

Medical food

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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

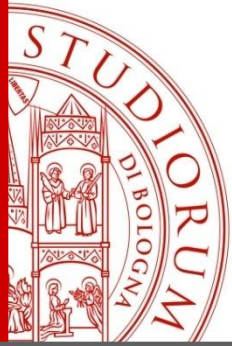
Mild cognitive decline. A position statement of the Cognitive Decline Group of the European Innovation Partnership for Active and Healthy Ageing (EIPAHA)

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

Age Lifestyle Malabsorption

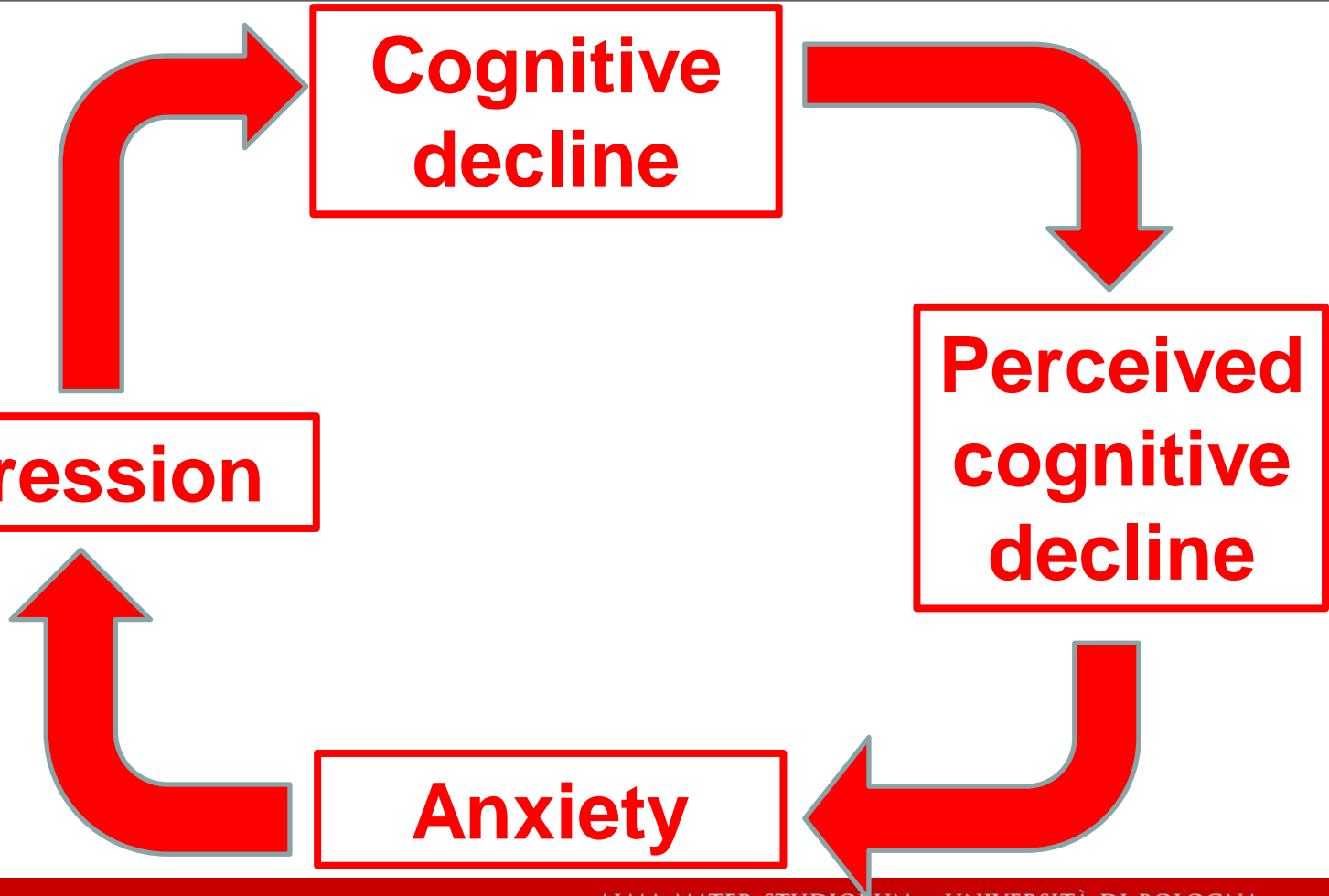


Cognitive decline

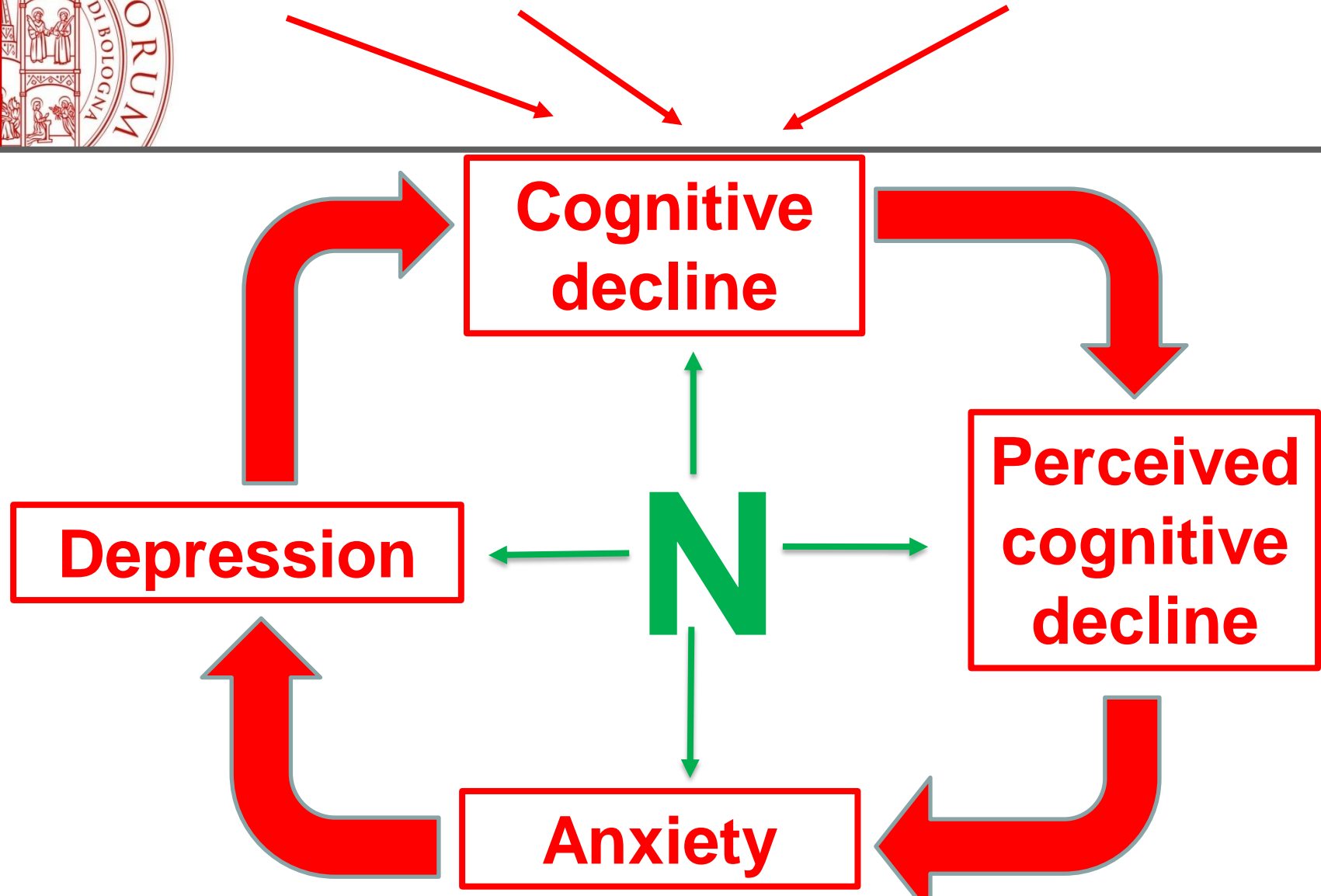
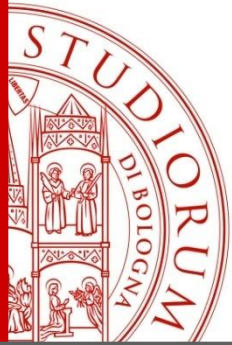
Perceived cognitive decline

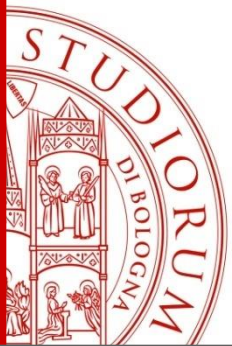
Depression

Anxiety




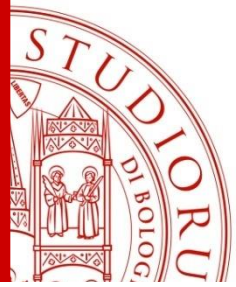
Age Lifestyle Malabsorption





A time-less war...

Epidemiology  **RCTs**



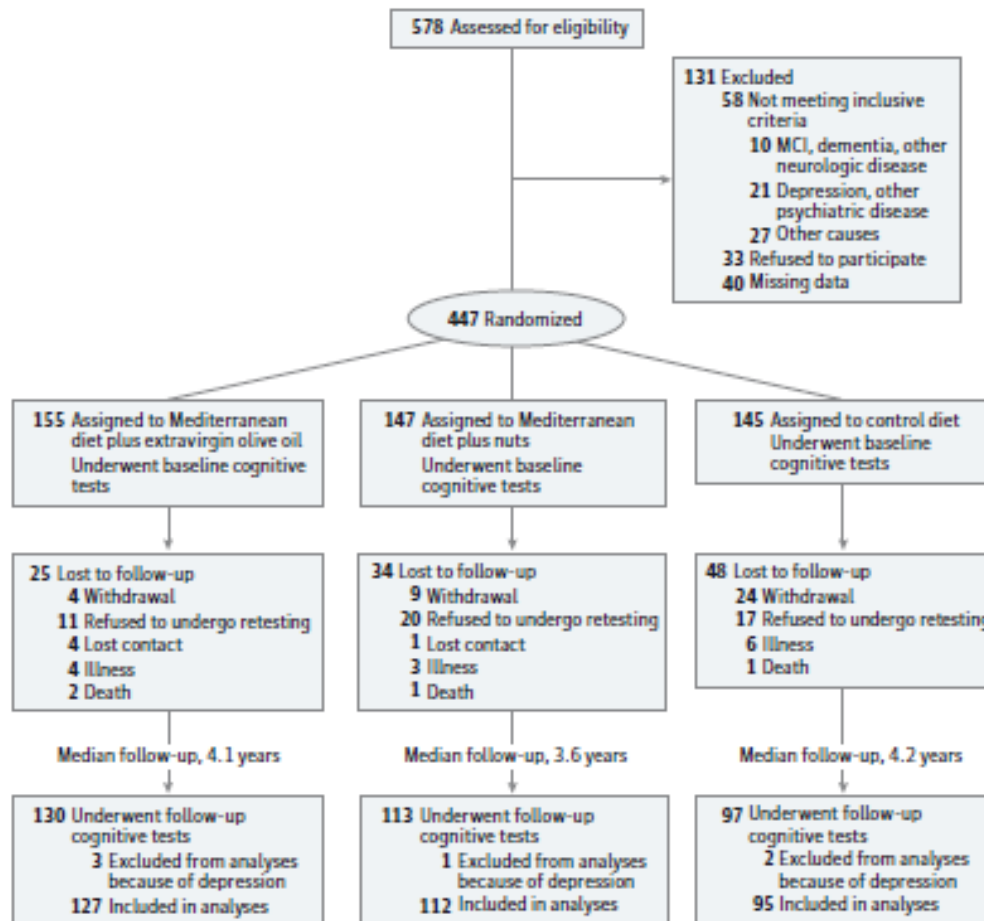
The «healthy diet»

Box 1 Milestones of a Healthy Diet

- Total energy intake proportional to physical activity
- Low salt intake
- Carbohydrates with low glycemic index as the main source of energy
- Very low intake of simple sugars
- Large intake of water, fresh vegetables, legumes, and berries
- Fish and nuts and moderate amount of nonprocessed meat
- Moderate doses of dairy products (preferably fermented, rich in probiotics, and low-fat)
- Coffee, high-quality dark chocolate, and low quantity of alcohol (from either wine or beer) not forbidden

