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Calorie Restriction, Longevity and Muscle Function: Emerging Research and Clinical Considerations

TODAY'S AGENDA:

- Introduction & Housekeeping
- Speaker Introduction
- Presentation
- Q&A
- Closing

WEBINAR HOST:

Keith Hine M.S., R.D.
Vice President of Healthcare, Sports & Professional Education
Orgain, LLC

WEBINAR PRESENTER:

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Assistant Professor - Research
Integrated Physiology and Molecular Metabolism
Pennington Biomedical Research Center

Owner
Cake Nutrition, LLC

Presentation Outline

- **Outline:**
  - Molecular basis of aging
  - Calorie restriction and anti-aging: the evidence
    - Preclinical trials
    - Human observational
    - Human clinical trials
  - Concerns & counterpoints

- **Objectives:**

  Understand the biological basis of aging

  Describe the proposed mechanisms by which calorie restriction slows aging

What do I do?

Clinical-Translational Research

Intersection of multiple approaches:

- Cell Culture
- Clinical Metabolism
- Lifestyle Intervention

Private Practice

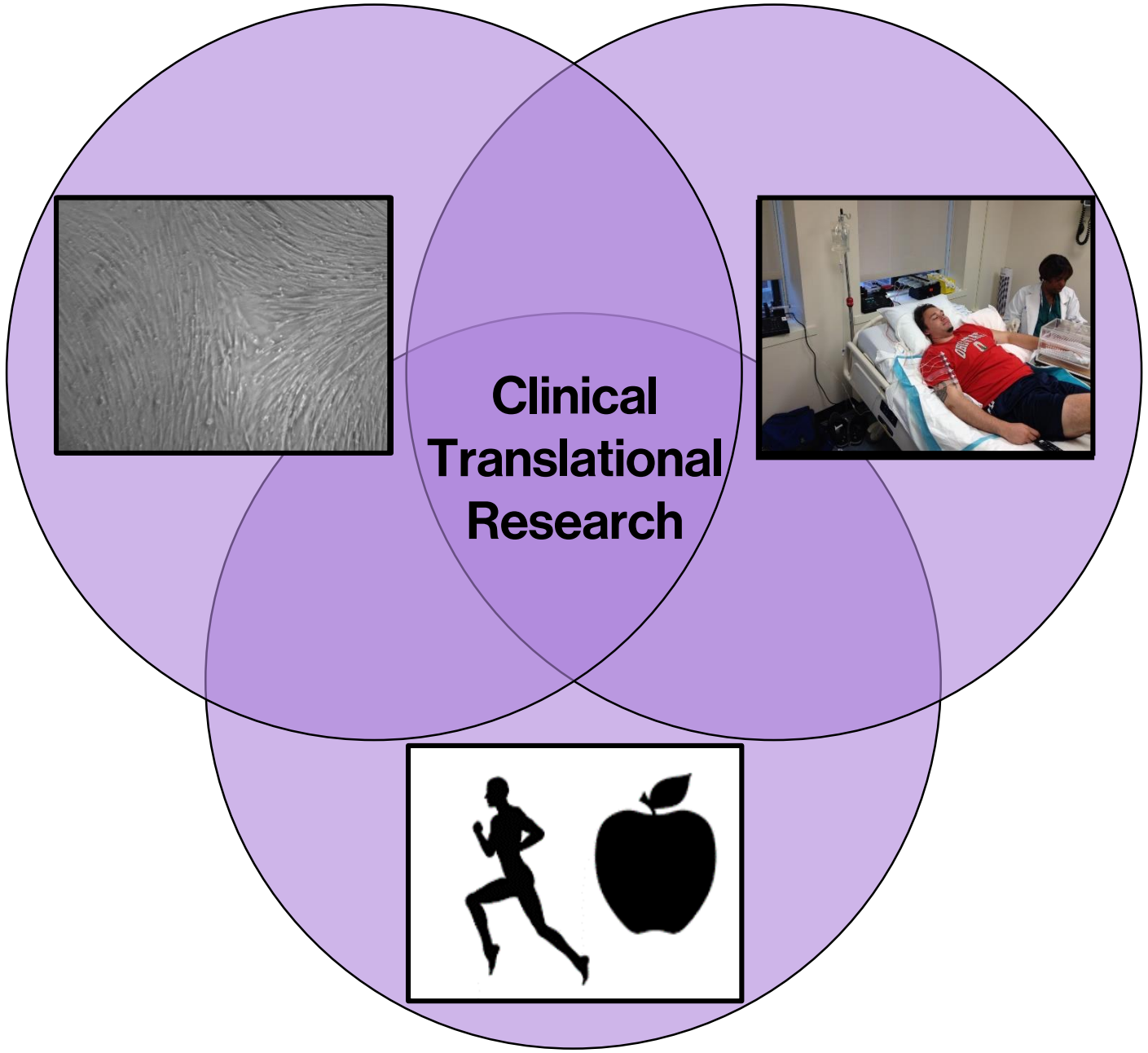
Cake Nutrition, LLC

- Metabolic Consultation
- Behavioral Counseling

Dietetic Leadership

Academy of Nutrition and Dietetics

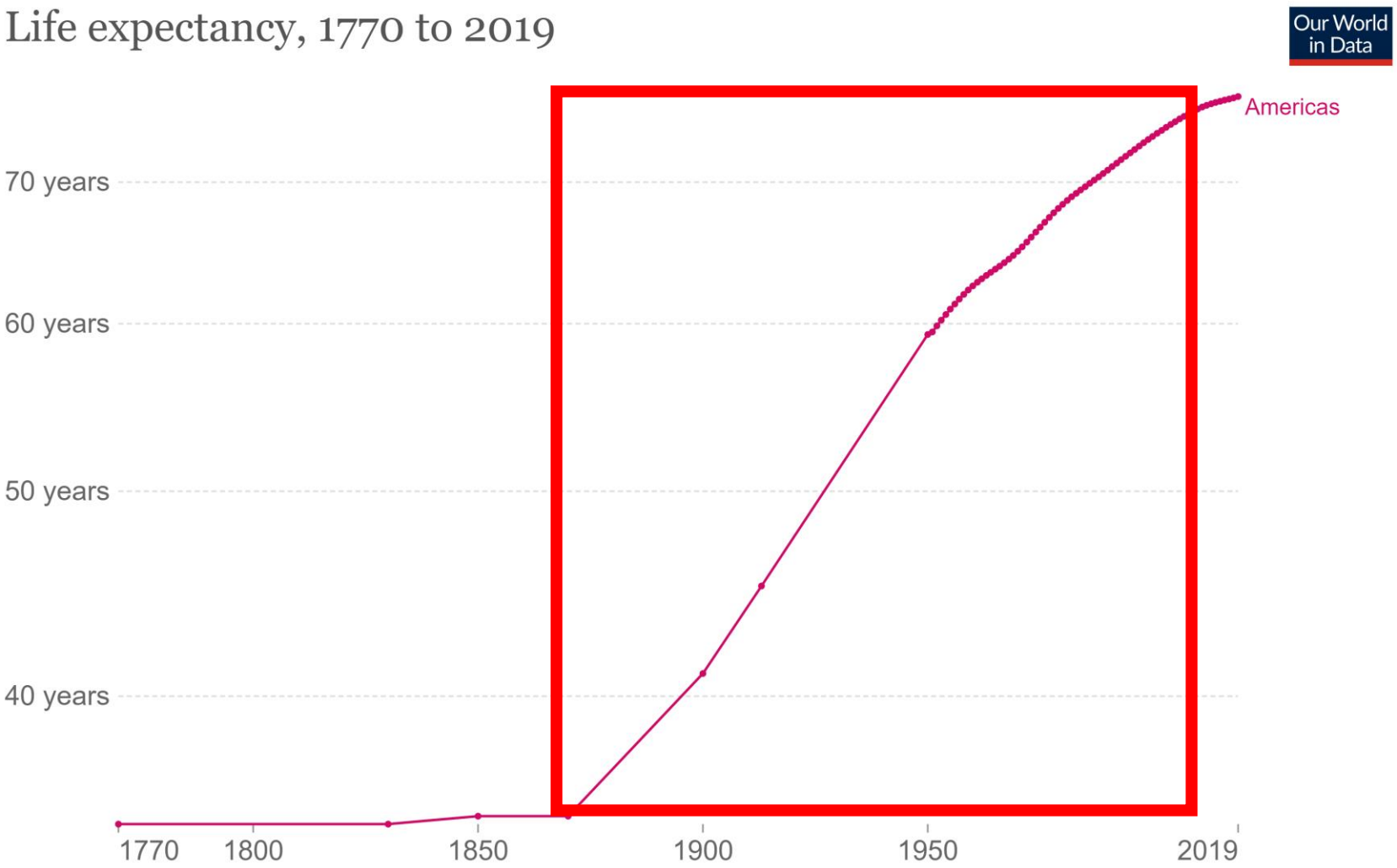
- Volunteer opportunities
- Writing, reviewing, presenting



Longevity is dictated by the aging process

- Longevity = lifespan.
- Aging = decline in physiological function.
  - Affected by intrinsic (primary) and extrinsic (secondary) factors.

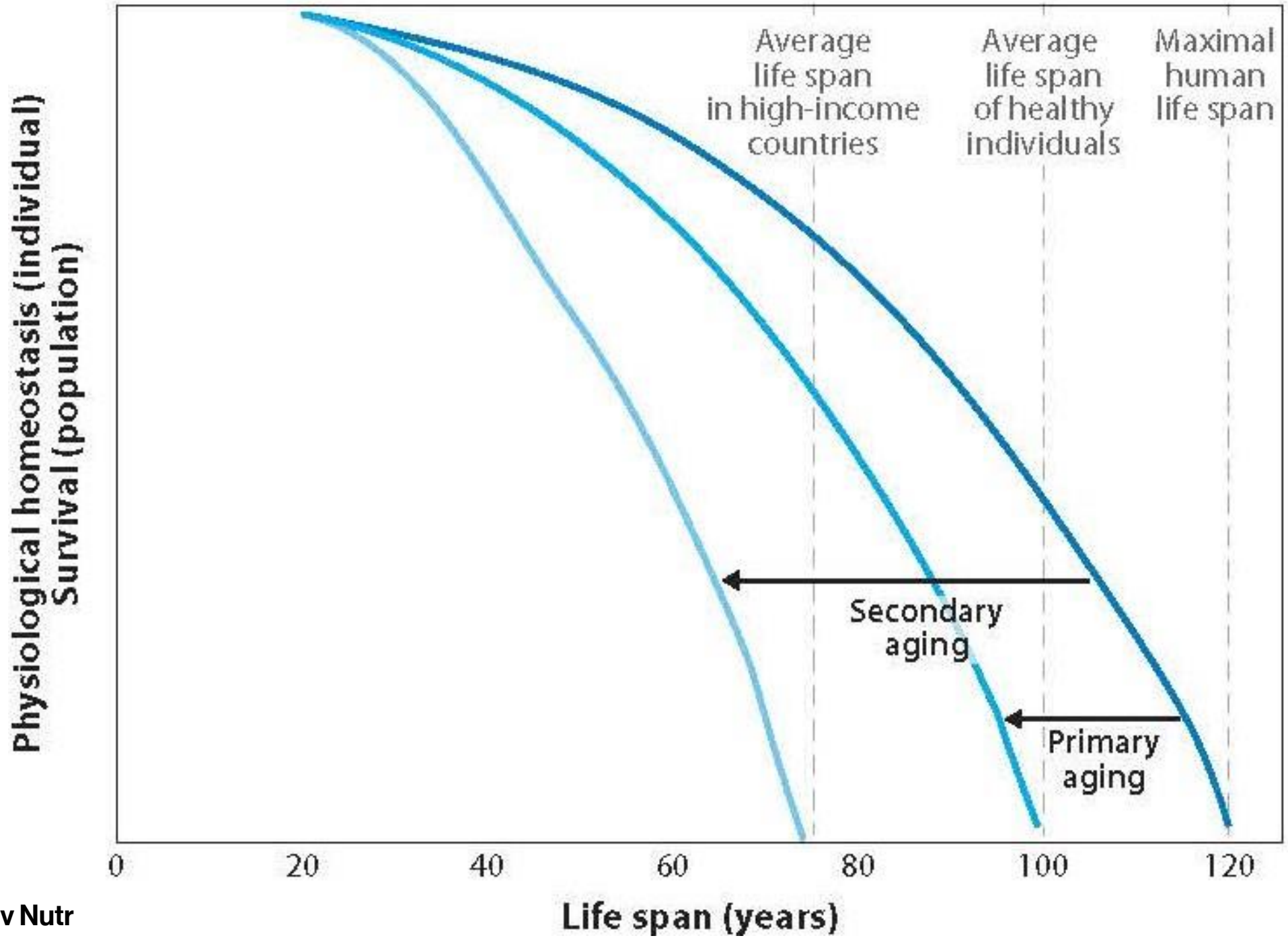
Longevity increasing … until recently



Source: Riley (2005), Clio Infra (2015), and UN Population Division (2019) OurWorldInData.org/life-expectancy • CC BY
Note: Shown is period life expectancy at birth, the average number of years a newborn would live if the pattern of mortality in the given year were to stay the same throughout its life.

- **Sanitation**
- **Public Health**
- **Food Supply**
- **Malnutrition**
- **Healthcare**

