63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI: LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018 Auditorium della Tecnica, Roma

L'APPROCCIO NUTRIZIONALE AL MILD COGNITIVE IMPAIRMENT

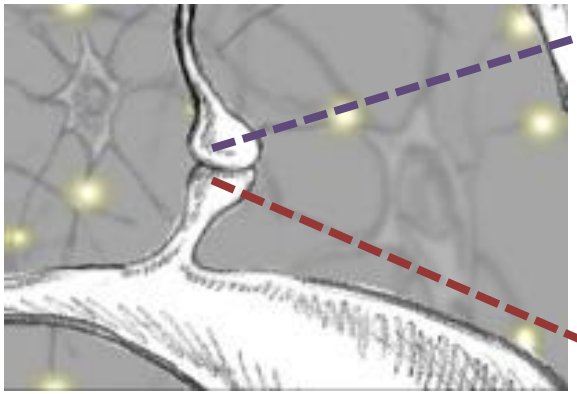
Francesco Landi

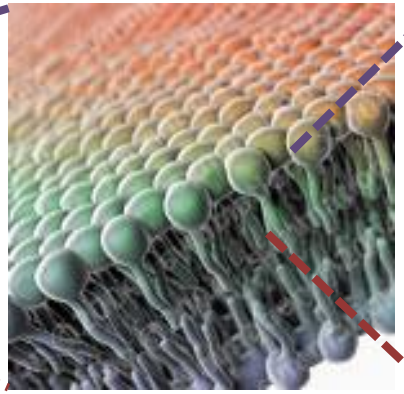
Dipartimento di Geriatria, Neuroscienze e Ortopedia

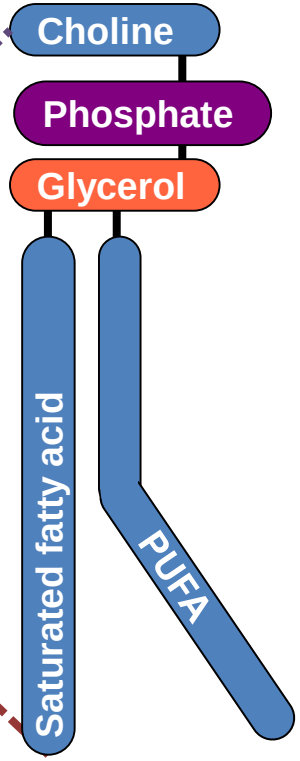
Università Cattolica, Roma

Amyloid damages neurones and synapses...

Beta Amyloid particles increase oxidation of membranes

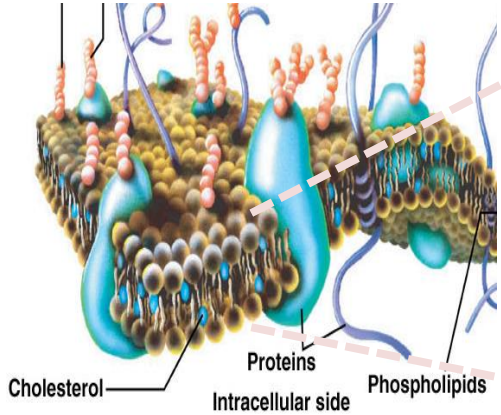


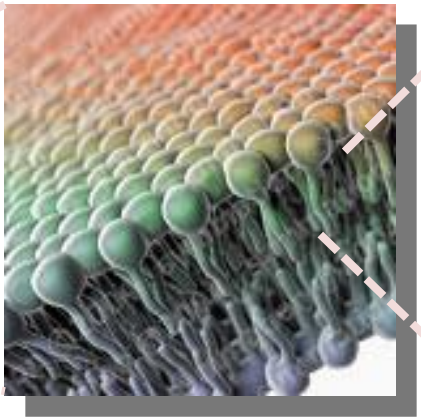


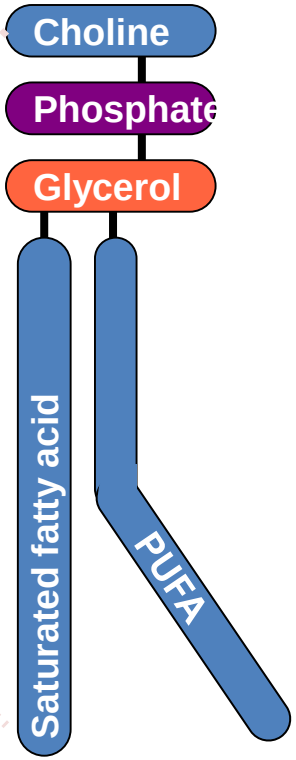


This greatly increases membrane turnover

Membranes are made of phospholipids

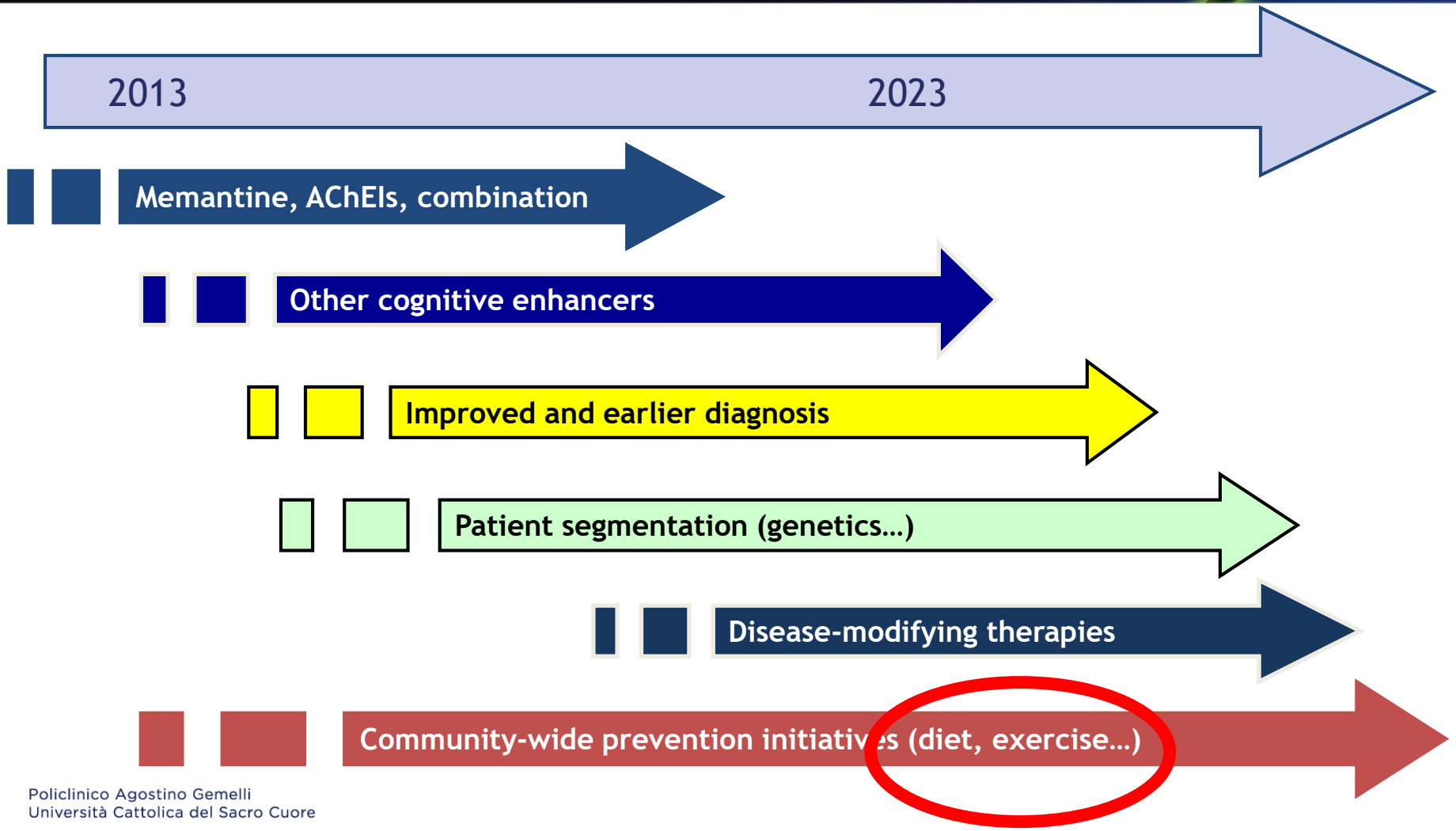






An increased proportion of omega 3 PUFAs increase membrane fluidity, essential for cell signalling Docosahexaenoic acid (DHA) is concentrated in synapses

Dementia treatment 2013 and beyond

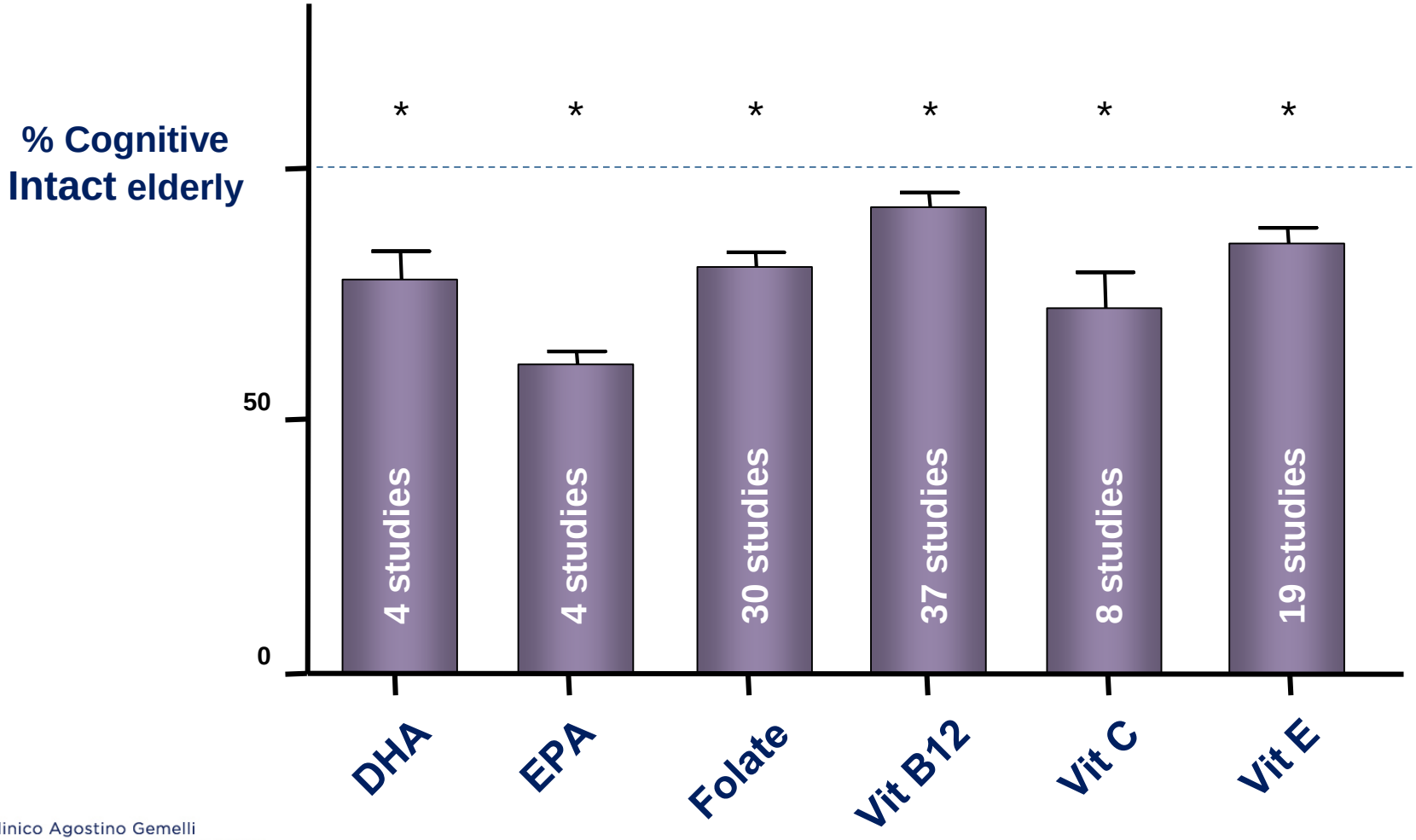


Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Two pillars of defining nutritional needs in Mild Cognitive Impairment

