Cognitive Decline and Alzheimer’s Disease: The Influence of Nutrition

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Objectives

• Describe nutrients and foods that negatively affect cognitive function or increase the risk for Alzheimer’s Disease (AD)
• Describe nutrients and foods that positively affect cognitive function or reduce the risk for AD
• Design a nutritional plan to reduce the risk of cognitive decline and AD

Dementia: decline in mental ability severe enough to interfere with daily life

• Alzheimer’s disease (AD): most common type
  – Brain changes may begin 20 years before symptoms begin
• Other types of dementia:
  – Vascular dementia
  – Frontal-temporal dementia
  – Parkinson’s dementia
  – Lewy-Body dementia
• Subjective cognitive decline (SCD)
  – Subjectively perceived subtle cognitive deficits
  – Neuropsychological testing: normal performance
• Mild cognitive impairment (MCI)
  – Neuropsychological test results: mildly reduced
• Neuropsychological tests
  – Memory, visuoconstruction, attention/processing speed, executive functioning
• Pathophysiological processes take place years before AD manifestation

**Warning signs of Alzheimer’s**

• Memory loss that disrupts daily life
• Challenges in planning or solving problems
• Difficulty completing familiar tasks at home, at work or at leisure
• Confusion with time or place
• Trouble understanding visual images & spatial relationships
• New problems with words in speaking or writing
• Misplacing things & losing the ability to retrace steps
• Decreased or poor judgment
• Withdrawal from work or social activities
• Changes in mood & personality

**Tests used for AD & cognitive impairment**

• Mini-Mental State Examination (MMSE)
  – Overall measure of cognitive impairment
  – 30 point questionnaire
  – 20-24 = mild dementia; 13-20 = moderate dementia; <12 = severe dementia.
• Alzheimer Disease Assessment Scale (ADAS-cog)¹
  – Evaluates memory, attention, language, orientation, and praxis
  – 70-point scale
  – Higher scores indicate greater impairment

• Alzheimer’s Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory\(^1\)
  – Assesses functional ability to perform activities of daily living in patients with AD
  – Scores range from 0 to 78
  – Lower scores indicate worse function
• Neuropsychiatric Inventory (NPI)\(^2\)
  – Assessment of severity and frequency of psychological and behavioral disturbances in patients with dementia
    • Delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, disinhibition, irritability, apathy, and aberrant motor activity
  – Provides scores for 10 subscales

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**Alzheimer's Disease Facts & Figures, U.S.**

- 2018:
  - 5.7 million Americans
  - 2025, estimated: 7.1 million
  - 2050, projected: nearly 14 million
  - Projected health & long-term care, individual with AD: $242,000
  - Alzheimer’s & other dementias, cost of care: $277 billion
  - 2050, projected: $1.1 trillion
  - Leading cause of disability & poor health
  - 6th leading cause of death in US
  - 5th leading cause of death, 65 & older
  - 1 in 3 seniors dies with Alzheimer’s or another dementia

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**Risk Factors**

- Apolipoprotein E (ApoE) \(\varepsilon4\) allele\(^1\)
- Oxidative stress\(^2\)
  – Transition metal accumulation
  – Mitochondrial dysfunction
  – Amyloid-\(\beta\)
- Diabetes\(^3\)
- Elevated blood homocysteine (Hcy) levels\(^4\)
Risk Factors – Nutrition-Related

- Significantly low protein intake
- Very low sodium diets
- Calcium supplementation
- Aluminum-containing additives in food/water
- Dietary patterns associated with mild cognitive impairment
  - Lower consumption of fish & more red meat
  - Low plasma concentration of HDL cholesterol
  - Low total antioxidant capacity & alpha-tocopherol


Risk Factors – Nutrition-Related

- Increased cerebral amyloid plaque burden
  - High glycemic load diet
  - High carbohydrate intake
  - High sugar intake
  - Reduced cognitive performance


Nutritional Interventions: Dietary Supplements

- Vitamin B12 & B6
- Folic acid
- Antioxidants
- Vitamin D
- Omega 3
- Herbs
Elevated Homocysteine

- Risk factor for cognitive impairment, dementia
  - Vascular mechanisms
  - Regional brain atrophy
  - Neurofibrillary tangle & amyloid plaque formation
  - Neuronal death
  - Epigenetic mechanisms
- Studies: variety of cut-offs
- 2018 international consensus: suggested threshold, 10-11 umol/L

