HOW TO STAY HEALTHY? EAT LESS?

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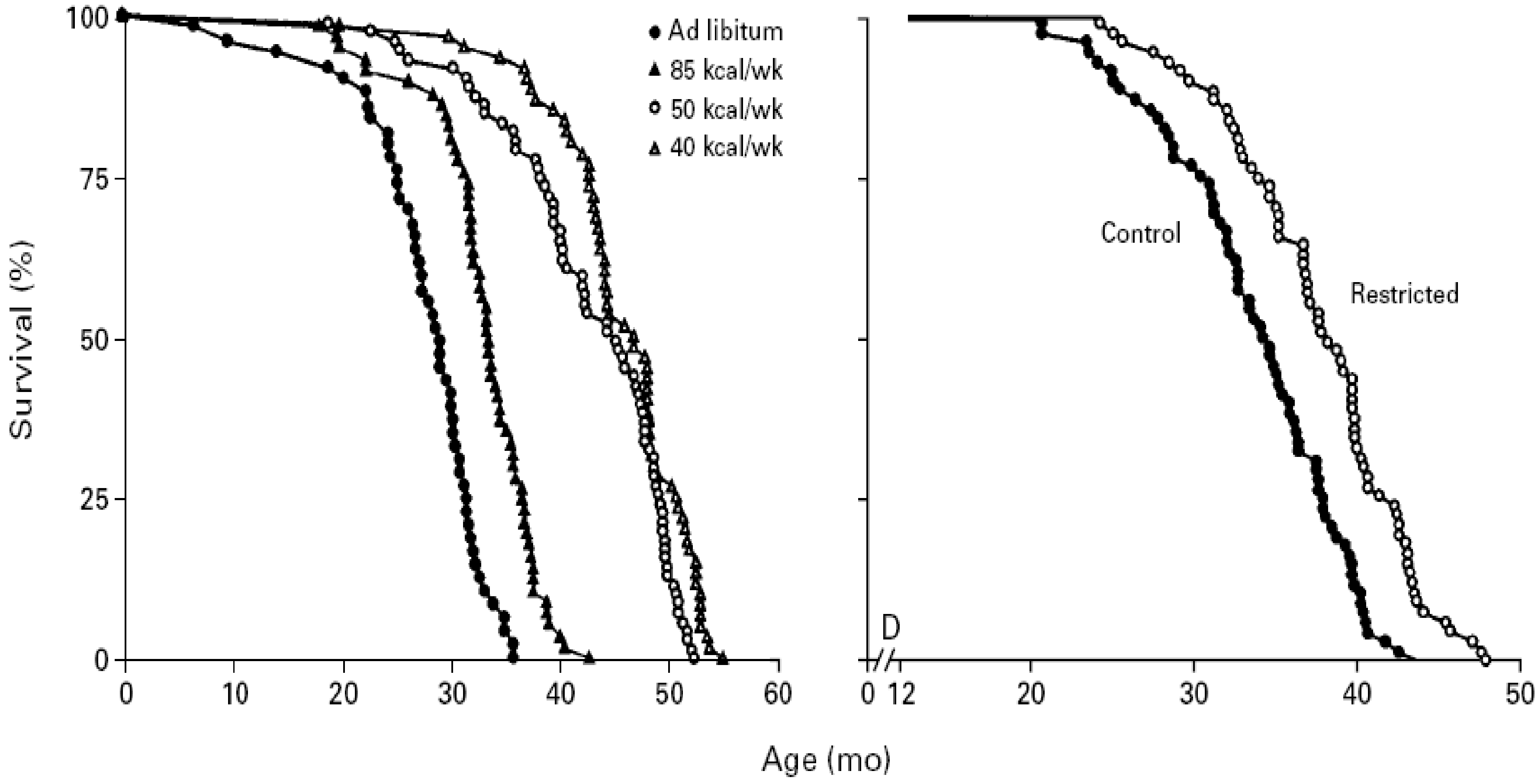
Definition of “OPTIMAL HEALTH”

- “Optimal health” is the state in which there is the highest possible attainment of physical, mental and social well-being and the lowest risk of developing future diseases.
- From a biological point of view, optimal health can be defined as the ability of an organism to maintain or regain homeostasis in an ever changing environment, and especially in response to a wide range of stressors.

Calorie restriction without malnutrition increases maximal lifespan up to 50% in rodents



Masoro EJ. Mech Ageing Dev. 2005

Weindruch R. N Engl J Med 1999

Calorie restriction and metabolic health

Calorie restricted animals are:

- Metabolically and physiologically younger
- More metabolically flexible
- More Resistant to many types of stresses (e.g. surgery, radiation, acute inflammation, exposure to heat, and oxidative stress)

as compared to ad-libitum fed animals

Masoro EJ. Mech Ageing Dev. 2005

Weindruch R. N Engl J Med 1999

Calorie restriction protects against spontaneous, radiation- and chemical- induced tumors

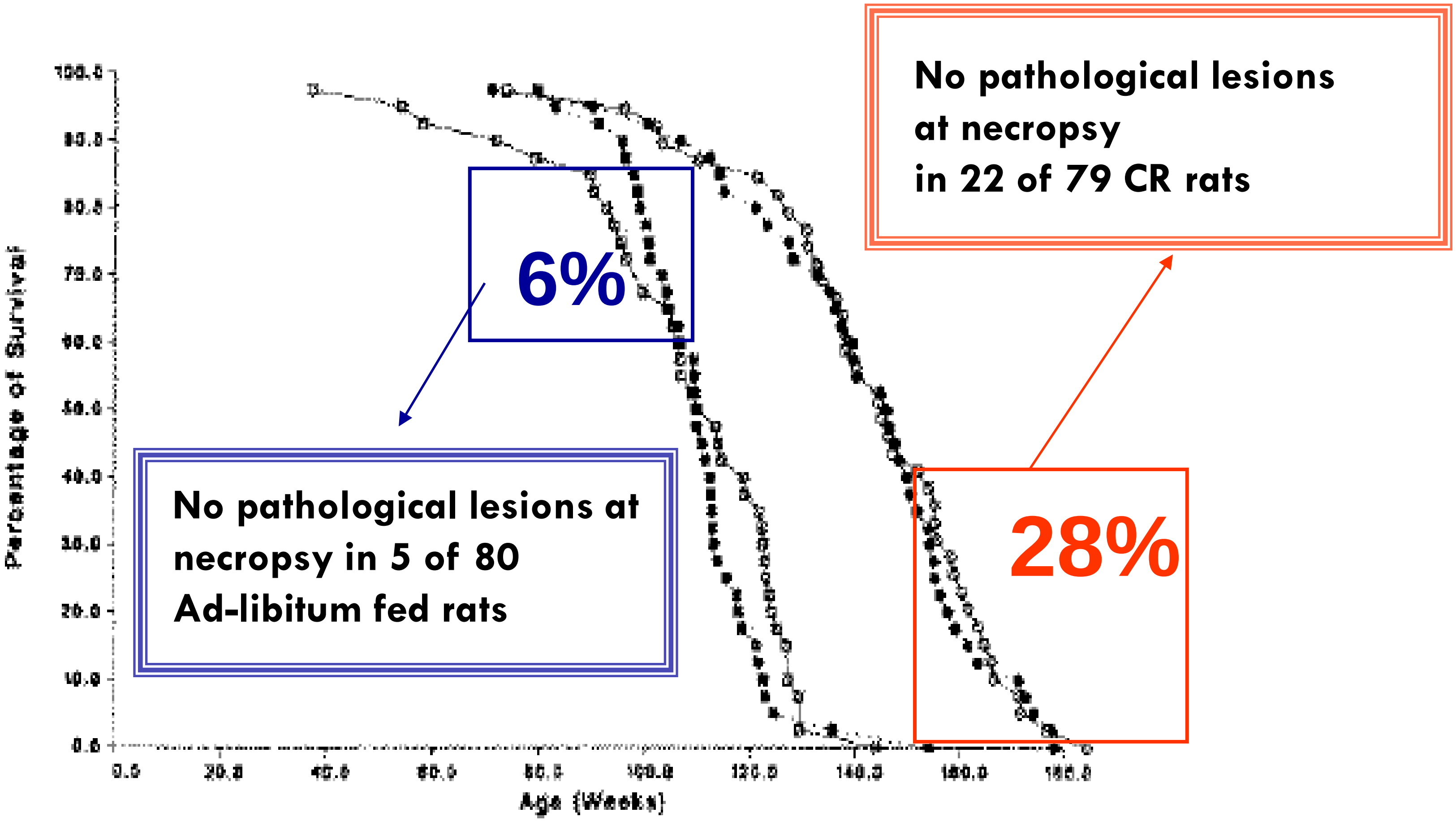
Number of experiments	Caloric restriction (%)		Tumor reduction (%)
	Range	Mean (SE)	Mean (SE)
9	0	0 (1.5)	−9.5 (10.2)
18	7–20	15.3 (1.2)	20.2 (8.1)
22	21–30	25.9 (1.1)	49.6 (6.4)
17	31–40	37.0 (1.2)	52.5 (7.8)
16	41–58	52.9 (1.1)	62.2 (7.6)

Site- and fat-adjusted means ± SE, weighted by number of animals per experimental group.

Data from 82 published experiments involving several tumor sites in mice

Albanes D. Cancer Research 1987

~30% of the CR rodents dies without any gross pathological lesion



Shimokawa I et al. J Gerontol 1993

~20% of centenarians are escapers

In a longitudinal study of the 424 centenarians:

- 19% were ESCAPERS (= without common age-associated disease before 100 years of age)
- 43% were delayers (= age-associated disease after the age of 80 years)
- 38% were survivors (= age-associated disease before the age of 80 years)

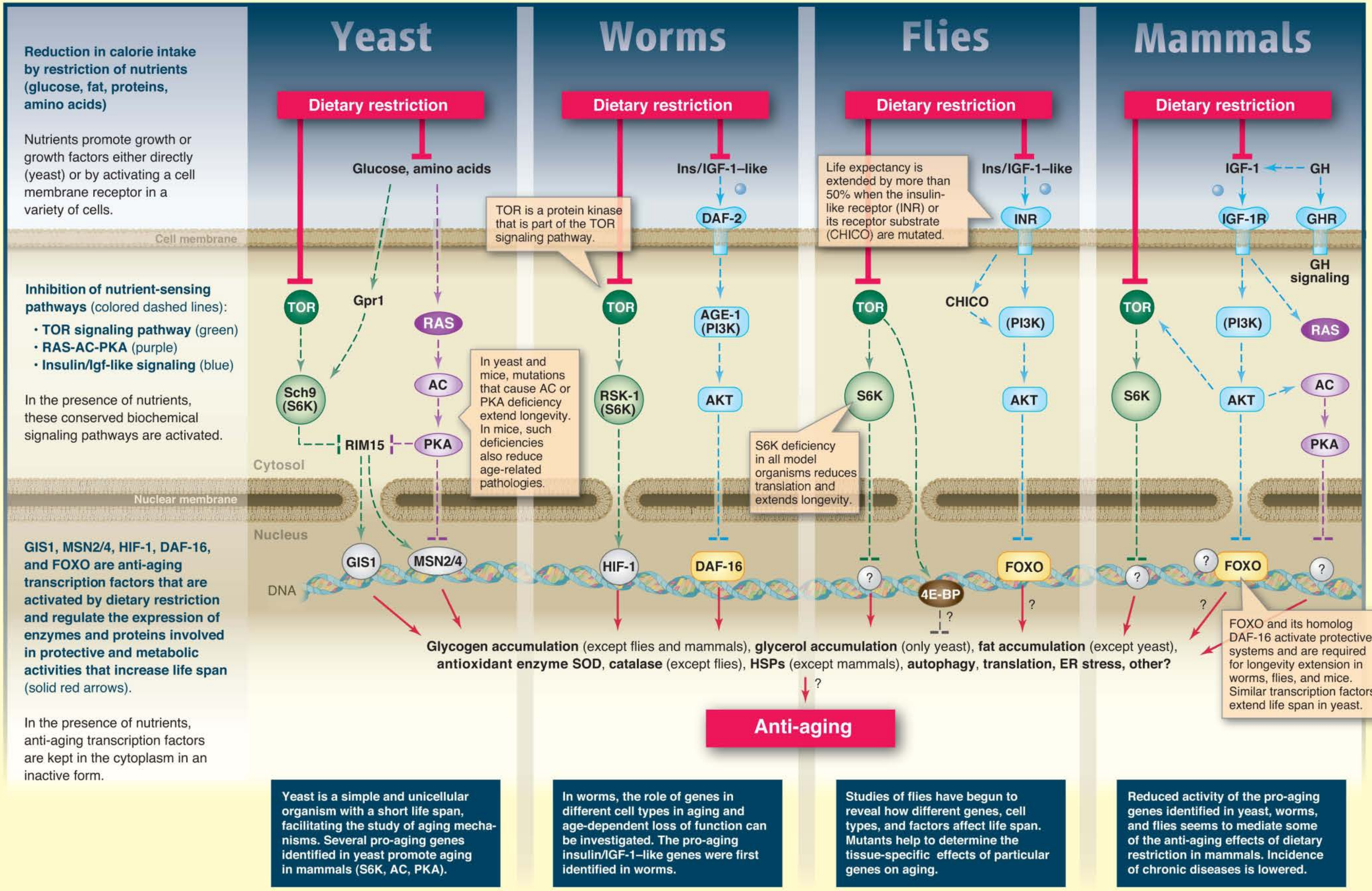
Evert *et al., J. Gerontol. A Biol. Sci. Med. Sci 2003*

Mammalian animal models of longevity

- Calorie restriction and intermittent fasting
- Methionine restriction
- Ames and Snell dwarf mice
- Growth hormone receptor KO mice
- IGF-1 receptor deficient mice
- Klotho overexpressing mice
- Fat Insulin Receptor KO (FIRKO) mice
- Insulin Receptor Substrate 1 KO mice
- Brain IRS-2 KO mice
- PAPP-A KO mice
- Ribosomal S6 protein kinase-1 KO mice
- Rapamycin supplementation
- p66shc KO mice
- Type 5 Adenylyl Cyclase KO mice
- Angiotensin II type 1 receptor KO mice
- Mice overexpressing catalase targeted to mitochondria

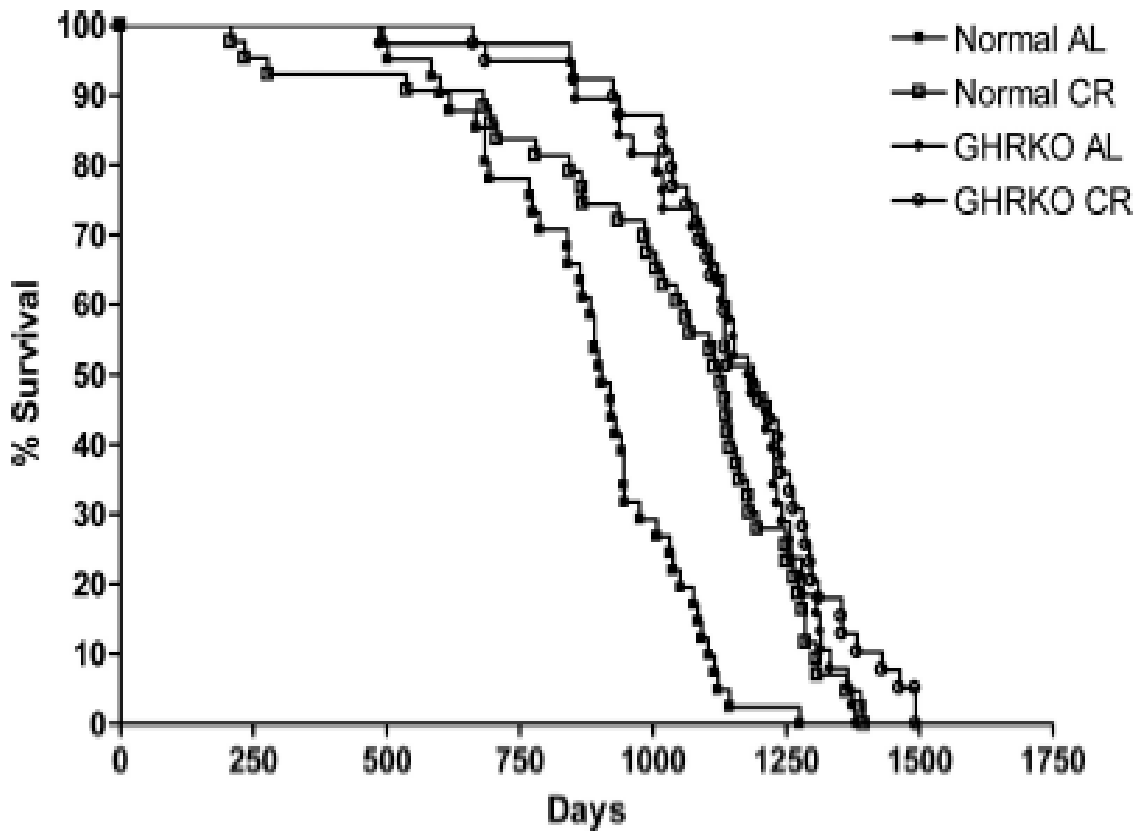
Down regulation Insulin/IGF-1/mTOR pathways = Nutrient –sensing signaling pathways

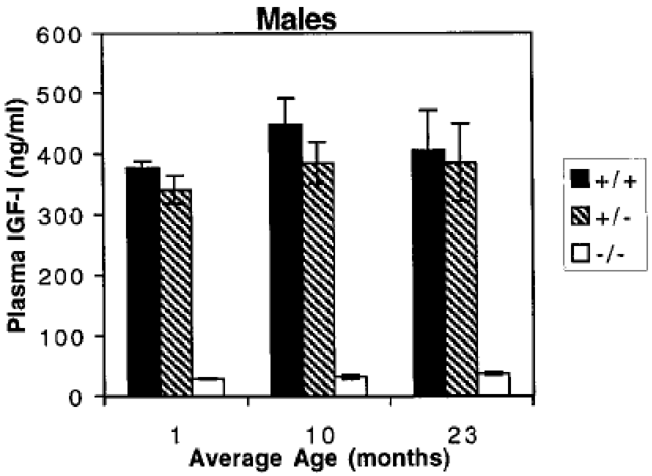
Conserved Nutrient Signaling Pathways Regulating Longevity



