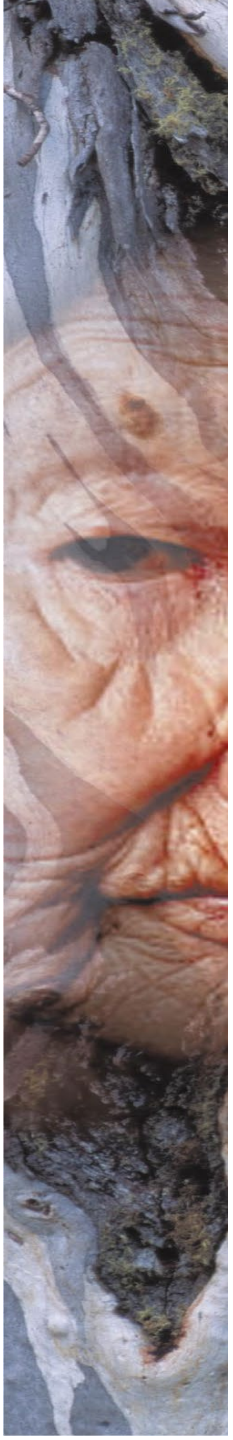


Blanchette Rockefeller Neurosciences Institute
West Virginia University

SINut
Società Italiana di Nutraceutica

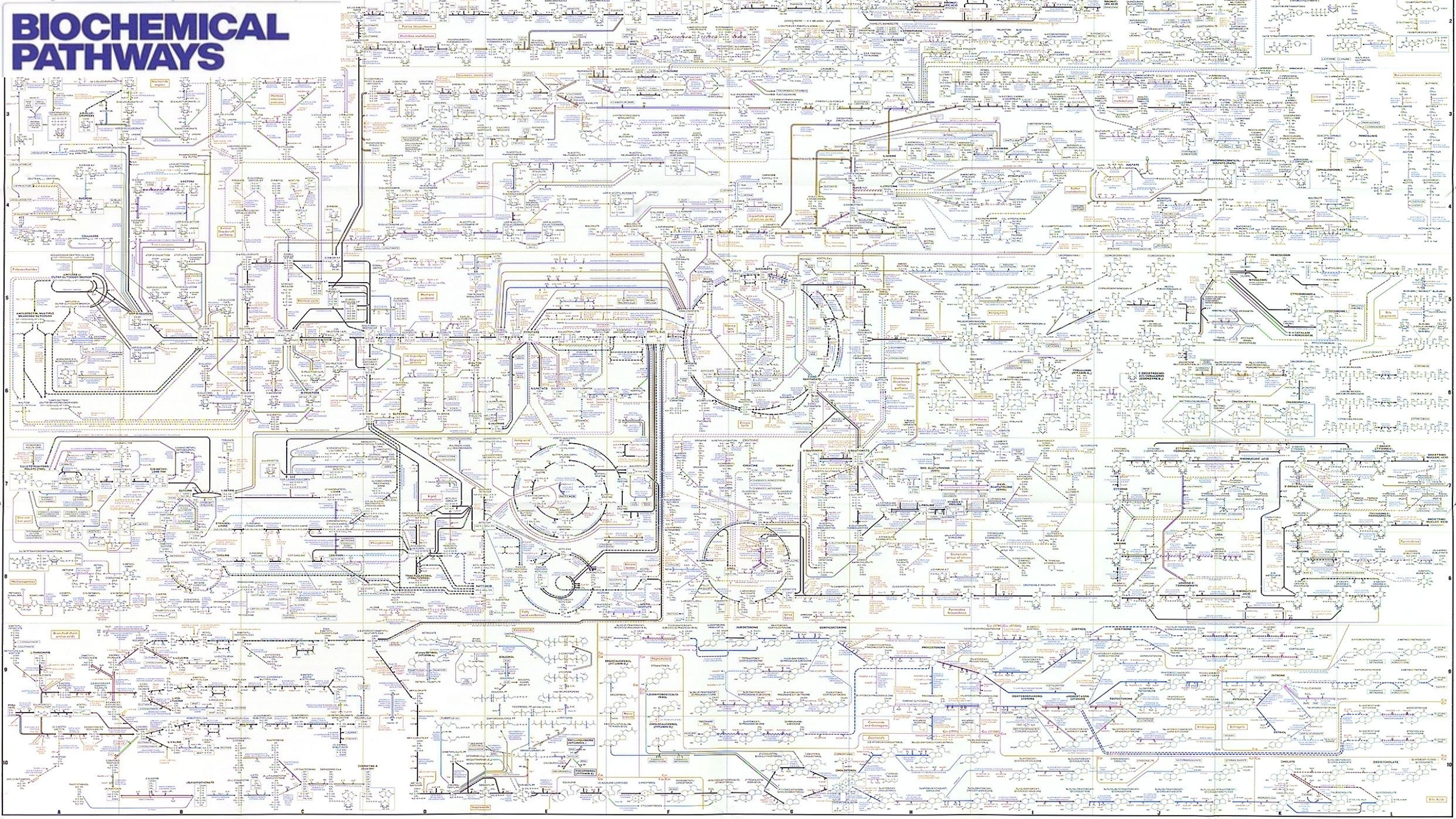
Consiglio Nazionale delle Ricerche
Istituto di Scienze Neurologiche

Università degli Studi del Molise
Via De Sanctis - 86100 Campobasso - Tel. +39 0874 4041

1° lecture

Giovanni Scapagnini, MD, PhD

BIOCHEMICAL PATHWAYS



Fauja Singh, here aged 100, prepares for Britain's Edinburgh marathon in 2011.

Treat ageing

By 2050, the number of people over the age of 80 will triple globally. These demographics could come at great cost to individuals and economies. Two groups describe how research in animals and humans should be refocused to find ways to delay the onset of frailty.

CLINICAL STUDIES

Prepare for human testing

Luigi Fontana, Brian K. Kennedy *and* Valter D. Longo

The problems of old age come as a package. More than 70% of people over 65 have two or more chronic conditions such as arthritis, diabetes, cancer, heart disease and stroke[1]. Studies of diet, genes and drugs indicate that delaying one age-related disease probably staves off others. At least a dozen molecular pathways seem to set the pace of physiological ageing.

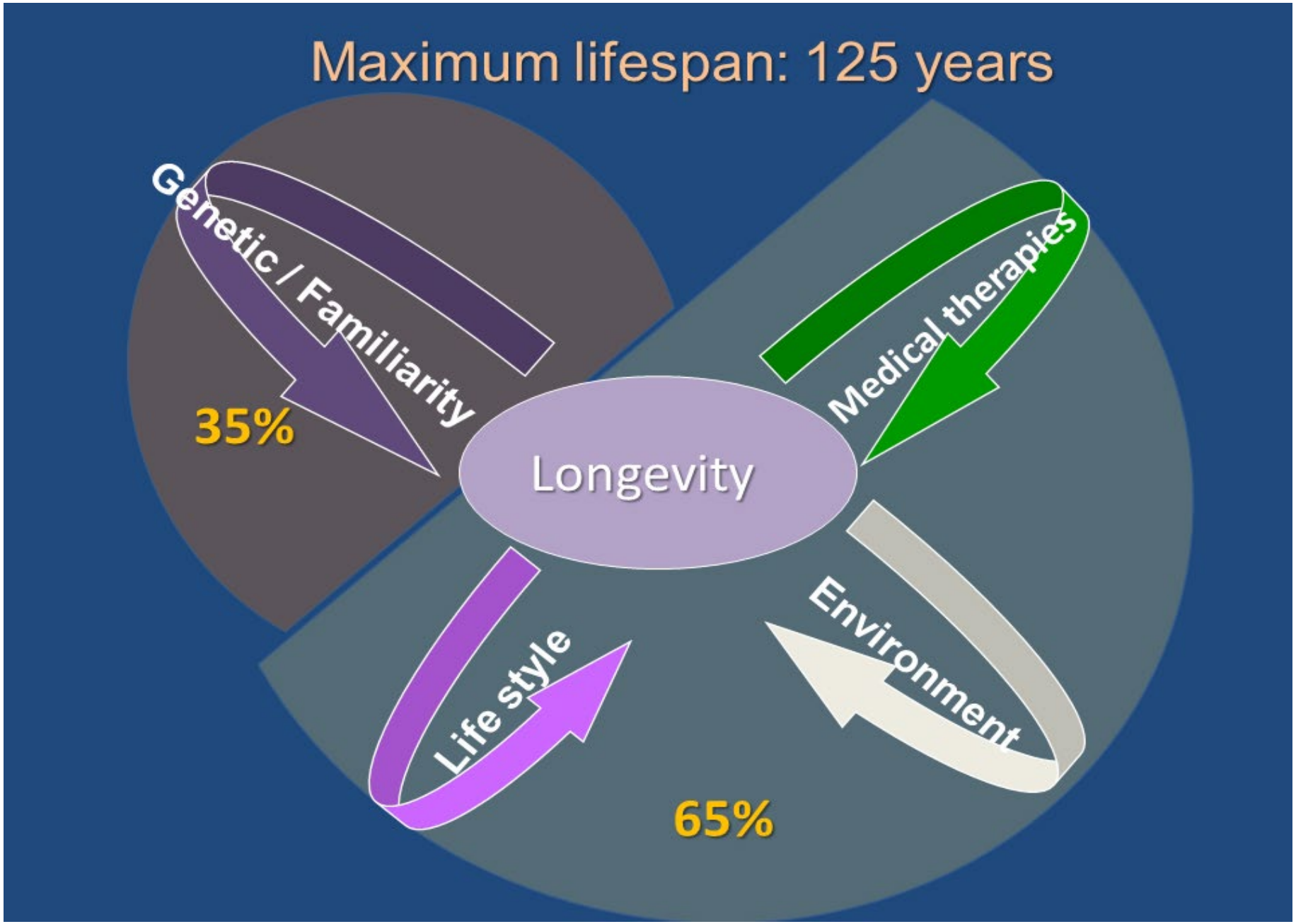
Researchers have tweaked these pathways to give rodents long and healthy lives. Restricting calorie intake in mice or introducing mutations in nutrient-sensing pathways can extend lifespans[2] by as much as 50%. And these 'Methuselah mice' are more likely than controls to die without any apparent diseases[3]. Post-mortems reveal that tumours, heart problems, neurodegeneration and metabolic disease are generally reduced or delayed in long-lived mice. In other words, extending lifespan also seems to increase 'healthspan', the time lived without chronic age-related conditions.

These insights have made hardly a dent in human medicine. Biomedicine takes on conditions one at a time — Alzheimer's disease, say, or heart failure. Rather, it should learn to stall incremental cellular damage and changes that eventually yield several infirmities.

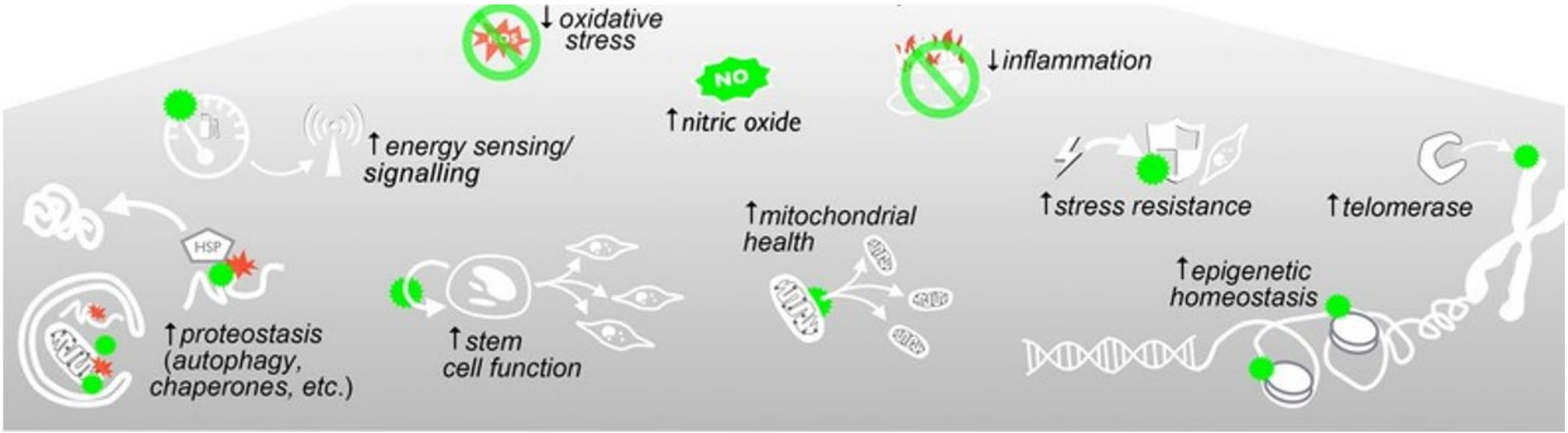
The current tools for extending healthy life — better diets and regular exercise — are effective. But there is room for improvement, especially in personalizing treatments. Molecular insights from animals should be tested in humans to identify interventions to delay ageing and associated conditions. Together, preclinical and clinical researchers must develop meaningful endpoints for human trials.

Longevity pathways identified in model organisms seem to be conserved in humans and can be manipulated in similar ways[2,4]. Genetic surveys of centenarians implicate hormonal and metabolic systems[5]. Long-term calorie restriction in humans induces drastic metabolic and molecular changes ▶

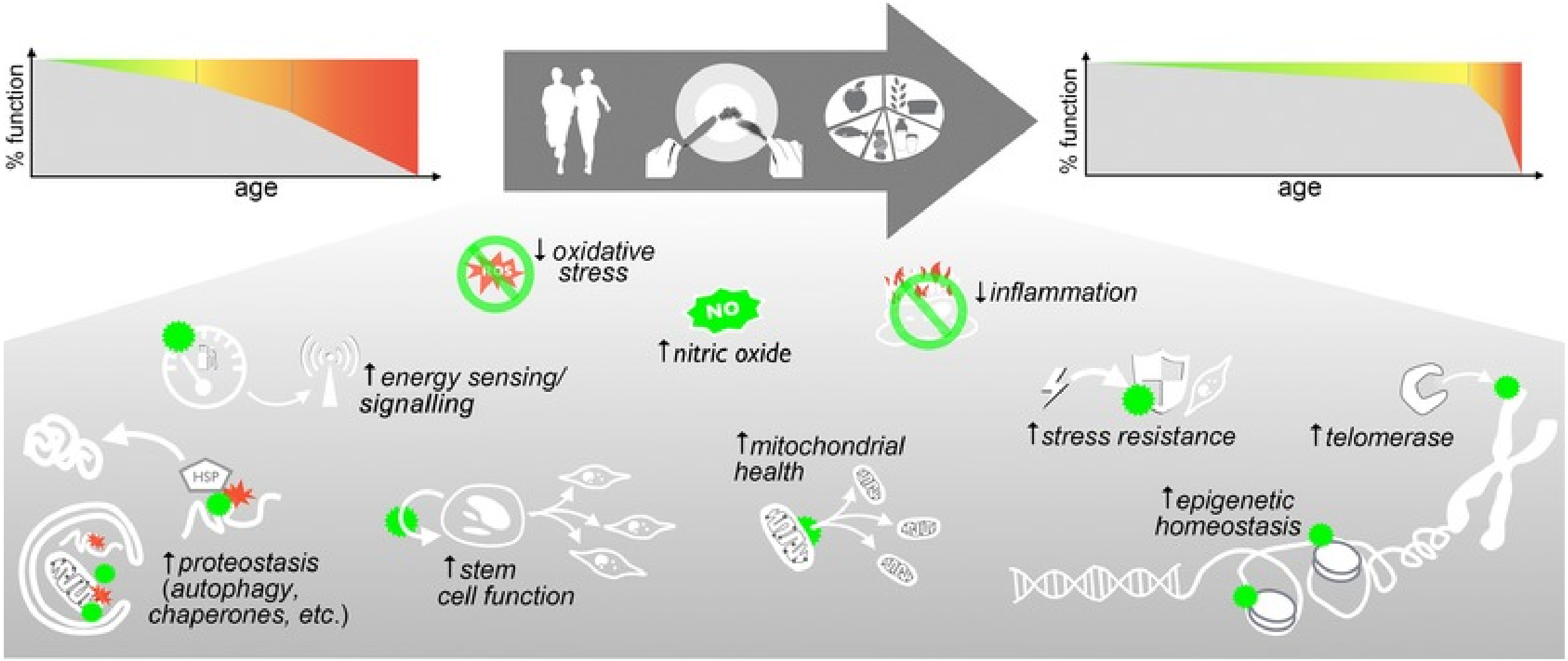
Environment is stronger than genes !




% function
age

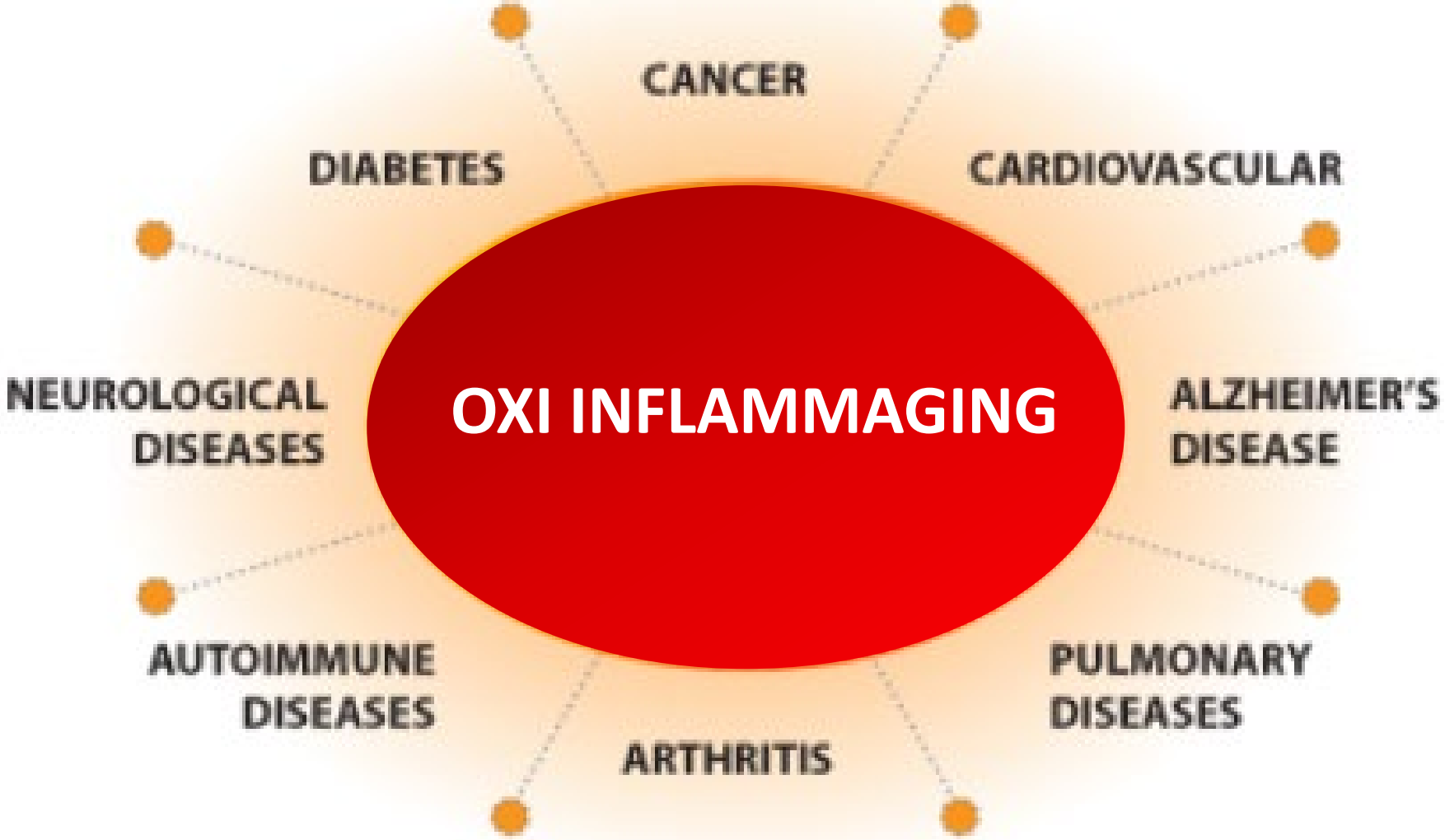

↓ oxidative stress
ROS
NO
↑ nitric oxide
↓ inflammation
↑ energy sensing/ signalling
HSP
↑ proteostasis (autophagy, chaperones, etc.)
↑ stem cell function
↑ mitochondrial health
↑ stress resistance
↑ telomerase
↑ epigenetic homeostasis

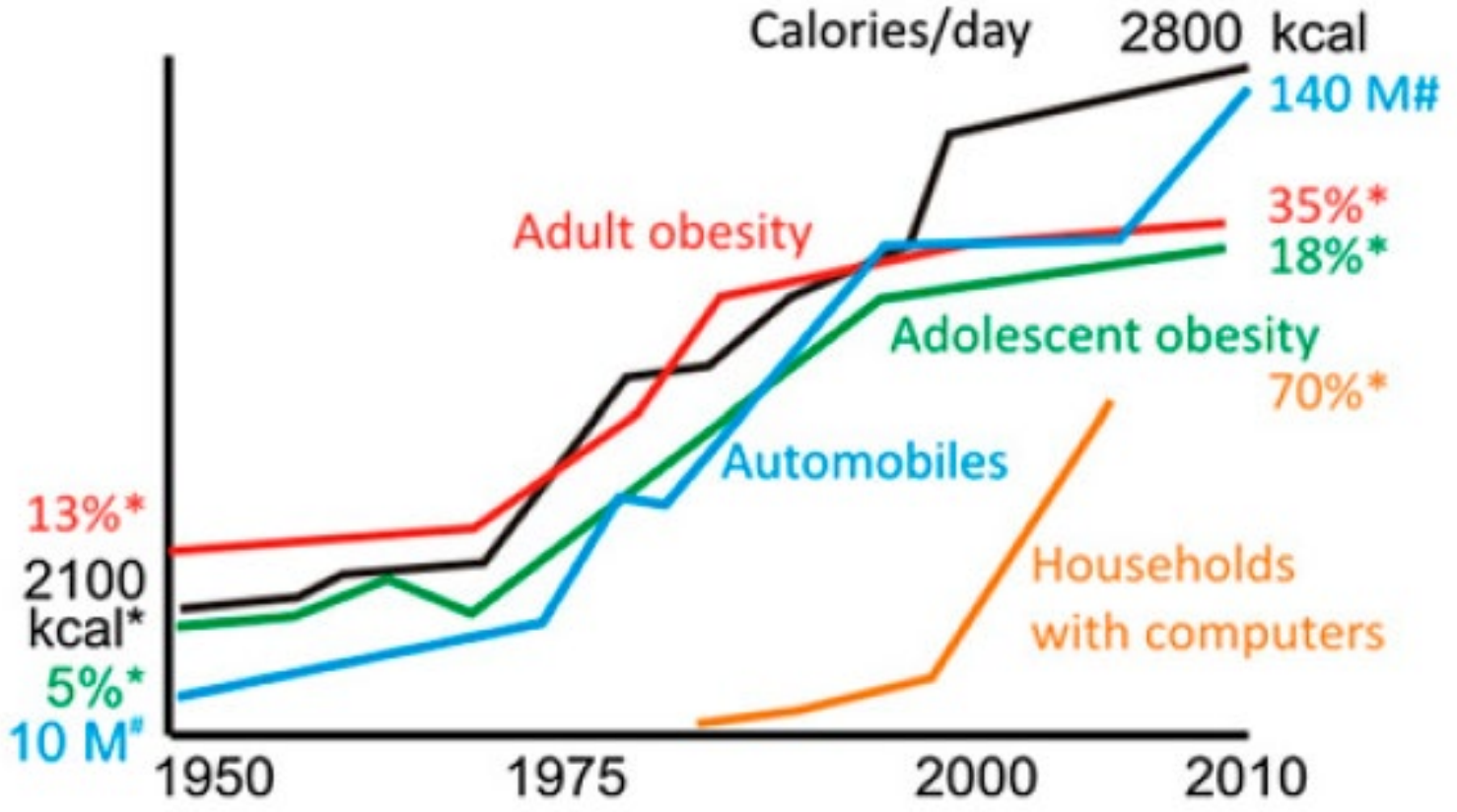
Lifestyle–behavioural Strategies that Increase Function and Healthspan



J Physiol. 2016 ;594(8):2001-24

Oxidation and Inflammation
The link with age related chronic diseases



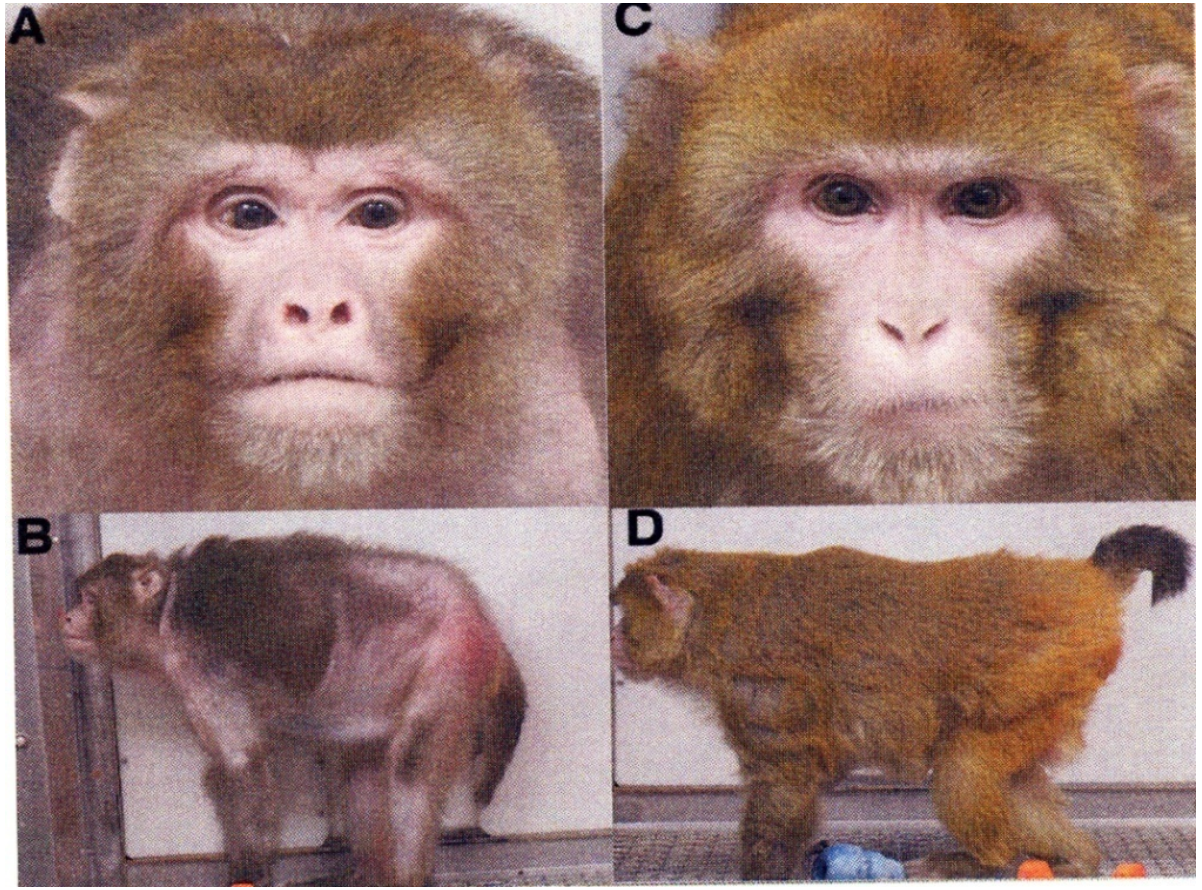


The rising tide of obesity is strongly associated with daily calorie intake and sedentary lifestyle-promoting transportation
*US, approximate value. #Worldwide auto production.

