Associazione Geriatri Extraospedalieri

ASSOCIAZIONE ITALIANA PSICOGERIATRIA

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

SIGOT

CONVENGNO CONGIUNTO AGE AIP SIGOT SIGG

La GERIATRIA in EMILIA ROMAGNA 2017: La demenza in Ospedale

Il trattamento della persona con demenza in ospedale

Supplementi nutrizionali nell'MCI

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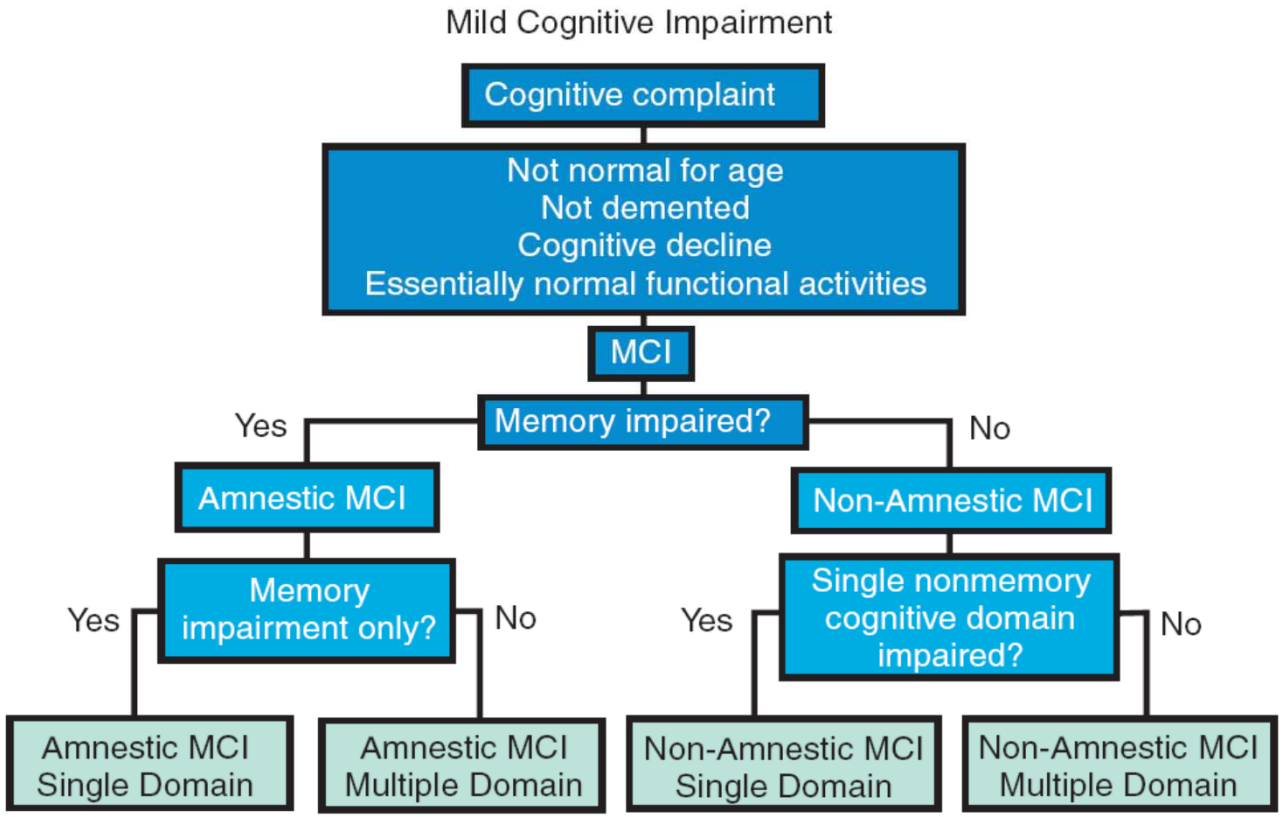
Dipartimento Medico ad Attività Integrata – OSPFE

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Università di Ferrara
- ex labore fructus -

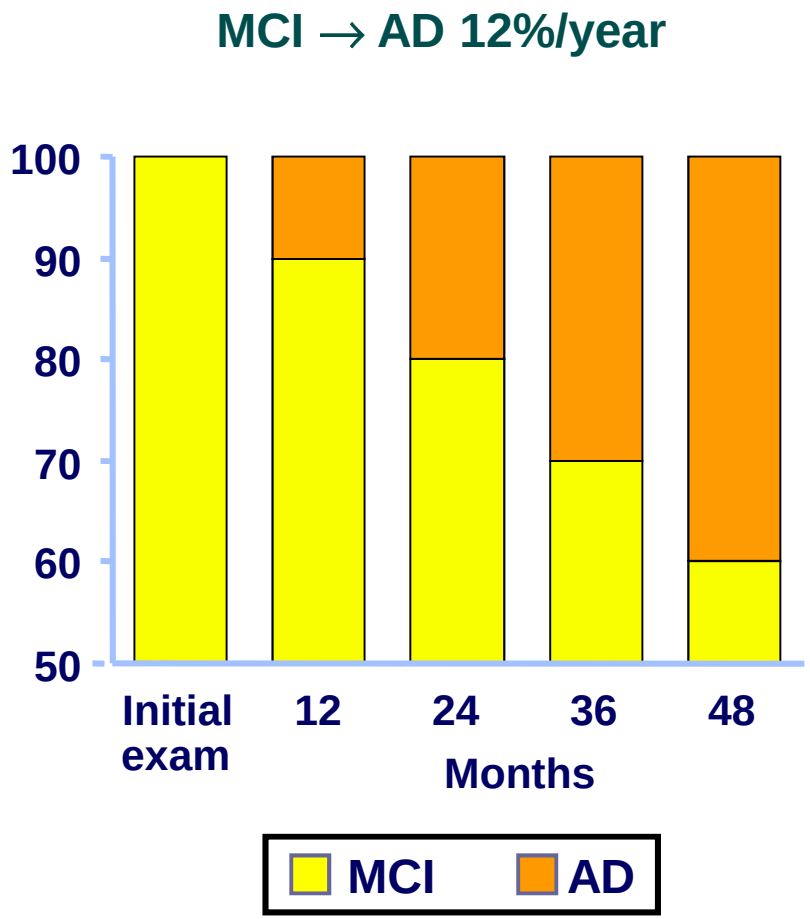
Mild Cognitive Impairment: definition

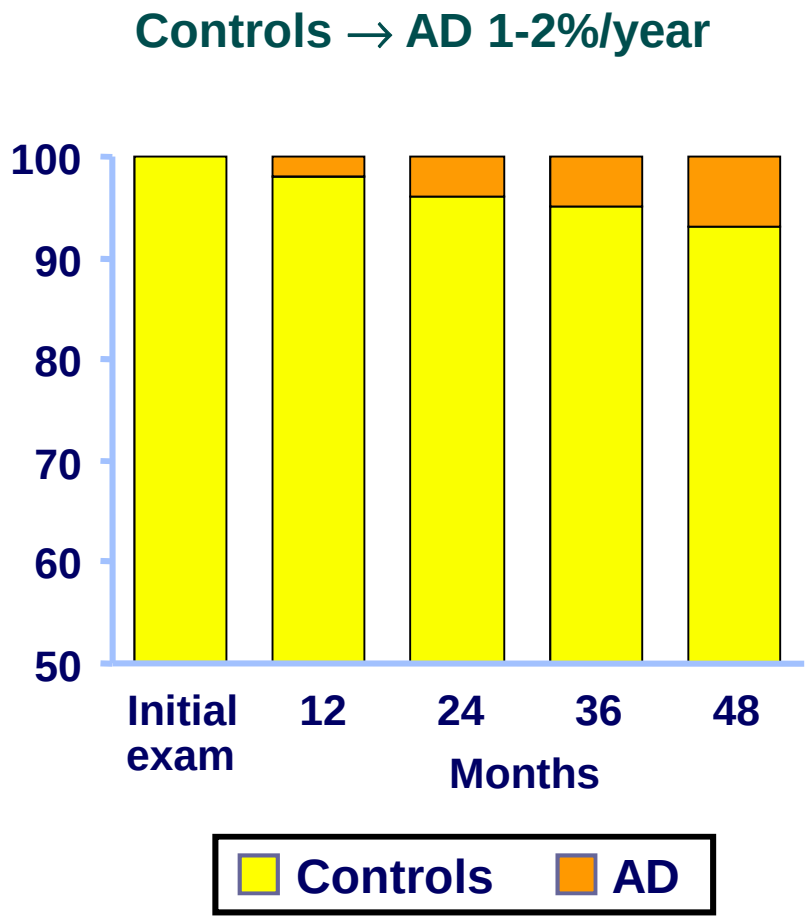
(Mild neurocognitive disorder DSM-5)



Petersen RC Journal of Internal Medicine 2004; 256: 183–194

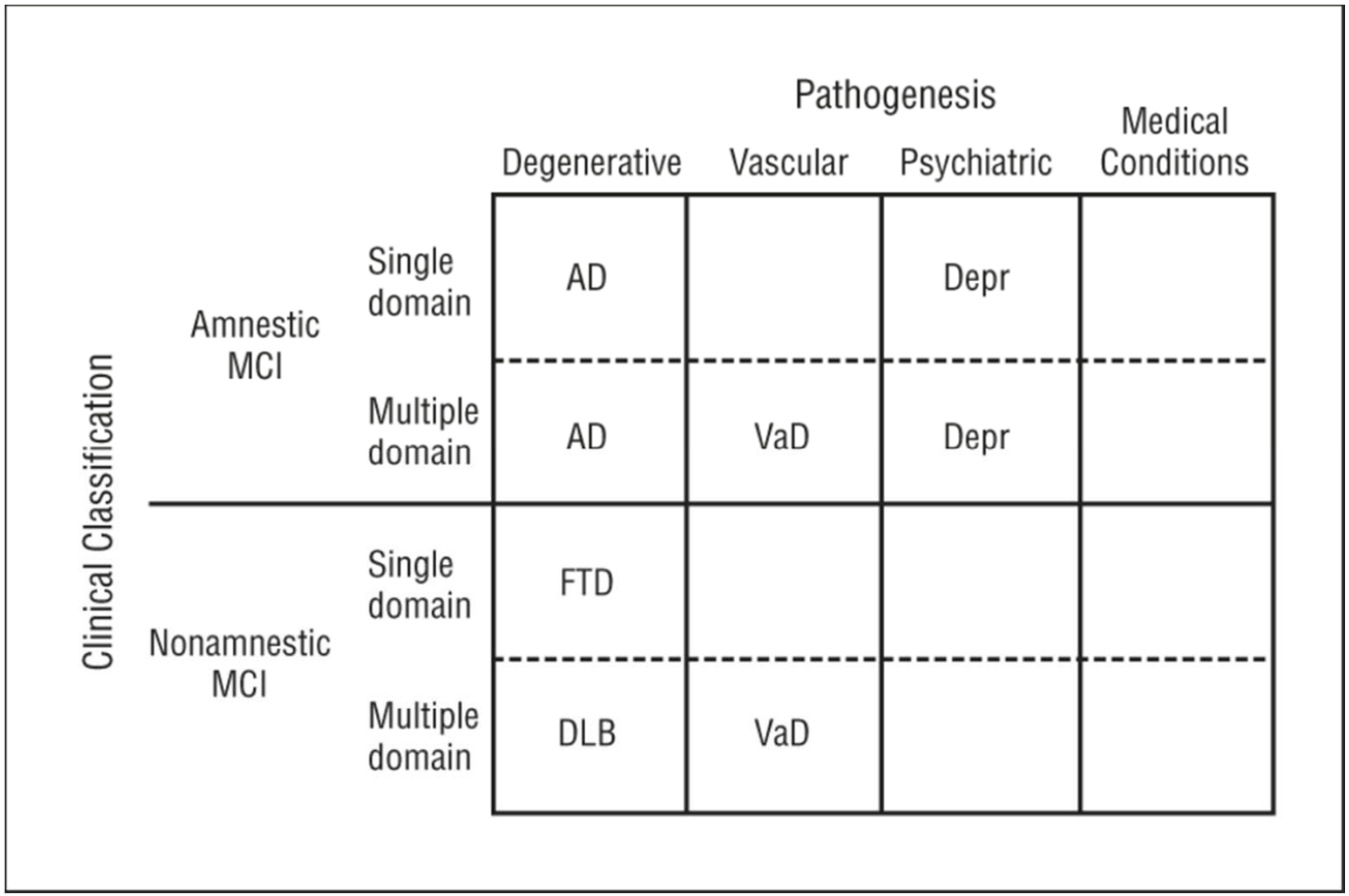
MCI & mNCD: Natural History





Petersen RC et al: Arch Neurol 56:303-308, 1999

Classification and Pathogenesis



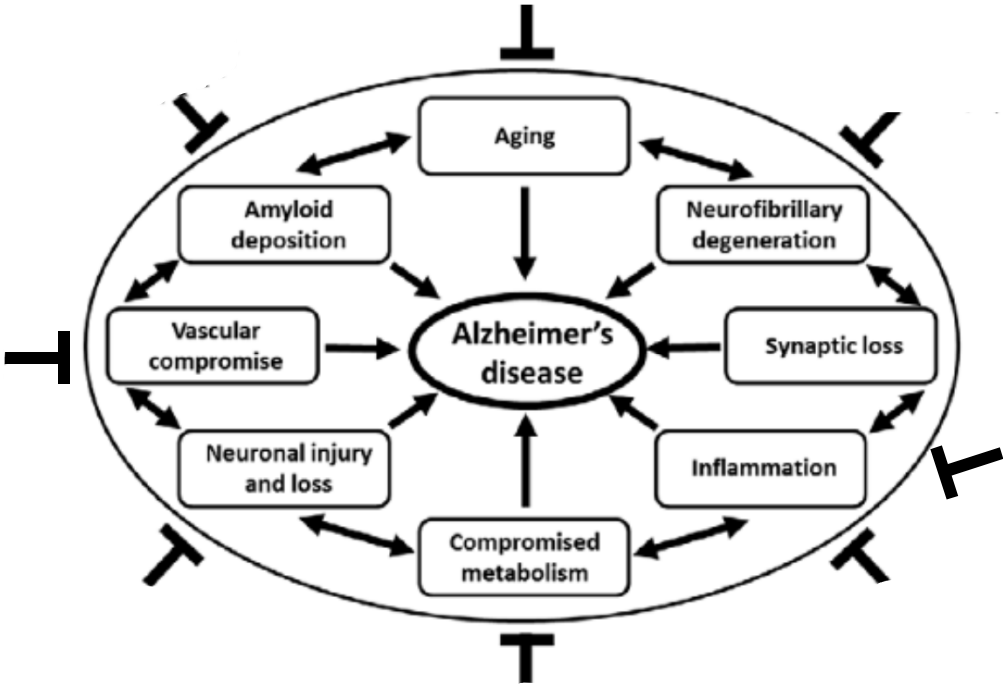
Petersen RC Journal of Internal Medicine 2004; 256: 183–194

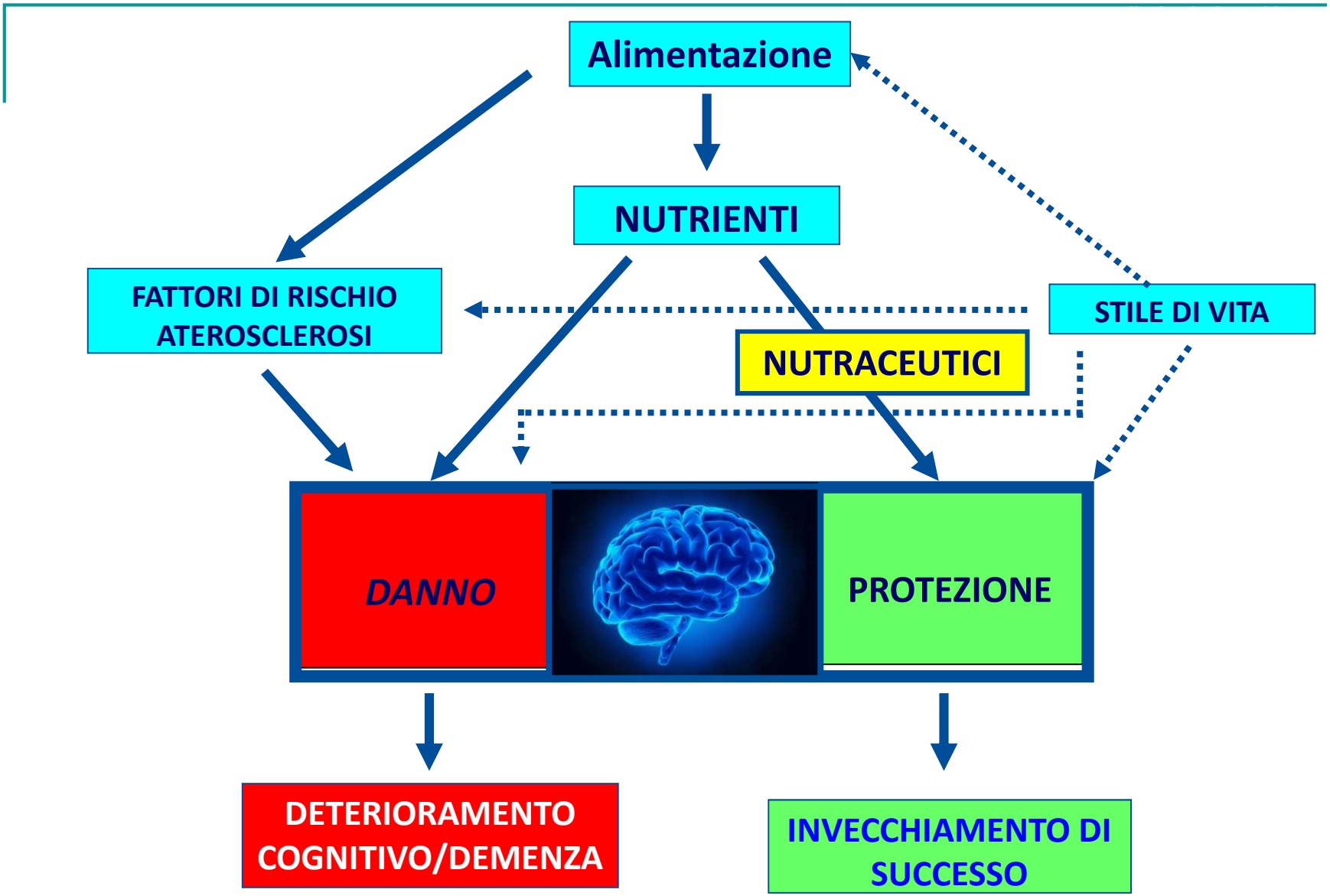
frontiers in
AGING NEUROSCIENCE

REVIEW ARTICLE
published: 20 October 2014
doi: 10.3389/fnagi.2014.00282

Nutrition and prevention of Alzheimer's dementia

*Arun Swaminathan and Gregory A. Jicha**




Alimentazione
NUTRIENTI
FATTORI DI RISCHIO
ATEROSCLEROSI
STILE DI VITA
NUTRACEUTICI
DANNO
PROTEZIONE
DETERIORAMENTO
COGNITIVO/DEMENZA
INVECCHIAMENTO DI
SUCCESSO