Mediterranean Diet and Age-Related Cognitive Decline

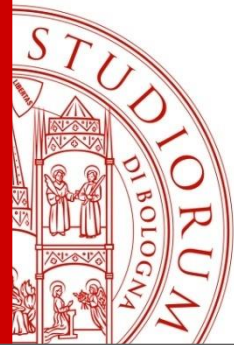
A Randomized Clinical Trial



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

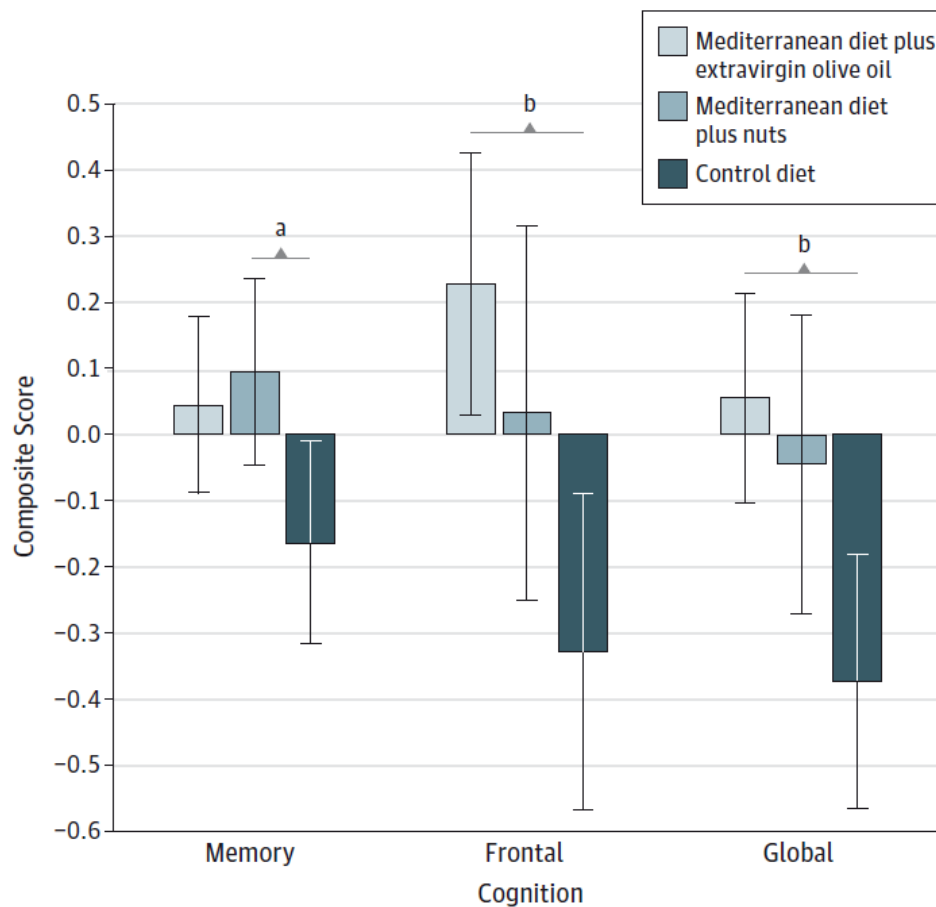
Median follow-up: 4.1 years

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

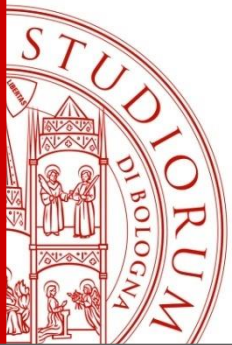


Mediterranean Diet and Age-Related Cognitive Decline

A Randomized Clinical Trial

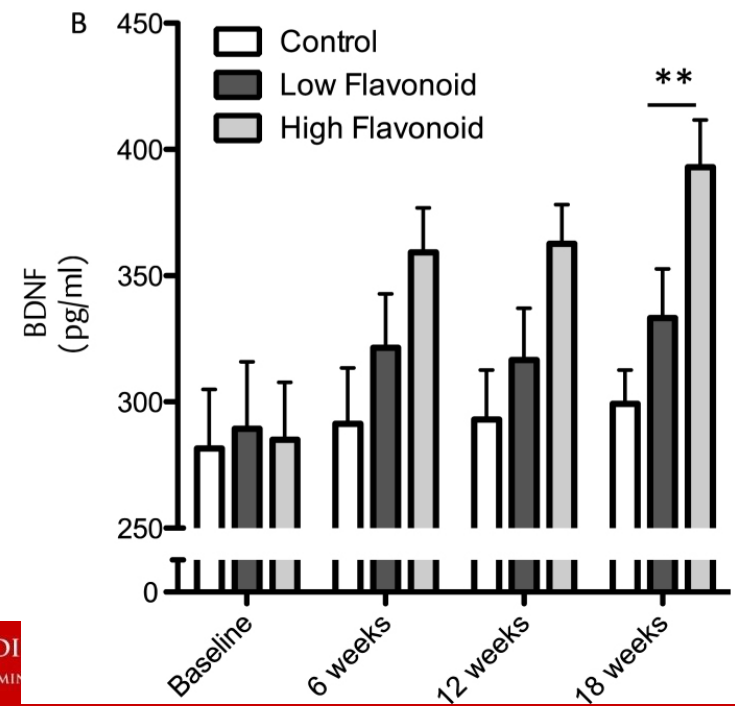
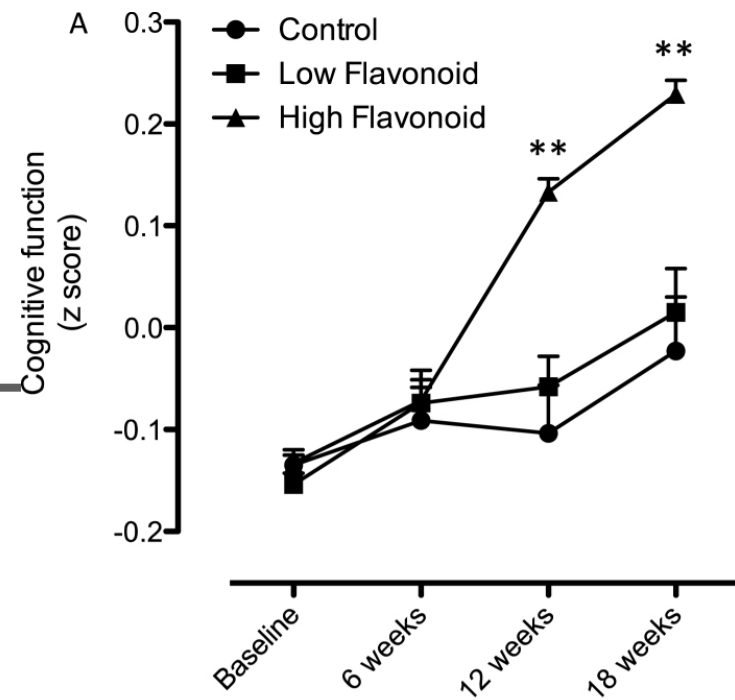


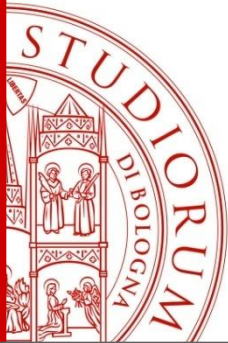
JAMA Intern Med.
2015;175(7):1094-
1103



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

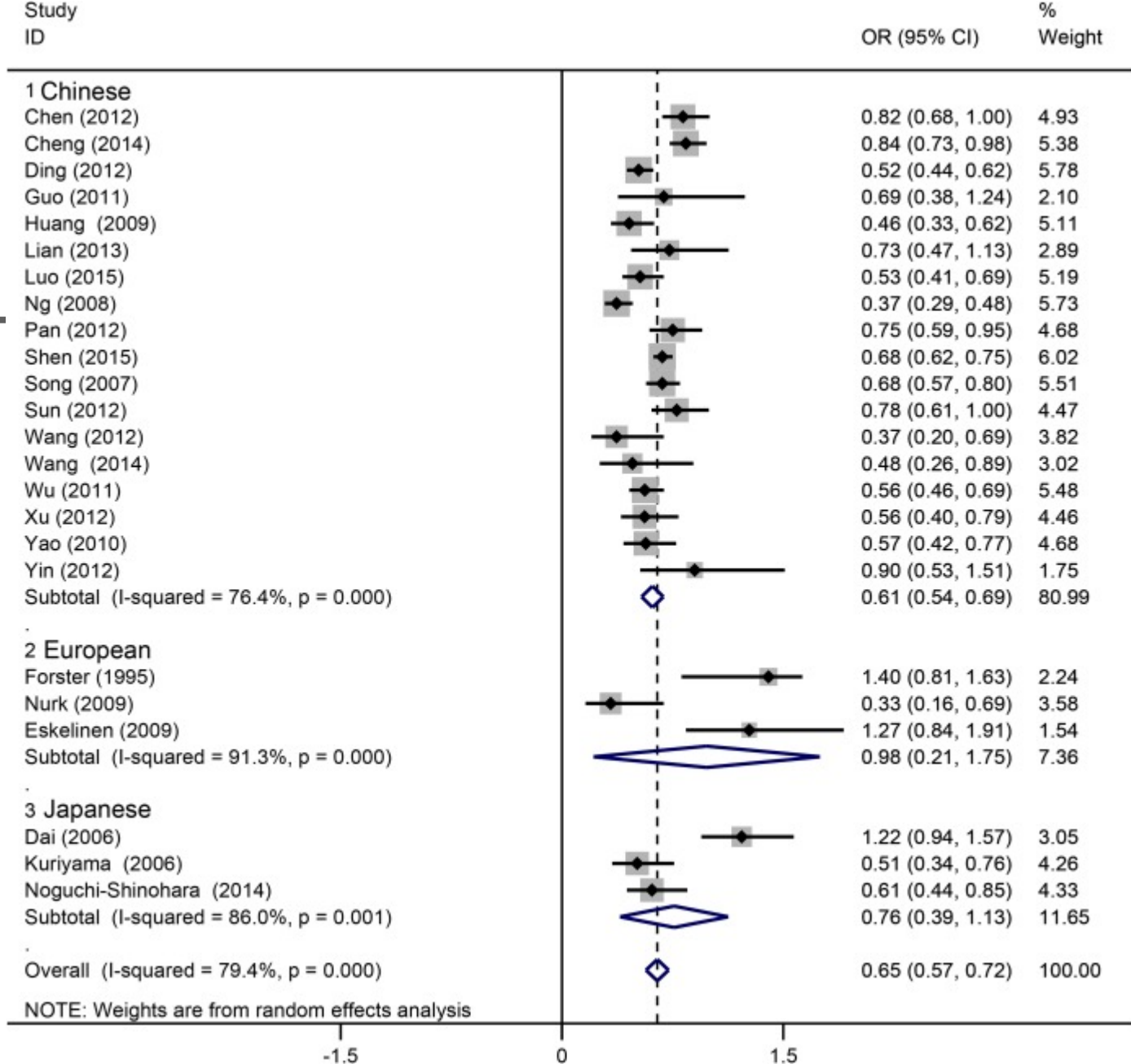
[Nutr Healthy Aging](#). 2016; 4(1): 81–93.

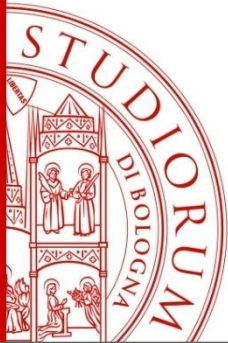




Association between tea intake and the cognitive disorders based on ethnicity

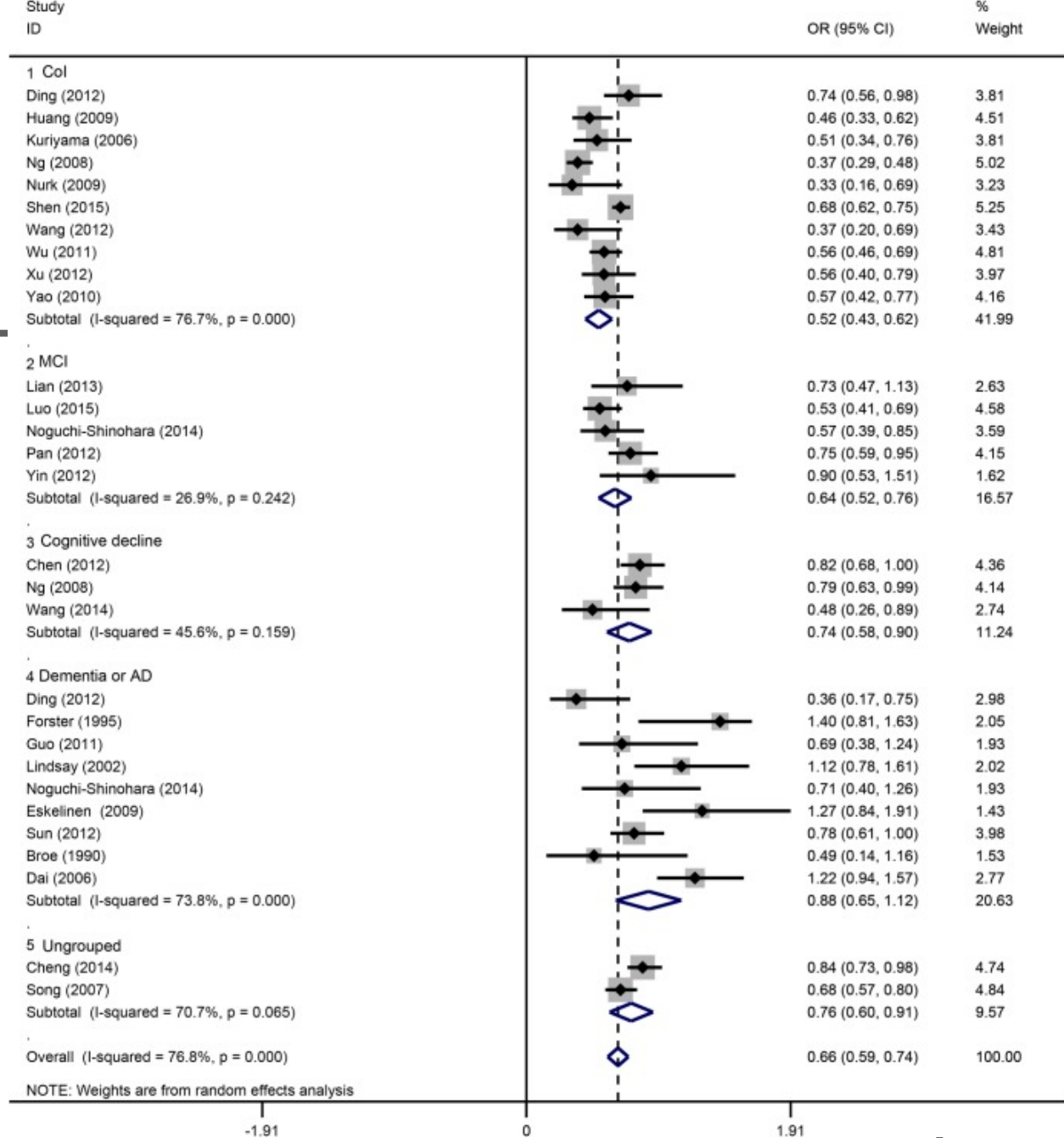
[PLoS One. 2016; 11\(11\): e0165861.](https://doi.org/10.1371/journal.pone.0165861)

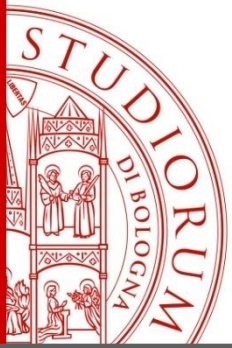




Association between tea intake and the cognitive disorders based on type of cognitive disorders

PLoS One. 2016;
11(11): e0165861.