Largely extrinsic/secondary factors



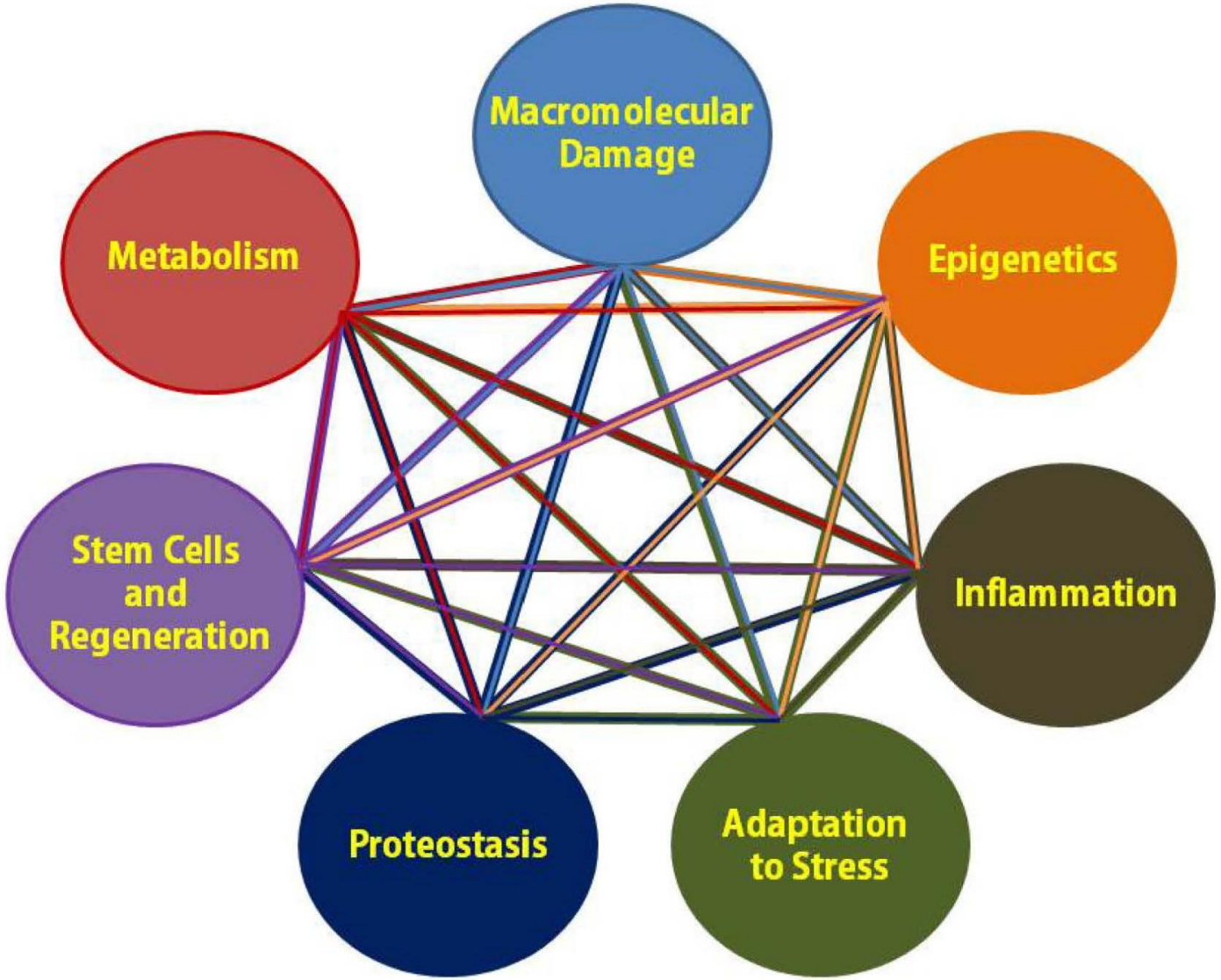
Flanagan 2020 Annu Rev Nutr

The aging process is inevitable

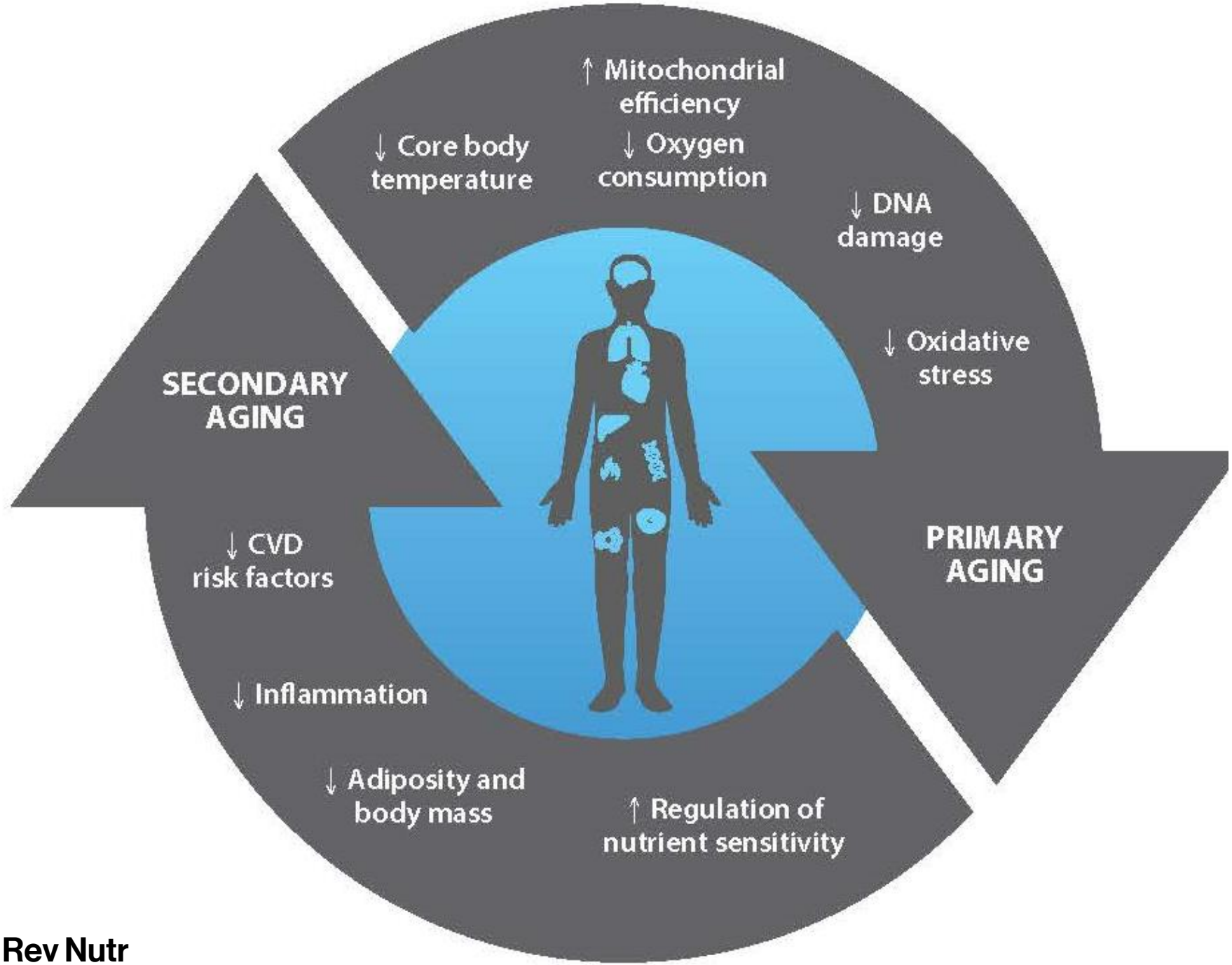
- Decline in multiple physiological functions.
- Culminates in death of the organism.
- Humans: ↓fat-free mass, ↑weight & fat mass

- Primary aging – intrinsic factors; associated with:
  - Oxidative stress
  - Metabolic rate
- Secondary aging – extrinsic factors
  - Accelerates primary aging & mortality

Molecular basis of aging: “Seven Pillars”



Kennedy Cell 2016



Flanagan 2020 Ann Rev Nutr

Endless Pursuit for a Fountain of Youth

Calorie Restriction

1. Dietary energy intake < requirements
2. Maintain optimal essential nutrient intake

Unique potential to slow aging!

