RUTGERS–NEW BRUNSWICK
Nutritional Sciences
School of Environmental
and Biological Sciences

Alzheimer's Prevention - New Frontiers
Food for the Brain Symposium
April 28, 2026

Is Homocysteine Causative for Alzheimer's and How to Lower Risk

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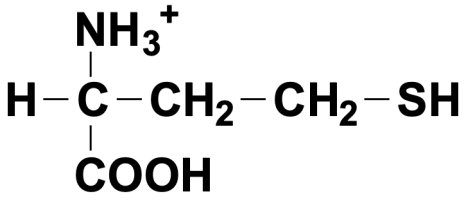
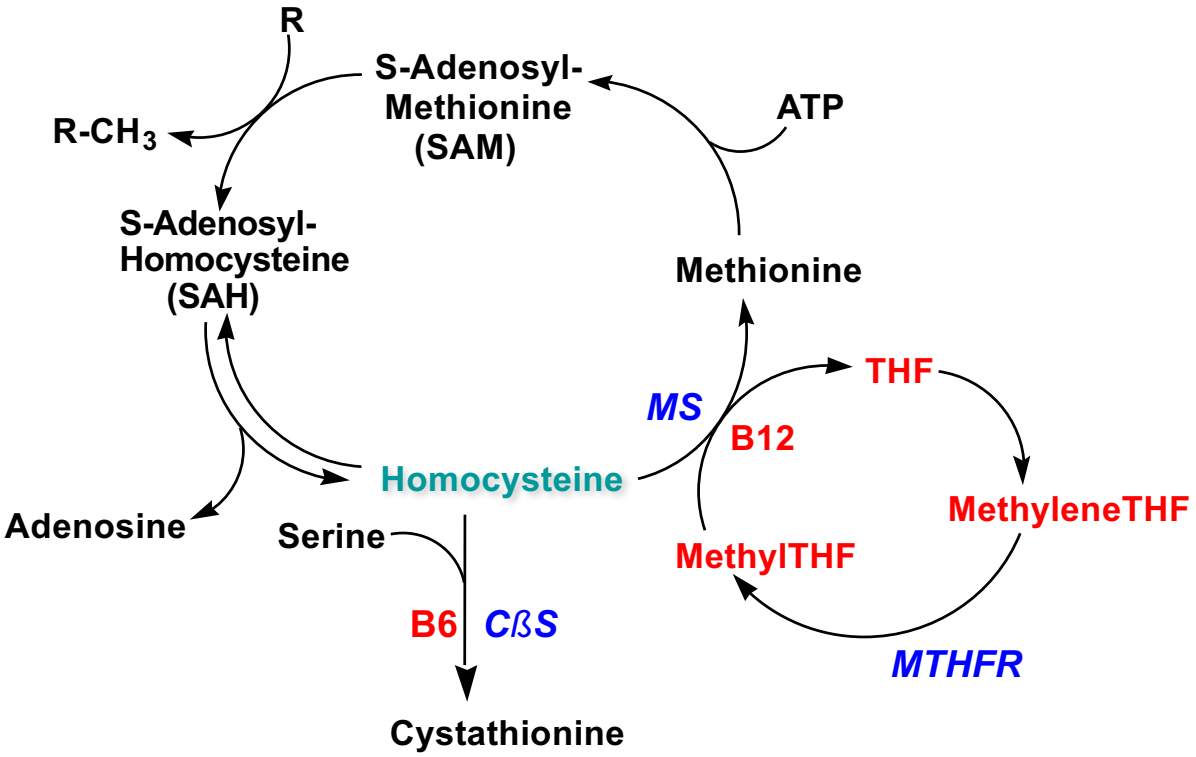
Presentation Goals

- What is homocysteine?
- Review of key historical evidence supporting the association between homocysteine and risk of age-related cognitive decline, Alzheimer's disease, and dementia.
- Review of evidence against the association.
- Key issues in considering the evidence.
- Recommendations for lowering homocysteine and possible risk reduction.

