Herbals, Supplements and Dementia

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Overview

- *Ginkgo Biloba*
- ω3 Fatty Acids
- Antioxidants (Vitamins E and C)
- Huperzine A

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- There is a relationship between nutrient deficiency and dementia onset.
- There is evidence to suggests that antioxidants and ω-3 fatty acids may be neuroprotective.
- *Ginkgo Biloba* and Huperzine A have a long history of use in Chinese medicine for the treatment of cognitive disorders and memory.

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Ginkgo biloba

- History
  - Used in traditional Chinese medicine for thousands of years. Only used in Western medicine since the 1960’s.
- Botanical aspects
  - A deciduous tree where leaves, fruits and seeds are all used for medicinal purposes.

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Ginkgo biloba: Pharmacology

- Antioxidant/Anti-inflammatory
- Free radical scavenger
- Anti-amyloid formation (*in vitro*)
- Anti-platelet activation factor

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Ginkgo biloba: Pharmacology

- Vasodilation
- Lower blood pressure
- Increased capillary flow and decreased blood viscosity
- Stimulation of endothelium-derived relaxing factor
- Increased nitric oxide and decreased endothelin-1 in vivo
- Neuroprotective effects and neurotransmitter modulation in animal and *in vitro* studies

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EGb761

- Well studied standardized extract preparation of the ginkgo leaf
  - 24% flavanoid glycosides
  - 6% terpene lacones (ginkgolides & bilobalide)
  - < 5ppm ginkgolic acid
  - A large number of the published clinical studies have been funded by "Dr. Willimar Schwabe GmbH & Co. Kg, Karlsruhe, Germany", the manufacturer of EGb761.

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Ginkgo biloba: Dementia and Alzheimer's Disease

- > 30 double blind, placebo controlled trials evaluating *Ginkgo biloba* have been published.
- Most early smaller studies showed *Ginkgo biloba* to be more efficacious than placebo.
- Large multi-center placebo controlled studies in US and Europe (GEM and GuidAge) found no preventative effect.

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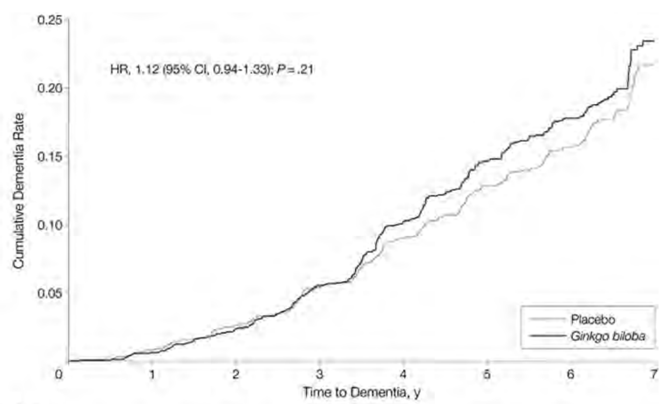
Ginkgo biloba for Prevention of Dementia
A Randomized Controlled Trial

- Randomized double blind, placebo controlled trial conducted in 5 academic medical centers. (GEM study)
- N=3,069 subjects age ≥ 75 yrs with normal cognition (n=2587) or mild cognitive impairment (n=482)
- Treatment: *Ginkgo biloba* 120 mg twice daily or placebo (EGb761 extract) with a mean follow-up of 6.1 years.
- Primary outcome: Incidence of dementia and Alzheimer's disease as evaluated every 6 months.

DeKosky et al. JAMA 2008:300:2253-62 9



No. at risk	0	1	2	3	4	5	6	7
Placebo	1524	1485	1423	1342	1243	1148	792	81
G biloba	1545	1521	1458	1369	1254	1129	775	97

No. with incident dementia							
Placebo	13	26	40	50	51	36	30
G biloba	10	26	47	66	60	40	27

Conclusion: *G. Biloba* was not effective in reducing the incidence rate of dementia or AD