Fontana L et al. Science 2010

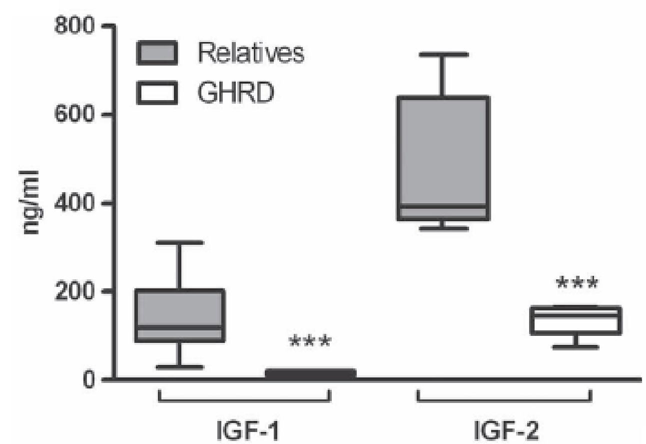
GH receptor KO mice live 40-50% longer than WT mice

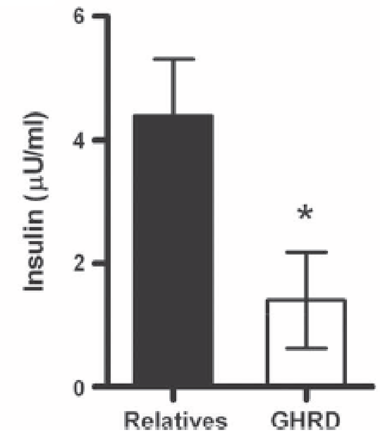


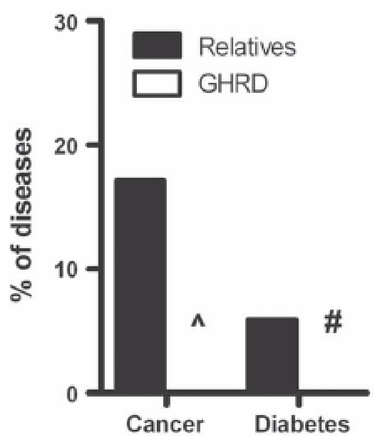


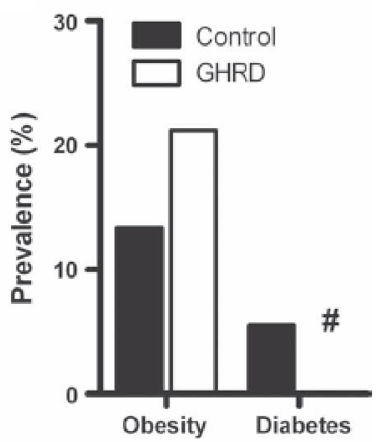
Bonkowski MS et al., PNAS 2006
COSCHIGANO KT et al., Endocr 2000

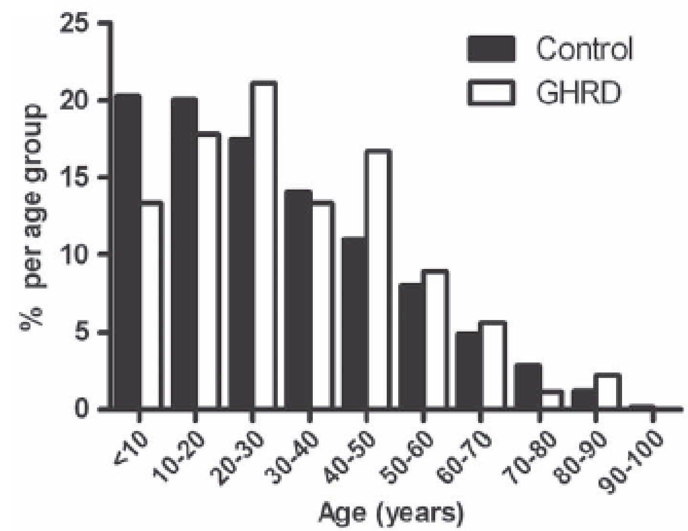
GHR deficient humans are protected against cancer and diabetes, but are not living longer



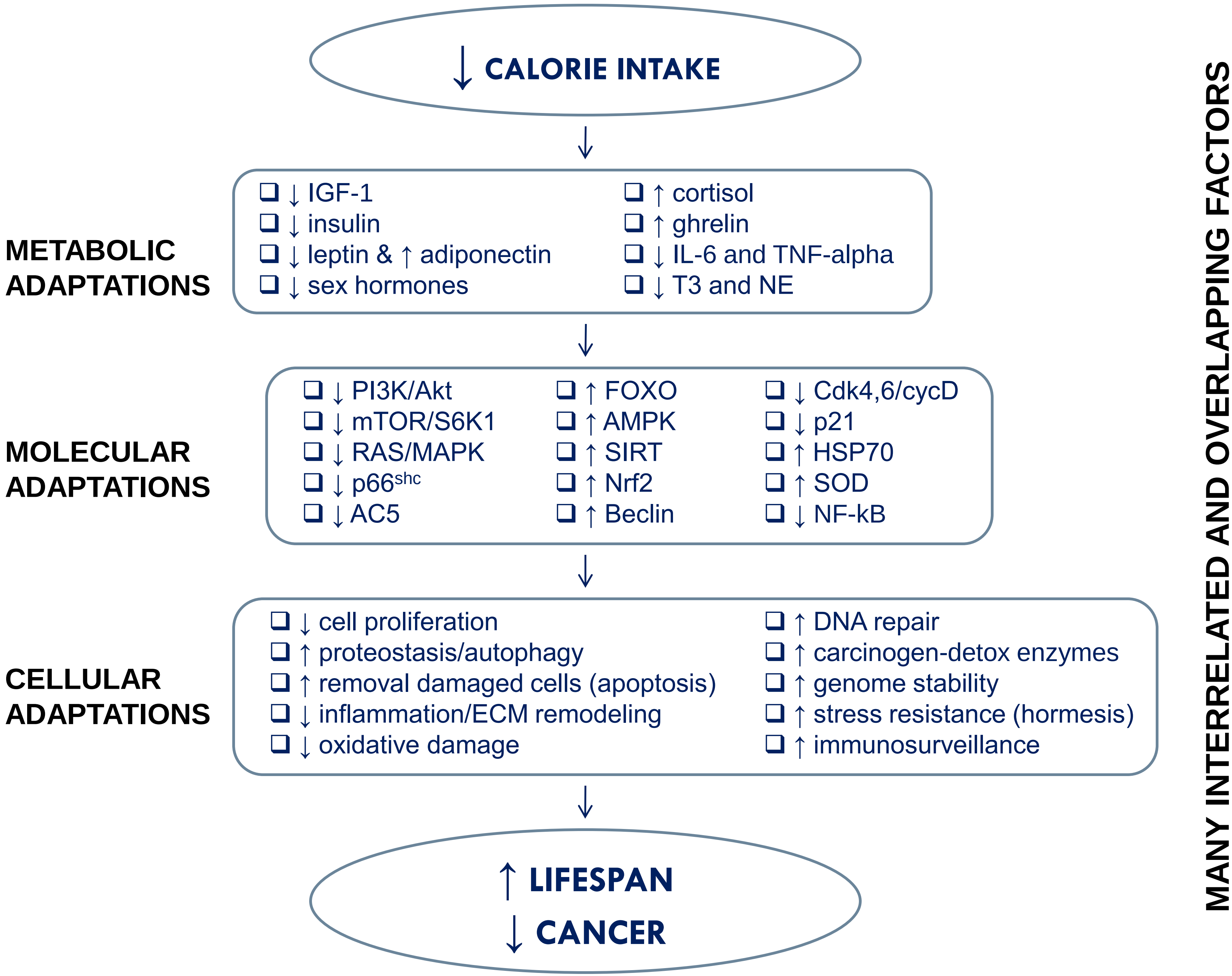




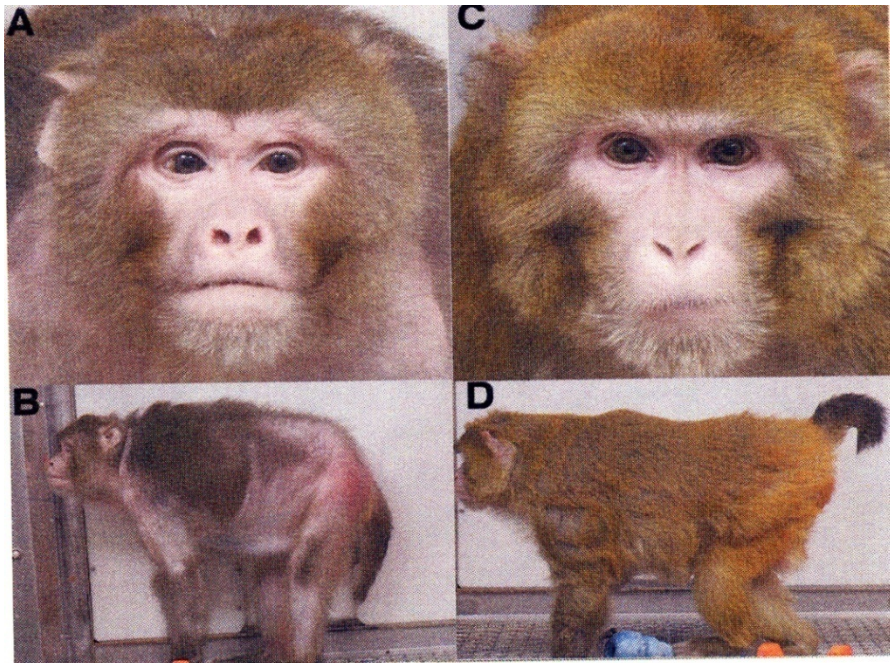




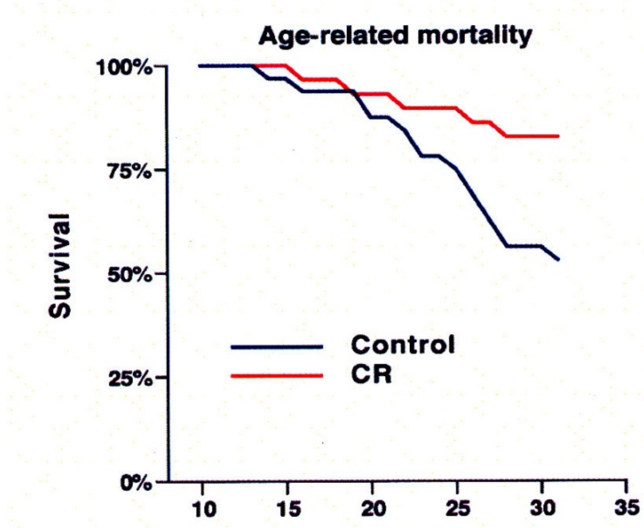
Guevara-Aguirre et al. Sci Transl Med 2011


↓ CALORIE INTAKE
METABOLIC ADAPTATIONS
❑ ↓ IGF-1
❑ ↓ insulin
❑ ↓ leptin & ↑ adiponectin
❑ ↓ sex hormones
❑ ↑ cortisol
❑ ↑ ghrelin
❑ ↓ IL-6 and TNF-alpha
❑ ↓ T3 and NE
MOLECULAR ADAPTATIONS
❑ ↓ PI3K/Akt
❑ ↓ mTOR/S6K1
❑ ↓ RAS/MAPK
❑ ↓ $p66^{shc}$
❑ ↓ AC5
❑ ↑ FOXO
❑ ↑ AMPK
❑ ↑ SIRT
❑ ↑ Nrf2
❑ ↑ Beclin
❑ ↓ Cdk4,6/cycD
❑ ↓ p21
❑ ↑ HSP70
❑ ↑ SOD
❑ ↓ NF-kB
CELLULAR ADAPTATIONS
❑ ↓ cell proliferation
❑ ↑ proteostasis/autophagy
❑ ↑ removal damaged cells (apoptosis)
❑ ↓ inflammation/ECM remodeling
❑ ↓ oxidative damage
❑ ↑ DNA repair
❑ ↑ carcinogen-detox enzymes
❑ ↑ genome stability
❑ ↑ stress resistance (hormesis)
❑ ↑ immunosurveillance
↑ LIFESPAN
↓ CANCER
MANY INTERRELATED AND OVERLAPPING FACTORS

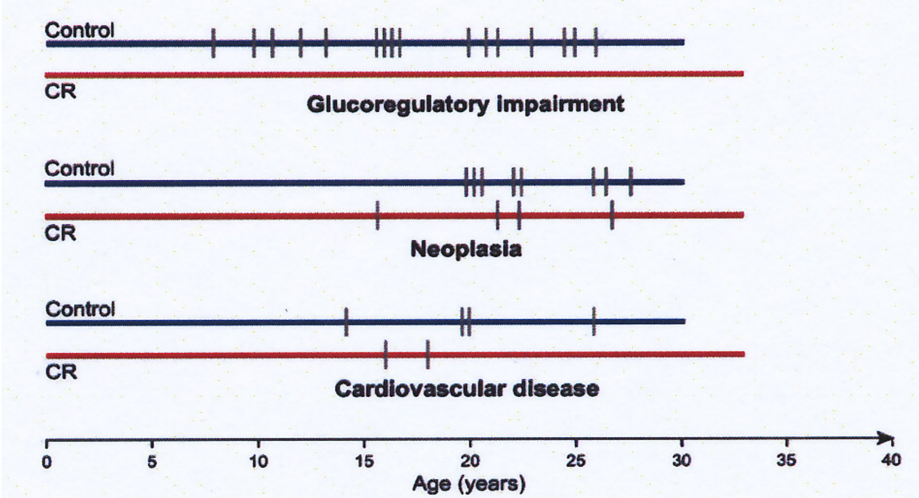
Calorie restriction reduces cardiovascular and cancer mortality by 50% in non-human primates



