Guardians of Healthy Longevity

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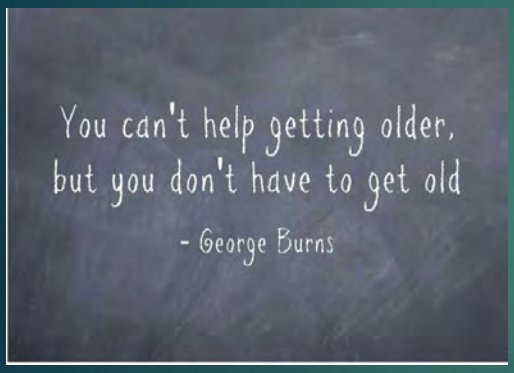
Poll

A 65 year old man arrives for his Welcome to Medicare wellness exam. He says that he is active and feels like he can live to 100 years of age. His mother lived to be 99 years old. He asks what you can do to give him another 35 active years. Your best answer is

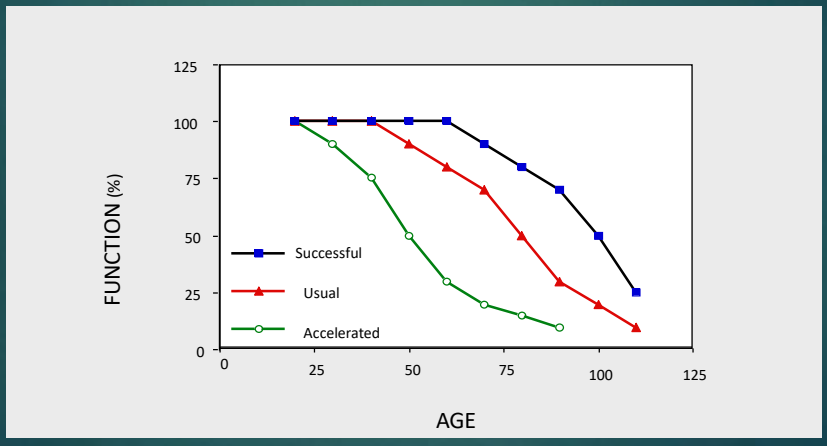
A. Mediterranean diet
B. Exercise
C. Caloric restriction
D. Daily ginkgo biloba

Objectives

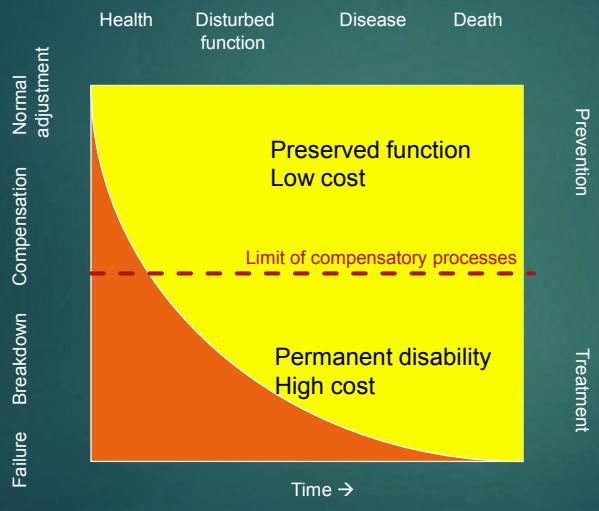


- Define successful aging
- Measure biological aging
- Invest in the longevity dividend

The Aging Process



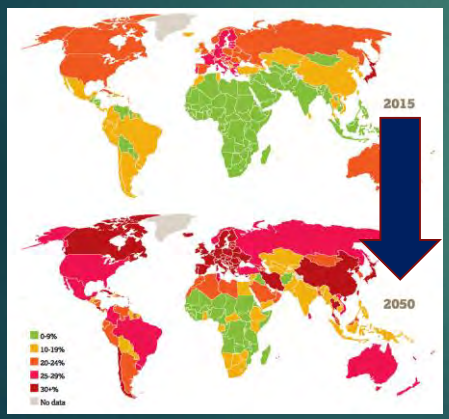
Environment: homeostasis, stress and aging



