Università di Modena e Reggio Emilia
Dipartimento di Scienze Biomediche
Metaboliche e Neuroscienze
Unità Operativa di Geriatria

Marco Bertolotti

Nutrizione e Deterioramento Cognitivo

Parma, 31 Maggio 2019

Nutrizione e Deterioramento Cognitivo

Potenziali conflitti di interesse collegati alla presente relazione:

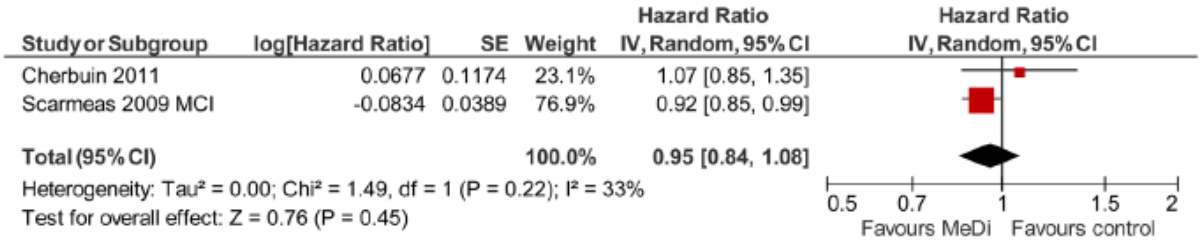
Nessuno

Nutrizione e Deterioramento Cognitivo

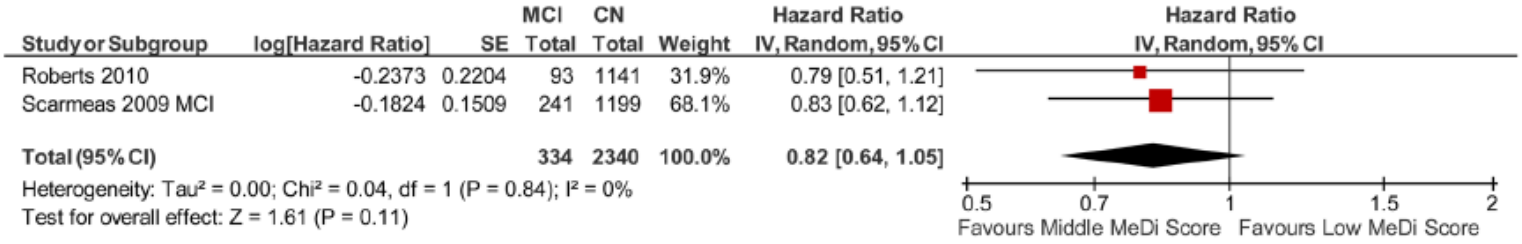
- Approccio dietetico e deterioramento cognitivo
- Evidenze su singole componenti della dieta
- Nutrizione e prevenzione cerebrovascolare
- Possibile ruolo dei nutraceutici - integratori

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

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



2.2 Middle vs Lowest MeDi tertile



2.3 Highest vs Lowest MeDi tertile

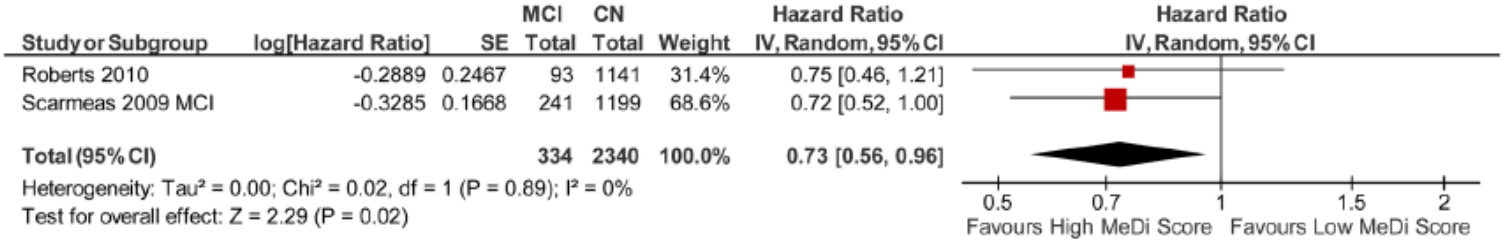


Figure 2.
Summary of adherence to the Mediterranean diet and risk of mild cognitive impairment among cognitively normal individuals at baseline

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

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

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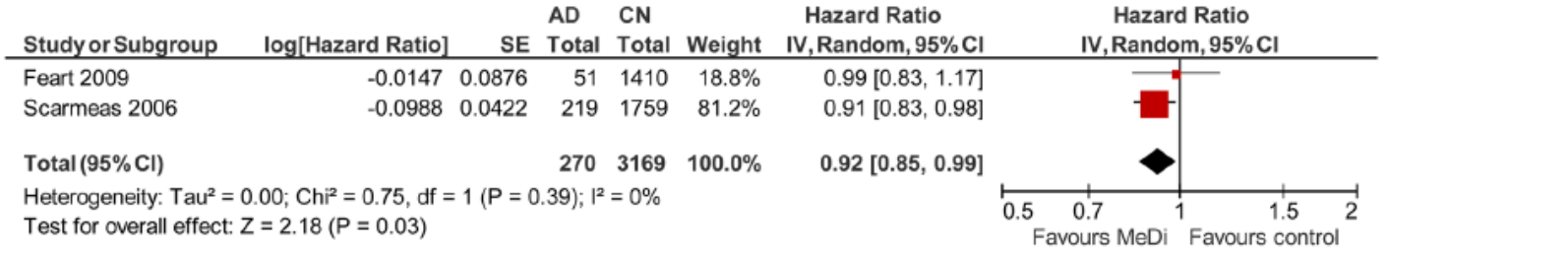
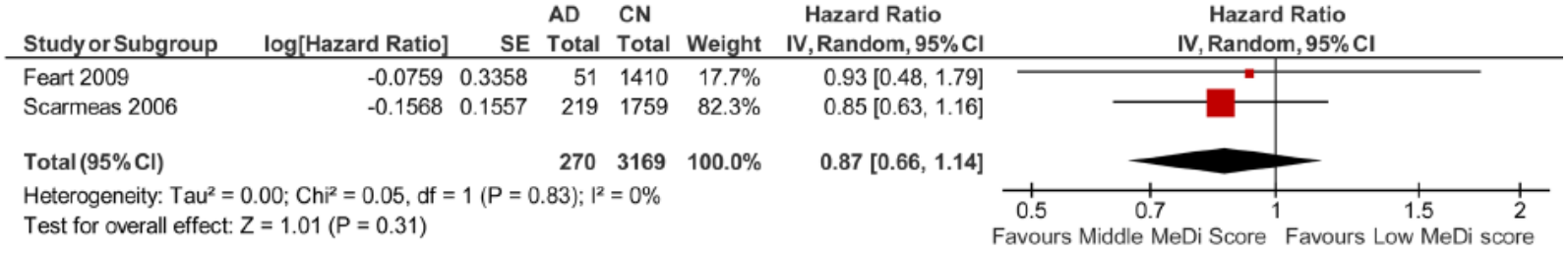


3.2 Middle vs Lowest MeDi tertile



3.3 Highest vs Lowest MeDi tertile

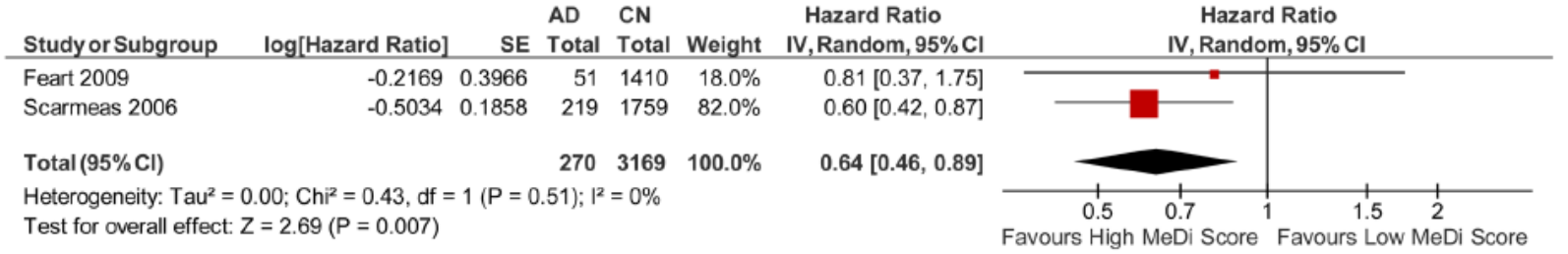


Figure 3.
Summary of adherence to the Mediterranean diet and risk of Alzheimer's disease among cognitively normal individuals at baseline.

