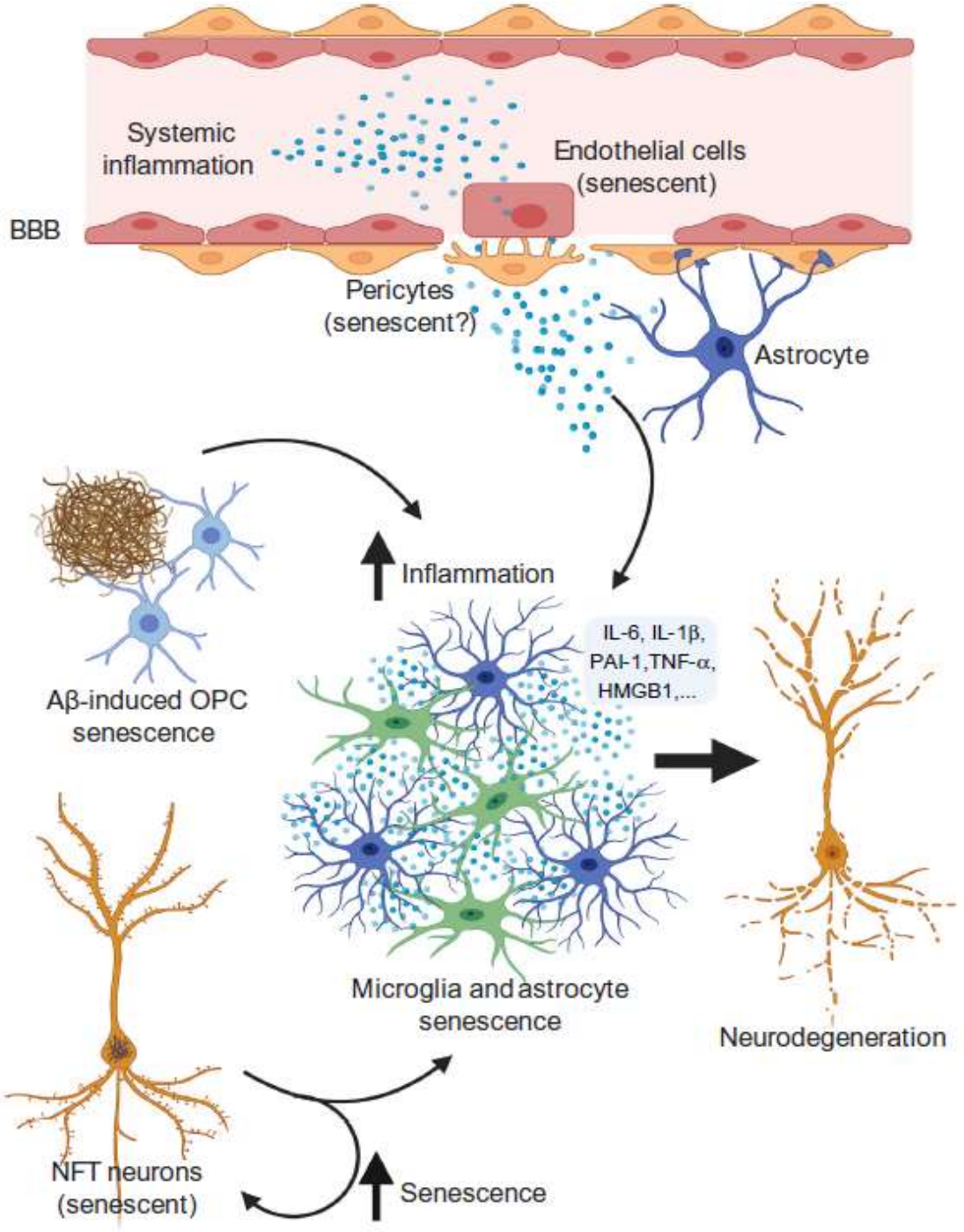
Cellular senescence at the crossroads of inflammation and Alzheimer's disease

Trends in Neurosciences, September 2021, Vol. 44, No. 9

Ana Guerrero [1,2] Bart De Strooper, [1,2,3,4] and I. Lorena Arancibia-Cárcamo [1,2,*]

Brain cell type	Markers of age-related senescence
Neurons	Elevated p16, p21, γH2AX, p-p38, SASP, mH2A, SA-βGal, lipofuscin, GATA4; loss of lamin B1 and HMGB1 [51,68,70,92]
Microglia	Dystrophic morphology; elevated p16, p21, SASP, lipofuscin [51,76,79]
Astrocytes	Elevated p16, p21, GATA4, SASP; loss of lamin B1 [51,68,86,87]
Oligodendrocyte progenitor cells	Elevated p16, p21 [51]
Oligodendrocytes	Elevated p21 [51]
Endothelial cells	Elevated p16, SA-βGal [97]

Senescence markers in the brain during age

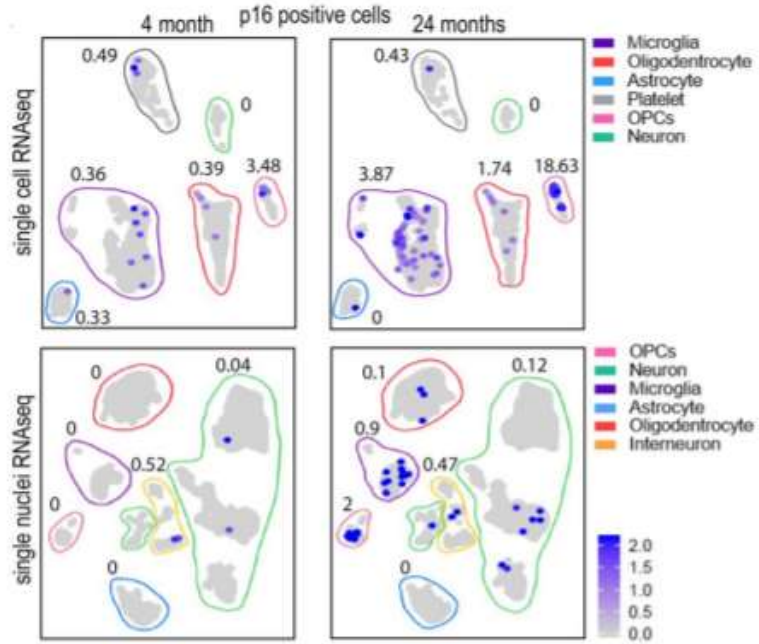


Aging Cell. 2021;20:e13296

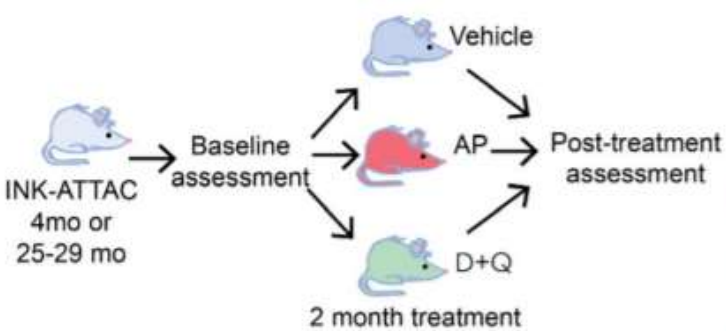
Aging Cell

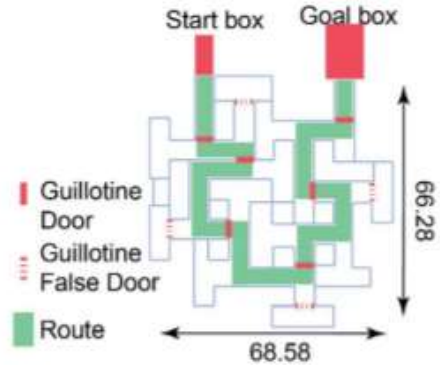
Whole-body senescent cell clearance alleviates age-related brain inflammation and cognitive impairment in mice

