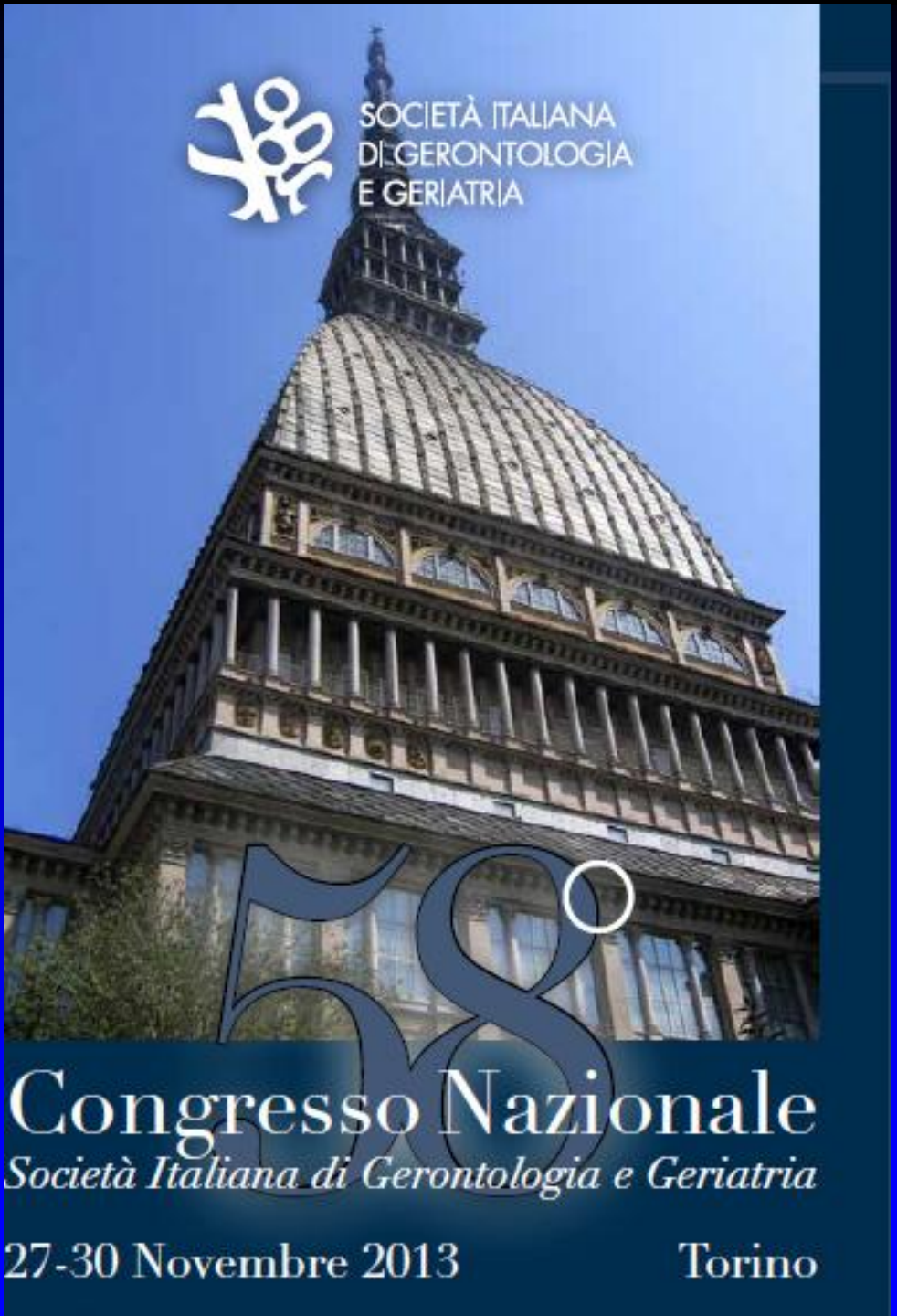

Lunch symposium

LA FARMACONUTRIZIONE NEL TRATTAMENTO DELLA MALATTIA DI ALZHEIMER IN FASE INIZIALE: EVIDENZA O EFFIMERA ILLUSIONE?

Angelo Bianchetti

Gruppo di Ricerca Geriatrica
Dip.to Medicina e Riabilitazione, Istituto Clinico S.Anna – Brescia
Scuola di Specializzazione in Geriatria, Università degli Studi di Brescia

Nutrizione e malattia di Alzheimer

L'AD influenza la nutrizione

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

La nutrizione influenza l'AD

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

Nutrizione e malattia di Alzheimer

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La nutrizione influenza l'AD

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- Prognosi delle malattie acute
- Rischio di decubito

- **Rischio di sviluppare demenza e AD**
- **Progressione della malattia**
- **Funzioni cognitive**

I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell'AD/demenza e le prestazioni cognitive anche in soggetti non dementi

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

I fattori nutrizionali influenzano il rischio di AD/demenza, la progressione dell'AD/demenza e le prestazioni cognitive anche in soggetti non dementi

- **Dati clinici**
  - In soggetti anziani sani, elevati livelli plasmatici di vitamine del gruppo B (B1, B2, B6, folati, B12), C, D, e E, e di acidi grassi ω-3 si associano a migliori prestazioni cognitive e minore atrofia cerebrale alla RMN *(Bowman GL et al Neurology 2012)*
  - In soggetti sedentari, ipertesi e in sovrappeso, una dieta ipocalorica, povera di sodio, ricca di potassio, calcio e magnesio, di frutta e vegetali, a basso contenuto di grassi animali, ricca di fibre, si associa a miglioramento delle prestazioni cognitive. *(Smith PJ et al, Hypertension 2010)*
  - Una dieta ricca di cibi ad elevata capacità antiossidante (olio di oliva, noci) si associa a migliori prestazioni cognitive mnesiche;. associazione indipendente fra escrezione urinaria di polifenoli e prestazioni mnesiche. *(Valls-Pedret et al, JAD 2012)*

The NEW ENGLAND JOURNAL of MEDICINE

OCCASIONAL NOTES

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Franz H. Messerli, M.D.

