Effects of Lovastatin on Cognitive Function and Psychological Well-being*

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PURPOSE: Animal research and cross-sectional studies suggest that serum lipid concentrations may influence cognitive function, mood, and behavior, but few clinical trials have studied these effects.

SUBJECTS AND METHODS: In this double-blind investigation, 209 generally healthy adults with a serum low-density-lipoprotein (LDL) cholesterol level of 160 mg/dL or higher were randomly assigned to 6-month treatment with lovastatin (20 mg) or placebo. Assessments of neuropsychological performance, depression, hostility, and quality of life were conducted at baseline and at the end of the treatment period. Summary effect sizes were estimated as *z* scores on a standard deviation (SD) scale.

RESULTS: Placebo-treated subjects improved between baseline and posttreatment periods on neuropsychological tests in all five performance domains, consistent with the effects of practice on test performance (all $P < 0.04$), whereas those treated with lovastatin improved only on tests of memory recall ($P = 0.03$). Comparisons of the changes in performance between placebo- and lovastatin-treated subjects revealed small, but statistically significant, differences for tests of attention (*z* score = 0.18; 95% confidence interval (CI), 0.06 to 0.31; $P = 0.005$) and psychomotor speed (*z* score = 0.17; 95% CI, 0.05 to 0.28; $P = 0.004$) that were consistent with greater improvement in the placebo group. Psychological well-being, as measured several ways, was not affected by lovastatin.

CONCLUSION: Treatment of hypercholesterolemia with lovastatin did not cause psychological distress or substantially alter cognitive function. Treatment did result in small performance decrements on neuropsychological tests of attention and psychomotor speed, the clinical importance of which is uncertain. **Am J Med. 2000;108:538–547.** ©2000 by Excerpta Medica, Inc.

In the early 1990s, meta-analysis revealed that cholesterol lowering via diet modifications or older pharmacologic agents was apparently associated with a significant increase in death from suicides, accidents, and violence (1,2). Increased mortality from these causes, however, has not been observed in more recent trials that used "statin" drugs, such as lovastatin, simvastatin, and pravastatin, which inhibit cholesterol synthesis (3,4). Nonetheless, this issue has underscored our limited understanding of the influences that serum lipids have on the brain and on behavior (5,6). Hypercholesterolemia increases the risk of ischemic stroke, but atherosclerosis may not be the only way that serum lipids affect the central nervous system. Research in animals, including nonhuman primates, suggests that circulating lipid levels can influence neurochemistry, neurophysiology, learning, and other aspects of behavior (7–12), leading to speculation about the psychological and behavioral effects of changes in serum lipid levels in humans (13,14).

Low serum cholesterol levels have been associated with depression, suicide, and suicide attempts, aggression, and antisocial behavior (15–19). Monkeys consuming low-fat, low-cholesterol diets have substantially lower serum cholesterol levels, increased aggression, and decreased social affiliation compared with controls eating diets that were high in fat or cholesterol (12,20). There is also evidence that hypercholesterolemia is associated with better scores on some tests of cognitive function in young, middle-aged, and older humans (21–26).

To the extent that long-term reductions of serum cholesterol levels are widely advised and prescribed, it is important to determine whether quality of life is affected by such treatment, and whether patients experience changes in mood, well-being, or cognitive function. Therefore, we studied the potential psychological effects of treatment of hypercholesterolemia with lovastatin, a prototypic statin medication.

MATERIAL AND METHODS

Subjects were generally healthy men and women with hypercholesterolemia, defined as a serum low-density-lipoprotein (LDL) cholesterol level 160 mg/dL or higher, between the ages of 24 and 60 years. After stratification by

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Supported by the Public Health Service (HL46328). The placebo and lovastatin tablets were donated by Merck and Co.

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Manuscript submitted May 17, 1999, and accepted in revised form January 6, 2000.

