Strategies to mitigate age-associated declines in skeletal muscle mass and function

Professor Bethan E. Phillips PhD
Professor of Translational Physiology,
University of Nottingham

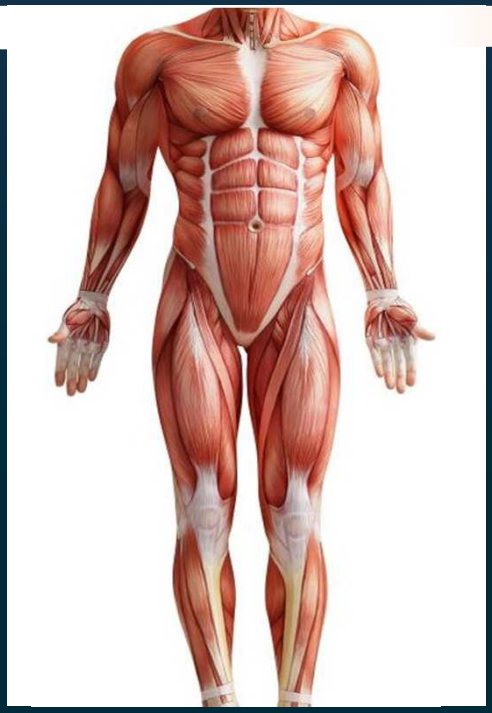
beth.phillips@nottingham.ac.uk

The University of Nottingham
ARTHRITIS RESEARCH UK
MRC Medical Research Council
BBSRC bioscience for the future
The Dunhill Medical Trust

Muscle has a central role in mobility and much more

STRUCTURAL FUNCTIONS

- Physical Movement
- Physical Strength
- Posture and Balance

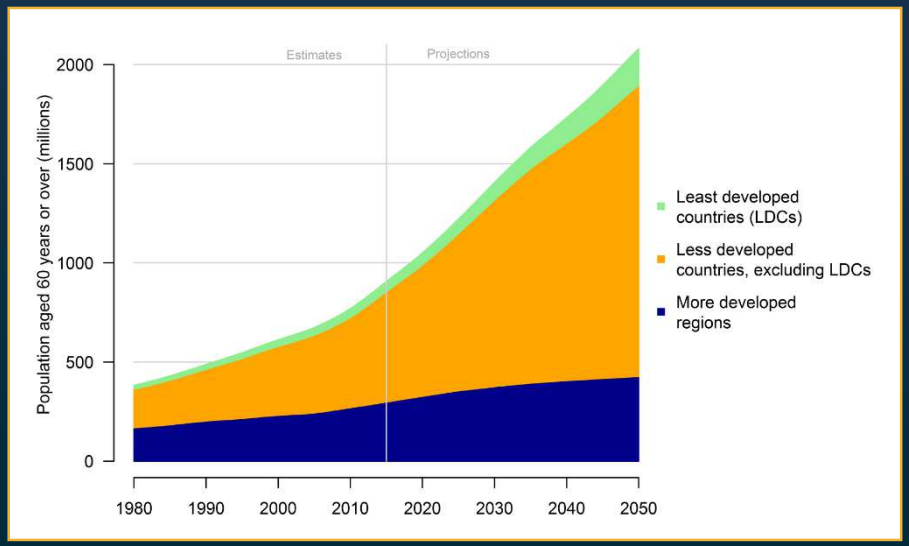


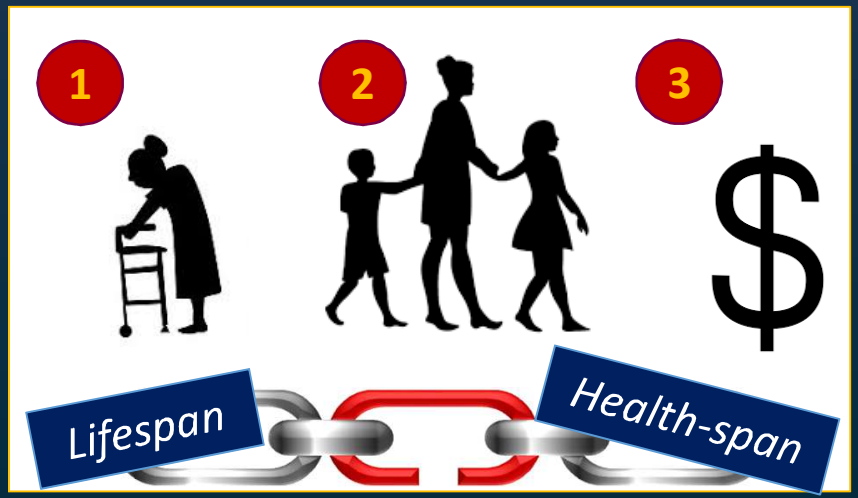
METABOLIC FUNCTIONS

- Main reservoir of proteins
- Glutamine synthesis and storage
- Regulator of glucose levels

Argiles JM, et al. *J Am Med Dir Assoc*. 2016;17(9):789-796.

Population ageing





Now:

- More people over 60 y than under 5 y

By 2050:

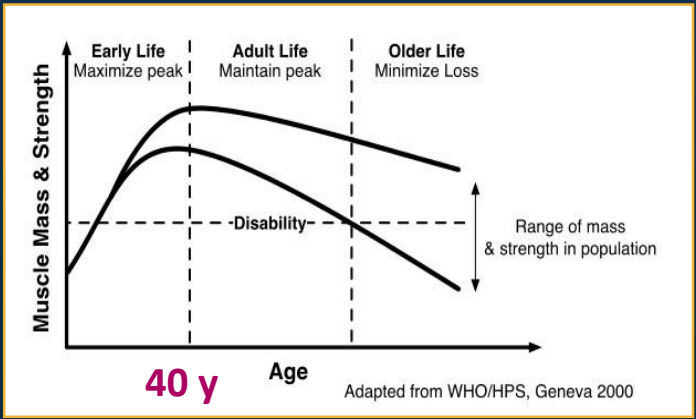
- Those over 60 y will rise from 12-22%
- 80% of over 60 y will live in low & middle-income countries

Decade of healthy ageing

United Nations, 2017: World Population Prospects: the 2017 Revision. Available online: https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2017_Highlights.pdf Last accessed April 2024.

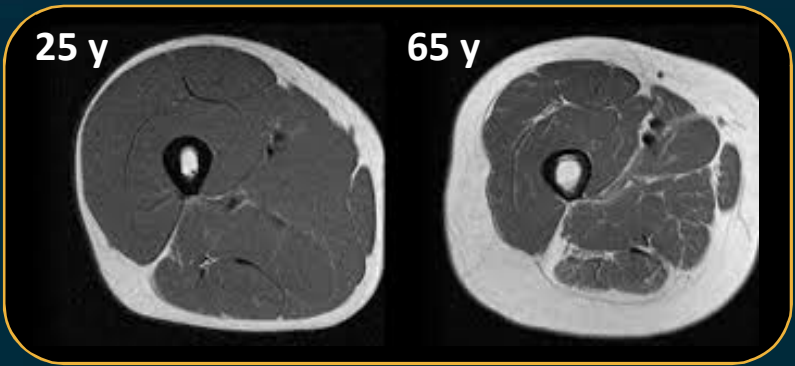
Muscle health for older adults: sarcopenia

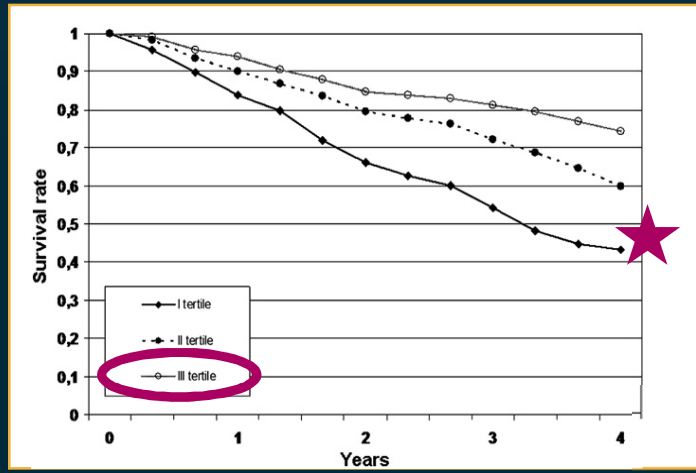
ICD10-CM Code for Sarcopenia



Sarcopenia:
The age-associated loss of muscle mass and function

Sarcopenia Prevalence:
- 5-13% 60-70 y olds
- > 50% in 80+ y olds





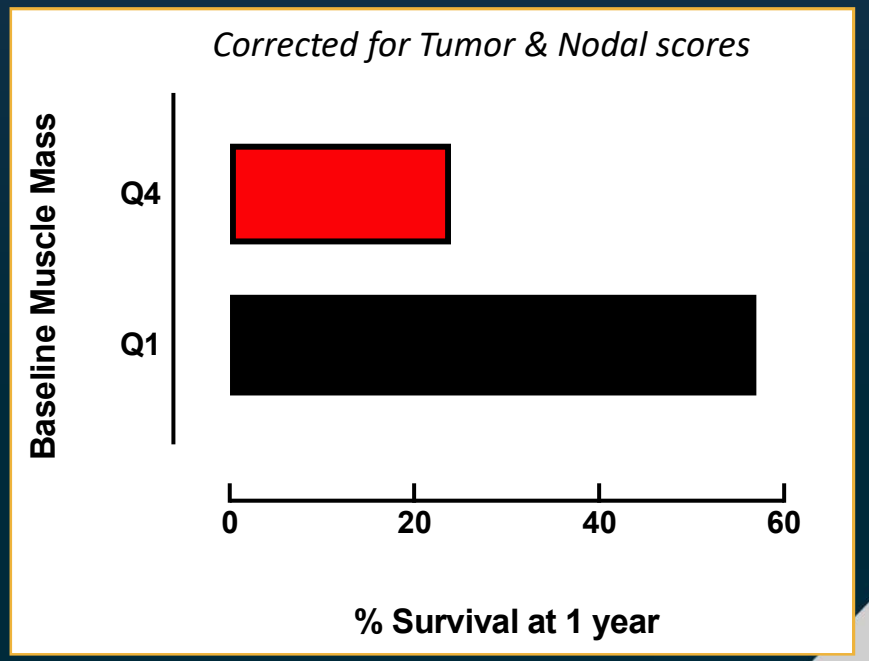
1. McLeod M, et al. *Biogerontology*. 2016;17(3):497-510; 2. WHO, 2000: The implications for training of embracing a life course approach to health. Available online: https://apps.who.int/iris/bitstream/handle/10665/69400/WHO_NMH_HPS_00.2_eng.pdf Last accessed April 2024; 3. Mitchell WK, et al. *Front Physiol*. 2012;3:260; 4. von Haehling S, et al. *J Cachexia Sarcopenia Muscle*. 2012;3(4):213-217; 5. Landi F, et al. *Clin Nutr*. 2010;29(4):441-447.

