

UNIVERSITÀ DEGLI STUDI DI VERONA

Simposio  
Active and Healthy Aging  
**Nutrizione**

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Clinica Geriatrica  
Università di Verona

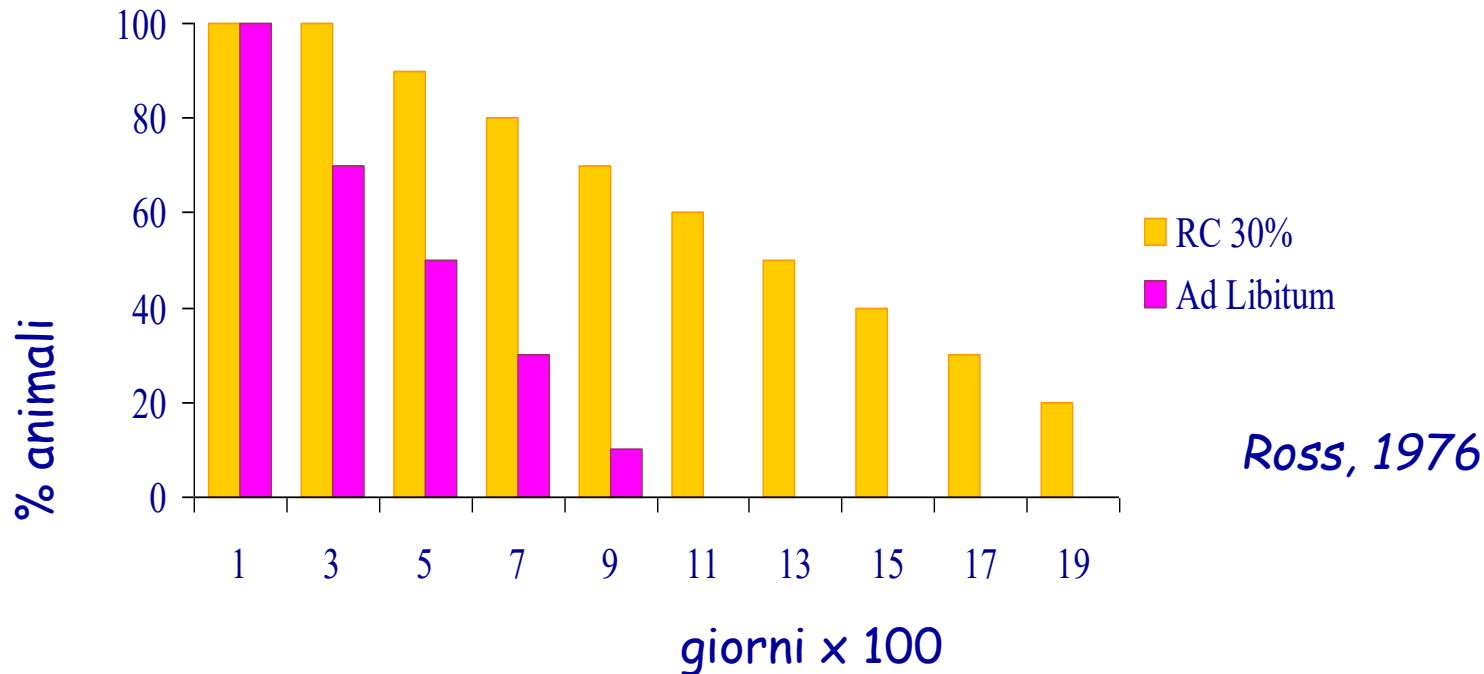


McCay C, Crowell M, Maynard L

*The effect of retarded growth  
upon the length of life and upon  
the ultimate size*

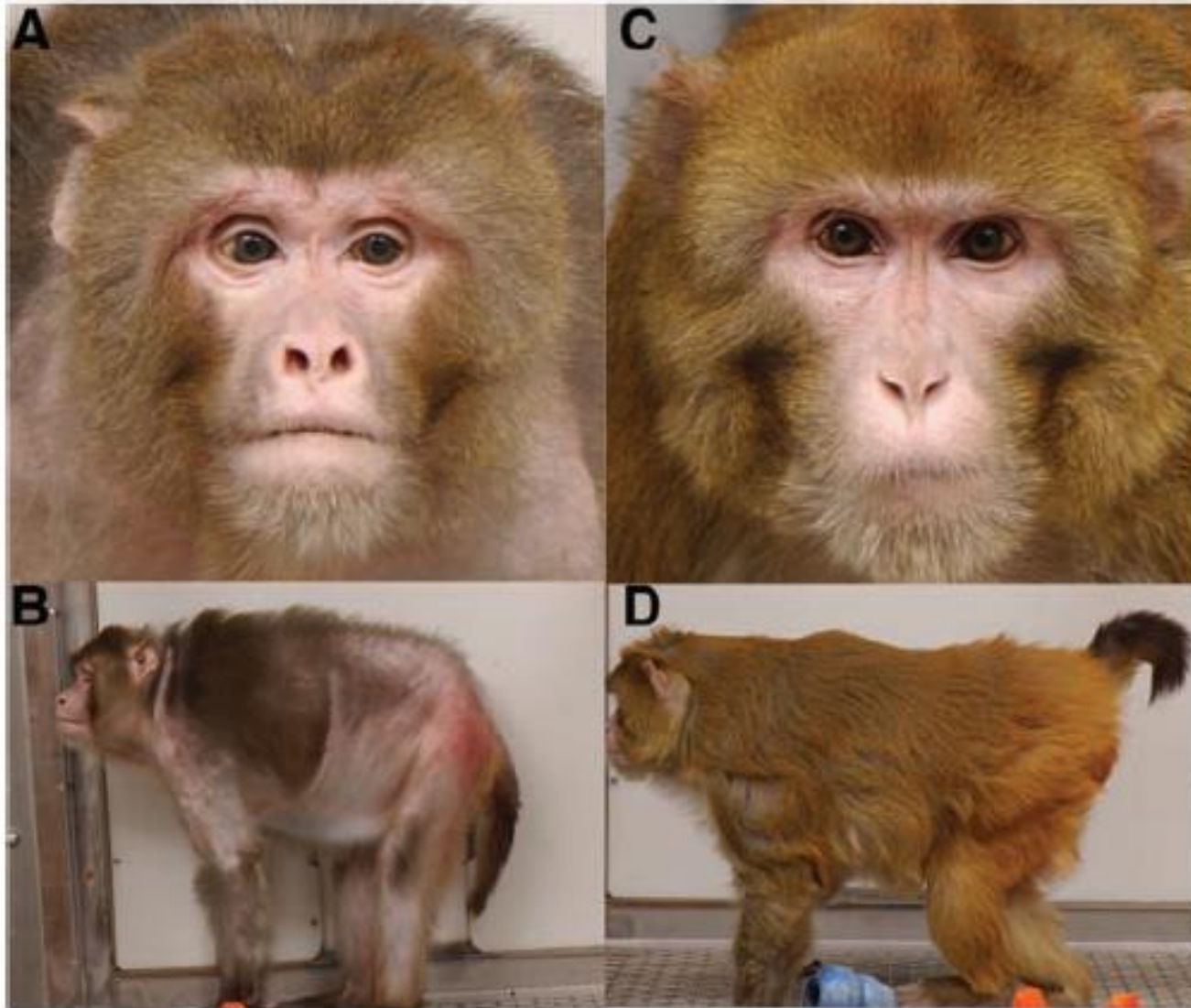
J Nutr, 10, 63-79, 1935

# Restrizione Calorica e durata media della vita in roditori



Dal 1996 al 2008 aumentano in modo esponenziale i lavori scientifici pubblicati su CR e longevità  
Nel 2007/8 200 citazioni/anno

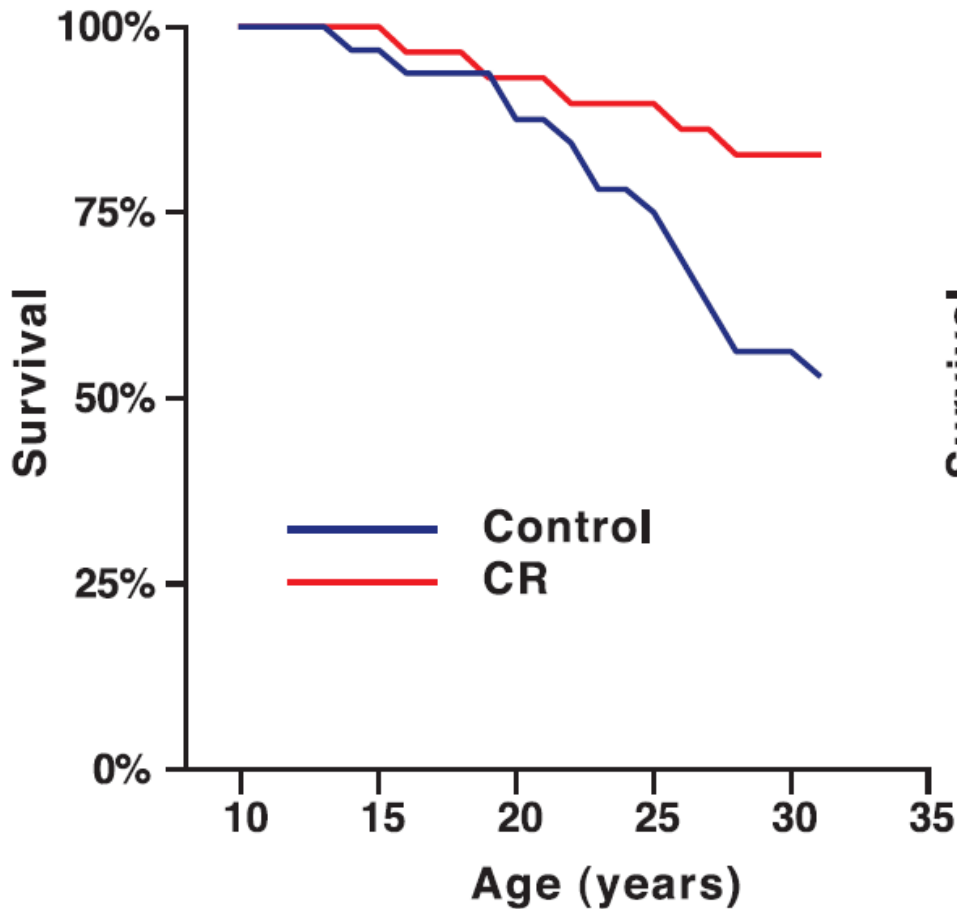
# Winsconsin National Primate Research Center (WNPRC) Study (30 % RC *versus* ad libitum)



**Fig. 1.** Animal appearance in old age. (A and B) Photographs of a typical control animal at 27.6 years of age (about the average life span). (C and D) Photographs of an age-matched animal on CR.

