Paving the way to successful ageing

Dr Giuseppe Maltese

Consultant in Diabetes, Endocrinology and Older People's Medicine
Epsom and St Helier University Hospitals

Honorary Clinical Lecturer
King's College London

Diabetes UK Clinical Champion

@docmaltese

Introduction

What is ageing?

What is the definition of successful ageing?

The role of Klotho in ageing and cardiovascular renal disease

Strategies to slow down the ageing process

Calorie restriction

Mediterranean diet

Physical activity

Conclusions


SARDINIA
ITALY
Tyrrhenian Sea
Mediterranean Sea
Aegadian Islands
Palermo
Messina
SICILY
Strait of Sicily
Ionian Sea
Gulf of Tunis
Tunis
Pantelleria
Modica

I Am a Geriatrician

How often have I been asked over the past 30 years, "What is a geriatrician"? I cannot count the times and the ways that I have tried to answer this question. But clearly, even as the field has grown and matured, the public continues to have at best a vague idea of what a geriatrician is and does and why. In this essay, I attempt to capture the essence of my various attempts to respond to this query (e.g., [1]) from my friends and neighbors, who still do not understand what I do. I hope that my answer is factually informative while emphasizing that the real magnetic force binding me to the field is my love for the patients we serve, each with an old lives tale to share.

I am a geriatrician. I specialize in the medical, psychological, and social care of old people.

How old is old? Perhaps 75 for starters, 85 as an average, even 90, 95, 100, and older.

I like old people. I love old people. I enjoy their stories. I respect and admire them. They inspire me. They have survived the trials of youth and middle age. They have learned from those trials and all of their experiences. They have so much to teach me about life and what's important. They have given so much and have so much to give.

How do you get to be a geriatrician? First, 4 years in medical school to become a doctor, of course. Then 3 years of residency to become an internist or a family doctor, a generalist skilled in diagnosis and treatment of the vast array of medical problems of adults. Finally, 1 or more years in a geriatrics fellowship to become a specialist in the management of the special problems of old people. This is tremendously challenging, because in old folks, multiple coexisting chronic and progressive diseases are the rule, and simple self-limited problems or cures are the exception. In addition, those diseases commonly interact to produce an atypical or nonspecific presentation, making any specific diagnosis obscure. The limited reserves and resiliency of the old person increase the risk of weight loss and malnutrition, dehydration, and bad reactions to drugs and medical and surgical procedures. The complex web of these factors frequently produces one or more of the geriatric syndromes that perhaps best define our specialty: confusion, falls and fractures, urinary incontinence, depression, and dementia, to name just a few. Perhaps my most typical patient is the old-fashioned picture of frailty, a man—or more often a woman—who lives on the razor's edge between independence and triggering a tragic cascade of diseases, disabilities, and complications that all too often prove irreversible.

So, as a geriatrician, I am by definition an expert in subtlety and complexity. I am acutely aware of the interaction between physical, psychological, and social factors that affects the lives of each of my elderly patients. Because the care of my patients is so demanding and so complicated, I often work with family members and other professionals who contribute to the care of my patients and try to orchestrate the best care as their primary physician. Our team includes nurses, social workers, rehabilitation therapists, psychological and spiritual counselors, and frequently others.

As a geriatrician, I have also come to terms with the reality that most of my sick old patients are unlikely to recover completely. Hence, by training, by temperament, and by experience, I am skilled in continuing and long-term care. This includes palliative care of patients in their last illness, that is, care focused on preserving their comfort and dignity throughout their final days or months.

Because the training of doctors in geriatrics and the science of aging lags so far behind the oncoming wave of baby-boomers who will soon begin to experience the challenges of old age—a product of long-standing ageism in health care and society in general—I am most likely to practice my profession in an academic health center. There, as a teacher and researcher, I can best transmit my special knowledge and skills to the next generation of physicians and other health professionals who will care for those aging baby-boomers.

My inspiration and my passion will always come from my older patients. One day I hope to be like them; when that day comes, I hope that my doctor will be a geriatrician.

William R. Hazzard, MD
Division of Gerontology and Geriatric Medicine
University of Washington School of Medicine
VA Puget Sound Health Care System
Seattle, WA

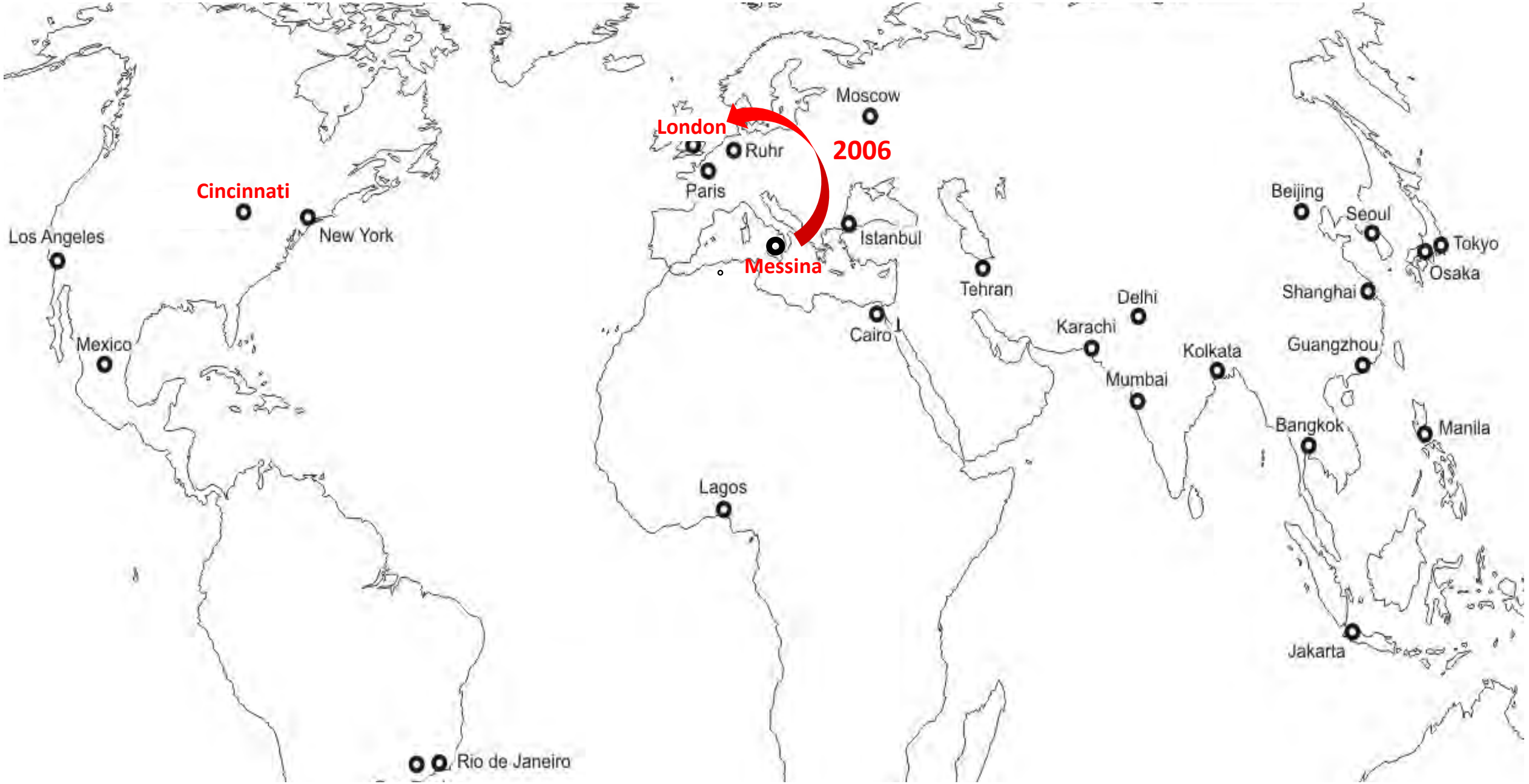
REFERENCE

1. Hazzard WR. Geriatrics? But why? Ann Intern Med 1987;106:785.

Journal of the AMERICAN GERIATRICS SOCIETY

JAGS 52:161, 2004

0002-8614/04/$15.00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Circulating Vascular Progenitor Cells in Patients With Type 1 Diabetes and Microalbuminuria

CECILE DESSAPT, PHD[1]
JANAKA KARALLIEDDE, MRCP[1]
MARIA HERNANDEZ-FUENTES, PHD[2]
PAZ PRIETO MARTIN, MS[1]
GIUSEPPE MALTESE, MD[1]
NIKESH DATTANI, MBBS[1]
RAVINDER ATKAR, MBBS[1]
GIANCARLO VIBERTI, FRCP[1]
LUIGI GNUDI, MD[1]

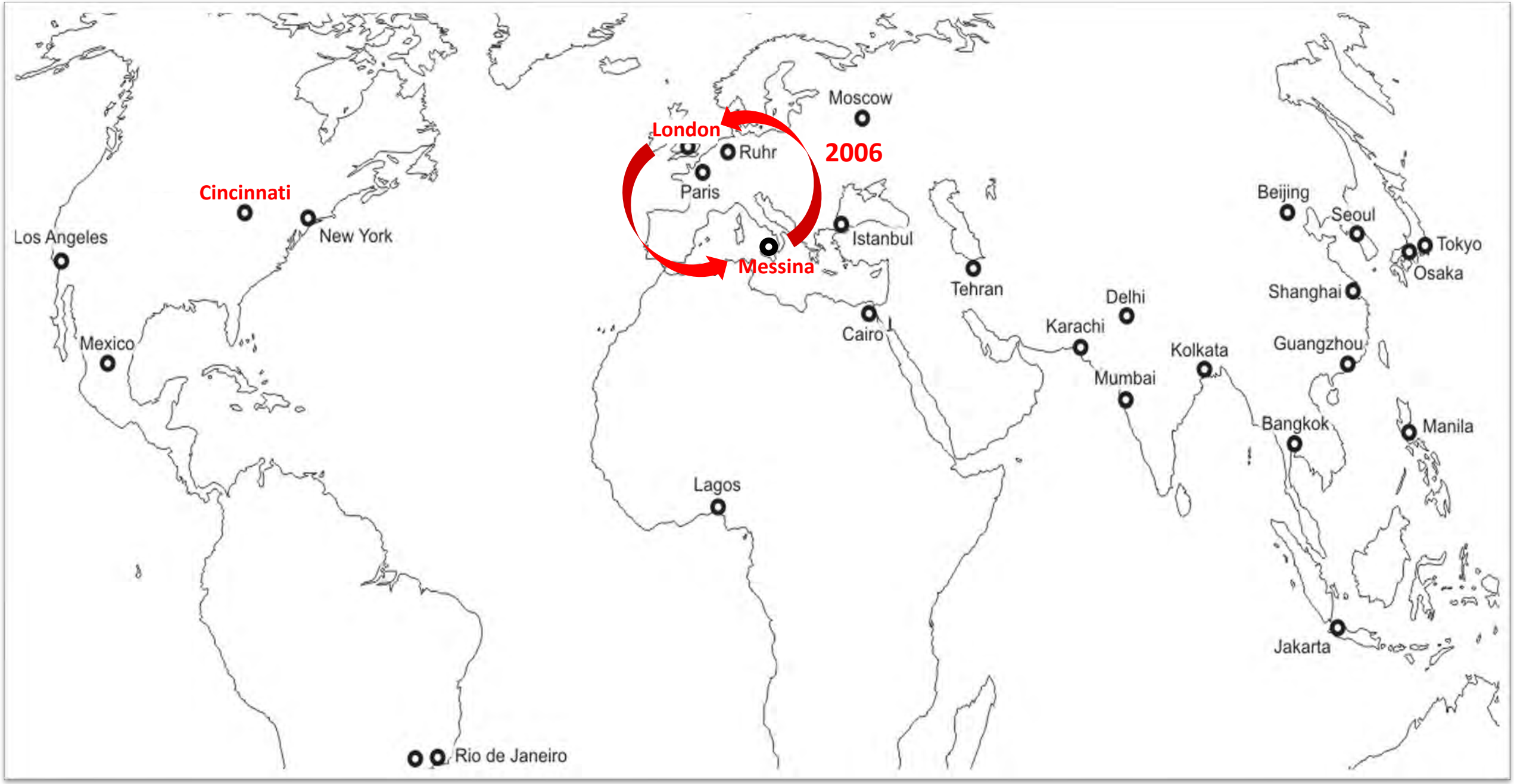
OBJECTIVE — Patients with type 1 diabetes and microalbuminuria are at increased risk of cardiovascular disease (CVD). Abnormalities in vascular progenitor cells, which participate in vascular repair, may be implicated in this susceptibility.

RESEARCH DESIGN AND METHODS — We studied the number and function of vascular progenitor cells in 22 type 1 diabetic patients with history of microalbuminuria (MA^+) and 22 type 1 diabetic patients without history of microalbuminuria (MA^-), of similar age, diabetes duration, glycemic control, renal function, and no history of CVD.

RESULTS — MA^+ patients had lower circulating $CD34^+$ and $CD34^+/CD133^+$ cell numbers compared with MA^- patients ($P < 0.006$). In in vitro functional assays, MA^+ patients had a significantly lower number of colony-forming units and impaired vascular endothelial growth factor (VEGF)-A–mediated tube formation, when compared with MA^- patients ($P < 0.01$).

CONCLUSIONS — In type 1 diabetic patients with microalbuminuria, a marker of microvascular injury and a risk factor for CVD, circulating vascular progenitor cell number is reduced and function is impaired.