Ad libitum **CR**

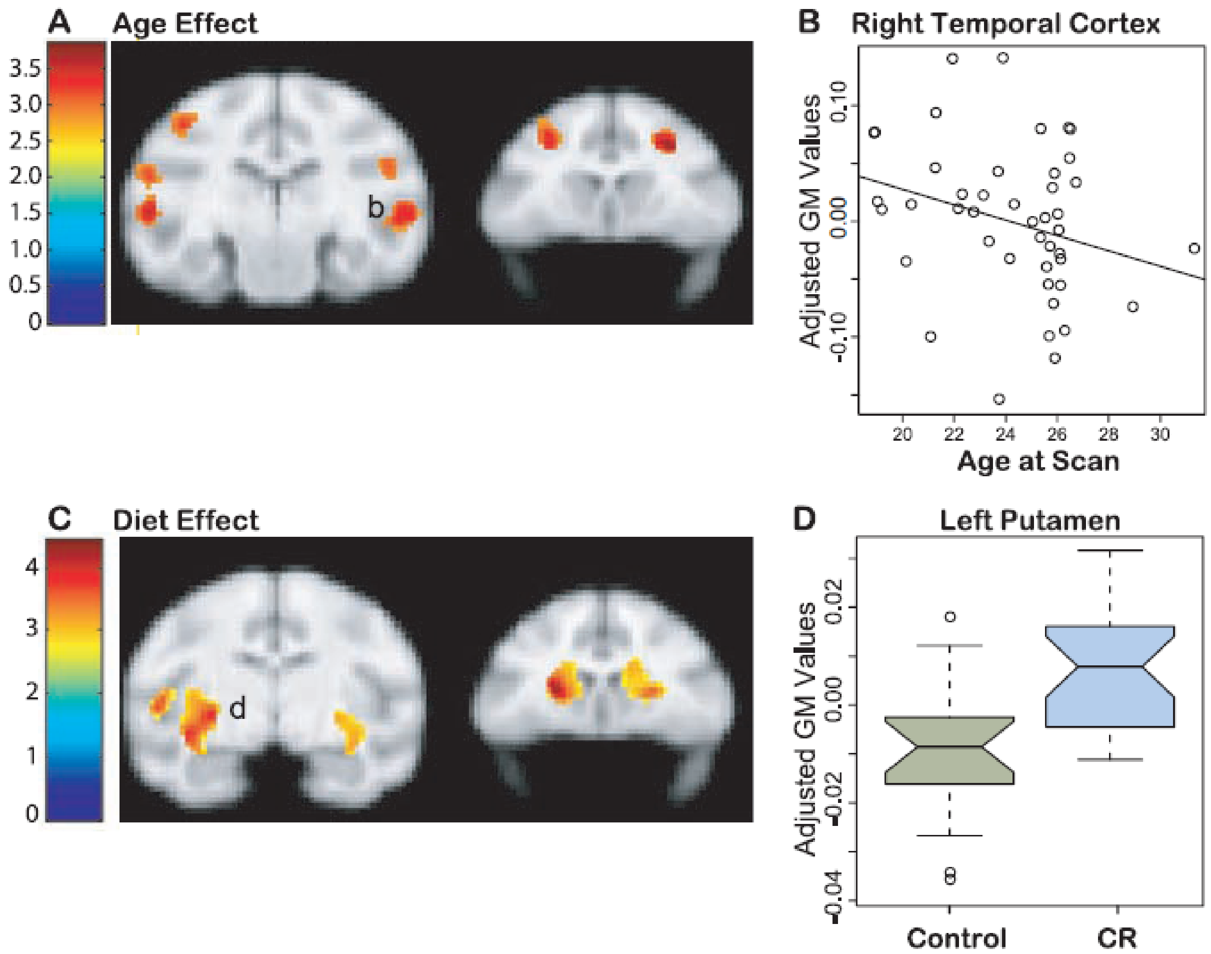


P = 0.03
HR = 3.0



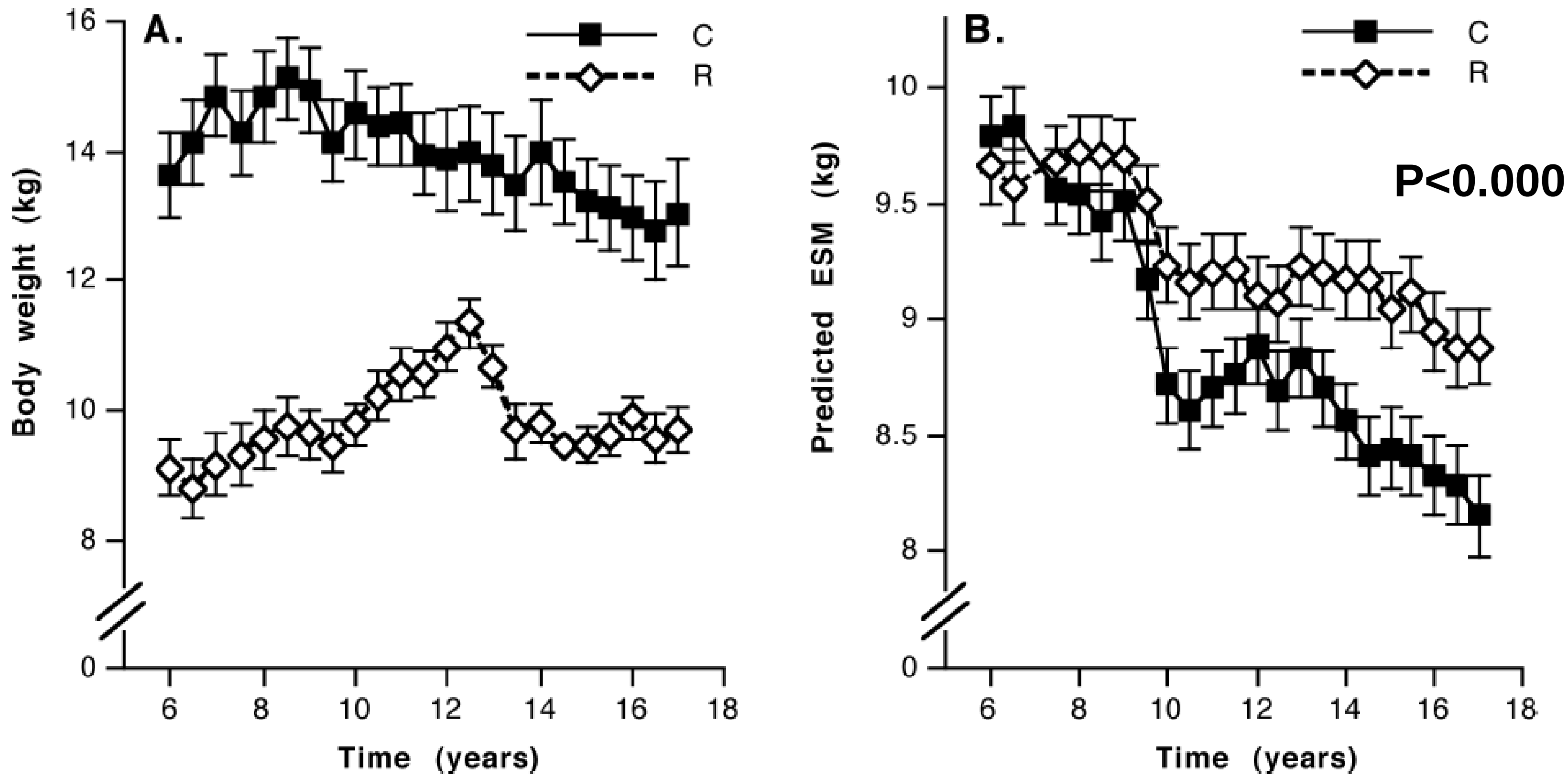
Colman et al. Science 2009

Calorie restriction reduces the age-associated brain atrophy in non-human primates



Colman et al. Science 2009

Attenuation of sarcopenia by CR in non-human primates



Colman et al. J Gerontol 2008

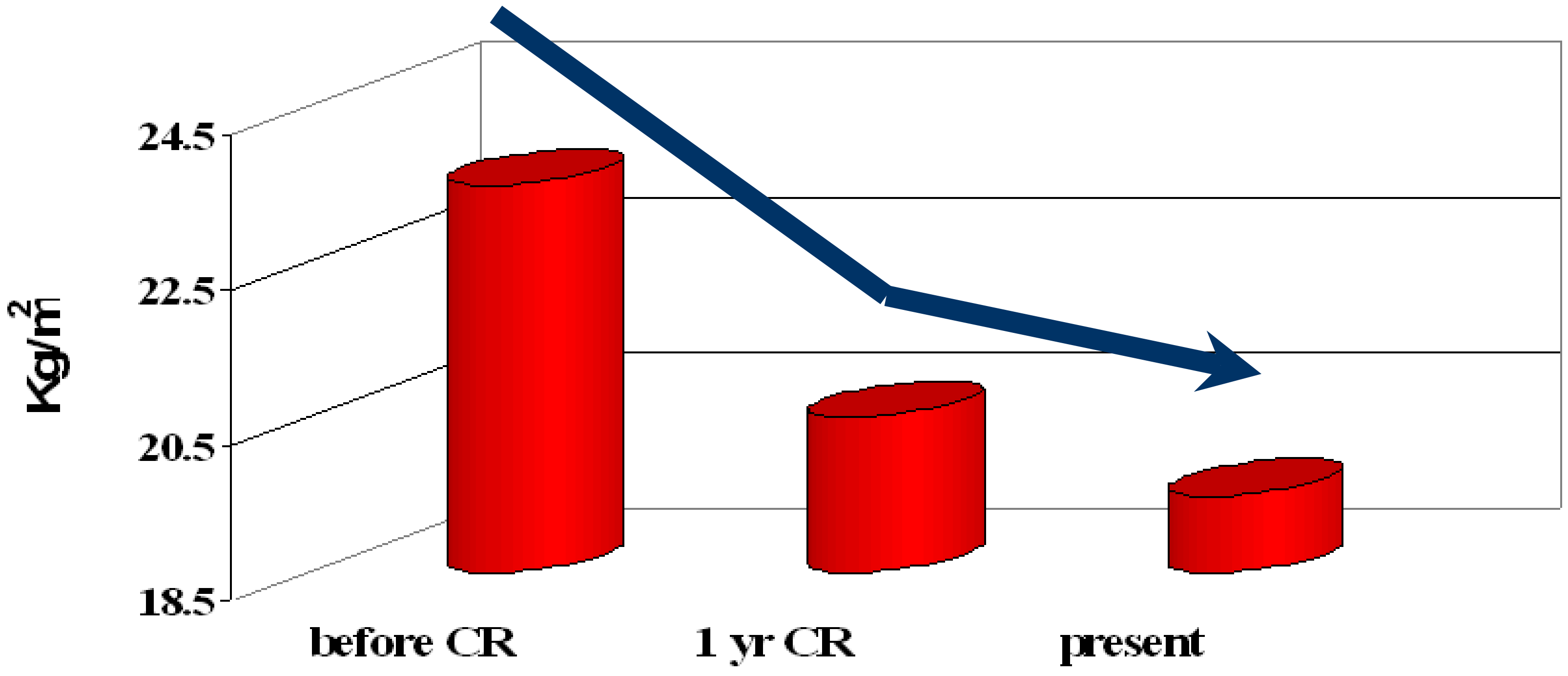
Effects of long-term CR in humans

	CR group (*n*=28)	EX group (*n*=28)	WD group (*n*=28)	Among group P
Age (years)	53.0±11	54.0±11	53.0±10	ns
Sex (M/F)	24/4	24/4	24/4	
Height (m)	1.73±0.1	1.75±0.1	1.76±0.1	ns
Weight (kg)	58.1±6.0*,**	68.0±7.6*	81.1±14.5	0.0001
BMI (kg/m^2)	19.5±1.7*,**	22.2±2.1*	26.0±3.0	0.0001
Total body fat (%)				
Men	9.7±4.6*	10.9±4.5*	23.2±6.2	0.0001
Women	20.5±9.9	20.1±1.7	32.0±7.8	0.085
Trunk fat (%)				
Men	7.0±5.0*	8.4±6.0*	25.2±8.4	0.0001
Women	14.1±8.8	13.2±2.6	27.5±10.4	0.056
Lean mass (kg)				
Men	51.7±4.8*,**	59.2±5.0	59.9±8.8	0.0001
Women	38.9±5.3	40.3±3.0	35.6±2.0	ns

Values are means ± SD

*$P \leq 0.0001$, significantly different from Western diet group; **$P \leq 0.001$, significantly different from EX group

BMI changes during CR Historical data (n=32)



CR practitioner before starting CR and after 7 years of CR

Body weight	180 lb or 81.6 kg (BMI 26.0 kg/m^2)	134 lb, or 60.8 kg (BMI 19.4 kg/m^2)
T-chol and LDL-c	244 mg/dl and 176 mg/dl	165 mg/dl and 97 mg/dl
Fasting glucose	87 mg/dl	74 mg/dl
Blood pressure	144/87 mmHg	94/61 mmHg

Fontana L et al. Science 2010

Circulating adipokines and cytokines

	CR group (*n*=28)	EX group (*n*=28)	WD group (*n*=28)	Among group P
Adiponectin (μg/mL)	15.7±8.2*,**	11.1±5.5	9.5±4.3	0.001
Resistin (pg/mL)	7.0±2.2***	8.1±1.7	8.7±2.3	0.015
IL-6 (pg/ml)	0.73±0.3*	0.71±0.3*	1.21±0.8	0.001
s-TNF R-I (ng/mL)	1.05±0.33***	0.95±0.28*	1.30±0.27	0.0001
s-TNF R-II (ng/mL)	2.77±0.83***	2.81±0.69***	3.40±0.84	0.008
Fructosamine (μmol/L)	269±40**	241±17	262±34	0.005
sRAGE (μg/mL)	1.27±0.66	1.63±0.53***	1.11±0.69	0.01
Free fatty acids (mEq/L)	0.72±0.35***	0.59±0.18	0.51±0.20	0.015

All values are means ± SD

*$P \leq 0.003$, significantly different from Western diet group; **$P \leq 0.05$, significantly different from EX group; ***$P \leq 0.05$, significantly different from Western diet group

Glucose tolerance and insulin action

	CR	EX	WD
HOMA-IR index	0.3±0.1*	0.4±0.3*	1.6±1.3
ISI Matsuda index	18.5±6.7*	20.4±9.2*	7.0±3.6
Fasting glucose (mg/dl)	83±8*,†	91±8	95±8
Fasting Insulin (μU/ml)	1.4±0.7*	2.0±1.3*	6.9±5.6
2-hr glucose (mg/dl)	132±42†	103±28	116±28
2-hr insulin (μU/ml)	37.7±24†	16.8±11*	60.4±55
Glucose AUC (mg•min/dl)	16.1±3.2	14.9±2.6*	16.8±3.0
Insulin AUC (μU•min/dl)	3.5±1.7*	2.7±1.8*	6.2±3.6

Fontana et al. Age 2009

Cardiometabolic risk factors

	CR	EX	WD	P value
Total cholesterol (mg/dl)	162±36*	166±35*	202±36	0.0001
LDL cholesterol (mg/dl)	88±24*	92±26*	122±33	0.0001
HDL cholesterol (mg/dl)	63±19*	61±17*	50±11	0.004
T Chol/HDL Chol ratio	2.7±0.5*	2.8±0.6*	4.3±1.1	0.0001
Triglycerides (mg/dl)	58±18*	65±22*	159±94	0.0001
SBP (mm Hg)	103±9*,†	125±17	131±13	0.0001
DBP (mm Hg)	62±7*,†	72±8*	84±8	0.0001
Fasting glucose (mg/dl)	82±7*,†	90±7	95±9	0.0001
hsCRP (mg/L)	0.2±0.3*,†	0.8±1.1	1.1±1.1	0.004

Fontana et al., PNAS 2004

CR ameliorates the decline in diastolic function

	Parameter	Western Diet Mean±SD	CR Mean±SD	p value
Diastolic Function				
	E_{peak} (cm/sec)	64.3 ± 12.6	70.8 ± 13.4	ns
	A_{peak} (cm/sec)	53.0 ± 10.2	45.7 ± 9.0	0.011
	E/A	1.24 ± 0.28	1.61 ± 0.44	0.001
	Atrial filling fraction	0.35 ± 0.05	0.29 ± 0.06	0.0001
Tissue Doppler Imaging				
	$E'_{Lateral}$ (cm/sec)	10.2 ± 2.8	14.3 ± 3.0	0.001
Model Derived Parameters				
	c (g/sec)	19.6 ± 3.6	14.9 ± 5.0	0.001
	k (g/sec^2)	218.9 ± 44.6	180.1 ± 41.6	0.003

Meyer T et al. JACC 2006

Long-term CR reduces metabolic factors associated with cancer in humans

- Reduces adiposity
- Reduces insulin
- Reduces growth factors such as IGF-1

  (if associated with lower protein intake)
- Reduces sex hormones
- Reduces inflammation
- Reduces oxidative stress

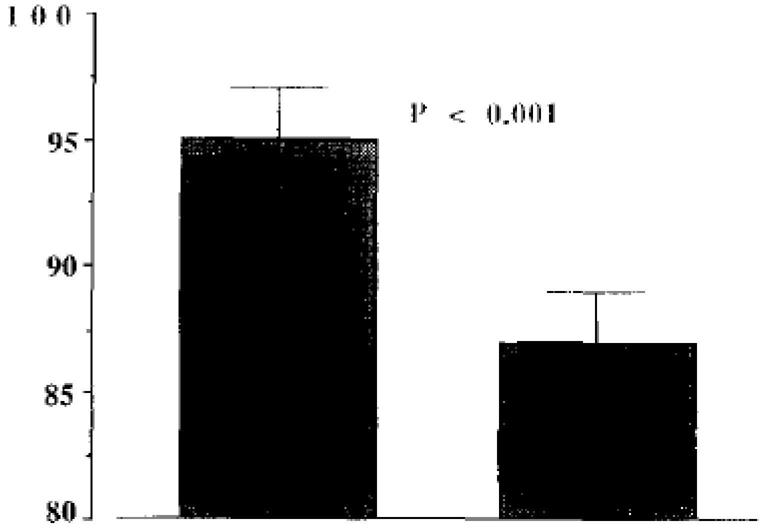
Longo and Fontana. Trends Pharmacol Sci 2010

