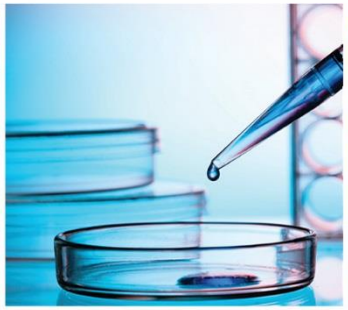
JEAN MAYER USDA HUMAN NUTRITION RESEARCH CENTER ON AGING

HNRCA



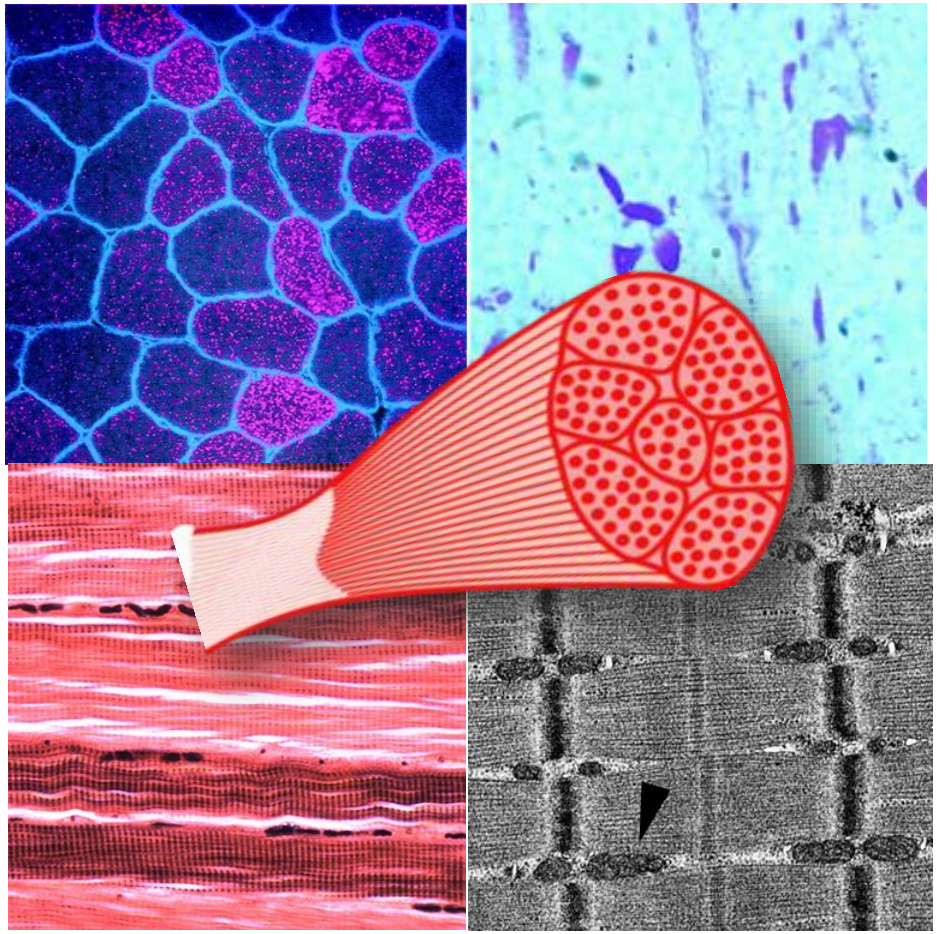
Roger A. Fielding, PhD
Director and Senior Scientist
Professor of Nutrition and Medicine
Nutrition, Exercise Physiology, and Sarcopenia Laboratory

Nutrition Across the Lifespan for Healthy Aging: muscular systems.

Food Forum Workshop
September 13, 2016

Tufts UNIVERSITY

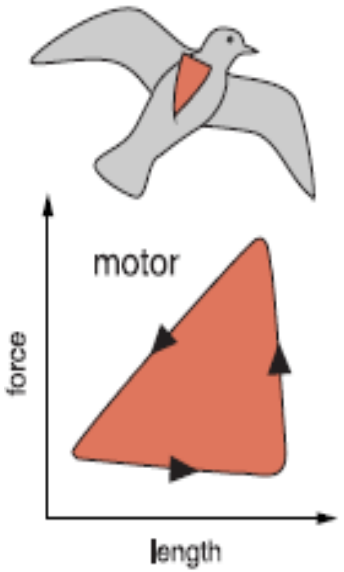
Skeletal Muscle Matters!

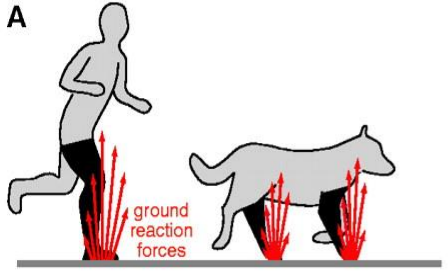


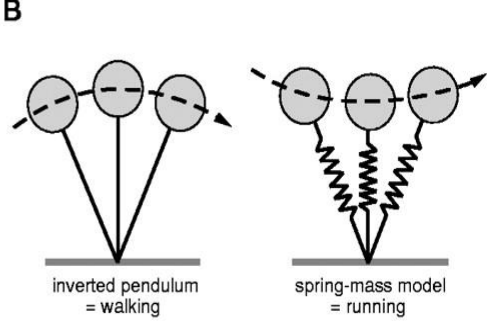
- Makes up 45-50% of body mass
- Fundamental role in locomotion, O_2 consumption, whole-body energy metabolism, and substrate turnover and storage
- Secretory organ (“myokines”)
- Robust skeletal muscle is a central factor in whole-body health and essential for maintaining energy homeostasis

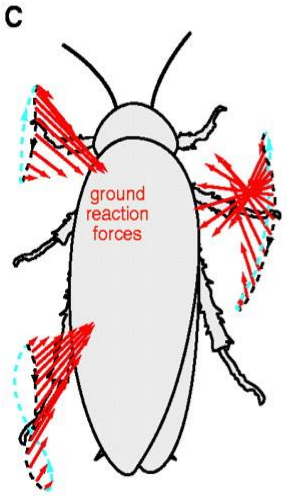
Rivas & Fielding. Muscle. Encyclopedia of Human Nutrition (3rd Ed.) 2012

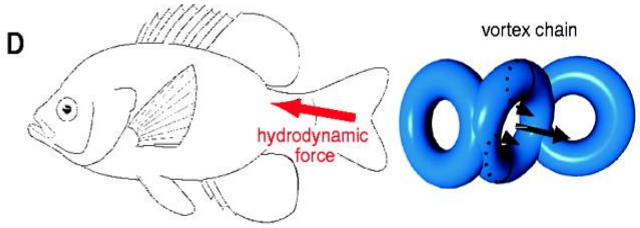
Mobility across species

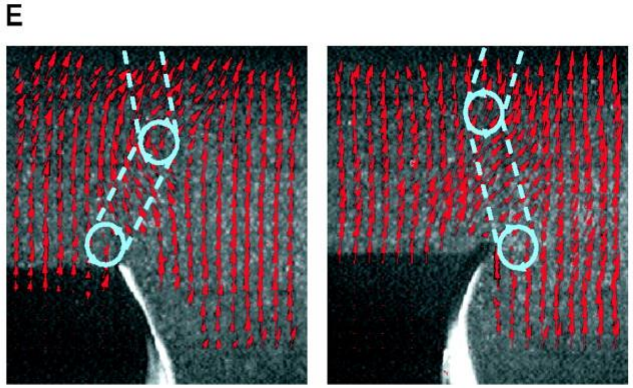


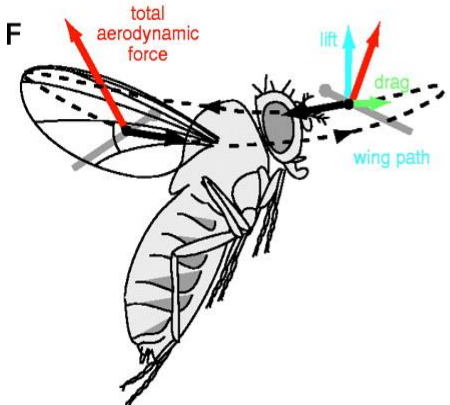


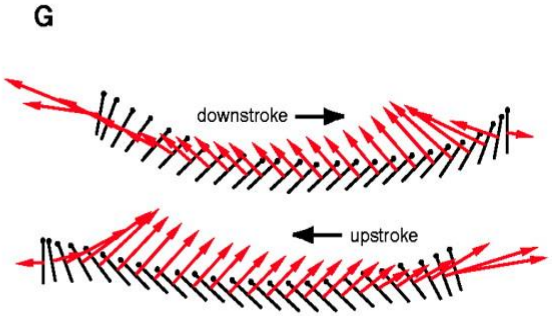






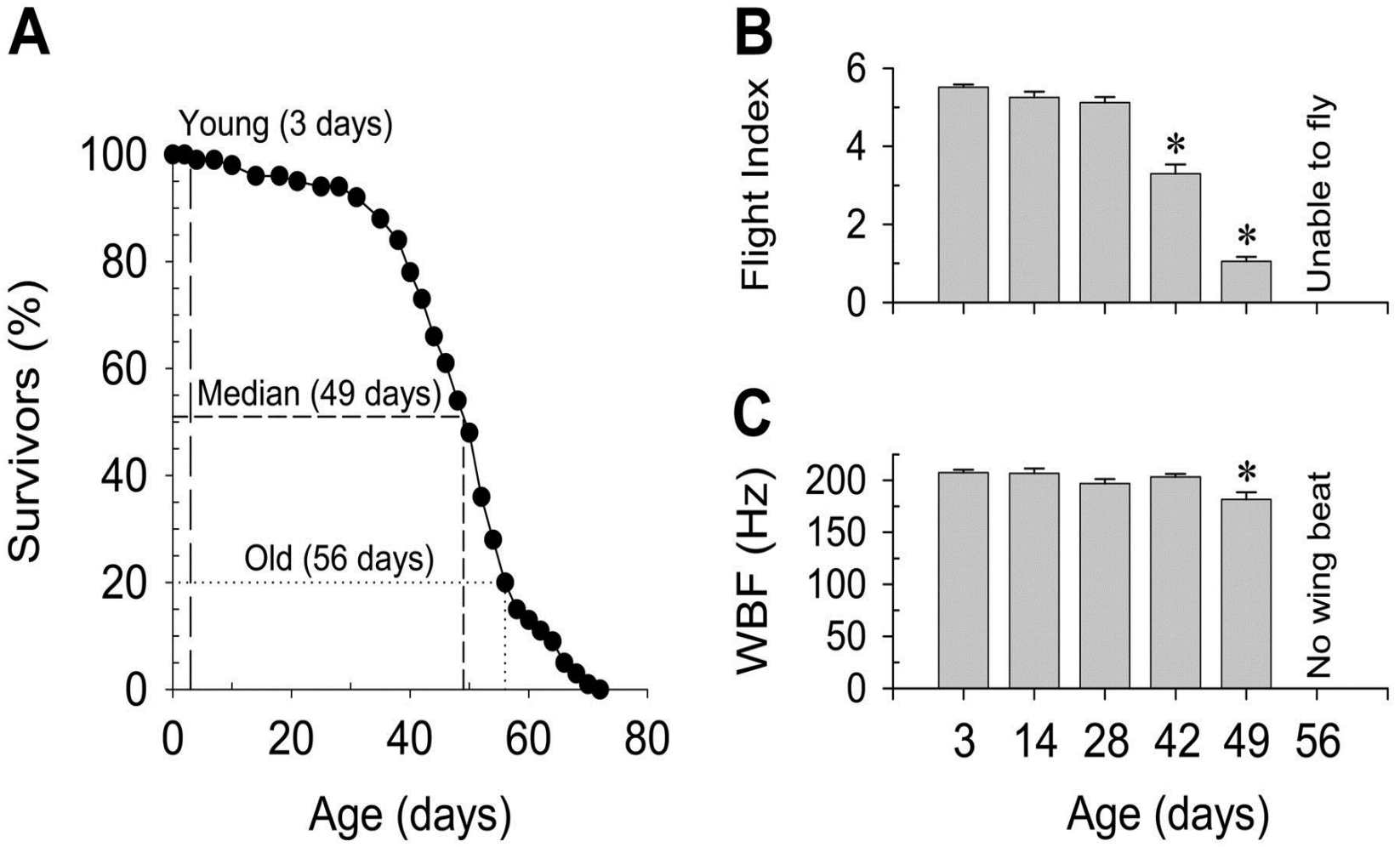






Dickinson et al. *Science 2000; 288:5463*

Aging drosophila and performance



Miller et al. *Biophys J 2008;95:2391*

Medicare Current Beneficiary Survey Ability to walk ¼ mile, health care cost and hospitalization rates