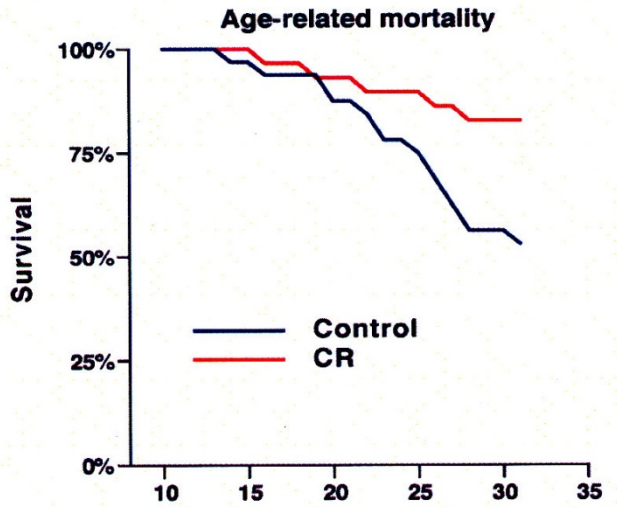
Mattson et al. PNAS 2015

Caloric Restriction : Most Powerful Anti-Aging Intervention

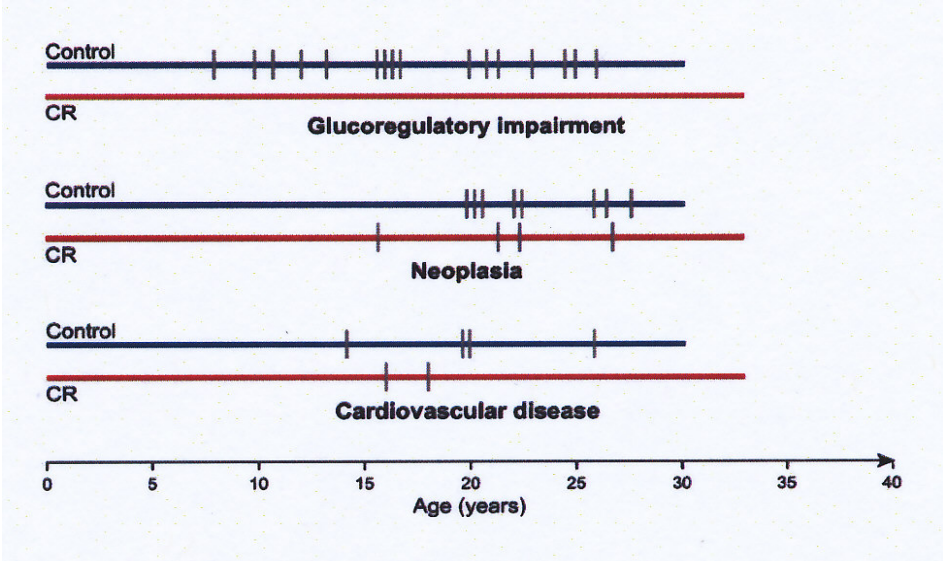
Caloric restriction reduces age-related and all-cause mortality in rhesus monkeys.
Colman RJ, Beasley TM, Kemnitz JW, Johnson SC, Weindruch R, Anderson RM.
Nat Commun. 2014 Apr 1;5:3557

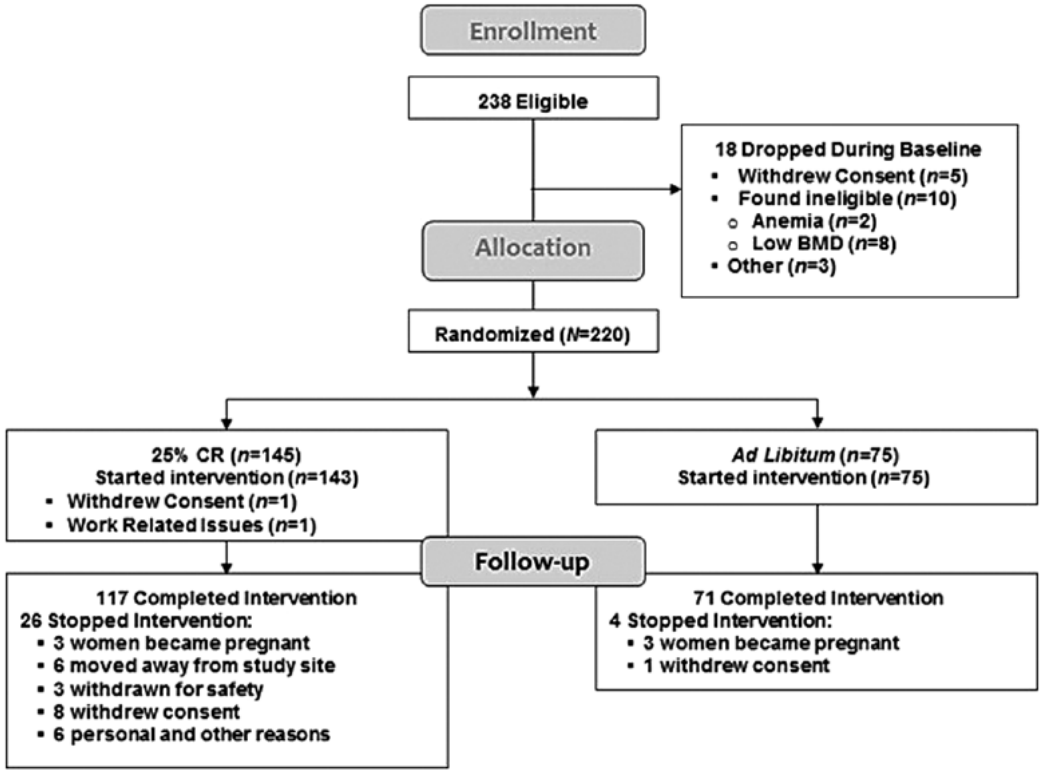


Ad libitum **CR**



P = 0.03
HR = 3.0





CALERIE CENTERS

PENNINGTON BIOMEDICAL RESEARCH CENTER LSU

Tufts UNIVERSITY | Jean Mayer USDA Human Nutrition Research Center on Aging

Washington University in St. Louis SCHOOL OF MEDICINE

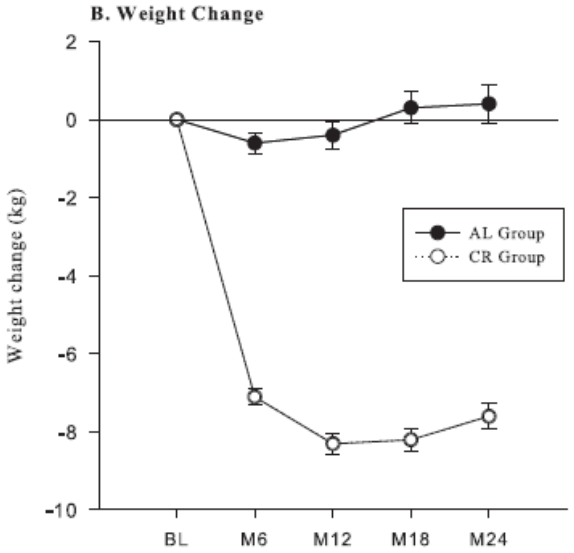
THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2015, Vol. 70, No. 9, 1097–1104
doi:10.1093/gerona/glv057
Advance Access publication July 17, 2015

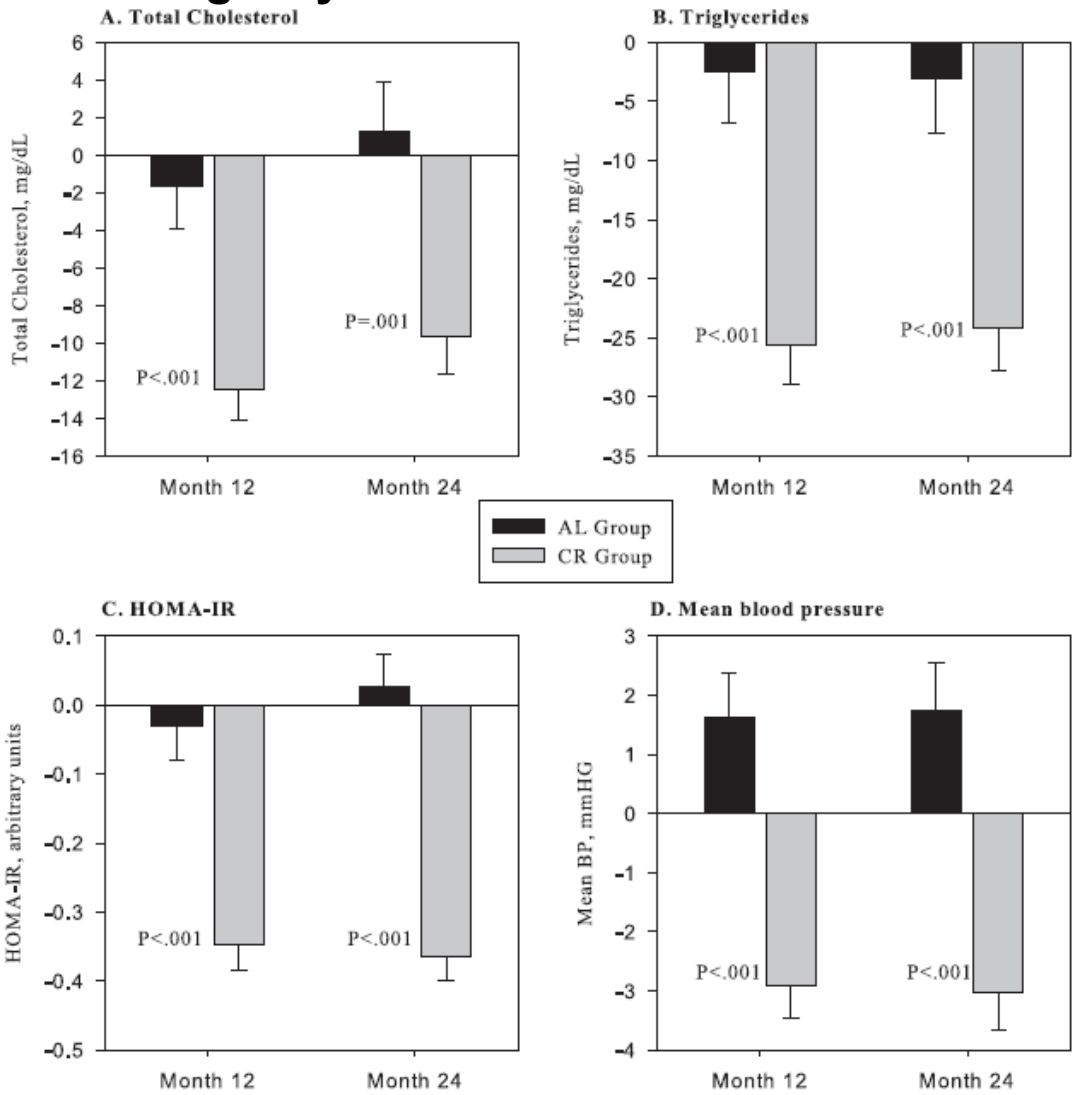
OXFORD

A 2-Year Randomized Controlled Trial of Human Caloric Restriction: Feasibility and Effects on Predictors of Health Span and Longevity

Ravussin E et al.



weight change over the course of the intervention in ad libitum (---) and CR (___) groups (values are means ± standard error)



Changes in total cholesterol (**A**), mean triglycerides (**B**), HOMA-IR (**C**), and mean blood pressure (**D**) at month 12 and month 24 in the AL control (black
bars) and CR (gray bars) groups

JAMA Intern Med. **2016;176(6):743-752.**

Effect of Calorie Restriction on Mood, Quality of Life, Sleep, and Sexual Function in Healthy Nonobese Adults The CALERIE 2 Randomized Clinical Trial

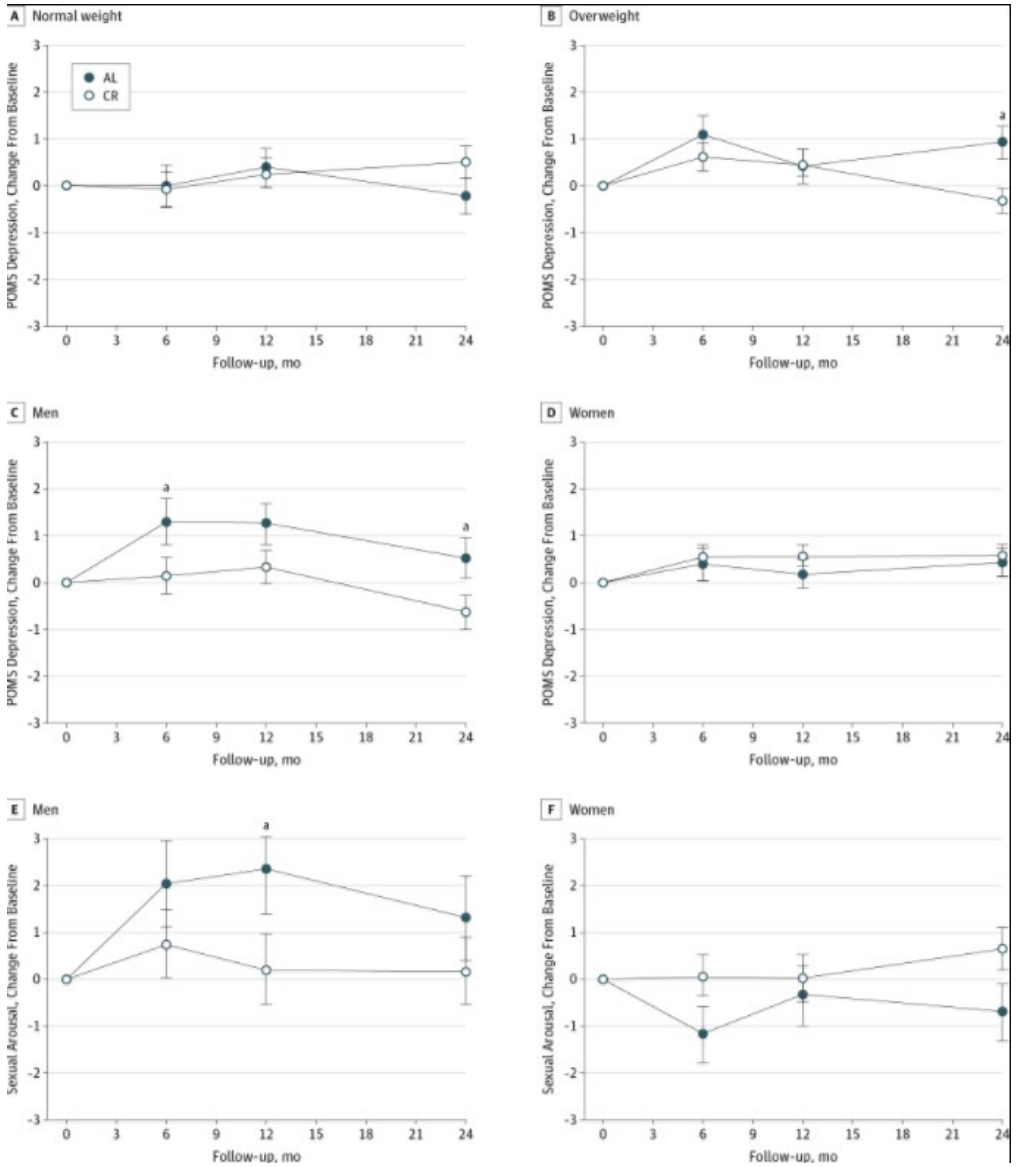
Martin CK et al

Key Points

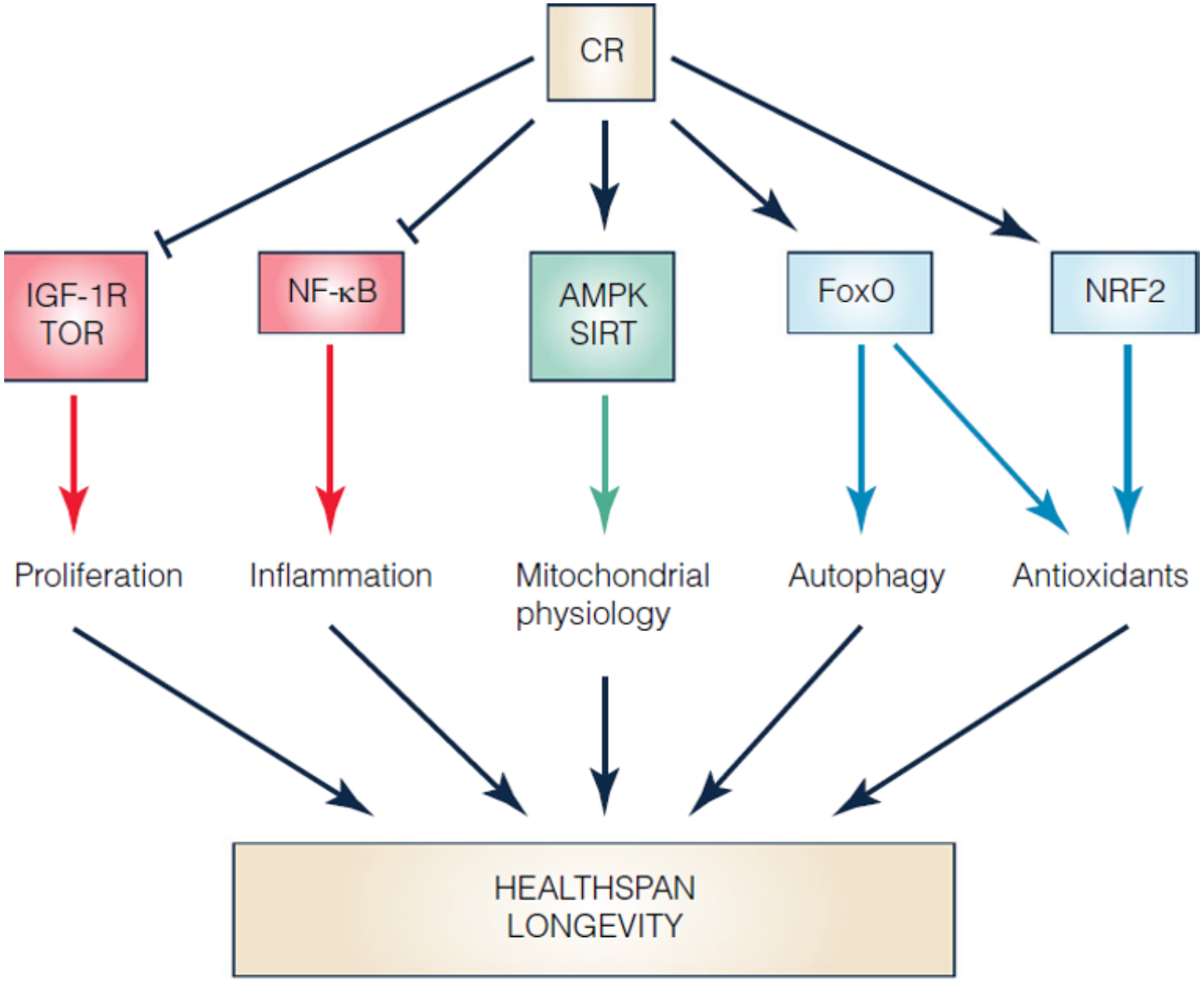
Question What are the effects of 2 years of calorie restriction on the health-related quality of life of nonobese adults?

Findings In this randomized clinical trial that enrolled 220 healthy nonobese adults, long-term (2-year) calorie restriction had no negative effects and some positive effects on health-related quality of life.

Meaning In nonobese adults, calorie restriction, marked by approximately 10% weight loss, can be undertaken with little concern about negative effects on quality of life, mood, sexual function, and sleep.



Images depicting the evolutionary basis for the importance of optimal brain function under conditions of food deprivation and physical exertion.



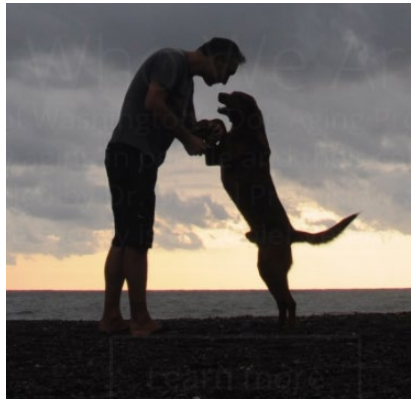
The Journal of
Physiology

Dog Aging Project

Vet Pathol. 2016 March ; 53(2): 291–298. doi:10.1177/0300985815591082.

The biology of aging: citizen scientists and their pets as a bridge between research on model organisms and human subjects

Matt Kaeberlein[1,*]
[1]Department of Pathology, University of Washington, 1959 NE Pacific ST, Seattle WA 98195



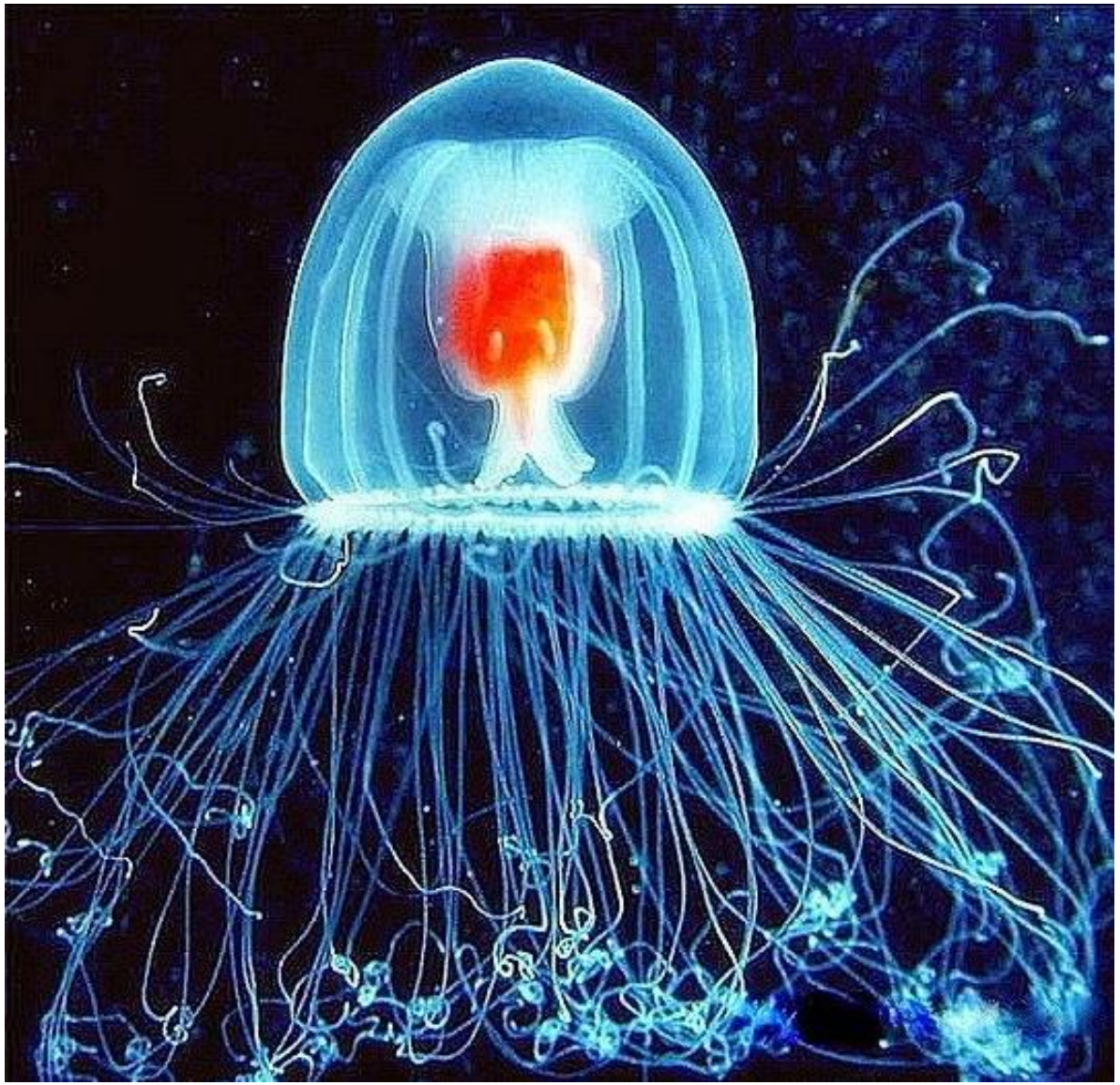
GeroScience (2017) 39:117–127
DOI 10.1007/s11357-017-9972-z

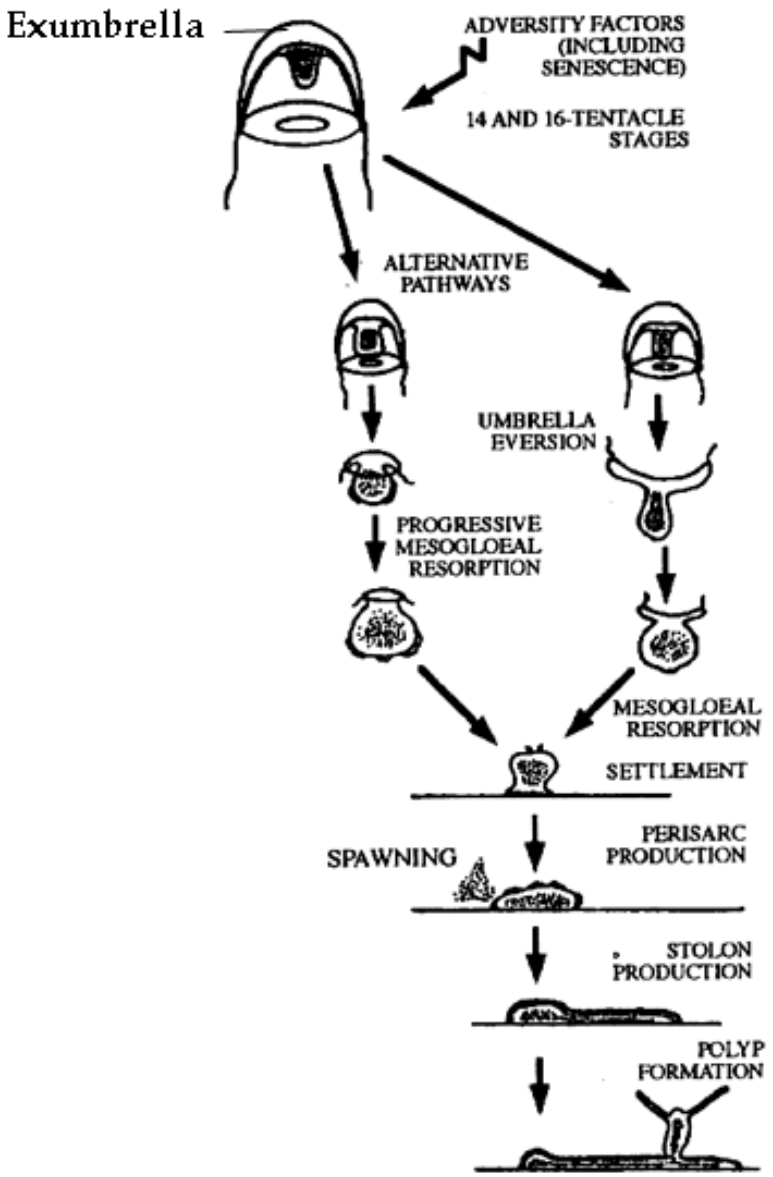
ORIGINAL ARTICLE

A randomized controlled trial to establish effects of short-term rapamycin treatment in 24 middle-aged companion dogs

Silvan R. Urfer · Tammi L. Kaeberlein · Susan Mailheau · Philip J. Bergman · Kate E. Creevy · Daniel E. L. Promislow · Matt Kaeberlein

Piraino, S., Boero, F., Aeschbach, B., and Schmid, V. 1996. Reversing the life cycle: Medusae transforming into polyps and cell transdifferentiation in *Turritopsis nutricula* (Cnidaria, Hydrozoa). *Biol. Bull.* 90: 302-312.

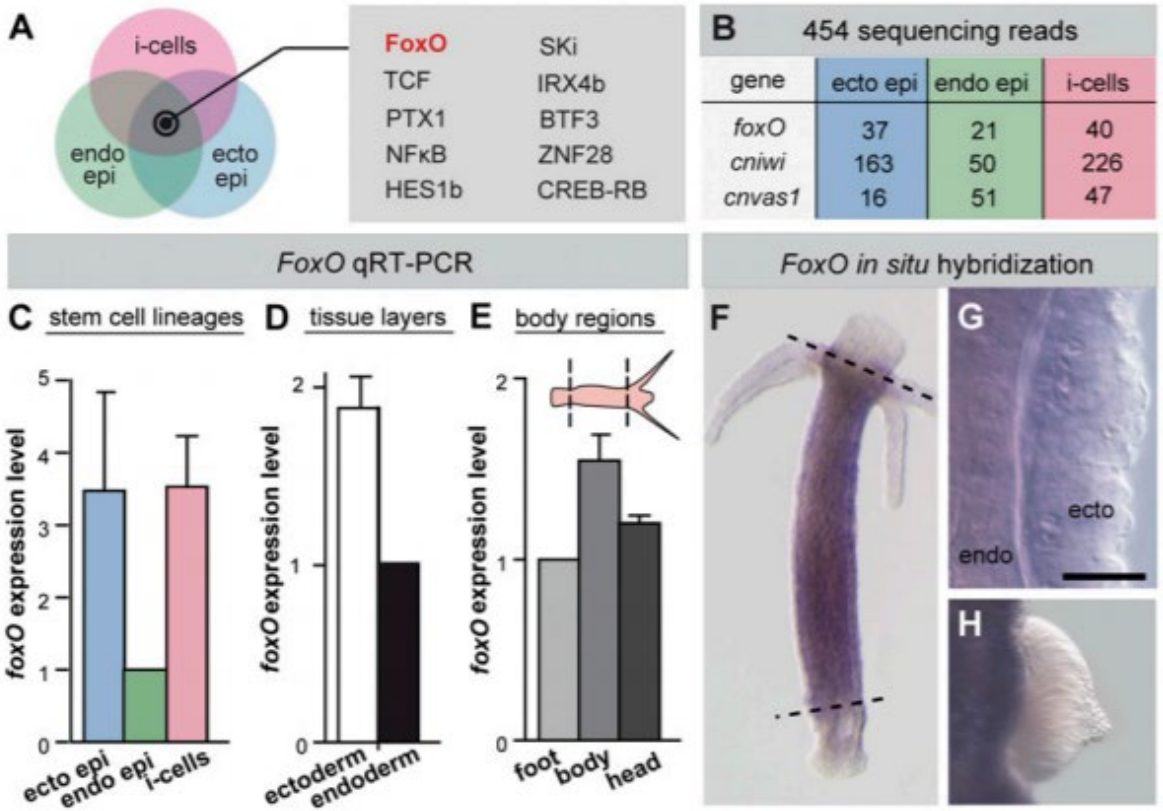


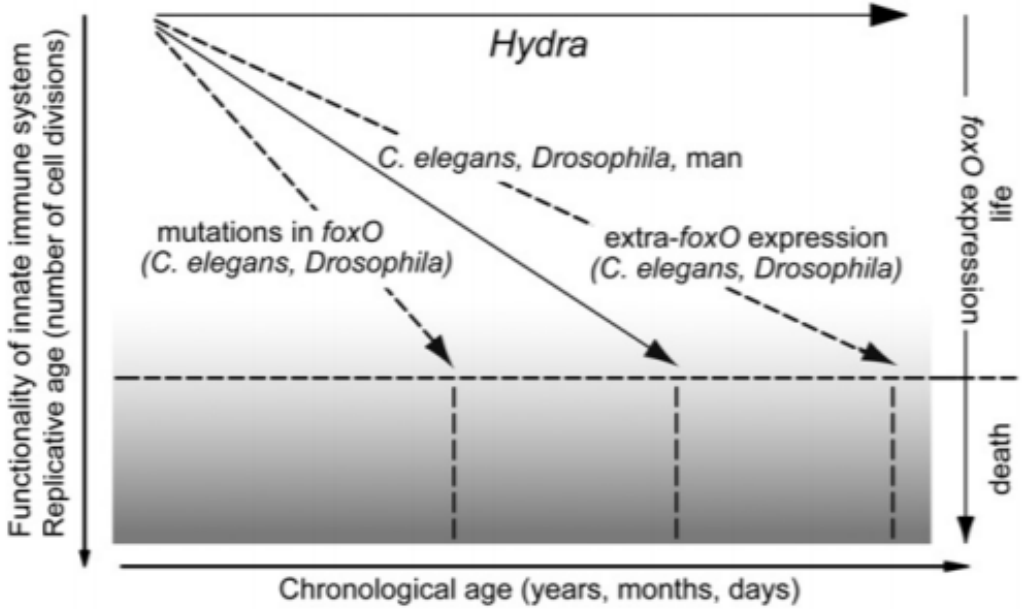


FoxO is a critical regulator of stem cell maintenance in immortal *Hydra*

Anna-Marei Boehm[a,1], Konstantin Khalturin[a,1], Friederike Anton-Erxleben[a], Georg Hemmrich[a], Ulrich C. Klostermeier[b], Javier A. Lopez-Quintero[a], Hans-Heinrich Oberg[c], Malte Puchert[a], Philip Rosenstiel[b], Jörg Wittlieb[a], and Thomas C. G. Bosch[a,2]

PNAS | January 8, 2013 | vol. 110 | no. 2 |





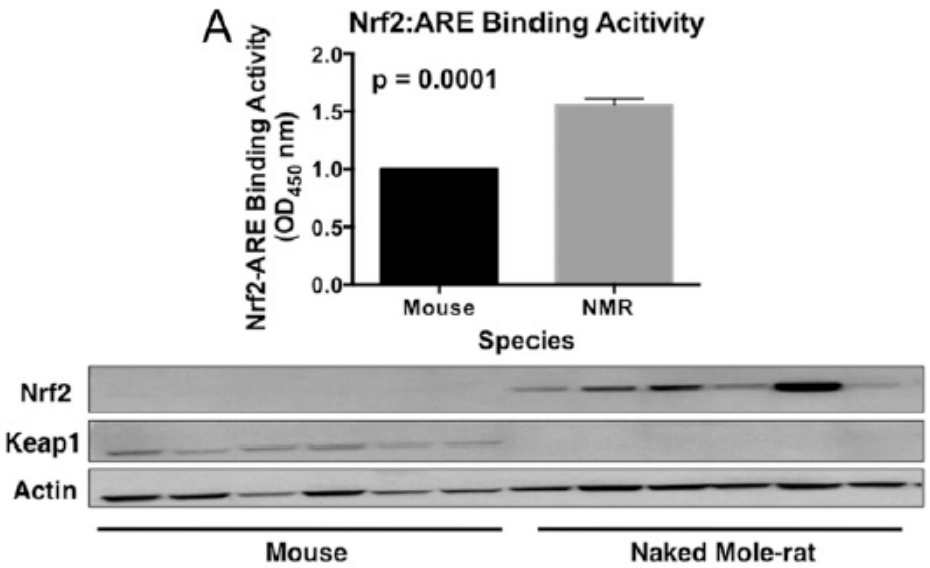
Model of the role of FoxO in controlling longevity. Decline of foxO expression results in aging and death. Mutations in DAF-16 and dfoxO reduce life span in both C. elegans and flies. Increase of foxO expression delays aging by maintaining stem cell self-renewal and functionality of the immune system. Universally expressed foxO in Hydra results in a continuous selfrenewal capacity of stem cells and immortality.