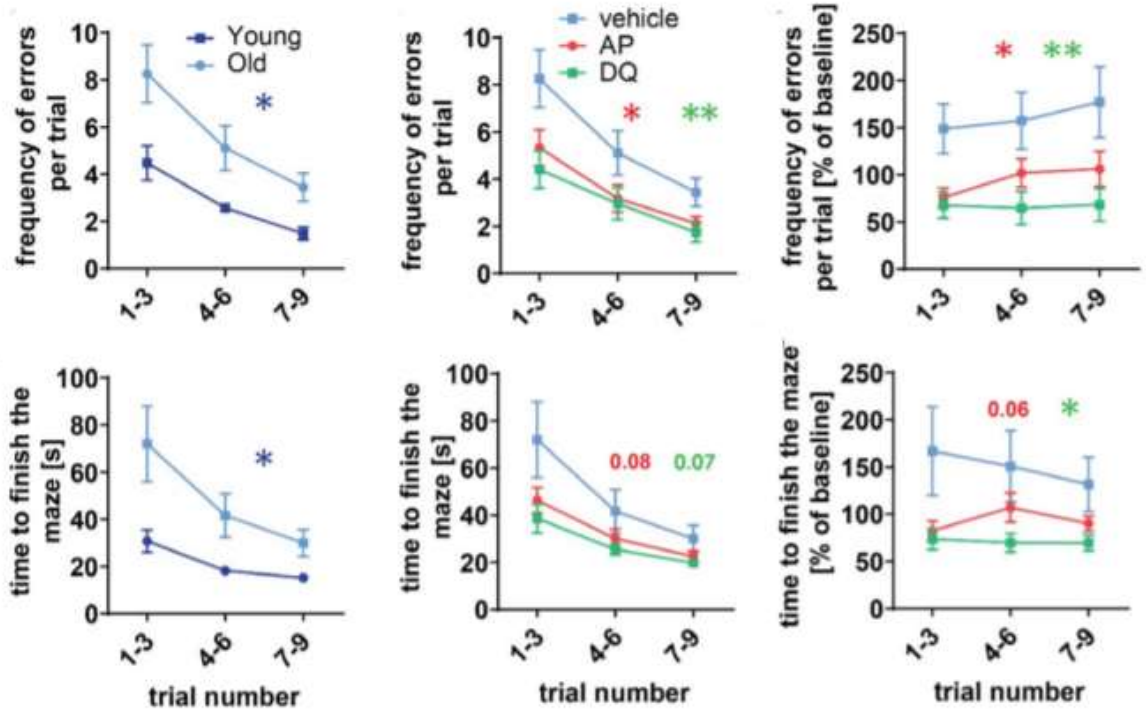
Ogrodnik M. et al



	Dose
AP20187	10 mg/kg body weight
Dasatinib and quercetin (D + Q)	Dasatinib 5 mg/kg body weight Quercetin 10 mg/kg body weight







This Red Color is Astaxanthin

nutrients

MDPI

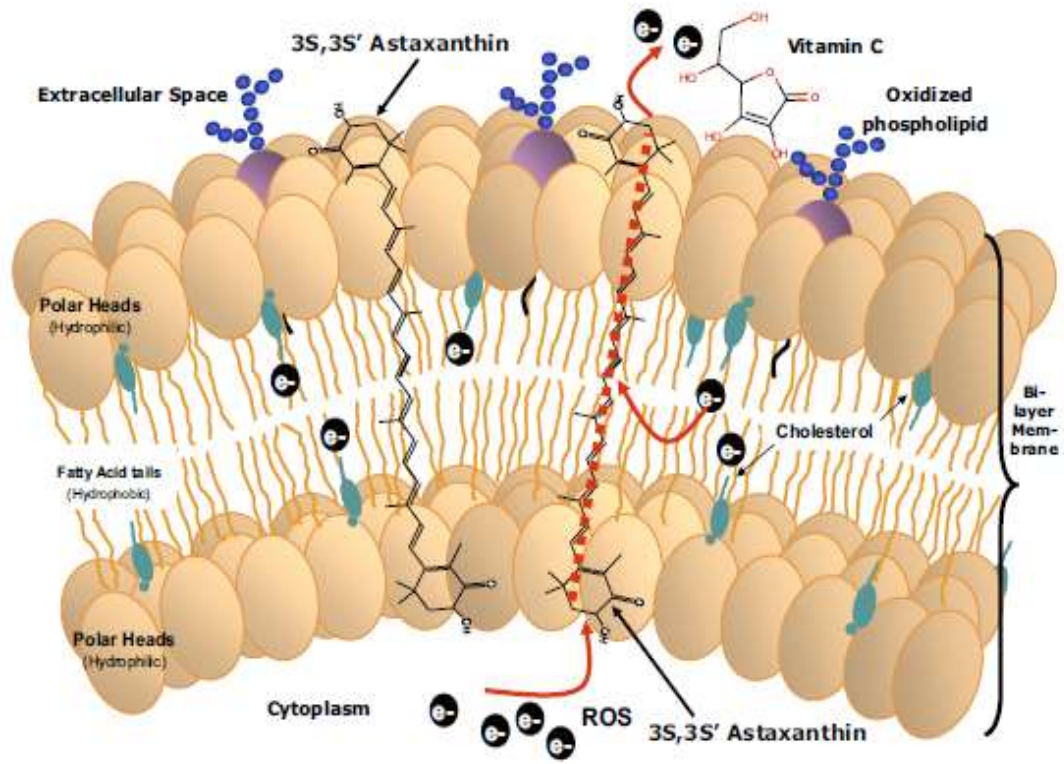
Review

Astaxanthin in Skin Health, Repair, and Disease: A Comprehensive Review

Sergio Davinelli [1,*], Michael E. Nielsen [2] and Giovanni Scapagnini [1]

Table 1. Summary of human intervention studies on skin and astaxanthin.

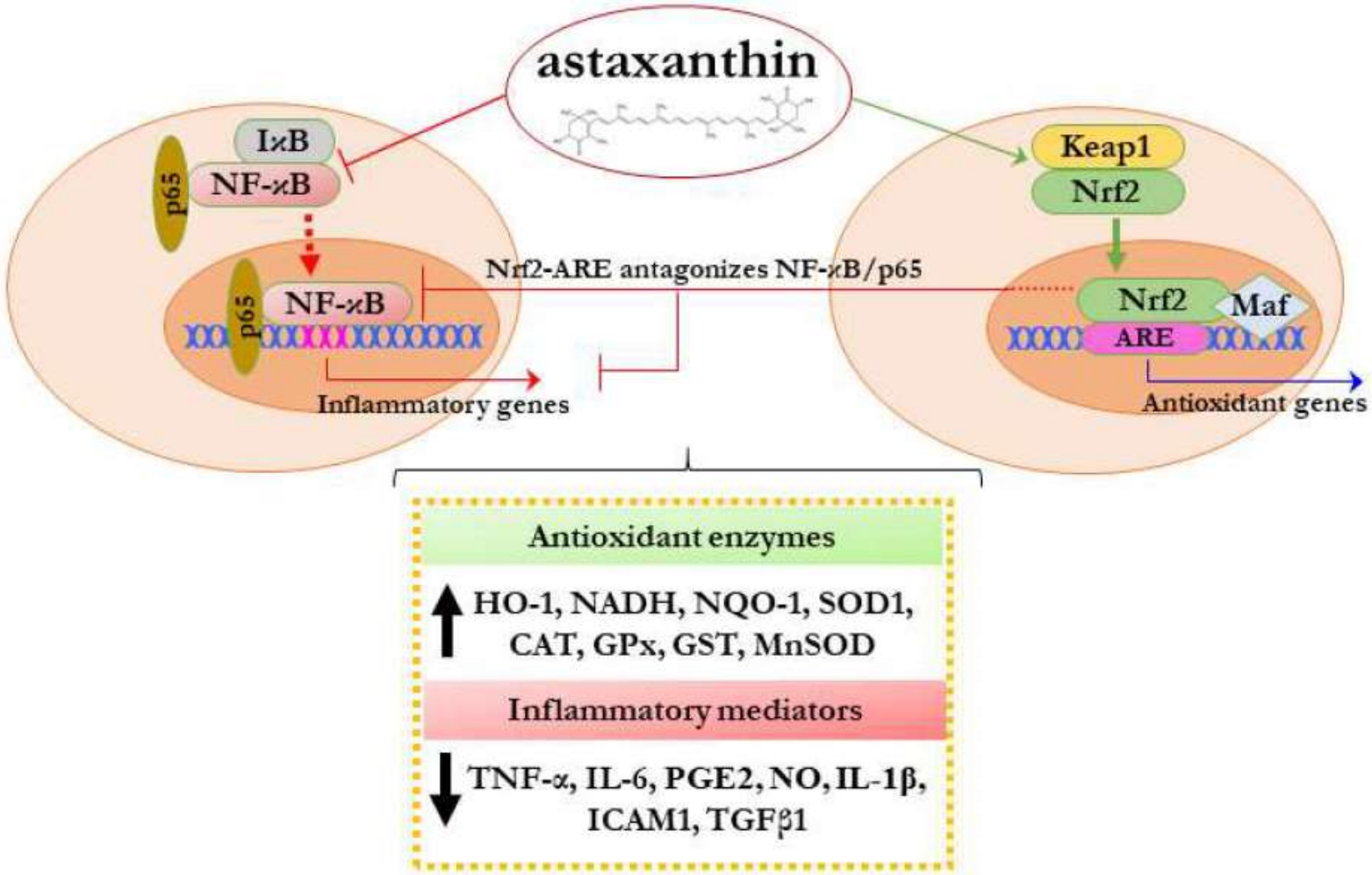
Intervention	Study Design	Control	Population (*n*)	Duration	Outcomes	Dosage	Author, Year
Administration of ASX capsules	Randomized double-blind, controlled study	Placebo	Healthy female subjects (14/diet group)	8 weeks	↓ DNA damage biomarkers; ↑ of NK cells, T cells, B cells, and IL-6	2 or 8 mg	Park, 2010
Administration of ASX capsules	Monitoring of oxidative stress and skin aging	None	31 middle-aged volunteers	4 weeks	↓ MDA; ↓ RSSC	4 mg	Chalyk, 2017
Administration of ASX capsules	Randomized, double-blind, parallel-group, placebo-controlled	Placebo	65 healthy female subjects	16 weeks	↓ Wrinkle parameters; ↓ IL-α	6 or 12 mg	Tominaga, 2017
Administration of ASX cream	Pilot study	None	3 healthy female subjects	2 weeks	↓ Wrinkle parameters	0.7 mg/g of ASX cream	Seki, 2001
Topical application of ASX	Pilot study	None	3 healthy male subjects	N/S	↓ erythema	N/S	Yamashita, 1995
Administration of ASX capsules	Randomized, single-blind, placebo-controlled	Placebo	49 healthy female subjects	6 weeks	↓ Wrinkle parameters	2 mg	Yamashita, 2006
Oral and topical treatment with ASX	N/S	N/S	28 healthy female subjects	8 weeks	↓ Wrinkle parameters	6 mg	Tominaga, 2009
Two oral forms (ASX capsules; tablets collagen)	Randomized, double-blind placebo-controlled	Placebo	44 healthy female volunteers	12 weeks	↑ viscoelastic parameters; ↓ TEWL; ↑ procollagen type I; ↓ MMP-1 and MMP-12	2 mg	Yoon, 2014
Capsules of ASX combined with topical application of ASX	Open-label noncontrolled	None	30 healthy female subjects	8 weeks	↓ wrinkles; ↓ age spot size; ↑ elasticity; ↑ skin texture	6 mg and 2 mL (78.9 μM solution)	Tominaga, 2012
Administration of ASX capsules	Randomized double-blind controlled	Placebo	36 healthy male subjects	6 weeks	↓ wrinkles; ↑ elasticity; ↓ TEWL; ↑ moisture content; ↓ sebum oil	6 mg	Tominaga, 2012