Homocysteine



Homocysteine Metabolism



Homocysteine and Cognitive Function

- "…individuals exposed to chronic low levels of vitamin B12, vitamin B6, and folate might be at risk of homocysteine toxicity, and therefore proposes cerebrovascular disease as a possible cause of the neuropathologies and cognitive disturbances associated with low concentrations of these vitamins."

Rosenberg and Miller, Am J Clin Nutr, 1992

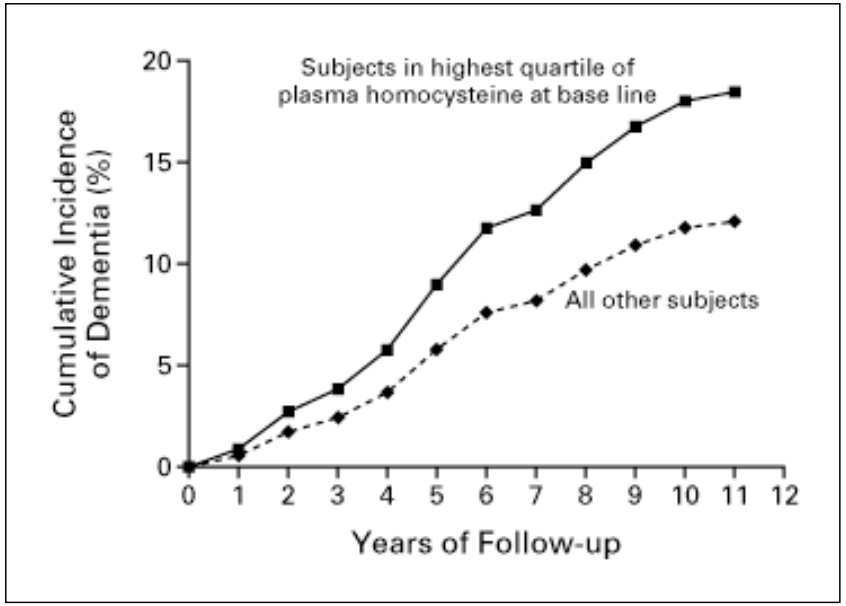
Homocysteine and Risk of Alzheimer's Disease

Plasma Homocysteine	Odds Ratio for Histologically-Confirmed Alzheimer's Disease
≤ 11.0 μM	1.0 (reference)
> 14.0 μM	4.6

Older adults with high homocysteine are more likely to have Alzheimer's Disease (and vice versa).

