UNIVERSITÀ DEGLI STUDI DI VERONA

La Sarcopenia
Definizione, Patogenesi e Trattamento


REMDICONTO
DELLE ADUNANZE
dell' Accademia
MEDICO-CHIRURGICA
DI FERRARA
DEGLI ANNI
1846 -- 1847 -- 1848 -- 1849

L'approccio Nutrizionale e Farmacologico

Prof Mauro Zamboni

Clinica Geriatrica

Università di Verona

Società Medico Chirurgica di Ferrara

19 Ottobre 2013
Aula Magna Nuovo Ospedale S. Anna
Cona, Ferrara

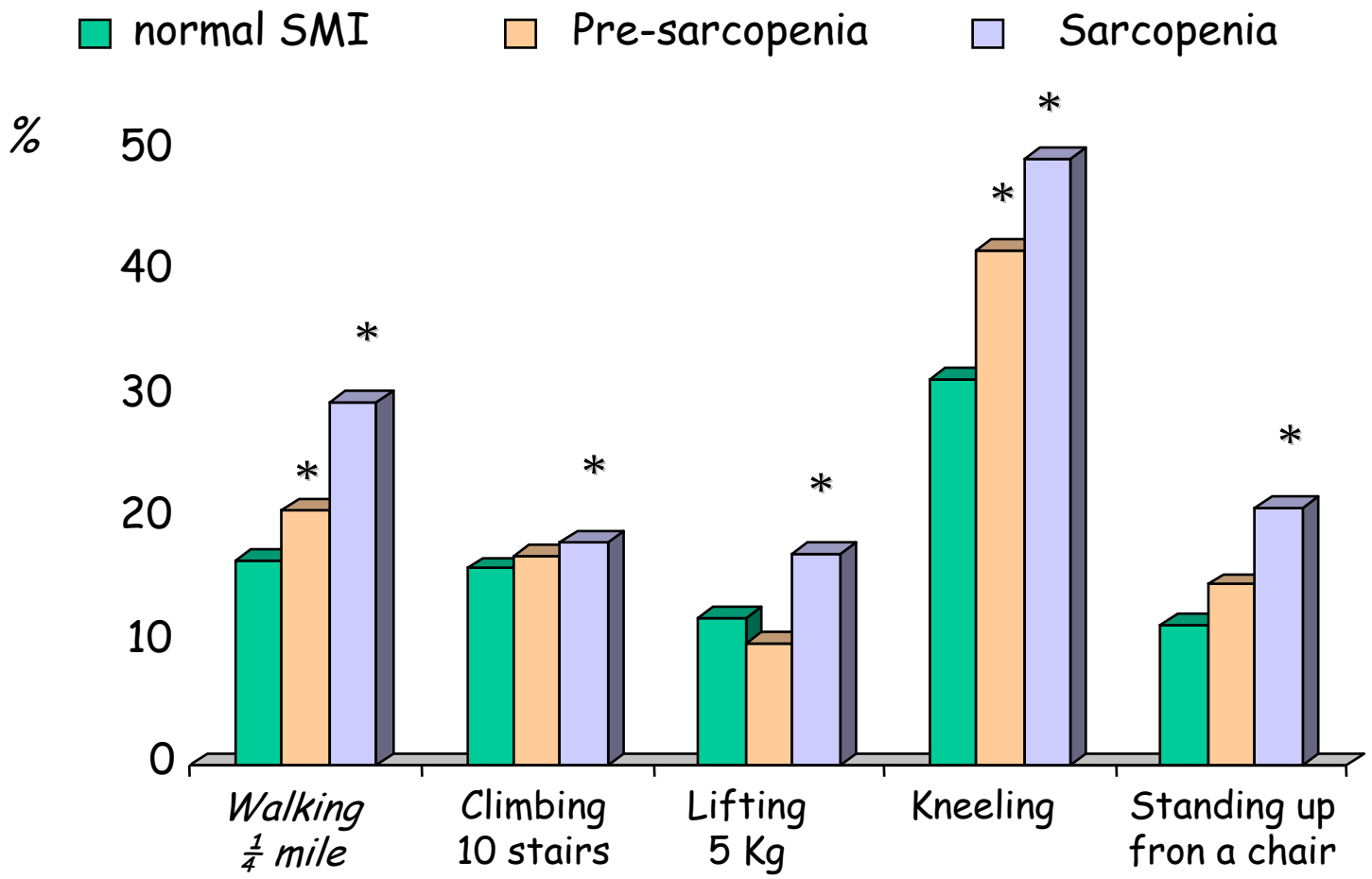
Why to identify Sarcopenia ?

"Sarcopenia is becoming recognized as a major cause of disability and morbidity in the elderly population".

Roubenoff and Hughes, 2000

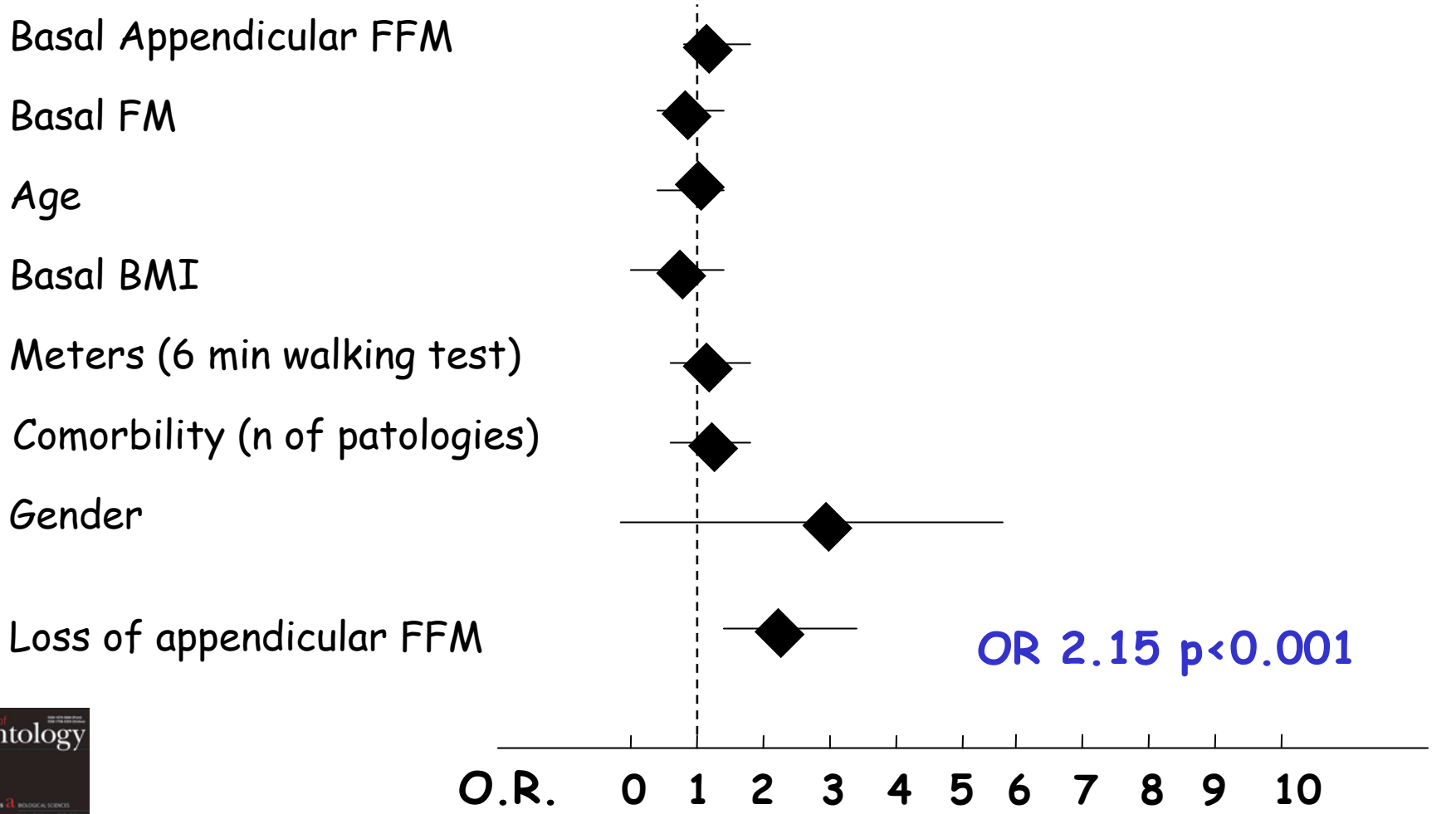
Functional impairment according to skeletal muscle index

NHANES III (n =2224 men older than 60 years)



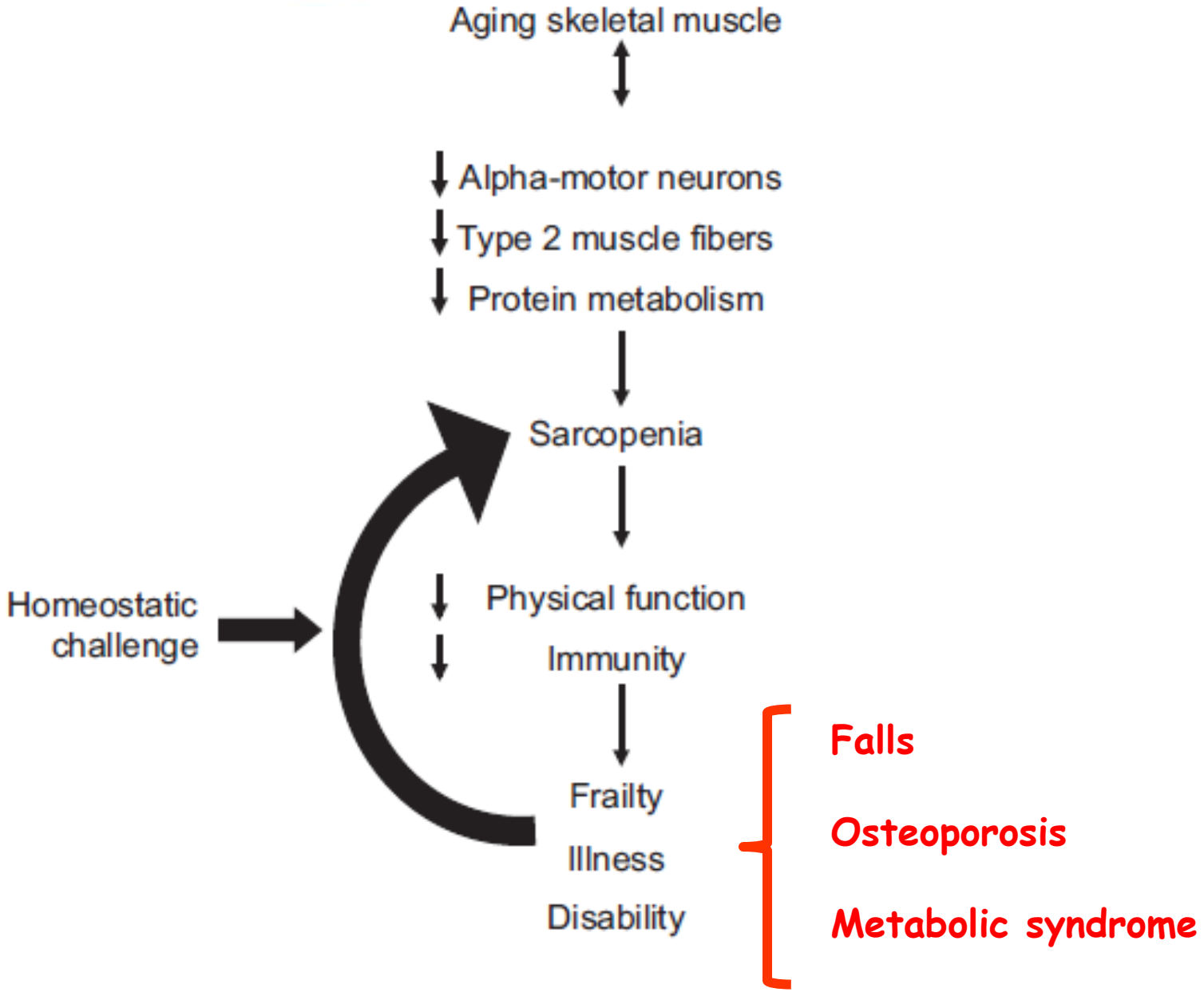
Janssen et al, 1998

Predictors of worsening disability during the follow-up period 5.5 years (160 subjects older 70)



Fantin et al, 2007

Clinical Interventions in Aging



Waters et al, 2010

Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study

197 subjects living in community
7- years follow up

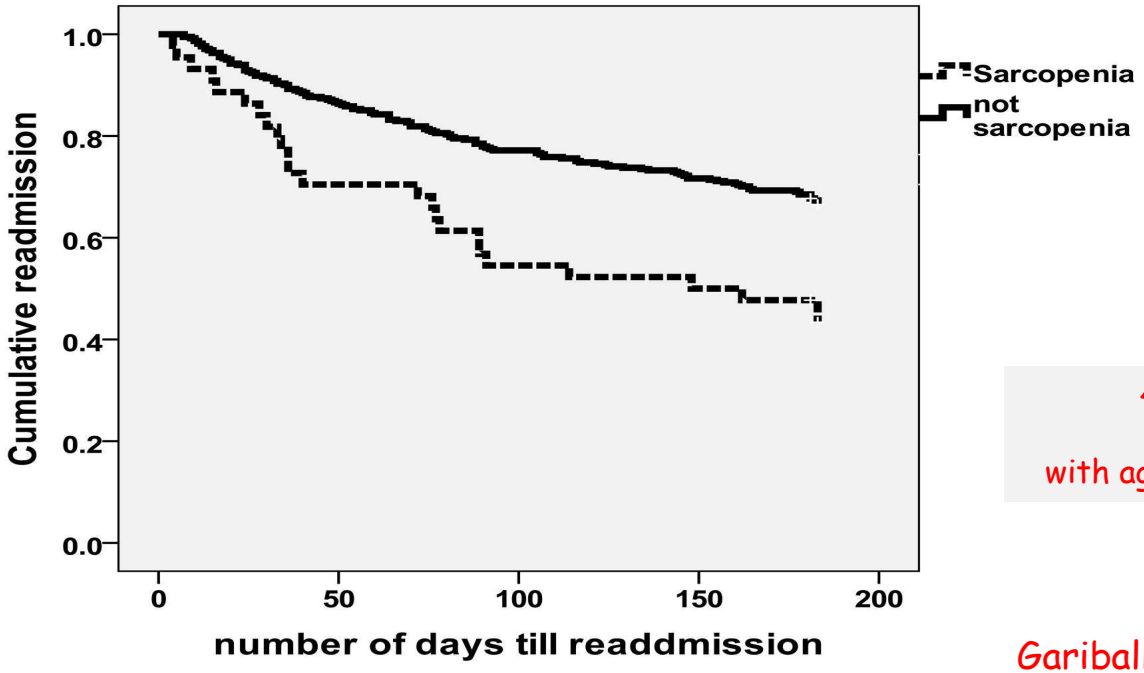
FRANCESCO LANDI[1,2], ALFONSO J. CRUZ-JENTOFT[3,†], ROSA LIPEROTI[1,†], ANDREA RUSSO[1], SILVIA GIOVANNINI[1], MATTEO TOSATO[1], ETTORE CAPOLUONGO[4], ROBERTO BERNABEI[1], GRAZIANO ONDER[1]

	Unadjusted	Model 1	Model 2	Model 3
	Hazard ratio (95% confidence interval)			
Sarcopenia	2.95 (1.44–6.04)	2.89 (1.40–5.96)	2.40 (1.07–5.42)	2.32 (1.01–5.43)
Age		1.15 (0.93–1.42)	1.08 (0.85–1.36)	1.12 (0.87–1.43)
Gender (female)		0.55 (0.29–1.03)	0.49 (0.25–0.99)	0.49 (0.23–1.04)
Education			0.87 (0.72–1.04)	0.87 (0.72–1.05)
ADL impairment			1.91 (1.29–2.83)	1.75 (1.20–2.56)
Body mass index			0.92 (0.86–0.99)	0.93 (0.86–1.01)
Hypertension				0.60 (0.26–1.35)
Congestive heart failure				6.71 (0.70–64.1)
COPD				1.46 (0.50–4.21)
Number of diseases				1.29 (0.92–1.80)
TNF-α				0.99 (0.85–1.15)

Model 1: adjusted for age, gender.
Model 2: adjusted for age, gender, education, ADL impairment, body mass index.
Model 3: adjusted for age, gender, education, ADL impairment, body mass index, hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), number of diseases, TNF-α.
Age, education, ADL impairment, body mass index, number of diseases, TNF-α was treated as a continuous variable.

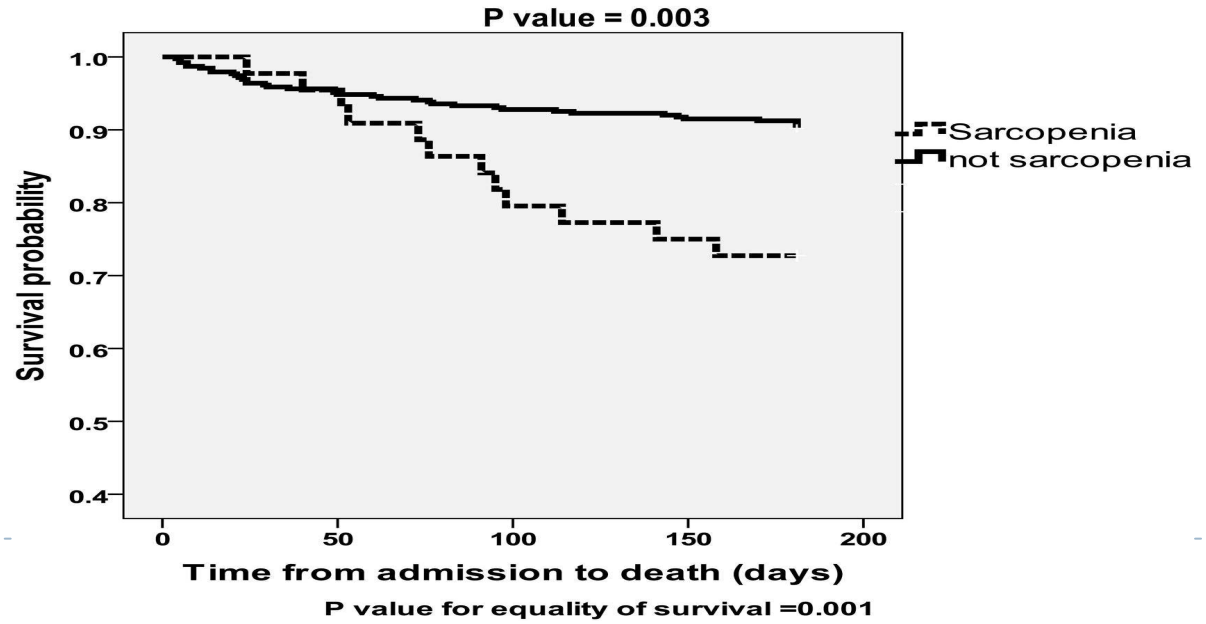
Age and Ageing 2013; **0:** 1–7
doi: 10.1093/ageing/afs194