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Conclusions—While the overall number of studies is small, pooled results suggest that a higher adherence to the MeDi is associated with a reduced risk of developing MCI and AD, and a reduced risk of progressing from MCI to AD. Further prospective-cohort studies with longer follow-up and randomized controlled trials are warranted to consolidate the evidence.

Mediterranean Diet, Cognitive Function, and Dementia: A Systematic Review of the Evidence[1–3]

Sara Danuta Petersson[4] and Elena Philippou[4,5]*

 Adv Nutr 2016;7:889–904; doi:10.3945/an.116.012138.

on the findings and the limitations in study design, we conclude that adherence to the MD is associated with better cognitive performance. However, it should be noted that the majority of findings come from epidemiologic studies that provide evidence for a correlation between the MD and cognition but not for a cause-and-effect relation. More controlled trials are required to establish a causational relation. *Adv Nutr* 2016;7:889–904.

The Association between the Mediterranean Dietary Pattern and Cognitive Health: A Systematic Review

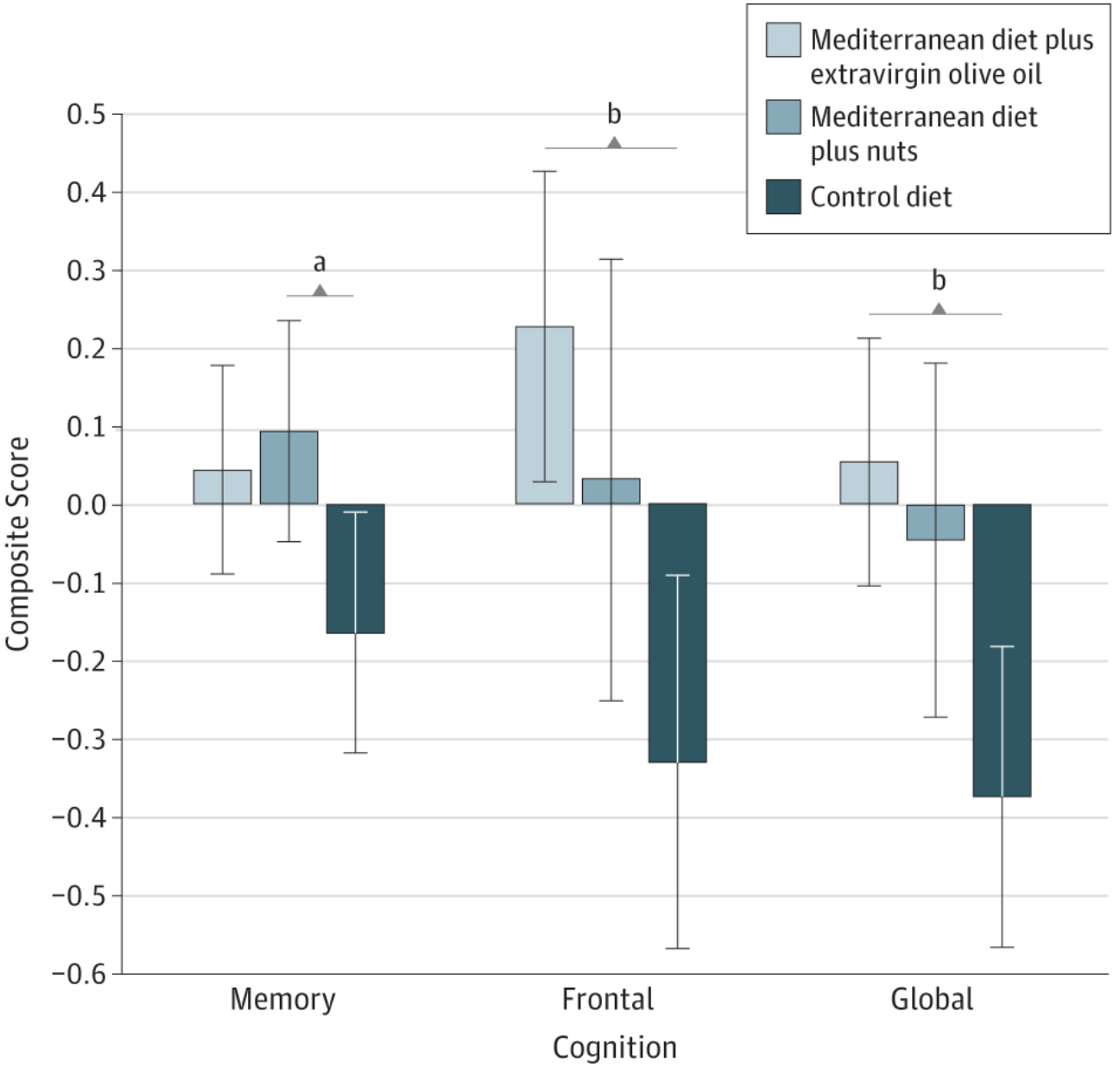
Yasmine S. Aridi *, Jacqueline L. Walker and Olivia R. L. Wright

Nutrients **2017**, *9*, 674; doi:10.3390/nu9070674

of the MD on cognitive function. Although more standardized and in-depth studies are needed to strengthen the existing body of evidence, results from this review indicate that the Mediterranean diet could play a major role in cognitive health and risk of Alzheimer's disease and dementia.

Mediterranean Diet and Age-Related Cognitive Decline: A RCT

In an older population, a Mediterranean diet supplemented with olive oil or nuts was associated with improved composite measures of cognitive function.

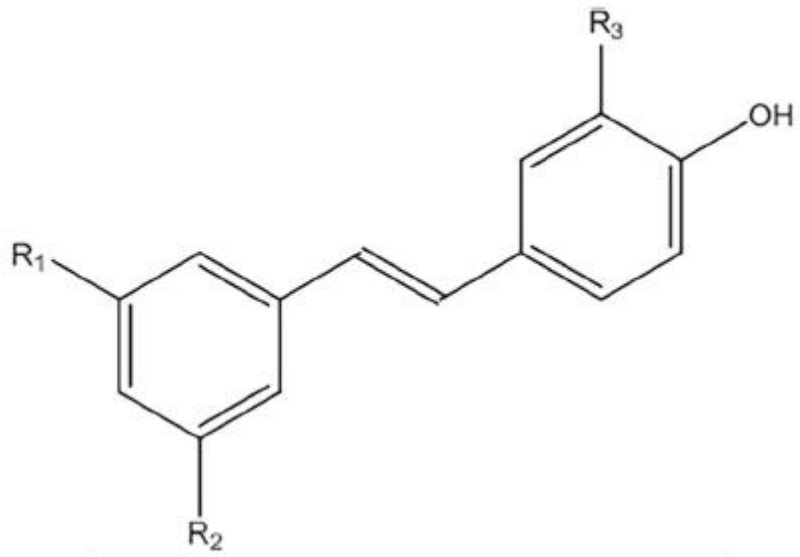


Valls-Pedret C. et al., JAMA Intern Med 2015: 175: 1094-1103

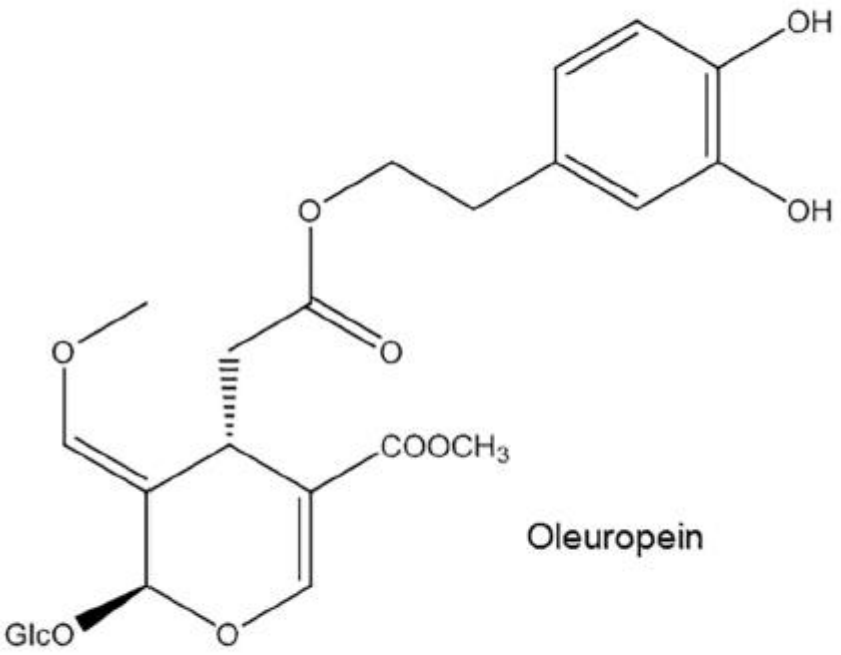
Phenolic Compounds Characteristic of the Mediterranean Diet in Mitigating Microglia-Mediated Neuroinflammation

Front. Cell. Neurosci. 12:373.
doi: 10.3389/fncel.2018.00373

*Ruth Hornedo-Ortega[1], Ana B. Cerezo[2], Rocio M. de Pablos[3], Stéphanie Krisa[1], Tristan Richard[1], M. Carmen Garcia-Parrilla[2] and Ana M. Troncoso[2]**



	R_1	R_2	R_3
Resveratrol	OH	OH	H
Piceatannol	OH	OH	OH
Pterostilbene	OCH_3	OCH_3	H



Oleuropein

FIGURE 1 | Chemical structure of RV and derivatives and OLE.

