

Approccio nutraceutico alla gestione del declino cognitivo iniziale

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Review article

Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA)

- **Prevalence: 5.5-7.7% over 60 years, 22% over 70**
- **Evolution to dementia 10%/year (strongly variable data)**
- **Reversibility each year: till 45% of cases !!!**

[Maturitas](#). 2016 Jan;83:83-93

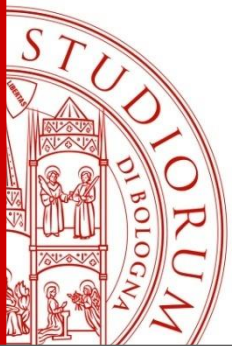
Review article

Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA)

RISK FACTORS

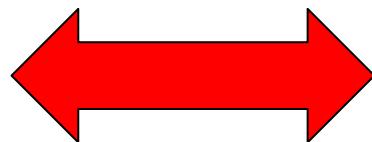
- **Age**
- **ApoE**
- **Behavioural: Smoking, Sedentariety, Alcoholic abuse, Wrong dietary habits**
- **Cardiovascular: Diabetes, Hypertension, Dyslipidemia, Obesity, Arrhythmia**
- **Psychosocial: Low educational, Isolation, Depression**

[Maturitas](#). 2016 Jan;83:83-93



A time-less war...

Epidemiology

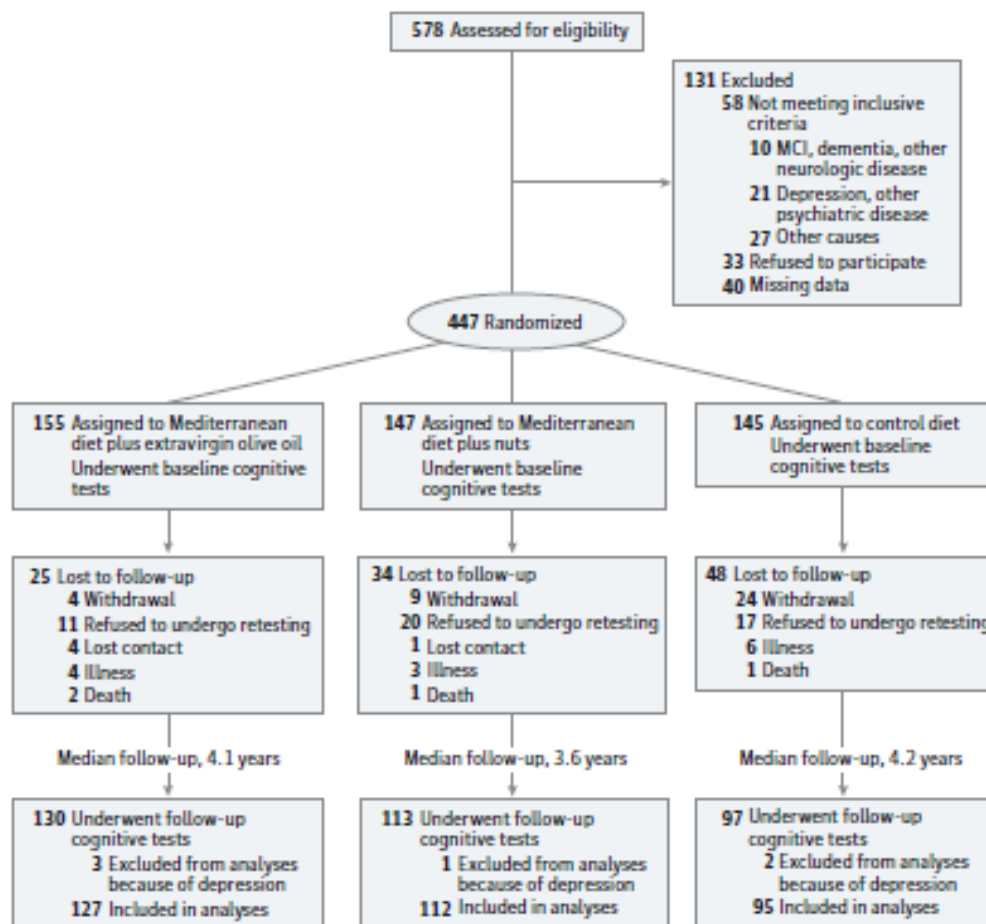


RCTs

- **Dietary approach**
- **Single nutraceutical approach**
- **Combined nutraceutical approach**

Mediterranean Diet and Age-Related Cognitive Decline

A Randomized Clinical Trial



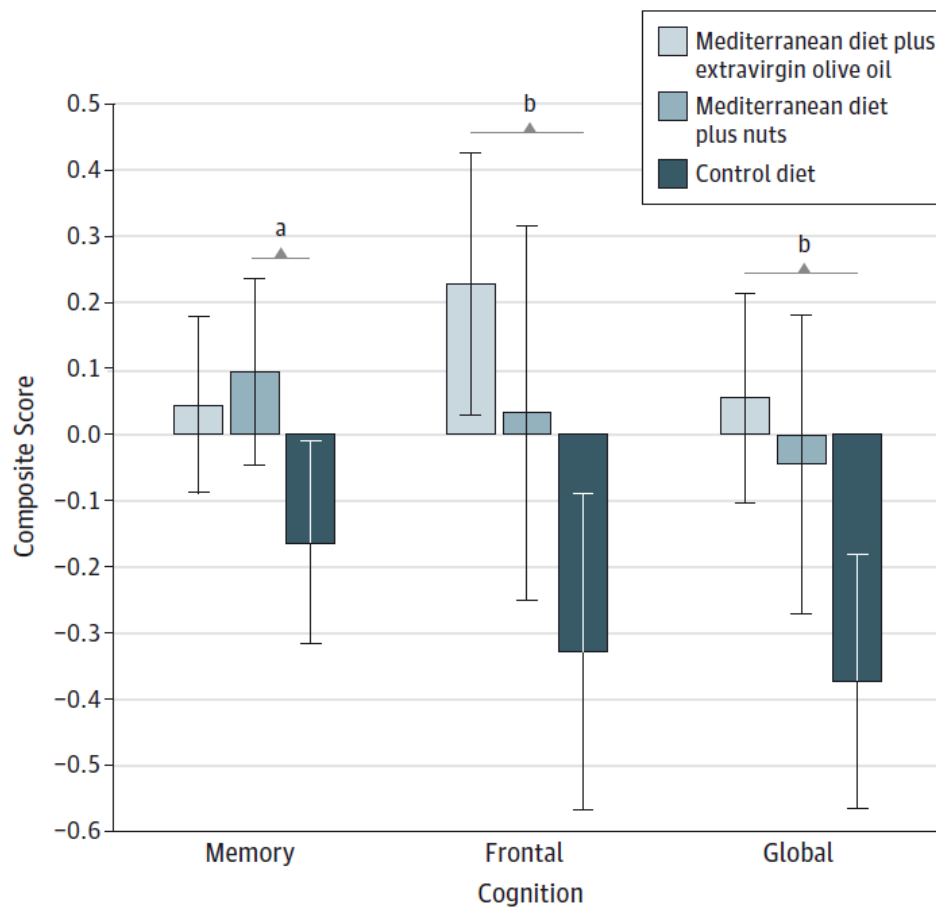
1 l olive oil/wk
+/-
30 gr nuts/day

Median follow-up: 4.1 years

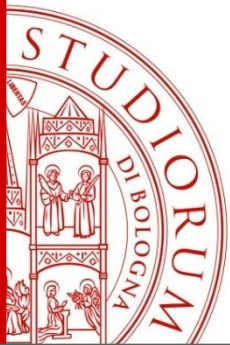
JAMA Intern Med.
2015;175(7):1094-1103

Mediterranean Diet and Age-Related Cognitive Decline

A Randomized Clinical Trial

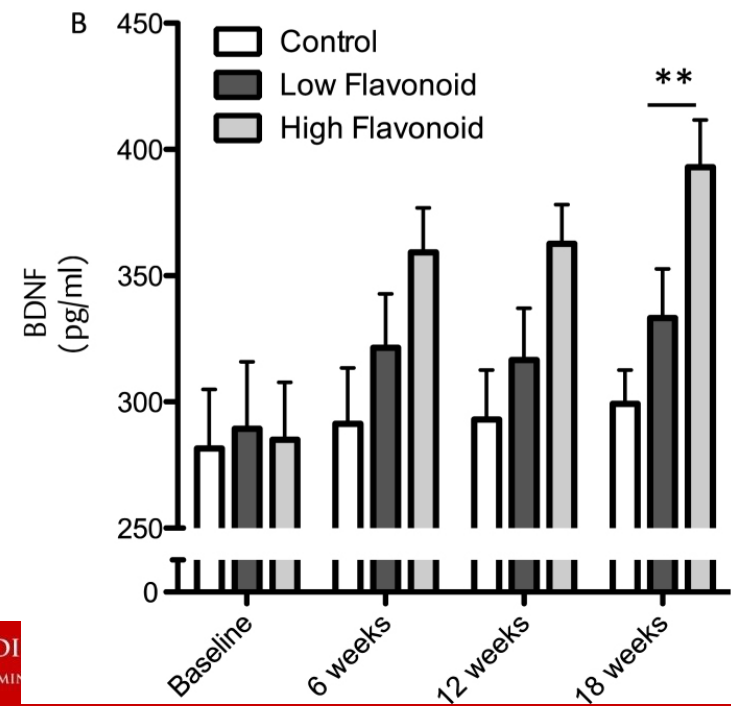
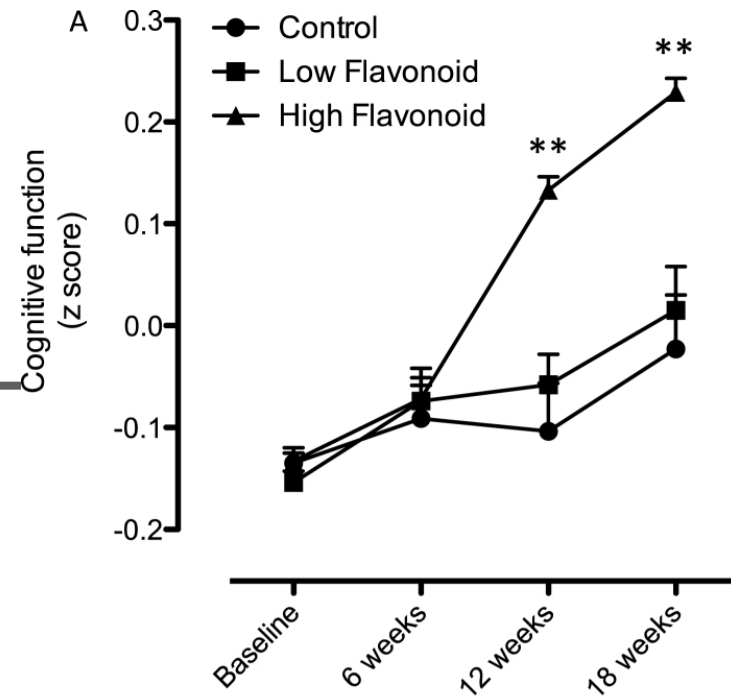


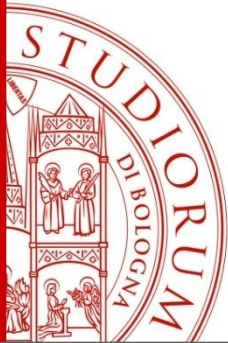
JAMA Intern Med.
2015;175(7):1094-103



Influence of fruit and vegetable (flavonoid) intake on cognition and serum brain-derived neurotrophic factor