Folic Acid (FA, Vitamin B9)

<table>
<thead>
<tr>
<th>Dose/Duration</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid 15 mg/d x 60 days 1</td>
<td>N = 30 Age = 65+ Cognitive decline Folate levels &lt; 3 ng/ml (low)</td>
<td>FA vs placebo: Attention efficiency score significantly improved</td>
</tr>
<tr>
<td>FA 800 mcg/d x 3 years 2</td>
<td>N = 818 Age = 50-70 From Netherlands Hcy levels ≥ 13 umol/L (elevated)</td>
<td>FA vs placebo: Plasma Hcy decreased by 26% Global cognitive function improved (based on 5 cognitive tests)</td>
</tr>
</tbody>
</table>

Combination Supplements

<table>
<thead>
<tr>
<th>Dose/Duration</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit 12 1 mg/d &amp; FA 5 mg/d x 2 months 1</td>
<td>N = 28: mean age = 74 Mild to moderate dementia (VaD, FTD, AD, mixed dementia, or other dementia)</td>
<td>High Hcy at baseline: Improved MMSE &amp; memory &amp; attention scores Normal baseline Hcy: No changes</td>
</tr>
<tr>
<td>Vit B12 1000 mcg/d alone or with FA 400 mcg/d x 24 weeks 2</td>
<td>N = 195: age = 70+ No to moderate cognitive impairment From Netherlands Mild vit B12 deficiency Mean plasma Hcy 14.5-15.8 (high)</td>
<td>Supplement (vit B12 or vit B12 + FA) vs placebo: vit B12 levels corrected &amp; Hcy levels reduced by 16% (vit B12 group) &amp; 37% (vit B12 + FA) No improvement in cognitive function vs placebo Improved memory in placebo group vs vit B12 group</td>
</tr>
</tbody>
</table>

Dose/Duration | Participants | Results
---|---|---
Vit B12 1 mg/d, FA 5 mg/d, vit B6 25 mg/d, x 18 months\(^1\) | N = 344 Age = 50+ yrs Probable AD Normal vit B12 & folate levels Mean plasma Hcy = 9.2 (SD = 3.2) | Supplement vs placebo: Hcy levels decreased by -2.4 vs -0.9 No improvement in cognitive function

Vit B12 0.5 mg/d, FA 0.8 mg/d & vit B6 20 mg/d vs placebo, x 2 yrs | N = 223 Age = 70+ yrs MCI | Supplement vs placebo: Hcy decreased (increased with placebo) High Hcy: Decline in rate of brain atrophy Slowed cognitive decline (significant decline with placebo)


**Antioxidants**

Oxidative Stress in AD

- Cellular respiration generates free radical intermediates (ROS formation)
- Sequestration mechanisms unable to capture all ROS
- Neurons vulnerable to oxidative damage
- Lipid peroxidation
- Reactive carbonyls
- Nitration
- Nucleic acid oxidation
- Formation of Aβ in neurons
- Compensatory mechanism: partial protection against oxidative damage in neurons

**Oxidative Damage**

**Amyloid-β**

**Antioxidants**

Protection against neurotoxicity due to oxidative stress
### Vitamin E

<table>
<thead>
<tr>
<th>Dose/Duration</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Vit E 2000 IU/day in 2 divided doses, vs memantine 20 mg/day, vs vit E + memantine, vs placebo, x 6 months-4 years&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N = 613 Mean age 78.8; 97% men (veterans) Possible or probably AD MMSE = 21</td>
<td>Delayed decline in ADCS-ADL &amp; reduced caregiver time in vit E group Effect not seen in other treatment groups No statistically significant differences in MMSE, ADAS-cog, or NPI</td>
</tr>
</tbody>
</table>

