The role of (micro) nutrients in ageing societies: implications for Alzheimer Disease

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Ageing, a global phenomenon

2014
- 0-9%
- 10-19%
- 20-24%
- 25-29%
- 30+%
- No data

2050

Map showing global aging trends compared to 2014 and projected for 2050.
Maintaining functional capacity

Disability Threshold:

Functional Capacity

Maintaining highest possible level of function

Growth & Development

Maintaining independence & avoiding disability

Range of function in individuals

Disability Threshold:

Rehabilitation & ensuring quality of life

Life Course

Nutrition can help to maintain the functional capacity

WHO, Active Aging: A Policy Framework, 2005
Alzheimer’s Fact & Figures

Alzheimer’s disease is the 6TH LEADING CAUSE of death in the United States.

MORE THAN 5 MILLION Americans are living with Alzheimer’s.

EVERY 67 SECONDS, someone in the United States develops the disease.

Alzheimer’s is the only cause of death among the top 10 in America that CANNOT BE PREVENTED, CURED OR EVEN SLOWED.

In 2013, 15.5 million caregivers provided an estimated 17.7 BILLION HOURS of unpaid care valued at more than $220 billion.

THERE ARE APPROXIMATELY 500,000 PEOPLE DYING each year because they have Alzheimer’s disease.

1 in 3 Seniors DIES WITH ALZHEIMER’S or another dementia.

http://www.alz.org/alzheimers_disease_facts_and_figures.asp
Alzheimer Disease death rates increase despite medical advancement

Progress in the development of medical drugs for Alzheimer Disease is slow

Adapted from: M. Hasan Mohajeri, Ph.D. Barbara Troesch, Ph.D. Peter Weber, MD., Ph.D DOI: 10.1016/j.nut.2014.06.016
Lifestyle and genetics are risk factors for Alzheimer Disease

- Age
- Family history
- APO-E
- Education
- Head trauma
- Depression
- Homocysteine
- Diabetes
- Hypertension
- Cholesterol
- Obesity
- Physical inactivity
- Smoking

Nutrition?
Impact of aging on nutrient intake & utilisation

- Decreased energy requirements due to changes in body composition & activity
- Changes in appetite & therefore nutrient intake due to factors such as medication, decrease taste & smell
- Impaired absorption due to changes in the GI tract
- Reduced food intake due to disease, disability, mental disorders or drugs
- Social factors such as low income & isolation affect intake

Various physiological & social factors make it more difficult to maintain a balanced diet & to use the nutrients properly
The nutritional situation is critical in the elderly even in affluent countries & even more so once they become ill or frail

Vitamin intake: German elderly (≥65 yrs)

Verzehrsstudie 2008; Ernährungsbericht 2008 & 2012
Inadequate supply of vitamins and DHA in the elderly: implications for brain aging and Alzheimer’s type dementia
M. Hasan Mohajeri, Ph.D. Barbara Troesch, Ph.D. Peter Weber, MD., Ph.D
DOI: 10.1016/j.nut.2014.06.016

Abstract
Alzheimer’s disease (AD) is the most prevalent, severe and disabling cause of dementia worldwide. To date, AD therapy is primarily targeted toward palliative treatment of symptoms rather than prevention of disease progression. So far, no pharmacological interventions have changed the onset or progression of AD and their use is accompanied by side effects. The major obstacle in managing AD and designing therapeutic strategies is the difficulty in retarding neuronal loss in the diseased brain once the pathological events leading to neuronal death have started. Therefore, a promising alternative strategy is to maintain a healthy neuronal population in the aging brain for as long as possible. One factor evidently important for neuronal health and function is the optimal supply of nutrients necessary for maintaining normal functioning of the brain. Mechanistic studies, epidemiological analyses and randomized controlled intervention trials provide insight to the positive effects of docosahexaenoic acid (DHA) and micronutrients such as the vitamin B family, and vitamins E, C and D, in helping neurons to cope with aging. These nutrients are cheap in use, have virtually no side effects when used at recommended doses, are essential for life, have established modes of action, and are broadly accepted by the general public. We provide here some evidence that the use of vitamins and DHA for the aging population in general, and for individuals at-risk in particular, is a viable alternative approach to delaying brain aging and for protecting against the onset of AD pathology.
Vit B intake slows rate of brain atrophy

- 168 mild cognitive impaired (MCI) elderly (>70 yrs) received 0.8 mg folic acid, 0.5 mg vit B12 & 20 mg B6 or placebo daily for 2 yrs
- Intervention lowered plasma concentrations of homocysteine
- Mean rate of brain atrophy per year was 0.8% [95% CI, 0.63-0.90] in intervention vs 1.1% [0.94-1.22] in placebo group (P = 0.001)
- A greater rate of atrophy was associated with a lower final cognitive test scores

Accelerated rate of brain atrophy in elderly with MCI can be slowed by treatment with B vitamins

Schmid et al, PLoSOne 2010
**MIDAS – Memory Improvement with Docosahexaenoic Acid Study**

**Goal:** Evaluate the effects of algal DHA on cognitive outcomes in healthy elderly (≥55 yrs.) with a mild memory complaint

**Trial Design**
- Randomized, double-blind, placebo-controlled, parallel, multi-center (19 US sites)
- Oral Dose: 900 mg algal DHA/day or placebo (corn/soy)
- Study treatment: 6 mos.
- Sample size: 485 subjects
- Primary Endpoint: cognitive test of memory & learning (CANTAB® PAL)
- Secondary Endpoints: cognitive tests of executive function, Activity of Daily Living (ADL) skills, plasma phospholipid fatty acid levels, safety and tolerability

