Alimentazione e Declino Cognitivo. Intuizioni e certezze.

Valeria Drago
Neurologo

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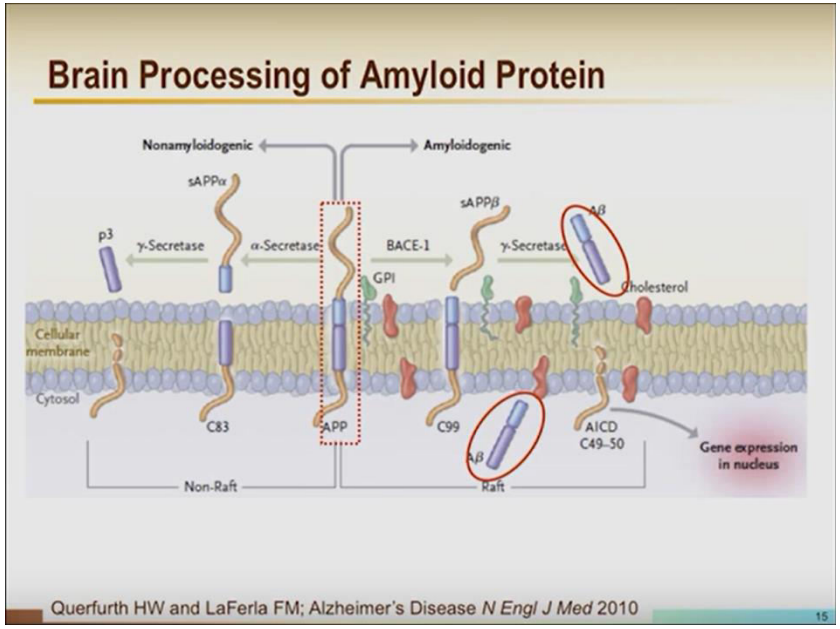
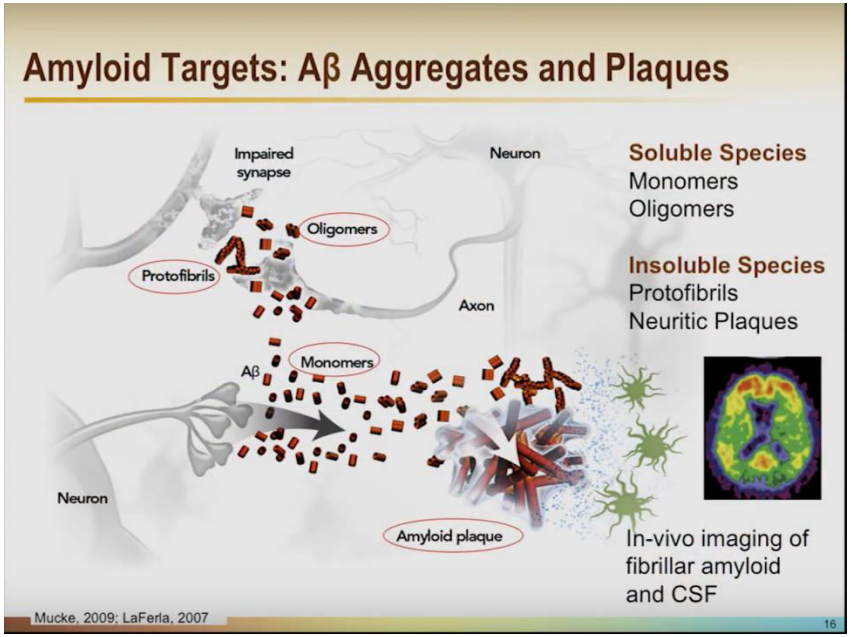
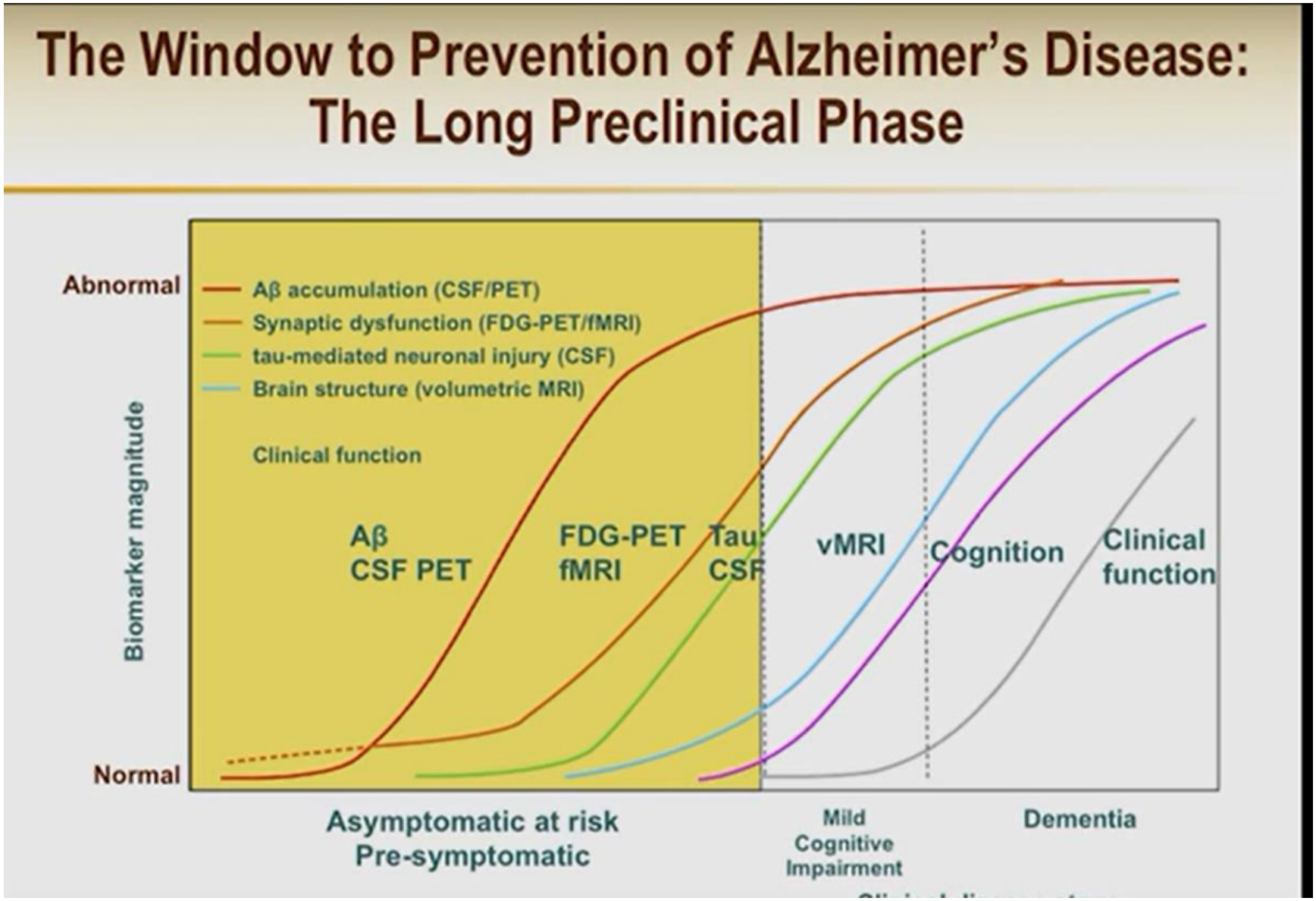
LA PATOGENESI DELLA M DI ALZHEIMER E' COMPLESSA E COINVOLGE UNA ANOMALIA NEL METABOLISMO DI ABETA, IPERFOSFORILAZIONE DELLA PROTEINA TAU, STRESS OSSIDATIVO, REATTIVITA' DELLA GLIA E MICROGLIA ETC







