Supporti nutrizionali nel trattamento della malattia di Alzheimer: quali evidenze

Angelo Bianchetti
Le persone che sono affette da decadimento cognitivo, in particolare AD presentano importanti modificazioni dello stato nutrizionale per numerosi fattori:

- Modificazione delle abitudini alimentari (riduzione dell’appetito, riduzione del numero dei pasti, monotonia dei cibi)
- Limitazione delle opportunità di approvvigionamento
- Alterazioni dello stato funzionale (difficoltà a preparare gli alimenti e a nutrirsi correttamente, problemi masticatori)
- Compromissione delle funzioni cognitive (dimenticanza di assumere i cibi, difficoltà nel cucinare correttamente)
- Comparsa di disturbi del comportamento (rifiuto del cibo, depressione, bulimia)
- Modificazioni delle richieste energetiche (più frequentemente un aumento)
- Nelle fasi avanzate comparsa di disfagia
Why are Alzheimer patients thin?

We observed that none of our long-stay elderly patients with AD was obese: most of them were thin and some become cachetic. Alzheimer’s patients lose weight and on average weigh 21% less then non demented patients and 14% less then MID patients. This weight loss is not accounted for by any obvious deficit in food intake, or by malabsorption.

Weight loss in Alzheimer’s Disease

• during the natural history almost twice as many AD patients as control subjects lost ≥5% of their initial body weight
• the same finding was observed for a loss of ≥10% of initial body weight
• AD patients were also more likely to gain ≥5% of their initial body weight than were control subjects
• the risk of weight loss tends to increase with the severity and progression of AD
• weight loss is a predictor of mortality in subjects with AD
• weight gain appears to have a protective effect.

BK Tamura et al, J Nutr Eld, 2007
Age-adjusted mean weight over time by dementia status.

* P < .01; weight loss over time. Errors bars show 1 standard error

Average weight loss (men and women combined) over time by group. T0 indicates the time of dementia diagnosis; T − 1 through T − 6, times of assessment before diagnosis; and T + 1 through T + 3, times of assessment after diagnosis.
Nutrizione e malattia di Alzheimer

L’AD influenza la nutrizione

- Abitudini e comportamento alimentare
- Opportunità di approvvigionamento
- Modalità di consumo del cibo
- Richieste energetiche
- Digestione e assorbimento
- Rifiuto del cibo e disfagia
I fattori nutrizionali influenzano le manifestazioni cliniche della malattia di Alzheimer e le complicanze

- Riduzione delle difese immunitarie
- Aumento del rischio di caduta
- Riduzione della massa muscolare e della forza
- Peggioramento dello stato funzionale
- Peggioramento della prognosi delle malattie acute
Nutrizione e malattia di Alzheimer

**L’AD influenza la nutrizione**

- Abitudini e comportamento alimentare
- Opportunità di approvvigionamento
- Modalità di consumo del cibo
- Richieste energetiche
- Digestione e assorbimento
- Rifiuto del cibo e disfagia

**La nutrizione influenza l’AD**

- Difese immunitarie
- Massa muscolare e forza
- Stato funzionale
- Rischio di caduta
- Prognosi delle malattie acute
- Rischio di decubito
Nutrizione e malattia di Alzheimer

L’AD influenza la nutrizione

- Abitudini e comportamento alimentare
- Opportunità di approvvigionamento
- Modalità di consumo del cibo
- Richieste energetiche
- Digestione e assorbimento
- Rifiuto del cibo e disfagia

La nutrizione influenza l’AD

- Difese immunitarie
- Massa muscolare e forza
- Stato funzionale
- Rischio di caduta
- Prognosi delle malattie acute
- Rischio di decubito

- Rischio di sviluppare demenza e AD
- Progressione della malattia
- Funzioni cognitive
I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell’AD/demenza e le prestazioni cognitive anche in soggetti non dementi

• **Dati epidemiologici:**
  - un elevato consumo di frutta e vegetali riduce del 38% il rischio di sviluppare demenza in uno studio osservazionale di 7 anni (*Ritchie et al, BMJ 2010*)
  
  - una elevata assunzione di vitamina C e vitamina E è associata ad un rischio più basso di sviluppare malattia di Alzheimer (82%) (*Engelhart et al, JAMA 2002*)
  
  - una dieta ricca di insalata, noci, pesce, pomodori, pollame, verdura, frutta e ortaggi a foglia verde si associa a una riduzione del rischio di sviluppare malattia di Alzheimer del 48% (*Gu et al, Arch Neurol. 2010*)
  
  - Una dieta “mediterranea” riduce il rischio di sviluppare AD e MCI (*Scarmeas et al, Ann Neurol 2006; Scarmeas et al, Arch Neurol 2009*)
I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell’AD/demenza e le prestazioni cognitive anche in soggetti non dementi

- Dati clinici
  - In soggetti anziani sani, elevati livelli plasmatici di vitamine del gruppo B (B1, B2, B6, folati, B12), C, D, e E, e di acidi grassi ω-3 si associano a migliori prestazioni cognitive e minore atrofia cerebrale alla RMN (Bowman GL et al Neurology 2012)

  - In soggetti sedentari, ipertesi e in sovrappeso, una dieta ipocalorica, povera di sodio, ricca di potassio, calcio e magnesio, di frutta e vegetali, a basso contenuto di grassi animali, ricca di fibre, si associa a miglioramento delle prestazioni cognitive. (Smith PJ et al, Hypertension 2010)

  - Una dieta ricca di cibi ad elevata capacità antiossidante (olio di oliva, noci) si associa a migliori prestazioni cognitive mnesiche; associazione indipendente fra escrezione urinaria di polifenoli e prestazioni mnesiche. (Valls-Pedret et al, JAD 2012)
Dietary Patterns in Alzheimer’s Disease and Cognitive Aging