MIDAS – Results

- Primary endpoint: **Paired Associate Learning** test - learning and memory recall test that discriminates well between aging, MCI, AD and is sensitive to early episodic memory changes. (de Jager, 2002; Fowler, 2002; Egerhazi, 2007)
  
  - ~50% less errors were made on this test with DHA
    (DHA -4.5±0.64 vs. -2.4±0.62 placebo, p=0.032, ITT)
MAPT (Multi-Domain Alzheimer’s Prevention Trial): Clinical, Biomarkers results and lessons for the future


• Multicenter RCT in 1680 elderly with subjective memory complaint
• Primary endpoint: change of cognitive function at 3 years
• Intervention:
  - 800 mg docosahexaenoic acid (DHA) per day
  - Multidomain intervention (training sessions in the following three areas: nutrition, physical activity, and cognition)
• Results:
  - Improvement of a composite cognition score in the DHA plus multi-domain intervention is the only significant change compared with placebo
  - Higher effects in people with low DHA levels

Reference: CTAD Meeting, Barcelona 2015
<table>
<thead>
<tr>
<th>Source</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Sano et al., 1997, N Engl J Med</td>
<td>341 AD patients of moderate severity received daily the selective monoamine oxidase inhibitor selegiline (10 mg), α-tocopherol (vitamin E, 2000 IU) for 2 years. <strong>Treatment with selegiline or alpha-tocopherol slows the progression of disease</strong> (MMSE measures).</td>
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<td>Klatte et al., 2003, Alzheimer Dis Assoc Disord.</td>
<td>Retrospective review of 130 patients AD patients receiving VitE (at least 1000 mg/d, and at least 5mg donepezil/d for 1y). <strong>Long-term combination therapy of donepezil and vitamin E appears beneficial for patients with AD</strong>.</td>
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<td>Petersen et al. N. Engl. J. Med. 2005</td>
<td>Time to the development of possible or probable AD (starting from MCI). 1000 IU/day for first 6 weeks, thereafter 2000 IU/day for 3 years. Results: <strong>No significant differences in the probability of progression from MCI to AD</strong>. No side effects.</td>
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<td>Chui &amp; Greenwood, 2008, Nutrition Research</td>
<td>Open trial in 16 adults (age 63.5±2 y) with type 2 diabetes mellitus. Antioxidant vitamins C (1000mg) &amp; E (800 IU) <strong>reduced acute meal-induced memory deficits in adults with type 2 diabetes</strong>.</td>
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<td>Lloret et al. J. Alzheimers Dis. 2009</td>
<td>33 AD patients (25 with mild, 26 with moderate and 6 with severe dementia) were treated with 800IU/day for 6 months. Primary outcome: Glutathione oxidation (GSSG). Higher GSSG/GSH ratio for severely demented patients when compared to moderated demented patients. Also, <strong>Respondents to vitE treatment (lower blood GSSG levels) were slightly better in cognitive testing than non-responders</strong>. No side effects.</td>
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<td>Dysken et al., JAMA, 2014</td>
<td>613 patients with mild to moderate AD were given 2000 IU/d a-tocopherol for up to 4 y. Treatment resulted in <strong>slower functional decline, in reduction of caregiver time (2h/d) and no additional side-effects</strong>.</td>
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Vitamin E slows the progression of AD

341 Patients with moderate and severe AD cases who were assigned to treatment with Selegiline (10 mg/d), α-tocopherol (2000 IU/d), both, or placebo for 2 years.

- Event-free Survival significantly improved in the vitamin E group (p=0.001) in comparison with the selegiline (p=0.012) or combination therapy (p=0.049), respectively).

- No statistically significant differences were observed among the groups in adverse-event categories after adjustment for multiple comparisons.

2000 IU/d of α-tocopherol resulted in slower functional decline of AD patients

613 patients with mild to moderate AD received either 2000 IU/d of synthetic α-tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152).

➤ Over the mean follow-up of 2.27 years, participants receiving α-tocopherol had slower decline than those receiving placebo as measured by the ADCS-ADL.

➤ The change translates into a delay in clinical progression of 19% per year compared with placebo (approximately 6.2 months over the follow-up period).

➤ Caregiver time increased least in the α-tocopherol group.

➤ No differences in the occurrence of adverse effects was observed.

Dysken et al. JAMA. 2014;311(1):33-44
Alzheimer’s Disease, progression & symptoms

Delaying AD / cognitive impairment by months is a significant achievement

Cognitive performance

- Memory
- Orientation
- Language

- Daily competences
- Affective disorders
- Decision making

- Behavior disturbance
- Dependency on caregivers
- Hygiene

- Agitation
- Immobility

Time (7-9 years)
mild moderate severe
Conclusions

• (Micro)nutrient inadequacy is widespread in the elderly.
• The need for essential nutrients is increased in the aging brain.
• AD prevalence is age dependent, it is the most common form of dementia, accounting for 60-80% of dementia cases for which no pharmacological interventions have changed the onset or progression of AD and their use is accompanied by side effects.
• Epidemiological findings and results of controlled clinical trials (RCTs) report vitamins B, E and n-3 PUFA to have a great potential in delaying the onset of AD.
• Delaying AD, either onset or deterioration of clinical course by micronutrients has a great potential to benefit the patients as well as the public health care
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