Fasting, gene expression and life span

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Our Region

Lake Plastira

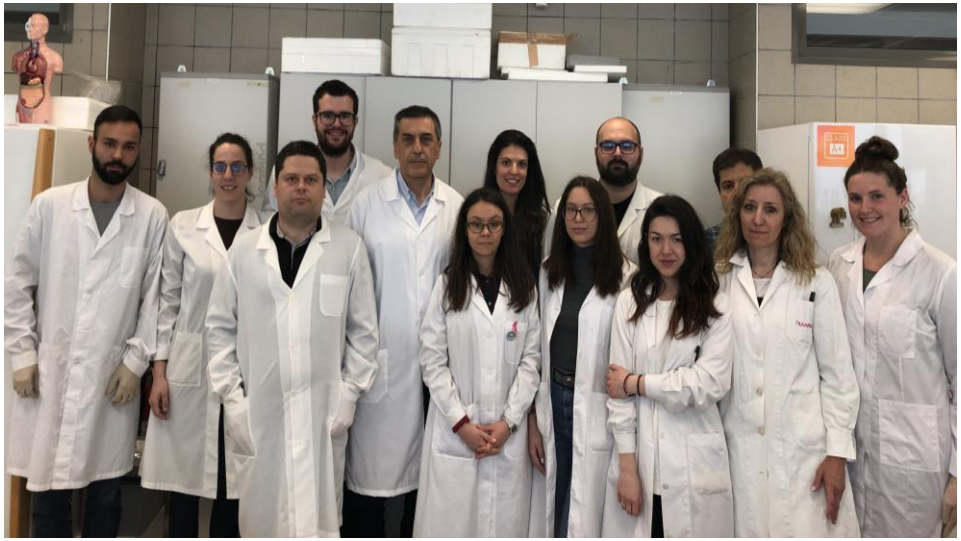
Thessaly, Greece

Meteora

Pelion

Mount Olympus

Our Laboratory



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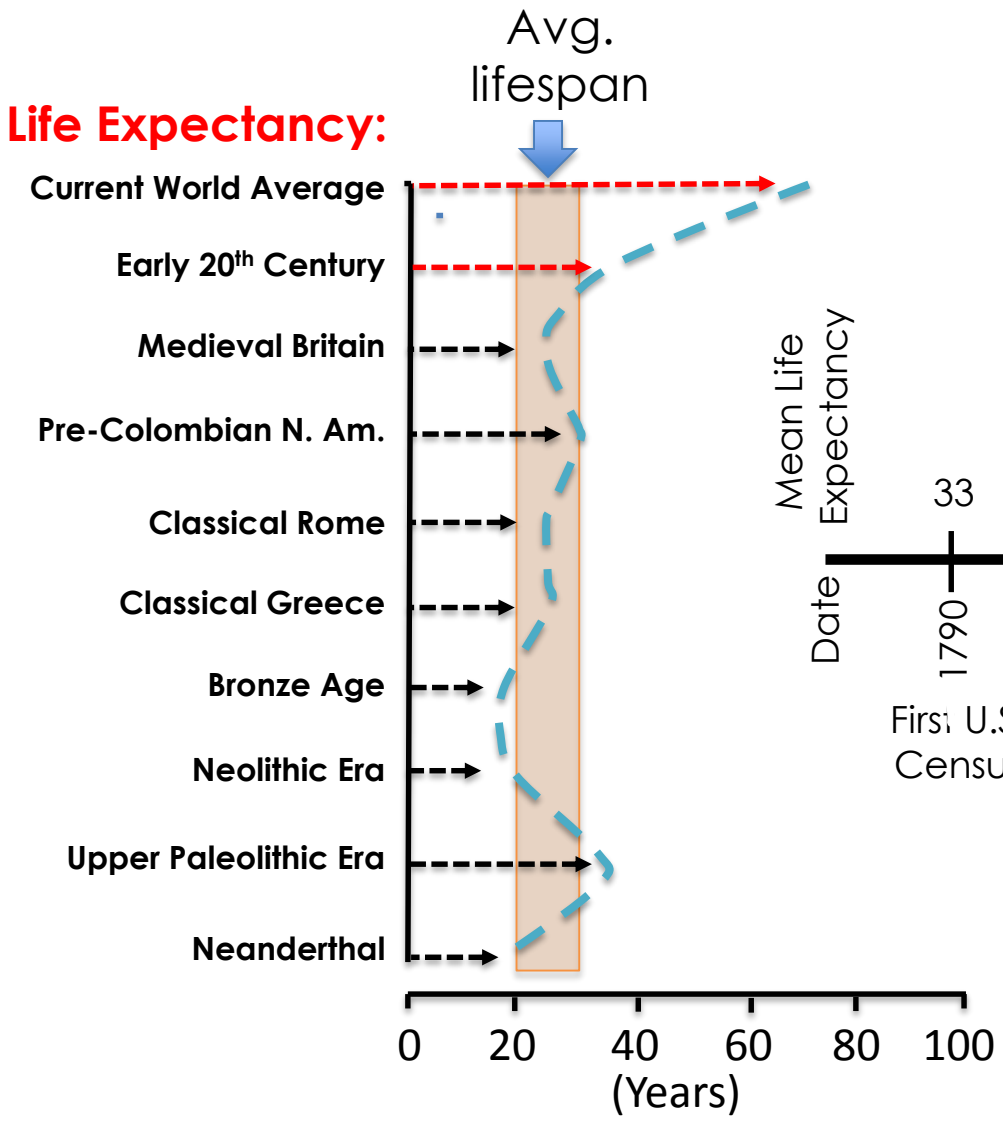
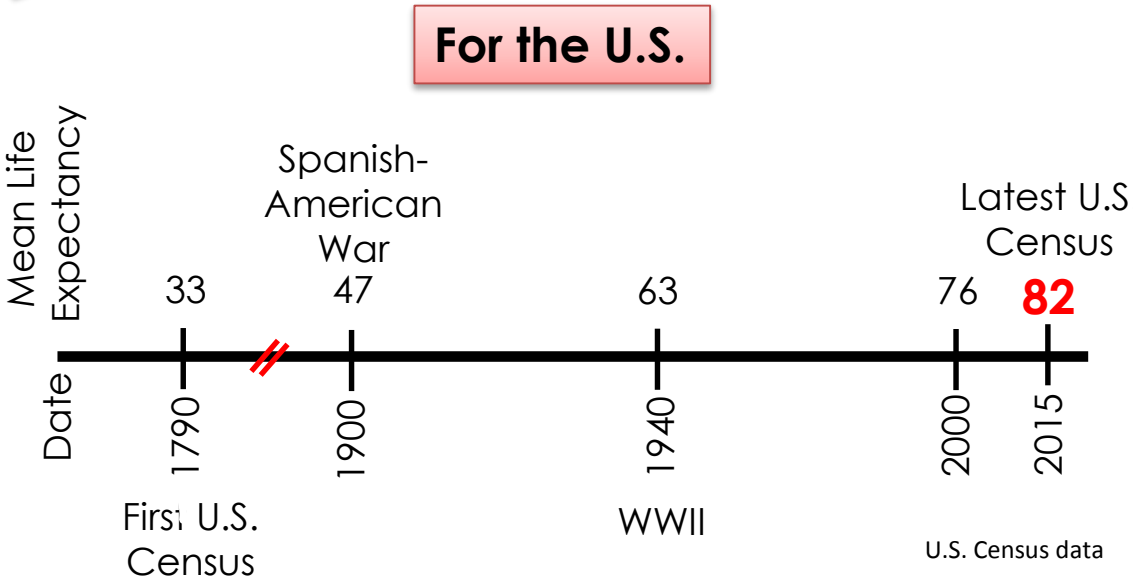
Spin-off company from
our Laboratory in U.TH

The Good News…We Are Living Far Longer Than Our Fore-bearers





Medicine Has Extended Our Life Expectancy

Better Sanitation

Antibiotics

Dramatically decreased mortality from infectious diseases

Pre- & post-natal care

Lowered mortality in childbirth & infant mortality

Drugs

Has made otherwise lethal diseases "chronic" in nature

"Assist" Devices

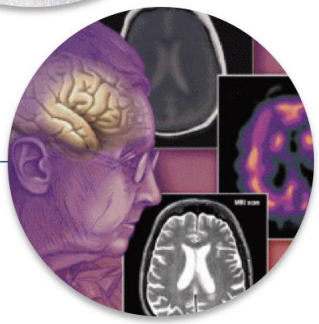
Compensates for loss of physiological function