Astaxanthin as a Modulator of Nrf2, NF-κB, and Their Crosstalk: Molecular Mechanisms and Possible Clinical Applications

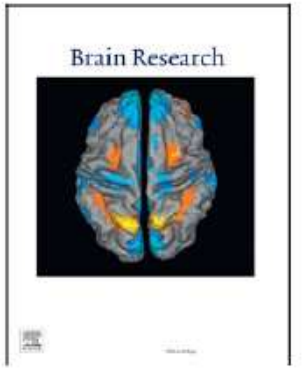
Molecules 2022, 27, 502.

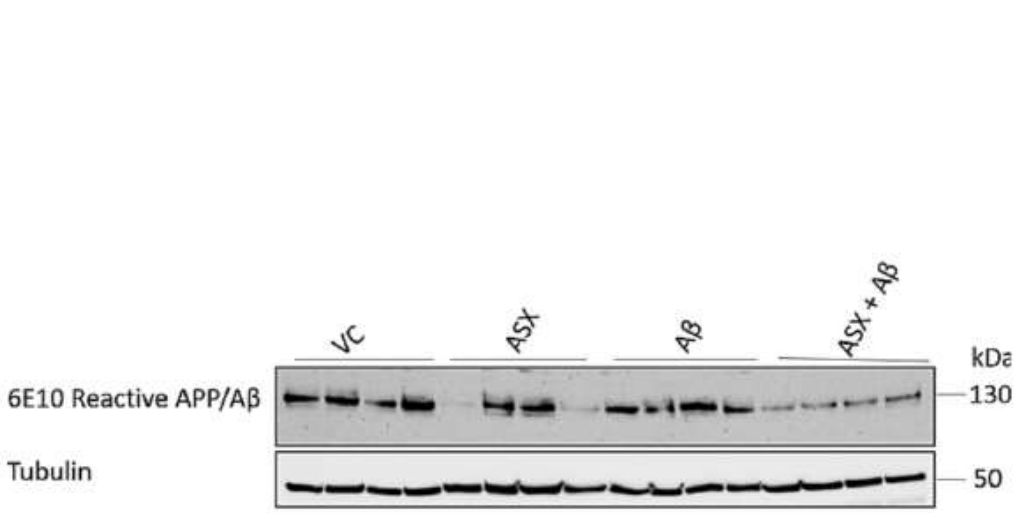
Sergio Davinelli [1,*], Luciano Saso [2], Floriana D'Angeli [3], Vittorio Calabrese [3], Mariano Intrieri [1] and Giovanni Scapagnini [1]

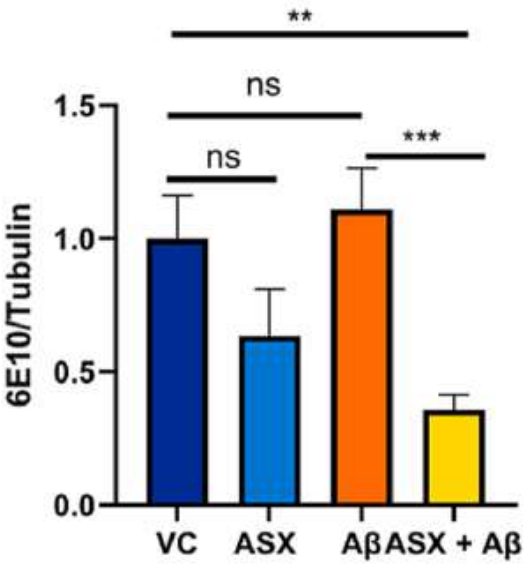


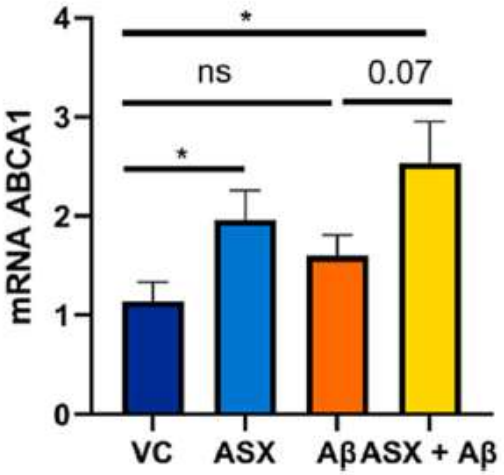
Brain Research 1819 (2023) 148518

Astaxanthin enhances autophagy, amyloid beta clearance and exerts anti-inflammatory effects in *in vitro* models of Alzheimer's disease-related blood brain barrier dysfunction and inflammation







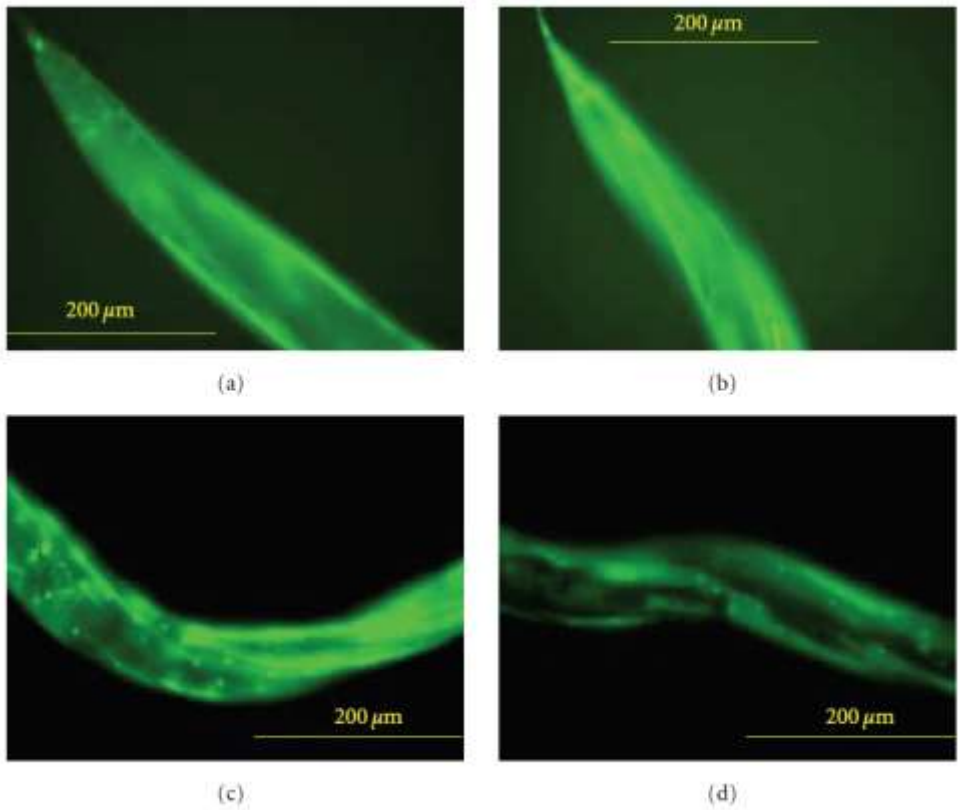


ASX reduces protein expression of APP/Aβ as well as increases expression of genes involved in Aβ clearance in Aβ-treated pBCECs.

