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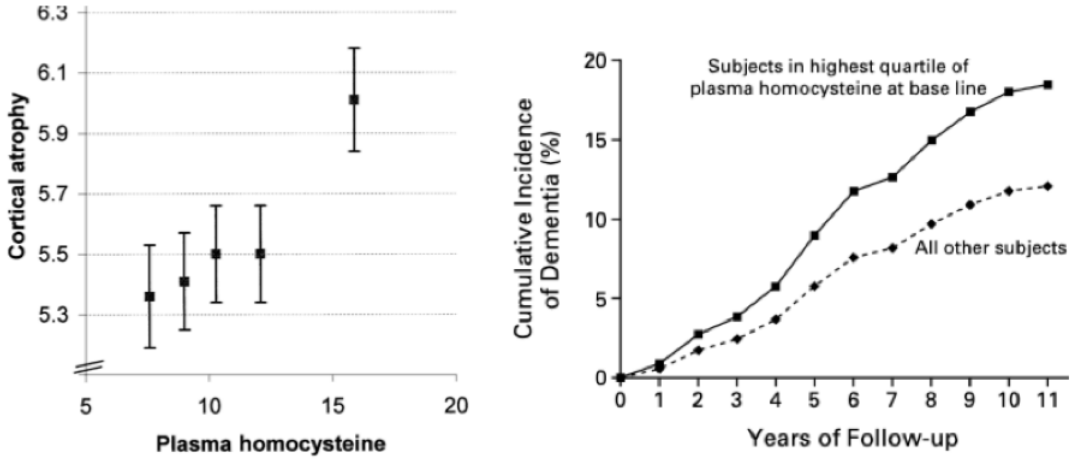
Smith AD, Smith SM, de Jager CA, Whitbread P, Johnston C, Agacinski G, et al. Homocysteine-lowering by b vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: A randomized controlled trial. PLoS One. 2010;5(9):1–10.

What We Know, Think We Know, or Are Starting to Know

The first indication that B-vitamins may have a role in neurological health is in fact one of the earliest observations of nutrient deficiency in nutritional sciences: 'Beriberi' , a colloquial name of obscure origin given to a condition common in East and South Asia in the 19th and early 20th Centuries, which caused cognitive impairment resulting from vitamin B1 [thiamine] deficiency.

These early nutrient deficiency findings placed B-vitamins on the neurological radar. From its synthesis in 1948, vitamin B12 [cobalamin] became available to treat pernicious anaemia, but B12 deficiency also has neurological presentations, including cognitive disturbance and peripheral neuropathy [(1)]. Vitamin B6 [pyridoxine] is an important co-factor in the conversion of dopamine precursors into active dopamine in the brain [(2)] [NB Nutritionists: this is why B6 supplements are contraindicated in anyone taking levodopa for Parkinson's Disease]. For vitamin B9 [folate], while there is no specific neurological condition associated with B9 deficiency, the intimate relationship between B9 and B12 in the methylation cycle* is critical, and high B9 intake may mask B12 deficiency [(3)]. Moreover, there is evidence to suggest that in people with low B12 status, high B9 intake may increase cognitive impairment [(4,5)].

This relationship between B-vitamins and homocysteine has resulted in interest in their potential therapeutic effect, based on associations between homocysteine and dementia and Alzheimer's Disease [(4,5)]. In the Framingham Study, elevated homocysteine was associated with a 40% increase in risk for AD after 8yrs follow-up [(4)]. In the Rotterdam Scan Study, a population - based MRI study in 60-90yo, elevated plasma homocysteine levels was associated with significant atrophy of the hippocampus, a brain region with vital roles in memory consolidation [(5)].

