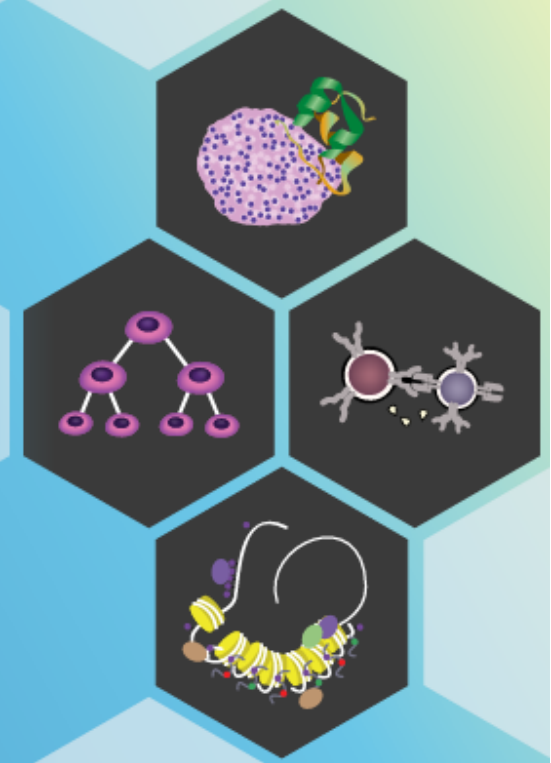
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Sarcopenia with GLP-1/Activin



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Disclosures

- Grant/Research Support from Pfizer and Novo Nordisk.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

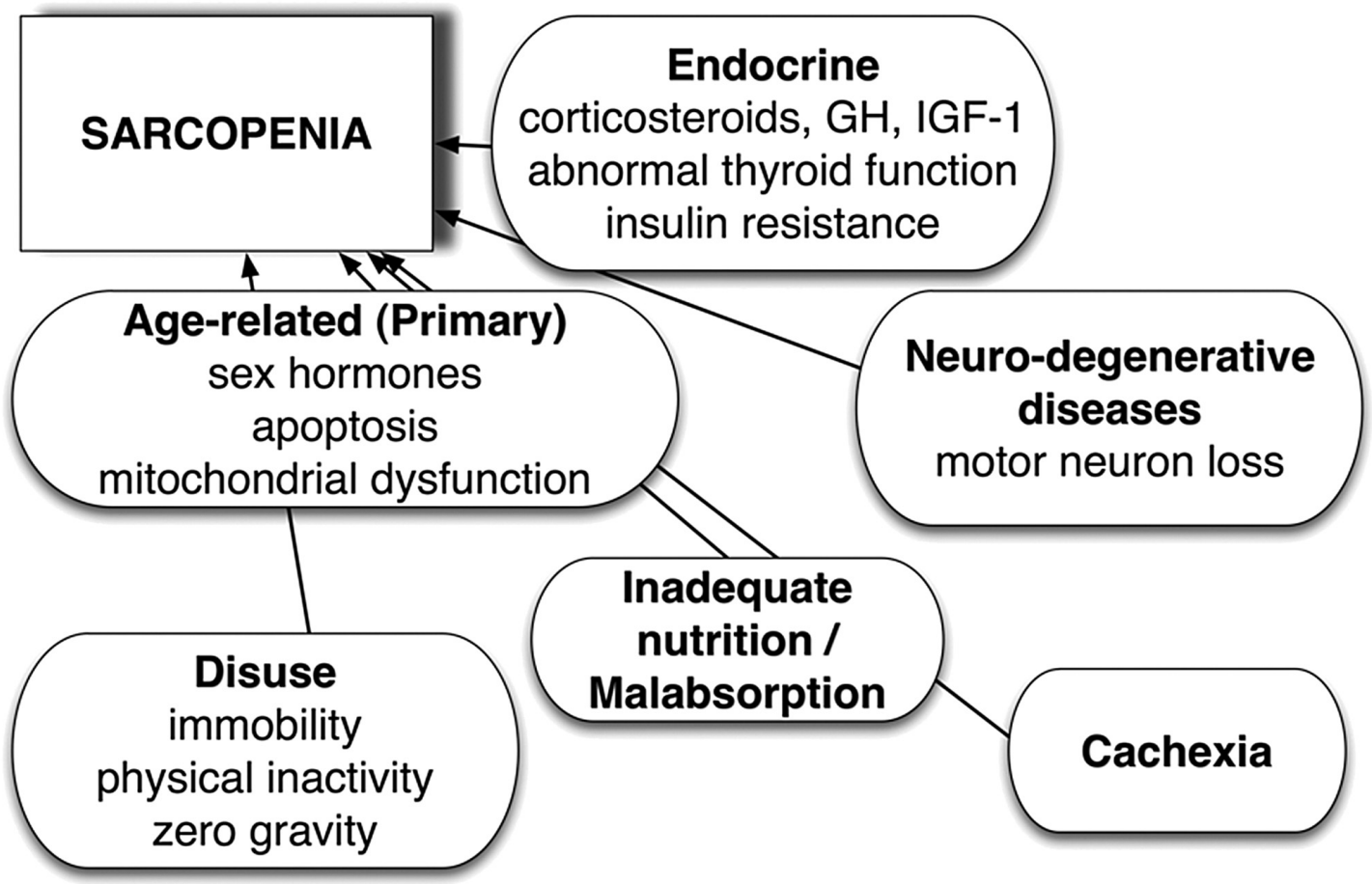
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Sarcopenia

The progressive loss of muscle mass and strength with a risk of adverse outcomes such as disability, poor quality of life and death.



Sarcopenia affects >50 million people today and will affect >200 million in the next 40 years.

Cruz-Jentoft et al., 2010

Clinical Definition of Sarcopenia

Table 1. Sarcopenia Staging Criteria[a]

Stage	Muscle Mass[b]	Muscle Strength[c]		Performance[d]
Presarcopenia	✓			
Sarcopenia	✓	✓	or	✓
Severe Sarcopenia	✓	✓		✓

Falcon, L. J. and M. O. Harris-Love (2017). "Sarcopenia and the New ICD-10-CM Code: Screening, Staging, and Diagnosis Considerations." Fed Pract **34(7): 24-32.**

Table 1. 2018 operational definition of sarcopenia

Probable sarcopenia is identified by Criterion 1.
Diagnosis is confirmed by additional documentation of Criterion 2.
If Criteria 1, 2 and 3 are all met, sarcopenia is considered severe.

(1) Low muscle strength
(2) Low muscle quantity or quality
(3) Low physical performance

	Men	Women
Grip strength (kg)	<27	<16
Appendicular skeletal muscle mass divided by height² (kg/m²)	<7	<5·5
Gait speed (m/sec)	≤0·8	≤0·8
Timed Up and Go test (sec)	≥20	≥20

Values shown are those recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2).[15]

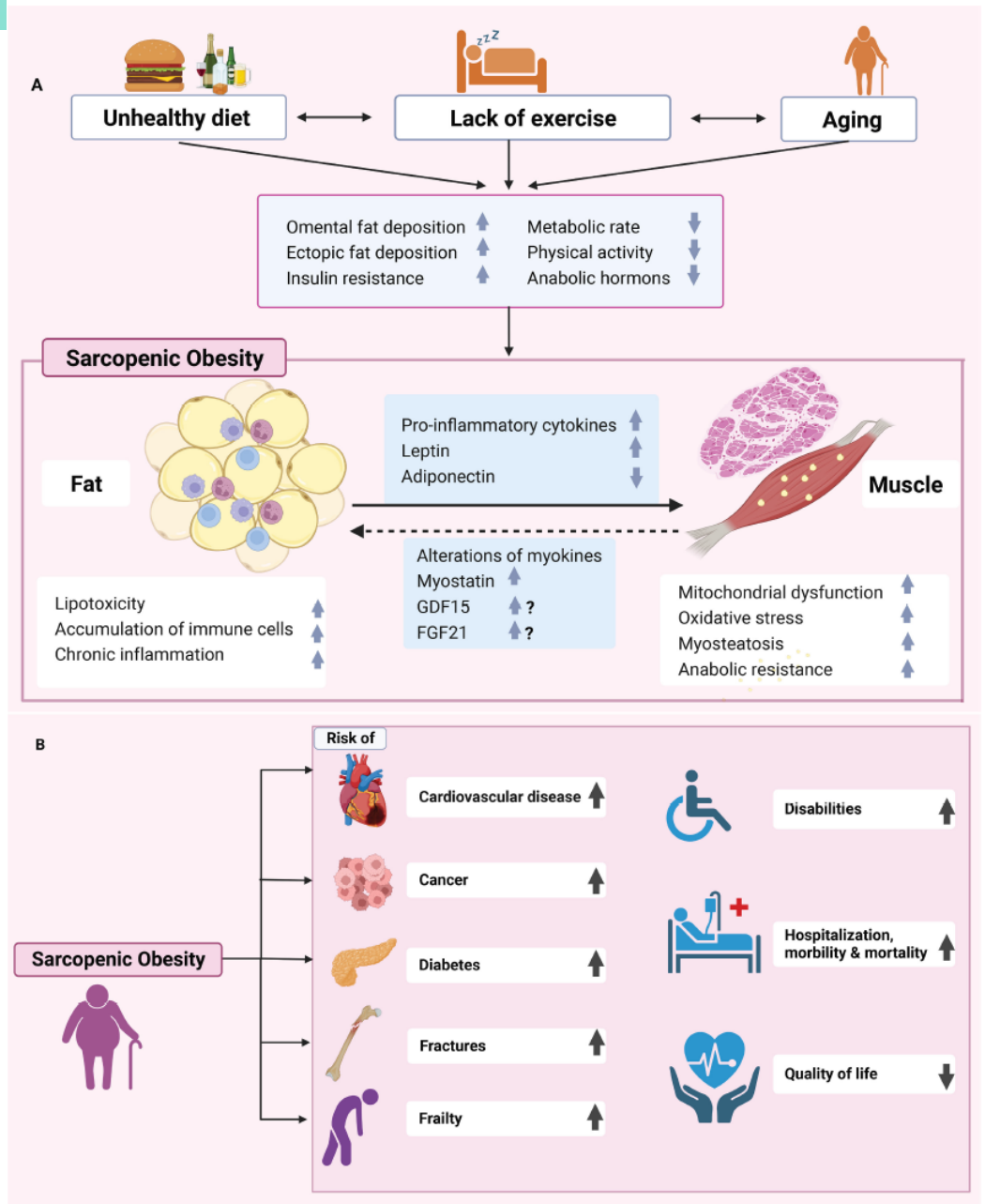
Table: **Reference values used to diagnose sarcopenia**

Cruz-Jentoft 2019

The prevalence is variable based on the methods (10-27%, mean age: 68.5 years)

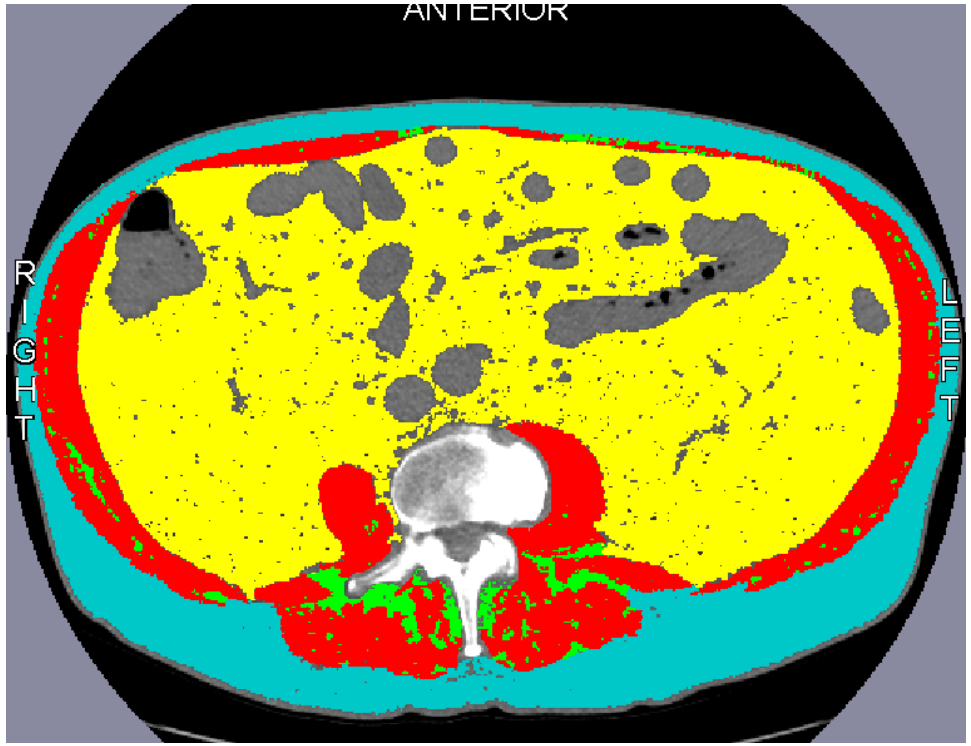
Sarcopenic Obesity

- Diagnostic criteria for sarcopenic obesity are yet to be established but prevalence of sarcopenic obesity is ~11% in those >60 yo
- Obese elderly individuals, have decreased muscle performance despite having increased muscle mass
- Potential mechanisms include IR, inflammation, myosteatosis, oxidative stress, hormonal changes and mitochondrial dysfunction, among others.
- Treatments for sarcopenic obesity are insufficient and limited to lifestyle modifications

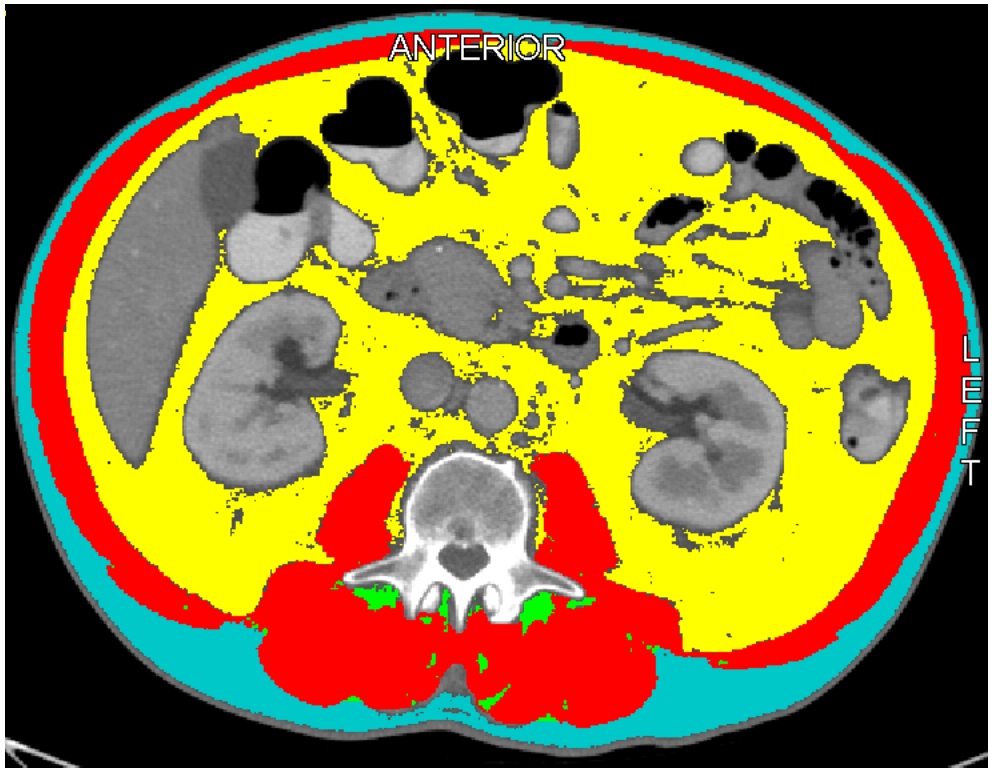


Wei et al. Frontiers in Endoc, 2023

Sarcopenic Obesity



Normal Muscle Mass

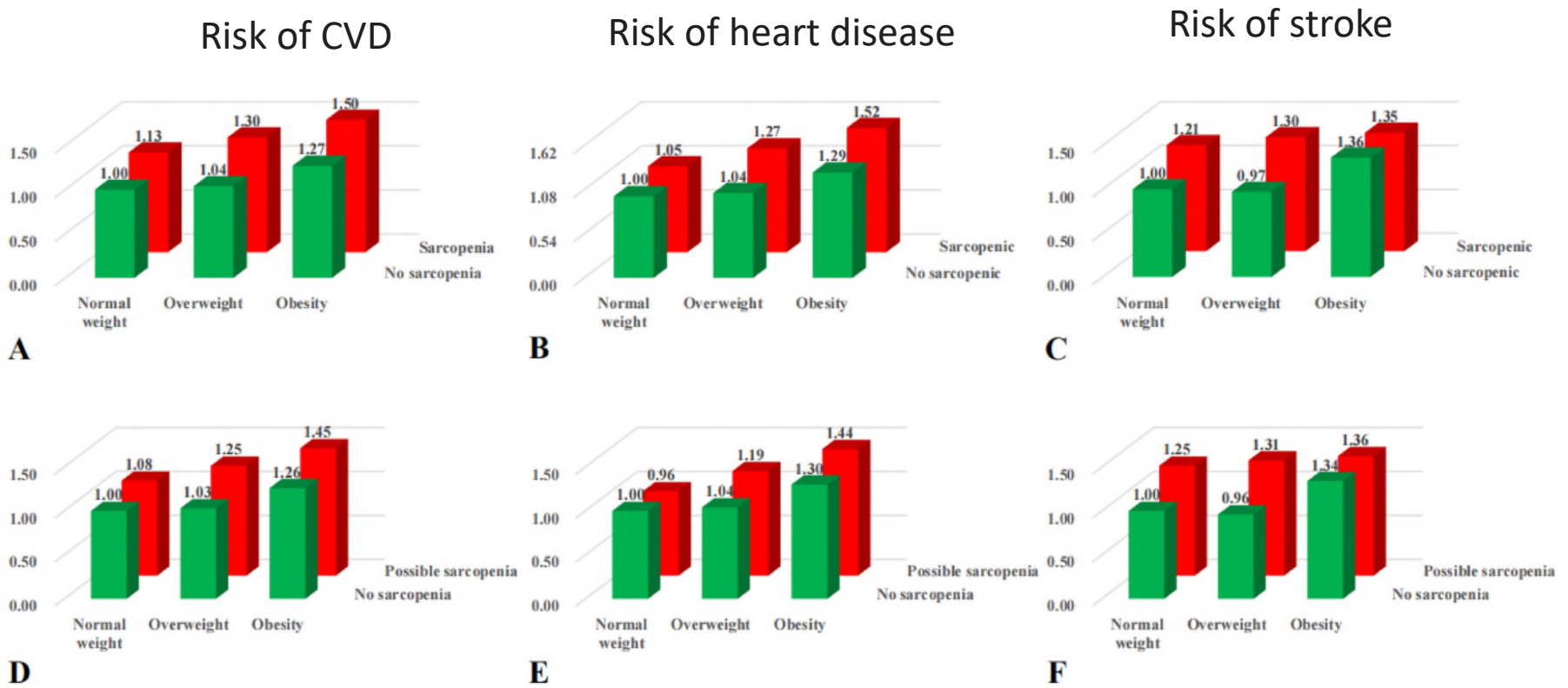


ID	Weight (kg)	BMI	Muscle Area (cm^2)	Sk. Muscle Index	Intramuscular Fat Area	Visceral Fat Area	Subcutaneous Fat Area
34	95.5	30.3	135.9	43.0 (low)	17.71	402.8	159.4
76	96.0	28.8	178.4	53.3	4.86	318.9	87.49

Sarcopenic Obesity Increases the Risk of CVD more than Sarcopenia and Obesity Alone

Sarcopenic obesity participants

Possibly sarcopenic obesity participants



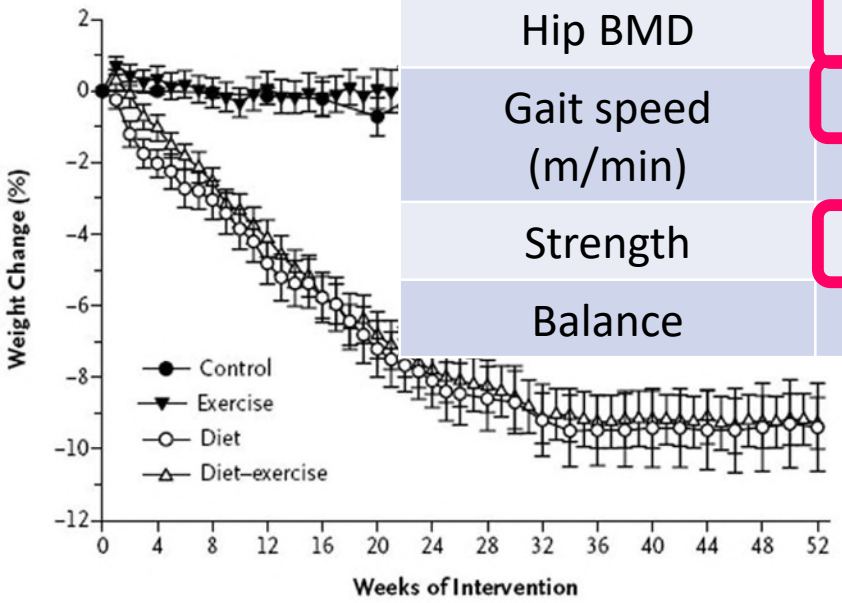
Jiang et al., Clinical Nutrition, 2024

Obesity Treatment in Older Patients and Sarcopenia Outcome

- Energy restriction with a hypocaloric diet results in the loss of approximately one-quarter of lean mass per unit weight, which could worsen sarcopenia and osteopenia
- Calorie restriction without resistance training leads to the loss of muscle mass and loss of handgrip strength of up to 4.6% and 1.7 kg, respectively