Diabetes Care 33:875–877, 2010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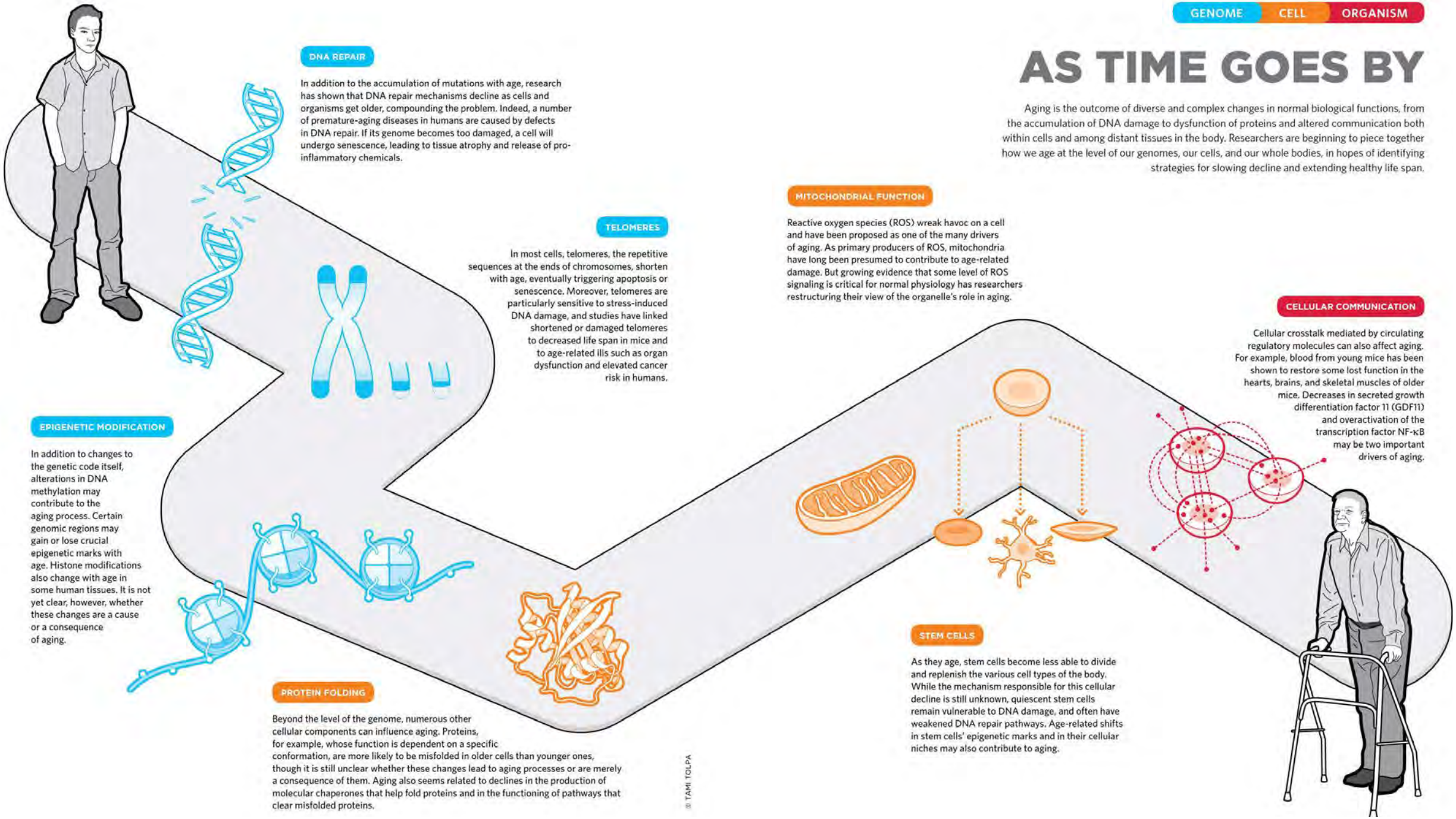
GENOME CELL ORGANISM

AS TIME GOES BY

Aging is the outcome of diverse and complex changes in normal biological functions, from the accumulation of DNA damage to dysfunction of proteins and altered communication both within cells and among distant tissues in the body. Researchers are beginning to piece together how we age at the level of our genomes, our cells, and our whole bodies, in hopes of identifying strategies for slowing decline and extending healthy life span.



DNA REPAIR

In addition to the accumulation of mutations with age, research has shown that DNA repair mechanisms decline as cells and organisms get older, compounding the problem. Indeed, a number of premature-aging diseases in humans are caused by defects in DNA repair. If its genome becomes too damaged, a cell will undergo senescence, leading to tissue atrophy and release of pro-inflammatory chemicals.

TELOMERES

In most cells, telomeres, the repetitive sequences at the ends of chromosomes, shorten with age, eventually triggering apoptosis or senescence. Moreover, telomeres are particularly sensitive to stress-induced DNA damage, and studies have linked shortened or damaged telomeres to decreased life span in mice and to age-related ills such as organ dysfunction and elevated cancer risk in humans.

EPIGENETIC MODIFICATION

In addition to changes to the genetic code itself, alterations in DNA methylation may contribute to the aging process. Certain genomic regions may gain or lose crucial epigenetic marks with age. Histone modifications also change with age in some human tissues. It is not yet clear, however, whether these changes are a cause or a consequence of aging.

PROTEIN FOLDING

Beyond the level of the genome, numerous other cellular components can influence aging. Proteins, for example, whose function is dependent on a specific conformation, are more likely to be misfolded in older cells than younger ones, though it is still unclear whether these changes lead to aging processes or are merely a consequence of them. Aging also seems related to declines in the production of molecular chaperones that help fold proteins and in the functioning of pathways that clear misfolded proteins.

MITOCHONDRIAL FUNCTION

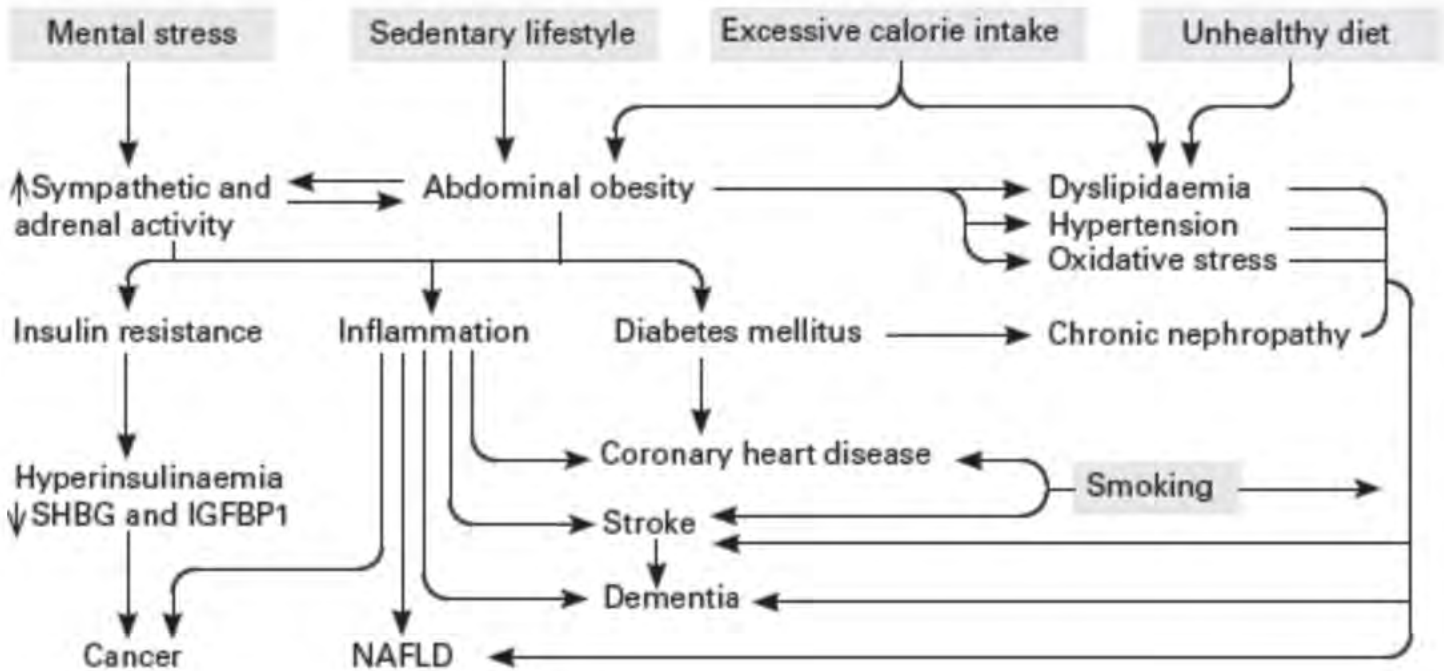
Reactive oxygen species (ROS) wreak havoc on a cell and have been proposed as one of the many drivers of aging. As primary producers of ROS, mitochondria have long been presumed to contribute to age-related damage. But growing evidence that some level of ROS signaling is critical for normal physiology has researchers restructuring their view of the organelle's role in aging.

CELLULAR COMMUNICATION

Cellular crosstalk mediated by circulating regulatory molecules can also affect aging. For example, blood from young mice has been shown to restore some lost function in the hearts, brains, and skeletal muscles of older mice. Decreases in secreted growth differentiation factor 11 (GDF11) and overactivation of the transcription factor NF-κB may be two important drivers of aging.

STEM CELLS

As they age, stem cells become less able to divide and replenish the various cell types of the body. While the mechanism responsible for this cellular decline is still unknown, quiescent stem cells remain vulnerable to DNA damage, and often have weakened DNA repair pathways. Age-related shifts in stem cells' epigenetic marks and in their cellular niches may also contribute to aging.



Luigi Fontana. The Path to Longevity.

Arch. Immunol. Ther. Exp. (2016) 64:111–126
DOI 10.1007/s00005-015-0377-3

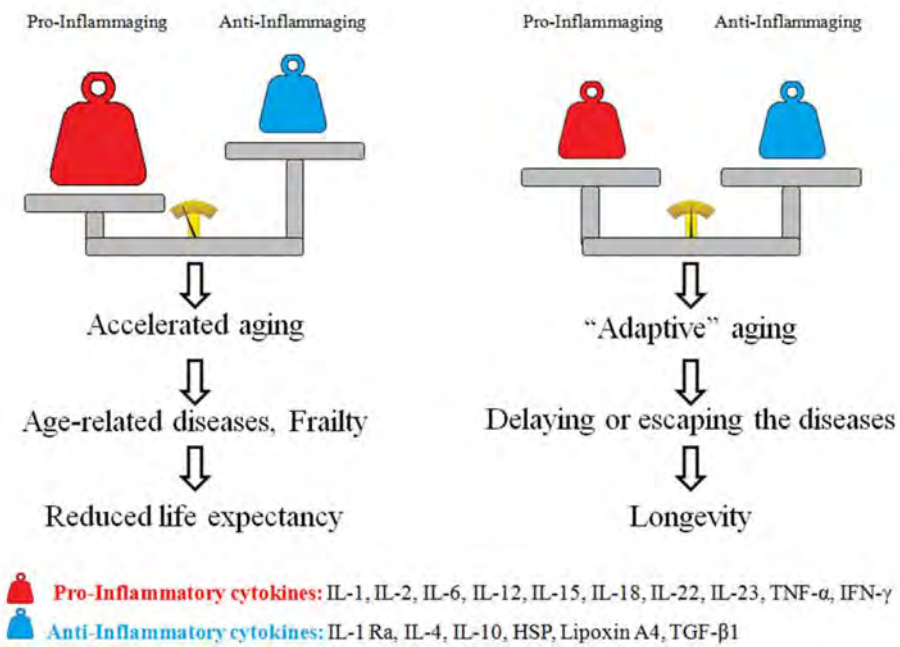
REVIEW

Inflammaging and Anti-Inflammaging: The Role of Cytokines in Extreme Longevity

Paola Lucia Minciullo[1] · Antonino Catalano[2] · Giuseppe Mandraffino[3] · Marco Casciaro[1] · Andrea Crucitti[2] · Giuseppe Maltese[4] · Nunziata Morabito[2] · Antonino Lasco[2] · Sebastiano Gangemi[1] · Giorgio Basile[2]

One of the most recent theories on aging focuses on immune response, and takes into consideration the activation of subclinical, chronic low-grade inflammation which occurs with aging, named ‘‘inflammaging’’.

Long-lived people, especially centenarians, seem to cope with chronic subclinical inflammation through an anti-inflammatory response, called therefore ‘‘anti-inflammaging’’.



What is successful ageing?

“Successful ageing is defined as high physical, psychological, and social functioning in old age without major diseases”

Immunity & Ageing

BioMed Central

Short report

Open Access

Smoking, health and ageing

Vittorio Nicita-Mauro[1], Giorgio Basile[1], Giuseppe Maltese[1], Claudio Nicita-Mauro[1], Sebastiano Gangemi[2] and Calogero Caruso*[3]

Int Urol Nephrol (2014) 46:481–482
DOI 10.1007/s11255-013-0518-8

NEPHROLOGY - LETTER TO THE EDITOR

Estimating glomerular filtration rate in centenarians: comparison of the chronic kidney disease epidemiology collaboration (CKD-EPI) and modification of diet in renal disease (MDRD) study equations

Giorgio Basile · Andrea Crucitti · Sergio Fusco · Maria D. Cucinotta · Giuseppe Maltese · Antonino Catalano · Antonino Lasco

Gerontology

Clinical Section / Short Communication

Gerontology 2012;58:216–220
DOI: 10.1159/000330801

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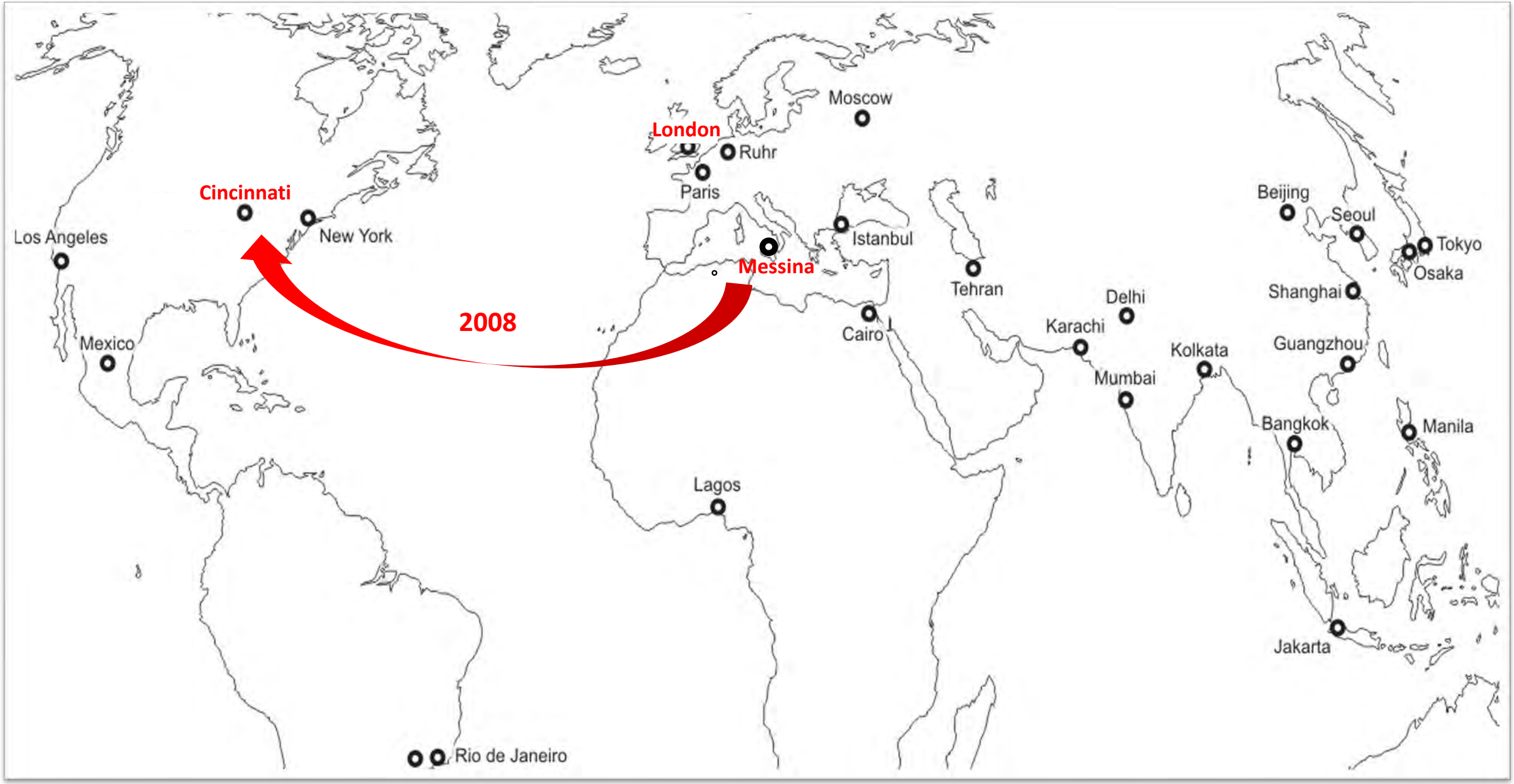
Electrocardiographic Changes in Centenarians: A Study on 42 Subjects and Comparison with the Literature

