Evaluation of the Strength of Evidence for Supplementation Use for Healthy Cognitive Function

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A. The Cognitive Continuum

Peterson et al. (1996)

Normal Aging (Successful Aging),
Age-Associated Memory Impairment (AAMI)

Mild Cognitive Impairment (MCI)

Dementia/Alzheimer’s
Dietary Supplements/variables

- Antioxidants
- Ginkgo
- Folate, B6, B12, homocysteine
- Cholesterol intake and statins
- Fatty acids
- (anti-inflammatory agents, estrogen)
Oxidative Damage and Brain Aging

• Aged animals and people accumulate oxidative damage to lipids, proteins and nucleic acids

• Antioxidant treatments in rodents can “reverse” the decline in learning and motor function, e.g., Vit. E, lipoic acid and ALCAR, PBN, blueberry extracts, etc.
MORRIS WATER MAZE
REVERSAL AGE DIET STUDY (J. Joseph, 2002)

LATENCY TO PLATFORM (sec)

<table>
<thead>
<tr>
<th>DIET GROUP</th>
<th>CONTROL</th>
<th>STRAWBERRY</th>
<th>SPINACH</th>
<th>BLUEBERRY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIAL 1</td>
<td>54</td>
<td>54</td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>TRIAL 2</td>
<td>36</td>
<td>36</td>
<td>72</td>
<td>36</td>
</tr>
</tbody>
</table>

* Significant difference
** Highly significant difference
Observational Studies of the Effect of Antioxidant Intake on the Risk of Dementia and Alzheimer’s Disease

**Intake**

**Morris (2002)**
- Vit E 3rd Q
- Vit E 4th Q
- Vit E 5th Q
- Vit C 3rd Q
- Vit C 4th Q
- Vit C 5th Q

**Engelhart (2002)**
- Vit E
- Vit C

**Corrada (2002)**
- Vit E 3rd Q
- Vit E 2nd Q
- Vit E 1st Q
- Vit C 3rd Q
- Vit C 2nd Q
- Vit C 1st Q

**Ortega**
- Vit E

vit = Vitamin
Q = quartile
sign. = Significant
Observational Studies of the Effect of Antioxidant Supplement Use on the Risk of Dementia and Alzheimer’s Disease

**Supplement**

- **Morris (1998)**
  - vit E
  - vit C
  - sign. ↓ AD risk
  - non sign. ↓ AD risk

  - vit E or C

- **Grundman (2001)**
  - vit E or C

- **Zandi (2002)**
  - vit E
  - vit C

![Graph showing risk ratio and confidence intervals for antioxidant supplement use on AD risk](image)

**Risk (Odds) Ratio and 95% Confidence Interval (log scale)**

- Decreased Risk
- Increased Risk

`vit` = Vitamin

`sign.` = Significant
# Cognitive Function and Serum Vitamin E Status

**Pfeiffer Mental Status Questionnaire**

<table>
<thead>
<tr>
<th></th>
<th>No Errors</th>
<th>Some Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin E</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>19.7 ± 8.6 µmol/l</td>
<td>15.1 ± 5.6 µmol/l</td>
</tr>
<tr>
<td>Women</td>
<td>20.8 ± 8.4 µmol/l</td>
<td>14.9 ± 6.1 µmol/l</td>
</tr>
<tr>
<td><strong>Vitamin E / Cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3.5 ± 2.0 µmol/l</td>
<td>2.4 ± 20.8 µmol/l</td>
</tr>
<tr>
<td>Women</td>
<td>2.9 ± 1.4 µmol/l</td>
<td>2.3 ± 1.3 µmol/l</td>
</tr>
</tbody>
</table>

Ortega, 2002; similar data in Perkins, 1999
Cox Survival Functions – ITT
By Treatment Arm
Covariate: Baseline Mini Mental State Exam (Sano, 1997)
Challenges

• Studies to date are descriptive except for Vit. E in AD.
• Foods rich in antioxidants are also enriched in other dietary components that may be beneficial.
• Supplement doses, form unclear, eg., d.l vs. d vit E
• Peripheral markers may not reflect brain state, e.g., plasmaVit E/chol.
• Supplements may not be as effective as diet and it is likely combinations of antiox. are needed
• Life style is not taken into account
• Animal studies may help, particularly on higher mammals.
Canine (Dog) Aging and Cognition

Exhibit age-associated cognitive decline similar to humans, e.g., capable of complex learning tasks

Exhibit similar neuropathology to humans, e.g., β-amyloid, oxidative stress

Share many environmental conditions and the genome is similar to humans.
Protocol and Data Collection
Dietary rationale

Intervention with antioxidants may slow or reverse changes associated with mental aging

