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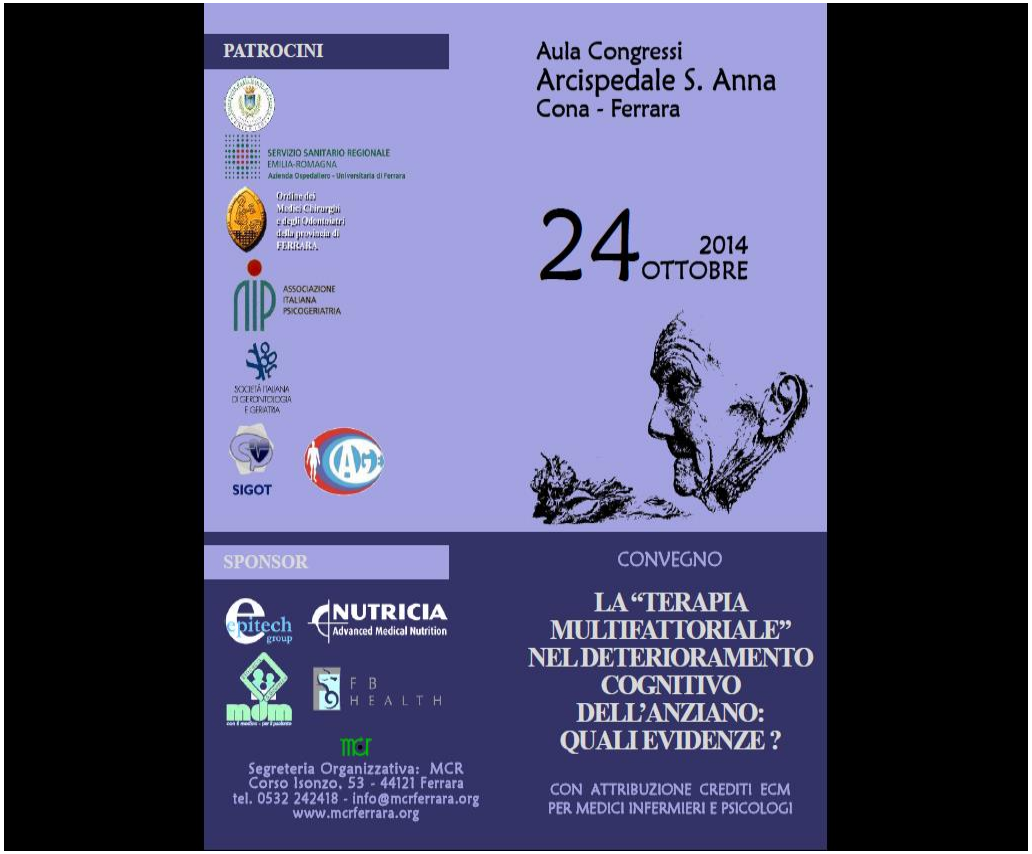

Dieta e Medical Food nel declino cognitivo lieve

MEDICAL FOOD

A medical food is in USA defined in 21 U.S.C. as :

A food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognisable scientific principles, are established by medical evaluation

Medical foods are foods that are specially formulated and intended for the dietary management of a disease that has distinctive nutritional needs that cannot be met by normal diet alone. They were defined in the Food Drug Administration's and are subject to the general food and safety labeling requirements of the Federal Food Drug and cosemtic act.

Medical foods are distinct from the broader category of foods for special dietary use and from traditional foods that bear a health claim. In order to be considered a medical food the product must, at a minimum: be a food for oral ingestion or tube feeding (nasogastric tube); be labeled for the dietary management of a specific medical disorder, disease or condition for which there are distinctive nutritional requirements and be intended to be used under medical supervision.

MEDICAL FOOD

Federal regulation requires that a product meet all of the following criteria to be considered a medical food.

1. It is a specially formulated and processed product (as opposed to a naturally occurring foodstuff used in its natural state) for the partial or exclusive feeding of a patient by means of oral intake or enteral feeding by tube.

2. It is intended for the dietary management of a patient who, because of therapeutic or chronic medical needs, has limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foodstuffs or certain nutrients, or who has other special medically determined nutrient requirements, the dietary management of which cannot be achieved by the modification of the normal diet alone.

3.The product label specifies that the product is for the dietary management of a medical disorder, disease or condition. It provides nutritional support specifically modified for the management of the unique nutrient needs that result from the specific disease or condition, as determined by medical evaluation.

4. It is intended to be used under medical supervision, and is labeled as such.

5. It is intended only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the medical food.

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Use of medical foods and nutritional approaches in the treatment of Alzheimer's disease

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SUMMARY

Alzheimer's disease, the most common cause of dementia, has a high global economic impact. To date, there is no curative treatment; therefore, many efforts are directed not only at novel potential disease-modifying treatments and interventions, but also to develop alternative symptomatic and supportive treatments. Examples of these efforts include the medical foods. There are three medical foods that claim to offer symptomatic benefits: Axona®, Souvenaid® and CerefolinNAC®. Axona supplies ketone bodies as alternative energy source to neurons. Souvenaid provides precursors thought to enhance synaptic function. CerefolinNAC addresses the role of oxidative stress related to memory loss. The current scientific evidence on these medical foods is reviewed in this article. Furthermore, we also review the concept and evidence supporting use of the Mediterranean diet, a possible alternative to medical foods that, if implemented correctly, may have lower costs, fewer side effects and stronger epidemiological health outcomes.

Alzheimer's disease (AD) is the most common cause of dementia, affecting over 5 million North Americans and 14 million individuals worldwide [1]. In its early stages, AD affects predominantly short-term memory and language ability, with progressive changes in

Mediterranean diet

The Mediterranean diet does not comprise of medical foods, however, the concept is very similar to medical food whereby a specific healthy dietary pattern is adhered to, which may help in the prevention or delay of AD progression. There are a number of dietary approaches and interventions that have been proposed for the prevention and/or treatment of AD. We included a single dietary approach (i.e., the Mediterranean diet) and its scientific evidence to give one example of possible alternative nutritional approaches that may have lower costs, lower side effects and stronger epidemiologic evidence of health outcomes.

The most common version of the Mediterranean diet was presented by Dr Walter Willett of Harvard University's School of Public Health in the mid-1990s [44]. This diet emphasizes plant-based foods in abundance, fresh fruit as the typical daily dessert, olive oil as the principal source of fat, dairy products (principally cheese and yogurt), fish and poultry consumed in low to moderate amounts, zero to four eggs consumed weekly, red meat consumed in low amounts and wine consumed in low to moderate amounts. The total fat in this diet is 25–35% of daily calorie allowance, with saturated fat at 8% or less of daily calorie allowance [44].

A number of published studies found the benefits of adhering to the Mediterranean diet are being less likely to develop depression [45], more than 50% lowering of early death rates [46] and 83% relative reduction in the risk of developing diabetes [47]. The Seven Countries Study report also found the Cretan diet – a type of traditional Mediterranean diet consisting mostly of olive oil, bread, an abundance of fruits and vegetables, fish and moderate amounts of dairy foods and wine – can help lower death rates from heart disease [48]. The Lyon Diet Heart Study was a randomized, controlled trial with free-living subjects. Its goal was to test the effectiveness of a Mediterranean-type diet on the rate of coronary events in people who have had a first heart attack. A total of 302 experimental and 303 control subjects were randomized in the study. The results suggest that a Mediterranean-style diet may help reduce recurrent events in patients with heart disease [49]. The Mediterranean diet is low in

LIEVE DECLINO COGNITIVO

ELSEVIER

Alzheimer's & Dementia 7 (2011) 270–279

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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the text, which incorporate the use of biomarkers, are currently intended to be used only in research settings, including academic centers and clinical trials. There are several reasons for this limitation: (1) more research needs to be done to ensure that the criteria that include the use of biomarkers have been appropriately designed, (2) there is limited standardization of biomarkers from one locale to another, and limited experience with cut-points for diagnosis, and (3) access to biomarkers may be limited in different settings.

As a result, some aspects of the clinical research criteria may need to be revised, as these criteria are put into practice and new findings emerge. The clinical research criteria include an outline of additional data that need to be acquired so as to refine and improve their application. From that perspective, the clinical research criteria are designed to be a work-in-progress that will be updated regularly, as new information becomes available.

In these recommendations, we use the term "mild cognitive impairment (MCI) due to AD" to refer to the symptomatic predementia phase of AD. This degree of cognitive impairment is not normal for age and, thus, constructs such as age-associated memory impairment and age-associated cognitive decline do not apply. From this perspective, MCI due to AD can be considered as a subset of the many causes of cognitive impairment that are not dementia (CIND), including impairments resulting from head trauma, substance abuse, or metabolic disturbance [4].

Thus, the concept of "*MCI due to AD*" is used throughout this article to reflect the fact that the ultimate focus of these criteria is to identify those symptomatic but nondemented individuals whose primary underlying pathophysiology is

2.1.1. *Concern regarding a change in cognition*

There should be evidence of concern about a change in cognition, in comparison with the person's previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.

2.1.2. *Impairment in one or more cognitive domains*

There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic memory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to a diagnosis of AD dementia. (See the section on the cognitive characteristics later in the text for further details).

2.1.3. *Preservation of independence in functional abilities*

Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance. It is recognized that the application of this criterion is challenging,

Continuum

- Deficit soggettivo di memoria
- Mild cognitive impairment
- Declino cognitivo
  - Lieve
  - Lieve moderata
  - Moderata
  - Moderata grave
  - Grave

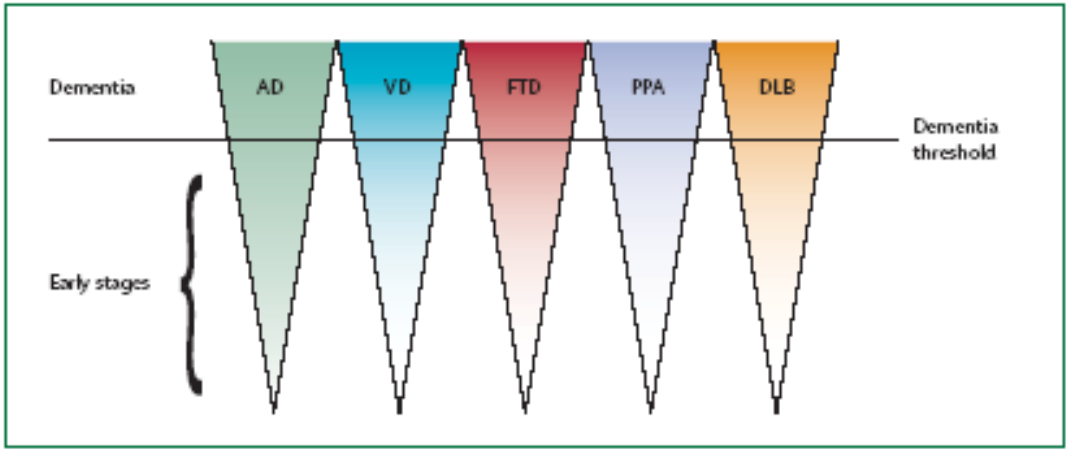

Figure: Alzheimer's disease starts and should be identified before the occurrence of full-blown dementia (as for other dementing conditions)

ELSEVIER

Alzheimer's & Dementia 6 (2010) 1–10

Alzheimer's & Dementia

Featured Articles

Efficacy of a medical food in mild Alzheimer's disease: A randomized, controlled trial

Philip Scheltens[a,*], Patrick J. G. H. Kamphuis[b], Frans R. J. Verhey[c], Marcel G. M. Olde Rikkert[d], Richard J. Wurtman[e], David Wilkinson[f], Jos W. R. Twisk[g], Alexander Kurz[h]

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Abstract

Objective: To investigate the effect of a medical food on cognitive function in people with mild Alzheimer's disease (AD).

