WEBINAR | Stronger Longer: Muscle Mass and Aging

afar american federation for aging research

NIH National Institute on Aging

nextavenue where grown-ups keep growing

American Federation of Aging Research Webinar 26September2019

Stronger, Longer
Muscle Mass & Aging

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@NKLeBRASSEUR

Strength

Lasha Talakhadze
2016 Olympic Games
258 kg dead lift
Image: Fernando Frazão/Agência Brasil

Image: Clive Brunskill/Getty Images

Image: Paul Childs/Reuters

Endurance

Eliud Kipchoge
2019 London Marathon
2:02:37 (4:41/mile)

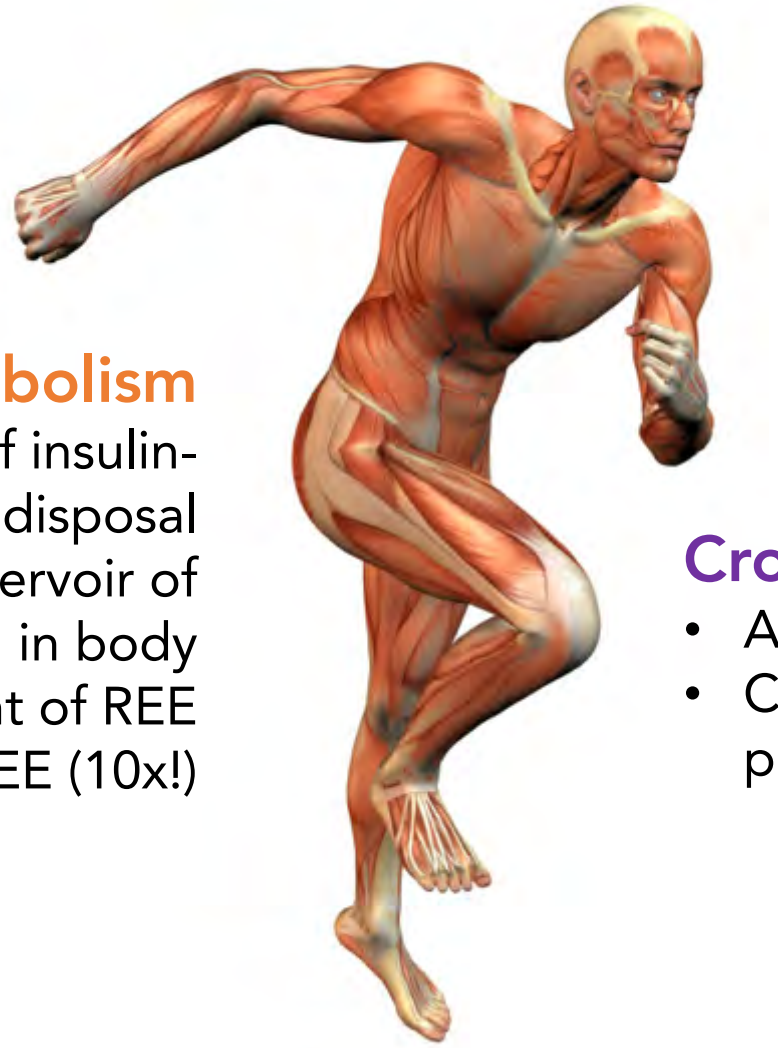
Beyond Superhumans: Why Muscle Matters

Physical Performance

- Powers movement
- Enables activity/function

Metabolism

- Primary sight of insulin-mediated glucose disposal
- Largest reservoir of glycogen in body
- Primary determinant of REE and driver of AEE (10x!)



Resilience

- Strength and mobility predict resistance to, and recovery, from stressors
- More muscle = better medical/surgical outcomes

Cross-talk

- An endocrine organ: "myokines"
- Communicates with liver, brain, pancreas, adipose tissue, bone….

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Aversa et al., *Bone*, 2019

Image: Leslie Samuel, Interactive Biology

Threats to Skeletal Muscle Health

Aging (sarcopenia)

Chronic disease (cachexia)

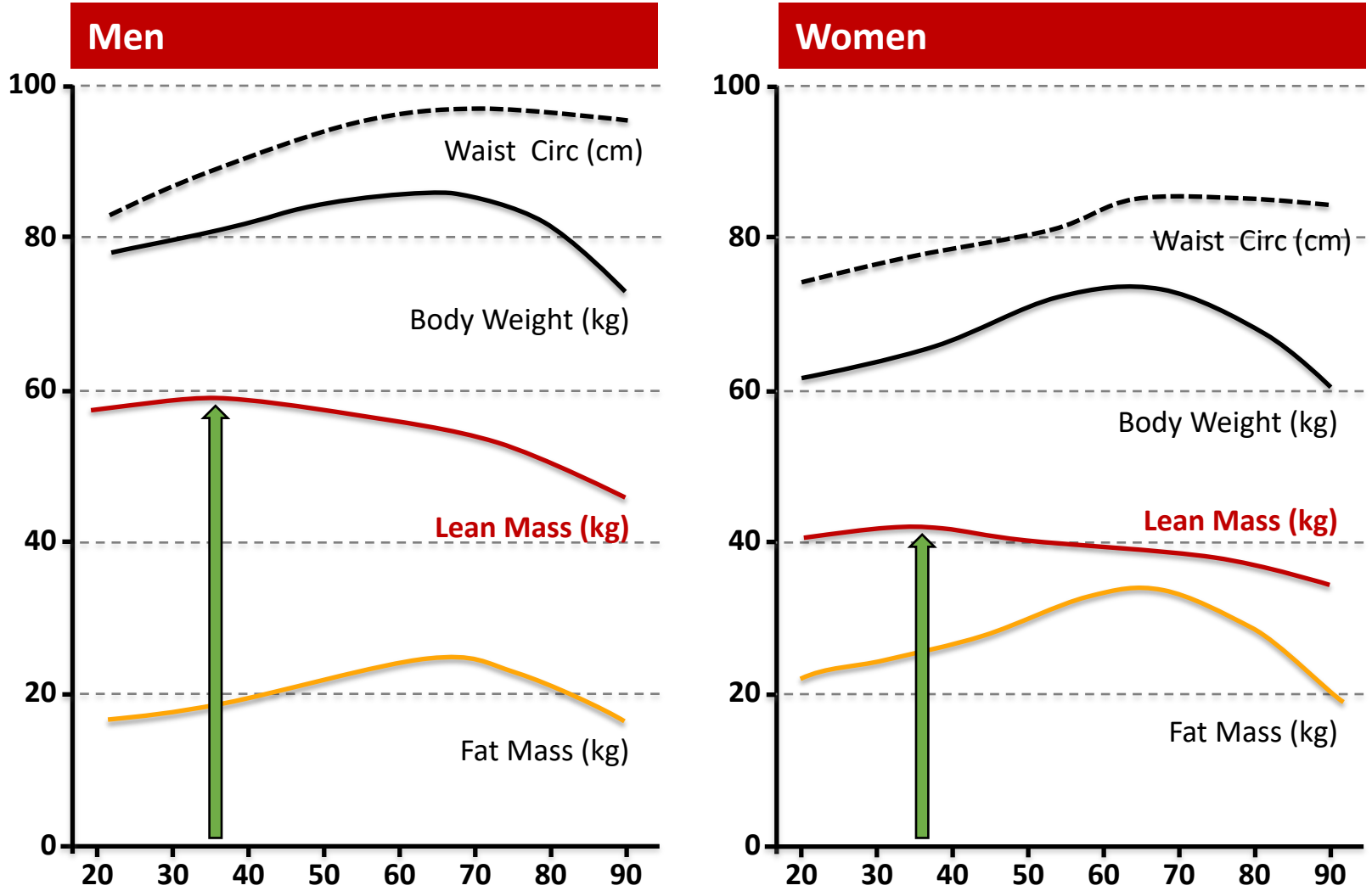
Inactivity (disuse)

Congenital disease (degeneration)

Obesity (lipotoxicity)

Skeletal Muscle: An Early Casualty of Aging

Baltimore Longitudinal Study of Aging (Luigi Ferrucci)
1300 subjects, 5200 longitudinal observations



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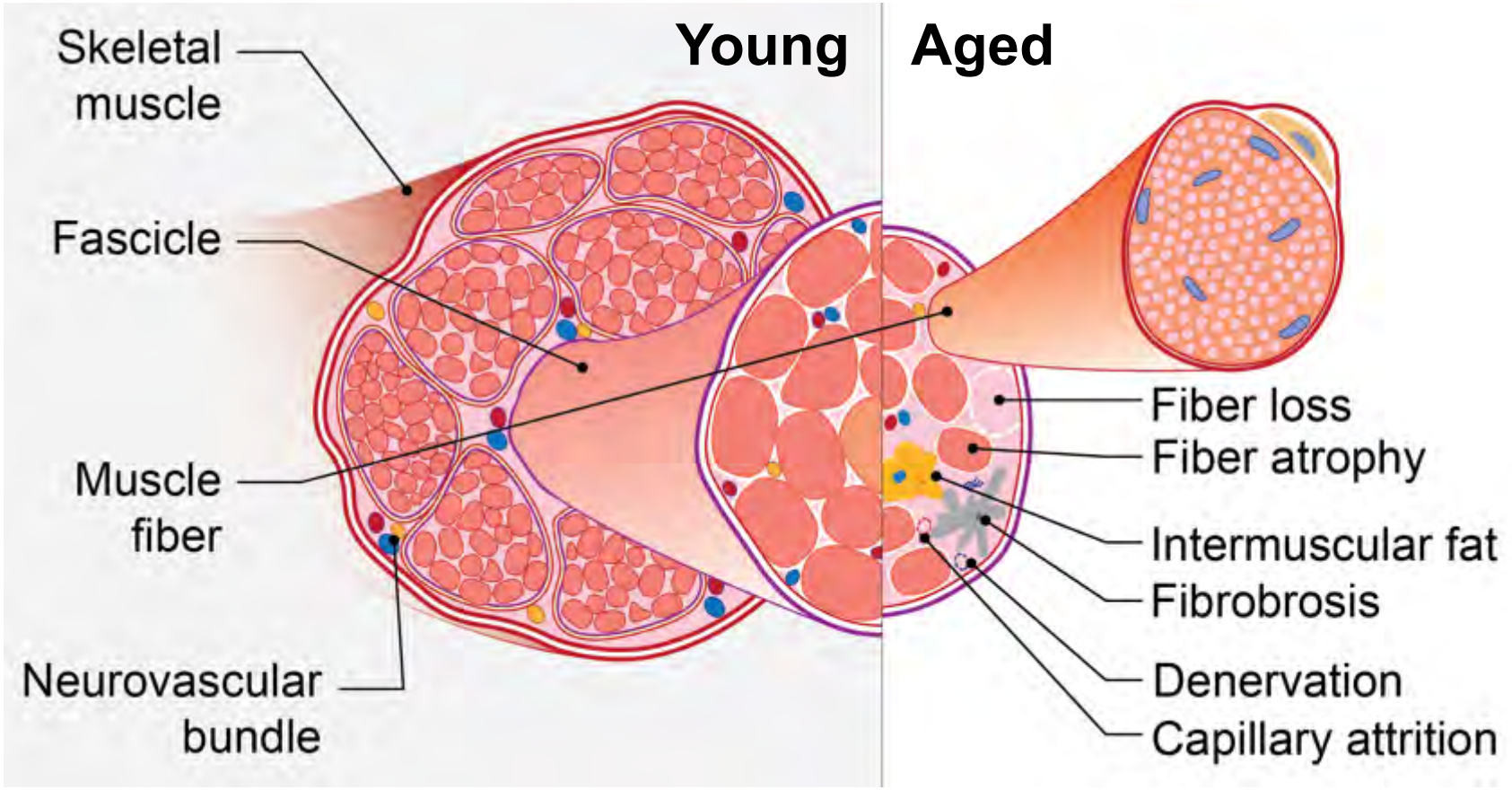
Sarcopenia- poverty (penia) of the flesh (sarx)

The Age-Related Loss of Skeletal Muscle Mass and Function

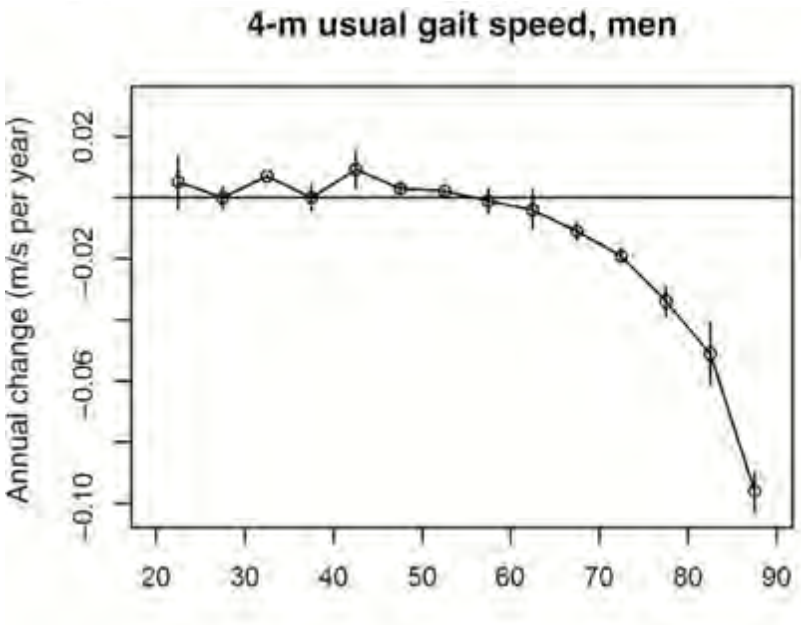
Image: Leslie Samuel
Interactive Biology