0002-9343/00/$–see front matter
PII S0002-9343(00)00353-3

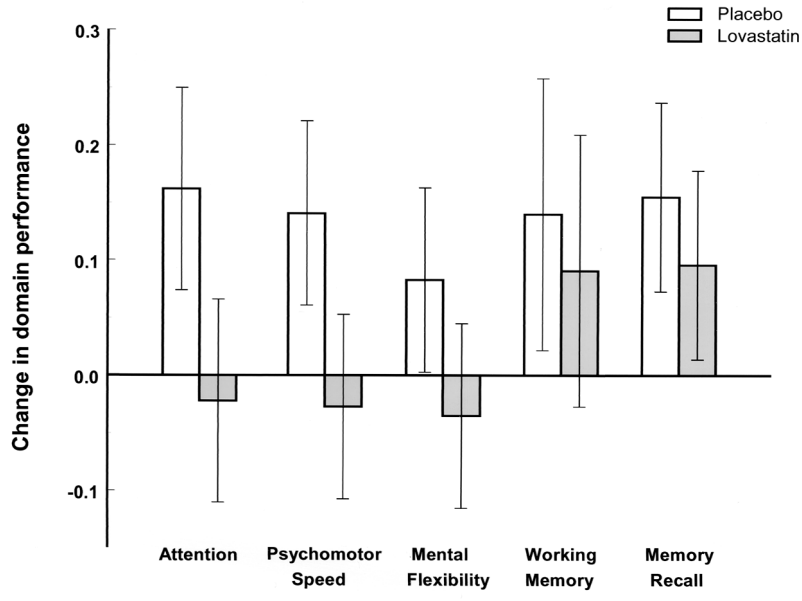

Figure. Mean change in cognitive function between baseline and 6-month follow-up in the two treatment groups. Results are expressed as the change in summary *z* scores (and 95% confidence intervals) for each of the five domains of neuropsychological performance. A positive deflection indicates performance improvement and a negative deflection indicates performance decrement. See text for results of statistical analyses.

sex and age (45 years and younger, older than 45 years), each participant was randomly assigned to daily treatment with lovastatin (Mevacor, Merck and Co., Rahway, New Jersey, 20 mg) or matching placebo for 6 months. Exclusion criteria included secondary hyperlipidemia (chronic hepatitis, renal failure, diabetes requiring medication, untreated hypothyroidism), hypertriglyceridemia (fasting serum triglyceride level 400 mg/dL or higher), untreated hypertension (diastolic blood pressure greater than 95 mm Hg), major illnesses such as cancer or schizophrenia, and treatment with any lipid-lowering or psychotropic medications, glucocorticoids, or opiates. Women likely to become pregnant were excluded. Participants were recruited from Allegheny County in southwestern Pennsylvania through newspaper advertisements and distribution of study brochures and posters. Written informed consent was obtained from all subjects, as approved by the University of Pittsburgh Biomedical Institutional Review Board. Subjects were paid for their participation.

A total of 209 hypercholesterolemic subjects were eligible, agreed to participate, and underwent randomization. Fifteen subjects withdrew from the study, 8 for personal reasons, such as moving or inability to comply with the appointment schedule, and 6 developed exclusion criteria during the treatment period. A single subject was withdrawn because of a suspected adverse drug reaction (rash). Two additional subjects either did not complete or did not follow instructions for the end-of-treatment neuropsychological assessments. Comparisons between subjects who completed the study and dropouts revealed marginally more education in the completers (15 $\pm$ 3 vs 14 $\pm$ 2 years, $P = 0.06$), but no differences in age, sex, race, income, alcohol consumption, or LDL-cholesterol levels.

Measurements

During screening, fasting blood samples for serum lipid determinations were drawn on two occasions separated by 1 to 3 weeks. Subsequent fasting samples were obtained after 8, 16, 23, and 24 weeks of treatment. The two baseline samples and the two end-of-treatment samples were averaged. Determinations of serum total and high-density lipoprotein cholesterol and triglyceride levels were performed by the Heinz Nutrition Laboratory at the University of Pittsburgh, which has met the criteria of the Centers for Disease Control National Heart, Lung, and Blood Institute Lipid Standardization Program since 1982. LDL-cholesterol levels were calculated using the Friedewald equation (27).

Participants completed measures of cognitive function, using neuropsychological tests, and measures of self-reported quality of life and psychological distress, encompassing depression, anxiety, and hostility. Trained testers were blinded to subjects' treatment assignment. Neuropsychological testing sessions, which lasted approximately 90 minutes, were conducted at baseline and the end of treatment. Before testing, each subject attended a preliminary (practice) session to be familiarized with test materials and instructions. Neuropsychological

Table 1. Baseline Characteristics of Subjects in the Placebo and Lovastatin Groups

Characteristic	Placebo (n = 96)	Lovastatin (n = 98)
	Number (percent) or Mean ± SD	
Age (years)	46.6 ± 8.4	46.2 ± 9.5
Female sex	47 (49)	43 (44)
White race	87 (91)	84 (86)
Body mass index (kg/m^2)	27 ± 4	27 ± 4
Systolic blood pressure (mm Hg)	120 ± 11	124* ± 12
Diastolic blood pressure (mm Hg)	81 ± 7	82 ± 7
Education (years)	15 ± 3	15 ± 3
Employed (%)	79	73
Annual family income (median in $1,000)	35–50	35–50
Alcohol (drinks/week)	3 ± 7	3 ± 3
Total cholesterol (mg/dL)	265 ± 28	263 ± 31
LDL cholesterol (mg/dL)	187 ± 24	184 ± 27
HDL cholesterol (mg/dL)	49 ± 9	49 ± 13
Triglycerides (mg/dL)	142 ± 70	147 ± 74
Cognitive function		
Digit Span (longest correct span)	7.1 ± 1.2	6.9 ± 1.3
Digit Symbol (age-scaled score, 0–20)	11.9 ± 2.5	11.7 ± 2.6
Trail Making B (time required in seconds)	62 ± 22	68 ± 2.0
Associative Learning (number correct out of 36)	23 ± 12	23 ± 12
Controlled Oral Word Association (number of words generated)	42 ± 11	43 ± 13
Quality of life† (scaled scores, 0–100)		
General health	77 ± 16	76 ± 16
Vitality	61 ± 20	62 ± 20
Bodily pain	73 ± 22	73 ± 22
Physical function	91 ± 12	89 ± 16
Physical role	84 ± 29	77 ± 36

* Lovastatin group greater than placebo group, $P < 0.05$.

