Sepsis en Daarna Lotgenotendag
Zaterdag 17 september 2022, Zwolle

Post Sepsis
ICU acquired weakness

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Disclosures

Prof. van Zanten has received honoraria for advisory board meetings, lectures, research and travel expenses from:

- **Abbott**
- **AOP Pharma**
- **Baxter**
- **Cardinal Health**
- **Dim-3**
- **Fresenius Kabi**
- **Lyric**
- **Mermaid**
- **Nestlé-Novartis**
- **Nutricia-Danone**
- **Rousselot**

Inclusion fees for patients in trials were paid to the local ICU research foundation.

Chair Sepsis Guideline Program The Netherlands
ESPEN guidelines committee Critical Care Nutrition for Adults
ESICM Working Group Gastrointestinal Failure
NESPEN Executive Team

REVIEW

CURRENT OPINION

Poor physical recovery after critical illness: incidence, features, risk factors, pathophysiology, and evidence-based therapies

Yente Floriine Niké Boelens[a,b], *Max Melchers*[a,b], *and Arthur Raymond Hubert van Zanten*[a,b]

- **Injured satellite cells, epigenetic differences and hormonal and mitochondrial disturbances may be involved in sustained ICU-AW.**

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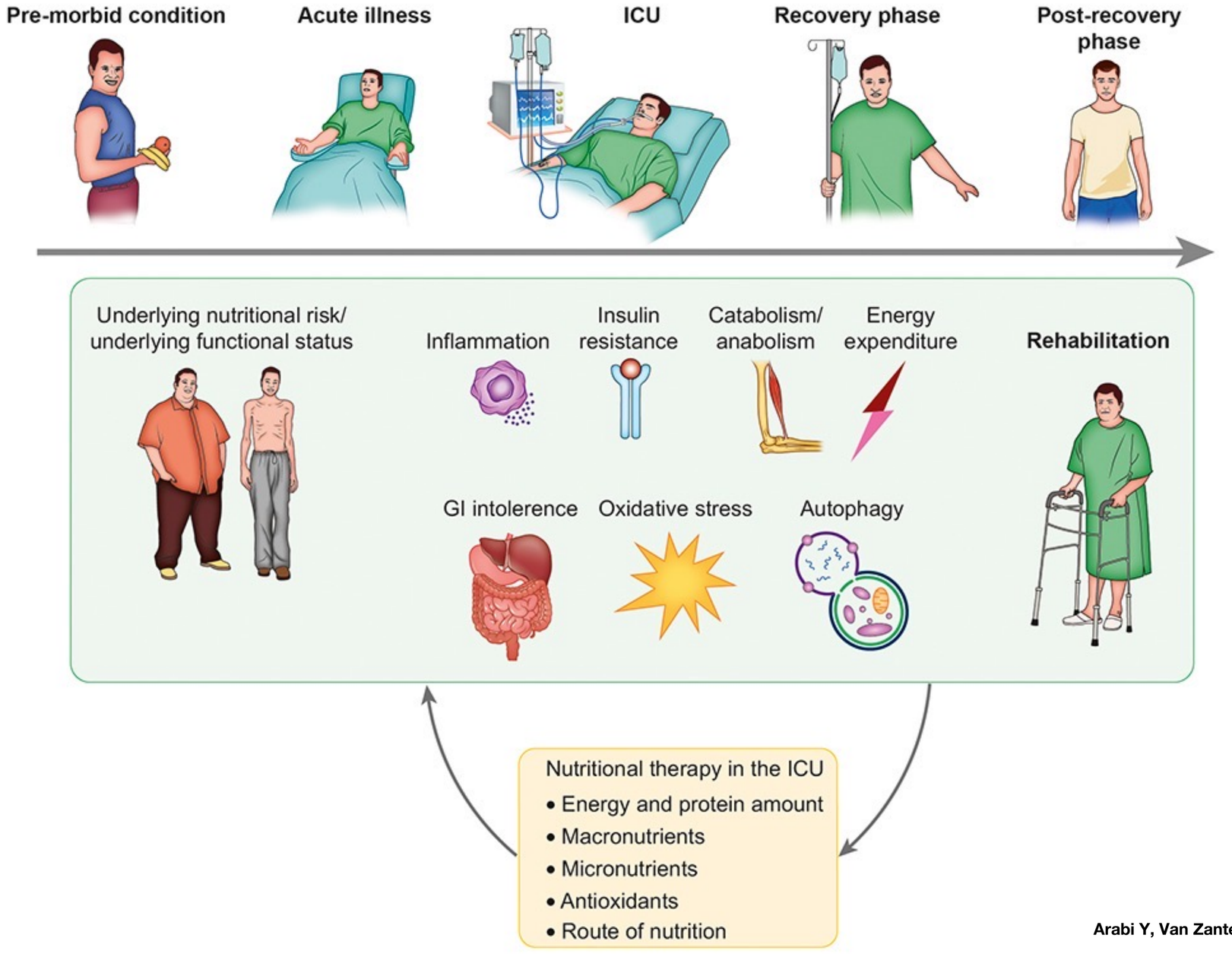
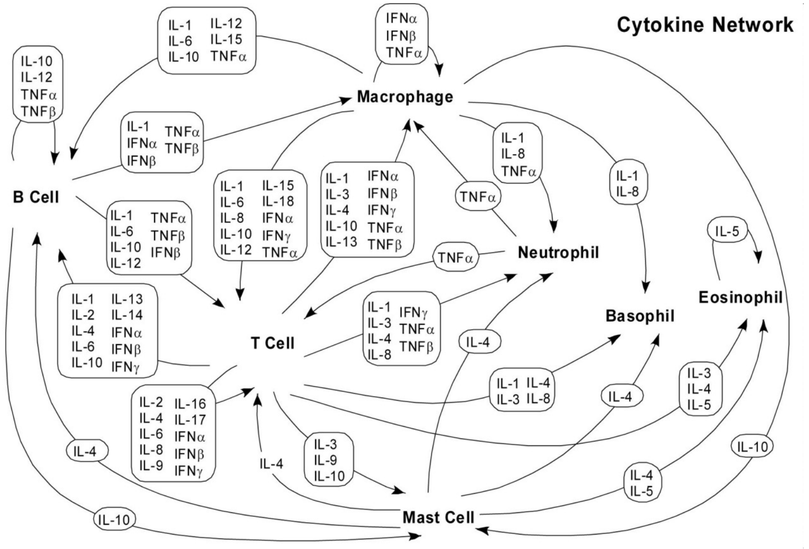
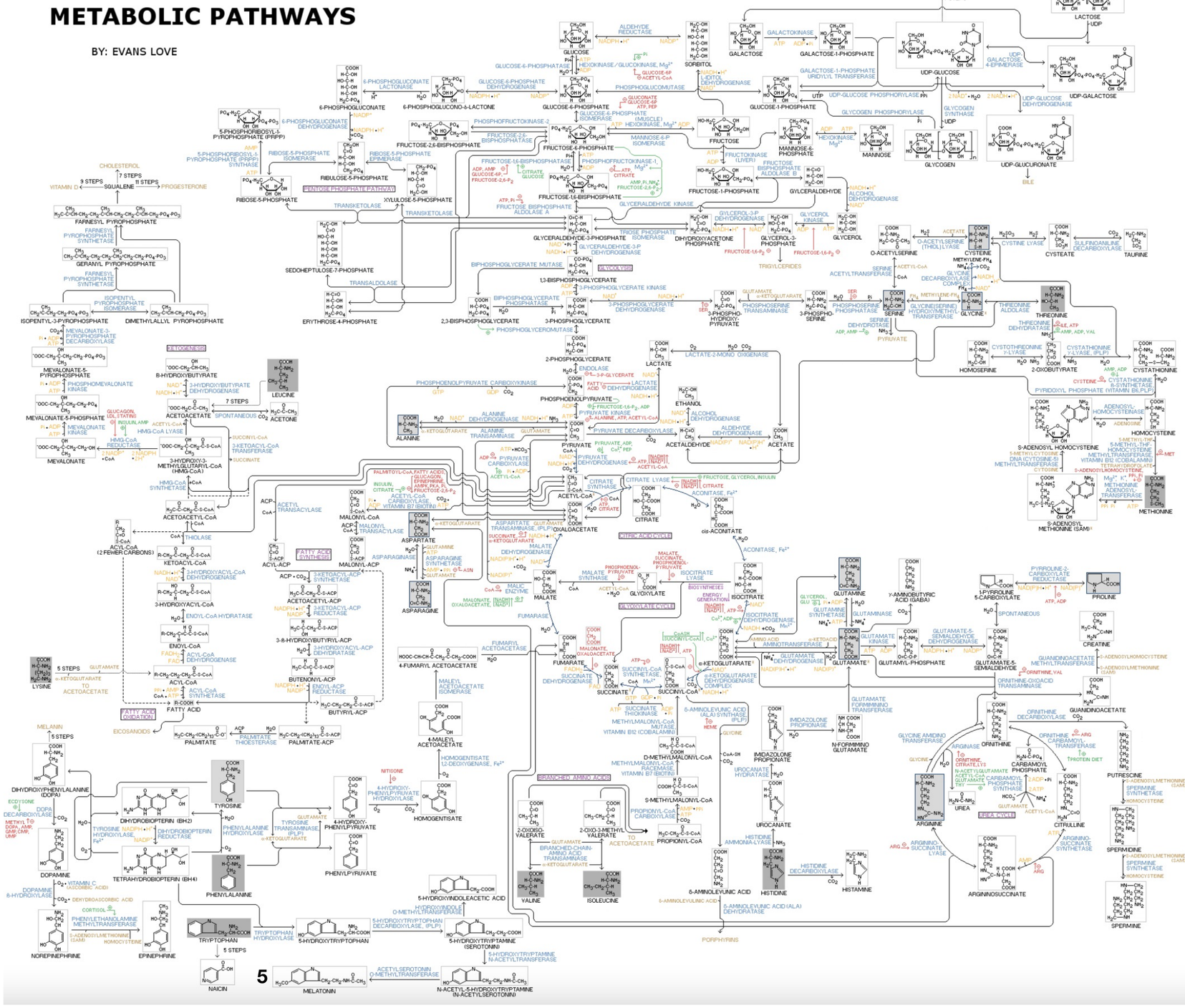


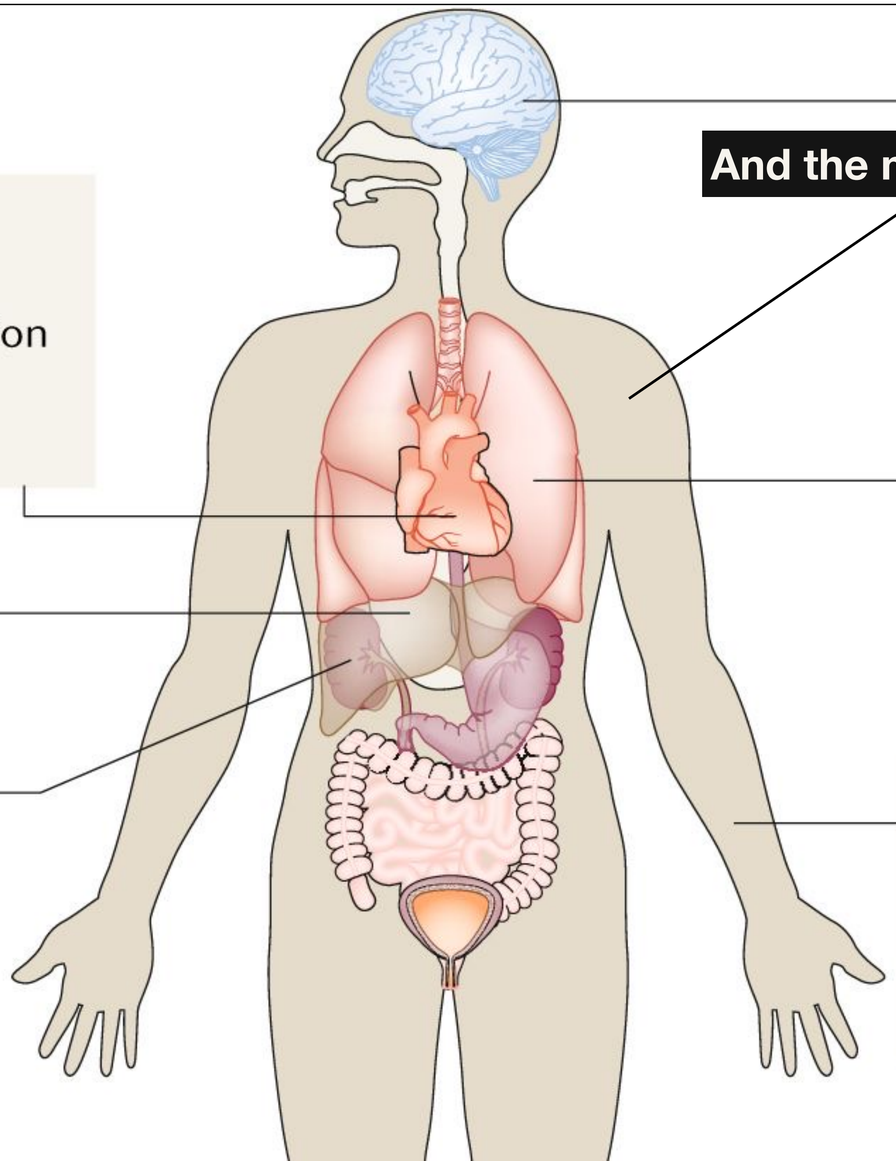
Arabi Y, Van Zanten AR: Intensive Care Med 2017



Interactions between critical illness and metabolism



Failing organ systems in sepsis



Neurological system
- Altered mentation
- Confusion
- Disorientation

And the muscles?

Cardiovascular system
- Hypotension
- Mottled skin and altered microcirculation
- ↑ Lactate levels (in septic shock)
- Altered echocardiography variables

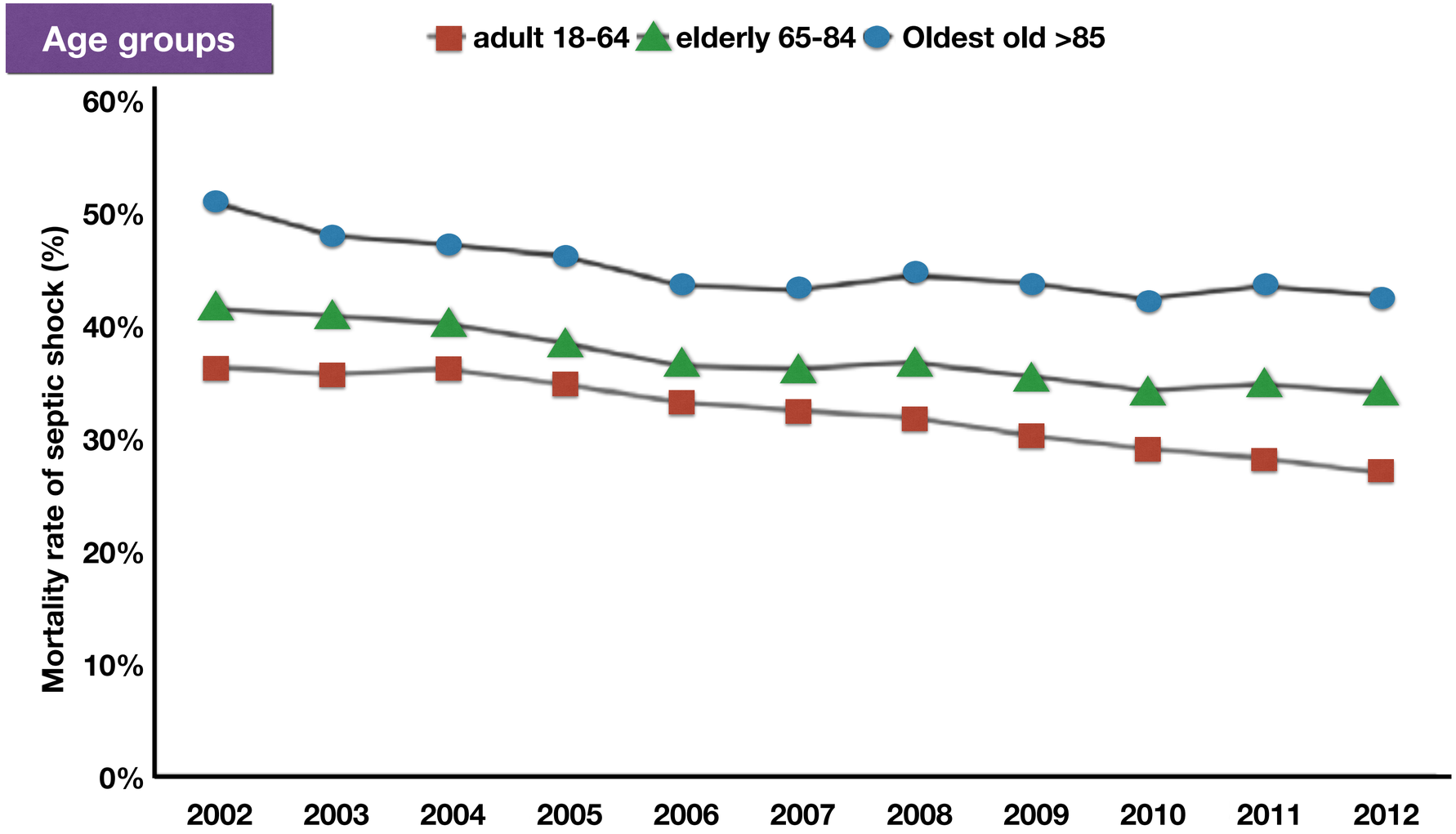
Respiratory system
- Hypoxaemia
- ↓ PaO_2:FiO_2 ratio

Hepatic system
- ↑ Bilirubin levels
- ↑ Liver enzymes

Renal system
- Oliguria
- ↑ Serum creatinine
- ↑ Blood urea nitrogen
- ↑ Biomarkers

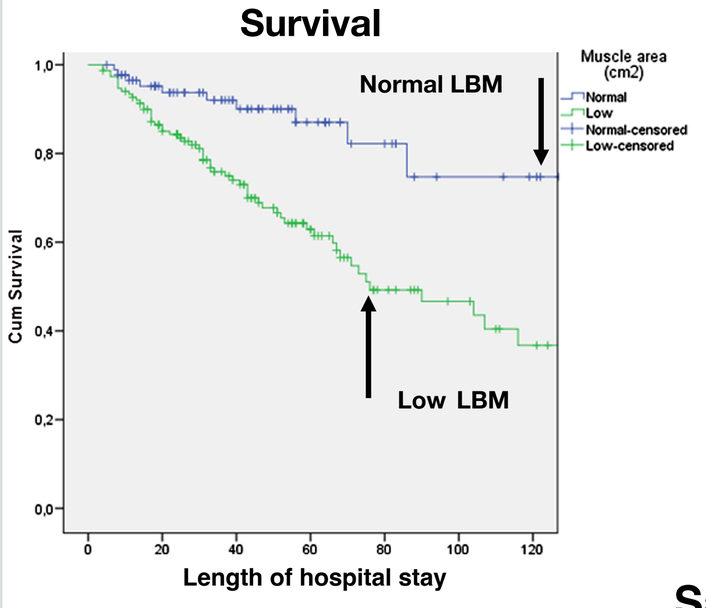
Haematological system
- Low platelet count
- Disseminated intravascular coagulation
- Petechiae (in some severe cases)

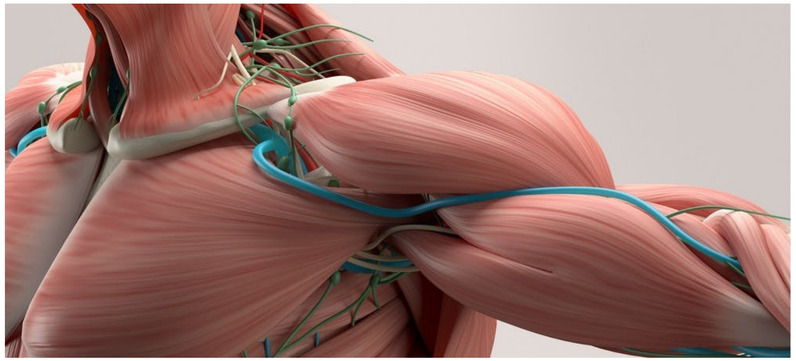
In-hospital mortality in septic shock patients in USA

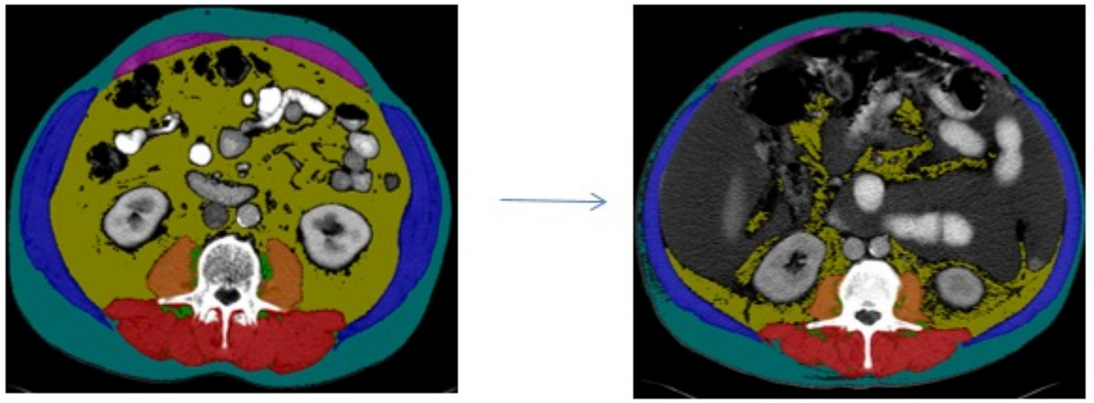


Si-Huei Lee et al. Crit Care Med 2018

LBM: CT-scan and mortality







- The Obesity paradox
- Patients with a high BMI have better survival odds in the ICU: “obesity paradox”
- BMI is not an independent predictor of mortality when muscle area is accounted for.