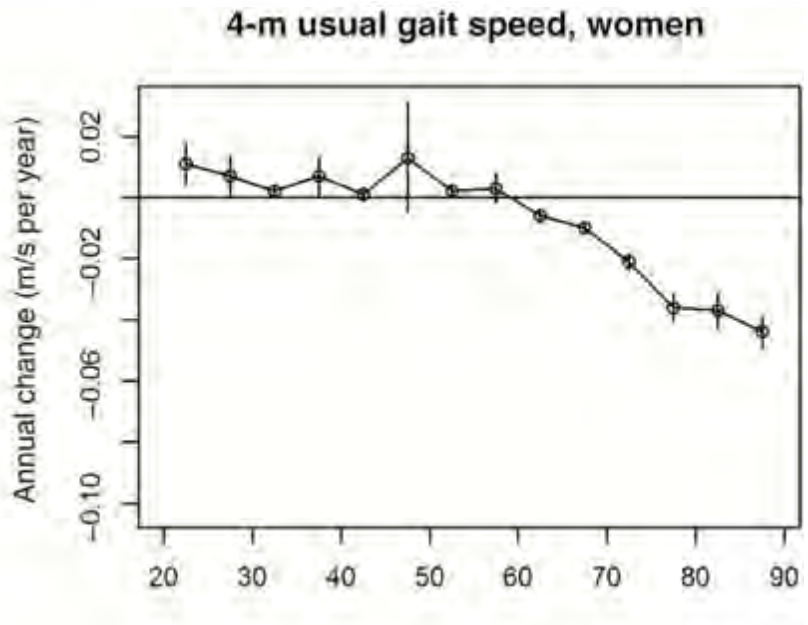


Aversa et al., *Bone*, 2019

Sarcopenia
The Age-Related Loss of Skeletal Muscle Mass and Function

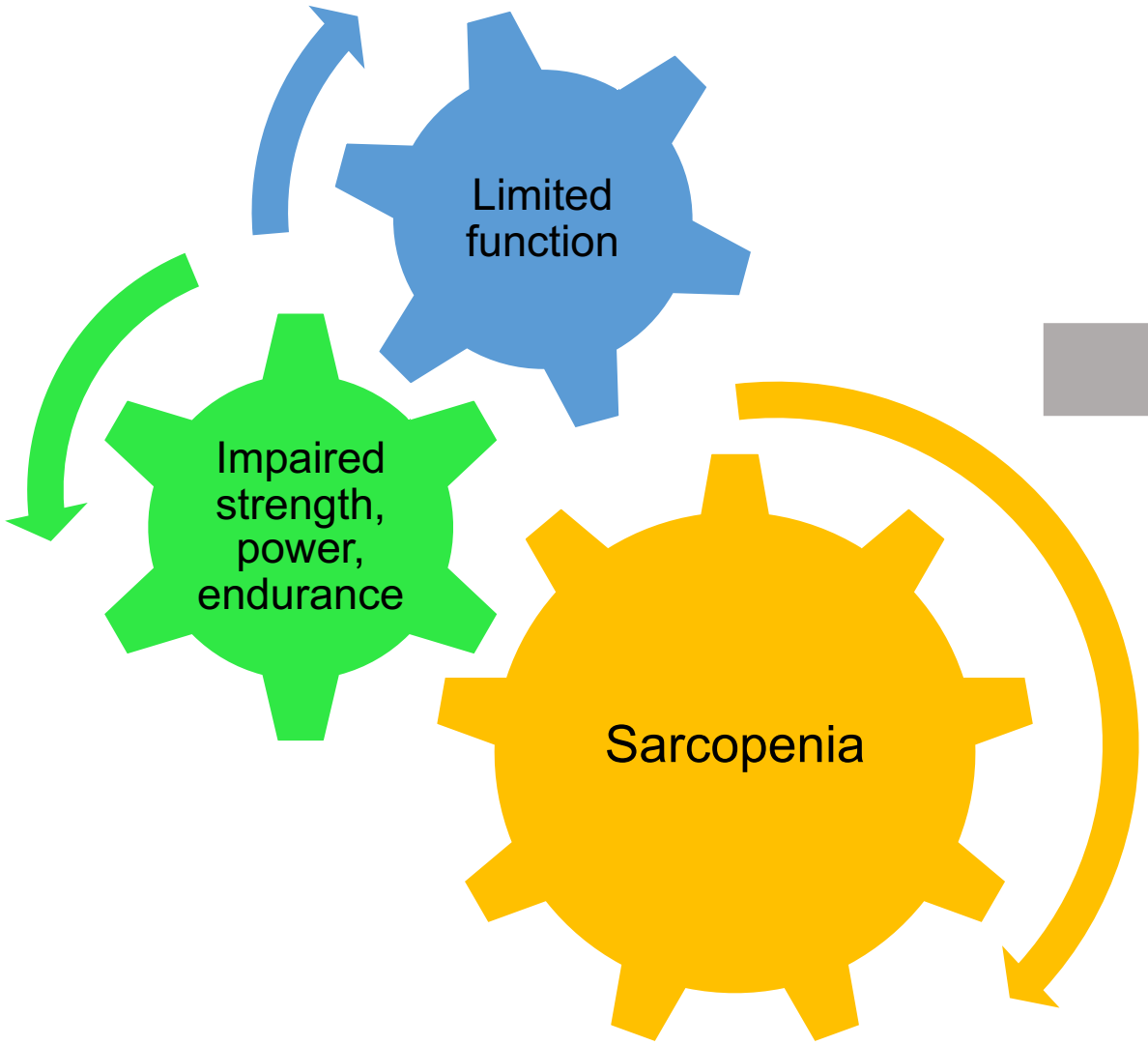
Image: Leslie Samuel
Interactive Biology





Ferrucci et al., *J of Gerontolgy*, 2016

The Impact of Sarcopenia

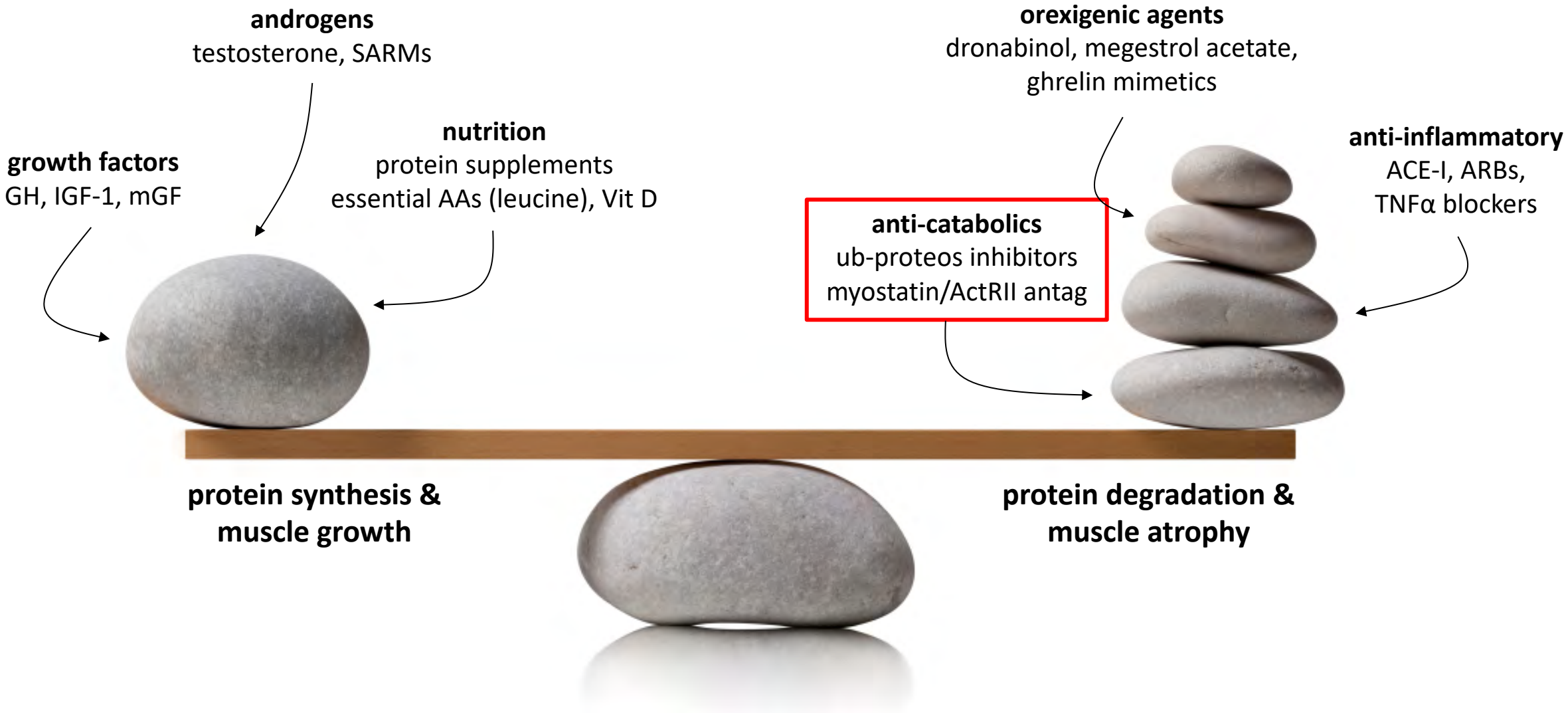


Falls
Disability
Institutionalization
Death

$19B

Janssen, *J Am Geriat Soc*, 2004

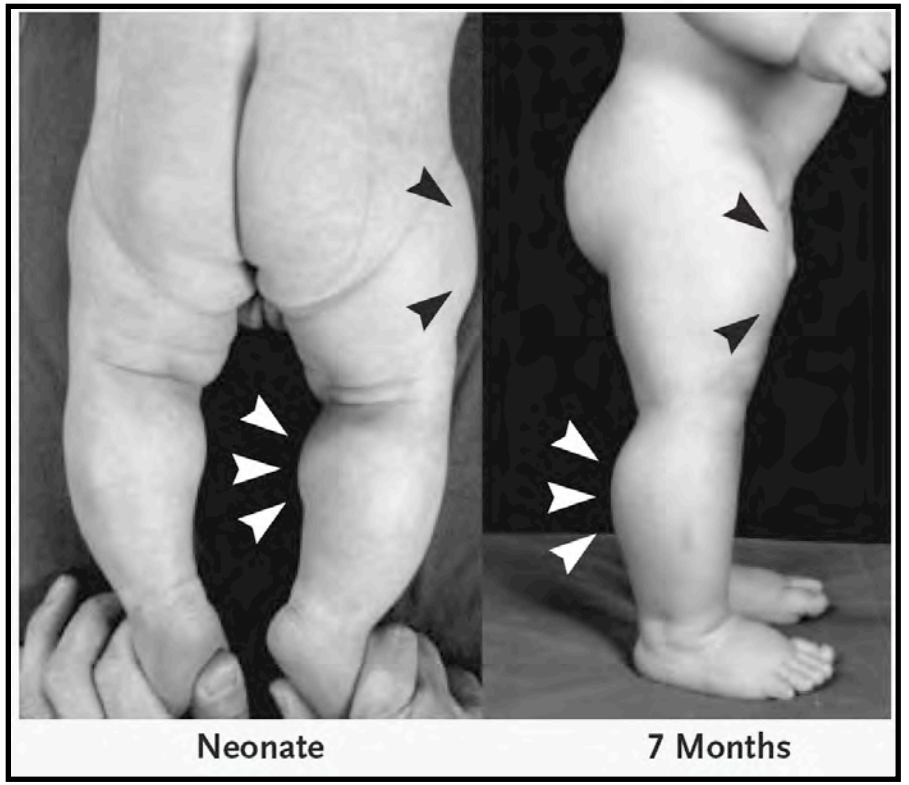
Pharmacological "Growth Promoting" Strategies for Sarcopenia



Myostatin (GDF-8): *A highly conserved and powerful negative regulator of muscle mass*

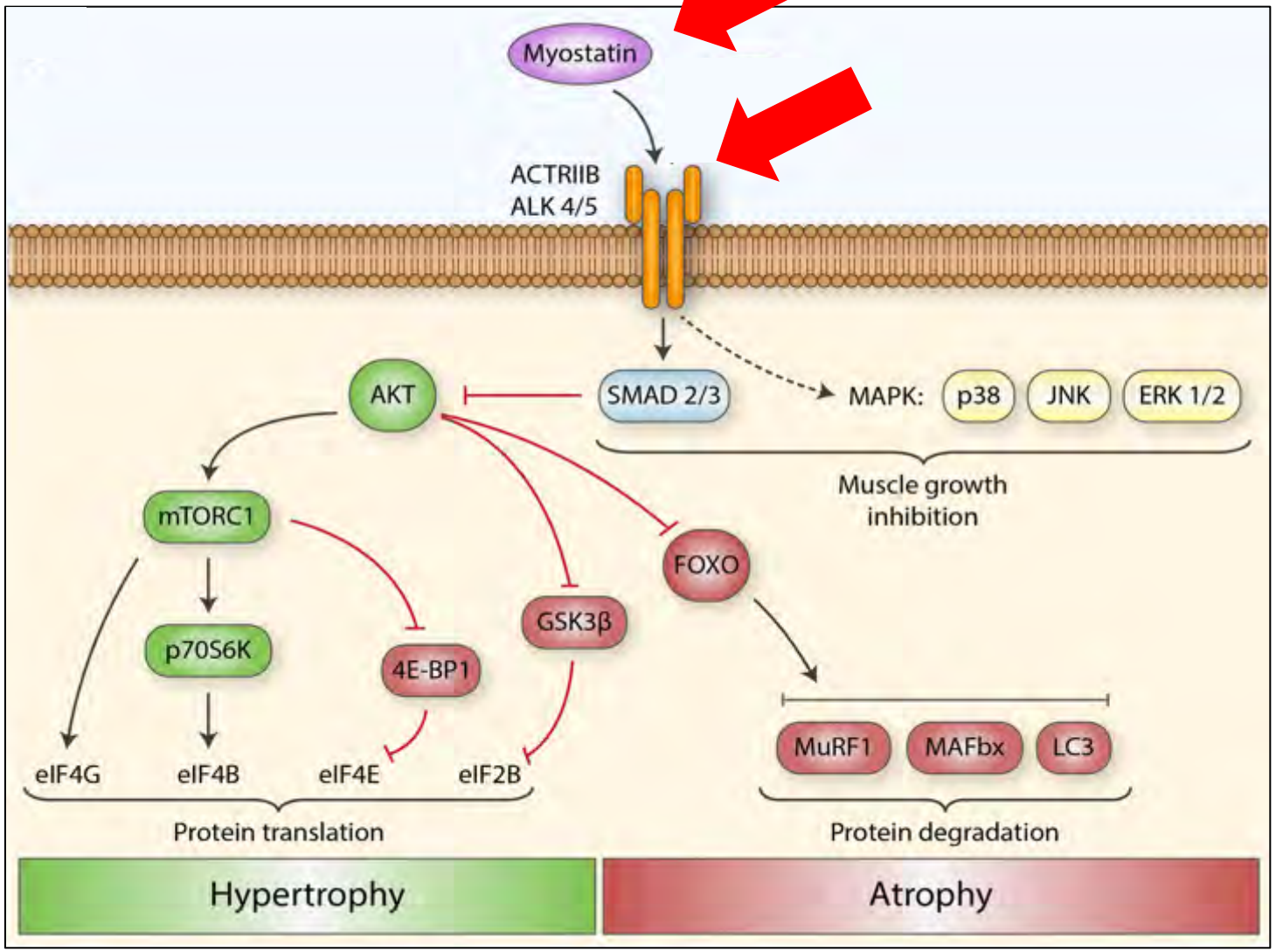
Myostatin Mutation Associated with Gross Muscle Hypertrophy in a Child

Markus Schuelke, M.D., Kathryn R. Wagner, M.D., Ph.D., Leslie E. Stolz, Ph.D., Christoph Hübner, M.D., Thomas Riebel, M.D., Wolfgang Kömen, M.D., Thomas Braun, M.D., Ph.D., James F. Tobin, Ph.D., and Se-Jin Lee, M.D., Ph.D.