Muscle health for older patients

Low muscle mass in medical and surgical admissions (Geneva):

- Hospitalisation
- Increased length of stay
- Hospital outcomes:
  - Complications and mortality

Surgical (spinal) cancer patients:

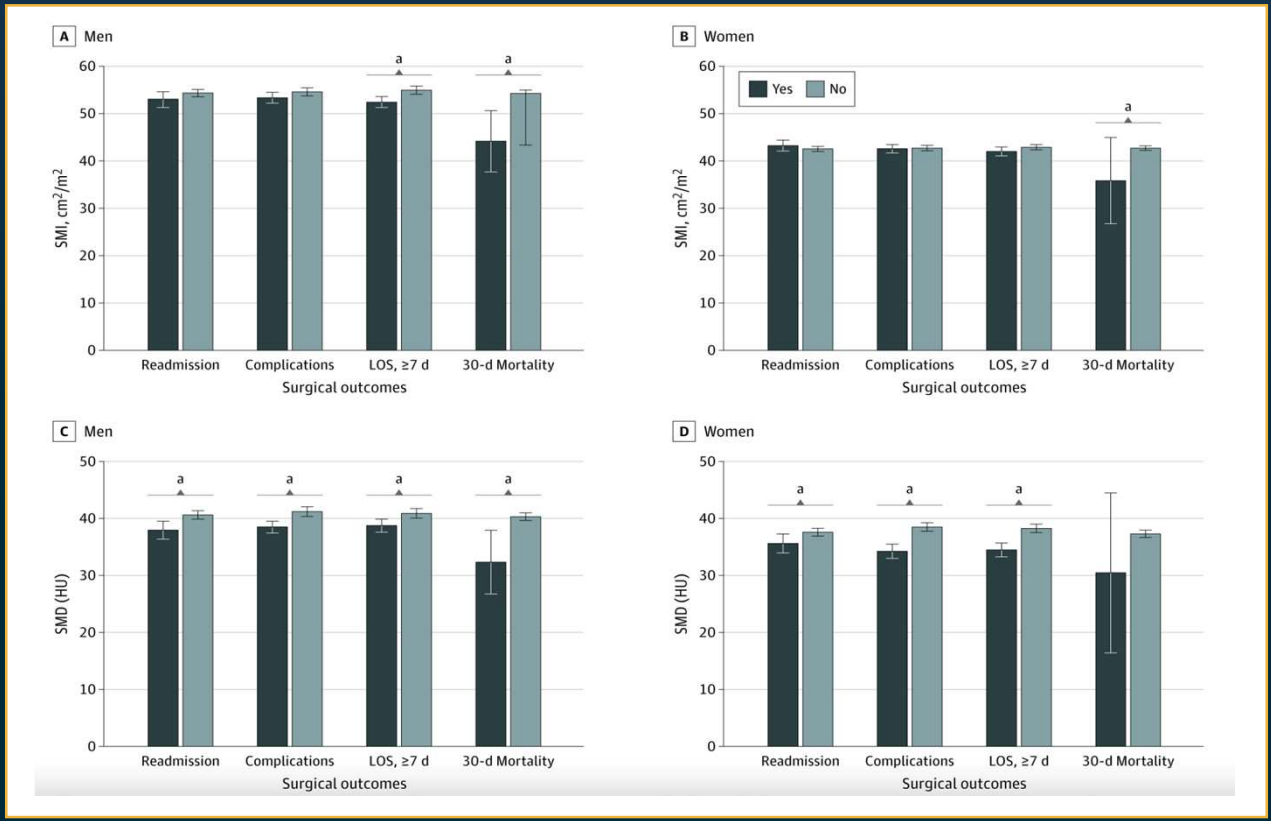


1. NIH, 2024: Ependymoma: Diagnosis and Treatment. Available online: https://www.cancer.gov/rare-brain-spine-tumor/tumors/ependymoma Last accessed February 2024; 2. Thibault R, et al. *Intensive Care Med*. 2016;42(9):1445-1453;
3. Gakhar H, et al. *Eur Spine J*. 2015;24(10):2150-2155.

Muscle health for older surgical patients

Muscle mass:

Muscle quality:



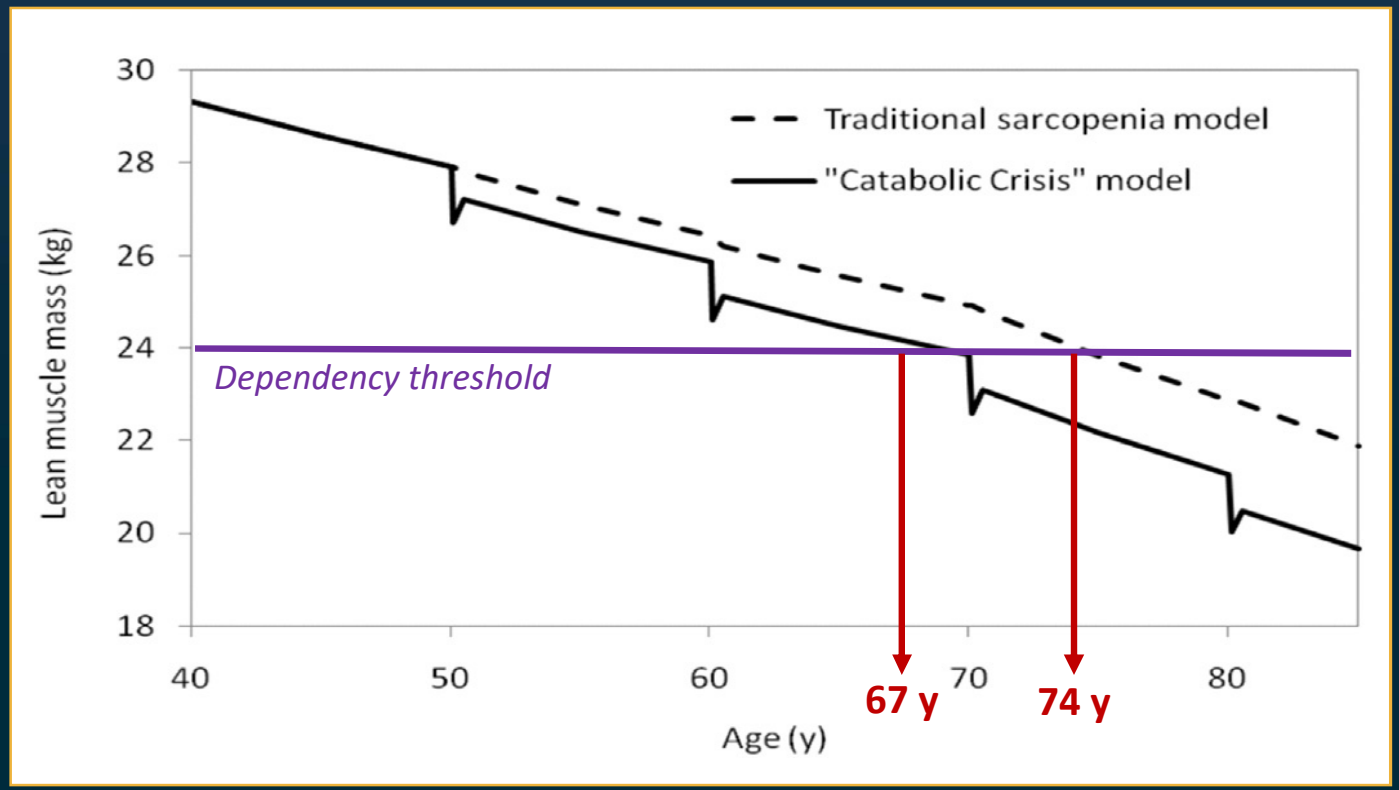
N=1,637

a = P < 0.05

LOS=Length of Stay; SMI=Skeletal Muscle Index; SMD=Skeletal Muscle Radiodensity

Xiao J, et al. *JAMA Surg*. 2020;155(10):942-949.

Sarcopenic trajectory and hospitalisation

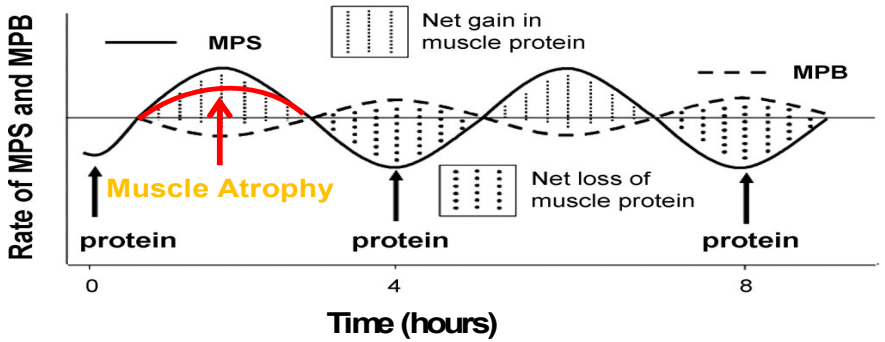


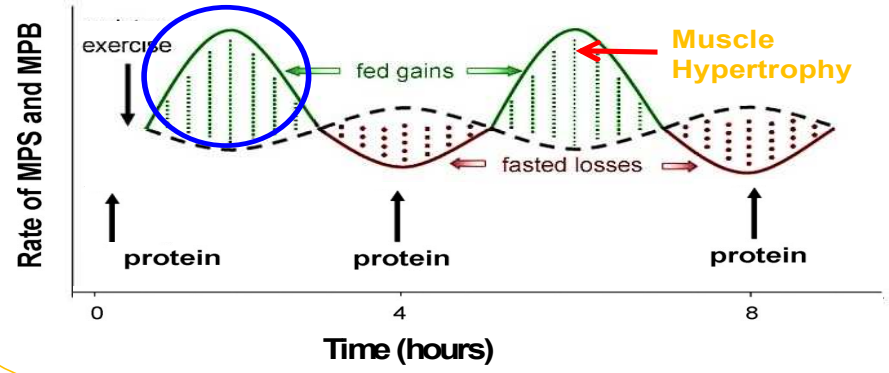
Rates of atrophy in older vs. younger adults:
10 d = 28 d, bed rest
~3x faster

Rates of atrophy in patients vs. research participants:
Faster in ICU and even ankle fracture patients

1. English KL, et al. *Curr Opin Clin Nutr Metab Care*. 2010;13(1):34-39; 2. Kortebein P, et al. *JAMA*. 2007;297(16):1772-1774;
3. Hardy EJO, et al. *J Cachexia Sarcopenia Muscle*. 2022;13(6):2616-2629.