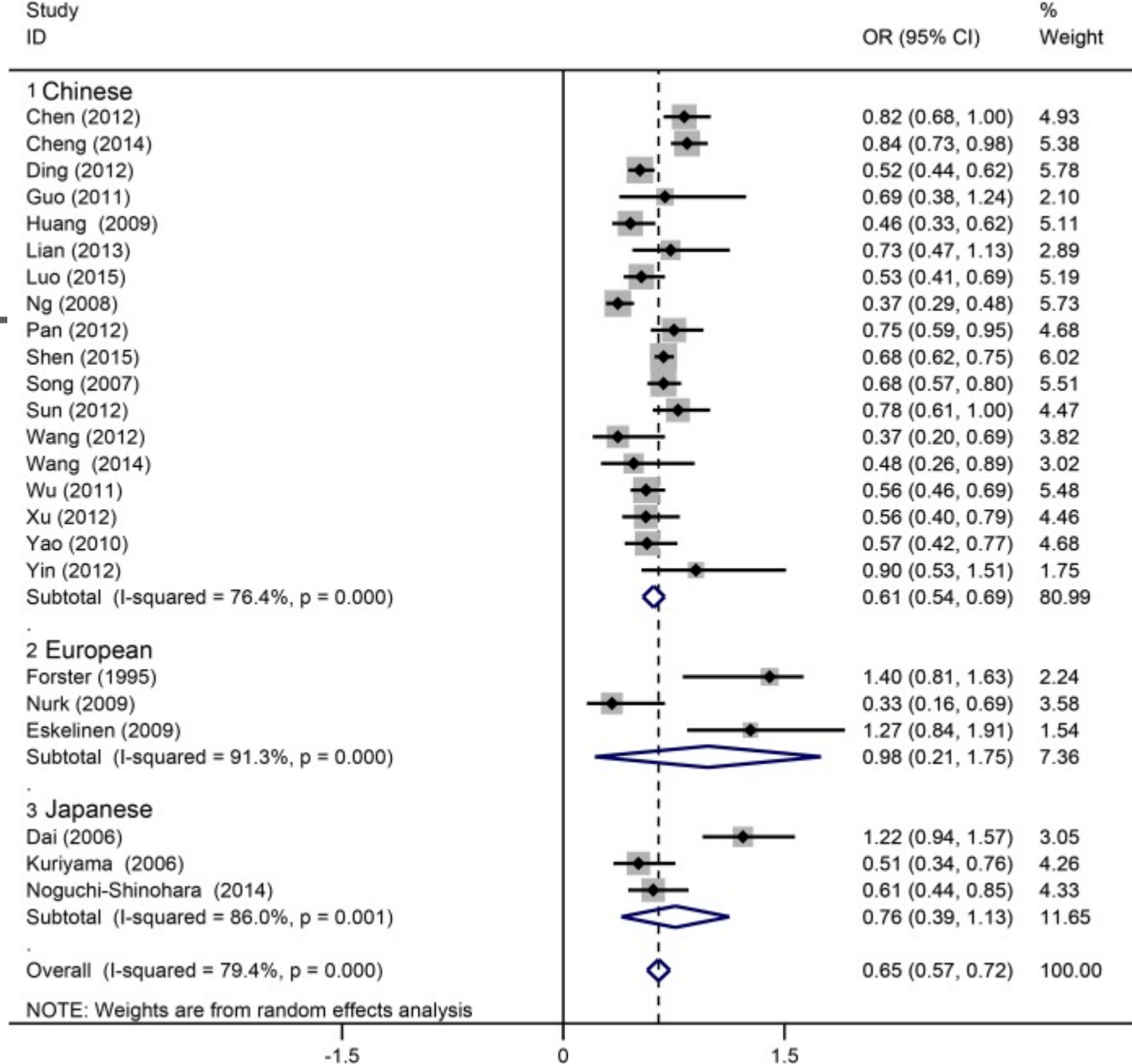
[Nutr Healthy Aging](#). 2016; 4(1): 81–93.

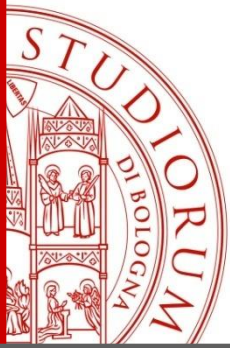




Association between tea intake and the cognitive disorders based on ethnicity

[PLoS One. 2016; 11\(11\): e0165861.](https://doi.org/10.1371/journal.pone.0165861)

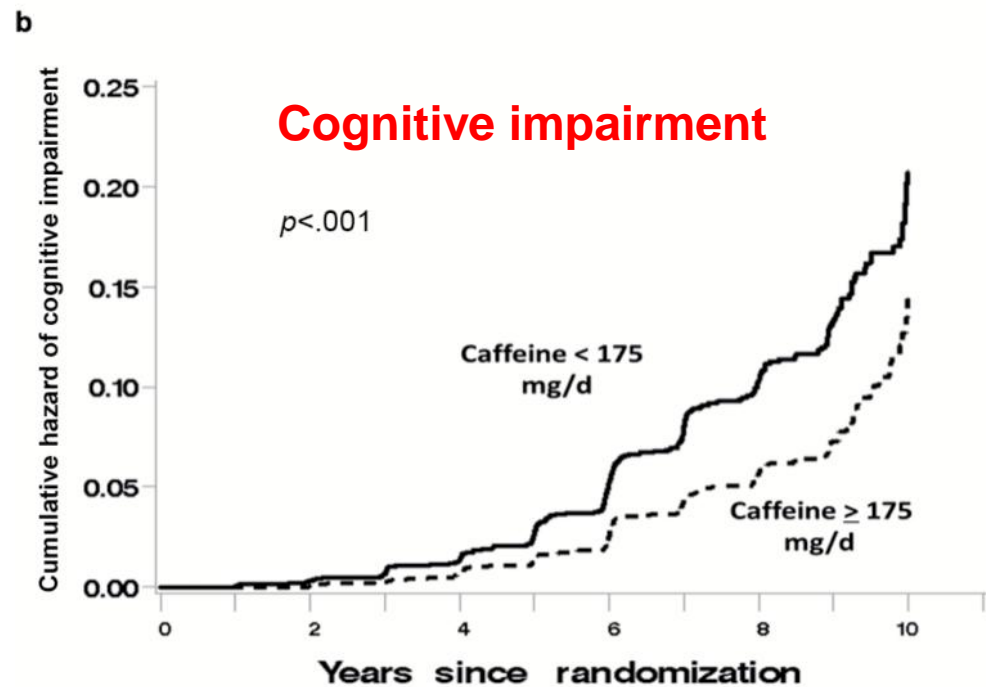
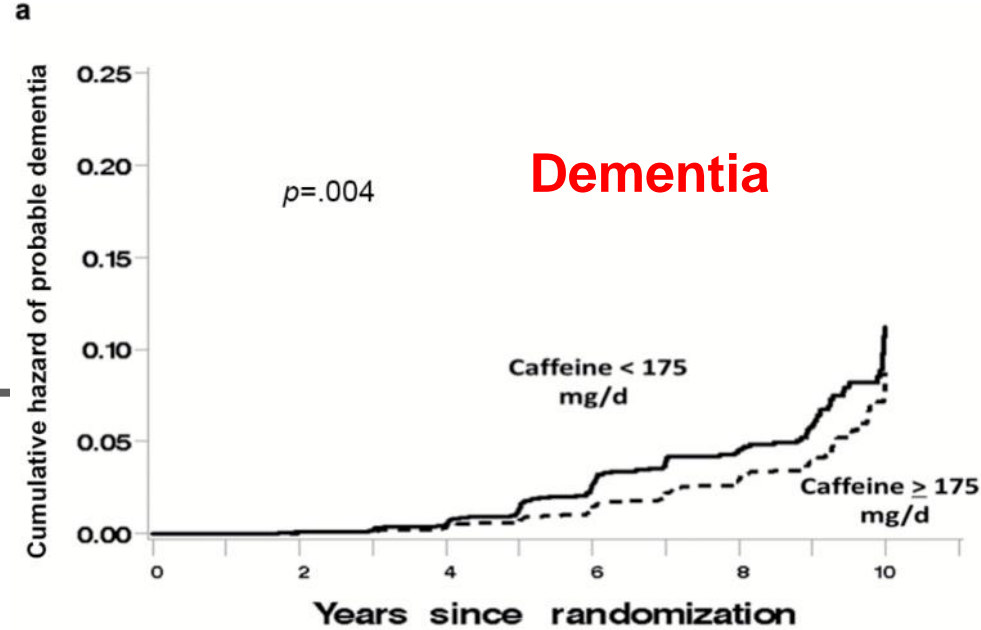


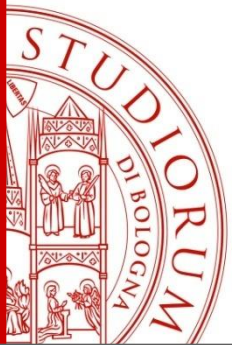


The Women's Health Initiative Memory Study

Association that baseline self-reported caffeine intake has with the distribution of times until
(a) probable dementia and
(b) composite cognitive impairment (mild cognitive impairment + dementia).

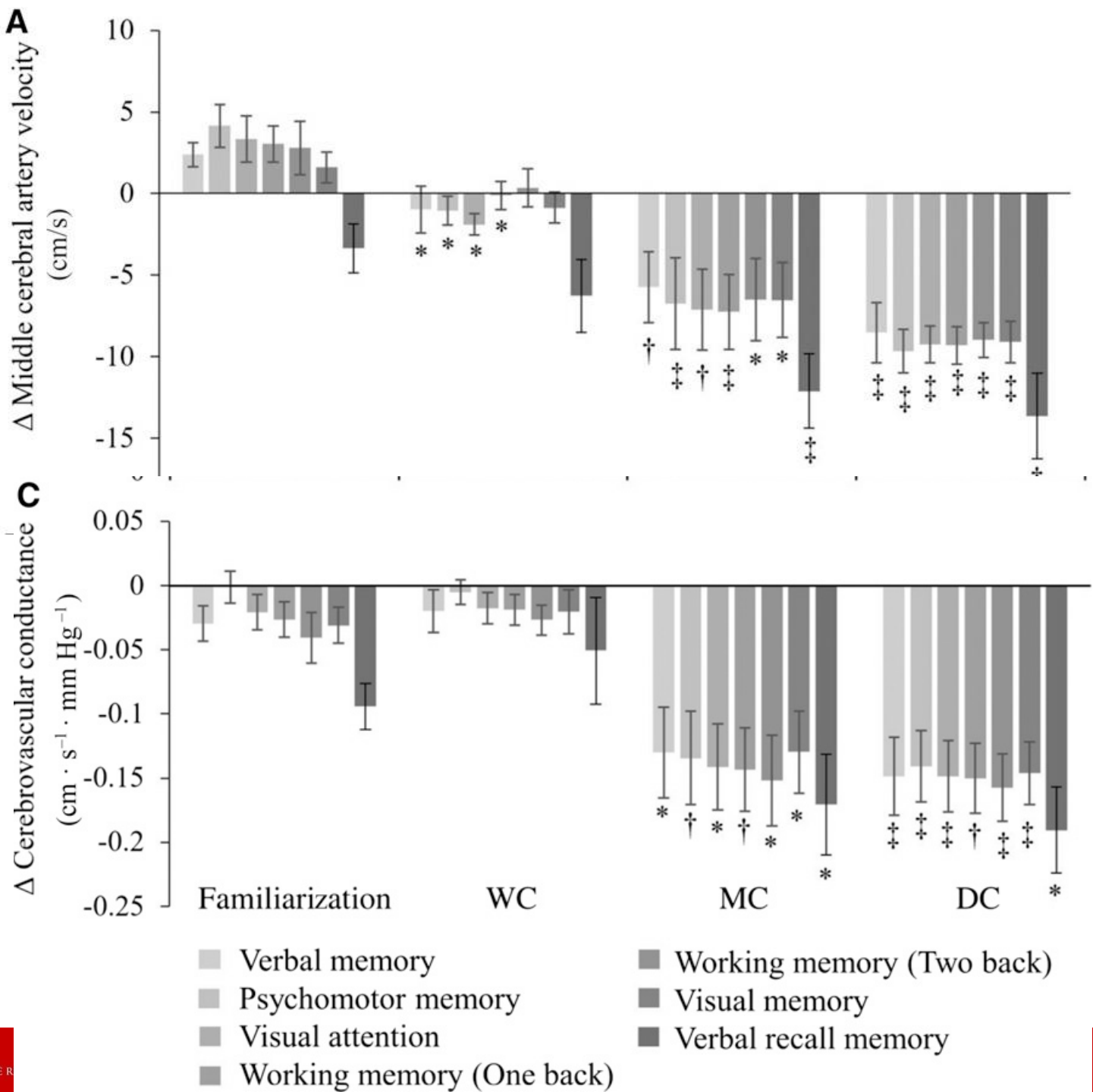
[J Gerontol A Biol Sci Med Sci. 2016; 71\(12\): 1596–1602.](#)





Impacts of chocolate containing different concentrations of cocoa on cerebral blood flow velocity in response to individual cognitive tasks performed by postmenopausal women

