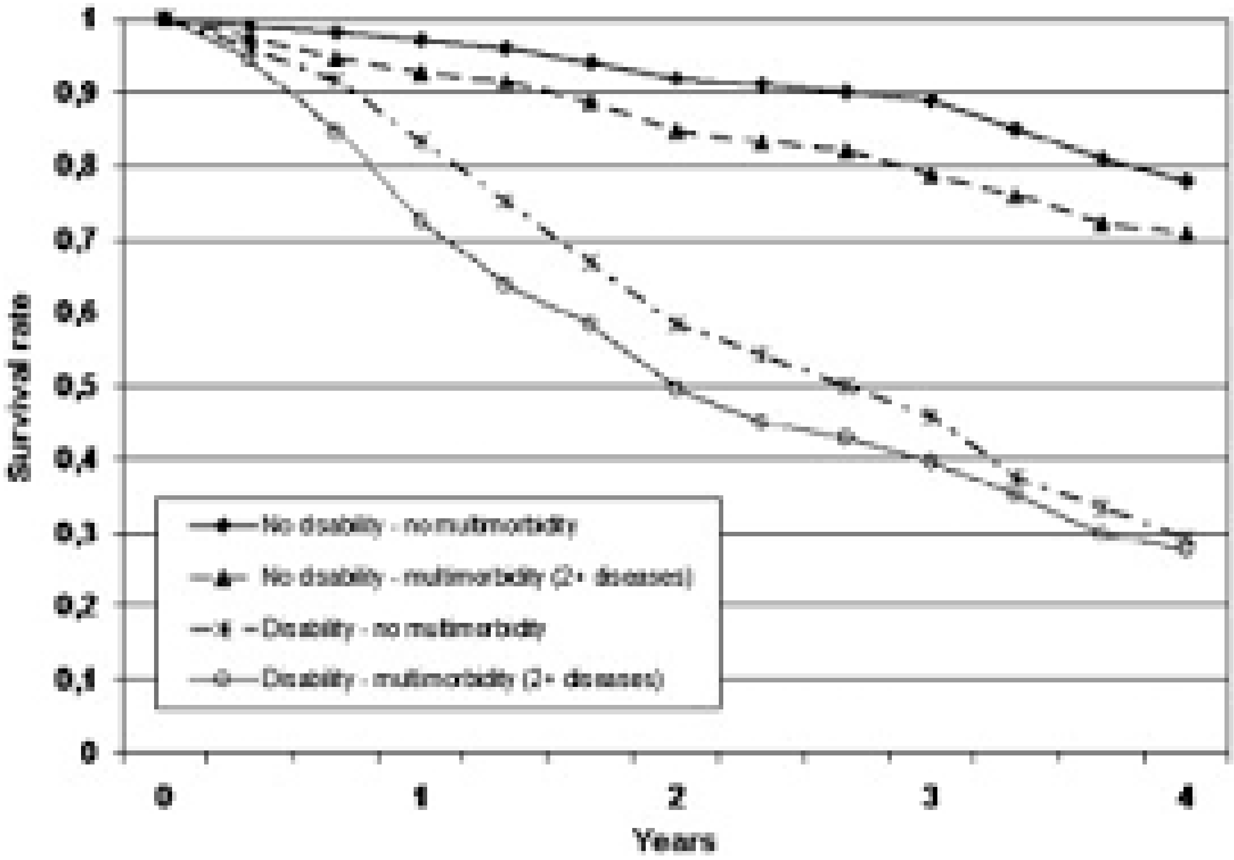
An overview of Sarcopenia

What matters to older adults

- Disability or Multimorbidity



"No Disability"

Journal of Clinical Epidemiology 63 (2010) 752-759

Healthy Ageing

the process of developing and maintaining the Functional Ability

- Every person – in every country in the world – should have the opportunity to live a long and healthy life. Yet, the environments in which we live can favour health or be harmful to it. Environments are highly influential on our behaviour, our exposure to health risks (for example, air pollution or violence), our access to quality health and social care and the opportunities that ageing brings.

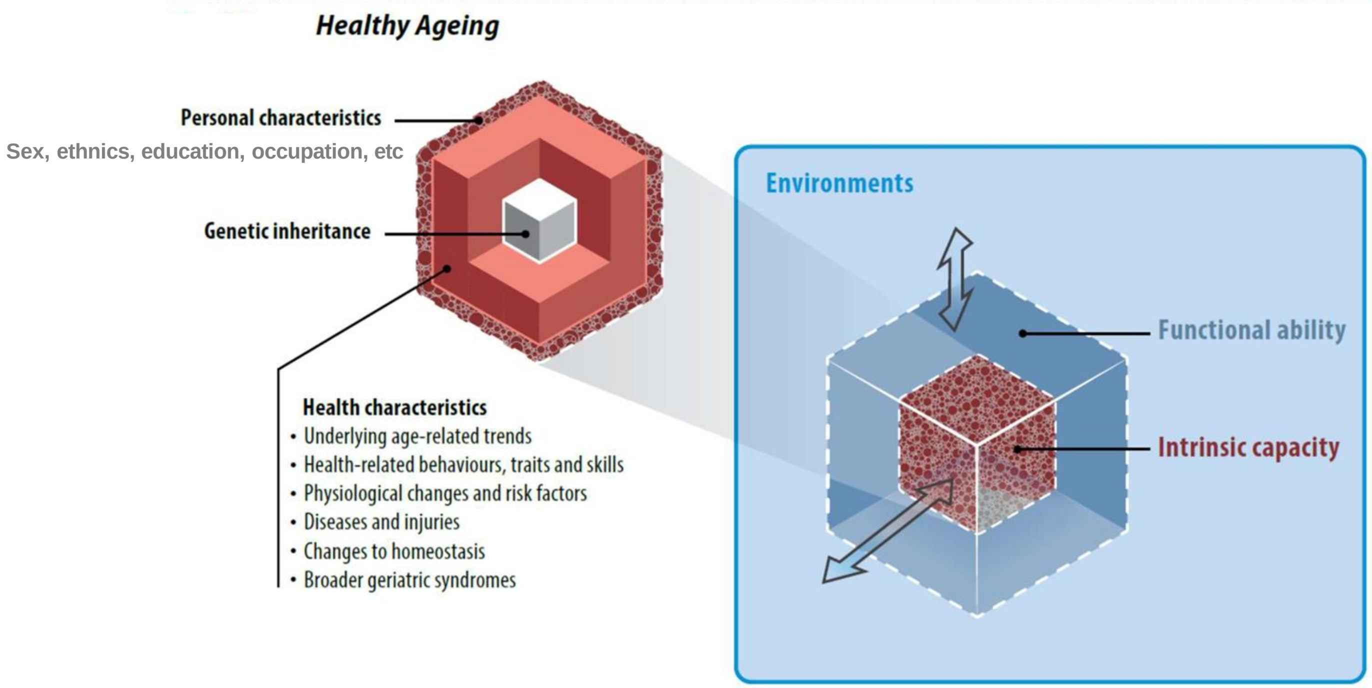
- Healthy ageing is about creating the environments and opportunities that enable people to be and do what they value throughout their lives. Everybody can experience healthy ageing. Being free of disease or infirmity is not a requirement for healthy ageing, as many older adults have one or more health conditions that, when well controlled, have little influence on their wellbeing.

WHO, World Report on Ageing and Health, 2015

Functional Ability

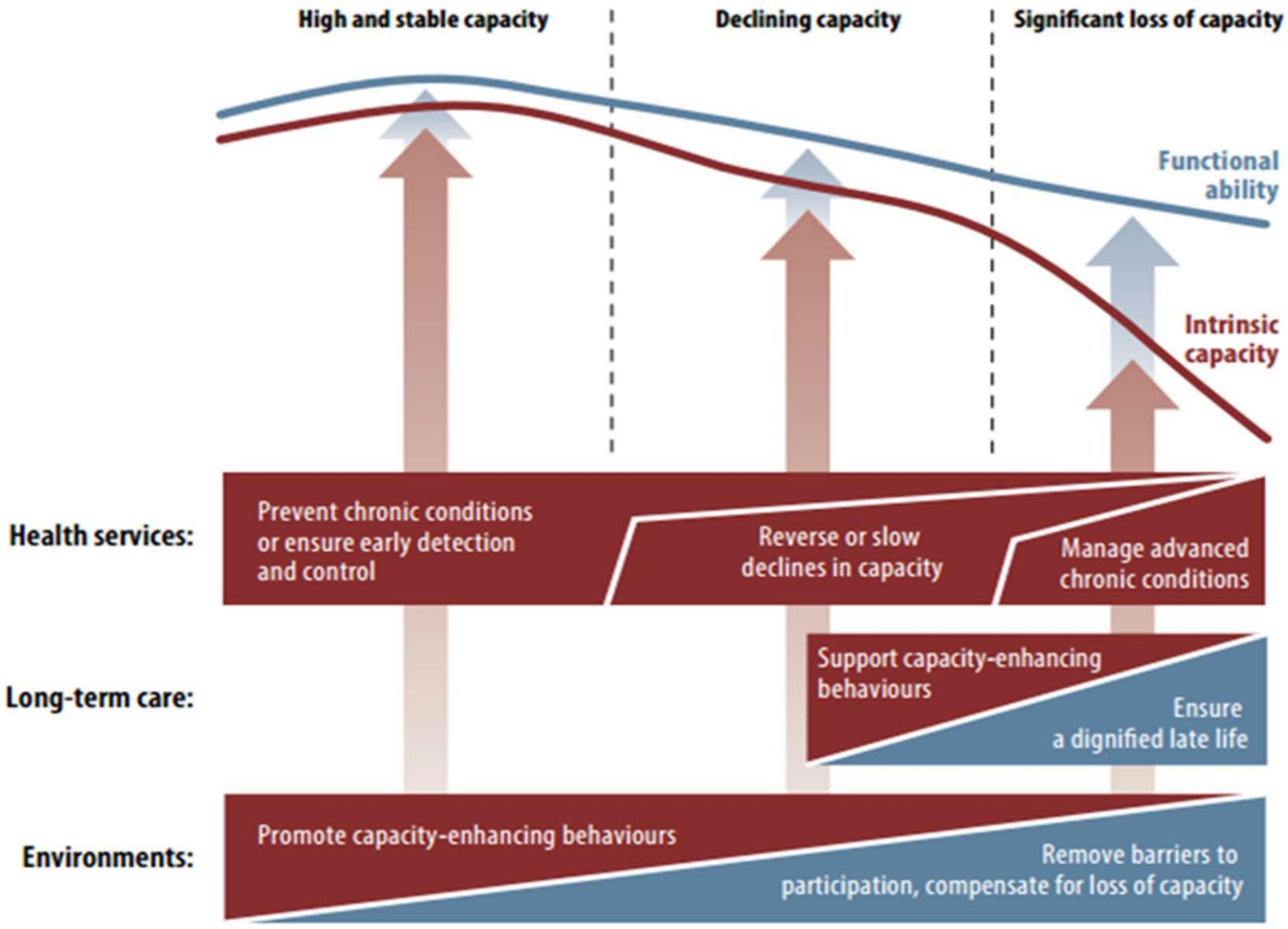
is made-up of

- the intrinsic capacity of the individual
- relevant environmental characteristics
- the interactions between the individual & these characteristics



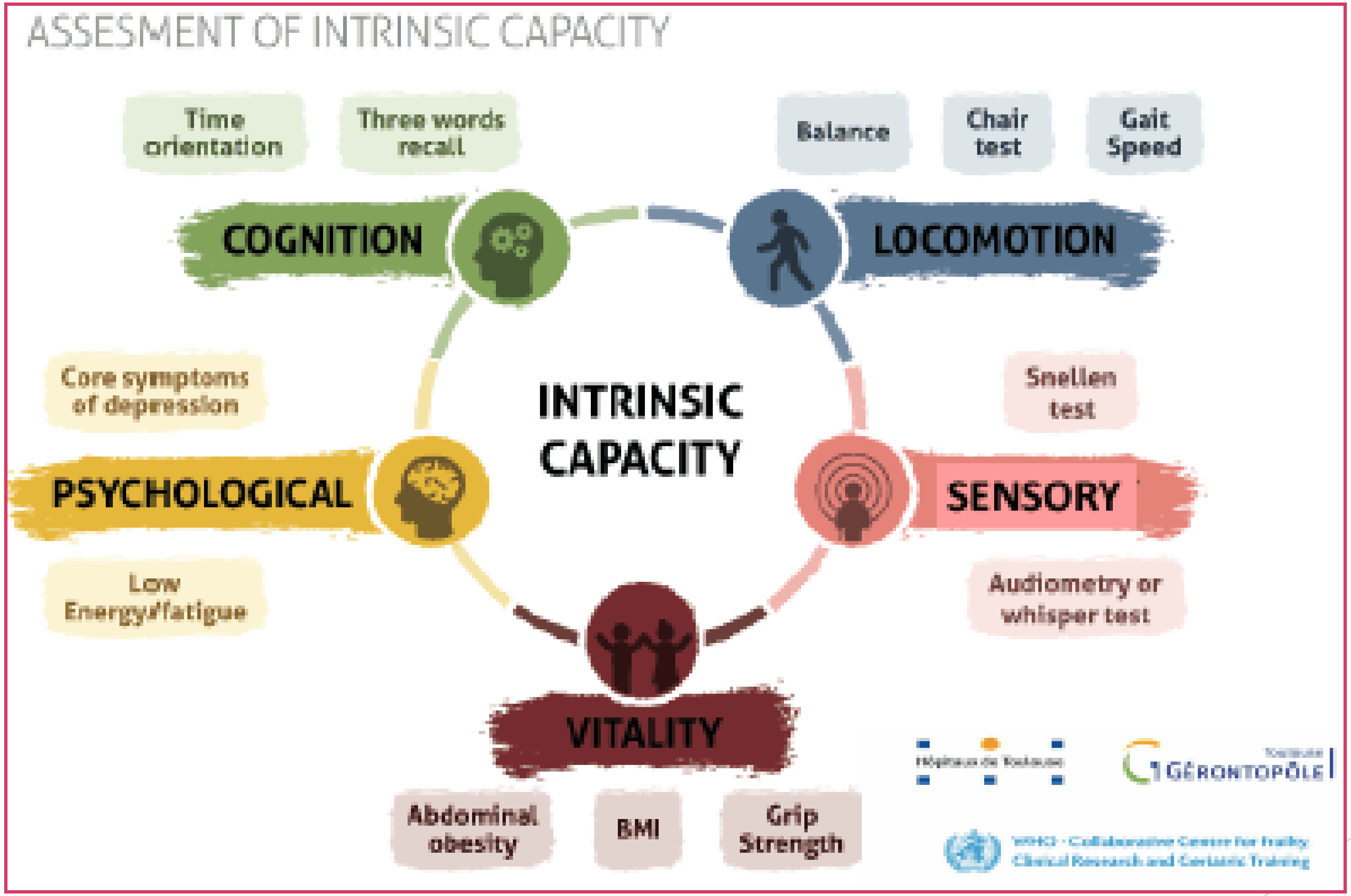
WHO, World Report on Ageing and Health, 2015