DOI: 10.1056/NEJMon1211064

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Dietary flavonoids, abundant in plant-based foods, have been shown to improve cognitive function. Specifically, a reduction in the risk of dementia, enhanced performance on some cognitive tests, and improved cognitive function in elderly patients with mild impairment have been associated with a regular intake of flavonoids.[1,2] A subclass of flavonoids called flavanols, which are widely present in cocoa, green tea, red wine, and some fruits, seems to be effective in slowing down or even reversing the reductions in cognitive performance that occur with aging. Dietary flavanols have also been shown to improve endothelial function and to lower blood pressure by causing vasodilation in the peripheral vasculature and in the brain.[3,4] Improved cognitive performance with the administration of a cocoa polyphenolic extract has even been reported in aged Wistar–Unilever rats.[5]

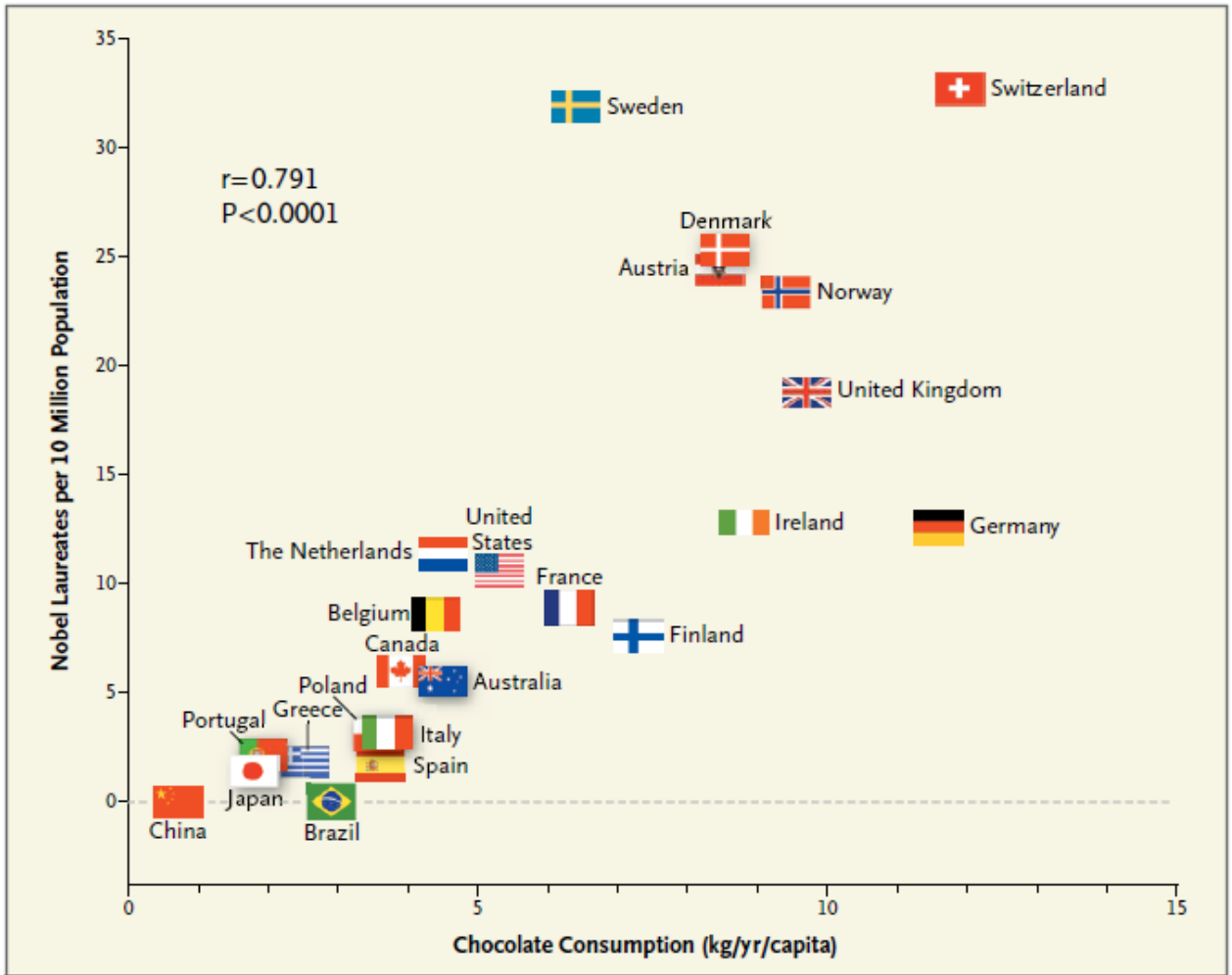

Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

ABSTRACT

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Estruch at the Department of Internal Medicine, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain, or at restruch@clinic.ub.es, or to Dr. Martínez-González at the Department of Preventive Medicine and Public Health, Facultad de Medicina–Clínica Universidad de Navarra, Irunlarrea 1, 31008 Pamplona, Spain, or at mamartinez@unav.es.

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

Drs. Estruch and Martínez-González contributed equally to this article.