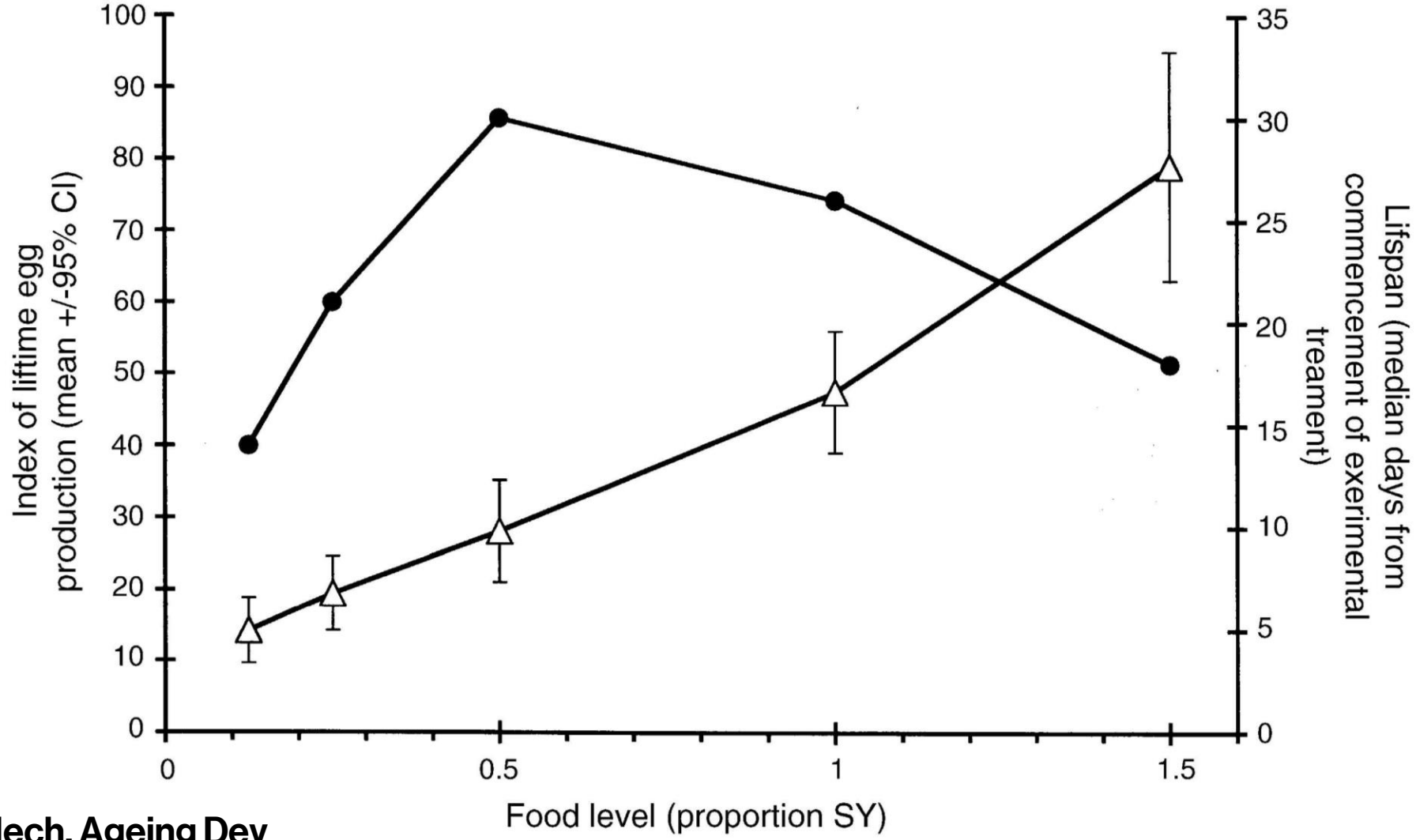
Diving into the Evidence

Pre-clinical evidence

Human observational reports

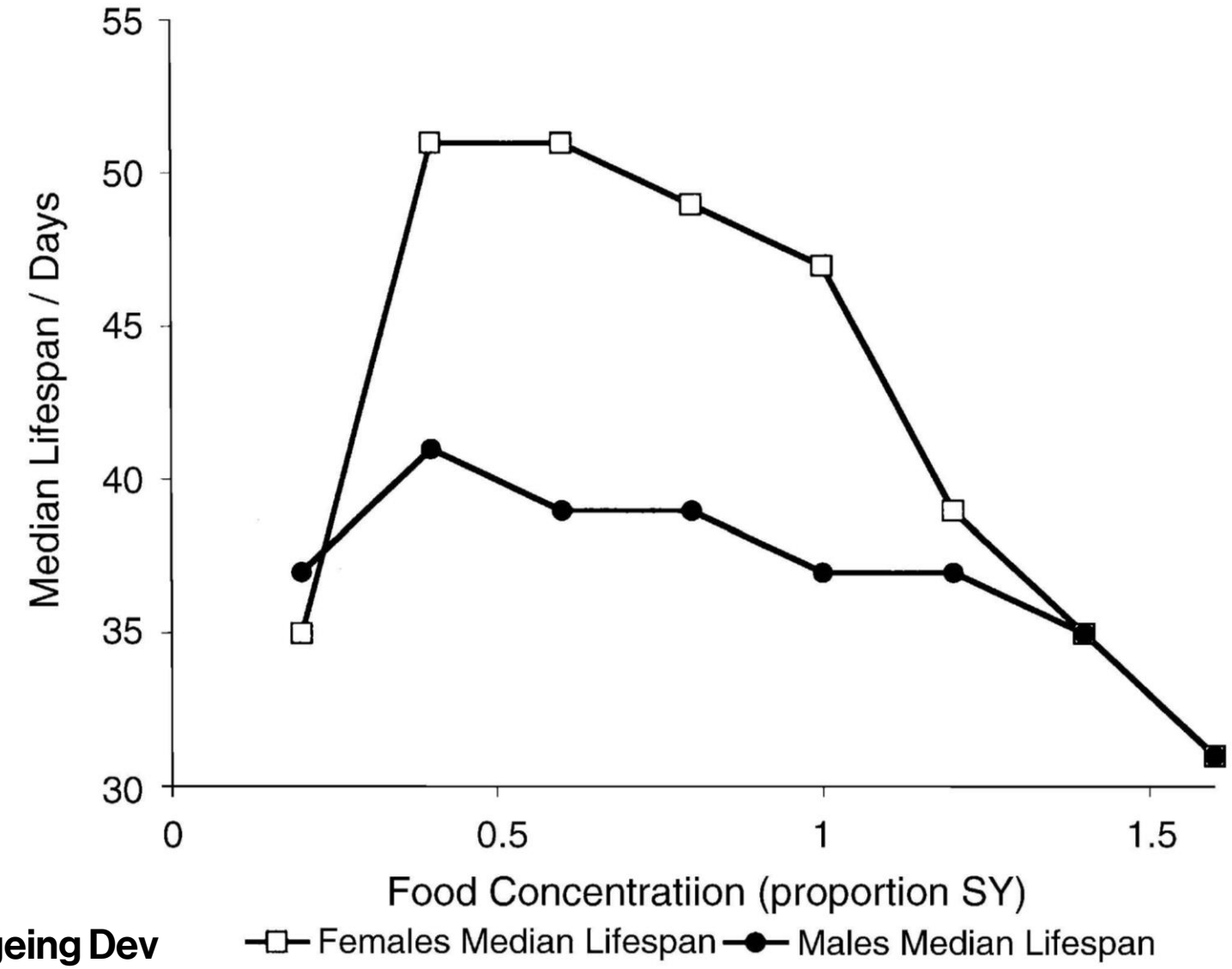
Clinical Trials

Pre-clinical: Drosophila



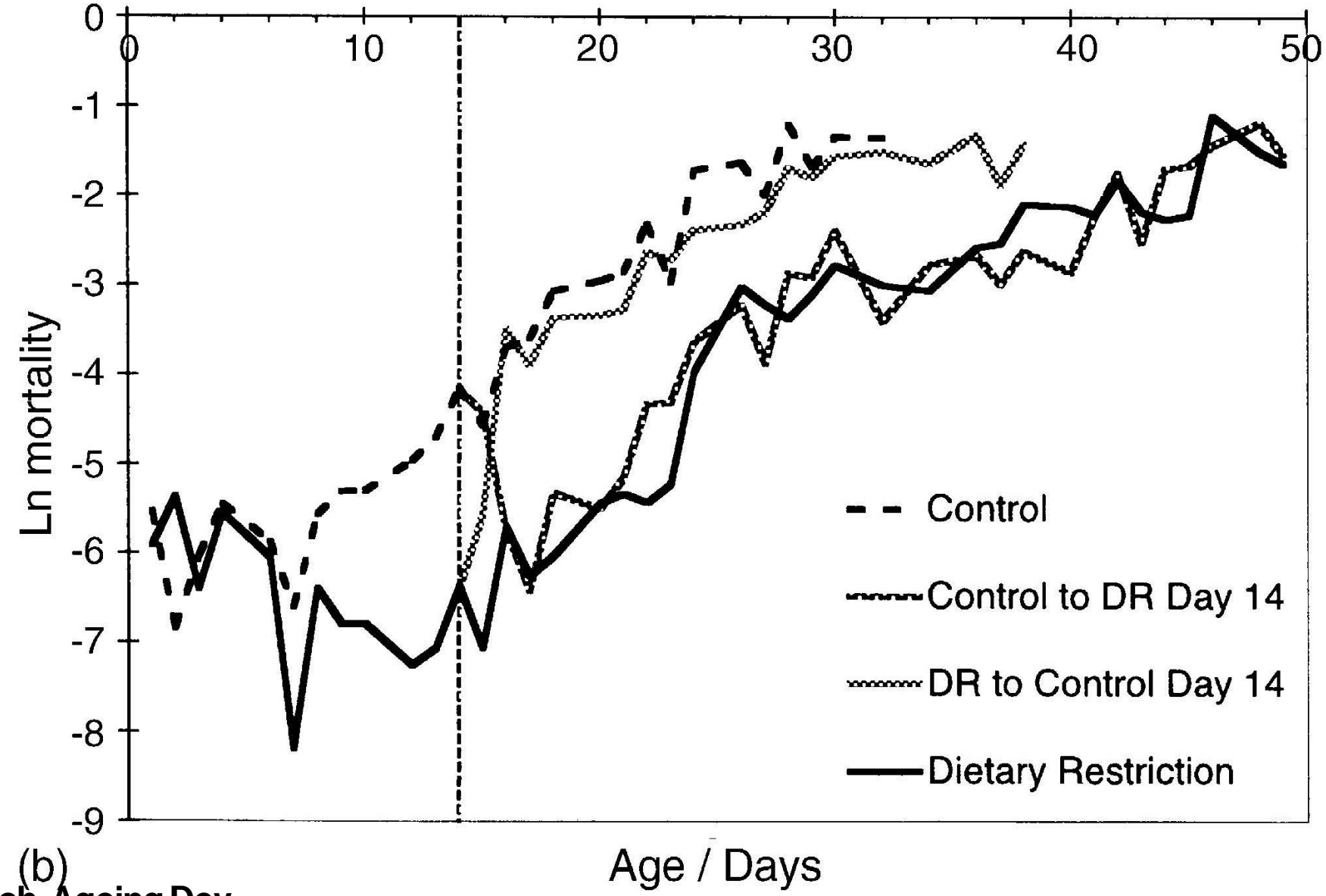
Partridge 2005 Mech. Ageing Dev

Pre-clinical: Drosophila



Partridge 2005 Mech. Ageing Dev

Pre-clinical: Drosophila

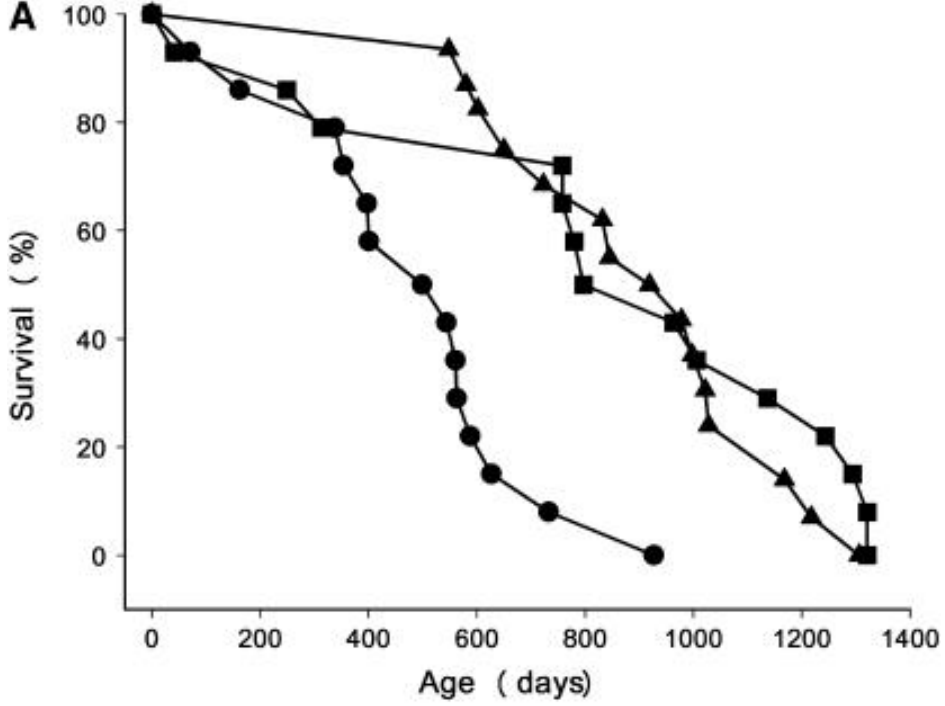


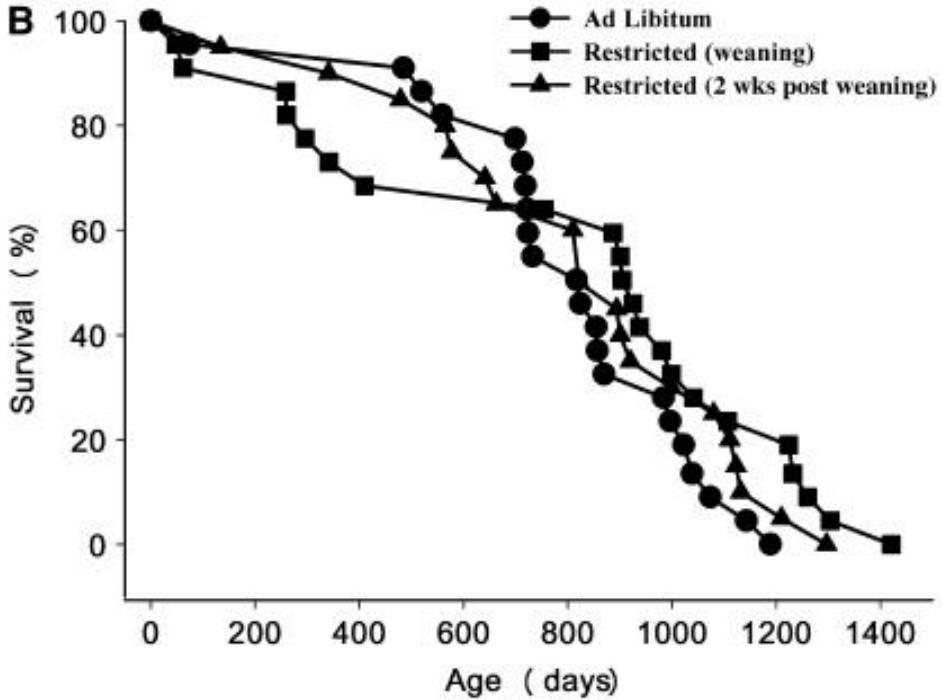
(b)

Partridge 2005 Mech. Ageing Dev

Pre-clinical: Murine Models

- Classic trial 1935
- McCay, Crowell, and Maynard
- "The Effect of Retarded Growth upon the Length of Life Span and upon the Ultimate Body Size"

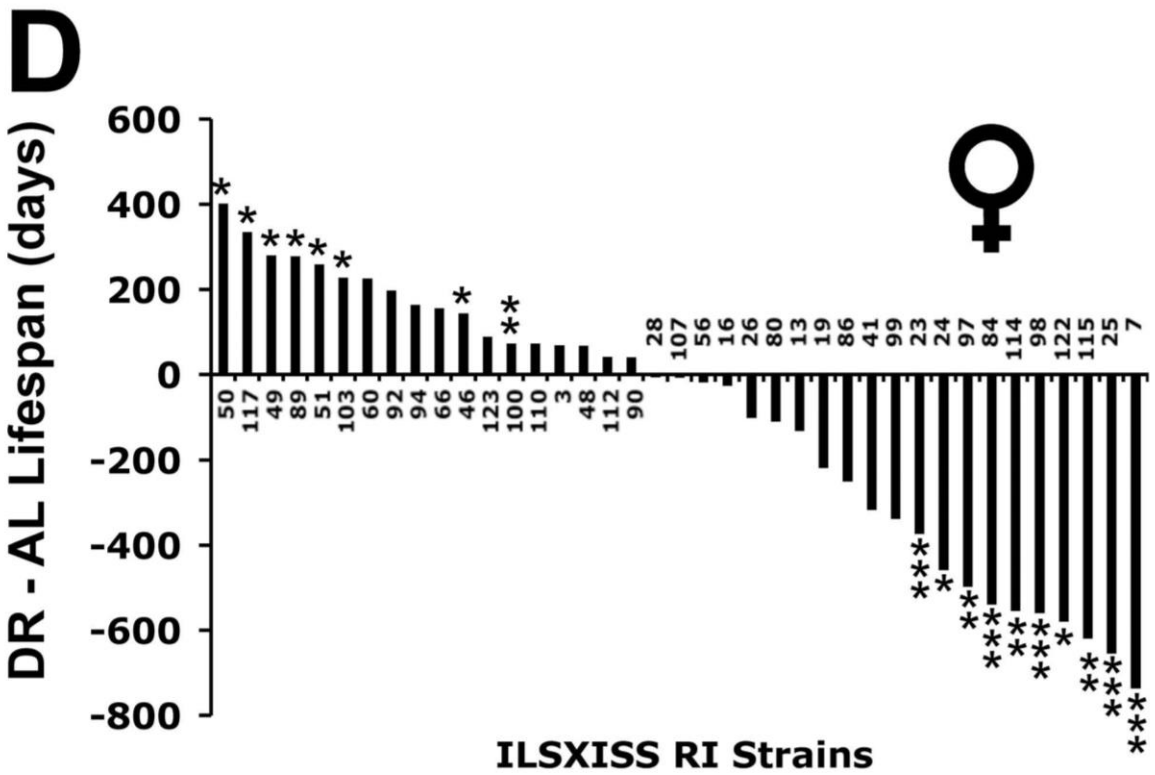




McCay 1935 J Nutr
McDonald 2010 J Nutr

Pre-clinical: Murine Models

- MANY different murine models
- 40% restriction in 41 genetic strains



Liao 2010 Aging Cell

Raises concerns for translation to humans

Pre-clinical: Non-human Primates

- Genome shares 93% sequence identity with humans
- More similar to humans (decades of life, grey hair, muscle loss) than other models

<u>Three overlapping studies</u>

- U of Maryland
- U of Wisconsin
- National Institutes of Health

Pre-clinical: Non-human Primates

- University of Maryland rhesus monkey study
- 117 monkeys (Macaca mulatta)

Data collection started 1977

- Caloric restriction increases median age of survival ~7 years

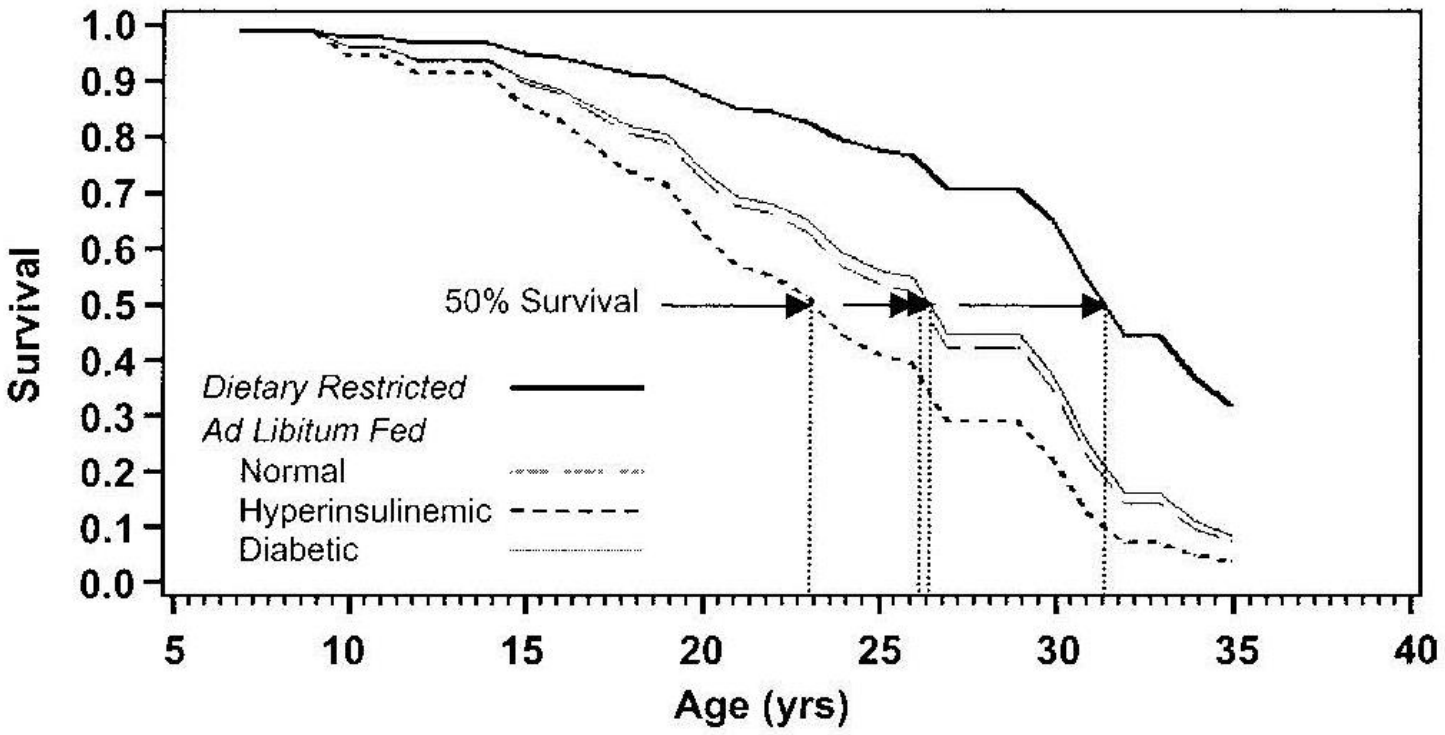


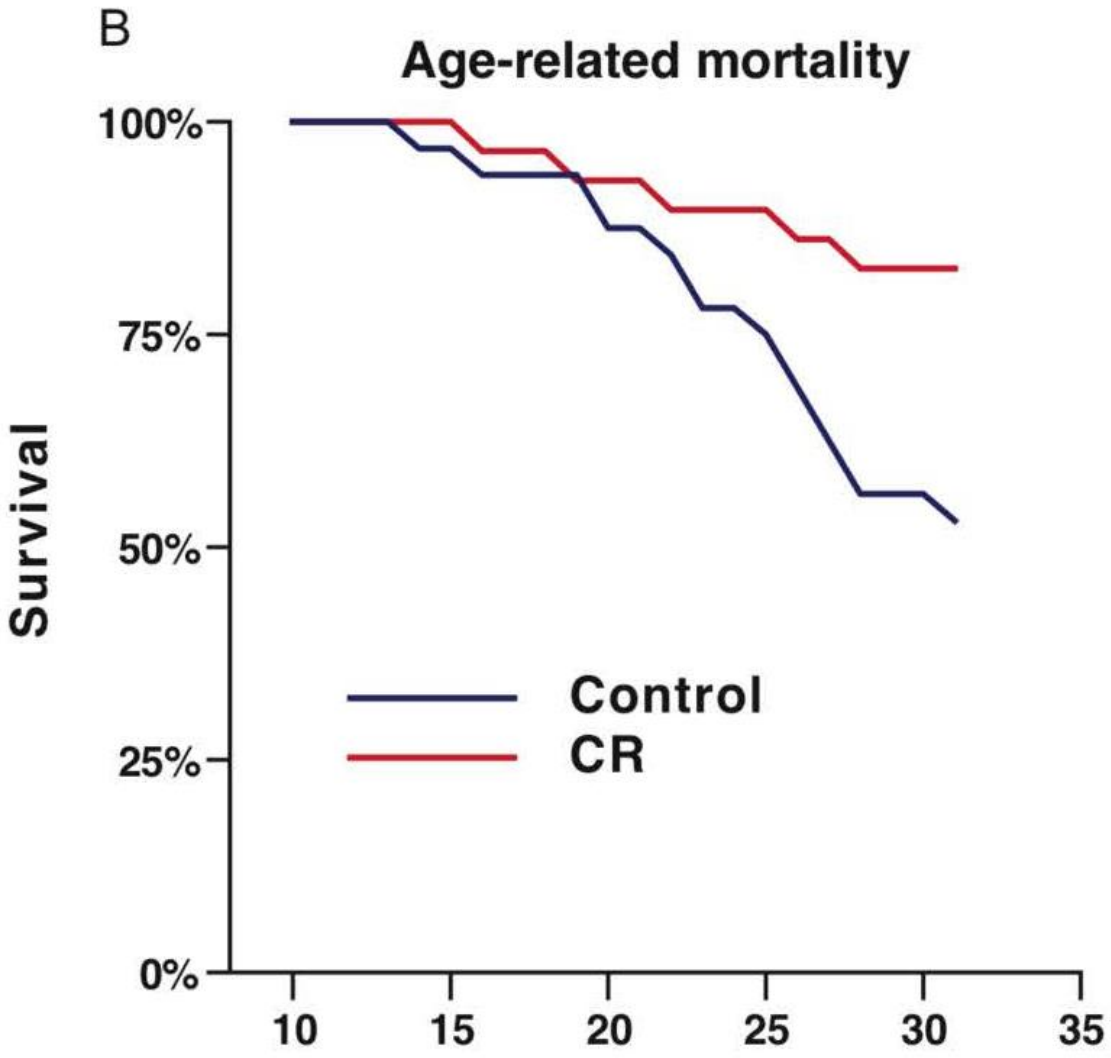
Figure 1. Estimated survival curves comparing the dietary-restricted monkeys

Bodkin 2003 J Gerontol A Biol Sci Med Sci

Pre-clinical: Non-human Primates

- University of Wisconsin

- Most prominent effects
  1. Delays the onset of age-associated pathologies
  2. Promotes survival