6-months hospital readmission

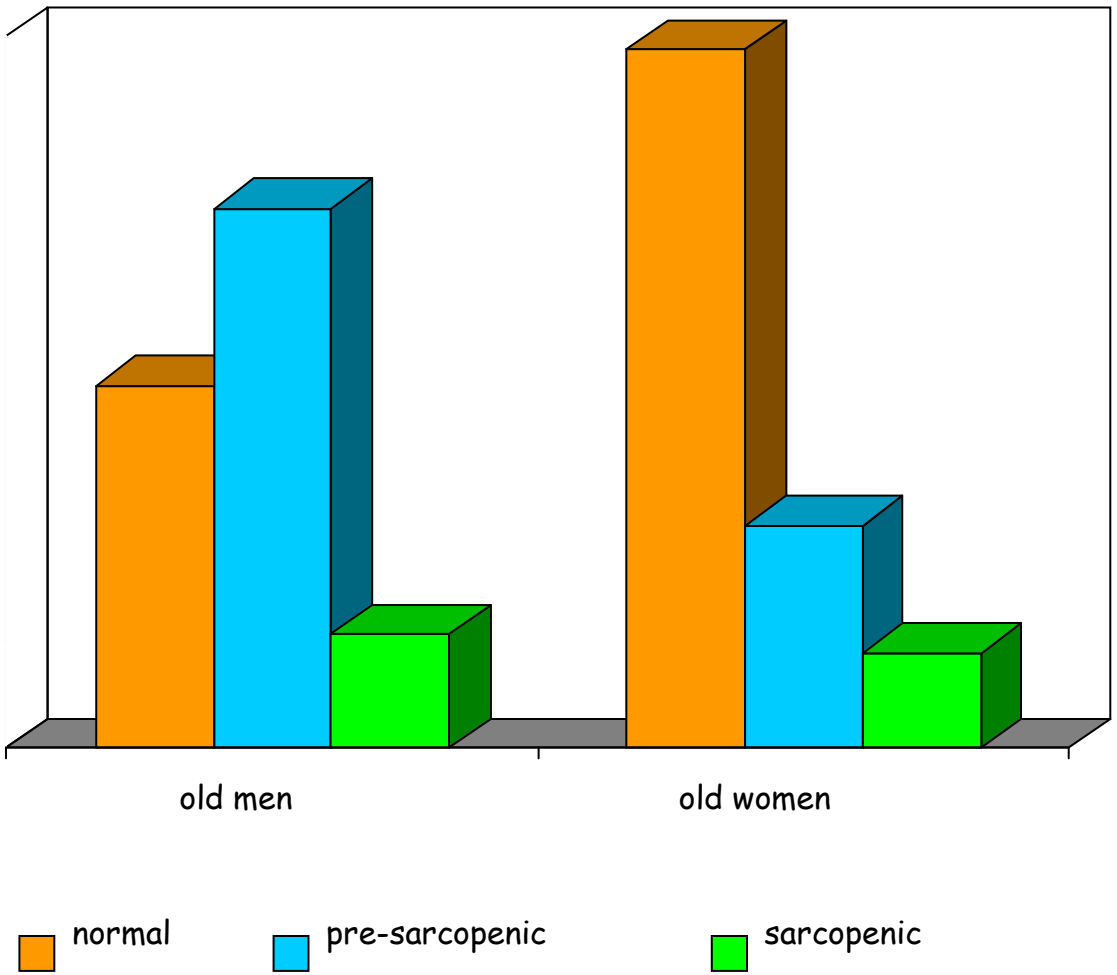


432 hospitalized
ill older patients
with age higher than 65 years

Gariballa and Alessa, 2013



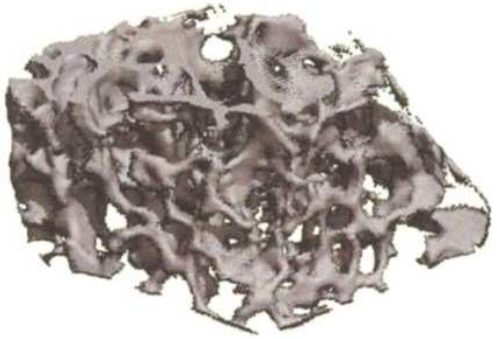
Bilions $			7.18	3.63		2.7	4.96
Relative Risk disability%	1	3.48	4.6		1	1.46	3.15



Janssen et al, J am Geriatri Soc 2004, 52, (1), 80-85

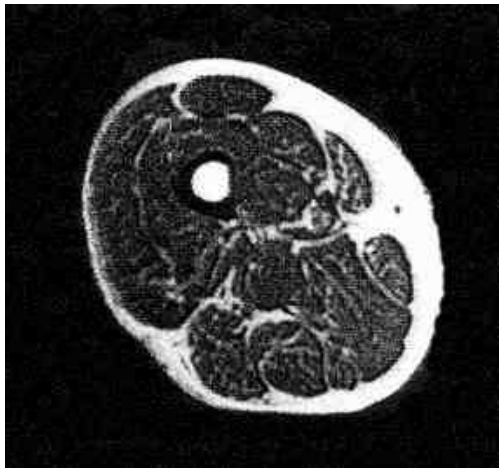
Yearly costs, (US)

Osteoporotic fractures



$16.3 billion

Sarcopenia

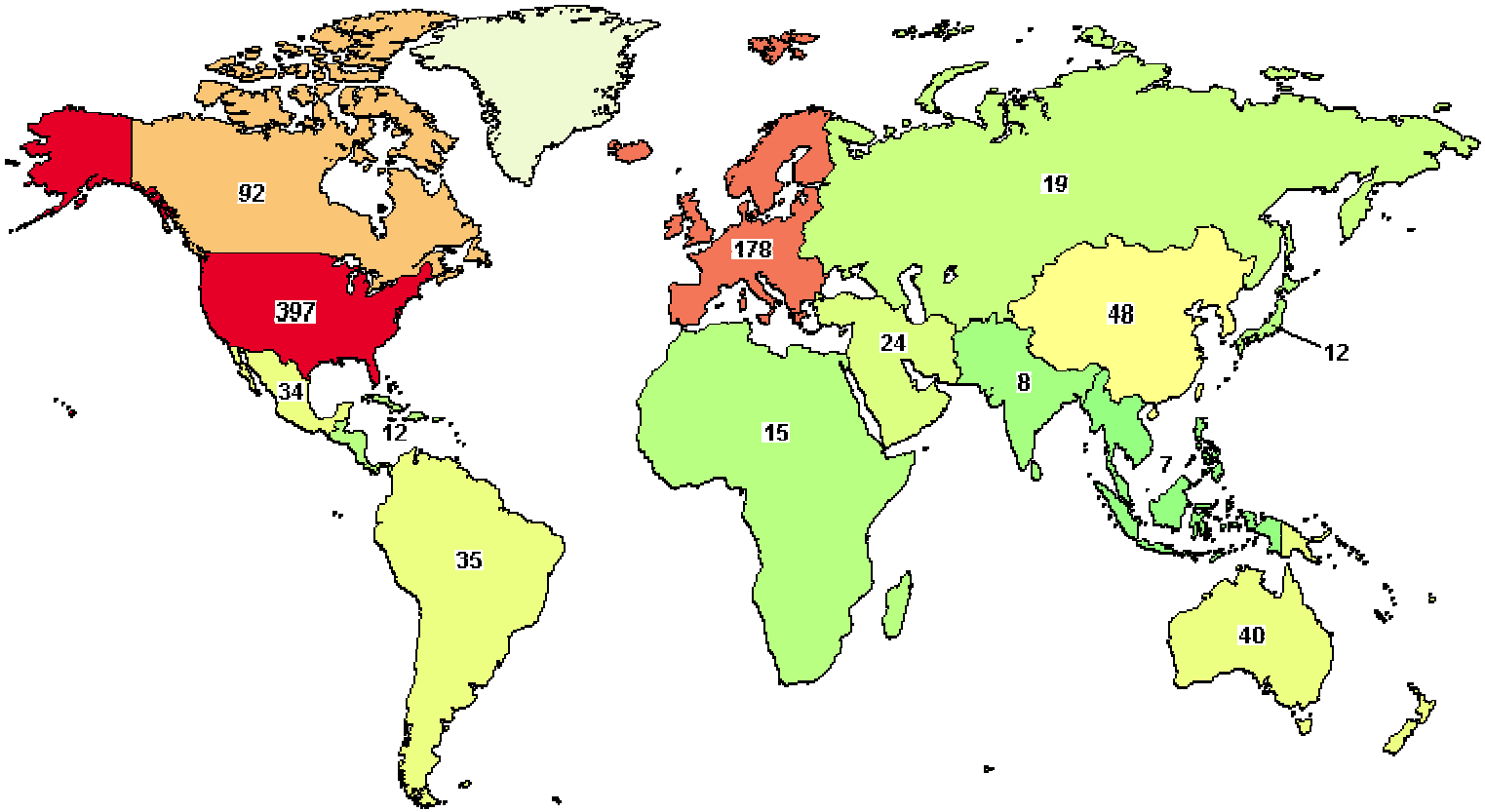


$18.5 billion

J Am Geriatr Soc 52:80–85, 2004

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

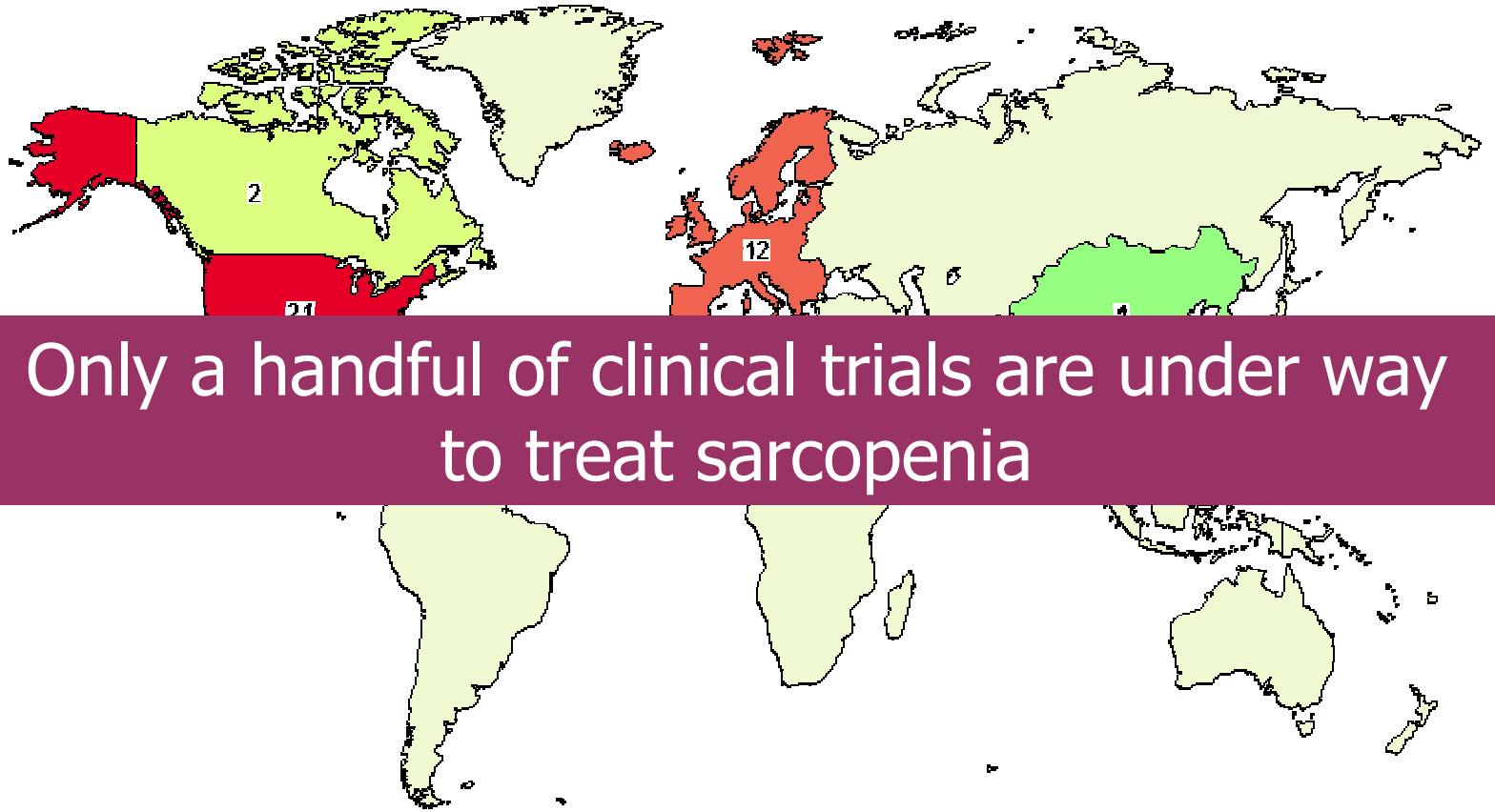
March 2013



Map of 1121 studies found by search of: osteoporosis

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

March 2013



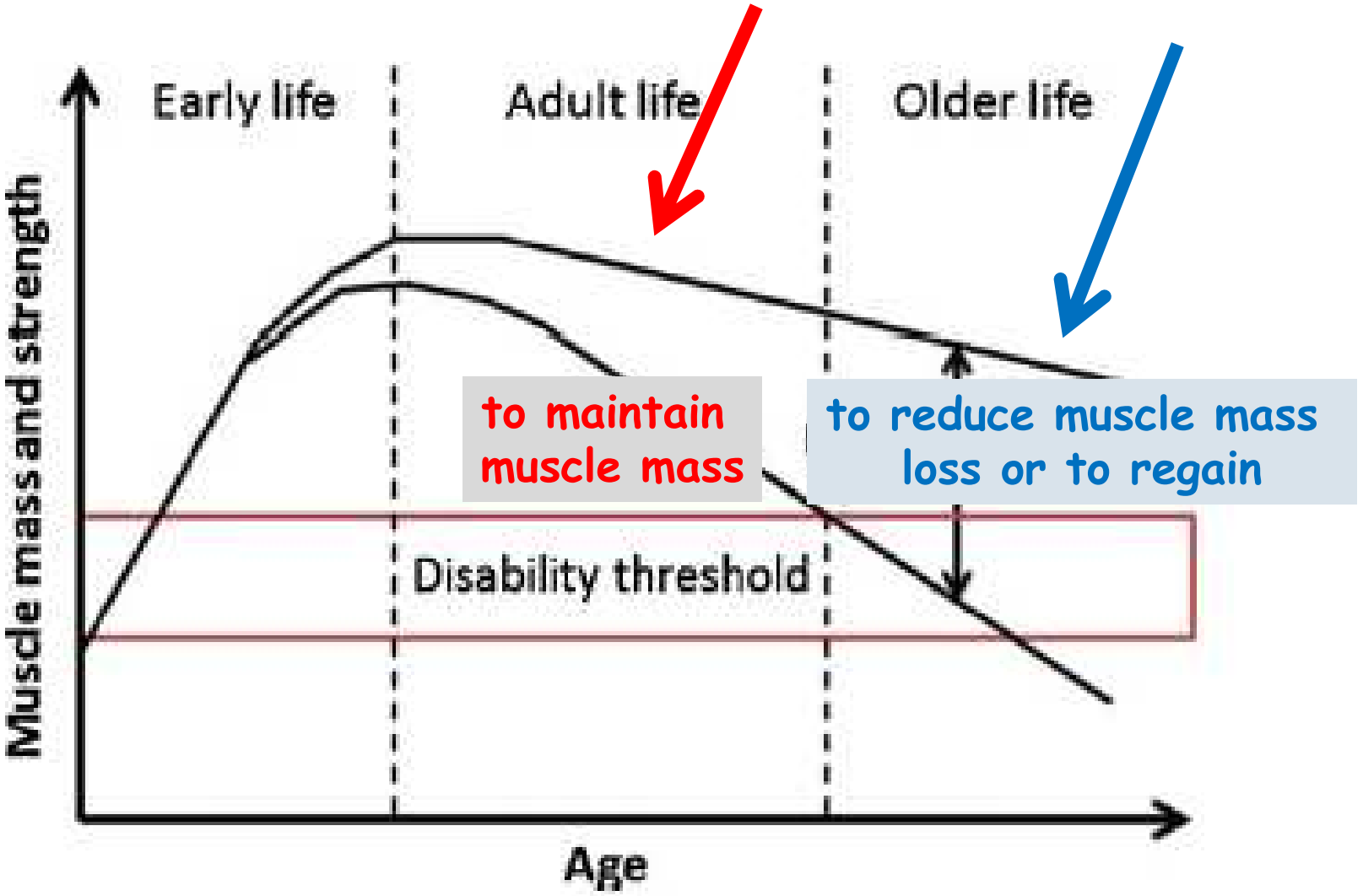
Only a handful of clinical trials are under way to treat sarcopenia

Map of 101 studies found by search of: sarcopenia

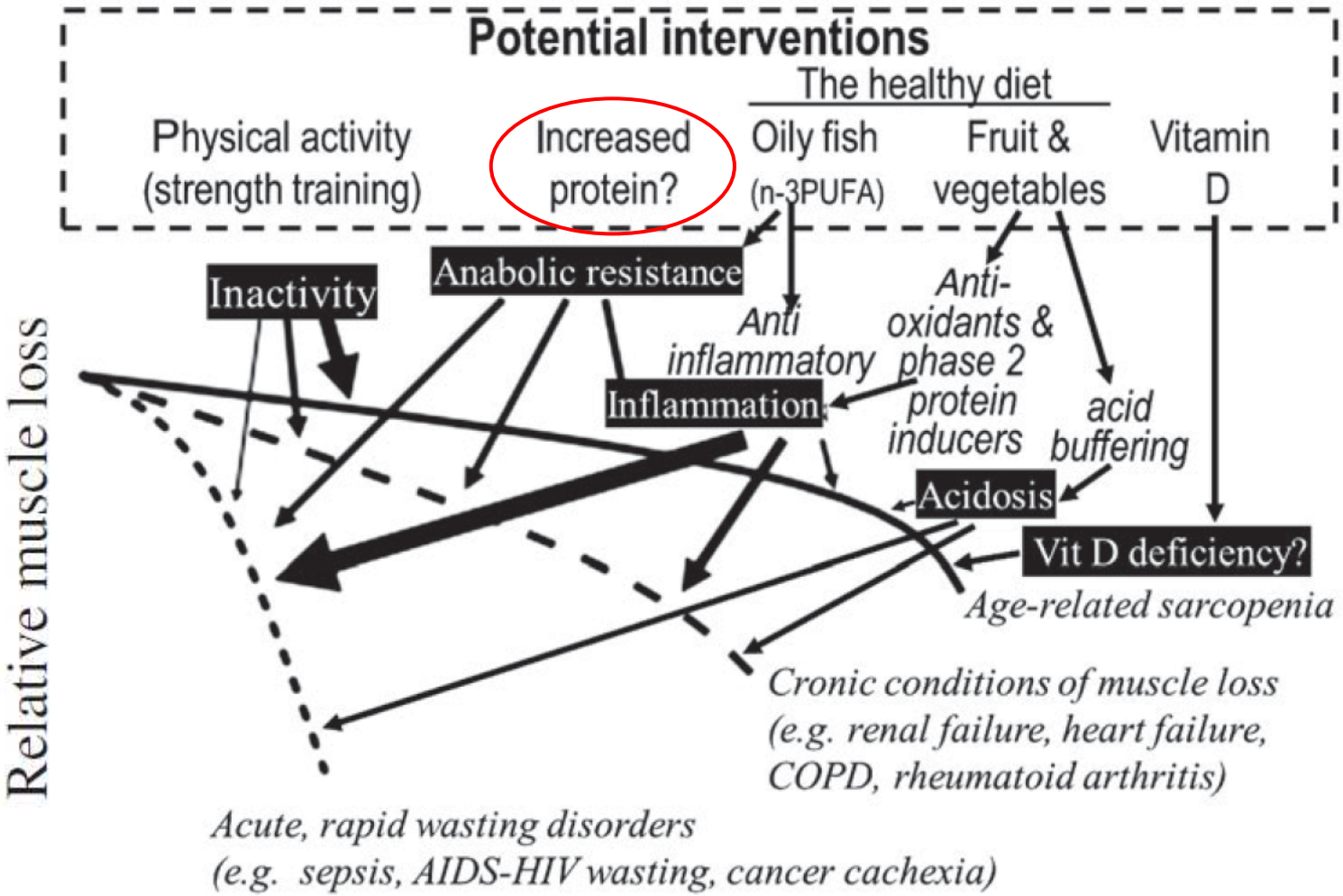
A. Mithal · J.-P. Bonjour · S. Boonen · P. Burckhardt · H. Degens · G. El Hajj Fuleihan · R. Josse · P. Lips · J. Morales Torres · R. Rizzoli · N. Yoshimura · D. A. Wahl · C. Cooper · B. Dawson-Hughes · for the IOF CSA Nutrition Working Group

Osteoporos Int 18 December 2012

different aims

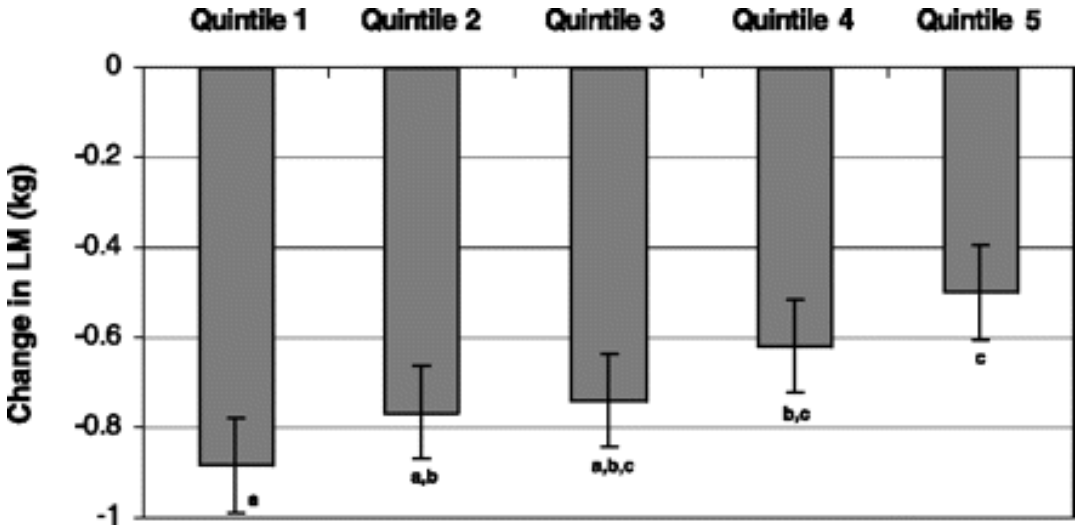


Nutrition and sarcopenia: evidence for an interaction



D. Joe Millward

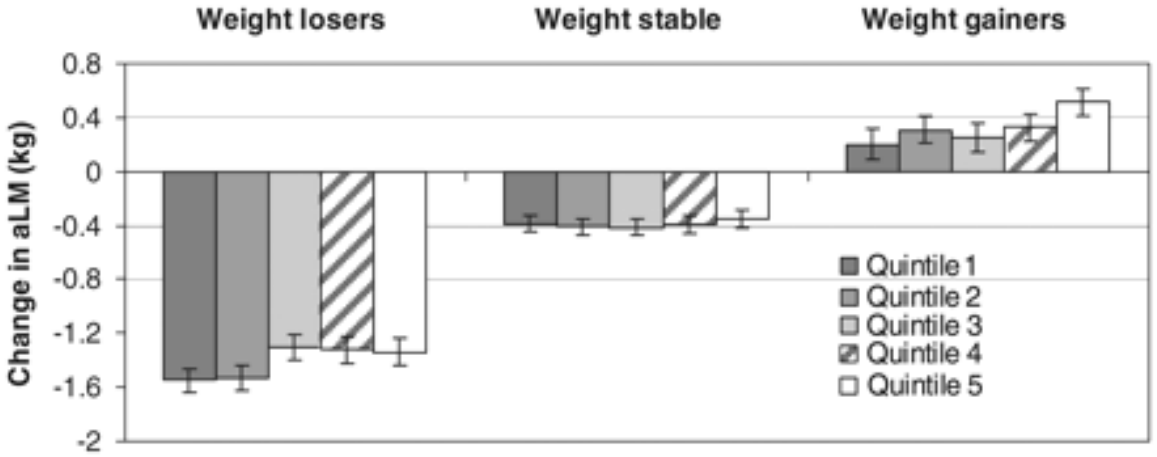
Proceedings of the Nutrition Society (2012), **71**, 566–575