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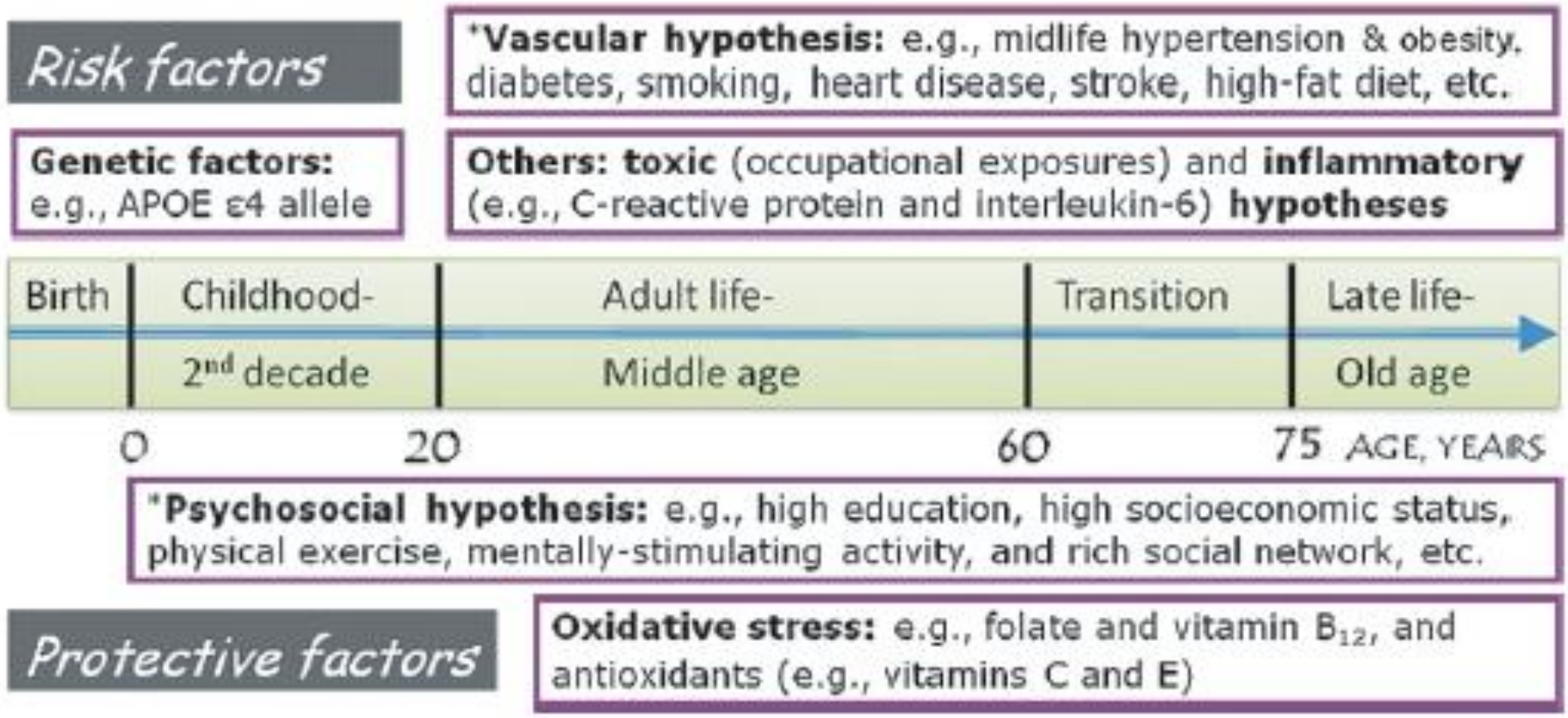


Qiu, Xu and Fratiglioni, JAD, 2010

ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of Apolipoprotein E Genotype and Diet on Apolipoprotein E Lipidation and Amyloid Peptides

Randomized Clinical Trial

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

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

Objective: To characterize the lipidation states of Aβ peptides and apolipoprotein E in the cerebrospinal fluid in adults with respect to cognitive diagnosis and *APOE* ε4 allele carrier status and after a dietary intervention.

Design: Randomized clinical trial.

Setting: Veterans Affairs Medical Center clinical research unit.

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

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

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

Results: Baseline levels of LD Aβ were greater for adults with mild cognitive impairment compared with adults with normal cognition (LD Aβ42, $P=.05$; LD Aβ40, $P=.01$). These findings were magnified in adults with mild cognitive impairment and the ε4 allele, who had higher LD apolipoprotein E levels irrespective of cognitive diagnosis ($P<.001$). The Low diet tended to decrease LD Aβ levels, whereas the High diet increased these fractions (LD Aβ42, $P=.01$; LD Aβ40, $P=.15$). Changes in LD Aβ levels with the Low diet negatively correlated with changes in cerebrospinal fluid levels of insulin (LD Aβ42 and insulin, $r=-0.68$ [$P=.01$]; LD Aβ40 and insulin, $r=-0.78$ [$P=.002$]).