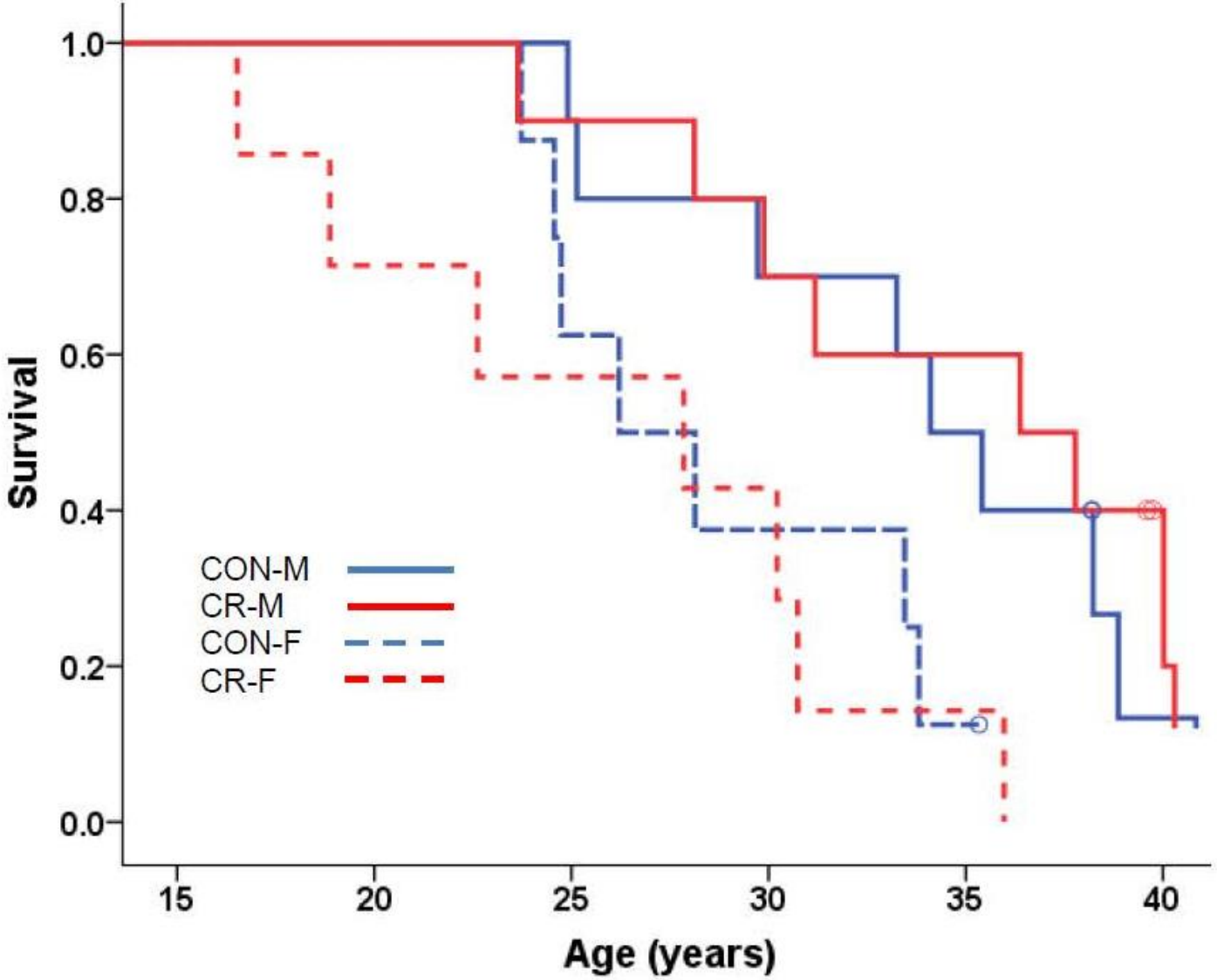


Colman 2009 Science

Pre-clinical: Non-human Primates

- National Institutes of Health
- No significant effect on survival
- Why?
  - Variability in environment and/or unknown factors

  (study design, housing animals, diet composition)



Mattison 2012 Nature

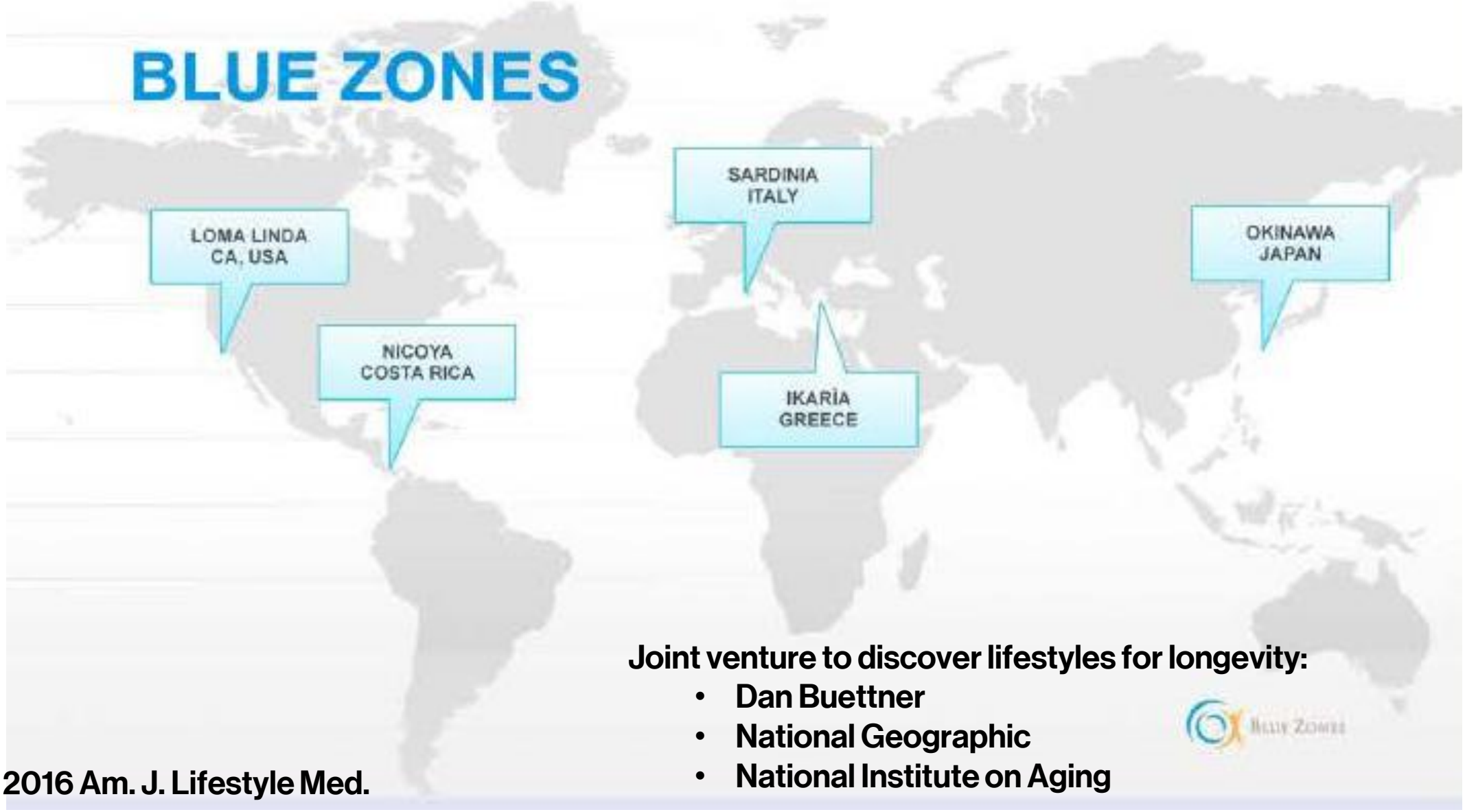
Summary of the Evidence

Preclinical

- Calorie restriction is the only non-genetic method that extends lifespan in every species studied (50–300%)
  - Variability between and among species exist.
  - Translation to human remains in question.

Human Observational: Blue Zones

5 Areas with highest prevalence of centenarians



Joint venture to discover lifestyles for longevity:

- Dan Buettner
- National Geographic
- National Institute on Aging

Buettner 2016 Am. J. Lifestyle Med.

Human Observational: Okinawans

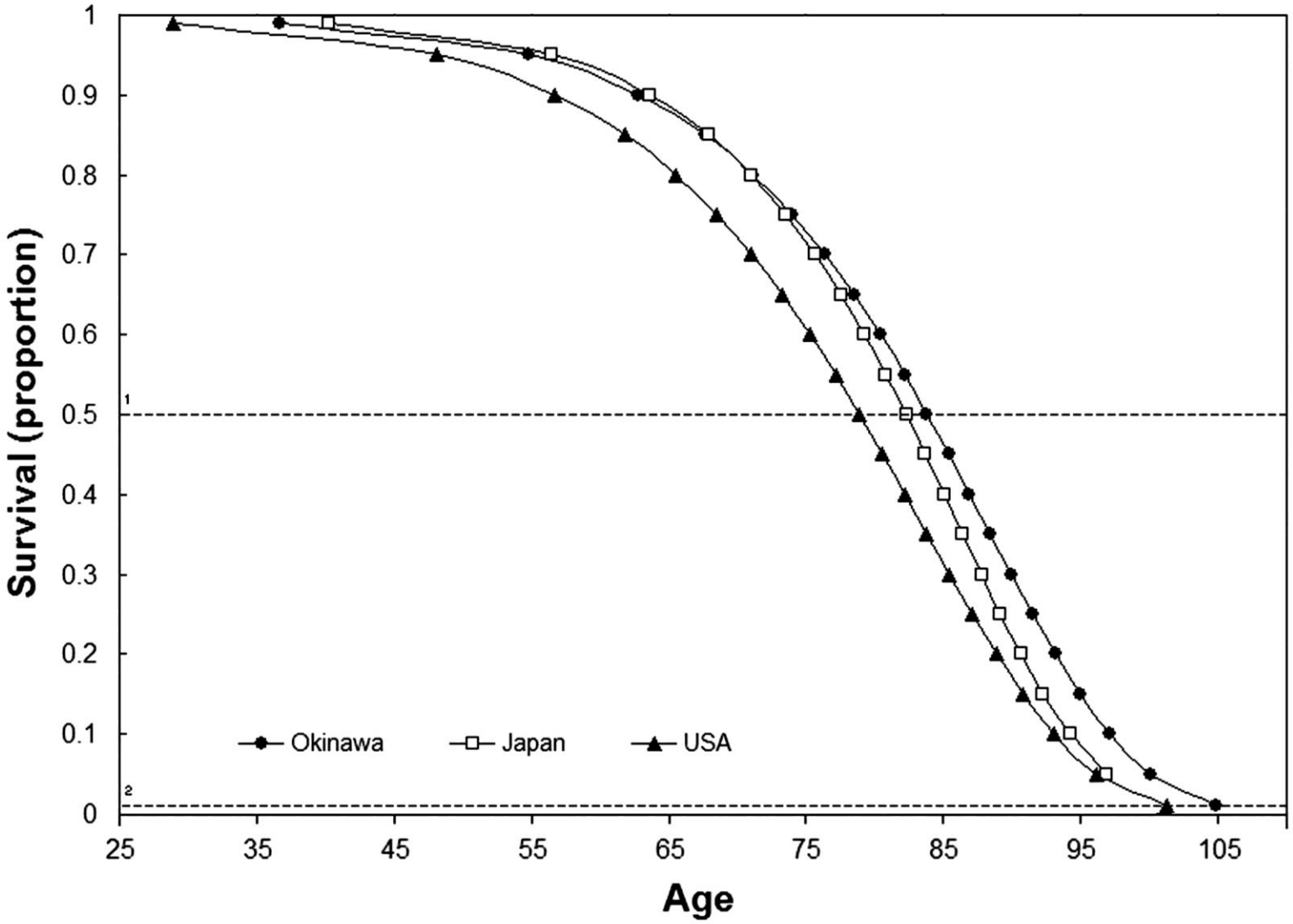
- Small island of Japan
- Unique dietary habits
- Naturally restricted dietary intake to ~11% less than mainland

Willcox 2007 Ann. N.Y. Acad. Sci.

Human Observational: Okinawans

- Longer lifespan
- More centenarians
- Less age-related diseases

- Effects dissipated after Westernization
- Today, similar to other Westernized countries

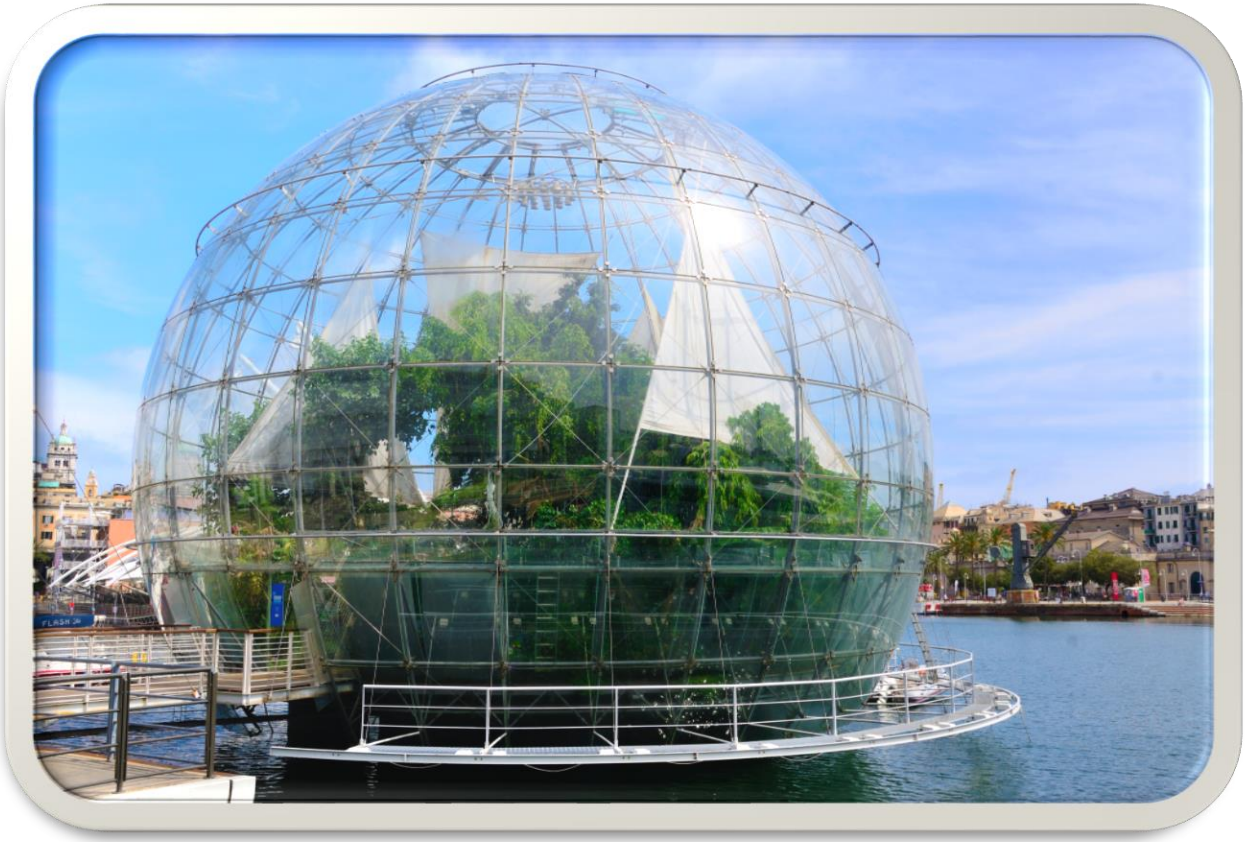


[1] Average life span (50th percentile survival).
[2] Maximum life span (99th percentile survival).

Willcox 2007 Ann. N.Y. Acad. Sci.

