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Dementia Prevention by Disease-Modification through Nutrition

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It is agreed that disease-modification is the most desirable approach to tackling dementia (1), but we are often told that it is not yet feasible and that "no disease modifying therapy has proven effective in clinical trials" (2). The purpose of our Editorial is to show that disease-modification is not only feasible but that there is good evidence that it has already been achieved in subjects with Mild Cognitive Impairment (MCI). An important approach to dementia prevention is to identify modifiable risk factors and to administer treatments that reduce the exposure to the risk factor. One such risk factor is raised plasma total homocysteine (tHcy), which is considered to be one of the most significant modifiable risk factors for incident AD, along with low education and low physical activity (3). In a meta-analysis on 5 observational studies (4,412 subjects) it was found that raised tHcy was associated with a pooled relative risk of AD of 1.93 (C.I. 1.5, 2.49) and had a population attributable risk for AD of 21.7% (3). Raised tHcy can readily be lowered by supplementation with B vitamins (folic acid, B12 and B6) and there have been a number of trials in which one or more of these B vitamins have been administered. It has been pointed out that the majority of these trials were poorly designed or interpreted and so few conclusions can be drawn (4, 5). However, two of the trials were well designed and gave clear results. The FACIT trial in the Netherlands selected 818 subjects (mean age 60y) with tHcy > 13 μmol/L and gave half of them a supplement of 0.8 mg of folic acid for 3 years, which led to a lowering of tHcy concentrations by 26%. Significant slowing of age-related decline was found in memory and several other cognitive domains, compared with subjects taking a placebo (6). Of direct relevance to the topic of disease-modification is the VITACOG trial in the UK which was done on 271 people with MCI (mean age 77y) (7). A subgroup (n = 168) volunteered for MRI scans and half of these were randomised to a supplement of three B vitamins (0.8 mg folic acid, 0.5 mg B12, 20 mg B6) for 2 years. The trial was designed to see if the B vitamins slowed down the accelerated rate of brain atrophy that occurs in MCI and whether the treatment effect was influenced by the baseline concentration of tHcy. After 2 years of treatment, the tHcy concentration in the B vitamins group was 30.2% lower than that in the placebo group and, in the intention to treat analysis, there was a 29.6% slower rate of brain atrophy in the B vitamin group than in the placebo group. Importantly, the rate of brain atrophy in the placebo group was strongly influenced by the baseline tHcy concentration, with subjects in the top quartile (> 13μmol/L) showing a rate of atrophy (1.52% per y) almost twice that of those in the bottom quartile (≤ 9.5μmol/L). The effect of B vitamin treatment was greater the higher the baseline tHcy, with subjects in the top quartile showing a 53% slowing of brain atrophy. If we accept that the rate of brain atrophy is a valid biomarker of disease progression (1), then these results imply the modification of progression by B vitamin treatment. The VITACOG trial was not powered to detect an effect on cognition and indeed it was found that there was no overall effect of B vitamin treatment on most cognitive test scores, although executive function was better maintained in the B vitamin group. However, when baseline tHcy was taken into account, there was a striking difference: for those with tHcy below the median (11.3 μmol/L) there was no treatment effect, but in those with tHcy above the median the B vitamin treatment significantly slowed decline in episodic memory, semantic memory and global cognition (MMSE) (8). A marked effect on the CDR was found in those with high baseline tHcy (> 13 μmol/L): in the placebo group, there was no significant change in the proportion having a CDR score of zero over 2 y, but in the B vitamin group 25% had a zero score at baseline and after 2 y of treatment this had increased to 58.3%. In other words, clinically the B vitamin group showed a significant improvement over time. Logistic regression showed that the odds of having CDR=0 at follow-up is five times greater in the B vitamin group compared with placebo (8). On the basis that the CDR is a valid outcome measure for disease progression (1), these results are consistent with a disease-modifying effect of B vitamin treatment. Further evidence of a disease-modifying action of B vitamins came from analysis of the changes in brain regional gray matter in the participants in VITACOG (9). Voxel-based morphometry was used to identify the regions where gray matter atrophy was protected by B vitamin treatment. No significant effect of the treatment was found in participants whose baseline tHcy was below 11 μmol/L, but in those with high baseline tHcy the following regions showed significant atrophy in the