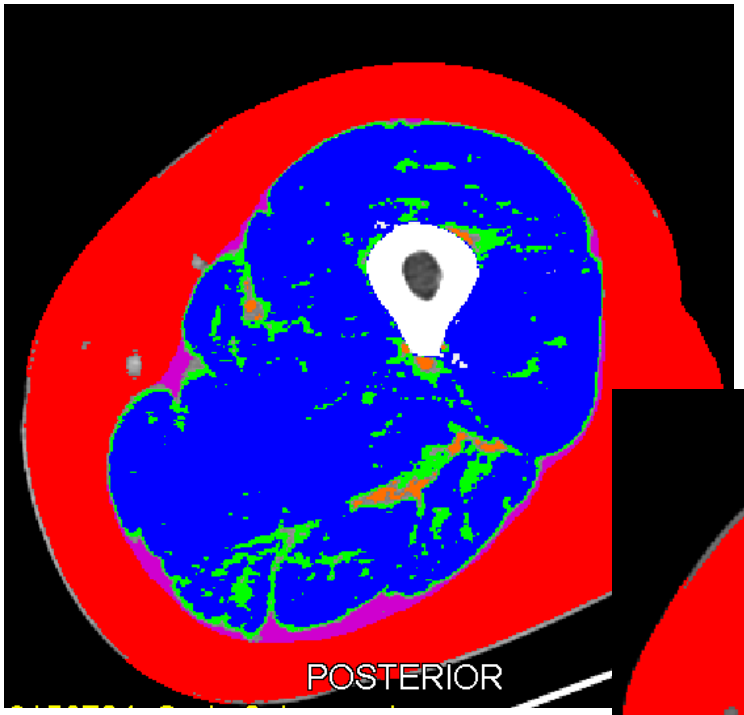
Table 4. Adjusted 2004 Health Care Costs and Hospitalization Rates for Community-Dwelling Medicare Beneficiaries Aged 65 or Older by Self-Reported Ability to Walk 1/4 Mile (N=5493)*

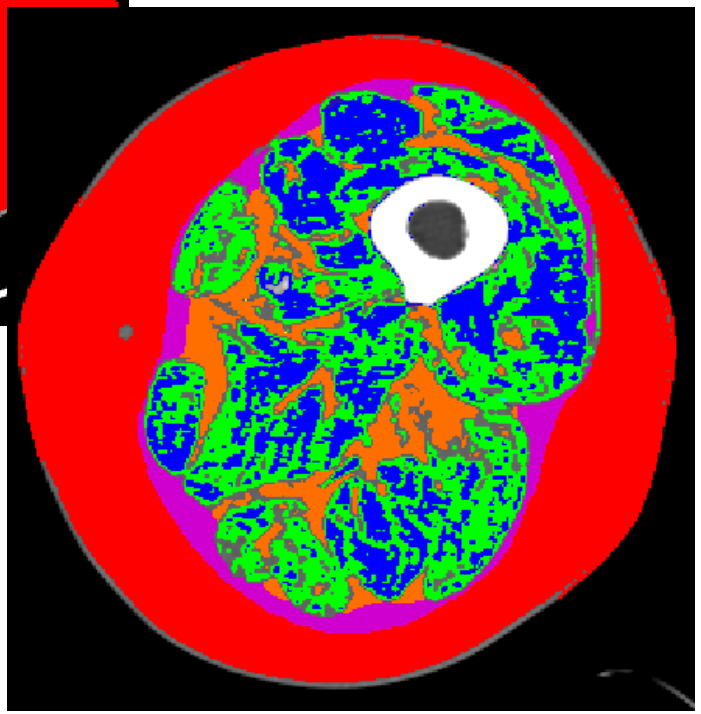
	Ability to Walk 1/4 Mile		
	No Difficulty	Difficulty	Unable
Mean annual cost, in $1000 s†			
Total	9.51 (8.80-10.21)	12.28 (11.17-13.39)	13.42 (11.73-15.12)
Out-of-pocket	1.75 (1.60-1.91)	2.03 (1.79-2.26)	1.85 (1.61-2.10)
Hospitalizations per 100 persons‡	25.1 (21.8-28.4)	39.2 (34.0-44.3)	47.3 (40.6-54.0)

Hardy et al. *J Gen Intern Med Online; 2010:Oct 23*

Sarcopenia: Age-associated loss in muscle mass and function

Female 70 yrs.
BMI = 23.3

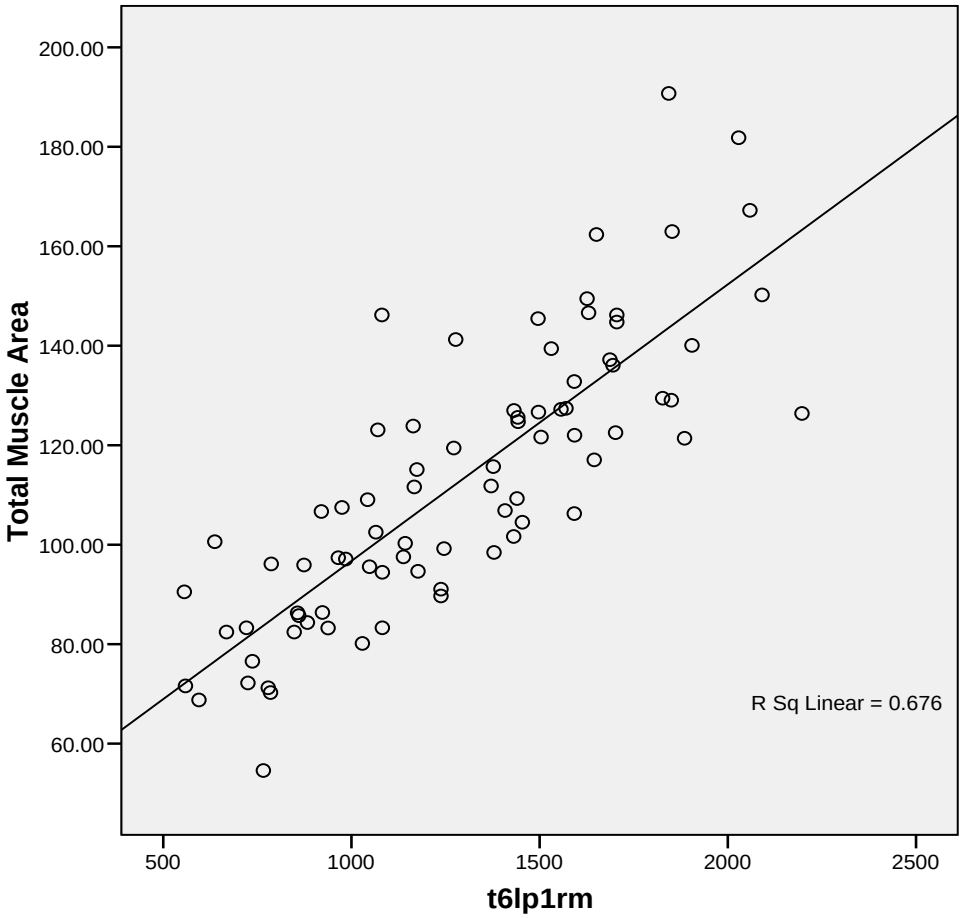




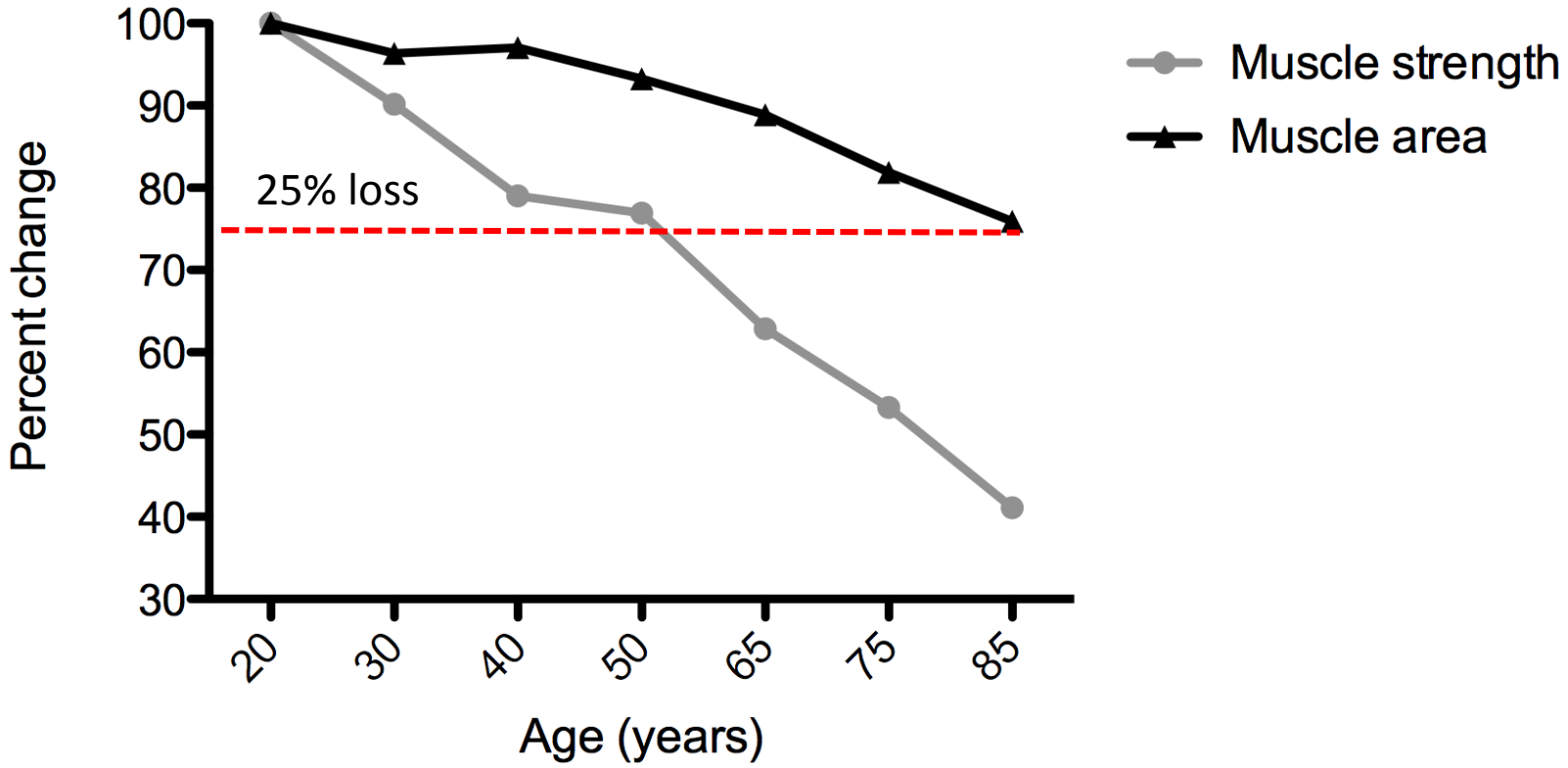
Female 85 yrs.
BMI = 24.6

STRENGTH-MASS CONVERGENCE: Correlation of Quadriceps Total Muscle Area vs. Muscle Strength

$R^2 = 0.676$



Age-related loss in muscle performance



Lauretani et al. 2003

Despite high prevalence & major implications

- Sarcopenia still has no:
  - Broadly accepted clinical definition
  - Consensus diagnostic criteria
  - Treatment guidelines

- Since 2005 – renewed efforts to define sarcopenia:
  - Several organizations from Europe and US
    - **October 2016 establishement of ICD 10 code for sarcopenia**

Agreement Among Sarcopenia Consensus Definitions:

- All have included objective measure of muscle/lean mass.
- All have incorporated muscle weakness or reduced physical functioning into the definition.
- Encouraging evidence-based data from FNIH project.