Clarke et al, Arch Neurol, 1998

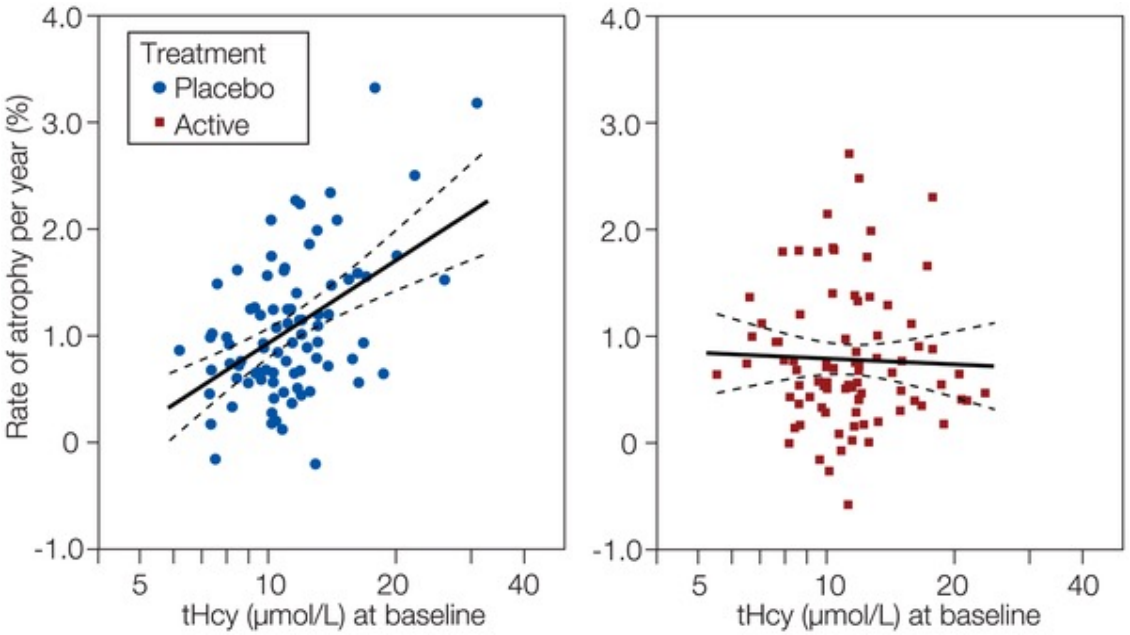
Homocysteine and Incident Dementia



Older adults with high homocysteine are more likely to be diagnosed with Alzheimer's Disease or dementia in the future.

Seshadri et al, N Engl J Med, 2002

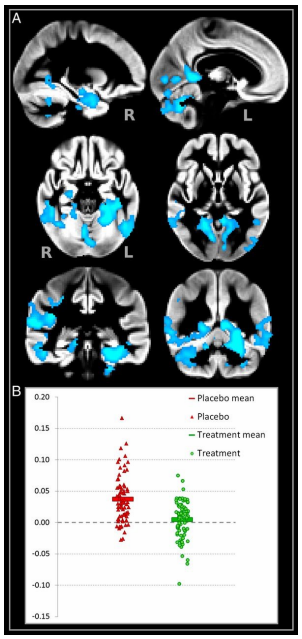
Effect of B Vitamin Supplements on Brain Atrophy in Older Adults with MCI

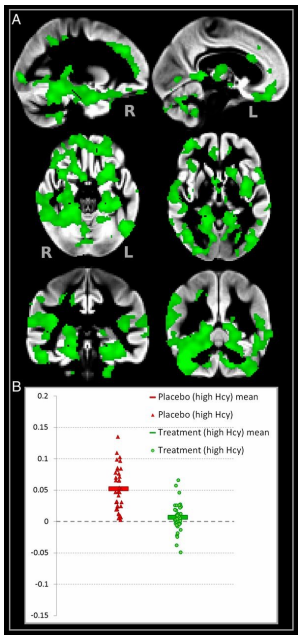


Smith et al, PLoS One, 2010

Effect of B Vitamin Supplements on Regional Brain Atrophy

All Subjects





High Homocysteine

B vitamin supplements slow brain atrophy in older adults with mild cognitive impairment and high homocysteine.

Douaud et al, PNAS, 2013

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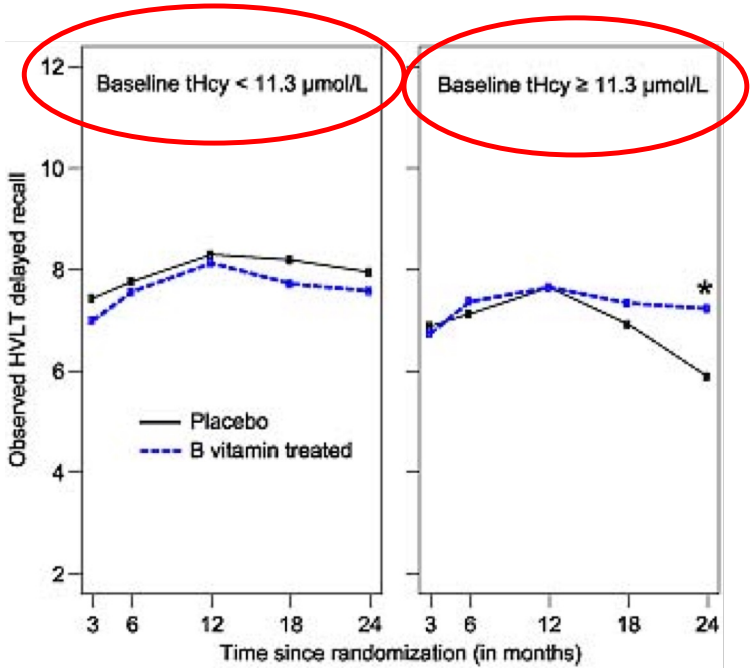
Effect of B Vitamin Supplements on Delayed Recall (Short-Term Memory)



B vitamin supplements slow cognitive decline in older adults with mild cognitive impairment and high homocysteine.