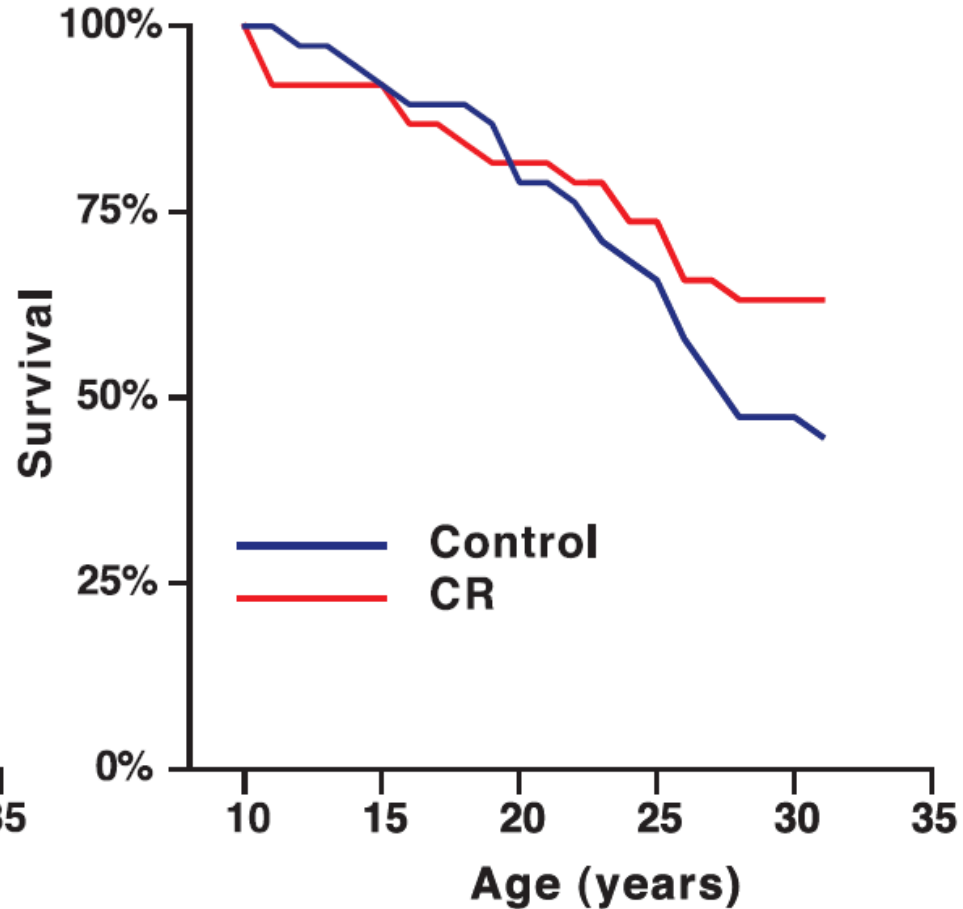
# WNPRC study: Survival curves

## Age-related mortality



$p=0.03$  HR=3.0

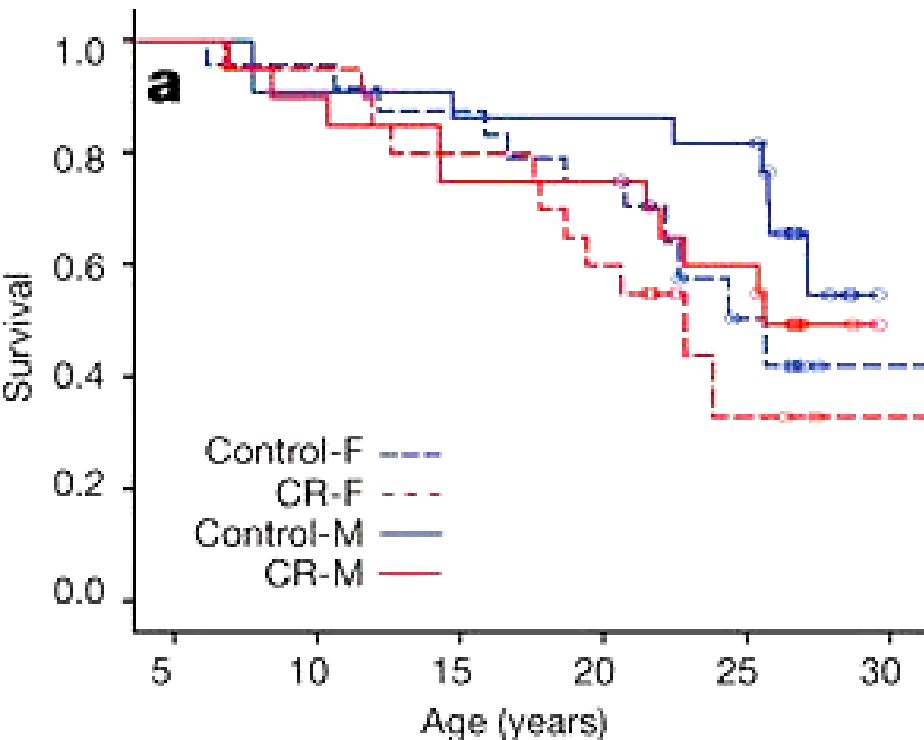
## Overall mortality



$p=0.16$

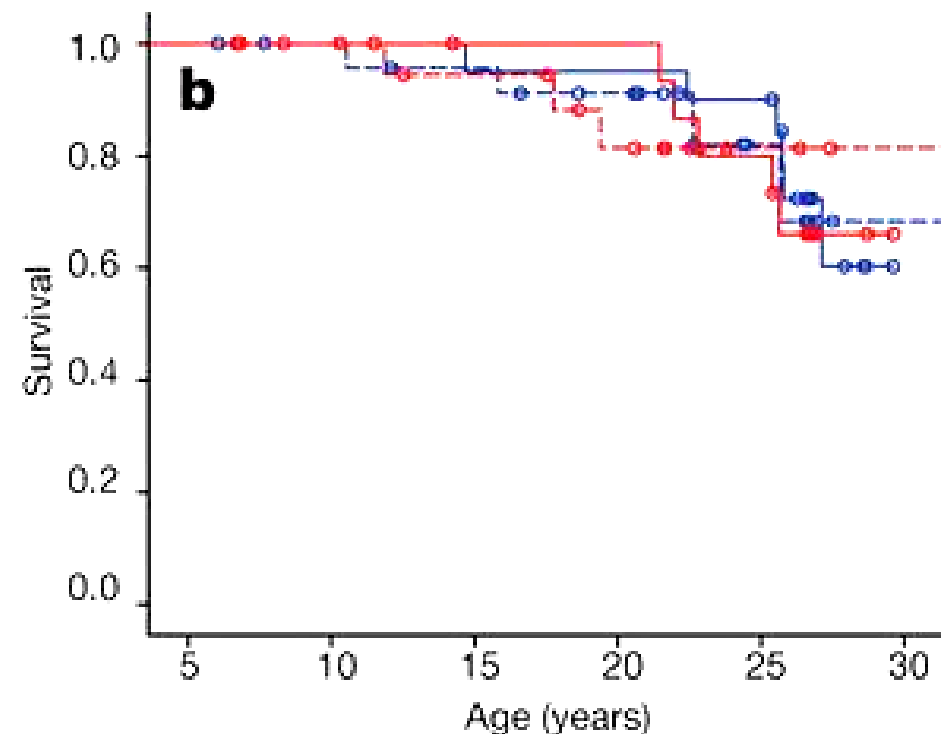
# NIA study: Kaplan-Meier survival curves for young-onset monkeys (7-14 years)

all causes mortality



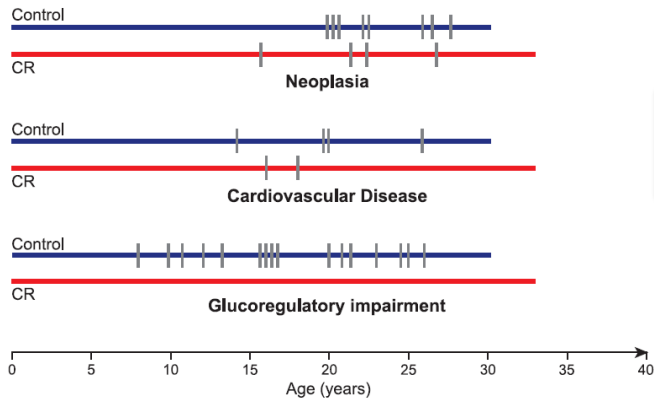
**p=0,255**

age-related mortality



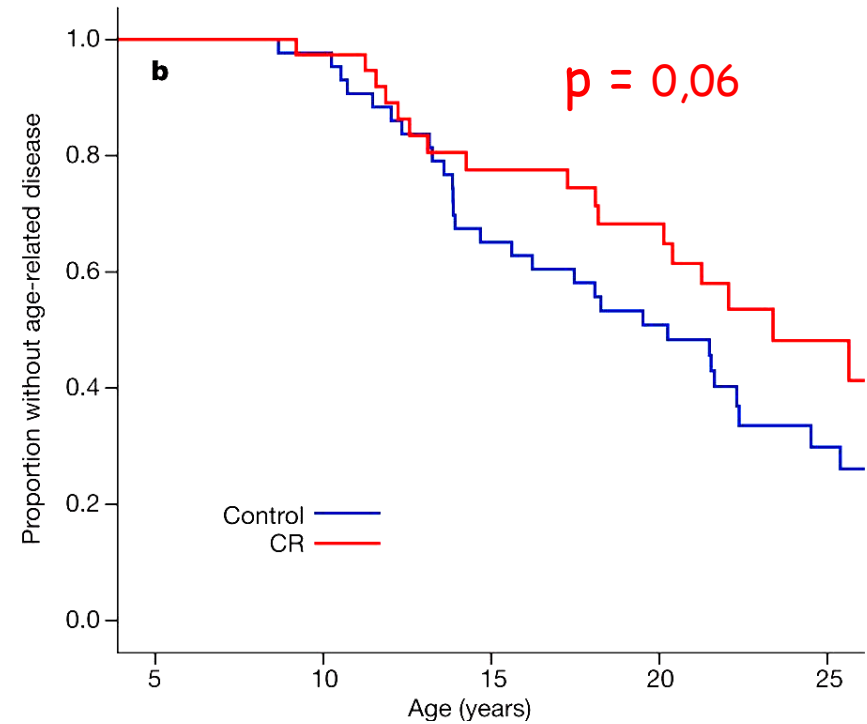
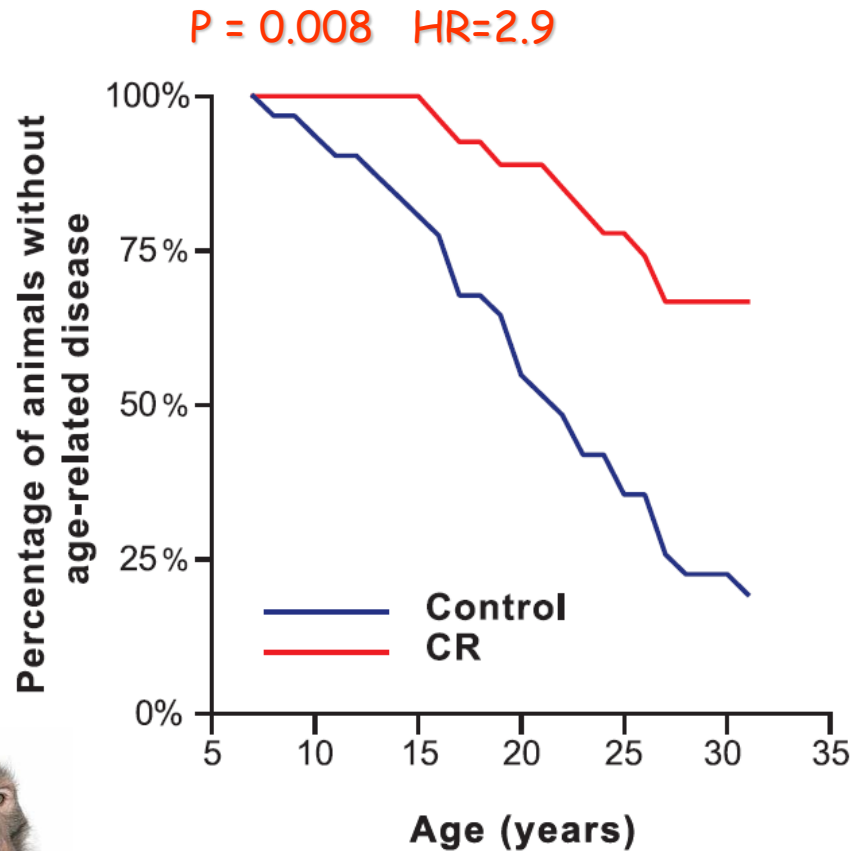
**p=0,975**