Healthy Ageing trajectories



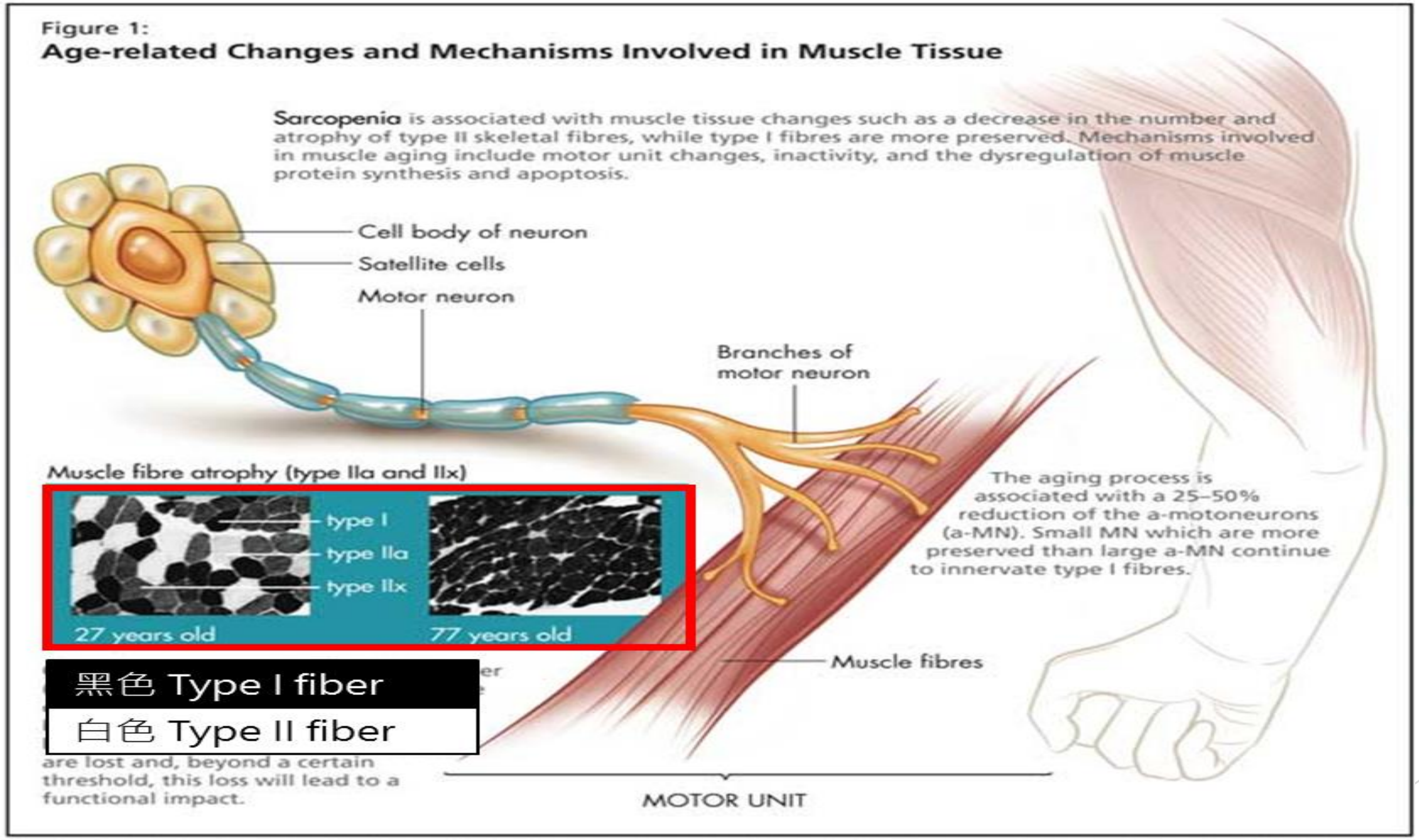
WHO, World Report on Ageing and Health, 2015

Intrinsic Capacity



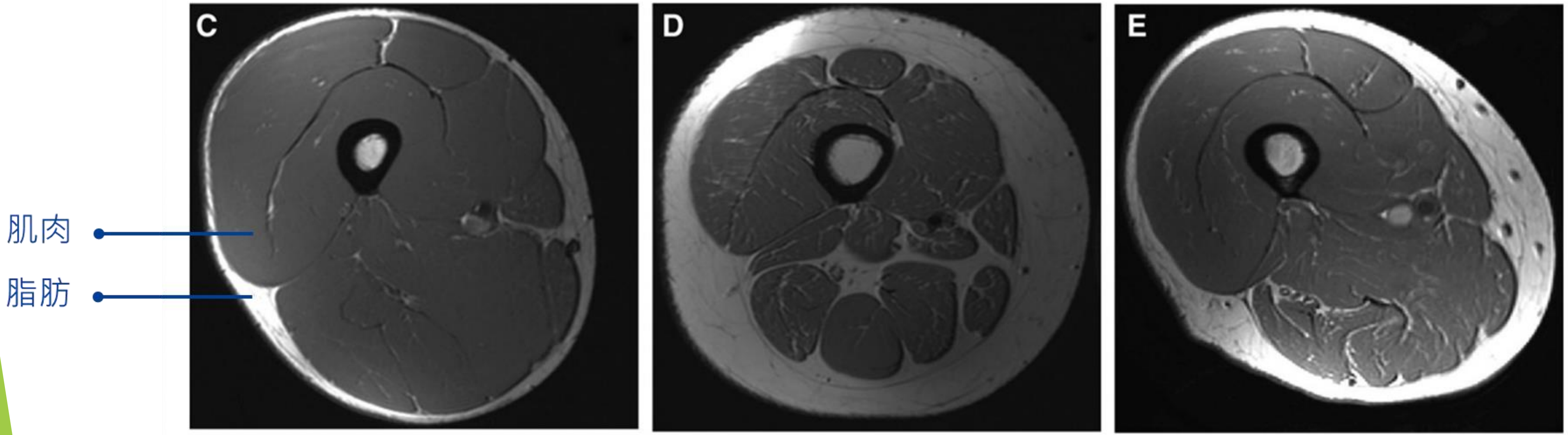
Aged-related muscle fibers change

- Type II fiber ↓
- Imbalance of Type I &Type II fiber ratio



Source: Photographic images drawn from Lee WS, Cheung WH, Qin L, et al. Age-associated decrease of type II A/B human skeletal muscle fibers. Orthop Relat Res 2006;450: 231–7.

Muscle with Ageing



Young male	Older male (Inactive)	Older male (Active)
Male – 24 yrs	Male – 66 yrs	Male – 66 yrs
Body mass – 76kg	Body mass – 81kg	Body mass – 79kg
Fat mass – 10kg	Fat mass – 57kg	Fat mass – 34kg
Fat free mass – 57kg	Fat free mass – 13kg	Fat free mass – 36kg
	Average daily steps = 3141	Average daily steps = 12445
	PA >3MET per/day = 22mins	PA >3MET per/day = 130mins

Etiology of Muscle loss

Primary

Age-related
- Physical performance
- Muscle /strength
- Muscle mass

Secondary

Activity related
- Bed rest
- Sedentary lifestyle
- Deconditioning

Disease related
- Advanced organ failure
- Inflammatory diseases
- Malignancy
- Endocrine diseases

Nutrition related
- Inadequate diet
- Malabsorption
- Gastrointestinal disorders
- Drug induced anorexia

↑
- Pro-inflammatory markers
- Oxidative stress
- Catabolic hormones
- Denervation

↑
- Myocyte apoptosis
- Protein degradation
- Myofibre necrosis
- Fibre-type grouping
- Intramyocelluar lipids

→ **Sarcopenia**

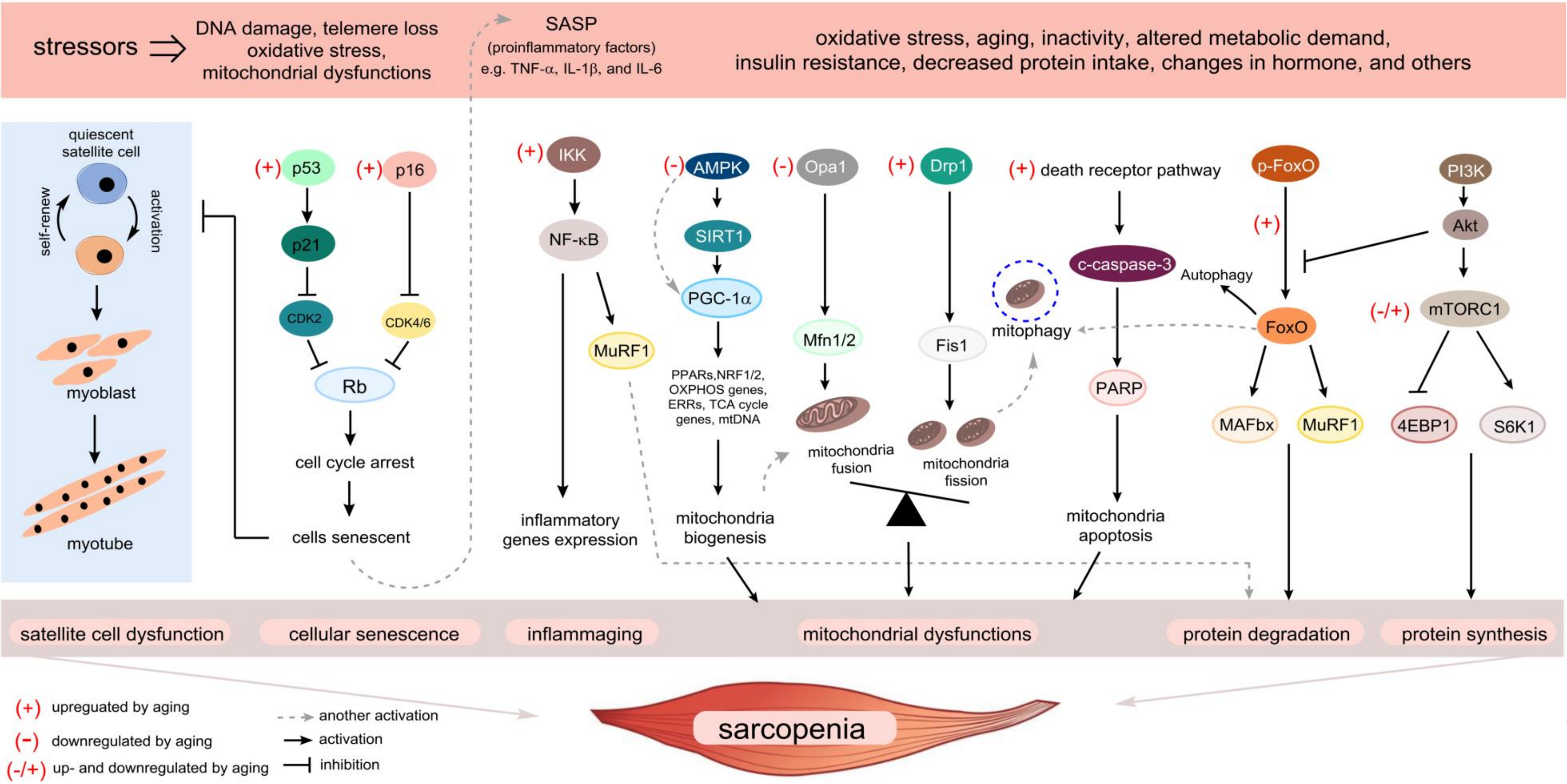
↓
- Vascular perfusion
- Amino acid availability
- Anabolic hormones

↓
- Protein synthesis
- Motor neuron function
- Mitochondrial biogenesis
- Satellite cell regeneration

- Diabetes/CKD
- Obesity
- GH deficiency
- Vit D deficiency
- Osteoporosis
- Cancer
- PAD/CHF
- COPD
- Cirrhosis
- Rheumatoid arthritis

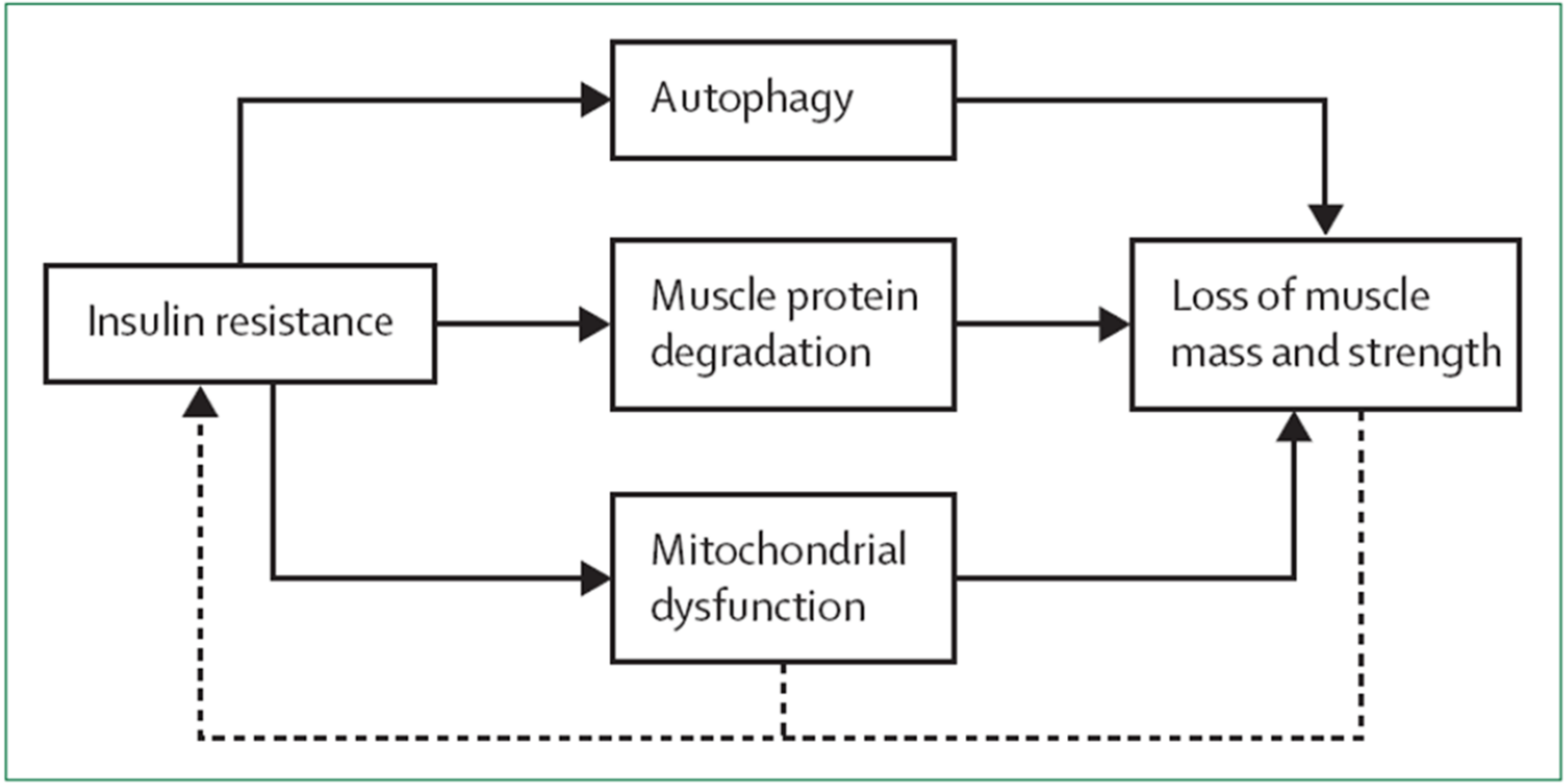
1. *Rita Rastogi Kalyani, et al. Lancet Diabetes Endocrinol. 2014 Oct; 2(10): 819–829.*
2. *Cruz-Jentoft AJ et al. Sarcopenia: European consensus on definition and diagnosis. Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010.*
3. *Kalyani, R. R., Corriere, M., & Ferrucci, L. (2014). Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases.*
4. *The lancet Diabetes & endocrinology, 2(10), 819-829.*

Aging mechanisms contribute to Sarcopenia



Mankhong S , et al. Experimental Models of Sarcopenia: Bridging Molecular Mechanism and Therapeutic Strategy. Cells. 2020 Jun 2;9(6):1385. doi: 10.3390/cells9061385.