NEUROENDOCRINE ADAPTATIONS OF LONG-TERM CR

Long-term CR depresses serum T3 concentration in the rat

Serum T3

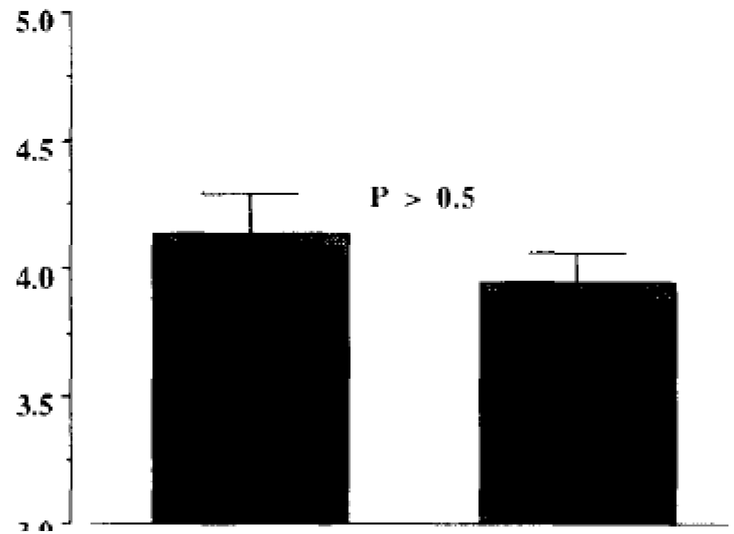
ng/ml



Ad lib CR

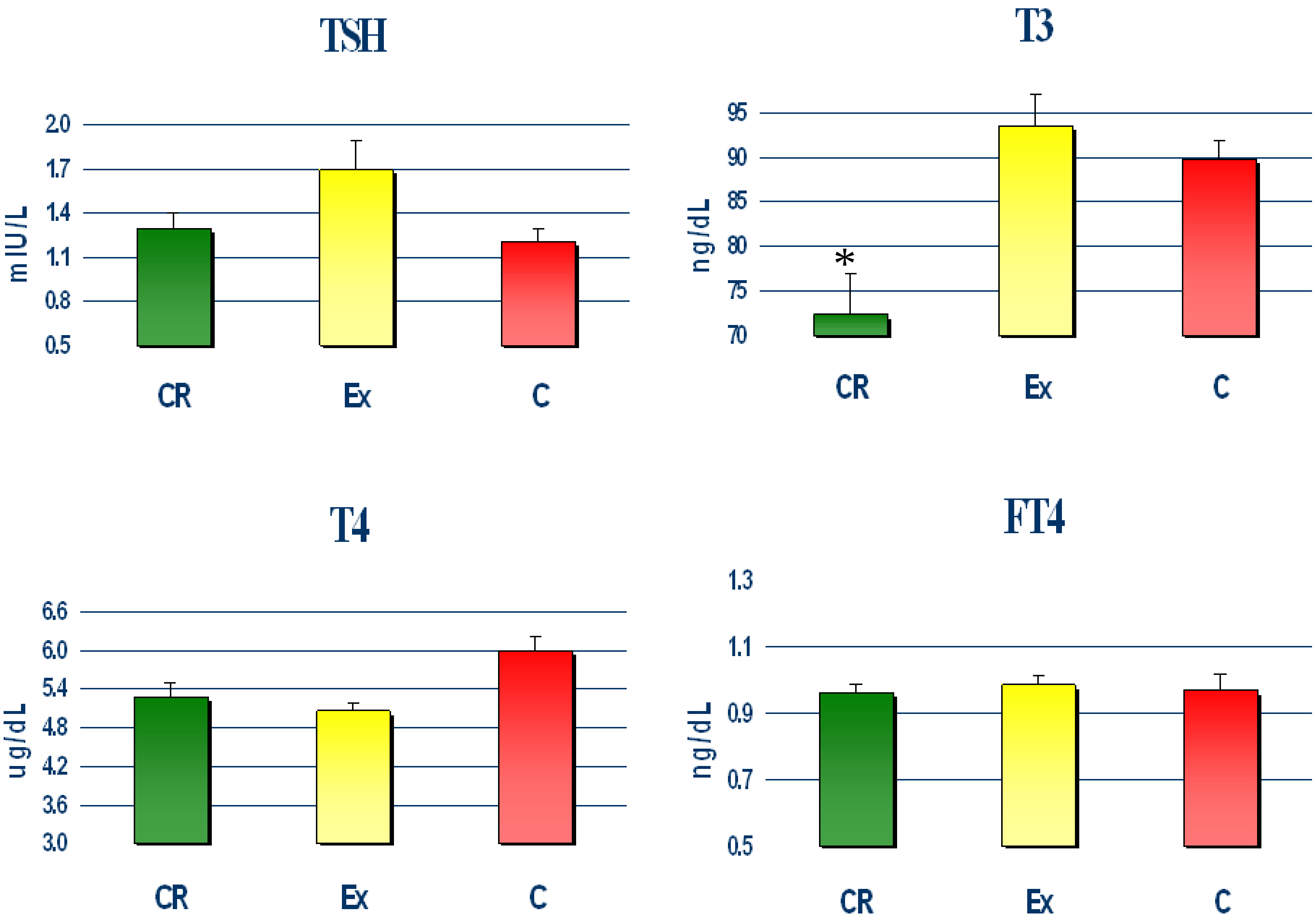
Serum T4

µg/ml



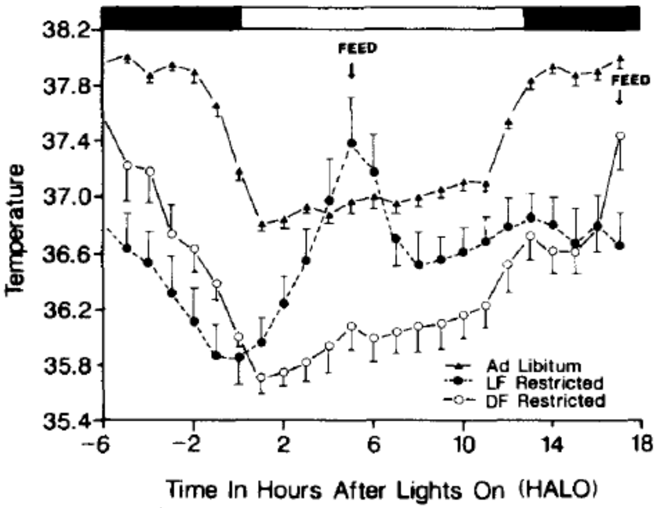
Ad lib CR

Herlihy et al. Mech Ageing Dev 1990

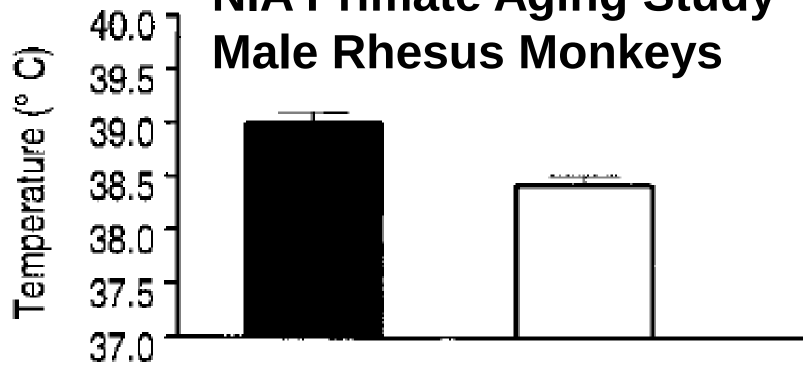


Fontana L et al. JCEM 2006

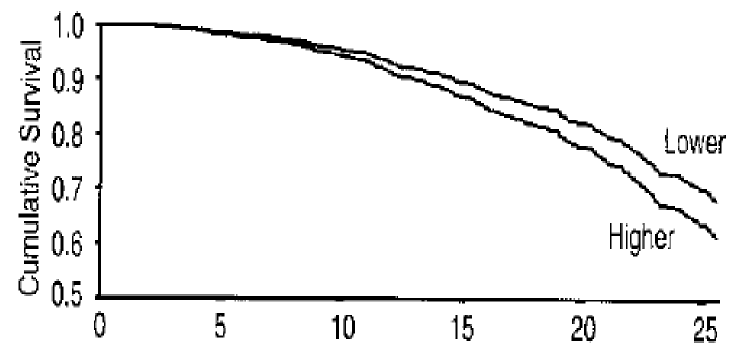
Body temperature and longevity



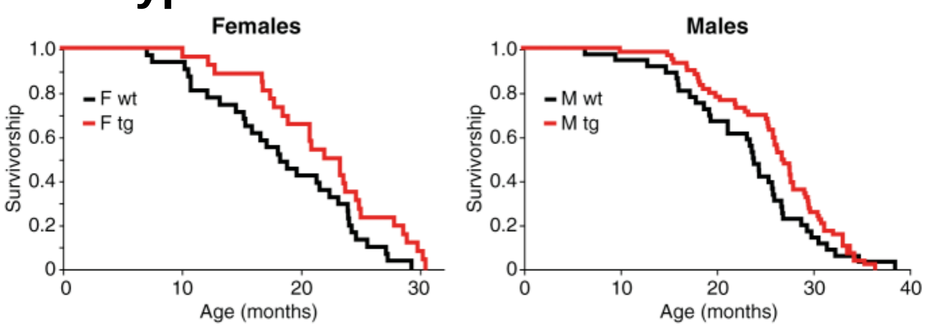
NIA Primate Aging Study
Male Rhesus Monkeys



Baltimore Longitudinal Study of Aging: Male Humans



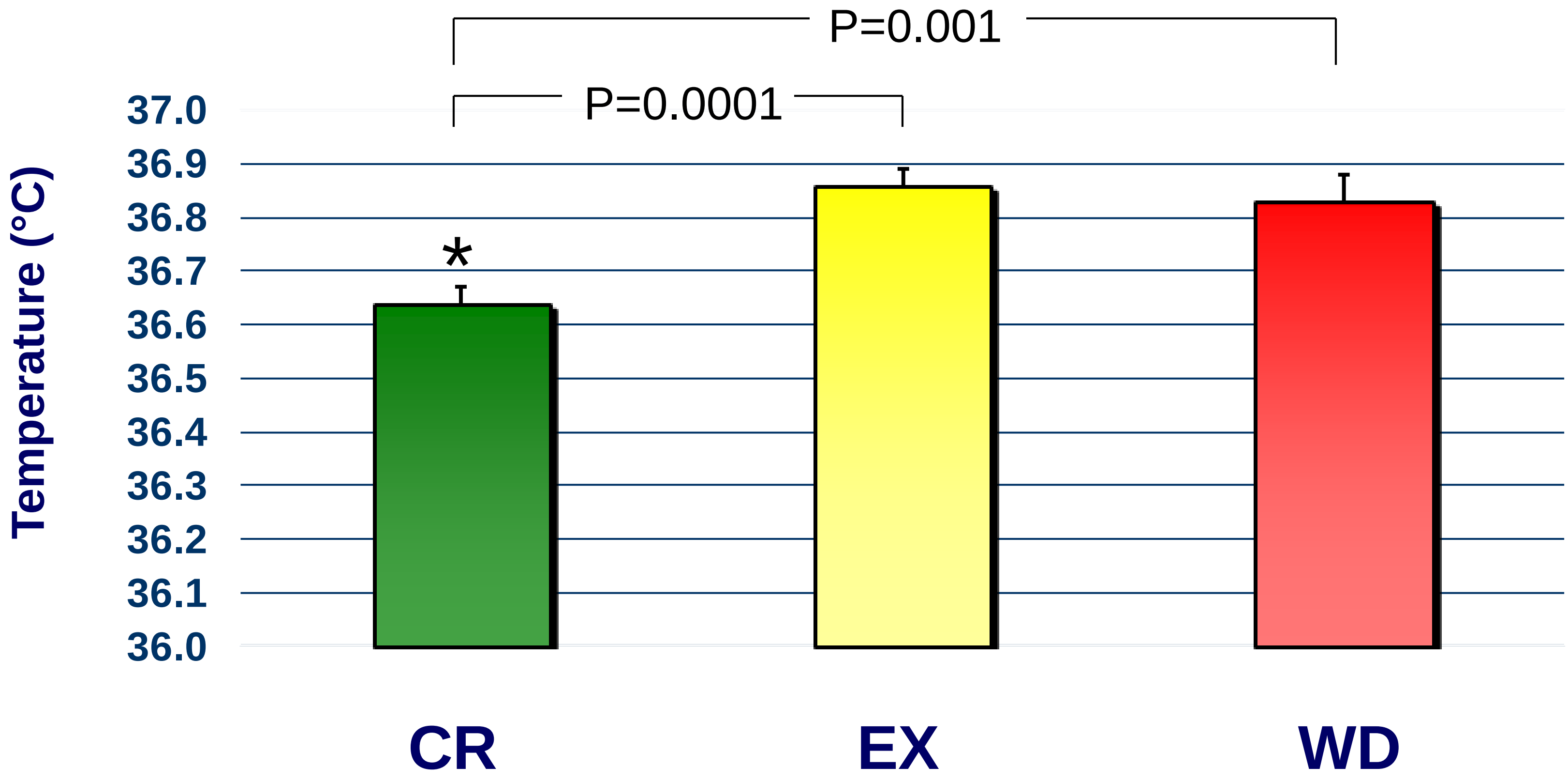
Transgenic mice overexpress UCP2 in hypocretin neurons