Adjusted lean mass (LM) loss by quintile of energy-adjusted total protein intake. N= 2066

Protein intake: from 0.7 g/kg to 1.2 g/kg

Adjusted lean mass (LM) loss by quintile of energy-adjusted total protein intake and weight change status. N= 2066

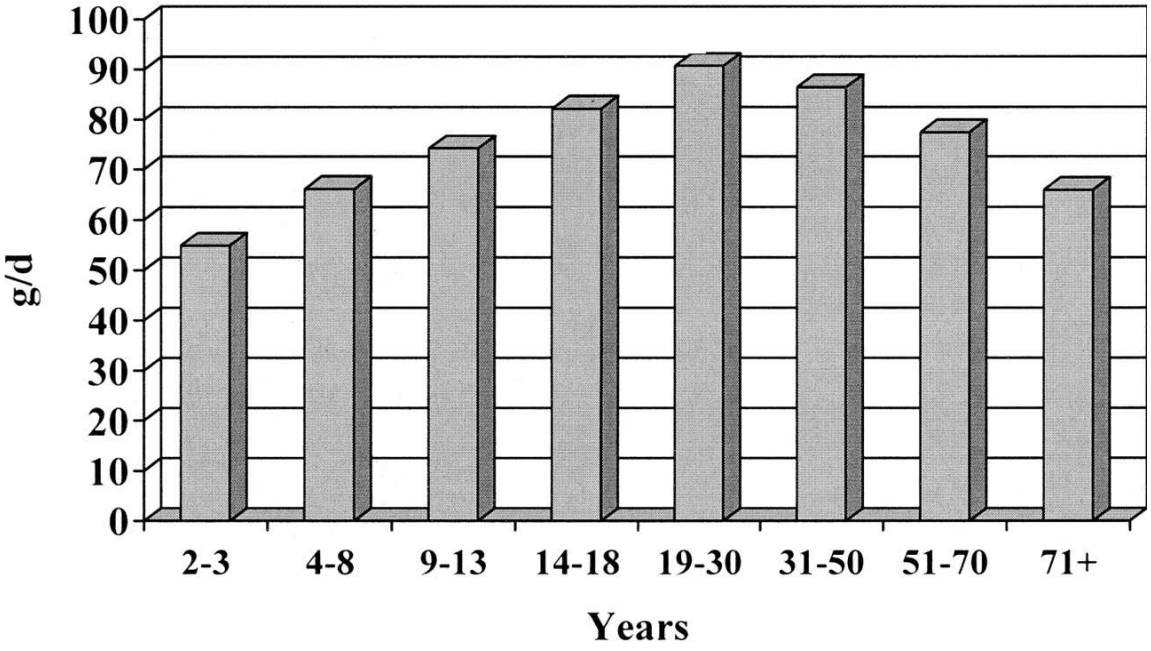


Low protein intake means higher risk of Sarcopenia

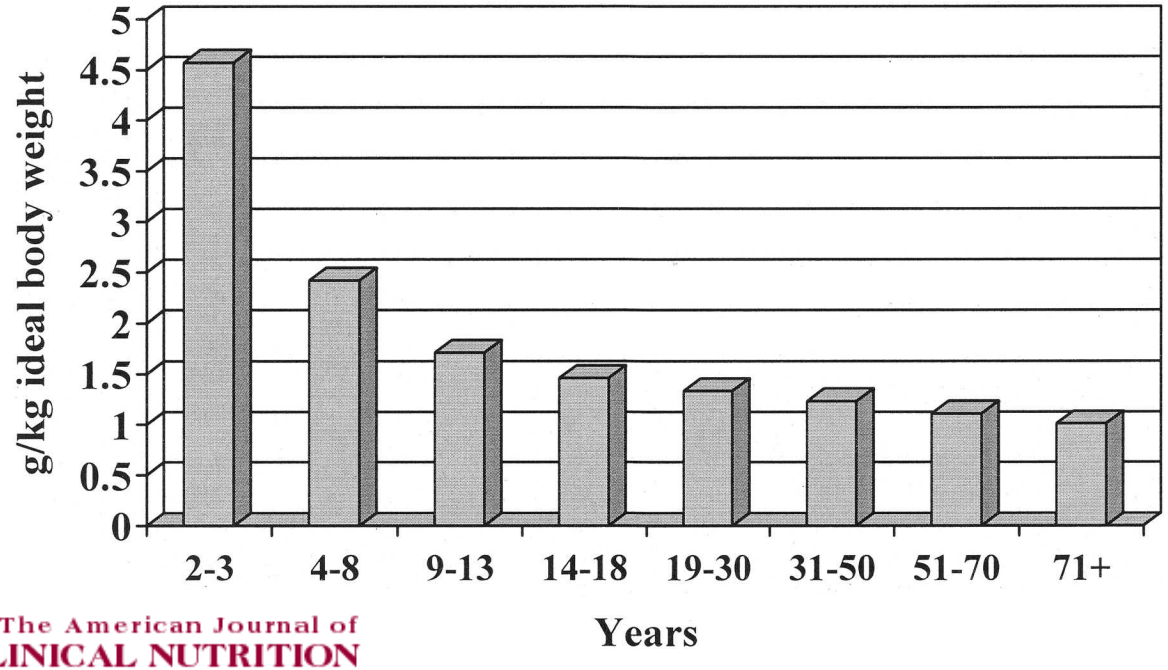
The American Journal of CLINICAL NUTRITION

Denise K Houston, 2008

NHANES 2003-2004



Protein intake (g/d) by age

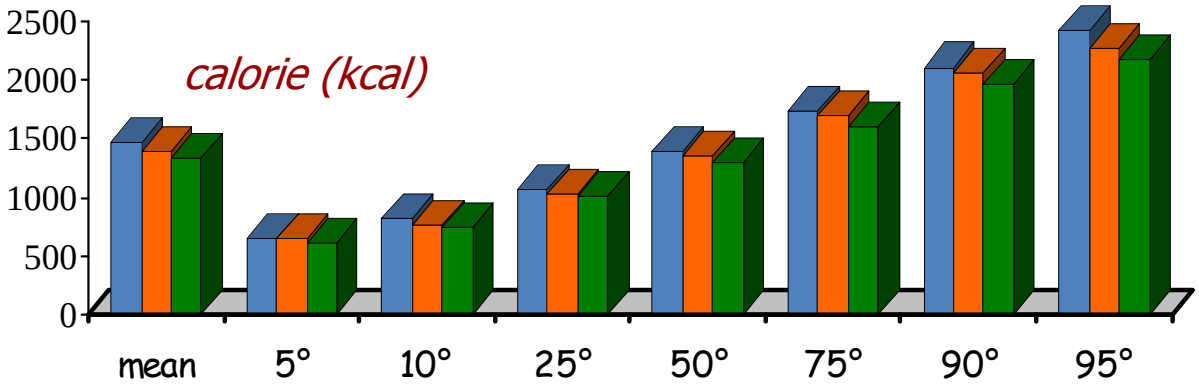


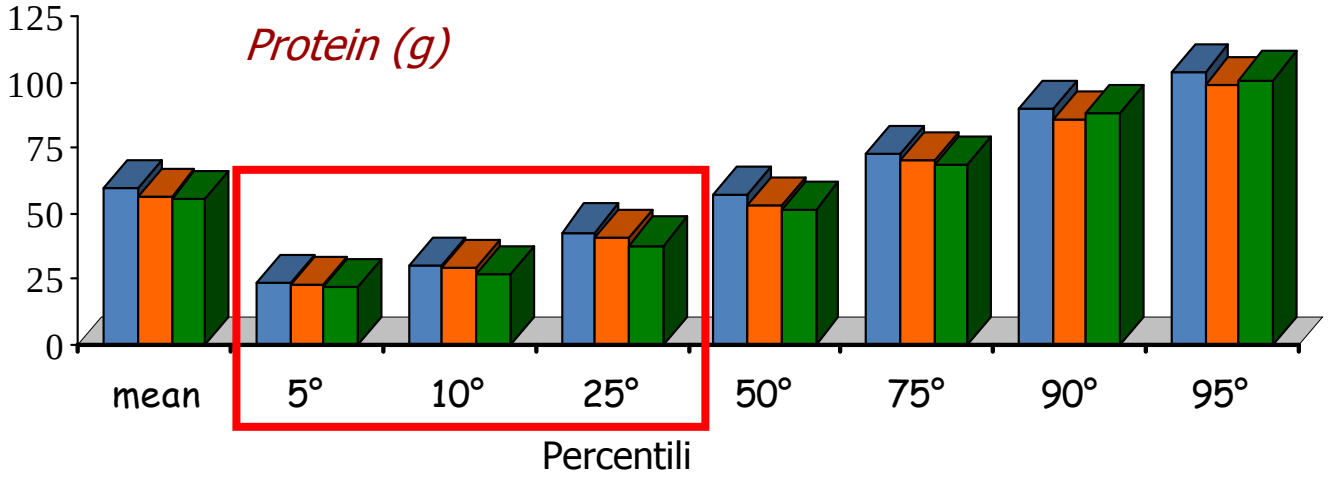
Protein intake (g/kg body weigth) by age

The American Journal of CLINICAL NUTRITION

Fulgoni ,2008

Introito calorico e proteico in soggetti anziani di sesso femminile
Continuing Survey of Food Intakes by Individuals
(15000 soggetti, con età di 60, 70, 80 e oltre)





60-69 anni 70-79 anni 80+ anni

Wakimoto & Block, 2001

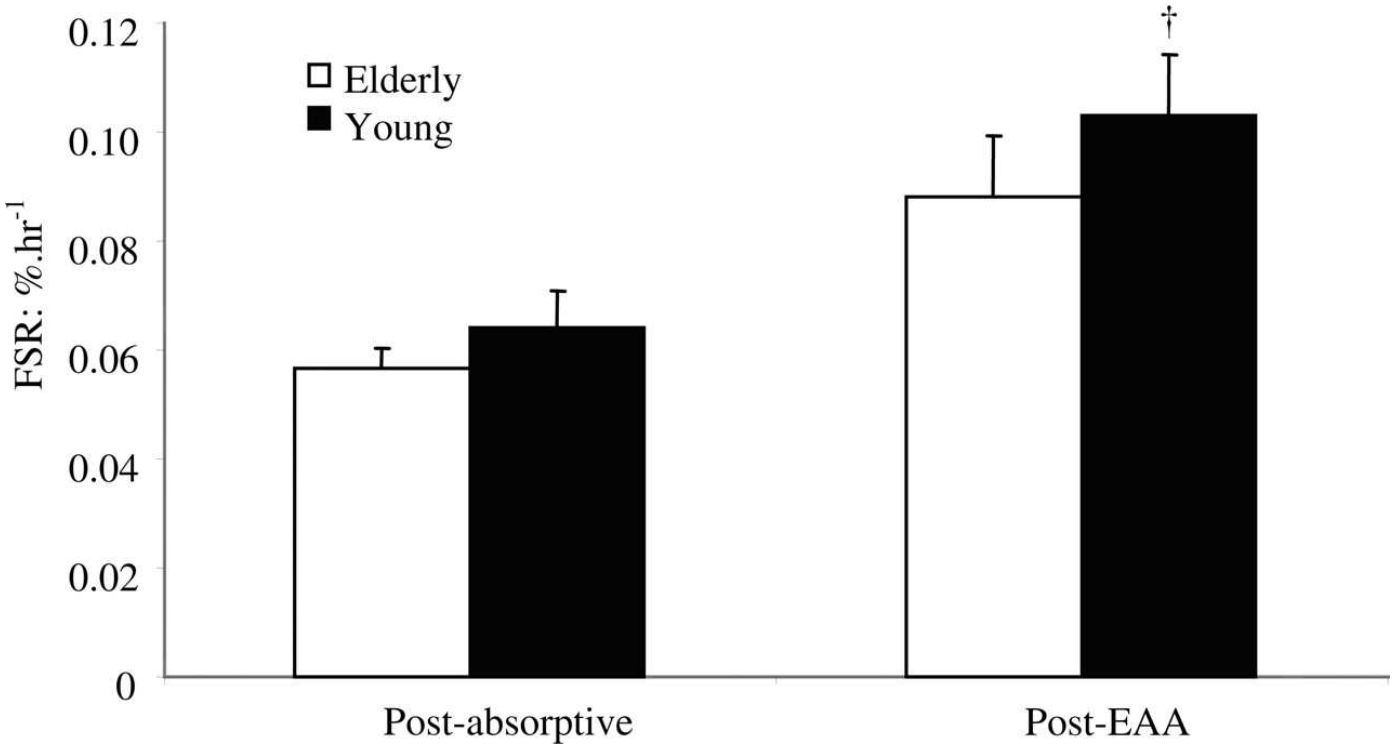
Essenziali	Non essenziali	Conditionally Indispensable
Istidina	Alanina	Arginina
Isoleucina	Acido Aspartico	Cisteina
Leucina	Asparagina	Glutamina
Lisina	Acido Glutammico	Glicina
Metionina	Serina	Prolina
Fenilalanina		Tirosina
Treonina		
Triptofano		
Valina		

Essenziali

Istidina
Isoleucina
Leucina
Lisina
Metionina
Fenilalanina
Treonina
Triptofano
Valina

AA ramificati
30%
proteine muscolari

Mixed muscle fractional synthetic rate (FSR) in young and elderly before and after ingestion of 15 g of EAA

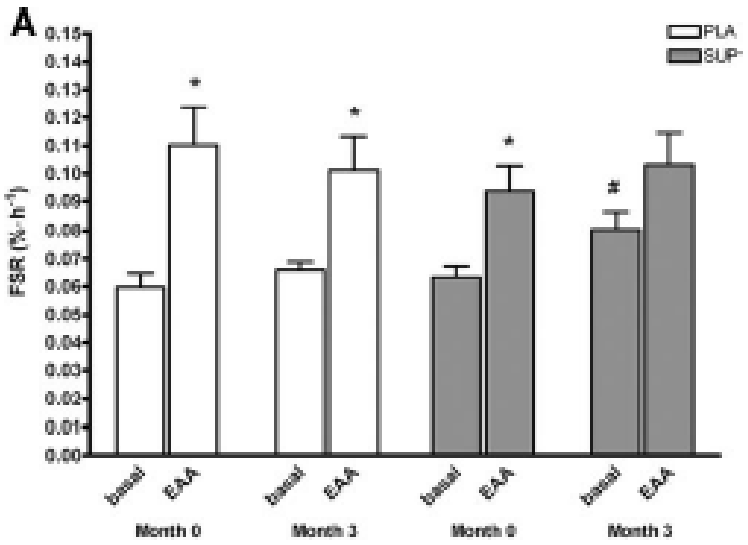


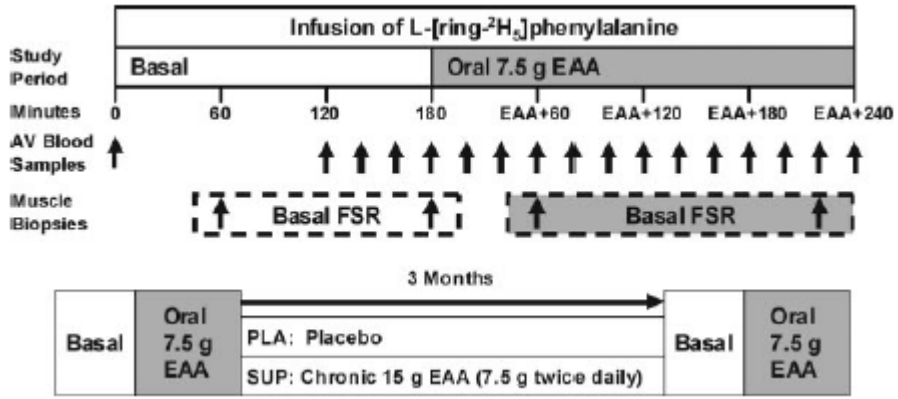
AJP - Endocrinology and Metabolism

Paddon-Jones, D. et al. 2003

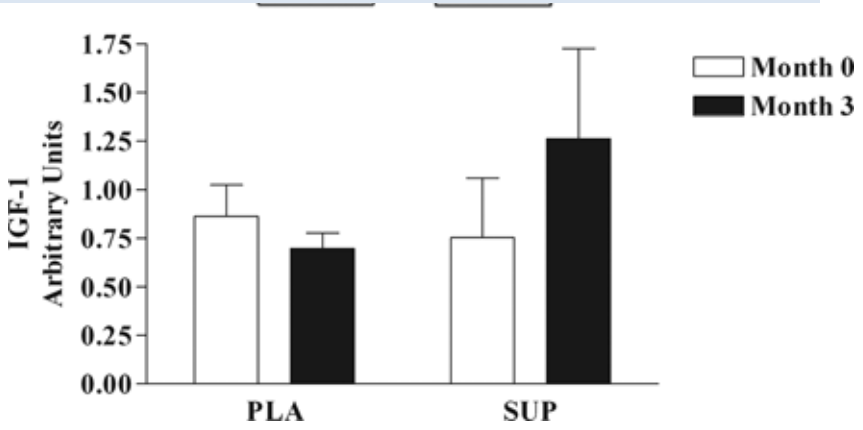
Amino Acid Supplementation Increases Lean Body Mass, Basal Muscle Protein Synthesis and IGF-1 Expression in Older Women

Objective and Design: The objectives of this study were to determine whether: 1) chronic essential amino acid (EAA) supplementation improves postabsorptive muscle protein fractional synthesis rate (FSR), lean body mass (LBM), and one-repetition maximum muscle strength, and androgen receptor and IGF-I muscle protein expression; and 2) the acute anabolic response to EAA ingestion is preserved after a 3-month supplementation period. Using a randomized, double-blinded, placebo-controlled design, older women (68 ± 2 yr) were assigned to receive either placebo (n = 7), or 15 g EAA/d [supplemented treatment group (SUP)] (n = 7) for 3 months. Metabolic outcomes were assessed in association with stable isotope studies conducted at 0 and 3 months.