***J Nutr*
2017;147:
1686–92**



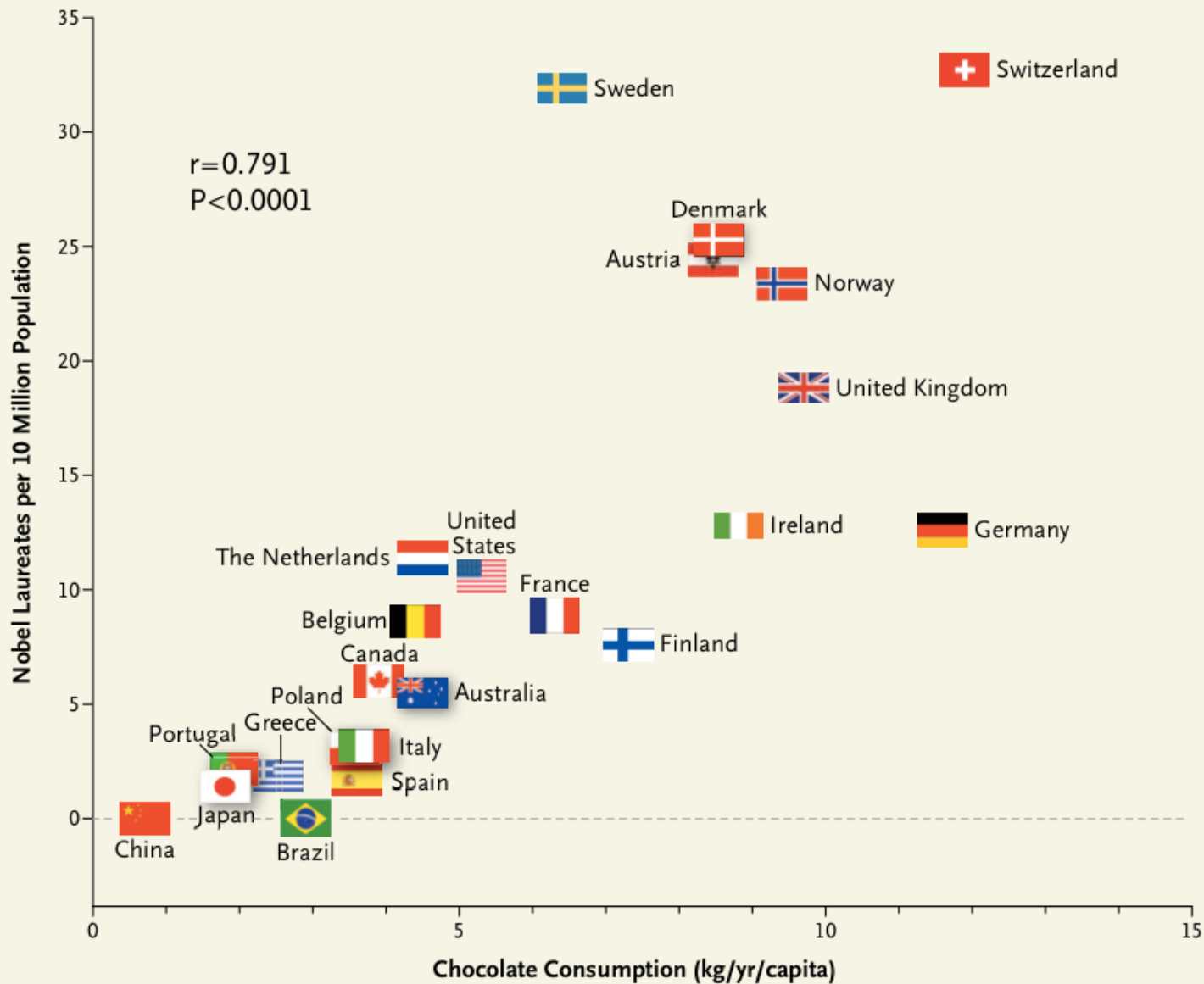
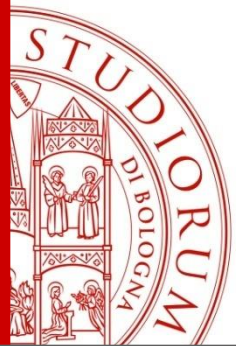
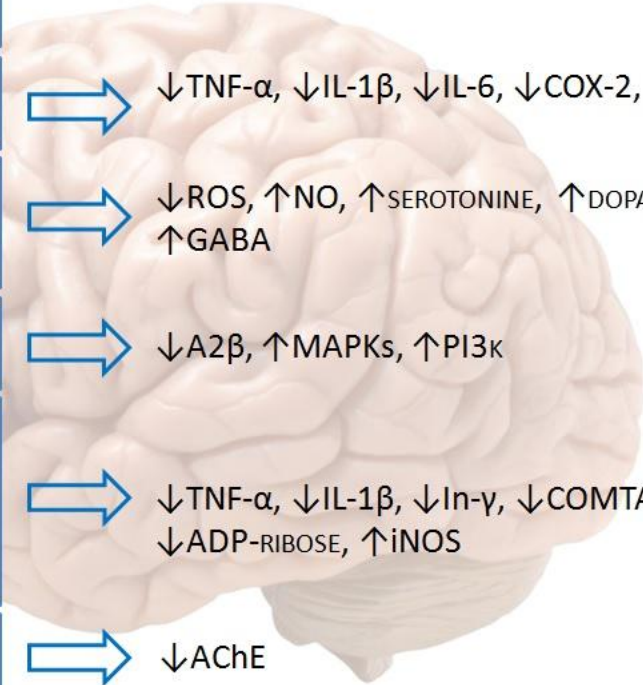


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.

Botanicals active on cognitive decline



<u>GINKGO BILOBA</u> <i>proanthocyanidins</i> <i>flavonol glycosides</i> <i>terpenoids</i>	⇒ ↓PAF, ↓iNOS
<u>VITIS VINIFERA</u> <i>trans-resveratrol</i>	⇒ ↓TNF- α , ↓IL-1 β , ↓IL-6, ↓COX-2, ↑NO
<u>CAMMELIA SINESIS</u> <i>epigallocatechin-3-gallate</i> <i>L-theanine</i>	⇒ ↓ROS, ↑NO, ↑SEROTONINE, ↑DOPAMINE, ↑GABA
<u>THEOBROMA CACAO</u> <i>cocoa flavanols</i>	⇒ ↓A2 β , ↑MAPKs, ↑PI3k
<u>BACCOPA MONNIERI</u> <i>bacoside A</i> <i>bacoside B</i> <i>alkaloids</i> <i>saponins</i>	⇒ ↓TNF- α , ↓IL-1 β , ↓In- γ , ↓COMT A2 β , ↓PE, ↓ADP-RIBOSE, ↑iNOS
<u>CROCUS SATIVUS</u> <i>crocin</i>	⇒ ↓AChE
<u>CURCUMA LONGA</u> <i>curcumin</i>	⇒ ↓AChE, ↓ γ -SECRETASE

**Cicero AF
et al.
Pharmacol
Res. 2017**

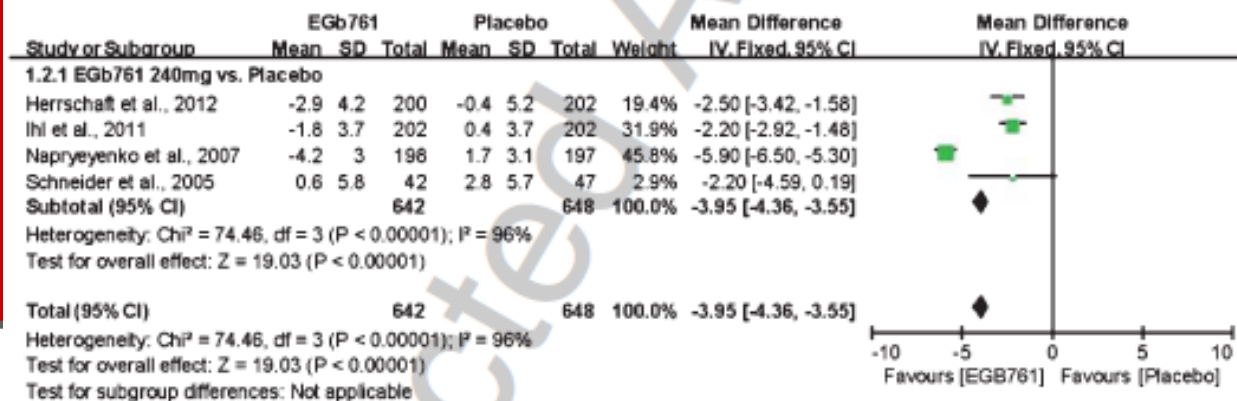


Gingko biloba: metanalysis of RCT

- **9 RCTs, 22–26 weeks duration, 2,561 patients.**
- **EGb761 at 240 mg/day is able to stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.**
- **No important safety concerns with EGb761.**

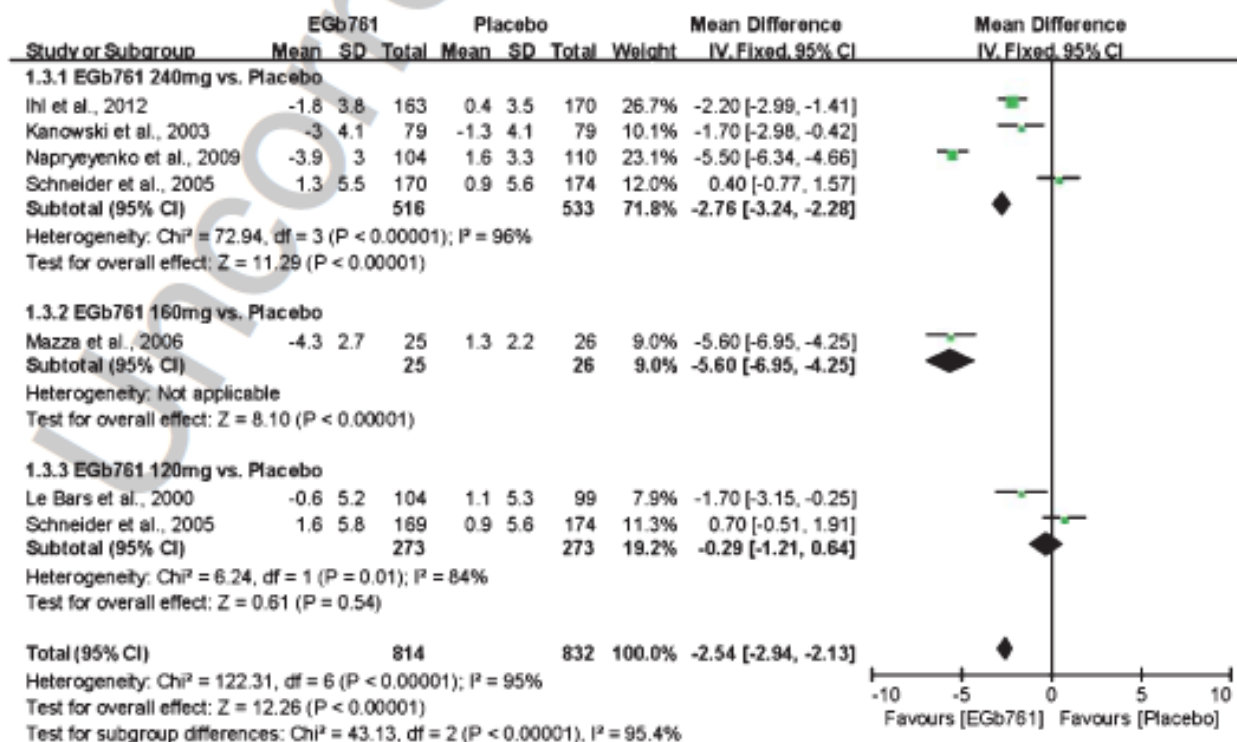
J Alzheimers Dis. 2015;43(2):589-603.

1.2 Patients with NPS subgroup



Efficacy on the ADAC Score

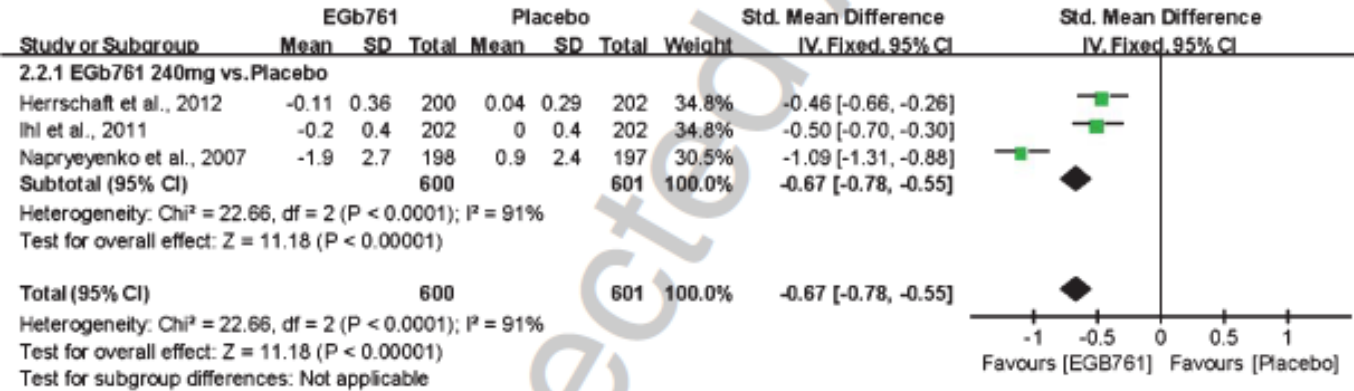
1.3 AD subgroup



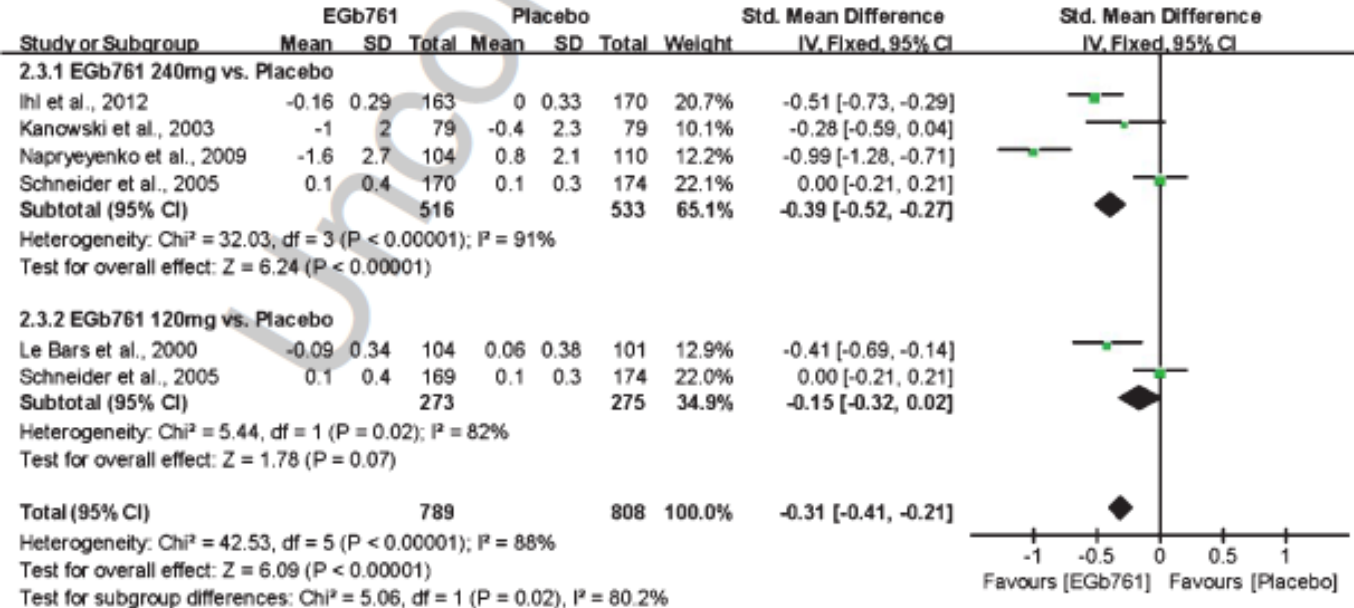
**J Alzheimers Dis.
2015;43(2):589-603.**