<sup>1</sup>Dysken, et al. JAMA. 2014;311(1):33-44

### Antioxidants

<table>
<thead>
<tr>
<th>Dose/Duration</th>
<th>Participants</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Acetyl-L-carnitine (ALCAR) 1 g TID x 1 year&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N = 229 Age = 45-65 Probable AD (young-onset)</td>
<td>ALCAR vs placebo: No significant difference in the rate of decline in ADAS-cog score Less decline in MMSE</td>
</tr>
<tr>
<td>Alpha-lipoic acid (ALA) 600 mg/d x 16 months&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N = 126 AD with T2DM (Group A) &amp; without T2DM (Group B)</td>
<td>Group A vs Group B: Significant improvements in MMSE, ADAS-cog, CIBIC scores</td>
</tr>
<tr>
<td>N-Acetylcysteine (NAC) 50 mg/kg/day in 3 divided doses x 6 months&lt;sup&gt;3&lt;/sup&gt;</td>
<td>N = 43 Probable AD MMSE scores between 12 &amp; 26</td>
<td>NAC vs placebo: Trend to perform better on MMSE &amp; the Wechsler Memory Scale Performed significantly better on letter fluency task</td>
</tr>
</tbody>
</table>


### Combination Supplements

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<tr>
<td>ALCAR 500 mg, NAC 600 mg, S-adenosylmethionine (SAM) 400 mg (200 mg active ion), vit E 30 IU, FA 400 mcg &amp; vit B12 6 mcg x 3-6 months&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N = 106 Probable AD &amp;/or senile dementia of the Alzheimer type</td>
<td>Supplement vs placebo: Cognitive performance (Clox-1 &amp; DRS) improved No statistical change in BPSD</td>
</tr>
</tbody>
</table>

Vitamin D deficiency

- Serum 25-hydroxyvitamin D concentrations ≤ 20 ng/mL (50 nmol/L)
- 41.6% deficient in the US general population
- 82.1% blacks, 69.2% Hispanics
- No college education, obese, poor health status, HTN, no daily milk consumption, high cholesterol


Vitamin D

- Amyloid-B
- Inflammatory stress
- Oxidative stress
- Neuronal death
- Vascular stress
- Decline in Memory & learning

- Role of vitamin D mediated by VDRs
  - Clearance of AB peptide
  - Anti-inflammatory action
  - Antioxidant action
  - Primary prevention and reduction of ischemic zone size


Vitamin D

<table>
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</tr>
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<tbody>
<tr>
<td>Vit D1</td>
<td>6 studies on AD patients 319 patients, 573 controls Age 65+</td>
<td>AD patients: Either vit D deficient or had insufficient plasma vit D levels (Insufficient &lt;20 ng/ml; Deficient &lt;10 ng/ml)</td>
</tr>
<tr>
<td>Vit D2</td>
<td>N = 10,186 White Danish individuals 30 years follow up</td>
<td>Lower plasma vit D levels: Increase risk of AD &amp; vascular dementia</td>
</tr>
<tr>
<td>Vit D3</td>
<td>N = 1182 Swedish men Mean age 71 18 years follow up (&lt;20ng/mL, 20-30ng/mL, &gt;30ng/mL)</td>
<td>No association between baseline vit D status &amp; long term risk of dementia or cognitive decline</td>
</tr>
</tbody>
</table>


Vitamin D Combination

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<tr>
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<tbody>
<tr>
<td>Memantine 20 mg, vs vit D 400-1000 IU, vs Memantine + vit D, x 6 mo.</td>
<td>43 white patients New diagnosis of AD, No anti-dementia drug or vit D supplementation before</td>
<td>Memantine + vit D group: Increased MMSE score by 4 points No test score changes for the other two groups</td>
</tr>
</tbody>
</table>


Omega 3 PUFAs: DHA & EPA

- Brain requires DHA:
  - Production and clearance of β-amyloid
  - Maintenance of neuronal membranes
  - Modulation of inflammation
  - Improvement of vascular health
- Dementia:
  - Decreased DHA
  - Decreased EPA
  - Decreased total n-3 PUFAs
- Predementia:
  - Decreased EPA


