Sarcopenia and frailty – preventable and treatable geriatric syndromes

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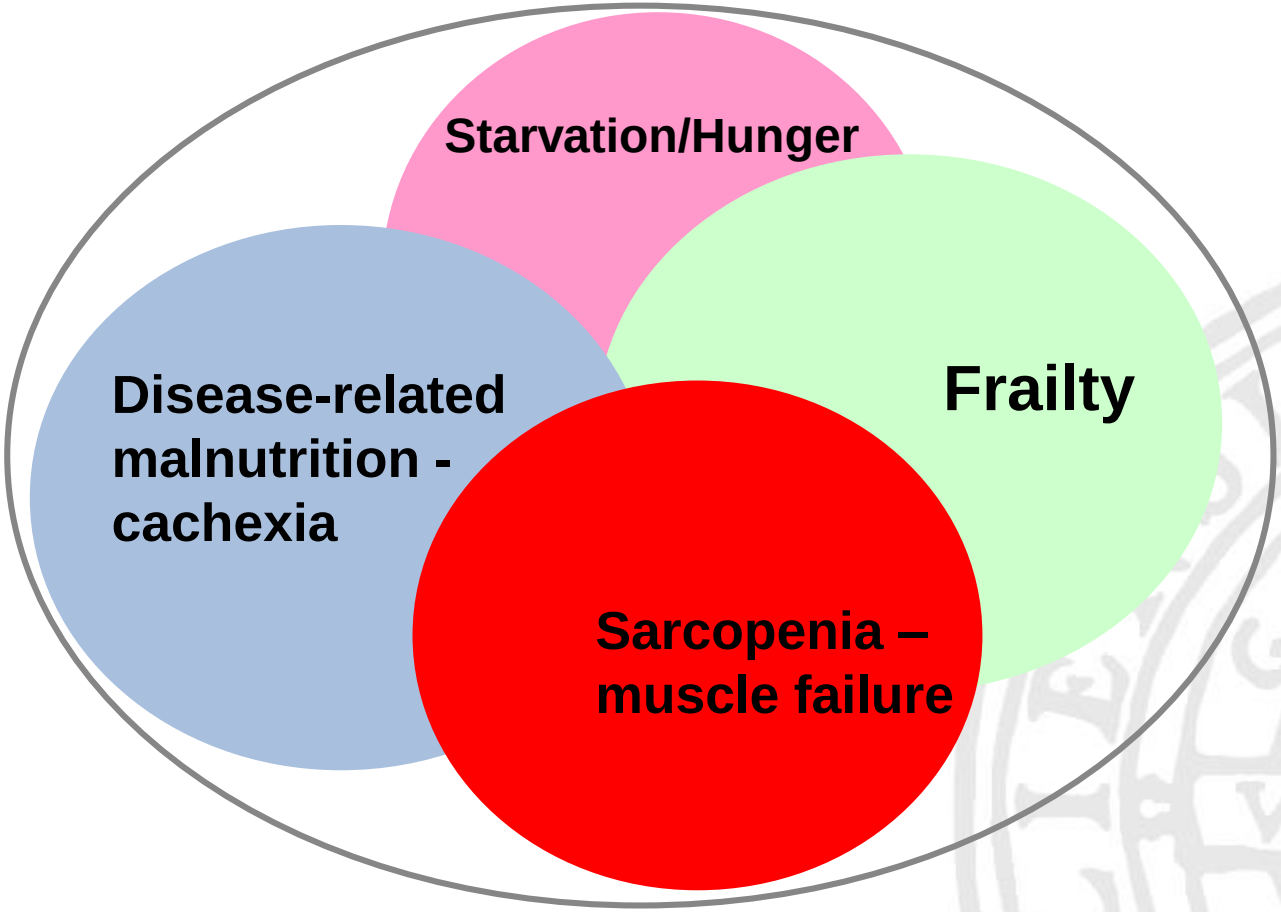
Overlapping catabolic conditions that affect function and survival



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Ageing & Disease→ disability & †

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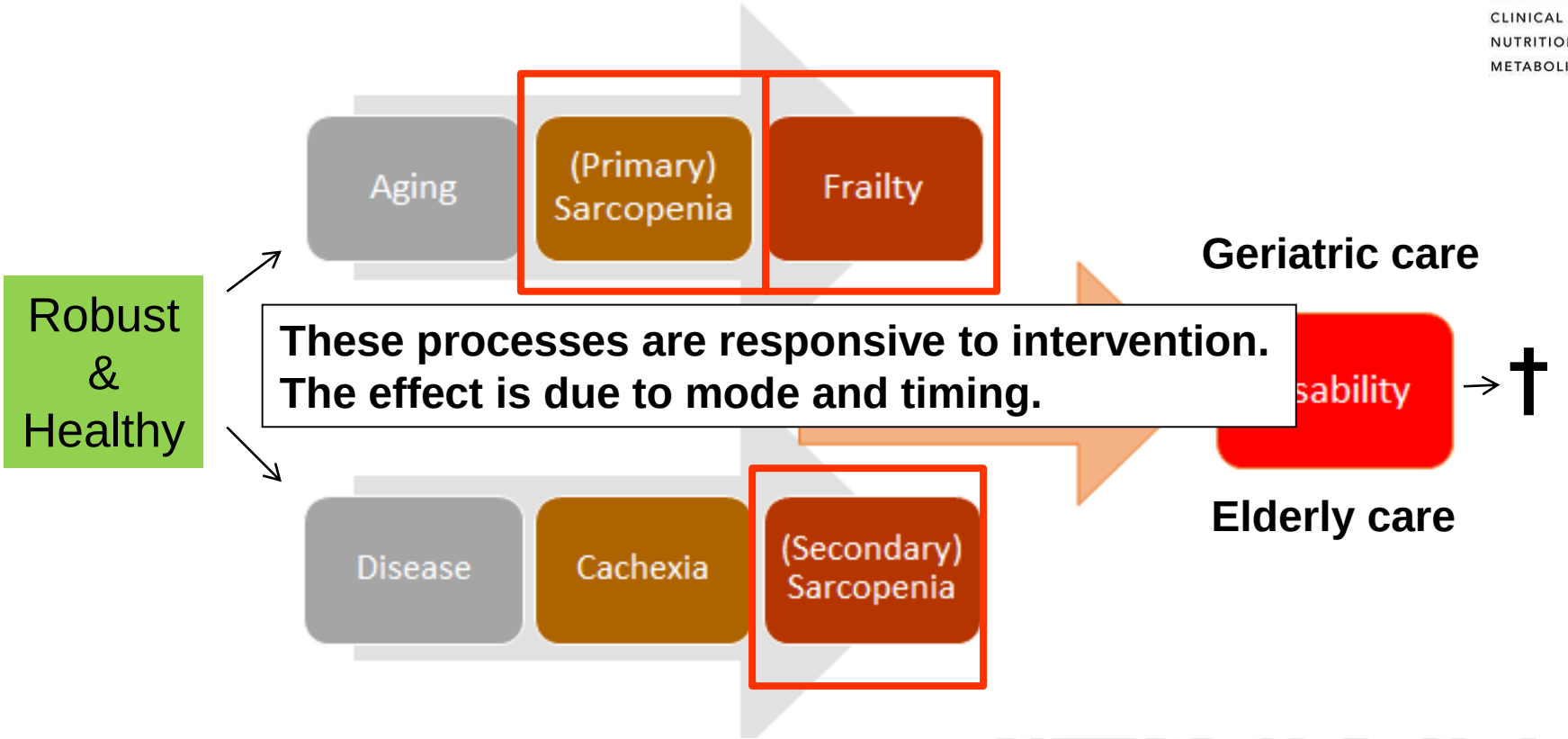


Frailty and sarcopenia are risk factors for disability and death

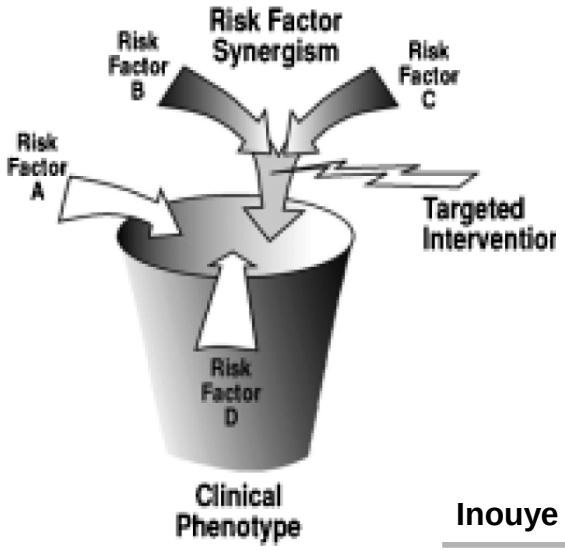
Geriatric syndromes –
Sarcopenia and Frailty new GS/Giants

Falls
Pressure ulcers
Malnutrition
Confusion
Sarcopenia
Frailty

A geriatric syndrome is/has

- **multi-factorial pathogenesis**
- **one phenotype**
- **linked to co-morbidity**
- **bad prognosis**