Physiology of muscle mass maintenance





INACTIVITY

E.g.,
- Hospitalization
- Inactivity of ageing

EXERCISE

E.g.,
- Resistance exercise training (RET)

HYPERTROPHY

=

EXERCISE

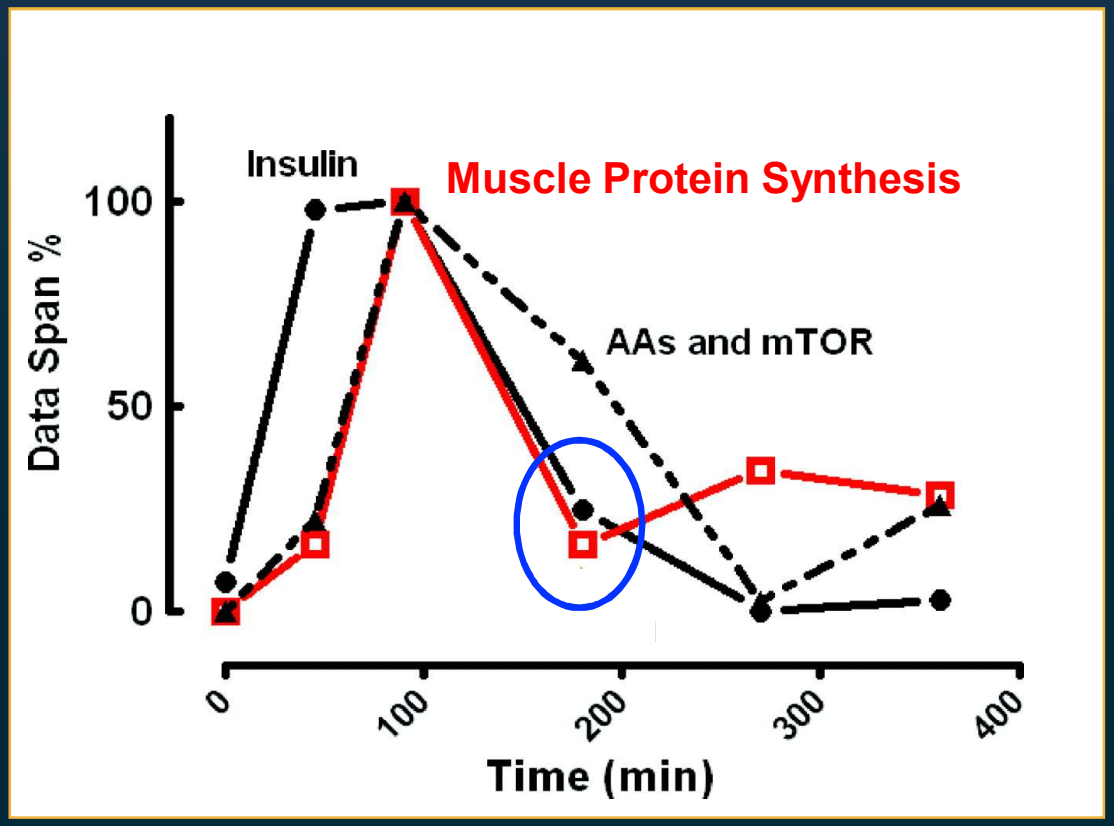
+

PROTEIN

MPS=Muscle Protein Synthesis;
MPB=Muscle Protein Breakdown

1. Burd N, et al. *J Physiol.* 2009;106(5):1692-701; 2. Breen L, et al. *J Clin Endocrinol Metab*. 2013;98(6):2604-2612;
3. Bukhari SS, et al. *Am J Physiol Endocrinol Metab*. 2015;308(12):E1056-E1065.

Protein consumption does not = unlimited hypertrophy



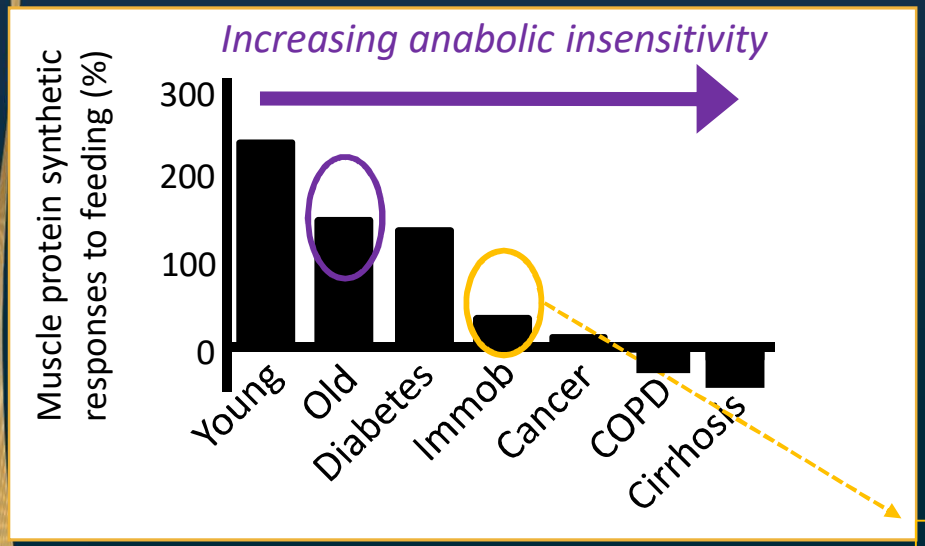
"Muscle Full" Phenomenon

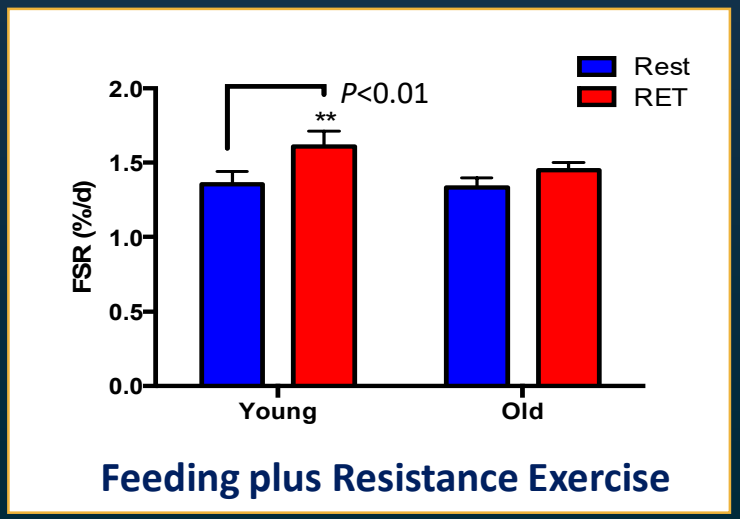
MPS "switches-off" despite continued availability of circulating EAAs and anabolic signaling

AA=Amino Acids; EAA=Essential Amino Acid; mTOR=Mechanistic Target of Rapamycin; MPS=Muscle protein synthesis

Atherton PJ, et al. *J Physiol*. 2012;590(5):1049-1057.

Anabolic resistance of advancing age



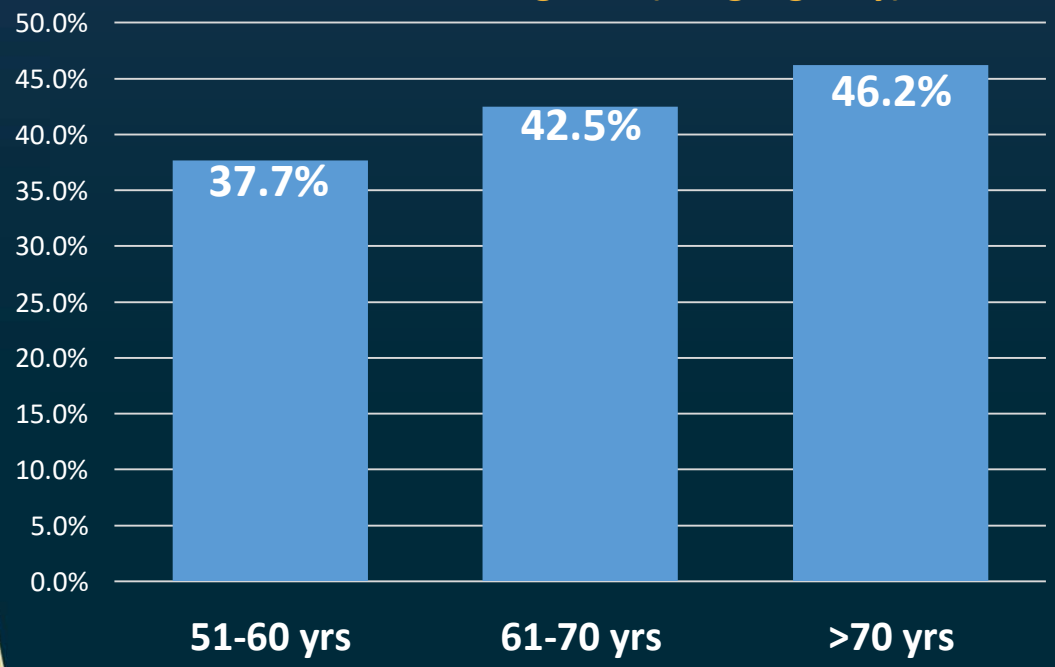


COPD=Chronic Obstructive Pulmonary Disorder;
LBM=Lean Body Mass, FSR=Fractional Synthetic Rate

- Inactivity of Ageing
- Illness
- Post-fall
- Post-surgery

1. Moore DR, et al. *J Gerontol: Series A.* 2015;70(1):57-62; 2. Brook MS, et al. *Curr Opin Clin Nutr Metab Care*. 2017;20(6):433-439;
3. Brook MS, et al. *J Physiol*. 2016;594(24):7399-7417.

