SINdem4Juniors

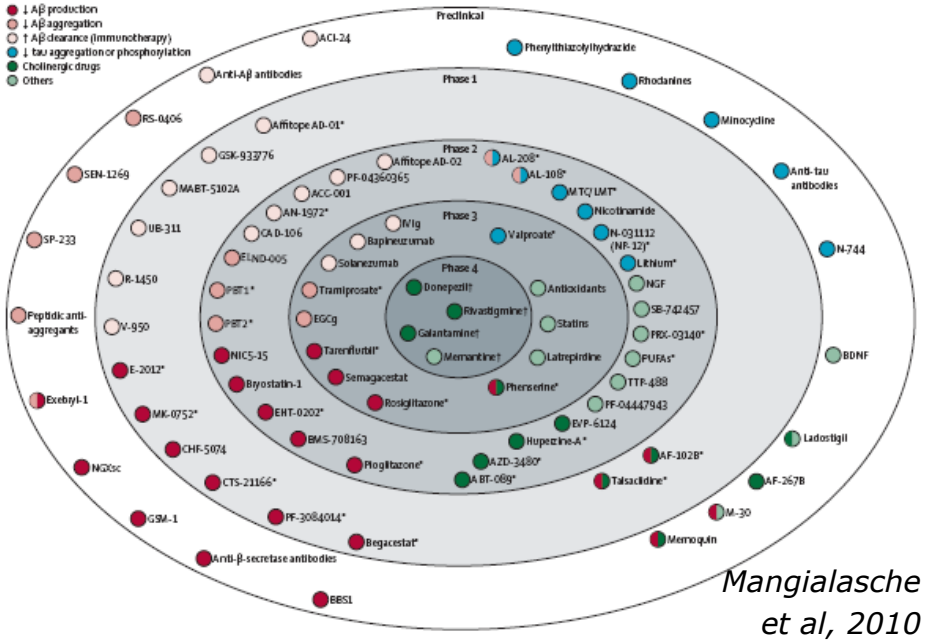
6th Winter Seminar on Dementia and Neurodegenerative Disorders

Diet style

dott. Cherubino Di Lorenzo

Dipartimento di Scienze medico-chirurgiche e Biotecnologie, Università La Sapienza Roma - Fondazione Don Gnocchi Onlus

DISEASE MODIFYING TREATMENTS?



Mangialasche et al, 2010

PREVENTION

Conuteracts the risk factors and the transition from MCI to AD

The prevention

Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Sandrine Andrieu, Nicola Coley*, Simon Lovestone, Paul S Aisen, Bruno Vellas*

The projected effects of preventive interventions with even quite modest effects at the individual level are impressive, dramatically reducing the future burden of dementia. For example, an intervention that delays disease onset and progression by 1 year, or a reduction in the prevalence of several modifiable lifestyle risk factors of 10% per decade, could potentially reduce the number of Alzheimer's disease dementia cases worldwide in 2050 by around 9 million.[5,6]

Andrieu et al, 2015

Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

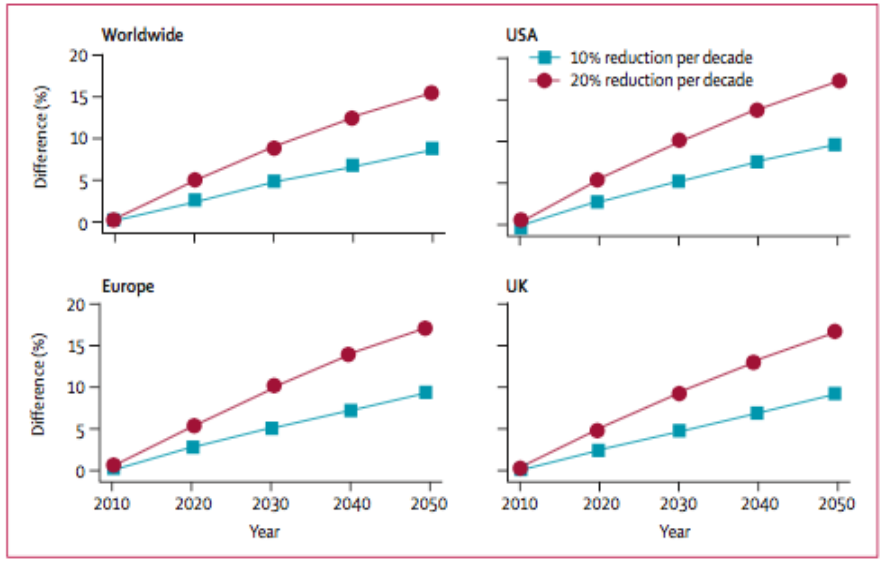


Figure: Projected percentages of Alzheimer's disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

Norton S et al, 2014

Epidemiology of AD

(nature or nurture?)

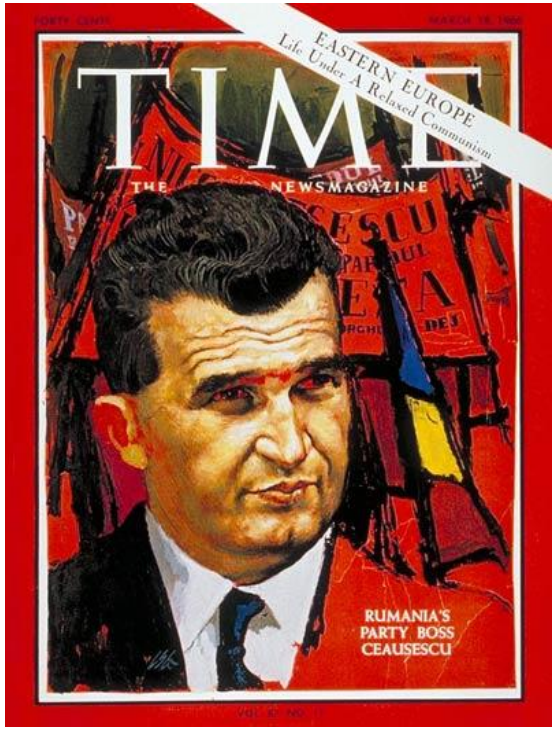
GBD region	Population >60 years of age (millions 2010)	Crude estimated prevalence (%, 2010)	Number of people with dementia (millions)			Proportionate increases (%)	
			2010	2030	2050	2010–2030	2010–2050
Asia	406.6	3.9	15.9	33.0	60.9	107.0	282.0
Europe	160.2	6.2	10.0	14.0	18.7	40.0	87.0
The Americas	120.7	6.5	7.8	14.8	27.1	89.0	246.0
Africa	71.1	2.6	1.9	3.9	8.7	111.0	370.0
World	758.5	4.7	35.6	65.7	115.4	85.0	225.0

	1990		2010	
	Alzheimer's disease	Dementia	Alzheimer's disease	Dementia
55–59 years	0·0014 (0·0000–0·8378)	0·0047 (0·0000–0·6702)	0·0023 (0·0000–0·7227)	0·0068 (0·0000–0·5451)
60–64 years	0·0033 (0·0000–0·6410)	0·0094 (0·0000–0·5266)	0·0055 (0·0000–0·4982)	0·0135 (0·0000–0·3830)
65–69 years	0·0076 (0·0000–0·5304)	0·0180 (0·0000–0·4438)	0·0127 (0·0000–0·3612)	0·0258 (0·0000–0·2816)
70–74 years	0·0164 (0·0000–0·4946)	0·0332 (0·0000–0·4170)	0·0273 (0·0000–0·3178)	0·0476 (0·0000–0·2460)
75–79 years	0·0330 (0·0000–0·5040)	0·0592 (0·0000–0·4323)	0·0552 (0·0000–0·3391)	0·0850 (0·0000–0·2639)
80–84 years	0·0625 (0·0000–0·5337)	0·1019 (0·0000–0·4782)	0·1044 (0·0000–0·3862)	0·1463 (0·0000–0·3137)
85–89 years	0·1109 (0·0000–0·5785)	0·1694 (0·0000–0·5564)	0·1854 (0·0000–0·4500)	0·2432 (0·927–0·3937)
90–94 years	0·1847 (0·0000–0·6549)	0·2720 (0·0000–0·6840)	0·3086 (0·0595–0·5578)	0·3903 (0·2416–0·5389)
95–99 years	0·2884 (0·0000–0·7974)	0·4214 (0·0000–0·8892)	0·4819 (0·1904–0·7735)	0·6047 (0·3967–0·8128)

Data are prevalence (95% CI).

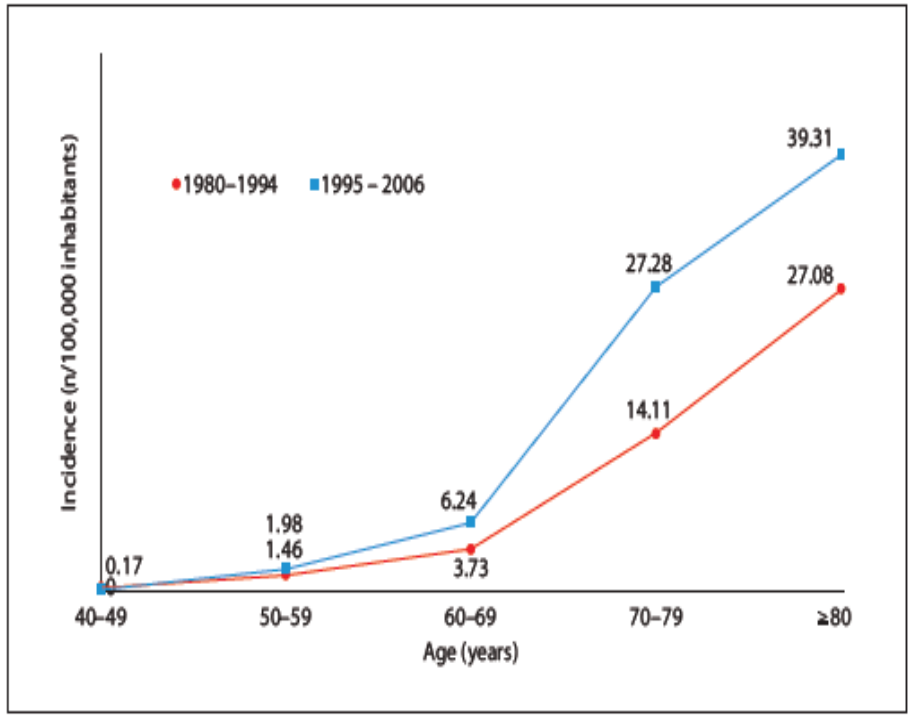
CHINA

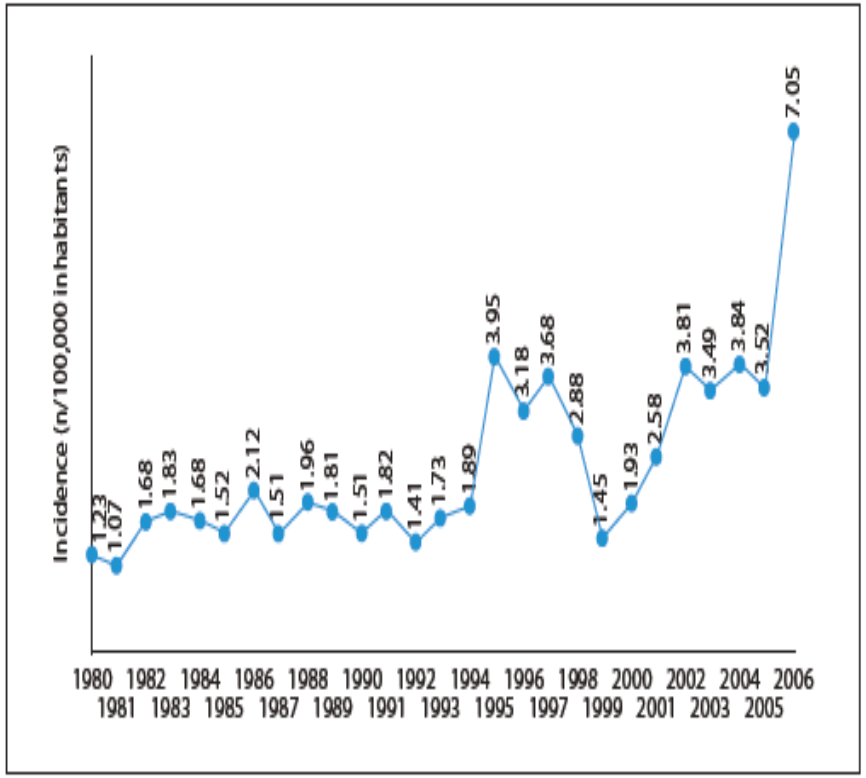
Nature and nurture: the case of Romania



AD Incidence in Romania between 1980 and 2006:

Stable levels untill 1994, than significant increase





WHY?

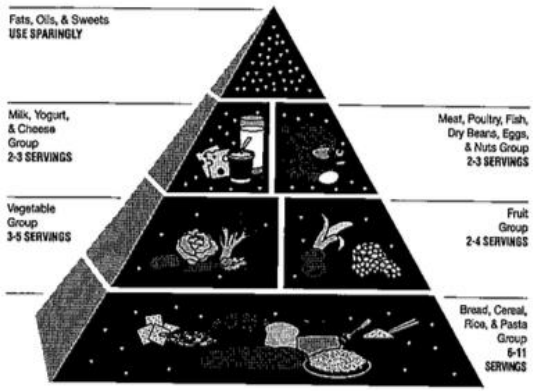
G. Cornutiu, Neurodegenerative Dis., 2011

Industrial foods availability

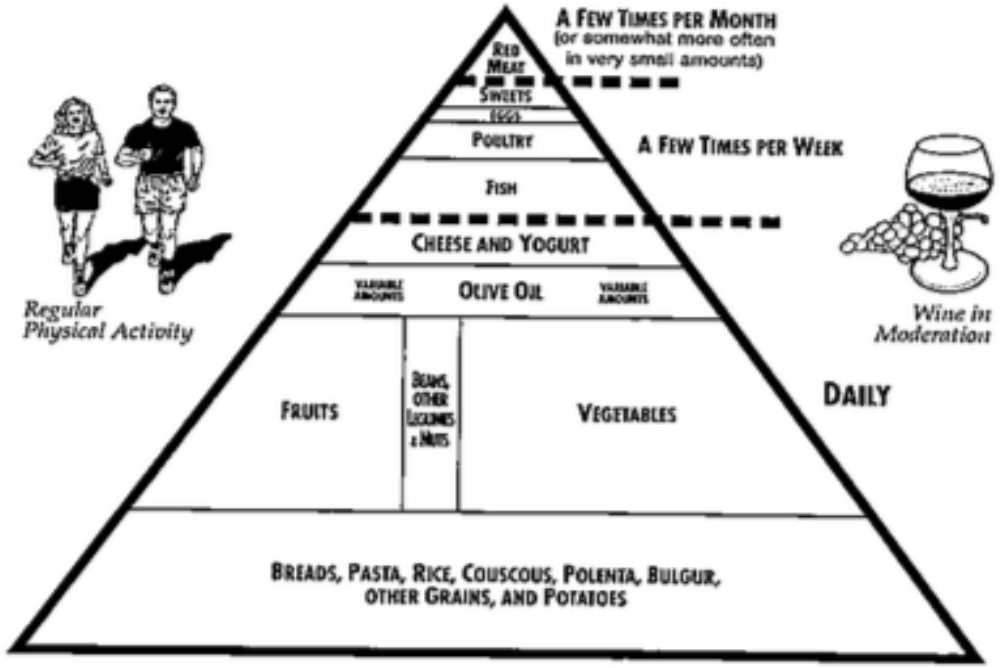
(rich in refined sugars, unhealty fats and calories)

Mediterranean Pyramid

- 1993 – International Conference on the Diet of the Mediterranean



1992 – US Department of Agriculture food guide pyramid



1994 – Mediterranean diet pyramid

Willett WC, 1995

Ann Neurol. 2006 June ; 59(6): 912–921. doi:10.1002/ana.20854.