De Jager et al, Int J Geriatr Psychiatry, 2011

Systematic Review and Meta-Analysis

Guidelines for Preventing Alzheimer's Disease

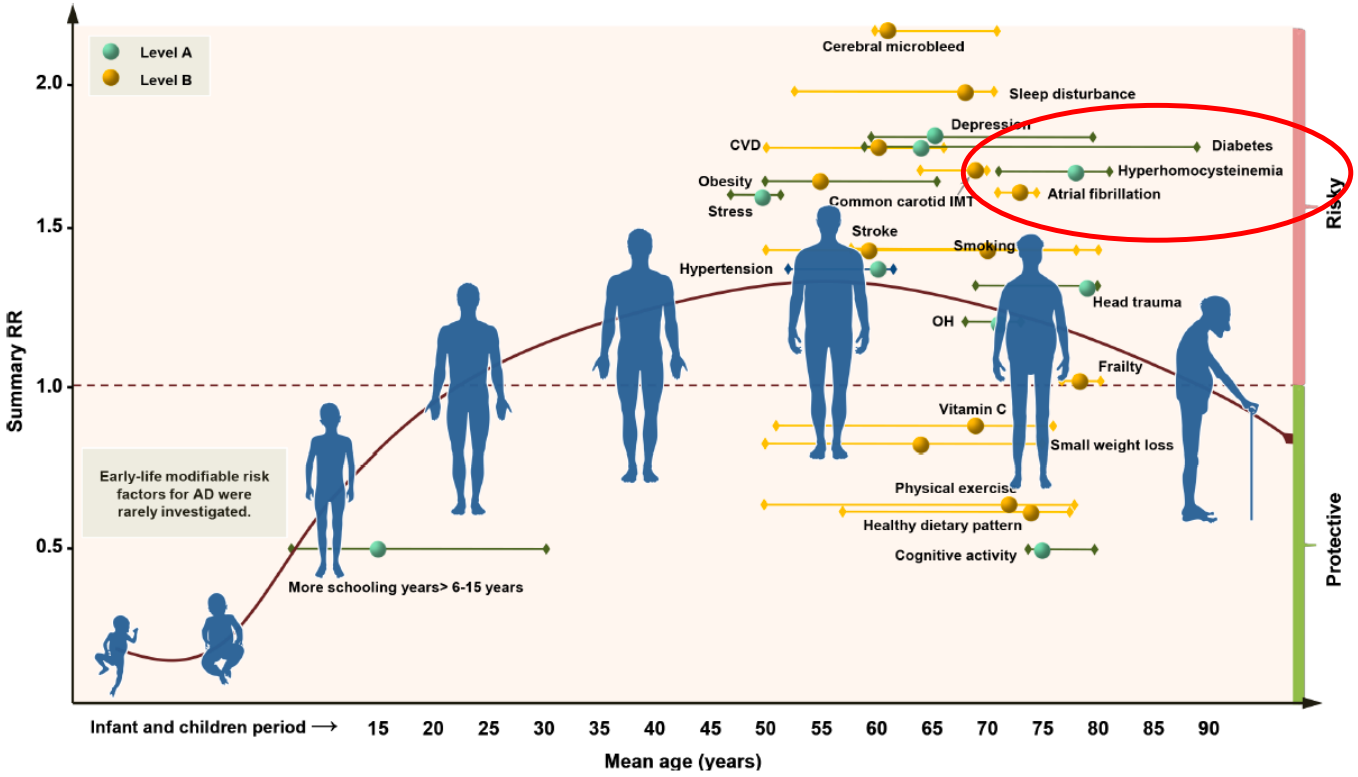
Table 1 Guideline for prevention of AD: preliminary clinical suggestions*