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

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

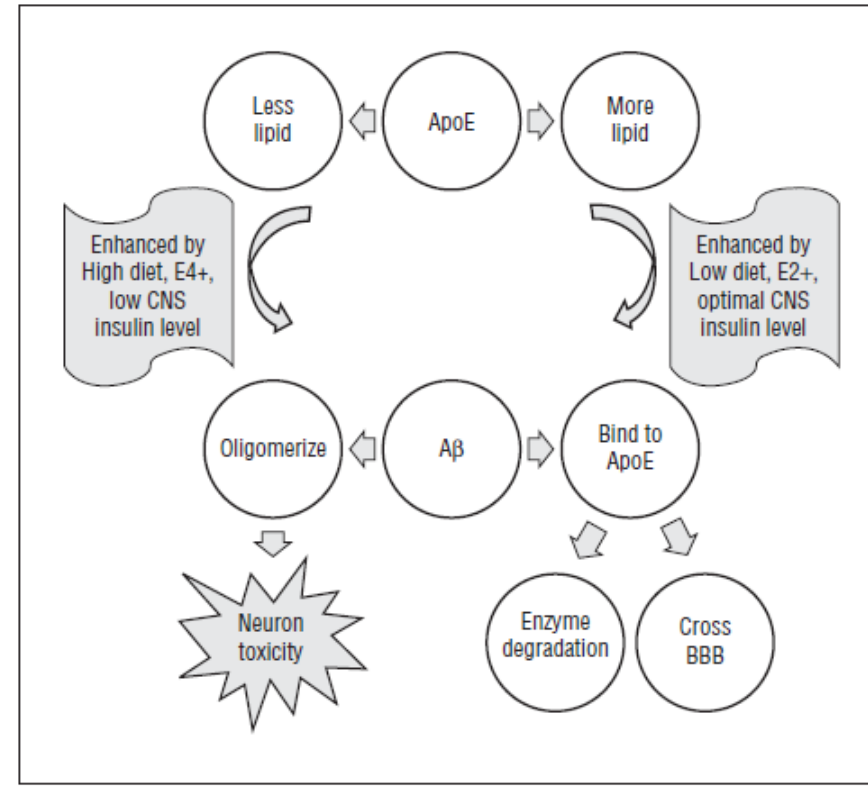


Figure 6. Theoretical model of β-amyloid (Aβ) peptide and apolipoprotein E (ApoE) interaction in the central nervous system (CNS). In the top panel, when ApoE is more lipidated, such as with an ε2 allele (E2+) or a healthy diet, it may be more able to bind Aβ and facilitate its clearance and degradation.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

EDITORIAL

JAMA NEUROL PUBLISHED ONLINE JUNE 17, 2013

ONLINE FIRST

Food for Thought

Deborah Blacker, MD, ScD

- cardiovascular risk factors such as poor diet, obesity and higher body mass index, diabetes and insulin resistance, and other aspects of the metabolic syndrome contribute to risk for AD dementia.
- part of the increased risk for AD dementia associated with vascular risk factors is surely related to an **increase in cerebrovascular burden**, but there may be a direct contribution to the development of Alzheimer pathology as well
- the important lesson from the study is that **dietary intervention can change brain amyloid chemistry** in largely consistent and apparently meaningful ways—and in a short period of time.
- it adds another small piece to the growing evidence that **taking good care of your heart is probably good for your brain too**.

WFN-RGD members now have access to
Journal of Alzheimer's Disease

Journal of Alzheimer's Disease 33 (2013) 177–190
DOI 10.3233/JAD-2012-112039
IOS Press

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

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

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

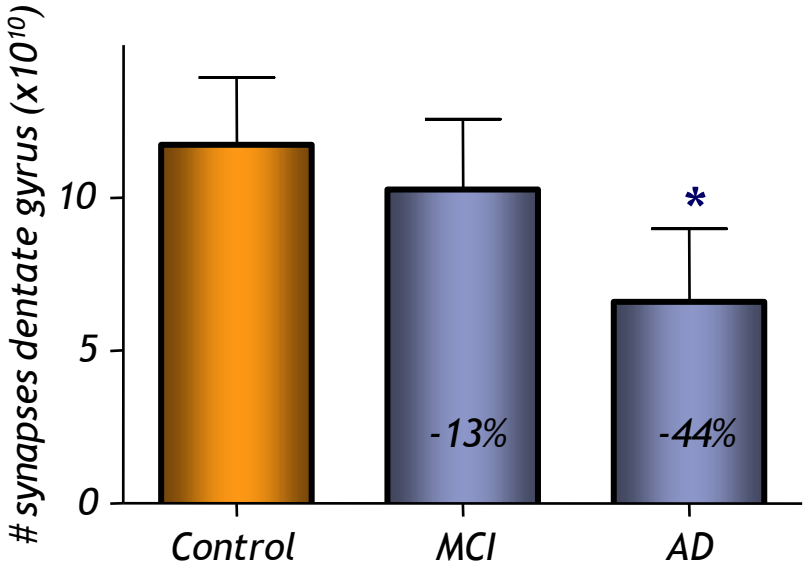
VIEWPOINT

Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002

- Synaptic loss occurs very early in the disease process and is considered the most structural correlate to cognitive performance.



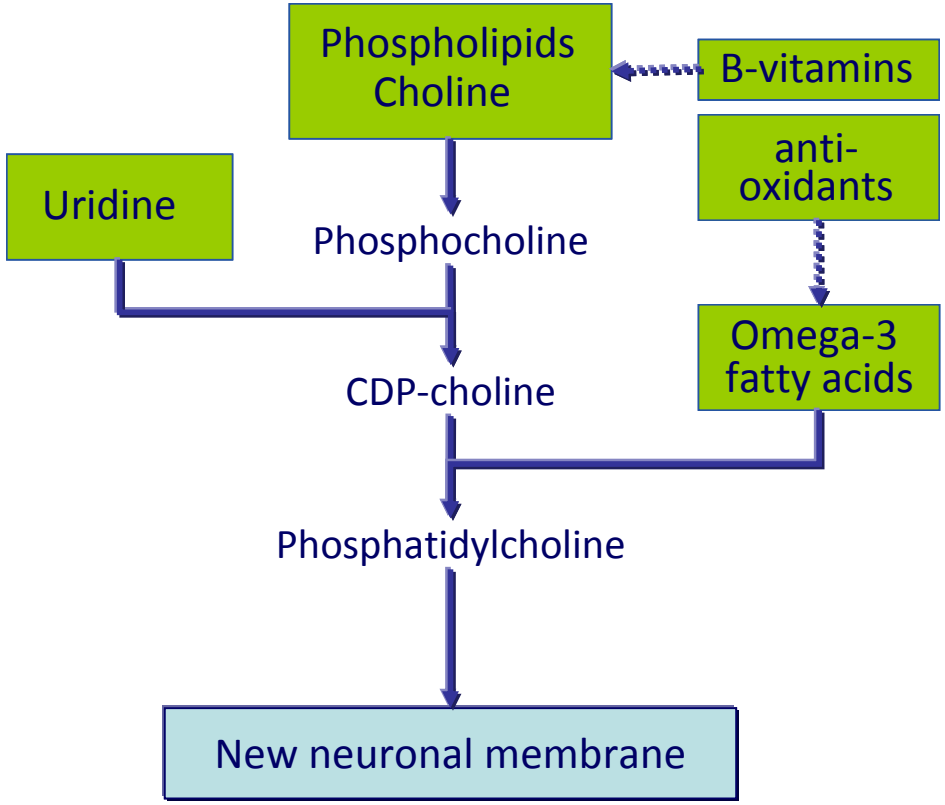
Physical Basis of Cognitive Alterations in Alzheimer's Disease: Synapse Loss Is the Major Correlate of Cognitive Impairment