Giorgio Basile Maria Despina Cucinotta Paolo Figliomeni Claudia Lo Balbo Giuseppe Maltese Antonino Lasco

School and Division of Geriatrics, University Hospital, University of Messina, Messina, Italy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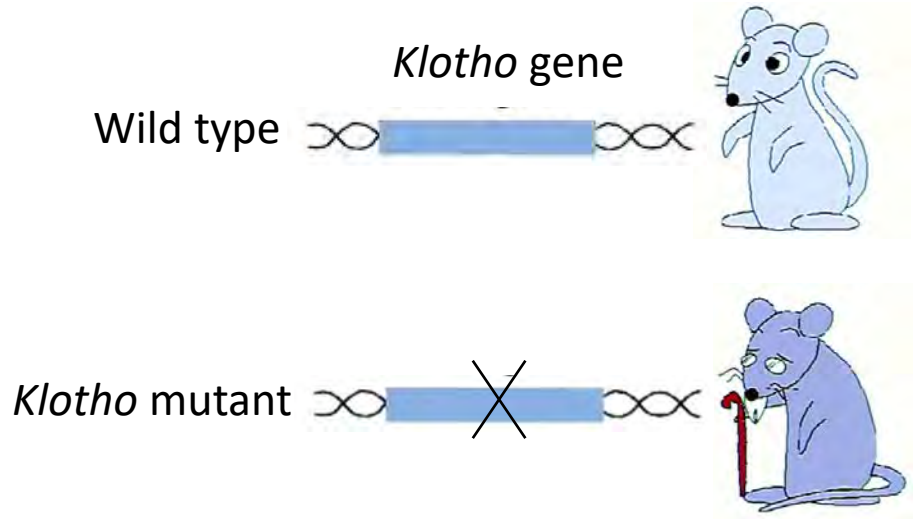
atropos
lachesis
clotho

Nature 390; 45-51, 1997

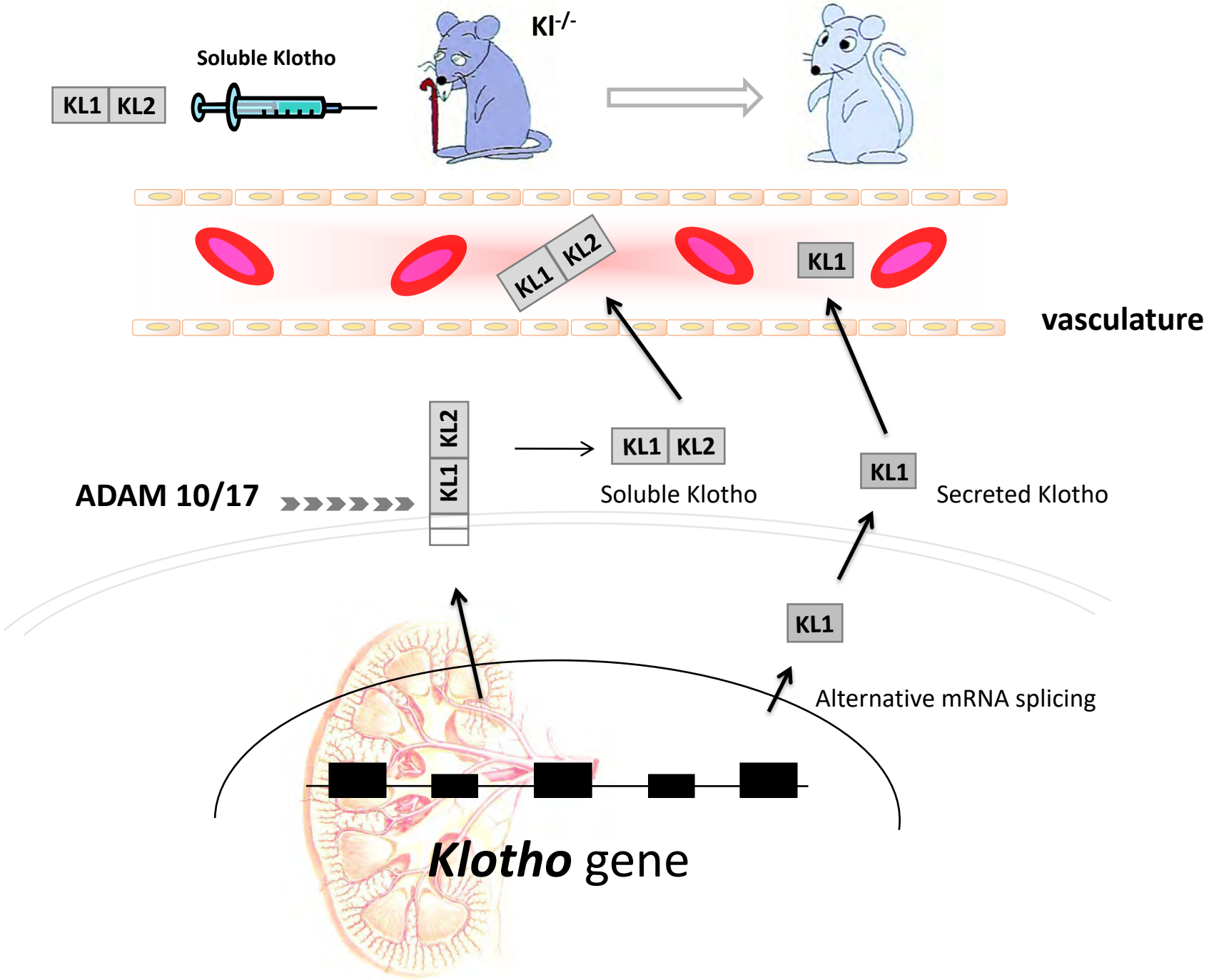
Mutation of the mouse *klotho* gene leads to a syndrome resembling ageing

Makoto Kuro-o*, Yutaka Matsumura*†, Hiroki Aizawa*†, Hiroshi Kawaguchi‡, Tatsuo Suga†, Toshihiro Utsugi†, Yoshio Ohyama†, Masahiko Kurabayashi†, Tadashi Kaname§, Eisuke Kume‖, Hitoshi Iwasaki‖, Akihiro Iida¶, Takako Shiraki-Iida*¶, Satoshi Nishikawa#, Ryozo Nagai†☆ & Yo-ichi Nabeshima*☆††

* *Division of Molecular Genetics, National Institute of Neuroscience, NCNP, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187, Japan*
† *The 2nd Department of Internal Medicine, University of Gunma School of Medicine, 3-39-22, Showa, Maebashi, Gunma 371, Japan*
‡ *Department of Orthopaedic Surgery, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113, Japan*
§ *Institute of Molecular Embryology and Genetics, Kumamoto University School of Medicine, Kumakoto 862, Japan*
‖ *Lead Optimization Research Laboratory, Tanabe Seiyaku Co. Ltd, 2-2-50 Kawagishi, Toda, Saitama 335, Japan*
¶ *Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd, 3-6-6 Asahimachi, Machidashi, Tokyo 194, Japan*
# *Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co. Ltd, 118 Shimotagari, Nagaizumi, Sunto, Shizuoka 411, Japan*
☆ *Core Research for Evolutional Science & Technology (CREST), JRDC and †† Institute for Molecular and Cellular Biology, Osaka University, 1-3 Yamada-oka, Suita, Osaka 565, Japan*



- Short lifespan
- Vascular calcification
- Renal fibrosis
- High levels serum Pi, FGF23


Soluble Klotho
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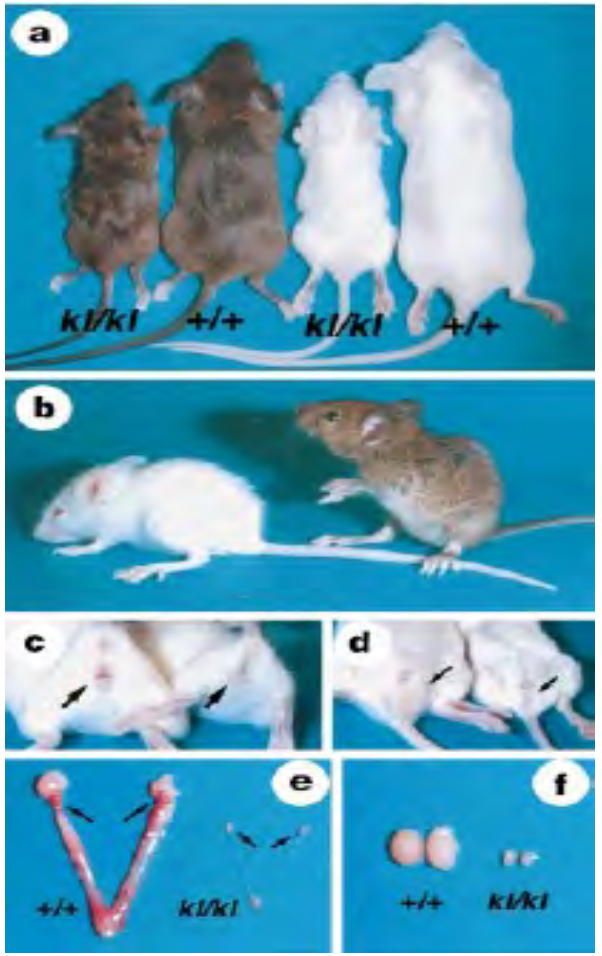
KL1
KL2
KL1
vasculature
ADAM 10/17
KL2
KL1
KL1
KL2
Soluble Klotho
KL1
Secreted Klotho
KL1
Alternative mRNA splicing
Klotho gene

KLOTHO DEFICIENT MOUSE

- Short lifespan
- Arteriosclerosis
- Ectopic calcification
- Pulmonary emphysema
- Impaired maturation of sexual organs
- Senile atrophy of the skin
- Osteopenia
- Altered mineral-ion homeostasis



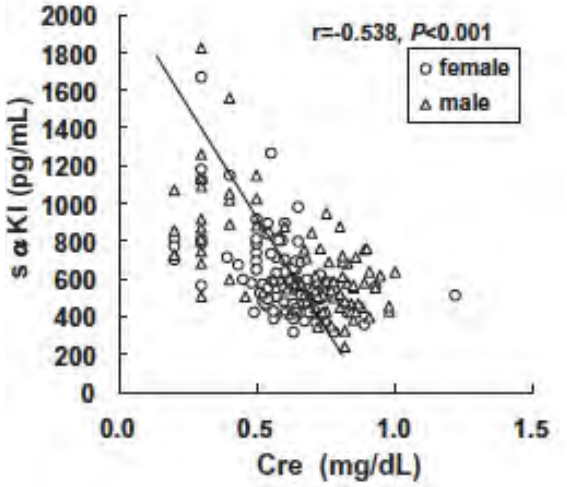
Nature 390; 45-51, 1997

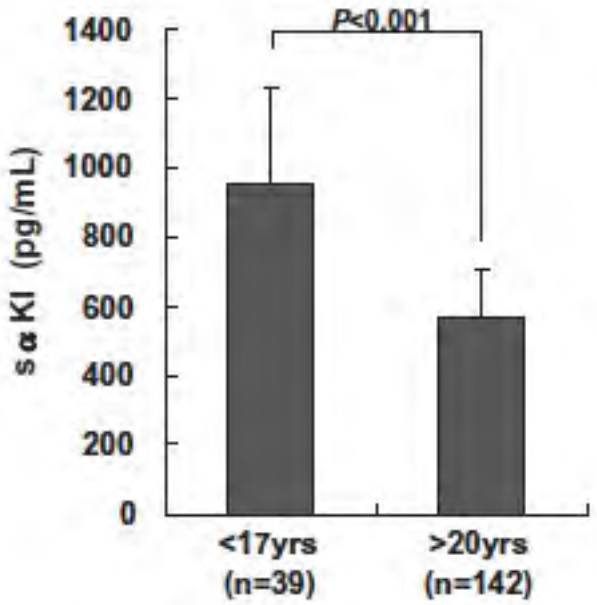
Establishment of sandwich ELISA for soluble alpha-Klotho measurement: Age-dependent change of soluble alpha-Klotho levels in healthy subjects

Objectives: to establish a sandwich ELISA system enabling detection of circulating serum sKl in healthy volunteers (n = 142, males 66) of ages (61.1 ± 18.5 year)

Results: serum levels of sKl ranged from 239 to 1266 pg/mL (mean ± SD; 562 ± 146 pg/mL) in normal adults

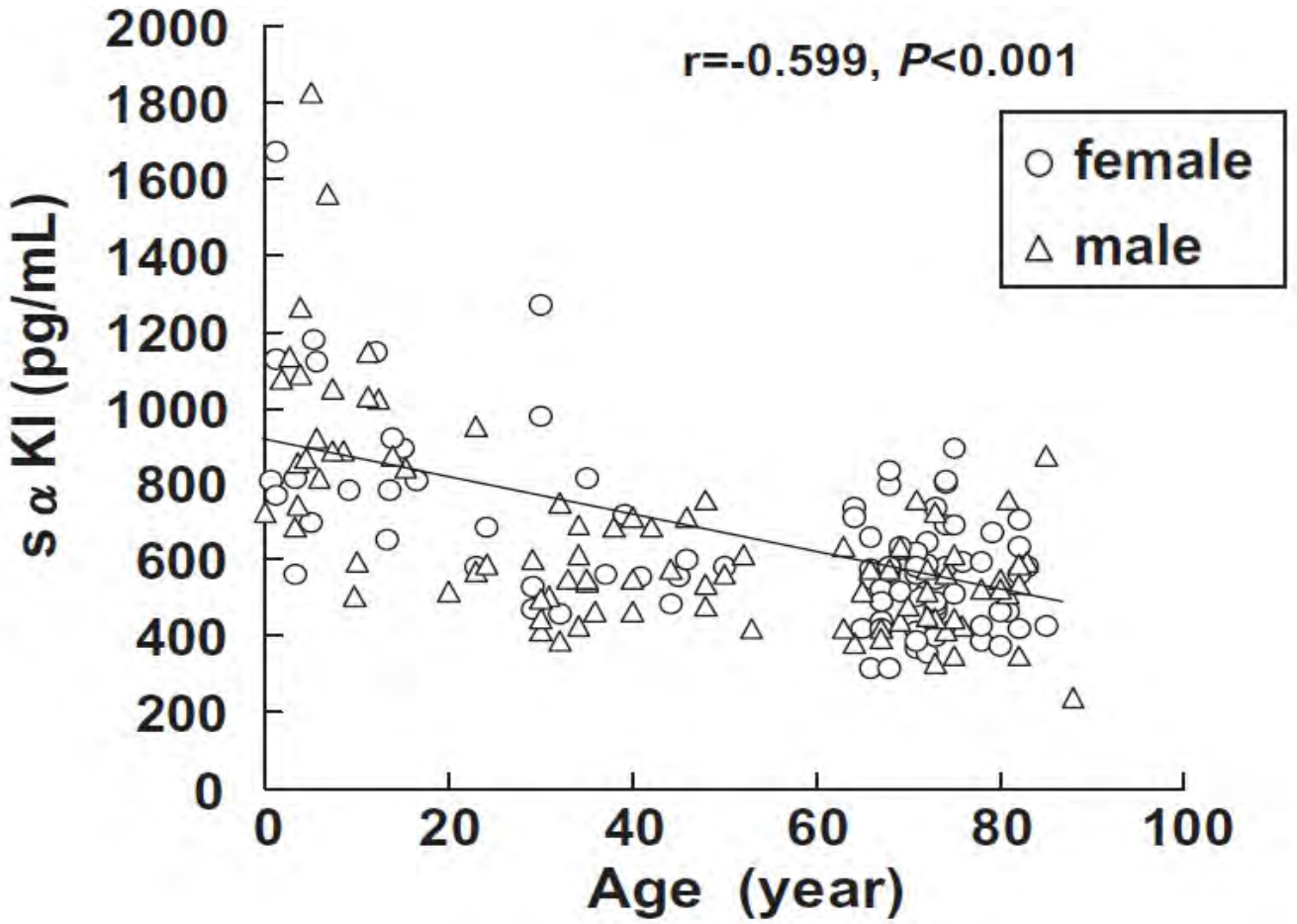
sKl levels in normal children (n = 39, males 23, mean ± SD; 7.1 ± 4.8 years) were significantly higher (mean ± SD; 952 ± 282 pg/mL) than those in adults (mean ± SD; 562 ± 146, P < 0.001)





