Cummings *et al. Alzheimer's Research & Therapy* 2014, 6:37
http://alzres.com/content/6/4/37

alzheimer's research&therapy

RESEARCH Open Access

# Alzheimer's disease drug-development pipeline: few candidates, frequent failures

Jeffrey L Cummings[1*], Travis Morstorf[2] and Kate Zhong[1]

**Abstract**

**Introduction:** Alzheimer's disease (AD) is increasing in frequency as the global population ages. Five drugs are approved for treatment of AD, including four cholinesterase inhibitors and an *N*-methyl-D-aspartate (NMDA)-receptor antagonist. We have an urgent need to find new therapies for AD.

**Methods:** We examined Clinicaltrials.gov, a public website that records ongoing clinical trials. We examined the decade of 2002 to 2012, to better understand AD-drug development. We reviewed trials by sponsor, sites, drug mechanism of action, duration, number of patients required, and rate of success in terms of advancement from one phase to the next. We also reviewed the current AD therapy pipeline.

**Results:** During the 2002 to 2012 observation period, 413 AD trials were performed: 124 Phase 1 trials, 206 Phase 2 trials, and 83 Phase 3 trials. Seventy-eight percent were sponsored by pharmaceutical companies. The United States of America (U.S.) remains the single world region with the greatest number of trials; cumulatively, more non-U.S. than U.S. trials are performed. The largest number of registered trials addressed symptomatic agents aimed at improving cognition (36.6%), followed by trials of disease-modifying small molecules (35.1%) and trials of disease-modifying immunotherapies (18%). The mean length of trials increases from Phase 2 to Phase 3, and the number of participants in trials increases between Phase 2 and Phase 3. Trials of disease-modifying agents are larger and longer than those for symptomatic agents. A very high attrition rate was found, with an overall success rate during the 2002 to 2012 period of 0.4% (99.6% failure).

**Conclusions:** The Clinicaltrials.gov database demonstrates that relatively few clinical trials are undertaken for AD therapeutics, considering the magnitude of the problem. The success rate for advancing from one phase to another is low, and the number of compounds progressing to regulatory review is among the lowest found in any therapeutic area. The AD drug-development ecosystem requires support.

La “terapia multifattoriale” nel deterioramento cognitivo dell’anziano: quali evidenze ?

Ferrara 24 Ottobre 2014

# Nutrizione e deterioramento cognitivo nell’anziano

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Sezione di Medicina Interna e CardioPolmonare
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# Potential preventive strategies for dementia

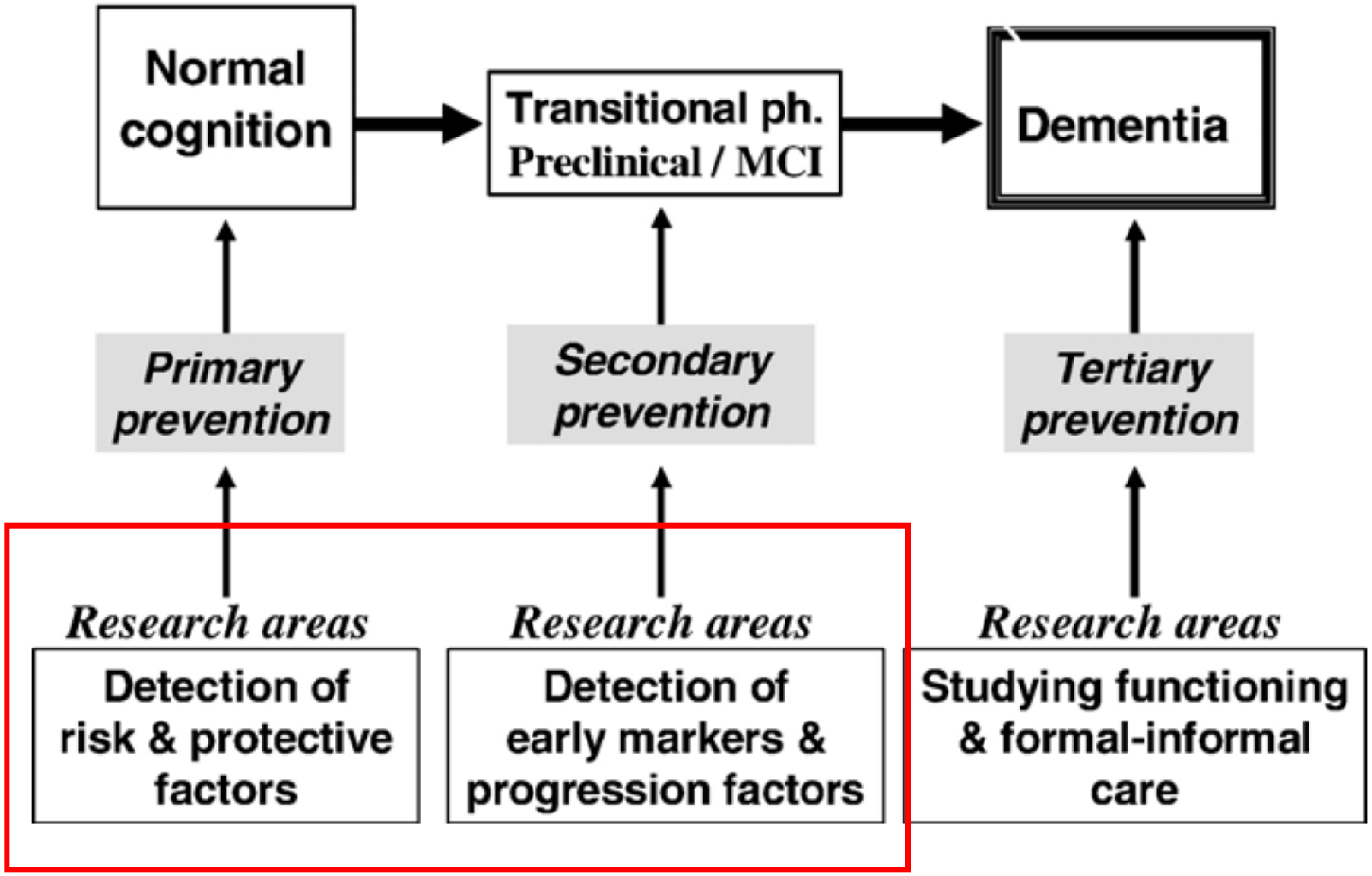
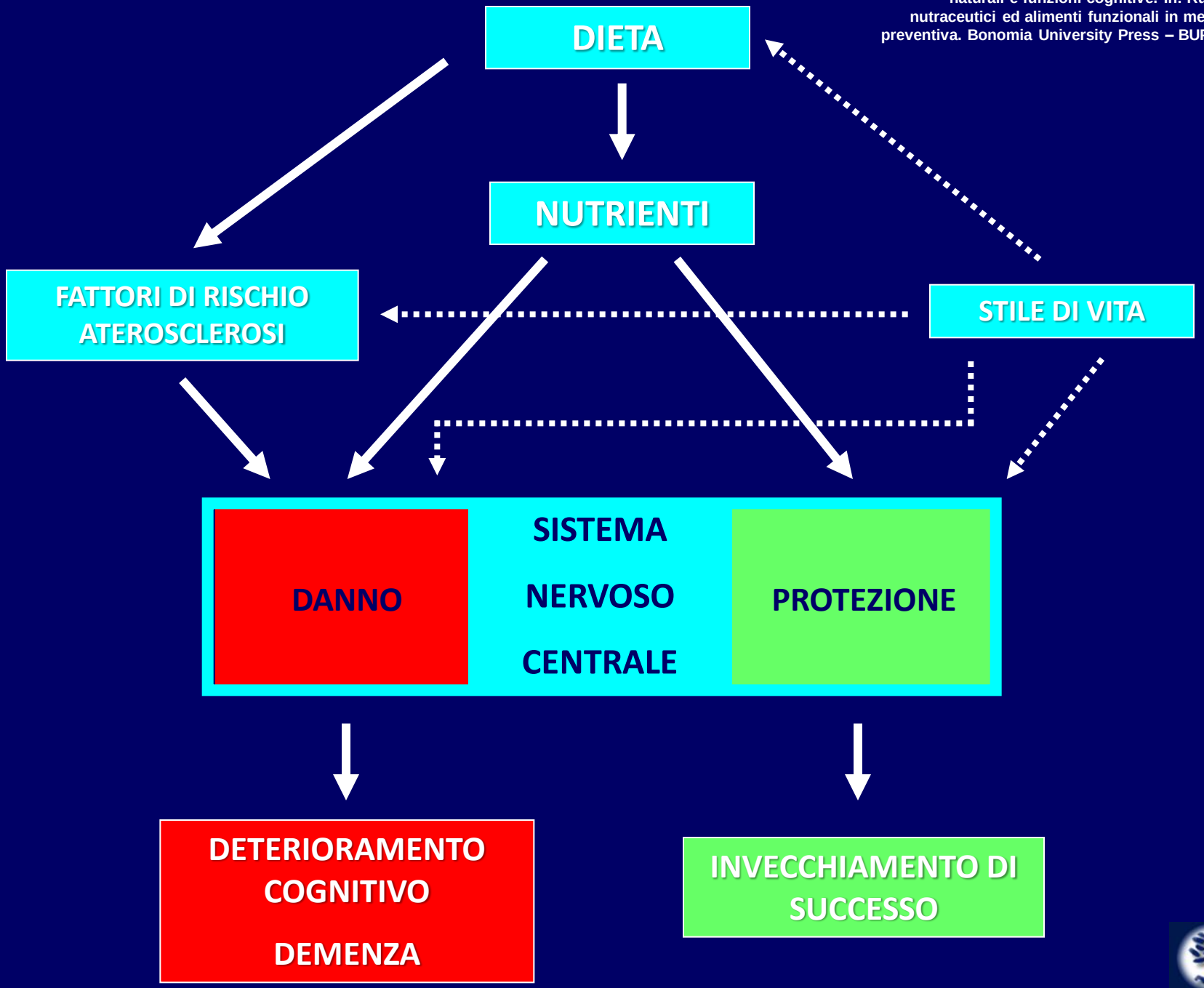
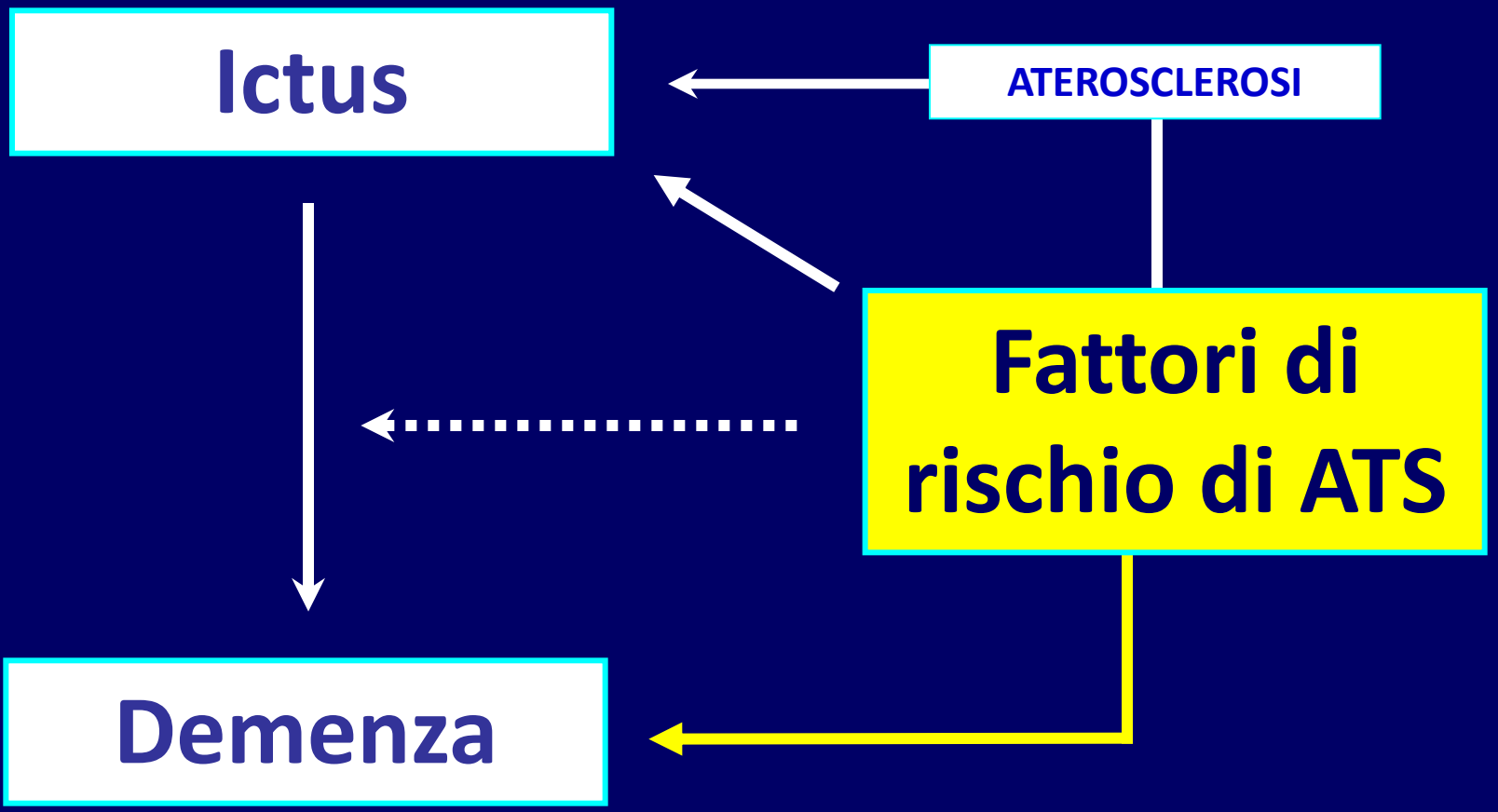



Fig. 1. Potential preventive strategies for dementing disorders at different times of disease development.