DeKosky et al. JAMA 2008:300:2253-62 10

Table 3. Specific Serious Adverse Events

Type	No. (%) Placebo	Ginkgo Biloba	HR (95% CI)	P Value
Death	188 (12.3)	197 (12.8)	1.04 (0.85-1.26)	.72
Bleeding, total	140 (9.2)	138 (8.9)	0.97 (0.77-1.23)	.81
Gastrointestinal	77 (5.1)	83 (5.4)	1.06 (0.78-1.45)	.70
All other	71 (4.7)	64 (4.1)	0.89 (0.64-1.25)	.52
CHD total	204 (13.4)	211 (13.7)	1.02 (0.84-1.24)	.83
Myocardial infarction	76 (5.0)	90 (5.8)	1.18 (0.87-1.59)	.30
Angina	99 (6.5)	107 (6.9)	1.06 (0.81-1.40)	.65
Angioplasty	65 (4.3)	79 (5.1)	1.20 (0.87-1.67)	.27
CABG	49 (3.2)	51 (3.3)	1.02 (0.69-1.52)	.90
CHD death	47 (3.1)	48 (3.1)	1.01 (0.67-1.50)	.98
Stroke, total	71 (4.7)	80 (5.2)	1.12 (0.81-1.54)	.50
Ischemic	62 (4.1)	62 (4.0)	0.99 (0.70-1.41)	.96
Hemorrhagic	8 (0.5)	16 (1.0)	1.97 (0.84-4.61)	.12
Unknown	2 (0.1)	3 (0.2)		

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.

It was concerning even if it was not statistically significant

DeKosky et al. JAMA 2008:300:2253-62

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Ginkgo biloba for Preventing Cognitive Decline in Older Adults

A Randomized Trial

- The GEM trial To determine whether *Ginkgo biloba* slowed the rate of global or domain-specific cognitive function.
- Treatment: *Ginkgo biloba* 120 mg twice daily vs. placebo (EGb761 extract)
- Primary outcome evaluated: Rate of change over time in the Modified Mini-Mental State Examination, the cognitive subscale of the Alzheimer's Disease Assessment Scale and in neuropsychological domains of memory, attention, visual-spatial construction, language, and executive function.
- Results: "Compared with placebo, the use of *G. biloba*, 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild impairment."

Snitz et al. JAMA 2009:302:2663-70

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Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): a randomised placebo-controlled trial

- GuidAge study: Randomized placebo controlled trial
- n=2,854 adults age $\geq$ 70 y with reported memory complaints
- Treatment: 120 mg twice daily standardized *Ginkgo biloba* extract (EGb761) or matched placebo
- Primary outcome: Diagnosis of Alzheimer's disease.
- Results: Long term use of standard ginkgo biloba did not reduce the progression of Alzheimer's disease in patients with memory complaints.

Safety: No increased risk of stroke in this study

Vellas et al. Lancet Neurol. 2012;11:851-9

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Ginkgo biloba for cognitive impairment and dementia

Cochrane Database of Systematic Reviews

- Effect of *Ginkgo biloba* any strength or duration compared to placebo in patients with cognitive impairment, including dementia, of any degree or severity.
- N = 36 trials, most were small and < 3 months
  - 9 trials (2,016 patients) were 6 months of duration.
  - Most used EGb761 at different doses
- Results: Inconsistent results for cognition, activities of daily living, mood, depression and caregiver burden.
  - 4 most recent trials were longer and of adequate size, 3 found no difference between placebo and *Ginkgo biloba* and one reported a large treatment effect in favor of *Ginkgo biloba* (neuropsychiatric features)
- Sub-analysis of Alzheimer's disease patients (n=925) found no consistent pattern of any benefit compared to placebo

Birks et al. Cochrane Database of Systematic Reviews 2009:

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Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg

- Multi-center double blind, randomized, placebo-controlled, 24-week trial.
- N=410 patients with mild to moderate dementia (Alzheimer's disease and vascular dementia).
- Treatment: *Ginkgo biloba* extract EGb 761® 240 mg once daily.
- Primary outcome: SKT, a 9-item cognitive test battery and the Neuropsychiatric Inventory (NPI), 12 item test.

- Funded by "Dr. Willimar Schwabe GmbH & Co. Kg, Karlsruhe, Germany", the manufacturer of EGb761.

Herrschaft et al. J Psychiatric Research 2012:46:716-723

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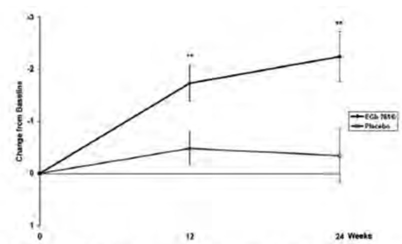

Fig. 2. Change in SKT total score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals; $^{**}p < 0.001$. ANCOVA with treatment and centre as factors and the baseline value as covariate.

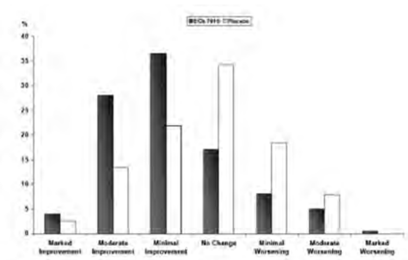

Fig. 4. Clinical global impression of change (ADCS-CGIC) at week 24; full analysis set ($n = 410$); $p < 0.001$. Chi-square test.