Higher nutrient need for synapses	• Loss of synapses • Basic science: nutrients needed to increase synapse formation
Lower nutrients levels in CI	• Lower levels in blood • Lower levels in the brain • Lower intake • Compromised nutrient metabolism & uptake

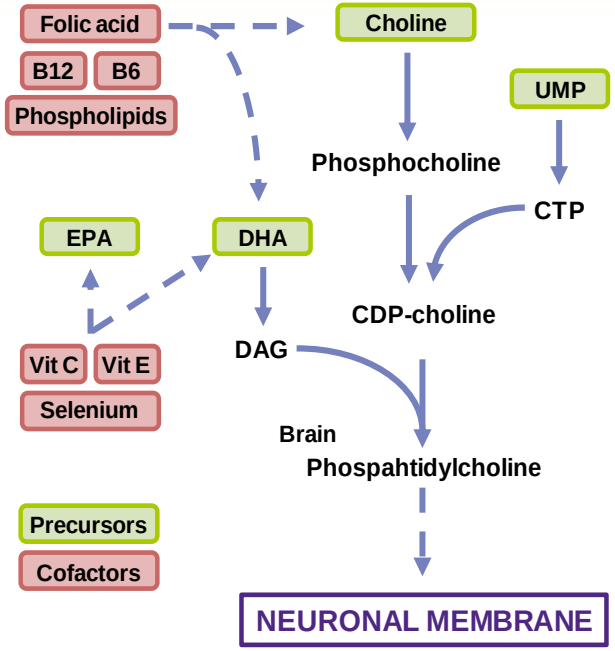
Systematic review and meta-analysis of literature: Lower levels in MCI/AD of specific nutrients

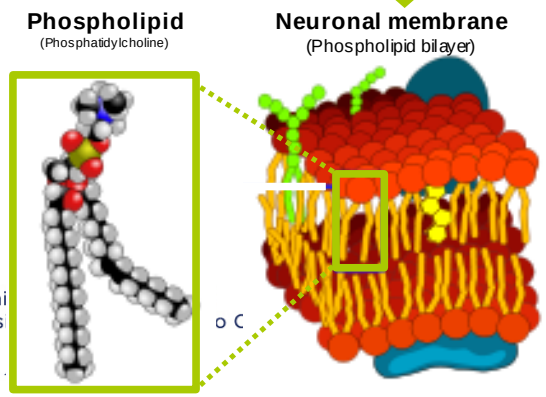


Lopes da Silva et al, *Alzheimers Dement*, 2013

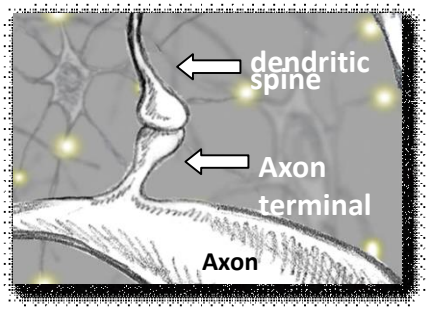
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Synapse formation requires nutritional precursors and cofactors

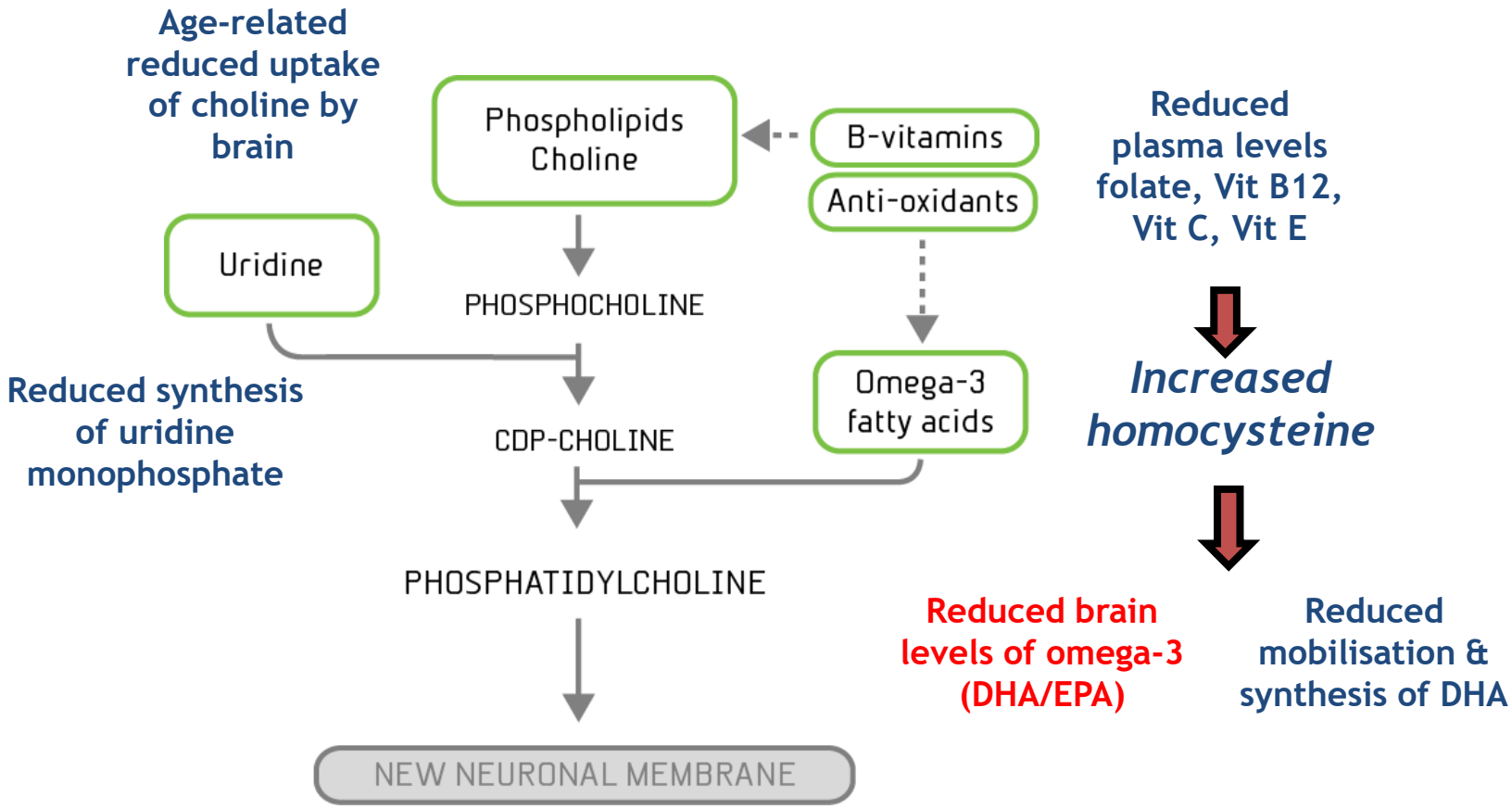




- Synapses are continuously being remodeled
- Synapses are part of the neuronal membrane
- Membranes consist of phospholipids
- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- Co-factors facilitate phospholipid synthesis by enhancing precursor bioavailability

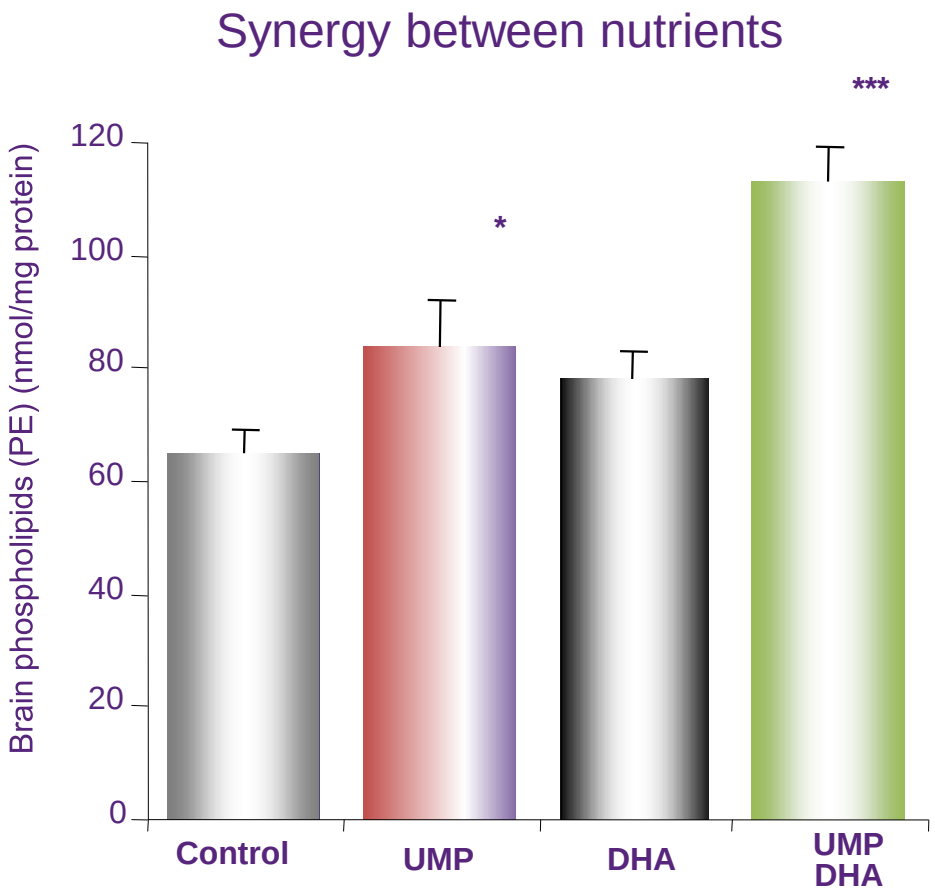


MCI is not primarily a nutritional disorder – but age-related nutritional deficiencies occur



These deficiencies reduce capacity to replace membrane

A combination of dietary precursors increases membrane synthesis



Wurtman *et al*. (2005) Brain Res; Wurtman *et al.* (2006) Brain Res

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Nutrient combination enhances synapse formation and function – basic science data

JAD
Journal of Alzheimer's Disease

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

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

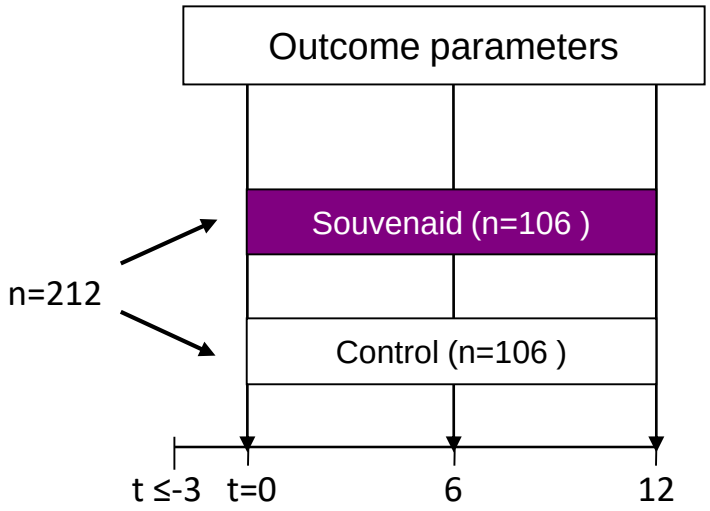
Full clinical trial programme

	Prodromal	Mild	Moderate
Souvenir		WMS-r & ADAS-cog MMSE 20–26, drug-naïve 28 sites	
connect			ADAS-cog MMSE 14–24, stable on AD drugs 48 sites
Souvenir II		NTB + EEG/MEG MMSE ≥ 20, drug-naïve 27 sites	
LipiDiDiet	NTB + MRI/CSF MMSE ≥ 24, drug-naïve 13 sites		

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

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)

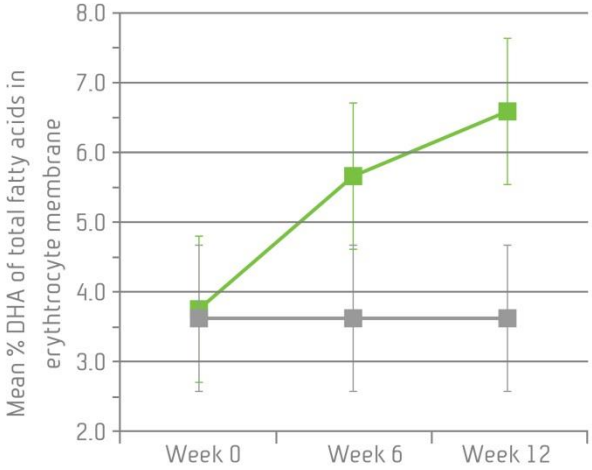
  Randomised, double-blind, controlled, parallel-group
- Intervention: Souvenaid, a once-a-day (125 ml / day) drink for 12 weeks
- Co-primary outcomes: delayed verbal recall WMS-r and modified ADAS-cog

Scheltens et al. *Alz & Dement* 2010.