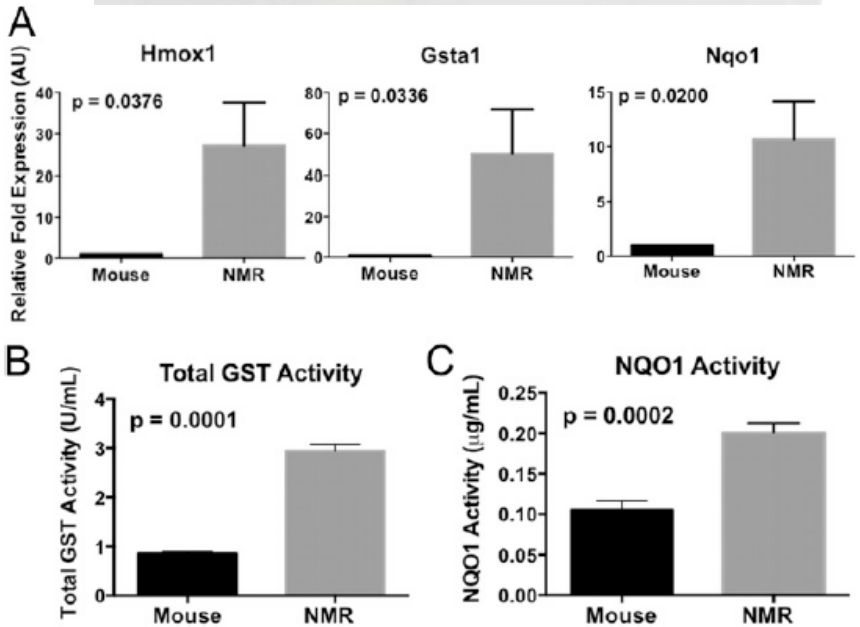
Regulation of Nrf2 signaling and longevity in naturally long-lived rodents

Kaitlyn N. Lewis[a,b], Emily Wason[c], Yael H. Edrey[b,c], Deborah M. Kristan[d], Eviatar Nevo[e], and Rochelle Buffenstein[a,b,c,1]

[a]Departments of Cellular and Structural Biology and [c]Physiology and [b]Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center at San Antonio, San Antonio, TX 78229; [d]Department of Biological Sciences, California State University, San Marcos, CA 92096; and [e]Institute of Evolution, University of Haifa, Haifa 31905, Israel

3722–3727 | PNAS | March 24, 2015 | vol. 112 | no. 12



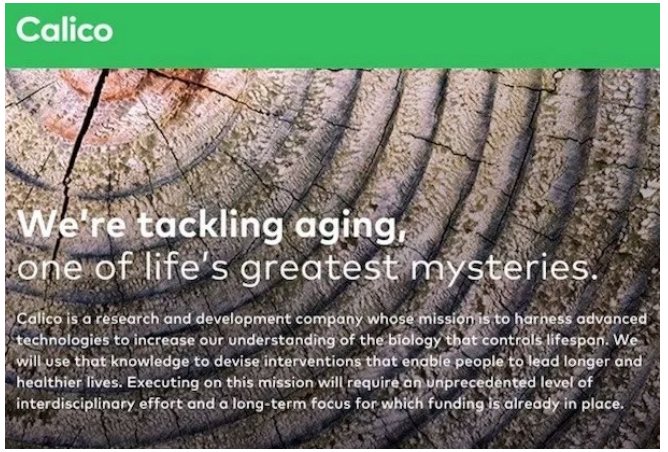


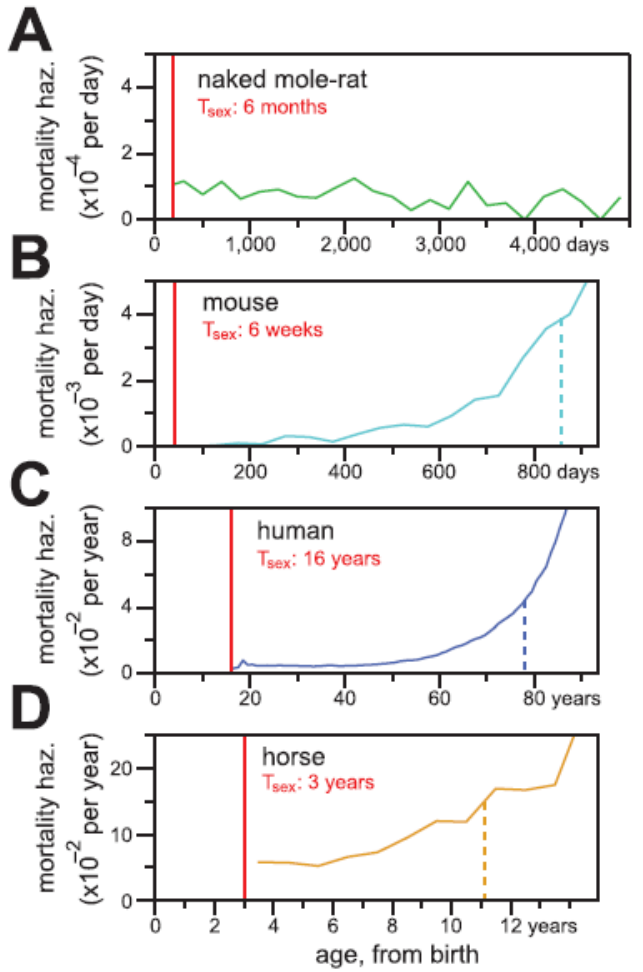
Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age

J Graham Ruby, Megan Smith, Rochelle Buffenstein*

Calico Life Sciences LLC, South San Francisco, United States

Google's Calico Labs announces discovery of a "non-aging mammal."





EMBO reports

EMBO reports VOL 13 | NO 3 | 2012

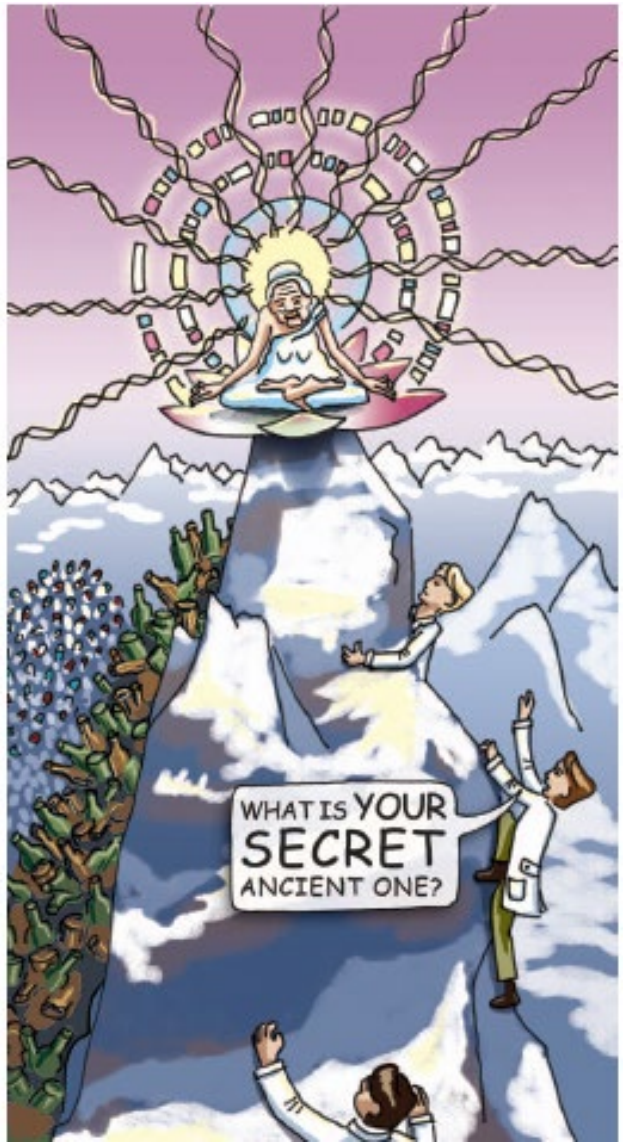
science & society

‘Positive biology’ as a new paradigm for the medical sciences

Focusing on people who live long, happy, healthy lives might hold the key to improving human well-being

Colin Farrelly

Eliminating all types of cancer would increase life expectancy in the USA by approximately only three years



Centenarians are a great model of Positive Biology
Study the escapers to keep their secret of long life

Mechanisms of Ageing and Development 136-137 (2014) 148–162

Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet

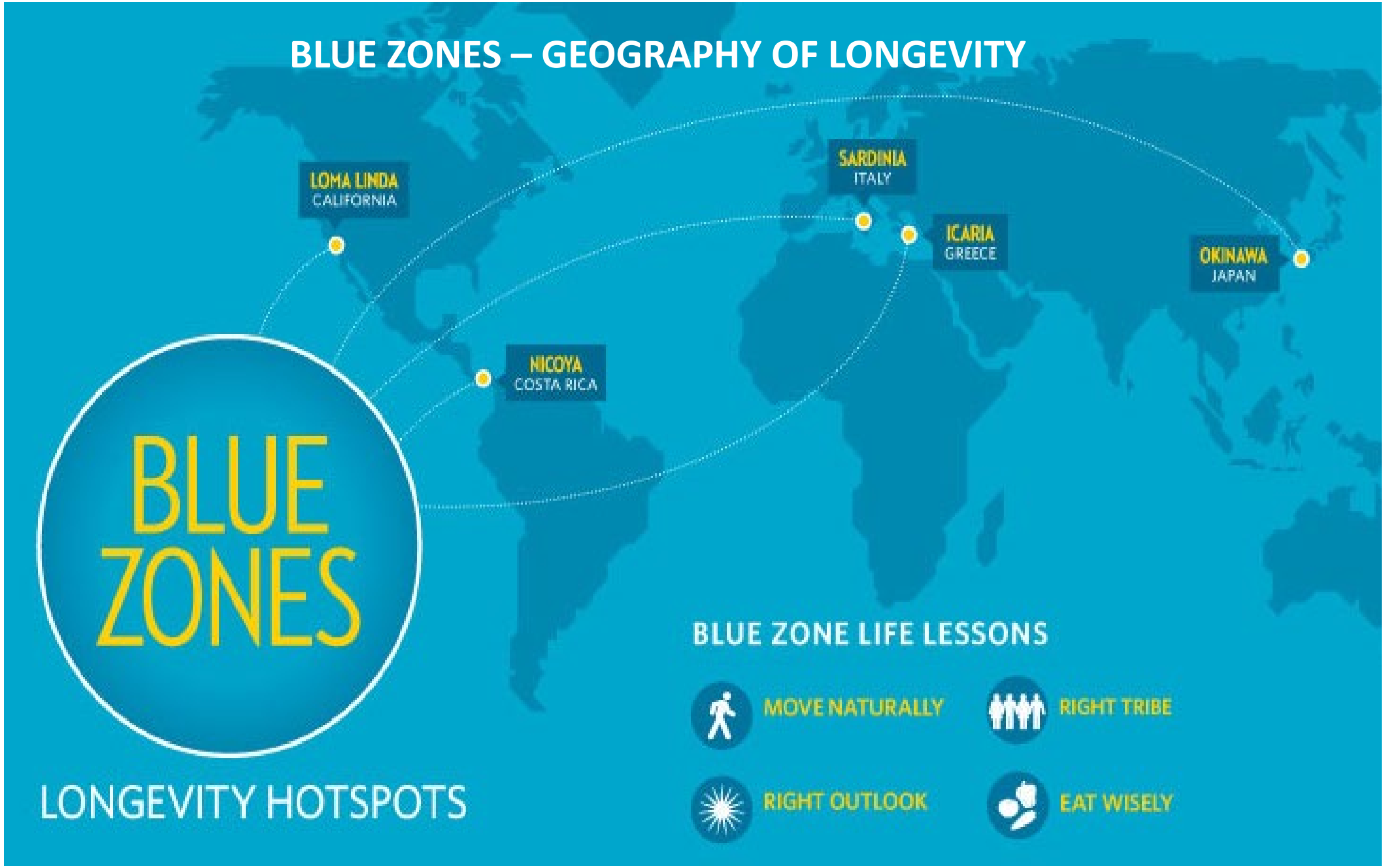
Donald Craig Willcox [a,b,c,*], Giovanni Scapagnini [d], Bradley J. Willcox [b,c]

REJUVENATION RESEARCH
Volume 15, Number 2, 2012
© Mary Ann Liebert, Inc.
DOI: 10.1089/rej.2011.1280

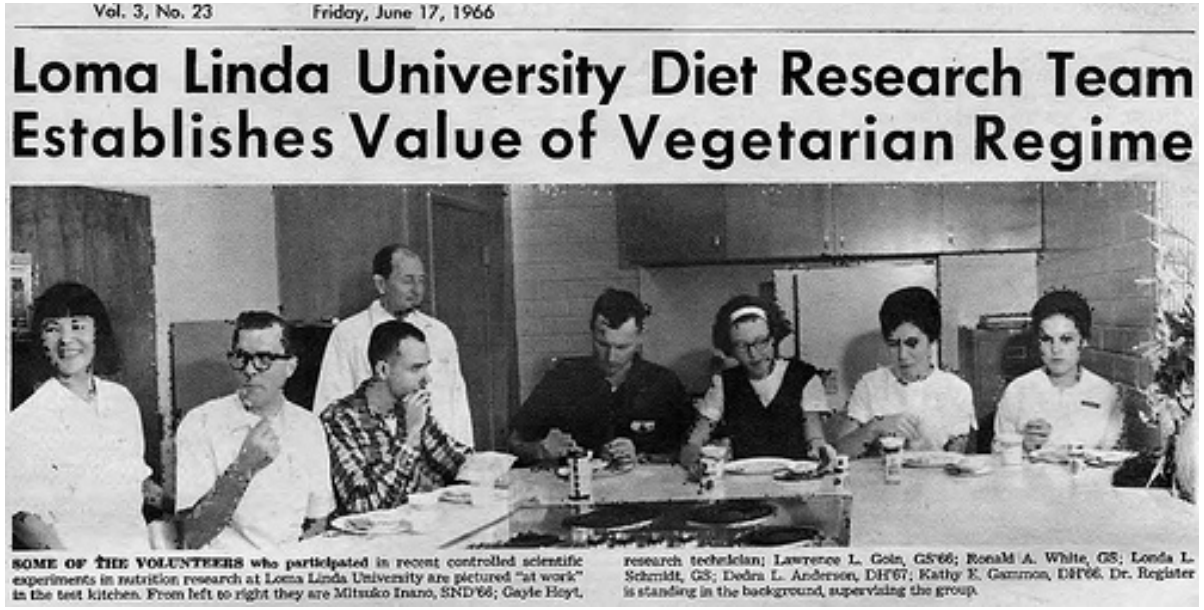
Mediterranean Diet and Longevity in Sicily: Survey in a Sicani Mountains Population

Sonya Vasto,[1] Giovanni Scapagnini,[2] Claudia Rizzo,[2] Roberto Monastero,[3] Antonio Marchese,[4] and Calogero Caruso[1]

BLUE ZONES – GEOGRAPHY OF LONGEVITY



Seventh-Days Adventists



Vol. 3, No. 23 Friday, June 17, 1966

Loma Linda University Diet Research Team Establishes Value of Vegetarian Regime

SOME OF THE VOLUNTEERS who participated in recent controlled scientific experiments in nutrition research at Loma Linda University are pictured "at work" in the test kitchen. From left to right they are Mitsuko Inano, SND'68; Gayle Hoyt, research technician; Lawrence L. Goin, GS'66; Ronald A. White, GS; Londa L. Schmidt, GS; Dedra L. Anderson, DH'67; Kathy E. Gammon, DH'66. Dr. Register is standing in the background, supervising the group.

HHS Public Access
Author manuscript
J Relig Health. Author manuscript; available in PMC 2018 August 14.

Published in final edited form as:
J Relig Health. 2016 April ; 55(2): 695–708. doi:10.1007/s10943-015-0102-x.

Intrinsic Religiosity and Hypertension Among Older North American Seventh-Day Adventists

Sherma J. Charlemagne-Badal[1] and **Jerry W. Lee**[2]

The American Journal of
CLINICAL NUTRITION

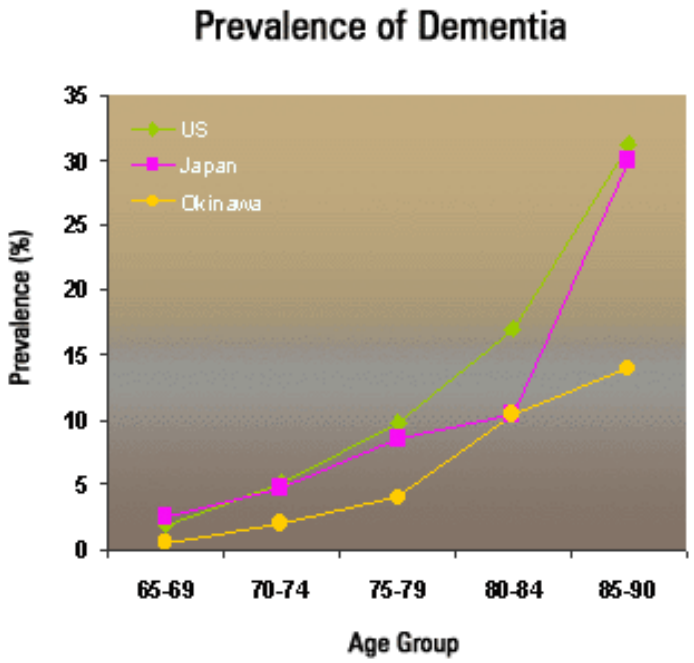
Vegetarian diets in the Adventist Health Study 2: a review of initial published findings[1–4]

Michael J Orlich and Gary E Fraser

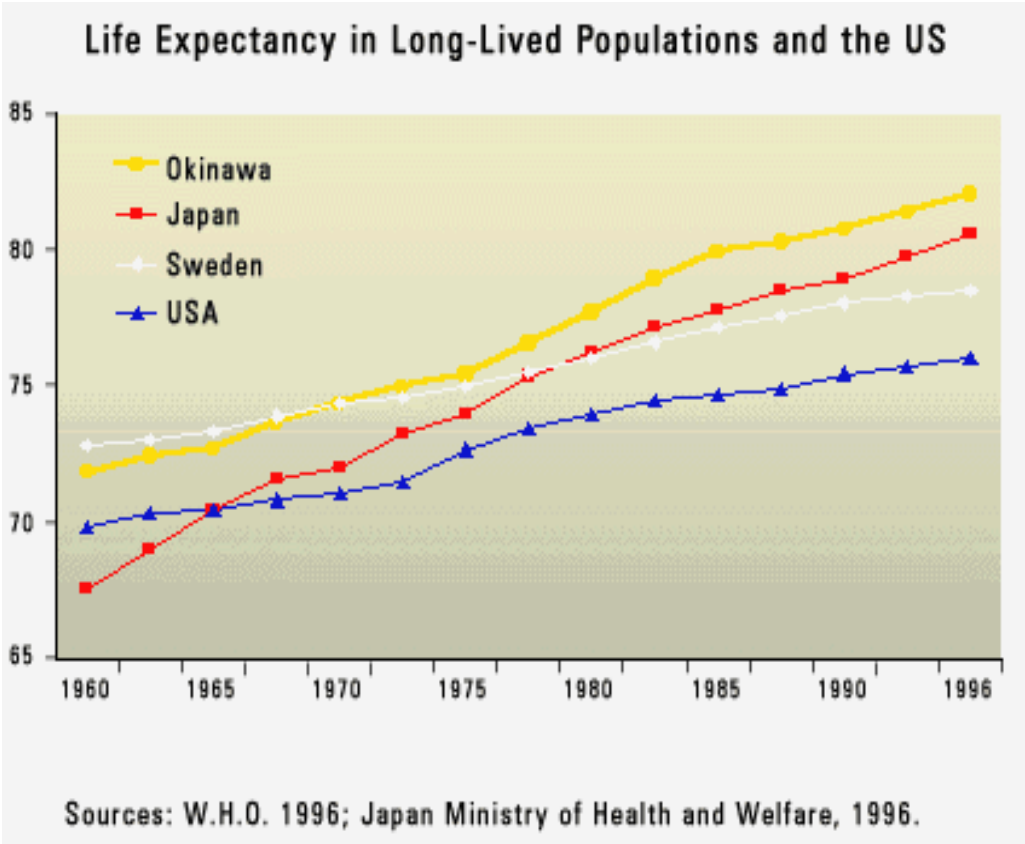
A lifestyle characterized by a series of lifestyle choices such as exercise, vegetarian diet, abstinence from smoking, consumption of nuts, and favorable psychosocial functioning (lower depression and authoritarianism, higher time urgency), all hinged on religious beliefs, has been found to predict a longer life among SDAs

In Okinawa, centenarian ratios may be the world's highest at approximately 50 per 100,000 population

Almost 1000 Okinawan centenarians and numerous other elderly in their seventies, eighties, and nineties, have been studied from 1975



Sources: Yamada, M., et al. J Am Geriatr Soc 1999;47:189-95. Kokmen, E., et al. Mayo Clin Proc 1996;71:275-82. Ogura, C., et al. Internatl J Epidemiol 1995;24:373-80.



Sources: W.H.O. 1996; Japan Ministry of Health and Welfare, 1996.

Gene Varient in Insulin Signaling Pathway Strongly Associated with Healthy Aging and Longevity (Willcox et al. Proc Nat Acad Sci 2008)

HONOLULU Star-Bulletin

TUESDAY SEPTEMBER 2, 2008 • HAWAII'S OLDEST DAILY NEWSPAPER, SINCE 1882 • 50¢

STARBULLETIN.COM

"Most people my age would get into the starting block and never be able to get up," says Chuck Yogi, 89. A lifelong runner of Okinawan decent, Yogi's mother lived to 102 and his father to 98. "If worrying made you live longer, I would do it, but it doesn't help so I never do," he says. Here, Yogi runs on a high school track in Hilo.

COURTESY PHOTO / 2004

LONGEVITY GENE FOUND

Isle scientists isolate the gene using decades of data

Hawaii scientists say they have identified a human "longevity" gene prevalent in men who have led long, healthy lives.

The gene, labeled FOXO3A, was identified by Kuakini Medical Center and Pacific Health Research Institute investigators. They studied biological specimens and clinical data collected and maintained at Kuakini since 1965 on 8,006 Japanese-American men recruited for the Honolulu Heart Program and Honolulu-Asia Aging study.

Discovery of the FOXO3A gene is part of a Hawaii Lifespan Study that is continuing to mine information from the cohort to increase understanding of diseases and aging.

Findings of the team, led by Dr. Bradley Willcox, were published yesterday in the National Academy of Sciences' journal.

"Some humans are just built stronger, built to last, and other humans are more frail. That's our genetic endowment," Willcox said.

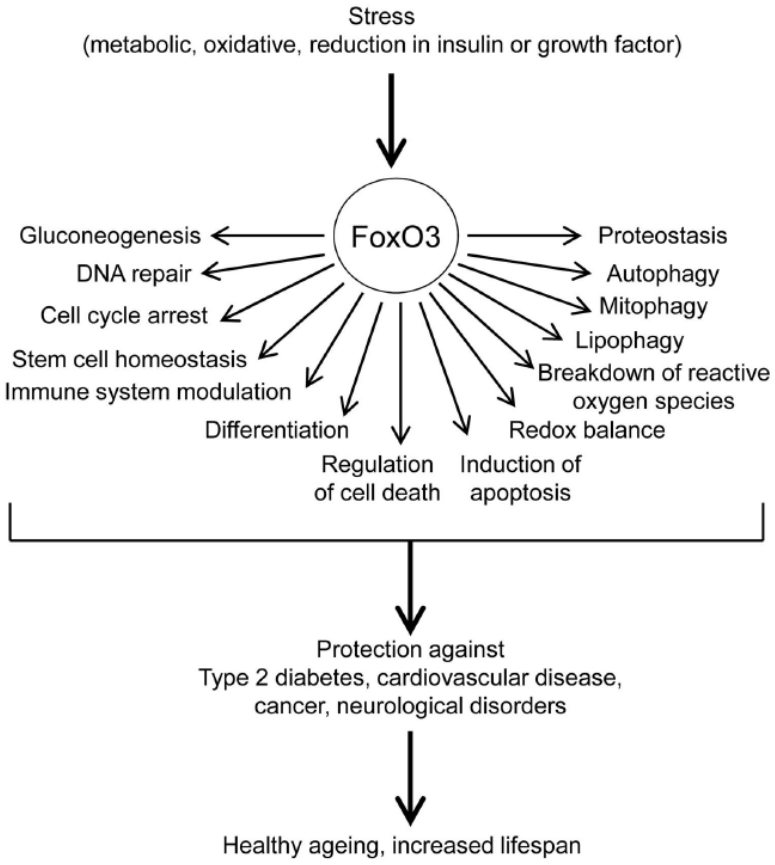
HELEN ALTONN / PAGE A6

MORNING DIGEST

HAWAII

TT
TG
GG

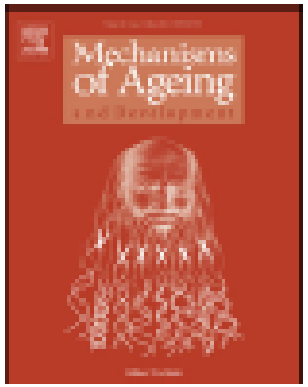
Lower prevalence of cancer, CVD, better self-reported health, and higher physical and cognitive function, despite significantly older ages than controls. Greater insulin sensitivity and this was associated with homozygosity for the *FOXO3A* GG genotype.