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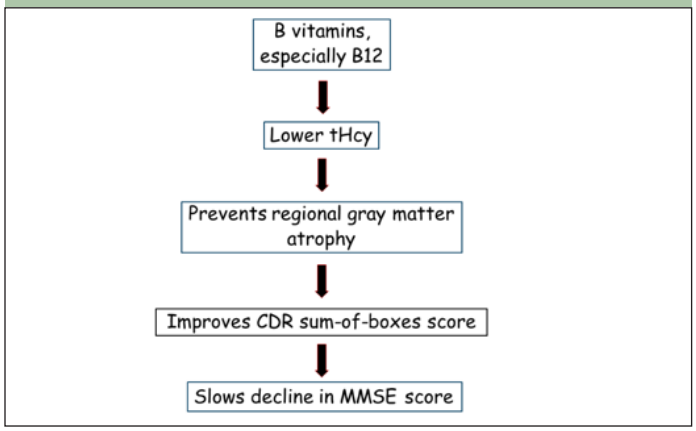
placebo group that was markedly slowed in the B vitamin group: hippocampus, parahippocampal gyrus, inferior parietal lobule and retrosplenial cortex, fusiform gyrus and inferior temporal gyrus. It is notable that these regions are among those that best discriminate normal ageing from MCI and which also show the fastest atrophy rate in conversion from MCI to AD. For these specific regions, there was a striking quantitative difference between the placebo group (n=35), with an average loss of gray matter of 5.2% over 2 y, and the B vitamin group (n=42) where the gray matter loss was only 0.6% over 2 y. Thus, the B vitamin treatment slowed atrophy in these regions by 8.7-fold compared with the placebo treatment. A directed acyclic graph was used to model the relationships between the measured parameters. The resultant optimal Bayesian network is shown in Figure 1. Thus, the VITACOG trial has identified possible causal links in the disease-modifying process in MCI that results from administration of high-doses of B vitamins (9). It must be stressed that the above results in VITACOG were only found for participants with baseline tHcy concentrations above the median, which indicates that the B vitamin status of these subjects was not ideal. In a later study the baseline concentrations of total fatty acids were measured and it was found that the B vitamins only had a beneficial effect on brain atrophy (10) and on cognition (11) in participants who had a good baseline status of omega-3 fatty acids. Possible mechanisms for the beneficial effects of B vitamins and for the interaction between B vitamins and omega-3 fatty acids are discussed in detail elsewhere (5). To summarise, the evidence of disease-modification by B vitamin treatment for two years in MCI subjects with high tHcy is as follows: 1. Whole brain atrophy rate was slowed by B vitamin treatment by up to 53%, depending on the baseline tHcy concentration. 2. The rate of decline in cognitive test scores (episodic and semantic memory) was slowed by B vitamin treatment. 3. The proportion of MCI subjects reverting to a CDR score of zero was more than doubled in the B vitamin group. 4. The rate of gray matter atrophy specifically in brain regions that are susceptible to AD, such as the hippocampus, was reduced by almost 9-fold after B vitamin treatment. 5. A causal pathway, via slowing of regional atrophy, mediating the beneficial cognitive effects of B vitamin treatment was identified. Individually each the above findings is consistent with disease-modification, but taken together they surely offer very convincing evidence. While we believe that the VITACOG trial has demonstrated that disease-modification can be achieved in MCI by a nutritional intervention, it will be crucial to establish in a new trial that this intervention (ideally with the addition of omega-3 fatty acids) slows or prevents the conversion from MCI to dementia. Pending the outcome of such trials, many people with MCI could benefit by a policy that screens for tHcy and then treats those who have elevated concentrations with B vitamins; such a policy operates in Sweden (12) and would be highly cost-effective (13). Furthermore, the results should encourage others to explore other nutritional interventions in subjects whose nutritional status is not optimal.

Figure 1. Directed acyclic graph analysis of B vitamin treatment and consequential changes in brain structure and function in MCI. The mediating pathway shows the optimal Bayesian network that explains the findings from the VITACOG trial. For details see reference (9)



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