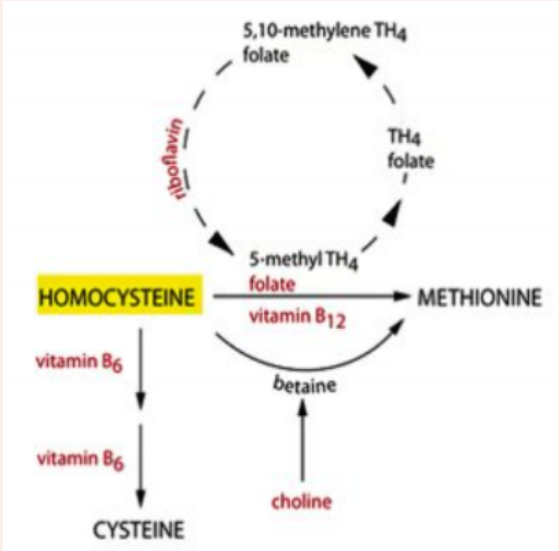


Left Figure *from the Rotterdam Scan Study [(5)] illustrating the rate of global brain atrophy associated with homocysteine levels, with the most profound increase of brain atrophy observed at homocysteine levels of >15µmol/L.* ***Right Figure*** *from the Framingham Study [(4)] illustrating the incidence of dementia in participants with the highest homocysteine levels at baseline, which in this study was >14µmol/L.*

Thus, the interest in B-vitamins, homocysteine, and cognitive health has a solid mechanistic basis. The present study investigated the effects of a vitamin B6/B9/B12 combination supplement on homocysteine levels and brain atrophy in elderly adults with mild cognitive impairment.

*Geek Box: The Methylation Cycle

It's important for the context of this study, and anything related to homocysteine, to understand the methylation cycle. A methyl group is one carbon atom [C] bonded with 3 hydrogen atoms [H3], so collectively this is written as CH3. Methylation is the process of adding a CH3 methyl group to another pre-existing molecule, and adding a methyl group to a molecule may either inhibit or initiate reactions. Thus, methylation is responsible for regulating genetic and epigenetic expression and repairing of DNA and RNA, along with neurotransmitter regulation and energy production. The methyl donor responsible for transferring methyl groups to other molecules is known as S-adenosylmethionine [SAMe]. The cycle responsible for producing SAMe is also knows as the 'methylation cycle', and is where homocysteine is produced as a byproduct. You can see this cycle in the diagram below. The cycle begins with 5-methyltetrahydrofolate [5-methylTH4], which is the active form of dietary folate - vitamin B9. This step requires the function of an enzyme, methyltetrahydrofolate reductase [MTHFR], through which folate enters the cycle. A series of methyl group donations result in a cycle ultimately producing homocysteine. As you can see from the red names of vitamins, B2 [riboflavin], B6 [pyridoxine], B9 [folate] and B12 [cobalamin] are all important cofactors in order to recycle this homocysteine back into the amino acids methionine and cysteine. Of these co-factors, however, it appears that B9 and B12 are the most important, as the recycling of homocysteine into methionine is a fundamental step in the functioning of these cycles. There are two common genetic variants in the MTHFT enzyme, C677T and A1298C, result in the enzyme under-functioning and require supplemental folate for normal functioning of the methylation cycle, and lower homocysteine levels. This methylation cycle provides a mechanistic understanding for how inadequate levels of B-vitamins, folate and B12 in particular, may lead to elevated homocysteine levels.



The Study

The 'Homocysteine and B vitamins in cognitive impairment' VITACOG Study was a randomised, double-blind, and placebo-controlled trial comparing a combined 0.8mg B9, 0.5mg B12, and 20mg B6 supplement taken daily to a placebo. The primary outcome measures were brain atrophy [shrinkage] assessed by MRI, and cognitive performance.

The present study investigated whether the combined B-vitamin supplement would slow the rate of brain atrophy by lowering plasma homocysteine levels. Participants were >70yo with a diagnosis of mild cognitive impairment [MCI]. The intervention lasted for 2yrs, and participants consented to a brain MRI scan and blood samples at baseline and at the end of the intervention period.

The analysis examined the difference in the rate of brain atrophy between the intervention and placebo groups as determined by MRI scan at baseline and follow-up. In addition, the rate of brain atrophy was also examined in relation to changes in plasma concentrations of B6, B9, and B12, over the 2yrs. As age was significantly associated with rate of brain atrophy, results presented here are adjusted for age.

Results: 168 participants completed both baseline and final MRI scans [85 in the intervention group, 83 in the placebo group]. In the intervention group, adherence was confirmed by the plasma analysis which indicated that mean B9 levels increased by 266% [22.4 to 82.1nmol/L], while B12 increased by 103% [330pmol/L to 672pmol/L]. No significant changes in plasma B9/B12 occurred in the placebo group, also indicating compliance.