Mechanisms of Ageing and Development 136-137 (2014) 148–162

Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet

Donald Craig Willcox [a,b,c,*], Giovanni Scapagnini [d], Bradley J. Willcox [b,c]



Key Features of Traditional Okinawa Diet

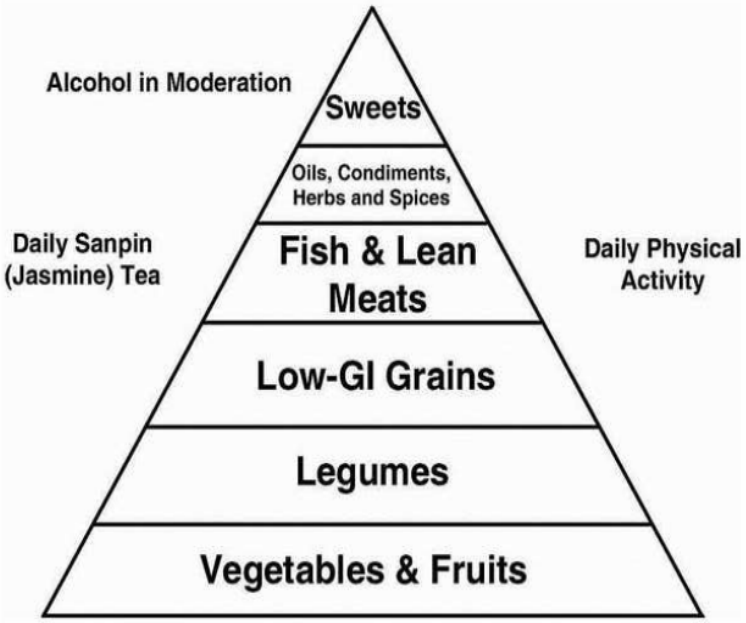
1) Low Caloric Density (plant-based, low fat, moderate protein from soy, fish, lean meats)

2) High Nutrient Density (Vitamins A,C, E, potassium, magnesium, folate, and healthy oils)

3) Phyto-nutrient Rich (polyphenols, carotenoids mostly from green leafy, yellow root vegetables and seaweed)

4) Low in Glycemic Load (high quality carbohydrates from staple sweet potato)

5) Anti-inflammatory (CR, polyphenols, omega 3 fatty acids)

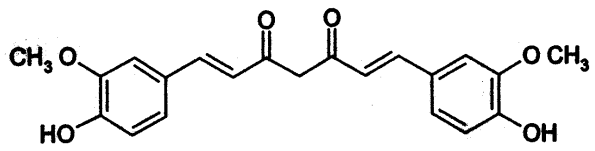


Traditional Okinawan diet food pyramid

Healthy aging diets other than the Mediterranean: A focus on the Okinawan diet.

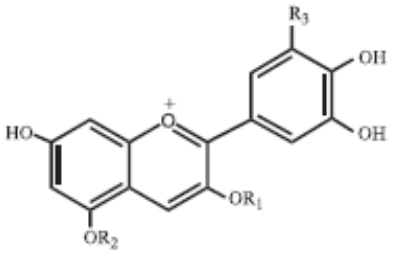
Willcox DC, Scapagnini G, Willcox BJ. Mech Ageing Dev. 2014 Jan 21.

Curcuma longa



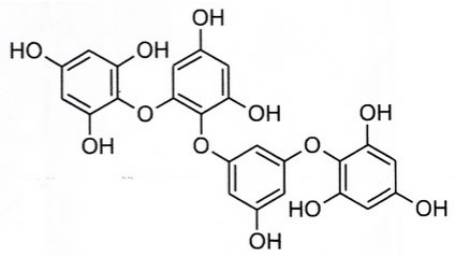
Curcumin

Ipomoera batatas cultivar Ayamurasaki



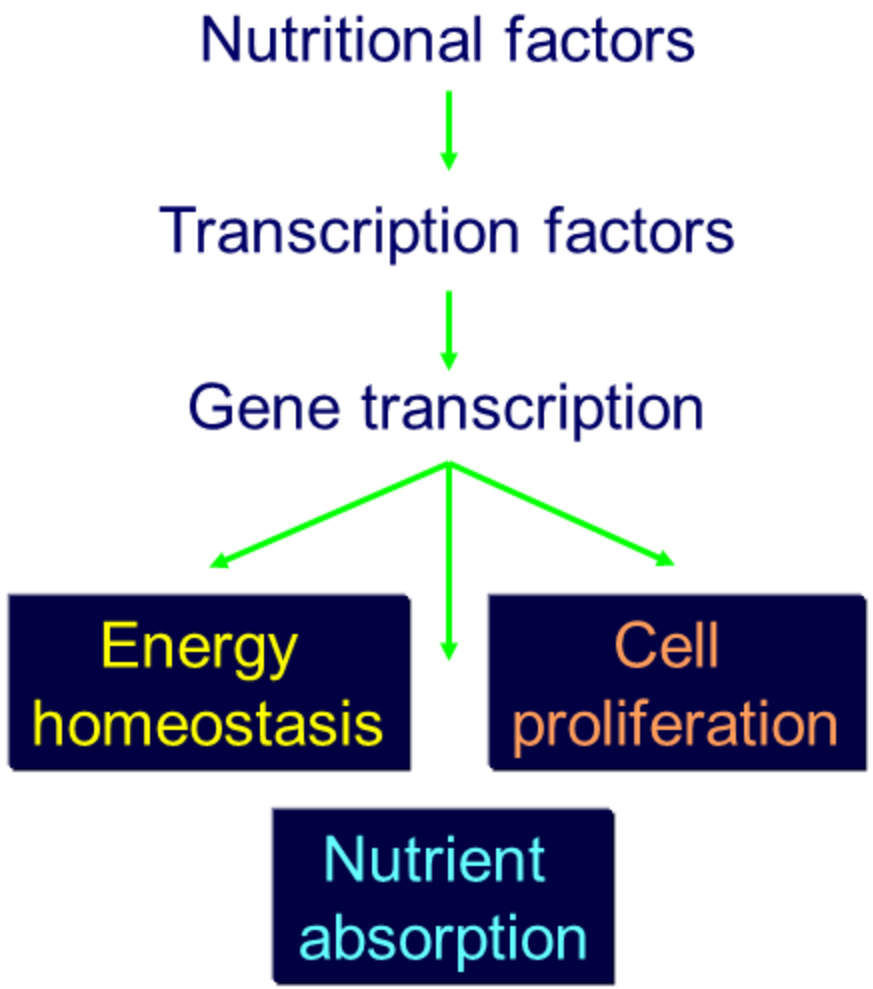
Anthocyanin

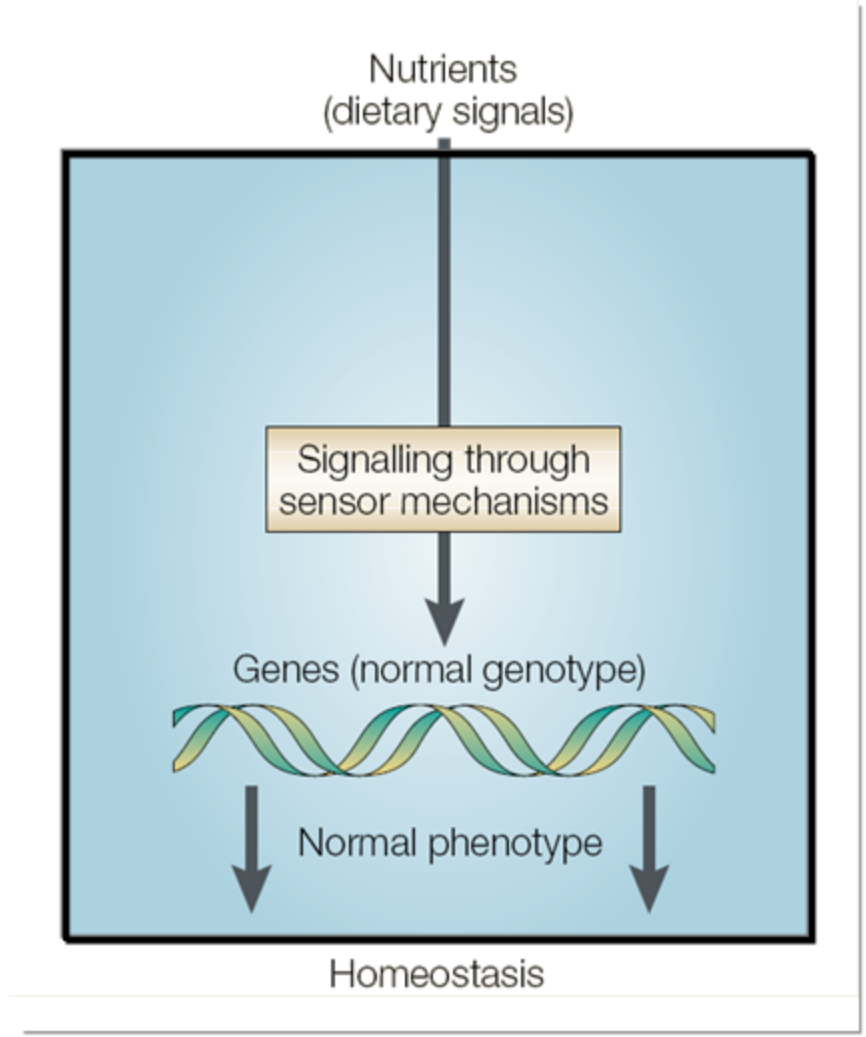
Wakame Undaria pinnatifida

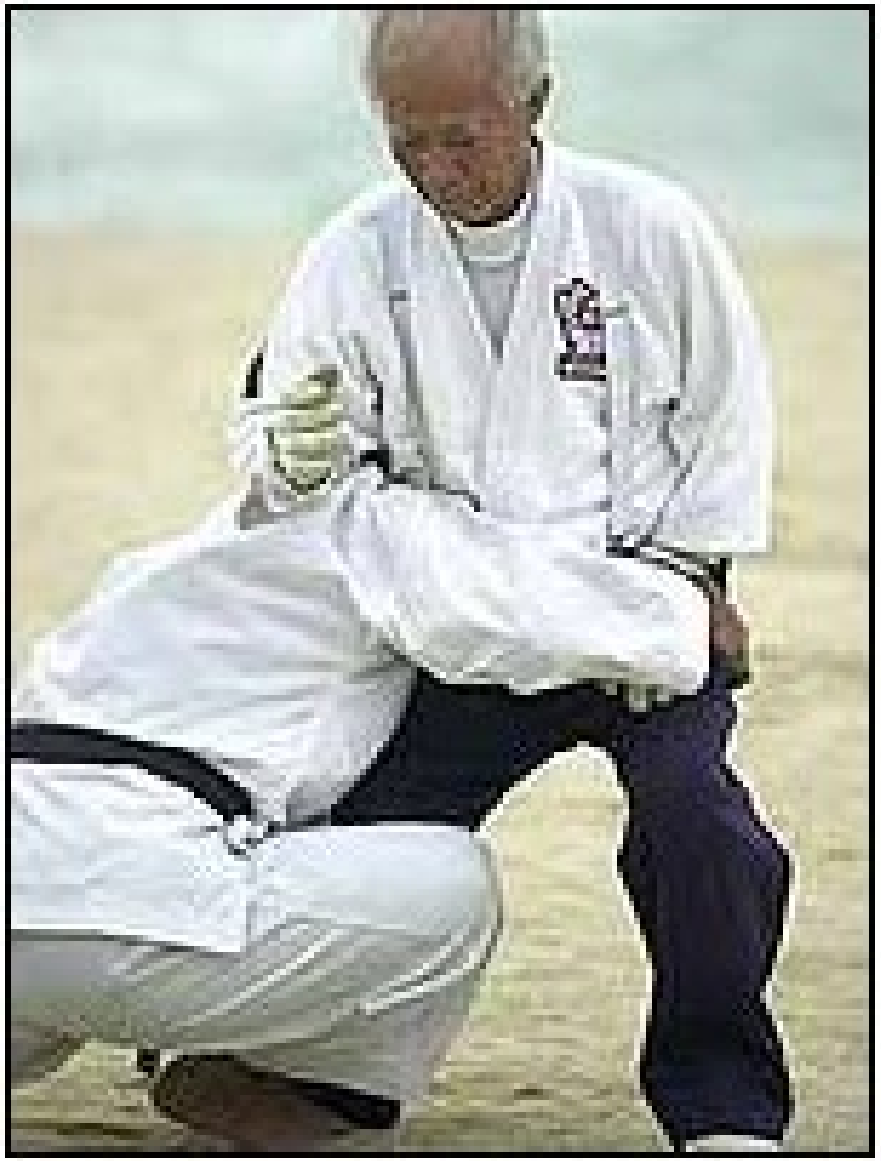


Phlorotannin

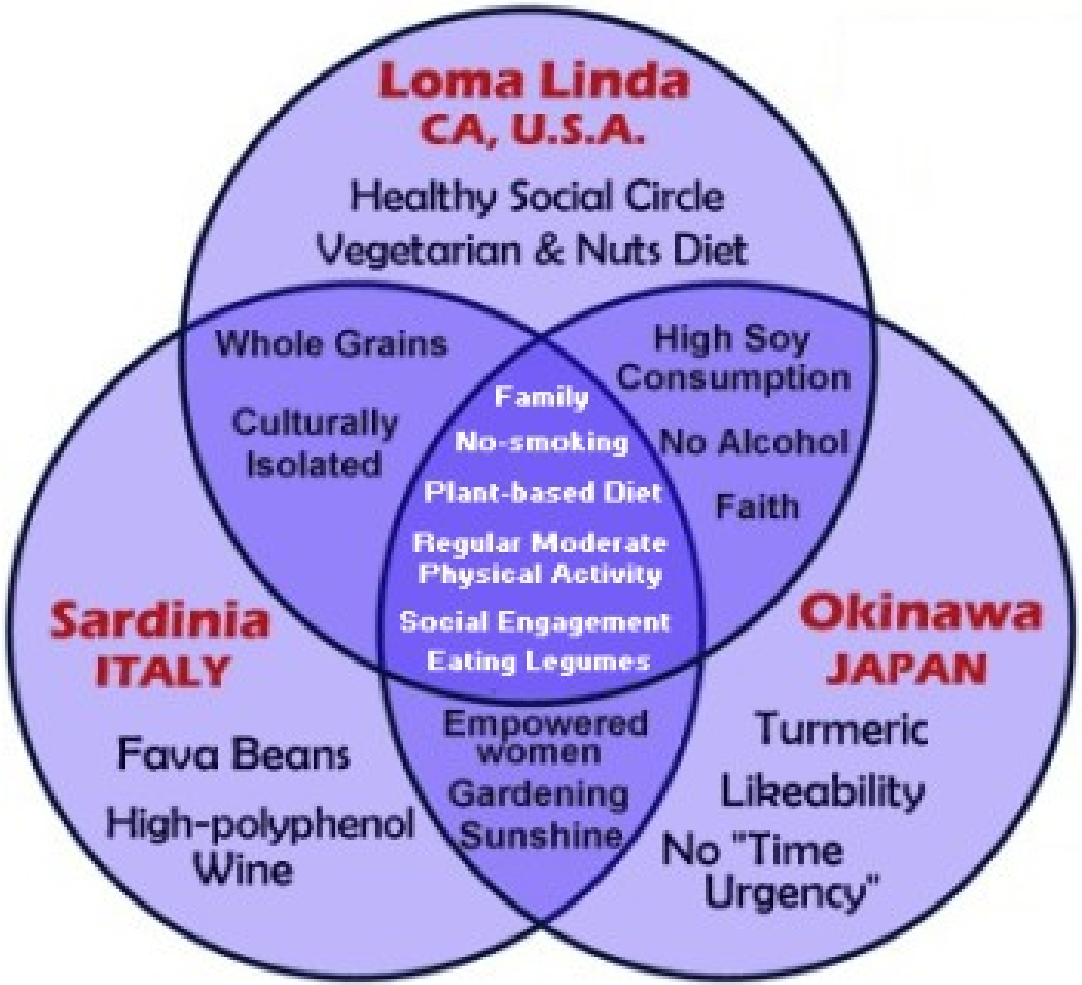
Nutrients acts as dietary signals







Physical Activity and psychological and social aspects, all play an important role in Okinawan longevity.

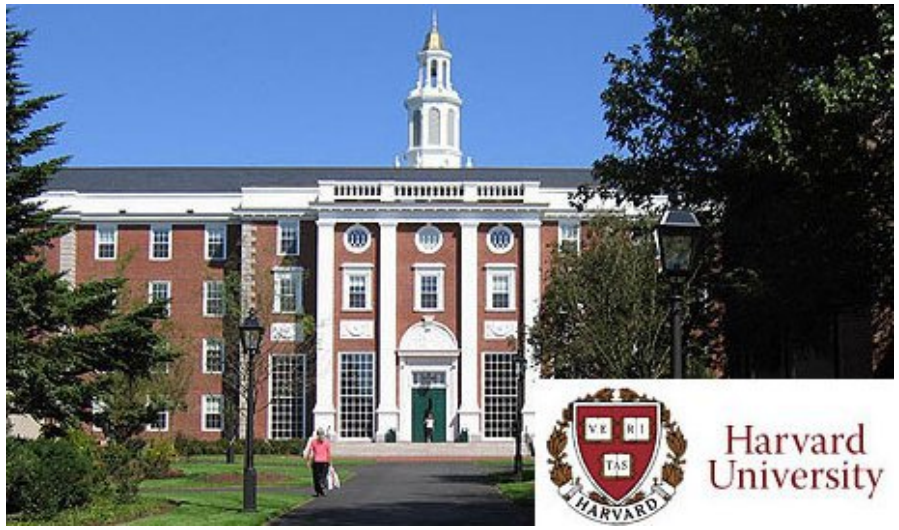


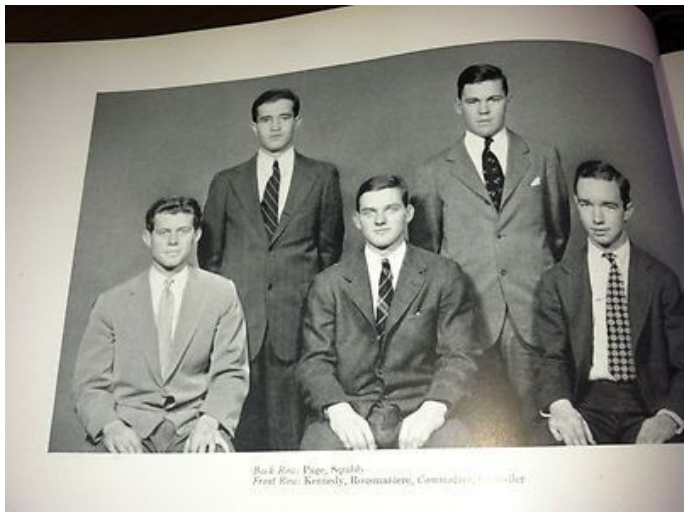
Move Naturally

Right Outlook
- Purpose Now
- Downshift

Eat Wisely
- 80% Rule
- Plant Slant
- Wine@5

Belong
- Right Tribe
- Community
- Loved Ones First





Harvard students 1940

JFK

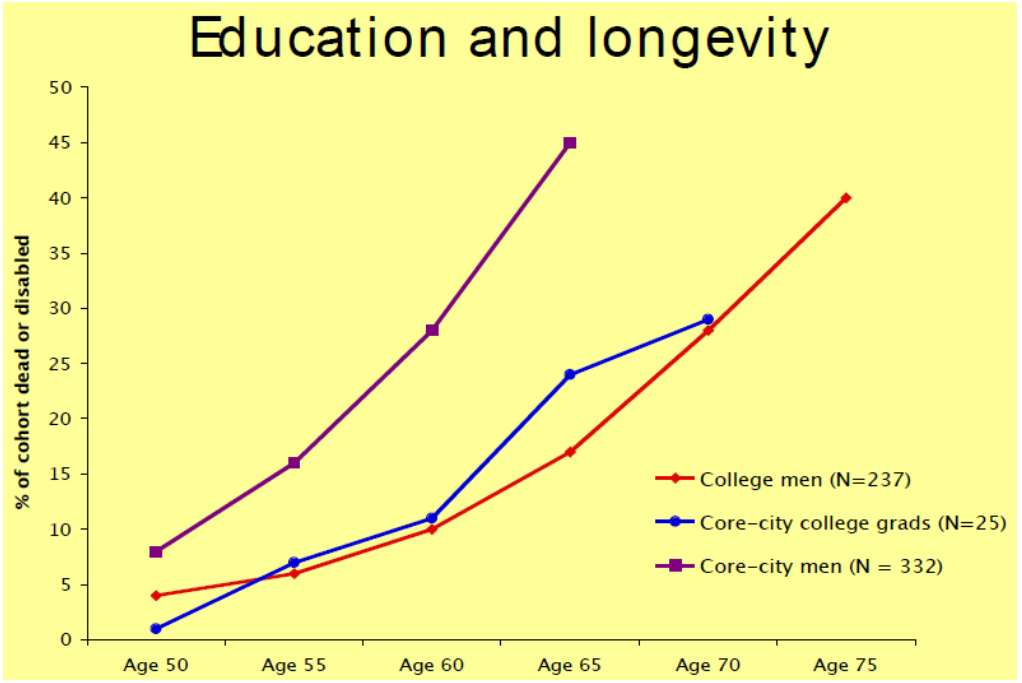
The Study of Adult Development

268 Harvard Sophomores

350 Boston Core-City boys

Have been studied from 1937 until today

Boston 1940



Childhood factors do not predict much about life at age 70- 80

	Age 70- 80			
	Physical Health	Length of Active Life	Life Satisfaction	Mental Health
Warmth of Childhood	+	no	no	++
Childhood Temperament	no	no	no	no
Parental social class	no	no	no	no
Ancestral longevity	no	+	no	no

Factors in midlife that predict how we age

		Age 70- 80			
Age 50		Physical Health	Length of Active Life	Life Satisfaction	Mental Health
	Smoking	↓↓	↓↓	no	↓↓
	Alcohol Abuse	↓↓	↓	↓↓	↓↓
	Exercise	++	++	no	+
	Stable Marriage	+	no	++	++

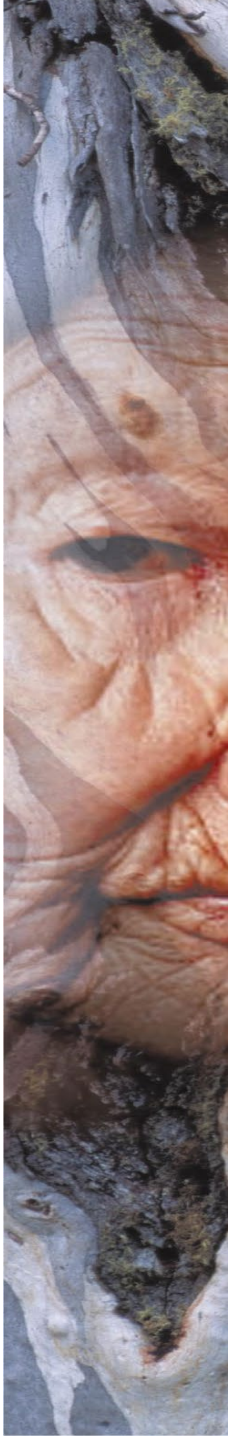
The Harvard Gazette

HEALTH & MEDICINE

Good genes are nice, but joy is better

Harvard study, almost 80 years old, has proved that embracing community helps us live longer, and be happier

Robert J. Waldinger
Harvard Medical School



Blanchette Rockefeller Neurosciences Institute
West Virginia University

SINut
Società Italiana di Nutraceutica

CONSIGLIO NAZIONALE DELLE RICERCHE
ISTITUTO DI SCIENZE NEUROLOGICHE

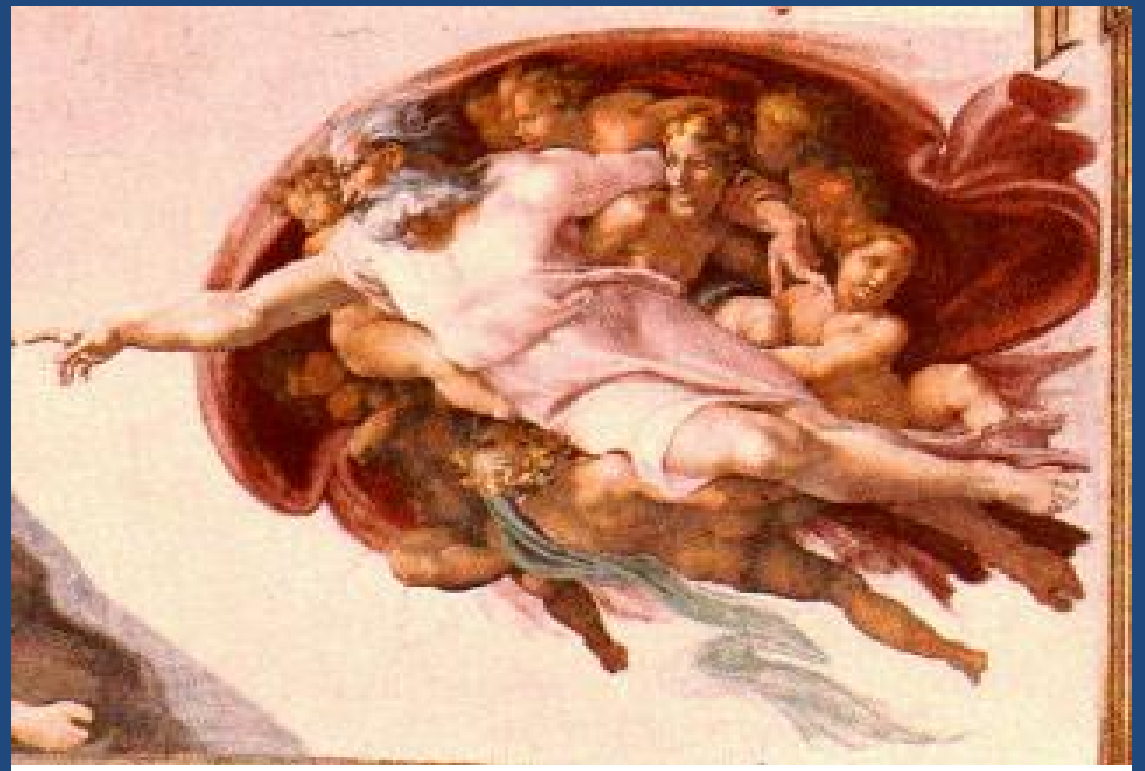
Università degli Studi del Molise
Via De Sanctis - 86100 Campobasso - Tel. +39 0874 4041

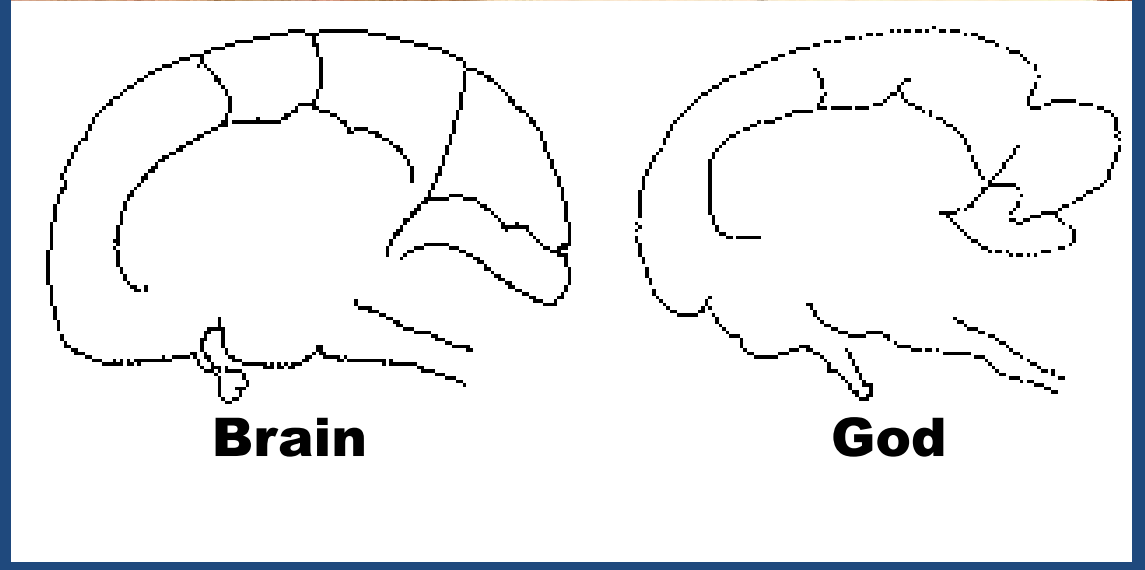
2° lecture

Giovanni Scapagnini, MD, PhD

The creation of Adam by Michelangelo

F.L. Meshberger, *An interpretation of Michelangelo's Creation of Adam Based on Neuroanatomy*, in: "journal of American Medical Ass.", 264, 1990, pp. 1837-41)




Brain
God

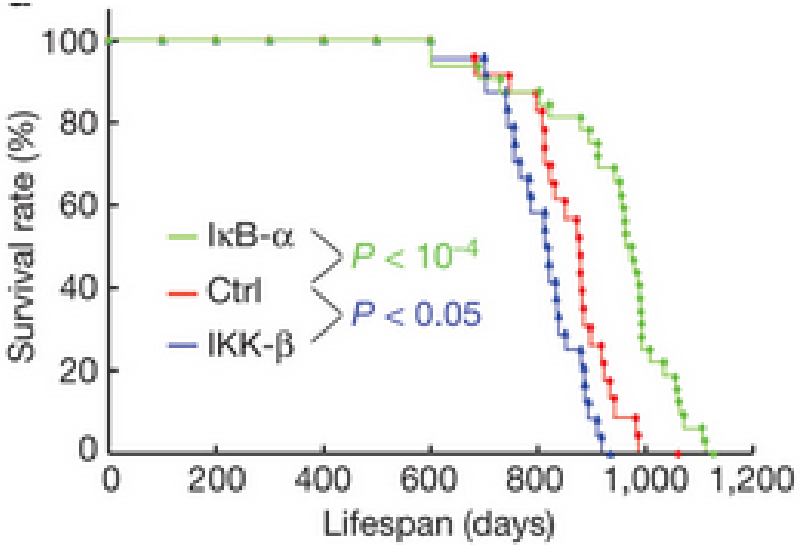
The link between brain and longevity

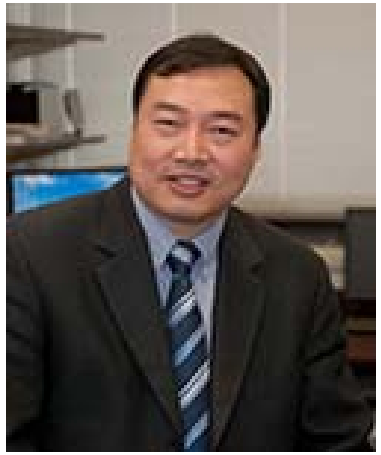
Hypothalamic programming of systemic ageing involving IKK-β, NF-κB and GnRH

Guo Zhang[1,2,3*], Juxue Li[1,2,3*], Sudarshana Purkayastha[1,2,3*], Yizhe Tang[1,2,3*], Hai Zhang[1,2,3*], Ye Yin[1,2,3], Bo Li[1,2,3], Gang Liu[1,2,3] & Dongsheng Cai[1,2,3]

Nature. 2013 May 9;497(7448):211-6. May 1.