Robert D. Terry, MD,* Eliezer Masliah, MD,* David P. Salmon, PhD,* Nelson Butters, PhD,†
Richard DeTeresa, BS,* Robert Hill, PhD,* Lawrence A. Hansen, MD,* and Robert Katzman, MD*

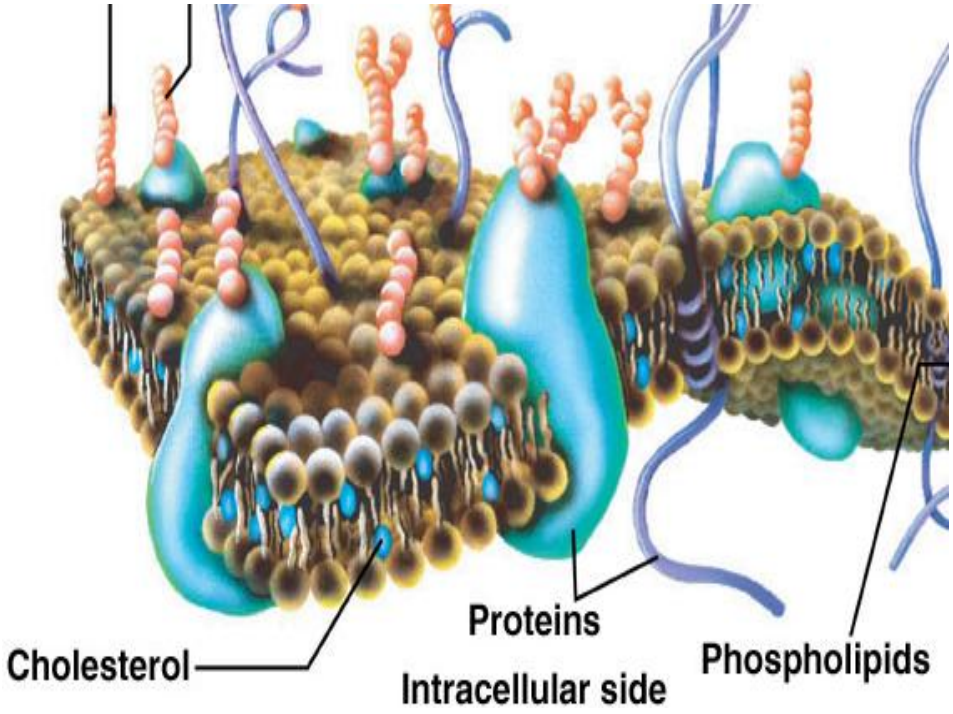
Terry RD, Masliah E, Salmon DP, Butters N, DeTeresa R, Hill R, Hansen LA, Katzman R.
Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580

Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis neuronal membrane



Phospholipids are main constituents of synapses



Fattori nutrizionali e AD: le modalità di relazione.

- Effetto di protezione dai fattori vascolari
- Effetto di riduzione del carico infiammatorio
- Effetto su specifici meccanismi coinvolti nella patogenesi della malattia di Alzheimer (tossicità a-β, integrità sinaptica)

Single nutrient interventions in MCI and AD: No effect on cognitive functioning

Author	Journal		Nutrient	#Subjects/ Duration	Outcome
Stein 2011	J Alz Disease		Vitamin D2	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
Quinn 2010	JAMA		DHA	402 18 months	DHA compared with placebo **did not slow the rate of cognitive and functional decline** in mild-moderate AD patients.
DeKosky 2008	JAMA		Ginkgo biloba	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.
Aisen 2008	JAMA		B-vitamins	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		B-vitamins	276 24 months	The results of this trial do **not support the hypothesis that homocysteine lowering with B vitamins improves cognitive performance**.
Freund-Levi 2006	Arch Neurol		n3 PUFAs	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.
Petersen 2005	N Eng J Med		Vitamin E	769 36 months	Vitamin E had **no benefit in patients with mild cognitive impairment**.

