



Nutrizione e Nutraceutica
per l'invecchiamento attivo della popolazione

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

Francesco Landi

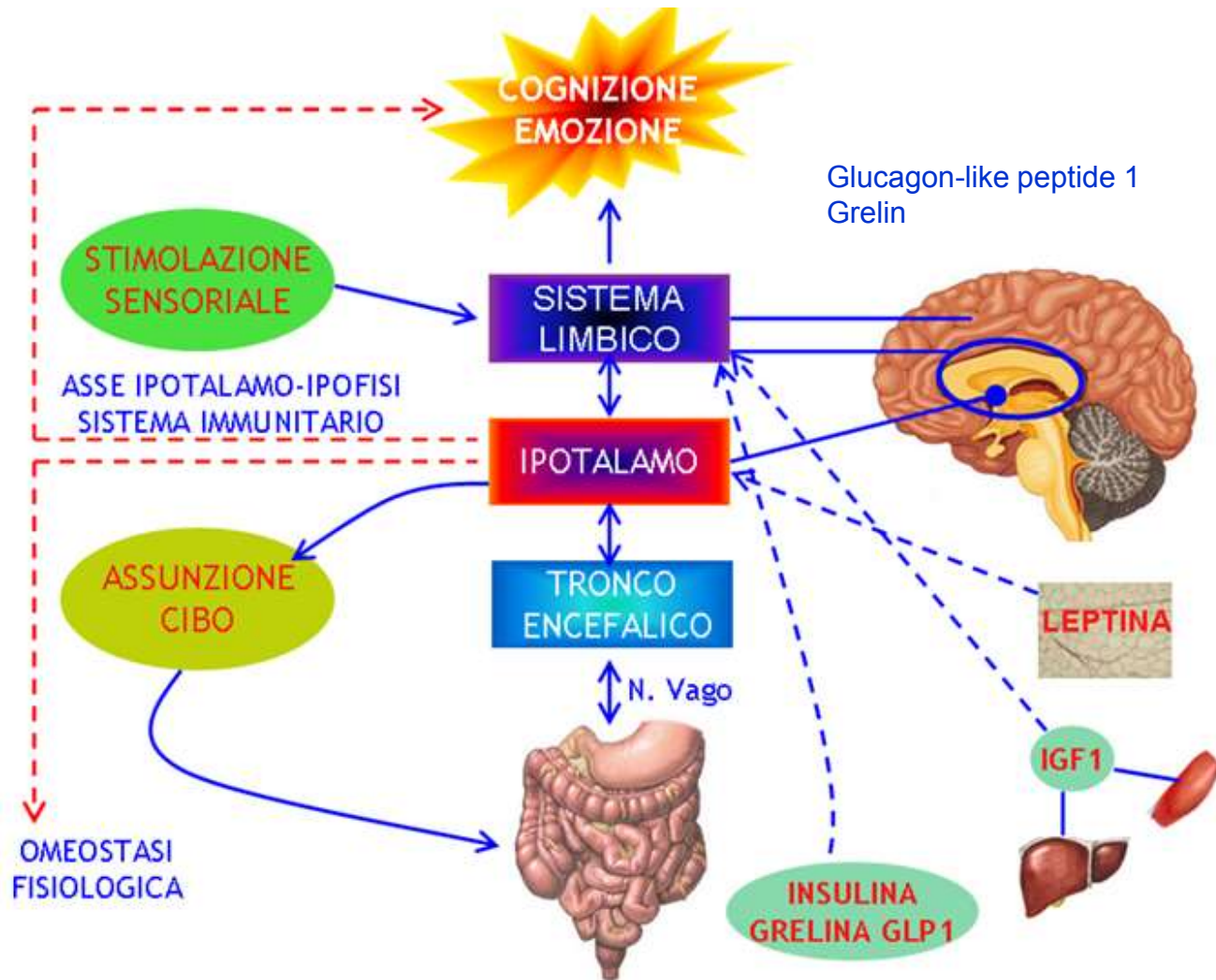
Dipartimento di Geriatria, Neuroscienze e Ortopedia

Università Cattolica, Roma

Roma, 17 dicembre 2014



Correlation nutrition - cognition



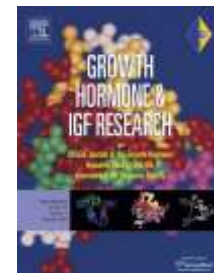
Unadjusted and adjusted mean of IGFBP-3 concentration (lg/ml) according to cognitive skills

	No. of subjects	Unadjusted mean (standard error)	<i>p</i>	Adjusted mean (standard error)	<i>p</i>
<i>Short-term memory problem</i>					
Yes	111	4.25 ± 0.12	0.11	4.30 ± 0.08	0.23
No	242	4.51 ± 0.09		4.51 ± 0.13	
<i>Procedural memory problem</i>					
Yes	65	4.00 ± 0.15	0.005	4.07 ± 0.08	0.02
No	288	4.53 ± 0.08		4.53 ± 0.18	
<i>Cognitive skills for daily decision making problem</i>					
Yes	95	4.10 ± 0.13	0.006	4.20 ± 0.15	0.07
No	258	4.55 ± 0.08		4.53 ± 0.08	
<i>Verbal expression problem</i>					
Yes	20	3.68 ± 0.15	0.01	3.73 ± 0.32	0.02
No	333	4.47 ± 0.07		4.48 ± 0.07	
<i>Comprehension problem</i>					
Yes	24	3.74 ± 0.23	0.01	3.74 ± 0.29	0.01
No	329	4.48 ± 0.07		4.49 ± 0.07	

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.

Free insulin-like growth factor-I and cognitive function in older persons living in community

Francesco Landi ^{a,*}, Ettore Capoluongo ^b, Andrea Russo ^a, Graziano Onder ^a,
Matteo Cesari ^{a,c}, Paola Lulli ^b, Angelo Minucci ^b, Marco Pahor ^c,
Cecilia Zuppi ^b, Roberto Bernabei ^a

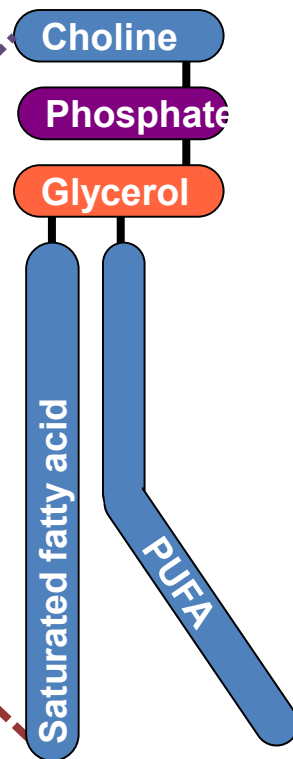
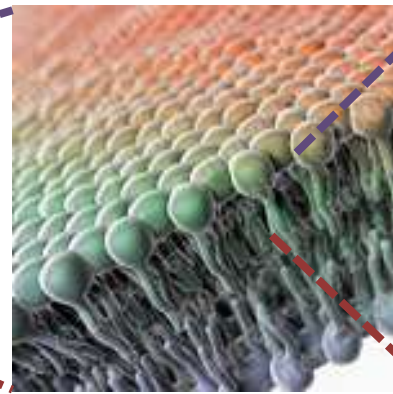
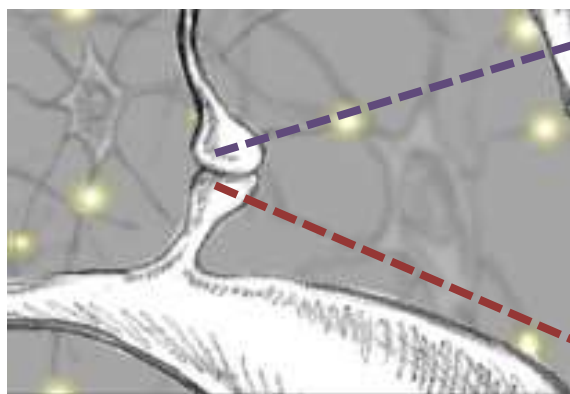
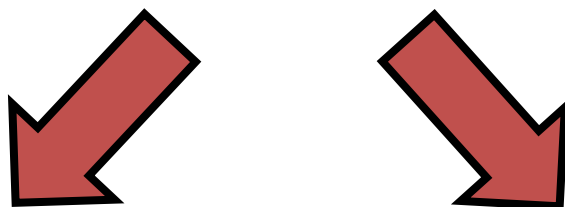


Growth Hormone & IGF Research 17 (2007) 58–66

Amyloid damages neurones and synapses...

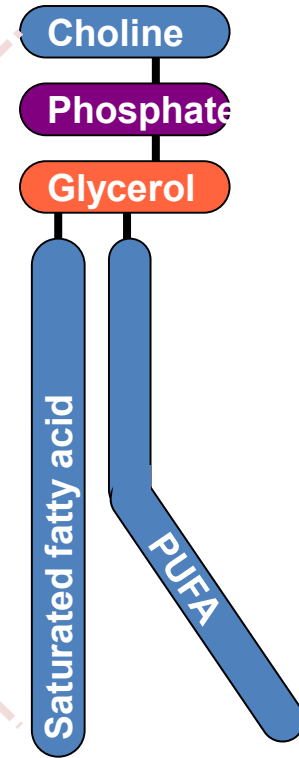
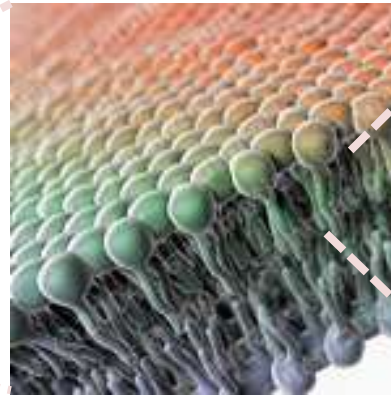
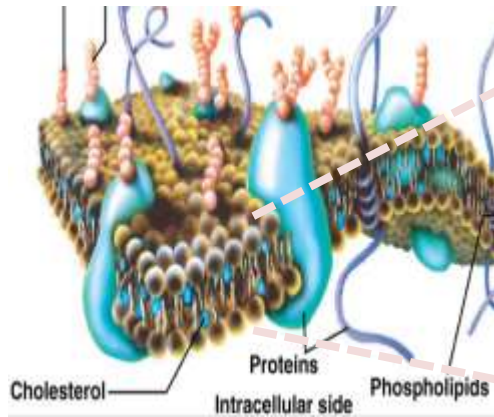