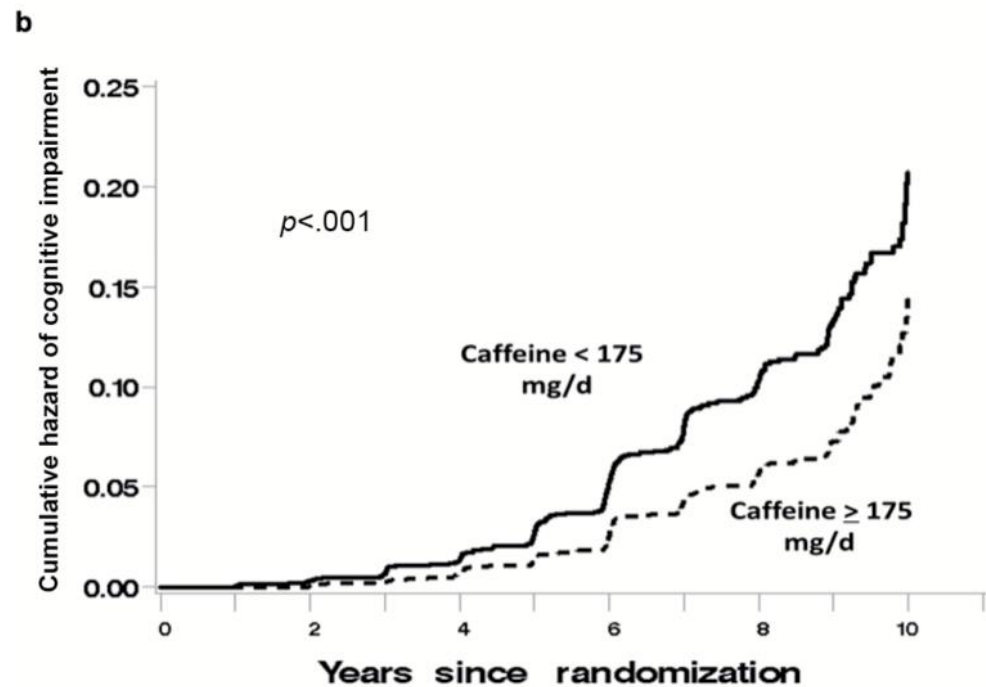
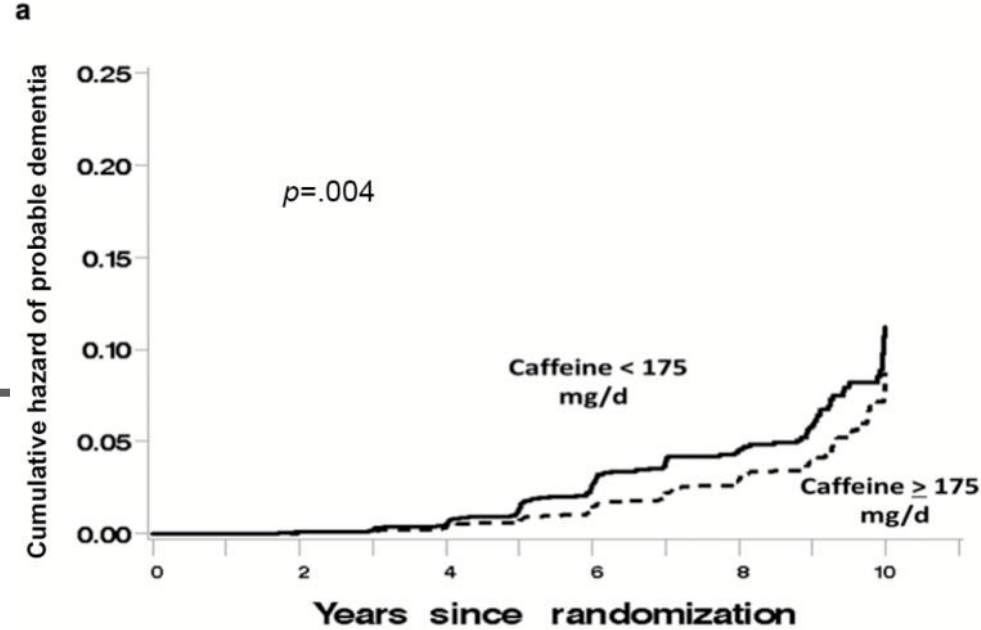


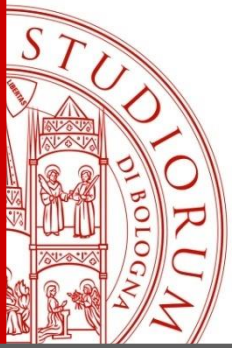


The Women's Health Initiative Memory Study

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).

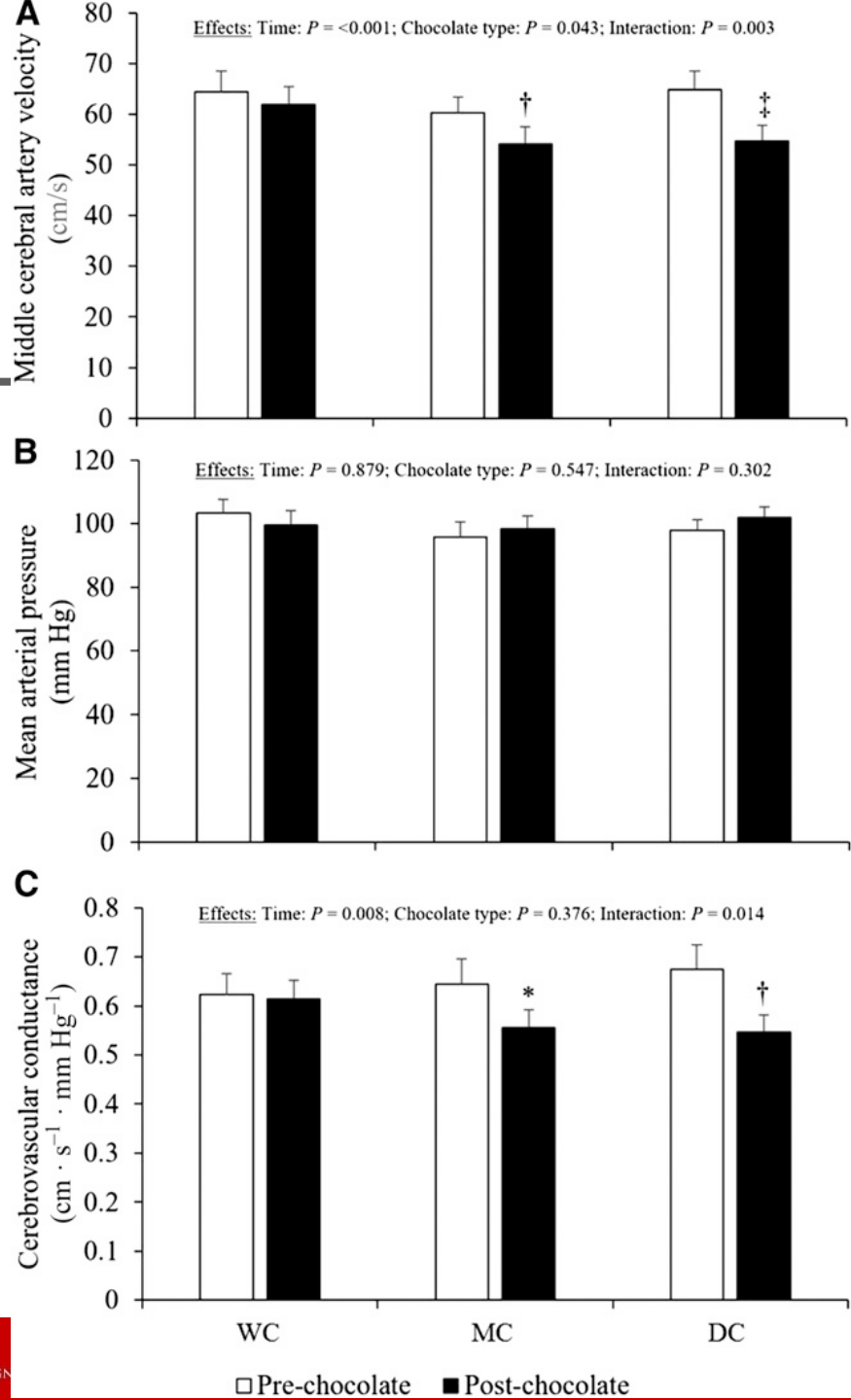
[J Gerontol A Biol Sci Med Sci. 2016; 71\(12\): 1596–1602.](#)

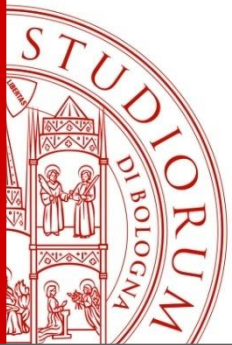




Impacts of chocolate containing different concentrations of cocoa on cerebral blood flow velocity and BP in postmenopausal women at rest

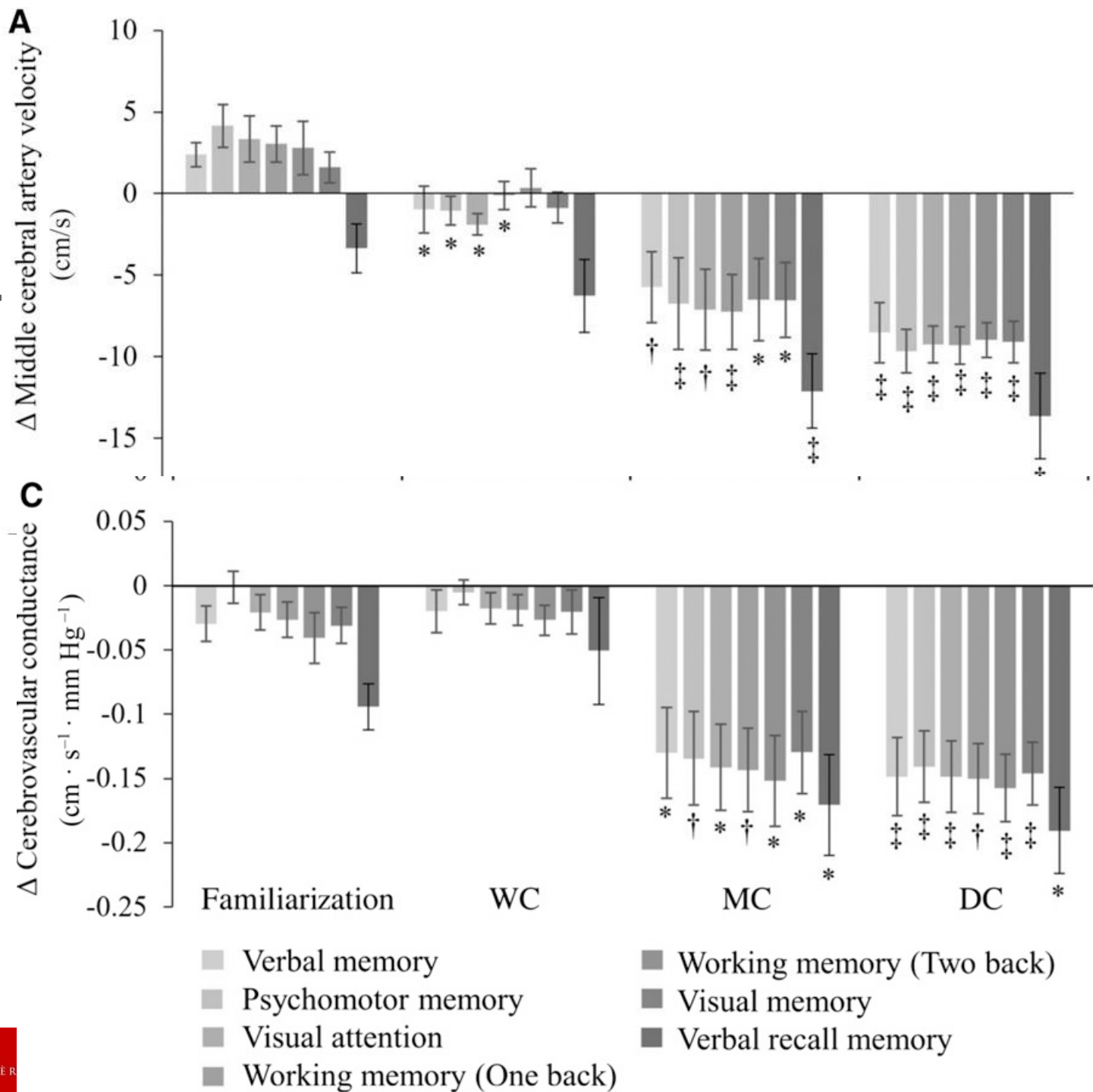
J Nutr 2017;147:1686–92





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

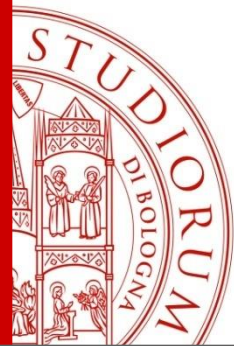
***J Nutr*
2017;147:
1686–92**



Changes in neuropsychological test scores during the study period in the 3 treatment groups¹

