Secondo focus di approfondimento: l’impatto della nutrizione per prevenire la demenza e le principali patologie neurodegenerative

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Università Cattolica, Roma
Roma, 17 dicembre 2014
Correlation nutrition - cognition

- Glucagon-like peptide 1
- Grelin
### Unadjusted and adjusted mean of IGFBP-3 concentration (lg/ml) according to cognitive skills

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Unadjusted mean (standard error)</th>
<th>p</th>
<th>Adjusted mean (standard error)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term memory problem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>111</td>
<td>4.25 ± 0.12</td>
<td>0.11</td>
<td>4.30 ± 0.08</td>
</tr>
<tr>
<td>No</td>
<td>242</td>
<td>4.51 ± 0.09</td>
<td></td>
<td>4.51 ± 0.13</td>
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<tr>
<td><strong>Procedural memory problem</strong></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>65</td>
<td>4.00 ± 0.15</td>
<td>0.005</td>
<td>4.07 ± 0.08</td>
</tr>
<tr>
<td>No</td>
<td>288</td>
<td>4.53 ± 0.08</td>
<td></td>
<td>4.53 ± 0.18</td>
</tr>
<tr>
<td><strong>Cognitive skills for daily decision making problem</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>95</td>
<td>4.10 ± 0.13</td>
<td>0.006</td>
<td>4.20 ± 0.15</td>
</tr>
<tr>
<td>No</td>
<td>258</td>
<td>4.55 ± 0.08</td>
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<td>4.53 ± 0.08</td>
</tr>
<tr>
<td><strong>Verbal expression problem</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>3.68 ± 0.15</td>
<td>0.01</td>
<td>3.73 ± 0.32</td>
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<tr>
<td>No</td>
<td>333</td>
<td>4.47 ± 0.07</td>
<td></td>
<td>4.48 ± 0.07</td>
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<tr>
<td><strong>Comprehension problem</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>3.74 ± 0.23</td>
<td>0.01</td>
<td>3.74 ± 0.29</td>
</tr>
<tr>
<td>No</td>
<td>329</td>
<td>4.48 ± 0.07</td>
<td></td>
<td>4.49 ± 0.07</td>
</tr>
</tbody>
</table>

Analyses are adjusted for age, gender, education, cerebrovascular disease, ischemic heart disease, congestive heart failure, diabetes, depression, Parkinson diseases, smoking status, alcohol abuse, body mass index, and number of diseases.
Amyloid damages neurones and synapses...

Beta Amyloid particles increase oxidation of membranes

This greatly increases membrane turnover
Membranes are made of phospholipids

An increased proportion of omega 3 PUFAs increase membrane fluidity, essential for cell signalling. DHA is concentrated in synapses.
What correlates best with severity of dementia?

- Synapse loss/neurone loss
- Neurotransmitter loss - acetylcholine
- Neurofibrillary tangles
- Amyloid plaques
Synaptic loss occurs early and accelerates.

Adapted from: Scheff et al. (2006) Neurobiol Aging

**VIEWPOINT**

*Alzheimer’s Disease Is a Synaptic Failure*

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002
AD is a multi-faceted disease requiring a multi-domain approach

- Multiple pathologies occur in AD, including neuroinflammation, neurovascular pathology and neurodegeneration

- Approaches that have targeted single pathologies, such as amyloid aggregation or inflammatory responses, or individual nutrients have had limited success

- A multi-modal approach may therefore be required, as has been effective in other conditions such as heart failure.

AD treatment 2014 and beyond

2014

Memantine, AChEIs, combination

Other cognitive enhancers

Improved and earlier diagnosis

Patient segmentation (genetics...)

Disease-modifying therapies

Community-wide prevention initiatives (diet, exercise...)

2023
Vicious circle of malnutrition

Cognitive status

Malnutrition

Nutrition

ANOREXIA

> Mortality
> Disability
> Cost

DIET
CHOLINE
VITAMIN B
VITAMINS A, C, D, E
PUFA
Two pillars of defining nutritional needs in AD

<table>
<thead>
<tr>
<th>Higher nutrient need for synapses</th>
<th>Lower levels in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Loss of synapses in AD</td>
<td>• Lower levels in blood</td>
</tr>
<tr>
<td>• Basic science: nutrients needed to increase synapse formation</td>
<td>• Lower levels in the brain</td>
</tr>
<tr>
<td></td>
<td>• Lower intake</td>
</tr>
<tr>
<td></td>
<td>• Compromised nutrient metabolism &amp; uptake</td>
</tr>
</tbody>
</table>
Changes in regulation of appetite
- Hypometabolism of hypothalamus, Hippocampus atrophy, impairment of olfaction and taste
- Genetic predisposition
- Metabolic changes: increase TNF-alpha levels ...