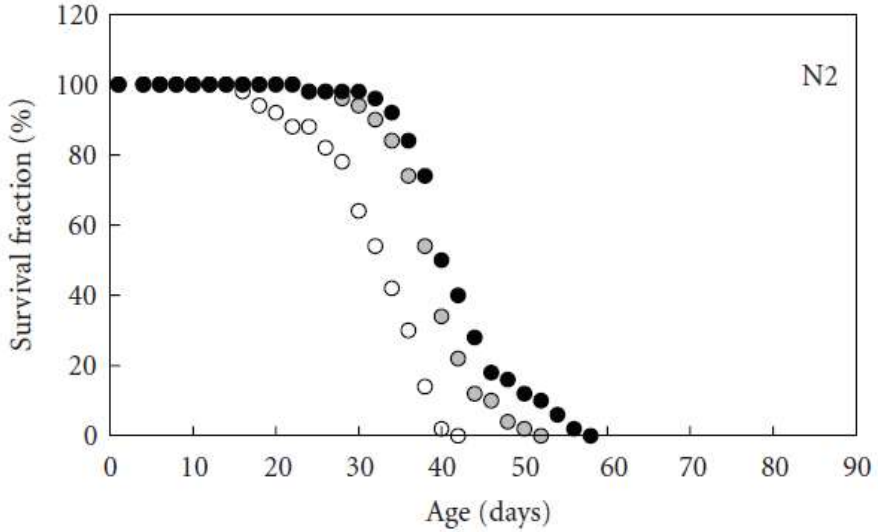
Oxidative Medicine and Cellular Longevity 2011

Supplemental Cellular Protection by a Carotenoid Extends Lifespan via Ins/IGF-1 Signaling in *Caenorhabditis elegans*

Koumei Yazaki, Chinatsu Yoshikoshi, Satoru Oshiro, and Sumino Yanase



Localization of DAF-16/FOXO : GFP



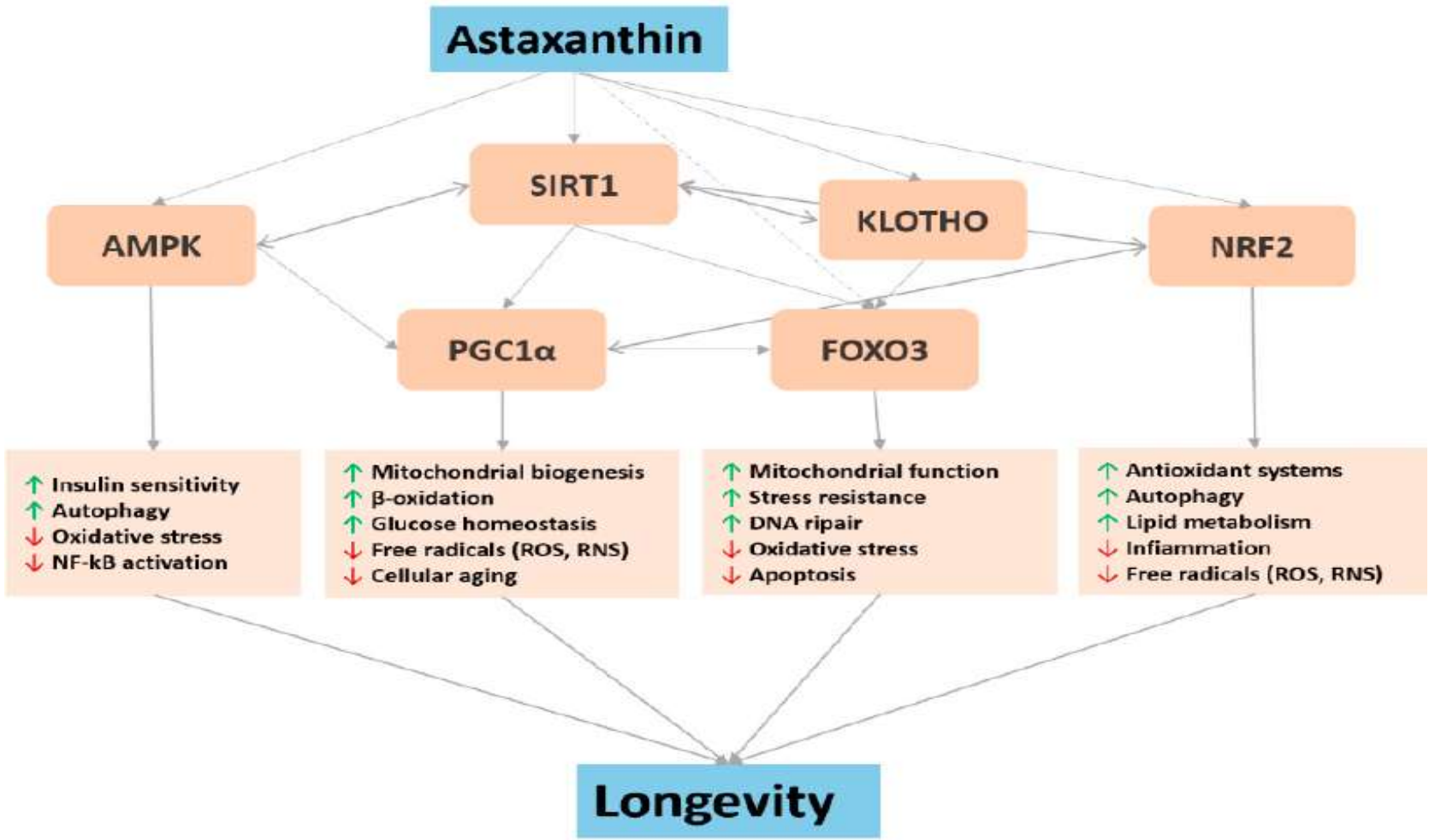
AX-containing NGM plates for measurement of lifespan in nematode

Astaxanthin as a Putative Geroprotector: Molecular Basis and Focus on Brain Aging

marine drugs

Mar. Drugs 2020, *18*, 351

Vincenzo Sorrenti [1,2,*], Sergio Davinelli [3], Giovanni Scapagnini [3], Bradley J. Willcox [4,5], Richard C. Allsopp [6] and Donald C. Willcox [4,5,7]