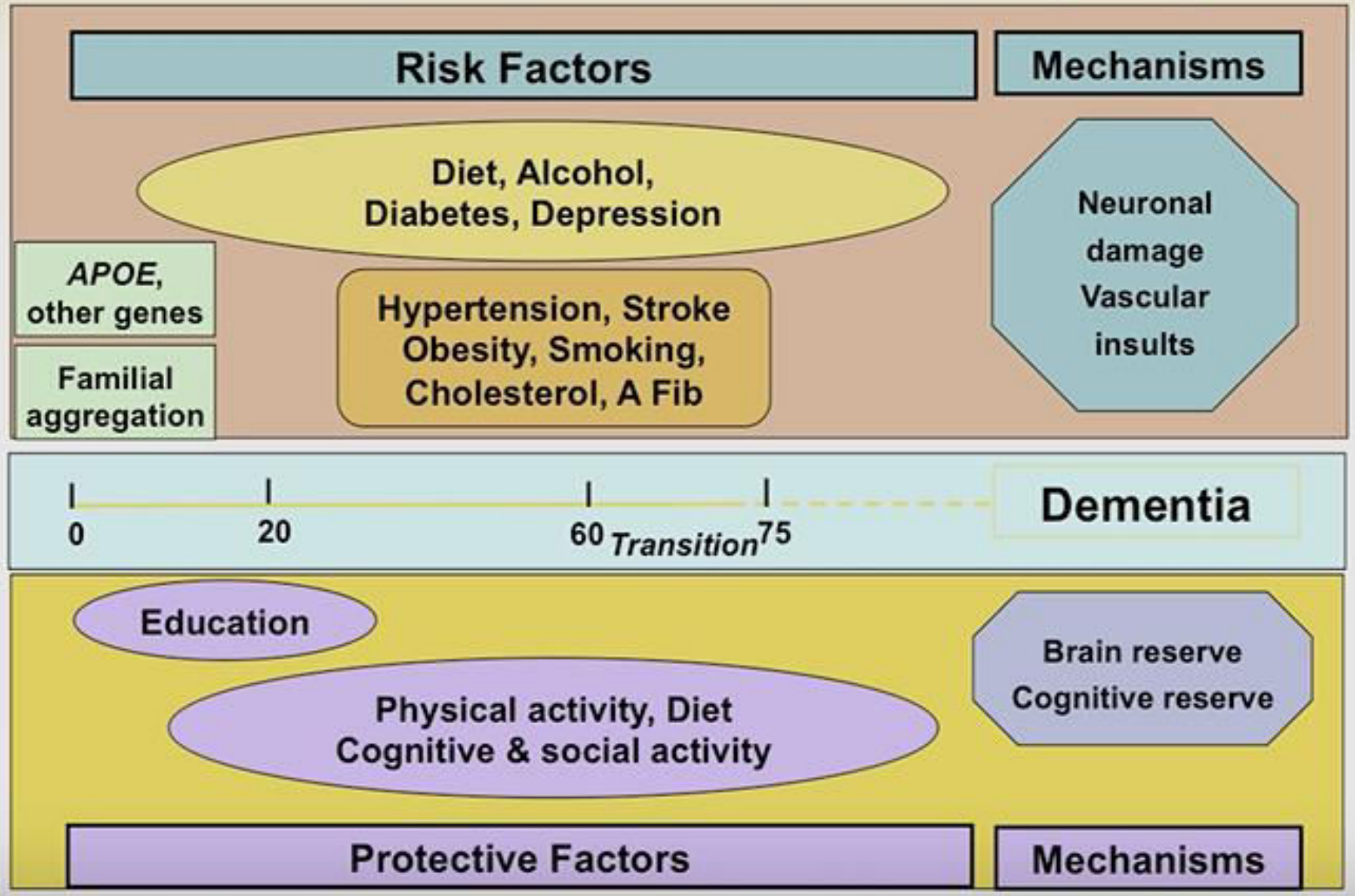
IMPORTANZA DEL TRATTAMENTO PRECOCE O DELLA PREVENZIONE DELLA MA

OBIETTIVI

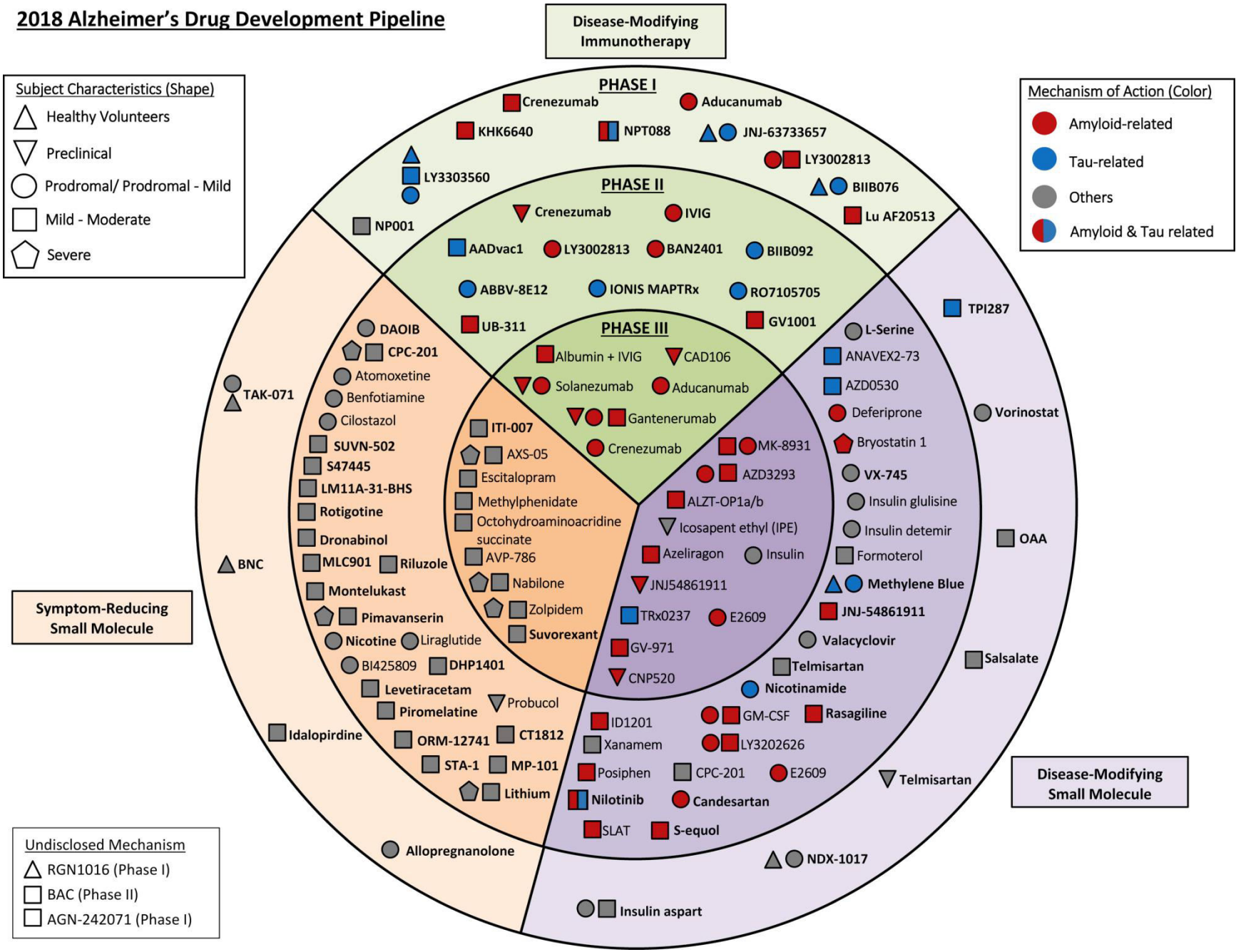
- FATTORI DIETETICI CHE POSSONO INFLUENZARE L'EZIOPATOGENESI DELLA MA

- SE C'E'UN ARCO DI TEMPO DOVE LA DIETA POTREBBE AVERE UN RUOLO NEL PROTEGGERE DA EVENTUALI PROCESSI DEGENERATIVI

Risk Factors for Dementia: Lifetime Trajectory



Adapted from Kivipelto, Mangialasche et al., Oxford Geriatr Text Medicine 2015.

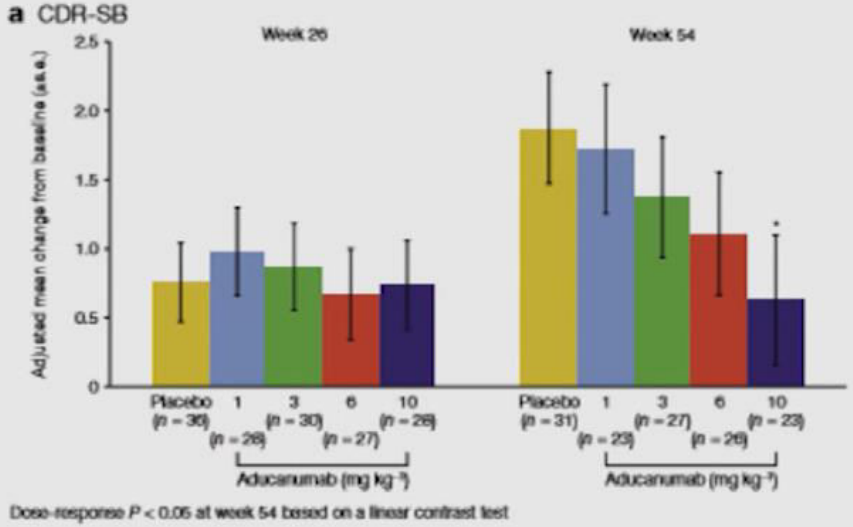

2018 Alzheimer's Drug Development Pipeline
Disease-Modifying Immunotherapy
Subject Characteristics (Shape)
Healthy Volunteers
Preclinical
Prodromal/ Prodromal - Mild
Mild - Moderate
Severe
Mechanism of Action (Color)
Amyloid-related
Tau-related
Others
Amyloid & Tau related
PHASE I
Crenezumab
Aducanumab
KHK6640
NPT088
JNJ-63733657
LY3002813
LY3303560
BIIB076
NP001
Lu AF20513
PHASE II
Crenezumab
IVIG
AADvac1
LY3002813
BAN2401
BIIB092
ABBV-8E12
IONIS MAPTRx
RO7105705
UB-311
GV1001
PHASE III
Albumin + IVIG
CAD106
Solanezumab
Aducanumab
Gantenerumab
Crenezumab
TPI287
L-Serine
ANAVEX2-73
AZD0530
Deferiprone
Bryostatin 1
VX-745
Insulin glulisine
Insulin detemir
Formoterol
Methylene Blue
JNJ-54861911
Valacyclovir
Telmisartan
Nicotinamide
Vorinostat
OAA
Salsalate
Telmisartan
NDX-1017
Insulin aspart
DAOIB
CPC-201
Atomoxetine
Benfotiamine
Cilostazol
SUVN-502
S47445
LM11A-31-BHS
Rotigotine
Dronabinol
MLC901
Riluzole
Montelukast
Pimavanserin
Nicotine
Liraglutide
BI425809
DHP1401
Levetiracetam
Piromelatine
Probucol
ORM-12741
CT1812
STA-1
MP-101
Lithium
Idalopirdine
Allopregnanolone
TAK-071
BNC