Weakness and lean mass cut points:

Lean Mass in Men and Women

Cutpoint	Men	Women
Weakness		
Recommended: grip strength (GSMAX)	<26 kg	<16 kg
Alternate: grip strength adjusted for BMI ($GSMAX_{BMI}$)	<1.0	<0.56
Appendicular lean body mass		
Recommended: ALM adjusted for BMI (ALM_{BMI})	<0.789	<0.512
Alternate: ALM	<19.75 kg	<15.02 kg

What is the prevalence of sarcopenia among older adults?

- Range varies depend on operational definition employed
- Gender differences
- Increases with advancing age
- Depends on the population (health status, dietary patterns, comorbidities)
- Varies anywhere from 0.5 to 13% (FNIH data)

Prevalence of sarcopenia by definition:

Criteria	Operational Definition: Physical Performance	Operational Definition: Muscle Strength	Operational Definition: ALM	Prevalence (%): Men (n = 7,113)	Prevalence (%): Women (n = 2,950)
Foundation of NIH Sarcopenia Project					
Weakness and low lean mass	—	Grip strength Men: <26 kg Women: <16 kg	ALM_{BMI} Men: <0.789 Women: <0.512	1.3	2.3
Slowness with weakness and low lean mass	Gait speed: ≤0.8 m/s	Grip strength Men: <26 kg Women: <16 kg	ALM_{BMI} Men: <0.789 Women: <0.512	0.5	1.8
International Working Group	Gait speed: <1.0 m/s	—	ALM/ht^2 Men: ≤7.23 kg/m^2 Women: ≤5.67 kg/m^2	5.1	11.8
European Working Group on Sarcopenia Older Persons					
Sarcopenia	Gait speed: <0.8 m/s or Grip strength Men: <30 kg Women: <20 kg		ALM/ht^2 Men: ≤7.23 kg/m^2 Women: ≤5.67 kg/m^2	5.3	13.3
Severe sarcopenia	Gait speed: <0.8 m/s	Grip strength Men: <30 kg Women: <20 kg	ALM/ht^2 Men: ≤7.23 kg/m^2 Women: ≤5.67 kg/m^2	0.7	2.9

Dam et al. *J Gerontol; 2014 FNIH*

Multifactorial origins of sarcopenia

Young muscle

Decreased physical activity

Increased homocysteine → Increased Atherosclerosis

Anorexia of Aging

Increased cytokine activity
- Interleukin-1
- Tumor Necrosis Factor-α
- Interleukin-6-I

Decreased number and increased irregularity of motor unit firing

Decreased anabolic hormones
- Testosterone
- DHEA
- Growth hormone
- Insulin Growth factor-I

Morley JE et al. J Clin Lab Med 2001

Nutrition/physical activity interventions*:

- Dietary Interventions:
  - Protein nutrition/adequacy
  - Vitamin D intake/sufficiency
  - Other micronutrients (anti-inflammatory diet patterns, anti-oxidants, B-vitamins)
- Physical activity/Exercise interventions:
  - Resistance exercise
  - Aerobic exercise
  - Combined
- Multi-modality interventions

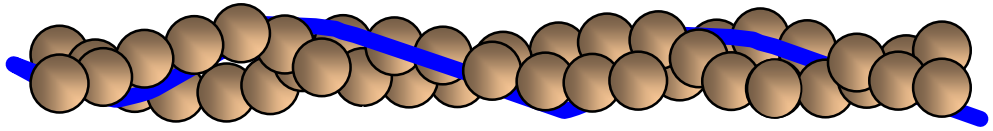
***Potentially important targets for therapy but may also be modifiers of response in Pharma trials.**

Protein metabolism and sarcopenia

- Balance of protein synthesis and degradation
- Adequacy of dietary intake of protein in older adults
- Evidence of relationship between protein intake and change in muscle mass with aging

Metabolic Control of Muscle Mass

CONTRACTILE PROTEINS



Synthesis Breakdown

FREE AMINO ACID POOL

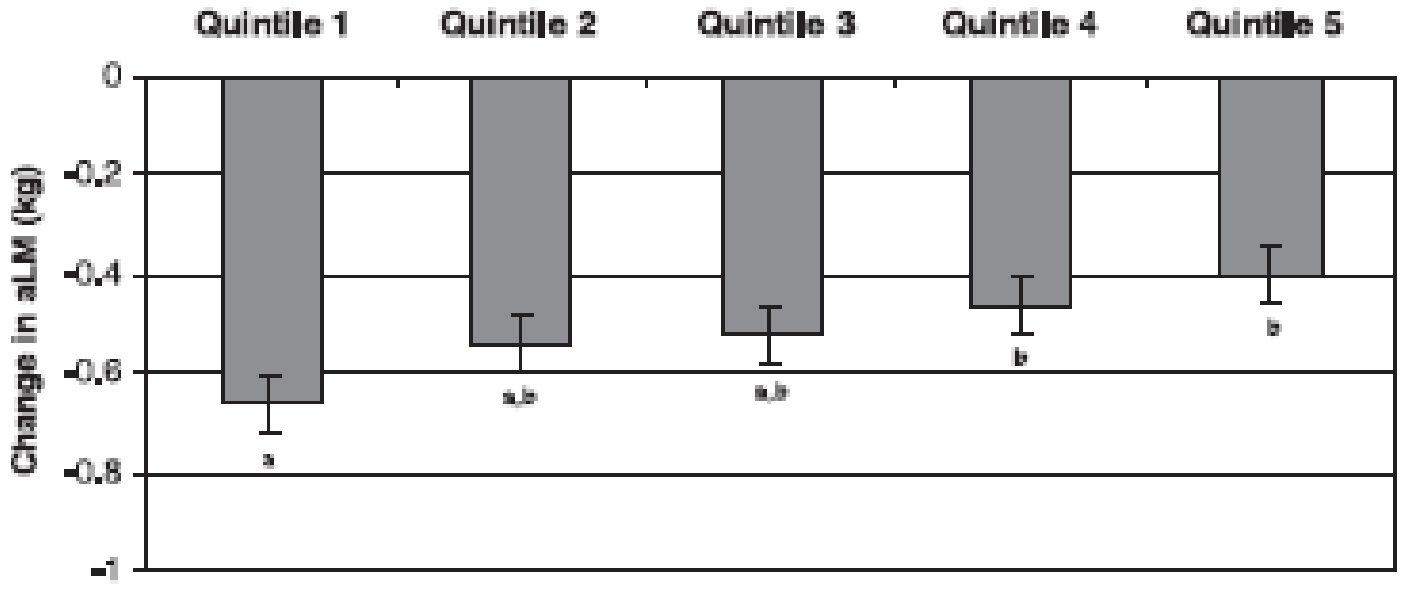
Blood

AMINO ACIDS

Synthesis – Breakdown = Net Balance

Biolo et al Am J Physiol, 1995

Dietary protein intake and change in lean mass



Protein intake ranged from 0.7 to 1.1 g/kg/day

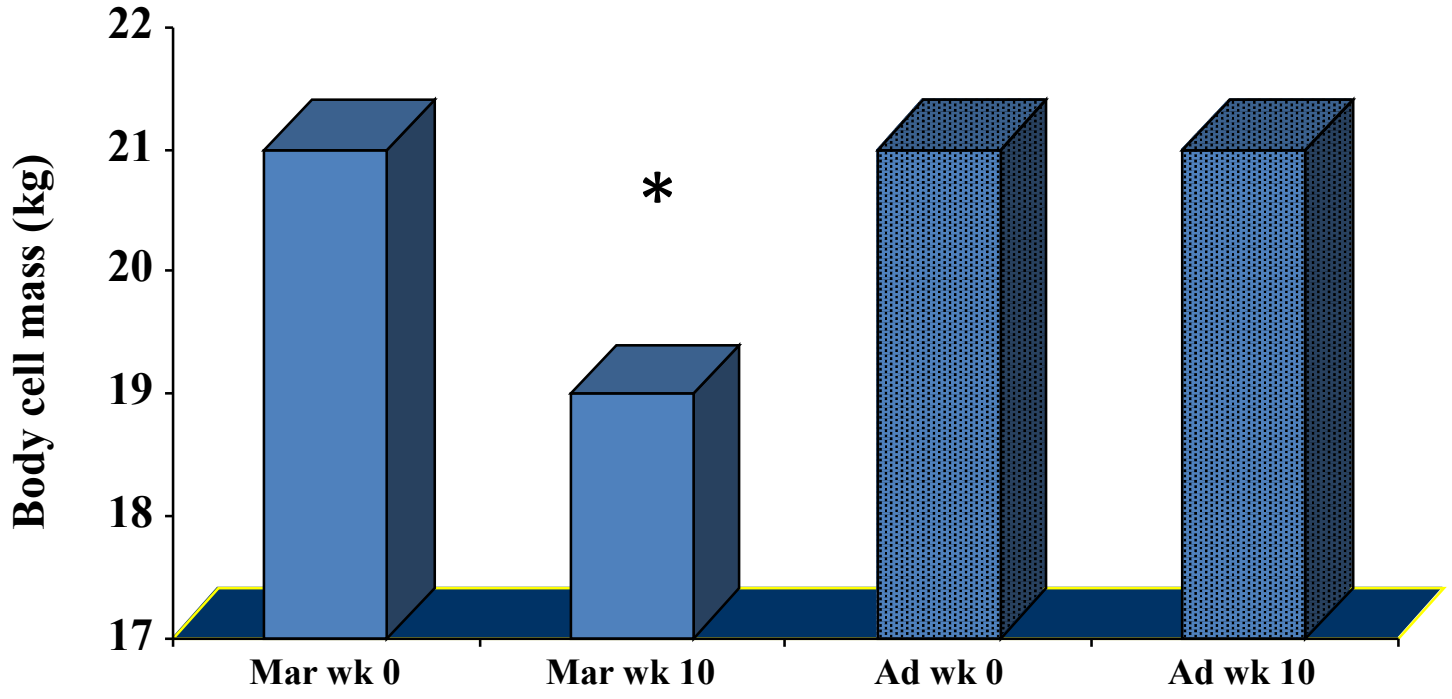
Houston et al. J Gerontol 2008

Influence of dietary protein on Sarcopenia in elderly women

- Randomized double-blind intervention 10-wks.
- 12 healthy older women (66 – 79 yrs)
- Subjects received 0.45 (**Mar**) or 0.92 (**Ad**) g protein/kg/day.
- Energy intake adjusted through Day 28.