Methods: A total of 225 drug-naïve AD patients participated in this randomized, double-blind controlled trial. Patients were randomized to active product, Souvenaid, or a control drink, taken once-daily for 12 weeks. Primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale–revised, and the 13-item modified Alzheimer's Disease Assessment Scale–cognitive subscale at week 12.

Results: At 12 weeks, significant improvement in the delayed verbal recall task was noted in the active group compared with control ($P = .021$). Modified Alzheimer's Disease Assessment Scale–cognitive subscale and other outcome scores (e.g., Clinician Interview Based Impression of Change plus Caregiver Input, 12-item Neuropsychiatric Inventory, Alzheimer's disease Co-operative Study–Activities of Daily Living, Quality of Life in Alzheimer's Disease) were unchanged. The control group neither deteriorated nor improved. Compliance was excellent (95%) and the product was well tolerated.

Conclusions: Supplementation with a medical food including phosphatide precursors and cofactors for 12 weeks improved memory (delayed verbal recall) in mild AD patients. This proof-of-concept study justifies further clinical trials.

Keywords: Alzheimer's disease; Nutritional intervention; Synapse formation; Membrane phosphatide synthesis; B vitamins; Omega-3 fatty acids; Nucleotides; Uridine; Phospholipids; Choline; Antioxidants; ADAS-cog, delayed verbal recall; Medical food; Dietary management; Randomized clinical trial; Dementia

Journal of Alzheimer's Disease 31 (2014) 225–236
DOI 10.3233/JAD-2012-121189
IOS Press

Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized, Controlled Trial

Philip Scheltens[a,*], Jos W.R. Twisk[b], Rafael Blesa[c], Elio Scarpini[d], Christine A.F. von Arnim[e], Anke Bongers[f], John Harrison[g,h], Sophie H.N. Swinkels[f], Cornelis J. Stam[i], Hanneke de Waal[a], Richard J. Wurtman[j], Rico L. Wieggers[f], Bruno Vellas[k] and Patrick J.G.H. Kamphuis[f]

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Accepted 1 June 2012

Abstract. Souvenaid aims to improve synapse formation and function. An earlier study in patients with Alzheimer's disease (AD) showed that Souvenaid increased memory performance after 12 weeks in drug-naïve patients with mild AD. The Souvenir II study was a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial to confirm and extend previous findings in drug-naïve patients with mild AD. Patients were randomized 1 : 1 to receive Souvenaid or an iso-caloric control product once daily for 24 weeks. The primary outcome was the memory function domain Z-score of the Neuropsychological Test Battery (NTB) over 24 weeks. Electroencephalography (EEG) measures served as secondary outcomes as marker for synaptic connectivity. Assessments were done at baseline, 12, and 24 weeks. The NTB memory domain Z-score was significantly increased in the active *versus* the control group over the 24-week intervention period ($p = 0.023$; Cohen's d = 0.21; 95% confidence interval [−0.06]–[0.49]). A trend for an effect was observed on the NTB total composite z-score ($p = 0{\cdot}053$). EEG measures of functional connectivity in the delta band were significantly different between study groups during 24 weeks in favor of the active group.

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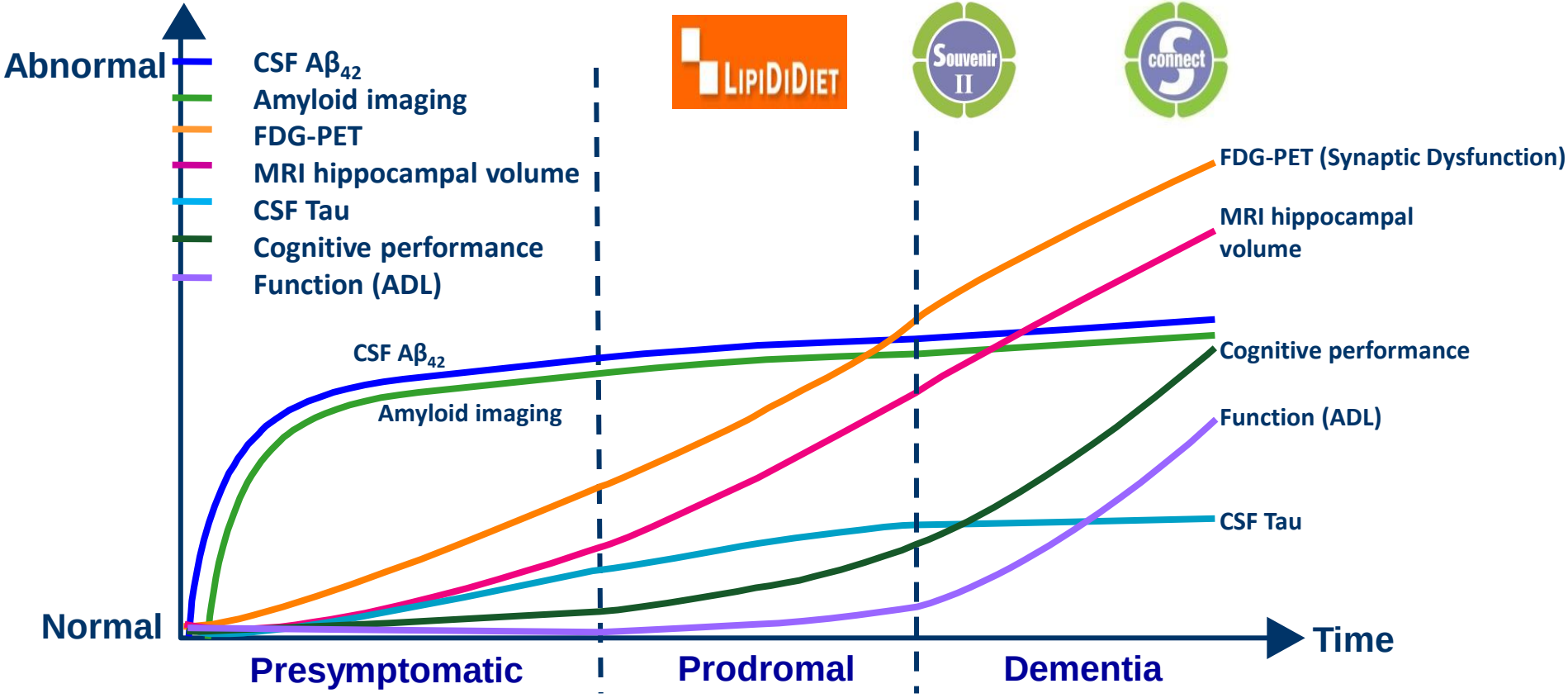
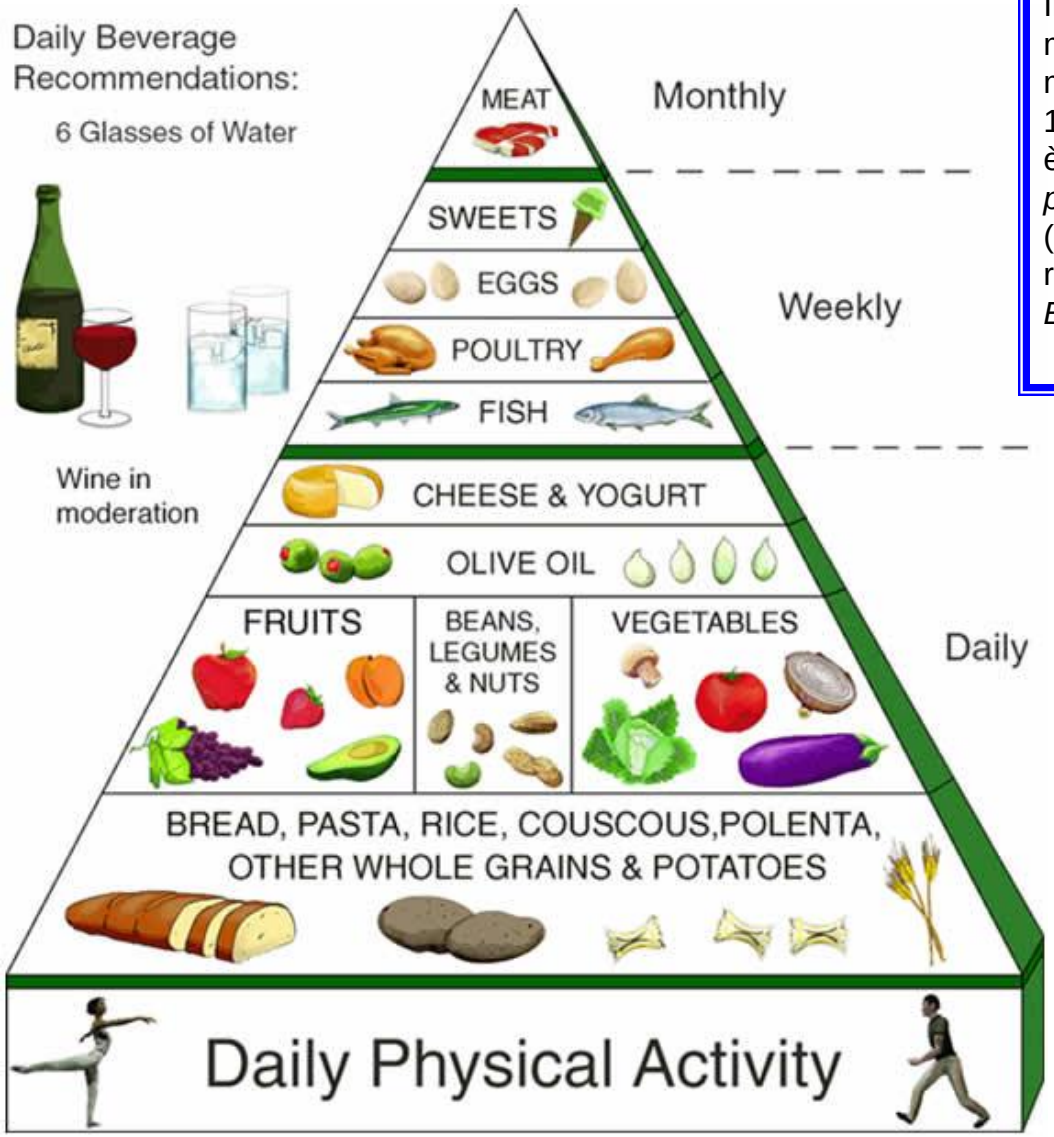
ISSN 1387-2877/14/$27.50