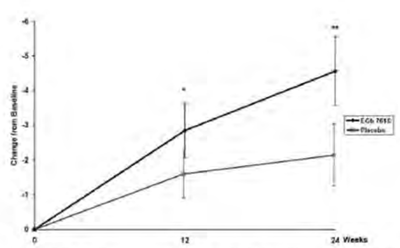

Fig. 3. Change in NPI composite score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals; $^{*}p < 0.01$, $^{**}p < 0.001$. ANCOVA with treatment and centre as factors and the baseline value as covariate.

Table 3
Adverse events reported by at least 3% of patients of either treatment group with onset during and within two days after randomised treatment (safety analysis set); number and per cent of patients with adverse events.

	EGb 761® ($N = 205$)		Placebo ($N = 205$)		EGb 761® – placebo Diff. of rates with 95% CI[a]
	N	%	*N*	%	
Headache	15	7.3	17	8.3	−1.0 [−6.4; 4.4]
Dizziness	4	2.0	15	7.3	−5.4 [−9.9; −1.3]
Viral respiratory tract infection	8	3.9	6	2.9	1.0 [−2.9; 4.9]
Hypertension	5	2.4	8	3.9	−1.5 [−5.3; 2.2]
Somnolence	8	3.9	4	2.0	2.0 [−1.6; 5.8]
Upper abdominal pain	5	2.4	7	3.4	−1.0 [−4.7; 2.6]

[a] 95% confidence intervals calculated according to Newcombe (1998), Method 10.

"There was a significant and clinically relevant improvement in cognition, psychopathology, functional measures and quality of life in patients and caregivers"

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Ginkgo biloba: Summary

- Efficacy: Lack of evidence demonstrating a benefit in large studies using a standardize product.
  - "If *Ginkgo biloba* were a drug, and not marketed as a food supplement, clinical testing for efficacy against Alzheimer's disease and cognitive impairment would have ended long ago."
    - *Schneider LS. Lancet Neurol. 2012:11:836-7.*
- Question: Is there a role for Ginkgo biloba in dementia with neuropsychiatric features?

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Ginkgo biloba: Summary

- Safety: Overall good, except reports of rare bleeding episodes.
- Drug Interactions: Use cautiously or avoid use in patients receiving anti-platelet drugs. (i.e. aspirin, clopidogrel) and anticoagulants (i.e. warfarin, dabigatran, apixaban)

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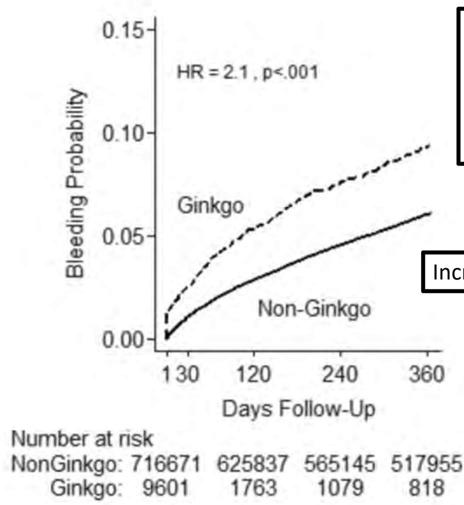
Ginkgo and Warfarin Interaction in a Large Veterans Administration Population



VA data base 2008-2014
N=807,399 patients
N=11,003 had used ginkgo + warfarin
Bleeding: GI bleeds, Intracranial Bleeds

Increased risk of bleeding adverse event

Stoddard et al. AMIA Annu Symp Proc
2015: Nov 5: 1174-83 eCollection

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Product selection: EGb761 is the best studied.
Dose: 120-240 mg twice daily or 240 mg tablet once daily.

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Fish Oil (ω-3)

- Many health benefits of eating fatty fish are well established, especially lowering of triglycerides and general cardiovascular health.
- According to the latest questionnaire from the National Institutes of Health's National Center for Complementary and Integrative Health and CDC's National Center for Health Statistics, omega-3 fish oil was the top natural product used by adults.
- Significant evidence for CV disease

Fish Oil Supplements ≠ Eating fatty fish

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Fish Oil (ω-3)

- Usually contains ~ 30% omega-3 fatty acids
  - Are <u>essential</u> unsaturated fatty acids
    - vital to normal metabolism and can not be synthesized by the human body
- EPA and DHA are the most prevalent
  - Eicosapentaenoic acid (EPA) – C20
  - Decosahexanoc acid (DHA) – C22
- EPA and DHA: highest amounts in oily fish
  - mackerel, trout, salmon, herring and sardines