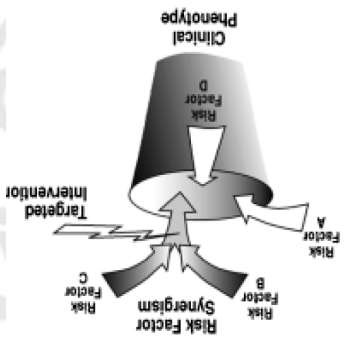
Compare a medical syndrome



Risk factors in common

- **high age**
- **cognitive decline**
- **reduced mobility**

One disease



Many symptoms

Inouye S et al. J Am Geriatr Soc 2007;55:780-91

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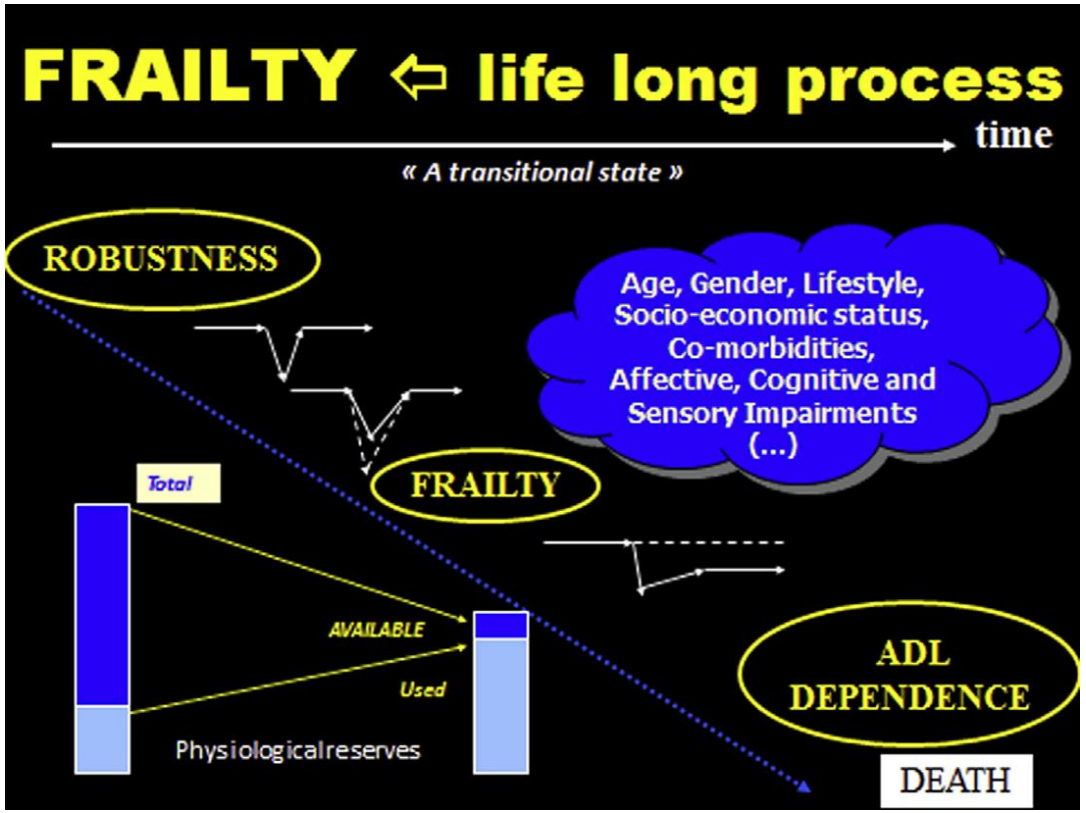
Frailty – a new geriatric giant

Definition:

- **Vulnerability**
- **Non-resilience**
- **Reserve capacity↓**
- **Risk of morbidity and dependency**

Prevalence :
6-26% of older people in Europe (SHARE) (Frieds criteria)



Michel, Cruz & Cederholm. Clin Ger Med 2015

Borsch-Supan et al. Int J Epidemiol 2013

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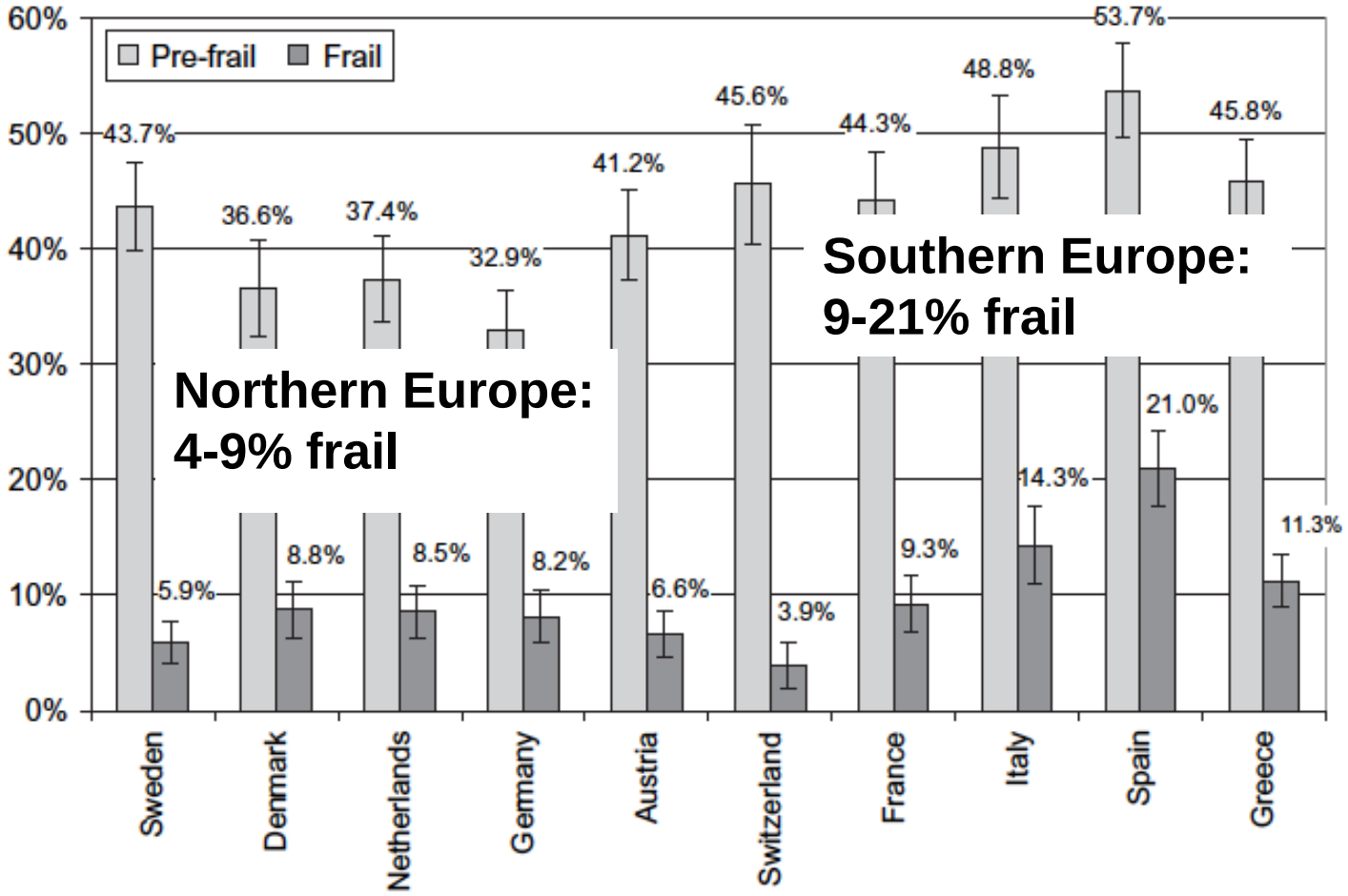
Prevalence of frailty in Europe in persons > 65 y – The SHARE Study



Santos-Eggimann B et al, J Gerontol A Biol Sci Med Sci 2009; 64:675-681

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Frailty is reversible – The SHARE Study

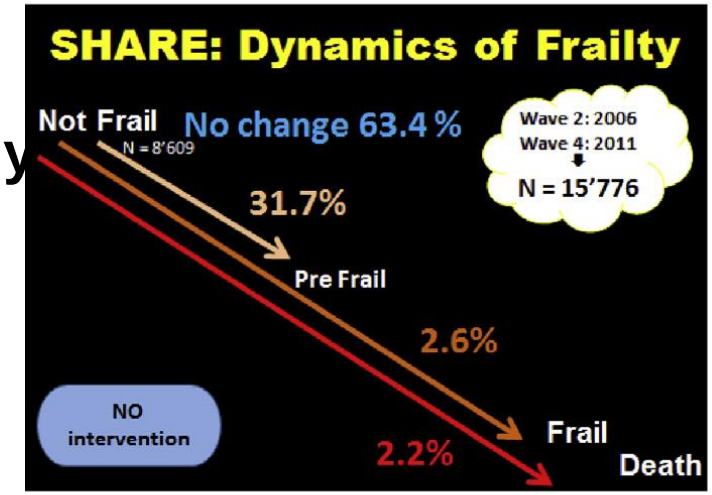
The SHARE Study

80.000 >65 y

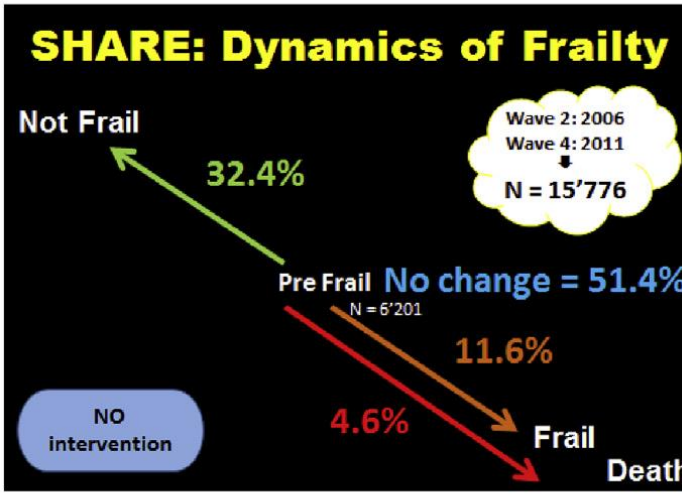
5-y f-up

A: Not Frail
B: Pre Frail
C. Frail (40% improved)