Le fasi della malattia di Alzheimer fino alla demenza

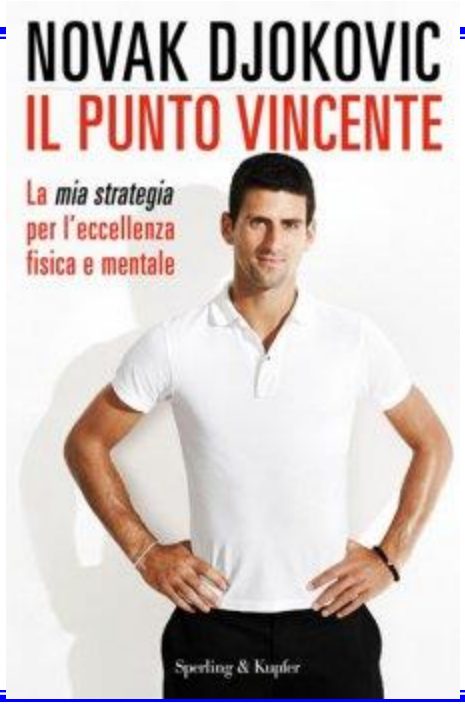


Modified from Aisen PS *Alzheimers Dement*. 2010

La dieta mediterranea: patrimonio culturale dell' umanità dal 2010



Il primo a intuire la connessione tra alimentazione e malattie del ricambio, quali diabete, bulimia, obesità, fu il medico nutrizionista italiano ***Lorenzo Piroddi*** (Genova 1911-1999). Considerato il "padre" della dieta mediterranea è anche autore del libro *Cucina Mediterranea. Ingredienti, principi dietetici e ricette al sapore di sole*. Ancel Keys (1904-2004) si fece promotore dell'ampio programma di ricerca noto come *Seven Countries Study* e autore del libro *Eat well and stay well, the Mediterranean way*.



frutta, legumi, ortaggi, pesce e olio d'oliva

Fin dalla prima infanzia
a scuola e in famiglia

Cultura ed educazione
alimentare

Dieta mediterranea : ridotto rischio malattie cardiovascolari, diabete e neoplasie maligne.

Quali sono le abitudini alimentari sbagliate?

Un'alimentazione con cibi ricchi di grassi saturi (grassi di origine animale) e di colesterolo aumenta il livello di colesterolo nel sangue, favorendo l'accumulo di questa sostanza sotto forma di placche nella parete stessa dei vasi sanguigni (arterie), che diventano più rigidi: questo processo viene chiamato **"aterosclerosi"**.

Cibi ricchi di grassi saturi o di zuccheri semplici come i dolci apportano nella dieta molte calorie, quasi sempre superiori a quelle necessarie, con conseguente **aumento del peso corporeo fino all'obesità**. Il sovrappeso e l'obesità, specie se addominale, predispongono al diabete ed aumentano il rischio di malattie cardiovascolari.

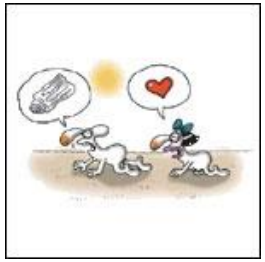
Mangiare cibi molto salati favorisce l'aumento della pressione arteriosa, uno dei fattori di rischio più importanti per le malattie cardiovascolari.

L'abitudine di "saltare" i pasti, non mantenendo la giusta cadenza dei 3-5 pasti in cui suddividere l'alimentazione della giornata, favorisce il "senso di fame" e porta a mangiare grandi quantità di cibo in un pasto unico, con conseguente difficile consumo delle calorie introdotte (specialmente se l'unico pasto è quello serale). Tutto ciò facilita l'aumento del peso corporeo e predispone all'obesità.

PREDIMED Study Investigators:

Primary prevention of cardiovascular disease with a Mediterranean diet.

N Engl J Med 2013;368:1279-90.

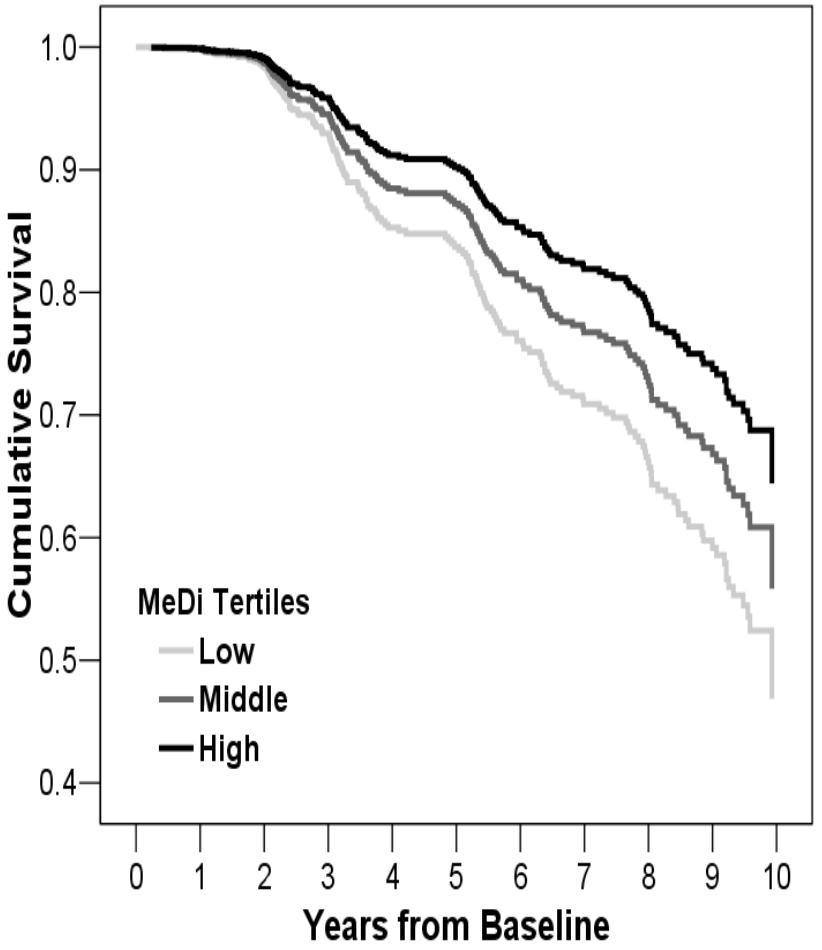


AD Risk and combination of nutrients

Observational studies suggest a link between Mediterranean diet & AD risk, but data not fully consistent

Mediterranean diet:

- High vegetables, legumes, fruits, and cereals
- High unsaturated fatty acids
- Low saturated fatty acids
- Moderately high fish
- Low-to-moderate dairy
- Low meat and poultry
- Regular but moderate amount of ethanol, primarily in the form of wine and generally, during meals



Scarmeas et al, *Ann Neurol,* 2006

Scarmeas et al, *Ann Neurol,* 2006; Psaltopoulou et al, *Public Health Nutr,* 2008;
Feart et al, *JAMA*, 2009; Cherbuin et al, *Am J Geriatr* Psychiatry, 2011; Tangney et al, *Am J Clin Nutr*, 2011

Alcuni riferimenti bibliografici su malattia di Alzheimer e dieta mediterranea e sul ruolo nella conversione da MCI ad AD

Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. Singh et all. J. Alzheimer Disease 2014;39(2):271-82. doi: 10.3233/JAD-130830.

Aderence to a Mediterranean diet and Alzheimer's disease risk in Australian population. Gardener et all. Transl Psychiatry. 2012 Oct 2; 2:e 164.

Mediterranean diet and Mild Cognitive Impairment . Scarmeas et all. Arch Neurol 2009 Feb; 66(2); 216-25.

Diet, cognition and Alzheimer's disease: food for Thought. Otaegui-Arrazola et all. Eur J Nutr 2014 Feb ; 53 (1) : 1-23.

Mediterranen diet improves cognition : the PREDIMED-NAVARRA randomised trial. Martinez et all. J Neurol Neurosurg Psychiatry 2013. Dec; 84 (12): 1318-25.

Synaptic proteins and phospholipids are increased in gerbil brain by administering uridine plus docosahexaenoic acid orally. Wutman et all. Brain Res 2006 May 9; 1088 (1): 83-92.

Uridine enhaces neurite outgrowth in nerve growth factor differentiated PC 12. Pooler et all. Neuroscience 2005; 134 (1): 207-14.

Utility of imaging for nutrinional intervention studies in Alzheimer's disease. De Wilde et all. Eur J Pharmacol 2011 Sep; 668 Suppl 1: S59-69.

The role of nutrition and diet in Alzheimer disease: a systematic review. Shah R. J Am Med Dir Asoc. 2013 Jun; 14(6): 398-402.

Delay onset of Alzheimer's disease

Aim for at least 30 minutes of aerobic exercise five times per week.
Try walking, swimming, or any other activity that gets your heart rate up. Even routine activities such as gardening, cleaning, or doing laundry count as exercise.

Follow a Mediterranean diet. Eating a heart-healthy Mediterranean diet rich in fish, nuts, whole grains, olive oil, and abundant fresh produce. Treat yourself to the occasional glass of red wine and square of dark chocolate.

Avoid trans fats and saturated fats. Reduce your consumption by avoiding full-fat dairy products, red meat, fast food, fried foods, and packaged and processed foods.

Eat a heart-healthy diet. What's good for the heart is also good for the brain, so by reducing your risk of heart disease, you also lower your risk of Alzheimer's disease.

Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease

Cassia R. Overk [a], Eliezer Masliah [a,b,*]

C.R. Overk, E. Masliah / Biochemical Pharmacology 88 (2014) 508–516

Considerable progress has been made in the past few years in the fight against Alzheimer's disease (AD) and Parkinson's disease (PD). Neuropathological studies in human brains and experimental *in vivo* and *in vitro* models support the notion that synapses are affected even at the earliest stages of the neurodegenerative process. The objective of this manuscript is to review some of the mechanisms of synaptic damage in AD and PD. Some lines of evidence support the notion that oligomeric neurotoxic species of amyloid β, α-synuclein, and Tau might contribute to the pathogenesis of synaptic failure at early stages of the diseases. The mechanisms leading to synaptic damage by oligomers might involve dysregulation of glutamate receptors and scaffold molecules that results in alterations in the axonal transport of synaptic vesicles and mitochondria that later on lead to dendritic and spine alterations, axonal dystrophy, and eventually neuronal loss. However, while some studies support a role of oligomers, there is an ongoing debate as to the exact nature of the toxic species. Given the efforts toward earlier clinical and preclinical diagnosis of these disorders, understanding the molecular and cellular mechanisms of synaptic degeneration is crucial toward developing specific biomarkers and new therapies targeting the synaptic apparatus of vulnerable neurons.

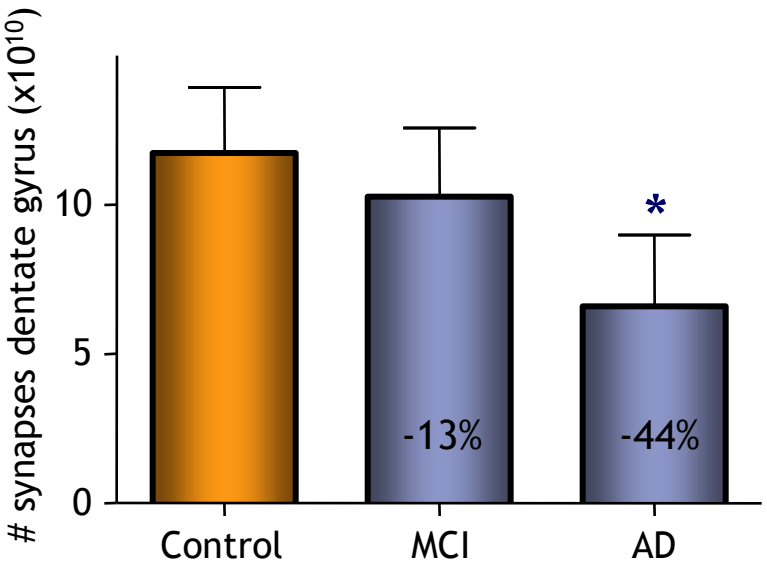
Synapse loss is structural basis of deficits in people with AD – Our lead for intervention target

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

Reduced number of synapses



VIEWPOINT

Alzheimer's Disease Is a Synaptic Failure

Dennis J. Selkoe

SCIENCE VOL 298 25 OCTOBER 2002

A Nutrient Combination that Can Affect Synapse Formation

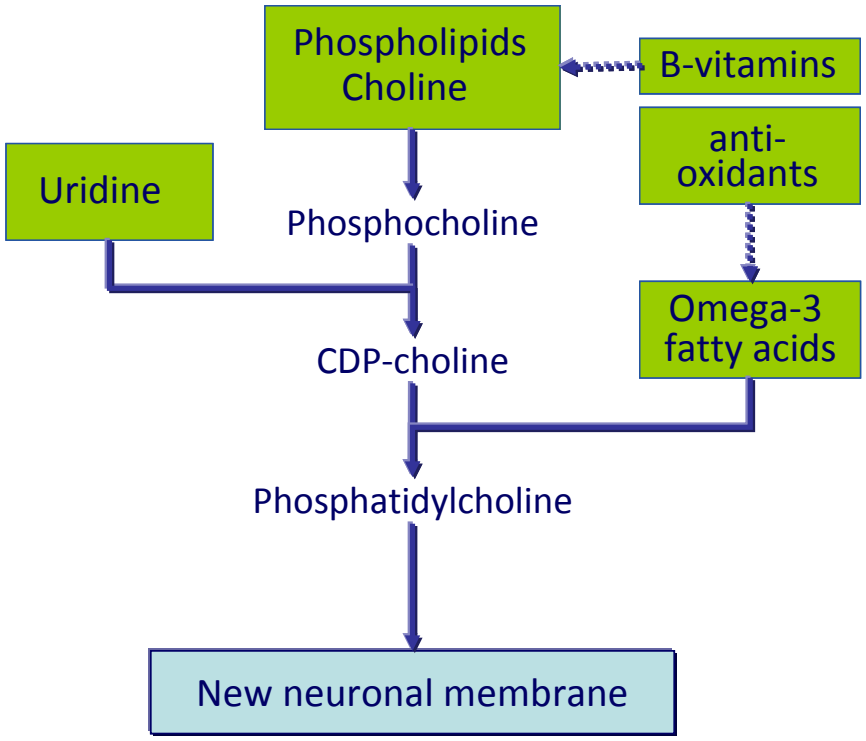
Richard J. Wurtman

Nutrients **2014**, *6*, 1701-1710

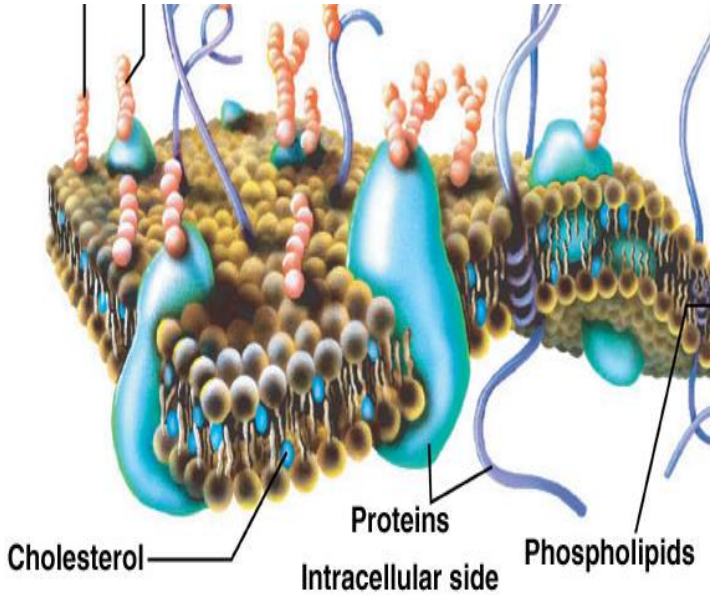
All cells utilize DHA and other fatty acids (e.g., EPA); uridine; and choline to form the phosphatide compounds that constitute the major components of their membranes. PC, the most abundant phosphatide in brain, is synthesized from these precursor-nutrients by a set of enzymes that comprise the CDP-choline cycle (or "*Kennedy Cycle*"). This biochemical pathway also generates a related is formed from PC. Thus, all of the principal lipid components of synaptic membranes are affected by the rate at which PC is being formed. In addition, since each of the reactions needed to convert choline, uridine, and DHA to PC is catalyzed by a low-affinity enzyme, blood levels of the three nutrient-precursors can determine not only PC's rate of synthesis but also the rates at which almost all of the brain's membrane lipids are produced. When all three of the nutrients are provided concurrently the resulting increase in PC production is greater than the sum of the increases produced by giving each separately [1,2]. This probably occurs because if just one of the nutrient-precursors were to be provided, the concentrations of the other two would continue to be limiting.

Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis neuronal membrane

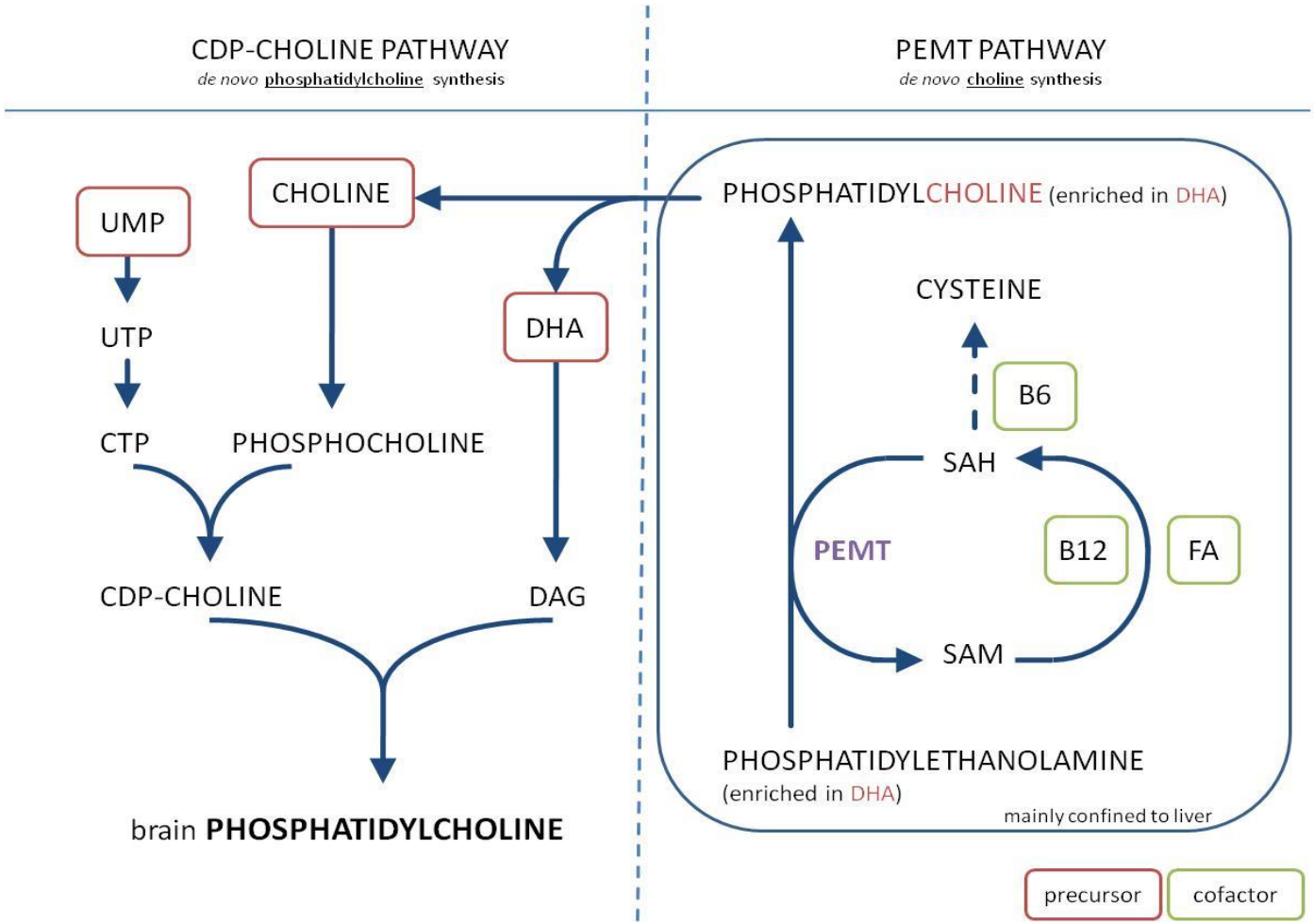


Phospholipids are main constituents of synapses



Kennedy pathway is dependent on a supply of precursors from the circulation

B vitamins as cofactor needed for endogenous production of membrane precursors



PEMT = phosphatidylethanolamine -N-methyltransferase

Development of Souvenaid
Contains the investigated key nutrients

Esame del sangue ci dirà se avremo la malattia di Alzheimer con tre anni di anticipo. Il 'test della demenza' è già validato e potrebbe arrivare nella pratica clinica tra meno di due anni. E' stato messo a punto da un gruppo di ricercatori americani del Georgetown University Medical Center, che hanno pubblicato la loro ricerca su Nature Medicine.Potrebbe aiutare a sviluppare una nuova generazione di farmaci anti-Alzheimer da usare in fase preclinica o precoce di malattia per rallentarne lo sviluppo o bloccarlo