1 in 3 ‘older’ adults are not consuming enough protein



NHANES Dietary intake data (US)
N=11,728

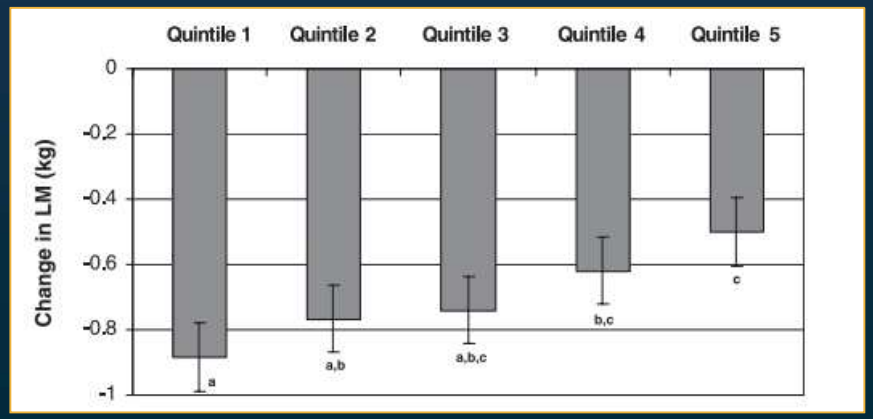
50% of hospitalised patients do not consume the full meal provided by the hospital

Post-operative patients after major abdominal surgery consumed ~12% of the new ESPEN recommendation for protein (1.5 g/kg/day)

RDA=Recommended Dietary Allowance; NHANES=National Health and Nutrition Examination Survey; ESPEN=European Society for Clinical Nutrition and Metabolism.

1. Krok-Schoen JL, et al. *J Nutr Health Aging*. 2019;23(4):338-347; 2. Hardy EJO et al. *Eur J Clin Nutr.* 2023:77(4):503-505.

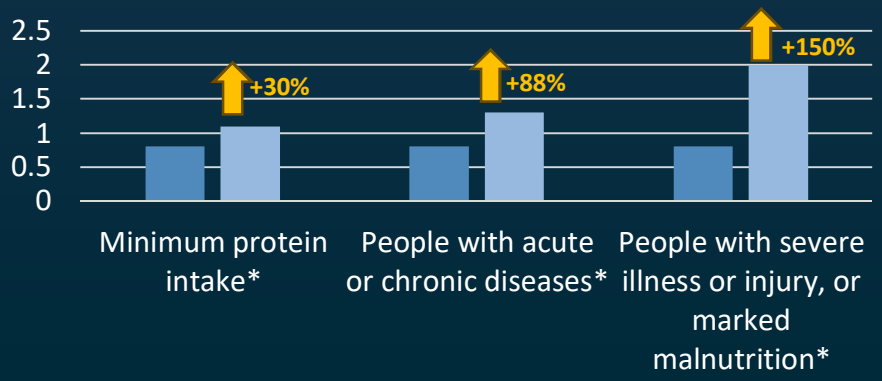
Dietary protein and muscle mass in older adults



Protein intake ranged from 0.7 to 1.1 g/kg/day

Higher protein intake was associated with better preservation of lean mass over a 3-year period

New recommendations call for higher protein intake (g per kg of body weight) in those aged >65 years

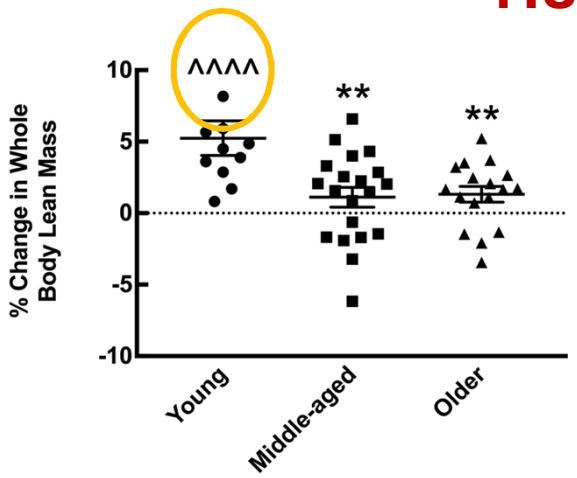


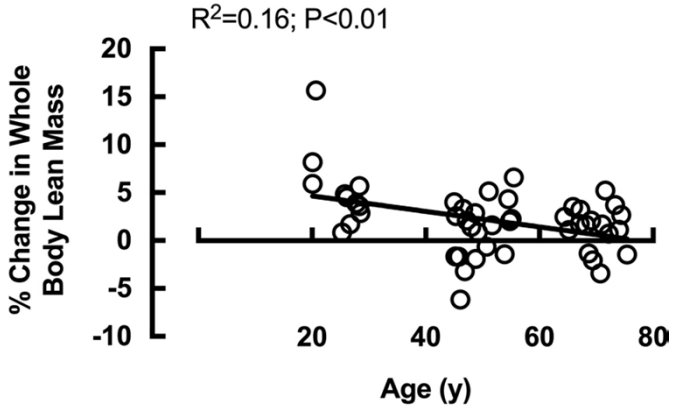
LM=Lean Mass

1. Houston DK, et al. *Am J Clin Nutr*. 2008;87(1):150-155; 2. Bauer J, et al. *J Am Med Dir Assoc*. 2013;14(8):542-559; 3. Deutz NE, et al. *Clin Nutr*. 2014;33(6):929-936; 3. Bauer J, et al. *JAMDA*. 2013;14:542-559.

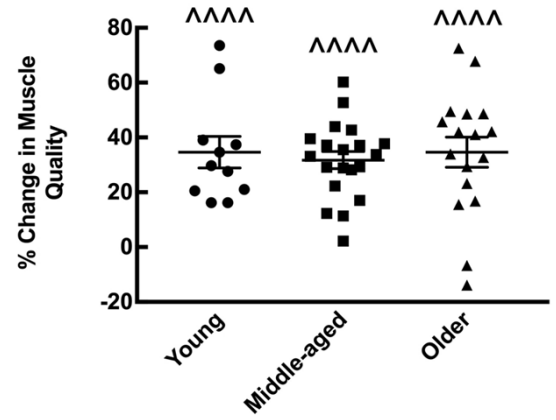
Resistance exercise training (RET) for older adults

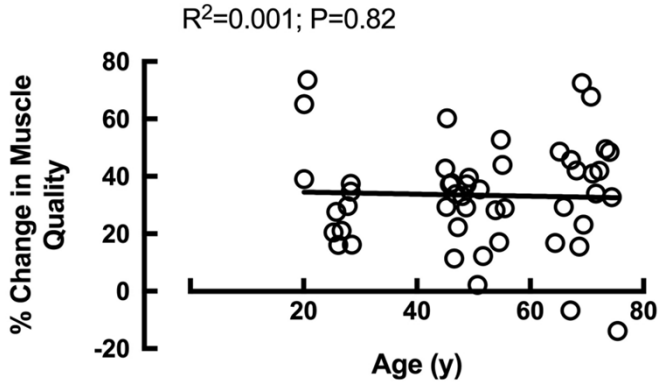
MUSCLE MASS





MUSCLE FUNCTION





^ = vs. pre-RET;
* = vs. young response

Muscle Mass & Cardiorespiratory Fitness

Cardiorespiratory Fitness Predicts Mortality and Hospital Length of Stay After Major Elective Surgery in Older People

Snowden, Chris P. MD[*,†]; Prentis, James FRCA[*,†]; Jacques, Byron FRCS[‡]; Anderson, Helen FRCA[†]; Manas, Derek FRCS[*,‡]; Jones, Dave PhD[*]; Trenell, Michael PhD[*]

Annals of Surgery: June 2013 - Volume 257 - Issue 6 - p 999–1004
doi: 10.1097/SLA.0b013e31828dbac2
Feature

Related to CRF at time of operation

Tech Coloproctol. 2014 Dec;18(12):1153-9. doi: 10.1007/s10151-014-1232-y. Epub 2014 Nov 8.

One-third of patients fail to return to work 1 year after surgery for colorectal cancer.

20000 40000 60000 80000

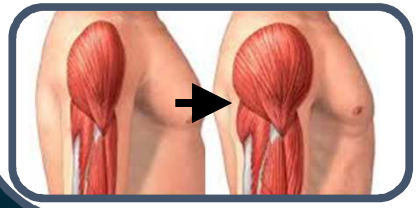
Lean muscle mass (g)

Williams JP et al., 2013

Traditional forms of exercise training

‘RESISTANCE’

Physiological Adaptation: MUSCLE MASS



HEALTH

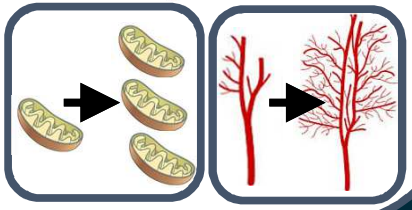
- ↓ BLOOD PRESSURE
- ↓ BLOOD SUGAR
- ↓ LIPID PROFILES
- ↓ OBESITY
- ↑ MUSCLE QUALITY
- ↑ PSYCHOLOGICAL HEALTH

↓

- ↓ CHRONIC DISEASE RISK
- ↑ HEALTHY LIFE YEARS
- ↑ LONGEVITY

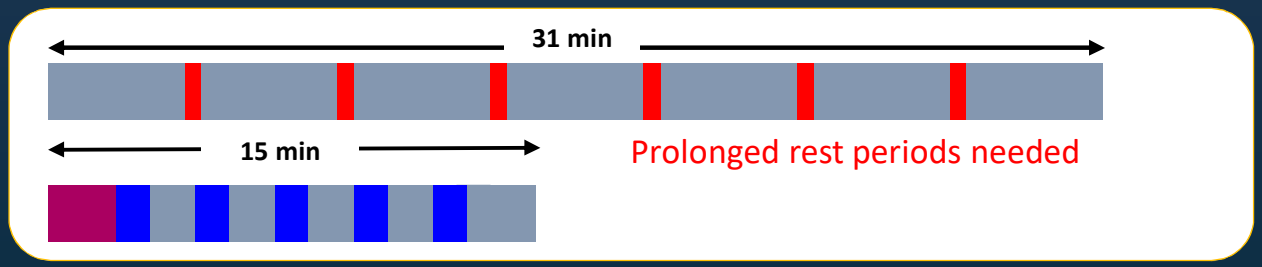
‘ENDURANCE’