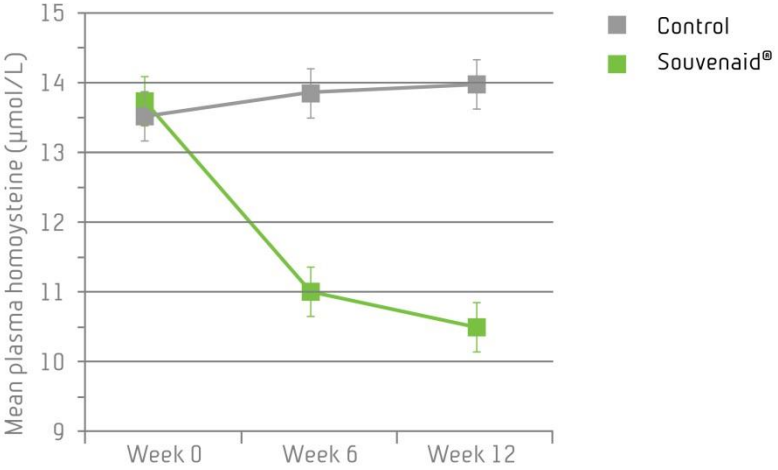
Souvenir I: Well tolerated with good adherence

- 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 ($p<0.001$)



Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

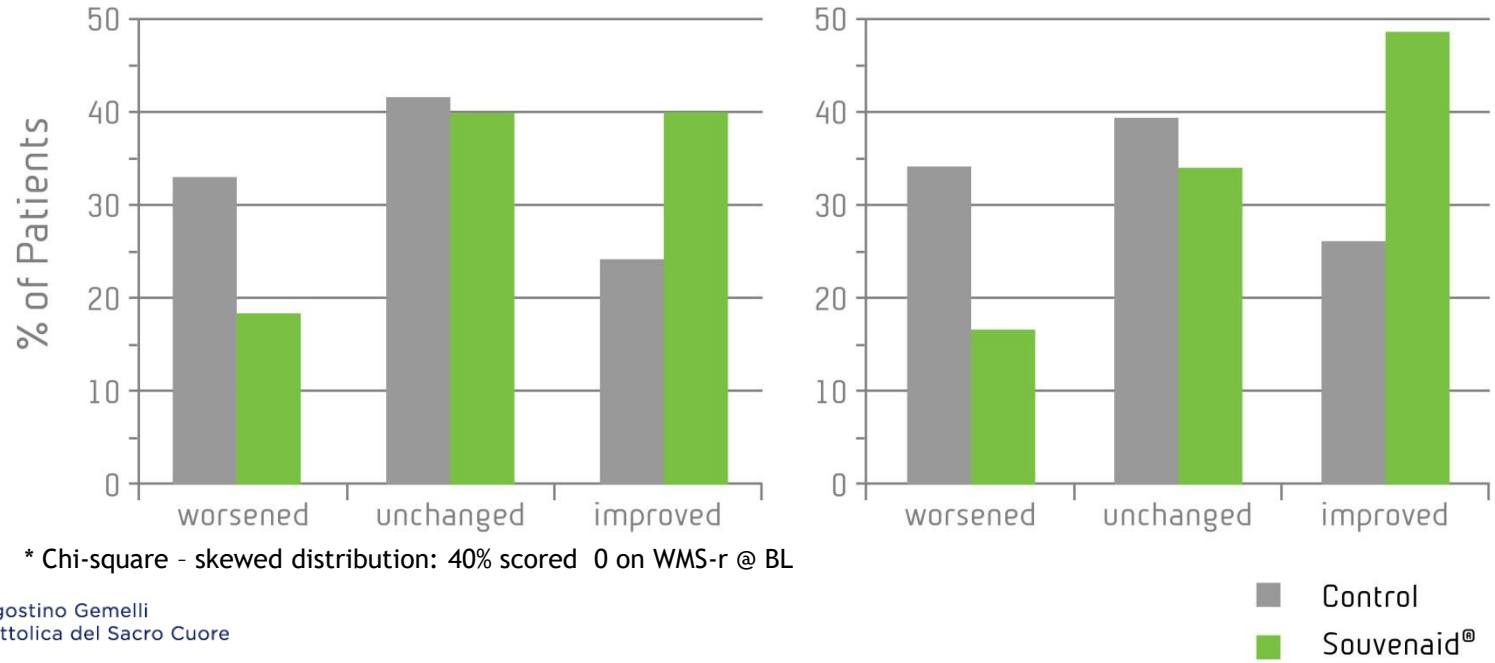
Scheltens et al. *Alzheimers Dement*. 2010;6:1-10.

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

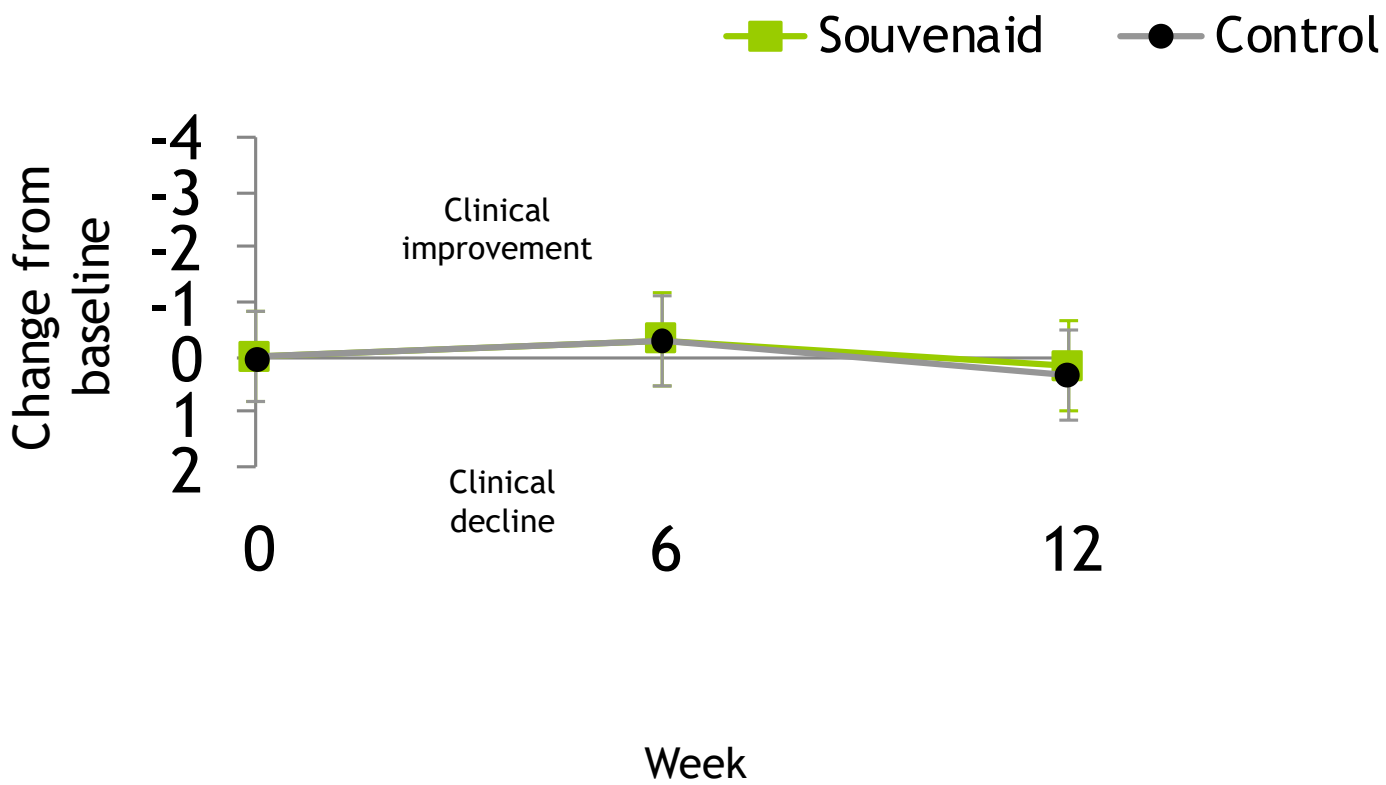
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

Scheltens et al. *Alzheimers Dement*. 2010;6:1-10.

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

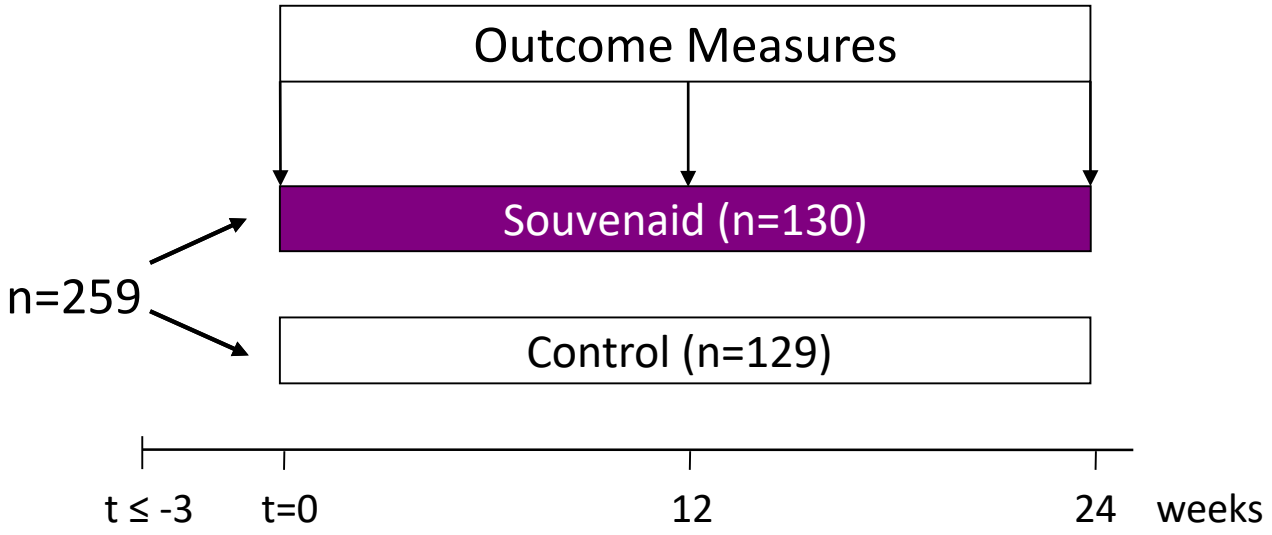
Repeated-Measures Mixed Model analysis



Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Scheltens et al. *Alzheimers Dement*. 2010;6:1-10.