ITI-007
AXS-05
Escitalopram
Methylphenidate
Octohydroaminoacridine succinate
AVP-786
Nabilone
Zolpidem
Suvorexant
MK-8931
AZD3293
ALZT-OP1a/b
Icosapent ethyl (IPE)
Azeliragon
Insulin
JNJ54861911
TRx0237
E2609
GV-971
CNP520
ID1201
GM-CSF
Rasagiline
Xanamem
LY3202626
Posiphen
CPC-201
E2609
Nilotinib
Candesartan
SLAT
S-equol
Symptom-Reducing Small Molecule
Disease-Modifying Small Molecule
Undisclosed Mechanism
RGN1016 (Phase I)
BAC (Phase II)
AGN-242071 (Phase I)

Scorecard for Amyloid Immunotherapy: 2016

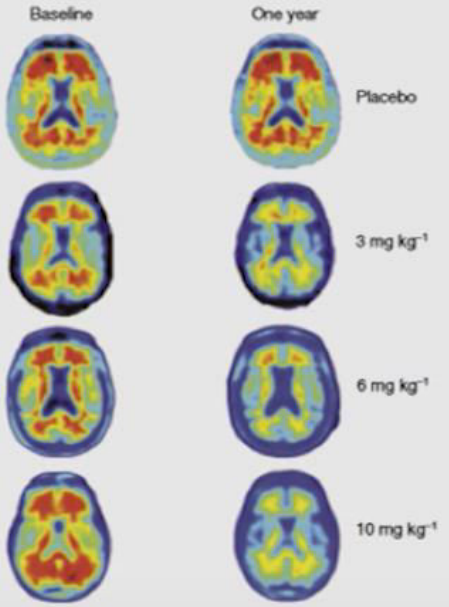
Name of drug	Status of Completed Trials	Comment and Current Status
Bapineuzumab	Phase 3 studies (x2) Mild to Moderate AD	Negative trials Terminated program
Solaneuzumab	Phase 3 studies (x2) Mild to Moderate AD	Negative trials Current trials: Mild AD Prevention in DIAN, Prevention in A4 trials
Gammagard IVIG	Phase 2-3 (x1) Mild to Moderate AD	Negative trial No active program
Gantenerumab	Phase 2 trial in prodromal AD	Negative trial Prevention of AD in DIAN Phase 3 Prodromal AD
Crenezumab	Phase 1-2	Negative trial Phase 2 API trial Prevention in PS 1 FAD
Aducanumab	Phase 1b	***Positive*** trial Phase 3 trials x2 Early AD

Aducanumab: Clinical and PET Results

- **Key findings:**
  - Dose response relationship
  - Significant effect at 12 and not 6 months
  - Converging evidence of clinical and PET response
  - Caveats: Small samples and ARIA at higher doses (30-40%)



Dose-response $P < 0.05$ at week 54 based on a linear contrast test



Sevigny J et al *Nature* 2016

IL 21 MARZO LA BIOGEN HA INTERROTTO I DUE TRIAL CLINICI DI FASE III CON ADUCANUMAB.