Ageing is a result of gradual and overall functional deteriorations across the body; however, it is unknown whether an individual tissue primarily works to mediate the ageing progress and control lifespan. Here we show that the hypothalamus is important for the development of whole-body ageing in mice, and that the underlying basis involves hypothalamic immunity mediated by IκB kinase-β (IKK-β), nuclear factor κB (NF-κB) and related microglia–neuron immune crosstalk. Several interventional models were developed showing that ageing retardation and lifespan extension are achieved in mice by preventing ageing-related hypothalamic or brain IKK-β and NF-κB activation. Mechanistic studies further revealed that IKK-β and NF-κB inhibit gonadotropin-releasing hormone (GnRH) to mediate ageing-related hypothalamic GnRH decline, and GnRH treatment amends ageing-impaired neurogenesis and decelerates ageing. In conclusion, the hypothalamus has a programmatic role in ageing development via immune–neuroendocrine integration, and immune inhibition or GnRH restoration in the hypothalamus/brain represent two potential strategies for optimizing lifespan and combating ageing-related health problems.



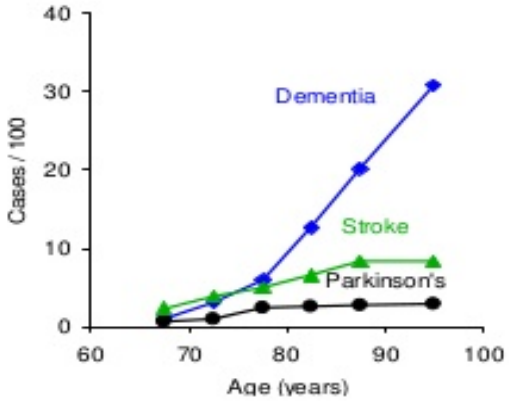


Dongsheng Cai, M.D., Ph.D,
professor of molecular pharmacology
at Albert Einstein College of Medicine, NY

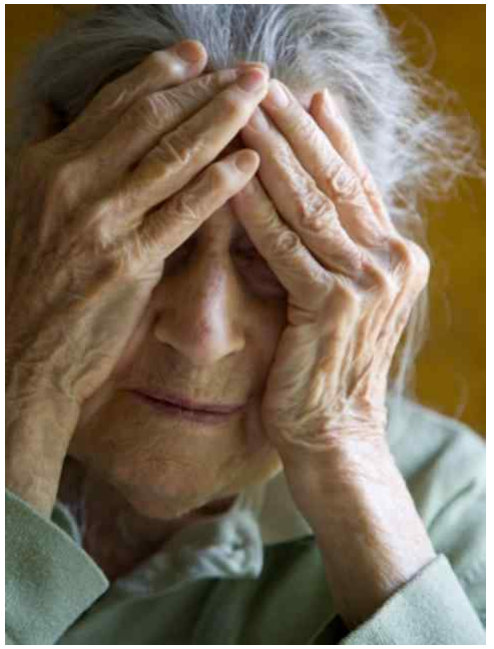
."Scientists have long wondered whether aging occurs independently in the body's various tissues or if it could be actively regulated by an organ in the body,"

"It's clear from our study that many aspects of aging are controlled by the hypothalamus. What's exciting is that it's possible — at least in mice — to alter signaling within the hypothalamus to slow down the aging process and increase longevity."

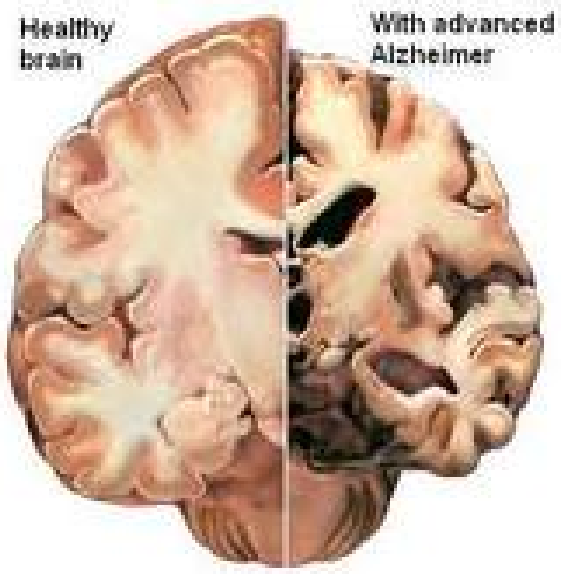
How many dementia cases in the future?

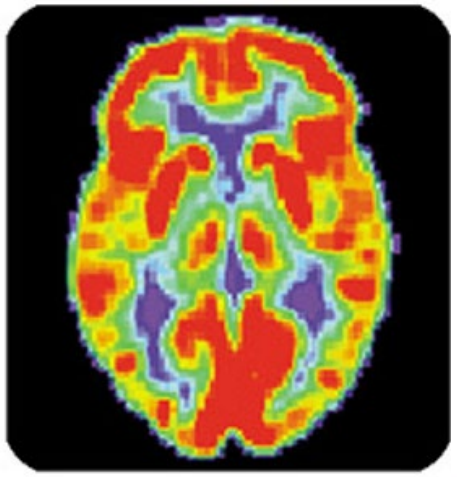


	Number of cases	Societal costs (€)
2010	6,000,000	72,000,000,000
2040	12,000,000	144,000,000,000

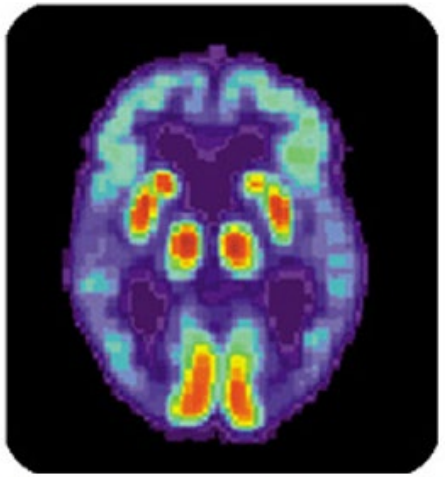


A major societal challenge for the coming years



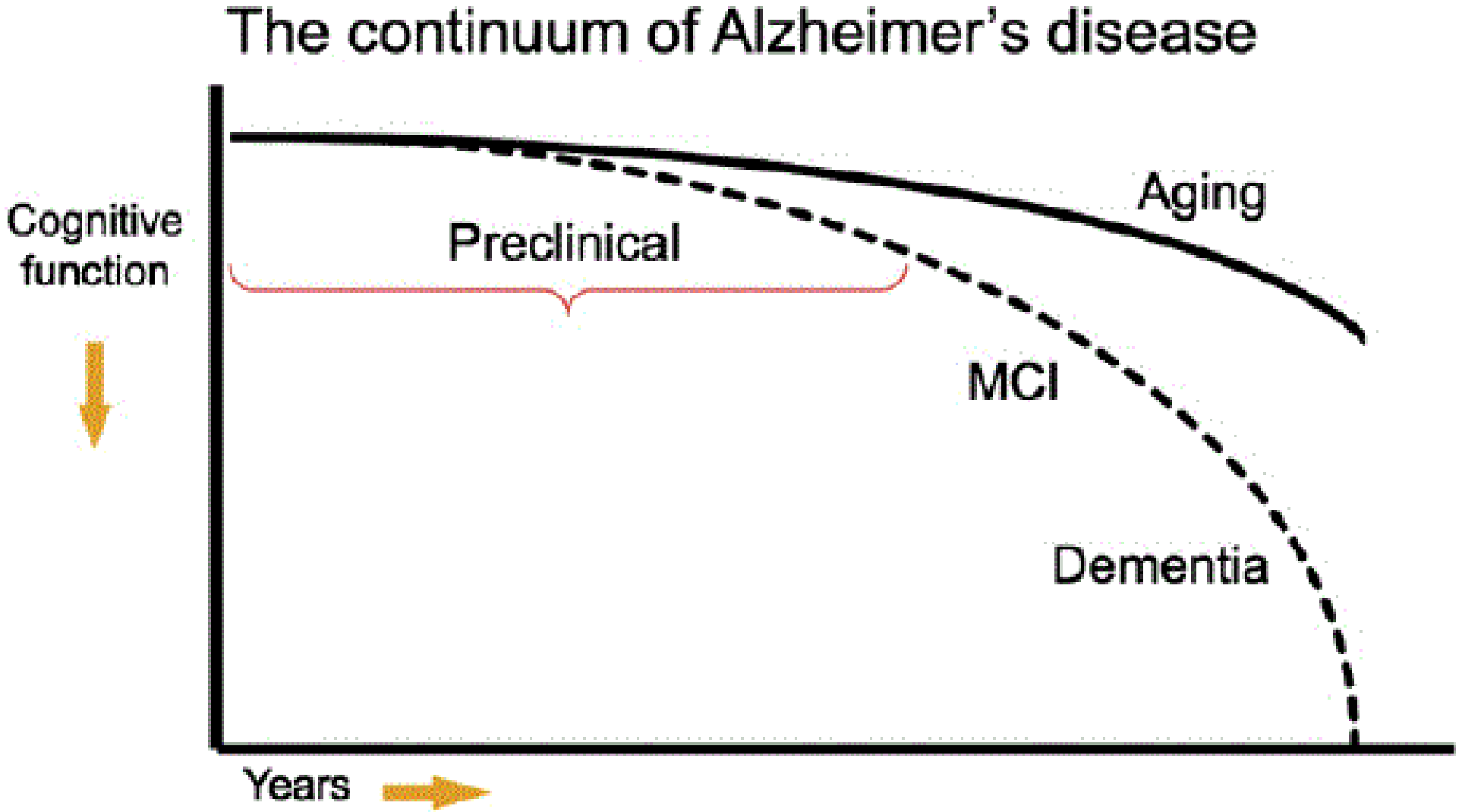


Pet Scan of Normal Brain



Pet Scan of Alzheimer's Disease Brain

Toward defining the preclinical stages of Alzheimer's disease:
Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup



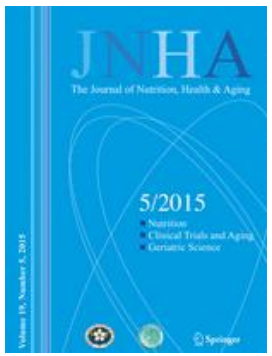
THE JOURNAL OF NUTRITION, HEALTH & AGING©

EPIGENETIC NUTRACEUTICAL DIETS IN ALZHEIMER'S DISEASE

S. DAVINELLI[1,2], V. CALABRESE[2,3], D. ZELLA[4], G. SCAPAGNINI[1,2]

1. Department of Medicine and Health Sciences, University of Molise, Campobasso 86100, Italy; 2. Inter-University Consortium "Sannio Tech", Benevento, 82030, Italy; 3. Department of Biomedical Sciences, University of Catania, Catania, 95124 Italy; 4. Department of Biochemistry and Molecular Biology, University of Maryland-School of Medicine, Baltimore, MD 21201, USA. Corresponding author: Giovanni Scapagnini, Department of Medicine and Health Sciences, University of Molise, Campobasso 86100, Italy, g.scapagnini@gmail.com

Abstract: There is growing support that environmental influences and individual genetic susceptibility may increase the incidence and accelerate the onset of Alzheimer's disease (AD). Epigenetic mechanisms encompass a complex regulatory network of modifications with considerable impact on health and disease risk. Abnormal epigenetic regulation is a hallmark in many pathological conditions including AD. It is well recognized that numerous bioactive dietary components mediate epigenetic modifications associated with the pathophysiology of several diseases. Although the influences of dietary factors on epigenetic regulation have been extensively investigated, only few studies have explored the effects of specific food components in regulating epigenetic patterns during neurodegeneration and AD. Epigenetic nutritional research has substantial potential for AD and may represent a window of opportunity to complement other interventions. Here, we provide a brief overview of the main mechanisms involved in AD, some of which may be epigenetically modulated by bioactive food.



Potentially Relevant Effects of Epigenetic Dietary Compounds in AD

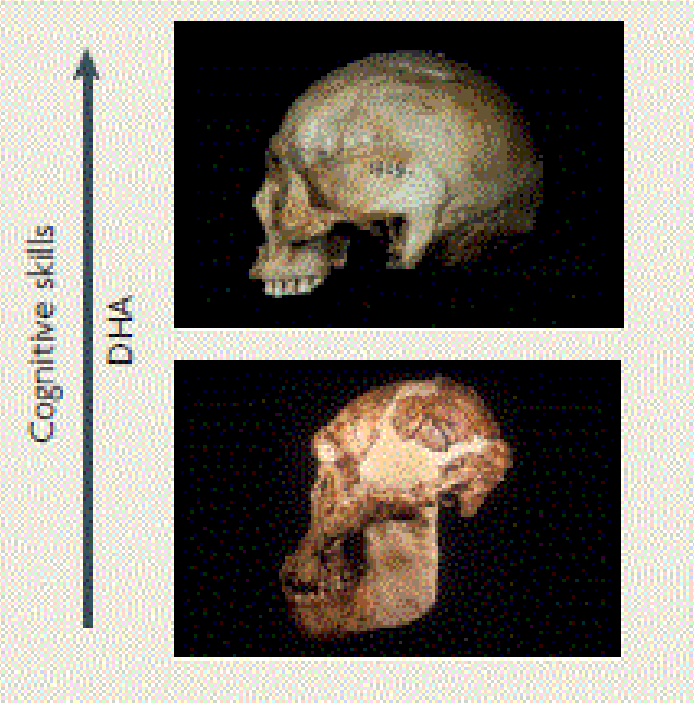
Dietary components	Sources	Epigenetic effects	References
B vitamins	meat and vegetables but B12 vitamin is not available from plant products	DNA methylation	(23, 24)
Resveratrol	grapes, red wine, peanuts	DNA methylation, Histone-modifications, miRNA	(26, 53, 72)
Catechins	green tea, cocoa, blackberries	DNA methylation, Histone-modifications, miRNA	(31, 57, 70, 76)
Caffeic acid	coffee, barley grain	DNA methylation	(32)
Chlorogenic acid	apples, pears, berries	DNA methylation	(32)
Isoflavones	soy products	DNA methylation, Histone-modifications, miRNA	(33, 34, 58, 74)
Isothiocyanates	cruciferous vegetables	DNA methylation	(35)
Sodium butyrate	cheese, butter	Histone-modifications	(45, 46)
Flavonols	grape, blueberry, citrus fruits	Histone-modifications, miRNA	(48, 49, 55, 56, 73)
Curcumin	tumeric	miRNA	(70, 75)

NIH Public Access
Author Manuscript
Nat Rev Neurosci. Author manuscript; available in PMC 2010 January 12.

Published in final edited form as:
Nat Rev Neurosci. 2008 July ; 9(7): 568–578. doi:10.1038/nrn2421.

Brain foods: the effects of nutrients on brain function

Fernando Gómez-Pinilla
Departments of Neurosurgery and Physiological Science, University of California at Los Angeles School of Medicine, Los Angeles 90095, California, USA

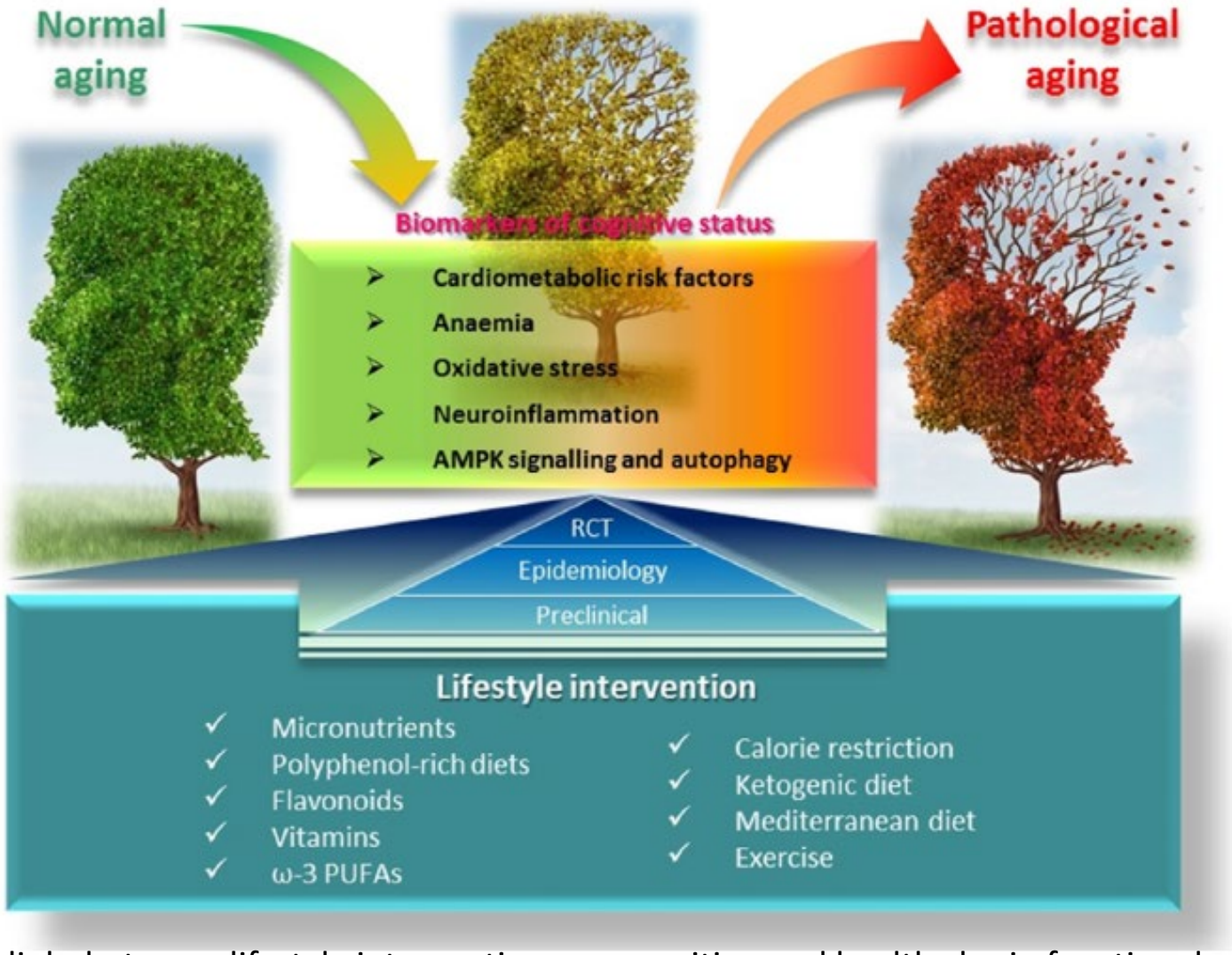


Crawford MA, et al. Evidence for the unique function of docosahexaenoic acid during the evolution of the modern hominid brain. Lipids 1999;34 (Suppl):39–47.

Ageing Research Reviews

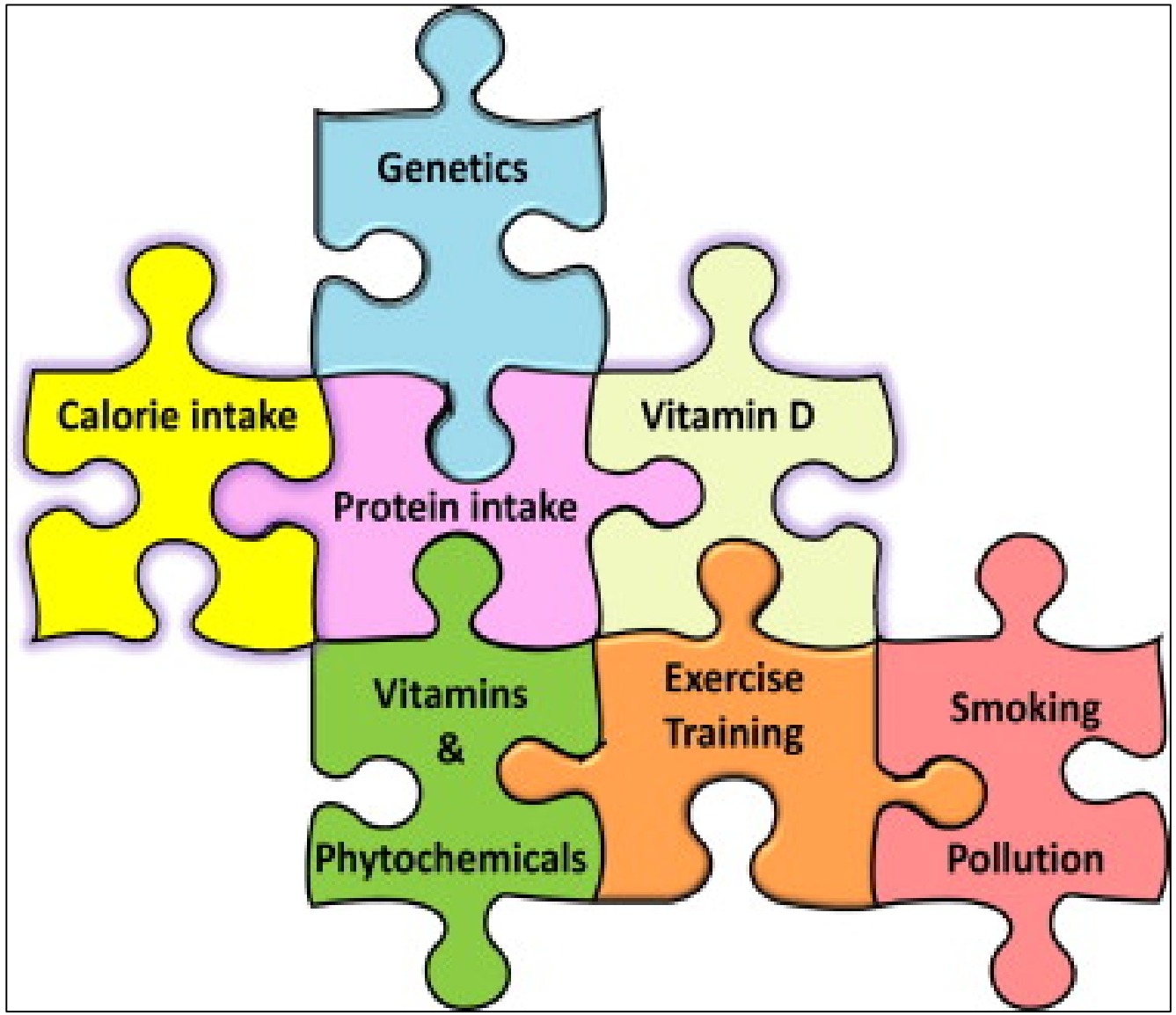
Nutrition for the ageing brain: Towards evidence for an optimal diet

Vauzour D, et al. 2016



Overview of links between lifestyle interventions on cognition and healthy brain function during ageing.

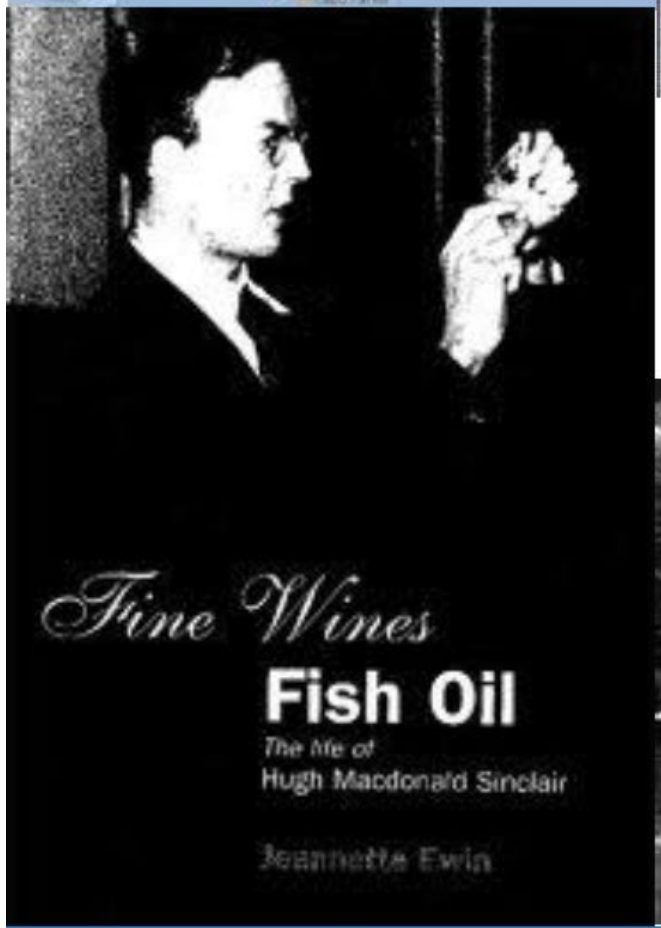
The Longevity Puzzle:
Determinants of Healthy Longevity



Interaction between:

- **Genes**
- **Environment**
- **Lifestyle factors**
  - ✓ **Diet**
  - ✓ **Physical activity**

Ageing Res Rev. 2014; 13:38-45

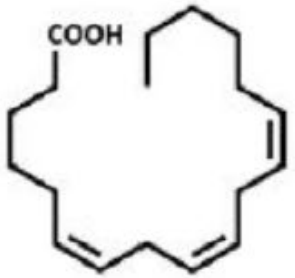


The Connection Between Fats and Heart Diseases

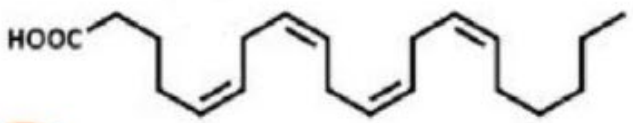
1969, Bang & Dyerberg: investigation in Greenland near absence of thrombotic heart diseases in Greenlanders

OMEGA 6

linoleic acid
LA

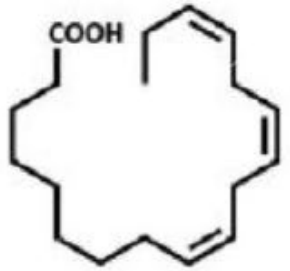


gamma linolenic acid
GLA

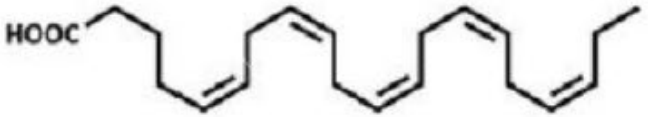


arachidonic acid
AA

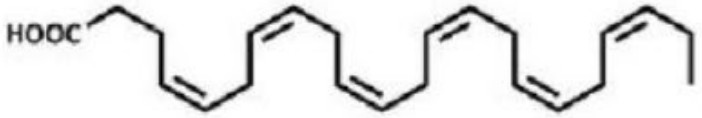
OMEGA 3



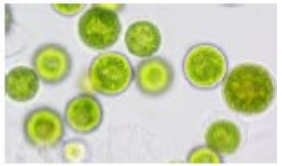
alpha linolenic acid
ALA



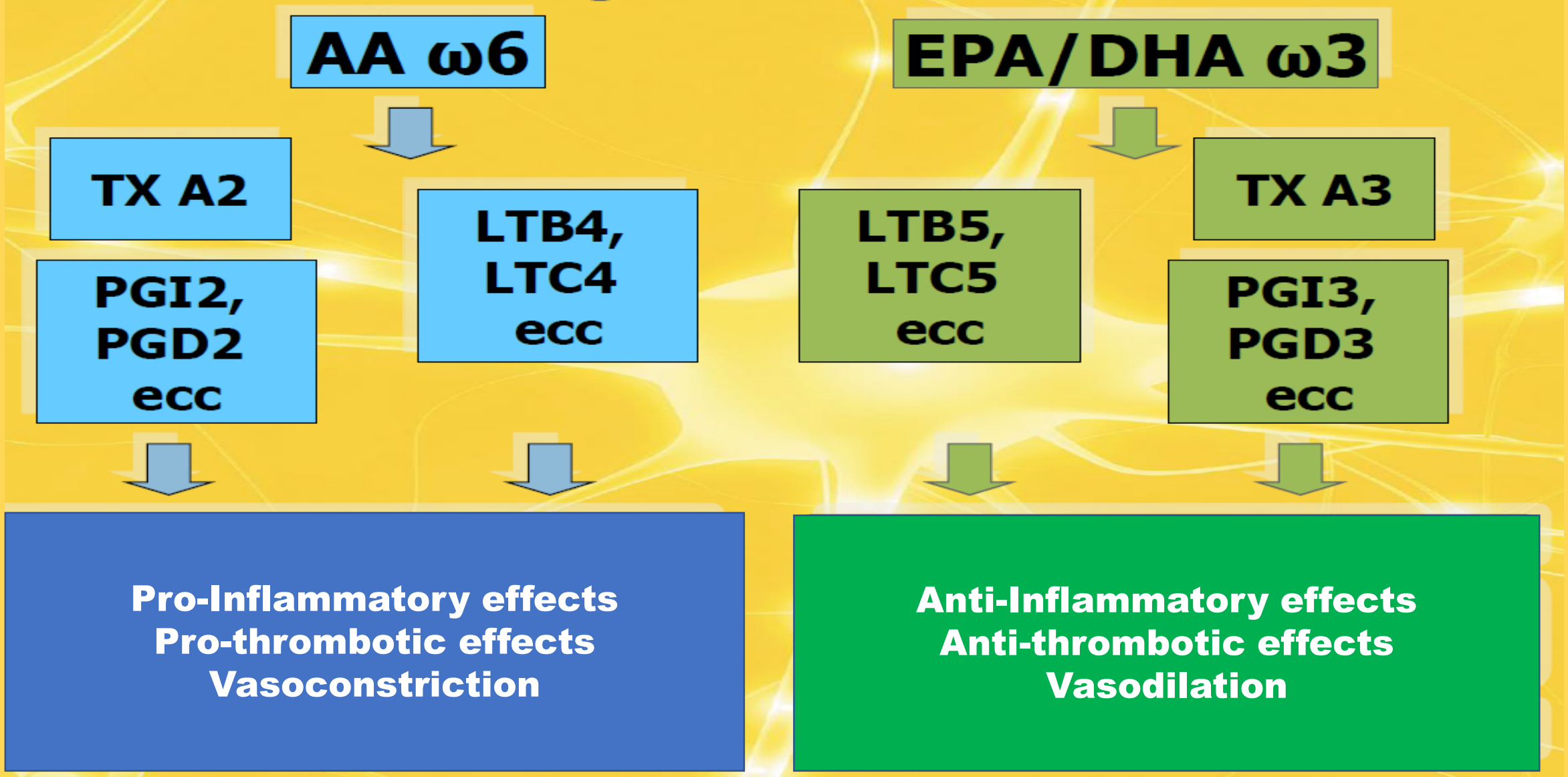
eicosapentaenoic acid
EPA



docosahexanoic acid
DHA



Long Chain PUFA

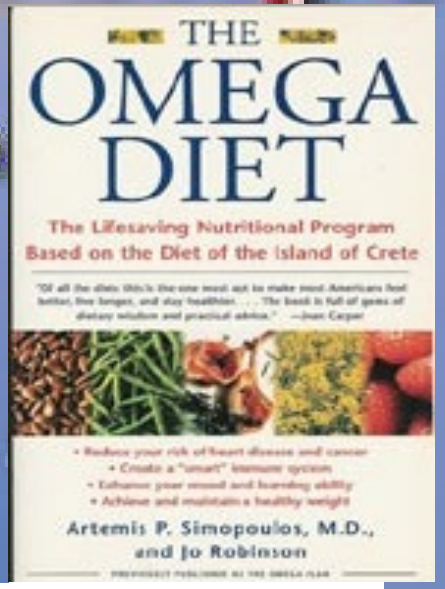


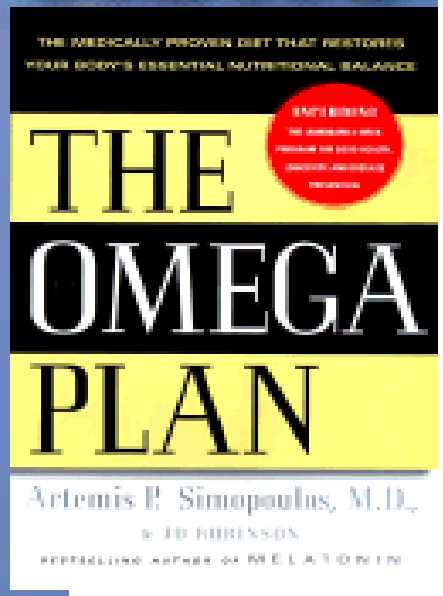
Evolutionary Aspects of Diet: Omega-6/Omega-3 Fatty Acid Ratio