Diabetes & muscle loss



Kalyani, R. R., Corriere, M., & Ferrucci, L. (2014).
Age-related and disease-related muscle loss: the effect of diabetes, obesity, and other diseases. The lancet Diabetes & endocrinology, 2(10), 819-829.

Obesity & muscle loss

- Total and Intra-abdominal fat ↑
- Adipocyte size and number of macrophages ↑
- Pro-inflammatory ↑
- ROS ↑
- Insulin resistance ↑
- Leptin ↑
- Adiponectin ↓

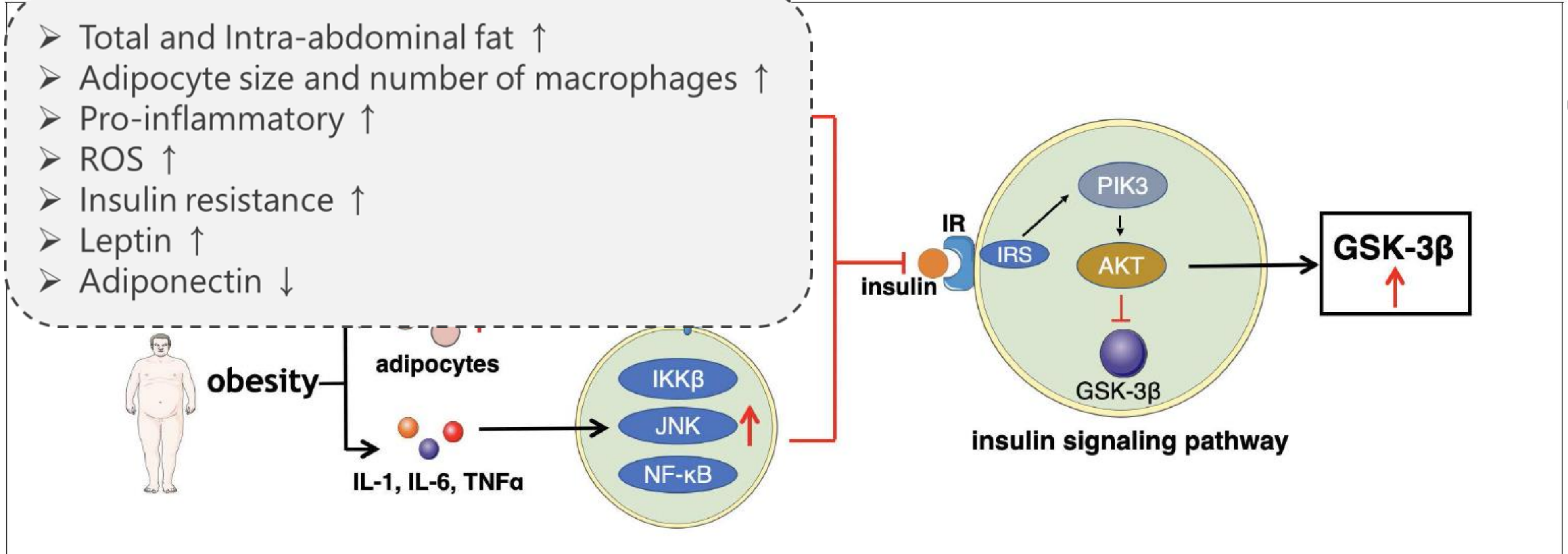
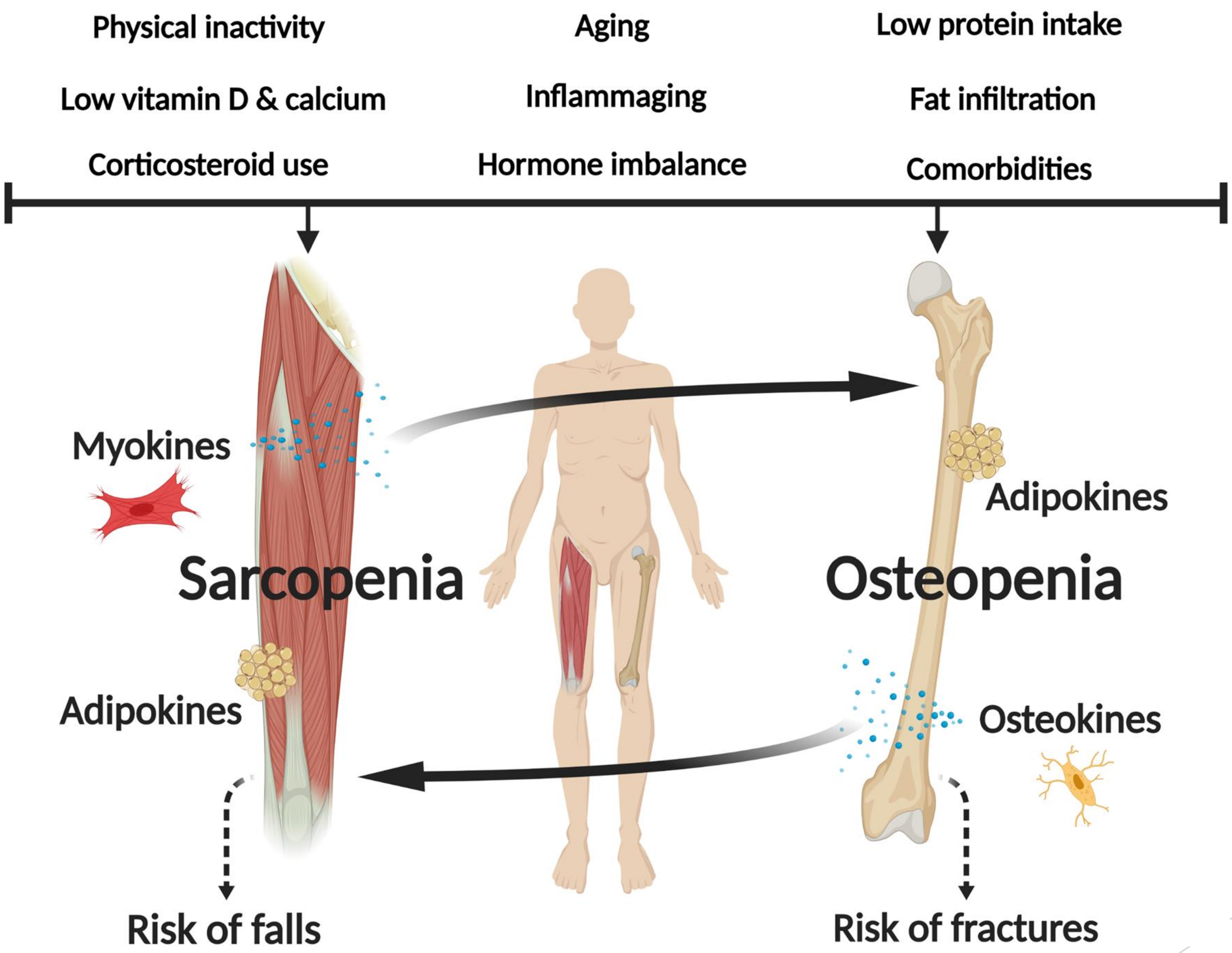


FIGURE 3 | This figure illustrates the main mechanism of impaired insulin action that excessive insulin secretion, adipocytes, and inflammatory factors directly affect IR or indirectly interfere the insulin signaling pathway.

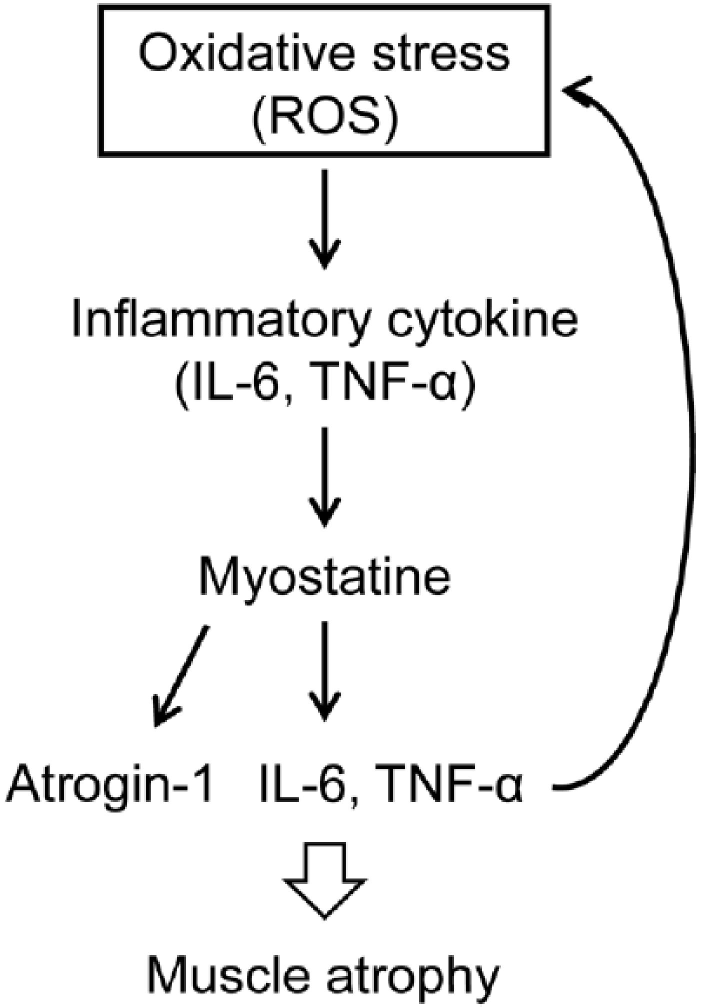
Wang, M., Tan, Y., Shi, Y., Wang, X., Liao, Z., & Wei, P. (2020). Diabetes and sarcopenic obesity: pathogenesis, diagnosis, and treatments. Frontiers in Endocrinology, 11.

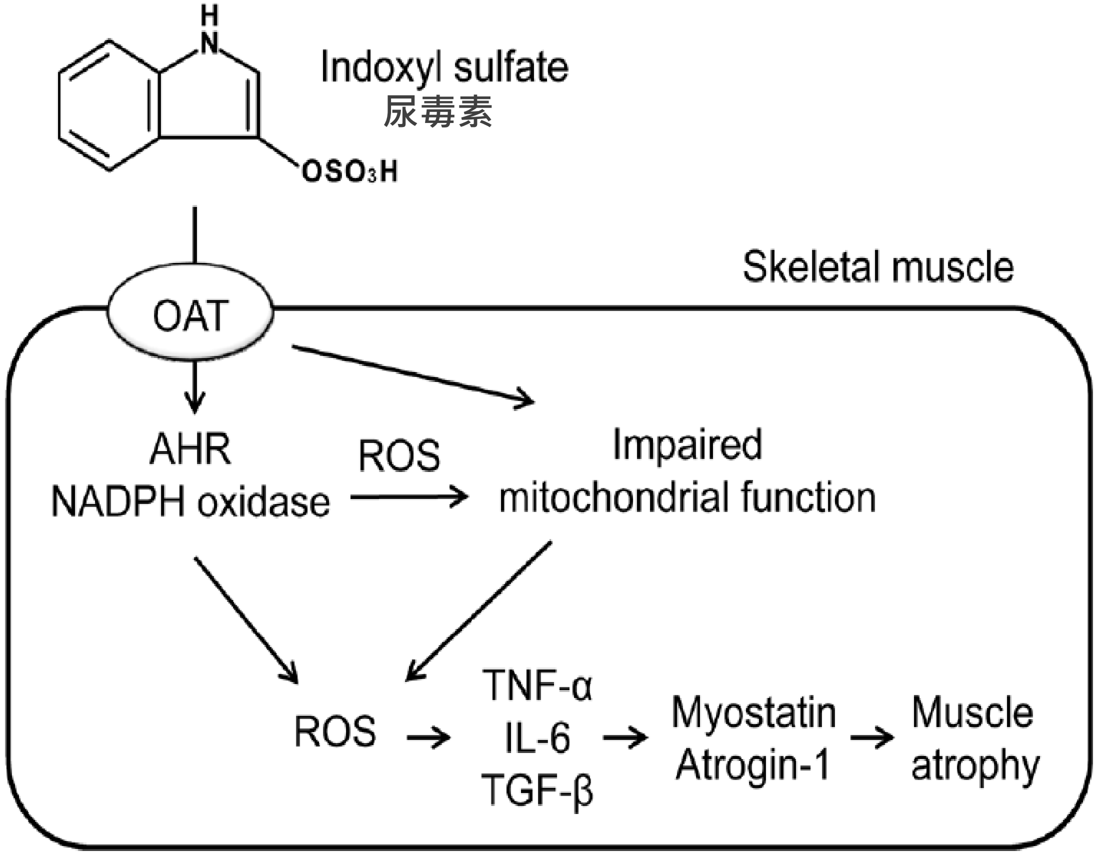
Osteoporosis & muscle loss



Kirk, B., Zanker, J., & Duque, G. (2020). Osteosarcopenia: epidemiology, diagnosis, and treatment—facts and numbers. Journal of cachexia, sarcopenia and muscle, 11(3), 609-618.