Our Increased Longevity Often Comes at a Price:

chronic diseases and "disuse" syndromes

Chronic Diseases

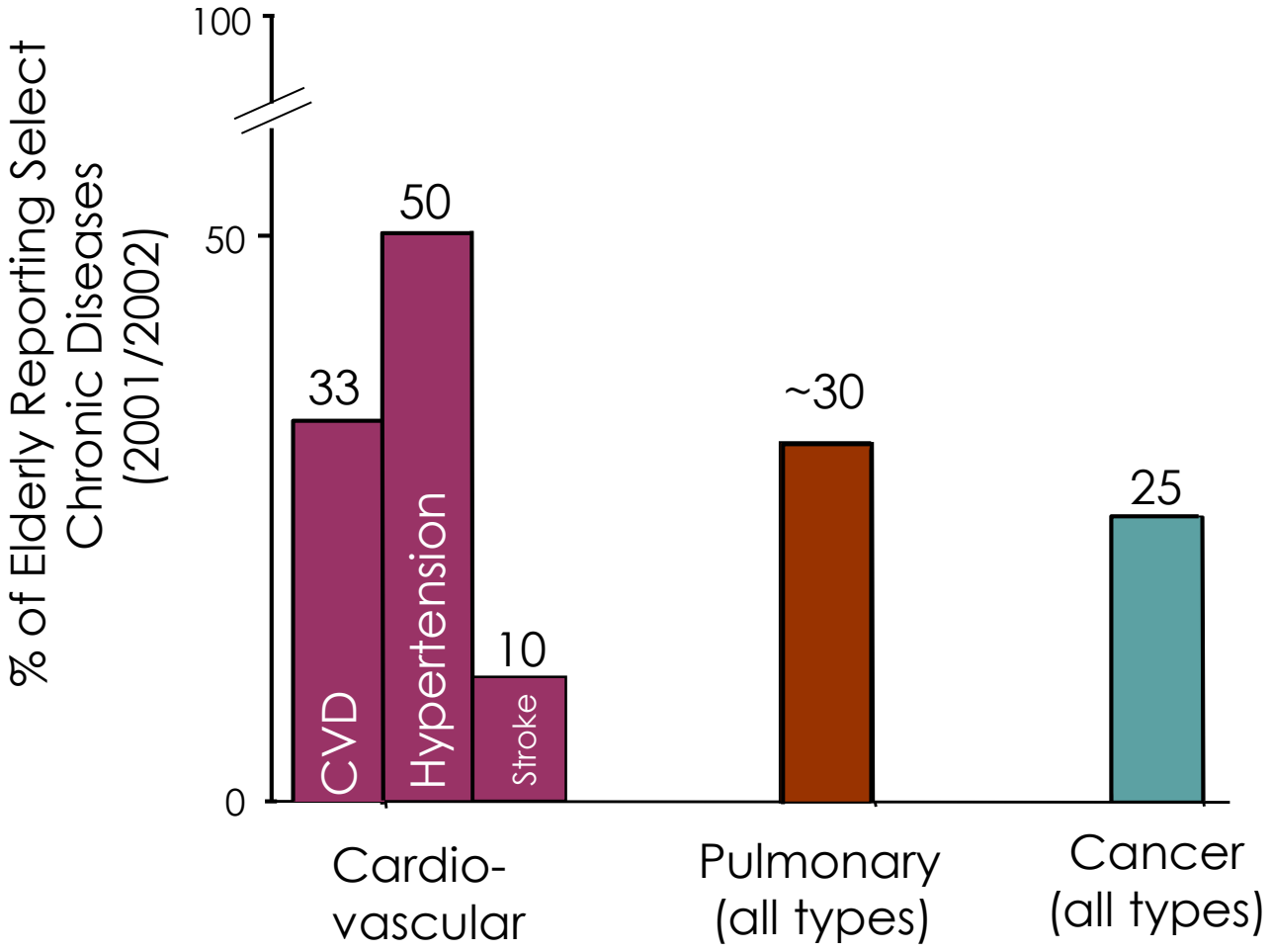
Frailty & Loss of Activities of Daily Living



Cognitive Decline

Older Adults are at High Risk for Chronic Disease

80% of Americans >65 yrs of age have at least 1 chronic disease



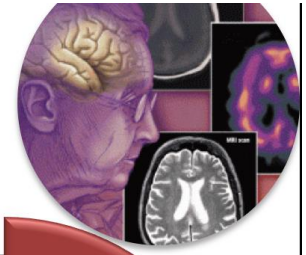
Source: CDC, National Center for Health Statistics, National Health Interview Survey

Age-related Loss in "Activities of Daily Living" (ADL)

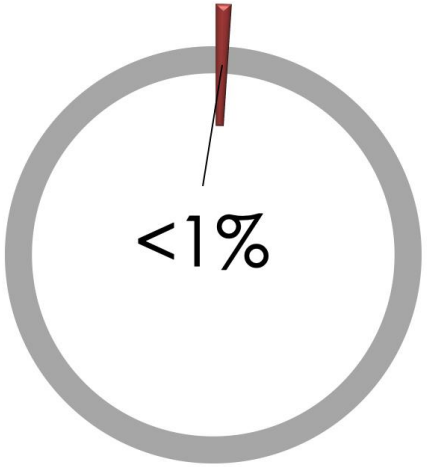
Characteristic	% of those ≥ 65 years
Weight loss	17.5
Exhaustion	15.5
Low Energy	27.0
Slowness	43.2
Weakness	21.8

J Gerontol A Biol Sci Med Sci (2007) 62: 738-743.

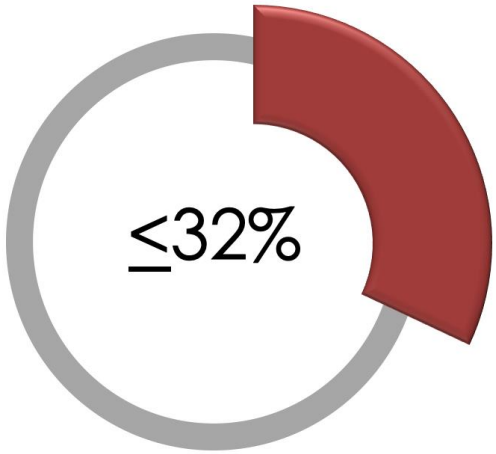
Dementias Become Increasingly Common With Age



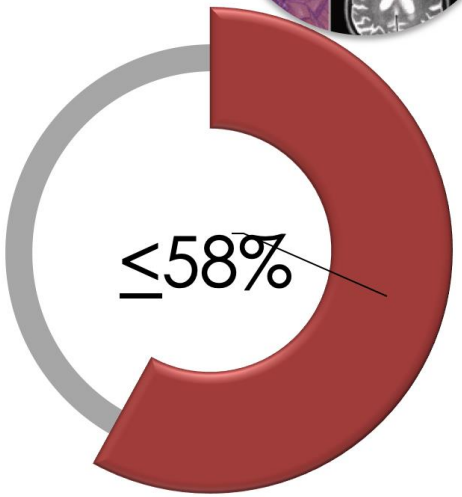
Alzheimer's Disease:



Under 65 years



80 to 89 years

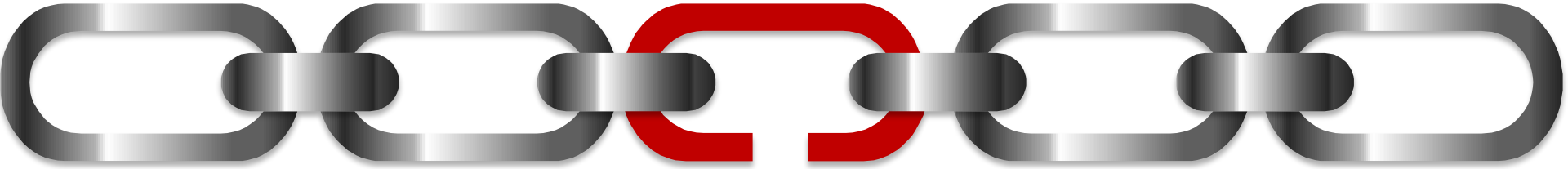


90 to 95 years

…Mild cognitive impairment is even more widespread with age:

Beydoun et al. BMC Public Health 14: 643, 2014

There is a Break in the Link Between Life Expectancy vs. "Healthspan"



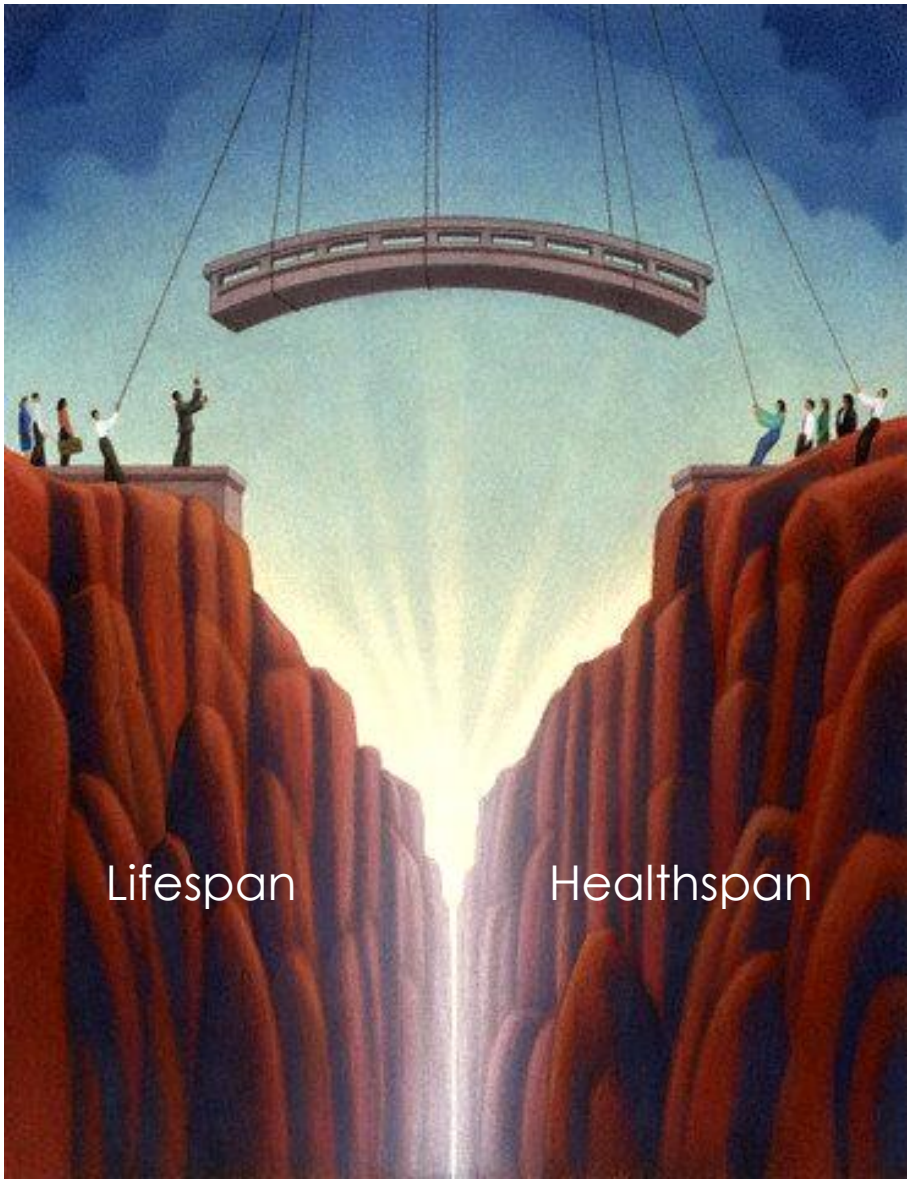
The Disconnect:

Lifespan

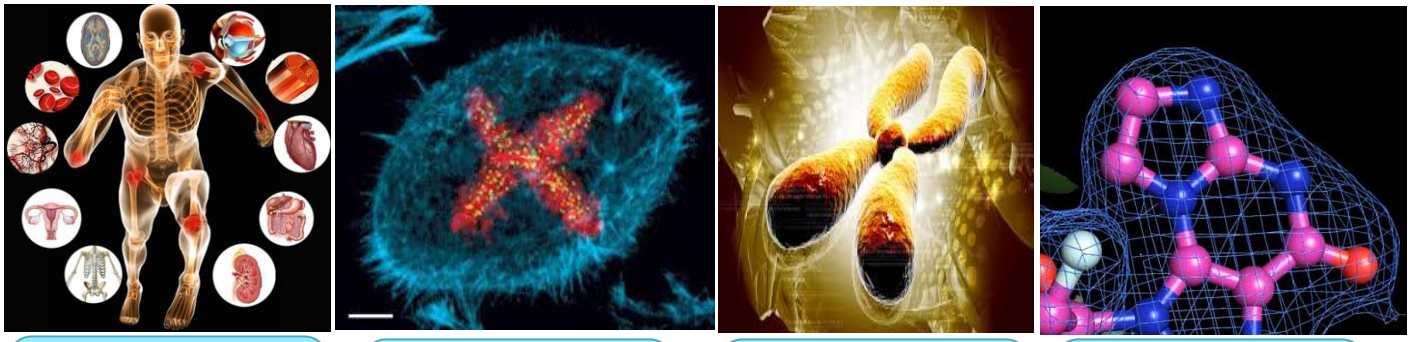
- Life expectancy continues to rise
- Parameters of healthspan have stagnated for at least a decade

"healthspan"

Is There a Way to Bridge the Gap Between Lifespan and Healthspan?



Additional Benefits to Life- and Health-span Will Now Likely Come From a Better Understanding Of the Basic Biology of Aging

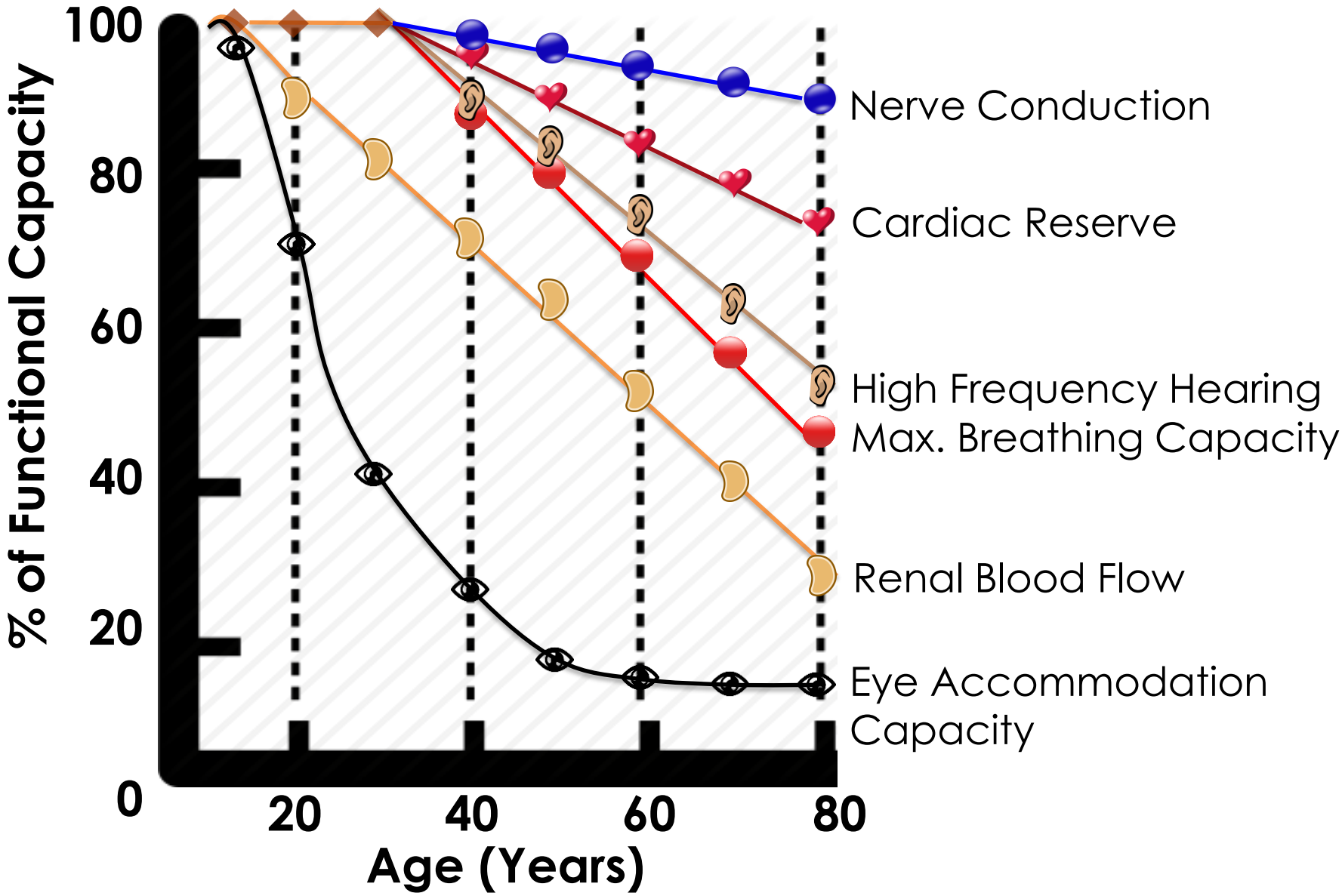


Physiological/ anatomical | Cellular | Sub-cellular | Biochemical

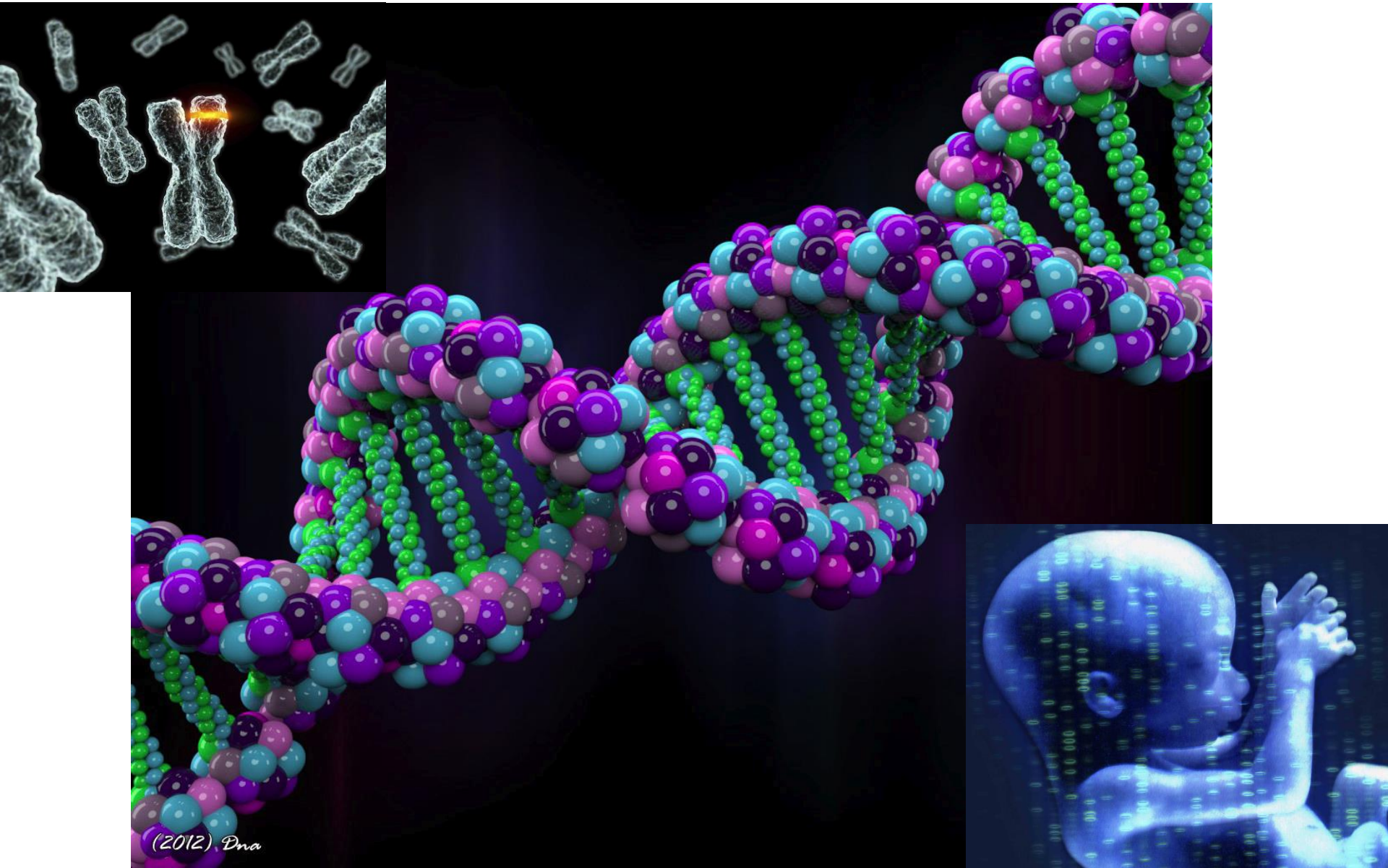
Senescence:

The biological processes of aging that lead to increased risk for mortality

The Rate of Physiological Deterioration Coincides the Force of Mortality with a Given Species



Is Your Lifespan (and/or Healthspan) "Programmed" in Your Genes?