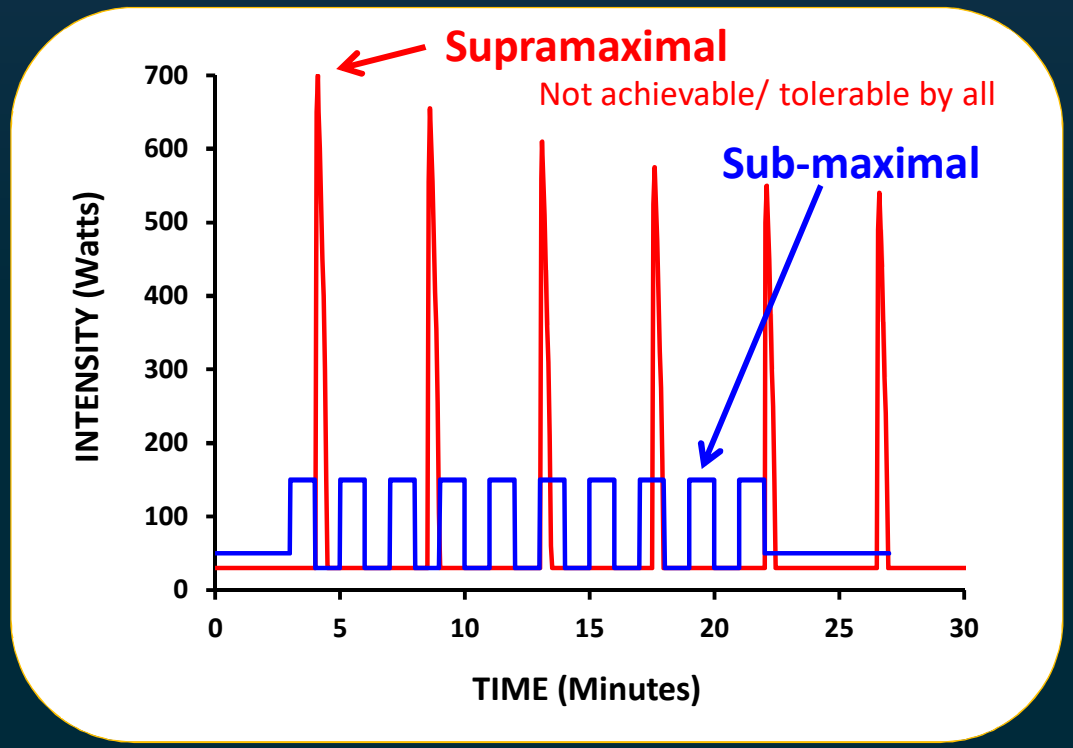
Physiological Adaptation: AEROBIC FITNESS



HIGH INTENSITY INTERVAL TRAINING (HIIT)???

High intensity interval training (HIIT)





Time Efficiency

Intensity

Format/Modality

~~7 x 1 m @ 100%~~

5 x 1 min @ ~120%

Study 1 - Healthy HIIT: 68.4±0.9 years, BMI:26±2 kg/m^2

Study 2 - Colorectal HIIT: 67.6±2.6 years, BMI:27±1 kg/m^2

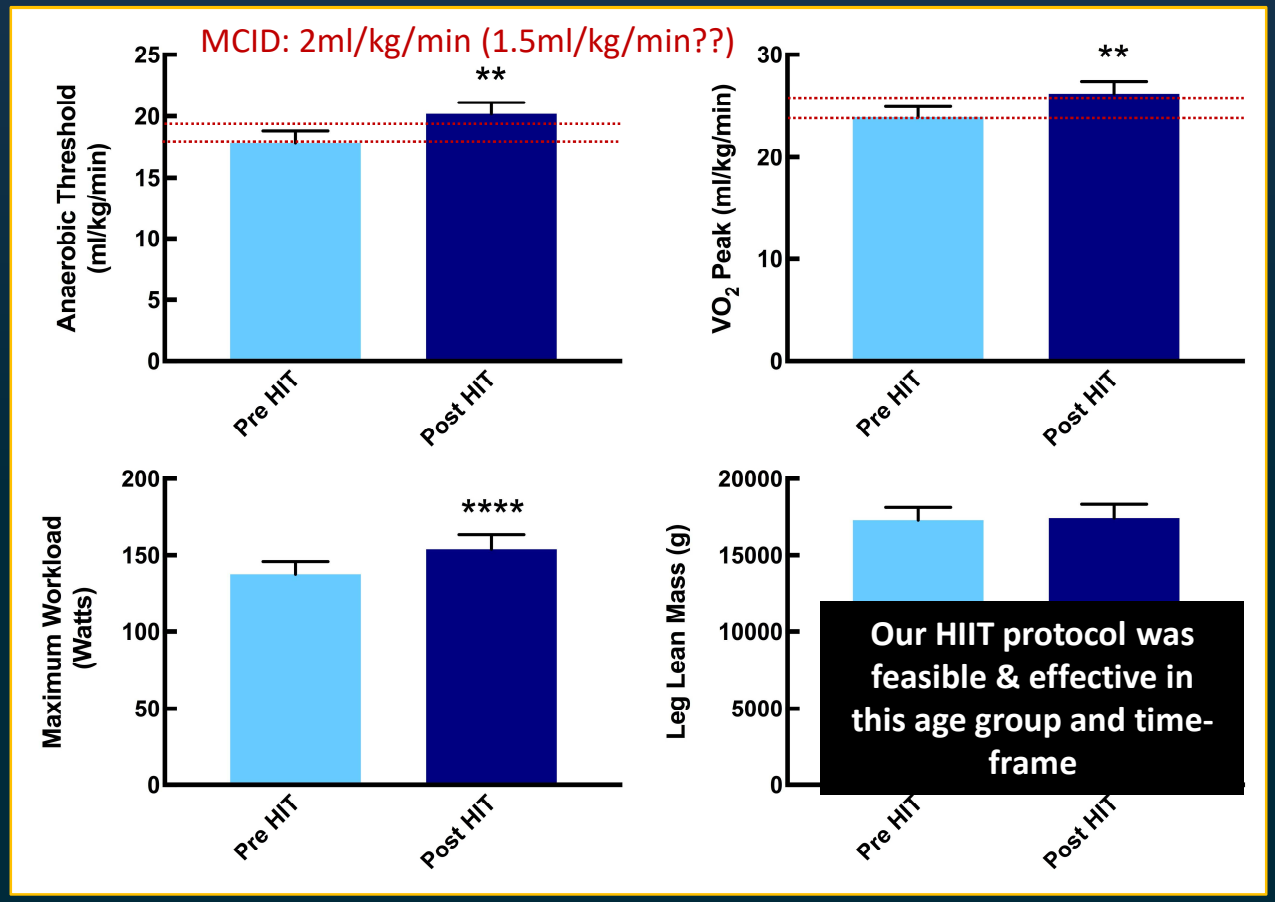
Study 3 - Urological HIIT: 71.3±0.8 years, BMI:26±3 kg/m^2

Study 4 - 'Elderly' eHIIT: 84.6±3.8 years, BMI:27±3 kg/m^2

Pre & Post HIIT Assessments:

* Anaerobic threshold
* VO_2 peak
* Exercise performance
* Muscle mass/architecture
* Blood pressure/heart rate/O_2 utilisation

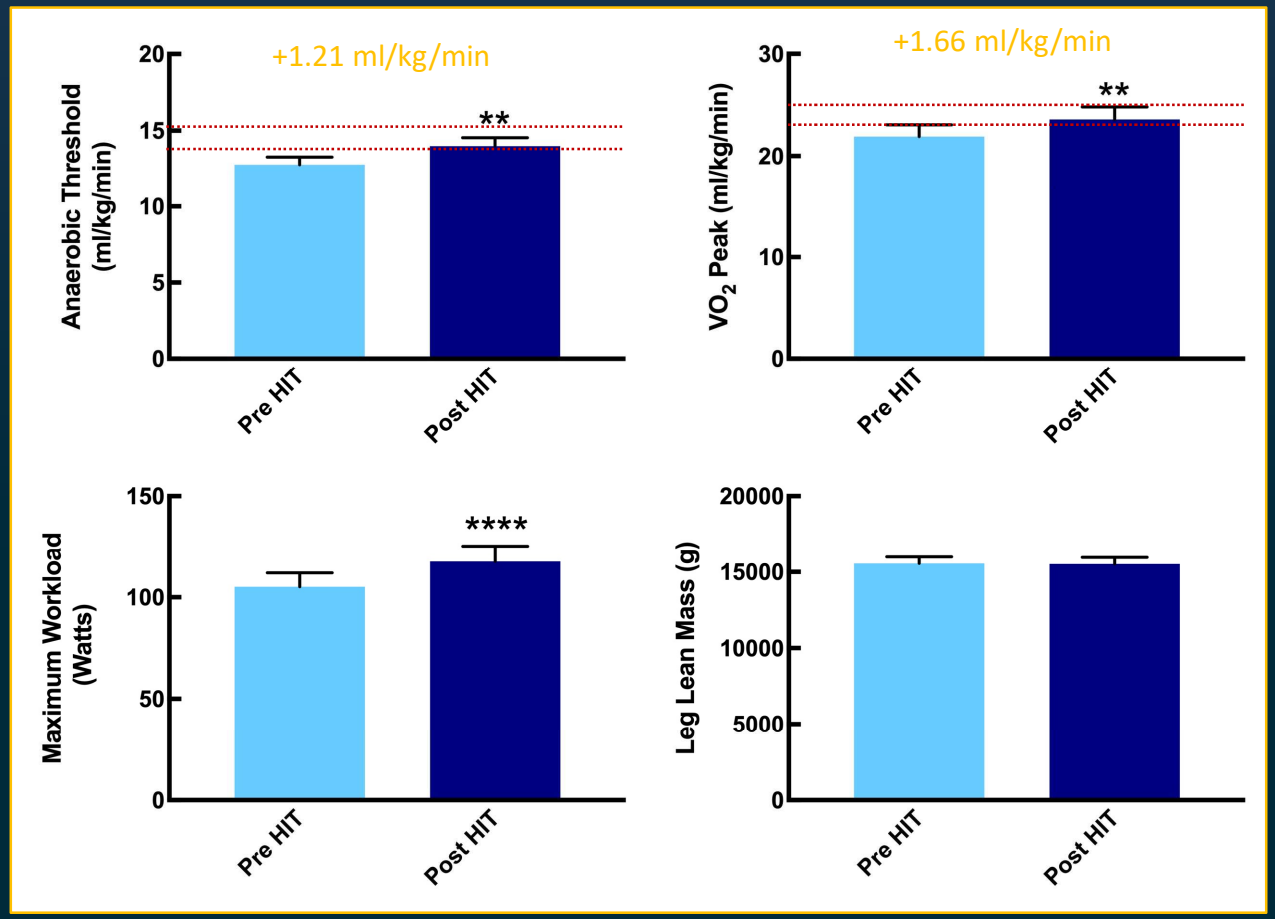
Healthy HIIT: 68.4±0.9 years, BMI:26±2 kg/m^2



