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The impact of homocysteine and B vitamins on Alzheimer's disease, cognitive performance and structural brain changes

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ABSTRACT

The overall aim of this thesis was to investigate the relation of homocysteine (tHcy), vitamin B12, and folate with Alzheimer's disease (AD), cognitive performance, and structural brain changes in population-based studies of Finnish and Swedish elderly individuals.

Study I. Serum levels of tHcy, holotranscobalamin (holoTC, the active fraction of vitamin B12), and folate were assessed in 274 individuals aged 65-79 years and without dementia from the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study. Participants were followed-up for 7 years to detect incident AD. The odds ratios (OR) (95% confidence interval [CI]) for AD were 1.16 (1.04-1.31) for each increase of 1 μmol/L tHcy and 0.980 (0.965-9.995) for each increase of 1pmol/L holoTC. While adjusting for holoTC attenuated the tHcy-AD relation, the holoTC-AD link was less influence by controlling for tHcy. The protective effects of holoTC were more pronounced with increasing age.

Study II. In the CAIDE study, performance in several cognitive domains was assessed on two occasions. Higher tHcy values among 65-79 years old persons were associated with worse performance on global cognition, episodic memory, executive functions and verbal expression 7 years later. Elevated holoTC was related to better performance on global cognition, executive functions, and psychomotor speed. After excluding participants with incident dementia, tHcy and holoTC remained associated with several cognitive domains, and folate became associated with global cognition and verbal expression. The protective effects of holoTC were present over the whole normal range of holoTC.

Study III. The associations of baseline plasma tHcy with neuropathological and post-mortem magnetic resonance imaging (MRI) findings up to 10 years later were investigated in the Vantaa 85+ study including individuals aged >85 years. tHcy levels in the highest quartile were related to about 2.5-fold increased OR for higher neurofibrillary tangles burden. This association was present particularly in subjects with dementia, cerebral infarcts, and with longer follow-up duration. tHcy tended to relate to amyloid -β accumulation in people with longer follow-up time. Higher tHcy levels were also associated with more severe medial temporal lobe atrophy and periventricular white matter hyperintensities on post-mortem MRI.

Study IV. Plasma B12 and red blood cell folate were examined in relation to brain volumes in a Swedish population-based study (The Swedish National Study of Aging and Care in Kungsholmen (SNAC-K)), including dementia-free individuals aged >60 years with MRI scans at 2-3 occasions over 6 years. Higher baseline plasma B12 concentrations were associated with decreased rate of total brain tissue and grey matter volume loss, even in non-demented elderly. The protective effects of vitamin B12 were present over the whole distribution of vitamin B12 levels.

Conclusions: Results of this project indicate that lower B12, elevated tHcy, and lower folate levels are involved in late-life cognitive impairment. Assessments of B12 and folate status (including functional indicators such as tHcy or holoTC) are recommendable in elderly at risk of dementia. Adequately timed and powered randomized controlled trials are needed to determine the impact of B-vitamin supplementation on preventing cognitive decline and dementia-related pathology.

Keywords: Alzheimer's disease, Alzheimer pathology, cerebrovascular pathology, cognition, elderly, dementia, folate, holotranscobalamin, homocysteine, population-based study, vitamin B12

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