VI Congresso Nazionale SINut

BOLOGNA 27-28 MAGGIO 2016

Evidenze epidemiologico-cliniche dell'utilità di nutraceutici neuroprotettivi - *2016*

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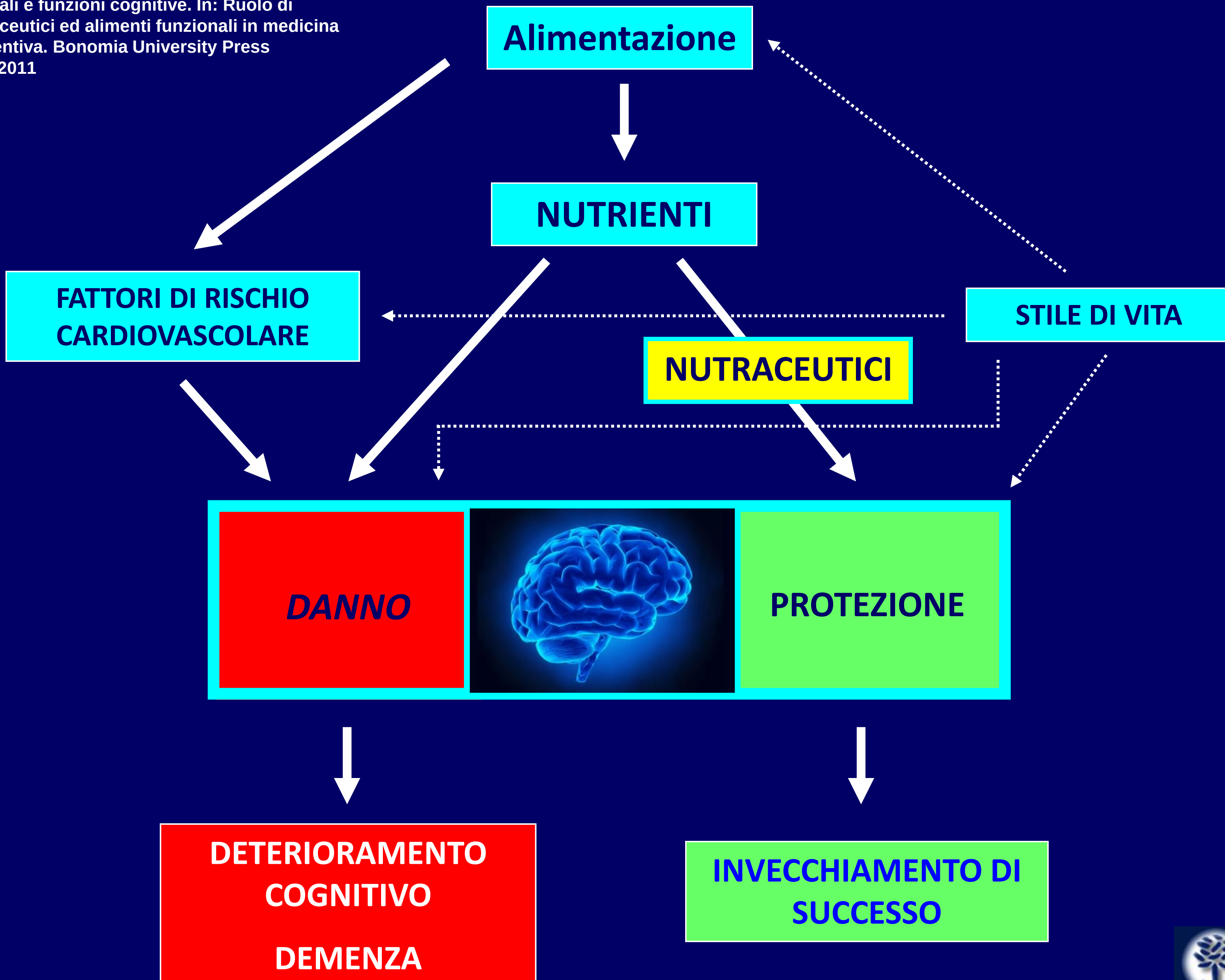
Nutrizione e decadimento cognitivo
Giovanni Zuliani

"NON HO ALCUN CONFLITTO DI INTERESSI DA DICHIARARE"

Riassunto della puntata precedente ...

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



Fattori di rischio per aterosclerosi/ demenza

↑ 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 - sovrappeso

Ipertensione arteriosa

Diabete

Dislipidemia

Insulinoresistenza - diabete

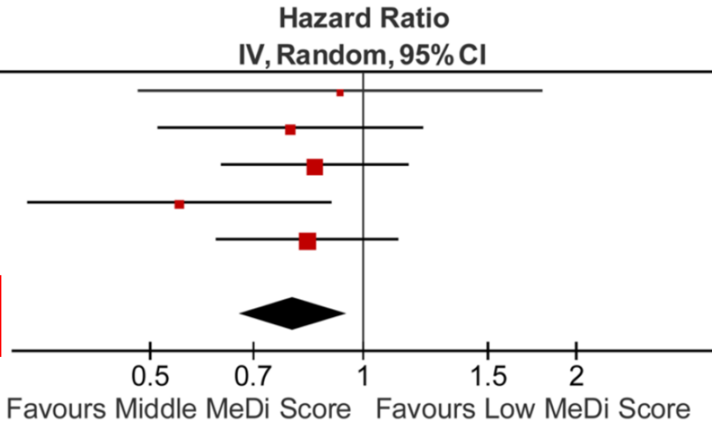
Infiammazione cronica

Deterioramento cognitivo e 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]**

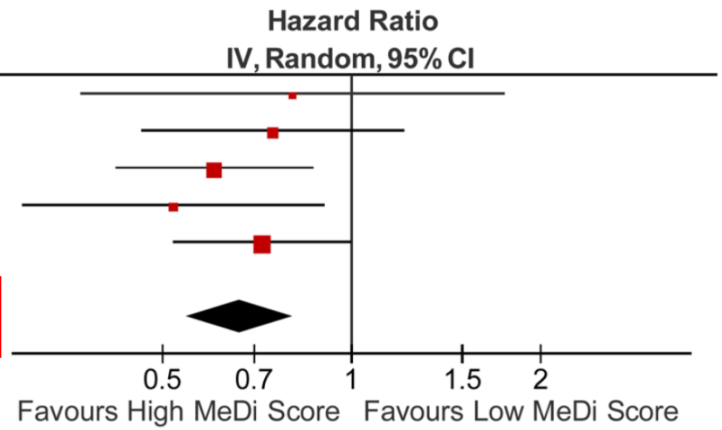
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.57 (P = 0.01)



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]**

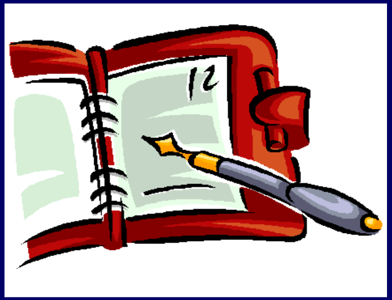
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 4.06 (P < 0.0001)

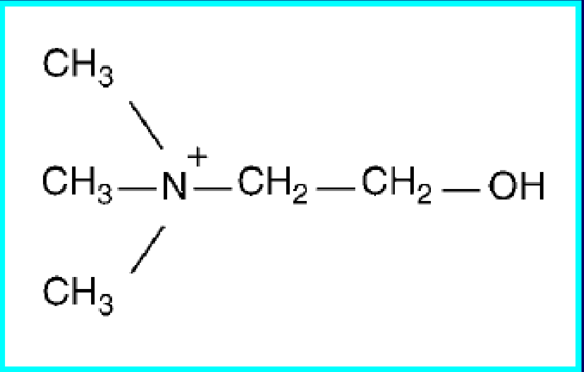


Singh et al. J Alzheimer's Disease 2014

Agenda

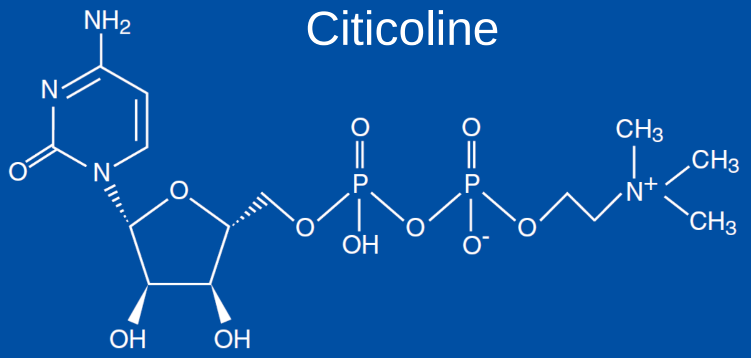
- ✓ ***Colina***
- ✓***Omotaurina / Tramiprosato***
- ✓ ***Vitamina D***
- ✓ ***Tè verde***
- ✓ ***Alcool***





Colina (Vitamina J)

Citicoline



From: Secades JJ, Frontera G. Meth Find Exp Clin Pharmacol 1995;17(Suppl. B):1-54.

Colina

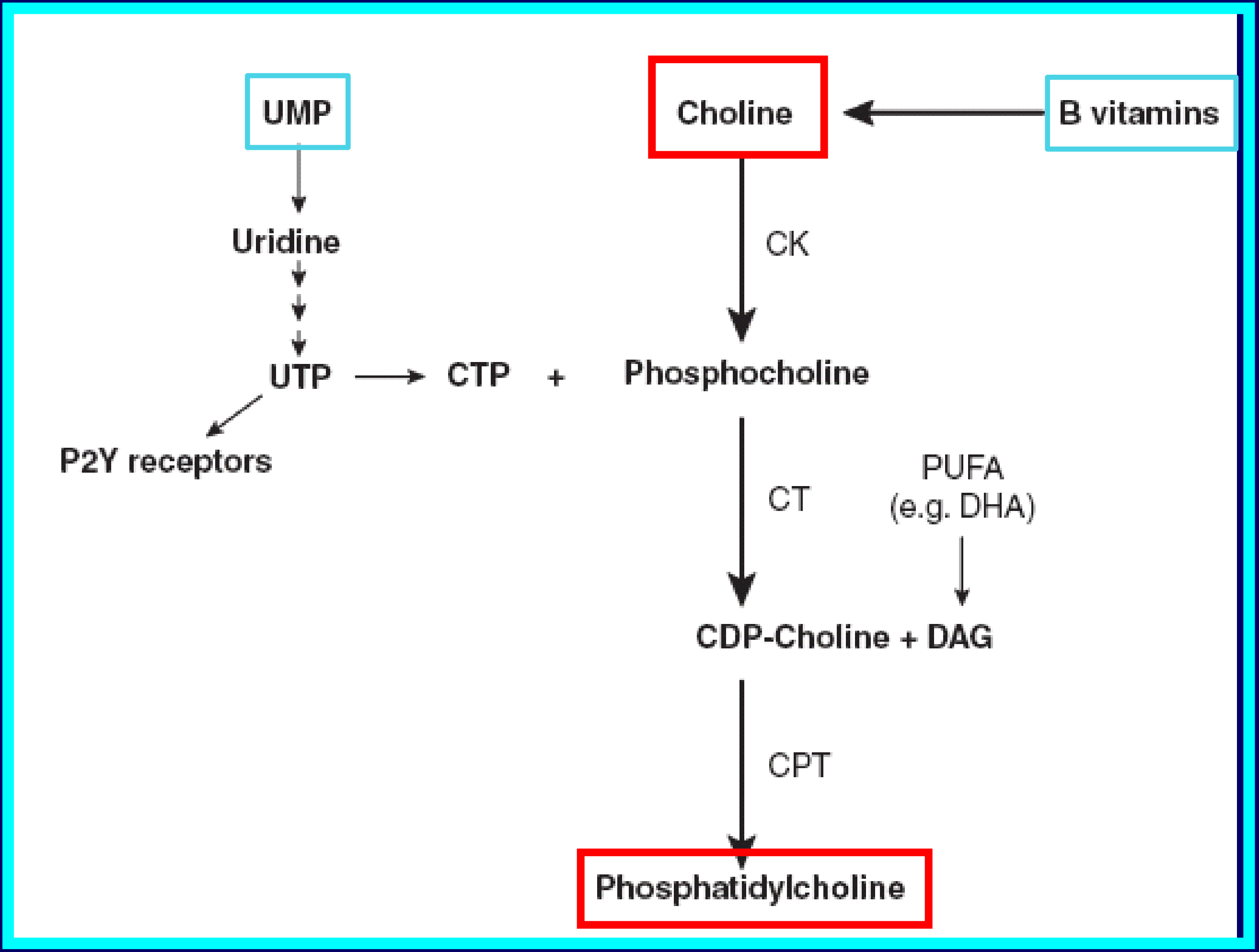
La colina ed i suoi derivati sono coinvolti in tre importanti processi metabolici:

1. integrità strutturale della **Membrana Cellulare**

2. trasmissione dei segnali nervosi dopo trasformazione in **Acetilcolina**

3. principale **sorgente di Gruppi Metile** tramite il suo derivato, la betaina, intermedio nella biosintesi della S-adenosilmetionina.

Sintesi della Fosfatidilcolina



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

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

ABSTRACT

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

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

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

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

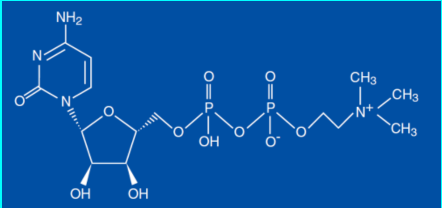
Conclusion: In this community-based population of nondemented individuals, higher concurrent choline intake was related to better cognitive performance, whereas higher remote choline intake was associated with little to no WMHV. *Am J Clin Nutr* 2011;94:1584–91.

Lecitina

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

NESSUNA EVIDENZA DI EFFETTI SUPERIORI AL PLACEBO

Citicolina



From: Secades JJ, Frontera G. Meth Find Exp Clin Pharmacol 1995;17(Suppl. B):1-54.

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

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

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

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

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

F. Amenta 2014

Cytidinediphosphocholine (CDP-choline) for cognitive and behavioural disturbances associated with chronic cerebral disorders in the elderly (Review)

THE COCHRANE COLLABORATION

Cochrane Database of Systematic Reviews 2005

Fioravanti M, Yanagi M

THE COCHRANE COLLABORATION

Authors' conclusions

There was some evidence that CDP-choline has a positive effect on memory and behaviour in at least the short to medium term. The evidence of benefit from global impression was stronger, but is still limited by the duration of the studies. Further research with CDP-choline should focus on longer term studies in subjects who have been diagnosed with currently accepted standardised criteria, especially Vascular Mild Cognitive Impairment (VaMCI) or vascular dementia.

Colina alfoscerato

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

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

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

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

F. Amenta 2014

Colina alfoscerato

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

2014

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

Francesco Amenta[a,*], Anna Carotenuto[a], Angiola Maria Fasanaro[b], Raffaele Rea[a] and Enea Traini[a]
[a]*Centro Ricerche Cliniche, Scienze del Farmaco e dei Prodotti della Salute, Università di Camerino, Camerino, Italy*
[b]*Unità Valutativa Alzheimer e Malattie Involutive Cerebrali, Azienda Ospedaliera di Rilievo Nazionale A. Cardarelli, Napoli, Italy*

Colina alfoscerato

Studio ASCOMALVA

2014

Studio controllato, randomizzato ed in doppio cieco.