Weijs et al. Critical Care 2014 18:R12

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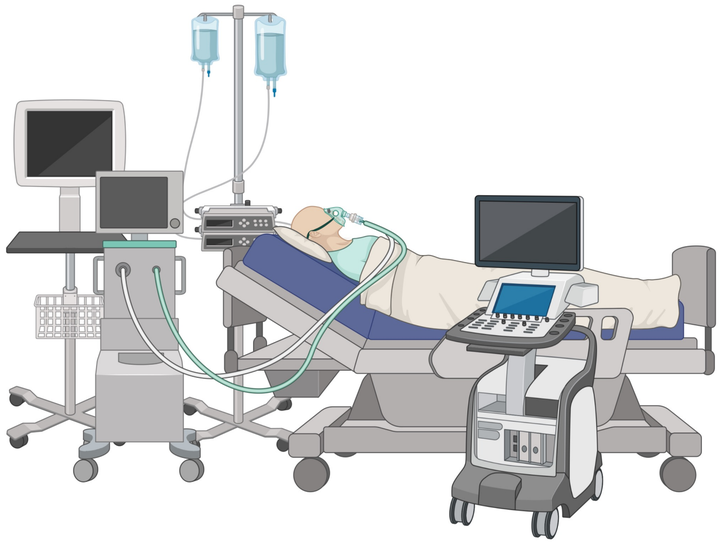
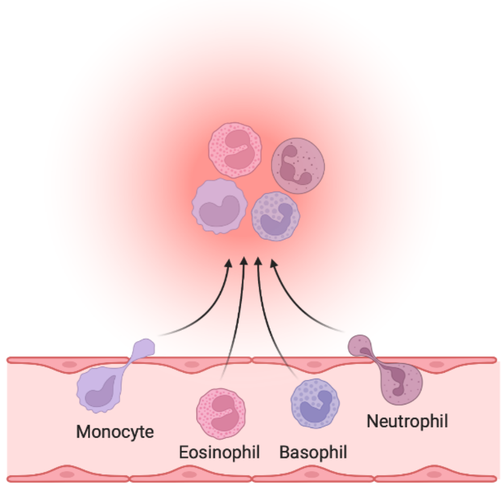
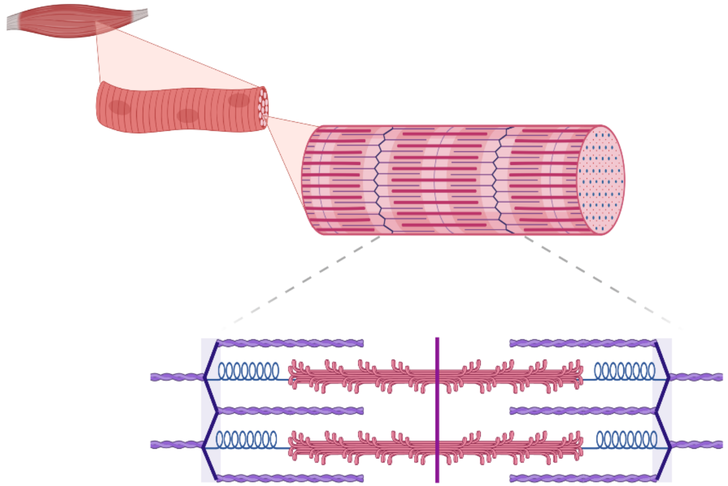
Why do we lose the muscles?



Immobilization



Inflammation



Loss of Muscle Mass

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- Our survivors have to learn walking

- Swallowing is very difficult after prolonged intubation
- Progressive loss of body weight and LBM is imminent
- Concentration disturbances, decline of cognitive functions and Anxiety,

Depression and Post-traumatic stress disorder do not help nutrition intake

- Prolonged Nutrition Therapy combined with Exercise rehabilitation is crucial

CURRENT OPINION

Are we creating survivors. . .or victims in critical care? Delivering targeted nutrition to improve outcomes

Paul E. Wischmeyer

Despite the improvements in ICU outcome, data indicating we have reduced sepsis in-hospital mortality

by half in the last 10 years, reveal ‘we have tripled the number of patients going to rehabilitation settings’

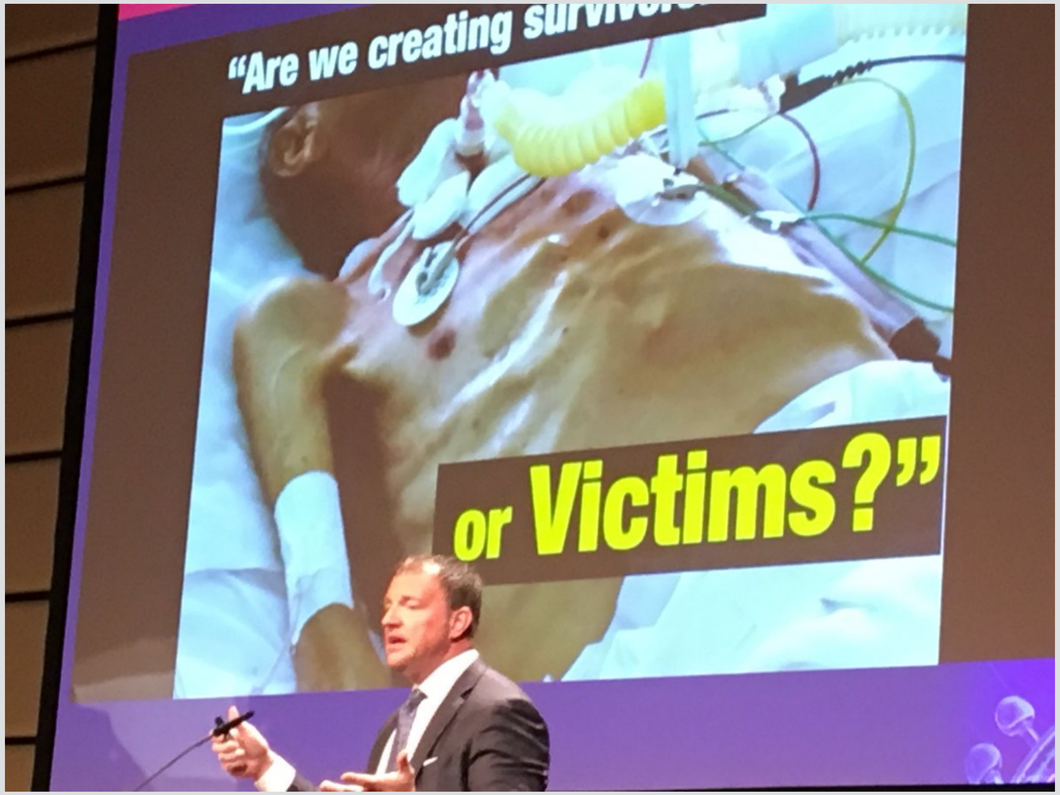
Sepsis: Survivors or Victims

33% die during first year

50% recover

17% persistent impairments

1 to 2 new functional limitations
(eg, inability to bathe or dress independently)



Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

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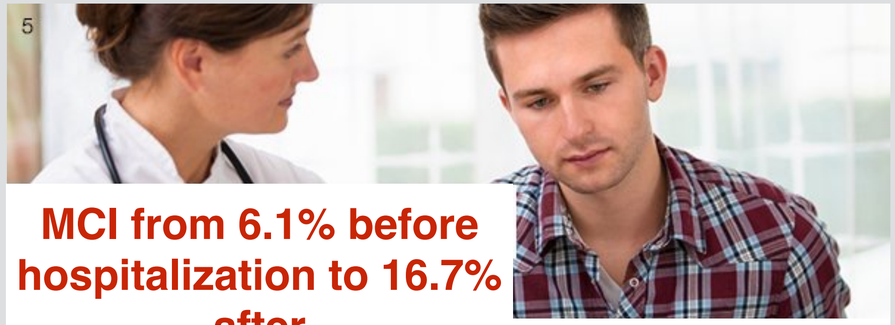
Sepsis: long-term consequences

40% of patients are rehospitalized within 90 days of discharge.

Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

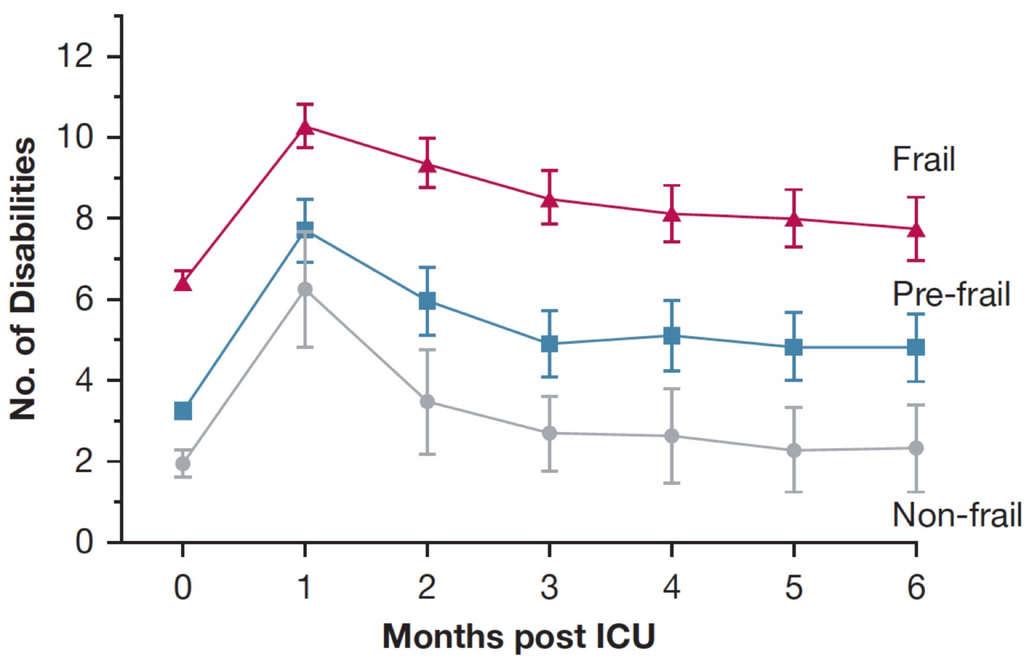
Sepsis: long-term consequences

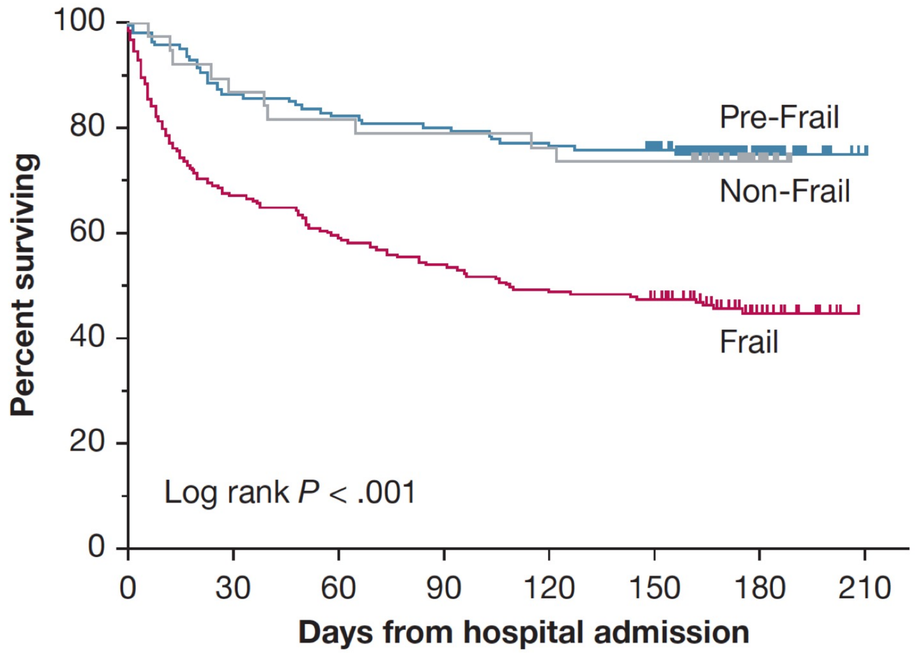


MCI from 6.1% before hospitalization to 16.7% after

Prescott HC, Angus DC. JAMA. 2018;319(1):62–75.

Increase in disabilities and long-term mortality in frailty





Ferrante LE et al. Chest. 2018 Jun;153(6):1378-1386.

What is essential for the (elderly) ICU patient?

- Functional independence is the #1 health priority for older adults
- Risk for poor functional outcomes is conferred by vulnerability factors not by chronological age
- Baseline frailty increases risk for disabilities by 3-4 times, almost doubles 9-month mortality risk
- The patient (usually) cannot recover beyond their functional baseline

Ferrante LE et al. Chest. 2018 Jun;153(6):1378-1386.

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Factors associated with performance at 1 year

Baseline characteristics

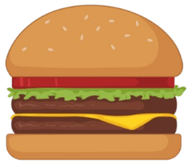
- Baseline performance
- Female
- Being married
- Urgent heart surgery as reason for admission

Better performance

- Severity of illness in ICU
- Charlson comorbidity index
- Frailty scale
- Stroke as reason for admission

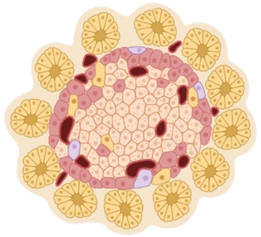
Worse performance

Heyland et al. Crit Care Med 2016



Anabolic state

Glucose ↑

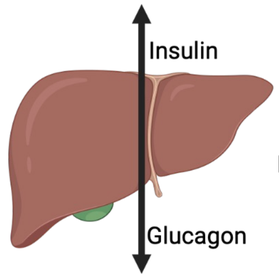


Pancreatic islet cells

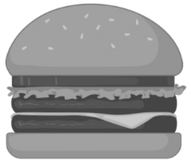
Insulin ↑

Glycogen

Glucose

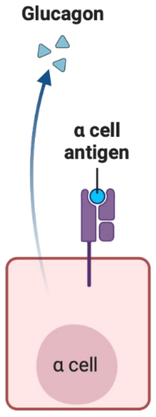


Glycogenolysis



Catabolic state

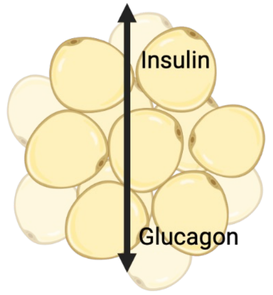
Glucose ↓



Glucagon ↑

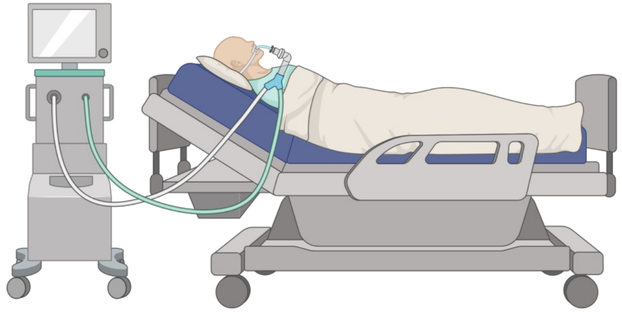
Lipogenesis

Free fatty acids



Lipolysis

Persistent Catabolic state



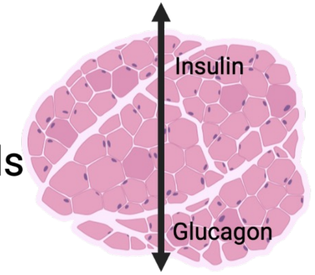
Despite

IV insulin

Medical nutrition

Protein synthesis

Amino acids



Proteolysis

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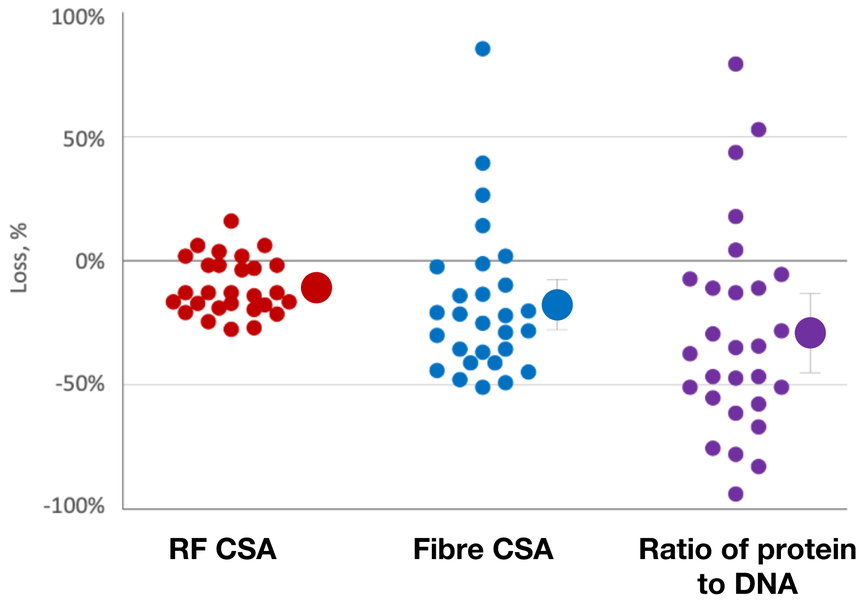
MODS: Muscle mass loss 1 kg per day

Rectus femoris Cross Sectional Area % change

*P<.001 for difference between failure of 2-3 organs and 4-6 organs from day 1 to day 7 and day 10.

Muscle wasting % loss day 7 versus day 1 (n=28)



Measurements of Muscle Wasting During Critical Illness Summary data ● ● ● are expressed as medians and 95% confidence intervals.

Puthucheary ZA et al., JAMA 2013

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Muscle wasting:
Most common complication of critical illness

The impact of loss of lean body mass can lead to significant effects:

per day in first 10 days in MODS patients

-10%
Impaired Immunity, increased infection

-20%
Decreased healing and weakness

-30%
Spontaneous development of wounds, pressure ulcers

-40%
Mortality

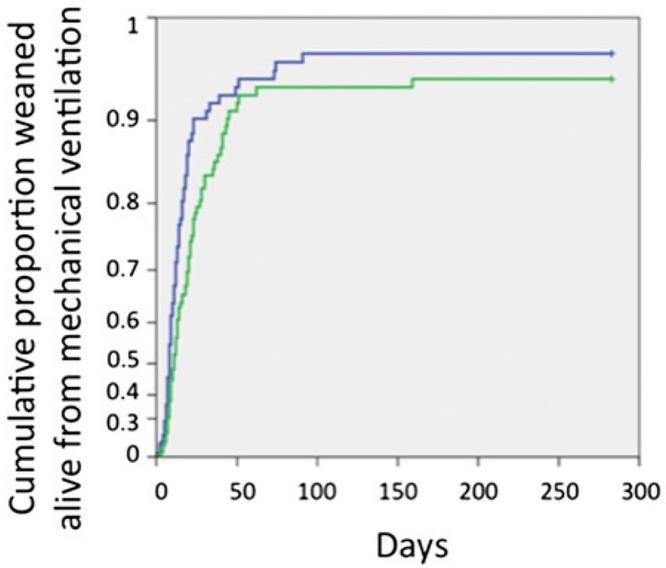
up to 50% of patients

This loss of muscle has a major impact on a patients ability to survive and recover

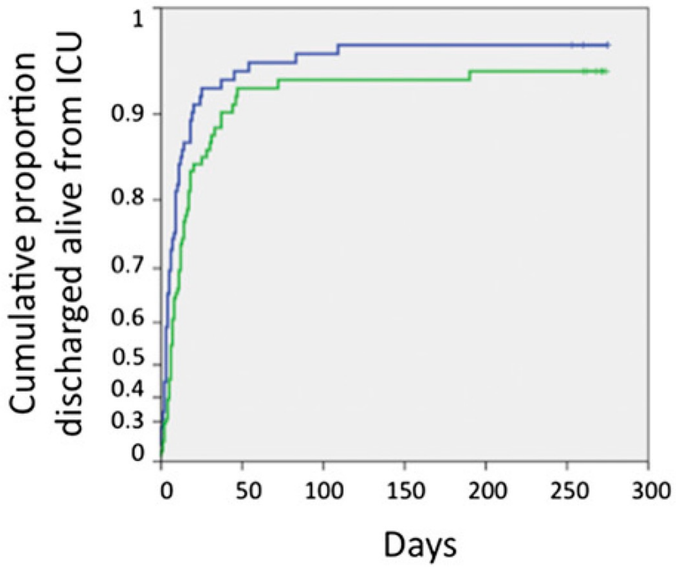
Puthucheary ZA. SIGNA VITAE. 2017;13(3): 30-31.
Puthucheary ZA, Rawal J, McPhail M, et al. JAMA. 2013; 310:1591-1600.
Demling RH. Journal of Plastic Surgery. 2009;9(e9):65-94.