Evidenza in modello sperimentale animale di effetti antiinfiammatori (ridotta attivazione di astrociti e microglia) da parte di alcune componenti dell'olio d'oliva (Oleuropenina)

Prospective Associations between Single Foods, Alzheimer's Dementia and Memory Decline in the Elderly

Karina Fischer [1,2,3,†], Debora Melo van Lent [4,*,†], Steffen Wolfsgruber [4,5], Leonie Weinhold [6], Luca Kleineidam [4,5], Horst Bickel [7], Martin Scherer [8], Marion Eisele [8], Hendrik van den Bussche [8], Birgitt Wiese [9], Hans-Helmut König [10], Siegfried Weyerer [11], Michael Pentzek [12], Susanne Röhr [13,14], Wolfgang Maier [5], Frank Jessen [4,15], Matthias Schmid [4,6], Steffi G. Riedel-Heller [13,†] and Michael Wagner [4,5,†]

Nutrients **2018**, *10*, 852; doi:10.3390/nu10070852

Table 3. Longitudinal joint modeling associations between food intake and incident AD and memory decline over a 10-year follow-up period.

Associations between Food Intake and Incident AD or Memory Decline	*HR* (95% CI) for Incident AD and UnstandardizedRegression Coefficients (95% CI) for Memory Decline		Significant *P*-Values for Interaction ($P < 0.10$)	
	Model 2		Gender	*APOE* ε4 status
Incident AD				
(survival sub-model)	*HR* (95%CI)	*P*		
Fruits and vegetables	1.08 (0.80; 1.46)	0.609	-	0.085
Fresh fish	0.98 (0.87; 1.11)	0.754	-	-
Olive oil	1.00 (0.93; 1.07)	0.969	-	-
Meat and sausages	1.09 (0.94; 1.26)	0.236	-	0.083
Red wine	0.92 (0.85; 0.99)	0.045	0.001	-
White wine	1.00 (0.91; 1.12)	0.875	-	0.074
Coffee	0.97 (0.90; 1.04)	0.338	-	-
Green tea	0.94 (0.86; 1.02)	0.129	-	-
Memory decline				
(repeated-measures sub-model)	*B* (95%CI)	*P*		
Fruits and vegetables	0.10 (−0.14; 0.33)	0.408	-	-
Fresh fish	−0.03 (−0.14; 0.08)	0.610	-	-
Olive oil	−0.03 (−0.09; 0.04)	0.388	0.064	-
Meat and sausages	0.01 (−0.11; 0.14)	0.845	-	-
Red wine	−0.04 (−0.11; 0.03)	0.302	-	-
White wine	−0.03 (−0.12; 0.06)	0.494	0.085	-
Coffee	−0.02 (−0.08; 0.05)	0.241	-	0.056
Green tea	0.02 (−0.06; 0.09)	0.681	-	-

Based on imputed data (n = 2622). Model 2 was adjusted for age, gender, BMI, education, *APOE* ε4 carrier status, smoking status, physical activity score, depression, hypercholesterolemia, and a modified CCI score (for model 1 see Table S3 in the Supplementary Materials part). $P < 0.05$ was considered statistically significant. Abbreviations: HR, hazard ratio; AD, Alzheimer's dementia; BMI, body mass index.

Prospective Associations between Single Foods, Alzheimer's Dementia and Memory Decline in the Elderly

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White wine				
Coffee				
Green tea	0.02 (−0.06; 0.09)	0.681	-	-

No evidence for single foods to be protective against cognitive decline, with the exception of red wine, which reduced the risk for AD in men

Based on imputed data (n = 2622). Model 2 was adjusted for age, gender, BMI, education, *APOE* ε4 carrier status, smoking status, physical activity score, depression, hypercholesterolemia, and a modified CCI score (for model 1 see Table S3 in the Supplementary Materials part). $P < 0.05$ was considered statistically significant. Abbreviations: HR, hazard ratio; AD, Alzheimer's dementia; BMI, body mass index.

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment (Review)

McCleery J, Abraham RP, Denton DA, Rutjes AWS, Chong LY, Al-Assaf AS, Griffith DJ, Rafeeq S, Yaman H, Malik MA, Di Nisio M, Martínez G, Vernooij RWM, Tabet N

The evidence on vitamin and mineral supplements as treatments for MCI is very limited. Three years of treatment with high-dose vitamin E probably does not reduce the risk of progression to dementia, but we have no data on this outcome for other supplements. Only B vitamins have been assessed in more than one RCT. There is no evidence for beneficial effects on cognition of supplementation with B vitamins for six to 24 months. Evidence from a single study of a reduced rate of brain atrophy in participants taking vitamin B and a beneficial effect of vitamin B on episodic memory in those with higher tHcy at baseline warrants attempted replication.

Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD011905.
DOI: 10.1002/14651858.CD011905.pub2.

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life (Review)

Rutjes AWS, Denton DA, Di Nisio M, Chong LY, Abraham RP, Al-Assaf AS, Anderson JL, Malik MA, Vernooij RWM, Martínez G, Tabet N, McCleery J

We did not find evidence that any vitamin or mineral supplementation strategy for cognitively healthy adults in mid or late life has a meaningful effect on cognitive decline or dementia, although the evidence does not permit definitive conclusions. There were very few data on supplementation starting in midlife (< 60 years); studies designed to assess cognitive outcomes tended to be too short to assess maintenance of cognitive function; longer studies often had other primary outcomes and used cognitive measures which may have lacked sensitivity. The only positive signals of effect came from studies of long-term supplementation with antioxidant vitamins. These may be the most promising for further research.

Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD011906.
DOI: 10.1002/14651858.CD011906.pub2.

Cochrane Library

Cochrane Database of Systematic Reviews

Vitamin E for Alzheimer's dementia and mild cognitive impairment (Review)

Farina N, Llewellyn D, Isaac MGEKN, Tabet N

We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.

Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD002854.
DOI: 10.1002/14651858.CD002854.pub5.

Cochrane Library

Cochrane Database of Systematic Reviews

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

Sydenham E, Dangour AD, Lim WS

Cochrane Database of Systematic Reviews 2012, Issue 6. Art. No.: CD005379.
DOI: 10.1002/14651858.CD005379.pub3.

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

Further studies of longer duration are required. Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

Omega-3 fatty acids for the treatment of dementia (Review)

Burckhardt M, Herke M, Wustmann T, Watzke S, Langer G, Fink A

We found no convincing evidence for the efficacy of omega-3 PUFA supplements in the treatment of mild to moderate AD. This result was consistent for all outcomes relevant for people with dementia. Adverse effects of omega-3 PUFAs seemed to be low, but based on the evidence synthesised in this review, we cannot make a final statement on tolerability. The effects on other populations remain unclear.

Cochrane Database of Systematic Reviews 2016, Issue 4. Art. No.: CD009002.
DOI: 10.1002/14651858.CD009002.pub3.

9. NUTRACEUTICI E STIMOLAZIONE INTELLETTIVA

Marco Bertolotti[1], Giovambattista Desideri[2], Damiano Rizzoni[3]

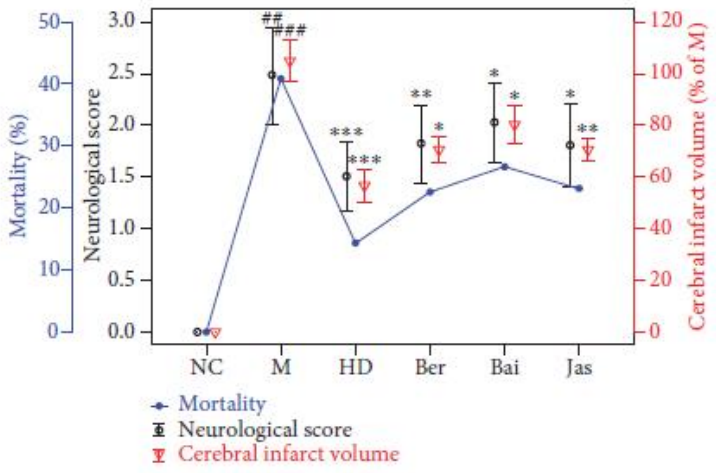
Tabella 1. Nutraceutici e prevenzione cerebrovascolare