LA DECISIONE E' DOVUTA AD UNA ANALISI DI FUTILITA' SVOLTA DA UN COMITATO INDIPENDENTE CHE INDICA COME IMPROBABILE IL RAGGIUNGIMENTO DEGLI ENDOPOINT PRIMARI STABILITI

How do we combat cognitive decline?

At present, healthy diets, antioxidant supplements, the prevention of nutritional deficiencies and moderate physical activity could be considered the first line of defence against the development and progression of pre-dementia and dementia syndromes

Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Santamato A, Ranieri M, Fiore P, Capurso A, Panza F. Lifestyle-related factors in predementia and dementia syndromes. Expert Rev Neurother. 2008 Jan;8(1):133-58. Review.

QUALI SONO I PRINCIPALI FATTORI NUTRIZIONALI CHE POTREBBERO AVERE UN RUOLO PROTETTIVO O DISTRUTTIVO NELL'INSORGENZA DEL DECLINO COGNITIVO?

Additional nutrient & lifestyle factors

Risk factor	Modifiable?
High HbA1c (with or without diabetes)	✓
Poor adherence to Mediterranean diet	✓
Low omega-3 intake/ fish consumption	✓
Low intake of B vitamins	✓
Low vitamin D exposure/ intake/ status	✓
Low antioxidant intake	✓
High oxidative stress	✓
High alcohol consumption	✓
Low intake of polyphenols	✓
High stress/ cortisol/ HPA axis activity	✓
Poor sleep quality/ sleep deprivation	✓

Glicemia e deterioramento cognitivo

Morris JK et al. (2014)
Impaired glycemia increases disease progression in mild cognitive impairment.
Neurobiol Aging. 35:585-589.

Il diabete accelera la conversione da MCI a demenza

Journals of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2015 April;70(4):471–479
doi:10.1093/gerona/glu135

Advance Access publication August 22, 2014

Blood Glucose, Diet-Based Glycemic Load and Cognitive Aging Among Dementia-Free Older Adults

Shyam Seetharaman,[1,] Ross Andel,[2,3] Cathy McEvoy,[2] Anna K. Dahl Aslan,[4,5] Deborah Finkel,[6] and Nancy L. Pedersen[4,7]

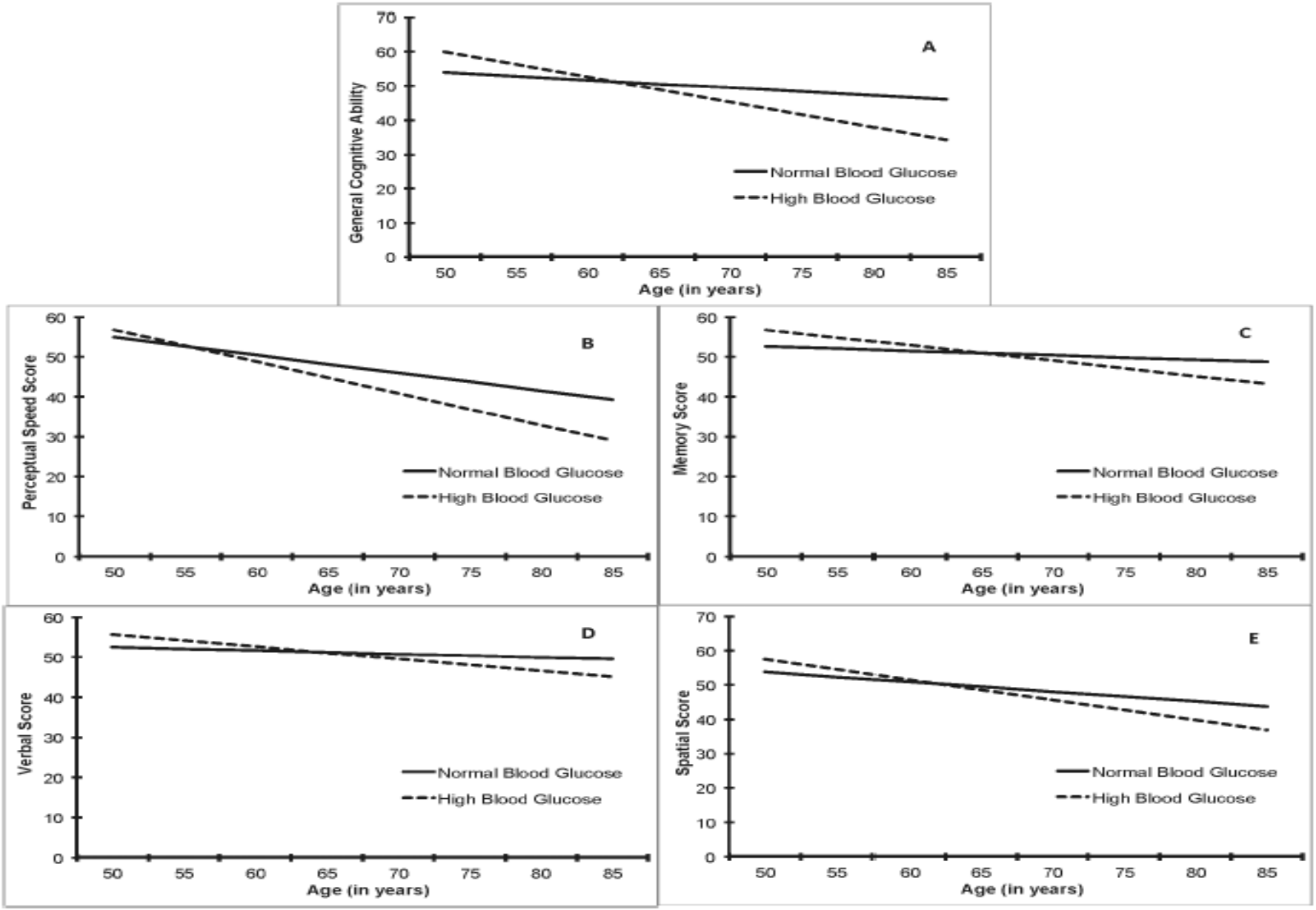


Figure 2. Fully adjusted growth models of cognitive aging as a function of normal vs high blood glucose. Compared with normal blood glucose, high blood glucose was significantly related to greater rates of decline in general cognitive ability (**A**), perceptual speed (**B**), as well as verbal (**D**) and spatial (**E**) scores. The differences between normal vs high blood glucose in terms of change in memory scores over time were not statistically significant (**C**).