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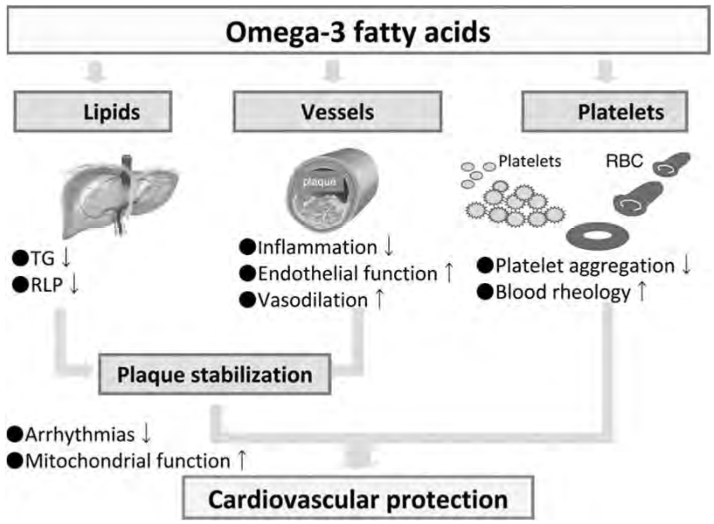
Summary of Proposed Beneficial effects of omega-3 fatty acids



Kromhout D et al. Eur Heart J 2011;eurheartj.ehr362

European Heart Journal

The pleiotropic effects of omega-3 docosahexaenoic acid on the hallmarks of Alzheimer's disease

- 60% of PUFA in neuronal membranes consists of DHA. It is the most common PUFA in the brain.
  - Involved in neurogenesis, synaptogenesis, neuronal differentiation, neurite outgrowth and maintenance of membrane fluidity.
- Normal aging and neurodegenerative disease characterized by cognitive decline is correlated with a deficiency in DHA in blood and brain.
  - Cause vs Consequence?

Belkouch et al. J Nutritional Biochemistry 2016:38:1-22

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Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies[1–3]

- 181,580 subjects with 4,428 cases identified during the 2.1-21 year follow-up.
- At least 1 serving/wk increment of dietary fish is associated with 5% lower risk of dementia and a 7% lower risk of AD.
- 0.1 g/day increment of dietary DHA was associated with a 14% lower risk of dementia and a 37% lower risk of AD.
- "Significant curvilinear relations between fish consumption and risk of AD and between total PUFAs and mild cognitive impairment."

Zhang et al. Am J Clin Nutr 2016:103:330-40

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Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline

- Randomized, double-blind, placebo controlled study in US.
- Aged ≥ 55 y with MMSE > 26 and a Logical Memory (Wechsler Memory Scale III) baseline score ≥ 1 standard deviation below young adults.
- Treatment: 900 mg/d DHA or placebo for 24 weeks.
- Results: DHA improved the CANTAB Paired Associated Learning (PAL).
- Conclusion: DHA improved learning and memory function in age related cognitive decline.

Yurko-Mauro et al. Alzheimer's & Dementia 2010:6:456-64

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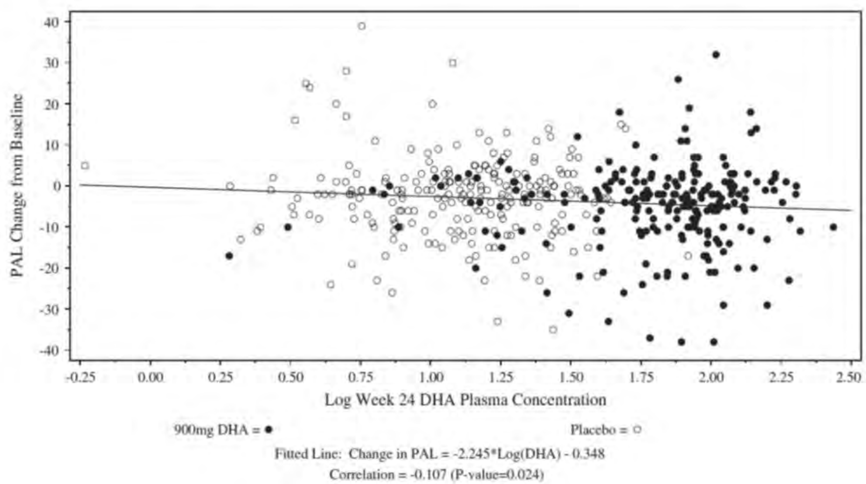
K. Yurko-Mauro et al. / Alzheimer's & Dementia 6 (2010) 456–464



Plasma levels of DHA doubled and correlated with improved PAL scores.