Obesity Treatment in the Elderly

	Control	Diet	Exercise	Both
Body weight (Kg)	-0.1	-9.7	-0.5	-8.6
Muscle mass(cm^3)	-7	-81	30	-28
Fat mass (Kg)	1.2	-7.1	-1.8	-6.3
Hip BMD	-7	-27	13	-11
Gait speed (m/min)	1.1	4.7	8.2	16.9
Strength	-6	1	174	164
Balance	-2.3	4.7	3.4	7.9



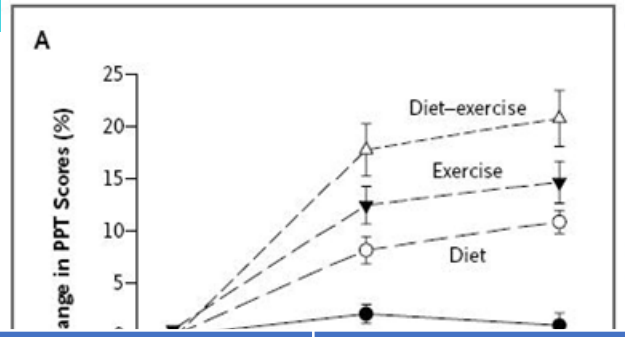


Table 2. Effect of Diet, Exercise, or Both on Primary and Secondary Outcome Variables in Obese Older Adults.*

Outcome Variable	Control (N=27)	Diet (N=26)	Exercise (N=26)	Diet–Exercise (N=28)	P Value†				
					Interaction between Group and Time	Diet vs. Control	Exercise vs. Control	Diet–Exercise vs. Diet	Diet–Exercise vs. Exercise
Primary outcome									
PPT score†									
Baseline	26.8±4.5	28.6±1.9	27.1±3.1	28.0±2.9					
Change at 6 mo	0.6±1.7	2.3±1.8‡	3.4±2.4‡	4.7±2.4‡					
Change at 1 yr	0.2±1.8	3.1±1.4‡	4.0±2.5‡	5.4±2.4‡	<0.001	<0.001	<0.001	<0.001	0.04
Secondary outcomes									
Other frailty measures									
VO_{2peak} (ml/kg/min)									
Baseline	16.3±3.8	17.6±2.2	17.4±3.5	17.3±3.5					
							<0.001	0.01	0.002
							0.005	0.04	0.19
							0.71	0.67	<0.001
							<0.001	0.04	<0.001
							0.004	0.57	<0.001
							0.045	<0.001	<0.001
							0.19	0.44	0.02
							0.001	0.005	<0.001
Total 1RM (lb)‖									
Baseline	505±143	607±213	519±187	539±218					
Change at 6 mo	−16±78	8±60	110±138§	96±108§					
Change at 1 yr	−6±101	1±85	174±166‡	164±124‡	<0.001	0.90	<0.001	<0.001	0.32
Obstacle course (sec)									
Baseline	11.6±3.3	11.0±2.2	10.9±3.3	10.7±3.3					
Change at 6 mo	−0.1±1.2	−0.7±1.3	−1.6 ±1.6‡	−1.1±2.2					
Change at 1 yr	0.0±1.0	−1.1±1.1	−1.5±1.4‡	−1.7±2.2‡	0.002	0.03	0.004	0.18	0.68
One-leg stance (sec)									
Baseline	10.7±10.6	11.7±8.7	13.4±10.4	10.5±9.5					
Change at 6 mo	−2.4±8.2	0.8±6.1	1.4±7.7	6.3±7.6‡					
Change at 1 yr	−2.3±9.4	4.7±5.0‡	3.4±5.9¶	7.9±7.8‡	<0.001	0.001	0.02	0.18	0.04
Gait speed (m/min)									
Baseline	75.5±17.6	87.5±15.8	76.0±18.3	72.9±14.9					
Change at 6 mo	−3.0±10.5	1.7±5.4	7.6±14.8§	5.5±7.6§					
Change at 1 yr	1.1±11.0	4.7±5.2	8.2±15.5§	16.9±42.3§	0.02	0.45	0.003	0.04	0.39

* Plus–minus values are means ±SD. Scores on the modified Physical Performance Test (PPT, the primary outcome) range from 0 to 36, with higher scores indicating better physical

Villareal et al. N Engl J Med. 2011

Clinical Endpoints

Clinical (Direct) Endpoints

- Measures of how a patient feels (i.e. fatigue, quality of life), or functions (i.e. mobility, activities of daily living), or survives
  - Patient Reported Outcome (PRO) measures must be validated
- Decrease the chances of developing a condition or disease complication that is itself apparent to the patient and is undesirable (hospitalization, tolerance to treatment)

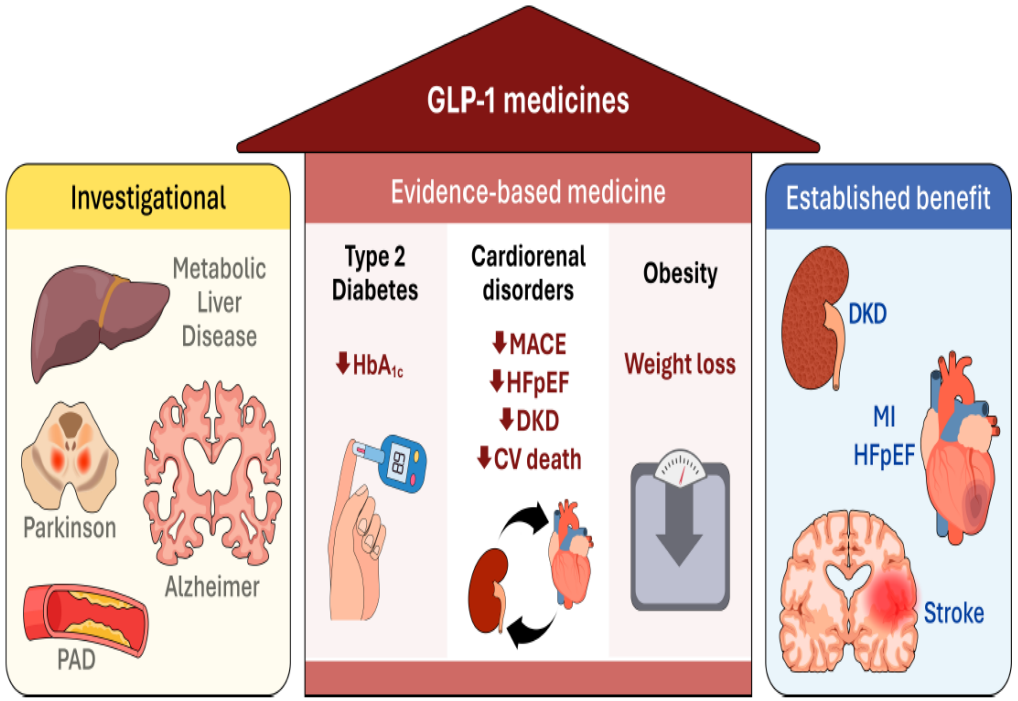
Surrogate endpoints

- Biomarkers: a validated outcome that is not a direct measurement of clinical benefit but predicts clinical benefit

Endpoints should be assessed in the target population and the magnitude of effect must be large enough to be **clinically meaningful**

GLP-1R Agonists

- Activation of GLP-1R have well-established benefits on a range of metabolic and cardiovascular outcomes
- GLP-1 may directly enhance skeletal muscle by improving microvascular recruitment, glucose uptake, inflammation and mitochondrial biogenesis via AMPK
- A hypocaloric diet results in the loss of one-quarter of lean mass/unit weight, which could worsen sarcopenia and osteopenia
- Calorie restriction without resistance training leads to the loss of muscle mass and handgrip strength of up to 4.6% and 1.7 kg, respectively



Drucker D. Diabetes Care 2024

GLP-1R Agonists

- Body composition in people with T2DM treated with GLP-1RA have not revealed consistent evidence for disproportionate loss of lean mass or impaired muscle strength
- Semaglutide and/or tirzepatide decrease FM and LBM (FM>LBM) whereas PROs (exercise capacity, QOL) are stable or improved

End Point	Semaglutide (N=1306)	Placebo (N=655)	Difference between Semaglutide and Placebo (95% CI)†	Odds Ratio	P Value
Coprimary end points assessed in the overall population					
Percent body-weight change from baseline to wk 68	−14.85	−2.41	−12.44 (−13.37 to −11.51)		<0.001
Participants with body-weight reduction ≥5% at wk 68 — %‡	86.4	31.5		11.2 (8.9 to 14.2)	<0.001
Confirmatory secondary end points assessed in the overall population					
Participants with body-weight reduction ≥10% at wk 68 — %‡	69.1	12.0		14.7 (11.1 to 19.4)	<0.001
Participants with body-weight reduction ≥15% at wk 68 — %‡	50.5	4.9		19.3 (12.9 to 28.8)	<0.001
Change from baseline to wk 68					
Waist circumference — cm	−13.54	−4.13	−9.42 (−10.30 to −8.53)		<0.001
Systolic blood pressure — mm Hg	−6.16	−1.06	−5.10 (−6.34 to −3.87)		<0.001
SF-36 physical functioning score	2.21	0.41	1.80 (1.18 to 2.42)		<0.001
IWQOL-Lite-CT physical function score	14.67	5.25	9.43 (7.50 to 11.35)		<0.001

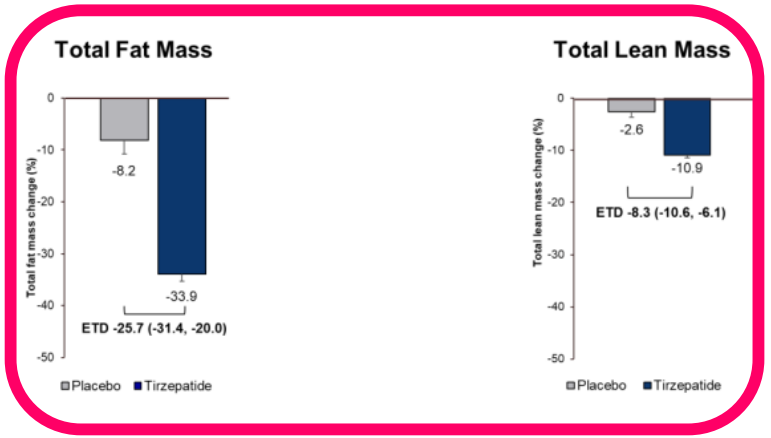
	N=95	N=45	
Body composition change from baseline to week 68 (DEXA)			
Total fat mass			
Kg change	−10.40	−1.17	ETD: −9.23 [−12.72; −5.74]
Percentage-points change in total fat mass proportion§	−4.19	−0.19	ETD: −4.00 [−6.27; −1.73]
Regional visceral fat mass¶			
Kg change	−0.47	−0.03	ETD: −0.45 [−0.60; −0.30]
Percentage-points change in regional visceral fat mass proportion‖	−2.65	0.58	ETD: −3.23 [−5.35; −1.10]
Total lean body mass			
Kg change	−6.92	−1.48	ETD: −5.44 [−7.07; −3.81]
Percentage-points change in total lean body mass proportion§	3.61	0.11	ETD: 3.50 [1.35; 5.64]

Wilding et al. N Engl J Med 2021

GLP-1R Agonists

Table 3. Key Secondary and Additional Secondary End Points for Pooled Tirzepatide Dose Groups (Treatment-Regimen Estimand).*

End Points	Pooled Tirzepatide Groups†	Placebo (N=643)	Estimated Treatment Difference from Placebo (95% CI)
	least-squares mean (95% CI)		
Key secondary end points‡			
Change from baseline to week 20 in body weight — kg§	−12.8 (−13.1 to −12.5)	−2.7 (−3.2 to −2.2)	−10.1 (−10.7 to −9.6)
Change in measure			
SF-36 physical function score§¶	3.6 (3.2 to 4.0)	1.7 (0.8 to 2.6)	1.9 (1.0 to 2. 9)



Jastreboff et al. N Engl J Med 2022

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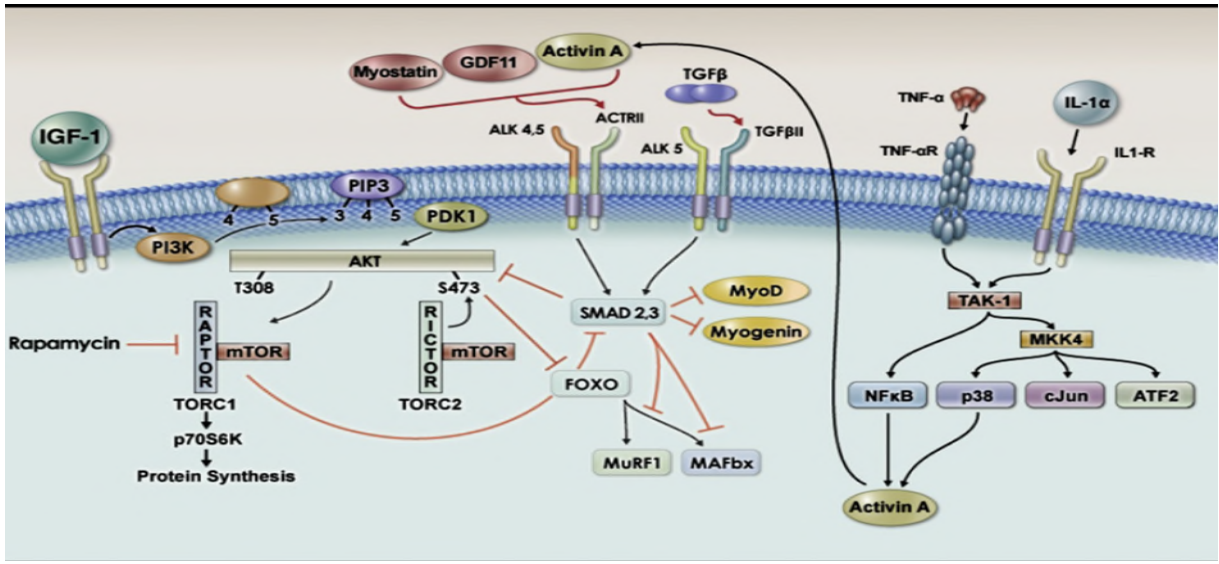
Wilding et al. N Engl J Med 2021

Activin and Muscle Health

- Myostatin and activin A are members of the (TGF-β) family that negatively regulate muscle growth by binding to the activin type II receptors (ActRIIA and ActRIIB) on myocytes
- By activating Smad2/3, they lead to protein degradation and inhibit protein synthesis, inhibit satellite cell activation and promote the ubiquitin-proteasome system and autophagy
- Pharmacological inhibitors could target muscle mass and strength, improve insulin sensitivity, reduce adiposity, and attenuate systemic inflammation

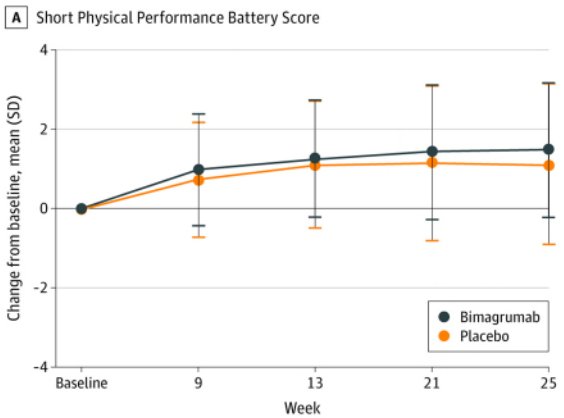


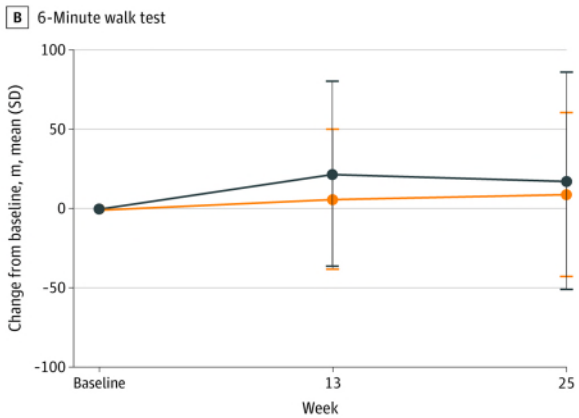
Fearon et al. Cell Metab 2012

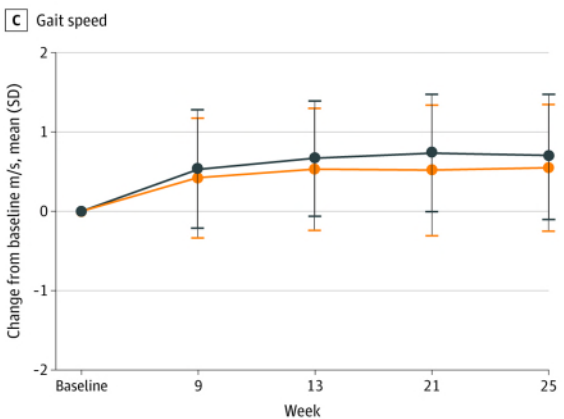
Activin Receptor Antagonists

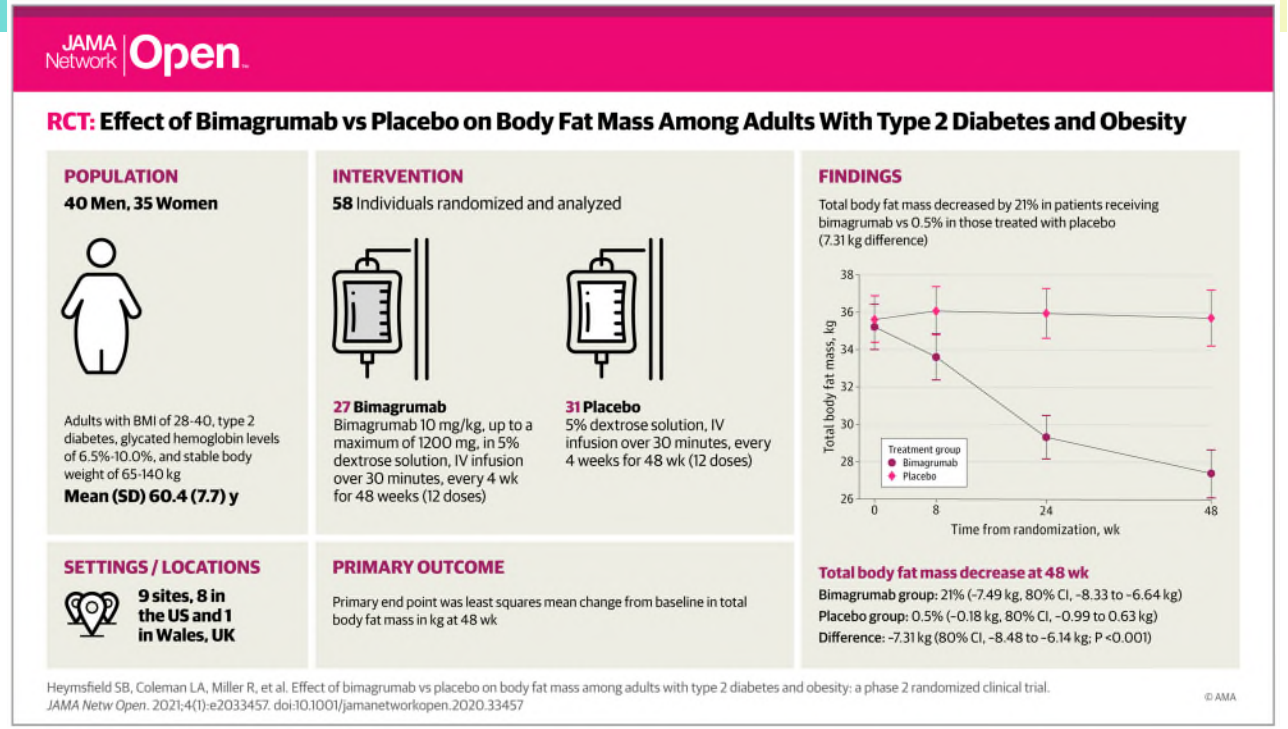
- Three mechanisms of action have been shown to increase LBM: 1) antiligand (primarily to myostatin), 2) a soluble ActRIIB, and 3) a receptor antagonist
- Muscle hypertrophy is enhanced by the blockade of ActRIIA and ActRIIB achieved with bimagrumab, with muscle mass increasing approximately 2-fold that seen with myostatin inhibition alone
- Bimagrumab is an antagonist that improves LBM but not function when given to sarcopenic older individuals with adequate nutritional support, vit. D and light exercise
- In diabetics with a BMI >25, bimagrumab decreased FM (~20%) without impacting Lean Mass or grip strentgh