Boereboom CL *et al.*, 2016

**=P<0.01; ****=P<0.001 vs. Pre HIIT

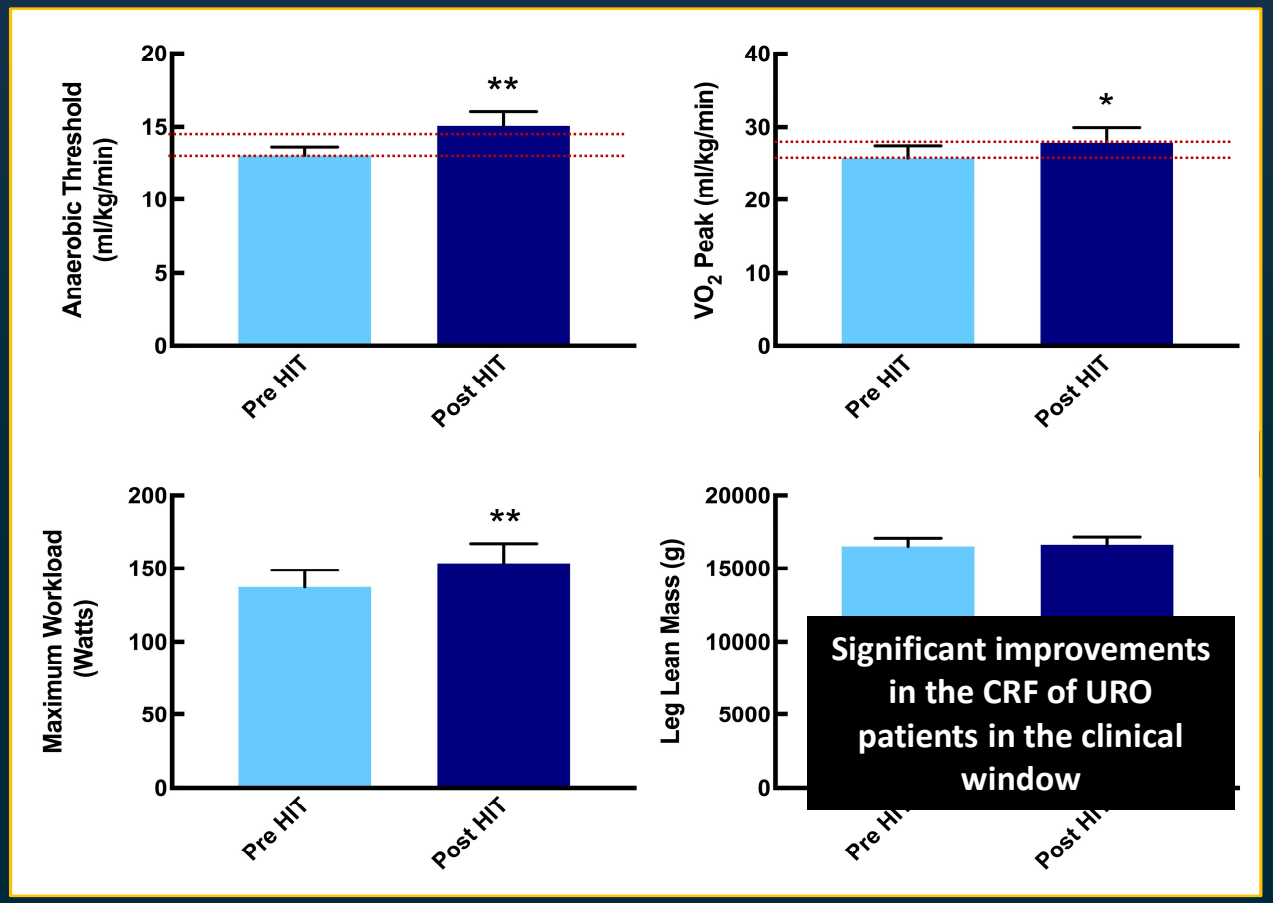
eHIIT: 84.6±3.8 years, BMI:27±3 kg/m^2



Blackwell JEM et al., 2019

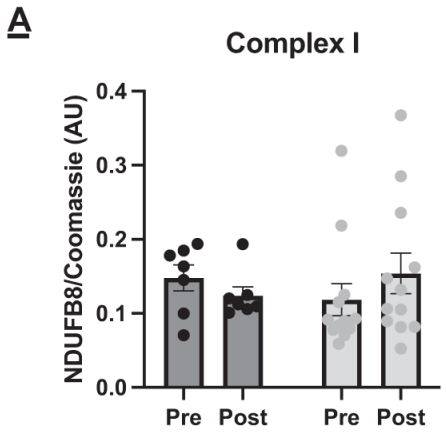
**=P<0.01; ****=P<0.001 vs. Pre HIIT

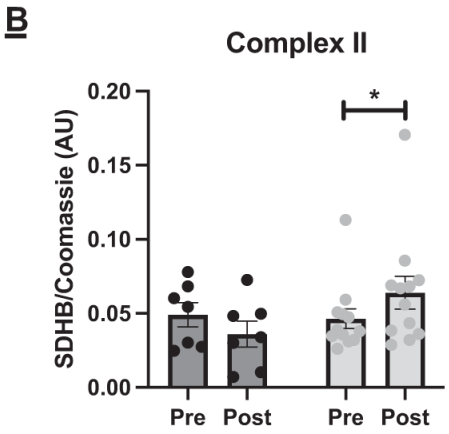
Urological HIIT: 71.3±0.8 years, BMI:26±3 kg/m^2

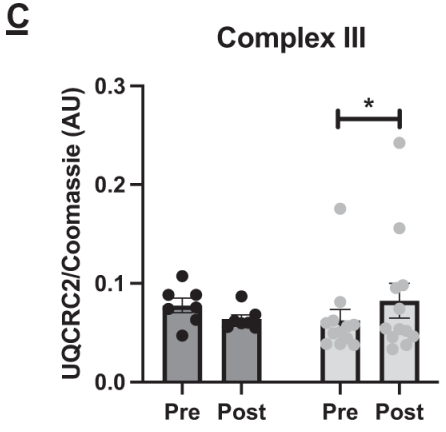


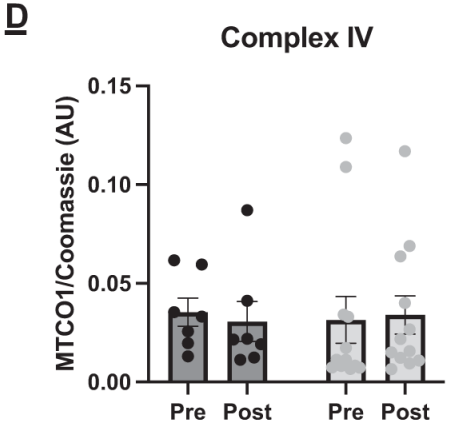
Blackwell JEM et al., 2019

*=P<0.05; **=P<0.01 vs. Pre HIIT





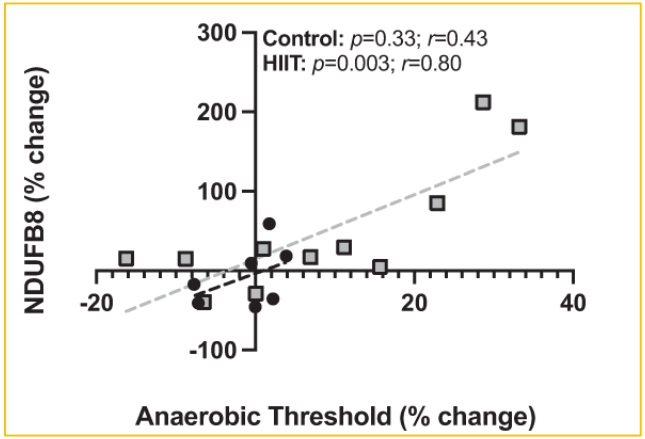




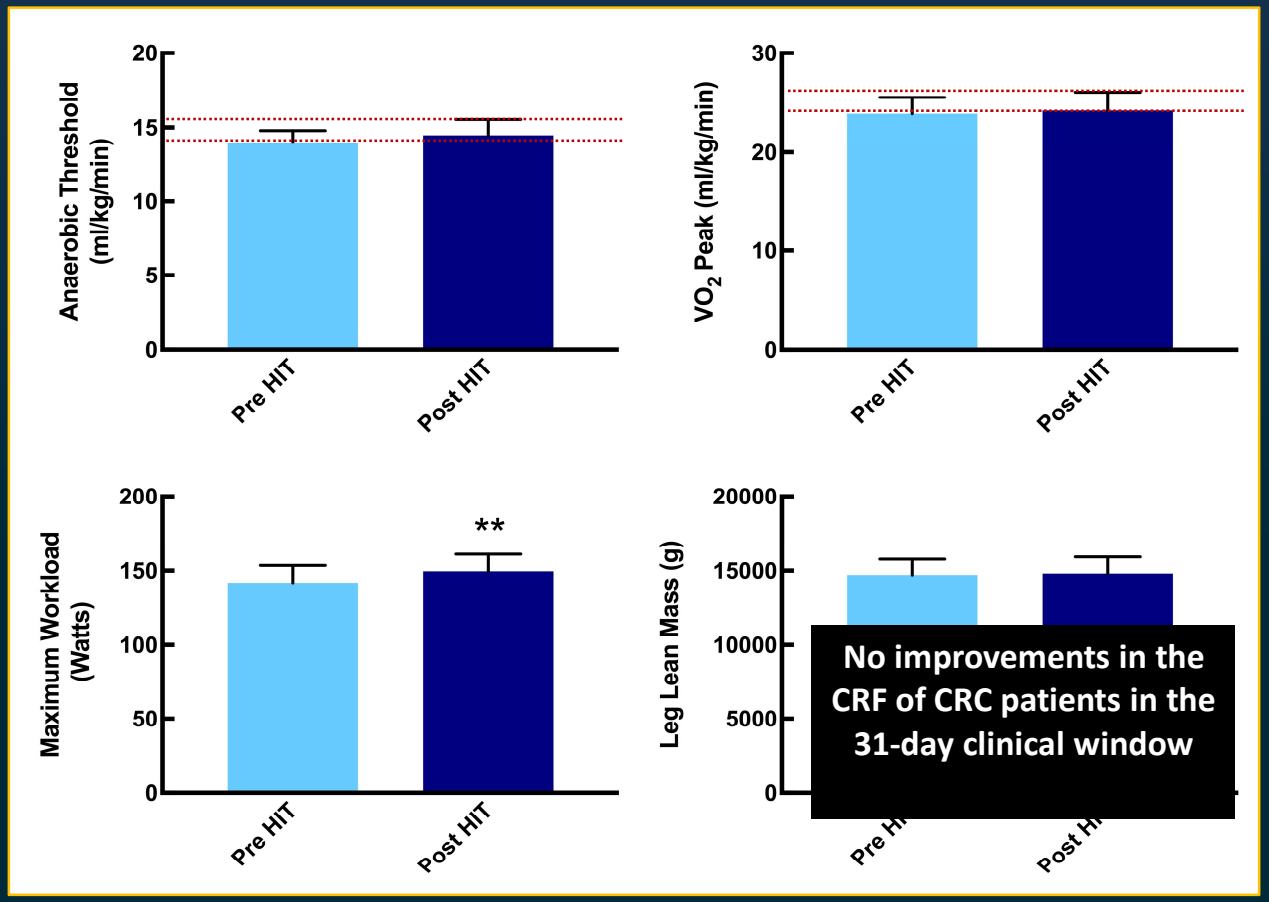
Control
HIIT

Blackwell JEM et al., 2023

HIIT improves the mitochondrial function of patients with colorectal cancer, and this is related to improvements in CRF