Human Observational: Biosphere II

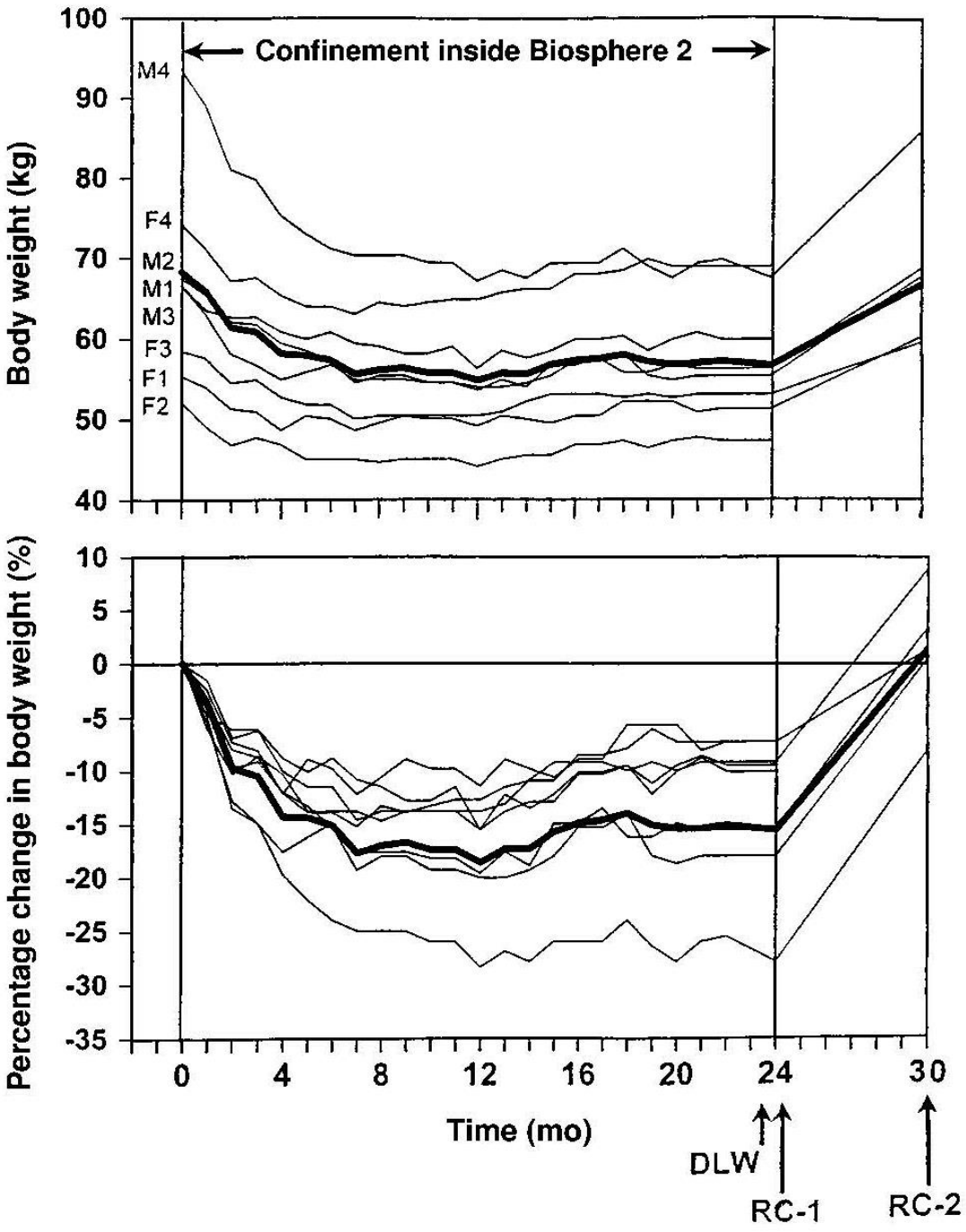
- Biosphere-II experiment
- American Earth system science (closed ecosystem)
- Oracle, Arizona
- Studies to inform life in outer space



Biosphere II

- 8 volunteers, 2 years, 3.15 acre system
- Insufficient food production – unintentional calorie restriction
  - Low energy, but sufficient micronutrients

- Improved cardiovascular risk factors
- ↓ metabolic rate



Weyer 2000 Am J Clin Nutr

Human Observational: Calorie Restriction Society International

- Started by Roy Walford (Biosphere II volunteer)
- Free-living group
- Practice Caloric Restriction with Optimal Nutrition
  - “CRONies”
- Restrict energy intake ~1100-1950 kcals/day
  - Meet micronutrient needs
- BMI 19.6 ± 1.9
- Healthier cardiovascular markers vs controls

Fontana 2004 PNAS

Summary of the Evidence

Preclinical

- Calorie restriction is the only non-genetic method that extends lifespan in every species studied (50–300%)
  - Variability between and among species exist.
  - Translation to human remains in question.

Human Observational

- **Calorie restriction reduces age-related disease and mortality risk.**
- **Improves secondary aging.**
- **Impact on primary aging suggestive, but unclear.**

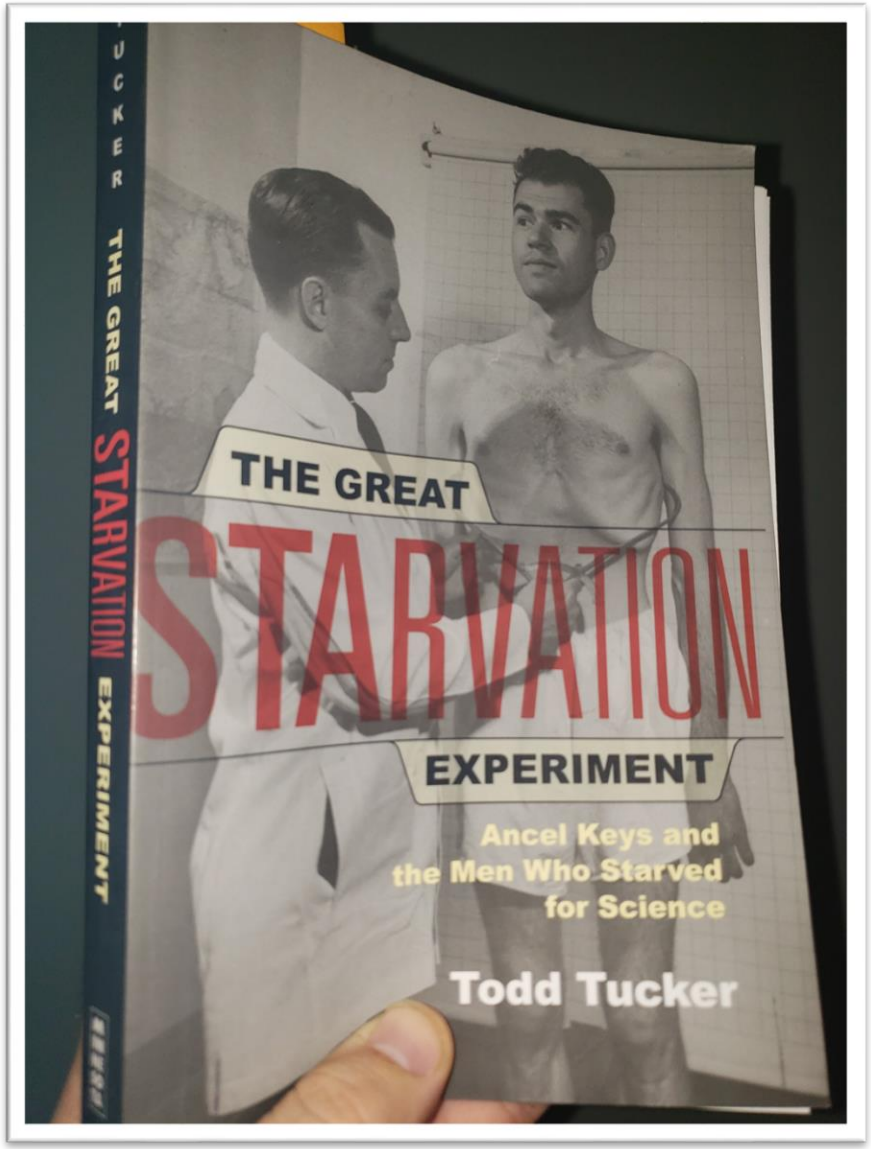
Clinical Trials: Minnesota Starvation Experiment

Classic landmark trial by Ancel Keys
1944, University of Minnesota
The Laboratory of Physiological Hygiene

Motivation: post-war rehabilitation
→ instrumental in famine relief programs today

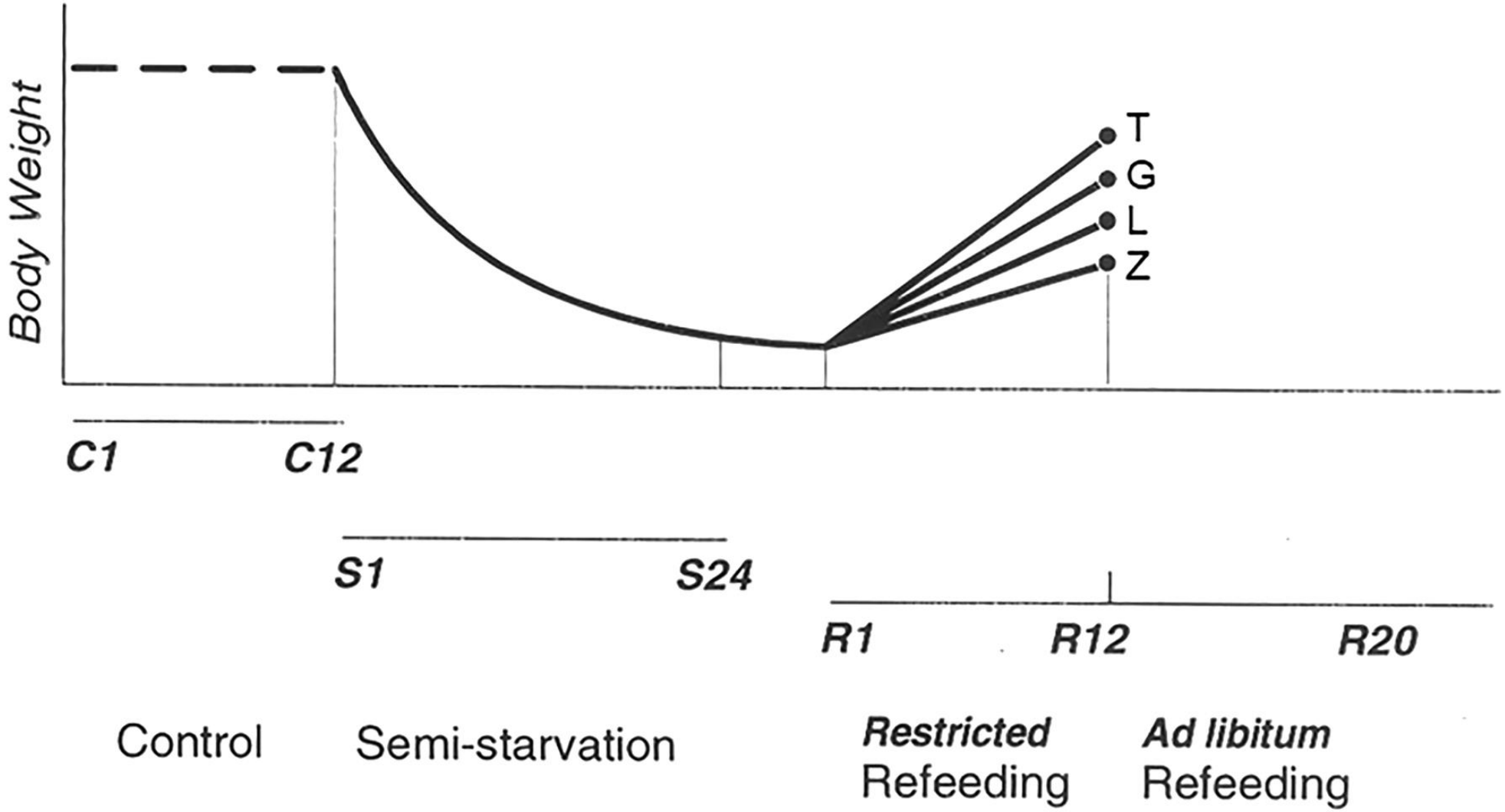
Goal: observe physical and mental effects of semi-starvation

Subjects: 36 conscientious objectors



Keys A 1950 University of Minnesota Press

Clinical Trials: Minnesota Starvation Experiment



Dulloo AG 2021 Obesity Reviews

Clinical Trials: Minnesota Starvation Experiment

Methods:

~60% of habitual dietary intake, foods mimic starvation conditions

e.g., bland, low variety, missing micronutrients

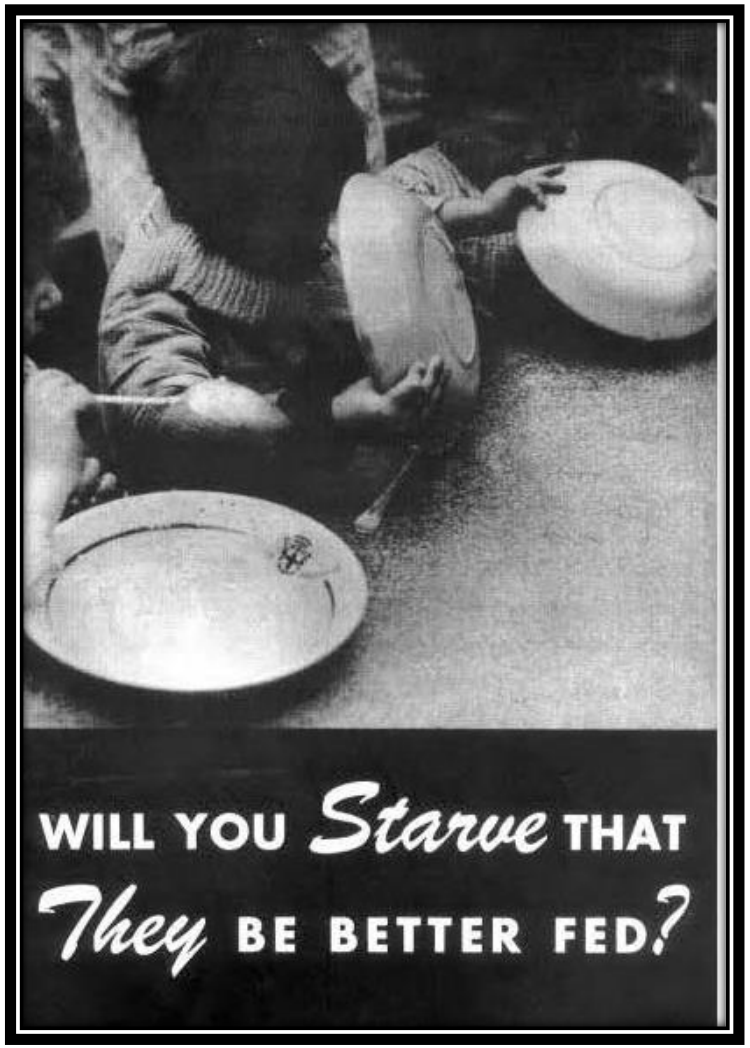
Walk 22 miles/week

Results:

~24% weight loss

Malnutrition with multiple nutrient deficiencies

First report of physical & psychological effects



Clinical Trials: Minnesota Starvation Experiment

<u>Recall</u>

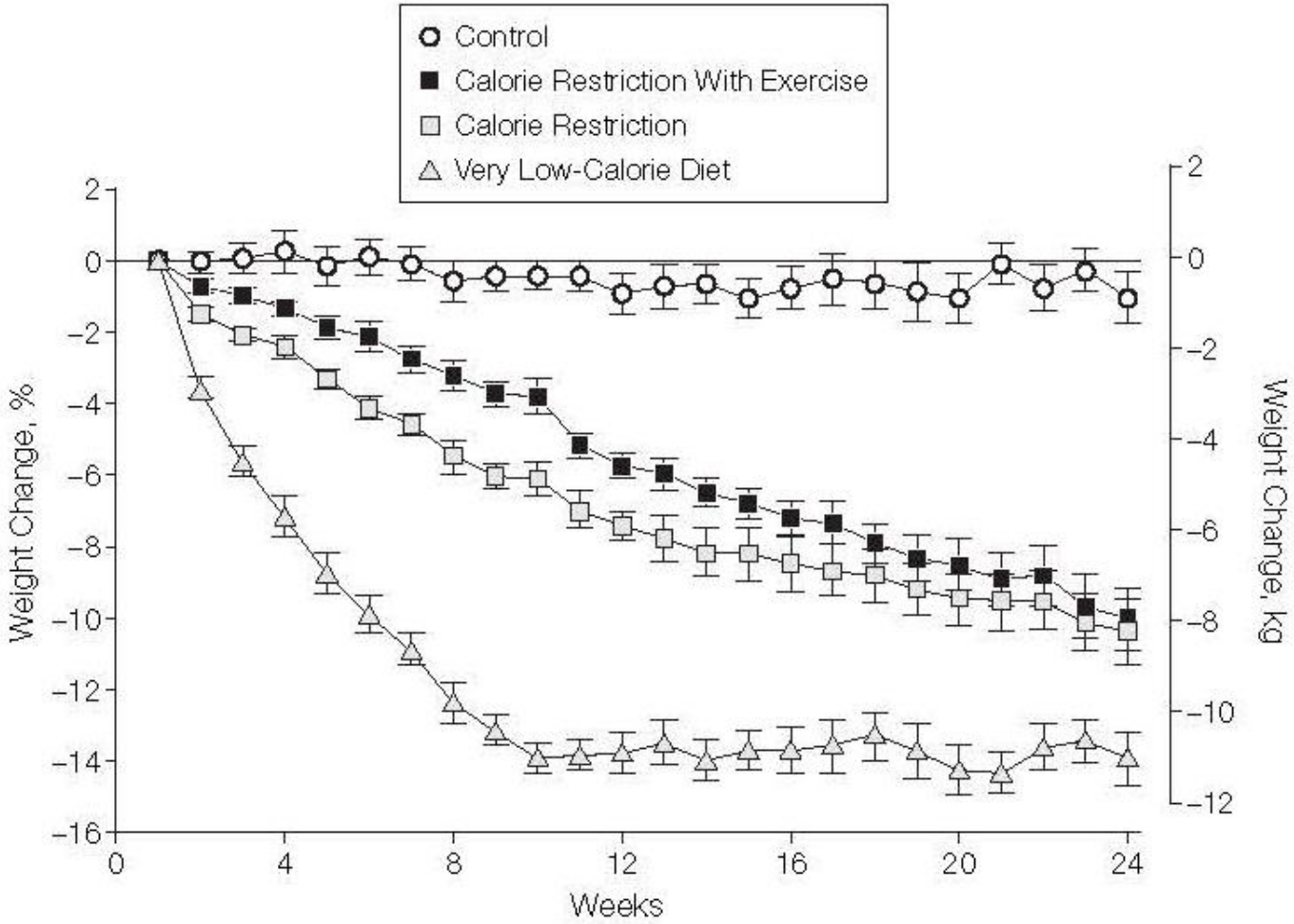
Calorie Restriction

1. **Dietary energy intake < requirements**
2. **Maintain essential nutrient intake**