| Neuropsychological tests | Treatment group | | | ANOVA | <i>P</i> Time × treatment interaction |
|--------------------------|---------------------------|-----------------------------|---------------------------|---------|--|
| | HF (<i>n</i> = 30) | IF (<i>n</i> = 30) | LF (<i>n</i> = 30) | | |
| MMSE | | | | | |
| Week 0 | 29.07 ± 0.20 | 29.27 ± 0.20 | 29.23 ± 0.22 | 0.76 | 0.52 ² |
| Week 8 | 29.20 ± 0.17 | 29.27 ± 0.18 | 29.20 ± 0.19 | | |
| Change | 0.13 ± 0.13 | 0.00 ± 0.10 | -0.03 ± 0.09 | | |
| TMT A, s | | | | | |
| Week 0 | 33.87 ± 1.81 | 32.27 ± 1.67 | 33.07 ± 1.75 | 0.81 | <0.0001 |
| Week 8 | 25.25 ± 1.45 ^a | 25.58 ± 1.53 ^a | 32.13 ± 1.82 ^b | 0.0035 | |
| Change | -8.57 ± 0.38 ^a | -6.67 ± 0.45 ^a | -0.77 ± 1.57 ^b | <0.0001 | |
| <i>P</i> (ANOVA) | <0.0001 | <0.0001 | 0.63 | | |
| TMT B, s | | | | | |
| Week 0 | 79.23 ± 3.37 | 78.27 ± 3.43 | 77.45 ± 4.17 | 0.94 | <0.0001 |
| Week 8 | 62.71 ± 2.80 ^a | 63.99 ± 3.14 ^a | 76.43 ± 4.21 ^b | 0.01 | |
| Change | -16.50 ± 0.8 ^a | -14.20 ± 0.49 ^a | -1.10 ± 0.68 ^b | <0.0001 | |
| <i>P</i> (ANOVA) | <0.0001 | <0.0001 | 0.12 | | |
| VFT, words/60 s | | | | | |
| Week 0 | 24.87 ± 1.08 | 26.13 ± 1.11 | 23.72 ± 1.28 | 0.38 | <0.0001 |
| Week 8 | 32.58 ± 1.60 ^a | 29.62 ± 1.35 ^{a,b} | 25.05 ± 1.44 ^b | 0.002 | |
| Change | 7.70 ± 1.09 ^a | 3.57 ± 1.23 ^b | 1.33 ± 0.45 ^b | <0.0001 | |
| <i>P</i> (ANOVA) | <0.0001 | 0.007 | 0.01 | | |
| z Score | | | | | |
| Week 0 | -0.058 ± 0.10 | 0.083 ± 0.10 | -0.026 ± 0.17 | 0.72 | <0.0001 |
| Week 8 | 0.656 ± 0.10 ^a | 0.582 ± 0.10 ^a | 0.063 ± 0.15 ^b | 0.0013 | |
| Change | 0.714 ± 0.03 ^a | 0.498 ± 0.05 ^b | 0.089 ± 0.7 ^c | <0.0001 | |
| <i>P</i> (ANOVA) | <0.0001 | <0.0001 | 0.19 | | |

¹Values are means ± SEs. Differences within groups were analyzed by ANOVA. Differences between groups were analyzed by ANOVA followed by Tukey's honestly significant difference test. Values within a row not sharing a common superscript letter are significantly different, *P* < 0.05. HF, high flavanol intake; IF, intermediate flavanol intake; LF, low flavanol intake; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Test.



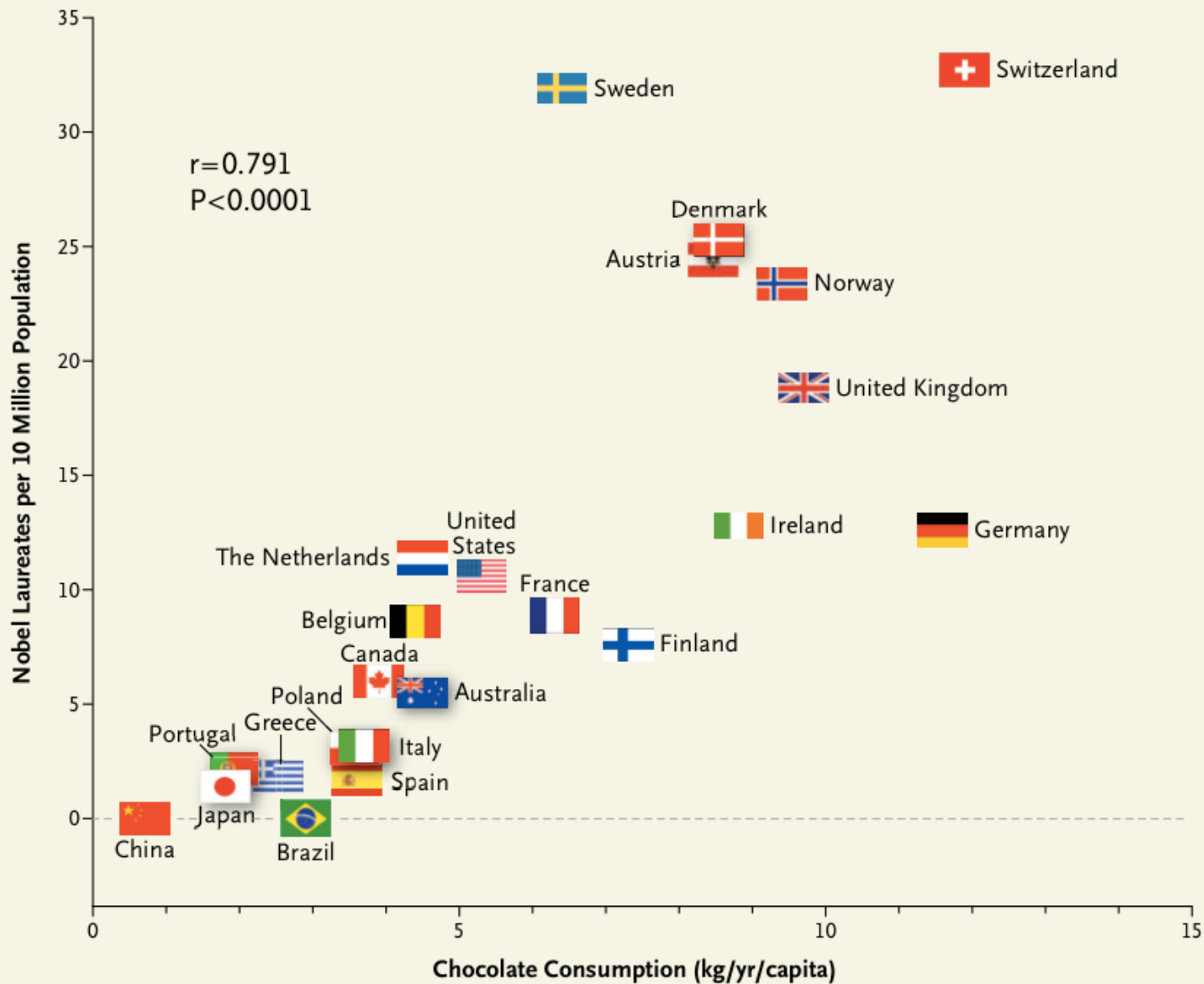
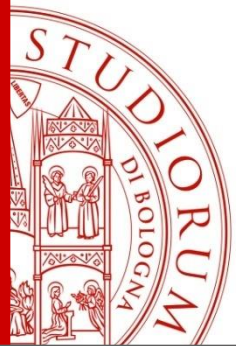
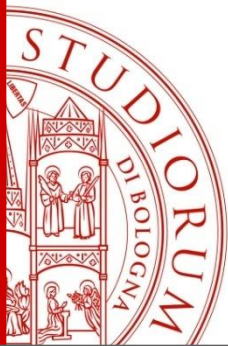


Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.



The Nutrition Society Irish Section Meeting was held at the Queens University, Belfast on 21–23 June 2017

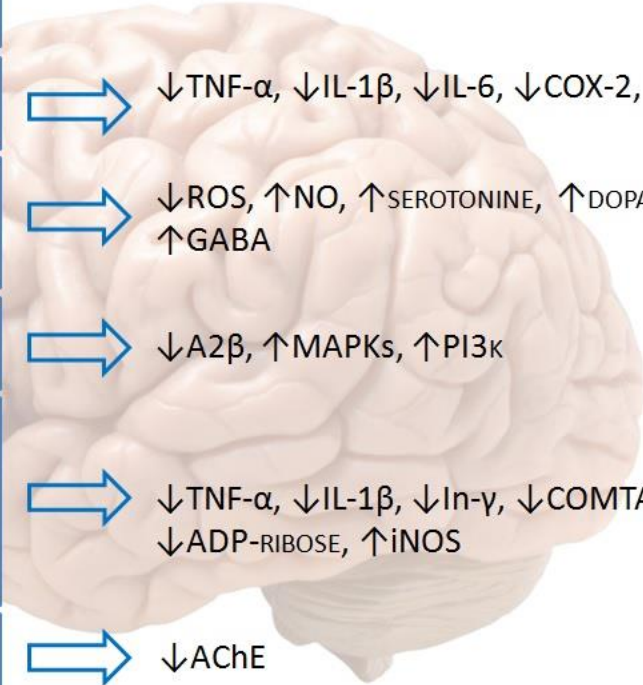
Conference on ‘What governs what we eat?’ Irish section postgraduate meeting

Diet, nutrition and the ageing brain: current evidence and new directions

Katie Moore, Catherine F. Hughes, Mary Ward, Leane Hoey and Helene McNulty*
*Nutrition Innovation Centre for Food and Health, School of Biomedical Sciences, Ulster University Coleraine,
Coleraine, Northern Ireland*

ority. There is some evidence linking certain dietary patterns, particularly the Mediterranean diet, with a reduced risk of dementia and depression. Specific dietary components have also been investigated in relation to brain health, with emerging evidence supporting protective roles for *n*-3 PUFA, polyphenols, vitamin D and B-vitamins. At this time, the totality of