Omega 3

<table>
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<tr>
<th>Dose/Duration</th>
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</tr>
</thead>
<tbody>
<tr>
<td>4 capsules 1.6 g EPA &amp; 0.8 g DHA/day</td>
<td>Healthy older adults Age = 62-80 Subjective memory impairment (not meeting criteria for MCI or AD)</td>
<td>Red blood cell omega 3 content, working memory performance &amp; blood oxygen level dependent (BOLD) signal increased</td>
</tr>
<tr>
<td>High dose DHA/EPA ranging from 150-2000 mg/d</td>
<td>Mice: APOE4 carriers &amp; non-carrier with or without AD</td>
<td>Incidence of AD was reduced significantly in APOE4 carriers</td>
</tr>
<tr>
<td>1.7 g of DHA + 0.6 g of EPA, vs. placebo, x 6 mo</td>
<td>N = 204 Mean age = 74 AD MMST score of 15</td>
<td>No delay in rate of cognitive decline in patient with mild-moderate AD Positive effect on patient with very mild AD</td>
</tr>
</tbody>
</table>

N-3 PUFAs on dementia

- Observational studies:
  - Beneficial in 17 studies
    - Higher level of ALA: decreased risk
    - Higher level of DHA: decreased risk
    - Fatty fish > 2/wk vs < 1/month: decreased risk
  - No benefit in 3 studies
- Intervention studies:
  - Beneficial in 8 studies
  - No benefit in 5 studies
- APOE e4 carriers:
  - More vulnerable to dietary n-3 deficits
  - Supplementation with DHA as early as possible might help to prevent onset of AD


Dementia can be improved or prevented by n-3 PUFA

- Mild memory &/or cognitive impairment
  - Subjective memory impairment
  - Mild cognitive impairment
  - Cognitive impairment no dementia
  - Mild Alzheimer’s disease
- Higher intake of fish
- Additional daily n-3 PUFA intake > 2 g
- Additional daily DHA intake > 900 mg
- Duration of treatment > 6 mos


Herbs
Curcumin

- Compound in turmeric
  - Herb in the ginger family
  - *Curcuma longa* L.
- Spice in curry powder
- Anti-inflammatory\(^1\)
- Powerful antioxidant\(^2\)
- Inhibits amyloid β formation\(^2\)

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<tr>
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</tr>
</thead>
</table>
| Curcumin 80 mg single dose\(^1\) | N = 60       | Healthy adults
Age 60-85 Acute curcumin vs placebo: Significantly improved sustained attention & working memory tasks 1 hour post dose |
| Curcumin 80 mg/d x 4 weeks\(^1\)   | N = 160      | Healthy adults
Age 40-90 Chronic curcumin vs placebo: Significantly improved working memory & mood |
| Curcumin 1500 mg capsules/d x 12 months\(^2\) | N = 160      | Healthy adults
Age 40-90 No cognitive impairments Curcumin vs placebo: Improved cognitive performance at 6 months No differences between groups at 12 months |
| Theracurmin: curcumin 90 mg twice/d x 18 months\(^3\) | N = 40       | Healthy adults
Age 51-84 Non-demented Curcumin vs placebo: Improved memory & attention Benefit associated with decreases in amyloid & tau accumulation |

Curcumin

Sage

- Herbal supplement
- Antioxidant and anti-inflammatory
- Inhibits acetylcholinesterase (AChE)\(^1,2\)
- CNS depressant
- *Salvia officinalis*
- *S. lavandulaefolia*
# Sage Extract

<table>
<thead>
<tr>
<th>Dose/Duration</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. lavandulaefolia</em> essential oil 50 mg capsules QD x 1 week, then BID x 1 week, then TID x 4 weeks&lt;sup&gt;1&lt;/sup&gt;</td>
<td>N = 11 Age = 76-95 Mild to moderate probable AD MMSE = 10-26</td>
<td>After 6 weeks of treatment: 14.4% decrease in AChE activity Improvements in Neuropsychiatric Inventory (NPI) measurements MMSE scores stayed the same</td>
</tr>
<tr>
<td><em>S. lavandulaefolia</em> essential oil 65 uL single dose&lt;sup&gt;2&lt;/sup&gt;</td>
<td>N = 36 Mean age = 23 Healthy participants</td>
<td><em>S. lavandulaefolia</em> vs placebo: Improved cognitive performance &amp; mood Improved attention &amp; memory performance 1-h post dose Reduced mental fatigue &amp; increased alertness more prominent 4-h post-dose</td>
</tr>
</tbody>
</table>

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### Sage Extract

<table>
<thead>
<tr>
<th>Dose/Duration</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. officinalis</em> extract 60 drops (~4 mL)/day x 4 months</td>
<td>N = 42 Age = 65-80 Mild to moderate AD Score ≥ 12 on the ADAS-cog</td>
<td><em>S. officinalis</em> vs placebo: Improved cognitive functions (ADAS-cog &amp; CDR-SB scores) May reduce agitation</td>
</tr>
</tbody>
</table>