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Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial

- 3-year multi-center, randomized, placebo-controlled superiority trial with 4 parallel groups at 13 memory centers in France and Monaco.
- N=1680, participants without dementia with a spontaneous memory complain to their physician; aged ≥ 70 yr) MMSE score > 24
- DHA 800 mg + EPA 225 mg per day for 3 years.
  Multi-domain intervention (cognitive stimulation, physical activity and nutrition)
- Results: No significant effect of the multi-domain intervention and/or ω3 fatty acids on cognitive decline.

Andrieu et al. Lancet Published online March 27, 2017

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

Cochrane Database of Systematic Reviews

- 3 studies with 632 subjects with mild to moderate Alzheimer's disease on a stable dose of cholinesterase inhibitors or memantine.
  - Freund-Levi 2006, Quinn 2010, Shinto 2014
- EPA + DHA 1750 – 2300 gm/day for 6 months.
- Results: No significant effect on cognition function, severity of dementia, quality of life or mental health at 6 months.

Burckhardt et al. Cochrane Database Syst Rev 2016:April 11: 4

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Plasma Fatty Acid Profiles in Relation to Cognition and Gender in Alzheimer's Disease Patients During Oral Omega-3 Fatty Acid Supplementation: The OmegAD Study

- Subgroup analysis of OmegAD study, found that an effect of ω3 fatty acids on very mild cognitive dysfunction (MMSE > 27) and not advanced disease.
- Relationship between plasma ω3 to cognitive studies.
  - Dose-response relationship between plasma levels of ω3 fatty acids and preservation of cognition.
  - Levels were dependent on body weight. Females had higher plasma levels but the effect disappeared when adjusted for body weight.
- Conclusion: Future studies should use body weight adjusted does of ω3 fatty acids.

Eriksdotter et al. J Alzheimer's Disease 2015:48:805-12

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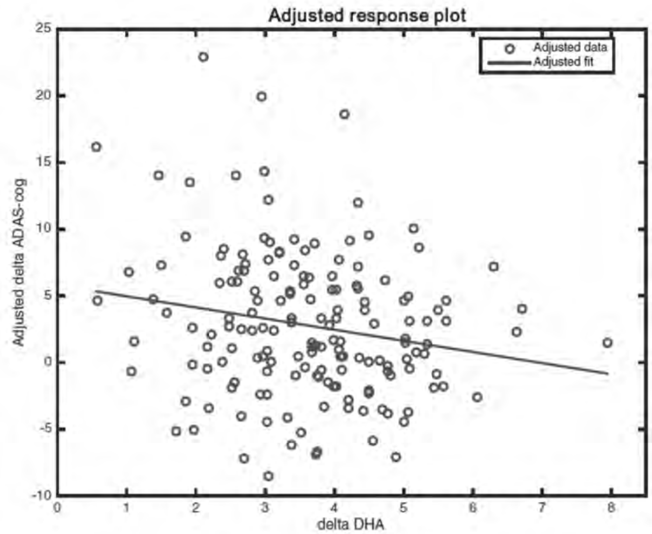

Fig. 1. Scatter plot of the changes of DHA versus the changes of ADAS-cog during 6 months of ω3 FA supplementation, adjusted for baseline ADAS-cog scores, baseline weight, and gender ($B = -0.834$, $p = 0.016$).

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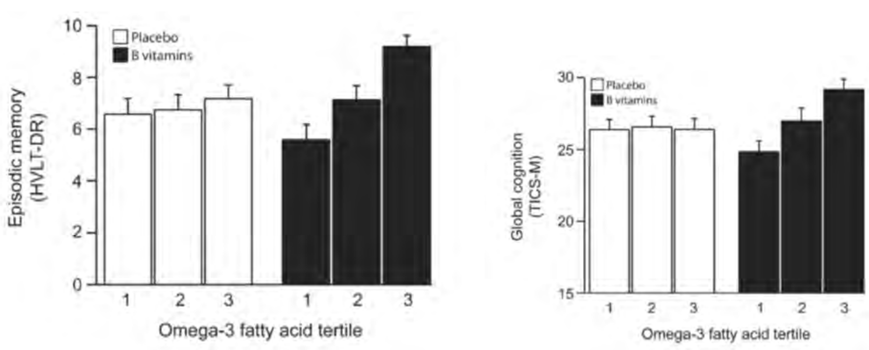
Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment

N=266 subjects, > 7- years with MCI. Treated with high dose B vitamins Or placebo for 2 years.