- ***Homocysteine:*** Plasma homocysteine levels decreased by 22.5% in the intervention group, and increased by 7% in the placebo group.
- ***Brain Atrophy:*** After adjusting for age and other covariates [i.e., smoking, BMI, alcohol, and specific genetic variants], brain atrophy was 27.1% lower in the B-vitamin intervention group. Confining the analysis to participants with high compliance, the effect was greater at a 31.1% lower rate of atrophy.
- ***Relationship Between Homocysteine & Brain Atrophy:*** Rate of brain atrophy was positively associated with baseline homocysteine levels. Participants in the placebo group with higher baseline homocysteine levels had greater brain atrophy over 2yrs. Conversely, participants in the intervention group who had higher baseline homocysteine levels had a reduction in brain atrophy of 43%, compared to an 11% slower rate of atrophy in intervention group participants with lower baseline levels.
- ***Relationship Between B-vitamins & Homocysteine:*** Greater increases in plasma levels of vitamin B9 and B12 were associated with greater reductions in rate of brain atrophy, mediated by homocysteine. The investigators divided participants in the intervention group in quartiles [i.e., 4 tiers], and analysed the effects of treatment with B-vitamins relative to baseline homocysteine levels: there was no effect of B-vitamin supplementation in participants in the lowest quartile of homocysteine, but a 53.3% slower rate of brain atrophy in participants in the highest quartile. Despite greater rate of brain atrophy in the placebo group, neither baseline B9 or B12 was associated with this rate of atrophy; only baseline homocysteine levels were.