Conundrum

Unprecedented growth in global aging

Percent of population > 65 y/o



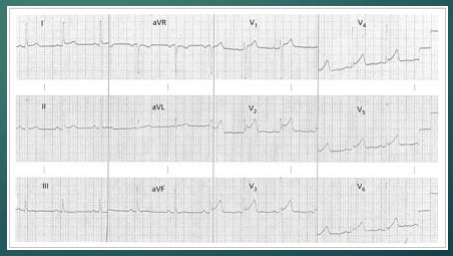
Subgroups with worsening health in late life

Latent effects of childhood obesity (doi: 10.1056/NEJMsr043743)

Lower life expectancy of poorly educated white men

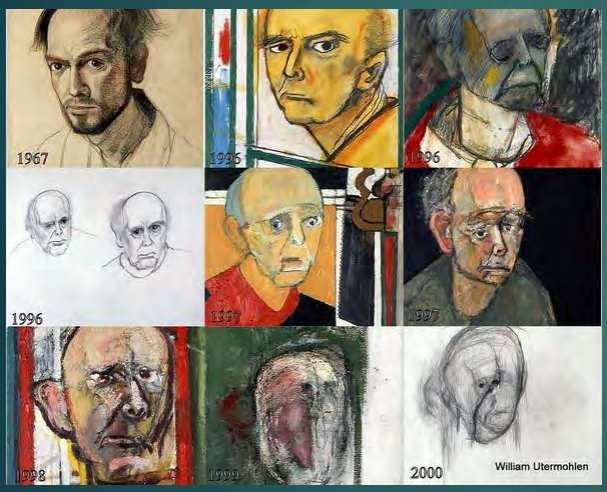
(doi: 10.1377hlthaff.2011.0746)

Unsuccessful Aging: physical decay



Early repolarization in AA men mimics acute pattern of injury

Unsuccessful aging: brain failure



Self – portraits with Alzheimer's Disease

Unsuccessful aging: psycho – social destitution

Successful aging

Multi – dimensional

- Functional independence
- Healthy brain
- Psycho – social integrity

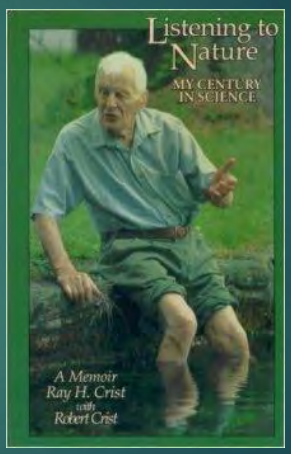
Successful aging: physically robust

Robert Marchand, 105 year old cyclist

Fauja Singh, 104 year old distance runner

Successful aging: cognitive maintenance

Stanislaw Skrowaczewski (93)
Minnesota Orchestra



Ray H. Crist, PhD (105), former Manhattan Project leader, oldest US professor

What determines successful aging ?

Genetic versus Environment

Genetics of aging

- Danish twin study: 25% inheritability

Human Genet (2006) 119:312

- Longevity genes vs disease resistance

SNP	Function	Disease correlates
APOE / TOMM40	Lipid metabolism	APOE4 = Alz Dx
CDKN2B / ANRIL	Cell senescence	CAD, DM
ABO	"O" Blood group	
SH2B3 / ATXN2	Lifespan gene	CAD, DM, cancer, ALS

PLOS Genetics (2015) doi: 10.1371/journal.pgen.1005728

Danish twin study

Monozygotic twins 67 years old

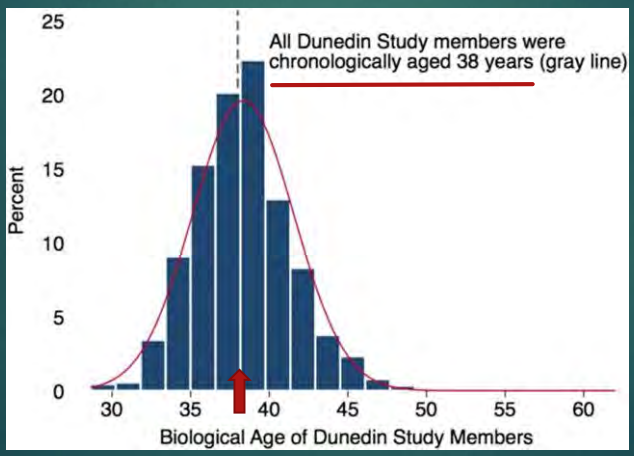
Perceived age A = 64 (57 – 70 y.o.)
B = 70 (60 - 85 y.o.)