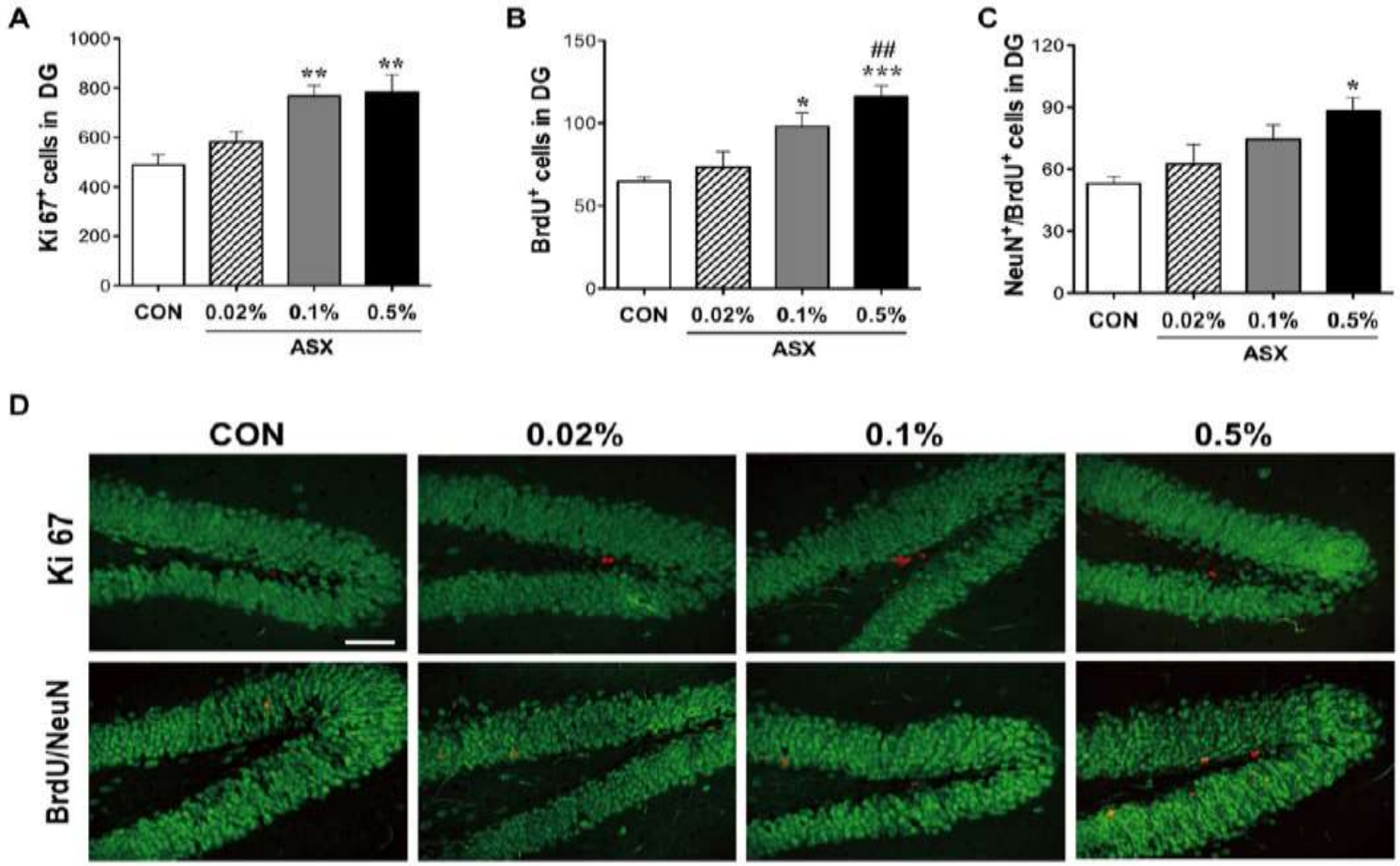


Mol. Nutr. Food Res. 2016, *60*, 589–599

RESEARCH ARTICLE

Astaxanthin supplementation enhances adult hippocampal neurogenesis and spatial memory in mice

Jang Soo Yook[1], Masahiro Okamoto[1], Randeep Rakwal[2], Junko Shibato[1], Min Chul Lee[1,3], Takashi Matsui[1], Hyukki Chang[4], Joon Yong Cho[5] and Hideaki Soya[1]



antioxidants

Antioxidants 2021, 10, 223.

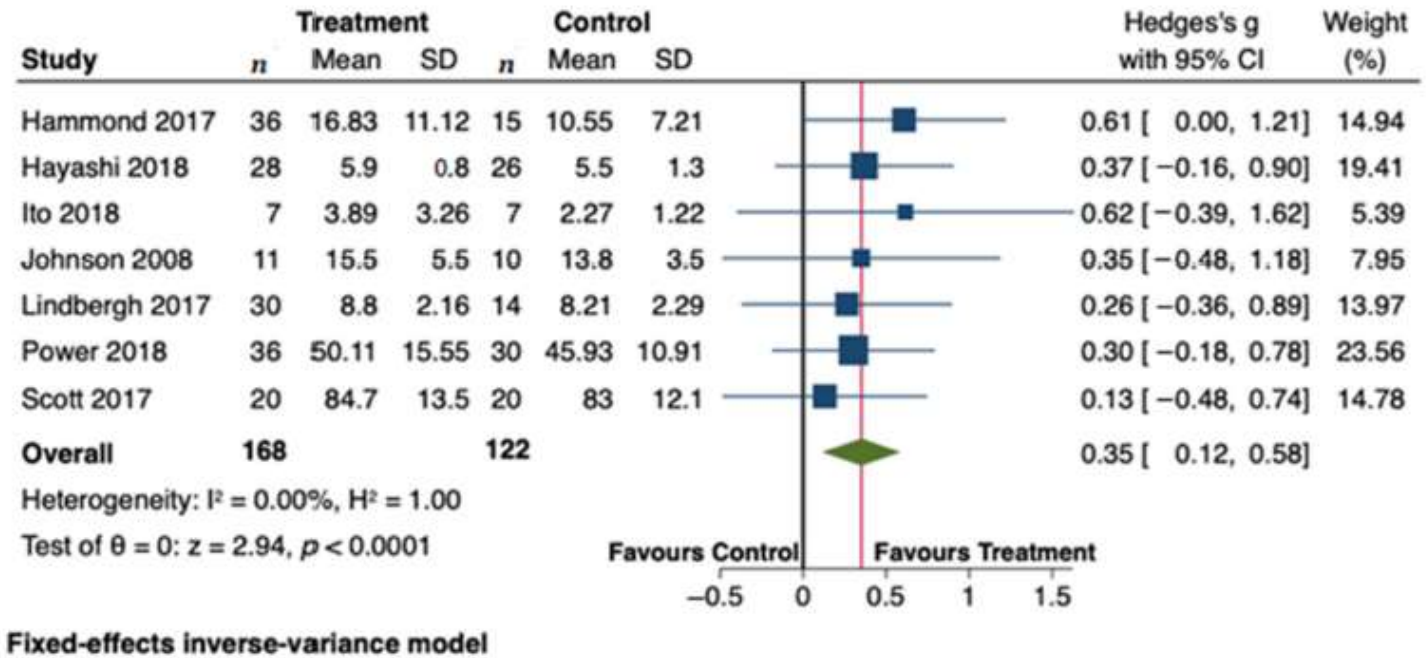
MDPI

Review

Carotenoids and Cognitive Outcomes: A Meta-Analysis of Randomized Intervention Trials

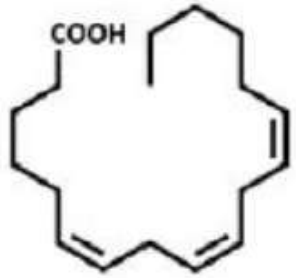
Sergio Davinelli [1,*], Sawan Ali [1], Vincenzo Solfrizzi [2], Giovanni Scapagnini [1] and Graziamaria Corbi [1]

In conclusion, these results highlight the potential role of carotenoids in the protection of mental functions even in subjects without cognitive impairment.