Genetics

Your Genetic Make-up Influences Life Expectancy

A glance at your family tree may indicate whether you have a tendency to live a long, healthy life

Family History

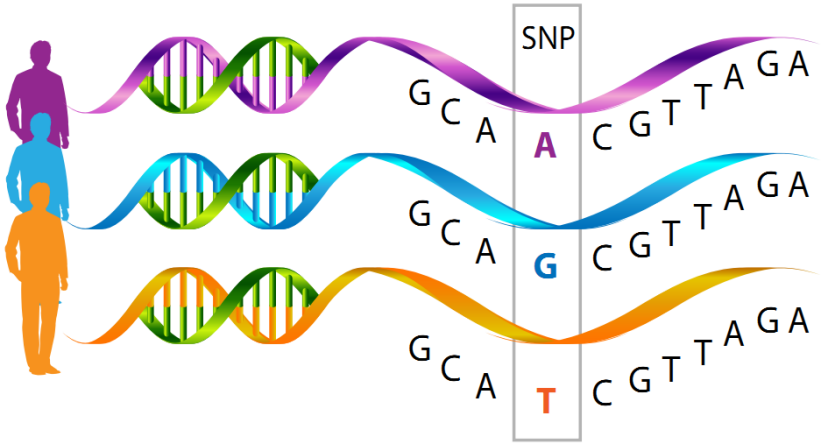
1. Exceptional longevity (1 to 3 decades longer than average) tends to run in families

2. Siblings of "super-centenarians" tend to live longer than average

What Does Genetic Analysis of Exceptionally Long-lived People Reveal About Longevity?

There are "nodes" of exceptionally long-lived people throughout the world

Genome Analysis [with "single nucleotide polymorphisms" (SNPs)] of Exceptionally Long-lived People Reveal…



Complex Genetic Signatures

19 different genetic groupings

Very Few Genes Consistently Involved

- FOXO3A
- APOE
- Many SNPs

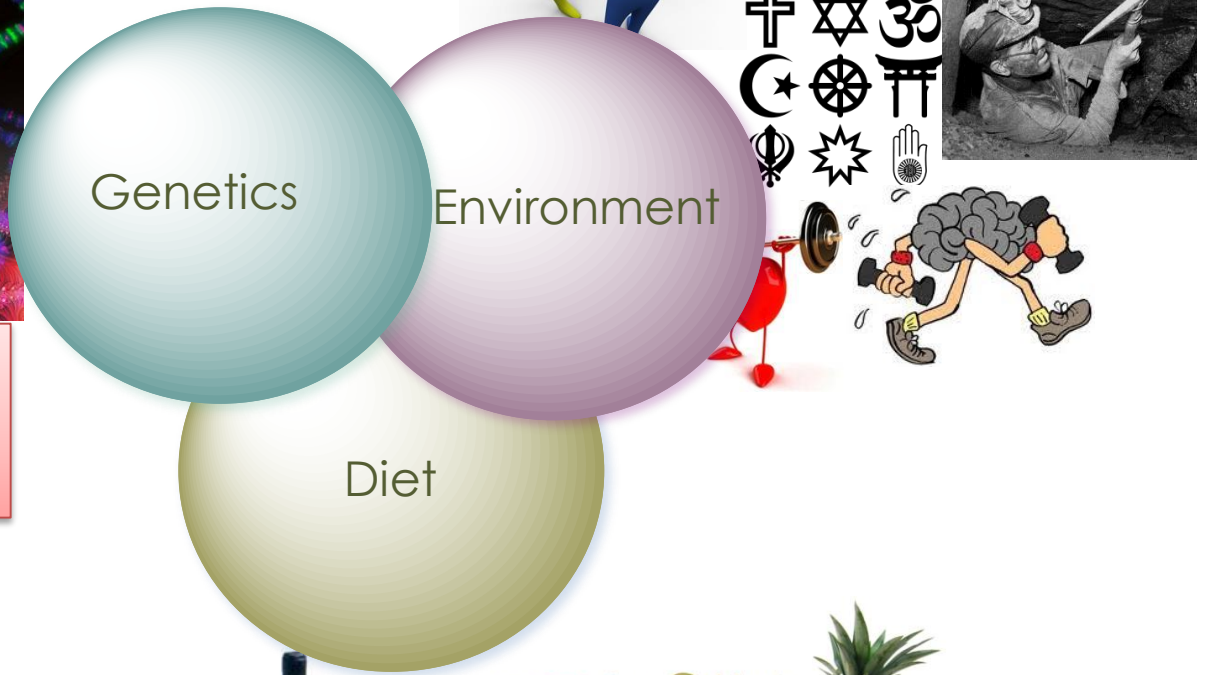
No Genes Associated With Diseases

Longevity genes confer resiliency

Genes do not solely govern whether you will live longer than an average lifespan

Genetic Analysis Suggests that Environment & Diet are the Major Determinants for Healthy Aging

15-25% of longevity quotient



Five Modifiable Factors Negatively Associated Life Expectancy

- **Sedentary**:

Frailty & disuse syndromes

- **Hypertension**:

Stroke; kidney failure; cardiovascular diseases

- **Obesity (BMI > 25)**:

Metabolic syndrome; cardiovascular diseases; dementias; and cancers

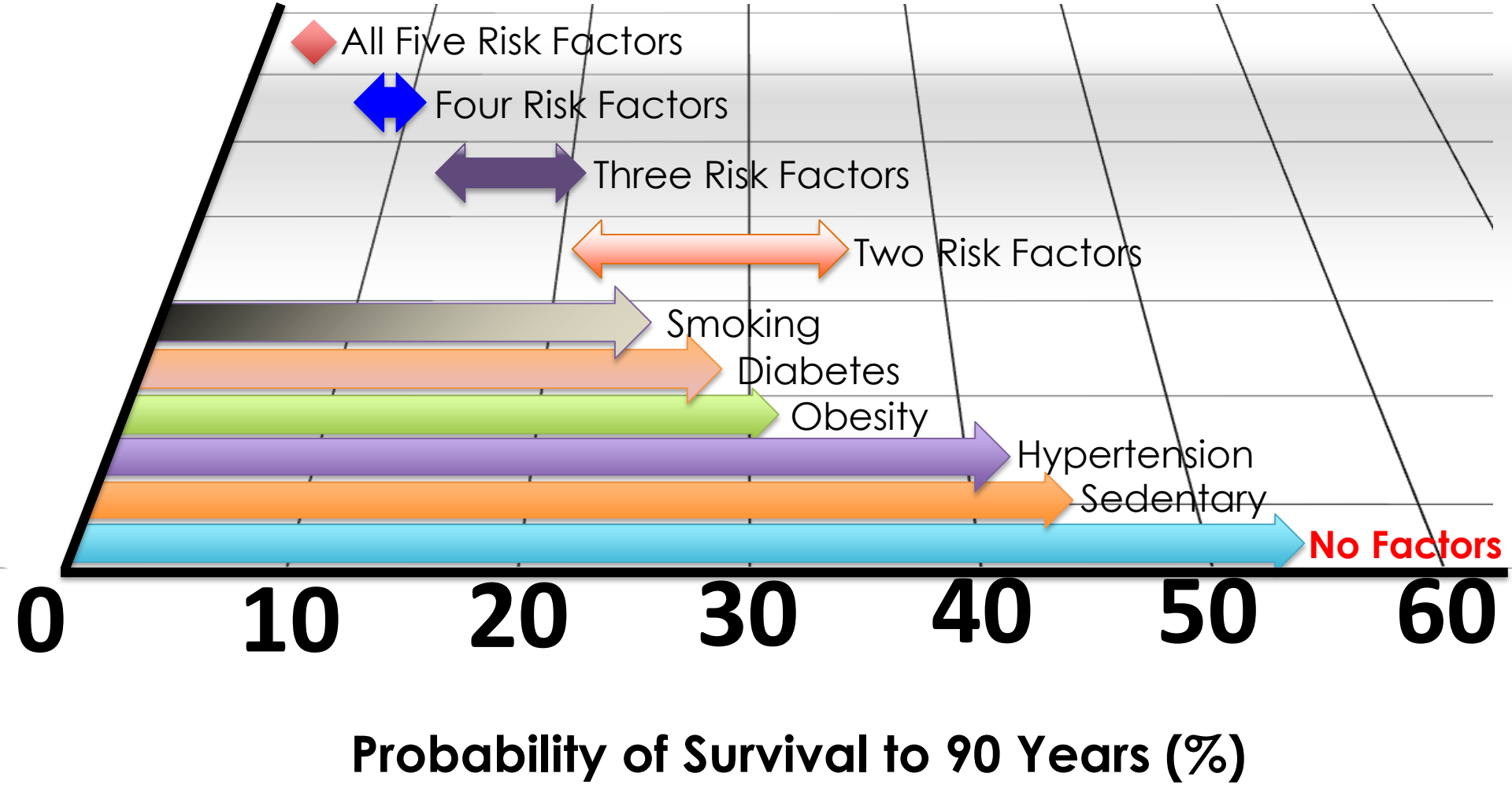
- **Diabetes**:

insulin resistance; cardiovascular; cognitive decline

- **Smoking**:

Cancer; cardiovascular diseases; pulmonary diseases; and cognitive decline

Probability of 70 Year Old Men to Survive to 90 Years of Age



Yates, LB et al. Arch Internal Medicine. 168: 284-290 (2008)

Are Other Lifestyle Factors Associated with High Life Expectancy?

1	Marriage	✓
2	High Social Contacts	✓
3	Alcohol Intake	?
4	Early Life Exposure to Infectious Diseases	✗
5	Moderate Physical Activity	✓

Are Lifestyle Risks Different Between Mid-life Versus Late-Life?