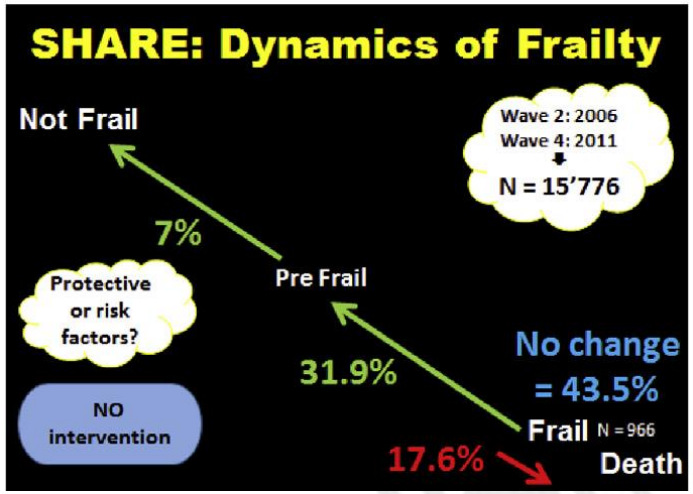
A



B



C



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Diagnosis of frailty?

The Frailty Phenotype

Cardiovascular Health Study "Linda Fried Criteria" (2001)

- **Weight loss**
- **Weakness**
- **Exhaustion**
- **Slowness**
- **Low physical activity**

≥3 Frailty

1-2 Pre-Frailty

Fried L et al. Frailty in older adults: evidence for a phenotype. J Gerontol 2001

The Frailty Index

- "Cumulative deficit model" (60-70 items)

Canadian Study of Health and Aging (Rockwood 2002)

A 60-point Frailty Index score, based on data routinely collected in a Comprehensive Geriatric Assessment.

Health deficit	Scoring instructions
Cognition	Score 0 if within normal limits, 0.5 if "Cognitive Impairment, No Dementia", 1 if "dementia
Dementia stage	0 = absent, 0.33 = mild; 0.67 = moderate; 1 = severe
Delirium	0 = absent, 1 = present
Affect/mood	0 = normal; 0.5 = low mood; 1 = depression
Anxiety	0 = absent; 1 = present
Behavioural and psychological symptoms of dementia	0 = absent; 1 = present
Violence	0 = absent; 1 = present
Health attitude	0 = excellent/good; 1 = fair/poor
Mobility	0 = walks on own; 0.25 = slow 0.5 needs assistance; 1 = cannot walk
Walking aid	0 = absent 0.25 = cane; 0.75 = walker; 1 = wheelchair
Balance	0 = unimpaired; 1 = impaired
Falls	0 = none; 0.5 present, not in last month; 1 = within last month
Transfers	0 = independent; 0.5 = standby; 1 = any hands-on assistance
Bowels	0 = normal; 0.5 = constipation; 1 = incontinence
Bladder	0 = normal; 0.5 = occasional incontinence; 1 = incontinence
Hobbies	0 = retained; 0.5 = reduced; 1 = abandoned
Banking	0 = independent; 0.5 = needs some assistance; 1 = dependent
Medications	0 = independent; 0.5 = needs some assistance; 1 = dependent
Shopping	0 = independent; 0.5 = needs some assistance; 1 = dependent
Transportation	0 = independent; 0.5 = needs some assistance; 1 = dependent
Climbs stairs	0 = independent; 0.5 = needs some assistance; 1 = dependent
Bathing	0 = independent; 0.5 = needs some assistance; 1 = dependent
Dressing	0 = independent; 0.5 = needs some assistance; 1 = dependent
Toileting	0 = independent; 0.5 = needs some assistance; 1 = dependent
Grooming	0 = independent; 0.5 = needs some assistance; 1 = dependent
Feeding	0 = independent; 0.5 = needs some assistance; 1 = dependent
Weight	0 = independent; 0.5 = needs some assistance; 1 = dependent
Appetite	0 = normal; 1 = reduced
Sleep	0 = normal; 0.5 = sometimes disrupted; 1 = problem
Daytime drowsiness	0 = absent; 0.5 = occasional; 1 = present
Smoking	0 = never; 0.25 none in last 25 years; 0.5 = past; 1 = present
In Emergency Department in last 30 days	0 = no; 1 point for each visit (maximum 3)
In hospital in last 6 months	0 = 1; 1 point for each week in hospital (maximum = 6)
Co-morbidities	Score 1 for each; maximum is 16
Medications	<5 = 0; 5–7 = 1.0; 8–11 = 2; 12–15 = 3; >15 = 4

Note on scoring: 1 point is added for each deficit; the total points are divided by 60 to achieve a Frailty Index score, where 0 = no deficits present, and 1.0 = all 60 deficits present. In practice, many fewer than 1% of people would have a Frailty Index score >0.67.

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Fried L et al. Frailty in older adults: evidence for a phenotype. J Gerontol 2001

The Frailty Index

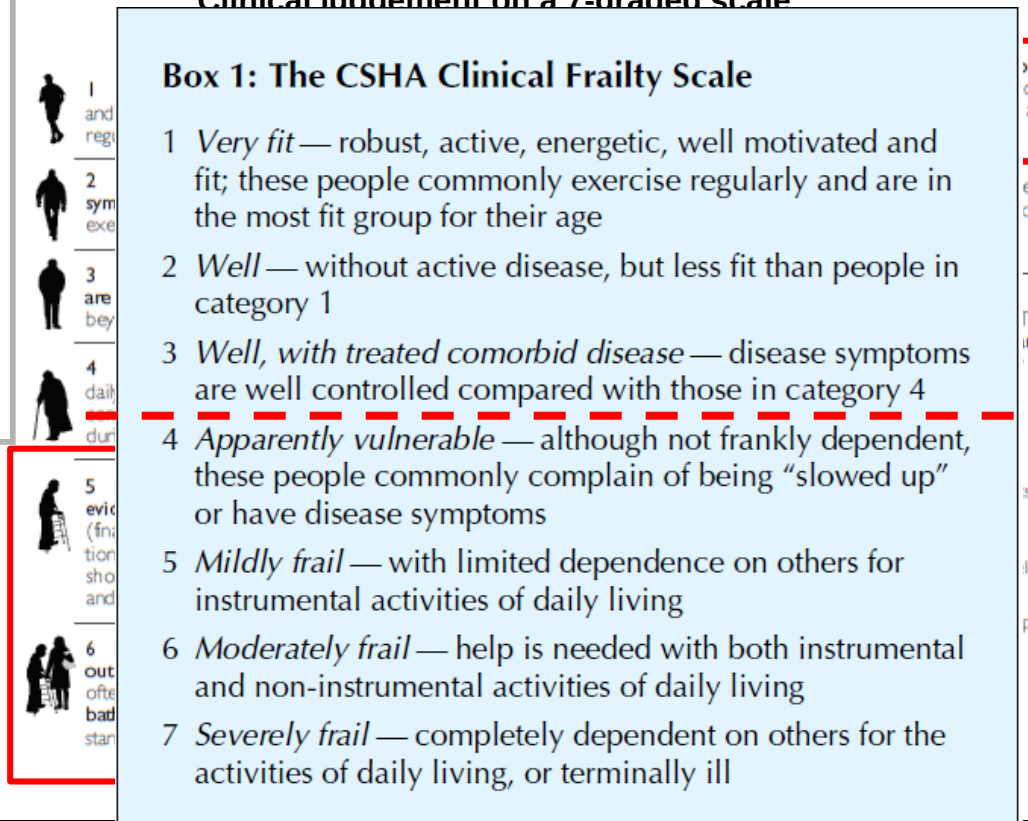
- "Cumulative deficit model" (70 items)

Canadian Study of Health and Aging

(Rockwood 2002)

- Clinical Frailty Scale (Rockwood 2006)

Clinical judgement on a 7-graded scale



Box 1: The CSHA Clinical Frailty Scale

1 *Very fit* — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 *Well* — without active disease, but less fit than people in category 1

3 *Well, with treated comorbid disease* — disease symptoms are well controlled compared with those in category 4

4 *Apparently vulnerable* — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms

5 *Mildly frail* — with limited dependence on others for instrumental activities of daily living

6 *Moderately frail* — help is needed with both instrumental and non-instrumental activities of daily living

7 *Severely frail* — completely dependent on others for the activities of daily living, or terminally ill

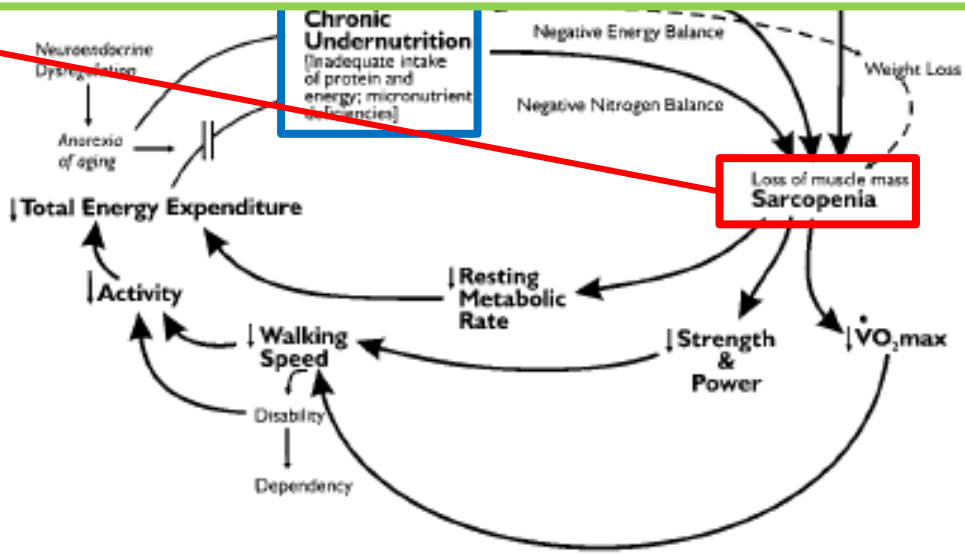
Q: What is frailty?