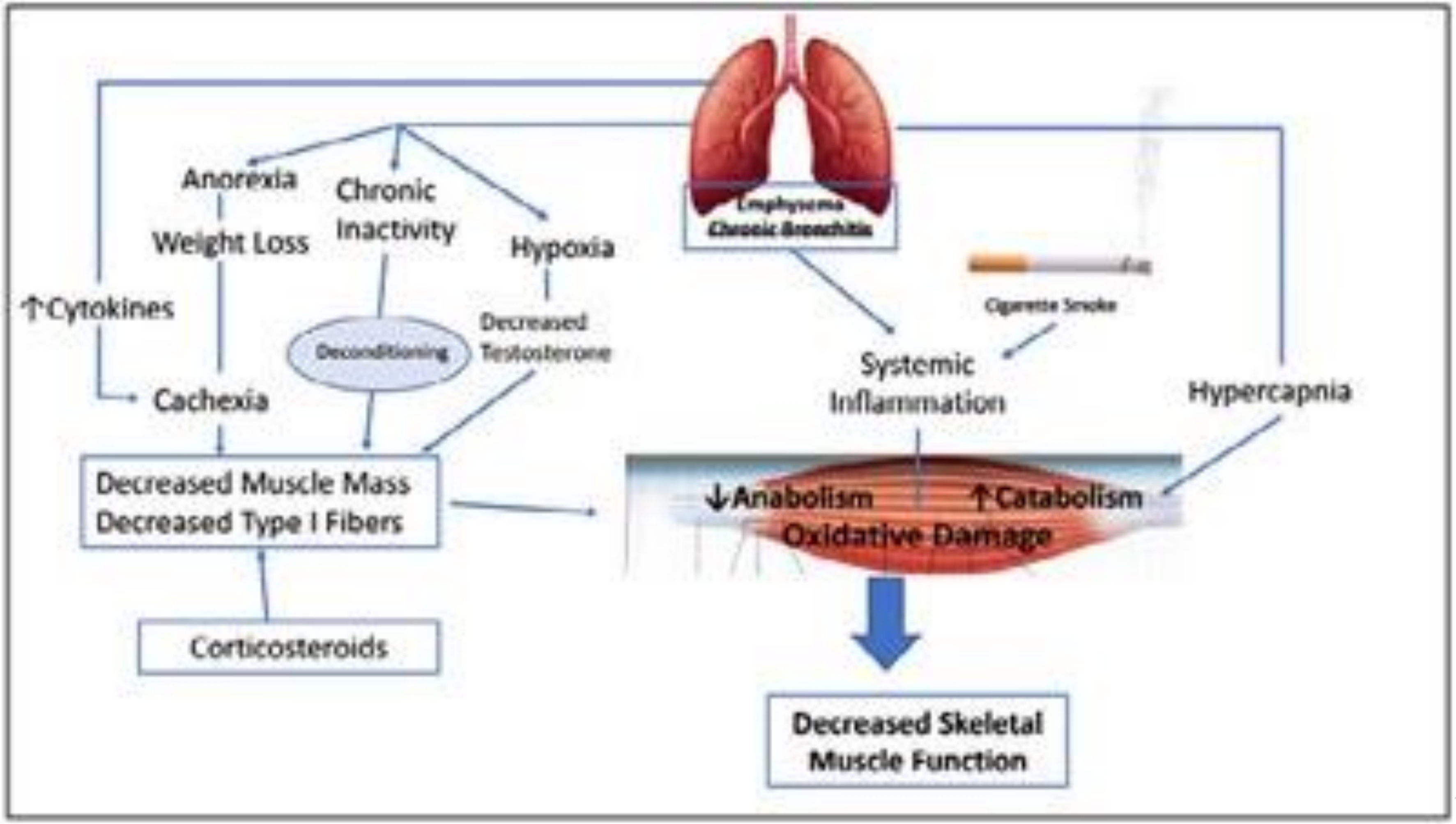
CKD & muscle loss





Watanabe, H., Enoki, Y., & Maruyama, T. (2019). Sarcopenia in chronic kidney disease: factors, mechanisms, and therapeutic interventions. Biological and Pharmaceutical Bulletin, 42(9), 1437-1445.

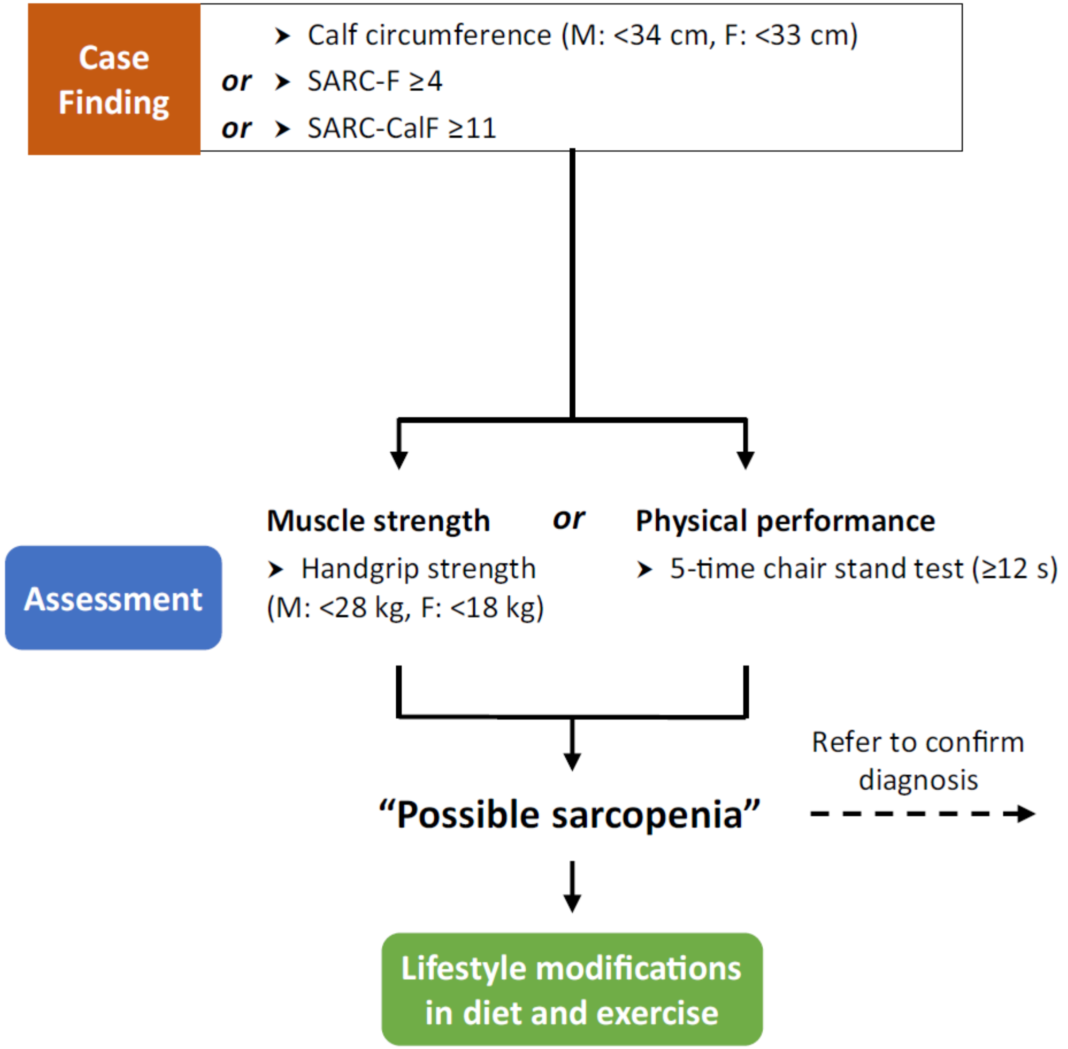
COPD & muscle loss



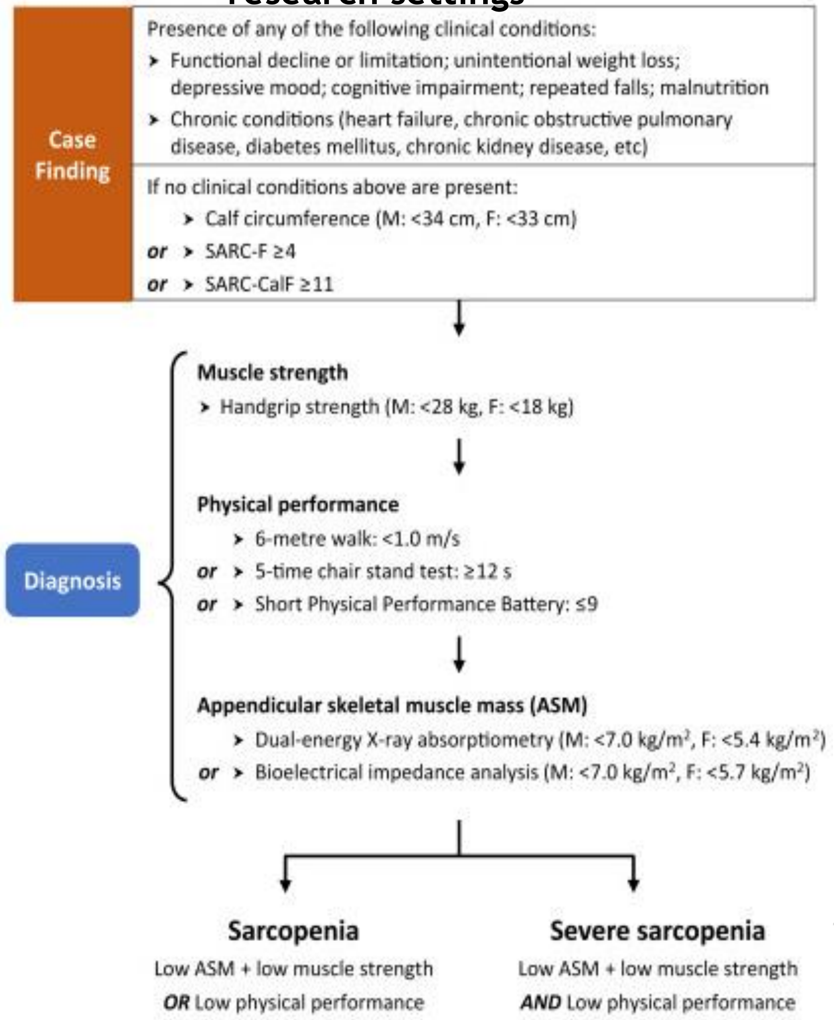
J Nutr Health Aging. 2018;22(8):876-879.

AWGS 2019 Identifying

Primary health care or community preventive services settings

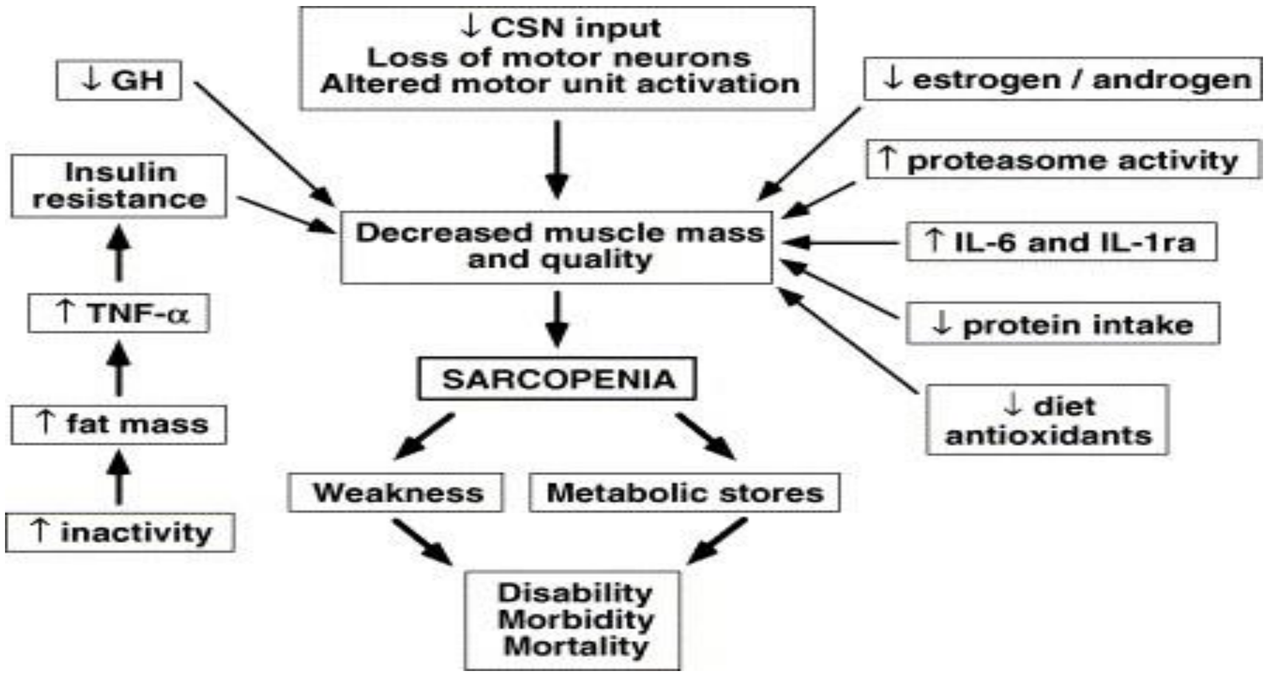


Acute to chronic health care Clinical research settings



Potential therapeutic approaches

Etiology of sarcopenia



Argiles JM, et al. Int J Biochem Cell Biol 2005;37:1084-1104

Etiology of Sarcopenia

- Inactivity
- Poor Nutrition
- Hormone Change
- Chronic Inflammation
- Loss of muscle fiber Loss of motor units

Treament Options

- Exercise
- Nutrition Supplement
- Hormone Therapy?
- Antioxidants
- Potential new treatments

Interventions for Sarcopenia Exercise

Table 3: Exercise and nutritional interventions for sarcopenia.

	Exercise [33]		
Type of training	Frequency	Intensity	Duration/set
Aerobic exercise	Minimum 5 days/week for moderate intensity or 3 days/week for vigorous intensity	Moderate intensity at 5-6 on a 10-point scale Vigorous intensity at 7-8 on a 10-point scale	Accumulate at least 30 min/day of moderate intensity activity in bouts of at least 10 min each continuous vigorous activity for at least 20 min/day
Resistance exercise (for major muscle groups using free weights and machines)	At least 2 days/week	Slow-to-moderate velocity 60–80% of 1 RM	8–10 exercises 1–3 sets per exercise 8–12 repetitions 1–3 min rest
Power training (to practice only after the resistance training)	Two days a week	High repetition velocity Light-to-moderate loading 30–60% of 1 RM	1–3 sets 6–10 repetitions

Solomon C. Y. Y, et al. Current Gerontology and Geriatrics ResearchVolume 2016, Article ID 5978523, 10 pages.