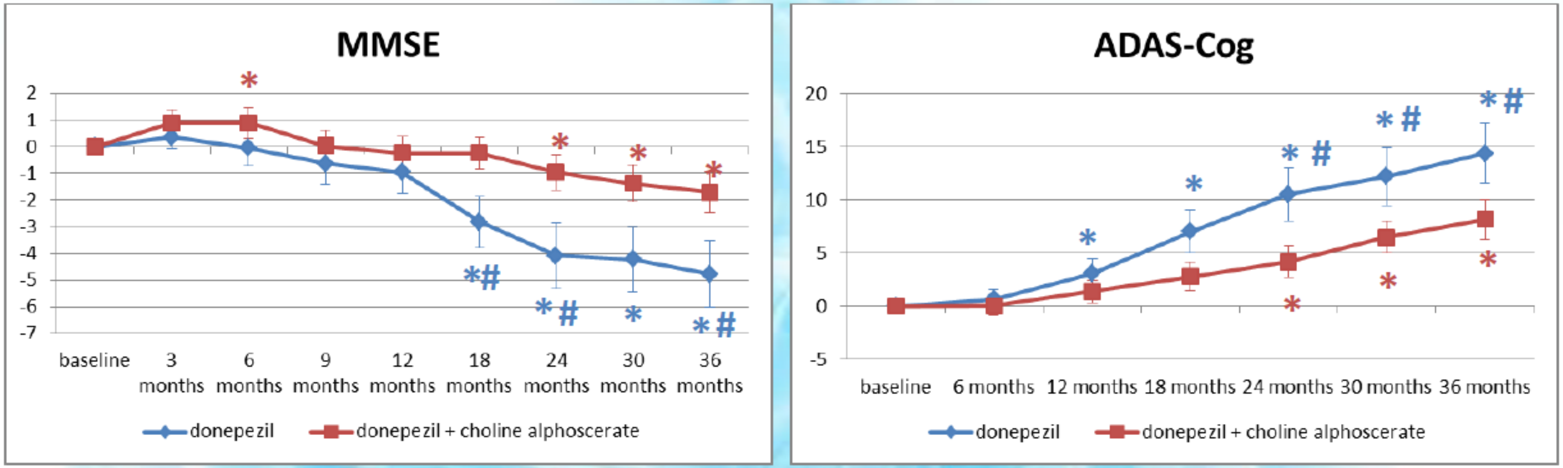
Numero OsSC: 2008-004667-19

Trattamento farmacologico

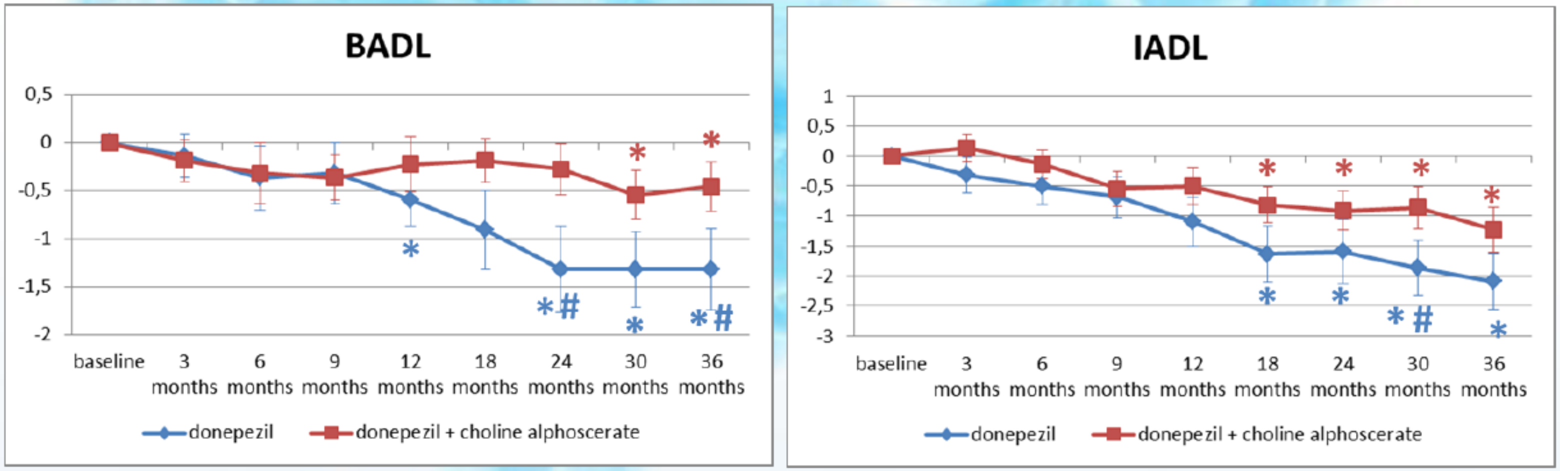
***Trattamento 1*: Donepezil cp, dose pro/die 10 mg, (oppure Donepezil 5 mg, se non tollerata la dose di 10 mg) associato a placebo**

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

Colina alfoscerato



Valutazione funzionale



Omotaurina - Tramiprosato

acido 3-amino-1-propansulfonico
(3-APS o Tramiprosato)

acido 2-aminoetansulfonico
(3-AES o Taurina)

Meccanismi di azione 1

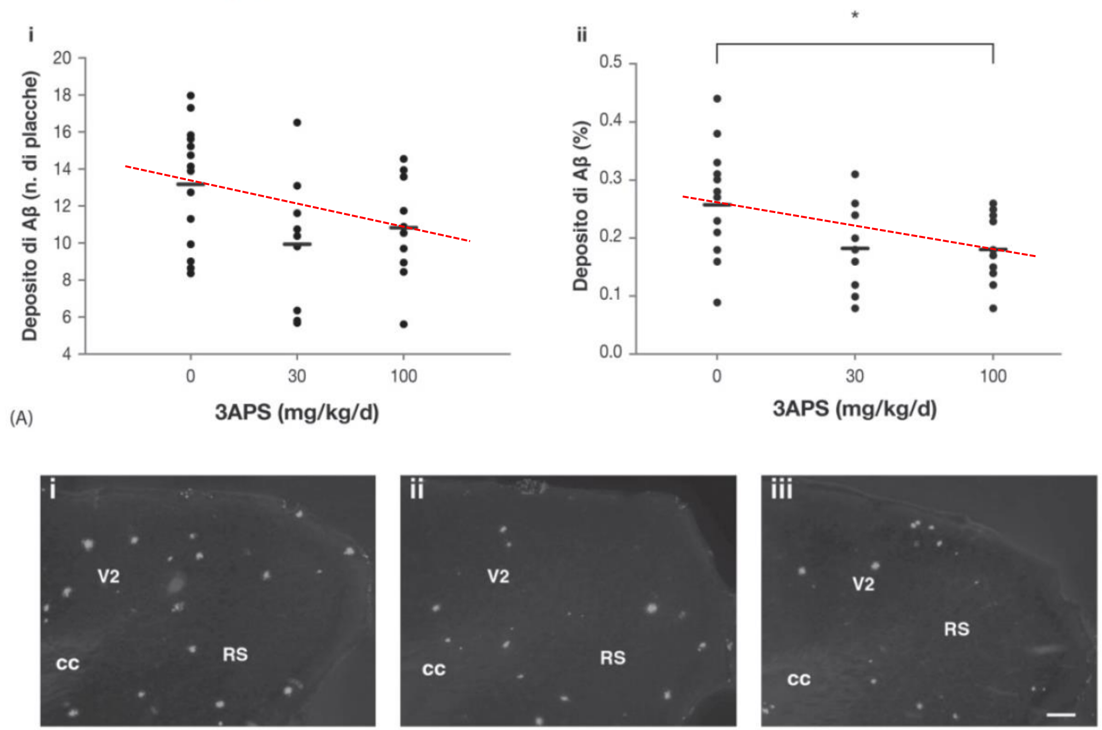
- Nel topo transgenico TgCRND8 con amiloidosi cerebrale precoce, Tramiprosato riduce del 30% la Beta amiloide 40-42 solubile/insolubile e la deposizione di placche amiloidi; riduce del 60% i livelli plasmatici di Beta amiloide (Gervais 2007).

- Tramiprosato sembra proteggere i neuroni ippocampali in coltura dall'effetto neurotossico della Beta amiloide (Kryzwkowski 2007).

- Tramiprosato potrebbe anche ridurre la fosforilazione della proteina Tau attraverso la inibizione della kinasi (Delacourte 2006).

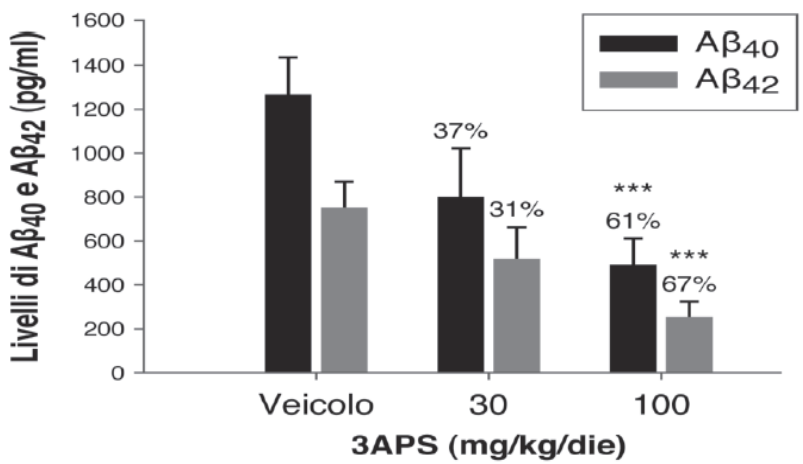
Nel topo: riduzione deposito Beta amiloide nella corteccia cerebrale

Figura 2: IG 2: Il trattamento con tramiprosato riduce la formazione di placche Aβ corticali.
(A) Numero di placche ThS+ per intera sezione neocorticale (i) e percentuale di area corticale occupata da placche (ii). I punti rappresentano i valori per i singoli animali e le barre rappresentano i valori medi.*Analisi della varianza a una via ($F_{0.05}[2,31] = 3.615$, $P = 0.039$) seguita dal metodo di Dunnett, confronti multipli vs. controllo, $P < 0.05$.
(B) Deposizione di Aβ nel cervello degli animali di controllo (i) e in topi trattati per 8 settimane con tramiprosato (s.c.): 30 mg/kg/d (ii) o 100 mg/kg/d (iii). Fotomicrografie a campo illuminato (iv, v, vi) corrispondenti rispettivamente a (i, ii, iii),.
Abbreviazioni: cc – corpus callosum; RS – corteccia retrospleniale; V2 – corteccia visiva secondaria. Scala = 100μm.
Fonte: Gervais F, Paquette J, Morissette C, et al. Targeting soluble Aβ peptide with Tramiprosate for the treatment of brain amyloidosis. Neurobiol Aging 2007; 28:537-547.



Nel topo: riduzione Beta amiloide plasmatica

Figura 3: IG 3: Il trattamento con tramiprosato riduce i livelli di Aβ plasmatica in topi TgCRND8. Livelli plasmatici di Aβ40 e Aβ42 dopo 8 settimane di trattamento con veicolo o tramiprosato (30 o 100 mg/kg/d). I livelli plasmatici sono stati determinati con ELISA. I risultati sono espressi come pg Aβ/ml plasma±S.E.M. ***Analisi di Aβ40: $F0.05[2,43] = 5.953, P = 0.005$ e Aβ42: $F0.05[2,43] = 6.106, P = 0.005$ seguita da metodo di Dunnett, confronti multipli vs. controllo, $P < 0.05$. Fonte: *Gervais F, Paquette J, Morissette C, et al. Targeting soluble Aβ peptide with Tramiprosate for the treatment of brain amyloidosis. Neurobiol Aging 2007; 28:537-547.*



Meccanismi di azione 2

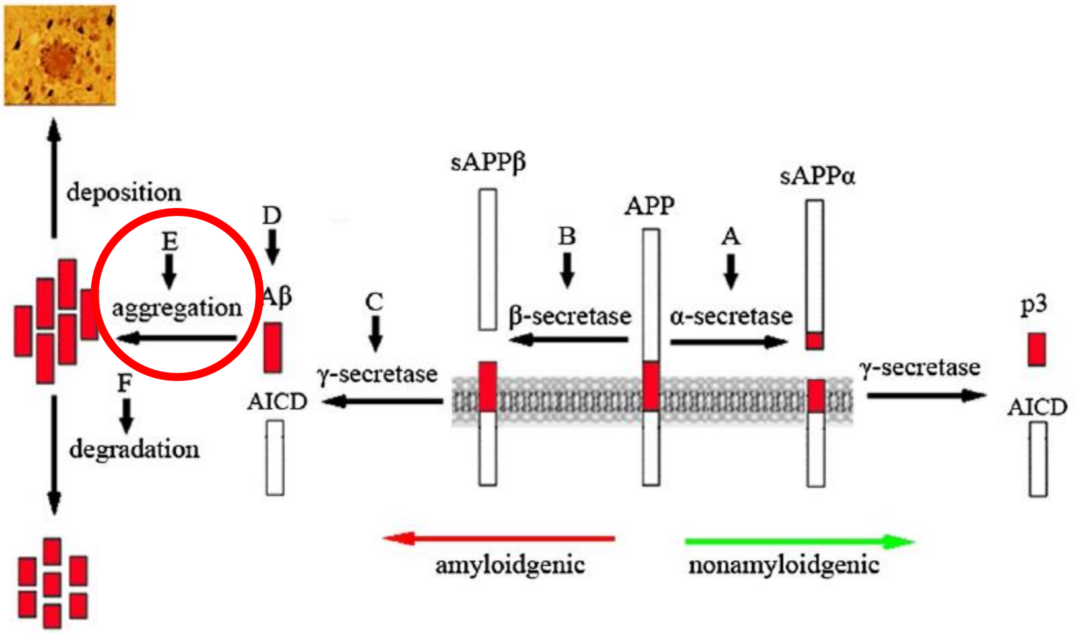
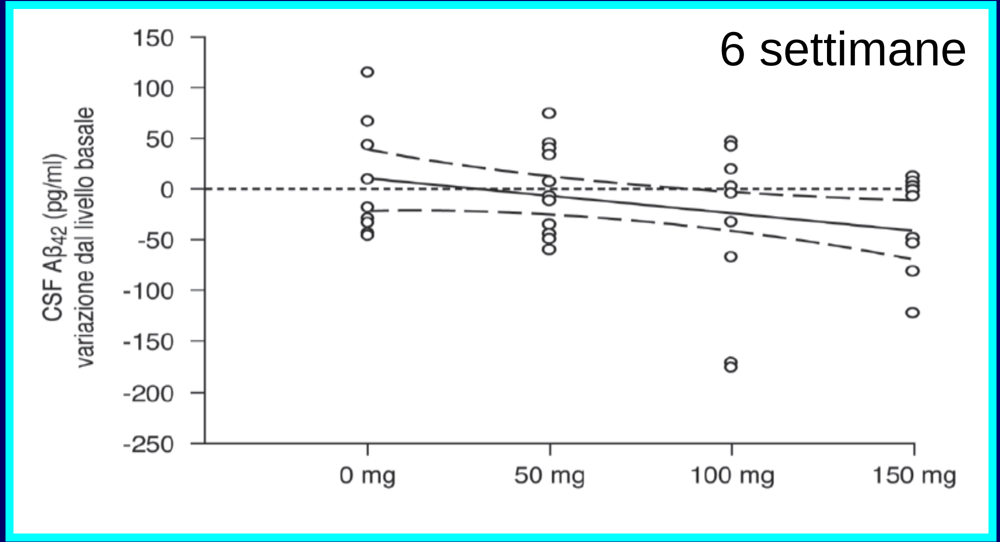
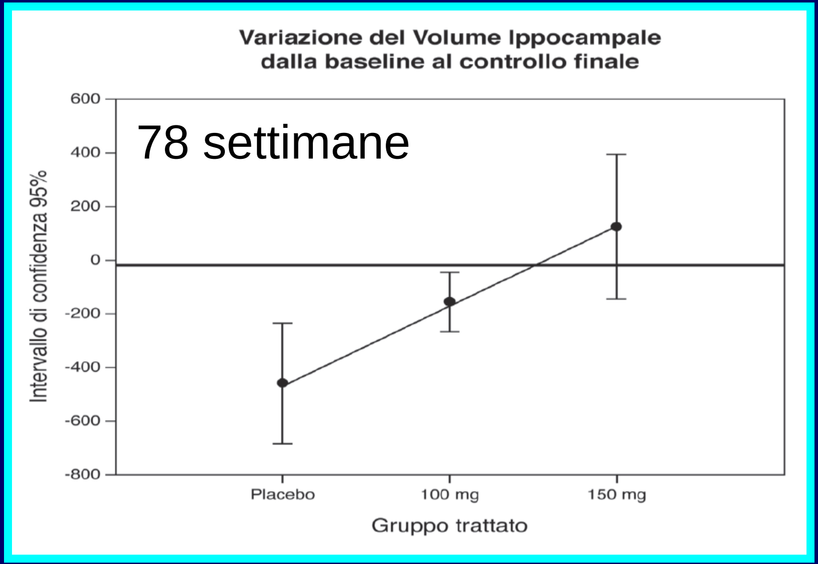