PRODOTTO	PRINCIPI ATTIVI	MECCANISMO D'AZIONE
Riso rosso fermentato	Monacolina K	Ipocolesterolemizzante Riduzione rigidità vascolare
Fibre cereali		Insulino-sensibilizzante
Berberina		Ipocolesterolemizzante Insulino-sensibilizzante
Tè nero Tè verde	Polifenoli (Catechine)	Antiossidante
Acidi grassi omega-3	Acido linolenico	Neuroprotettivo
Steroli-stanoli vegetali		Riduzione assorbimento di colesterolo
Lactotripeptidi		Riduzione pressione arteriosa
Citrus Depressa	Nobiletina	Antiossidante
Policosanolo		Ipocolesterolemizzante Antiaggregante
Aglio	Allicina	Ipocolesterolemizzante Riduzione pressione arteriosa
Cacao	Flavonoidi	Antiossidante Insulino-sensibilizzante Miglioramento funzione endoteliale

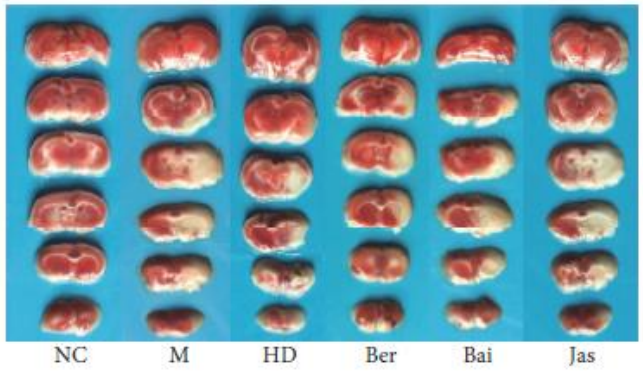
Treatment Effects of Ischemic Stroke by Berberine, Baicalin, and Jasminoidin from Huang-Lian-Jie-Du-Decoction (HLJDD) Explored by an Integrated Metabolomics Approach

Qian Zhang,[1] Xiaowei Fu,[1] Junsong Wang,[2] Minghua Yang,[1] and Lingyi Kong[1]

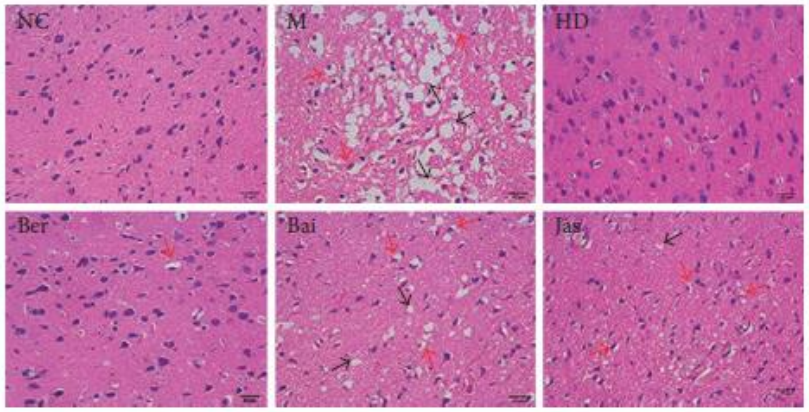
Oxidative Medicine and Cellular Longevity
Volume 2017, Article ID 9848594, 20 pages
https://doi.org/10.1155/2017/9848594



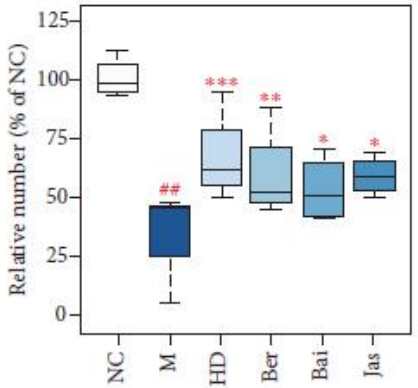
(a)



(b)



(c)



(d)

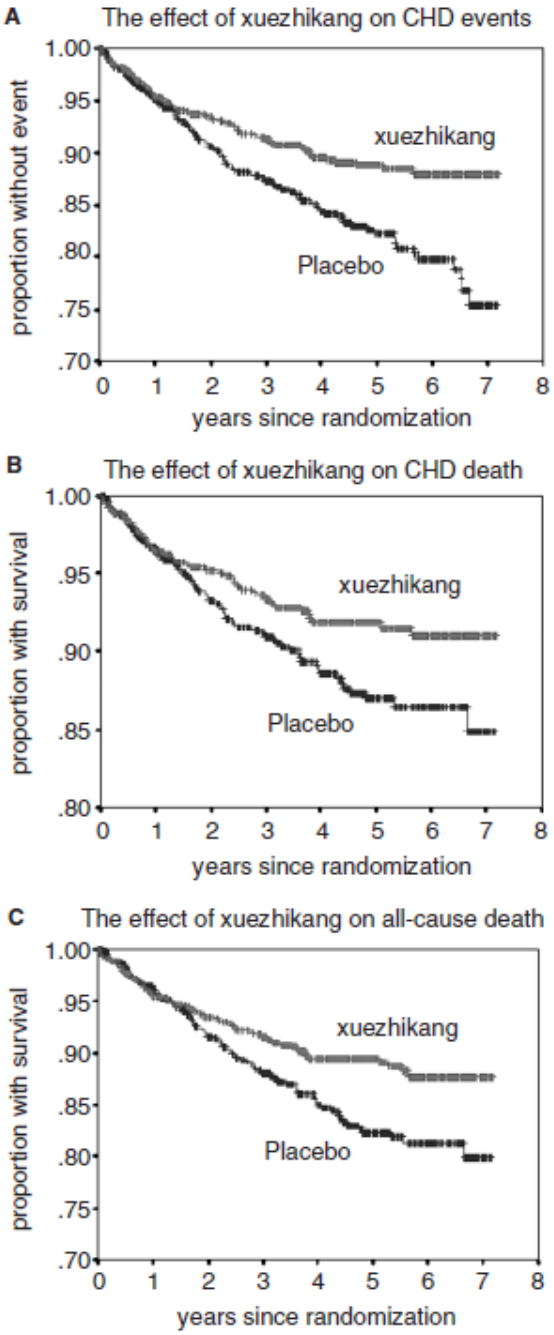
FIGURE 2: Neurological deficit, ischemic infarct, and histopathological assessment. (a) Mortality, infarct volume examinations, and neurobehavioral scores. (b) TTC sting of brains ($n = 6$). (c) Histopathological examination of brain tissues by hematoxylin-eosin (H&E) staining (×400 magnification; $n = 4$): neuronal loss and presence of numerous vacuolated spaces (black arrow) and disordered neuron arrangement (red arrow). (d) The abnormal neurons were counted and expressed relatively to the sham group ($n = 4$ in each group). $^{\#\#}p < 0.01$ and $^{\#\#\#}p < 0.001$, MCAO group versus sham group; $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$, drug-treated groups versus MCAO group.

Effect of Xuezhikang on Cardiovascular Events and Mortality in Elderly Patients with a History of Myocardial Infarction: A Subgroup Analysis of Elderly Subjects from the China Coronary Secondary Prevention Study

Ping Ye, MD, PhD, Zong-Liang Lu, MD,† Bao-min Du, MD,† Zuo Chen, MD, PhD,† Yang-Feng Wu, MD, PhD,†Xue-Hai Yu, MD,† and Yu-Cheng Zhao, MD,† for the CCSPS Investigators*

Table 3. Clinical Events in Two Groups

Clinical Event	Xuezhikang Group (n = 735) n (%)	Placebo Group (n = 710) n (%)	Intergroup Difference	P-Value*
Total CHD events	69 (9.4)	106 (14.9)	−36.9	.001
Nonfatal AMI	18 (2.4)	35 (4.9)	−51.0	.01
Fatal AMI	13 (1.38)	11 (1.55)	12.3	.74
Sudden death	24 (3.3)	31 (4.4)	−25.0	.27
Other CHD death	14 (1.9)	29 (4.1)	−53.6	.02
Total CHD death	51 (6.9)	71 (10.0)	−31.0	.04
Total death	68 (9.2)	96 (13.5)	−31.9	.01
Total stroke	24 (3.3)	42 (5.9)	−44.1	.04
Stroke survival	17 (2.3)	39(5.5)	−58.2	.006
Stroke death	7 (0.9)	3 (0.4)	125.0	.22
Percutaneous coronary intervention/coronary artery bypass graft	14 (1.9)	26 (3.7)	−48.6	.07
Cancer†	13 (1.8)	26 (3.7)	−51.4	.03
Cancer survival	7 (0.9)	9 (1.2)	−25.0	.57
Cancer death	6 (0.8)	17 (2.4)	−66.7	.02



J Am Geriatr Soc 55:1015–1022, 2007.