Dr. Artemis P. Simopoulos

President and Founder
The Center for Genetics, Nutrition and Health,

Washington, DC





Journal of Nutrigenetics and Nutrigenomics

J Nutrigenet Nutrigenomics 2014;7:191–211
DOI: 10.1159/000375495
Received: December 30, 2014
Accepted: January 24, 2015
Published online: March 4, 2015

© 2015 S. Karger AG, Basel
1661–6499/15/0076–0191$39.50/0
www.karger.com/jnn

Original Paper

The Impact of the Bellagio Report on Healthy Agriculture, Healthy Nutrition, Healthy People: Scientific and Policy Aspects and the International Network of Centers for Genetics, Nutrition and Fitness for Health

Artemis P. Simopoulos

The Center for Genetics, Nutrition and Health, Washington, D.C., USA

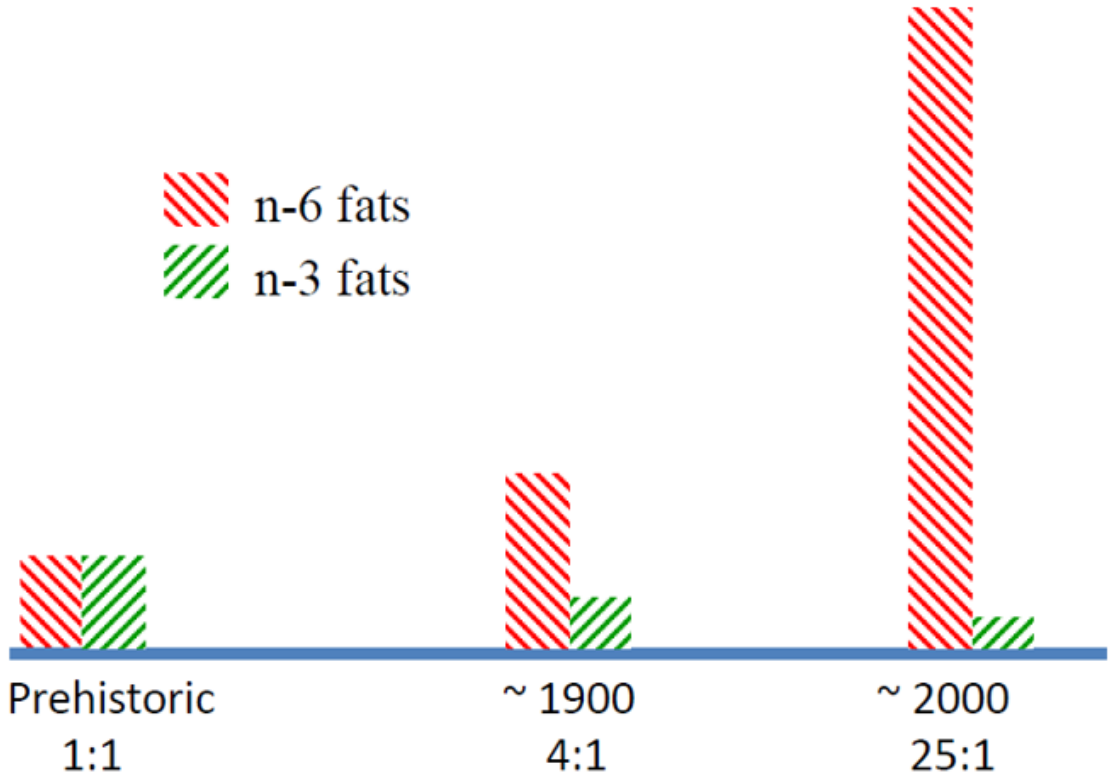
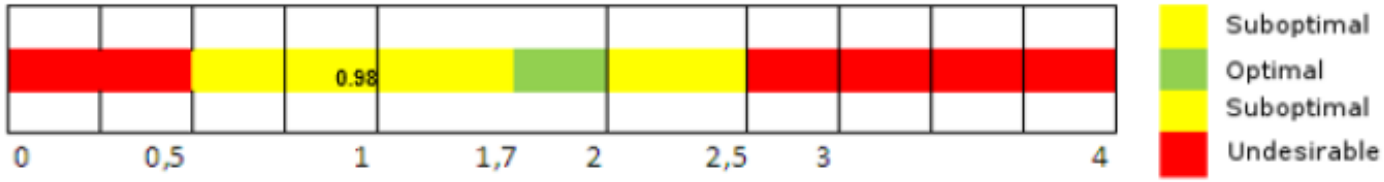


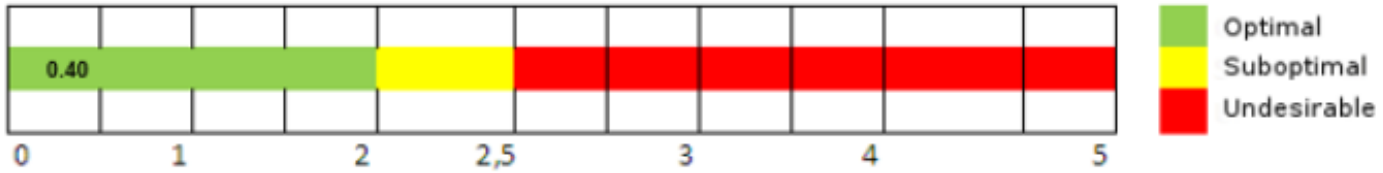
Table 5. International Network of Centers for Genetics, Nutrition and Fitness for Health (directors)

Last name	First name	Title/affiliation	City/country
Allayee	Hooman	Associate Professor, Department of Preventive Medicine, University of Southern California Keck School of Medicine, Los Angeles, Calif., USA	Los Angeles, Calif., USA
Cesuroglu	Tomris	Researcher, Department of Social Medicine, Maastricht University, Maastricht, The Netherlands	Maastricht, The Netherlands
Chrousos	George	Professor and Chairman, Department of Pediatrics, University of Athens, Athens, Greece	Athens, Greece
Gopalan	Sarath	Executive Director, Centre for Research on Nutrition Support Systems (CRNSS), New Delhi, India	New Delhi, India
Johnson	Richard	Professor of Medicine, Chief, Division of Renal Diseases and Hypertension, University of Colorado, Denver, Colo., USA	Denver, Colo., USA
Kang	Jing	Associate Professor of Medicine, Director, Laboratory for Lipid Medicine and Technology, Massachusetts General Hospital and Harvard Medical School, Boston, Mass., USA	Boston, Mass., USA
Kohlmeier	Martin	Professor, University of North Carolina School of Public Health, Chapel Hill, N.C., USA	Raleigh, N.C., USA
Li	Duo	Professor, Department of Food Science and Nutrition, Zhejiang University, Hangzhou, China	Shanghai Pudong, China
Marcos	Ascensión	Research Professor, Spanish National Research Council, Madrid, Spain	Madrid, Spain
Savas	Serdar	President, Turkish Society of Public Health Genomics and Personalized Medicine, Istanbul, Turkey	Istanbul, Turkey
Scapagnini	Giovanni	Associate Professor, Department of Medicine and Heath Science, University of Molise, Campobasso, Italy	Campobasso, Italy
Schmidt	Laura	Professor, Philip R. Lee Institute for Health Policy Studies and Department of Anthropology, History and Social Medicine, School of Medicine, University of California at San Francisco, San Francisco, Calif., USA	San Francisco, Calif., USA
Simopoulos	Artemis	President, The Center for Genetics, Nutrition and Health, Washington, D.C., USA	Washington, D.C., USA
Waitzberg	Dan	Associate Professor, Department of Gastroenterology, University of São Paulo Medical School, São Paulo, Brazil	São Paulo, Brazil

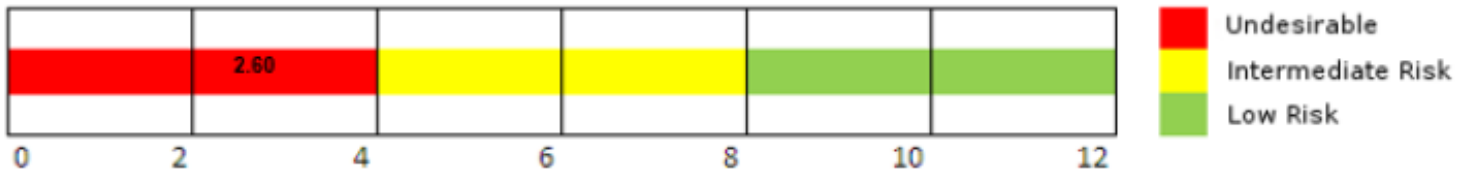
SFA/MUFA



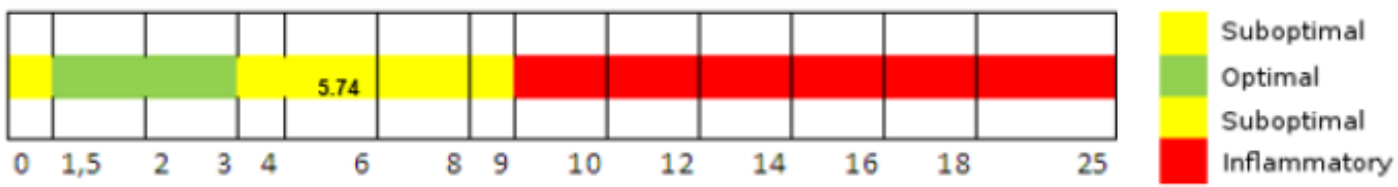
Trans Fat Index



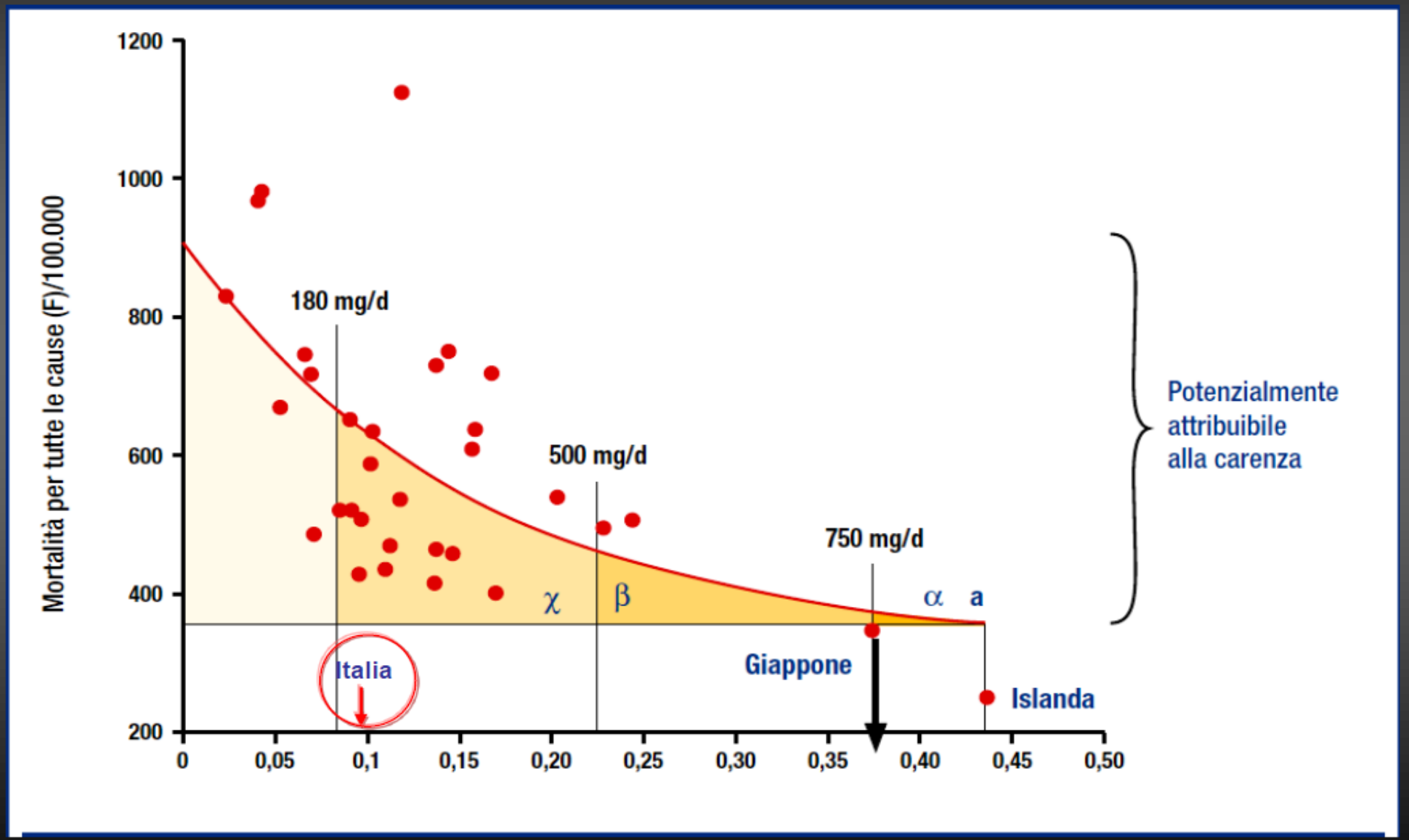
Omega-3 Index



AA/EPA Ratio



Livelli di assunzione di omega 3 con la dieta e riduzione del rischio di mortalità per tutte le cause (da Hibbeln et al., 2006, mod.)

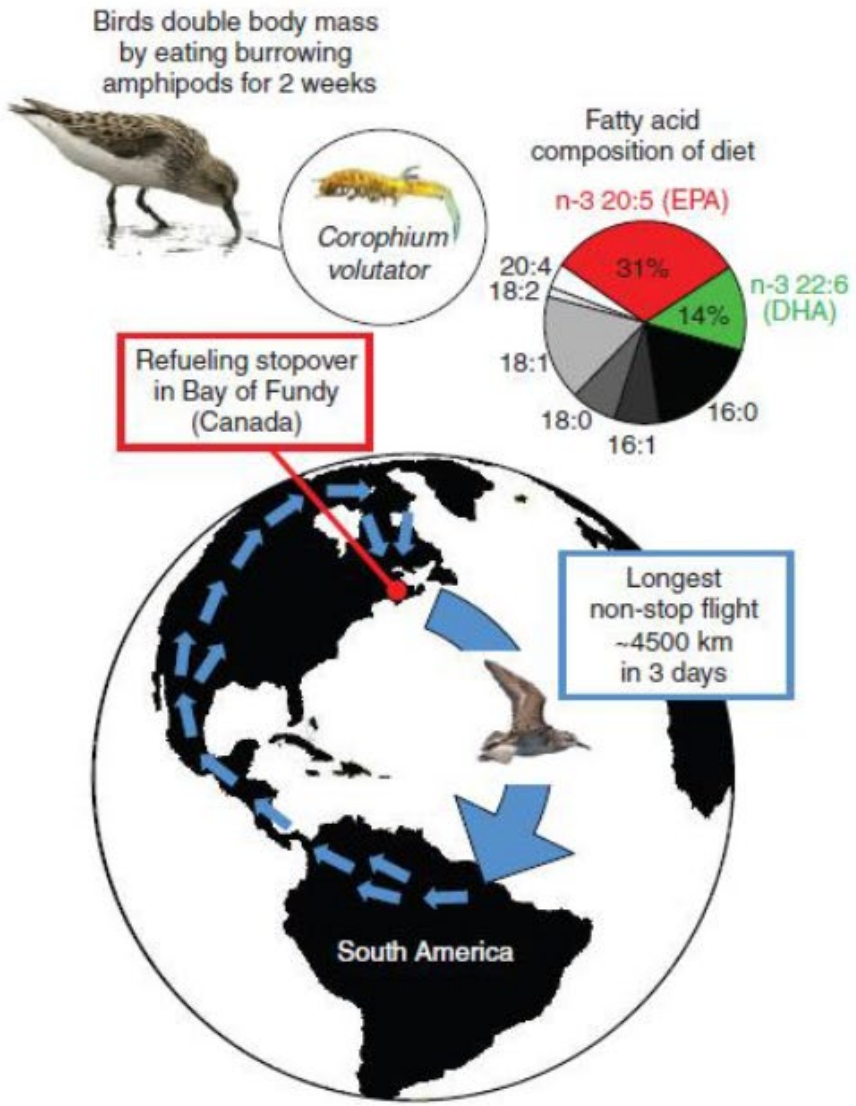


The physiology of long-distance migration: extending the limits of endurance metabolism

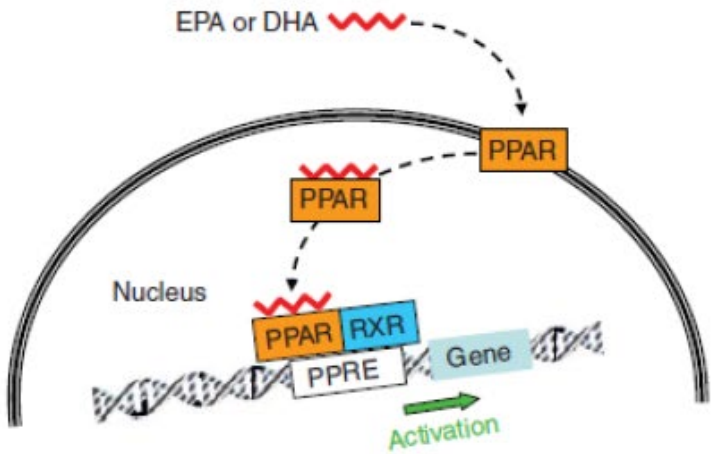
Jean-Michel Weber
Department of Biology, University of Ottawa, Ontario, Canada

The Journal of Experimental Biology 212, 593-597
Published by The Company of Biologists 2009
doi:10.1242/jeb.015024

Migration cycle of the semipalmated sandpiper (*Calidris pusilla*)



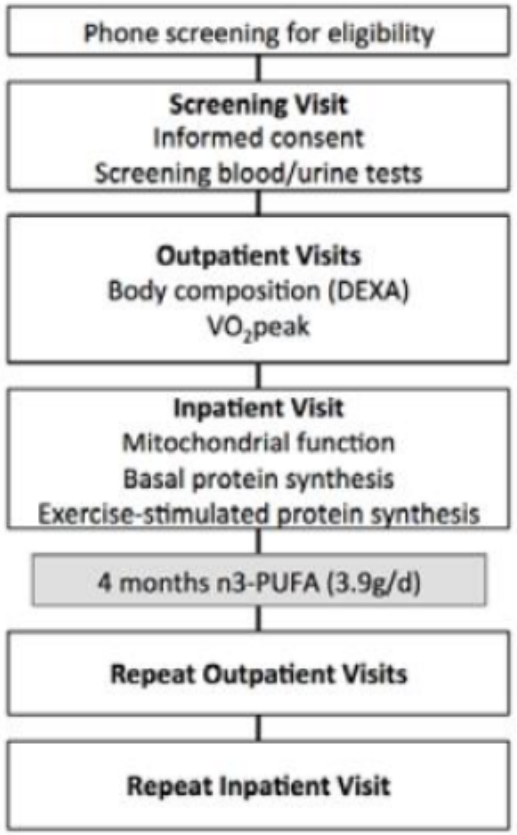
Natural doping by binding of n-3 fatty acids to PPARα and β

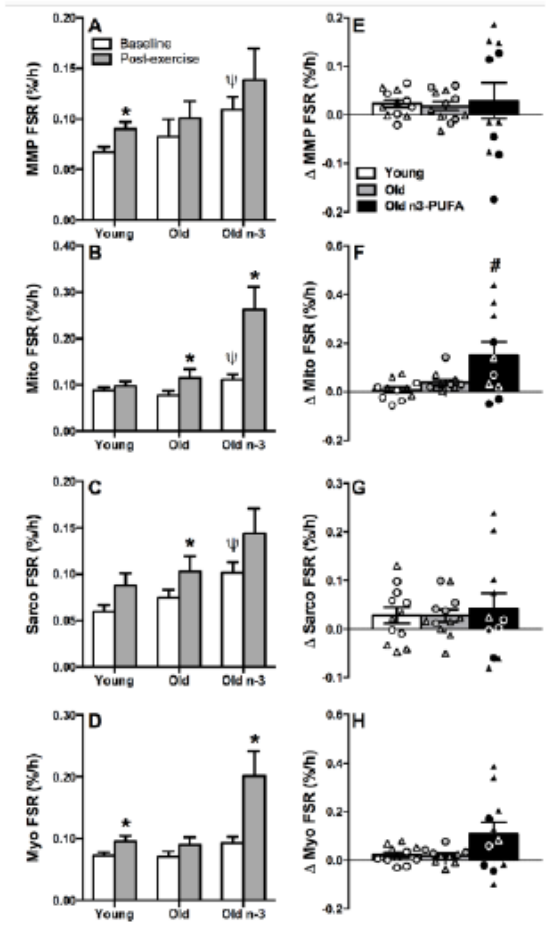


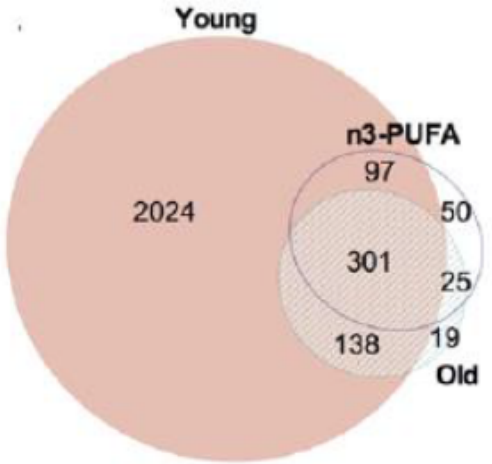
Research Paper

Influence of omega-3 fatty acids on skeletal muscle protein metabolism and mitochondrial bioenergetics in older adults

Antigoni Z. Lalia[1], Surendra Dasari[1], Matthew M. Robinson[1], Hinnah Abid[1], Dawn M. Morse[1], Katherine A. Klaus[1], Ian R. Lanza[1]







Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging

Z.S. Tan, MD, MPH
W.S. Harris, PhD
A.S. Beiser, PhD
R. Au, PhD
J.J. Himali, MS
S. Debette, MD
A. Pikula, MD
C. DeCarli, MD
P.A. Wolf, MD
R.S. Vasan, MD
S.J. Robins, MD
S. Seshadri, MD

Neurology 78 February 28, 2012

ABSTRACT

Objective: Higher dietary intake and circulating levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have been related to a reduced risk for dementia, but the pathways underlying this association remain unclear. We examined the cross-sectional relation of red blood cell (RBC) fatty acid levels to subclinical imaging and cognitive markers of dementia risk in a middle-aged to elderly community-based cohort.

Methods: We related RBC DHA and EPA levels in dementia-free Framingham Study participants (n = 1,575; 854 women, age 67 ± 9 years) to performance on cognitive tests and to volumetric brain MRI, with serial adjustments for age, sex, and education (model A, primary model), additionally for *APOE* ε4 and plasma homocysteine (model B), and also for physical activity and body mass index (model C), or for traditional vascular risk factors (model D).

Results: Participants with RBC DHA levels in the lowest quartile (Q1) when compared to others (Q2–4) had lower total brain and greater white matter hyperintensity volumes (for model A: $\beta \pm SE = -0.49 \pm 0.19$; $p = 0.009$, and 0.12 ± 0.06; $p = 0.049$, respectively) with persistence of the association with total brain volume in multivariable analyses. Participants with lower DHA and ω-3 index (RBC DHA+EPA) levels (Q1 vs Q2–4) also had lower scores on tests of visual memory ($\beta \pm SE = -0.47 \pm 0.18$; $p = 0.008$), executive function ($\beta \pm SE = -0.07 \pm 0.03$; $p = 0.004$), and abstract thinking ($\beta \pm SE = -0.52 \pm 0.18$; $p = 0.004$) in model A, the results remaining significant in all models.

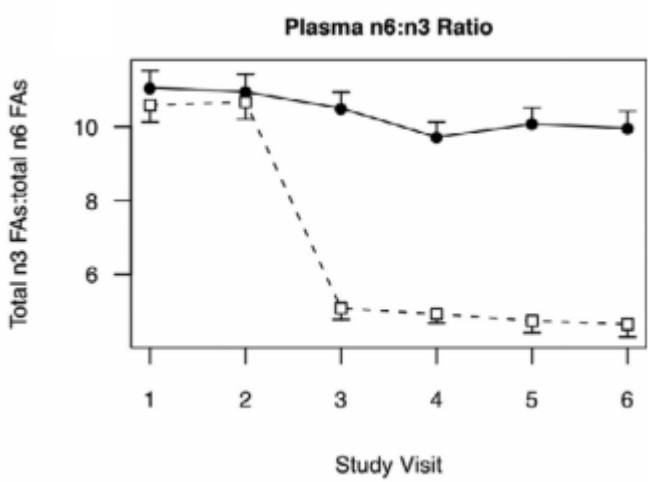
Conclusion: Lower RBC DHA levels are associated with smaller brain volumes and a "vascular" pattern of cognitive impairment even in persons free of clinical dementia. *Neurology*® 2012;78:658–664

Brain Behav Immun. 2011 November ; 25(8): 1725–1734.

Omega-3 Supplementation Lowers Inflammation and Anxiety in Medical Students: A Randomized Controlled Trial

Janice K. Kiecolt-Glaser[a,b,*], **Martha A. Belury**[c], **Rebecca Andridge**[d], **William B. Malarkey**[a,b,e], and **Ronald Glaser**[a,f]

planned secondary analyses that used the plasma n-6:n-3 ratio in place of treatment group showed that decreasing n-6:n-3 ratios led to lower anxiety and reductions in stimulated IL-6 and tumor necrosis factor alpha (TNF-α) production, as well as marginal differences in serum TNF-α.



Results from models using continuous *n*-6:*n*-3 plasma ratio to predict primary and secondary outcomes (natural log-transformed)

	Estimate (SE)	95% CI	P value
Primary Outcomes			
Serum Cytokines			
log(IL-6)	0.0095 (0.012)	−0.014 to 0.033	.43
log(TNF-α)	0.0089 (0.0047)	−0.0004 to 0.018	.06
Stimulated Cytokines			
log(IL-6)	0.021 (0.010)	0.0016 to 0.040	.03
log(TNF-α)	0.021 (0.010)	0.0006 to 0.042	.04
Secondary Outcomes			
Mood			
Beck Anxiety, log	0.039 (0.015)	0.0098 to 0.069	.01
CES-D, log	0.0061 (0.017)	−0.027 to 0.039	.72

* Least squares means adjusted for baseline value, visit, and gender. Cytokine models additionally adjusted for SAD

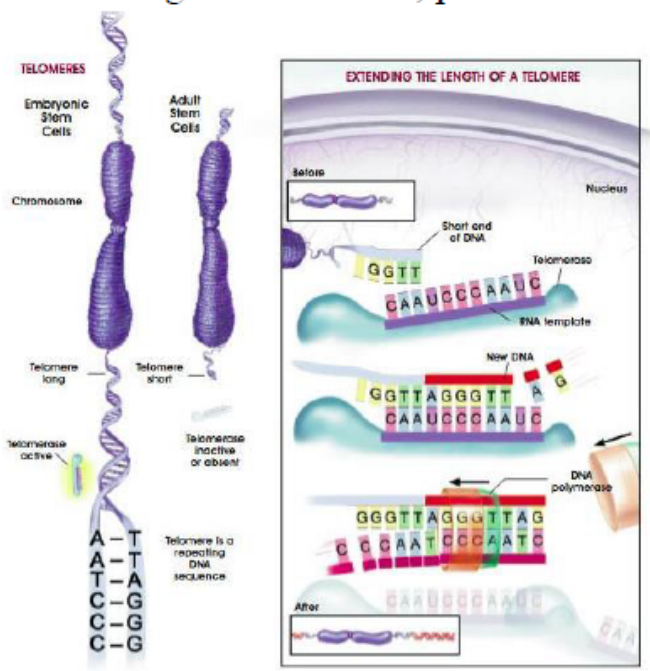
Note: All outcomes are natural log-transformed.