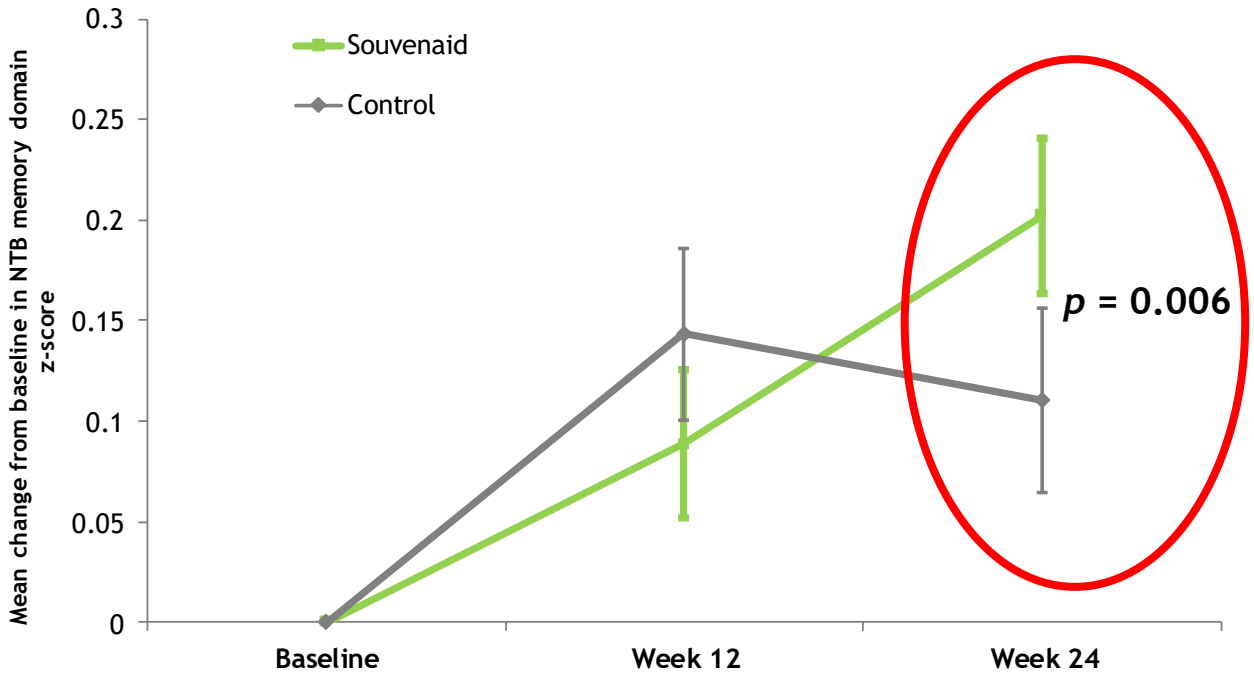
Souvenir II: Design & methodology



- 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

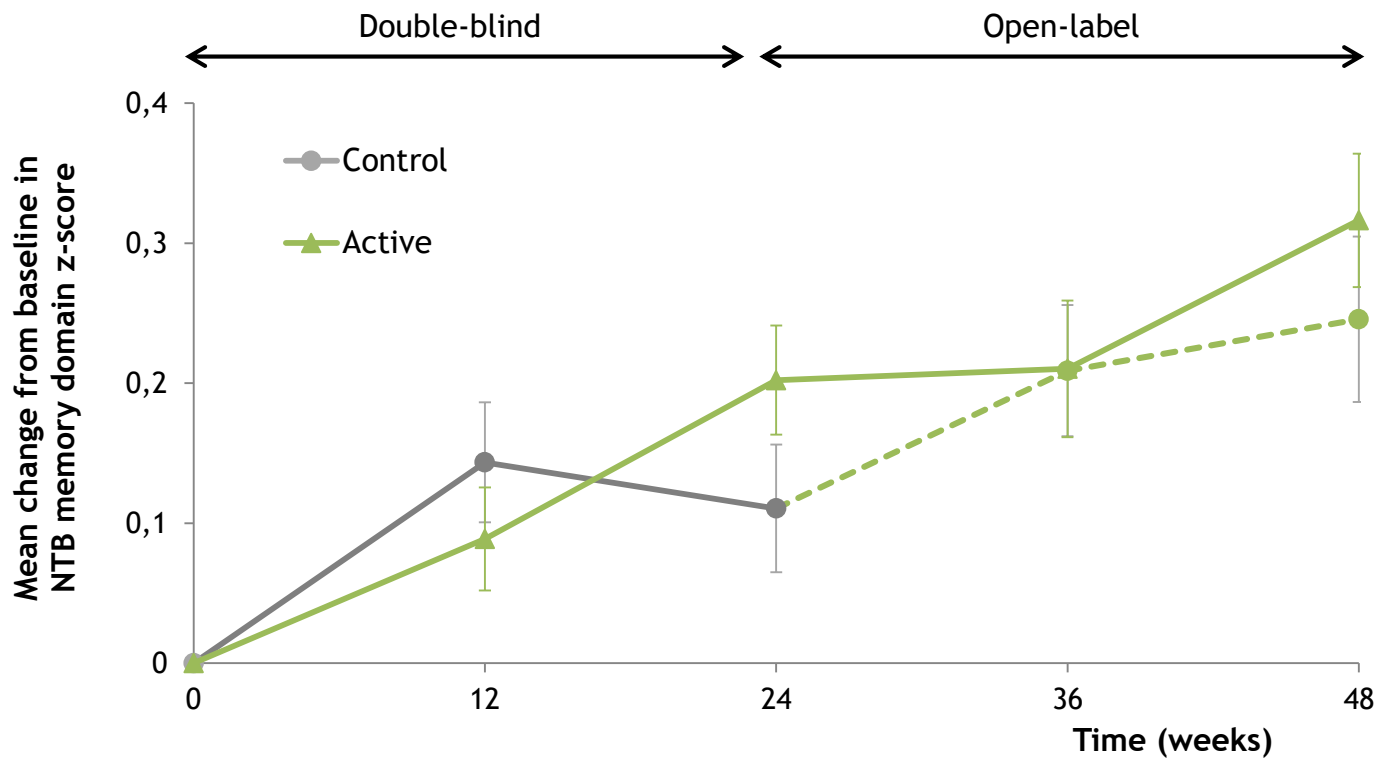
Significant effect* on NTB memory domain over 24 weeks
(whole period trajectory; *p*=0.023)



Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

*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



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

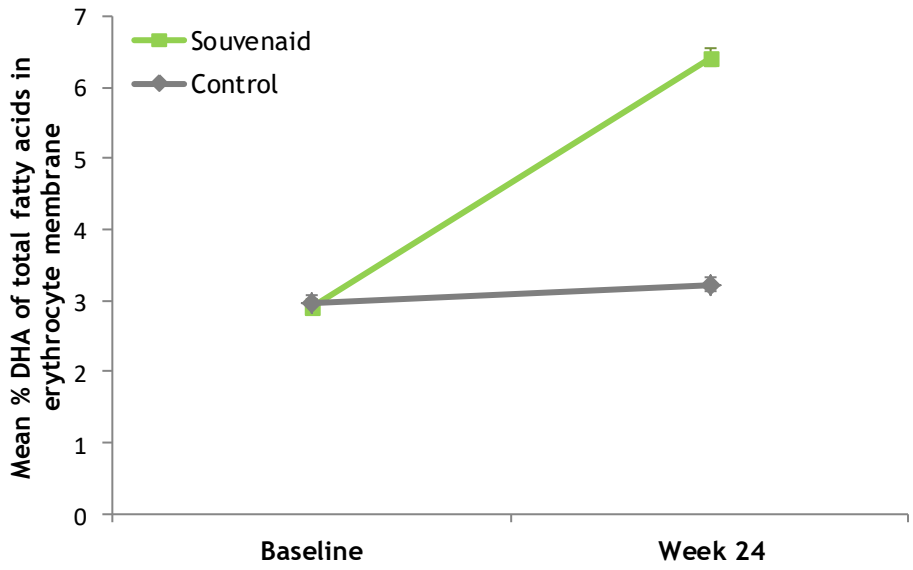
Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

Significant increase from week 24 to week 48 in both groups.
Active - Active: p=0.038
Control - Active: p=0.029

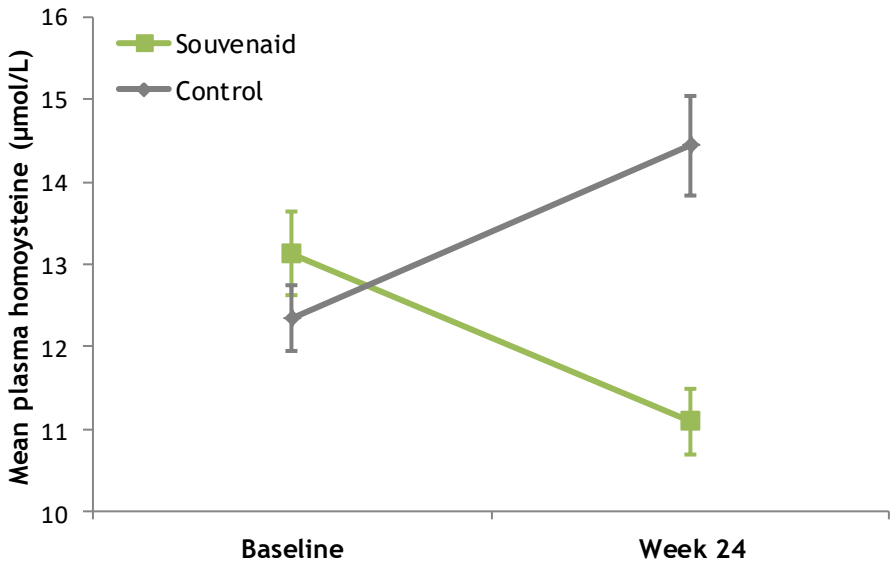
Souvenir II: Positive safety profile and biochemical changes

- 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)

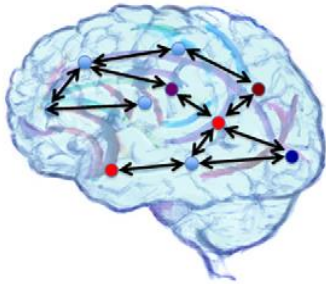


Reduced plasma homocysteine (*p*<0.001)

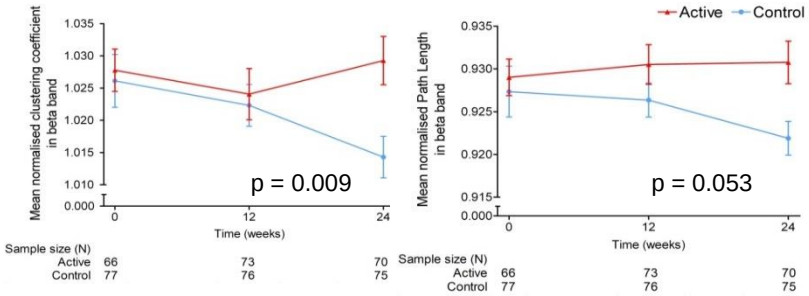


Combined Nutrients increases EEG biomarkers for functional connectivity, derivatives of synaptic activity

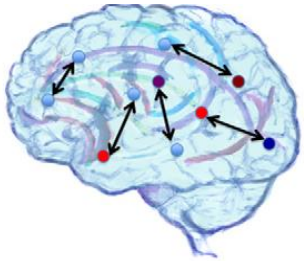
Level 3: network analysis



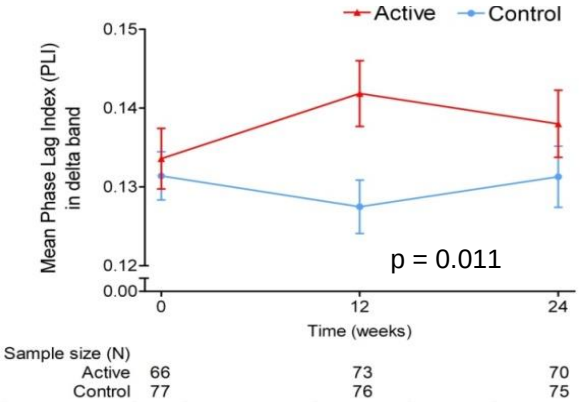
Network organization



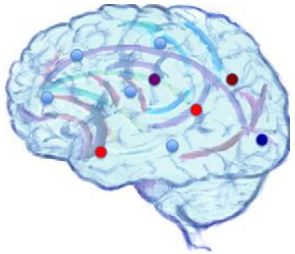
Level 2: connectivity analysis



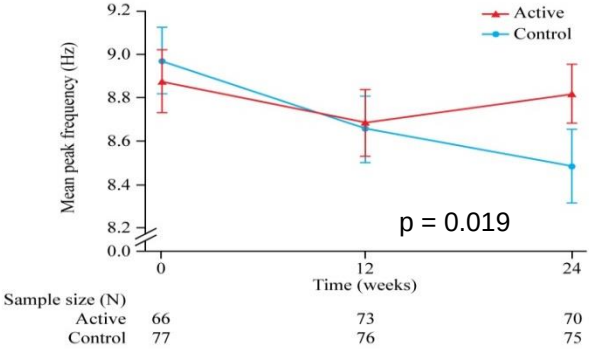
Pair-wise interactions



Level 1: basic signal analysis



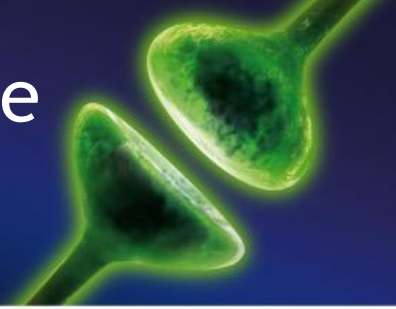
Local activation



Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

PLoS One. 2014 Jan 27;9(1):e86558.