Oulhaj et al. J Alzheimer's disease 2016:50:547-557

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Fish Oil - Summary

- Efficacy
  - Higher fish and fish oil intake has been linked to a decreased risk of developing Alzheimer's disease (AD) in population studies.
  - Treatment with ω-3 supplements (6 months) had no effect on cognitive function in patients with AD.
  - Conflicting data on whether or not ω-3 supplements are effective in age-related cognitive decline.

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Fish Oil: Adverse Effects

- Fishy odor, fishy taste
- Nausea/vomiting/diarrhea/constipation
- Decrease appetite
- Eructation (burping!)
- LDL-cholesterol: increased by 5%
- Mercury Contamination:
  - Shark, swordfish, king mackerel, tilefish, albacore tuna contain significant amount of mercury
    - However, they are seldom used in fish oil production
- Increased risk of prostate cancer in men
  - SELECT trial and other reports of increased risk in men with high ω-3 concentrations.

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Fish Oil -

- Safety
  - Excellent safety in doses less than 4 gm/day
  - In very high doses, there have been reports of an increased risk of bleeding.
  - Risk of prostate cancer in men needs to be considered.
- Drug Interactions
  - In high doses (> 3 g/d) fish oil may interact with warfarin and possibly with aspirin and other antiplatelet adhesion drugs and cause an increase risk of bleeding.
    - A theoretical interaction with few case reports
    - However, use cautiously in patient receiving anti-platelet drugs (i.e. aspirin, clopidogrel) and anticoagulants (i.e. warfarin, dabigatran, apixaban)

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Fish Oil - Summary

- Unresolved efficacy issues
  - There is not good evidence for:
    - the optimal dose (of fish or DHA/EPA)
    - the ratio of DHA to EPA
    - Whether or not supplementation with EPA and DHA is associated with prostate cancer?
      - And/or is DHA protective?
    - the role of the omega-3/omega-6 ratio
    - duration of supplement treatment that would be needed for an effect, if supplements are effective.

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Use products from small, oily fish like sardines and anchovies. These have the lowest risk for heavy metal and other contaminants.

Antioxidants: Vitamin E & C

- Oxidative stress may play a role in Alzheimer's disease. Use of anti-oxidants has been suggested as a preventative measure to reduce dementia risk.
- Vitamin E is a family of 8 different fatty soluble compounds with varying degrees of anti-oxidant activity.
  - α-Tocopherol is the most biologically important form of Vitamin E and is the only form recognized to meet human requirements.
- Vitamin C: Ascorbic acid is a water soluble vitamin, a coenzyme and an electron donor involved in formation of collage, muscle and blood vessels.

- Several large randomized controlled trials have found that supplementation with Vitamin E ± Vitamin C does not maintain cognitive performance in cognitively intact individuals nor delay the onset of AD in patient with mild cognitive impairment.
- Observational studies have found conflicting results.

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Antioxidant Vitamin Supplement Use and Risk of Dementia or Alzheimer's Disease in Older Adults

Shelly L. Gray, PharmD, MS, Melissa L. Anderson, MS,† Paul K. Crane, MD, MPH,‡ John C. S. Breitner, MD, MPH,‡§ Wayne McCormick, MD, MPH,‖ James D. Bowen, MD,# Linda Teri, PhD,**††‡‡ and Eric Larson, MD, MPH†*

Use of Vitamin E and C Supplements for the Prevention of Cognitive Decline

Luta Luse Basambombo, MSc[1], Pierre-Hugues Carmichael, MSc[1], Sharlène Côté, MD, MSc[2], and Danielle Laurin, PhD[1]

Reduced Risk of Alzheimer Disease in Users of Antioxidant Vitamin Supplements

The Cache County Study

Peter P. Zandi, PhD; James C. Anthony, PhD; Ara S. Khachaturian, PhD; Stephanie V. Stone, PhD; Deborah Gustafson, PhD; JoAnn T. Tschanz, PhD; Maria C. Norton, PhD; Kathleen A. Welsh-Bohmer, PhD; John C. S. Breitner, MD; for the Cache County Study Group

Gray et al. JAGS 2008:56:291-295; Zandi et al. Arch Neurol 2004:51:82-88;
Basambombo et al. Ann Pharmacotherapy 2016:1-8

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Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

Vit E: 2000 IU/daily (3 y)