Clinical Trials: CALERIE

Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy

- 6 month calorie restriction
- 48 overweight men & women
- 25% restriction
  - 25% diet
  - 12.5% diet + 12.5% exercise
  - VLCD to 15% weight loss



Heilbronn 2006 JAMA

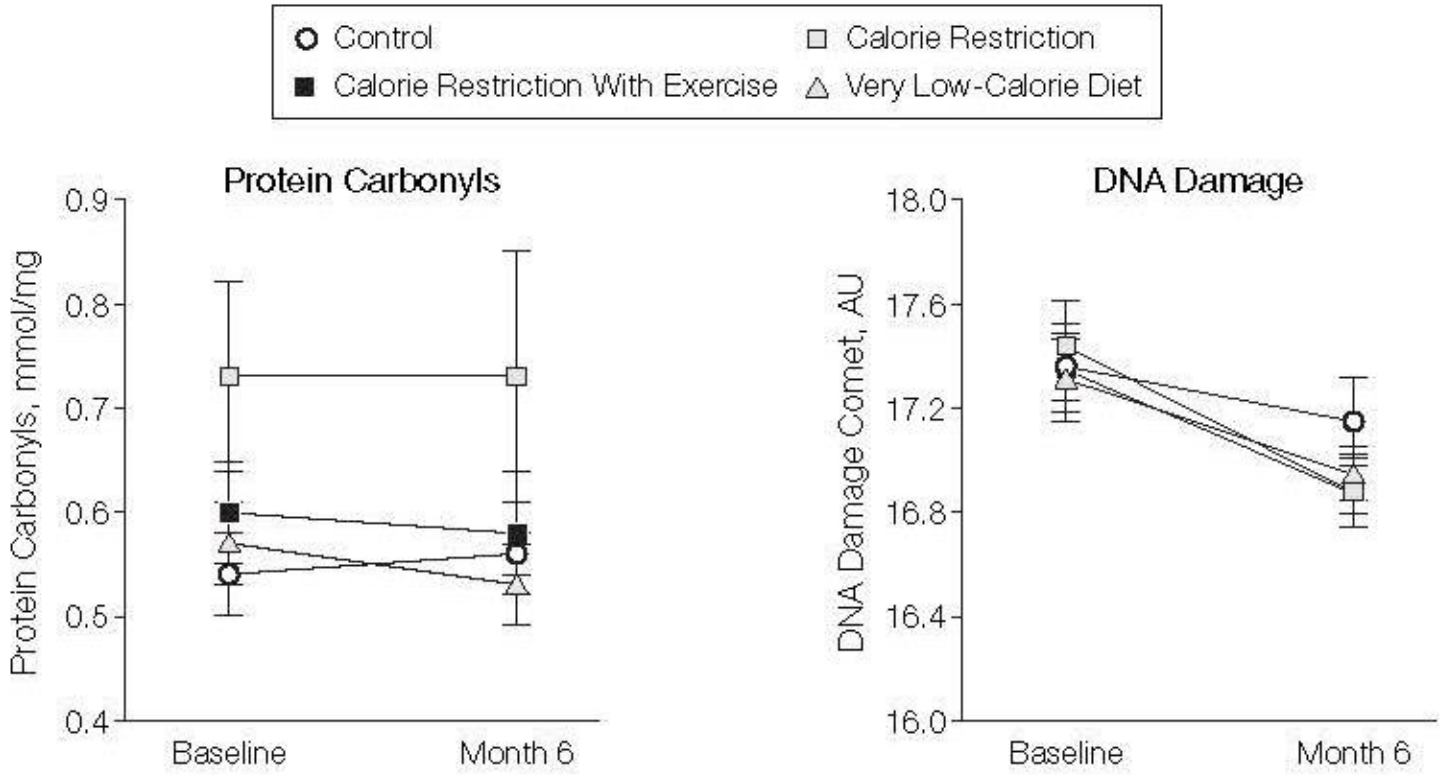
Clinical Trials: CALERIE

Slowed intrinsic factors to aging (primary aging)

↓fasting insulin

↓body temperature

Figure 6. Fasting Plasma Protein Carbonyls and DNA Damage Measured by the Comet Assay



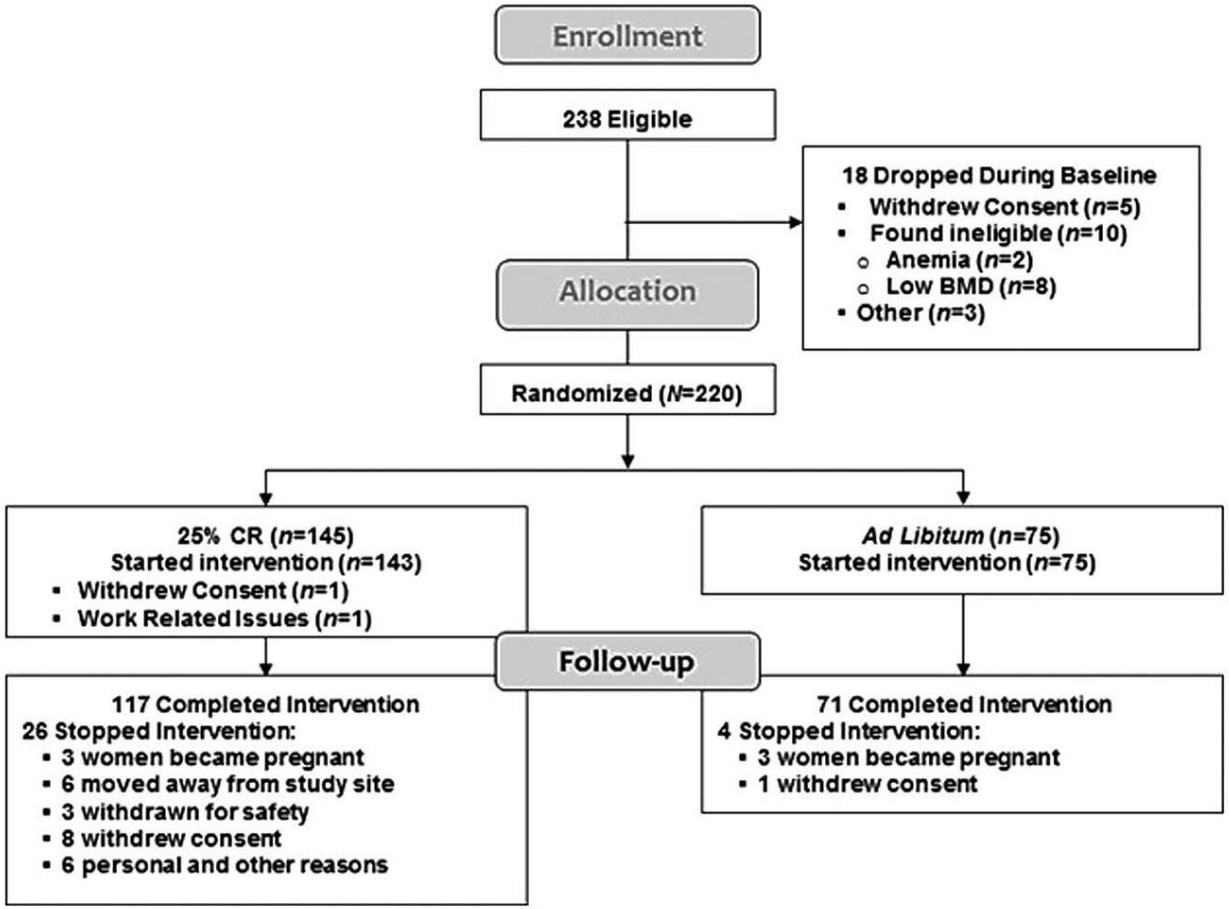
DNA damage was significantly reduced from baseline in the calorie restriction, calorie restriction with exercise, and very low-calorie diet groups at month 6 (all $P<.005$).

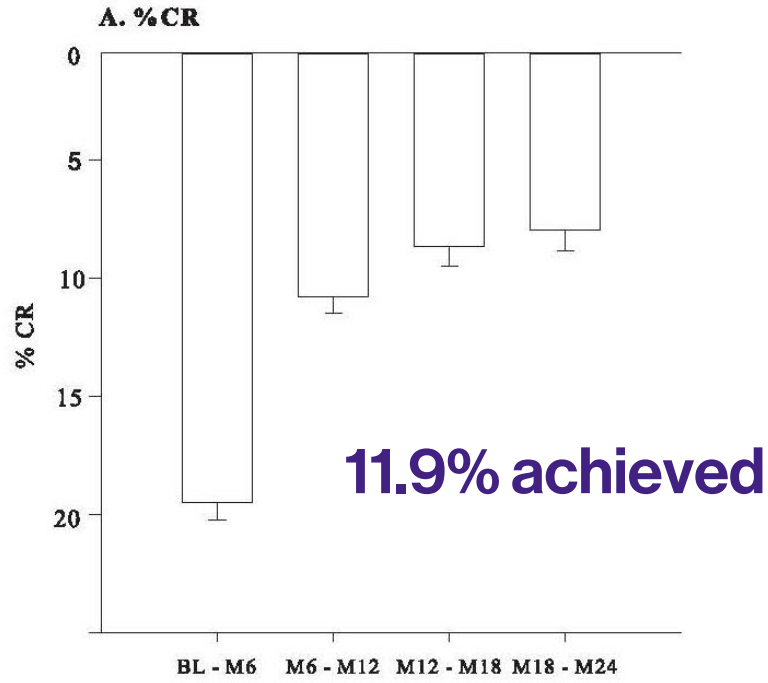
Heilbronn 2006 JAMA

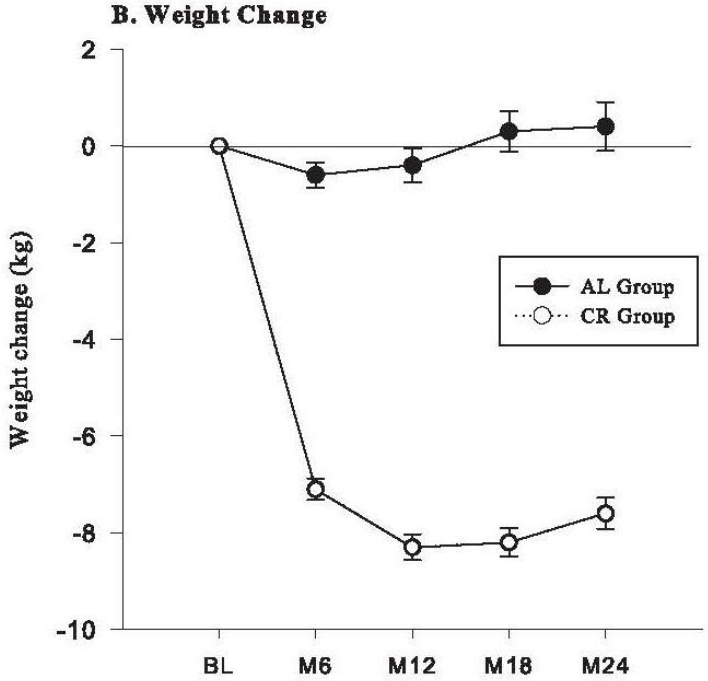
Clinical Trials: CALERIE II

- Larger, longer follow-up to CALERIE
- 2 years of calorie restriction (goal: 25% reduction from baseline)
- 220 adults 21-50 years old, without obesity