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### Foods/Diet Plans
Specific Foods/Fluids

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Food Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA, vitamin D</td>
<td>Fatty fish</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td>Olive oil</td>
</tr>
<tr>
<td>Tocopherols (vitamin E)</td>
<td>Leafy green vegetables</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>Berries</td>
</tr>
<tr>
<td>Polyphenols</td>
<td>Red wine, green tea</td>
</tr>
</tbody>
</table>

Studies on Specific Foods

<table>
<thead>
<tr>
<th>Foods</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish1</td>
<td>N = 2233</td>
<td>Lean fried fish: no effect</td>
</tr>
<tr>
<td></td>
<td>Age = 65+ yrs</td>
<td>Fatty fish: APOE e4: no protective effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>APOE e4 negative: reduced risk of dementia &amp; AD</td>
</tr>
<tr>
<td>Fish2</td>
<td>N = 5395</td>
<td>No association between fish intake &amp; dementia risk</td>
</tr>
<tr>
<td></td>
<td>Age = 55+ yrs</td>
<td></td>
</tr>
<tr>
<td>Olive oil3</td>
<td>N = 6947</td>
<td>High or moderate consumption of olive oil:</td>
</tr>
<tr>
<td></td>
<td>Age = 65+ yrs</td>
<td>Lower odds of cognitive deficit in visual memory &amp; verbal fluency</td>
</tr>
</tbody>
</table>

Leafy green vegetables1

<table>
<thead>
<tr>
<th>Foods</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 3,718</td>
<td>Greater consumption of leafy green vegetables:</td>
</tr>
<tr>
<td></td>
<td>Age = 65-102 yrs</td>
<td>Slower rate of cognitive decline</td>
</tr>
<tr>
<td></td>
<td>Chicago 60% Black, 62% F</td>
<td>cognition 5 yrs younger</td>
</tr>
<tr>
<td></td>
<td>Food frequency questionnaire</td>
<td>Fruit consumption:</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 3 &amp; 6 yrs</td>
<td>No cognition benefit</td>
</tr>
</tbody>
</table>

Leafy green vegetables2

<table>
<thead>
<tr>
<th>Foods</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 960</td>
<td>Green leafy vegetable consumption (highest quintile: mean 1.3 servings/d; higher intakes of folate, phylloquinone &amp; lutein):</td>
</tr>
<tr>
<td></td>
<td>Age = 58-99 yrs</td>
<td>Slower cognitive decline</td>
</tr>
<tr>
<td></td>
<td>Food frequency questionnaire &amp; cognitive assessments</td>
<td>Equivalent to 11 yrs younger vs rarely or never consumed green leafy vegetables</td>
</tr>
</tbody>
</table>

References:
## Foods Participants Results

### Berries¹
- **Participants**: N = 16,010 women
  - Age = 70+ yrs
  - Nurses' Health Study
  - Food frequency questionnaire
- **Results**: Higher total flavonoid intake:
  - Slower rates of cognitive decline
  - Blueberries & strawberries (2+ servings/wk):
    - Delayed cognitive aging by up to 2.5 yrs

### Berries²
- **Participants**: N = 9
  - Age = 76.2 +/- 5.2 yrs
  - Early memory changes
  - Wild blueberry juice daily vs grape juice vs placebo, x 12 wks
- **Results**: Blueberry juice:
  - Improved paired associate learning, word list recall

### Wine¹
- **Participants**: N = 980
  - Age = 65 yrs
- **Results**: Up to 3 servings of wine daily:
  - Lower risk of AD

### Green tea²
- **Participants**: N = 1003
  - Age = 70+ yrs
- **Results**: Green tea (> 3 cups/week):
  - Lower prevalence of cognitive impairment

### Tea³
- **Participants**: N = 490
  - Age = 60+ yrs
  - Green tea every day vs none:
    - Cognitive decline (dementia or MCI): OR 0.32 (P=0.001)
    - Dementia: OR 0.26 (P=0.06)
    - Black tea or coffee: no association for dementia or cognitive decline