Biochemical and Biophysical Research Communications 398 (2010) 513–518

Age-related decline in soluble Klotho levels in humans



Biochemical and Biophysical Research Communications 2010;398:513-518

Perturbations of the anti-ageing hormone Klotho in patients with type 1 diabetes and microalbuminuria

Giuseppe Maltese[1] · Nikolaos Fountoulakis[1] · Richard C. Siow[1] · Luigi Gnudi[1] · Janaka Karalliedde[1]

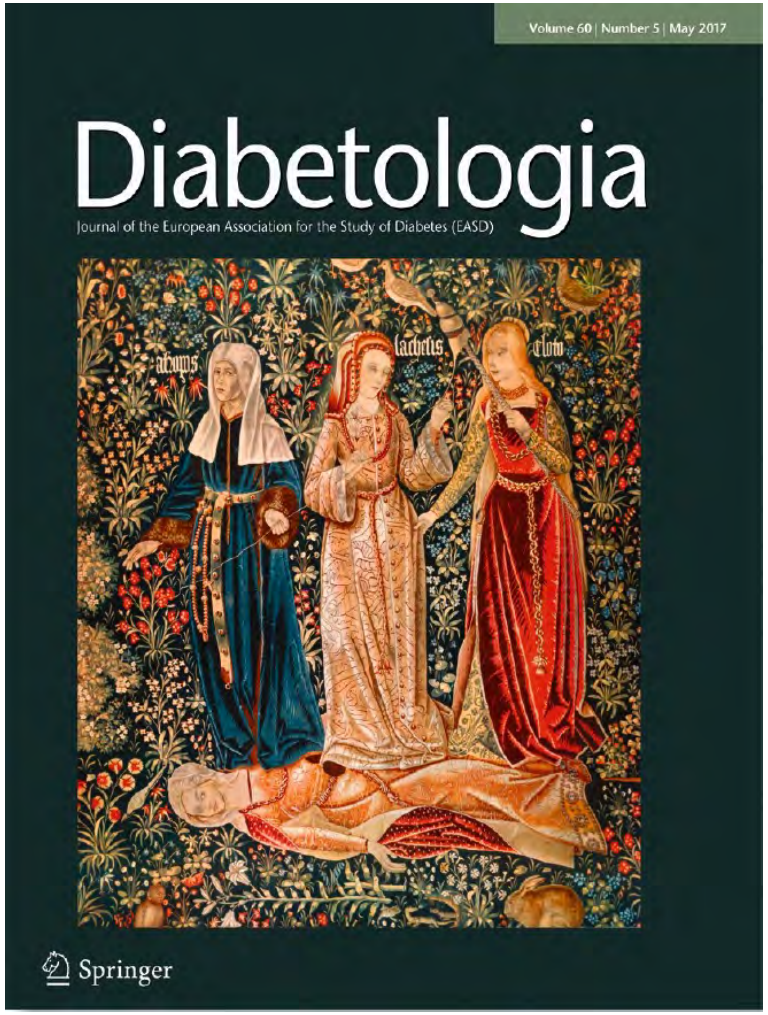
Variable	MA^+ ($n=33$)	MA^- ($n=45$)	p value
Age, years	54.4 ± 11.6	43.3 ± 9.6	<0.001
Sex, % male (M/F)	70 (23/10)	44 (20/25)	0.03
Retinopathy, %	100	100	NS
Use of RAS inhibitors, %	100	0	<0.001
Use of statins, % (n)	70 (23)	29 (13)	<0.001
Diabetes duration, years	32.7 ± 10.2	29.5 ± 9.7	0.21
HbA_{1c}, %	7.7	7.9	0.30
HbA_{1c}, mmol/mol	60.9 ± 10.7	63.0 ± 10.0	
SBP, mmHg	132.6 ± 12.4	126.3 ± 13.1	0.06
DBP, mmHg	72.3 ± 9.2	74.8 ± 8.5	0.26
eGFR, ml/min	90.2 ± 21.7	100.2 ± 20.4	0.054
ACR, mg/mmol[a]	1.1 (0.5, 8.1)	0.7 (0.5, 1.05)	0.013
Soluble Klotho, pg/ml[a]	659.3 (525.3, 827.6)	787.7 (629.5, 1007)	0.023

All data are mean ± SD unless otherwise stated

[a] Median (interquartile range)

DBP, diastolic BP; SBP, systolic BP

"This is the first study to demonstrate that individuals with type 1 diabetes and MA+ have significantly lower serum soluble Klotho levels compared with MA− individuals".



Diabetologia 2017, 60:911–914

Reduced Levels of Anti-Ageing Hormone Klotho Predict Renal Function Decline in Type 2 Diabetes

Nikolaos Fountoulakis,[1]* Giuseppe Maltese,[1]* Luigi Gnudi,[1] and Janaka Karalliedde[1]

[1]School of Cardiovascular Medicine & Sciences, Faculty of Life Sciences & Medicine, King's College London, London, SE1 9NH, United Kingdom

Variable	Residual Albuminuria (n = 53)	Normoalbuminuria (n = 39)	*P* Value
Age, y	59.7 ± 9.4	61.5 ± 9.3	0.40
Sex, % male	66	54	0.20
Diabetes duration,[a] y	9.0 (4.6–11.6)	9.9 (5.0–14.1)	0.3
Statin use, %	77	56	0.03
Oral antidiabetic agents, %	96	82	0.03
eGFR, mL/min	90.2 ± 20.3	88.7 ± 17.3	0.70
SBP, mm Hg	159.7 ± 10.7	155.1 ± 11.8	0.06
DBP, mm Hg	82.4 ± 10.9	79.8 ± 7.3	0.20
BMI, kg/m^2	32.0 ± 5.2	29.6 ± 5.2	0.04
HbA1c, %	7.5 ± 1.1	7.3 ± 1.3	0.40
FGF-23,[b] RU/mL	12.1 (9.8–24.0)	19.2 (15.4–22.5)	0.16
sKlotho,[b] pg/mL	184.7 (130.5–271.8)	235.2 (172.0–289.4)	0.03

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

[a]Mean (range).

[b]Median (IQR).

In patients with T2DM with relatively preserved eGFR, reduced levels of sKlotho predict renal function decline independent of traditional risk markers. sKlotho is a biomarker of renal dysfunction and a potential treatment target for renoprotection in T2DM.

J Clin Endocrinol Metab 2018, 103(5):2026–2032

Ageing in the UK

- In the UK, 1 in 4 adults are predicted to be aged over 65 by the year 2050 and 20% of boys and 26% of girls born in 2019 are expected to reach their 100th birthday

- In the period from 2009-2011 to 2016-2018, life expectancy in the UK increased by 0.8 years and 0.6 years for males and females, respectively

- In contrast, healthy life expectancy for males increased by 0.4 years and for females it actually decreased by 0.2 years in the same period

Can we prevent/slow down ageing?

Leading Edge
Review

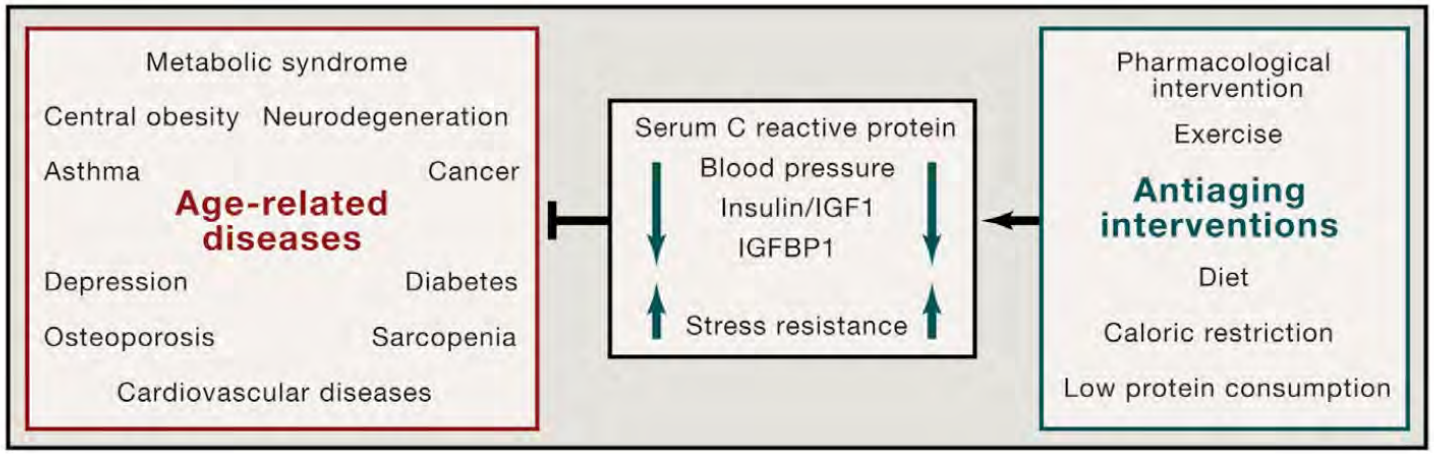
Cell

The Search for Antiaging Interventions: From Elixirs to Fasting Regimens

Rafael de Cabo,[1,*] Didac Carmona-Gutierrez,[3] Michel Bernier,[1] Michael N. Hall,[2] and Frank Madeo[3,*]
[1]Translational Gerontology Branch, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA
[2]Biozentrum, University of Basel, Basel 4056, Switzerland
[3]Institute of Molecular Biosciences, University of Graz, Graz 8010, Austria
*Correspondence: decabora@mail.nih.gov (R.d.C.), frank.madeo@uni-graz.at (F.M.)
http://dx.doi.org/10.1016/j.cell.2014.05.031

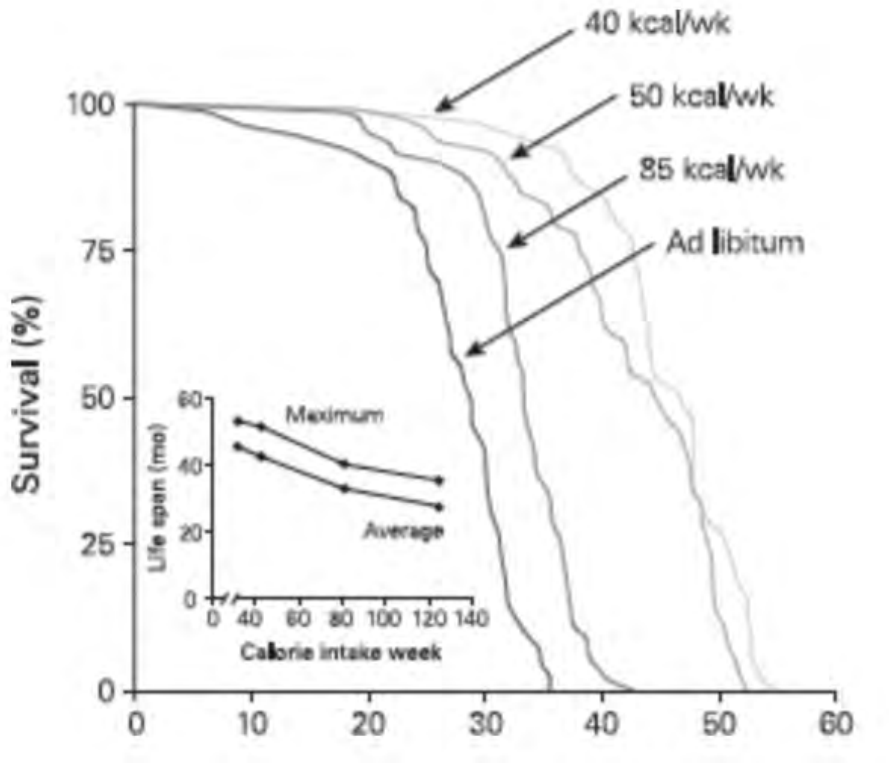
Table 1. Positive and Negative Effects of Lifestyle and Pharmacological Interventions on Humans; Where No Direct Data Are Available for Humans, Corresponding Effects on Mice Are Listed

Treatment	Positive Effects	Negative Effects
Caloric restriction	decreased body fat, blood pressure, resting heart rate and improved lipid profile	danger of malnutrition (e.g. neurologic deficits, lowered fertility and libido, wound healing problems, amenorrhea, osteoporosis, decreased potential to combat infections)
Fasting strategies	longer lifespan; decreased hypertension and of other features of metabolic syndrome; improved verbal memory loss in the aged and overweight; weight loss in the obese	limited if not integrated with health-associated diets; might be harmful in children, underweight people and during pregnancy as well as in some disease states
Exercise	prevents cardiovascular diseases, diabetes, osteoporosis, sarcopenia and depression; prolongs independent living by the elderly	excessive exercise in the elderly is correlated to mortality
Resveratrol	(in mice) prevents oxidative stress in the aging heart, neurodegeneration, vascular disease and diabetes; increases lifespan under metabolic stress conditions (high-fat diet or every other day feeding)	(in humans) at high doses, nausea, gastrointestinal discomfort; (in mice) at high doses, nephrotoxicity
Rapamycin	(in mice) extends lifespan; exerts antiproliferative effects	potent immunosuppressive properties; long-term administration has adverse effects (e.g. impaired wound healing, proteinuria, or pneumonitis)
Spermidine	(in mice) extends lifespan; inhibits neurodegeneration	
Metformin	(in mice) decreases hepatic gluconeogenesis and increases insulin sensitivity; lifespan extension	



