ± 2.3	183.6 ± 1.9	214.2 ± 2.3	236.6 ± 3.5	90.5 ± 1.3	85.7 ± 1.0	4.3 ± 0.3	4.1 ± 0.2
Intermediate	149.3 ± 1.2	132.9 ± 1.2	225.8 ± 2.4[3]	240.8 ± 2.1	94.0 ± 1.1	86.3 ± 0.8	4.5 ± 0.2	4.6 ± 0.2
Low	101.3 ± 1.4	97.2 ± 0.7	231.7 ± 2.7[3]	239.3 ± 2.5	94.4 ± 1.2	86.3 ± 0.9	4.0 ± 0.2	4.1 ± 0.2
P for trend			<0.001	0.58	0.16	0.91	0.07	0.06

[1] The variables race-ethnicity and years of education were significant in all multivariable models. Other terms in the final multivariable models for sex-specific models were as follows: immediate memory models (men: visuomotor speed, coding speed, dietary energy intake, serum β-carotene, and leisure-time physical activity; women: visuomotor speed, coding speed, serum iron, and waist-to-hip ratio), visuomotor speed models (men: family income, waist-to-hip ratio, and serum albumin, lead, iron, and total protein; women: age, β-carotene, current alcohol consumption, and leisure-time physical activity), speed models (men: age, income, visuomotor speed, and dietary energy intake; women: age, serum glucose, immediate memory test score, and visuomotor speed). Because of a high correlation between total cholesterol and non-HDL cholesterol, the regression model using total cholesterol as the main effect did not include non-HDL cholesterol, and the model using non-HDL cholesterol as the main effect did not include total cholesterol.

[2] Sex-specific distribution: high, at or above the 75th percentile; intermediate, between the 25th and 75th percentiles; low, below the 25th percentile.

[3] Significantly different from the reference group, $P < 0.05$ (Bonferroni adjustment).

not supported by the findings of the current study. Adjustment for β-carotene and vitamin E did not weaken the association. Alternatively, other investigators suggested that any intellectual impairment might be related to some illness or environmental variable (including dieting) that resulted in energy deprivation or weight loss and not to low serum cholesterol concentrations (30, 31). Our results suggest that this is not the case because inclusion of serum total protein, serum albumin, glucose, and daily dietary energy intake did not materially change the estimates of the main effects.

Compared with the typical findings that occur in intoxicated or brain-injured patients, the association between low serum cholesterol and visuomotor speed observed in the current study might be considered small. Its clinical relevance, however, would be well demonstrated when compared with the aging-related declines in visuomotor speed. After adjustment for potential confounders, we observed that visuomotor speed increased by 0.09 ± 0.15 ms for each 1-y age increase ($P > 0.10$; data not shown in detail). Therefore, from the ages of 30–59 y, the cumulative increase in mean visuomotor speed would be ≈3 ms, which was only 25% of the difference (12.7 ms) between the men with a TC concentration at or above the 75th percentile and men with a TC concentration below the 25th percentile. In other words, the contribution of the difference in TC to the variance in visuomotor speed was several fold greater than that from aging from 30 to 59 y. The major concern of clinical relevance was that if the association observed in the current study and in previous studies proves to be robust, the effects could be widespread and substantial because more and more people are encouraged to lower their serum cholesterol concentrations (32). Equally important, if the difference widens over time, it may have an effect on quality of life and even survival, because relative small impairments in cognitive function may shorten survival in later life (26). For example, the impairment could affect automobile driving, a situation encountered in everyday life and a task that requires the integration of a broad array of cognitive abilities: sustained attention and speed and accuracy of psychomotor performance (13). The findings of the current study might be helpful in explaining the high incidence of deaths from accidents in persons with low serum cholesterol concentrations (33–38).

Perhaps the greatest limitation of the current study was its cross-sectional design. The inherent limitation of cross-sectional data prevented us from investigating causality. Both serum cholesterol and cognition are strongly influenced by genetic factors, and any observed covariation could have been due to the concomitant expression of genotype without cholesterol and cognitive function being causally related to one another (9). Although the richness of the NHANES III data allowed us to delineate the relation between serum cholesterol and cognition after adjustment for a wide array of potential confounding factors, we were unable to control for the fasting or feeding status or the use of medications other than cholesterol-lowering drugs (eg, psychotropic medication, β-blockers, oral contraceptives, and estrogen). All these factors can affect lipid concentrations and cognitive function. Also, it has been documented that cognitive performance fluctuates across menstrual rhythms (39). Serum samples were collected only once, which may misrepresent true cholesterol concentrations. All these factors could lead to measurement errors with ensuing loss of precision, which would likely result in the attenuation of the true relations rather than in the production of spurious ones. The absence of menstrual

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rhythm data or other sex-related factors might be one reason for our failure to identify an association in women.

The current study has unique strengths as well. An increasing number of studies indicate that hormones play an important role in cognitive function (39–41) and that lipid metabolism differs by sex (42). The relatively large sample size of each sex in the current study allowed us to sufficiently control for the potential confounding or modifying effects from sex by analyzing the sexes separately. In addition, the NHANES III participants had been randomly selected from the community-dwelling US population; therefore, our results should be fairly generalizable to adults in the United States.

In conclusion, our findings indicate that a low concentration of serum TC or NHDLC is associated with relatively slower reaction times in men, and this association is independent of sociodemographic variables, risk factors for cerebrovascular diseases, and serum trace elements and vitamins. The clinical significance of this association is unclear but may be inferred from comparison with the age-related decline in visuomotor speed. Given the consistency of the findings, this association deserves more detailed and sustained study in large prospective investigations.

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All authors contributed to the study design and data analyses and participated in critically revising the manuscript for important intellectual content. MFM and REM supervised the study. JZ obtained the data, performed the data analysis, and drafted the manuscript. None of the authors had any financial or personal interest, including advisory board affiliations, in any company or organization within the food or pharmaceutical industries.

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