### Coffee¹
- **Participants**: N = 1409
  - Age: 65-79 yrs
  - Avg follow-up 21 yrs
- **Results**: Coffee consumption at midlife vs no/little coffee:
  - Lower risk of dementia & AD later in life
  - Lowest risk (65% decrease): 3-5 cups/day

### Coffee²
- **Participants**: N = 676 men
  - 10-yr prospective cohort study
  - Finland, Italy, Netherlands
- **Results**: Coffee consumption vs non-consumers:
  - Smaller cognitive decline
  - Inverse & J-shaped association
  - Least cognitive decline: 3 cups of coffee/day

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**DASH (Dietary Approaches to Stop Hypertension)**

- Emphasis on:
  - Vegetables
  - Fruits
  - Whole grains
  - Low-fat or fat-free dairy products
  - Lean meat, poultry, & fish
  - Nuts, seeds, legumes
- Increased amounts:
  - Potassium
  - Calcium
  - Magnesium
  - Fiber
- Limit:
  - Saturated fat
  - Sugar-sweetened beverages & sweets
  - Sodium

**DASH Diet**

<table>
<thead>
<tr>
<th>Participants</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 16,144 Age = 70+ yrs Women¹</td>
<td>Prospective cohort study Nurses’ Health Study</td>
<td>Long-term adherence: Better average cognitive function</td>
</tr>
<tr>
<td>N = 124 Middle age Elevated BP Sedentary &amp; overweight or obese (BMI 25-40)²</td>
<td>Randomized control trial DASH alone vs DASH + weight management vs usual diet control group</td>
<td>DASH + weight management and DASH alone: Greater neurocognitive improvements</td>
</tr>
</tbody>
</table>


**Mediterranean Diet**

- High intake of:
  - Extra virgin olive oil
  - Vegetables, including leafy green vegetables
  - Fruits
  - Cereals
  - Nuts & pulses/legumes
- Moderate intake of:
  - Fish & poultry
  - Dairy products
  - Red wine
- Low intake of:
  - Red meat
  - Eggs
  - Sweets
### Mediterranean Diet

<table>
<thead>
<tr>
<th>Participants</th>
<th>Study Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 2258&lt;sup&gt;1&lt;/sup&gt; No dementia</td>
<td>Prospective study, NY Food frequency questionnaire Evaluated Q 1.5 yrs Adherence: 0-9 pts</td>
<td>262 cases of AD 4 yr (0.2-13.9) follow-up For AD vs lowest tertile: Highest tertile: HR 0.60 Middle tertile: HR 0.85</td>
</tr>
<tr>
<td>N = 522&lt;sup&gt;2&lt;/sup&gt; Age 55-80 yrs (74.6 +/- 5.7) High vascular risk</td>
<td>Randomized control trial, Spain MedDiet+EVOO vs MedDiet+Nuts vs low-fat diet (control) Mean follow-up: 6.5 yrs</td>
<td>MedDiet enhanced with EVOO or nuts: Better cognitive performance MCI (60): 18 vs 19 vs 23 Dementia (35): 12 vs 6 vs 17</td>
</tr>
</tbody>
</table>


### Dietary Plans

- **DASH**
- **MedDiet**

**MIND**

### Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)

- Whole grains ≥3/d
- Green leafy vegetables ≥1/d
- Other vegetables ≥1/d
- Berries ≥2/wk
- Fish ≥1/wk
- Poultry ≥2/wk
- Beans ≥3/wk
- Nuts ≥5/wk
- Alcohol/wine 1/d
- Olive oil = primary oil

- Fast/fried food <1/wk
- Butter, margarine <17/d
- Cheese <1/wk
- Red meats and products <4/wk
- Pastries, sweets <5/wk

Rush Memory and Aging Project

- Prospective study, 2004-2013
- N = 923, 58-98 years old
- Evaluated 3 dietary patterns to incidence of AD
- Food frequency questionnaire
  - Usual frequency of intake over previous 12 mos
  - 144 items
- Mean of 4.5 years follow-up
  - 151 AD cases developed

DASH (max total score 10)