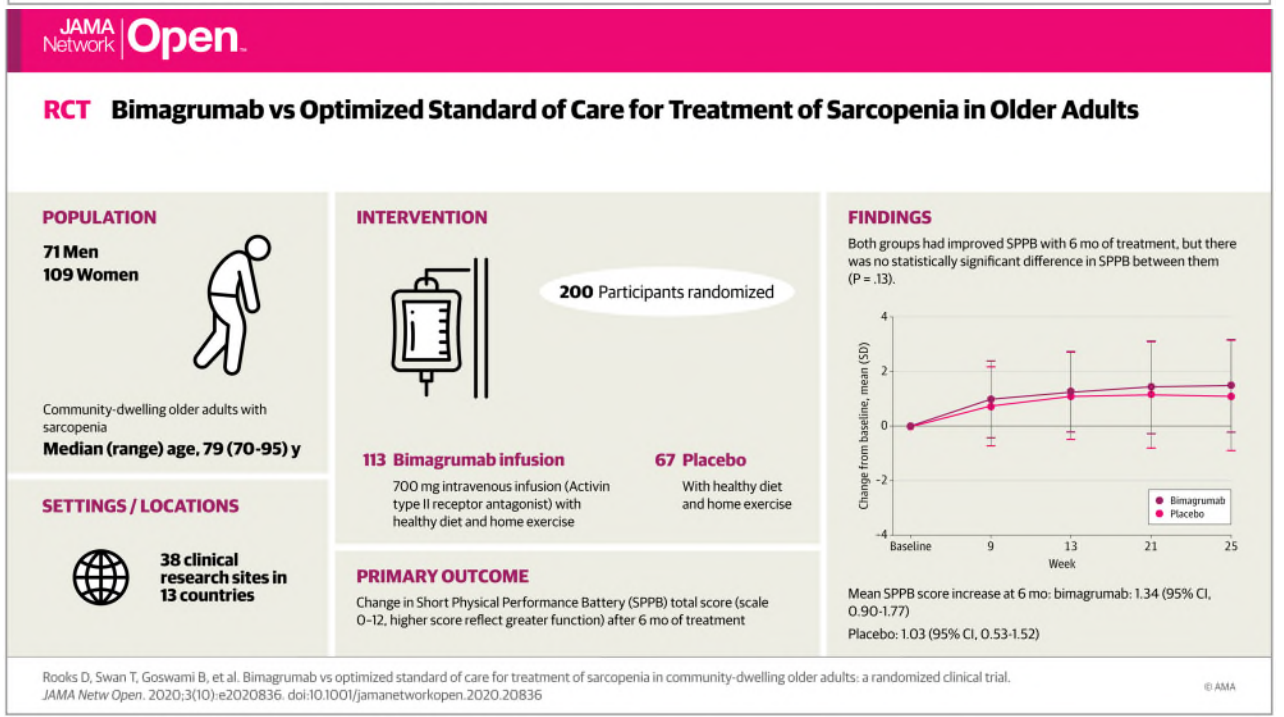
Activin Receptor Antagonists







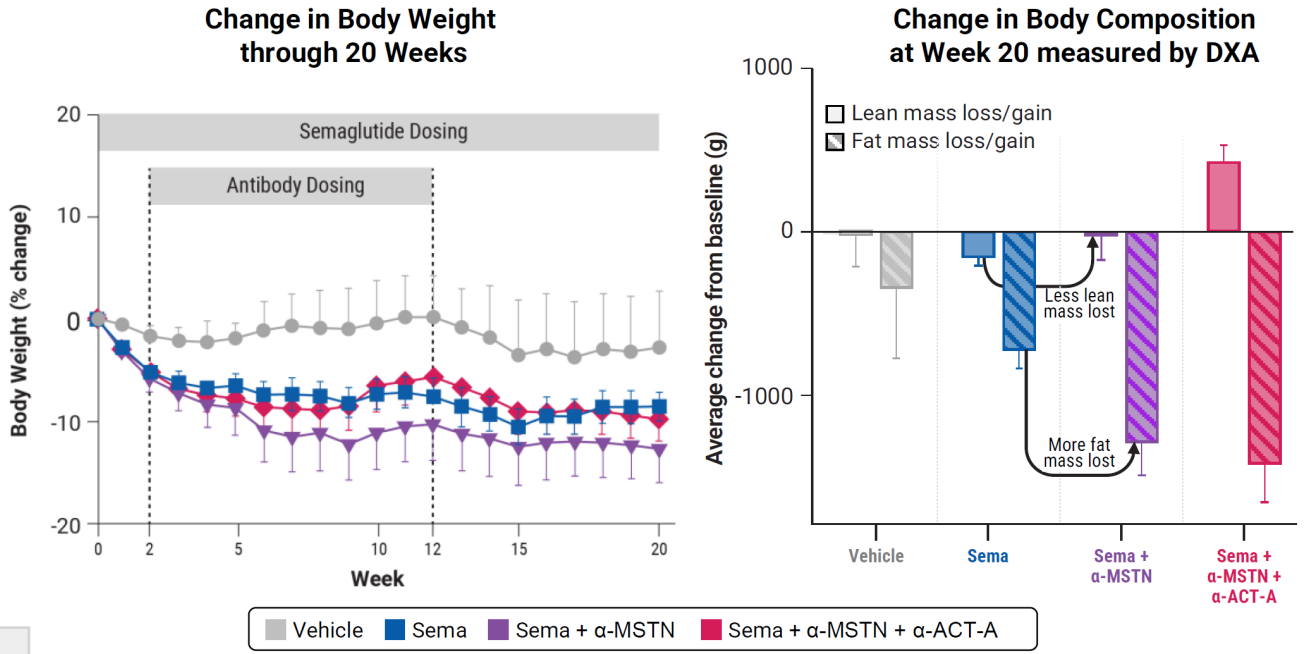




Future Directions

- Combination therapies
  - Tremogrumab/Garetosmab (myostatin/activin A MABs)+semaglutide (NCT06299098)
  - Bimagrumab and Semaglutide (NCT05616013)

Adding myostatin blockade to semaglutide leads to greater fat loss and less lean mass loss compared to semaglutide monotherapy in obese non-human primates[2]



Sponsor	Drug	Target	Details
University of Texas Health Science Center at San Antonio	Metformin	AMPK activator	Phase 2; NCT02570672
Biophytis	Ruvembri (BIO101)	MAS receptor agonist	Phase 2b
BioAge	Azelaprag (BGE-105) + Mounjaro	Apelin receptor agonist + GLP-1/GIP receptor agonist	Phase 2
Biohaven	Taldefgrobep alfa	Myostatin inhibitor	Phase 3 for spinal muscular atrophy
Immunis	IMMUNA	Non-cell-based secretome product	Phase 1/2a; NCT05211986
Juvena	JUV-161	Non-cell-based secretome product	IND-enabling
MyMD	MYMD-1	TNF inhibitor	Phase 2

GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; IND, Investigational New Drug; TNF, tumor necrosis factor. Source: company websites, Clinicaltrials.gov.

Mastaitits J et al, ADA 2023
https://investor.regeneron.com/
Nat Biotechnology, 2024

Mouse sarcopenia model reveals sex- and age-specific differences in phenotypic and molecular characteristics

Haiming L. Kerr,[1,2] Kora Krumm,[1,2] Barbara Anderson,[1,2] Anthony Christiani,[1,2] Lena Strait,[1,2] Theresa Li,[1,2] Brynn Irwin,[1,2] Siyi Jiang,[1,2] Artur Rybachok,[1,2] Amanda Chen,[1,2] Elizabeth Dacek,[1,2] Lucas Caeiro,[1,2] Gennifer E. Merrihew,[3] James W. MacDonald,[4] Theo K. Bammler,[4] Michael J. MacCoss,[3] and Jose M. Garcia[1,2]

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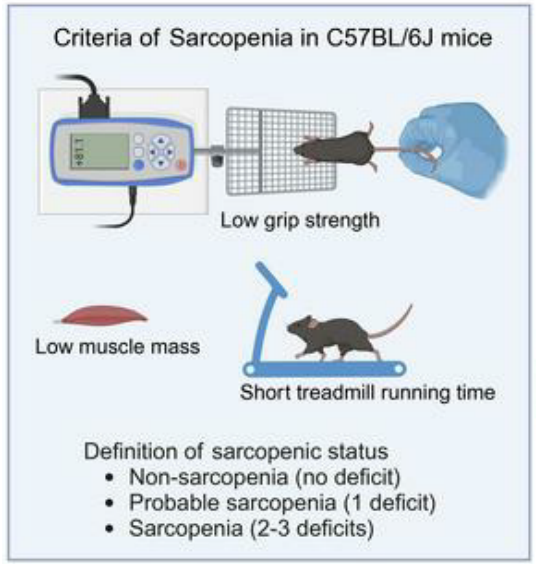
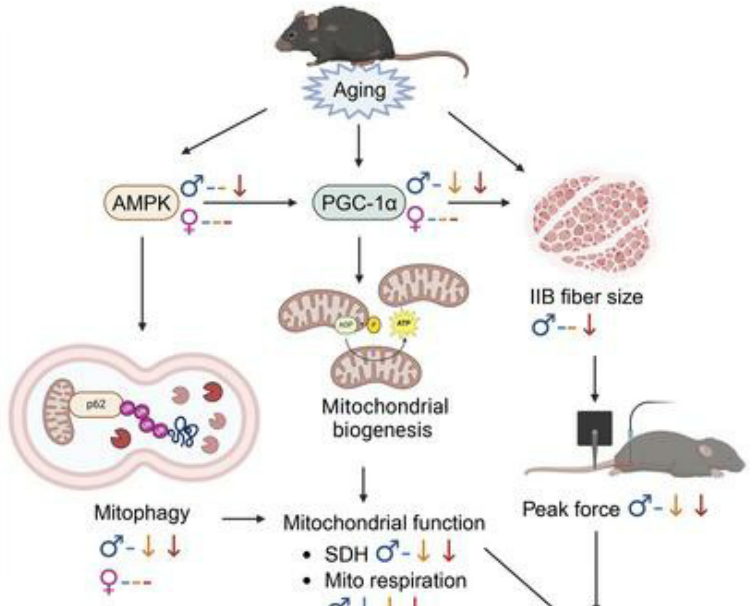
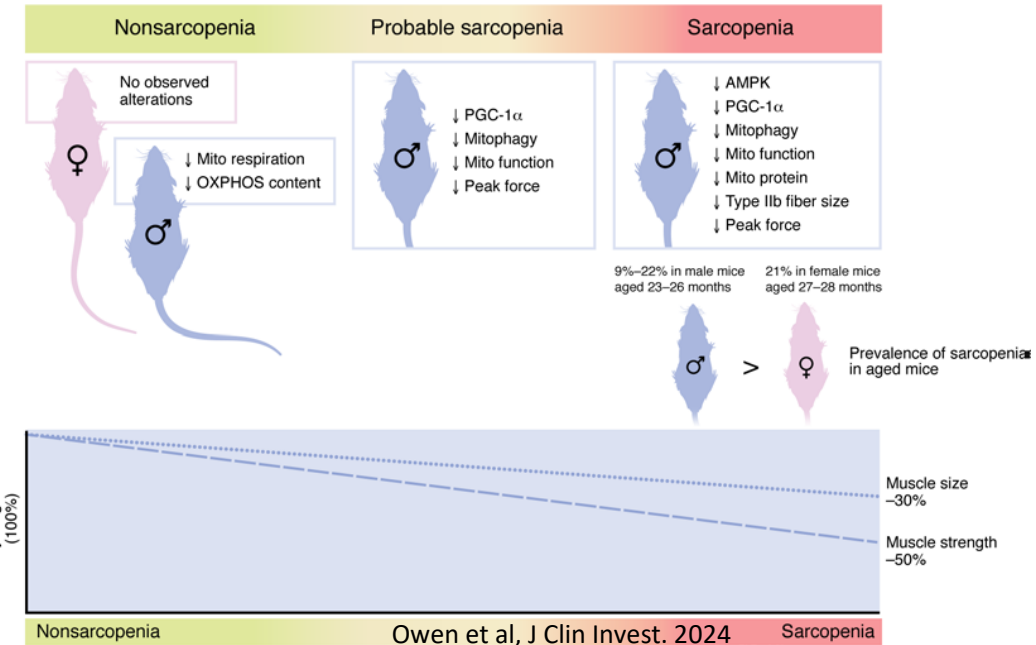
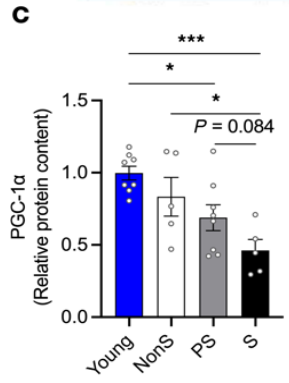
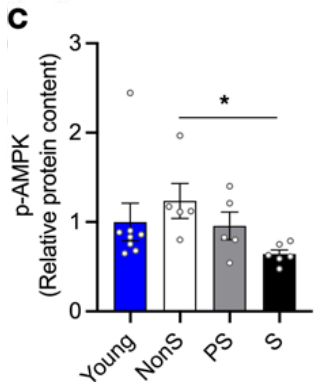
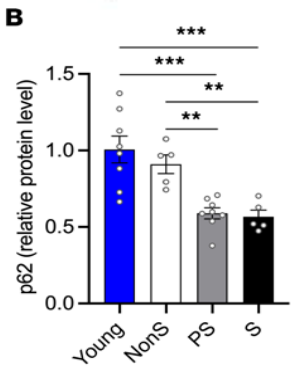


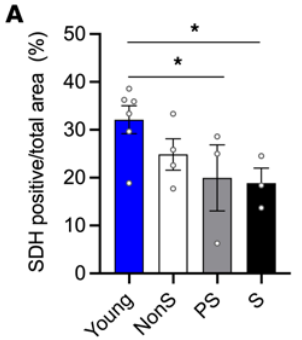


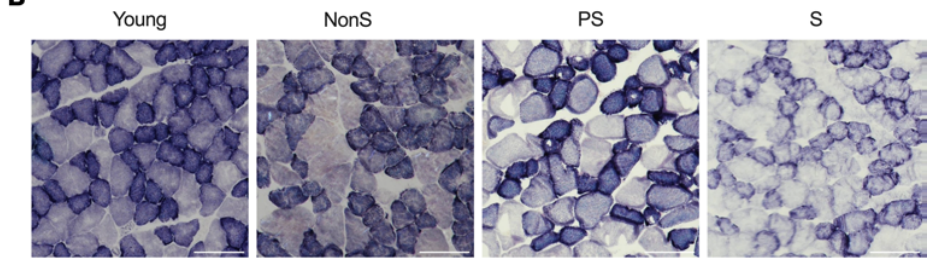












Muscle Mass, Function and QOL in Prostate Cancer patients

- Baseline ALM is directly associated with strength but inversely associated with endurance and PROs
- Cachexia and frailty are prevalent in this population
- For frail individuals, weight loss is the most prevalent component of the syndrome

				Muscle Endurance				Muscle Strength		FACT-P				EORTC QLQ C-30						
	BW	ALM	Fat mass	VO_2 Peak	6MWT	Steps/d	TotACT /d	SCP	Mean HGS	PWB	FWB	ADD	Total	QOL	PF	RF	SF	Fatigue	Pain	Dyspnea
BW		.78**	.88**	-.37**					.30*	-.37**		-.29*			-.34**	-.30*	-.37**	.31*		.33*
ALM			.48**					.34*	.36**	-.42**		-.28*			-.26*	-.27*	-.44**	.33*		.36**
Fat Mass				-.39**												-.27*				
VO_2 Peak					.69**	.43**	.50**	.38**	.31*	.42**	.29*	.36**	.28*	.44**	.57**	.43**	.43**	-.38**	-.40**	-.39**
6MWT						.42**	.53**	.59**	.38**	.47**	.26*	.36**	.26*	.43**	.66**	.47**	.42**	-.48**	-.40**	-.47**
Steps/d							.91**			.38**		.33*	.30*		.51**	.38**	.30*	-.45**	-.42**	-.28*
Tot ACT/d								.40**	.30*	.37**		.35**	.29*		.54**	.38**		-.43**	-.39**	-.29*
SCP									.53**						.36**					
Mean HGS																				
State 3u[A]															.32*					
Maximum ATP[B]	-.51**	-.41*	-.53**	.57**	.57**		.39*		-.37*	.44*				.42*	.42*	.54**	.42*	-.41*		
Muscle Size[B]								.42*	.59**											
Muscle Strength[B]								.40*												
Muscle Endurance[B]								.44*										-.40*		

Spearman's rho correlation

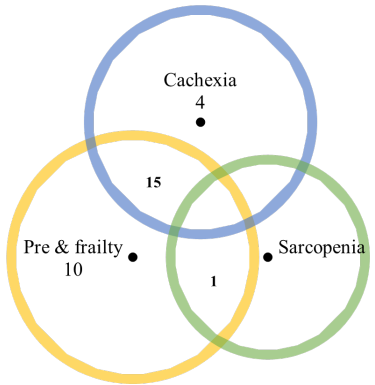
-1 -.5 0 .5 1

Table 2

N (%)	*N=59*
Age (yrs.)[1]	69.3 (6.9)
Body Weight (kg)[1]	87.2 (16.0)
Body Mass Index (kg/m²)[1]	27.8 (4.1)
Tumor stage	
2	16 (27.1)
3	24 (40.7)
4	19 (32.2)

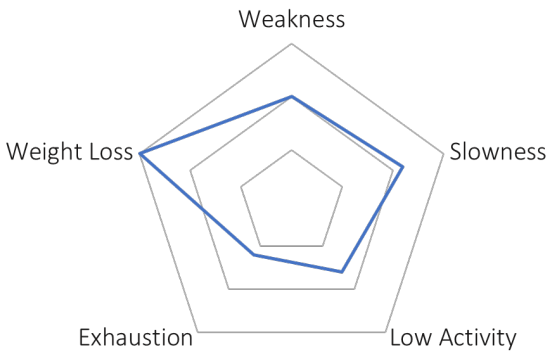
Mean (SD)	
Body Composition (DEXA)	*N=59*
Total Mass (kg)	87.5 (16.0)
Total Fat (kg)	25.9 (8.5)
Fat Percent (%)	29.0 (5.4)
Lean Mass (kg)	58.9 (9.0)
ALM (kg)	25.2 (4.0)
ASMI (kg/m²)	8.0 (1.0)

Baseline Prostate Cancer Patients Assessment
N=59



N=28

Frequency of Components by Phenotype Characteristic



Final Thoughts

- Lean mass ≠ muscle mass
- Muscle mass ≠ muscle function
- Muscle function is a multidimensional construct
  - Subjective (PROs for Physical function, fatigue)
  - Objective (Strength and power [HGS, SCP], endurance [6MWT, VO_2 Peak], balance)
- More clinical trials are needed to establish the effects of GLP-1- and activin-related therapies to determine their impact on sarcopenia-related clinically meaningful outcomes and indications

U.S. Department of VA(BX002807), DOD (PC170059), and NIH (R01CA239208, R01AG061558)

Paradigms of Frailty

- Increased vulnerability to stressors and adverse outcomes seen often late in life
  - Frailty as accumulation of deficits: “the more things that are wrong, the more likely that person is frail” (Rockwood 2007)
  - Frailty as a biologic syndrome of decreased reserve resulting from cumulative declines across multiple physiologic systems (Fried et al. 2001)

Physical Frailty Phenotype (PFP)

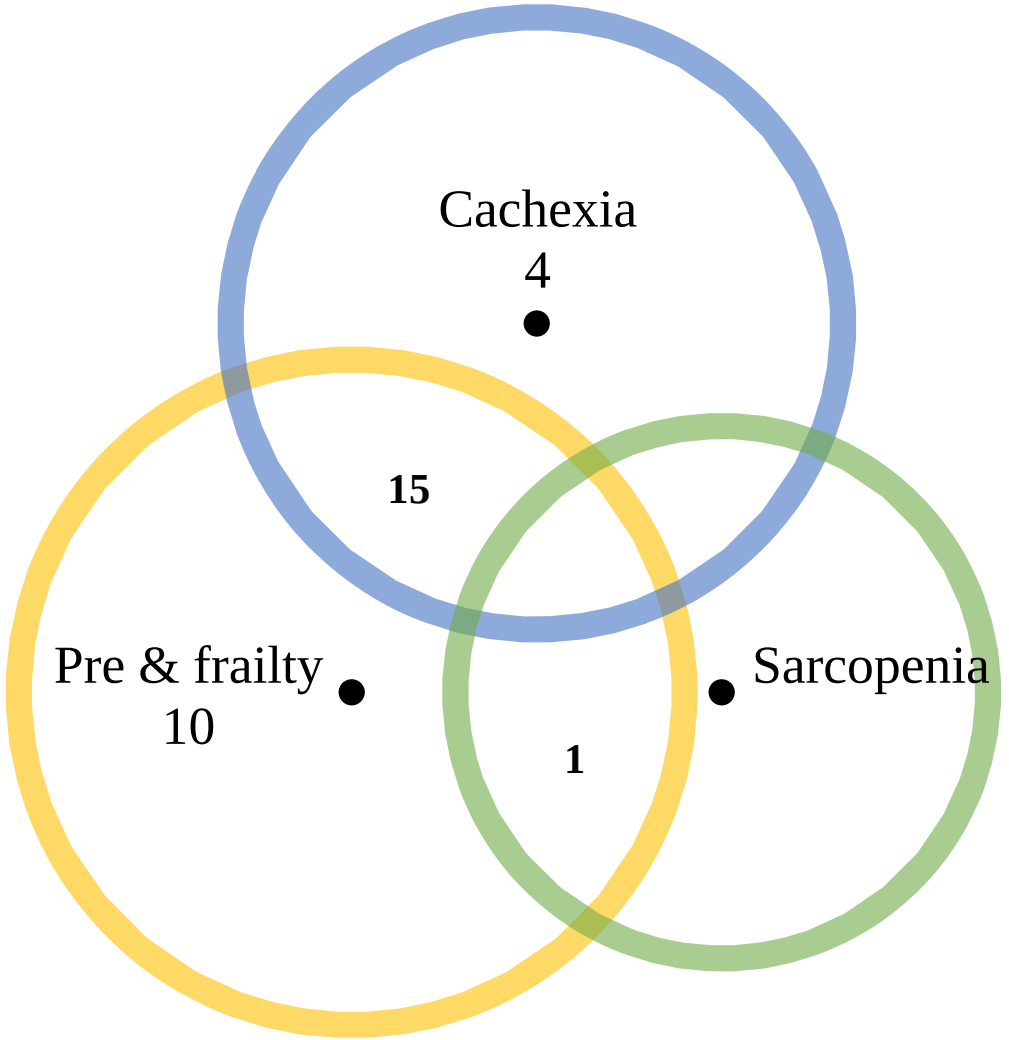
- Weight loss (more than 10 lbs or 5% over the previous year)
- Weakness (grip strength lowest 20% by gender, BMI)
- Exhaustion (self-report)
- Walking Speed (>6-7s to walk 15 feet)
- Physical Activity (<383♂ or 270♀ Kcals/week)
  - Not Frail: 0
  - Intermediate: 1-2
  - Frail: ≥3

Fried et al., Frailty in older adults: evidence for a phenotype, *J Gerontol A Biol Sci Med Sci,* 2001.

Table 1
46 deficits included in frailty index.

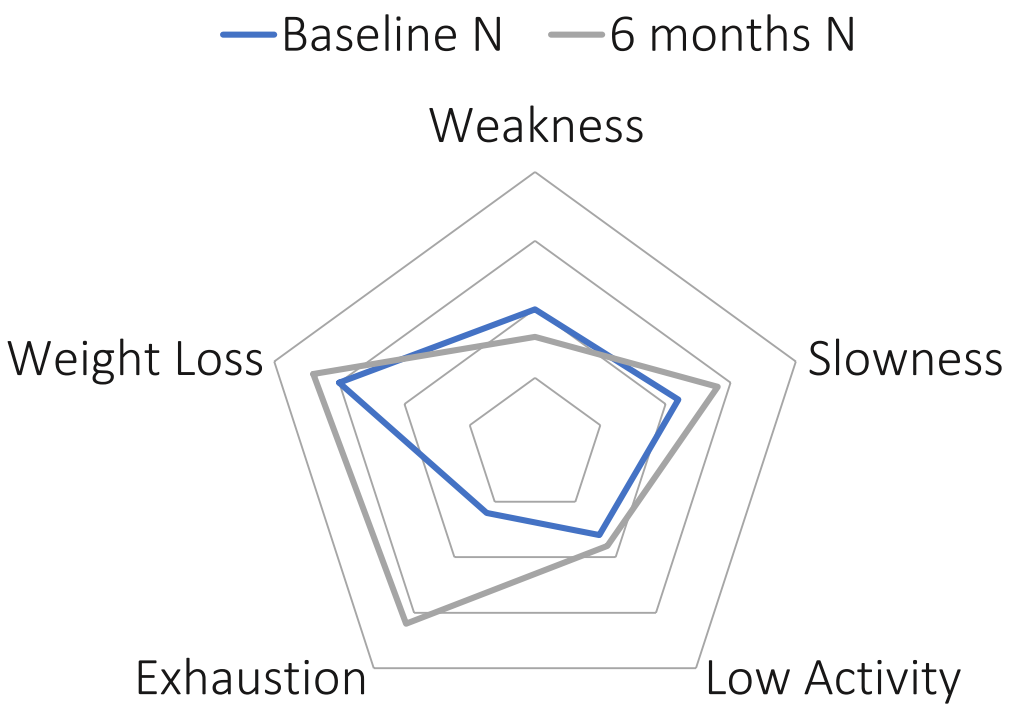
Comorbidities	*Signs/symptoms*
• Stroke	• Heart rate at rest
• Thyroid condition	• Systolic blood pressure
• Cancer	• Cough regularly
• Heart attack	• Leaked/lost control or urine
• Heart disease	• General vision
• Ever had high blood pressure	• Difficulty seeing steps/curbs in dim light
• Angina/angina pectoris	• General hearing
• Osteoporosis	• Confusion or inability to remember things
• Diabetes	
• Arthritis	*Lab values*
• Ever had broken hip	• Homocysteine (μmol/L)
	• Folatc, scrum (nmol/L)
• Cataract operation	• Glycohemoglobin (%)
• Weak/failing kidneys	• Red blood cell count (million cells/μL)
	• Hemoglobin (g/dL)
Function	• Red cell distribution width (%)
• Difficulty using fork and knife	• Lymphocyte percent (%)
• Difficulty dressing yourself	• Segmented neutrophils percent (%)
• Difficulty getting in/but of bed	
• Difficulty standing up from armless chair	*Other*
• Difficulty managing money	• Medications
• Difficulty preparing meals	• Self-reported health
• Difficulty standing for long periods of time	• Health compared to 1 year ago
• Difficult stooping, crouching, kneeling	• Frequency of healthcare use
• Difficulty grasping/holding small objects	• Overnight hospital stays
• Difficulty lifting or carrying	
• Difficulty pushing or pulling large objects	
• Difficult attending social event	

Baseline Prostate Cancer Patients Assessment
N=59

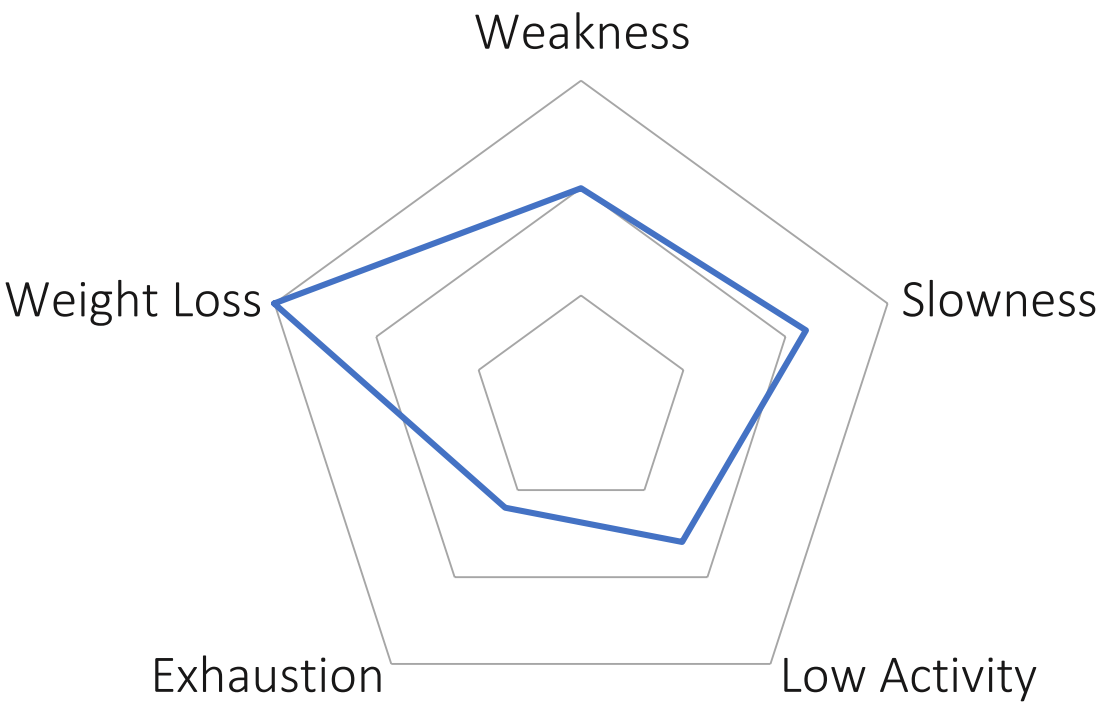


N=28

Frequency of Components by Phenotype Characteristic



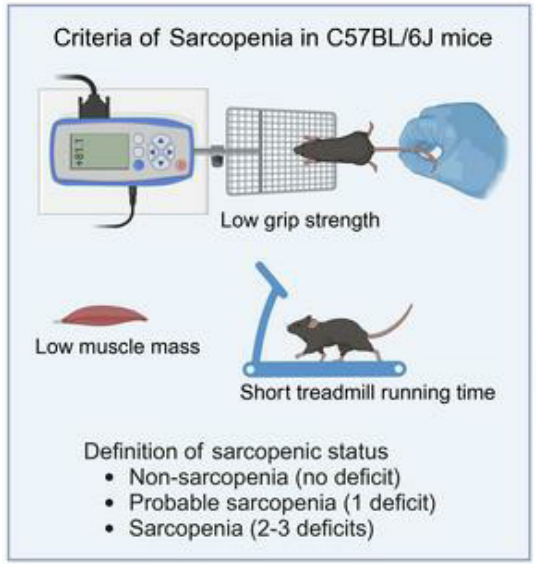
Frequency of Components by Phenotype Characteristic



Mouse sarcopenia model reveals sex- and age-specific differences in phenotypic and molecular characteristics

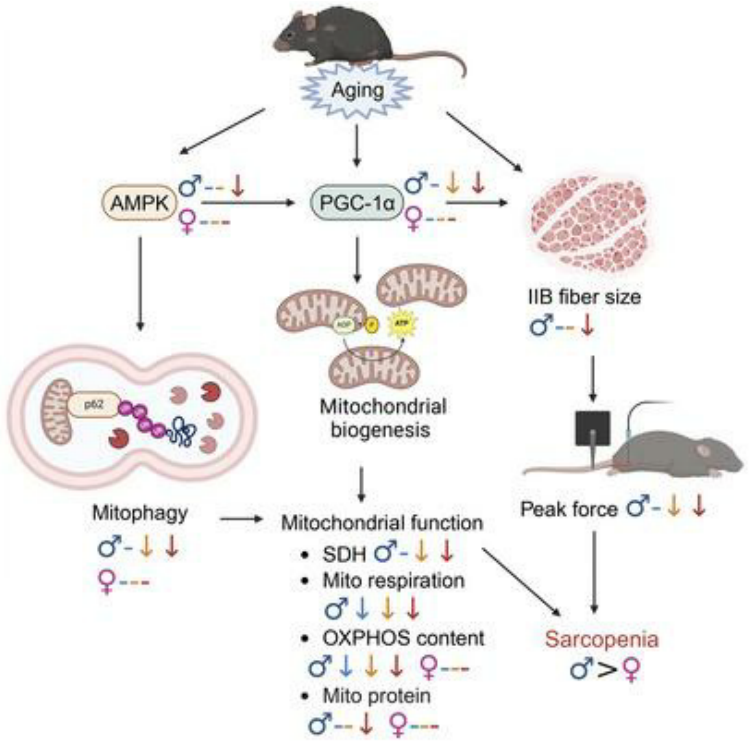
Haiming L. Kerr,[1,2] Kora Krumm,[1,2] Barbara Anderson,[1,2] Anthony Christiani,[1,2] Lena Strait,[1,2] Theresa Li,[1,2] Brynn Irwin,[1,2] Siyi Jiang,[1,2] Artur Rybachok,[1,2] Amanda Chen,[1,2] Elizabeth Dacek,[1,2] Lucas Caeiro,[1,2] Gennifer E. Merrihew,[3] James W. MacDonald,[4] Theo K. Bammler,[4] Michael J. MacCoss,[3] and Jose M. Garcia[1,2]

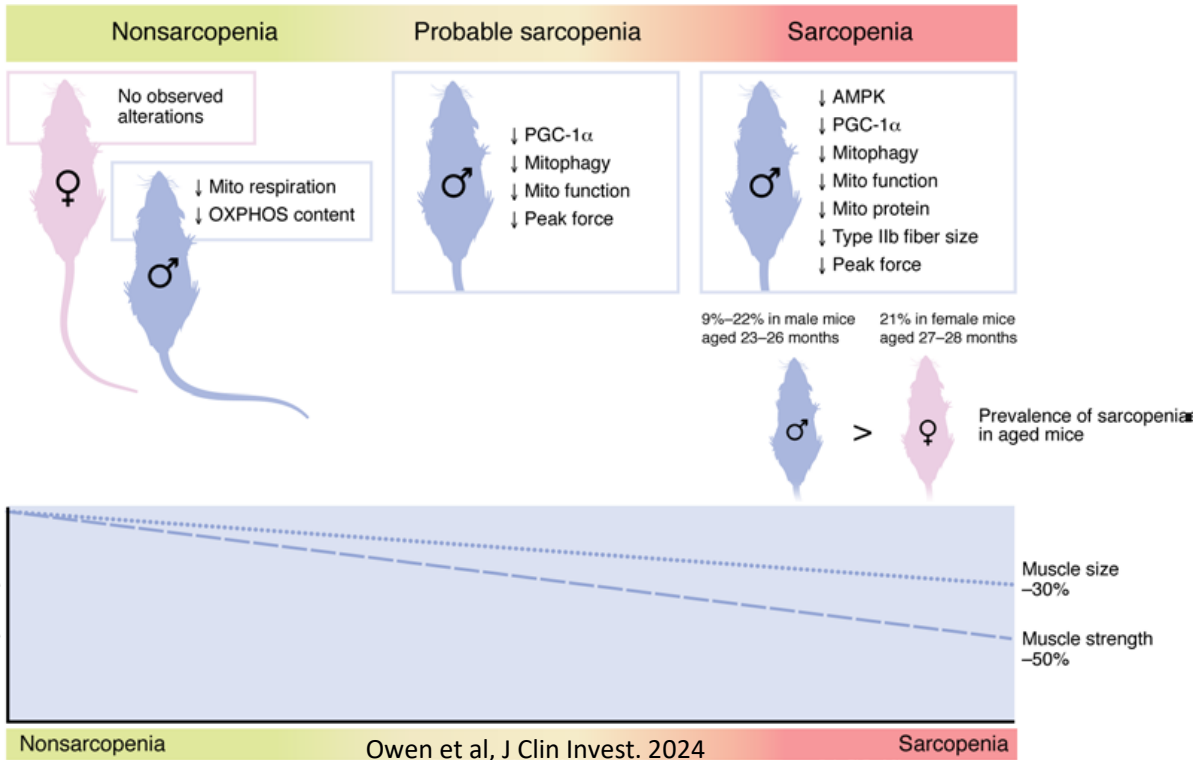
[1]Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA. [2]Division of Gerontology and Geriatric Medicine, Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA. [3]Department of Genome Sciences, and [4]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA.

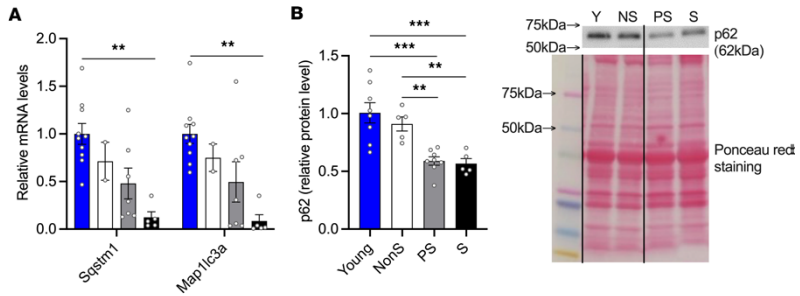


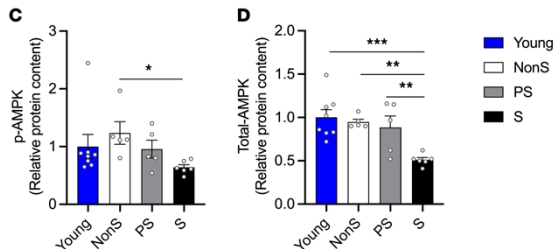
♂: 23-32-month-old males
♀: 27-28-month-old females

Age-related changes:
Increase (↑), decrease (↓), or no change (-) in Non-sarcopenia, Probable sarcopenia, or Sarcopenia









Owen et al, J Clin Invest. 2024

				Muscle Endurance				Muscle Strength		FACT-P				EORTC QLQ C-30						
	BW	ALM	Fat mass	VO_2 Peak	6MWT	Steps/d	TotACT/ d	SCP	Mean HGS	PWB	FWB	ADD	Total	QOL	PF	RF	SF	Fatigue	Pain	Dyspnea
BW		.78**	.88**	-.37**					.30*	-.37**		-.29*			-.34**	-.30*	-.37**	.31*		.33*
ALM			.48**					.34*	.36**	-.42**		-.28*			-.26*	-.27*	-.44**	.33*		.36**
Fat Mass				-.39**												-.27*				
VO_2 Peak					.69**	.43**	.50**	.38**	.31*	.42**	.29*	.36**	.28*	.44**	.57**	.43**	.43**	-.38**	-.40**	-.39**
6MWT						.42**	.53**	.59**	.38**	.47**	.26*	.36**	.26*	.43**	.66**	.47**	.42**	-.48**	-.40**	-.47**
Steps/d							.91**			.38**		.33*	.30*		.51**	.38**	.30*	-.45**	-.42**	-.28*
Tot ACT/d								.40**	.30*	.37**		.35**	.29*		.54**	.38**		-.43**	-.39**	-.29*
SCP									.53**						.36**					
Mean HGS																				
State 3u[A]															.32*					
Maximum ATP[B]	-.51**	-.41*	-.53**	.57**	.57**		.39*		-.37*	.44*				.42*	.42*	.54**	.42*	-.41*		
Muscle Size[B]								.42*	.59**											
Muscle Strength[B]								.40*												
Muscle Endurance[B]								.44*										-.40*		

Spearman's rho correlation

-1 -.5 0 .5 1

Table 2

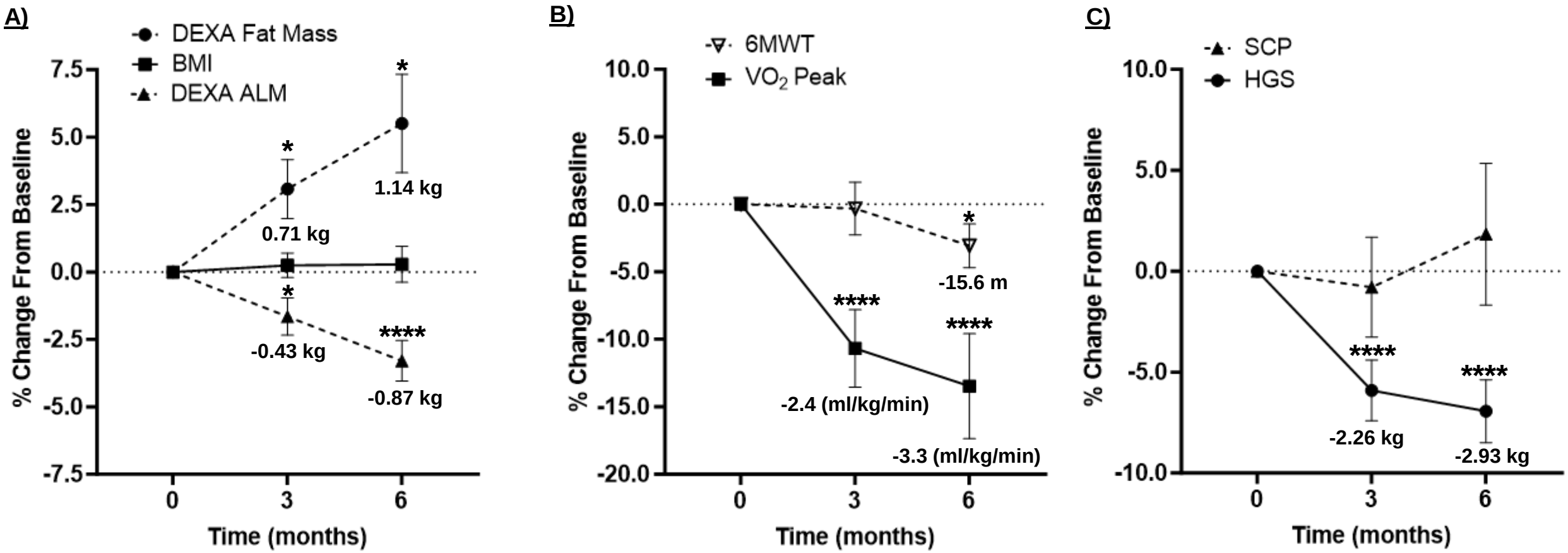

A)
DEXA Fat Mass
BMI
DEXA ALM
% Change From Baseline
Time (months)
0.71 kg
1.14 kg
-0.43 kg
-0.87 kg
B)
6MWT
VO2 Peak
% Change From Baseline
Time (months)
-15.6 m
-2.4 (ml/kg/min)
-3.3 (ml/kg/min)
C)
SCP
HGS
% Change From Baseline
Time (months)
-2.26 kg
-2.93 kg

Figure 2

Six-month Change

QLQ C-30

Baseline

	▲%BW	▲%BMI	▲ %DEXA Fat	▲%DEXA ALM	▲%VO_2 Peak	▲% 6MWT	▲ % HGS	▲%SCP	▲FACT-P ADD	▲PF	▲RF	▲CF
BW				-.35**								
BMI	-.32*	-.30*		-.43**		-.28*						
Fat Mass				-.33*	.34*							
ALM												
VO_2 Peak				.33*		.52**				.37**		.28*
6MWT							.27*					
HGS												
SCP												
State 3				.37*				.38*	.40*		.33*	
State 3u									.42**			
Maximum ATP				.40*					.41*	.40*		
Muscle Endurance				.43*								

Spearman's rho correlation

-1 -.5 0 .5 1

Table 3

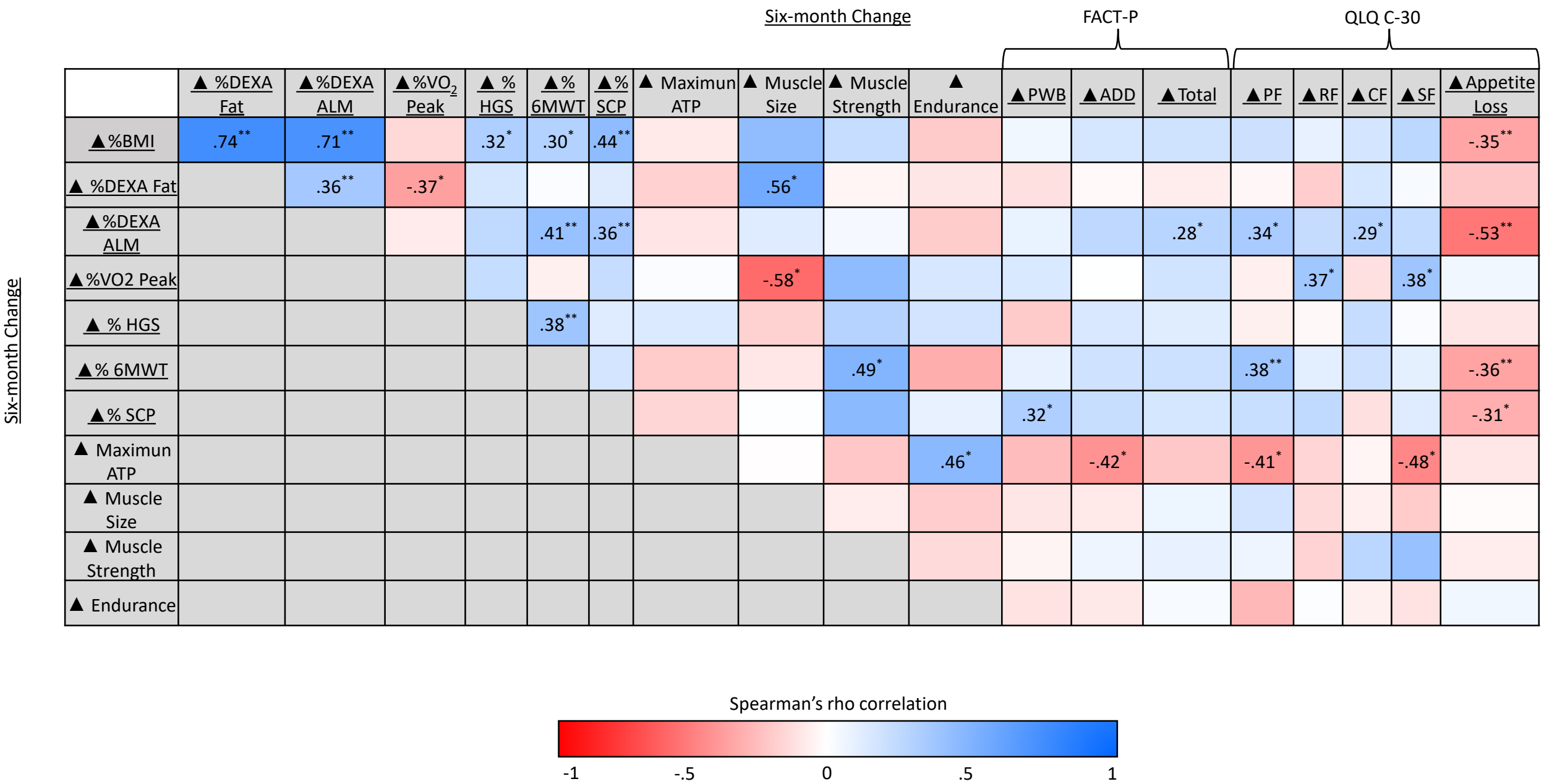

Six-month Change
FACT-P
QLQ C-30
Six-month Change
▲%BMI .74** .71** .32* .30* .44** -.35**
▲ %DEXA Fat .36** -.37* .56*
▲%DEXA ALM .41** .36** .28* .34* .29* -.53**
▲%VO2 Peak -.58* .37* .38*
▲ % HGS .38**
▲% 6MWT .49* .38** -.36**
▲% SCP .32* -.31*
▲ Maximun ATP .46* -.42* -.41* -.48*
▲ Muscle Size
▲ Muscle Strength
▲ Endurance
Spearman's rho correlation
-1
-.5
0
.5
1

Table 4

Effect of Bimagrumab on Body Fat Mass Among Adults With Type 2 Diabetes and Obesity

Table 2. Major End Points

End Point	Change (80% CI) [Participants, No.][a]			*P* value
	Bimagrumab[b]	Placebo[b]	Difference[b]	
Primary				
FM, kg	−7.49 (−8.33 to −6.64) [26]	−0.18 (−0.99 to 0.63) [29]	−7.31 (−8.48 to −6.14)	<.001
Secondary				
Lean mass, kg	1.70 (1.14 to 2.26) [26]	−0.44 (−0.97 to 0.09) [29]	2.14 (1.36 to 2.93)	<.001
Body weight, kg	−5.90 (−7.08 to −4.71) [26]	−0.79 (−1.92 to 0.33) [30]	−5.10 (−6.74 to −3.47)	<.001
BMI	−2.19 (−2.60 to −1.78) [26]	−0.28 (−0.67 to 0.11) [30]	−1.91 (−2.48 to −1.34)	<.001
Waist circumference, cm	−9.00 (−10.3 to −7.68) [26]	0.45 (−0.79 to 1.69) [30]	−9.46 (−11.3 to −7.64)	<.001
Waist-to-hip ratio	−0.05 (−0.06 to −0.04) [26]	0.01 (0.00 to 0.02) [30]	−0.06 (−0.08 to −0.04)	<.001
HbA_{1c}, %	−0.76 (−1.05 to −0.48) [26]	0.04 (−0.23 to 0.31) [30]	−0.80 (−1.20 to −0.41)	.005
HOMA2, week 36	−0.09 (−0.44 to 0.25) [25]	0.57 (0.24 to 0.90) [27]	−0.66 (−1.14 to −0.18)	.08
QUICKI, week 36	0.01 (0.01 to 0.01) [26]	0.00 (0.00 to 0.00) [30]	0.01 (0.00 to 0.01)	.03
Matsuda Index	3.15 (2.39 to 3.91) [26]	1.78 (1.05 to 2.51) [28]	1.37 (0.31 to 2.43)	.10
Exploratory				
Hepatic fat fraction, %				
Week 24	−4.60 (−6.07 to −3.12) [18]	0.23 (−1.61 to 2.08) [11]	−4.83 (−7.20 to −2.46)	.006
Week 48	−7.00 (−8.58 to −5.43) [5]	−2.33 (−4.16 to −0.51) [5]	−4.67 (−7.09 to −2.25)	.01
Abdominal SAT, L				
Week 24	−0.97 (−1.37 to −0.56) [18]	−0.14 (−0.65 to 0.37) [11]	−0.83 (−1.48 to −0.18)	.05
Week 48	−1.71 (−2.40 to −1.03) [5]	−0.52 (−1.30 to 0.26) [4]	−1.19 (−2.23 to −0.15)	.07
Abdominal VAT, L				
Week 24	−1.49 (−1.69 to −1.29) [18]	0.22 (−0.03 to 0.48) [11]	−1.71 (−2.04 to −1.39)	<.001
Week 48	−1.52 (−2.42 to −0.62) [5]	−0.01 (−1.05 to 1.03) [4]	−1.51 (−2.87 to −0.14)	.08

JAMA Network Open. 2021

Sarcopenia

- "Progressive loss of muscle mass and strength with a risk of adverse outcomes (disability, poor QOL, and death)"
- Public health issue particularly in the elderly
- Pathophysiology and different phenotypes are incompletely characterized
- Many pathways regulate muscle mass, but **function is the clinically-meaningful outcome**
- Anabolic interventions maintain mass, but do not ameliorate loss of function
- **There are no approved pharmacologic interventions for sarcopenia**

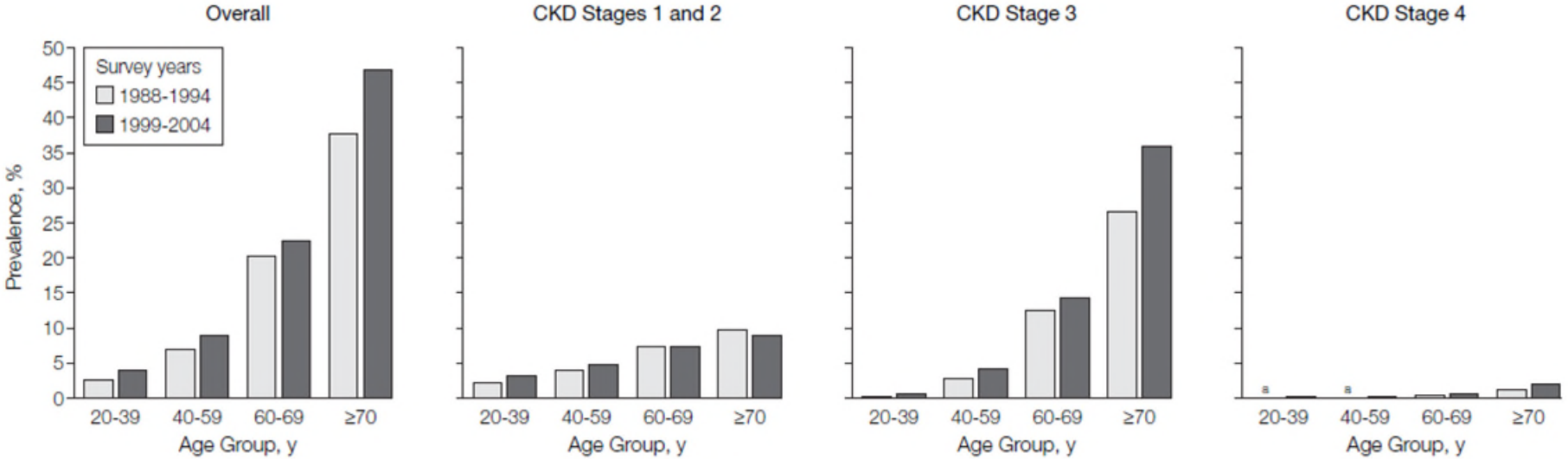
1 Fielding et al, J Am Med Dir Assoc 2011 2 Temel et al, Lancet Oncol 2016 3 Nass et al, 2008

Risk Factors for Frailty

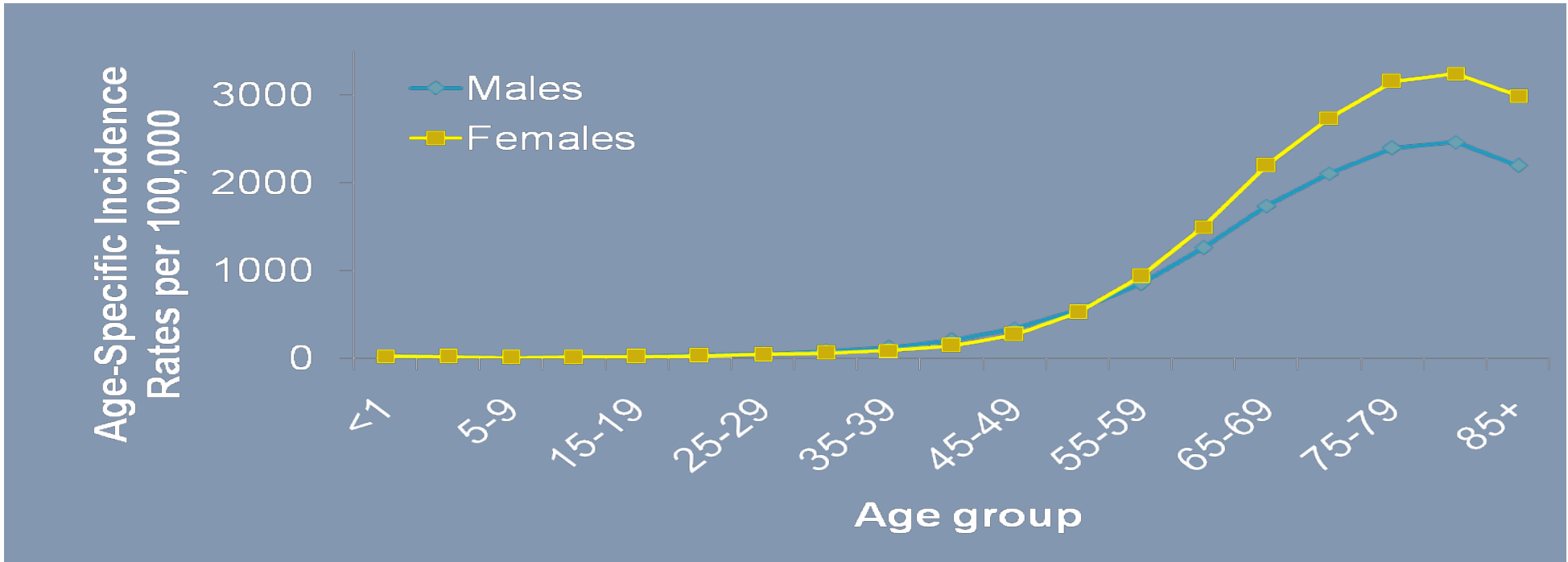
- Older age
- Lower educational level
- Current smoker
- African-American or Hispanic ethnicity
- Not married
- Depression, or use of antidepressants
- Intellectual disability

Cancer, Renal Dz and Aging

Figure 2. Prevalence of Chronic Kidney Disease (CKD) Stages by Age Group in NHANES 1988-1994 and 1999-2004

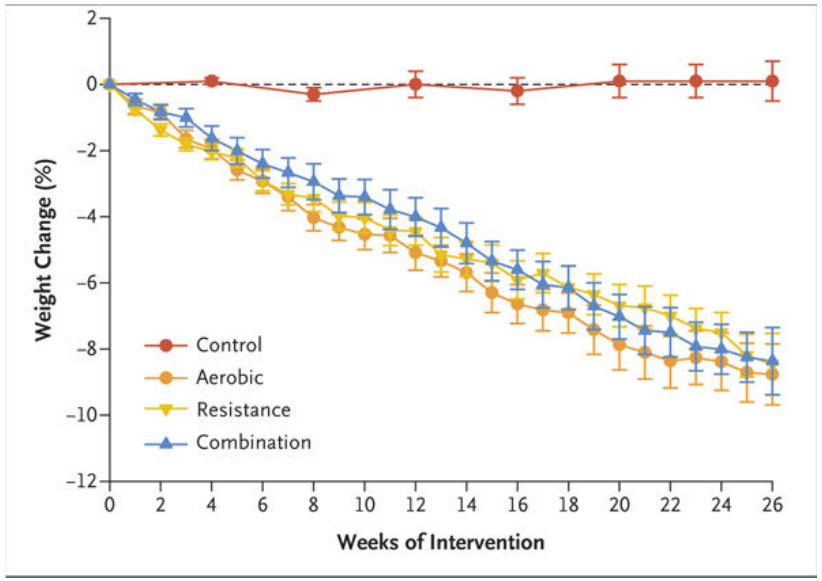


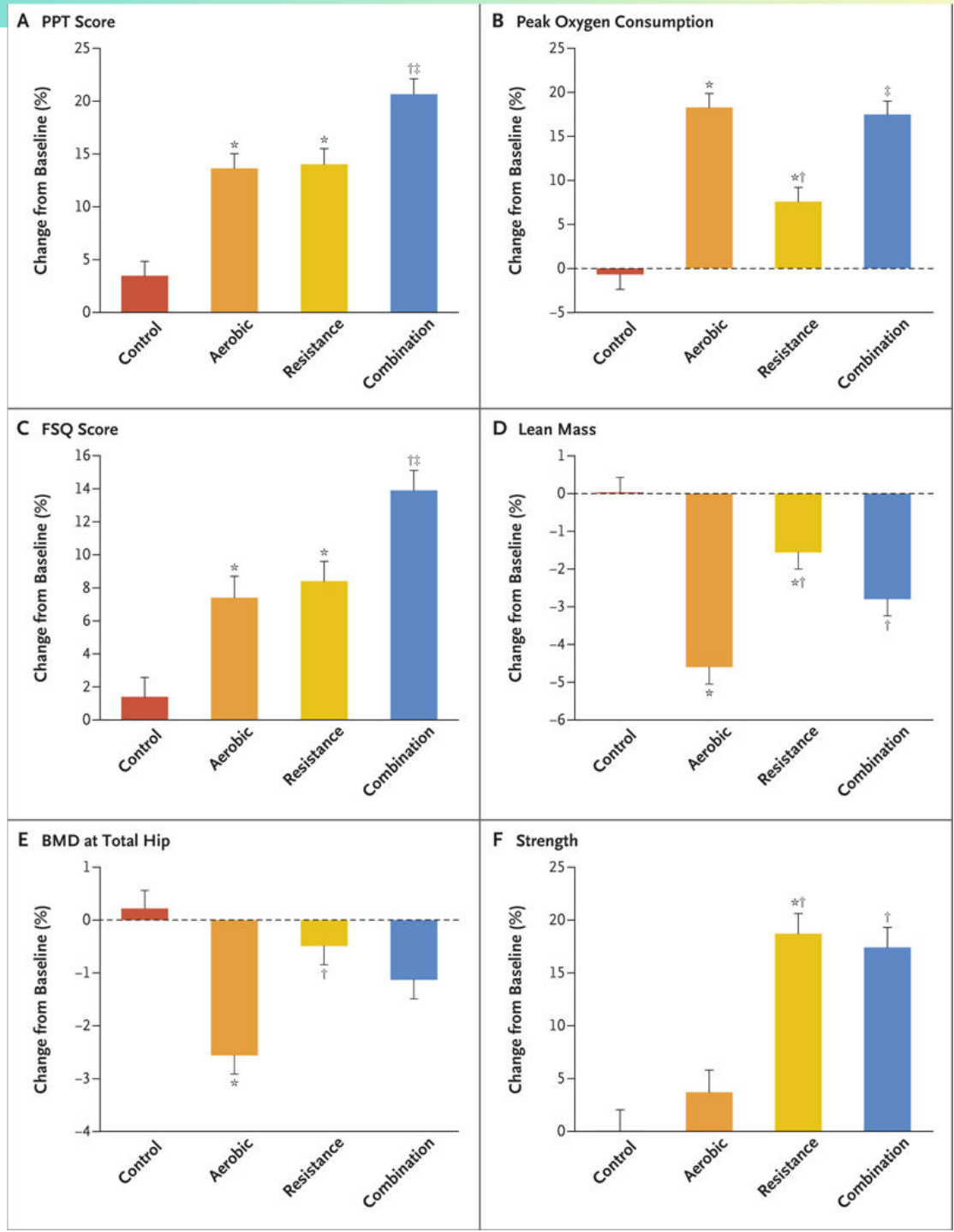
NHANES indicates National Health and Nutrition Examination Surveys.
[a]There were no cases in 1988-1994.



Coresh, 2007, seer.cancer.gov

Obesity treatment and frailty

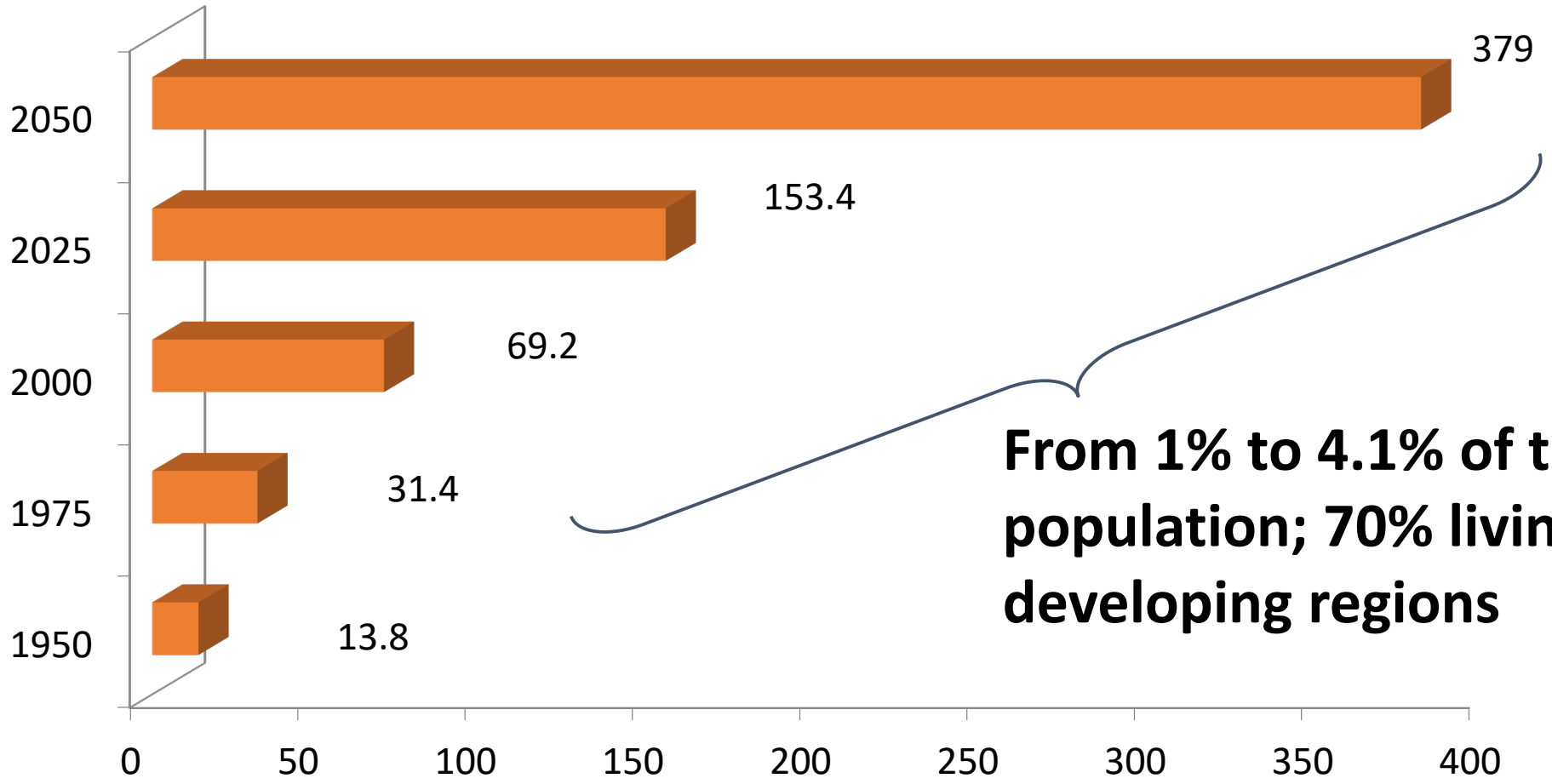




Villareal et al. N Engl J Med. 2017

Population aged 80 or over
World, 1950-2050

(UN 2001)

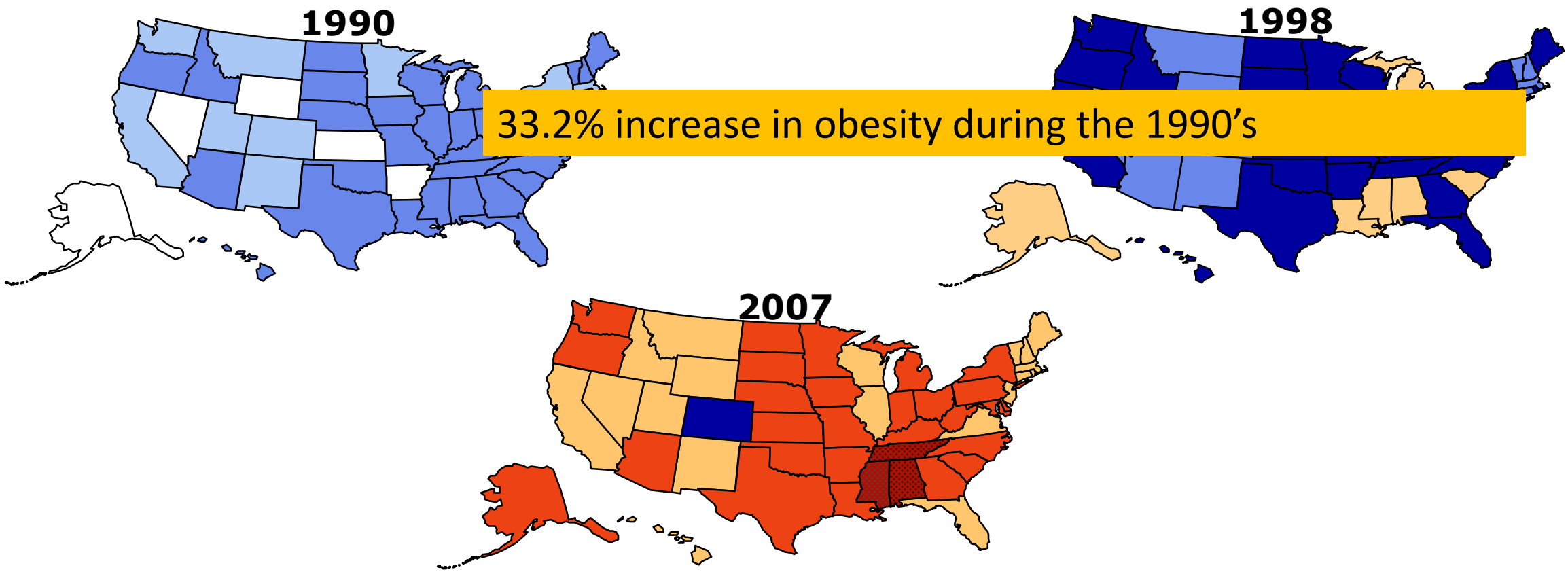


From 1% to 4.1% of the population; 70% living in developing regions

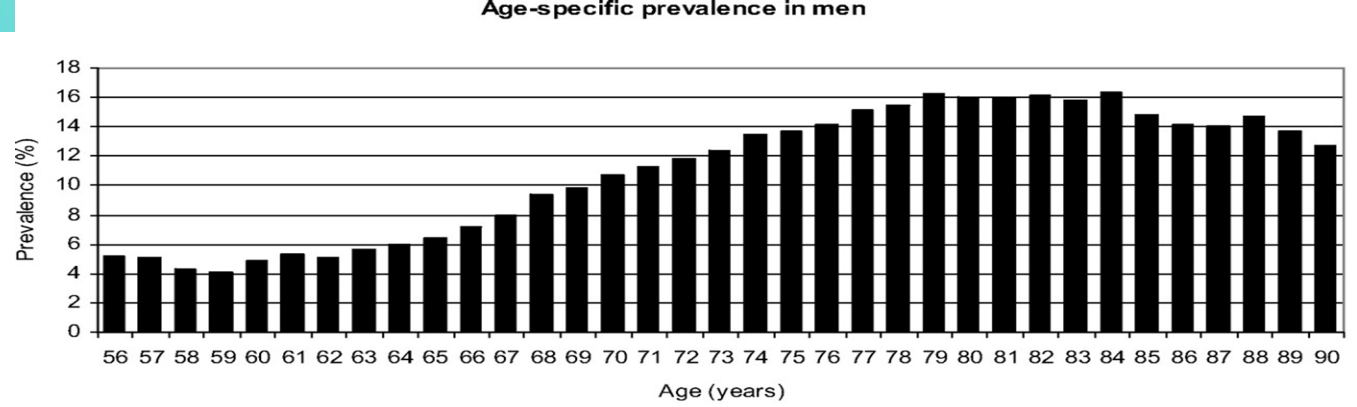
Obesity Trends* Among U.S. Adults

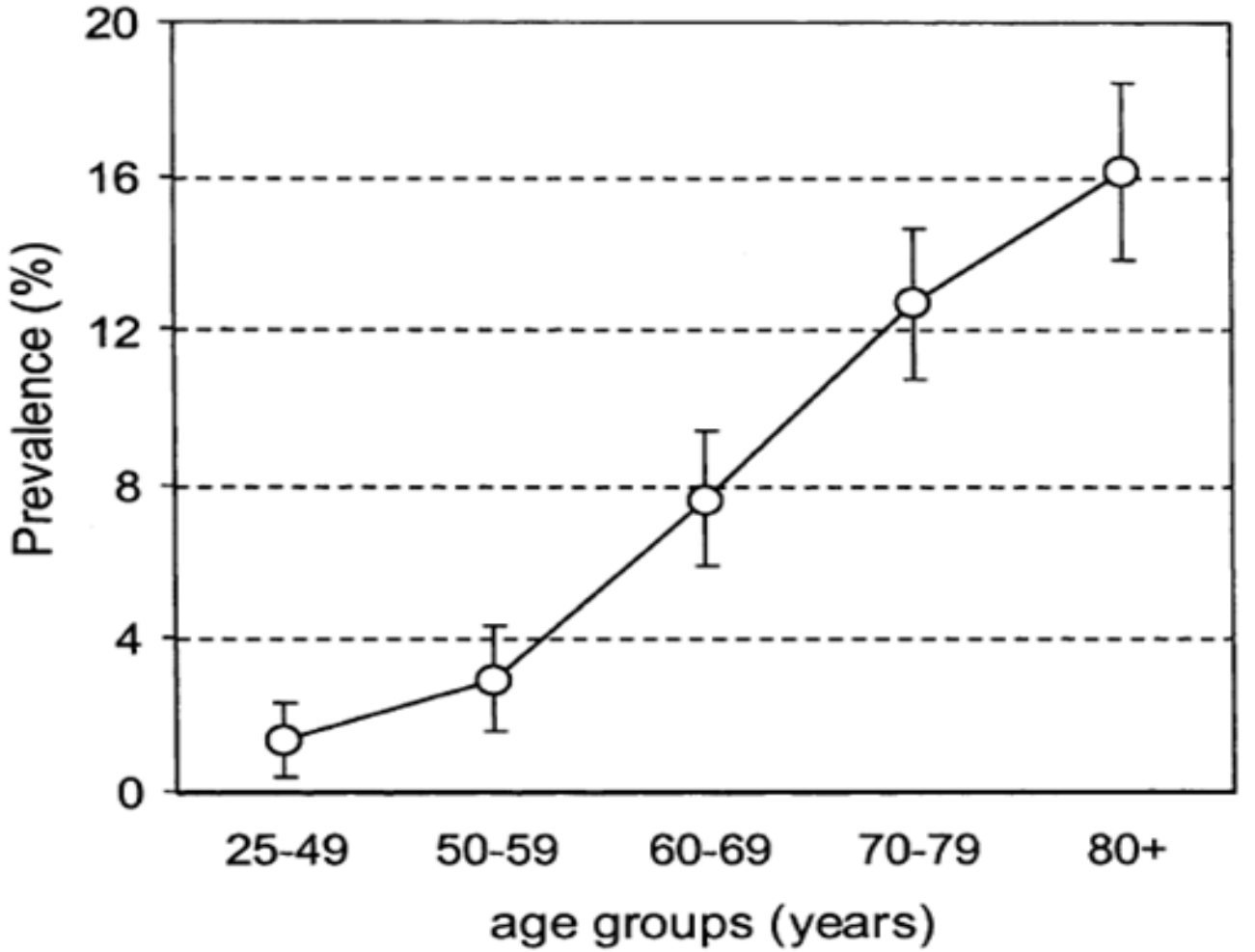
BRFSS, 1990, 1998, 2007

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)



CHF, COPD and Aging



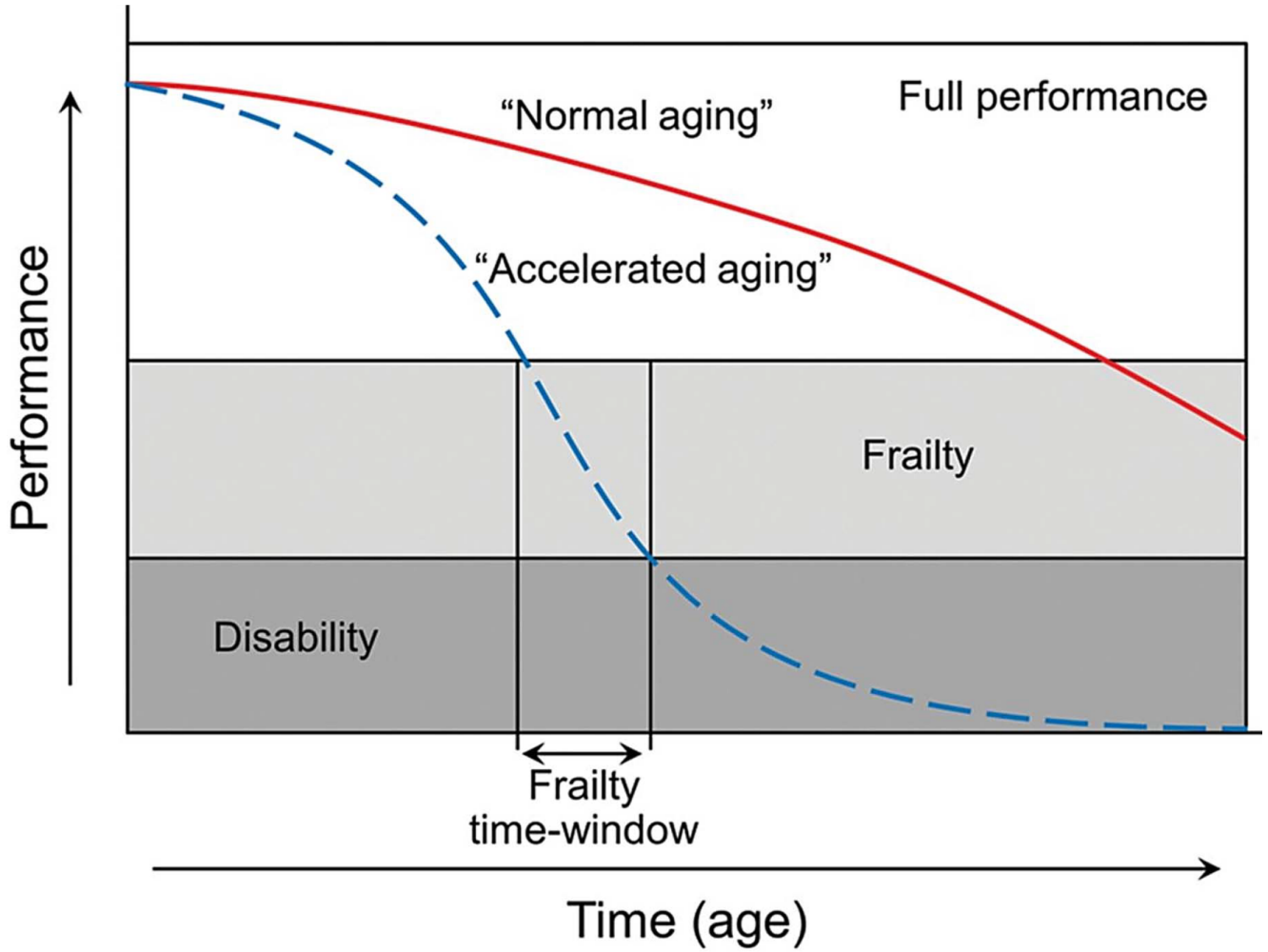


Ceia, 2002
Yannick, 2009

Diseases associated with increased risk of frailty

- COPD
- Chronic inflammatory diseases
- Hip fractures
- Pressure ulcers and chronic wounds
- AIDS, Tuberculosis, other chronic infections
- Congestive Heart Failure
- ESRD
- Diabetes
- Dementia
- Depression
- Advanced cancer

Frailty Trajectory



Ferrucci L et al. Biomarkers of frailty in older persons. J Endocrinol Invest 2002;25(10 Suppl):10-15

Physical Frailty Phenotype (PFP)

- Weight loss (more than 10 lbs or 5% over the previous year)
- Weakness (grip strength lowest 20% by gender, BMI)
- Exhaustion (self-report)
- Walking Speed (>6-7s to walk 15 feet)
- Physical Activity (<383♂ or 270♀ Kcals/week)
  - Not Frail: 0
  - Intermediate: 1-2
  - Frail: ≥3

Fried et al., Frailty in older adults: evidence for a phenotype, *J Gerontol A Biol Sci Med Sci,* 2001.

Frailty Index

- Ratio of deficits present out of the total number of possible deficits, gives a continuous score from total fitness (0) to total frailty (1)
  - 0-0.1: not frail
  - 0.11-0.2: vulnerable
  - 0.21-0.45: frail
  - 0.46-1: Most frail

Blodgett et al. Archives of Gerontology and Geriatrics 60 (2015) 464–470

Table 1
46 deficits included in frailty index.

Comorbidities
- Stroke
- Thyroid condition
- Cancer
- Heart attack
- Heart disease
- Ever had high blood pressure
- Angina/angina pectoris
- Osteoporosis
- Diabetes
- Arthritis
- Ever had broken hip
- Cataract operation
- Weak/failing kidneys

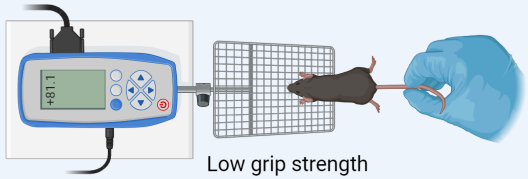
Function
- Difficulty using fork and knife
- Difficulty dressing yourself
- Difficulty getting in/but of bed
- Difficulty standing up from armless chair
- Difficulty managing money
- Difficulty preparing meals
- Difficulty standing for long periods of time
- Difficult stooping, crouching, kneeling
- Difficulty grasping/holding small objects
- Difficulty lifting or carrying
- Difficulty pushing or pulling large objects
- Difficult attending social event

Signs/symptoms
- Heart rate at rest
- Systolic blood pressure
- Cough regularly
- Leaked/lost control or urine
- General vision
- Difficulty seeing steps/curbs in dim light
- General hearing
- Confusion or inability to remember things

Lab values
- Homocysteine (μmol/L)
- Folatc, scrum (nmol/L)
- Glycohemoglobin (%)
- Red blood cell count (million cells/μL)
- Hemoglobin (g/dL)
- Red cell distribution width (%)
- Lymphocyte percent (%)
- Segmented neutrophils percent (%)

Other
- Medications
- Self-reported health
- Health compared to 1 year ago
- Frequency of healthcare use
- Overnight hospital stays

Criteria of Sarcopenia in C57BL/6J mice



Low grip strength

Low muscle mass

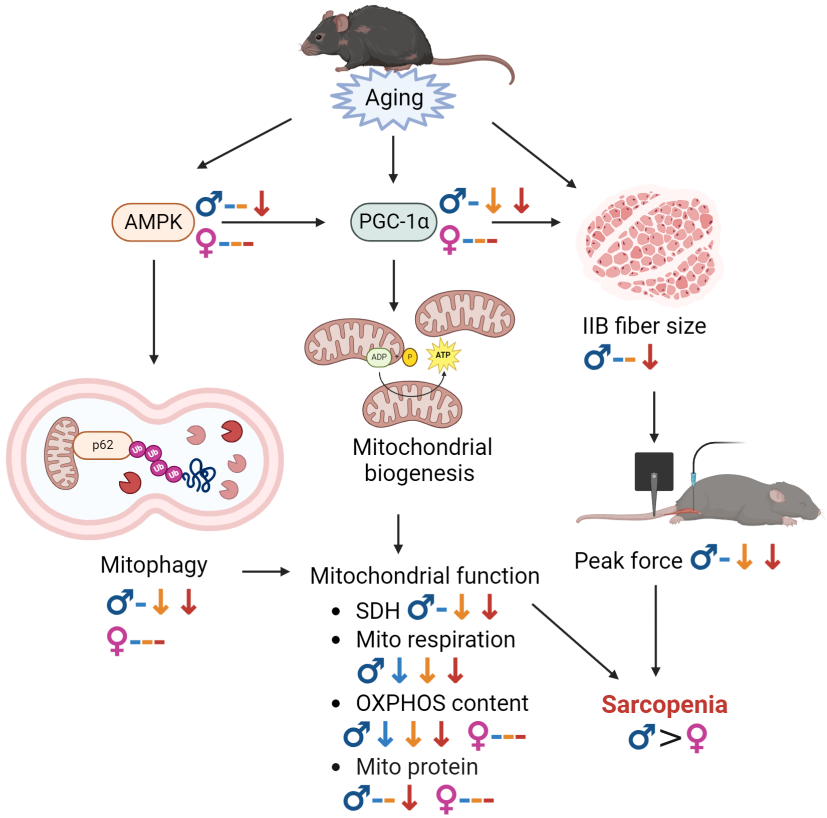
Short treadmill running time

Definition of sarcopenic status

- Non-sarcopenia (no deficit)
- Probable sarcopenia (1 deficit)
- Sarcopenia (2-3 deficits)

♂: 23-32-month-old males
♀: 27-28-month-old females

Age-related changes:
Increase (↑), decrease (↓), or no change (-) in Non-sarcopenia, Probable sarcopenia, or Sarcopenia



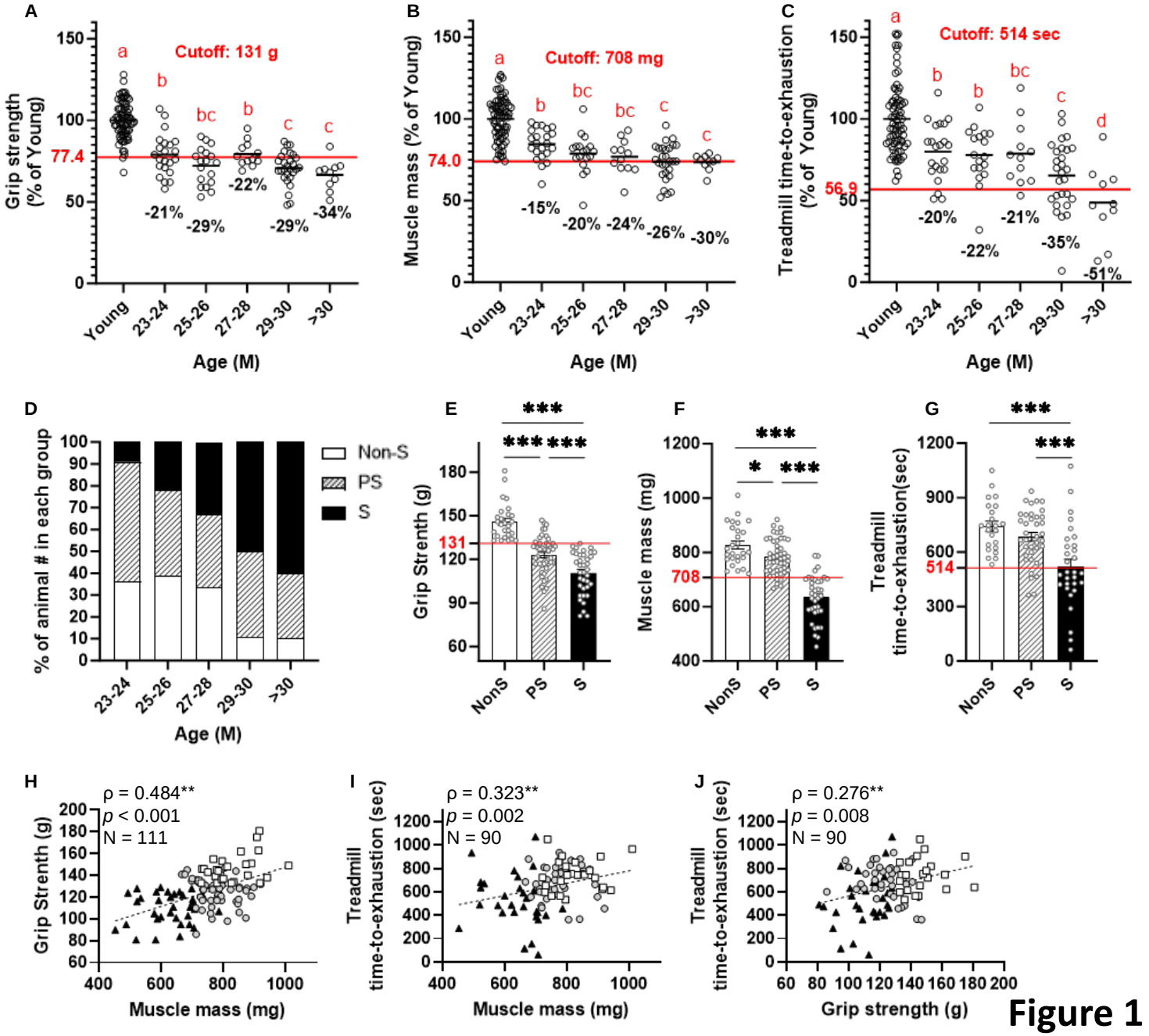

A
Grip strength (% of Young)
Cutoff: 131 g
77.4
-21%
-29%
-22%
-29%
-34%
Young
23-24
25-26
27-28
29-30
>30
Age (M)
B
Muscle mass (% of Young)
Cutoff: 708 mg
74.0
-15%
-20%
-24%
-26%
-30%
Age (M)
C
Treadmill time-to-exhaustion (% of Young)
Cutoff: 514 sec
56.9
-20%
-22%
-21%
-35%
-51%
Age (M)
D
% of animal # in each group
Non-S
PS
S
Age (M)
E
Grip Strenth (g)
131
NonS
PS
S
F
Muscle mass (mg)
708
G
Treadmill time-to-exhaustion(sec)
514
H
ρ = 0.484**
p < 0.001
N = 111
Grip Strenth (g)
Muscle mass (mg)
I
ρ = 0.323**
p = 0.002
N = 90
Treadmill time-to-exhaustion (sec)
Muscle mass (mg)
J
ρ = 0.276**
p = 0.008
N = 90
Treadmill time-to-exhaustion (sec)
Grip strength (g)

Figure 1

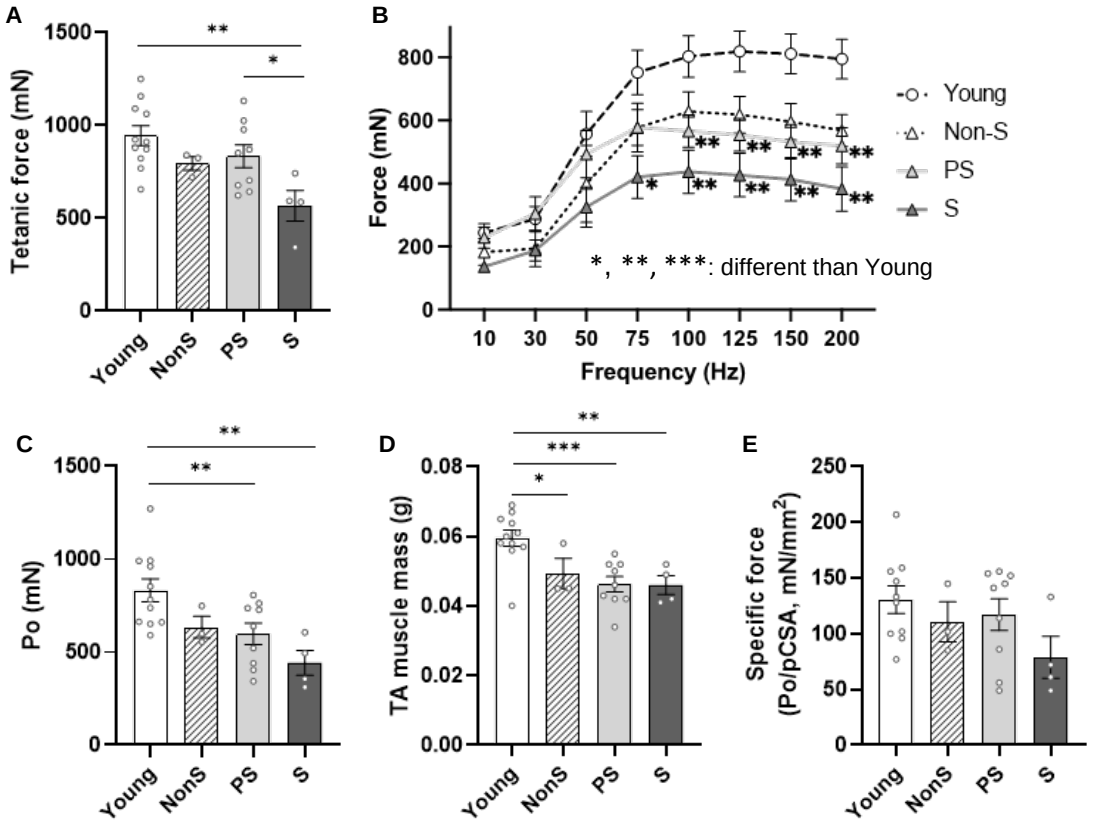

A
Tetanic force (mN)
1500
1000
500
0
**
*
Young
NonS
PS
S
B
Force (mN)
800
600
400
200
0
10
30
50
75
100
125
150
200
Frequency (Hz)
Young
Non-S
PS
S
*, **, ***: different than Young
C
Po (mN)
1500
1000
500
0
**
**
Young
NonS
PS
S
D
TA muscle mass (g)
0.08
0.06
0.04
0.02
0.00
**
***
*
Young
NonS
PS
S
E
Specific force
(Po/pCSA, mN/mm2)
250
200
150
100
50
0
Young
NonS
PS
S

Figure2

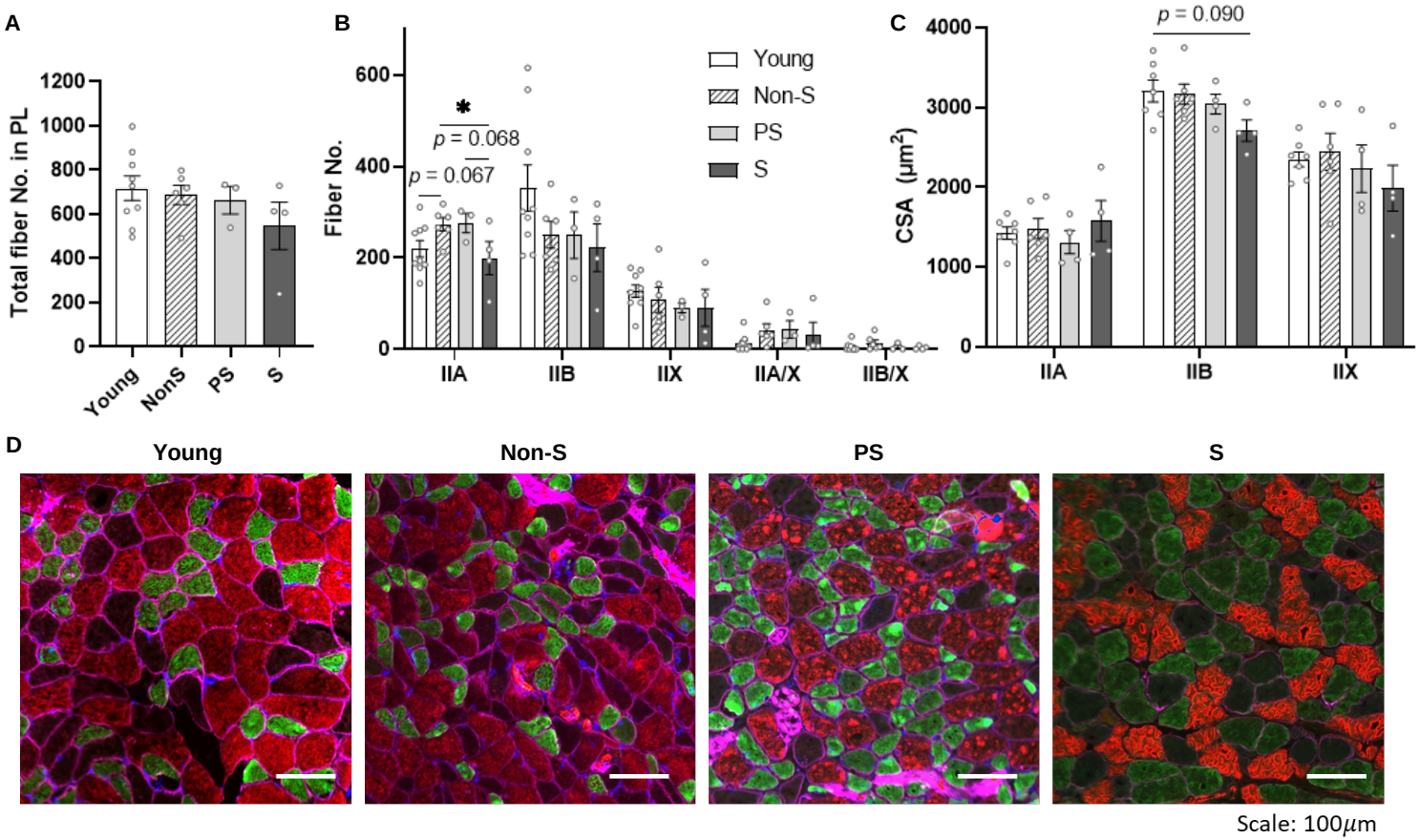

A
Total fiber No. in PL
1200
1000
800
600
400
200
0
Young
NonS
PS
S
B
Fiber No.
600
400
200
0
*
p = 0.068
p = 0.067
Young
Non-S
PS
S
IIA
IIB
IIX
IIA/X
IIB/X
C
CSA (μm²)
4000
3000
2000
1000
0
p = 0.090
IIA
IIB
IIX
D
Young
Non-S
PS
S
Scale: 100μm

Figure3

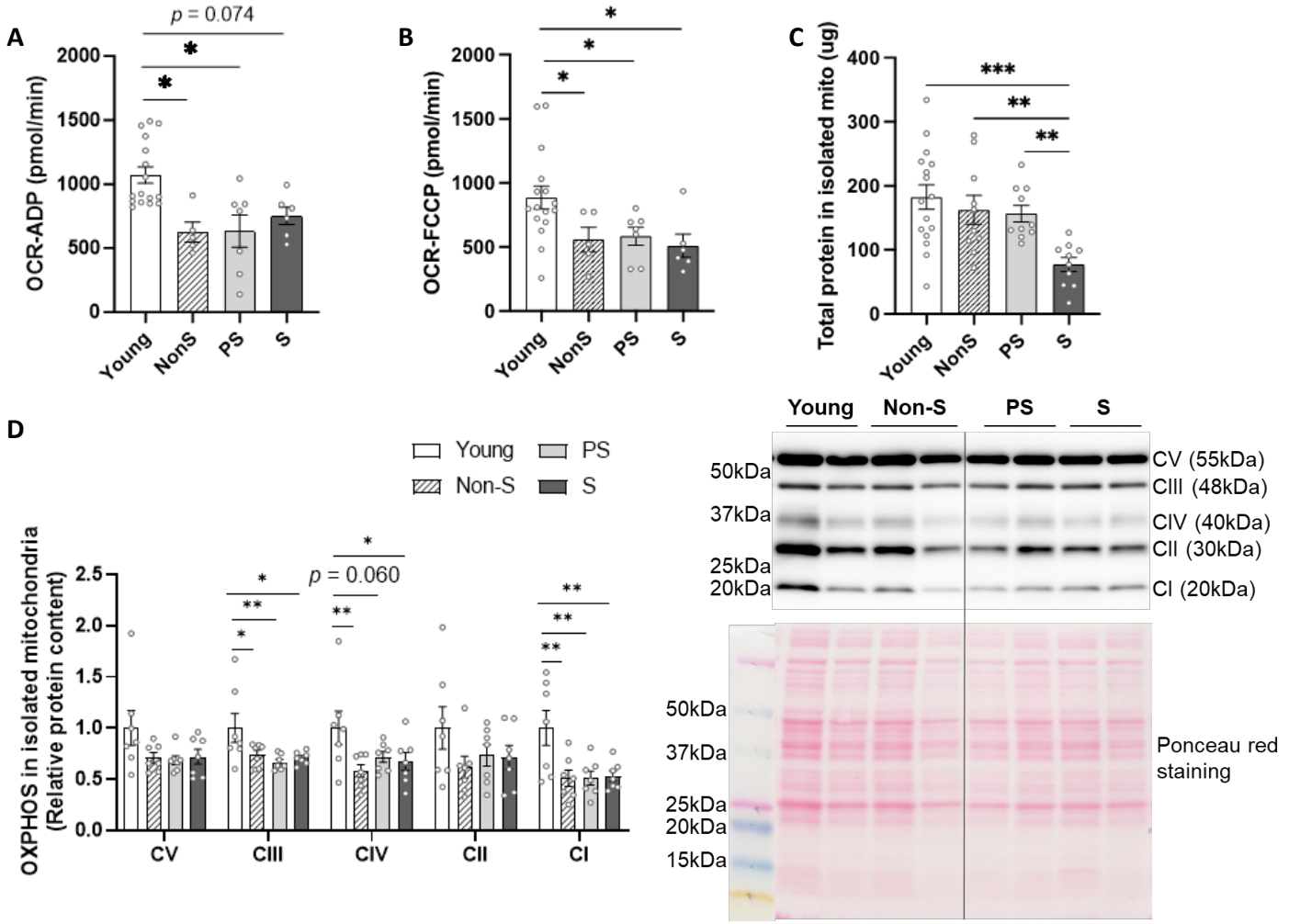

A
p = 0.074
OCR-ADP (pmol/min)
2000
1500
1000
500
0
Young
NonS
PS
S
B
OCR-FCCP (pmol/min)
C
Total protein in isolated mito (ug)
400
300
200
100
D
Young
Non-S
PS
S
OXPHOS in isolated mitochondria (Relative protein content)
2.5
2.0
1.5
1.0
0.5
0.0
p = 0.060
CV
CIII
CIV
CII
CI
Young
Non-S
PS
S
50kDa
37kDa
25kDa
20kDa
CV (55kDa)
CIII (48kDa)
CIV (40kDa)
CII (30kDa)
CI (20kDa)
50kDa
37kDa
25kDa
20kDa
15kDa
Ponceau red staining

Figure4

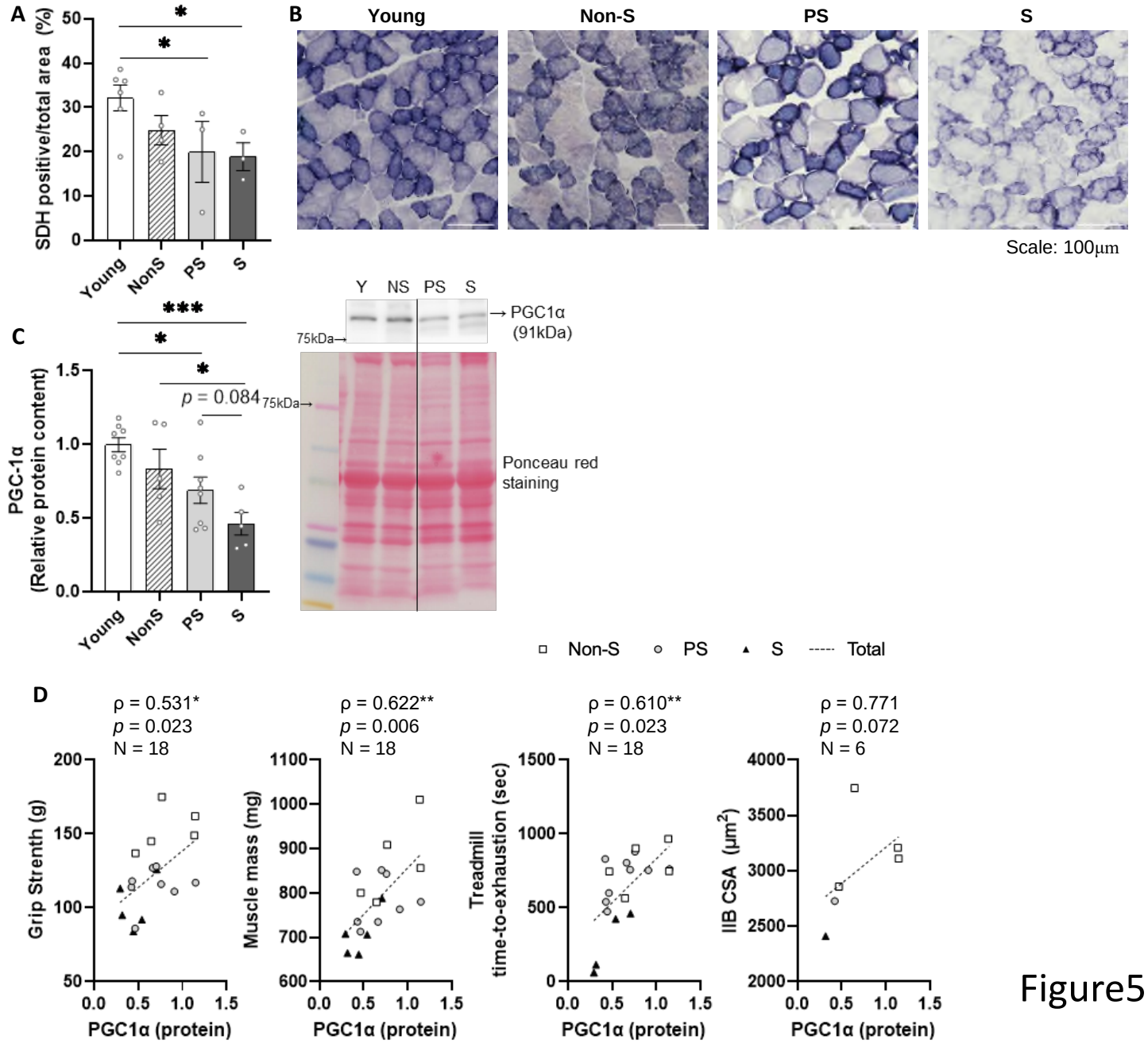

A
SDH positive/total area (%)
Young
NonS
PS
S
B
Young
Non-S
PS
S
Scale: 100μm
C
PGC-1α
(Relative protein content)
p = 0.084
Y NS PS S
75kDa→
→ PGC1α
(91kDa)
Ponceau red
staining
Non-S
PS
S
Total
D
ρ = 0.531*
p = 0.023
N = 18
ρ = 0.622**
p = 0.006
N = 18
ρ = 0.610**
p = 0.023
N = 18
ρ = 0.771
p = 0.072
N = 6
Grip Strenth (g)
Muscle mass (mg)
Treadmill
time-to-exhaustion (sec)
IIB CSA (μm²)
PGC1α (protein)

Figure5

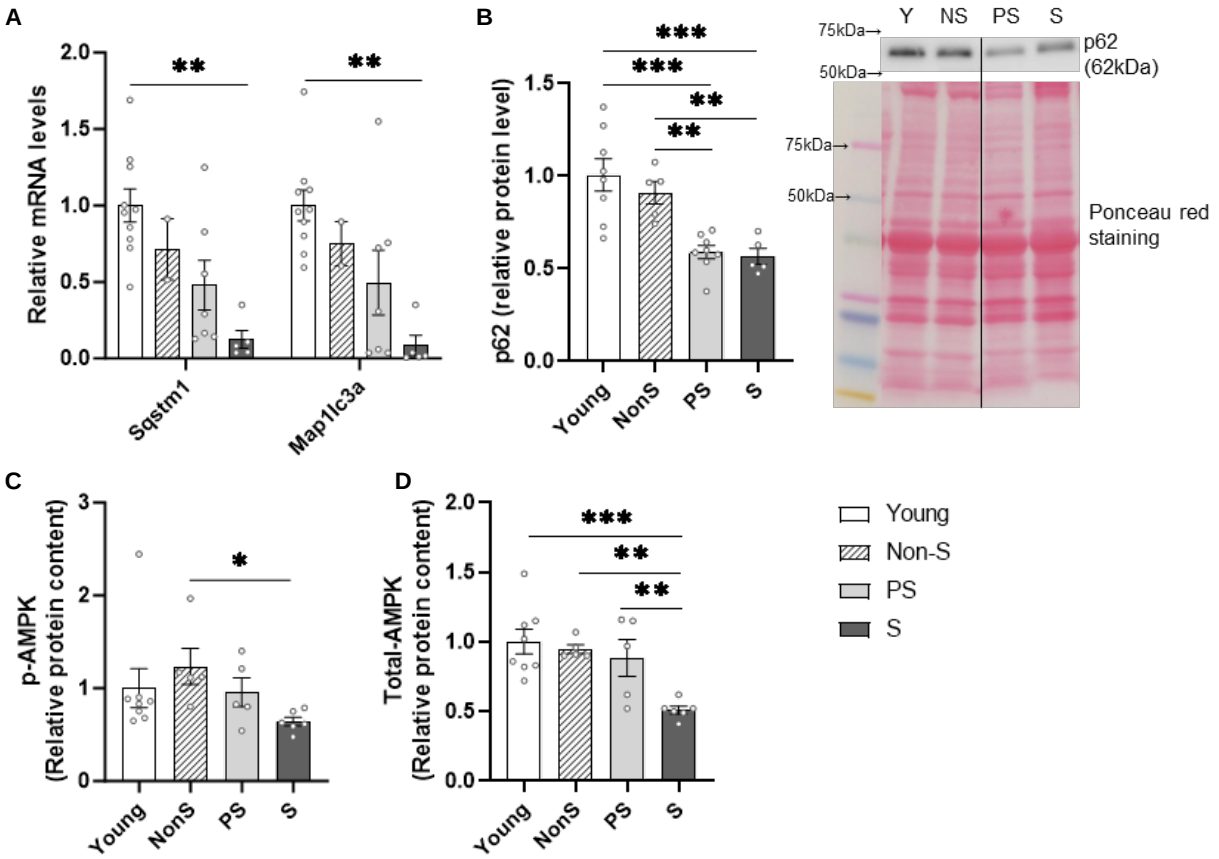

A
Relative mRNA levels
2.0
1.5
1.0
0.5
0.0
**
**
Sqstm1
Map1lc3a
B
p62 (relative protein level)
1.5
1.0
0.5
0.0
***
***
**
**
Young
NonS
PS
S
75kDa→
50kDa→
Y
NS
PS
S
p62
(62kDa)
75kDa→
50kDa→
Ponceau red
staining
C
p-AMPK
(Relative protein content)
3
2
1
0
*
Young
NonS
PS
S
D
Total-AMPK
(Relative protein content)
2.0
1.5
1.0
0.5
0.0
***
**
**
Young
NonS
PS
S
Young
Non-S
PS
S