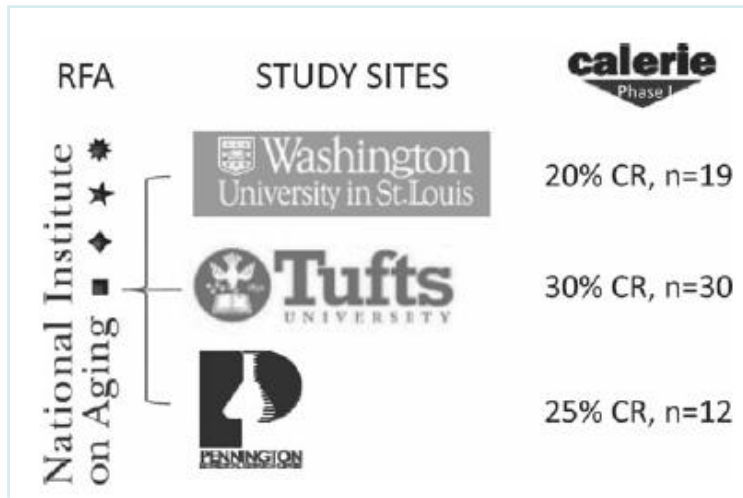
## WNPRC study

## NIA study

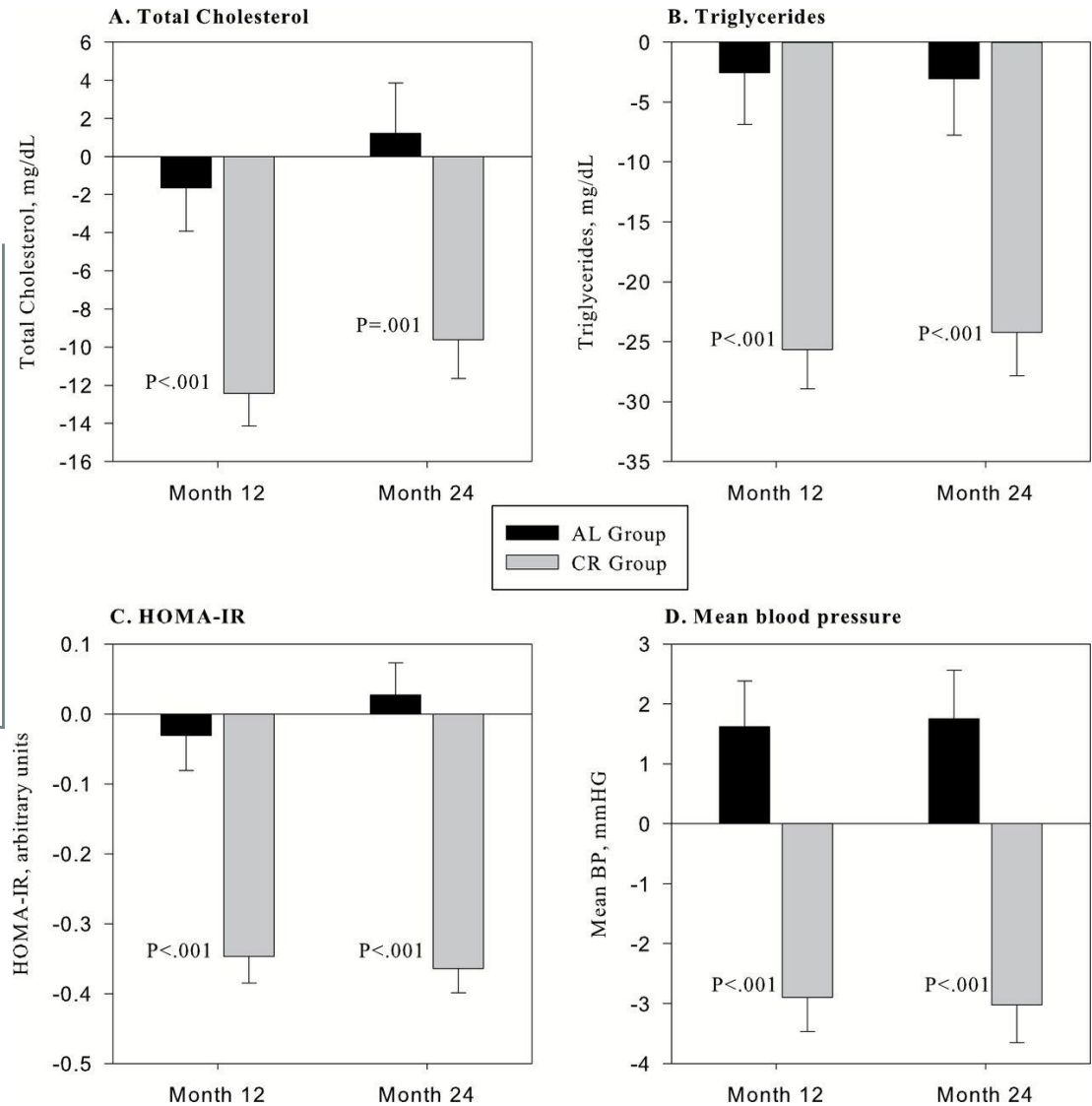


*Mattison JA et al., 2012*

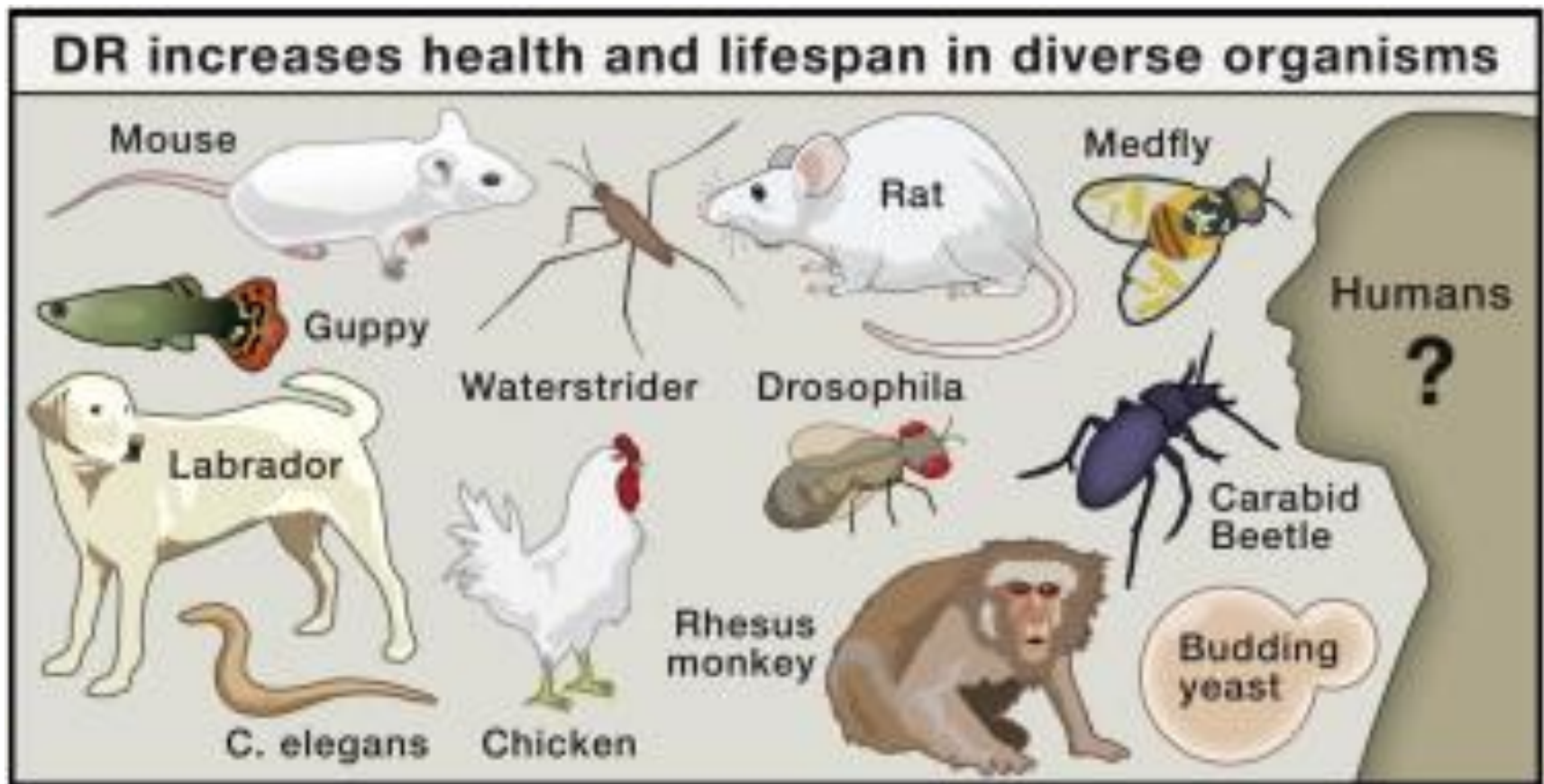
# Changes in cholesterol, triglycerides, HOMA-IR and pressure at month 12 and month 24 in the AL control (black) and CR (gray bars) groups