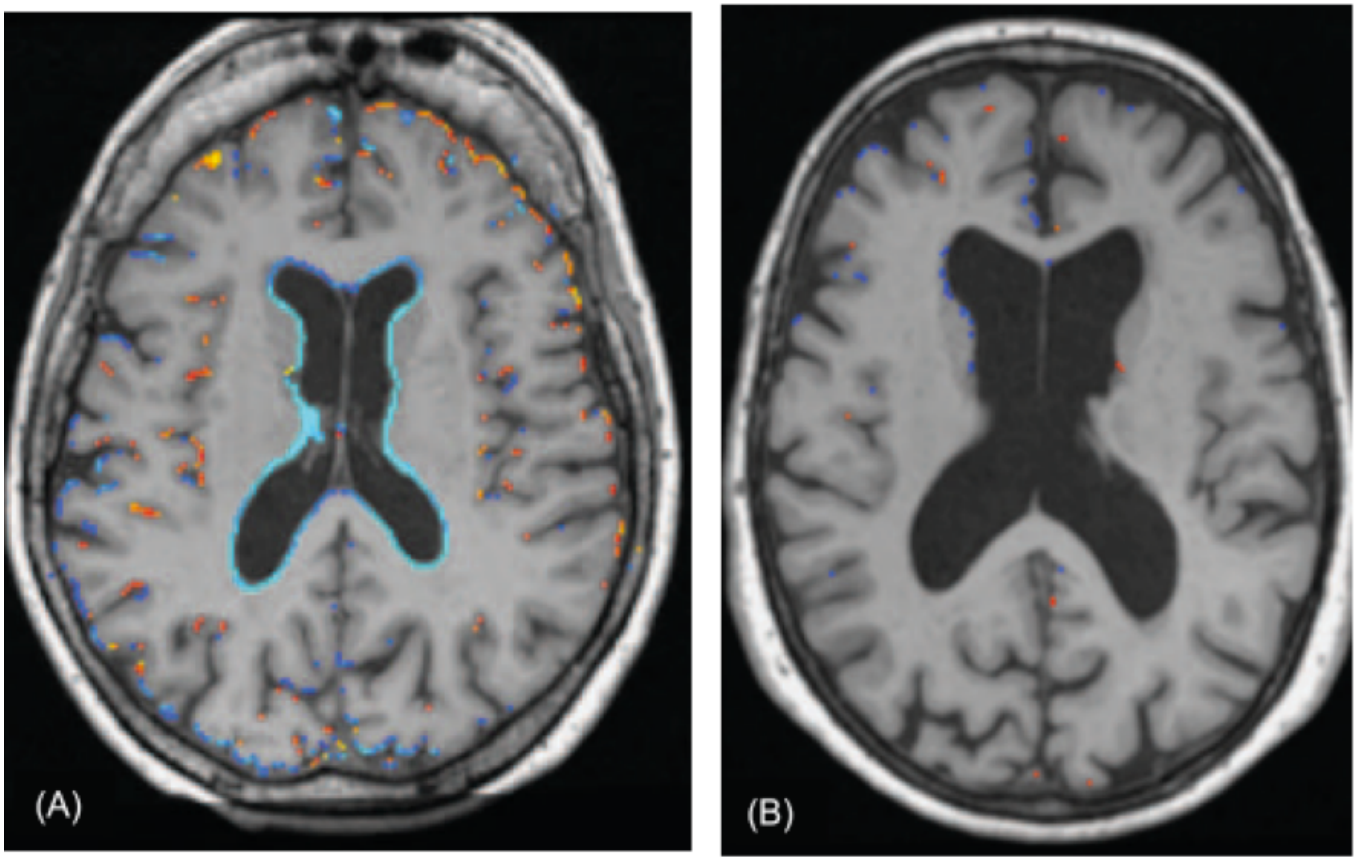


Figure *image from MRI scans in study of brain atrophy, highlighted by the orange/red and blue/light blue colourings. Image* ***(A)*** *shows the atrophy in a participant in the placebo group with baseline levels of homocysteine >22µmol/L, in whom homocysteine levels increased by 8µmol/L over the course of the 2yrs intervention. In contrast, image* ***(B)*** *shows the effects of B-vitamin supplementation over 2yrs in a participant from the intervention group with baseline levels of homocysteine of 24µmol/L, in whom the intervention resulted in a 12µmol/L decrease in homocysteine levels, and no clear pattern of brain atrophy.*

The Critical Breakdown

Pros: The study was a well-designed intervention meeting 'gold-standard' criteria. The maintenance of blinding was achieved by providing tablets labelled with the trial name, which meant the placebo group remained constant. The 2yr duration of the trial, with >75% compliance, were positives. Finally, the use of MRI to quantify brain atrophy, and the measurement of biomarkers of B-vitamin intake, provided strong mechanistic insight into the effects of the intervention.

Cons: Although the VITACOG study reported on cognitive outcomes, it was statistically underpowered to detect effects on cognition alone. While the analysis indicated B6 may not be related to the outcome, the intervention was a combination supplement and thus it is not possible to truly tease apart the interrelationships between the included nutrients.

Key Characteristic

Measuring compliance with plasma samples. The investigators choose particular blood levels as cut-off points to deem a participant compliant, i.e., if their plasma B-vitamin levels were over a certain threshold, it indicated high compliance with taking the supplemental intervention. This allowed for a clear picture to be presented from the data showing the relationship between levels of B-vitamins, homocysteine, and brain atrophy.

For example, there was no reduction in brain atrophy in the 31 participants from the intervention group who were deemed non-compliant, in whom the homocysteine reduction was only 13%. Conversely, the greater the improvement in B9 and B12 levels, the slower the rate of brain atrophy.

This also allowed examination into the relationship between changes in B-vitamin status, and changes in plasma homocysteine levels. The effect of B-vitamin supplementation was greatest in participants with higher baseline homocysteine levels.

Interesting Finding

There are two that deserve comment. The first is that there was no association noted between cystathionine levels, a biomarker of vitamin B6 status, and brain atrophy. This suggests that the beneficial effect of the intervention related specifically to improvements in levels of B9 and B12, but that B6 may not be related to protection against brain atrophy. This doesn' t mean that B6 isn' t important for brain health, however, it appears that the primary effect in the present study relates to the remethylation of homocysteine [lowering homocysteine levels], for which B9 and B12 may be more specifically required.

Which brings us to the second interesting finding, which is the relationship between baseline homocysteine levels and treatment effects of B-vitamin supplementation. In participants with homocysteine <9.5µmol/L, there was no effect of supplementation; in participants with homocysteine >13.0µmol/L, there was a 53.3% reduction in rate of brain atrophy. This indicates that the effect of B9 and B12 supplementation was clearly mediated by homocysteine levels, i.e., there may be no benefit to supplementation - even in individuals with MCI - if homocysteine levels are not elevated.