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD[1,2,3], **Yaakov Stern, PhD**[1,2,3], **Ming-Xin Tang, PhD**[1,4], **Richard Mayeux, MD**[1,2,3], and **Jose A. Luchsinger, MD**[1,5]

Association between high adherence to the Mediterranean Diet
and lower risk for AD
mediated by
the composite effect of some of its beneficial components, such as
higher intake of fish, fruits, and vegetables rich in antioxidants such as vitamin C, vitamin E, and flavonoids and higher intake of unsaturated fatty acids

None of the individual components was a significant AD predictor.
An overall dietary pattern,
with possible additive and interactive (antagonistic or synergistic) effects among nutritional components,
is likely to have a greater effect on health than a single nutrient.

Ann Neurol. 2006 June ; 59(6): 912–921. doi:10.1002/ana.20854.

Mediterranean Diet and Risk for Alzheimer's Disease

Nikolaos Scarmeas, MD[1,2,3], **Yaakov Stern, PhD**[1,2,3], **Ming-Xin Tang, PhD**[1,4], **Richard Mayeux, MD**[1,2,3], and **Jose A. Luchsinger, MD**[1,5]

Arch Neurol. 2006 December ; 63(12): 1709–1717. doi:10.1001/archneur.63.12.noc60109.

Mediterranean Diet, Alzheimer Disease, and Vascular Mediation

Dr. Nikolaos Scarmeas, MD, **Dr. Yaakov Stern, PhD**, **Dr. Richard Mayeux, MD**, and **Dr. Jose A. Luchsinger, MD**

JAMA. 2009 August 12; 302(6): 627–637. doi:10.1001/jama.2009.1144.

Physical Activity, Diet, and Risk of Alzheimer Disease

Nikolaos Scarmeas, MD, **Jose A. Luchsinger, MD**, **Nicole Schupf, PhD**, **Adam M. Brickman, PhD**, **Stephanie Cosentino, PhD**, **Ming X. Tang, PhD**, and **Yaakov Stern, PhD**

In MCI patients: the mediterranean diet halfs the risk of AD developement (follow up: 4,3 years)

Mediterranean Diet, Stroke, Cognitive Impairment, and Depression: A Meta-Analysis

Theodora Psaltopoulou, PhD,[1] Theodoros N. Sergentanis, MD,[1]
Demosthenes B. Panagiotakos, PhD,[2] Ioannis N. Sergentanis, MD,[1,3]
Rena Kosti, PhD,[1] and Nikolaos Scarmeas, MD, MSc, PhD[4,5]

Objective: This meta-analysis aims to quantitatively synthesize all studies that examine the association between adherence to a Mediterranean diet and risk of stroke, depression, cognitive impairment, and Parkinson disease.
Methods: Potentially eligible publications were those providing effect estimates of relative risk (RR) for the association between Mediterranean diet and the aforementioned outcomes. Studies were sought in PubMed up to October 31, 2012. Maximally adjusted effect estimates were extracted; separate analyses were performed for high and moderate adherence.
Results: Twenty-two eligible studies were included (11 covered stroke, 9 covered depression, and 8 covered cognitive impairment; only 1 pertained to Parkinson's disease). High adherence to Mediterranean diet was consistently associated with reduced risk for stroke (RR = 0.71, 95% confidence interval [CI] = 0.57–0.89), depression (RR = 0.68, 95% CI = 0.54–0.86), and cognitive impairment (RR = 0.60, 95% CI = 0.43–0.83). Moderate adherence was similarly associated with reduced risk for depression and cognitive impairment, whereas the protective trend concerning stroke was only marginal. Subgroup analyses highlighted the protective actions of high adherence in terms of reduced risk for ischemic stroke, mild cognitive impairment, dementia, and particularly Alzheimer disease. Meta-regression analysis indicated that the protective effects of Mediterranean diet in stroke prevention seemed more sizeable among males. Concerning depression, the protective effects of high adherence seemed independent of age, whereas the favorable actions of moderate adherence seemed to fade away with more advanced age.
Interpretation: Adherence to a Mediterranean diet may contribute to the prevention of a series of brain diseases; this may be of special value given the aging of Western societies.

ANN NEUROL 2013;74:580–591

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]

[a]Department of Neurology, Mayo Clinic, Rochester, MN, USA

[b]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[c]Mayo Medical Libraries, Mayo Clinic, Rochester, MN, USA

[d]Department of Clinical Neuroscience, University of North Dakota School of Medicine and Health Sciences, Fargo, North Dakota, USA

Abstract

Background/Objective—To conduct a systematic review of all studies to determine whether there is an association between the Mediterranean diet (MeDi) and cognitive impairment.

Methods—We conducted a comprehensive search of the major databases and hand-searched proceedings of major neurology, psychiatry, and dementia conferences through November 2012. Prospective cohort studies examining the MeDi with longitudinal follow-up of at least 1 year and reporting cognitive outcomes (mild cognitive impairment [MCI] or Alzheimer's disease [AD]) were included. The effect size was estimated as hazard-ratio (HR) with 95% confidence intervals (CIs) using the random-effects model. Heterogeneity was assessed using Cochran's Q-test and I^2-statistic.

Results—Out of the 664 studies screened, five studies met eligibility criteria. Higher adherence to the MeDi was associated with reduced risk of MCI and AD. The subjects in the highest MeDi tertile had 33% less risk (adjusted HR=0.67; 95% CI, 0.55–0.81; P<0.0001) of cognitive impairment (MCI or AD) as compared to the lowest MeDi score tertile. Among cognitively normal individuals, higher adherence to the MeDi was associated with a reduced risk of MCI (HR=0.73; 95% CI, 0.56–0.96; P=0.02) and AD (HR=0.64; 95% CI, 0.46–0.89; P=0.007). There was no significant heterogeneity in the analyses.

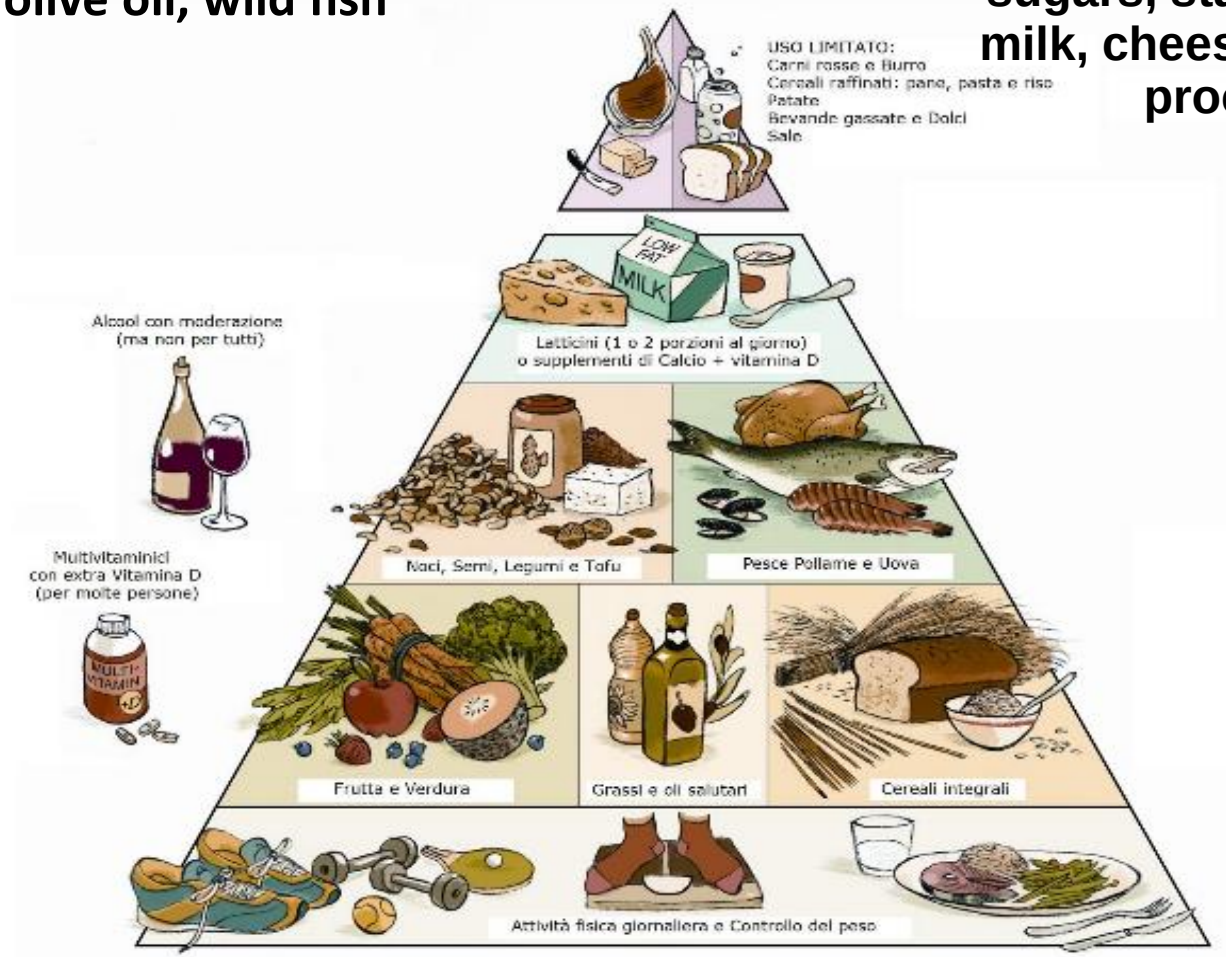
Singh B, 2014

Preventive way of life Pyramid?

(Beyond medirranean diet)

Preventive foods: **whole grains, low glycemic index vegetables, seeds, olive oil, wild fish**

Unhealthful foods: **white bread, sugars, refined flours and sugars, starch, potatoes, corn, milk, cheese, butter, read meet, processed foods**



Diet under an evolutionary pint of view? The Paleo diet!

(a fashionable diet: myth or reality?)

Low glicemicc index foods, no grains, no legumes, no diary, wild fruits

Grass-feed beef ⟶ lean (but rich in omega-3)

Meat from factory farming ⟶ rich in non-healthy fats (saturated and mono-insaturateded fatty acids)

E. Bufill et al., Journal of Anthropological Sciences 2013

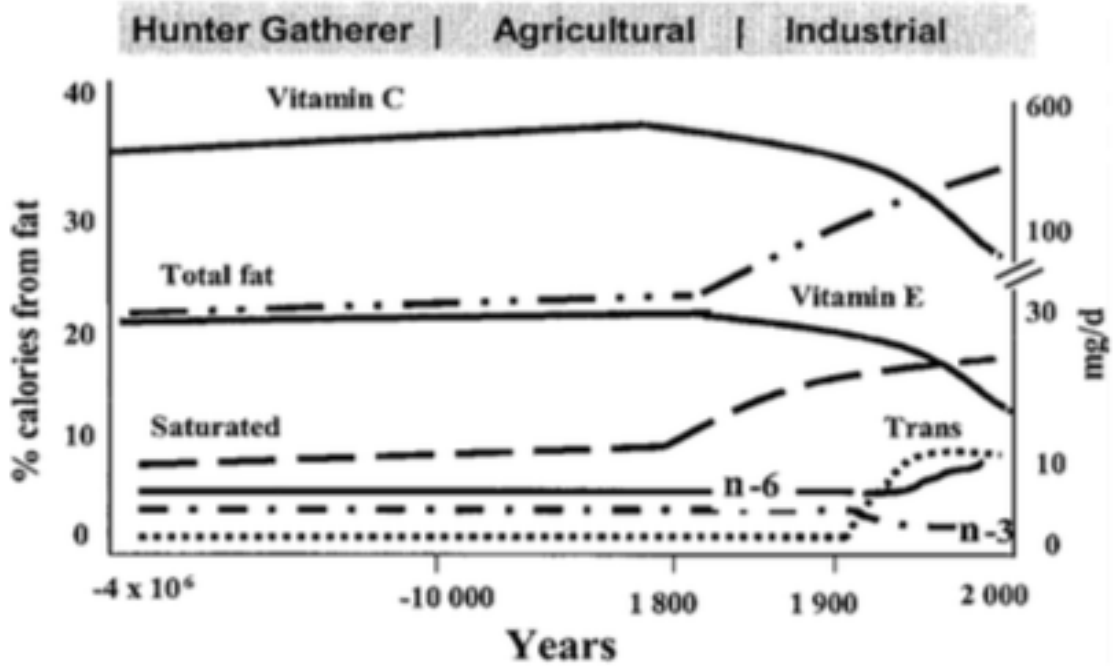


FIGURE 1 Hypothetical scheme of fat, fatty acid (n-6, n-3, *trans* and total) intake (as percentage of energy from fat) and intake of vitamins E and C (mg/d). Data were extrapolated from cross-sectional analyses of contemporary hunter-gatherer populations and from longitudinal observations and their putative changes during the preceding 100 y (12).

Ratios of (n-6) to (n-3) fatty acids in various populations

Population	(n-6):(n-3)	Reference
Paleolithic	0.79	8
Greece before 1960	1.00–2.00	9
Current United States	16.74	8
Current United Kingdom and northern Europe	15.00	10
Current Japan	4.00	11

Industrialized societies diet:

- an increase in energy intake and decrease in energy expenditure
- an increase in saturated fat, (n-6) fatty acids and *trans* fatty acids and a decrease in (n-3) fatty acid intake
- a decrease in fiber intake
- an increase in cereal grains
- a decrease in fruit and vegetable intake
- a decrease in protein, anti-oxidant and calcium intake

Simopoulos et al , 2001

Alzheimer's disease: an evolutionary approach

- Fat storage: an evolutionary evolutinary advantage!
- And now? evolutinary mismatch diseases (Obesity AD, type2 diab, etc.)