Duffy et al., Mech Ageing Dev 1990 & Conti et al., Science 2006

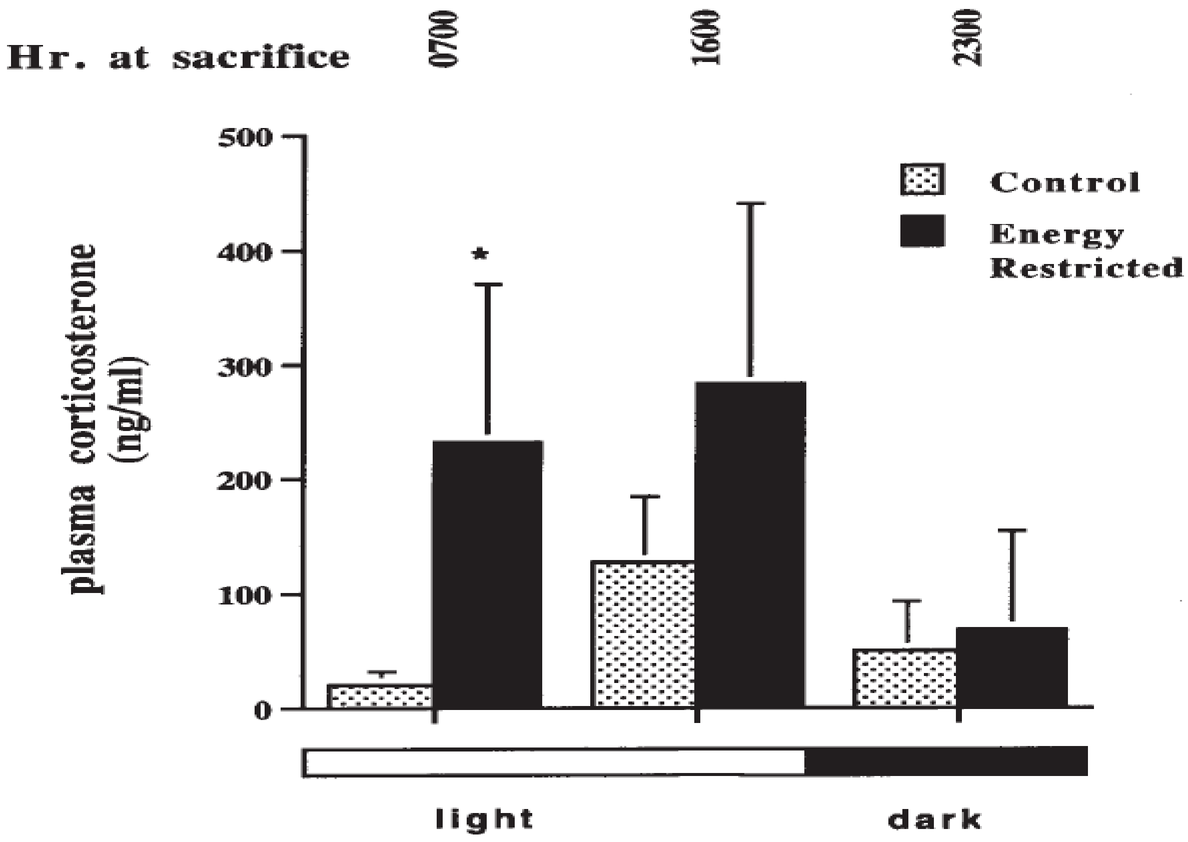
Roth G et al. Science 2000

Long-term CR reduces 24-hrs core body temperature in humans



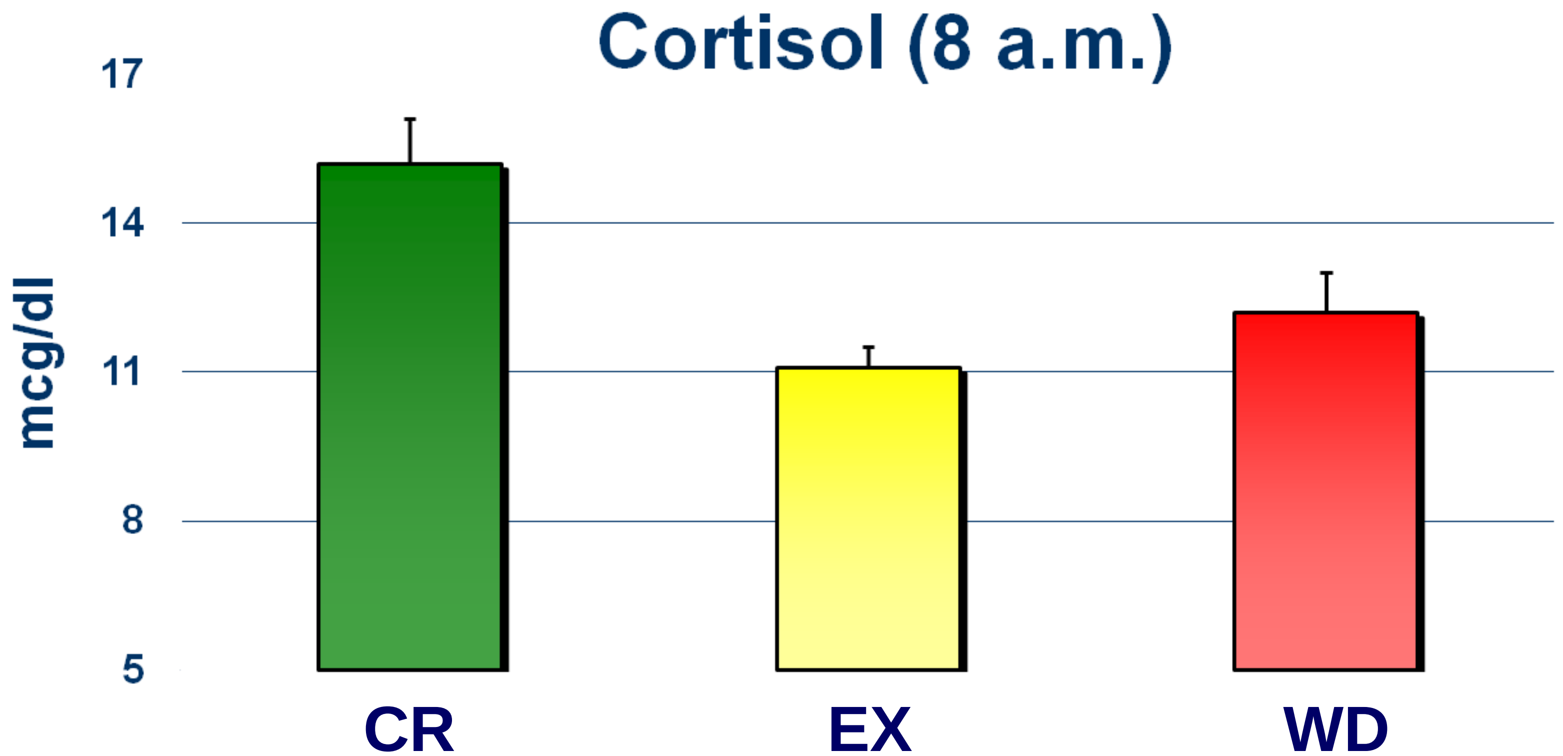
Soare A et al. Aging 2011

Long-term CR increases plasma corticosterone concentration in mice



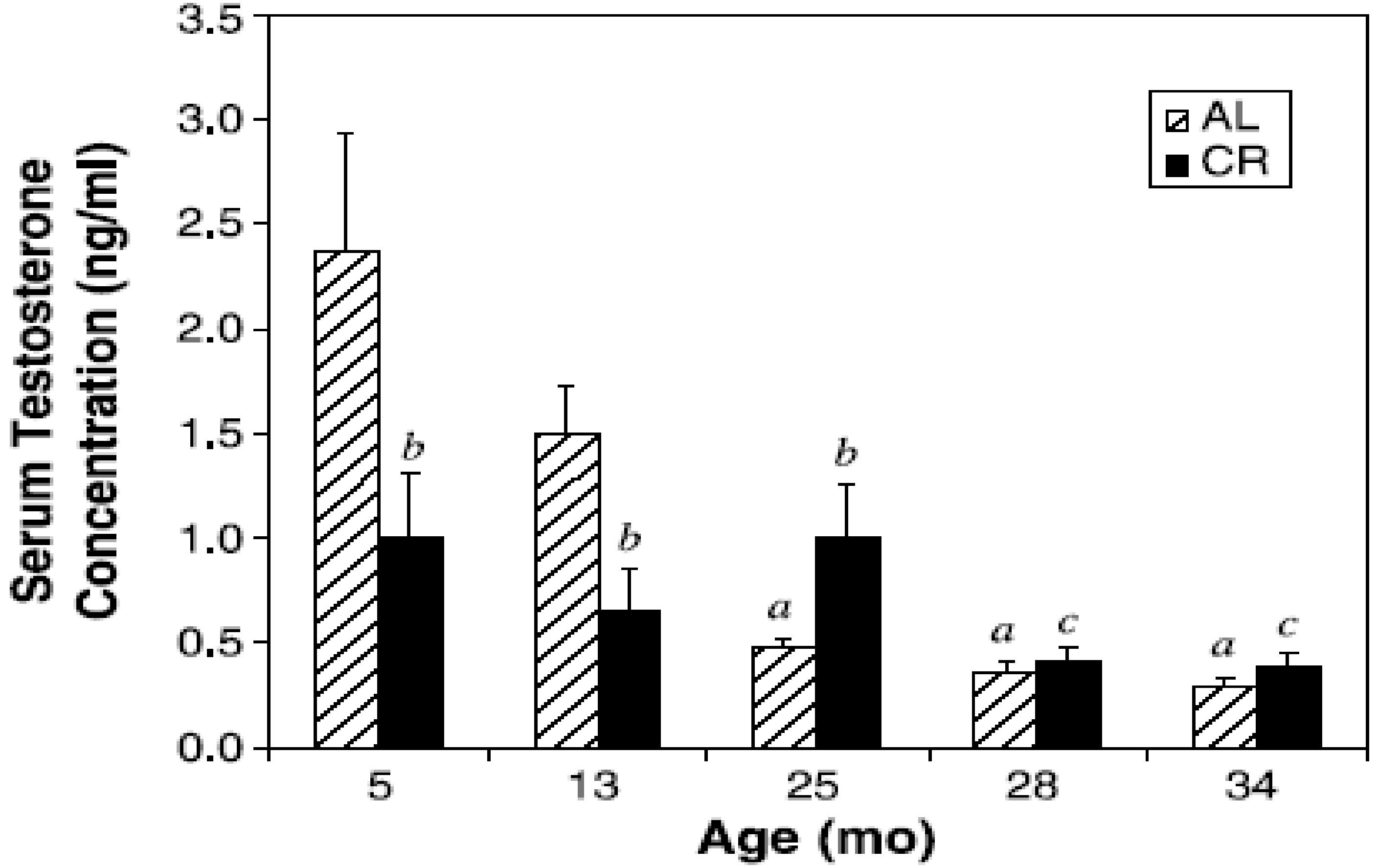
Yaktine et al. Mol Carc 1998

Long-term CR increases plasma cortisol concentration in humans

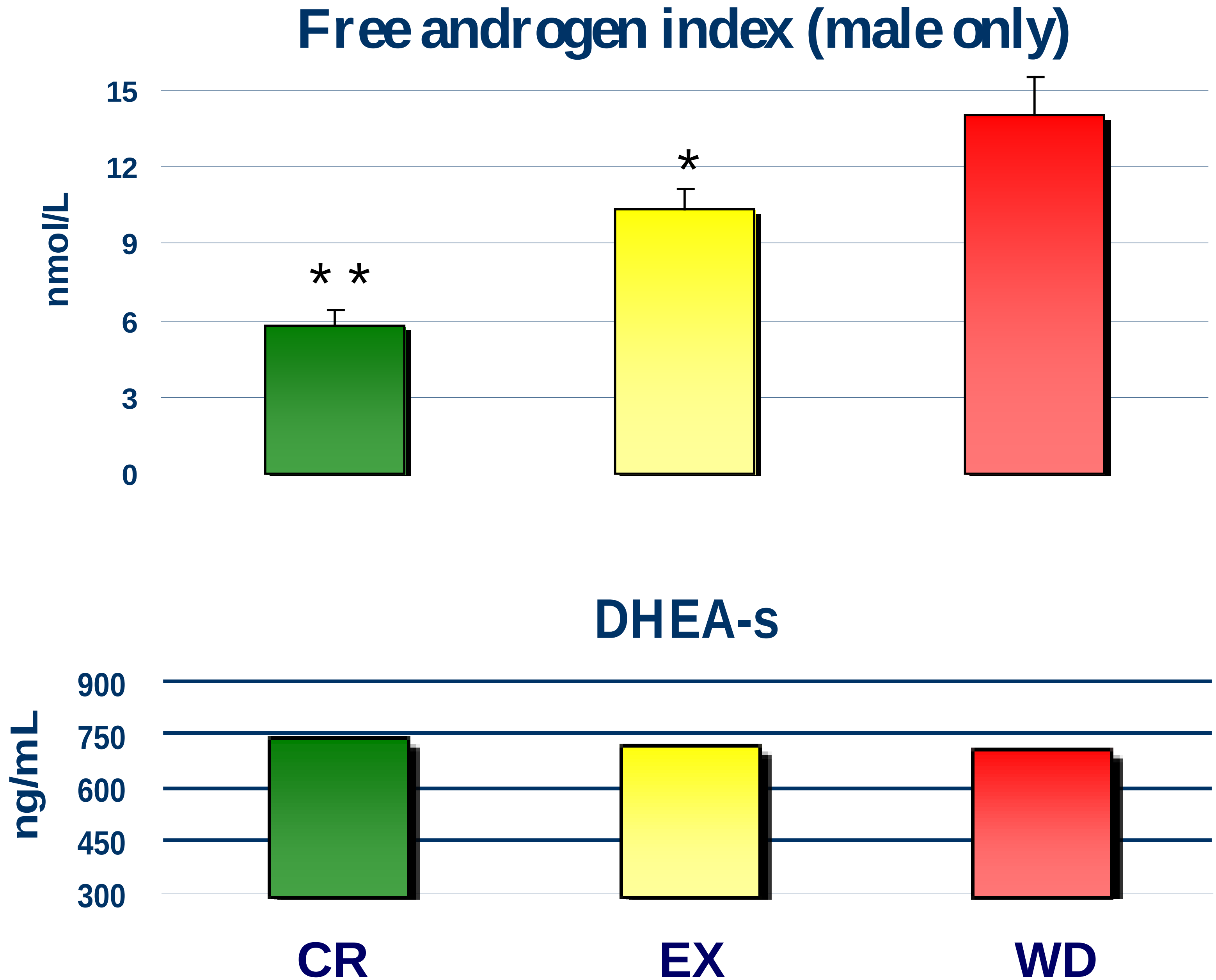


Unpublished data

Long-term CR reduces serum testosterone concentration in rats

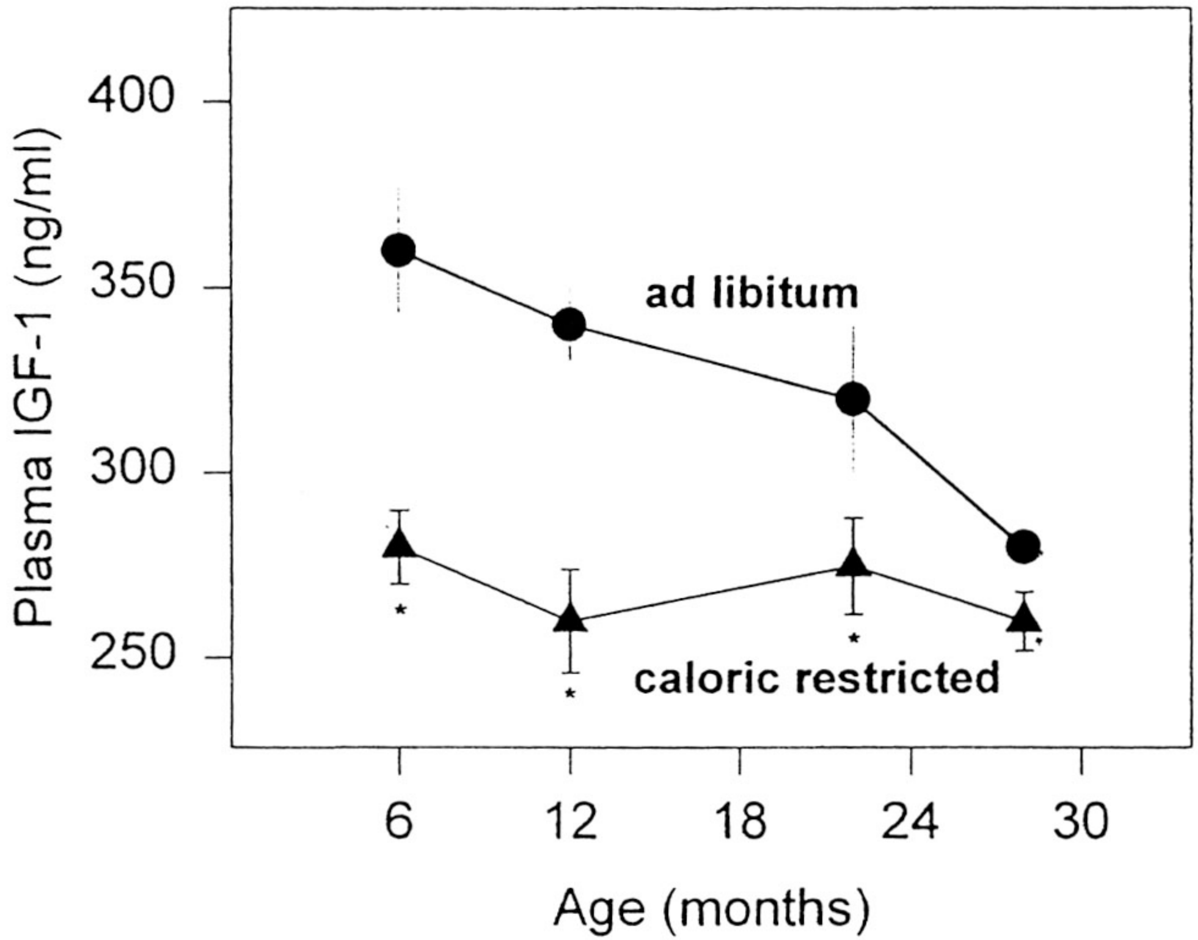


Chen et al. Exp Gerontol 2005



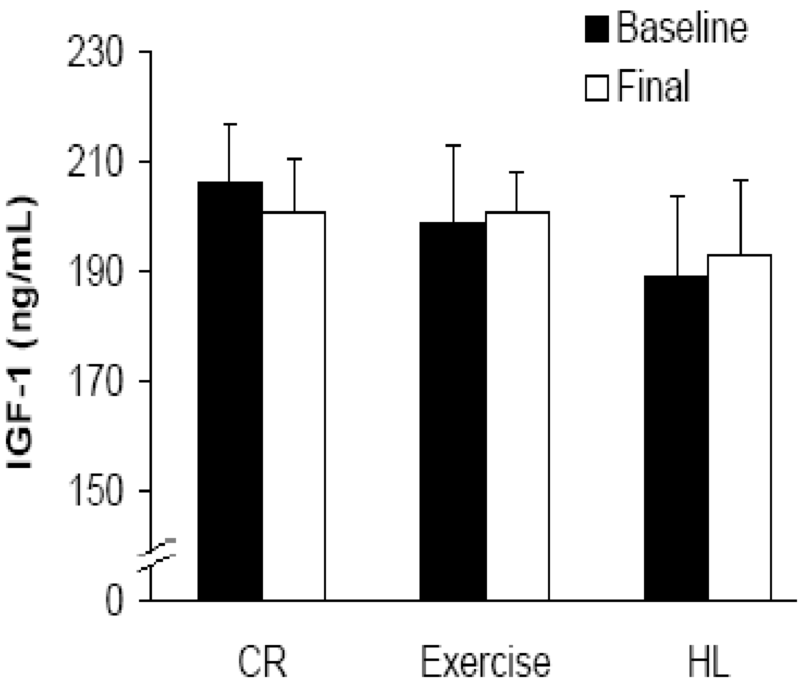
Cangemi R et al. Aging Cell 2010

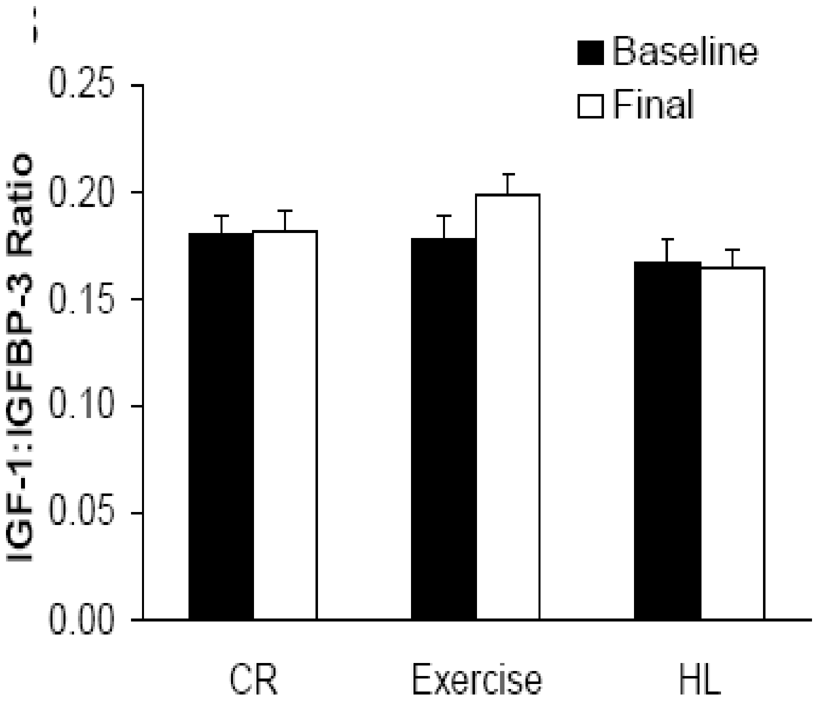
Long-term CR reduces plasma IGF-1 concentration by 20-40% in rats