Calorie restriction in rodents: the “fountain of youth”

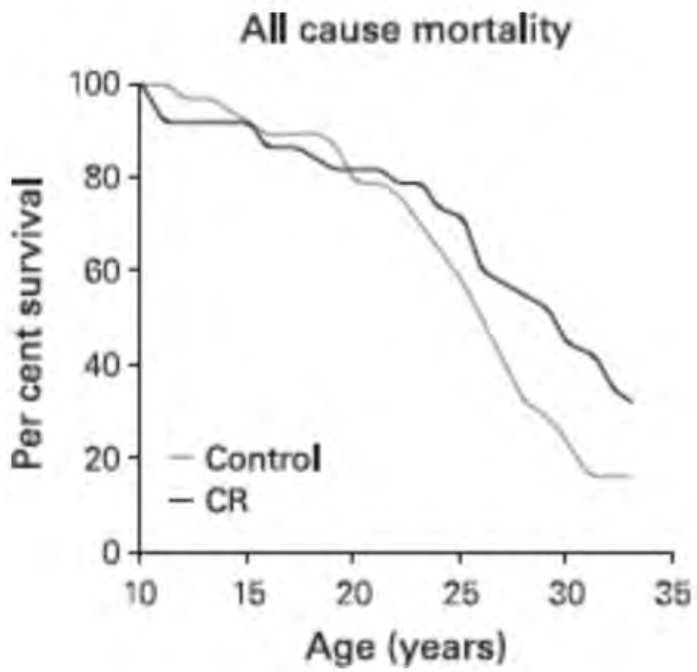
- Several animal studies have demonstrated that a 20-40% reduction in calorie intake without malnutrition causes a proportionate 20-50% increase in lifespan[1]
- Calorie restriction increase longevity by preventing or delaying the occurrence of chronic degenerative disease associated with ageing[2]
- A 15-53% reduction in calorie intake causes an equal linear 20-62 per cent reduction in incidence of cancer (the main cause of cancer in rodents)
- These animals die without any disease and the effects of calorie restriction are seen even in models of accelerated ageing (progeria)



Effects of different degree of calorie restriction on lifespan in mice

1. Calorie restriction in rodents: caveats to consider. Ageing Res Rev 2017 Oct;39:15-28.
2. **Aging, adiposity, and calorie restriction** JAMA 2007 Mar 7;297(9):986-94.
3. Luigi Fontana. The Path to Longevity.

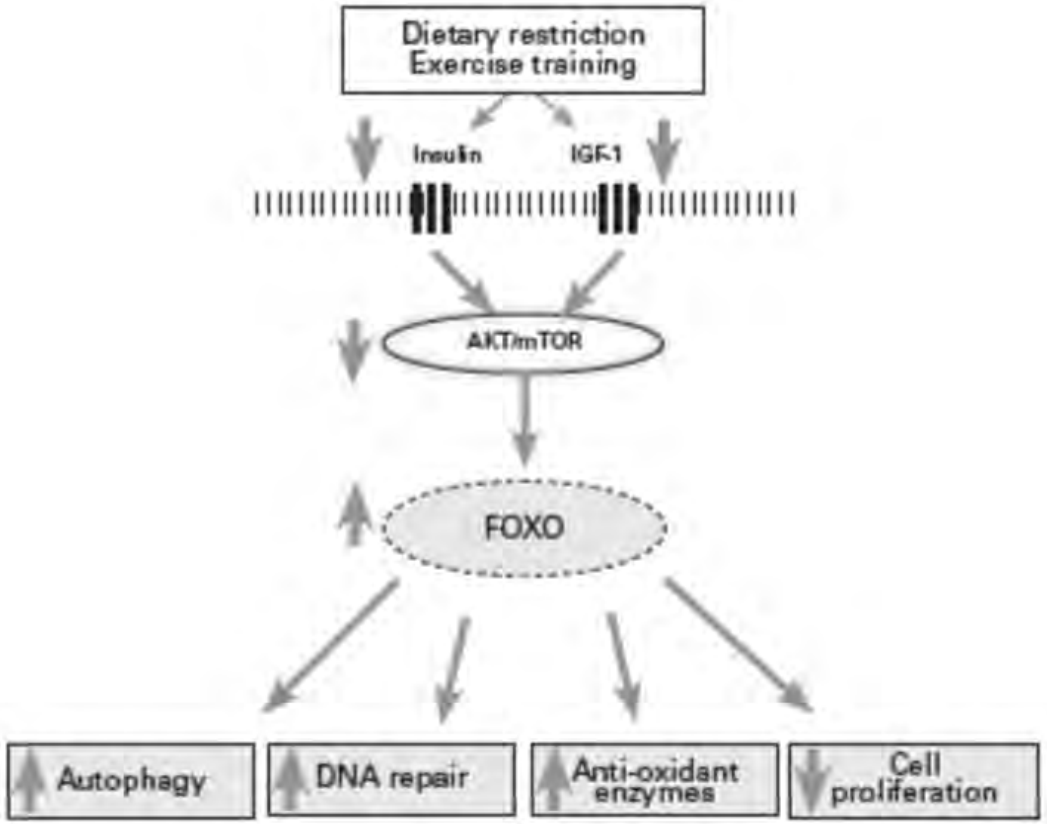
Effects of calorie restriction in Rhesus Monkeys



Effects of 30% calorie restriction in Rhesus monkeys

Luigi Fontana. The Path to Longevity.

Inhibition of nutrient-sensing and inflammatory pathways protects against damage



Luigi Fontana. The Path to Longevity.

Does calorie restriction work in humans?

- 20-30% reduction of calorie intake improves CV risk factors including blood pressure, cholesterol levels
- A 13% reduction of calorie intake improve all cardiometabolic risk factors beyond normal levels even in young adults
- The heart function of subjects decreasing the daily calorie intake to about 1800 calories is similar to that of people 15-20 years younger

Protective mechanisms underlying calorie restriction

- Reduction in markers of oxidative stress
- Inhibition of inflammatory pathways
- An activation of cellular pathways that help recycle molecular debris and remove toxic misfolded proteins and malfunctioning organelles
- An elevation of enzymes protecting cells against the damage of free radicals
- An increased level of genes that repair DNA damage
- A drastic reduction in markers of cell senescence

Excessive calorie restriction can be dangerous

- Increased cold sensitivity

- Menstrual irregularities
- Low libido

- Bone density loss

Tips to control calorie intake

- Substitute refined and processed foods with foods rich in fibre
- Eat your food slowly and stop eating before becoming full
- Once or twice a week eat only non starchy raw or cooked vegetables
- Consume most food within a restricted time frame, 8-10 hours

CNN health Life, But Better Fitness Food Sleep Mindfulness Relationships

life but better
Food

Mediterranean diet named best diet for 2022

By Sandee LaMotte, CNN
Published 8:30 AM EST, Tue January 4, 2022

(CNN) — It's a winning streak that just won't quit. For the fifth year in a row, the Mediterranean diet was first across the finish line in the annual race for best diet, according to ratings announced Tuesday by U.S. News & World Report.

RELATED ARTICLE
How to stock your kitchen with Mediterranean grocery staples

Tied for silver was the DASH diet, which stands for dietary approaches to stop hypertension, and the Flexitarian diet, which encourages being a vegetarian most of the time, but is flexible enough to allow a burger now and again.

What do all of these diets have in common? They stress reducing or eliminating processed foods, and focus on meals full of fruits, vegetables, beans, lentils, whole grains, nuts and seeds.

"I think it's important to note that the top three diets – Mediterranean, DASH and flexitarian – all offer variety, flexibility and few, if any, rules," said Gretel Schueller, managing editor of health for U.S. News & World Report, who puts out an annual ranking of diets, in an email.

"All the diets that perform well are safe, sensible and backed by sound science. The diet winners also all provide adequate calories with a focus on vegetables, fruits and whole grains; a modest amount of lean protein, dairy; and an occasional treat," Schueller added.

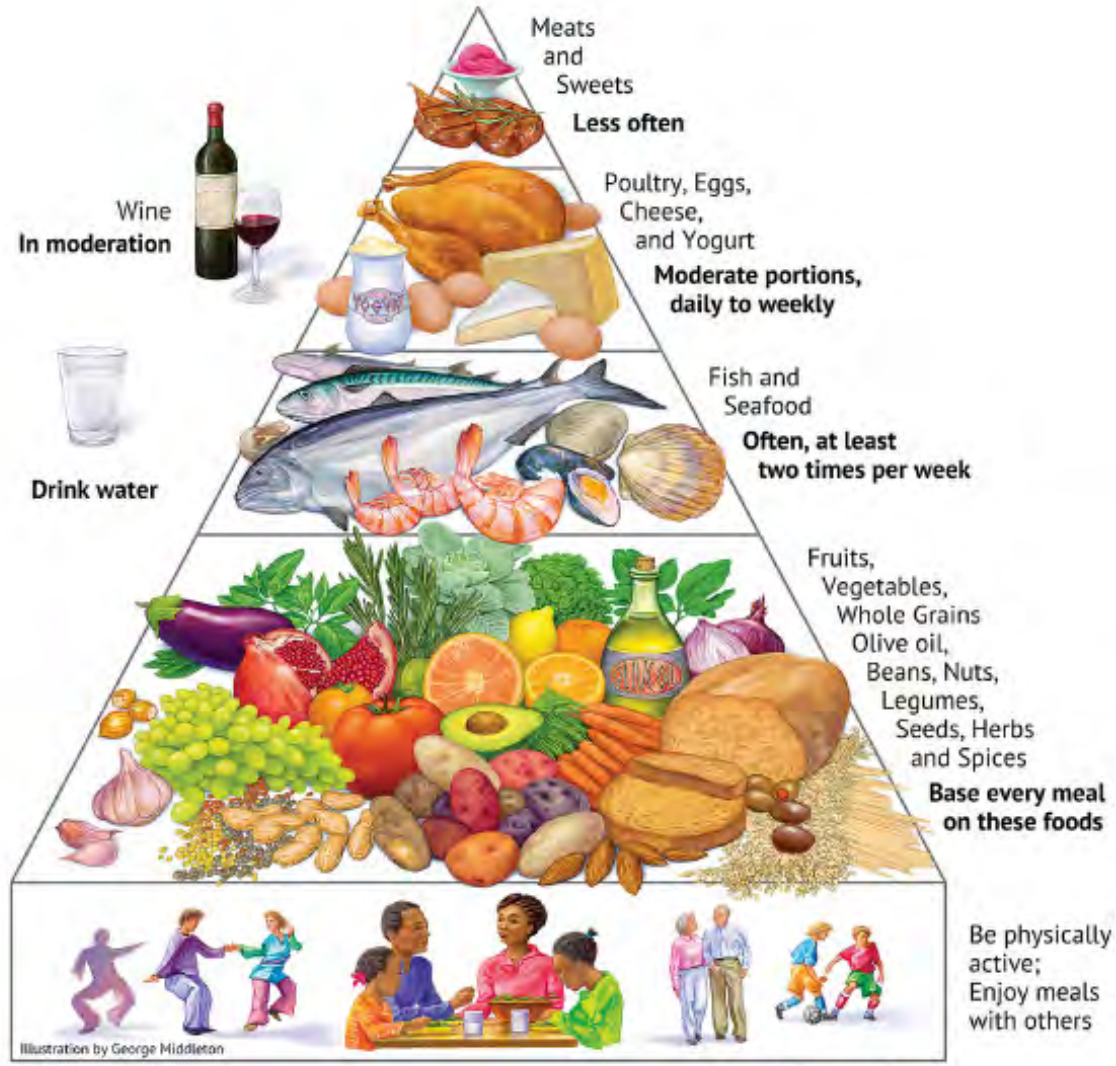
A panel of 27 experts examined 40 diets and ranked them on several categories: How easy is the diet to follow; how likely is a person to lose significant weight, both in the short and long term; how effective the diet is in preventing cardiovascular disease or diabetes; and the diet's nutritional completeness.

"Generally speaking, the top diets are driven by what you can eat – not what you can't eat. And right now – during these stressful times of the pandemic – that's especially helpful for people," Schueller said. "We want food we can enjoy. And we want food that will maintain our health, maybe even boost our immunity. The top-ranked diets offer this."

A panel of 27 experts examined 40 diets and ranked them on several categories:

1. How easy is the diet to follow
2. How likely is a person to lose significant weight, both in the short and long term
3. How effective the diet is in preventing cardiovascular disease or diabetes
4. The diet's nutritional completeness.

Mediterranean Diet Pyramid



eets health

JOURNAL ARTICLE

THE DIET AND 15-YEAR DEATH RATE IN THE SEVEN COUNTRIES STUDY

Get access >

ANCEL KEYS, ALESSANDRO MIENOTTI, MARITI J. KARVONEN, CHRIST ARAVANIS, HENRY BLACKBURN, RATKO BUZINA, B. S. DJORDJEVIC, A. S. DONTAS, FLAMINIO FIDANZA, MARGARET H. KEYS ... Show more

American Journal of Epidemiology, Volume 124, Issue 6, December 1986, Pages 903–915,
https://doi.org/10.1093/oxfordjournals.aje.a114480
Published: 01 December 1986 **Article history** ▾

- 15-year observational study including nearly 12,000 men living in Italy, Greece, Yugoslavia, Finland, Holland, Japan and US
- High association between the amount of dietary saturated fat intake, blood cholesterol levels and the risk of death from CV diseases
- Finland, Holland and the US had the highest animal food consumption, the highest saturated fat intake, the highest blood cholesterol levels and the highest percentage of CV deaths; in contrast the Mediterranean countries and Japan were at the opposite end of the spectrum
- Interestingly both the inhabitants of Crete in Greece and North Karelia in Finland obtained more than 40% of their calories from fat. However the % of deaths from heart attack was much higher in Finland than in Crete
- The average middle-aged Finnish man was consuming butter, milk, and cheese, while men for men in Crete was fish, nuts and extra-virgin olive oil

Journal List > J Gerontol A Biol Sci Med Sci > PMC7190876

OXFORD JOURNALS | The Journals of Gerontology Series A: Biological Sciences and Medical Sciences

J Gerontol A Biol Sci Med Sci. 2018 Mar; 73(3): 318–326.
Published online 2017 Dec 13. doi: 10.1093/gerona/glx227
PMCID: PMC7190876
PMID: 29244059