*L. Fratiglioni et al. / Physiology & Behavior 92 (2007) 98–104*

G. Zuliani & F. Bonetti: Nutraceutici, nootropi naturali e funzioni cognitive. In: Ruolo di nutraceutici ed alimenti funzionali in medicina preventiva. Bonomia University Press – BUP 2011




Ictus
ATEROSCLEROSI
Fattori di rischio di ATS
Demenza

# Fattori di rischio

↑ Calorie-overnutrition

↑ Zuccheri semplici

↑ Proteine animali

↑ Ac. Grassi saturi

↑ Ac. Grassi polinsaturi "trans"

↑ Sodio cloruro

↓ Fibre

↓ Acidi grassi poliinsaturi omega 3

↑ Omega 6/3 ratio

↓ Vitamine

**Età**

**Sesso maschile**

**Dieta di tipo "occidentale"**

**Obesità**

**Ipertensione arteriosa**

**Diabete**

**Ridotto C-HDL**

**Insulino-resistenza - diabete**

**Infiammazione cronica**

# RISERVA CEREBRALE

## RISERVA RIDOTTA

- ETA’
- APO E 4
- IPERCOLESTEROLEMIA
- IPEROMOCISTEINEMIA
- DIABETE
- IPERTENSIONE
- ALCOOL
- STRESS PSICOLOGICO
- TRAUMA CRANICO
- FUMO

## RISERVA AUMENTATA

- SCOLARITA’
- TEMPO LIBERO “ATTIVO”
- ESERCIZIO FISICO
- DIETA
- ALCOOL MODERATO
- STATINE
- ANTI-INFIAMMATORI NON STEROIDEI (FANS)

NEUROLOGICAL REVIEW

# Promising Strategies for the Prevention of Dementia

*Laura E. Middleton, PhD; Kristine Yaffe, MD*

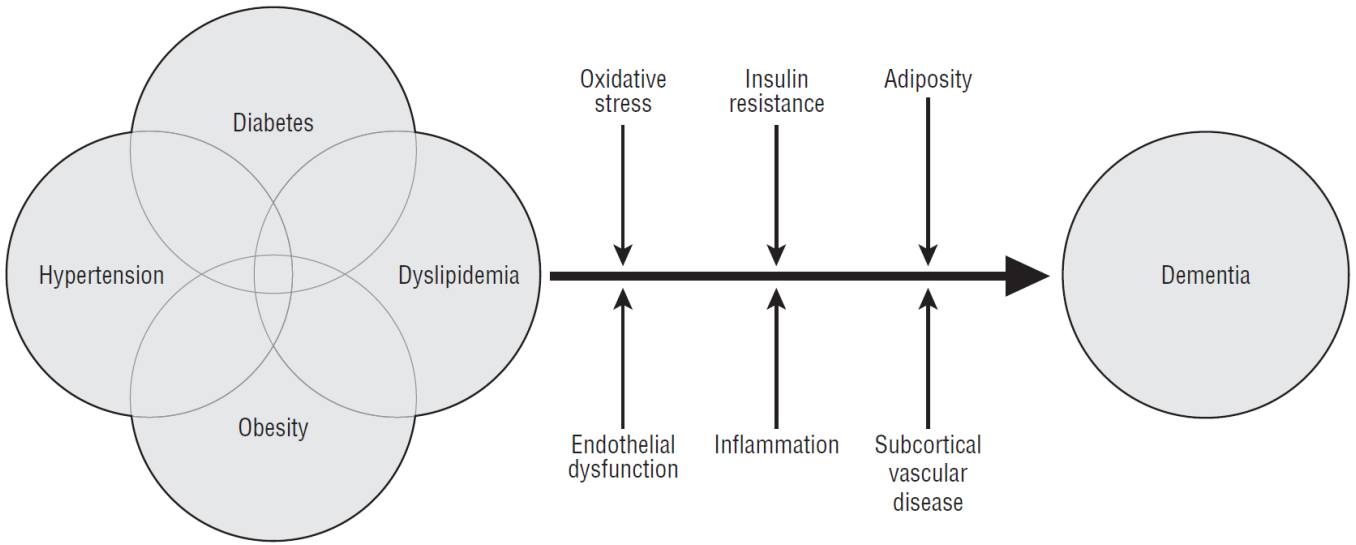


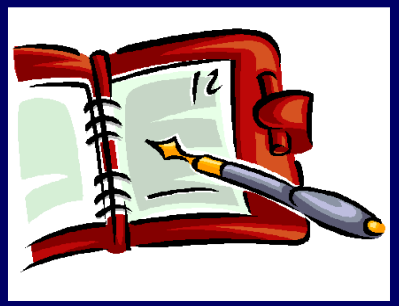

**Figure.** Possible mechanisms that may explain the association between vascular risk factors and an increased risk of developing dementia.

Arch Neurol 2009

# Nutrizione e deterioramento cognitivo nell'anziano

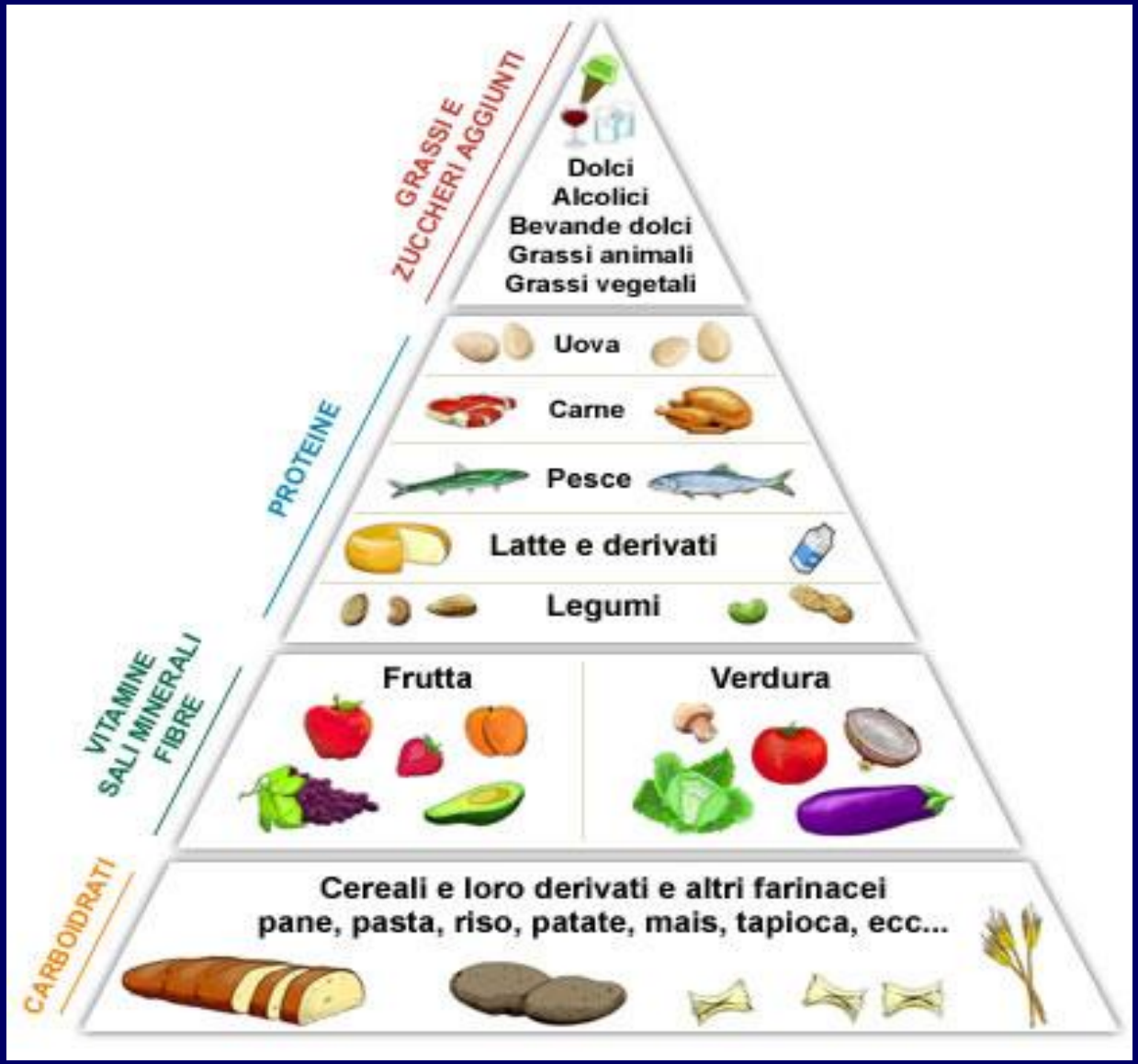
## *Agenda*

- ✓ *DIETA E DEMENZA*
- ✓ *ACIDI GRASSI*
- ✓ *VITAMINE & ANTIOSSIDANTI*
- ✓ *CONCLUSIONI*



# 1. Dieta & Demenza

# Dieta Mediterranea



Dieta mediterranea

# Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD,[1–3] Yaakov Stern, PhD,[1–3] Ming-Xin Tang, PhD,[1,4] Richard Mayeux, MD,[1–3] and Jose A. Luchsinger, MD[1,5]

**Objective:** Previous research in Alzheimer's disease (AD) has focused on individual dietary components. There is converging evidence that composite dietary patterns such as the Mediterranean diet (MeDi) is related to lower risk for cardiovascular disease, several forms of cancer, and overall mortality. We sought to investigate the association between MeDi and risk for AD.

**Methods:** A total of 2,258 community-based nondemented individuals in New York were prospectively evaluated every 1.5 years. Adherence to the MeDi (zero- to nine-point scale with higher scores indicating higher adherence) was the main predictor in models that were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index.

**Results:** There were 262 incident AD cases during the course of 4 (±3.0; range, 0.2–13.9) years of follow-up. Higher adherence to the MeDi was associated with lower risk for AD (hazard ratio, 0.91; 95% confidence interval, 0.83–0.98; $p = 0.015$). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had a hazard ratio of 0.85 (95% confidence interval, 0.63–1.16) and those at the highest tertile had a hazard ratio of 0.60 (95% confidence interval, 0.42–0.87) for AD ($p$ for trend = 0.007).

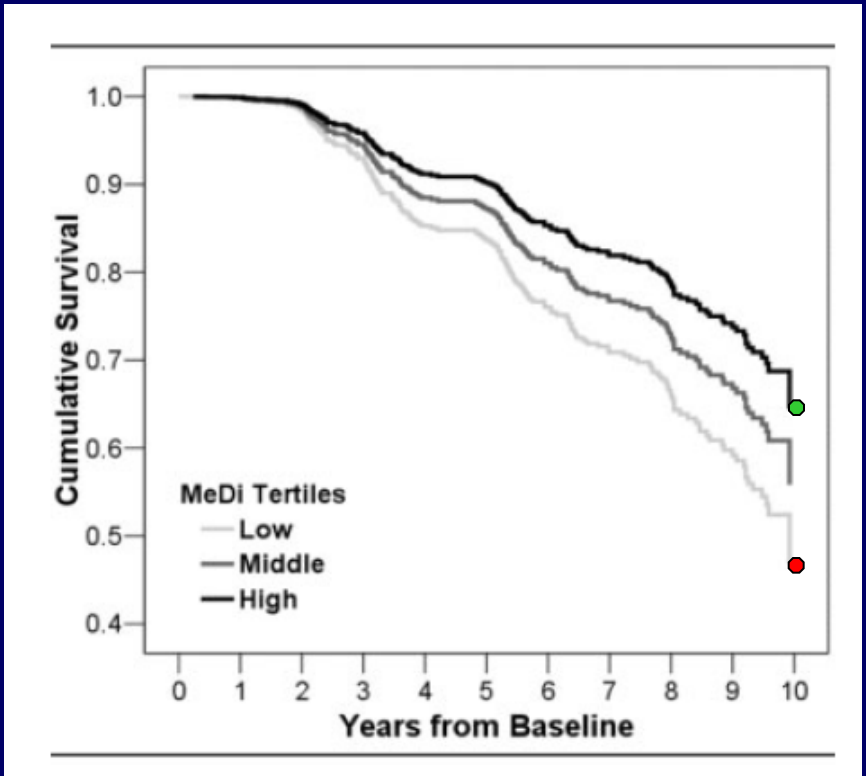
**Interpretation:** We conclude that higher adherence to the MeDi is associated with a reduction in risk for AD.

Ann Neurol 2006;59:912–921

*Table 1. Median Daily Intake for Individual Food Categories by Mediterranean Diet Score Tertiles and Overall*

| Food Categories | Low Tertile (MeDi score 0–3) | Middle Tertile (MeDi score 4–5) | High Tertile (MeDi score 6–9) | All (25th, 75th percentiles) |
|---|---|---|---|---|
| Dairy, gm/day | 246 | 174 | 151 | 182 (128–292) |
| Meat, gm/day | 101 | 86 | 65 | 85 (60–119) |
| Vegetable, gm/day | 165 | 202 | 243 | 197 (153–250) |
| Fruit, gm/day | 406 | 471 | 556 | 472 (372–582) |
| Legumes, gm/day | 44 | 58 | 78 | 57 (38–90) |
| Cereal, gm/day | 155 | 186 | 215 | 184 (140–233) |
| Fish, gm/day | 15 | 21 | 47 | 20 (14–47) |
| MUFA/SFA ratio | 0.57 | 0.82 | 0.97 | 0.80 (0.18–1.37) |
| Mild-to-moderate ethanol, % | 21 | 33 | 45 | 32 |

## Sopravvivenza libera da demenza




Dieta mediterranea

ORIGINAL CONTRIBUTION

# Mediterranean Diet and Mild Cognitive Impairment

*Nikolaos Scarmeas, MD; Yaakov Stern, PhD; Richard Mayeux, MD; Jennifer J. Manly, PhD; Nicole Schupf, PhD; Jose A. Luchsinger, MD*

Dieta mediterranea

**Background:** Higher adherence to the Mediterranean diet (MeDi) may protect from Alzheimer disease (AD), but its association with mild cognitive impairment (MCI) has not been explored.

**Objective:** To investigate the association between the MeDi and MCI.

**Design, Setting, and Patients:** In a multiethnic community study in New York, we used Cox proportional hazards to investigate the association between adherence to the MeDi (0-9 scale; higher scores indicate higher adherence) and (1) the incidence of MCI and (2) the progression from MCI to AD. All of the models were adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and duration between baseline dietary assessment and baseline diagnosis.

**Main Outcome Measures:** Incidence of MCI and progression from MCI to AD.

**Results:** There were 1393 cognitively normal participants, 275 of whom developed MCI during a mean (SD) follow-up of 4.5 (2.7) years (range, 0.9-16.4 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 17% less risk (hazard ratio [HR] = 0.83; 95% confidence interval [CI], 0.62-1.12; $P = .24$) of developing MCI and those in the highest tertile had 28% less risk (HR = 0.72; 95% CI, 0.52-1.00; $P = .05$) of developing MCI (trend HR = 0.85; 95% CI, 0.72-1.00; $P$ for trend = .05). There were 482 subjects with MCI, 106 of whom developed AD during a mean (SD) follow-up of 4.3 (2.7) years (range, 1.0-13.8 years). Compared with subjects in the lowest MeDi adherence tertile, subjects in the middle tertile had 45% less risk (HR = 0.55; 95% CI, 0.34-0.90; $P = .01$) of developing AD and those in the highest tertile had 48% less risk (HR = 0.52; 95% CI, 0.30-0.91; $P = .02$) of developing AD (trend HR = 0.71; 95% CI, 0.53-0.95; $P$ for trend = .02).

**Conclusions:** Higher adherence to the MeDi is associated with a trend for reduced risk of developing MCI and with reduced risk of MCI conversion to AD.

*Arch Neurol. 2009;66(2):216-225*

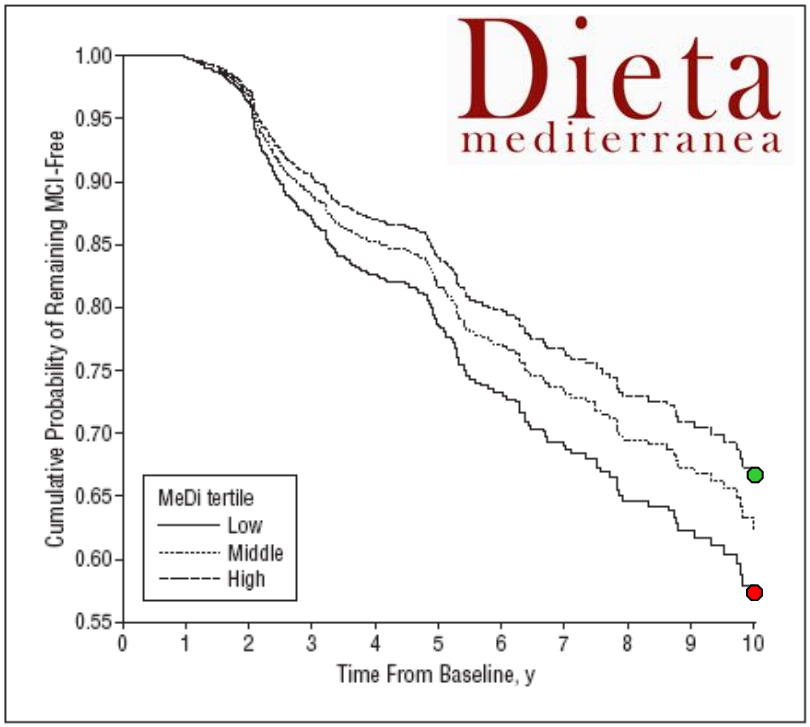



**Figure 2.** Survival curves based on Cox analysis comparing cumulative mild cognitive impairment (MCI) incidence in subjects who were cognitively normal at the first evaluation by each Mediterranean diet (MeDi) adherence tertile (*P* for trend=.05). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile, $\chi^2$=0.91, *P*=.33; low vs high tertile, $\chi^2$=3.72, *P*=.05; and middle vs high tertile, $\chi^2$=1.22, *P*=.26.