Consequences of ICU Acquired Weakness y/n

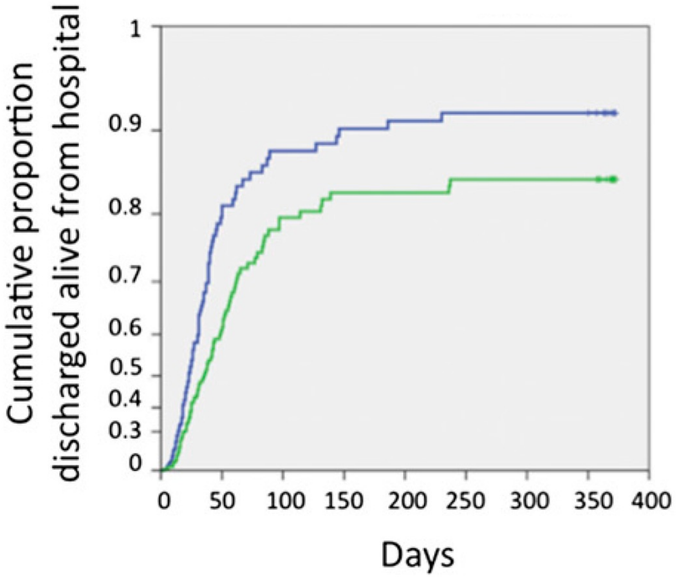
Weaning from ventilation



Alive discharge ICU



Alive discharge hospital



Hermans G et al. Am J Resp Crit Care Med 2014;190:410-420

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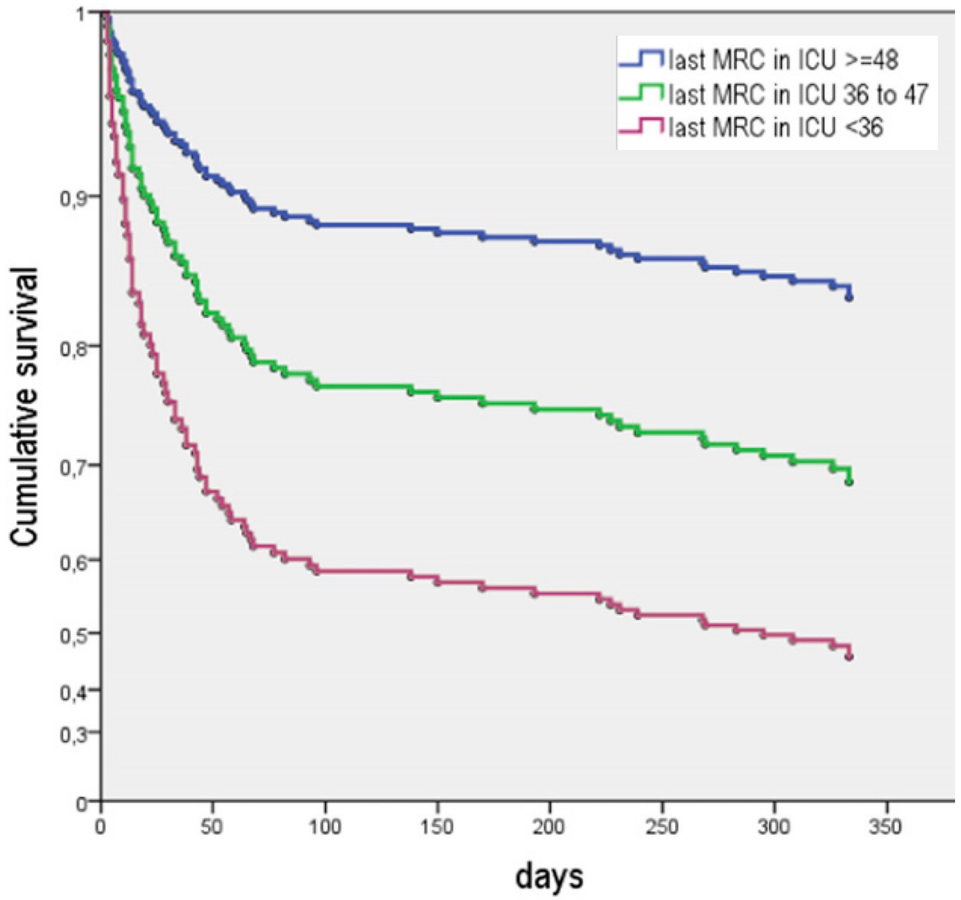
Consequences of ICU Acquired Weakness and survival



Last MRC sum score recorded in the ICU

MRC sum score

- Involves the assessment of muscle power from 3 movements of each limb:
  - Shoulder abduction
  - Elbow flexion
  - Wrist extension
  - Hip flexion
  - Knee extension and
  - Ankle dorsiflexion.
- Maximal power graded according to MRC scale.
- Total score =60

- Deltoid
- Biceps
- Wrist extensor
- Ileopsoas
- Quadriceps femoris
- Tibialis anterior

Strong association of ICU discharge weakness and 1 year mortality

Hermans G et al. Am J Resp Crit Care Med 2014;190:410-420

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WAGENINGEN UNIVERSITY & RESEARCH

Ziekenhuis Gelderse Vallei

Post-Intensive Care Syndrome (PICS) ⟷ **Post-Acute COVID Syndrome (PACS)**

Muscle strength
Pulmonary function
Pain
Exercise capacity
Gait speed
Balance
ADL
iADL

Cognitive

Attention
Memory
Executive function
Visuo-spatial
Mental processing speed

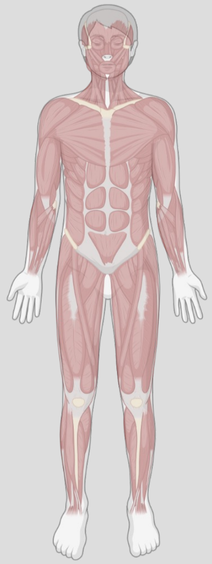
Mental

Anxiety
Depression
Post-traumatic Stress Disorder (PTSD)

↓

PICS-F

Physical



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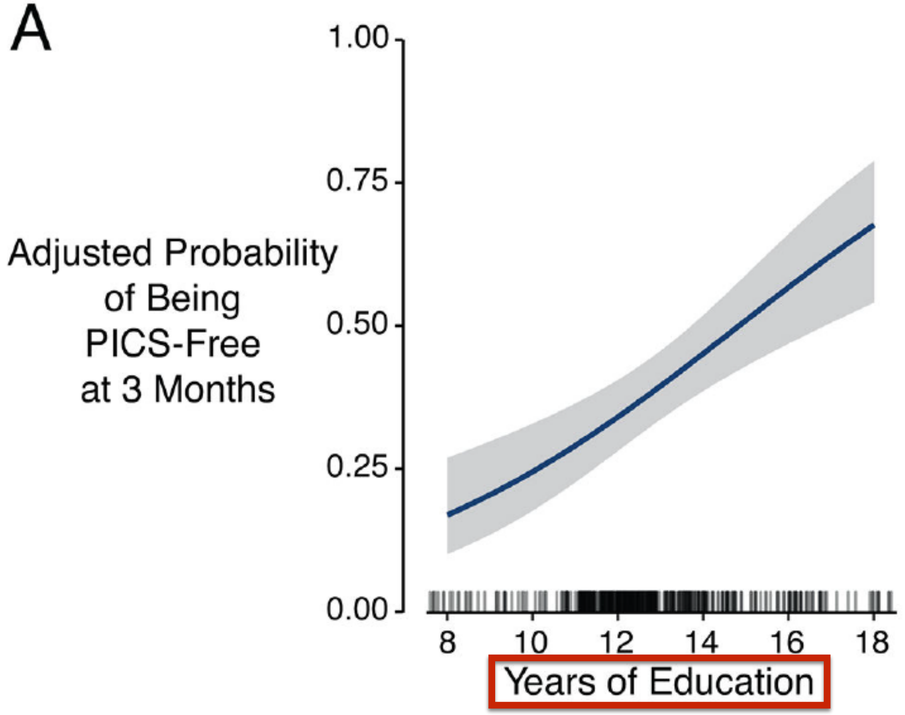
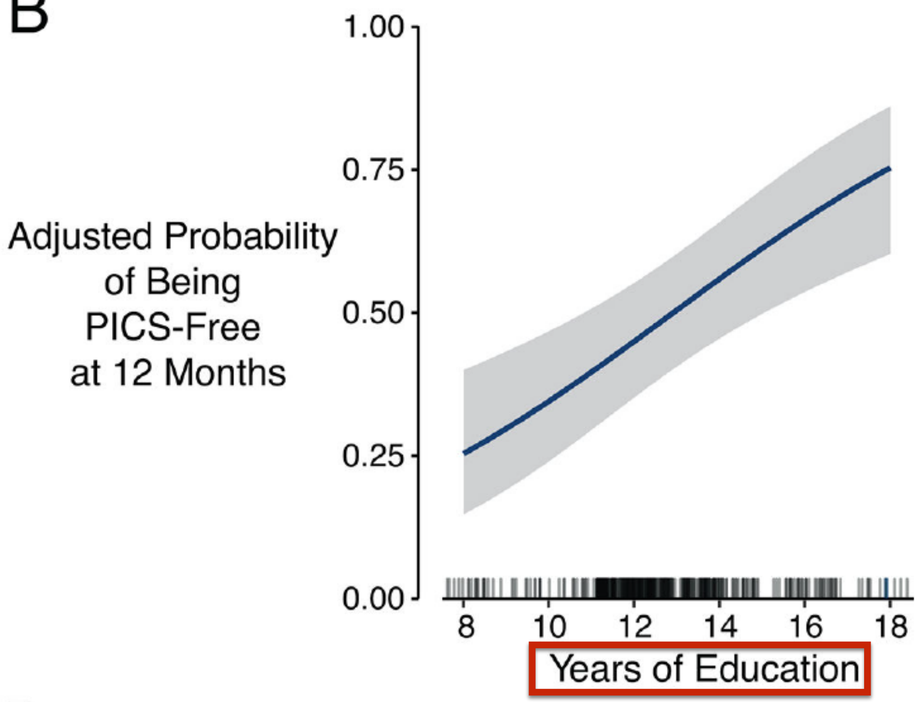
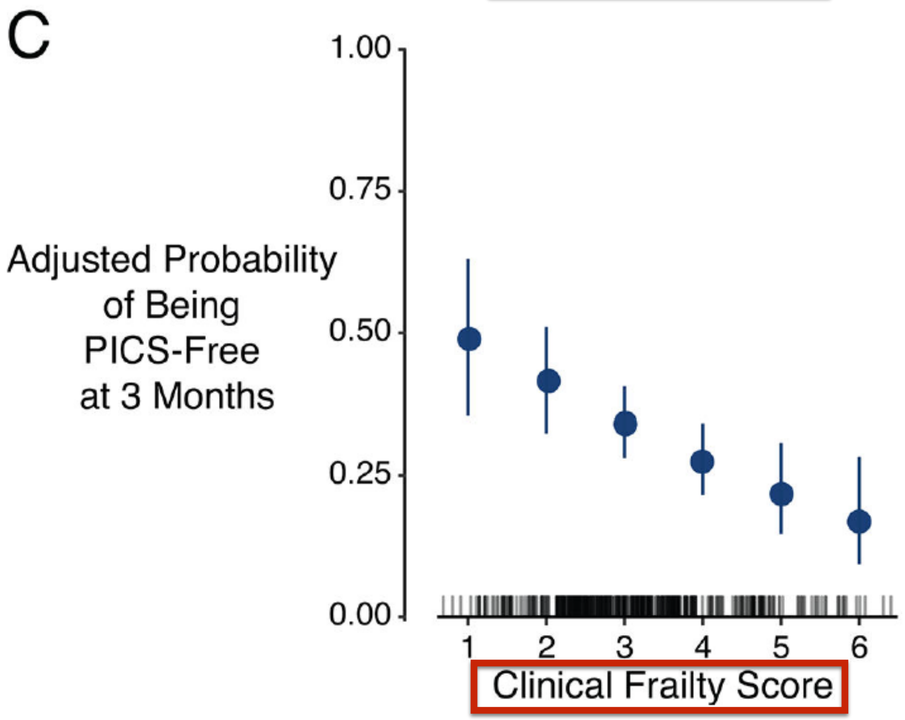
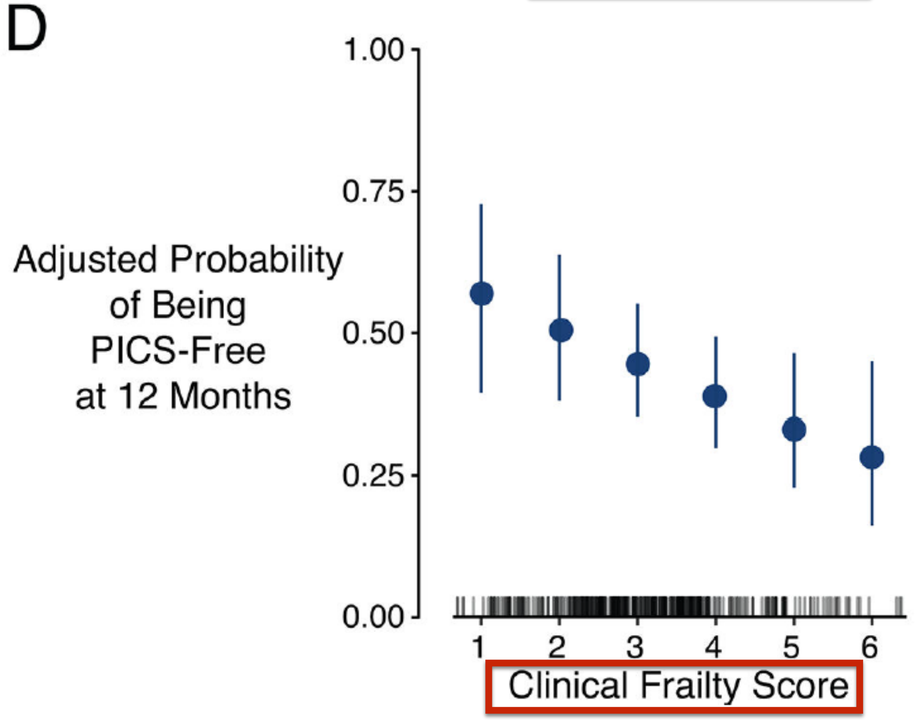

A
Adjusted Probability of Being PICS-Free at 3 Months
1.00
0.75
0.50
0.25
0.00
8
10
12
14
16
18
Years of Education


B
Adjusted Probability of Being PICS-Free at 12 Months
1.00
0.75
0.50
0.25
0.00
8
10
12
14
16
18
Years of Education


C
Adjusted Probability of Being PICS-Free at 3 Months
1.00
0.75
0.50
0.25
0.00
1
2
3
4
5
6
Clinical Frailty Score


D
Adjusted Probability of Being PICS-Free at 12 Months
1.00
0.75
0.50
0.25
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1
2
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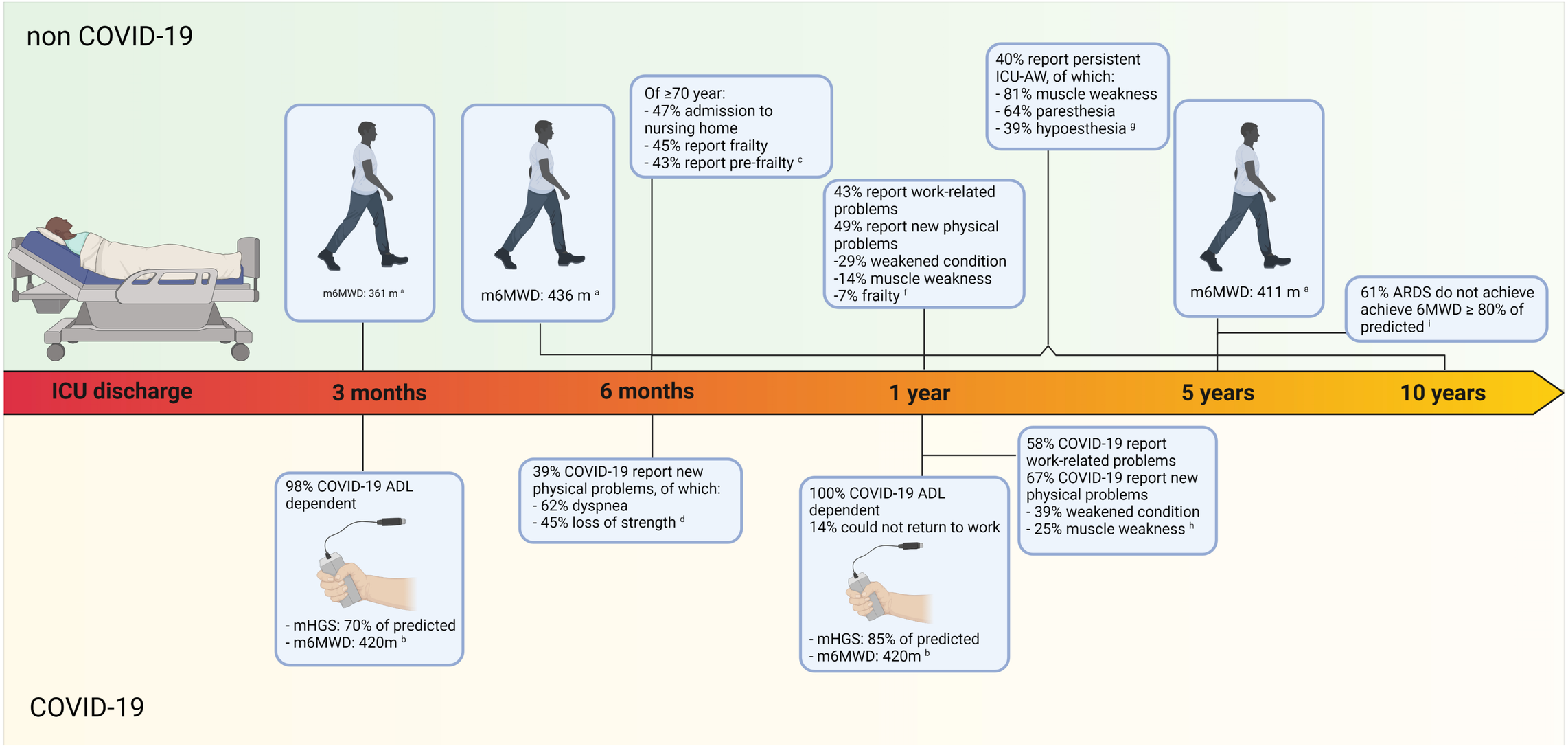
4
5
6
Clinical Frailty Score

Functional recovery after pneumonia and COVID-19



Boelens Y, Melchers M, Van Zanten AR. Curr Opinion Crit Care 2022 accepted.

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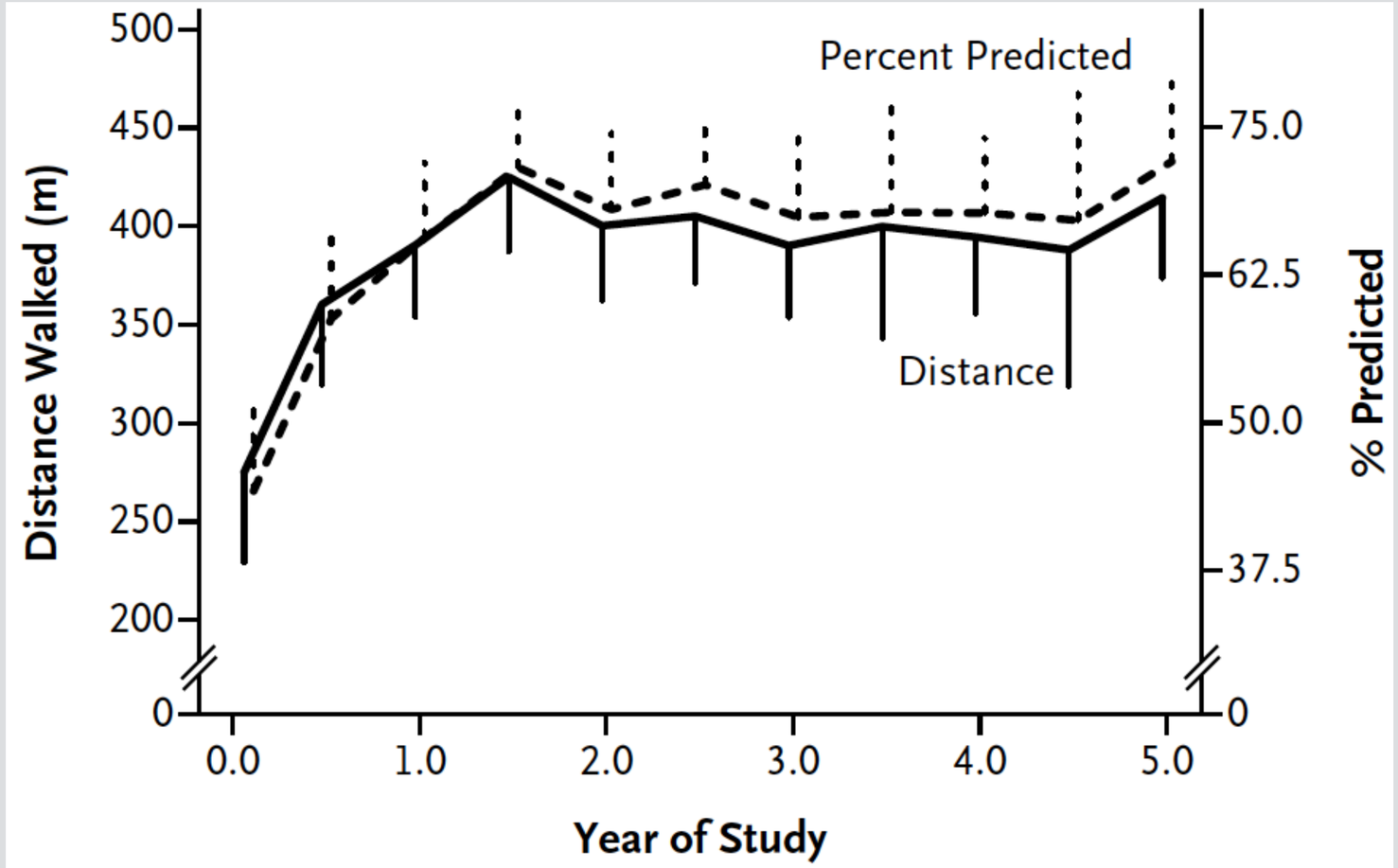
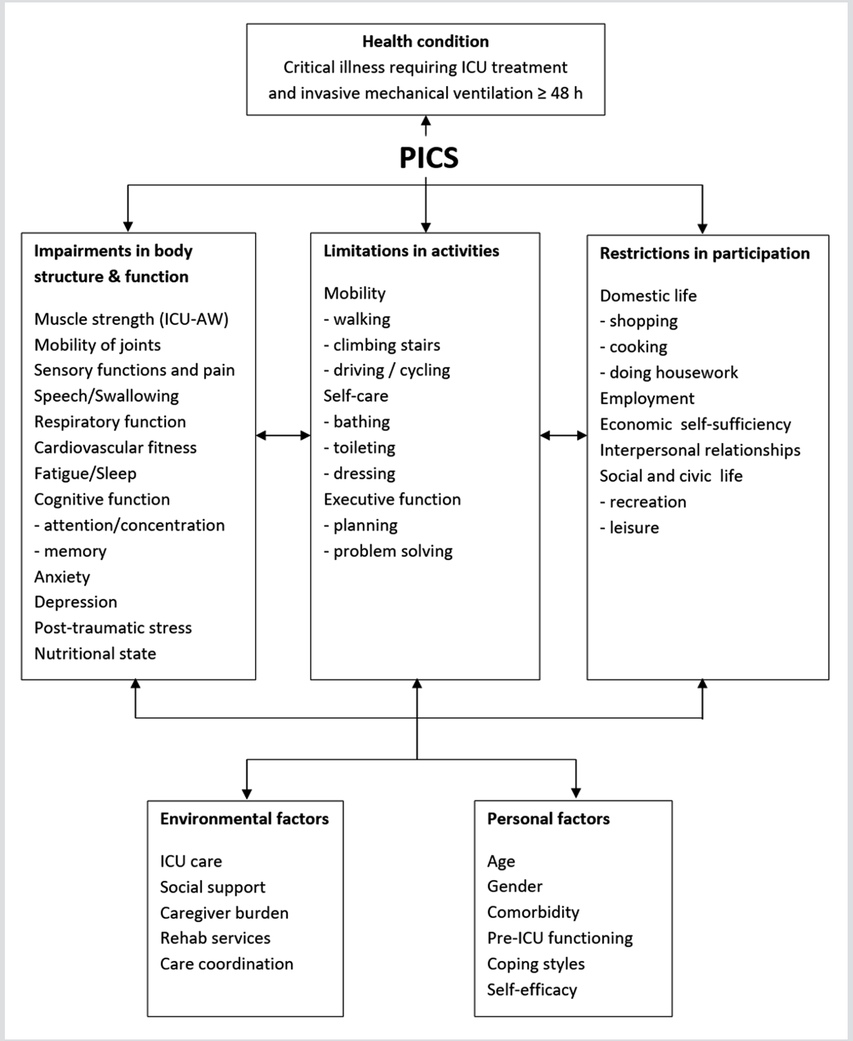
5 years after ARDS ICU treatment: ICU acquired weakness persists for years…..



- Muscles renew every 3-4 months
- What is wrong? Muscle mass? Muscle function? Innervation?
- Can we improve the outcome?