Figure 1 The Aβ-targeting strategies based on the Aβ cascade hypothesis. The processing of APP and the production, degradation of Aβ are illustrated and the therapeutic potential of targets are indicated with vertical arrows marked by alphabet: **A**, α-secretase activators; **B**, β-secretase inhibitors; **C**, γ-secretase inhibitors/modulators; **D**, immunotherapy; **E**, Aβ-aggregation inhibitors; F, Aβ-degradation activators. Modified and reproduced with permission from Yang et al. (2012) and see reference [2] for further details.

Nell'uomo: riduzione Beta amiloide nel liquor e stabilizzazione del volume ippocampale

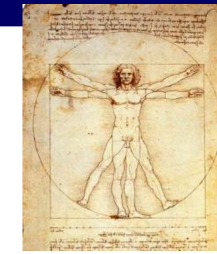
Aisen et al. Neurology 2006





Saumier et al. JNHA 2009

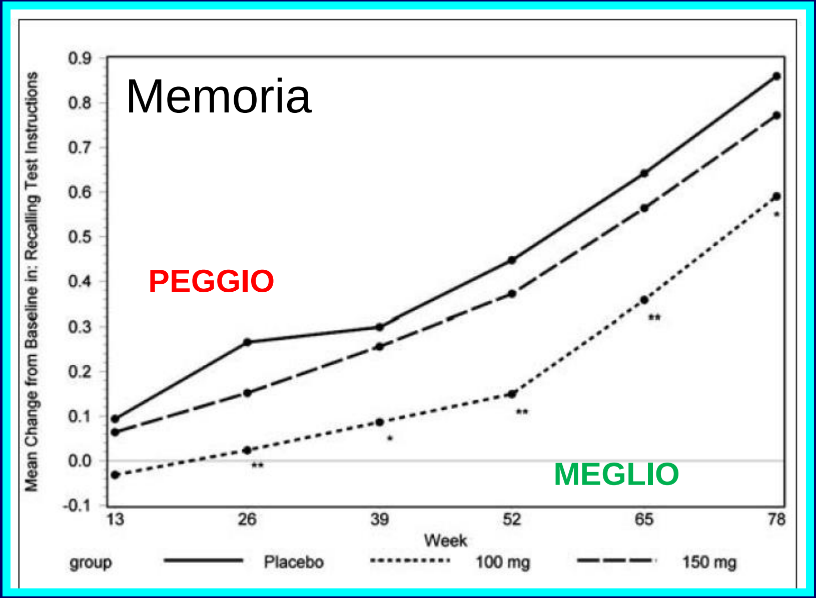
The Journal of Nutrition, Health & Aging©
Volume 13, Number 9, 2009



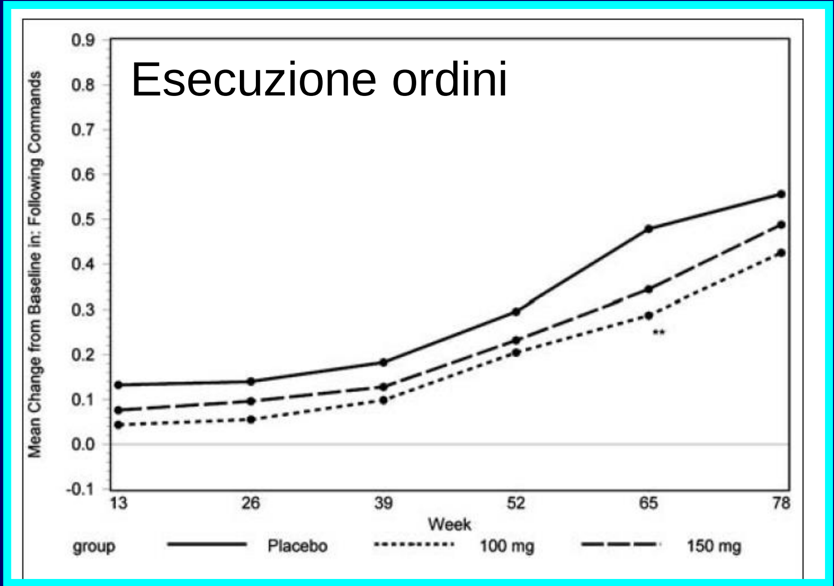
DOMAIN-SPECIFIC COGNITIVE EFFECTS OF TRAMIPROSATE IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE: ADAS-COG SUBSCALE RESULTS FROM THE ALPHASE STUDY

D. SAUMIER[1], A. DUONG[2,5], D. HAINE[2], D. GARCEAU[3], J. SAMPALIS[2,4]

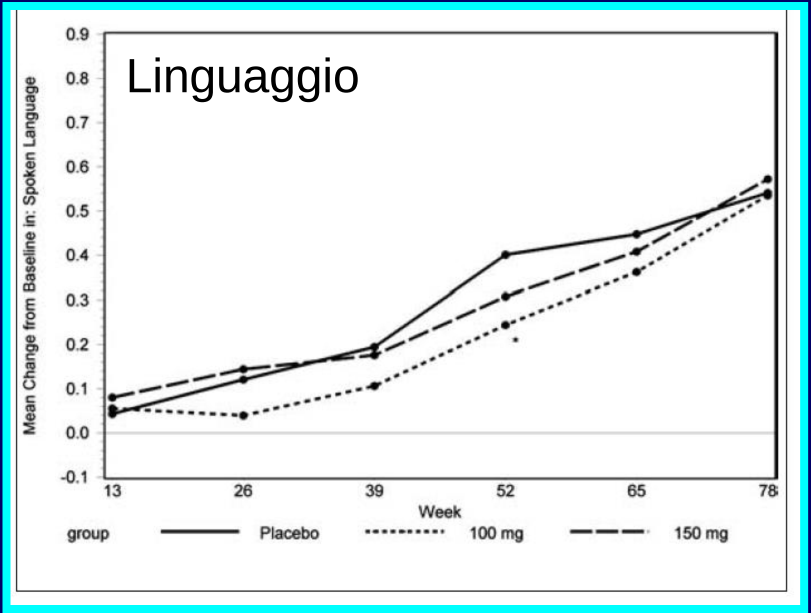
Abstract: *Objectives:* Tramiprosate (homotaurine, ALZHEMED^{TM}) was recently investigated for its efficacy, safety and disease-modification effects in a Phase III clinical study in mild to moderate Alzheimer's disease (AD) patients (the Alphase study). The primary cognitive endpoint measure of that study was the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). To characterize potential cognitive benefits of tramiprosate, the present study describes exploratory analyses performed on scores obtained from the specific ADAS-cog subscales in order to determine whether specific domains of cognition may be differentially affected by tramiprosate, which would not have been evident from the measure's total score. *Design:* Multi-center, double-blind, randomized, placebo-controlled study. *Setting:* 67 investigative sites in the United States and Canada. *Participants:* A total of 1,052 patients were randomized. Interventions: Patients were randomized to receive twice a day Placebo (n=353), tramiprosate 100 mg (n=352) and tramiprosate 150 mg (n=347). *Measurements:* ADAS-cog assessments were conducted every three months over the 78-week study period. Exploratory analyses were performed by comparing ADAS-cog subscale scores between Placebo and each active treatment arm at each visit. *Results:* The findings of this analysis revealed statistically significant differences or statistical trends in favour of tramiprosate on six ADAS-cog subscales, namely Following Commands, Language Comprehension, Ideational Praxis, Object Naming, Remembering Test Instructions, and Spoken Language Ability. Differences in favor of Placebo were only observed on the Constructional Praxis subscale. *Conclusion:* This exploratory analysis suggests that tramiprosate may have some benefit on memory, language and praxis skills in mild to moderate AD individuals. Future clinical studies of tramiprosate should include specialized neuropsychological tests to validate its effects within these cognitive domains.



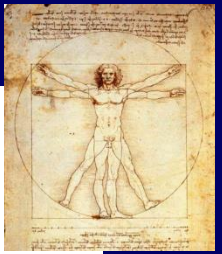
Memoria
PEGGIO
MEGLIO
Mean Change from Baseline in: Recalling Test Instructions
Week
group Placebo 100 mg 150 mg



Esecuzione ordini
Mean Change from Baseline in: Following Commands
Week
group Placebo 100 mg 150 mg



Linguaggio
Mean Change from Baseline in: Spoken Language
Week
group Placebo 100 mg 150 mg



Journal of Alzheimer's Disease 50 (2016) 807–816
DOI 10.3233/JAD-150484
IOS Press

Homotaurine Effects on Hippocampal Volume Loss and Episodic Memory in Amnestic Mild Cognitive Impairment

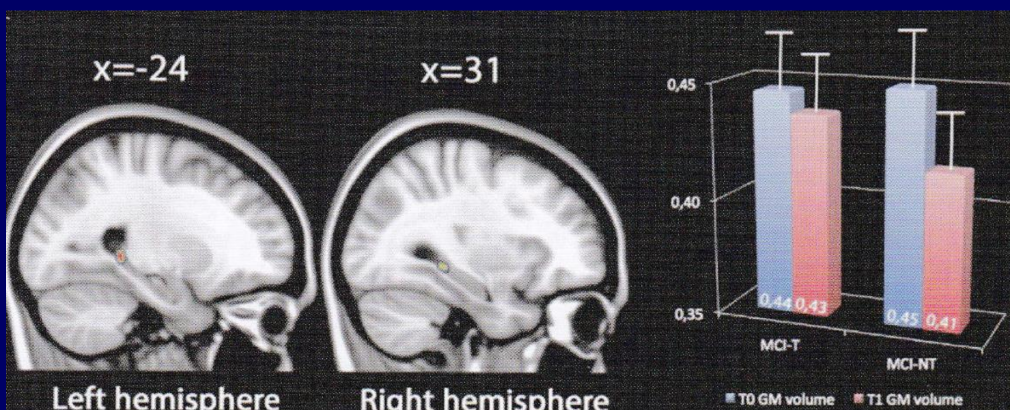
Gianfranco Spalletta[a,*], Luca Cravello[a], Walter Gianni[b], Federica Piras[a], Mariangela Iorio[a], Claudia Cacciari[a], Anna Rosa Casini[c], Chiara Chiapponi[a], Giuseppe Sancesario[d], Claudia Fratangeli[a], Maria Donata Orfei[a], Carlo Caltagirone[a,d] and Fabrizio Piras[a,e]

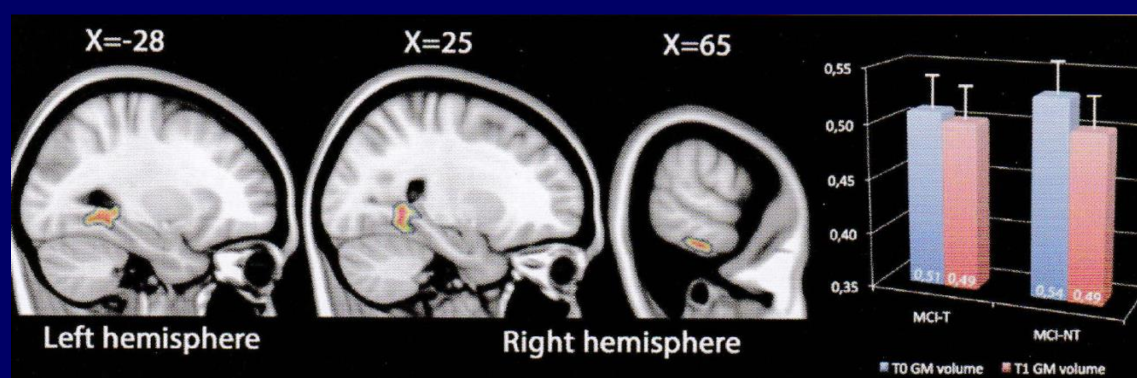
Abstract. Homotaurine supplementation may have a positive effect on early Alzheimer's disease. Here, we investigated its potential neuroprotective effect on the hippocampus structure and episodic memory performances in amnestic mild cognitive impairment (aMCI). Neuropsychological, clinical, and neuroimaging assessment in 11 treated and 22 untreated patients were performed at baseline and after 1 year. Magnetic resonance data were analyzed using voxel-based morphometry to explore significant differences (Family Wise Error corrected) between the two groups over time. Patients treated with homotaurine showed decreased volume loss in the left and right hippocampal tail, left and right fusiform gyrus, and right inferior temporal cortex which was associated with improved short-term episodic memory performance as measured by the recency effect of the Rey 15-word list learning test immediate recall. Thus, homotaurine supplementation in individuals with aMCI has a positive effect on hippocampus atrophy and episodic memory loss. Future studies should further clarify the mechanisms of its effects on brain morphometry.