Anabolic response to EAA supplementation is maintained over time

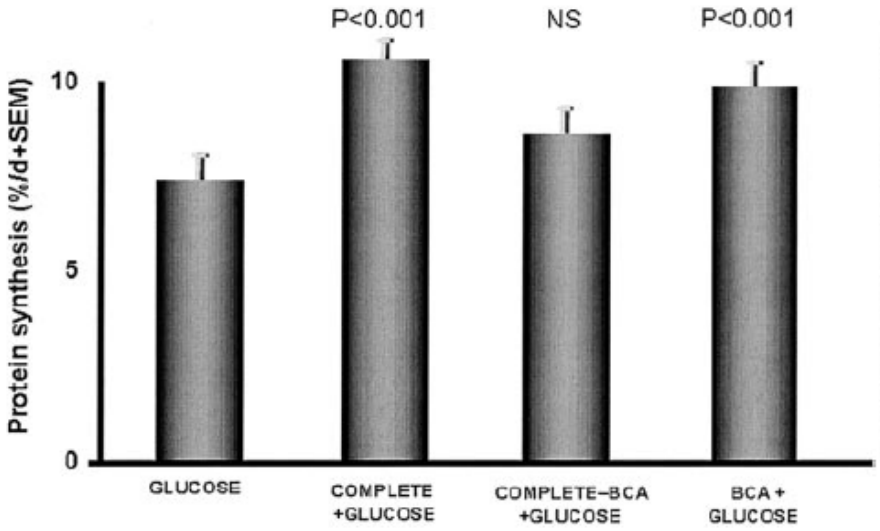


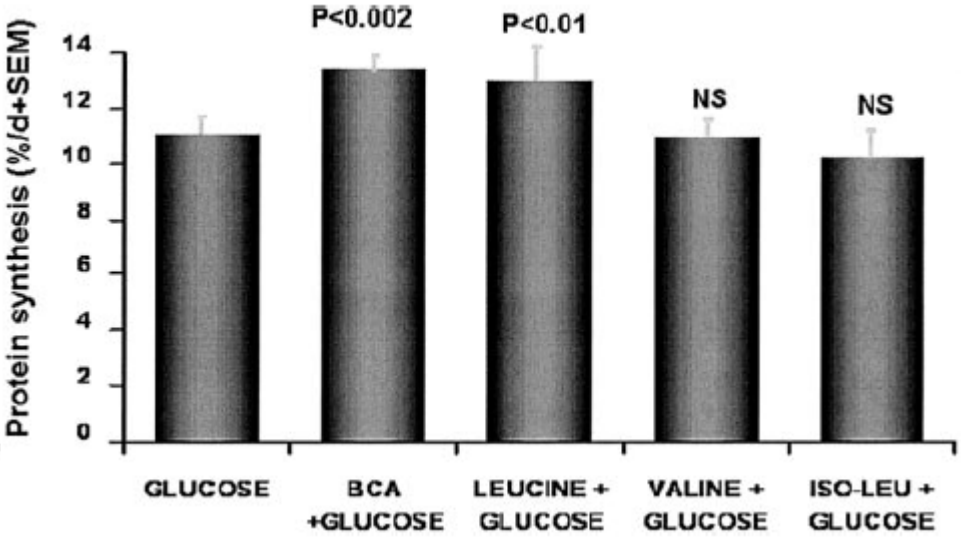
Edgar L. Dillon, 2008

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

The Role of Leucine in the Regulation of Protein Metabolism[1,2]

Peter J. Garlick[3]





ABSTRACT Studies both in vivo and in vitro have shown that leucine at a very high dose can stimulate muscle protein synthesis, an effect that is enhanced in vivo by insulin secreted in response to the leucine dose. High leucine can also inhibit protein degradation in skeletal muscle, as well as in liver. In contrast, at normal physiological levels, increasing leucine concentration by infusion stimulates muscle protein synthesis by enhancing its sensitivity to insulin. It is concluded that the role of leucine in vivo is to provide a signal that amino acids are available, which in combination with the signal of energy availability from insulin, stimulates muscle protein synthesis. J. Nutr. 135: 1553S–1556S, 2005.

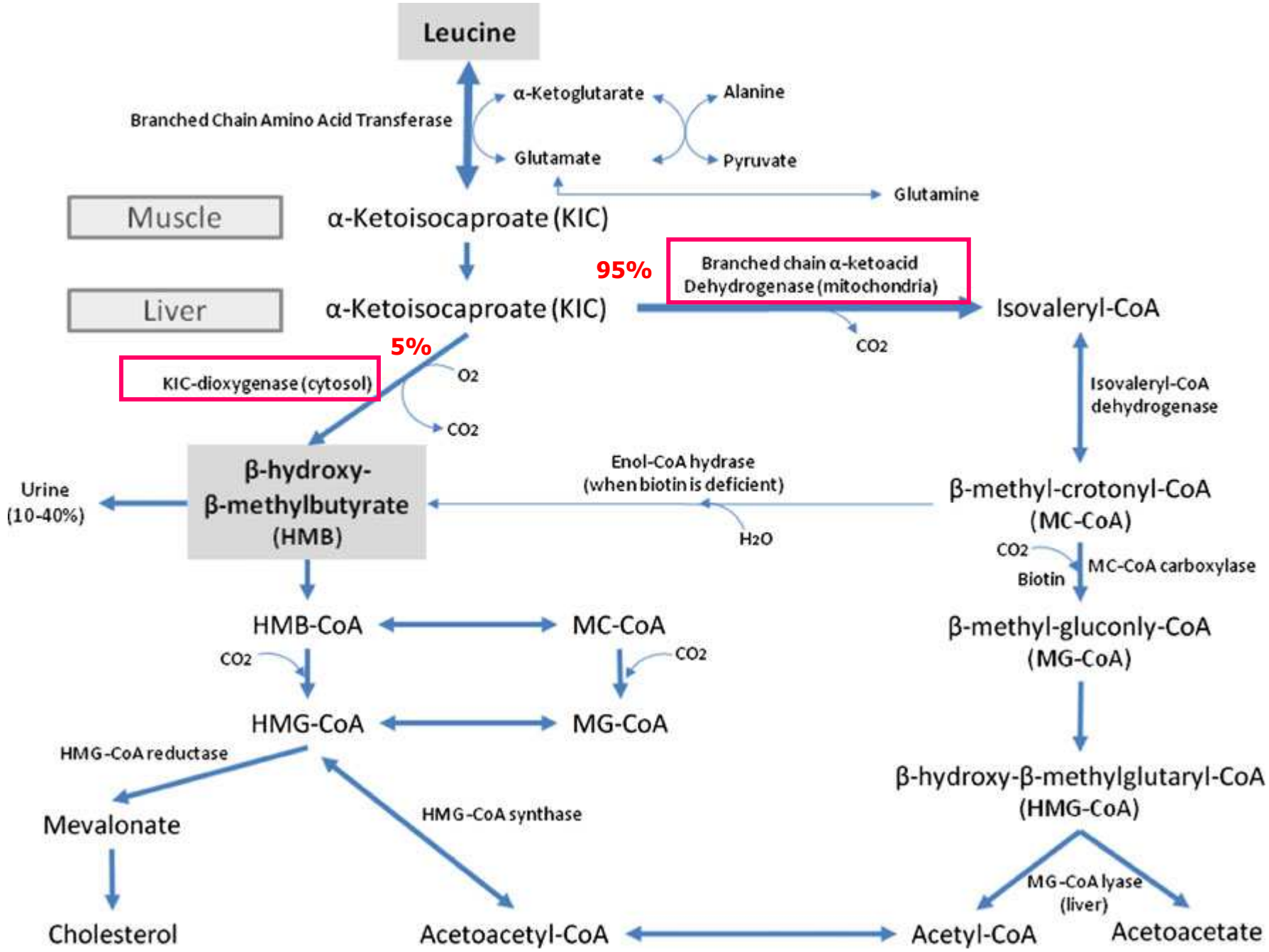
Aminoacidi essenziali in diete a vario contenuto calorico

Dieta kcal	Valina	Isoleucina	Leucina	Lisina	Metionina	Fenilalanina	Treonina	Triptofano	Istidina
1500	2,84	2,47	**4,25**	4,171	1,19	2,40	2,47	0,59	1,51
1800	3,59	3,12	**5,37**	5,27	1,542	3,03	3,07	0,75	1,92
2000	3,73	3,24	**5,57**	5,50	1,622	3,14	3,19	0,77	2,00

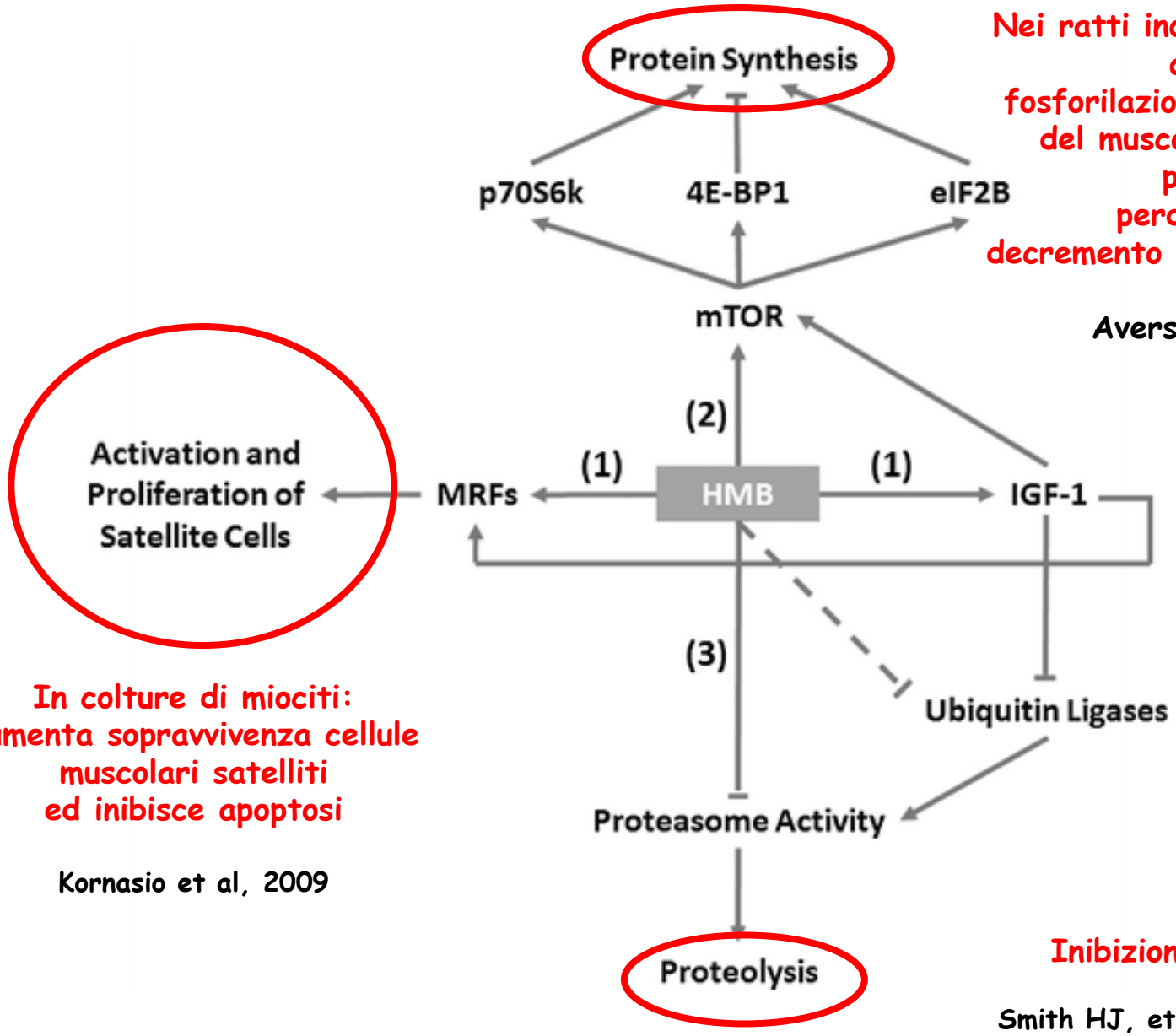
Introito medio di Leucina negli USA: 6.1 g/die
(da alimenti e/o supplementi) (1988-1994 NHANES III)

Hydroxy-β-Methylbutyrate: metabolita della Leucina

Essenziali	Non essenziali	Conditionally Indispensable
Istidina	Alanina	Arginina
Isoleucina	Acido Aspartico	Cisteina
Leucina	Asparagina	Glutamina
Lisina	Acido Glutammico	Glicina
Metionina	Serina	Prolina
Fenilalanina		Tirosina
Treonina		
Triptofano		
Valina		


Leucine
Branched Chain Amino Acid Transferase
α-Ketoglutarate
Alanine
Glutamate
Pyruvate
Glutamine
Muscle
α-Ketoisocaproate (KIC)
Liver
α-Ketoisocaproate (KIC)
95%
Branched chain α-ketoacid Dehydrogenase (mitochondria)
CO2
Isovaleryl-CoA
Isovaleryl-CoA dehydrogenase
5%
KIC-dioxygenase (cytosol)
O2
CO2
Urine (10-40%)
β-hydroxy-β-methylbutyrate (HMB)
Enol-CoA hydrase (when biotin is deficient)
H2O
β-methyl-crotonyl-CoA (MC-CoA)
CO2
Biotin
MC-CoA carboxylase
β-methyl-gluconly-CoA (MG-CoA)
HMB-CoA
MC-CoA
CO2
CO2
HMG-CoA
MG-CoA
HMG-CoA reductase
Mevalonate
HMG-CoA synthase
β-hydroxy-β-methylglutaryl-CoA (HMG-CoA)
MG-CoA lyase (liver)
Cholesterol
Acetoacetyl-CoA
Acetyl-CoA
Acetoacetate

Studi in vitro: meccanismi d'azione



Nei ratti inoculati con epatoma aumenta fosforilazione mTOR a livello del muscolo gastrocnemio previene:
perdita di peso
decremento massa gastrocnemio

Aversa et al 2011

In colture di miociti:
aumenta sopravvivenza cellule muscolari satelliti
ed inibisce apoptosi

Kornasio et al, 2009

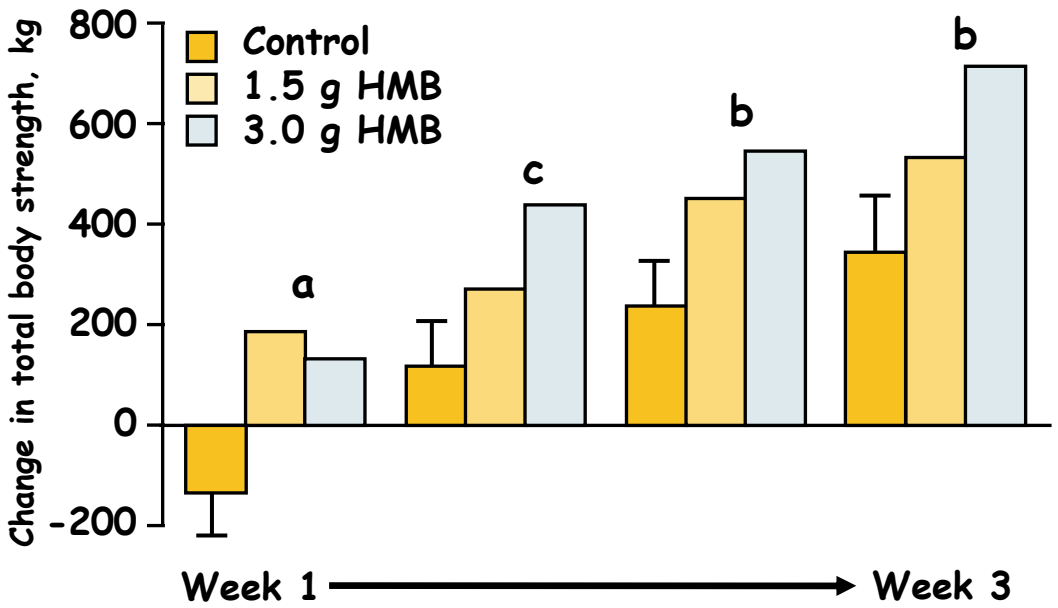
Inibizione caspasi 8 e 3

Smith HJ, et al. *Cancer Res.* 2005

Change in Muscle Strength During HMB Supplementation

- 41 healthy young adults (19-29 years), untrained
- 2 protein levels: 117 g/day (control) or 175 g/day
  - Diet was controlled, nutrient powder in a shake
- 3 HMB supplementation doses randomized and blinded within each protein group
  - 0, 1.5, or 3.0 g/day Mixed in orange juice
- Weight training for 1.5 hours 3 days/week for 3 weeks

- Data from control and high protein groups were pooled because there was no difference in HMB results
- Overall muscle strength increased at 3 weeks
  - 8% in control group
  - 13% in 1.5 g HMB group
  - 18% in 3.0 g HMB group



[a]$P < .03$
[b]$P < .02$
[c]$P < .01$

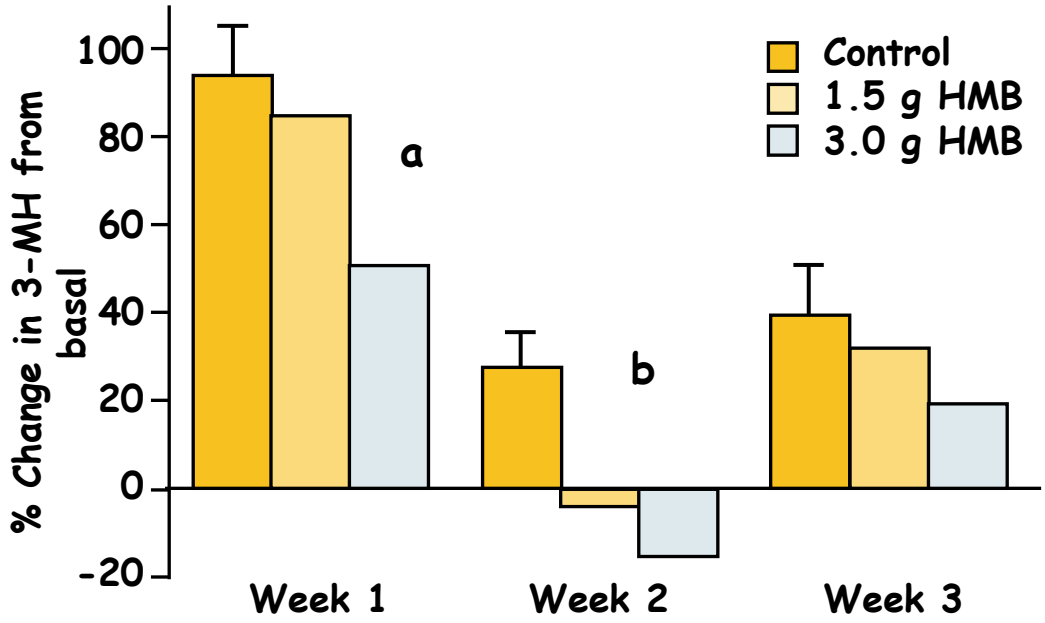
Nissen S, et al. *J Appl Physiol.* 1996;81(5):2095-2104.

Change in Urinary 3-Methylhistidine (3-MH) Excretion During HMB Supplementation

- 3-MH is a muscle-specific amino acid
  - Formed during breakdown of muscle proteins (actin and myosin)
  - Excreted unchanged in urine

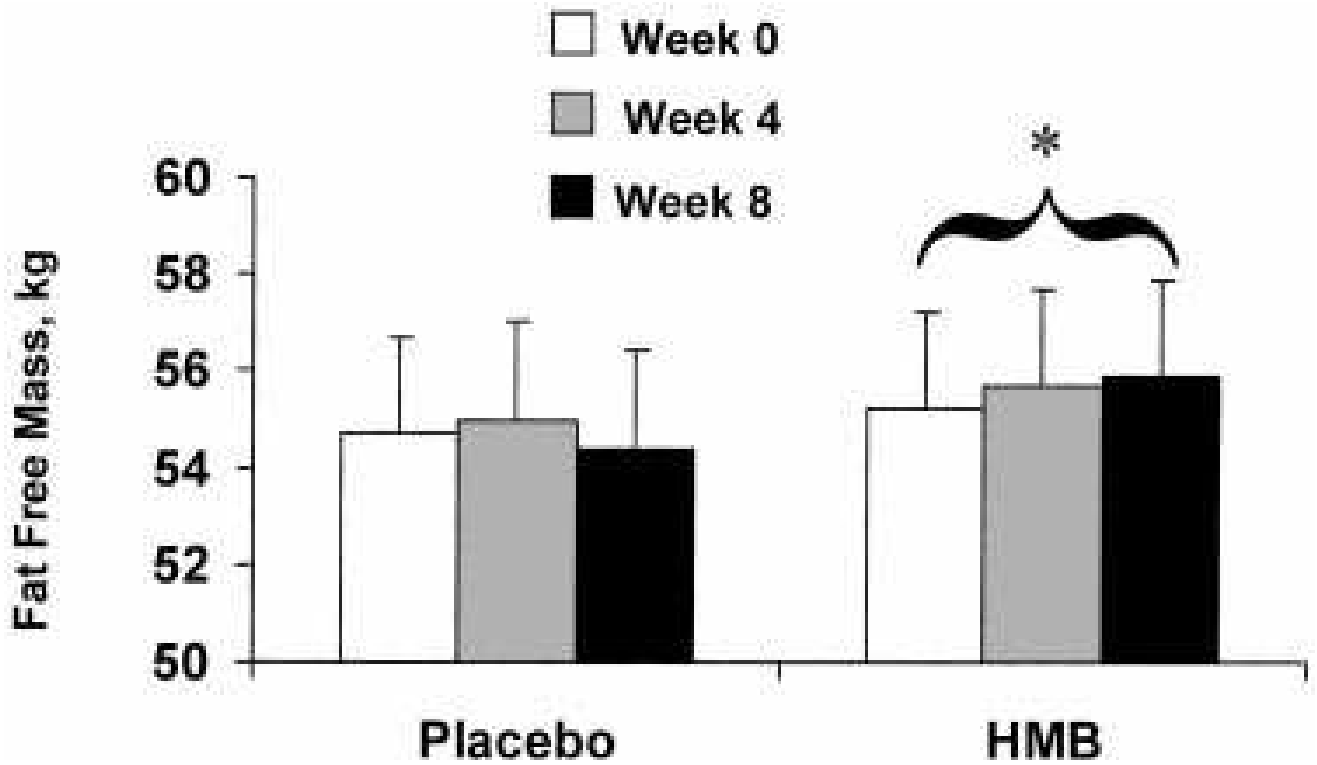
- Total muscle breakdown per day increased from 3% at baseline to
- 6% at week 3 in control group
- 5.5% at week 3 in 1.5 g HMB group
- 4.5% at week 3 in 3.0 g HMB group