Efficacy on the ADL Score

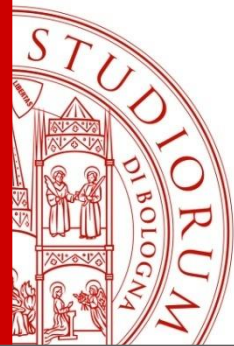
2.2 Patients with NPS subgroup



2.3 AD subgroup

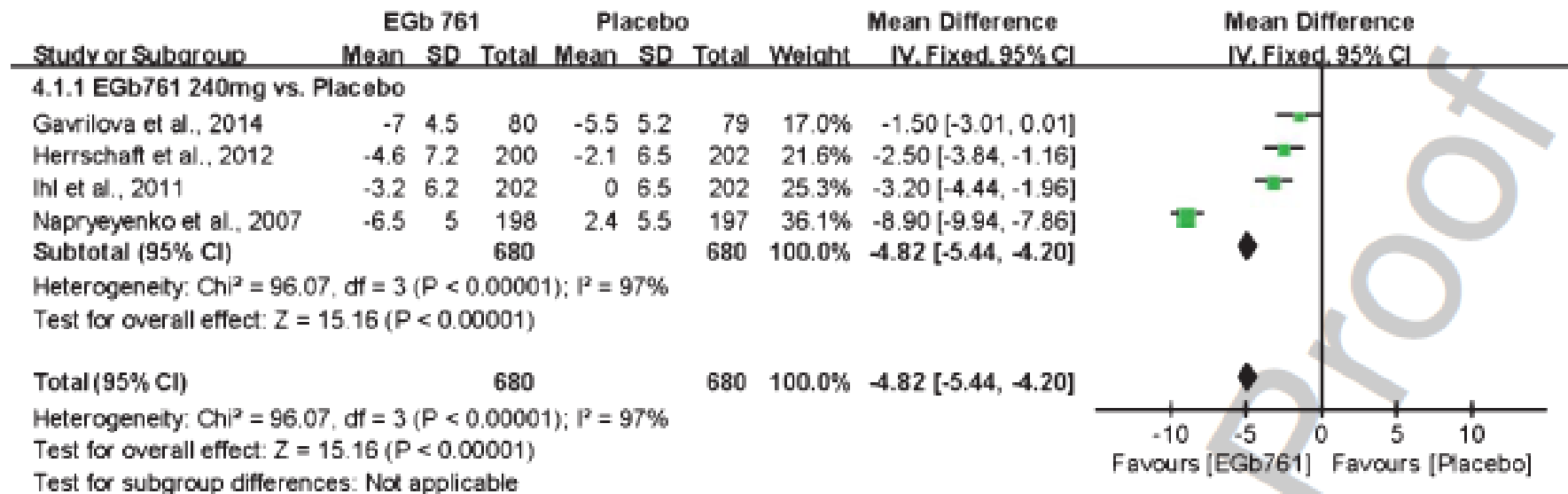


J Alzheimers
Dis. 2015;
43(2):589-603.

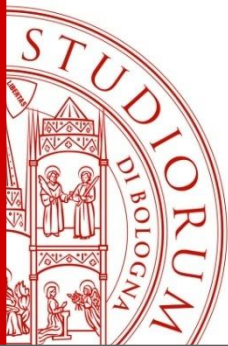


Efficacy on the NeuroPsychiatric Index (NPI) Score

4.1 Patients with NPS subgroup

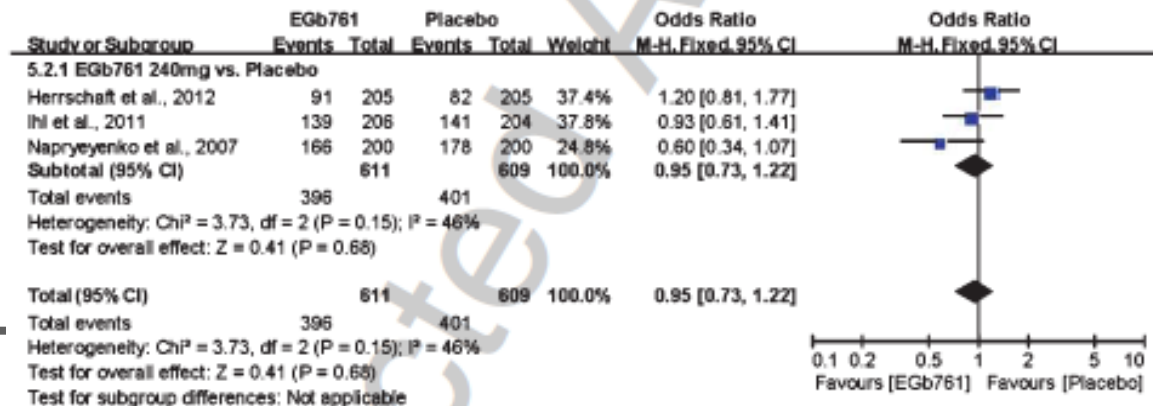


**J Alzheimers Dis.
2015;43(2):589-603.**

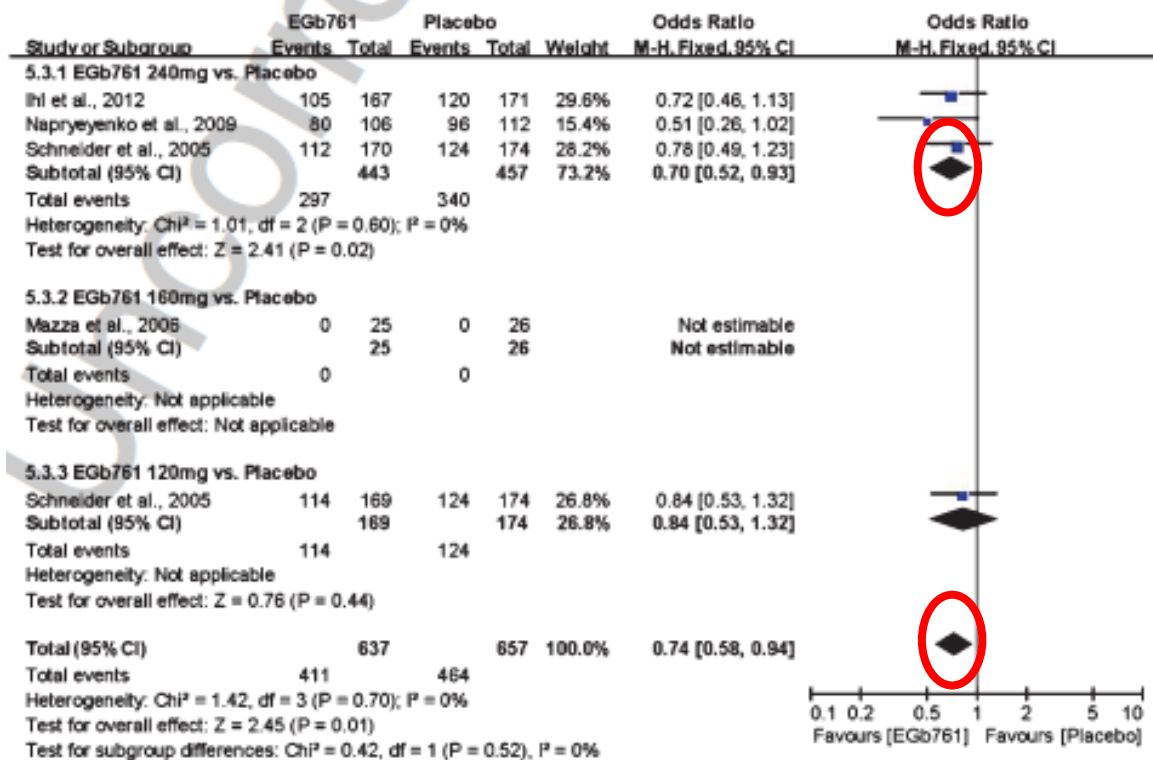


Adverse events

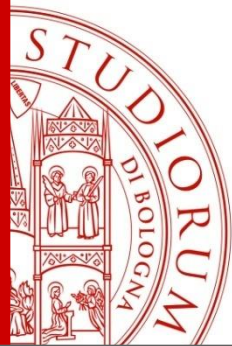
5.2 Patients with NPS subgroup



5.3 AD subgroup



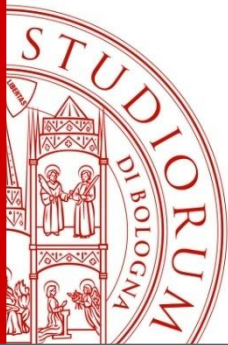
J Alzheimers Dis.
2015;43(2):589-603.



RCTs on resveratrol

Molecules 2016, 21, 1243

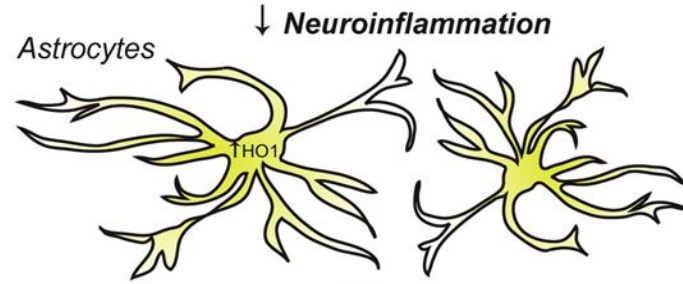
Reference or ID (Location)	Study Design	Resveratrol Preparation and Dose [Other Medication]	Duration	Subjects n Age Disorder/Status	Purpose Outcome Measures	Main Results
Kennedy et al. [111] (Newcastle upon Tyne, UK)	R, DB, PC, CO	<i>Trans</i> -resveratrol from Biotivia Bioceuticals (Vienna, Austria) 250 mg or 500 mg	21 days	24 18–25 years Healthy 9 further subjects underwent bioavailability assessment	To investigate the ability to modulate mental function and increase cerebral blood flow	Cognitive function not affected. <u>Increase in cerebral flow</u>
Wong et al. [112] (Adelaide, Australia) ACTRN1261100060943	R, DB, PC, CO	Resvida (resveratrol 75 mg/day)	12 weeks	28 45–70 years Obese but otherwise healthy	Effects of resveratrol on circulatory function and cognitive performance in obese adults	<u>Increase of circulatory function.</u> No effects on blood pressure, arterial compliance, and cognitive function
Witte et al. [113] (Berlin, Germany)	R, DB, PC,	Resveratrol 200 mg/day in a formula with quercetin	26 weeks	46 50–80 years Healthy overweight	To investigate the ability to enhance cognitive performance	<u>Significant retention of memory, significant increase of hippocampal FC, improvement of glucose metabolism</u>
Wightman et al. [114] (Newcastle upon Tyne, UK)	R, DB, PC, CO	<i>Trans</i> -resveratrol 250 mg/day or <i>trans</i> -resveratrol 250 mg/day with 20 mg piperine	21 days	23 19–34 years Healthy 6 healthy men underwent bioavailability assessment	To assess if piperine affects the efficacy and bioavailability of resveratrol	<u>Piperine enhances the effect of resveratrol on cerebral blood flow but not the cognitive performance and bioavailability</u>
Turner et al. [115] (Georgetown, USA) NCT01504854	R, DB, PC, MC Phase 2	Resveratrol 500 mg/day with dose escalation by 500 mg increments ending with 2 g/day	52 weeks	119 >49 years Mild-to-moderate AD	To assess safety and efficacy	<u>Decrease of CSF and plasma Aβ₄₀ levels.</u> No significant effects on cognitive score
Wong et al. [116] ACTRN12614000891628 (Newcastle, Australia)	R, DB, PC, CO Phase 2	Resvida 75 mg/day, 150 mg/day, 300 mg/day	4 weeks	36 40–80 years Type 2 diabetes mellitus	Improvement of cerebrovascular responsiveness	<u>Increase of cerebrovascular responsiveness</u>



