Background: Few strategies are available for the prevention of cognitive impairment in elderly persons. Serum lipoprotein levels may be important predictors of cognitive function, and drugs that lower cholesterol may be effective for the prevention of cognitive impairment.

Objective: To determine whether serum lipoprotein levels, the 4-year change in serum lipoprotein levels, and the use of statin drugs are associated with cognition in older women without dementia.

Design, Setting, and Participants: An observational study of 1037 postmenopausal women with coronary heart disease enrolled in the Heart and Estrogen/Progestin Replacement Study (participants at 10 of 20 centers).

Main Outcome Measure: The Modified Mini-Mental State Examination was administered at the end of the study after 4 years of follow-up. Women whose score was less than 84 points (≥1.5 SDs below the mean) were classified as having cognitive impairment. Lipoprotein levels (total, high-density lipoprotein, and low-density lipoprotein [LDL] cholesterol and triglycerides) were measured at baseline and at the end of the study; statin use was documented at each visit.

Results: Compared with women in the lower quartiles, women in the highest LDL cholesterol quartile at cognitive testing had worse mean ± SD Modified Mini-Mental State Examination scores (93.7±6.0 vs 91.9±7.6; P=.002) and an increased likelihood of cognitive impairment (adjusted odds ratio, 1.76; 95% confidence interval, 1.04-2.97). A reduction in the LDL cholesterol level during the 4 years tended to be associated with a lower odds of impairment (adjusted odds ratio, 0.61; 95% confidence interval, 0.36-1.03) compared with women whose levels increased. Higher total and LDL cholesterol levels, corrected for lipoprotein(a) levels, were also associated with a worse Modified Mini-Mental State Examination score and a higher likelihood of impairment, whereas high-density lipoprotein cholesterol and triglyceride levels were not associated with cognition. Compared with nonusers, statin users had higher mean ± SD Modified Mini-Mental State Examination scores (92.7±7.1 vs 93.7±6.1; P=.02) and a trend for a lower likelihood of cognitive impairment (odds ratio, 0.67; 95% confidence interval, 0.42-1.05), findings that seemed to be independent of lipid levels.

Conclusions: High LDL and total cholesterol levels are associated with cognitive impairment, and lowering these lipoprotein levels may be a strategy for preventing impairment. The association between statin use and better cognitive function in women without dementia requires further study.
Subjects and Methods

Subjects

Women were enrolled in the Heart Estrogen/progestin Replacement Study trial. The design and main outcomes of the trial have been published previously. Subjects were postmenopausal women younger than 80 years with established coronary disease who had not undergone a hysterectomy. None of the women had a history of dementia or were taking antidepressant medications at enrollment. Women were randomly assigned (stratified by clinical center) to treatment with daily oral estrogens, conjugated, 0.625 mg, and medroxyprogesterone acetate, 2.5 mg, or an identi
cal placebo. Because treatment was not associated with cognitive performance, we combined treatment groups for this study.

Measurements

At the end of the 4-year trial, women at 10 of the 20 clini
cal centers underwent cognitive testing. Trained clinical staff administered the Modified Mini-Mental State Examination (3MS), a brief cognitive test with components for orientation, concentration, language, praxis, and immediate and delayed memory. Scores range from 0 to 100, with higher scores denoting better cognitive performance. We defined cognitive impairment to be a 3MS score less than 84 points, which is greater than 1.5 SDs below the mean.

At baseline and at cognitive testing (year 4), particip-
ants completed questionnaires that included informa
tion on demographics, smoking, general health, and medi
cal conditions. All medications, including statins and other lipid-lowering drugs, were recorded. We defined statin use to be present if a woman had regularly taken statins within the past month. Height and weight were measured, and the body mass index was calculated. Depression was mea-
sured with the 15-item Geriatric Depression Scale. Incident stroke was defined as a rapid onset of a neurological deficit attributable to a vascular territory that lasted longer than 24 hours or that was confirmed by a lesion compatible with an acute stroke on a computed tomographic or magnetic resonance imaging scan. All strokes were adjudicated by medical record review by 2 blinded Heart and Estrogen/progestin Replacement Study physicians. Incident nonfatal myocardial infarction cases were adjudicated by an independent subcommittee blinded to treat-
ment assignment; a history of coronary artery bypass graft (CABG) surgery at cognitive testing was verified by surgi
cal report.