Relevance

The role of B-vitamins in epidemiology of diet and dementia has been difficult to elucidate, possible due to the tight correlations between B9 and B12, the potential for B9 intake to mask B12 deficiency, and the effect of food fortification, which is undertaken for B9, but not B12 [8]. Nonetheless, the strong epidemiological associations between homocysteine and dementia, and the mechanistic knowledge of the critical role for B9 and B12 in the methylation cycle, have meant interest in the potential for B-vitamins to benefit cognitive health has been sustained. The present study adds good evidence of both efficacy of a B-vitamin intervention in adults with MCI, and interventional evidence for the biological plausibility of the B-vitamins>homocysteine>brain hypothesis.

The fact that baseline B9 and B12 were not associated with rate of brain atrophy in the placebo group may not be surprising: levels of these nutrients were both within normal range. This again points to homocysteine as the factor negatively influencing rate of brain atrophy. It also indicates that the particular benefit of B9 and B12 supplementation relates specifically to the role of both these highly correlated nutrients in reducing homocysteine levels. This makes the actual causal factor difficult to elucidate, as the authors ponder in their discussion: is elevated homocysteine the direct cause of brain atrophy, or is elevated homocysteine a marker for low levels of B-vitamins, i.e., B9 and B12 are the causal factors? This is arguably overly reductionist thinking: in a "sufficient cause" framework, both may be causal.

Nonetheless, arguably all roads of analysis in this study appear to point to homocysteine as the moderating factor, giving high-quality interventional evidence to the observational epidemiology associating elevated homocysteine levels with increased risk for dementia and Alzheimer' s Disease [6,7]. Notably, the homocysteine levels in the highest quartile in the present study of >13.0µmol/L are consistent with levels of homocysteine in prospective cohort studies associated with profound increases in risk. For example, in the Aberdeen 1921 Birth Cohort, homocysteine levels of >14µmol/L were associated with a 272% increased risk for dementia, while in the Framingham Study >14µmol/L a 90% increase in dementia and Alzheimer' s Disease risk [6,7].

Application to Practice

Supporting healthy brain ageing is important given the predicted increase in dementia prevalence over the next 25yrs. This study indicates that in elderly adults with MCI and elevated homocysteine, combination B-vitamin supplementation [in particular B9 and B12] is a safe and well-tolerated supplemental intervention to protect the brain against atrophy.

References

1. Savage D, Lindenbaum J. Neurological complications of acquired cobalamin deficiency: clinical aspects. Baillière' s Clinical Haematology. 1995;8(3):657-678.
2. Allen G, Neergheen V, Oppenheim M, Fitzgerald J, Footitt E, Hyland K et al. Pyridoxal 5′-phosphate deficiency causes a loss of aromatic l-amino acid decarboxylase in patients and human neuroblastoma cells, implications for aromatic l-amino acid decarboxylase and vitamin B6 deficiency states. Journal of Neurochemistry. 2010;:no-no.
3. Ellison A. Pernicious anemia masked by multivitamins containing folic acid. Journal of the American Medical Association. 1960;173(3):240.
4. Morris M, Evans D, Bienias J, Tangney C, Hebert L, Scherr P et al. Dietary Folate and Vitamin B12 Intake and Cognitive Decline Among Community-Dwelling Older Persons. Archives of Neurology. 2005;62(4):641.
5. Moore EM, Ames D, Mander AG, et al. Among vitamin B12 deficient older people, high folate levels are associated with worse cognitive function: combined data from three cohorts. J Alzheimers Dis. 2014;39(3):661-668.
6. Seshadri S, Beiser A, Selhub J, Jacques P, Rosenberg I, D' Agostino R et al. Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer' s Disease. New England Journal of Medicine. 2002;346(7):476-483.
7. den Heijer T, Vermeer S, Clarke R, Oudkerk M, Koudstaal P, Hofman A et al. Homocysteine and brain atrophy on MRI of non-demented elderly. Brain. 2003;126(1):170-175.
8. Morris M. Nutritional determinants of cognitive aging and dementia. Proceedings of the Nutrition Society. 2011;71(1):1-13.