Herridge MS et al NEJM 2011

Long-term consequences of ICU treatment



- Personal burden
- Family burden
- Healthcare burden
- Societal burden
- Economic burden

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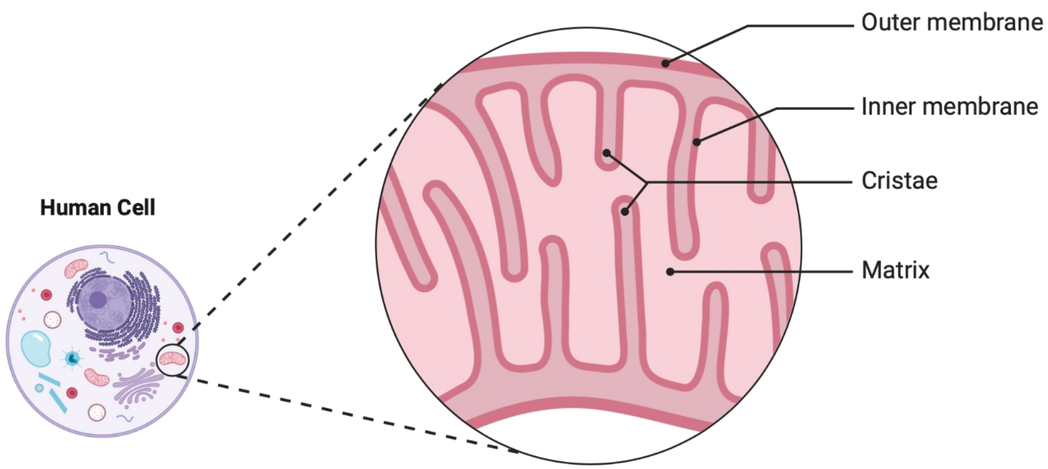
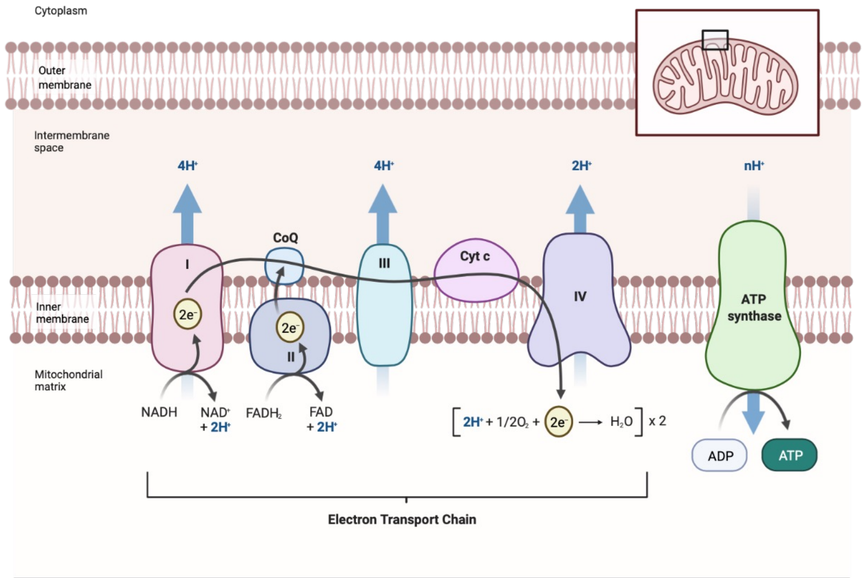
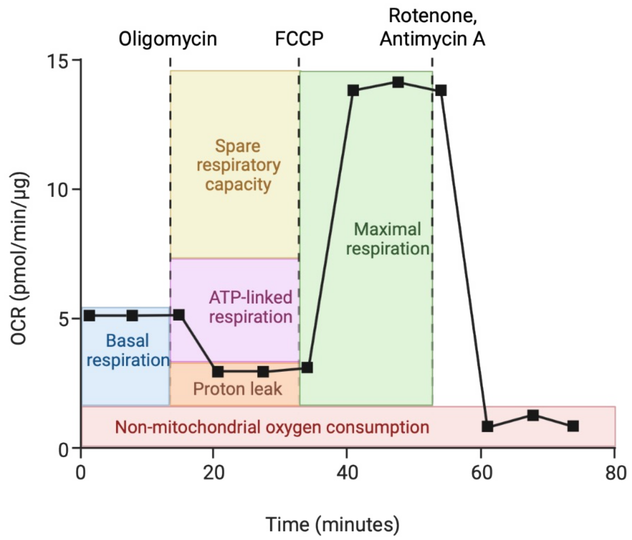
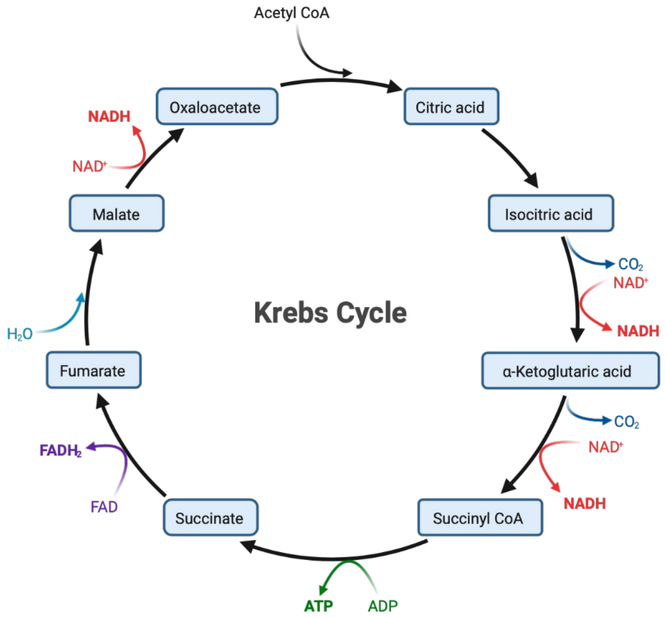
Mitochondria









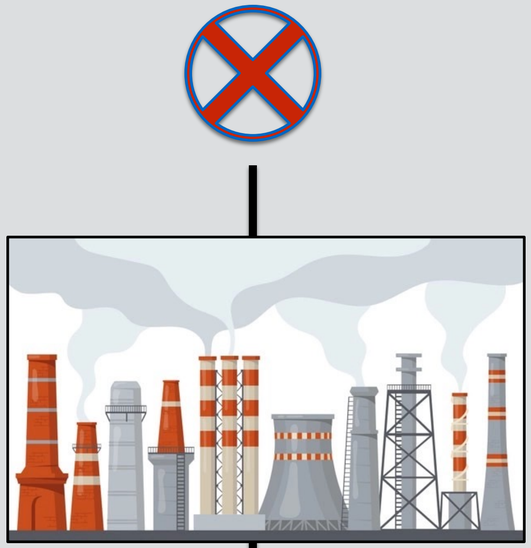
PRODUCTS
2 ATP
8 NADH
2 $FADH_2$
6 CO_2

27

ATP stores 0.2% of daily need

Actual storage

ATP 50-100 g



Daily demand

100-150 mol

507.2 g/mol

50-75 kg

50,720 - 76,080 g

adapted from M. Hiesmayr ISICEM 2021

Singer *Critical Care* 2017, **21**(Suppl 3):309
DOI 10.1186/s13054-017-1913-9

Critical Care

REVIEW

Open Access

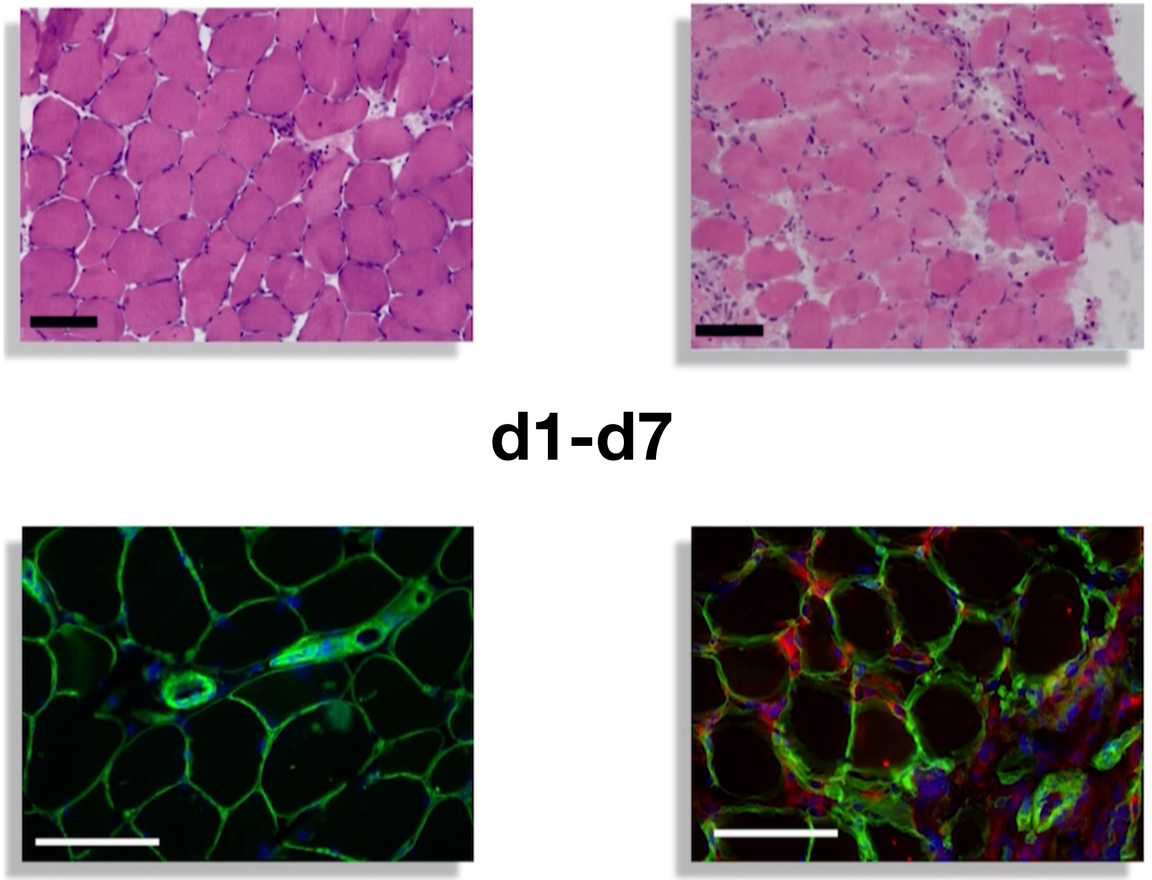
Critical illness and flat batteries

Mervyn Singer

Myonecrosis and inflammation: Myositis
Low ATP content

- **Protein synthesis** measured by the muscle protein fractional synthetic rate **was depressed in patients on day 1** (0.035%/hour; 95% CI, 0.023% to 0.047%/hour) compared with rates observed in fasted healthy controls (0.039%/hour; 95% CI, 0.029% to 0.048%/hour) (P = .57) and i**ncreased by day 7** (0.076% [95% CI, 0.032%-0.120%/hour]; P = .03) to rates associated with fed controls (0.065%/hour [95% CI, 0.049% to 0.080%/hour]; P = .30), **independent of nutritional load.**

- **Unexpectedly, higher protein delivery in the first week was associated with greater muscle wasting.**

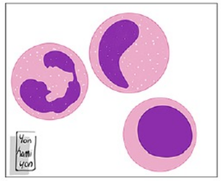


d1-d7

Puthucheary ZA et al., JAMA 2013

Potential role in sepsis associated MODS

IMMUNE CELLS

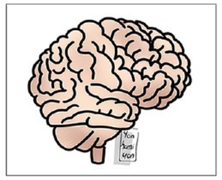


- **Resting metabolism:**
  - Low levels of ATP consumption
  - Specific of cell-phenotype
- **Activation of immune cells:**
  - Reprioritization of protein synthesis
  - ↑ nucleotide and FA synthesis
  - ↑ ATP consumption
  - => aerobic glycolysis
  - => PPP / aerobic glycolysis

Energetic changes potentially leading to IMMUNE-PARALYSIS

- Cell phenotype-specific mechanisms
- Impaired metabolism plasticity

BRAIN

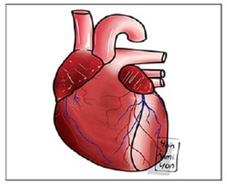


- **Basal metabolism:**
  - High levels of ATP consumption
  - Neuronal signalling
  - Maintenance of brain functions
  - => glucose oxidation / OXPHOS
- **Brain acute stimulation:**
  - Moment-to-moment variations
  - ↑ ATP consumption
  - => aerobic glycolysis

Energetic changes potentially leading to ENCEPHALOPATHY

- Mitochondrial dysfunction
- Impaired ATP production

HEART

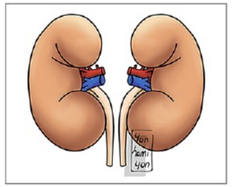


- **Basal metabolism:**
  - High levels of ATP consumption
  - Continuous rhythmic contractile activity
  - => OXPHOS
  - => 60 to 100% FA oxidation
- **Metabolism adaptation to sepsis:**
  - ↑ lactate uptake and oxidation
  - ↓ expression of genes involved in ATP consumption (e.g. sarcomere proteins)

Energetic changes potentially leading to CARDIOMYOPATHY

- Mitochondrial dysfunction
- ↓ glucose and FA oxidation
- Accumulation of toxic lipids and dysfunctional mitochondria

KIDNEY



- **Basal metabolism:**
  - High levels of ATP consumption
  - Tubular reabsorption by TECs
  - => OXPHOS
- **Metabolism adaptation to sepsis:**
  - ↓ protein synthesis
  - ↑ gluconeogenesis during adrenergic stimulation

Energetic changes potentially leading to RENAL FAILURE

- Time-dependent metabolic switch from OXPHOS to a more glycolytic phenotype
- Mitochondrial dysfunction
- ↓ FA oxidation

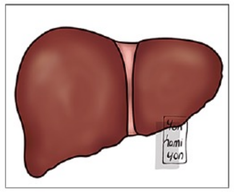
DIAPHRAGM

- **Basal metabolism:**
  - High levels of ATP consumption
  - Continuous rhythmic contractile activity
  - => OXPHOS

Energetic changes potentially leading to MUSCLE WEAKNESS and/or MUSCLE FATIGUE

- Mitochondrial dysfunction
- ↓ FA oxidation
- Intracellular lipid accumulation

LIVER



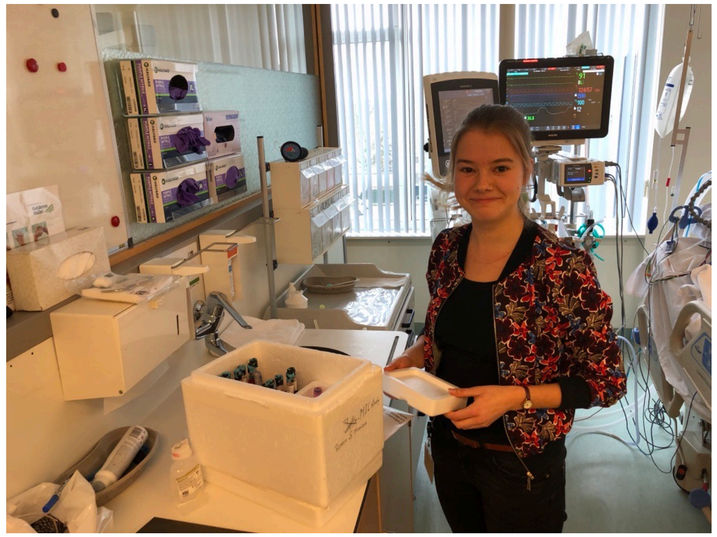
- **Basal metabolism:**
  - High levels of ATP consumption
  - => OXPHOS
- **Metabolic alterations during sepsis:**
  - ↑ gluconeogenesis

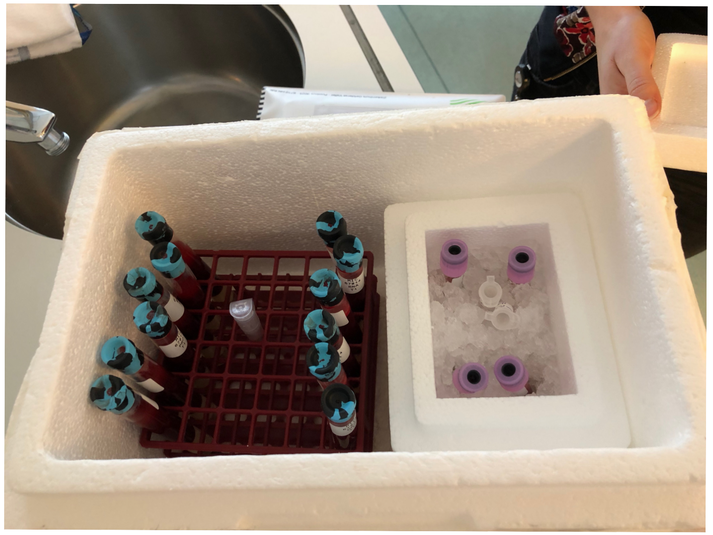
Energetic changes potentially leading to LIVER DYSFUNCTION

- Mitochondrial dysfunction
- ↓ FA oxidation
- Accumulation of lipids and dysfunctional mitochondria

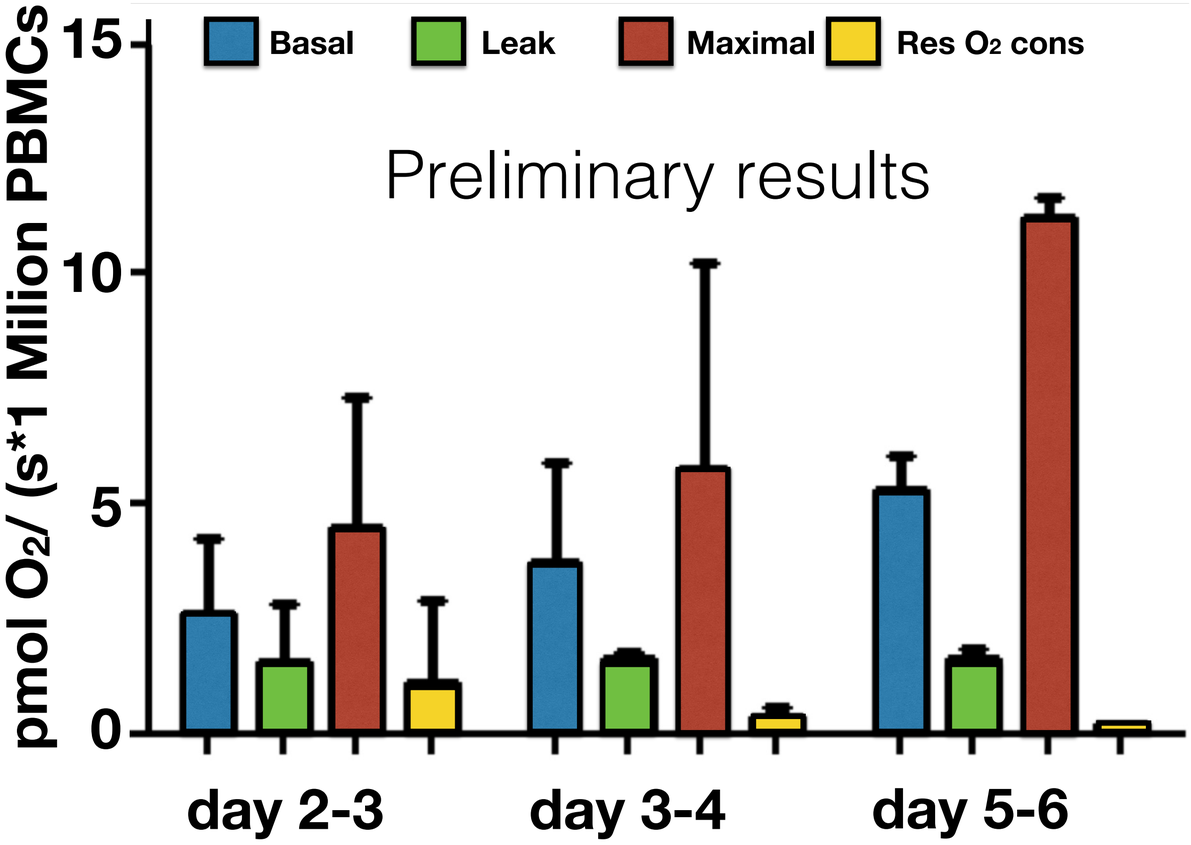
Preau, S., Vodovar, D., Jung, B. et al. Ann. Intensive Care 11, 104 (2021).

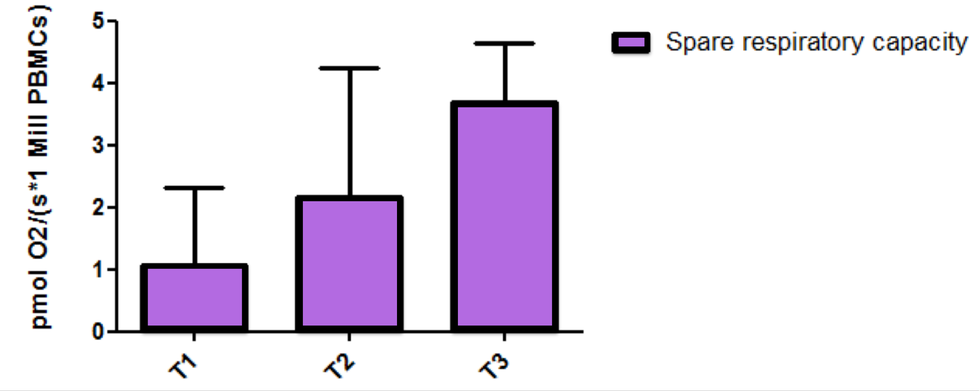
Study logistics in the Netherlands

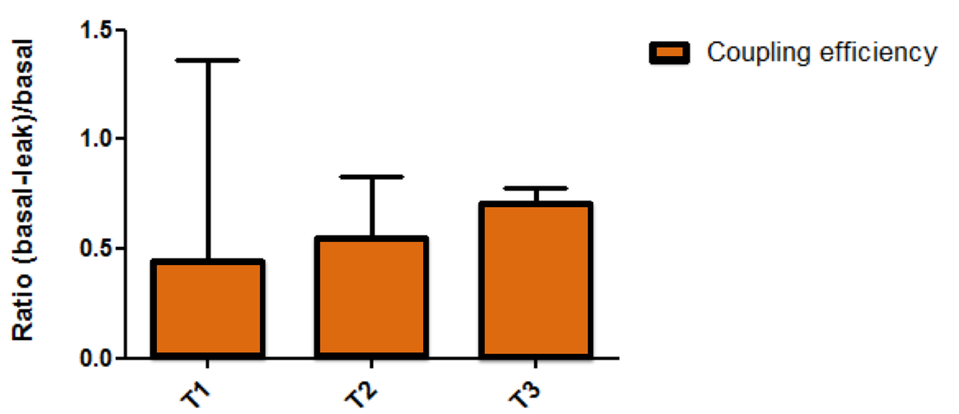




The concept of adaptive mitochondrial metabolic-bio-energetic downregulation







Mitochondria work slower than they can! Adaptation?