Lipoprotein levels were measured at baseline and at the end of the study. All subjects were instructed to fast for 12 hours before measurement. Total, LDL, and high-density lipoprotein (HDL) cholesterol levels and triglyceride levels were determined by the Lipoprotein Analytical Labo
ratory, The Johns Hopkins University, Baltimore, Md, in compliance with the standards of the Centers for Disease Control and Prevention location. Lipoprotein(a) levels were measured immunochemically with a sandwich enzyme-linked immunosorbent assay (Strategic Diagnostics Inc, Newark, Del). Low-density lipoprotein cholesterol levels were corrected for lipoprotein(a) levels with the follow-
ing formula: corrected LDL cholesterol level=LDL cholesterol level–[0.3×lipoprotein(a) level].

For this study, the analytic cohort consisted of the 1037 women who underwent cognitive testing at the end of the trial and serum lipoprotein measurements at the beginning and end of the trial.

Statistical Analysis

Statistical analyses were performed using SAS statistical soft-
ware, version 6.12 (SAS Institute Inc, Cary, NC), and all sig
nificance levels reported are 2-sided, with P<.05 consid
ered statistically significant. Because the distributions of serum lipoprotein levels were not normal, we divided subjects into approximate quartiles. Subject characteristics were com-
pared by analysis of variance for continuous variables and the χ2 test for dichotomous variables across quartile of total cholesterol level. To determine whether serum lipoprotein level at cognitive testing was associated with the 3MS score, we compared scores on the 3MS across lipid quartiles using an analysis of variance. Linear trends across quartiles were tested using linear contrasts. We adjusted the 3MS scores for variables that differed among subjects in the lipoprotein quartiles with P≤.05 (aspirin use), variables known to be associated with cognition (age and educational level), con
tions that might affect cognitive function (diabetes, self-
reported health status, or CABG surgery), and hormone treat-
ment group. We also compared models with and without statin use. To determine if change in lipoprotein level during the trial was associated with cognitive performance, we calculated the approximate 4-year change in level (follow-up level−baseline level). We compared mean unad
djusted and multivariate-adjusted 3MS scores among the quar
tiles of change in lipoprotein level. We used logistic regression to examine the odds of cognitive impairment (an a priori 3MS cutoff score >1.5 SDs of the cohort mean) as a function of lipoprotein quartile and change quartile using the lowest 3 quartiles as the reference group for total and LDL choles
terol and triglyceride levels and the highest 3 quartiles as the reference for HDL cholesterol level. To determine if any association between level and cognitive function was pri
marily due to stroke, we repeated all analyses after exclud
ing subjects with incident stroke.

We compared mean 3MS scores by statin use at cog
tive testing with the t test. Multivariate models were con
ducted using an analysis of covariance; we first ad
justed the models for age and total cholesterol level. We then adjusted the models for variables that were statisti
cally different between statin and nonstatin users (educa
tional level, current smoking, and CABG surgery), age, treat
ment group, and total cholesterol level. We used logistic regression analyses to determine if statin use, and use of other lipoprotein-lowering drugs, was associated with the odds of cognitive impairment.
of cognitive impairment, we asked whether serum lipoprotein levels and the 4-year change in levels are associated with cognitive impairment in a cohort of older women with known cardiovascular disease. We also investigated whether the use of lipid-lowering drugs, such as statins, is associated with cognitive function. Several small trials of statins have included cognitive outcomes, initially out of concern for harmful effects, and have yielded inconsistent results. Most of these trials9-13 were short-term and enrolled young adults who are not at risk for cognitive impairment. Two recent observational studies, one case-control14 and one nested case-control,15 reported a 60% to 70% lower odds of developing dementia among statin users. Serum lipoprotein levels were not measured directly in either study and, therefore, it is uncertain whether the protective effect of statin use was related to lipoprotein level or whether the effect was due to an unknown selection bias. However, in their study, Jick and colleagues15 found that the medical record diagnosis of untreated hyperlipidemia was not associated with a risk of developing dementia. Our goal was to determine if statin use is associated with cognitive function and risk of cognitive impairment in older women without dementia and, if so, if it is mediated by lipoprotein level.

**RESULTS**

Serum lipoprotein concentration and ranges in each quartile at cognitive testing are shown in Table 1, along with mean 4-year changes from the baseline level. During the 4 years, most women (those in the lowest 3 quartiles of lipoprotein change) had reductions or little change in their lipoprotein levels. The mean ± SD age of the women was 71.1 ± 6.3 years. The characteristics of the participants did not differ across total cholesterol quartile, except that women in the lowest quartile were more likely to be taking statins and aspirin (Table 2). None of the women were taking medications for AD, such as donepezil.