Antioxidant activities

- ↓ ROS
- ↓ free radicals
- ↓ metals (i.e. copper)
- ↓ NO
- ↓ QR2 activity

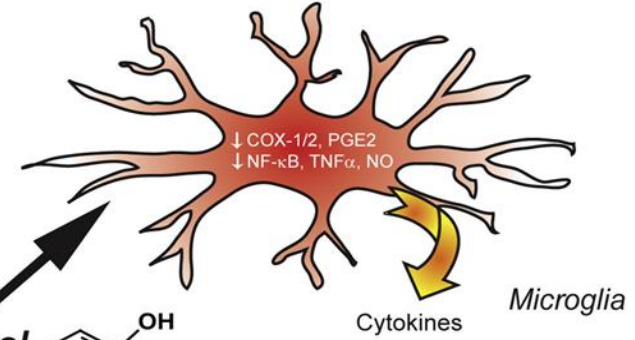
↑ glutathione peroxidase, HO1, AMPK, LKB1



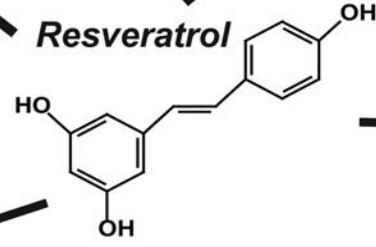
Sirtuins activator

AMPK
↓
NAD
↓
SIRT1
↓

- Akt → Cell survival
↓ Apoptosis
↓ Neuroinflammation
↓ Oxidative stress

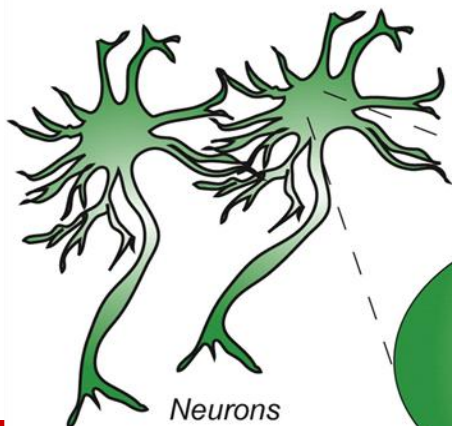


Resveratrol

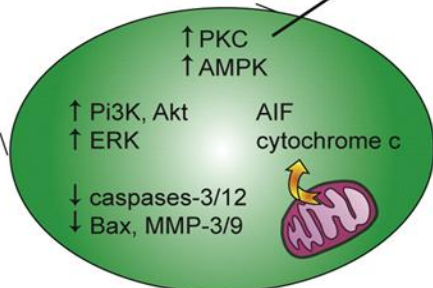
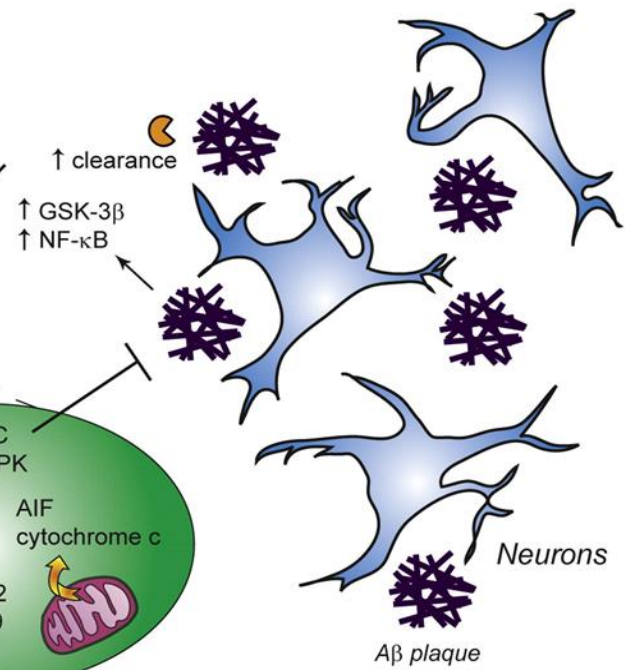


Synaptic plasticity

↑ neuronal interconnections

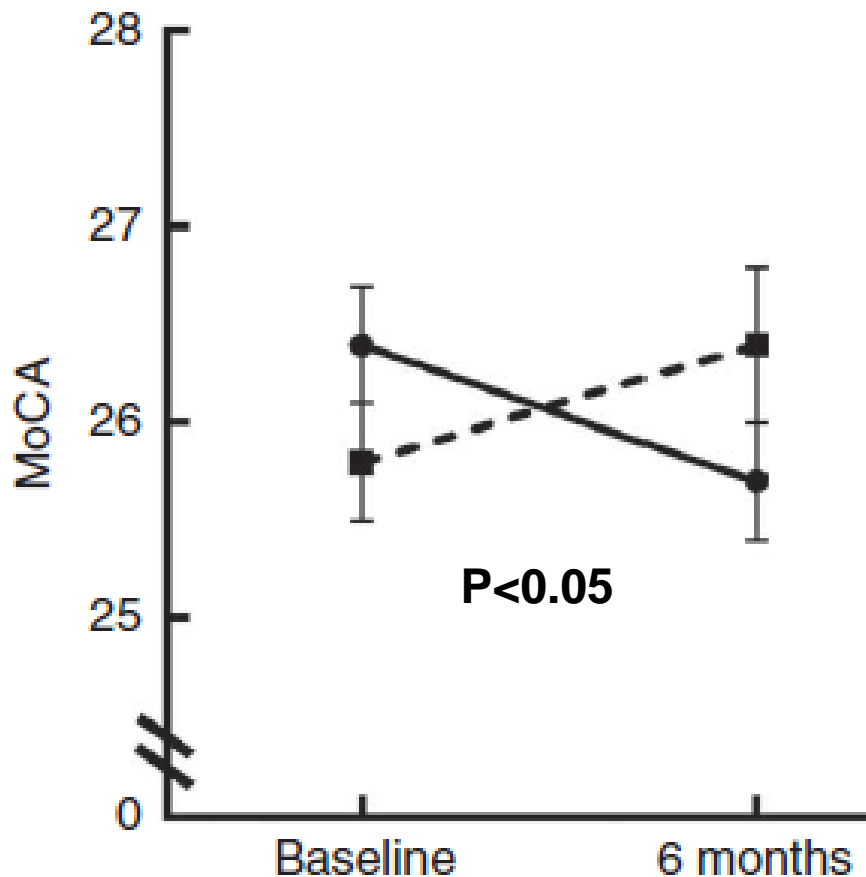
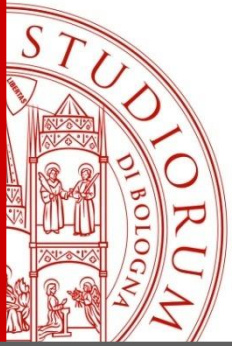


↓ **Amyloidogenesis**



Cicero et al. Arch Med Sci 2018; in press.

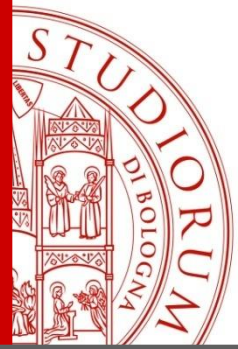
Curcumin and cognition: a RCT of community-dwelling older adults



Montreal Cognitive Assessment (MoCA) scores (adjusted for age, sex, years of education and APOE ε4 allele carriage)

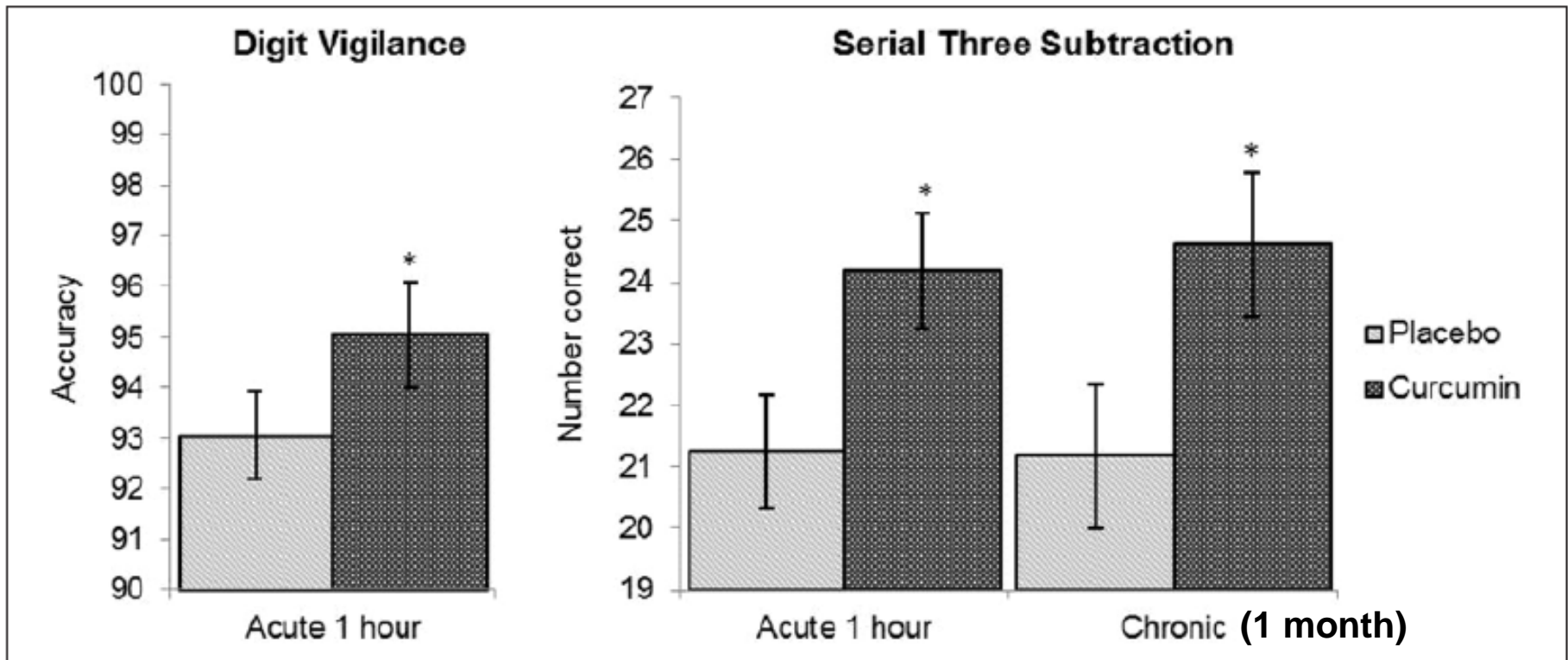
—■—, Curcumin group; —●—, placebo group.