New Engl J Med, 2004

Pharmacological Strategies to Inhibit Myostatin Signaling



Adapted from Brun & Rudnicki, Cell Metabolism, 2015

Targeting Myostatin: Preclinical Promise

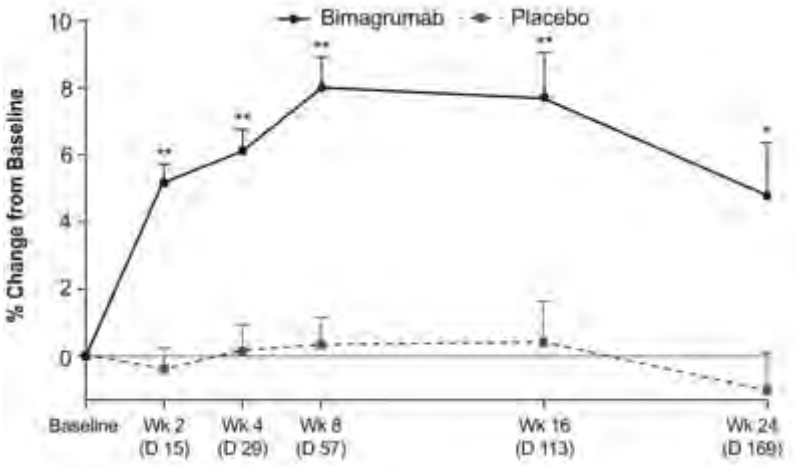
- Increased **muscle mass and function** in mouse models of aging and disease
- Improved **body composition and metabolism** in models of obesity/diabetes
- Enhanced **resilience** in models of cancer
- Diminished **age- and disease-associated pathology** in other organs (i.e., bone, liver, heart, blood vessels)
- Marked excitement for translation!

Myostatin Therapies in Older Adults

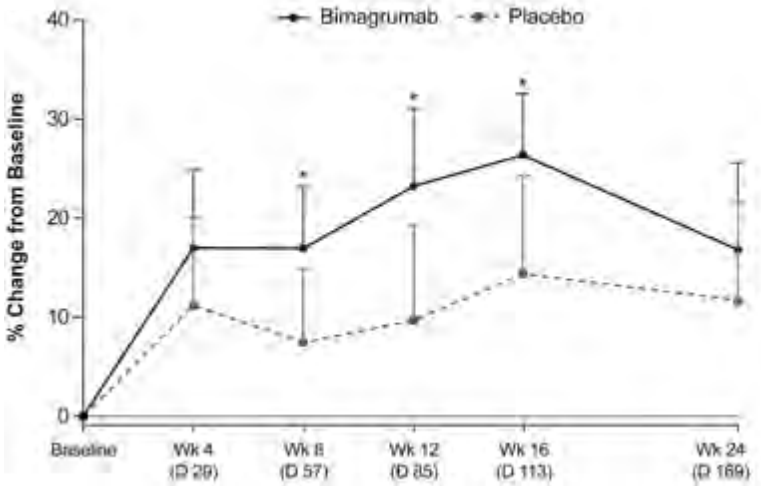
Sarcopenic (low muscle mass, slow gait speed) older adults
Placebo vs. Bimagrumab (IV infusion): 1 or 2 (day 56) doses

Rooks et al., J of Am Geriatrics Soc, 2017

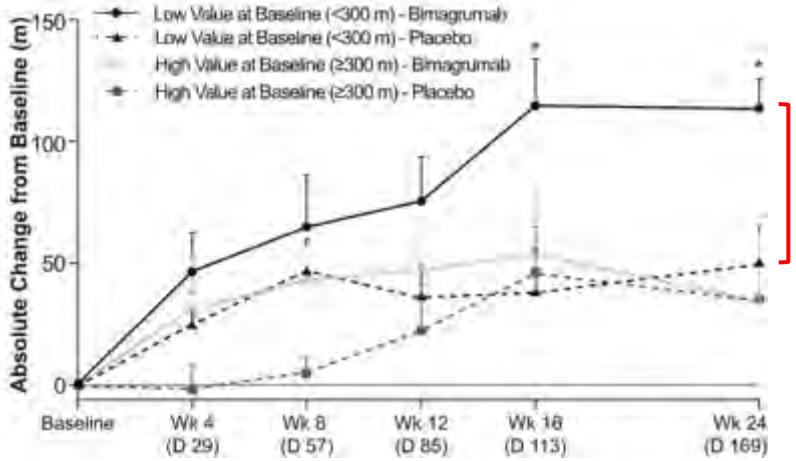
Muscle Volume



Grip Strength



6-minute Walk Distance

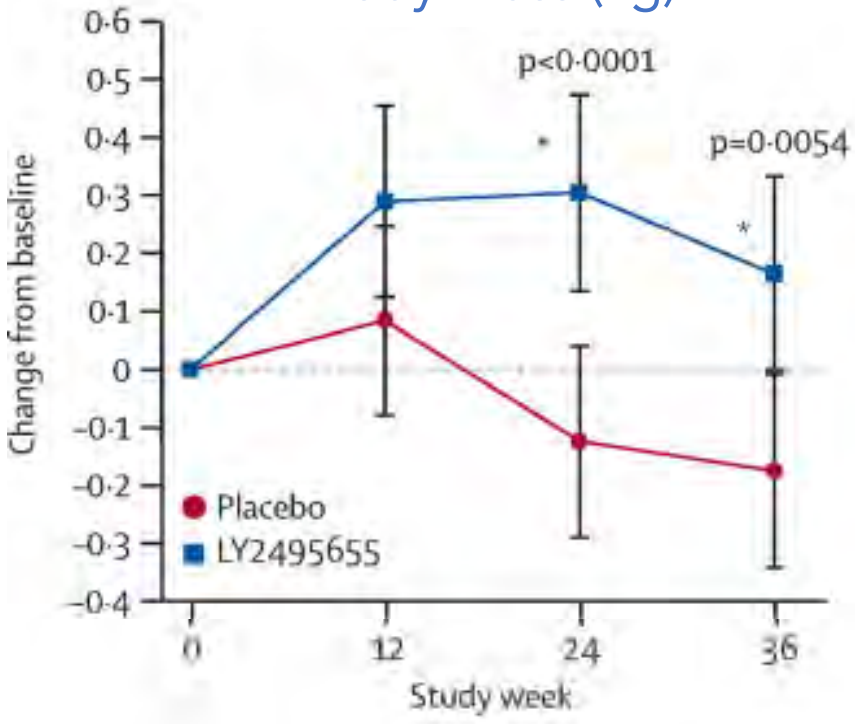


Myostatin Therapies in Older Adults

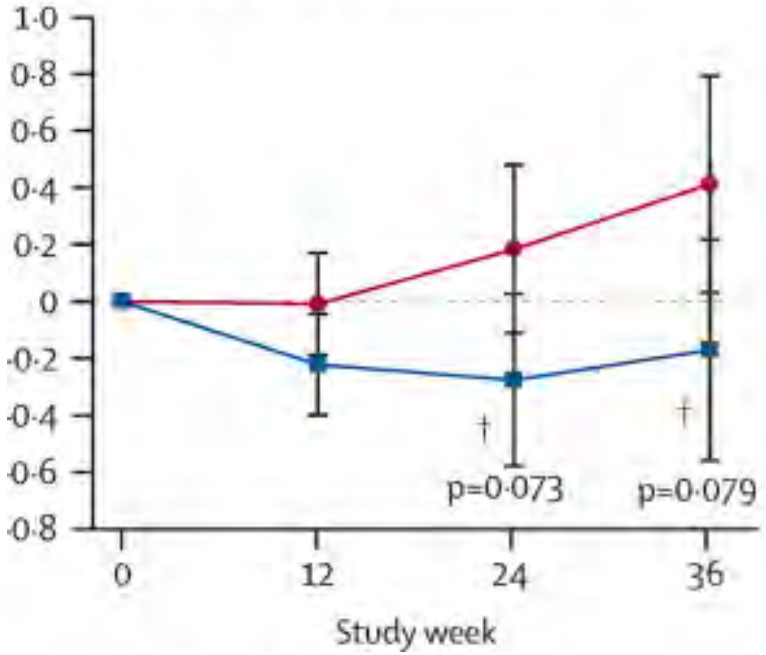
Older adults with a fall in past year
Placebo vs. LY2495655 (SQ injections): Every 4 wks x 5 weeks

Becker et al., Lancet Diabetes & Endo, 2015

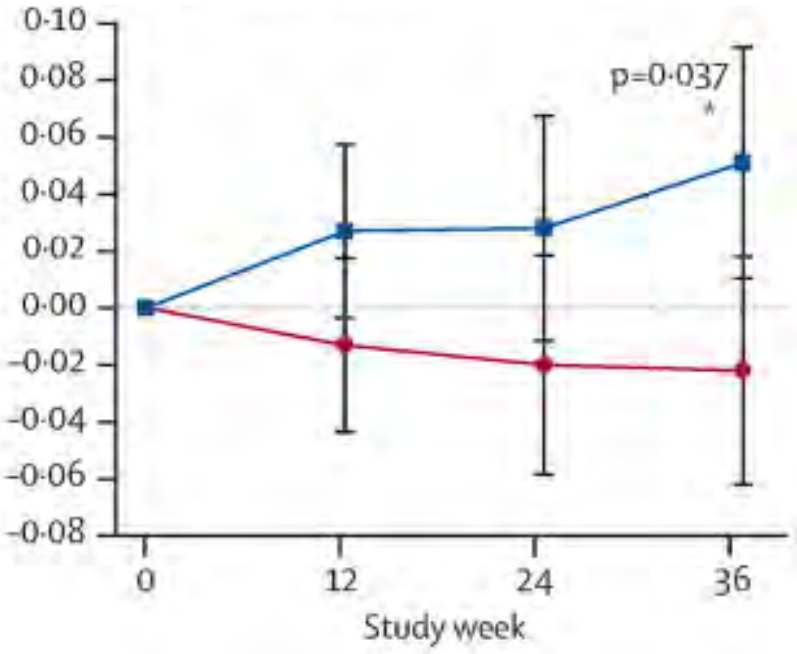
Appendicular Lean Body Mass (kg)



4-step Stair Climb Minimum Time (s)



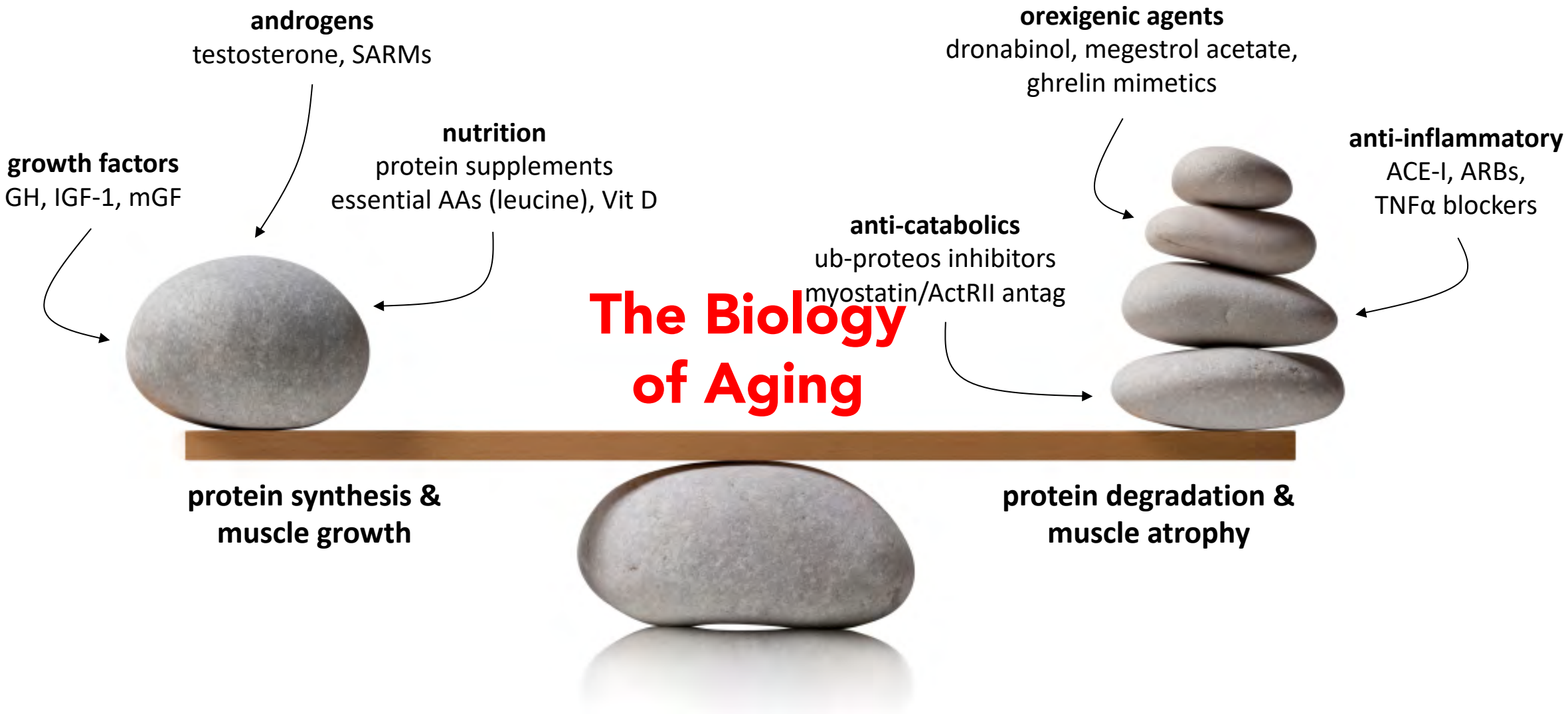
Fast Gait Speed (m/s)



Lost in Translation: Myostatin-based Therapies

- Short-term interventions exhibit moderate effects on muscle mass, but **limited effects on measures of function** (FDA)
- Some evidence that individuals who exhibit best response are **most affected** by sarcopenia. Challenging to recruit/retain in randomized clinical trials
- Agreement that pharmacological interventions are most effective when **combined with nutrition and exercise** programs. Challenging and expensive to design and run a RCT
- Future is, unfortunately, uncertain….

