Micronutrient Supplementation and the Aging Brain
Can Supplements Prevent Age-Related Cognitive Decline?

Joshua W. Miller, PhD
Professor and Chair
Dept. of Nutritional Sciences
School of Environmental and Biological Sciences
Rutgers, The State University of New Jersey
7 WAYS TO CUT YOUR ALZHEIMER’S DISEASE RISK

Research suggests that certain diet and exercise habits may lower Alzheimer’s disease risk by more than half.

Steps to Prevent Alzheimer’s

1. Avoid saturated fats and trans fats.
   Dairy products, meats, and certain oils (coconut and palm oils) that are listed on labels as “partially hydrogenated oils” contain saturated fat. Many snacks, pastries, and fried foods are filled with trans fats.

2. Eat a healthy diet.
   Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should be staples in your diet.

3. Go nuts for nuts.
   One ounce of raw nuts — a small handful — is a great source of vitamin E.

4. Make vitamin B12 a priority.
   Eat fortified foods or take a supplement to get at least the recommended daily allowance (2.4 mcg per day for adults).

5. Choose your multivitamin wisely.
   Avoid multivitamins with iron and copper, and take iron supplements only when directed by your doctor.

6. Cook with caution.
   Avoid aluminum cookware, which has been linked to Alzheimer’s-related dementia. Instead choose stainless steel or cast iron pots and pans.

   Get at least 40 minutes of aerobic exercise three times a week — such as brisk walking, running, or cycling.

Source: Dietary Guidelines for Alzheimer’s Prevention 2013, Physicians Committee for Responsible Medicine

Help improve Memory

Vitamin B12

PLAN B POSITIVE ACTION ON ALZHEIMER’S

HOMOCYSTEINE AND B VITAMINS

Link Found between Vitamin D Deficiency and Dementia

VITAMIN D & DEMENTIA

www.alzinfo.org

Taking B vitamins won’t prevent Alzheimer’s disease

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

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
Do Supplements Prevent Cognitive Decline?

Answer…

Probably, but...

The devil is in the details
B Vitamins, Homocysteine, and Vascular Disease

**Vitamin Deficiencies**
- Folate (vitamin B9)
- Vitamin B12 (cobalamin)
- Vitamin B6 (pyridoxine)

**Homocysteine**
- Increased in Blood

**Increased Risk of Vascular Disease and Dementia**
- Heart Attacks
- Strokes
- Brain Atrophy
- Cognitive Decline
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 Total Brain Atrophy

Placebo

B Vitamins

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

ΔHcy: 22 to 30 µmol/L
Atrophy Rate: 2.5%/yr

ΔHcy: 24 to 12 µmol/L
Atrophy Rate: 0.46%/yr

Smith et al, PLoS One, 2010
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.

Taking B vitamins won’t prevent Alzheimer’s disease

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

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
Effects of B Vitamins and Homocysteine Lowering on Global Cognitive Function


title

Meta-Analysis of RCTs

<table>
<thead>
<tr>
<th>Trial (Reference)</th>
<th>Z-score difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stott (11)*</td>
<td>0.01 (-0.29, 0.31)</td>
</tr>
<tr>
<td>HOPE-2 (12)</td>
<td>-0.00 (-0.11, 0.11)</td>
</tr>
<tr>
<td>SU.FOL.OM3 (13)*</td>
<td>-0.05 (-0.17, 0.07)</td>
</tr>
<tr>
<td>WAFACS (14)</td>
<td>0.01 (-0.09, 0.10)</td>
</tr>
<tr>
<td>VISP (15)</td>
<td>0.01 (-0.06, 0.09)</td>
</tr>
<tr>
<td>VITATOPS (16)</td>
<td>0.00 (-0.06, 0.06)</td>
</tr>
<tr>
<td>SEARCH (17)</td>
<td>-0.01 (-0.05, 0.03)</td>
</tr>
<tr>
<td>All</td>
<td>-0.01 (-0.03, 0.02)</td>
</tr>
</tbody>
</table>
Effects of B Vitamins and Homocysteine Lowering on Domains of Cognitive Function
Meta-Analysis of RCTs