<table>
<thead>
<tr>
<th>Components</th>
<th>Max score</th>
<th>Components</th>
<th>Max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total grains ≥ 7/d</td>
<td>1</td>
<td>Total fat ≤ 27% of kcal</td>
<td>1</td>
</tr>
<tr>
<td>Vegetables ≥ 4/d</td>
<td>1</td>
<td>Saturated fat ≤ 6% of kcal</td>
<td>1</td>
</tr>
<tr>
<td>Fruits ≥ 4/d</td>
<td>1</td>
<td>Sweets ≤ 5/wk</td>
<td>1</td>
</tr>
<tr>
<td>Dairy ≥ 2/d</td>
<td>1</td>
<td>Sodium ≤ 2400 mg/d</td>
<td>1</td>
</tr>
<tr>
<td>Meat, poultry &amp; fish ≤ 2/d</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuts, seeds &amp; legumes ≥ 4/wk</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MedDiet (max total score 55)

<table>
<thead>
<tr>
<th>Components</th>
<th>Max score</th>
<th>Components</th>
<th>Max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonrefined Grains &gt; 4/d</td>
<td>5</td>
<td>Legumes, nuts &amp; beans &gt; 6/wk</td>
<td>5</td>
</tr>
<tr>
<td>Vegetables &gt; 4/d</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potatoes &gt; 2/d</td>
<td>5</td>
<td>Olive oil ≥ 1/d</td>
<td>5</td>
</tr>
<tr>
<td>Fruits &gt; 3/d</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-fat Dairy ≤ 10/wk</td>
<td>5</td>
<td>Alcohol &lt; 300 mL/d but &gt; 0</td>
<td>5</td>
</tr>
<tr>
<td>Red meat ≤ 1/wk</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish &gt; 6/wk</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry ≤ 3/wk</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MIND (max total score 15)

<table>
<thead>
<tr>
<th>Components</th>
<th>Max score</th>
<th>Components</th>
<th>Max score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole grains ≥ 3/d</td>
<td>1</td>
<td>Nuts ≥ 5/wk</td>
<td>1</td>
</tr>
<tr>
<td>Green leafy ≥ 6/wk</td>
<td>1</td>
<td>Fast/fried food &lt; 1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Other Vegetables ≥ 1/d</td>
<td>1</td>
<td>Olive Oil primary oil</td>
<td>1</td>
</tr>
<tr>
<td>Berries ≥ 2/wk</td>
<td>1</td>
<td>Butter, margarine &lt; 1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Red Meats &amp; products &lt; 4/wk</td>
<td>1</td>
<td>Cheese &lt; 1/wk</td>
<td>1</td>
</tr>
<tr>
<td>Fish ≥ 1/wk</td>
<td>1</td>
<td>Pastries, sweets &lt; 5/wk</td>
<td>1</td>
</tr>
<tr>
<td>Poultry ≥ 2/wk</td>
<td>1</td>
<td>Alcohol/wine 1d</td>
<td>1</td>
</tr>
<tr>
<td>Beans ≥ 3/wk</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Diet Scores

<table>
<thead>
<tr>
<th>Diet Score</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
<th>P for Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DASH</strong></td>
<td>1.0 - 3.5</td>
<td>4.0 - 4.5</td>
<td>5.0 - 8.5</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>0.98</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>Referent</td>
<td>0.66, 1.46</td>
<td>0.38, 0.97</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Mediterranean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score range</td>
<td>18 - 29</td>
<td>30 - 34</td>
<td>35 - 46</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>0.81</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>Referent</td>
<td>0.54, 1.24</td>
<td>0.27, 0.79</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>MIND</strong></td>
<td>2.5 - 6.5</td>
<td>7 - 8</td>
<td>8.5 - 12.5</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.0</td>
<td>0.65</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>Referent</td>
<td>0.44, 0.98</td>
<td>0.29, 0.76</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CerefolinNAC: L-methylfolate 6 mg, methylcobalamin 2 mg, N-acetylcysteine 600 mg

<table>
<thead>
<tr>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHcy+CFLN (N=34) vs NoHHcy+NoCFLN (N=82)²</td>
<td>AD, VD, mixed dementia</td>
</tr>
<tr>
<td>HHcy+CFLN (N=30) vs NoHHcy+NoCFLN (N=37)²</td>
<td>AD or cognitive impairment due to cerebrovascular disease</td>
</tr>
</tbody>
</table>