Green and Black Tea Consumption and Risk of Stroke
A Meta-Analysis

Lenore Arab, PhD; Weiqing Liu, MS; David Elashoff, PhD

Background and Purpose—Experimental models of stroke provide consistent evidence of smaller stroke volumes in animals ingesting tea components or tea extracts. To assess whether a similar association of black or green tea consumption with reduced risk is evident in human populations, we sought to identify and summarize all human clinical and observational data on tea and stroke.

Methods—We searched PubMed and Web of Science for all studies on stroke and tea consumption in humans with original data, including estimation or measurement of tea consumption and outcomes of fatal or nonfatal stroke. Data from 9 studies involving 4378 strokes among 194 965 individuals were pooled. The main outcome was the occurrence of fatal or nonfatal stroke. We tested for heterogeneity and calculated the summary effect estimate associated with consumption of ≥3 cups of tea (green or black) per day using random-effects and fixed-effects models for the homogeneous studies. Publication bias was also evaluated.

Results—Regardless of their country of origin, individuals consuming ≥3 cups of tea per day had a 21% lower risk of stroke than those consuming <1 cup per day (absolute risk reduction, 0.79; CI, 0.73 to 0.85). The proportion of heterogeneity not explained by chance alone was 23.8%.

Conclusions—Although a randomized clinical trial would be necessary to confirm the effect, this meta-analysis suggests that daily consumption of either green or black tea equaling 3 cups per day could prevent the onset of ischemic stroke.
(***Stroke***. **2009;40:1786-1792.**)

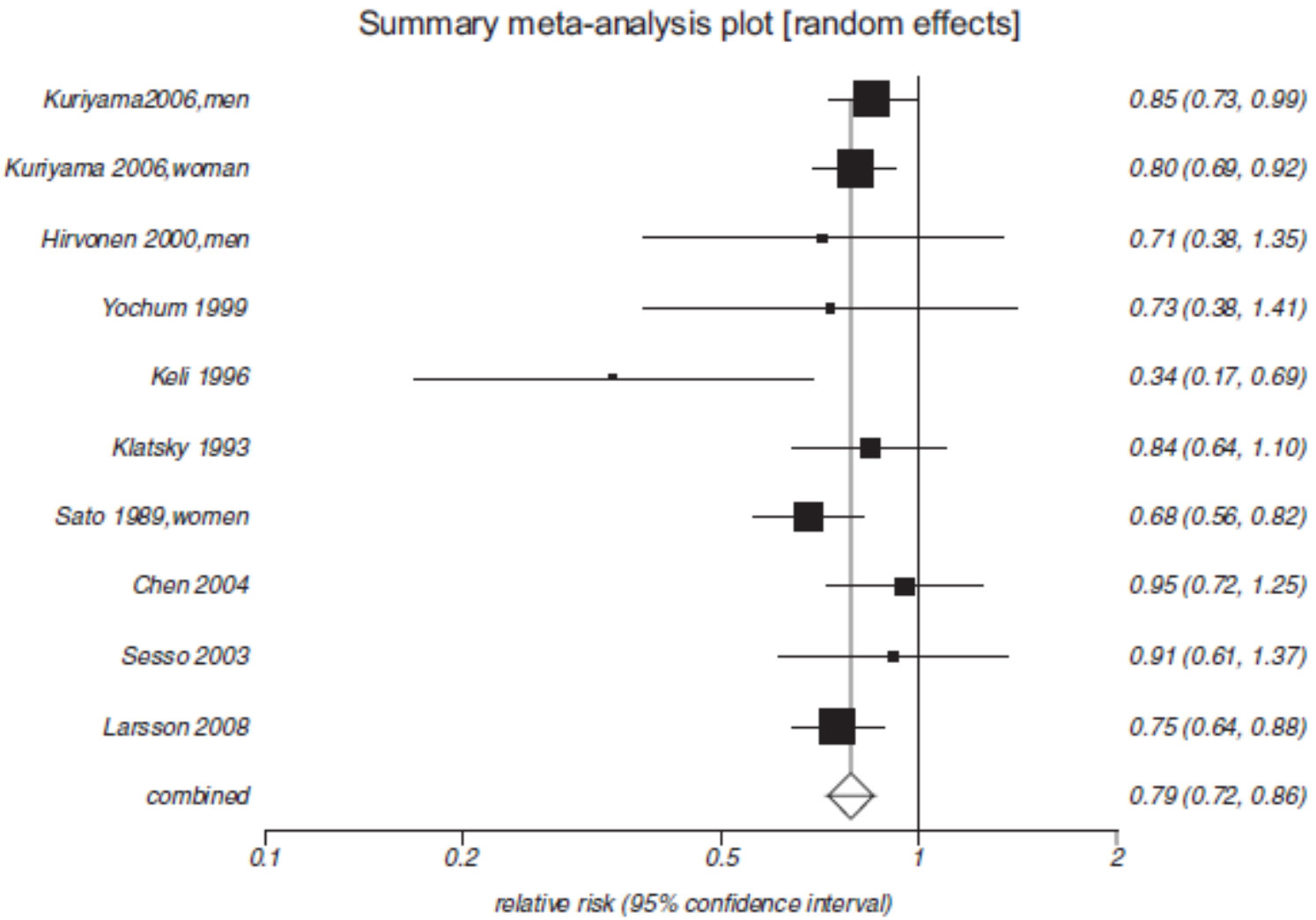


Figure 2. Forest plot of studies of stroke and tea consumption.

Combination Medical Foods: Fortasyn Connect

DHA	1200 mg
EPA	300 mg
UMP	625 mg
Choline	400 mg
Folic acid	400 µg
Vit B6	1 mg
Vit B12	3 µg
Vit C	80 mg
Vit E	40 mg
Se	60 µg
Phospholipids	106 mg

Designed to support the formation and function of synapses

125 ml, once-per-day, milk-based liquid

Vanilla or strawberry flavours

Macronutrients:

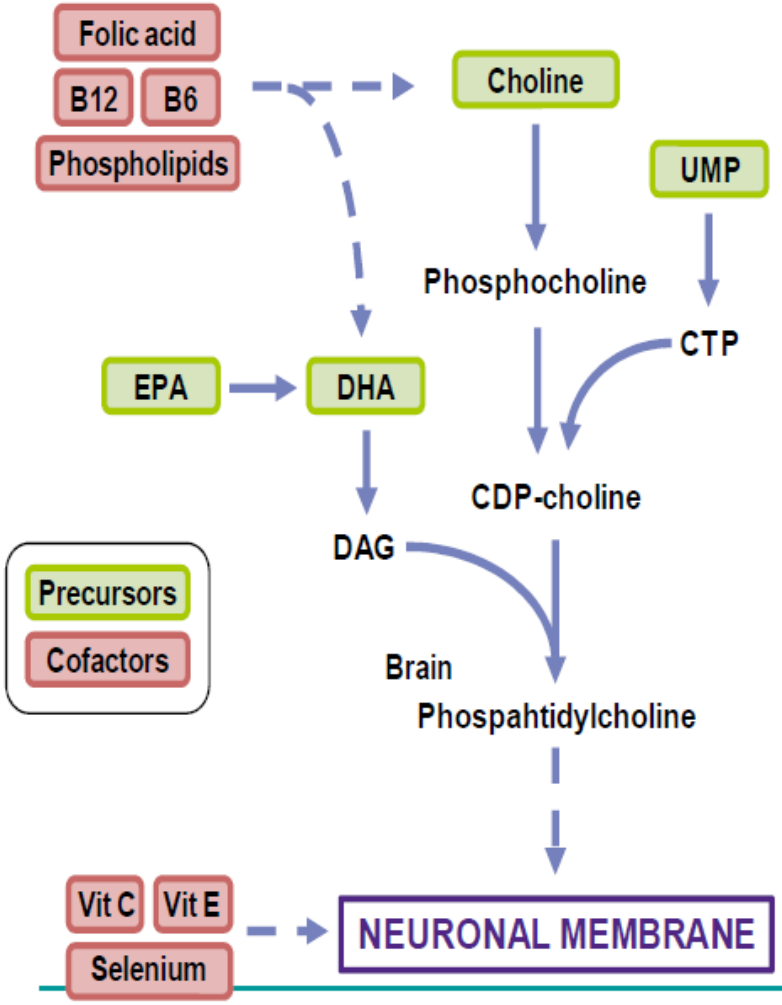
125 kcal, as protein (12%), fat (34%), CHO (53%)

Micronutrients

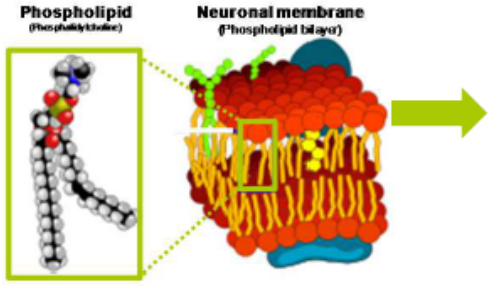
Other micronutrients according to FSMP levels