LOW BATTERY

Jiroutková *et al. Critical Care* (2015) 19:448
DOI 10.1186/s13054-015-1160-x

Critical Care

Ziekenhuis Gelderse Vallei

RESEARCH Open Access

Mitochondrial function in skeletal muscle of patients with protracted critical illness and ICU-acquired weakness

Kateřina Jiroutková[1*], Adéla Krajčová[1,2], Jakub Ziak[1], Michal Fric[4], Petr Waldauf[4], Valér Džupa[3], Jan Gojda[2], Vlasta Němcova-Fürstová[5], Jan Kovář[5], Moustafa Elkalaf[1], Jan Trnka[1] and František Duška[1,6]

Compared to healthy controls, in ICU patients this group demonstrated a ~50 % reduction of the ability of skeletal muscle to synthetize ATP in mitochondria and found a depletion of complex III and IV concentrations

Biopsy day: d28 (9) after ICU admission

Latronico and Friedrich *Critical Care* (2019) 23:33
https://doi.org/10.1186/s13054-019-2331-y

WAGENINGEN UNIVERSITY & RESEARCH

Ziekenhuis Gelderse Vallei

EDITORIAL Open Access

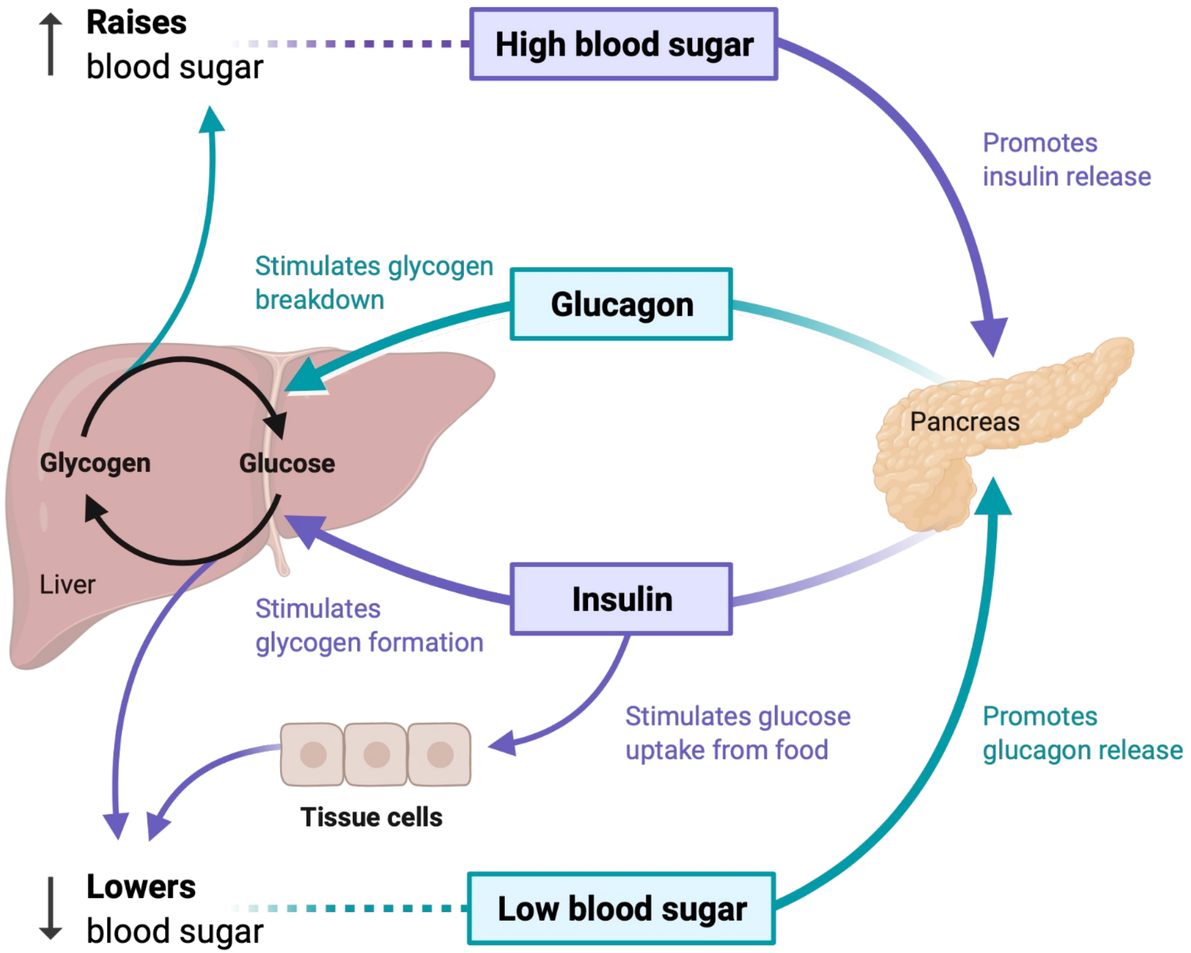
Electrophysiological investigations of peripheral nerves and muscles: a method for looking at cell dysfunction in the critically ill patients

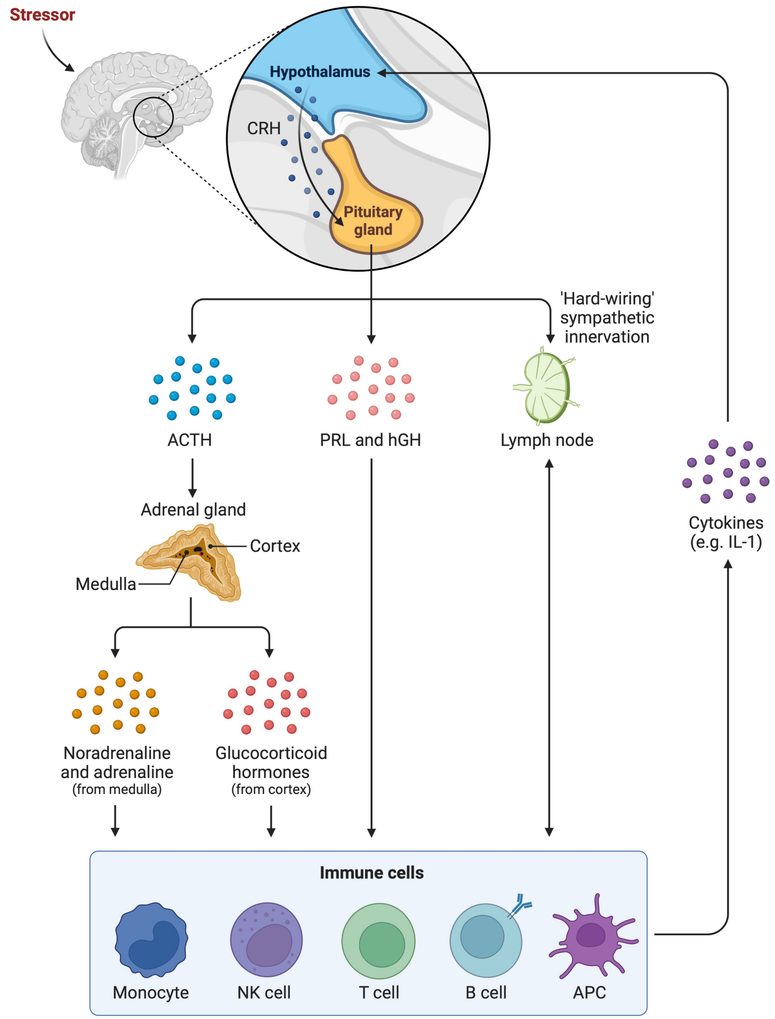
Nicola Latronico[1,2*] and Oliver Friedrich[3,4,5]

Keywords: Muscle weakness, Polyneuropathy, Myopathy, Organ dysfunction, Mitochondrial dysfunction, Energy metabolism

Inflammation, hypoxia, and ischemia increase NO and ROS production associated with mitochondrial dysfunction and ATP depletion in nerve axons

Glucose regulation: stress hyperglycemia in critical illness





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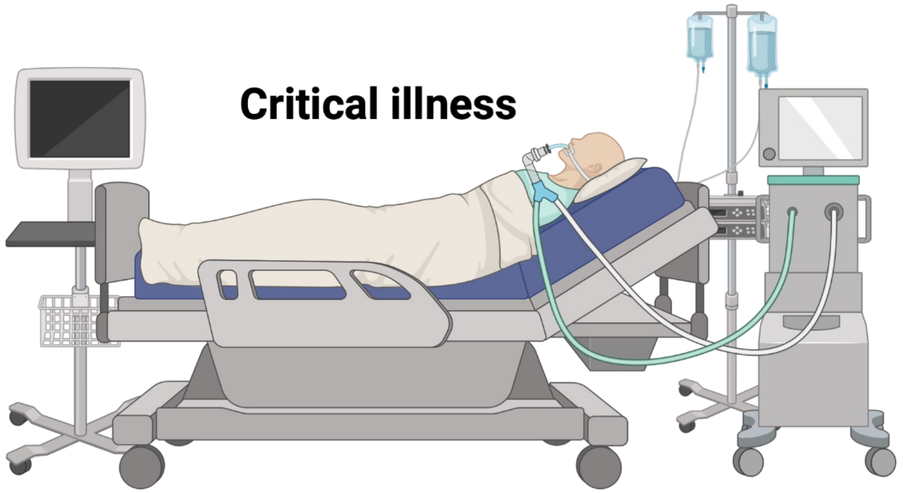
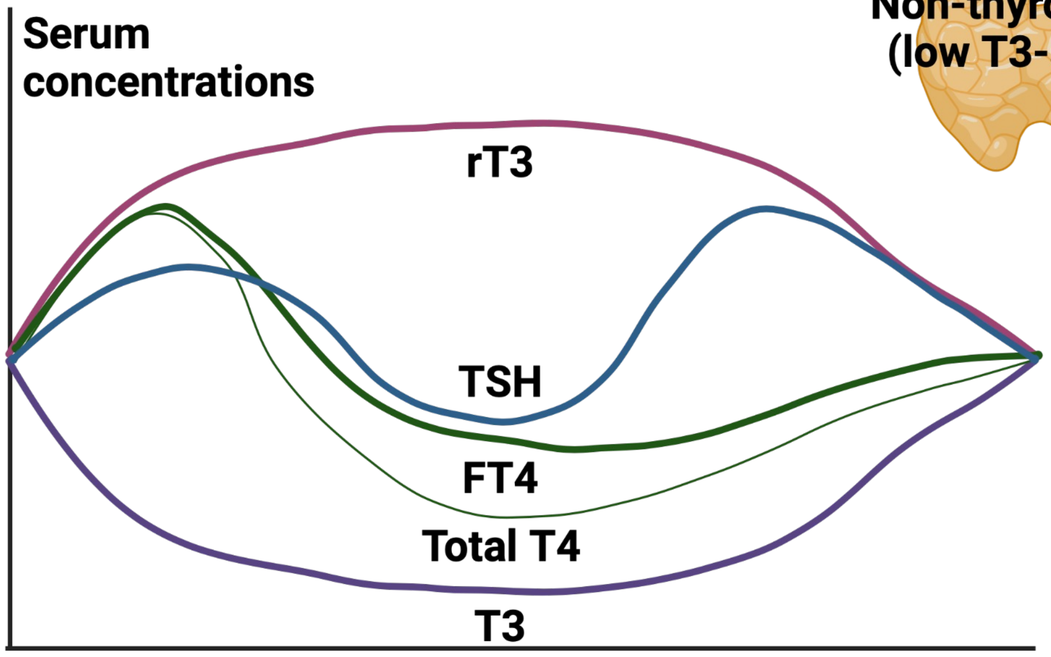
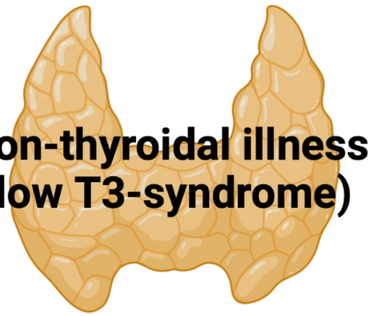
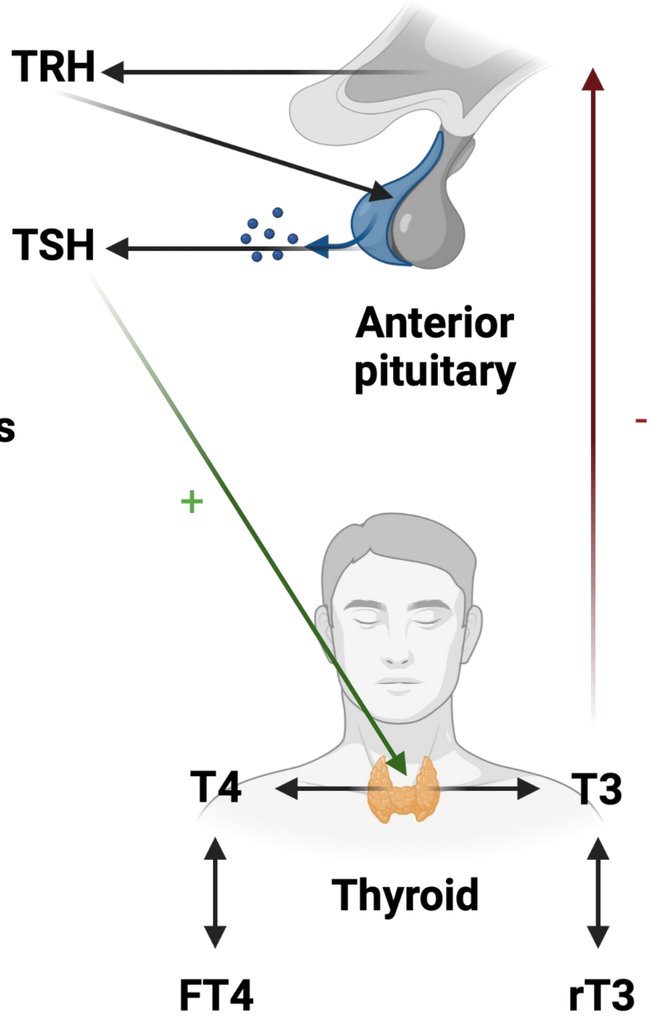
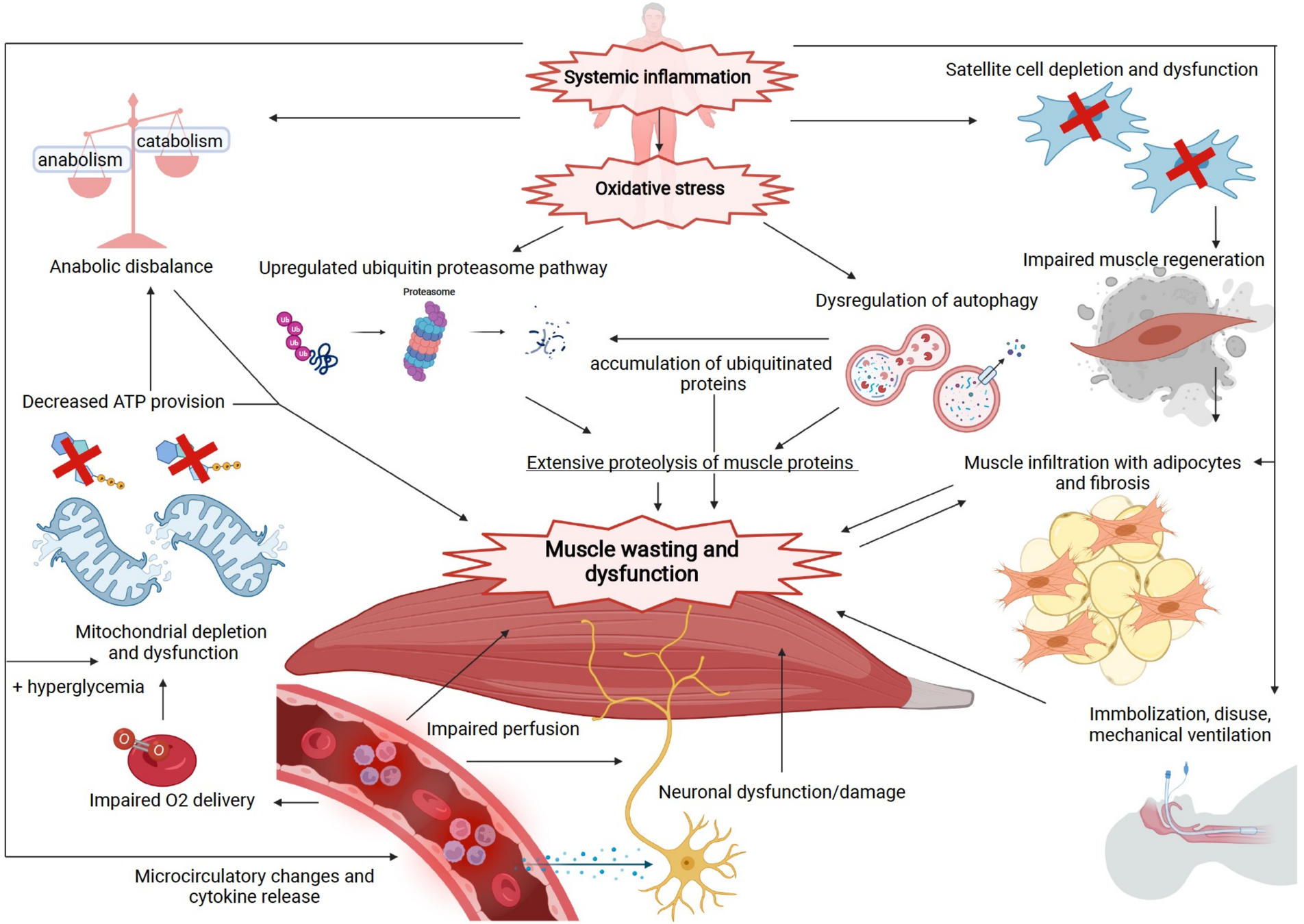

Critical illness


Serum
concentrations
rT3
TSH
FT4
Total T4
T3
Mild
Moderate
Severe
Recovery


Non-thyroidal illness
(low T3-syndrome)


Hypothalamus
TRH
TSH
Anterior
pituitary
+
-
T4
T3
Thyroid
FT4
rT3

38



Boelens Y, Melchers M, Van Zanten AR. Curr Opinion Crit Care 2022

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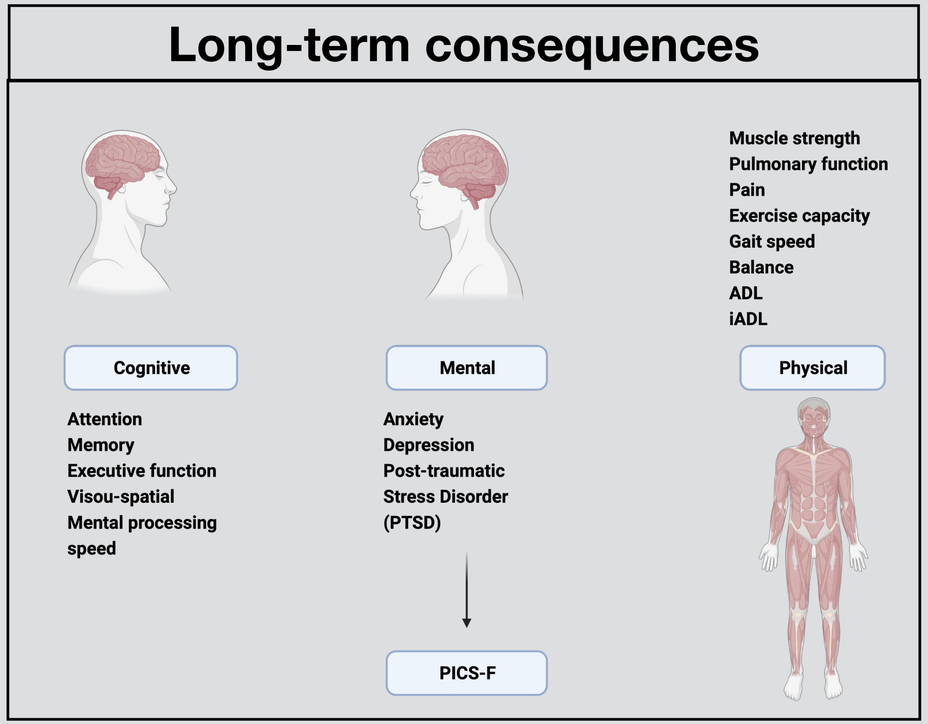
What we have learned?

Metabolic alterations are common in ICU patients:

- Stress hyperglycemia (insulin resistance)
- Persistent catabolism
- Muscle mass loss
- Mitochondrial dysfunction
- Autophagy deficiency
- Thyroid hormone abnormalities
- Refeeding syndrome



Clinical Nutrition xxx (2018) 1–32

Contents lists available at ScienceDirect

Clinical Nutrition

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

ESPEN Guideline

ESPEN guideline on clinical nutrition in the intensive care unit

Pierre Singer [a, *], Annika Reintam Blaser [b, c], Mette M. Berger [d], Waleed Alhazzani [e], Philip C. Calder [f], Michael P. Casaer [g], Michael Hiesmayr [h], Konstantin Mayer [i], Juan Carlos Montejo [j], Claude Pichard [k], Jean-Charles Preiser [l], Arthur R.H. van Zanten [m], Simon Oczkowski [e], Wojciech Szczeklik [n], Stephan C. Bischoff [o]

- **Statement 1**
- **Every critically ill patient staying for more than 48 h in the ICU should be considered at risk for malnutrition.**
- **Strong consensus (96 % agreement)**

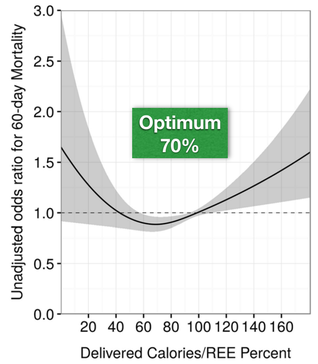
Early ICU nutrition a metabolic challenge

Hyperglycemia

Calories

Calories

Overfeeding



Refeeding syndrome

Clinical Nutrition xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Nutrition

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

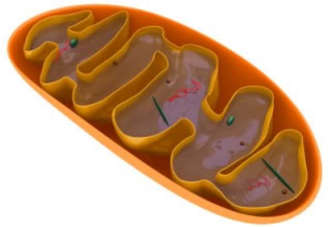
Original article

Impact of caloric intake in critically ill patients with, and without, refeeding syndrome: A retrospective study

Laura E. Olthof [a], W.A.C. Kristine Koekkoek [b], Coralien van Setten [a], Johannes C.N. Kars [c], Dick van Blokland [a], Arthur R.H. van Zanten [a, *]

[a] Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands
[b] Department of Internal Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands
[c] Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands

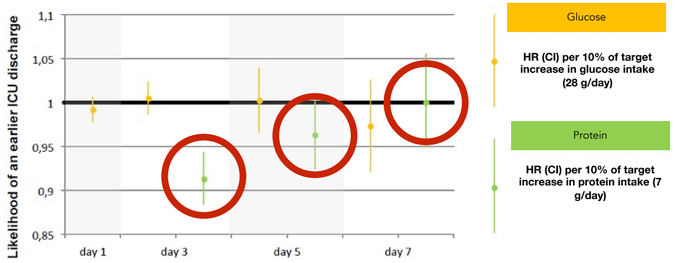
Calories and Proteins?