Dizygotic twins 69 years old

Perceived age C = 64 (59 – 74 y.o.)
D = 76 (69 – 84 y.o.)

PLoS One. 2009; 4(12): e8021. doi: 10.1371/journal.pone.0008021

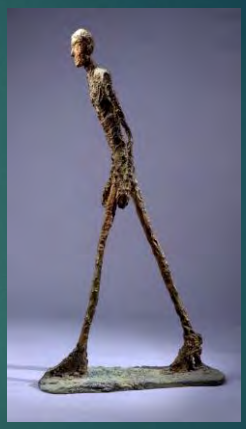
The older we get, the less we look alike physiologically.



How can we measure aging ?

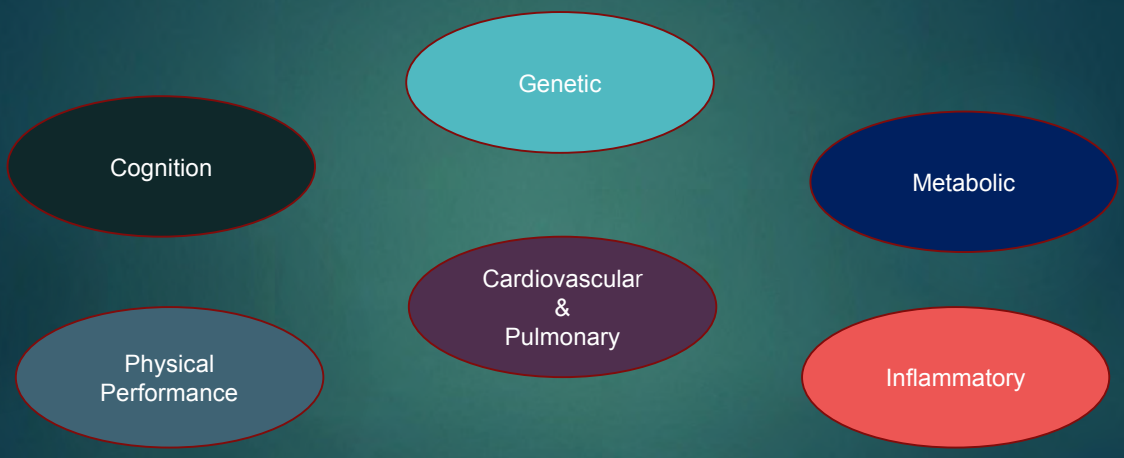
Processes:

- Physiologic measurements
  - Function
  - Biologic
- Psychological measurements
  - Happiness
  - Sense of purpose