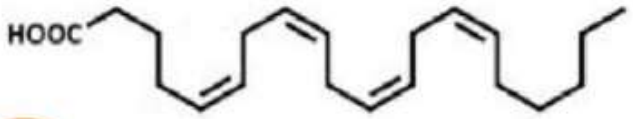


OMEGA 6

linoleic acid
LA

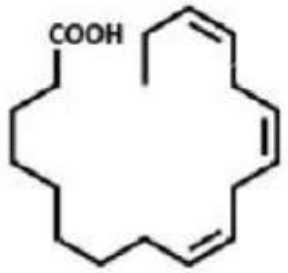


gamma linolenic acid
GLA

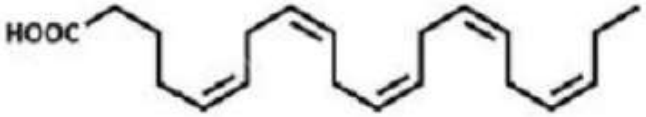


arachidonic acid
AA

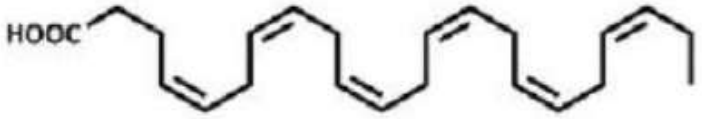
OMEGA 3



alpha linolenic acid
ALA

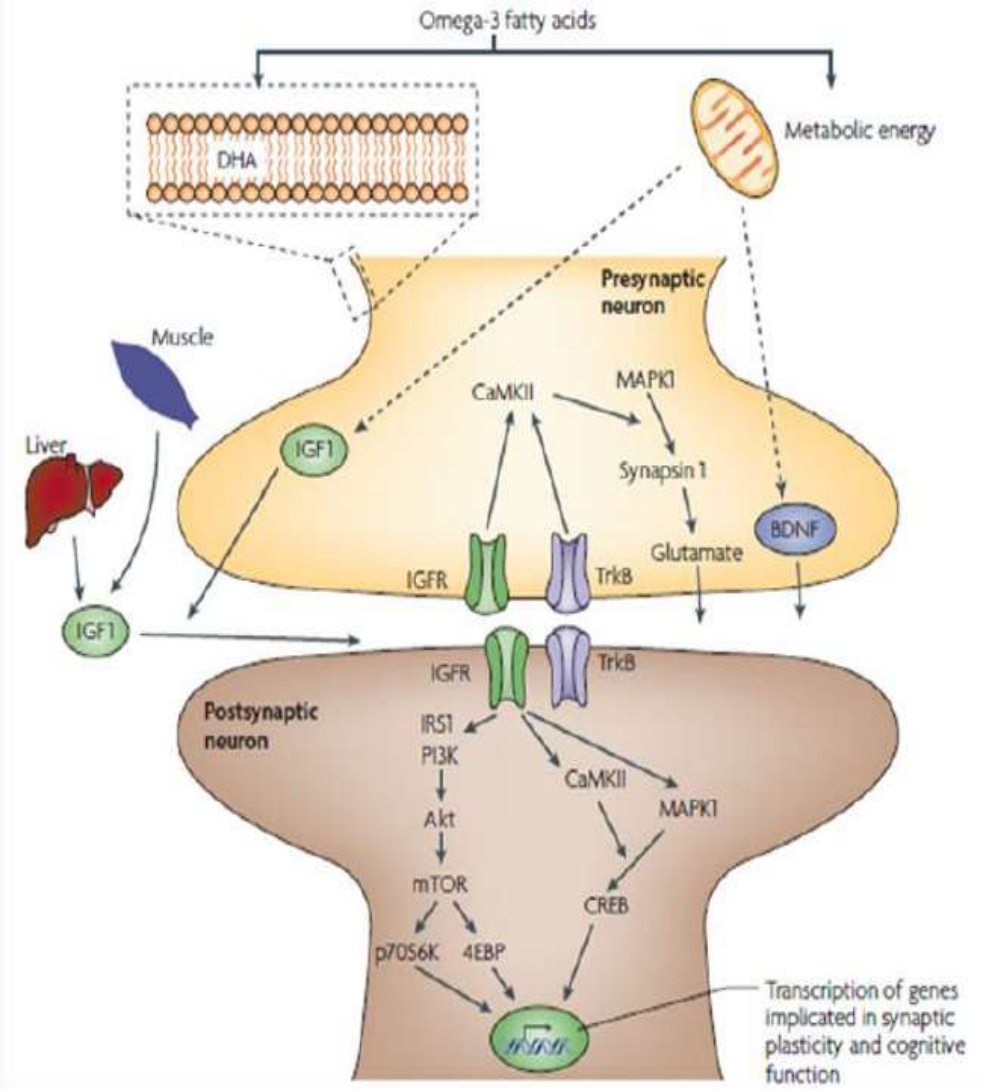


eicosapentaenoic acid
EPA



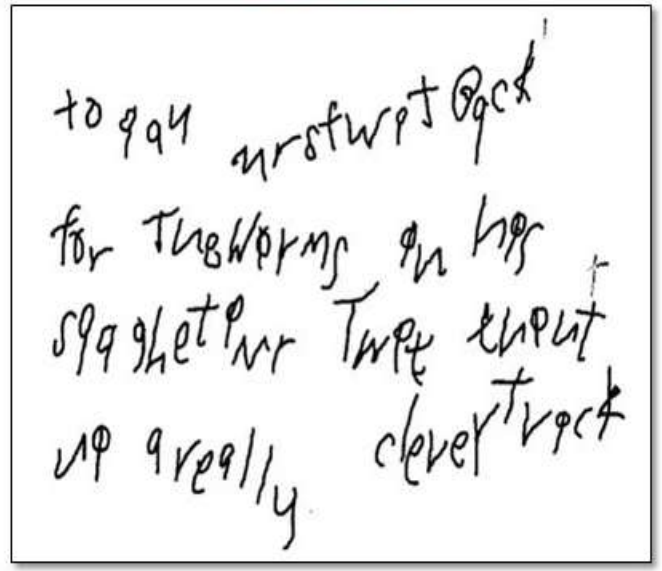
docosahexanoic acid
DHA

Dietary omega-3 fatty acids can affect synaptic plasticity and cognition.



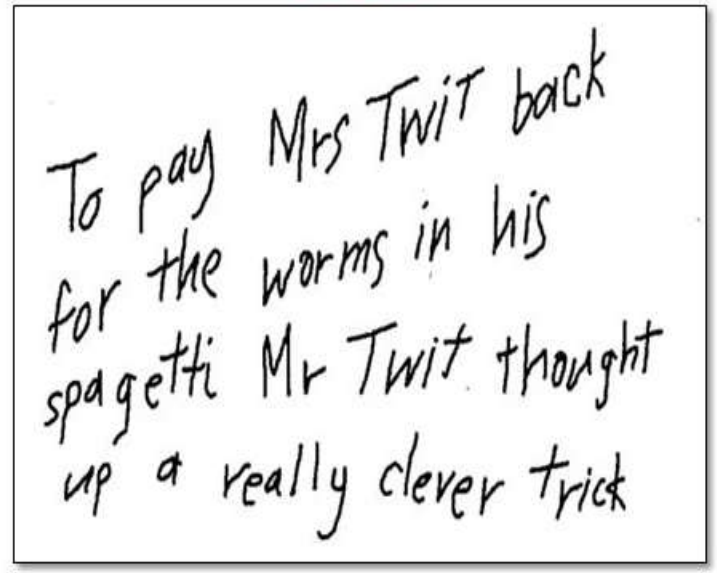
Performance & Learning

BEFORE



A six year old child's handwriting on a Junk Food diet.

AFTER



Six year old child's handwriting after one month of *change in diet.

Published in final edited form as:

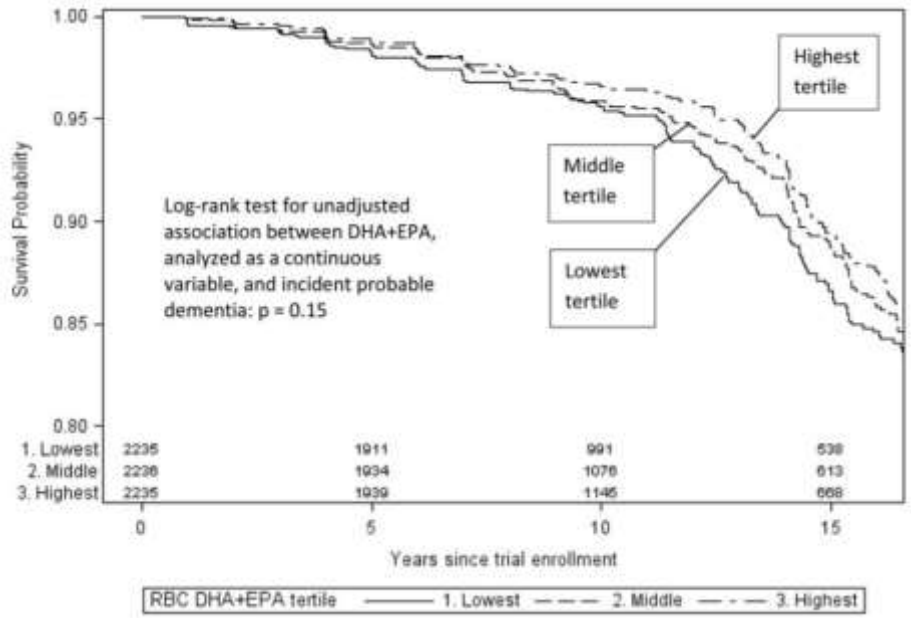
Prostaglandins Leukot Essent Fatty Acids. 2017 June ; 121: 68–75. doi:10.1016/j.plefa.2017.06.006.