Interventions for Sarcopenia Nutrition

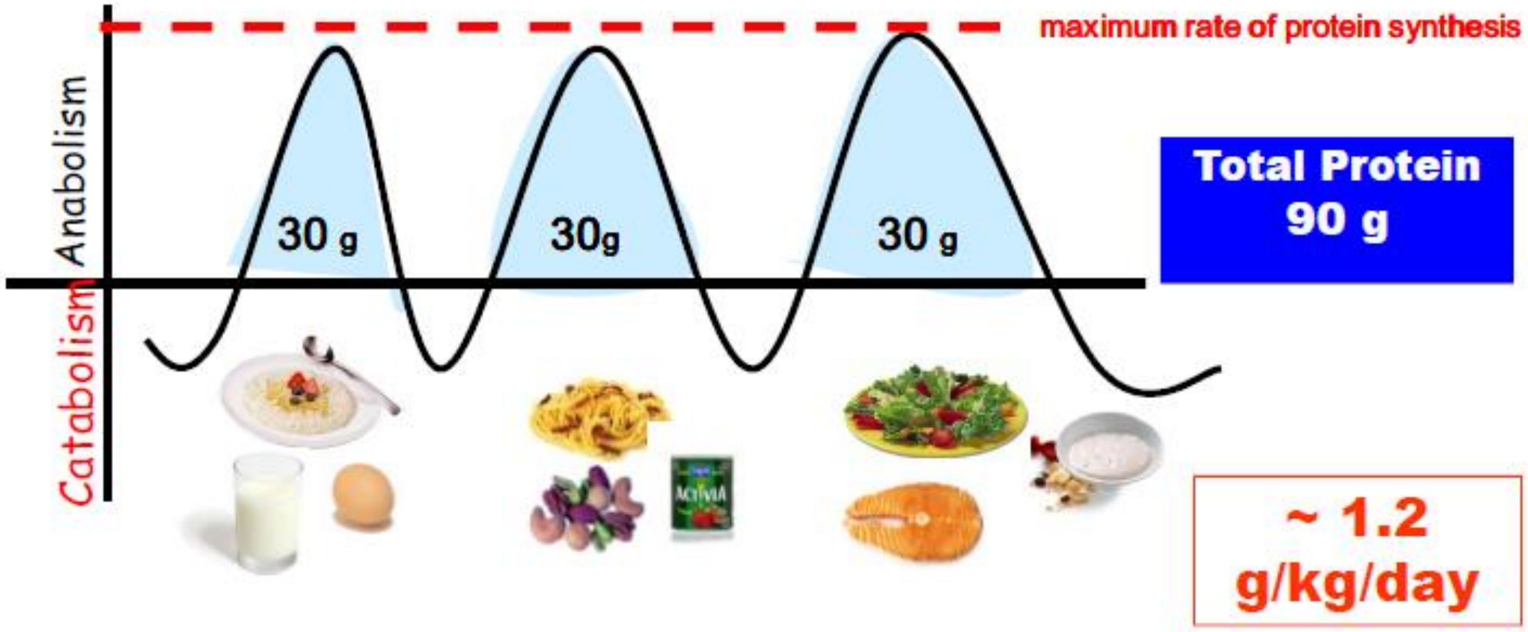
Nutritional supplementation

1. To maintain sufficient protein intake, we recommend a daily protein intake of ≥1.0 g/kg BW for healthy older adults and ≥1.2 g/kg BW for those with sarcopenia and/or frailty. This target protein intake should be achieved primarily by diet, and where that is not possible, then protein supplementation can be considered.
2. For older adults who are candidates for supplementation, high-quality protein, amino acids such as leucine and L-carnitine, or oral nutritional supplement (ONS) containing beta-hydroxy-beta-methylbutyrate (HMB) may be considered and should be taken according to the specific prescribing information.
3. Determination of serum 25-OH vitamin D levels can be considered in patients at risk of malnutrition or sarcopenia. Oral vitamin D supplementation (800–1000 IU/day) may be beneficial for older adults with vitamin D insufficiency. Higher doses may be required for those who are deficient in 25-OH vitamin D.

Solomon C. Y. Y, et al. Current Gerontology and Geriatrics ResearchVolume 2016, Article ID 5978523, 10 pages.

Distribution of protein intake is also relevant:

REGULAR intakes maximize protein synthesis

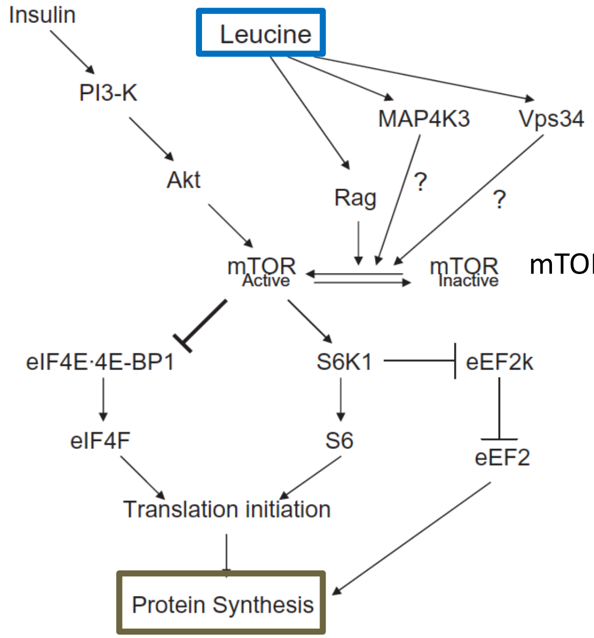


Repeated maximal stimulation of protein synthesis
→ increase / maintenance of muscle mass

Amino acid: prevent and treat sarcopenia

BCAA (Branched-chain amino acids): Leucine, Isoleucine, Valine

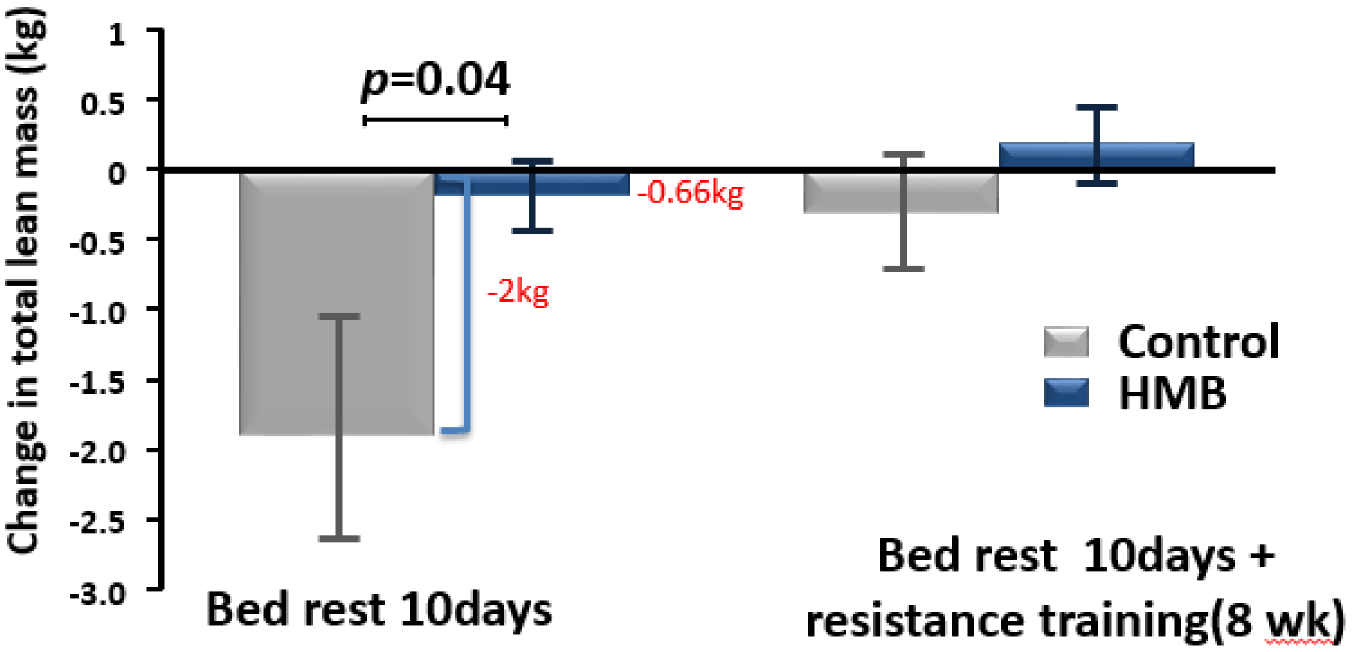
→regulate the rate of protein synthesis and degradation



mTOR:mammalian target of rapamycin

Effect of **HMB** on bed rest-associated muscle loss

Lean body mass is maintained by HMB during 10 days of bed rest in elderly women



HMB (β-hydroxy-β-methylbutyrate)： a metabolite of Leucine

Deutz NE et al. Clin Nutr. 2013;32:704-12.

Vitamin D supplement to prevent sarcopenia

- 96 elderly women with poststroke hemiplegia were followed for two years.
- 48 patients received 1,000 IU ergocalciferol daily, and the remaining 48 received placebo.
- Outcome measurement: number of falls per person and incidence of hip fractures, strength and tissue ATPase of skeletal muscles on the nonparetic side

Falls	Before therapy (8 weeks)		With therapy (2 years)	
	Placebo group	Vitamin D_2 group	Placebo group	Vitamin D_2 group
0	23	24	9	32
1	15	14	8	6
2–5	10	10	13	5
6–7	0	0	10	0
>7	0	0	2	0
Total	46	44	136	22
Fallers	25	24	33	11

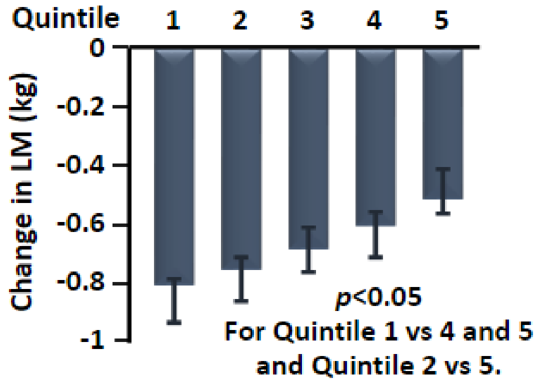
	Placebo group	Vitamin D_2 group	p value
Muscle strength on intact side			
Baseline	4.6 ± 1.5	4.7 ± 1.8	0.81[b]
2 years	3.5 ± 1.3[a]	6.9 ± 1.1[a]	
Change from baseline, %	–28.2 ± 12.1	56.5 ± 40.5	<0.01
Routine ATPase			
Mean type I fiber diameter, μm			
Baseline	50.8 ± 3.6	50.8 ± 3.3	0.98[b]
2 years	49.2 ± 2.6	49.3 ± 2.9	
Change from baseline, %	–2.9 ± 6.8	–2.7 ± 6.9	0.93
Mean type II fiber diameter, μm			
Baseline	12.7 ± 2.8	12.6 ± 2.9	0.89[b]
2 years	9.8 ± 2.3[a]	24.3 ± 4.4[a]	
Change from baseline, %	–22.5 ± 6.7	96.5 ± 26.7	<0.0001
Percentage of type II fiber			
Baseline	7.0 ± 1.9	7.0 ± 1.9	0.92[b]
2 years	5.3 ± 1.8[a]	20.4 ± 3.5[a]	
Change from baseline, %	–24.8 ± 9.0	202.4 ± 65.0	<0.0001
Serum 25-hydroxyvitamin D, ng/ml			
Baseline	9.8 ± 1.3	9.8 ± 1.2	0.95[b]
2 years	5.3 ± 1.1[a]	33.4 ± 3.3[a]	
Change from baseline, %	–25.0 ± 9.0	246.2 ± 69.0	<0.0001
Serum ionized calcium, mEq/l			
Baseline	2.65 ± 0.03	2.65 ± 0.03	0.84[b]
2 years	2.64 ± 0.03	2.64 ± 0.03	
Change from baseline, %	–0.2 ± 0.3	–0.2 ± 0.3	0.81
Serum parathyroid hormone, pg/ml			
Baseline	18.4 ± 2.4	18.5 ± 3.0	0.91[b]
2 years	21.6 ± 2.1[a]	21.7 ± 2.4[a]	
Change from baseline, %	17.6 ± 5.5	18.5 ± 8.5	0.68
Serum 1,25-dihydroxyvitamin D, pg/ml			
Baseline	21.8 ± 5.3	22.0 ± 5.3	0.86[b]
2 years	19.7 ± 4.7[a]	32.6 ± 5.7[a]	
Change from baseline, %	–8.2 ± 14.4	51.9 ± 17.2	<0.0001
Serum creatinine, mg/dl			
Baseline	1.2 ± 0.2	1.2 ± 0.2	0.92[b]
2 years	1.3 ± 0.2[a]	1.3 ± 0.2[a]	
Change from baseline, %	11.4 ± 19.9	11.7 ± 16.1	0.75

Cerebrovasc Dis. 2005;20:187–192.