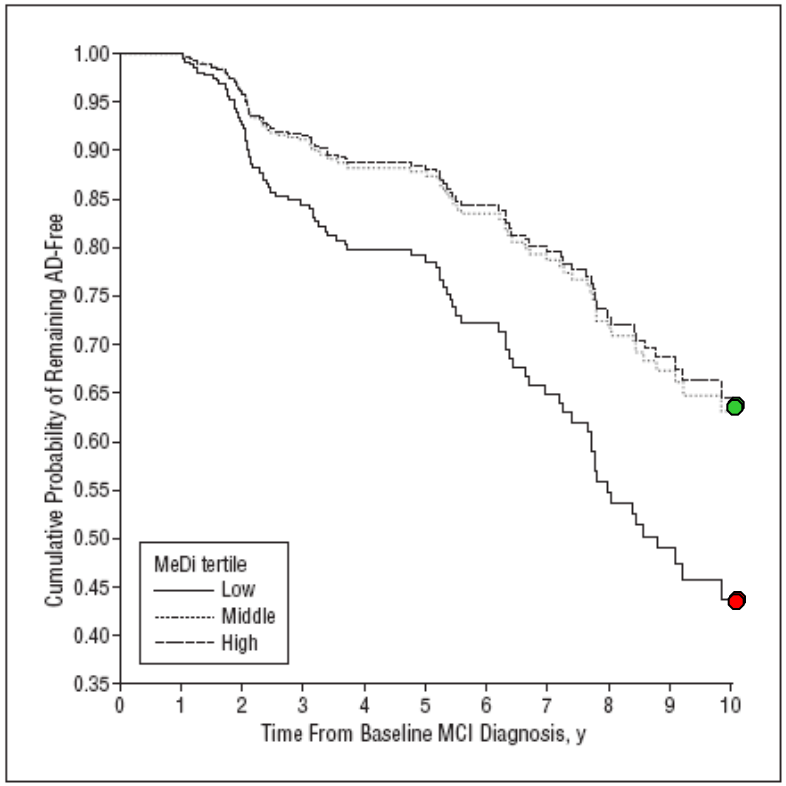



**Figure 3.** Survival curves based on Cox analysis comparing cumulative Alzheimer disease (AD) incidence in subjects with mild cognitive impairment (MCI) at the first evaluation by Mediterranean diet (MeDi) adherence tertile (*P* for trend=.02). The figure is derived from a model that is adjusted for cohort, age, sex, ethnicity, education, *APOE* genotype, caloric intake, body mass index, and time between the first dietary assessment and the first cognitive assessment. Duration of follow-up is truncated at 10 years. Results of log-rank tests for pairwise comparisons are as follows: middle vs low tertile, $\chi^2$=4.26, *P*=.03; low vs high tertile, $\chi^2$=1.39, *P*=.23; and middle vs high tertile, $\chi^2$=0.12, *P*=.72.

**Sopravvivenza libera da MCI**

**Sopravvivenza libera da demenza in soggetti con MCI**

# Mediterranean diet and Alzheimer disease mortality

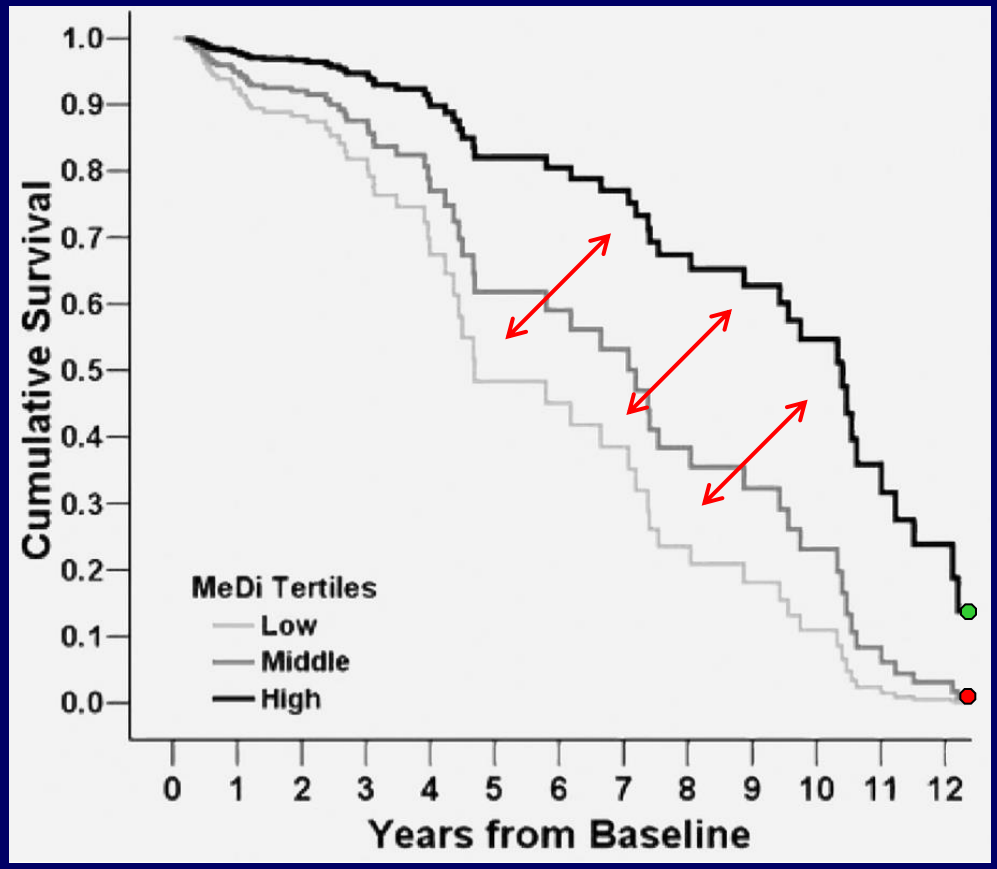
Neurology 2007

**Nikolaos Scarmeas, MD**, **Jose A. Luchsinger, MD**, **Richard Mayeux, MD**, and **Yaakov Stern, PhD**

*From the Taub Institute for Research in Alzheimer's Disease and the Aging Brain (N.S., J.A.L., R.M., Y.S.), Gertrude H. Sergievsky Center (N.S., R.M., Y.S.), and Departments of Neurology (N.S., R.M., Y.S.) and Medicine (J.A.L.), Columbia University Medical Center, New York.*

## Sopravvivenza cumulativa

Dieta mediterranea



*J Alzheimers Dis*. 2014 January 1; 39(2): 271–282. doi:10.3233/JAD-130830.

Dieta mediterranea

# Association of Mediterranean diet with Mild Cognitive Impairment and Alzheimer's disease: A Systematic Review and Meta-Analysis

**Balwinder Singh, MD**[a,d], **Ajay K. Parsaik, MD**[a], **Michelle M. Mielke, PhD**[b], **Patricia J. Erwin**[c], **David S. Knopman, MD**[a], **Ronald C. Petersen, MD, PhD**[a,b], and **Rosebud O. Roberts, MB, ChB**[a,b]

## Abstract

**Background/Objective—**To conduct a systematic review of all studies to determine whether there is an association between the Mediterranean diet (MeDi) and cognitive impairment.

**Methods—**We conducted a comprehensive search of the major databases and hand-searched proceedings of major neurology, psychiatry, and dementia conferences through November 2012. Prospective cohort studies examining the MeDi with longitudinal follow-up of at least 1 year and reporting cognitive outcomes (mild cognitive impairment [MCI] or Alzheimer's disease [AD]) were included. The effect size was estimated as hazard-ratio (HR) with 95% confidence intervals (CIs) using the random-effects model. Heterogeneity was assessed using Cochran's Q-test and $I^2$-statistic.

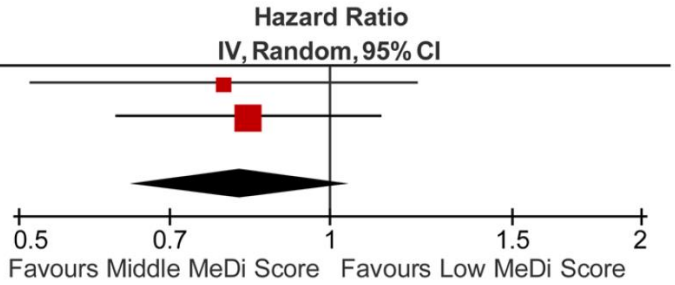
**Results—**Out of the 664 studies screened, five studies met eligibility criteria. Higher adherence to the MeDi was associated with reduced risk of MCI and AD. The subjects in the highest MeDi tertile had 33% less risk (adjusted HR=0.67; 95% CI, 0.55–0.81; P<0.0001) of cognitive impairment (MCI or AD) as compared to the lowest MeDi score tertile. Among cognitively normal individuals, higher adherence to the MeDi was associated with a reduced risk of MCI (HR=0.73; 95% CI, 0.56–0.96; P=0.02) and AD (HR=0.64; 95% CI, 0.46–0.89; P=0.007). There was no significant heterogeneity in the analyses.

# Controlli vs MCI

**2.2 Middle vs Lowest MeDi tertile**

| Study or Subgroup | log[Hazard Ratio] | SE | MCI Total | CN Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Roberts 2010 | -0.2373 | 0.2204 | 93 | 1141 | 31.9% | 0.79 [0.51, 1.21] |
| Scarmeas 2009 MCI | -0.1824 | 0.1509 | 241 | 1199 | 68.1% | 0.83 [0.62, 1.12] |
| **Total (95% CI)** | | | **334** | **2340** | **100.0%** | **0.82 [0.64, 1.05]** |

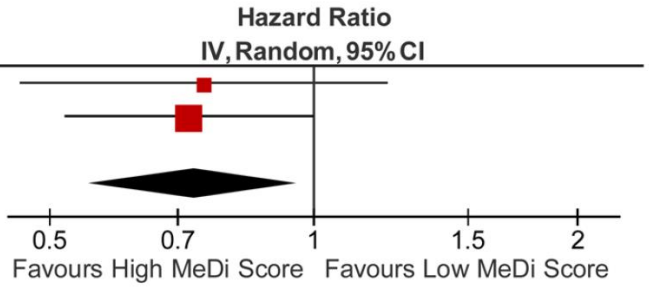
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.61 (P = 0.11)




**2.3 Highest vs Lowest MeDi tertile**

| Study or Subgroup | log[Hazard Ratio] | SE | MCI Total | CN Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Roberts 2010 | -0.2889 | 0.2467 | 93 | 1141 | 31.4% | 0.75 [0.46, 1.21] |
| Scarmeas 2009 MCI | -0.3285 | 0.1668 | 241 | 1199 | 68.6% | 0.72 [0.52, 1.00] |
| **Total (95% CI)** | | | **334** | **2340** | **100.0%** | **0.73 [0.56, 0.96]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)



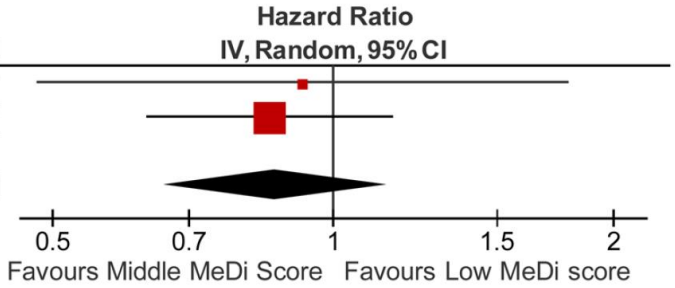
# Controlli vs Alzheimer

Dieta mediterranea

**3.2 Middle vs Lowest MeDi tertile**

| Study or Subgroup | log[Hazard Ratio] | SE | AD Total | CN Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Feart 2009 | -0.0759 | 0.3358 | 51 | 1410 | 17.7% | 0.93 [0.48, 1.79] |
| Scarmeas 2006 | -0.1568 | 0.1557 | 219 | 1759 | 82.3% | 0.85 [0.63, 1.16] |
| **Total (95% CI)** | | | **270** | **3169** | **100.0%** | **0.87 [0.66, 1.14]** |

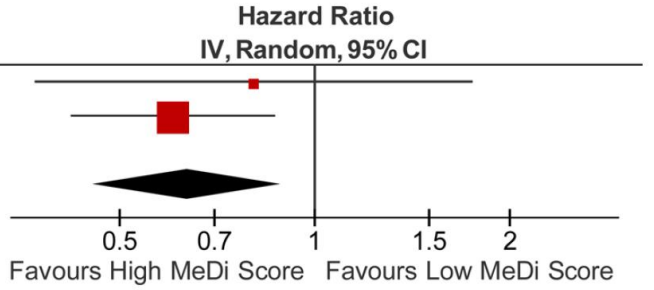
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)




**3.3 Highest vs Lowest MeDi tertile**

| Study or Subgroup | log[Hazard Ratio] | SE | AD Total | CN Total | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|---|---|
| Feart 2009 | -0.2169 | 0.3966 | 51 | 1410 | 18.0% | 0.81 [0.37, 1.75] |
| Scarmeas 2006 | -0.5034 | 0.1858 | 219 | 1759 | 82.0% | 0.60 [0.42, 0.87] |
| **Total (95% CI)** | | | **270** | **3169** | **100.0%** | **0.64 [0.46, 0.89]** |

Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)



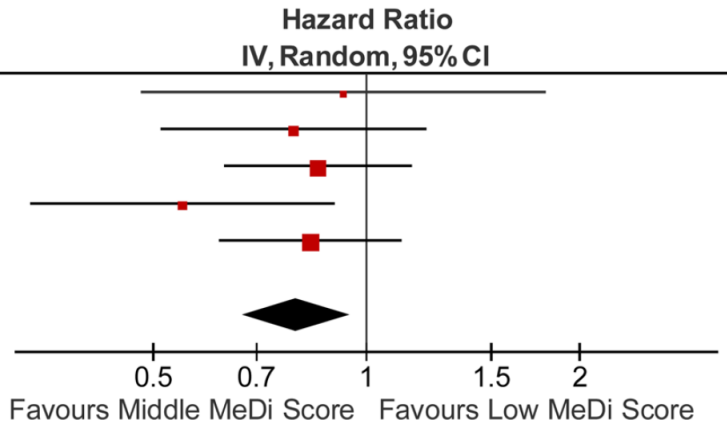
# Deterioramento cognitivo

Dieta mediterranea

**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]** |

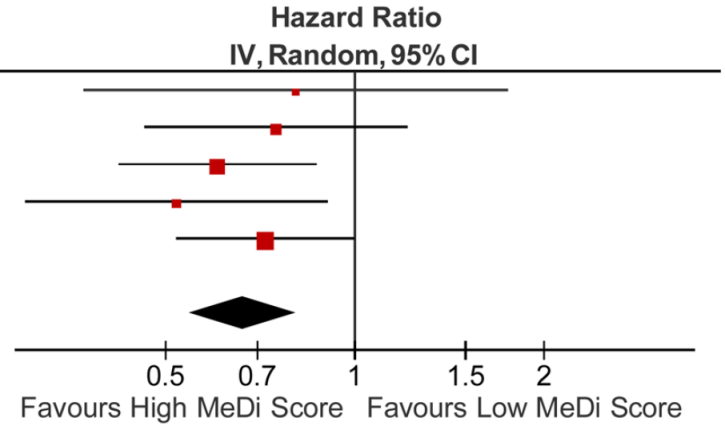
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)




**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)



# Physical Activity, Diet, and Risk of Alzheimer Disease

Dieta mediterranea

Nikolaos Scarmeas, MD
Jose A. Luchsinger, MD
Nicole Schupf, PhD
Adam M. Brickman, PhD
Stephanie Cosentino, PhD
Ming X. Tang, PhD
Yaakov Stern, PhD

**Context** Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk but their combined association has not been investigated.

**Objective** To investigate the combined association of diet and physical activity with AD risk.

**Design, Setting, and Patients** Prospective cohort study of 2 cohorts comprising 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available. Standardized neurological and neuropsychological measures were administered approximately every 1.5 years from 1992 through 2006. Adherence to a Mediterranean-type diet (scale of 0-9; trichotomized into low, middle, or high; and dichotomized into low or high) and physical activity (sum of weekly participation in various physical activities, weighted by the type of physical activity [light, moderate, vigorous]; trichotomized into no physical activity, some, or much; and dichotomized into low or high), separately and combined, were the main predictors in Cox models. Models were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, depression, leisure activities, a comorbidity index, and baseline Clinical Dementia Rating score.