Summary of reasoning – Address the cognitive impairment specific nutrient need



CI 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

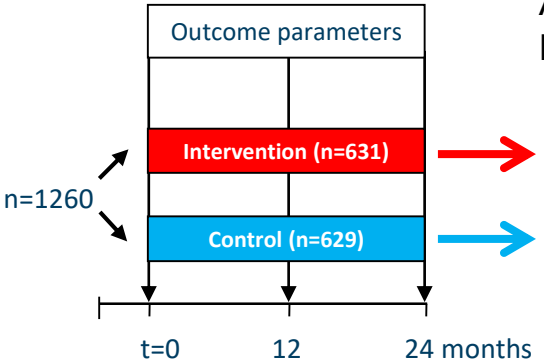
Addressing the nutritional need in CI by increasing intake of dietary precursors and co-factors results in improved memory performance due to enhanced synapse formation & function

FINGER: multidomain intervention can improve or maintain cognitive function in at-risk elderly

THE LANCET
Published online: March 11, 2015
Articles

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

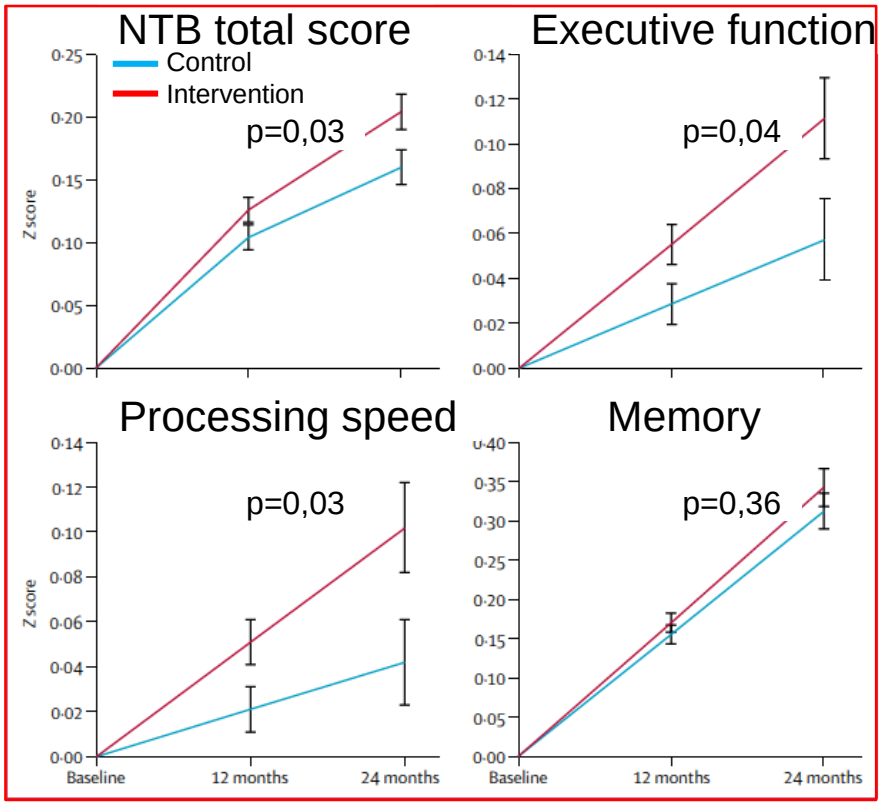
Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto



Age: 69,4
MMSE: 26,7

diet, exercise, cognitive training, vascular risk monitoring

general health advice



Interpretation Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

LIPIDIDIET

24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial

*Hilkka Soininen, Alina Solomon, Pieter Jelle Visser, Suzanne B Hendrix, Kaj Blennow, Miia Kivipelto, Tobias Hartmann, on behalf of the LipiDiDiet clinical study group**

Springfield 2016 Athens, 10 March 2016

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

Lancet Neurol 2017; 16: 965–75

Study centres & investigators

	Study centre	Principal investigator
01	University of Eastern Finland, Kuopio	Prof. Dr. H. Soininen
02	VU University Medical Centre, Amsterdam	Prof. Dr. P. Scheltens
03	Heidelberg University Hospital, Heidelberg	Prof. Dr. J. Schröder
04	Karolinska Institutet, Stockholm	Prof. Dr. L-O. Wahlund
05	Saarland University, Homburg	Prof. Dr. K. Faßbender
06	St. Elisabeth Hospital, Tilburg	Dr. G. Roks
07	Zuwe Hofpoort Hospital, Woerden	Dr. H. Henselmans
08	University of Tubingen, Tübingen	Prof. C. Laske
09	Saarland University, Homburg	Prof. Dr. M. Riemenschneider
10	Central Institute for Mental Health, Mannheim	Prof. Dr. Frölich
11	University Hospital Regensburg, Regensburg	Dr. S. Shiekofer

Prodromal AD:
Novel area for clinical research

LIPIDIDIET

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria[3]

Start pilot study in prodromal AD

LIPIDIDIET

NIA-AA criteria for MCI due to AD[2]

LipiDiDiet RCT results
First clinical trial on nutrition in prodromal AD[1] completed

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria[1]

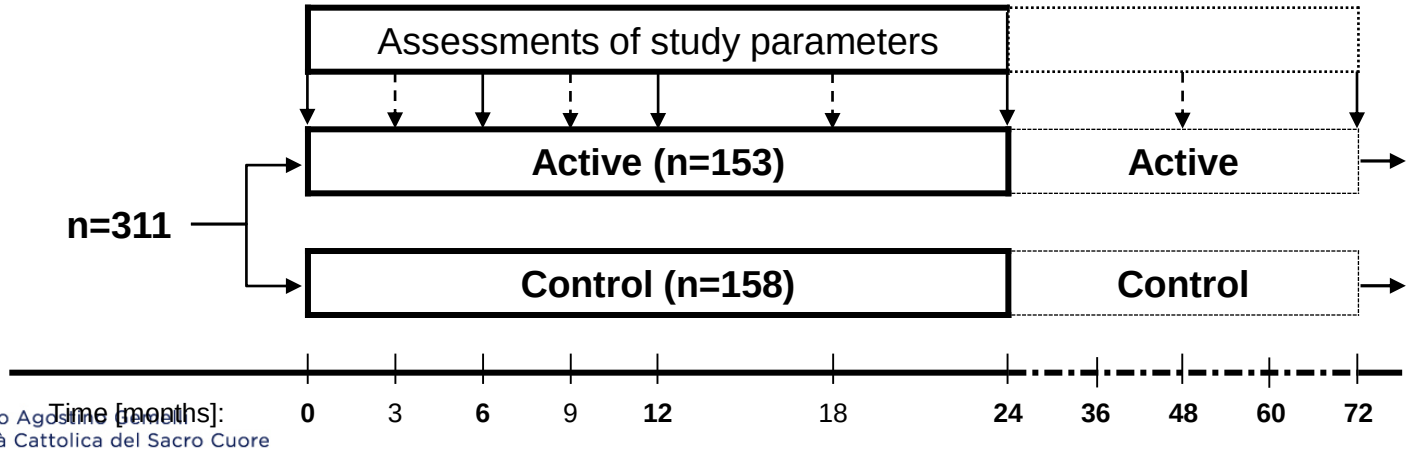
Funding European Commission 7th Framework Programme.

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore
Gemelli

[1]Dubois et al. Lancet Neurol 2007; [2]Albert et al. Alzheimers Dement 2007; [3]Dubois et al. Lancet Neurol 2014

Objective and study design

Objective	Pilot study to investigate the effects of Fortasyn Connect (Souvenaid) in prodromal AD on cognition, function, MRI volumes, progression to dementia, blood and CSF
Study design	**Randomised, controlled, double-blind, parallel-group** Rescue medication allowed after progression to dementia
Subjects	**311 subjects** with **prodromal AD**[1]
Intervention	Active (incl. **Fortasyn Connect**) vs. iso-caloric control, 125 ml daily
Duration	**24 months**
Centres	11 sites in 4 countries
Main assessments	Baseline, 6, 12, 24 months
Optional	4 x 1 year double-blind extension period

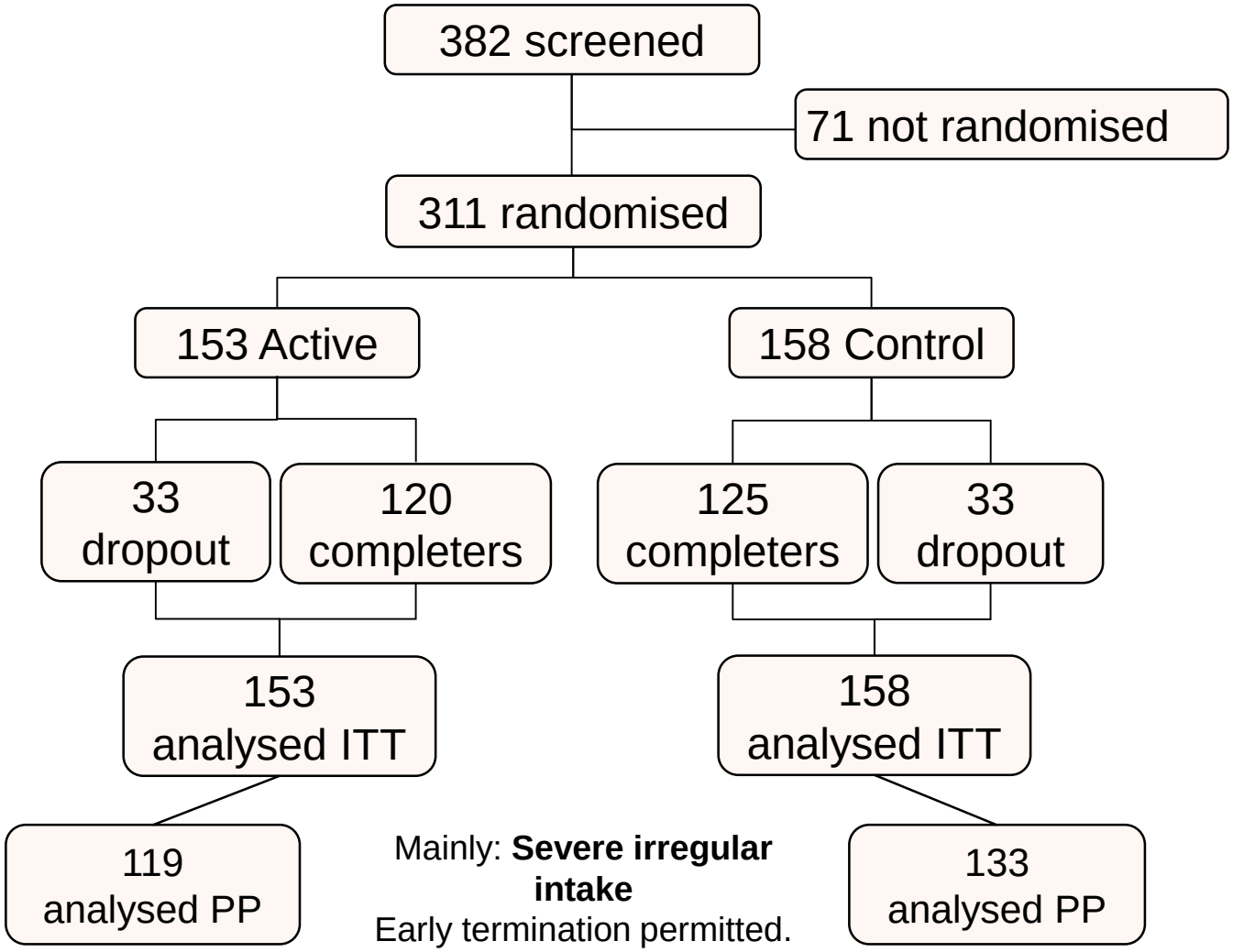


Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli

[1]Dubois et al. Lancet Neurol 2007

Flow chart


382 screened
71 not randomised
311 randomised
153 Active
158 Control
33 dropout
120 completers
125 completers
33 dropout
153 analysed ITT
158 analysed ITT
119 analysed PP
Mainly: **Severe irregular intake**
Early termination permitted.
133 analysed PP