Factors/interventions	Suggestion
Lifestyle	
BMI and weight management	► Adults aged <65 years should maintain or lose weight through an appropriate balance of physical activity, caloric intake and formal behavioural programmes when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m^2 (*Class I, level B*) ► Adults aged >65 years should not to be too skinny (*Class I, level A4*) ► Adults aged >65 years with a trend of weight loss should be closely monitored for their cognitive status (*Class I, Level B*)
Physical exercise	► Individuals, especially those aged ≥65 years, should stick to regular physical exercise (*Class I, Level B**)
Cognitive activity	► Mentally stimulating activities should be encouraged, such as reading, playing chess, etc (*Class I, Level A4*)
Smoking	► People should not smoke and should avoid environmental tobacco smoke. Counselling, nicotine replacement and other pharmacotherapy as indicated should be provided in conjunction with a behavioural programme or formal smoking cessation programme (*Class I, Level B*)
Sleep	► Get sufficient and good quality sleep and consult a doctor or receive treatment when you have problem with sleep (*Class I, Level B*)
Comorbidities	
Diabetes	► Stay away from diabetes via a healthier lifestyle and diabetic patients should be closely monitored for their cognitive decline (*Class I, Level A4*)
CVD	► Maintain a good condition of the cerebral vessels via a healthier lifestyle or medications to avoid atherosclerosis, low cerebral perfusion and any CVD. Individuals with stroke, especially cerebral microbleeding, should be carefully monitored for their cognitive change and take preventative measures as indicated to protect cognition (*Class I, level B*)
Head trauma	► Protect your head from injuries (*Class I, level A4*)
Frailty	► Stay healthy and strong in late life. Those with increasing frailty should be especially monitored for their cognition (*Class I, Level B*)
Blood pressure	► Individuals aged < 65 years should avoid hypertension via a healthier lifestyle (*Class I, Level A4*) ► Individuals with OH should be closely monitored for their cognition (*Class I, Level A4*)
Depression	► Maintain a good condition of mental health and closely keep an eye on the cognitive status for those with depressive symptoms (*Class I, Level A4*)
AF	► Maintain a good cardiovascular condition and manage AF using pharmaceuticals (*Class I, level B*)
Stress	► Relax your mind and avoid daily stress (*Class I, Level A4*)
Other domains	
Education	► Receive as much education as possible in early life (*Class I, level A4*)
Hyperhomocysteinaemia	► Have a regular blood examination for homocysteine level. Individuals with hyperhomocysteinaemia should be treated with vitamin B and/or folic acid and be followed with a focus on their cognition (*Class I, Level A2*)
Vitamin C	► Vitamin C in the diet or taken as supplements might help (*Class I, Level B*)
Not recommended	
ERT	► Oestrogen replacement therapy should not be specifically used for AD prevention in postmenopausal women (*Class III, Level A2*)
ACI	► ACI should not be used for AD prevention in cognitively impaired individuals (*Class III, Level B*)