**Beta Amyloid particles
increase oxidation of membranes**



**This greatly increases
membrane turnover**

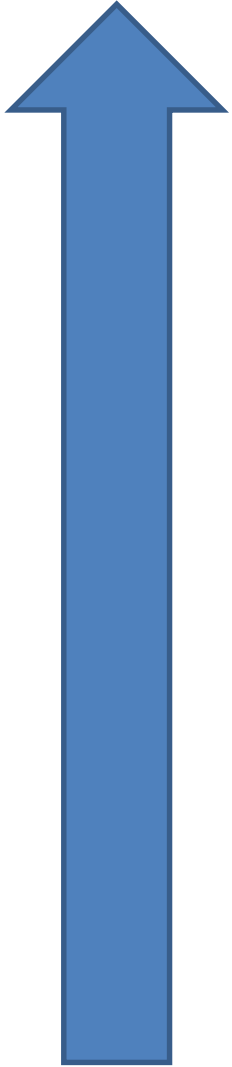
Membranes are made of phospholipids



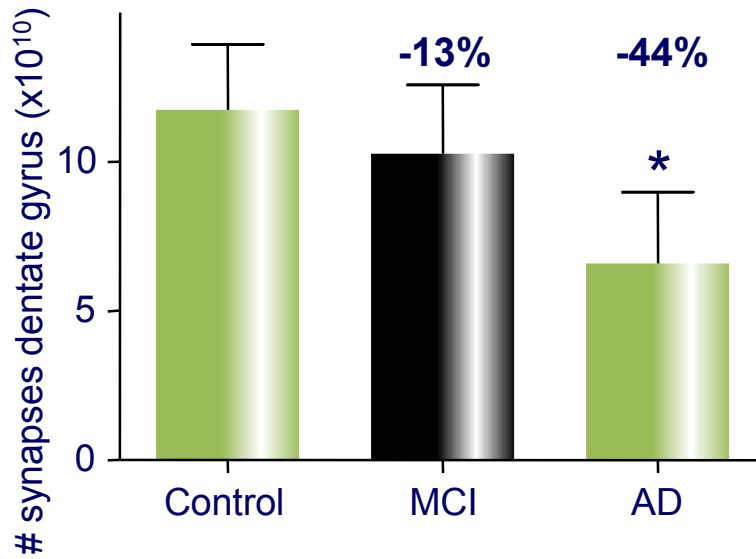
An increased proportion of omega 3 PUFAs increase membrane fluidity, essential for cell signalling DHA is concentrated in synapses

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*

Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Richard D. Terry, MD,* Thomas Birdsall, MD,* David E. Scheff, PhD,* Melissa Dennis, PhD†, Richard D. Terry, MD,* Robert E. M. Frye, PhD,* Lawrence A. Klapper, MD,* and Robert G. Thomas, MD*

Terry RD, Birdsall T, Scheff DE, Dennis M, DeGroot B, Hill R, Hunter LA, Klapper L. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. *Ann Neurol* 1991;30:573-580

VIEWPOINT

Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002

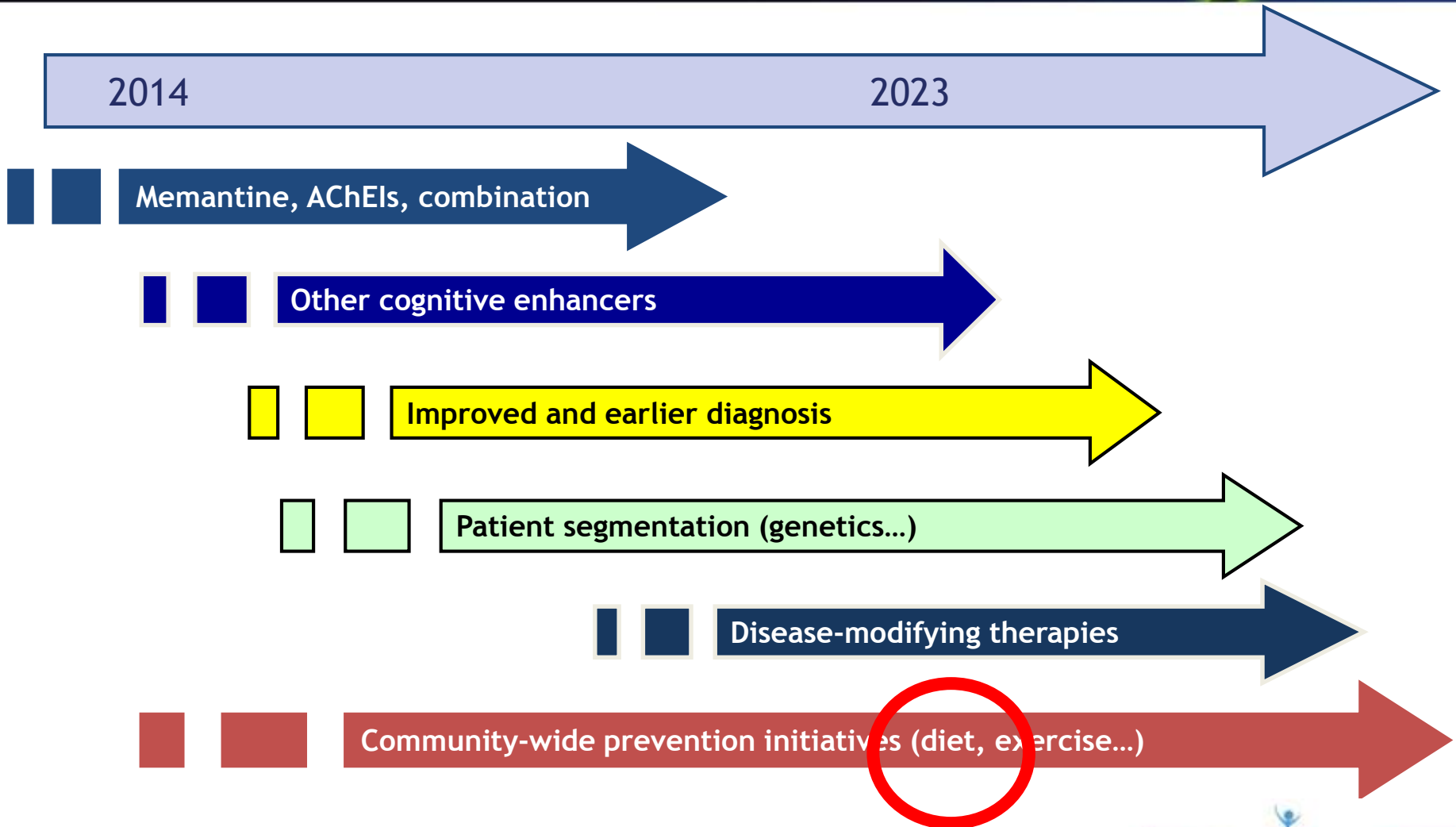
AD is a multi-faceted disease requiring a multi-domain approach



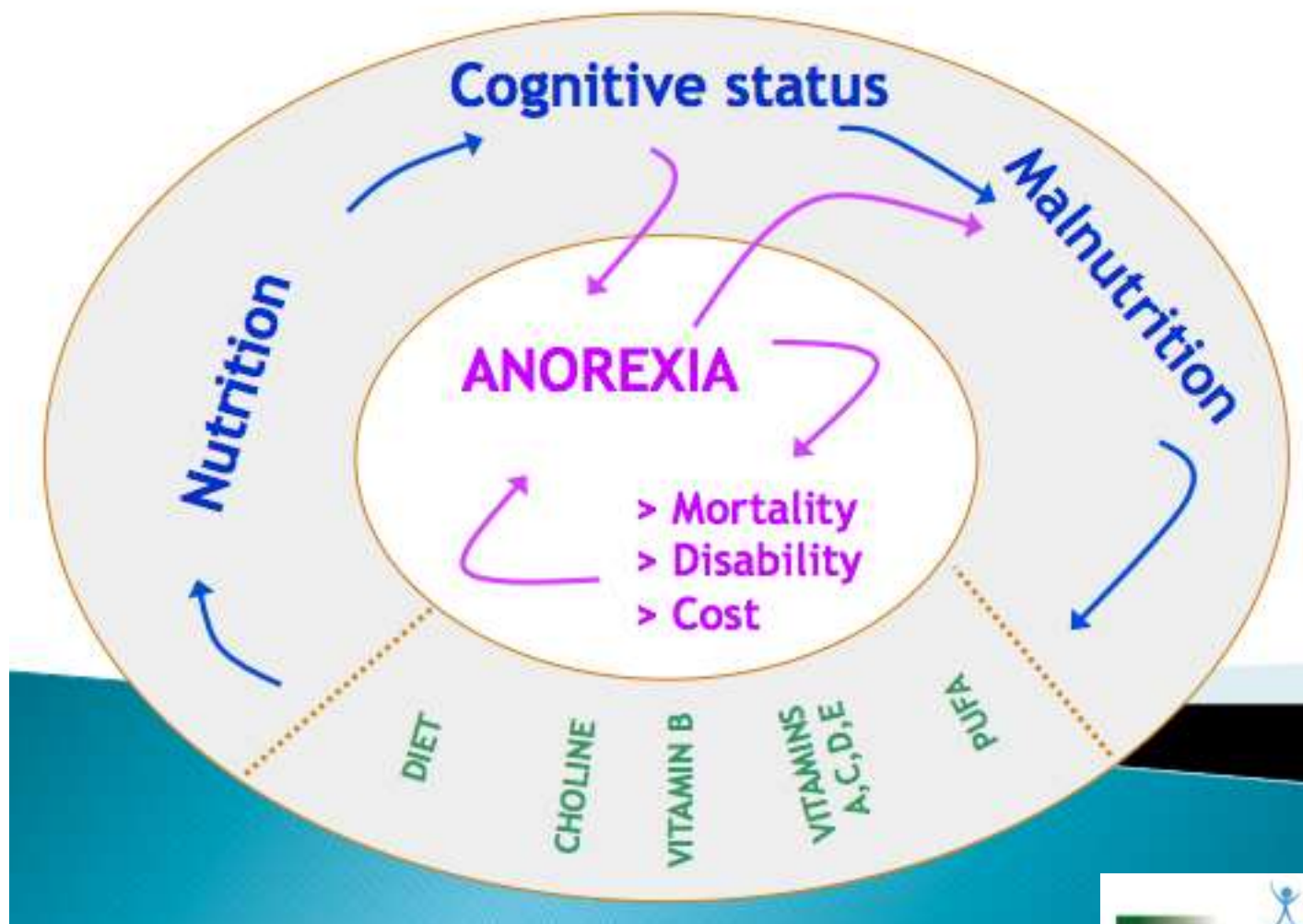
- Multiple pathologies occur in AD, including neuroinflammation, neurovascular pathology and neurodegeneration
- Approaches that have targeted single pathologies, such as amyloid aggregation or inflammatory responses, or individual nutrients have had limited success
- A multi-modal approach may therefore be required, as has been effective in other conditions such as heart failure.