† Component scales of the Medical Outcomes Study Short Form 36-item Health Survey. Higher scores indicate better quality of life.

tests were chosen to assess general mental efficiency, attention, psychomotor skills, learning, and memory, which are essential for routine daily activities (Appendix A). Alternative forms were employed for tests on which recall of prior test materials might affect performance on subsequent testing, and the order of these alternative forms was randomly assigned.

To examine treatment effects on psychological well-being, participants underwent assessments of mood, hostility, anxiety, depression, hopelessness, anger, and social function at baseline and during the last week of enrollment. Widely used pencil-and-paper trait and state measures were complemented by interview (depression) and daily diary (mood state) assessments (Appendix B). Participants were instructed to answer questions in reference to the preceding 6 months.

Statistical Analyses

All analyses were conducted on an intention-to-treat basis. Baseline characteristics of the placebo- and lovastatin-treated subjects were compared using Student's *t* tests, Mann-Whitney U tests, or chi-square analyses. Treatment effects on serum lipid levels were examined with Student's *t* tests and repeated-measures analysis of variance. The between-subject factors were treatment (lovastatin, placebo) and sex; the within-subject factor was visit (baseline, treatment).

In several instances, neuropsychological test scores were transformed to ensure normality. To limit experiment-wise error, performance scores were grouped into five cognitive domains, based on prior experience (28), which were labeled attention, psychomotor speed, mental flexibility, working memory, and memory recall. We examined the correlation matrix among baseline scores to confirm our "clinical clustering" procedure; in a few instances we reassigned tests to ensure that the scores within each cluster were maximally intercorrelated. The composition of the five performance domains is provided in Appendix A. A repeated-measures multivariate analy-

Table 2. Cognitive Function at Baseline and after 6 Months of Treatment, by Treatment Group, for Tests That Showed a Significant Difference ($P < 0.05$) in Changes in Scores between the Two Treatment Groups

	Placebo		Lovastatin	
	Baseline	Treatment	Baseline	Treatment
	Mean (95% confidence interval)*			
Digit vigilance (errors)	6.9 (5.8–8.0)	5.4 (4.5–6.4)	6.3 (5.7–7.6)	6.2 (5.2–7.3)
Recurrent words (% correct)	82 (79–86)	84 (80–88)	88 (85–91)	86 (83–89)
Maze completion time (seconds)	106 (99–113)	99 (92–108)	101 (95–108)	106 (99–112)
Grooved pegboard insertion time (seconds)	133 (129–137)	132 (128–137)	134 (130–139)	137 (132–142)

* Geometric means.

sis of covariance was conducted for each of the five clusters of performance scores. Sex and test form were included as between-subjects factors, and age was included as a covariate. Significant effects resulting from drug treatment (as indicated by the omnibus F statistic for the interaction of treatment with visit) were followed by univariate analyses to identify which neuropsychological tests differed by treatment assignment. In addition, standardized *z* scores were computed for the individual neuropsychological tests (follow-up values were standardized using baseline means and standard deviations), and "summary" *z* scores were calculated for the five performance domains by averaging the component *z* scores within each domain. Changes in performance within treatment groups were examined with *t* tests for paired observations. For testing treatment effects (eg, lovastatin vs placebo), changes in performance were calculated as the change in the summary *z* score and compared between the two groups with unpaired *t* tests. Summary effect sizes were estimated from these *z* score analyses.

In subjects assigned to lovastatin, supplementary analyses were conducted to determine if any treatment effects were related to either the reduction in the serum LDL-cholesterol level, or to the final level of LDL cholesterol. For that purpose, treatment effects on performance domains were averaged and examined in relation to LDL-cholesterol change or level by correlation analysis or by comparing high and low responders (median split) with a *t* test.

For the purposes of data reduction, the 17 psychological well-being variables were entered into a principal components analysis, allowing the components to correlate (oblique rotation), and the four components with eigenvalues greater than 1 were extracted, accounting for 67.5% of the variance. For convenience, these four factors were labeled mood, anger and hostility, role function, and anger-internal (Appendix B). All 17 variables were standardized (follow-up values were standardized using baseline means and standard deviations) and averaged to create four component scores. To evaluate treatment effects, the four component scores were analyzed using a single, repeated-measures analysis of variance, with treatment and sex as between-subject factors and visit as a within-subject factor.