Omocisteina

CORRELAZIONE

- AVERE ALTI LIVELLI PLASMATICI DI OMOCISTEINA RAPPRESENTA UN FATTORE DI RISCHIO PER INSORGENZA DI DEMENZA
- I MALATI DI AD PRESENTANO LIVELLI DI OMOCISTEINA PIU' ALTI DEI CONTROLLI

NON CORRELAZIONE

- NEUROLOGY 2008 L'INTEGRAZ CON AC FOLICO E B 12 PER 18 MESI IN MALATI DI AD PORTAVA AD UNA RIDZIONE DELLA OMOCISTEINA MA LE PRESTAZIONI COGNITIVE DEI PAZ ALL'ADAS COG NON DIFFERNZIAVANO DA QUELLE DEL GRUPPO TRATTATO CON PLACEBO

Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals[1–5]

Robert Clarke, Derrick Bennett, Sarah Parish, Sarah Lewington, Murray Skeaff, Simone JPM Eussen, Catharina Lewerin, David J Stott, Jane Armitage, Graeme J Hankey, Eva Lonn, J David Spence, Pilar Galan, Lisette C de Groot, Jim Halsey, Alan D Dangour, Rory Collins, and Francine Grodstein on behalf of the B-Vitamin Treatment Trialists' Collaboration

Conclusion: Homocysteine lowering by using B vitamins had no significant effect on individual cognitive domains or global cognitive function or on cognitive aging. *Am J Clin Nutr* 2014;100: 657–66.

Journal of Alzheimer's Disease 62 (2018) 561–570
DOI 10.3233/JAD-171042
IOS Press

Editorial

Homocysteine and Dementia: An International Consensus Statement

Abstract. Identification of modifiable risk factors provides a crucial approach to the prevention of dementia. Nutritional or nutrient-dependent risk factors are especially important because dietary modifications or use of dietary supplements may lower the risk factor level. One such risk factor is a raised concentration of the biomarker plasma total homocysteine, which reflects the functional status of three B vitamins (folate, vitamins B12, B6). A group of experts reviewed literature evidence from the last 20 years. We here present a Consensus Statement, based on the Bradford Hill criteria, and conclude that elevated plasma total homocysteine is a modifiable risk factor for development of cognitive decline, dementia, and Alzheimer's disease in older persons. In a variety of clinical studies, the relative risk of dementia in elderly people for moderately raised homocysteine (within the normal range) ranges from 1.15 to 2.5, and the Population Attributable risk ranges from 4.3 to 31%. Intervention trials in elderly with cognitive impairment show that homocysteine-lowering treatment with B vitamins markedly slows the rate of whole and regional brain atrophy and also slows cognitive decline. The findings are consistent with moderately raised plasma total homocysteine (>11 μmol/L), which is common in the elderly, being one of the causes of age-related cognitive decline and dementia. Thus, the public health significance of raised tHcy in the elderly should not be underestimated, since it is easy, inexpensive, and safe to treat with B vitamins. Further trials are needed to see whether B vitamin treatment will slow, or prevent, conversion to dementia in people at risk of cognitive decline or dementia.

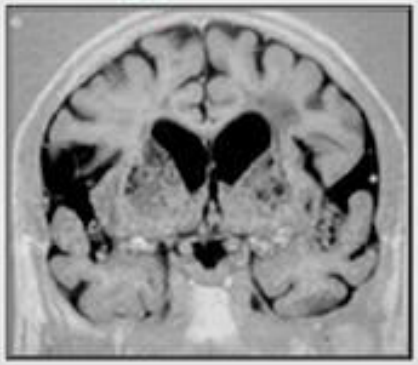
Keywords: Homocysteine, folate, vitamin B12, cobalamin, vitamin B6, cognitive impairment, dementia, Alzheimer's disease, brain atrophy, risk-factor, causation

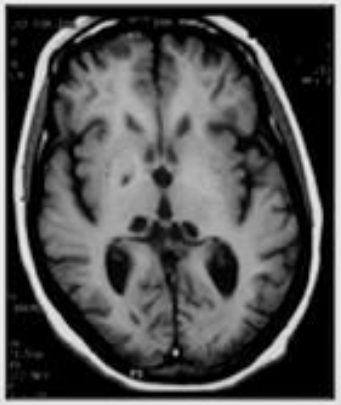
IL RISCHIO RELATIVO DI SVILUPPARE DEMENZA IN SOGG CON ALTA OMOCISTEINEMIA VA DA 1.15 A 2.5 (RR: la probabilità di malattia nel gruppo degli esposti rispetto ai controlli)

Il rischio attribuibile anche aumenta (RA: la quota di rischio supplementare attribuibile al fattore di rischio iperomocisteina, ossia la quota di malati che eviterebbe la malattia se fosse completamente rimosso dalla popolazione il suddetto fattore di rischio)

Interactions of Vascular and Alzheimer Pathology

- "Fewer neuropathologic lesions of AD appeared to result in dementia in those with lacunar infarcts in the basal ganglia, thalamus, or deep white matter than those without infarcts."
- The presence of cerebral infarcts even is small and scarce raise the risk of dementia by as much as 20 times in those with AD type lesions [1]



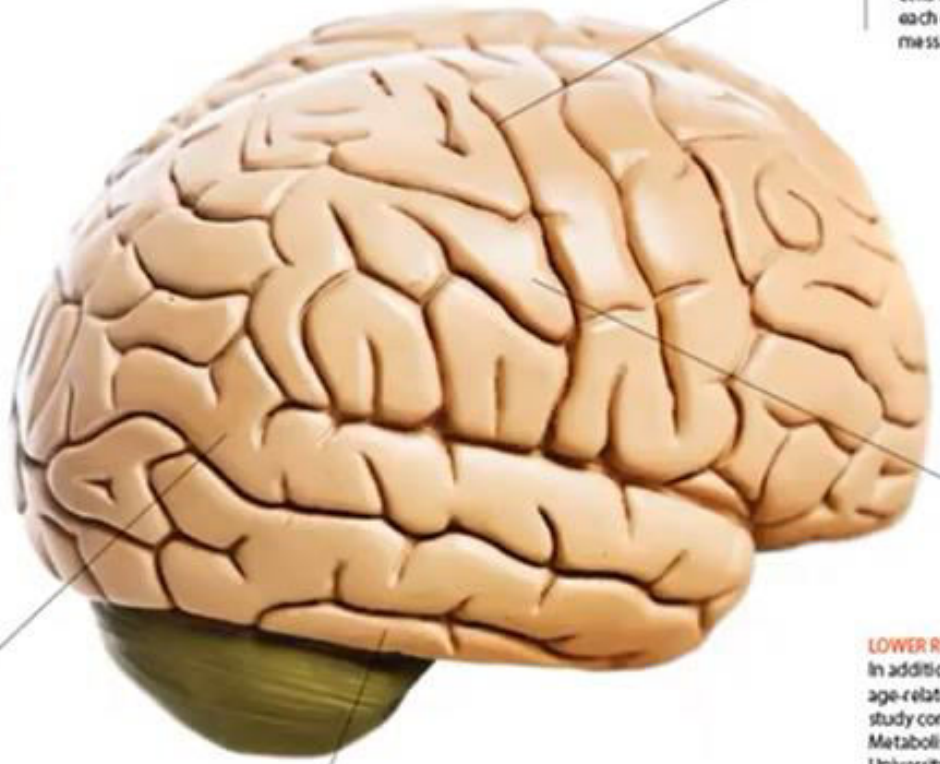


1Snowdon DS et al *JAMA* 1997; 2Pendlebury ST et al *Lancet Neurol* 2009

Omega-3s

your daily dose of smart.