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Abstract

Much of the attention on diet and Alzheimer’s disease (AD) or cognition among the elderly has focused on the role of single nutrients or foods, while available information on dietary pattern (DP) analysis, which better reflects the complexity of the diet, is sparse. In this review, we describe different patterning approaches and present studies performed to date that have assessed the associations between DPs and risk of AD or cognitive function in the elderly. Three patterning approaches have been most commonly used: (i) hypothesis-based that use dietary quality indexes or scores (e.g., Mediterranean pattern), (ii) data-driven that use factor or cluster analysis to derive DPs, (iii) reduced rank regression which combines characteristics of the former two approaches. Despite differences existing among the approaches, DPs characterized by higher intake of fruits, vegetables, fish, nuts and legumes, and lower intake of meats, high fat dairy, and sweets seemed to be associated with lower odds of cognitive deficits or reduced risk of AD. Overall, the inherent advantages as well as the existing evidence of DP analyses strongly suggest that this approach may be valuable in AD and aging research. Further studies are warranted, though, to confirm the findings in different population settings, to address some methodological issues, and possibly utilize the information for future clinical trial design.
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<th>Conclusion</th>
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<tr>
<td>Huijbregts et al. 1998 [26]</td>
<td>Cross-sectional</td>
<td>1049 men aged 70–91 years; the Seven Countries Study</td>
<td>MMSE. A score of 23 or lower was used to indicate cognitive impairment.</td>
<td>Cross-check dietary history</td>
<td>HDI</td>
<td>After multivariable adjustment, OR (95% CI) for cognitive impairment per unit increase of HDI = 0.75 (0.58–0.97) and 0.81 (0.63–1.04) in two cohorts.</td>
<td>A healthy diet (higher HDI) might be associated with a better cognitive function in elderly men.</td>
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<tr>
<td>Corrêa Leite et al. 2001 [27]</td>
<td>Cross-sectional</td>
<td>560 men and 1091 women aged ≥65 years; Italy.</td>
<td>Neuropsychological test score (≥53 for normal cognition; 40–52 for mild cognitive deficit; 24–39 for moderate cognitive deficit; ≤23 or less for severe deficit).</td>
<td>180-item FFQ</td>
<td>HDI</td>
<td>After multivariable adjustment, OR (95% CI) for any level of cognitive deficit per unit increase of HDI = 0.85 (0.77–0.93).</td>
<td>A better HDI was associated with a lower prevalence of cognitive deficit in the elderly.</td>
</tr>
<tr>
<td>Wengreen et al. 2009 [29]</td>
<td>Prospective</td>
<td>3634 subjects ≥ 65 years of age followed up for an average ~11 years; Cache County Study on Memory and Aging in Utah.</td>
<td>3MS</td>
<td>142-item FFQ</td>
<td>RFS</td>
<td>Subjects in the highest quartile (Q4) of RFS scored 1.80 points higher on the baseline 3MS test than did those in the Q1 (P &lt; 0.001). Subjects with Q4 RFS declined less (3.41 points) than those with Q1 RFS (5.15 points) (P = 0.0013) over 11 years.</td>
<td>Consuming a diverse diet that includes a variety of recommended foods may help to attenuate age-related cognitive decline among the elderly.</td>
</tr>
<tr>
<td>Scarmeas et al. 2006a [35]</td>
<td>Prospective</td>
<td>2,258 nondemented subjects ≥ 65 years old followed up for an average 4 years; WHICAP.</td>
<td>Comprehensive Neuropsychological test battery. Physicians screened subjects for potential AD consensus diagnosis by neurologists and neuropsychologists.</td>
<td>61-item FFQ</td>
<td>MeDi</td>
<td>Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a HR (95% CI) of 0.85 (0.63–1.18) and in the highest tertile 0.60 (0.42–0.87) for AD (p-for-trend=0.007).</td>
<td>MeDi is associated with a reduction in risk for incident AD.</td>
</tr>
<tr>
<td>Scarmeas et al. 2006b [33]</td>
<td>Case-control</td>
<td>194 patients with AD and 1790 nondemented participants of WHICAP.</td>
<td>As Scarmeas N 2006a.</td>
<td>61-item FFQ</td>
<td>MeDi</td>
<td>Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had an OR (95% CI) of 0.47 (0.29–0.76) and those at the highest tertile an OR (95% CI) of 0.32 (0.17–0.59) for AD (p-for-trend=0.001).</td>
<td>Higher adherence to the MeDi is associated with a reduced risk for AD.</td>
</tr>
<tr>
<td>Scarmeas et al. 2009 [34]</td>
<td>Prospective</td>
<td>1393 cognitively normal</td>
<td>As Scarmeas N 2006. MCI diagnosis</td>
<td>61-item FFQ</td>
<td>MeDi</td>
<td>Compared with subjects in the lowest MeDi tertile,</td>
<td>Higher adherence to the MeDi is</td>
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<td>Paliotopoulou et al. 2008 [36]</td>
<td>Prospective</td>
<td>732 subjects ≥60 years old followed up for 6–13 years: EPIC–Greece cohort</td>
<td>MMSE</td>
<td>61-item FFQ</td>
<td>MeDi</td>
<td>Adherence to the MeDi exhibited weakly positive (multiple regression for 1 unit increase of MeDi β=0.05) but not significant (p=0.485) associations.</td>
<td>Adherence to the MeDi was very weakly positively and not significantly associated with MMSE score.</td>
</tr>
<tr>
<td>Feart et al. 2009 [37]</td>
<td>Prospective</td>
<td>1410 adults (≥65 years) from Bordeaux, France, included in the Three-City cohort in 2001–2002. Median follow-up time was 4.1 years.</td>
<td>MMSE for global cognitive performance, IST for semantic verbal fluency and speed of verbal production. BVRT for immediate visual memory. FCSRT for verbal episodic memory.</td>
<td>FFQ</td>
<td>MeDi</td>
<td>Higher MeDi score associated with fewer MMSE errors (β = -0.006; 95% CI: -0.01 to -0.0003; P=0.04 for 1 point increase of the MeDi score). MeDi was associated with the risk for incident dementia: HR (95% CI) = 1.12 (0.60–2.10) comparing the highest to the lowest tertile. P = 0.72.</td>
<td>Higher adherence to MeDi was associated with slower MMSE cognitive decline but not consistently with other cognitive tests. Higher adherence was not associated with risk for incident dementia or AD.</td>
</tr>
<tr>
<td>Smith et al. 2010 [38]</td>
<td>Randomized clinical trial</td>
<td>124 participants with elevated blood pressure who were sedentary and over-weight or obese</td>
<td>A battery of neurocognitive tests at baseline and again after the 4-month intervention.</td>
<td>N/A</td>
<td>DASH</td>
<td>Compared with subjects on the usual diet, subjects on DASH+ weight management arm and the DASH diet alone arm both exhibited greater neurocognitive improvements.</td>
<td>Combining aerobic exercise with the DASH diet and caloric restriction improves neurocognitive function among sedentary and overweight/obese individuals with pre-hypertension and hypertension.</td>
</tr>
<tr>
<td>Barberas-Gateau et al. 2007 [41]</td>
<td>Prospective</td>
<td>8,085 participants (≥ 65 years) of the Three-City cohort study in France. Median</td>
<td>3 steps: neuropsychological tests; neurologists screened subjects for potential AD patients;</td>
<td>FFQ</td>
<td>Good and Poor DPs</td>
<td>A poor DP (infrequent consumption of fish, fruits and vegetables, and no regular use of omega-3 rich oils) was associated with an increased risk for dementia.</td>
<td>A combination of dietary sources of omega-3 PUFA and antioxidants seems therefore necessary.</td>
</tr>
<tr>
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<tr>
<td>Samieri et al. 2006 [42]</td>
<td>Cross-sectional</td>
<td>1,724 subjects aged 65 years; the Three-City cohort in France.</td>
<td>MMSE</td>
<td>FFQ</td>
<td>Cluster analysis</td>
<td>Mean MMSE score was higher in the &quot;healthy&quot; cluster and lower in the &quot;biscuit and snacking&quot; cluster in both sexes.</td>
<td>A &quot;healthy&quot; dietary pattern characterized by higher consumption of fish in men and fruits and vegetables in women was related to better cognitive performance.</td>
</tr>
<tr>
<td>Akbaraly et al. 2009 [45]</td>
<td>Cross-sectional</td>
<td>4,692 aged 35–55 years white European participants of the Whitehall II study</td>
<td>Cognitive test battery consisted of 5 standard tasks</td>
<td>127-item FFQ</td>
<td>PCA</td>
<td>The 'whole food' pattern was associated with lower (OR=0.5-0.8, p&lt;0.05 for all 5 domains) and the &quot;processed food&quot; pattern with increased (OR=1.0–1.8, p&lt;0.05 for all domains except memory) odds of cognitive deficit.</td>
<td>A diet rich in fruits, vegetables and fish ('whole food' pattern) is associated with lower odds of cognitive deficit while 'processed food' DP rich in processed meat, chocolates and sweeteners, desserts, fried food, refined grains and high-fat dairy products is associated with greater odds of cognitive deficit. Education shapes the relationships.</td>
</tr>
<tr>
<td>Cer et al. 2010 [48]</td>
<td>Prospective</td>
<td>2148 nondemented individuals &gt; 65 years, followed up for an average 4 years, WHICAP</td>
<td>As Scarmans N 2006a</td>
<td>61-item FFQ</td>
<td>RRR</td>
<td>A DP was identified and it was strongly associated with lower AD risk compared to subjects in the lowest tertile of adherence to this pattern. AD HR (95% CI) for subjects in the highest DP tertile was 0.85 (0.43–0.89) after multivariable</td>
<td>Higher consumption of salad dressing, nuts, fish, tomatoes, poultry, cruciferous vegetables, fruits, dark- and green-leafy vegetables and lower of high fat dairy, red meat, organ meats, and butter may be associated with decreased risk of AD via a more favorable profile of nutrients (i.e. lower ingestion of SFAs and higher ingestion of PUFAs, Vitamin E and folate).</td>
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</table>
Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids. A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging. Dietary flavanols have also been shown to improve endothelial function and to lower blood pressure by causing vasodilation in the peripheral vasculature and in the brain. Improved cognitive performance with the administration of a cocoa polyphenolic extract has even been reported in aged Wistar–Unilever rats.

Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.
### Risk factors

- **Vascular hypothesis:** e.g., midlife hypertension & obesity, diabetes, smoking, heart disease, stroke, high-fat diet, etc.

- **Genetic factors:** e.g., APOE ε4 allele

- **Others:** toxic (occupational exposures) and inflammatory (e.g., C-reactive protein and interleukin-6) hypotheses

### Protective factors

- **Oxidative stress:** e.g., folate and vitamin B₁₂, and antioxidants (e.g., vitamins C and E)

### Psychosocial hypothesis

- e.g., high education, high socioeconomic status, physical exercise, mentally-stimulating activity, and rich social network, etc.

<table>
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<th>Birth</th>
<th>Childhood-2nd decade</th>
<th>Adult life-Middle age</th>
<th>Transition</th>
<th>Late life-Old age</th>
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<tr>
<td>0</td>
<td>20</td>
<td>60</td>
<td>75 Age, Years</td>
<td></td>
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</table>

Qiu, Xu and Fratiglioni, JAD, 2010
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gomez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutierrez, Ph.D., Miguel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Llamuela-Raventos, D.Pharm., Ph.D., Luis Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorli, M.D., Ph.D., José Alfredo Martinez, D.Pharm., M.D., Ph.D., and Miguel Angel Martinez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND
Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events.

METHODS
In a multicenter trial in Spain, we randomly assigned participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years.

RESULTS
A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported.

CONCLUSIONS
Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events. (Funded by the Spanish government’s Instituto de Salud Carlos III and others; Controlled-Trials.com number, ISRCTN35739639.)

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*The PREDIMED (Prevención con Dieta Mediterránea) study investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on February 25, 2013, at NEJM.org.

DOI: 10.1056/NEJMoa1300368
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Perspective

New Insights into the Dementia Epidemic

Eric B. Larson, M.D., M.P.H., Kristine Yaffe, M.D., and Kenneth M. Langa, M.D., Ph.D.
November 27, 2013 | DOI: 10.1056/NEJMp1311405

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<td>Manton et al. (United States)</td>
<td>Prevalence of severe cognitive impairment</td>
<td>National long-term care survey interviews, 1982–1999</td>
<td>Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)</td>
<td>Higher educational level, decline in stroke incidence</td>
</tr>
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<td>Langa et al. (United States)</td>
<td>Prevalence of cognitive impairment</td>
<td>Ongoing population-based survey of people ≥51 yr of age</td>
<td>Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)</td>
<td>Higher educational level; combination of medical, lifestyle, demographic, and social factors</td>
</tr>
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<td>Schrijvers et al. (Rotterdam)</td>
<td>Incidence of dementia</td>
<td>Population-based cohort ≥55 yr of age in 1990, extended in 2000</td>
<td>Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)</td>
<td>Higher educational level, reduction in vascular risk, decline in stroke incidence</td>
</tr>
<tr>
<td>Qiu et al. (Stockholm)</td>
<td>Prevalence of DSM-III-R dementia*</td>
<td>Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004</td>
<td>Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004; lower hazard ratio for death in later cohort suggests decreased dementia incidence</td>
<td>Favorable changes in risk factors, especially vascular risk; healthier lifestyles</td>
</tr>
<tr>
<td>Matthews et al. (England)†</td>
<td>Prevalence of dementia in 3 regions</td>
<td>Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)</td>
<td>Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)</td>
<td>Higher educational level, better prevention of vascular disease</td>
</tr>
</tbody>
</table>

* In the study by Qiu et al., dementia was diagnosed according to the criteria provided in the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R).
† CFAS denotes Cognitive Function and Ageing Study.
Effect of Apolipoprotein E Genotype and Diet on Apolipoprotein E Lipidation and Amyloid Peptides

Randomized Clinical Trial

Angela J. Hanson, MD; Jennifer L. Bayer-Carter, PhD; Pattie S. Green, PhD; Thomas J. Montine, MD, PhD; Charles W. Wilkinson, PhD; Laura D. Baker, PhD; G. Stennis Watson, PhD; Laura M. Bonner, PhD; Maureen Callaghan, MD; James B. Leverenz, MD; Elaine Tsai, MD; Nadia Postuma, PhD; Jing Zhang, PhD; Johanna Lampe, PhD; Suzanne Craft, PhD

**Importance:** Sporadic Alzheimer disease (AD) is caused in part by decreased clearance of the β-amyloid (Aβ) peptide breakdown products. Lipid-depleted (LD) apolipoproteins are less effective at binding and clearing Aβ, and LD Aβ peptides are more toxic to neurons. However, not much is known about the lipid states of these proteins in human cerebrospinal fluid.

**Objective:** To characterize the lipidation states of Aβ peptides and apolipoprotein E in the cerebrospinal fluid in adults with respect to cognitive diagnosis and APOE e4 allele carrier status and after a dietary intervention.

**Design:** Randomized clinical trial.

**Setting:** Veterans Affairs Medical Center clinical research unit.

**Participants:** Twenty older adults with normal cognition (mean [SD] age, 69 [7] years) and 27 with amnestic mild cognitive impairment (67 [6] years).

**Interventions:** Randomization to a diet high in saturated fat content with a high glycemic index (High diet; 45% of energy from fat >25% saturated fat, 35%-40% from carbohydrates with a mean glycemic index >70, and 15%-20% from protein) or a diet low in saturated fat content and with a low glycemic index (Low diet; 25% of energy from fat <7% saturated fat, 55%-60% from carbohydrates with a mean glycemic index <55, and 15%-20% from protein).

**Main Outcomes and Measures:** Lipid-depleted Aβ42 and Aβ40 and apolipoprotein E in cerebrospinal fluid.

**Results:** Baseline levels of LD Aβ were greater for adults with mild cognitive impairment compared with adults with normal cognition (LD Aβ42, \(P = .05\); LD Aβ40, \(P = .01\)). These findings were magnified in adults with mild cognitive impairment and the e4 allele, who had higher LD apolipoprotein E levels irrespective of cognitive diagnosis (\(P < .001\)). The Low diet tended to decrease LD Aβ levels, whereas the High diet increased these fractions (LD Aβ42, \(P = .01\); LD Aβ40, \(P = .15\)). Changes in LD Aβ levels with the Low diet negatively correlated with changes in cerebrospinal fluid levels of insulin (LD Aβ42 and insulin, \(r = -0.68\) [\(P = .01\)]; LD Aβ40 and insulin, \(r = -0.78\) [\(P = .002\)].

**Conclusions and Relevance:** The lipidation states of apolipoproteins and Aβ peptides in the brain differ depending on APOE genotype and cognitive diagnosis. Concentrations can be modulated by diet. These findings may provide insight into the mechanisms through which apolipoprotein E4 and unhealthy diets impart risk for developing AD.