Brain Behav Immun. 2013 February ; 28: 16–24. doi:10.1016/j.bbi.2012.09.004.

Omega-3 Fatty Acids, Oxidative Stress, and Leukocyte Telomere Length: A Randomized Controlled Trial

Janice K. Kiecolt-Glaser[a,1], **Elissa S. Epel**[b], **Martha A. Belury**[c], **Rebecca Andridge**[d], **Jue Lin**[e], **Ronald Glaser**[a], **William B. Malarkey**[a], **Beom Seuk Hwang**[d], and **Elizabeth Blackburn**[e]

The double-blind 4-month trial included 106 healthy sedentary overweight middle-aged and older adults who received (1) 2.5 g/day n-3 PUFAs, (2) 1.25 g/day n-3 PUFAs, or (3) placebo capsules that mirrored the proportions of fatty acids in the typical American diet. Supplementation significantly lowered oxidative stress as measured by F2-isoprostanes (p=0.02). The estimated geometric mean log-F2-isoprostanes values were 15% lower in the two supplemented groups compared to placebo. Telomere length increased with decreasing n-6:n-3 ratios, p=0.02. The data suggest that lower n-6:n-3 PUFA ratios can impact cell aging.



Linear regression analysis for change in telomere length with change in n-6:n-3 fatty acid plasma ratio, controlling for baseline telomere length.

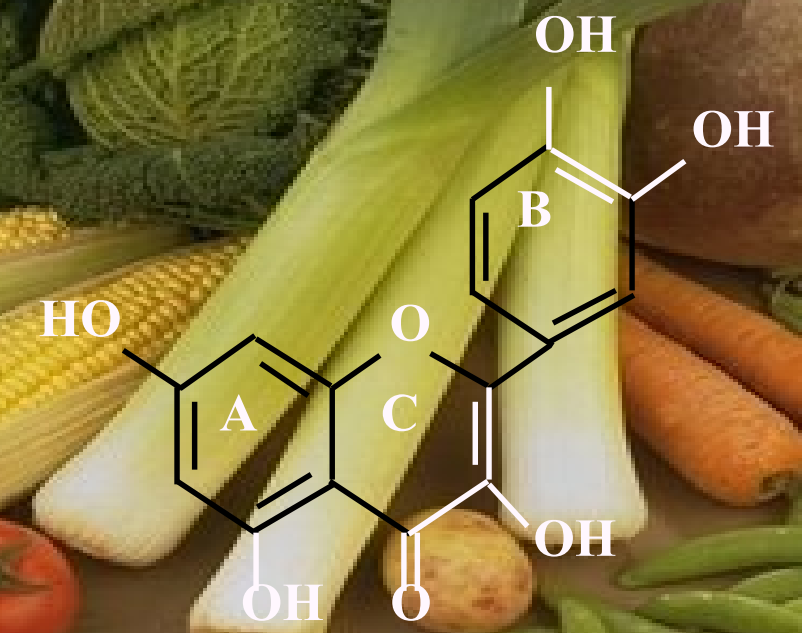
Effect	Estimate	95% CI	P-value
Intercept	1040	(296, 1785)	0.007
Telomere length, baseline	−0.15	(−0.27, −0.031)	0.01
n-6:n3 fatty acids, baseline	−21	(−44, 2.0)	0.07
Decrease in n6:n3 fatty acids[a]	20	(4, 36)	0.02

Units: telomere length = base pairs.

Regression model with change in telomere length (4 months minus baseline) as the outcome

[a]Decrease in *n*-6:n-3 PUFA ratio is calculated as baseline minus 4 months so that a positive value is a decrease in *n*-6:*n*-3 PUFA ratio.

Phenolic Compounds



1998-2001

Azienda Sanitaria Firenze
Servizio Sanitario della Toscana

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2015, Vol. 70, No. 9, 1141–1147

The Relationship Between Urinary Total Polyphenols and the Frailty Phenotype in a Community-Dwelling Older Population: The InCHIANTI Study

Mireia Urpi-Sarda,[1,2] Cristina Andres-Lacueva,[1,2] Montserrat Rabassa,[1,2] Carmelinda Ruggiero,[3] Raul Zamora-Ros,[4] Stefania Bandinelli,[5] Luigi Ferrucci,[6] and Antonio Cherubini[7]

The Journal of Nutrition
Nutritional Epidemiology

J. Nutr. 143: 1445–1450, 2013

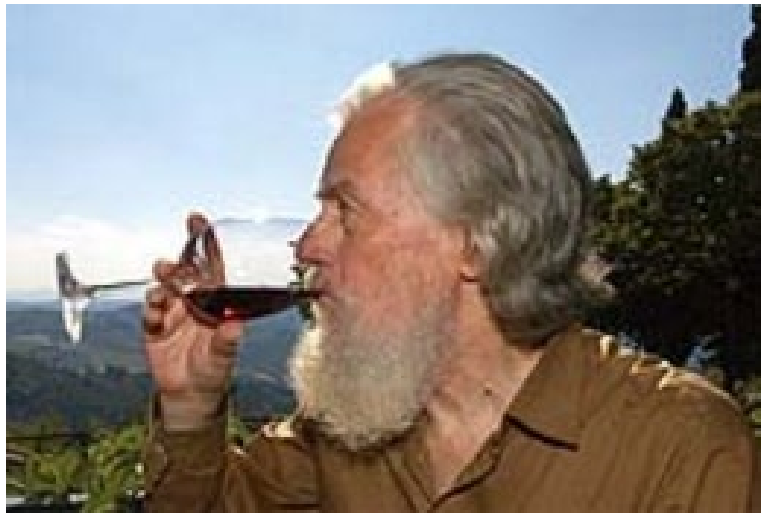
High Concentrations of a Urinary Biomarker of Polyphenol Intake Are Associated with Decreased Mortality in Older Adults[1,2]

Raul Zamora-Ros,[3,4] Montserrat Rabassa,[3] Antonio Cherubini,[5,6]* Mireia Urpí-Sardà,[3] Stefania Bandinelli,[7] Luigi Ferrucci,[8] and Cristina Andres-Lacueva[3]

JAGS 63:938–946, 2015

Low Levels of a Urinary Biomarker of Dietary Polyphenol Are Associated with Substantial Cognitive Decline over a 3-Year Period in Older Adults: The Invecchiare in Chianti Study

Montserrat Rabassa, MSc, Antonio Cherubini, MD, PhD,† Raul Zamora-Ros, PhD,‡ Mireia Urpi-Sarda, DPharm, PhD,* Stefania Bandinelli, MD,§ Luigi Ferrucci, MD, PhD,‖ and Cristina Andres-Lacueva, DPharm, PhD**

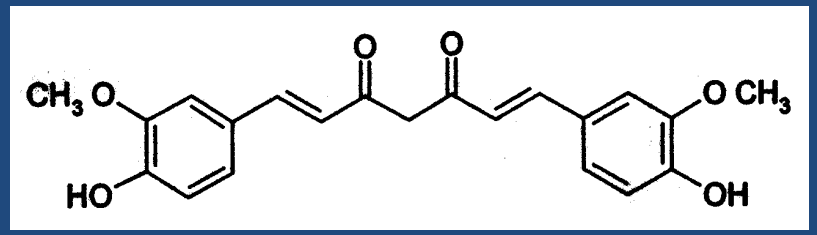


Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A, Calabrese V.

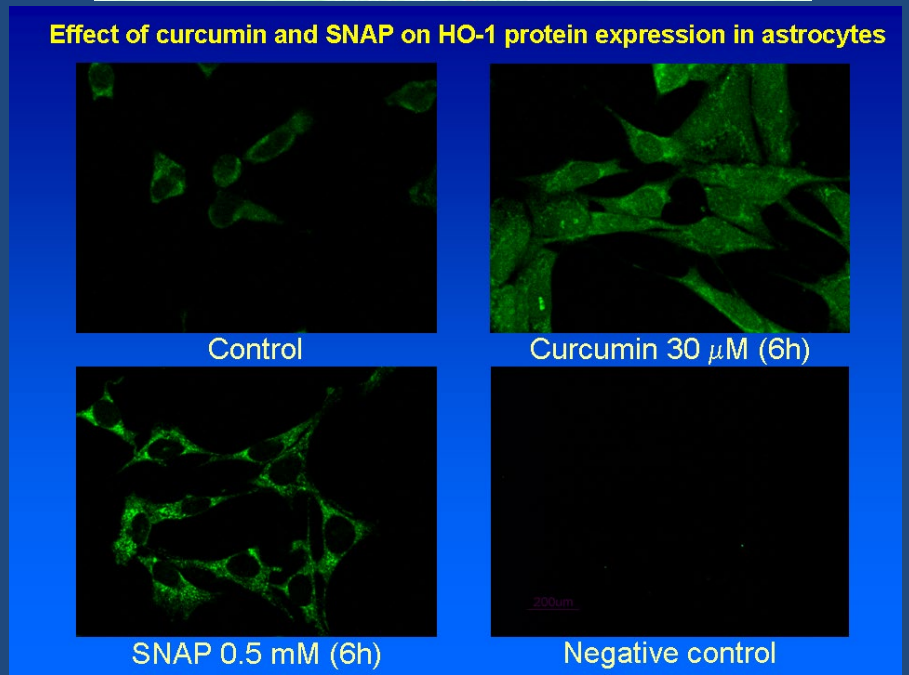
Curcumin activates defensive genes and protects neurons against oxidative stress.

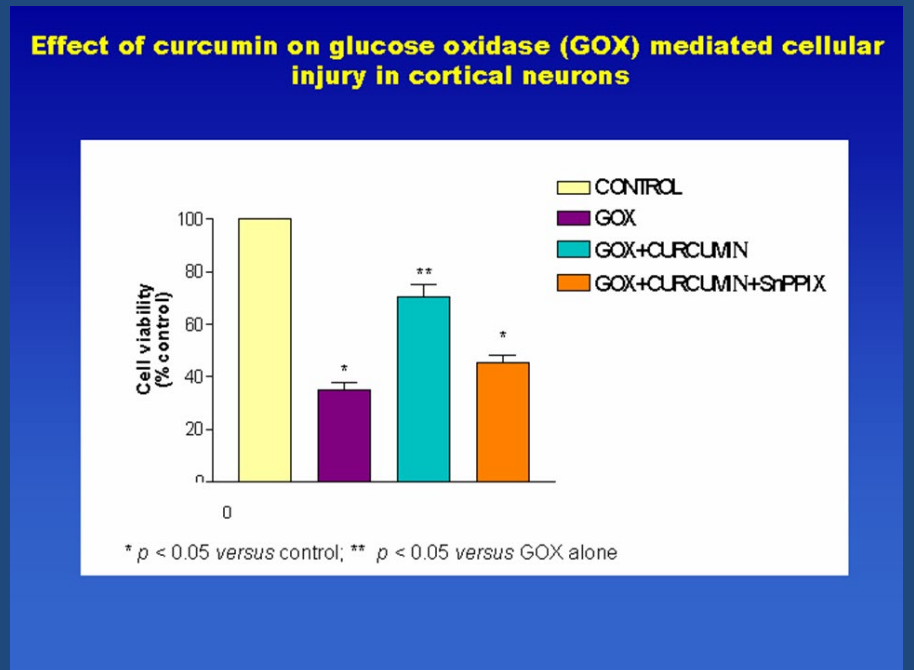
Antioxid Redox Signal. 2006 Mar-Apr;8(3-4):395-403.

Institute of Neurological Sciences, National Research Council (CNR), Catania, Italy.,
Blanchette Rockefeller Neurosciences Institute, West Virginia University, Rockville, Maryland.



CURCUMIN





THE TIMES

April 19, 2004

Health news

Curry keeps Alzheimer's at bay

BY SAM LISTER

THEY may be a challenge to the consumer's constitution, but hot curries do not just test the taste buds and the stomach, they also guard against the deterioration of the brain.

A study into the health benefits of curcumin, found in everything from the mildest korma to the hottest vindaloo, has revealed its power to protect against the onset of Alzheimer's disease.

Scientists have identified curcumin oil as a chemical trigger that enhances enzyme activity, protecting the brain against the progression of neurodegenerative disease.

TIME

FROM THE MAGAZINE

May 3, 2004 Vol. 163 No. 18

YOUR TIME/HEALTH/PAGING DR. GUPTA

Spicing Up Your Life

Got a taste for zesty food? The things that give it zing may also ward off disease

By SANJAY GUPTA

Monday, May. 03, 2004

Since I'm of Indian descent, spicy foods have long been a part of my diet. The distinctive smell of curry often wafted through my childhood home as my mom prepared her deliciously spicy dishes, often served with a dose of "it's good for you." She is a fantastic cook, and it turns out she may have been right about the health benefits of curry as well. According to preliminary research presented last week at a meeting of the American Physiological Society, curcumin, which gives the curry spice tumeric its yellow color, may help protect the brain against Alzheimer's disease.

Scientists have long theorized that free radicals released as we age could be a major cause of Alzheimer's. The new study, conducted by researchers at three centers in Italy, as well as New York Medical

NEW YORK POST

LATE CITY FINAL

CURRY PUTS HEAT ON ALZHEIMER'S

April 20, 2004 -- If you want to protect against Alzheimer's disease, better get some curry in a hurry.

A new study reveals that hot curries can prevent the deterioration of the brain and help prevent the onset of Alzheimer's.

Scientists at New York Medical College and the University of Catania in Italy made the discovery as they looked at the health benefits of curcumin, which is found in most Indian foods.

Guardian Unlimited

The Guardian

Spice of life

It's high in fat and can contain dangerous levels of artificial colourings. But curry, reports Clint Witchalls, could well be good for your health

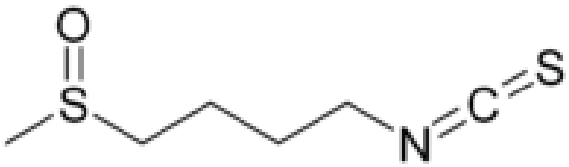
Tuesday April 20, 2004
The Guardian

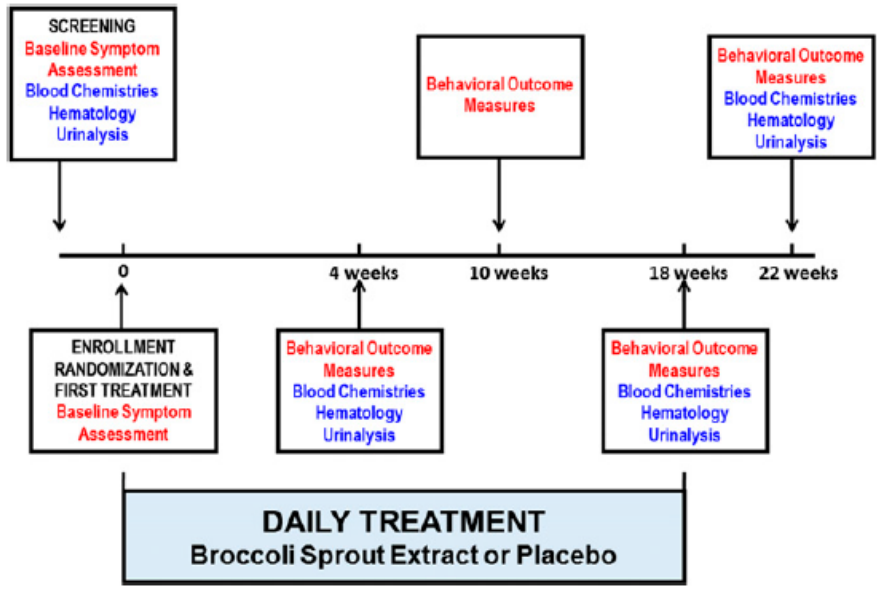
Chicken tikka masala is said to be Britain's favourite dish, but the recent scare about artificial colourings may have put some people off it. Last month, trading standards officers in Surrey found that 58 out of 102 chicken tikka masala samples contained illegal and potentially dangerous levels of artificial colourings. The dyes, such as tartrazine, ponceau, and sunset yellow, have been implicated in a number of disorders, ranging from hyperactivity in children to cancer.

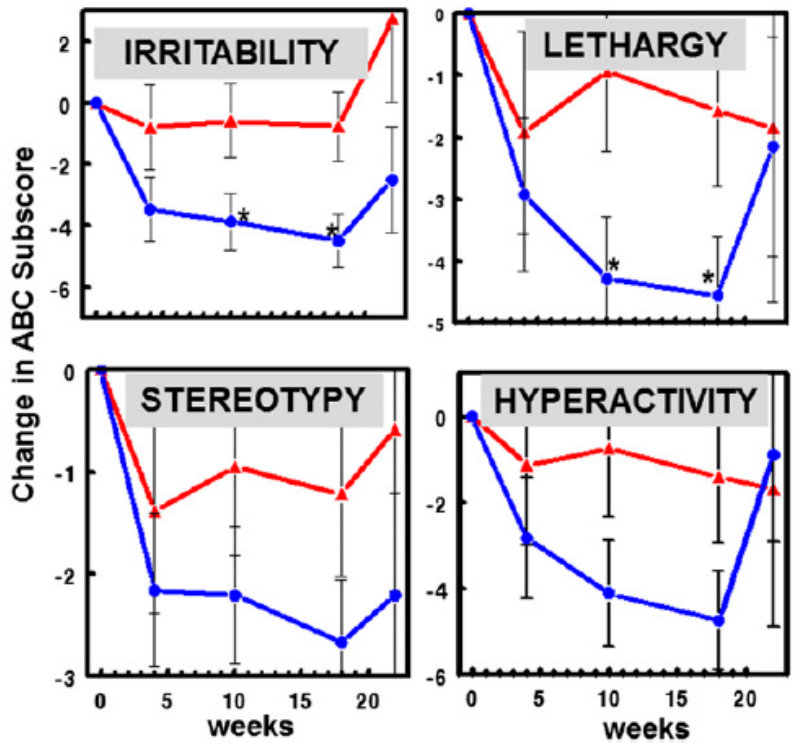
Sulforaphane treatment of autism spectrum disorder (ASD)

PNAS | October 28, 2014 | vol. 111 | no. 43

Kanwaljit Singh[a,b], Susan L. Connors[a], Eric A. Macklin[c], Kirby D. Smith[d], Jed W. Fahey[e], Paul Talalay[e,1], and Andrew W. Zimmerman[a,b,1]







Cocoa phytochemicals, a story of positive biology

International Journal of Medical Sciences
ISSN 1449-1907 www.medsci.org 2007 4(1):53-58
© Ivyspring International Publisher. All rights reserved

Research Paper

Does Flavanol Intake Influence Mortality from Nitric Oxide-Dependent Processes? Ischemic Heart Disease, Stroke, Diabetes Mellitus, and Cancer in Panama

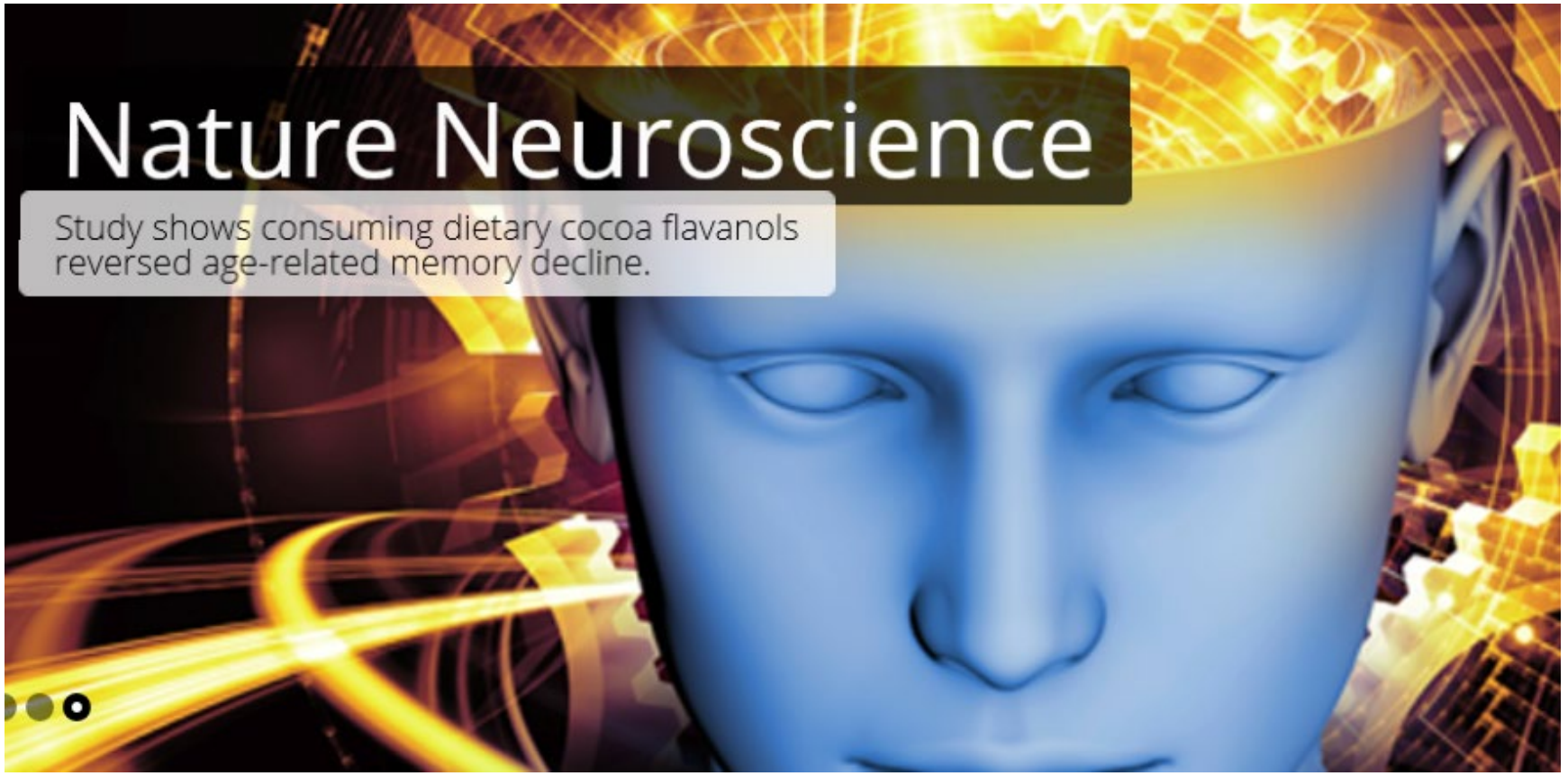
Vicente Bayard [1], Fermina Chamorro [1], Jorge Motta [2], and Norman K. Hollenberg [3]

1. Instituto Commemorative Gorgas de Estudios de la Salud and The Department of Preventive Medicine, School of Medicine, University of Panama, Panama City, PANAMA, and Gorgas Institute, Panama City, PANAMA;
2. Instituto Commemorative Gorgas de Estudios de la Salud, Panama City, PANAMA;
3. Brigham and Women's Hospital, and Harvard Medical School, Boston, Massachusetts, USA.

Correspondence to: Norman K. Hollenberg, M.D., Ph.D., Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Tel: (617) 732-6682; Fax: (617) 232-2869; e-mail: djpagecapo@rics.bwh.harvard.edu

Panama

Cocoa epicatechins improve cognition

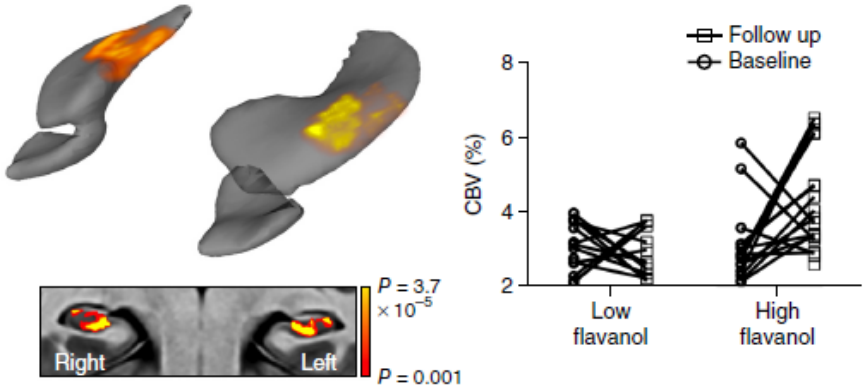


VOLUME 17 | NUMBER 12 | DECEMBER 2014 NATURE NEUROSCIENCE

Enhancing dentate gyrus function with dietary flavanols improves cognition in older adults

Adam M Brickman[1,2,8], Usman A Khan[1,2,8], Frank A Provenzano[1,2,8], Lok-Kin Yeung[1,2], Wendy Suzuki[3], Hagen Schroeter[4], Melanie Wall[5,6], Richard P Sloan[5,6] & Scott A Small[1,2,5,7]

In a controlled randomized trial, healthy 50–69-year-old subjects consumed either a high or low cocoa flavanol–containing diet for 3 months. A high-flavanol intervention was found to enhance DG function, as measured by fMRI and by cognitive testing.



USA, COcoa Supplement and Multivitamin Outcomes Study (COSMOS)

COSMOS will enroll 18,000 women and men nationwide, making it the largest dietary intervention study to evaluate the health benefits of cocoa flavanols and a multivitamin.

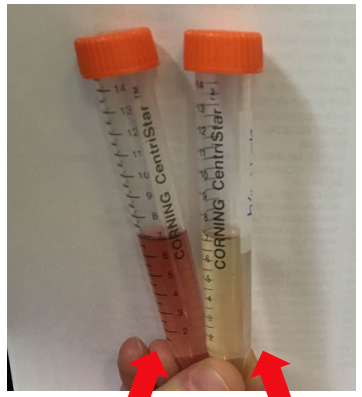
BRIGHAM AND WOMEN'S HOSPITAL
Cardiovascular Division

HARVARD MEDICAL SCHOOL
Teaching Affiliate

MARS
center for Cocoa health science

Pfizer

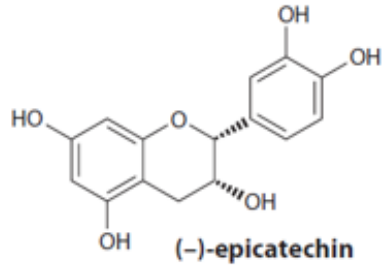
Colombian High Flavanols Cocoa



Colombian High Flavanol Cocoa

Ordinary Cocoa extract

Comparition between colombia High Flavanols Cocoa and others								
		Total polyphenols (g/Kg) gallic acid	Gallic acid	theofyl line	Caffeine	Procyanidin B2	epicatechin	theobromine
Colombia 3870	Colombia coca powder	55,50	1,8800	1,4000	6,3800	11,7000	21,7070	28,0000
526	Coca powder Lotto LC743	34,21	0,0383	0,3198	2,9004	3,6515	3,8388	26,9669
527	Coca powder Lotto 00466732	39,40	0,1302	0,3236	3,2174	3,8932	4,0506	25,1874
528	Coca powder Lotto 00010513	37,16	0,0540	0,2879	2,7879	4,1799	4,1381	24,6174
529	Tumaco 85%	15,62	0,0473	0,1120	1,2478	1,0966	1,4551	9,3337
530	Colombia bar 70%	14,55	0,0300	0,0715	0,8653	0,4401	0,7373	7,0097
531	Cumbia milk chocolate	3,77	0,0115	0,0521	0,5235	0,4528	0,5383	3,0160
532	Arauca	15,89	0,0464	0,0545	0,9496	0,8230	1,1426	7,2328
533	Nevado	0,34	0,0007	0,0017	0,2544	0,0297	0,0547	0,3189
534	Pàramo	0,41	0,0030	0,0014	0,1792	0,0299	0,0292	0,2075



(–)-epicatechin

Available online at www.sciencedirect.com

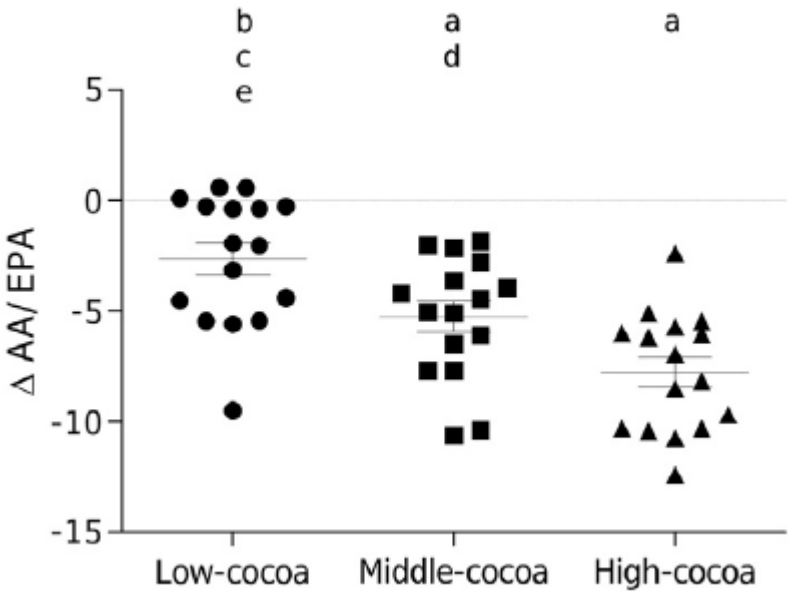
ScienceDirect

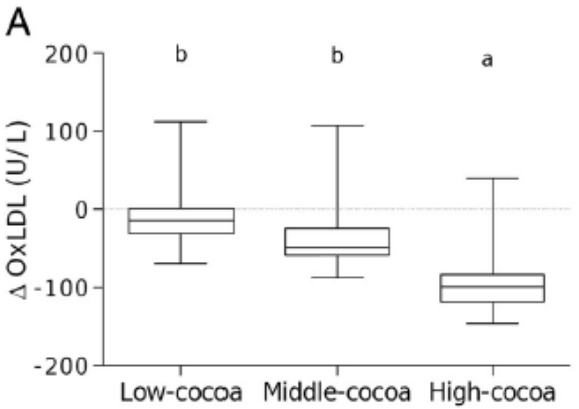
Journal of Nutritional Biochemistry 61 (2018) 33–39

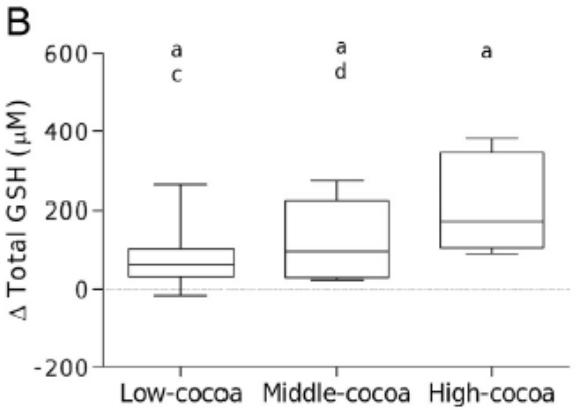
Journal of Nutritional Biochemistry

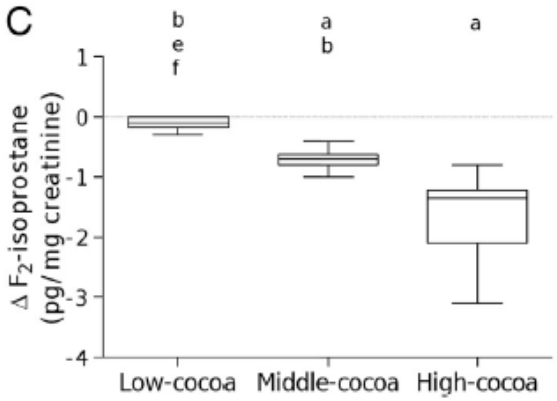
Short-term supplementation with flavanol-rich cocoa improves lipid profile, antioxidant status and positively influences the AA/EPA ratio in healthy subjects

Sergio Davinelli[a,b,1], Graziamaria Corbi[a,1], Armando Zarrelli[c], Mariachiara Arisi[d], Piergiacomo Calzavara-Pinton[d], Davide Grassi[e], Immaculata De Vivo[b,f], Giovanni Scapagnini[a,*]









Mediterranean Fashion: a treasure of functional food

Public Health Nutrition: 9(8A), 1136–1140 DOI: 10.1017/S1368980007668530

Importance of functional foods in the Mediterranean diet

RM Ortega*
Departamento de Nutrición, Facultad de Farmacia, Universidad Complutense, 28040-Madrid (Spain)

Submitted 18 April 2006: Accepted 26 November 2006

Abstract

Objective: Analyse the importance of components of Mediterranean diet in functional feeding.