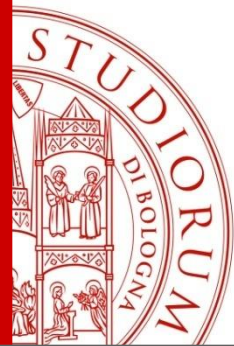
British Journal of Nutrition (2016), **115**, 2106–2113



Effects of solid lipid curcumin 400 mg on cognition and mood in 60 healthy elderly (60-85 yo)

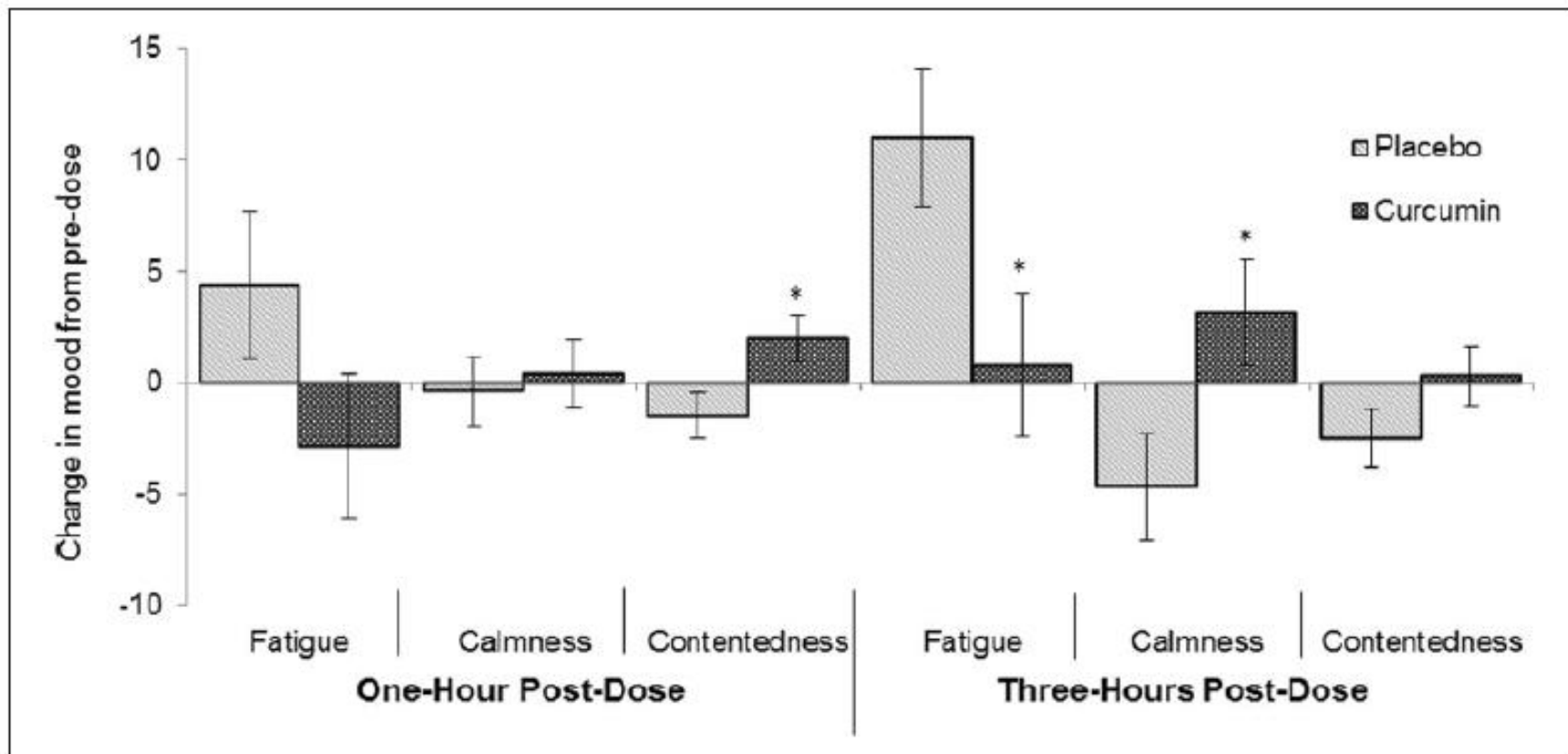
[J Psychopharmacol.](#) 2015 May;29(5):642-51



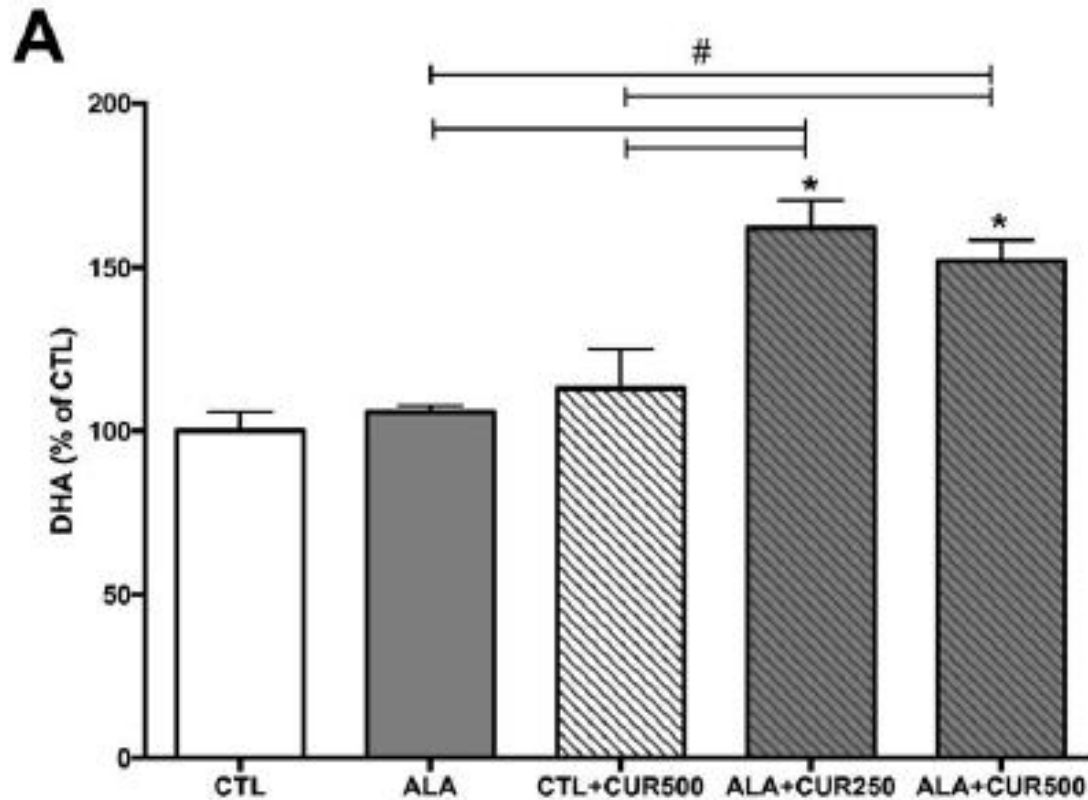


Effects of solid lipid curcumin 400 mg on cognition and mood in 60 healthy elderly (60-85 yo)

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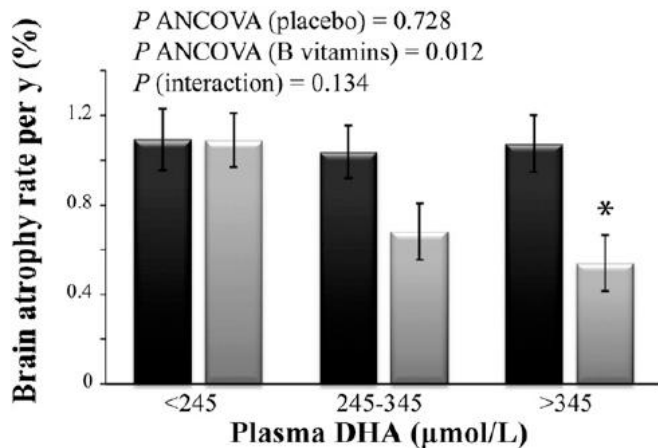
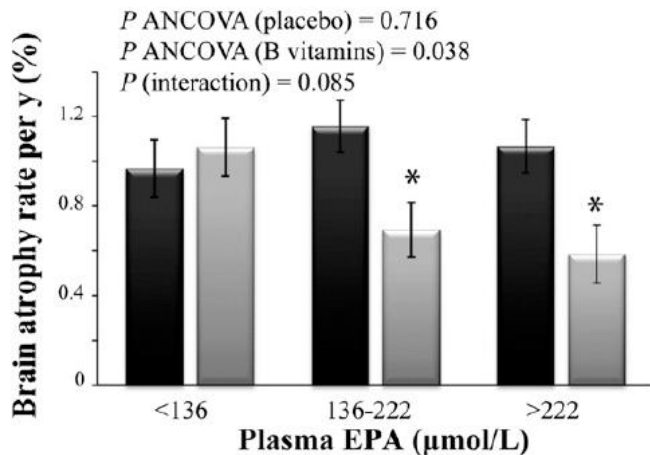
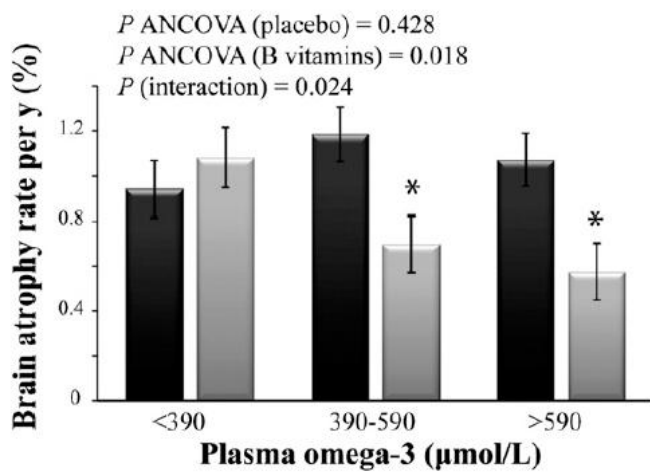


Curcumin boosts DHA in the brain: implications for the prevention of anxiety disorders



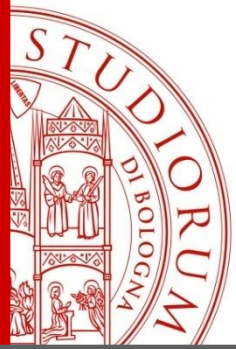
Biochim Biophys Acta. 2015;
1852(5): 951–961.

Omega 3 and B vitamins

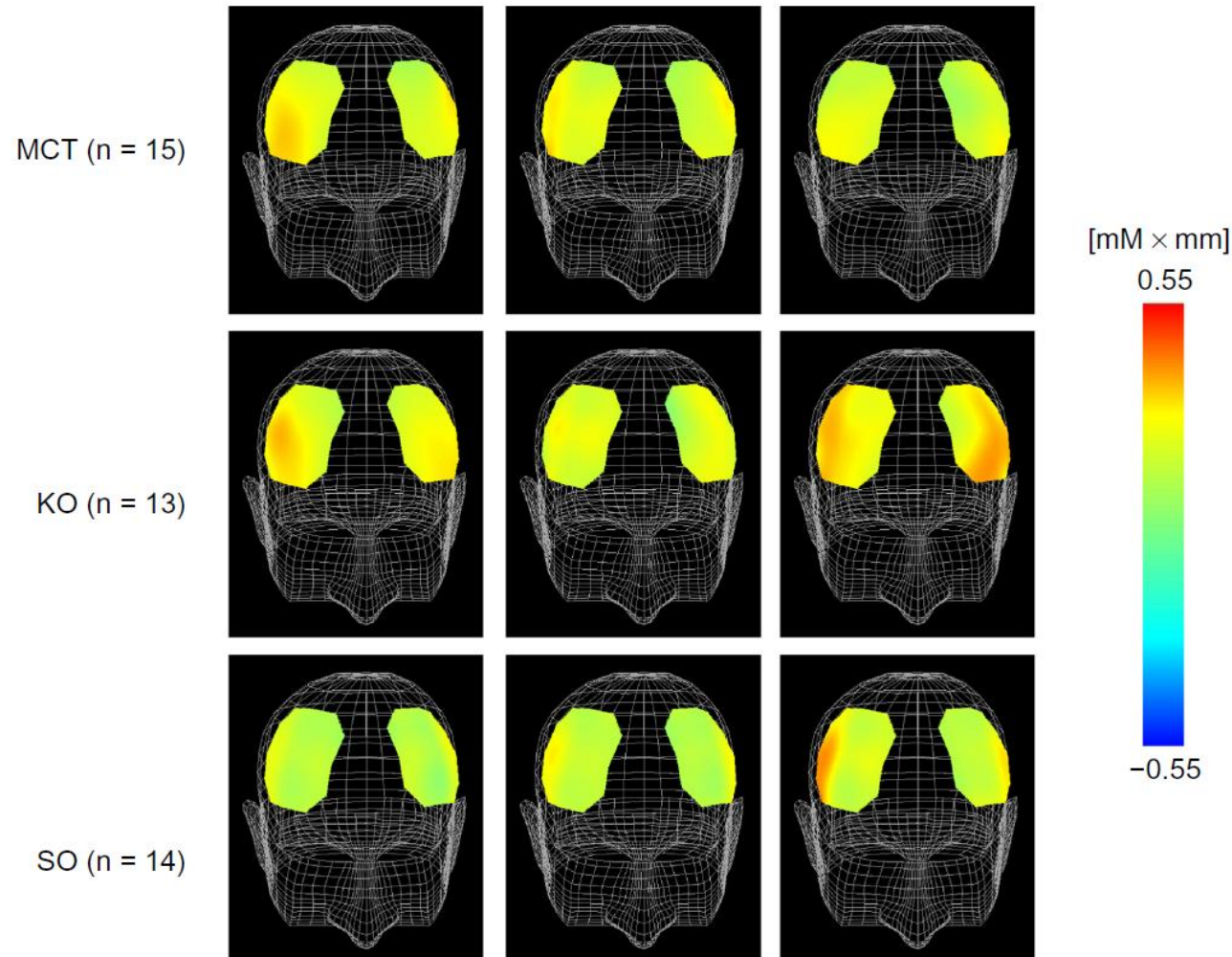


Brain atrophy rates (mean \pm 6 SEM) among subjects receiving placebo (black) and high-dose B vitamins (gray) according to tertiles of plasma baseline combined ω -3 (top)

Am J Clin Nutr 2015;102:215–21.