1. Gillete-Guyonnet et al. *Br J Clin Pharmacol*. 2013;75:738-755.

AD treatment 2014 and beyond



Vicious circle of malnutrition



Two pillars of defining nutritional needs in AD



Higher
nutrient
need for
synapses

- Loss of synapses in AD
- Basic science: nutrients needed to increase synapse formation

Lower
nutrients
levels in AD

- Lower levels in blood
- Lower levels in the brain
- Lower intake
- Compromised nutrient metabolism & uptake

Changed eating behaviour in AD

Preclinical stage

- **Changes in regulation of appetite**
- Hypometabolism of hypothalamus, Hippocampus atrophy, **impairment of olfaction and taste**
- Genetic predisposition
- Metabolic changes: increase TNF-alpha levels ...

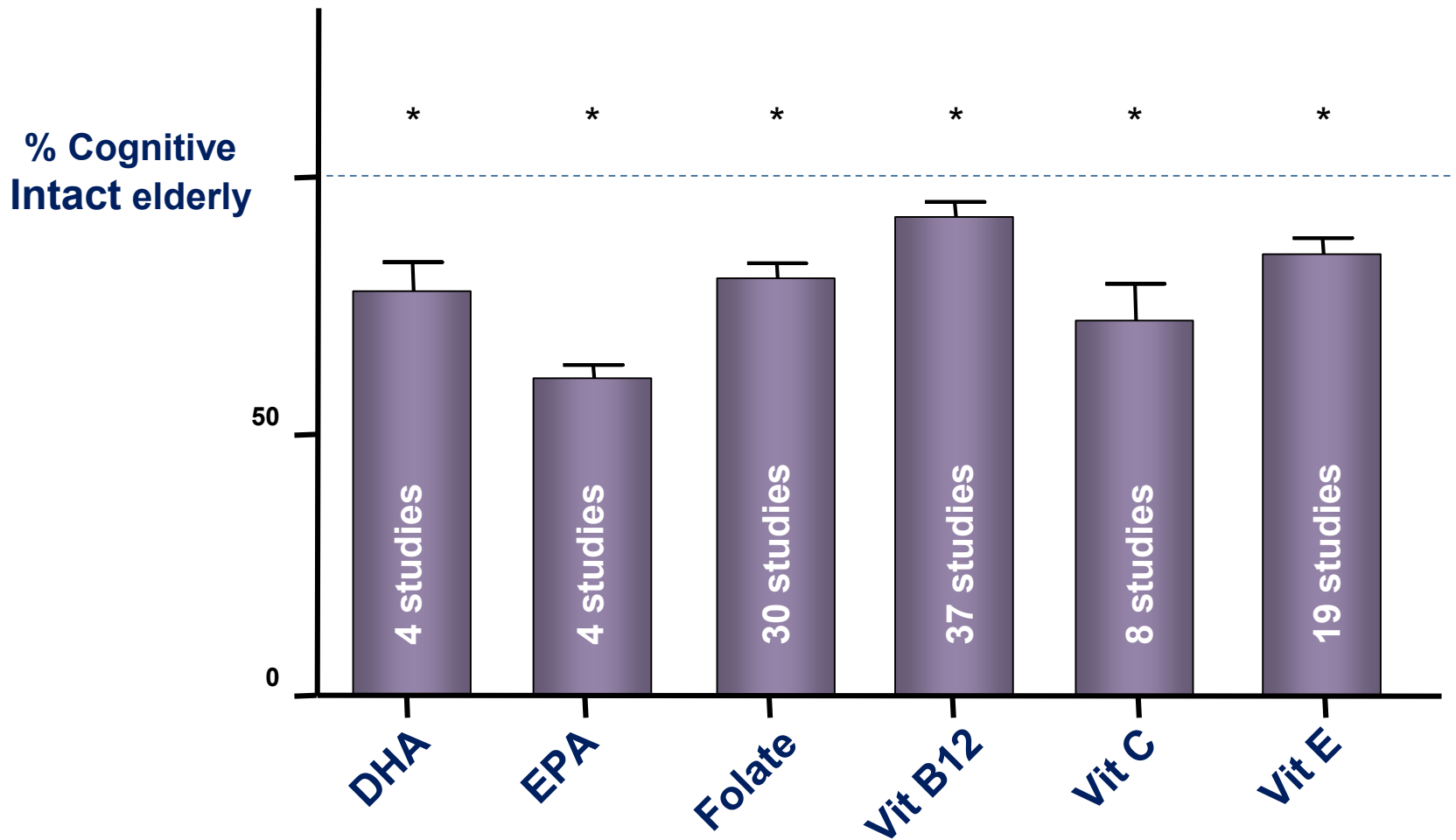
Early stage of AD

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

Late stage of AD

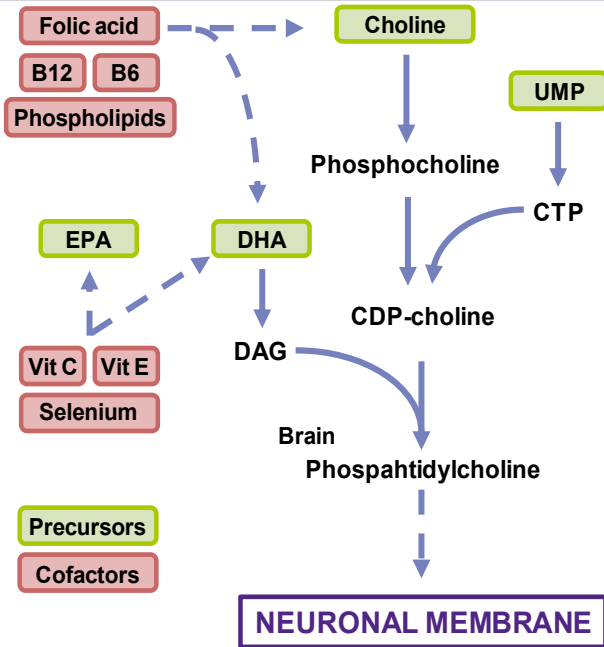
- **Reduced energy intake**
- Apraxy, dependency...
- Dysphagia
- Medication with sedative effects

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



Lopes da Silva et al, *Alzheimers Dement*, 2013

Synapse formation requires nutritional precursors and cofactors

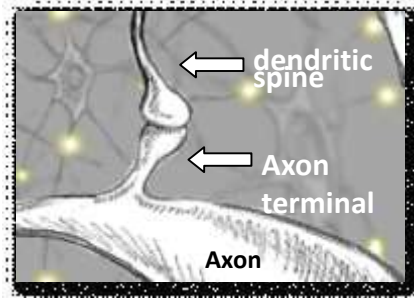


- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- Co-factors facilitate phospholipid synthesis by enhancing precursor bioavailability

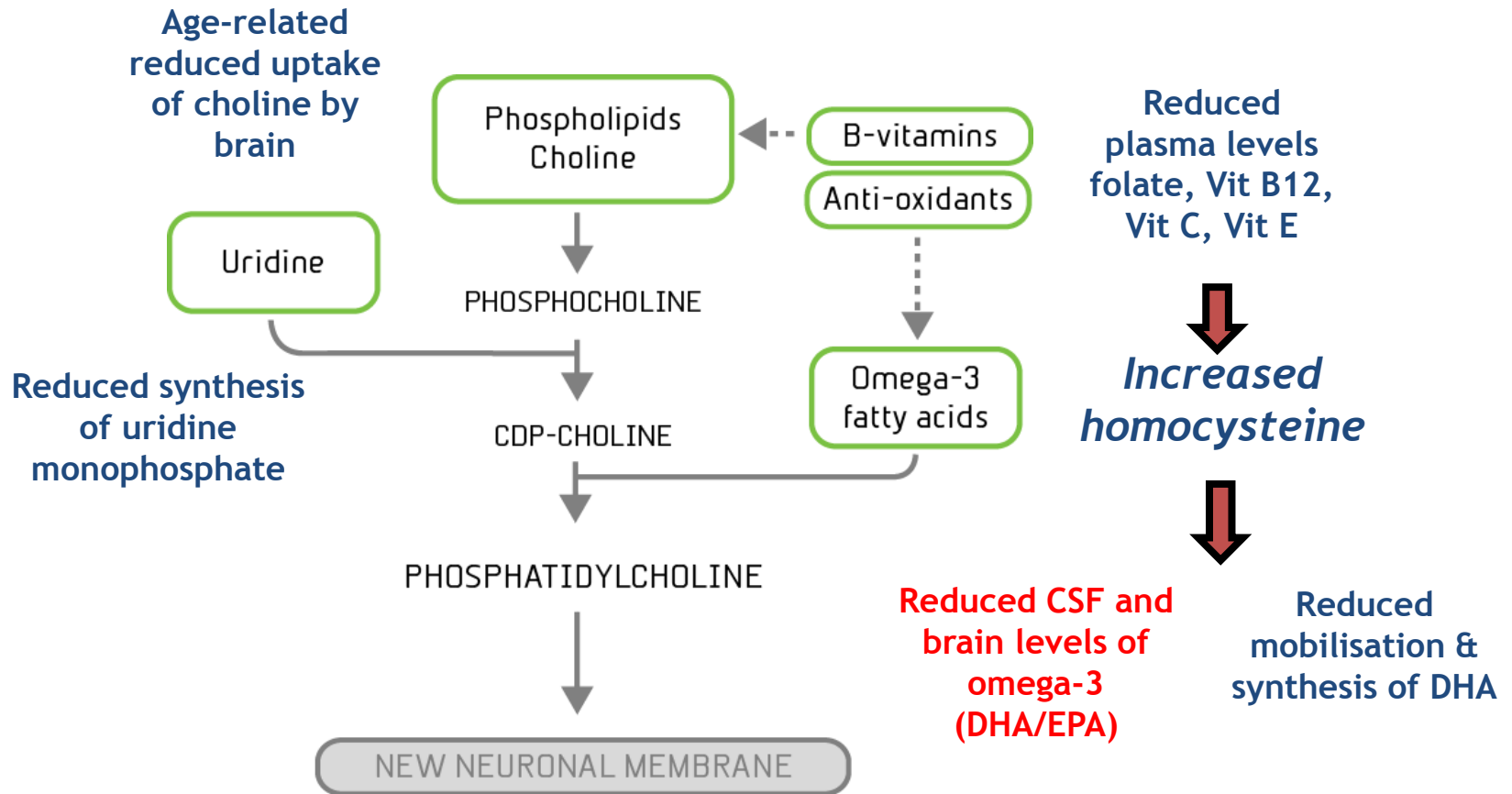
Phospholipid
(Phosphatidylcholine)