Clinical Trials: CALERIE II





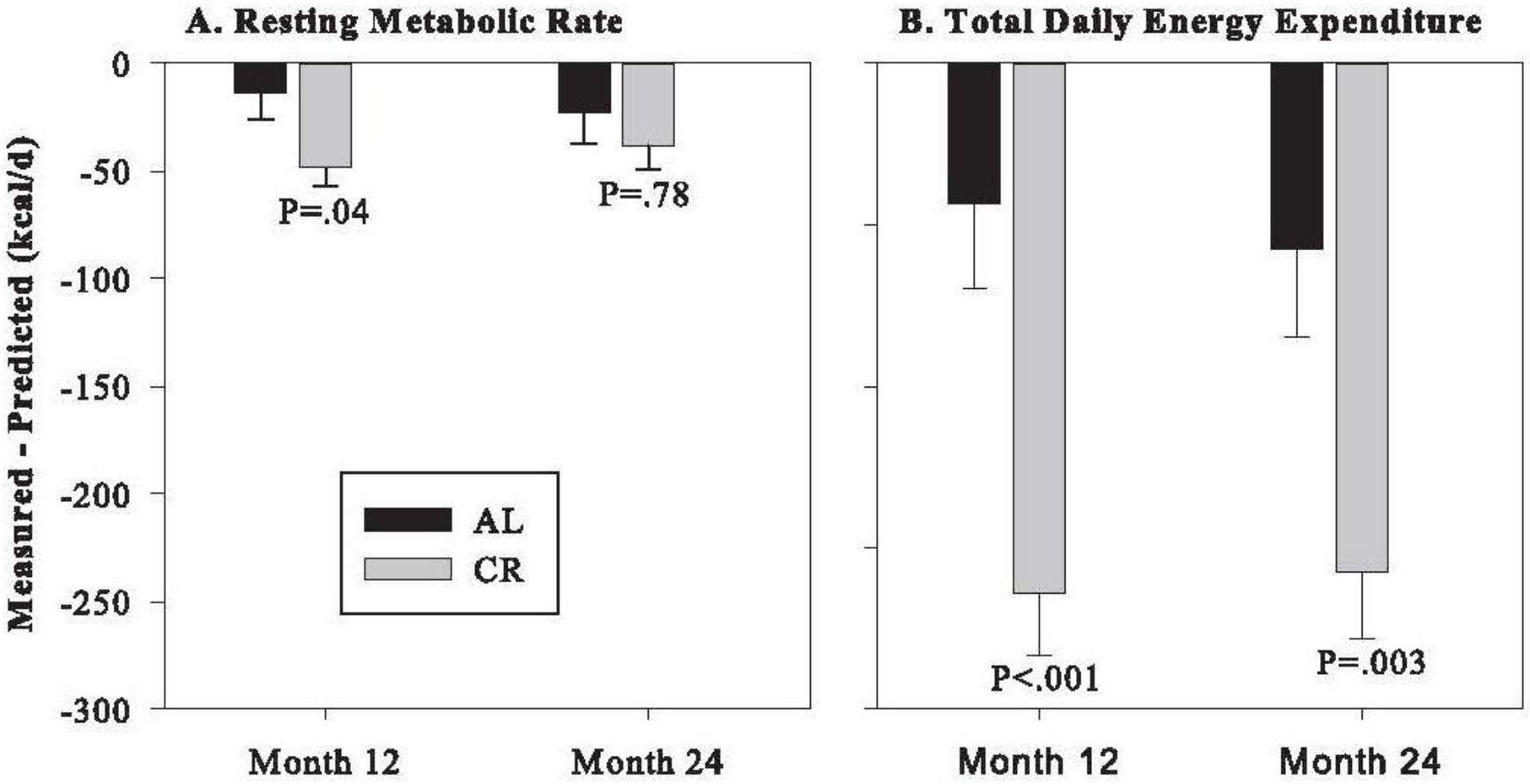


Ravussin 2015 Journals of Gerontology

Clinical Trials: CALERIE II

- **Primary outcomes**
  - Resting metabolic rate
  - Core body temperature

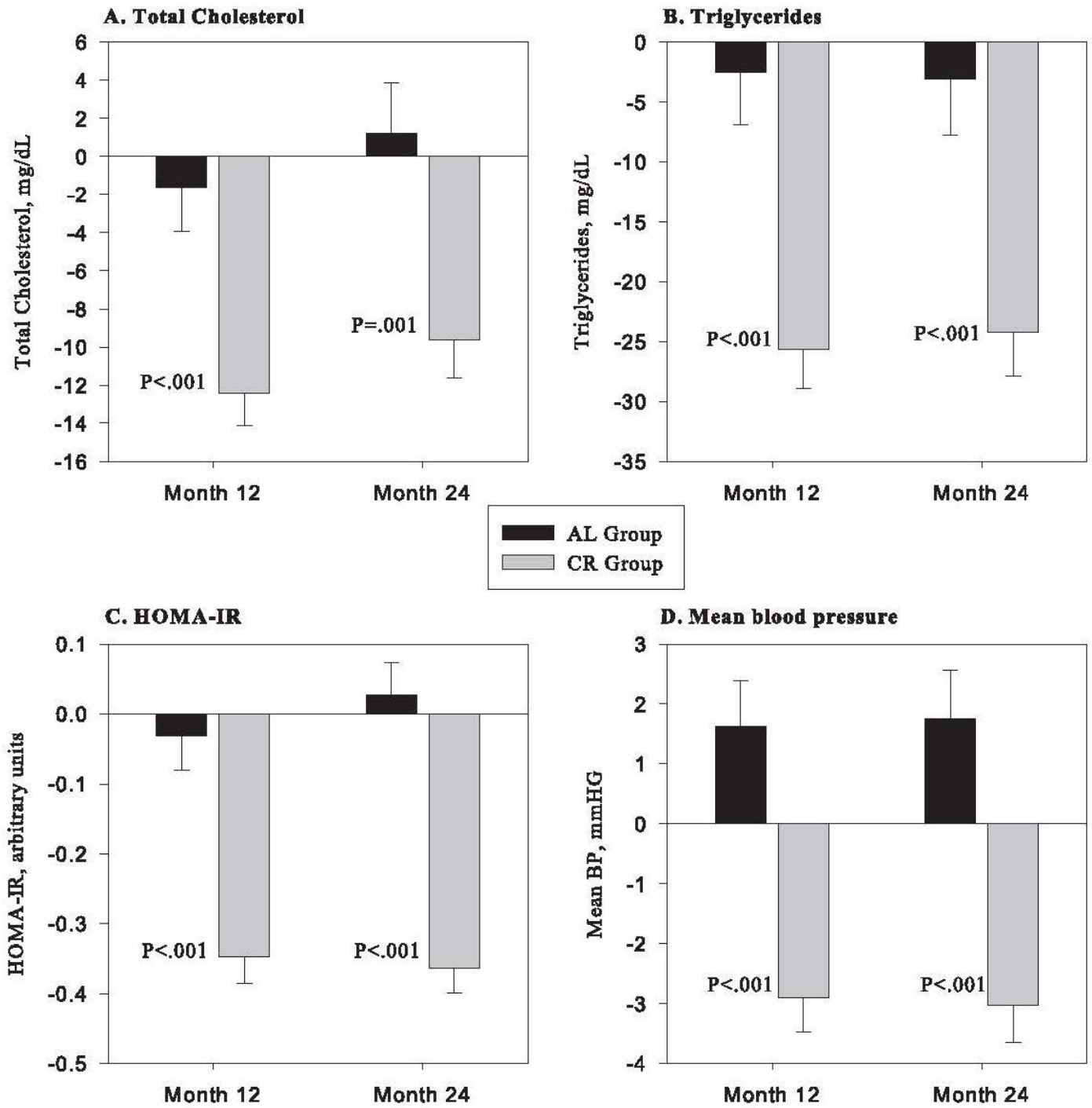
  - No change



Ravussin 2015 J Gerontol A Biol Sci Med Sci

CALERIE II

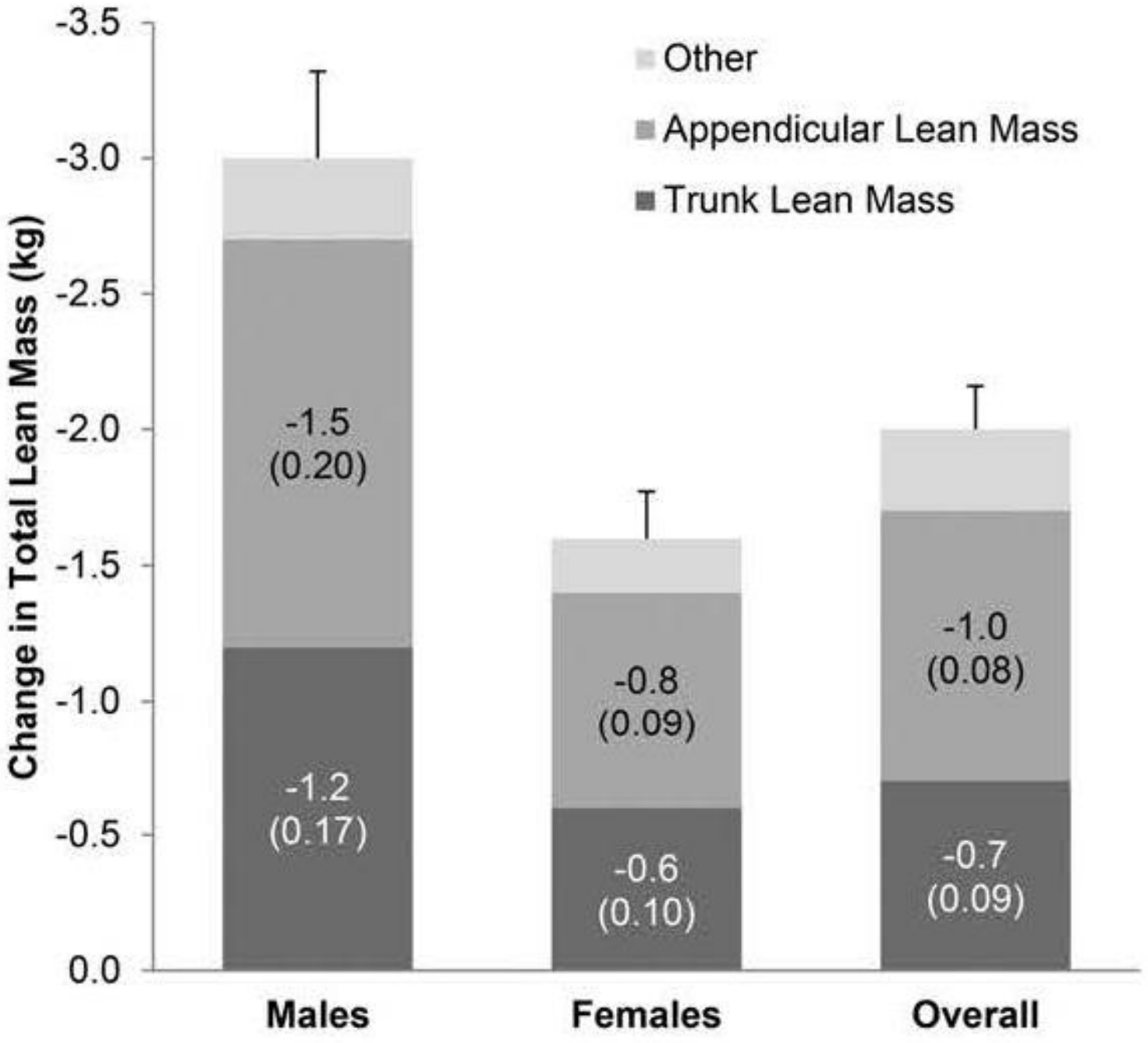
- Other Cardiovascular outcomes
  - Significantly improved
  - Secondary aging/extrinsic factors



Ravussin 2015 J Gerontol A Biol Sci Med Sci

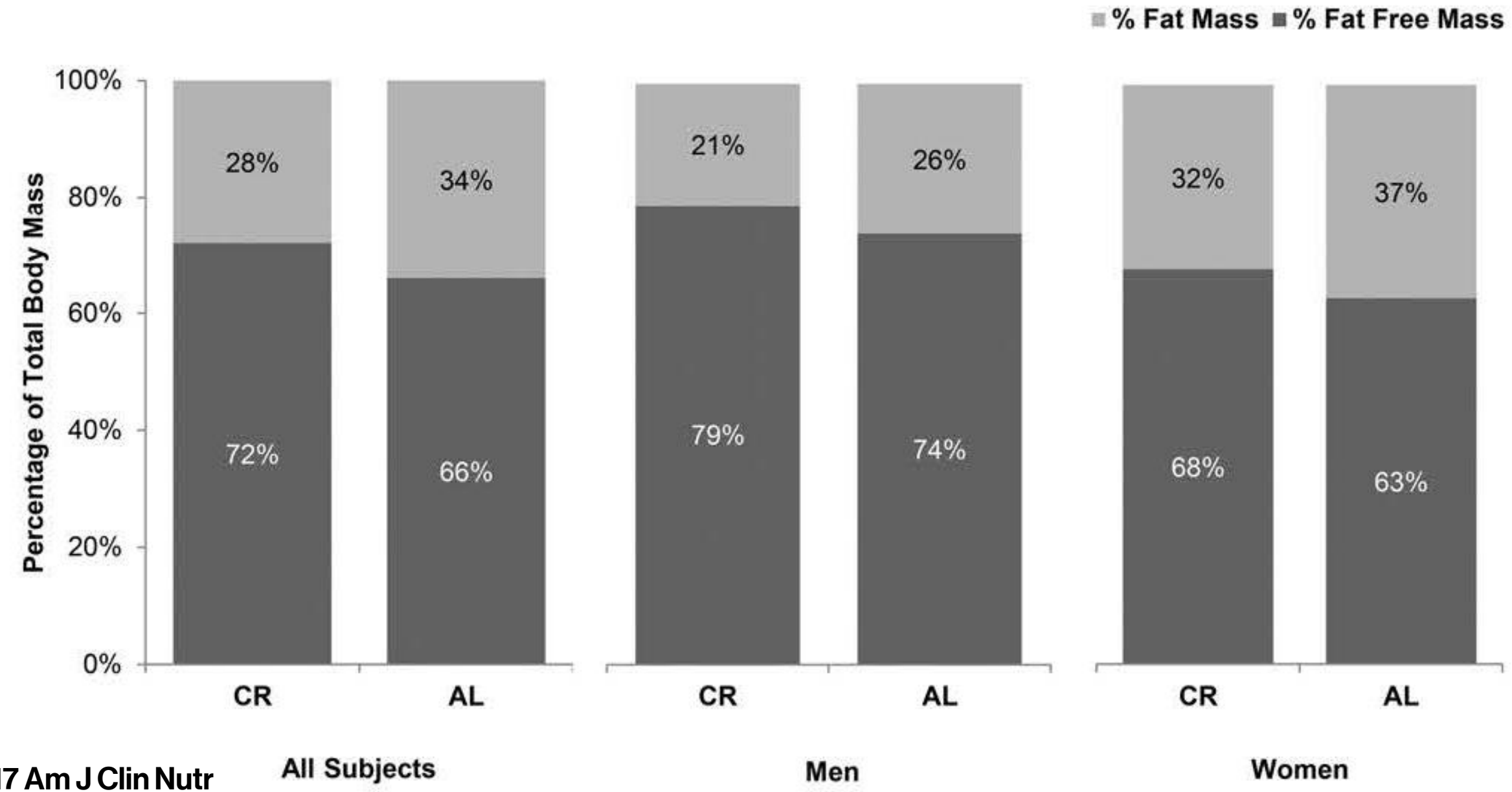
CALERIE II

Significant loss of lean mass



Das 2017 Am J Clin Nutr

CALERIE II Lean mass loss relatively proportional to overall mass loss



Das 2017 Am J Clin Nutr

Summary of the Evidence

Preclinical

- Calorie restriction is the only non-genetic method that extends lifespan in every species studied (50–300%)
  - Variability between and among species exist.
  - Translation to human remains in question.

Human Observational

- Calorie restriction reduces age-related disease and mortality risk.
- Improves secondary aging,
- Impact on primary aging suggestive, but unclear.

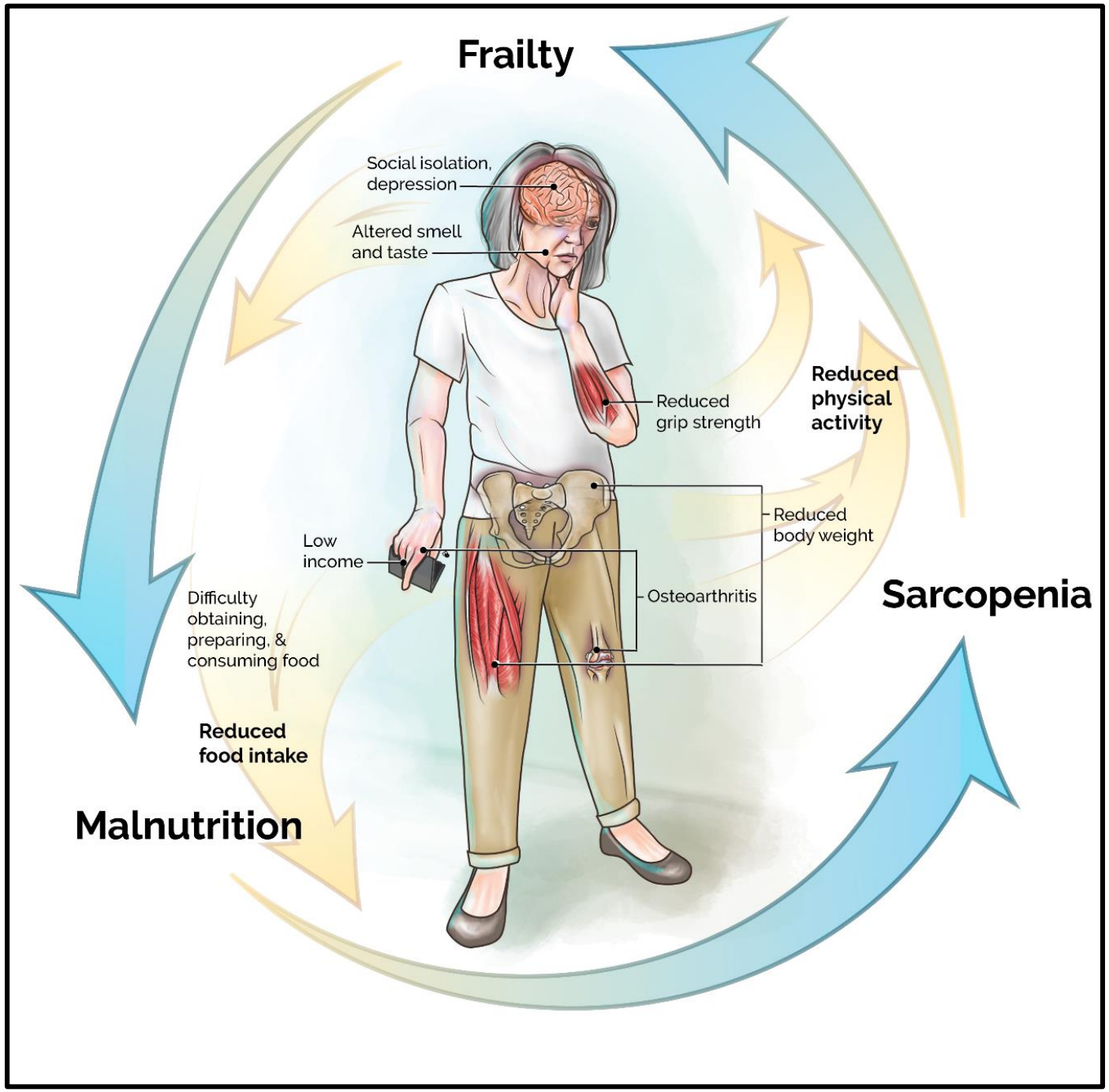
Clinical Trials

- **Prolonged calorie restriction is safe and tolerated well**
  - Appears to improve some mechanisms of primary aging
  - Reduces biomarkers related to age-related disease and secondary aging
  - No incidence of eating disorder development
- **Few clinical trials have been conducted**

Williamson 2008 Health Psychol.