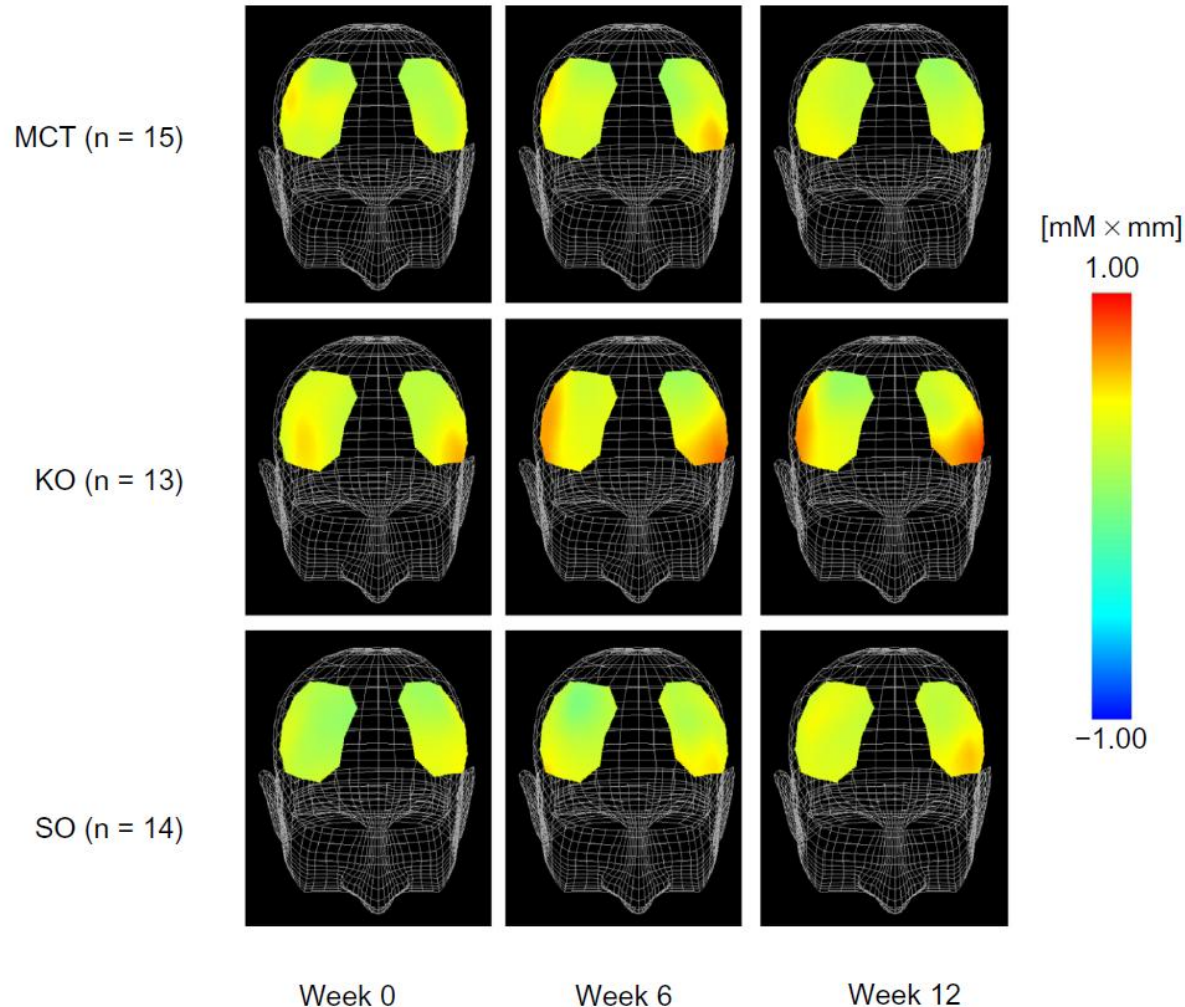


Topographic maps of changes in oxy-hb concentration at 225.0 seconds during working memory task



**Clin Interv Aging
2013:8 1247–1257**

Topographic maps of changes in oxy-hb concentration at 150.0 seconds during the calculation task



**Clin Interv Aging
2013:8 1247–1257**

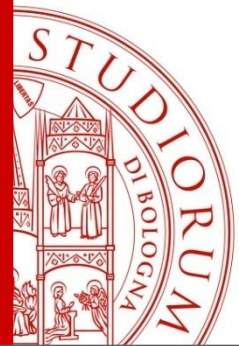


A multicomponent approach: the possible solution?

Gingko + DHA + Vitamin B

Variable	Baseline Mean (SD)	Six Months Mean (SD)	Adjusted Mean (SD)	p Value
Cognition				
MOT latency (ms)				
Placebo	1171 (276)	1162 (180)	1170 (162)	.038
Intervention	1171 (275)	1058 (190)	1052 (162)	
VRM immediate free recall (words)				
Placebo	9.2 (1.7)	8.0 (2.2)	7.7 (1.7)	.029
Intervention	8.7 (2.3)	8.8 (2.1)	9.0 (1.7)	
Mobility				
HW Speed (m/s)				
Placebo	1.35 (0.20)	1.32 (0.15)	1.29 (0.08)	.031
Intervention	1.30 (0.24)	1.33 (0.25)	1.36 (0.10)	

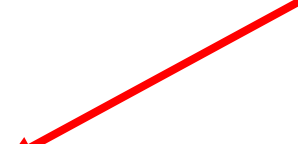
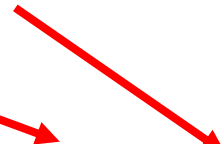
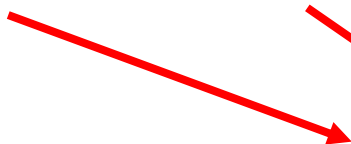
J Gerontol A Biol Sci Med Sci, 2016;71(2):236–242



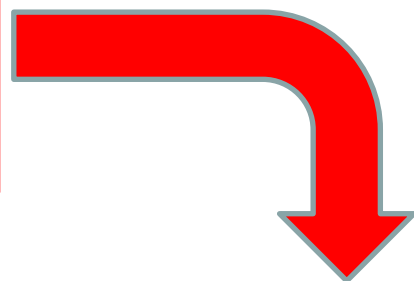
Età

Disnutrizione

Malassorbimento

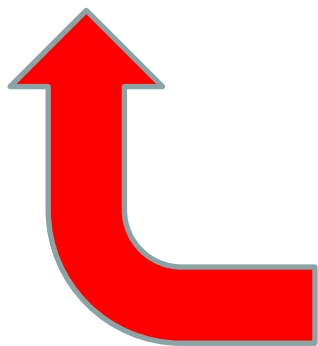


**Declino
cognitivo**

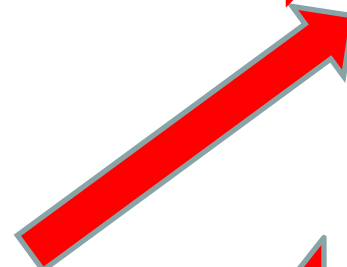


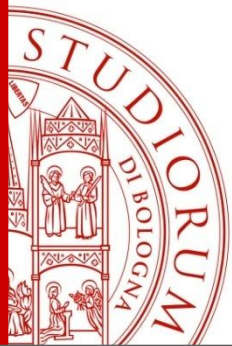
**Declino
cognitivo
percepito**

Depression

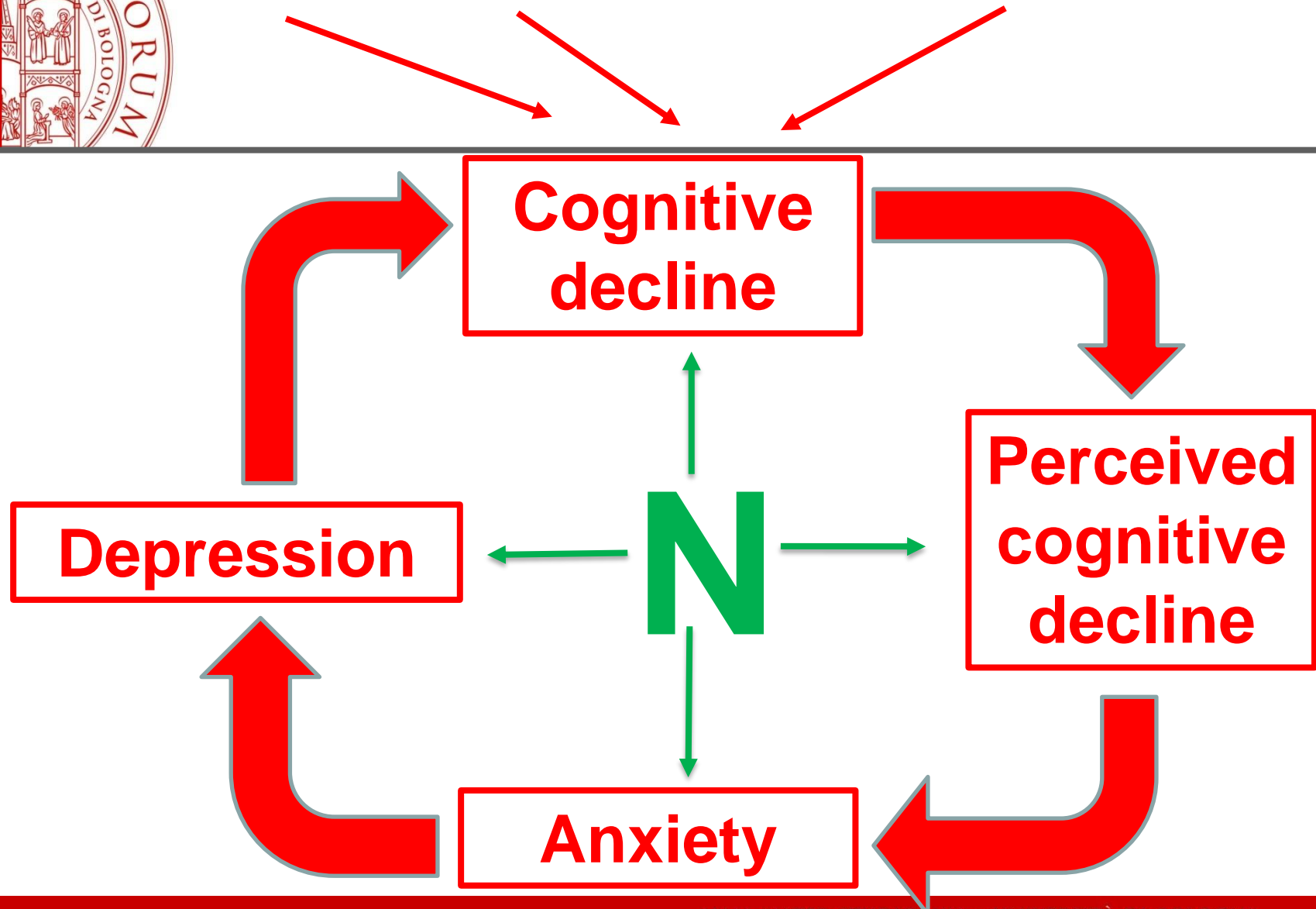


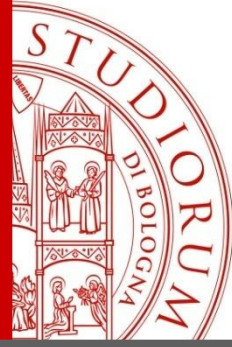
Ansia





Age Lifestyle Malabsorption





Età **Disnutrizione** **Malassorbimento**

VITAMINE B6, B9, B12, H, D, Rame

Declino cognitivo

Declino cognitivo percepito

CROCUS



Depressione



BACOPA

TEANINA



Alzheimer

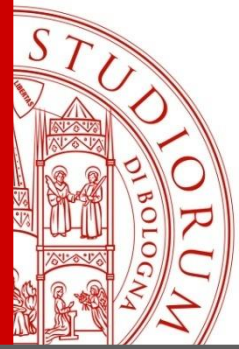
An Acute, Double-Blind, Placebo-Controlled Crossover Study of 320 mg and 640 mg Doses of a Special Extract of *Bacopa monnieri* (CDRI 08) on Sustained Cognitive Performance

Luke A. Downey,¹ James Kean,¹ Fiona Nemeh,¹ Angela Lau,¹ Alex Poll,¹ Rebecca Gregory,¹ Margaret Murray,¹ Johanna Rourke,¹ Brigit Patak,¹ Matthew P. Pase,¹ Andrea Zangara,^{1,2} Justine Lomas,¹ Andrew Scholey¹ and Con Stough^{1*}

¹Centre for Human Psychopharmacology, Swinburne University of Technology, Melbourne, Australia