Yu et al, J Neurol Neurosurg Psychiatry, 2020

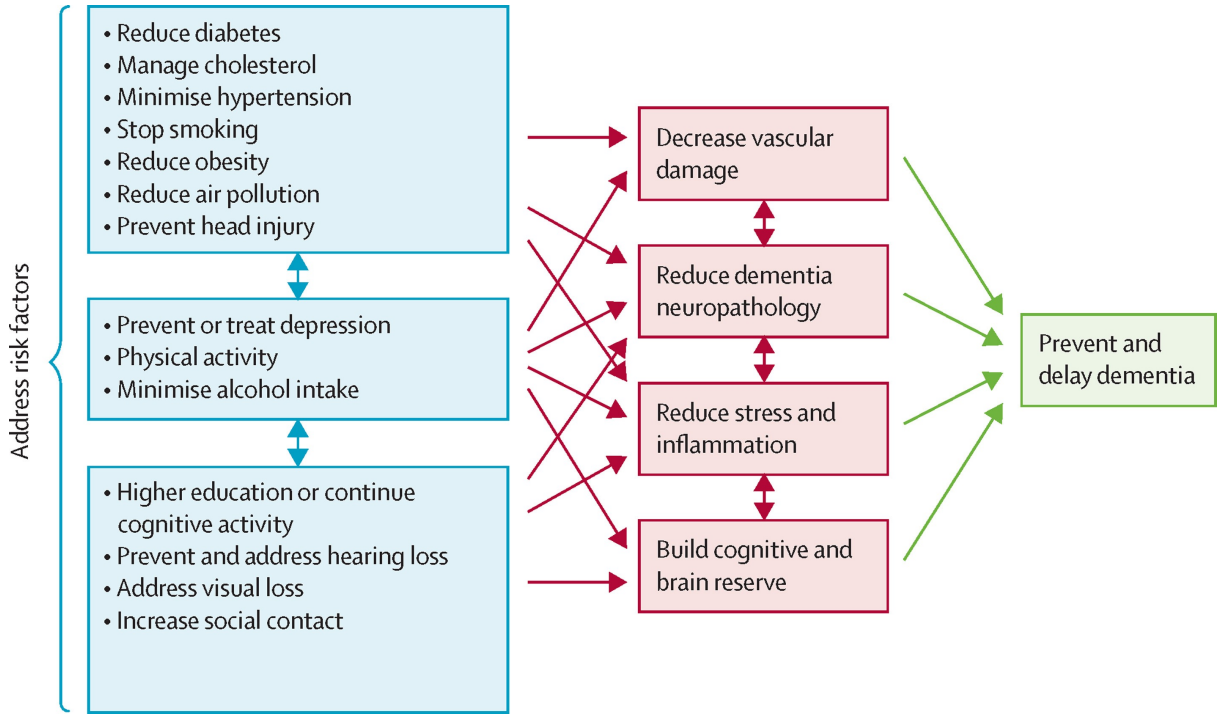
Systematic Review and Meta-Analysis

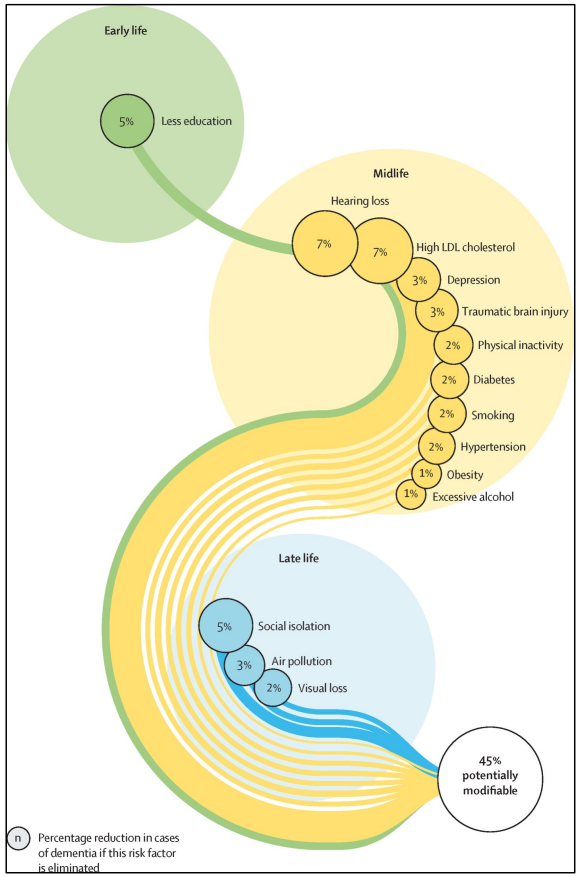
Guidelines for Preventing Alzheimer's Disease



Yu et al, J Neurol Neurosurg Psychiatry, 2020

2024 *Lancet* Commission on Dementia Prevention, Intervention, and Care





No recommendation for B vitamins or lowering homocysteine!

Livingston et al, *Lancet*, 2024.