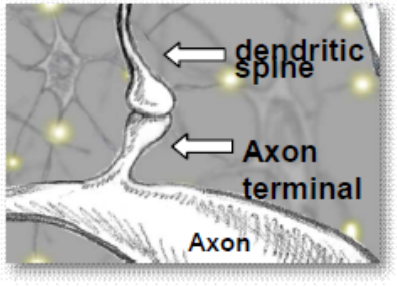
FORTASYN CONNECT

Mechanism of action: enhancing synaptic membranes



- Phospholipid synthesis depends on the presence of uridine, choline and DHA
- B-vitamins enhance precursor bioavailability
- Antioxidants protect the neuronal membrane and maintain its integrity, stability and function





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

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

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

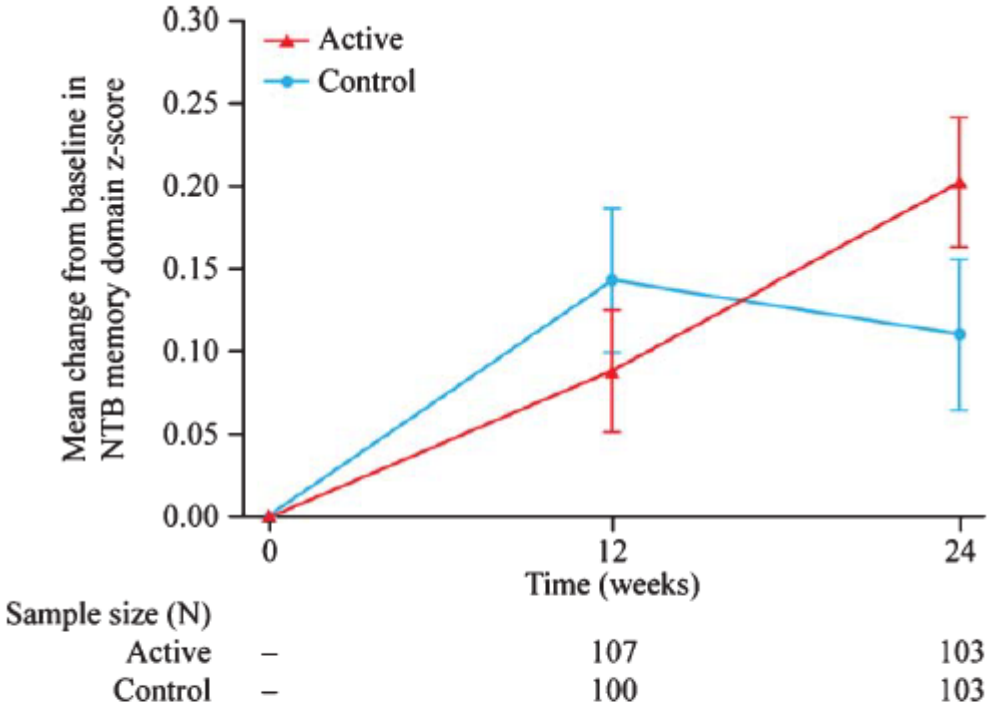


Fig. 2. Mean change from baseline in the Neuropsychological Test Battery (NTB) memory composite score. Error bars represent standard errors. The difference in trajectories over time between active and control groups during the 24-week intervention period: $p = 0.023$ (mixed model for repeated measures, 2 degrees of freedom contrast).

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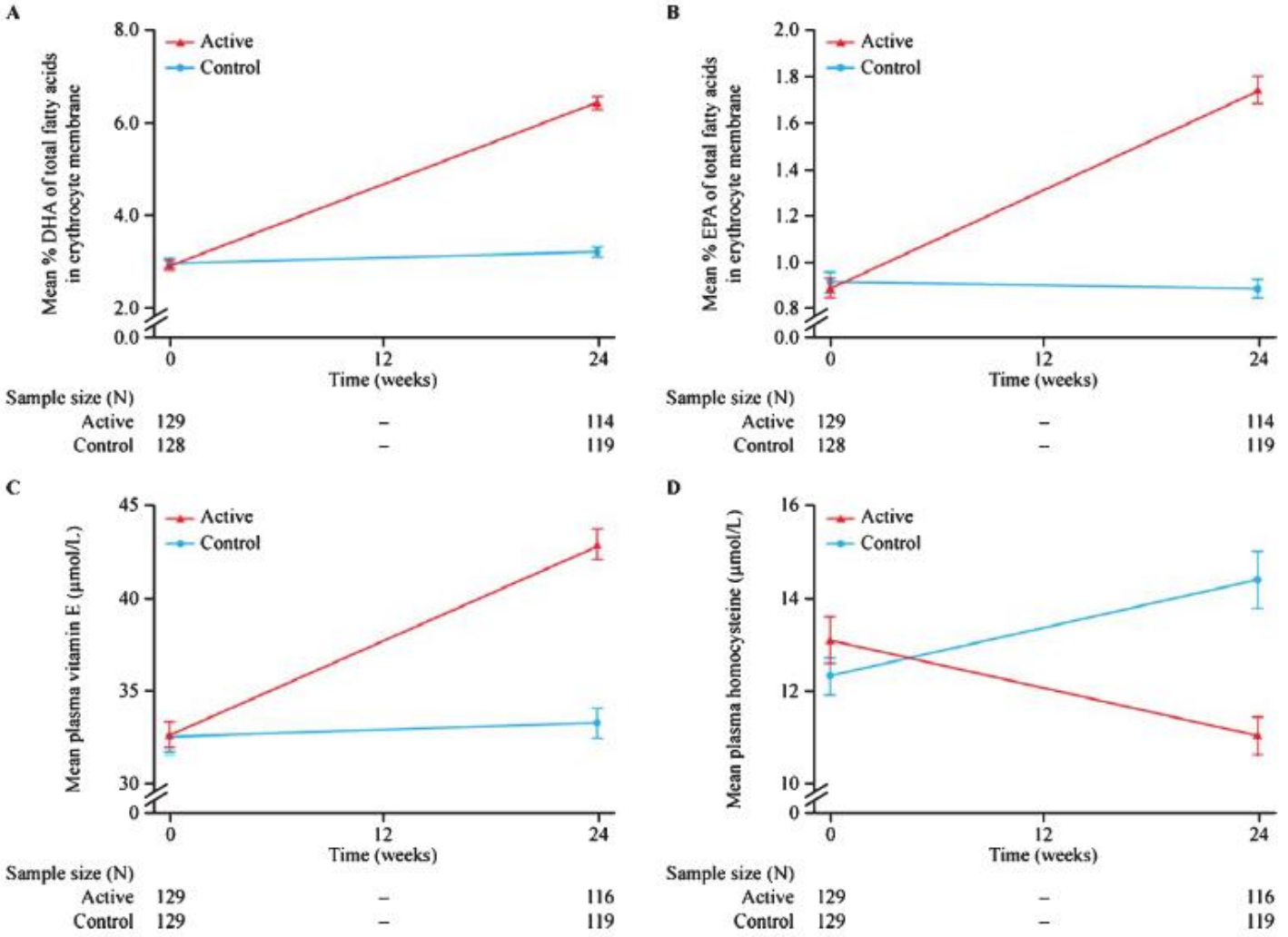


Fig. 5. Mean (A) docosahexaenoic acid (DPA) percentage of fatty acids in erythrocyte membrane, (B) eicosapentaenoic acid (EPA) percentage of fatty acids in erythrocyte membrane, (C) plasma vitamin E levels, and (D) plasma homocysteine. Error bars represent standard errors $p < 0.001$ (Mann-Whitney U test).