Preclinical stage

Ability to maintain attention & concentration
- Reduced intake, unbalanced nutrient choice
- Increased energy requirements
- Restless, wandering...
- Co-morbid medical illness...

Early stage of AD

Reduced energy intake
- Apraxia, dependency...
- Dysphagia
- Medication with sedative effects

Late stage of AD

Changed eating behaviour in AD
Systematic review and meta-analysis of literature: Lower levels in AD of specific nutrients

Synapse formation requires nutritional precursors and cofactors

- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- Co-factors facilitate phospholipid synthesis by enhancing precursor bioavailability

**Precursors**
- Folic acid
- B12
- B6
- Phospholipids
- EPA
- DHA
- Vit C
- Vit E
- Selenium

**Cofactors**
- Choline
- UMP
- Phosphocholine
- CDP-choline
- Phosphatidylcholine
- CTP
- DAG

**Neuronal membrane (Phospholipid bilayer)**
- Brain
- Phosphatidylcholine
- Neuronal membrane (Phospholipid bilayer)
- Neurite
- Dendritic spine
- Axon terminal
- Axon
Alzheimer’s disease is not primarily a nutritional disorder - but age-related nutritional deficiencies occur.

Reduced plasma levels of folate, Vit B12, Vit C, Vit E

Increased homocysteine

Reduced CSF and brain levels of omega-3 (DHA/EPA)

Reduced mobilisation & synthesis of DHA

These deficiencies reduce capacity to replace membrane

Phosphatidylcholine

NEW NEURONAL MEMBRANE

Reduced synthesis of uridine monophosphate

Age-related reduced uptake of choline by brain

Uridine

Reduced mobilisation & synthesis of DHA

Omega-3 fatty acids

B-vitamins

Anti-oxidants

Phospholipids Choline
A combination of dietary precursors increases membrane synthesis

Synergy between nutrients

Wurtman et al. (2005) Brain Res; Wurtman et al. (2006) Brain Res
Nutrient combination enhances synapse formation and function – basic science data

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

Nick van Wijk\textsuperscript{a,*}, Laus M. Broersen\textsuperscript{a}, Martijn C. de Wilde\textsuperscript{a}, Robert J.J. Hageman\textsuperscript{a}, Martine Groenendijk\textsuperscript{a}, John W.C. Sijben\textsuperscript{a} and Patrick J.G.H. Kamphuis\textsuperscript{a,\textit{b}}

\textsuperscript{a}Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands
\textsuperscript{b}Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands
Nutrient combination enhances synapse formation and function

- Omega-3 fatty acids
- UMP
- Choline
- Phospholipids
- B vitamins
- Antioxidants

- DHA 1200 mg
- EPA 300 mg
- UMP 625 mg
- Choline 400 mg
- Folic acid 400 µg
- B6 1 mg
- B12 3 µg
- Vit C 80 mg
- Vit E 40 mg
- Se 60 µg
- Phospholipids 106 mg
Intake of Combined Nutrients cannot be met on top of normal diet

- 400 mg Choline
- 300 mg EPA
- 625 mg UMP
- 3 mcg Vit B12
- 1 mg Vit B6
- 80 mg Vit C
- 1200 mg DHA
- 40 mg Vit E
- 106 mg Phospholipids
- 400 mcg Folate
- 60 mcg Selenium

No studies showing foods substantially increase plasma uridine exist
### Full clinical trial programme

<table>
<thead>
<tr>
<th>Prodromal</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
</table>
| WMS-r & ADAS-cog  
MMSE 20-26, drug-naïve  
28 sites | ADAS-cog  
MMSE 14-24, stable on AD drugs  
48 sites | NTB + EEG/MEG  
MMSE ≥ 20, drug-naïve  
27 sites |
| NTB + MRI/CSF  
MMSE ≥ 24, drug-naïve  
13 sites | | |

**Souvenir I:** this project receives funding from NL STW.

**Souvenir II:** This project receives funding from the NL Food & Nutrition Delta project, FND N° 10003.

**LipiDiDiet:** Funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696.
Souvenir I: Design and methodology

- Multi-centre (28 sites in NL, Bel, Ger, UK) PI Prof Philip Scheltens,
- Drug-naive subjects with probable AD of mild severity (MMSE 20-26)
  Randomised, double-blind, controlled, parallel-group
- Intervention: Souvenaid, a once-a-day (125 ml / day) drink for 12 weeks
- Co-primary outcomes: delayed verbal recall WMS-r and modified ADAS-cog

Souvenir I: Well tolerated with good adherence

- No significant differences in the number of AEs or serious AEs
- No differences in blood safety parameters
- 94% > 75% over 24 weeks
  - No difference in product appreciation (taste and amount)

Increased % DHA in plasma erythrocyte membrane ($p<0.001$)