Lifestyle Factor	Mid-life	Late Life
BMI	High BMI = Poor Health & Shorter Lifespan	Low BMI = High Risk for Death
Hypertension	Non-survival & poor health	Non-survival & poor health
Smoking	Non-survival & poor health	Non-survival & poor health
Alcohol	≥ 3 drinks/day	>1 drink/day (15 oz/month)
Physical Activity	Not protective if stopped	Protective even if started late in life

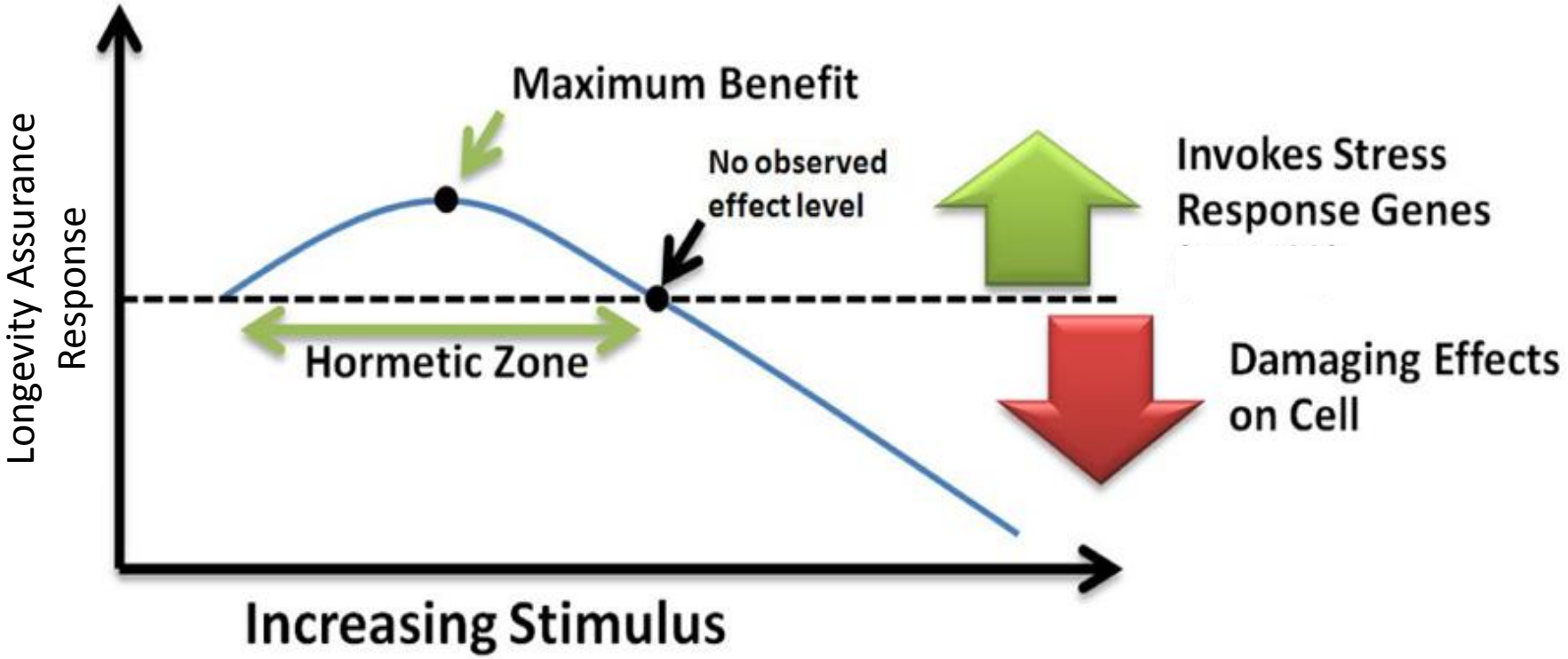
Being a bit overweight is not so risky

High risk at all ages

Increasing risk with age

The Benefits Exercise is an Example of "Hormesis": Low to Moderate Stress is Beneficial

Hormesis



Accentuating Positive Lifestyle Factors & Eliminating the Adverse Ones Promotes Healthy Aging

Activities of Daily Living

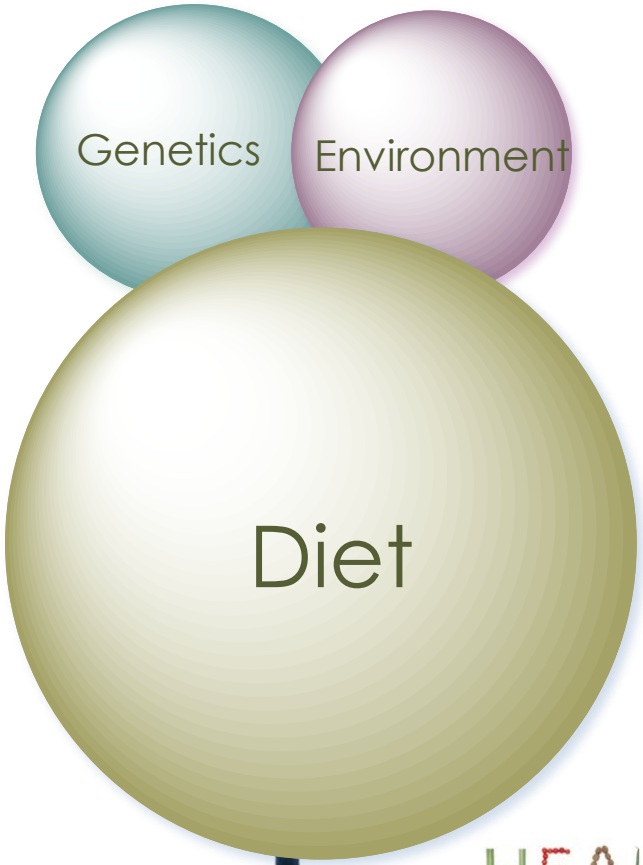
- Faster Walk Times
- Greater Handgrip Strength

Life- and health-span can be increased by as much as ***10 years***!

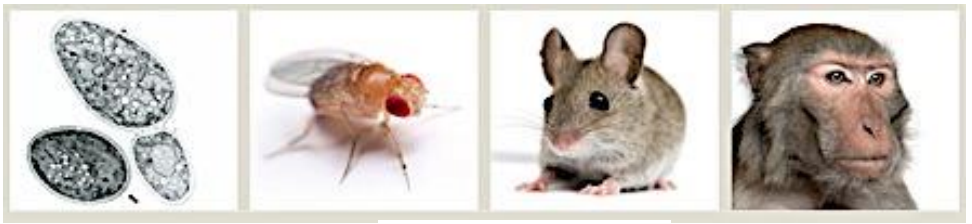
Physiological

- Lower Blood Pressure & glucose
- Lower Indices of Inflammation

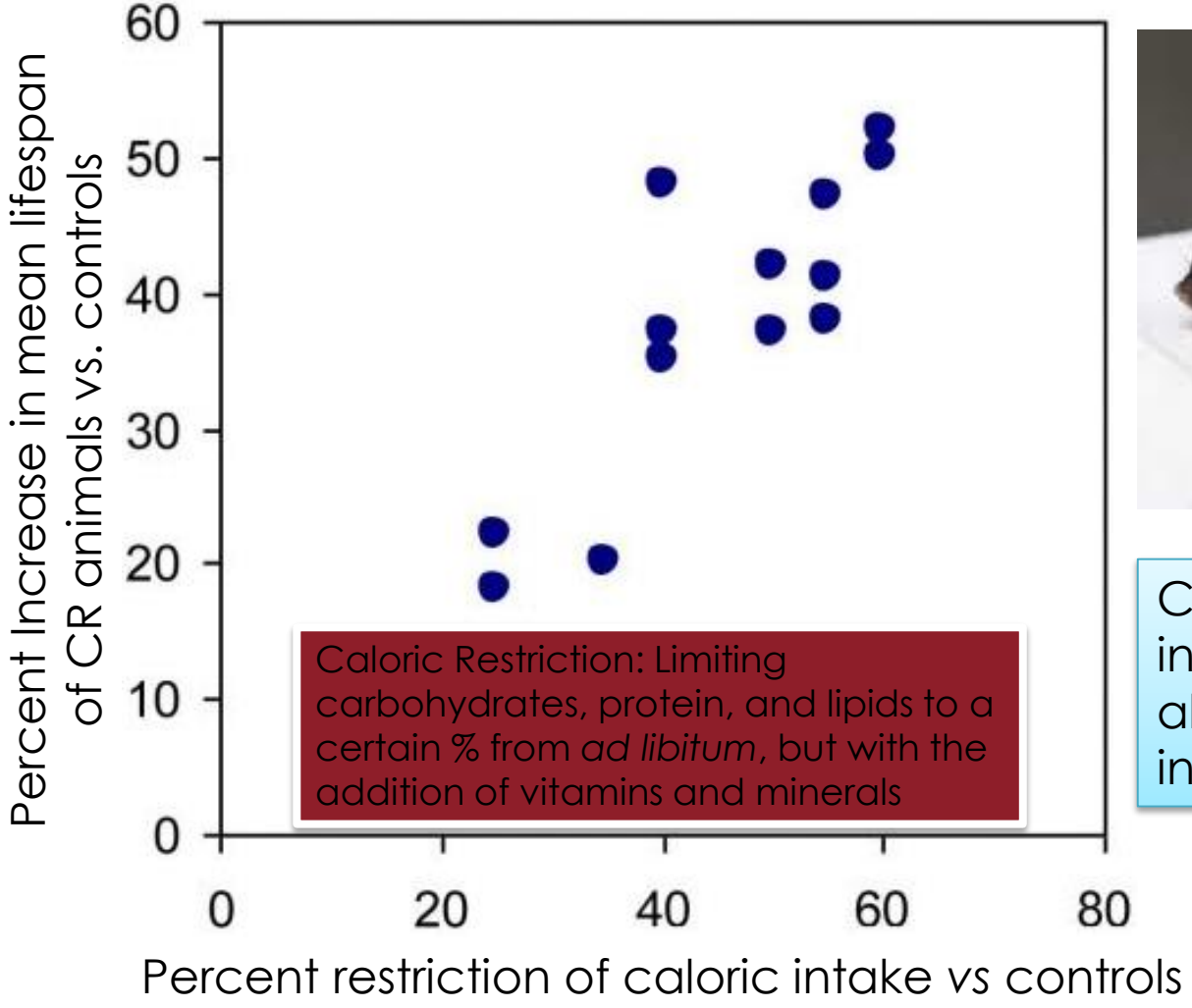
Diet is the Largest Factor Affecting Longevity and Healthy Aging