Women’s scores on the 3MS ranged from 53 to 100, with a mean ± SD score of 93.3 ± 6. Unadjusted and multivariate-adjusted 3MS scores by lipoprotein quartile at cognitive testing are shown in Table 3. Compared with women in the lower quartiles, women in the highest LDL cholesterol quartile had worse performance on the 3MS. Almost identical results were obtained for total cholesterol quartiles and for LDL cholesterol levels after correcting for lipoprotein(a) levels. There was no association between HDL cholesterol or triglyceride quartile and 3MS score (P > .10). The results of these analyses did not change after adjusting cognitive test scores for age, educational level, treatment group, diabetes status, health status, CABG surgery, and aspirin use (Table 3). Adjusting for statin use also did not change the magnitude or statistical significance of the results.

Change in lipoprotein level during the 4 years was also associated with the 3MS score. Of the 1037 women who were taking medications for AD, such as donepezil.
triglyceride level quartile and odds of cognitive impairment. Reduction or no change in total and LDL cholesterol levels during the 4 years was associated with a lower odds of impairment, comparing women in the lowest 3 quartiles (those whose lipoprotein levels were reduced or stayed the same) with women in the highest quartile (those whose lipoprotein levels increased) (total cholesterol level: unadjusted OR, 0.55 [95% CI, 0.34-0.91]; and adjusted OR, 0.53 [95% CI, 0.31-0.89]; LDL cholesterol level: unadjusted OR, 0.64 [95% CI, 0.39-1.03]; and adjusted OR, 0.61 [95% CI, 0.36-1.03]; LDL cholesterol level corrected for lipoprotein[a] level: unadjusted OR, 0.56 [95% CI, 0.34-0.92]; and adjusted OR, 0.50 [95% CI, 0.30-0.85]). There was no association between 4-year change in HDL cholesterol or triglyceride level and odds of impairment.

To determine if the association between cognitive scores and the odds of cognitive impairment and lipoprotein levels was explained by stroke incidence, we excluded the 32 women who developed stroke during the trial. The results were nearly identical when these subjects were excluded.

At cognitive testing, 583 (56%) of the women were taking statins (simvastatin, atorvastatin calcium, pravastatin sodium, lovastatin, or fluvastatin sodium). Statin users tended to be more educated (12.9 vs 12.5 years; \(P = .02\)), tended to smoke less (10% vs 15%; \(P = .01\)), and were more likely to have undergone CABG surgery (43% vs 37%; \(P = .05\)), but they did not differ from nonusers on other characteristics. The mean±SD 3MS score among statin users was 93.7±6.1 compared with 92.7±7.1 among women not taking statins (Table 5). Adjustment for age

Table 2. Subject Characteristics by Total Cholesterol Quartile at Cognitive Testing in the 1037 Women Enrolled in the HERS Trial*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lowest (106-184 mg/dL)</th>
<th>Second (185-207 mg/dL)</th>
<th>Third (208-234 mg/dL)</th>
<th>Highest (235-432 mg/dL)</th>
<th>(P) Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>69.9 ± 6.1</td>
<td>72.2 ± 6.1</td>
<td>70.9 ± 6.2</td>
<td>71.0 ± 6.6</td>
<td>.21</td>
</tr>
<tr>
<td>White</td>
<td>91</td>
<td>91</td>
<td>91</td>
<td>90</td>
<td>.80</td>
</tr>
<tr>
<td>Education, mean ± SD, y</td>
<td>12.8 ± 2.8</td>
<td>12.7 ± 2.4</td>
<td>12.9 ± 2.7</td>
<td>12.5 ± 2.6</td>
<td>.38</td>
</tr>
<tr>
<td>Body mass index, mean ± SD, kg/m²</td>
<td>28.1 ± 5.6</td>
<td>28.3 ± 4.4</td>
<td>28.2 ± 6.1</td>
<td>28.9 ± 5.2</td>
<td>.10</td>
</tr>
<tr>
<td>Geriatric Depression Scale score,</td>
<td>2.1 ± 2.7</td>
<td>1.8 ± 2.4</td>
<td>2.0 ± 2.6</td>
<td>2.1 ± 2.6</td>
<td>.72</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair or poor health</td>
<td>22</td>
<td>22</td>
<td>21</td>
<td>23</td>
<td>.92</td>
</tr>
<tr>
<td>Current smoking</td>
<td>14</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td>.55</td>
</tr>
<tr>
<td>Hypertension history</td>
<td>57</td>
<td>53</td>
<td>55</td>
<td>57</td>
<td>.93</td>
</tr>
<tr>
<td>CABG surgery history</td>
<td>41</td>
<td>45</td>
<td>38</td>
<td>35</td>
<td>.10</td>
</tr>
<tr>
<td>Diabetes history</td>
<td>21</td>
<td>20</td>
<td>18</td>
<td>18</td>
<td>.29</td>
</tr>
<tr>
<td>Incident myocardial infarct</td>
<td>11</td>
<td>5</td>
<td>8</td>
<td>10</td>
<td>.99</td>
</tr>
<tr>
<td>Incident stroke</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>.68</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>81</td>
<td>82</td>
<td>77</td>
<td>72</td>
<td>.006</td>
</tr>
<tr>
<td>Statin use</td>
<td>72</td>
<td>65</td>
<td>65</td>
<td>36</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are given as percentage of subjects unless otherwise indicated. HERS indicates Heart and Estrogen/progestin Replacement Study; CABG, coronary artery bypass graft.
†The conversion factor is given in the first footnote to Table 1.