AD Prevalence > 65 aa:
- in Nigeria 1.15%
- in USA 6.7%

Brain energy expenditure:

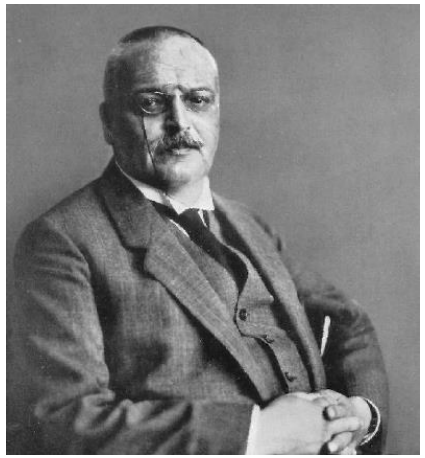
- mammalians 2-8%
- Monkeys 11-13%
- humans 20-25%

E. Bufill et al., Journal of Anthropological Sciences, 2013

Alzheimer's disease

A modern disease?

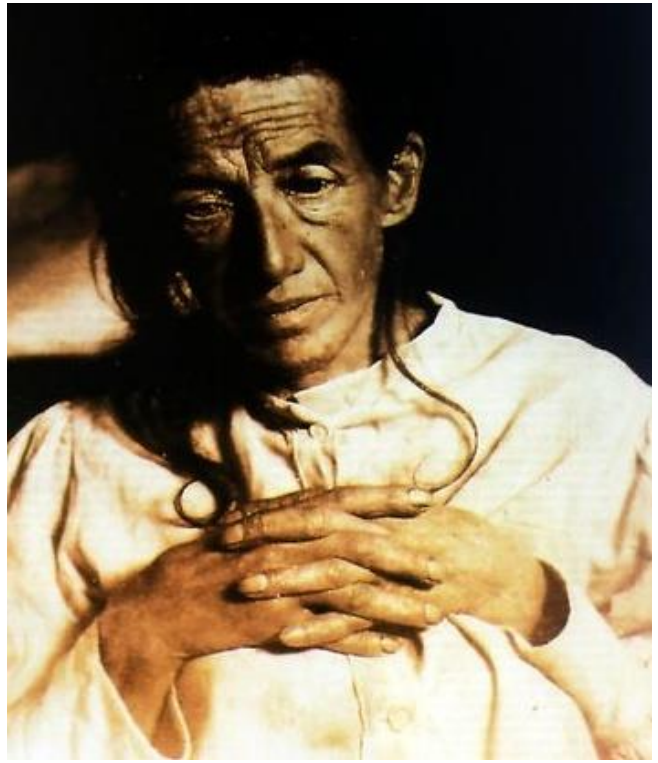
The type 3 diabetes

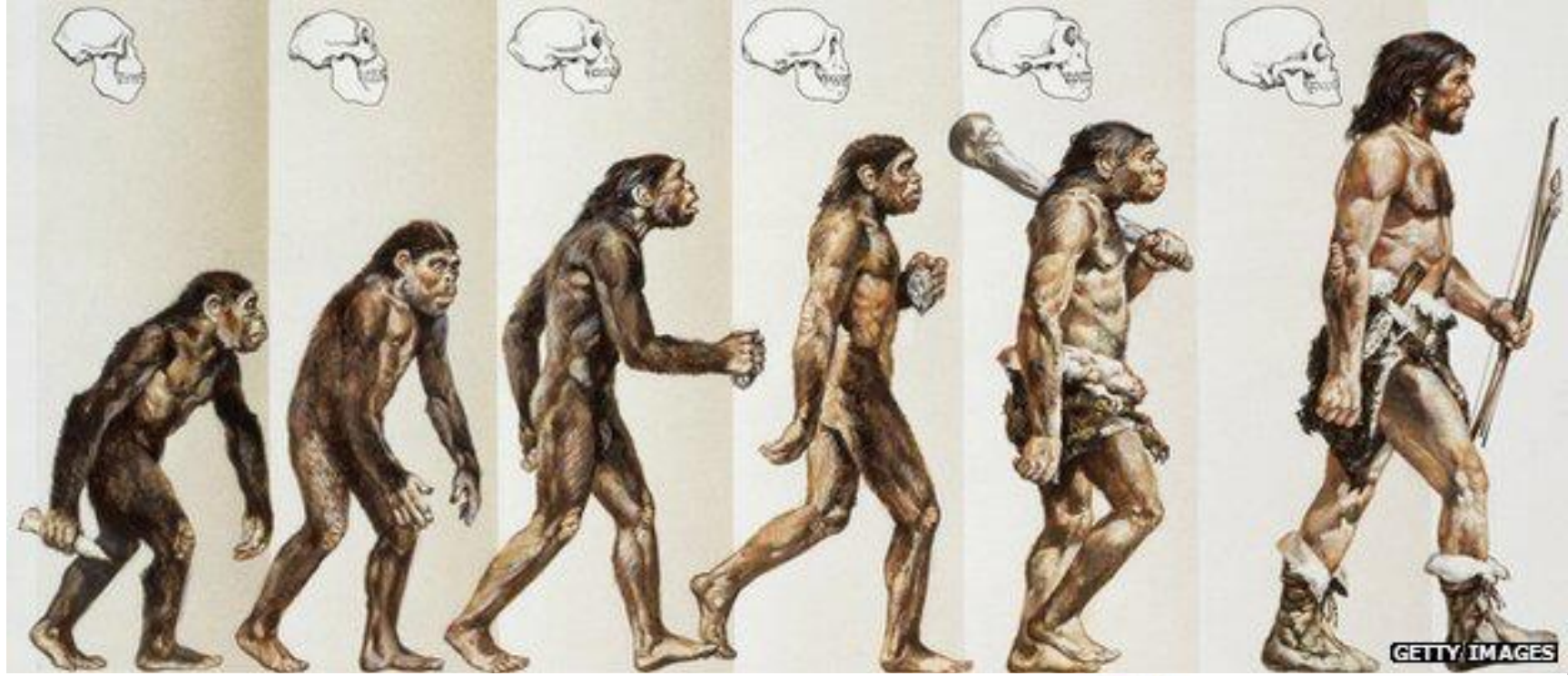


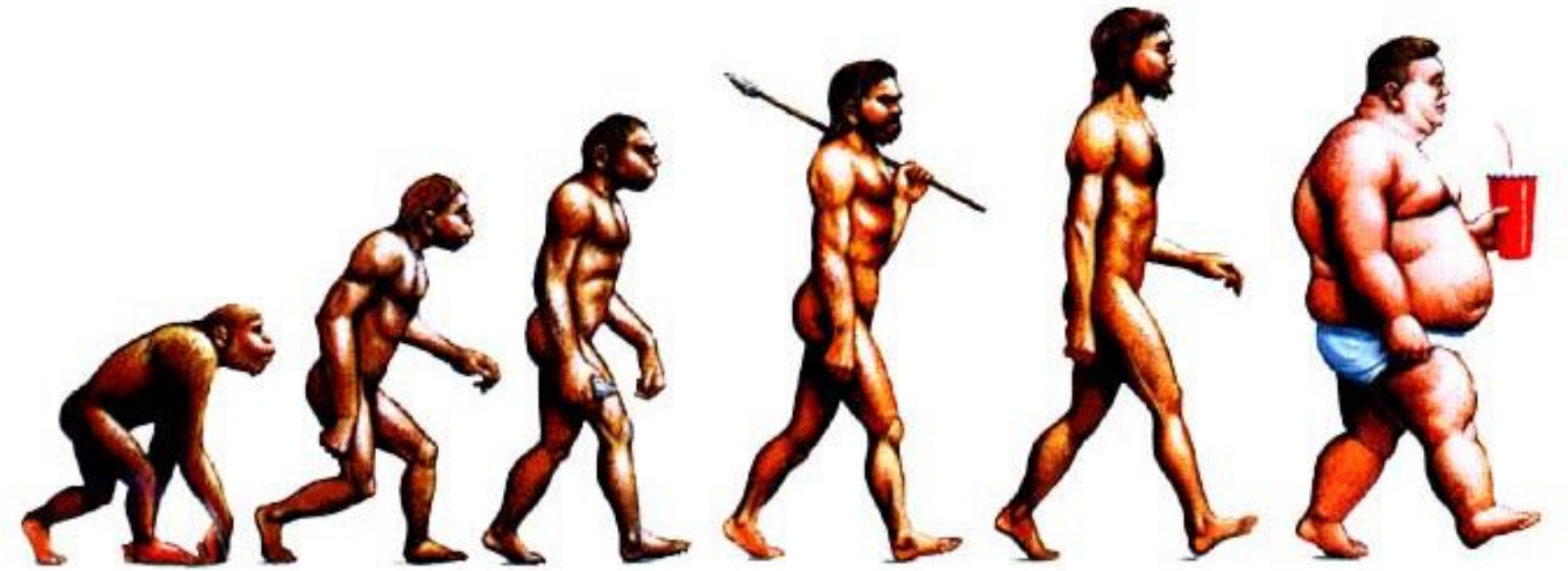
Alois Alzheimer
(*1863-1915*)

Gaetano Perusini
(*1879-1915*)

1906: first case described
(Auguste Deter, 51 yrs)




GETTY IMAGES



What about apes?

β-amyloid deposits, aggregated forms of intracellular hyperphosphorylated tau protein and neurofibrillary tangles in captive chimpanzee

Obese chimpanzee *with high bloood levels of colesterol*

Caleb E. Finch & Steven N. Austa, AGE 2012

Bufill et al. Journal of Anthropological Sciences 2013

Disease-modifying strategies

How to counteract the risk factors?

Behavioral approach:

- diet
- specific food supplements

Nutrients in AD

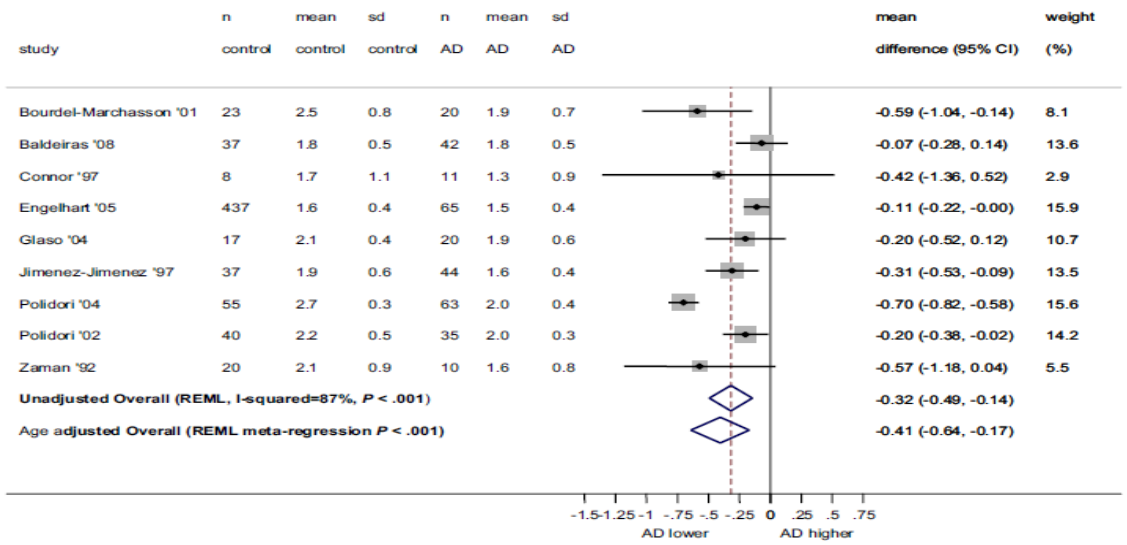
Alzheimer's & Dementia 10 (2014) 485–502

Review Article

Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis

Sofia Lopes da Silva[a,b], Bruno Vellas[c], Saskia Elemans[a], José Luchsinger[d], Patrick Kamphuis[a,b], Kristine Yaffe[e], John Sijben[a,*], Martine Groenendijk[a], Theo Stijnen[f]

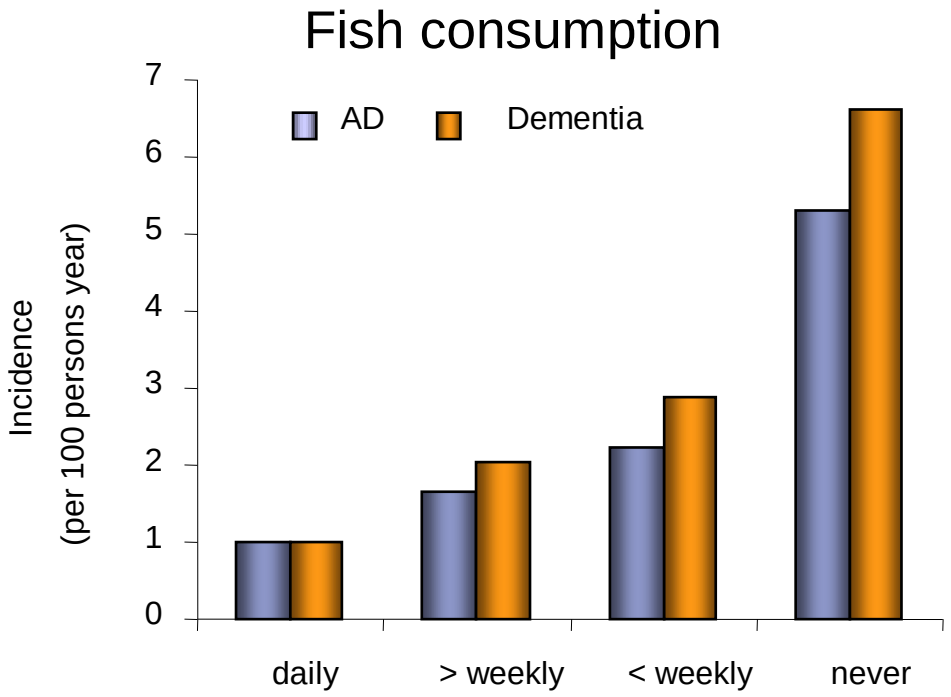
vitamin A

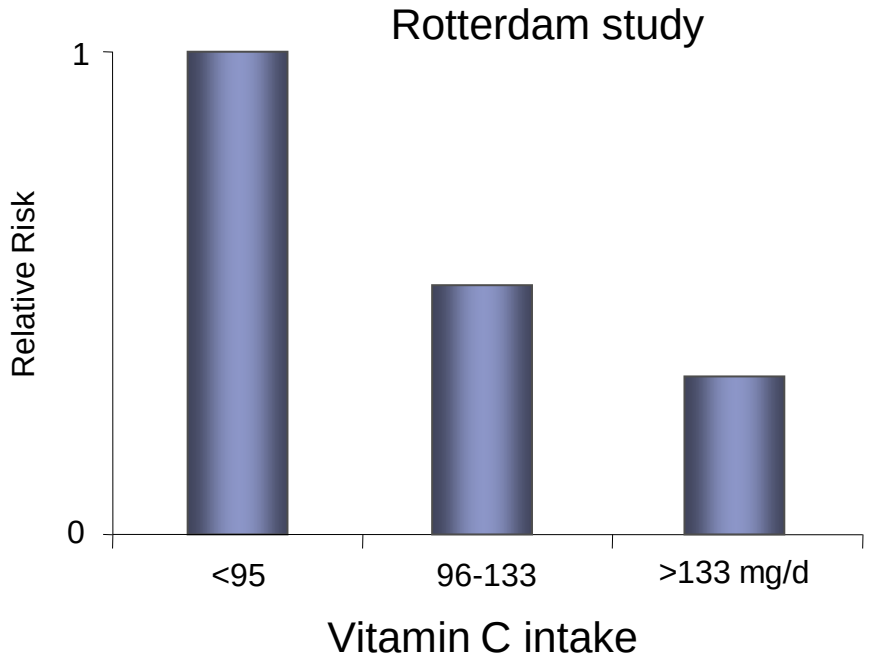


Lower plasma levels of vitamin A in patients as compared with elderly controls (-20%, *P*<0.001)