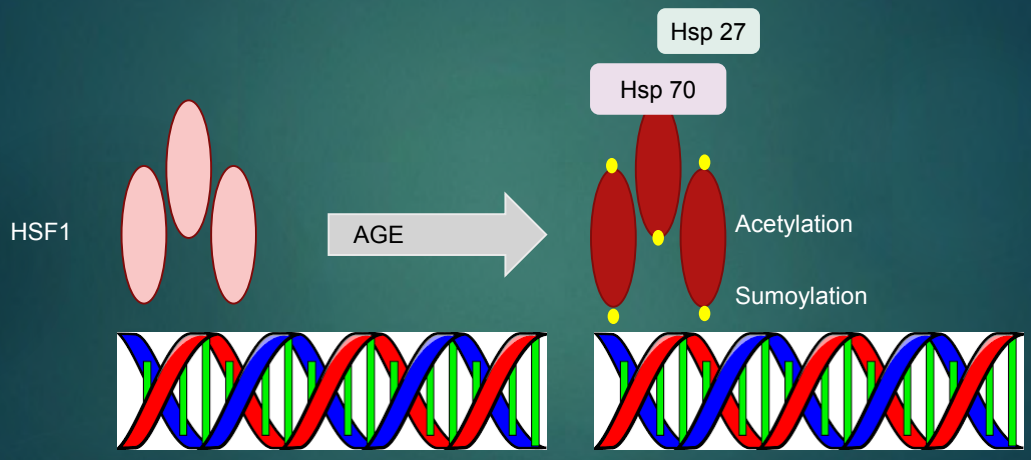


Alberto Giacometti

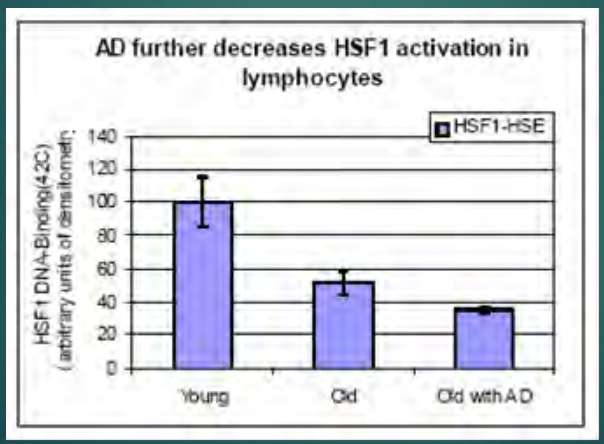
Biomarker categories



Biomarkers of aging: cellular stress



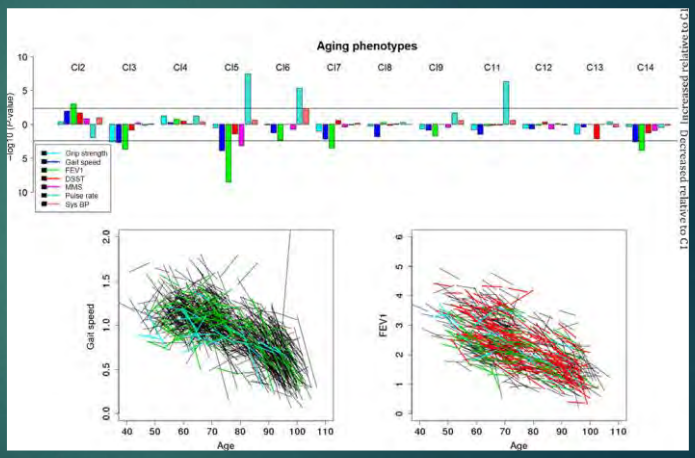
HSF1 – activation in old donors with cognitive impairment



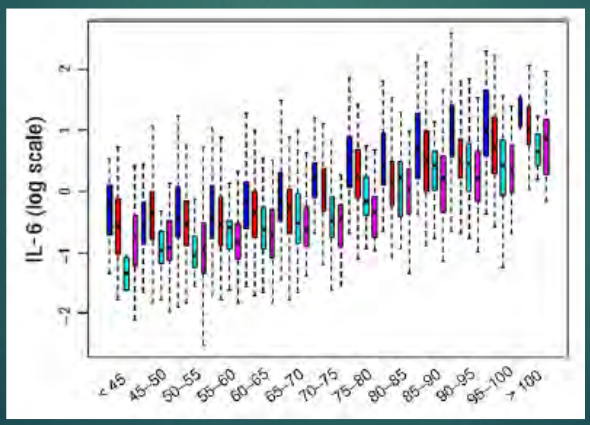
Biomarkers of aging: Long Life Family Study