JAMA Neurol. Published online June 17, 2013. doi:10.1001/jamaneurol.2013.396

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**Figure 6.** Theoretical model of β-amyloid (Aβ) peptide and apolipoprotein E (ApoE) interaction in the central nervous system (CNS). In the top panel, when ApoE is more lipidated, such as with an ε2 allele (E2+) or a healthy diet, it may be more able to bind Aβ and facilitate its clearance and degradation. When ApoE is less lipidated, such as with the E4+ state or a diet with a high level of saturated fat and a high glycemic index (High diet), it may be less able to bind Aβ. In the bottom panel, when ApoE binds to carrier proteins, such as ApoE, it is more likely to be cleared by enzymatic degradation or by crossing the blood-brain barrier (BBB). However, when Aβ is not bound to proteins, it can form oligomers that are toxic to synapses and neurons. High diets may decrease Aβ-lipoprotein binding, which will increase the toxic forms of Aβ. Conversely, diets with low levels of saturated fat and glycemic index (Low diet) may enhance Aβ-lipoprotein binding, in part by raising CNS insulin levels to optimal.
cardiovascular risk factors such as poor diet, obesity and higher body mass index, diabetes and insulin resistance, and other aspects of the metabolic syndrome contribute to risk for AD dementia.

part of the increased risk for AD dementia associated with vascular risk factors is surely related to an increase in cerebrovascular burden, but there may be a direct contribution to the development of Alzheimer pathology as well

the important lesson from the study is that dietary intervention can change brain amyloid chemistry in largely consistent and apparently meaningful ways—and in a short period of time.

it adds another small piece to the growing evidence that taking good care of your heart is probably good for your brain too.
Single nutrient interventions in MCI and AD: No effect on cognitive functioning

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Nutrient</th>
<th>#Subjects/Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein 2011</td>
<td>J Alz Disease</td>
<td>Vitamin D2</td>
<td>32 8 weeks</td>
<td>We conclude that high-dose vitamin D provides no benefit for cognition or disability over low-dose vitamin D in mild-moderate AD</td>
</tr>
<tr>
<td>Quinn 2010</td>
<td>JAMA</td>
<td>DHA</td>
<td>402 18 months</td>
<td>DHA compared with placebo did not slow the rate of cognitive and functional decline in mild-moderate AD patients.</td>
</tr>
<tr>
<td>DeKosky 2008</td>
<td>JAMA</td>
<td>Ginkgo biloba</td>
<td>3069 median f-up 6.1 Y</td>
<td>Ginkgo biloba at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or AD incidence in elderly individuals with normal cognition or those with MCI.</td>
</tr>
<tr>
<td>Aisen 2008</td>
<td>JAMA</td>
<td>B-vitamins</td>
<td>409 18 months</td>
<td>This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.</td>
</tr>
<tr>
<td>McMahon 2006</td>
<td>N Eng J Med</td>
<td>B-vitamins</td>
<td>276 24 months</td>
<td>The results of this trial do not support the hypothesis that homocysteine lowering with B vitamins improves cognitive performance.</td>
</tr>
<tr>
<td>Freund-Levi 2006</td>
<td>Arch Neurol</td>
<td>n3 PUFAs</td>
<td>174 6 months</td>
<td>Administration of n3PUFA in mild -moderate AD patients did not delay the rate of cognitive decline according to the MMSE or the cognitive portion of the ADAS.</td>
</tr>
<tr>
<td>Petersen 2005</td>
<td>N Eng J Med</td>
<td>Vitamin E</td>
<td>769 36 months</td>
<td>Vitamin E had no benefit in patients with mild cognitive impairment.</td>
</tr>
</tbody>
</table>
Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease
The TEAM-AD VA Cooperative Randomized Trial

Maurice W. Dysken, MD; Mary Sano, PhD; Sanjay Asthana, MD; Julia E. Vertrees, PharmD, BCPP; Muralidhar Pallaki, MD; Maria Llorente, MD; Susan Love, MA; Gerard D. Schellenberg, PhD; J. Riley McCarten, MD; Julie Malphurs, PhD; Susana Prieto, MD; Peijun Chen, MD, MPH, PhD; David J. Loreck, MD; George Trapp, MD, JD; Rajbir S. Bakshi, MD; Jacopo E. Mintzer, MD; Judith L. Heidebrink, MD; Ana Vidal-Cordona, MD; Lillian M. Arroyo, MD; Angel R. Cruz, MD; Sally Zachariah, MD; Neil W. Kowall, MD; Mohit P. Chopra, MD; Suzanne Craft, PhD; Stephen Thielke, MD; Carolyn L. Turvey, PhD; Catherine Woodman, MD; Kimberly A. Monnell, MD; Kimberly Gordon, MSN, RN, FNP-BC; Julie Tomaska, PhD; Yoav Segal, MD, PhD; Peter N. Peduzzi, PhD; Peter D. Guarino, MPH, PhD

**IMPORTANCE** Although vitamin E and memantine have been shown to have beneficial effects in moderately severe Alzheimer disease (AD), evidence is limited in mild to moderate AD.

**OBJECTIVE** To determine if vitamin E (alpha tocopherol), memantine, or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitor.

**DESIGN, SETTING, AND PARTICIPANTS** Double-blind, placebo-controlled, parallel-group, randomized clinical trial involving 613 patients with mild to moderate AD initiated in August 2007 and concluded in September 2012 at 14 Veterans Affairs medical centers.

**INTERVENTIONS** Participants received either 2000 IU/d of alpha tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or placebo (n = 152).

**MAIN OUTCOMES AND MEASURES** Alzheimer’s Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) inventory score (range, 0-78). Secondary outcomes included cognitive, neuropsychiatric, functional, and caregiver measures.

RESULTS  Over the mean (SD) follow-up of 2.27 (1.22) years, participants receiving alpha 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 alpha tocopherol group. All-cause mortality and safety analyses showed a difference only on the serious adverse event of “infections or infestations” with greater frequencies in the memantine (31 events in 23 participants) and combination groups (44 events in 31 participants) compared with placebo (13 events in 11 participants).

<table>
<thead>
<tr>
<th>ADCS-ADL Inventory</th>
<th>Vitamin E (n = 140)</th>
<th>Memantine (n = 142)</th>
<th>Vitamin E + Memantine (n = 139)</th>
<th>Placebo (n = 140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline score, mean (SD)</td>
<td>57.20 (14.38)</td>
<td>57.77 (13.78)</td>
<td>57.16 (13.59)</td>
<td>56.93 (13.61)</td>
</tr>
<tr>
<td>Least squares mean (SE) change from baseline</td>
<td>-13.81 (1.11)</td>
<td>-14.98 (1.10)</td>
<td>-15.20 (1.11)</td>
<td>-16.96 (1.11)</td>
</tr>
<tr>
<td>Mean change difference compared with placebo (95% CI)</td>
<td>3.15 (0.92 to 5.39)</td>
<td>1.98 (-0.24 to 4.20)</td>
<td>1.76 (-0.48 to 4.00)</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS AND RELEVANCE  Among patients with mild to moderate AD, 2000 IU/d of alpha tocopherol compared with placebo resulted in slower functional decline. There were no significant differences in the groups receiving memantine alone or memantine plus alpha tocopherol. These findings suggest benefit of alpha tocopherol in mild to moderate AD by slowing functional decline and decreasing caregiver burden.
Medical food:
una nuova opportunità di terapia

• Un cibo formulato per essere consumato o somministrato per via enterale sotto la supervisione di un medico.
• Prodotto per la gestione dietetica di una specifica malattia o condizione per la quale esistano necessita alimentari peculiari, basate su principi scientifici.
• Prescritto dopo una valutazione medica.
• Quindi, “medical food” è un prodotto nutrizionale prescritto per il trattamento di una specifica condizione clinica.