Reduced plasma homocysteine ($p<0.001$)

Souvenir I: Primary endpoint
MMSE 20-26, drug-naïve 12 weeks

Delayed verbal memory (Wechsler Memory Scale - recall task)

- Significantly more responders in **mild** AD after 12 weeks ($p=0.021$)*
- Significantly more responders in **very mild** (MMSE 24-26) AD after 12 weeks ($p=0.019$)*

* Chi-square - skewed distribution: 40% scored 0 on WMS-r @ BL

Souvenir I: ADAS-cog 13 was similar in the 2 groups

Repeated-Measures Mixed Model analysis

Souvenir II: Design & methodology

Outcome Measures

Souvenaid (n=130)

Control (n=129)

n=259

- Multi-centre (27 sites) in Europe (NL, Ger, Bel, Fr, It, Sp)
- Mild AD patients (MMSE > 20), AD drug-naïve
- Primary outcome NTB + EEG/MEG
- Randomized, double-blind, controlled, parallel-group
- Intervention: Souvenaid® or an isocaloric control
Souvenir II: Primary endpoint
MMSE > 20, drug-naïve 24 weeks

Significant effect* on NTB memory domain over 24 weeks
(whole period trajectory; \( p=0.023 \))

*Statistical analysis re-run by Rush Alzheimer’s Disease Center, Rush University Medical Center
ITT, MMRM, trajectory, mean ± SE.
**Souvenir II: Primary endpoint**

**MMSE > 20, drug-naïve 24-48 weeks**

Significant increase from week 24 to week 48 in both groups.

Active - Active: $p=0.038$
Control - Active: $p=0.029$
Souvenir II: Positive safety profile and biochemical changes

- No differences in renal and liver parameters or AEs
- Overall adherence during 24 weeks was very high in both groups (97.1% in the active group vs. 96.6% in the control group)

**Increased % DHA in plasma erythrocyte membrane ($p<0.001$)**

**Reduced plasma homocysteine ($p<0.001$)**
Combined Nutrients increases EEG biomarkers for functional connectivity, derivatives of synaptic activity

Level 3: network analysis

Level 2: connectivity analysis

Level 1: basic signal analysis

De Waal et al. Manuscript submitted
Combined Nutrients increases EEG biomarkers for functional connectivity, derivatives of synaptic activity

**Level 1: basic signal analysis**

Souvenaid preserves oscillatory frequency (that decreases in AD)

**Level 2: connectivity analysis**

Souvenaid increases delta band functional connectivity (the implications of which remain to be studied)

**Level 3: network analysis**

Souvenaid preserves organization of functional brain networks

De Waal et al. *Manuscript submitted*
Summary of reasoning - Address the AD specific nutrient need

- AD is characterized by synapse loss that results in cognitive decline
- Stimulating synapse formation requires specific nutrients
  - Uridine (UMP), Omega-3 fatty acids, Phosholipids & Choline, B-Vitamins, Antioxidants
- Lower Nutrient status & altered nutrient metabolism
- Increased nutritional need not met by the regular diet

Addressing the nutritional need in AD by increasing intake of dietary precursors and co-factors results in improved memory performance due to enhanced synapse formation & function.
Providing the nutritional precursors and co-factors for synapse formation

Hypothesized to:

Increase the formation and function of synapses in AD

- UMP
- DHA, EPA
- Choline
- Phospholipids
- B vitamins
- Antioxidants
Mediterranean diet and dementia

Higher adherence to the MeDi is associated with a trend for reduced risk for developing MCI and with reduced risk for MCI conversion to AD.