Main inclusion criteria

LIPIDIDIET

1. Subjects with prodromal AD[1] defined by:
   a) Episodic memory disorder *and*
   b) Evidence for underlying AD pathology:
      - Medial temporal lobe atrophy (MTA) ≥ 1 on MRI (82%) *OR*
      - CSF (β-amyloid or tau) (41%) *OR*
      - Abnormal FDG PET (8%)
2. Age 55 - 85 years
3. MMSE ≥ 24*

cation (≤ 6 years) MMSE ≥ 20

[1]Dubois et al. Lancet Neurol 2007

Study outcome parameters

LIPIDIDIET

Primary

- Neuropsychological Test Battery subset: Cognitive function composite z-score:
  - CERAD 10-word list (immediate recall, delayed recall, recognition)
  - Category Fluency
  - Letter Digit Substitution Test

Secondary

- CDR Sum of Boxes*: Combined measure of cognition and function
- MRI brain volumes: whole-brain, total hippocampal, ventricular
- The other NTB composite z-scores: Episodic Memory, Executive function/working memory composite, Total composite (16 subtests)
- Progression to (AD) dementia, analyses ongoing
- Blood and CSF biomarkers, analyses ongoing

Exploratory (several predefined, analyses ongoing)

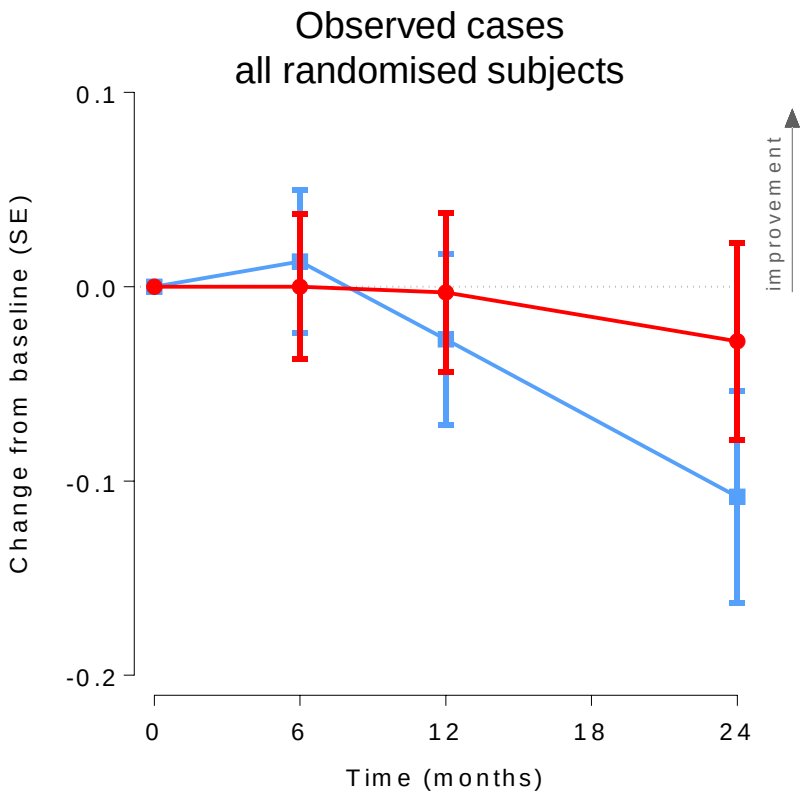
Baseline characteristics

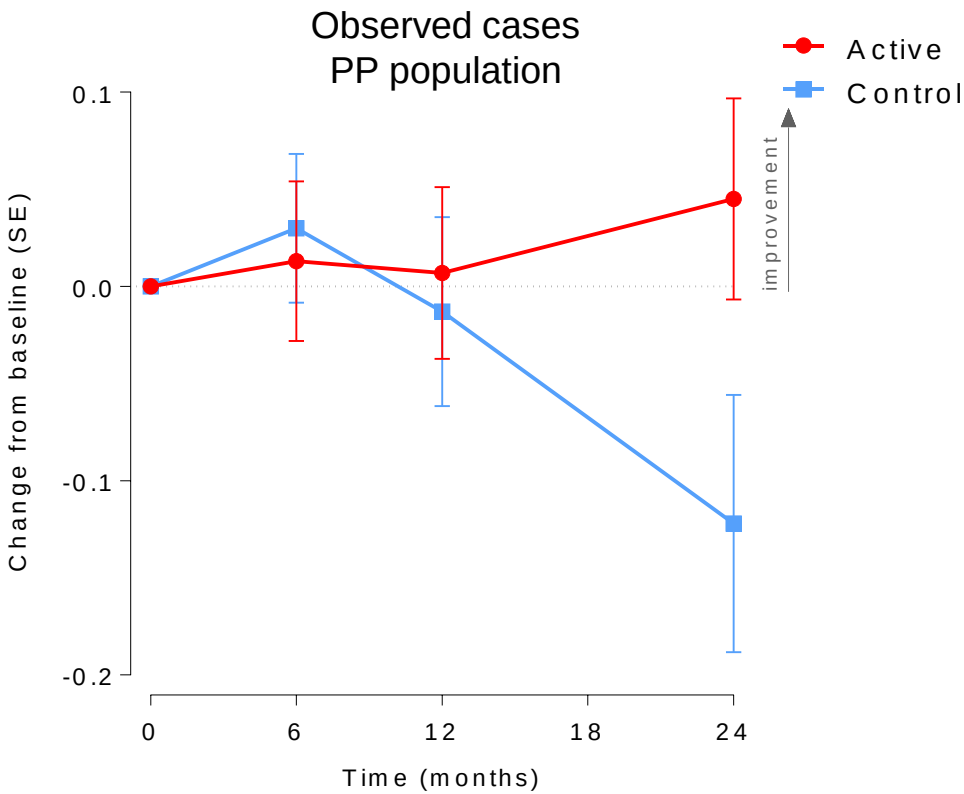
LIPIDIDIET

	Active (n=153)	**Control** (n=158)
Age, yr (SD)	71.3 (7.0)	70.7 (6.2)
Men, n (%)	81 (52.9%)	73 (46.2%)
Years of education (SD)	10.6 (3.9)	10.7 (3.6)
MMSE, total score (SD)	26.4 (2.1)	26.9 (1.9)
APOE ε4 carriers, n (%)	83 (60.1%)	90 (62.9%)
Duration prodromal AD, yr (SD)	0.4 (0.9)	0.4 (0.8)
BMI, kg/m^2 (SD)	26.0 (3.5)	25.9 (4.0)

Primary: 5-item NTB composite z-score
(CERAD 10-word list, Category Fluency, LDST)

LIPIDIDIET





ITT

MM	p=0.166
MMsensitivity	p=0.214

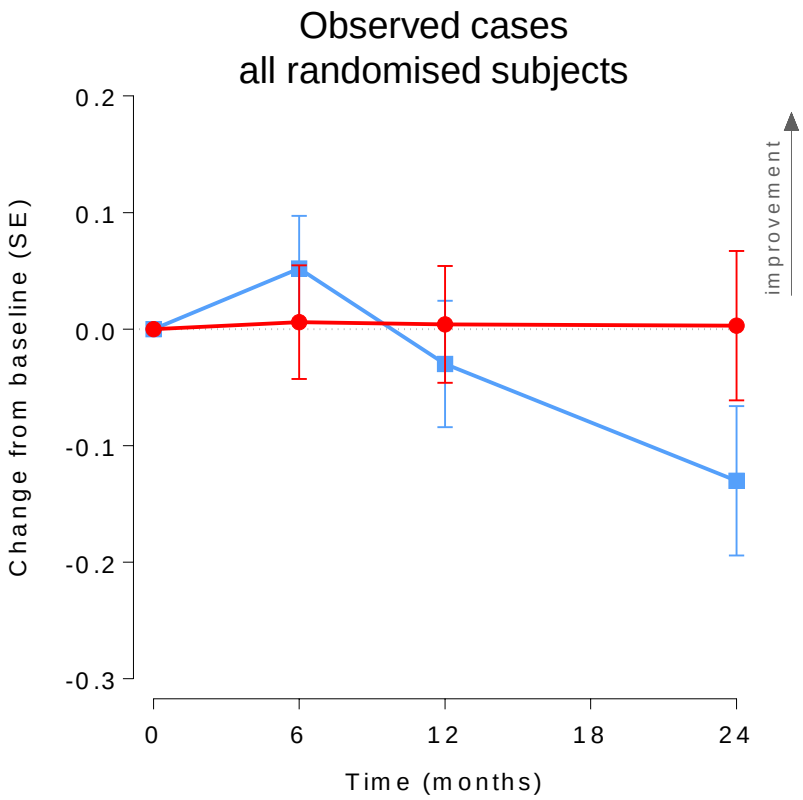
PP

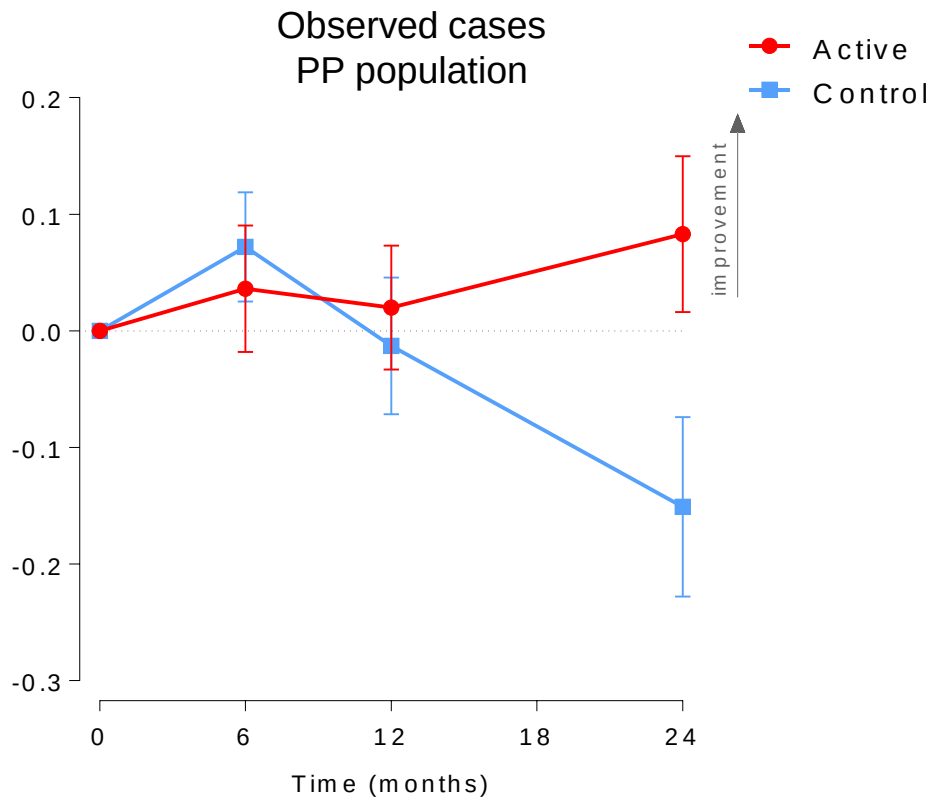
MM	p=0.080
MMsensitivity	p=0.043

Less decline than expected

Observed: -0.11 Expected: -0.40

Secondary: 3-item memory composite z-score (CERAD 10-word list; immediate, delayed, recognition)