Impact of antioxidants, zinc, and copper on cognition in the elderly

A randomized, controlled trial*

Age-Related Eye Disease Study Research Group

Vit C: 500 mg (6.9 y)
Vit E: 400 IU

A Randomized Trial of Vitamin E Supplementation and Cognitive Function in Women

Jae Hee Kang, ScD; Nancy Cook, ScD; JoAnn Manson, MD, DrPH; Julie E. Buring, ScD; Francine Grodstein, ScD

Vit E: 600 IU qod (5.6 y)

Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE)

Richard J. Kryscio, PhD; Erin L. Abner, PhD; Allison Caban-Holt, PhD; Mark Lovell, PhD; Phyllis Goodman, MS; Amy K. Darke, MS; Monica Yee, BA; John Crowley, PhD; Frederick A. Schmitt, PhD

Vit E: 400 IU/d (5.4 y)

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

- 2-Double-blind, randomized, placebo controlled trials met inclusion criteria for review.
  - Alzheimer's disease (n=304)
  - Mild cognitive impairment (n=516)
- No evidence of any clinically important effect on cognition in people with AD over 6 to 48months.
- No evidence that Vitamin E affected the progression of MCI to dementia due to AD over 36 months.

Farina et al. Cochrane Review 2017

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Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology

- Type 1 evidence that Vitamin E is not effective in reducing the risk of AD disease in mild cognitive impairment.

O'Brien et al. J Psychopharm 2017:31:147-68

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Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease
The TEAM-AD VA Cooperative Randomized Trial

- Vitamin E (alpha tocophenol)2000 IU/d (n=152), Memantine 20 mg/day (n=155) Combination (n=154) or Placebo (n=152)
- Mean follow-up of 2.27 (1.22) years

ADCS-ADL Inventory	Vitamin E (n = 140)	Memantine (n = 142)	Vitamin E + Memantine (n = 139)	Placebo (n = 140)
Baseline score, mean (SD)	57.20 (14.38)	57.77 (13.78)	57.16 (13.59)	56.93 (13.61)
Least squares mean (SE) change from baseline	−13.81 (1.11)	−14.98 (1.10)	−15.20 (1.11)	−16.96 (1.11)
Mean change difference compared with placebo (95% CI)	3.15 (0.92 to 5.39)	1.98 (−0.24 to 4.20)	1.76 (−0.48 to 4.00)	

Results
- Vitamin E participants had a slower function decline than placebo
- Delay in clinical progression of 19% per year
- Caregiver time increased the least in the Vitamin E group

Dysken et al. JAMA 2014:311:34-44

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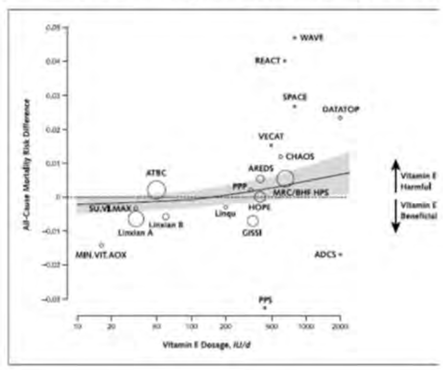
Safety

- High dose Vitamin E increases all cause-mortality
  - Meta-analysis of 10 studies found that Vitamin E ≥ 400 IU/day may increase all-cause mortality

Figure 3. Dose–response relationship between vitamin E supplementation and all-cause mortality in randomized, controlled trials.



Miller et al. Ann Intern Med 2005:142: 37-46

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Souvenaid

- Nutrition formulation designed to support synapse formation and function in early Alzheimer's’ disease
- Composition
  - EPA: 300 mg
  - DHA: 1200 mg
  - Phospholipids: 106 mg
  - Choline: 400 mg
  - Uridine monophosphate: 625 mg
  - Vitamin E: 40 mg
  - Selenium: 60 µg
  - Vitamin B12: 3 µg
  - Vitamin B6: 1 mg
  - Folic Acid: 400 µg
  - Vitamin C: 80 mg
- 3 randomized placebo controlled trials showed that Souvenaid was ineffective at decreasing rate of cognitive decline or progression of Alzheimer’s disease.

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Huperzine A

- Alkaloid derived from the Chinese club moss *Huperzia serrata*
- Used for hundred of years in Chinese medicine to improve cognition and memory.
- Marketed as a dietary supplement to "enhance memory".

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Huperzine A: Pharmacology

- Naturally occurring acetylcholinesterase inhibitor that increases acetylcholine levels in the synapse and in peripheral tissues
  - More potent ACHe inhibitor than donepezil, tacrine and pyridostigmine in pre-clinical studies.
- Increases GABAergic signaling and may augment inhibitory tone and decrease seizure susceptibility
  - Huperzine A has anti-seizure activity and is being developed by Biscayne Pharmaceutical for the treatment of seizure disorders (Dravet syndrome and refractory complex partial seizures).