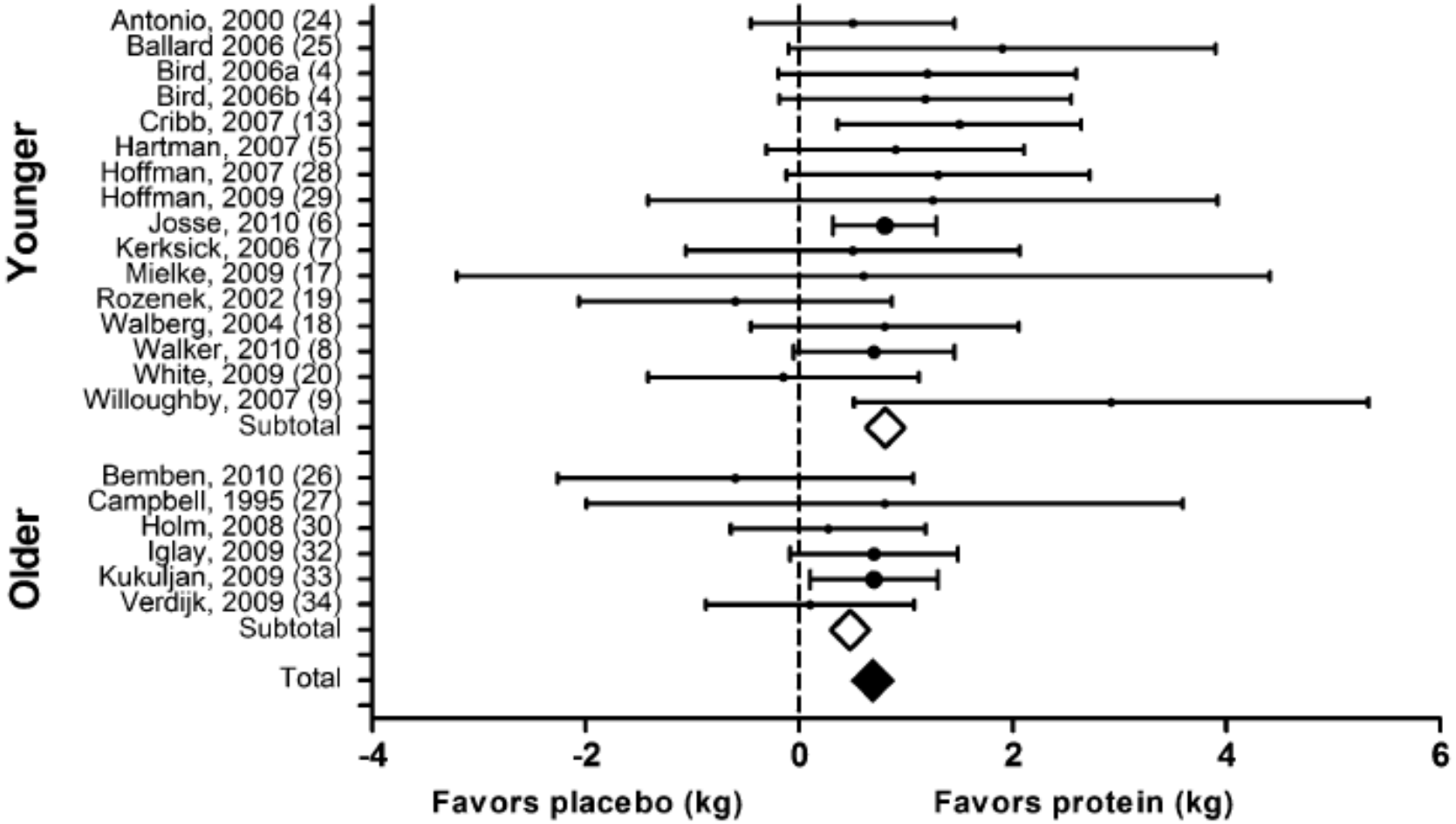
Castaneda, Gordon, Fielding, et al. J. Nutr. Health 2000

Body cell mass after marginal protein intake



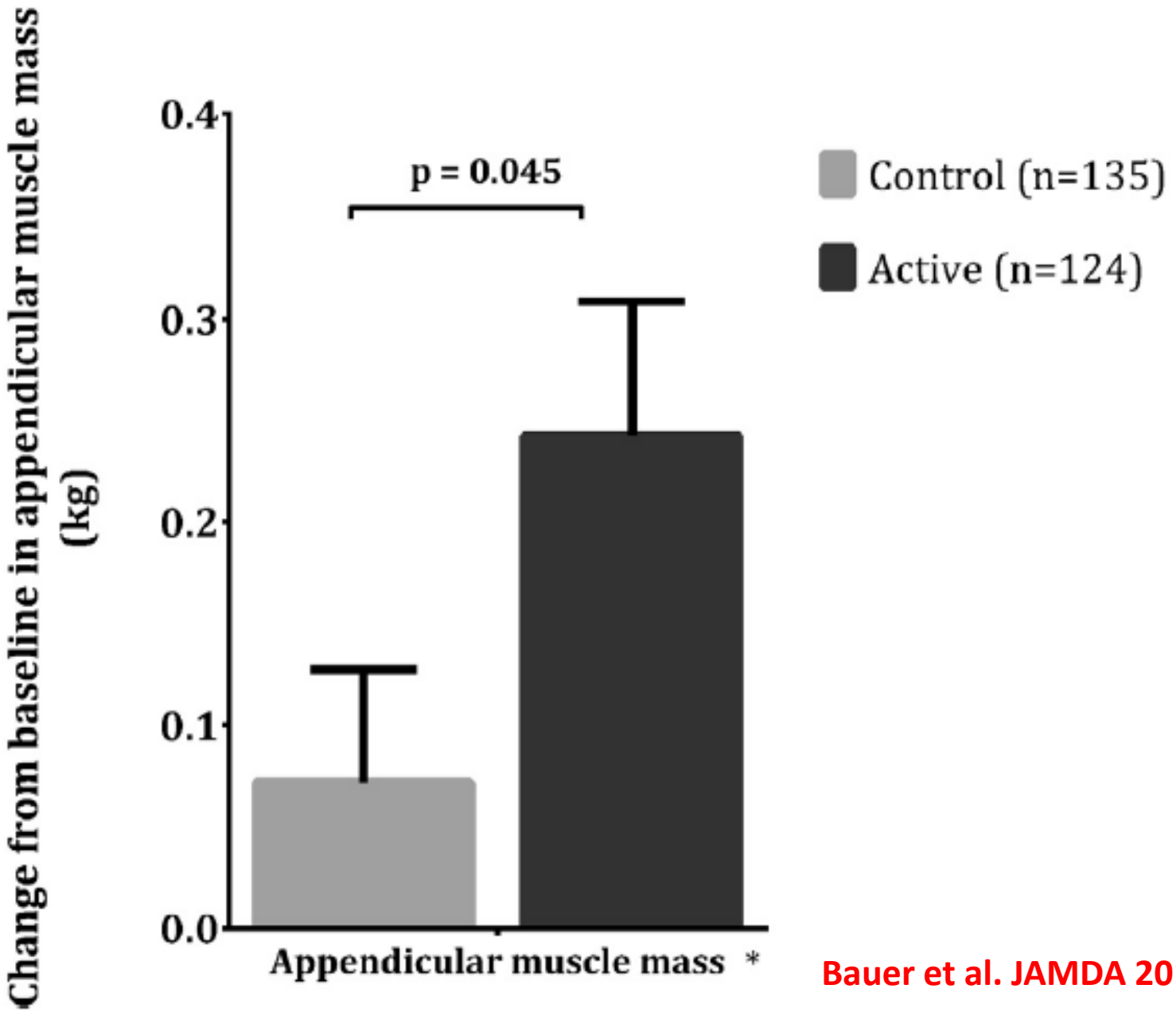
* Different from wk 0 P < 0.01

Meta-analysis of protein supplementation/exercise and gains in lean mass



Cermak, Van Loon 2012 Am J Clin Nutr

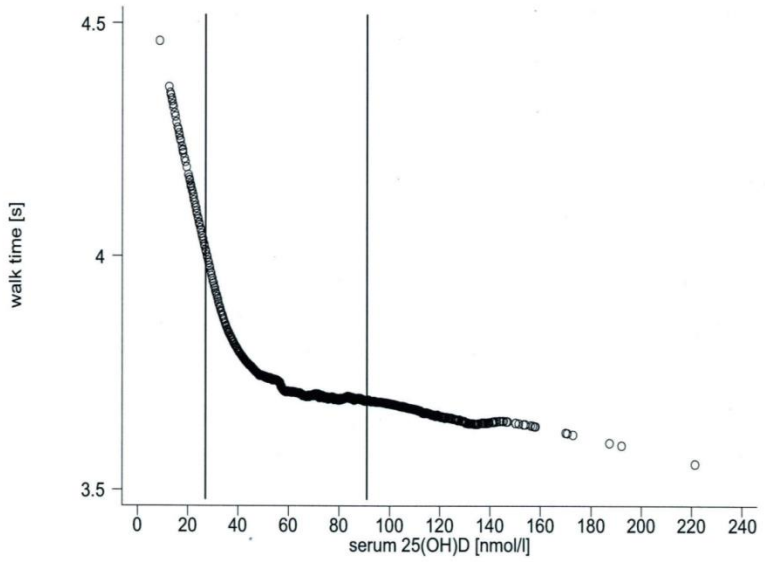
Supplemental protein in frail elders with sarcopenia



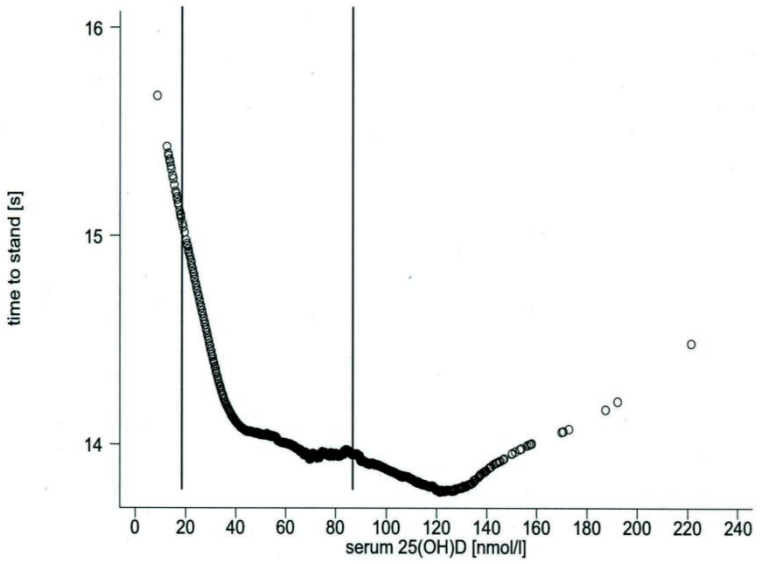
Bauer et al. JAMDA 2015

NHANES III – Serum 25(OH)D and Performance in Men and Women Age 60 and Older

Walk time

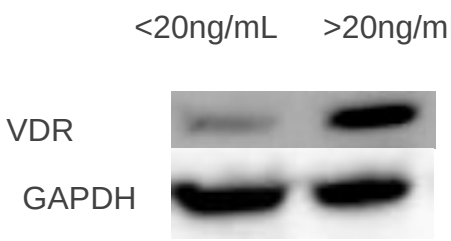


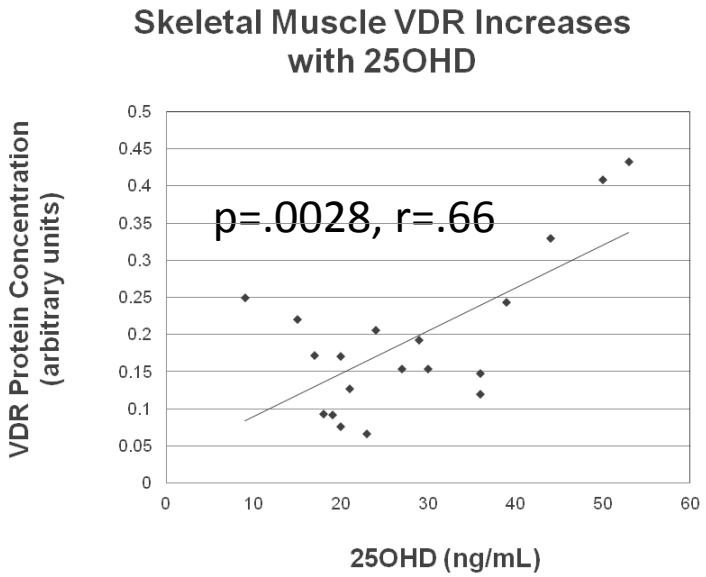
Sit-to-stand

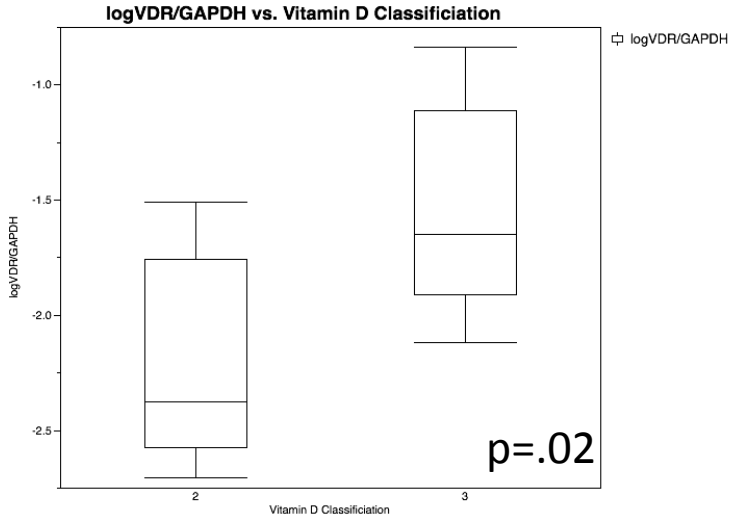


Bischoff-Ferrari HA. Am J Clin Nutr 2004;80:752-8.