[a]$P < .04$
[b]$P < .001$



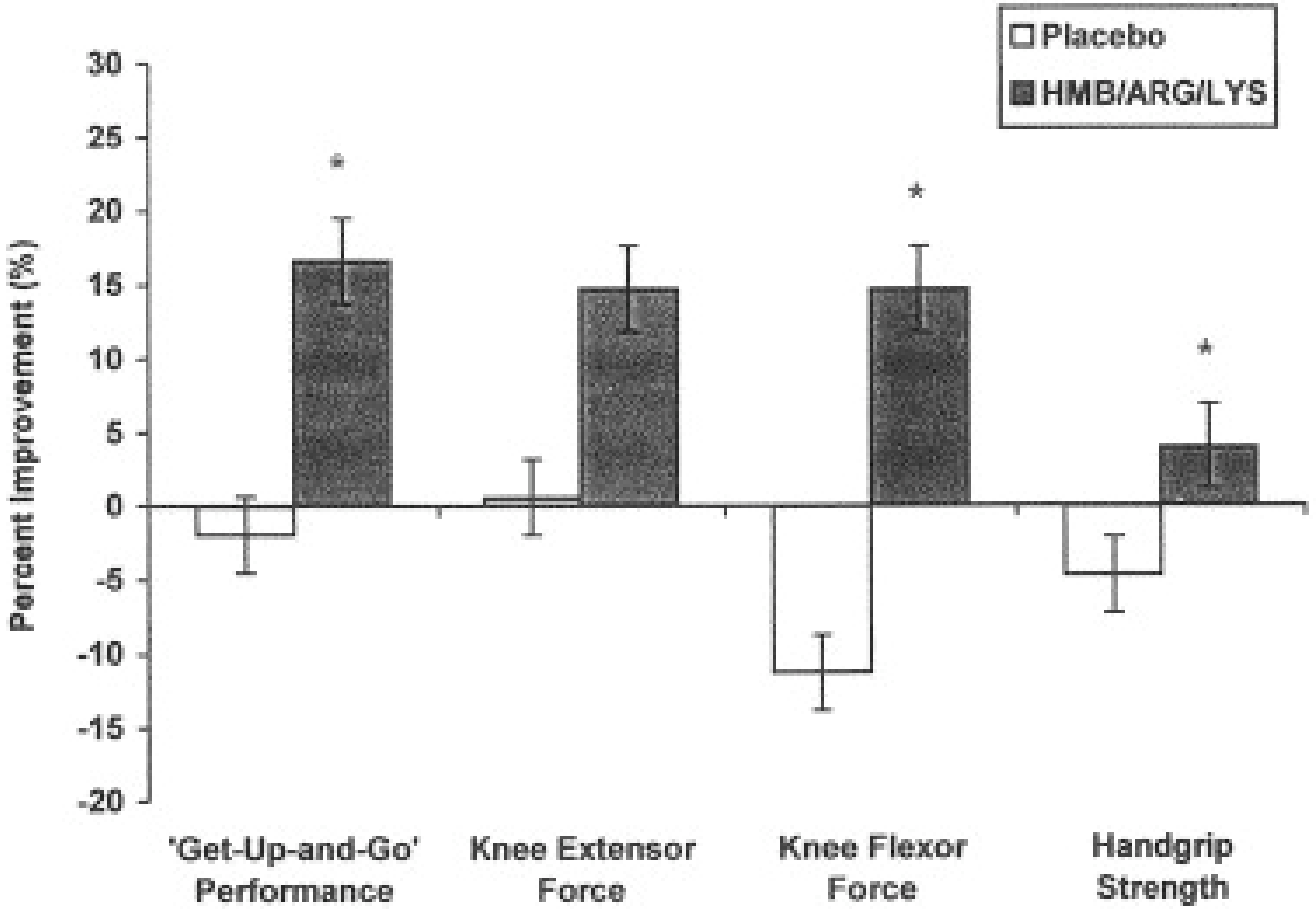
Nissen S, et al. *J Appl Physiol.* 1996;81(5):2095-2104.

Randomized, double-blind study:
31 adults (men, 15; women, 16) 70 years of age
Received 3 g/day HMB or placebo for 8 weeks
Participants underwent an exercise program 5 day/week
diet not controlled



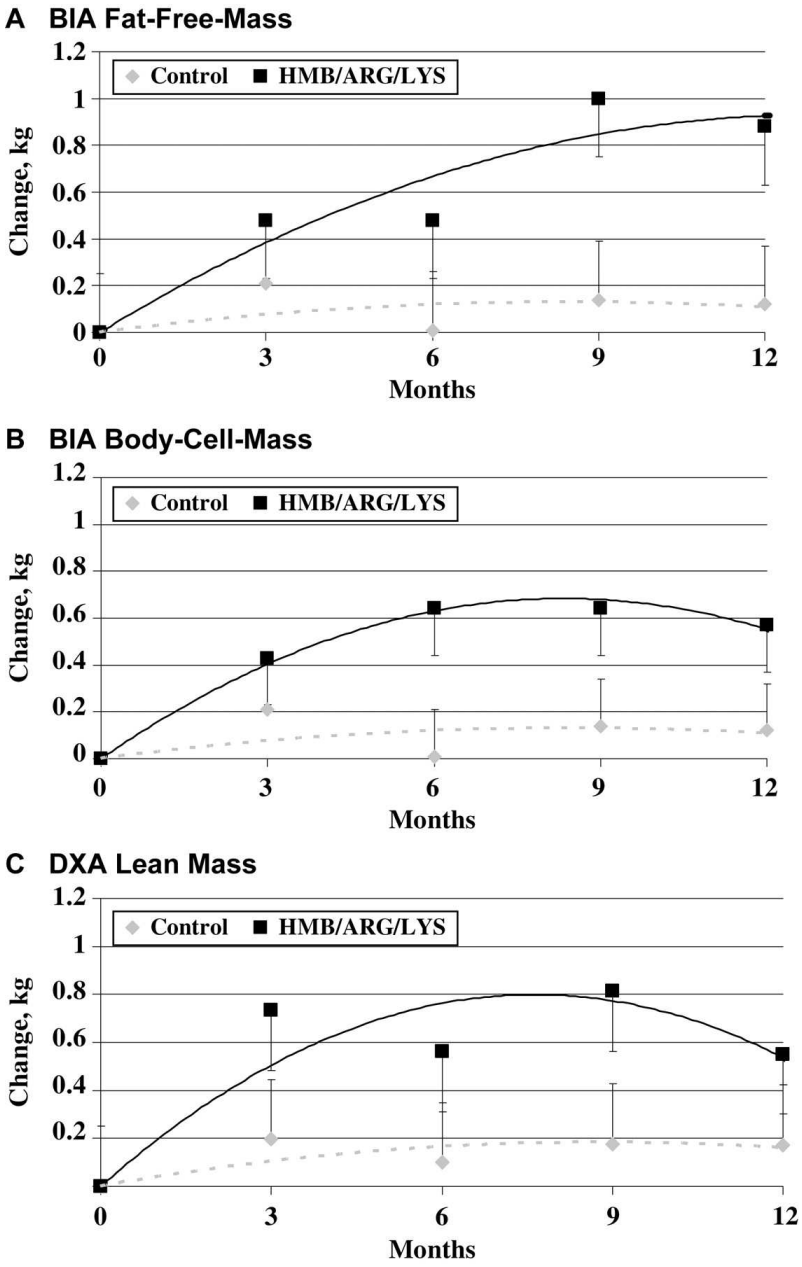
Vukovich et al,J Nutrition, 2000

Double-blind study in old women (76,7 years)
2 g HMB (n 23) vs placebo (n 27)
12 weeks: no exercise



Flakol et al, 2004

Body composition data for elderly men and women



12 months
double-blinded study

127 elderly adults

Received:
2 to 3 g HMB + 1.5 to 2.25 g lysine + 5 to 7.5 g arginine per day

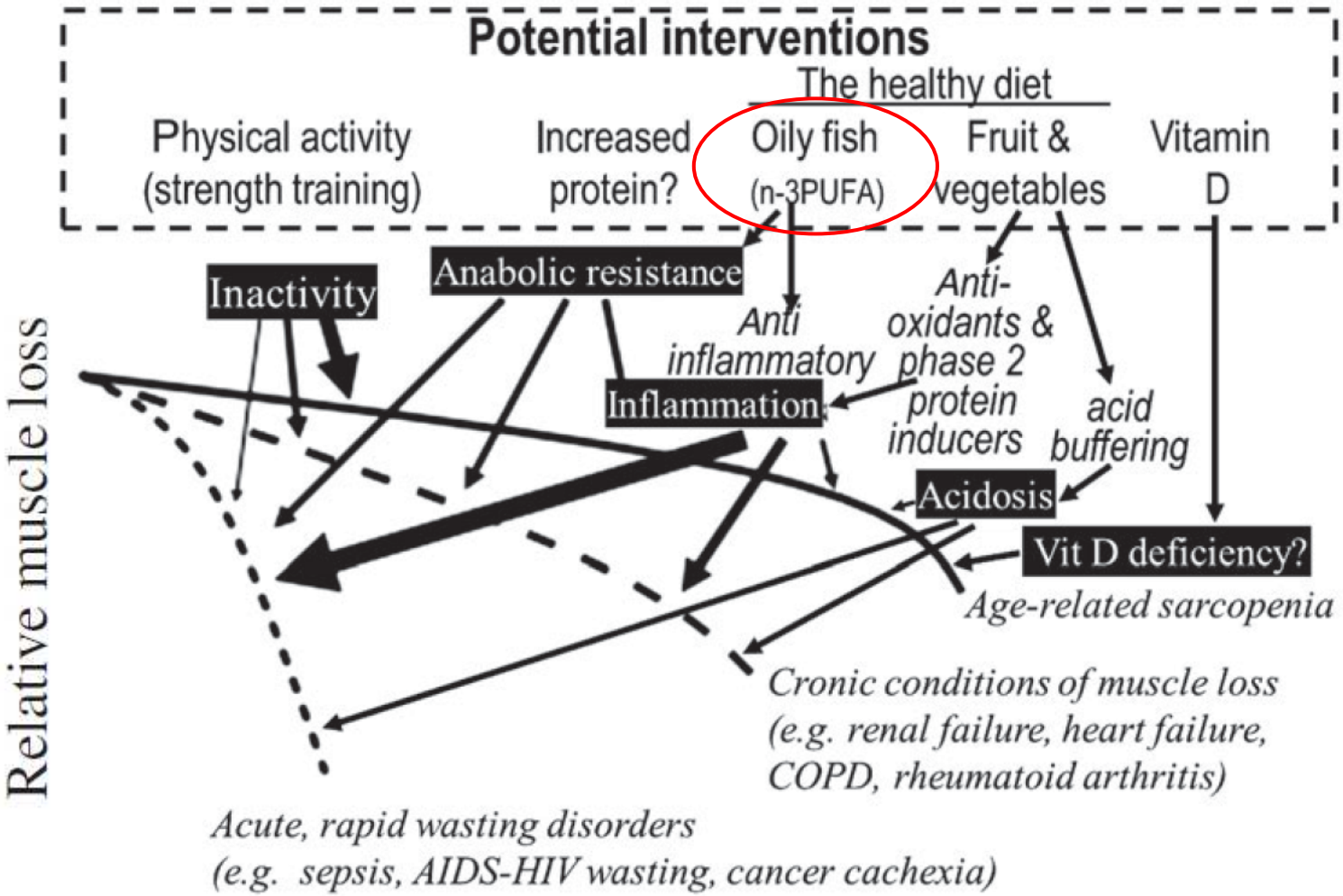
or isocaloric, isonitrogenous placebo

No exercise component

Baier S et al., 2009

JPEN JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

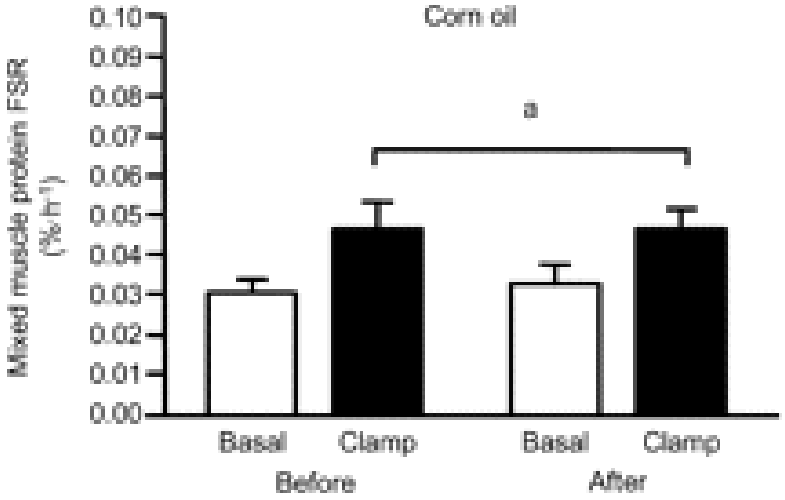
Nutrition and sarcopenia: evidence for an interaction

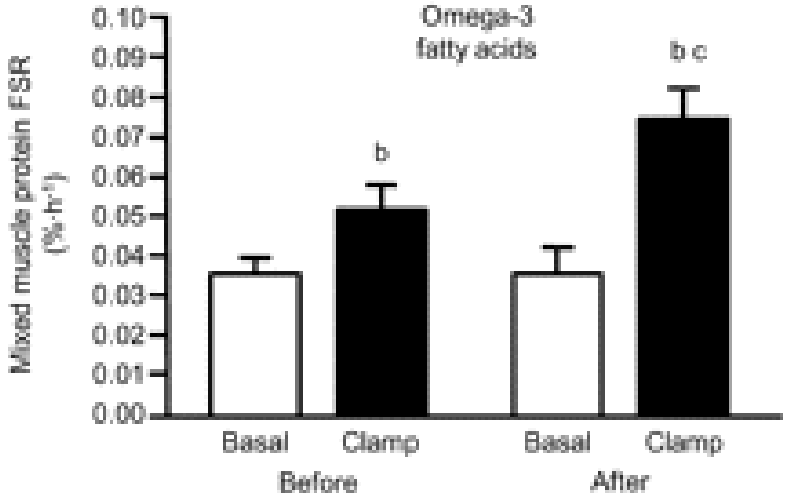


D. Joe Millward

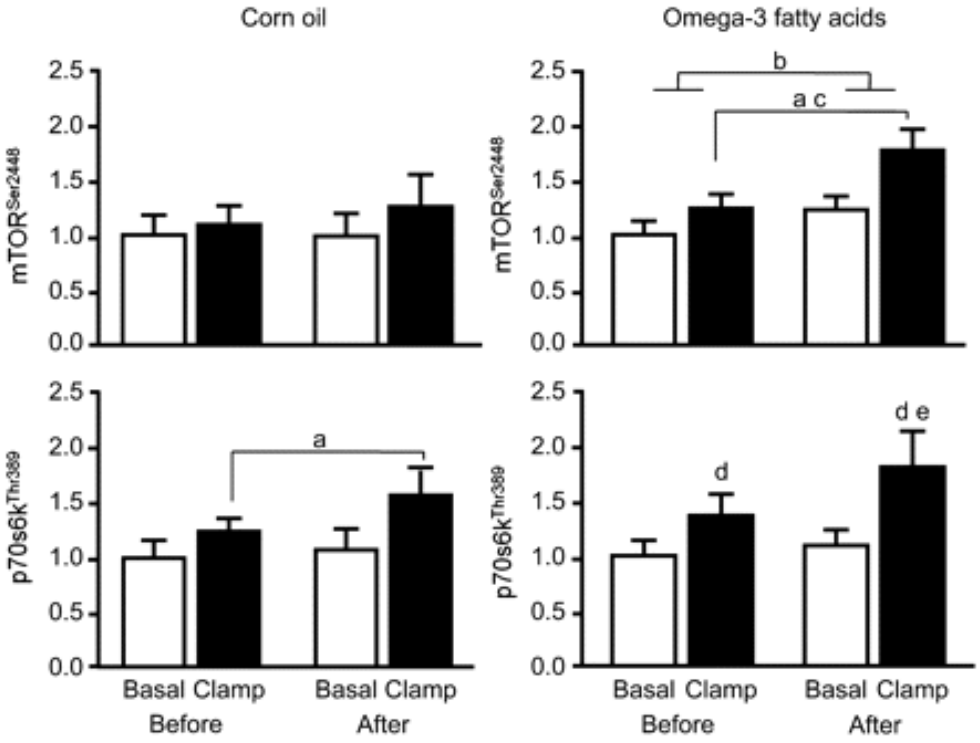
Proceedings of the Nutrition Society (2012), **71**, 566–575

Dietary omega-3 fatty acid supplementation increase the rate of muscle protein synthesis in older adults: a randomized controlled trial





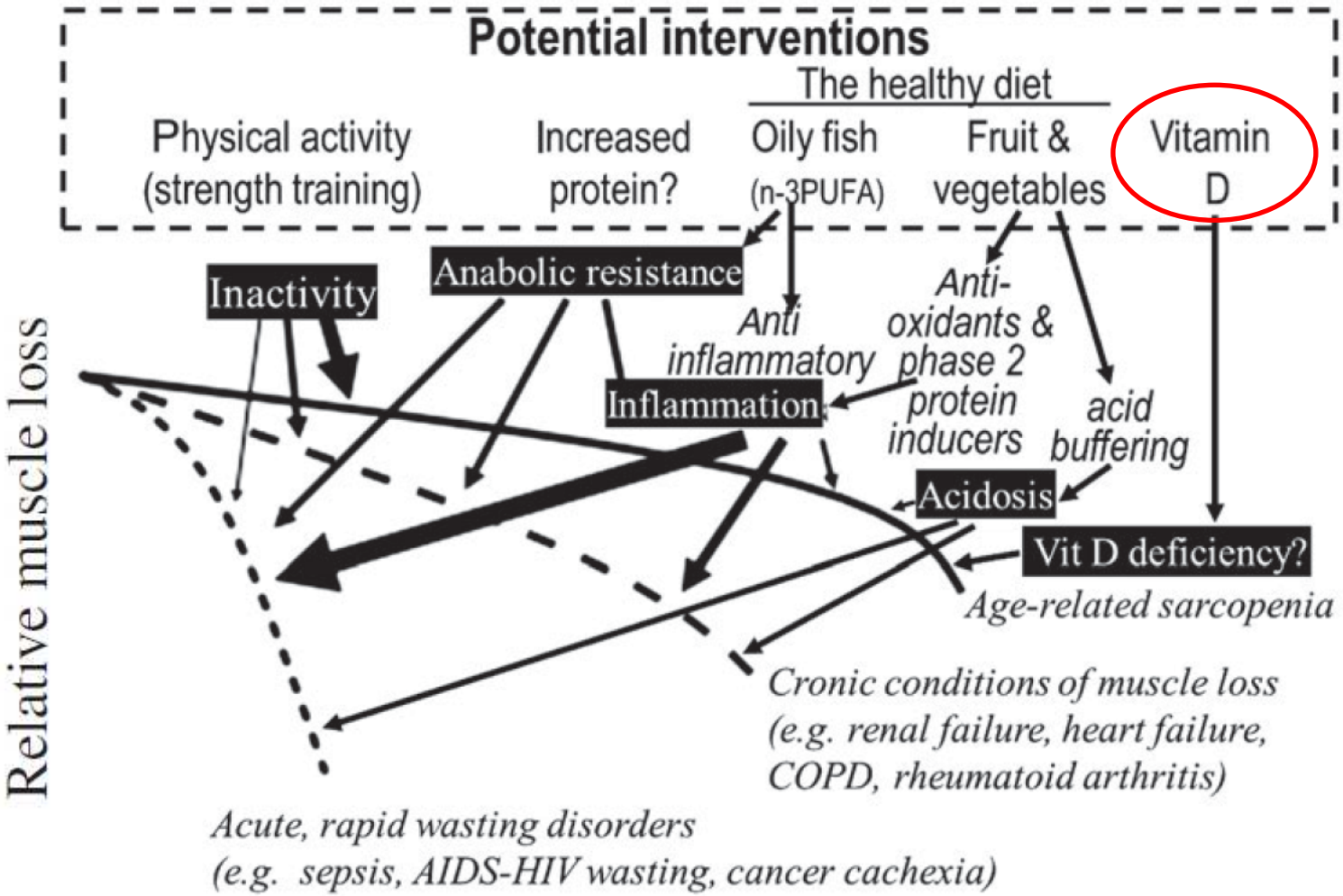
16 anziani randomizzati a ricevere omega 3 (4 g) o corn oil (4 g) per 8 sett
In condizioni basali e dopo clamp iperinsulinemico e iperaminoacidemico.