Potential useful nutrients

- ✓ Acidi grassi omega 3
- ✓ Vitamine e antiossidanti
- ✓ Ginkgo biloba
- ✓ Ashwagandha
- ✓ Resveratrolo
- ✓ Huperzia serrata
- ✓ Curcumina
- ✓ Illumina (bacopa monnieri)
- ✓ Tè verde
- ✓ Agent AC-1202
- ✓ Palmitoiletanolamide
- ✓ Colina
- ✓ Omotaurina
- ✓ Alcool
- ✓ Dieta Mediterranea
- ✓ Combination medical food

- ✓ Acidi grassi omega 3
- ✓ Vitamine e antiossidanti
- ✓ Palmitoiletanolamide
- ✓ Colina
- ✓ Dieta Mediterranea
- ✓ Combination medical foods

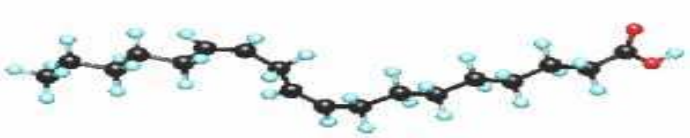
Acidi Grassi

Saturi

Palmitico (16:0)

Stearico (18:0)

Insaturi



Polinsaturi

Omega-6 (n-6)

Ac. Linoleico (18:2)

Arachidonico (20:4)

Omega-3 (n-3)

Ac. α-Linolenico (18:3)

Eicosapentenoico (20:5) (EPA)

Docosaexenoico (22:6) (DHA)

Monoinsaturi

Omega-9 (n-9)

Ac. Oleico (18:1)

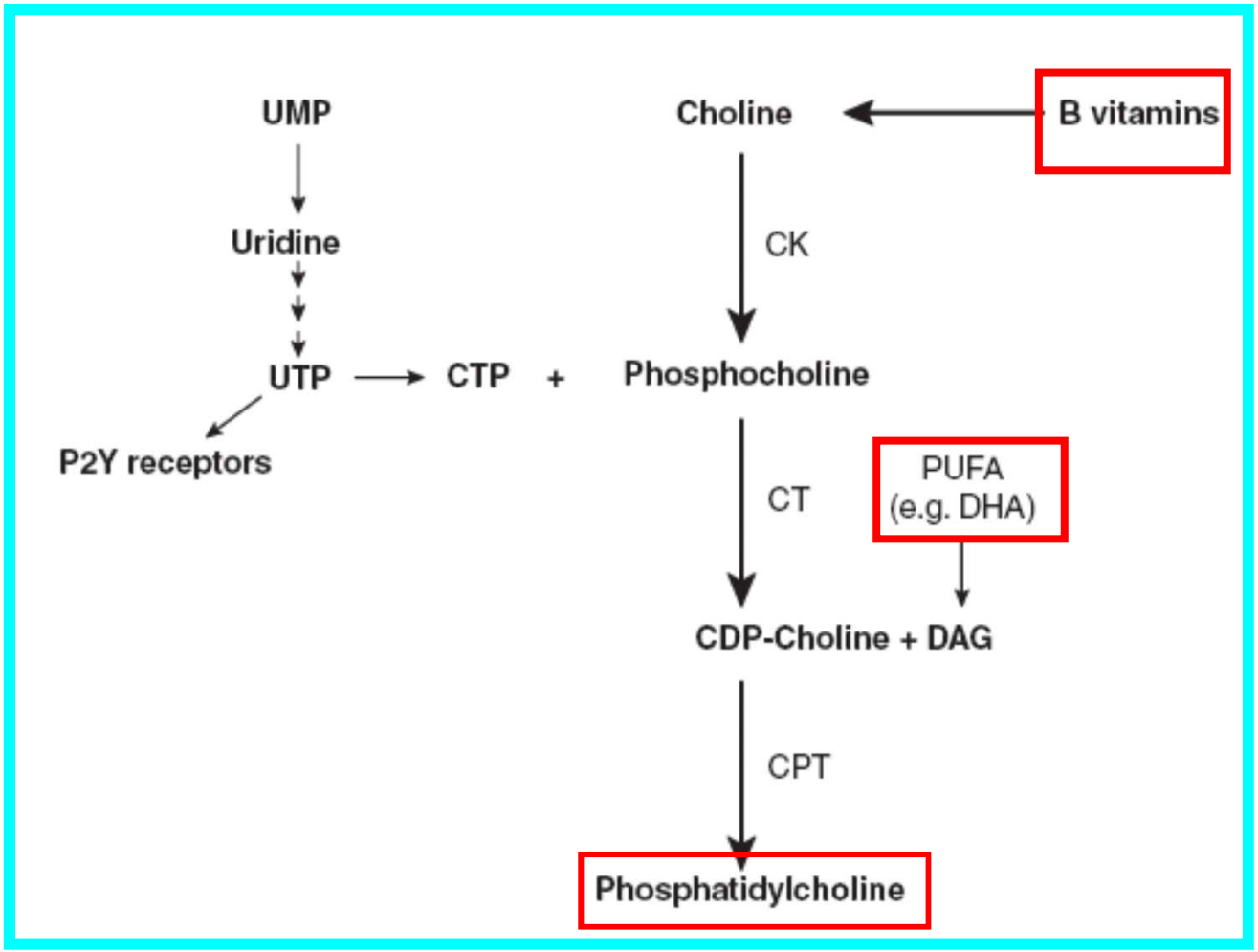
ACIDI GRASSI & SISTEMA NERVOSO CENTRALE

- Il SNC ha la **2° maggiore concentrazione di lipidi** dopo il tessuto adiposo

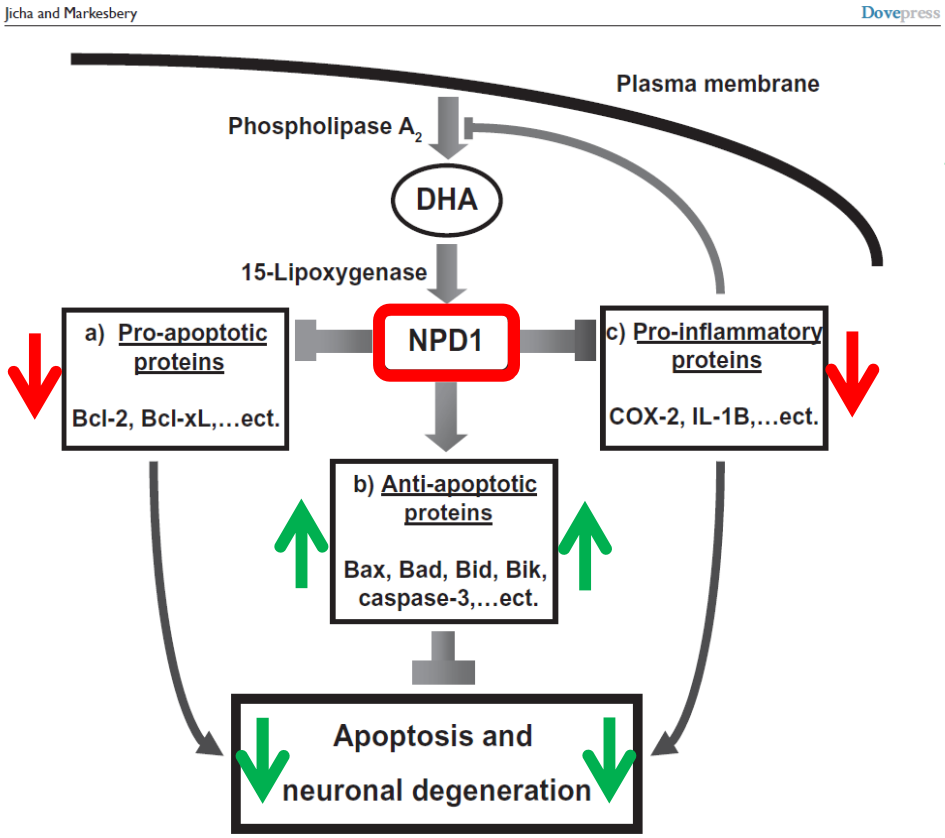
- I fosfolipidi della membrana neuronale e della mielina contengono quantità elevate di **acido Arachidonico** e **Docosaexenoico (DHA)**

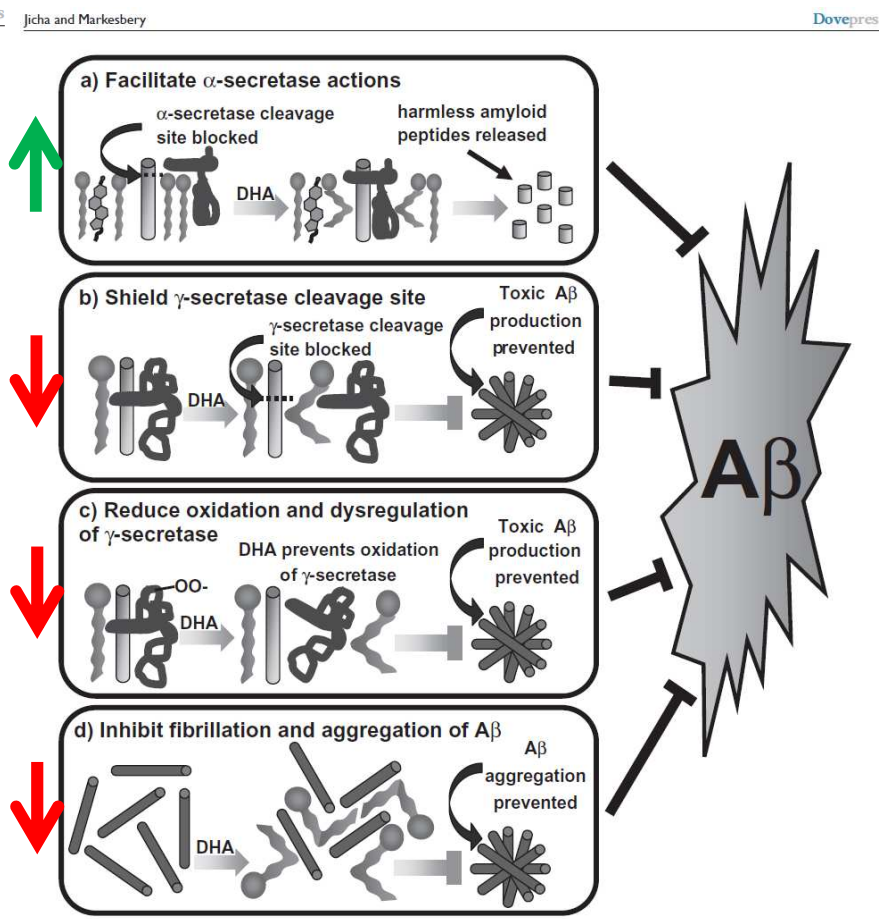
- Il **contributo della dieta sembra fondamentale** poichè la capacità di sintesi di EPA e DHA è bassa, è variabile tra individuo e individuo e può declinare ulteriormente con l'età.

Sintesi della Fosfatidilcolina



n-3 PUFA: attività anti-apoptotica/anti infiammatoria e produzione di Beta-Amiloide



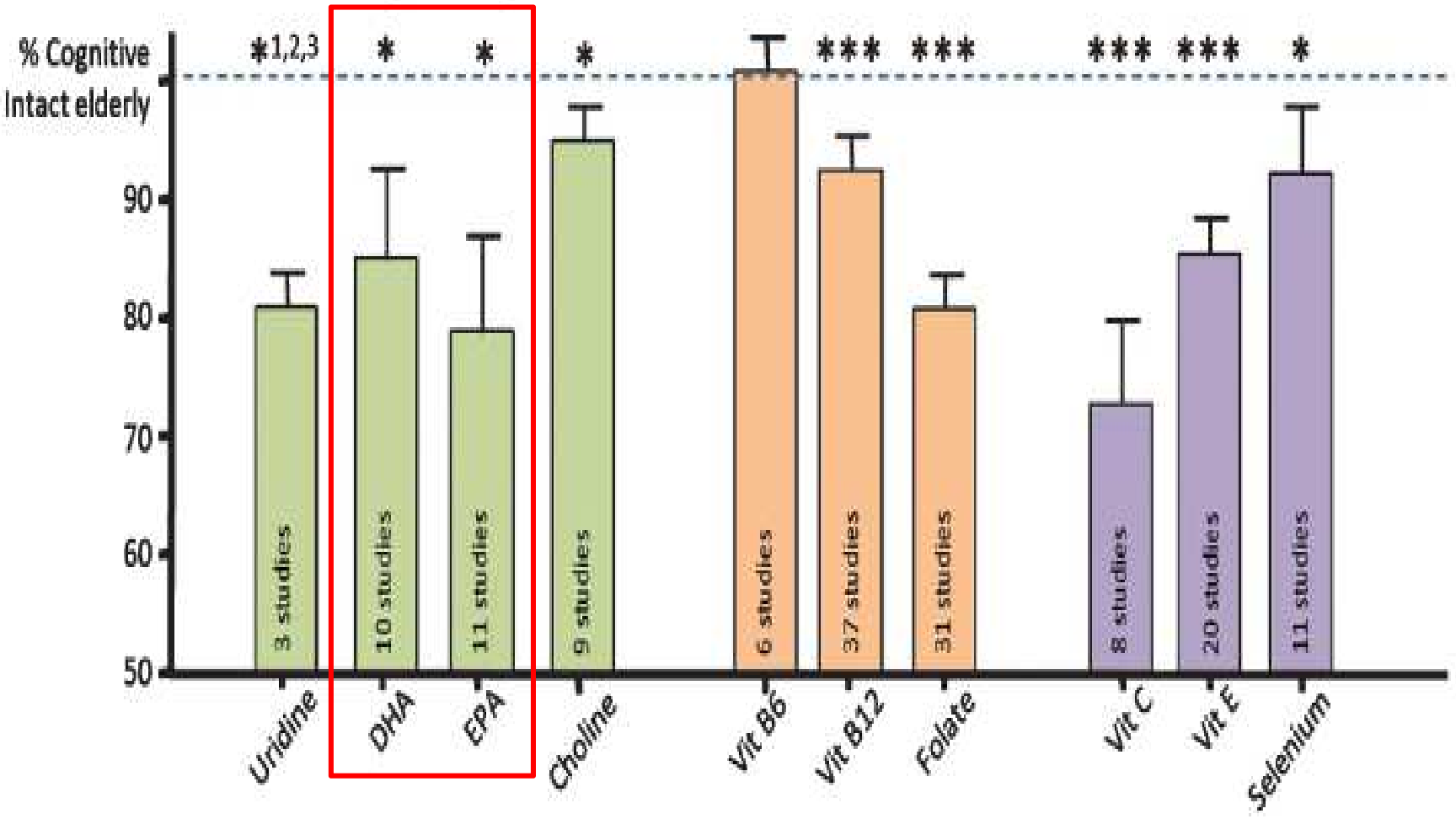


NPD1: neuroprotectin1

DHA: Docosaexenoico

Plasma nutrient status in AD

Meta-analyses, systematic review and observations



DHA: Docosaexenoico

EPA: Eicosapentenoico

da Silva SL et al. Alzheimer's & Dementia 2014

Omega-3 fatty acids and cognitive decline: observational studies

Study	Population	Methods	Findings	Other
Kalmijn et al. 1997 (70)	Zutphen N=476 men, 64-89 yrs	Diet history, MMSE	Fish intake reduced in 153 impaired men, but n-3 not associated with 3 yr cognitive decline	Fish intake inversely correlated with cognitive decline (adjusted OR = 0.45, $p = 0.09$); Linoleic Acid raised risk.
Kalmijn et al. 1997 (71)	Rotterdam, N=5,386, 55+ yrs	Diet history, dementia	High fish, RR (D)=0.4; RR (AD)=0.3	Saturated fat and cholesterol increased risk
Morris et al., 2003 (72)	Chicago, N=815 unimpaired, 65-94 yrs	Diet history, 2.3 yr follow-up test for AD	131/ 815 developed AD, 60% less risk of AD with fish	DHA but not EPA associated with low AD risk
Kalmijn et al., 2004 (73)	Zutphen N=1,613, 45-70 yrs,	Diet history, Cog testing	High n-3 reduces risk of cognitive impairment	Cholesterol and sat. fat increased risk
Morris et al., 2005 (74)	Chicago, N=3,718 65+, mean 74 yrs	Diet history, Cog testing	Fish consumption associated with reduced cognitive decline over 6 yrs	No clear association with n-3 intake
Huang et al., 2005 (75)	Boston	Diet history, Dementia/ AD	Fish consumption reduces AD risk by 41%, dementia by 28%	Risk reduction only in non-ApoE4
Nurk et al., 2007 (76)	Norway, N=2031, 70-74 yrs	Diet history, Cog testing	Less than 10 g/ day fish intake predicts poor Cog performance	Most Cog function improved dose-dependently up to 75 g/ d fish
Barberger-Gateauet al. 2007 (77)	France, 3-City, n=8,085, Non-demented, 65+	Diet history, 4 yr follow-up, Dementia/AD	281 dementia (183 AD) Fish reduced dementia (HR=0.46) and AD (HR=0.65)	Fish only protective for AD in non-ApoE4 (HR=0.60)
van Gelder et al. 2007 (78)	Zutphen, (N=210, men 70-89 yrs)	Diet history, 5 yr follow-up, MMSE	~400 mg/day DHA+EPA associates with reduced decline	Dose-dependent effect

Cole MG. et al. Prostaglandins Leukot Essent Fatty Acids 2009

Omega 3 fatty acid for the prevention of cognitive decline and dementia (Review)

Sydenham E, Dangour AD, Lim WS

Cochrane Database Syst Rev. 2012

Authors' conclusions

Direct evidence on the effect of omega-3 PUFA on incident dementia is lacking. The available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people. Omega-3 PUFA supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.