AL = ad libitum;  
CR = caloric restriction





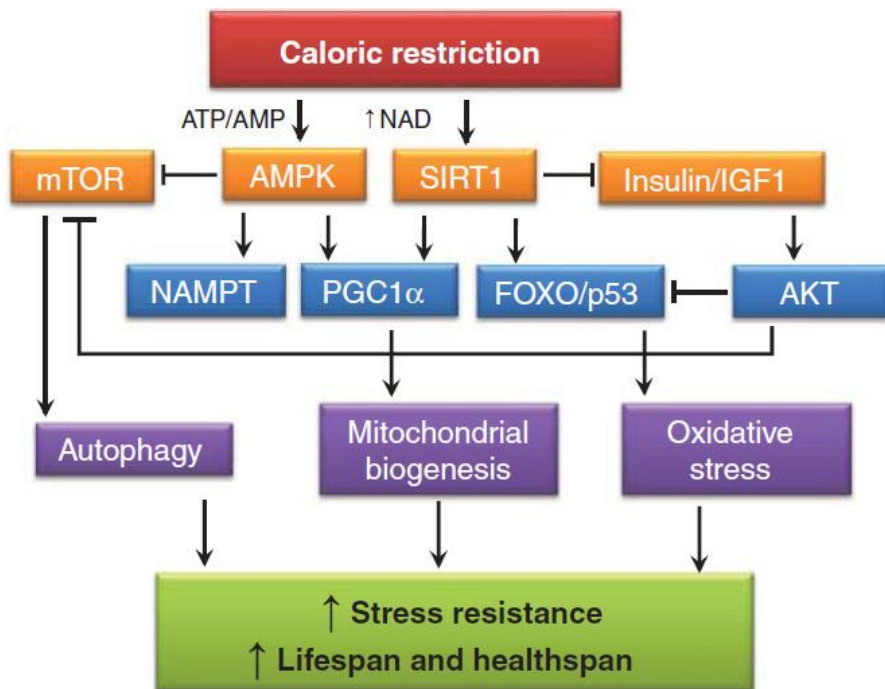


CR has been reported to delay or **prevent the occurrence of many chronic diseases** in a variety of animals.

CR is often reported as the most robust non-genetic mechanism to **extend lifespan and healthspan**

## Cellular mechanisms responsible for CR-mediated beneficial effects in rats and monkeys

## Mechanisms responsible for CR-mediated beneficial effects in rats and monkeys



- Lower body weight and fat mass
- Lower body temperature and Energy Expenditure
- Decrease T3
- Improvement on CVD risk factors
- Decrease inflammation and oxidative stress
- Delayed immune senescence

# Caloric Restriction in Humans: Impact on Physiological, Psychological, and Behavioral Outcomes

Redman LM and Ravussin E, 2011



25 y old

**Albert Einstein on CR**  
(14 March 1879 – 18 April 1955)

20% CR

Five year of Albert Einstein's  
productivity is worth it

+ 4.7 yr  
81 y old



60 y old

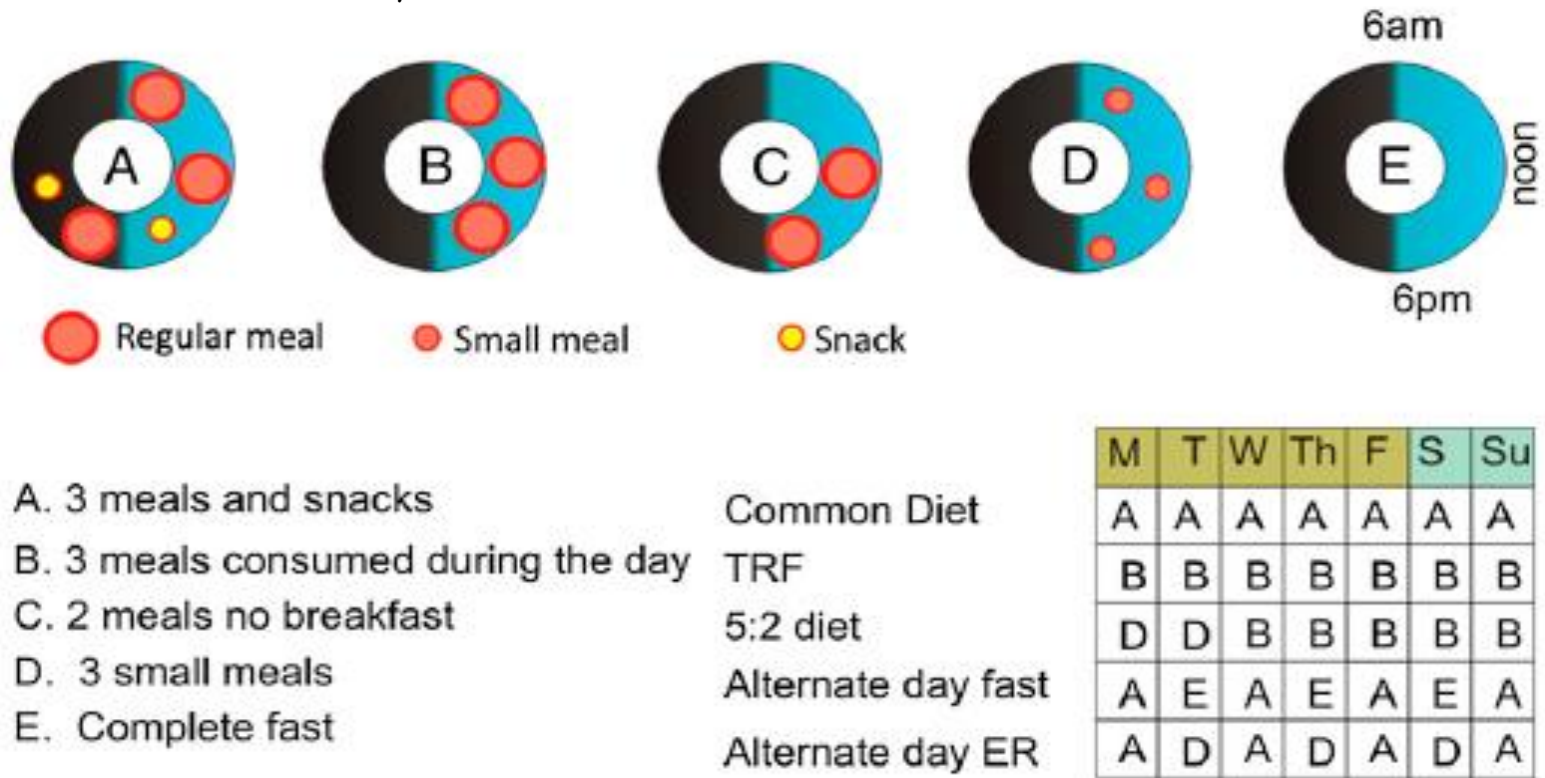
30% CR

+ 2 mo  
76 y old

Early in adult life to significantly increase life expectancy  
However it is challenge for most individuals to practice CR in a  
obesogenic environment so conducive to overfeeding

# Pattern of daily and weekly food consumption and healthy aging

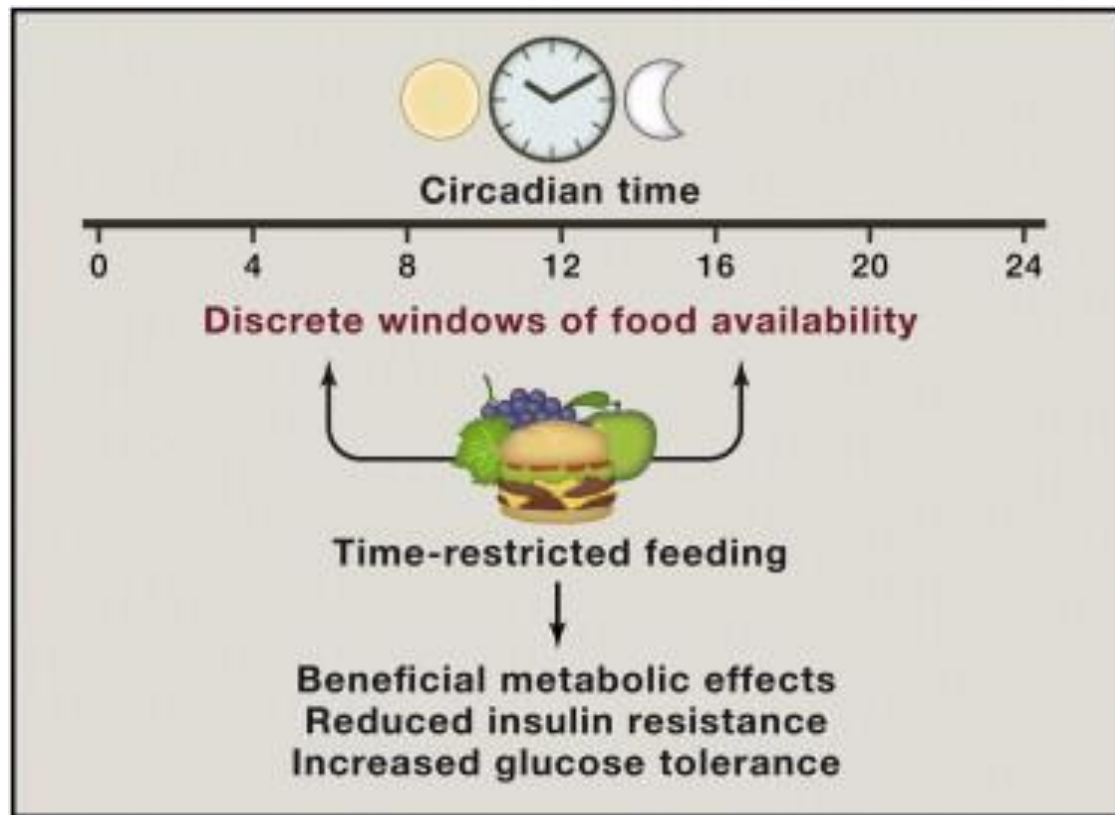
Mattson MP et al , 2014 PNAS



Obese- overweight women: fasting 2 non consecutive days per week for 6-months show greater WL and metabolic improvment

Non obese and obese individuals with alternate day fasting for 8-12 weeks improved CVD risk factors

# Meal timing



Energy restriction periods  
(IER)  
of at least 16 h  
can improve health indicators

Mechanisms involve  
a metabolic shift  
to fat metabolism,  
stimulation of adaptative  
stress responses that  
prevent and repair  
molecular damage

