A major component of circulating manganese is bound to hemoglobin in erythrocytes. Whole blood manganese concentrations may be 10 times more than serum and a better biomarker of manganese exposure. Manganese has been implicated in the pathogenesis of extrapyramidal features seen in liver failure. There is no evidence that chelation therapy is effective in treating hepatic encephalopathy.

Neeraj Kumar, MD, Rochester, MN

Disclosure: The author reports no disclosures.

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Reply from the Authors: We thank Drs. Nehrlich and Vos for their comments. We accounted for indication bias by including only cases that occurred after baseline, only statin use that occurred at a visit prior to the diagnosis, and by adjusting for access to health care.

We went beyond a simple cholesterol test and obtained lipids 6 times during study follow-up. Low-density lipoprotein cholesterol (LDL-C) was lower in statin users at study baseline and declined over time more rapidly than among nonusers. In additional analyses, adjustment for LDL-C as a time-dependent covariate does not influence the association between dementia/CIND and statin use over time.

Drs. Nehrlich and Vos compared our study to one of elderly hospitalized patients with heart failure. Our study was population-based and included healthy and younger people. Horwich et al. showed that sick, elderly people with low cholesterol are more likely to die. The lower LDL reported by Horwich et al. was probably due to underlying pathology, declining weight, or frailty. The association of cholesterol measurement of the statin-treated population is higher than that of the general population.

The Framingham Heart study found that those with high cholesterol—defined as 240–380 mg/dL [6.1–9.7 mmol/L]—had significantly better cognition scores than those with lower levels of 150–199 mg/dL (3.85–5.1 mmol/L; p < 0.01 for group test scores).

Statin prescriptions naturally select a higher cholesterol population where cognitive status tends to be better. Cramer et al. should have conducted a simple cholesterol test as was done in the Framingham study. In the abstract, the conclusion of Cramer et al. suggests a protective effect of statin use on cognitive outcomes. However, this is not supported by other data and cannot be concluded from this patient selection study where baseline cholesterol pre-statin use is the one factor for which there was not adjustment. The authors, later in the article, mention that no randomized study date to has reported a cognitive benefit from statin use. This contradicts the assertion made in the abstract.

Cholesterol is vital to memory and the aging brain and the message the authors convey may promote non-evidence-based drug use. At an age where cognitive decline, low cholesterol, and heart failure become major health issues, a recent observational study found 2.6 times the in-hospital mortality from heart failure in those with lowest cholesterol, an effect that became highly significant among statin users.

Eddie Vos, Herbert H. Nehrlich, Sutton, Quebec, Canada

Disclosure: The authors report no disclosures.

USE OF STATINS AND INCIDENCE OF DEMENTIA AND COGNITIVE IMPAIRMENT WITHOUT DEMENTIA IN A COHORT STUDY

To the Editor: Cramer et al. reported less dementia and cognitive decline among statin users in the SALSA study participants. This study implied that less cognitive decline may be a statin benefit yet the authors did not attribute the finding to the selection and prescribing bias.

The only on-label prescribing rationale for statin is elevated cholesterol, thereby unselecting those with lower levels of cholesterol. This was recently confirmed by a study asserting that, “Overall, the mean baseline cholesterol measurement of the statin-treated population is higher than that of the general population.”

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lower LDL with higher mortality is expected in this sample and it does not follow that community-dwelling elderly would be at similar risk.

Elias et al. averaged change over time in total cholesterol rather than modeling decline and evaluated means or odds ratios for cognition rather than incidence of dementia. Neither study addressed the role of statins. In a statin-free sample, Curb et al. found a quadratic (U-shaped) association between LDL and coronary heart disease, attributed the effects of low LDL-C to aging-related metabolic/physiologic changes, and concluded statin treatment as appropriate in healthy elderly. Decline in LDL-C due to underlying disease is not the same as lowering LDL-C by statins or another intervention in relatively healthy, non-frail individuals.

It is inappropriate to compare our study to randomized clinical trials of statin treatment in demented patients with established disease. These trials may have failed because statins cannot slow decline or reverse pathology. The mechanistic roles of statins in neurodegeneration are unclear; our results may be due to the effect statins have on subclinical cerebrovascular disease. For example, the SPARCL trial recently reported that aggressive treatment with atorvastatin reduced stroke risk by 16%.

Cerebrovascular disease is a major contributor to cognitive impairment and dementia so we adjusted for stroke. Cognitive decline and dementia in statin users appear to be less than in nonusers. However, this is not a recommendation for treatment for the purpose of preventing dementia. Only a randomized trial in people with normal cognition can determine whether statin treatment will prevent cognitive decline and dementia.

M.N. Haan, C. Cramer, S. Galea, K.M. Langa, J.D. Kålblesisch, Ann Arbor, MI

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