Development of Souvenaid
Targeted to improve formation of synapses

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

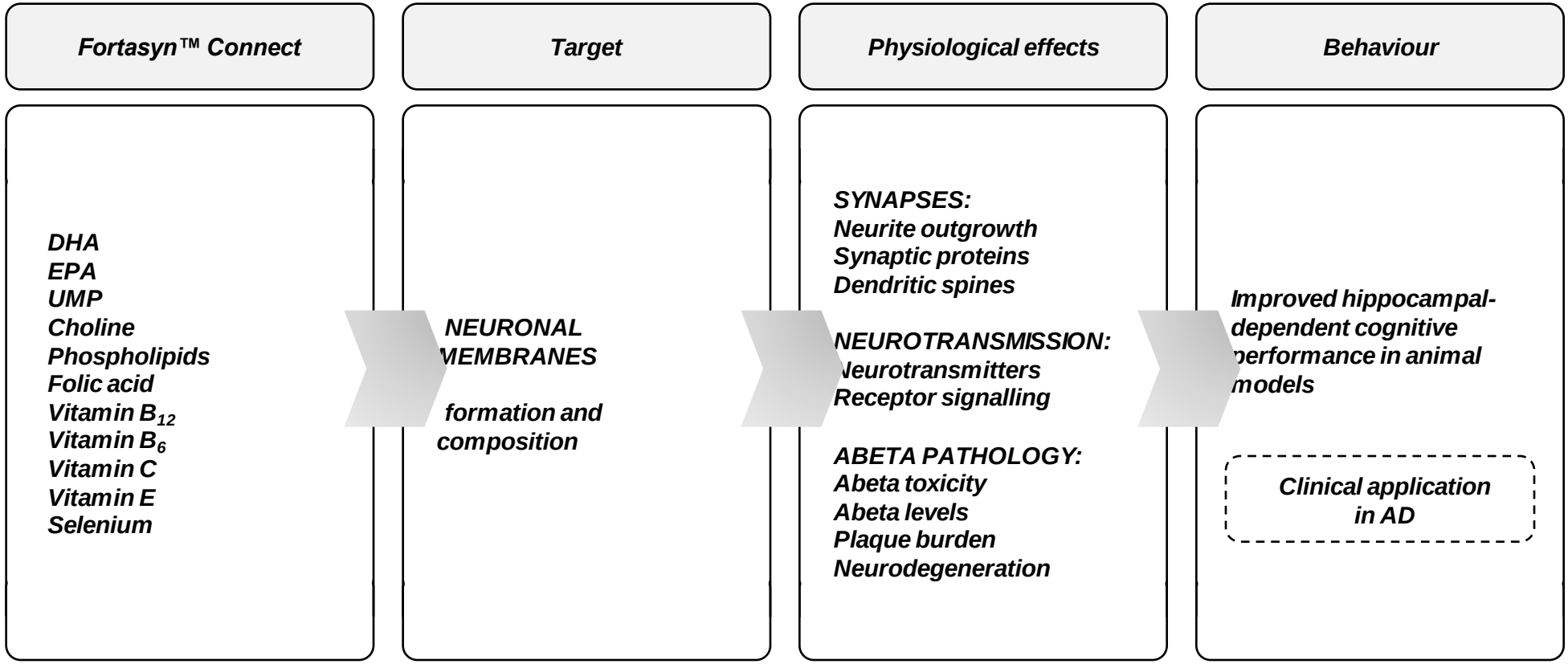
- Uridine (UMP)
- Omega-3 fatty acids
- Choline
- Phospholipids
- B vitamins

Fortasyn™ Connect PATENTED

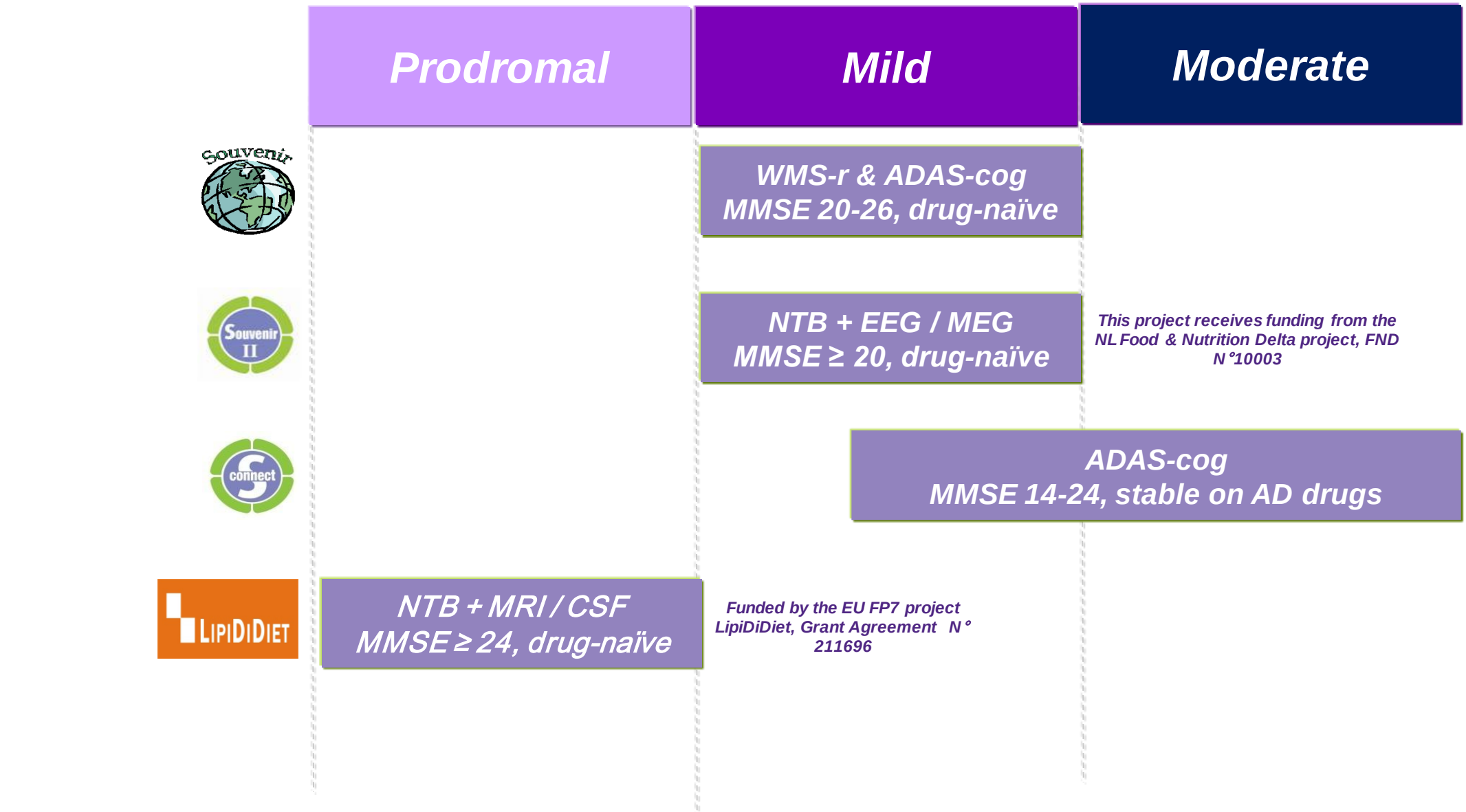
HYPOTHESIS:
Souvenaid successfully addresses an unmet nutritional need in people with AD by increasing their intake of these dietary precursors and co-factors