Calories?

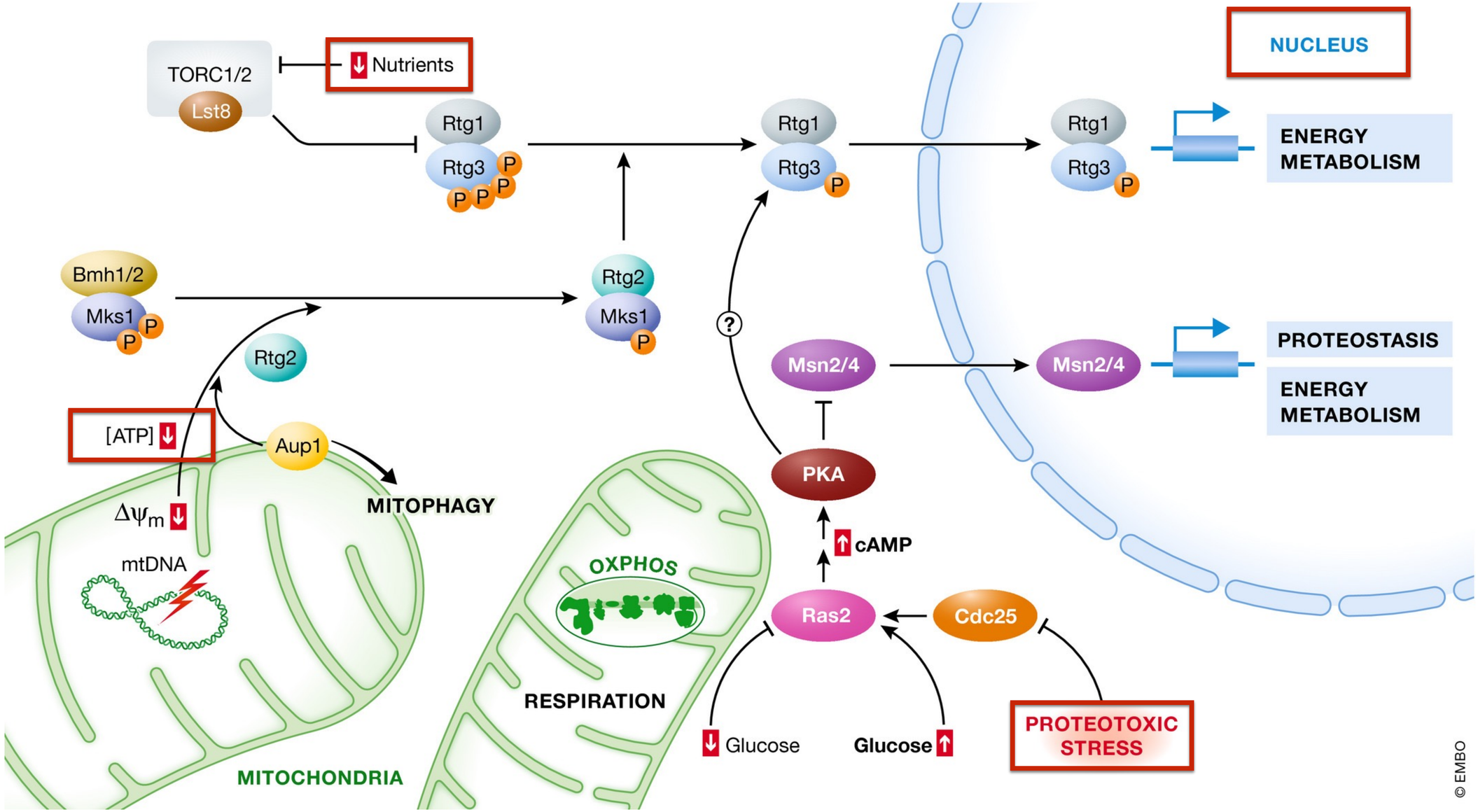
Mitochondrial dysfunction

Autophagy deficiency

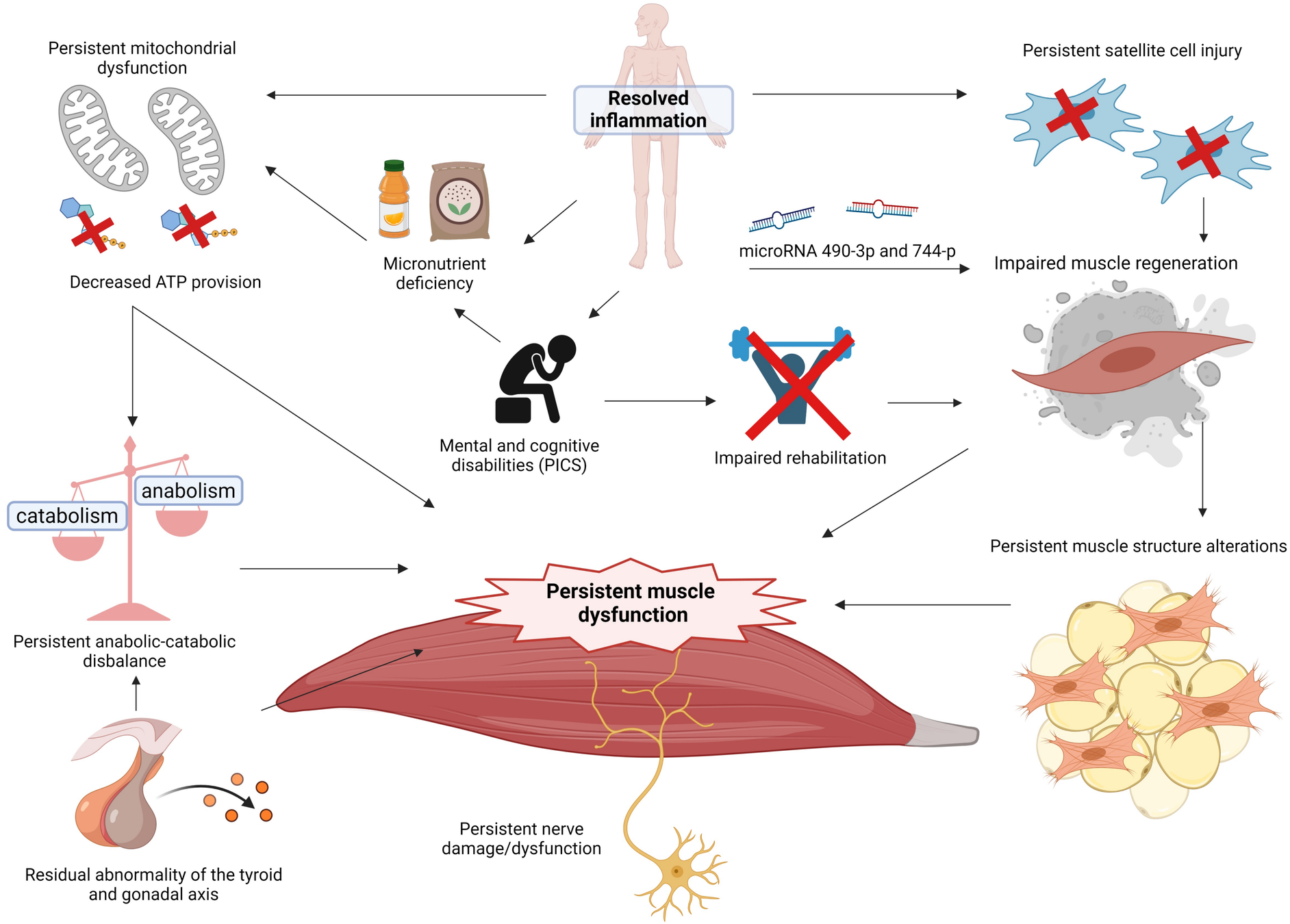


Proteins?

Mitochondria: hubs that integrate metabolic and proteostatic fluxes to modulate stress responses to various insults



Andreasson A et al. EMBO Rep (2019)20:e47865



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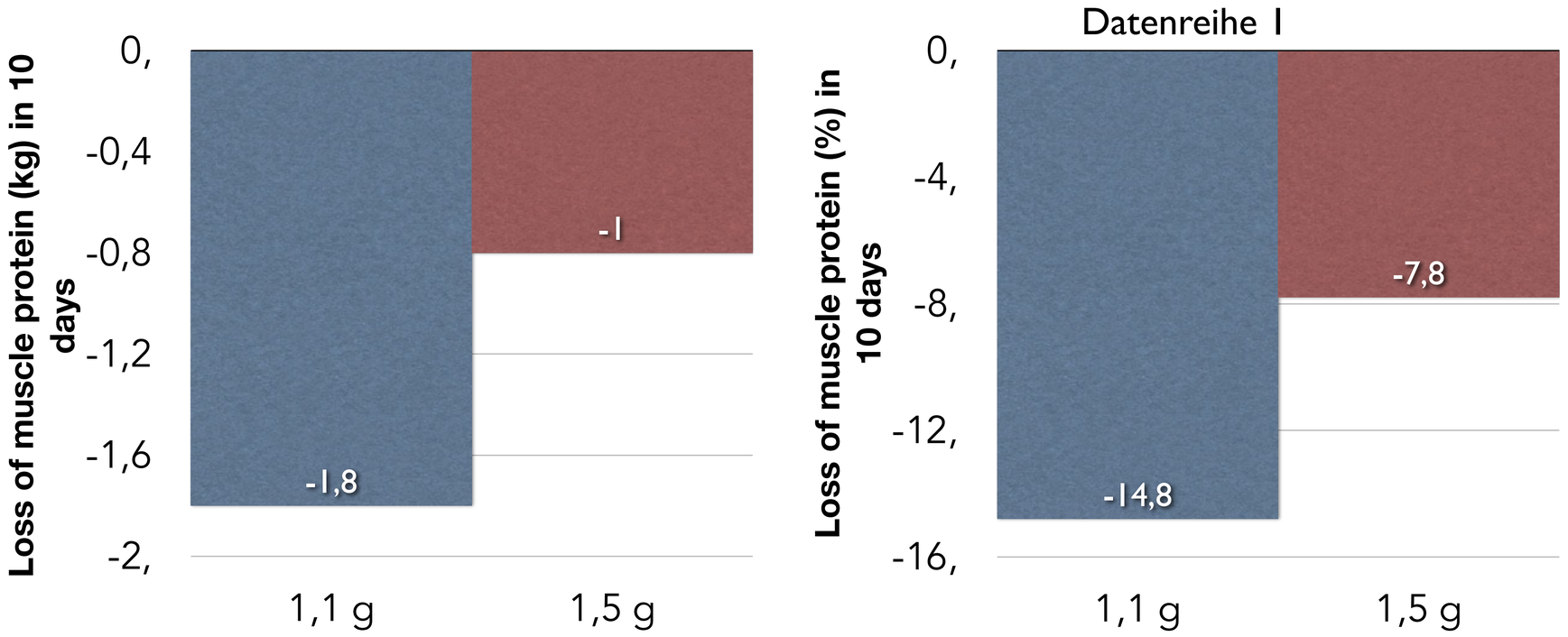
Boelens Y, Melchers M, Van Zanten AR. Curr Opinion Crit Care 2022

Effect of high protein intake on lean body mass (LBM)

in vivo neutron activation



-1.8 kg of proteins reflects 9 kg of muscle mass

Ishibashi N et al. Crit Care Med 1998

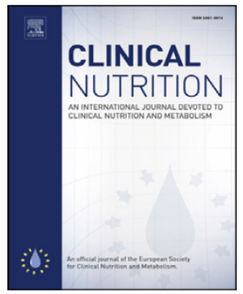
Role of timing protein intake: PROTINVENT study

Clinical Nutrition xxx (2018) 1–8

Contents lists available at ScienceDirect

Clinical Nutrition

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



Original article

Timing of PROTein INtake and clinical outcomes of adult critically ill patients on prolonged mechanical VENTilation: The PROTINVENT retrospective study

W.A.C. (Kristine) Koekkoek [a, 1], C.H. (Coralien) van Setten [a, 1], Laura E. Olthof [a], J.C.N. (Hans) Kars [b], Arthur R.H. van Zanten [a, *]

[a] *Department of Intensive Care Medicine, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands*
[b] *Department of Information Technology and Datawarehouse, Gelderse Vallei Hospital, Willy Brandtlaan 10, 6716 RP, Ede, The Netherlands*

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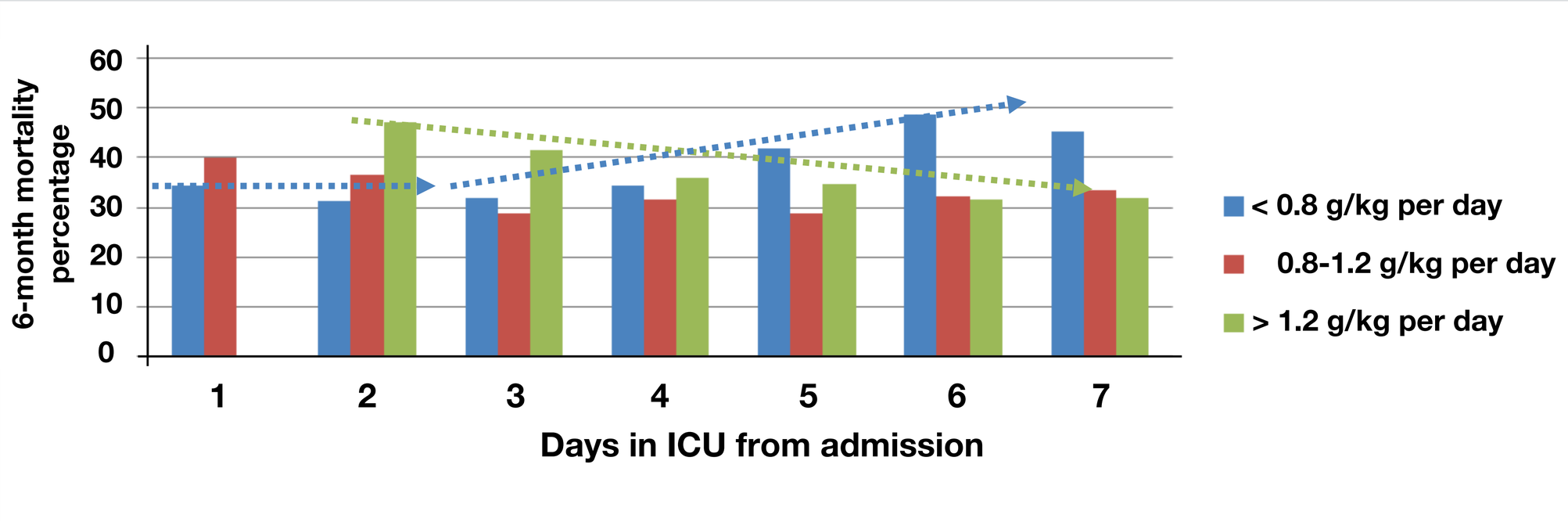
PROTINVENT study:
Role of timing protein intake and 6-month mortality

PROTein INtake and clinical outcome in adult critically ill patients on prolonged mechanical VENTilation: n=456; 2011-2015, Mechanical Ventilation > 7 days; Primary endpoint 6 month mortality

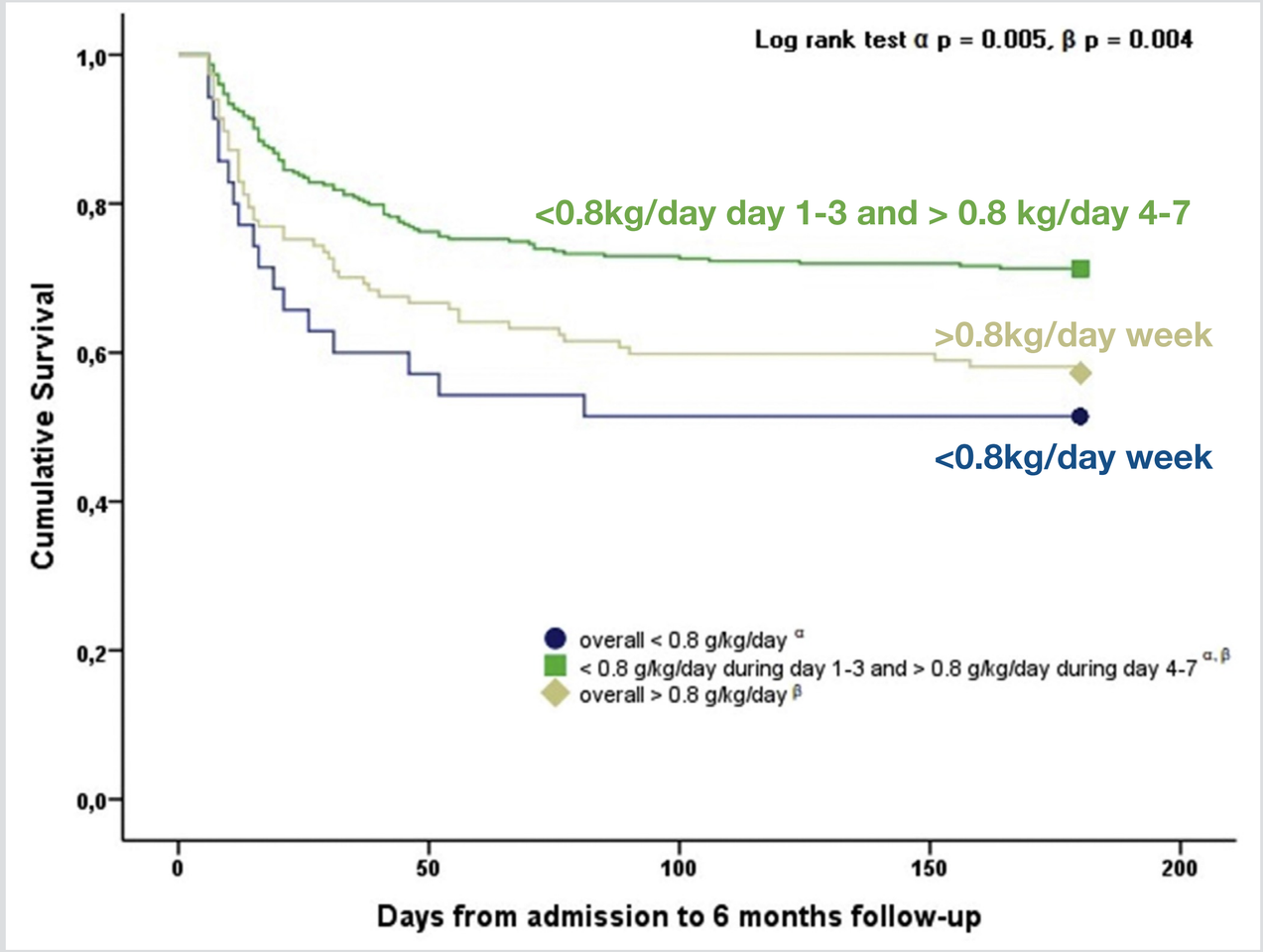


Early (< 3 days) high protein intake associated with higher mortality, after day 3 high intake is better. Is low to high intake after 3 days better?

47

Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17

Effect on protein intake (day 1-3) and (day 4-7) 6-month mortality



Time-dependent effect of protein intake.

Gradual increase from low protein intake during first 2 days of ICU stay to intermediate on day 3-5 and high protein intake from day 6 is associated with lower 6-month mortality.

Overall low protein intake associated with e highest 6-month, ICU and hospital mortality.

48

Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17

High protein intake

Days after ICU admission

1 2 3 4 5 6 7

Meta-analysis high protein in ICU

- 0.48 g/kg higher protein delivery (with similar energy delivery between groups) started within 3 days of ICU admission and lasting for 3 - 28 days in the ICU was **not** associated with a significant effect on:

overall mortality	hospital LOS
mortality at any time point	ICU LOS
duration of ventilation	infectious complications

Lee, ZY., Yap, C.S.L., Hasan, M.S. Heyland, DK et al. Crit Care 25, 260 (2021).