**Main Outcome Measure** Time to incident AD.

**Results** A total of 282 incident AD cases occurred during a mean (SD) of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence (compared with low diet score, hazard ratio [HR] for middle diet score was 0.98 [95% confidence interval {CI}, 0.72-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; $P=.008$ for trend) and physical activity (compared with no physical activity, the HR for some physical activity was 0.75 [95% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; $P=.03$ for trend) were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; $P=.03$ for trend).

**Conclusion** In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.

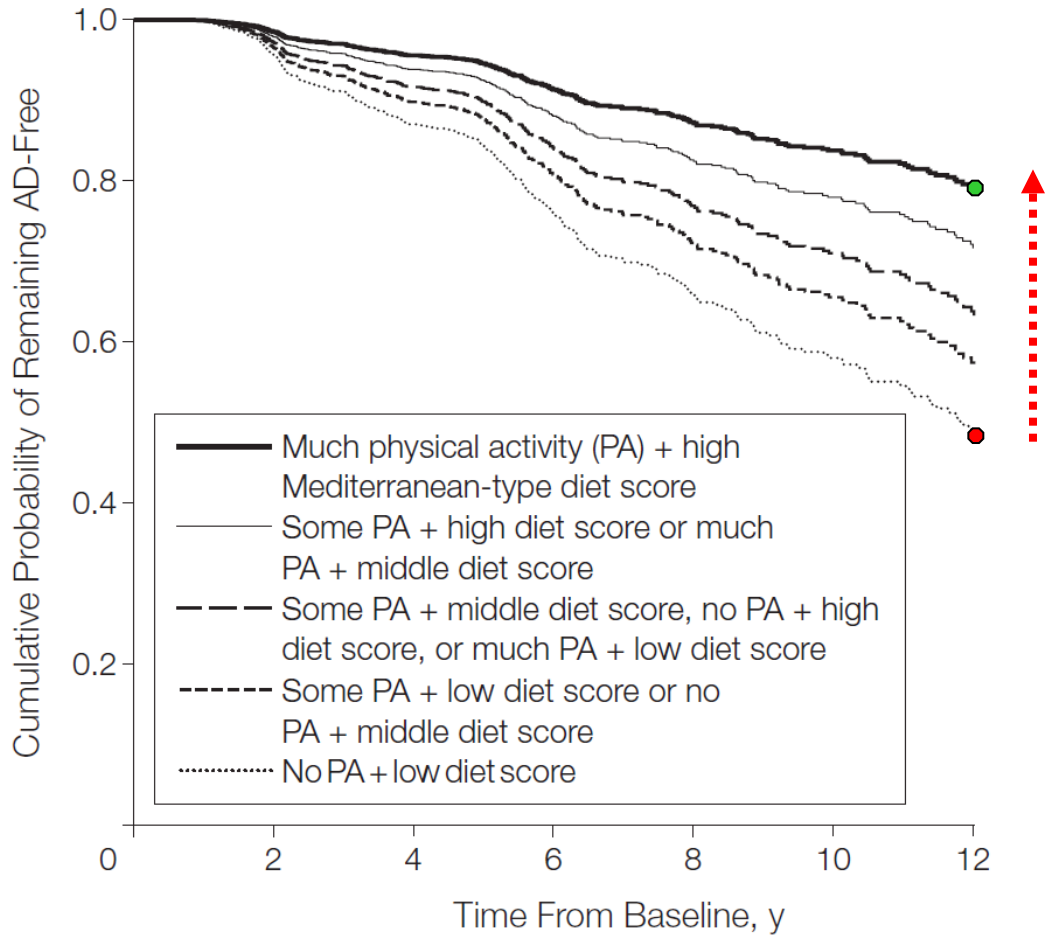
*JAMA. 2009;302(6):627-637* www.jama.com

PREVIOUS RESEARCH HAS SHOWN that physical activity can slow down or prevent functional decline associated with aging and improve health in older individuals.[1,2] However, regarding Alzheimer disease (AD) or dementia, the relationship is less clear, with many studies reporting exercise being associated with lower rates of cognitive decline[1,3] or dementia[4-7] and others reporting no significant association.[8-10] Dietary habits also may play an important role but epidemiological data on diet and AD have been conflicting.[11] In this cohort, we previously found that higher adherence to a Mediterranean-type diet is associated with lower risk for AD[12,13] and mild cognitive impairment.[14]

Nevertheless, it is important to know whether physical activity and diet confer independent associations because individuals who exercise often belong to higher educational-socioeconomic strata, are more health conscious, and in general

**Figure 3.** Alzheimer Disease (AD) Incidence in Individuals by No, Some, or Much Physical Activity and Low, Middle, and High Mediterranean-Type Diet Adherence Scores

Dieta mediterranea



# Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study[1–3]

*Emiliano Albanese, Alan D Dangour, Ricardo Uauy, Daisy Acosta, Mariella Guerra, Sara S Gallardo Guerra, Yueqin Huang, KS Jacob, Juan Llibre de Rodriguez, Lisseth Hernandex Noriega, Aquiles Salas, Ana Luisa Sosa, Renata M Sousa, Joseph Williams, Cleusa P Ferri, and Martin J Prince*



FISH

| Country | PRs (95% CI) |
|---|---|
| Cuba | 0.81 (0.65 to 1.02) |
| Dominican Republic | 0.80 (0.65 to 1.00) |
| Perú | 0.76 (0.56 to 1.05) |
| Venezuela | 0.87 (0.56 to 1.34) |
| Mexico | 0.81 (0.62 to 1.08) |
| China | 0.58 (0.39 to 0.85) |
| India | 1.47 (0.92 to 2.35) |
| **Pooled Effect** Fixed-Effect Method | 0.81 (0.72 to 0.91) |
| **Test for heterogeneity** $I^2$ Higgins (%) | Q= 9.31 (df=6) (p=0.16) $I^2$= 35.51 (95%CI: 0 to 71) |
| **Test for Overall Effect:** Fixed-Effects Model | z=-3.72 (p<0.001) |

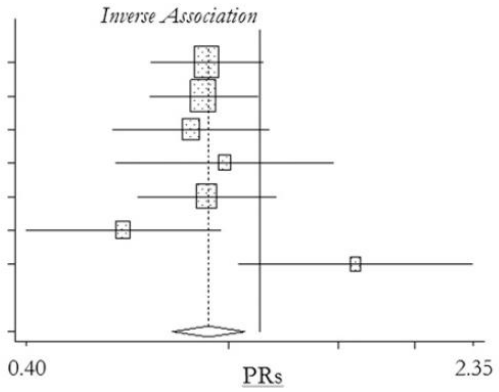



**FIGURE 1.** Meta-analysis (fixed-effect model) of country prevalence ratios (PRs) (and 95% CIs) for the association between fish consumption and 10/66 dementia. PRs are from robust Poisson regression models adjusted for household clustering as for model 3 in Table 4, ie, adjusted for age, sex, educational level, and family history of dementia and controlled for number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoking habit; living arrangements (live alone or only with spouse); number of assets; meat intake; and number of daily portions of fruit and vegetables.

**Am J Clin Nutr 2009**

# Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study[1–3]

*Emiliano Albanese, Alan D Dangour, Ricardo Uauy, Daisy Acosta, Mariella Guerra, Sara S Gallardo Guerra, Yueqin Huang, KS Jacob, Juan Llibre de Rodriguez, Lisseth Hernandex Noriega, Aquiles Salas, Ana Luisa Sosa, Renata M Sousa, Joseph Williams, Cleusa P Ferri, and Martin J Prince*

MEAT



| Country | PRs (95% CI) |
|---|---|
| Cuba | 1.31 (1.07 to 1.60) |
| Dominican Republic | 1.19 (0.98 to 1.45) |
| Perú | 1.41 (1.09 to 1.81) |
| Venezuela | 0.91 (0.59 to 1.40) |
| Mexico | 1.24 (0.94 to 1.64) |
| China | 0.95 (0.69 to 1.31) |
| India | 0.77 (0.48 to 1.21) |
| **Pooled Effect** Fixed-Effect Method | 1.19 (1.07 to 1.31) |
| **Test for heterogeneity**[1] $I^2$ Higgins (%) | Q= 9.46 (6 df) (p=0.15) $I^2$= 36.55 (95% C.I. 0 to 57.4) |
| **Test for Overall Effect:** Fixed-Effects Model | z=3.37 (p=0.001) |

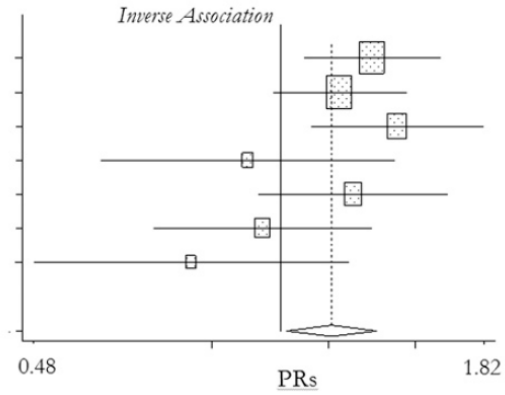
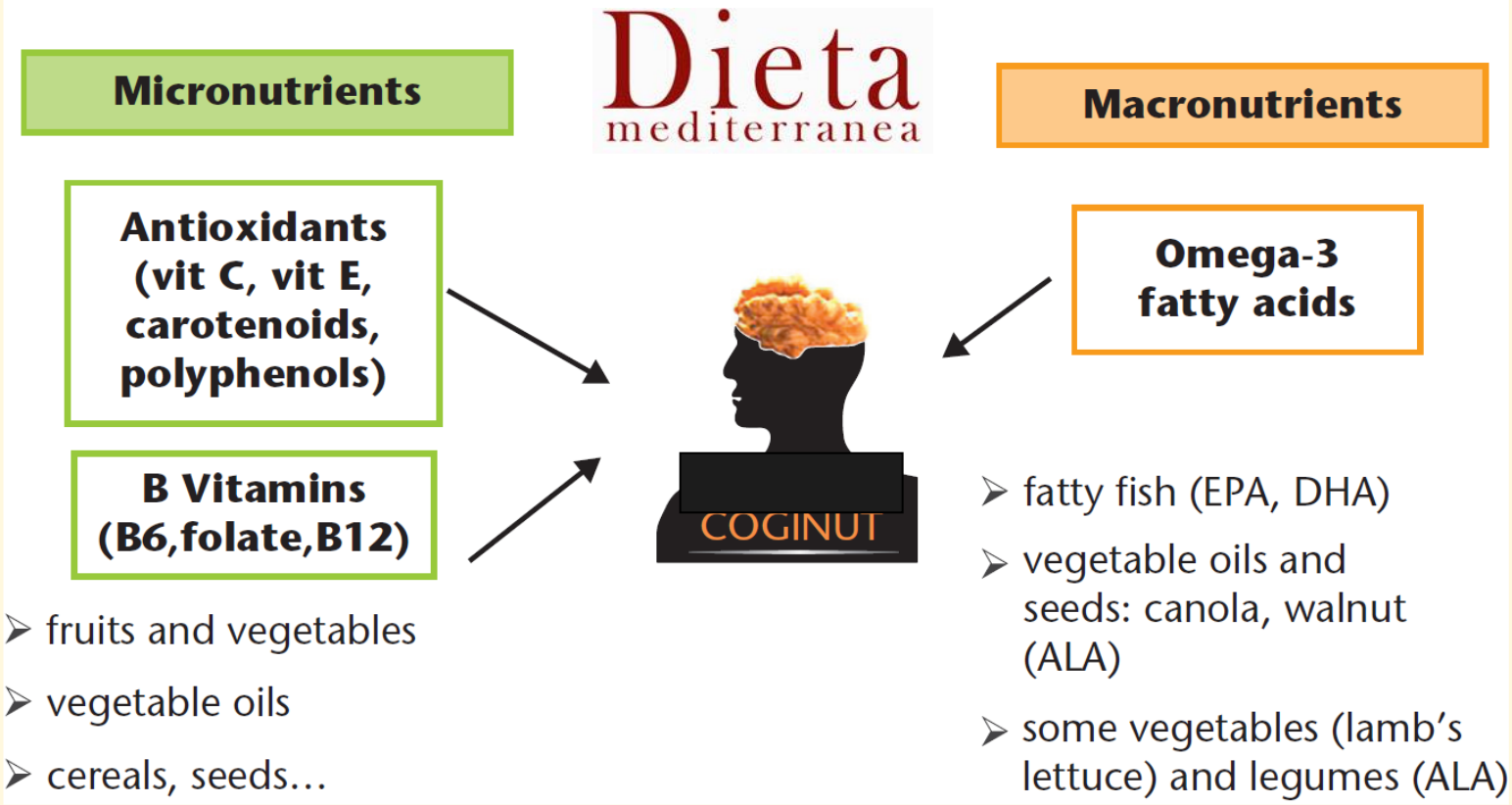



**FIGURE 2.** Meta-analysis (fixed-effect model) of country prevalence ratios (PRs) (and 95% CIs) for the association between meat consumption and 10/66 dementia. PRs are from robust Poisson regression models adjusted for household clustering as for model 3 in Table 5, ie, adjusted for age, sex, educational level, and family history of dementia and controlled for the number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoke habit; living arrangements (live alone or only with spouse); number of assets; fish intake; and number of daily portions of fruit and vegetables.

**Am J Clin Nutr 2009**

# Dieta mediterranea e funzioni cognitive



# Olive-Oil-Derived Oleocanthl Enhances β-Amyloid Clearance as a Potential Neuroprotective Mechanism against Alzheimer's Disease: In Vitro and in Vivo Studies

**Abuznait AH, Qosa H, Busnena BA, El Sayed KA, Kaddoumi A**

Department of Basic Pharmaceutical Science, University of Louisiana at Monroe, Louisiana, USA

## Abstract

Oleocanthal, a phenolic component of extra-virgin olive oil, has been recently linked to reduced risk of Alzheimer's disease (AD), a neurodegenerative disease that is characterized by accumulation of β-amyloid (Aβ) and tau proteins in the brain. However, the mechanism by which oleocanthal exerts its neuroprotective effect is still incompletely understood. **Here, we provide in vitro and in vivo evidence for the potential of OLEOCANTHAL to enhance Aβ clearance from the brain via up-regulation of P-glycoprotein (P-gp) and LDL lipoprotein receptor related protein-1 (LRP1), major Aβ transport proteins, at the blood-brain barrier (BBB).** Results from in vitro and in vivo studies demonstrated similar and consistent pattern of oleocanthal in controlling Aβ levels. In cultured mice brain endothelial cells, oleocanthal treatment increased P-gp and LRP1 expression and activity. Brain efflux index (BEI%) studies of (125)I-Aβ(40) showed that administration of oleocanthal extracted from extra-virgin olive oil to C57BL/6 wild-type mice enhanced (125)I-Aβ(40) clearance from the brain and increased the BEI% from 62.0 ± 3.0% for control mice to 79.9 ± 1.6% for oleocanthal treated mice. Increased P-gp and LRP1 expression in the brain microvessels and inhibition studies confirmed the role of up-regulation of these proteins in enhancing (125)I-Aβ(40) clearance after oleocanthal treatment. Furthermore, our results demonstrated significant increase in (125)I-Aβ(40) degradation as a result of the up-regulation of Aβ degrading enzymes following oleocanthal treatment. **In conclusion, these findings provide experimental support that potential reduced risk of AD associated with extra-virgin olive oil could be mediated by enhancement of Aβ clearance from the brain.**

**ACS Chem Neurosci 2013 Feb 25 [Epub ahead of print]**

frontiers in
AGING NEUROSCIENCE

MINI REVIEW ARTICLE
published: 09 May 2014
doi: 10.3389/fnagi.2014.00088

# Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia

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Both obesity and Alzheimer's disease (AD) are major health burdens in Western societies. While commonly viewed as having separate etiologies, this review highlights data suggesting that intake of "Western diets", diets high in saturated fatty acids (SFA) and simple carbohydrates, may pose a common environmental risk factor contributing to the development of both of these adverse pathologies. We discuss the effects of Western Diet intake on learning and memory processes that are dependent on the hippocampus, as well as the importance of this brain region in both obesity development and the onset of Alzheimer's and other dementias. A putative mechanism is discussed that mechanistically links Western diet consumption, blood brain barrier (BBB) degradation, and subsequent hippocampal damage and dementia pathology.