Health Benefits of the Mediterranean Diet: Metabolic and Molecular Mechanisms

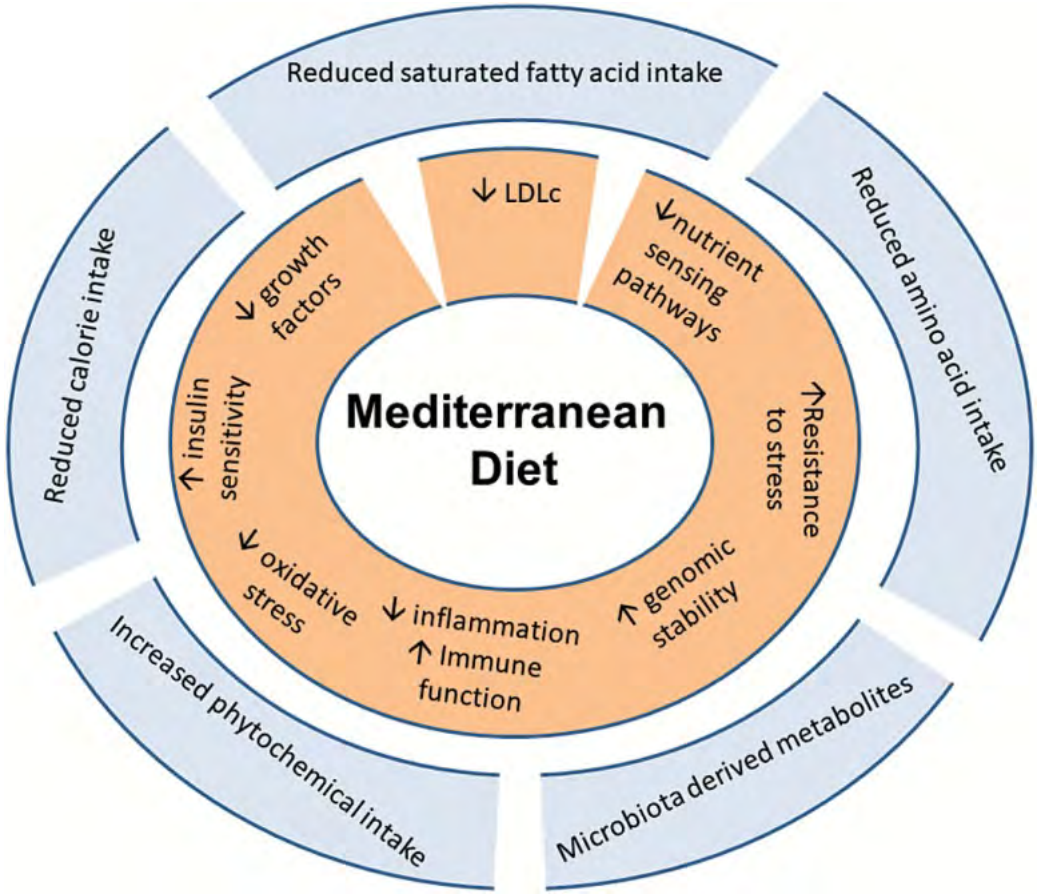
Valeria Tosti, MD,[1] Beatrice Bertozzi, PhD,[1] and Luigi Fontana, MD, PhD[1,2]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Protective effects of the MD against:

- Diabetes
- Hypertension
- Several type of cancers
- Allergic reactions

- Alzheimer Disease
- Parkinson's Disease



Circulation
Volume 99, Issue 6, 16 February 1999; Pages 779-785
https://doi.org/10.1161/01.CIR.99.6.779

CLINICAL INVESTIGATION AND REPORTS

Mediterranean Diet, Traditional Risk Factors, and the Rate of Cardiovascular Complications After Myocardial Infarction

Final Report of the Lyon Diet Heart Study

Michel de Lorgeril, Patricia Salen, Jean-Louis Martin, Isabelle Monjaud, Jacques Delaye, and Nicole Mamelle

- 605 men and women who had already had a heart attack were randomized to either the diet recommended by the AHA or a Mediterranean Diet
- Patients randomized to the MD consumed more breath, vegetables, fruit and fish and less red and meat (replaced with poultry)
- After only two years, the study was terminated because people adhering to the MD experienced a 70% reduction in mortality (due to a 73% reduction in coronary artery disease death and major reductions in non fatal complications.

Mechanisms behind the benefits of the Mediterranean diet

- Reduction in cholesterol level
- Reduction in oxidative stress and inflammation
- Positive changes in the composition and function of the gut microbiome

Food rich in saturated fat

- Dairy products including butter, cream, whole milk, cheese
- Meat fatty cuts of beef, pork, lamb
- Lard and processed meats (salami)
- Chicken skin

Mediterranean diet lower the cholesterol levels through

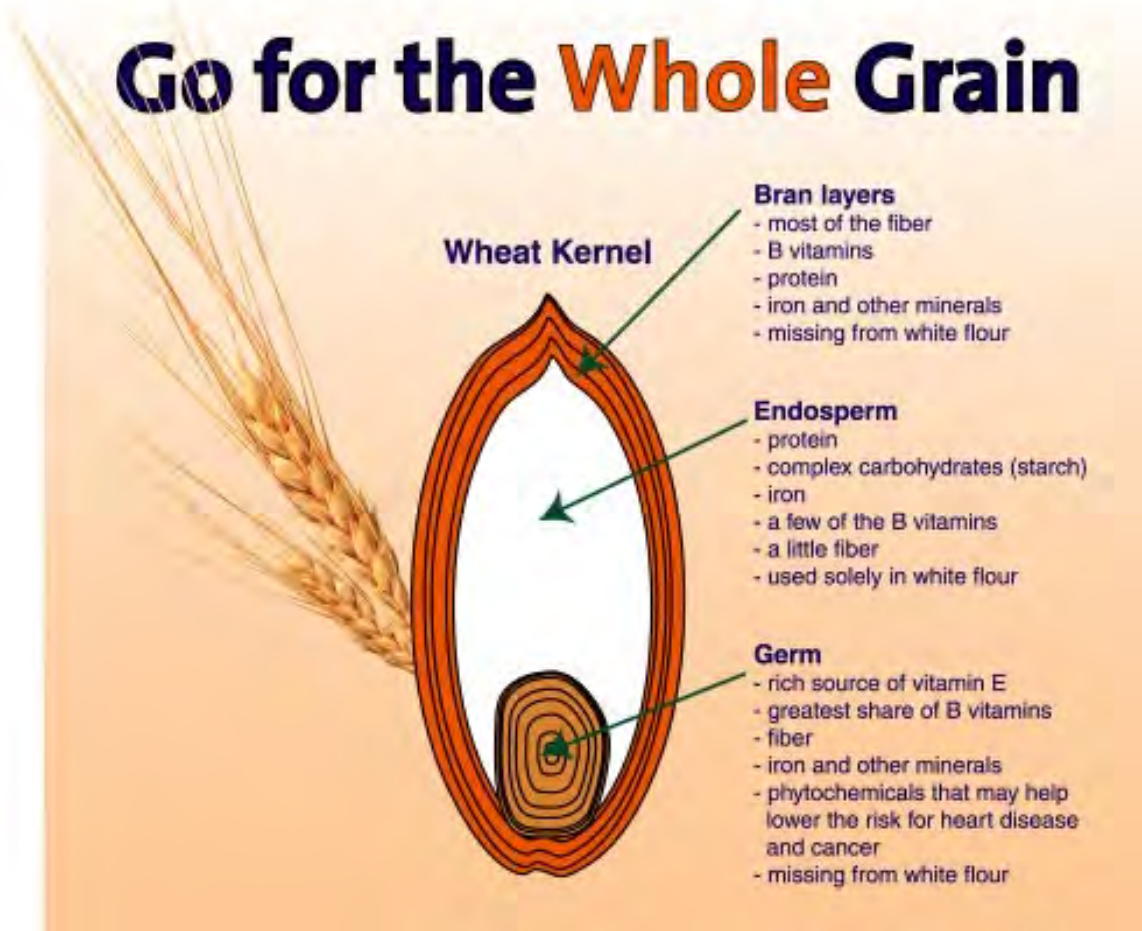
- Polyunsaturated omega-3 fatty acids (e.g. fish, walnuts)
- Omega-6 fatty acids and plant sterols (e.g. almonds, hazelnuts, pine nuts)

- Fibre intake (whole grains, legumes, vegetable, nuts)

Reduced oxidative stress and inflammation

Vegetables, beans, unrefined whole grains, seeds, nuts, fruits, and extra virgin olive oil are rich in *antioxidant vitamins* and *minerals* (vitamin C, vitamin E, beta-carotene, selenium folate) and a variety of *phytochemicals*

Go for the Whole Grain



Gut health

- A Mediterranean diet rich in insoluble fibre has been shown to increase the production of certain bacteria (called Bacteroidetes and Firmicutes) producing high levels of short chain fatty acids (butyrate and propionate)

- These metabolites by binding to specific receptors inhibit inflammation and increase the levels of certain immune cells, called regulatory T cells which protect from the development of autoimmune disorders

- The reduced intake of fibre rich vegetables, whole grains, legumes may be responsible for the increased incidence of type 1 diabetes, asthma, IBD

Large dark green leafy vegetables

- Rich in chlorophyll, folic acid, carotenoids and vitamin K
- Lutein and zeaxanthin which protect eye tissues
- Great source of *Vitamin K* and *Vitamin A.*

Beet greens

Mustard Greens

Silver beet

Spinach

Cruciferous vegetables

- Part of the family *Brassicaceae*

- High levels of **Vitamin C** and some phytochemicals such as isothiocyanates, indol-3 –carbinol and **sulforaphane** which play an important role in cancer prevention and longevity.

Savoy cabbage

Cabbage

Brussels sprouts

Broccoli

Kale

Arugula (rocket)

Pumpkin, carrots, sweet potatoes

Rich in **carotenoids** responsible for the orange colour and the production of Vitamin A

Pumpkin

Health eye and immune function health

Carrots

Carrots like parsley are members of the *Apiaceae* or *Umbelliferae f*amily and all contain a compound called **polyaceylene** which has preventative effects against thrombosis and cancer

Sweet potatoes

Tomatoes

As well as watermelon they contain *lycopene* a strong antioxidant, important in the prevention of some certain cancers, including prostate, digestive tract and cervical

Anti-cancer effect due to reduction in IGF-1.

Legumes (beans or pulses)

Source of healthy proteins and vitamins

B vitamins, folate, iron, copper, magnesium, manganese, zinc, and phosphorus

Low in fat (apart from soya)

One serving of legumes provides on average
- 120 calories
- 20 g of complex carbohydrate
- 6 -10 g of fibre
- 8 g proteins

Recommended for overweight people, and those individuals at risk of diabetes

They can replace red meat, and they lower fasting blood glucose levels, insulin, triglycerides and LDL cholesterol

Chickpeas

Fava beans

Lentils

Borlotti beans

Nuts and seeds

- Nutritional powerhouses
- Amino acids and fatty acids (monounsaturated and polyunsaturated) and dietary fibre

- Vitamins (group B, folic acid and Vitamin E)

- Minerals (K, Mg, Ca, iron, and Zn)
- Anti-oxidants minerals (Selenium, Manganese, and Copper)

- Phytochemicals (Flavonoids, resveratrol, and plant sterols)

Meta-Analysis > Curr Atheroscler Rep. 1999 Nov;1(3):204-9.
doi: 10.1007/s11883-999-0033-7.

Nut consumption and risk of coronary heart disease: a review of epidemiologic evidence

F B Hu [1], M J Stampfer

Affiliations + expand

PMID: 11122711 DOI: 10.1007/s11883-999-0033-7

A growing body of epidemiological studies suggests that people who consume at least 5 servings of nuts per week experience a 40-60% lower risk of developing heart disease.

Six reasons why nuts can protect our CV system:

1. Nuts are low in saturated fats and rich in cardioprotective *monounsaturated* and *polyunsaturated* fats

2. They are rich in *soluble fibre* that reduce the absorption of cholesterol in our intestine

3. All nuts, particularly almonds and walnuts are the main dietary source of antioxidant vitamin E and antioxidants minerals such as selenium, copper and manganese

4. Raw nuts are low in *Na*, and high in *K* and *Mg*, factors that have an important effect in lowering blood pressure

5. Pines nuts are rich in *arginine* and amino acid that is converted to an anti-atherogenic molecule the NO

6. Walnuts are a source of omega-3 alpha-linolenic acid which lower triglycerides levels, inflammation and protects against several irregular heartbeat conditions

Fish: substitute meat with fish for the goof of your heart

Fish eating Inuit and Japanese populations traditionally had lower rates of heart disease compared to meat-eaters living in the US and North Europe

Eating four or more servings per week of fish rich in long chain omega 3 polyunsaturated fatty acids seems to lower the risk of having a heart attack by 22% when compared to people who consumed seafood less than once a month

It is not necessary to eat four servings of fish every week. Several studies have shown that even consuming one to four servings of oily fish per month has a significant cardioprotective effect compared with no consumption

Extra Virgin Olive oil

- Nutritionally balanced and healthy condiment

- Extracted from the ripe fruit of the olive tree without using chemical solvents

- Unrefined cold pressed juice rich in monounsaturated fats
- The mixture of phenolic compounds is responsible for the fruity, pungent and slightly bitter taste

- More than 30 phytocompounds have been described (oleuropein, tyrosol, hydroxytyrosol)

- Contains alpha-tocopherol and carotenoids which are potent antioxidants

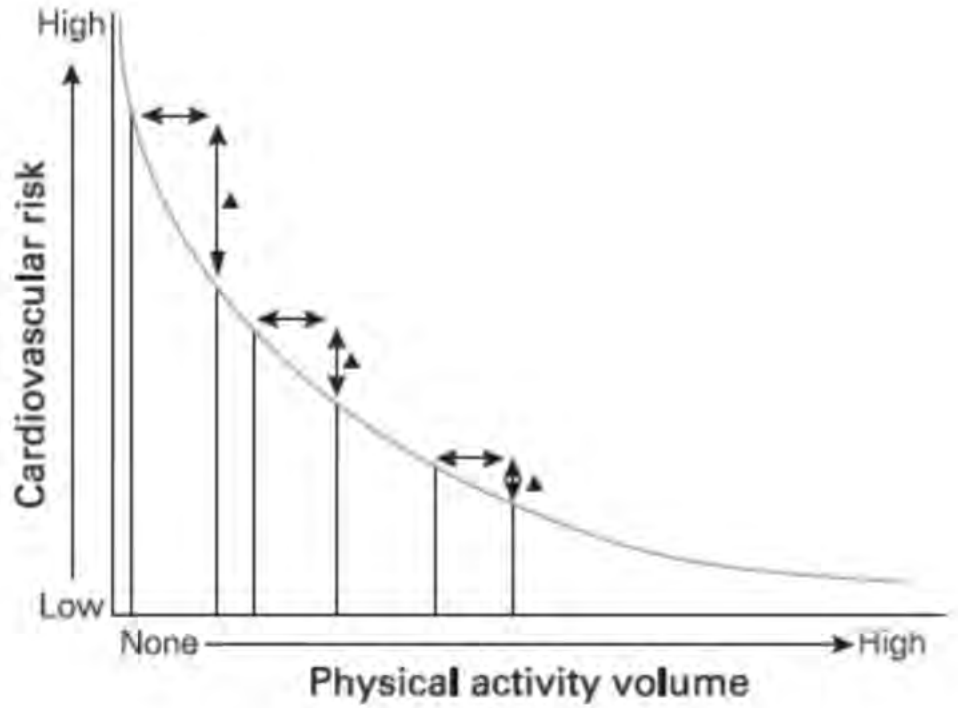
How to choose the best olive oil

- Buy only olive oil labelled “extra virgin”. Extra virgin olive oil is the highest quality olive oil with the very lowest acidity (<0.8%). It is extracted through a cold mechanical process without using any chemical refining methods.