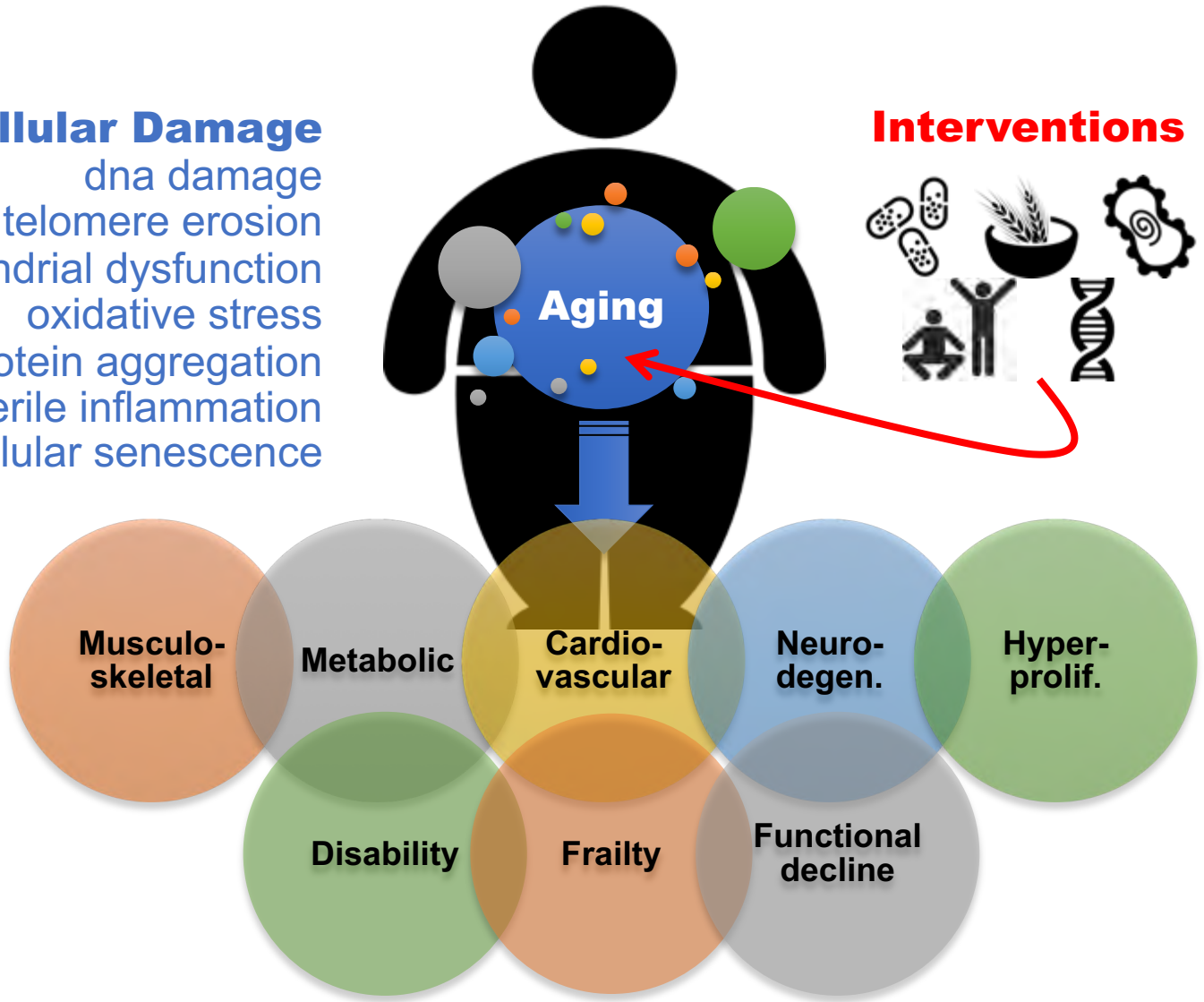
"Geroscience" Strategies for Sarcopenia and Age-related Functional Decline



What is Aging?

Molecular & Cellular Damage

dna damage
telomere erosion
mitochondrial dysfunction
oxidative stress
protein aggregation
sterile inflammation
cellular senescence



Interventions

Metformin
Rapamycin
Senolytics
….

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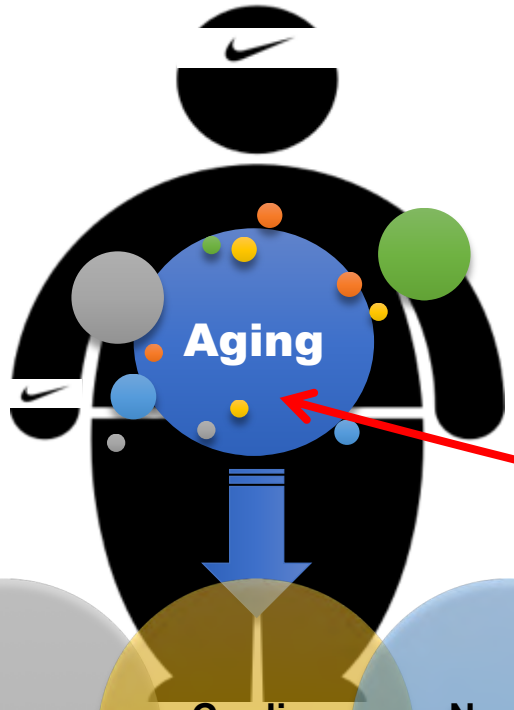
What is Aging? Can We Intervene?

Molecular & Cellular Damage

dna damage ✓
telomere erosion ✓
mitochondrial dysfunction ✓
oxidative stress ✓
protein aggregation ✓
sterile inflammation ✓
cellular senescence ✓

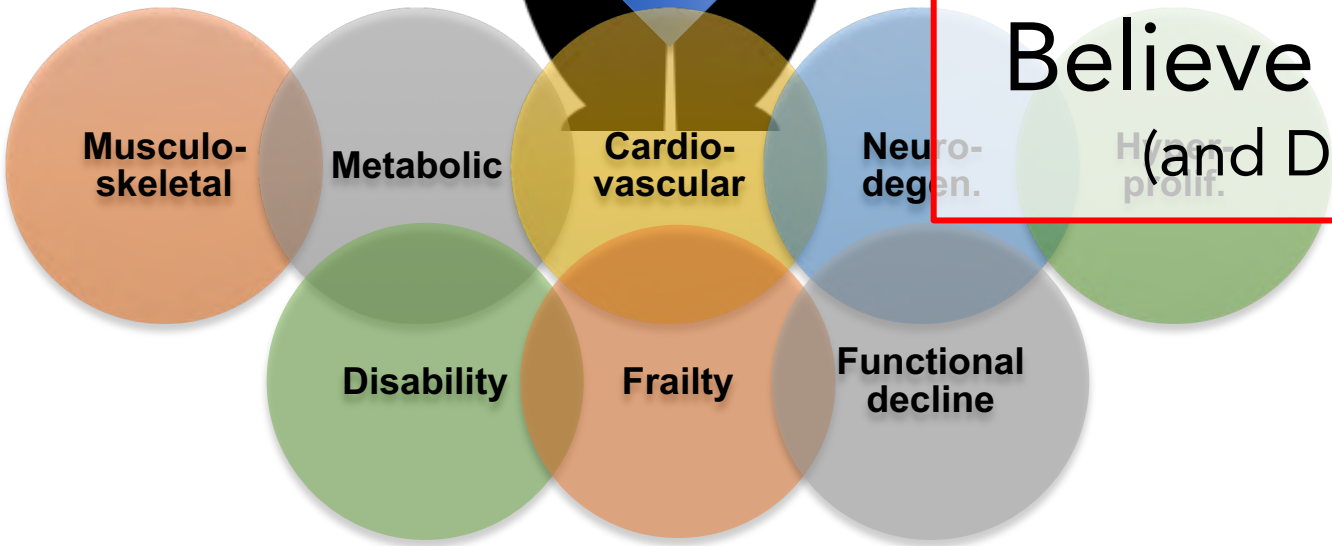


Interventions

Exercise

Believe the hype!

(and Dr. Joseph)



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Geroscience
A New Era in Science and Medicine

- Targeting the biology of aging **is a fundamentally different approach** to optimizing human health
- Interventions targeting the effects of aging hold promise for extending **human healthspan**; delaying the onset of age-related conditions as a group
- Though early, there is significant promise that such interventions will positively affect **skeletal muscle health and physical function**

American Federation for Aging Research

Stronger, Longer: Muscle Mass and Aging.

Lyndon Joseph, PhD
Division of Geriatrics and Clinical Gerontology
National Institute on Aging

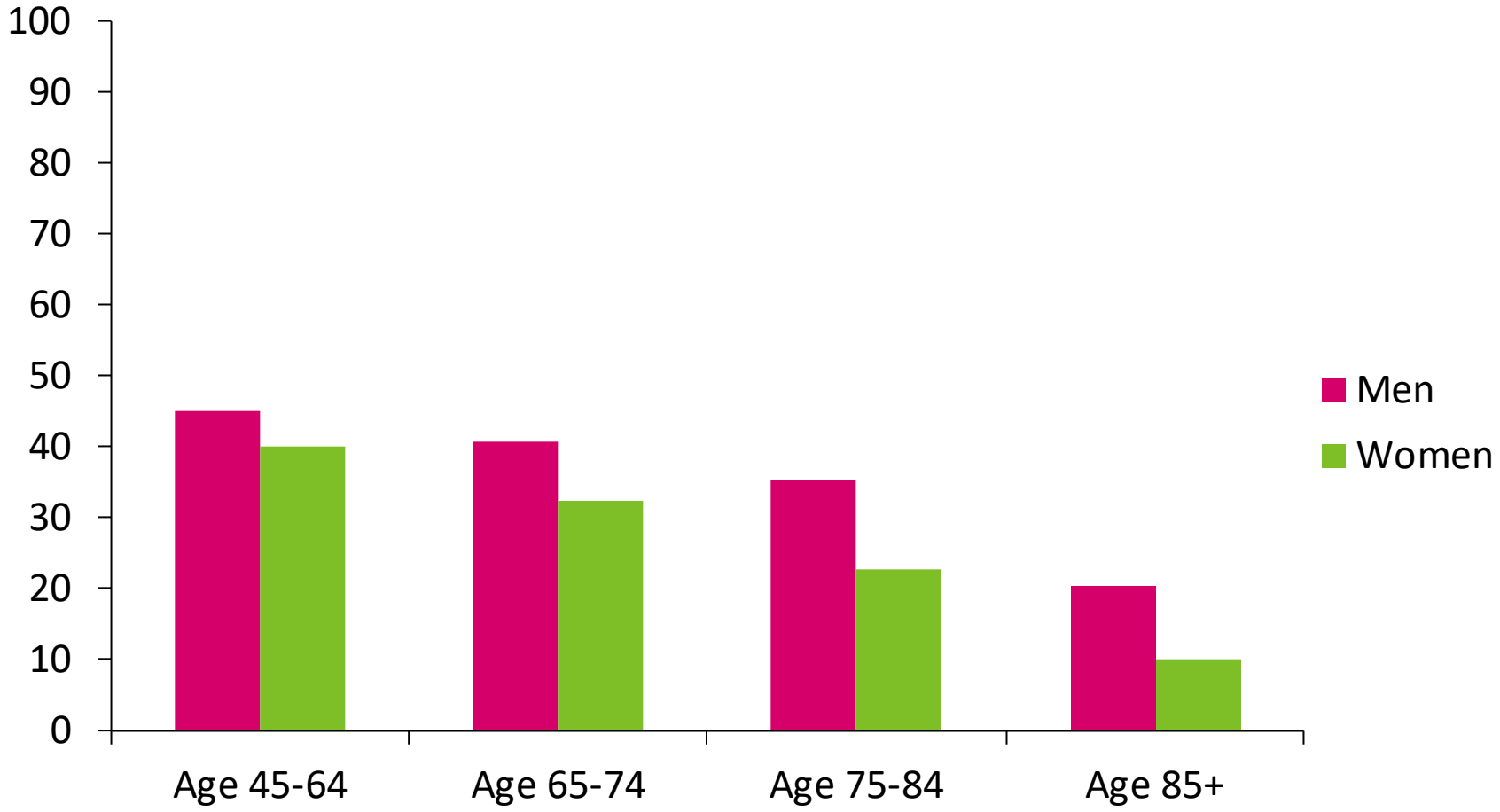
NIH National Institute on Aging

September 26, 2019

Hippocrates
(c. 460 B.C. - c. 370 B.C.)

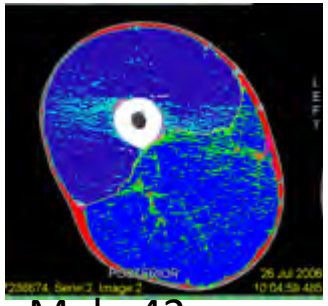
- Even when all is known, the care of a man is not yet complete, because eating alone will not keep a man well; he must also take exercise. For food and exercise, while possessing opposite qualities, yet work together to produce health.

Percentage of people age 45+ who reported engaging in regular leisure-time physical activity (by age group, 1998-2009)

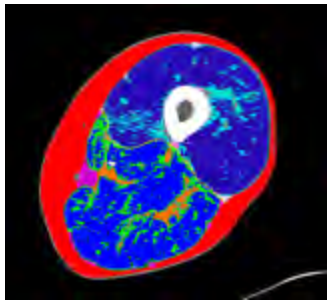


Source: CDC, National Center for Health Statistics, National Health Interview Survey 2007-2008

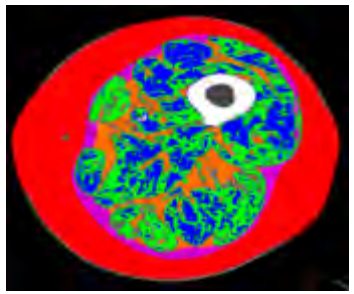
Sarcopenia: Age-associated loss in muscle mass and function



Male 43 yrs.



Male 76 yrs.



Male 85 years

- Associated with weakness & poor physical function
  - **Difficulty in rising from a chair**
  - **Problems with climbing stairs**
  - **Impaired gait/walking**
  - **Increased Falls**
- Associated with lower survival
- Loss of independence
- Reduce quality of life
- Important for Skeletal Health
  - **Osteoporosis**
  - **Vertebral compression fractures**

Muscle quality affects performance:
muscle size & composition are affected with age and mobility limitation

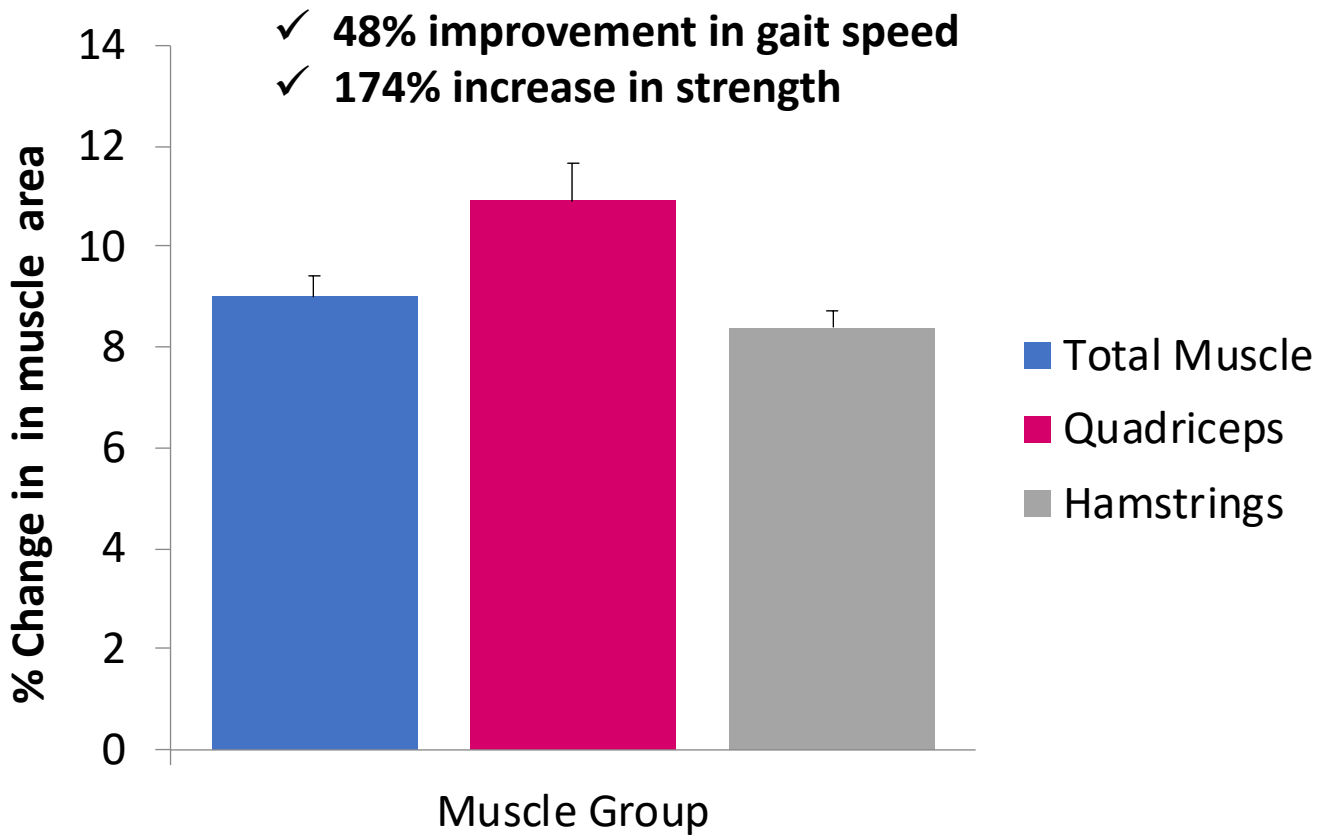
Mobility disability in the US in 2010

- About 23.9 million people living in the community had difficulty walking a quarter mile or 400m, including 13.1 million who could NOT perform the activity