A Specific Multi-Nutrient Diet Reduces Alzheimer-Like Pathology in Young Adult AβPP_{swe}/PS1_{dE9} Mice

Laus M. Broersen\textsuperscript{a,}\textsuperscript{*}, Almar A.M. Kuipers\textsuperscript{a}, Martin Balvers\textsuperscript{a}, Nick van Wijk\textsuperscript{a}, Paul J.M. Savelkoul\textsuperscript{a}, Martijn C. de Wilde\textsuperscript{b}, Eline M. van der Beek\textsuperscript{a}, John W.C. Sijben\textsuperscript{a}, Robert J.J. Hageme\textsuperscript{a}, Patrick J.G.H. Kamphuis\textsuperscript{a,}\textsuperscript{b} and Amanda J. Kiliaan\textsuperscript{c}

Abstract. Diet is an important lifestyle factor implicated in the etiology of Alzheimer’s disease (AD), but so far it is not fully elucidated to which nutrients the suggested protective effect of diet can be attributed. Recent evidence obtained in the amyloid-\(\beta\) 1-42 (A\(\beta_{42}\)) infusion model in rats has shown that a multi-nutrient intervention known as Fortasyn™ Connect (FC) may protect the central cholinergic system against A\(\beta_{42}\)-induced toxicity. FC comprises the nutritional precursors and cofactors for membrane synthesis, viz. docosahexaenoic acid (DHA), eicosapentaenoic acid, uridine-mono-phosphate (UMP), choline, phospholipids, folic acid, vitamins B6, B12, C, E, and selenium. In order to investigate whether the combined administration of these nutrients may also affect AD-like pathology, we now evaluated the effects of the FC diet intervention in the transgenic AβPP_{swe}/PS1_{dE9} mouse model with endogenous Aβ production. In addition we evaluated the effects of diets containing the individual nutrients DHA and UMP and their combination in this model. Between the age of 3 and 6 months, FC diet decreased brain Aβ levels and amyloid plaque burden in the hippocampus of AβPP/PS1 mice. The FC diet also reduced ongoing disintegrative degeneration in the neocortex, as indicated by Amino Cupric Silver staining. Although all three DHA-containing diets were equally effective in changing brain fatty acid profiles, diets differentially affected amyloid-related measures, indicating that effects of DHA may depend on its dietary context. The current data, showing that dietary enrichment with FC reduces AD-like pathology in AβPP/PS1 mice, confirm and extend our previous findings in the A\(\beta_{42}\) infusion model and favor the combined administration of relevant nutrients.
Amyloid cascade hypothesis

**APP**

- **BACE1 inhibitors**
- **γ-secretase inhibitors**
  - *Semagacestat (terminated)*

**Production of Aβ**

**Aβ oligomers**

**Toxic Aβ monomers**

**Synaptic dysfunction**

**β-amyloid plaque**

**Tau targets**

**Tau pathology** ➔ **Neuronal loss**

**Aβ antibodies**

**ApoE**

**Clearance mechanisms**
Synaptic loss occurs very early in the disease process and is considered the most structural correlate to cognitive performance.
Putative model of enhanced membrane formation by nutritional membrane precursors and cofactors

**LIPID ABSORPTION**
- DHA & EPA in triglycerides
- PL
- Digestion
- Micelle formation
- Absorption
- Reassembly
- Chylomicron formation

**PEMT PATHWAY**
- Phosphatidylethanolamine (enriched in DHA)
- Met
- B12
- FO
- Cysteine
- Phosphatidylcholine (enriched in DHA)
- Liver-derived lipoproteins
- PL Choline
- EPA
- AO
- Uridine
- DHA
- CDP-Choline
- DAG
- Choline
- DHA
- Increased membrane formation
- Brain Phosphatidylcholine

**KENNEDY PATHWAY**
- PL
- EPA
- AO
- Uridine
- DHA
- CTP
- CDP-Choline
- DAG
- SEL
- Increased membrane formation

---

*Phospholipids* enhance the bioavailability of DHA and EPA by facilitating emulsification and by increasing chylomicron formation.

*B-vitamins* enhance the bioavailability of DHA and choline via the PEMT pathway.

*Phospholipids* are a direct source of precursors, e.g., choline.

*Antioxidants* enhance the bioavailability of DHA and EPA.

*Selenium* can also enhance the activity of a key enzyme in the Kennedy pathway.

*DHA, EPA, uridine, and choline* are precursors of phospholipid synthesis via the Kennedy pathway.

*Fortasyn Connect* is designed to enhance the formation of synaptic membranes.

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*Journal of Alzheimer’s Disease 38 (2014) 459–479*
A specific multi-nutrient formulation enhances M1 muscarinic acetylcholine receptor responses in vitro

Abstract
Recent evidence indicates that supplementation with a specific combination of nutrients may affect cell membrane synthesis and composition. To investigate whether such nutrients may also modify the physical properties of membranes, and affect membrane-bound processes involved in signal transduction pathways, we studied the effects of nutrient supplementation on G protein-coupled receptor activation in vitro. In particular, we investigated muscarinic receptors, which are important for the progression of memory deterioration and pathology of Alzheimer’s disease. Nerve growth factor differentiated pheochromocytoma cells that were supplemented with specific combinations of nutrients showed enhanced responses to muscarinic receptor agonists in a membrane potential assay. The largest effects were obtained with a combination of nutrients known as Fortasyn™ Connect, comprising docosahexaenoic acid, eicosapentaenoic acid, uridine monophosphate as a uridine source, choline, vitamin B6, vitamin B12, folic acid, phospholipids, vitamin C, vitamin E, and selenium. In subsequent experiments, it was shown that the effects of supplementation could not be attributed to single nutrients. In addition, it was shown that the agonist-induced response and the supplement-induced enhancement of the response were blocked with the muscarinic receptor antagonists atropine, telenzepine, and AF-DX 384. In order to determine whether the effects of Fortasyn™ Connect supplementation were receptor subtype specific, we investigated binding properties and activation of human muscarinic M1, M2 and M4 receptors in stably transfected Chinese hamster ovary cells after supplementation. Multi-nutrient supplementation did not change M1 receptor density in plasma membranes. However, M1 receptor-mediated G protein activation was significantly enhanced. In contrast, supplementation of M2- or M4-expressing cells did not affect receptor signaling. Taken together, these results indicate that specific combinations of nutrients act synergistically in enhancing muscarinic M1 receptor responses, probably by facilitating receptor-mediated G protein activation.

Keywords: Alzheimer’s disease, docosahexaenoic acid, G protein-coupled receptors, muscarinic receptor, PC12, uridine.

Hypothetical model of increased nutrient requirements throughout the whole AD stages. Lower nutrient status (e.g. of DHA, vitamins A, C, E, folate, and vitamin B12) has been reported in patients with AD compared with cognitively intact elderly controls. Such compromised nutritional status may result from alteration in nutrient intake, uptake, metabolism, and utilization. First, worsening of appetite, altered taste and smell might lead to smaller portions of food being consumed, to food neglect, and to changes in food preferences, resulting in lower intake of specific nutrients. Second, compromised nutrient uptake and metabolism (e.g., due to compromised liver function) result in lower concentration in the circulation. Third, AD-specific pathology may result in higher utilization and needs of specific nutrients (e.g., for neuronal membrane and synapse formation). Collectively, these factors result in a putative increased nutrient requirement that is specific to AD.
Fattori nutrizionali e AD: le modalità di relazione.