ITT

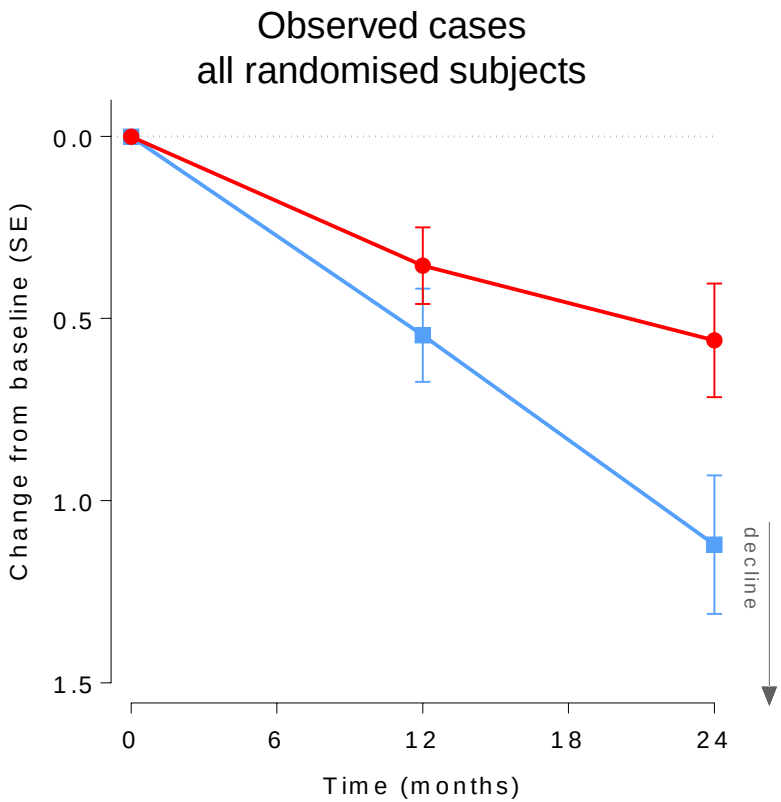
MM	p=0.101
MMsensitivity	p=0.112

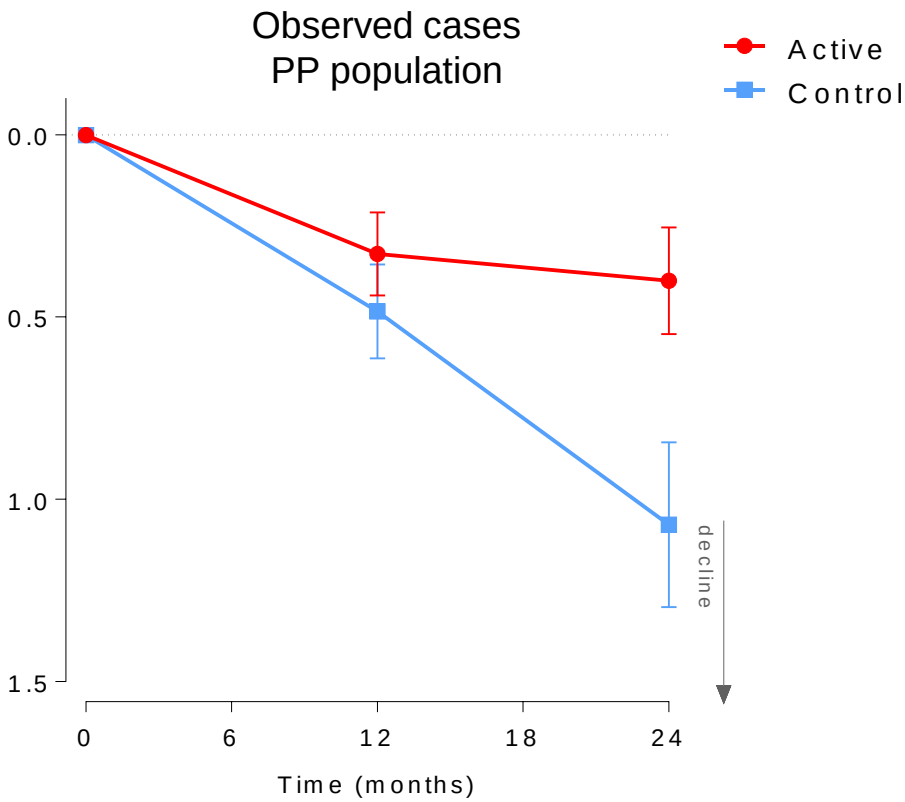
PP

MM	p=0.057
MMsensitivity	p=0.026

Generally, regular intake increased the intervention effects

Secondary: CDR-SB
Combined measure cognition and function





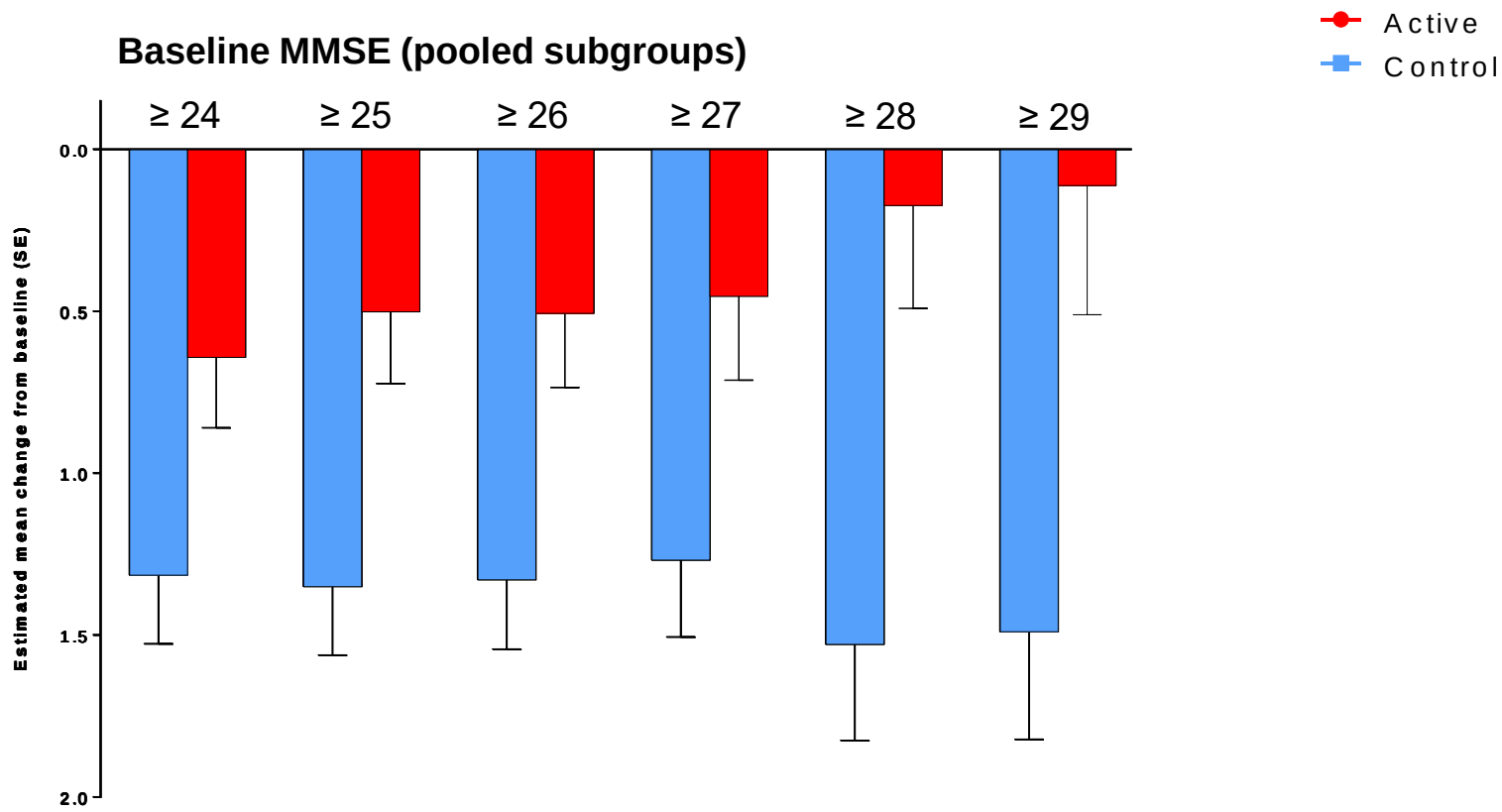
ITT

MM	p=0.005
MMsensitivity	p=0.004

PP

MM	p=0.002
MMsensitivity	p=0.002

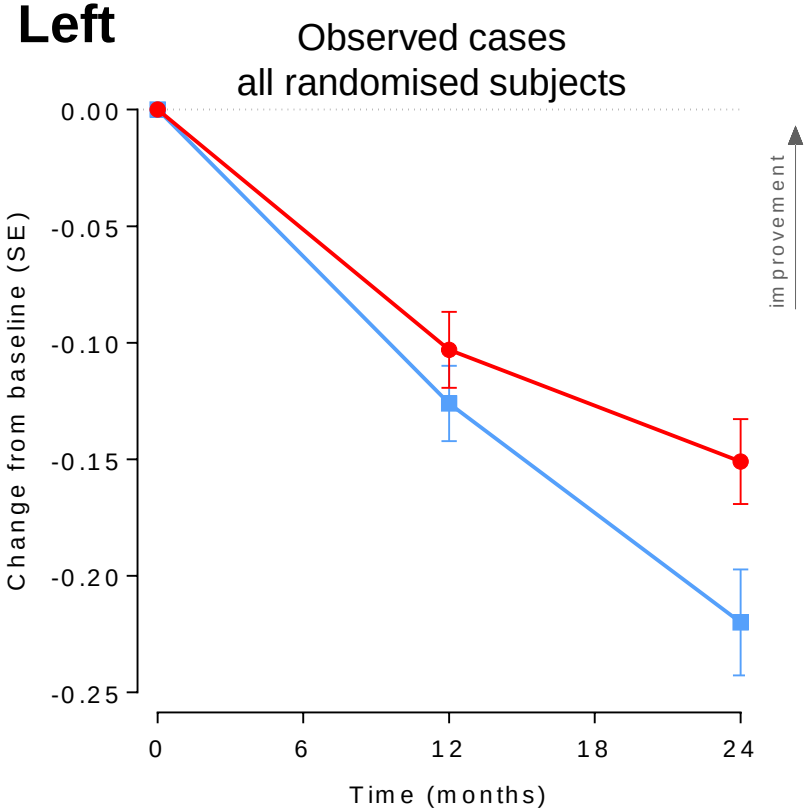
CDR-SB
Baseline MMSE subgroup exploratory analysis



	≥ 24	≥ 25	≥ 26	≥ 27	≥ 28	≥ 29
N control / active	96 / 89	86 / 75	78 / 66	66 / 53	48 / 37	24 / 19
Change from baseline	1.3 / 0.6	1.3 / 0.5	1.3 / 0.5	1.3 / 0.5	1.5 / 0.2	1.5 / 0.1
MM	p=0.004	p=0.0007	p=0.001	p=0.003	p<0.0001	p=0.013