Neuronal membrane
(Phospholipid bilayer)



Alzheimer's disease is not primarily a nutritional disorder - but age-related nutritional deficiencies occur

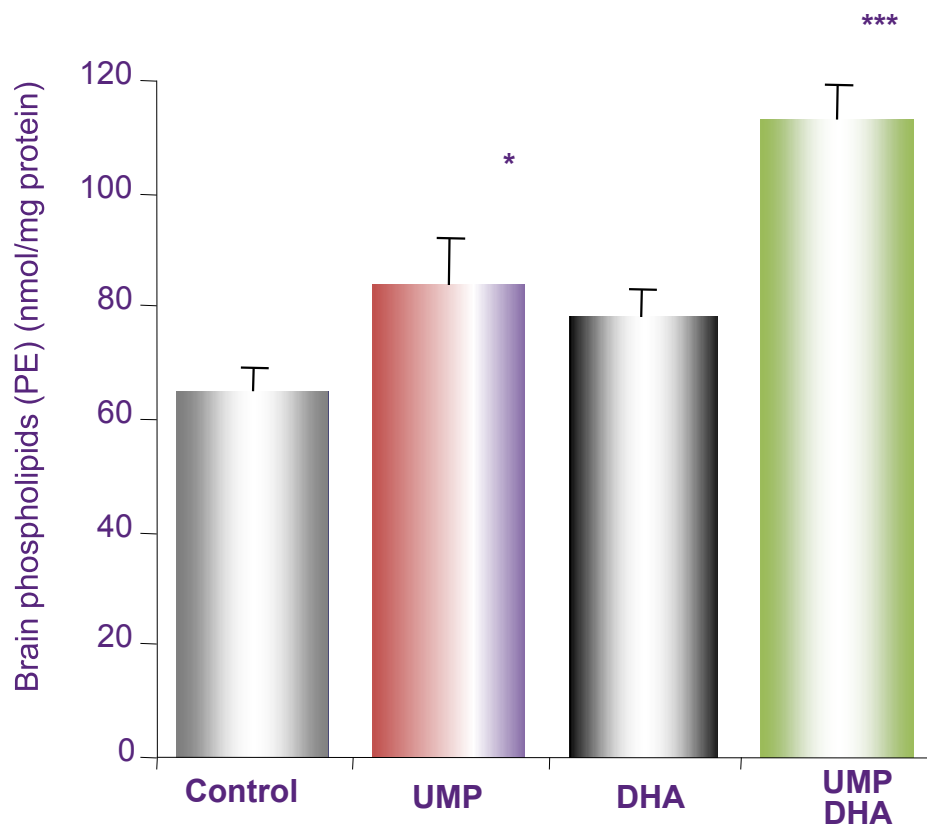


These deficiencies reduce capacity to replace membrane

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^{a,*}, Laus M. Broersen^a, Martijn C. de Wilde^a, Robert J.J. Hageman^a, Martine Groenendijk^a, John W.C. Sijben^a and Patrick J.G.H. Kamphuis^{a,b}

^a*Nutricia Advanced Medical Nutrition, Nutricia Research, Utrecht, The Netherlands*

^b*Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands*

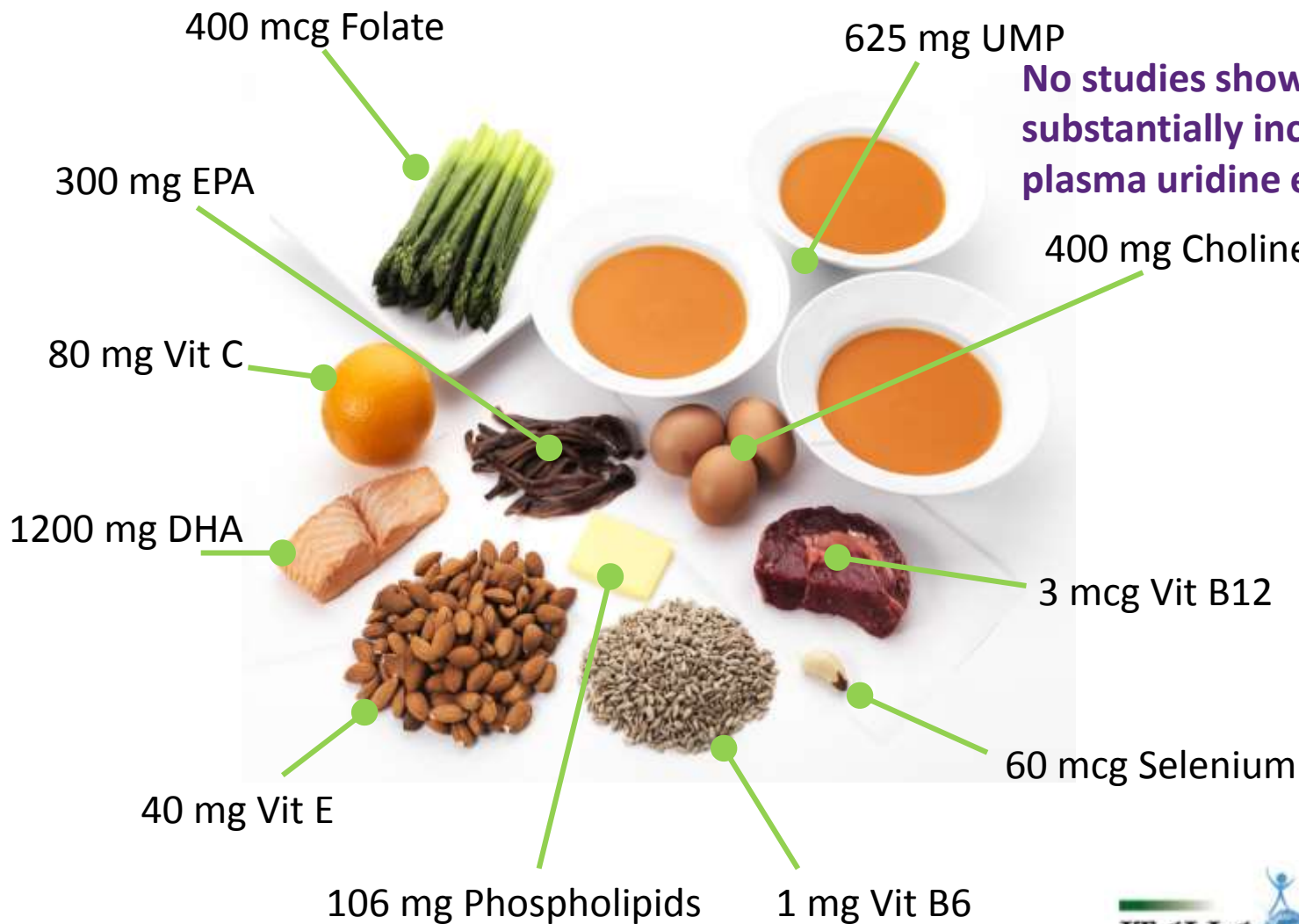
Nutrient combination enhances synapse formation and function