We tested whether drug treatment affected cognitive function or psychological well-being in the six defined

Table 3. Scores on Selected Tests of Psychological Well-being at Baseline and after 6 Months of Treatment, by Treatment Group*

	Placebo Group		Lovastatin Group	
	Baseline	Treatment	Baseline	Treatment
	Mean ± SD			
Hamilton Depression Rating Scale	2.6 ± 3.4	2.7 ± 3.3	3.7 ± 5.1	3.1 ± 4.3
NEO-Depression†	13.5 ± 6.5	10.1 ± 6.0	12.6 ± 5.5	9.4 ± 5.8
Cook-Medley Hostility	9.1 ± 4.8	8.5 ± 5.1	9.1 ± 4.2	8.0 ± 4.7
MOS SF-36‡				
Role Functioning—Physical	84 ± 29	86 ± 29	77 ± 36	85 ± 30
Social Functioning	91 ± 16	90 ± 18	86 ± 19	88 ± 19
Role Functioning—Emotional	80 ± 30	83 ± 33	81 ± 31	86 ± 29

* Higher scores indicates higher levels of the characteristic. There were no significant differences in changes in scores between the two treatment groups.
† Depression scale of the NEO Personality Inventory.
‡ Component scales of the Medical Outcomes Study Short Form 36-item Health Survey.

multivariate or summary score analyses comparing lovastatin and placebo; all other analyses were supplementary to those primary comparisons. Statistical significance was set at $P < 0.05$ (two sided), without adjustment for multiple comparisons.

RESULTS

Overall, subjects were young to middle aged, mostly employed with some college education and moderate hypercholesterolemia (Table 1). Five of the 192 participants who completed the study had a history of ischemic heart disease. Baseline measures from a sample of neuropsychological tests and quality-of-life scales are provided in Table 1; additional pretreatment data appear in Tables 2 and 3. Mean systolic blood pressure was somewhat greater in the subjects assigned to lovastatin, but it was not significantly correlated with neuropsychological performance.

Compliance and Changes in Serum Lipid Levels

Compliance data based on pill counts indicated that median adherence was 92% and did not differ between treatment groups. Serum lipid levels changed only slightly in the placebo-treated subjects. Compared with placebo, lovastatin lowered the serum total cholesterol level by 18% [95% confidence interval (CI), 16% to 21% and the LDL-cholesterol level by 25% (95% CI, 22% to 28%). At the end of the treatment period, the mean (± SD) serum cholesterol level was 209 ± 34 mg/dL, and the LDL-cholesterol level was 131 ± 30 mg/dL in the lovastatin group.

Effects on Cognitive Function

At 6-month follow-up, placebo-treated subjects had improved significantly (all $P < 0.04$) in all five domains of cognitive function (Figure). These changes represent learning or practice effects that are commonly observed upon re-administration of cognitive tests. Subjects receiving lovastatin improved only on tests of memory recall ($P = 0.03$). The differences in performance change between placebo- and lovastatin-treated subjects were statistically significant for tests of attention, (z score = 0.18; 95% CI, 0.06–0.31; $P = 0.005$) and for tests of psychomotor speed (z score = 0.17; 95% CI, 0.05–0.28; $P = 0.004$), indicating greater improvement in the placebo group. Repeated measures multivariate analysis of covariance confirmed these findings. Excluding subjects who reported alcohol consumption in excess of 21 drinks per week did not alter the findings.

Analyses of individual tests of attention and psychomotor speed revealed significant effects (all $P < 0.05$) for four tests (Table 2). After treatment, the lovastatin group failed to show an improvement in the error rate for Digit Vigilance, made slightly fewer correct responses on Recurrent Words, and took several seconds longer to complete the Elithorn Maze and Grooved Pegboard tests.

Among subjects receiving lovastatin, change in performance was unrelated to the percent change in serum LDL-cholesterol but was significantly related to the post-treatment level ($r = 0.21$; $P = 0.04$). When subjects were divided into those whose final serum LDL-cholesterol level was above or below the median level, only those in the lower group (who had a mean LDL-cholesterol level at follow-up of 109 ± 11 mg/dL) had a decrease in cognitive function (z score = 0.15; 95% CI, 0.04 to 0.26; $P = 0.007$).

Effects on Psychological Well-being

Compared with baseline, most scores on measures of psychological well-being improved in both the lovastatin and the placebo group, as commonly occurs in clinical trials. Lovastatin-treated subjects had similar improvement. Table 3 presents results from select measures of mood, hostility, and quality of life. In the multivariate repeated measures analysis, there was no significant effect of lovastatin treatment ($P > 0.2$). Supplementary analyses failed to reveal evidence of a deterioration in psychological measures in subjects experiencing the greatest reduction in serum LDL-cholesterol level or in those reaching the lowest LDL-cholesterol level during treatment.