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**

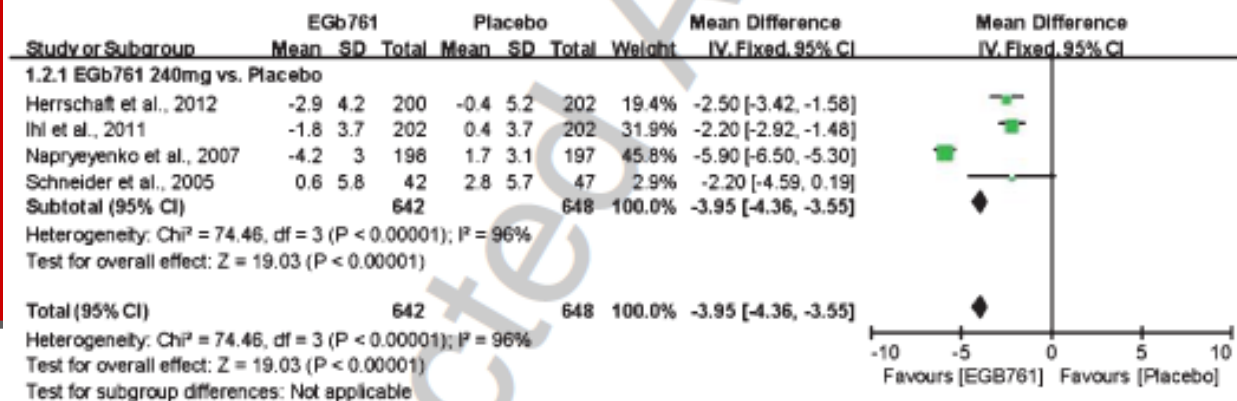


Gingko biloba: metanalysis of RCT

- **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.**

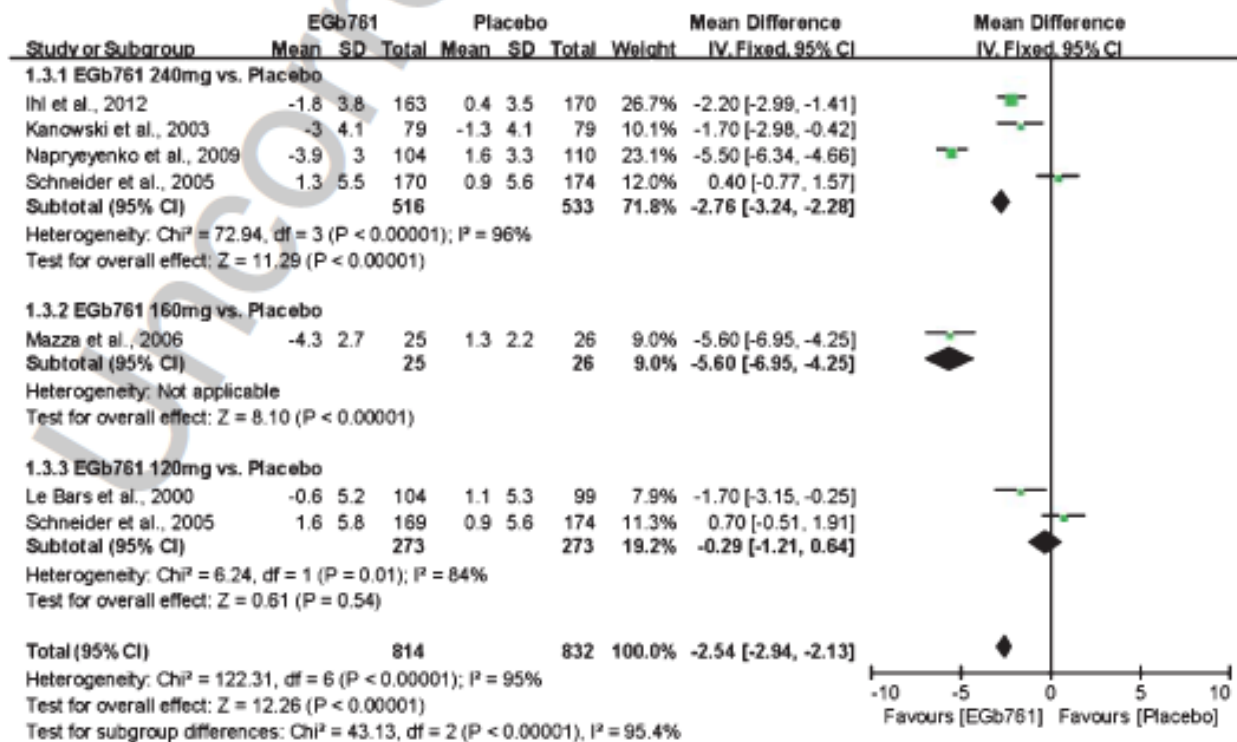
J Alzheimers Dis. 2015;43(2):589-603.

1.2 Patients with NPS subgroup



Efficacy on the ADAC Score

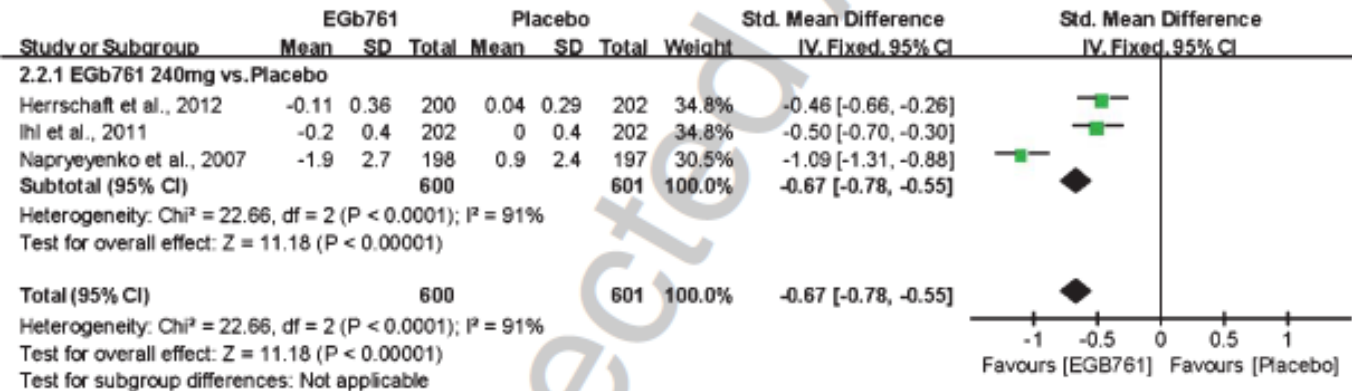
1.3 AD subgroup



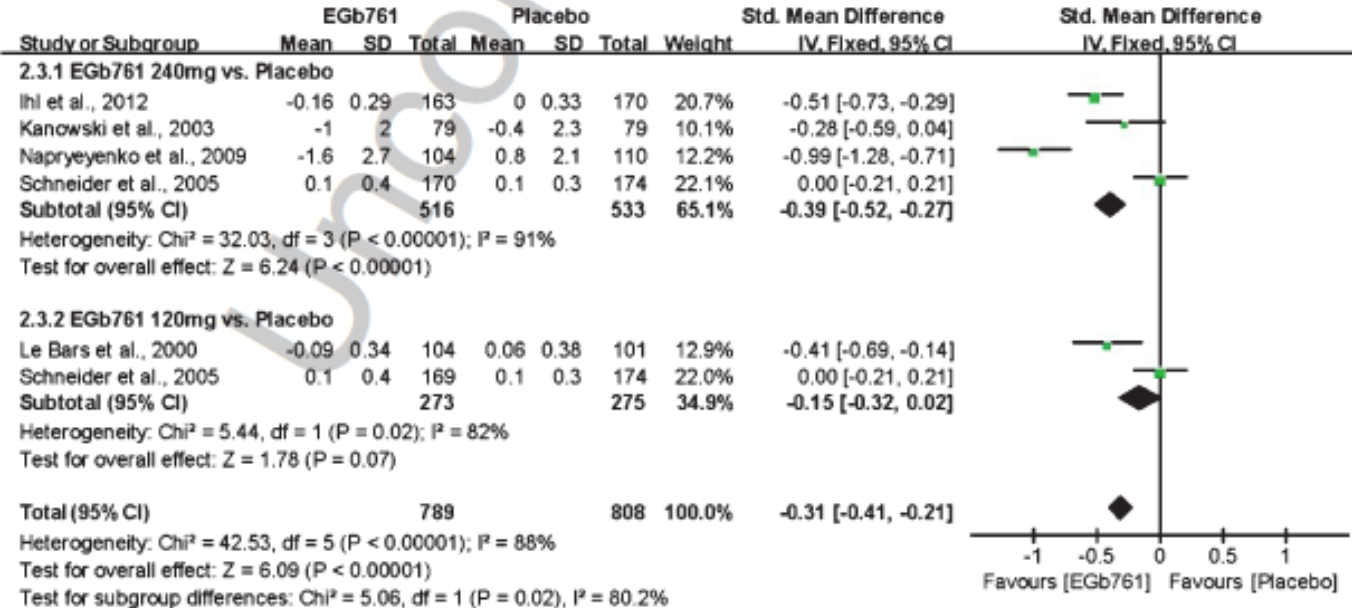
**J Alzheimers Dis.
2015;43(2):589-603.**

Efficacy on the ADL Score

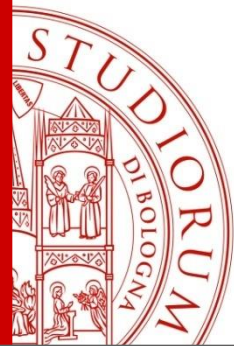
2.2 Patients with NPS subgroup



2.3 AD subgroup

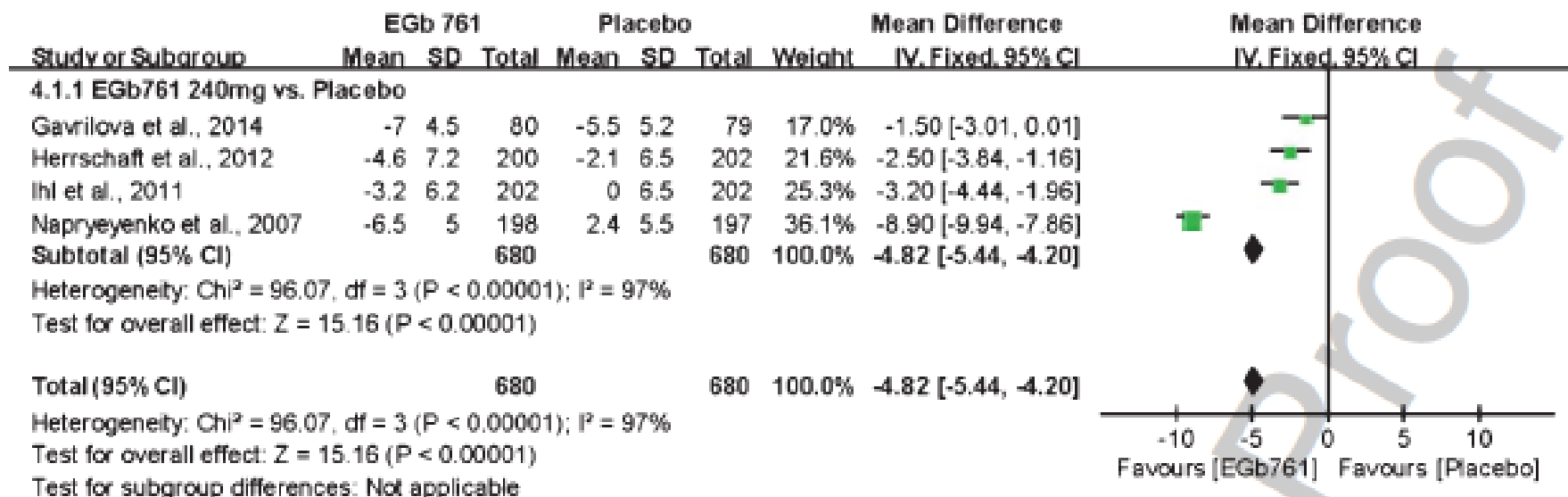


**J Alzheimers
Dis. 2015;
43(2):589-603.**

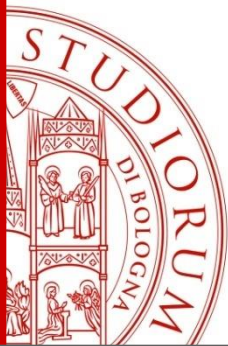


Efficacy on the NeuroPsychiatric Index (NPI) Score

4.1 Patients with NPS subgroup

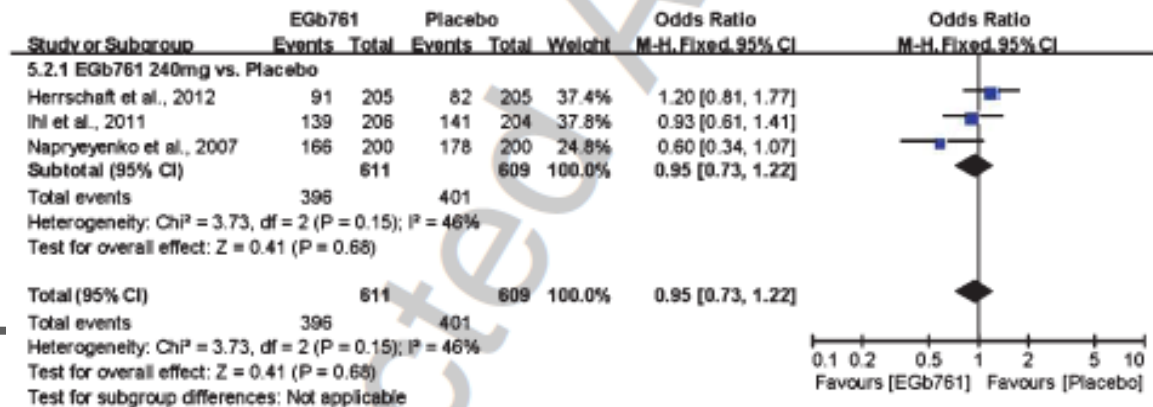


**J Alzheimers Dis.
2015;43(2):589-603.**

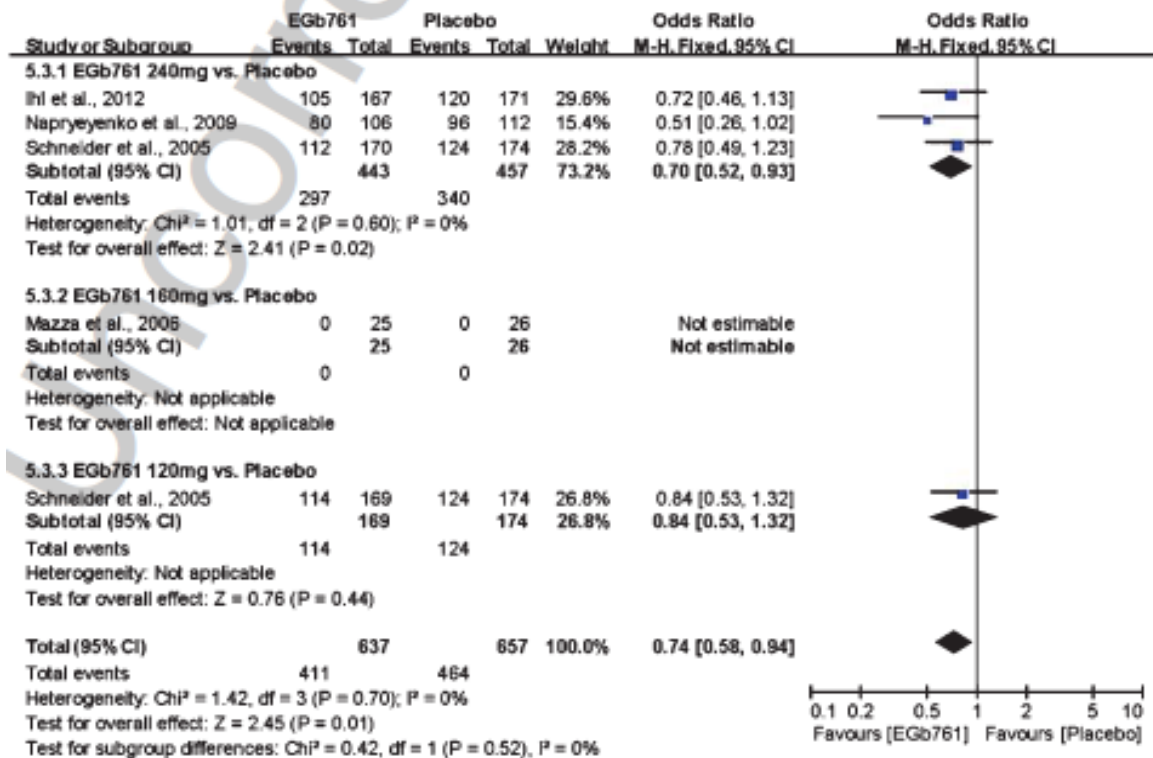


Adverse events

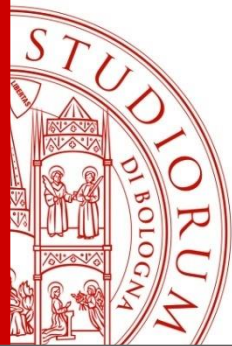
5.2 Patients with NPS subgroup



5.3 AD subgroup



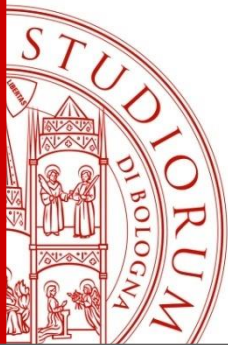
**J Alzheimers Dis.
2015;43(2):589-603.**