Nutrient influence on healthy aging is being extensively studied in humans and in many animal models of aging



A connection between nutrient energy intake and aging is best experimentally seen in "Caloric Restriction"



Calorically restricted old mouse

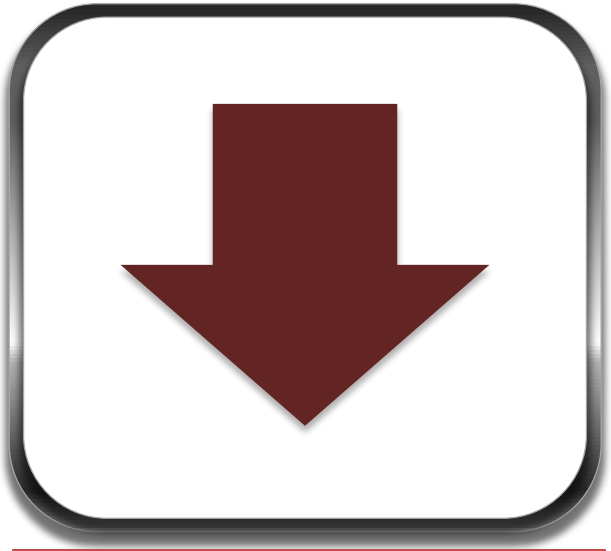
Ad libitum fed old mouse

Caloric restriction not only increases mean lifespan but it also extends maximal lifespan in some species!

Caloric Restriction Improves Healthspan in Lab Animals

Increases

- Memory/learning
- Muscle mass
- Mitochondrial function
- Insulin sensitivity



Decreases

- Cancer
- Renal Disease
- Autoimmune Disease
- Alzheimer's Disease
- Atherosclerosis
- Sarcopenia

Diets that Mimic Periods of Fasting

= Very low caloric intake

	Mon	Tue	Wed	Thu	Fri	Sat	Sun
Week 1							1
Week 2	Fasting mimicked diet					7	8
Week 3	9	10	11	12	13	14	15
Week 4	16	17	18	19	20	21	22
Week 5	23	24	25	26	27	28	29
Week 6	30	Fasting mimicked diet					

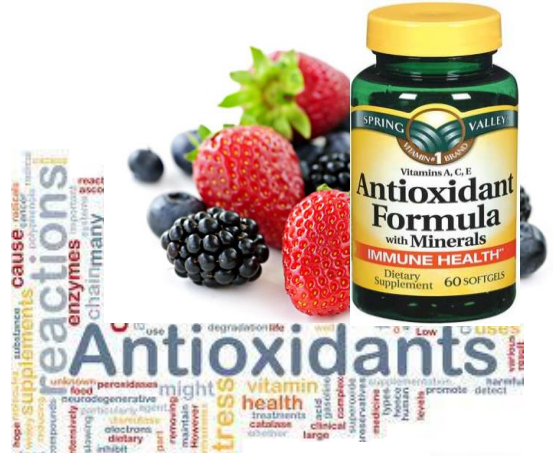
- 34-54% of normal caloric intake: 750-1090 kcals/day
- 9-10% protein; 34-47% carbs; 44-56% fat
- After 5 days, subjects could eat their normal diets for 25 days
- The fasting/normal eating cycle was repeated for 3 times

Risk Factors & Biomarkers of Health

- ↓ Diabetes
- ↓ Cardiovascular disease
- ↓ Cancer
- ↓ …Aging (?)

Brandhorst, S. et al. Cell Metabolism 22: 1-14, 2015

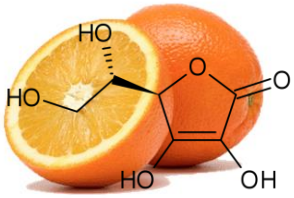
Are There Micronutrients or Other Small Molecules From the Diet That Mimic Caloric Restriction?



1. Antioxidants and Phytochemicals
2. Anti-Inflammatory Compounds
3. Drugs and Small Molecules

Antioxidant Supplements Fail to Significantly Improve Lifespan

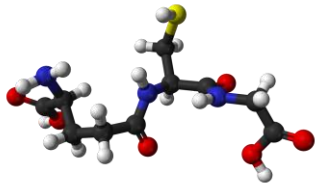
Vitamin E



Vitamin C

Does supplementation lower <u>oxidative damage in older animals?</u>

➢ Vitamin E	short-lived mice, but not humans
➢ Vitamin C	No
➢ Glutathione	No
➢ Coenzyme Q	fruit flies, but not mice



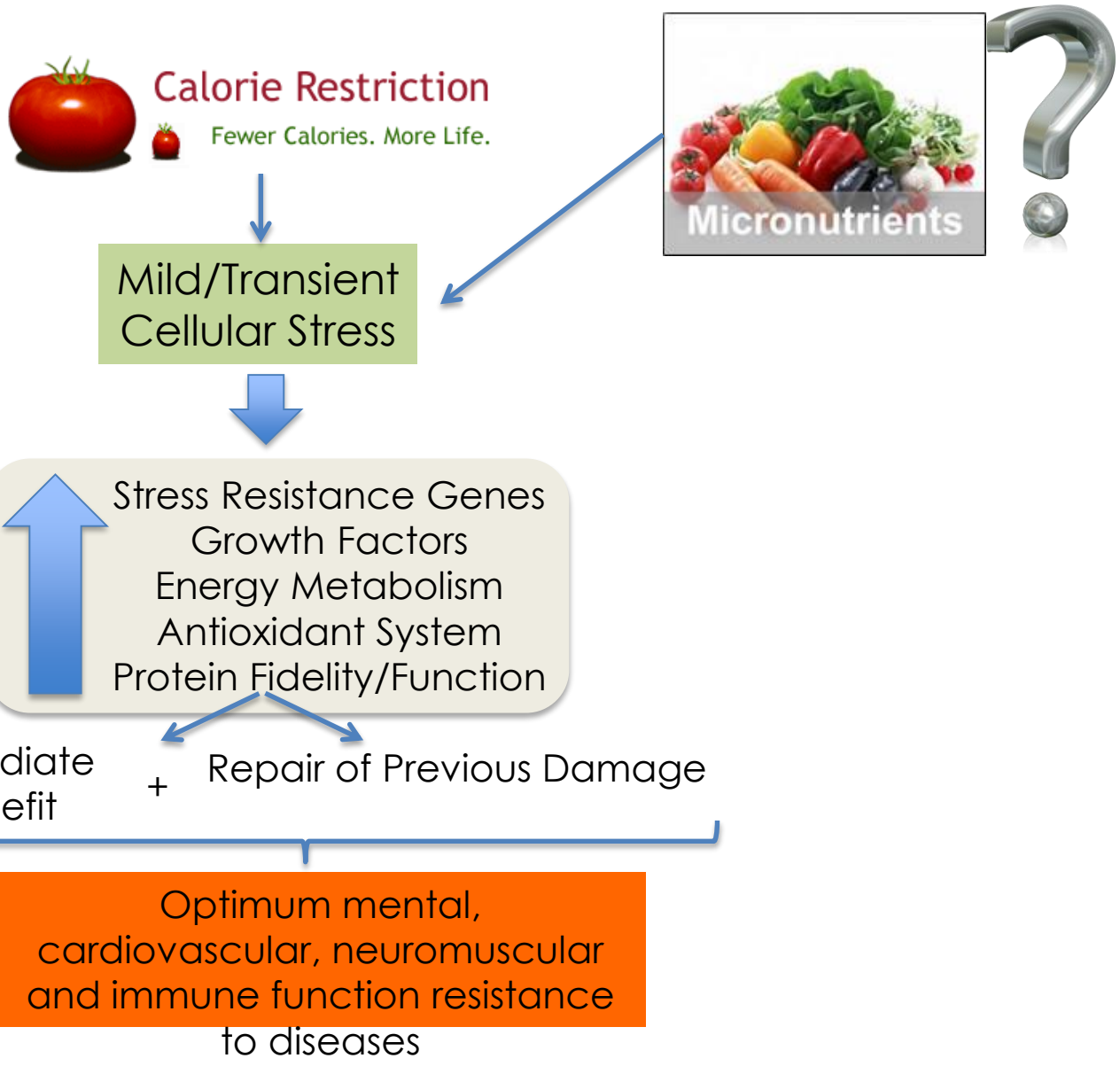
Glutathione

Does supplementation extend lifespan?

➢ Vitamin E	Small increase in avg. but not maximal lifespan (some mice)
➢ Vitamin C	Small increase in avg. but not maximal lifespan (mice)
➢ Glutathione	No
➢ Coenzyme Q	No

Coenzyme Q

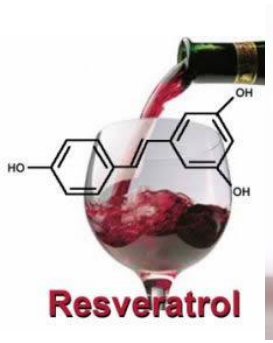
What About Caloric Restriction Mimetics?



Candidate Agents to Improve Healthspan

Over 600 candidates!

Red Wine Constituents & Alcohol




- Alcohol (1 or 2 drinks/d only!)
- Resveratrol (?)