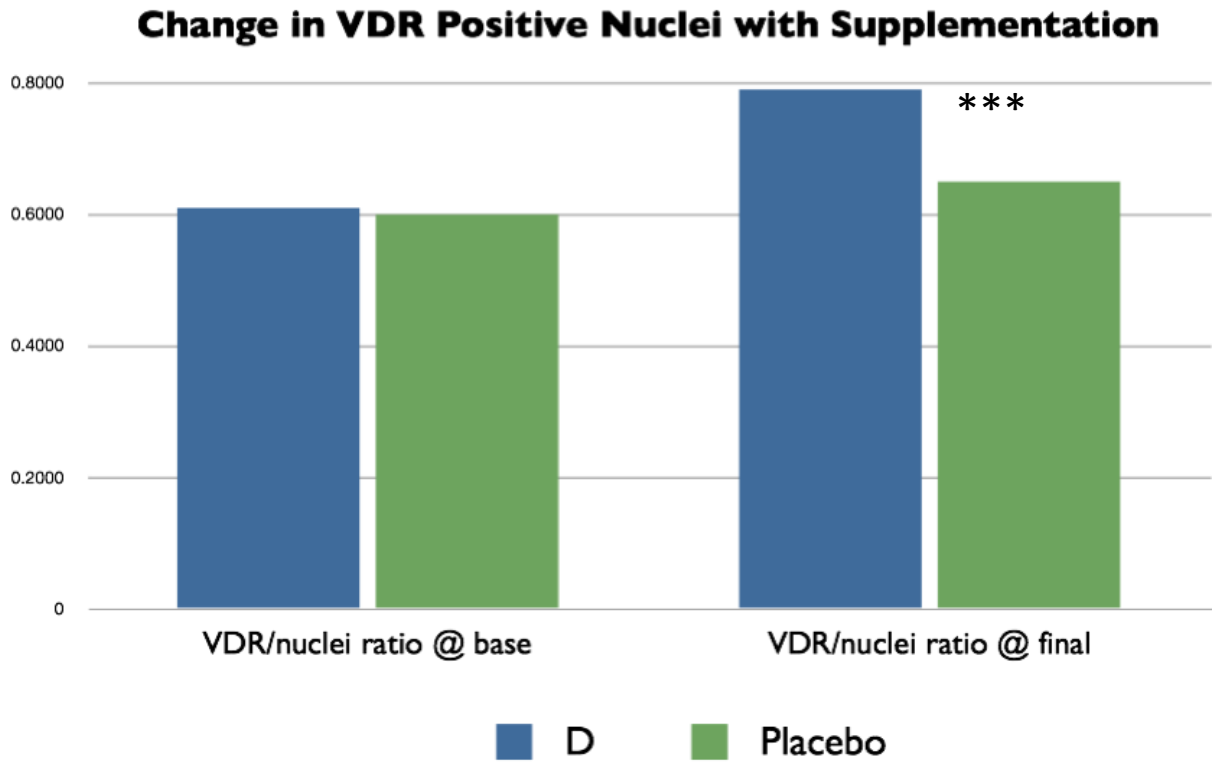
VDR vs 25OHD


<20ng/mL
>20ng/mL
VDR
GAPDH


Skeletal Muscle VDR Increases with 25OHD
VDR Protein Concentration (arbitrary units)
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
p=.0028, r=.66
0
10
20
30
40
50
60
25OHD (ng/mL)

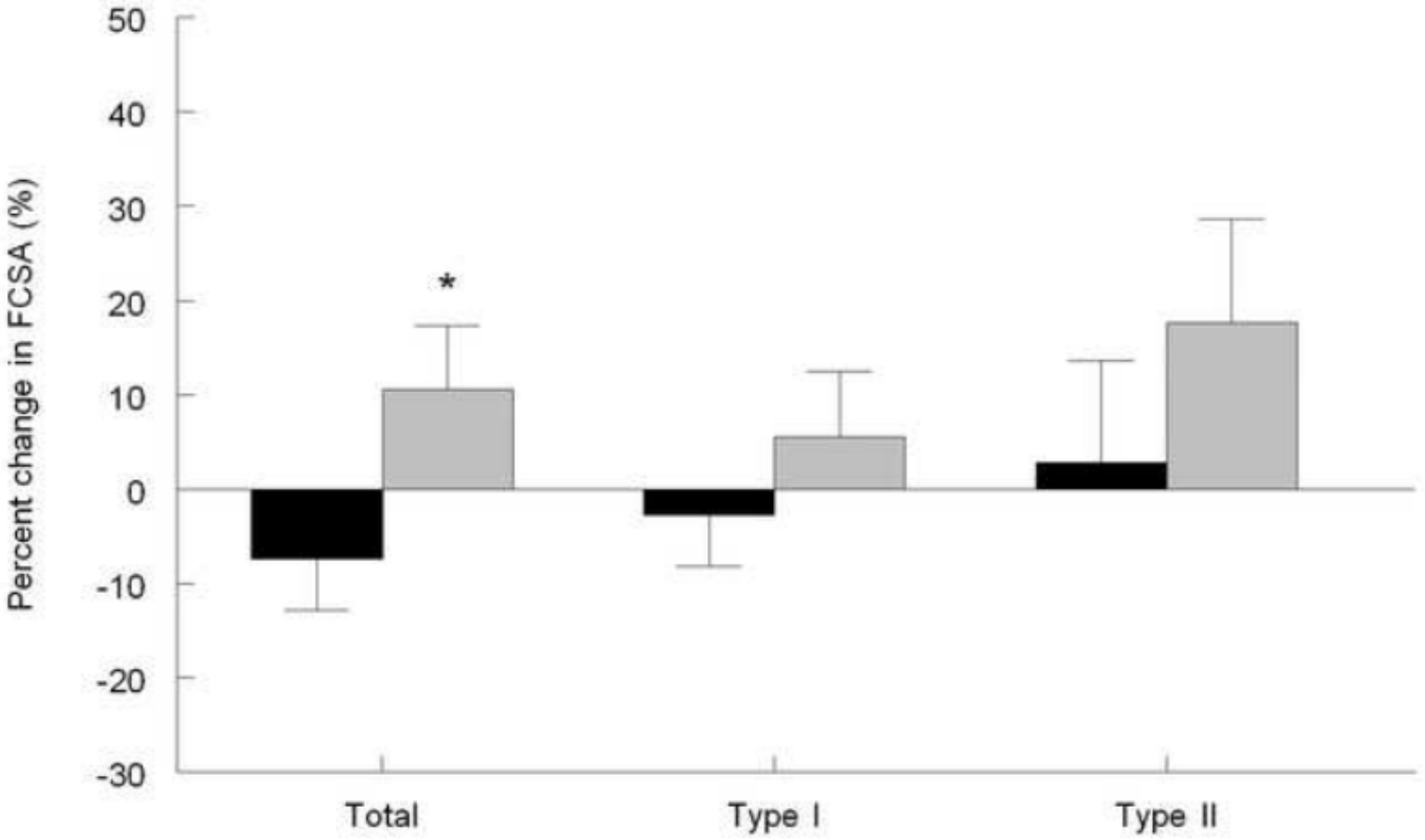

logVDR/GAPDH vs. Vitamin D Classificiation
logVDR/GAPDH
-1.0
-1.5
-2.0
-2.5
p=.02
2
3
Vitamin D Classificiation

29% Increase in Nuclear VDR with D Supplementation



Niramitmahapanya et al, 2012 (unpublished)

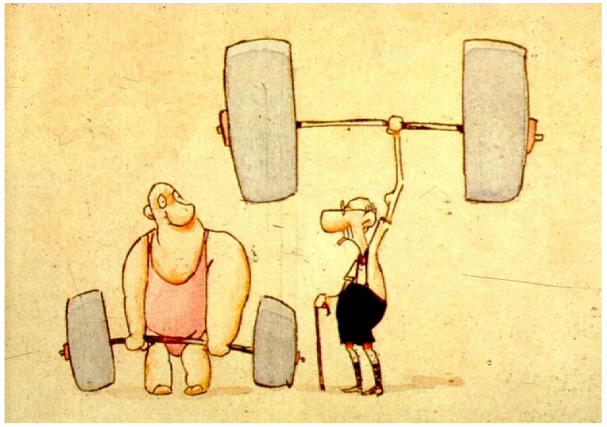
Change in muscle size with Vitamin D



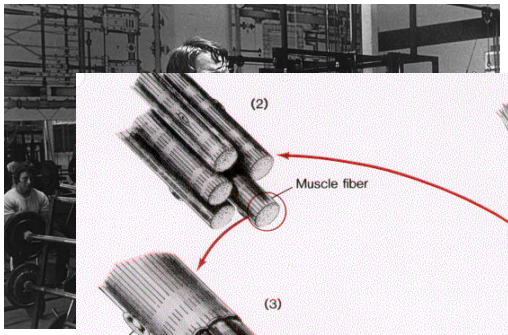
Ceglia et al. JCEM 2013

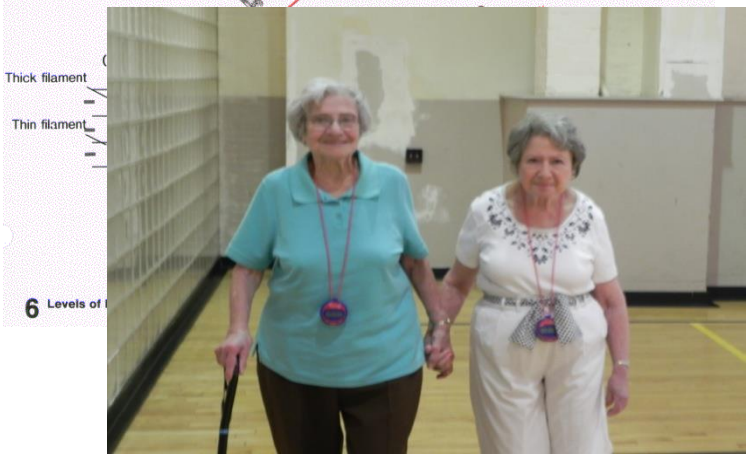
Awareness and Acceptance of Sarcopenia as a Clinical Syndrome/Disease has lagged: limited effective therapies currently available

- Objective definition linked to “hard” end points (mortality, falls, fractures).
- Agreement on appropriate outcomes for efficacy and registration trials.
- Establishment of treatment guidelines and billing codes (ICD 10 stablished).
- **Treatments are emerging but indications are lagging.**



Summary:





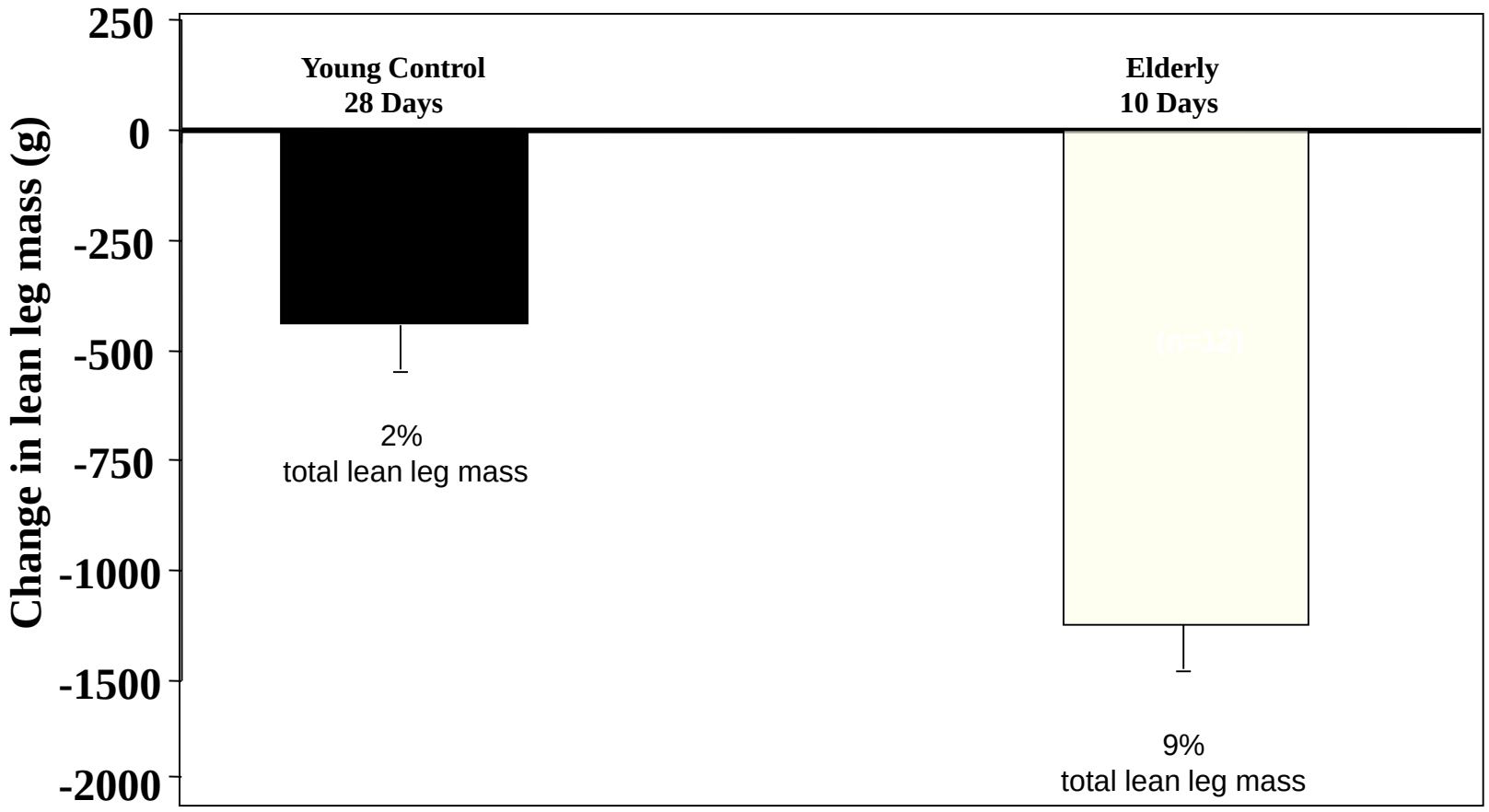
- Sarcopenia is the age-related loss in muscle mass and function.
- Nutritional factors related to protein intake and specific micronutrients affect sarcopenia progression.
- Nutritional interventions may play a role in the prevention and treatment of sarcopenia.

Bedrest and Aging

- 10 days complete bedrest
- 12 subjects, 67 ± 5 years
- Eucaloric diet, 0.8g protein/kg/d
- Body composition (DEXA)
- Fractional Synthetic Rate of muscle protein
  - 24-h infusion of $^{13}C_6$-phenylalanine, vastus lateralis biopsy pre-post infusion

Loss of Leg Muscle Mass: DEXA

Effect of 10 days of bed rest on skeletal muscle in Healthy older adults, *JAMA* 297: 2007



Whole body muscle loss: >2kg (~5% total lean mass)

Essential Amino Acid Composition (3 X day)

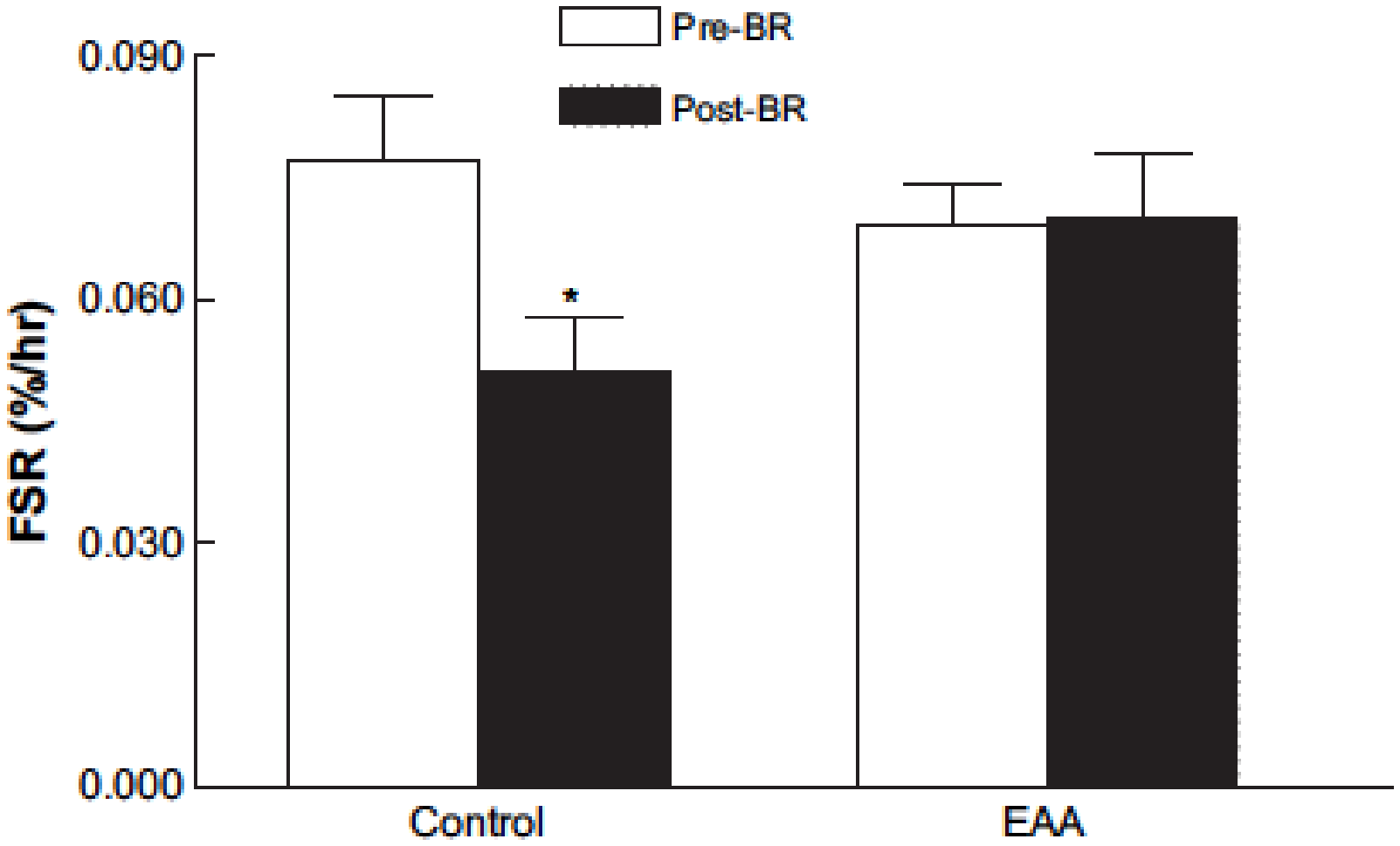
Composition of essential amino acid (EAA) drink.

Amino Acid	Amount (g)	Proportion of total (%)
Histidine	0.488	3.26
Isoleucine	1.286	8.57
Leucine	5.382	35.88
Lysine (HCl)	2.561	17.08
Methionine	0.538	3.59
Phenylalanine	0.698	4.65
Threonine	1.435	9.57
Valine	1.116	7.44
Arginine	1.495	9.97
Total	15.000	100.00

Caloric content = 45 kcal.