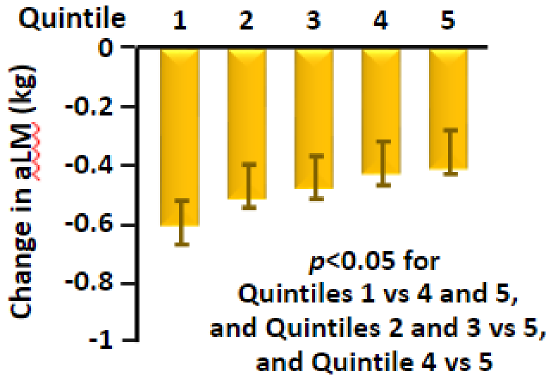
Nutrition-muscle connection

Prospective Analysis including 2000+ elderly adults in the health, aging, and body composition (Health ABC) study

Overall lean body mass (LM) **by quintile of protein intake**



Appendicular (ARM+LEG) **lean mass** (aLM) **by quintile of protein intake**

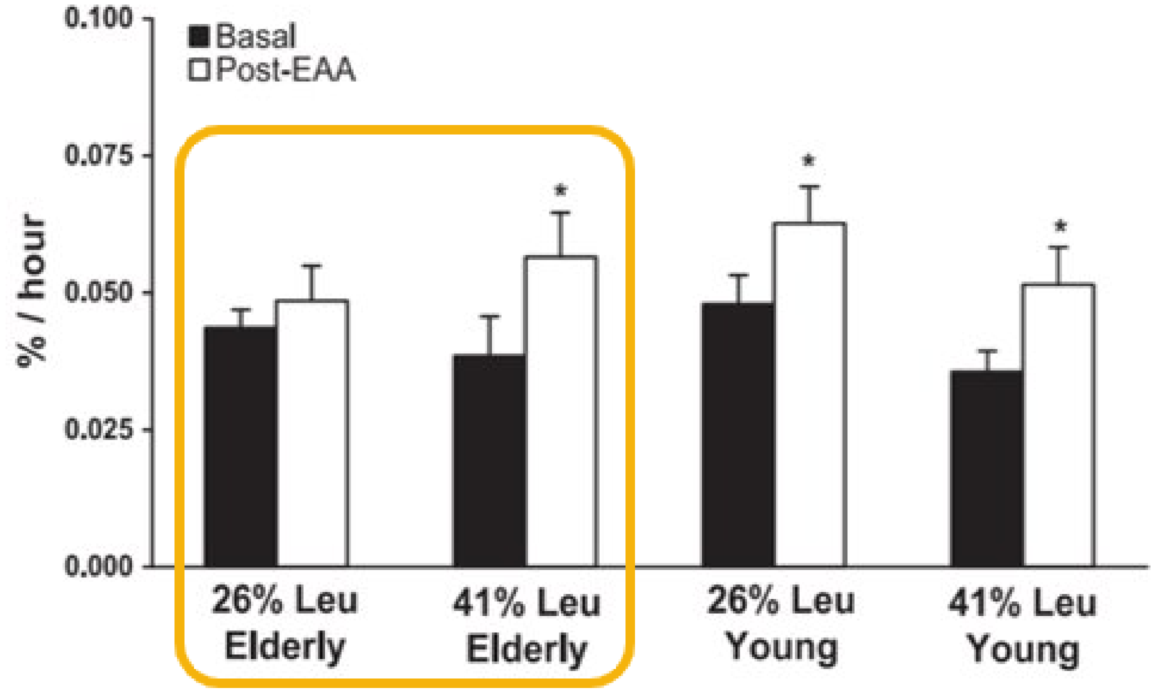


Protein is important in the maintenance and rebuilding of lean body mass in aging adults: participants in the top fifth of protein intake lost 40% less lean mass (LM) – Overall and appendicular – than did those in the bottom fifth of protein intake, a difference that is statistically significant ($p < 0.01$)

Houston DK, et al. Am J Clin Nutr.: 2008:87:150–155.

Muscle protein synthesis to EAA

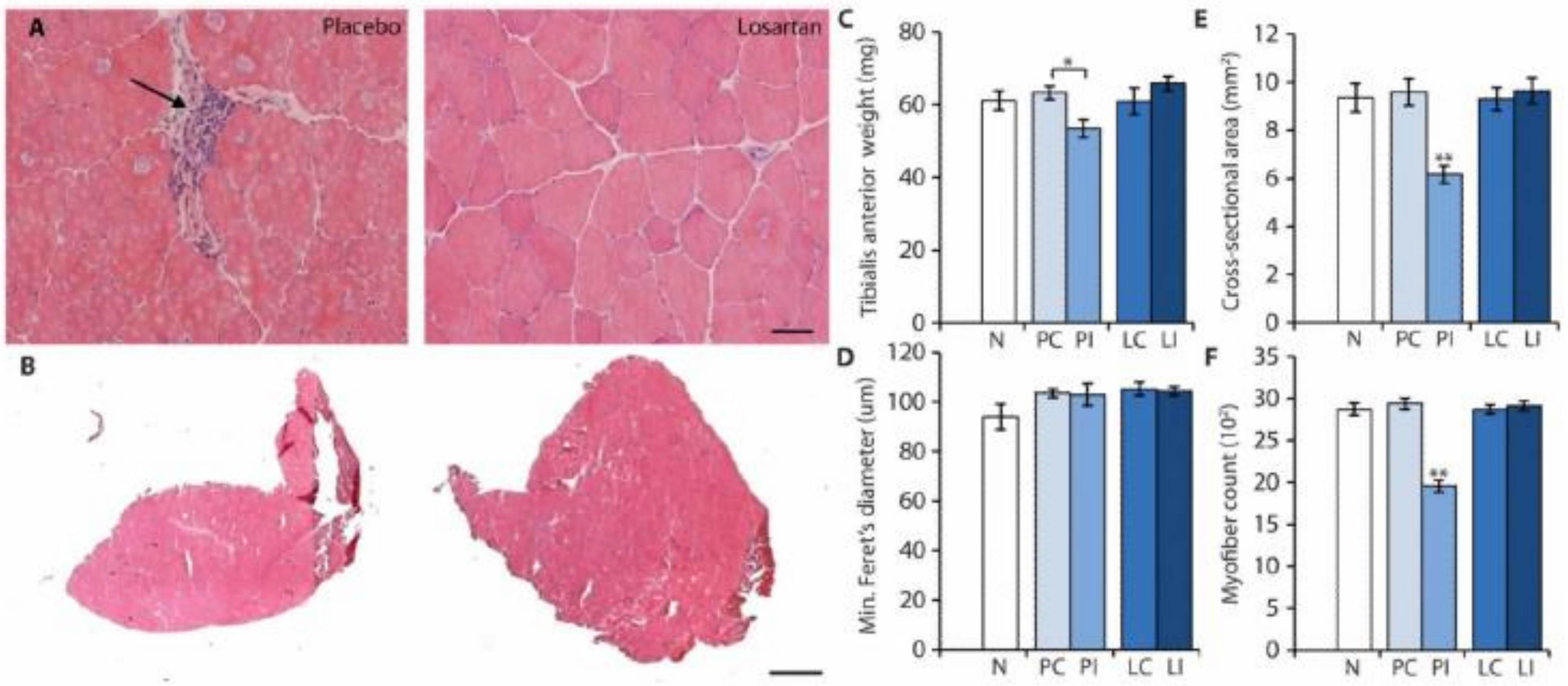
- Leucine (Leu), at daily amount of either 2.5 g or 2.8 g in combination with resistance exercise may affect muscle protein synthesis, muscle recovery following illness, and muscle mass.[1]
- A high proportion of Leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly.[2]



Ingestion of 6.7 g of EAA (Post-EAA) containing either 1.7 (26% Leu) or 2.8 (41% Leu) g of leucine.

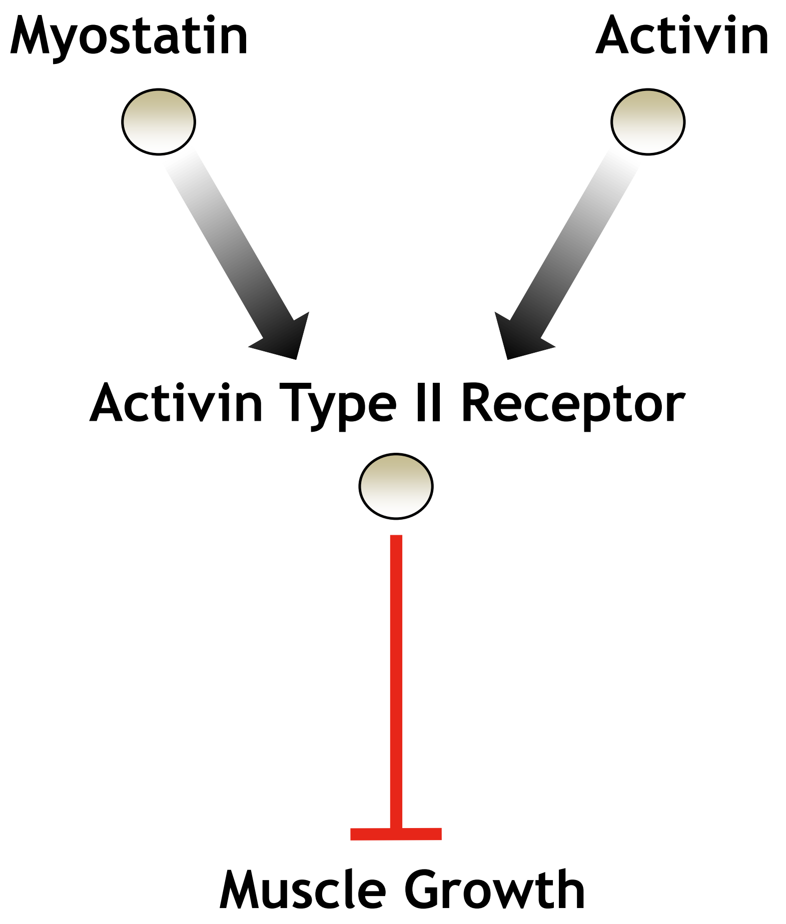
1. Solomon C. Y. Y, et al. Current Gerontology and Geriatrics Research Volume 2016, Article ID 5978523, 10 pages.
2. Christos S. Katsanos, et al. Am J Physiol Endocrinol Metab 291: E381–E387, 2006.