Breese CR et al. J Gerontol Biol sci 1991

1-yr CR intervention does NOT reduce serum IGF-1 concentration

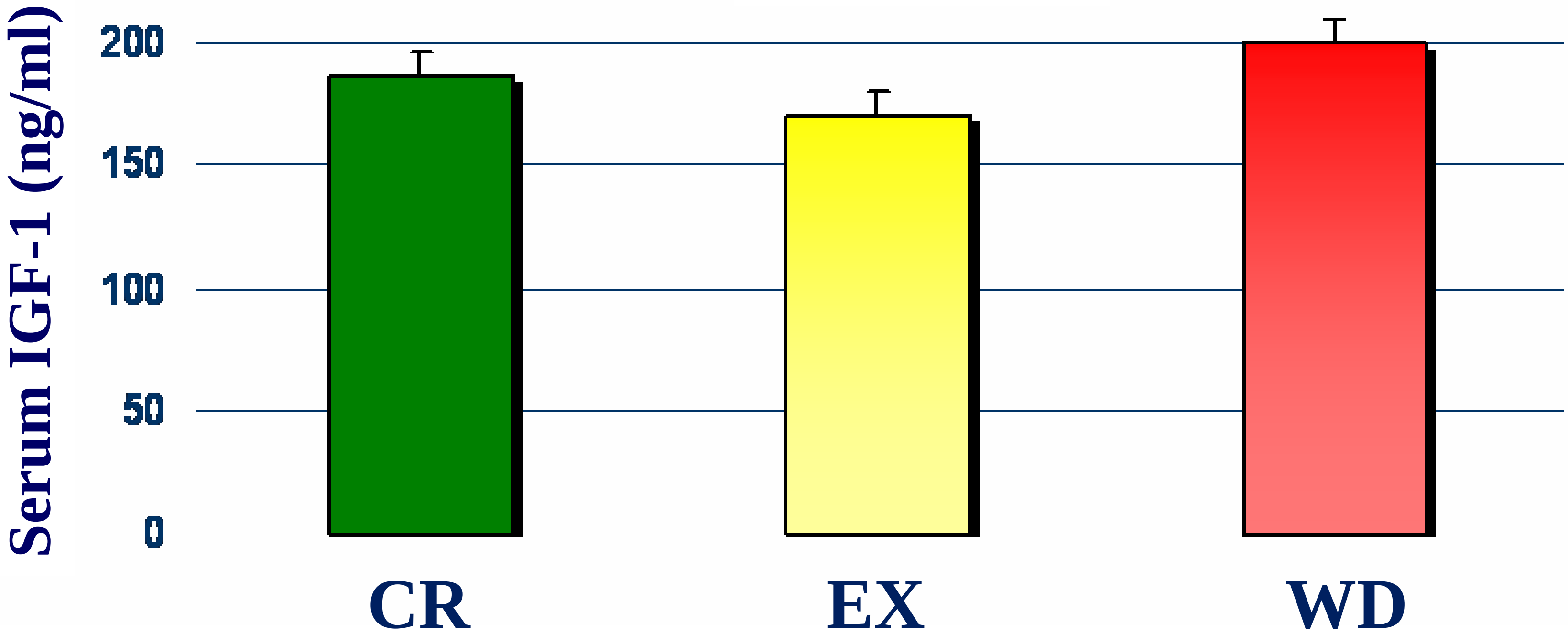




calerie

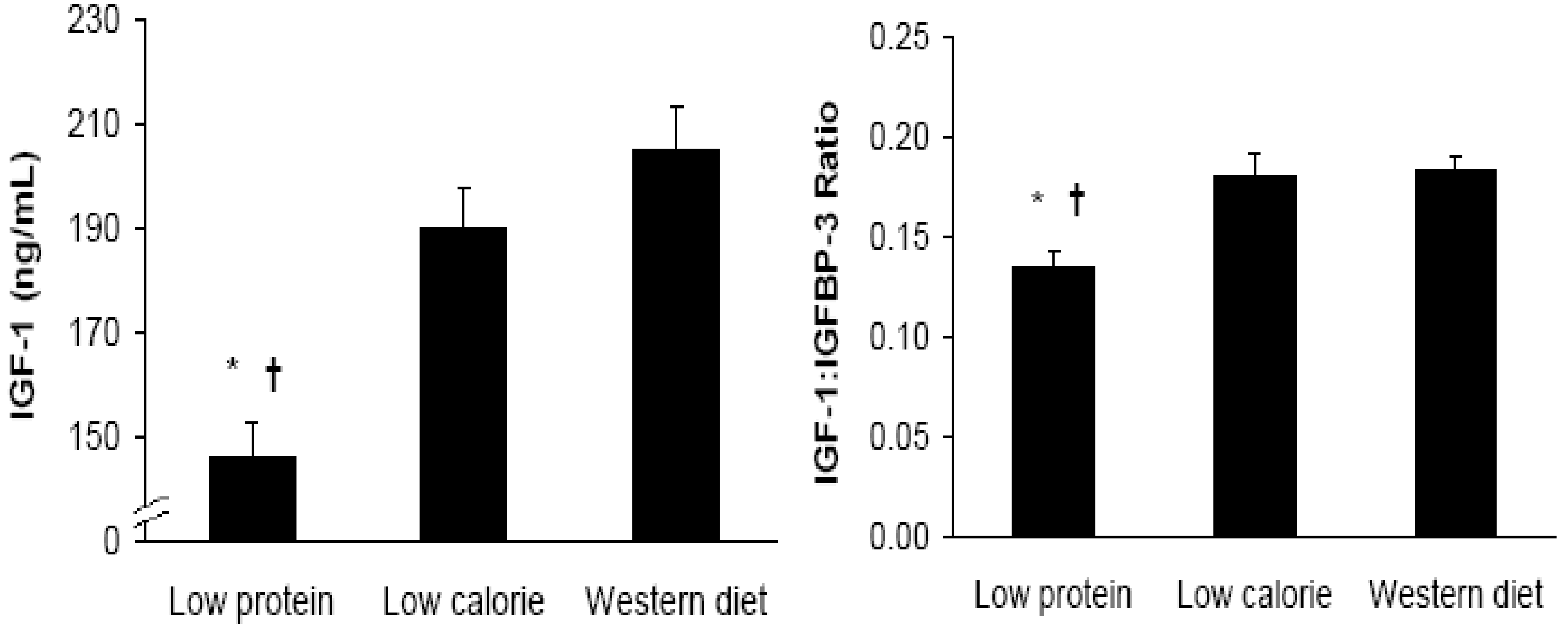
Fontana et al., Aging Cell 2008

Long-term CR does NOT reduce serum IGF-1 concentration



Fontana et al., Aging Cell 2008

Moderate protein restriction reduces serum IGF-1 concentration



Fontana et al., Aging Cell 2008

Diet composition: protein restricted vegan diet versus CR diet

	PR vegan (n=28)	CR diet (n=28)	WD (n=28)
Age (yrs)	53.4±11	52.2±12	53.7±8.2
Body fat (%)			
men	15.2±5.4*,†	7.1±4.6*	23.6±6.5
women	25.8±7.7*	20.5±9.9*	36.9±3.9
Calorie intake (kcal/d)	1980±535*	1772±351*	2505±522
Protein intake			
(%)	9.6±3.3*,†	23.5±5.7*	15.9±3.0
(g/Kg/day)	0.76±0.2*,†	1.73±0.4*	1.24±0.3
Fat intake (%)	41.3±10*,†	28.1±9*	33.6±6

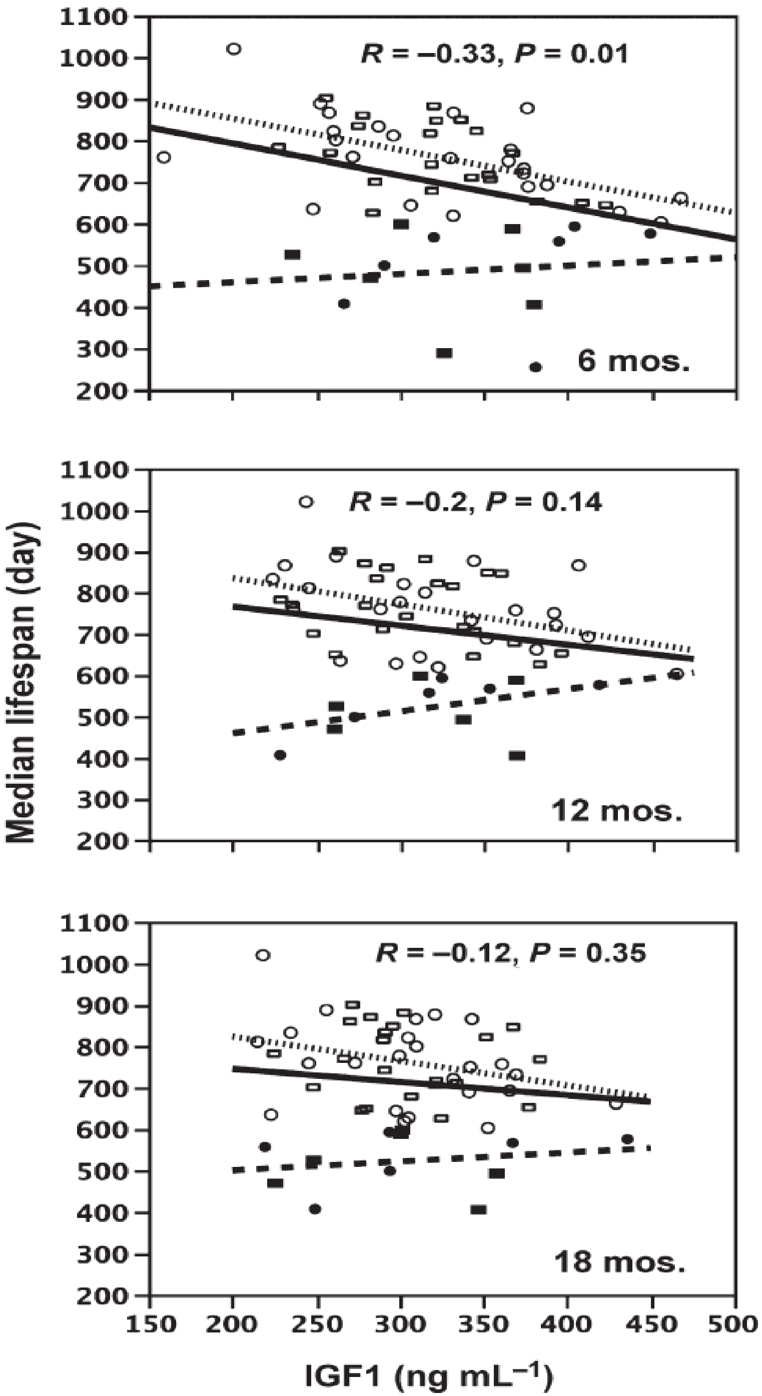
Fontana et al., Aging Cell 2008

Serum IGF-1 is associated with increased risk of breast and prostate cancer

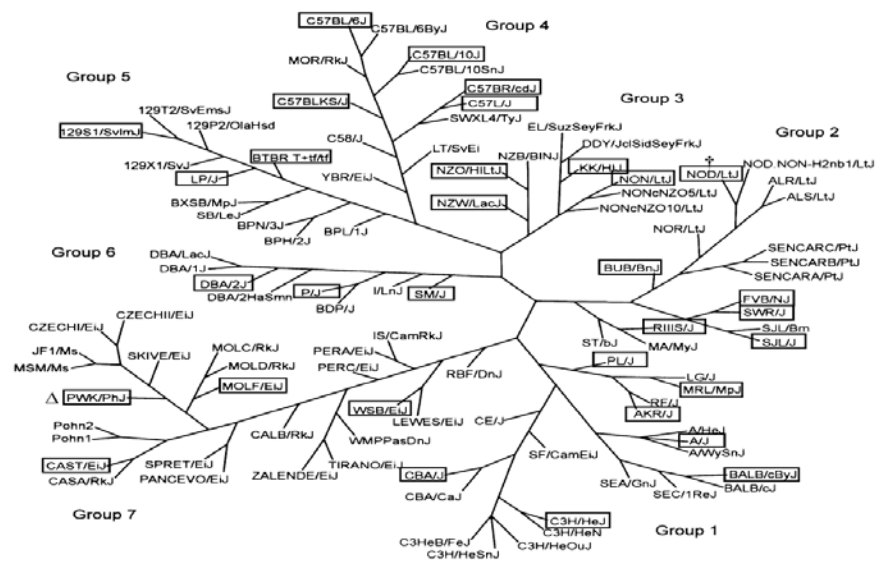
Plasma IGF	RR	RAR
Breast cancer (premenopausal, <50 years)		
<158 ng/mL	1·0	1·0
158–206 ng/mL	2·64	3·12
>207 ng/mL	4·58	7·28
Prostate cancer		
99–184 ng/mL	1·0	1·0
185–236 ng/mL	1·32	1·94
237–293 ng/mL	1·81	2·83
294–500 ng/mL	2·41	4·32

RR, relative risk; RAR, risk adjusted for IGFBP3.

Hankinson SE, Lancet 1998 & Chan JM, Science 1998



Plasma IGF-1 levels are negatively correlated with median lifespan in mice



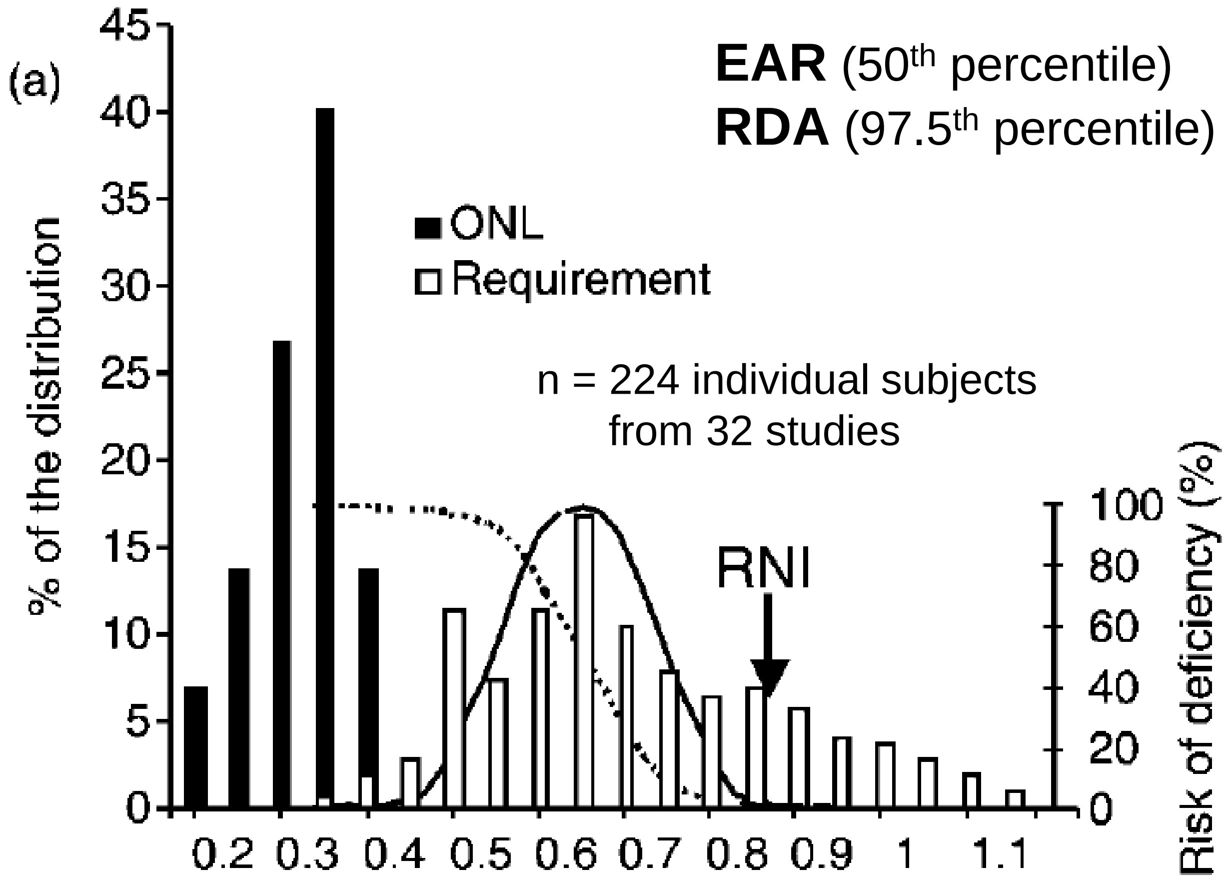
31 genetically-diverse inbred mouse strains
(median lifespan: 251-964 days)

For the longer-lived strains (>600 days), the negative correlation between lifespan and IGF-1 is stronger: 6 mos R=-0.53, P<0.01; 12 mos R=-0.39, P<0.01; 18 mos R=-0.3, P<0.05.

Yuan et al., Aging Cell 2009

Protein requirements for healthy adults

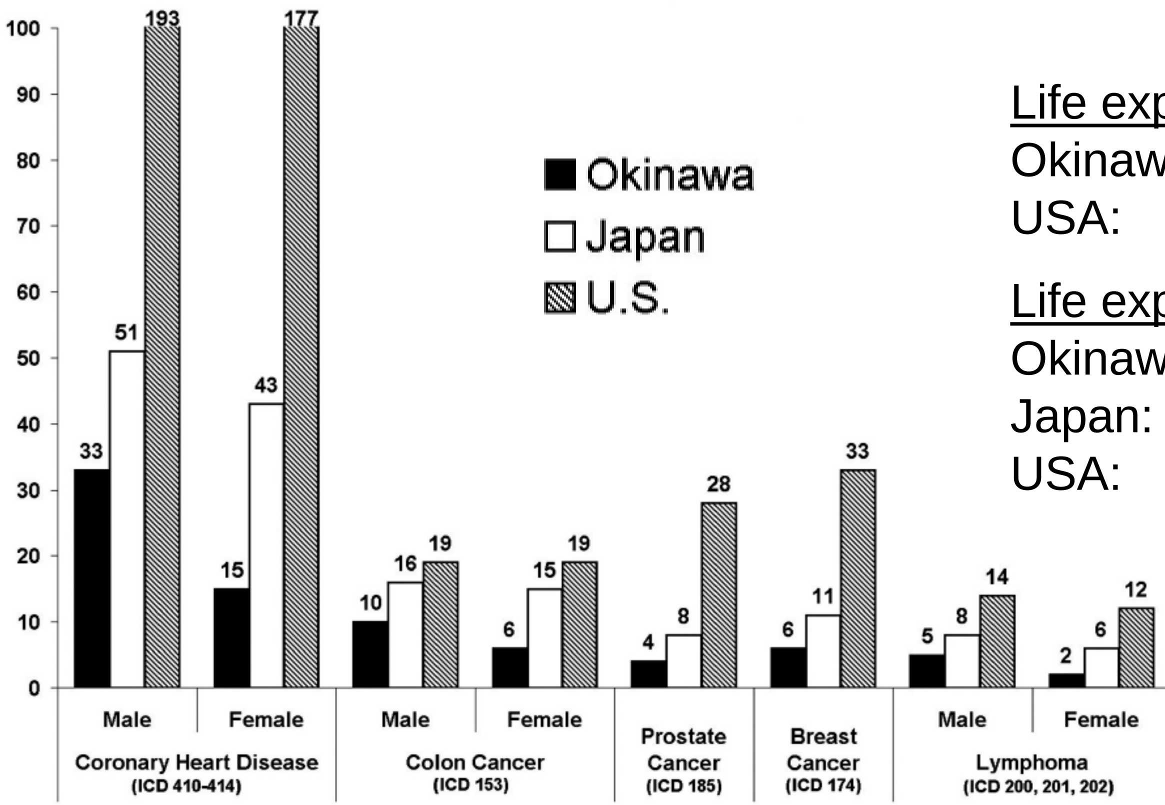
EAR (50th percentile) = **0.65 g/kg/d**
RDA (97.5th percentile) = **0.83 g/kg/d**



Rand WM et al. AJCN 2003

Traditional dietary intake of Okinawans and Japanese in 1950

	Okinawa, 1949[a]	Japan, 1950[b]
Total calories	1785[c]	2068
Total weight (grams)	1262	1057
Caloric density (calories/gram)	1.4	2.0
Total protein in grams (% total calories)	39 (9)	68 (13)
Total carbohydrate in grams (% total calories)	382 (85)	409 (79)
Total fat in grams (% total calories)	12 (6)	18 (8)



<u>Life expectancy at birth</u>:

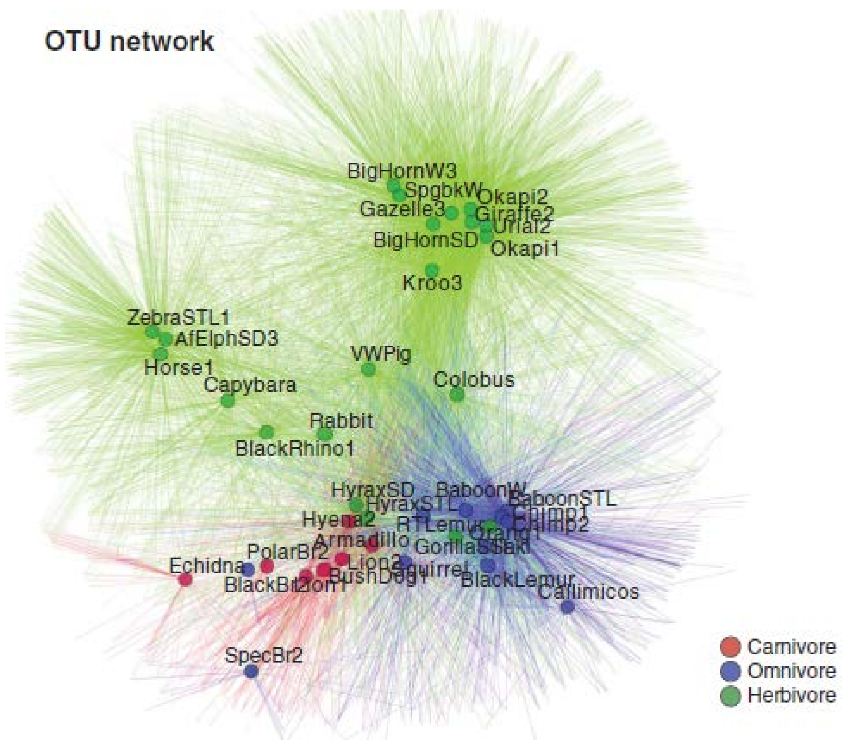
Okinawa:	86 y F; 77.6 y M
USA:	80 y F; 75 y M