- The label should also state “First cold pressed”. This means the olives were crushed in a mill and pressed only once at a temperature that did not exceed 30C (86F). Lower quality olive oils are crushed multiple times and at higher temperatures to extract more oil from the fruit.

- Look for the harvest and bottled date. You should consume extra-virgin olive oil within 12-14 months from the time of the production.

Physical exercise as a daily medicine



Relationship between physical activity and CV risk

Physical inactivity is associated with the highest risk, whereas high aerobic exercise volumes are associated with the lowest risk

Luigi Fontana. The Path to Longevity.

How much exercise do we need?

According to the **2018 Physical Activity Guidelines Advisory Committee Scientific Report**, to achieve substantial health benefits, we should undertake:

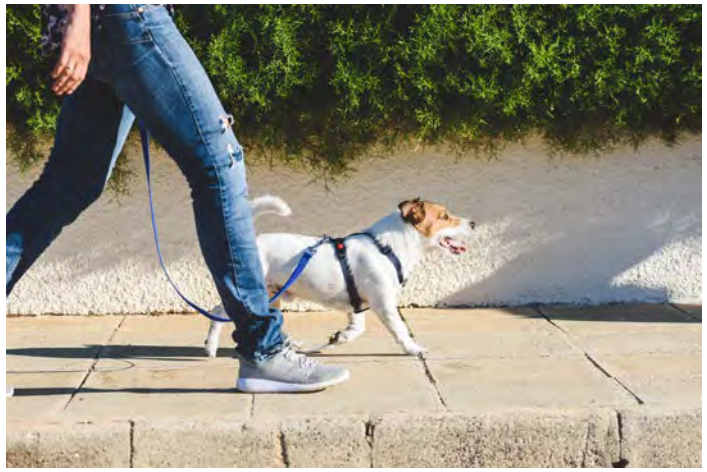
1. At least *150-300 minutes a week of moderate-intensity* or *75-150 minutes a week of vigorous-intensity aerobic physical exercise*, or an equivalent combination of moderate and vigorous-intensity aerobic training

2. Muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups on two or more days a week.

Examples of aerobic activities to achieve exercise guideline recommendations

***Moderate intensity activities**:*

- Brisk walking
- Cycling (less than 16 km/h)
- Water aerobics
- Tennis (double)
- Volleyball
- Ballroom dancing
- Raking the yard



***Vigorous-intensity aerobic activities**:*

- Uphill walking or race walking
- Running or jogging
- Cycling (at more than 16 km/h)
- Tennis single
- Strenuous fitness class
- Aerobic dancing
- Heavy gardening (digging/hoeing)

Beneficial effects of aerobic exercise

- Even in non obese people aerobic exercise is the most powerful intervention to improve *insulin sensitivity* and *glucose tolerance* (more potent than calorie restriction)
- Walking for ~18 km a week, 2.5 km (1.5 miles) a day, is very effective *in improving oral glucose tolerance* despite a modest 2 Kg (4.4 lb) reduction in body fat
- Walking for 18 km/week more effective than multicomponent intervention (diet and exercise induced weight loss) for preventing the progression to diabetes in individuals affected by pre-diabetes
- Regular endurance training also decreases systolic and diastolic blood pressure (the largest reduction occurs in systolic BP, especially in patients with hypertension)
- Vascular health (arterial function and parasympathetic tone).

Aerobic exercise helps to reduce cancer risk

- Epidemiological studies suggest that aerobic exercise reduces the risk of at least 13 cancers in particular breast, colon, endometrium
- It can help to improve the prognosis after being treated for breast, colon and prostate cancer
- Breast cancer studies suggest that 30-40 minutes per day of brisk waking can reduce mortality by 50%
- Reduction in abdominal fat and insulin seem to play a key role

Sitting
Breaking sitting with bouts of slow walk (every 30 min)

Stepping
An increase of with 2-9% decr and all cause m

Sleep
The quantity associated with health outcomes with both long (>8 h) and short (<6 h) sleep durations having negative impacts

Sweating
A reasonable target for physical activity is at least

Journal of Diabetes
Open Access

LETTER TO THE EDITOR | Open Access

The importance of sleep quality, quantity, and chronotype in the management of diabetes: Is it time to wake up?

Theocharis Koufakis, Giuseppe Maltese, Djordje S. Popovic, Kalliopi Kotsa

First published: 09 September 2022 | https://doi.org/10.1111/1753-0407.13313

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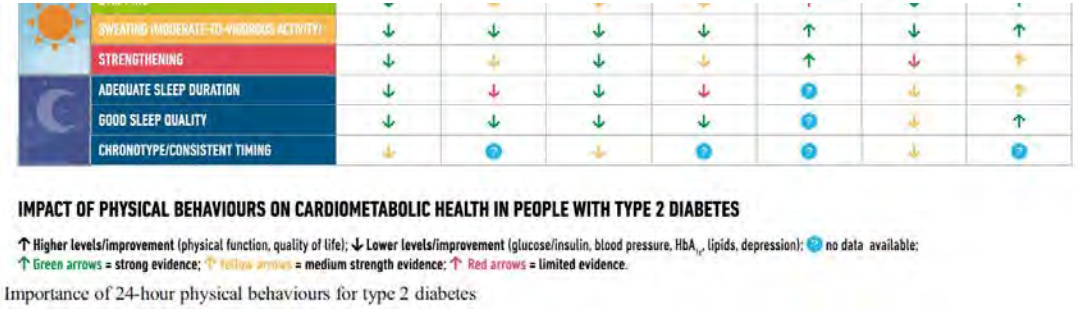
y and glucose



Importance of 24-hour physical behaviours for type 2 diabetes

nutrients

MDPI

Article

Adherence to Mediterranean Diet and Soluble Klotho Level: The Value of Food Synergy in Aging

Shou-En Wu [1], Ying-Jen Chen [2] and Wei-Liang Chen [3,4,5,*]

[1] Department of Dermatology, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei 11490, Taiwan
[2] Department of Ophthalmology, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei 11490, Taiwan
[3] Division of Family Medicine, Department of Family and Community Medicine, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei 11490, Taiwan
[4] Division of Geriatric Medicine, Department of Family and Community Medicine, Tri-Service General Hospital, School of Medicine, National Defense Medical Center, Taipei 11490, Taiwan
[5] Department of Biochemistry, National Defense Medical Center, Taipei 11490, Taiwan
* Correspondence: weiliang0508@gmail.com; Tel.: +886-2-8792-3311 (ext. 16567); Fax: +886-2-8792-7057

Abstract: Diets for healthy aging have long been an intriguing issue. The current study makes a head-to-head comparison of four dietary patterns and their associations with soluble Klotho (s-Klotho) levels, an aging-related marker. The dietary data of 7906 subjects were obtained from the National Health and Nutrition Examination Survey 2007–2016. Each participant was given a score or was grouped according to four dietary patterns, namely the Mediterranean adherence diet score (MDS), the low-carbohydrate-diet score, a low-fat diet, and a low-carbohydrate diet. Subsequently, the associations with s-Klotho were examined using linear regression analyses. In addition, we calculated the odds ratio (OR) for aging in different dietary patterns, taking the lowest quartile of s-Klotho as a reference for aging. The MDS was the only dietary pattern that revealed a relationship with s-Klotho levels. The positive association (β coefficient: 9.41, $p < 0.001$) remained significant when dividing the MDS into tertiles (Tertile 2: β coefficient: 36.87, $p < 0.001$; Tertile 3: β coefficient: 45.92, $p < 0.001$) and grouping participants into subsets by sex, age, and BMI. A lower OR for aging was observed in higher MDS groups (Tertile 2: OR = 0.86, $p = 0.026$; Tertile 3: OR = 0.77, $p < 0.001$). However, when analyzed separately, merely three out of nine components of the MDS, namely alcohol consumption (β coefficient: 42.54, $p < 0.001$), fruit (β coefficient: 11.59, $p = 0.029$), and dairy products (β coefficient: 8.55, $p = 0.032$), showed a significant association with s-Klotho. The Mediterranean diet adopts a food-based approach, which has the merit of valuing the complex interactions between foods and their constituents, and further brings benefits to healthy aging.

Keywords: soluble Klotho; Mediterranean diet; low-carbohydrate diet; low-fat diet; aging

Citation: Wu, S.-E.; Chen, Y.-J.; Chen, W.-L. Adherence to Mediterranean Diet and Soluble Klotho Level: The Value of Food Synergy in Aging. *Nutrients* **2022**, *14*, 3910. https://doi.org/10.3390/nu14193910

Academic Editors: Nicola Di Daniele and Annalisa Noce

Received: 2 September 2022
Accepted: 17 September 2022
Published: 21 September 2022

"This study shows a positive association between Mediterranean Diet and soluble Klotho. No association was found with low carb diet and low fat diet".

> Free Radic Biol Med. 2014 Oct;75 Suppl 1:S14-5. doi: 10.1016/j.freeradbiomed.2014.10.588. Epub 2014 Dec 10.

Induction of antioxidant genes by sulforaphane and klotho in human aortic smooth muscle cells

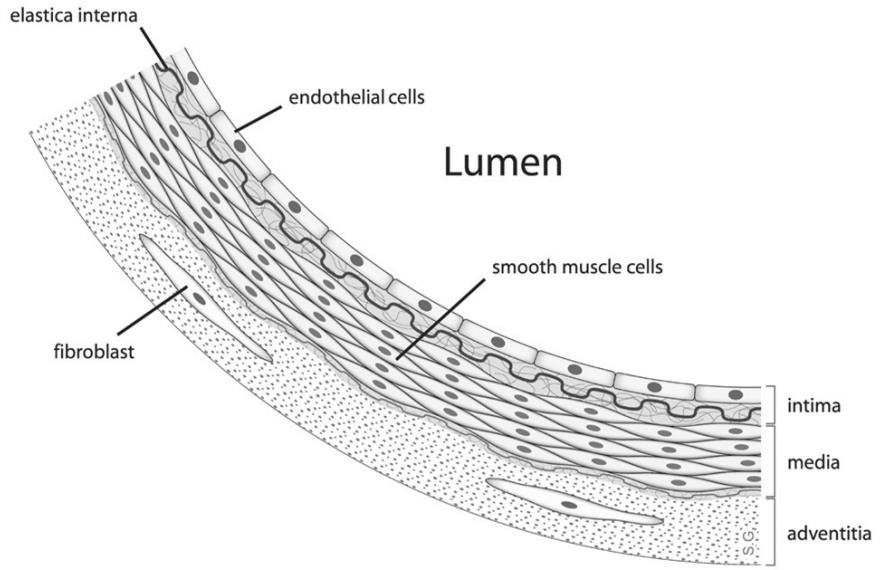
Benedetta Rizzo [1], Giuseppe Maltese [2], Maria Psefteli Paraskevi [2], Silvana Hrelia [1], Giovanni Mann [2], Richard Siow [3]

Affiliations + expand

PMID: 26461289 DOI: 10.1016/j.freeradbiomed.2014.10.588

Abstract

Vascular smooth muscle cell (SMC) dysfunction due to enhanced oxidative stress contributes to age-related cardiovascular diseases such as atherosclerosis and calcification. Klotho, a protein with multiple pleiotropic effects associated with anti-ageing, can extend lifespan when overexpressed while its deficiencies result in rapid aging. It exists in membrane and secreted forms with distinct pleiotropic functions, with the secreted form regulating ion channels, suppressing growth factor signaling and oxidative stress while the transmembrane protein forms a co-receptor for FGF23, although the mechanisms involved in its actions remain to be fully elucidated. Sulforaphane (SFN) is an isothiocyanate present in cruciferous vegetables that can induce antioxidant defence enzymes such as heme oxygenase-1 (HO-1) and peroxiredoxin-1 (Prx-1). The present study investigates whether SFN or klotho increases antioxidant defences in cultured human aortic SMC. Cells were treated (0-24h) with either SFN (0-5μM) or klotho (0-1nM) and HO-1, Prx-1 expression determined by western blot analyses and glutathione (GSH) levels measured using the o-phthalaldehyde fluorescence assay. SFN significantly ($p<0.05$, $n=3$) enhanced both HO-1 and Prx-1 protein expression and GSH levels in SMC at 12 and 24h while klotho treatments significantly ($p<0.05$, $n=3$) augmented HO-1 and Prx-1 expression only at 24h but significantly increased GSH levels after both 8h and 24h. Interestingly preliminary data suggest that treatment of SMC with SFN for 12 or 24h enhances the expression of klotho. Taken together, these findings demonstrate that both SFN and klotho can enhance antioxidant defences which may protect against vascular SMC dysfunction in age-related cardiovascular diseases.Supported by the British Heart Foundation, Heart Research UK and the 'Marco Polo' Program, University of Bologna.



Key findings

- Vascular smooth muscle cells (VSMC) were cultured in vitro
- Klotho was found to be expressed in VSMC
- The *in vitro* treatment of VSMC with sulforaphane enhances the expression of Klotho

Exercise training increases levels of the anti-ageing Klotho protein: health-related cardiometabolic implications. The FIT-AGEING randomised controlled trial (PhD Academy Award)

Francisco J Amaro-Gahete

After that, a 12-week randomised controlled trial was performed recruiting a total of 89 middle-aged adults (53.5±4.9 years old; ~53% women). The participants were randomly assigned to one of the following treatment groups: (1) no exercise (control group), (2) concurrent training based on international physical activity recommendations (PAR group), (3) high intensity interval training (HIIT group) or (4) HIIT plus whole-body electromyostimulation (HIIT+EMS group). Healthy ageing–related outcomes included the baseline

WHAT DID I FIND?

- *Section 1*: Higher lean mass,[1] physical fitness,[1] and fat oxidation in basal conditions and during exercise[2] were associated with greater levels of S-Klotho, while a poorer cardiometabolic profile and insulin resistance[3] were associated with lower levels of S-Klotho.
- *Section 2*: Exercise training induces an improvement in S-Klotho,[4] physical fitness,[1] energy metabolism[5] and cardiometabolic health,[6] obtaining slightly better results with the application of a HIIT+EMS intervention, independently of several confounders factors (ie, age and sex among others).[1]

Amaro-Gahete FJ. Br J Sports Med 2020;54:1233–1234.

Trends in Endocrinology & Metabolism Supports open access

FORUM | ONLINE NOW

Can sodium-glucose cotransporter 2 inhibitors 'spin the thread of life'?

Giuseppe Maltese • Theocharis Koufakis • Kalliopi Kotsa • Janaka Karalliedde • Show footnotes

Published: November 07, 2022 • DOI: https://doi.org/10.1016/j.tem.2022.10.002

- SGLT2i are antidiabetic agents lowering the blood glucose levels by promoting glycosuria
- In recent years, randomised clinical trials have demonstrated that SGLT2i reduce cardiovascular-renal events and all-cause mortality in people with and without diabetes
- SGLT2i can exert anti-ageing effects on the vasculature and other body organs through several signalling pathways and the induction of antioxidant enzymes
- We speculate that the pro-longevity effects of the SGLT2i are mediated by soluble Klotho.