Spaghetti plots of

- gait speed
- FEV1 changes

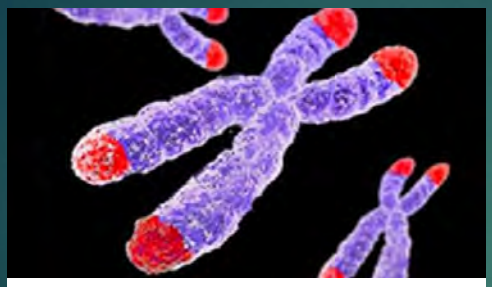


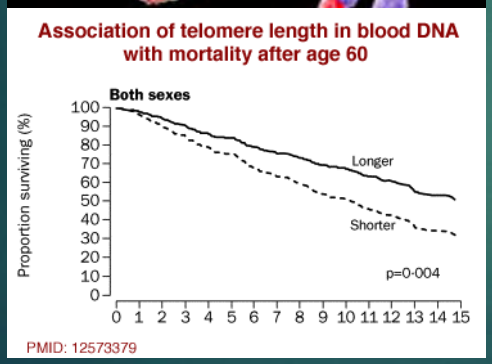
Inflammatory markers and age

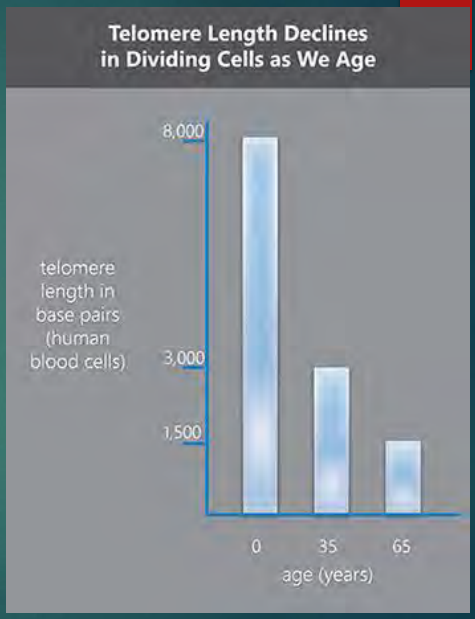


CRP
IL-6

Long Life Family Study

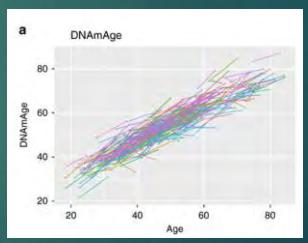






Lifespan changes in DNA methylation

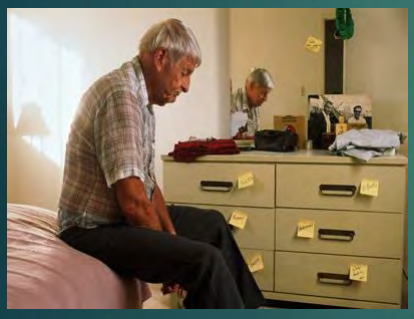
Global decline in DNA methylation



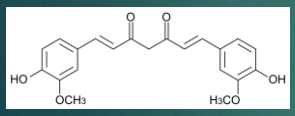
Hyper methylation at promoters and CpG rich regions

What is the evidence that we can change the course of aging ?

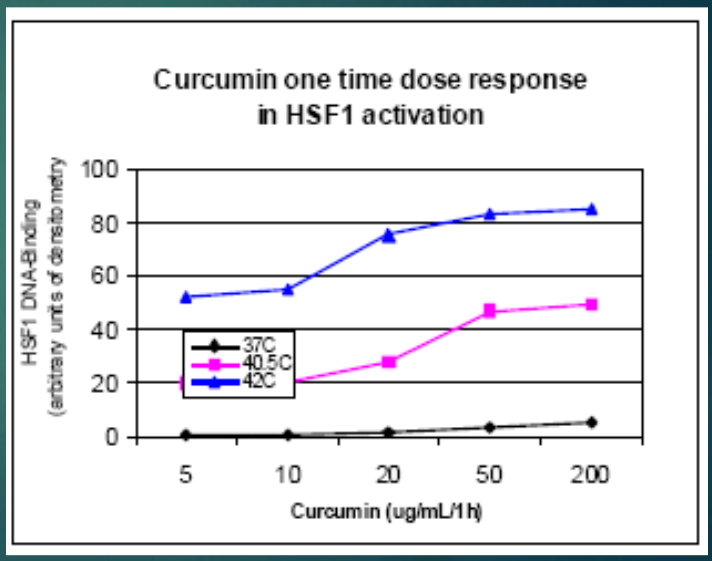
Can the stress response be revived with age ?