**not yet examined  
in humans**

composizione della dieta  
vs  
restrizione calorica

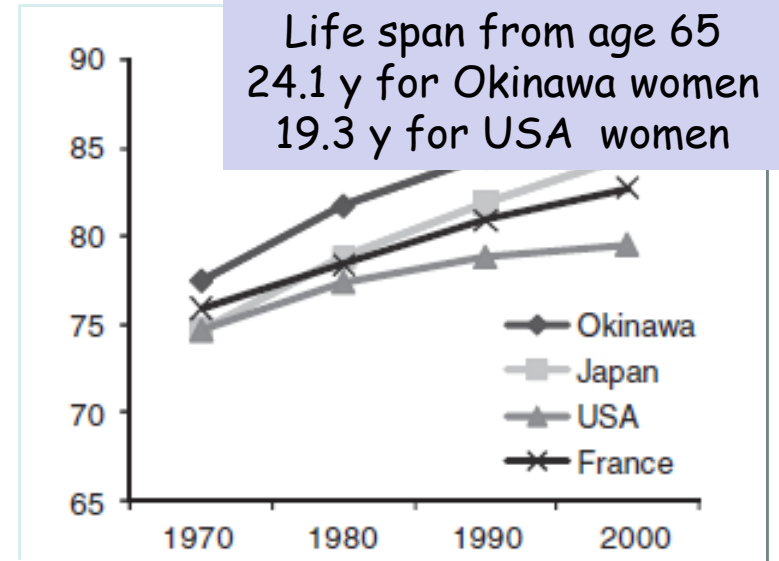
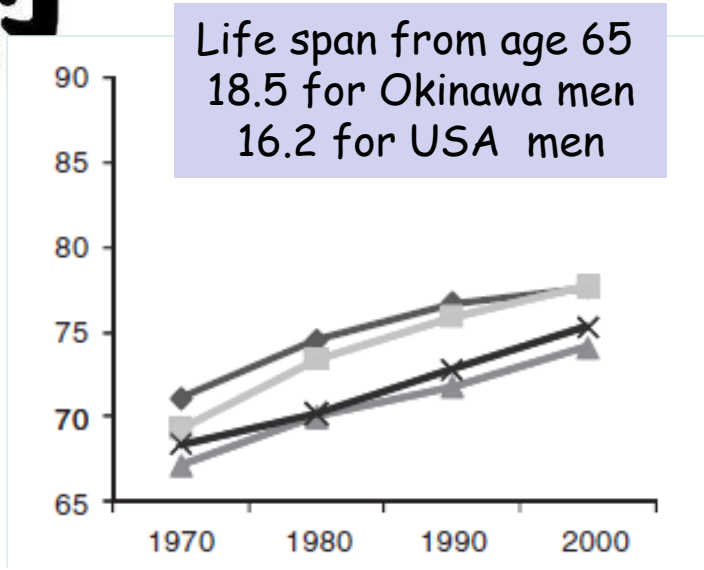


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# Centenarians from Okinawa

## Life expectancy at birth

Longevity



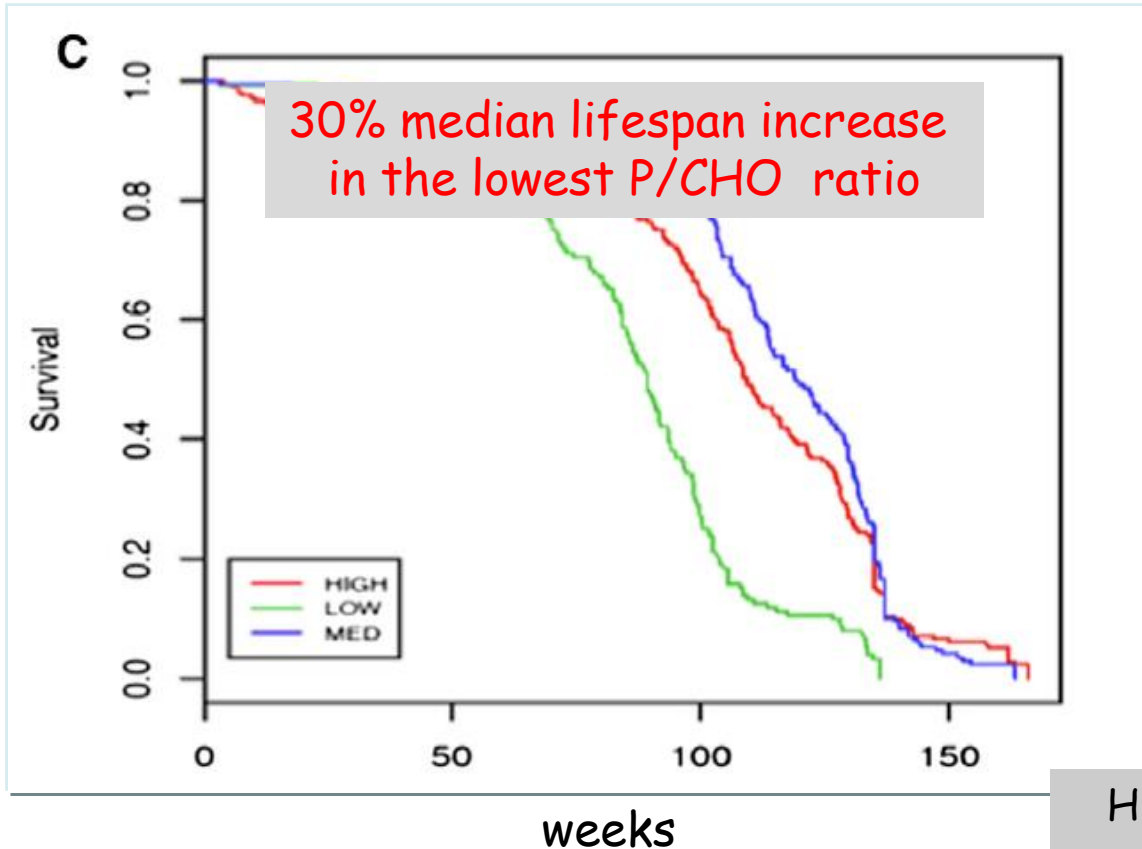
- Low calorie diet reported in school children on Okinawa 40 years ago and later studies confirmed a 20% CR in adults
- The diet, rich in green leafy vegetables, soy and some fish is similar with CR interventions providing adequate amounts of nutrients, essential vitamins and minerals

Redman LM et al., 2008

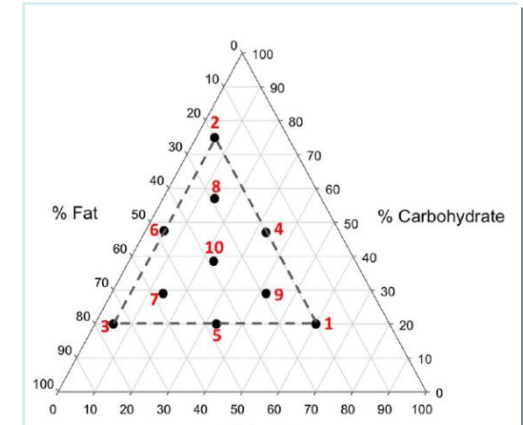
Redman LM and Ravussin E, 2011

# The Ratio of Macronutrients, Not Caloric Intake, Dictates Cardiometabolic Health, Aging, and Longevity in Ad Libitum-Fed Mice

Male and female mice (3 weeks old, n 858)



3 levels of energy density diets  
Differing in content of protein,  
fat and CHO  
1/3 culled at 15-months of age  
the remainder until they died

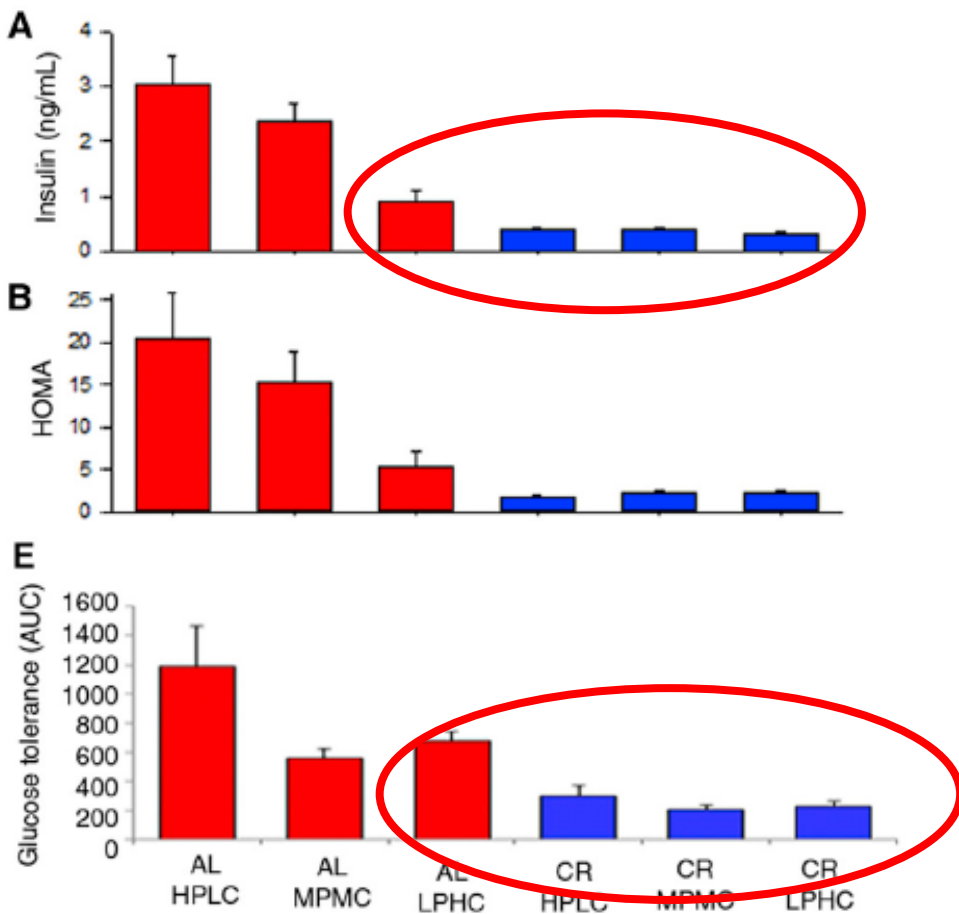
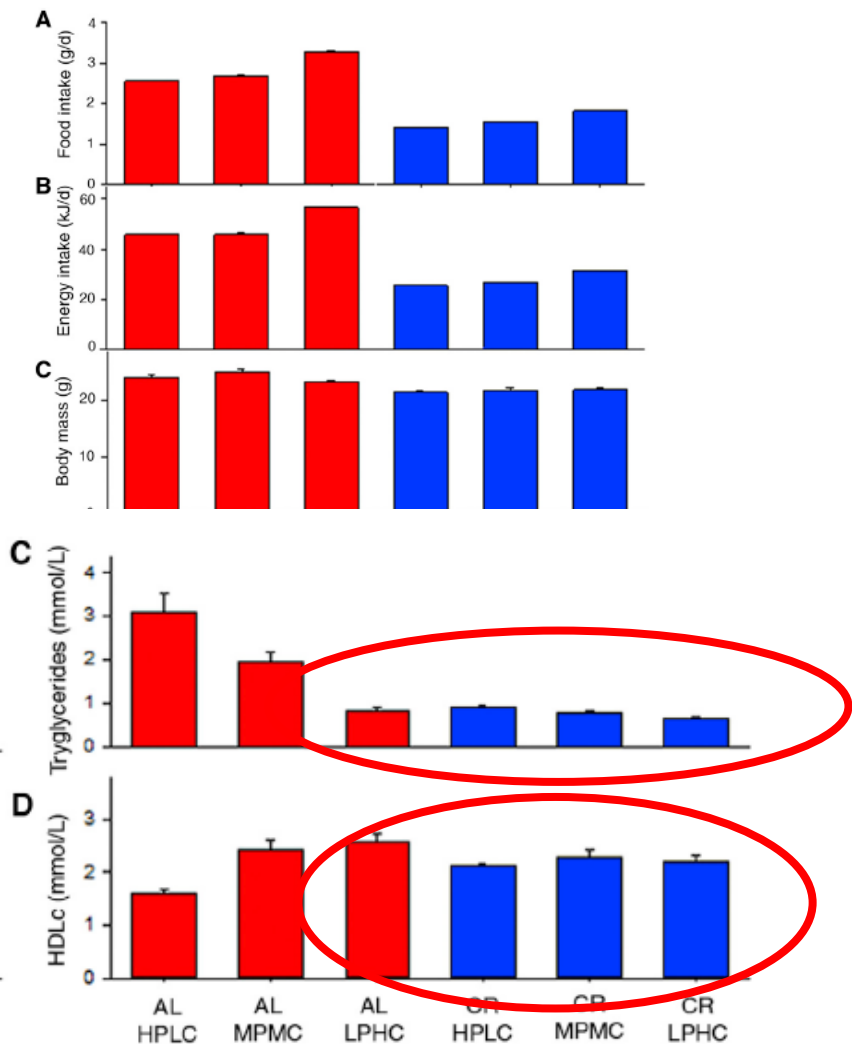