As a major structural component of the brain, omega-3s are crucial to supporting almost every area of brain function and development through every stage of life.



SUPPORTS MEMORY, FOCUS AND ATTENTION

Regular intake of omega-3s boosts DHA levels in the hippocampus—the area of the brain responsible for memory and recall. DHA helps memory cells communicate better with each other and better relay messages.[1]

HELPS PREVENT BRAIN SHRINKAGE

Brain volume maxes out at about age 20, and then slowly deteriorates, losing up to 11% by age 45. This shrinkage is most pronounced in the forebrain region responsible for personality, memory and cognitive function. Regular omega-3 intake has been linked to increased brain volume as well as a reduction in the risk of brain shrinkage.

ESSENTIAL TO BRAIN STRUCTURE AND MASS

DHA omega-3s are one of the few substances that can cross the blood brain barrier and be incorporated into the structure of the brain. In doing so, they help maintain optimal brain mass.

LOWER RISK OF DEMENTIA

In addition to helping slow age-related memory loss, a study conducted at the Lipid Metabolism Laboratory of Tufts University found that high levels of DHA in the brain can result in a significant 47% reduction in the risk of developing dementia.[2]

IMPROVED SIGNAL TRANSMISSION

The brain relies on synapses to transfer signals around the brain and to other parts of the body. DHA omega-3 boosts this process by allowing an increase in signal transmission from the surface of the membrane to the interior of the nerve cells.

Fish consumption, cognitive decline and dementia

Brain lipids contain a high proportion of polyunsaturated fatty acids (PUFAs), which are a main component of cell membranes

The physiological roles of omega-3 PUFA in the brain include regulation of cell membrane fluidity, dopaminergic and serotonergic transmission, regulation of cellular signal transduction, brain glucose metabolism, eicosanoid synthesis, gene expression and cell cycle control

- High fish consumption tends to be inversely associated with cognitive impairment and decline (Kalmijn 2000)

- Elderly people who eat fish or seafood at least once a week are at lower risk of developing dementia, including Alzheimer's disease (Barberger-Gateau *et al.* 2002)

- Meta analysis of 21 studies (181,580 participants) with 4438 cases identified during follow-up periods (2.1-21 y) found increased fish and omega-3 fatty consumption was associated with a statistically significant lower risk of dementia, AD, MCI and PD (Zhang *et al.* 2016)

Barberger-Gateau P, Letenneur L, Deschamps V, Pérès K, Dartigues JF, Renaud S. Fish, meat, and risk of dementia: cohort study. BMJ. 2002 Oct 26;325(7370):932-3.

Kalmijn S. Fatty acid intake and the risk of dementia and cognitive decline: a review of clinical and epidemiological studies. J Nutr Health Aging. 2000;4(4):202-7. Review.

Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. Am J Clin Nutr. 2016 Feb;103(2):330-40.

Omega-3 and cognitive decline

- Meta-analysis examined the neuropsychological benefit of omega-3 in randomized RCTs including healthy people, Alzheimer's disease and milder forms of cognitive impairment (e.g. cognitive impairment no dementia [CIND])

- Omega-3 fatty acid treatment was associated with a small, but significant, benefit for immediate recall and attention and processing speed in subjects with CIND but not in healthy subjects or those with AD (similar findings from OmegAD study)

"Nevertheless, the present findings suggest that the effects of omega-3 on cognitive decline are not uniform, and that there is a need to identify potentially responsive populations"

Furthermore it is likely that nutrients work synergistically rather than in isolation!

Mazereeuw G, Lanctôt KL, Chau SA, Swardfager W, Herrmann N. Effects of ω-3 fatty acids on cognitive performance: a meta-analysis. Neurobiol Aging. 2012 Jul;33(7):1482.e17-29.

- **Alzheimer's disease (AD)** is the most common neurodegenerative disorder in the aged population

- Main pathological features of AD include β-amyloid (Aβ) accumulation and hyper-phosphorylation of the microtubule-associated protein *tau*, leading to the neuropathological hallmarks of AD, senile plaques and neurofibrillary tangles

- Amyloidogenic Aβ peptides are generated by sequential proteolytic processing of the amyloid precursor protein (APP) involving β- and γ-secretase activity

- DHA has been shown to reduce Aβ production *in vitro* and in animal models of AD

- DHA is decreased in post-mortem AD brains, and AD patients have reduced blood DHA levels

- *DHA has therefore become of major interest for nutritional intervention in AD*

Grimm MO, Haupenthal VJ, Mett J, Stahlmann CP, Blümel T, Mylonas NT, Endres K, Grimm HS, Hartmann T. Oxidized Docosahexaenoic Acid Species and Lipid Peroxidation Products Increase Amyloidogenic Amyloid Precursor Protein Processing. Neurodegener Dis. 2016;16(1-2):44-54.

Gut microbiota and cognitive behaviour

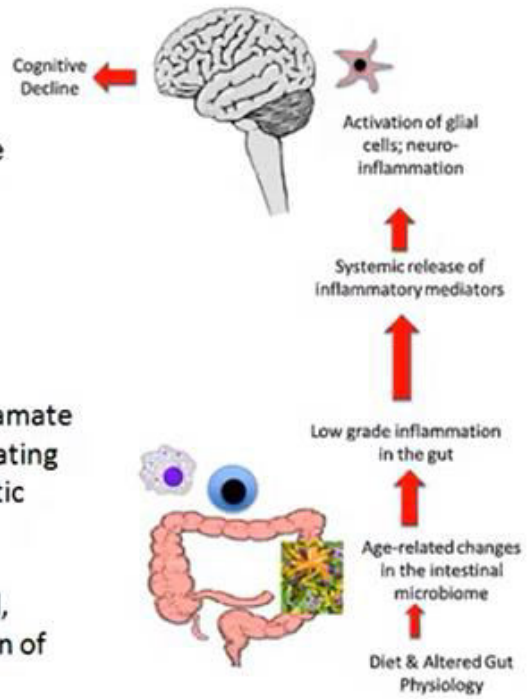
Dysbiosis is known to result in low grade inflammation

Recent studies suggest a significant correlation between the changes of gut microbiota and cognitive behaviour:

Neurotransmitters including γ-aminobutyric acid (GABA), glutamate and serotonin are influenced by gut flora

Disruption of gut microbiota by antibiotic treatment also significantly reduces the level of N-methyl-D-aspartate glutamate receptor (NMDA) in the hippocampus – important for regulating neuronal survival, dendrite & axon development and synaptic plasticity

The development of HPA-axis in germ free mice is abnormal, leading to altered response to stress and reduced expression of brain-derived neurotrophic factor (BDNF)



Caracciolo B, Xu W, Collins S, Fratiglioni L. Cognitive decline, dietary factors and gut-brain interactions. Mech Ageing Dev. 2014 Mar-Apr;136-137:59-69.