DISCUSSION

We studied the effects of pharmacologic cholesterol lowering on a broad range of cognitive skills and indexes of psychological well-being among nonelderly subjects with moderate hypercholesterolemia. We found significant effects of lovastatin treatment on measures of psychomotor and attentional processes, as compared with placebo. Performance in three other domains—mental flexibility, working memory, and memory recall—also tended to decrease compared with placebo, but the differences were not statistically significant. Subjects with the lowest post-treatment LDL-cholesterol levels had the greatest decrements in function. There were no effects of treatment on measures of psychological well-being.

A few previous studies have evaluated cognitive functioning during treatment with statins. The pharmaceutical industry sponsored four studies that were briefer and smaller than the current investigation. Three found no effects of treatment (29–31), whereas the fourth reported that lovastatin, but not pravastatin, significantly lowered scores on tests of attentional processes in normo-cholesterolemic volunteers (32). An additional trial in elderly patients found no effects of lovastatin on a single neuropsychological test (33).

Standard neuropsychological tests attempt to separate cognitive function into its component processes, but the distinctions are imperfect, and individual tests measure

more than one skill. Therefore, the observed treatment effects on cognitive function may not be selective for attentional and psychomotor processes. Equally important, the magnitude of the effects of treatment on test scores was small. Such changes in neuropsychological performance would not be considered clinically significant if compared with the typical findings that occur in intoxicated or brain-injured patients. Also, the performance of placebo-treated subjects generally improved from baseline to the 6-month assessment. Such learning or practice effects are common in studies involving repeated testing (34,35). Thus, the small adverse effects that were associated with cholesterol lowering were primarily an absence of practice effects, rather than an absolute decline in performance.

We also evaluated the effects of cholesterol reduction on psychological well-being using a diverse battery of psychological assessments, including interview, questionnaire, and daily mood ratings. Despite this range of measures, no adverse effects were observed, irrespective of the magnitude of cholesterol reduction. Small changes in specific psychological symptoms may have been missed, and it is possible that subjects with preexisting psychiatric disorders may develop psychological or behavioral changes that were not observed in this community sample. Nonetheless, these data suggest that lipid-lowering therapy with statins does not lead to increased depression, anxiety, hostile attitude, or anger. Our results are consistent with a previous study that compared simvastatin with placebo (36).

Several reviews have concluded that the empiric evidence generally supports the hypothesis that low or lowered cholesterol levels are associated with depression and violent behavior (14,37). However, we observed no increases in self-reported hostility, anger expression, or aggression. While these measures are at best moderately related to violence, they should be sensitive to an increase in violent tendencies. It is possible that other factors, such as impulsivity or more objective measures of aggressive disposition, would be related to serum cholesterol levels. Because of the potential importance of this relation, we believe our results do not warrant discarding the possibility of violent outcomes after cholesterol reduction.

The mechanism by which lovastatin might affect cognitive function is unknown. Lovastatin penetrates the central nervous system, and the cognitive effects that we observed may be the result of neuropharmacologic actions that are independent of cholesterol lowering. Large doses of statins can produce substantial neurotoxicity in dogs (38,39). Statins lower circulating levels of vitamin E and ubiquinone (40) and may affect the synthesis of polyunsaturated fatty acids that are integral to neuronal membranes (41). Even cholesterol-lowering diets may affect the brain. Modifications in the dietary fat of laboratory animals changes the fatty acid and cholesterol content of neural tissue and affects the pain threshold and learning behaviors (7–11). In nonhuman primates, cholesterol-lowering diets appear to increase aggression while decreasing affiliative social behavior (12,20,42). Preliminary evidence from clinical studies indicates that adoption of calorie-restricted diets, which lower serum cholesterol and triglyceride levels, may slightly impair mental efficiency (43–45).

Any potential adverse effects of an intervention on the quality of life are important, especially for preventive treatments that are widely prescribed. To the extent that someone's perceptions and self-appraisal are central to the concept of quality of life, this study and others (46,47) found that treatment of hypercholesterolemia with lovastatin causes no ill effects. However, actual abilities and level of function are equally germane. Self-reported measures of function may be inaccurate or insensitive to small changes; direct assessment of performance may be needed (48). Our results indicate that lovastatin causes small decrements in scores on tests of psychomotor speed and attention. Although these effects may be inconsequential, they could affect performance on tasks, such as automobile driving, which require the integration of a broad array of cognitive abilities (eg, sustained attention, and speed and accuracy of psychomotor performance). An appropriate extension of this research would entail an evaluation of the effects of cholesterol lowering on the performance of tasks that impose complex cognitive and psychomotor demands that are analogous to situations encountered in everyday life.