- Effetto di protezione dai fattori vascolari
- Effetto di riduzione del carico infiammatorio
- Effetto su specifici meccanismi coinvolti nella patogenesi della malattia di Alzheimer (tossicità a-β, integrità sinaptica, neurotrasmissione)
<table>
<thead>
<tr>
<th>Ongoing studies</th>
<th>Participants</th>
<th>Mean follow up</th>
<th>Nutrients</th>
<th>1) Primary outcome</th>
<th>2) Secondary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIPIDIMET NTR1705</td>
<td>1) 300 Prodromal AD as defined by episodic memory disorder and evidence for underlying AD pathology (Dubois et al, 2007) 2) 55 – 85 years 3) MMSE ≥ 20</td>
<td>2 y</td>
<td>125 mL of Souvenaid®, once daily</td>
<td>Cognitive performance during 24 mo of intervention as measured by a modified version of the NTB (Harrison et al, 2007) 2) Progression to dementia; cognitive performance (MMSE, 13-item ADAS-cog); functional abilities (ADCS-ADL); occurrence of depressive symptoms (MADRS); plasma biomarkers; atrophy rates on MRIs; nutritional (blood) parameters; tolerance and safety</td>
<td>Change in cognitive test performance 2) Change in body mass distribution; change in oxidative stress and inflammatory markers as measured in blood and urine</td>
</tr>
<tr>
<td>BERRY NCT01515098</td>
<td>1) 132 MCI s 2) ≥ 65 y</td>
<td>6 mo</td>
<td>35 g freeze-dried blueberries</td>
<td>1) Memory performance 2) Cortisol</td>
<td>1) Improved cognitive performance</td>
</tr>
<tr>
<td>NCT005599508</td>
<td>1) 60 MCI s 2) ≥ 65 y</td>
<td>16 wk</td>
<td>Purple grape juice</td>
<td></td>
<td></td>
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<tr>
<td>NCT01571193</td>
<td>1) 212 nondemented participants with either normal cognition or amnestic MCI s 2) 50–75 y</td>
<td>1 y</td>
<td>1000 mg pomegranate extract</td>
<td>1) ADAS-cog 2) Functional/structural brain changes and plasma biomarkers</td>
<td></td>
</tr>
<tr>
<td>NCT01219244</td>
<td>1) 330 participants with mild cognitive impairment 2) 50–80 y 3) Moderate to heavy weight (BMI 25–35 kg/m²)</td>
<td>Dietary intervention: 6 mo Exercise/cognitive training: NA</td>
<td>Dietary intervention (caloric restriction, ω-3 fatty acids and resveratrol) and in combination with exercise and cognitive training</td>
<td>1) Changes in memory function scores determined by Gröber and Buscke test 2) Changes in other cognitive functions; changes in functional capacities. To study the long-term safety and tolerability of DHA treatment. To study compliance and adherence to “multidomain” intervention program</td>
<td></td>
</tr>
<tr>
<td>MAPT NCT00672868 [113]</td>
<td>1) 1200 frail elderly with subjective memory complaints 2) ≥ 70 y</td>
<td>3 y</td>
<td>Multidomain intervention (nutritional, physical, and cognitive training) and DHA (800 mg/d)</td>
<td>1) Cognitive performance (attention, memory, executive function) 2) Cerebral hemodynamics; mood/well-being</td>
<td></td>
</tr>
<tr>
<td>EFAlex Active 50+ NCT01185379</td>
<td>1) 250 healthy elderly 2) 50–70 y 3) MMSE ≥ 24; 4) Participants suffering from a memory complaint (MAC-Q score &gt; 24)</td>
<td>6 mo</td>
<td>EFAlex Active 50+, a dietary supplement containing DHA, phosphatidylserine, vitamin B12, folic acid and Ginkgo biloba</td>
<td>1) Cognitive performance during 24 mo of intervention as measured by a modified version of the NTB (Harrison et al, 2007) 2) Progression to dementia; cognitive performance (MMSE, 13-item ADAS-cog); functional abilities (ADCS-ADL); occurrence of depressive symptoms (MADRS); plasma biomarkers; atrophy rates on MRIs; nutritional (blood) parameters; tolerance and safety</td>
<td></td>
</tr>
<tr>
<td>Alois de Montauba n study</td>
<td>1) 4000 individuals 2) ≥ 87 y 3) 400 elderly; 4) 65–90 y; 3) Score ≥ 24</td>
<td>5 y</td>
<td>DHA</td>
<td>1) Prevent development of neurodegenerative disease 2) Prevent development of AD 1a) Rate of cognitive decline b) Change in well-being measures; 2) Plasma fatty acid changes, blood pressure, oxidative stress, and inflammation</td>
<td></td>
</tr>
<tr>
<td>EPOCH ACTRN 12607000278437 [116]</td>
<td>1) 10 400 males with no neurologic or psychiatric illness 2) 60–90 y 3) 300 healthy adults; 4) 50–80 y; 5) Moderate to heavy weight (BMI 25–30 kg/m²)</td>
<td>7–12 y</td>
<td>Vitamin E + Selenium (400 IU + 200 mcg/d)</td>
<td>1) Prevention of AD as measured by Memory Impairment Screen</td>
<td></td>
</tr>
<tr>
<td>PREADVSE NCT00040378</td>
<td>1) 40 healthy elderly 2) 60–90 y 3) Moderate to heavy weight (BMI 25–30 kg/m²)</td>
<td>6 mo</td>
<td>Caloric restriction or dietary supplementation (2 g/d DHA/EPA or resveratrol)</td>
<td>1) Auditory verbal learning task 2) Functional/structural brain changes and plasma biomarkers</td>
<td></td>
</tr>
<tr>
<td>NCT00996229</td>
<td>1) 300 healthy elderly 2) ≥ 65 y 3) Fasting plasma homocysteine ≥12 and &lt;50 μmol/L</td>
<td>2 y</td>
<td>Folic acid (400 mcg) + vitamin B12 (500 μg) + vitamin D3 (600 IU); placebo (vitamin D3 600 IU)</td>
<td>1) Fractures 2) Cognitive decline; bone health; physical performance; QoL; nutritional status</td>
<td></td>
</tr>
<tr>
<td>B-PROOF NCT00696514 [117]</td>
<td>1) 80 healthy women</td>
<td>23–24 wk</td>
<td>Creatine supplementation (20 g/d for 7 d followed by 5 g/d for 23 wk) in combination with resistance training</td>
<td>1) Cognitive function 2) Physical capacity, muscle strength, and function</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Duration</td>
<td>Intervention</td>
<td>Outcomes</td>
<td></td>
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</tbody>
</table>
| Oxi-Stress NCT01234506 [118] | 1) 154 healthy adults
2) 60-80 years | 24 wk | Flax lignan SDG (300 mg SDG/d) + 1000 IU vitamin D; placebo (1000 IU vitamin D) | 1) Safety of 300 mg/d SDG consumption; effect of SDG on oxidative stress and inflammation
2) Effect of SDG on QoL including cognitive function; effect of SDG supplement on blood levels of flax lignan metabolites, bone resorption, and blood lipids |
| M00201109 NCT01625195 | 1) 300 healthy adults;
2) 20-80 y | 6 mo | 1.2 g/d of DHA and 2.4 g/d of EPA | 1) Change from baseline in cognition
2) DHA level in plasma at baseline, monthly DHA metabolism |
| WAHA NCT01634841 | 1) 700 healthy adults;
2) 65-75 y | 2 y | 30-45 g/d walnuts | 1) Change in cognitive decline from baseline
2) Change in macular degeneration from baseline |
| NCT01620567 | 1) 44 healthy adults
2) ≥ 50 y
3) MMSE > 24 | 6 mo | 1 avocado/d; placebo: equivalent calories of chickpeas/potatoes | 1) Cognition
2) Inflammation (markers in plasma) |