Smith GI et al , 2011

The American Journal of CLINICAL NUTRITION

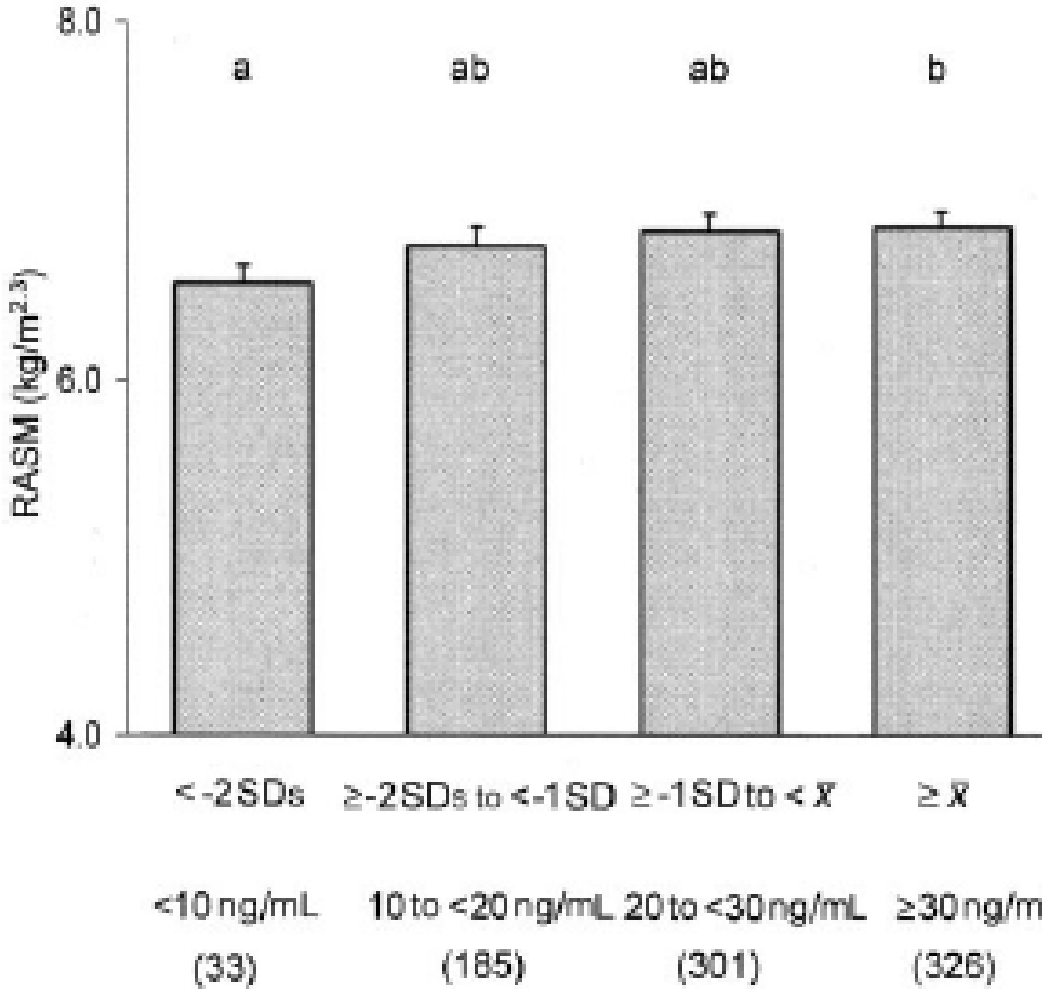
Nutrition and sarcopenia: evidence for an interaction



D. Joe Millward

Proceedings of the Nutrition Society (2012), **71**, 566–575

The Minos study: 845 men aged 45-85 years



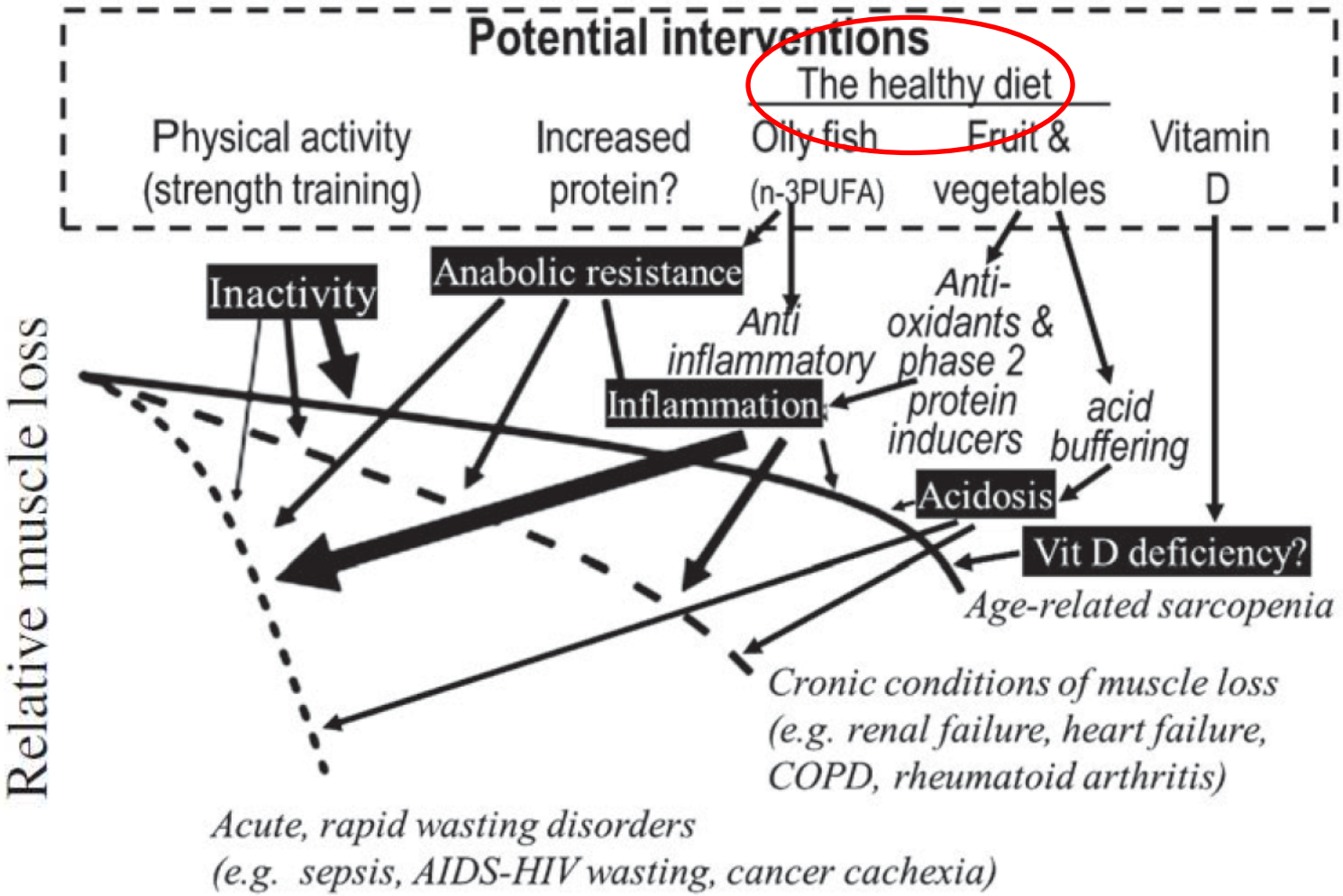
The American Journal of CLINICAL NUTRITION

Szulc et al, 2004

Vitamina D

- Ipovitaminosi D associata ad atrofia fibre di tipo II
- Livelli Vitamina D associati a forza muscolare
- Supplemantazione Vitamina D aumenta forza muscolare e sembra ridurre il rischio di caduta
- Bassi livelli di vitamina D associati ad aumentato rischio di miopatia da statina

Nutrition and sarcopenia: evidence for an interaction

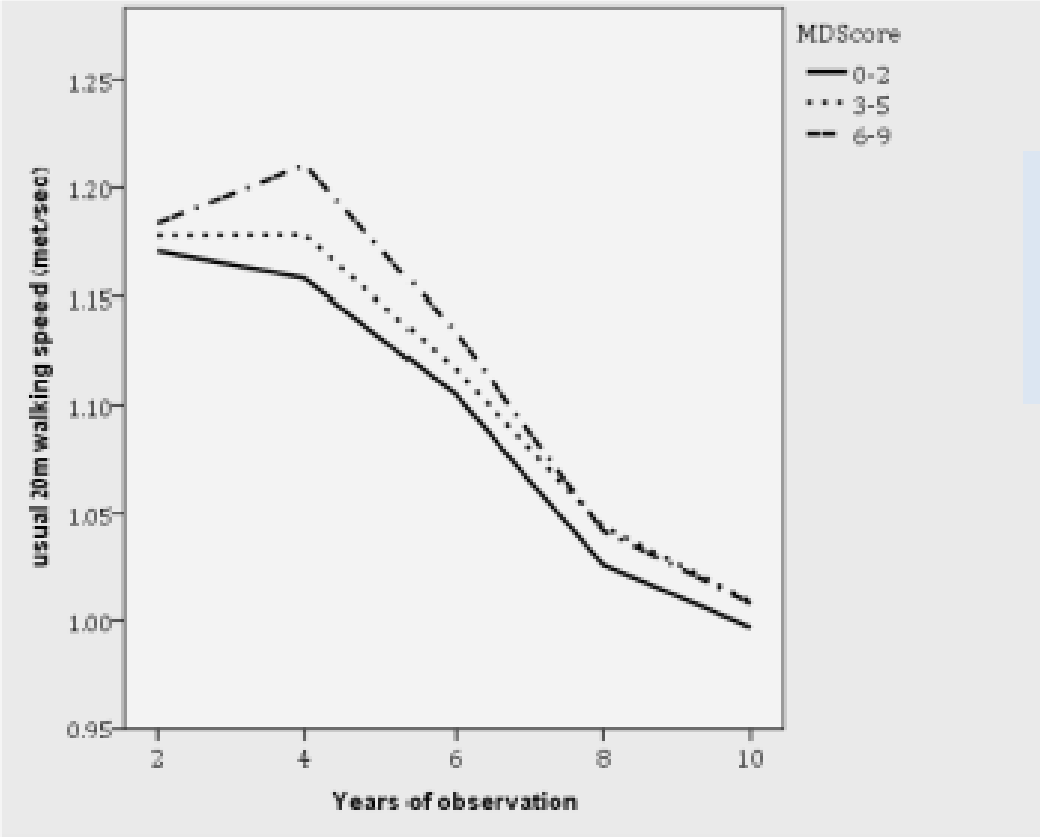


D. Joe Millward

Proceedings of the Nutrition Society (2012), **71**, 566–575

Shahar DR, 2012

Adherence to Mediterranean diet and decline in walking speed over 8 years in community-dwelling older adults



H-ABC study

2225 well functionining participants

older than 70 years

Conclusion—Walking speed over 8 years was faster among those with higher MedDiet adherence at baseline. The differences remained significant over 8y, suggesting a long-term effect of diet on mobility performance with aging.

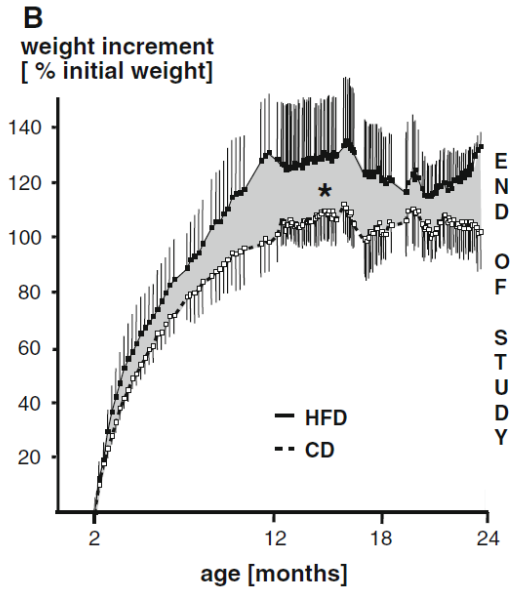
Sarcopenia in the aging high-fat fed rat: a pilot study for modeling sarcopenic obesity in rodents

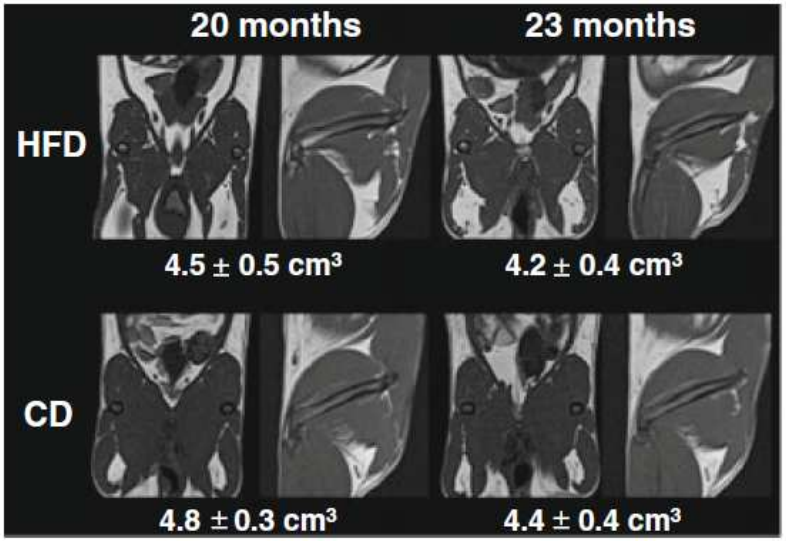
L. Cornelius Bollheimer ·

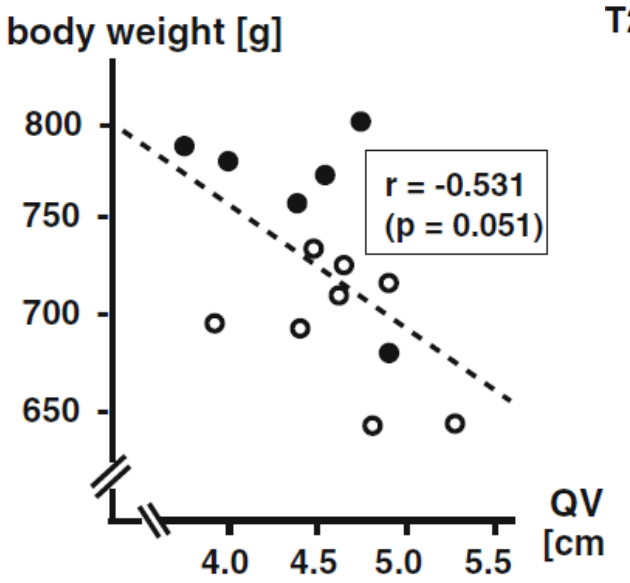
Biogerontology (2012) 13:609–620

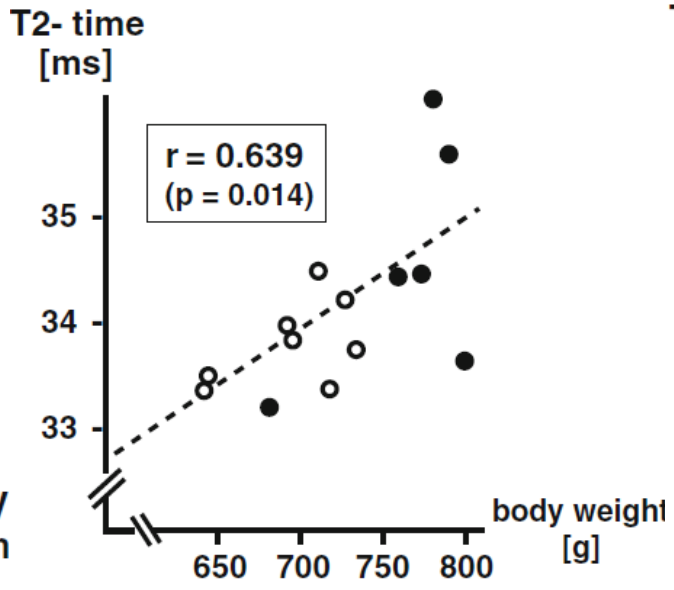
Male rats
CD 25% fat

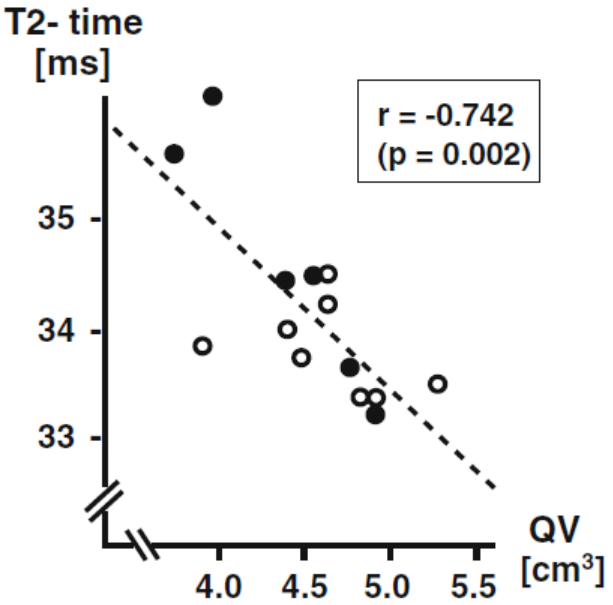
HFD 45% fat
Isocaloric
Starting 2 months









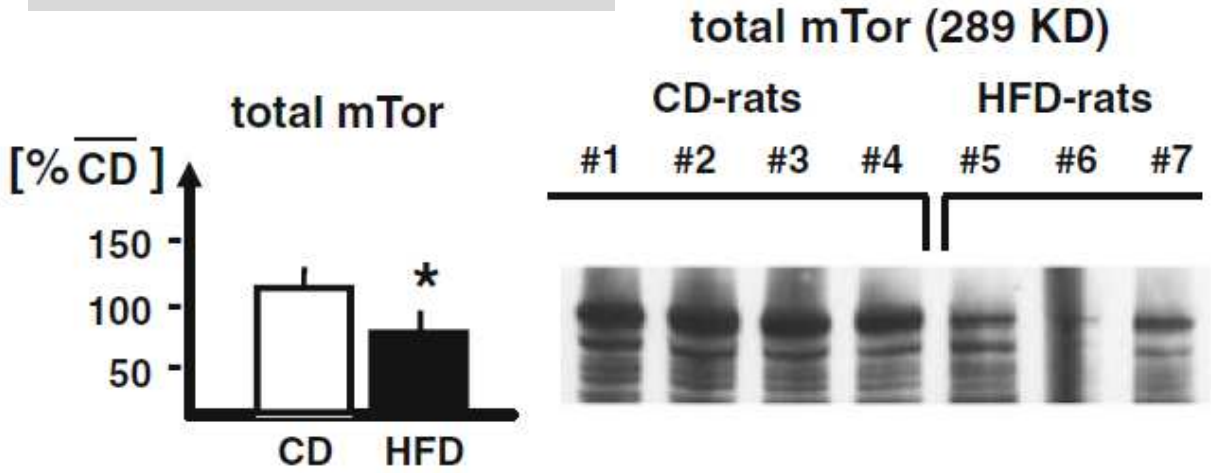


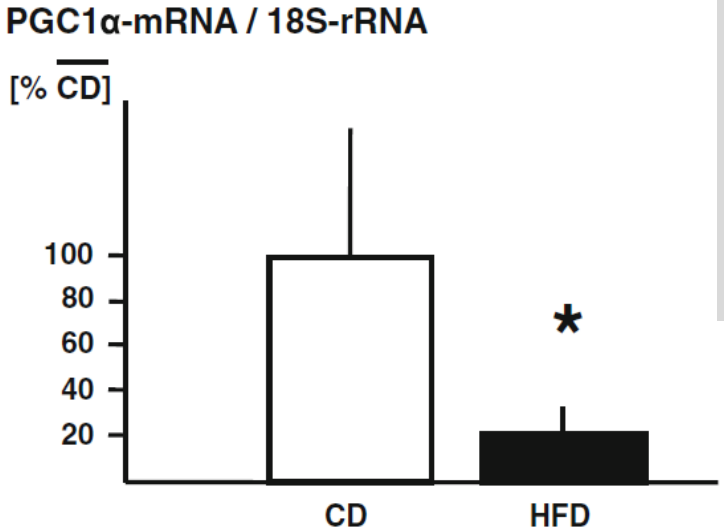
Sarcopenia in the aging high-fat fed rat: a pilot study for modeling sarcopenic obesity in rodents

L. Cornelius Bollheimer ·

Biogerontology (2012) 13:609–620

Vastus lateralis biopsies at 24 months





At 12 months in HFD rats:

Plasma insulin 3-fold higher
Plasma leptin 1.6-fold higher
Plasma adiponectin 20% lower

Sarcopenia nutritional recommendations

Metabolic efficiency in older persons is decreasing, requiring a higher protein intake: a 15%-38% of older men and 27%-41% of old women ingest less than the RDA for protein (B)

A trial of balanced amino-acid supplementation (leucine enriched?) alone and with exercise is recommended (B)

Vitamin D should be measured in all sarcopenic subjects (A)