Summary mode of action Fortasyn Connect – based on preclinical observations

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



Souvenaid Clinical trial programme

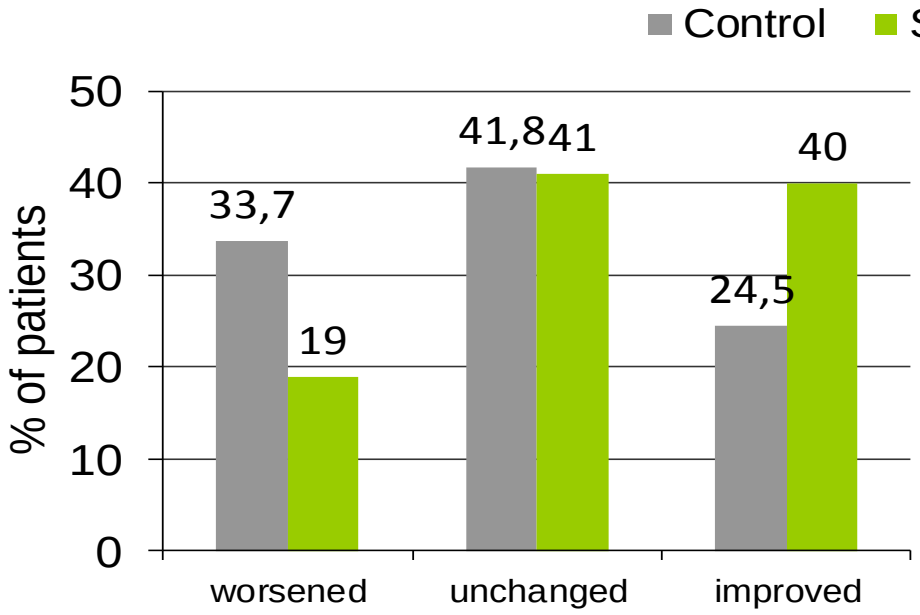


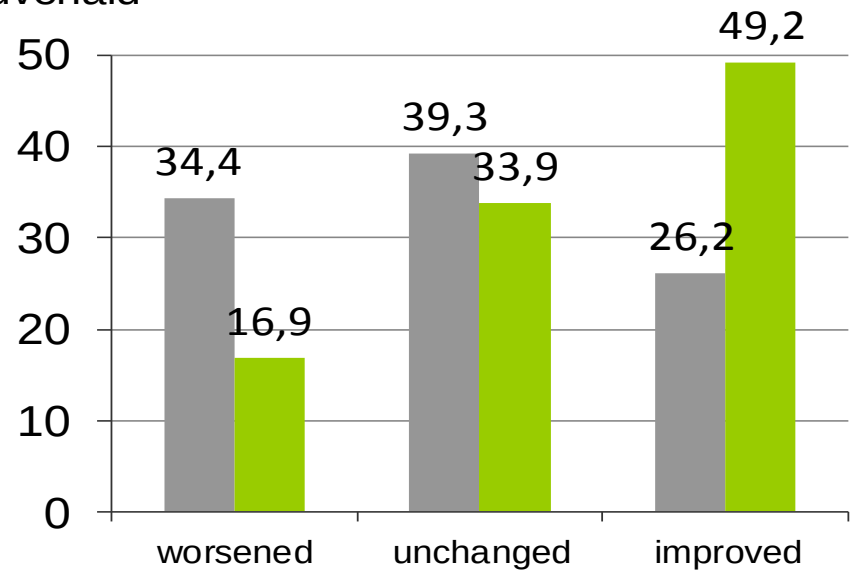
Souvenir I: Souvenaid improves memory

Delayed verbal memory WMS-r

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

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

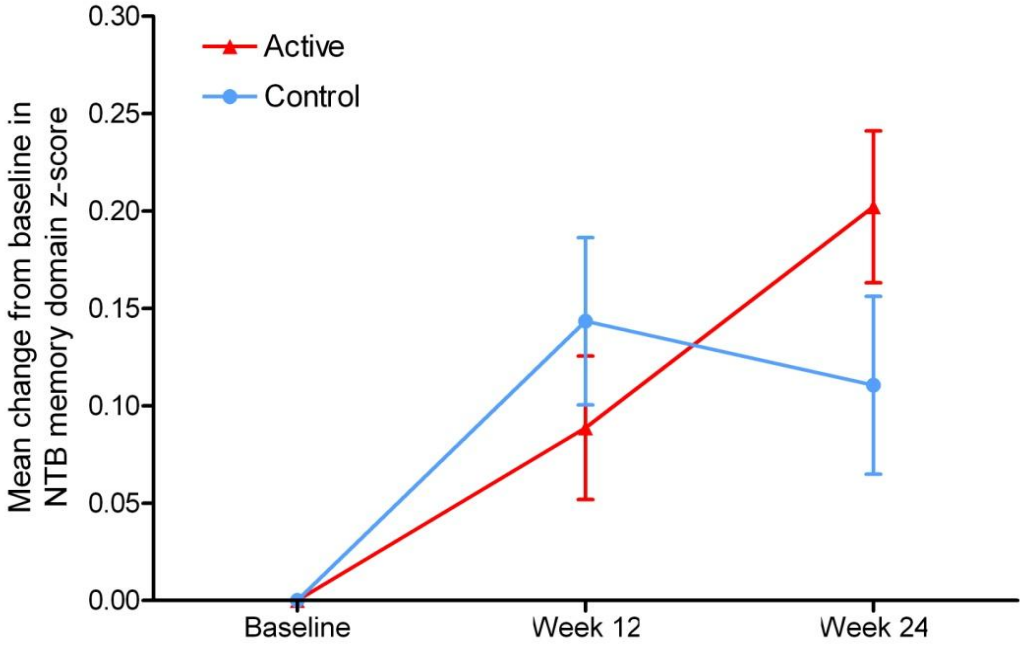




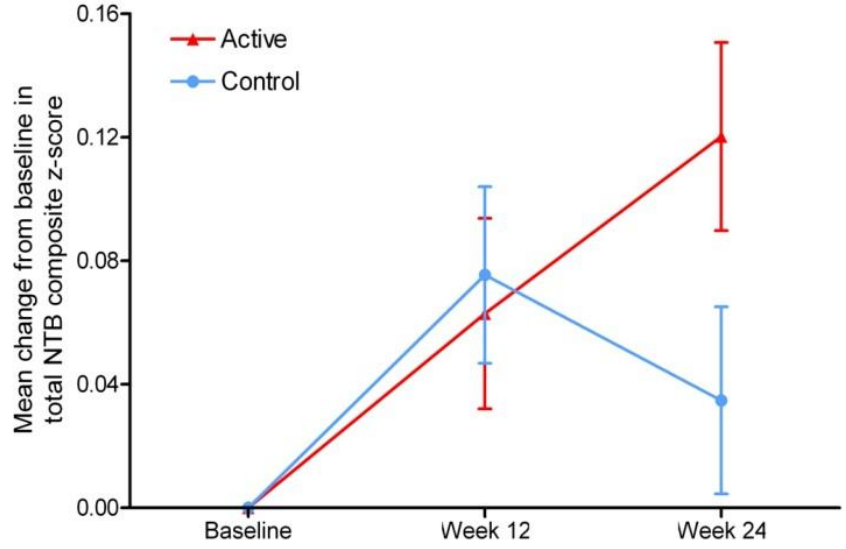
** Chi-square*

Souvenir II: memory improvement

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



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



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

Survey sui benefici di Souvenaid nei pazienti con Malattia di Alzheimer in fase iniziale.

Introduzione:

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

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

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

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

Obiettivo:

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

Metodo:

- descrizione da parte di un gruppo di 30 medici afferenti a centri per la diagnosi e cura delle demenze (UVA) degli effetti della somministrazione di Souvenaid sulle funzioni cognitive, sul comportamento e sulla funzione osservati dal caregiver e condivisione delle opinioni osservate
- la descrizione del comportamento del paziente avverrà al termine di un periodo di utilizzo di Souvenaid minimo 3 mesi
- per la raccolta delle opinioni, che saranno anonime e non prevedono la raccolta di dati sensibili dei pazienti e dei caregiver, verrà utilizzato un questionario anonimo da compilarsi on line
- non è prevista la raccolta di dati che permettano l'identificazione del paziente né l'identificazione del centro