- Vitamin E slowed progression of Alzheimer’s in people (Sano 1997)
- Carnitine and lipoic acid improved mitochondrial health and impairments in old rats (Hagen 1999; McGahon 2000)
- Blueberry extract reversed aged rat learning disabilities (Joseph 1999)
- High intake of fruits/veg. decrease dementia risk by 19% (Engelhart 2000)
Oddity Task

Harder Version

Easy Version
6 months
Dog Aging and Cognition Project

Oddity testing in young and aged dogs

Mistakes

Oddity Task

Young dogs

Aged dogs

Task 1  Task 2  Task 3  Task 4
Effect of diet on oddity discrimination in aged beagles

The dietary enrichment group performed significantly better than the control group on the more difficult discriminations.
Spatial Memory and Antioxidant Diet

![Bar chart showing errors to criterion for Year 1, Year 2, and Year 3 spatial memory for control and antioxidant conditions.](chart)

- Year 1 Spatial Memory
- Year 2 Spatial Memory
- Year 3 Spatial Memory

**P<.05**

**P<.08**
Plaque Accumulation in Unimpaired and Impaired Dogs: Comparison with Normal Elderly and Alzheimer’s disease Human Brain
Effect of Treatment on Total Amyloid Load (6E10)

By Brain Region

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>C/C</th>
<th>C/E</th>
<th>A/C</th>
<th>A/E</th>
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</thead>
<tbody>
<tr>
<td>Prefrontal</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>9</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Parietal</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Occipital</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

*Includes archival data
Beta-amyloid in Canines after A/E treatments
Ginkgo

- Widely prescribed and used
- Over 50 report showing effects on one or more measures of cognitive function
- No effect on healthy non-demented subjects (n=230, 6 months) (Solomon, JAMA, 2002)
- Dementia patients (n=202) treated with ginkgo show 0.1 decline on ADAS-Cog vs. 1.48 in placebo. No subjective differences reported by family or physicians (LeBars, JAMA, 1997)
Ginkgo for Memory Enhancement
A Randomized Controlled Trial

Solomon, JAMA, August 21, 2002
Homocysteine; folate, B6,12 and the decline in cognitive function
High homocysteine increases risk for neuronal damage

- Increases neuronal DNA damage
- Sensitizes neurons to oxidative damage and degeneration
- Folate, B6, B12 protect in animal models, eg., AD mouse.
High Homocysteine and Low Folate and Vitamin B12 as a Risk Factor for Cognitive Decline (AD)

Seshadri (2002)*

Clarke (1998)**

Homocysteine
Folate
B12

*An increase in plasma homocysteine levels of 5 µmol/l increases risk by 40%

**Radiologic evidence of AD also greater in those with high homocysteine at entry
Incidence of Dementia among subjects with HC in highest quartile (Seshadri, NJM, 2002)
Fatty acids and dementia

• Animal studies indicate that select fatty acid improve learning and memory in rats
• Human studies are unclear as to whether or not high total fat, sat. and trans fat and low mono and polyunsat and unsat. fatty acids protect
• Cholesterol - probably
Fatty Acids and Dementia, The Rotterdam Study (2002)

• Total fat  0.93 (95% CI 0.79-1.05)
• Sat. fat  0.91 (95% CI 0.91-1.10)
• n-3 polyunsat  1.07 (95% CI 0.94- 1.07)

When corrected for age, education, total energy intake and Vit. E
Clinical trial suggests improvement possible

• Supplementation with essential fatty acids in AD patients (n=100) was reported to improve quality of life and short term memory (Yehuda, 1996)
High Serum Cholesterol is a Risk Factor for Alzheimer’s Disease

Notkola (1998)
Cholesterol lowering drugs

• Statins delay onset of dementia, e.g., levostatin

• Reduce B-amyloid in rodent models
Cholesterol Depletion Inhibits Beta Amyloid Cleavage

Observational Studies of the Effect of Statin Use on the Risk of Dementia and Alzheimer’s Disease

Wolozin (2000)
Jick (2000)
Rockwood (2002)

sign. ↓ AD prevalence 60%-70% lower

sign. = Significant
Conclusions

• Select antioxidants; folate/B6,12; cholesterol lowering strategies may provide benefit
• Animal data are strong for all 3
• Human studies to date are descriptive though trials are ongoing
• Gingko data are unclear but a primary prevention trail for AD is ongoing
• Cognitive measures need to be challenging, graded for endpoints other than dementia
• Environmental enrichment and lifestyle interact with diet and are not taken into account
Methodology

• Larger populations?
• Better mechanistic-based cognitive tests
• Informatics approaches to facilitate data collection and more data points
• Biomarkers as pre-endpoints
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