Concerns & Caveats

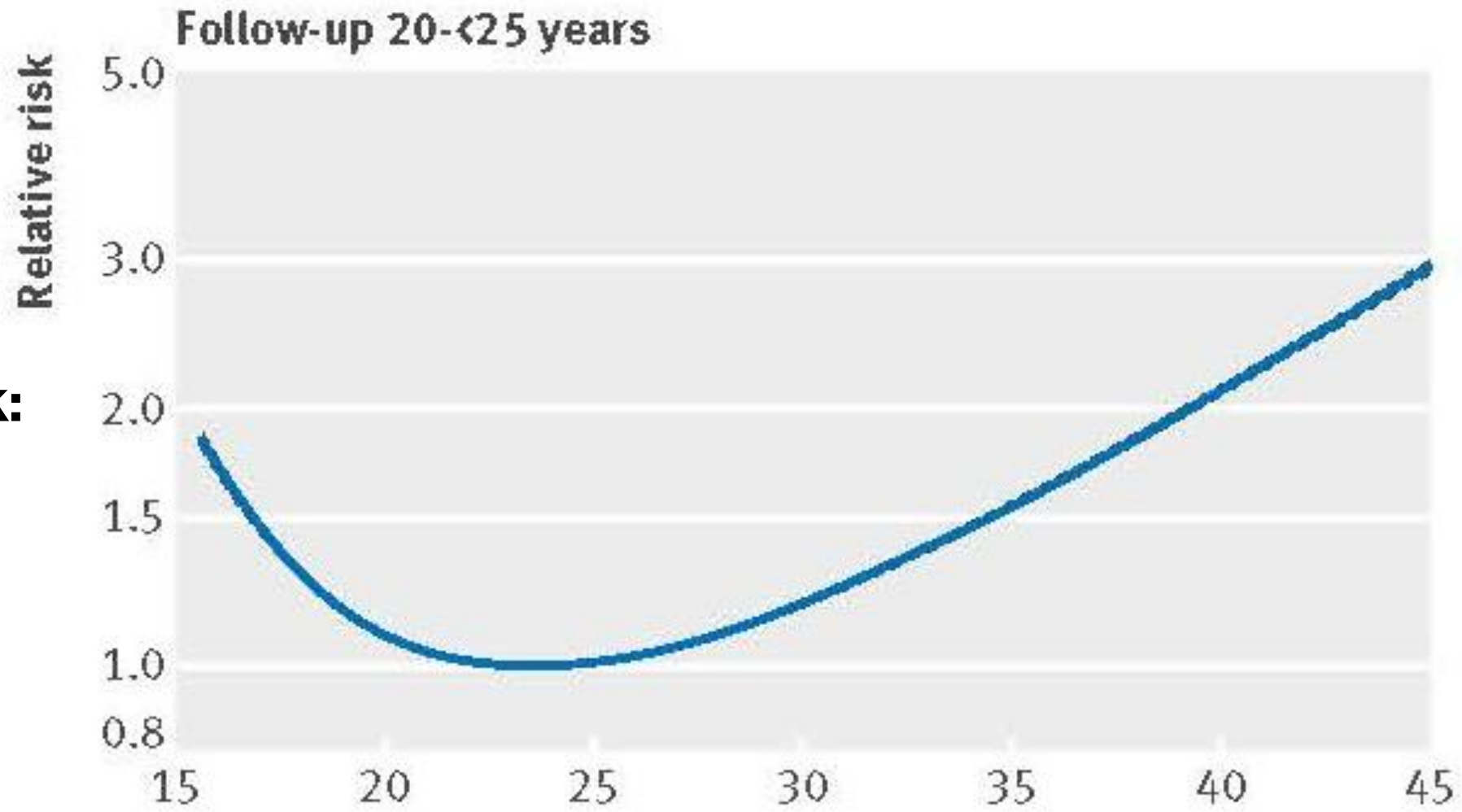
- Loss of bone mineral density
- Loss of muscle mass
- Sarcopenia definition only recently defined and ICD10 established



Severin 2018 Topics in Geriatric Rehabilitation

Concerns and Caveats: Protective effects of BMI

Lowest mortality risk:
BMI 23-25 kg/m²

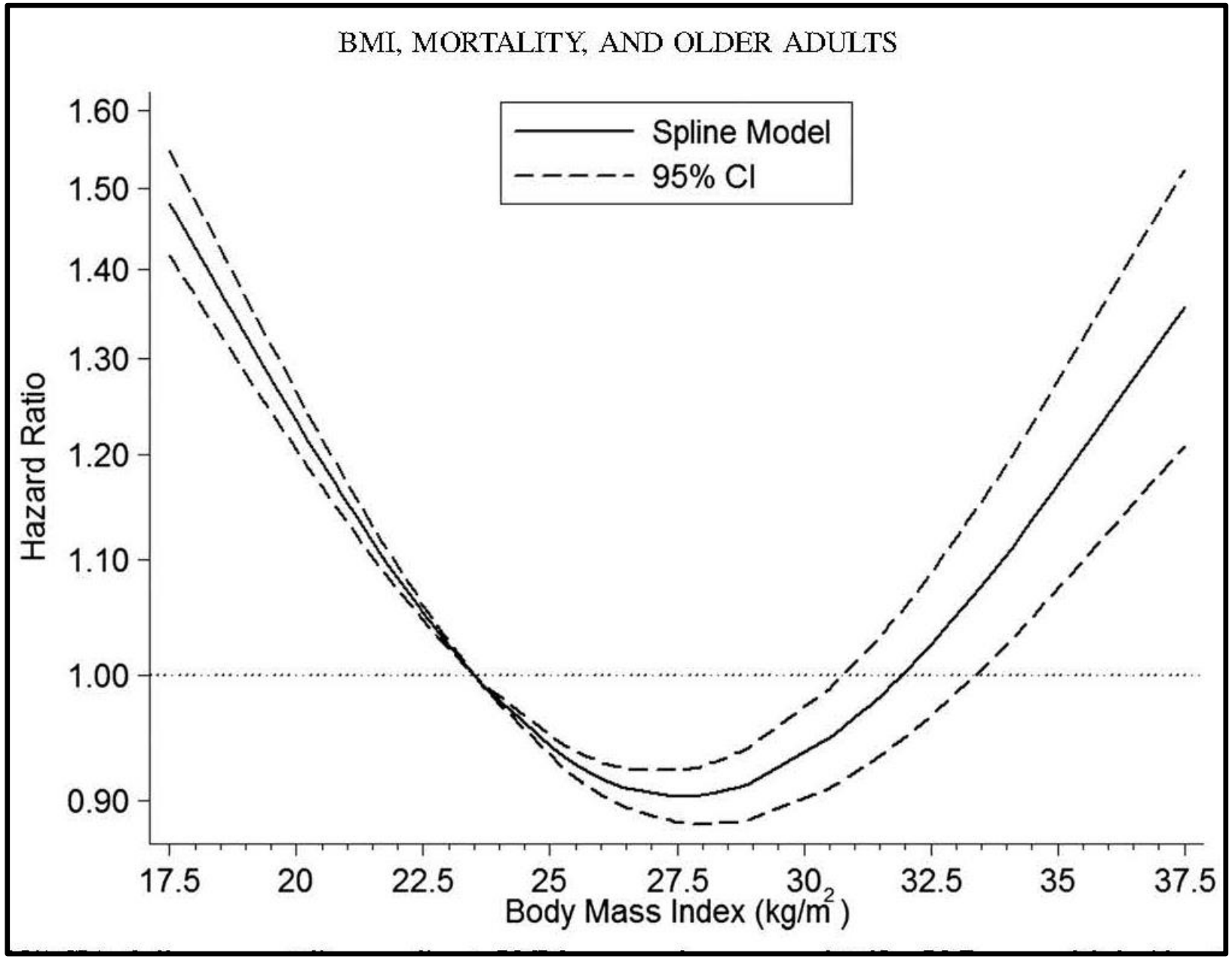


Aune 2016 Br Med J

Concerns and Caveats: Protective effects of BMI

Right-shifted in Aging

Lowest mortality risk: BMI 27-28 kg/m^2

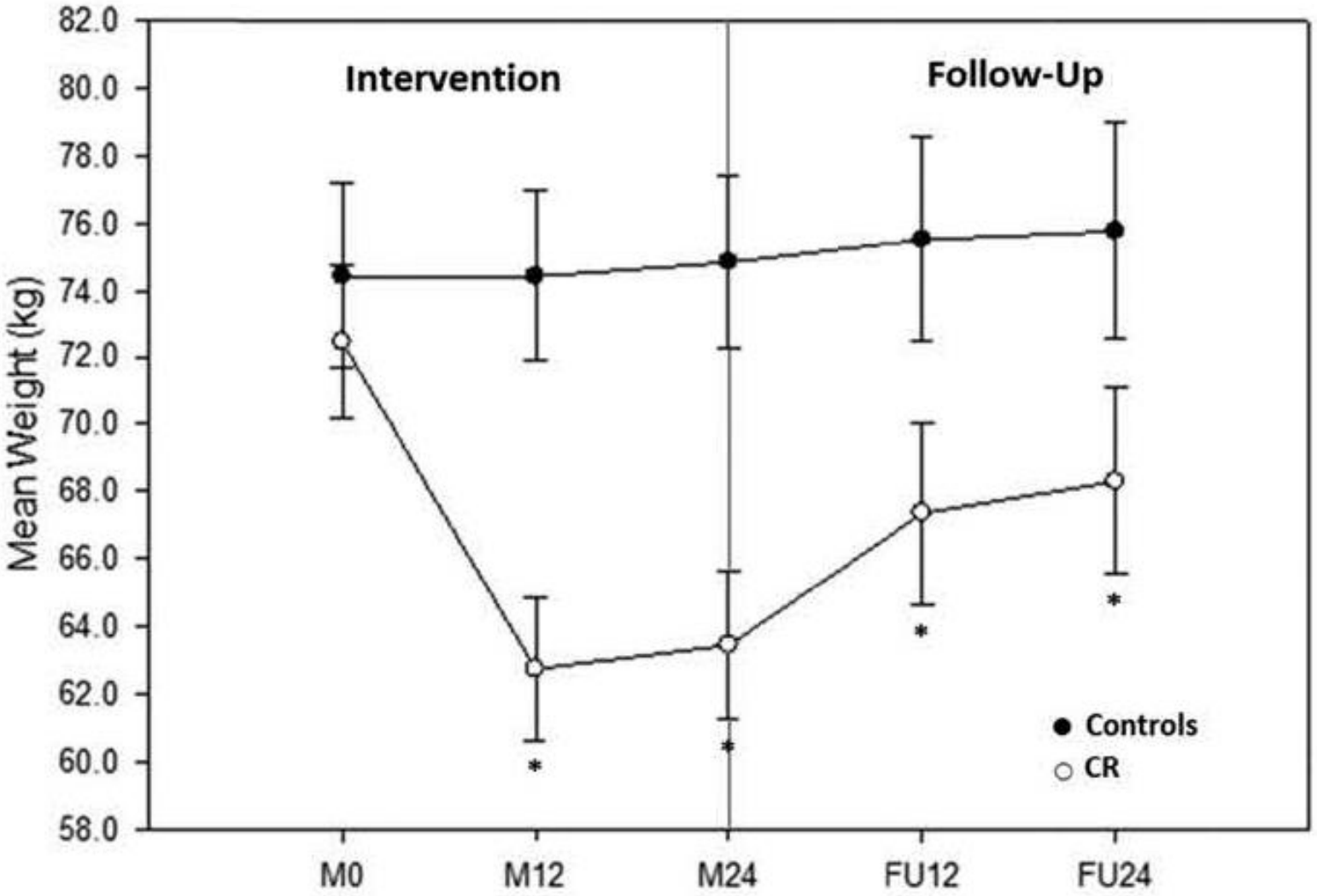


Winter 2014 Am J Clin Nutr

Concerns and Caveats: Restriction Forever or Bust?

~50% lost weight was ...

Maintained vs Regained

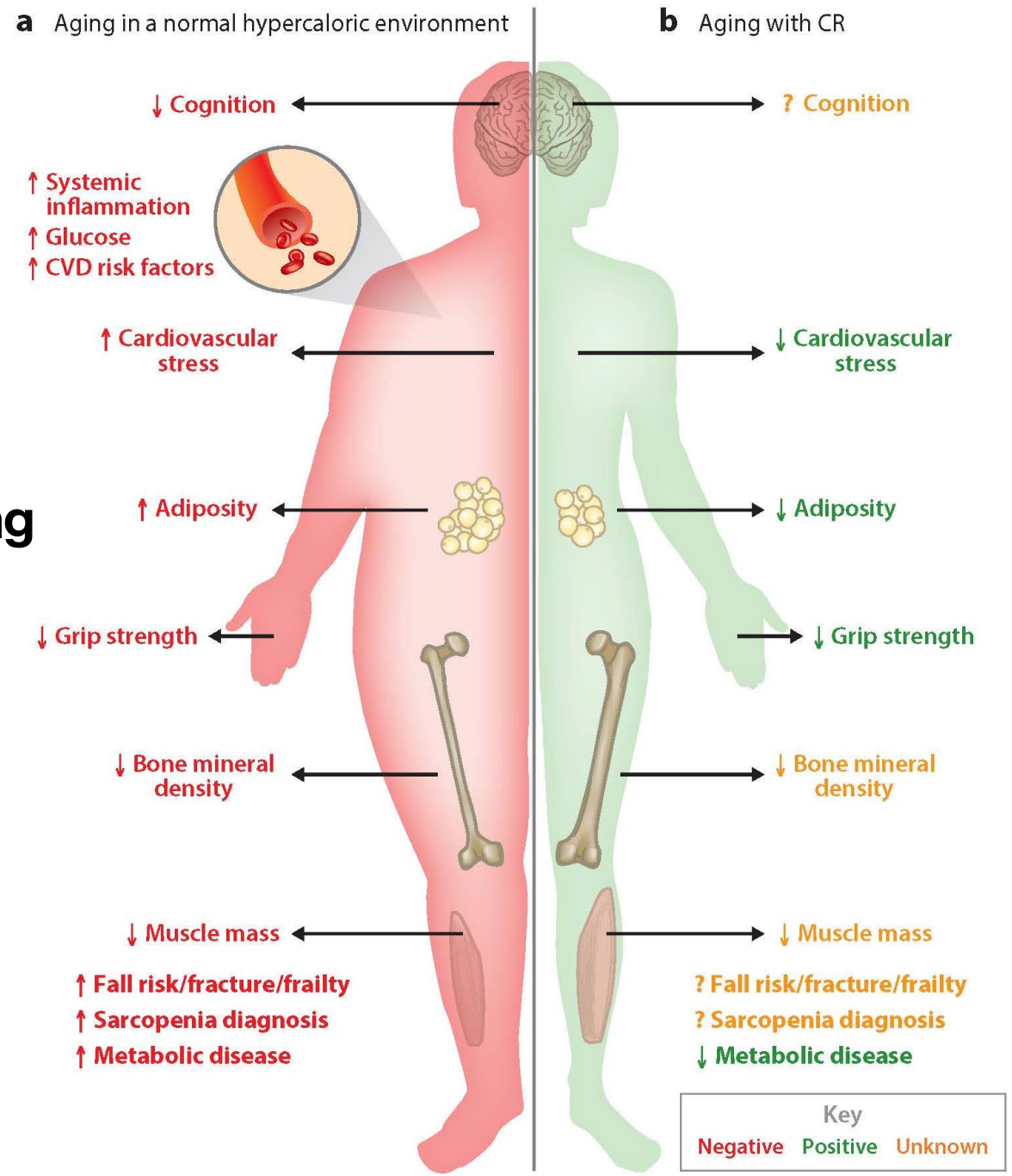


Marlatt 2017 Am J Clin Nutr

Overall State of the Evidence

Additional Limitations:

- Inherent issues to longevity research
- Variable effect on different factors of aging
- Few clinical trials



Flanagan 2020 Ann Rev Nutr

Take-home Message

- **Prolonged calorie restriction:**
  - Increases lifespan in preclinical models
  - Is viable in humans
  - Is the only approach evidenced (not proven) to slow primary aging
  - Consistently improves factors of secondary aging in humans
  - Has significant limitations and concerns

Deciphering a Clinical Application

- Flys, worms, mice = 50-300% increased lifespan
- Rhesus monkeys = 0-25% increased median survival
- Bluezones/Okinawa/CRONies = increased mean survival, reduced disease
- Minnesota Starvation Study = Critical concept
  - calorie restriction must come with optimal nutrition
- CALERIE I & II = Calorie restriction in healthy humans:
  1. is the only intervention that impacts facets of primary aging
  2. produces profound benefits on secondary aging
     - 10-15% caloric restriction w/ optimal nutrition
     - May be less useful to initiate as an older adult (65+)

Potential Clinical Utility

Thank you!

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