

# Who benefits more from the cognitive effects of B vitamins?

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## Further understanding of the characteristics of the responders may shed light on how B vitamins benefit brain health and the formulation of more effective forms of B vitamins

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B vitamins are often prescribed for or bought over the counter by older people with mild cognitive impairment (MCI). The cognitive responses of B vitamins, notably vitamin B12 and folic acid, have been inconsistent in randomised placebo controlled trials. A probable explanation is that B vitamins benefit some but not all people with cognitive impairment.

## The importance of Omega3 for cognitive function in people with AD

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The VITACOG trial in Oxford was one of the few that showed positive B vitamins results in older people with MCI. The trial showed that the combination of vitamin B12, folic acid and vitamin B6 reduced brain atrophy over a two-year period in older people with amnesic MCI, i.e. the subtype of MCI characterised by impaired short-term memory. (Smith et al. 2010) On subsequent subgroup analysis, it was found that only those with high serum omega3 responded to the B vitamins. (Smith et al. 2021)

Since then, there has been more evidence that B vitamins and omega3 supplements have additive effects on cognitive function in those with MCI. It is known that B vitamins enhance the formation of phosphatidylcholine (PC), a form of phospholipid which is important for brain function. It is possible that PC containing omega3, produced in the liver, is important to cognitive function in people with AD. (Smith et al. 2021) More research into this nutrient interaction is warranted.

## Negative interaction effect of concomitant use of aspirin

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Inspired by the VITACOG trial, we performed a similar randomised trial of B vitamins (vitamin B12 and folic acid) in older Chinese people with MCI in Hong Kong. Although we did not observe significant cognitive improvement in the supplemented subjects, we found a significant negative interaction effect of concomitant use of aspirin. (Kwok et al., 2020) Among those aspirin users, B vitamins actually led to more cognitive decline than placebo.

When we combined our data with that of VITACOG trial, this negative interaction effect of aspirin was still significant. We believe that the negative interaction was between aspirin and folic acid, as in our earlier trial of vitamin B12 supplementation in older people with diabetes mellitus; no trend of an interaction effect of aspirin on the cognitive response was observed. More investigations are needed to explain the mechanisms of this interaction. Meanwhile, folic acid supplements should be avoided in those on aspirin.

## Dihydrofolate reductase (DHFR) gene polymorphism

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Folate is an important nutrient for brain health. Borderline low folate status is common in older people because of the relatively low intake of green leafy vegetables and poor dental status. Folic acid is, therefore, a common constituent of B vitamin supplements. However, folic acid requires conversion to active folates by an enzyme called DHFR in the liver.

The activity of DHFR is known to be significantly influenced by DHFR 19-bp deletion gene polymorphism. Those with DHFR del/del genotype had greatly reduced DHFR activity. Therefore it is plausible that folic acid may be less effective in those with DHFR del/del genotype.

In a post hoc analysis of the combined data set of the VITACOG trial and our trial of a similar design in Hong Kong, we found that only those with DHFR in/in genotype, i.e. intact DHFR function (accounting for 26% of the subjects) responded cognitively to B vitamins. (Wu et al., 2022) This suggested that folic acid is not the ideal form of folate supplement, even though this formulation is favoured because of its chemical stability.

Alternative forms of folate supplement, e.g. folinic acid or methylfolate which do not require conversion by DHFR may therefore be more effective than folic acid in the majority of people, especially among Chinese people who have a relatively low prevalence of DHFR in/in genotype.

## Metabolomic changes in B vitamin responders

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In our randomised trial of B vitamins in older Chinese people with MCI, some subjects did improve with B vitamins, even though the overall result was negative. To understand why some subjects responded to B vitamins, we performed extensive metabolomics analysis on the archived serum samples at baseline and month 24 in the responders. Pathway analysis showed that the most significant effect of B vitamins was the enhancement of gluconeogenesis and Warburg effect among the responders.

Warburg effect was first described in cancer cells where there was a preponderance towards glucose utilisation irrespective of oxygen availability. It is well known that beta amyloid deposition, a hallmark of Alzheimer's disease (AD), impairs glucose metabolism. It is plausible that this shift towards glycolysis by B vitamins may help neurons to survive the negative effects of beta amyloid accumulation. This suggested that B vitamins may be more effective for cognitive function in those with incipient AD.

## Frontal lobe atrophy and vitamin B

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To further explore the characteristics of the positive responders in our randomised trial, we performed another postdoc analysis to identify MRI markers of a positive cognitive response to B vitamins. It was found that the most significant predictor was left frontal lobe atrophy. (Gong et al., 2022) This is interesting because frontal lobe atrophy is a later stage development in AD. The implication is that B vitamins may not be as effective in

older people with MCI if the underlying AD is at its earlier stages. Clinically it is possible to identify patients with frontal lobe atrophy by administering Frontal Assessment Battery or Stroop test.

Older MCI patients with AD and frontal lobe dysfunction will benefit from vitamin B In conclusion, among older people with MCI, those with AD and frontal lobe dysfunction are most likely to benefit from vitamin B12 and folate supplementation. Folinic acid or methylfolate may be superior to folic acid in efficacy, especially in Chinese people with a high prevalence of DHFR 19-BP deletion genotypes. B vitamins may be more effective when they have combined with omega 3 supplements. The use of folic acid should be avoided by aspirin users.

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