Highest survival for animals with  
low protein and high CHO  
Not influenced by CR



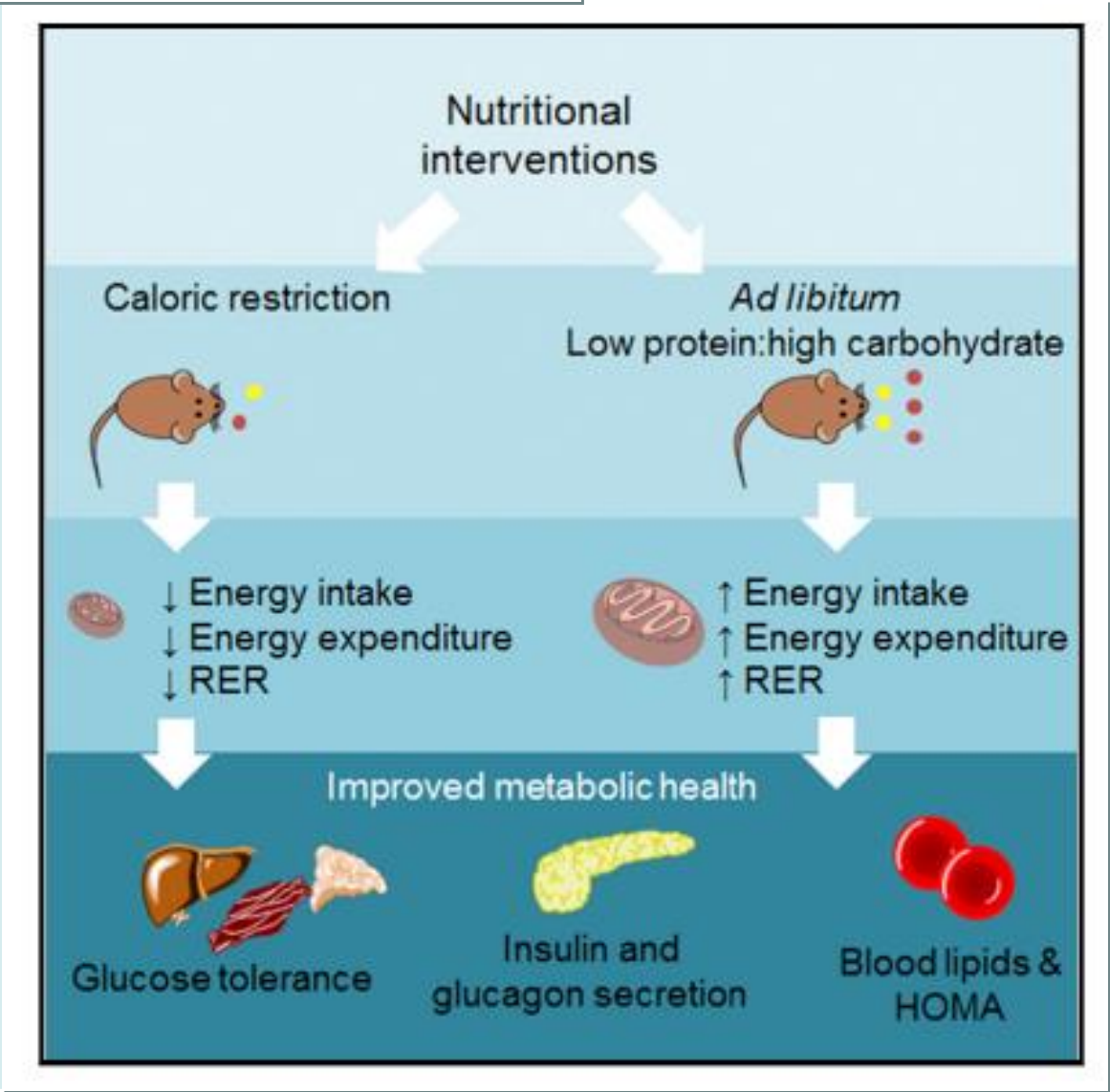
Dietary Protein to Carbohydrate Ratio and Caloric Restriction: Comparing Metabolic Outcomes in Mice

8-weeks  
dietary intervention  
in mice

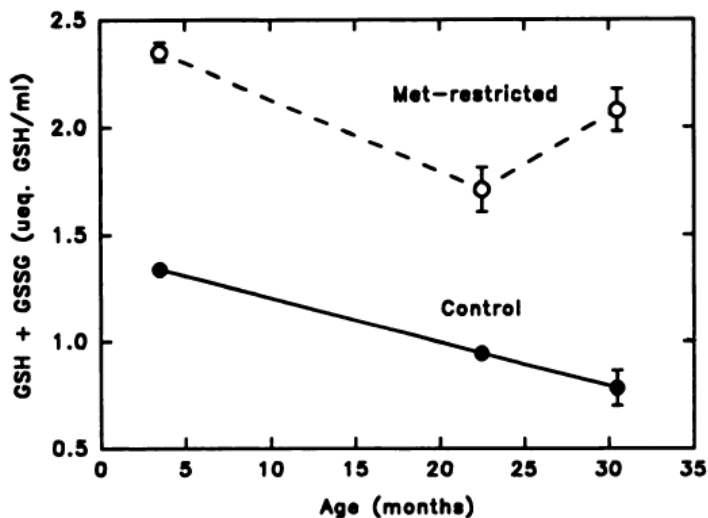
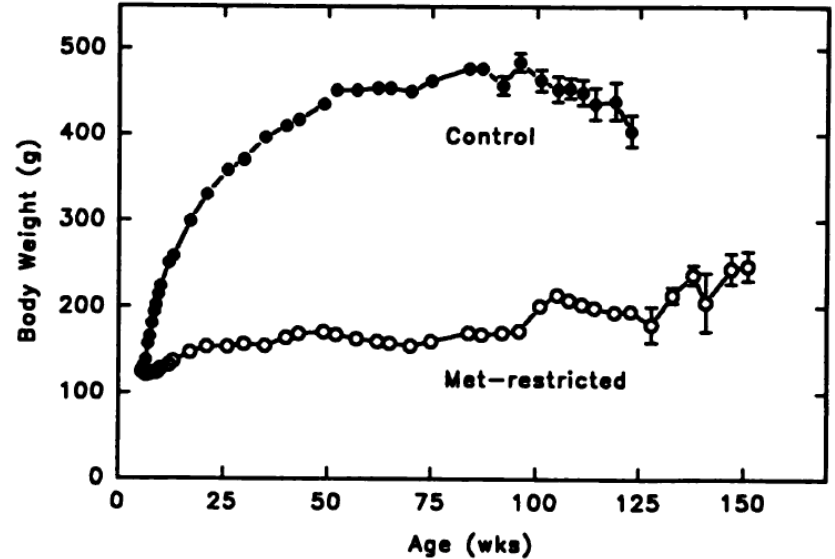
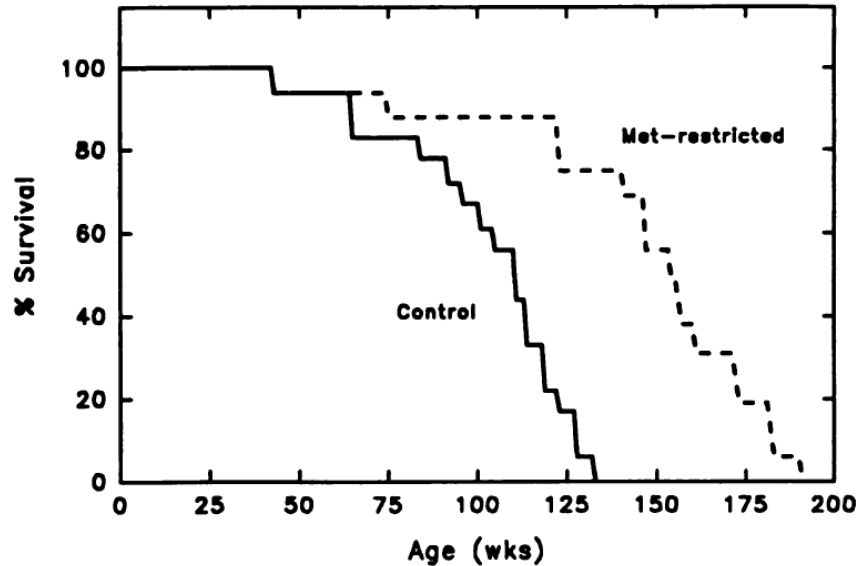


Dietary Protein to Carbohydrate Ratio and Caloric Restriction: Comparing Metabolic Outcomes in Mice

Solon-Biet et al., 2015, Cell Reports 11, 1529–1534  
June 16, 2015 ©2015 The Authors  
<http://dx.doi.org/10.1016/j.celrep.2015.05.007>