Modulators of the human heat shock response



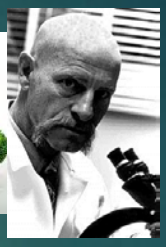
curcuminoid



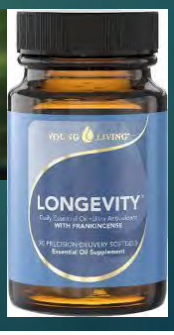
Calment credited her longevity to Port wine, a diet rich in olive oil, and her sense of humor. "I will die laughing," she predicted.

Healthy Longevity interventions

- Nutrition
  - Caloric Restriction
- Physical activity
- Supplements

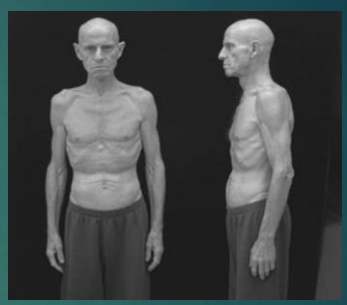


Roy Walford, MD



Caloric Restriction to prolong life

- Gene activation
  - Metabolic and Stress Genes
- Gene suppression
  - DNA methylation, IGF1 signaling
- Controversies
  - Not all animal models benefit from CR
  - Intermittent versus continuous intervention
  - Total calorie versus protein restriction



Roy Walford, MD

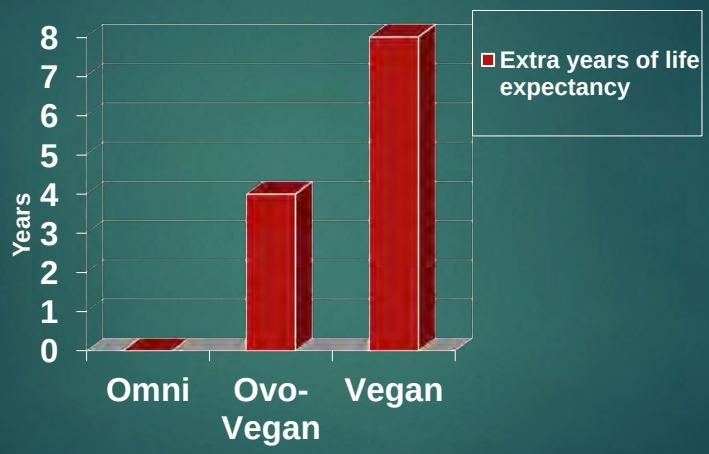
Intermittent caloric restriction

VD Longo, PhD

- Intermittent fasting: 60 % caloric intake twice weekly or qod
- Periodic fasting: 5 day diet ~ 1000 calories
- Time restricted feeding: limit feeding within 8 hour period

Ageing Res Rev. 2016 Oct 31. pii: S1568-1637(16)30251-3. doi: 10.1016/j.arr.2016.10.005

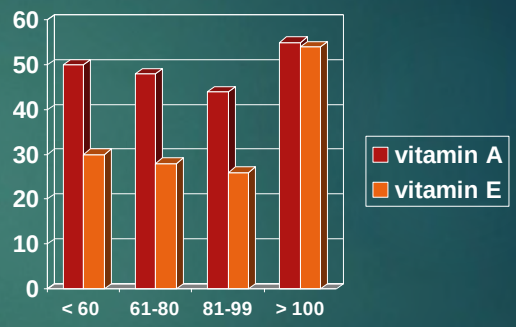
Adventist Health Study 1



Centenarian Diets

	Meat	Fish	Milk / cheese	Beans	Vegies	Fruits	Bread
Sardinia	+	+	++++	++++	++++	++++	++++
Okinawa		+++		++++	++++	++++	++++
Costa Rica	++	+		++++	++++	++++	++++
Loma Linda				++	++++	++++	++

