

Elevated plasma total homocysteine levels increased the risk for dementia in the elderly

Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med.* 2002 Feb 14;346:476-83.

QUESTION

Is an elevated plasma total homocysteine level a risk factor for dementia in the elderly?

DESIGN

Cohort study with a median follow-up of 8 years.

SETTING

Framingham, Massachusetts, USA.

PARTICIPANTS

1092 elderly participants (mean age 76 y, 61% women) from the Framingham Study cohort who were free from dementia and had plasma total homocysteine levels measured at their 20th biennial examination.

ASSESSMENT OF RISK FACTORS

Baseline data were collected on the plasma total homocysteine level. Analyses were adjusted for baseline age; sex; apolipoprotein E genotype (93% of participants); plasma

levels of folate (98% of participants), vitamin B₁₂ (85% of participants), and vitamin B₆ (92% of participants); educational status; history of stroke; cigarette smoking; alcohol intake; diabetes mellitus; systolic blood pressure; and body mass index.

MAIN OUTCOME MEASURES

Dementia (*Diagnostic and Statistical Manual of Mental Disorders, 4th edition*) criteria; symptoms > 6 months in duration; and Clinical Dementia Rating scale severity of dementia score ≥ 1) and Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for definite, probable, or possible Alzheimer disease). Outcome assessors were blinded to plasma total homocysteine levels.

MAIN RESULTS

Dementia was diagnosed in 111 participants (10% of the cohort), and of those, 83 partic-

ipants (8% of the cohort) were diagnosed with Alzheimer disease. After adjustment for all collected variables using a Cox proportional hazards model ($n = 680$), risks for dementia (relative risk [RR] 1.4, 95% CI 1.1 to 1.9) and Alzheimer disease (RR 1.8, CI 1.3 to 2.5) were increased; the RRs were per increment of 1 standard deviation in the log-transformed baseline plasma total homocysteine levels. Hyperhomocysteinemia (plasma homocysteine > 14 $\mu\text{mol/L}$) increased the risks for dementia (RR 1.9, CI 1.3 to 2.8) and Alzheimer disease (RR 1.9, CI 1.2 to 3.0).

CONCLUSION

An elevated plasma total homocysteine level was a risk factor for dementia in the elderly.

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COMMENTARY

A risk factor may show disease causation; if it suggests a plausible intervention, then it is all the more interesting. It is even better if that intervention is preventive. Robust risk factors for Alzheimer disease are now well established: increased age, the Down syndrome, poor education, and apolipoprotein E status. These risks are not easily altered. Biological risk factors that can be altered are especially attractive. Some, such as estrogen use and middle-life vascular risk-factor control, have accumulating evidence and suggest obvious, if awkward, interventions. The homocysteine story includes a plausible mechanism for causing Alzheimer disease, and the suggested intervention (dietary folate supplementation) is cheap, easy, and available to all. Folate prevents neural tube defects, a finding that has already led to dietary supplementation with folate in the United States.

The study by Seshadri and colleagues is hypothesis generating and prospectively studies 1092 participants from the Framingham Study, of whom 111 subsequently developed dementia. The wide confidence intervals of the RRs reported in the study suggest the need for caution in interpreting these results. Can they be explained because of inadequate adjustment for possible confounding factors? In addition, the findings of Seshadri and colleagues are contrary to those from the other large prospective study of homocysteine and cognition (1). Some of these uncertainties can be resolved by doing larger studies that provide

estimates of the association between homocysteine and dementia in a range of different circumstances (such as at different levels of other risk factors and at different times in the evolution of risk). Analogy with plasma risk factors in cardiovascular disease is instructive. Initial studies overestimated the role of homocysteine, and a recent synthesis of the evidence suggests that its role remains uncertain (2), even though > 10 times the amount of information is available for cardiovascular disease than for dementia. Understanding the exact nature of the relation between homocysteine and dementia is important because the implications of this link are far reaching.

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2. Danesh J, Lewington S. Plasma homocysteine and coronary heart disease: systematic review of published epidemiological studies. *J Cardiovasc Risk.* 1998;5:229-32.