**Keywords: obesity, Western diet, Alzheimer's, hippocampus, cognitive impairment, blood-brain barrier**

Frontiers in Aging Neuroscience 2014

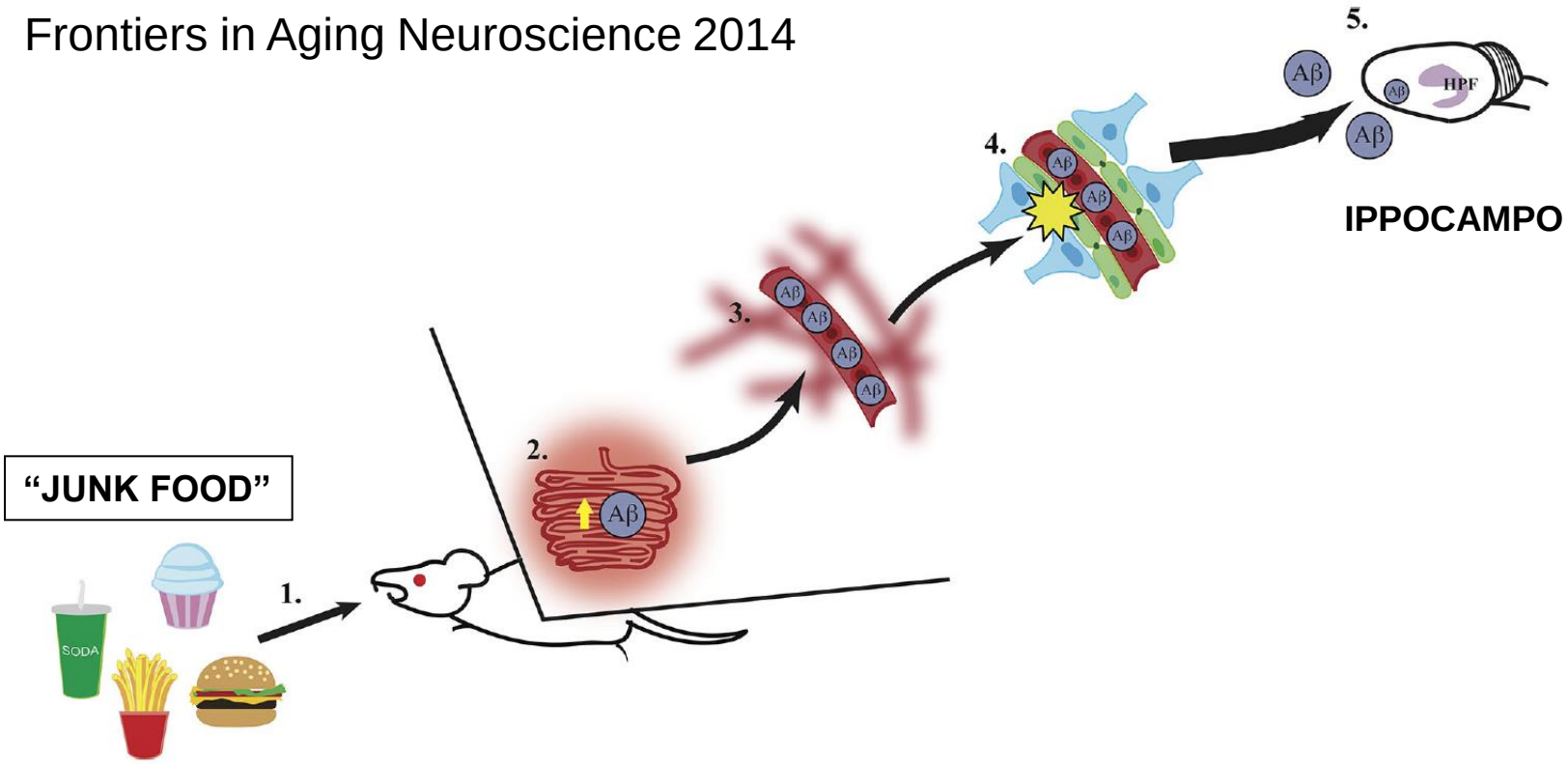



**FIGURE 1 | A putative mechanism for hippocampus dysfunction by Western Diet intake. (1)** Intake of a Western Diet (simple carbohydrates, saturated fatty acids) results in **(2)** elevated secretion of amyloid-β (Aβ) from the small intestines, **(3)** thus elevating circulating Aβ levels within the vasculature system. **(4)** High circulating levels of Aβ contribute to blood-brain barrier damage via reduction of gene expression of tight junction proteins (e.g., occludin, claudin 5; illustrated in green), **(5)** which leaves the hippocampal formation (HPF) vulnerable to damage by excessive Aβ accumulation and other circulating toxins (e.g., heavy metals, inflammatory markers).

# 2. Acidi Grassi

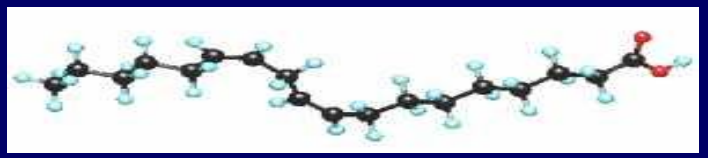
# Acidi Grassi

## 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)

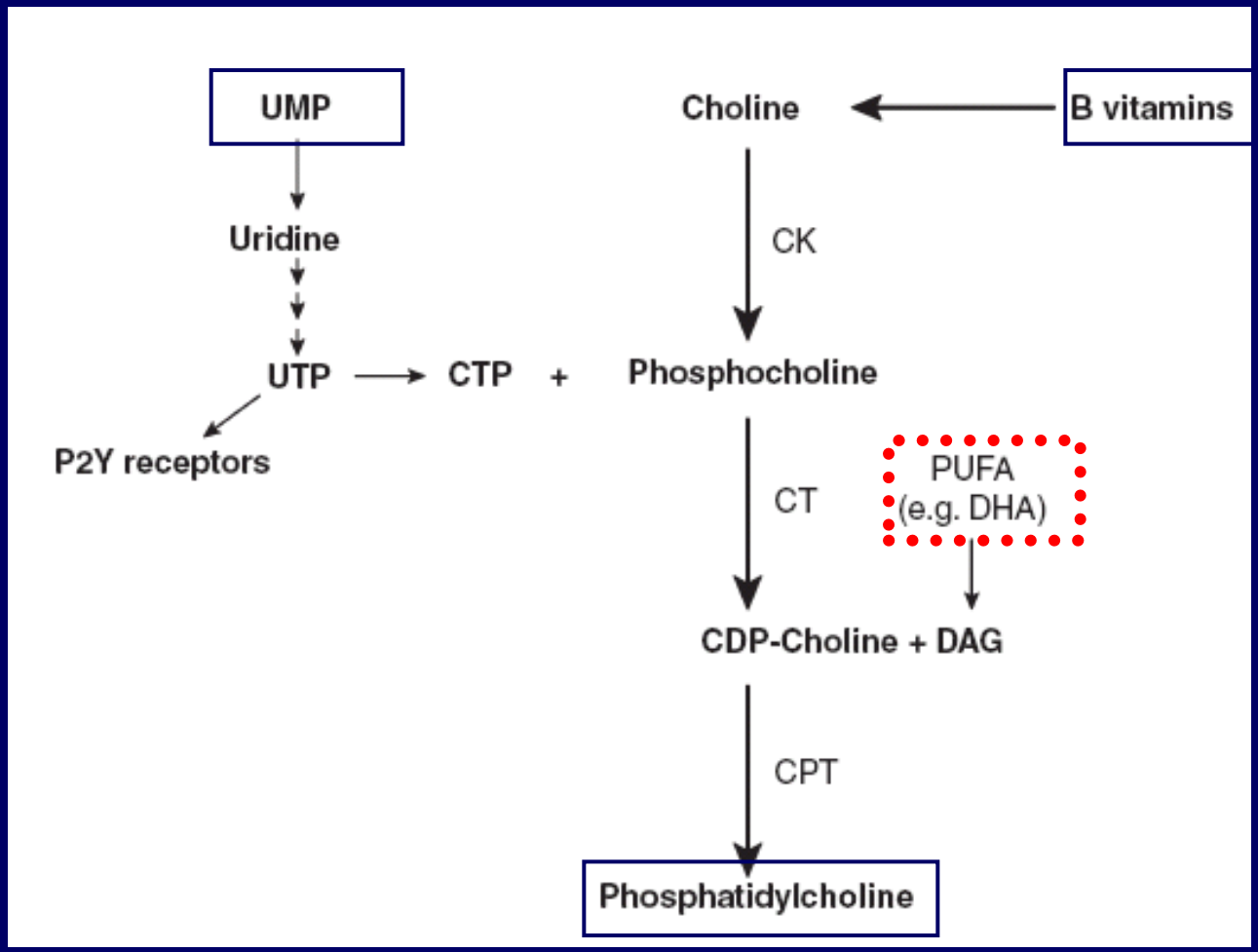
# ACIDI GRASSI & SISTEMA NERVOSO CENTRALE

- 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



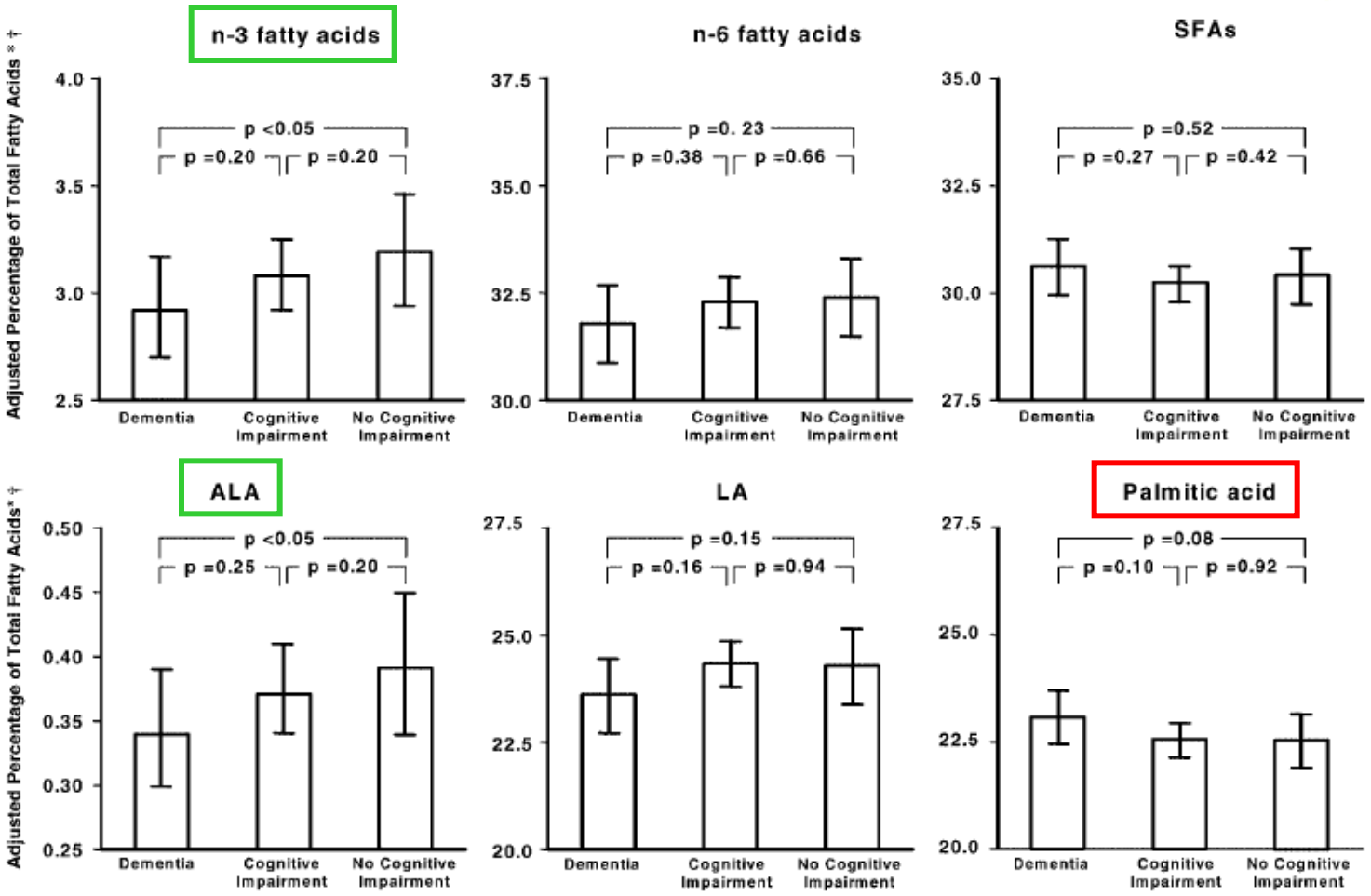



Figure 1. Means ± 95% confidence intervals of the relative concentration of n-3 fatty acids (FA), n-6 FA, and saturated FA (SFAs) (*top*); and alpha-linolenic acid (ALA), linolenic acid (LA), and palmitic acid (*bottom*) in participants with dementia, cognitive impairment, or normal cognitive function. *Based on mg/L total plasma FA. †Adjusted for age, gender, education, smoking status, body mass index, weight loss, alcohol intake, total energy intake, low density lipoprotein and high density lipoprotein cholesterol levels, triglyceride levels, coronary heart disease, cerebrovascular disease, congestive heart failure, diabetes, hypertension, depression, and plasma levels of the other two FA variables in the same panel.