Table 4
Anatomical brain locations of ROI and whole-brain analysis results

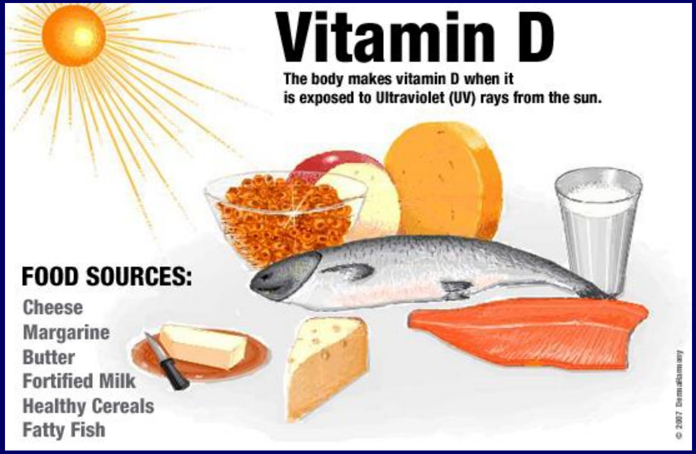
Anatomical Region	Cluster extent	Equiv Z	p_{FWE}	MNI statis
ROI-based analysis				
Left Hippocampus	61	4.58	0.001	–24, –40, 1
Right Hippocampus	42	4.24	0.004	32, –37, –5
Whole-brain analysis				
Left fusiform gyrus (extending to the hippocampus tail)	540	5.01	0.021	–27, –43, –11
Right fusiform gyrus (extending to the hippocampus tail)	862	4.97	0.025	34, –51, –15
Right inferior temporal lobe	221	4.92	0.031	63, –31, –21

ROI, regions of interest; FWE, family-wise error; MNI, Montreal Neurological Institute.





Vitamina D

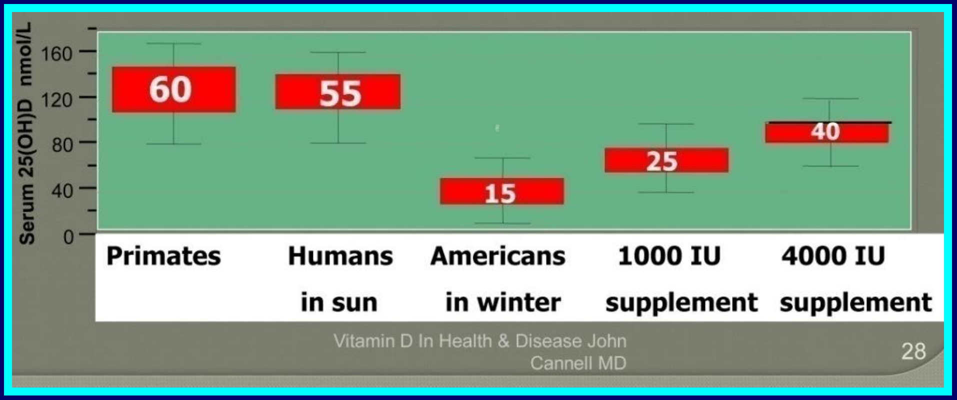

Vitamin D
The body makes vitamin D when it
is exposed to Ultraviolet (UV) rays from the sun.
FOOD SOURCES:
Cheese
Margarine
Butter
Fortified Milk
Healthy Cereals
Fatty Fish

Livelli normali di Vitamina D

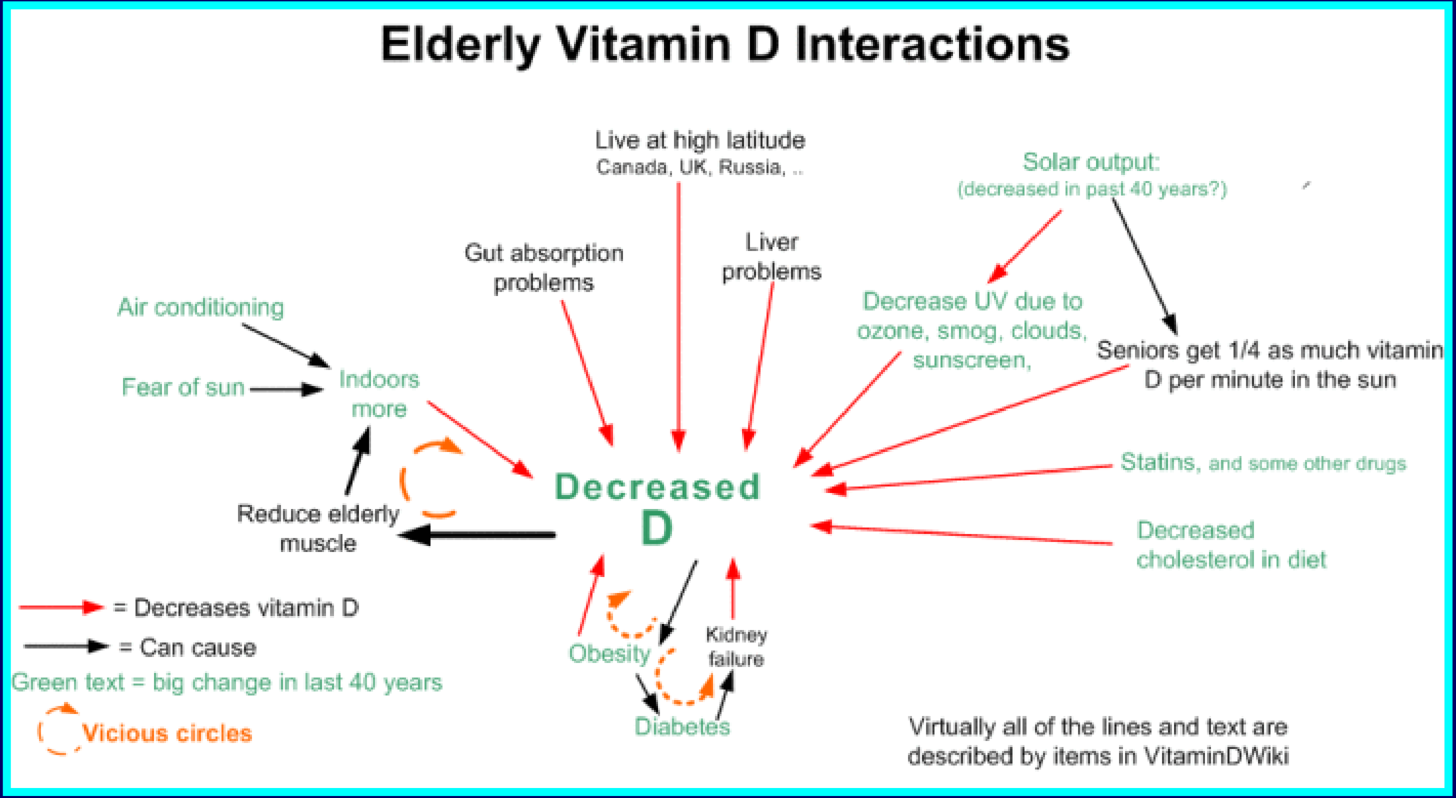
Vitamin D status classification	
Status	25-hydroxyvitamin D
Vitamin D deficiency	< 50 nM
Vitamin D insufficiency	50 to 74 nM
Vitamin D optimal range	75 to 100 nM
Vitamin D sufficiency	75 to 250 nM
Vitamin D intoxication	> 375 to 500 nM

Figure 1. Proposed vitamin D status classification.

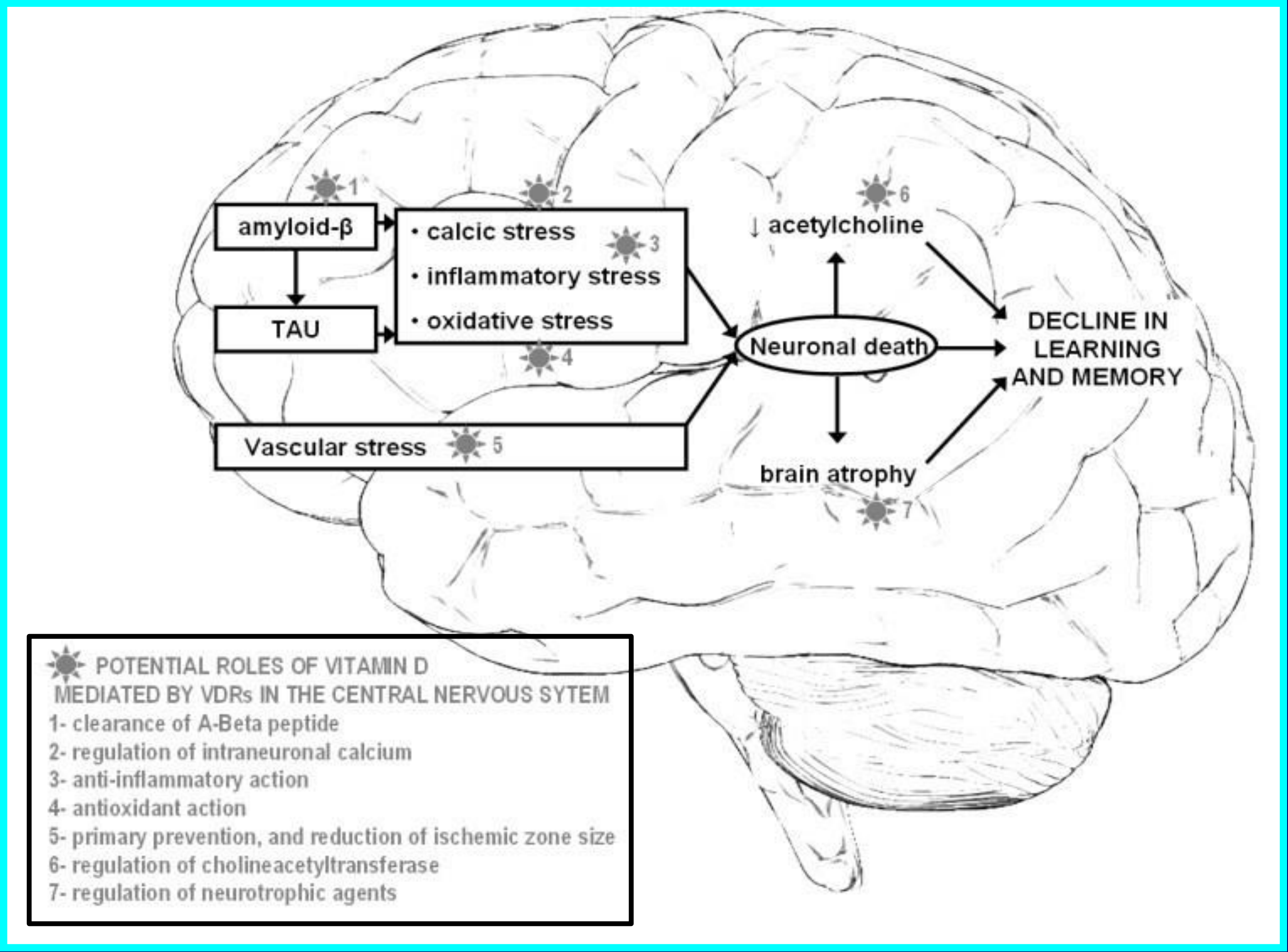
Livelli "reali" di Vitamina D



Vitamina D nell’anziano



Vitamina D e sistema nervoso centrale



Dementia and Geriatric Cognitive Disorders

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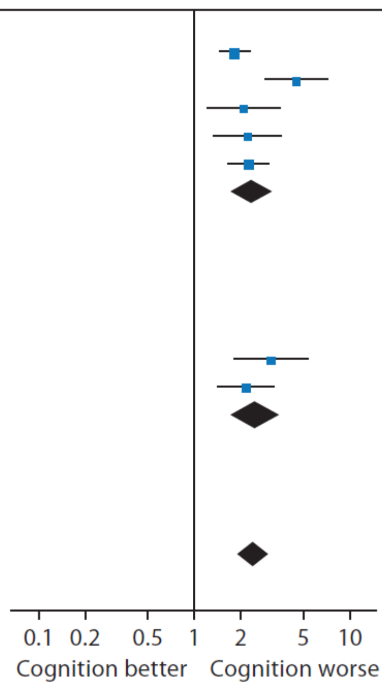
Vitamin D Deficiency, Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

Thorleif Etgen[a,b] Dirk Sander[c,d] Horst Bickel[a] Kerstin Sander[d] Hans Förstl[a]

Abstract
Background: Recent preventive strategies for patients with cognitive impairment include the identification of modifiable somatic risk factors like vitamin D deficiency. ***Methods:*** A systematic literature research and meta-analysis were conducted to assess the association of cognitive impairment and vitamin D deficiency. ***Results:*** Data from cross-sectional and longitudinal studies suggest an association between cognitive impairment and vitamin D deficiency. Meta-analysis of 5 cross-sectional and 2 longitudinal studies comprising 7,688 participants showed an increased risk of cognitive impairment in those with low vitamin D compared with normal vitamin D (OR 2.39, 95% CI 1.91–3.00; $p < 0.0001$). ***Conclusions:*** Methodological limitations of these studies comprise heterogeneity of study populations, different forms of cognitive assessment, the problem of reverse causality, different definitions of vitamin D deficiency and inconsistent control for confounders. As the value of vitamin D substitution in cognitive impairment remains doubtful, a long-time major placebo-controlled randomized trial of vitamin D supplementation in participants with mild cognitive impairment (MCI) should be started.