Medical Foods

<table>
<thead>
<tr>
<th>Medical Foods</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souvenaid\textsuperscript{1,2}</td>
<td>N = 26</td>
<td>Treatment vs placebo: Significant reduction of behavioral symptoms and increase in Theory of Mind skill. No effect on executive functions.</td>
</tr>
<tr>
<td>Contains DHA 1200 mg &amp; EPA 300 mg, B vitamins 1 mg, uridine monophosphate 625 mg, choline 400 mg, &amp; phospholipids 106 mg</td>
<td>Age = 50-65 yrs</td>
<td>Drug-naïve pts with mild AD: Improved memory performance.</td>
</tr>
<tr>
<td>Behavioral variant of frontotemporal dementia</td>
<td>N = 259</td>
<td>Age = 50+ yrs</td>
</tr>
</tbody>
</table>

Reversal of cognitive decline

- 10 patients, memory loss: Alzheimer’s disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI)
- Nine of 10: subjective or objective improvement in cognition beginning within 3-6 months; one failure: very late stage AD
- Six patients:
  - Discontinued working or were struggling with their jobs at time of presentation
  - All able to return to work or continue working with improved performance
- Longest patient f/u: 2½ years from initial treatment, with sustained & marked improvement

Metabolic enhancement for neurodegeneration (MEND) protocol

<table>
<thead>
<tr>
<th>Goal</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize diet: minimize simple CHO, minimize inflammation</td>
<td>Choice of several low glycemic, low inflammatory, low grain diets</td>
</tr>
<tr>
<td>Enhance autophagy, ketogenesis</td>
<td>Fast 12 hr each night, including 3 hr prior to bedtime</td>
</tr>
<tr>
<td>Reduce stress</td>
<td>Yoga or meditation or music, etc</td>
</tr>
<tr>
<td>Optimize sleep</td>
<td>8 hr sleep per night, melatonin 0.5 mg po qhs, Tryptophan 500 mg po 3x/wk if awakening. Exclude sleep apnea.</td>
</tr>
<tr>
<td>Brain stimulation</td>
<td>Posit or related</td>
</tr>
</tbody>
</table>
Metabolic enhancement for neurodegeneration (MEND) protocol

<table>
<thead>
<tr>
<th>Goal</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of A-beta</td>
<td>Curcumin, Ashwagandha</td>
</tr>
<tr>
<td>Cognitive enhancement</td>
<td>Bacopa monniera, Mg Threonate</td>
</tr>
<tr>
<td>25(OH)D3 = 50-100 ng/mL</td>
<td>Vitamins D3, K2</td>
</tr>
<tr>
<td>Increase NGF</td>
<td>H. Erinaceus or ALCAR</td>
</tr>
<tr>
<td>Provide synaptic structural components</td>
<td>Citicoline, DHA</td>
</tr>
<tr>
<td>Optimize antioxidants</td>
<td>Mixed tocopherols &amp; tocotrienols, Se, blueberries, NAC, ascorbate, α-lipoic acid</td>
</tr>
</tbody>
</table>

Aging 2014; 6: 707-717
Metabolic enhancement for neurodegeneration (MEND) protocol

- Decrease in:
  - hs-CRP
  - Fasting insulin
  - HbA1c
  - Homocysteine

- Increase in:
  - 25OH vitamin D
  - MMSE
  - MoCA
  - Hippocampal volume

- Improvement in:
  - Memory
  - Recall
  - Processing speed
  - Executive function

Conclusion

<table>
<thead>
<tr>
<th>Nutritional Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>Lowered Hcy and improved cognition</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Improvement in cognition</td>
</tr>
<tr>
<td>Alpha-lipoic acid</td>
<td>Improved cognition in patients with diabetes</td>
</tr>
<tr>
<td>Omega 3</td>
<td>Reduced incidence of dementia; improvements in cognition in healthy adults and in very mild dementia</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Improved cognition in healthy adults</td>
</tr>
<tr>
<td>Sage</td>
<td>Decreased AChE activity and improvements in cognition in patients with dementia</td>
</tr>
<tr>
<td>DASH and MeDi diets</td>
<td>Only high adherence was associated with cognitive improvement</td>
</tr>
<tr>
<td>MIND diet</td>
<td>Even moderate adherence reduced risk of AD</td>
</tr>
</tbody>
</table>

Thank You!

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