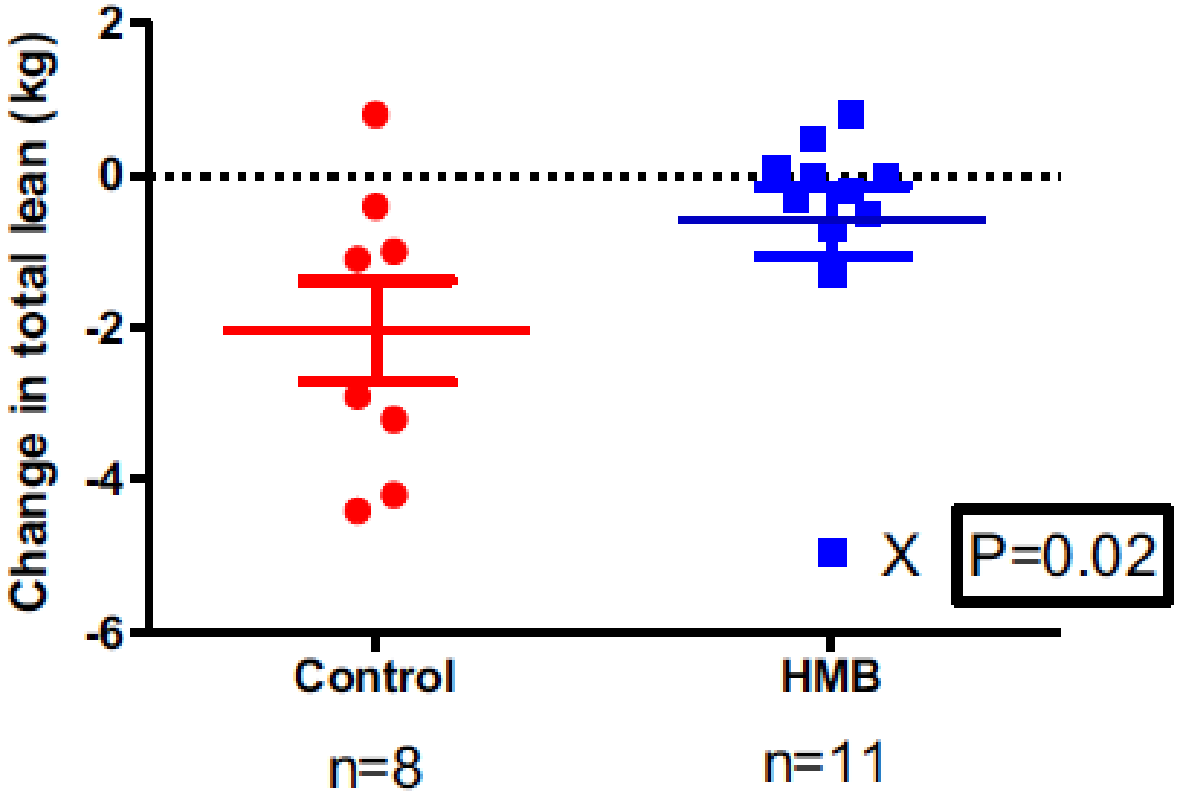
Ferrando et al. 2010

10 days of bedrest with EAA supplementation

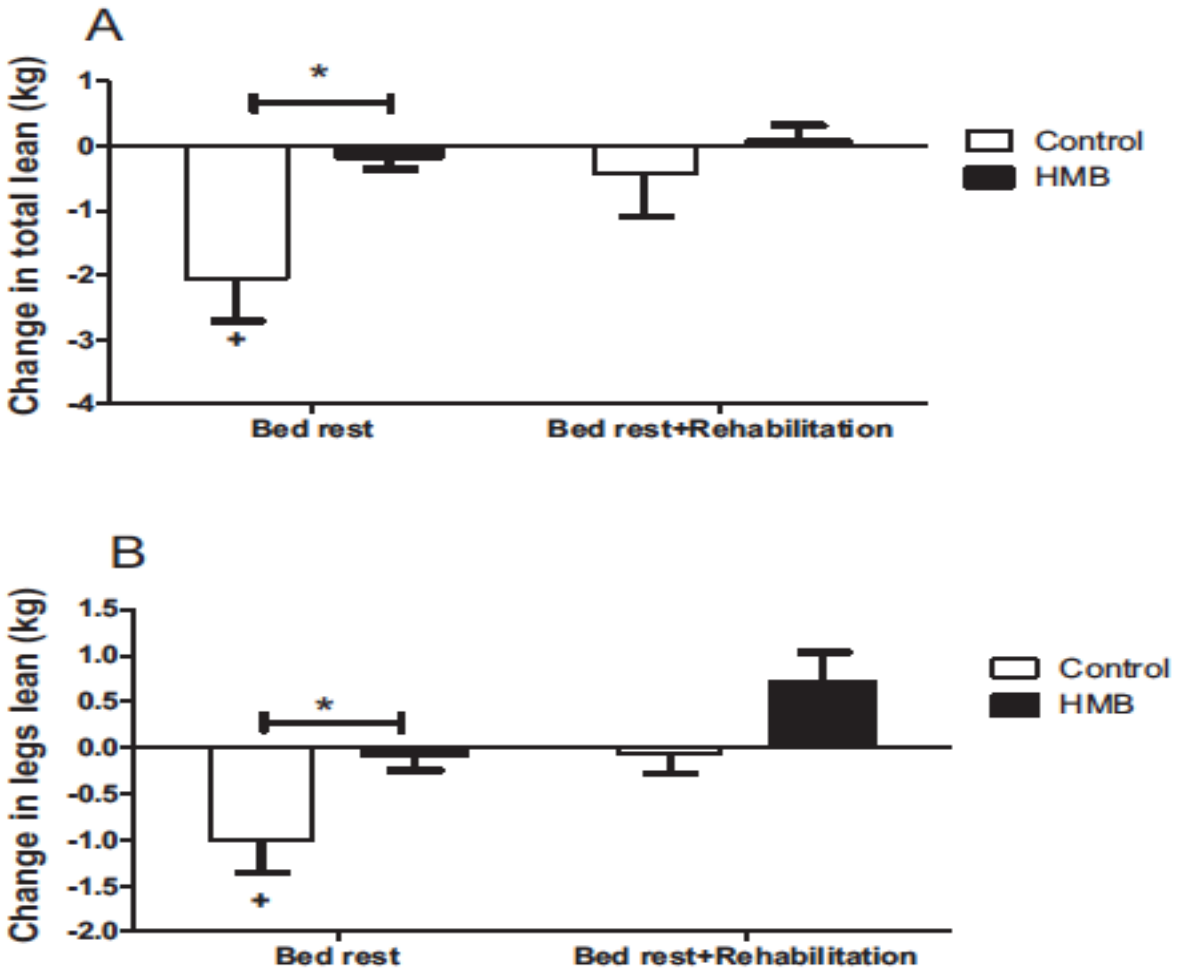


Ferrando et al. 2010

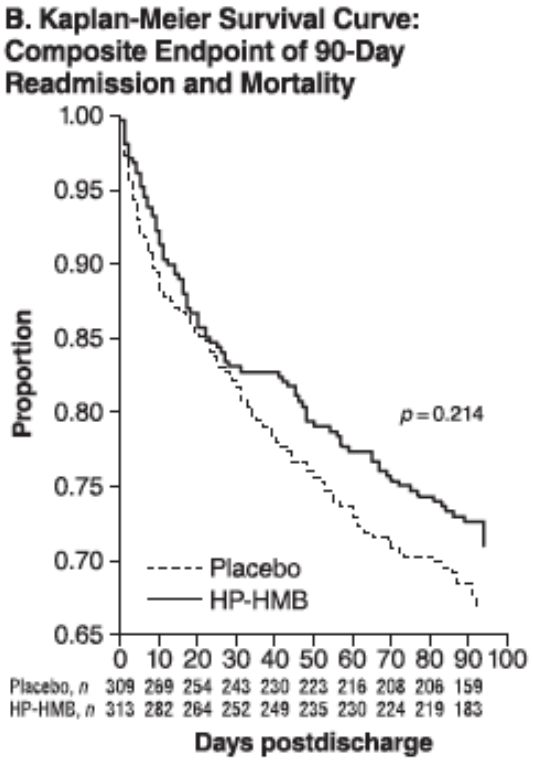
10 days of bedrest with HMB intervention

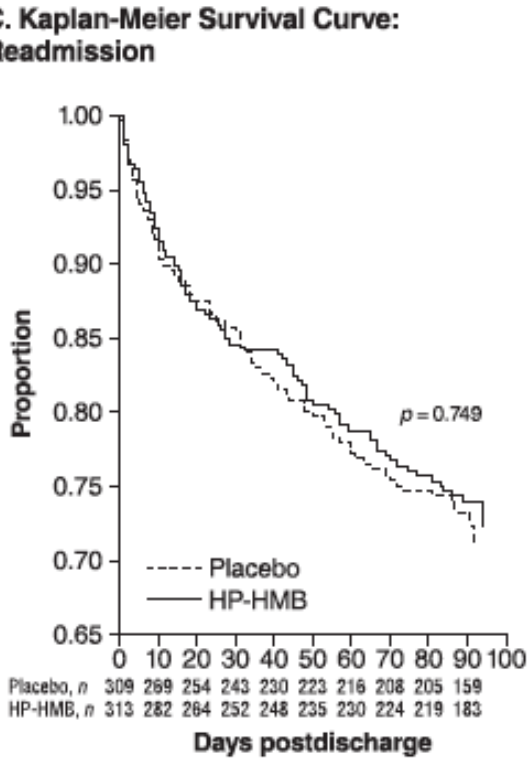


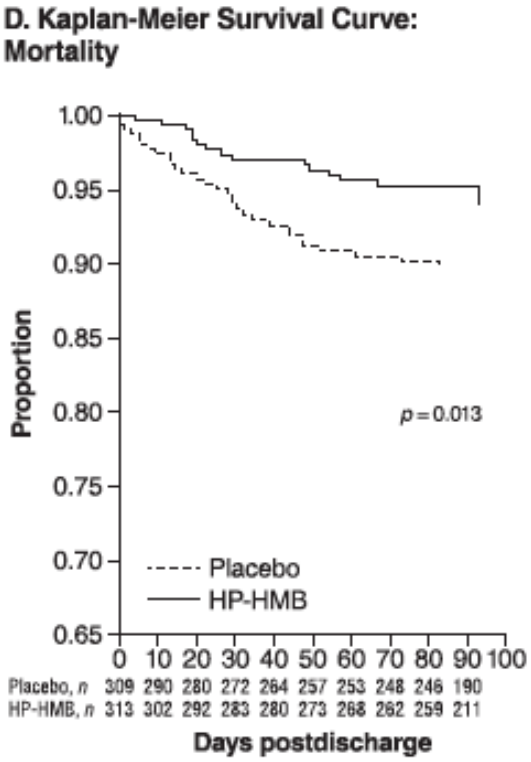
10 days of bedrest with HMB intervention



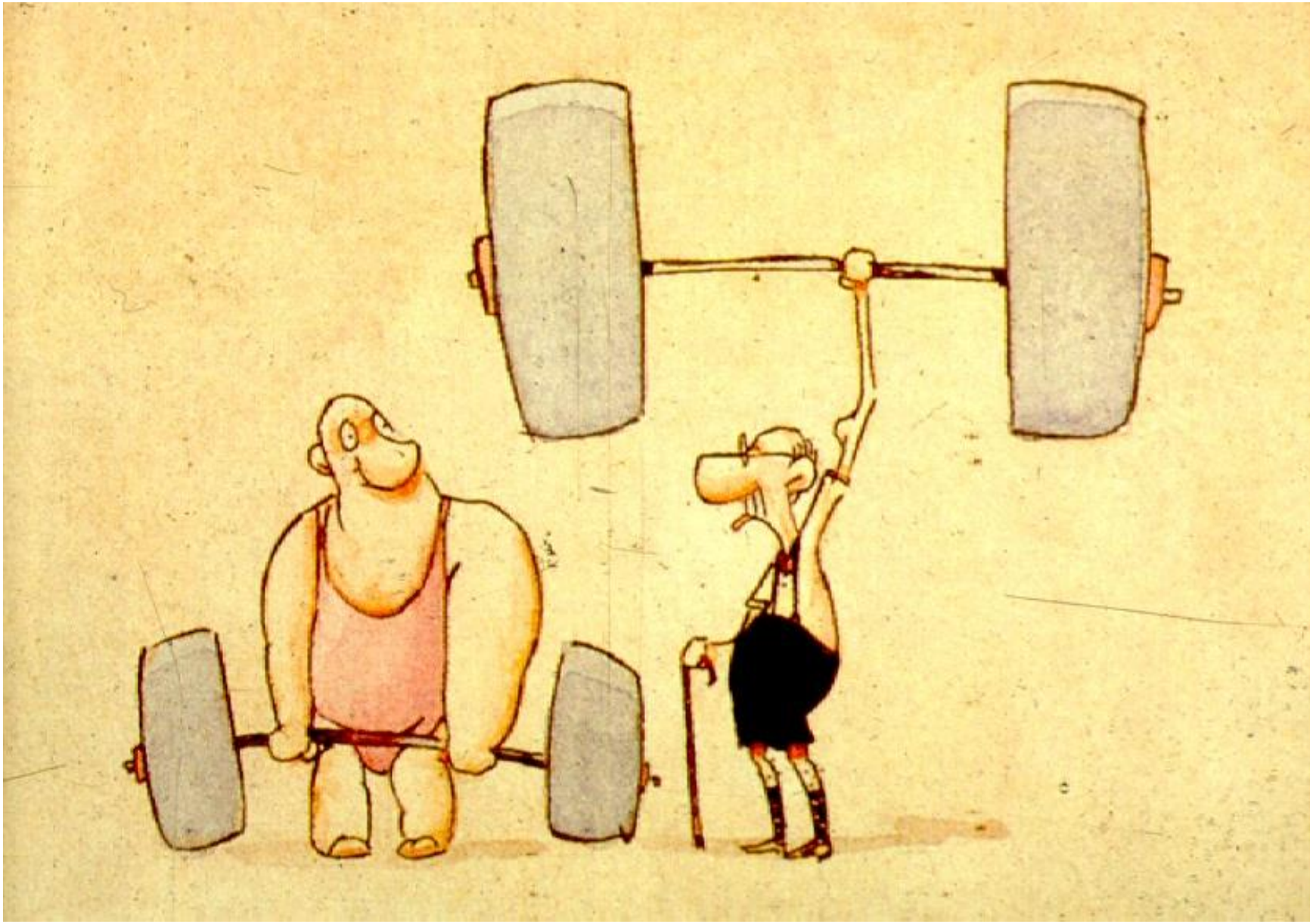
HMB and mortality in hospitalized patients







Deutz et al. Clin Nutr 2016



Nutritional intervention:

Whey Protein/Placebo(2 packets/day*)

- **Supplement packets were given to subjects weekly.**
- **Adherence was assessed by empty packet return/logs and urinary PABA recovery (200 mg per packet).**
- **Subjects were instructed to consume supplements after regular meals.**