Table 3. 3MS Scores by Quartile of Lipoprotein at Cognitive Testing in the 1037 Women Enrolled in the HERS Trial*

<table>
<thead>
<tr>
<th>Lipoprotein Quartile</th>
<th>Total Cholesterol</th>
<th>HDL Cholesterol</th>
<th>LDL Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
<td>Adjusted</td>
</tr>
<tr>
<td>Lowest</td>
<td>93.9 ± 5.9</td>
<td>93.5 ± 0.4</td>
<td>93.0 ± 6.7</td>
<td>93.2 ± 0.4</td>
</tr>
<tr>
<td>Second</td>
<td>93.7 ± 6.1</td>
<td>94.0 ± 0.4</td>
<td>93.3 ± 6.5</td>
<td>93.5 ± 0.4</td>
</tr>
<tr>
<td>Third</td>
<td>93.7 ± 6.2</td>
<td>93.6 ± 0.4</td>
<td>93.4 ± 6.6</td>
<td>93.2 ± 0.4</td>
</tr>
<tr>
<td>Highest</td>
<td>91.9 ± 7.6</td>
<td>92.3 ± 0.4</td>
<td>93.5 ± 6.4</td>
<td>93.5 ± 0.4</td>
</tr>
<tr>
<td>(P) Value for Linear Trend</td>
<td>.002</td>
<td>.01</td>
<td>.38</td>
<td>.82</td>
</tr>
</tbody>
</table>

*Data are given as mean ± SD scores for unadjusted models and mean ± SE scores for adjusted models. Adjusted models were adjusted for age, educational level, treatment group, diabetes status, health status, coronary artery bypass graft surgery, and aspirin use. 3MS indicates Modified Mini-Mental State Examination; HERS, Heart and Estrogen/progestin Replacement Study; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.
we excluded women with stroke, there was still an increased risk of developing dementia from stroke. When a high LDL cholesterol level was associated with an increased risk of developing AD. One prospective study also found that between high total cholesterol levels and increased risk of cognitive impairment or dementia. Furthermore, we found a positive association between statin use and cognitive performance in the statin use group. Of the women taking statins, 6% (n=37) had cognitive impairment, whereas 9% (n=42) of the women not taking statins had cognitive impairment (OR, 0.67; 95% CI, 0.42-1.05). Sixty-three of the women were taking nonstatin lipoprotein-lowering agents, such as niacin (n=41) and cholestyramine resin (n=17). Use of nonstatin lipoprotein-lowering drugs was not associated with an adjusted odds of having cognitive impairment (OR, 0.97; 95% CI, 0.36-2.61).

Among elderly women with coronary heart disease, higher serum levels of total and LDL cholesterol were associated with worse cognitive scores and a greater likelihood of cognitive impairment. Reductions in total and LDL cholesterol levels during 4 years were associated with better cognitive functioning and approximately 50% less risk of having cognitive impairment. These findings suggest that lowering total and LDL cholesterol levels may be a potential strategy for preventing the development of cognitive impairment or dementia. Furthermore, we found a positive association between statin use and cognitive function that seems to be independent of total cholesterol level.

Our finding is supported by several, but not all, cross-sectional studies that found an association between high total cholesterol levels and increased risk of developing AD. One prospective study also found that a high LDL cholesterol level was associated with an increased risk of developing dementia from stroke. When we excluded women with stroke, there was still an association between high total and LDL cholesterol levels and worse cognition, suggesting that factors other than large-vessel ischemia may be involved. High total and LDL cholesterol levels may influence the risk of cognitive impairment by increasing subclinical vascular disease. Furthermore, recent evidence suggests that traditional vascular risk factors, such as carotid atherosclerosis, atrial fibrillation, and increase in coagulation factor I, may be also involved in the pathogenesis of AD. While we did not have a clinical assessment for cognitive impairment and cannot determine its cause, it is likely that the women in our study would have various neuropsychologic features, including AD and vascular dementia. Women with coronary heart disease have an increased risk of dementia of all types. The 8% incidence of cognitive impairment that we observed is consistent with a 1% to 2% annual dementia incidence for women of this age, assuming that most participants were free of cognitive impairment when they enrolled in the trial. Nevertheless, our study does not specifically address the efficacy of statins for the prevention of AD.