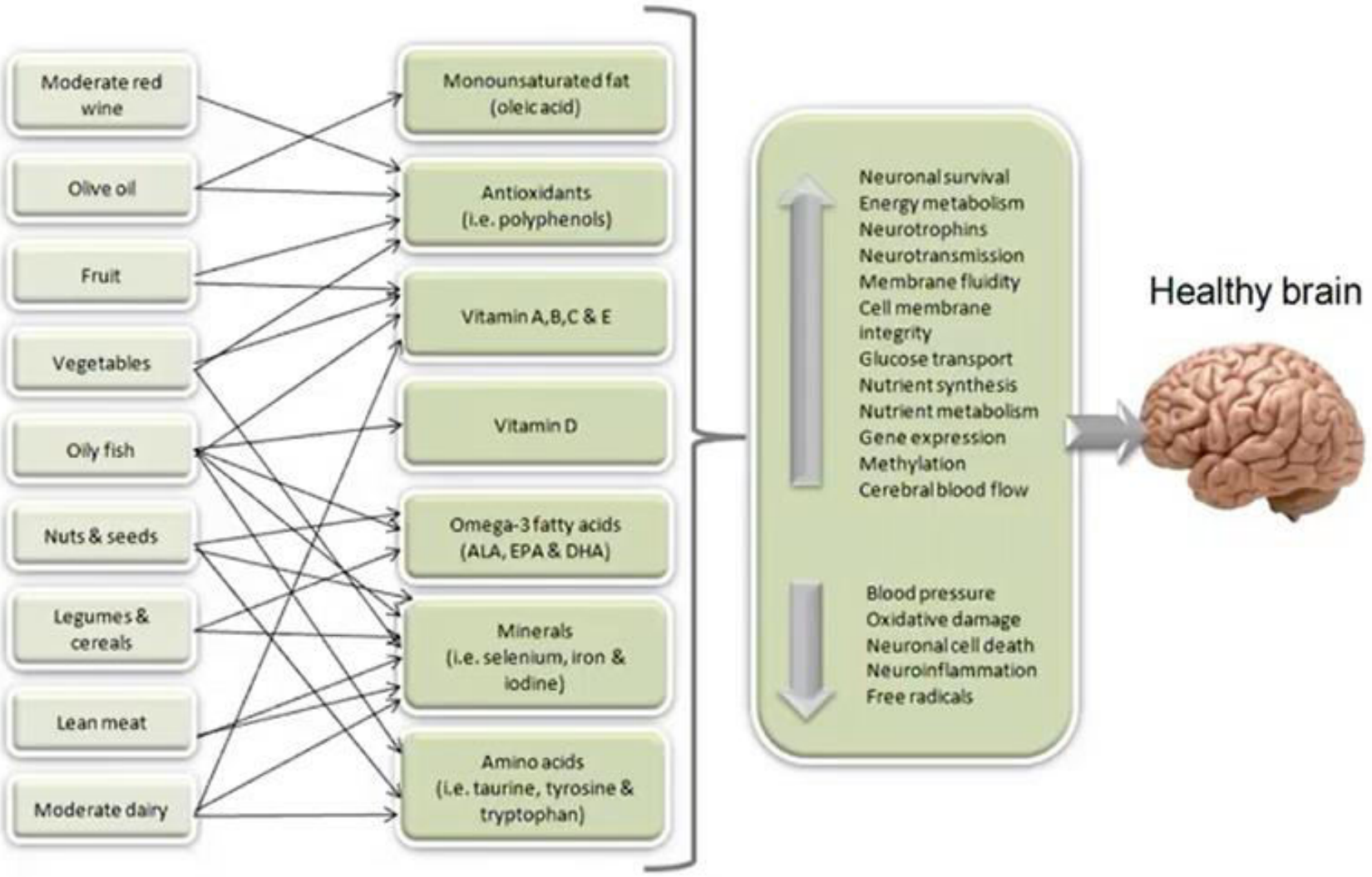
Inflamm-aging: basso grado di infiammazione alla base di ampio spettro di patologie correlate all'età incluso il declino cognitivo. (Franceschi 2000)

Giovani: Bacteroidi e Firmicuti
Adulti: Aumentano i pathobionti e diminuiscono i simbionti (aumento delle specie proto batteriche e diminuzione delle specie bifidobatteriche)

DIETA MEDITERRANEA

DAGLI STUDI EMERGE SEMPRE PIU' L'IPOTESI CHE PIU' CHE UN SINGOLO NUTRIENTE CIO' CHE E' DI PIU' BENEFICIO E' UNA DIETA BILANCIATA.

LA DIETA MEDITERRANEA E' LA PIU' STUDIATA IN RELAZIONE AI BENEFICI CIRCA LE FUNZIONI COGNITIVE (CHAO ET AL 2013) PER VIA DELL'APPORTO DI FRUTTA VERDURA OLIO DI OLIVA E LA POVERTA' DI GRASSI ANIMALI.



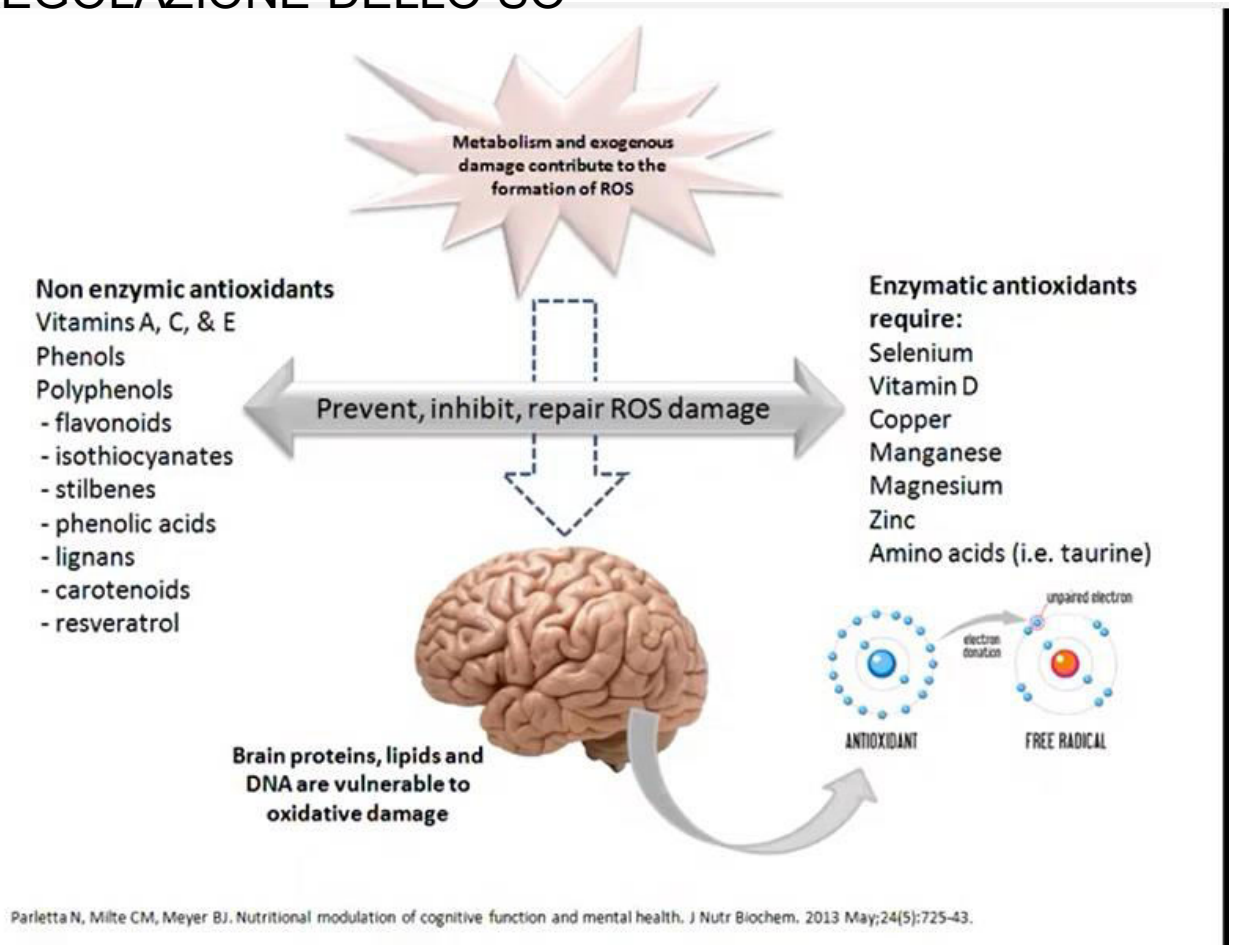
Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. J Nutr Biochem. 2013 May;24(5):725-43.