Low intake of nutrients is associated with cognitive decline

Low intake of some nutrients: associated with a loss of cognitive function and increased risk of AD

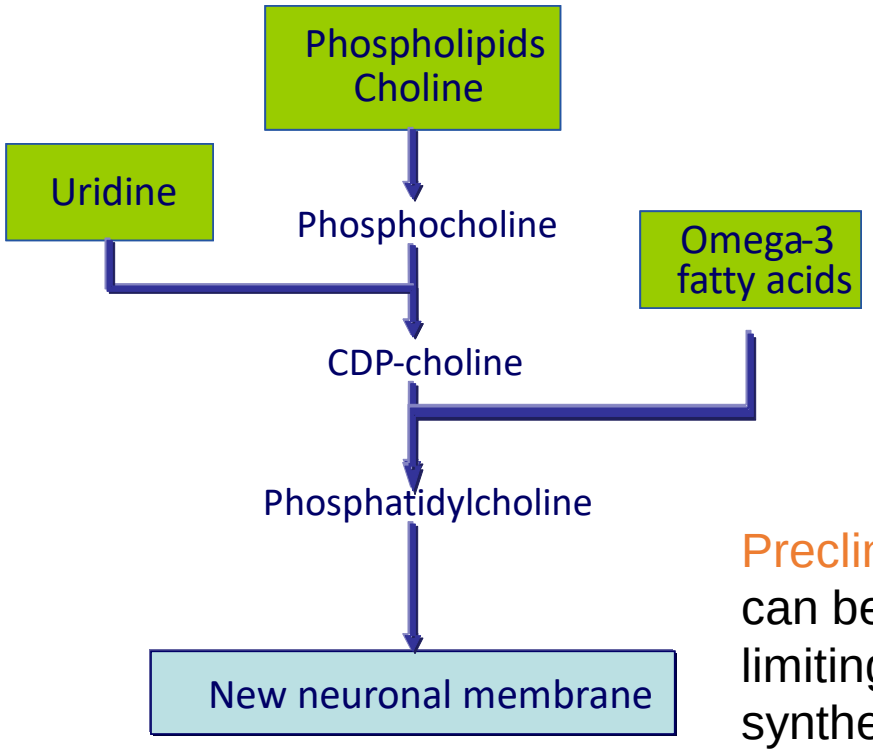




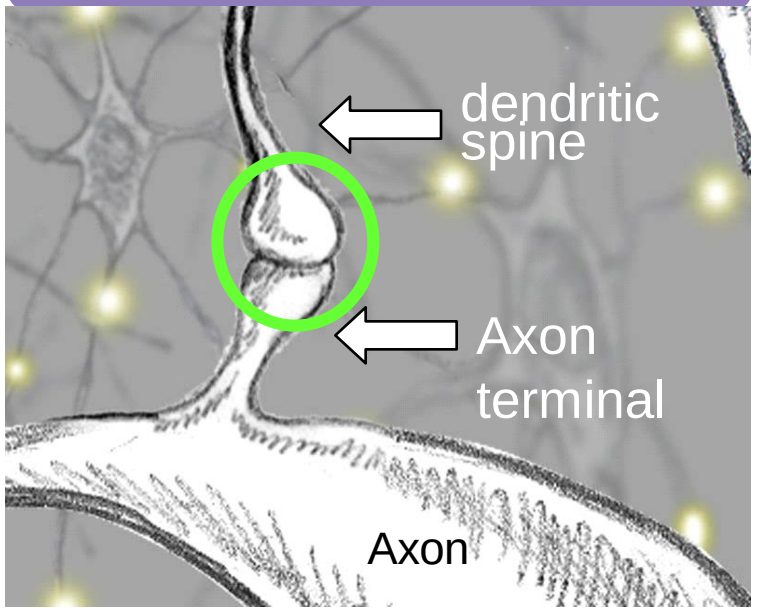
Barberger-Gateau et al. (2002) BMJ; Engelhart et al. (2002) JAMA

Dietary precursor control of neural membrane synthesis

The Kennedy pathway for biosynthesis neuronal membrane



Membranes are main constituents of synapses



Preclinical studies indicate that such an effect can be induced by co-administration of rate-limiting precursors for membrane phosphatide synthesis, such as:

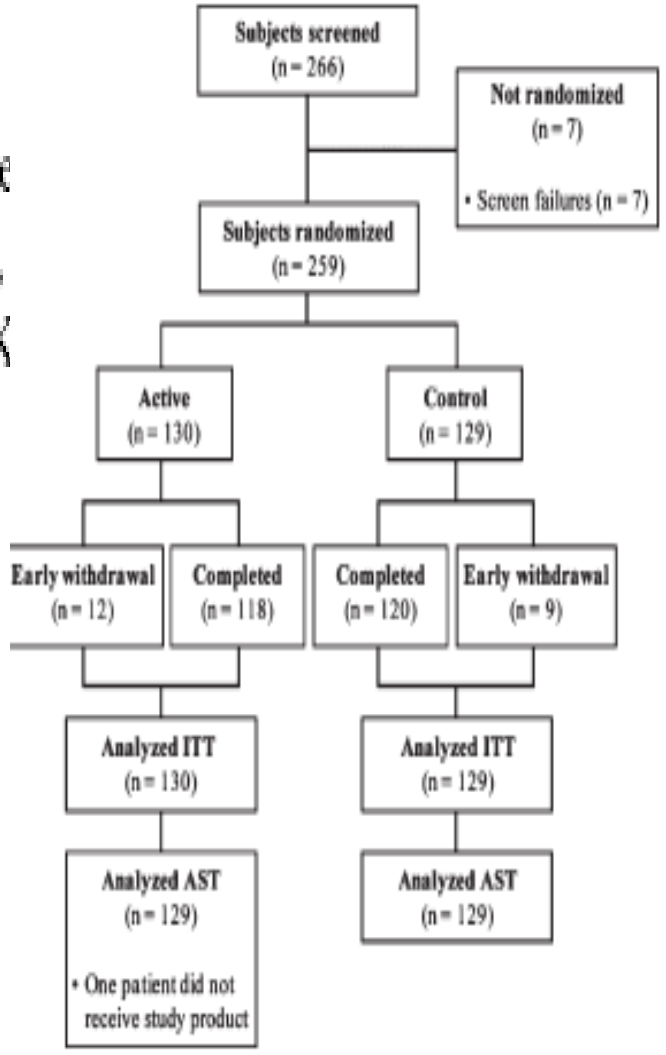
the nucleotide uridine, omega-3 polyunsat. fatty acids, choline

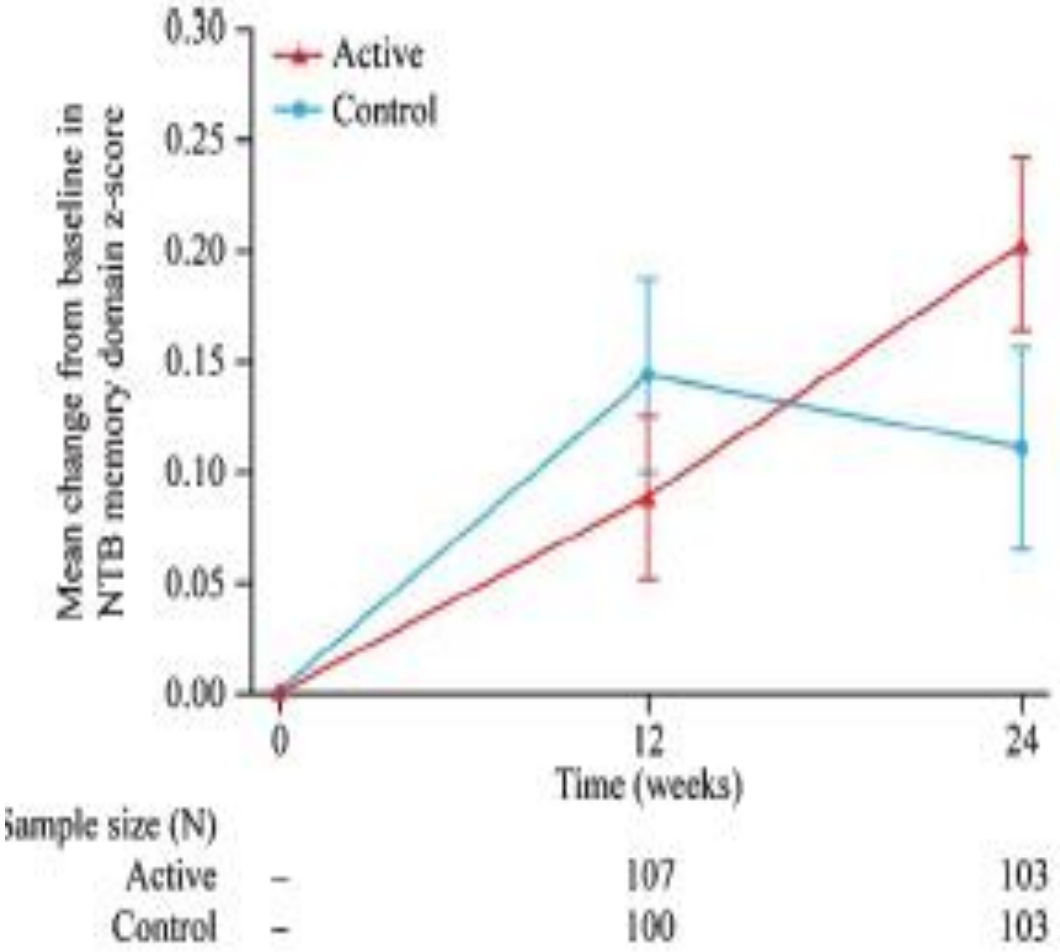
Efficacy of Souvenaid in Mild Alzheimer's Disease: Results from a Randomized, Controlled Trial

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

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

Memory domain





NTB memory domain

interventional period: 24 weeks

Significant difference between active and control groups (p=0.023)

A summary of evidences from literature

In a recent review 16 micronutrients resulted to have appropriate scientific evidence in terms of preventing elderly disorders: beta-alanine, calcium, creatine, fluorides, leucine, magnesium, omega-3, potassium, zinc, folic acid, vitamin B6 and B12, vitamin C, D, E and K2

Iolascon G, et al. J Nutr Health Aging. 2017

Ongoing nutritional studies

Preventive trials in elderly/at risk people

- 8 trials to test the efficacy of n-3 long-chain polyunsaturated fatty acids (PUFAs)-
- 5 trials with vitamin D
- 1 on caloric restriction

(clinicalTrials.gov)

In the future? Insects!

International Journal of Biological Sciences
2011; 7(3):301-307

Short Research Communication

Transgenic Rice Expressing Amyloid β-peptide for Oral Immunization

Taiji Yoshida[1,✉], Eiichi Kimura[1], Setsuo Koike[1], Jun Nojima[2], Eugene Futai[2], Noboru Sasagawa[2], Yuichiro Watanabe[2], and Shoichi Ishiura[2]

The future: engeneered sushi to treat AD?

Ketogenesis and Dementia

Blood levels	*Normal diet*	*Ketogenic diet*	*Diabetic ketoacidosis*
Glucose (mg/dl)	80-120	65-80	>300
Insulin (μU/l)	6-23	6.6-9.4	≅ 0
Glucagon	Low	High	High
KB produc. (gr/day)	Low	115-180	400
KB conc. (mmol/dl)	0.1	4-10	>20
pH	7.4	7.4	<7.3