Erythrocyte omega-3 fatty acids are inversely associated with incident dementia: Secondary analyses of longitudinal data from the Women's Health Initiative Memory Study (WHIMS)

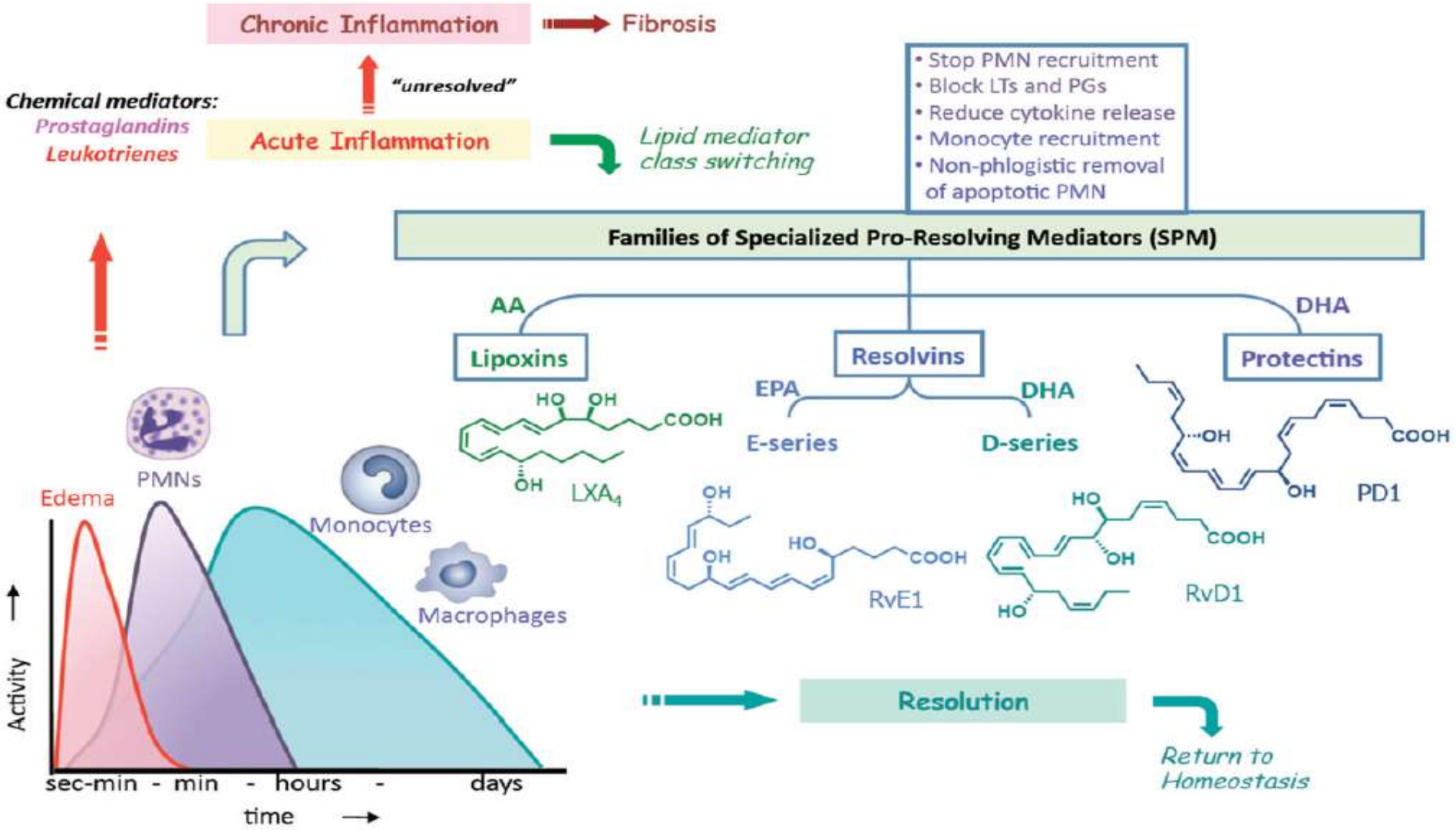
Eric M. Ammann, PhD[a], **James V. Pottala, PhD**[b], **Jennifer G. Robinson, MD MPH**[a,c], **Mark A. Espeland, PhD**[d], and **William S. Harris, PhD**[b,e,*]

Highlights

- We examined the association between erythrocyte EPA+DHA and risk for incident dementia in 6706 women in the USA.
- After about 10 years of follow-up and after appropriate adjustments, we found a significant, 8% decreased risk for probable dementia associated with a 1-SD increase in EPA+DHA.
- This large study confirms previous research suggesting that higher EPA+DHA levels may be protective against dementia.



Inflammatory response and resolution time course: Roles of pro-resolving lipid mediators.

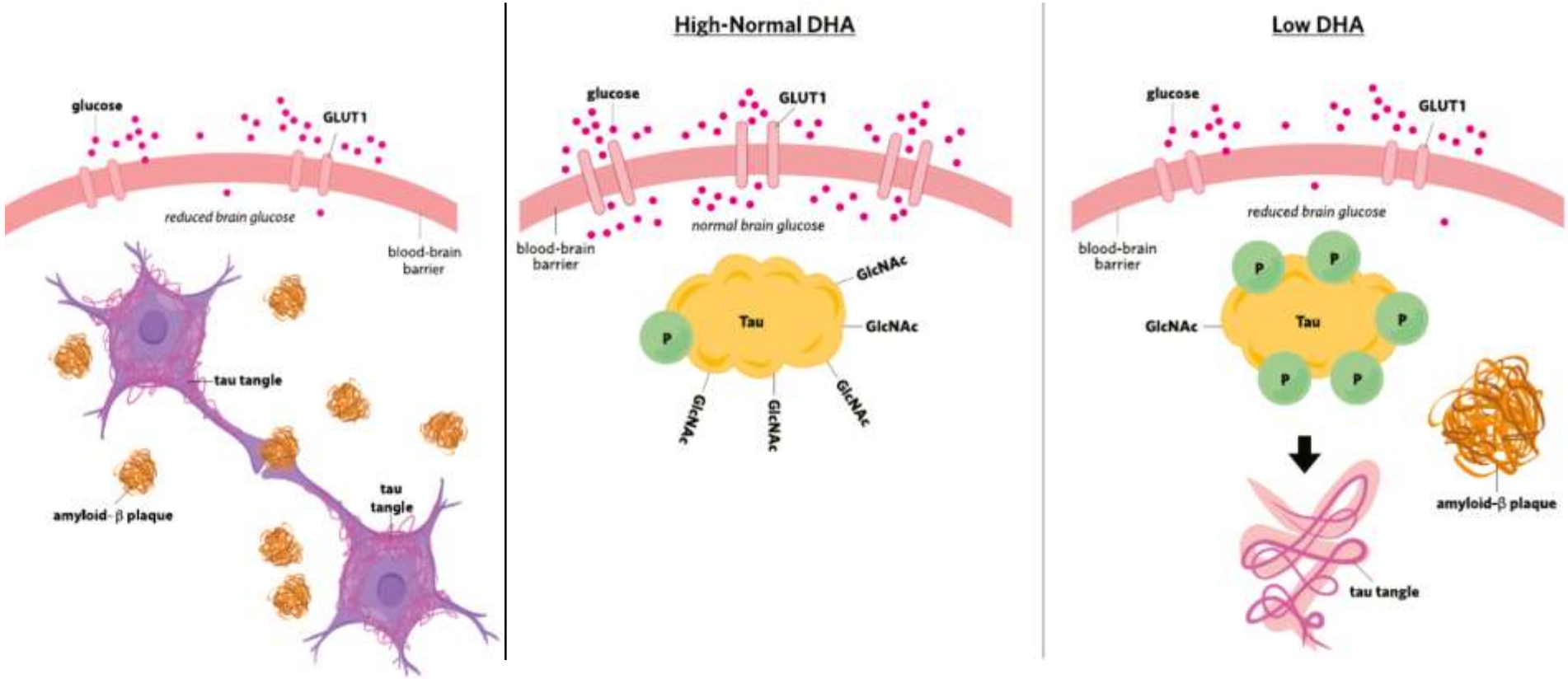


Serhan and Petasis Chem Rev. 2011

The FASEB Journal 2019

Role of phosphatidylcholine-DHA in preventing APOE4-associated Alzheimer's disease

Rhonda P. Patrick[1]



AD is associated with decreased GLUT1 transporters and glucose uptake, tau tangles inside of neurons, and amyloid-b plaques in the extracellular space between neurons.

DHA regulates brain glucose uptake, which prevents amyloid-b plaque and tau tangle formation

Low DHA concentrations in the brain reduce GLUT1 transporter expression, which leads to increased tau phosphorylation and promotes amyloid-b plaque formation.

First published:13 April 2020

alzheimer's association | Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Adherence to a Mediterranean diet and cognitive function in the Age-Related Eye Disease Studies 1 & 2

Tiarnán D. Keenan, Elvira Agrón, Julie A. Mares, Traci E. Clemons, Freekje van Asten, Anand Swaroop, Emily Y. Chew ✉, for the AREDS and AREDS2 Research Groups

7,756 participants enrolled in two randomized trials of nutritional supplements for age-related macular degeneration: Age-Related Eye Disease Study (AREDS) and AREDS2.

Closer Mediterranean diet adherence was associated with lower risk of cognitive impairment but not slower decline in cognitive function.

Fish intake was associated with higher cognitive function. In AREDS2, rate of cognitive decline over 5 to 10 years was not significantly different by a MED but was significantly slower (P = .019) with higher fish intake.