Centenarians exhibit high anti-oxidant vitamins in their serum



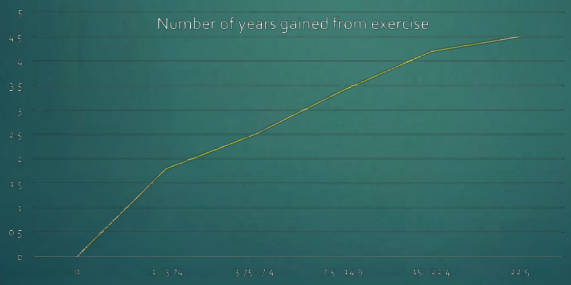
Free Radical Biology and Medicine (2000) 28:1243-1248

Physical inactivity accelerates aging processes

Telomere length is reduced by aging and inactivity

Healthy longevity through exercise

65 year old	Healthy Life Expectancy	Years gained
No exercise	77.7 years old	----
Exercise	83.4 years old	5.7 years



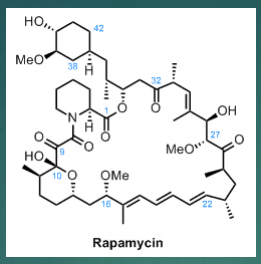
PLOS 2012

How much exercise is enough ?

Intensity	Duration (minutes)	Benefit (% CV risk reduction)
Low	30	10
Moderate	60	20 – 30
Intense	90	40

Longevity extension through chemistry ?

Rapamycin



Arlan Richardson, PhD

mTOR inhibitor

Animal studies:

Improve lifespan in mice 9 – 13 % (gender effects).

Nature 460, 392-395

Reduces old dog infirmities

Human Studies:

improved influenza vaccine response in elderly by 20%

Science Translational Medicine (2014) 6:268

Metformin

United Kingdom Prospective Diabetes Study

reduced CV events in diabetics

Meta-analyses

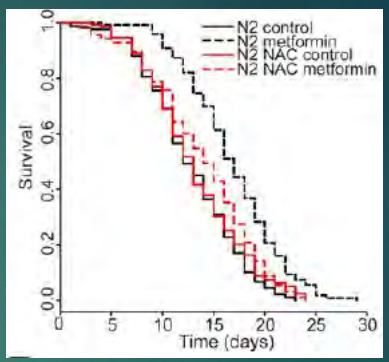
reduced cancer rates

Metformin in Longevity Extension (MILES)

NIH clinical trial NCT02432287

Action:

- reduces IGF1 signaling
- improves AMP kinase activity
- enhances mitochondria



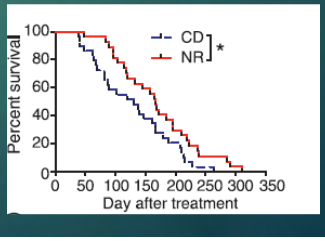
Metformin extends c. elegans lifespan via mito – oxidant hormesis

Naturally occurring anti – aging compounds ?

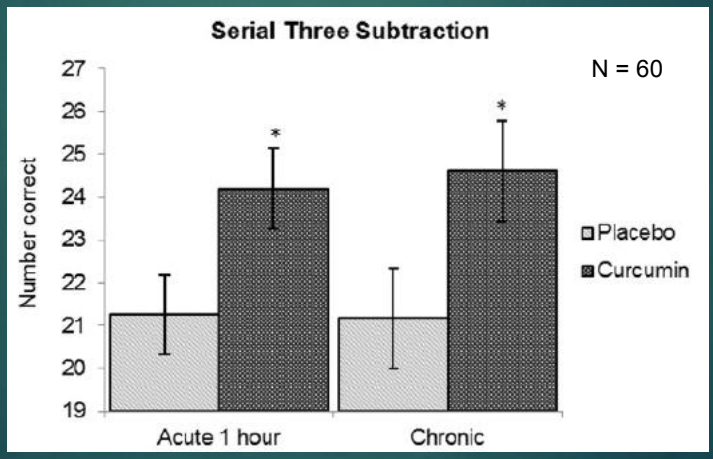
Nicotinamide Riboside therapy

- Skeletal muscle aging: animal models
- Age = loss of mitochondrial bioenergetics
  - Reduced NAD levels
  - Reduced sirtuin 1 (SIRT1) activity
- NR supplementation
  - Restores mitochondrial function
  - Extends lifespan