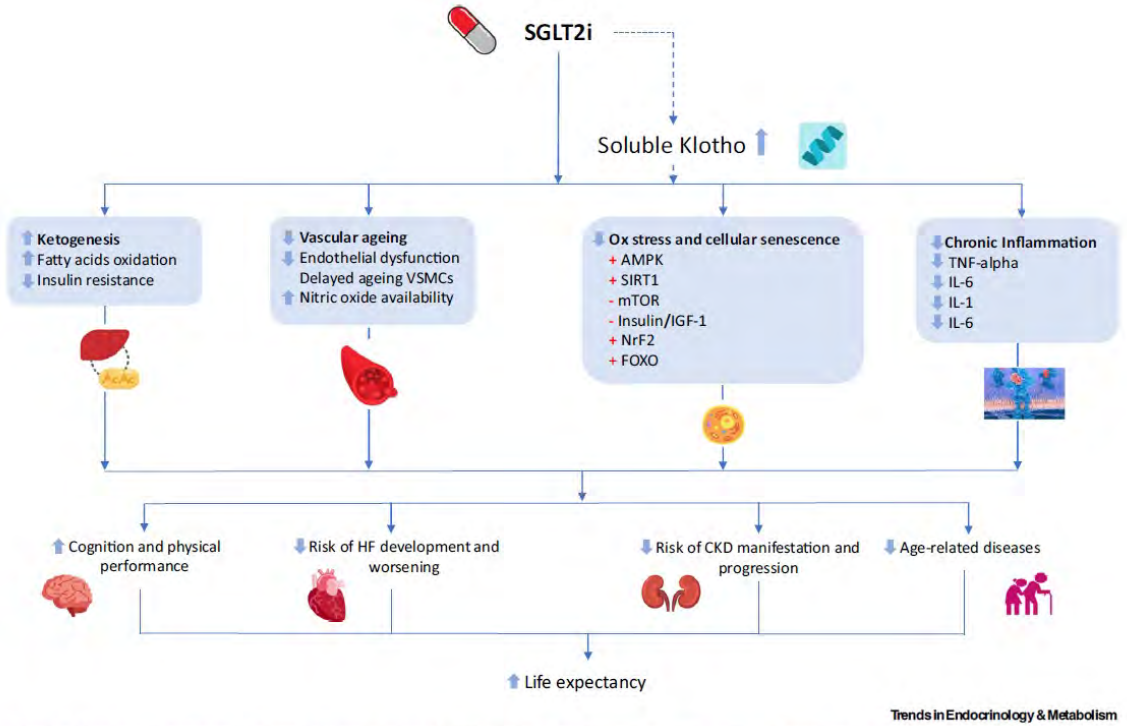
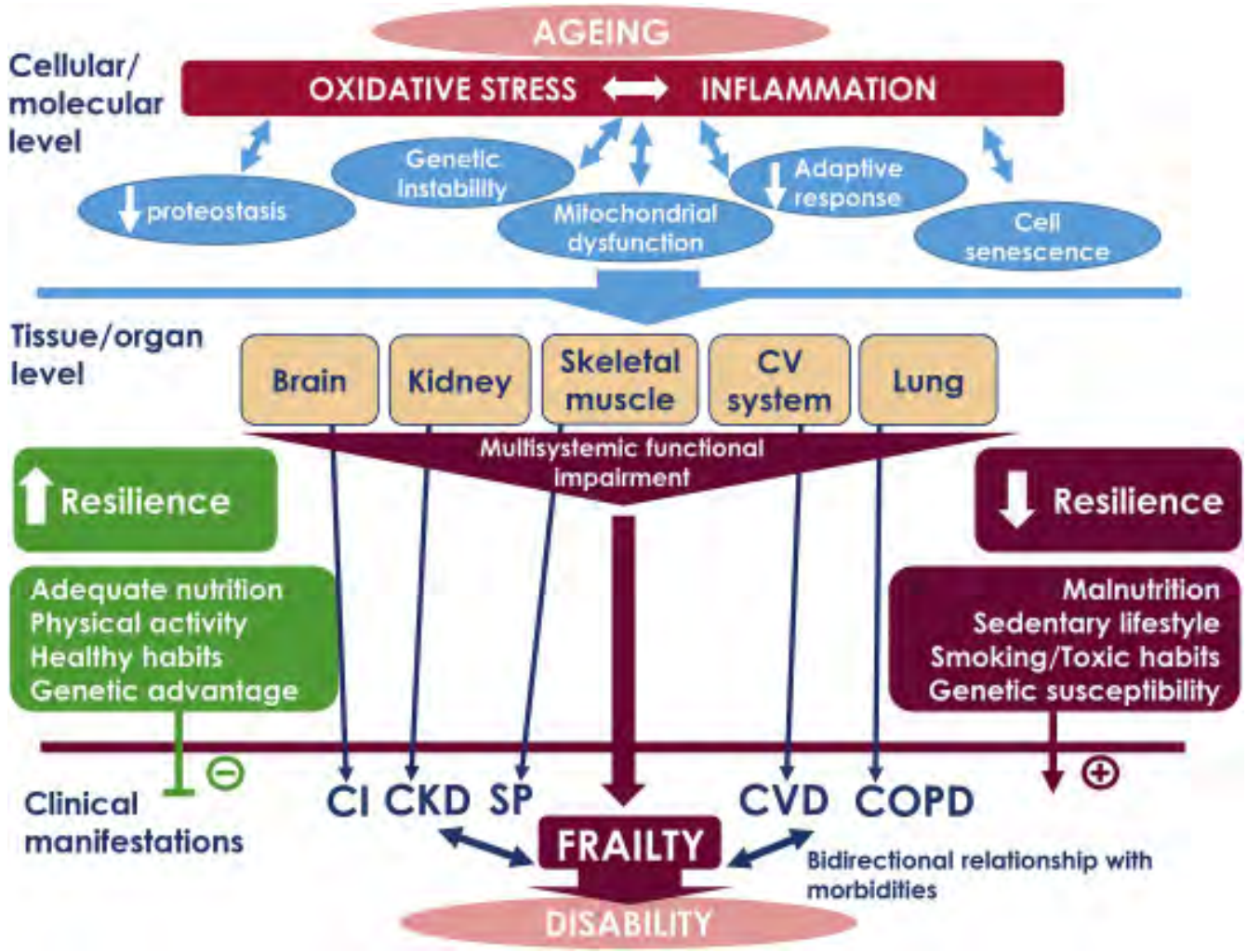
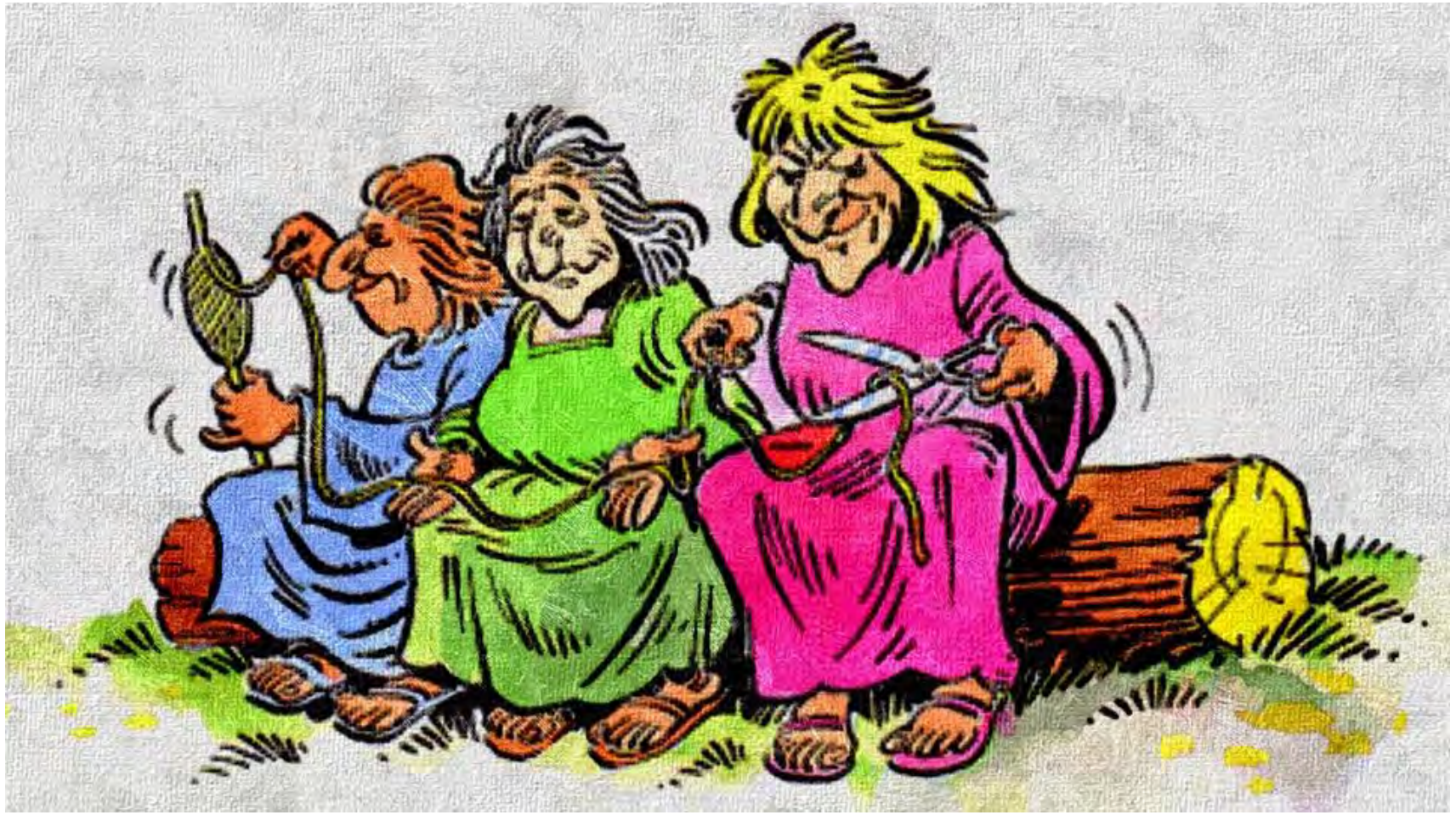
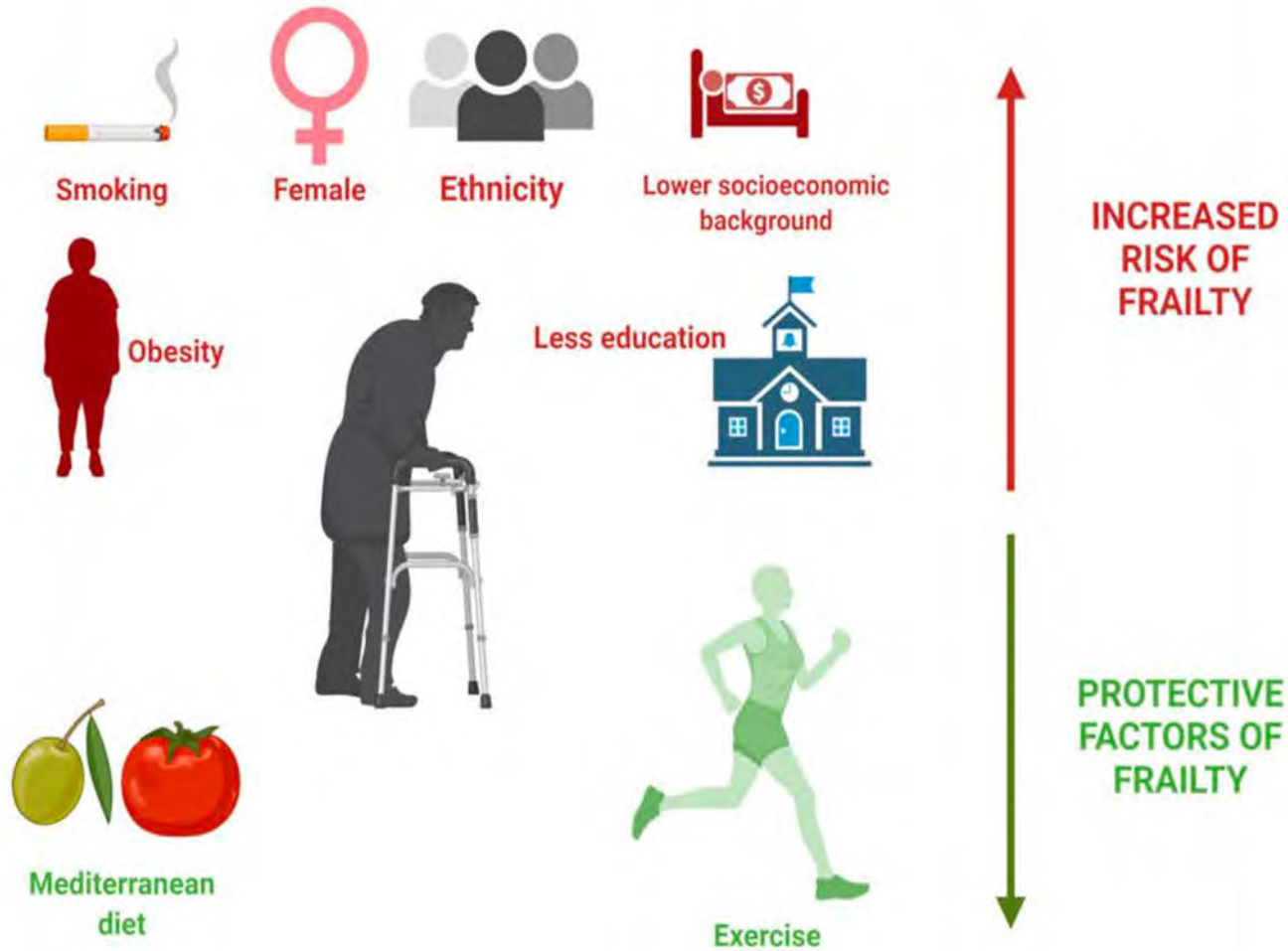


Figure 1. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and Klotho interplay in ageing and cardiovascular-renal disease. Abbreviations: CKD, chronic kidney disease; HF, heart failure; VSMC, vascular smooth muscle cells.


AGEING
Cellular/ molecular level
OXIDATIVE STRESS
INFLAMMATION
proteostasis
Genetic instability
Mitochondrial dysfunction
Adaptive response
Cell senescence
Tissue/organ level
Brain
Kidney
Skeletal muscle
CV system
Lung
Multisystemic functional impairment
Resilience
Adequate nutrition
Physical activity
Healthy habits
Genetic advantage
Resilience
Malnutrition
Sedentary lifestyle
Smoking/Toxic habits
Genetic susceptibility
Clinical manifestations
CI CKD SP
CVD COPD
FRAILTY
Bidirectional relationship with morbidities
DISABILITY

Thank you for the attention




Smoking
Female
Ethnicity
Lower socioeconomic background
Obesity
Less education
INCREASED RISK OF FRAILTY
Mediterranean diet
Exercise
PROTECTIVE FACTORS OF FRAILTY