<table>
<thead>
<tr>
<th>Memory (n=1338)</th>
<th>Speed (n=1344)</th>
<th>Executive function (n=1324)</th>
<th>Domain-composite global cognitive function (n=1306)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial (Reference)</strong></td>
<td><strong>Z-score difference (95% CI)</strong></td>
<td><strong>Z-score difference (95% CI)</strong></td>
<td><strong>Z-score difference (95% CI)</strong></td>
</tr>
<tr>
<td>Eussen (7)</td>
<td>-0.13 (-0.41, 0.15)</td>
<td>0.01 (-0.29, 0.32)</td>
<td>0.09 (-0.23, 0.40)</td>
</tr>
<tr>
<td>Lewerin (8)</td>
<td>-0.09 (-0.29, 0.11)</td>
<td>-0.16 (-0.39, 0.07)</td>
<td>0.00 (-0.21, 0.21)</td>
</tr>
<tr>
<td>McMahon (9)</td>
<td>-0.15 (-0.31, 0.01)</td>
<td>-0.24 (-0.42, -0.05)</td>
<td>-0.10 (-0.27, 0.07)</td>
</tr>
<tr>
<td>FACIT (10)</td>
<td>0.14 (0.03, 0.24)</td>
<td>0.07 (0.01, 0.13)</td>
<td>-0.07 (-0.19, 0.05)</td>
</tr>
<tr>
<td><strong>All</strong></td>
<td>0.02 (-0.06, 0.10)</td>
<td>0.03 (-0.02, 0.08)</td>
<td>-0.05 (-0.14, 0.03)</td>
</tr>
</tbody>
</table>
Trajectories of Cognitive Change

Brain Injury

Cognitive Ability

Dependent

Normal

Severe

Time

Prevention

Treatment

Charles DeCarli (unpublished)
Assessing the association between homocysteine and cognition: reflections on Bradford Hill, meta-analyses, and causality

Andrew McCaddon and Joshua W. Miller

Hyperhomocysteinemia is a recognized risk factor for cognitive decline and incident dementia in older adults. Two recent reports addressed the cumulative epidemiological evidence for this association but expressed conflicting opinions. Here, the evidence is reviewed in relation to Sir Austin Bradford Hill’s criteria for assessing “causality,” and the latest meta-analysis of the effects of homocysteine-lowering on cognitive function is critically examined. The meta-analysis included 11 trials, collectively assessing 22,000 individuals, that examined the effects of B vitamin supplements (follic acid, vitamin B₁₂, vitamin B₆) on global or domain-specific cognitive decline. It concluded that homocysteine-lowering with B vitamin supplements has no significant effect on cognitive function. However, careful examination of the trials in the meta-analysis indicates that no conclusion can be made regarding the effects of homocysteine-lowering on cognitive decline, since the trials typically did not include individuals who were experiencing such decline. Further definitive trials in older adults experiencing cognitive decline are still urgently needed.
## Change in Cognition in Healthy Older Adults

You can’t prevent something that isn’t happening...

### Table 2: Changes in cognitive domain scores of elderly people (only participants with baseline and 2-year data)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted mean (SD)</th>
<th>Change (95% CI)</th>
<th>Model 1, p value</th>
<th>Model 2, p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Episodic memory (n = 2,467)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.04 (0.69)</td>
<td>0.13 (0.75)</td>
<td>0.08 (0.05 to 0.12)</td>
<td>0.27</td>
</tr>
<tr>
<td>B vitamins</td>
<td>0.05 (0.69)</td>
<td>0.16 (0.75)</td>
<td>0.11 (0.07 to 0.14)</td>
<td></td>
</tr>
<tr>
<td><strong>Attention and working memory (n = 759)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.02 (0.86)</td>
<td>−0.04 (0.88)</td>
<td>−0.06 (−0.12 to 0.01)</td>
<td>0.38</td>
</tr>
<tr>
<td>B vitamins</td>
<td>−0.01 (0.84)</td>
<td>−0.10 (0.82)</td>
<td>−0.09 (−0.16 to −0.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Information processing speed (n = 731)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.08 (0.75)</td>
<td>0.06 (0.79)</td>
<td>−0.02 (−0.06 to 0.01)</td>
<td>0.65</td>
</tr>
<tr>
<td>B vitamins</td>
<td>0.04 (0.75)</td>
<td>0.01 (0.77)</td>
<td>−0.03 (−0.07 to 0.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Executive functioning (n = 720)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>0.04 (0.54)</td>
<td>0.10 (0.68)</td>
<td>0.06 (−0.00 to 0.12)</td>
<td>0.20</td>
</tr>
<tr>
<td>B vitamins</td>
<td>−0.01 (0.52)</td>
<td>0.13 (0.66)</td>
<td>0.13 (0.07 to 0.19)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: CI = confidence interval.
Differences between the 2 groups over time were measured using analyses of covariance. Model 1: adjusted for baseline domain scores. Model 2: adjusted for baseline domain scores, age, sex.

*Model 2 additionally adjusted for study center.

Van der Zwaluw et al, Neurology, 2014
Key Considerations

- **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?
Challenge and Opportunity

Challenge
• Applying what we’ve learned from population-based studies to inform personalized medicine and personalized nutrition.

Opportunity
• To design and implement smarter intervention trials with nutritional supplements to determine if age-related cognitive decline can be slowed or prevented.