A. A minimum single radomized- placebo controlled trial or meta-analysis. B. Small trials

J Morley, 2010

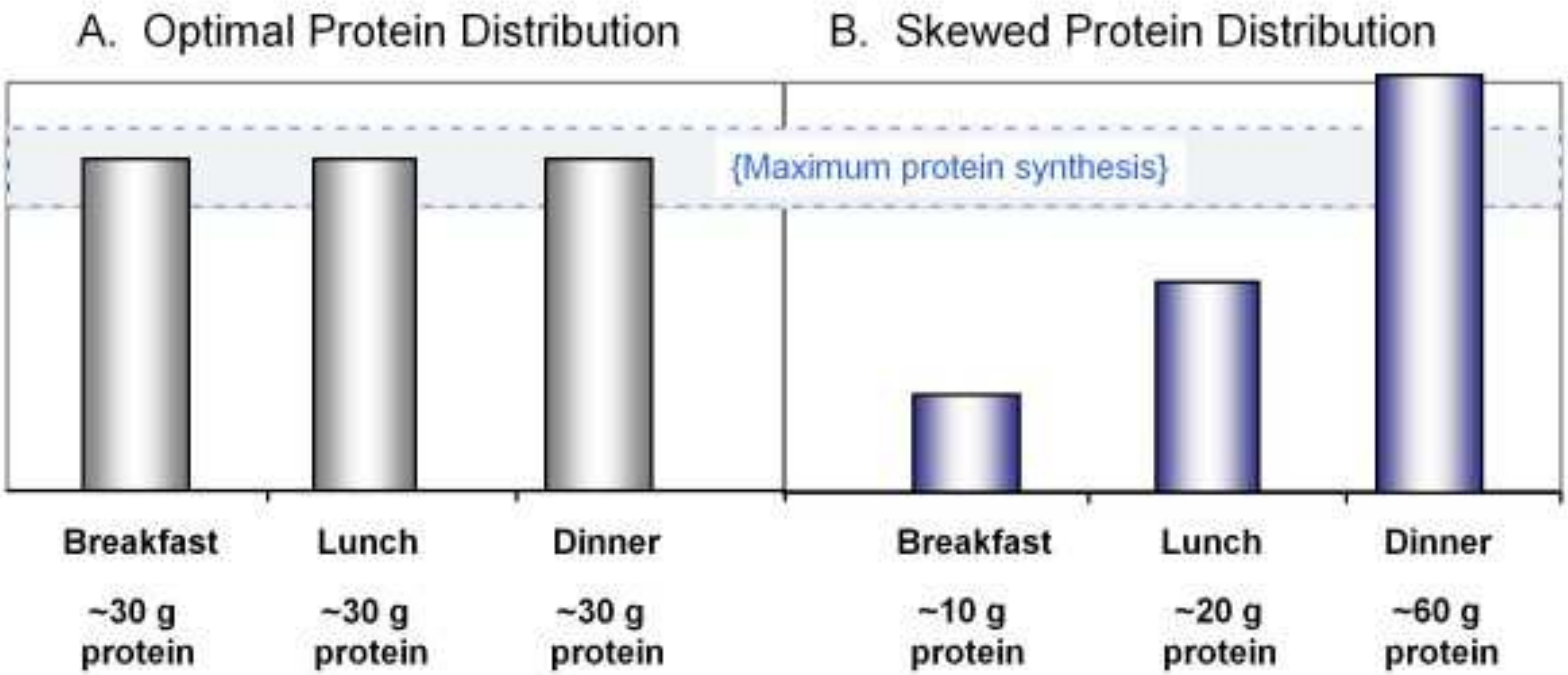
New concepts about protein for the Dietary Guidelines

- Protein is a critical part of the adult diet
- Protein needs are proportional to body weight; NOT energy intake
- Adult protein utilization is a function of intake at individual meals
- Most adults benefit from protein intakes above the minimum RDA (1-1.2g /kg/die)

Layman DK, 2009

Acceptable Macronutrient Distribution Ranges (AMDR) is more relevant to normal dietary intake than RDA

Wolfe et al, 2008



Protein distribution at meals. A) Ingestion of 90 grams of protein, distributed evenly at 3 meals. B) Ingestion of 90 grams of proteins unevenly distributed throughout the day. Stimulating muscle protein synthesis to a maximal extent during the meals shown in Figure 1A is more likely to provide a greater 24 hour protein anabolic response than the unequal protein distribution in Figure 1B.

Nutrition&Metabolism

Donald K Layman, 2009

Drugs for Sarcopenia Treatment

Myostatin

Inhibitors:

- **antibody**
- **recepetor decoy**
- **activity inhibitors**

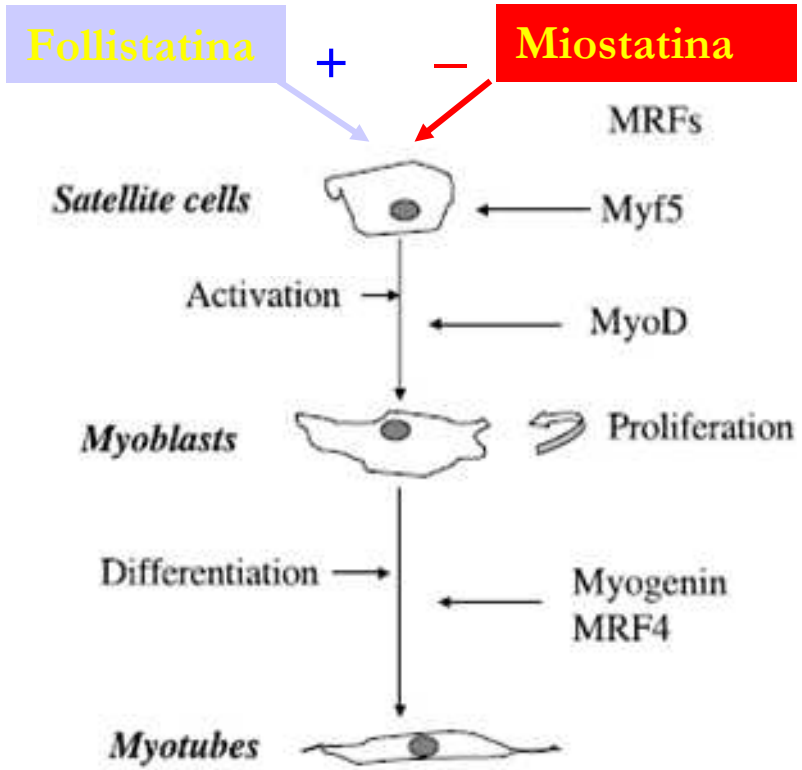
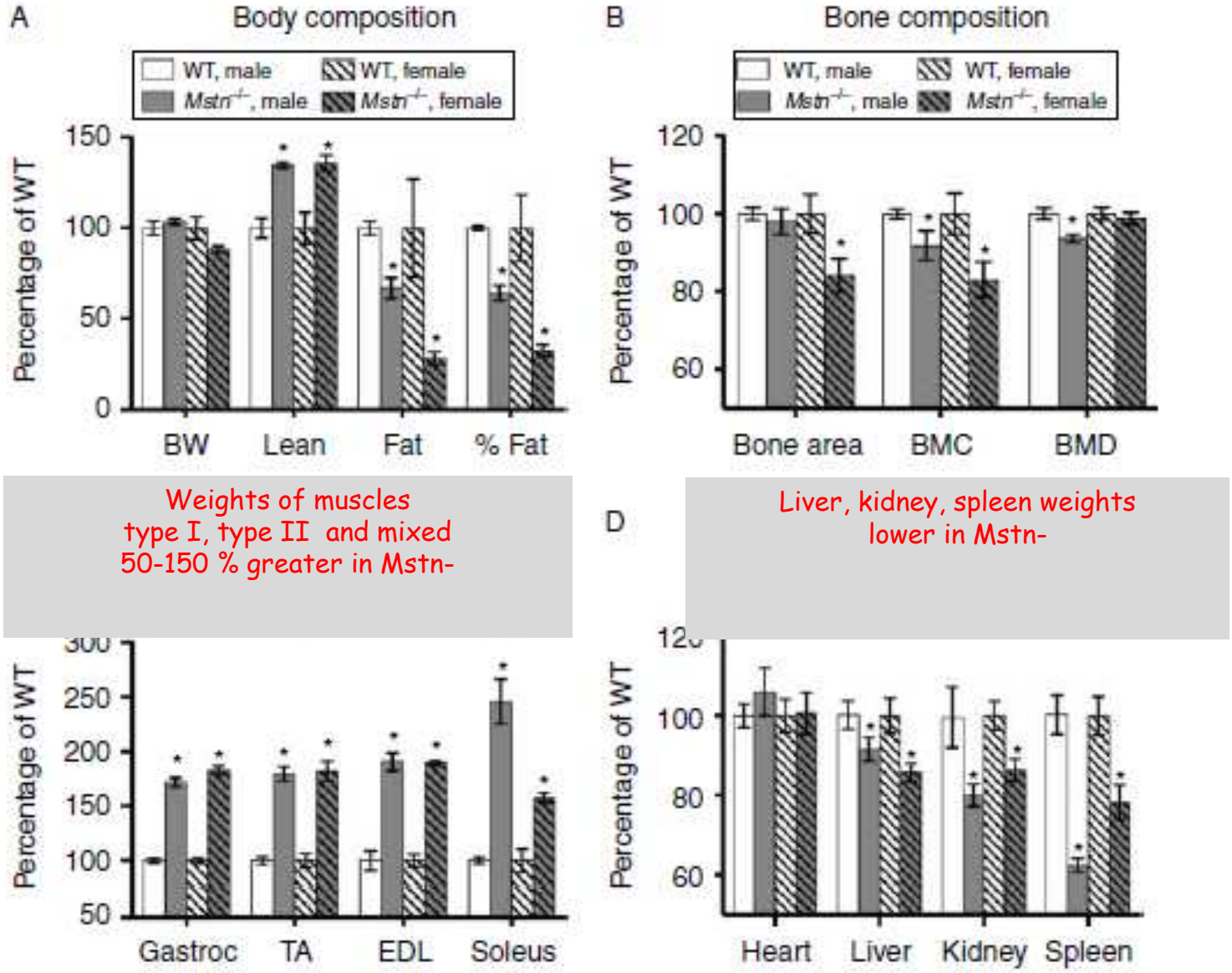
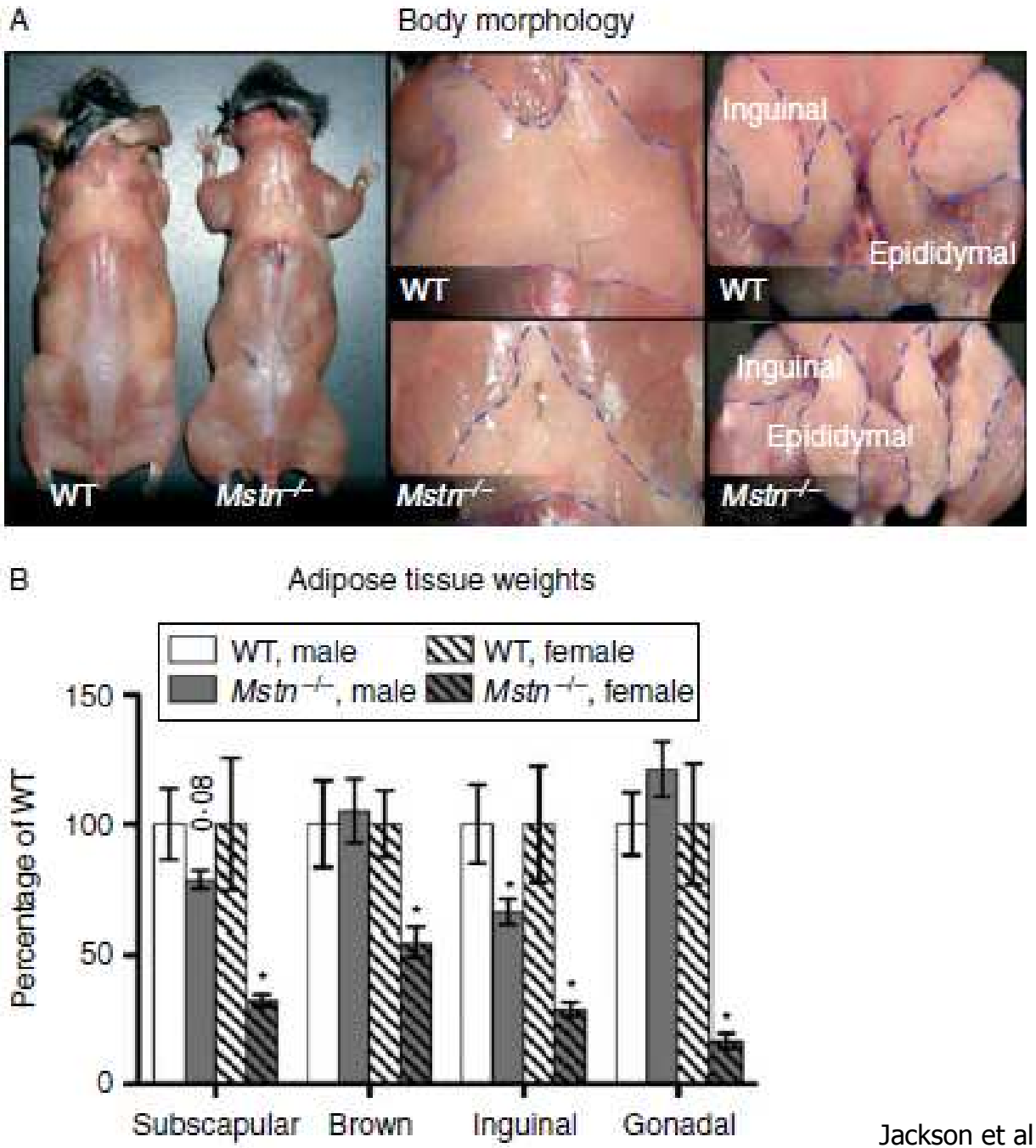


FIG. 2. A fullblood Belgian Blue bull showing the double muscling phenotype.

The aging myostatin null phenotype



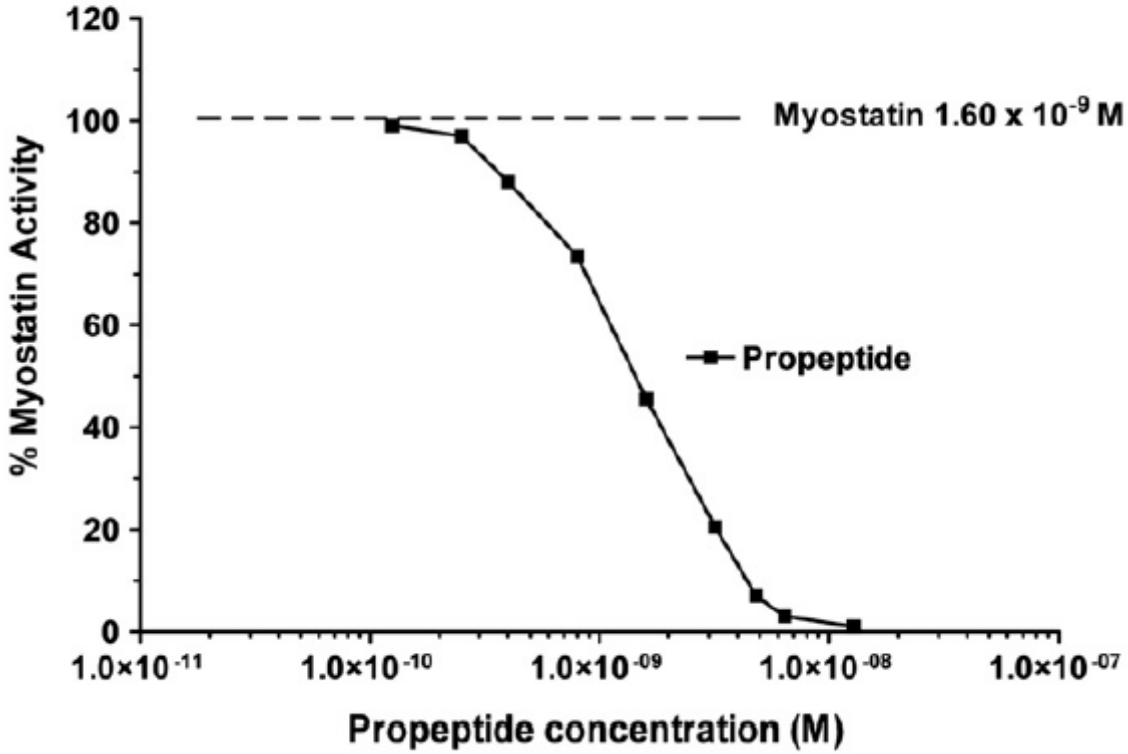
Jackson et al 2012

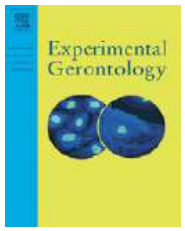


Jackson et al 2012

A myostatin inhibitor (propeptide-Fc) increases muscle mass and muscle fiber size in aged mice but does not increase bone density or bone strength ☆

Myostatin propetide prevents the binding of myostatin to its receptor

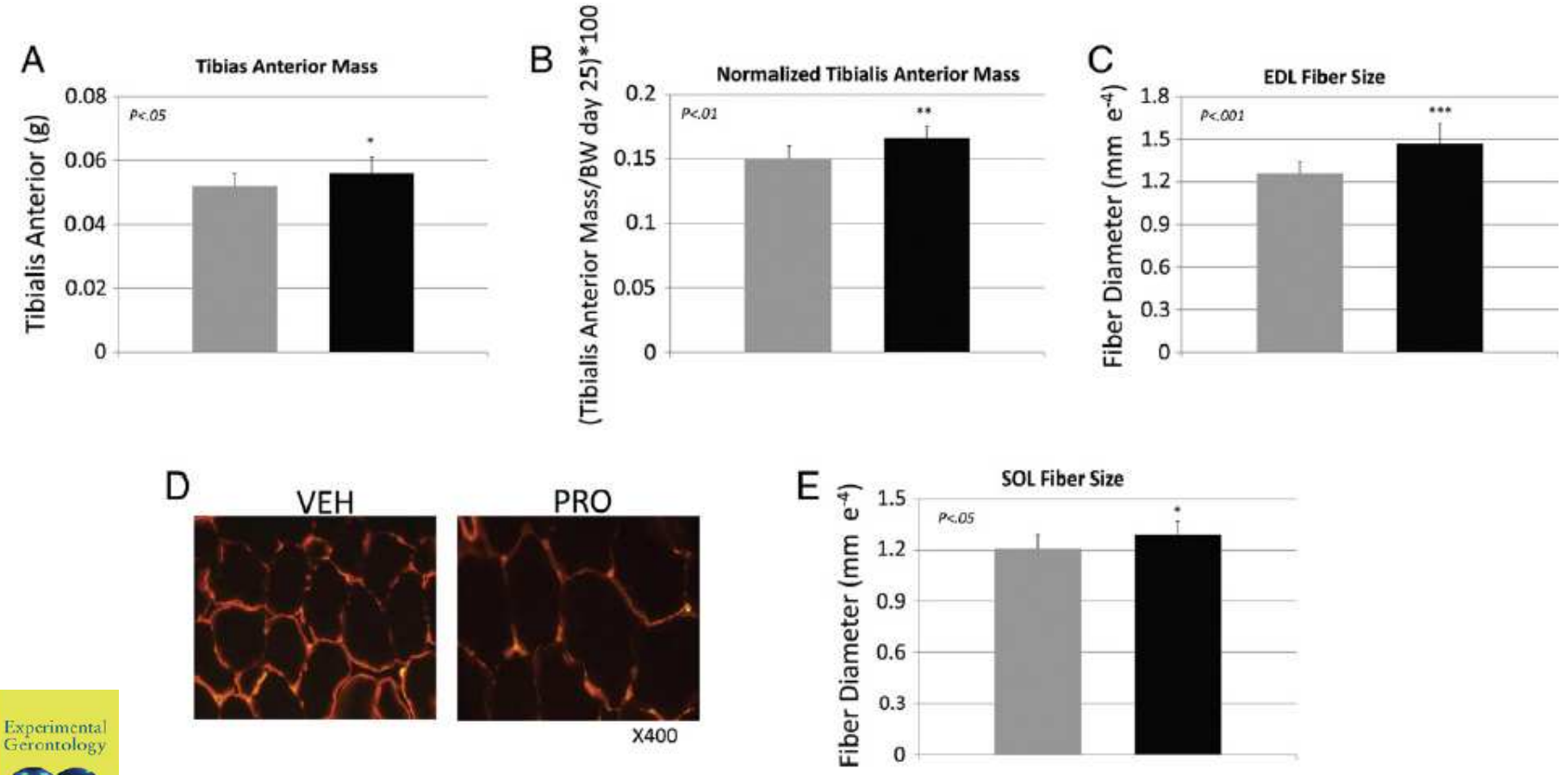


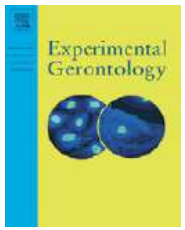


Arounleut et al, 2013

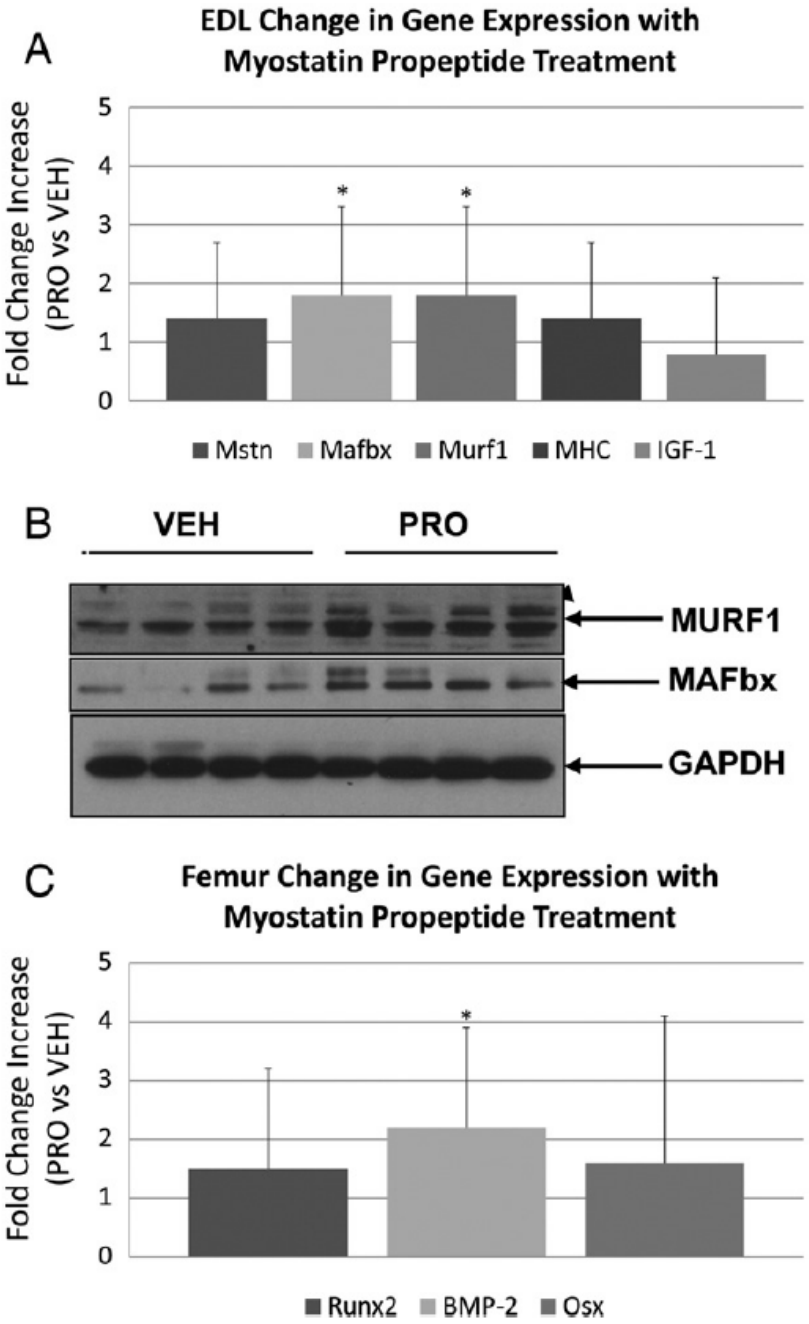
A myostatin inhibitor (propeptide-Fc) increases muscle mass and muscle fiber size in aged mice but does not increase bone density or bone strength ☆