Linda Fried's criteria (2001)

- **Weight loss**
- **Weakness**
- **Exhaustion**
- **Slowness**
- **Low physical activity**

Frailty is a complex state of reduced strength, power and resilience (WHO), that increases risk of dependence and mortality

A: A combination of reduced function and malnutrition



Fried L et al. Frailty in older adults: evidence for a phenotype. J Gerontol 2001

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The role of muscle

- ~40% of body weight
- 50-75% of body protein
- Mobility
- Strength
- Amino acid pool
- Glucose regulation
- Energy metabolism
- Endocrine functions
- ....

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Sarcopenia – a novel concept for an old problem in old and ill

Loss of muscle – Irvin Rosenberg 1989

"Muscle loss steals the freedom of the old"

Muscle mass decrease by

- **30-50% from 20 to 80 y**
- **1-2%/y after 50 y**

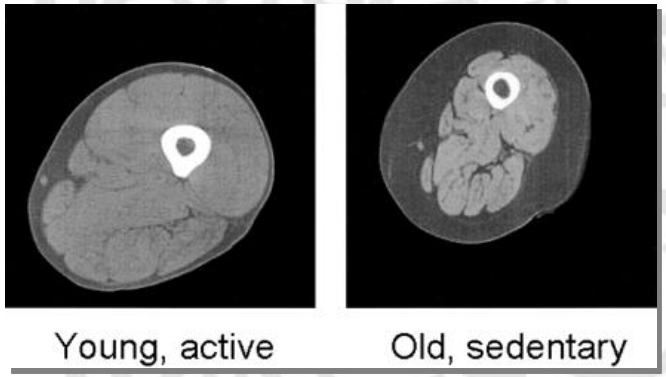
Selective typ II fibre atrophy

Muscle strength ↓ by

- **15% / 10 y between 50 and 70 y**
- **30% / 10 y thereafter**

Sarcopenia is a syndrome characterized by progressive loss of muscle mass and strength with a risk of adverse outcomes

Cruz-Jentoft et al. Age Aging 2010;39:412-23



Marzetti. Exp Gerontol 2006;41:1234-8

Classification of sarcopenia

Primary sarcopenia *(or age-related)* when there is no evident cause but ageing itself

Secondary sarcopenia when one or more causes are identified:

- **Activity-related sarcopenia**
  - bed rest, sedentarism, deconditioning, non-gravity
- **Disease-related sarcopenia**
  - advanced organ failure (heart, respiratory, liver, renal, brain, intestinal), inflammatory disease, malignancy, endocrine disease
- **Nutrition-related sarcopenia**

Cruz-Jentoft et al. Age Aging 2010

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Diagnostic criteria for sarcopenia

- adopted by ESPEN/EUGMS/IAGG/IANA/

Reduced muscle mass

≥2 SD below mean of muscle mass in a young ref population

...m)

Maximum walking speed of the Grim Reaper (Death) is 1.3 m/s (5 km/h)

BMJ Dec 2011;343
Stanaway

reduced grip strength; e.g. 20 k...

Cruz-Jentoft et al. Age Aging 2010;39:412-23
Fielding et al. JAMDA 2011;12:249-256
Morley et al. JAMDA 2011;12:403-09
Studenski et al. J Gerontol 2014;69:547-58

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Aetiology of sarcopenia → frailty

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Apoptosis↑,

Caspase activation, mitochondria DNA mutations

Inflammation

Inactivity/bed rest

Hormonopause

testosteron↓, estrogen↓, DHEA↓, GH↓, IGF-I↓

Insulin resistance

relative obesity, inflammation

Nutritional deficiencies

“anorexia of aging”, protein RDI 0.8 g/d/kg?

Motor-unit losses (~50% between 25 and 75 y)

neuro-muscular synaptic damage

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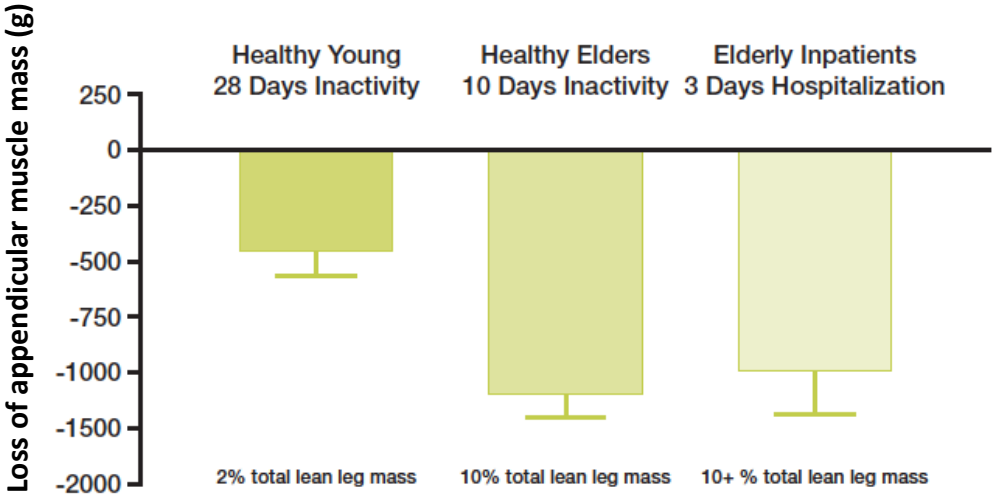
Loss of muscle mass as a consequence of immobility in young and old – is hospitalization a cause for sarcopenia in older adults?

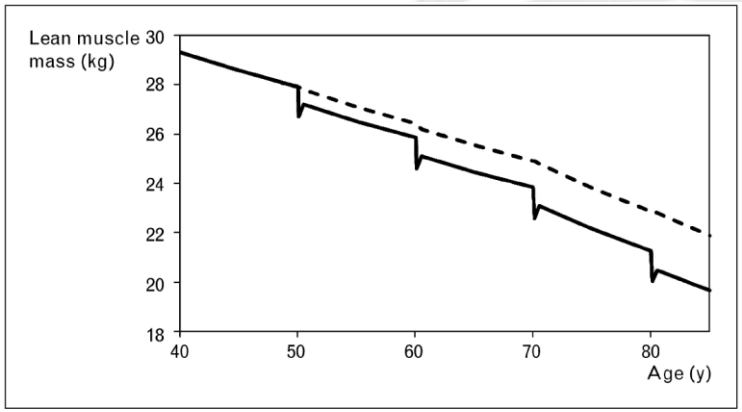


Kortebein P et al, JAMA 2007;297:1772-1774

Aging + "catabolic crisis":

Recurrent disease episodes aggravate the sarcopenic process

- **Bedrest**
- **Inflammatory bouts**



(– –), Traditional sarcopenia model; (—), Catabolic crisis model.

English&Paddon-Jones. COCNM 2010;13:34-39

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Disease/trauma/aging

Inflammation

Neuropeptid Y↓

Leptin↑

Insulin resistence

Cathepsin↑

Ubiquitin-proteasom↑

Hormon sensitive lipase↑

Lipoprotein lipase↓

Anorexia **Proteolysis** **Lipolysis**

Cachexia → Sarcopenia

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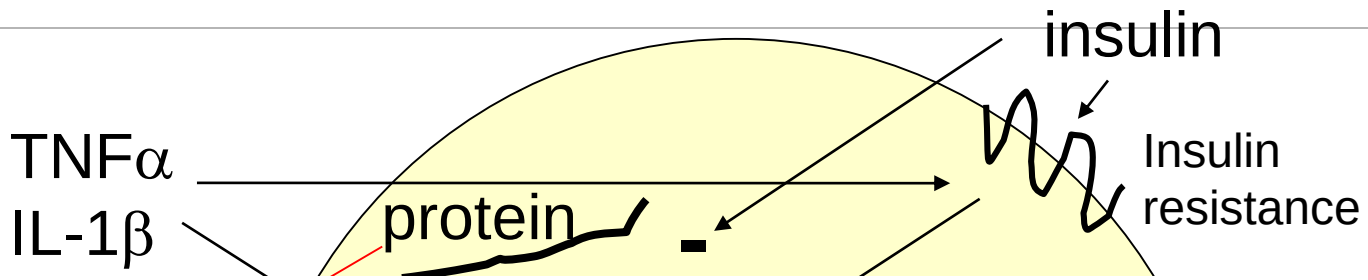
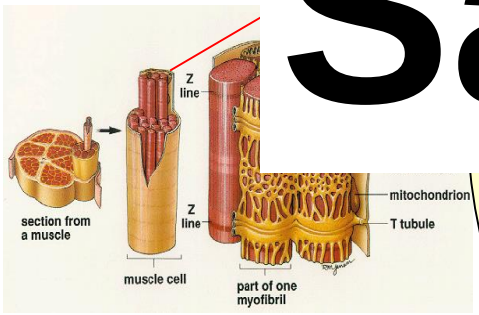
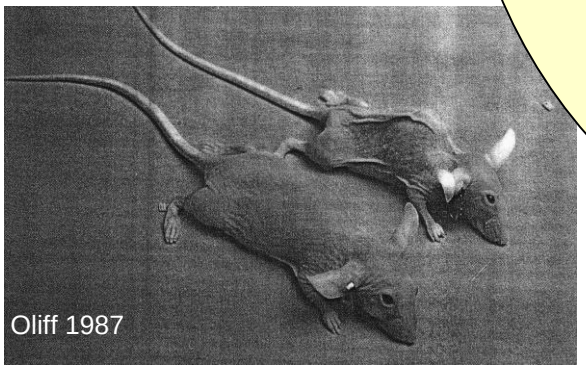
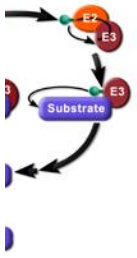
Inflammation and muscle breakdown