- Among individuals aged 65 and older living in the community, about 15.2 million (39.4 percent) had difficulty with ambulatory activities, of which 11.2 million had sever difficulty

US Census Bureau, Current Population Reports, MW Brault, July 2012, P70-131

High-intensity progressive strength training in frail, 90-yr-olds



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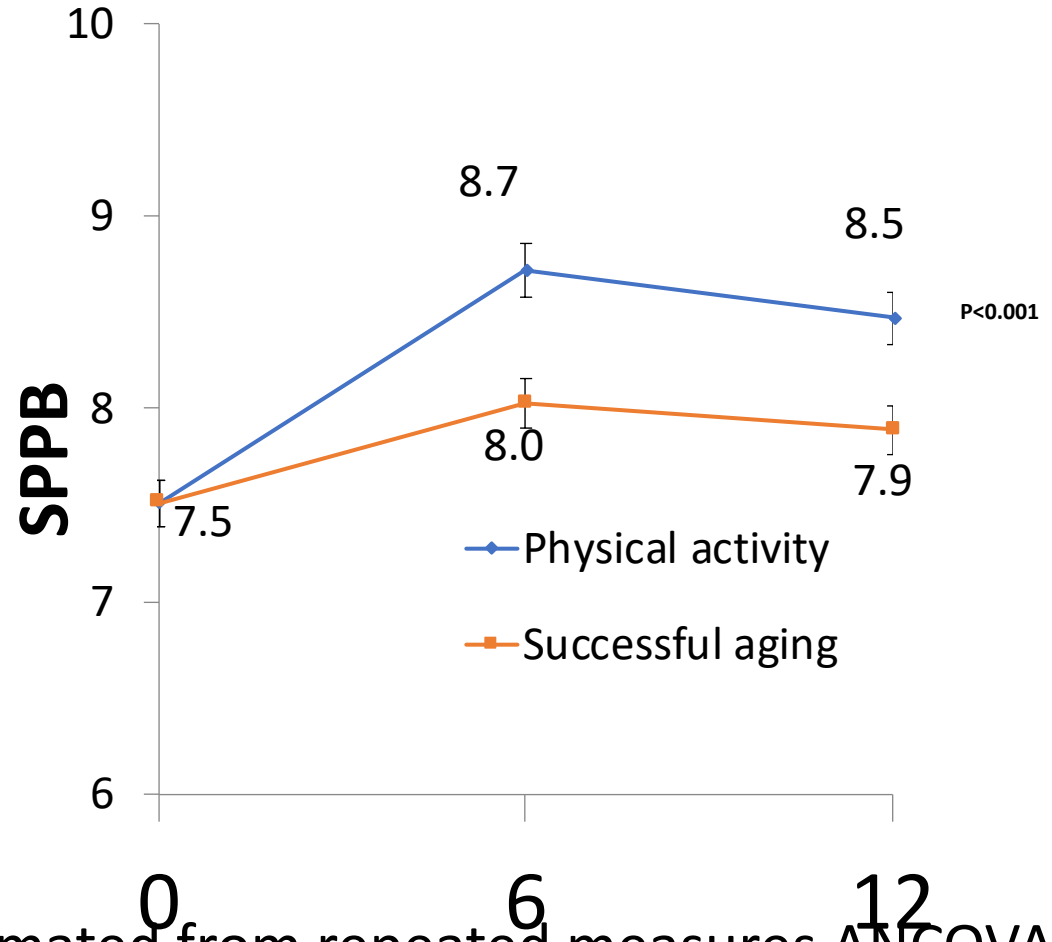
Fiatarone M., et al., JAMA, 1990

Exercise/Physical Activity LIFE-Pilot SPPB score

INTERVENTION

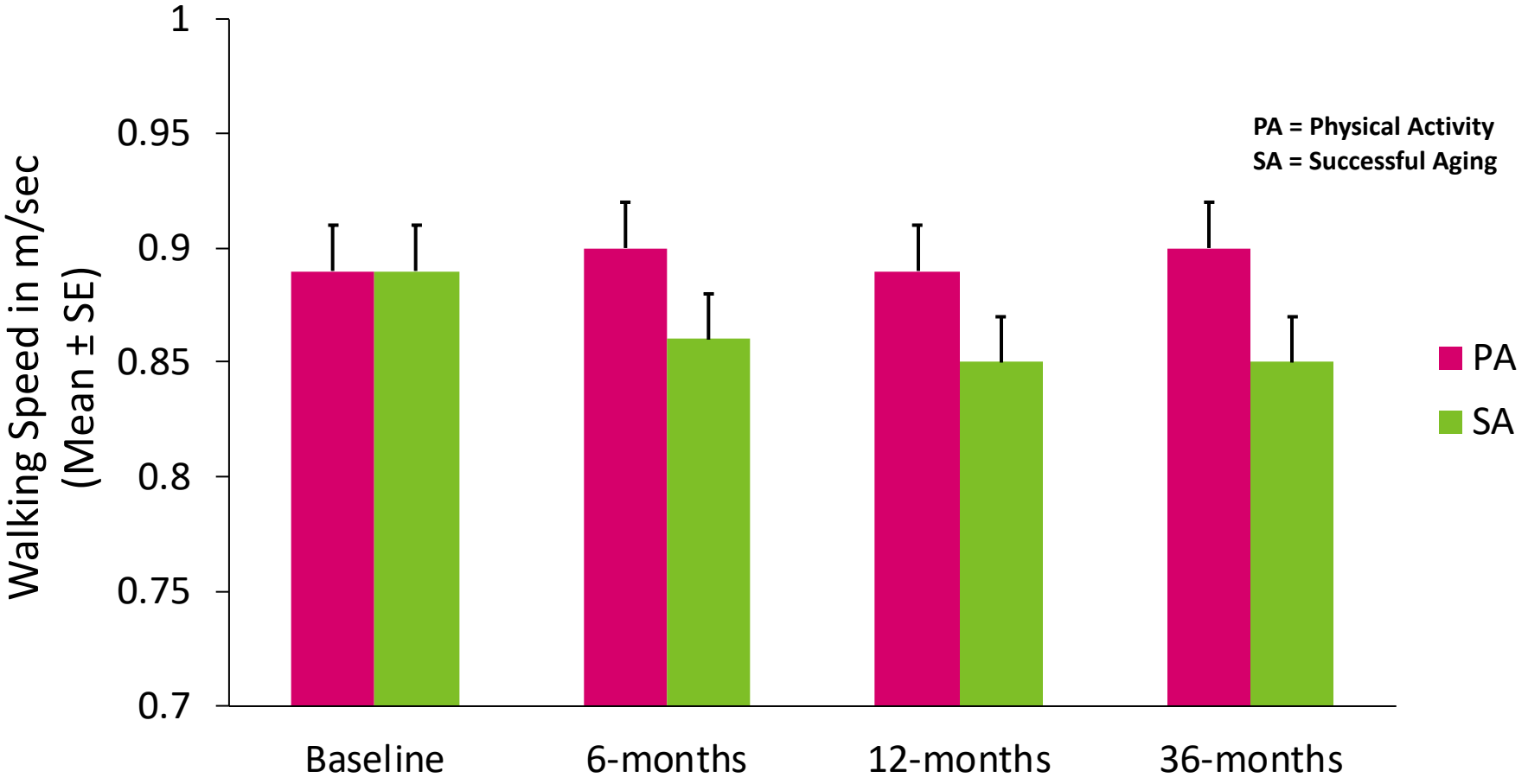
- Aerobic (walking)
- Strength (lower extremities)
- Balance
- Flexibility stretching
- Behavioral counseling



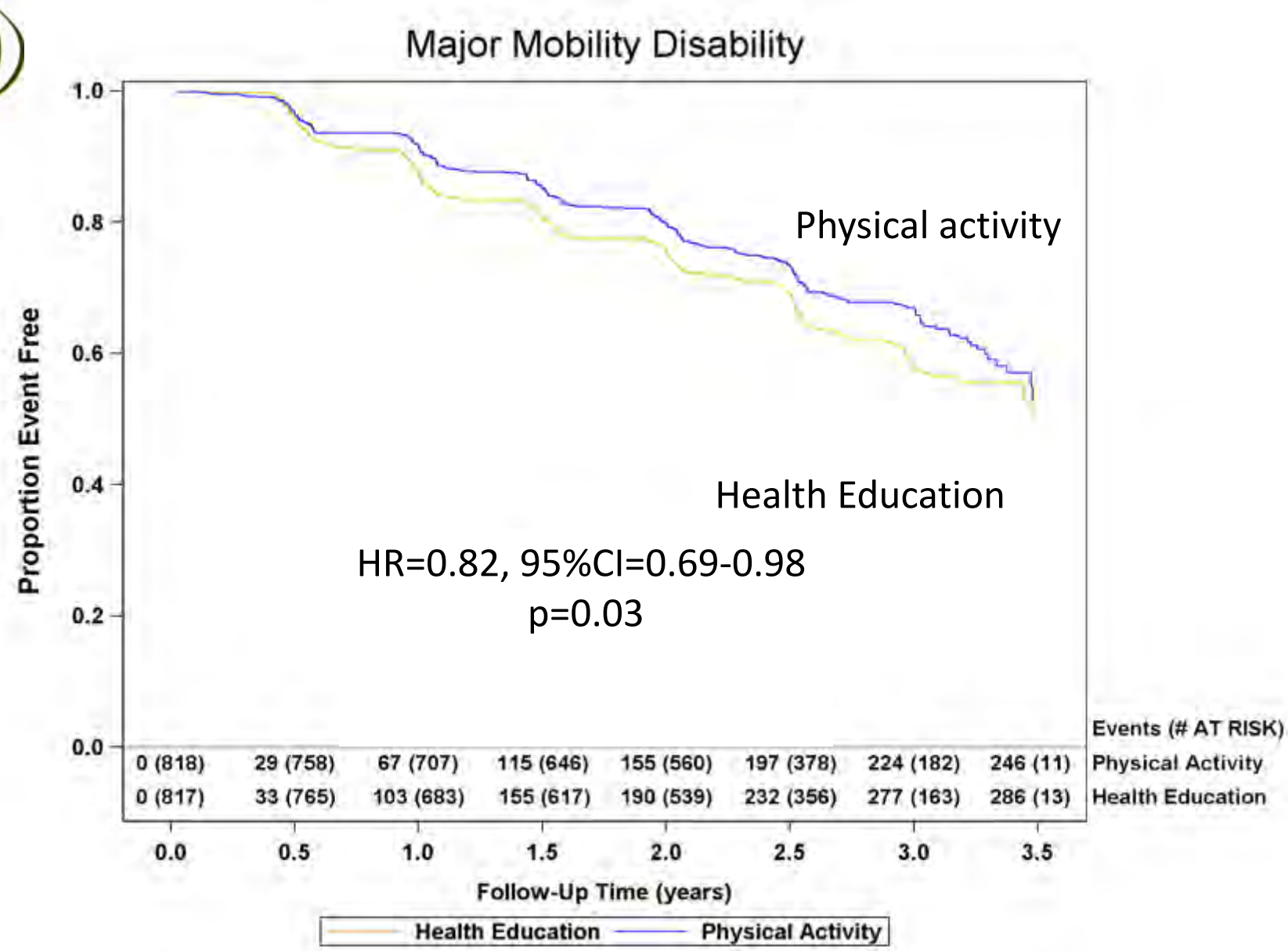
Means estimated from repeated measures ANCOVA adjusted for gender, field center and baseline values

Pahor et al *J Gerontol 2006;61:1157*

2-Year Follow-up of Life Pilot Participants

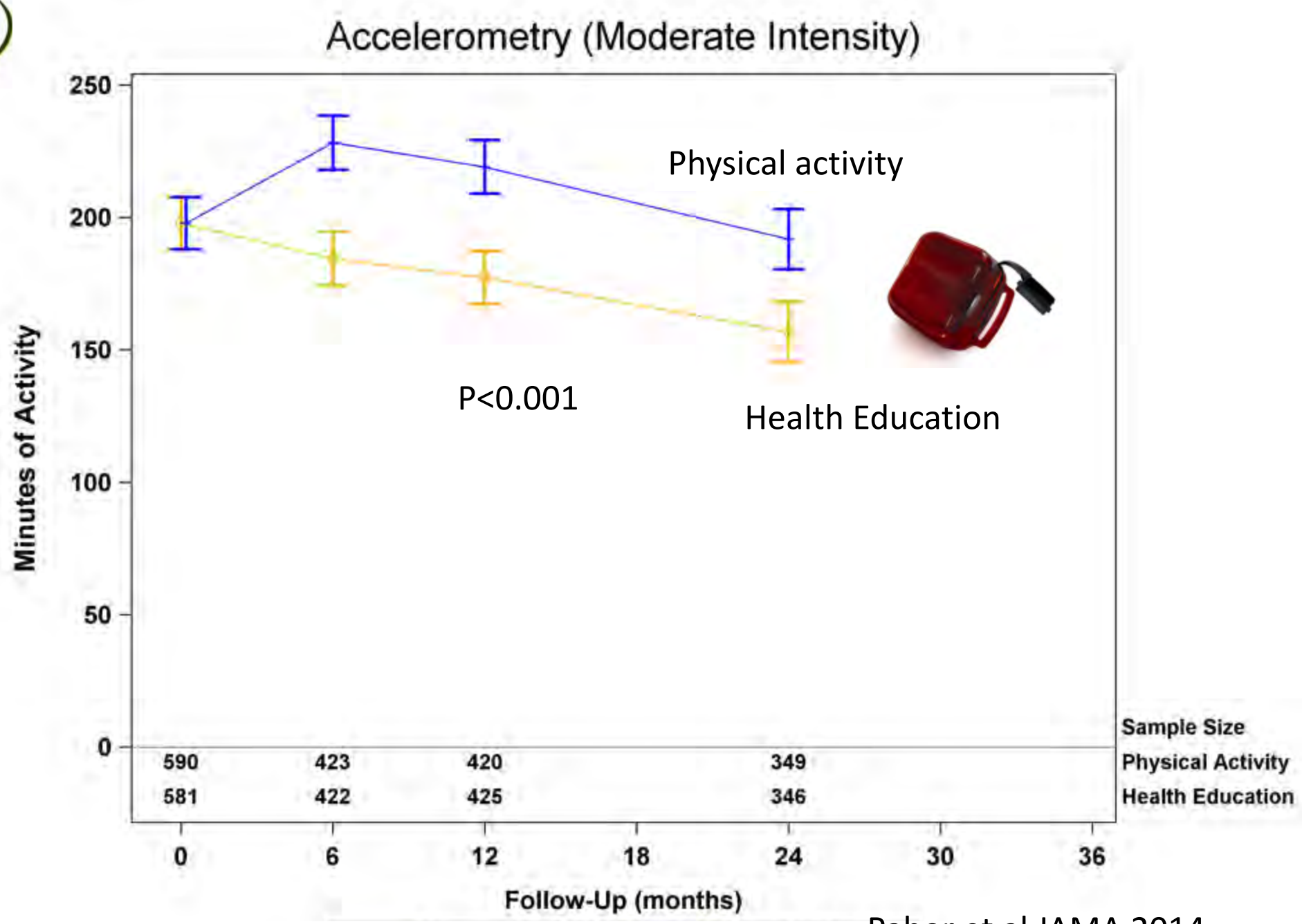


Source: J Gerontol A Biol Sci Med Sci 2009



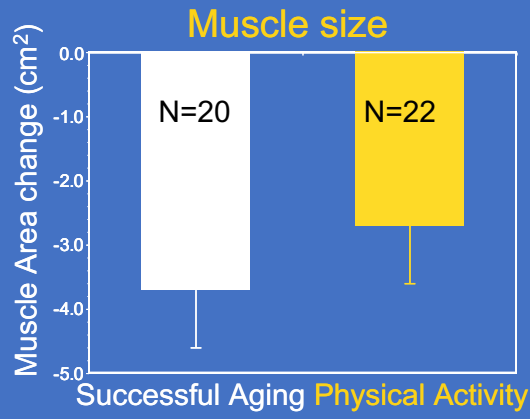
- **18% reduction in the risk of major mobility disability, defined as loss of ability to walk 400 m**
- **28% reduction in the risk of persistent mobility disability**