RCTs on resveratrol

Molecules **2016**, *21*, 1243

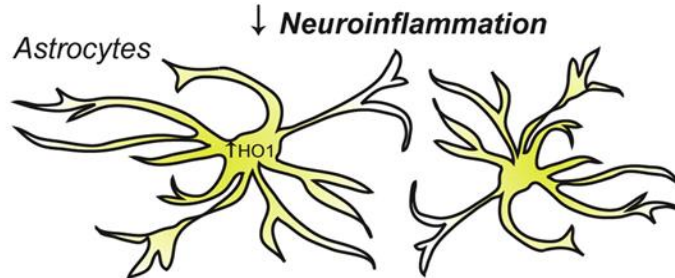
| Reference or ID (Location) | Study Design | Resveratrol Preparation and Dose [Other Medication] | Duration | Subjects <i>n</i> Age Disorder/Status | Purpose Outcome Measures | Main Results |
|--|-----------------------|--|----------|---|--|---|
| Kennedy et al. [111] (Newcastle upon Tyne, UK) | R, 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) ACTRN12611000060943 | 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

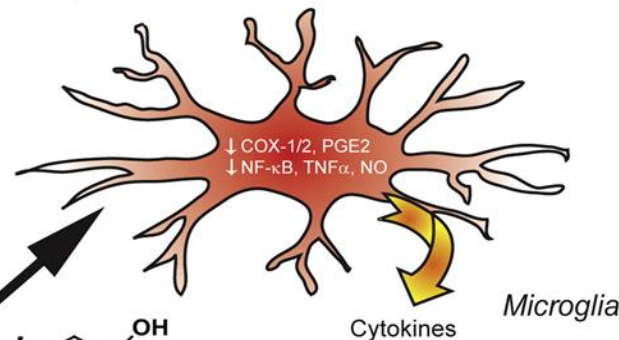
↑ glutathione peroxidase, HO1, AMPK, LKB1



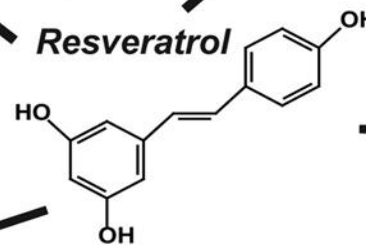
Sirtuins activator

AMPK
↓
NAD
↓
SIRT1
↓

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



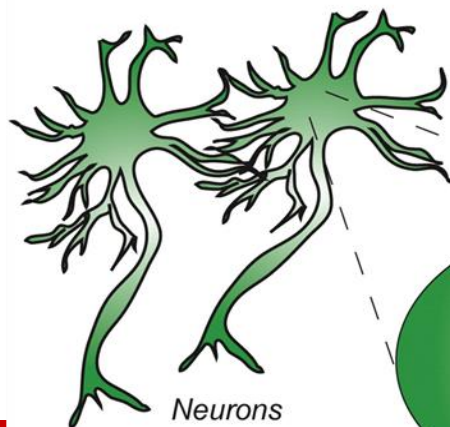
Resveratrol



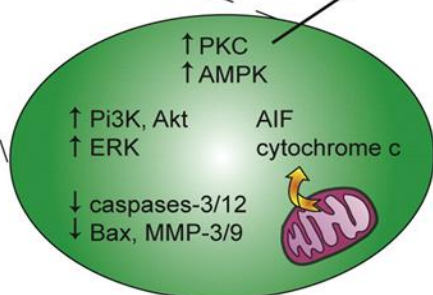
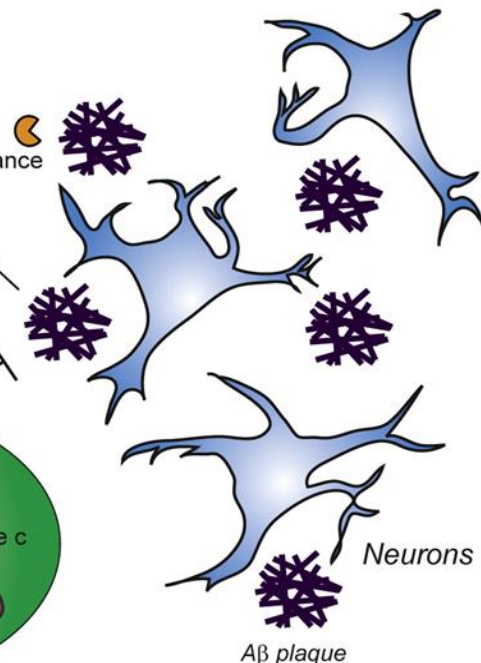
↓ Amyloidogenesis

Synaptic plasticity

↑ neuronal interconnections

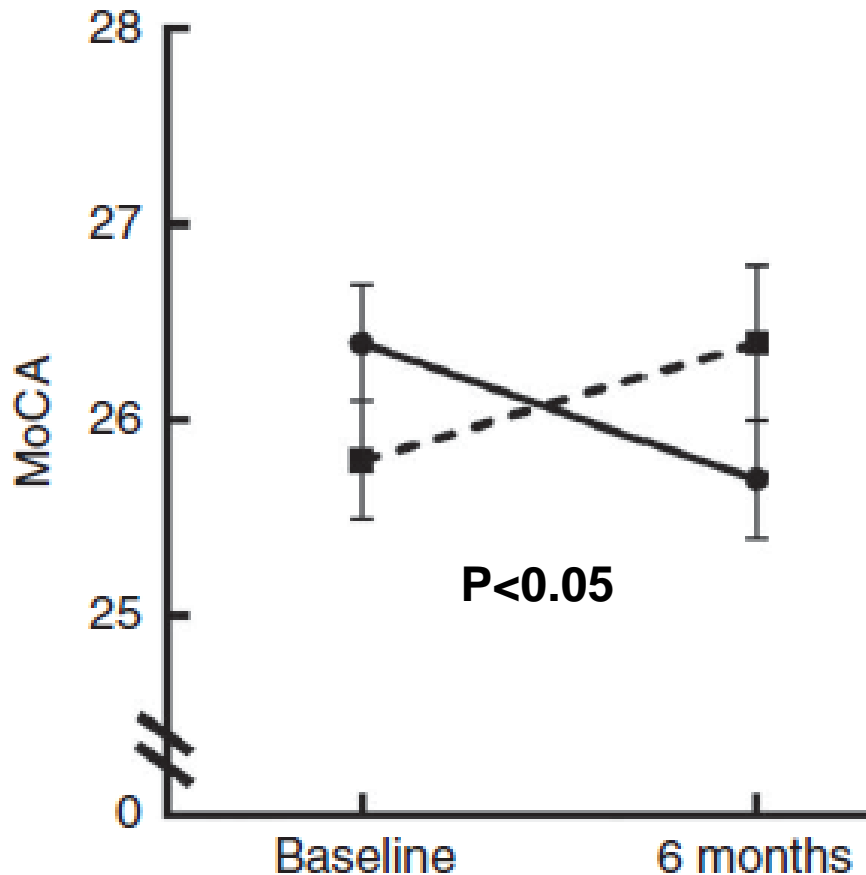
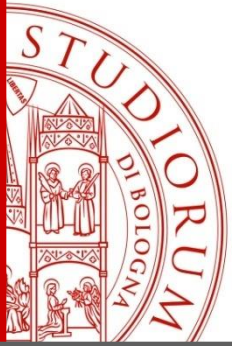


↑ clearance
↑ GSK-3β
↑ NF-κB



Cicero et al. 2018; in press.

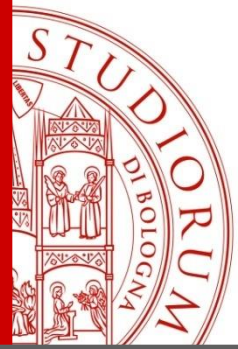
Curcumin and cognition: a RCT of community-dwelling older adults



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

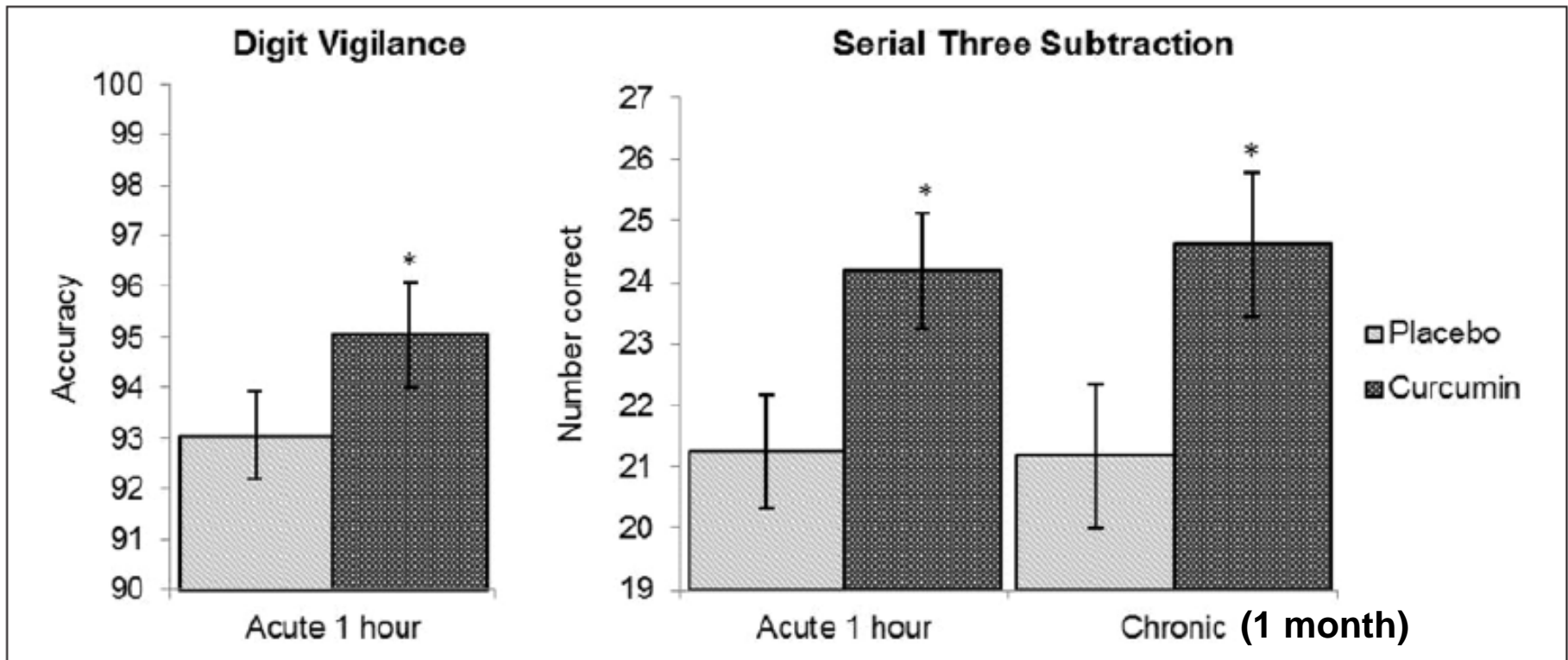
—■—, Curcumin group; —●—, placebo group.