Tolerability and Safety of Souvenaid in Patients with Mild Alzheimer's Disease: Results of Multi-Center, 24-Week, Open-Label Extension Study

Journal of Alzheimer's Disease 44 (2015) 471–480
DOI 10.3233/JAD-141305
IOS Press

Marcel G.M. Olde Rikkert[a,*], Frans R. Verhey[b], Rafael Blesa[c], Christine A.F. von Arnim[d], Anke Bongers[e], John Harrison[f], John Sijben[e], Elio Scarpini[g], Maurits F.J. Vandewoude[h], Bruno Vellas[i], Renger Witkamp[j], Patrick J.G.H. Kamphuis[e] and Philip Scheltens[k]

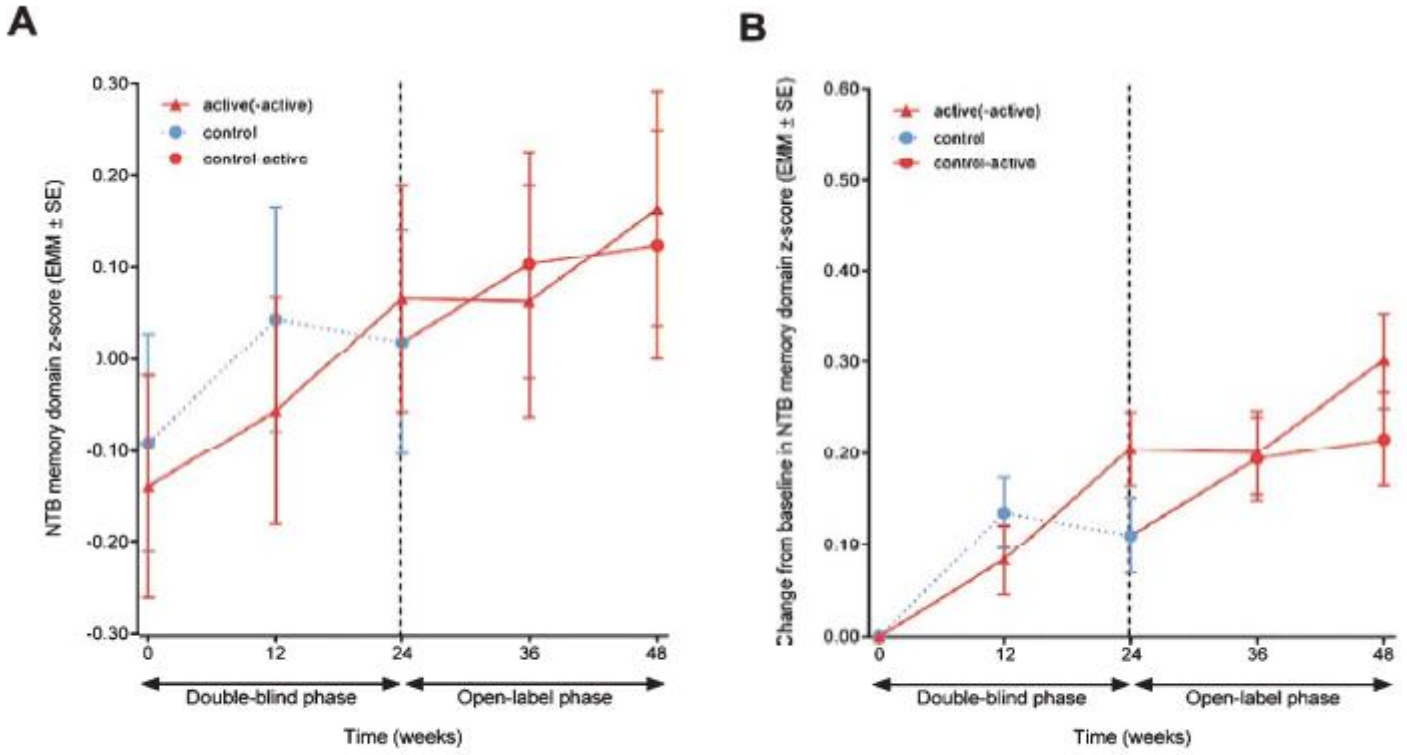


Fig. 3. NTB memory domain composite z-scores for both the double-blind RCT and OLE study period in (A) observed values and (B) change from baseline (RCT week 0). 24–48 week change for active-active group; paired *t*-test: $p = 0.025$; MMRM: $p = 0.015$ and for control-active group; paired *t*-test: $p = 0.008$; MMRM: $p = 0.007$. Data are estimated marginal mean (EMM) and standard error (SE).

24-month intervention with a specific multinutrient in people with prodromal Alzheimer's disease (LipiDiDiet): a randomised, double-blind, controlled trial

Lancet Neurol 2017; 16: 965–75

*Hilkka Soininen, Alina Solomon, Pieter Jelle Visser, Suzanne B Hendrix, Kaj Blennow, Miia Kivipelto, Tobias Hartmann, on behalf of the LipiDiDiet clinical study group**

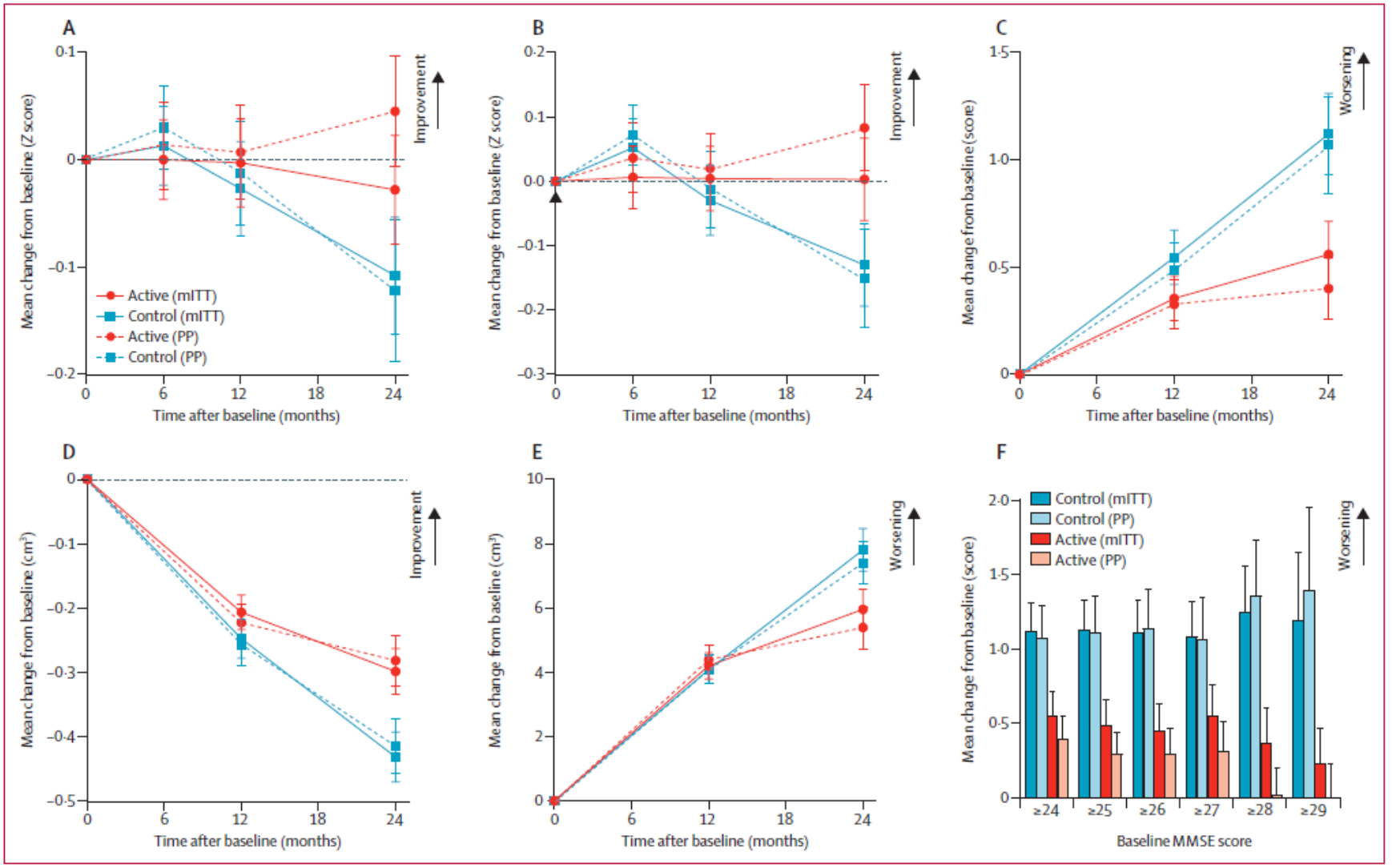
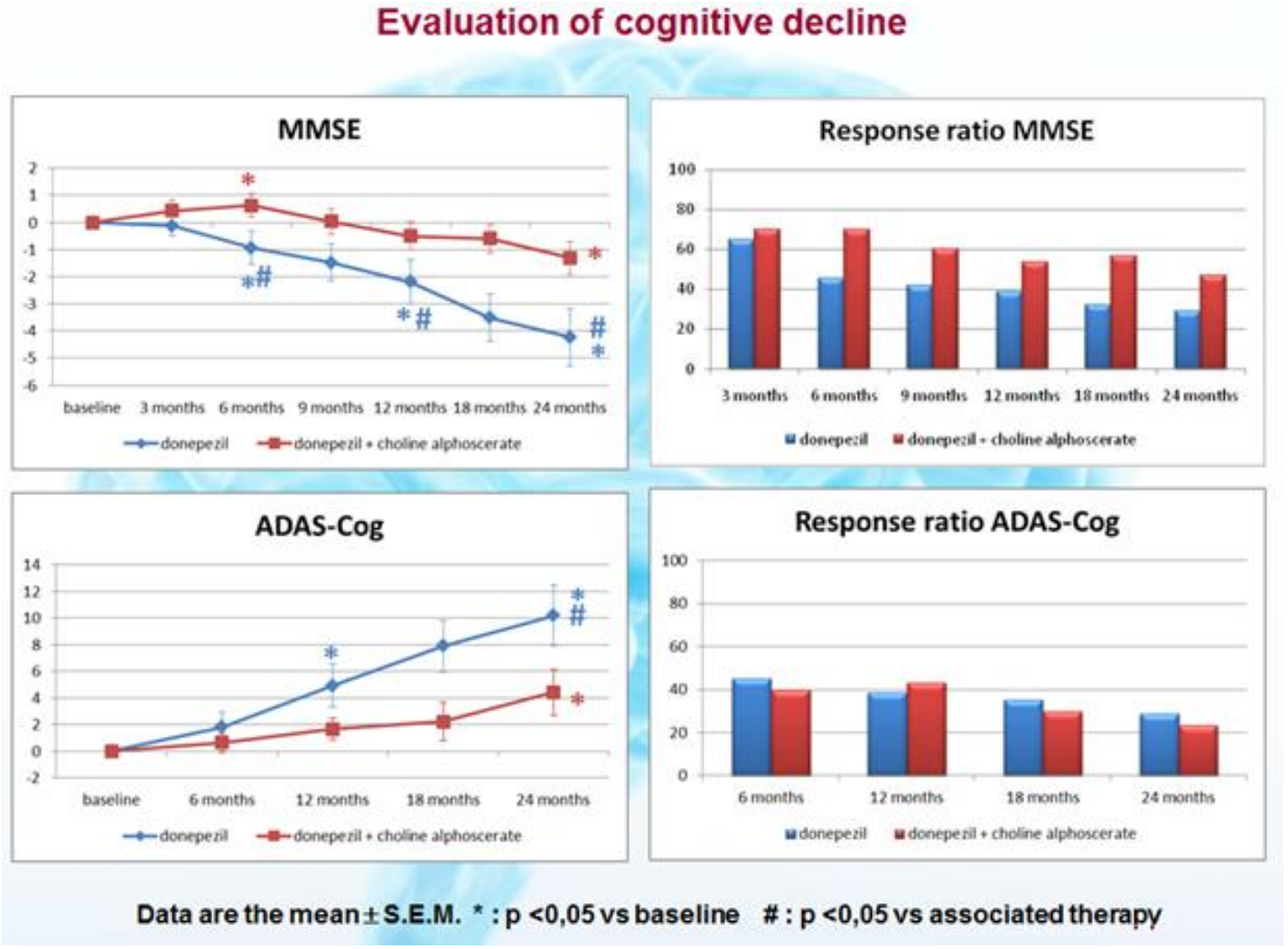