Male mice 22-m old:
20mg/kg myostatin propeptide (PRO) body weight i.p. for 25 days vs vehicle (VEH)

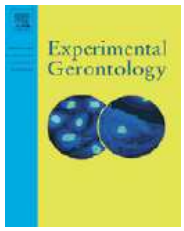




Arounleut et al, 2013

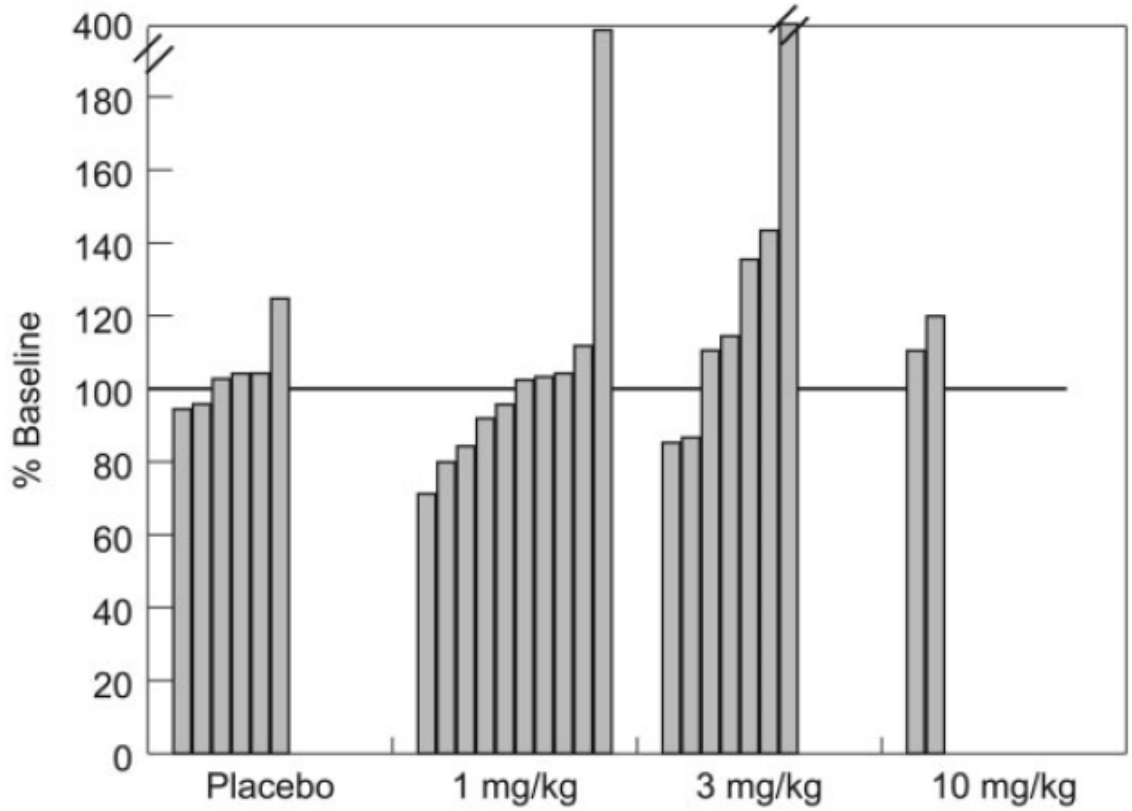


Arounleut et al, 2013



A Phase I/II trial of MYO-029 in Adult Subjects with Muscular Dystrophy

percentage change in muscle fiber diameter before and after treatment.



Methods: This double-blind, placebo-controlled, multinational, randomized study included 116 subjects divided into sequential dose-escalation cohorts, each receiving MYO-029 or placebo (Cohort 1 at 1mg/kg; Cohort 2 at 3mg/kg; Cohort 3 at 10mg/kg; Cohort 4 at 30mg/kg). Safety and adverse events were assessed by reported signs and symptoms, as well as by physical examinations, laboratory results, echocardiograms, electrocardiograms, and in subjects with facioscapulohumeral dystrophy, funduscopic and audiometry examinations. Biological activity of MYO-029 was assessed through manual muscle testing, quantitative muscle testing, timed function tests, subject-reported outcomes, magnetic resonance imaging studies, dual-energy radiographic absorptiometry studies, and muscle biopsy.

Wagner et al, 2008

Apoptosis in Skeletal Myocytes: A Potential Target for Interventions against Sarcopenia and Physical Frailty – A Mini-Review

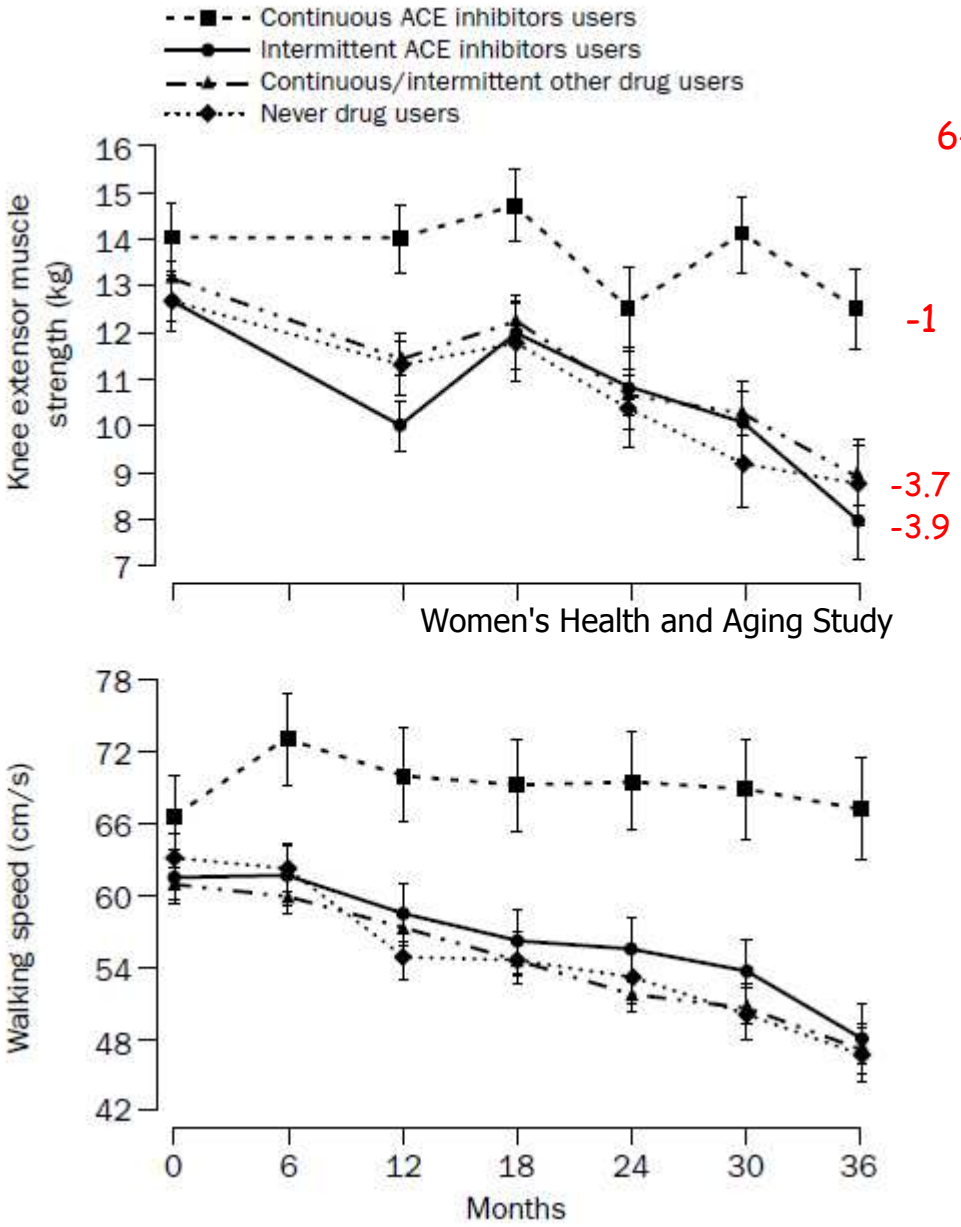
	Apoptotic signaling pathways			
	extrinsic	mitochondrial caspase-dependent	mitochondrial caspase-independent	sarcoplasmic reticulum pathway
Behavioral interventions				
CR	↓	↓	↓	↓
Resveratrol (CR mimetic)	–	↓	–	–
Exercise training	↓	↓	–	–
Drugs and hormones				
Enalapril	–	↓	↔	–
Acetaminophen	–	↓[a]	↓[a]	–
Antimyostatin antibody	↓[b]	↓[b]	–	↓[b]
Q10 + creatine + ginseng	–	↓[a]	↓[a]	–
Testosterone[c]	?	?	?	?
Genetic manipulations				
PGC-1α overexpression	–	↓	–	–

Emanuele Marzetti[a] Riccardo Calvani[b] Roberto Bernabei[b]
Christiaan Leeuwenburgh[c]

Gerontology 2012;58:99–106

Drugs for Sarcopenia Treatment: Ancillary Effects

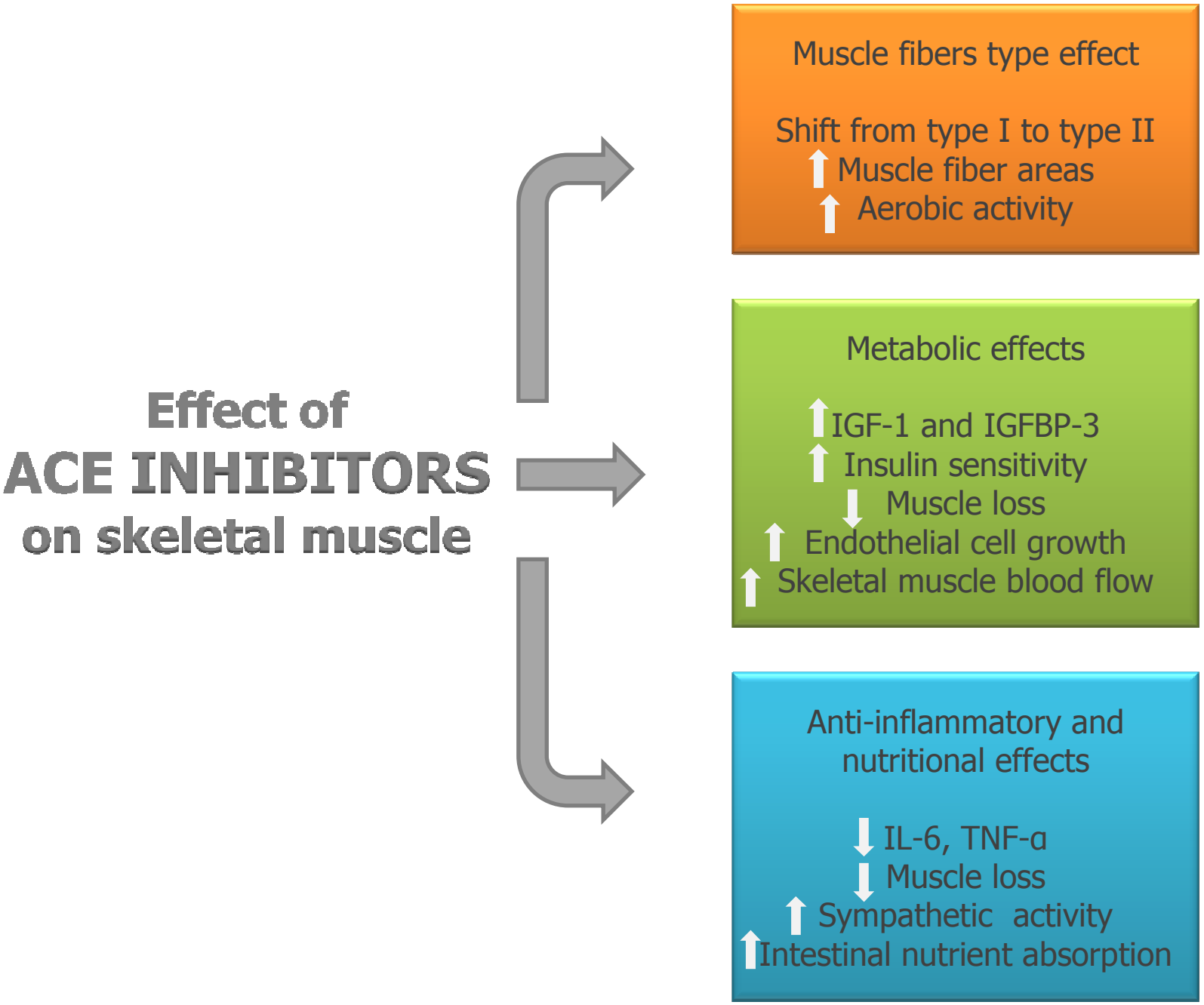
- Ace-Inhibitors ?
- Statin ?

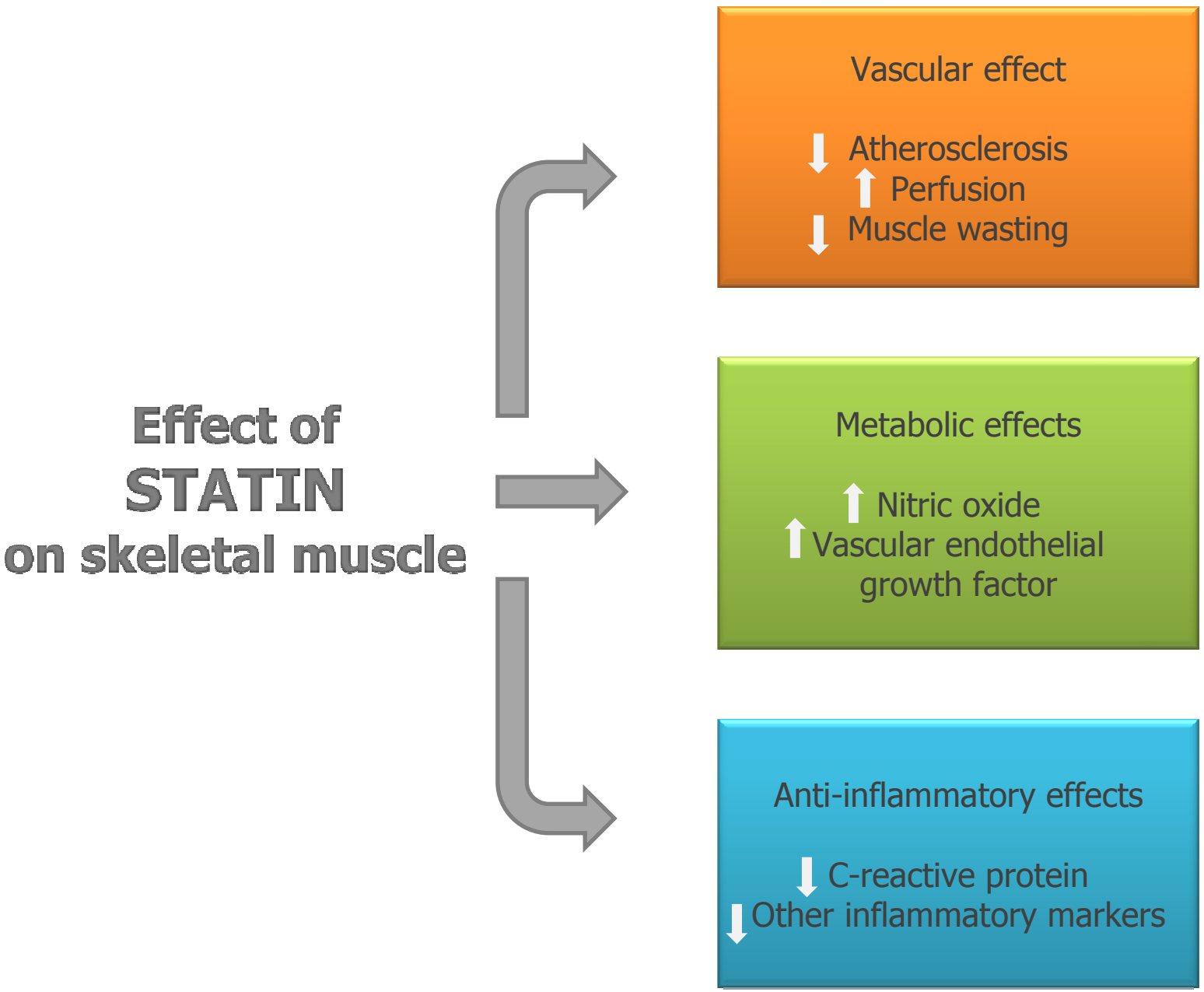


641 Women Health and Aging Study
old disabled women
without CHF

Follow-up 3 years

Onder et al, 2002


Effect of
ACE INHIBITORS
on skeletal muscle
Muscle fibers type effect
Shift from type I to type II
↑ Muscle fiber areas
↑ Aerobic activity
Metabolic effects
↑ IGF-1 and IGFBP-3
↑ Insulin sensitivity
↓ Muscle loss
↑ Endothelial cell growth
↑ Skeletal muscle blood flow
Anti-inflammatory and
nutritional effects
↓ IL-6, TNF-α
↓ Muscle loss
↑ Sympathetic activity
↑ Intestinal nutrient absorption


Effect of
STATIN
on skeletal muscle
Vascular effect
Atherosclerosis
Perfusion
Muscle wasting
Metabolic effects
Nitric oxide
Vascular endothelial growth factor
Anti-inflammatory effects
C-reactive protein
Other inflammatory markers

Potential Study End Point	Advantages
Muscle mass	Readily measured and central to the condition of sarcopenia; relevant to expected actions of several potential interventions (see Table 1)
Muscle strength	Easily measured; important component of physical function and correlates with clinical outcomes
Falls	Clinically important and of prognostic value
Fractures	Clinically important; accepted as regulatory endpoint in osteoporosis
Walking and other physical performance measures	Relevant to ambulatory function; treadmill assessments, walking speed and 6-minute walk accepted as regulatory endpoints for other indications
Patient-reported outcomes	Probably most relevant to patients' ambulatory function and quality of life

Considerations in the Development of Drugs to Treat Sarcopenia

Eric P. Brass, MD, PhD, and Kathy E. Sietsema, MD

JAGS 59:530–535, 2011