MRI brain volumes
Hippocampal volume - left and right

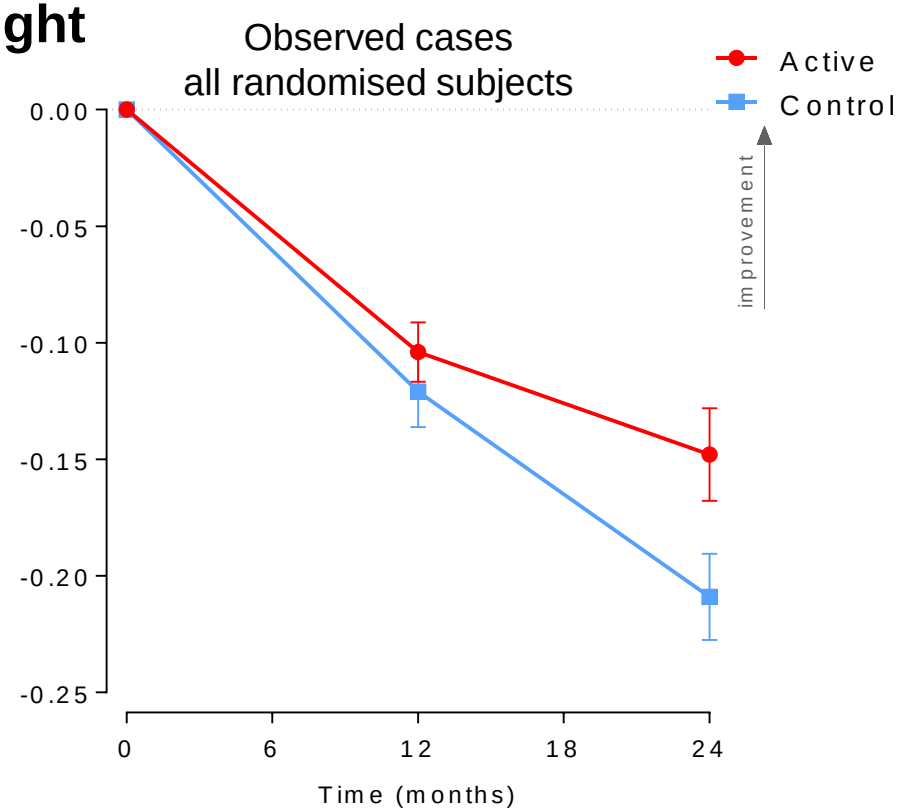
Left



ITT

MM	p=0.017
MMsensitivity	p=0.015

Right



ITT

MM	p=0.007
MMsensitivity	p=0.007

Levels of Homocystein, fatty acids and micronutrients

	Control		Active		*p* value
	Baseline	End of study	Baseline	End of study	
Vitamin B_6 (nM)					
RCT2 (0–24 wk)	45.6 [11.5, 182.3] (45)	42.6 [9.4, 128.0] (41)	37.2 [13.5, 257.2] (37)	59.5 [27.1, 377.4] (36)	<0.001*
OLE (24–48 wk), C-A, A-A			43.0 [12.9, 128.0] (38), 60.3 [27.1, 377.4] (33)	84.9 [44.8, 173.8] (17), 76.8 [33.0, 121.9] (13)	<0.001* (C-A), 0.244* (A-A)
Vitamin E (μM)					
RCT1 (0–24 wk)	31.9 [12.3, 66.2] (104)	30.9 [14.3, 78.5] (74)	33.1 [19.2, 75.2] (104)	39.6 [13.1, 83.6] (74)	<0.001**
RCT2 (0–24 wk)	32.0 [9.2, 70.6] (129)	33.2 [14.4, 61.6] (119)	32.1 [18.0, 71.4] (129)	41.6 [25.7, 73.6] (116)	<0.001*
OLE (24–48 wk), C-A, A-A			32.8 [14.4, 61.6] (103), 41.7 [25.7, 73.6] (96)	40.2 [20.7, 72.4] (93), 41.5 [20.1, 68.6] (88)	<0.001* (C-A), 0.319* (A-A)
RCT3 (0–24 wk)	29.9 [8.5, 99.8] (255)	30.6 [6.0, 78.4] (233)	29.6 [1.8, 84.3] (260)	38.5 [17.1, 109.4] (239)	<0.001
Selenium (μM)					
RCT1 (0–24 wk)	1.1 [0.6-1.8] (73)	1.0 [0.6-1.5] (68)	1.1 [0.6, 2.1] (75)	1.3 [0.7, 2.0] (72)	<0.001**
RCT2 (0–24 wk)	1.1 [0.3, 1.6] (129)	1.1 [0.5, 1.8] (119)	1.1 [0.6, 1.9] (129)	1.4 [0.7, 2.0] (116)	<0.001*
OLE (24–48 wk), C-A, A-A			1.1 [0.5, 1.8] (103), 1.4 [0.7, 2.0] (96)	1.3 [0.8, 1.7] (15), 1.3 [1.1, 1.5] (15)	0.007* (C-A), 0.017* (A-A)
Homocysteine (μM)					
RCT1 (0–24 wk)	11.7 [5.0, 83.0] (104)	12.0 [6.8, 42.1] (74)	12.5 [6.6, 36.7] (104)	9.7 [4.0, 19.1] (74)	<0.001**
RCT2 (0–24 wk)	11.7 [3.9, 28.3] (129)	13.4 [3.3, 38.8] (119)	12.1 [4.4, 37.3] (129)	10.5 [2.3, 20.3] (116)	<0.001*
OLE (24–48 wk), C-A, A-A			13.9 [3.3, 38.8] (103), 10.3 [2.3, 20.3] (96)	9.2 [4.7, 17.1] (93), 9.3 [4.3, 19.0] (86)	<0.001* (C-A), <0.001* (A-A)
RCT3 (0–24 wk)	10.6 [3.9, 100.5] (256)	11.0 [3.5, 102.5] (234)	10.4 [12.8, 50.5] (260)	9.8 [2.0, 46.1] (239)	0.004*

Rijpma *et al. Alzheimer's Research & Therapy* (2015) 7:51
DOI 10.1186/s13195-015-0134-1

alzheimer's research&therapy

RESEARCH Open Access

Effects of Souvenaid on plasma micronutrient levels and fatty acid profiles in mild and mild-to-moderate Alzheimer's disease

Anne Rijpma[1*], Olga Meulenbroek[1], Anneke M. J. van Hees[2], John W. C. Sijben[2], Bruno Vellas[3], Raj C. Shah[4], David A. Bennett[4], Philip Scheltens[5] and Marcel G. M. Olde Rikkert[1]

12-24 weeks supplementation with Fortasyn connect:

Increases the plasma levels of vitamins B (B6, B9, and B12) **selenium and vitamin E** compared to control

Increase levels of EPA and DHA and total fatty acids in erythrocyte membrane

Significantly reduces Homocysteine levels compared to control

Safety

Journal of Alzheimer's Disease 44 (2015) 471–480
DOI 10.3233/JAD-141305
IOS Press

Tolerability and Safety of Souvenaid in Patients with Mild Alzheimer's Disease: Results of Multi-Center, 24-Week, Open-Label Extension Study

Safety

Table 2
Number (%) of patients experiencing one or more AEs, by affected body system†

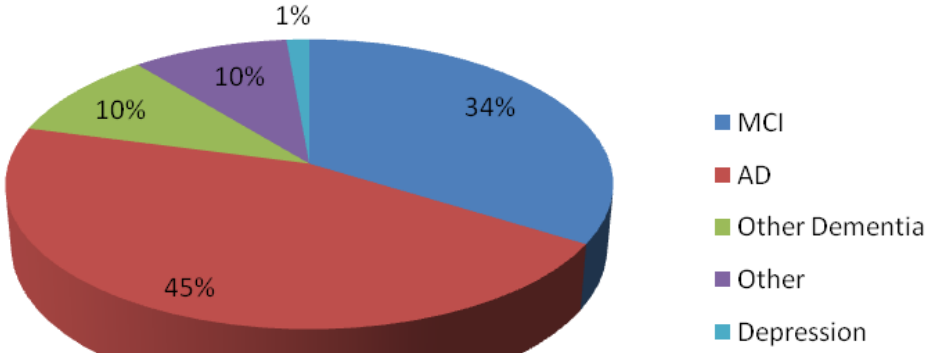
Body system (example AEs)	Control ($n=129$) RCT	Control-Active ($n=104$) OLE	Active ($n=129$) RCT	Active-Active ($n=97$) OLE
Body as a whole (back pain, syncope, fatigue)	20 (15.5%)	13 (12.5%)	11 (8.5%)	9 (9.3%)
Central and peripheral nervous system disorders (dizziness/vertigo, headache)	18 (14.0%)	7 (6.7%)	11 (8.5%)	9 (9.3%)
Gastrointestinal system disorders (diarrhea, dyspepsia, constipation, flatulence)	30 (23.3%)	10 (9.6%)	22 (17.1%)	10 (10.3%)
Metabolic and nutritional disorders (hypercholesterolemia, weight decrease, weight increase)	9 (7.0%)	3 (2.9%)	13 (10.1%)	6 (6.2%)
Musculo-skeletal system disorders (fracture, myalgia, skeletal pain)	9 (7.0%)	7 (6.7%)	10 (7.8%)	5 (5.2%)
Psychiatric disorders (aggressive reaction, anorexia, anxiety, depression)	16 (12.4%)	14 (13.5%)	15 (11.6%)	7 (7.2%)
Respiratory system disorders (bronchitis, pharyngitis)	15 (11.6%)	6 (5.8%)	10 (7.8%)	1 (1.0%)
Other (fall, surgical intervention)	8 (6.2%)	7 (6.7%)	8 (6.2%)	3 (3.1%)

Progetto Memento

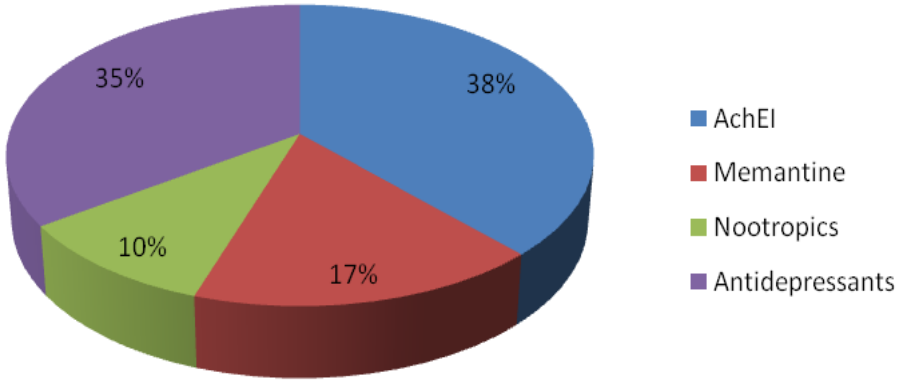
Results from a caregiver survey (real-world, 510 pts)

- Objective to assess the impact of Souvenaid on patients with cognitive impairment in a ‘real-world’ setting
- Total number of patients: 510 (female: 58,5%) recruited in 30 AD clinics in Italy
- Age: 76.0 y (+/- 6,9), range 50-99y
- Open label observation survey in patients taking Souvenaid for a mean of 4,02 months (range 2-33)

Diagnosis



Other medications



Gemelli

Methods and analysis

- Interview of caregivers and patients at the follow-up visit after taking Souvenaid for at least three months
- A structured interview was used to explore the modification of cognitive, behavioral and functional domains in a ‘real life’ situation

Domain	Caregiver interview	Patient interview
Behaviour	1. apathy/interest 2. agitation/irritability 3. sleep 4. eating behavior	1. depression complaints
Function	1. household activities/hobbies 2. outdoor activities 3. books/newspaper reading	1. household activities/hobbies
Cognition	1. remember appointments commitments dates 2. identify persons/remember names 3. orientation in new place	1. subjective memory 2. orientation in and out home

The answers were standardized using a hierarchical scale:

- 1: worsened, 2: slightly worsened, 3: unchanged, 4: slightly improved, 5: improved
- A single domain score and a global score were calculated for the analysis

Memento survey: conclusions

- Souvenaid is well tolerated in clinical practice (only 6.5% of patients discontinued)
- Following 3 months of Souvenaid, between 27% and 47% of caregivers reported an improvement, mainly in memory and apathy
- In the same time period, 36% and 43% of patients reported an improvement in the same domains
- The best results were seen in patients with **MCI** (compared to AD), in subjects with **higher MMSE scores** at baseline and in those who took Souvenaid for a **longer time period**

Take Home Message

- Cognitive impairment (MCI, AD) 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 MCI and early stage of AD
- This offers a nutritional approach to support patients with brain failure