Further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

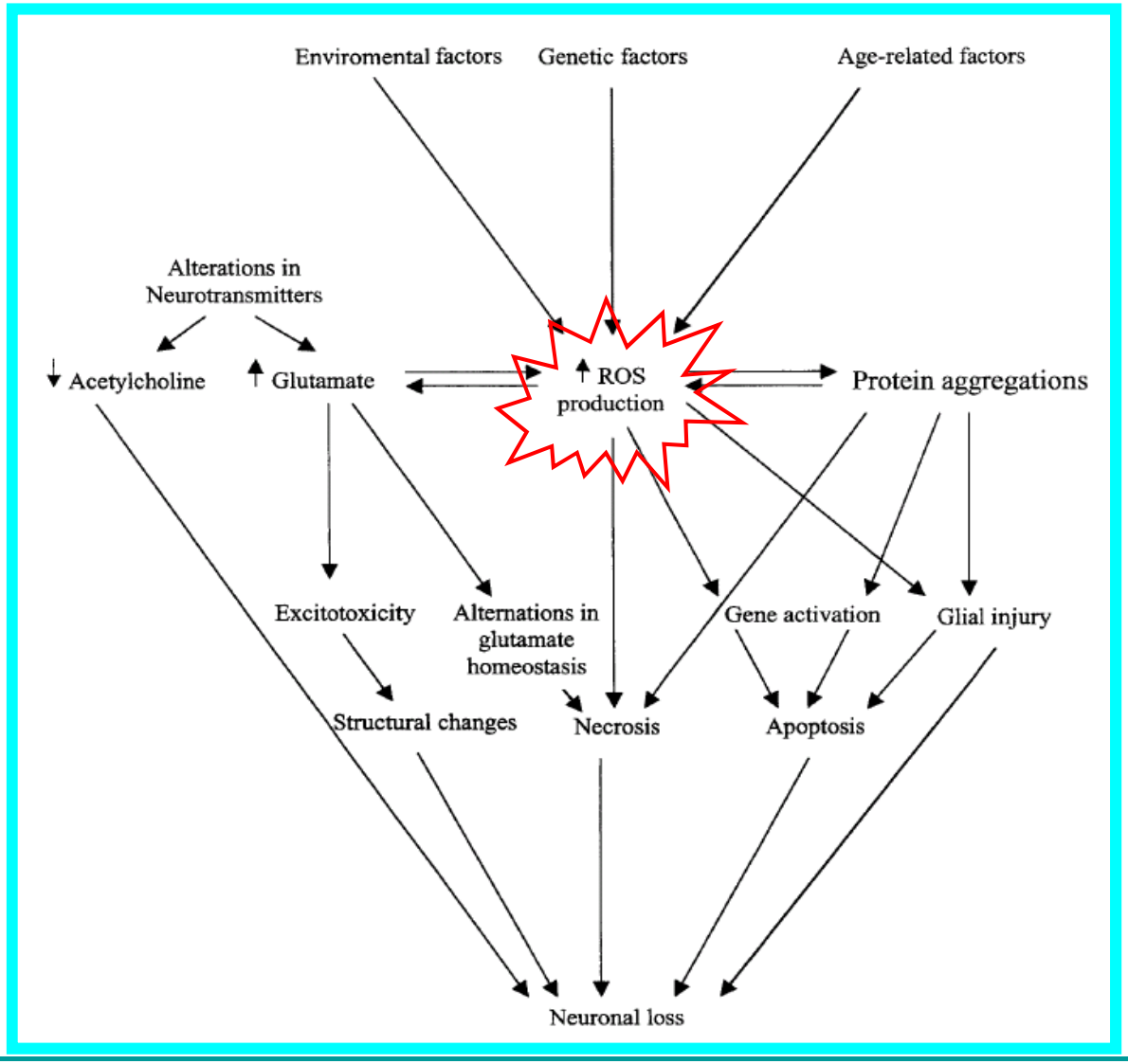
THE COCHRANE COLLABORATION®

Summary of DHA/EPA dietary intervention trials in patients with mild cognitive impairment

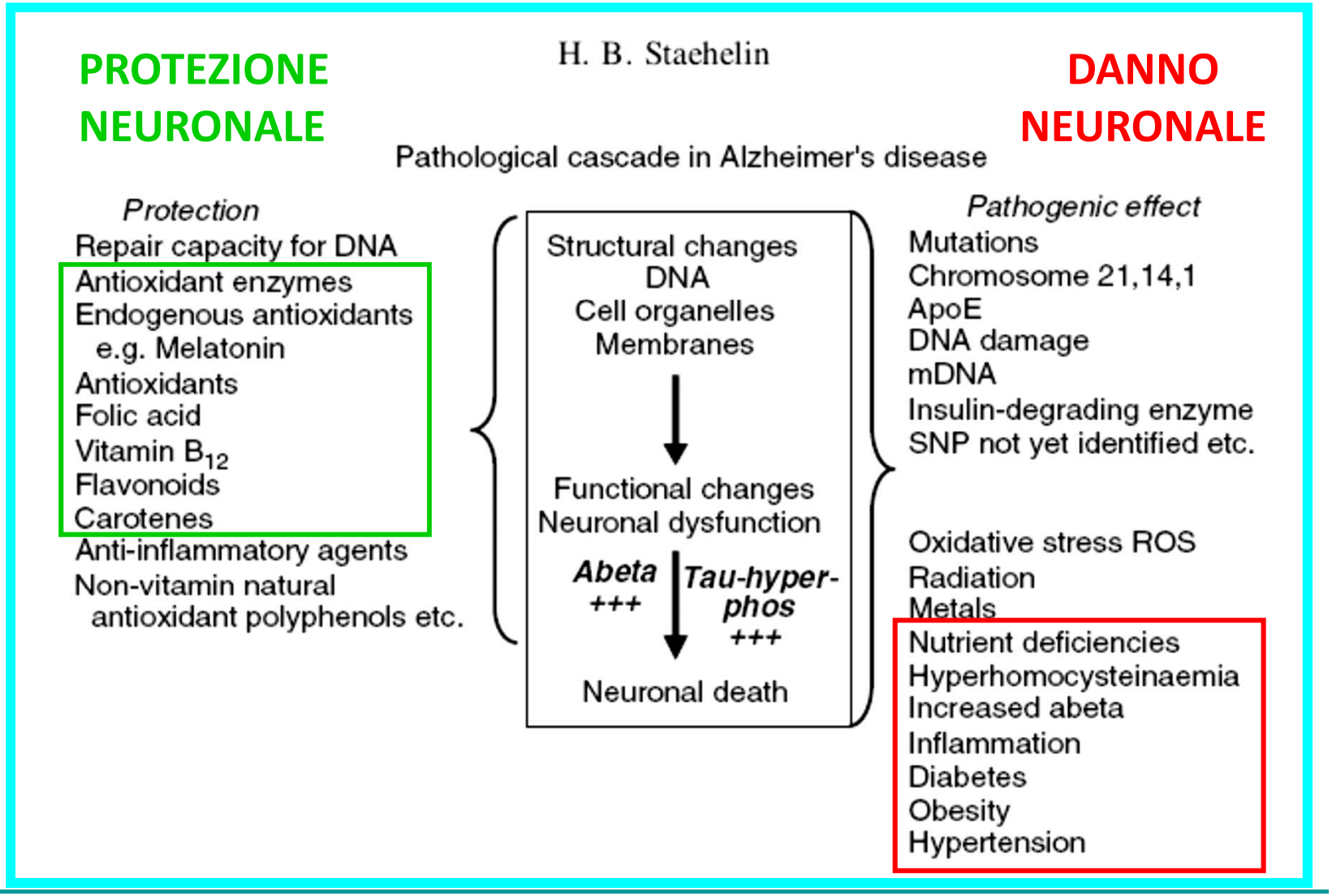
Reference	Clinical trials with MCI patients (n, mean age)	Dosage of DHA/EPA per day	Trial duration and design	Measures	Outcome
[15]	Patients with MCI (23, 74 yrs)	0.72 g DHA + 1.08 g EPA or placebo	6 mths randomized double-blinded placebo-controlled trials	ADAS-cog.; CIBIC plus	Significant improvement in ADAS-cog; in patients with MCI after omega-3 supplementation
[16]	Patients with MCI (23, 68 yrs)	240 mg DHA + 240 mg AA or placebo	3 mths, placebo controlled trial	Japanese version of RBANS (5 cognitive domains)	Improvement of immediate memory and attention in omega-3 supplemented group
[17]	Elderly persons with MCI (36, 66 yrs)	1.3 g DHA + 0.45 mg of EPA or placebo	12 mths, randomized double-blinded placebo controlled trial	RAVLT, MMSE, CDT, WAIS-R	Significant improvement in cognitive function in omega-3 supplemented group
[18]	Elderly patients suffering from MCI (11, 85 yrs)	1.4 g DHA + 572 g EPA or placebo	3 mths, randomized double-blinded placebo controlled trial	MMSE	Significant improvement in MMSE, semantic verbal fluency, and olfactory sensitivity assessment in omega-3 supplemented group
[19]	Older people with MCI (100, 74 yrs)	180 mg DHA + 120 mg EPA or placebo	6 mths, randomized double-blinded placebo controlled trial	MMSE, AMT	Low prescription dose had no effect on cognitive function in omega-3 supplemented group

Thomas J et a.. BioMed Research International 2015

Oxidative stress and cognitive decline

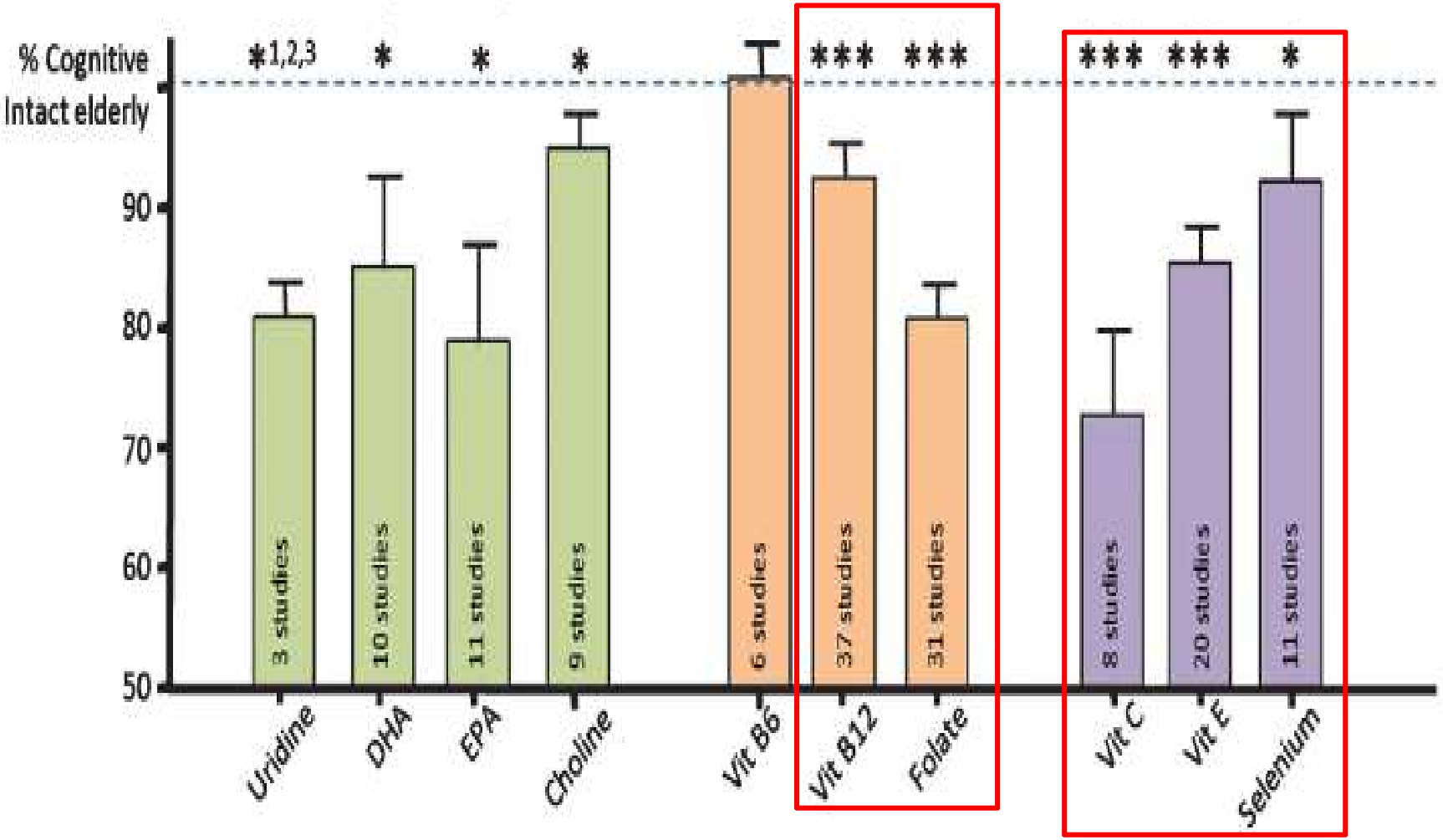


Oxidative stress and cognitive decline



Plasma nutrient status in AD

Meta-analyses, systematic review and observations



da Silva SL et al. Alzheimer's & Dementia 2014

B-vitamin deficiency causes hyperhomocysteinemia and vascular cognitive impairment in mice

Aron M. Troen*, Melissa Shea-Budgell, Barbara Shukitt-Hale, Donald E. Smith, Jacob Selhub, and Irwin H. Rosenberg

Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, 711 Washington Street, Boston, MA 02111-1524

Communicated by Leon E. Rosenberg, Princeton University, Princeton, NJ, June 5, 2008 (received for review July 20, 2007)

In older adults, mildly elevated plasma total homocysteine (hyperhomocysteinemia) is associated with increased risk of cognitive impairment, cerebrovascular disease, and Alzheimer's disease, but it is uncertain whether this is due to underlying metabolic, neurotoxic, or vascular processes. We report here that feeding male C57BL6/J mice a B-vitamin-deficient diet for 10 weeks induced hyperhomocysteinemia, significantly impaired spatial learning and memory, and caused a significant rarefaction of hippocampal microvasculature without concomitant gliosis and neurodegeneration. Total hippocampal capillary length was inversely correlated with Morris water maze escape latencies ($r = -0.757$, $P < 0.001$), and with plasma total homocysteine ($r = -0.631$, $P = 0.007$). Feeding mice a methionine-rich diet produced similar but less pronounced effects. Our findings suggest that cerebral microvascular rarefaction can cause cognitive dysfunction in the absence of or preceding neurodegeneration. Similar microvascular changes may mediate the association of hyperhomocysteinemia with human age-related cognitive decline.

cerebrovascular | homocysteine | mouse | nutrition

design of these studies makes it difficult to single out vitamin deficiency, excess methionine, or homocysteine as a primary cause of vascular dysfunction. Moreover, studies showing the association between vascular changes and cognition in experimental animals with hyperhomocysteinemia are lacking (5).

To better understand the role of hyperhomocysteinemia in cognitive impairment, we examined the relationship between impaired homocysteine metabolism and neurodegenerative, cerebrovascular, and cognitive outcomes in a mouse model of dietary hyperhomocysteinemia. We fed control or homocysteine-inducing diets to male WT C57Bl6/J mice for 10 weeks. The control group consumed an AIN93M diet containing 0.33% methionine, 2-mg folic acid, 25-μg cyanocobalamin (vitamin B_{12}), and 7-mg pyridoxal L-phosphate (vitamin B_6) per kg diet. Two different diets were formulated to induce hyperhomocysteinemia, the one through combined folate, vitamin B_{12}, and vitamin B_6 deficiency, the other through methionine enrichment with 1% L-methionine (10 g L-methionine/kg diet). Both diets induce hyperhomocysteinemia; however, they do so through markedly different metabolic impairments. B-vitamin deficiency

Vitamin B6 for cognition (Review)

Malouf R, Grimley Evans J

THE COCHRANE COLLABORATION

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that vitamin B6 supplementation has any effect an mood or cognitive functions of older people. Vitamin B6 supplementation improves biochemical indices of vitamin B6 status in older men, suggesting that some may be deficient in the vitamin.

Ontario
Health Quality Ontario
Qualité des services de santé Ontario

Ontario Health Technology Assessment Series; Vol. 13: No. 23, pp. 1–45, November 2013

Vitamin B12 and Cognitive Function: An Evidence-Based Analysis

Therefore, moderate quality evidence indicates treatment with vitamin B12 supplementation does not change cognitive function in patients with or without dementia or cognitive impairment and with or without vitamin B12 deficiency. Low to moderate quality of evidence indicates treatment with vitamin B12 and folate for patients with mild cognitive impairment slows the rate of brain atrophy compared with those who receive a placebo.

2006

Evidence Report/Technology Assessment

Number 134

B Vitamins and Berries and Age-Related Neurodegenerative Disorders

Results. In animal studies, deficiencies in vitamins B1 or folate generally cause neurological dysfunction; supplementation with B6, B12, or folate may improve neurocognitive function. In animal experiments folate and B12 protect against genetic deficiencies used to model AD; thiamine and folate also affect neurovascular function and health.

Human studies were generally of poor quality. Weak evidence suggests possible benefits of B1 supplementation and injected B12 in AD. The effects of B6 and folate are unclear. Overall, dietary intake studies do not support an association between B vitamin intake and AD. Studies evaluating B vitamin status were mostly inadequate due to poor study design. Overall, studies do not support an association between B vitamin status and age-related neurocognitive disorders.

Only one study evaluated human berry consumption, finding no association with PD. Animal studies of berries have almost all been conducted by the same research group. Several berry constituents have been shown to affect brain and nerve tissue function. Blueberry and strawberry extract were protective of markers of disease, although effects on neurocognitive tests were less consistent. Berry extracts may protect against the deleterious effects of compounds associated with AD.

Reporting of adverse events was uncommon. When reported, actual adverse events from B vitamins were rare and minor.