LO-MAPT STUDY

Making dementia a priority:
changing perceptions, practice and policy.

Clinicaltrials.gov identifier	NCT03691519

Study Design

Study Type : Interventional (Clinical Trial)
Actual Enrollment : 774 participants
Allocation: Randomized

1. Study Information	
Name of the study	Prevention of cognitive decline in older adults with low Dha/Epa index in red blood cells
Study sponsor	University Hospital, Toulouse
Disease	At risk of developing Alzheimer's disease
Phase	Phase III

2. Information about the drug that will be tested in the study	
Name of drug	Omega-3
Administration	Three capsules taken orally per day

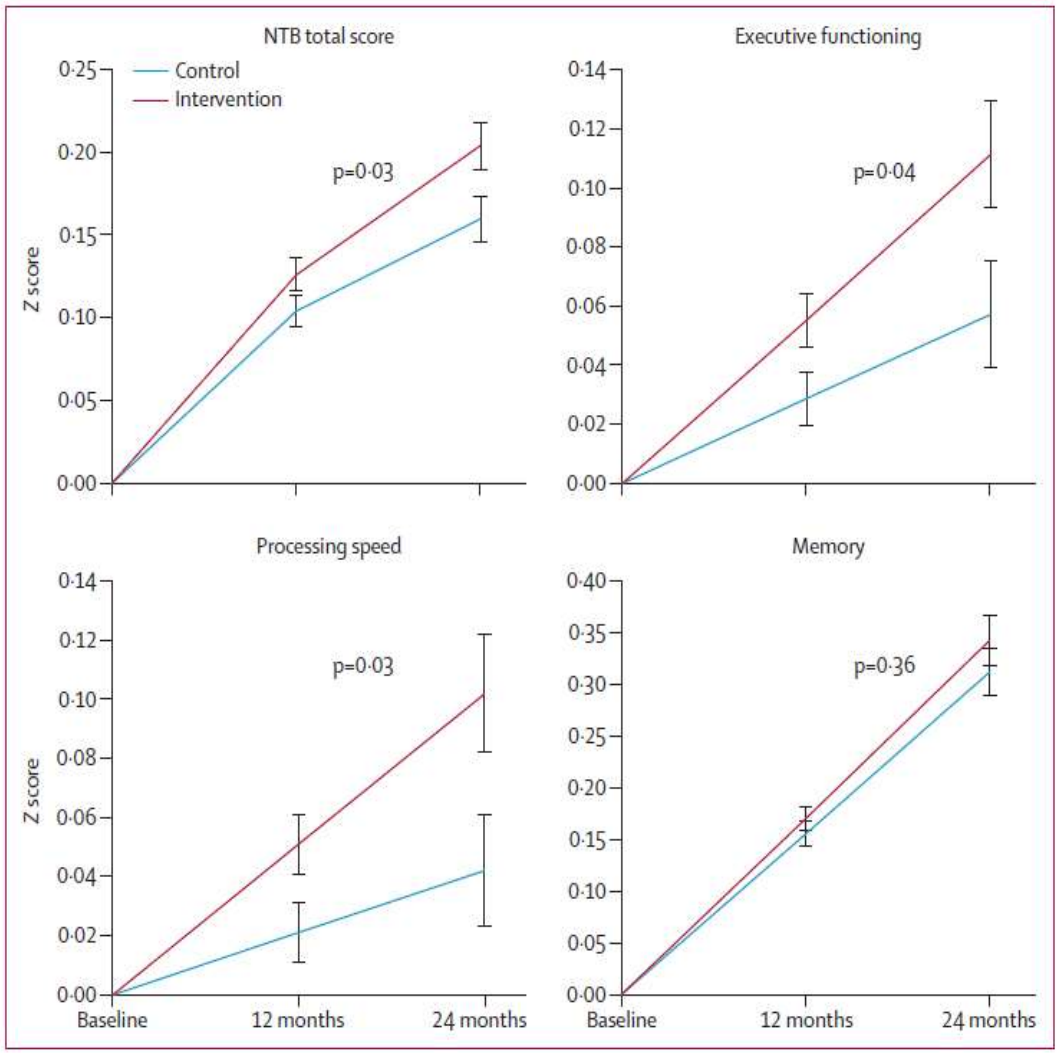
The lancet **Vol 385 June 6, 2015**

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto

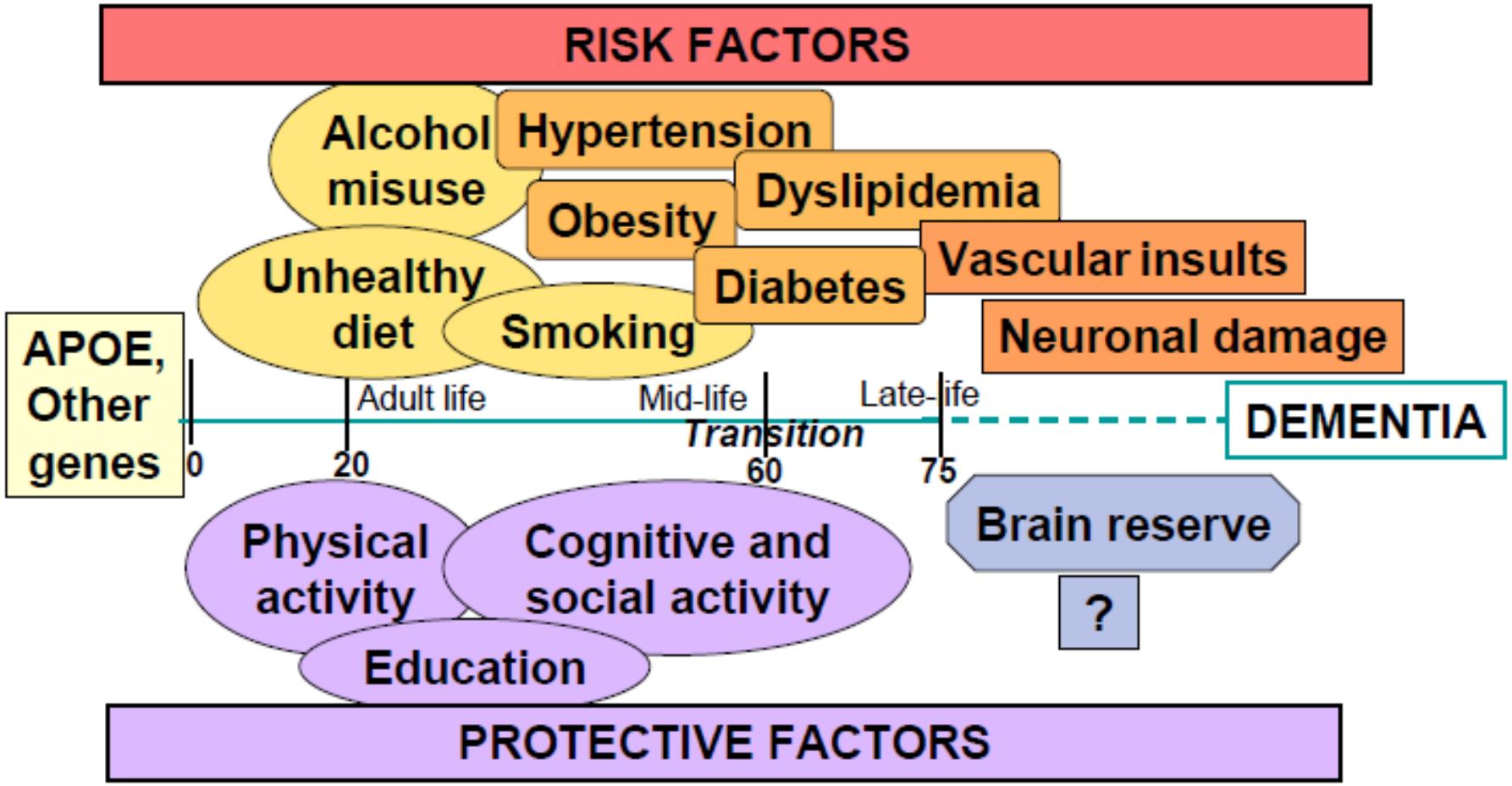
	Participants with information available	Intervention group (n=591)	Control group (n=599)
Demographic characteristics			
Age at the baseline visit, years	1190	69·5 (4·6)	69·2 (4·7)
Number of women	1190	267/591 (45%)	284/599 (47%)
Education, years	1179	10·0 (3·4)	10·0 (3·4)
Married or cohabiting	1189	436/590 (74%)	454/599 (76%)

Methods In a double-blind randomised controlled trial we enrolled individuals aged 60–77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.



Change in cognitive performance during the 2 year intervention

The bases for a multidomain approach



Alzheimer's Research and Prevention Foundation