AD, Alzheimer’s disease; ADAS, Alzheimer’s Disease Assessment Scale; ADL, activities of daily living; BMI, body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic; MADRS, Montgomery-Åsberg Depression Rating Scale; MCI, mild cognitive impairment; MIS, Memory Impairment Screen; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NTB, Neuropsychological Test Battery; SDG, secoisolaricresinol diglucoside; QoL, quality of life.
Axona (caprylidene)

- **Single-Administration Clinical Study in Patients With AD or MCI**
  This randomized, placebo-controlled, crossover-design study enrolled 20 subjects between the ages of 55-85 years old and diagnosed with probable AD or mild cognitive impairment (MCI). It was designed to measure the therapeutic effects of a single administration (40-80 grams) of medium-chain triglycerides (MCTs) on memory. Subjects were allowed to continue on stable concomitant AD treatments. A single 40-gram administration of MCTs led to elevated BHB serum levels (to approximately 0.5 mM at 90 minutes following administration) that were positively correlated with improvement in paragraph recall (a measure of cognition) (P = 0.02). APOE4(-) patients showed greater improvement compared to APOE4(+) patients in the AD Assessment Scale—Cognitive subscale (ADAS-Cog, which measures memory and other aspects of cognitive performance) (P = 0.039).
Clinical Study in Patients With Probable Mild to Moderate AD

This double blind, randomized, placebo-controlled, 90-day study enrolled 152 subjects with mild to moderate AD in the US. At day 45, ADASCog scores stabilized in the Axona group, whereas a decline in cognition was observed in the placebo group. The point difference in ADAS-Cog change from baseline scores at day 45 between groups was 1.91 (P = 0.024). This point difference in ADAS-Cog change from baseline scores at day 90 between groups was 1.54 (P = 0.0767). Final ADAS-Cog evaluations were performed following a 2-week washout period (day 104): the Axona group maintained a slight improvement from baseline, whereas the placebo group still demonstrated a decline, although the difference between groups was no longer statistically significant (P = 0.405). The ADAS-Cog change from baseline score was also analyzed in subgroups of patients based on APOE4 genotype. The APOE4(-) patients receiving Axona showed improved cognitive function when compared with APOE4(-) patients receiving placebo. The point difference in change from baseline ADAS-Cog scores for APOE4(-) Axona and placebo patients at day 45 was 4.77 (P < 0.0005), and was 3.36 at day 90 (P = 0.015; see Figure 2). In APOE4(+) patients, the mean change in ADAS-Cog total scores for the 2 groups was essentially identical at all time points, with more patients showing decline rather than improvement at day 45 and day 90.
• **Bridging Study in Healthy Elderly Volunteers**

This open-label, randomized bridging study enrolled 66 healthy elderly subjects and was designed to establish the tolerability, safety, and pharmacokinetic (PK) profile of 3 different formulations of Axona administered for 14 days either with a 7-day titration (7 days at 10 grams MCTs followed by 7 days at 20 grams MCTs) or without titration (14 days at 20 grams MCTs). The original formulation of Axona used in the AD controlled clinical trial required reconstitution with a meal replacement drink, (i.e Ensure), in order to enhance product tolerability. The two new formulations tested each contained an identical amount of MCTs as the original formulation, but different amounts of proteins and carbohydrates, and allowed for reconstitution in 6-8 ounces of water. The highest mean BHB levels (Cmax) and area-under-the-curve (AUC) values were observed in the cohort of subjects receiving the high-protein formulation at the 20-gram MCT level. This cohort of subjects receiving the high-protein formulation at the 20-gram MCT level also experienced the latest onset of most GI AEs.
Development of a Medical Food Targeted to improve formation of synapses

- 125 ml, 125 kcal, once-per-day drink, vanilla & strawberry flavours

Uridine (UMP)
Omega-3 fatty acids
Choline
Phospholipids
B vitamins

HYPOTHESIS:
Souvenaid successfully addresses an unmet nutritional need in people with AD by increasing their intake of these dietary precursors and co-factors
Summary mode of action a specific nutrient combination (Fortasyn Connect) based on preclinical observations

- FC primarily target neuronal membrane quantity and quality
- Resulting in increased synapse formation and function, and decreased pathology

<table>
<thead>
<tr>
<th>Fortasyn™ Connect</th>
<th>Target</th>
<th>Physiological effects</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>NEURONAL MEMBRANES</td>
<td>SYNAPSES: Neurite outgrowth Synaptic proteins Dendritic spines</td>
<td>Improved hippocampal-dependent cognitive performance in animal models</td>
</tr>
<tr>
<td>EPA</td>
<td>formation and composition</td>
<td>NEUROTRANSMISSION: Neurotransmitters Receptor signalling</td>
<td></td>
</tr>
<tr>
<td>UMP</td>
<td></td>
<td>ABETA PATHOLOGY: Abeta toxicity Abeta levels Plaque burden Neurodegeneration</td>
<td></td>
</tr>
<tr>
<td>Choline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phospholipids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical application in AD
Medical Food (FC) Clinical trial programme

Prodromal

MMSE ≥ 24, drug-naïve

Mild

WMS-r & ADAS-cog
MMSE 20-26, drug-naïve

NTB + EEG / MEG
MMSE ≥ 20, drug-naïve

Moderate

ADAS-cog
MMSE 14-24, stable on AD drugs

Funded by the EU FP7 project
LipiDiDiet, Grant Agreement N° 211696

This project receives funding from the NL Food & Nutrition Delta project, FND N° 10003
Souvenir I: memory improvement

Delayed verbal memory WMS-r

Significantly* (p=0.021) more responders in Mild (ITT) AD after 12 weeks

Significantly* (p=0.019) more responders in very Mild (MMSE 24-26) AD after 12 weeks

* Chi-square
Significant effect on NTB memory domain during 24 weeks (whole period trajectory; p=0.023)

Trend on NTB composite score during 24 weeks (whole period trajectory; p=0.053)

Statistical analysis re-run by Rush Alzheimer's Disease Center
ITT, Mixed Model for Repeated Measures (trajectory, mean ± SE)
Nutritional status in AD

Plasma concentration of selenium, uridine and the proportion of DHA and n-3 long chain PUFA in the erythrocyte membrane were lower in mild AD compared to healthy controls. In particular, this is the first time that a lower plasma uridine levels in mild AD compared to healthy controls has been observed.

Subjects
- Subgroup of 79 Dutch drug-naive patients with mild AD (MMSE ≥ 20) participating in the Souvenir II study (Scheltens, 2012)
- A group of 93 Dutch healthy control subjects, mainly relatives of the AD patients

Table 1 - Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>AD (n=79)</th>
<th>Healthy (n=93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>39 (49.4)</td>
<td>43 (46.2)</td>
<td>0.760</td>
</tr>
<tr>
<td>Age, yr</td>
<td>73.4 ± 7.2</td>
<td>71.5 ± 9.3</td>
<td>0.125</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.3 ± 2.7</td>
<td>28.8 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 Fisher’s Exact test, 2 T-test.
No significant differences between groups were found for the 24-week change from baseline in serum concentrations of plasma PT.
No significant differences between groups were found for the 24-week change from baseline in serum concentrations of plasma aPTT.
## Glycemic Index - Results

<table>
<thead>
<tr>
<th>Palatability rating (Mean ± SD)</th>
<th>Mean GI ± SEM (Standard Error of the Mean)</th>
<th>GI Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7 ± 1.05</td>
<td>50.0 ± 3.53</td>
<td>LOW</td>
</tr>
</tbody>
</table>

Rating scale palatability:
1 = not palatable, 7 = very palatable

<table>
<thead>
<tr>
<th>GI Classification</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>≤ 55</td>
</tr>
<tr>
<td>MODERATE</td>
<td>56 – 69</td>
</tr>
<tr>
<td>HIGH</td>
<td>≥ 70</td>
</tr>
</tbody>
</table>
Souvenir II: Open Label Extension Study

**ITT population**

- **Control (n=129)**
  - Age (y): 73.2 (8.4)
  - Sex: males (n[%]): 64 (49.6)
  - Total MMSE score: 25.0 (2.8)

- **Active (n=130)**
  - Age (y): 74.4 (6.9)
  - Sex: males (n[%]): 68 (52.3)
  - Total MMSE score: 24.9 (2.9)

- **Control - Active (n=104)**
  - Age (y): 73.9 (8.3)
  - Sex: males (n[%]): 52 (50.0)
  - Total MMSE score: 25.1 (3.4) #

- **Active - Active (n=97)**
  - Age (y): 74.5 (6.8)
  - Sex: males (n[%]): 51 (52.6)
  - Total MMSE score: 25.1 (3.3) #

Data are means (SD) unless stated otherwise.