Press Release – July 16, 2014

UNIVERSITY OF OXFORD

Taking B vitamins won't prevent Alzheimer's disease

HEALTH (/NEWS-LISTING?CATEGORY=249) RESEARCH (/NEWS-LISTING?CATEGORY=228)

Taking B vitamins doesn't slow mental decline as we age, nor is it likely to prevent Alzheimer's disease, conclude Oxford University researchers who have assembled all the best clinical trial data involving 22,000 people to offer a final answer on this debate.

Clarke et al, Am J Clin Nutr, 2014

Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals[1–5]

Robert Clarke, Derrick Bennett, Sarah Parish, Sarah Lewington, Murray Skeaff, Simone JPM Eussen, Catharina Lewerin, David J Stott, Jane Armitage, Graeme J Hankey, Eva Lonn, David Spence, Pilar Galan, Lisette C de Groot, Jim Halsey, Alan D Dangour, Rory Collins, and Francine Grodstein on behalf of the B-Vitamin Treatment Trialists' Collaboration

Press Release – November 13, 2014

BBC NEWS

HEALTH

13 November 2014 Last updated at 07:59 ET

Dementia study questions advice on taking supplements

By Emma Wilkinson
Health reporter, BBC News

Van der Zwaluw et al, Neurology, 2014

Results of 2-year vitamin B treatment on cognitive performance

Secondary data from an RCT

If *The Lancet*, Oxford and the BBC proclaim it, then it must be true, right?

Well...

Do B Vitamin Supplements Prevent Cognitive Decline?

Answer…

Probably, but...

The devil is in the details

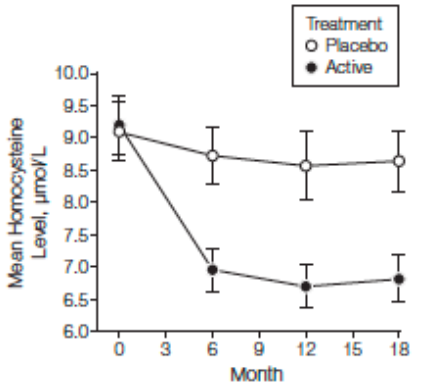
Key Issue in Considering the Evidence

- **What is the cognitive status of the subjects?**
  - Cognitively normal?
  - Mild cognitive impairment?
  - Dementia?
- **What is the B vitamin/homocysteine status of the subjects?**
  - Is homocysteine elevated?

Extent of Cognitive Impairment Matters

All AD Patients

Figure 2. Mean Homocysteine Level by Treatment and Visit

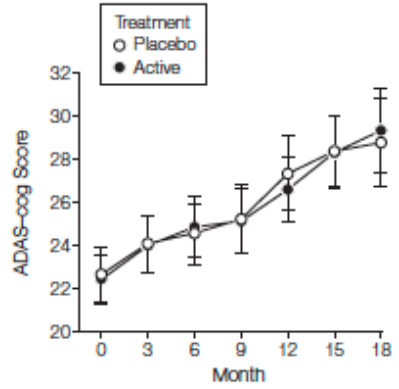


No. of patients

Placebo	155	138	126	119
Active	218	208	184	177

Error bars indicate standard deviation of the mean. Some patients had missing values; therefore, 155 patients in the placebo group and 218 patients in the active treatment group were used for the analysis.

Figure 3. Mean ADAS-cog Score by Treatment and Visit



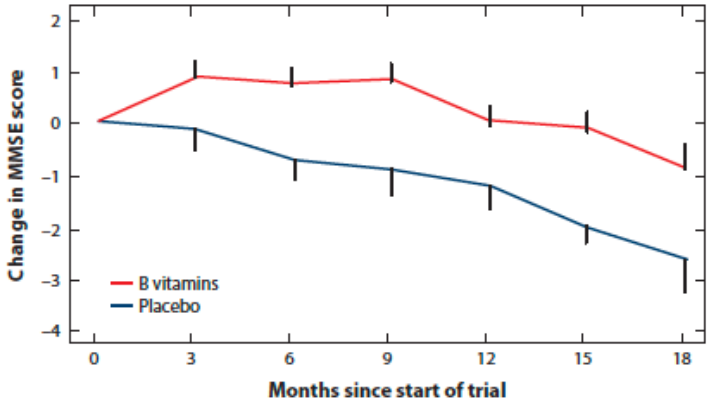
No. of patients

Placebo	166	161	156	146	143	140	136
Active	240	234	232	215	216	211	197

ADAS-cog indicates Alzheimer Disease Assessment Scale. Error bars indicate standard deviation of the mean. Three patients in the placebo group had missing values and were not included in the analysis.