# Methionine restriction increases longevity in F344 rats

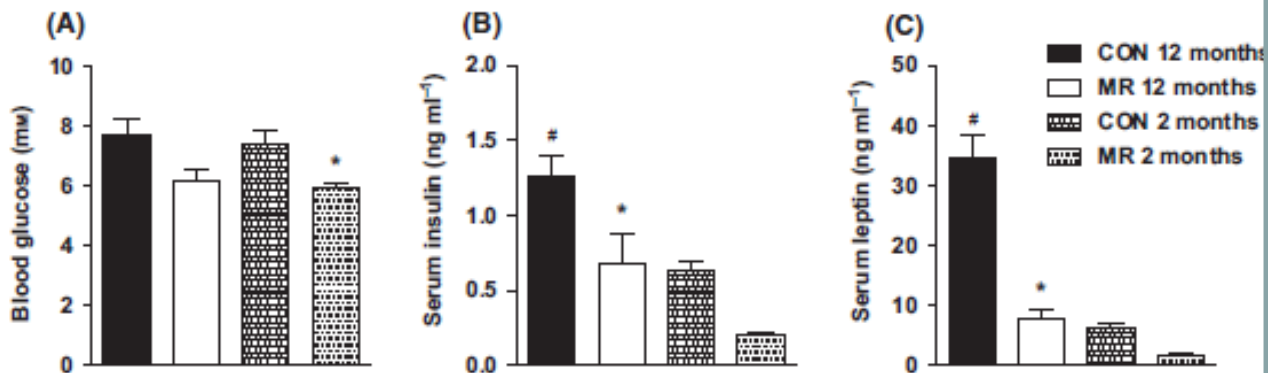
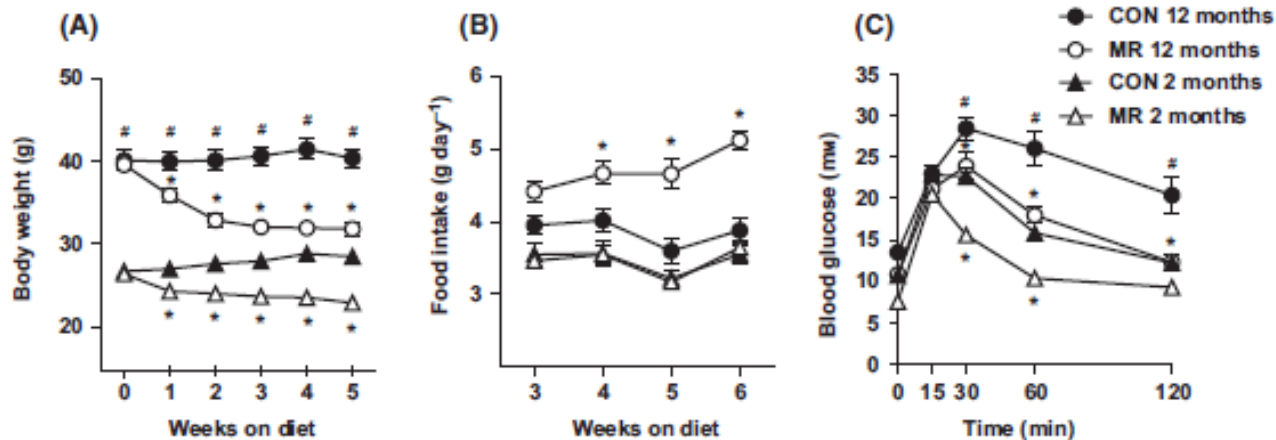


Male F344 rats fed Purina Chow until 6-8 wk of age when they were randomized into control and exp ad libitum diet (exp was restricted in methionine)

Richie JP et al, FASEB 1994

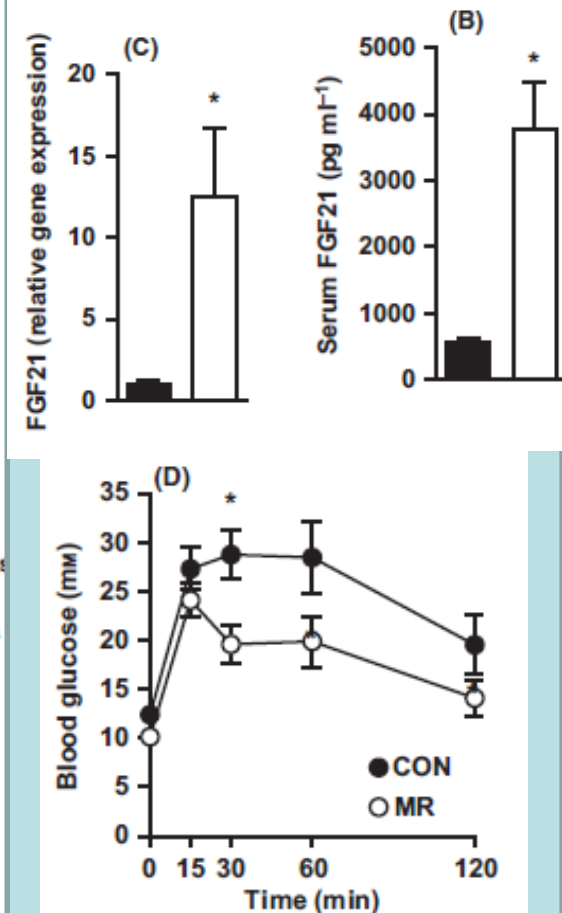
# Methionine restriction reverses age-related metabolic dysfunction