²Soho Flordis International, Sydney, Australia

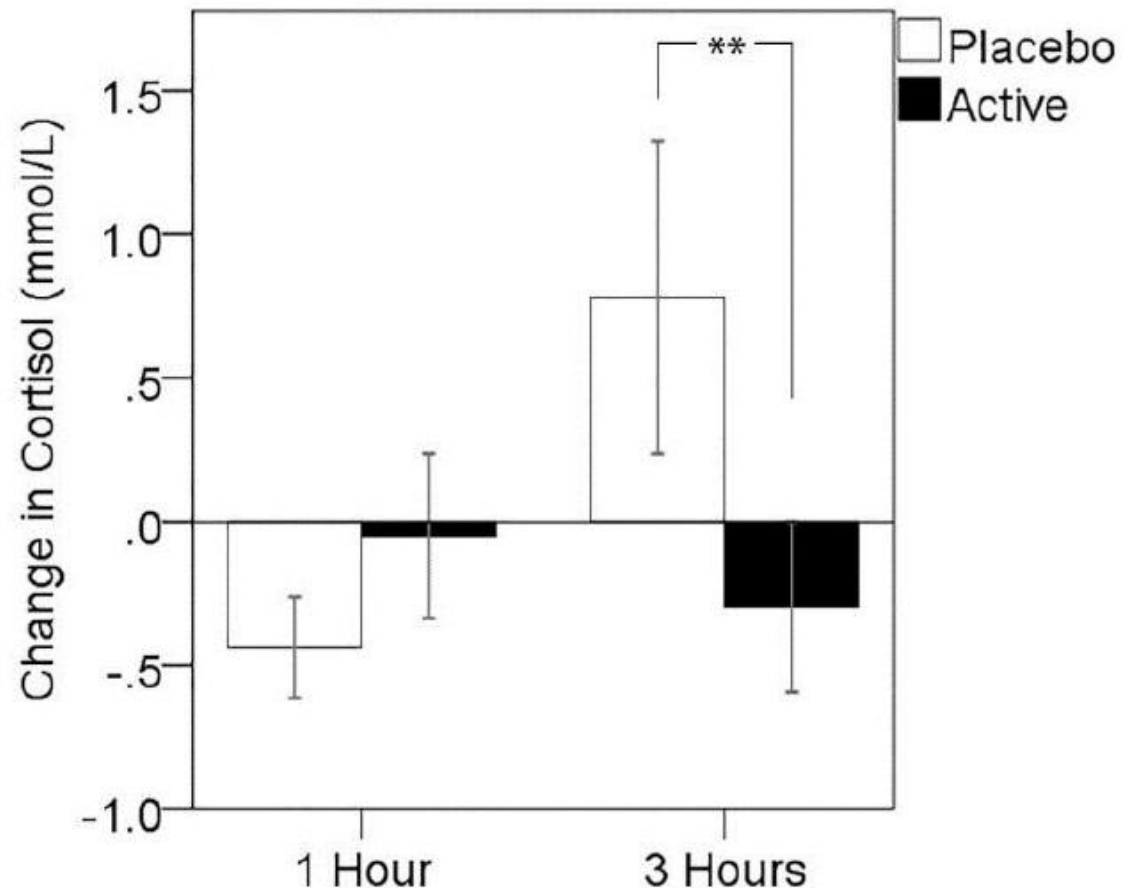
Standardized extracts of the traditional Ayurvedic medicine *Bacopa monnieri* (BM) (Brahmi) have been recently shown to have cognitive enhancing effects in chronic administration studies. Pre-clinical work has also identified a number of acute anxiolytic, nootropic, and cardiovascular effects of BM. There has, however, been little research on the acute effects of BM on cognitive function. The current study aimed to assess the acute effects of a specific extract of BM (KeenMind[®] - CDRI 08) in a double-blind, placebo-controlled study in normal healthy participants who completed a cognitively demanding series of tests. Twenty-four healthy volunteers completed six repetitions of the Cognitive Demand Battery (CDB) after consuming a placebo, 320 mg BM or 640 mg of BM in a cross-over design and provided cardiovascular and mood assessments before and after treatment. Change from baseline scores indicated that the 320 mg dose of BM improved performance at the first, second, and fourth repetition post-dosing on the CDB, and the treatments had no effect upon cardiovascular activity or in attenuating task-induced ratings of stress and fatigue. It was concluded that assessment of an earlier pharmacological window and use of less memory-specific cognitive tests together with more temporally sensitive measures of brain activity may improve our understanding of the acute neurocognitive properties of BM. Copyright © 2012 John Wiley & Sons, Ltd.

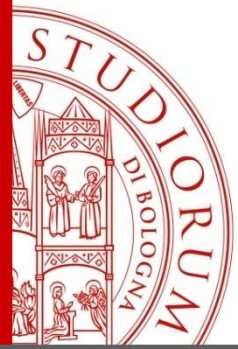


Anti-Stress Effects of L-Theanine: A Randomised, Double-Blind, Placebo-Controlled, Crossover Trial

Change in cortisol from pre- to post-stressor for both post-dose assessments and treatment visits

Nutrients 2016, 8, 53;
doi:10.3390/nu8010053

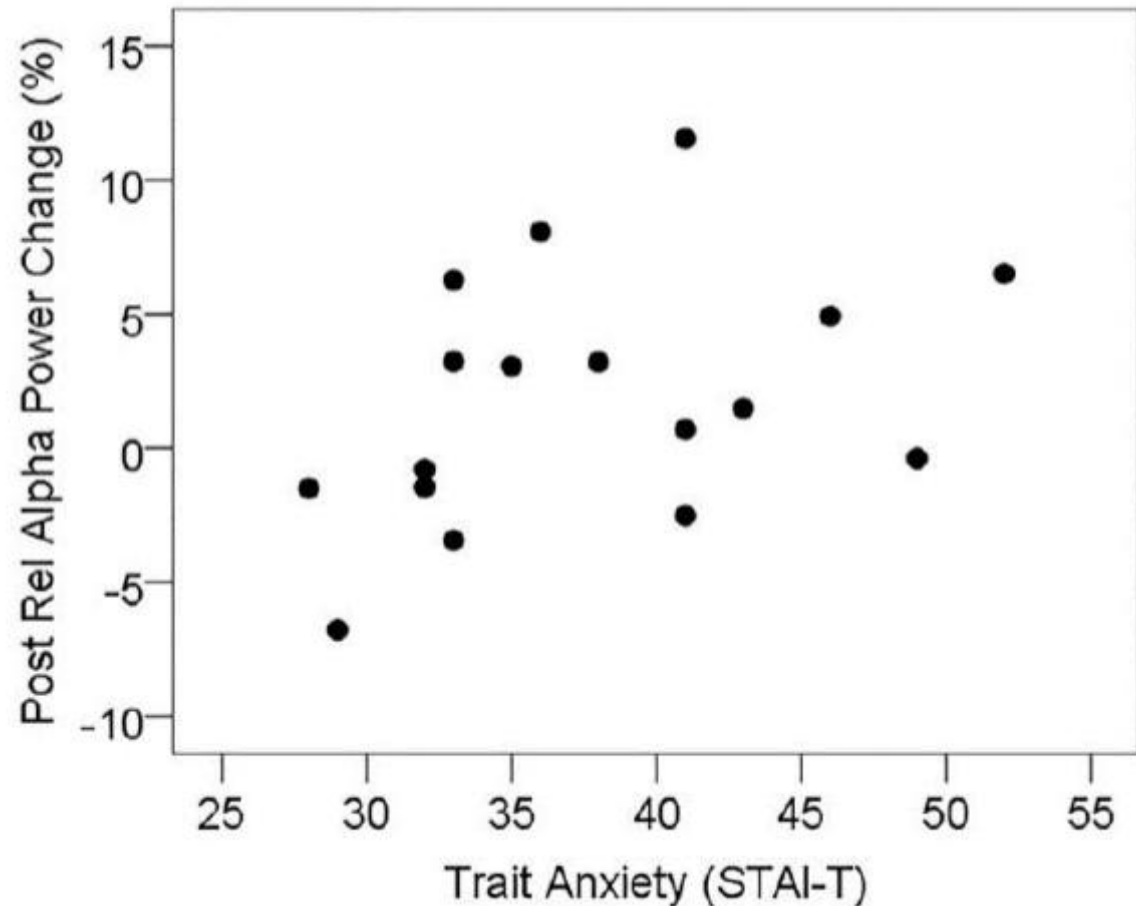




Anti-Stress effects of L-Theanine: the impact on magnetoencephalography

Association between trait anxiety and treatment-related change in resting relative alpha power in posterior sensor sites (positive change = increased alpha during active treatment visit).

Nutrients 2016, 8, 53;
doi:10.3390/nu8010053





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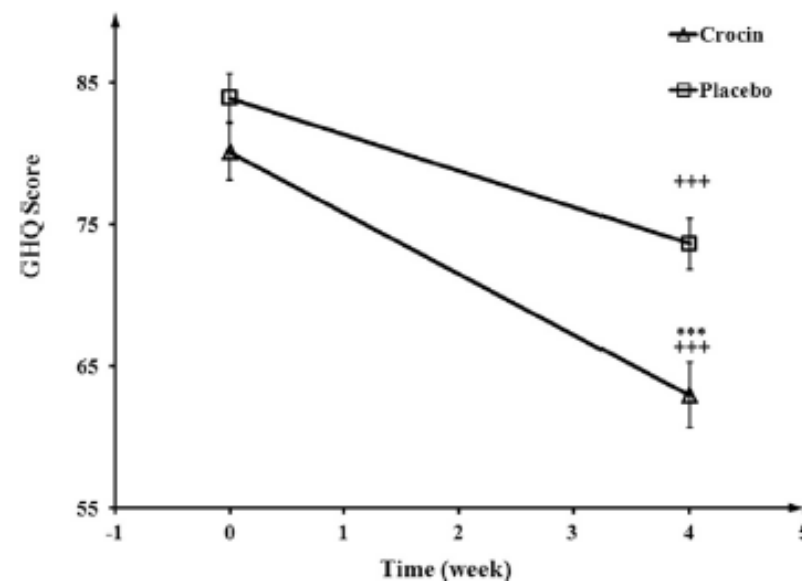
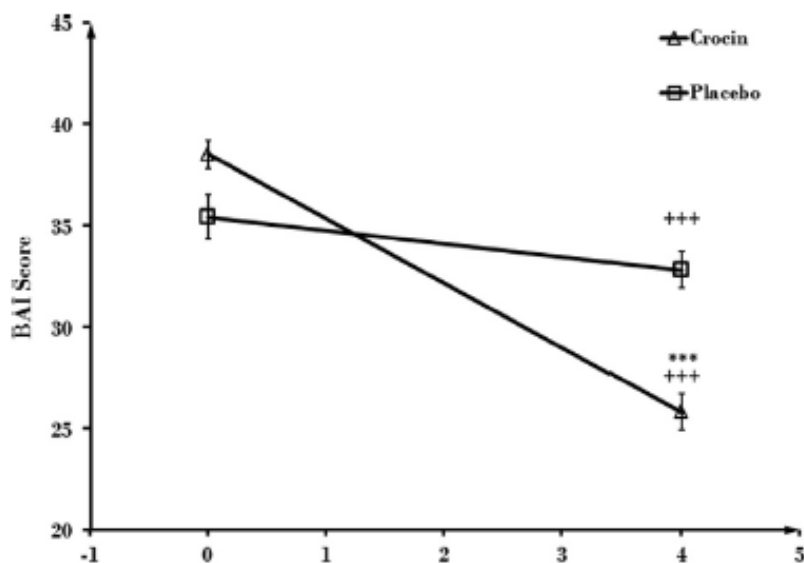
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Journal of Affective Disorders

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Research report




Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial



Short-Term Impact of a Combined Nutraceuticals on Cognitive Function, Perceived Stress and Depression in Young Elderly with Cognitive Impairment: A Pilot, Double-Blind, Randomized Clinical Trial

A.F. Cicero¹, M. Bove¹, A. Colletti¹, M. Rizzo², F. Fogacci¹, M. Giovannini¹, C. Borghi¹

Table 2. Modification of the biometric test carried out on the volunteers in both groups of treatment

	Active		Placebo	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
MMSE	23.1±0.9	24.5±1.0*° 	23.2±1.1	23.1±0.9
PSQ Index	2.7±0.4	2.2±0.7*° 	2.6±0.8	2.4±0.9
SRDS	42.8±8.4	37.1±7.6* 	43.6±9.3	40.9±8.8*

*P<0.05 Vs. baseline ; ° P<0.05 Vs. placebo

*Mini-Mental State Examination

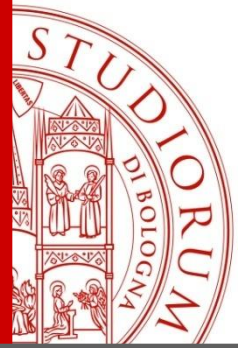
*Perceived Stress Questionnaire Index

*Self-rating Depression Scale



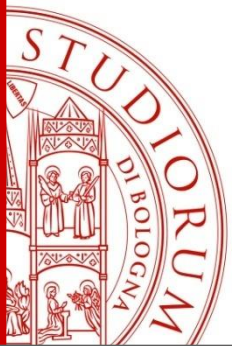
Interesting results but ...

- **Short term studies (compared with disease pathogenesis)**
- **Small studies (compared with large patient heterogeneity)**
- **Different botanical extracts (doses and bioavailability not always adequate)**
- **Risk factors not always optimized at the baseline !**
- **... beyond that they function !!!**



Patient target for the nutraceutical approach

- **>60 years (but also before)**
- **With perceived cognitive decline**
- **Asking help to manage the problem**
- **With psychological co-morbidity**
- **With cardiovascular disease risk factors**



ALMA MATER STUDIORUM - UNIVERSITÀ DI BOLOGNA

IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI