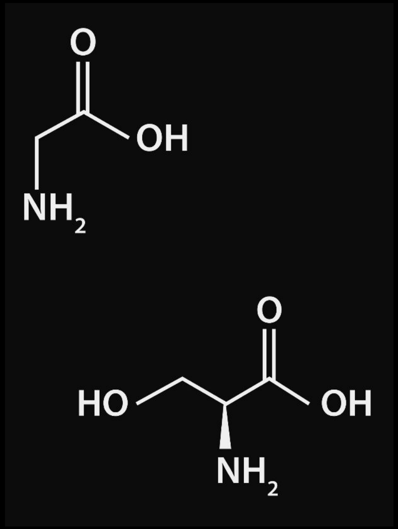
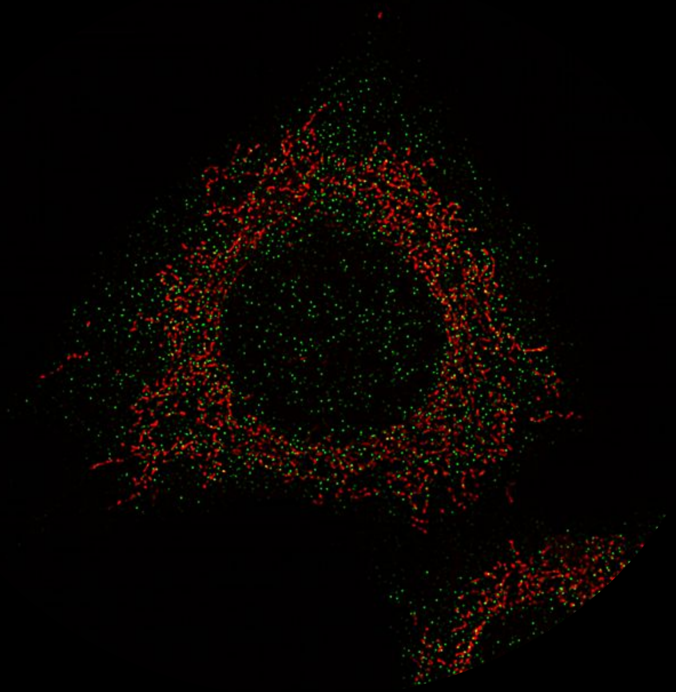
Skeletal Muscle Decline with Advancing Age

National Academies of Science: Food Forum
November 20, 2024





Anna Thalacker-Mercer, Ph.D.
UAHSF Endowed Professor of Regenerative and Translational Medicine
Associate Professor and Vice Chair of Training Programs and Mentorship
Associate Director, UAB Center for Exercise Medicine

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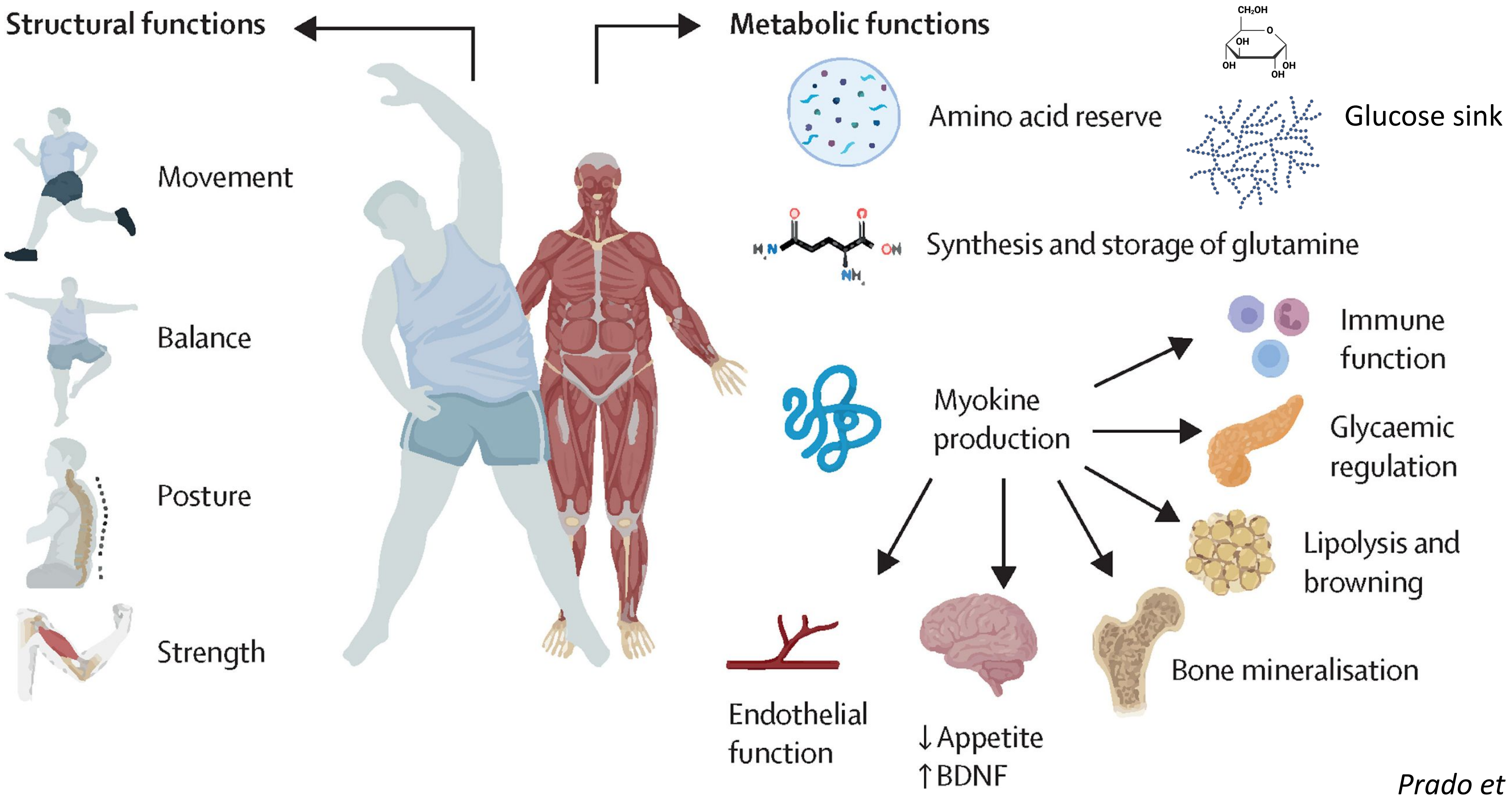
Skeletal muscle in human health

Skeletal muscle is the largest organ (system) in the body

~45% of body weight (BW) in young men

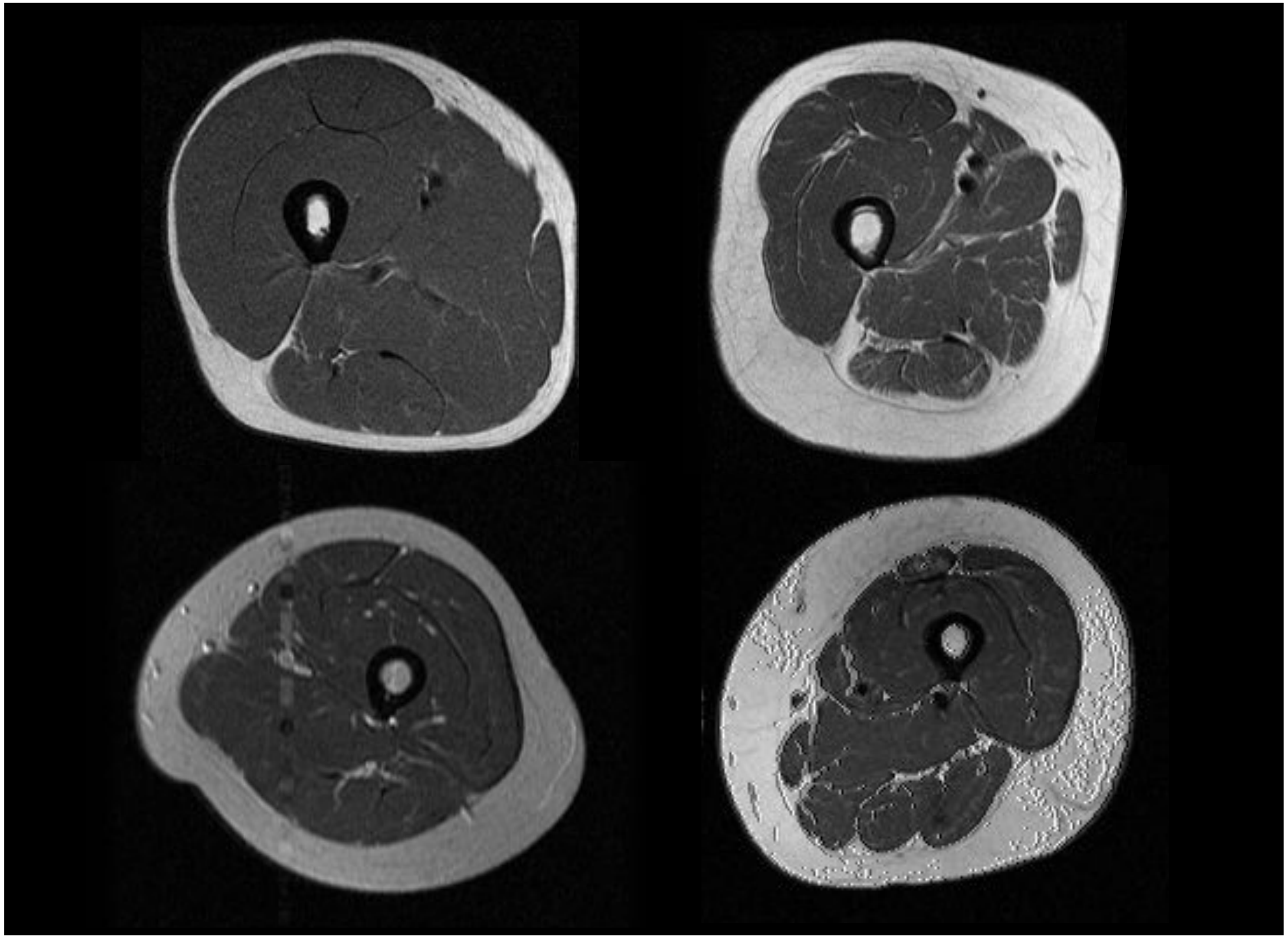
~35% of BW in young women

 25-30% of BW by 70 y—**sarcopenia**



Prado et al. Lancet 2024

Age-related change in thigh muscle, fat, and fibrotic masses in BMI and sex matched adults



Male Age 25

Male Age 63

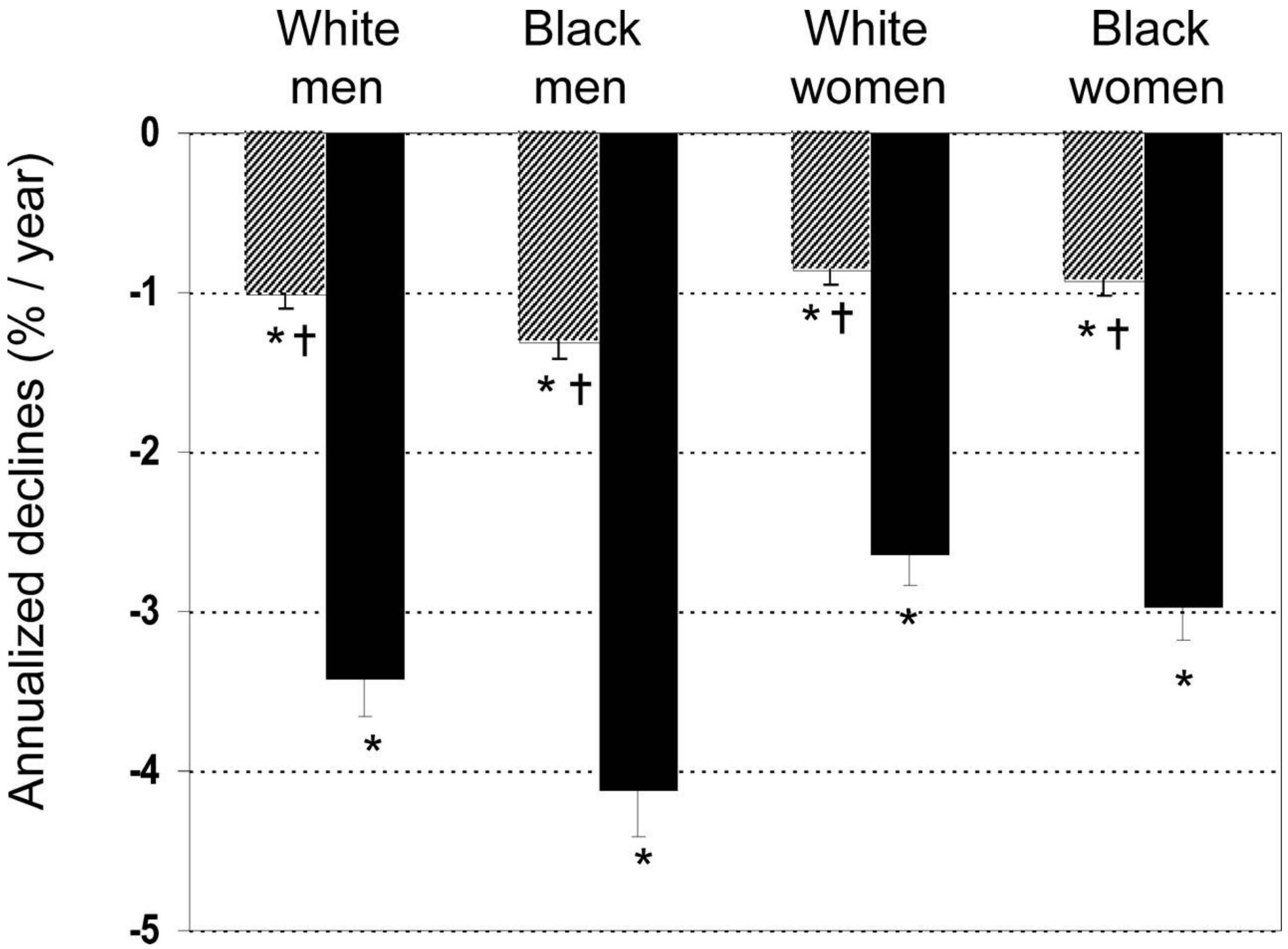
Female Age 30

Female Age 66

Similar BMI

UAB Core Muscle Research Laboratory

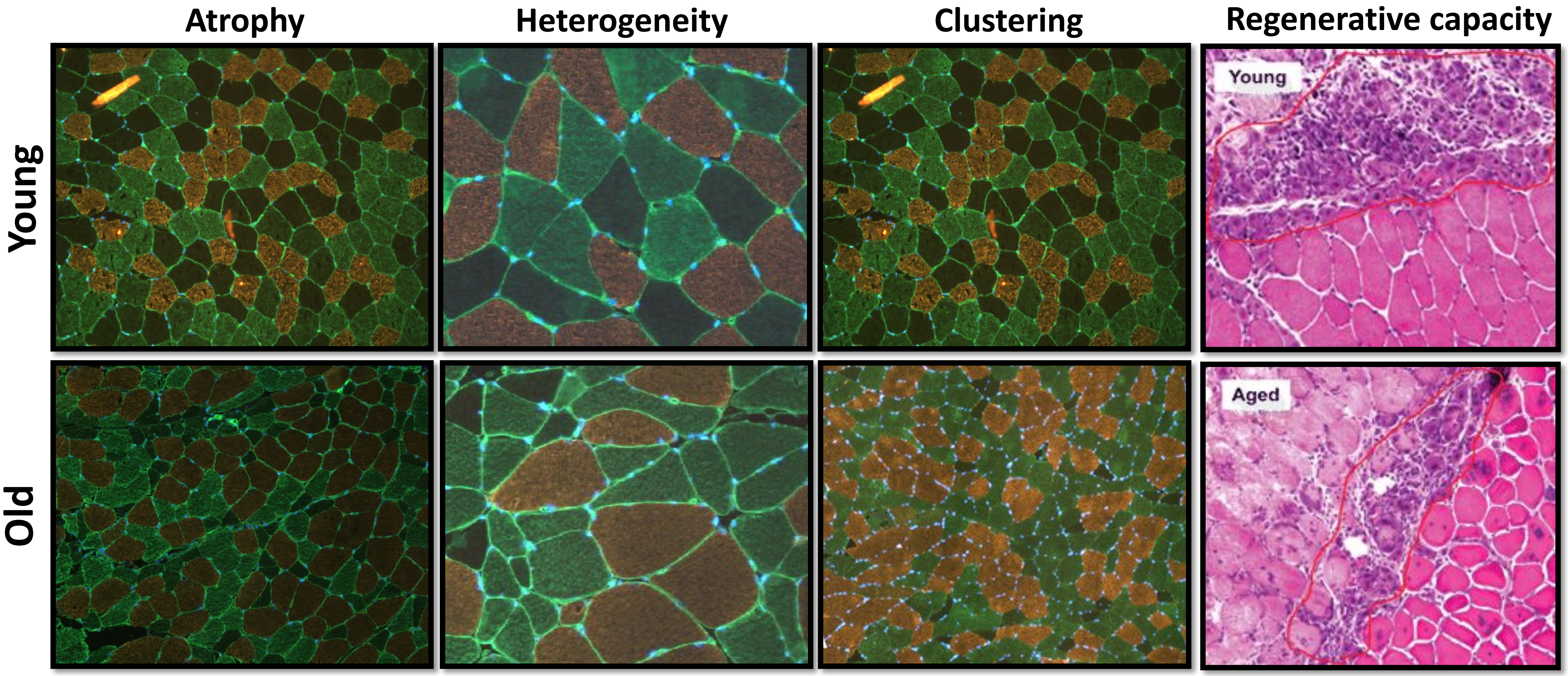
Loss of muscle strength and quality is 3X greater than the loss of muscle mass



Gender difference within race, p <0.01. Racial difference within gender, p <0.05
Leg lean mass (hatched bar); muscle strength (black bar)

Goodpaster et al. J. Geron A Biolo Sci Med Sci 2006

Complex (multi)cellular changes in skeletal muscle with aging



Copper = Type I
Green = Type IIa
Black = Type IIx

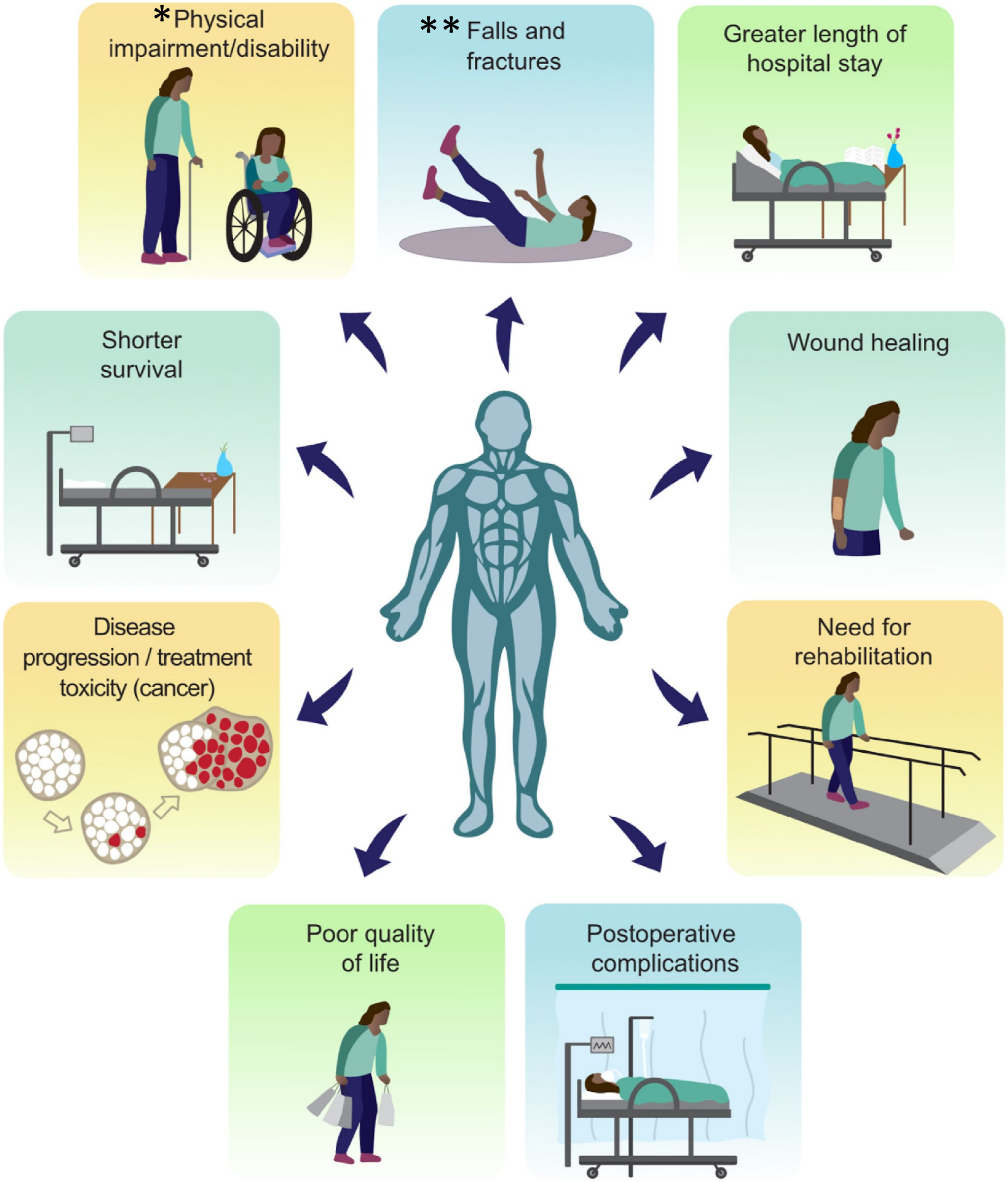
Atrophy: Females > Males

Heterogeneity: Females > Males

Clustering: Type I grouping: Both sexes
Type I cluster size: Females > Males

Roberts et al. Exp Gerontol. 2018, Jang et al. Cold Spring Harb Symp Quant Biol 2011; 76:101-11

The adverse effects of skeletal muscle deterioration



Reduced Activities of Daily Living (ADLs) and Instrumental ADLs

Loss of autonomy and independence

Institutionalization

*Mobility most common disability among older adults

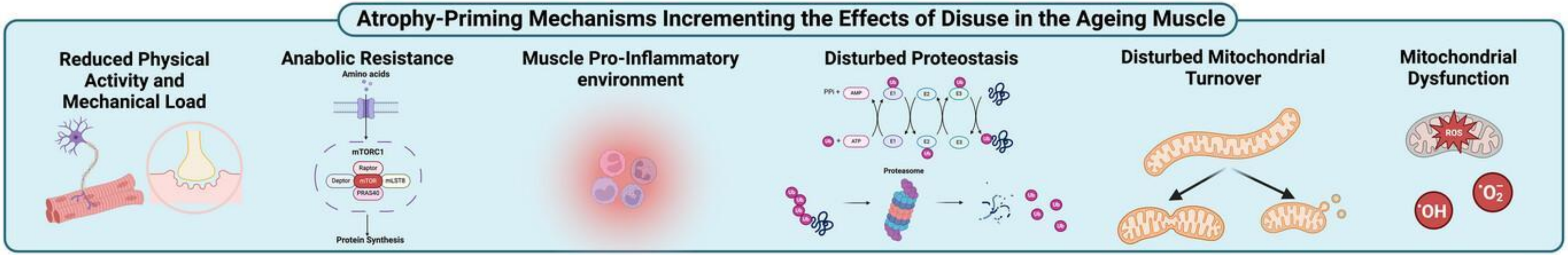
- 35% of adults 70 y
- Majority of adults >85 y

**Annual falls in older adults

- 1 in 4 older adults
- 41,000 deaths

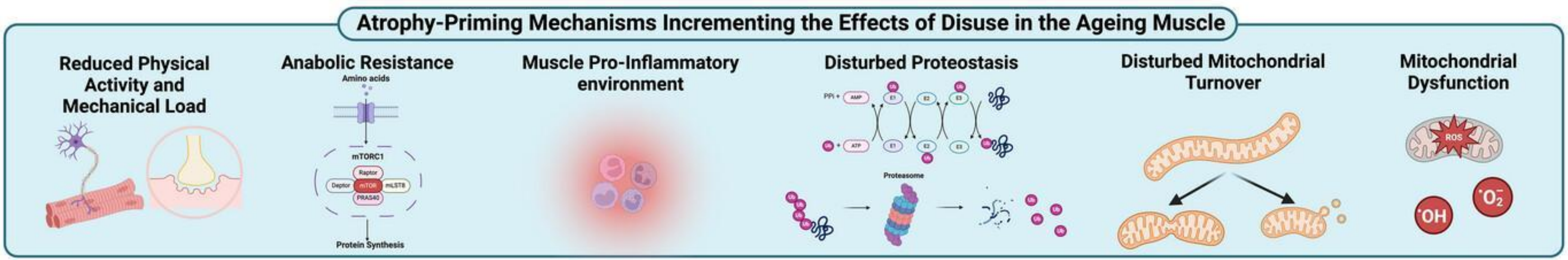
Adapted from *Prado et al. Clin. Nut. 2022*

Mechanisms are multi-factorial



Adapted from *McKendry et al. Exp. Phys. 2024*

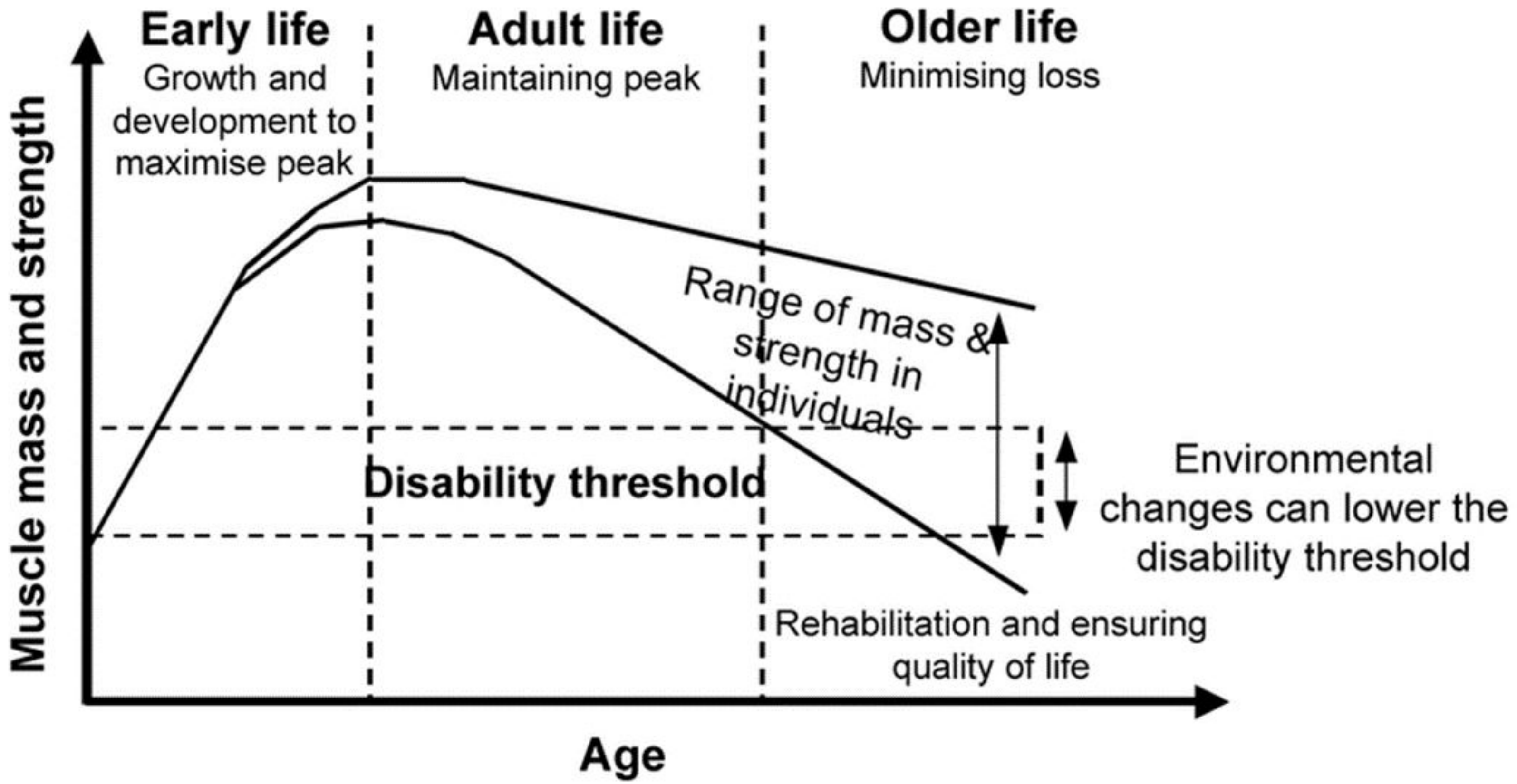
Mechanisms are multi-factorial



Understanding mechanisms will help us
identify biomarkers and **understand how to intervene**

Adapted from *McKendry et al. Exp. Phys. 2024*

Temporal changes in skeletal muscle mass and strength



Modified WHO/HPS, Geneva 2000

Level of evidence for dietary patterns, whole foods, and nutrients impacting indicators of sarcopenia

		Mid-Adult (<60 y)	Old Adult (≥65 y)
Dietary Patterns		Evidence (**limited**) of higher quality diets being beneficial for physical performance in later life.	Evidence (**moderate**) for higher quality diet patterns being better for muscle strength and physical performance.
Whole Foods	*Select examples*		
	Fruits and Vegetables	Evidence (**limited**) benefits physical performance later in life.	Evidence (**limited**) for benefits on physical performance with higher intakes
	Meat		Evidence (**mixed**) for mass and strength when mixed with exercise. Evidence for potential harmful effects of processed meats.
	Dairy / Dairy product		Evidence (**mixed**) of mass, strength, and functional benefits when mixed with exercise. Relationship between consumption, mass and strength.
Nutrients	*Select examples*		
	Protein	Evidence of benefits when mixed with exercise.	Evidence (**mixed**) of mass, strength, and functional benefits when mixed with exercise.
	Vitamin D	Evidence is **inconsistent**.	
	Antioxidants	**Very limited** evidence.	Evidence (**limited**) for benefits on mass, strength, and function particularly when coupled with exercise.
	B vitamins		Evidence (**limited**) of B12 status association with muscle mass and strength.

Robinson et al. AJCN 2023; Ganapathy and Nieves Nutrients 2020; Granic et al. Proc. Nutrition Society 2024; Campbell et al. J. Geron Med Sci 2023

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Whole	*Select examples*		
		exercise.	benefits when mixed with exercise.
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	B vitamins		Evidence (**limited**) of B12 status association with muscle mass and strength.

Timing of intake, dose, biological age, polypharma, exercise/physical activity level, habitual diet, etc. need to be accounted for.

Robinson et al. AJCN 2023; Ganapathy and Nieves Nutrients 2020; Granic et al. Proc. Nutrition Society 2024; Campbell et al. J. Geron Med Sci 2023

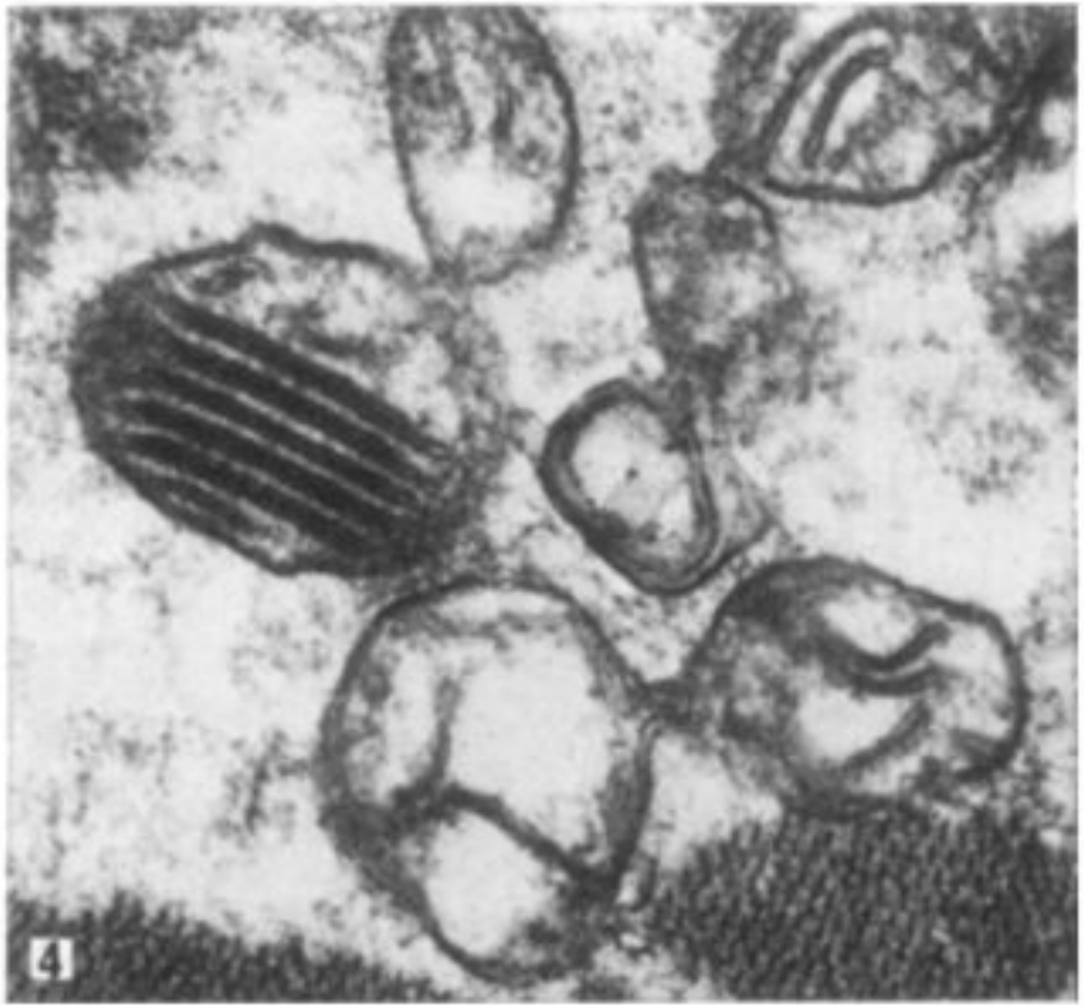
Muscle mass and strength are related to Vitamin B12 levels

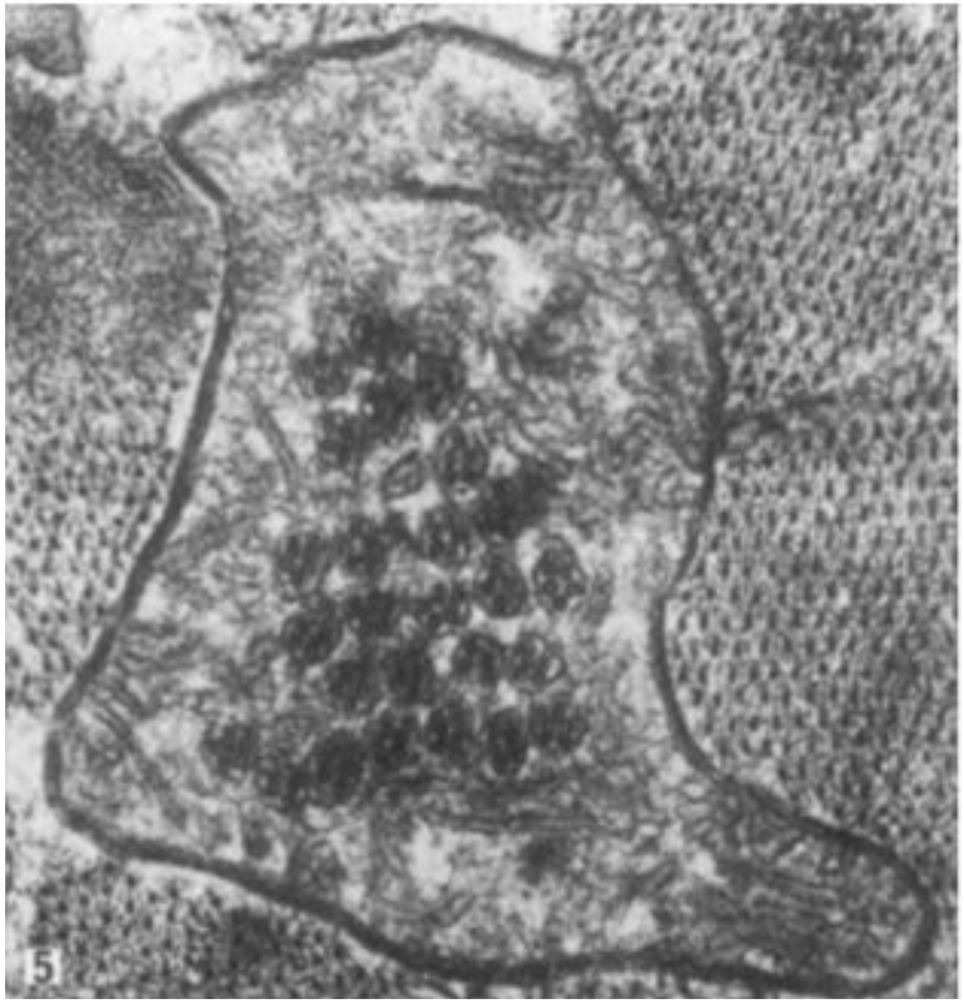
	Vitamin B12<400pg/mL n=240	Vitamin B12≥400pg/mL n=163	p
Age	73.7±7.19	72.9±7.81	0.30
Muscle strength (kg)	17.95±9.06	20.00±9.11	**0.03**
Fat (kg)	22.49±8.88	22.97±10.01	0.65
Lean body mass (kg)	45.98±8.14	49.42±9.52	**0.001**
Skeletal muscle mass (kg)	26.01±4.51	27.97±5.38	**0.001**
Muscle (kg)	43.58±7.66	46.92±9.06	**<0.001**
Skeletal muscle mass index (skeletal muscle mass/height^2)	7.14±1.32	7.74±1.43	**<0.001**

N = 403 human adults aged 70-84 y

Bulut, A.E., et al., 2017

Disrupted mitochondria cristae and inclusions are observed in muscle of B12 deficient sheep





J. Comp, Path. 1983. Vol, 93

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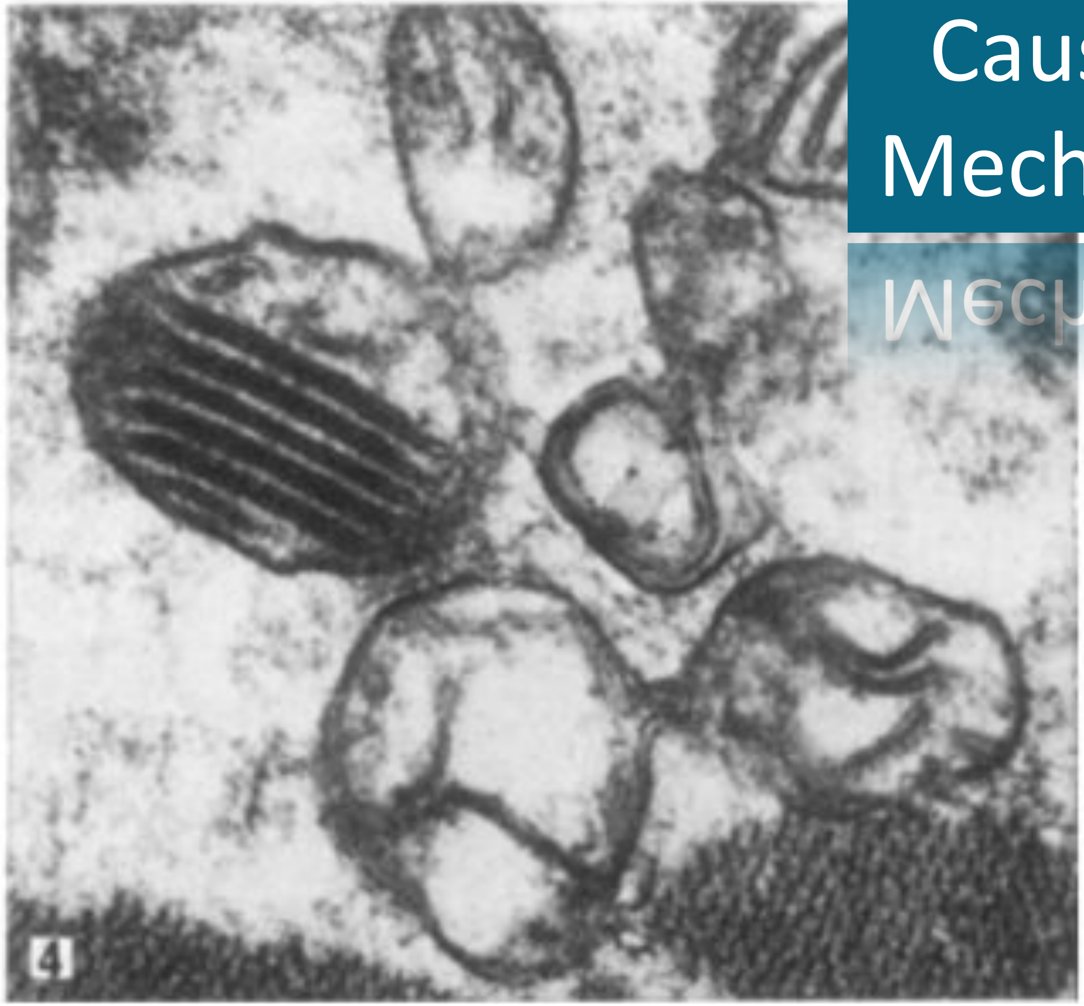
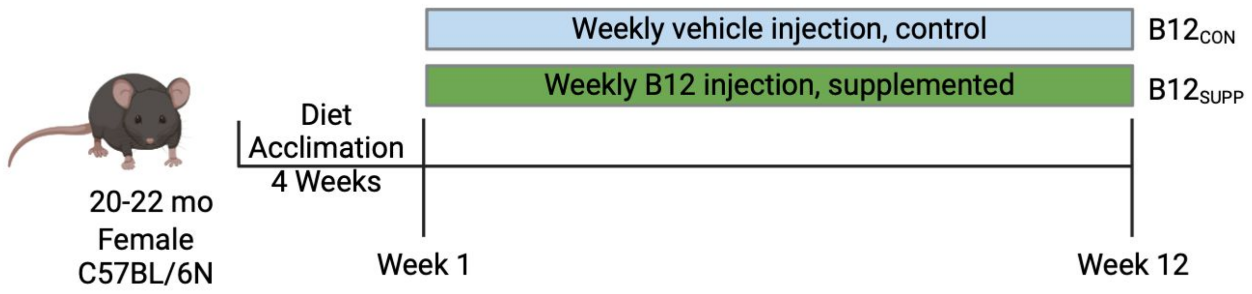


Causality?
Mechanism?

J. Comp, Path. 1983. Vol, 93

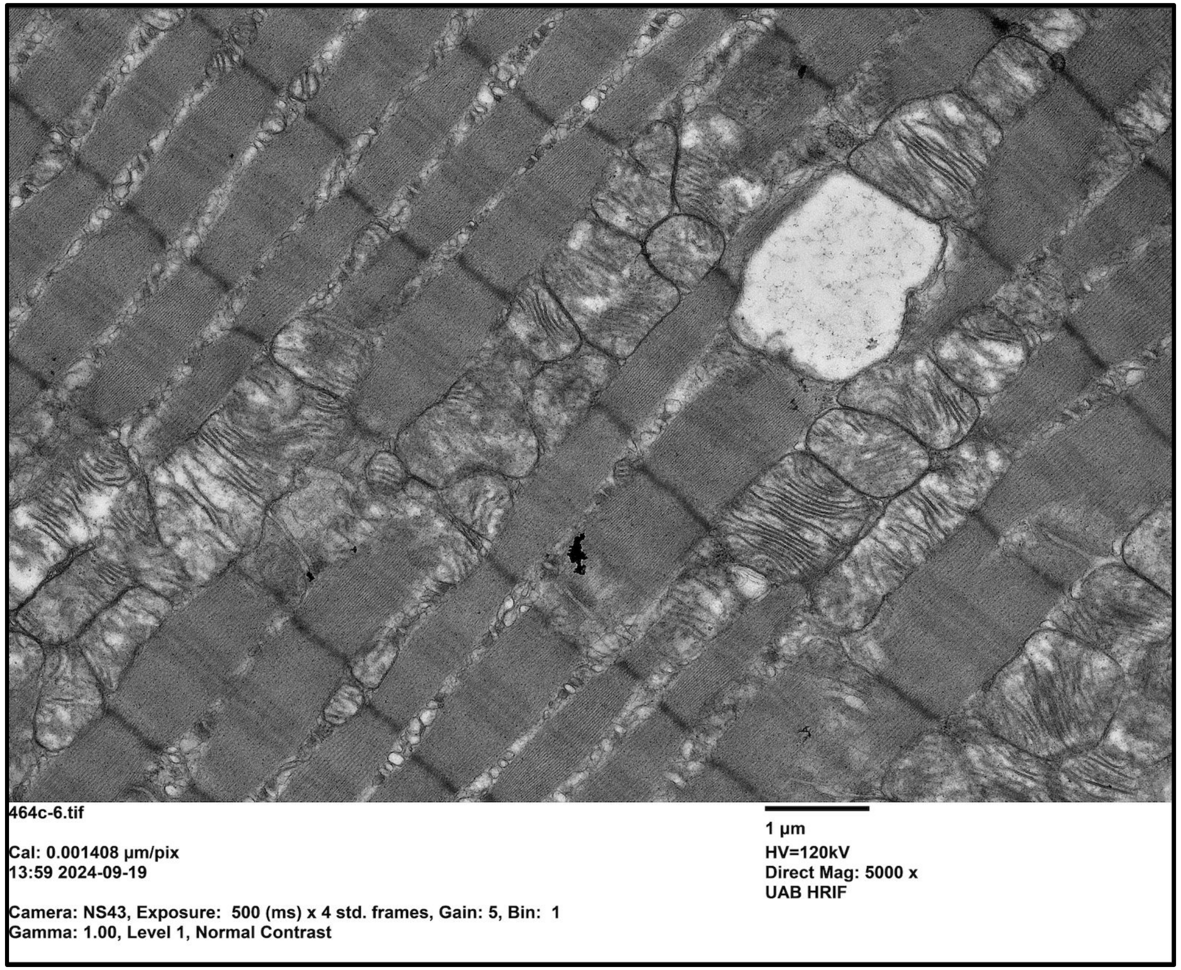
Examining the impact of B12 supplementation on aged skeletal muscle

- **Diet:** AIN93
- **Randomized 12 weeks treatment**:
  - 1.25 µg B12 in 0.9% saline
  - vehicle control (0.9% saline)
- **Assessments:**
  - Mitochondria architecture with electron microscopy
  - Global proteomics
- **Indicator of improved B12 status**
  - Increased ceruloplasmin levels (4.6-fold)

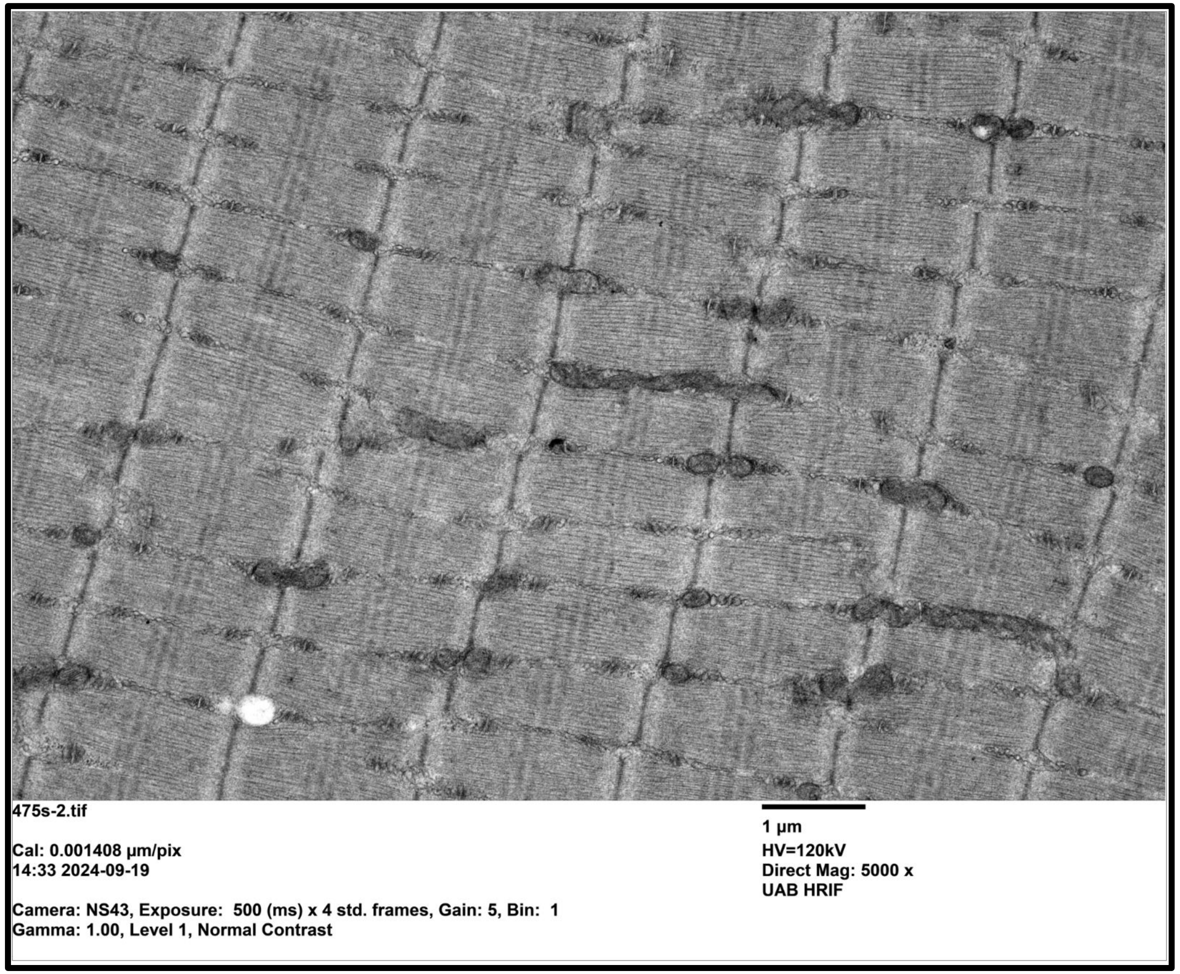


Preserved mitochondrial morphology with B12 supplementation

Vehicle control

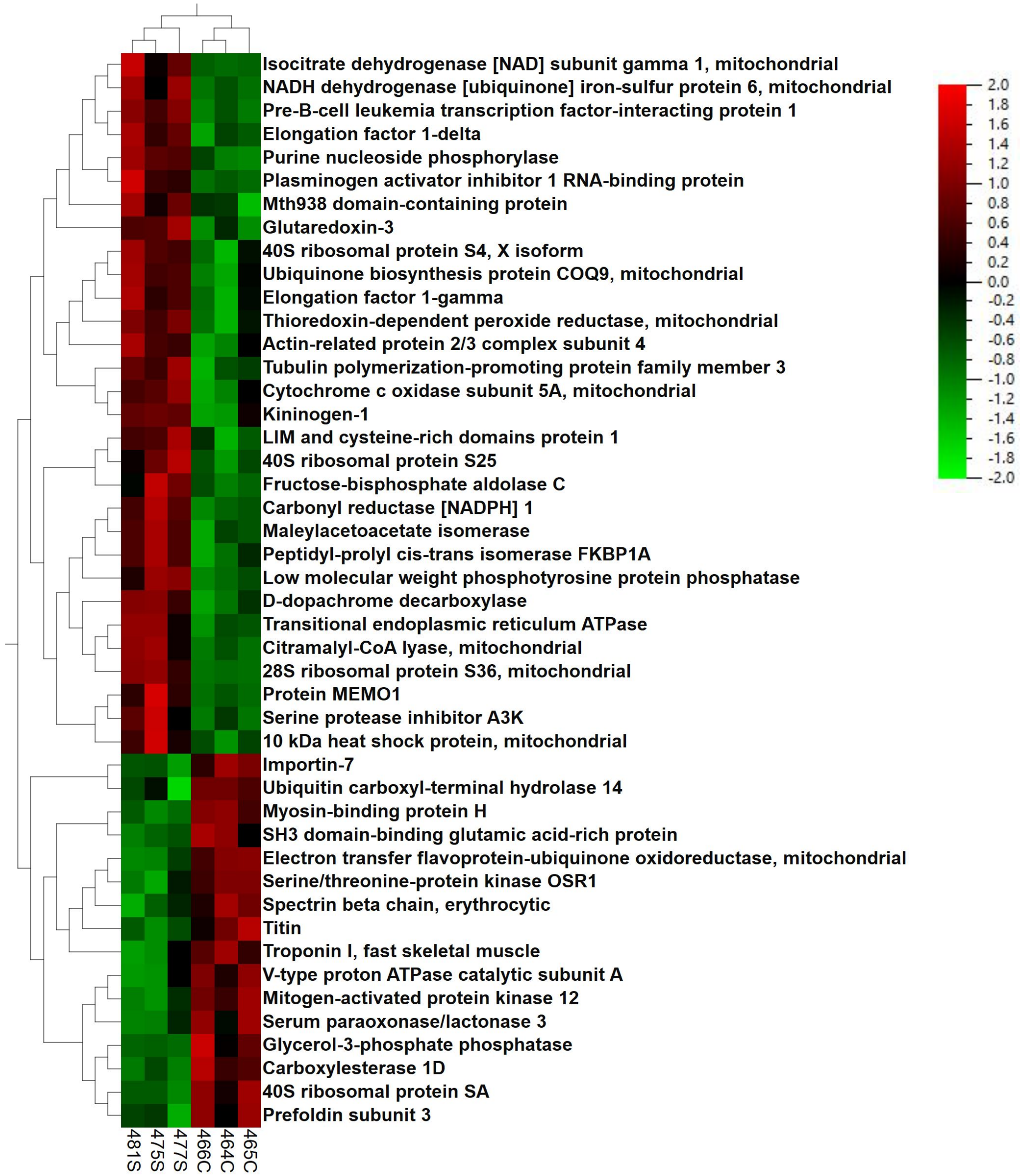


Supplemented



Unpublished data

B12 availability impacts skeletal muscle mitochondria and structure

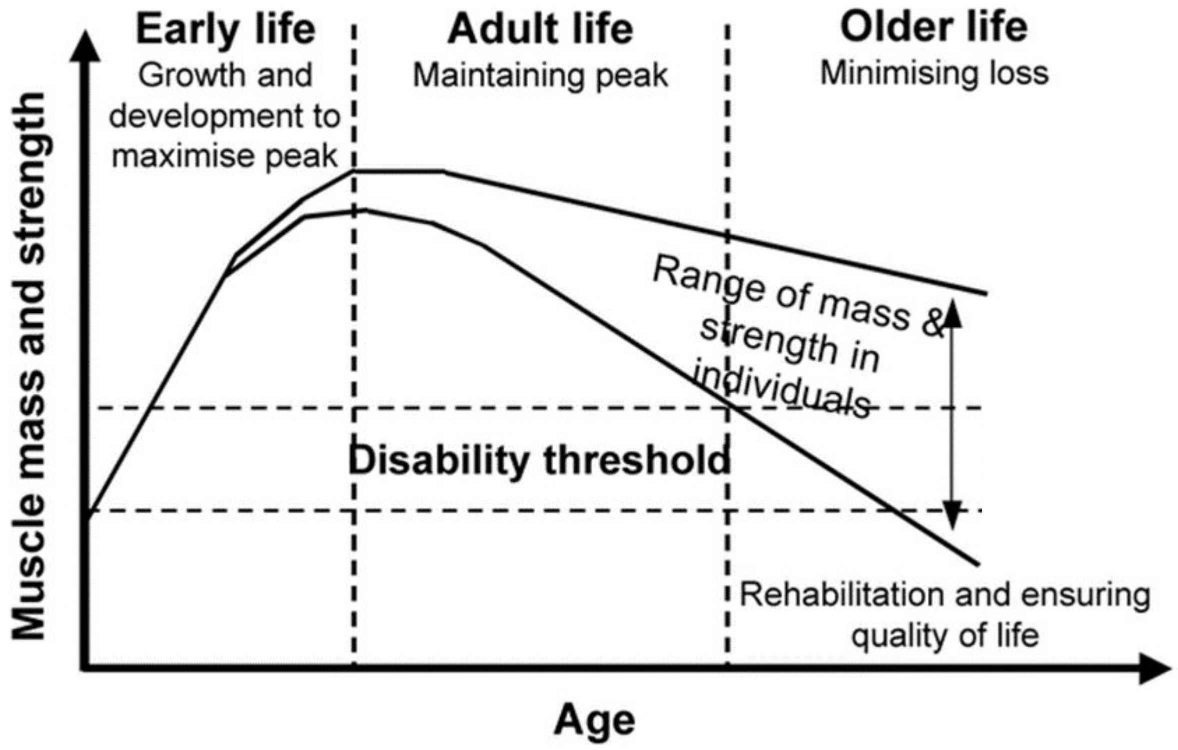


- Top differentially expressed proteins related
  - Mitochondria function
  - Skeletal muscle architecture / structure
- Top canonical pathways
  - Regulation of eIF4 and p70S6K (p = 1.30E-08)
  - mTOR signaling (p = 6.32E-07)
- Physiological system development and function
  - Skeletal muscular system development and function (p-value range 5.14E-03 – 1.07E-07)
  - Organismal survival (p-value range 1.77E-05 – 1.29E-07)

Unpublished data

Anticipated vs. unexpected sarcopenia

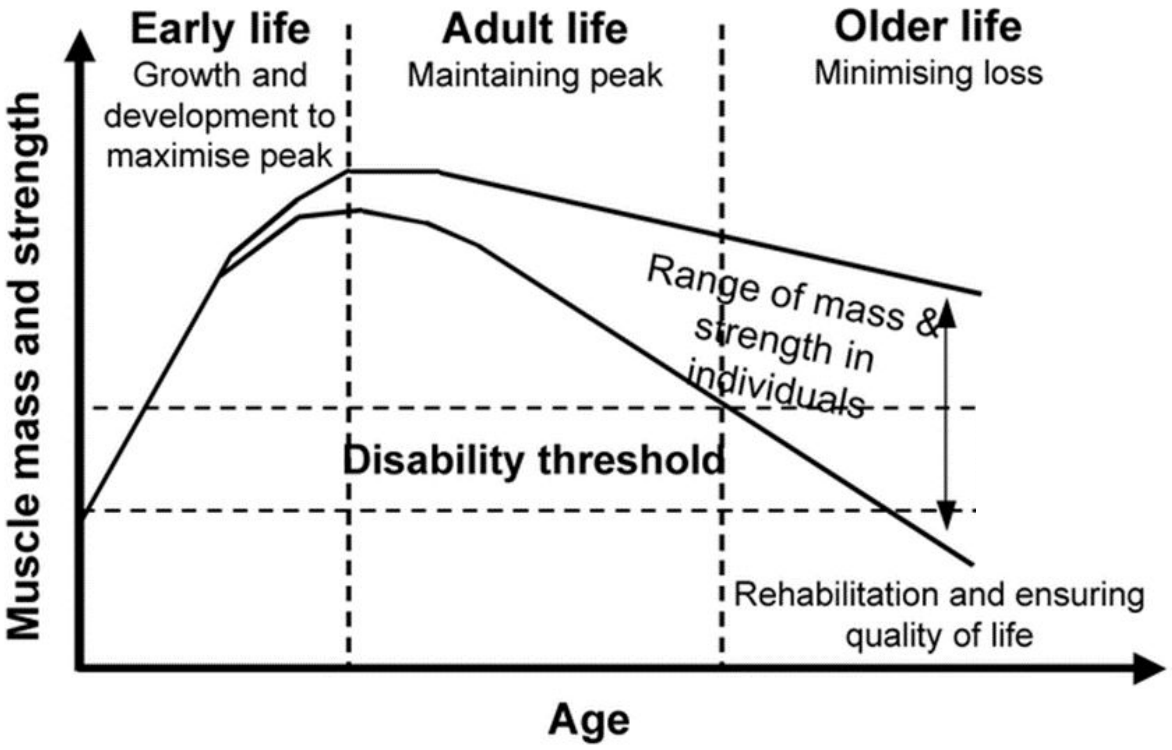
"Anticipated"



Modified WHO/HPS, Geneva 2000

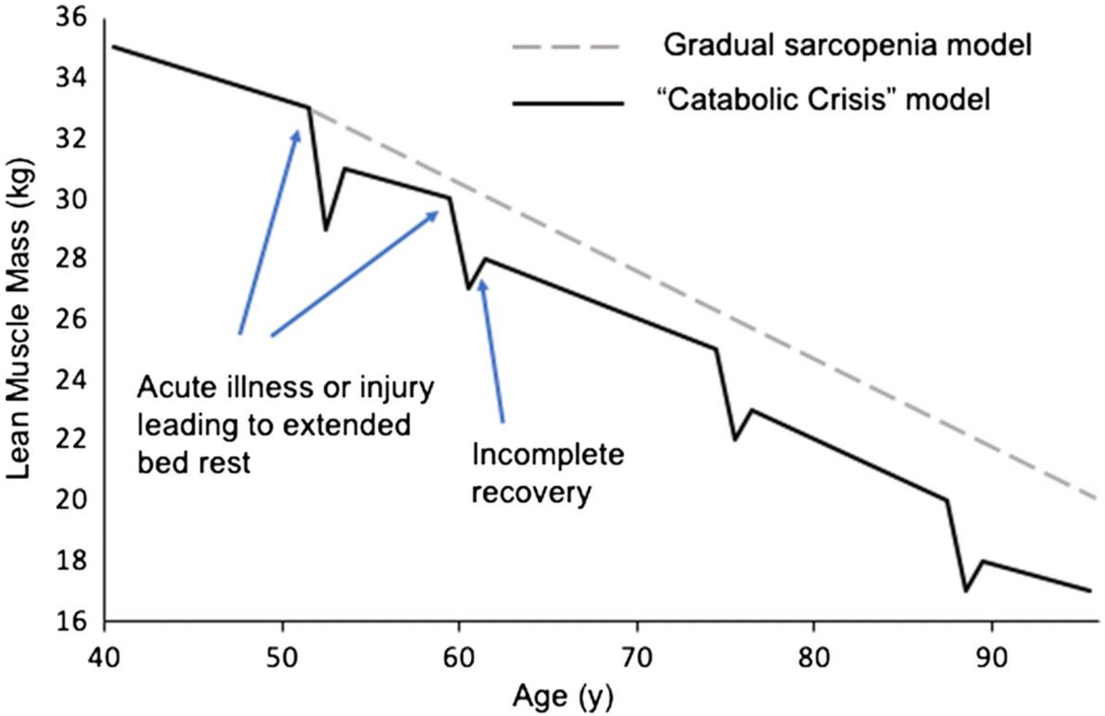
Anticipated vs. unexpected sarcopenia

"Anticipated"



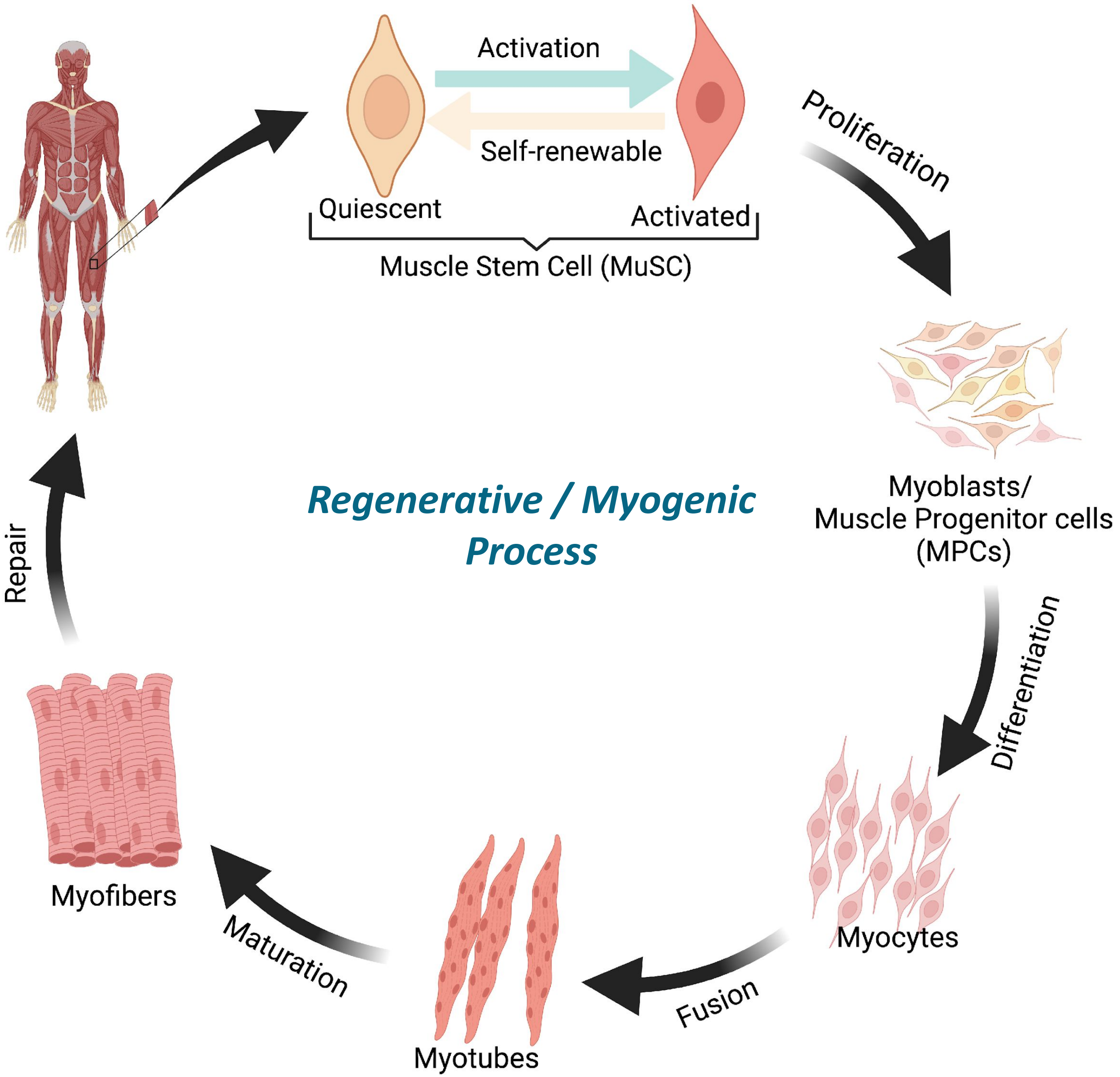
Modified WHO/HPS, Geneva 2000

"Unexpected"



Kirwan et al. GeroScience 2020

“Unexpected” stressors impact skeletal muscle health



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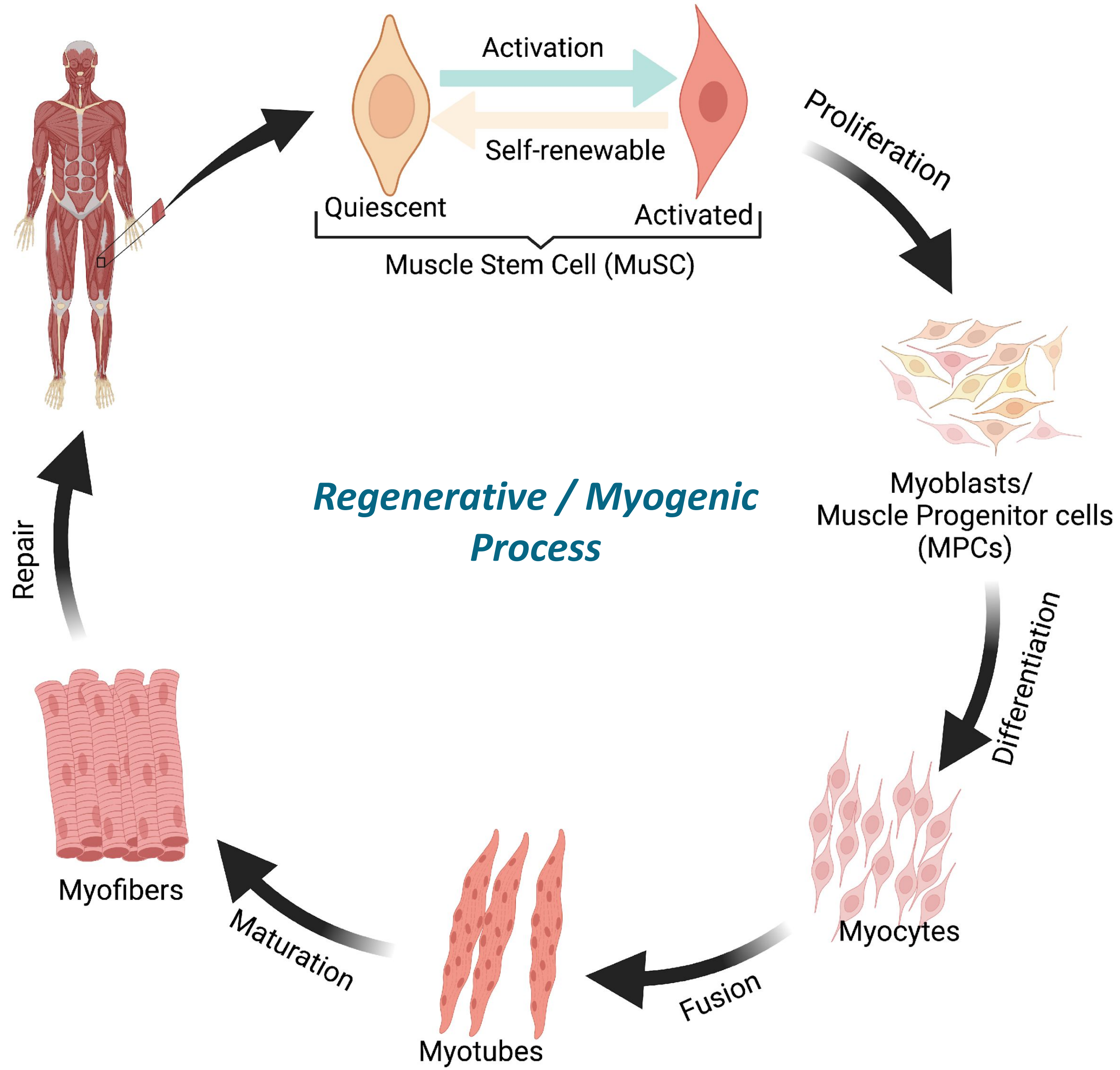
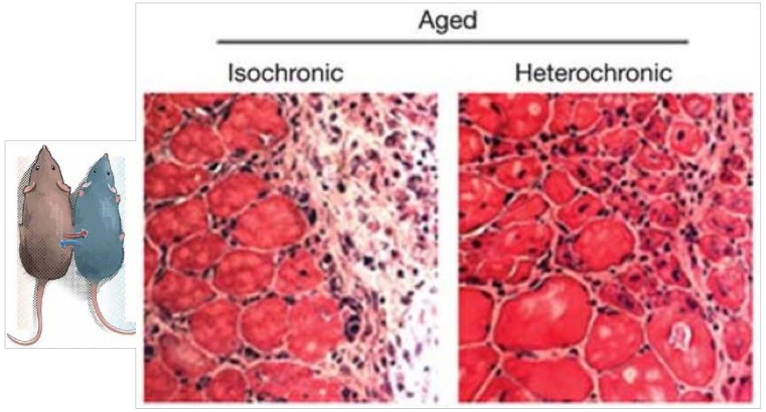
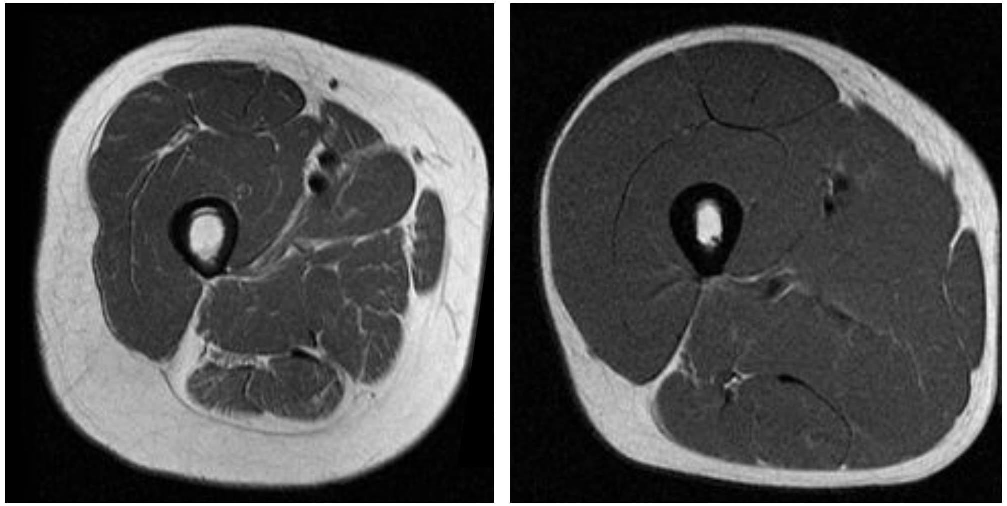




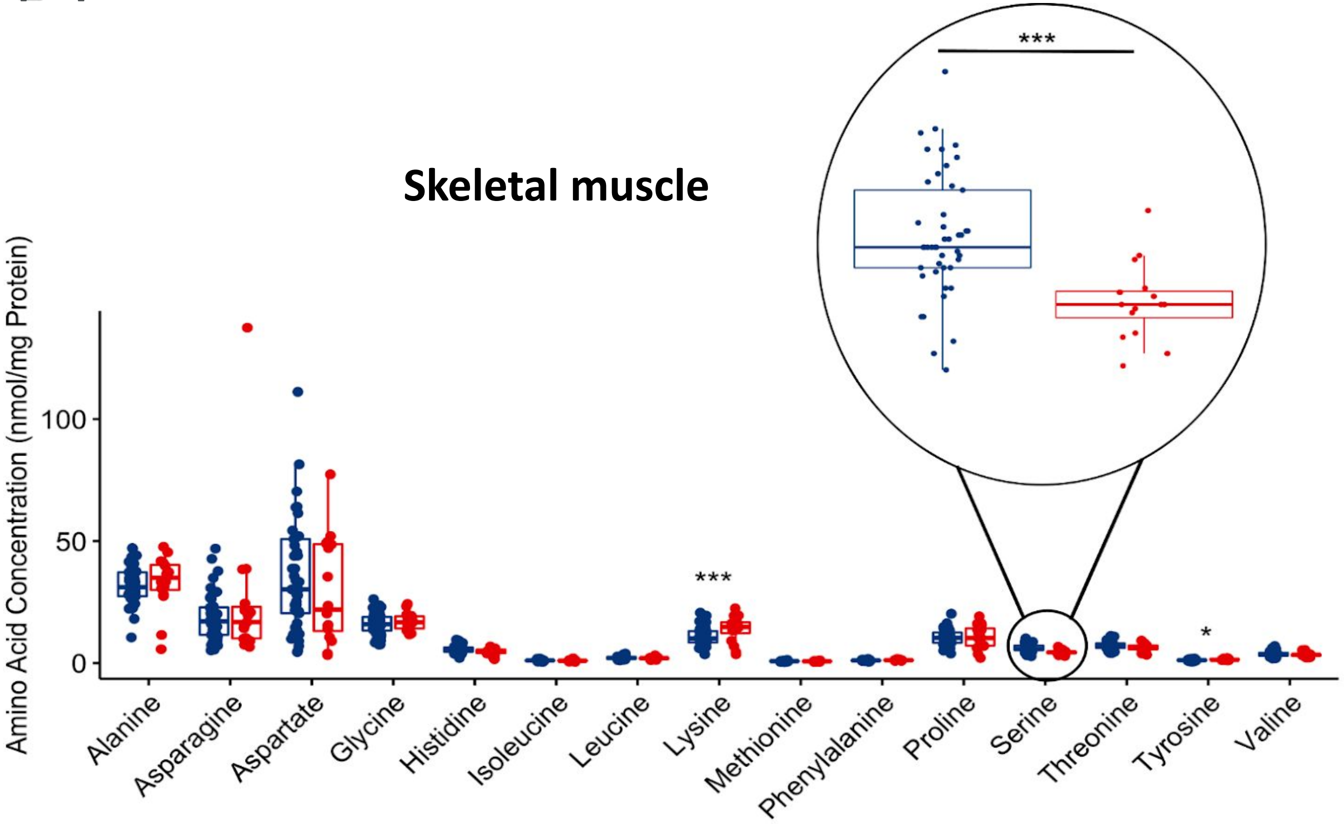
Conboy et al. Nature 2005



Endogenous serine (and glycine) availability is lost with advancing age

- Older and younger adults
- Metabolomics skeletal muscle, plasma and serum

Skeletal muscle



Circulating

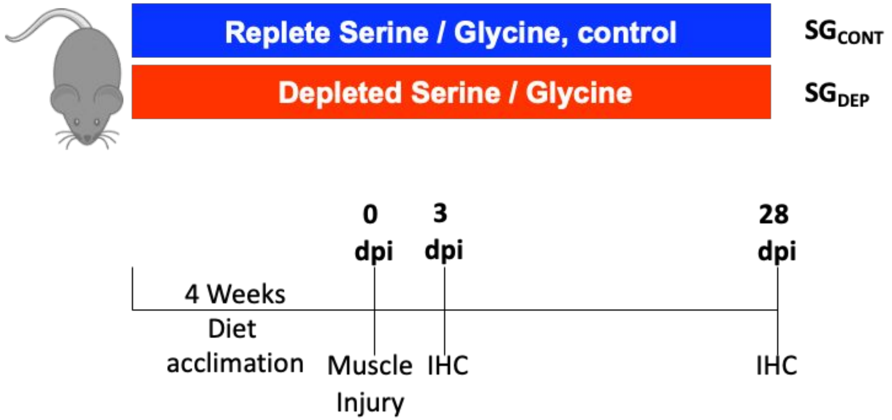
	Young *human adults		Older human adults	
	Plasma µM/L	Serum µM/L	Plasma µM/L	Serum µM/L
l-Serine	136	112	135	^98
Glycine	360	248	352	246

*changes with age also observed in mice
^different from young, p<0.05

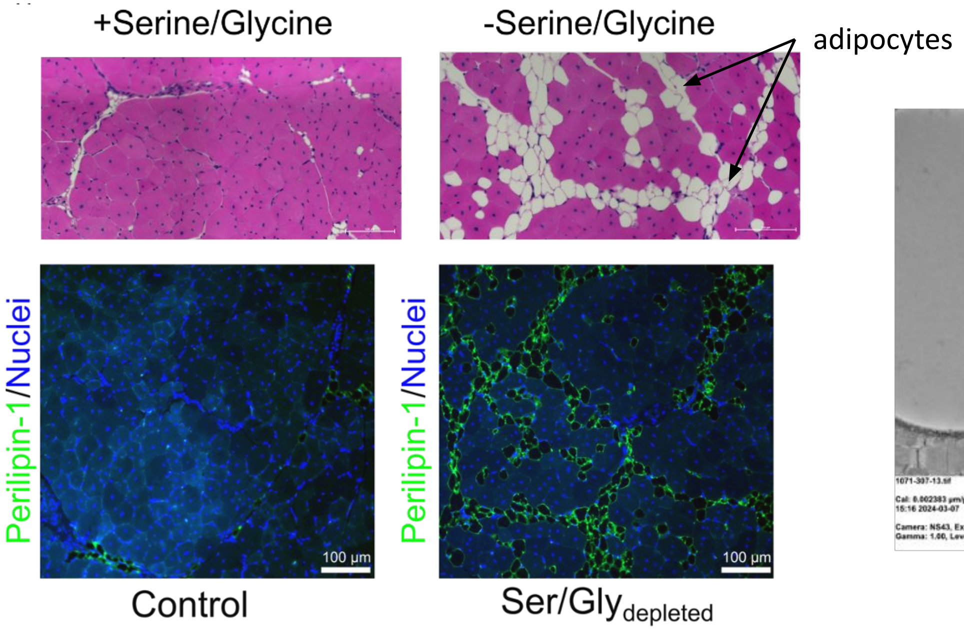
Gheller et al. Mol Metab. 2021

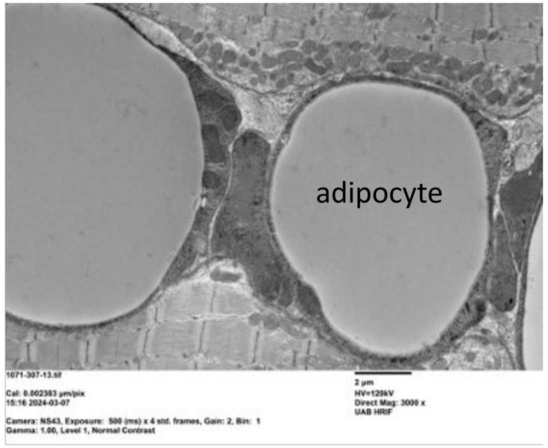
Enhanced skeletal muscle remodeling with reduced serine and glycine availability in older mice

- C57Bl/6N, aged (19-20 months)
- Diets: isonitrogenous, isoenergetic



Gheller et al. Mol Metab. 2021





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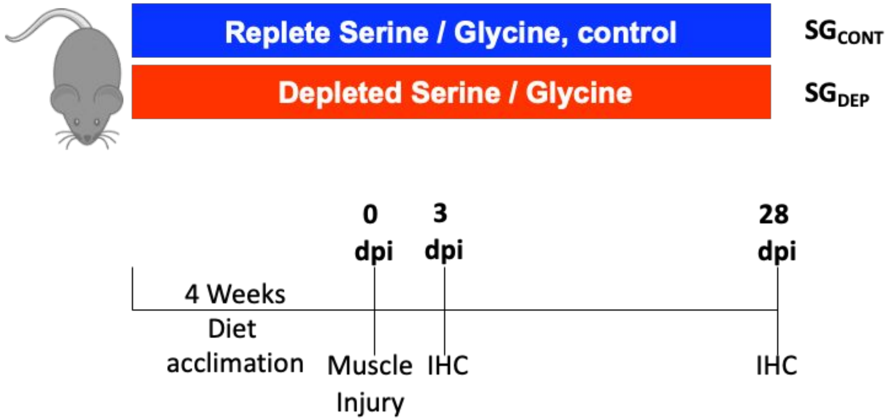

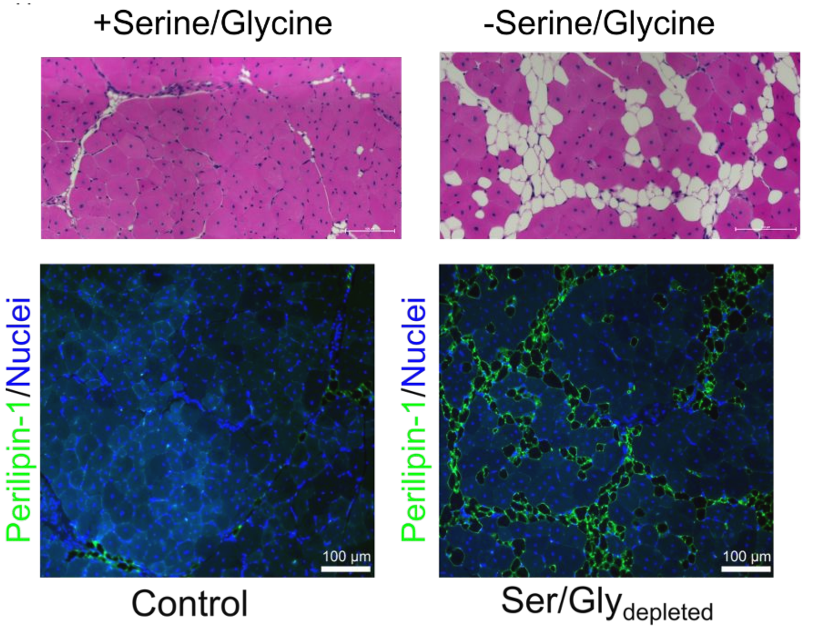

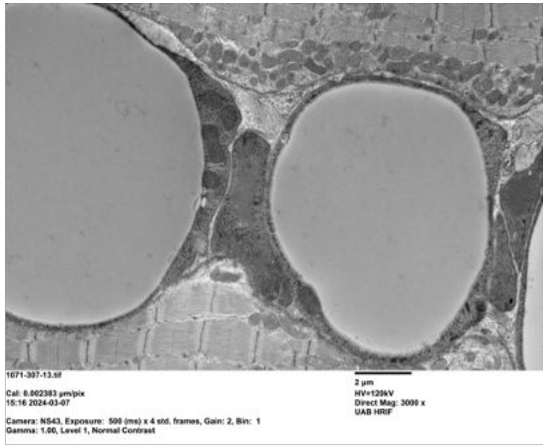

Gheller et al. Mol Metab. 2021

Lustgarten & Fielding, Exp. Gero. 2017

- **Older adults**: n=73 older adults, mean age 78 y
- Multivariate-adjusted linear regression model to evaluate the association between serum metabolites and skeletal muscle composition.
- Normal density (NDM) vs. low density thigh muscle area (LDM)
- Serine and Glycine were positively associated with NDM/LDM—***increasing adiposity of the muscle was associated with reduced Serine/Glycine availability***

Summary and Conclusions

- Skeletal muscle deterioration is the most prevalent phenotype observed with advancing age
- Mechanisms are multi-factorial and therapies are limited
- Nutrition and nutrient availability for the age-related muscle decline
  - Have potential benefits for attenuating the “anticipated” muscle deterioration trajectory
  - Are likely necessary for “unexpected” stressors that derail the trajectory

Summary and Conclusions

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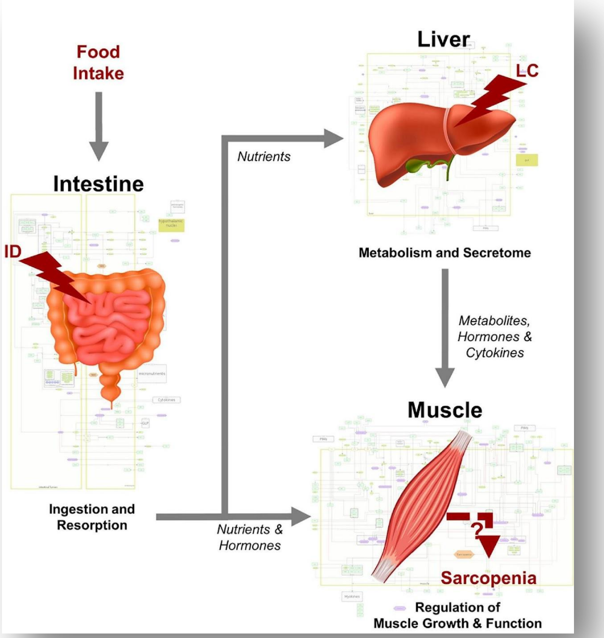
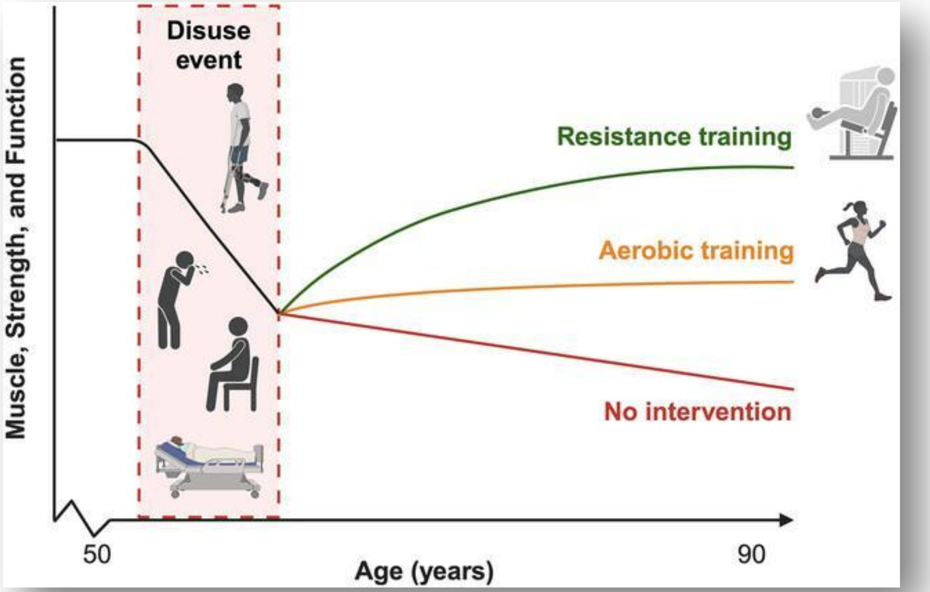
- Mechanisms are multi-factorial and therapies are limited
- Nutrition and nutrient availability for the age-related muscle decline
  - Have potential benefits for attenuating the “anticipated” muscle deterioration trajectory
  - Are likely necessary for “unexpected” stressors that derail the trajectory
- Muscle and nutrients don’t work in silos



Hoch et al. Front Nut. 2022



McKendry et al. Exp. Phys. 2024

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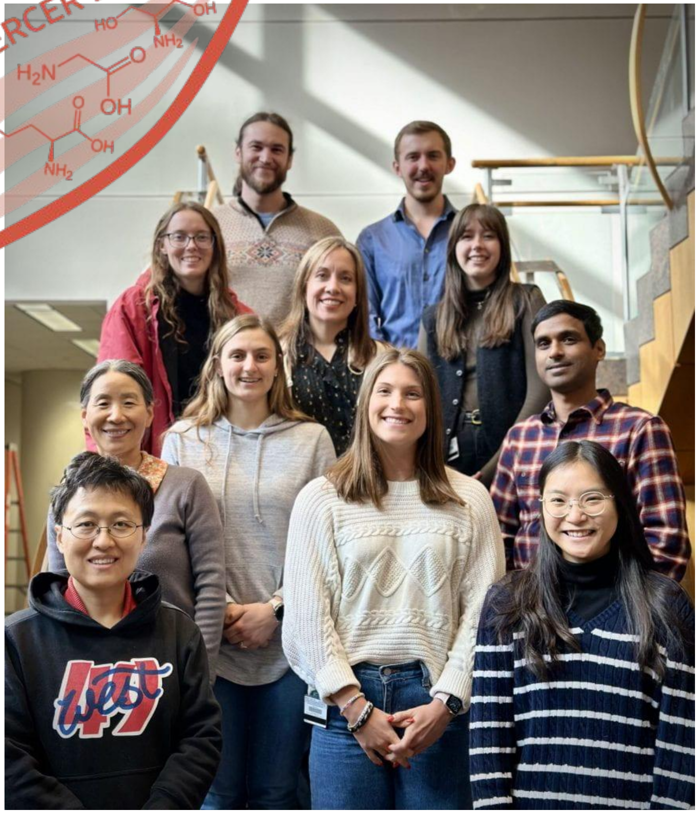
Thalacker-Mercer Research Team

Wenxia Ma, MS
Angad Yadav, PhD
Ryan Dannemiller NIH
Susan Ruby
Abigail Williamson
Lauren Odom
Shelby Rorrer
Dhanya Vadlapati

Alumni

Brandon Gheller, MS, RD, PhD CIHR IRSC
Jamie Blum, PhD NSF
Emily Riddle, RD, PhD
Dexten Retchloff
Esther Lim
Molly Gheller, MS, RD
Erica Bender, CNM, NP



Collaborators

UAB

Matthew Alexander, PhD
Merry-Lynn McDonald, PhD
James Mobley, PhD
Peter King, MD
Glenn Rowe, PhD
Thomas Buford, PhD
Adam Wende, PhD
Sufen Yang, PhD
Keith Saffold, MS, RD

IMHC

Marcas Bamman, PhD

Salk Institute

Christian Metallo, PhD
Michal Handzlik, PhD
Esther Lim, PhD

Cornell University

Ben Cosgrove, PhD
Martha Field, PhD
Hannah Fong, MS
Nathaniel Vacanti, PhD
Daniel Barry, PhD
Elena Vacanti, PhD

Texas A&M

Patrick Stover, PhD

U. Arkansas

Joanna Fiddler, PhD

Virginia Tech

Charlie Najt, PhD

Vanderbilt U.

A.J. Hinton, PhD

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