Omega-3 fatty acids
UMP
Choline
Phospholipids
B vitamins
Antioxidants



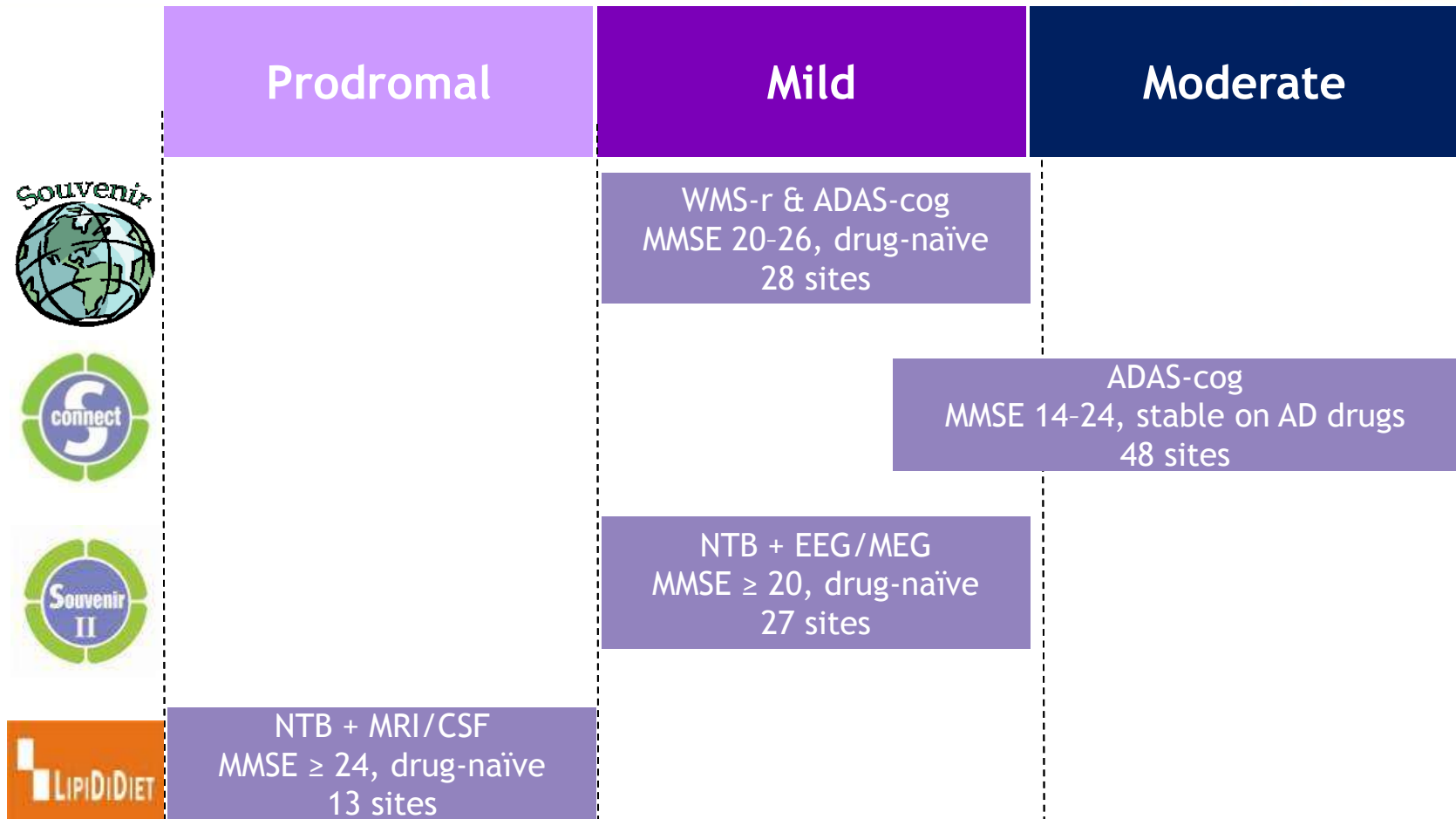
DHA 1200 mg
EPA 300 mg
UMP 625 mg
Choline 400 mg
Folic acid 400 µg
B6 1 mg
B12 3 µg
Vit C 80 mg
Vit E 40 mg
Se 60 µg
Phospholipids 106 mg

Intake of Combined Nutrients cannot be met on top of normal diet



No studies showing foods substantially increase plasma uridine exist

Full clinical trial programme

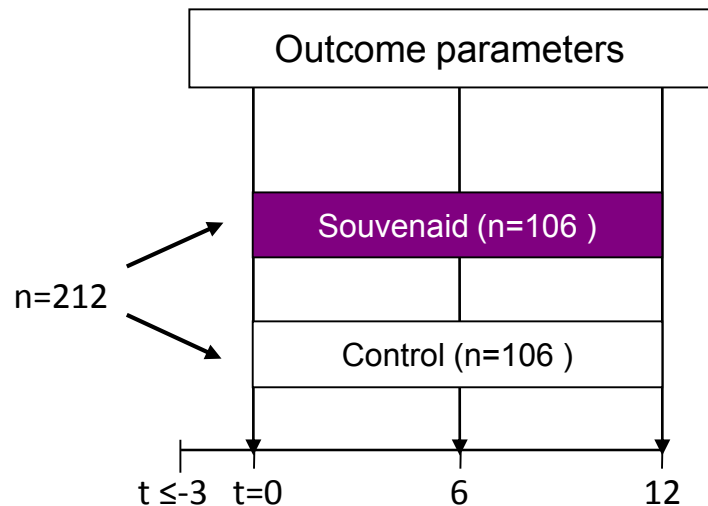


Souvenir I: this project receives funding from NL STW.

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

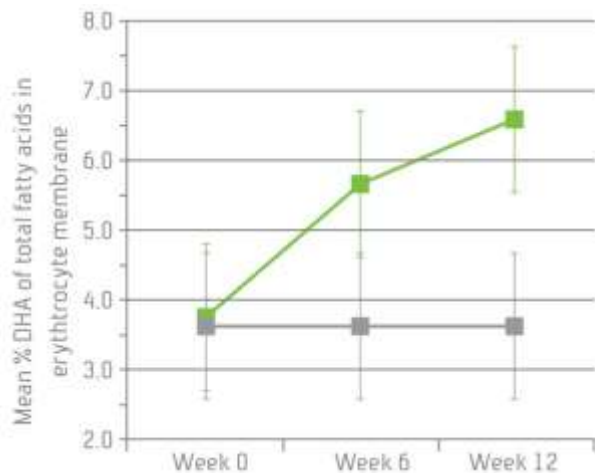


- Multi-centre (28 sites in NL, Bel, Ger, UK) PI Prof Philip Scheltens,
- Drug-naive subjects with probable AD of mild severity (MMSE 20-26)
Randomised, double-blind, controlled, parallel-group
- Intervention: Souvenaid, a once-a-day (125 ml / day) drink for 12 weeks
- Co-primary outcomes: delayed verbal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

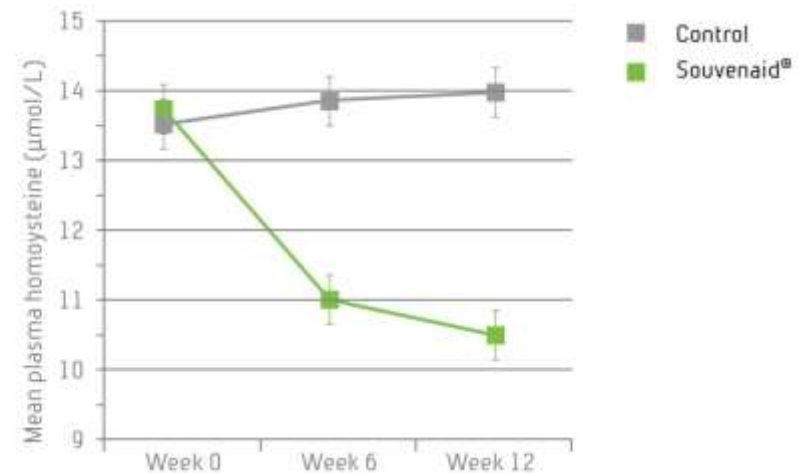
Souvenir I: Well tolerated with good adherence

- 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 ($p < 0.001$)



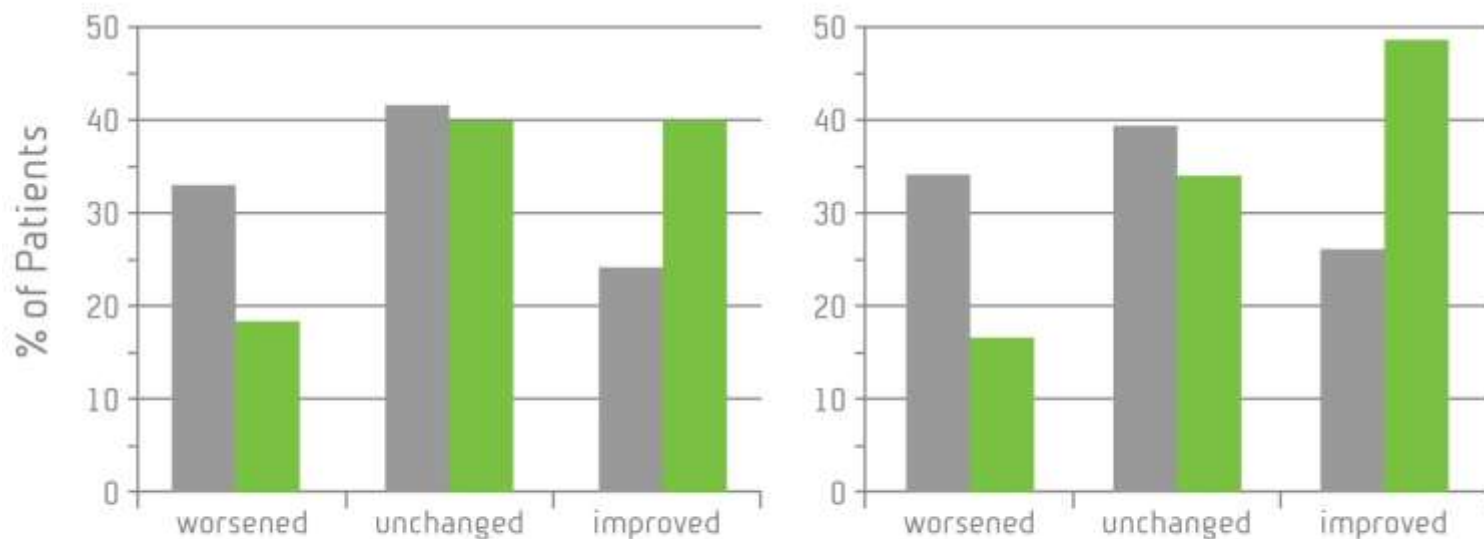
Souvenir I: Primary endpoint MMSE 20-26, drug-naïve 12 weeks