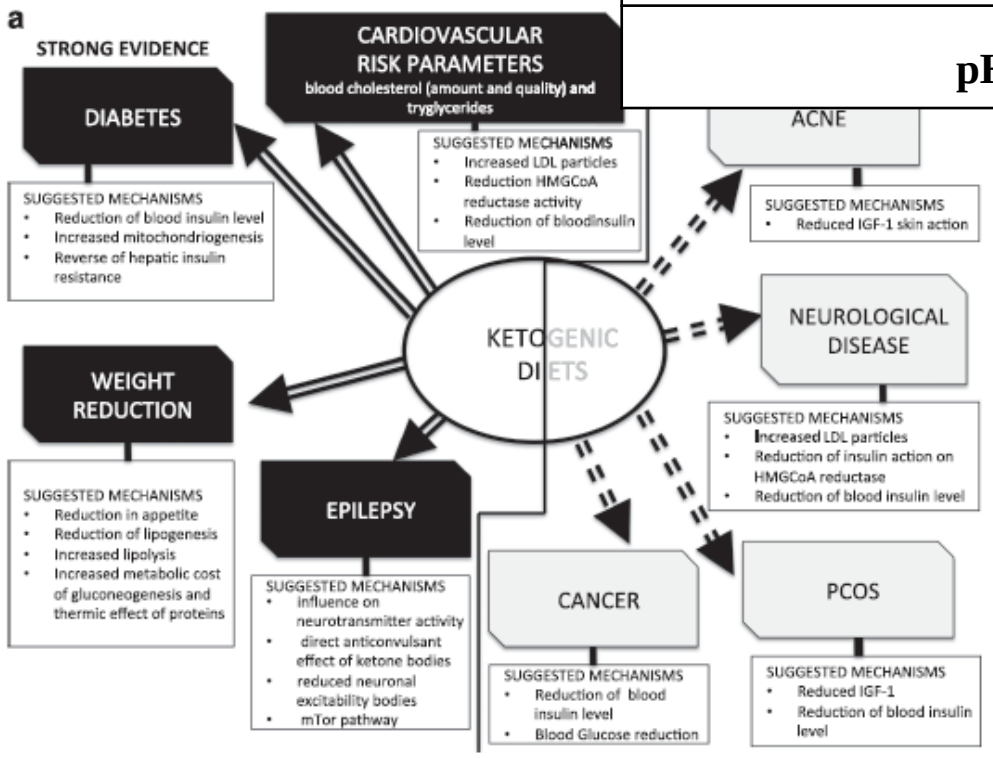
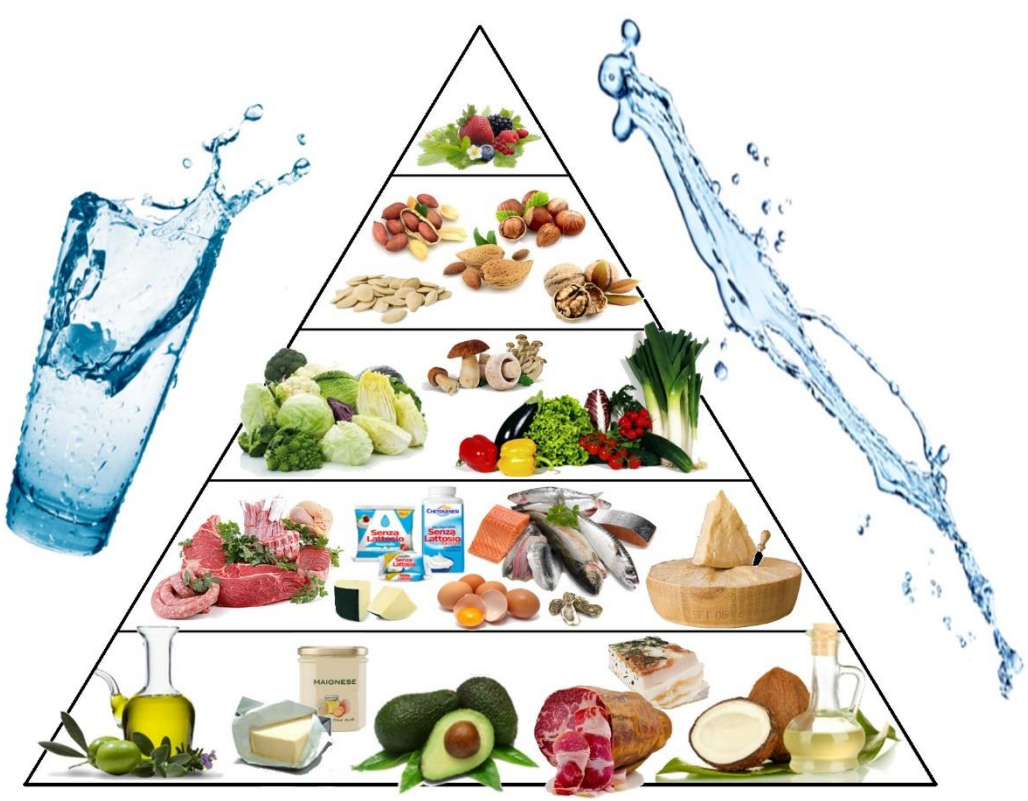


Figure 1. Suggested mechanisms for the therapeutic action of ketogenic diets in pathologies for which there exists strong (**a**) and emerging (**b**) evidence.

The Ketogenic Food Pyramid

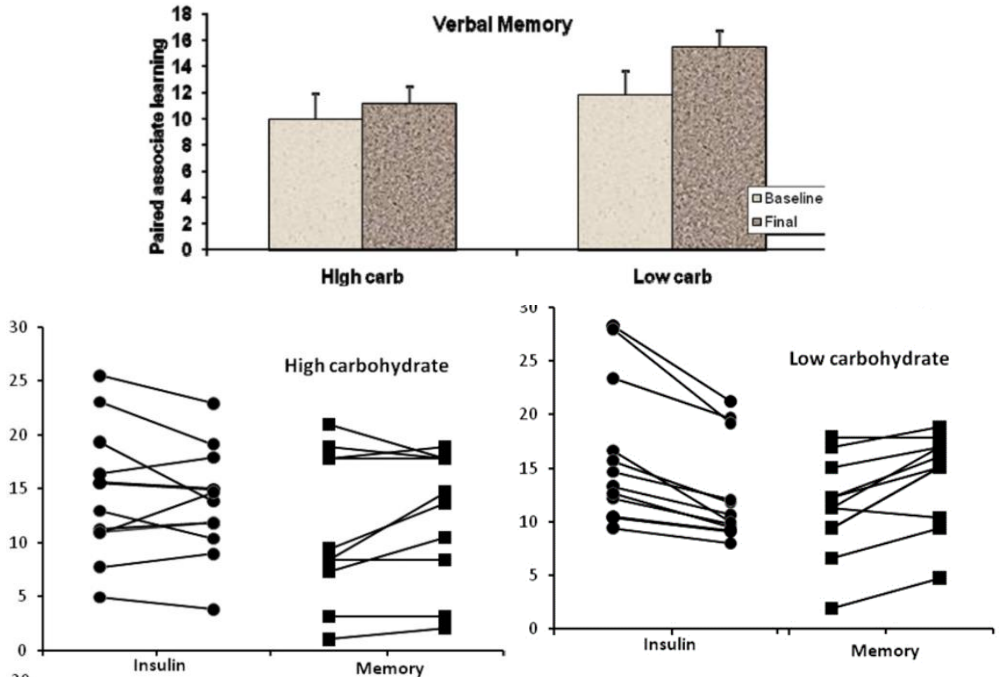


Omnivore vs Vegan

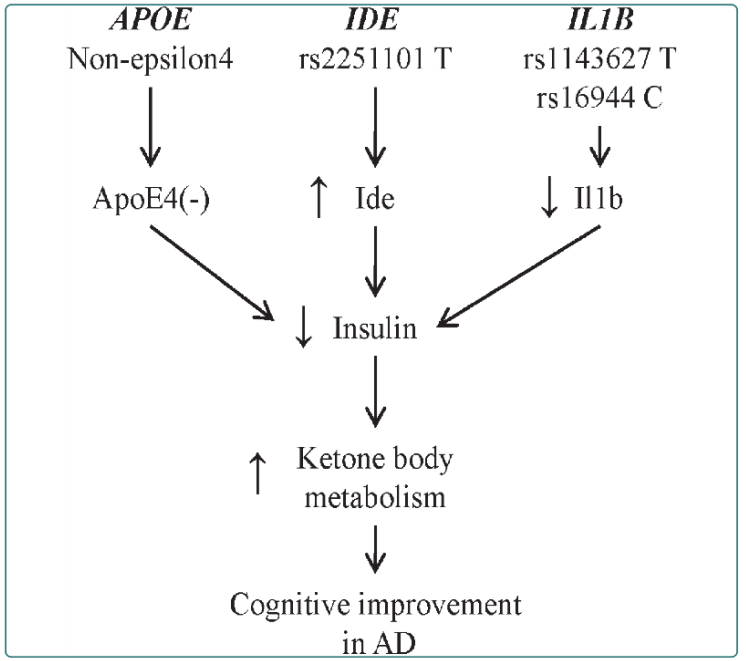
Ketogenesis and Cognition

Dietary ketosis enhances memory in mild cognitive impairment

Robert Krikorian[a,*], Marcelle D. Shidler[a], Krista Dangelo[b], Sarah C. Couch[b], Stephen C. Benoit[a], Deborah J. Clegg[c]



R. Krikorian et al. / Neurobiology of Aging 33 (2012) 425.e19–425.e27



Pharmacogenetic analysis of the effects of polymorphisms in *APOE*, *IDE* and *IL1B* on a ketone body based therapeutic on cognition in mild to moderate Alzheimer's disease; a randomized, double-blind, placebo-controlled study

Henderson and Poirier

BioMed Central

Henderson and Poirier *BMC Medical Genetics* 2011, **12**:137
http://www.biomedcentral.com/1471-2350/12/137 (12 October 2011)

ELSEVIER

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NEUROBIOLOGY OF AGING

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Brief communication

Effects of β-hydroxybutyrate on cognition in memory-impaired adults

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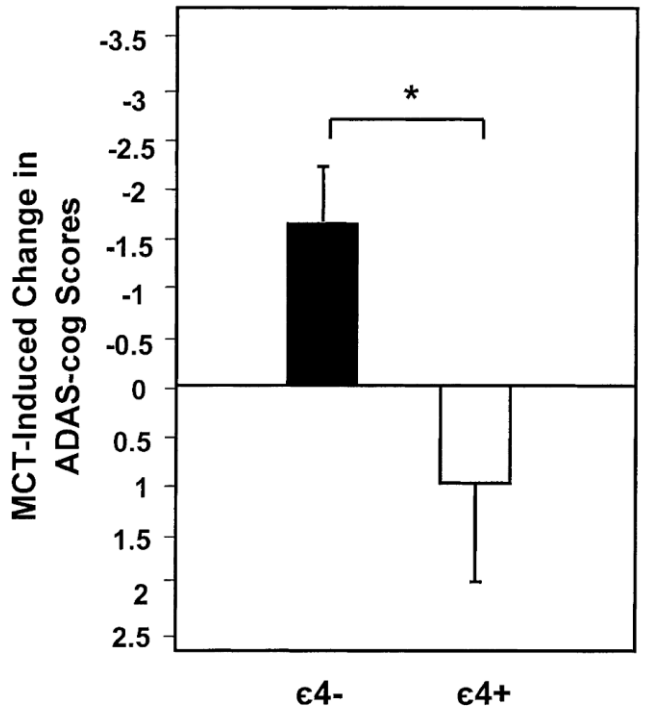

Fig. 1. ADAS-cog mean change with MCT treatment; benefits of treatment depended on $\varepsilon 4$ status ($^*P = 0.039$). Note: negative scores indicate improvement on the ADAS-cog.

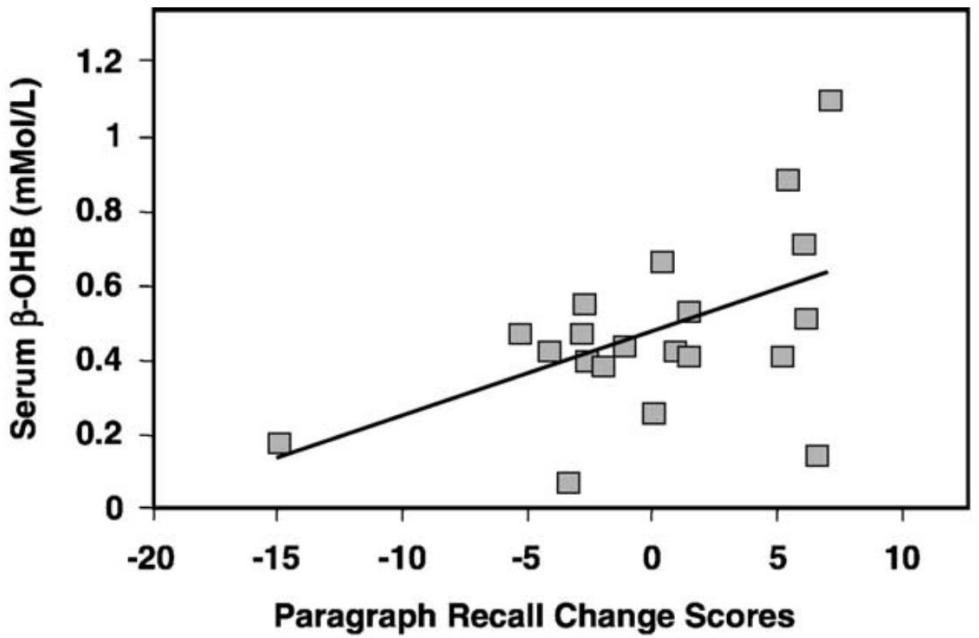

Fig. 2. Relationship between β-OHB levels at the time of cognitive testing and the change in paragraph recall following MCT treatment; $r = 0.50$, $P = 0.02$.

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Commentary

Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial

Candida J. Rebello[a,b], Jeffrey N. Keller[a], Ann G. Liu[a], William D. Johnson[a], Frank L. Greenway[a,*]

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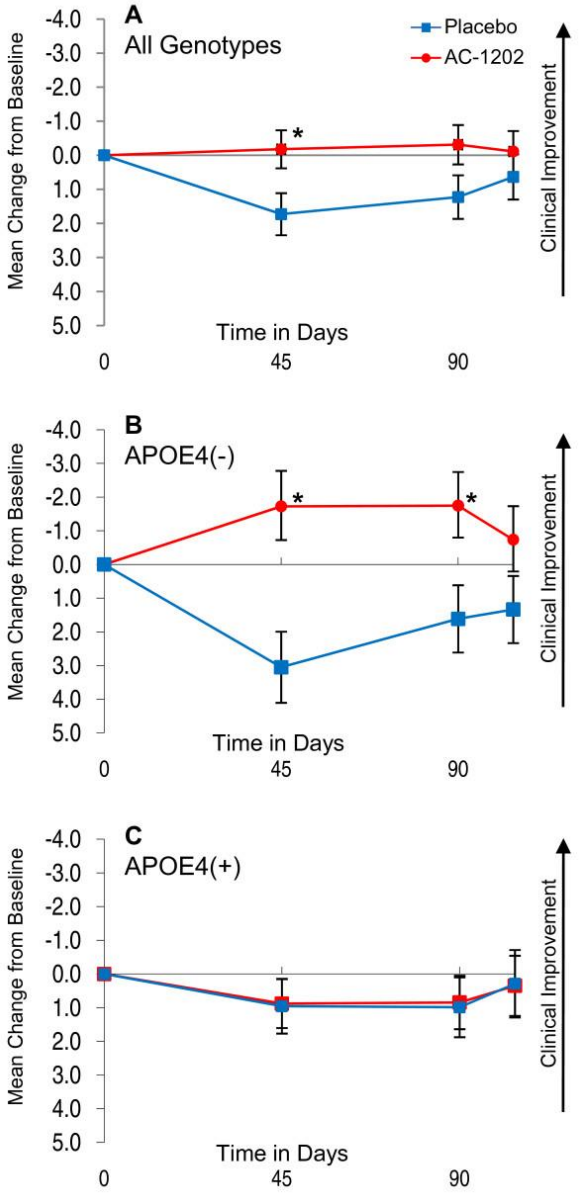
Results: Intake of MCT oil increased serum ketone bodies and improved memory, while intake of placebo did not show improvement in any of the cognitive measures tested.

Conclusions: Consumption of 56 g/day of MCTs for 24 weeks increases serum ketone concentrations and appears to be a candidate for larger randomized control trials in the future that quantify the modulation of cognitive function through supplementation with ketone precursors, in patients with MCI.