Conclusions. The current research on B vitamins is largely inadequate to confidently assess their mechanisms of action on age-related neurocognitive disorders, their associations with disease, or their effectiveness as supplements. B vitamin supplementation may be of value for neurocognitive function, but the evidence is inconclusive.

http://archive.ahrq.gov/clinic/epcarch.htm

ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Petersen RC et al: NEJM 2005

Vitamin E for Alzheimer's dementia and mild cognitive impairment (Review)

Farina N, Isaac MGEKN, Clark AR, Rusted J, Tabet N

Cochrane Database Syst Rev. 2017 Jan 27;1:CD002854.

We found no evidence that vitamin E affected the probability of progression from MCI to probable dementia due to AD over 36 months (RR 1.03, 95% CI 0.79 to 1.35, P = 0.81, 1 study, n = 516; moderate quality evidence). We were unable to extract data in accordance with the review protocol for other outcomes. However, the study authors found no evidence that vitamin E differed from placebo in its effect on cognitive function, global severity or activities of daily living . **Authors' conclusions**

We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.

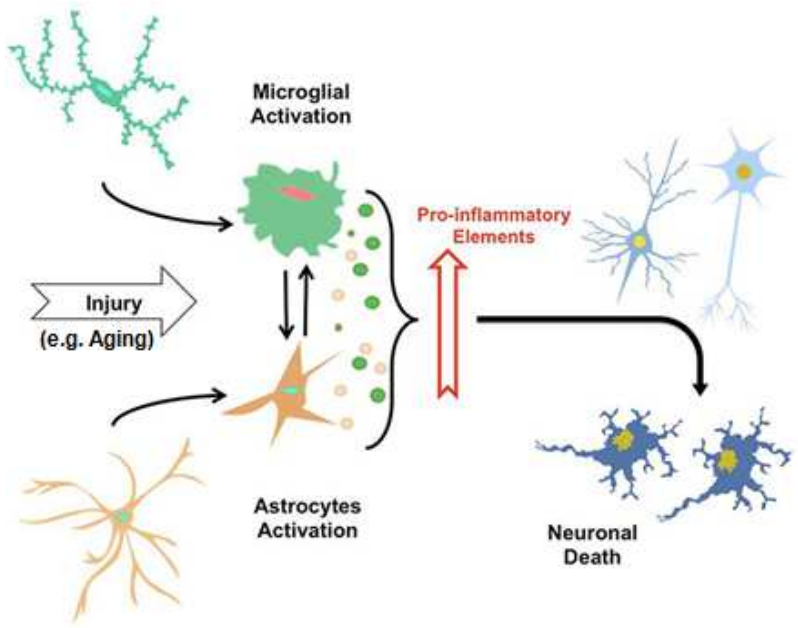
Il ruolo della glia nella disfunzione neuronale, neurodegenerazione e demenza

frontiers in
CELLULAR NEUROSCIENCE

REVIEW ARTICLE
published: 22 April 2014
doi: 10.3389/fncel.2014.00112

Neuroinflammation in the pathogenesis of Alzheimer's disease. A rational framework for the search of novel therapeutic approaches

*Inelia Morales[1,2], Leonardo Guzmán-Martínez[1,2], Cristóbal Cerda-Troncoso[1,2], Gonzalo A. Farías[1,2,3] and Ricardo B. Maccioni[1,2,4]**

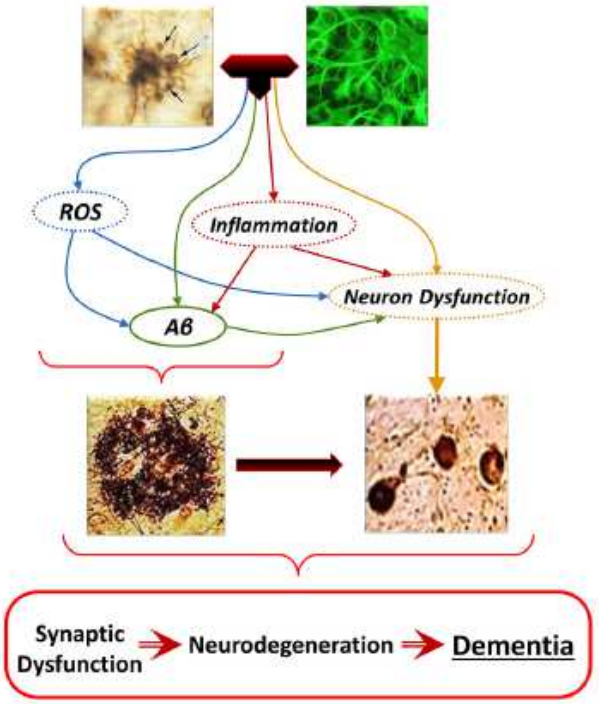


frontiers
in Aging Neuroscience

REVIEW
published: 20 July 2015
doi: 10.3389/fnagi.2015.00124

Microglial cell dysregulation in brain aging and neurodegeneration

Rommy von Bernhardi[1], Laura Eugenín-von Bernhardi[1] and Jaime Eugenín[2]**

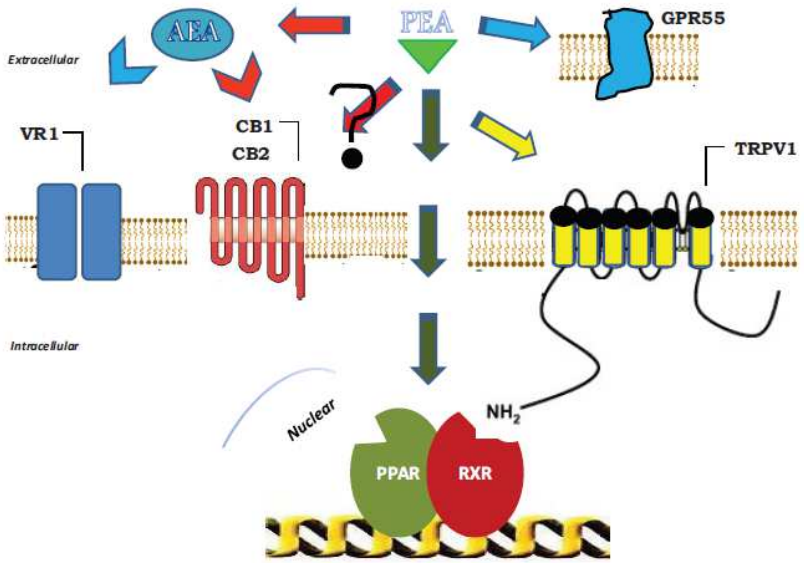


Azione della Palmitoiletanolamide sulle cellule non neuronali (effetto pleiotropico e sincronico)

Mini-Reviews in Medicinal Chemistry, 2013, *13*, 237-255 237

Palmitoylethanolamide is a New Possible Pharmacological Treatment for the Inflammation Associated with Trauma

Emanuela Esposito[1] and Salvatore Cuzzocrea[1,2,*]



British Journal of Pharmacology

British Journal of Pharmacology (2017) **174** 1349–1365 1349

Themed Section: Principles of Pharmacological Research of Nutraceuticals

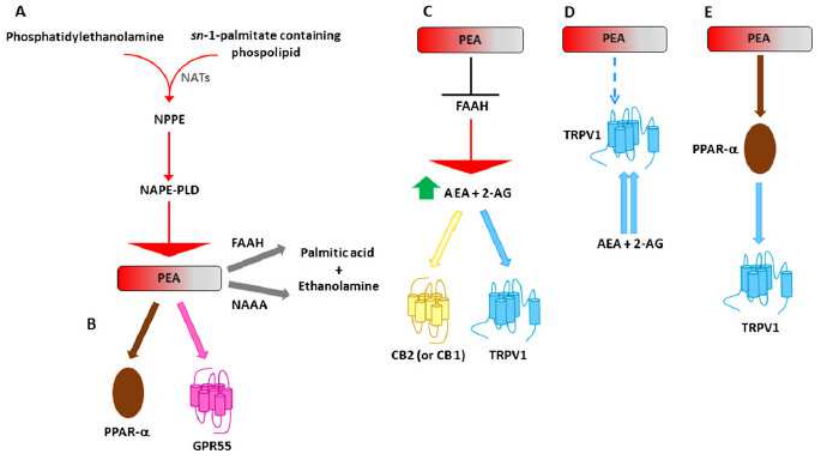
REVIEW ARTICLE

The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations

Correspondence Stefania Petrosino, Endocannabinoid Research Group, Istituto di Chimica Biomolecolare (ICB), Consiglio Nazionale delle Ricerche (CNR), Via Campi Flegrei 34, Comprensorio Olivetti, 80078 Pozzuoli (NA), Italy. E-mail: spetrosino@icb.cnr.it

Received 6 June 2016; **Revised** 1 August 2016; **Accepted** 5 August 2016

Stefania Petrosino[1,2] and Vincenzo Di Marzo[1]



Modulazione del fenotipo e ripristino della normofunzionalità gliale tramite l'azione su: recettore nucleare PPARα, recettori di membrana TRPV1 e GPR55, innalzamento del tono endogeno di endocannabinoidi.

Aging Clin Exp Res
DOI 10.1007/s40520-016-0533-6

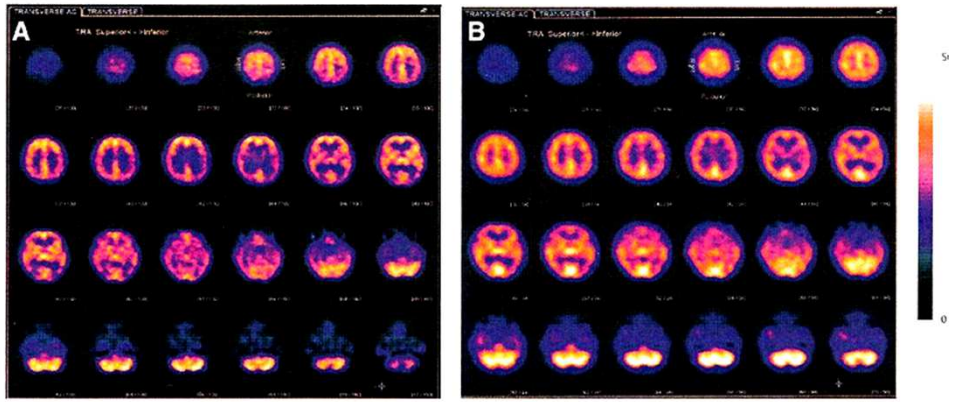
CASE REPORT

PEALut efficacy in mild cognitive impairment: evidence from a SPECT case study!

Rocco Salvatore Calabrò[1] · Antonino Naro[1] · Rosaria De Luca[1] · Simona Leonardi[1] · Margherita Russo[1] · Angela Marra[1] · Placido Bramanti[1]

Parameter	Normative	References	T_{PRE}	T_3	T_9	RCI	
						T_3–T_{PRE}	T_9–T_{PRE}
Neuropsychological							
MMSE	27.9 ± 2.2	[6]	26	26	30	NS	NS
MoCA	27.4 ± 2.2	[7]	24	26	29	NS	NS
BSRT	0.1 ± 0.5	[8]	7.5	10	12.5	NS	NS
RAVLT	38.1 ± 9.8	[9]	27	32	40	NS	3.4
AM	3.9 ± 3.1	[10]	3.3	4	4.9	2.5	6.2
TMT							
A	39.1 ± 11.8	[11]	48	45	43	NS	NS
B	91.3 ± 28.9		110	107	98	NS	4.6
BA			62	62	55	NS	2.7
VFT	21 ± 4.2	[12]	33	34	34	NS	NS
SPECT areas							
Parietal	43.6 ± 1.1	[13]	31	–	40	–	4.5
Inferior temporal	39.2 ± 2.1		22	–	36	–	7
Temporo-occipital	41.4 ± 1		27	–	37	–	5

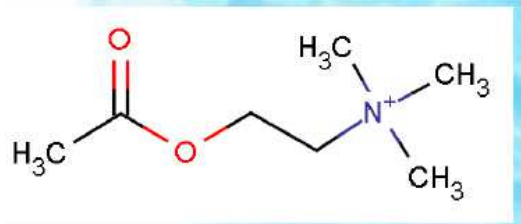
“La valutazione neuropsicologica è pressoché normale a T9.”

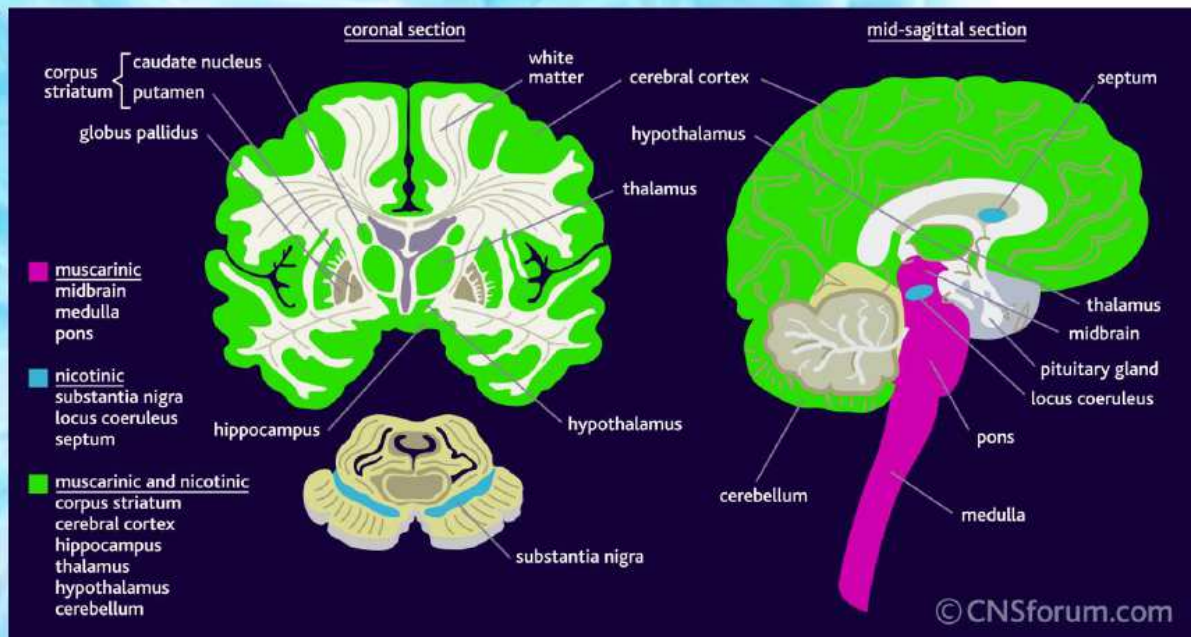


“A) **la perfusione valutata mediante SPECT al basale mostra significativa ipoperfusione** bilaterale nelle aree prietali, temporali inferiori e temporo-occipitali. B) **a T9 la SPECT mostra perfusione normale** pressoché in tutte le aree subcorticali.”

Colina

Choline is required to transport fats in and out of cells, and is a precursor of acetylcholine, the neurotransmitter required for several brain functions including learning and memory.





Journal of Alzheimer's Disease 42 (2014) S281–S288
DOI 10.3233/JAD-140150
IOS Press

The ASCOMALVA (Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease) Trial: Interim Results after Two Years of Treatment

Francesco Amenta[a,*], Anna Carotenuto[a], Angiola Maria Fasanaro[b], Raffaele Rea[a] and Enea Traini[a]
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Studio ASCOMALVA

Studio controllato, randomizzato ed in doppio cieco.