Aisen et al, JAMA, 2008

Only Mild AD Patients (CDR Score = 0.5)

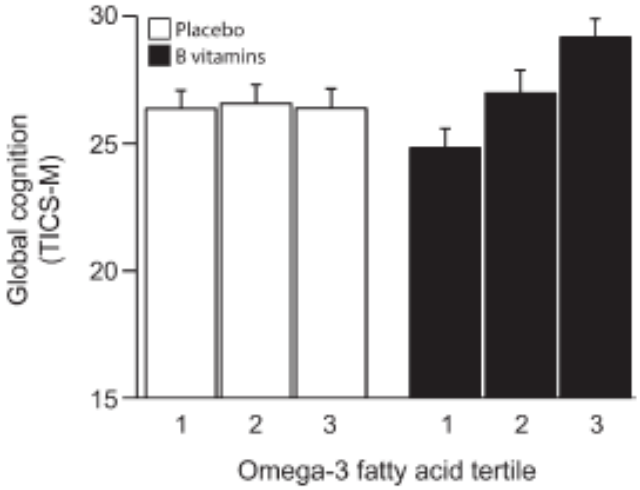


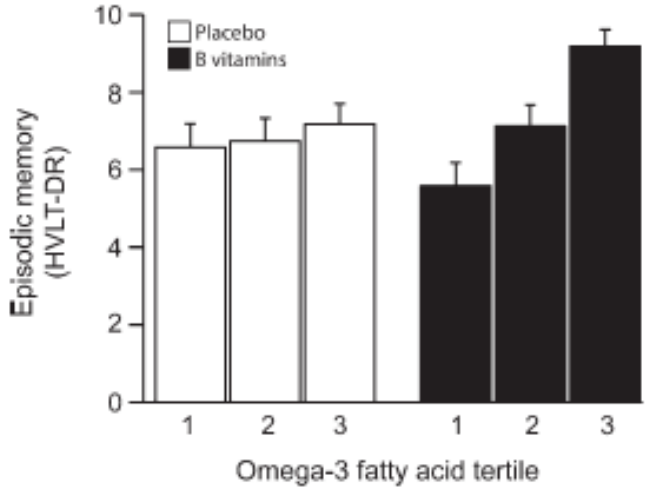
Smith and Refsum, Ann Rev Nutr, 2016

Key Issue in Considering the Evidence

- **What is the cognitive status of the subjects?**
  - Cognitively normal?
  - Mild cognitive impairment?
  - Dementia?
- **What are the cognitive outcomes?**
  - Improve cognitive function?
  - Slow or prevent cognitive decline?
- **What cognitive function tests are used?**
  - MMSE (global)?
  - Subdomains?
- **What is the B vitamin/homocysteine status of the subjects?**
  - Is homocysteine elevated?
- **How long is the intervention?**
  - Months?
  - Years?
- **Are there confounding factors not considered?**
  - Aspirin?
  - Omega-3 fatty acid status?

Synergistic Effect of Homocysteine Lowering and Omega-3 Fatty Acids





Oulhaj et al, AJCN, 2015

Conclusions

- B vitamin supplements may best protect against cognitive decline when taken prior to development of significant brain damage due to Alzheimer's disease or cerebrovascular disease.
- B vitamin supplements may only be effective in those individuals with metabolic evidence of deficiency or sub-optimal status (i.e., hyperhomocysteinemia).
- Older adults should be screened for elevated homocysteine. If elevated, B vitamin supplements (folic acid, B12, and B6) will lower homocysteine safely and inexpensively, and may slow or protect against age-related cognitive decline, Alzheimer's disease, and dementia.

Homocysteine and Neurodegenerative Disease

A Canary in the Coal Mine

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Thank You!