Sarcopenia







Amino acids

- alanine → gluconeogenesis
- glutamine → gut, immune system

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Clinical relevance of sarcopenia

- **QoL↓** Patel et al. Age Ageing 2013;42:378-84
- **Insulin resistence** Sanada et al. Eur J Clin Nutr 2012;66:1093-1098
- **Osteoporosis** Verschueren et al. Osteoporosis Int 2013;24:87-98
- **Falls** Landi F et al. Clin Nutr 2012;31:652-8
- **LoS↑** Gariballa&Alessa. Clin Nutr 2013;32:772-6
- **Re-admissions↑** Gariballa&Alessa. Clin Nutr 2013;32:772-6
- **Mortality↑** Landi F et al. Age Ageing 2013;42:203-9

- adjusted for several confounders

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Treatment options for malnutrition and sarcopenia

✓Nutrition

- Regular food
- *Oral supplementation*
- Energy enriched
- Protein enriched
  - Essential amino acids
- Vitamin D
- Essential fatty acids
- *Dietary patterns*
- *Enteral nutrition*
- Nasogastric tube
- PEG
- *Parenteral nutrition*

✓Reduce catabolism

- Myostatin inhibitors - decoy receptors
- Ghrelin agonists - anamorelin
- Megesterol acetate
- Proteasome inhibitors
- ACE inhibitors

✓Immuno modulation

- n-3 and n-6 fatty acids
- Arginine, glutamine
- Anti-oxidants

✓Anabolic treatment

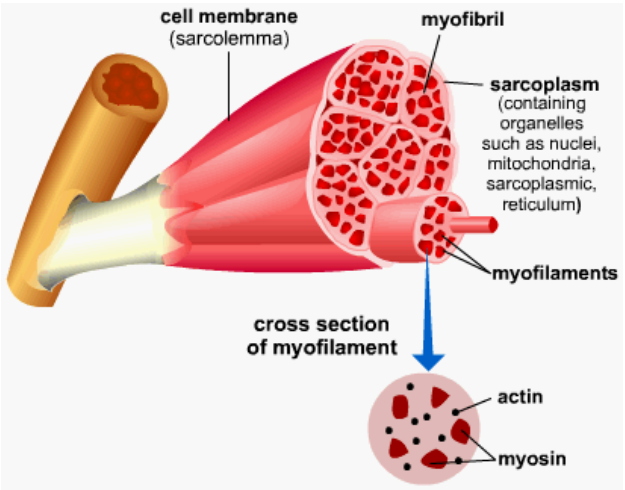
- BCAA, leucin, HMB
- GH, Nandrolon,
- SARMs

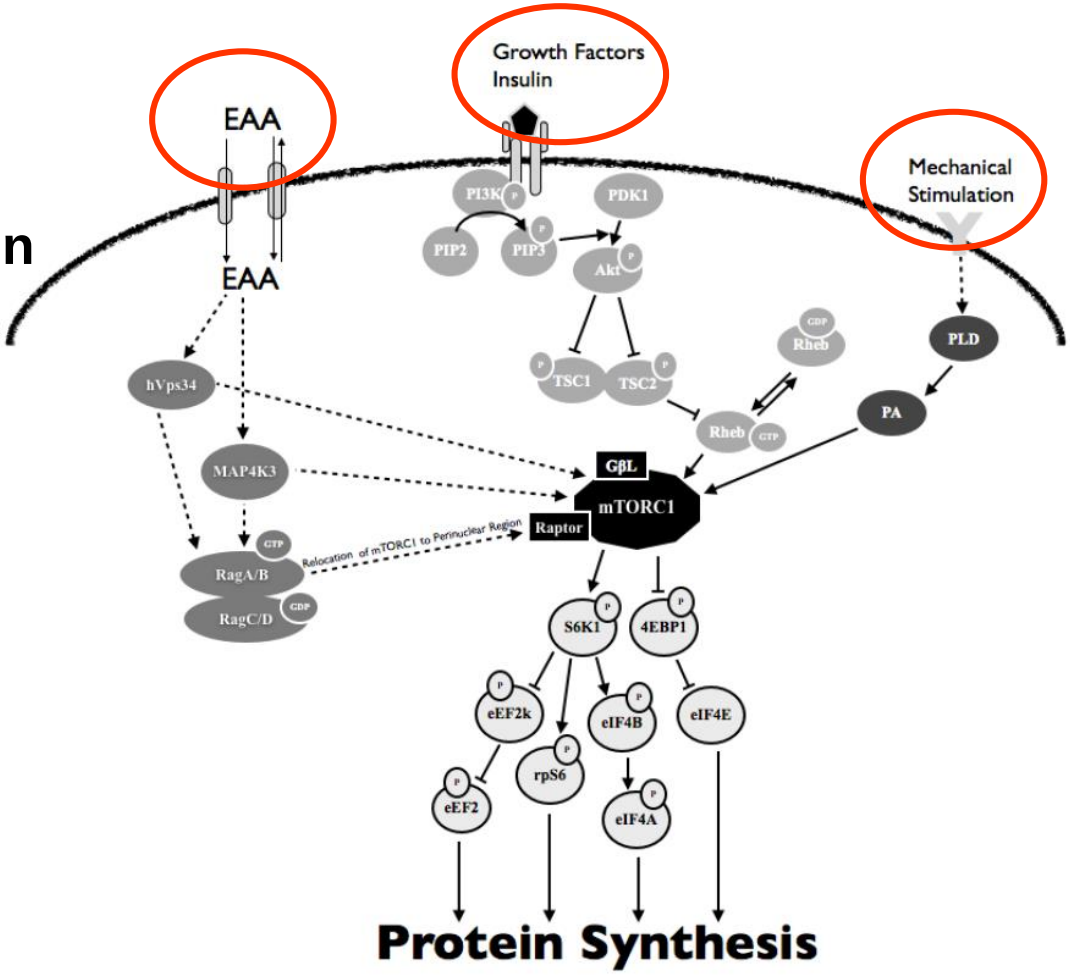
✓ Physical activity

Resistance training

How to generate protein synthesis?

- **mTOR activation**
  - **Amino acids**
  - **Mechanical stimulation**
  - **Anabolic hormones**
- **Transcription**
- **Translation**





Walker et al. Med Sci Sports Exerc 2011;43

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Resistance training

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Resistance training

15 RCT in a systematic review show in general positive effects

Strength↑ ~200%, muscle mass↑ 10%,

Improved stair-climb, gait-speed, chair.rise, 6 minutes walk test

Seguin&Nelson Am J Prev Med 2003;25:141

66 studies in a Cochrane meta-analysis 2003:

REVIEWER'S CONCLUSIONS: PRT appears to be an **effective intervention** to **increase strength** in older people and has a positive effect….

Latham et al. Cochrane Database Syst Rev 2003

Up-dated Cochrane analysis 2009 - 121 studies (RCT), 6700 subjects

- "modest improvement in gait speed"
- "moderate-large effect for getting out of chair"
- **"large effect on muscle strength"**

Liu & Latham. Cochrane 2009

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Protein intake - observational studies

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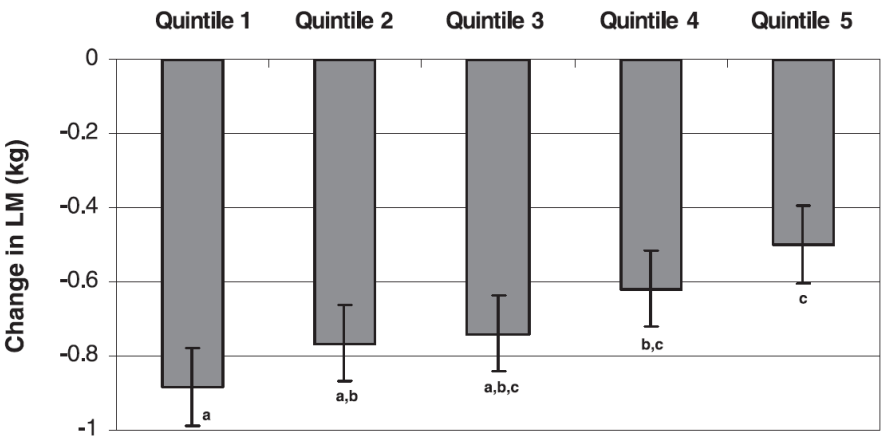
Protein intake and muscle mass in the Health ABC Study

2066 ♀/♂, 70-79 y

3-year follow-up

Lean Mass (DXA)

Quintiles of protein intake



Q1 – 0.8 g/kg bw, 11 E% protein
Q5 – 1.2 g/kg bw, 18 E% protein

Conclusion:

High protein intake preserves muscle mass

Houston DK et al. AJCN 2008

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Protein intake and mobility limitation in the Health ABC Study

1998 ♀/♂, 70-79 y com-dw

- **6-year follow-up**
- **Tertiles of protein intake (FFQ)**
- **Limited walking (400 m) or stair climbing (10 steps)**
- **1/3 developed mobility lim**

T1 – <0.7 g/kg bw/d
T2 – 0.7-1.0 g/kg bw/d
T3 – >1 g/kg bw/d

T1 vs T3: HR 1.89 (CI 1.41-2.44)
T2 vs T3: HR 1.49 (CI 1.20-1.84)
to develop mobility limitation when compared to >1 g prot/kg bw/d

Conclusion:
Protein intake >1 g/kg bw/d reduces 6-y risk of mobility limitation

Houston DK et al. JAGS 2017

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Proteins/amino acids - intervention studies

Effects of essential amino acid treatment after knee arthroplasty

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N=28, 70±5 y, *sarcopenic*?

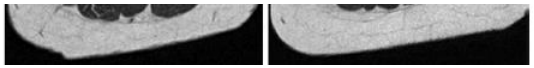
- **Knee arthroplasty**
- **RCT: 20 g EAA vs placebo for 6 weeks post-op**
- **MRI for lean mass**
- **Muscle performance**

Conclusion: EAA-treatment protect lean mass and accelerate functional mobility after knee arthroplasty

Lean mass

EAA: - 6±2 %

Plac: - 18±2 %



M. Quadriceps strength

EAA: + 7±7 %

Plac: - 16±7 %

Timed up-go-test

EAA: - 4±10 %

Plac: + 32±10 %

Dreyer et al. J Clin Invest 2013

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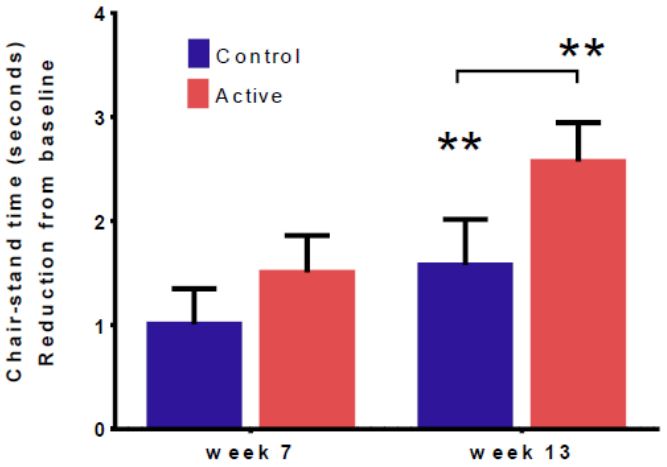
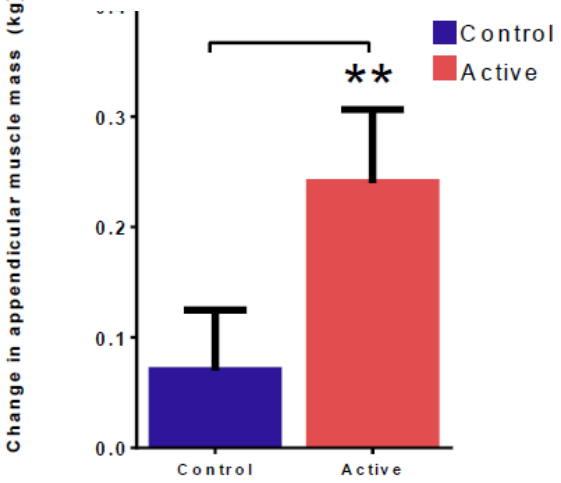
Protein + leucin + vitamin D to *sarcopenic non-malnourished* older adults: The Provide Study

- 380 >65 y, 77±1 y, sarcopenic, non-malnourished,
- RCT for 13 weeks
- 40 g prot, 3 g leucin, 1600 IU vit D, 300 kcal vs. isocaloric placebo
- Primary outcomes: SPPB, HGS,
- Secondary outcomes: Chair-stand, DXA

Chair-stand



App muscle mass



Conclusion:

- Faster 5 times chair stand
- Gains in appendicular muscle mass

Bauer et al. JAMDA 2015

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Proteins and exercise - combination studies

VIVE2 – 6 mo RCT combining exercise and protein/vitD suppl

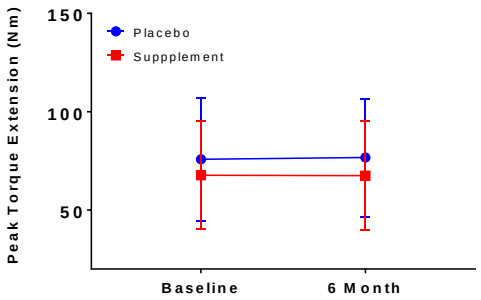
Subjects:
- 149 subjects, 78±5 y, 46% w
- BMI 28
- SPPB ~8 – *mobility-limited*
- Vit D <60 nmol/L; ~50/20 nM/L/ ng/ml

Intervention:
- Physical activity 3x/week for 24 w; walking, strength, balance, and flexibility.
- Randomized to a daily high protein/high leucine, vitamin D nutritional supplement or placebo.

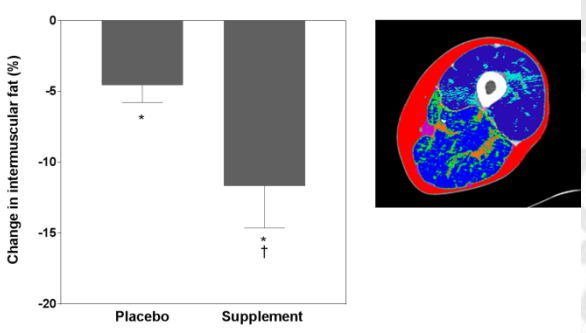
Primary outcome: Gait speed (400M walk).

Results – 400 m walk speed:
- Improved ~0.1 m/s in both groups.

Results – leg strength:



Results – im fat:



Conclusion: 24 w of intervention showed
- improvement in gait speed in both groups with no significant effect of the supplementation,
- no effect on leg strength
- reduced im fat infiltration by supplementation

Fielding et al. JNHA 2017
Englund et al. J Gerontol 2017

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Whey protein, EAA, leucin and vit D to exercising *sarcopenic* old adults

130 *sarcopenic* old adults, 80 y. BMI 24, Exercise for everybody for 12 w.

RCT: Whey prot + EAA + leucin + vit D or placebo

Effects of supplementation compare[1]

Variable	Diet				Treatment effect	
	Mean c			p P^2	Mean difference (95% CI)	P^3
Fat-free mass,[4] g	1382			6	1695 (892, 2498)	<0.001
Fat mass, g	−345			2	−114 (−786, 559)	0.689
Gynoid, %	−1.39			6	0.54 (−0.67, 1.75)	0.451
Android, %	−2.03				1.80 (0.30, 3.29)	0.021
RSMM, kg/m^2	0.21				0.27 (0.07, 0.47)	0.009
MNA score	1.76			5	1.52 (0.51, 2.52)	0.003
Weight, kg	1.12 (0.37, 1.87)	0.004	−0.89 (−1.62, −0.15)	0.019	2.00 (0.97, 3.04)	<0.001
BMI, kg/m^2	0.42 (0.11, 0.72)	0.008	−0.42 (−0.70, −0.14)	0.004	0.84 (0.43, −1.25)	<0.001
Waist circumfere					2)	0.449
ADL score						<0.001
SF-36 MCS scor					9)	0.166
SF-36 PCS score						0.030
CRP, mg/dL						0.038
IGF-I, ng/mL						0.002
Handgrip, kg					)	<0.001

Fat free mass ↑ 1.6 kg

ADL score ↑

IGF-I ↑

Handgrip ↑ 3.7 kg

	Inter-vention	BMI	Sarco-penia	Hand-grip (kg)	ONS outcome
VIVE2	Ex+ONS	28	y/n	26	? -/+
Rondinelli	Ex+ONS	24	Yes	18	+

Rondanelli et al. AJCN 2016

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Current recommendations on protein intake

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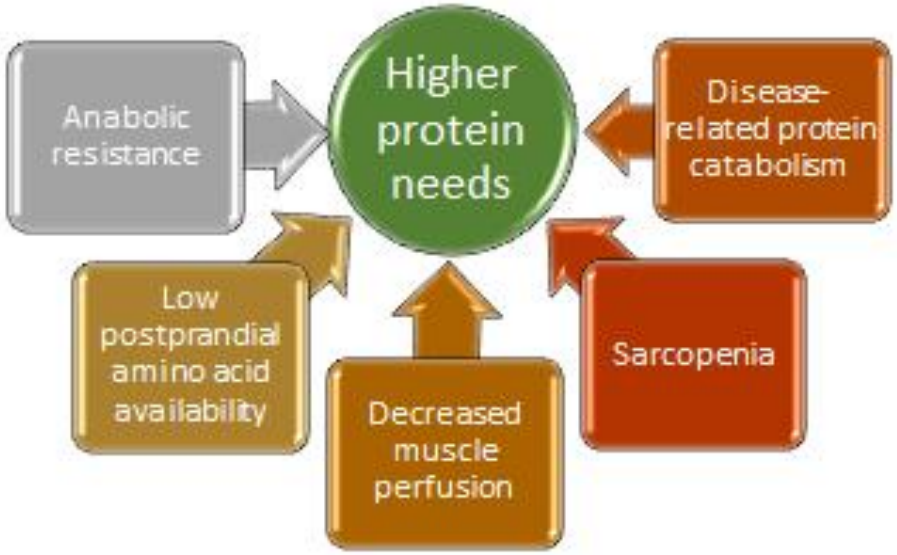
Nordic Nutrition Recommendation 2012: ... goal for protein intake in old adults is 18 E%, i.e. 1.2-1.4 g/kg bw/d...



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EUGMS – PROT-AGE 2013

... healthy old at least in the range of **1.0-1.2 g prot/kg bw/d**

...acute and chronic disease or frail need even more, i.e. **1.2-1.5 g prot/kg bw/d**

JAMDA 14 (2013) 542–559

ELSEVIER

JAMDA

journal homepage: www.jamda.com

Special Article

Evidence-Based Recommendations for Optimal Dietary Protein Intake in Older People: A Position Paper From the PROT-AGE Study Group

Jürgen Bauer MD [a,*], Gianni Biolo MD, PhD [b], Tommy Cederholm MD, PhD [c], Matteo Cesari MD, PhD [d], Alfonso J. Cruz-Jentoft MD [e], John E. Morley MB, BCh [f], Stuart Phillips PhD [g], Cornel Sieber MD, PhD [h], Peter Stehle MD, PhD [i], Daniel Teta MD, PhD [j], Renuka Visvanathan MBBS, PhD [k], Elena Volpi MD, PhD [l], Yves Boirie MD, PhD [m]

ESPEN EXPERT GROUP 2014

ESPEN

THE EUROPEAN SOCIETY FOR CLINICAL NUTRITION AND METABOLISM

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Clinical Nutrition

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journal homepage: http://www.elsevier.com/locate/clnu

ESPEN endorsed recommendation

Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group

Nicolaas E.P. Deutz [a,*], Jürgen M. Bauer [b], Rocco Barazzoni [c], Gianni Biolo [c], Yves Boirie [d], Anja Bosy-Westphal [e], Tommy Cederholm [f,g], Alfonso Cruz-Jentoft [h], Zeljko Krznariç [i], K. Sreekumaran Nair [j], Pierre Singer [k], Daniel Teta [l], Kevin Tipton [m], Philip C. Calder [n,o]

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- **Fat quality?**
- **Vitamin D?**

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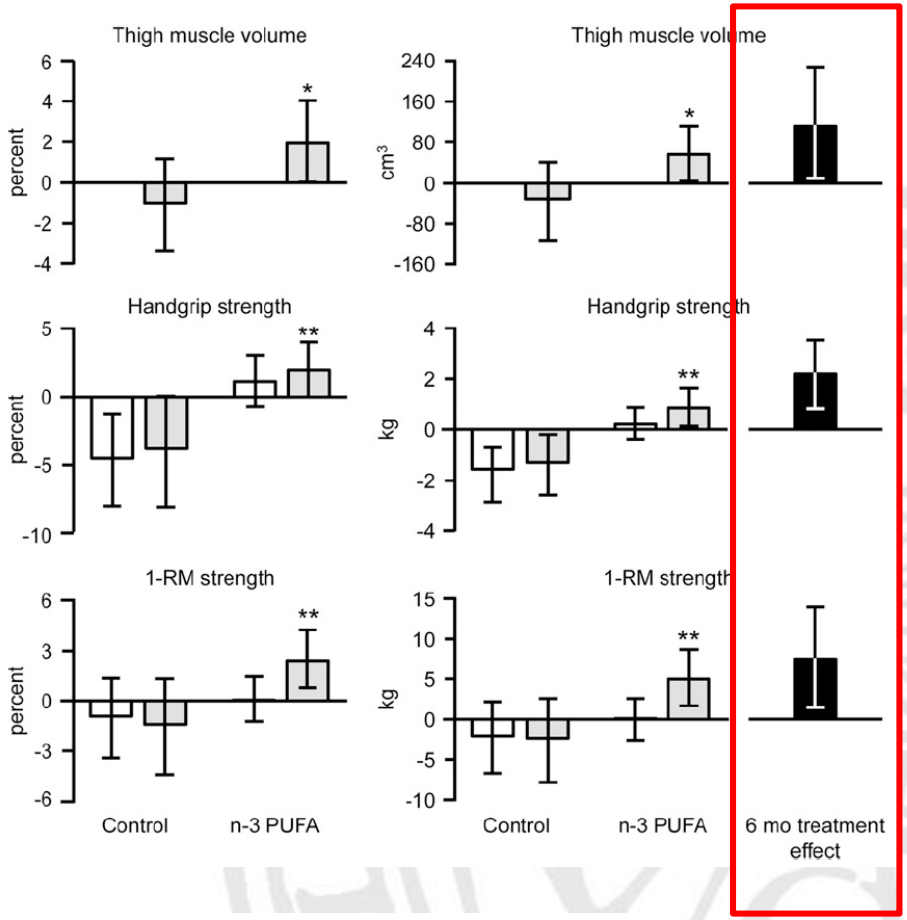
N-3 fatty acids may improve muscle mass and function in healthy old adults

- 60/44 ***healthy***, 60-85 y,
- 6 months RCT,
  - N-3 fatty acids – 3.3 g/d
  - Linoleic acid (C)
- Outcome;
  - Thigh volume,
  - Grip strength,
  - 1-RM strength

Conclusion:
6-mo treatment with n-3 FA increased muscle mass and improved muscle strength in healthy old adults

Treatment effect



Smith et al. AJCN 2015

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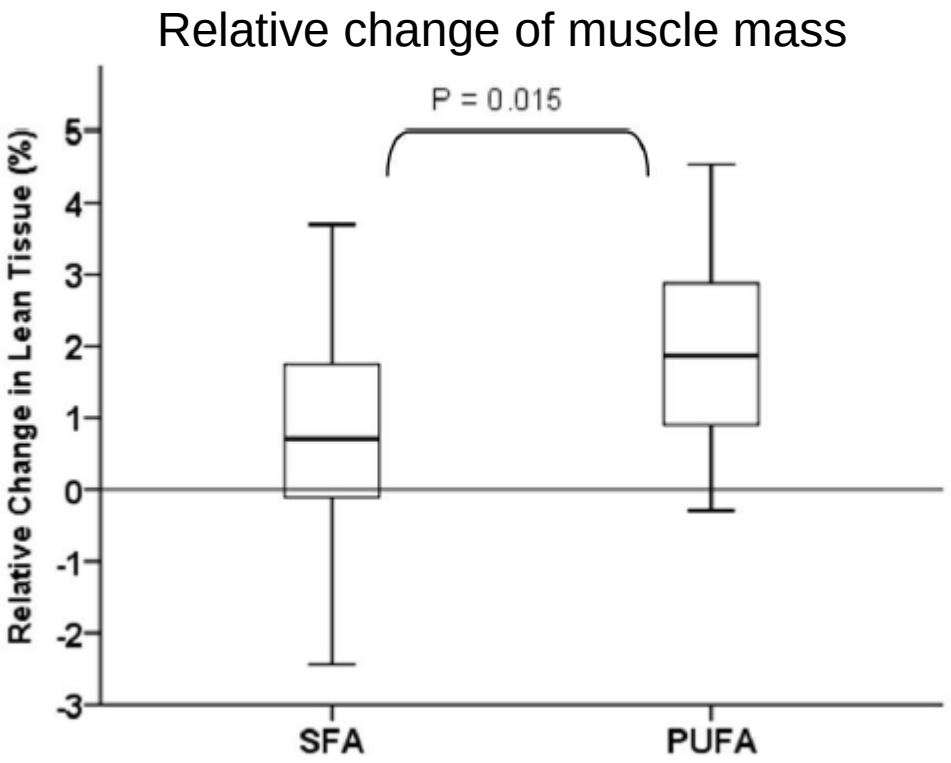
Effects on muscle mass by over-feeding n-6 PUFA vs. SFA

- Lipogain Study (RCT)
- N=41 (20-36 y)
- Palm oil (SFA) vs. Sun flower oil (n-6 PUFA) for 6 weeks
- 3% (intended) weight gain

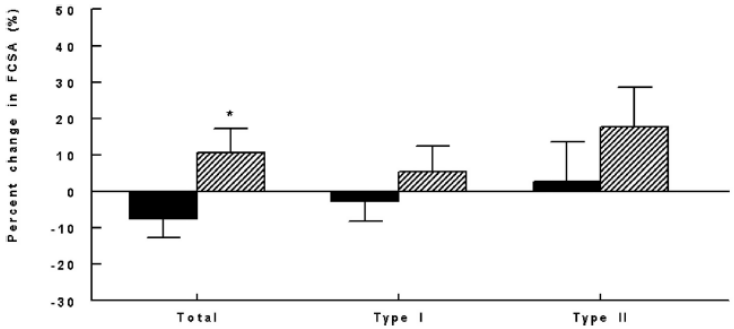


Conclusion: Muscle mass increased significantly more by PUFA (n-6) than by SFA

Rosqvist F et al. Diabetes 2014;63:2356-68

Vitamin D supplementation, muscle fiber area and leg strength

- 21 w, mobility limitation, 77 y
- RCT; 4000 IU Vit D for 4 mo



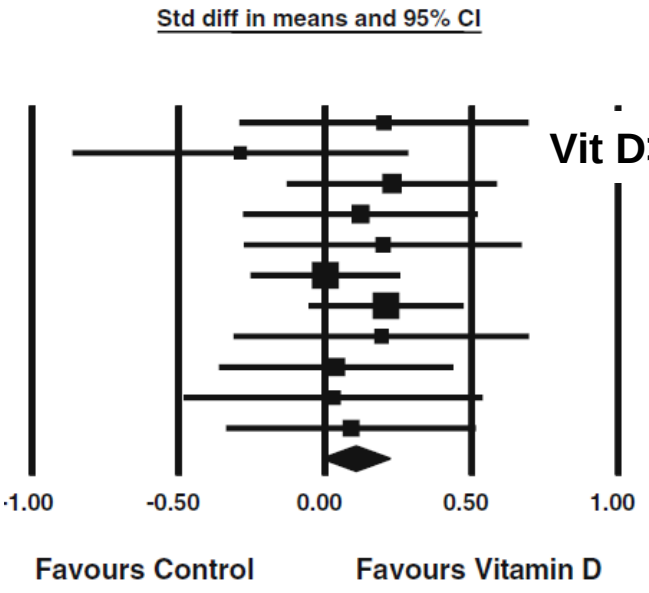
Result

- **Fiber area↑ 10%**
- **No effect on SPPB or knee-extension strength** (small study)