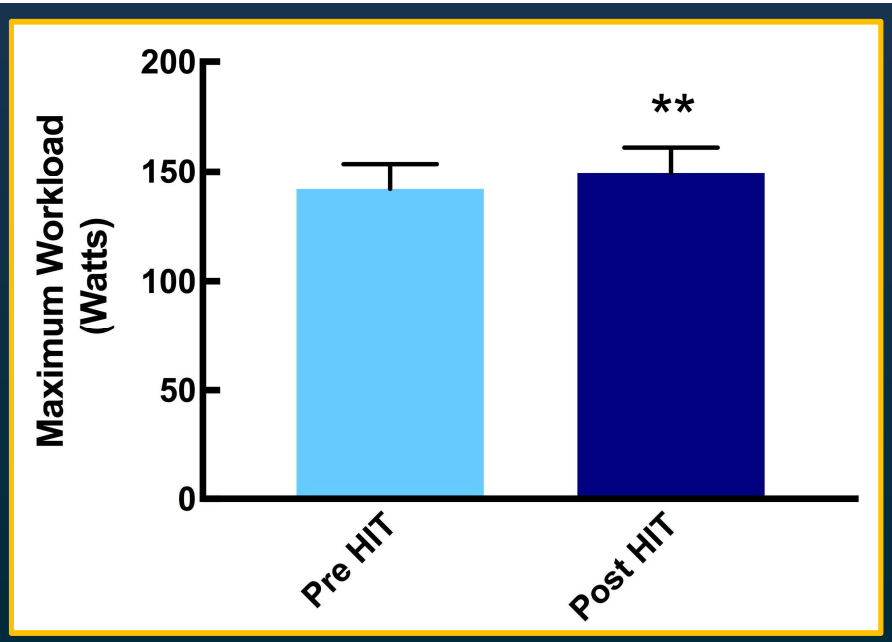


Colorectal HIIT: 67.6±2.6 years, BMI:27±1 kg/m^2



Boereboom CL *et al.*, 2019

**=P<0.01 vs. Pre HIIT



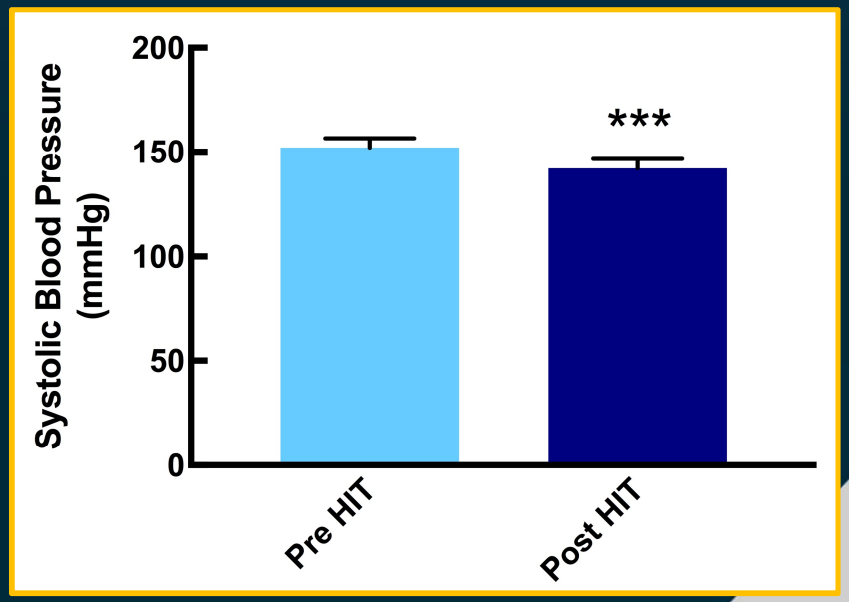
Plus, <u>may</u> improve post-operative outcomes?

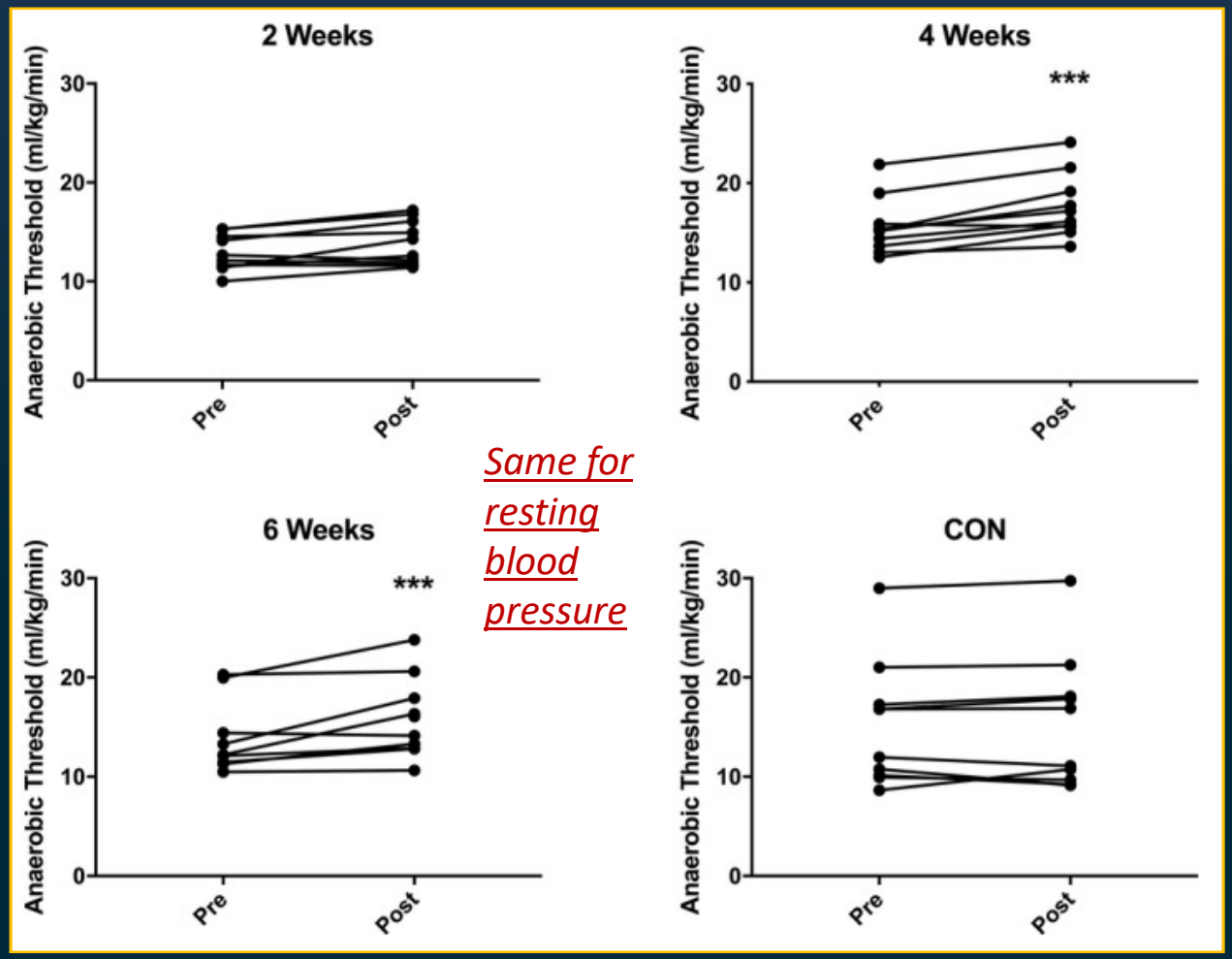
- Complications
- Length of stay
- Return to normal activities
- Reduced muscle loss

<u>Benefits for all:</u>

- Improved exercise efficiency
- Improved health perception
- Increased muscle thickness (trend)