REFERENCES

1. Muldoon MF, Manuck SB, Matthews KA. Effects of cholesterol lowering on mortality: a quantitative review of primary prevention trials. *Br Med J*. 1990;301:309–314.
2. Muldoon MF. Injury, death, and cholesterol. *Ann Intern Med*. 1994; 121:719.
3. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
4. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *NEJM*. 1996;335:1001–1009.
5. Ryman A. Cholesterol, violent death, and mental disorder. *Br Med J*. 1994;309:425–426.
6. Muldoon MF, Rossouw JE, Manuck SB, Glueck CJ, Kaplan JR, Kaufmann PG. Low or lowered cholesterol and risk of death from suicide and trauma. *Metabolism*. 1993;42:45–56.
7. Geiser F. Influence of polyunsaturated and saturated dietary lipids on adipose tissue, brain and mitochondrial membrane fatty acid composition of a mammalian hibernator. *Biochimica et Biophysica Acta*. 1990;1046:159–166.
8. McGee CD, Greenwood CE. Effects of dietary fatty acid composition on macronutrient selection and synaptosomal fatty acid composition in rats. *J Nutr*. 1989;119:1561–1568.
9. Hibbeln JR, Salem N. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr*. 1995; 62:1–9.

10. Yehuda S, Leprohon-Greenwood CE, Dixon LM, Coscina DV. Effects of dietary fat on pain threshold, thermoregulation and motor activity in rats. *Pharmacol Biochem Behav*. 1986;24:1775–1777.
11. Kessler AR, Kessler B, Yehuda S. In vivo modulation of brain cholesterol level and learning performance by a novel plant lipid: indications for interactions between hippocampal-cortical cholesterol and learning. *Life Sci*. 1986;38:1185–1192.
12. Kaplan JR, Fontenot MB, Manuck SB, Muldoon MF. Influence of dietary lipids on agonistic and affiliative behavior in Macaca fascicularis. *Am J Primatol*. 1996;38:333–347.
13. Mason RP, Herbette LG, Silverman DI. Can altering serum cholesterol affect neurologic functions? *J Mol Cell Cardiol*. 1991;23:1339–1342.
14. Golomb BA. Cholesterol and violence: is there a connection? *Ann Intern Med*. 1998;128:478–487.
15. Olusi SO, Fido AA. Serum lipid concentrations in patients with major depressive disorder. *Biol Psychiatry*. 1996;40:1128–1131.
16. Jacobs D, Blackburn H, Higgins M, et al. Report of the conference on low blood cholesterol: mortality associations. *Circulation*. 1992; 86:1046–1060.
17. Kunugi H, Takei N, Aoki H, Nanko S. Low serum cholesterol in suicide attempters. *Biol Psychiatry*. 1997;41:196–200.
18. Hillbrand M, Spitz RT, Foster HG. Serum cholesterol and aggression in hospitalized male forensic patients. *J Behav Med*. 1995;18:33–43.
19. Freedman DS, Byers T, Barrett DH, Stroup NE, Eaker E, Monroe-Blum H. Plasma lipid levels and psychologic characteristics in men. *Am J Epid*. 1995;141:507–517.
20. Kaplan JR, Muldoon MF, Manuck SB, Mann JJ. Assessing the observed relationship between low cholesterol and violence-related mortality: implications for suicide risk. *Ann New York Acad Sci*. 1997;836:57–80.
21. Muldoon MF, Flory JD, Ryan CM. Serum cholesterol, the brain, and cognitive functioning. In: Waldstein SR, Elias MF, eds. *Neuropyschology of Cardiovascular Disease*. Mahwah, NJ: Lawrence Erlbaum Associates, 2000.
22. Benton D. Do low cholesterol levels slow mental processing? *Psychosom Med*. 1995;57:50–53.
23. Muldoon MF, Ryan CM, Matthews KA, Manuck SB. Serum cholesterol and intellectual performance. *Psychosom Med*. 1997;59: 382–387.
24. Swan GE, LaRue A, Carmelli D, et al. Decline in cognitive performance in aging twins. Heritability and biobehavioral predictors from the National Heart, Lung, and Blood Institute Twin Study. *Arch Neurol*. 1992;49:476–481.
25. Cattin L, Bordin P, Fonda M, et al. Factors associated with cognitive impairment among older Italian inpatients. *J Am Geriat Soc*. 1997; 45:1324–1330.
26. Kuusisto J, Koivisto K, Mykkanen L, et al. Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *BMJ*. 1997;315:1045–1049.
27. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–503.
28. Waldstein SR, Jennings JR, Ryan CM, et al. Hypertension and neuropsychological performance in men: interactive effects of age. *Health Psych*. 1996;15:102–109.
29. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *Clin Pharm*. 1994;34:989–996.
30. Harrison RWS, Ashton CH. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin, pravastatin, and placebo in healthy volunteers. *Br J Clin Pharm*. 1994;37:231–236.
31. Gengo F, Cwudzinski D, Kinkel P, Block G, Stauffer L. Effects of treatment with lovastatin and pravastatin on daytime cognitive performance. *Clin Cardiol*. 1995;18:209–214.
32. Roth T, Richardson GR, Sullivan JP, Lee RM, Merlotti L, Roehrs T. Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. *Clin Cardiol*. 1992;15:426–432.
33. Santanello NC, Barber BL, Applegate WB, et al. Effect of pharmacologic lipid lowering on health-related quality of life in older persons: results from the cholesterol reduction in seniors program (CRISP) pilot study. *J Am Geriat Soc*. 1997;45:8–14.
34. McCaffrey RJ, Westervelt HJ. Issues associated with repeated neuropsychological assessments. *Neuropsych Rev*. 1995;5:203–221.
35. The Diabetes Control, and Complications Trial Research Group. Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. *Ann Intern Med*. 1996;124:379–388.
36. Wardle J, Armitage J, Collins R, Wallendszus K, Keech A, Lawson A. Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *Br Med J*. 1996;313:75–78.
37. Boston PF, Dursun SM, Reveley MA. Cholesterol and mental disorder. *Br J Psychiatry*. 1996;169:682–689.
38. Berry PH, MacDonald JS, Albert AW, et al. Brain and optic system pathology in hypocholesterolemic dogs treated with a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Am J Path*. 1988;32:427–443.
39. Walsh KM, Albassam MA, Clarke DE. Subchronic toxicity of atorvastatin, a hydroxymethylglutaryl-coenzyme A reductase inhibitor, in beagle dogs. *Toxicol Path*. 1996;24:468–476.
40. Palomaki A, Malminiemi K, Metsa-Ketela T. Enhanced oxidizability of ubiquinol and tocopherol during lovastatin treatment. *FEBS Letters*. 1997;410:254–258.
41. Rise P, Colombo C, Galli C. Effects of simvastatin on the metabolism of polyunsaturated fatty acids and on glycerolipid, cholesterol, and de novo lipid synthesis in THP-1 cells. *J Lipid Res*. 1997;38: 1299–1307.
42. Kaplan JR, Manuck SB, Fontenot MB, Muldoon MF, Shively SA, Mann JJ. The cholesterol-serotonin hypothesis: interrelationships among dietary lipids, central serotonergic activity, and antagonistic behavior in monkeys. In: Hillbrand M, Spitz RT, eds. *Lipids, Health, and Behavior*. Washington, DC: American Psychological Association, 1996:139–166.
43. Kretsch MJ, Green MW, Fong AKH, Elliman NA, Johnson HL. Cognitive effects of a long-term weight reducing diet. *Internatl J Obesity*. 1997;21:14–21.
44. Wing RR, Vazquez JA, Ryan CM. Cognitive effects of ketogenic weight-reducing diets. *Internatl J Obesity*. 1995;19:811–816.
45. Green MW, Rogers PJ. Impaired cognitive functioning during spontaneous dieting. *Psychosom Med*. 1995;25:1003–1010.
46. Downs JR. HMG CoA reductase inhibitors and quality of life. *JAMA*. 1993;269:24:3107–3108.
47. Keech A, Collins R, MacMahon S, et al. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J*. 1994;14:255–269.
48. Muldoon MF, Barger SD, Flory JD, Manuck SB. What are quality of life measurements measuring? *BMJ*. 1998;316:542–545.
49. Lewis RF, Rennick PM. *Manual for the Repeatable Cognitive-Perceptual-Motor Battery*. Clinton, MI: Axon, 1979.
50. Cedrus. Superlab. General Purpose Psychology Testing Software, Version 1.4. Wheaton, MD: Cedrus, 1991.
51. Wechsler D. *WAIS-R Manual*. New York: Psychological Corporation, 1981.
52. Waldstein SR, Jennings JR, Ryan CM, et al. Hypertension and neuropsychological performance in men: interactive effects of age. *Health Psych*. 1996;15:102–109.
53. Rourke BP, Yanni DW, MacDonald GW, Young G. Neuropsycho-