Overall Mortality among Nursing Home Residents with Advanced dementia

## Risk factors and mortality among Nursing Home Residents with dementia

**Table 3** Adjusted relative risks (95% CI), by baseline level of cognitive impairment

<table>
<thead>
<tr>
<th></th>
<th>Moderate (n=5393)</th>
<th>Severe (n=3160)</th>
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</thead>
<tbody>
<tr>
<td>Age (y):</td>
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<tr>
<td>65-74</td>
<td></td>
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<tr>
<td>75-84</td>
<td>1.40 (1.21 - 1.62)</td>
<td>1.29 (1.12 - 1.49)</td>
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<tr>
<td>85+</td>
<td>1.77 (1.52 - 2.05)</td>
<td>1.92 (1.65 - 2.23)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.94 (1.79 - 2.11)</td>
<td>1.80 (1.63 - 1.99)</td>
</tr>
<tr>
<td>Race / ethnicity:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>0.72 (0.60 - 0.87)</td>
<td>0.99 (0.81 - 1.26)</td>
</tr>
<tr>
<td>Other minorities</td>
<td>0.69 (0.52 - 0.92)</td>
<td>0.64 (0.47 - 0.87)</td>
</tr>
<tr>
<td>Behaviour problems:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.99 (0.91 - 1.08)</td>
<td>0.85 (0.76 - 0.94)</td>
</tr>
<tr>
<td>Indicators of delirium:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.15 (1.03 - 1.27)</td>
<td>1.19 (1.06 - 1.33)</td>
</tr>
<tr>
<td>Physical function:</td>
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<td></td>
</tr>
<tr>
<td>Normal</td>
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<td></td>
</tr>
<tr>
<td>Need supervision</td>
<td>1.26 (1.10 - 1.45)</td>
<td>1.66 (1.10 - 2.53)</td>
</tr>
<tr>
<td>Require assistance</td>
<td>1.44 (1.22 - 1.69)</td>
<td>1.98 (1.29 - 3.03)</td>
</tr>
<tr>
<td>Hearing problems:</td>
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<td></td>
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<tr>
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<tr>
<td>Yes</td>
<td>1.12 (1.00 - 1.27)</td>
<td>1.06 (0.94 - 1.26)</td>
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<td>Vision problems:</td>
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<td>1.20 (1.05 - 1.36)</td>
<td>1.06 (0.97 - 1.22)</td>
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<td>Urinary incontinence:</td>
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<td>1.16 (1.06 - 1.28)</td>
<td>1.09 (0.95 - 1.28)</td>
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<td>Pressure ulcers:</td>
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<td>1.26 (1.10 - 1.45)</td>
<td>1.23 (1.08 - 1.40)</td>
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<td>Cardiovascular disease:</td>
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<td>1.24 (1.14 - 1.35)</td>
<td>1.21 (1.10 - 1.34)</td>
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<td>Depression:</td>
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<td>1.07 (1.00 - 1.17)</td>
<td>1.19 (1.07 - 1.32)</td>
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<td>COPD:</td>
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<td>No</td>
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<tr>
<td>Yes</td>
<td>1.28 (1.13 - 1.45)</td>
<td>1.18 (1.00 - 1.42)</td>
</tr>
<tr>
<td>Diabetes mellitus:</td>
<td></td>
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<tr>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.27 (1.14 - 1.42)</td>
<td>1.36 (1.19 - 1.57)</td>
</tr>
<tr>
<td>Malnutrition (BMI &lt; 21):</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.33 (1.22 - 1.44)</td>
<td>1.30 (1.17 - 1.43)</td>
</tr>
</tbody>
</table>

**Conclusions**—Age, sex, functional limitation, and malnutrition seem to be the strongest predictors of death for patients with Alzheimer’s disease in nursing homes. Altogether, severity of dementia has no influence on survival, yet the predictive role of certain variables depends on the degree of impairment.

Take Home Message

• AD dementia is a result of multiple process failures, the most significant of which is synapse loss

• Combined Nutrients (gave by specific and balanced medical nutrition product) support synapse formation and have been shown to improve memory in early AD

• This offers a nutritional approach to support patients with brain failure
How humans experience food

The sense of taste has to be one of the most important human senses.

<table>
<thead>
<tr>
<th>BASIC TASTE SENSES:</th>
<th>ACCEPTABILITY</th>
<th>FLAVOUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweet</td>
<td>Environment</td>
<td>Aroma</td>
</tr>
<tr>
<td>Sour</td>
<td>Culture</td>
<td>‘Mouth-feel’</td>
</tr>
<tr>
<td>Salty</td>
<td>Memory</td>
<td>(texture/thickness)</td>
</tr>
<tr>
<td>Bitter</td>
<td>Genetics</td>
<td>Chemical senses</td>
</tr>
<tr>
<td>Umami</td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Personal condition (mood/health)</td>
<td></td>
</tr>
</tbody>
</table>

- Tip of the tongue: Sweetness
- Back of the tongue: Bitterness
- Sides of tongues: Saltiness and sourness

Areas of sensitivity on the tongue:

- Tip of the tongue: Sweetness
- Back of the tongue: Bitterness
- Sides of tongues: Saltiness and sourness
Allora all’improvviso mi ricordo. Dagli occhi mi sgorgano le lacrime … sono un uomo maturo in agonia, ripiombato nell’infanzia in punto di morte.

Devo farmi capire … “Và a comprarmi dei bignè … con la granella … di zucchero”.

Il bignè aderiva alle mucose più intime del mio palato. La sua molle sensualità sposava le guance e la sua indecente elasticità lo compattava in una pasta omogenea e cremosa, a cui la dolcezza dello zucchero conferiva una punta di perfezione.

Nell’unione quasi mistica della mia lingua con i bignè del supermercato … sono felice.

Alla fine dopo anni di erranza lo ritrovo sul letto di morte … il punto non è mangiare né vivere, è sapere perché … Muoio.