NATURE MEDICINE ADVANCE ONLINE PUBLICATION

5-year observational study, with 525 community-dwelling participants enrolled, aged 70 and older and otherwise healthy

(Converter$_{pre}$). The average time for phenoconversion to either aMCI or AD was 2.1 years (range 1–5 years). We defined three main participant groups in this paper: aMCI/AD, Converter and Normal Control (NC). The participants with aMCI and mild AD were combined into a single group (aMCI/AD) because this group was defined by a primary memory impairment, and aMCI is generally thought to reflect the earliest clinically detectable stage of AD. The aMCI/AD group included the Converters after phenoconversion.

This targeted analysis revealed significantly lower plasma levels of serotonin, phenylalanine, proline, lysine, phosphatidylcholine (PC), taurine and acylcarnitine (AC) in Converter$_{pre}$ participants who later phenoconverted to aMCI/AD (**Table 2**).

A notable finding of this targeted metabolomic and lipidomic analysis was the identification of a set of ten metabolites, comprising PCs, (PC diacyl (aa) C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:1, PC aa C40:2, PC aa C40:6, PC acyl-alkyl (ae) C40:6), lysophophatidylcholine (lysoPC a C18:2), and acylcarnitines (ACs) (Propionyl AC (C3) and C16:1-OH) that were depleted in the plasma of the Converter$_{pre}$ participants but not in that of the NC group (**Fig. 1b**). These metabolites remained depleted after phenoconversion to aMCI/AD (Converters$_{post}$) and were similar to the levels in the aMCI/AD group.

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Commentary

A Nutritional Approach to Ameliorate Altered Phospholipid Metabolism in Alzheimer's Disease

We previously tested, in drug-naïve patients with very mild to mild AD [8], the nutritional intervention Souvenaid® (125 mL, taken once daily) containing the specific nutrient combination Fortasyn® Connect in a 24-week, randomized, controlled, double-blind, parallel-group, multi-country trial.

In the present study, some baseline and 24-week plasma samples, chosen at random, of subjects taking either the investigational product (n=47) or a control product (n=49) were analysed for lipid profiles at the Kansas Lipidomics Research Center using electrospray ionization tandem mass spectrometry

Five of the 7 measured PCs reported by Mapstone et al. [1], were significantly increased following the 24-week treatment with the nutrient combination (see Table 1). These results indicate that a biomarker profile reflecting disturbed phospholipid metabolism and perhaps indicative of early neurodegeneration can be modified in AD by providing nutrients which ratelimit phospholipid biosynthesis. These nutrients are substrates in the Kennedy pathway which synthesizes the phospholipids present in synaptic membranes

our findings suggest that a nutritional intervention that raises levels of nutrients normally rate-limiting in phospholipid synthesis may also be useful in asymptomatic subjects with plasma lipid biomarker profiles predictive for phenoconversion to aMCI/AD.

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.

The NEW ENGLAND JOURNAL of MEDICINE

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

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Vitamin E had no benefit in patients with mild cognitive impairment

ORIGINAL INVESTIGATION

A Randomized Trial of Vitamin E Supplementation and Cognitive Function in Women

Jae Hee Kang, ScD; Nancy Cook, ScD; JoAnn Manson, MD, DrPH; Julie E. Buring, ScD; Francine Grodstein, ScD

Arch Intern Med. 2006;

Long-term use of vitamin E supplements did not provide cognitive benefits among generally healthy older women.

Development of Fortasyn connect
Targeted to improve formation of synapses

- **Uridine** (UMP): 625 mg
- **Omega-3 fatty acids**: EPA 1200 mg, DHA 300 mg
- **Choline**: 400 mg
- **Phospholipids**: 106 mg
- **B vitamins**: folic acid 400 mcg, Vit B6 1 mg, Vit B12 3 mcg
- **Antioxidants**: Vit C 80 mg, Vit E 40 mg, Selenium 60 mcg

Fortasyn™ Connect PATENTED

Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands), a Food for Special Medical Purposes (FSMP), has undergone an extensive, 12-year development programme. It has been designed to address the specific nutritional needs of patients with early Alzheimer's disease, the stage when there are still abundant functional synapses and intervention may be most effective. By targeting rate-limiting steps of the Kennedy pathway, Souvenaid® aims to increase synaptic membrane formation. Souvenaid® is a 125 mL, multi-nutrient drink to be (Table 1) (34). These nutrients are present in Souvenaid® at levels above those that can be achieved in the normal diet, and the aim of Souvenaid® is to rectify nutritional deficiencies that may limit synaptogenesis.

The Journal of Nutrition, Health & Aging©
Volume 18, Number 3, 2014

Key phenomena being studied

	Confirmed	Published	
• Increase precursor supply	✓	✓	2,3
• Increase phosphatide / membrane synthesis	✓	✓	3,4
• Increase neurite outgrowth	✓	✓	5,6
• Increase synapses	✓	✓	3,7
• Increase neurotransmission (ACh synthesis, release, receptors)	✓	✓	8,9,10
• Synergy between nutrients	✓	✓	3,7
• Improve learning	✓	✓	11-14
• Complete mixture (learning and memory, synapse)	✓	✓	15

1. de Wilde *et al.* (2003) Brain Res
2. Cansev *et al.* (2005) Brain Res
3. Ulus *et al.* (2006) Cell Mol Neurobiol
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5. Wang *et al.* (2005) J Mol Neurosci
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13. de Bruin *et al*. (2003) J Learn Mem Res
14. Holguin *et al.* (2008) Behav Brain Res
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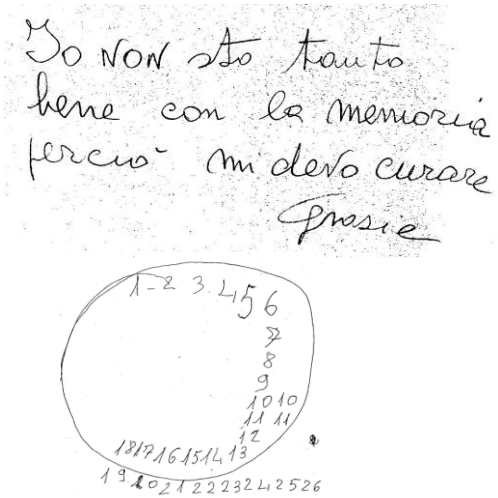
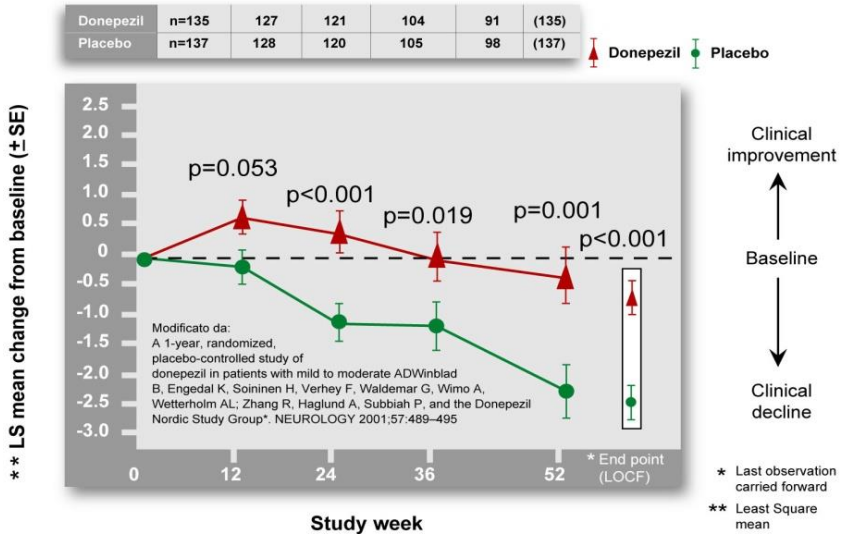
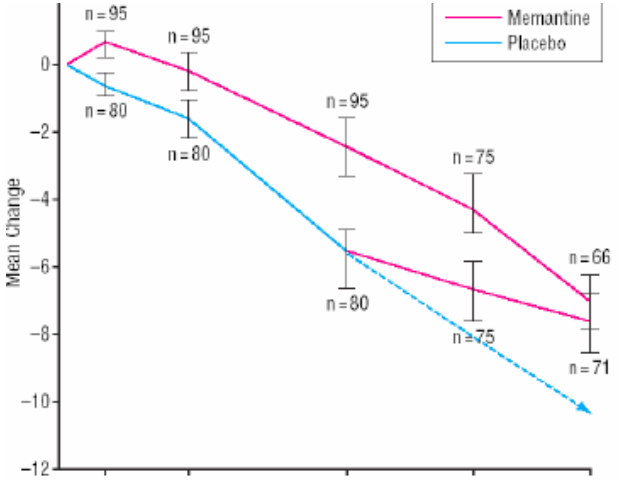






La terapia farmacologica della malattia di Alzheimer:

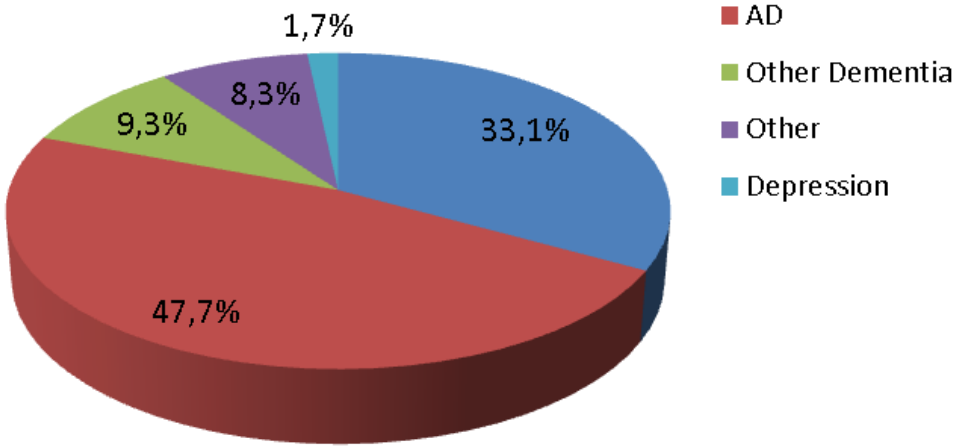
È multimodale (cioè rivolta sia al controllo dei sintomi cognitivi che comportamentali), si avvale degli inibitori delle colinesterasi, indicati e rimborsati in fase lieve-moderata (MMSE 26-10) e della memantina, indicata in fase moderata severa, rimborsata in fase moderata (MMSE 20-10)

1. Antonino Cotroneo (Torino),
2. Innocenzo Rainero (Torino),
3. Domenica La Milia (San Maurizio Canavese),
4. Loredana Seccia (Omegna),
5. Roberto Confalonieri (Monza),
6. Fabiola Teruzzi (Monza),
7. Daniele Perotta (Rho),
8. Manuela Teresa Mazzà (Milano),
9. Massimo Moleri (Bergamo),
10. Angelo Bianchetti (Brescia),
11. Simona Gentile (Cremona),
12. Annachiara Bonazzi (Verona),
13. Laura De Togni (Verona),
14. Giuseppe Gambina (Verona),
15. Carlo Gabelli (Padova),
16. Flavio Cursi (Roma),
17. Stefano Ronzoni (Roma),
18. Maria Carmela Lechiara (Avezzano),
19. Antonio Lera (Giulianova),
20. Nicola Serroni (Teramo),
21. Francesco Di Blasio (Teramo),
22. Gina Varricchio (Caserta),
23. Francesco Fiorillo (San Cipriano D'Aversa),
24. Carmine Fuschillo (Saviano),
25. Patrizia Bruno (Napoli),
26. Vincenzo Canonico (Napoli),
27. Anna Maria Papantonio (Foggia),

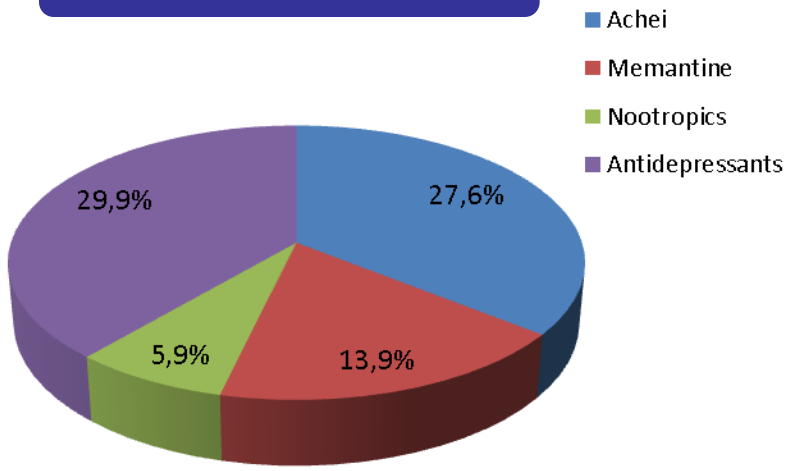
Preliminary results from a caregiver survey

- Objective to assess the impact of Souvenaid on patients with cognitive impairment in a ‘real-world’ setting
- Total number of patients: 387 (female: 60%) recruited in 30 AD clinics in Italy
- Age: 75,9y (+/- 7,2), range 50-99y
- Open label observation survey in patients taking Souvenaid for a mean of 3.6 months (range 1-12)

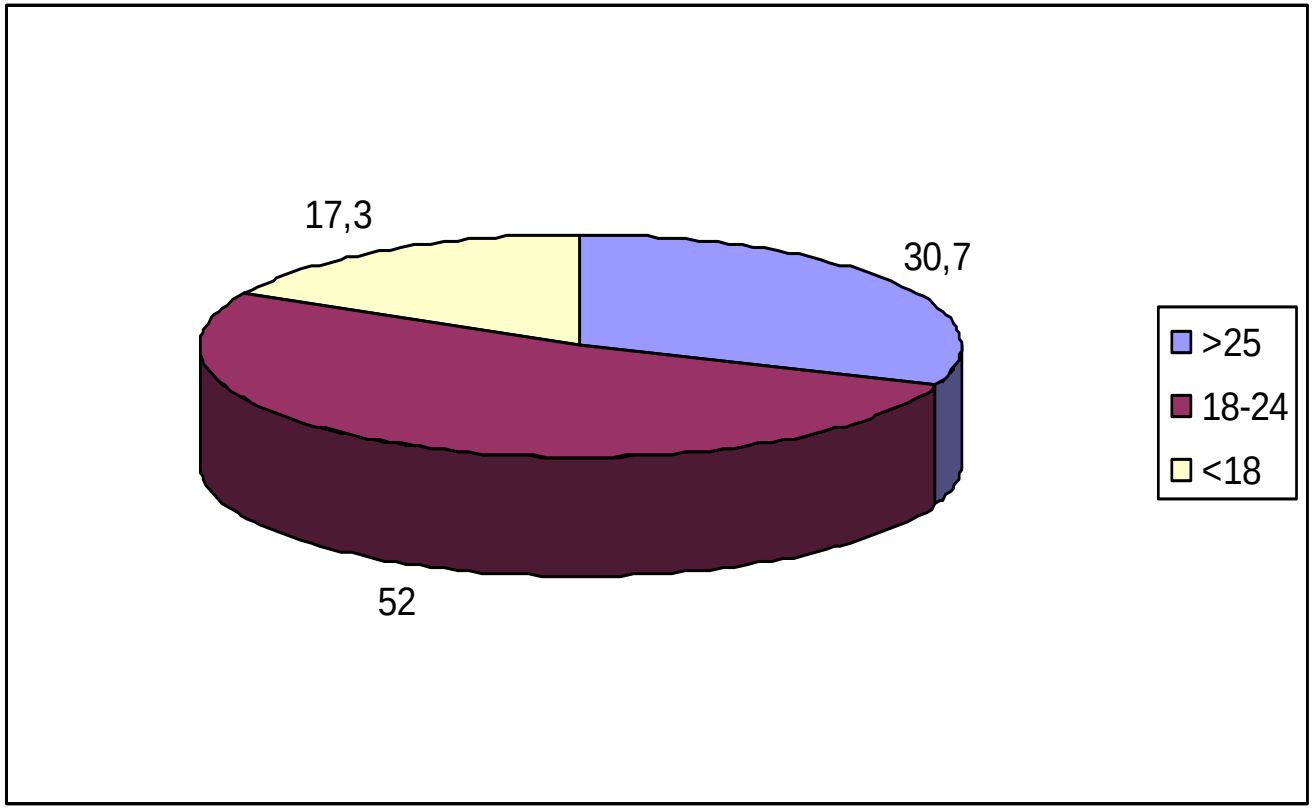
Diagnosis



Other medications



Distribuzione del campione in relazione ai valori di MMSE alla baseline



Il MMSE basale medio dell'intero campione era 21,0±4,97.

Tollerabilità

- Soltanto in 20 casi (6.5% del campione) si sono presentati problemi di tolleranza al trattamento.
- Il 24.0% dei soggetti ha riferito difficoltà legate al costo del trattamento.

- Compliance Souvenir II (24 w) 96.6% nei controlli e 97.1% nei trattati (*Scheltens et al, J Alzheimers Dis. 2012)*
- OLE a 1 anno 83% in trattamento (***Olde Rikkert et al. In press)***

Methods and analysis

- Interview of patients and caregivers 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 complain
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

RISPETTO ALLA PRESTAZIONI COGNITIVE

11. Ricordare appuntamenti/impegni/date: rispetto alla capacità di ricordare gli appuntamenti, gli impegni, ai comportamenti ripetitivi (chiedere più volte le stesse cose) lei ritiene che la situazione attuale sia

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

☐ lievemente migliorata ☐ decisamente migliorata

12. Riconoscere/ricordare nomi di persone: rispetto alla capacità di riconoscere le persone che incontra (familiari, amici, conoscenti) e ricordarne i nomi ritiene che la situazione attuale sia

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

☐ lievemente migliorata ☐ decisamente migliorata

13. Orientarsi in ambienti nuovi: rispetto alla capacità di orientarsi in ambienti nuovi (come centri commerciali, ristoranti, hotel, case di amici/conoscenti) ritiene che la situazione attuale sia

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

☐ lievemente migliorata ☐ decisamente migliorata

RELATIVAMENTE AGLI EFFETTI DEL TRATTAMENTO CON SOUVENAID, QUALI IMPRESSIONI DI EFFICACIA HA AVUTO IL PAZIENTE STESSO?
(le risposte vanno ottenute attraverso il colloquio clinico diretto al paziente quando lo stesso è in grado di rispondere; il giudizio soggettivo deve essere poi strutturato come indicato)

14. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi della memoria (difficoltà a ricordare le date, gli appuntamenti, necessità di chiedere più volte le cose) oggi si sente

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

☐ lievemente migliorata ☐ decisamente migliorata

15. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi di orientamento (difficoltà a orientarsi fuori casa, quando va a trovare amici o parenti, quando visita un luogo nuovo) oggi si sente