**The InCHIANTI Study: A. Cherubini et al. J Geront Med Sci 2007**

# Differences in Nutritional Status Between Very Mild Alzheimer's Disease Patients and Healthy Controls

**M.G.M. Olde Rikkert et al.**
**J Alzheimer's Disease 2014**

| | Erythrocyte fatty acids | | |
|---|---|---|---|
| | Healthy controls ($n=93$) | Mild AD ($n=79$) | $p$-value* |
| EPA (%) | 0.98 (0.40) | 0.97 (0.44) | 0.849 |
| DHA (%) | 3.44 (0.99) | 2.99 (1.14) | 0.006 |
| DPA (%) | 1.78 (0.36) | 1.64 (0.54) | 0.046 |
| DHA+EPA (%) | 4.42 (1.30) | 3.95 (1.48) | 0.028 |
| n-3 LC-PUFA (%) | 6.20 (1.54) | 5.59 (1.92) | 0.024 |
| Palmitic acid (%) | 24.82 (1.40) | 26.64 (2.76) | <0.001 |
| Stearic acid (%) | 9.00 (0.72) | 9.12 (0.84) | 0.309 |
| Elaidic acid (%) | 0.18 (0.11) | 0.23 (0.11) | 0.006 |
| Oleic acid (%) | 15.80 (1.72) | 15.59 (1.54) | 0.387 |
| Cis-vaccenic acid (%) | 1.14 (0.16) | 1.14 (0.17) | 0.981 |
| Linoleic acid (%) | 15.01 (2.53) | 13.06 (2.41) | <0.001 |
| Gamma linolenic acid (%) | 0.15 (0.10) | 0.09 (0.09) | <0.001 |
| Alpha linolenic acid (%) | 0.28 (0.10) | 0.16 (0.09) | <0.001 |
| Stearidonic acid (%) | 0.09 (0.04) | 0.11 (0.13) | 0.231 |
| Dihomo gamma linolenic acid (%) | 1.49 (0.30) | 1.30 (0.33) | <0.001 |
| Arachidonic acid (%) | 10.94 (1.43) | 9.76 (2.69) | <0.001 |
| Cis docosapentaenoic acid (%) | 0.63 (0.14) | 0.70 (0.25) | 0.026 |

# Acidi grassi e rischio di sviluppare demenza tipo Alzheimer

Adjusted relative risks[a] of incident AD by quintile of intake of specific types of dietary fats amongst 815 persons after 3.9 years of follow-up, CHAP, 1993–2000

| | Type of fat | |
|---|---|---|
| Quintile | Saturated | Trans |
| 1 | 1.0 (Referent) | 1.0 (Referent) |
| 2 | 1.8 (0.7–4.3) | 2.4 (1.1–5.3) |
| 3 | 1.1 (0.5–2.8) | 2.9 (1.2–7.2) |
| 4 | 1.4 (0.5–3.6) | 1.8 (0.8–4.2) |
| 5 | 2.2 (1.1–4.7) | 2.5 (1.0–6.2) |

| Quintile | Total omega-3 fatty acids | DHA | EPA |
|---|---|---|---|
| 1 | 1.0 (Referent) | 1.0 (Referent) | 1.0 (Referent) |
| 2 | 1.2 (0.5–3.0) | 0.8 (0.3–2.1) | _a |
| 3 | 0.6 (0.2–1.7) | 0.4 (0.1–1.0) | 1.1 (0.4–2.8) |
| 4 | 0.7 (0.3–1.6) | 0.2 (0.1–0.8) | 0.5 (0.2–1.2) |
| 5 | 0.4 (0.1–0.9) | 0.3 (0.1–0.9) | 0.9 (0.4–2.3) |
| *P*-value trend | 0.01 | 0.02 | 0.40 |

Chicago Health and Aging Study - Morris MC Eur J Neurol 2009

**BMC Public Health**

BioMed Central
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# Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis

*BMC Public Health* 2014, **14**:643 doi:10.1186/1471-2458-14-643

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## Methods

We systematically reviewed selected modifiable factors such as education, smoking, alcohol, physical activity, caffeine, antioxidants, homocysteine (Hcy), *n*-3 fatty acids that were studied in relation to various cognitive health outcomes, including incident AD. We searched MEDLINE for published literature (January 1990 through October 2012), including cross-sectional and cohort studies (sample sizes > 300). Analyses compared study finding consistency across factors, study designs and study-level characteristics. Selecting studies of incident AD, our meta-analysis estimated pooled risk ratios (RR), population attributable risk percent(PAR%) and assessed publication bias.

## Results

In total, 247 studies were retrieved for systematic review. Consistency analysis for each risk factor suggested positive findings ranging from ~38.9% for caffeine to ~89% for physical activity. Education also had a significantly higher propensity for "a positive finding" compared to caffeine, smoking and antioxidant-related studies. Meta-analysis of 31 studies with incident AD yielded pooled RR for low education (RR = 1.99; 95%CI: 1.30-3.04), high Hcy (RR = 1.93; 95%CI: 1.50-2.49), and current/ever smoking status (RR = 1.37; 95%CI: 1.23-1.52) while indicating protective effects of higher physical activity and *n*-3 fatty acids. Estimated PAR% were particularly high for physical activity (PAR% = 31.9; 95%CI: 22.7-41.2) and smoking (PAR%-31.0%; 95%CI: 17.9-44.3). Overall, no significant publication bias was found.

## Conclusions

Higher Hcy levels, lower educational attainment, and decreased physical activity were particularly strong predictors of incident AD. Further studies are needed to support other potential modifiable protective factors, such as caffeine.

MA Beydoun et al. BMC Publ Health 2014

# Nutrient intake and plasma β-amyloid


## ABSTRACT

**Objective:** The widely reported associations between various nutrients and cognition may occur through many biologic pathways including those of β-amyloid (Aβ). However, little is known about the possible associations of dietary factors with plasma Aβ40 or Aβ42. The aim of the current study was to evaluate the association between nutrient intake and plasma Aβ levels.

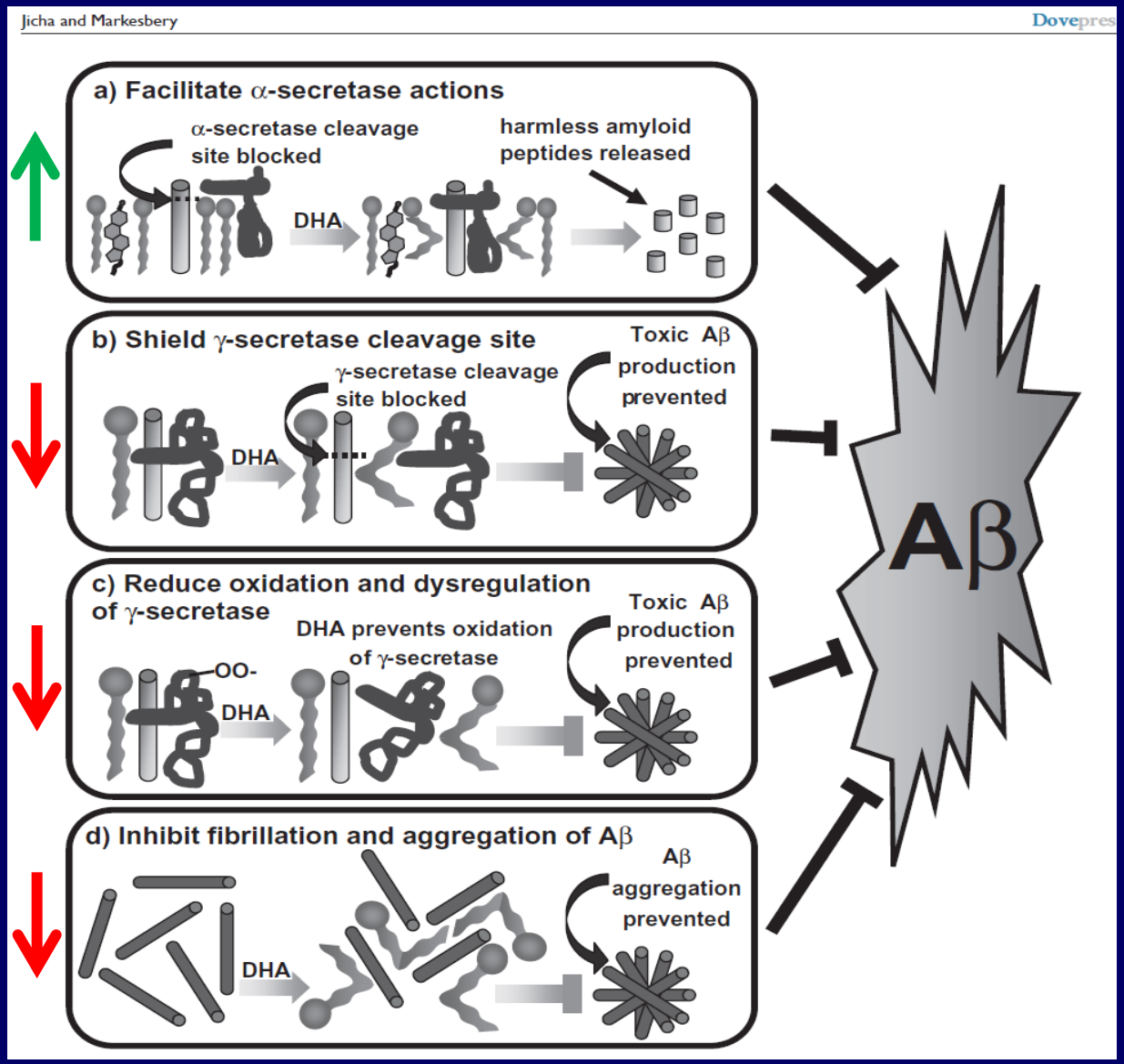
**Methods:** In this cross-sectional study, plasma Aβ40 and Aβ42 and dietary data were obtained from 1,219 cognitively healthy elderly (age >65 years), who were participants in a community-based multiethnic cohort. Information on dietary intake was obtained 1.2 years, on average, before Aβ assay. The associations of plasma Aβ40 and Aβ42 levels and dietary intake of 10 nutrients were examined using linear regression models, adjusted for age, gender, ethnicity, education, caloric intake, apolipoprotein E genotype, and recruitment wave. Nutrients examined included saturated fatty acid, monounsaturated fatty acid, ω-3 polyunsaturated fatty acid (PUFA), ω-6 PUFA, vitamin E, vitamin C, β-carotene, vitamin $B_{12}$, folate, and vitamin D.

**Results:** In unadjusted models that simultaneously included all nutrients, higher intake of ω-3 PUFA was associated with lower levels of Aβ40 ($\beta = -24.7$, $p < 0.001$) and lower levels of Aβ42 ($\beta = -12.3$, $p < 0.001$). In adjusted models, ω-3 PUFA remained a strong predictor of Aβ42 ($\beta = -7.31$, $p = 0.02$), whereas its association with Aβ40 was attenuated ($\beta = -11.96$, $p = 0.06$). Other nutrients were not associated with plasma Aβ levels.

**Conclusions:** Our data suggest that higher dietary intake of ω-3 PUFA is associated with lower plasma levels of Aβ42, a profile linked with reduced risk of incident AD and slower cognitive decline in our cohort. *Neurology*® 2012;78:1832-1840

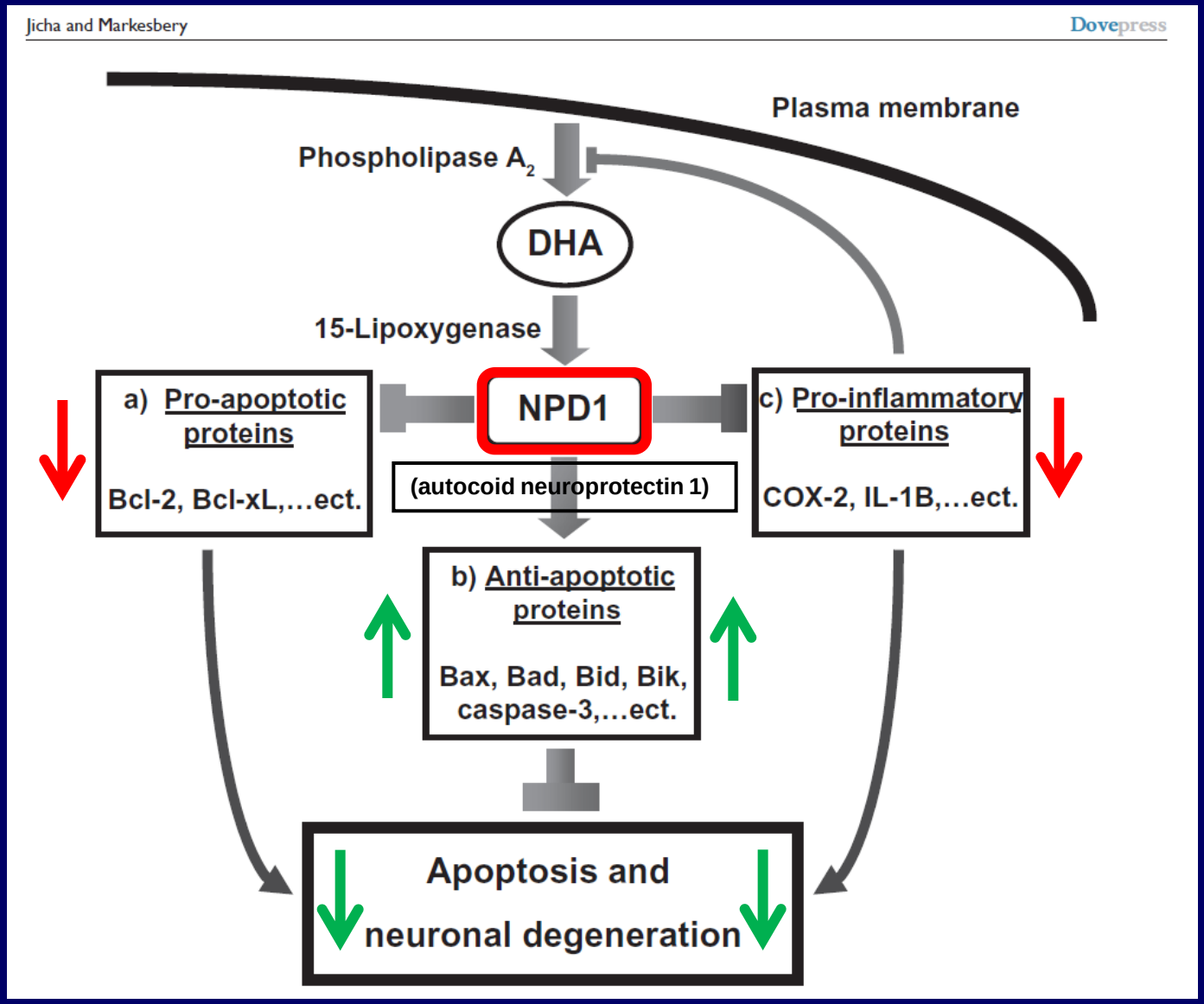

Y. GU et al. Neurology 2012

# n-3 PUFA e produzione di Beta-Amiloide




GA Jicha & WR Markesbery Clin Interv in Aging 2010

# n-3 PUFA: attività anti-apoptotica/infiammatoria




GA Jicha & WR Markesbery Clin Interv in Aging 2010

# Omega 3 fatty acids and cognitive health in older people

**Dangour AD, Andreeva VA, Sydenham E, Uauy R**

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alan.dangour@lshtm.ac.uk

## Abstract

Oily fish and other sources of long-chain n-3 polyunsaturated fatty acids (n-3 LCPs) have been proposed as protective against dementia and age related cognitive impairment. The basic mechanisms underlying these proposed benefits have been postulated and experimental studies supporting the plausibility of the putative effects have been published. **Observational epidemiological and case control studies also largely support a protective role of fish consumption on cognitive function with advancing age, albeit with important unexplained heterogeneity in findings.** In this review we report the findings of the latest Cochrane review on the benefits of n-3 LCP supplementation on cognitive function among cognitively healthy older people and expand the review by including trials conducted with individuals with prevalent poor cognitive function or dementia. We identified **seven relevant trials,** four among cognitively healthy older people, and three among individuals with pre-existing cognitive decline or dementia, and overall **conclude that there is NO EVIDENCE to support the routine use of n-3 LCPs supplements for the prevention, or amelioration, of cognitive decline in later life.** We identified several challenges in the design of intervention studies for the prevention of dementia and cognitive decline in older people that require careful consideration especially in recruitment and retention in long-term trials. Whether the lack of agreement in findings from mechanistic and observational data and from intervention studies reflects a real absence of benefit on cognitive function from n-3 LCP supplementation, or whether it reflects intrinsic limitations in the design of published studies remains open to question.