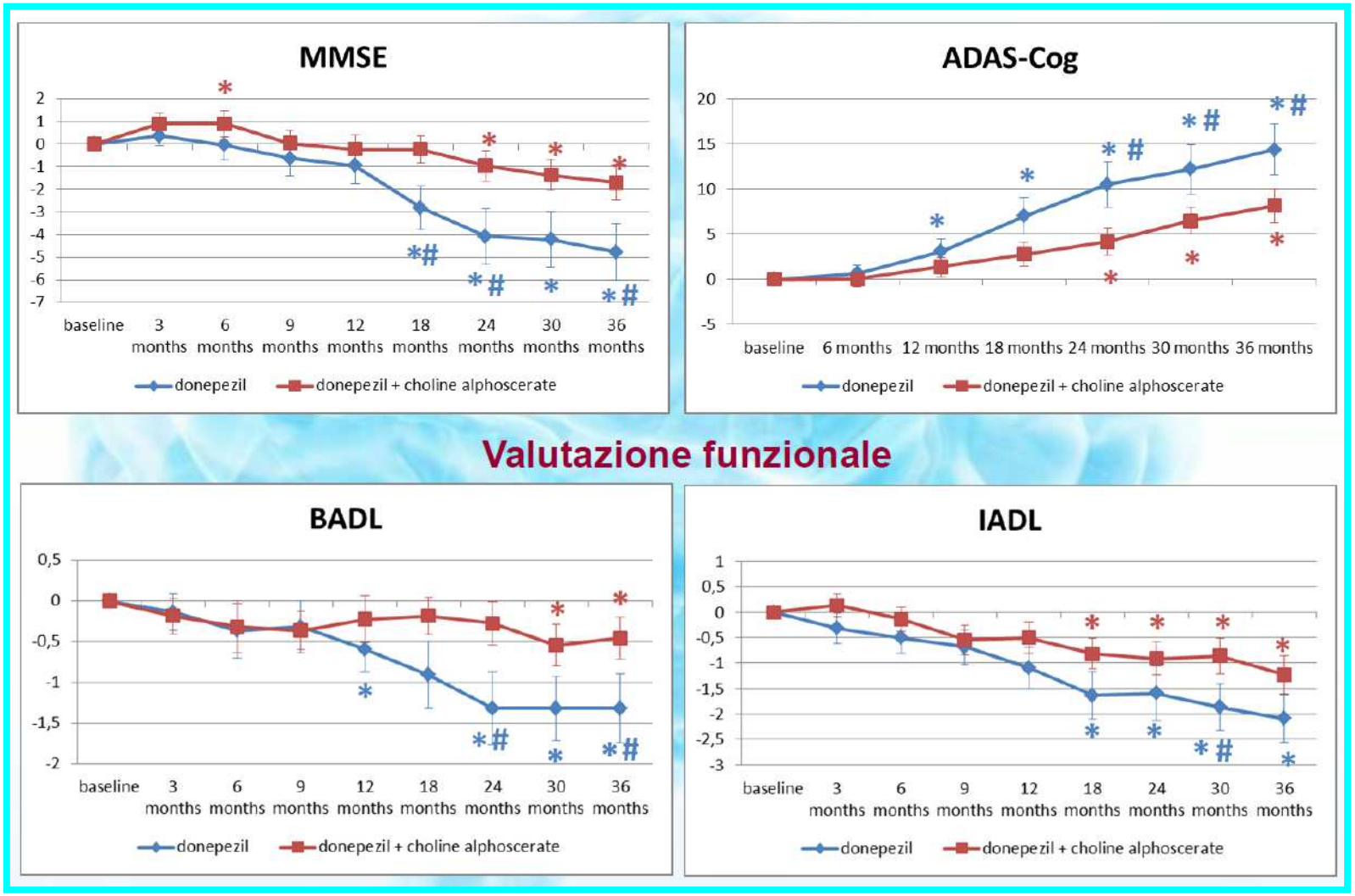
Numero OsSC: 2008-004667-19

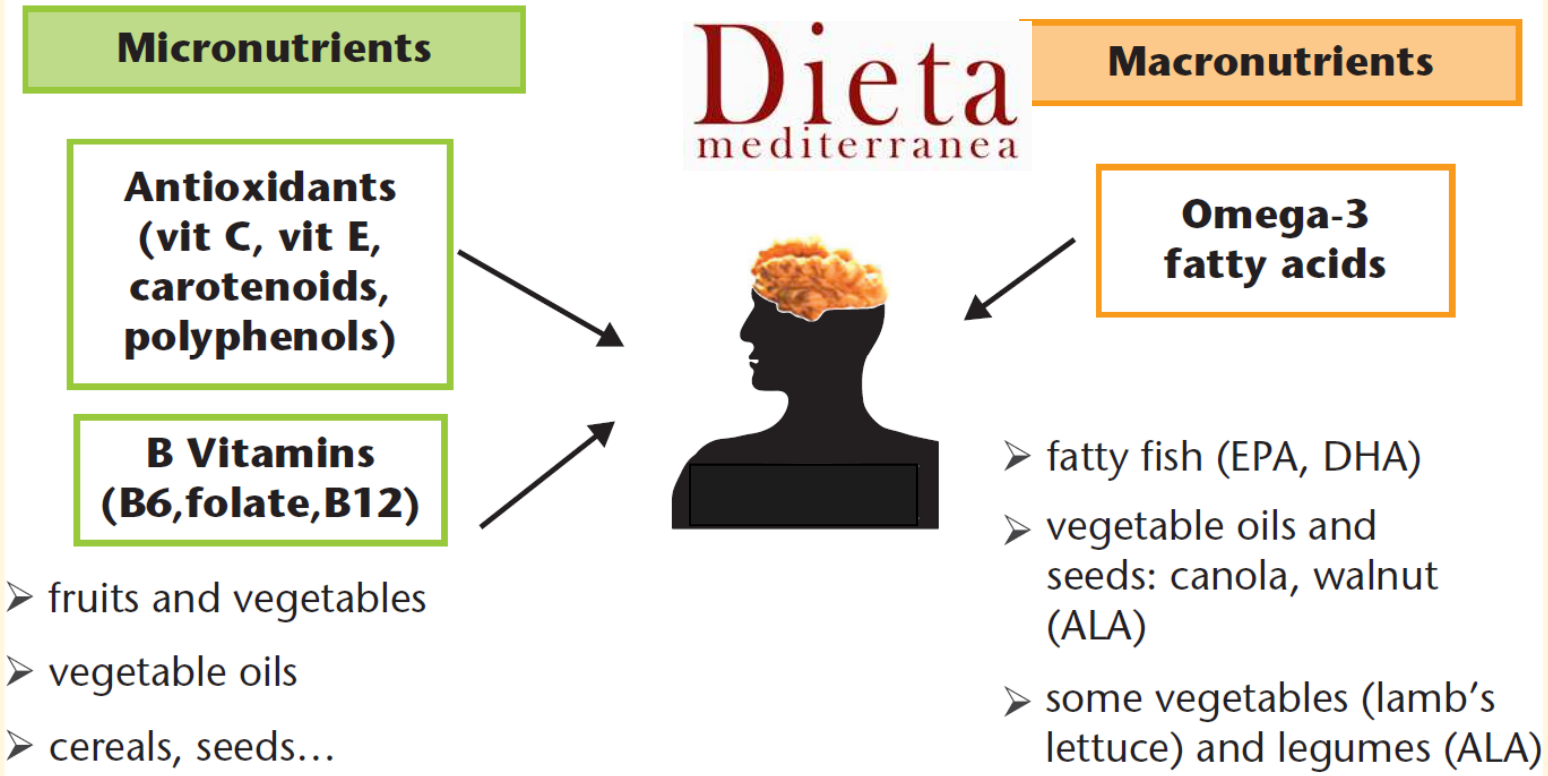
Trattamento farmacologico

***Trattamento 1*: Donepezil cp, dose pro/die 10 mg, (oppure Donepezil 5 mg, se non tollerata la dose di 10 mg) associato a placebo**

***Trattamento 2*: Donepezil cp, dose pro/die 10 mg (oppure Donepezil 5 mg, se non tollerata la dose di 10 mg) associato a Colina alfoscerato 2 x 600 mg/die in flaconcino bevibile.**

Colina alfoscerato



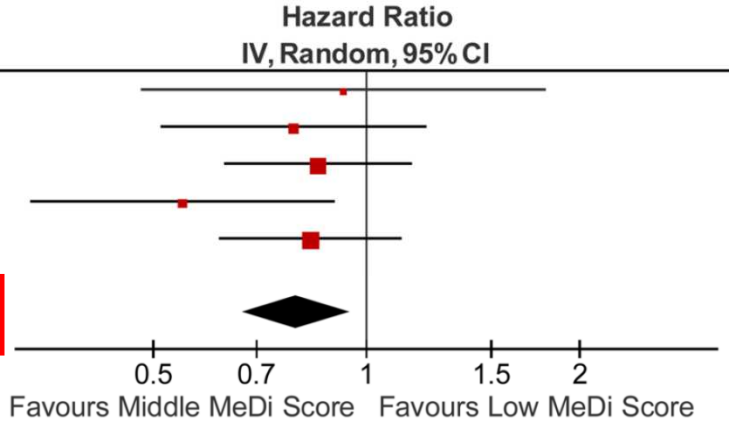

Micronutrients
Antioxidants (vit C, vit E, carotenoids, polyphenols)
B Vitamins (B6,folate,B12)
Dieta mediterranea
Macronutrients
Omega-3 fatty acids
fruits and vegetables
vegetable oils
cereals, seeds…
fatty fish (EPA, DHA)
vegetable oils and seeds: canola, walnut (ALA)
some vegetables (lamb's lettuce) and legumes (ALA)

Dieta mediterranea e Deterioramento cognitivo

4.2 Middle vs Lowest MeDi tertile

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Feart 2009	-0.0759	0.3358	6.8%	0.93 [0.48, 1.79]
Roberts 2010	-0.2373	0.2204	15.8%	0.79 [0.51, 1.21]
Scarmeas 2006	-0.1568	0.1557	31.7%	0.85 [0.63, 1.16]
Scarmeas 2009 AD	-0.5978	0.2529	12.0%	0.55 [0.34, 0.90]
Scarmeas 2009 MCI	-0.1824	0.1509	33.7%	0.83 [0.62, 1.12]
Total (95% CI)			**100.0%**	**0.80 [0.67, 0.95]**

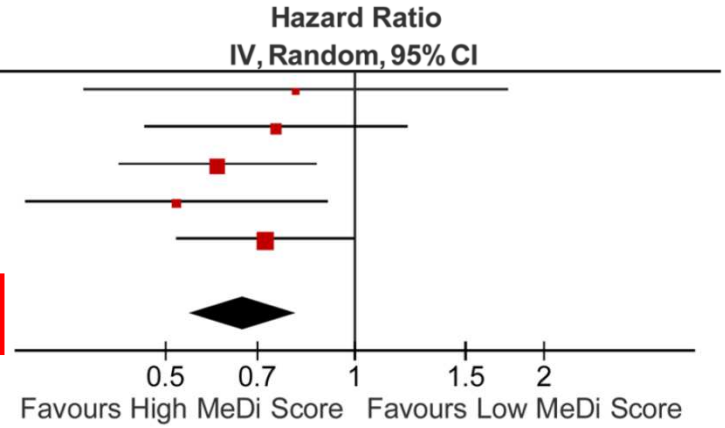
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



4.3 Highest vs Lowest MeDi tertile

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Feart 2009	-0.2169	0.3966	6.3%	0.81 [0.37, 1.75]
Roberts 2010	-0.2889	0.2467	16.4%	0.75 [0.46, 1.21]
Scarmeas 2006	-0.5034	0.1858	28.9%	0.60 [0.42, 0.87]
Scarmeas 2009 AD	-0.6539	0.2831	12.5%	0.52 [0.30, 0.91]
Scarmeas 2009 MCI	-0.3285	0.1668	35.9%	0.72 [0.52, 1.00]
Total (95% CI)			**100.0%**	**0.67 [0.55, 0.81]**

Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)



Singh et al. J Alzheimer's Disease 2014

Mediterranean Diet and Age-Related Cognitive Decline: A RCT

IMPORTANCE Oxidative stress and vascular impairment are believed to partly mediate age-related cognitive decline, a strong risk factor for development of dementia. Epidemiologic studies suggest that a Mediterranean diet, an antioxidant-rich cardioprotective dietary pattern, delays cognitive decline, but clinical trial evidence is lacking.

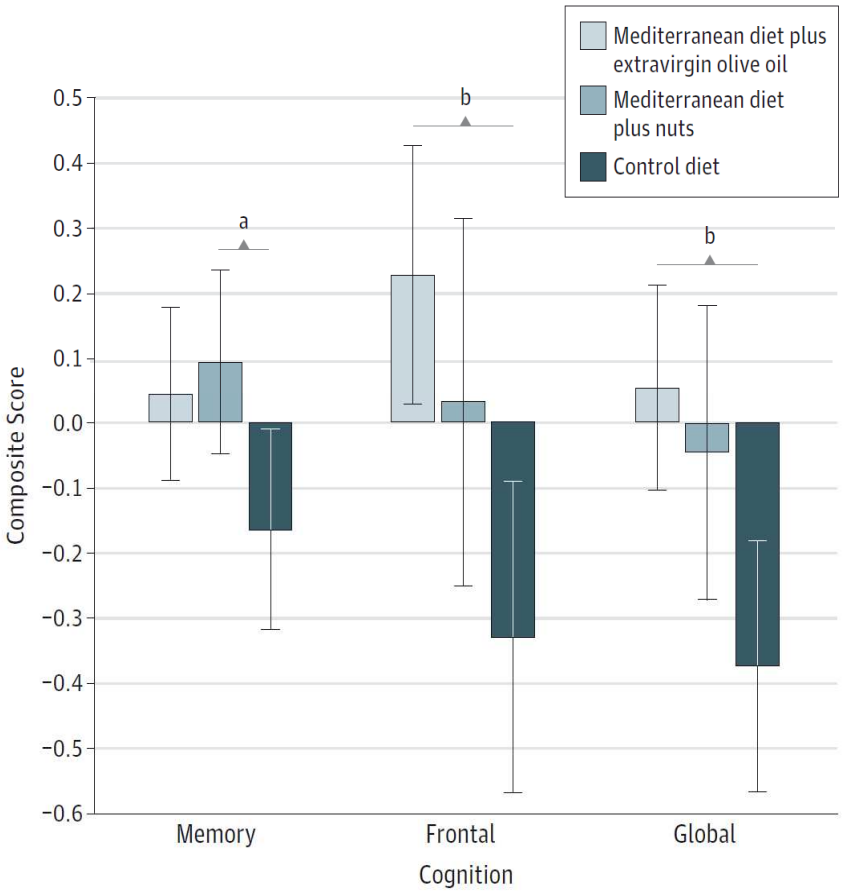
OBJECTIVE To investigate whether a Mediterranean diet supplemented with antioxidant-rich foods influences cognitive function compared with a control diet.

DESIGN, SETTING, AND PARTICIPANTS Parallel-group randomized clinical trial of 447 cognitively healthy volunteers from Barcelona, Spain (233 women [52.1%]; mean age, 66.9 years), at high cardiovascular risk were enrolled into the Prevención con Dieta Mediterránea nutrition intervention trial from October 1, 2003, through December 31, 2009. All patients underwent neuropsychological assessment at inclusion and were offered retesting at the end of the study.

INTERVENTIONS Participants were randomly assigned to a Mediterranean diet supplemented with extravirgin olive oil (1 L/wk), a Mediterranean diet supplemented with mixed nuts (30 g/d), or a control diet (advice to reduce dietary fat).

MAIN OUTCOMES AND MEASURES Rates of cognitive change over time based on a neuropsychological test battery: Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Animals Semantic Fluency, Digit Span subtest from the Wechsler Adult Intelligence Scale, Verbal Paired Associates from the Wechsler Memory Scale, and the Color Trail Test. We used mean *z* scores of change in each test to construct 3 cognitive composites: memory, frontal (attention and executive function), and global.

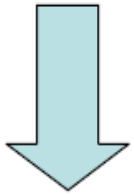
Figure 2. Changes in Cognitive Function Measured With Composites by Intervention Group



Valls-Pedret C. et al Jama Internal Medicine 20015

Mediterranean diet and cognitive decline

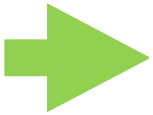
A **Mediterranean diet** might also have protective effects against cognitive decline in older individuals, because it **combines several foods and nutrients potentially protective** against cognitive dysfunction or dementia



- antioxidants (vitamin E, carotenoids, flavonoids),
- vitamins B12, folate
- PUFAs

Combination Medical Foods: Fortasyn Connect

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



Designed to support the formation and function of synapses

125 ml, once-per-day, milk-based liquid

Vanilla or strawberry flavours

Macronutrients:

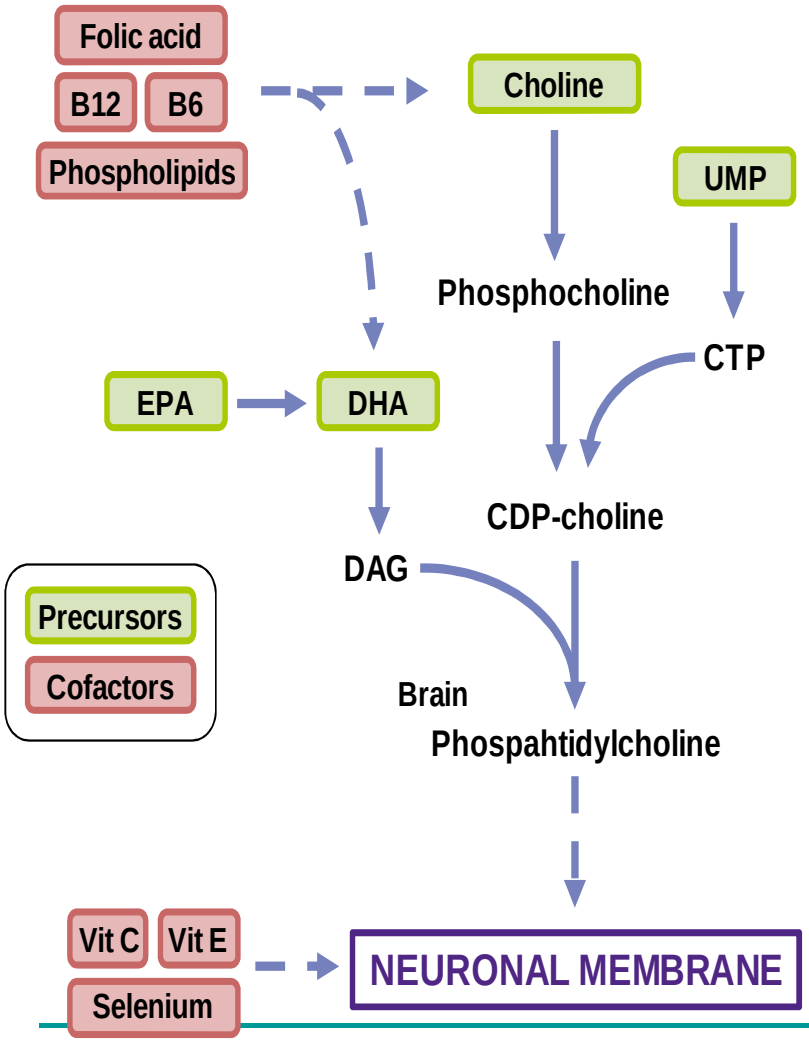
125 kcal, as protein (12%), fat (34%), CHO (53%)

Micronutrients

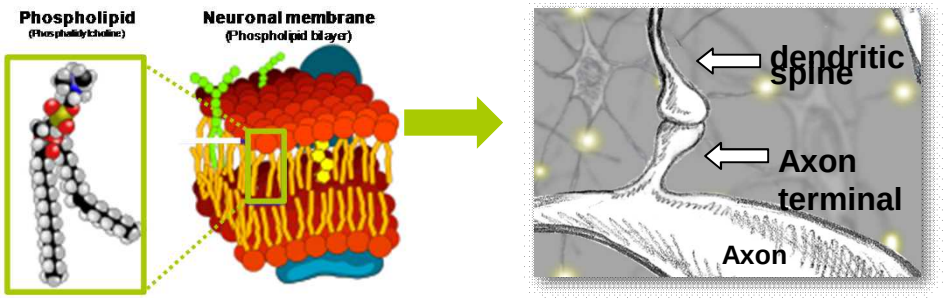
Other micronutrients according to FSMP levels