Figure6

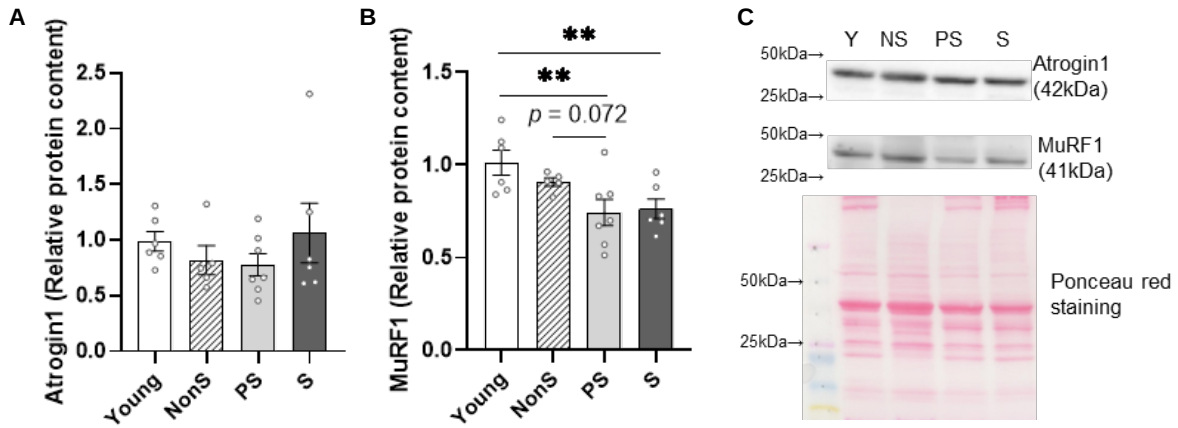
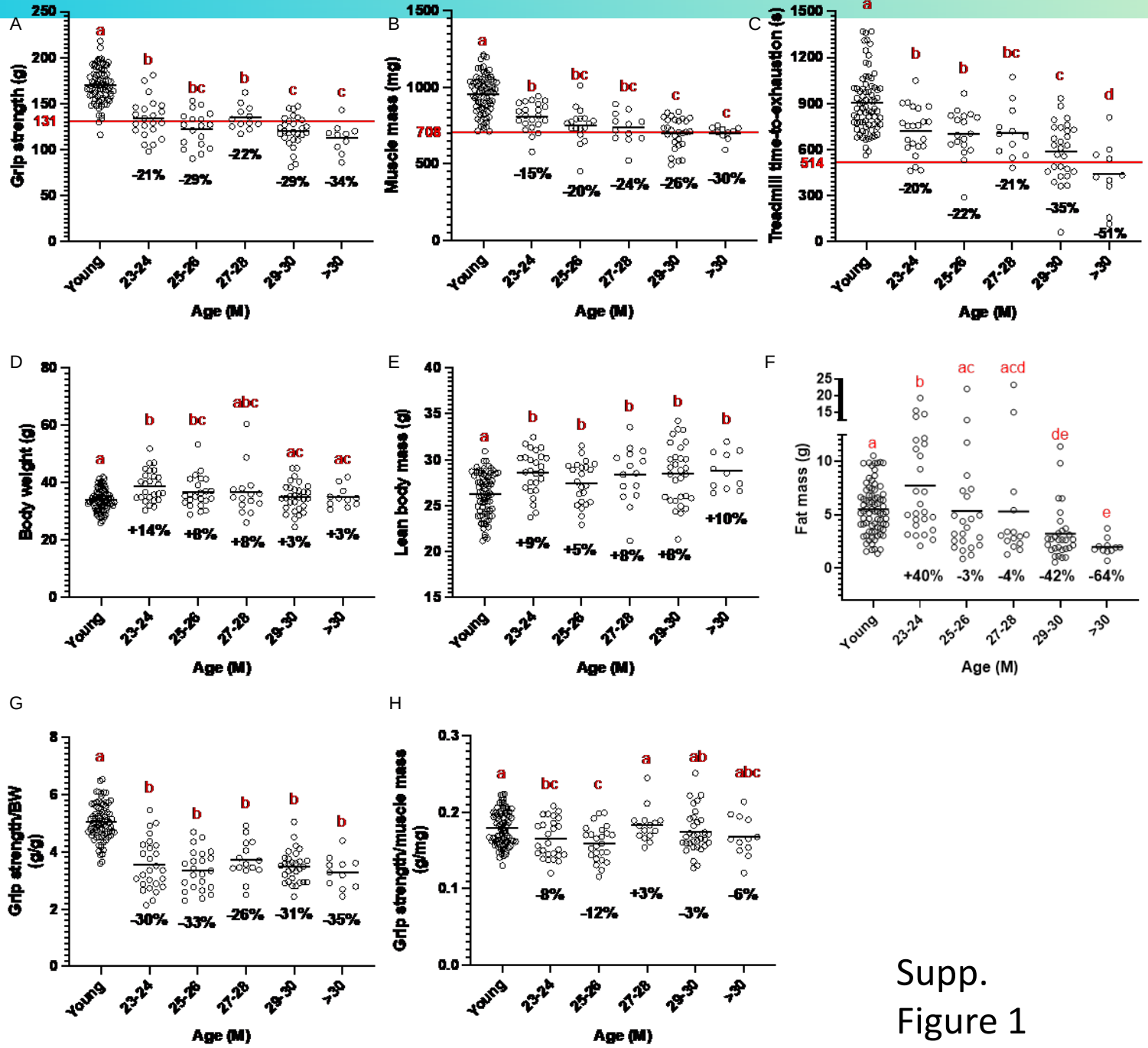
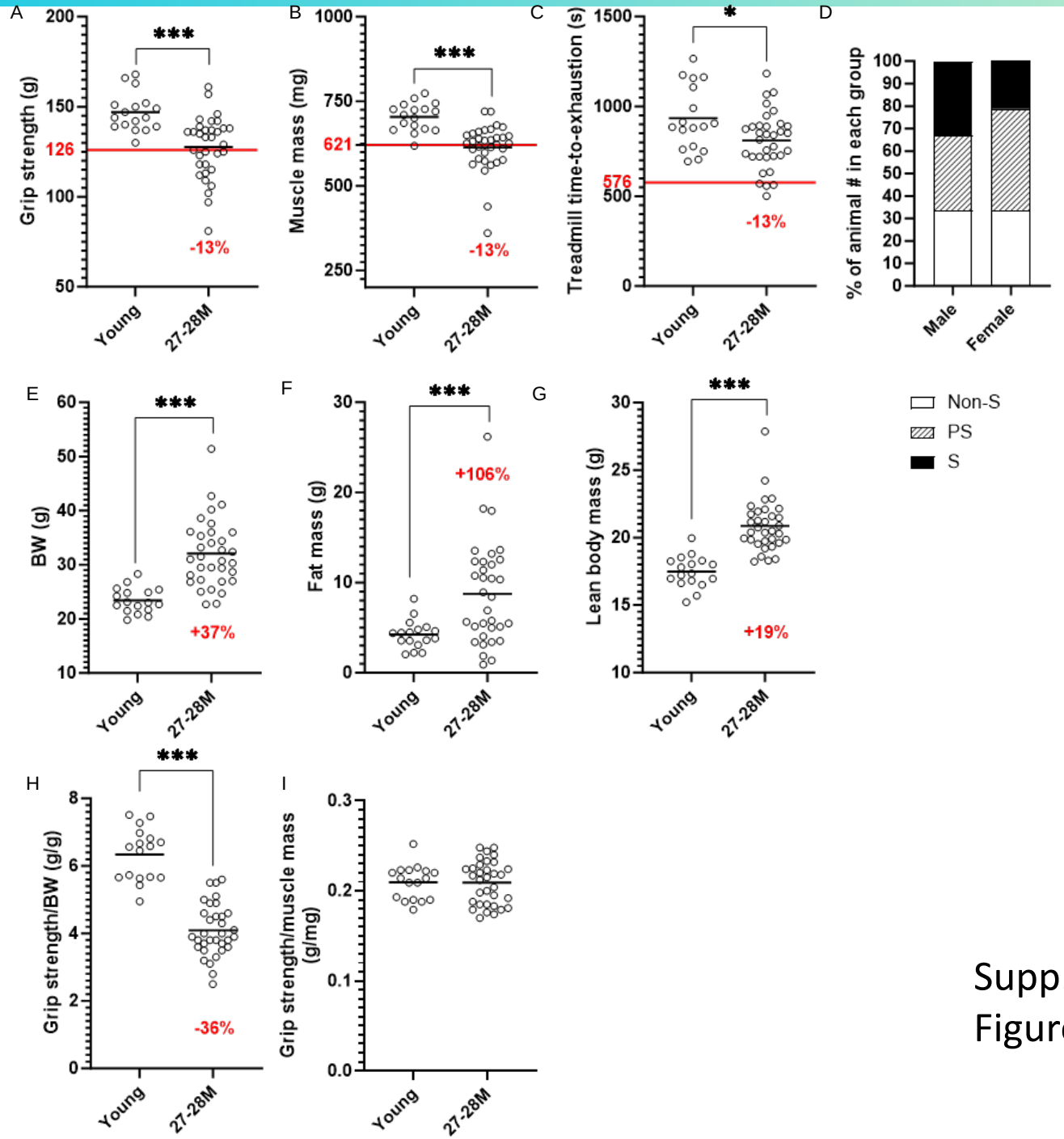

A
Atrogin1 (Relative protein content)
2.5
2.0
1.5
1.0
0.5
0.0
Young
NonS
PS
S
B
MuRF1 (Relative protein content)
**
**
p = 0.072
1.5
1.0
0.5
0.0
Young
NonS
PS
S
C
Y
NS
PS
S
50kDa→
25kDa→
Atrogin1
(42kDa)
50kDa→
25kDa→
MuRF1
(41kDa)
50kDa→
25kDa→
Ponceau red
staining

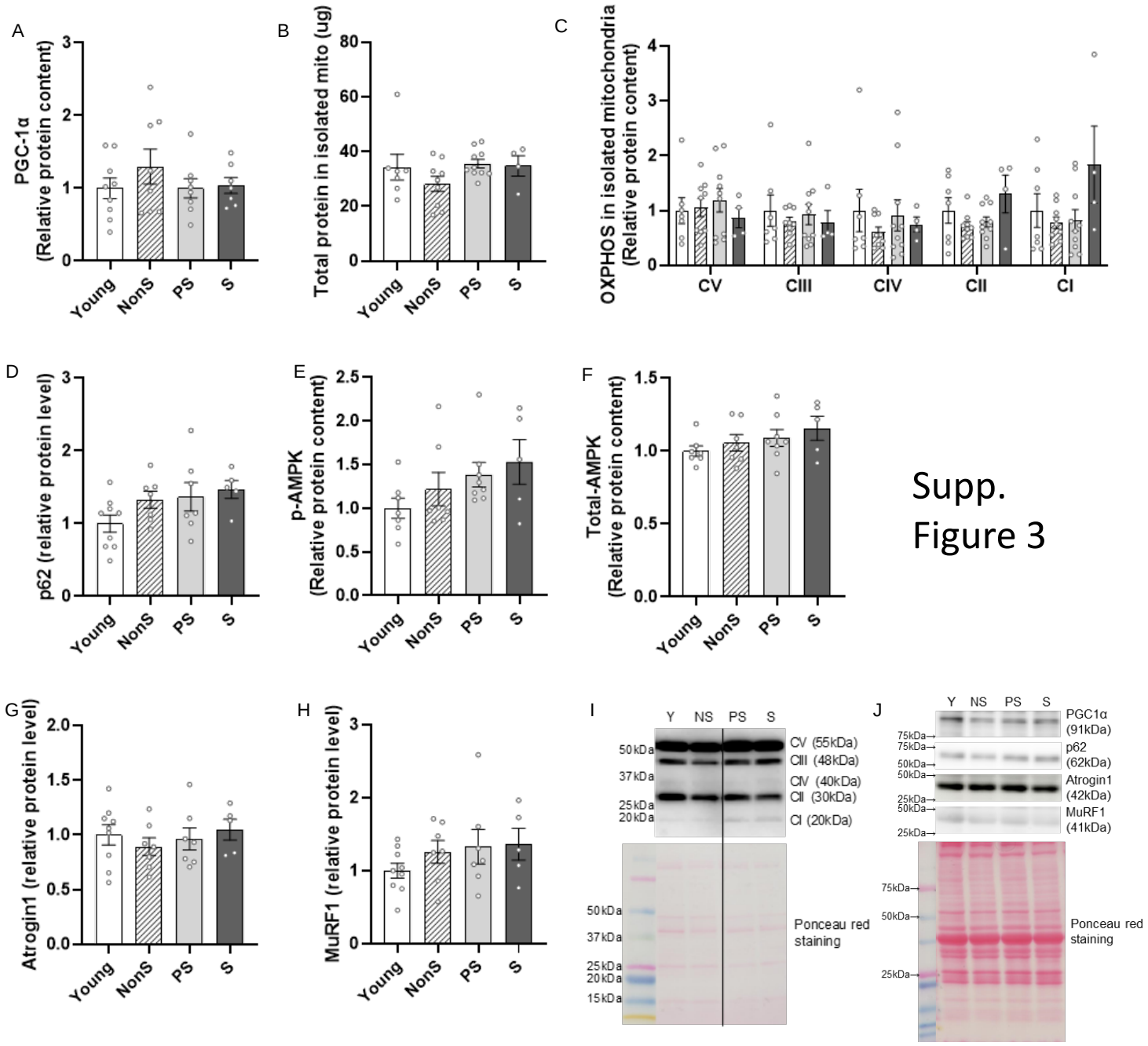
Figure7



Supp. Figure 1



Supp.
Figure 2



Supp. Figure 3

Validating a Biomarker

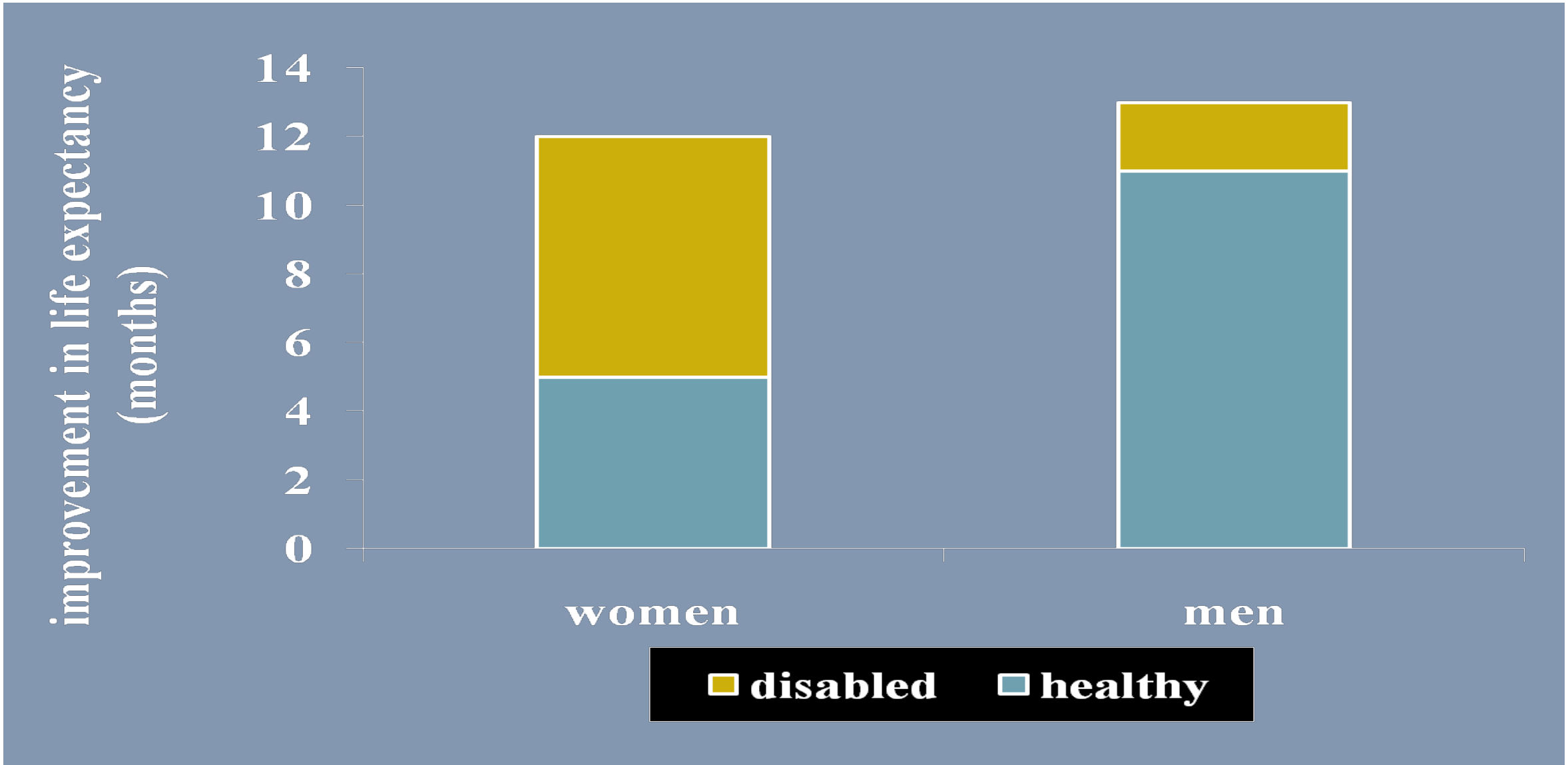
- The relationship between the surrogate and the “direct” endpoint must be firmly established. Correlations, are not enough.
- Ideal method: Analyses of multiple studies of known effective drugs, which assess both the direct and surrogate endpoints, in order to establish (and quantitate) the relationship.
- Once validated, a surrogate may be useful for future studies, particularly those with same mechanism of action

FDA.gov

Validating a Biomarker

- Disease-, host-, pathway-, target-specific
- Laboratory measurement (inflammatory markers [CRP, IL-6, IL1a], GDF-15, testosterone)
- Radiographic image (aLBM, muscle mass/density)
- Physical sign (BMI, weight history, weakness, poor performance)
- Other (non-biomarker) measures including PROs: physical dysfunction, anorexia, fatigue
  - Avoid a ceiling effect

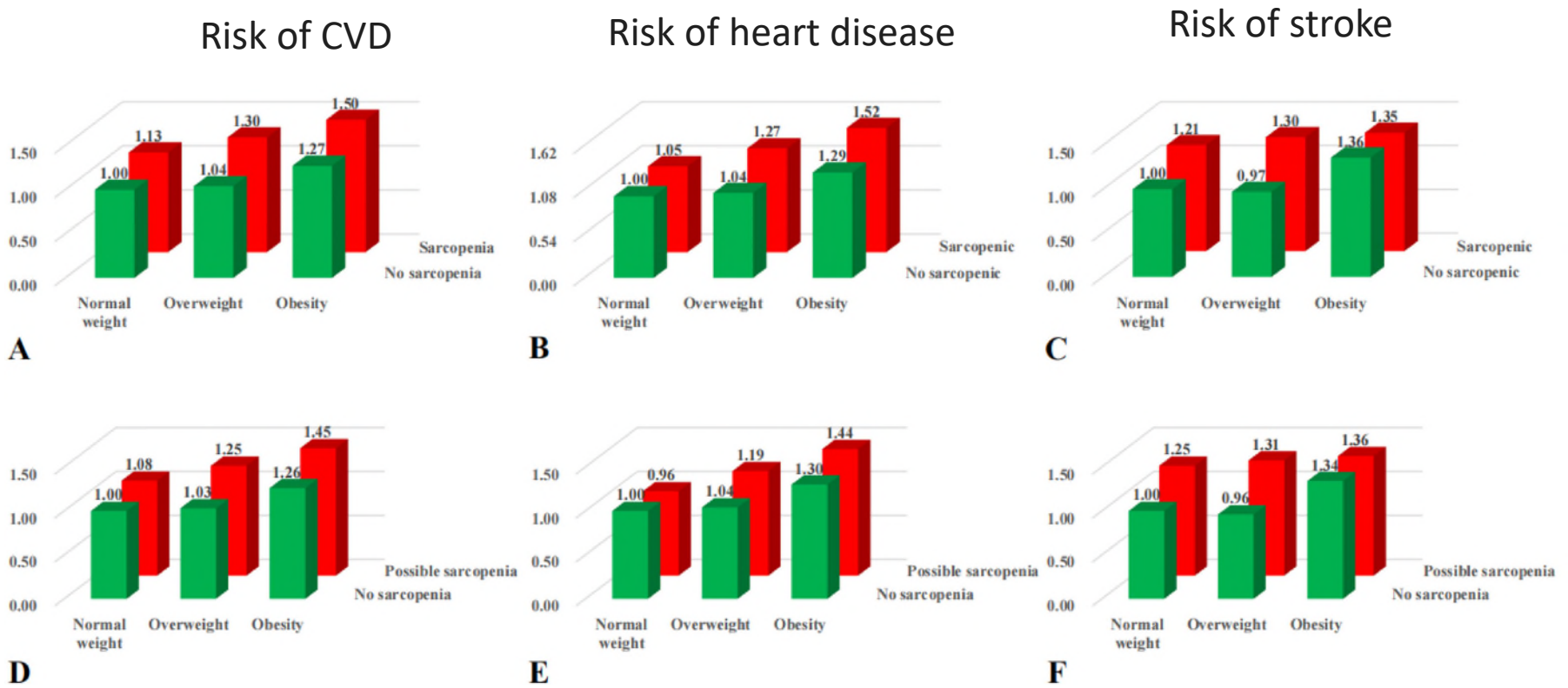
Improvement in Life Expectancy at 65 from 1987 to 1993 (Santé-Québec)



Sarcopenic Obesity Increases the Risk of CVD more than Sarcopenia and Obesity Alone

Sarcopenic obesity participants

Possibly sarcopenic obesity participants



Jiang et al., Clinical Nutrition, 2024