**British Journal of Nutrition 2012; 107 Suppl 2**

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

Sydenham E, Dangour AD, Lim WS

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**Authors' conclusions**

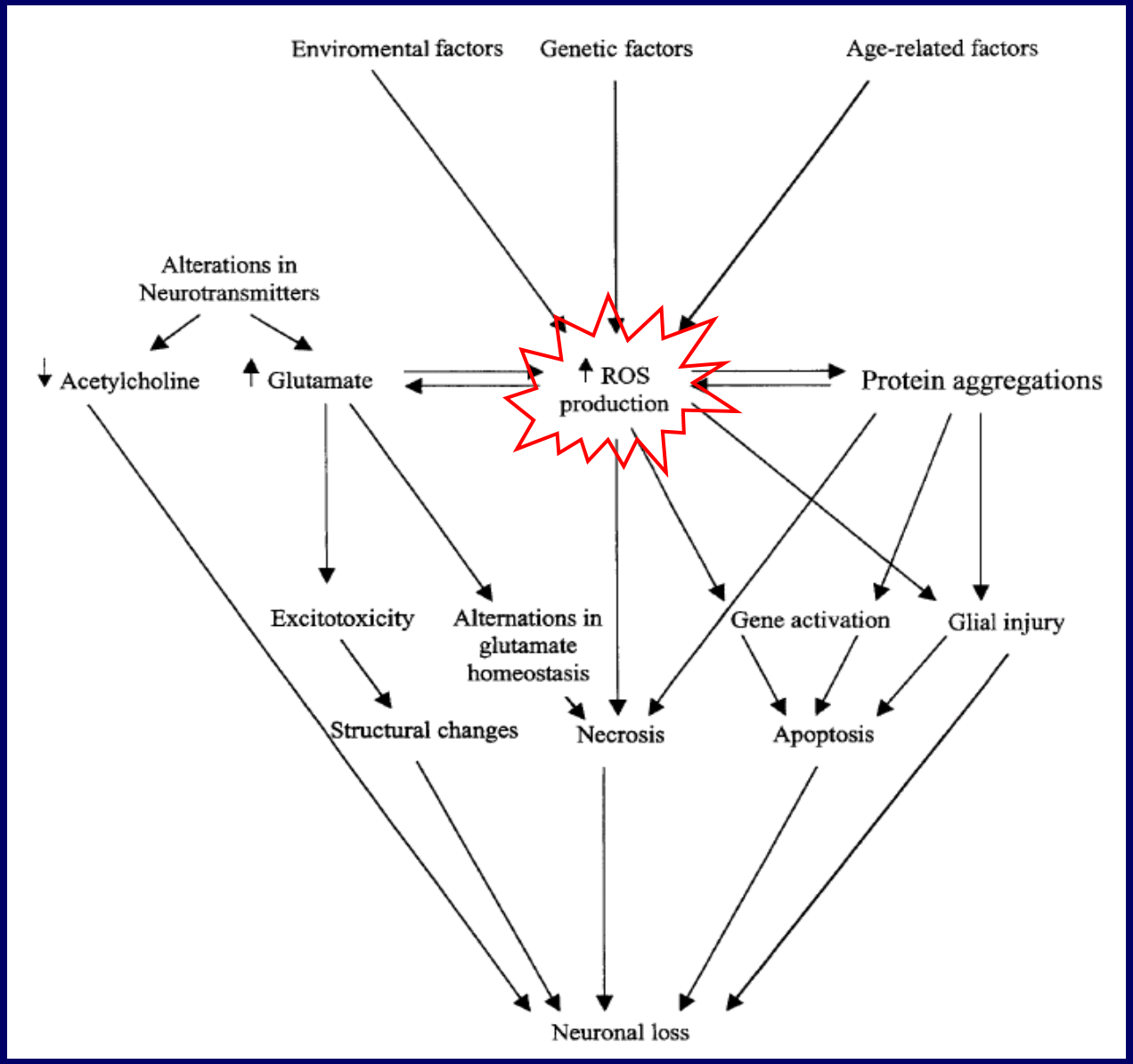
Direct evidence on the effect of omega-3 PUFA on incident dementia is lacking. The available trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people. Omega-3 PUFA supplementation is generally well tolerated with the most commonly reported side-effect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

**E. Sydhenam et al. 2012**

# 3. Vitamine & Antiossidanti

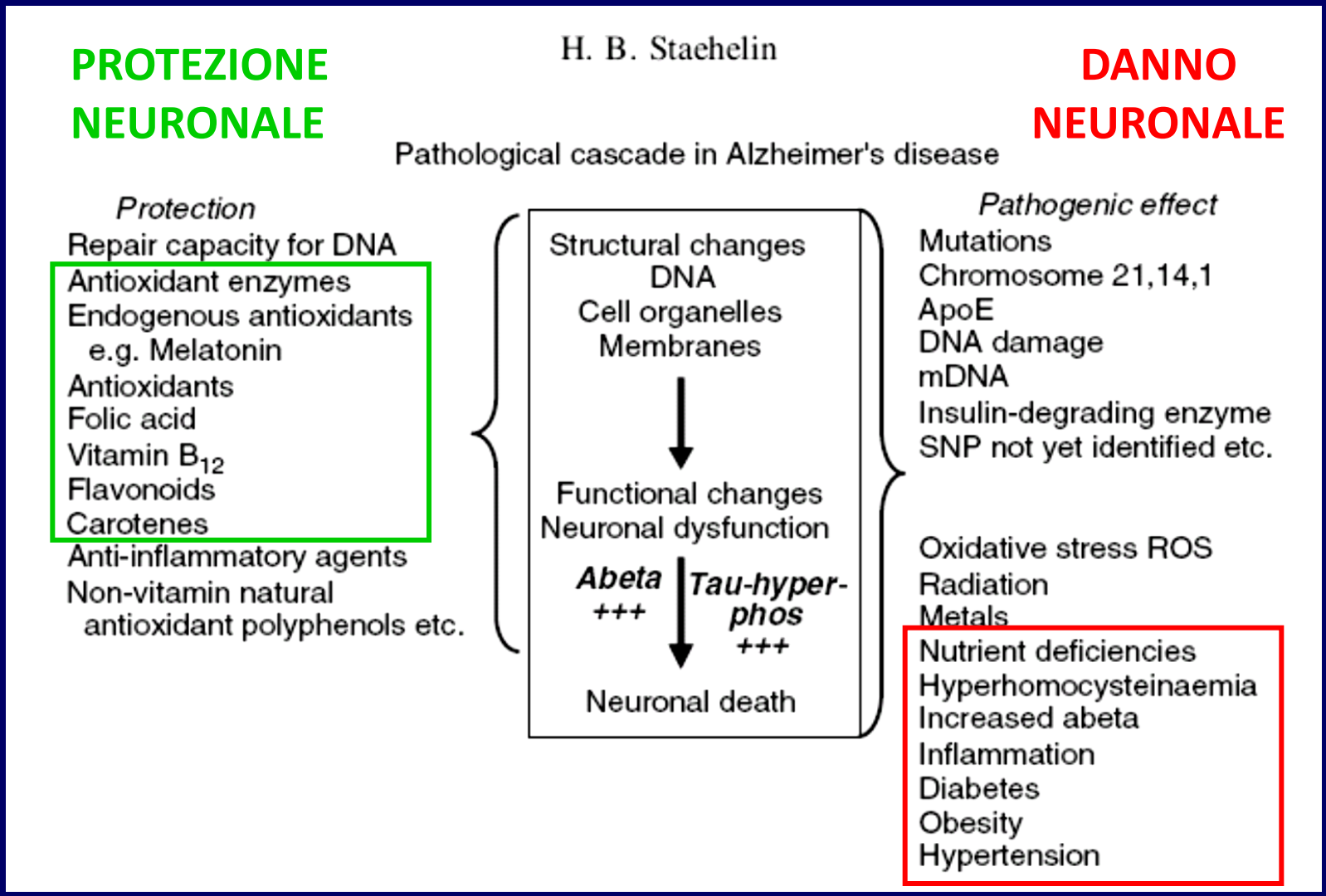
# Stress ossidativo e demenza



# Stress ossidativo e demenza

**PROTEZIONE NEURONALE**

**DANNO NEURONALE**




HB Stahelin Proocedings of Nutr Soc 2005

Review Article

# Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis

Sofia Lopes da Silva[a,b], Bruno Vellas[c], Saskia Elemans[a], José Luchsinger[d], Patrick Kamphuis[a,b], Kristine Yaffe[e], John Sijben[a,*], Martine Groenendijk[a], Theo Stijnen[f]

Results of meta-analyses **Alzheimer's & Dementia 2014**

**ALZHEIMER < CONTROLS**

| Nutrient | Number of publications | Meta-analysis In all cases levels were lower in AD patients than in controls |
|---|---|---|
| Vitamin A | 9 studies [44,65,72,74,75,78,100–102] | $P < .001$ |
| Folate | 31 studies [36,37,46,84,85,103–128] | $P < .001$ |
| Vitamin B12 | 33 studies [35–37,44,46,49,84,85,103,105, 107–112,114–123,125–131] | $P < .001$ |
| Vitamin C | 8 studies [44,74,75,77,79,132–134] | $P < .001$ |
| Vitamin D | 5 studies [47,98,99,135,136] | $P = .075$ |
| Vitamin E | 20 studies [44,65,69,71–78,100,101,132, 133,137–141] | $P < .001$ |
| Copper | 5 studies [39,40,51,53,142] | NS |
| Iron | 5 studies [39,51,53,129,142] | NS |
| Zinc | 5 studies [39,51,53,142,143] | $P = .05$ |

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PROTEGGEREBBERO DA ALZHEIMER E MALATTIE DEGENERATIVE

## *La dieta che fa bene al cervello*

***La ricchezza in determinati polifenoli e acidi grassi aumentano il numero e la differenziazione delle cellule staminali cerebrali. Almeno nei topi***

***Elena Meli 8 gennaio 2010***

Journal of Alzheimer's Disease 18 (2009) 849–865
DOI 10.3233/JAD-2009-1188
IOS Press

# A Diet Enriched in Polyphenols and Polyunsaturated Fatty Acids, LMN Diet, Induces Neurogenesis in the Subventricular Zone and Hippocampus of Adult Mouse Brain

Tony Valente[a,*], Juan Hidalgo[b], Irene Bolea[a], Bartolomé Ramirez[c], Neus Anglés[c], Jordi Reguant[c], José Ramón Morelló[c], Cristina Gutiérrez[a], Mercè Boada[d] and Mercedes Unzeta[a]

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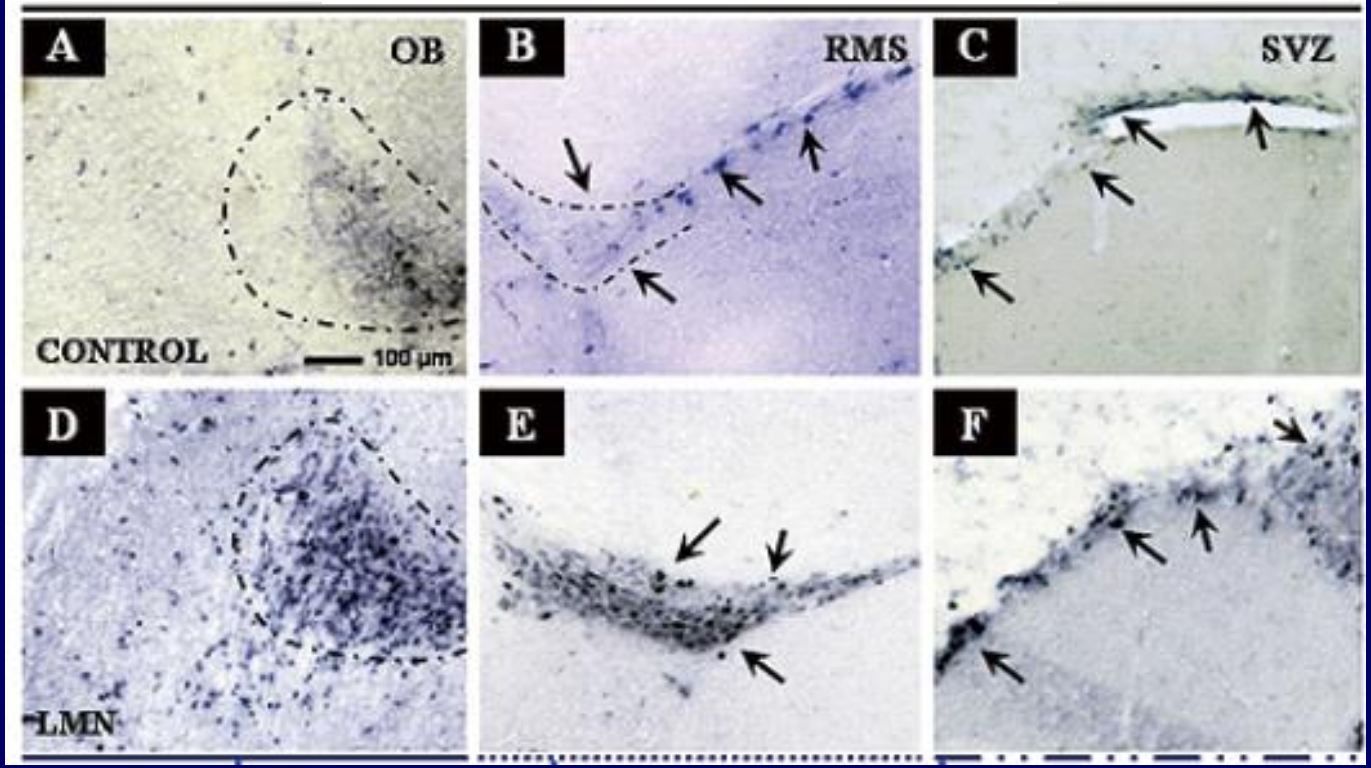
**LMN diet contains: nuts, cocoa, vegetable oils rich in unsaponifiable fatty acids, and flours rich in soluble fibers**