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 ($p=0.019$)*



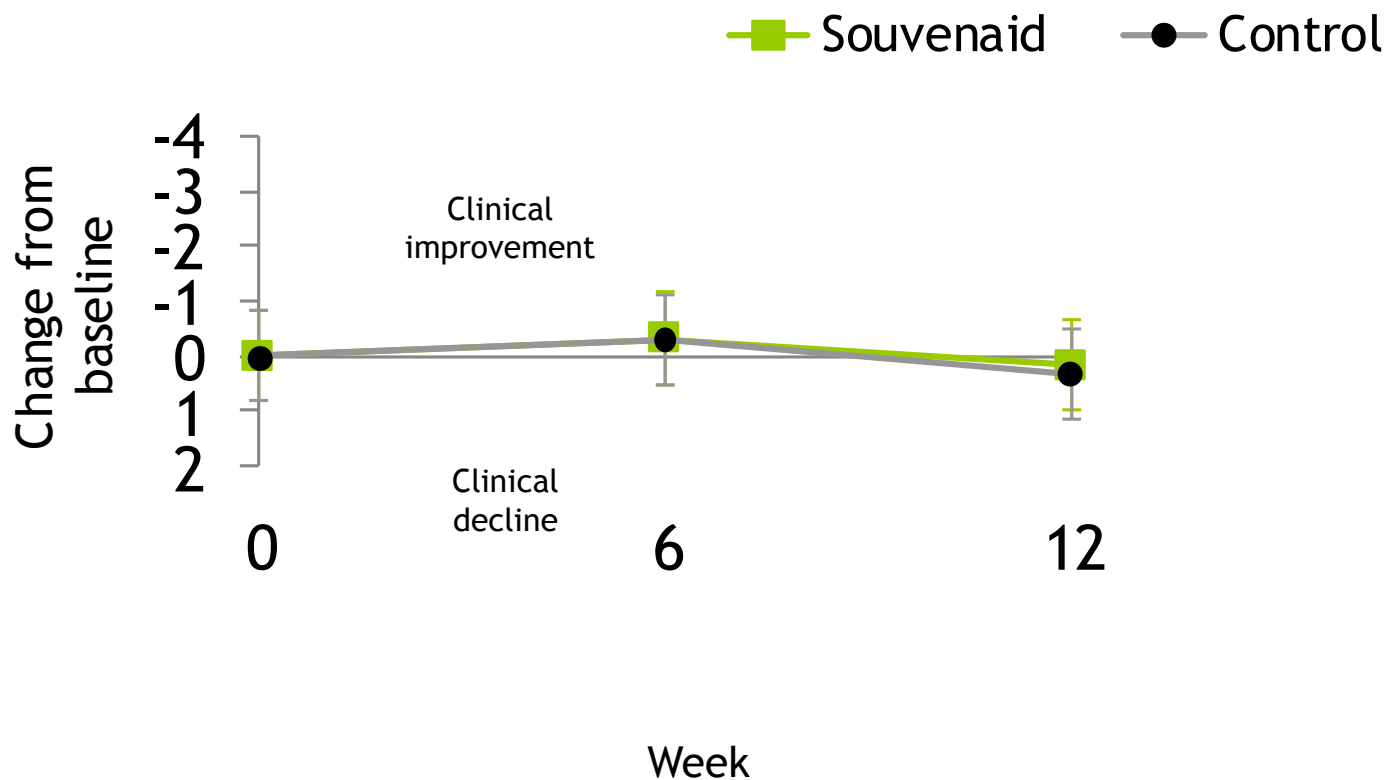
* Chi-square - skewed distribution: 40% scored 0 on WMS-r @ BL

■ Control
■ Souvenaid®

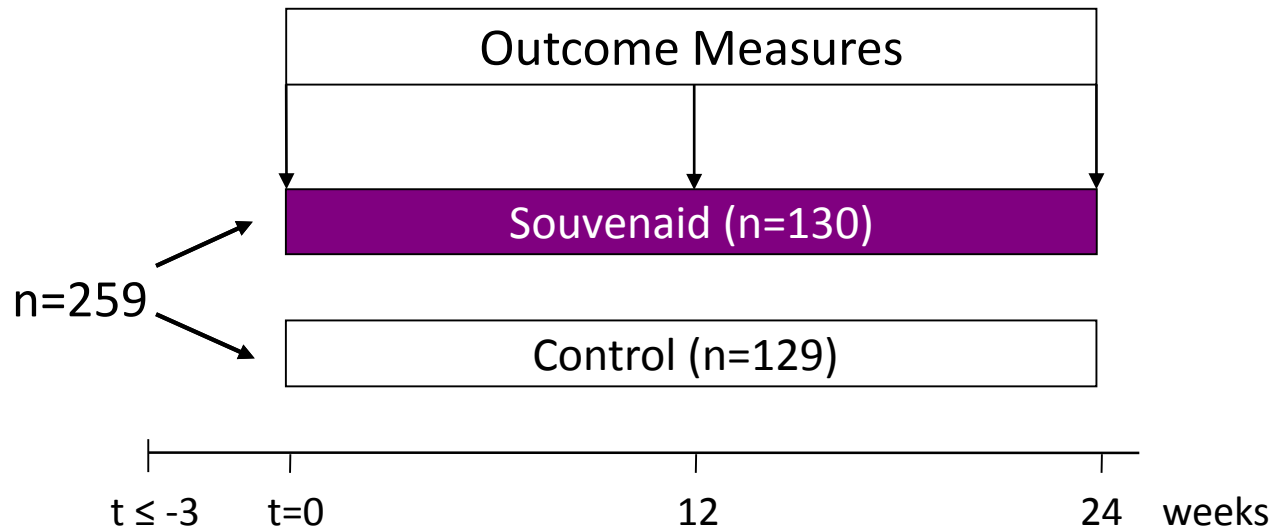
Souvenir I: ADAS-cog 13 was similar in the 2 groups



Repeated-Measures Mixed Model analysis



Souvenir II: Design & methodology

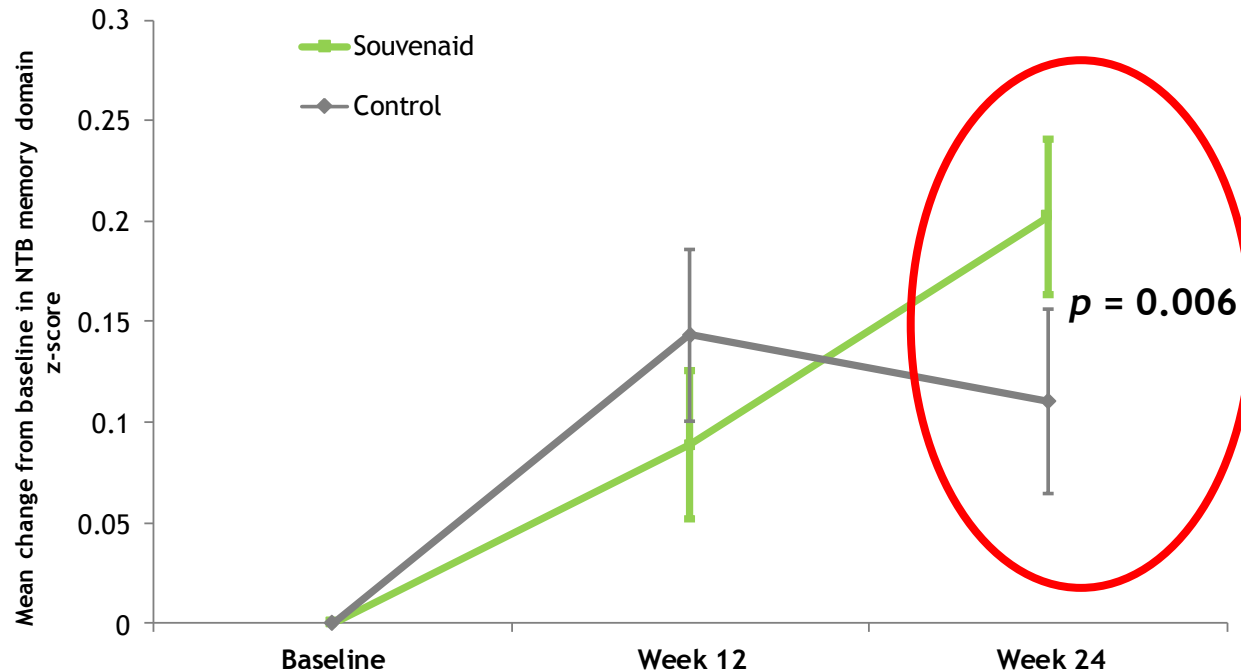


- Multi-centre (27 sites) in Europe (NL, Ger, Bel, Fr, It, Sp)
- Mild AD patients (MMSE > 20), AD drug-naïve
- Primary outcome NTB + EEG/MEG
- Randomized, double-blind, controlled, parallel-group
- Intervention: Souvenaid® or an isocaloric control