Ceglia et al. JCEM 2013

Meta-analysis -17 RCT

- **Quadriceps strength**



In 2 studies w. Vit D <25 nmol/l Vit D supplementation resulted in improved leg strength

Stockton et al. Osteopor Int 2011

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Pharmacology

- Myostatinab
  - Bimagrumab
- Ghrelin agonist
  - anamorelin

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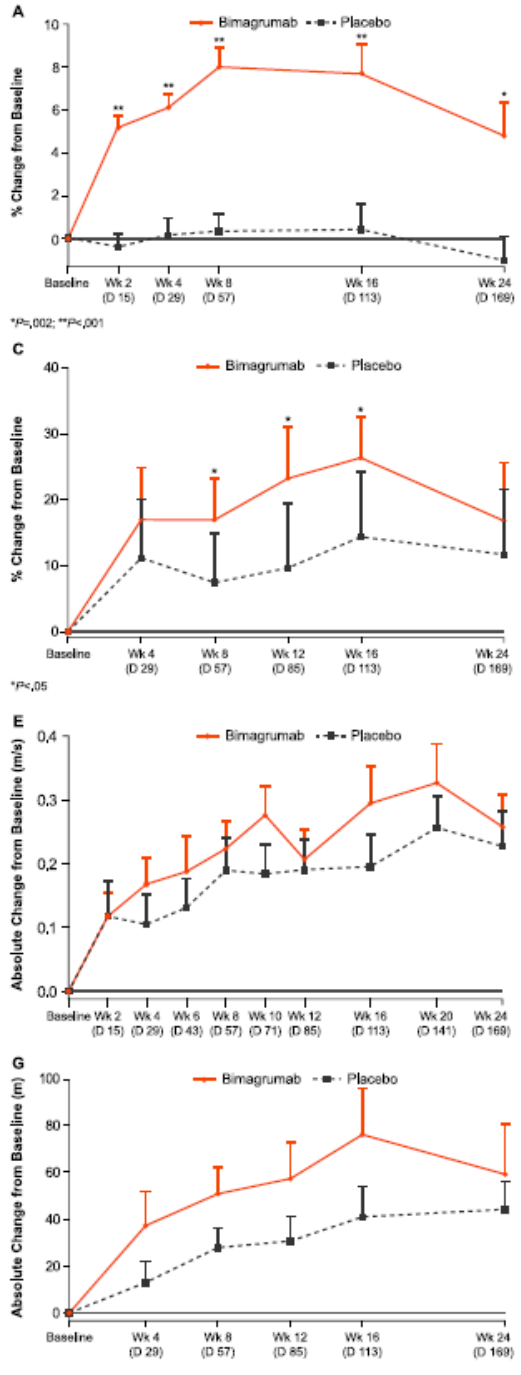
Myostatin ab (bimagrumab) to sarcopenic old

- 40 comm-dw subjects, >65 y
- Slow gait speed (<1 m/s) and reduced muscle mass (=*sarcopenia*)
- Myostatinab (bimagrumab) for 24 w

- Leg muscle volume
- Grip strength
- Walking speed
- 6-min walking distance

Conclusion: 6 mo treatment with bimagrumab improved muscle mass, grip strength and walking speed in old sarcopenic adults

Rooks et al. JAGS 2017



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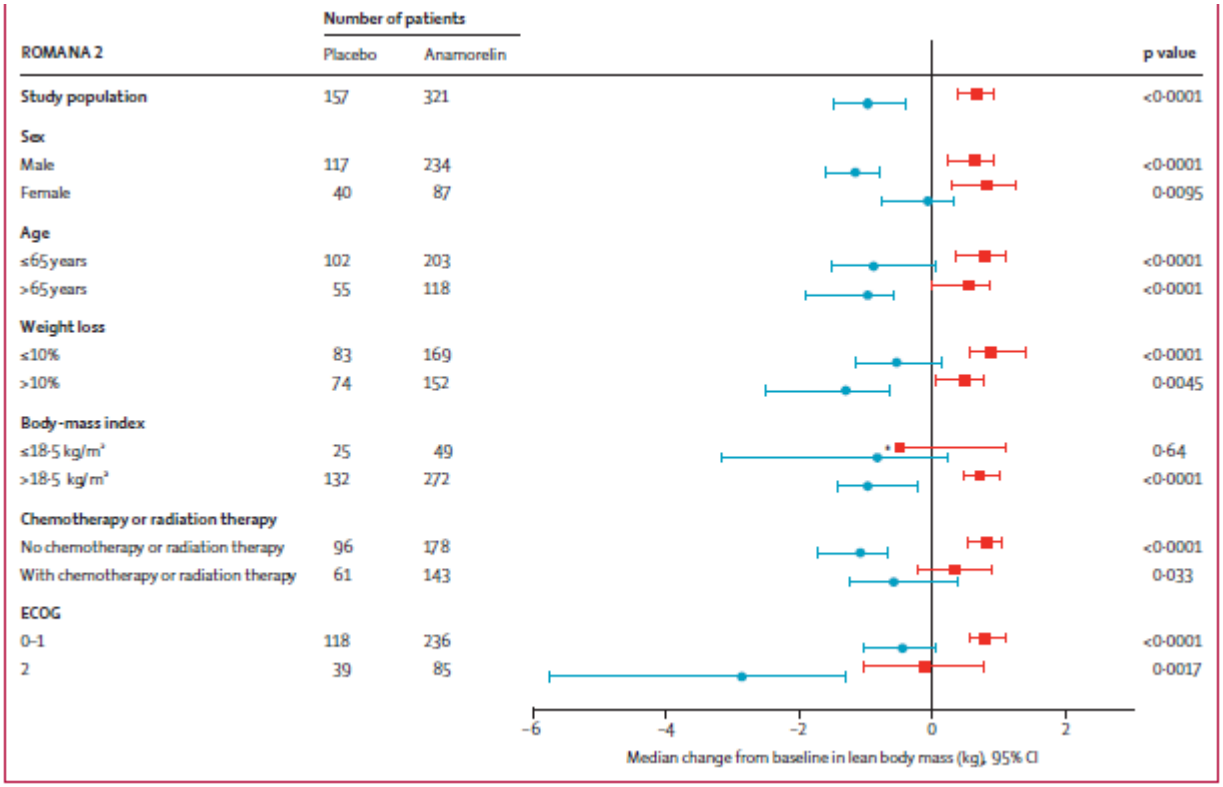
Ghrelin agonist in lung cancer

- 495 patients w. non small cell lung cancer och anorexia-cachexia.
- Ghrelin agonist (anamorelin) for 12 w.
- DXA/lean body mass (kg). Hand grip strength.



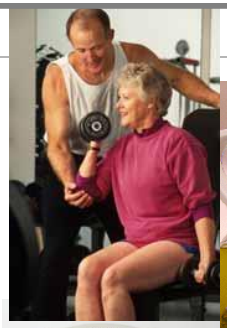
ROMANA 2	Number of patients: Placebo	Anamorelin	p value
Study population	157	321	<0·0001
Sex			
Male	117	234	<0·0001
Female	40	87	0·0095
Age			
≤65 years	102	203	<0·0001
>65 years	55	118	<0·0001
Weight loss			
≤10%	83	169	<0·0001
>10%	74	152	0·0045
Body-mass index			
≤18·5 kg/m²	25	49	0·64
>18·5 kg/m²	132	272	<0·0001
Chemotherapy or radiation therapy			
No chemotherapy or radiation therapy	96	178	<0·0001
With chemotherapy or radiation therapy	61	143	0·033
ECOG			
0–1	118	236	<0·0001
2	39	85	0·0017

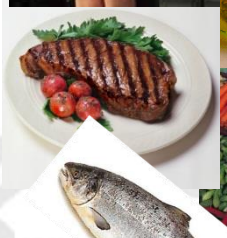
- **LBM↑**
- **HGS→**
- **Symtoms↓**

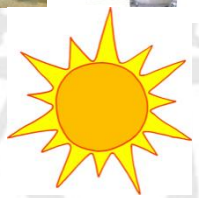
Temel et al. Lancet Oncol 2016;17:519-31

Take-home messages

Food, nutrients and exercise for treatment of malnutrition and sarcopenia







Exercise

- Resistance training - works always

Nutrition

- Protein and amino acid supplementation
  - Target 1.2-1.4 g/kg bw/d
  - Whey, essential AA and leucin/HMB

  Works mainly when there is a deficit (energy or proteins)
- Essential fatty acids (n3) supplementation?
  - Needs more research
- Vitamin D supplementation
  - Target 20 ug/800 IU per day

Pharmacological treatment

- Myostatinab, ghrelin, SARM…

  We are not there yet

Combinations…

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Thanks for your attention

+

…keys to successful rehab, survival and aging