# ↑ Proliferazione neuronale in vivo

## CONTROLLI

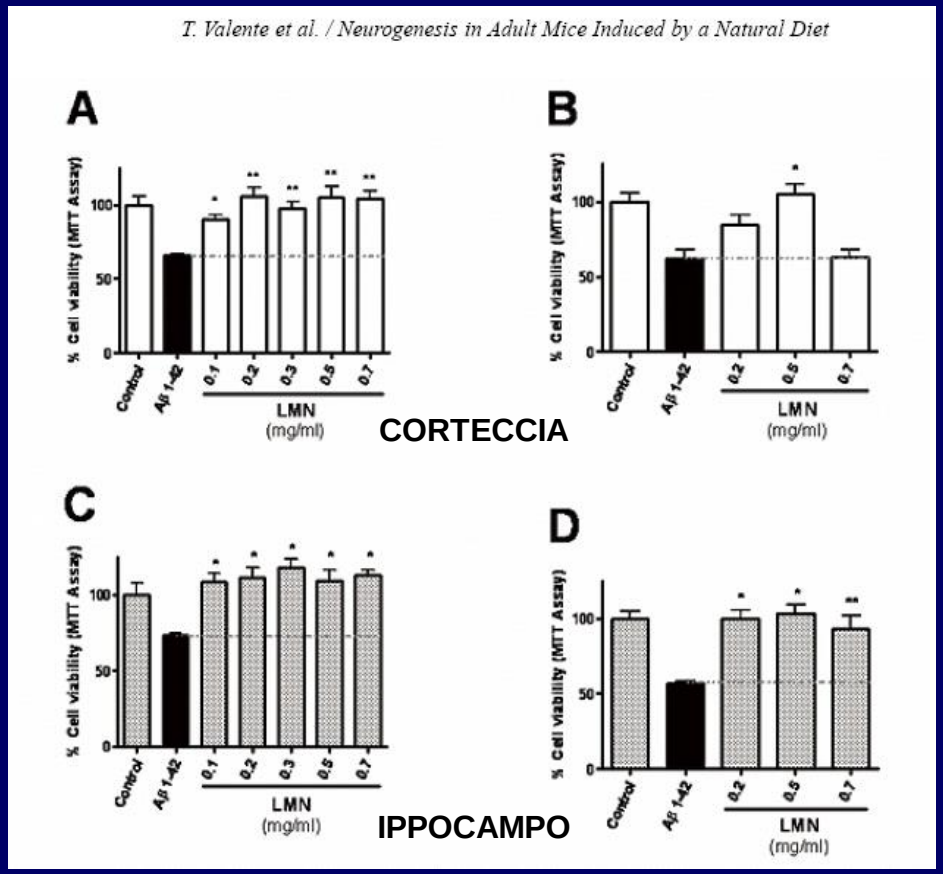
**BrdU** *(Bromodeoxyuridine) marcata*

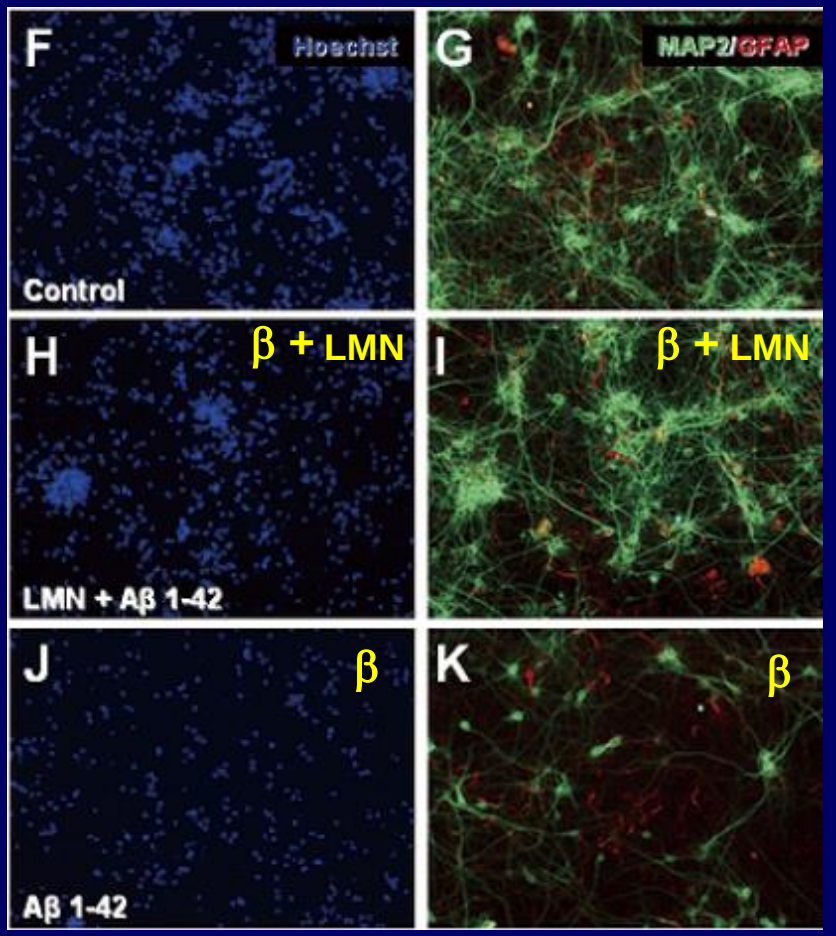



## DIETA LMN

T Valente et al. J Alzh Dis 2009

# Protezione neuronale in vitro




T Valente et al. J Alzh Dis 2009

*Evidence Report/Technology Assessment* **2006**
**Number 134**

# B Vitamins and Berries and Age-Related Neurodegenerative Disorders

**Prepared for:**
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

**Contract No. 290-02-0022**

**Prepared by:**
Tufts-New England Medical Center Evidence
Boston, Massachusetts

**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

*Journal of Molecular Neuroscience*

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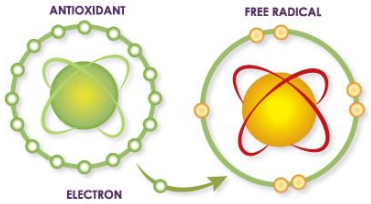


**REVIEW ARTICLE**

# Antioxidant Treatment in Alzheimer's Disease

*Current State*

***Yossi Gilgun-Sherki, Eldad Melamed, and Daniel Offen****

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## Abstract

Accumulating data from experimental and human studies indicate that oxidative stress (OS) plays a major role in the pathogenesis of Alzheimer's disease (AD). The production of reactive oxygen species (ROS), which leads to OS, can occur very early, even before the appearance of symptoms and molecular events (β-amyloid plaques and neurofibrillary tangles), leading to tissue damage via several different cellular molecular pathways. ROS can cause damage to cardinal cellular components such as lipids, proteins, and nucleic acids (e.g., RNA, DNA), causing cell death by modes of necrosis or apoptosis. The damage can become more widespread because of the weakened cellular antioxidant defense systems. Therefore, treatment with antioxidants might theoretically act to prevent propagation of tissue damage and improve both survival and neurological outcome. Indeed, several studies preformed to date examined whether dietary intake of several antioxidants, mainly vitamins, might prevent or reduce the progression of AD. Although a few of the antioxidants showed some efficacy in these trials, no answer is yet available as to whether antioxidants are truly protective against AD. Reasons for these results might include, in part, blood–brain barrier (BBB) permeability, inappropriate timing of administration, or suboptimal drug levels at the target site in the central nervous system. Thus, antioxidant cocktails or antioxidants combined with other drugs may have more successful synergistic effects. Further, well-designed intervention, as well as observational investigations based on large cohorts studied over a long period of time with several methods for assessing antioxidant exposure, including relation to BBB penetration, are needed to test this hypothesis.

*The Journal of Nutrition, Health & Aging©*
*Volume 16, Number 7, 2012*

# FRUIT, VEGETABLES AND PREVENTION OF COGNITIVE DECLINE OR DEMENTIA: A SYSTEMATIC REVIEW OF COHORT STUDIES

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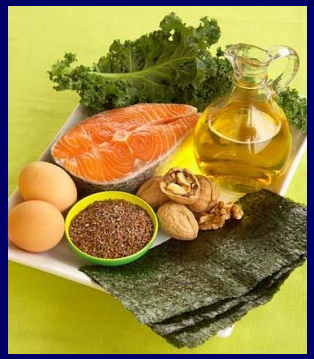
**Abstract:** *Background:* Regular consumption of fruit and vegetables has been considered to be associated with a reduced risk of dementia and age-associated cognitive decline, although the association is currently unsupported by a systematic review of the literature. *Methods:* We searched Medline, Embase, Biosis, ALOIS, the Cochrane library, different publisher databases as well as bibliographies of retrieved articles. All cohort studies with a follow-up of 6 months or longer were included if they reported an association of Alzheimer's disease or cognitive decline in regard to the frequency of fruit and vegetables consumption. *Findings:* Nine studies with a total of 44 004 participants met the inclusion criteria. Six studies analyzed fruit and vegetables separately and five of them found that higher consumption of vegetables, but not fruit is associated with a decreased risk of dementia or cognitive decline. The same association was found by three further studies for fruit and vegetable consumption analytically combined. *Conclusion:* Increased intake of vegetables is associated with a lower risk of dementia and slower rates of cognitive decline in older age. Yet, evidence that this association is also valid for high fruit consumption is lacking.

**Key words:** Fruit, vegetables, dementia, Alzheimer's disease, systematic review.

# STUDI EPIDEMIOLOGICI



OMEGA 3

DIETA
MEDITERRANEA

VERDURA

EFFETTO
PROTETTIVO

# STUDI DI INTERVENTO

OMEGA 3


VITAMINE

EFFETTO PROTETTIVO ?

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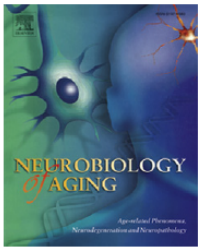


Review

# Dietary and lifestyle guidelines for the prevention of Alzheimer's disease

Neal D. Barnard [a,b,*], Ashley I. Bush [c], Antonia Ceccarelli [d], James Cooper [a], Celeste A. de Jager [e,1], Kirk I. Erickson [f], Gary Fraser [g], Shelli Kesler [h], Susan M. Levin [b], Brendan Lucey [i], Martha Clare Morris [j], Rosanna Squitti [k,l]

A B S T R A C T

Risk of developing Alzheimer's disease is increased by older age, genetic factors, and several medical risk factors. Studies have also suggested that dietary and lifestyle factors may influence risk, raising the possibility that preventive strategies may be effective. This body of research is incomplete. However, because the most scientifically supported lifestyle factors for Alzheimer's disease are known factors for cardiovascular diseases and diabetes, it is reasonable to provide preliminary guidance to help individuals who wish to reduce their risk. At the International Conference on Nutrition and the Brain, Washington, DC, July 19–20, 2013, speakers were asked to comment on possible guidelines for Alzheimer's disease prevention, with an aim of developing a set of practical, albeit preliminary, steps to be recommended to members of the public. From this discussion, 7 guidelines emerged related to healthful diet and exercise habits.

Seven guidelines emerged and are as follows:

1. Minimize your intake of saturated fats and trans fats. Saturated fat is found primarily in dairy products, meats, and certain oils (coconut and palm oils). Trans fats are found in many snack pastries and fried foods and are listed on labels as "partially hydrogenated oils."
2. Vegetables, legumes (beans, peas, and lentils), fruits, and whole grains should replace meats and dairy products as primary staples of the diet.
3. Vitamin E should come from foods, rather than supplements. Healthful food sources of vitamin E include seeds, nuts, green leafy vegetables, and whole grains. The recommended dietary allowance (RDA) for vitamin E is 15 mg per day.
4. A reliable source of vitamin B12, such as fortified foods or a supplement providing at least the recommended daily allowance (2.4 μg per day for adults), should be part of your daily diet. Have your blood levels of vitamin B12 checked regularly as many factors, including age, may impair absorption.
5. If using multiple vitamins, choose those without iron and copper and consume iron supplements only when directed by your physician.
6. Although aluminum's role in Alzheimer's disease remains a matter of investigation, those who desire to minimize their exposure can avoid the use of cookware, antacids, baking powder, or other products that contain aluminum.
7. Include aerobic exercise in your routine, equivalent to 40 minutes of brisk walking 3 times per week.

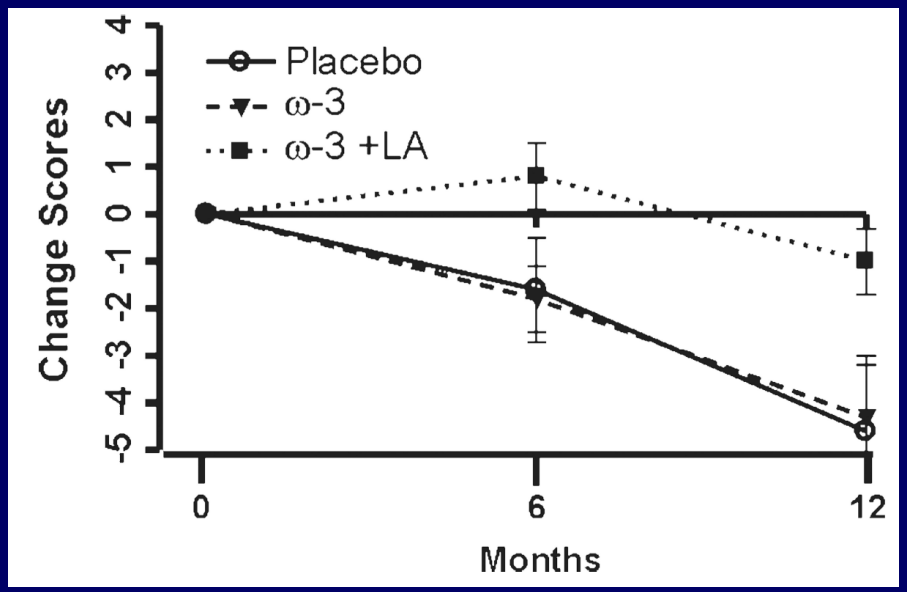
**Neurobiol Aging 2014; S74-S78**

*Grazie per la cortese attenzione …*

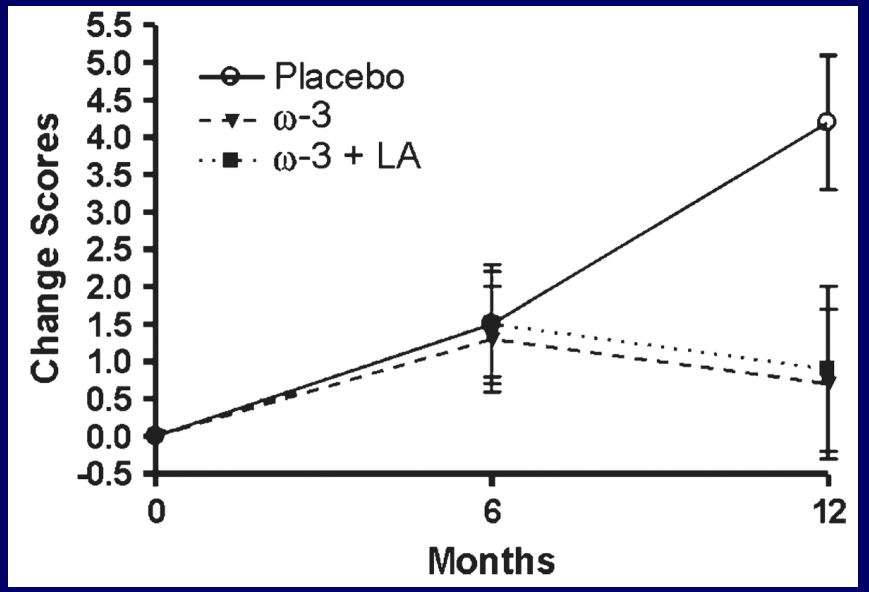
*J Alzheimers Dis*. 2014 ; 38(1): . doi:10.3233/JAD-130722.

# A Randomized Placebo-Controlled Pilot Trial of Omega-3 Fatty Acids and Alpha Lipoic Acid in Alzheimer's Disease

**Lynne Shinto**[a,*], **Joseph Quinn**[a,b], **Thomas Montine**[c], **Hiroko H. Dodge**[a], **William Woodward**[a], **Sara Baldauf-Wagner**[a], **Dana Waichunas**[a], **Lauren Bumgarner**[a], **Dennis Bourdette**[a,b], **Lisa Silbert**[a,b], and **Jeffrey Kaye**[a,b]




**MMSE**




**IADLs**

# 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

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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-$\mu$g 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

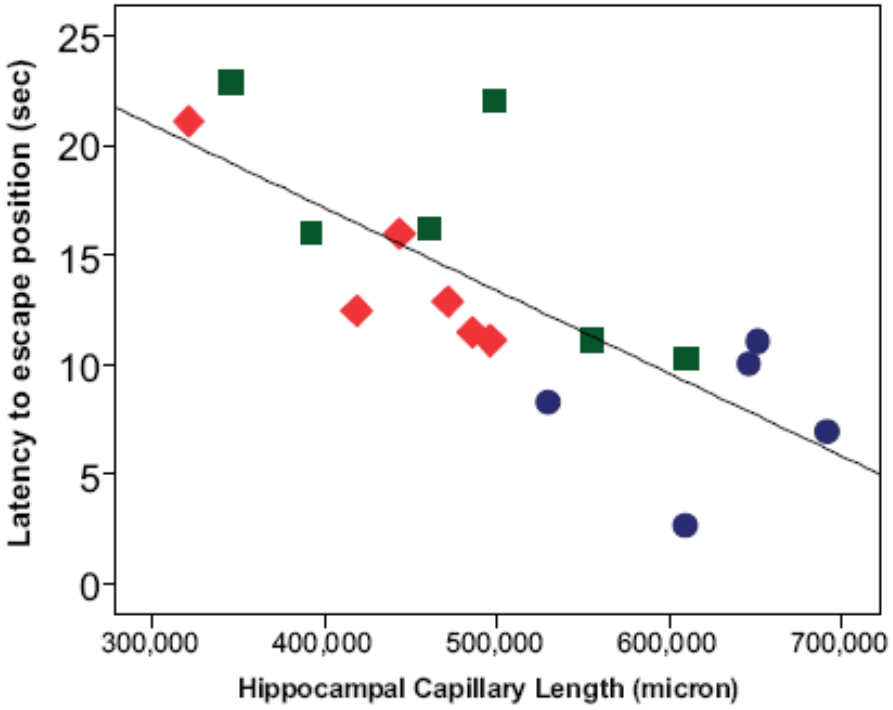
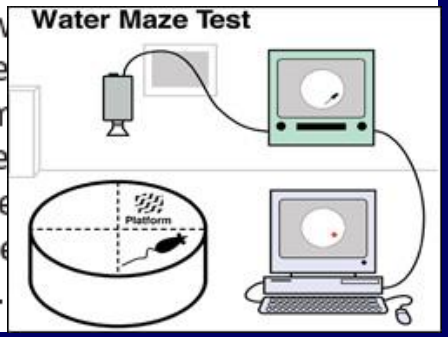



**Fig. 2.** Cognitive performance on Morris water maze correlates with hippocampal capillary length. Chart shows that hippocampal capillary length strongly predicts escape latencies on the Morris w probe trial (the shorter the latency, the better the there is little overlap between control and treatm hippocampal capillary length were highly correlate the escape position during the Morris water maze −0.757, $P < 0.001$). Blue circles = control diet; gree rich diet; red diamonds = B-vitamin-deficient diet.




AM Troen et al. PNAS 2008