Science (2016) 352 (6292)



Lipid emulsified curcumin to prevent brain aging

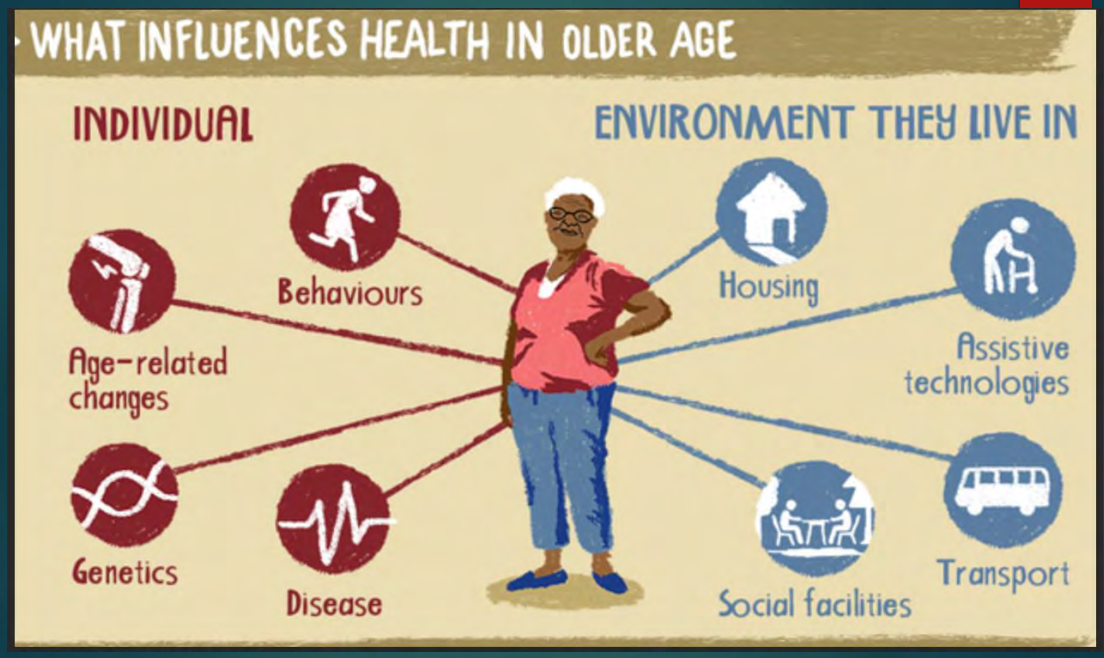


Journal of Psychopharmacology (2015) 29(5) 642 –651

Population Health and Healthy Aging

European Innovation Partnership on Active and Healthy Ageing

Goal: gain 2 years of healthy life years by 2020



Summary

- Biological age and rate of aging are measurable
- Anti-aging interventions include diet, physical activity and possibly chemical adjuvants
- Prescriptions for healthy lifespans can be part of personalized medicine as well as a population health metric
- The Longevity Dividend seeks to reduce disability and disease in late life by slowing the rate of aging.

Case Study

- A 67 year old woman arrives for her Medicare Annual Wellness exam and reports that she feels like she is losing her memory. Her mother died from Alzheimer's Disease and she is afraid of getting it too.

Case Study

- Her blood pressure is 148 / 88, her PHQ2 test is positive and states that things are not the same after retirement. She scored 23 / 30 on the SLUMS test.

4Ms assessment

- What matters: "getting her previous life back"
- Mobility: "household chores", no regular walking or exercise; gait speed 1.2 m / sec
- Mentation: + PHQ2, + SLUMS
- Medication: see next slide

Case study

Medication review:

- Ambien + / - Tylenol PM for insomnia
- Lisinopril for hypertension
- Tramadol prn for generalized joint and back pain
- Vitamin D for primary prevention of osteoporosis
- Gingko Biloba and Prevagen for memory
- Vitamin E for general health

Case study

- Does the patient have early Alzheimer's Disease ?
- Is she at risk for progressive dementia ?
- What are three evidence – based recommendations for dementia prevention ?
- What is your prescription for a healthy lifespan ?