***Figure 2*: Changes in main endpoints during the 24-month intervention**

(A) NTB primary endpoint. (B) NTB memory domain. (C) CDR-SB. (D) MRI total hippocampal volume. (E) MRI ventricular volume. (F) CDR-SB in subgroups defined by baseline MMSE. Data are observed mean change from baseline; error bars are SE. Sample size by baseline MMSE subgroup (control/active): ≥24: mITT 117/106 (PP 96/89), ≥25: 104/91 (86/75), ≥26: 95/79 (78/66), ≥27:77/63 (66/53), ≥28: 55/43 (48/37), ≥29 29/21 (24/19). CDR-SB=clinical dementia rating-sum of boxes. mITT=modified intention-to-treat analysis. MMSE=Mini-Mental State Examination. NTB=neuropsychological test battery. PP=per-protocol analysis.

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.



Amenta et al., J Alzheimer's Dis 2014; 42(s3): S281-8)

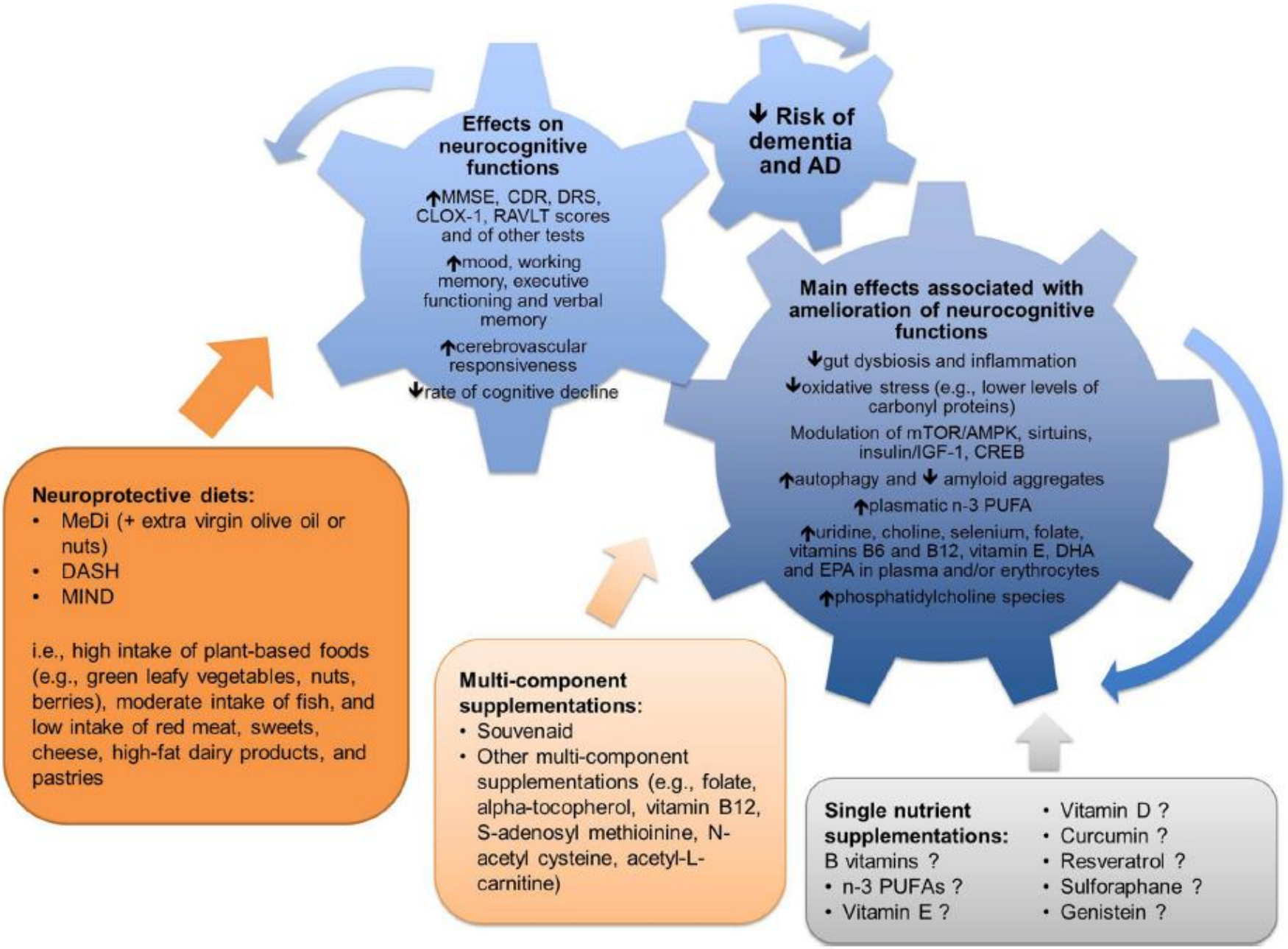


Fig. 1. Summary of the main effects elicited by single nutrient, multi-component supplementations, and specific healthy diets (e.g., MeDi, DASH and MIND), and their association with amelioration of neurocognitive functions and neuroprotection. Attention to overall diet compositions, rather than single nutrient supplementation strategies, may represent a more effective approach for the prevention and management of AD and dementia risk. The figure has been created according to the guidelines for preparing color figures [230].

Pistollato F. et al., Pharm Res 2018: 131: 32-43

Nutrizione e Deterioramento Cognitivo

- La adesione alla Dieta Mediterranea sembra associarsi a effetti benefici sugli aspetti cognitivi
- Un approccio dietetico globale (inquadrato in un corretto stile di vita) sembra avere effetti migliori, rispetto alla supplementazione con i singoli nutrienti (assenza di dati a favore dell'utilizzo di acidi grassi Omega-3, dati limitati con vitamine)
- E' plausibile che interventi in ambito di prevenzione cerebrovascolare possano avere effetti protettivi sul decadimento cognitivo
- Vi sono dati incoraggianti da singoli studi clinici con integratori (donatori di colina, agenti che aumentano la produzione di fosfolipidi)
- Qualsiasi approccio con dieta o nutraceutici deve essere condotto **precocemente**

University of Modena and Reggio Emilia

Department of Biomedical, Metabolic
and Neural Sciences