FORTASYN CONNECT

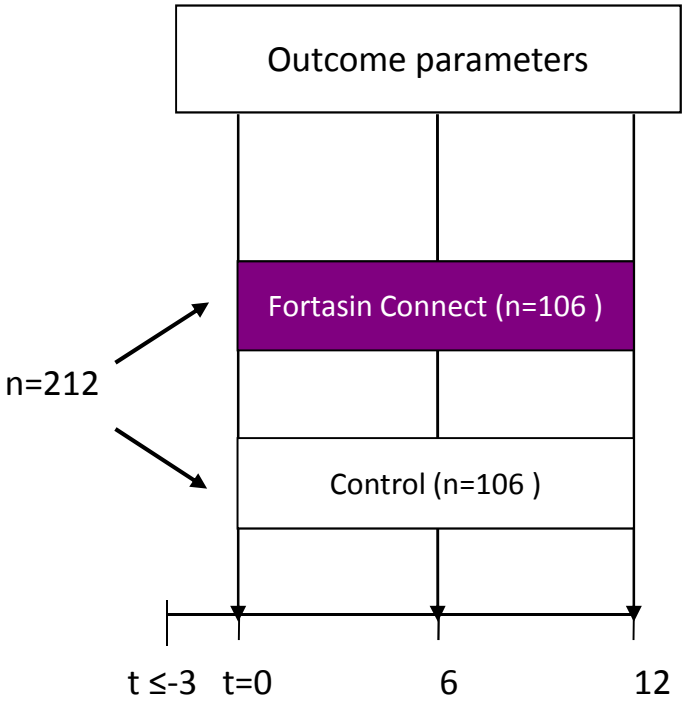
Mechanism of action: enhancing synaptic membranes



- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- B-vitamins enhance precursor bioavailability
- Antioxidants protect the neuronal membrane and maintain its integrity, stability and function



Souvenir I: Design and methodology



- Design: randomised,double-blind, controlled, parallel-group, multi centre (28 sites in NL, Bel, Ger, UK)
- Patients:drug-naive mild subjects with probable AD (MMSE 20–26)
- Intervention: Fortasin Connect, a once-a-day (125 ml / day) drink or an isocaloric control
- Co-primary outcomes: delayed verbal recall task of the WMS-r and modified ADAS-cog

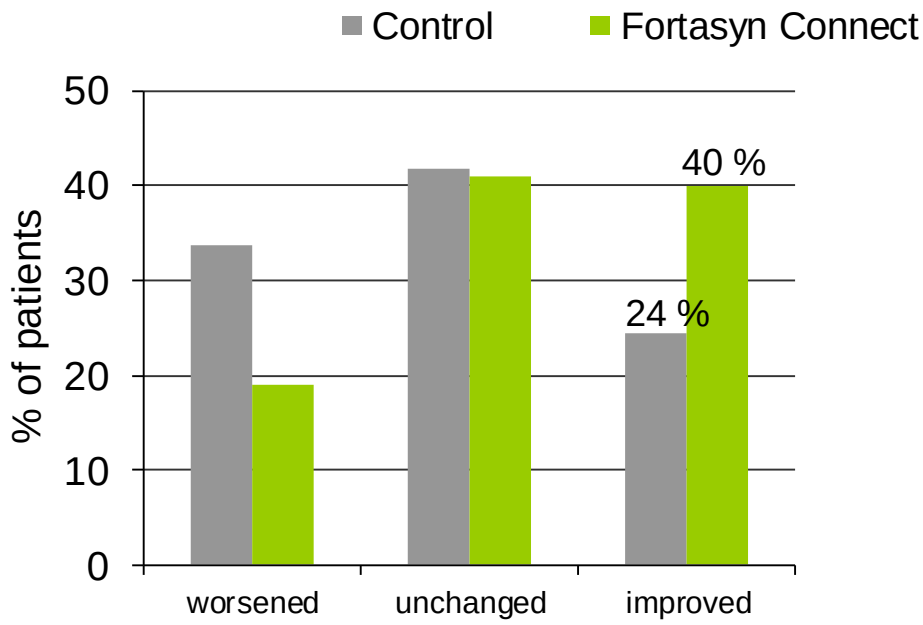
Scheltens et al. Alz & Dement 2010.

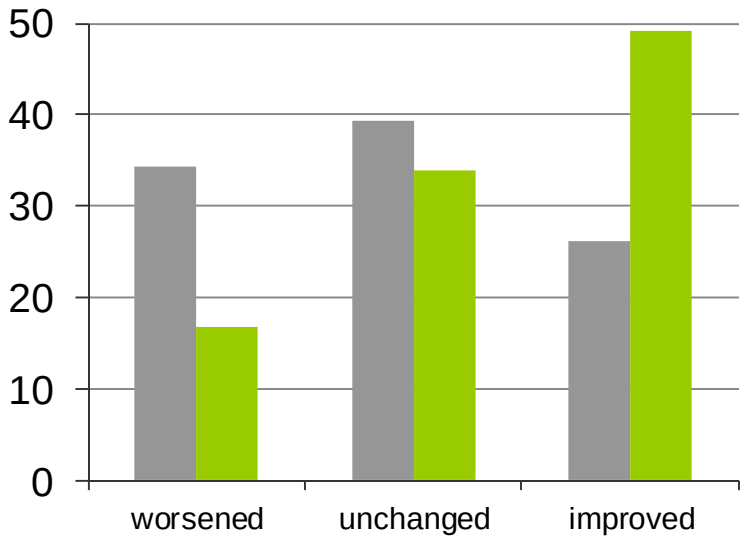
Souvenir I: Fortasyn Connect improves memory

Delayed verbal memory WMS-r

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

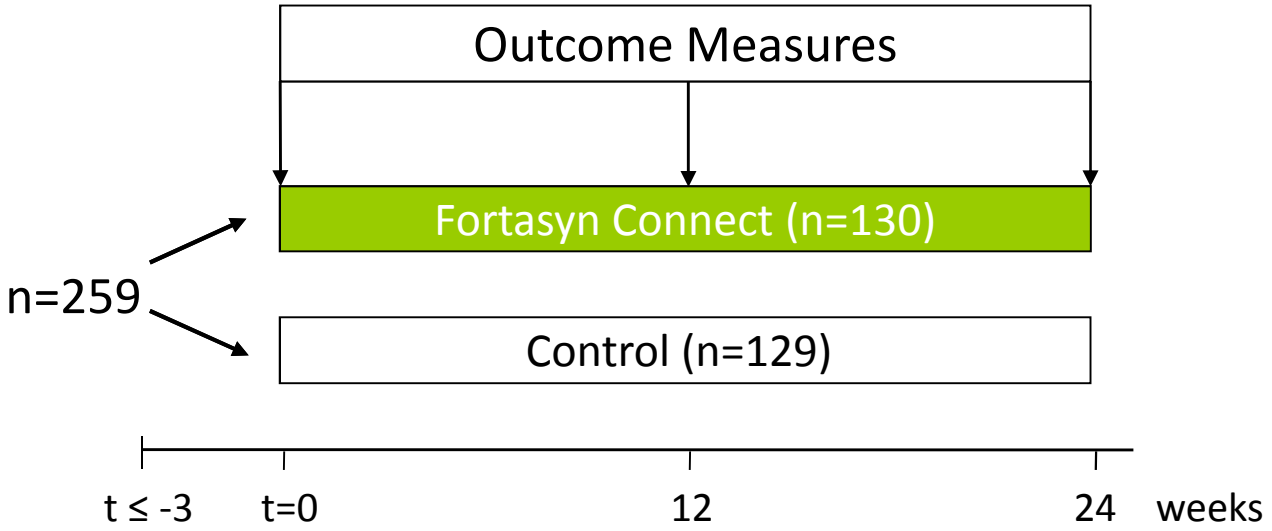
Significantly more responders in very mild (MMSE 24–26) AD after 12 weeks (p=0.019)*





Scheltens et al. Alz & Dement 2010.

Souvenir II: Design & Methodology

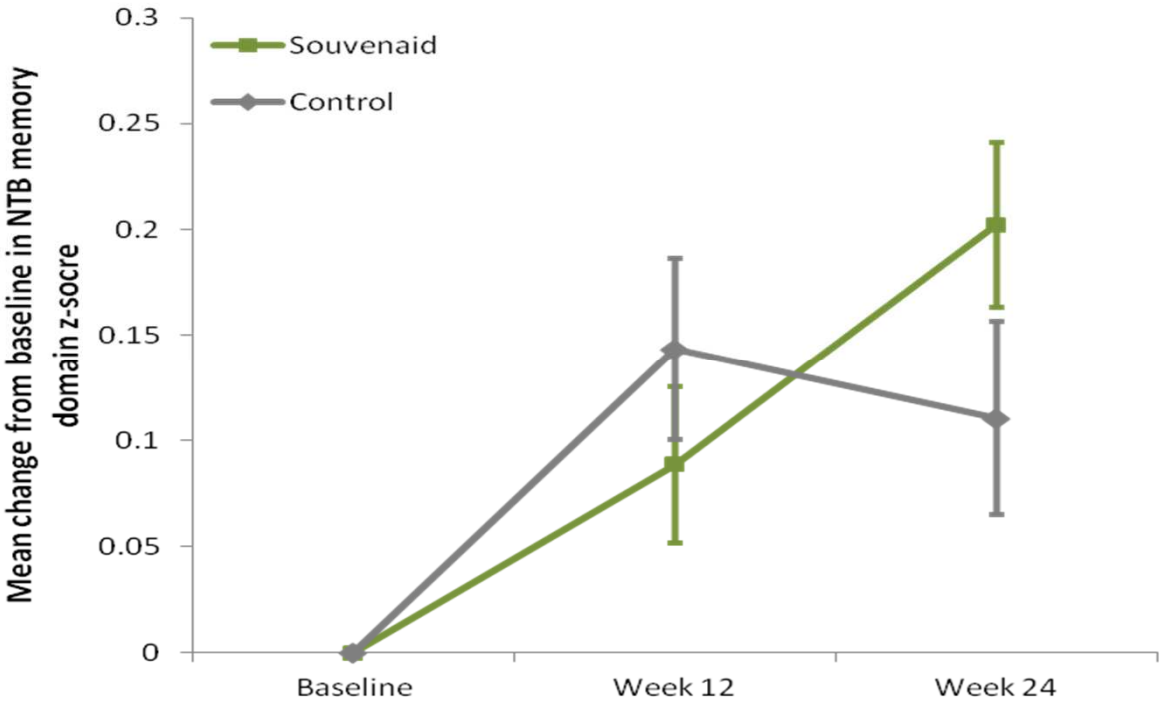


- Design: randomized, double-blind, controlled, parallel-group, multi-centre (27 sites) in Europe (NL, Ger, Bel, Fr, It, Sp)
- Patients: mild AD patients (MMSE > 20), AD drug-naïve
- Intervention: Fortasin Connect or an isocaloric control
- Outcomes: Memory domain score (z-score) of the NTB (primary); Executive domain of NTB & Total composite score of NTB (secondary)

Scheltens et al. Alz & Dement 2012

Primary Efficacy: Memory Domain Score of the Neuropsychological Test Battery

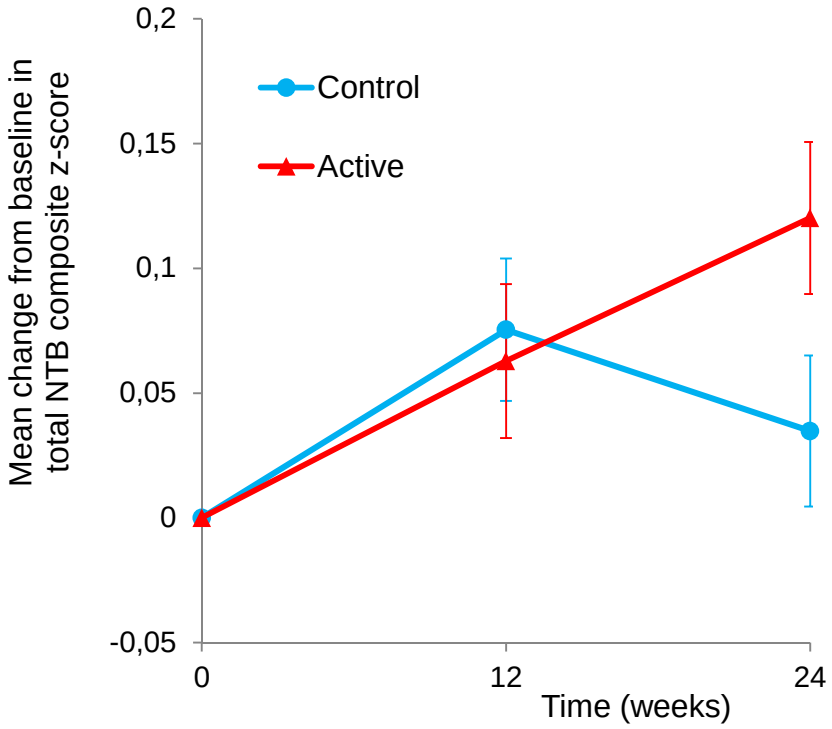
Significant effect on NTB memory domain during 24 weeks
(whole period trajectory; p=0.023)



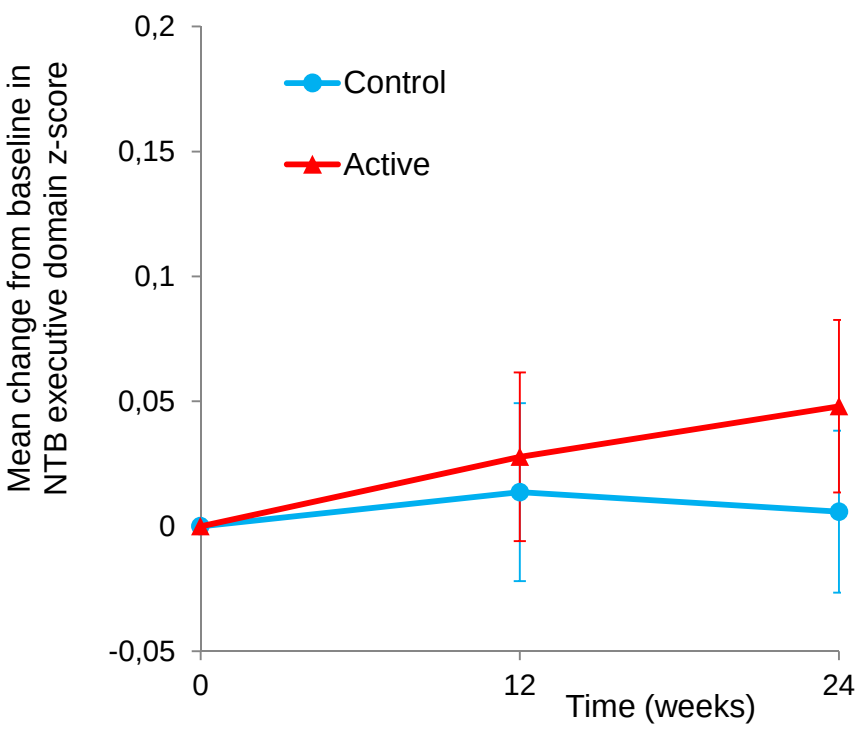
Scheltens et al. Alz & Dement 2012.

Secondary Efficacy: NTB Total and NTB Executive Domain

NTB composite score trend (p=0.053)



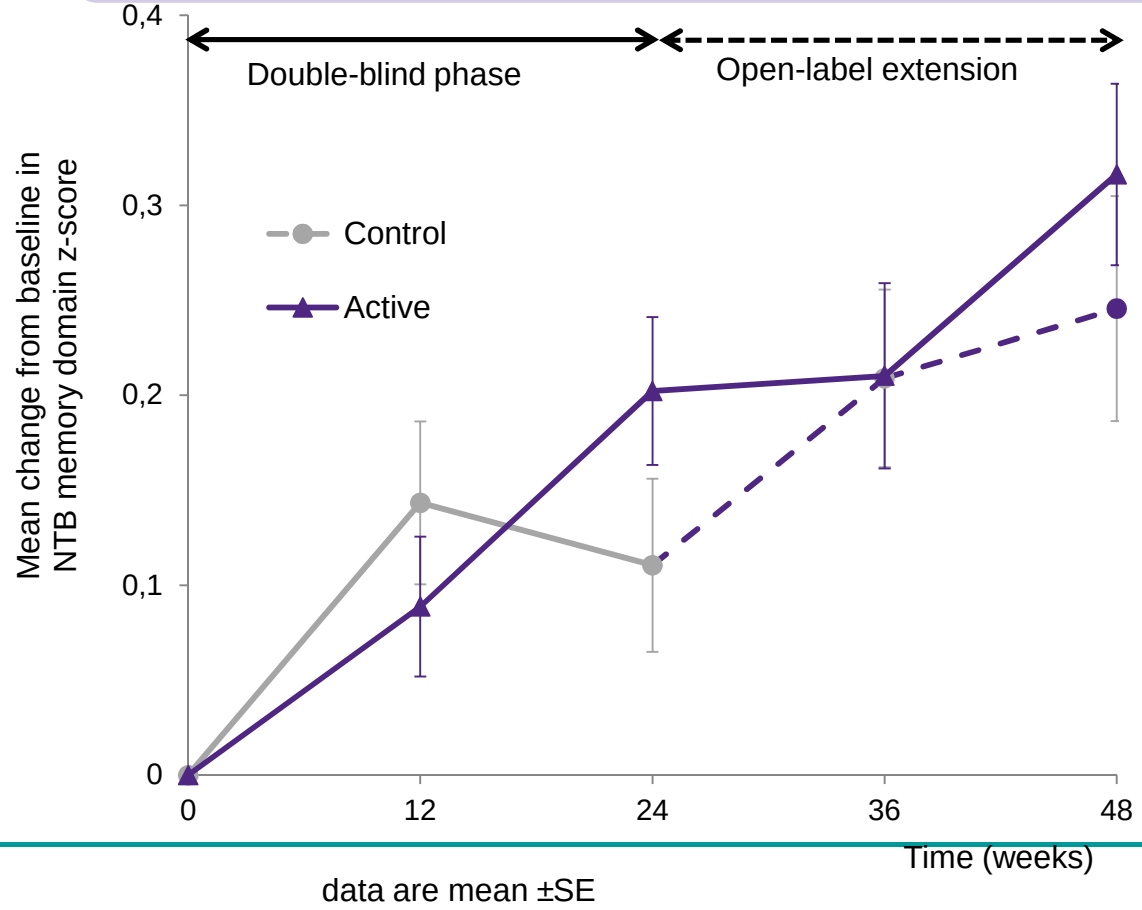
NTB executive domain score no significant effect (p=0.686)



Scheltens et al. Alz & Dement 2012.