Our finding that statins were associated with cognitive performance and protection against cognitive impairment is not supported by 5 small trials that did not find a consistent improvement on cognitive testing with statin treatment. However, most of these trials lasted only a few weeks, and all enrolled young or middle-aged adults who rarely develop cognitive deficits. In the only trial of older adults in which 431 subjects were randomized to placebo or to lovastatin for 6 months, no differences on performance on the Digit Symbol test were found. In that study, subjects with low Mini-Mental State Examination scores were excluded and there may have been limited ability to detect differences in cognitive scores. As with coronary disease, 1 to 2 years of statin use may be necessary to demonstrate any benefit on cognition.

Two recent observational studies found a lower likelihood of developing AD or dementia associated with use of statins. Our observation of better cognitive scores in statin users supports the hypothesis that statins may be associated with less risk of dementia. The mechanism for...
A positive association with cognitive function is not known, but several hypotheses have been suggested. One is a direct effect of lipid reductions. We doubt that this is the entire explanation because after adjusting for total cholesterol level, we still found that statins were associated with better cognitive performance. Furthermore, we, along with others, 

7 did not find an association between nonstatin lipid-lowering drugs and risk of cognitive impairment. Some of the statin trials 

25 for reduction of risk of coronary events also suggest that event reduction is not fully explained by lipid level lowering. Statins block the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol and for nonsterol intermediates, some of which are involved in signal transduction. Statins may prevent atherothrombotic events via nonsterol effects on smooth muscle function, macrophages, and platelets. 

26 Statins may also have a neuroprotective effect via enhancement of endothelial nitric oxide synthase and reduction of inflammatory responses, such as C-reactive protein and cytokine responses. 

26 Furthermore, cholesterol reduction with statins inhibits the formation of β-amyloid in hippocampal neurons, a finding that could explain how statins could lower the risk of cognitive impairment. 

27,28 Several limitations of our study deserve mention. Our subjects were mostly white women, and it is unclear whether our results would apply to other ethnic groups or to men. Furthermore, all of the women had known coronary heart disease and this could limit the generalizability of our findings. Unfortunately, apolipoprotein E genotyping was not performed. Some studies have found an interaction between apolipoprotein E ε4 and total cholesterol level on risk of AD 

14 or on cognitive decline, 

29 and further studies might investigate whether statin use differentially affects cognitive function by apolipoprotein E ε4 status. It is unclear whether the observed differences in mean 3MS scores between lipid groups are of clinical significance. However, we found the same association between lipid level and change in lipid level and risk of cognitive impairment. Finally, because statin use was not randomly assigned to women, and although we statistically adjusted for those characteristics that were different among statin and nonstatin users, it is possible that the differences in cognitive function were due to unmeasured confounders. Randomized controlled trials of statins are necessary to determine if they protect against cognitive decline.

In this study of 1037 women with cardiovascular disease, we found that lower serum levels of LDL and total cholesterol were associated with better cognitive performance and less risk of impairment. Furthermore, 4-year reductions in these lipoprotein levels and use of statins were independently associated with better cognitive scores. Aggressive lipoprotein management and statin use may be potential strategies for preventing cognitive decline in elderly persons. More studies, especially trials, aimed at understanding whether statins may lower the risk of cognitive impairment are needed.

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Author contributions: Study concept and design (Drs Yaffe and Grady); acquisition of data (Dr Barrett-Connor); analysis and interpretation of data (Drs Yaffe, Barrett-Connor, and Grady and Ms Lin); drafting of the manuscript (Drs Yaffe and Grady); critical revision of the manuscript for important intellectual content (Drs Yaffe, Barrett-Connor, and Grady and Ms Lin); statistical expertise (Dr Yaffe and Ms Lin); obtained funding (Dr Grady); and study supervision (Drs Yaffe, Barrett-Connor, and Grady).

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REFERENCES


8. Swan GE, LeRue A, Carmelli D, Reed TE, Fabsitz RR. Decline in cognitive per-


Announcement

Aging of the Nervous System: November 2002

We are planning an issue of the Archives of Neurology in November 2002 on aging of the nervous system and ask for original contributions, case reports, and reviews. Clinical or basic neuroscience papers covering the broad field of aging will be considered through June 2002.