male mice aged 2 and 12 months  
fed MR or control diet for 8 weeks



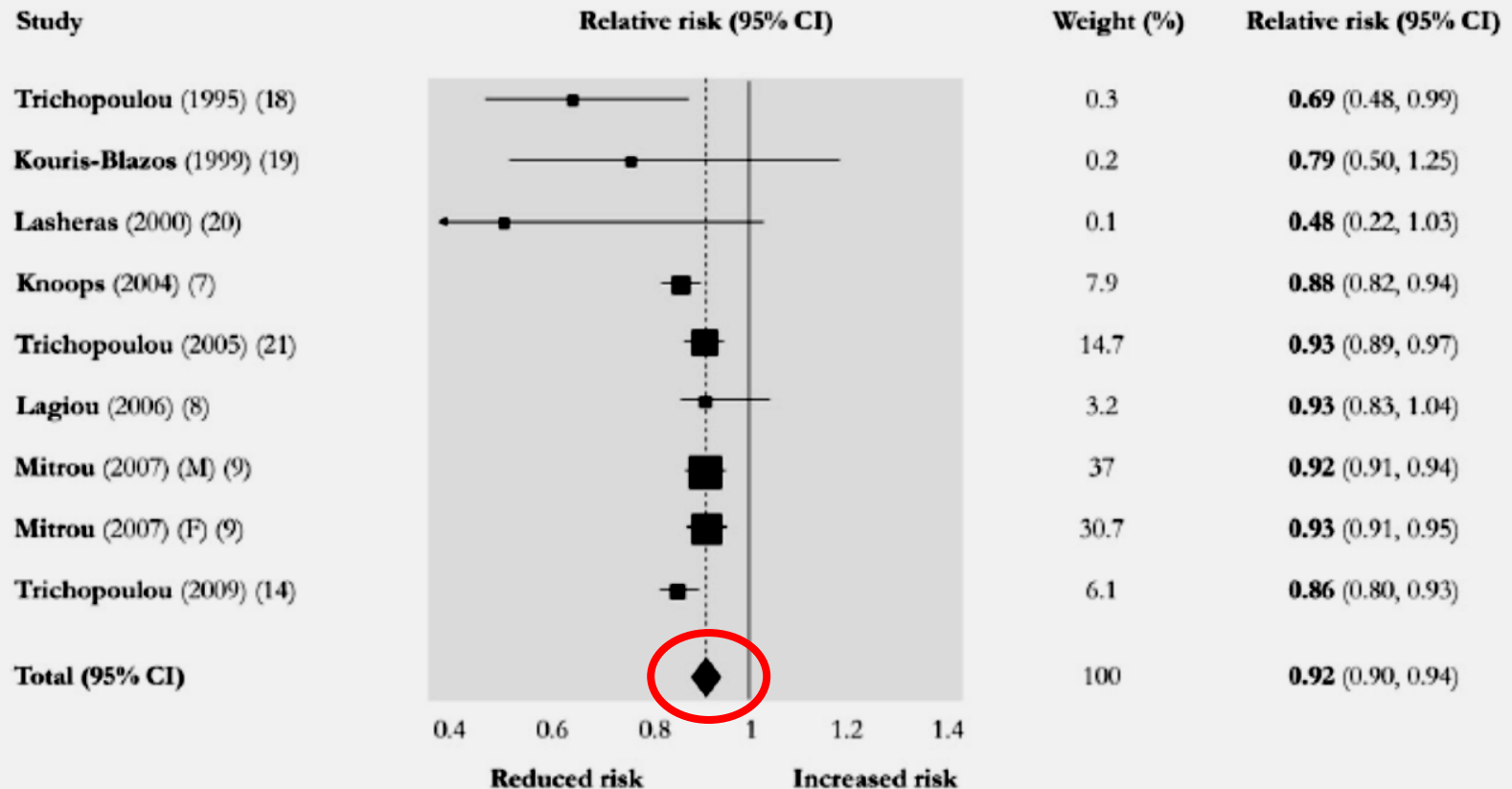
48-h MR  
effects

■ CON  
□ MR



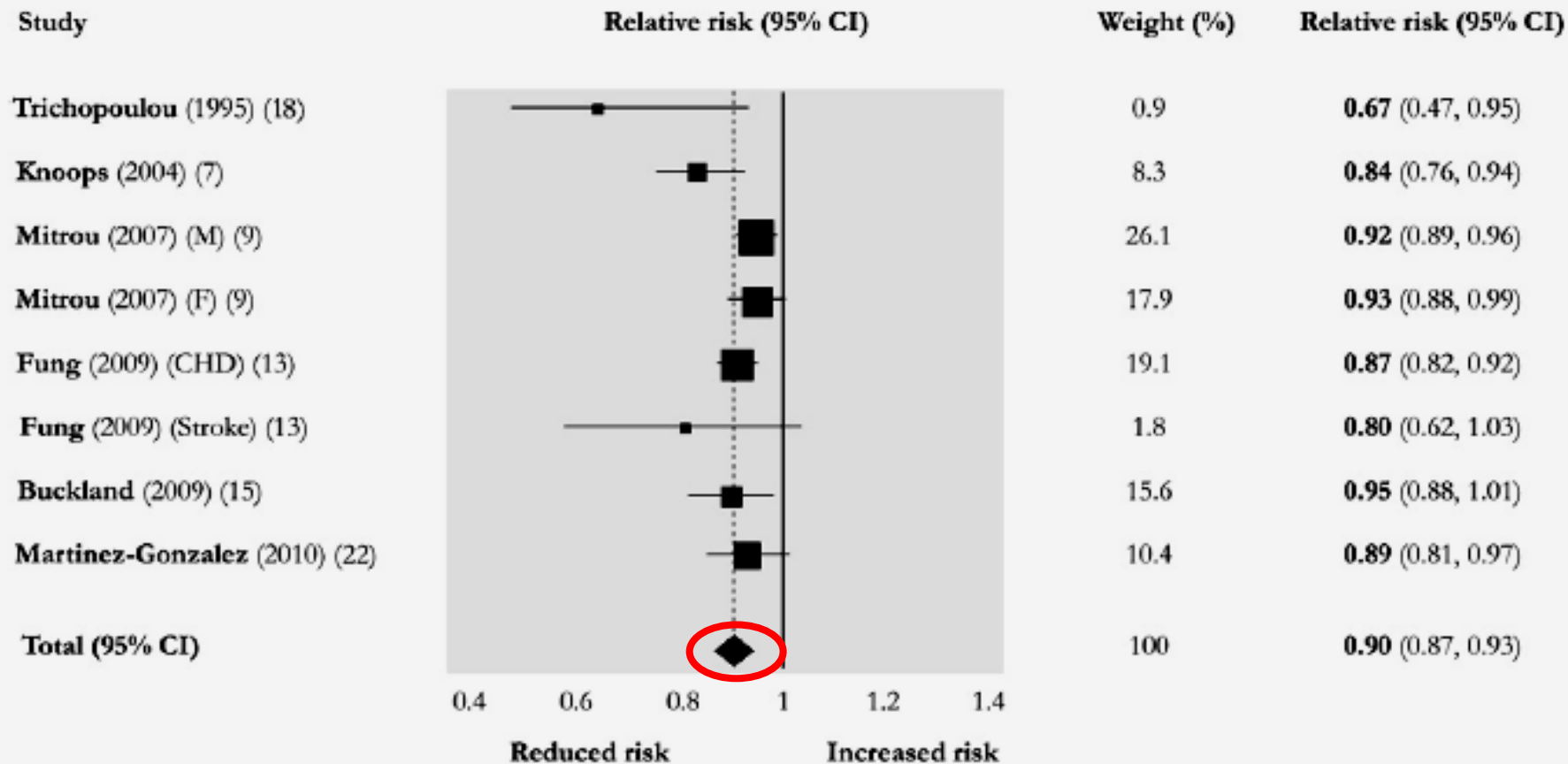
## 2 point increase adherences to the **Mediterranean diet** determines a decrease risk of the overall **mortality** rate

Meta-analysi of 9 studies, 514 118 subjects, 4-20 years follow-up ; no evidence of statistical heterogeneity across studies ( $I^2 = 33\%$ ;  $P = 0.15$ ).



## 2-point increase of adherence to the **Mediterranean diet** is associated with a reduced risk of mortality from and incidence of **CVD**

Meta-analysis of 8 studies, 534 064 subjects, 4-20 years follow-up ; no evidence of statistical heterogeneity across studies ( $I^2 = 35\%$ ;  $P = 0.15$ ).



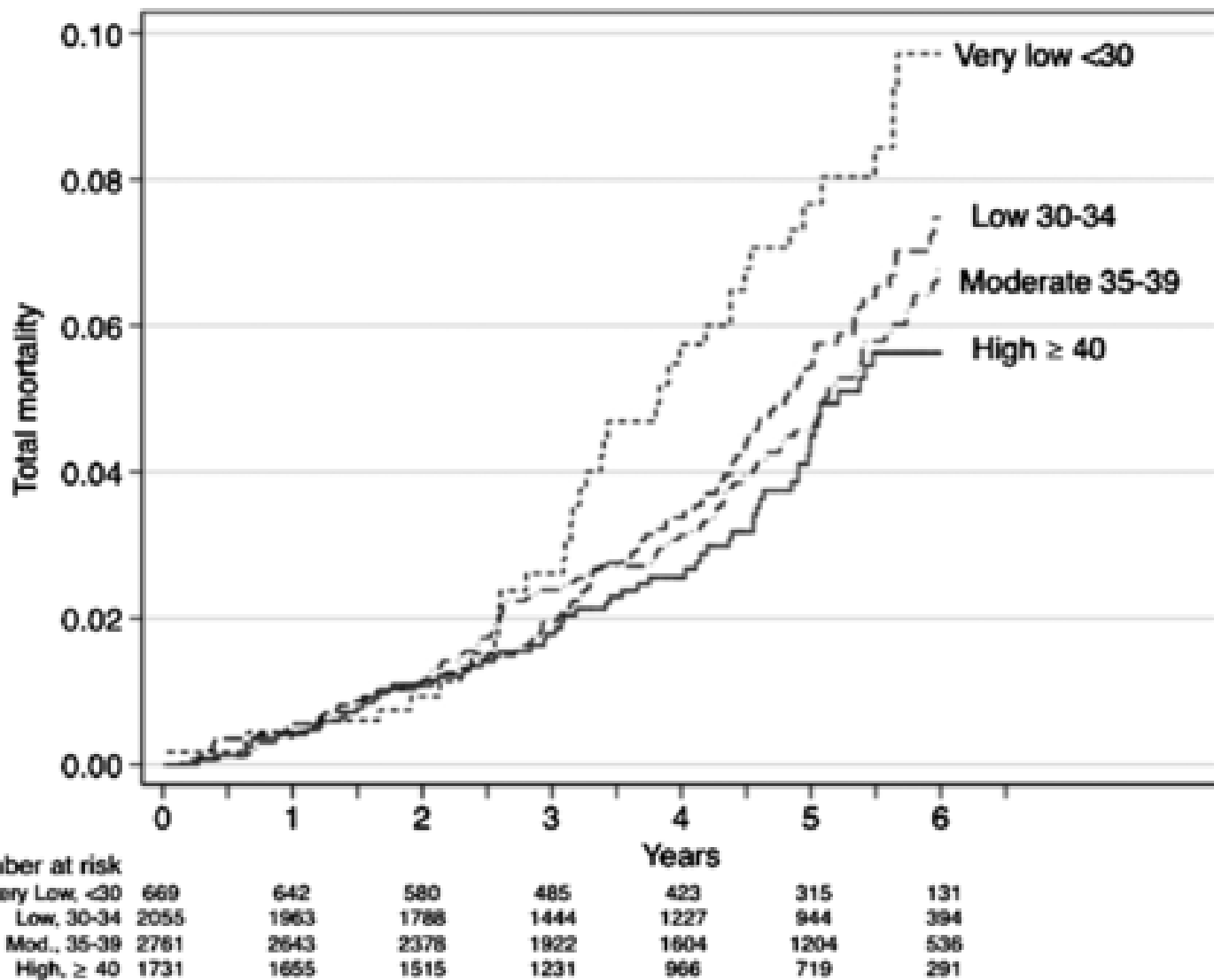


# PREDIMED study

7216 participants  
at high CVD risk

Follow-up 4.8 y

Categories  
of pro-vegetarian diet



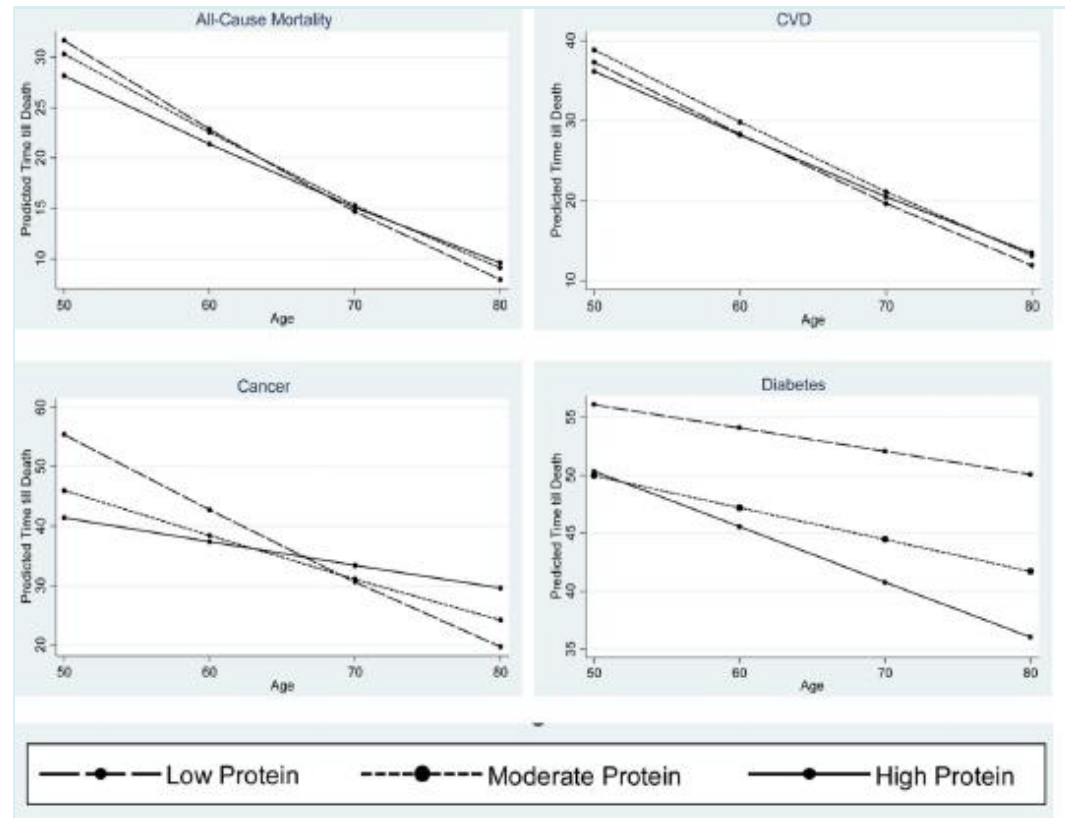
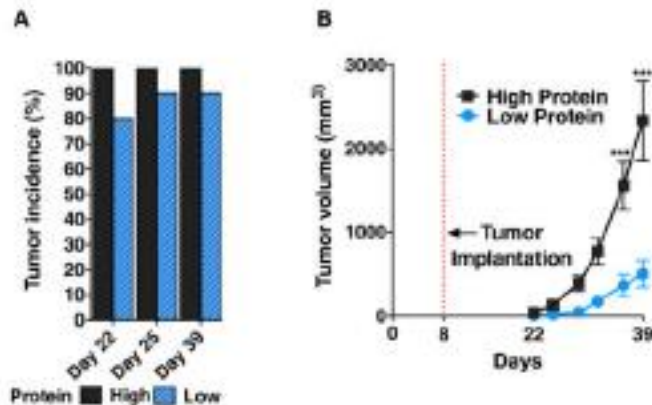
# Protein Intake, IGF-1 and mortality

Human population: 63  
High protein: 20% or more; Moderate protein: 10-20%; Low protein: less than 10%

Age 65 or more High Protein was associated with opposite outcomes but diabetes

## Mice study:

young (18 weeks old) male mice  
isocaloric diet 18% or 4 % protein  
Implanted subcutaneously  
with murine melanoma cells



Age 50-65 High Protein had  
74% increase in all cause mortality  
4 times higher risk of cancer



# Protein Intake, and mortality

Una alimentazione ad ad libitum a basso contenuto proteico in età giovanile e medio matura, seguito da una a moderato contenuto proteico, si associa a migliore spettanza di vita, in particolare di quella libera di malattia