Study of the ketogenic agent AC-1202 (that increases BHB levels in blood) in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial

[Henderson et al., 2009]



Mean change in ADAS-Cog scores from Baseline in the ITT population w/LOCF and stratified by APOE4 carriage status. Y axis is change from Baseline. X axis is time in days. Red circles and lines represent subjects taking AC-1202. Blue squares and lines represent subjects taking Placebo. Error bars represent standard error of the mean. Asterisks (*) indicate a significant (p-value < 0.05) difference in mean change from Baseline between AC-1202 and Placebo. **A)** Intention to treat subjects (N = 77AC, N = 63PL) administered AC-1202 demonstrate a significant difference from Placebo at Day 45. **B)** Genotyped subjects lacking the APOE4 allele (APOE4(-)) (N = 29AC, N = 26PL) and administered AC-1202 demonstrate a significant difference from Placebo at Days 45 and 90. **C)** Genotyped subjects carrying the APOE4 allele (APOE4(+)) (N = 38AC, N = 31PL) do not differ from Placebo at any time point.

Filippo M Santorelli

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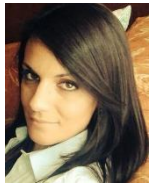

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Thank you for your kind attention

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Christa M. Studzinski , William A. MacKay , Tina L. Beckett , Samuel T. Henderson , M. Paul Murphy , Patrick G. Su...

Induction of ketosis may improve mitochondrial function and decrease steady-state amyloid-β precursor protein (APP) levels in the aged dog

Brain Research, Volume 1226, 2008, 209 - 217

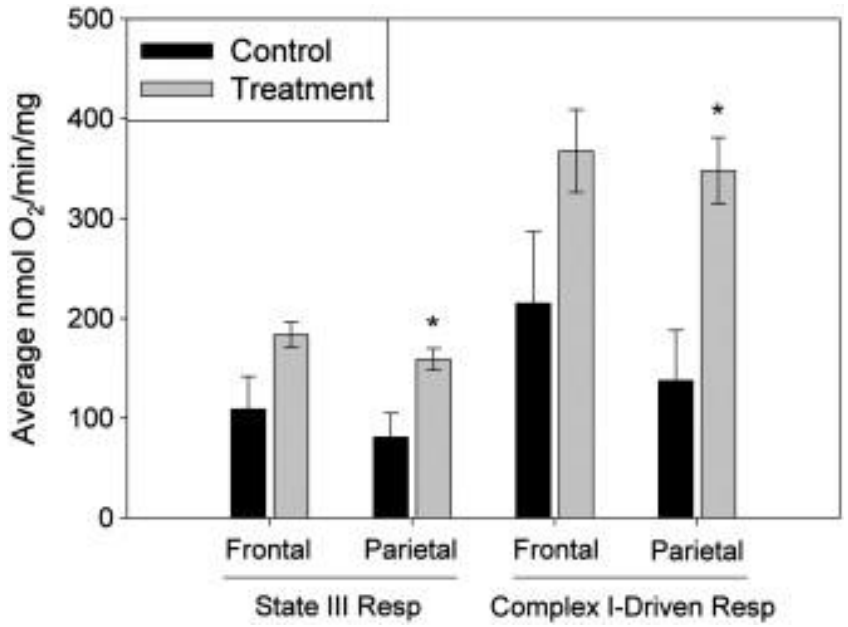
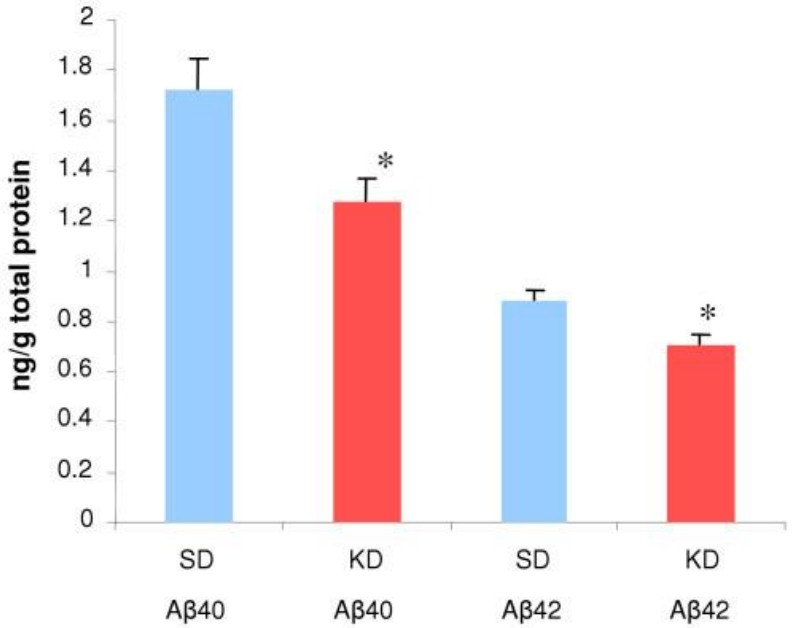


Fig. 2 Mitochondrial respiration. The treatment animals had larger rates of state III respiration in the parietal lobes, as compared to controls (*t* -test, *P* = 0.025). The treatment animals also had an increa...

In a mouse model of Alzheimer's disease, Ketogenic diet reduces amyloid beta 40 and 42 peptides

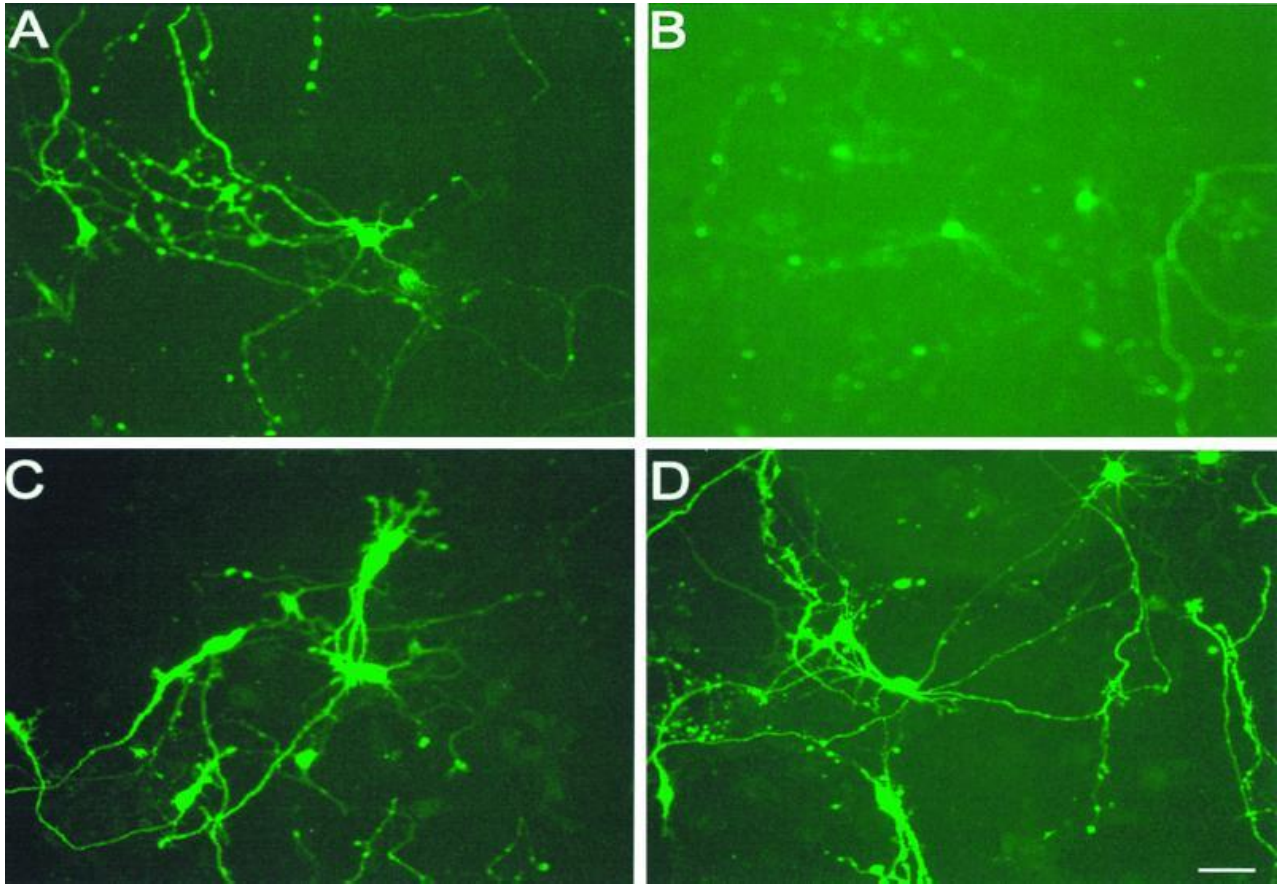
[Van der Auwera et al., 2005]



Ketogenic diet reduces Aβ40 and Aβ42. Aβ levels as ng/g of brain tissue. Standard diet (SD) group shown in blue, ketogenic diet (KD) group shown in red, error bars represent standard error of the mean. SD chow Aβ40 1.72 ± 0.12 ng/g vs. KD chow Aβ40 1.28 ± 0.09 ng/g, p= 0.012. SD chow Aβ42 0.88 ± 0.05 ng/g vs. KD chow Aβ42 0.71 ± 0.0.4 ng/g, p = 0.016.

β-Hydroxybutyrate protects neurons in models of Alzheimer's disease

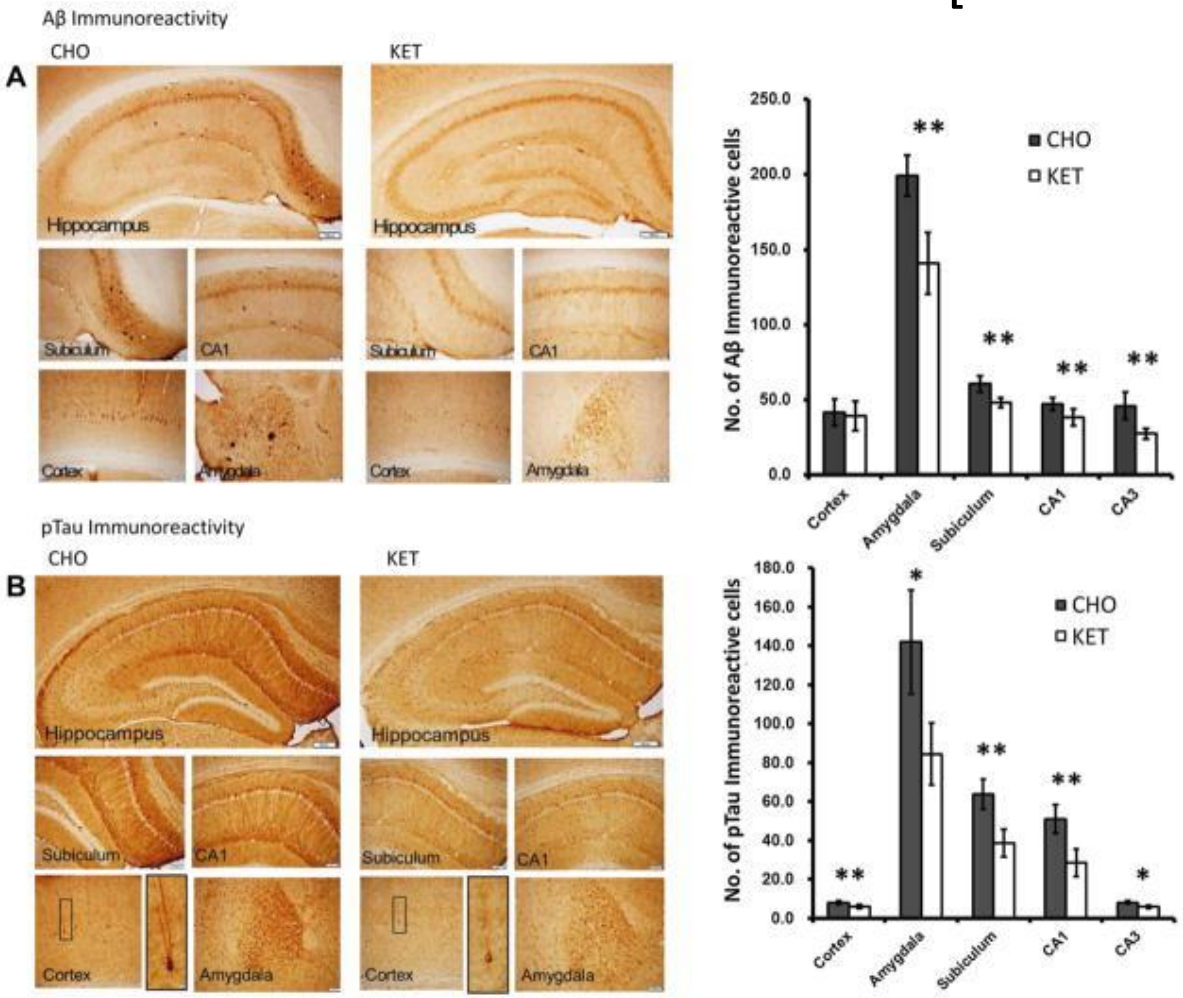
[Kashiwaya et al., 2000]



The effects on cultured rat hippocampal cells of $A\beta_{1-42}$, ketones, or the combination. (*A*) The 6-day control cultures of 18-day embryonic rat hippocampal tissue; (*B*) after 14 h exposure to 5 μM $A\beta_{1-42}$, (*C*) after exposure to both $A\beta_{1-42}$ and 4 mM d-β-hydroxybutyrate, and (*D*) the effects of ketone bodies alone. Addition of $A\beta_{1-42}$ resulted in a decrease in neuronal number and number of neurites (*B* versus *A*). Addition of ketones to cells exposed to $A\beta_{1-42}$ showed no decrease in neuron or neurite number, indicating that ketones act as neuroprotective agents against the toxicity of $A\beta_{1-42}$ on cultured hippocampal neurons (*C* versus *B*).