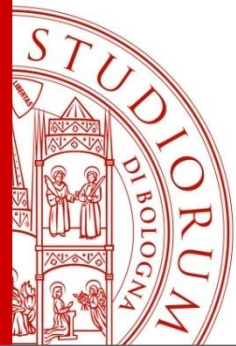
British Journal of Nutrition (2016), **115**, 2106–2113



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

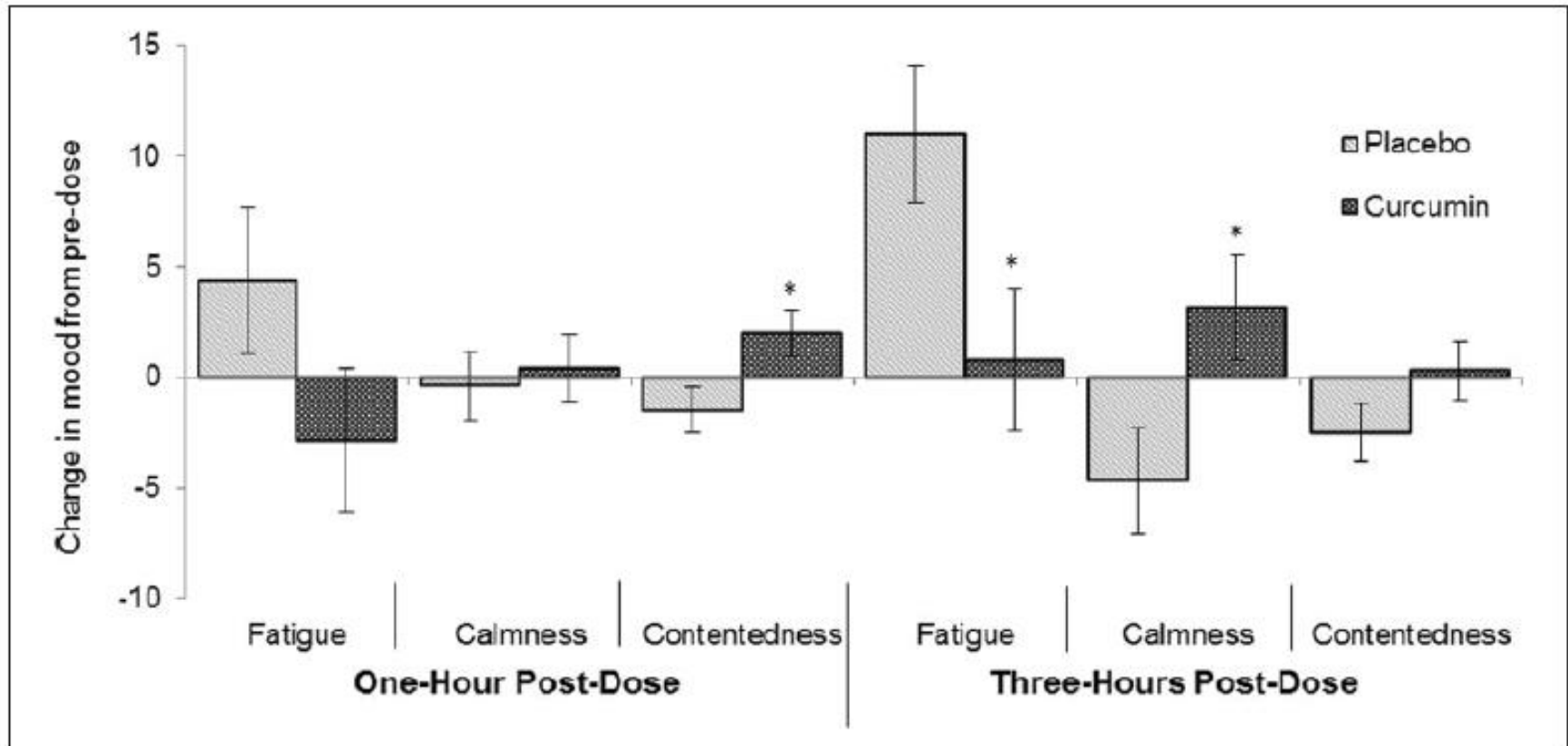
J Psychopharmacol. 2015 May;29(5):642-51



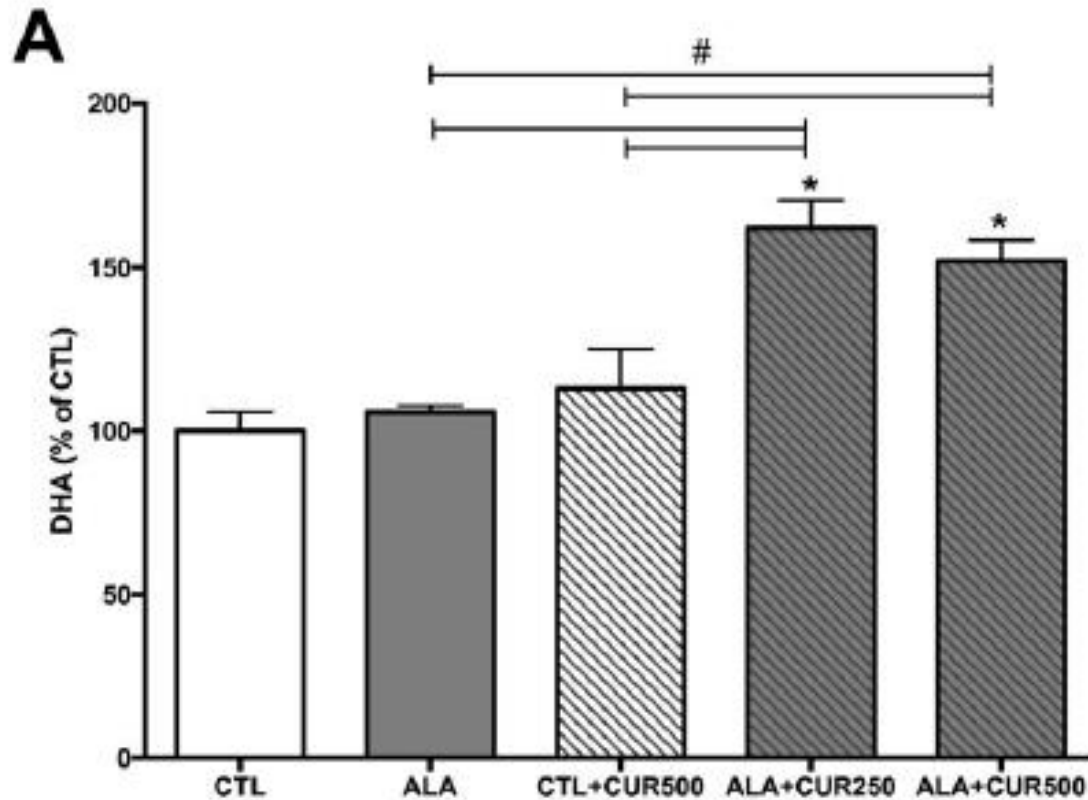


Effects of solid lipid curcumin 400 mg on cognition and mood in 60 healthy elderly (60-85 yo)

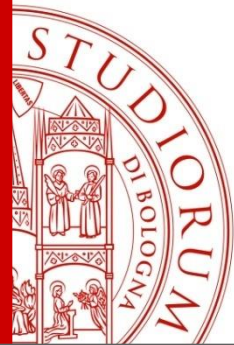
[J Psychopharmacol.](#) 2015 May;29(5):642-51



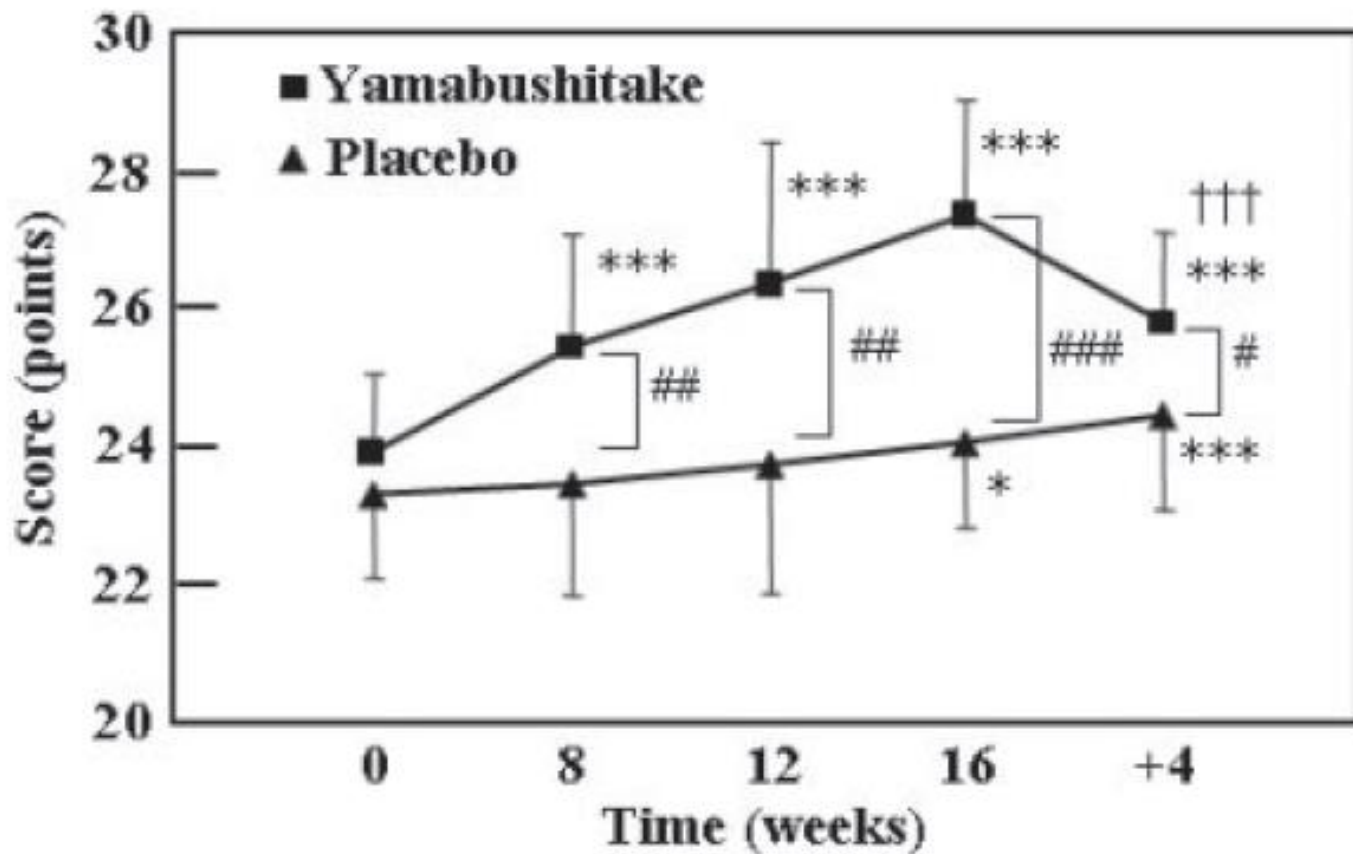
Curcumin boosts DHA in the brain: implications for the prevention of anxiety disorders



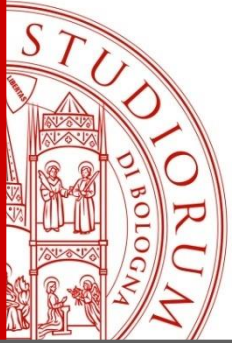
Biochim Biophys Acta. 2015;
1852(5): 951–961.



Score of the cognitive function scale: result of a RCT



Phytother.
Res. 2009;23:
367–372

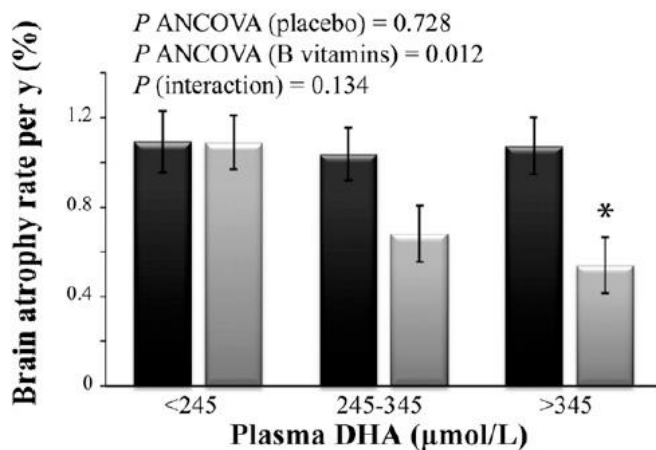
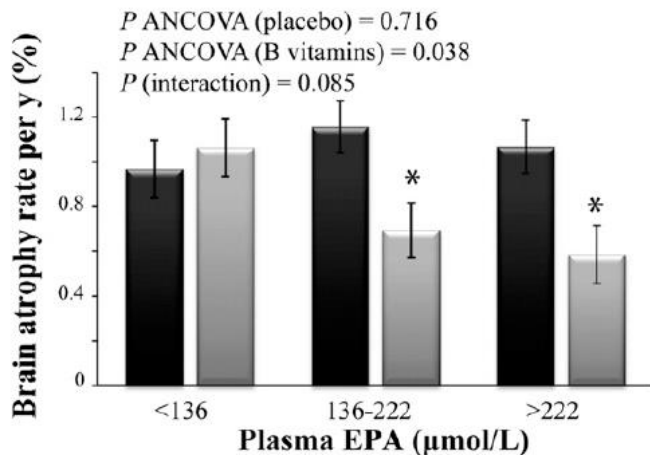
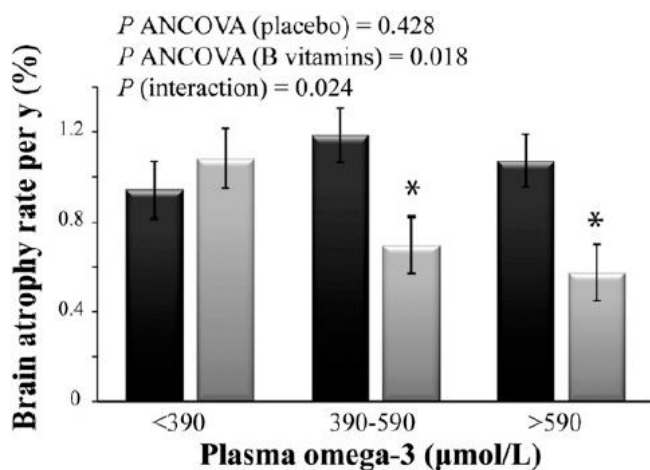