Sulfur-containing Compounds in Brassica and Onions

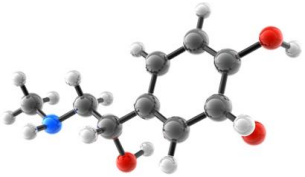


- Lipoic Acid
- Thioflavin T

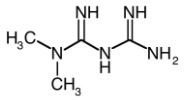
Other:


- Chocolate & coffee components

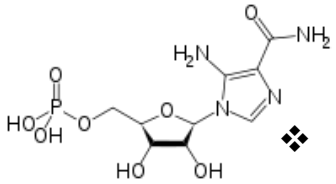
- Berries



- Rapamycin



- Metformin



- AICAR

Optimal dosage & the long-term benefits to people (as well as potential adverse consequences) are largely unknown

Make Sure Your Vitamin Intake is Optimal

Vitamin	RDA Men	RDA Women	LPI Recommendation
Vitamin B_{12}	*2.4 mcg/day#*	*2.4 mcg/day#*	*100-400 mcg/day of crystalline vitamin B_{12}*
Vitamin C	*90 mg/day*	*75 mg/day*	*≥ 400 mg/day*
Vitamin D	*600-800 IU/day*	*600-800 IU/day*	*2,000 IU/day from supplements; serum level ≥32 ng/ml*

Americans generally do not get enough vitamins E or D, and intake of many minerals are inadequate: magnesium, calcium, potassium, phosphorous

#Vitamin B_{12} intake should be from supplements or fortified foods due to the age-related increase in malabsorption

Summary: The Interplay of Genetics, Environmental Positive/Negative Risk Factors, and Diet Can Strongly Influence Healthspan

15-25% of longevity quotient

Genetics

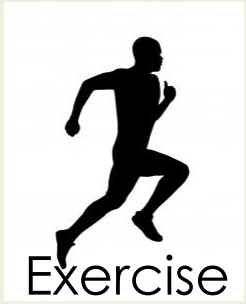
Environment

Diet

What Can You Do To Maximize Healthspan?

Keep your mind engaged

Limit overnutrition, eat "colorful foods", & have optimal intake of vitamins



Exercise

Optimum mental, cardiovascular, neuromuscular and immune function resistance to diseases

Limit the "Big 5" lifestyle risk factors

www.impactaging.com AGING, December 2009 Vol.1 No 12

Research paper

Fasting and Cancer Treatment in Humans: A Case series report

Fernando M. Safdie[1,6], Tanya Dorff [2,3,6], David Quinn[2,3], Luigi Fontana[4], Min Wei[1], Changhan Lee[1], Pinchas Cohen[5], and Valter D. Longo[1]

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[6] These authors contributed equally to this work