- *<u>Improved resting blood pressure</u>*



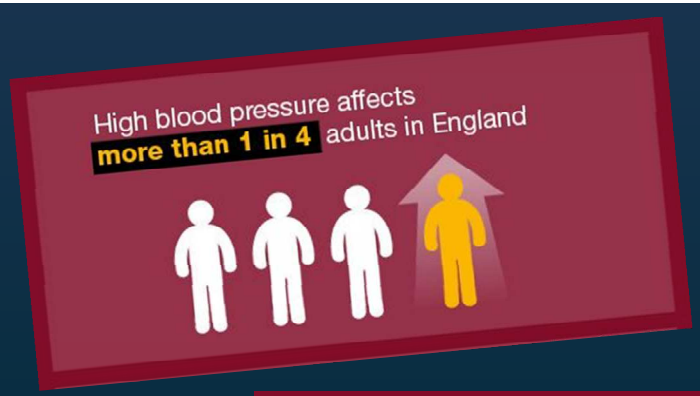


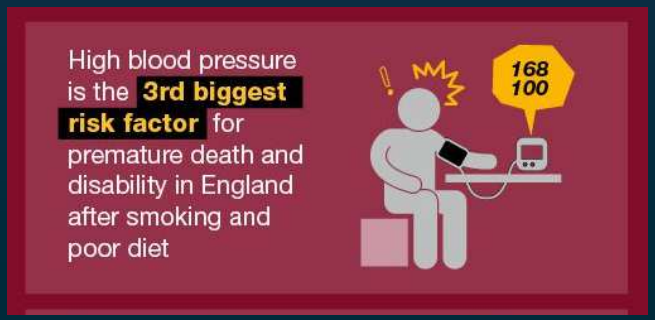
Same for resting blood pressure

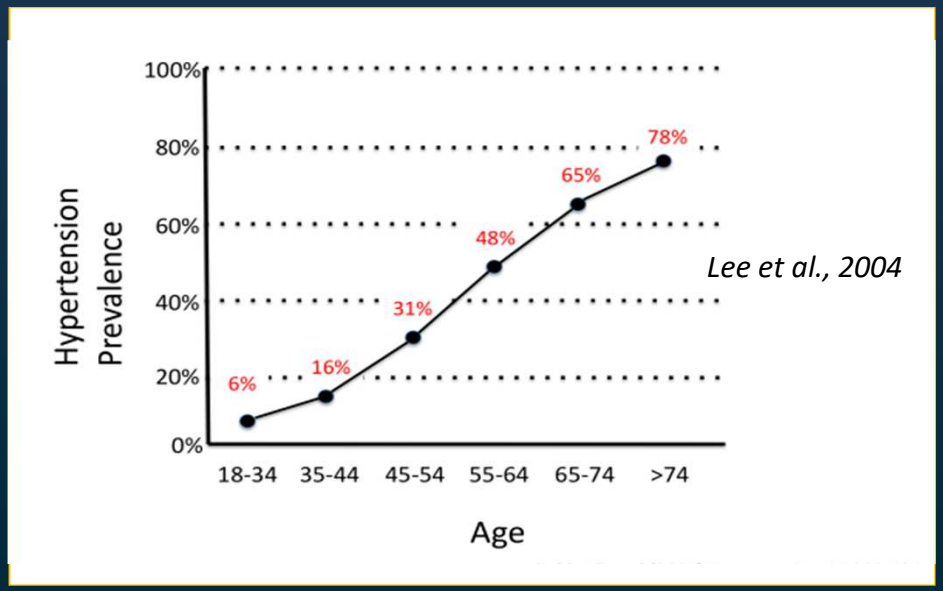
But what about CRF & muscle mass in CRC?

Exercise Prehabilitation in Colorectal Cancer

Herrod PJJ et al., 2020







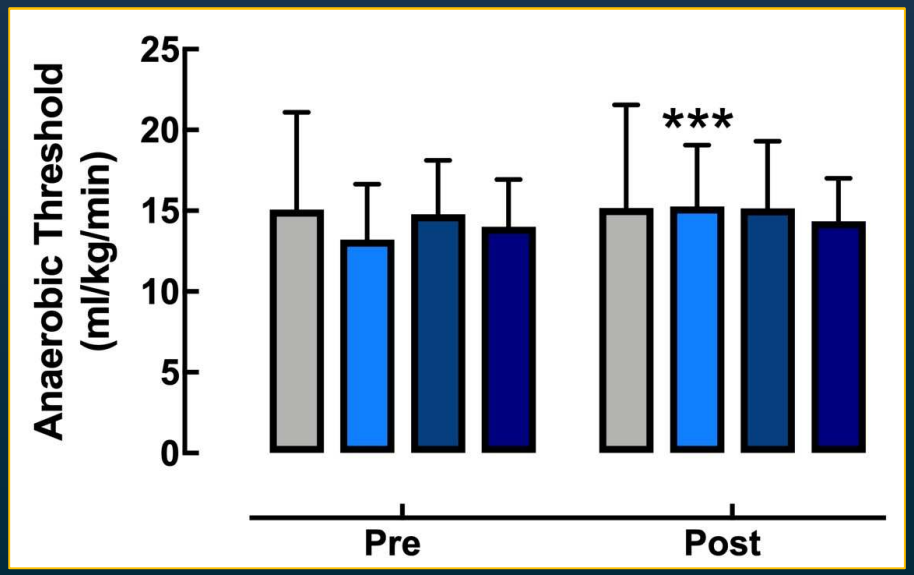
Lee et al., 2004

"Hypertension (HTN) is one of the most common chronic medical conditions in the elderly… (it) is an important risk factor for cerebro-cardiovascular disease, and it has a critical impact on quality of life and maintenance of activities of daily living (ADL) among the elderly."

Kang et al., 2017

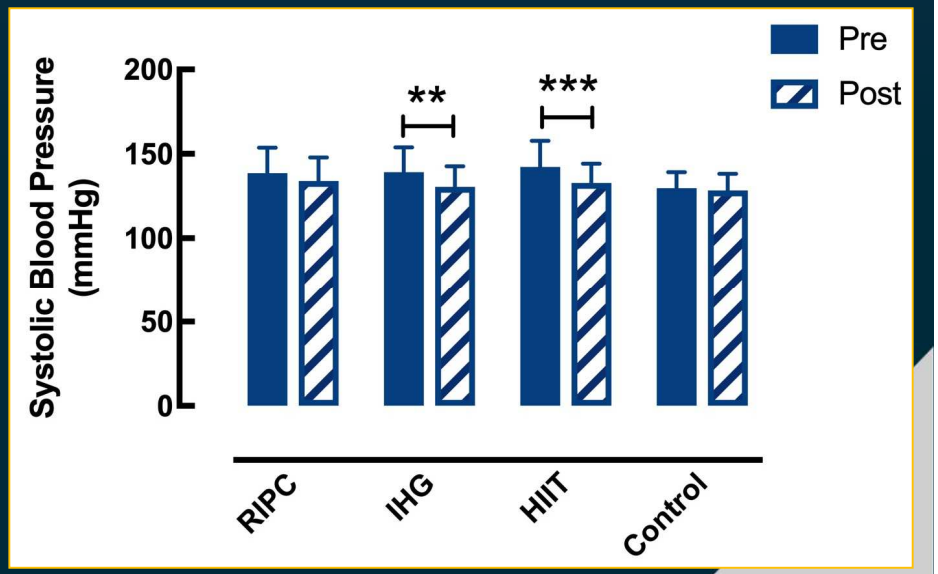
‘Static’ Exercise Interventions

			**CONTROL**
REPEATED REMOTE ISCHEMIC PRE-CONDITIONING	**ISOMETRIC HANDGRIP TRAINING**	**HIGH INTENSITY INTERVAL TRAINING**	**NO INTERVENTION**
3 x 3 min “on” 3 min “off” **15 min total**	**4 x 2 min “on” 2 min “off”** **14 min total**	**5 x 1 min “on” 1.5 min “off”** **15 min total**	**NO INTERVENTION**



Utility:

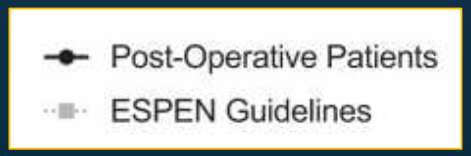
- A potential adjuvant or alternative to HIIT
- Easy home-based translation

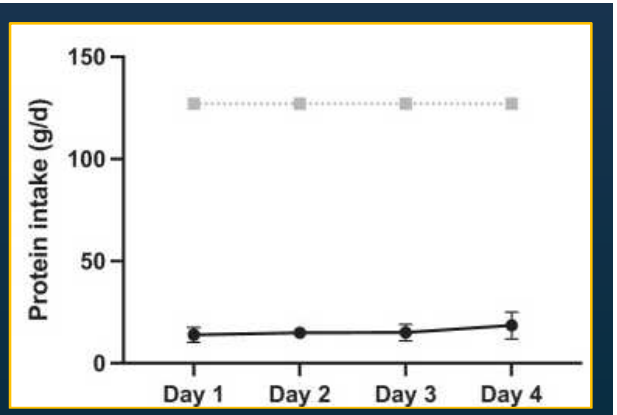


MCID: 10mmHg

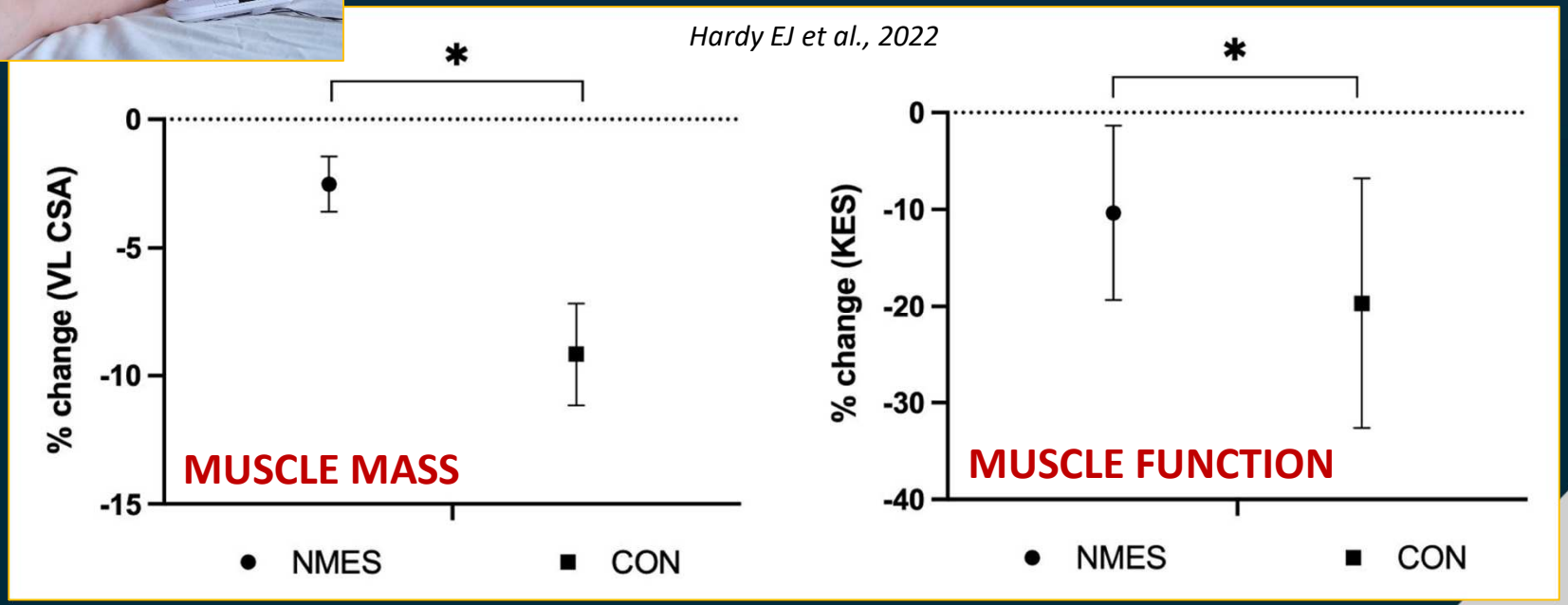
Herrod PJJ et al., 2019

Neuromuscular electrical stimulation (NMES)





Hardy EJ et al., 2022



THANK YOU…

- All of my colleagues in the Centre of Metabolism, Ageing & Physiology (CoMAP)
- Our national and international collaborators
- All of our research volunteers and R4U members

If you are interested in joining R4U please email:
amanda.gates@nottingham.ac.uk