A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease

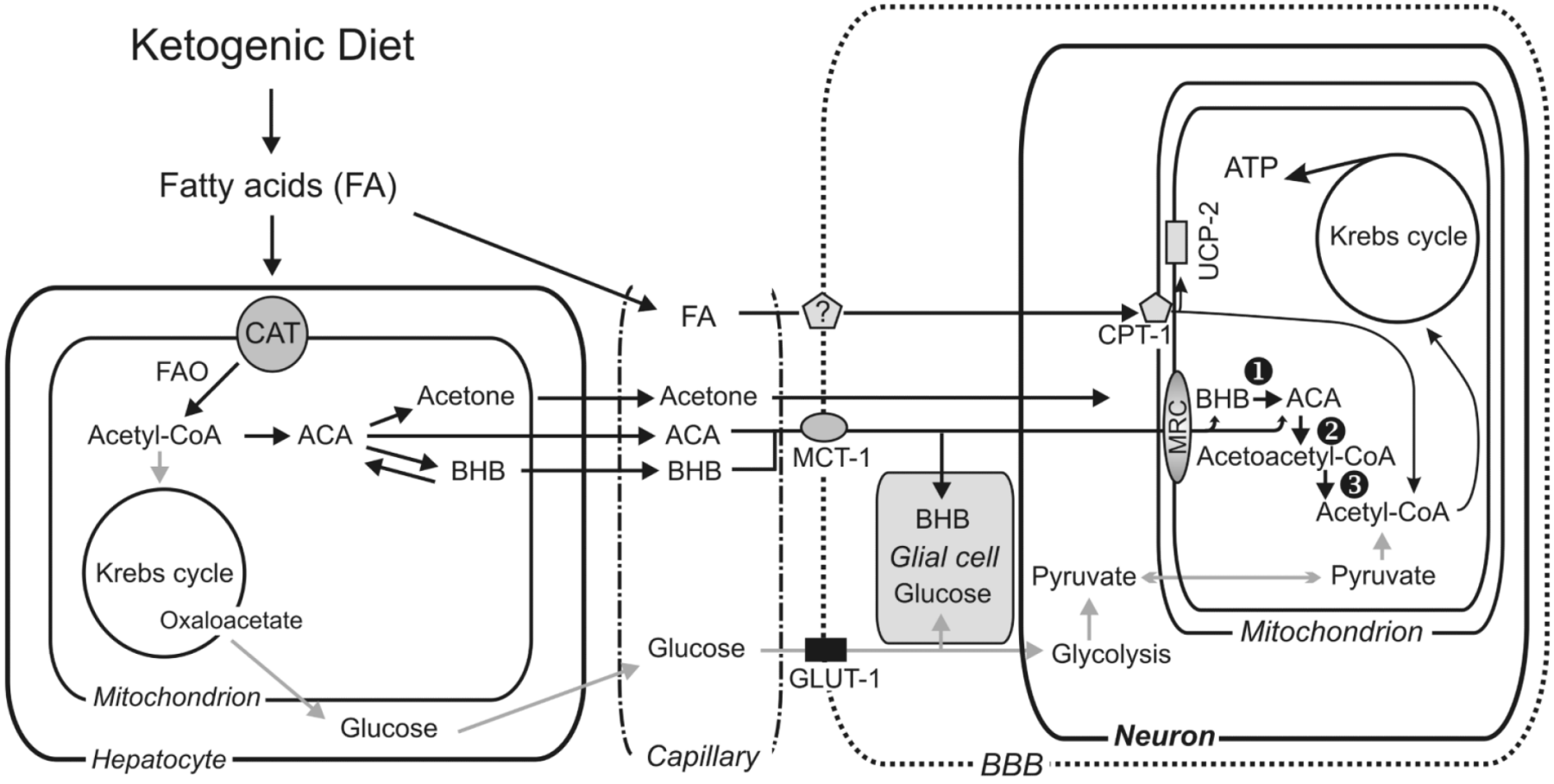
[Kashiwaya et al., 2013]



Ketone ester feeding reduces intracellular accumulations of amyloid β (Aβ) and phosphorylated tau (pTau) in the subiculum, CA1 and CA3 area of hippocampus, amygdala, and cerebral cortex of 3xTgAD mice. (A) Aβ immunoreactivity in brain sections from mice in the carbohydrate-enriched (CHO; left) and ketone ester (KET; right) diet groups. The upper panels are low magnification images of the regions of the hippocampus and the lower panels are high magnification images of the regions of the subiculum, CA1, cerebral cortex, and amygdala. The graph on the right shows the results of counts of Aβ immunoreactive cells in the indicated brain regions. (B) pTau immunoreactivity in brain sections from mice in the CHO (left) and KET (right) diet groups. The upper panels are low magnification images of the regions of the hippocampus and the lower panels are high magnification images of the regions of the subiculum, CA1, cerebral cortex, and amygdala respectively. The graph on the right shows the results of counts of pTau immunoreactive cells in the indicated brain regions. Scale bars: lower magnification images, 200 µm; high magnification images, 100 µm. Values are the mean ± SEM (n = 6–9 mice per group). *$p < 0.05$ and **$p < 0.001$ by the Student t test.

Ketone bodies and Mitochondria

Jasper's Basic Mechanisms of the Epilepsies



Edited by Jeffrey L. Noebels, Massimo Avoli, Michael A. Rogawski, Richard W. Olsen, Antonio V. Delgado-Escueta
JASPER'S BASIC MECHANISMS OF THE EPILEPSIES
Fourth Edition
NCBI Bookshelf Online Book Version

Mechanisms of Ketogenic Diet Action

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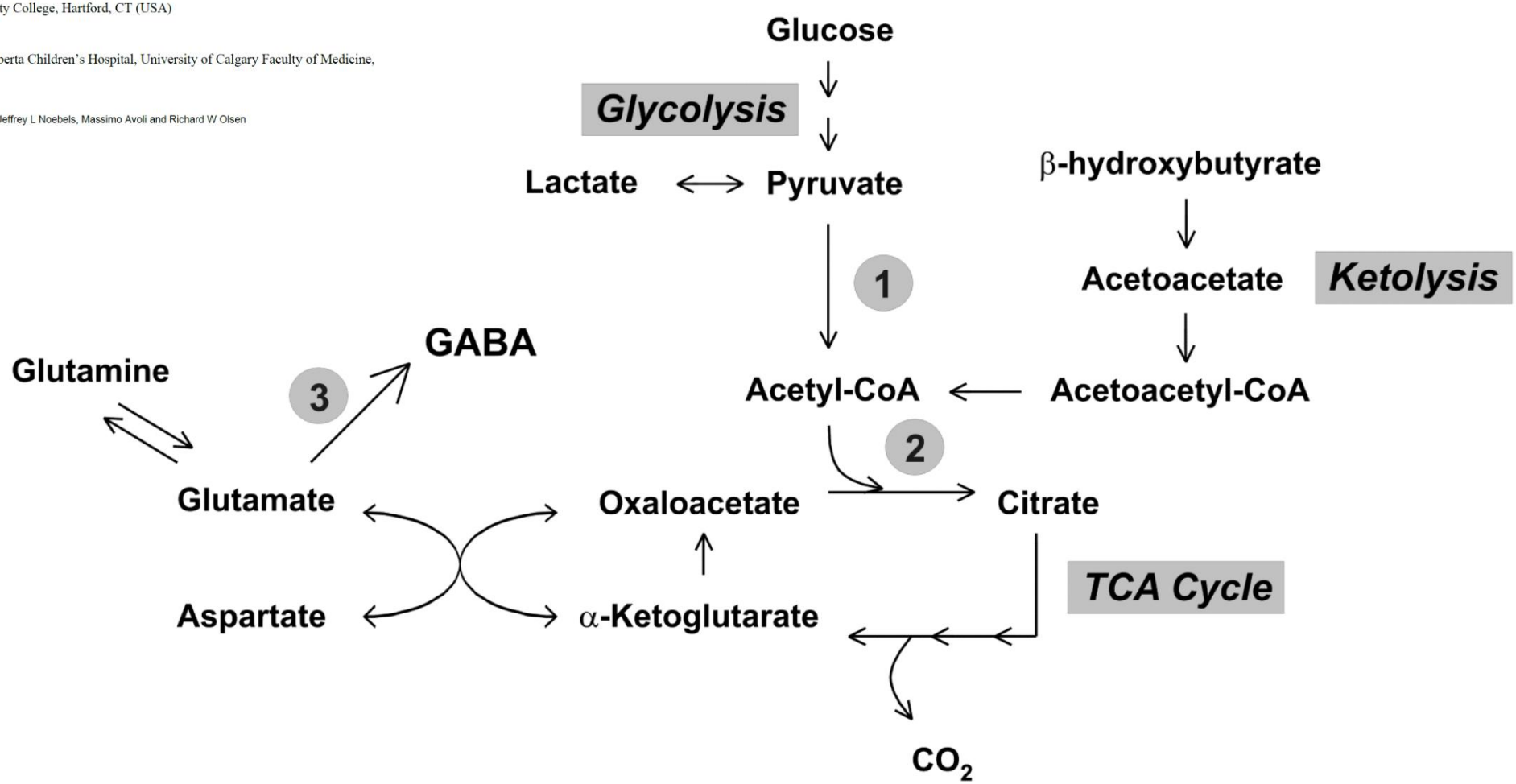
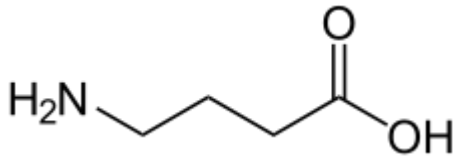


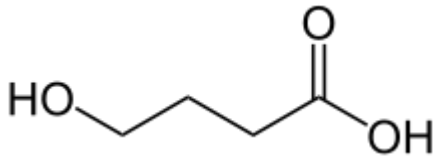
Figure 2. The metabolic inter-relationships between brain metabolism of glutamate, ketone bodies and glucose

GABAergic effect of ketone bodies

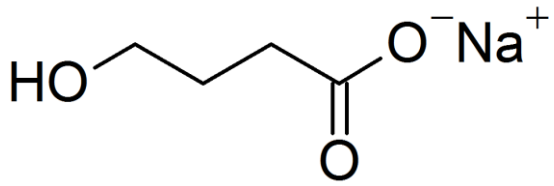
- Gamma-aminobutyric acid (GABA)



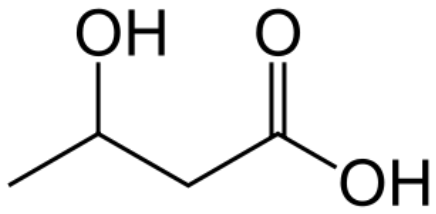
- Gamma-hydroxybutyric acid (GHB)



- Sodium Oxybate



- Beta-hydroxybutyric acid (BHB)



Epilepsia, **48**(1):43–58, 2007
Blackwell Publishing, Inc.