Open label exploratory Outcome: Sustainable Memory Improvement

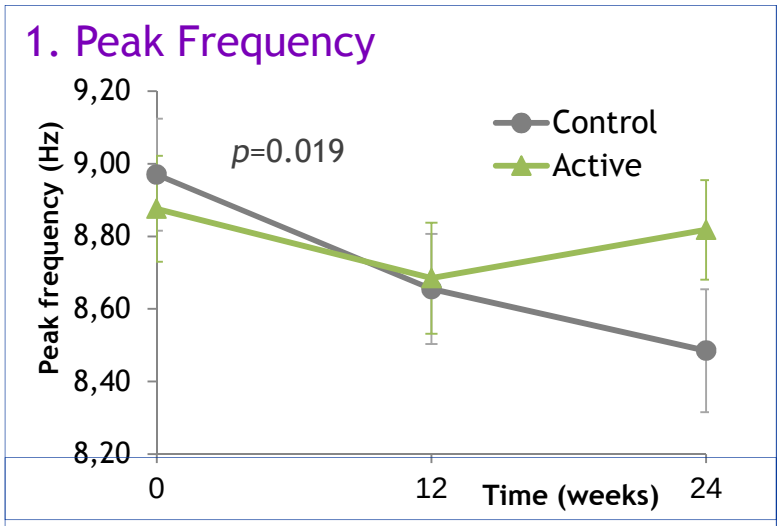
Significant increase from week 24 to week 48 in both groups.
Active - Active: p=0.025; Control - Active: p=0.008

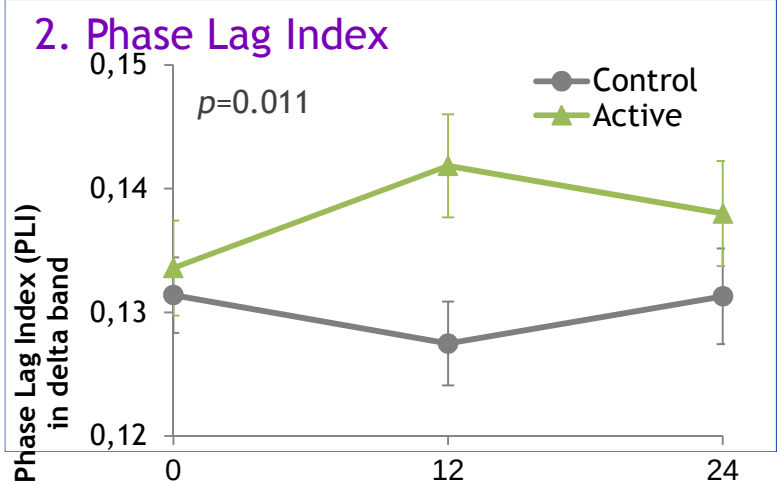


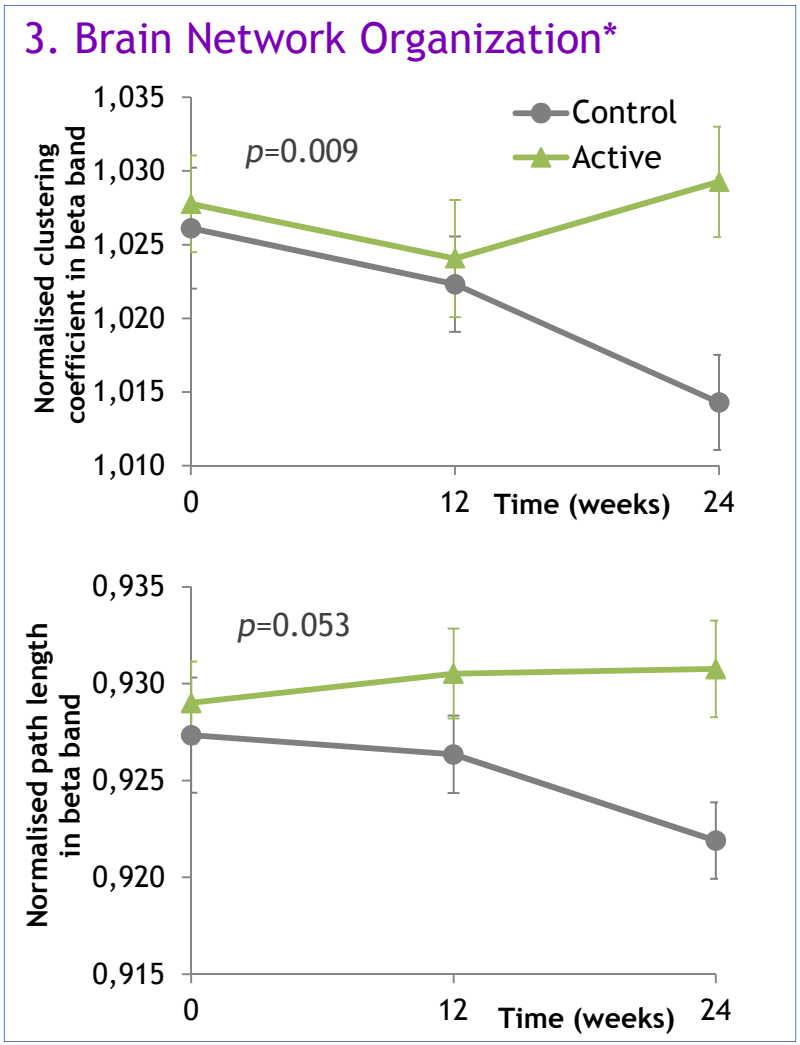
data are mean ±SE

Olde Rikkert et al. JAD 2014

Network parameters suggest preserved synaptic formation, function and network







Time (weeks)

ITT, MMRM, 2 df contrast, data are mean ±SE

Scheltens et al. *J Alzheimers Dis*. 2012;31:225-236.
de Waal et al. *Plos One 2014;9:1.*

A clinical trial investigating the effects of Fortasyn Connect in prodromal Allzheimer's disease: results of the LipiDiDiet study

Hilkka Soininen, Pieter-Jelle Visser, Miia Kivipelto, Tobias Hartmann
for the LipiDiDiet study group

e-mail: hilkka.soininen@uef.fi

Springfield 2016 Athens, 10 March 2016

Conclusioni

- MIC è una sindrome a patogenesi multifattoriale
- Nel paziente con deterioramento cognitivo sono spesso presenti deficit nutrizionali multipli
- Per numerosi “nutrienti” è stato ipotizzato un effetto neuroprotettivo
  - Meccansimi fisiopatologici
  - Studi osservazionali
- Gli studi di intervento suggerisco la superiorità di un approccio nutrizionale globale combinato rispetto alla supplementazione singola
- Effetti più marcati nelle forme iniziali di declino: *“the earlier the better”*

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Università di Ferrara

-Ex Labore Fructus-

The relation of dietary choline to cognitive performance and white-matter hyperintensity in the Framingham Offspring Cohort[1–4]

Coreyann Poly, Joseph M Massaro, Sudha Seshadri, Philip A Wolf, Eunyoung Cho, Elizabeth Krall, Paul F Jacques, and Rhoda Au0

ABSTRACT

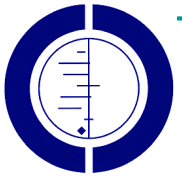
Background: Choline is the precursor to the neurotransmitter acetylcholine. Loss of cholinergic neurons is associated with impaired cognitive function, particularly memory loss and Alzheimer disease (AD). Brain atrophy and white-matter hyperintensity (WMH) are also associated with impaired cognitive function and AD.

Objective: The objective was to determine whether a relation exists between dietary choline intake, cognitive function, and brain morphology in a large, nondemented community-based cohort.

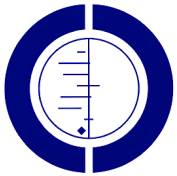
Design: A dementia-free cohort of 1391 subjects (744 women, 647 men; age range: 36–83 y; mean ± SD age: 60.9 ± 9.29 y) from the Framingham Offspring population completed a food-frequency questionnaire administered from 1991 to 1995 (exam 5; remote intake) and from 1998 to 2001 (exam 7; concurrent intake). Participants underwent neuropsychological evaluation and brain MRI at exam 7. Four neuropsychological factors were constructed: verbal memory (VM), visual memory (VsM), verbal learning, and executive function. MRI measures included WMH volume (WMHV).

Results: Performance on the VM and VsM factors was better with higher concurrent choline intake in multivariable-adjusted models for VM (average change in neuropsychological factor per 1-unit change in choline = 0.60; 95% CI: 0.29, 0.91; $P < 0.01$) and VsM (0.66; 95% CI: 0.19, 1.13; $P < 0.01$). Remote choline intake was inversely related to log-transformed WMHV (average change in log WMHV per 1-unit change in choline = −0.05; 95% CI: −0.10, −0.01; $P = 0.02$). Furthermore, an inverse association was observed between remote higher choline intake and presence of large WMVH (OR: 0.56; 95% CI: 0.34, 0.92; $P = 0.01$).

Conclusion: In this community-based population of nondemented individuals, higher concurrent choline intake was related to better cognitive performance, whereas higher remote choline intake was associated with little to no WMHV. *Am J Clin Nutr* 2011;94:1584–91.



THE COCHRANE COLLABORATION



THE COCHRANE COLLABORATION

Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people (Review)

Malouf R, Grimley Evans J

AUTHORS' CONCLUSIONS

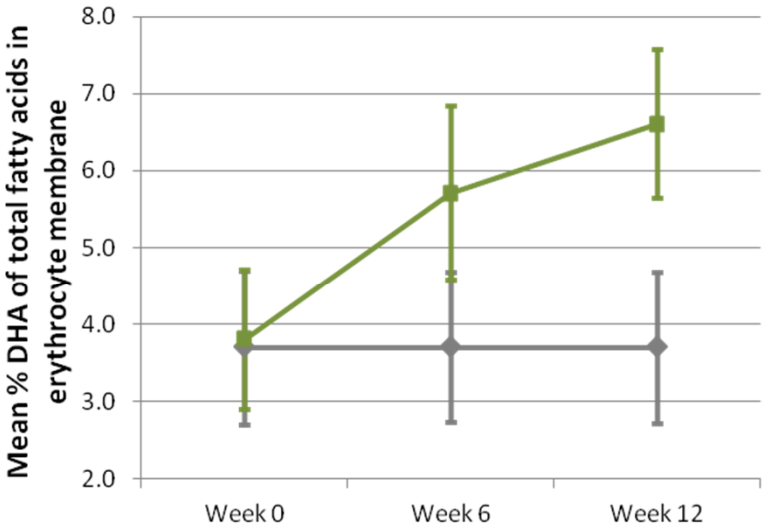
Implications for practice

The findings of a single large study suggest a possible benefit from folic acid supplementation over long periods in preserving some aspects of cognitive function of healthy people with high homocysteine levels. The risks of malignancy with long term folate supplementation are unknown and folate supplementation may worsen cognitive function in the presence of low B12. Until further safety data accrue, and the effect is replicated, the risk-benefit ratio remains unknown and practice should not change.

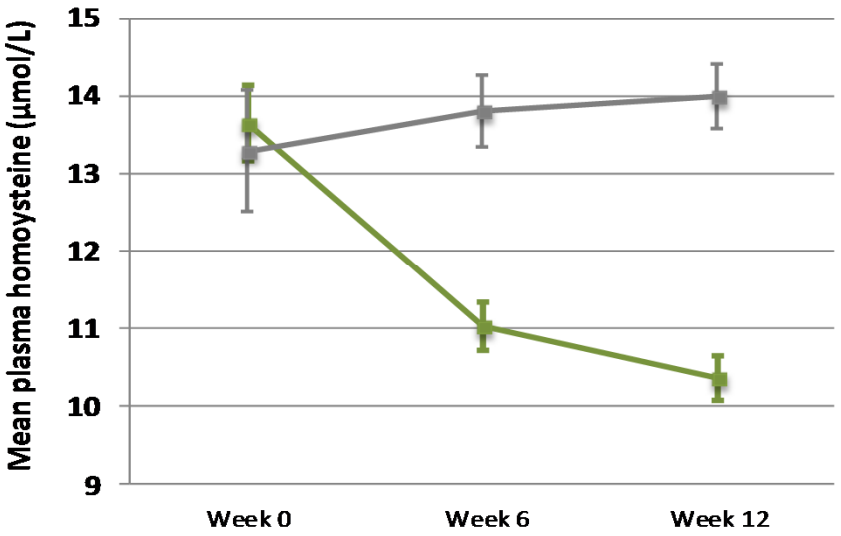
Souvenir I: Positive safety profile & biochemical changes

- No significant differences in the number of adverse events (AEs) or serious AEs
- No clinically relevant differences in blood safety parameters
- Overall adherence was very high (94%)

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

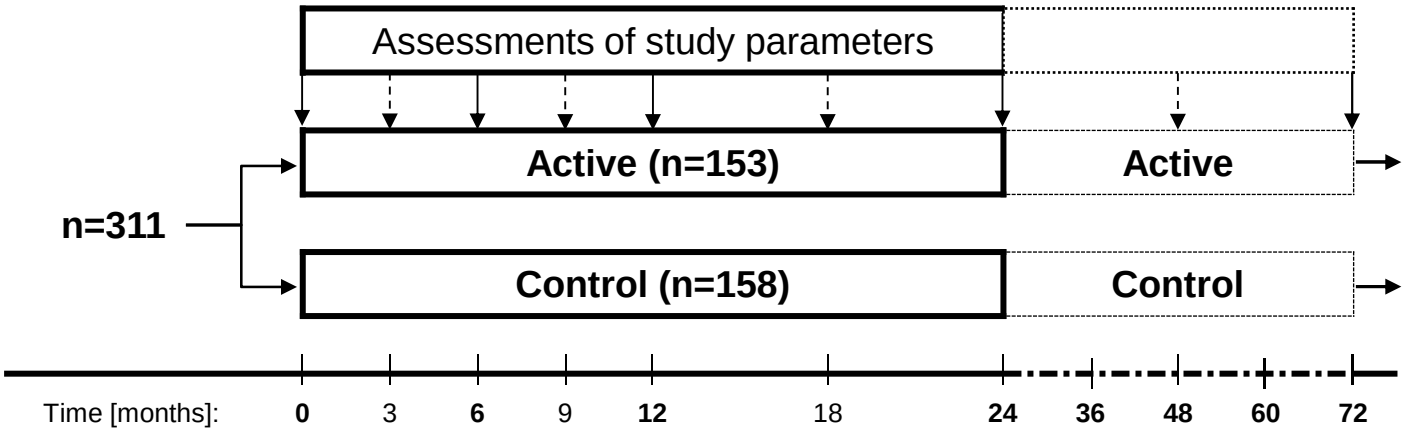


Reduced plasma homocysteine (p<0.001)



Scheltens et al. Alz & Dement 2010.

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



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)

Tea consumption and cognitive impairment and decline in older Chinese adults

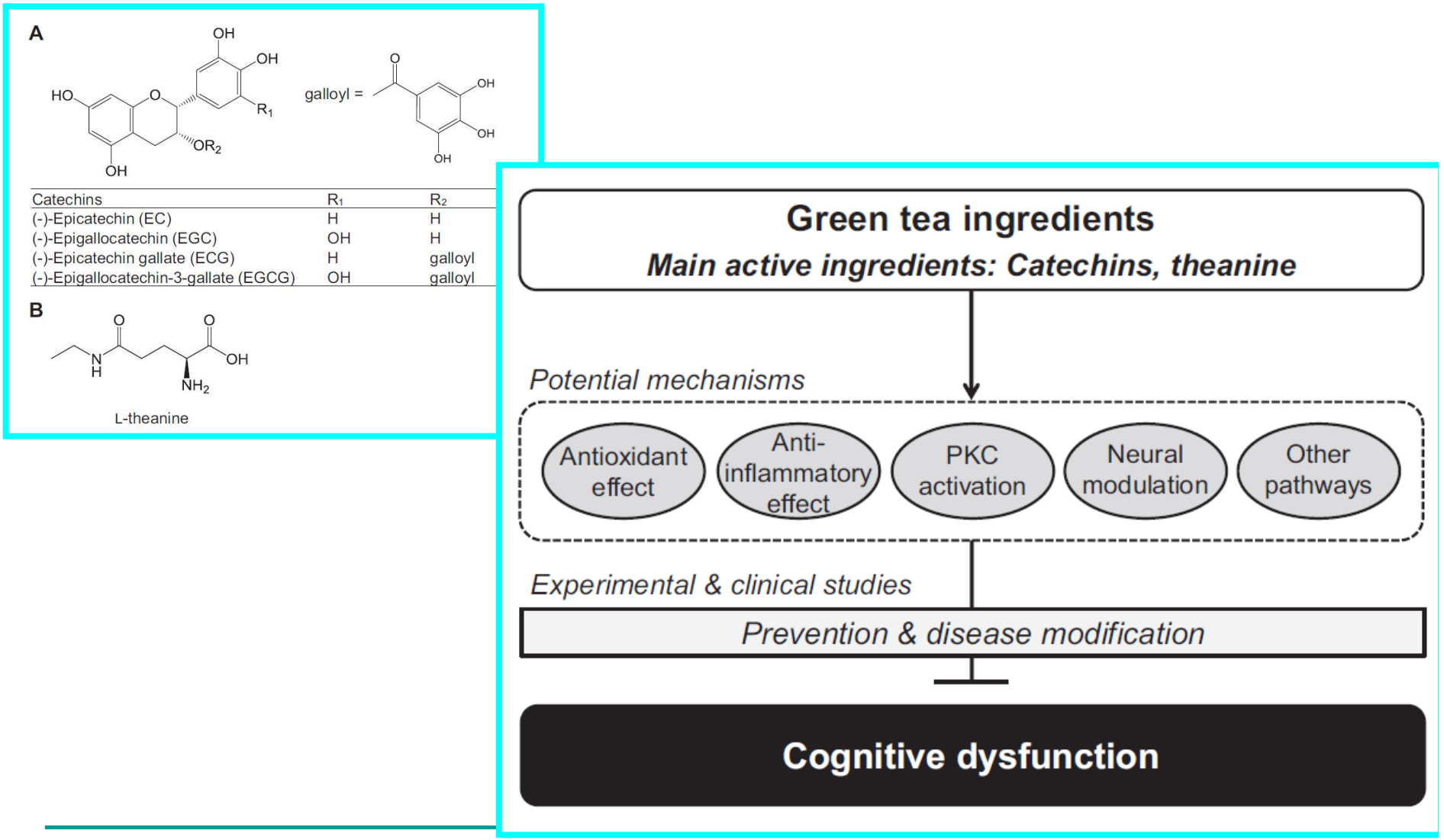
TABLE 4

Associations of types of tea with cognitive impairment and decline[1]