Souvenir II: Primary endpoint MMSE > 20, drug-naïve 24 weeks

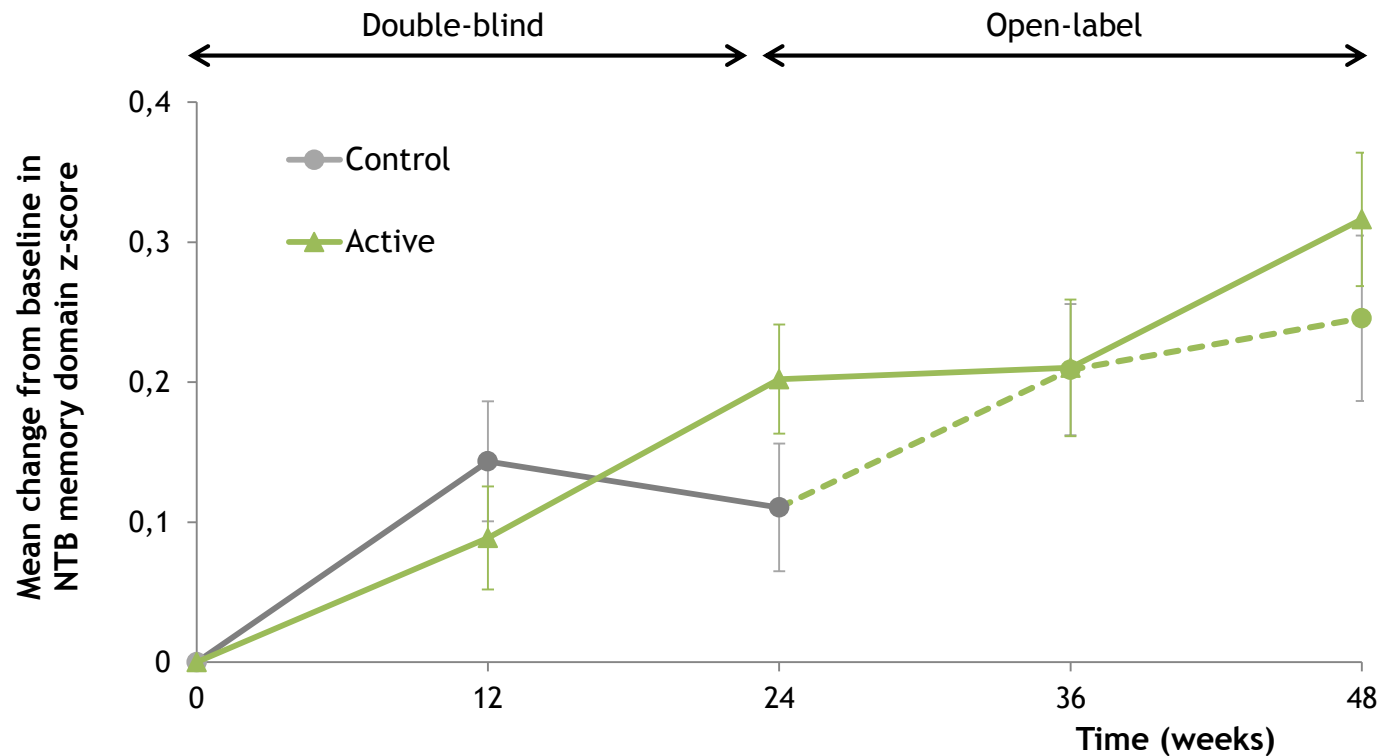
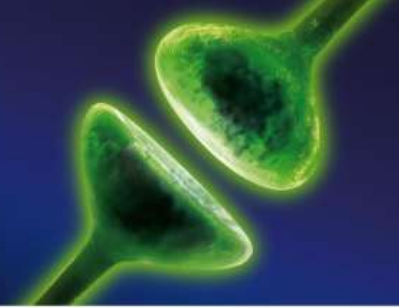


Significant effect* on NTB memory domain over 24 weeks
(whole period trajectory; $p=0.023$)



*Statistical analysis re-run by Rush Alzheimer's Disease Center, Rush University Medical Center ITT, MMRM, trajectory, mean \pm SE.

Souvenir II: Primary endpoint MMSE > 20, drug-naïve 24-48 weeks



	0	12	24	36	48
Control (N)	-	100	103	85	83
Active (N)	-	107	103	83	83

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

Active - Active: $p=0.038$

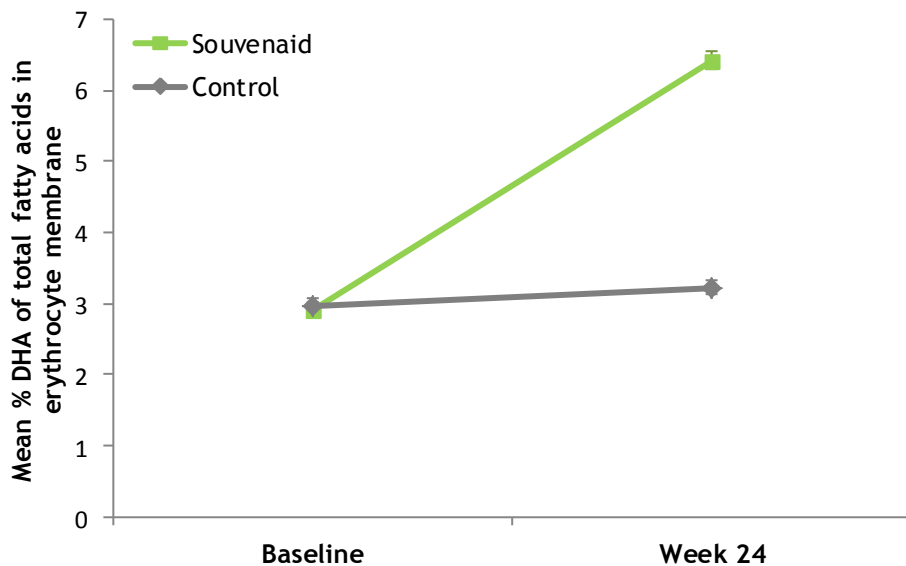
Control - Active: $p=0.029$

Souvenir II: Positive safety profile and biochemical changes

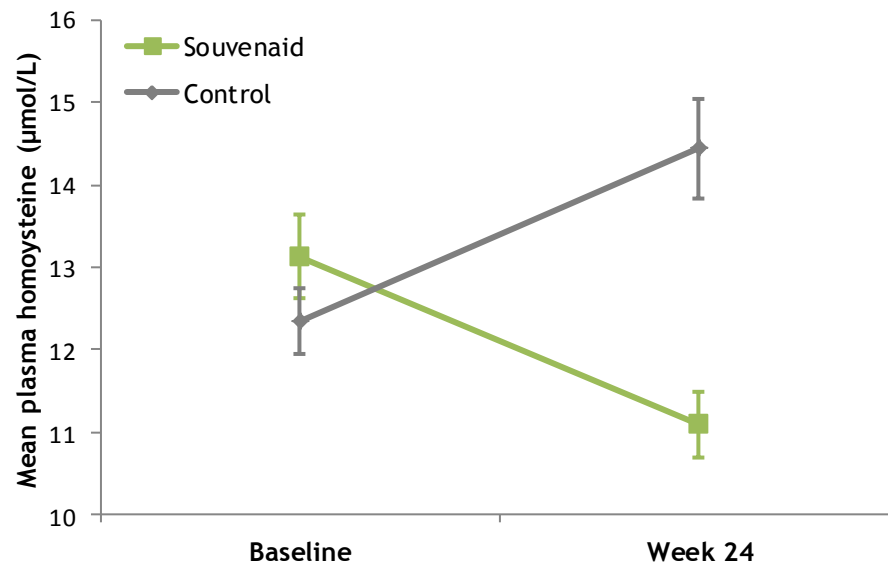


- No differences in renal and liver parameters or AEs
- Overall adherence during 24 weeks was very high in both groups (97.1% in the active group vs. 96.6% in the control group)

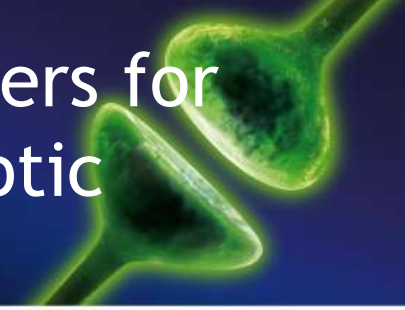
Increased % DHA in plasma erythrocyte membrane ($p < 0.001$)



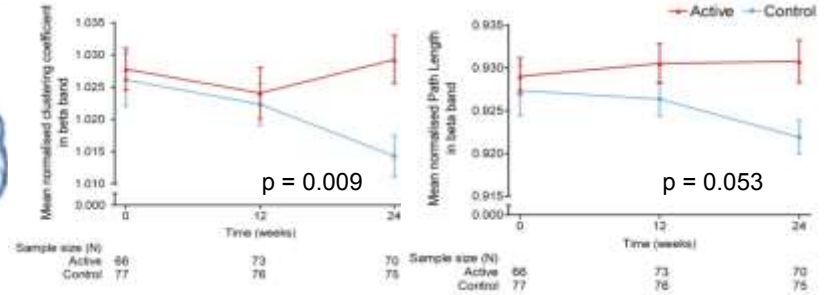
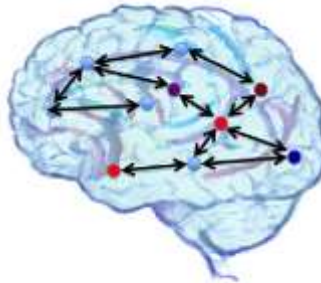
Reduced plasma homocysteine ($p < 0.001$)



Combined Nutrients increases EEG biomarkers for functional connectivity, derivatives of synaptic activity

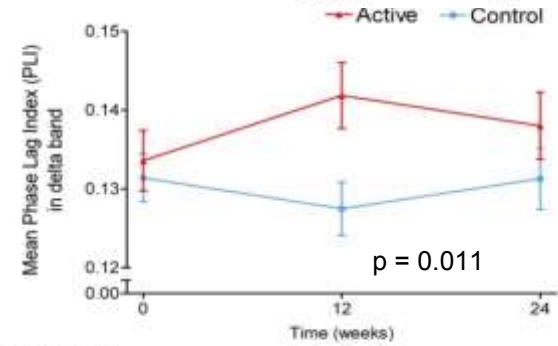
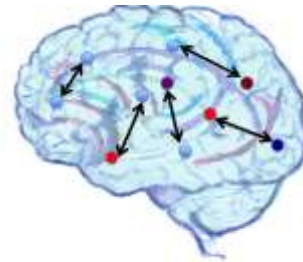


Level 3: network analysis



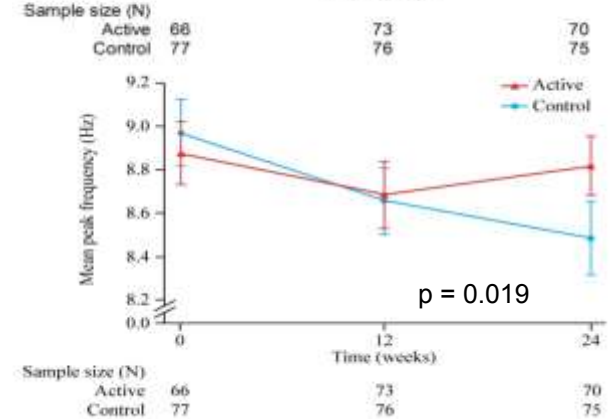
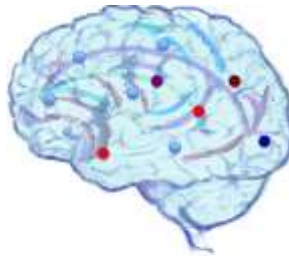
Network organization