Running title: *Fasting and Cancer Treatment*

Key words: *fasting, Cancer, Chemotherapy, Toxicity, Side-effect, IGF-I*

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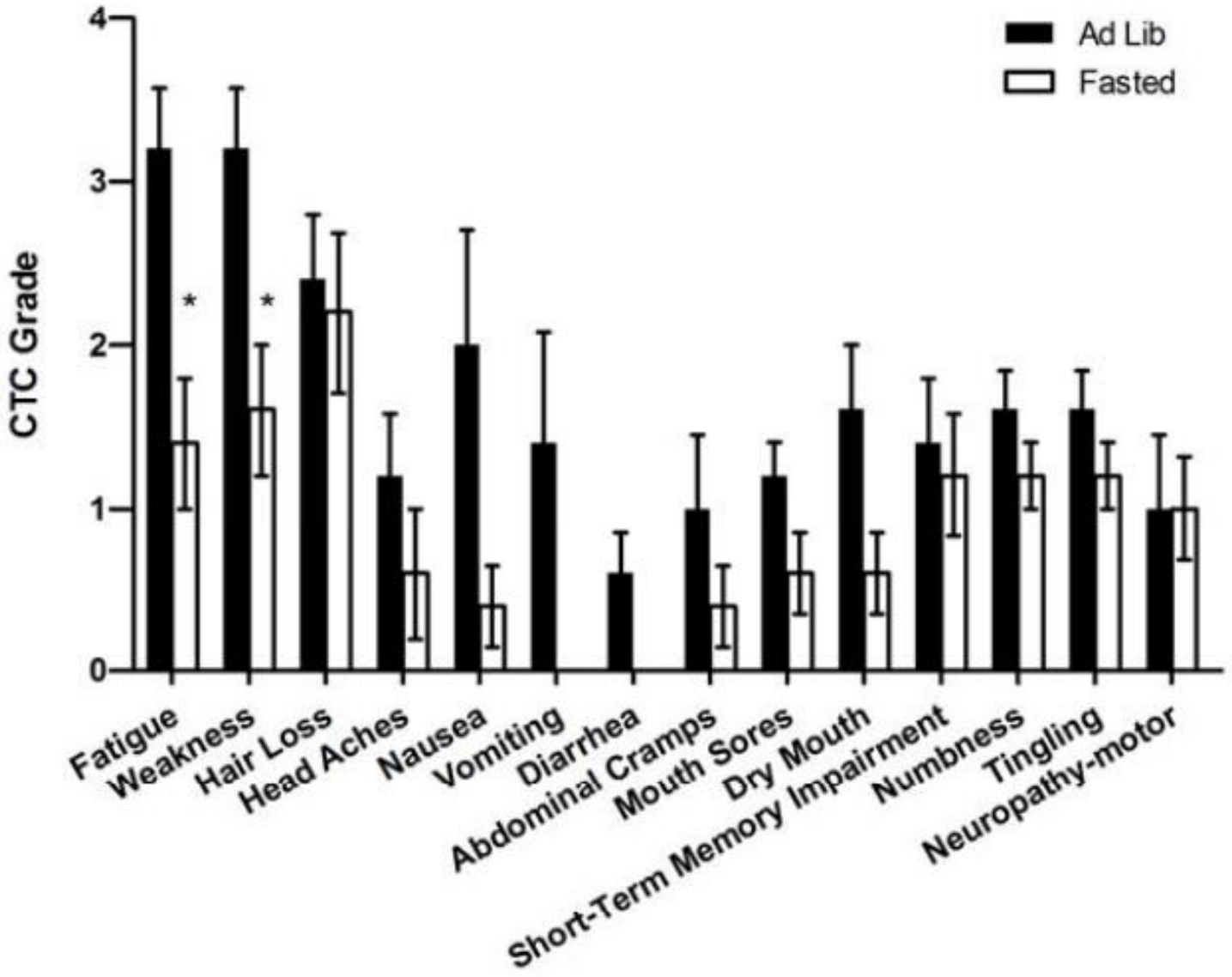
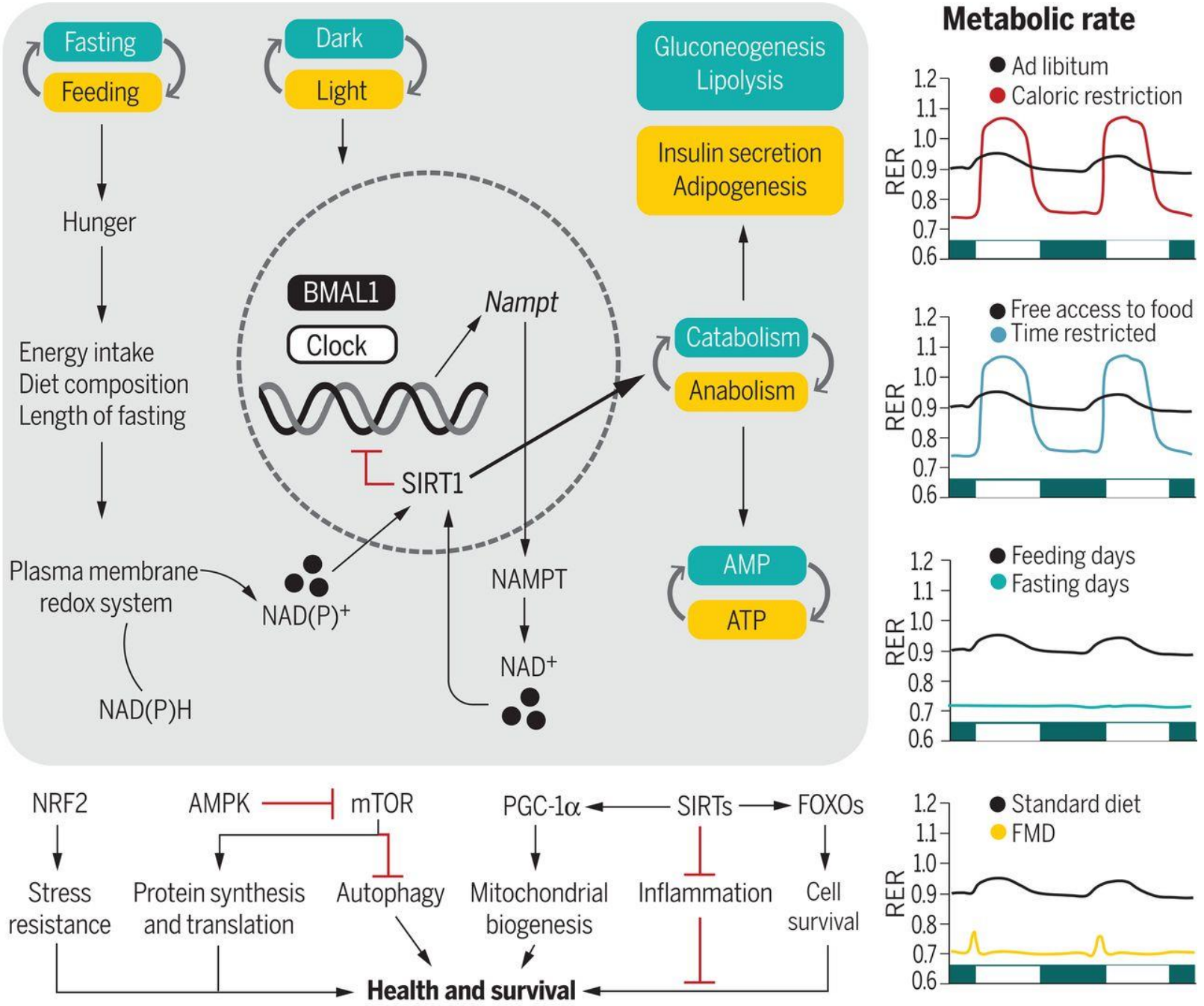
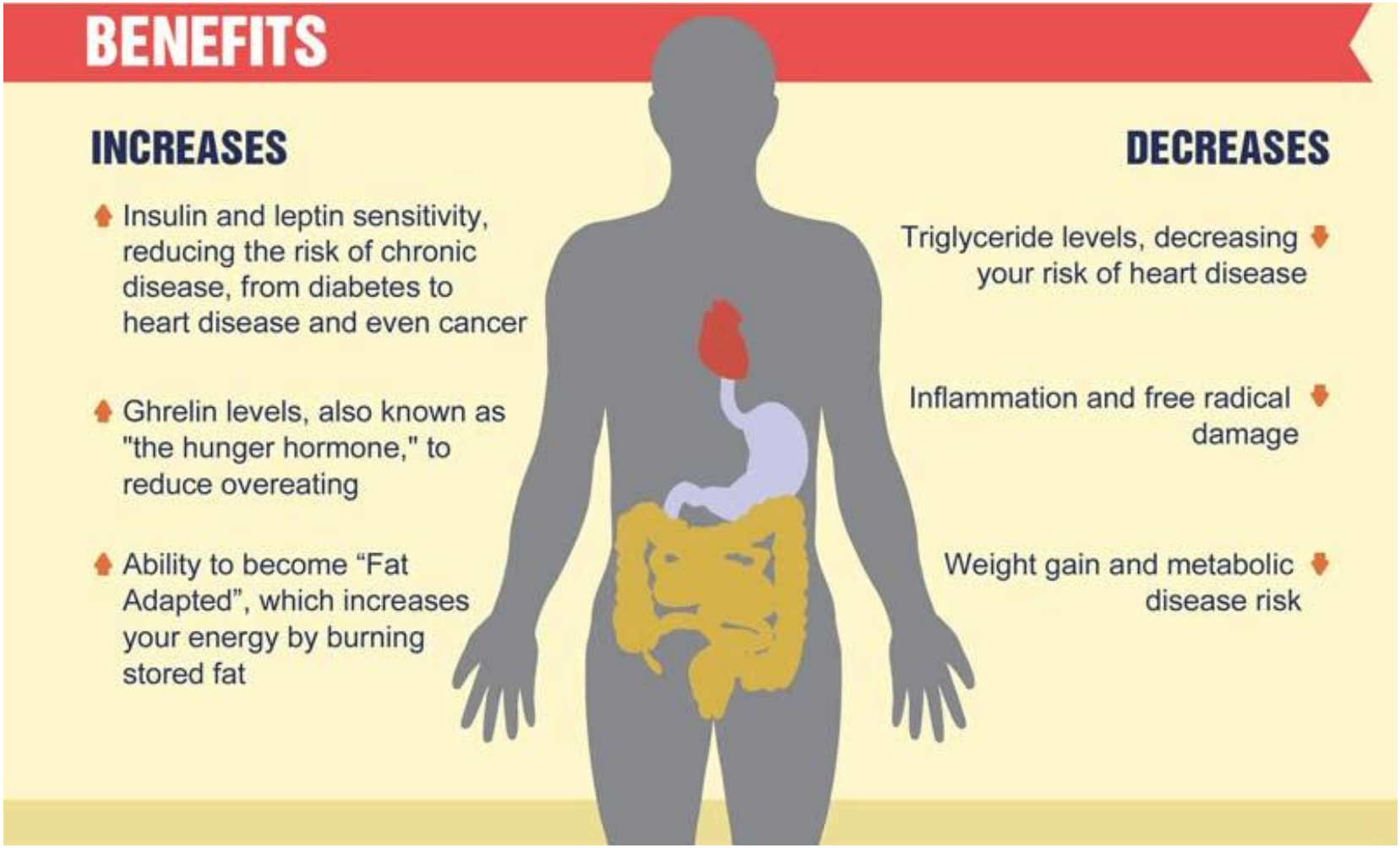
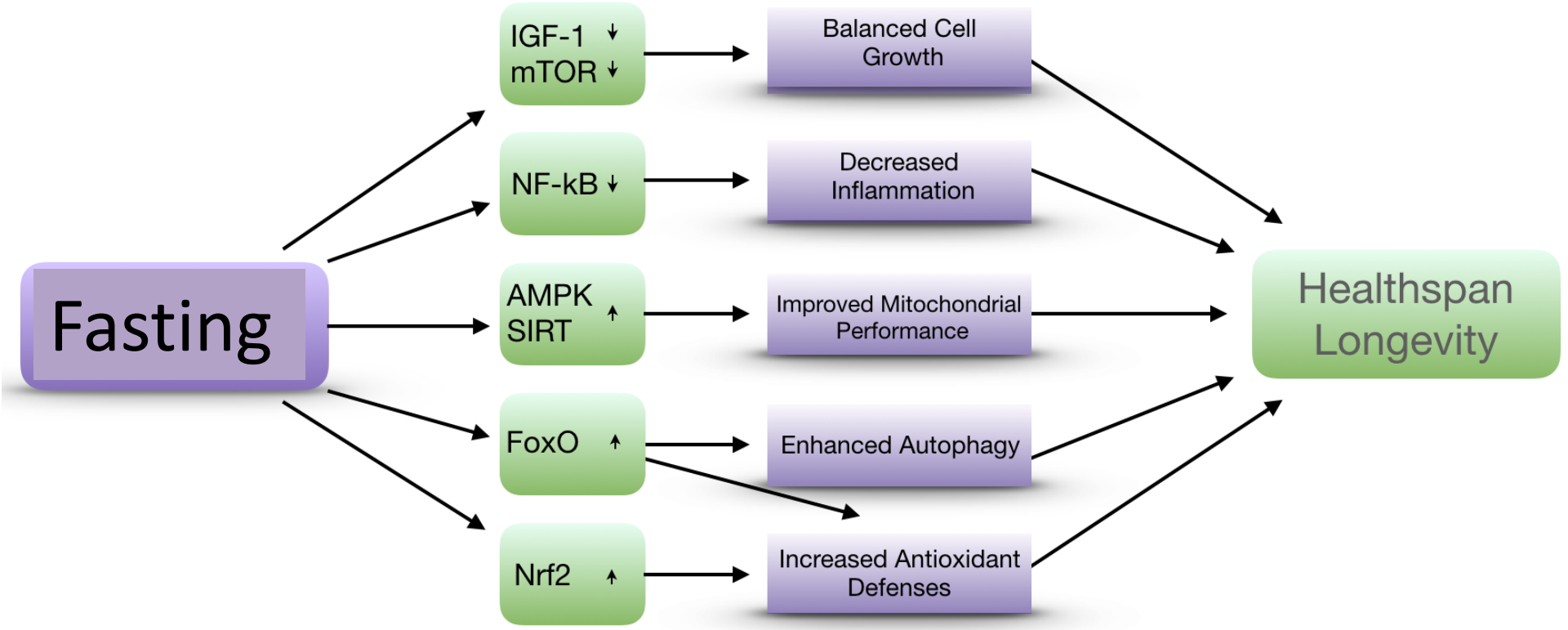

Ad Lib
Fasted
CTC Grade
4
3
2
1
0
*
*
Fatigue
Weakness
Hair Loss
Head Aches
Nausea
Vomiting
Diarrhea
Abdominal Cramps
Mouth Sores
Dry Mouth
Short-Term Memory Impairment
Numbness
Tingling
Neuropathy-motor



Andrea Di Francesco et al. Science 2018;362:770-775

Fasting


BENEFITS
INCREASES
Insulin and leptin sensitivity, reducing the risk of chronic disease, from diabetes to heart disease and even cancer
Ghrelin levels, also known as "the hunger hormone," to reduce overeating
Ability to become "Fat Adapted", which increases your energy by burning stored fat
DECREASES
Triglyceride levels, decreasing your risk of heart disease
Inflammation and free radical damage
Weight gain and metabolic disease risk


Fasting
IGF-1 ↓
mTOR ↓
NF-kB ↓
AMPK ↑
SIRT ↑
FoxO ↑
Nrf2 ↑
Balanced Cell Growth
Decreased Inflammation
Improved Mitochondrial Performance
Enhanced Autophagy
Increased Antioxidant Defenses
Healthspan Longevity

AUTOPHAGY BENEFITS

Detox, Renew, and Cleanse Your Body

What is Autophagy?

Autophagy is a well-regulated, orderly process to break down and recycle various cellular components.
A type of self-renewal method focusing on removing older structures so that the new ones can take their place..

Autophagy Prevents Cancer

Autophagy plays an important role in preventing the onset and early growth of cancer cells. It is has been known to suppress several processes leading to cancer, such as DNA damage, chronic inflammation, and genome instability.

Autophagy Enhances Muscle Performance

As you exercise, you are put stress on your cells. As this happens, energy use increases and the cell components get worn out at a faster rate. Autophagy makes sure to balance energy use within a cell.

Autophagy Prevents Neurodegenerative Diseases

Stimulating autophagy can help protect your brain by properly removing misfolded proteins inside neurons that cause cell death in your brain and loss of mental capacity.

Autophagy Regulates Inflammation

Autophagy can help decrease inflammation within your body. It also gets rid of any pro-immune response molecules from the body to lower down the level of inflammation.

Autophagy Reduces the Effects of Aging

Autophagy along with intermittent fasting boosts the production of Human Growth Hormone (HGH). HGH is largely associated with an increased healthy muscle growth but also provides powerful anti-aging benefits.

Enhances Cellular Energy

The mitochondria undergo an autophagy process called "mitophagy" that favors the development of new and stronger mitochondria that can produce more cellular energy.

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Thank you for your attention

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