ESPEN ICU guideline recommendation: proteins

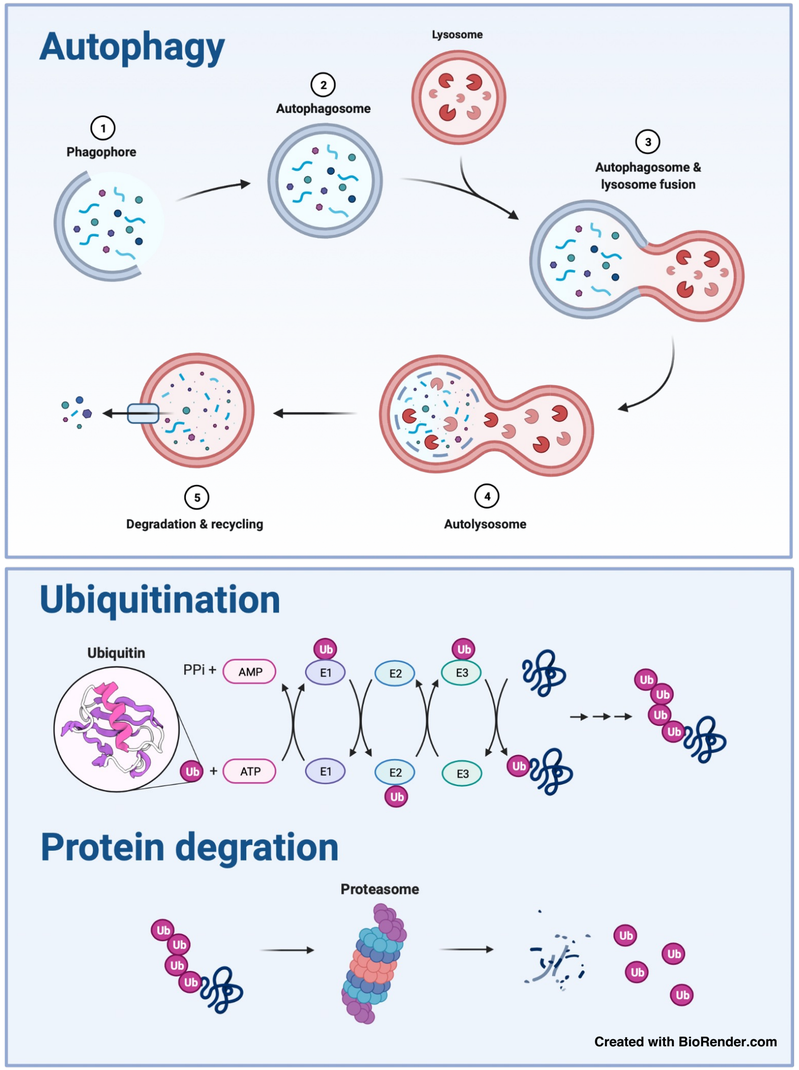
Recommendation 22

During critical illness, 1.3 g/kg protein equivalents per day can be delivered progressively

Grade of recommendation: 0 – strong consensus (91% agreement)

As enteral nutrition delivery is 80-85% in most patients for practical reasons we use 1.5 g/kg/day as a target

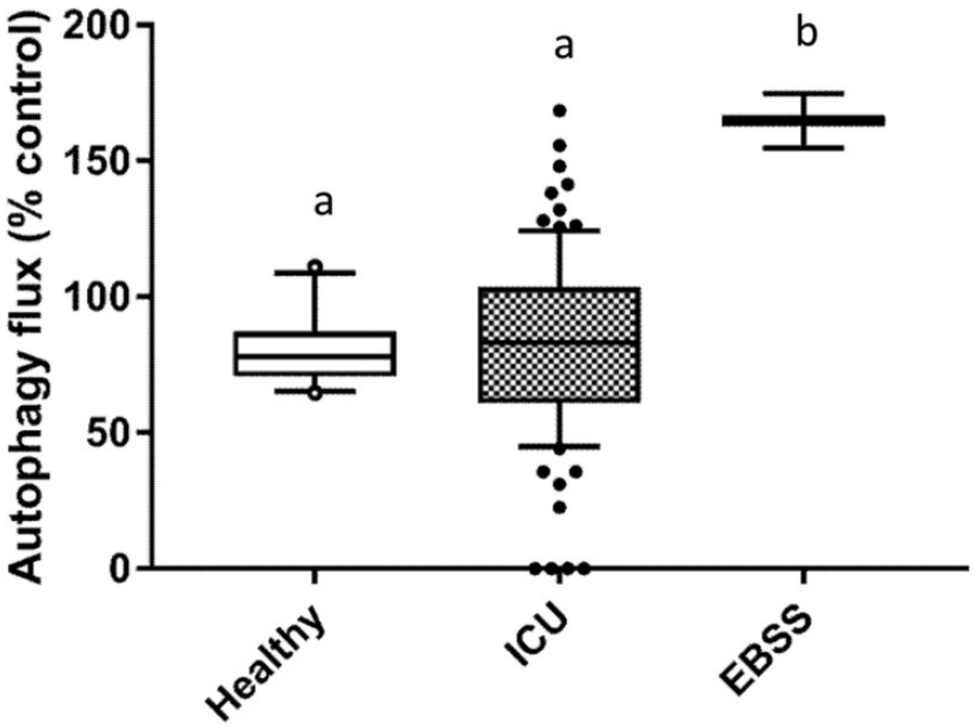
Proteins and Autophagy

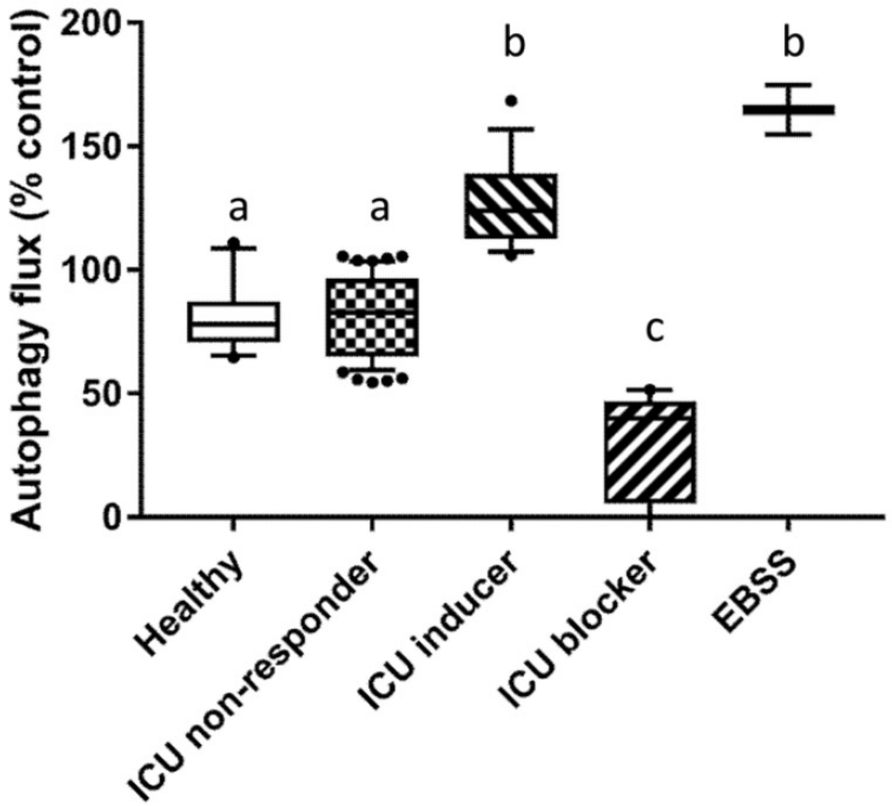


- Method eukaryotic cells dispose damaged organelles or protein aggregates too large for proteasome ubiquitin system
- Involves lysosomal system for removing unfolded proteins, virus, bacteria, fat/carb, organelles
- Autophagy role in immunity, inflammation, infection, cancer, aging, pulmonary diseases (COPD), metabolic and neurodegenerative diseases

AMK Choi et al NEJM 2013;368:651

Divergent autophagy response in critical illness





block was related to an accumulation of autophagosomes/autolysosomes, which indicates an impairment in the last steps of the autophagy process.

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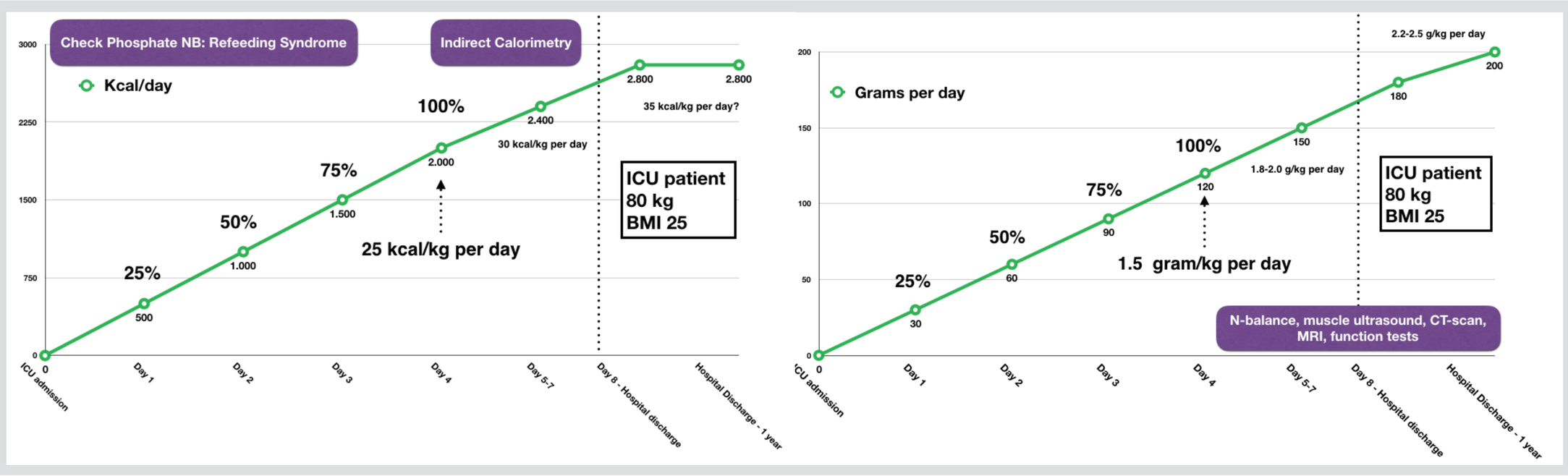
Tardif N, Rooijackers O et al. Nature Science Report 2019 45:1283–1287

Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding?

Kristine W.A.C. Koekkoek and Arthur R.H. van Zanten



Koekkoek WAC, Van Zanten AR. Curr Opin Anesthesiol 2018, 31:136–143

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DOI: 10.1002/jpen.2242

ORIGINAL COMMUNICATION

Physical recovery of COVID-19 pneumosepsis intensive care survivors compared with non-COVID pneumosepsis intensive care survivors during post–intensive care hospitalization: The RECOVID retrospective cohort study

Hanneke Pierre Franciscus Xaverius Moonen MD[1,3] | Bert Strookappe PhD[1,2] | Arthur Raymond Hubert van Zanten MDPhD[1,3]

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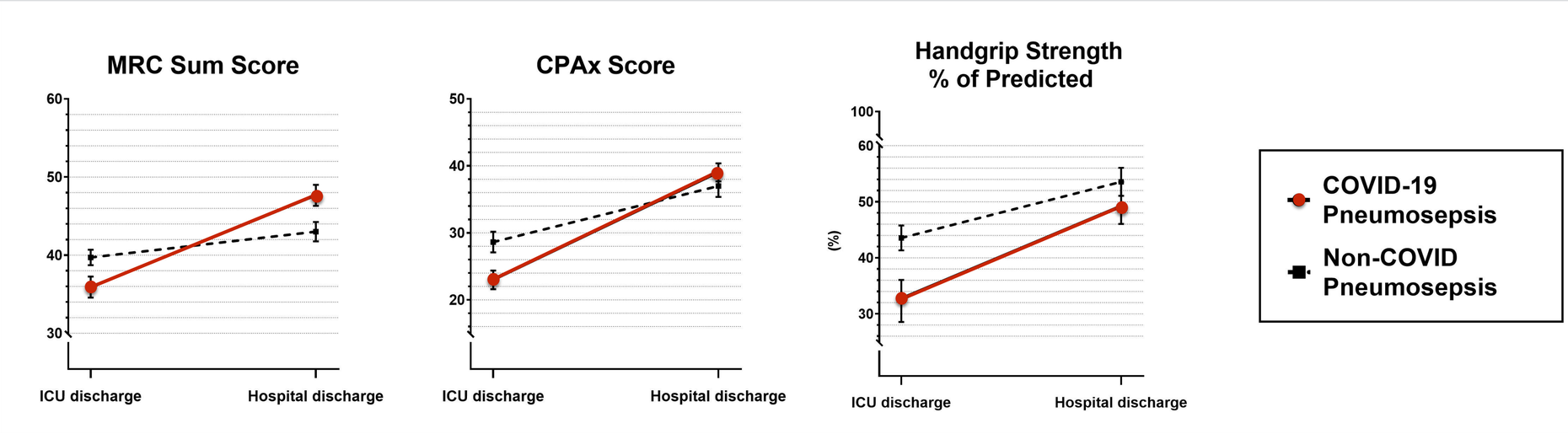
COVID-19 vs pneumosepsis non-COVID-19 ICU patients

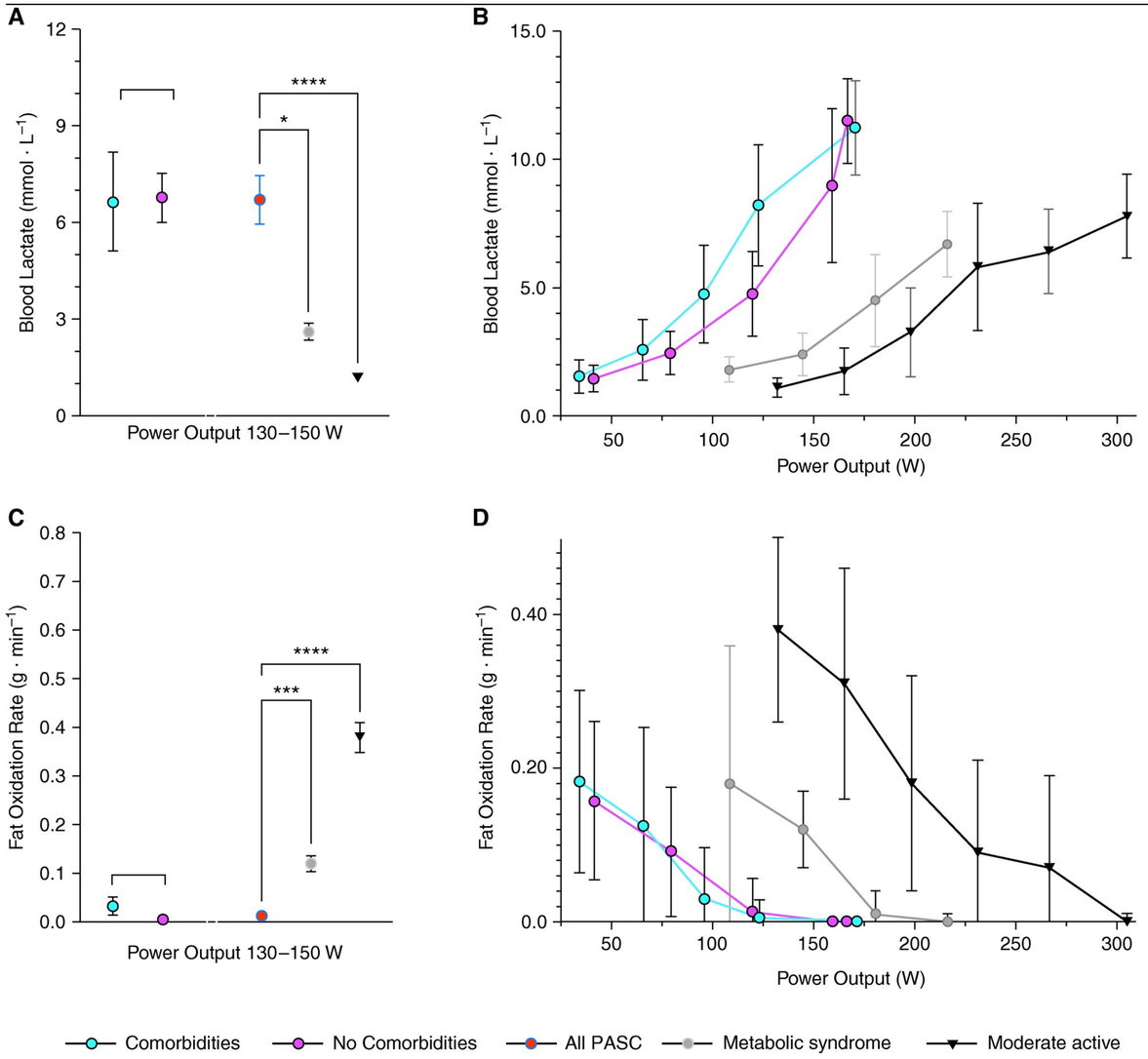


COVID-19 patients more severe ICU acquired weakness, however recover faster during post-ICU hospitalization

Moonen HPFX, Strookappe B, Van Zanten ARH. JPEN J Parenter Enteral Nutr. 2021;1–7

56

Decreased Fatty Acid Oxidation and Altered Lactate Production during Exercise in Patients with Post-acute COVID-19 Syndrome



- CPET
- In patients with PACS
- The transition from FATox to CHOox occurs prematurely, suggesting metabolic reprogramming and dysfunctional mitochondria
- Dysregulated lipid oxidation and decreased mitochondrial biogenesis have been reported in acute critically ill patients admitted to the ICU

de Boer E, et al. Am J Respir Crit Care Med. 2022 Jan 1;205(1):126-129

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6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Chaolin Huang, Lixue Huang*, Yeming Wang*, Xia Li*, Lili Ren*, Xiaoying Gu*, Liang Kang*, Li Guo*, Min Liu*, Xing Zhou, Jianfeng Luo, Zhenghui Huang, Shengjin Tu, Yue Zhao, Li Chen, Decui Xu, Yanping Li, Caihong Li, Lu Peng, Yong Li , Wuxiang Xie, Dan Cui, Lianhan Shang, Guohui Fan, Jiuyang Xu, Geng Wang, Ying Wang, Jingchuan Zhong, Chen Wang , Jianwei Wang†, Dingyu Zhang†, Bin Cao†*

- **At 6 months after COVID-19 survivors:**
- **Fatigue or muscle weakness, sleep difficulties, and anxiety or depression**
- **More severely ill had more severe impaired pulmonary diffusion capacities**

Huang L et al. Lancet 2021; 397: 220–32

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	Total (n=1733)	Seven-category scale			OR or β (95% CI)	
		Scale 3: not requiring supplemental oxygen (n=439)	Scale 4: requiring supplemental oxygen (n=1172)	Scale 5–6: requiring HFNC, NIV, or IMV (n=122)	Scale 4 *vs* 3	Scale 5–6 *vs* 3
Symptoms						
Any one of the following symptoms	1265/1655 (76%)	344/424 (81%)	820/1114 (74%)	101/117 (86%)	OR 0·70 (0·52 to 0·96)*	OR 2·42 (1·15 to 5·08)*
Fatigue or muscle weakness	1038/1655 (63%)	281/424 (66%)	662/1114 (59%)	95/117 (81%)	OR 0·74 (0·58 to 0·96)*	OR 2·69 (1·46 to 4·96)*
Sleep difficulties	437/1655 (26%)	116/424 (27%)	290/1114 (26%)	31/117 (26%)	OR 0·92 (0·71 to 1·21)	OR 1·15 (0·68 to 1·94)
Hair loss	359/1655 (22%)	93/424 (22%)	238/1114 (21%)	28/117 (24%)	OR 0·99 (0·74 to 1·31)	OR 1·17 (0·67 to 2·04)
Smell disorder	176/1655 (11%)	55/424 (13%)	107/1114 (10%)	14/117 (12%)	OR 0·69 (0·48 to 1·00)	OR 0·90 (0·43 to 1·87)
Palpitations	154/1655 (9%)	45/424 (11%)	96/1114 (9%)	13/117 (11%)	OR 0·86 (0·58 to 1·28)	OR 1·31 (0·61 to 2·80)
Joint pain	154/1655 (9%)	51/424 (12%)	86/1114 (8%)	17/117 (15%)	OR 0·56 (0·38 to 0·83)*	OR 0·74 (0·36 to 1·50)
Decreased appetite	138/1655 (8%)	42/424 (10%)	85/1114 (8%)	11/117 (9%)	OR 0·84 (0·56 to 1·27)	OR 1·56 (0·71 to 3·43)
Taste disorder	120/1655 (7%)	37/424 (9%)	75/1114 (7%)	8/117 (7%)	OR 0·84 (0·54 to 1·30)	OR 0·80 (0·32 to 2·02)
Dizziness	101/1655 (6%)	32/424 (8%)	60/1114 (5%)	9/117 (8%)	OR 0·77 (0·48 to 1·22)	OR 0·95 (0·39 to 2·31)
Diarrhoea or vomiting	80/1655 (5%)	27/424 (6%)	48/1114 (4%)	5/117 (4%)	OR 0·71 (0·42 to 1·22)	OR 0·39 (0·11 to 1·42)
Chest pain	75/1655 (5%)	19/424 (4%)	46/1114 (4%)	10/117 (9%)	OR 0·94 (0·52 to 1·67)	OR 2·55 (0·99 to 6·62)
Sore throat or difficult to swallow	69/1655 (4%)	20/424 (5%)	44/1114 (4%)	5/117 (4%)	OR 0·91 (0·50 to 1·65)	OR 1·21 (0·40 to 3·73)
Skin rash	47/1655 (3%)	16/424 (4%)	27/1114 (2%)	4/117 (3%)	OR 0·64 (0·32 to 1·26)	OR 0·71 (0·18 to 2·87)
Myalgia	39/1655 (2%)	11/424 (3%)	24/1114 (2%)	4/117 (3%)	OR 0·80 (0·38 to 1·69)	OR 1·72 (0·47 to 6·27)
Headache	33/1655 (2%)	10/424 (2%)	20/1114 (2%)	3/117 (3%)	OR 0·76 (0·35 to 1·69)	OR 1·53 (0·36 to 6·52)
Low grade fever	2/1655 (<1%)	1/424 (<1%)	1/1114 (<1%)	0	NA	NA
mMRC score						
0	1196/1615 (74%)	323/425 (76%)	802/1079 (74%)	71/111 (64%)	NA	NA
≥1	419/1615 (26%)	102/425 (24%)	277/1079 (26%)	40/111 (36%)	OR 1·11 (0·84 to 1·46)	OR 2·15 (1·28 to 3·59)*
EQ-5D-5L questionnaire†						
Mobility: problems with walking around	113/1622 (7%)	25/426 (6%)	72/1084 (7%)	16/112 (14%)	OR 1·06 (0·63 to 1·78)	OR 2·48 (1·12 to 5·48)*
Personal care: problems with washing or dishing	11/1622 (1%)	0	10/1084 (1%)	1/112 (1%)	NA	NA
Usual activity: problems with usual activity	25/1611 (2%)	5/425 (1%)	15/1076 (1%)	5/110 (5%)	OR 1·10 (0·35 to 3·50)	OR 3·42 (0·74 to 15·78)
Pain or discomfort	431/1616 (27%)	111/422 (26%)	274/1082 (25%)	46/112 (41%)	OR 0·86 (0·66 to 1·13)	OR 1·94 (1·19 to 3·16)*
Anxiety or depression	367/1617 (23%)	98/425 (23%)	233/1081 (22%)	36/111 (32%)	OR 0·88 (0·66 to 1·17)	OR 1·77 (1·05 to 2·97)*
Quality of life‡	80·0 (70·0 to 90·0)	80·0 (70·0 to 90·0)	80·0 (75·0 to 90·0)	80·0 (70·0 to 87·5)	β 2·68 (−1·55 to 6·91)	β −2·33 (−10·60 to 5·95)
Distance walked in 6 min, m	495·0 (440·0 to 538·0)	495·0 (446·0 to 542·0)	495·0 (439·0 to 537·0)	479·0 (434·0 to 515·5)	β −9·25 (−18·80 to 0·26)	β −32·50 (−51·40 to −13·60)§
Percentage of predicted value¶	87·7 (75·9 to 101·1)	87·8 (76·3 to 101·3)	87·9 (76·3 to 101·5)	85·2 (72·9 to 98·6)	β −1·58 (−3·59 to 0·43)	β −5·61 (−9·60 to −1·62)*
Less than lower limit of the normal range‖	392/1692 (23%)	103/423 (24%)	255/1153 (22%)	34/116 (29%)	OR 1·13 (0·81 to 1·57)	OR 2·18 (1·18 to 4·03)*
eGFR <90 mL/min per 1·73 m²	487/1393 (35%)	121/338 (36%)	326/967 (34%)	40/88 (45%)	OR 0·86 (0·63 to 1·19)	OR 1·44 (0·76 to 2·70)

ICU population

- 86% fatigue
- 14% mobility disorders
- 41% pain or discomfort
- 32% anxiety or depression
- 6-min walking 29% less than lower limit
- 45% eGFR< 90 mL/min/1,73 m^2

Huang L et al. Lancet 2021; 397: 220–32

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MONITOR Study

	Values at 1-y follow-up, No./total (%) [95% CI]
Physical symptoms	
Reported ≥1 physical symptom	182/245 (74.3) [68.3-79.6]
Clinical Frailty Scale score, median (IQR)[a]	2 (2-3)
Exceeded frailty cutoff[a]	15/245 (6.1) [3.5-9.9]
Checklist Individual Strength-8—fatigue subscale score, median (IQR)[b]	29 (18-39)
Exceeded fatigue cutoff[b]	138/246 (56.1) [49.7-62.4]
New or worsened physical problems, No. of problems, median (IQR)[c]	2 (0-5)
Reported ≥1 physical problem	165/246 (67.1) [60.8-72.9]
Mental symptoms	
Reported ≥1 mental symptom	64/244 (26.2) [20.8-32.2]
HADS scale-anxiety score, median (IQR)[d]	3 (1-6)
Exceeded anxiety cutoff[d]	44/246 (17.9) [13.3-23.3]
HADS scale-depression score, median (IQR)[d]	3 (1-5)
Exceeded depression cutoff[d]	45/246 (18.3) [13.7-23.7]
Impact of Event Scale-6 score, median (IQR)[e]	0.5 (0.2-1.2)
Exceeded posttraumatic stress disorder cutoff[e]	24/244 (9.8) [6.4-14.3]
Cognitive symptoms	
Cognitive Failure Questionnaire-14 score, median (IQR)[f]	24.8 (12.8-37.0)
Exceeded cognitive failure cutoff[f]	39/241 (16.2) [11.8-21.5]

Abbreviation: HADS, Hospital Anxiety and Depression Scale.