Study or subgroup	Vitamin D deficiency events	Vitamin D deficiency total	No vitamin D deficiency events	No vitamin D deficiency total	Weight	OR M-H, random, 95% CI	Year
1.1.1 Cross-sectional							
McGrath, 2007	245	950	151	944	21.4%	1.83 [1.45, 2.29]	2007
Llewellyn, 2009	100	458	25	432	12.8%	4.55 [2.87, 7.21]	2009
Annweiler, 2010	22	129	56	623	10.8%	2.08 [1.22, 3.55]	2010
Annweiler, 2011	59	138	38	150	11.7%	2.20 [1.34, 3.63]	2011
Llewellyn, 2011	143	843	85	1,019	19.0%	2.24 [1.69, 2.99]	2011
Subtotal (95% CI)		**2,518**		**3,168**	**75.7%**	**2.37 [1.77, 3.17]**	
Total events	569		355				
Heterogeneity: $Tau^2 = 0.07$, $\chi^2 = 12.25$, d.f. = 4 ($p = 0.02$); $I^2 = 67\%$							
Test for overall effect: $Z = 5.81$ ($p = 0.00001$)							
1.1.2 Longitudinal							
Llewellyn, 2010	19	92	85	1,104	10.4%	3.12 [1.80, 5.41]	2010
Slinin, 2010	71	405	36	401	13.8%	2.16 [1.41, 3.31]	2010
Subtotal (95% CI)		**497**		**1,505**	**24.3%**	**2.49 [1.74, 3.56]**	
Total events	90		121				
Heterogeneity: $Tau^2 = 0.01$, $\chi^2 = 1.11$, d.f. = 1 ($p = 0.29$); $I^2 = 10\%$							
Test for overall effect: $Z = 4.99$ ($p = 0.00001$)							
Total (95% CI)		**3,015**		**4,673**	**100%**	**2.39 [1.91, 3.00]**	
Total events	659		476				
Heterogeneity: $Tau^2 = 0.05$, $\chi^2 = 13.72$, d.f. = 6 ($p = 0.03$); $I^2 = 56\%$							
Test for overall effect: $Z = 7.55$ ($p = 0.00001$)							
Test for subgroup differences: $\chi^2 = 0.04$, d.f. = 1 ($p = 0.84$); $I^2 = 0\%$							

OR
M-H, random, 95% CI



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Vitamin D and the risk of dementia and Alzheimer disease

OPEN

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ABSTRACT

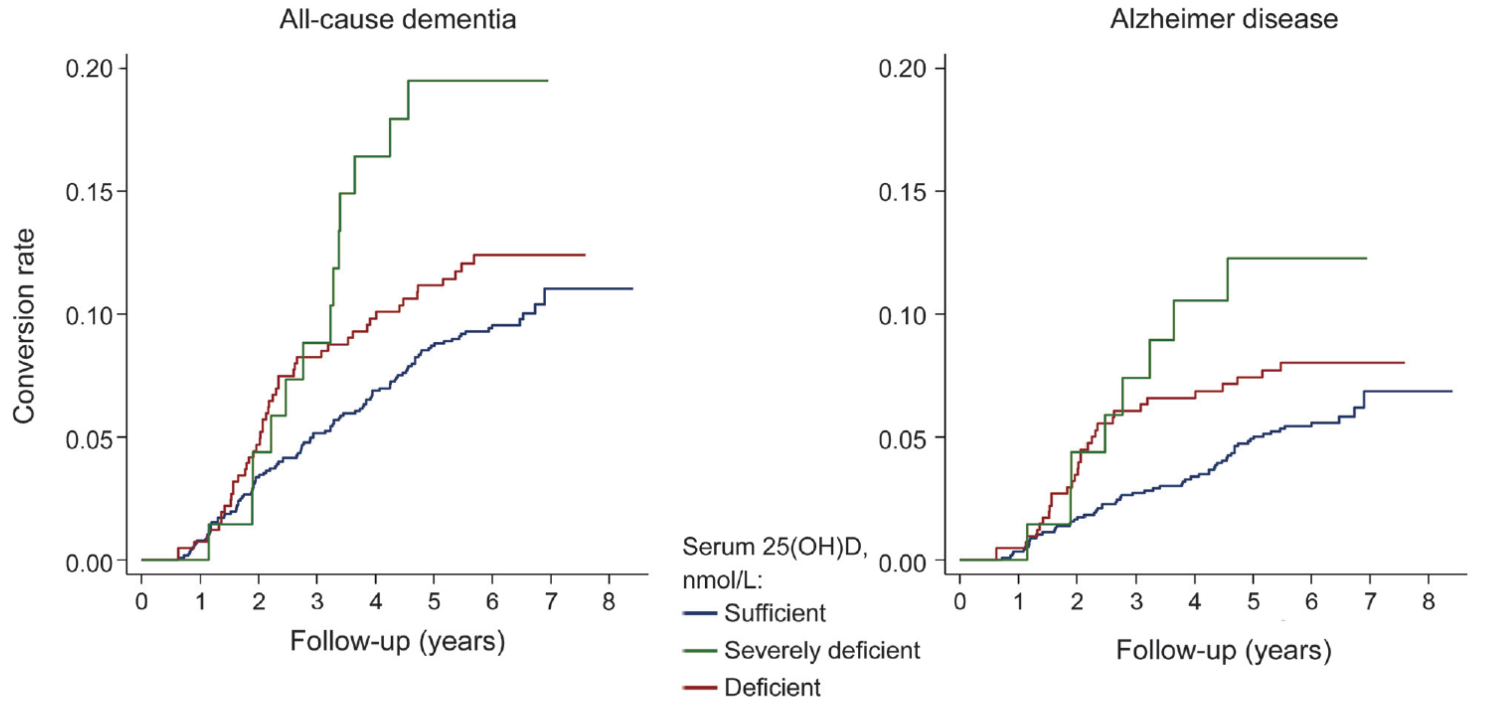
Objective: To determine whether low vitamin D concentrations are associated with an increased risk of incident all-cause dementia and Alzheimer disease.

Methods: One thousand six hundred fifty-eight elderly ambulatory adults free from dementia, cardiovascular disease, and stroke who participated in the US population-based Cardiovascular Health Study between 1992–1993 and 1999 were included. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were determined by liquid chromatography-tandem mass spectrometry from blood samples collected in 1992–1993. Incident all-cause dementia and Alzheimer disease status were assessed during follow-up using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

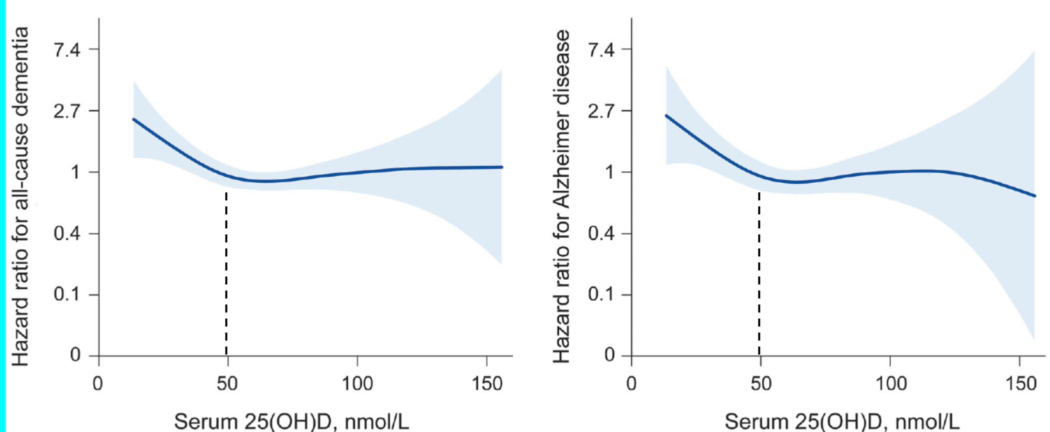
Results: During a mean follow-up of 5.6 years, 171 participants developed all-cause dementia, including 102 cases of Alzheimer disease. Using Cox proportional hazards models, the multivariate adjusted hazard ratios (95% confidence interval [CI]) for incident all-cause dementia in participants who were severely 25(OH)D deficient (<25 nmol/L) and deficient (≥25 to <50 nmol/L) were 2.25 (95% CI: 1.23–4.13) and 1.53 (95% CI: 1.06–2.21) compared to participants with sufficient concentrations (≥50 nmol/L). The multivariate adjusted hazard ratios for incident Alzheimer disease in participants who were severely 25(OH)D deficient and deficient compared to participants with sufficient concentrations were 2.22 (95% CI: 1.02–4.83) and 1.69 (95% CI: 1.06–2.69). In multivariate adjusted penalized smoothing spline plots, the risk of all-cause dementia and Alzheimer disease markedly increased below a threshold of 50 nmol/L.

Conclusion: Our results confirm that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer disease. This adds to the ongoing debate about the role of vitamin D in nonskeletal conditions. *Neurology®* 2014;83:1–9

Figure 1 **Kaplan-Meier curves for unadjusted rates of all-cause dementia and Alzheimer disease by serum 25-hydroxyvitamin D (25(OH)D) concentrations.**



Multivariate adjusted smoothing spline plots showing the hazard ratios for dementia and Alzheimer disease by serum 25(OH)D concentrations



Vitamin D deficiency predicts cognitive decline in older men and women

The Pro.V.A. Study

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ABSTRACT

Objective: To test the hypothesis that hypovitaminosis D is associated with a higher risk of cognitive decline over a 4.4-year follow-up in a large sample of older adults.

Methods: This research was part of the *Progetto Veneto Anziani* (Pro.V.A.), an Italian population-based cohort study of 1,927 elderly subjects. Serum 25-hydroxyvitamin D (25OHD) levels were measured at the baseline. Global cognitive function was measured with the Mini-Mental State Examination (MMSE); scores lower than 24 were indicative of cognitive dysfunction, and a decline of 3 or more points on the MMSE over the follow-up was considered as clinically significant. Analyses were adjusted for relevant confounders, including health and performance status.

Results: Participants with 25OHD deficiency (<50 nmol/L) or insufficiency (50–75 nmol/L) were more likely to have declining MMSE scores during the follow-up than those who were 25OHD sufficient (≥75 nmol/L). Among participants cognitively intact (baseline MMSE scores ≥24 and without diagnosis of dementia), the multivariate adjusted relative risk (95% confidence interval [CI]) of the onset of cognitive dysfunction was 1.36 (95% CI: 1.04–1.80; $p = 0.02$) for those with vitamin D deficiency and 1.29 (95% CI: 1.00–1.76; $p = 0.05$) for those with vitamin D insufficiency by comparison with individuals with normal 25OHD levels.

Conclusion: The results of our study support an independent association between low 25OHD levels and cognitive decline in elderly individuals. In cognitively intact elderly subjects, 25OHD levels below 75 nmol/L are already predictive of global cognitive dysfunction at 4.4 years.
Neurology® 2014;83:2292–2298

Figure Changes in MMSE scores over the follow-up according to 25OHD levels

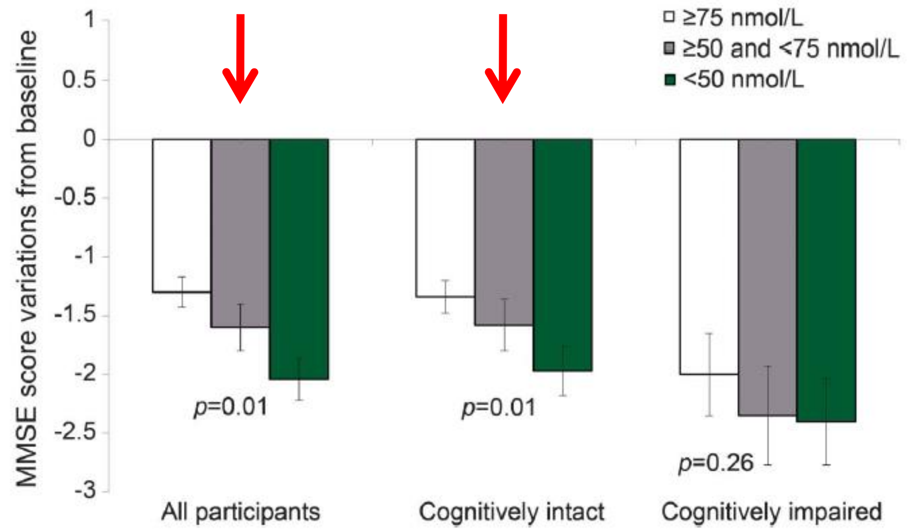

Table 3 Logistic regression model for the relative risk of the onset of cognitive impairment (MMSE score <24) at 4 years, in cognitively intact participants (with normal baseline MMSE score and without dementia), according to 25OHD serum levels

	Serum 25OHD cutoff levels, nmol/L				
	≥75	≥50 and <75	*p* Value	<50	*p* Value
Model 1	1 (ref.)	1.51 (1.16–1.97)	0.002	1.77 (1.40–2.26)	<0.0001
Model 2	1 (ref.)	1.40 (1.10–1.87)	0.03	1.57 (1.21–2.04)	0.01
Model 3	1 (ref.)	1.29 (1.00–1.76)	0.05	1.36 (1.04–1.80)	0.02

BJPsych
The British Journal of Psychiatry (2013)
202, 100–107. doi: 10.1192/bjp.bp.111.106666

Review article

Vitamin D deficiency and depression in adults: systematic review and meta-analysis

Rebecca E. S. Anglin, Zainab Samaan, Stephen D. Walter and Sarah D. McDonald

Background
There is conflicting evidence about the relationship between vitamin D deficiency and depression, and a systematic assessment of the literature has not been available.

Aims
To determine the relationship, if any, between vitamin D deficiency and depression.

Method
A systematic review and meta-analysis of observational studies and randomised controlled trials was conducted.

Results
One case–control study, ten cross-sectional studies and three cohort studies with a total of 31 424 participants were analysed. Lower vitamin D levels were found in people with depression compared with controls (SMD = 0.60, 95% CI 0.23–0.97) and there was an increased odds ratio of depression for the lowest *v.* highest vitamin D categories in the cross-sectional studies (OR = 1.31, 95% CI 1.0–1.71). The cohort studies showed a significantly increased hazard ratio of depression for the lowest *v.* highest vitamin D categories (HR = 2.21, 95% CI 1.40–3.49).

Conclusions
Our analyses are consistent with the hypothesis that low vitamin D concentration is associated with depression, and highlight the need for randomised controlled trials of vitamin D for the prevention and treatment of depression to determine whether this association is causal.

Declaration of interest
None.

Study or subgroup	log (OR)	s.e.	Weight, %	Odds Ratio IV, random, 95% CI
Ganji (2010)[33]	0.16	0.25	13.1	1.17 (0.72, 1.92)
Hoogendijk (2008)[2008)*]	0.29	0.19	16.1	1.34 (0.92, 1.94)
Lee (2011)[37]	0.55	0.27	12.2	1.73 (1.02, 2.94)
Nanri (2009)[30]	0.48	0.29	11.3	1.62 (0.92, 2.85)
Pan (2009)[11]	−0.3	0.19	16.1	0.74 (0.51, 1.08)
Stewart (2010)[38]	0.38	0.18	16.6	1.46 (1.03, 2.08)
Wilkins (2006)[8]	2.46	0.89	2.1	11.70 (2.05, 66.98)
Wilkins (2009)[39]	0.086	0.68	3.4	1.09 (0.29, 4.13)
Zhao (2010)[21]	0.11	0.35	9.2	1.12 (0.56, 2.22)
Total (95% CI)			100.0	1.31 (1.00, 1.71)

Heterogeneity: $\tau^2 = 0.08$; $\chi^2 = 17.24$, d.f. = 8 ($P = 0.03$); $I^2 = 54\%$

Test for overall effect: $Z = 1.98$ ($P = 0.05$)

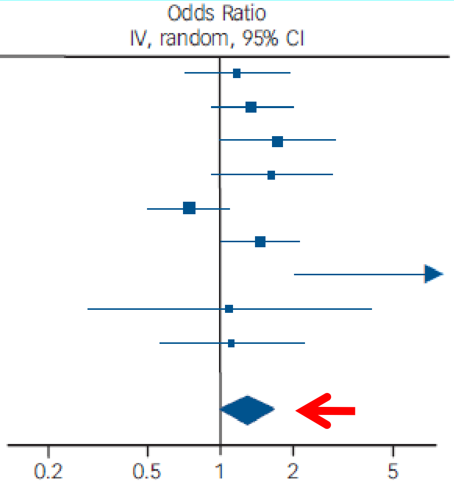

Fig. 2 Cross-sectional studies: forest plot of the odds ratio (OR) of depression for the lowest *v.* highest vitamin D categories. Squares to the right of the vertical line indicate that low vitamin D was associated with increased odds of depression, squares to the left of the vertical line indicate that low vitamin D was associated with decreased odds of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall OR of depression with low vitamin D from the meta-analysis and the corresponding 95% confidence interval (*OR provided by Dr B. Penninx, personal communication, 25 July 2011).