ARB restores skeletal muscle remodeling and prevents disuse atrophy

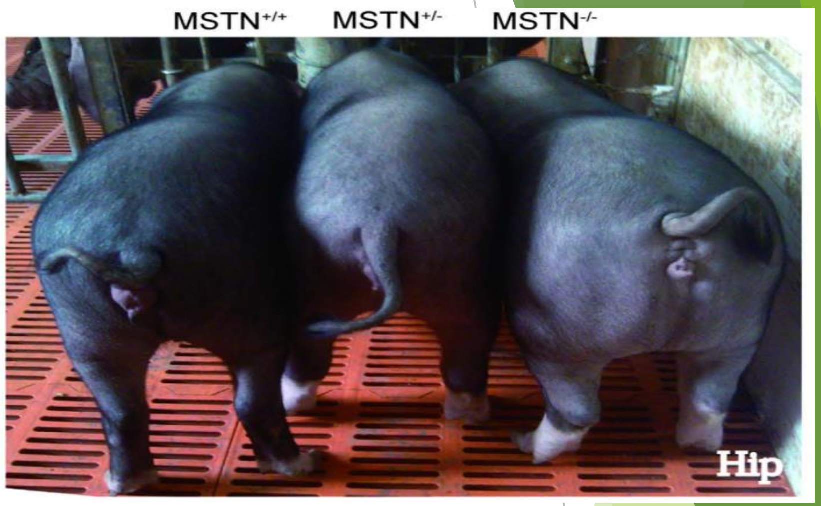


Burk TN, et al. Sci Tramsl Med 2011;3:82ra37

Controlling skeletal muscle growth

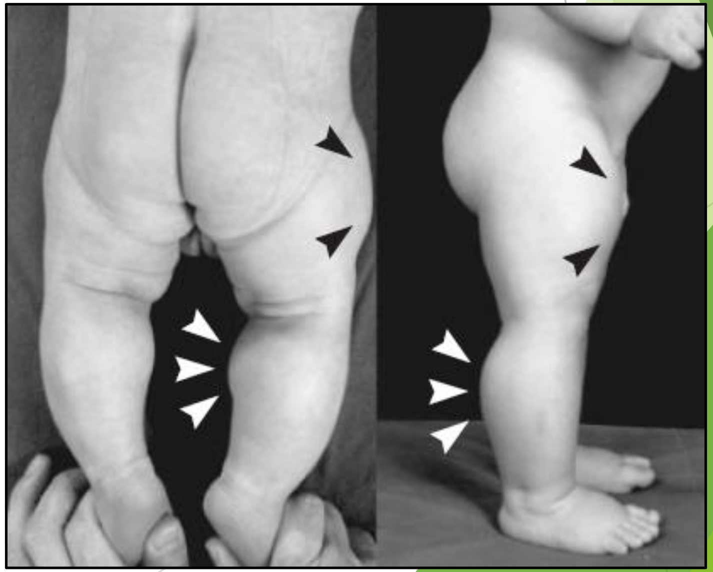


Meishan pig with myostatin mutation



Baby with myostatin mutation

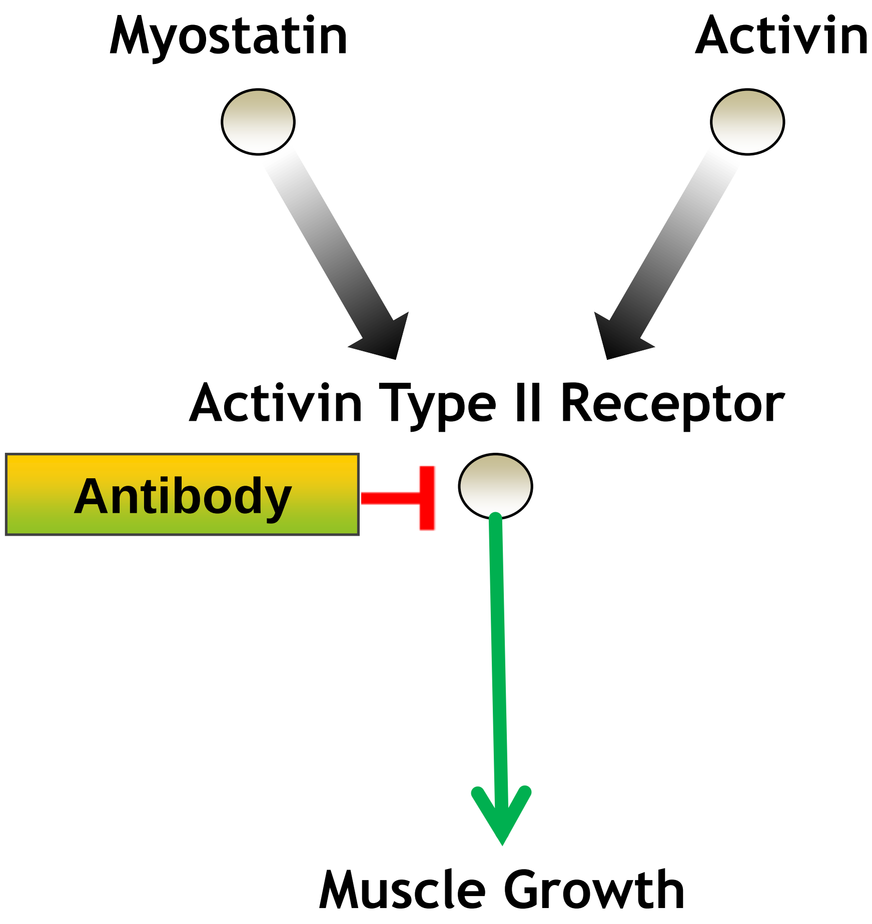
Neonate



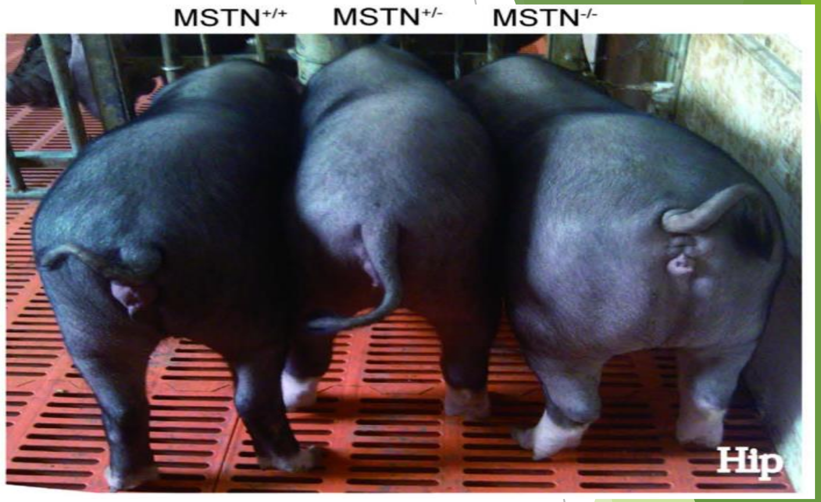
7 months

Source: n engl j med 350;26

Controlling skeletal muscle growth

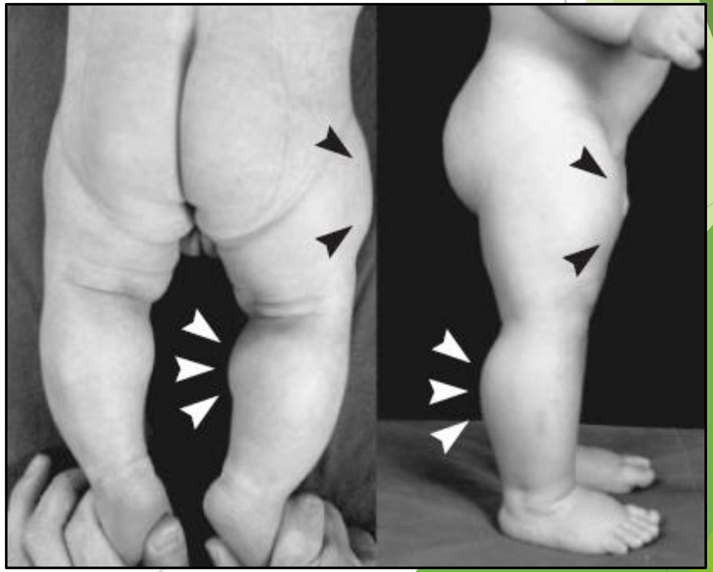


Meishan pig with myostatin mutation



Baby with myostatin mutation

Neonate

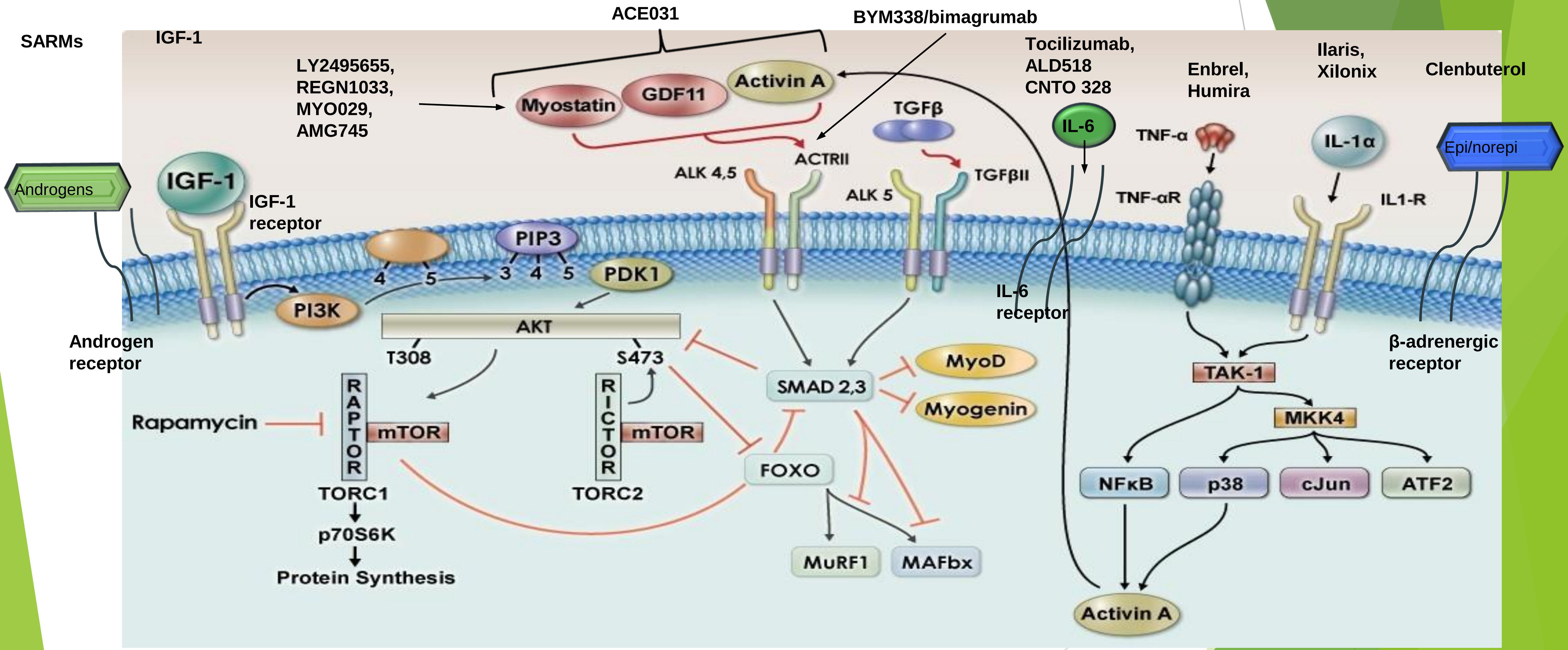


7 months

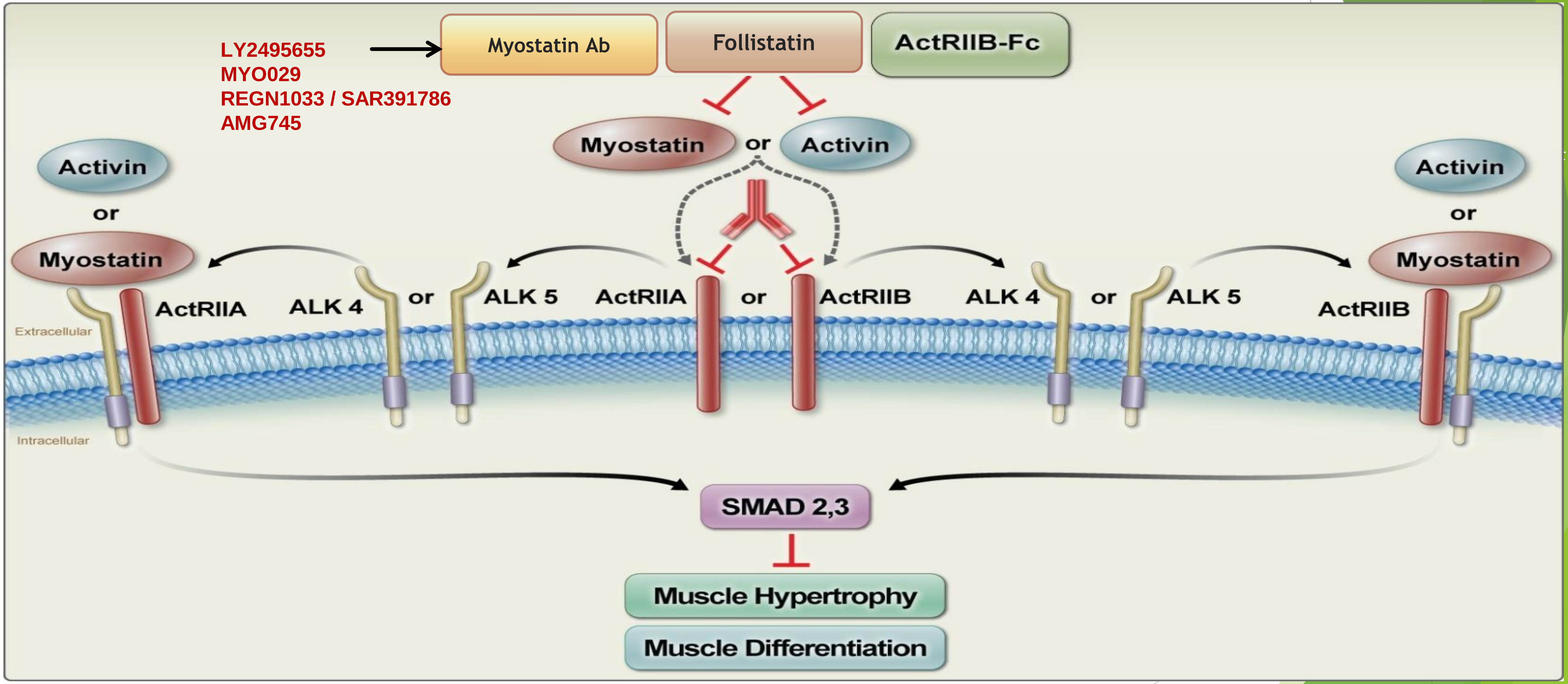
Source: n engl j med 350;26

Regulation of muscle protein balance

Many potential approaches to reverse muscle wasting



Approaches to inhibiting the inhibitor



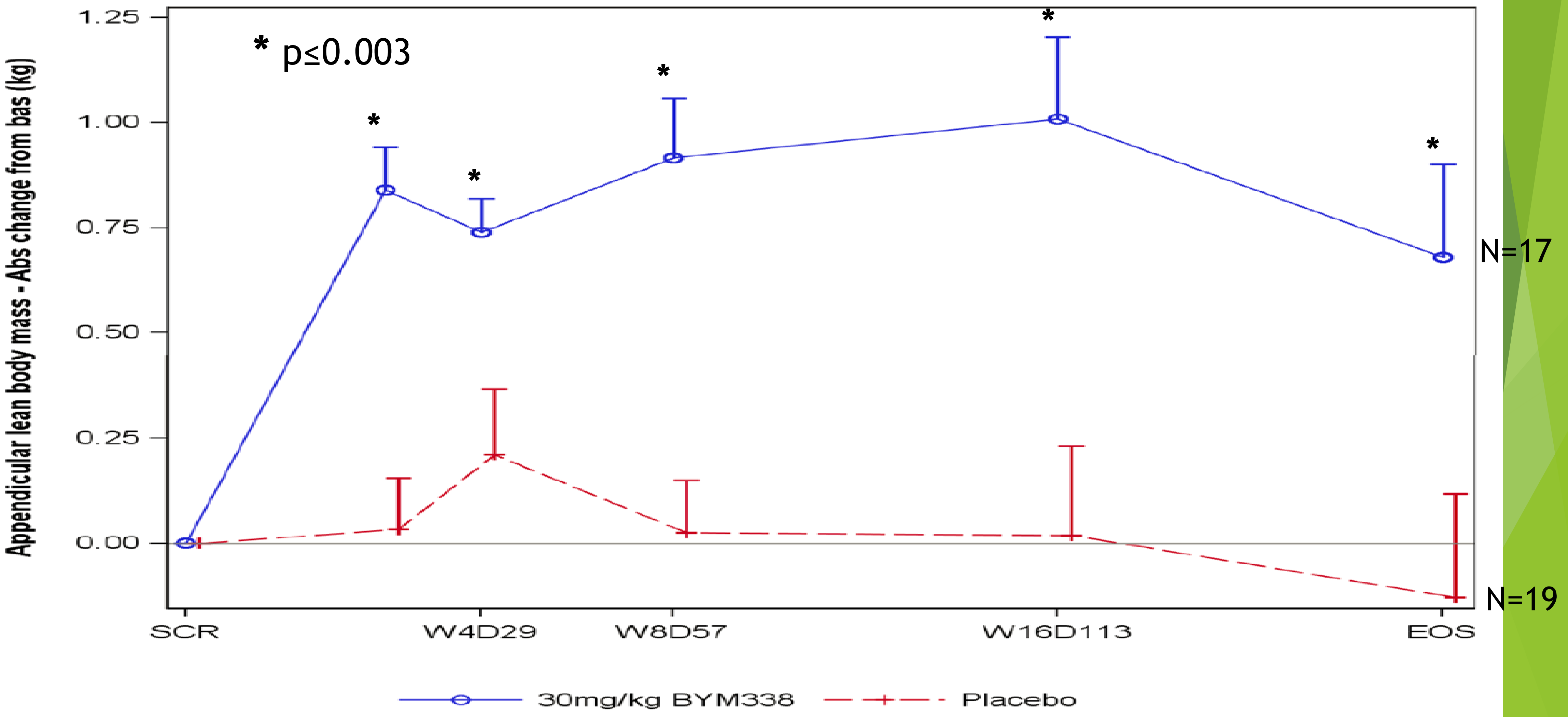
Myostatin antibody(LY2495655)

Phase 2 trial

- Randomized, placebo-controlled, double-blind, parallel
- N=201 (102 LY, 99 Placebo)
- 70% women
- ≥75 years of age (mean of 82 years)
- ≥1 fall in last 12 months
- Grip strength (≤37 kg men and ≤21 kg women)
- Extended time or unable to perform 5x chair rise without arms (>12sec)
- 21 sites, 6 countries
- 3 subcutaneous injections every 4 weeks for 20 weeks
- Primary endpoint – aLBM by DXA at week 24