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

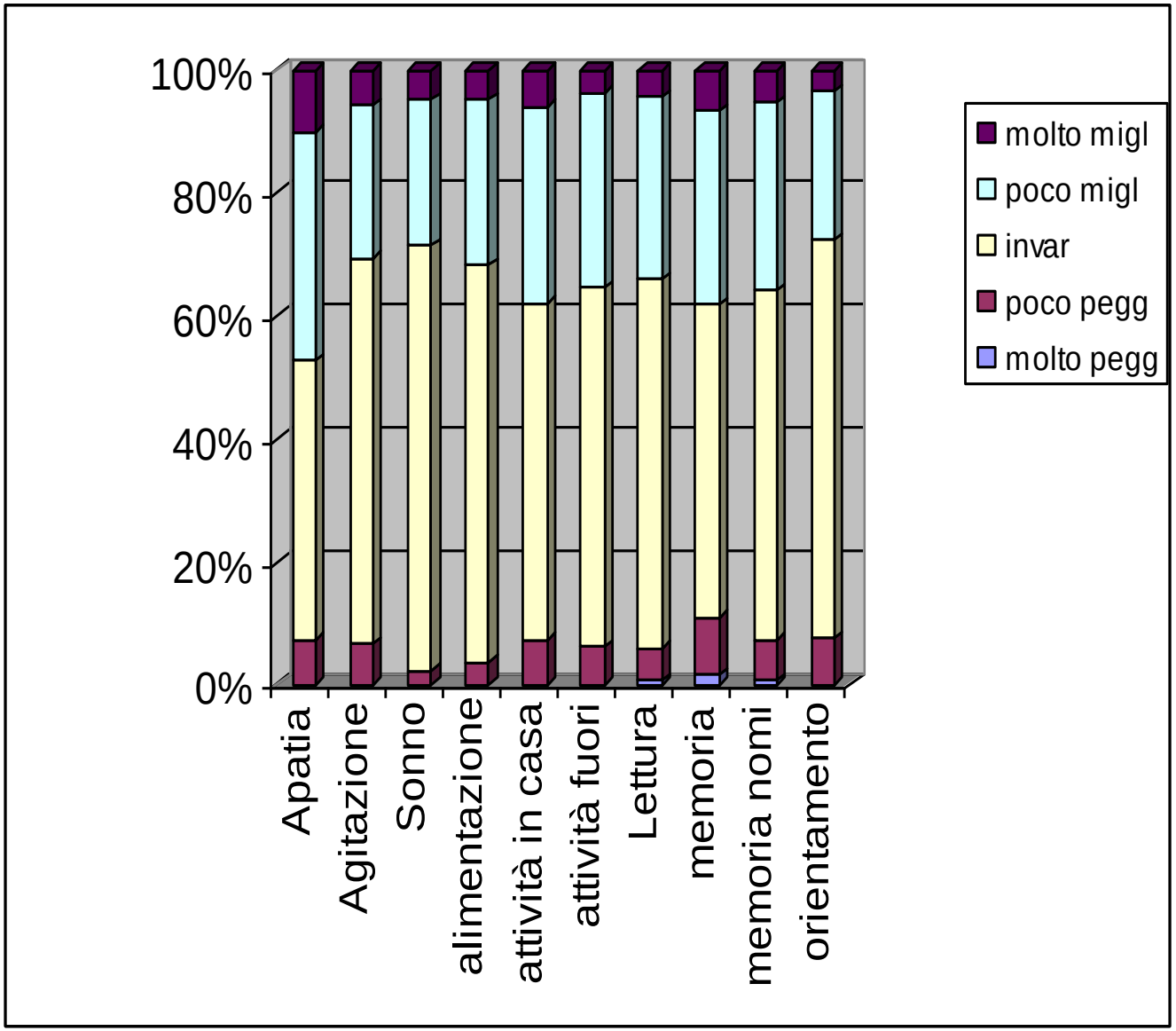
☐ lievemente migliorata ☐ decisamente migliorata

16. Lei ritiene che rispetto all'ultima visita riguardo ai suoi problemi nello svolgere le attività usuali (la gestione della casa, cucinare, fare la spesa, occuparsi dei suoi hobby) oggi si sente

☐ decisamente peggiorata ☐ lievemente peggiorata ☐ sostanzialmente invariata

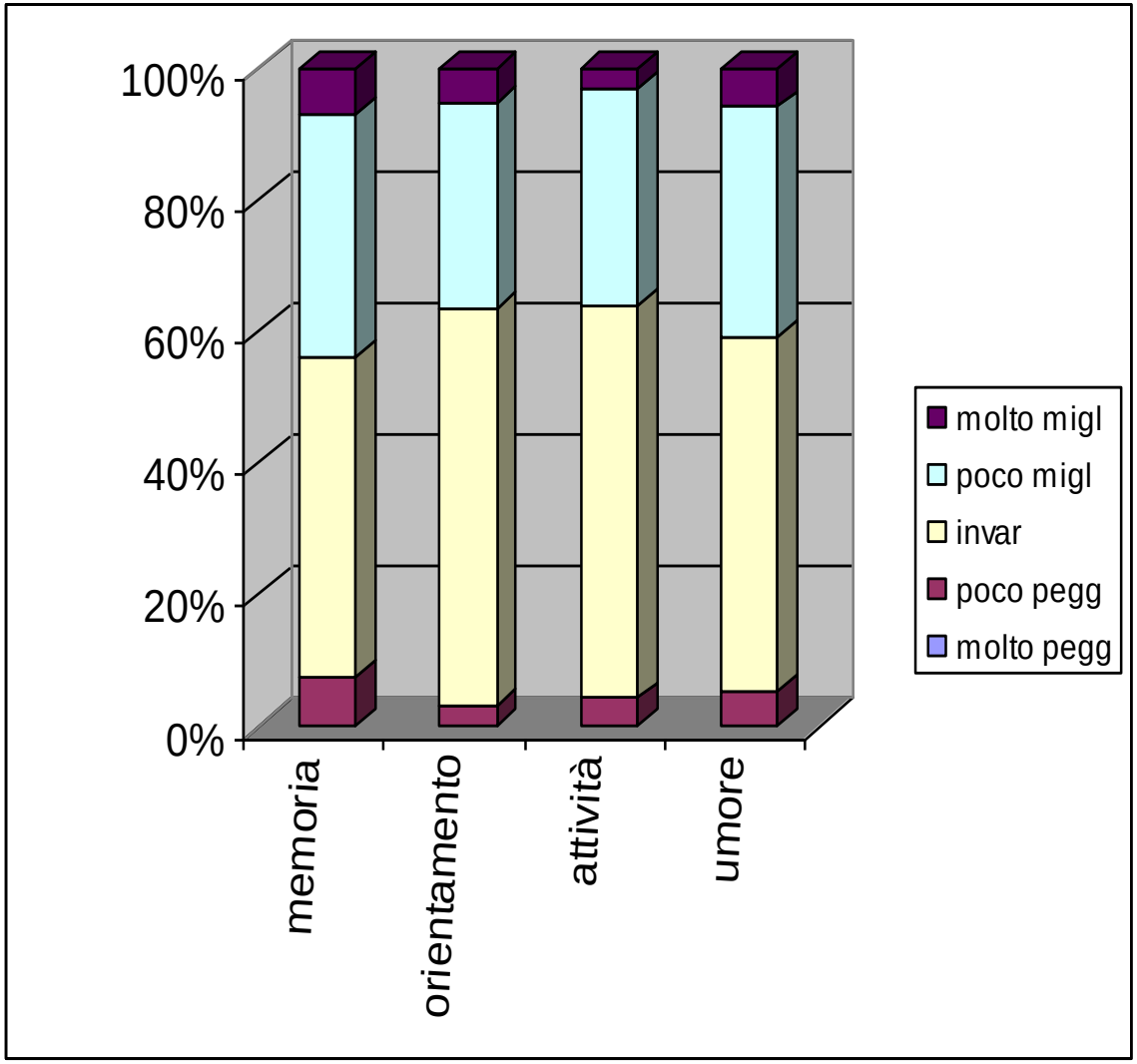
☐ lievemente migliorata ☐ decisamente migliorata

Descrizione dei giudizi di efficacia dei **caregiver** nella popolazione generale rispetto agli item considerati.



*Dal **27 al 47% dei caregiver fornisce un giudizio positivo** sull'efficacia del trattamento (lievemente/decisamente migliorato); **l'apatia e la memoria circa gli appuntamenti** sono le variabili che risultano migliorate con frequenza più elevata; l'orientamento e il comportamento alimentare mostrano i miglioramenti meno rilevanti.*

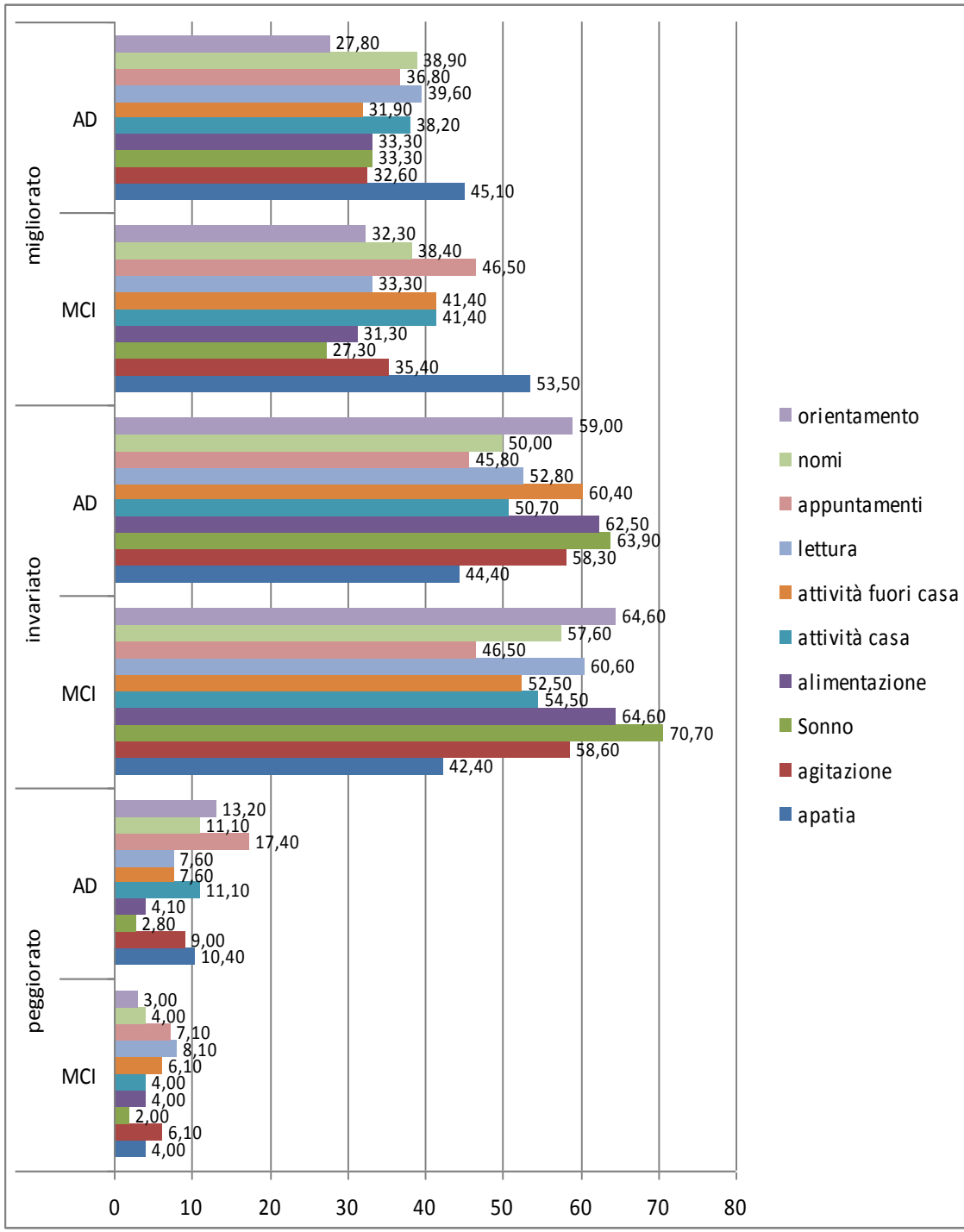
Descrizione dei giudizi di efficacia dei **pazienti** nella popolazione generale rispetto agli item considerati.