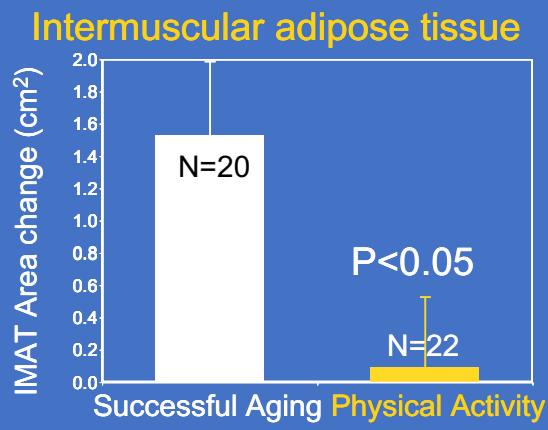
Pahor et al JAMA 2014

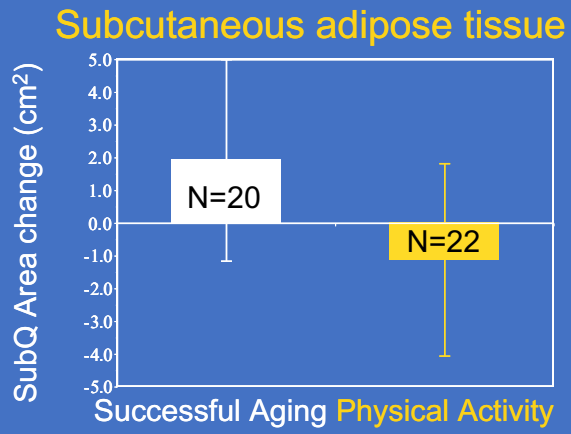


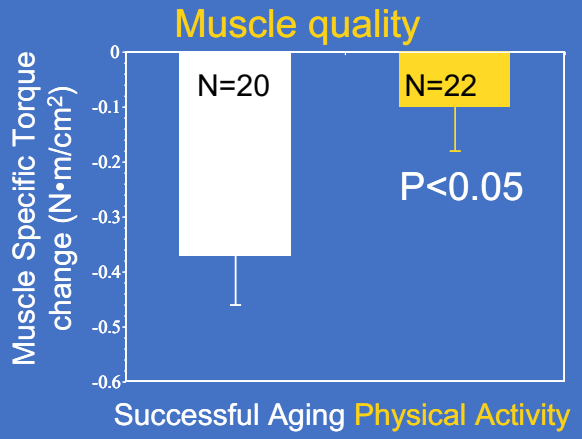
Pahor et al JAMA 2014

LIFE-P Muscle study





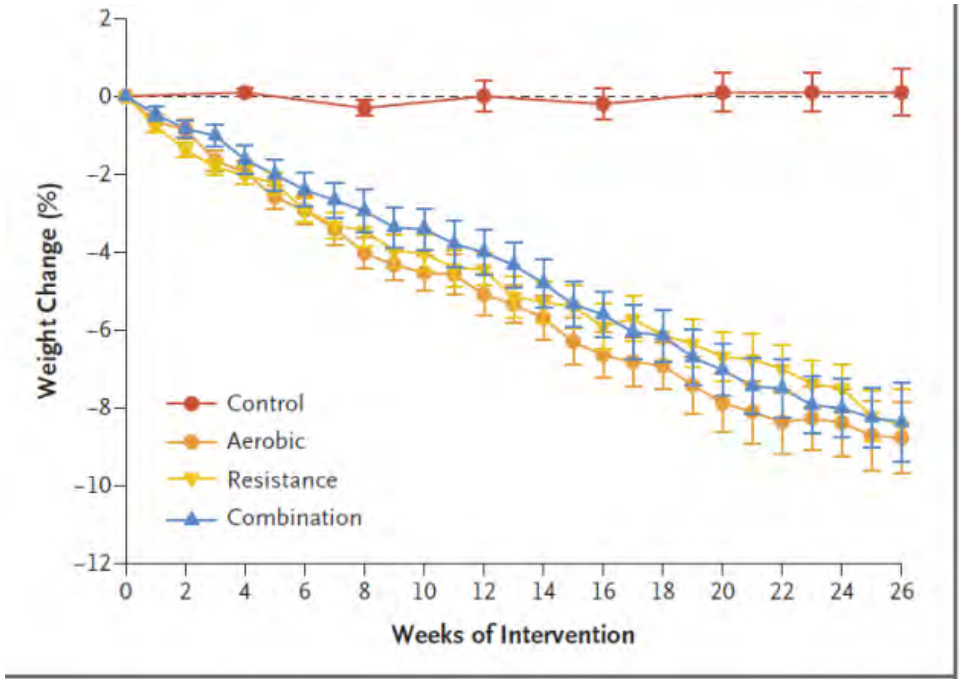


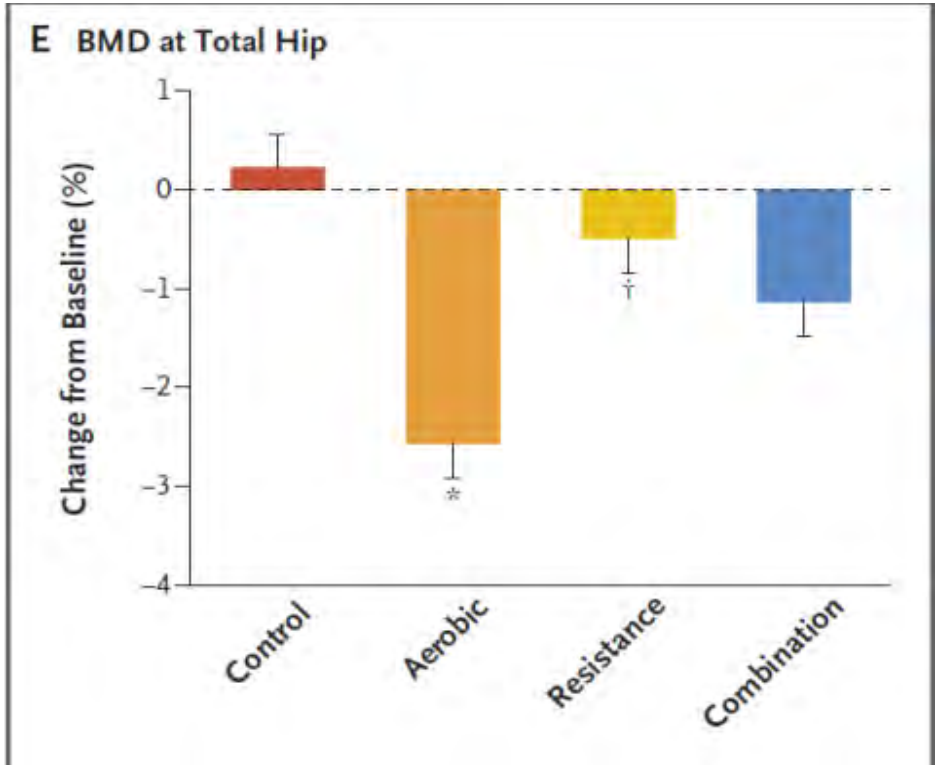


Physical activity may reduce the likelihood of falling and sustaining a serious injury by improving gait, balance, and lower extremity strength

- randomized to physical activity experienced
  - ✓ 46% reduction in all serious fall injuries
  - ✓53% reduction in the rate of fall related fractures
  - ✓59% reduction in the rate of fall injuries leading to hospital admission

Effectiveness of several exercise modes on bone mass (BMD) during weight loss





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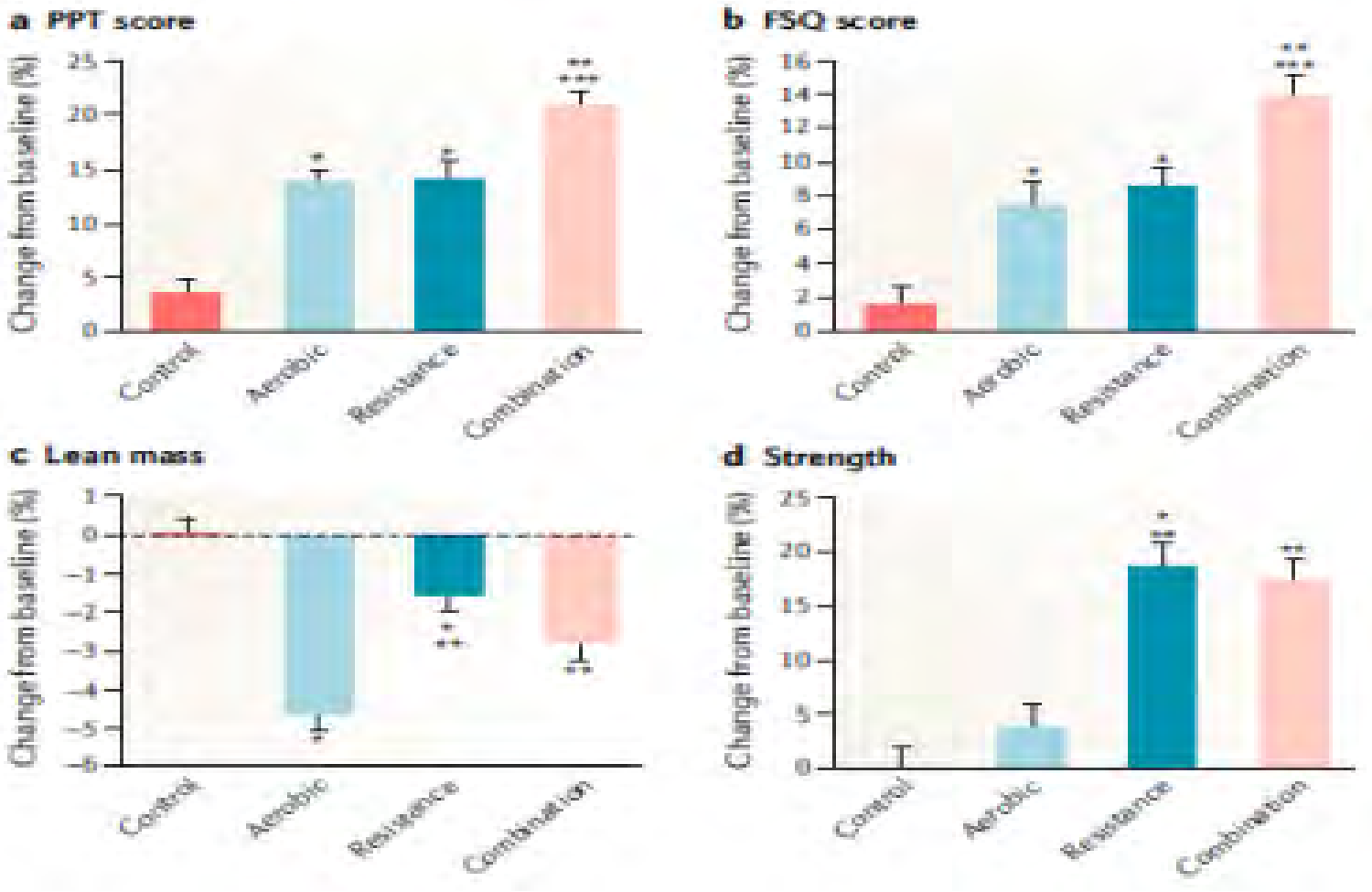
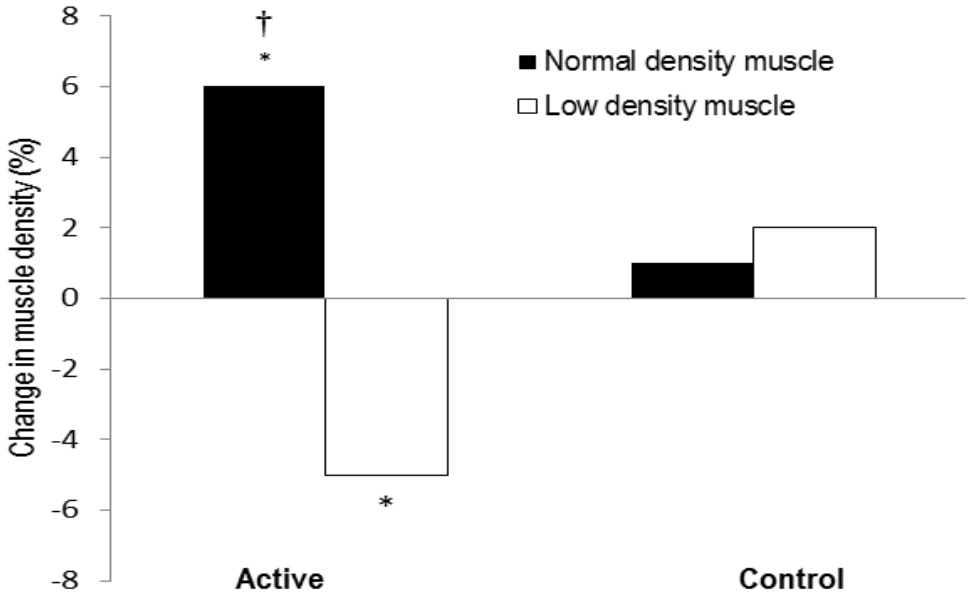
Villareal et al NEJM 2017

