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.[2] 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.[6]

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1. Kumar N, Boeve BF, Cowl CT, Ellison JW, Kamath PS, Swanson KL. Hypermanganesemia, hereditary hemorrhagic telangiectasia, brain abscess: the hepatic connection. Neurology 2008;71:1118–1119.
2. Smith D, Gwiazda R, Bowler R, et al. Biomarkers of Mn exposure in humans. Am J Ind Med 2007;50:801–811.
3. Peñalver R. Diagnosis and treatment of manganese intoxication. AMA Arch Ind Health 1957;16:64–66.
4. Herrero Hernandez E, Discalzi G, Valentini C, et al. Follow-up of patients affected by manganese-induced Parkinsonism after treatment with $CaNa_2EDTA$. Neurotoxicology 2006;27:333–339.
5. Tuschl K, Mills PB, Parsons H, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia: a new metabolic disorder. J Inherit Metab Dis 2008;31:151–163.
6. Dbouk N, McGuire BM. Hepatic encephalopathy: a review of its pathophysiology and treatment. Curr Treat Options Gastroenterol 2006;9:464–474.
7. Cook DG, Fahn S, Brait KA. Chronic manganese intoxication. Arch Neurol 1974;30:59–64.
8. Huang CC, Chu NS, Lu CS, et al. Chronic manganese intoxication. Arch Neurol 1989;46:1104–1106.
9. Crossgrove J, Zheng W. Manganese toxicity upon overexposure. NMR Biomed 2004;17:544–553.
10. Discalzi G, Pira E, Herrero Hernandez E, Valentini C, Turbiglio M, Meliga F. Occupational Mn parkinsonism: magnetic resonance imaging and clinical patterns following $CaNa_2EDTA$ chelation. Neurotoxicology 2000;21:863–866.
11. Klaassen CD. Heavy metals and heavy-metal antagonists. In: Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 11th ed. New York: McGraw Hill; 2005:1753–1775.


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

**To the Editor:** Cramer et al.[1] 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."[2]

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).[3]

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 to date 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[4] 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.[5]

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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.[6]

Drs. Nehrlich and Vos compared our study to one of elderly hospitalized patients with heart failure.[7] Our study was population-based and included healthy and younger people. Horwich et al.[5] 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



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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.[3] averaged change over time in total cholesterol rather than modeling decline and evaluated means or odds ratios for cognition rather than incidence of dementia.[4] Neither study addressed the role of statins. In a statin-free sample, Curb et al.[8] 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%.[9]

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.

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1. Cramer C, Haan MN, Galea S, Langa KM, Kalbfleisch JD. Use of statins and incidence of cognitive impairment without dementia in a cohort study. Neurology 2008;71:344–350.
2. Thompson R, O'Regan C, Morant A, Phillips B, Ong S. Measurement of baseline total cholesterol: new data from The Health Improvement Network (THIN) database. Prim Care Cardiovasc J 2008;1:107–111.
3. Elias PK, Elias MF, D'Agostino RB, Sullivan LM, Wolf PA. Serum cholesterol and cognitive performance in the Framingham Heart Study. Psychosom Med 2005;67: 24–30.
4. West R, Beeri MS, Schmeidler J, et al. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. Am J Geriatr Psychiatry 2008;16:781–785.
5. Horwich TB, Hernandez AF, Dai D, Yancy CW, Fonarow GC. Cholesterol levels and in-hospital mortality in patients with acute decompensated heart failure. Am Heart J 2008;156:1170–1176.
6. Haan MN. Use of statins, LDL-C and incidence of cognitive impairment or dementia in a seven year cohort study of older Mexican Americans. Presented at the International Congress on Alzheimer's Disease; August 2008; Chicago, IL.
7. Vos E. Nutrition, health & heart disease: tips on how to have a healthy heart. Available at: http://www.health-heart.org/. Accessed May 26, 2009.
8. Curb JD, Abbott RD, Rodriguez BL, et al. Prospective association between low and high total and low-density lipoprotein cholesterol and coronary heart disease in elderly men. J Am Geriatr Soc 2004;52:1975–1980.
9. Fitchett DH, Goodman SG, Langer A. Ischemic stroke: a cardiovascular risk equivalent? Lessons learned from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Can J Cardiol 2008;24: 705–708.