BMJ 2014;349:g6674 doi: 10.1136/bmj.g6674 (Published 2 December 2014)

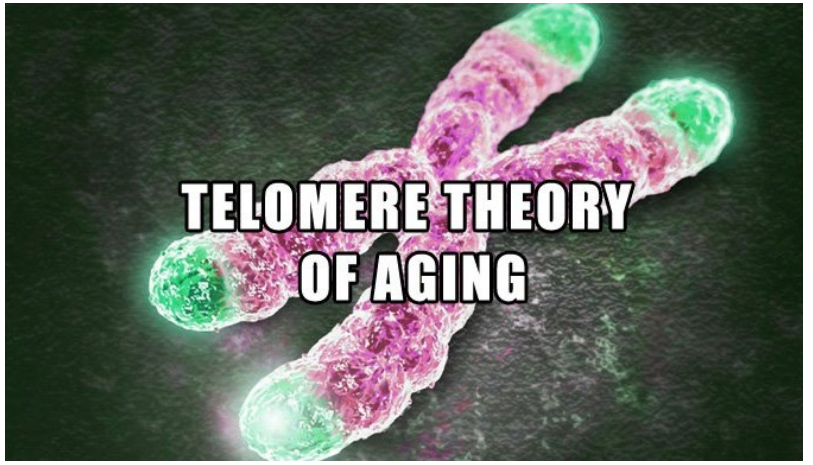
Mediterranean diet and telomere length in Nurses' Health Study: population based cohort study

OPEN ACCESS

Marta Crous-Bou *postdoctoral research fellow*[1] *research fellow*[2], Teresa T Fung *associate professor*[3] *adjunct associate professor*[4], Jennifer Prescott *instructor in medicine*[1], Bettina Julin *postdoctoral research fellow*[1] *research fellow*[2], Mengmeng Du *postdoctoral research fellow*[1] *research fellow*[5], Qi Sun *assistant professor*[1 4], Kathryn M Rexrode *associate professor*[7], Frank B Hu *professor*[1 2 4], Immaculata De Vivo *associate professor*[1 2]

Results Greater adherence to the Mediterranean diet was associated with longer telomeres after adjustment for potential confounders. Least squares mean telomere length z scores were –0.038 (SE 0.035) for the lowest Mediterranean diet score groups and 0.072 (0.030) for the highest group (P for trend=0.004).

Conclusion In this large study, greater adherence to the Mediterranean diet was associated with longer telomeres. These results further support the benefits of adherence to the Mediterranean diet for promoting health and longevity.



Brain Behav Immun. 2013 Aug;32:159-63. doi: 10.1016/j.bbi.2013.04.005. Epub 2013 Apr 19.

ELSEVIER

Loving-Kindness Meditation practice associated with longer telomeres in women.

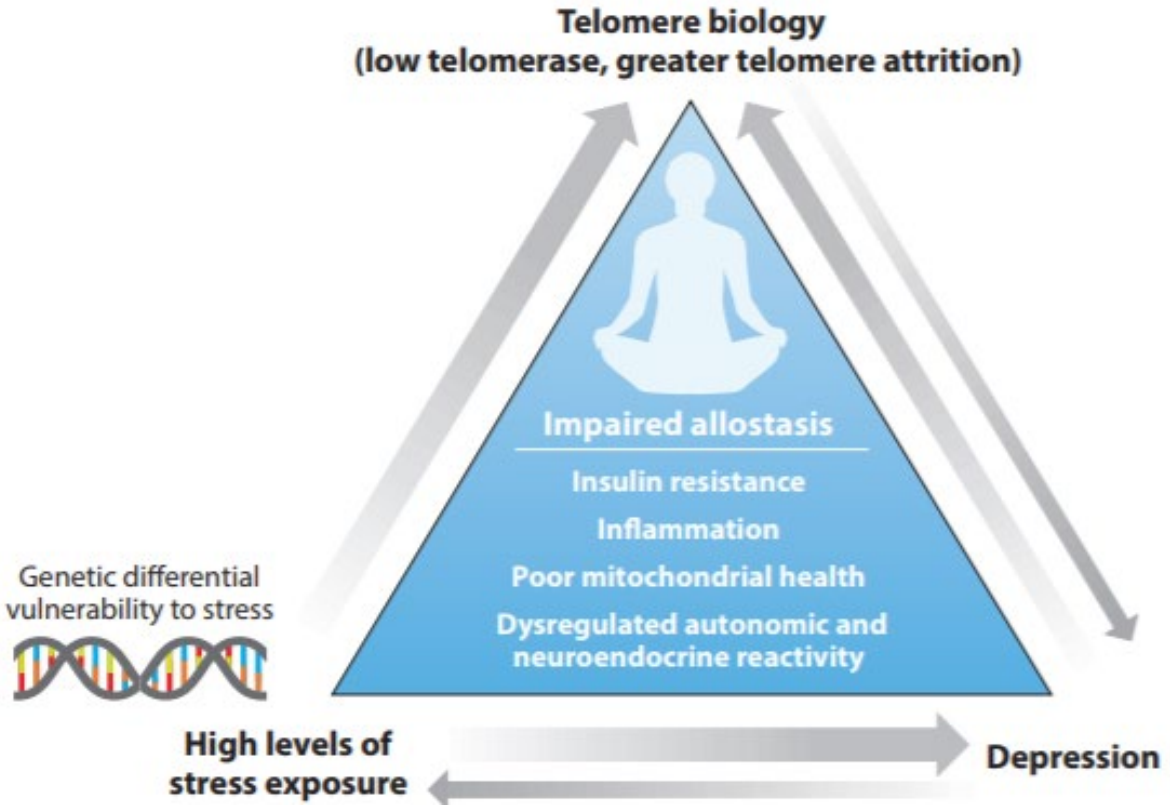
Hoge EA[1], Chen MM, Orr E, Metcalf CA, Fischer LE, Pollack MH, De Vivo I, Simon NM.

Relatively short telomere length may serve as a marker of accelerated aging, and shorter telomeres have been linked to chronic stress. Specific lifestyle behaviors that can mitigate the effects of stress might be associated with longer telomere lengths. Previous research suggests a link between behaviors that focus on the well-being of others, such as volunteering and caregiving, and overall health and longevity. We examined relative telomere length in a group of individuals experienced in Loving-Kindness Meditation (LKM), a practice derived from the Buddhist tradition which utilizes a focus on unselfish kindness and warmth towards all people, and control participants who had done no meditation. Our results offer the intriguing possibility that LKM practice, especially in women, might alter RTL, a biomarker associated with longevity.

Annu. Rev. Clin. Psychol. 2018

Stress, Telomeres, and Psychopathology: Toward a Deeper Understanding of a Triad of Early Aging

Elissa S. Epel and Aric A. Prather

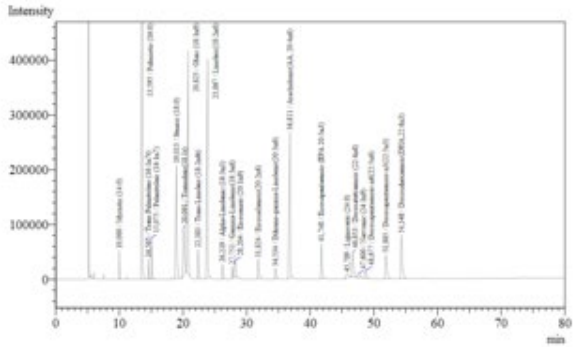


The triad of stress exposure, depression, and telomere biology

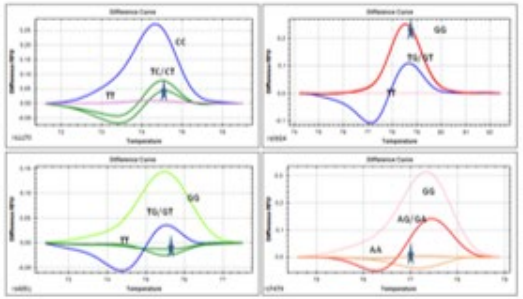
The most consistent and well-established relationships, from both longitudinal studies and experimental animal studies, show that greater exposure to major life stressors, especially early in life, leads to a greater rate of telomere attrition (as well as likelihood of major depression).

WHAT NEXT?

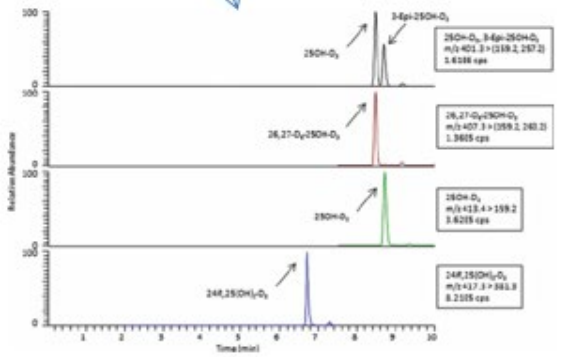
Lipidomic profile



SNP genotyping



LC-MS analysis

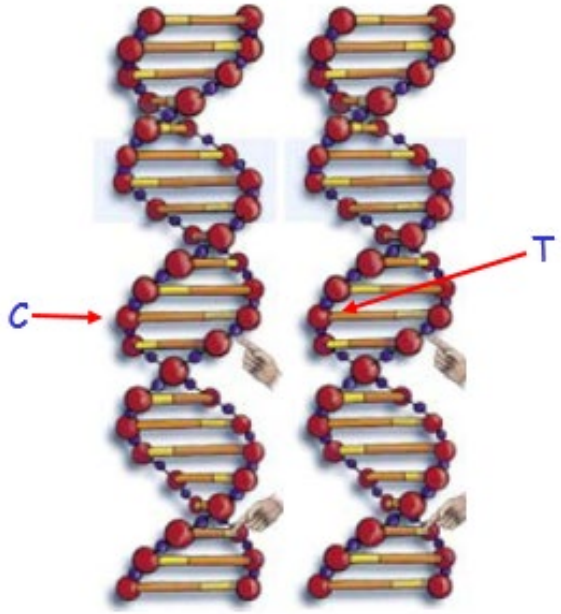


Protein assays

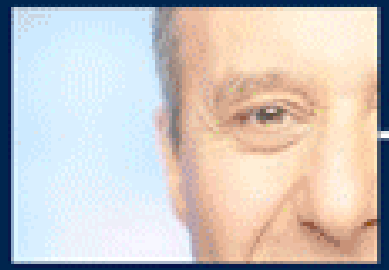
The nature of individuality

Natural genetic variation

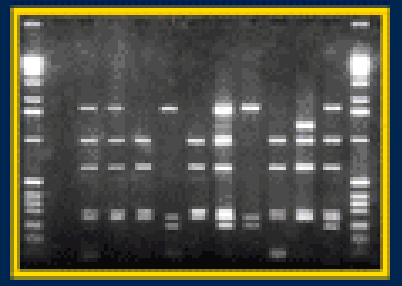
- Differences between individuals are known as polymorphisms
- Single nucleotide polymorphism (SNP) = a swap of a single letter in the code
- May make the protein product work more or less well
  - More than 1.5 million SNPs known in the genome
- Estimated 200,000 in the gene sequences alone



NuGO
the european nutrigenomics organisation



DNA - genes



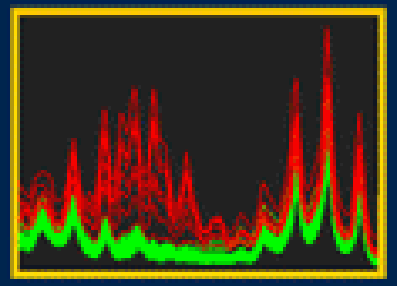
Genomics and Genotyping

Health Maintenance ⇄ Disease Development

Food

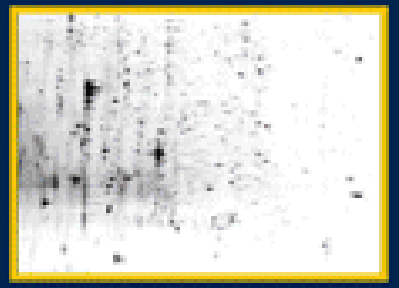
RNA

Metabolites

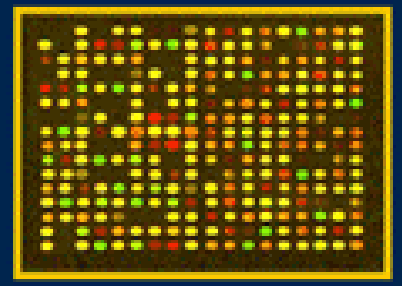


Metabolomics

Protein



Proteomics

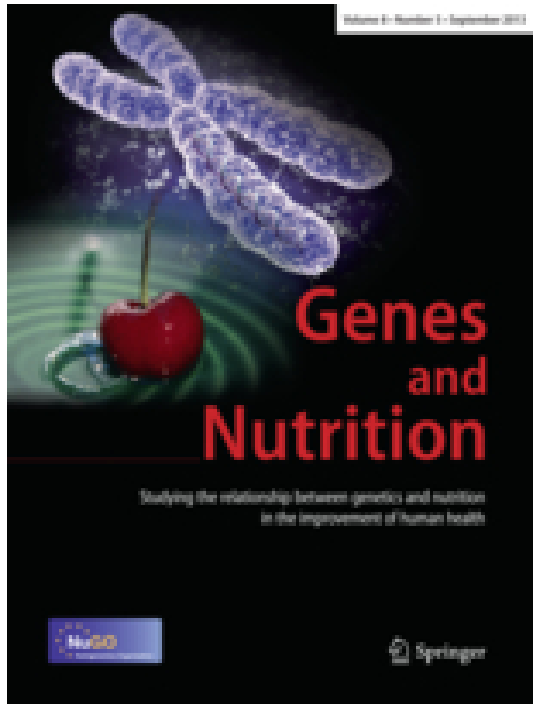


Transcriptomics

Do we know enough? A scientific and ethical analysis of the basis for genetic-based personalized nutrition

Genes Nutr (2013) 8:373–381

Ulf Görman · John C. Mathers · Keith A. Grimaldi · Jennie Ahlgren · Karin Nordström



The goal of personalized nutrition is not to substitute the official guidelines but to enhance or modify them for the individual where there is available evidence to do so. This is not a new development, but a practice that is old as the guidelines themselves: overweight people are advised to consume fewer calories than the recommended intake; lactose-intolerant individuals are advised to avoid or limit their intake of fresh dairy products; **now, we have the opportunity to consider the evidence from gene–diet interaction studies.**

Nutrigenetics is part of the information that contributes to personalized nutrition as a whole. Where there is supporting evidence, it should be added to other phenotypic information (such as health status, ethnicity, and gender), and genetic evidence should be assessed at the same level as phenotypic evidence. Preliminary studies suggest that including genetic information may be useful in several areas of health management. There is good evidence of some clinical and personal utility with respect to genotypebased personalized nutrition, and this should be made more widely available to allow individual decisions to be made.

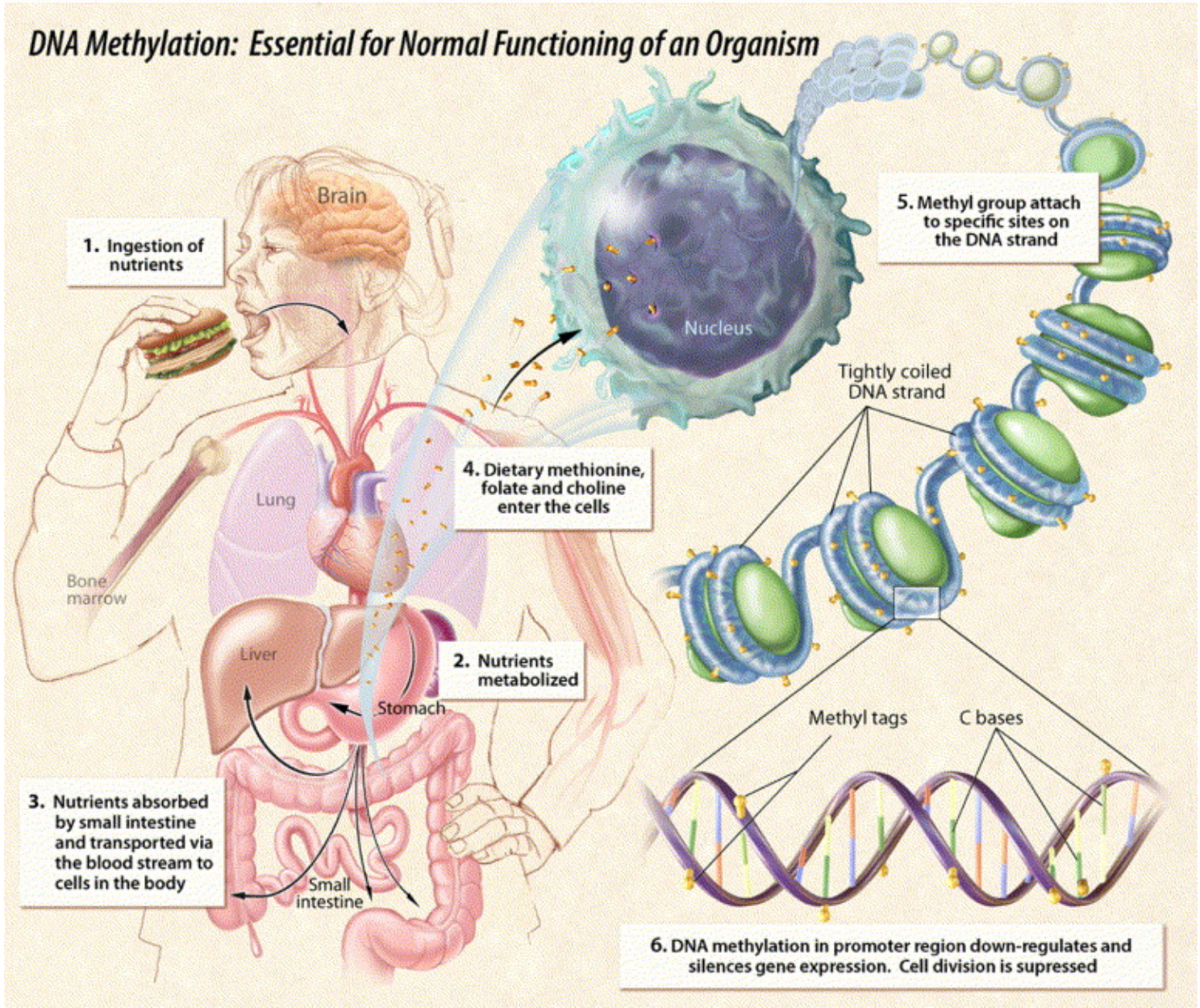
food4me.org

Food4Me is supported by the European Commission under the food, agriculture and fisheries, and biotechnology theme of the 7th Framework Programme for Research and Technological Development (contract no. 265494).

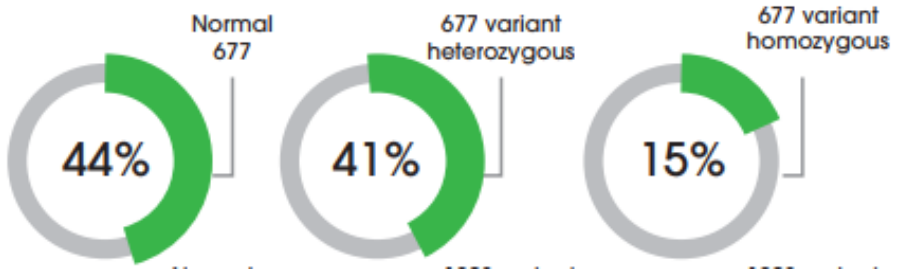
FUTURE SCENARIOS ABOUT PERSONALISED NUTRITION IN EUROPE

The **Food4Me** project looks to address the fundamental question of how we can best use our current understanding of food, genes, and physical traits to design healthier diets tailored for each individual, and to analyse the opportunities and challenges in the field of personalised nutrition.

Food4Me will explore the application of individualised nutrition advice. It will also investigate consumer attitudes and produce new scientific tools for implementation.



MTHFR variant genes are common!

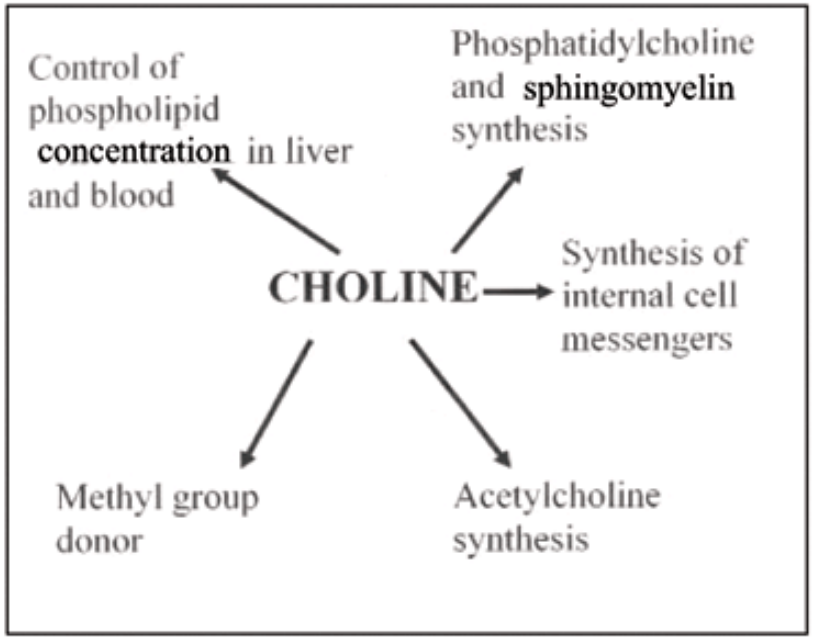


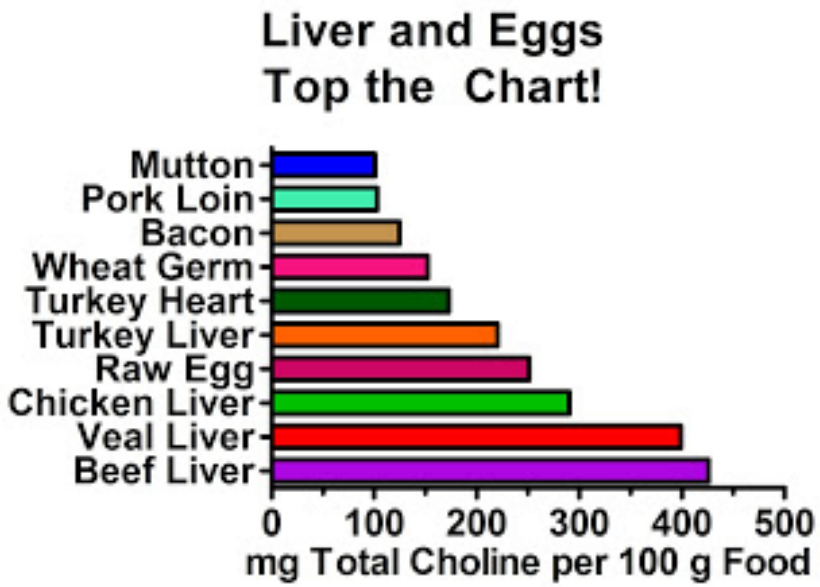
World Rev Nutr Diet. 2010 ; 101: 73–83. doi:10.1159/000314512.

Choline: Clinical Nutrigenetic/Nutrigenomic Approaches for Identification of Functions and Dietary Requirements

Steven H. Zeisel
Nutrition Research Institute, Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, N.C., USA

Choline, a nutrient found in many foods (especially in eggs, milk and meats), is important for making the neurotransmitter acetylcholine; for production of the membrane phospholipids phosphatidylcholine and sphingomyelin; and it is an important source of methyl-groups.



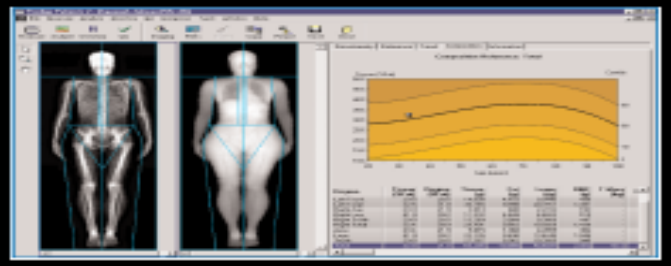


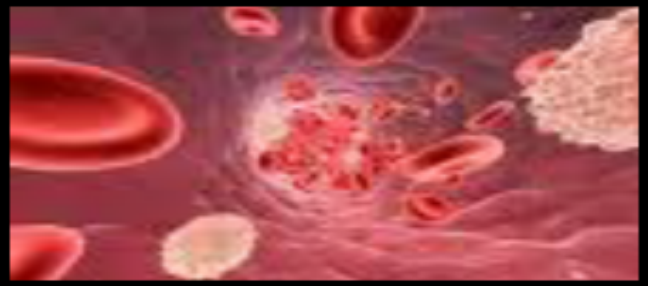
MTHFD1 rs2236225

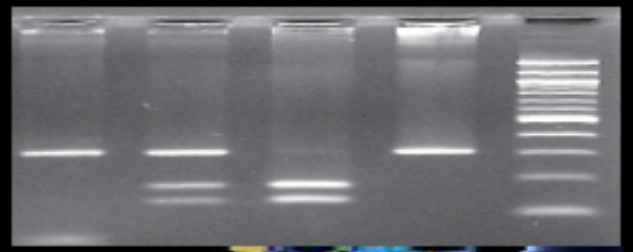
G1958A

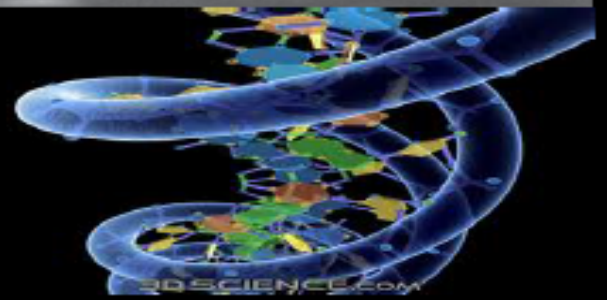
MORE CHOLINE IN THE DIET

Cross-over randomized clinical trial: the best intervention study(Kaput, 2008)
Accoding to Reg. CE 353/2008 All. I









1. medical history

2. Anthropometry & body composition

3Clinical-biochemical analysis

4. genetic and genomic analysis

Check variables

Assessment of nutritional status

nutritional intervention
based on the factors and conditions changeable