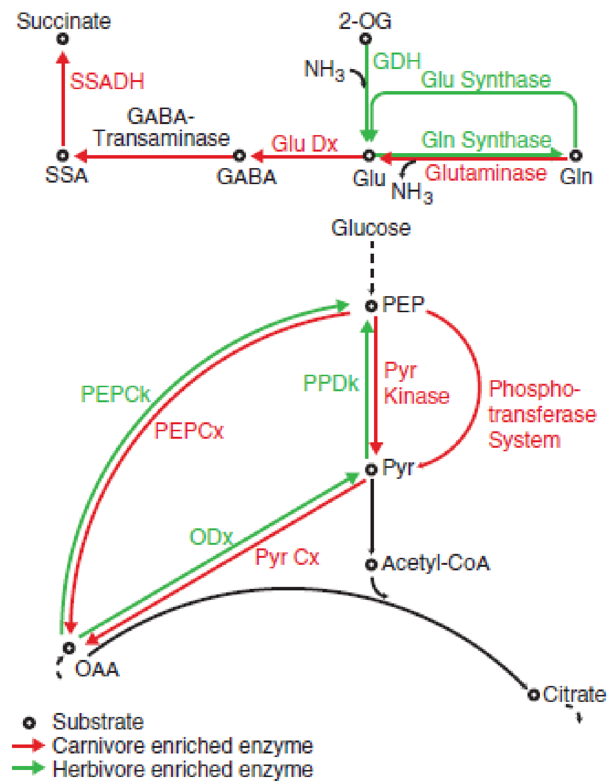
<u>Life expectancy at age 65</u>:

Okinawa:	24.1 y F; 18.5 y M
Japan:	22.5 y F; 17.6 y M
USA:	19.3 y F; 16.2 y M

Willcox BJ et al. Ann NY Acad Sci 2007

Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans





<u>In 18 CR individuals</u>:

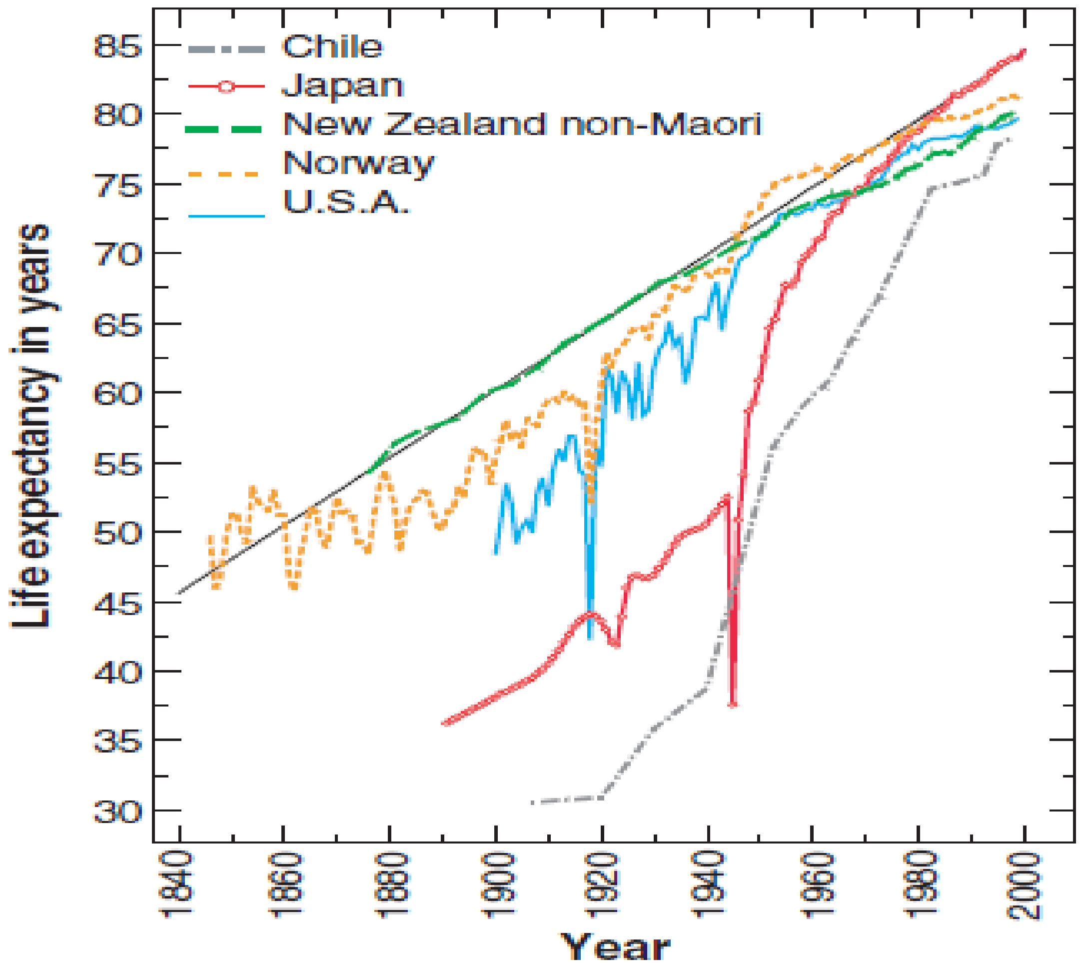
- ➢ Protein intake associated with KO data (R=0.307; adjusted p=0.030)
- ➢ Insoluble fiber associated with bacterial OTU (R=0.371; adjusted p=0.013

OTU = operational taxonomic units
KO = KEGG orthology groups

Muegge et al. Science 2011

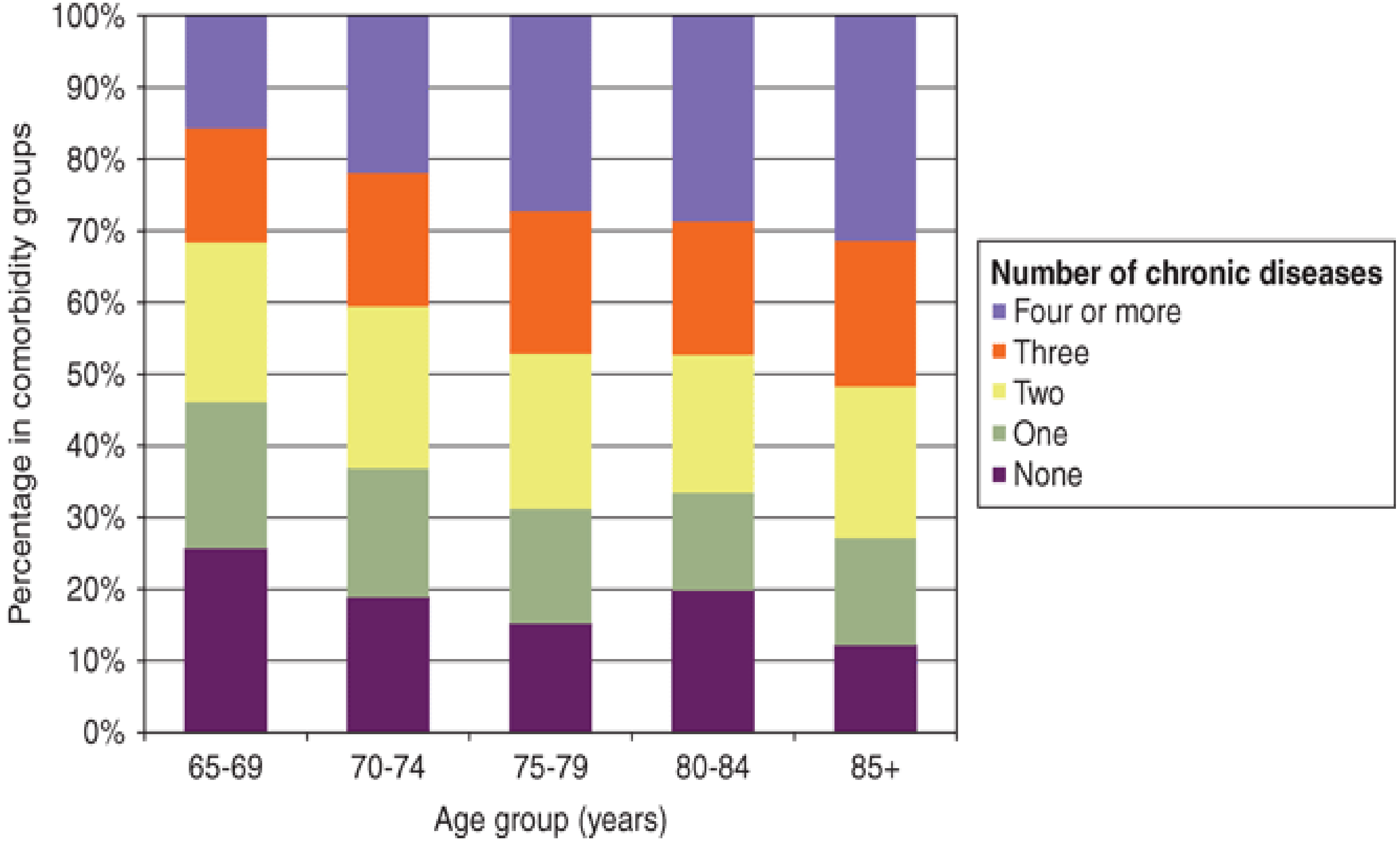
Conclusions and future directions

Life expectancy almost doubled between 1840 and 2007



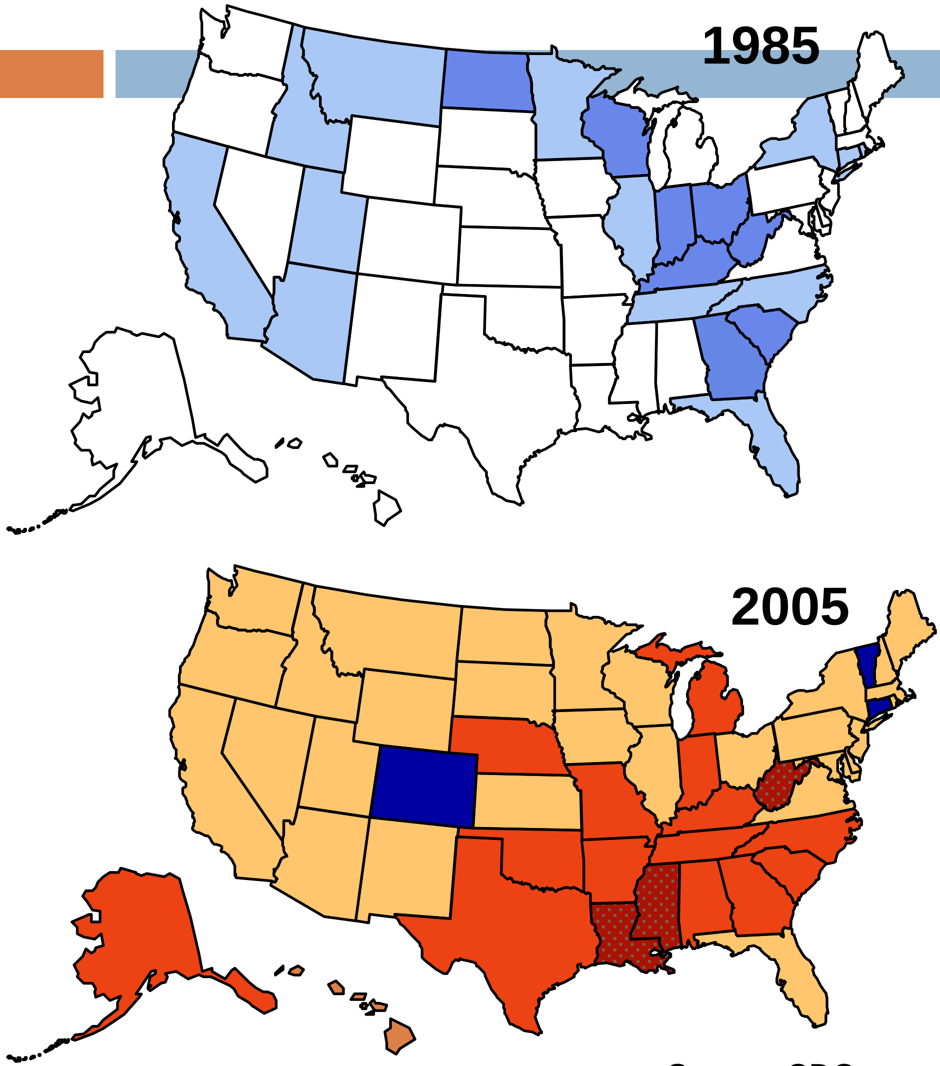
Christensen et al. Lancet 2009

Prevalence of chronic disease

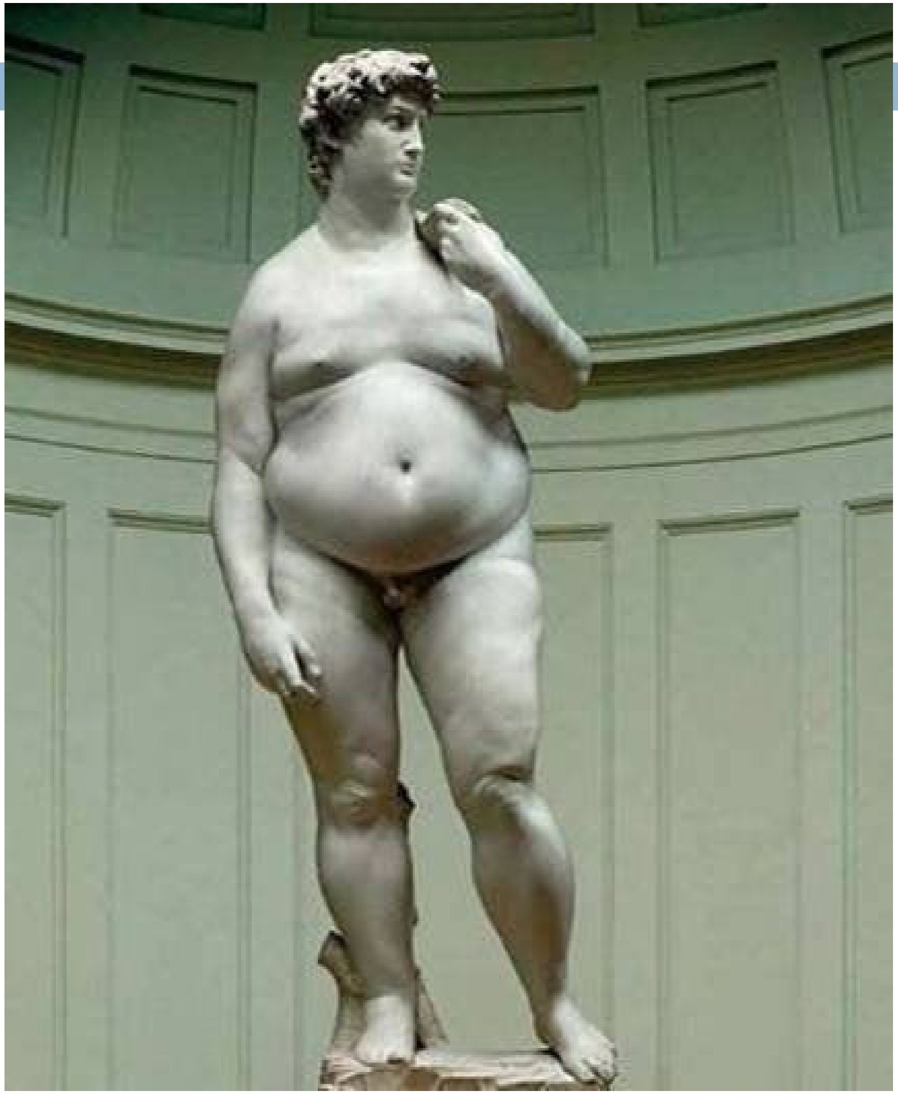


Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Epidemic of overweight/obesity