# At week 24 of Souvenir II study / start of OLE study.
Open label exploratory Outcome: Sustainable Memory Improvement

Significant increase from week 24 to week 48 in both groups.
Active - Active: $p=0.025$
Control - Active: $p=0.008$

**Graph**

- **Mean change from baseline in NTB memory domain z-score**
- **Time (weeks)**: 0, 12, 24, 36, 48
- **ITT, MMRM, data are mean ±SE**
- **Double-blind phase**
- **Open-label extension**

*Olde Rikkert et al. Manuscript submitted*
Key groups of interest –
Patient who did not start using AD medication during the OLE extension

In the subgroup of patients who did not receive AD medication, NTB memory domain scores were significantly increased between Week 24 and Week 48 (active-active and control-active groups combined; p=0.029)
Key groups of interest – Patients with a large gap between the 24 week and the start of OLE

- **Active-active group:** memory benefits present at Week 24 partially lost

- **Control-active group:** further decline of memory domain scores was observed

- **Souvenaid during the OLE phase in patients with a large study gap:** significant increase in NTB memory domain score between Week 36 and Week 48

### Sample size (N)

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>107</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>103</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>

Olde Rikkert et al. Manuscript submitted
The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease


Abstract

Introduction

Souvenaid® containing Fortasyn® Connect is a medical food designed to support synaptic synthesis in persons with Alzheimer's disease (AD). Fortasyn Connect includes precursors (uridine monophosphate; choline; phospholipids; eicosapentaenoic acid; docosahexaenoic acid) and cofactors (vitamins E, C, B12, and B6; folic acid; selenium) for the formation of neuronal membranes. Whether Souvenaid slows cognitive decline in treated persons with mild-to-moderate AD has not been addressed.

Methods

In a 24-week, double-masked clinical trial at 48 clinical centers, 527 participants taking AD medications [52% women; mean age 76.7 years (Standard Deviation, SD = 8.2), and mean Mini-Mental State Examination score 19.5 (SD = 3.1, range 14–24)] were randomized 1:1 to daily, 125-mL (125 kcal), oral intake of the active product (Souvenaid) or an iso-caloric control. The primary outcome of cognition was assessed by the 11-item Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-cog). Compliance was calculated from daily diary recordings of product intake. Statistical analyses were performed using mixed models for repeated measures.

Results

Cognitive performance as assessed by ADAS-cog showed decline over time in both control and active study groups, with no significant difference between study groups (difference = 0.37 points, Standard Error, SE = 0.57, p = 0.513). No group differences in adverse event rates were found and no clinically relevant differences in blood safety parameters were noted. Overall compliance was high (94.1% [active] and 94.3% [control]), which was confirmed by significant changes in blood (nutritional) biomarkers.

Conclusions

Add-on intake of Souvenaid during 24 weeks did not slow cognitive decline in persons treated for mild-to-moderate AD. Souvenaid was well tolerated in combination with standard care AD medications.
Survey sui benefici di Souvenaid nei pazienti con Malattia di Alzheimer in fase iniziale.

Introduzione:

Souvenaid è un prodotto nutrizionale concepito per rispondere in modo specifico alle esigenze delle persone che presentano problemi di memoria, inclusi i pazienti con malattia di Alzheimer in fase iniziale.

L'efficacia clinica di Souvenaid è stata valutata in trial randomizzati controllati che hanno dimostrato che

- nei soggetti con malattia di Alzheimer lieve migliorano la prestazione di memoria verbale dopo 12 settimane di trattamento
- nei soggetti con malattia di Alzheimer lieve migliora la memoria globale dopo 24 settimane di trattamento
- vi è un effetto biologico che favorisce il funzionamento delle sinapsi.

L'impatto dell'uso di Souvenaid su outcome soggettivi, quali la qualità della vita, e su outcome cognitivi e funzionali legati al vivere quotidiano in ampie popolazioni non sono ancora stati oggetto di valutazione.

Obiettivo:

- analizzare in modo descrittivo i risultati, osservati dai medici e dai caregiver, dell'uso di Souvenaid su un'ampia popolazione (prevalentemente composta da soggetti con malattia di Alzheimer in fase lieve).
- analizzare le modalità d'uso.

Metodo:

- descrizione da parte di un gruppo di 30 medici afferenti a centri per la diagnosi e cura delle demenze (UVA) degli effetti della somministrazione di Souvenaid sulle funzioni cognitive, sul comportamento e sulla funzione osservati dai caregiver e condivisione delle opinioni osservate
- descrizione del comportamento del paziente avverrà al termine di un periodo di utilizzo di Souvenaid minimo 3 mesi
- per la raccolta delle opinioni, che saranno anonime e non prevedono la raccolta di dati sensibili dei pazienti e dei caregiver, verrà utilizzato un questionario anonimo da compilarsi on line
- non è prevista la raccolta di dati che permettano l'identificazione del paziente né l'identificazione del centro
- la raccolta delle informazioni avverrà al momento della visita di controllo (la prima successiva alla prescrizione di Souvenaid)
- ogni partecipante alla Survey dovrà descrivere un minimo di 20 casi
A randomized, controlled, double-blind, parallel group, multicentre study to assess the effect of a Medical Food in pro-dromal AD subjects (Hilkka Soininen)

**Design and methodology**

- Proof-of-Concept, multi-country (EU) multi-centre study (10 sites in Netherlands, Finland, Sweden and Germany)
- 24-36 Months randomized, controlled trial in 300 drug-naive prodromal AD
- Eligibility:
  - Prodromal Alzheimer diagnosis (Dubois et al, 2007)
  - MMSE ≥ 24
- Outcome measures:
  - Primary: Neuropsychological Test Battery
  - Secondary: Progression to AD, functional (ADCS-ADL) and nutritional parameters, safety and tolerance
  - Biomarkers: CSF and MRI (0 – 12 – 24 – 36 months)
Review

Targeting Synaptic Dysfunction in Alzheimer’s Disease by Administering a Specific Nutrient Combination

Nick van Wijk, Laut M. Broersen, Martijn C. de Wilde, Robert J.J. Hageman, Martine Groenendijk, John W.C. Sijben and Patrick J.G.H. Kamphuis

L’AD influenza la nutrizione

- Abitudini e comportamento alimentare
- Opportunità di approvvigionamento
- Modalità di consumo del cibo
- Richieste energetiche
- Digestione e assorbimento
- Rifiuto del cibo e disfagia

La nutrizione influenza l’AD

- Difese immunitarie
- Massa muscolare e forza
- Stato funzionale
- Rischio di caduta
- Prognosi delle malattie acute
- Rischio di decubito
- Rischio di sviluppare demenza e AD
- Progressione della malattia
- Funzioni cognitive
Pharmacological treatment of AD