	Cross-sectional association with cognitive impairment at baseline in whole sample by type of tea					Longitudinal association with cognitive decline among 1438 participants without baseline cognitive impairment by type of tea[2]				
	No tea (n = 954)	Black and oolong tea only[3] (n = 965)	P	Green tea[4] (n = 582)	P	No tea (n = 513)	Black and oolong tea only[3] (n = 557)	P	Green tea[4] (n = 368)	P
Whole sample										
n (%)	182 (19.1)	99 (10.3)		26 (4.5)		182 (35.5)	169 (30.3)		110 (29.9)	
OR (95% CI)	1	0.55 (0.40,0.76)	< 0.001	0.42 (0.25, 0.69)	0.001	1	0.69 (0.51, 0.93)	0.02	0.82 (0.58, 1.16)	0.26
Stratified analyses										
Men										
n (%)	38 (14.0)	30 (7.6)		4 (1.7)		43 (30.7)	55 (24.6)		49 (31.8)	
OR (95% CI)	1	0.48 (0.24, 0.95)	0.036	0.25 (0.08, 0.79)	0.018	1	0.58 (0.32, 1.03)	0.06	1.04 (0.55, 1.94)	0.91
Women										
n (%)	144 (21.1)	69 (12.1)		22 (6.5)		139 (37.3)	114 (34.2)		61 (28.5)	
OR (95% CI)	1	0.56 (0.38, 0.82)	0.003	0.50 (0.28, 0.88)	0.016	1	0.75 (0.53, 1.08)	0.12	0.70 (0.45, 1.07)	0.10
Age < 75 y										
n (%)	112 (14.0)	63 (7.4)		20 (3.8)		162 (35.0)	149 (29.9)		103 (31.1)	
OR (95% CI)	1	0.52 (0.35, 0.78)	0.001	0.57 (0.33, 0.99)	0.045	1	0.70 (0.51, 0.96)	0.03	0.91 (0.63, 1.31)	0.62
Age ≥ 75 y										
n (%)	70 (45.5)	36 (29.3)		6 (11.1)		20 (40.0)	20 (34.5)		7 (18.9)	
OR (95% CI)	1	0.53 (0.27, 1.05)	0.068	0.13 (0.03, 0.51)	0.003	1	0.31 (0.07, 1.39)	0.13	0.09 (0.01, 0.68)	0.02

Tze-Pin N. et al. Am J Clin Nutr 2008

The verde


A
OH
OH
HO
O
R1
OR2
OH
galloyl =
O
OH
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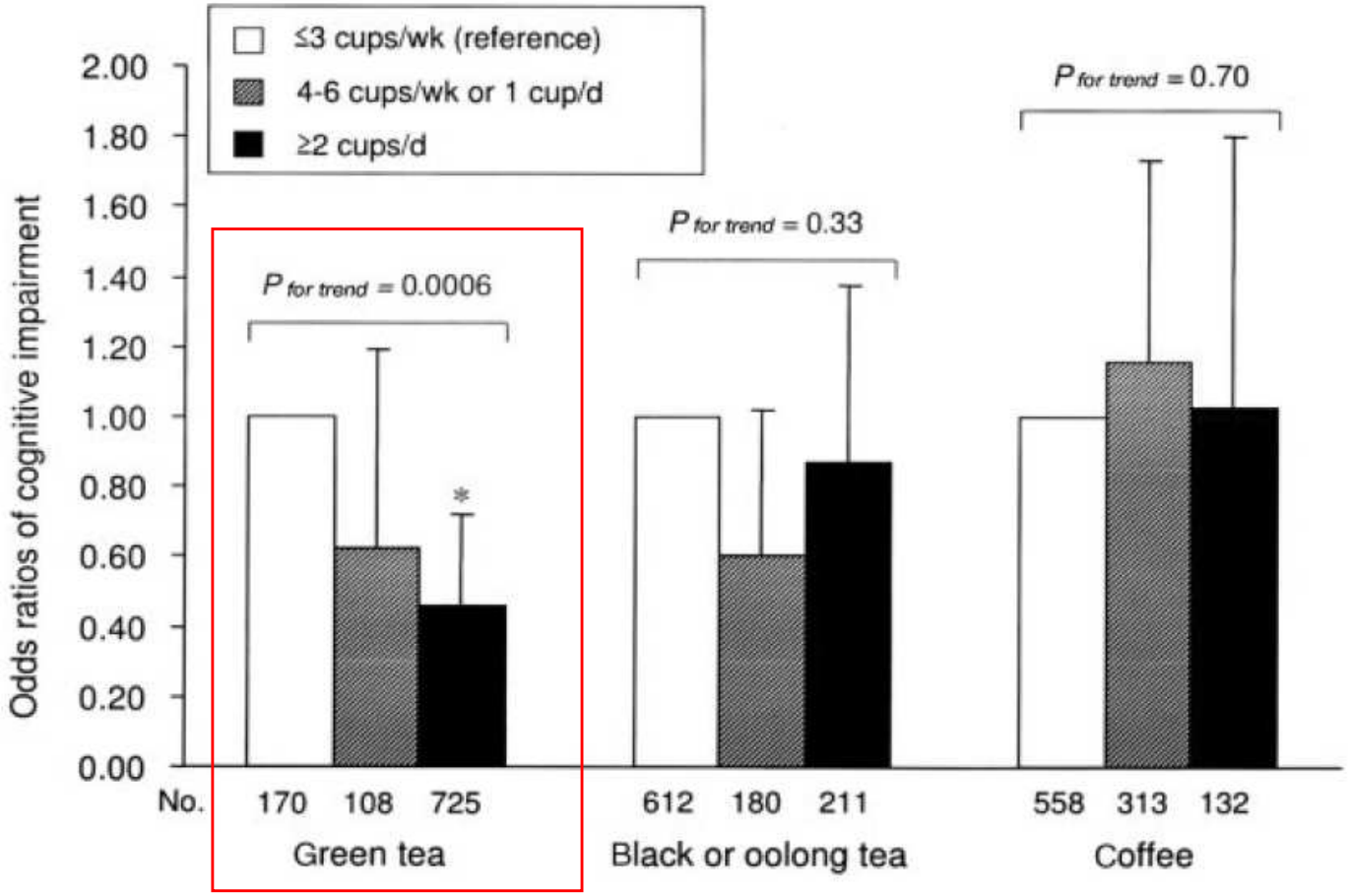
OH
Catechins R1 R2
(-)-Epicatechin (EC) H H
(-)-Epigallocatechin (EGC) OH H
(-)-Epicatechin gallate (ECG) H galloyl
(-)-Epigallocatechin-3-gallate (EGCG) OH galloyl
B
O
O
N
H
OH
NH2
L-theanine
Green tea ingredients
Main active ingredients: Catechins, theanine
Potential mechanisms
Antioxidant effect
Anti-inflammatory effect
PKC activation
Neural modulation
Other pathways
Experimental & clinical studies
Prevention & disease modification
Cognitive dysfunction

Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project[1–3]

Shinichi Kuriyama, Atsushi Hozawa, Kaori Ohmori, Taichi Shimazu, Toshifumi Matsui, Satoru Ebihara, Shuichi Awata, Ryoichi Nagatomi, Hiroyuki Arai, and Ichiro Tsuji



Kuriyama S. et al. Am J Clin Nutr 2006

Clinical Benefits of green Tea consumption for cognitive dysfunction

Table 2
Longitudinal studies.

Source	Population description	Types of tea	Outcomes	Reference no.
Ng et al. 2008	1438 Chinese residents, aged ≥55, 1- to 2-year follow-up	Green tea, black tea, oolong tea	Less decline of cognitive function in participants with higher level of tea consumption, $P = 0.042$	[138]
Eskelinen et al. 2009	1409 Finnish residents, aged 65–79, 21-year follow-up	Any type of tea	No association with dementia or Alzheimer's disease	[143]
Arab et al. 2011	4809 U.S. residents, aged ≥65, 7.9-year follow-up	Any type of tea	Reduced rate of cognitive decline in women, $P = 0.07$ for modified MMSE, $P = 0.04$ for modified MMSE with item response theory; non-linear relationship with the frequency of tea consumption	[144]
Feng et al. 2012	7139 Chinese residents, aged 80–115, 7-year follow-up	Any type of tea	Higher verbal frequency scores throughout the follow-up period; but steeper slope of cognitive decline compared with non-drinker from a higher baseline level; coefficient for the interaction term Time × Daily drinking = −0.12, $P = 0.02$	[147]
Noguchi-Shinohara et al. 2014	723 Japanese residents, aged≥ 60 years, 4.9-year follow-up	Green tea	Incidence of overall cognitive decline (dementia or mild cognitive impairment): 0.32 (95% CI: 0.16–0.64) for everyday drinker; 0.47 (95% CI: 0.25–0.86) for 1–6 days/week drinker *vs.* 1 (reference, non-drinker)	[145]

Table 3
Interventional studies.

Source	Population description	Intervention	Outcomes	Reference no.
Kataoka et al. 2009	29 Japanese participants with cognitive dysfunction, aged 85 years on average	Green tea with high theanine content (2040 mg/day) *vs.* placebo, 12 months	Improvement of cognitive function based on revised Hasegawa dementia scale, $P < 0.05$	[148]
Park et al. 2011	91 Chinese participants with mild cognitive impairment, aged 40–75 years	Green tea-based dietary supplement (LGNC-07, 1680 mg/day) *vs.* placebo, 4 months	Improvement of cognitive function based on Rey–Kim memory test (memory) in 16 weeks, $P = 0.0478$; and Stroop test (attention) in 8 weeks, $P = 0.0306$	[149]
Ide et al. 2014	12 Japanese participants with dementia, aged ≥65 years	Green tea powder (2000 mg/day), 3 months	Improvement of cognitive function based on MMSE Japanese version *vs.* before intervention, $P = 0.03$	[150]

Ide K. Et al PharmaNutrition 2015

Prevalence and natural history of MCI

Table 2. Prevalence Studies

Source	Study Location	No. of Participants	Participant Age, y	Prevalence of MCI, %
Unverzagt et al,[19] 2001	Indianapolis, IN	2212	≥65	23.4
Hänninen et al,[20] 2002	Finland	806	60-76	5.3
Lopez et al,[17] 2003	CHS	1690	≥75	22
Ganguli et al,[13] 2004	MoVIES	1248	≥65	3.2
Busse et al, [12] 2006	Leipzig, Germany	980	75-79	19.3
Das et al,[22] 2007	India	745	≥50	14.9
Di Carlo et al,[23] 2007	Italy	2830	65-84	16.1
Fischer et al,[24] 2007	Vienna, Austria	581	75	24.3
Manly et al,[25] 2008	Manhattan, NY	2364	≥65	21.8
Palmer et al,[21] 2008	Kungsholmen, Stockholm, Sweden	379	75-95	11.1
Plassman et al,[26] 2008	ADAMS	856	≥71	22.2
Roberts et al,[27] 2008	Rochester, MN	1969	70-89	14.8

Abbreviations: ADAMS, Aging, Demographics and Memory Study; CHS, Cardiovascular Health Study; MCI, mild cognitive impairment; MoVIES, Monongahela Valley Independent Elders Survey.

Table 3. Rates of Progression

Source	Study Location	No. of Participants	Participant Age, y	Reported Rate of Progression	Annual Crude Progression Rate, %[a]
Solfrizzi et al,[30] 2004	Italy	1524	≥65	3.8/100 person-years	3.8
Busse et al,[12] 2006	Leipzig, Germany	863	≥75	44% per 4.3 y	10.2
Tschanz et al,[31] 2006	Cache County, Utah	3266	≥65	46% per 3 y	15.3
Fischer et al,[24] 2007	Vienna, Austria	476	75-76	33.9% per 30 mo	13.6
Ravaglia et al,[32] 2008	Italy	937	≥65	14% per 1 yr	14.0
Farias et al,[28] 2009	California	111	>60	3% per 1 y[b]	3.0[b]
Petersen et al, unpublished data, 2009	Rochester, MN	1969	70-89	7.5% per 1 y	7.5

[a] Reported or crude rate estimated from data.
[b] Progression rate for clinic cohort reported as 13% per 1 year.

Acidi Grassi Omega 3

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Hindawi Publishing Corporation
BioMed Research International
Volume 2015, Article ID 172801, 13 pages
http://dx.doi.org/10.1155/2015/172801

Review Article

Omega-3 Fatty Acids in Early Prevention of Inflammatory Neurodegenerative Disease: A Focus on Alzheimer's Disease

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Alzheimer's disease (AD) is the leading cause of dementia and the most common neurodegenerative disease in the elderly. Furthermore, AD has provided the most positive indication to support the fact that inflammation contributes to neurodegenerative disease. The exact etiology of AD is unknown, but environmental and genetic factors are thought to contribute, such as advancing age, family history, presence of chronic diseases such as cardiovascular disease (CVD) and diabetes, and poor diet and lifestyle. It is hypothesised that early prevention or management of inflammation could delay the onset or reduce the symptoms of AD. Normal physiological changes to the brain with ageing include depletion of long chain omega-3 fatty acids and brains of AD patients have lower docosahexaenoic acid (DHA) levels. DHA supplementation can reduce markers of inflammation. This review specifically focusses on the evidence in humans from epidemiological, dietary intervention, and supplementation studies, which supports the role of long chain omega-3 fatty acids in the prevention or delay of cognitive decline in AD in its early stages. Longer term trials with long chain omega-3 supplementation in early stage AD are warranted. We also highlight the importance of overall quality and composition of the diet to protect against AD and dementia.

A critical review of Vitamin C for the prevention of age-related cognitive decline and Alzheimer's disease

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Abstract

Antioxidants in the diet have long been thought to confer some level of protection against the oxidative damage that is involved in the pathology of Alzheimer's disease as well as general cognitive decline in normal aging. Nevertheless, support for this hypothesis in the literature is equivocal. In the case of vitamin C (ascorbic acid) in particular, lack of consideration of some of the specific features of vitamin C metabolism has led to studies in which classification of participants according to vitamin C status is inaccurate, and the absence of critical information precludes the drawing of appropriate conclusions. Vitamin C levels in plasma are not always reported, and estimated daily intake from food diaries may not be accurate or reflect actual plasma values. The ability to transport ingested vitamin C from the intestines into blood is limited by the saturable sodium-dependent vitamin C transporter (SVCT1) and thus very high intakes, and the use of supplements are often erroneously considered to be of greater benefit that they really are. The current review documents differences among the studies in terms of vitamin C status of participants. Overall, there is a large body of evidence that maintaining healthy vitamin C levels can have a protective function against age-related cognitive decline and Alzheimer's disease, but avoiding vitamin C deficiency is likely to be more beneficial than taking supplements on top of a normal, healthy diet.

Single nutrient interventions in AD/MCI: in general no beneficial effects on cognition

Nutrient	Author	Journal	#Subjects/ Duration	Outcome
n3 PUFAs	Quinn 2010	JAMA	402 18 months	DHA compared with placebo did not slow the rate of cognitive and functional decline in mild-moderate AD patients.
	Freund-Levi 2006	Arch Neurol	174 6 months	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. However, positive effects were observed in a small group of patients with very mild AD (MMSE>27)
B-vitamins	Aisen 2008	JAMA	409 18 months	This regimen of high-dose B vitamin supplements does not slow cognitive decline in individuals with mild to moderate AD.
	McMahon 2006	N Eng J Med	276 24 months	The results of this trial do not support the hypothesis that homocysteine lowering with B vitamins improves cognitive performance.
Vitamin E / Antioxidants	Dysken 2014	JAMA	304 Mean f-up 27 months	Among patients with mild to moderate AD, 2000 IU/d of alpha-tocopherol compared with placebo resulted in slower functional decline.
	Petersen 2005	N Eng J Med	769 36 months	Vitamin E had no benefit in patients with mild cognitive impairment.
	Galasko 2012	Arch Neurol	52 16 weeks	However, this treatment (vitamin E + vitamin C plus α-lipoic acid) raised the caution of faster cognitive decline
Vitamin D2	Stein 2011	J Alz Disease	32 8 weeks	We conclude that high-dose vitamin D provides no benefit for cognition or disability over low-dose vitamin D in mild-moderate AD
Ginkgo biloba	DeKosky 2008	JAMA	3069 median f-up 6.1 Y	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.

- Lecitina (o fosfatidilcolina): principale fonte di colina di origine dietetica.
- Analisi: 12 trials condotti su pazienti affetti da malattia di Alzheimer, demenza vascolare, forme miste di demenza del tipo Alzheimer e vascolare e forme di decadimento cognitivo non chiaramente definite.

NESSUNA EVIDENZA DI EFFETTI SUPERIORI AL PLACEBO

La somministrazione di citicolina (citidina-5-difosfo-colina) da luogo alla formazione di citidina e colina, che entrano nel metabolismo dei fosfolipidi e determinano un incremento dei livelli cerebrali di acetilcolina e dopamina.

Studi clinici sul composto hanno valutato l'efficacia principalmente in patologie cerebrovascolari (funzioni cognitive; recupero a seguito di ictus cerebrale di lieve o moderata entità).

Modesto, ma significativo, effetto sulla memoria e sul comportamento rispetto al placebo .

Ictus cerebrale : 1.652 soggetti, di cui solo 1.372 erano comparabili (583 con placebo e 789 con citicolina) e la dose più studiata è stata di 2.000 mg al giorno).

Soggetti trattati con citicolina: maggiori capacità di recupero e minori sequele permanenti rispetto a quelli trattati con placebo .

La colina alfoscerato (alfa-gliceril-fosforil-colina) è, tra i precursori colinergici, quello che induce, in modelli animali, il più marcato aumento dei livelli cerebrali di acetilcolina.

Efficacia clinica : 9 trials controllati, randomizzati ed in doppio cieco.

1165 pazienti, di cui 486 affetti da malattia di Alzheimer, 421 da demenza vascolare e 208 da forme miste neurodegenerative e vascolari.

I risultati ottenuti hanno messo in evidenza, nelle forme neurodegenerative, una differenza di 3.4 punti medi rispetto al placebo per il MMSE ed una differenza di 4.3 punti medi rispetto al placebo per la SGAG nella demenza vascolare.