

Homocysteine and the Risk of Dementia

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Featured Article: Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346:476–83.³

In the late 1990s, I was working in a tertiary-care academic medical center in India and running a dementia clinic that had enrolled 120 patients in its first year. India is a country where centuries ago the influence of Buddhism and Jainism had persuaded a large proportion of the population to adopt a vegetarian diet; many others simply could not afford meat or fish. Perhaps as a consequence, as many as a fourth of the patients with dementia (and many without it) had low circulating vitamin B₁₂ concentrations, but correcting this deficiency did not improve their dementia. Nor did most of them have macrocytic anemia, peripheral neuropathy, or other clinical signs of vitamin B₁₂ deficiency. Vitamin B₁₂, along with folate and B₆, are essential cofactors in the conversion of homocysteine, a sulfur-containing amino acid, to methionine. A decade earlier, Lindenbaum et al. had drawn attention to cognitive deficits and neuropsychiatric manifestations in the absence of clinical signs of pernicious anemia and in the presence of low-normal serum B₁₂ concentrations. The symptoms of these patients correlated better with increased homocysteine concentrations, which Lindenbaum et al. were measuring as a marker of subclinical B₁₂ deficiency instead of concentrations of the vitamin itself (1).

The inherited metabolic disorder “homocystinuria” was initially described in “mentally backward” children who died young of vascular disease (2). Kilmer McCully had suggested that smaller increases in plasma homocysteine might increase vascular risk in a population sample, and observational studies were validating this hypothesis. The Framingham Heart Study (FHS) investigators, led by Philip Wolf, Peter Wilson, and Andrew Bostom, had collaborated with an outstanding team of researchers at the Tufts Human Nutrition Research Center—Jacob Selhub, Paul Jacques,

and Irv Rosenberg—to measure plasma homocysteine concentrations in stored serum samples obtained from FHS participants at their 16th biennial examination between the years 1978 and 1981. These homocysteine results had been related to a wide range of cardiovascular outcomes, including the risk of ischemic stroke (3). Even more intriguing, this team had also shown that the US government-mandated folate fortification of enriched cereal products, which was initiated in 1997, had significantly, if modestly, lowered plasma homocysteine concentrations among Framingham Offspring Study participants (4). Vascular risk factors, particularly stroke, increased the risk of dementia. Could McCully's hypothesis be extended to an association of mild increases in circulating homocysteine with the risk of dementia in the community as a whole?

Andrew McCaddon, Robert Clarke, and coworkers had shown in 1998 that circulating homocysteine concentrations were higher in patients with Alzheimer disease than in cognitively normal controls (5, 6). But the “chicken and egg” question remained: Were the observed increases in plasma homocysteine in Alzheimer disease patients a consequence of their dementia and resulting poor nutritional habits? Was this an instance of reverse causality? Only data from a prospective cohort in which homocysteine had been measured years before the onset of dementia could address that question.

I had completed a fellowship a few years earlier in the neurobiology of aging at the University of Massachusetts Medical Center. During that fellowship, I had volunteered some hours each week to examine FHS participants. The grace and graciousness of these participants (most of them belonging to what Tom Brokaw called “The Greatest Generation”), the reputation of the investigators, the friendliness of the staff, and the depth and breadth of the data available were as intoxicating to me as they have been to many others stronger and wiser than me!

I returned from India to Framingham in 1998, at a perfect time to join the “homocysteine team” in investigating the relationship of plasma homocysteine to the risk of incident dementia. We were astounded to find that the impact of homocysteine was considerable, as large as that of having an *APOE* (apolipoprotein E) e4 genotype. With the tantalizing thought that this link might lead to a relatively low-cost and harmless vitamin intervention to reduce the

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³ This article has been cited more than 1300 times since publication.

risk of dementia and Alzheimer disease, we submitted our manuscript to the *New England Journal of Medicine*. A year later, and after a 15-page response letter to the reviewers, the article was published with an editorial. Unfortunately, as for so many other leads involving the prevention of Alzheimer disease, this link has proved more complex than we had initially imagined. It remains a beacon and a challenge for our group and others to explore further.

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