Appendicular lean body mass

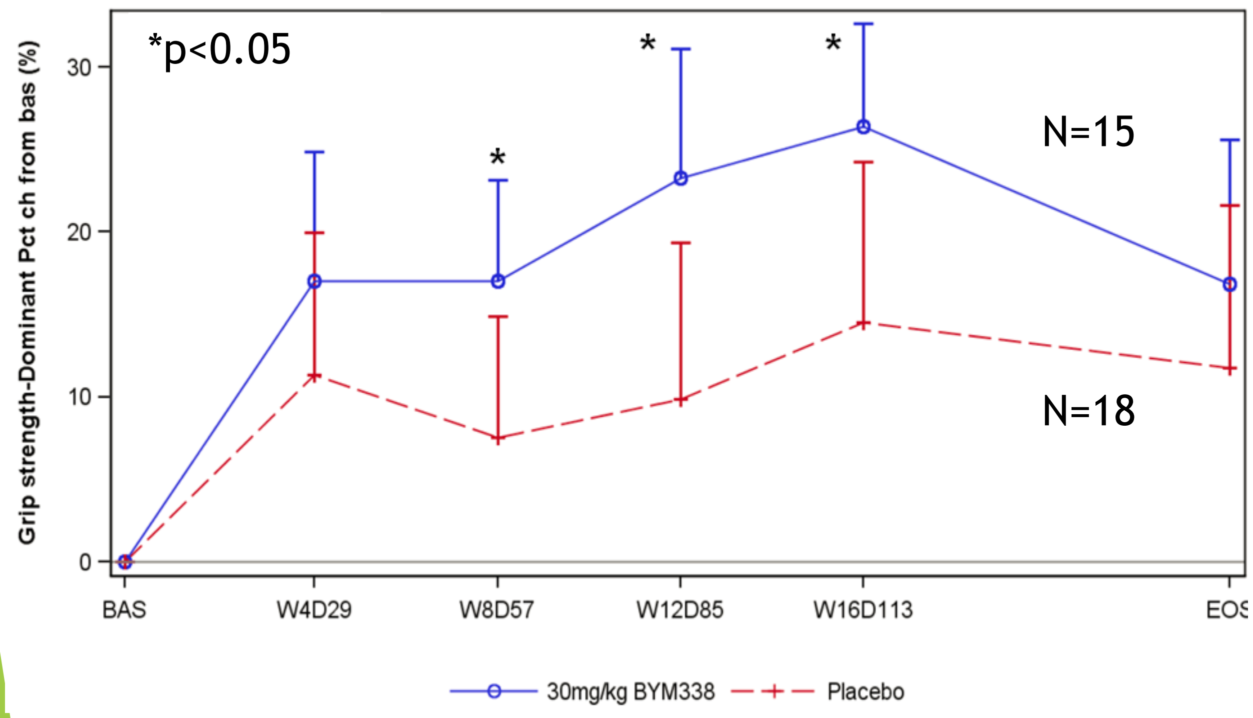
Absolute change from baseline in kg



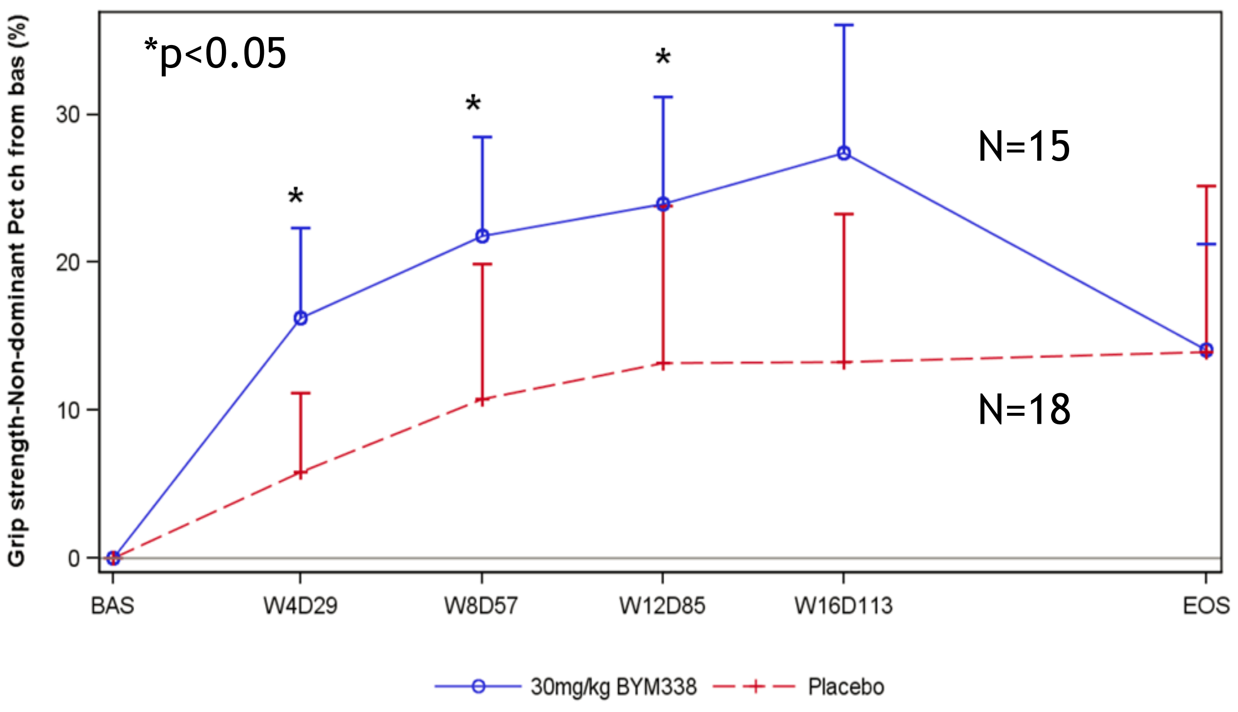
Grip strength

Percent change from baseline scores

Dominant hand

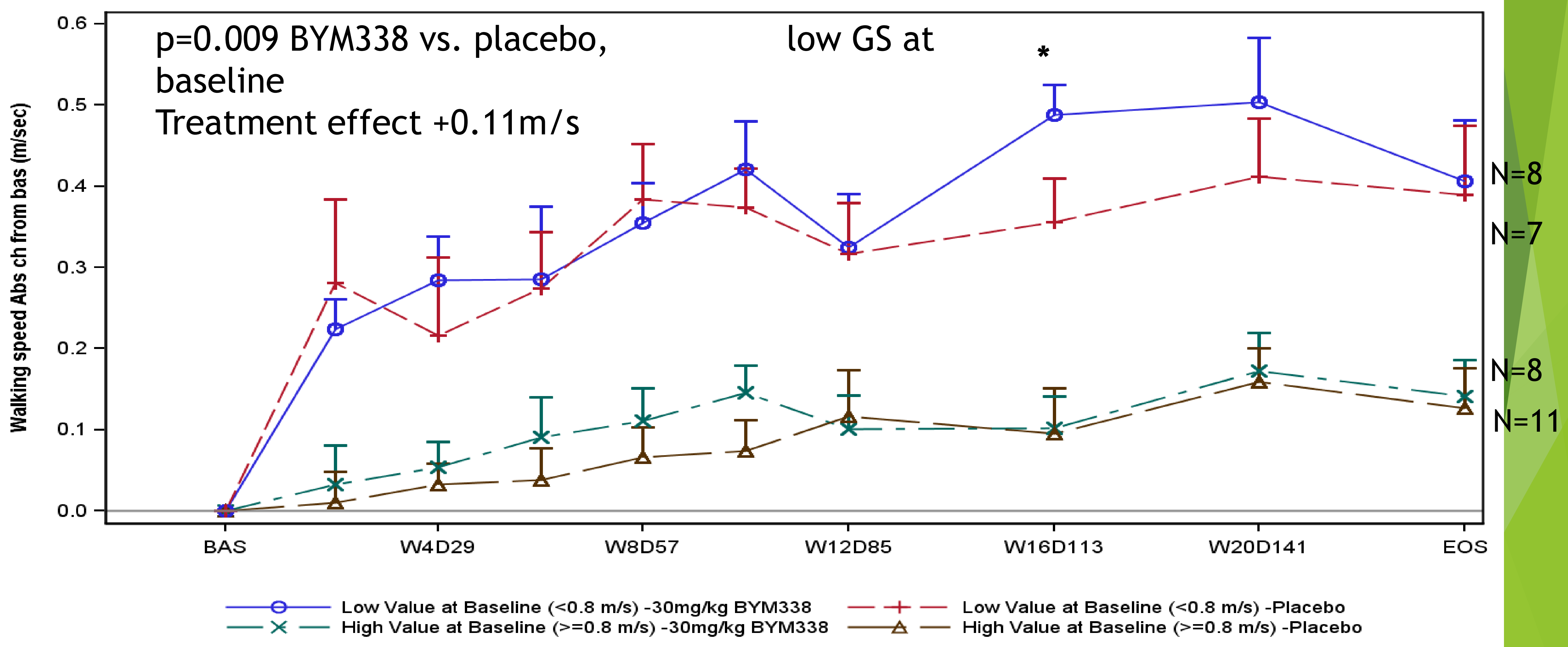


Non-dominant hand



Gait speed

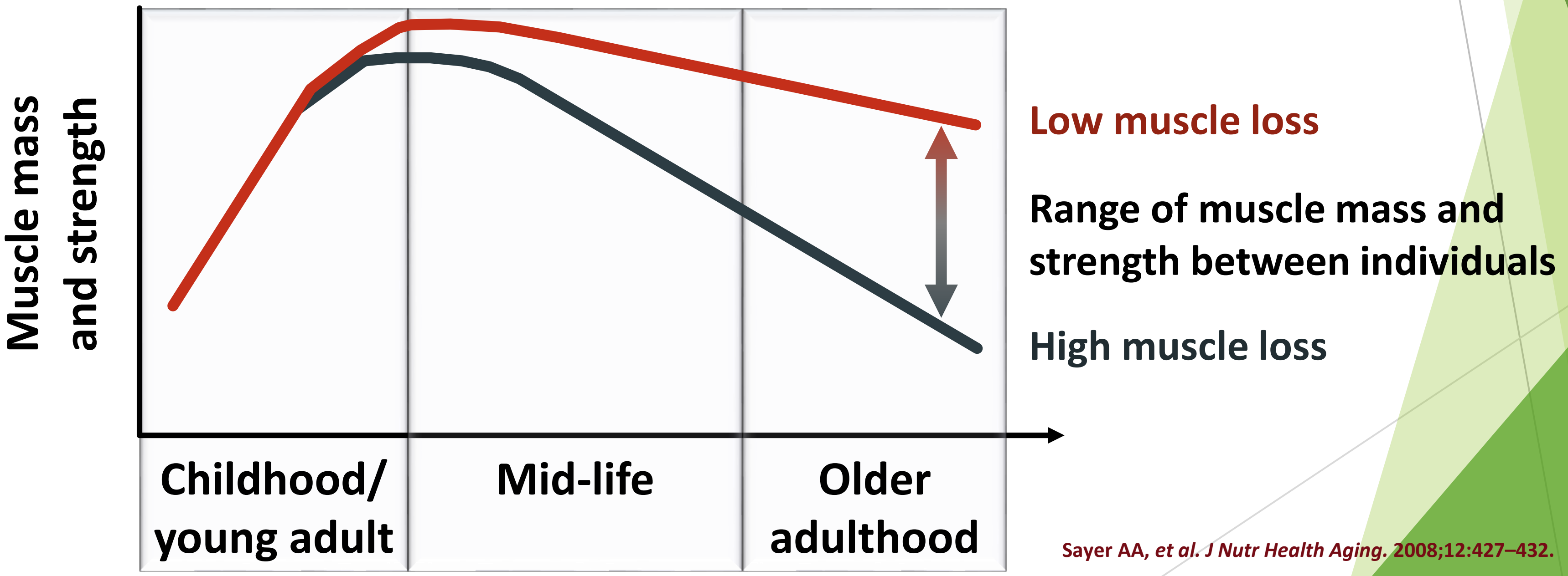
Absolute change from baseline in m/s stratified by baseline speed



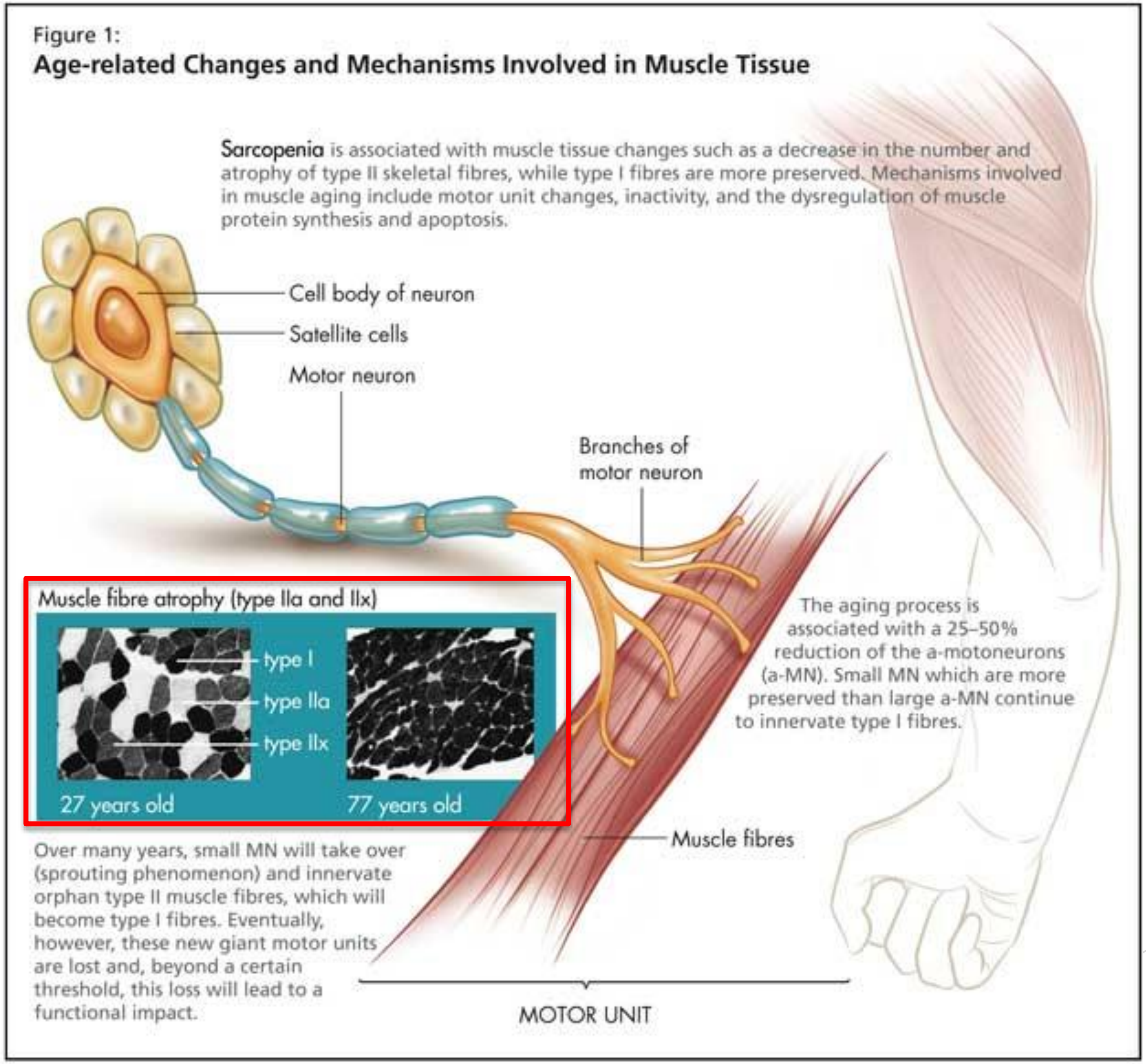
Optimize muscle mass across life

For optimal maintenance with aging, it is important to build muscle when young, maintain it in mid-life, and minimize loss in older adulthood

Build → **Maintain** → **Minimize Loss**



Sayer AA, *et al. J Nutr Health Aging.* 2008;12:427–432.



Source: Photographic images drawn from Lee WS, Cheung WH, Qin L, et al. Age-associated decrease of type II A/B human skeletal muscle fibers. Orthop Relat Res 2006;450: 231–7.

A life course approach for sarcopenia

- Exercise and good nutrition always
- Oral nutritional supplements when needed
- Potential benefits of ACEI/ARB
- Pharmaceutical intervention for severe sarcopenia