PERCHE' E' IMPORTANTE LA VARIETA'?

IL CERVELLO HA UN METABOLISMO MOLTO ATTIVO.
LO STRESS OSSIDATIVO E' UN FENOMENO MOLTO COMUNE NEL TESSUTO NEURALE
DUE PRINCIPALI ANTIOSSIDANTI SONO COINVOLTI NELLA REGOLAZIONE DELLO SO

Gli enzimi antiossidanti catalizzano reazioni neutralizzanti contro i radicali liberi e le specie reattive dell'ossigeno

I nutrienti antiossidanti aiutano come cofattori nelle attività catalitiche



Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. J Nutr Biochem. 2013 May;24(5):725-43.

Review | Journal of INTERNAL MEDICINE

Click here to view the article Editorial Comment by M. F. Holick

doi: 10.1111/joim.12279

'Vitamin D and cognition in older adults': updated international recommendations

C. Annweiler[1,2], E. Dursun[3], F. Féron[4], D. Gezen-Ak[3], A. V. Kalueff[5], T. Littlejohns[6], D. J. Llewellyn[6], P. Millet[4], T. Scott[7], K. L. Tucker[8], S. Yilmazer[3] & O. Beauchet[1]

REGOLA METABOLISMO OSSEO ED ESERCITA AZIONI BIOLOGICHE MULTIPLE MEDIATE DAL RECETTORE VDR

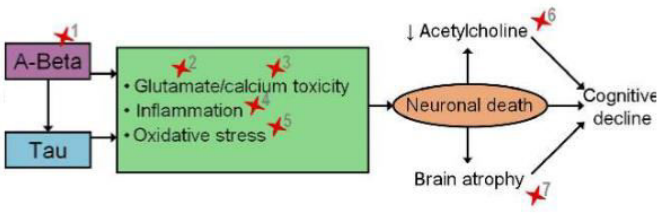


Fig. 1 *Potential targets and neuroprotective roles of vitamin D during the natural history of Alzheimer's disease.*

2014 raccomandazioni internazionali che riconoscono come il deficit di Vit D possa essere un fattore di rischio per declino cognitivo e demenza (ipovitaminosi molto comune nell'anziano; dati sui topi= diminuzione n placche amiloidi)

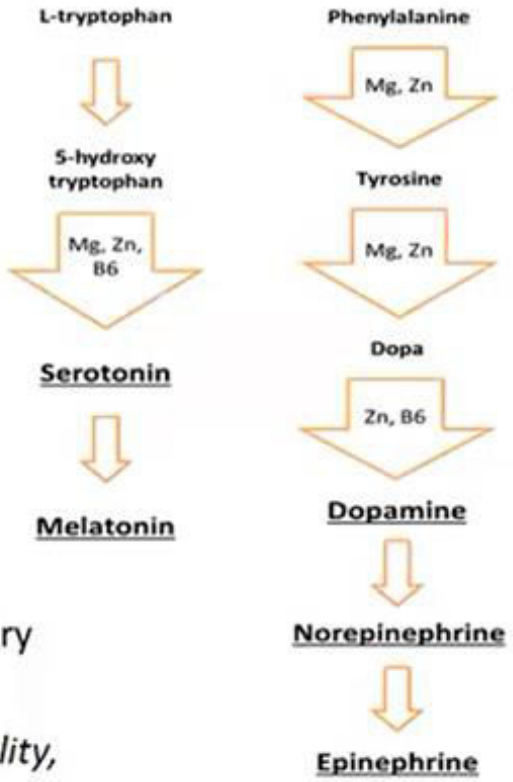
Supplementazione di Vit D=riduzione di più del doppio del rischio di ammalarsi di AD negli anni successivi (Neurology Llewellyn 2014)

Studio con Memantina+Vit D per 6 mesi (Neurology 2012)

Magnesium

- Regulates the CNS via
  - neurotransmitter synthesis
  - neurone activity
  - synaptic plasticity

- Vitamin B6 absorption
- Required by 325 enzymes (many of which act in the brain)
- Neurone health, synaptic plasticity, learning and memory



Low magnesium levels linked to anxiety, depression, irritability, insomnia, confusion....

Magnesium as glycinate provides a bioavailable and effective magnesium source

Glycine promotes healthy immune, digestive and central nervous systems, production of human growth hormones and creatine

Zinc

- Essential to the production of neurotransmitters
- Enhances neurotransmission via interaction with receptors, transporters and ion channels in the neurone and synapse
- Low zinc status is linked to cognitive impairment via epigenetic changes of the brain-derived neurotrophic factor (BDNF) gene

Selenium

- Up-regulates glutathione production
- Main component of antioxidant enzymes
- Supports proper adrenal function – commonly disrupted by high stress and poor diet – leads to poor sleep, memory problems and fatigue
- Low selenium status is a risk factor for cognitive decline!

Berr C, Arnaud J, Akbaraly TN. Selenium and cognitive impairment: a brief-review based on results from the EVA study. Biofactors. 2012 Mar-Apr;38(2):139-44.

Hu YD, Pang W, He CC, Lu H, Liu W, Wang ZY, Liu YQ, Huang CY, Jiang YG. The cognitive impairment induced by zinc deficiency in rats aged 0~2 months related to BDNF DNA methylation changes in the hippocampus. Nutr Neurosci. 2016 Jun 22:1-7.

CONCLUSIONI

La dieta mediterranea sembrerebbe essere quella con maggiore evidenza di benefici circa le funzioni cognitive probabilmente per la sua varietà di nutrienti

Sebbene vi siano molti studi sul potenziale effetto di vari nutrienti sullo sviluppo o la progressione di deterioramento cognitivo il tema risulta ancora non privo di incertezze

Una forte associazione tra fatt di rischio vascolari e demenza è ormai nota e oggi conosciamo quali sono i regimi dietetici che ci espongono maggiormente a problematiche vascolari e malattie metaboliche

Studi che includano l'assessment della dieta del paziente e il dosaggio di marcatori biologici correlati ai nutrienti in individui di mezza età potrebbe fornire preziose informazioni circa la relazione tra dieta e invecchiamento cerebrale.

GRAZIE