logical significance of lateralized deficits on the Grooved Pegboard Test for older children with learning disabilities. *J Consult Clin Psych*. 1973;41:128–134.
54. Elithorn A, Jones D, Kerr M, Lee D. The effects of the variation of two physical parameters on empirical difficulty in a perceptual maze test. *Br J Psych*. 1964;55:31–37.
55. Golden CJ. *Stroop Color and Word Test*. Chicago: Stoelting, 1978.
56. Reitan RM, Wolfson D. *The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation*, 2nd ed. Tucson, AZ: The Neuropsychology Press, 1993.
57. Ryan CM, Morrow LA, Bromet EJ, Parkinson DK. Assessment of neuropsychological dysfunction in the workplace: normative data from the Pittsburgh Occupational Exposures Test Battery. *J Clin Exp Neuropsych*. 1987;9:665–679.
58. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York: Oxford University Press, 1991.
59. Raikkonen K, Matthews KA, Flory JD, Owens JF, Gump BB. Effects of optimism, pessimism, and trait anxiety on ambulatory blood pressure and mood during everyday life. *J Pers Social Psychol*. 1999; 76:104–113.
60. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988;45:742–747.
61. Stewart AL, Hays RD, Ware JE. The MOS Short-Form General Health Survey: reliability and validity in a patient population. *Med Care*. 1988;26:724–735.
62. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. *J Consult Clin Psychol*. 1974;42: 861–865.
63. Spielberger CD. *State-Trait Anger Expression Inventory Professional Manual*. Odessa, FL: Psychological Assessment Resources, Inc, 1991.
64. Buss AH, Durkee A. An inventory for assessing different kinds of hostility. *J Consulting Psychol*. 1957;21:343–349.
65. Barefoot JC, Dodge KA, Peterson BL, Dahlstron WG, Williams RB. The Cook-Medley Hostility Scale: item content and ability to predict survival. *Psychosom Med*. 1989;51:46–57.
66. Costa PT, McCrae RR. *Revised NEO Personality Inventory (NEO PI-R) and NEO Five-factor Inventory Professional Manual*. Odessa, FL: Psychological Assessment Resources, Inc, 1992.
67. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1983.