Study or subgroup	log (HR)	s.e.	Weight, %	Hazard Ratio IV, random 95% CI
Chan (2011)[10]	−0.48	0.86	7.0	0.62 (0.11, 3.34)
May (2010)[9]	0.99	0.35	33.7	2.69 (1.36, 5.34)
Milaneschi (2010)[35]	0.83	0.23	59.3	2.29 (1.46, 3.60)
Total (95% CI)			100.0	2.21 (1.40, 3.49)

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 2.52$, d.f. = 2 ($P = 0.28$); $I^2 = 21\%$

Test for overall effect: $Z = 3.40$ ($P = 0.0007$)

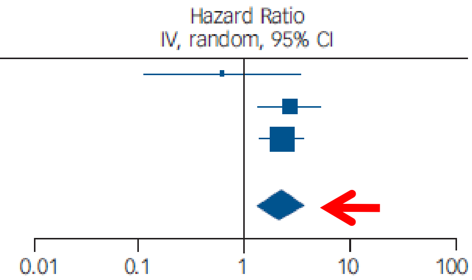

Fig. 3 Cohort studies: forest plot of the hazard ratio (HR) of depression for the lowest *v.* highest vitamin D categories. Squares to the right of the vertical line indicate that vitamin D deficiency was associated with an increased risk of depression, whereas squares to the left of the vertical line indicate that vitamin D deficiency was associated with a decreased risk of depression. Horizontal lines represent the associated 95% confidence intervals and the diamond represents the overall HR of depression with vitamin D deficiency from the meta-analysis and the corresponding 95% confidence interval.

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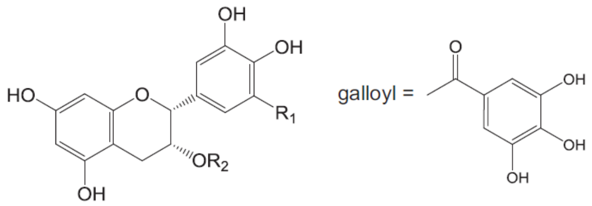
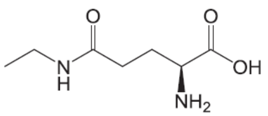
A

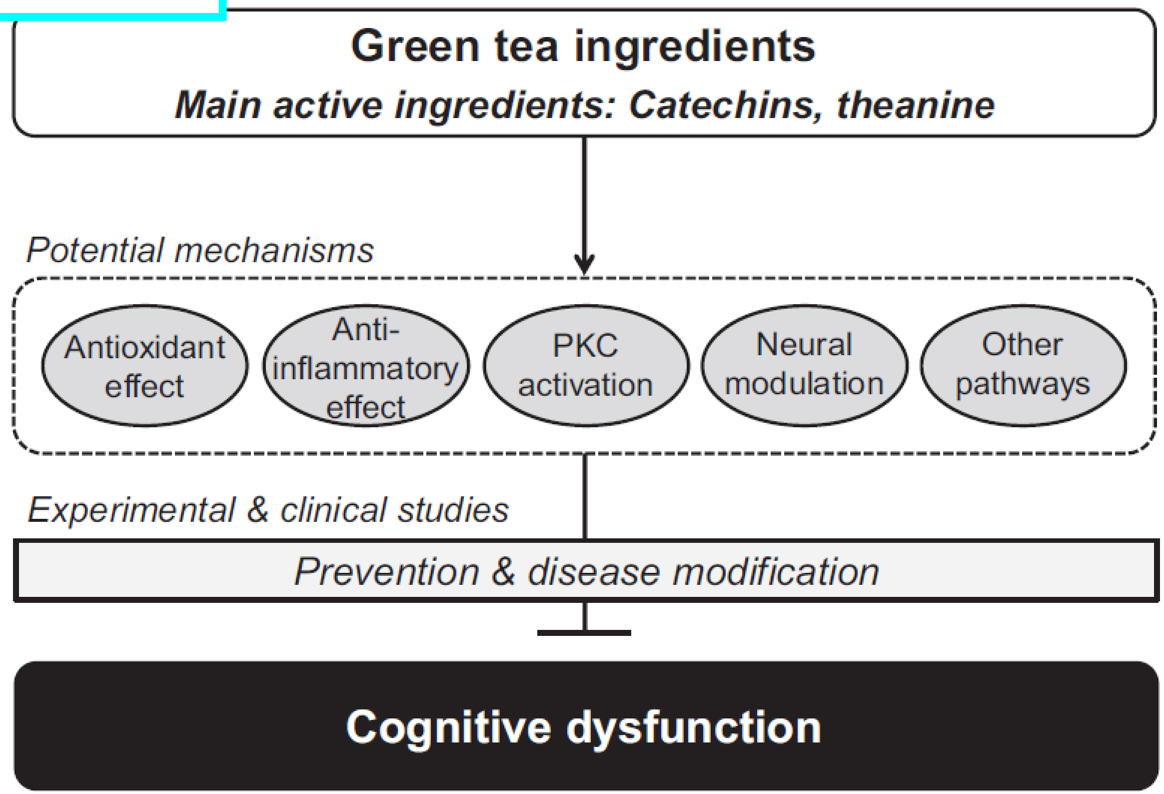


Catechins	R_1	R_2
(-)-Epicatechin (EC)	H	H
(-)-Epigallocatechin (EGC)	OH	H
(-)-Epicatechin gallate (ECG)	H	galloyl
(-)-Epigallocatechin-3-gallate (EGCG)	OH	galloyl

B



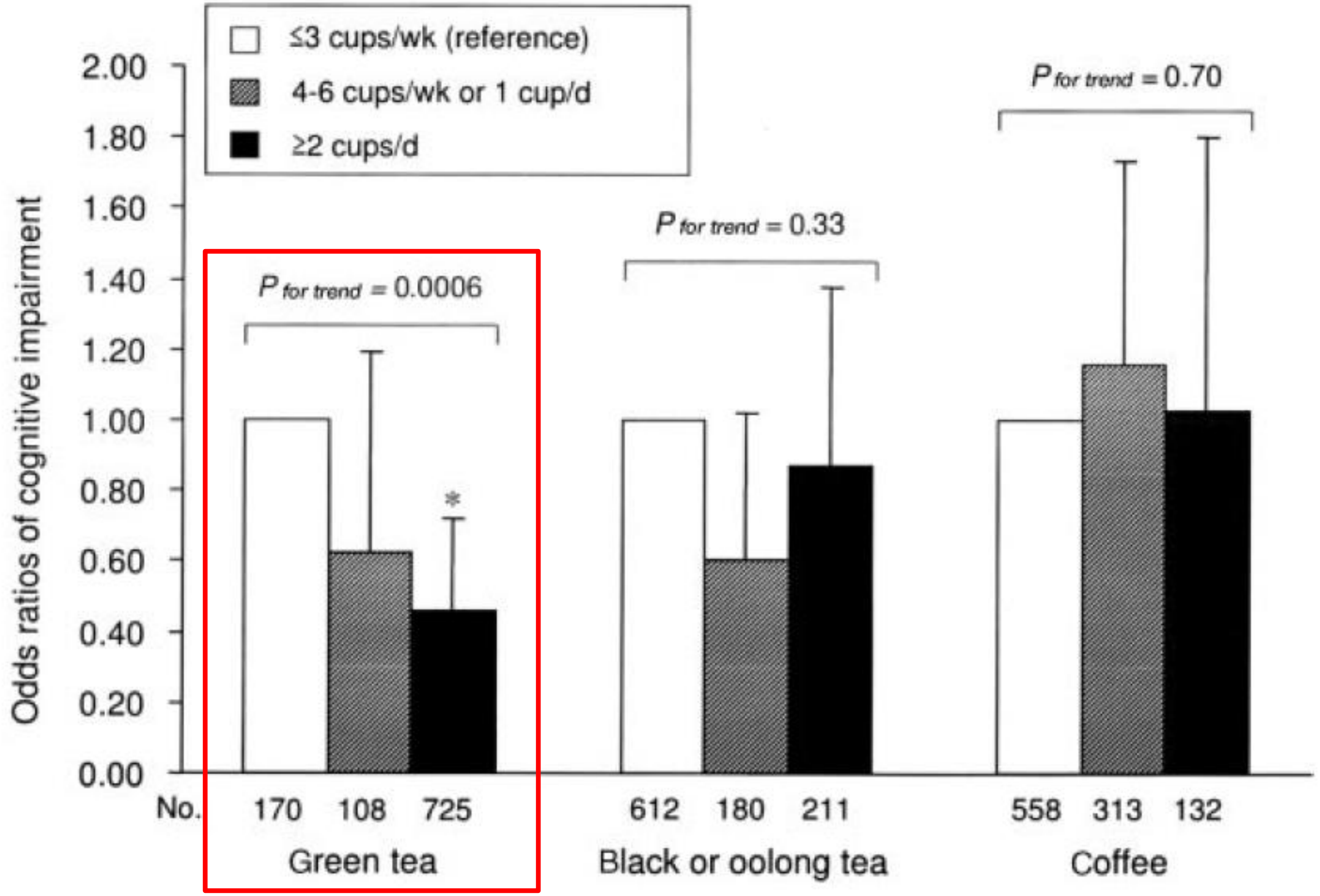
L-theanine



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

The American Journal of Clinical Nutrition

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



Am J Clin Nutr 2006

Tea consumption and cognitive impairment and decline in older Chinese adults[1–3]

The American Journal of Clinical Nutrition

Tze-Pin Ng, Lei Feng, Mathew Niti, Ee-Heok Kua, and Keng-Bee Yap

TABLE 4
Associations of types of tea with cognitive impairment and decline[1]

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

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PLOS ONE

Consumption of Green Tea, but Not Black Tea or Coffee, Is Associated with Reduced Risk of Cognitive Decline

Moeko Noguchi-Shinohara[1], Sohshi Yuki[1], Chiaki Dohmoto[1], Yoshihisa Ikeda[1], Miharu Samuraki[1], Kazuo Iwasa[1], Masami Yokogawa[2], Kimiko Asai[3], Kiyonobu Komai[4], Hiroyuki Nakamura[5], Masahito Yamada[1]*

2014

Table 4. Association between green tea consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of green tea consumption	None	1–6 days/week	Every day
Dementia			
Number of cases	12	11	3
Unadjusted Model	1	0.64 (0.27–1.49)	0.21 (0.06–0.76)*
Model 1†	1	0.89 (0.36–2.19)	0.26 (0.07–0.94)*
Model 2§	1	0.89 (0.35–2.28)	0.27 (0.07–1.07)
Model 3¶	1	0.90 (0.34–2.35)	0.26 (0.06–1.06)
Cognitive decline (MCI or dementia)			
Number of cases	43	29	18
Unadjusted Model	1	0.39 (0.23–0.67)**	0.29 (0.16–0.54)***
Model 1†	1	0.53 (0.30–0.93)*	0.34 (0.18–0.64)**
Model 2§	1	0.49 (0.27–0.89)*	0.33(0.17–0.66)**
Model 3¶	1	0.47 (0.25–0.86)*	0.32 (0.16–0.64)**

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PLOS ONE

Consumption of Green Tea, but Not Black Tea or Coffee, Is Associated with Reduced Risk of Cognitive Decline

Moeko Noguchi-Shinohara[1], Sohshi Yuki[1], Chiaki Dohmoto[1], Yoshihisa Ikeda[1], Miharu Samuraki[1], Kazuo Iwasa[1], Masami Yokogawa[2], Kimiko Asai[3], Kiyonobu Komai[4], Hiroyuki Nakamura[5], Masahito Yamada[1]*

2014

Table 6. Association between black tea consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of black tea consumption	None	1–7 days/week
Dementia		
Number of cases	20	6
Unadjusted Model	1	1.41 (0.55–3.61)
Model 1†	1	1.70 (0.64–4.47)
Model 2§	1	2.06 (0.76–5.61)
Model 3¶	1	2.14 (0.75–6.08)
Cognitive decline (MCI or dementia)		
Number of cases	74	16
Unadjusted Model	1	0.99 (0.54–1.81)
Model 1†	1	1.19 (0.64–2.24)
Model 2§	1	1.39 (0.72–2.68)
Model 3¶	1	1.52 (0.77–3.03)

Te nero

Table 5. Association between coffee consumption and the incidence of dementia or cognitive decline (MCI or dementia).

Frequency of coffee consumption	None	1–6 days/week	Every day
Dementia			
Number of cases	7	11	8
Unadjusted Model	1	0.86 (0.31–2.30)	0.51 (0.18–1.45)
Model 1†	1	1.06 (0.39–2.90)	0.69 (0.23–2.01)
Model 2§	1	1.13 (0.40–3.21)	0.71 (0.23–2.16)
Model 3¶	1	1.00 (0.34–2.99)	0.70 (0.22–2.17)
Cognitive decline (MCI or dementia)			
Number of cases	20	34	36
Unadjusted Model	1	0.93 (0.50–1.72)	0.80 (0.44–1.47)
Model 1†	1	1.22 (0.63–2.36)	1.19 (0.62–2.28)
Model 2§	1	1.23 (0.63–2.41)	1.09 (0.56–2.14)
Model 3¶	1	1.26 (0.62–2.54)	1.16 (0.58–2.32)

Caffè

PharmaNutrition 3 (2015) 136–145

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2015

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Review

Clinical benefits of green tea consumption for cognitive dysfunction

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ABSTRACT

The prevalence of cognitive dysfunction, and particularly dementia, is increasing rapidly among older adults worldwide. There is currently no cure for dementia. In this situation, pharmaceutical and non-pharmaceutical combination therapies capable of preventing or slowing the progression of cognitive dysfunction are important. Nutritional intervention provides an important non-pharmaceutical approach in clinical practice. Green tea has the potential to contribute to this nutritional approach. Experimental studies *in vitro* and *in vivo* have suggested that green tea and its components could affect cognition *via* several potential mechanisms; these include its antioxidant and anti-inflammatory properties, protein kinase C activation, and acetylcholinesterase inhibition. Although several epidemiological and interventional studies in humans have suggested an association between tea consumption and cognition, not all studies have reported consistent findings. The present review summarizes experimental studies of the mechanisms involved in these effects and clinical studies of green tea consumption and cognition. This review provides a basis for the development of an evidence-based approach to the use of green tea and its ingredients in individuals with cognitive dysfunction.

Table 1
Characteristics of cross-sectional studies.