Anticonvulsant Mechanisms of the Ketogenic Diet

*Kristopher J. Bough and †Jong M. Rho

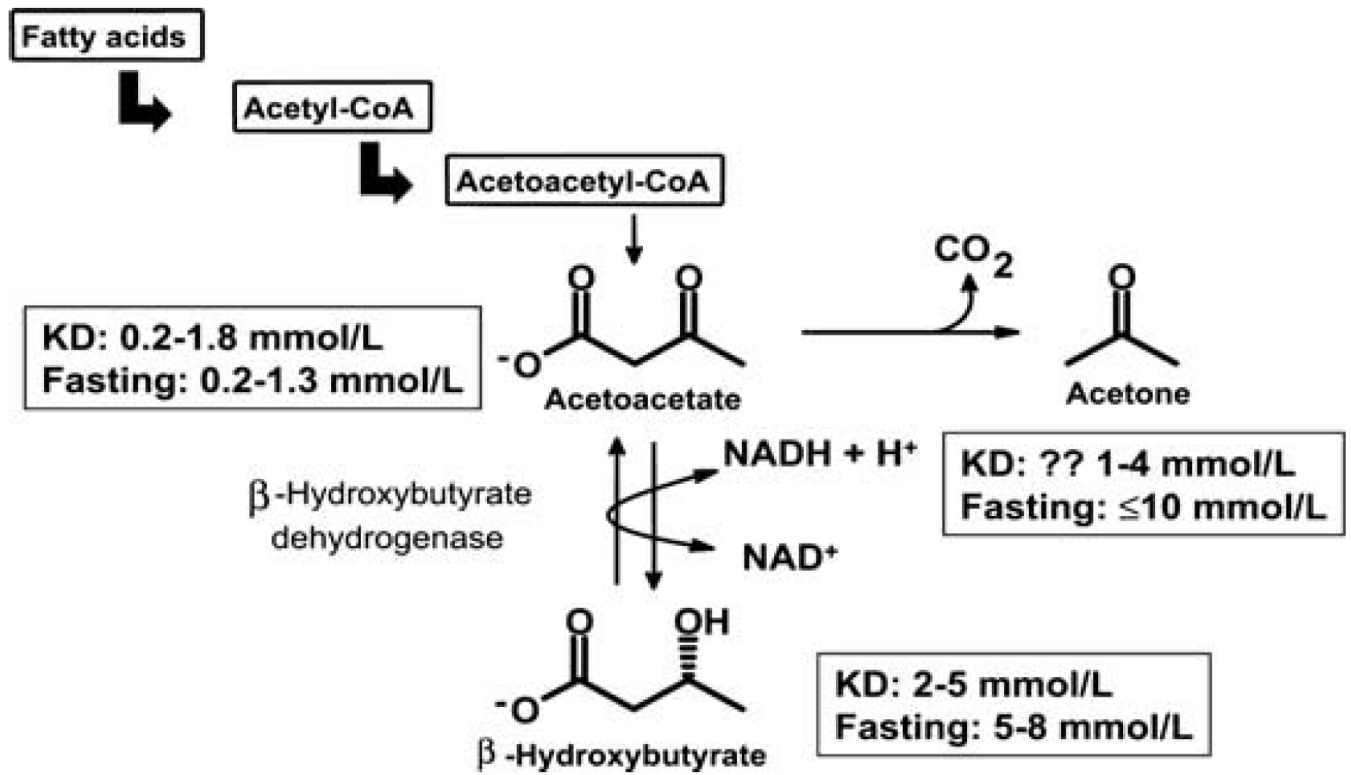
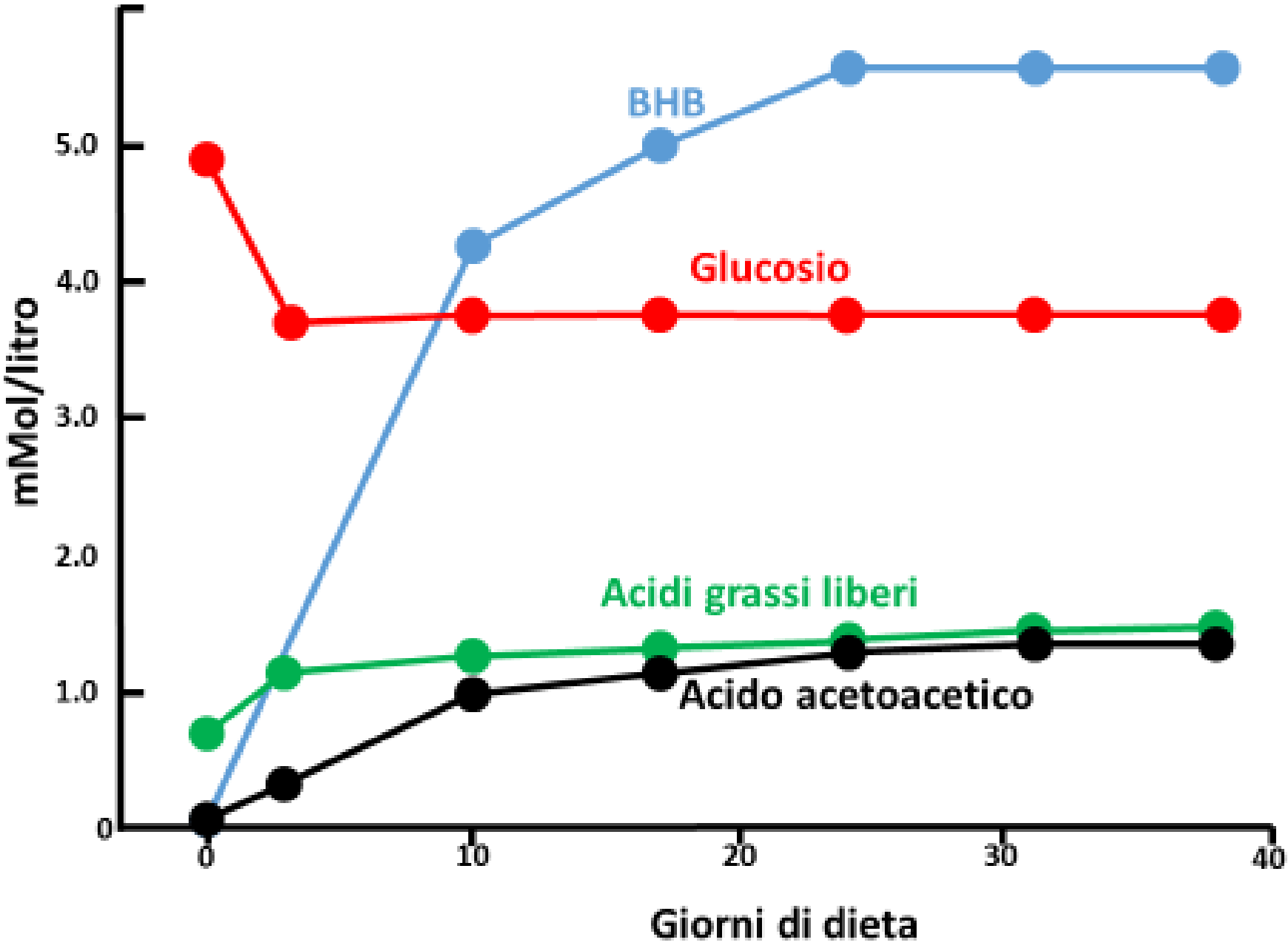
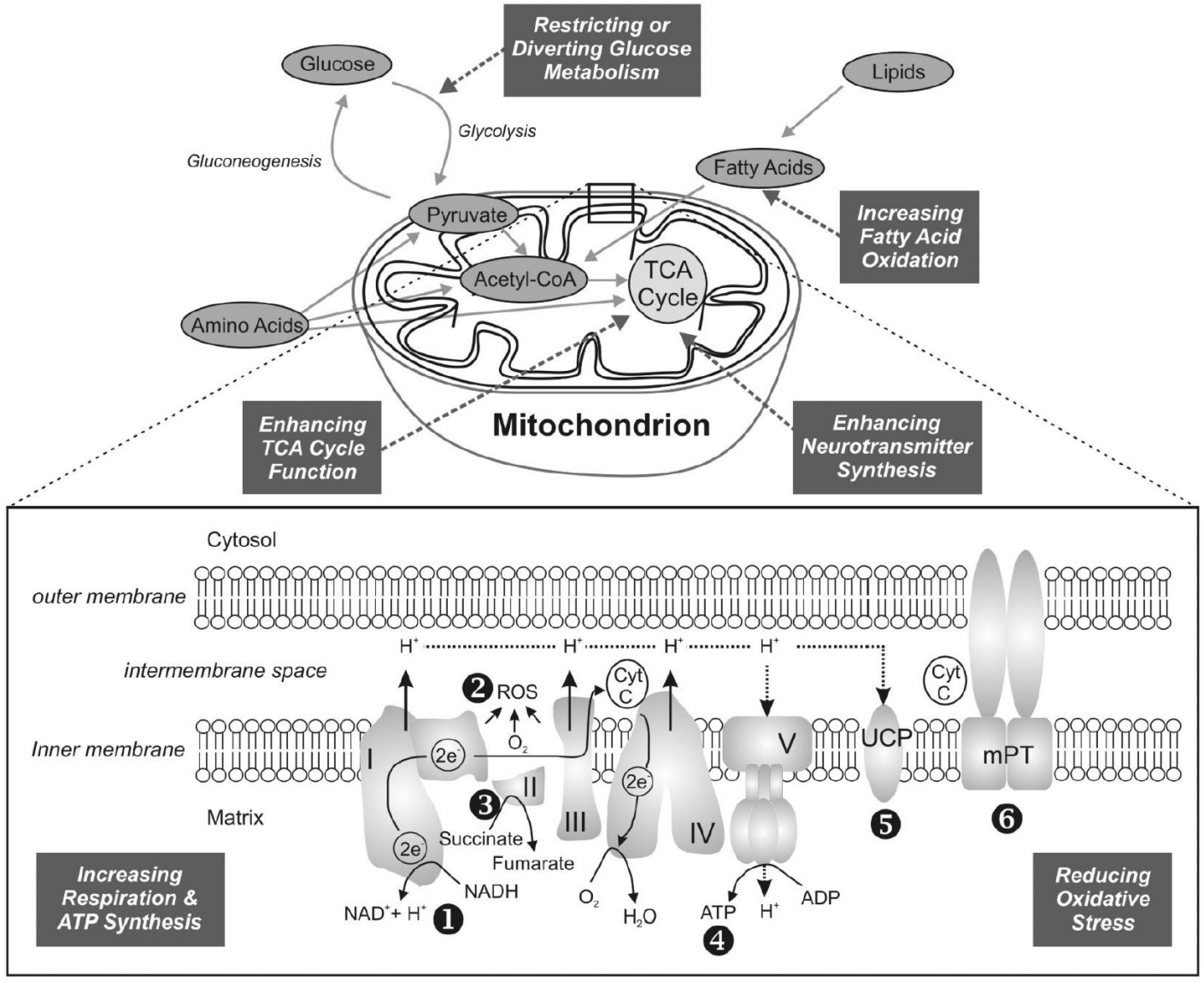


FIG. 1. Metabolic pathways highlighting the production of ketone bodies fatty acids during fasting or treatment with the ketogenic diet (KD). Estimated fasting- or KD-induced concentrations of beta-hydroxybutyrate, acetoacetate, and acetone in blood are listed (large boxes). Measures of beta-hydroxybutyrate levels in blood are most commonly used as the clinical indicator of successful KD treatment. From Likhodii and Burnham (2004).


BHB
Glucosio
Acidi grassi liberi
Acido acetoacetico
mMol/litro
5.0
4.0
3.0
2.0
1.0
0
0
10
20
30
40
Giorni di dieta

KD and Mitochondria

Jasper's Basic Mechanisms of the Epilepsies



Electron Transport & Oxidative Phosphorylation

Science. 2013 January 11; 339(6116): 211–214. doi:10.1126/science.1227166.

Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

Tadahiro Shimazu[1,2], **Matthew D. Hirschey**[1,2], **John Newman**[1,2], **Wenjuan He**[1,2], **Kotaro Shirakawa**[1,2], **Natacha Le Moan**[3], **Carrie A. Grueter**[4,5], **Hyungwook Lim**[1,2], **Laura R. Saunders**[1,2], **Robert D. Stevens**[6], **Christopher B. Newgard**[6], **Robert V. Farese Jr.**[2,4,5], **Rafael de Cabo**[7], **Scott Ulrich**[8], **Katerina Akassoglou**[3], and **Eric Verdin**[1,2,*]

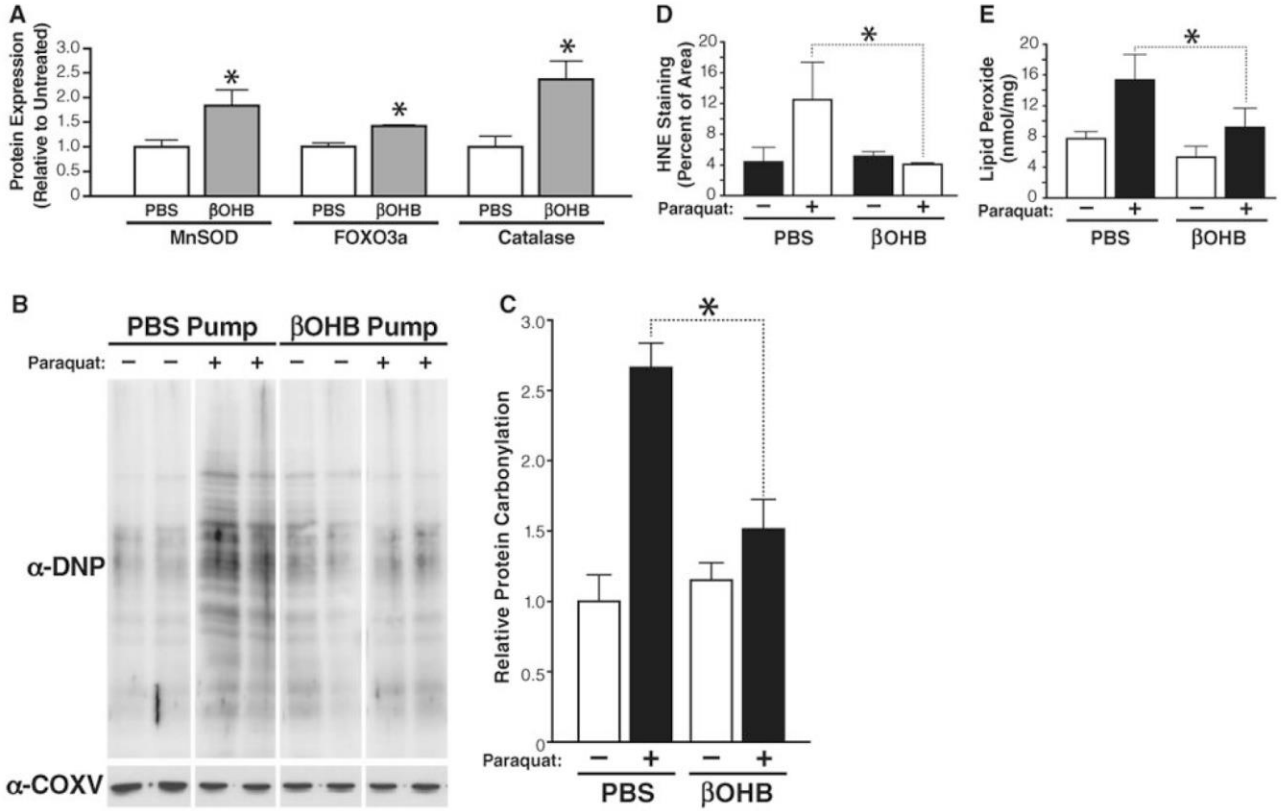


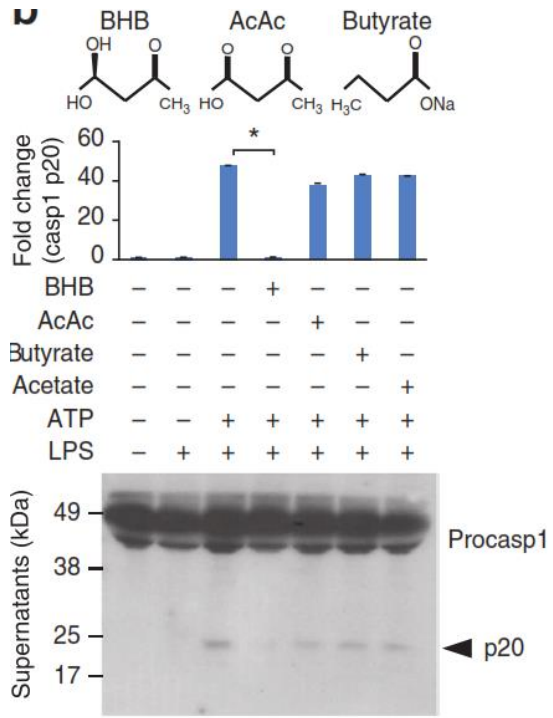
Fig. 4.

Protective effect of βOHB treatment against oxidative stress. (**A**) Amounts of catalase, MnSOD, or FOXO3A measured by protein immunoblotting in kidney tissue from 16-week-old mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$); mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**B**) Protein carbonylation in kidney samples from mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$) and treated with paraquat (50 mg/kg) or vehicle for 2 hours. Car-bonylation was measured by immunoblotting with anti-DNP. All samples were run on a single gel; after imaging, lanes were rearranged for presentation. (**C**) Quantification of protein carbonylation in (B). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**D**) Sections of kidney obtained from the same mice as in (B) were stained with anti-4-HNE and quantified (see fig. S16 for primary picture). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**E**). Lipid peroxides were quantified in mice kidneys (LPO assay kit, Cayman, Ann Arbor, MI). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions.

nature medicine

The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease

Yun-Hee Youm[1,11], Kim Y Nguyen[1,11], Ryan W Grant[2], Emily L Goldberg[1], Monica Bodogai[3], Dongin Kim[4], Dominic D'Agostino[5], Noah Planavsky[6], Christopher Lupfer[7], Thirumala D Kanneganti[7], Seokwon Kang[8], Tamas L Horvath[1], Tarek M Fahmy[4], Peter A Crawford[9], Arya Biragyn[3], Emad Alnemri[8] & Vishwa Deep Dixit[1,10]



Pediatr Neurol. 2007 May ; 36(5): 281–292.

The Neuropharmacology of the Ketogenic Diet

Adam L. Hartman, MD[*,†], **Maciej Gasior, MD, PhD**[†], **Eileen P. G. Vining, MD**[*], and **Michael A. Rogawski, MD, PhD**[†,‡]

Effects on Energy Metabolism

During consumption of the ketogenic diet, ketone bodies replace glucose as a source of energy for the brain. These ketone bodies may be a more efficient source of energy per unit oxygen than glucose [76]. In addition, the ketogenic diet causes a coordinated upregulation of mitochondrial genes and genes involved in energy metabolism, and appear to stimulate the biogenesis of mitochondria as assessed by electron microscopy [39]. Together, the availability of a more efficient fuel and an increase in the number of mitochondria provide an increase in cellular energy production capacity and reserves. It seems plausible that the greater energy reserve would enhance the capacity of neurons to withstand metabolic challenges and could account for the ability of the diet to confer neuroprotection in models of neurodegenerative diseases or stroke [5]. It also has been proposed that effects of the ketogenic diet on brain energetics contribute to the seizure protection conferred by the diet [37,42], although there is little experimental support for this concept.

Acqua (2 lit. die)

Supplemento proteico (10-15 gr X2-4)

Fino a 200 gr X2 (ben condita)

100-200 gr die

- 1.2-1.4 gr/Kg di proteine die
- <50 gr di carboidrati die
- 10-20 gr di grassi die
- integrazione minerale (K^+, Mg^+, Na^+, Se^+) e vitaminica