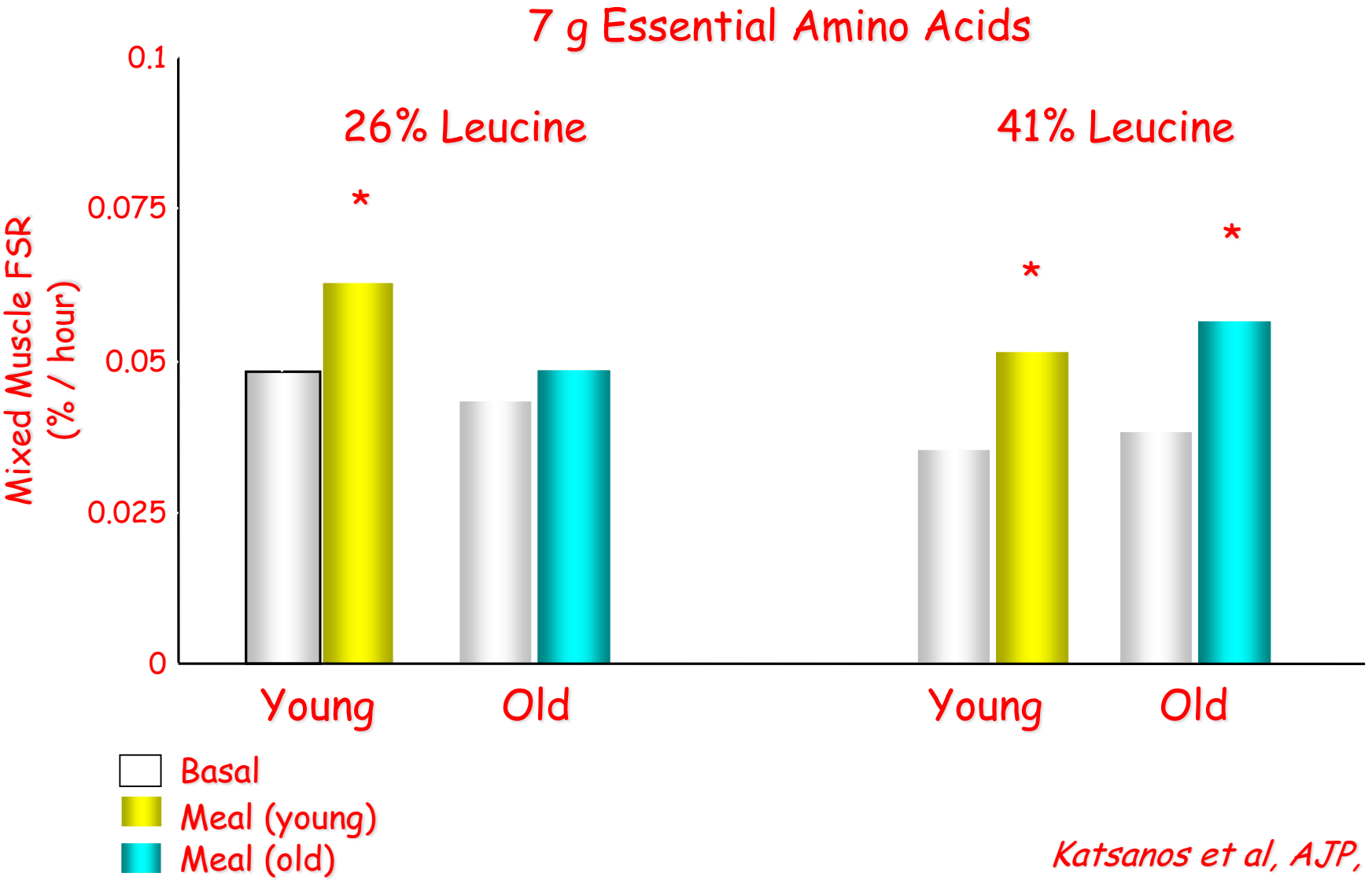
Whey	Placebo
20 g protein (whey concentrate)	NA
25 g maltodextrin	45 g maltodextrin
1 g fat	1 g fat
189 kcal (791 kJ)	189 kcal (791 kJ)

***On exercise training days supplements were consumed immediately after exercise (on site).**

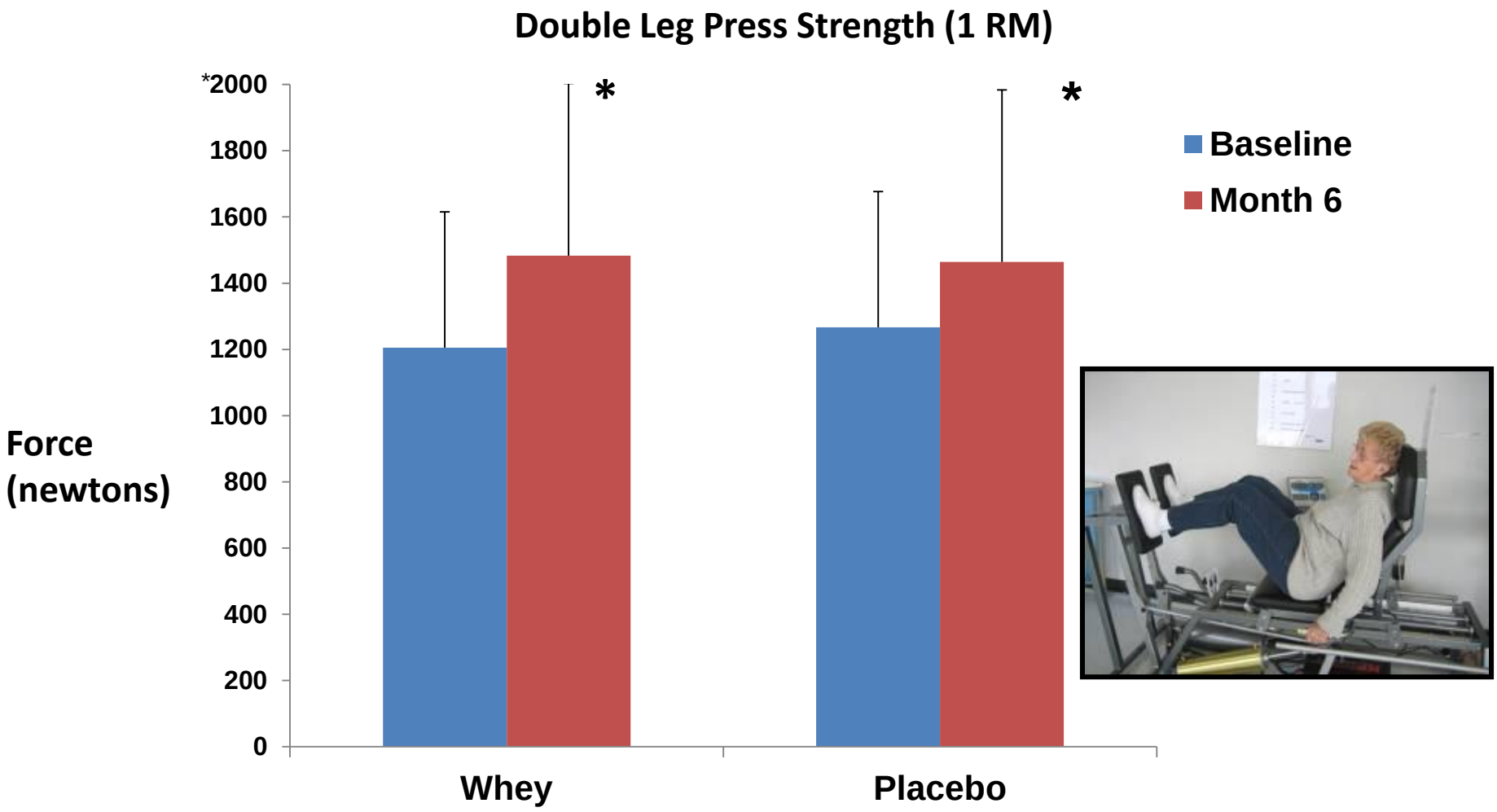
Intervention adherence

	Whey N=42 N (%)	Placebo N=38 N (%)
Study withdrawals	3	2
Exercise attendance	79.9 ± 20.8	80.2 ± 21.7
Supplement adherence (packets returned)	72.1 ± 29.3	82.3 ± 21.9
Completed both ≥ 70% of exercise & < 2 consecutive neg. urine PABA	28	31

Leucine Content is an Important Determinant of the Muscle Anabolic Response to Feeding in Aging



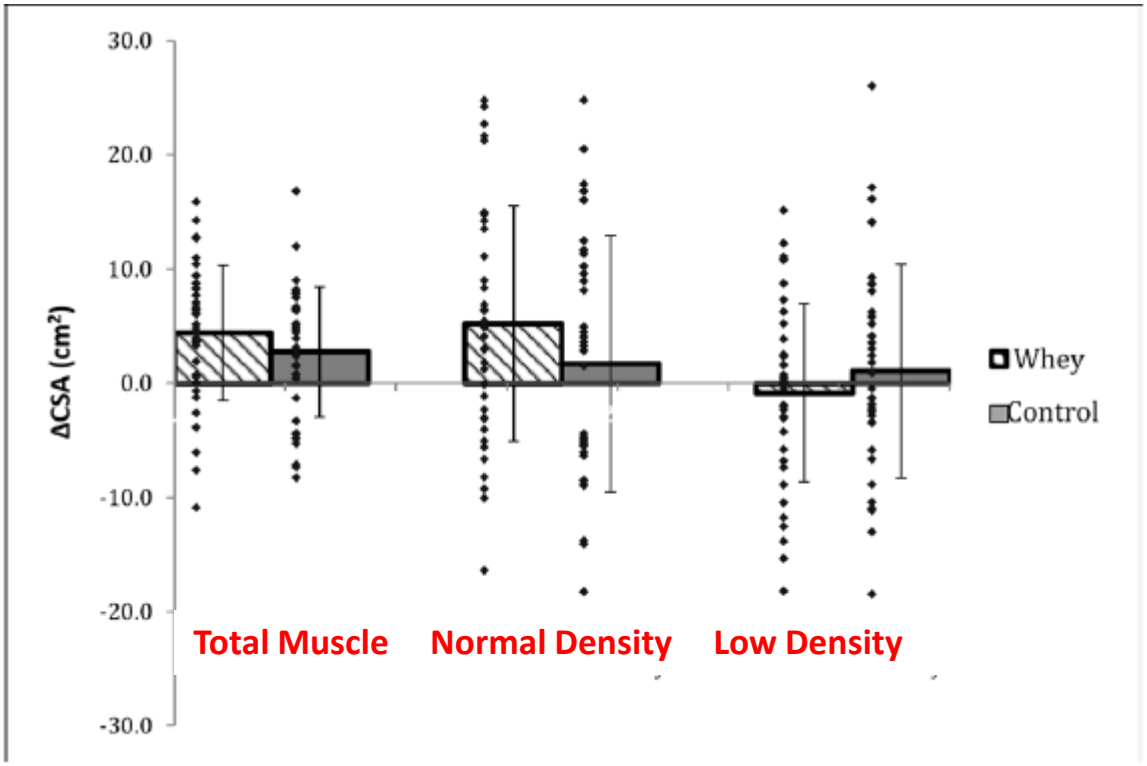
Katsanos et al, AJP, 2006

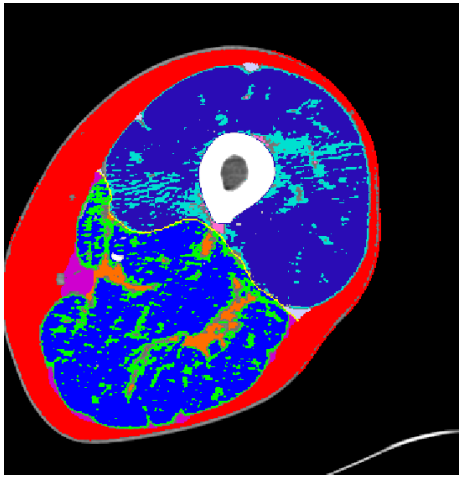


Time/supplement interaction P=0.43; * time effect P < 0.0001

Chale' et al. J Gerontol 2012

Change in Mid-thigh muscle cross sectional area (C-T)





Time/supplement interaction P=0.18; * time effect P < 0.008

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Physical Function measures

Physical Function measure	Baseline	6 months	P value interaction	P value time
Stair climb time (s)			0.64	0.03
Whey	7.6 ± 4.1	7.1 ± 3.9		
Placebo	8.6 ± 4.7	7.0 ± 3.2		
Chair rise time (s; 10X)			0.25	0.0001
Whey	32.1 ± 9.6	25.2 ± 6.9		
Placebo	33.9 ± 16.1	29.8 ± 16.0		
SPPB score			0.49	0.0001
Whey	8.5 ± 1.1	10.3 ± 1.5		
Placebo	8.4 ± 1.7	10.0 ± 1.8		
400 m walk (gait speed; $m \cdot s^{-1}$)			0.11	0.13
Whey	1.07 ± 0.19	1.12 ± 0.22		
Placebo	1,03 ± 0.18	1.04 ± 0.25		

Dietary Protein Intake

Protein Intake	Baseline	6 months	Point Estimates (95% C.I.)	P value time
Dietary Protein			-6 (-14,1)	0.015
Whey	71 ± 17	64 ± 15		
Placebo	72 ± 19	68 ± 18		
Total Protein (including supplement)			18 (8,29)	0.0001
Whey	71 ± 17	89 ± 22		
Placebo	72 ± 19	69 ± 19		