Source	Population	Types of tea	Outcomes	Reference no.
Kuriyama et al. 2006	1003 Japanese residents, aged ≥70 years	Green tea	1 (reference for ≤3 cups/week) *vs.* 0.46 (95% CI: 0.30, 0.72) for ≥2 cups/day, $P=0.0006$	[137]
Ng et al. 2008	2501 community-living Chinese residents, aged ≥55 years	Green tea, black tea, oolong tea	1 (reference for rare or no tea intake) *vs.* 0.56 (95% CI: 0.40, 0.78) for low level of intake; 1 *vs.* 0.45 (95% CI: 0.27, 0.72) for medium level of intake; 1 *vs.* 0.37 (95% CI: 0.14, 0.98) for high level of intake, $P<0.001$	[138]
Huang et al. 2009	681 Chinese residents, aged ≥90 years	Any type of tea	Lower prevalence of cognitive impairment in male but not female tea consumers, $P=0.041$ for former consumption, $P=0.044$ for current consumption	[139]
Nurk et al. 2009	2031 Norwegian residents, aged 70–74 years	Any type of tea (most common type during 1990s in Norway: black tea)	Dose-dependent effect of tea consumption on cognitive function (6 different cognitive tests) was observed up to ~200 ml/day, after which it plateaued or tended to be linear	[140]
Feng et al. 2010	716 Chinese residents, aged ≥55 years	Green tea, black tea, oolong tea	Total tea consumption was independently associated with better performances on global cognition, $P=0.03$; memory, $P=0.01$; executive function, $P=0.009$; and information processing speed, $P=0.001$	[141]

Table 2
Longitudinal studies.

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

Table 3
Interventional studies.

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

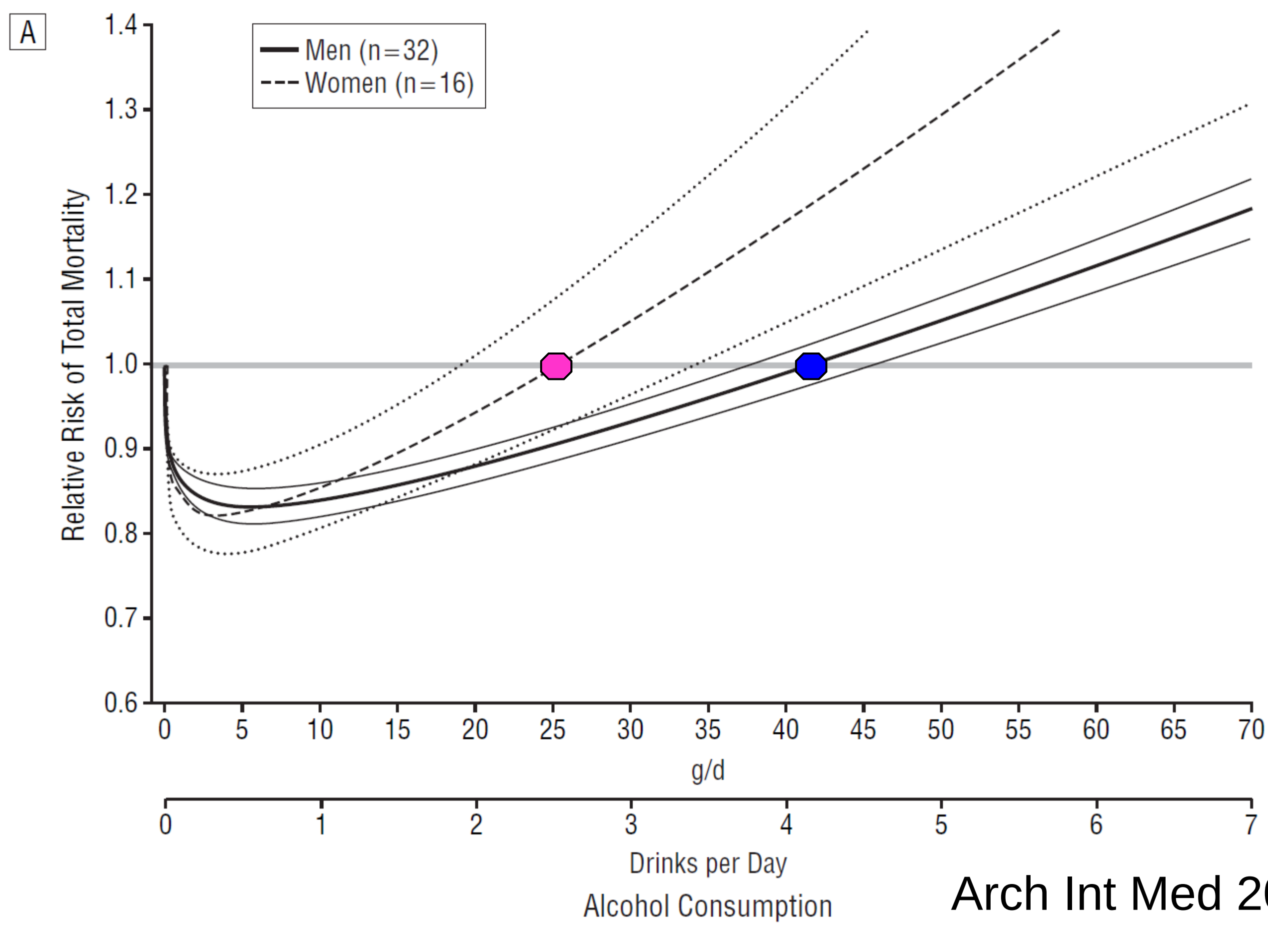
Alcol (etilico)

REVIEW ARTICLE

Alcohol Dosing and Total Mortality in Men and Women

An Updated Meta-analysis of 34 Prospective Studies

Augusto Di Castelnuovo, ScD; Simona Costanzo, ScD; Vincenzo Bagnardi, ScD; Maria Benedetta Donati, MD, PhD; Licia Iacoviello, MD, PhD; Giovanni de Gaetano, MD, PhD



Arch Int Med 2006

Association of Alcohol Consumption with Brain Volume in the Framingham Study

Arch Neurol. 2008 October ; 65(10): 1363–1367.

C. A. Paul, MS[1,3], **R. Au, PhD**[2,6], **L. Fredman, PhD**[3], **J. M. Massaro, PhD**[4,5,6], **S. Seshadri, MD**[2,6], **C. DeCarli, MD**[6], and **P. A. Wolf, MD**[2,6]

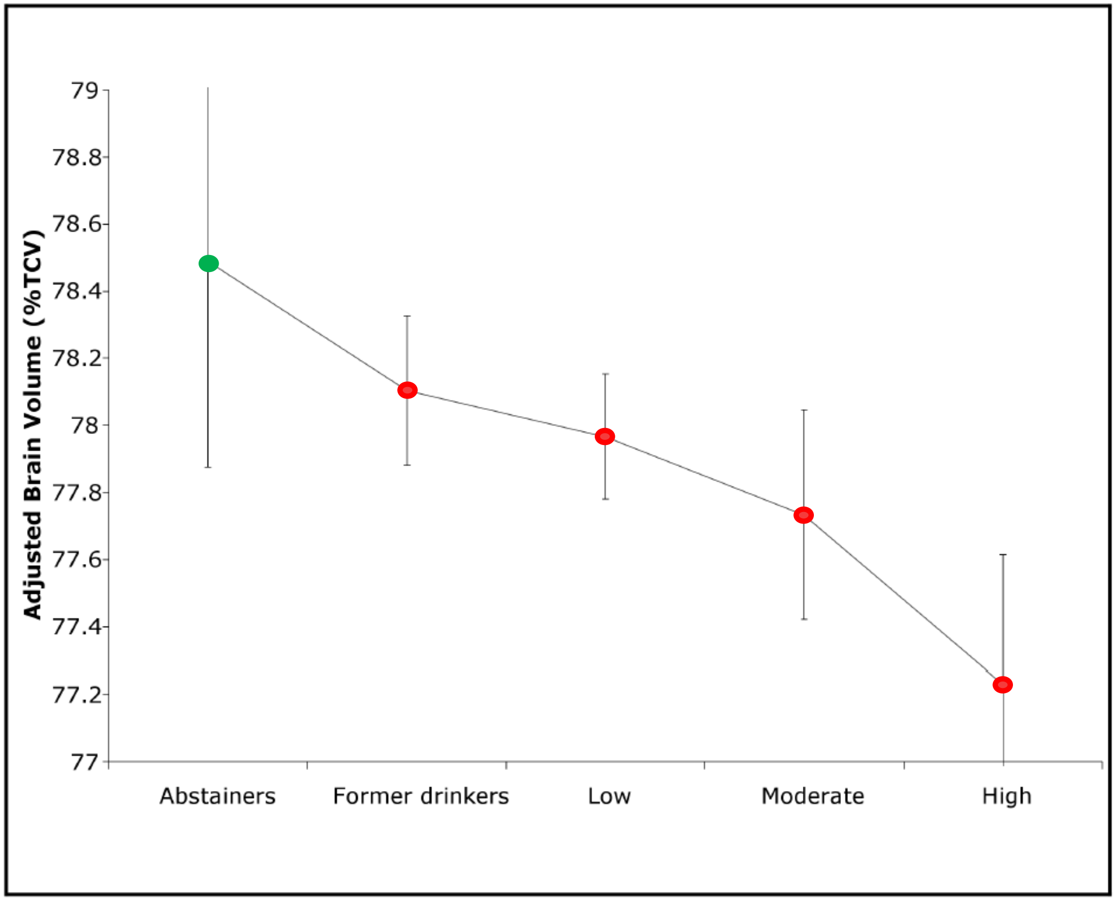


Figure 1.
Mean TCBV, including confidence intervals, illustrated as error bars, adjusted for age, sex, BMI and FSRP (slope = -0.25, $p < 0.01$, $R^2 = 0.96$).

Age and Ageing 2008; **37:** 505–512
doi:10.1093/ageing/afn095
Published electronically 16 May 2008

SYSTEMATIC REVIEW

Alcohol, dementia and cognitive decline in the elderly: a systematic review

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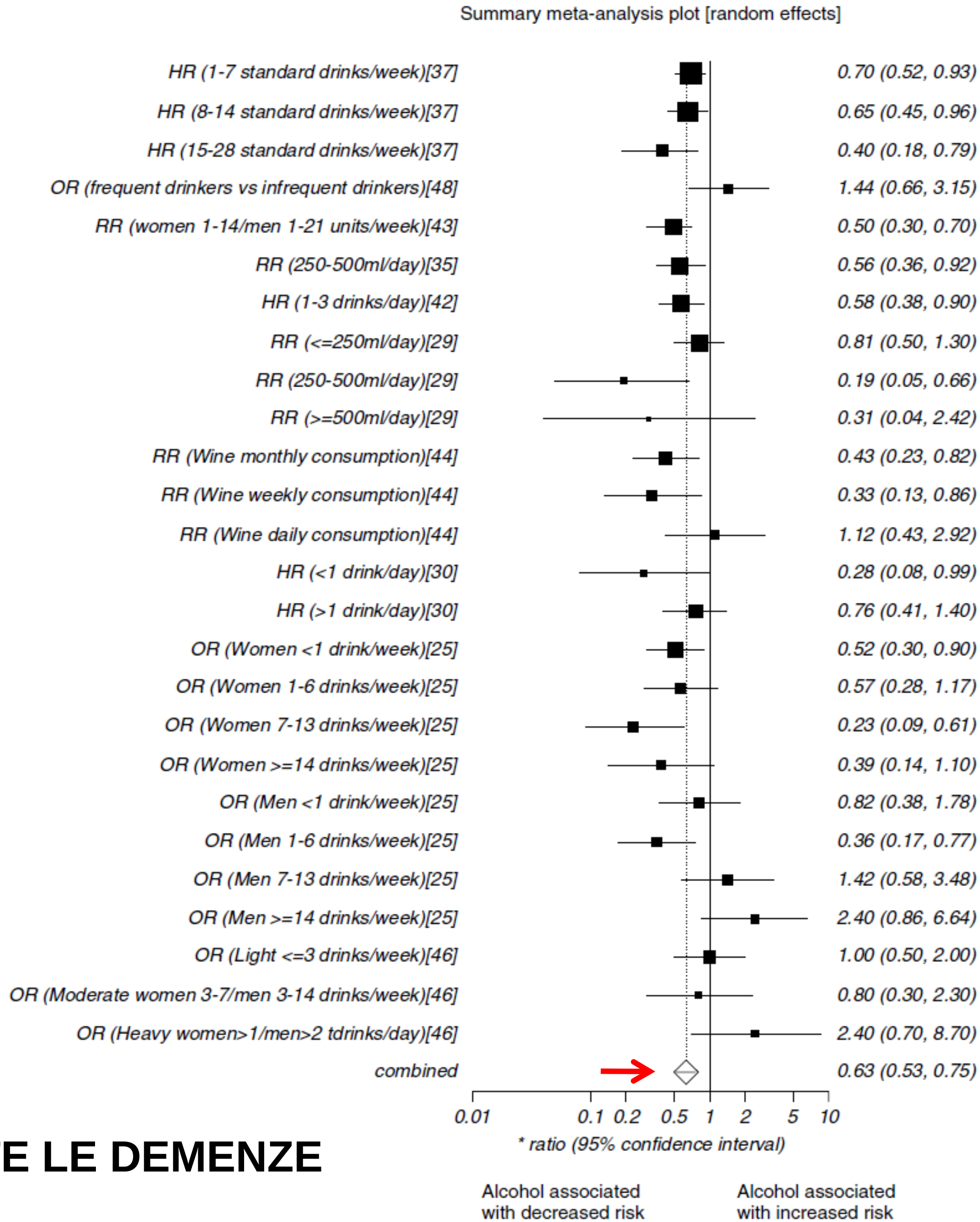
Abstract