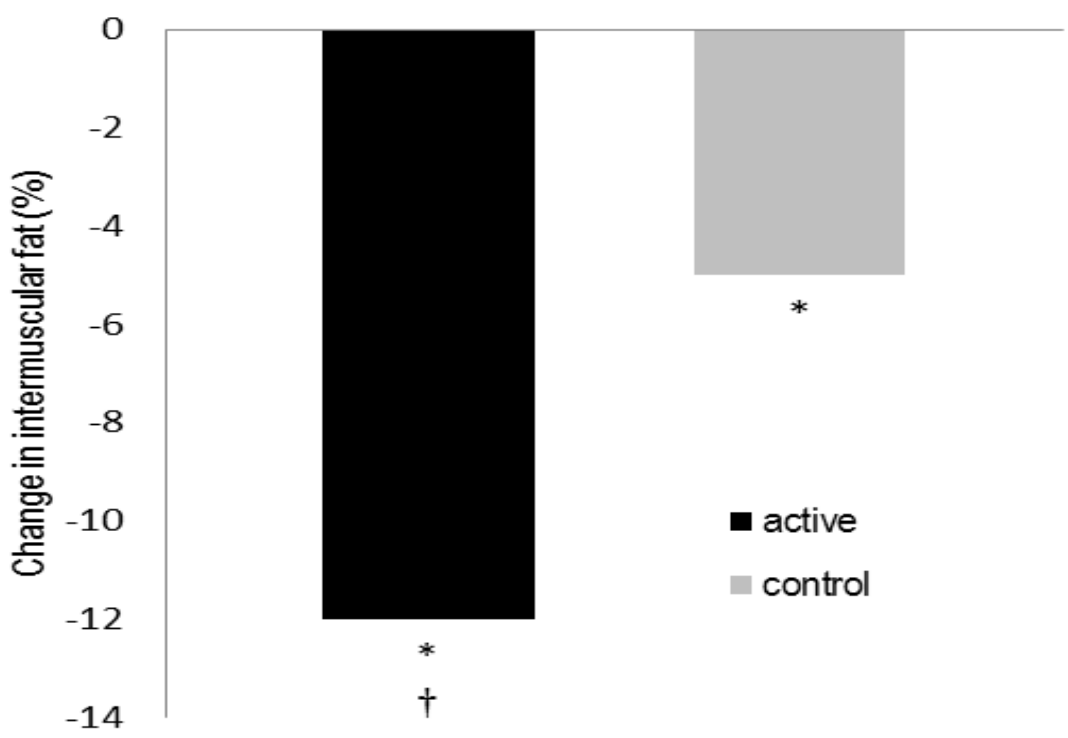
Effectiveness of several exercise modes on muscle mass/strength and functional status during weight loss



Villareal et al NEJM 2017

Effects of Physical activity plus nutritional supplement on thigh muscle quality and intermuscular fat in older individuals (>70 y)





VIVE2 Study: Walking, Strength, balance, flexibility
Nutritional supplement- Whey protein (20g), vitamin D (800 IU), calcium, vitamins + minerals (150 kcal)

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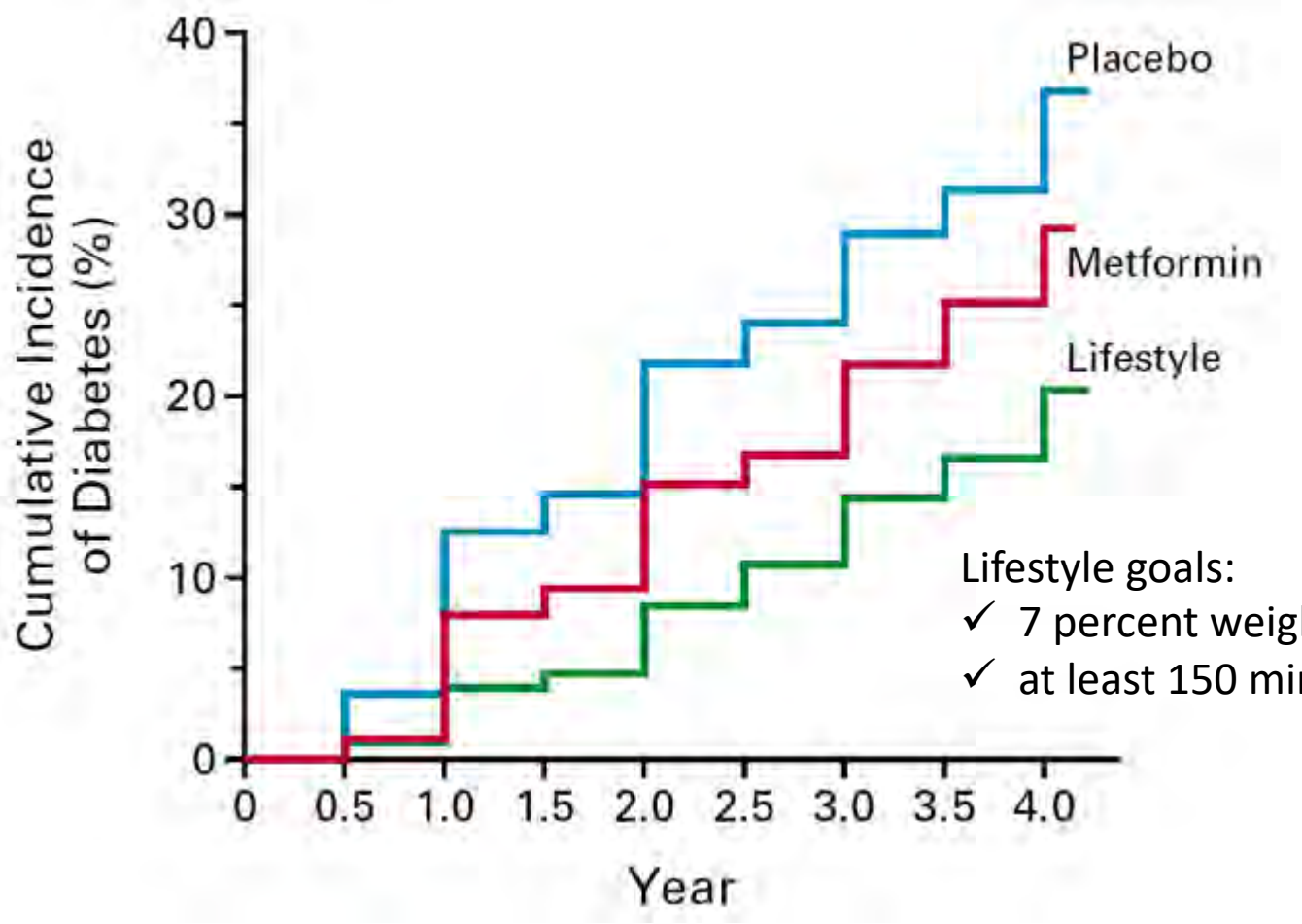
Englund et al J Gerontol 2018

Exercise and lifestyle changes substantially prevents the onset of diabetes compared to metformin alone or placebo



Lifestyle goals:

- ✓ 7 percent weight loss
- ✓ at least 150 minutes of PA per week

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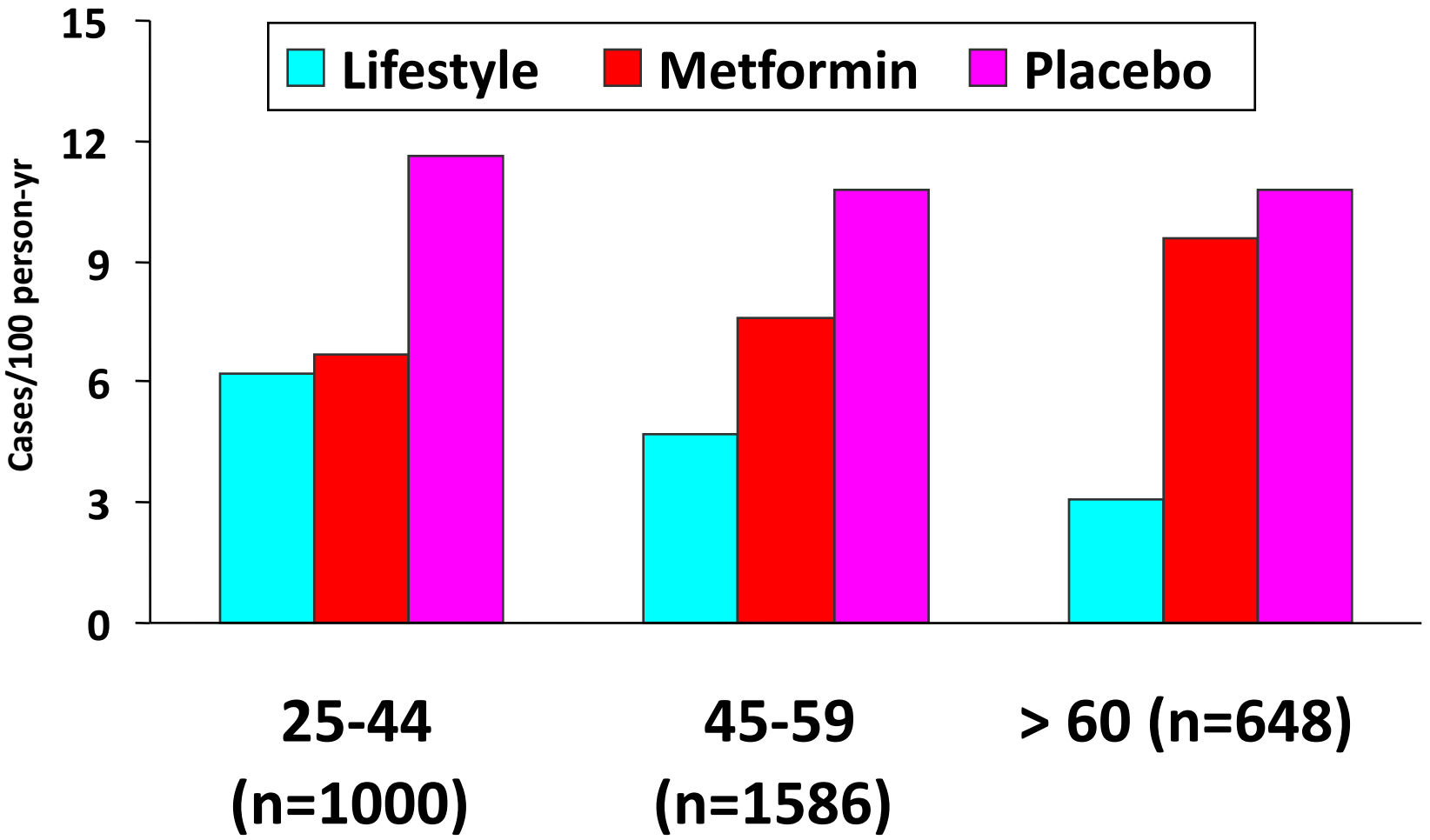
Diabetes Prevention Program Research Group. Knowler WC et al *NEJM. 2002;346:393-403*

Exercise and Lifestyle Influence on Diabetes Incidence



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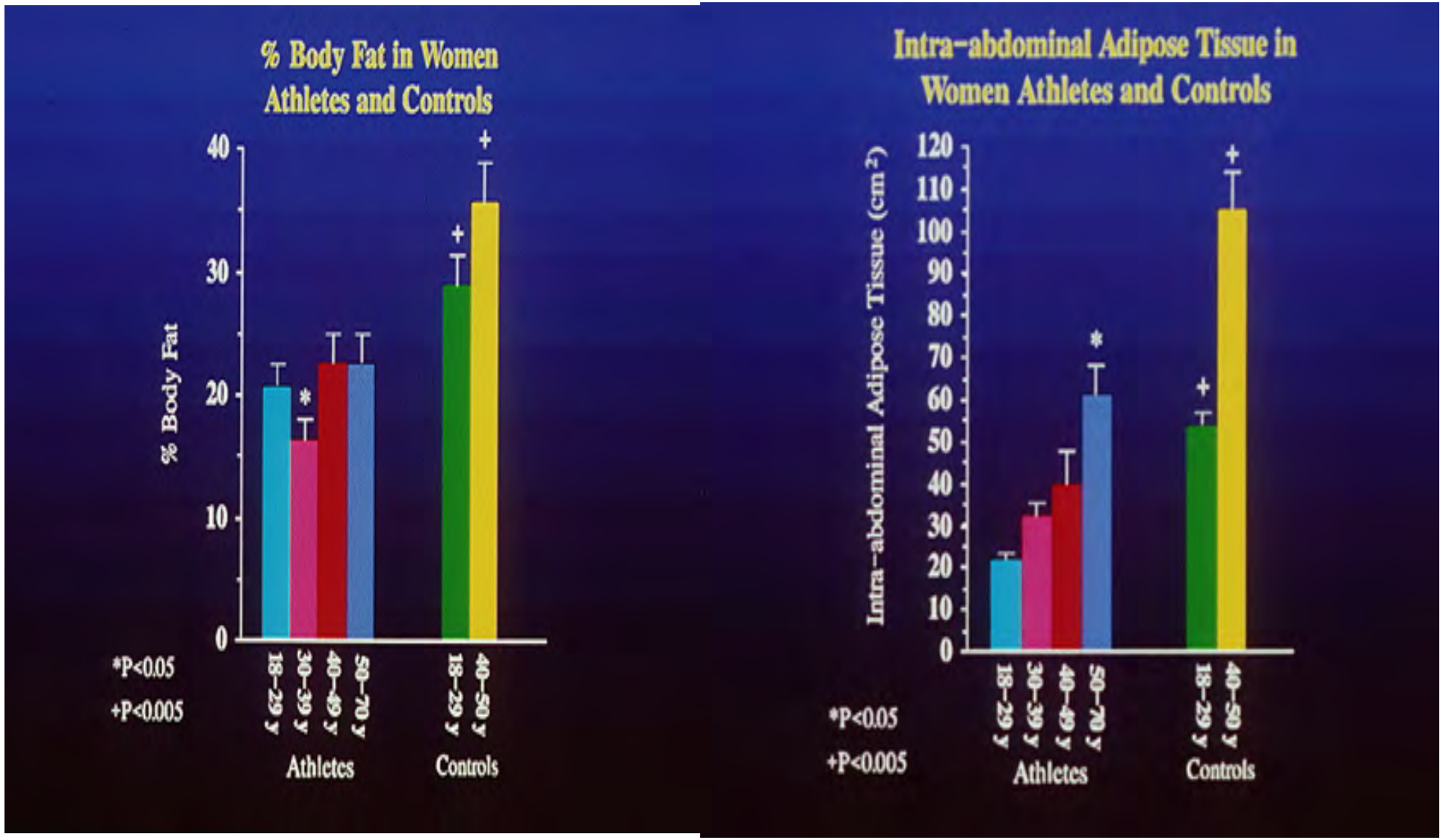
Source: Diabetes Prevention Program, 2001