Appendix A. Neuropsychological Performance Assessment Battery

Performance Domain	Test	Description	Reference
Attention	Digit Vigilance	Number of target stimuli (the number "6") missed when required to scan two pages of numbers	(49)
	Letter Rotation	Number of stimuli (the letters F, L, R rotated 0%, 30%, 60%, 90%, 120%, 150%, or 180%) misidentified as oriented normally or reversed missed	(50)
	Digit Span	Longest string of numbers (three to nine digits) repeated	(51)
	Recurring Words	Percent of words correctly identified as "new" or "repeated" when words are read (and repeated) using a continuous recognition test format	(52)
Psychomotor speed	Grooved Pegboard	Time required to insert 25 grooved pegs into slotted holes (dominant and nondominant hand trials)	(53)
	Elithorn Maze	Planning and drawing time to complete two complex lattice-type perceptual mazes	(54)
	Digit Symbol	Time required to recode numbers into symbols using a key that pairs each of nine numbers with a meaningless shape	(51)
Mental flexibility	Stroop Interference	Subjects are presented with color words printed in incongruously colored ink and instructed to state the name of the color of the ink (seeing "red" printed in blue ink, they respond "blue"). Derived score obtained by subtracting color-word score from a predicted score, where the color-word score is the number of correct responses made in 45 seconds.	(55)
	Trail Making	Time required to complete each of two tasks. Part A requires subjects sequentially to connect ascending numbers arrayed on page; Part B requires subjects to alternate between numbers and letters (1-A-2-B, etc).	(56)
	Digit Vigilance	Time required to scan two pages of numbers for target stimuli	(49)
	Letter Rotation	Median response latency for correct responses on this computer-run decision-making task	(50)
Working memory	Associative Learning	Total number of words correctly recalled when 12 unrelated word-pairs are presented for each of three study/test trials	(57)
	Digit Span	Longest string of digits (two to eight numbers) repeated backwards	(51)
Memory retrieval	Controlled Oral Word Association	Number of words, generated in 1 minute, that begin with a specific letter of the alphabet (3 trials)	(58)
	Digit Symbol Recall	Number of digit symbol associations correctly recalled after completing the Digit Symbol Substitution Test	(57)
	Verbal Recall	Number of word-pairs correctly recalled 30 minutes after completing the Associative Learning Test	(57)
	Complex Figure	Score on the reproduction of the Rey or Taylor Figure, 30 minutes after having copied the design	(58)

Appendix B. Psychological Assessment Battery

Psychological Domain	Measures	Description	Reference
Mood	Positive and Negative Daily Mood	Positive and negative mood items rated daily for at least 5 consecutive days	(59)
	Hamilton Depression Rating Scale	Presence and duration of depressive symptoms over the past week by clinical interview	(60)
	MOS SF-36 Mental Health	Feelings of nervousness or depression	(61)
	Beck Hopelessness Scale	The extent to which one holds negative expectations about the future	(62)
Anger and hostility	Anger-Out	Expression of anger toward others or the environment	(63)
	Buss-Durkee: Attitudinal Hostility	Resentment, suspicion, and guilt	(64)
	Trait Anger	Dispositional anger	(63)
	Cook-Medley Hostility	Cynicism, hostile affect, and aggressive responding	(65)
	NEO-Angry Hostility	Readiness to experience anger	(66)
Role function	MOS SF-36 Role Functioning—Physical	The degree to which physical health interferes with work or daily activities	(61)
	MOS SF-36 Social Functioning	The extent to which physical health or emotional problems interfere with social activities	(61)
	MOS SF-36 Role Functioning—Emotional	Problems with work or other daily activities as a result of emotional problems	(61)
Anger-internal	Anger-In	Suppression of angry feelings	(63)
	NEO-Depression	Feelings of guilt, sadness, hopelessness, and loneliness	(66)
	Buss-Durkee: Motor Hostility	Assault, irritability, negativism, and verbal hostility	(64)
	Trait Anxiety	Dispositional anxiety	(67)

MOS SF-36 = Medical Outcomes Study Short Form 36-item Health Survey; NEO = NEO Personality Inventory.