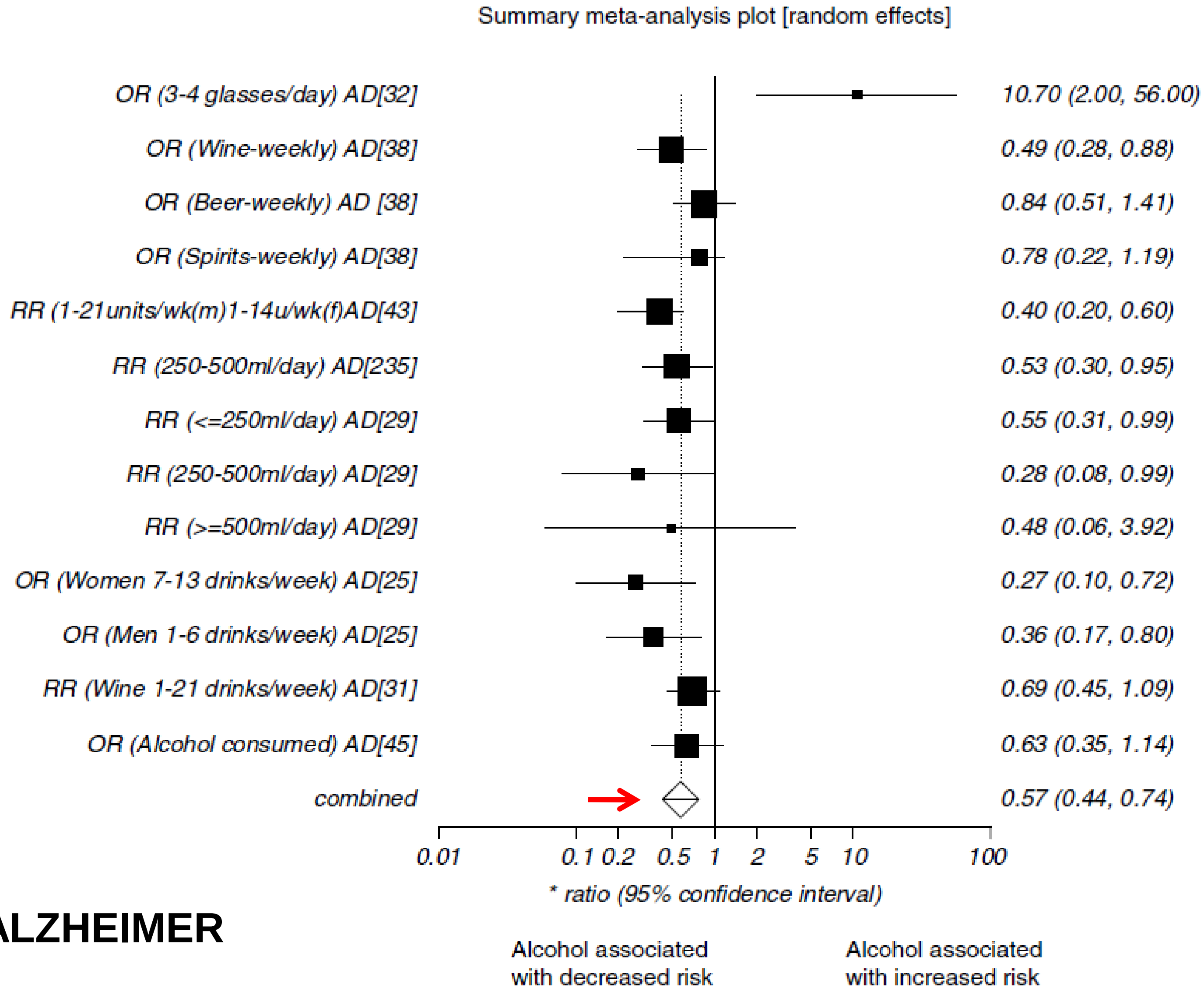
Background: dementia and cognitive decline have been linked to cardiovascular risk. Alcohol has known negative effects in large quantities but may be protective for the cardiovascular system in smaller amounts. Effect of alcohol intake may be greater in the elderly and may impact on cognition.
Methods: to evaluate the evidence for any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption, a systematic review and meta-analyses were carried out. Criteria for inclusion were longitudinal studies of subjects aged ≥65, with primary outcomes of incident dementia/cognitive decline.
Results: 23 studies were identified (20 epidemiological cohort, three retrospective matched case-control nested in a cohort). Meta-analyses suggest that small amounts of alcohol may be protective against dementia (random effects model, risk ratio [RR] 0.63; 95% CI 0.53–0.75) and Alzheimer's disease (RR 0.57; 0.44–0.74) but not for vascular dementia (RR 0.82; 0.50–1.35) or cognitive decline (RR 0.89; 0.67–1.17) However, studies varied, with differing lengths of follow up, measurement of alcohol intake, inclusion of true abstainers and assessment of potential confounders.
Conclusions: because of the heterogeneity in the data these findings should be interpreted with caution. However, there is some evidence to suggest that limited alcohol intake in earlier adult life may be protective against incident dementia later.

Keywords: *elderly, dementia, cognitive decline, alcohol*



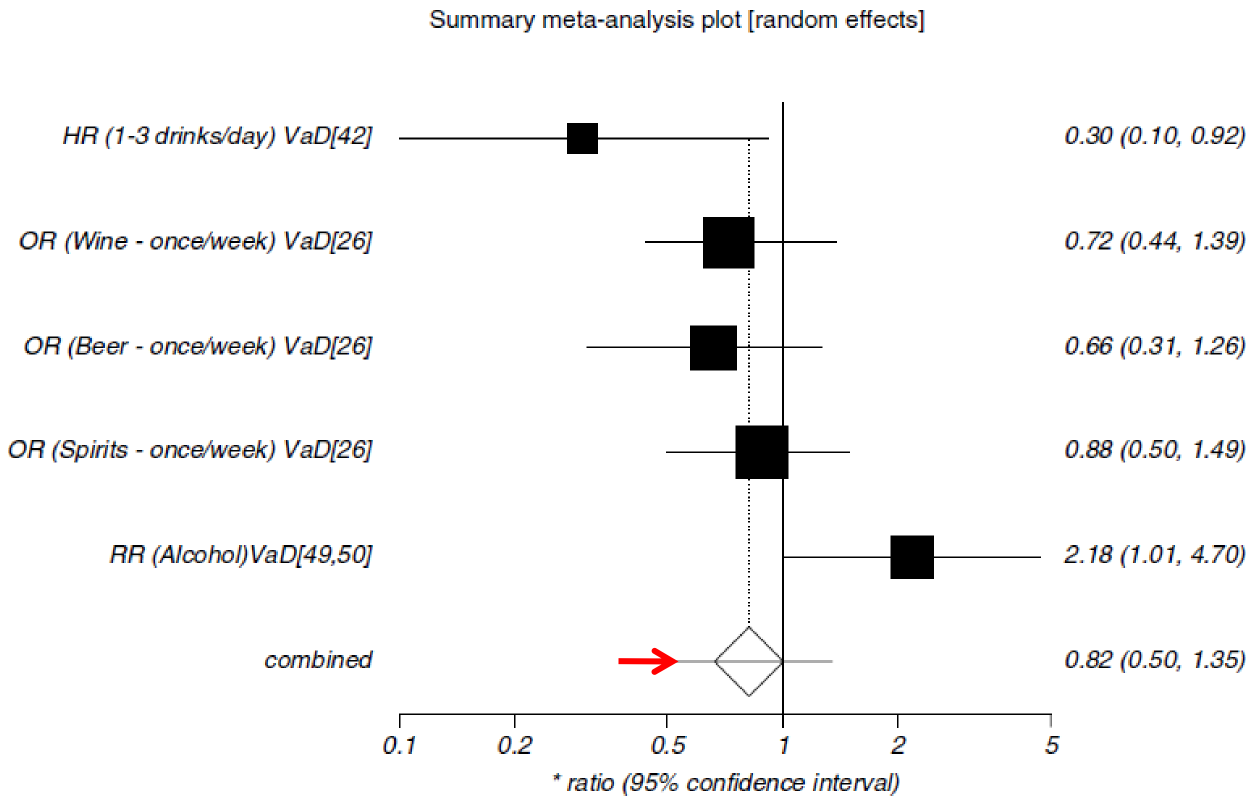
TUTTE LE DEMENZE

Figure 1. Dementia and alcohol.



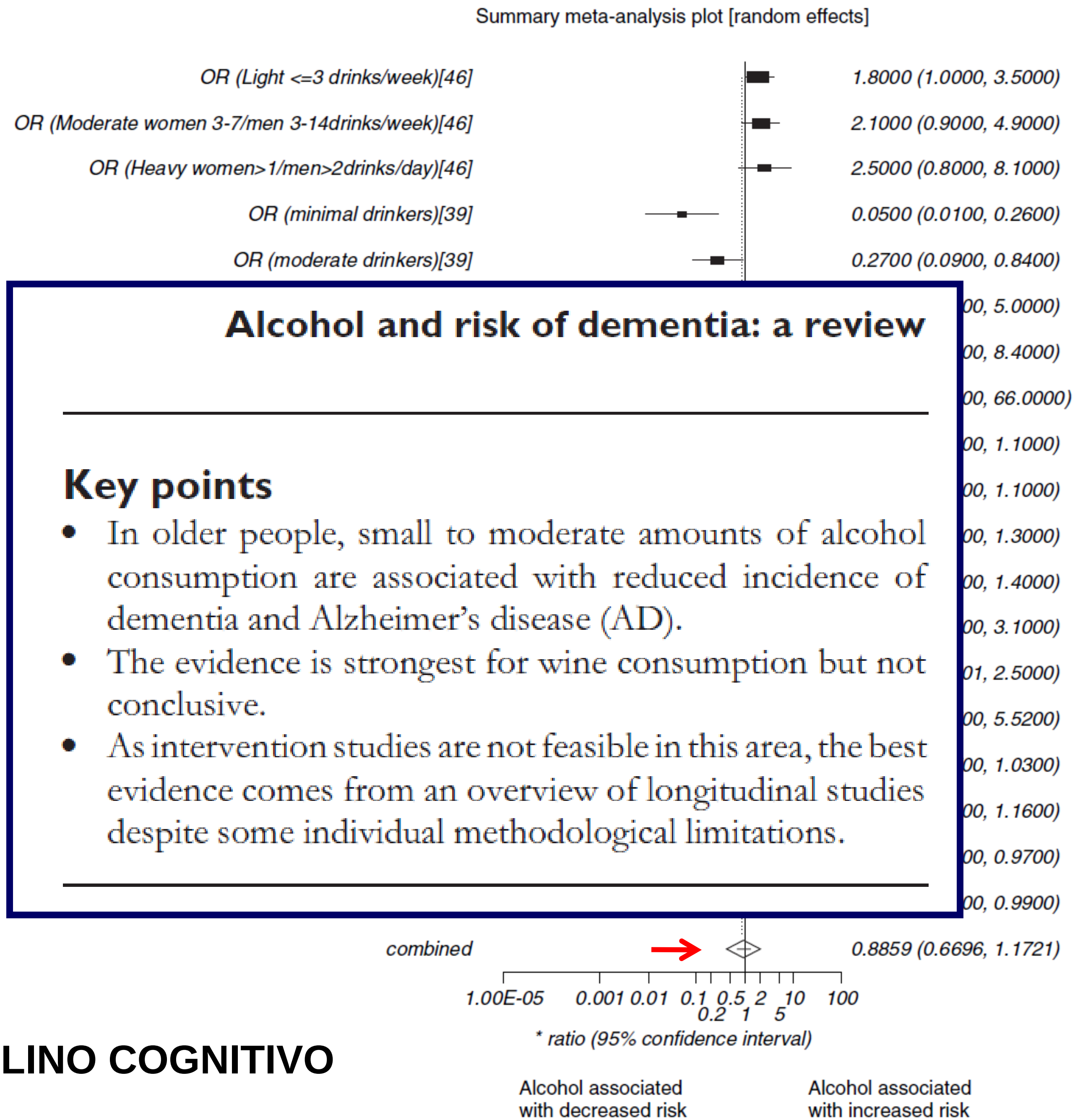
M. DI ALZHEIMER

Figure 2. AD and alcohol.



DEMENZA VASCOLARE

Figure 3. VaD and alcohol.



Alcohol and risk of dementia: a review

Key points

- In older people, small to moderate amounts of alcohol consumption are associated with reduced incidence of dementia and Alzheimer's disease (AD).
- The evidence is strongest for wine consumption but not conclusive.
- As intervention studies are not feasible in this area, the best evidence comes from an overview of longitudinal studies despite some individual methodological limitations.

DECLINO COGNITIVO

Figure 4. Cognitive decline and alcohol.

OPEN

Alcohol consumption and cognitive decline in early old age

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This study suggests that men consuming 36 g/d or more of alcohol in midlife were more likely to experience faster 10-year cognitive decline in all cognitive domains; in women, there was weaker evidence of this effect occurring at ≥19 g/d, but only for executive function. Our findings are in agreement with previous studies showing that moderate alcohol consumption is probably not deleterious for cognitive outcomes, but they also show that heavy alcohol consumption in midlife is likely to be harmful for cognitive aging, at least in men.

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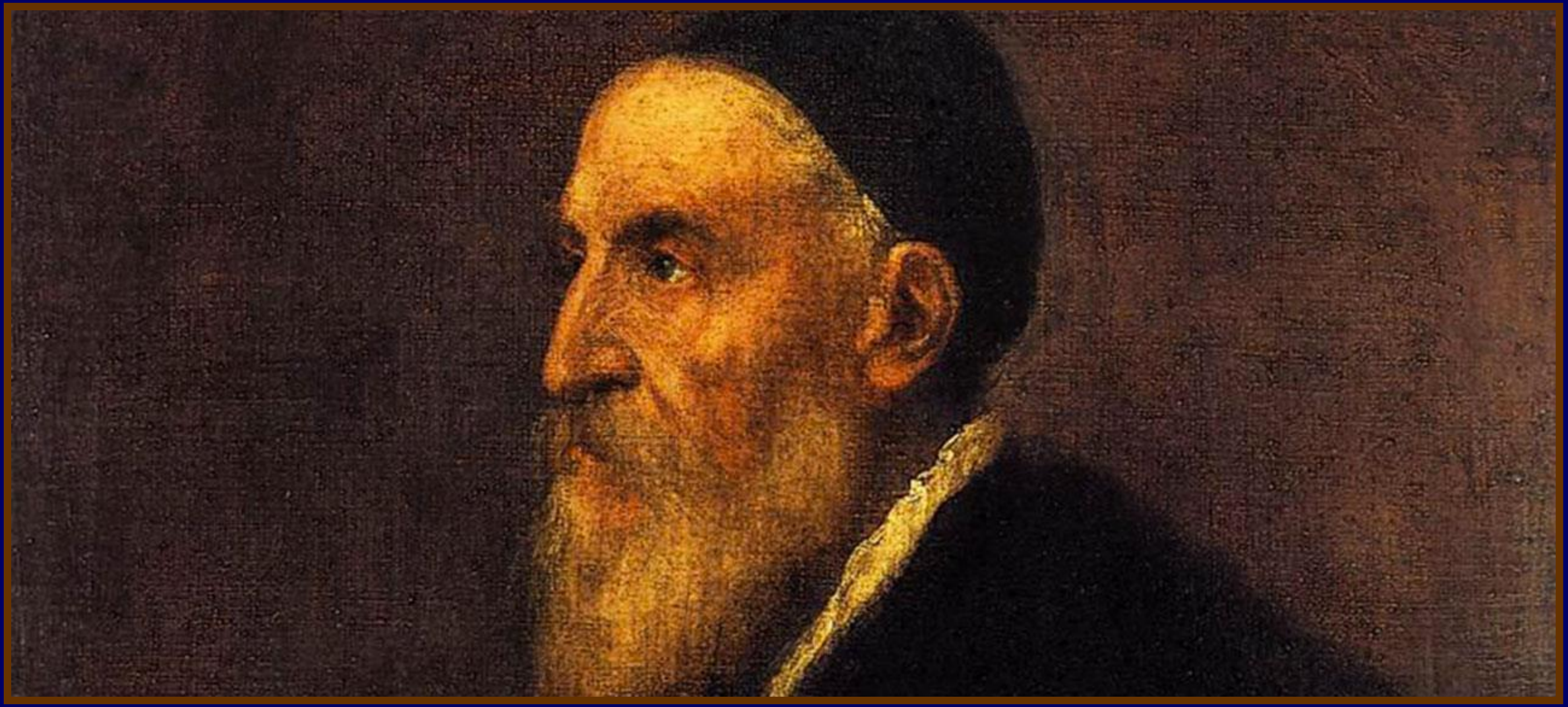
the association
n = 0, SD = 1).
ainers, quitters,
n ≥36 g/d was
mption between
ne in the global
.00), and mem-
9 g/d of alcohol,
−0.37, −0.04])

Conclusions: Excessive alcohol consumption in men (≥36 g/d) was associated with faster cognitive decline compared with light to moderate alcohol consumption. *Neurology®* 2014;82:332–339



Tiziano Vecellio

Grazie per la cortese attenzione …