- la raccolta delle informazioni avverrà al momento della visita di controllo (la prima successiva alla prescrizione di Souvenaid)
- ogni partecipante alla Survey dovrà descrivere un minimo di 20 casi

Design and methodology

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

SOUVENAID in clinica

I dati disponibili indicano che:

- *è ben tollerato, non interferisce con la coagulazione ed ha un indice glicemico basso*
- *nei soggetti con AD lieve migliora le prestazioni di memoria verbale a 12 settimane e la memoria globale a 24 settimane*
- *I miglioramenti proseguono a 48 settimane e rimangono presenti anche nei soggetti che non assumono farmaci per l'AD (OLE)*
- *vi e un effetto biologico che si esplica in un miglioramento del funzionamento sinaptico*

E' in corso di studio

- *l'effetto del trattamento sulla progressione da AD prodromico a AD conclamato (LipiDiDiet)*
- *Raccolta di dati in aperto «real world» sull'effetto sui domini funzione, comportamento auto ed etero osservati in soggetti con MCI e AD lieve (Memento)*

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Commentary

Food for Thought: Souvenaid® in Mild Alzheimer's Disease

Jeffrey L. Cummings*
From the Cleveland Clinic Lou Ruvo Center for Brain Health, Neurological Institute, Las Vegas, NV, Cleveland, OH, Weston, FL, USA

If Souvenaid® has an effect on a synaptic integrity as proposed by the investigators of Souvenaid® II, then its effects may not be limited to AD. An interesting challenge for the Souvenaid® development program is to prioritize potential target populations—normal aging, AD, Parkinson's disease, traumatic brain injury, stroke, etc. The results of the Souvenaid® II trial are sufficiently compelling to warrant advancing treatment trials of Souvenaid® into additional AD trials and consideration of testing in other conditions.