Chronic Exercise on Body Fat Composition and Distribution in Women

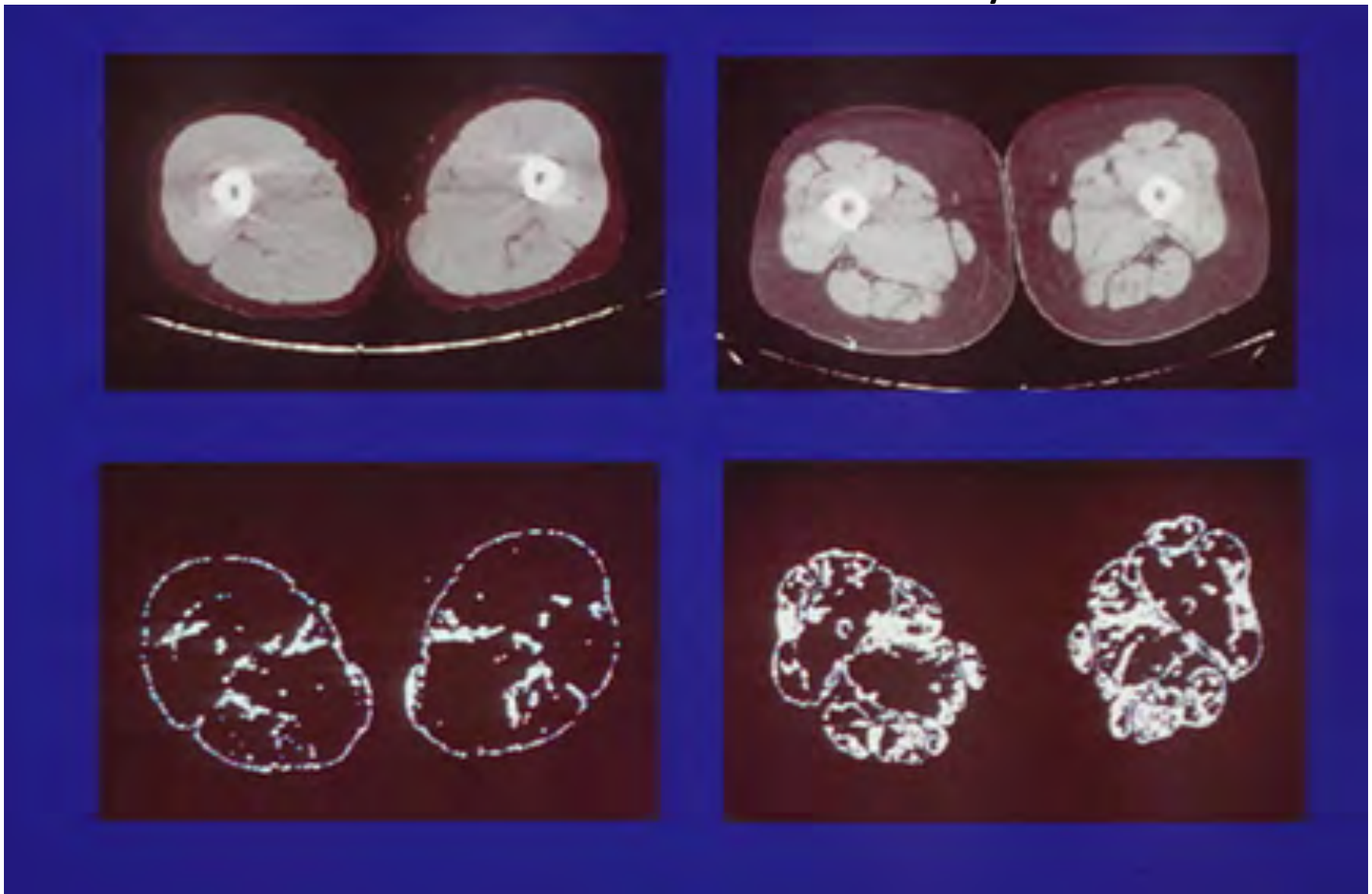


Ryan et al. AJP 1996

Chronic Exercise on thigh Adipose Tissue distribution of with Obesity

Trained older woman

Sedentary older woman



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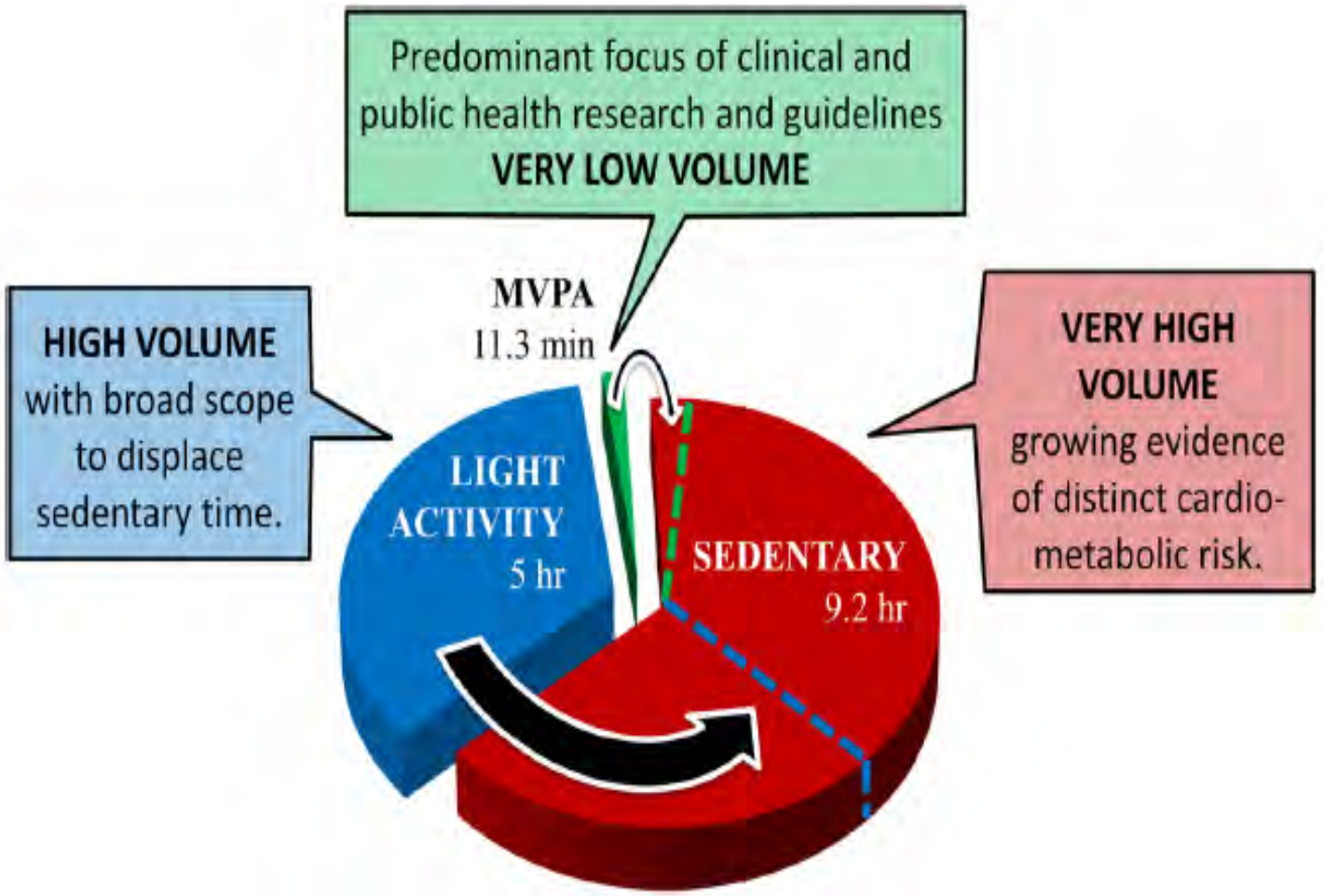
Managing sedentary behavior to reduce the risk of adverse outcomes associated with increased sedentary time



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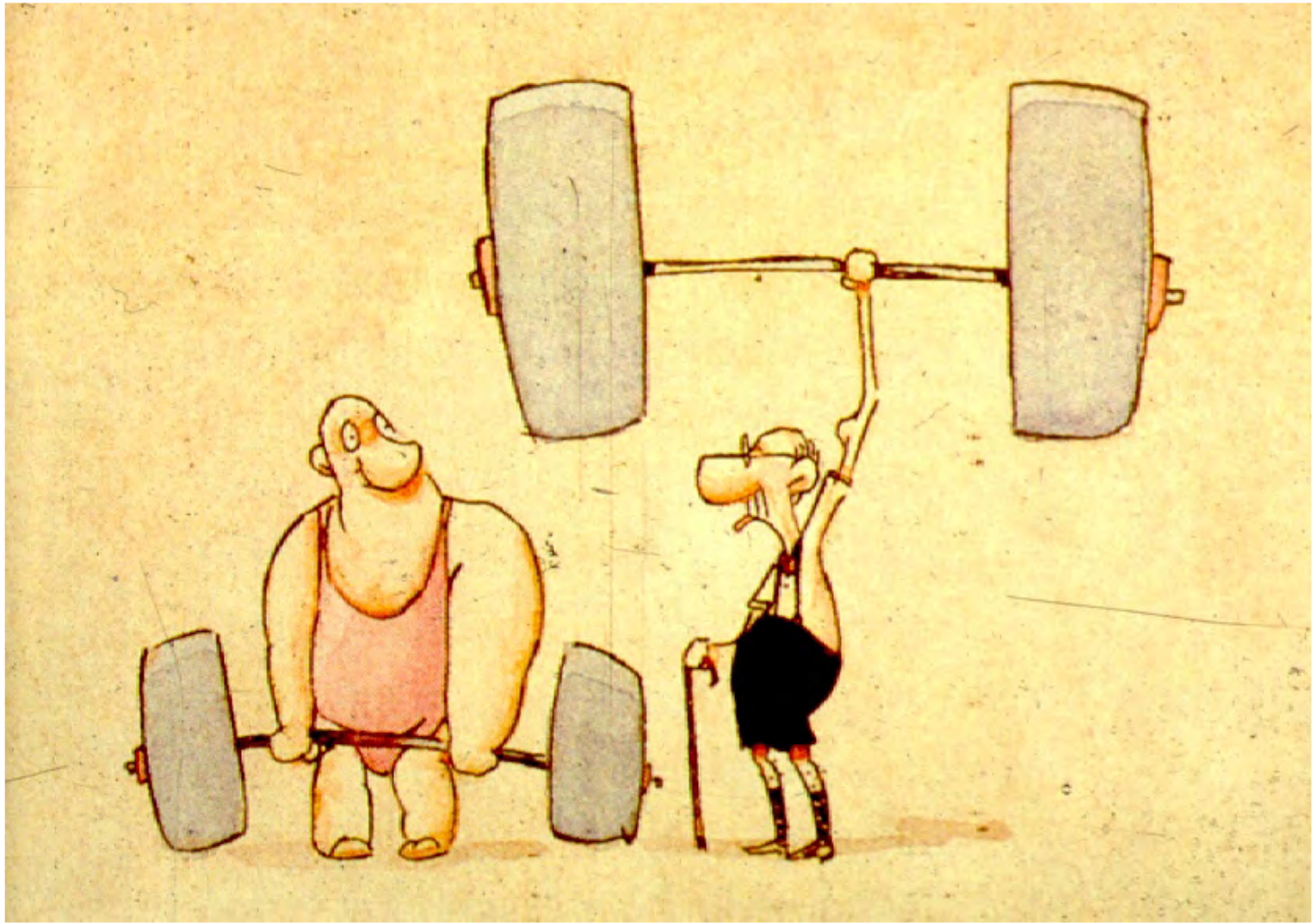
Dempsey et al., Curr Diab Rep 2014

Exercise/physical activity remains the only treatment for improving physical function and preventing disability



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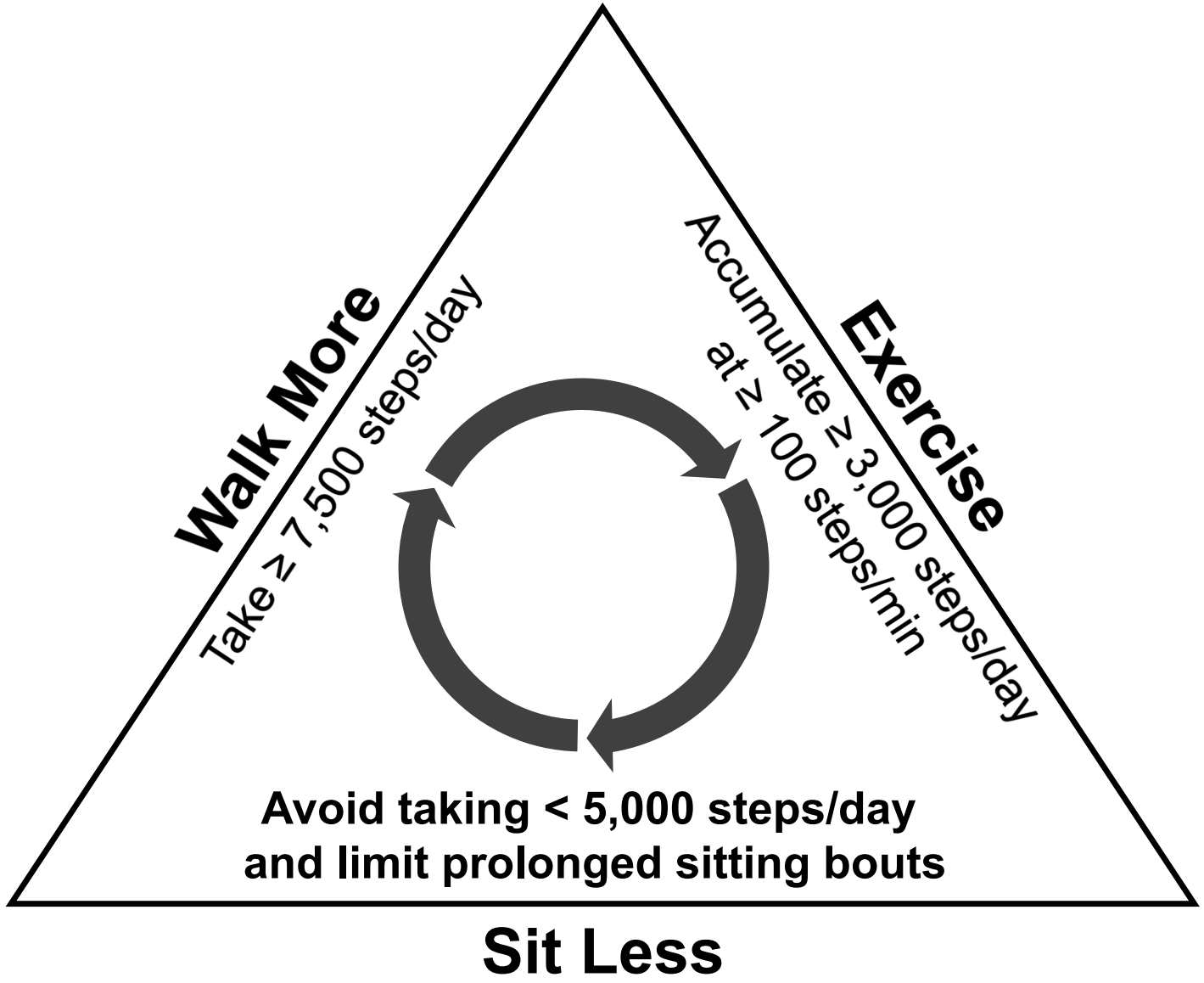
THANK YOU



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Tudor-Locke, Craig, Thyfault, & Spence, *APNM*, 2012

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