Reduction of depression or anxiety by 4 weeks Hericium erinaceus intake

| | before | | | | after | | | |
|----------|--------|------|---------|------|-------|------|---------|------|
| | HE | | Placebo | | HE | | Placebo | |
| | mean | SD | mean | SD | mean | SD | mean | SD |
| KMI | 16.5 | 10.2 | 17.1 | 8.1 | 11.2 | 6.2 | 11.1 | 9.9 |
| CES-D | 13.9 | 7.8 | 15.1 | 9.6 | 10.3 | 7.3 | 12.6 | 8.3 |
| PSQI | 6.3 | 2.3 | 6.2 | 2.6 | 6.0 | 2.7 | 6.4 | 2.7 |
| ICI | 46.1 | 23.4 | 40.4 | 17.5 | 29.6 | 21.5 | 31.6 | 22.3 |
| Total IC | 13.8 | 8.9 | 11.5 | 7.1 | 8.1 | 7.8 | 8.4 | 7.5 |

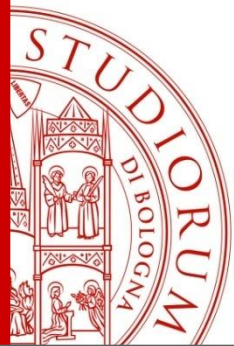
Biomed Res 2010;31(4):231-37

Omega 3 and B vitamins

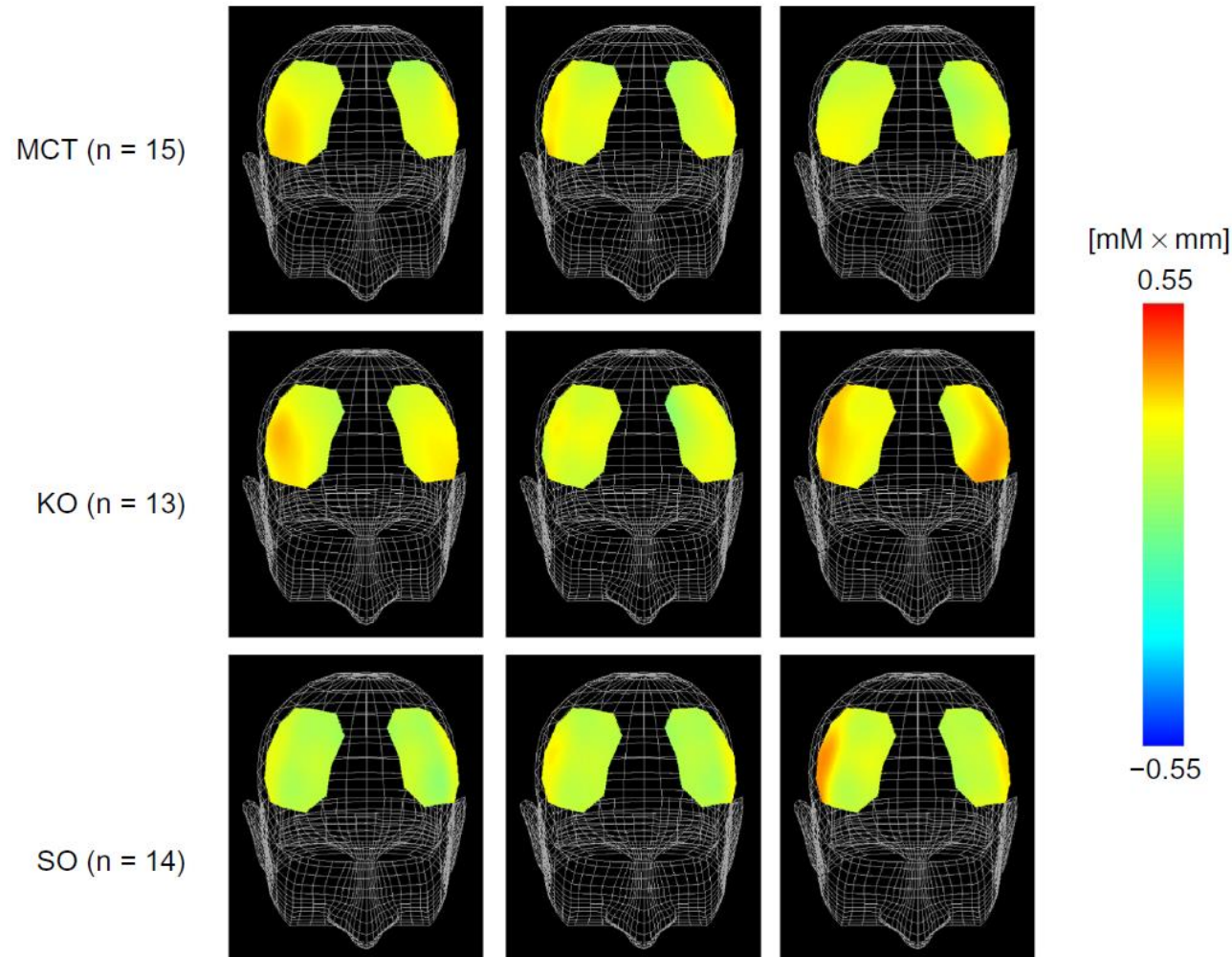


Brain atrophy rates (mean 6 SEM) among subjects receiving placebo (black) and high-dose B vitamins (gray) according to tertiles of plasma baseline combined ω-3 (top)

Am J Clin Nutr 2015;102:215–21.

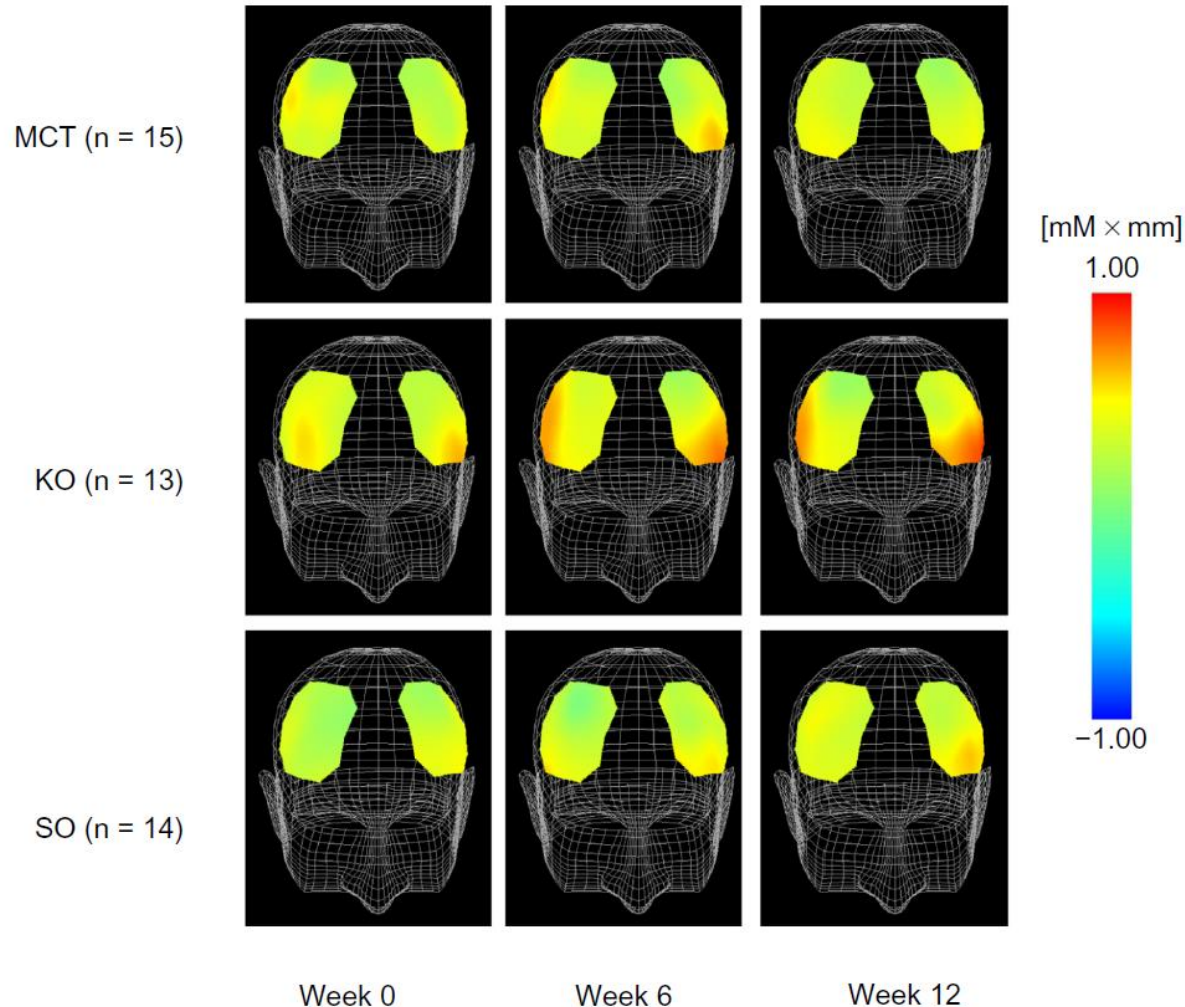


Topographic maps of changes in oxy-hb concentration at 225.0 seconds during working memory task



**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) | <i>p</i> 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



ELSEVIER

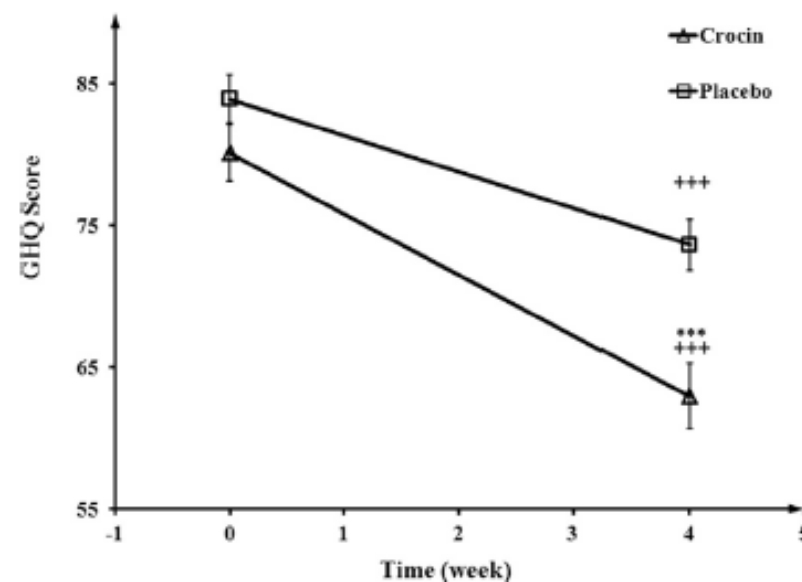
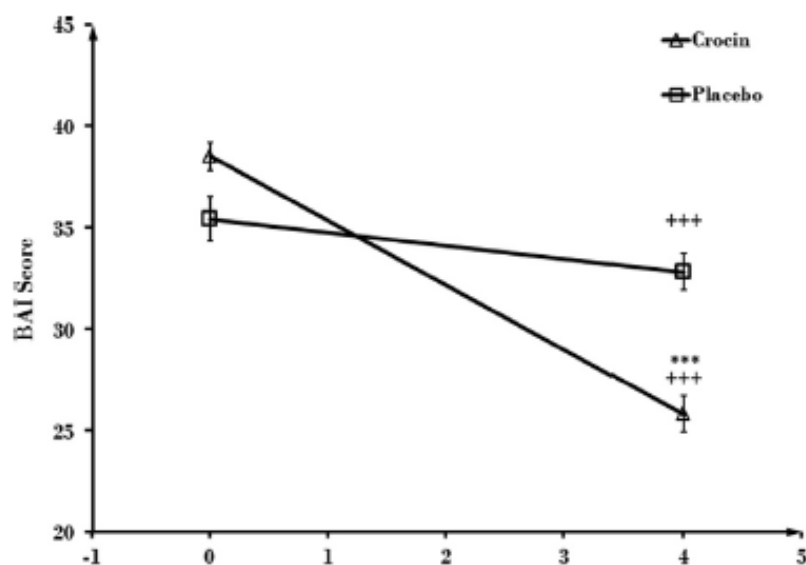
Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

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

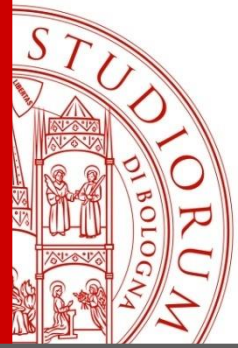
*Perceived Stress Questionnaire Index

*Self-rating Depression Scale



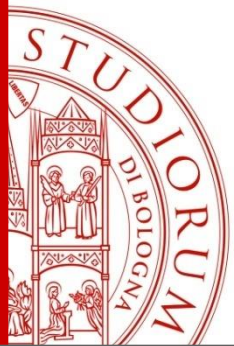
Interesting results but ...

- **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