Level 2: connectivity analysis



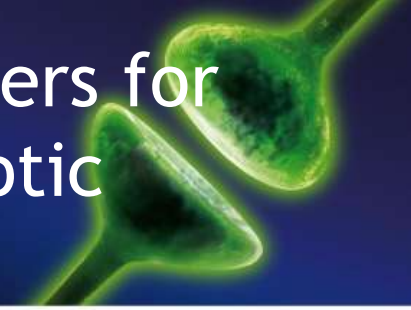
Pair-wise interactions

Level 1: basic signal analysis

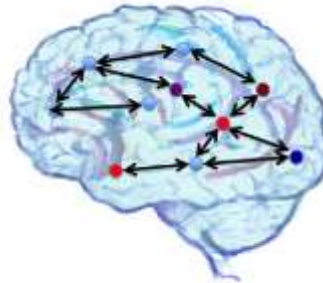


Local activation

Combined Nutrients increases EEG biomarkers for functional connectivity, derivatives of synaptic activity



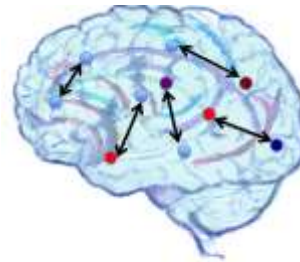
Level 3: network analysis



Network organization

Souvenaid preserves organization of functional brain networks

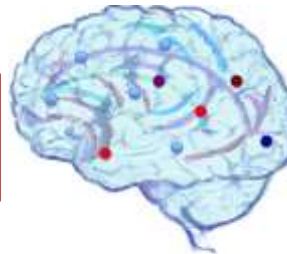
Level 2: connectivity analysis



Pair-wise interactions

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

Level 1: basic signal analysis



Local activation

Souvenaid preserves oscillatory frequency (that decreases in AD)

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,
Phospholipids & Choline, B-Vitamins, Antioxidants

Lower Nutrient status & altered nutrient metabolism

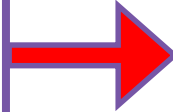
Increased nutritional need not met by the regular diet

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



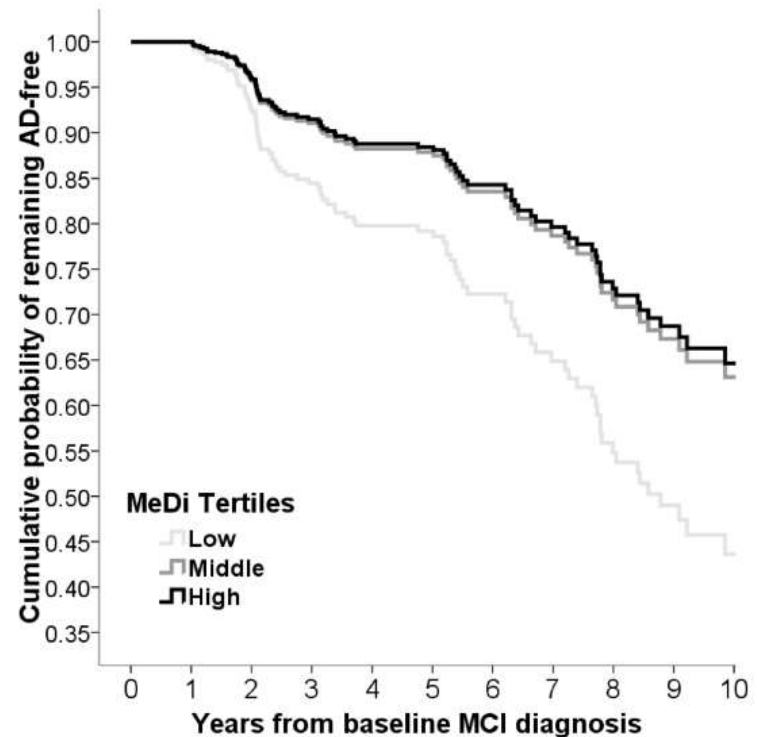
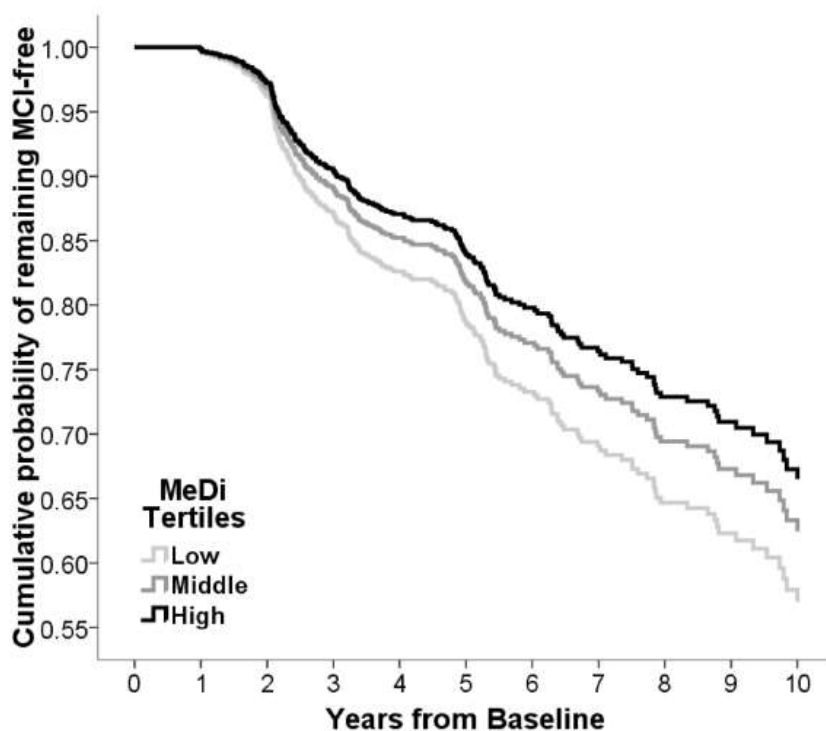
UMP
DHA, EPA
Choline
Phospholipids
B vitamins
Antioxidants



Hypothesized to:

Increase the formation and function of synapses in AD

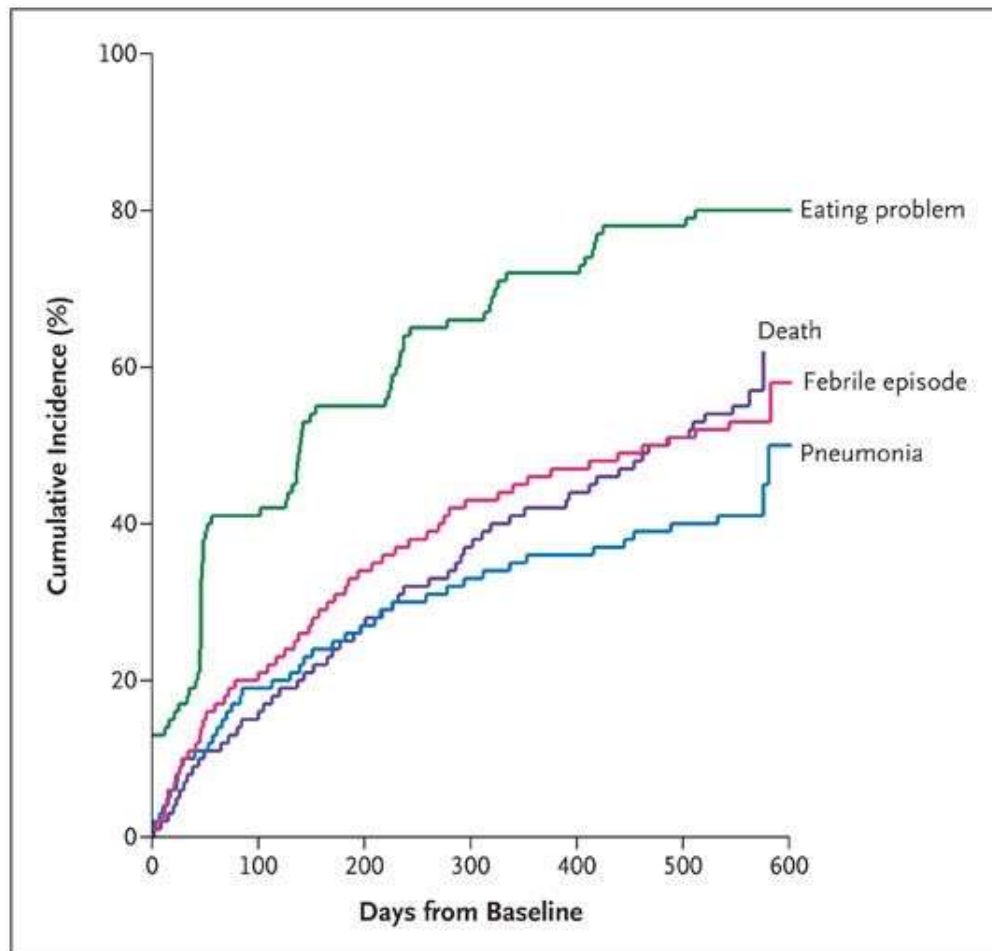
Mediterranean diet and dementia



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.

Arch Neurol. 2009 February ; 66(2): 216–225.

Overall Mortality among Nursing Home Residents with Advanced dementia



S.Mitchell; MB Hamel *N Engl J Med* 2009;361:1529-38

Risk factors and mortality among Nursing Home Residents with dementia

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

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

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.

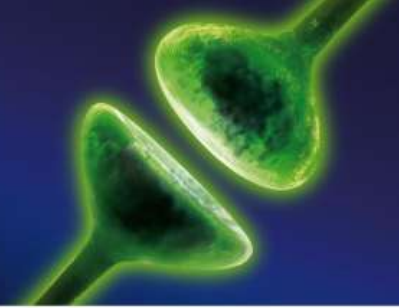
Landi et al. J Neurol Neurosurg Psychiatry 1999;67:59–65

Take Home Message



- AD dementia is a result of multiple process failures, the most significant of which is synapse loss
- Combined Nutrients (given 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

BASIC TASTE SENSES: Sweet Sour Salty Bitter Umami	ACCEPTABILITY Environment Culture Memory Genetics Age Personal condition (mood/health)
PALATABILITY Temperature Colour Shape Sound	FLAVOUR Aroma 'Mouth-feel' (texture/ thickness) Chemical senses



Areas of sensitivity on the tongue

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

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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.