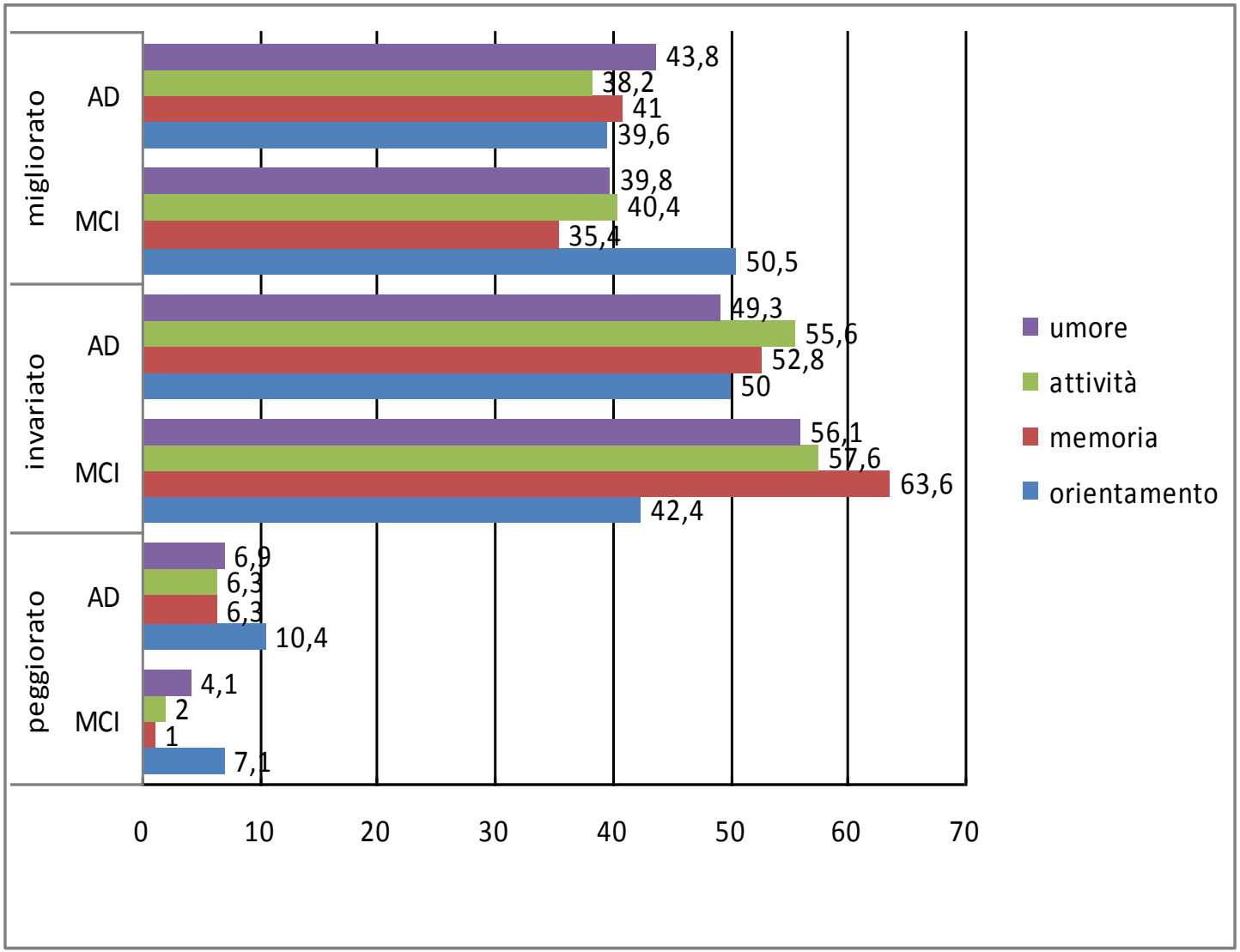
*Il giudizio dei **pazienti** è **positivo dal 36 al 43% dei casi** (massimo per la memoria, minimo per orientamento e attività).*

Confronto fra i **giudizi di efficacia espressi dai caregiver** dei pazienti con AD rispetto a quelli con MCI per gli item considerati (i dati rappresentano le percentuali).

Sono risultate statisticamente significative (test chi-square) le differenze per gli item *"memoria per appuntamenti"* (p=0.04) e *"orientamento"* (p=0.02).



Confronto fra i giudizi di efficacia espressi **dai pazienti** con AD rispetto a quelli con MCI per gli item considerati (i dati rappresentano le percentuali).
Sono risultate statisticamente significative (test chi-square) le differenze per gli item *"orientamento"* (p=0.06)



La risposta al trattamento si correla in modo significativo con la durata del trattamento (r=0.115; p=.05; fig A) e con i valori del MMSE alla baseline (r=.229; p=.0001).

Fig A

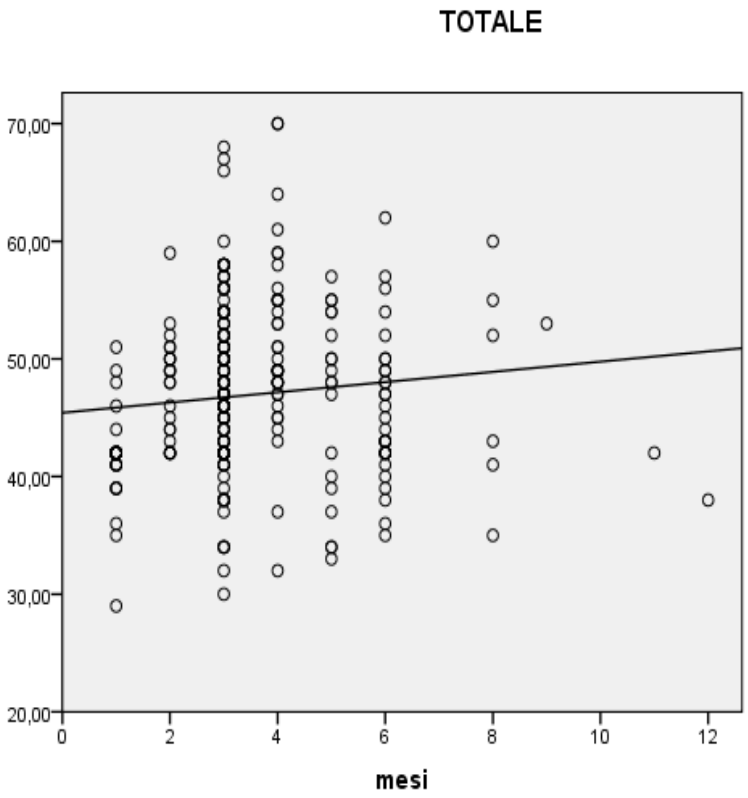
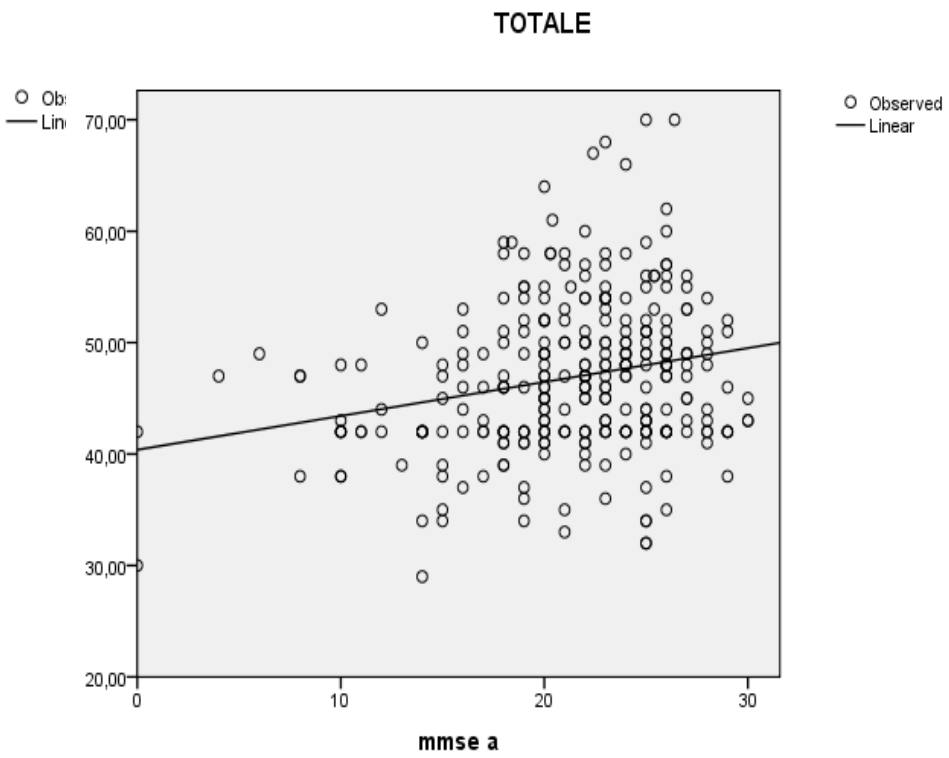


Fig B



Dalle sp clinici

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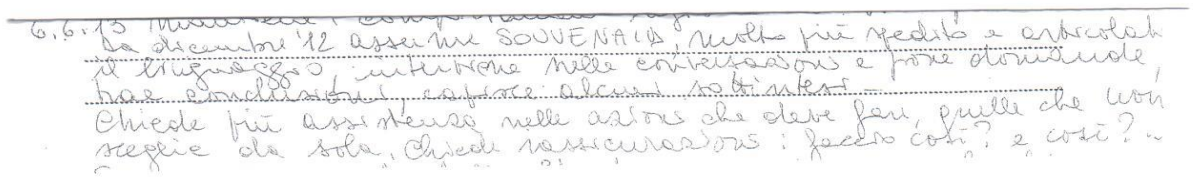

13/09/2013

19/03/2014

Caregiver: “ liorata
l’abulia, l
collabora

24/09/2014

Caregiver: “ cipe
anche se

Nel perioc ti e la

Arrivederci a Milano