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Huperzine A in the Treatment of Alzheimer's Disease and Vascular Dementia: A Meta-Analysis

- Huperzine A has shown promising results in the treatment of Alzheimer's disease in early and relatively small randomized clinical trials.
  - 8 studies in Alzheimer's patients (n=733)
  - 2 studies in Vascular dementia patients (n=92)
  - Results:
    - Huperzine A significantly improved mini mental state exam (MMSE) and the activities of daily living score (ADL).

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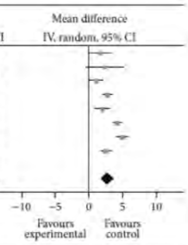
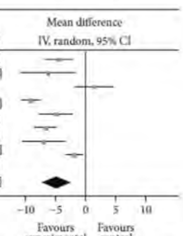
Study or subgroup	Huperzine			Placebo				Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI
Chai et al. 1998	3.5	2.99	22	1.81	2.99	26	10.5%	1.69 [−0.01, 3.39]
Liu et al. 1995	0.4	4.41	14	−2	3.1	14	6.6%	2.40 [−0.42, 5.22]
Rafii et al. 2011	0.65	2.85	59	−0.4	2.85	64	13.3%	1.05 [0.04, 2.06]
Shi et al. 2013	3.2	1.27	30	0.4	1.45	30	14.5%	2.80 [2.11, 3.49]
Xu et al. 1995	3	3.16	50	1	3.16	53	12.5%	2.00 [0.78, 3.22]
Yang et al. 2003	4.3	1.21	35	0.1	1.39	30	14.7%	4.20 [3.56, 4.84]
Zhang et al. 2006	5	2.45	52	0	2.45	57	13.7%	5.00 [4.08, 5.92]
Zhang et al. 2002	2.7	2.85	98	0.19	2.66	99	14.2%	2.51 [1.74, 3.28]
Total (95% CI)			**360**			**373**	**100.0%**	**2.79 [1.83, 3.74]**



Heterogeneity: $\tau^2 = 1.51$; $\chi^2 = 52.61$, df = 7 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: $Z = 5.72$ ($P < 0.00001$)

Figure 2: Forest plot with the weighted mean difference (WMD) on minimental state examination (MMSE) of Hup A relative to placebo in AD with 95% CI of the trials included in meta-analysis.

Study or subgroup	Hup A			Placebo				Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI
Chai et al. 1998	−4.77	4.61	22	−0.35	2.98	26	13.1%	−4.42 [−6.66, −2.18]
Liu et al. 1995	−3.6	5.75	14	2.6	6.44	14	9.7%	−6.20 [−10.72, −1.68]
Rafii et al. 2011	−1.18	9.1	59	−2.64	8.66	64	11.8%	1.46 [−1.69, 4.61]
Shi et al. 2013	−10	3.21	30	−0.9	3.1	30	13.9%	−9.10 [−10.70, −7.50]
Xu et al. 1995	−4	5.29	50	0.9	8.41	53	12.5%	−4.90 [−7.60, −2.20]
Yang et al. 2003	−6.6	3.99	35	0	3.32	30	13.7%	−6.60 [−8.38, −4.82]
Zhang et al. 2006	−5	7.91	52	2	10.54	57	11.3%	−7.00 [−10.48, −3.52]
Zhang et al. 2002	−2.39	4.88	98	−0.47	5.01	99	14.1%	−1.92 [−3.30, −0.54]
Total (95% CI)			**360**			**373**	**100.0%**	**−4.84 [−7.27, −2.42]**



Heterogeneity: $\tau^2 = 10.40$; $\chi^2 = 65.54$, df = 7 ($P < 0.00001$); $I^2 = 89\%$
Test for overall effect: $Z = 3.91$ ($P < 0.00001$)

Figure 3: Forest plot with the weighted mean difference (WMD) on daily living scale (ADL) of Hup A relative to placebo in AD with 95% CI of the trials included in meta-analysis.

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Huperzine A: Summary

- Efficacy: Phase II clinical trials in the United States and phase III trials in China are underway to investigate the use of huperzine A for the treatment of Alzheimer's disease .
- Safety: up to 400 µg/day.
  - Reported adverse effects include:
    Mild to moderate nausea, ankle edema, insomnia, sweating, high blood pressure, bradycardia, muscle twitching, increased saliva & urine.
- Drug Interactions: use with caution in individuals taking other acetylcholinesterase inhibitors
- Dose:
  - 100 µg tablet three times daily

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Consumerlab approved products

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