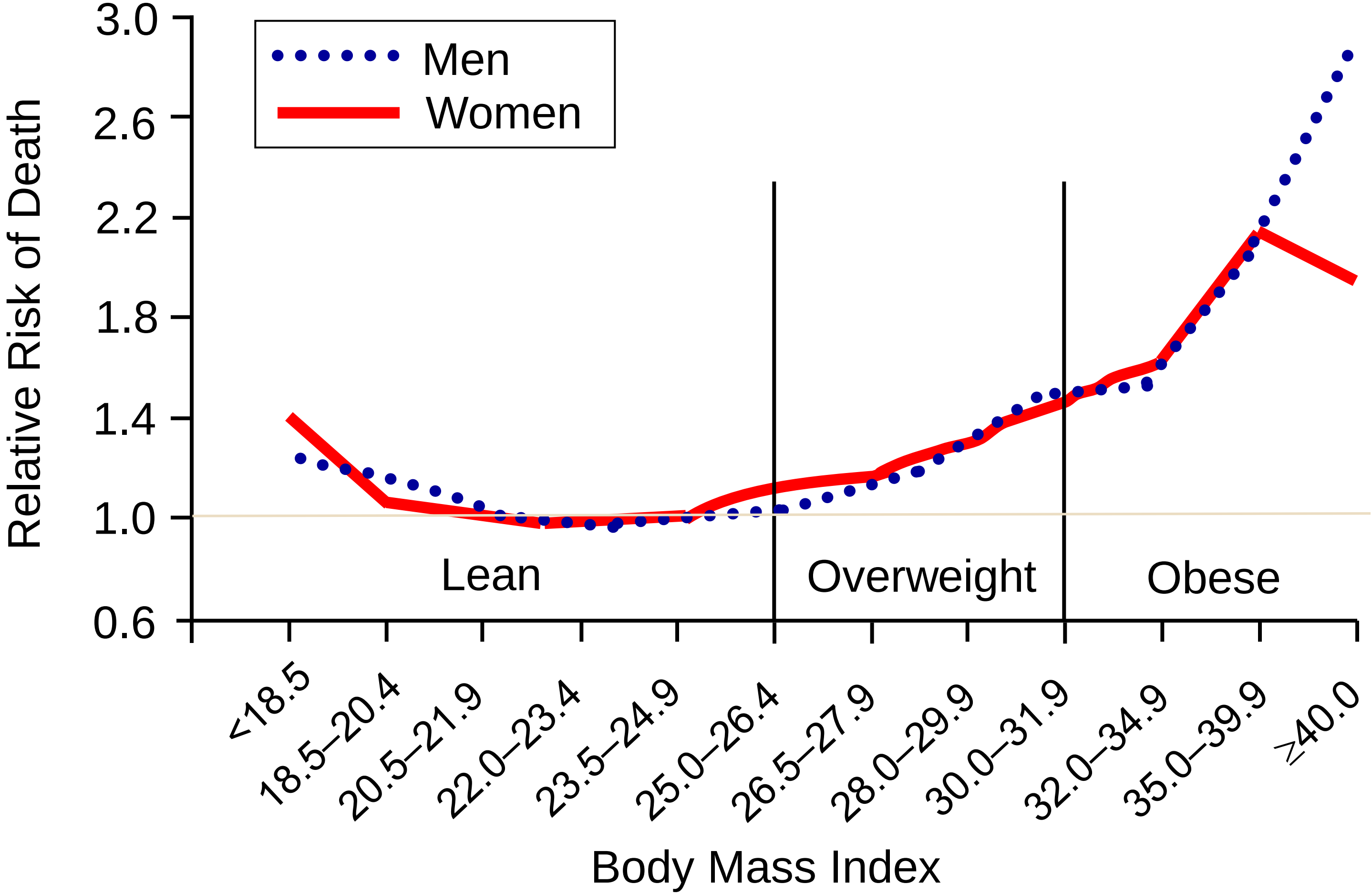


Source: CDC



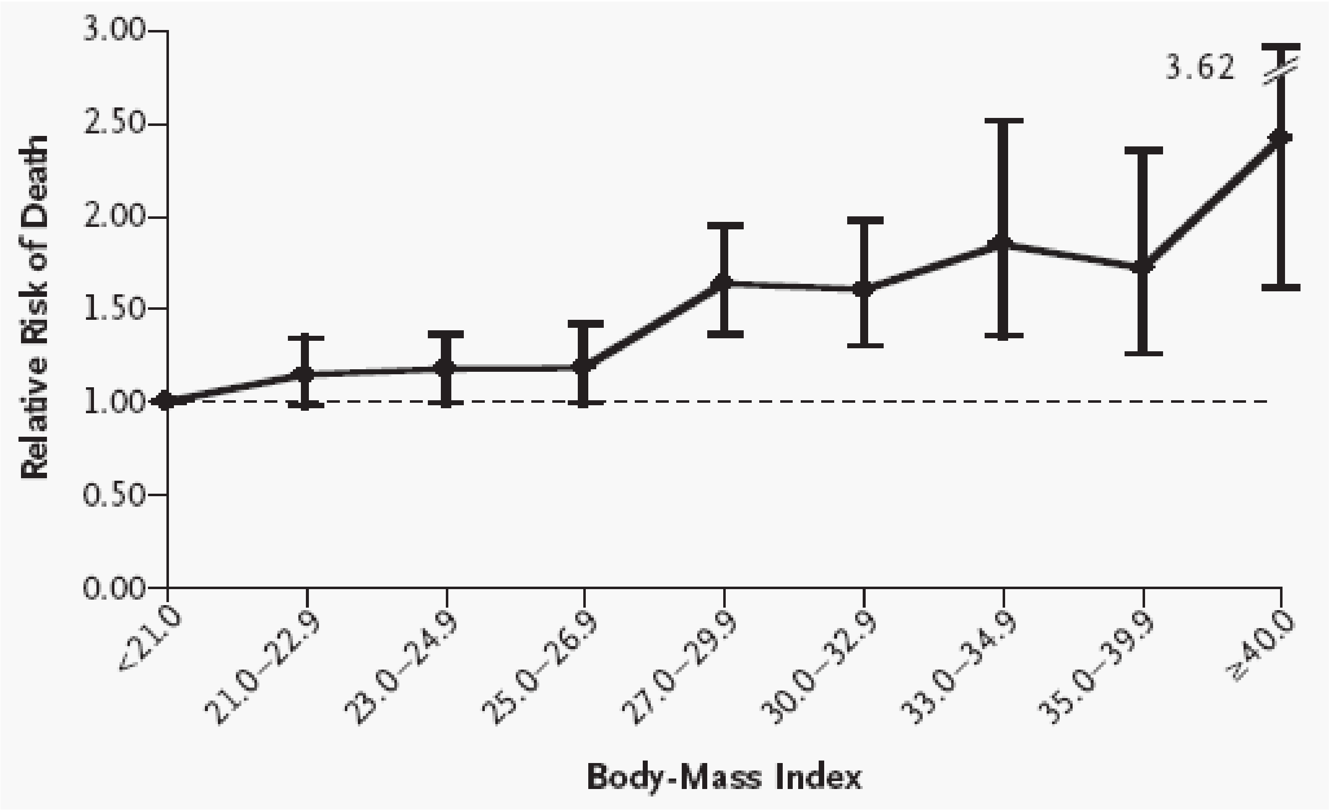
No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–**29%** | **≥30%**

Relationship Between BMI and Cardiovascular Disease Mortality



Calle et al. *N Engl J Med* 1999

Relationship Between BMI and Cancer Mortality in Women who never smoked



Hu FB et al., NEJM 2004

Our goal is to study and implement strategies for the promotion of SUCCESSFUL AGING

SUCCESSFUL AGING defined as

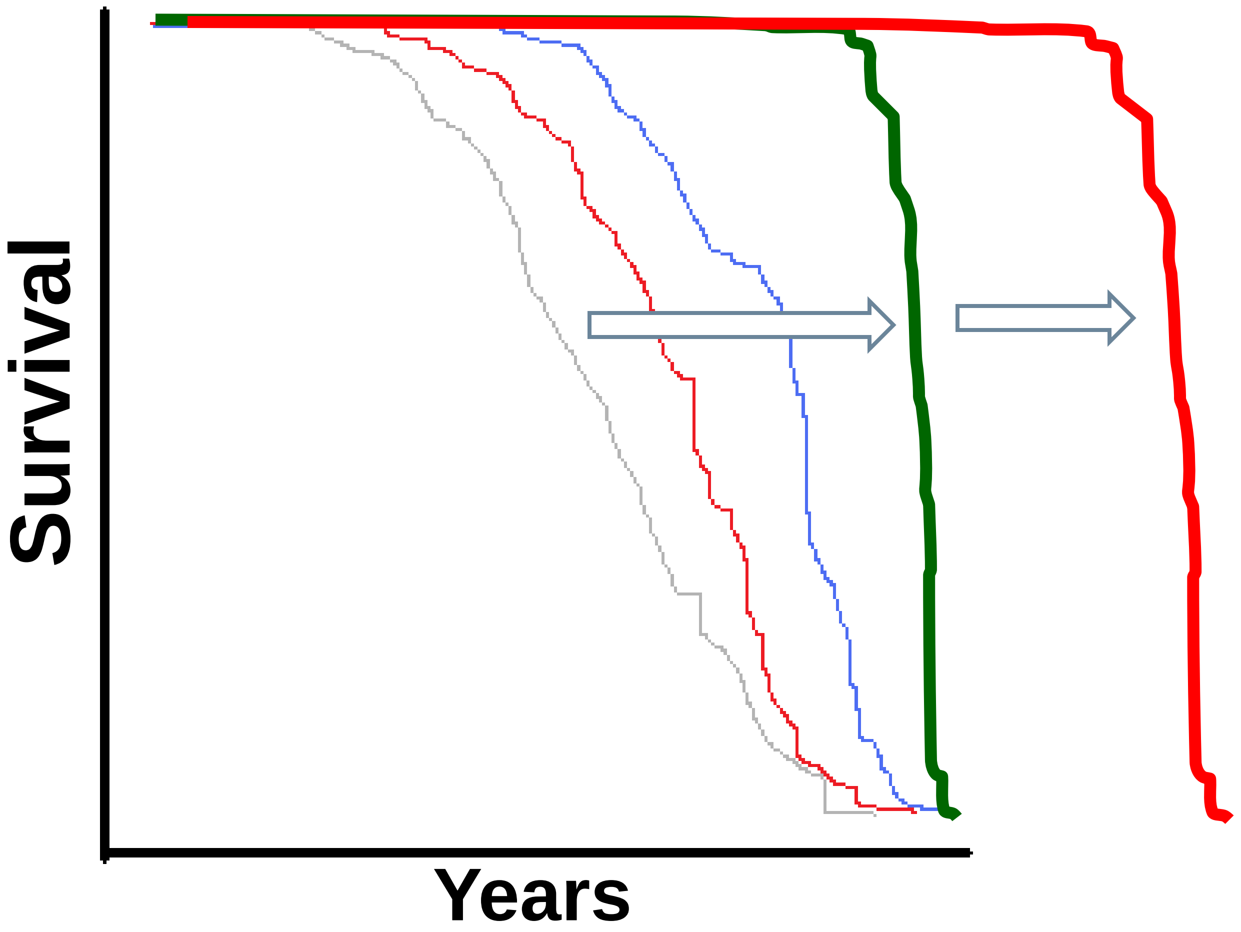
the ability of human beings to AVOID DISEASE AND DISABILITY and remain:

- physically and cognitively healthy
- happy and creative
- enpowered
- contributing to social and productive activities
- active & independent

..... for as long as possible.

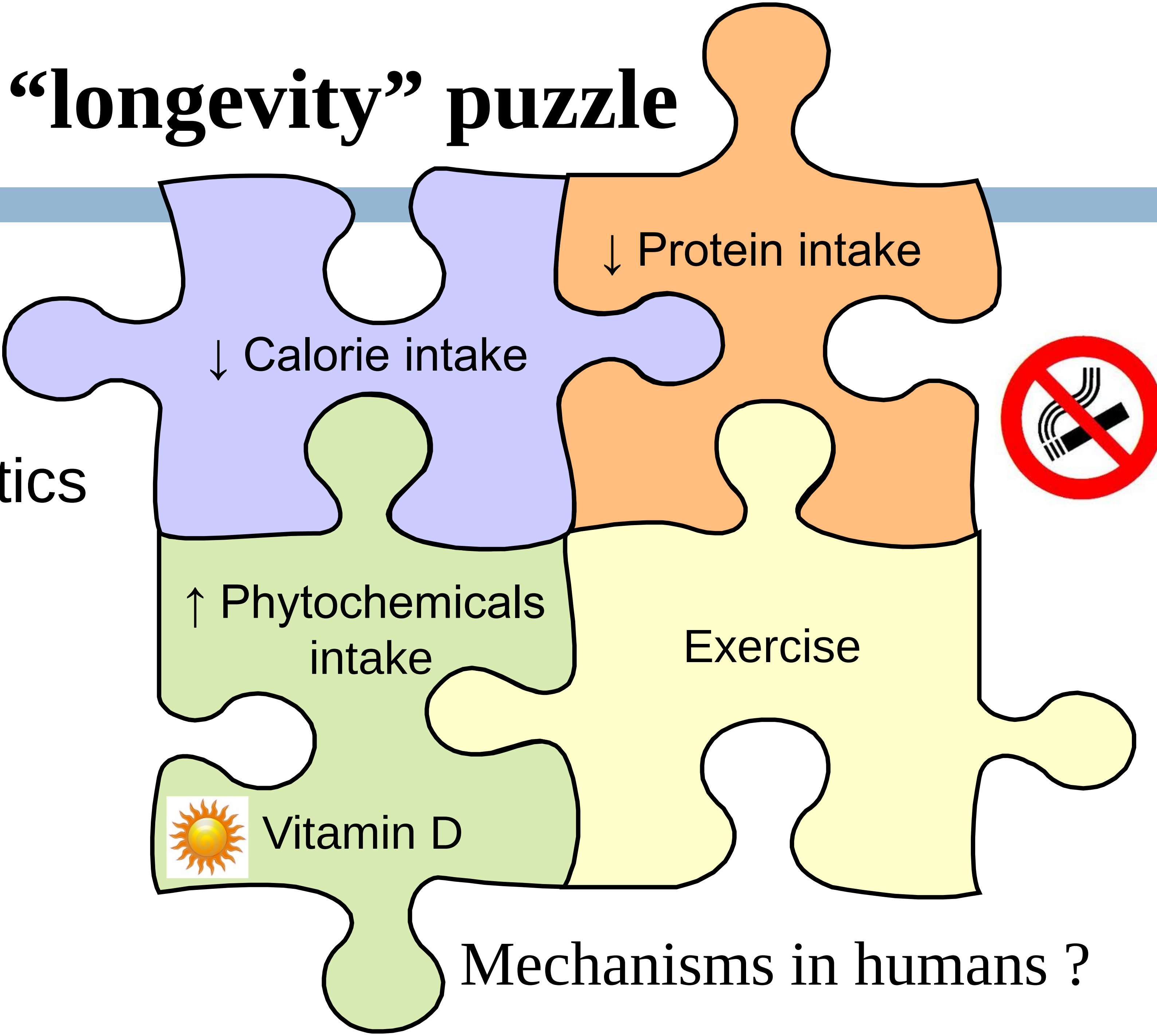
ISTITVTO SVPERIORE DI SANITÀ

Healthspan equals to lifespan



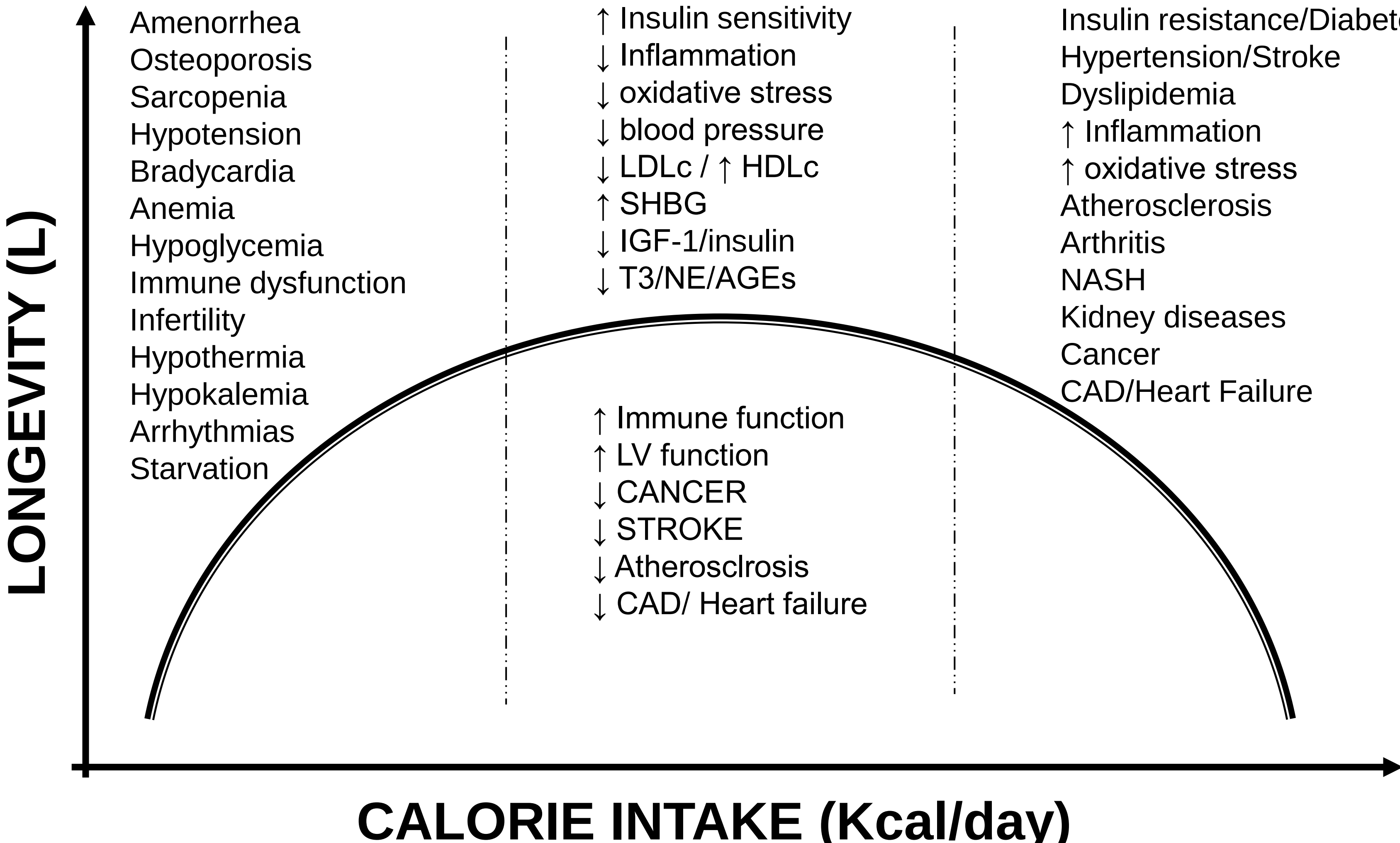
The “longevity” puzzle

Genetics



Mechanisms in humans ?

OPTIMAL CALORIE INTAKE FOR SUCCESSFUL/HEALTHY AGING



Fontana L. et al. JAMA 2007

Markers of biological aging ?

- In 2011 we have good risk factors for CVDs, stroke, type 2 diabetes
- In 2011 risk factors for cancer, Alzheimer's and autoimmune diseases are still missing
- In 2011 markers of aging are still missing

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