[a] Score range, 1 (very fit) to 9 (terminally ill), with a score of 5 or greater indicating frailty. A score of 2 describes a person who is fit, and higher scores indicate being more frail.

[b] A 7-point rating subscale of the Checklist Individual Strength-20 (score range, 8-56, with a score of 27 or greater indicating abnormal fatigue) and consisting of 8 statements.

[c] Physical problems were objectified by a list of 30 symptoms and were present if at least 1 symptom was moderate or severe.

[d] Score range, 0 (best) to 21 (worst), with higher scores indicating worse symptoms, with the presence of anxiety or depression symptoms defined by a subscale score of 8 or greater.

[e] Score range, 0 (not at all symptomatic) to 4 (extremely symptomatic), with a score of 1.75 or greater indicating presence of symptoms.

[f] Score range, 0 (never) to 100 (very often), with a score of 43 or greater indicating symptoms of daily life cognitive failure.

Heesakkers H, et al. JAMA. 2022;327(6):559–565.

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Table 3. Symptoms Experienced by Patients With COVID-19 1 Year After Intensive Care Unit Treatment[a]

	No./total (%) of patients with 1-y outcomes		
Domain	1 Domain	2 Domains	All 3 domains
Physical[b]	107/245 (43.5)	35/246 (14.2) + Mental	
Mental[c]	1/244 (0.4)		26/246 (10.5)
Cognitive[d]		15/246 (5.9) + Physical	

[a] Percentages will not sum to 100% because 25.5% of patients experienced no symptoms at 1 year. Percentages may differ from 1-year outcomes presented in Table 2 because only patients without any missing outcome variable were included in the analysis (N = 239). Empty cells indicate that zero patients fulfilled the category.

[b] Physical symptoms were defined as either being frail (Clinical Frailty Scale score of ≥5), fatigued (Checklist Individual Strength score of ≥27), or having at least 1 new or worsened physical problem.

[c] Mental symptoms were defined as either experiencing symptoms of anxiety (Hospital Anxiety and Depression Scale—anxiety subscale score of ≥8), depression (Hospital Anxiety and Depression Scale—depression subscale score of ≥8), or posttraumatic stress disorder (mean Impact of Event scale-6 score of ≥1.75).

[d] Cognitive symptoms were defined as having a Cognitive Failure Questionnaire score of 43 or greater.

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Heesakkers H, et al. JAMA. 2022;327(6):559–565.

New physical problems after COVID-19 ICU admission

Table 4. Prevalence of New Physical Problems in Patients With COVID-19 1 Year After Intensive Care Unit Admission

New physical problems[a]	No./total (%) [95% CI]
Weakened condition	95/244 (38.9) [33.0-45.1]
Joint stiffness	64/243 (26.3) [21.1-32.1]
Joint pain	62/243 (25.5) [20.3-31.2]
Muscle weakness	60/242 (24.8) [19.6-30.5]
Myalgia	52/244 (21.3) [16.5-26.7]
Dyspnea	51/245 (20.8) [16.1-26.2]
Tingling or numb sensation in limbs	50/243 (20.6) [15.8-26.0]
Lung disease	45/243 (18.5) [14.0-23.7]
Neuropathic pain	42/242 (17.4) [12.9-22.5]
Voice problems (eg, hoarseness)	29/244 (11.9) [8.2-16.3]
Dizziness or balance problems	28/243 (11.5) [7.9-15.9]
Hypotension or hypertension	28/245 (11.4) [7.9-15.8]
Sexual problems	18/240 (7.5) [4.6-11.3]
Skin problems	18/245 (7.3) [4.5-11.1]
Hair loss	17/243 (7.0) [4.2-10.7]
Loss of smell	17/245 (6.9) [4.2-10.6]
Loss of taste	15/245 (6.1) [3.6-9.6]
Headache	13/243 (5.3) [3.0-8.7]
Heart disease, chest pain	13/244 (5.3) [3.0-8.6]
Vision problems	12/244 (4.9) [2.7-8.1]
Loss of hearing	10/244 (4.1) [2.1-7.1]
Bowel problems	9/245 (3.7) [1.8-6.5]
Urinary problems	8/244 (3.3) [1.5-6.0]
Wound pain	5/245 (2.0) [0.7-4.3]
Pressure ulcers	5/243 (2.1) [0.7-4.4]
Abdominal pain	4/245 (1.6) [0.5-3.8]
Dysphagia	3/243 (1.2) [0.3-3.2]
Menstrual problems	1/200 (0.5) [0.0-2.2]
Other pain	13/206 (6.3) [3.5-10.2]
Other physical problems	22/194 (11.3) [7.4-16.3]

[a] New physical problems were selected from a list of 30 problems, and a condition or symptom was considered present if it was at least moderate or severe.

Heesakkers H, et al. JAMA. 2022;327(6):559–565.

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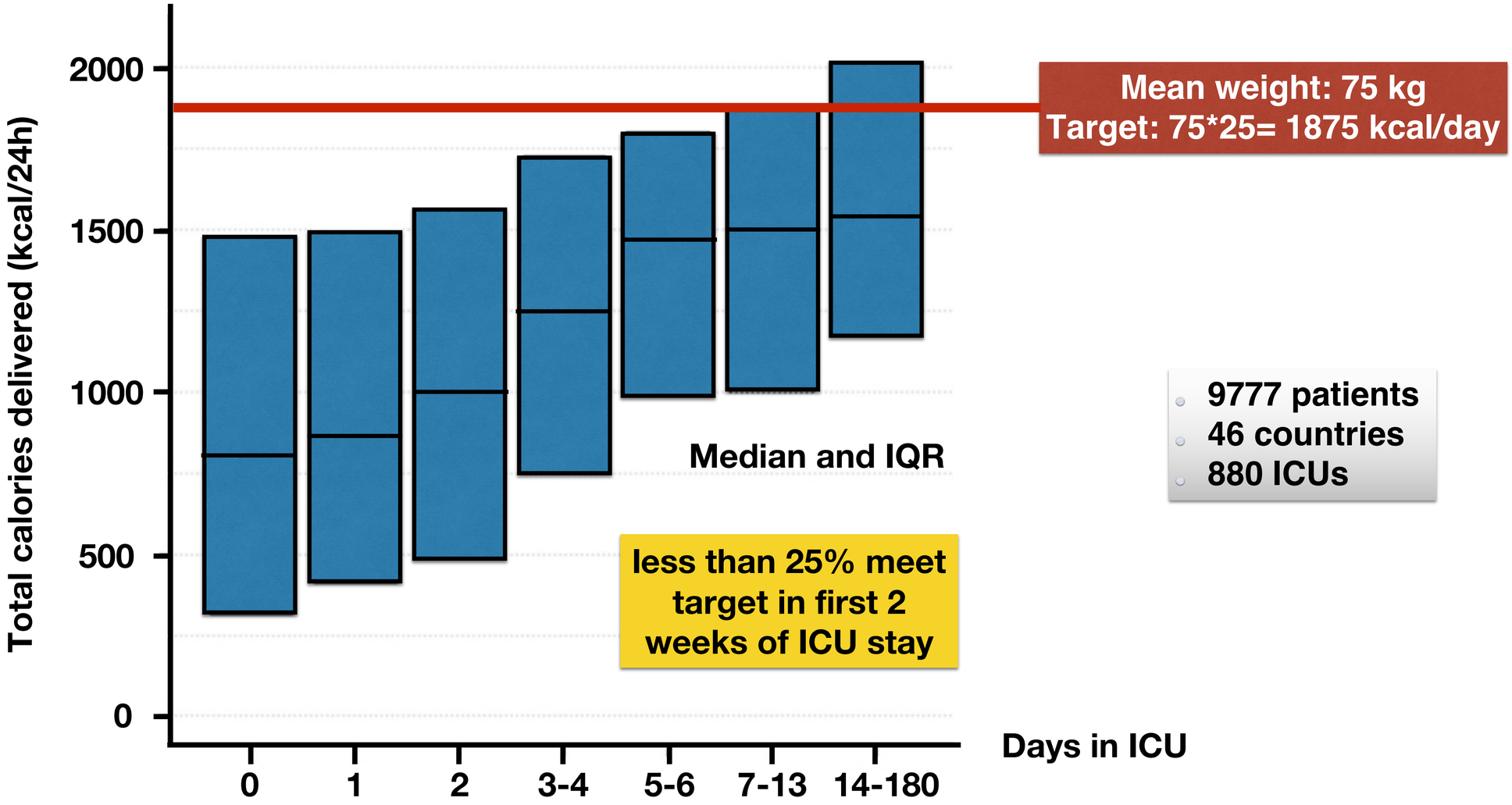
NutritionDay ICU: A 7 year worldwide prevalence study of nutrition practice in intensive care

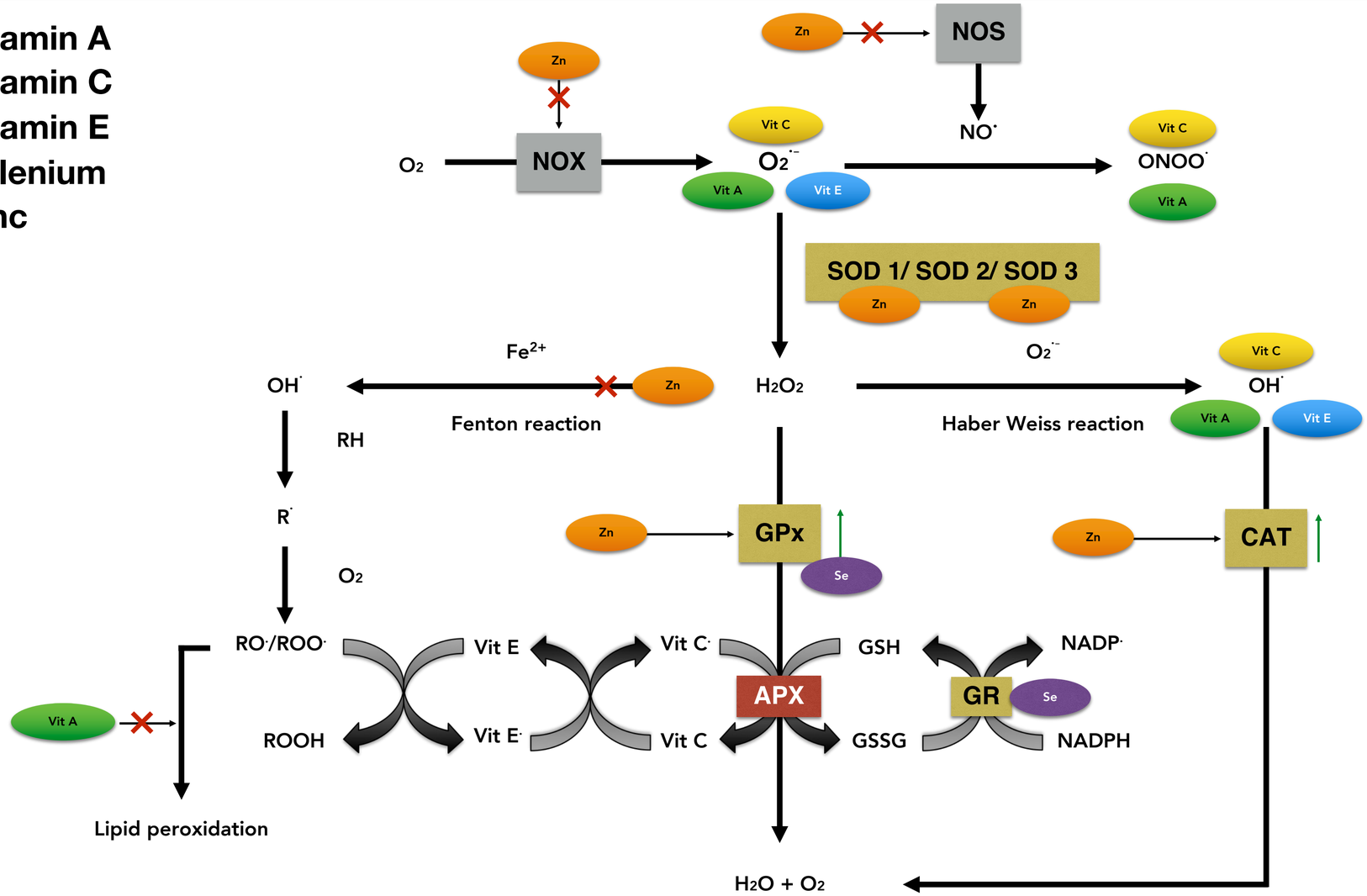


Bendavid I et al. Clin Nutr 2017;36:1122-1129

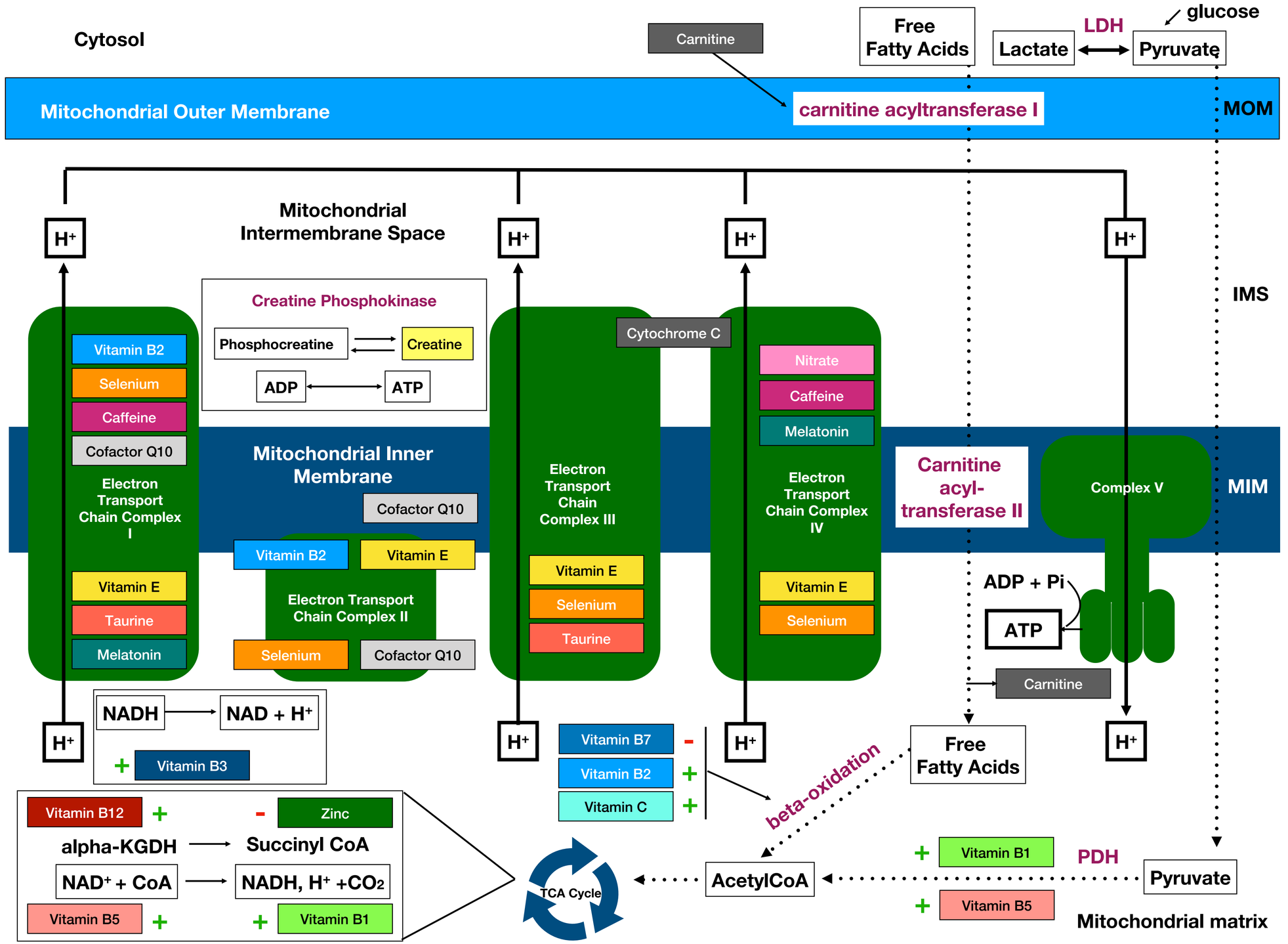
Early mobilization in the ICU

Antioxidant Network: Vitamins and trace elements

Vit A Vitamin A
Vit C Vitamin C
Vit E Vitamin E
Se Selenium
Zn Zinc

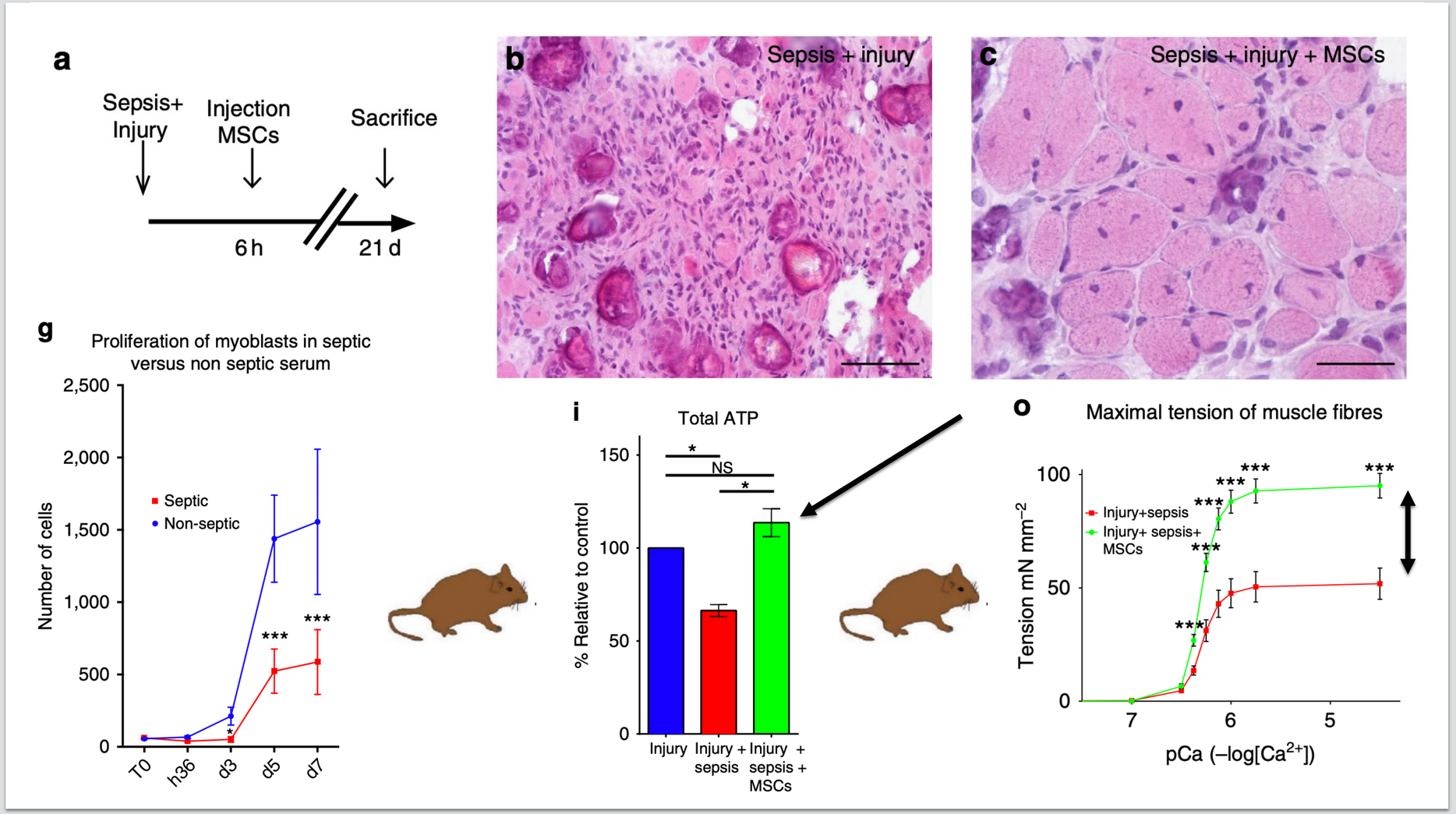


Koekkoek WA, van Zanten AR. Nutr Clin Pract. 2016;31(4):457-74.



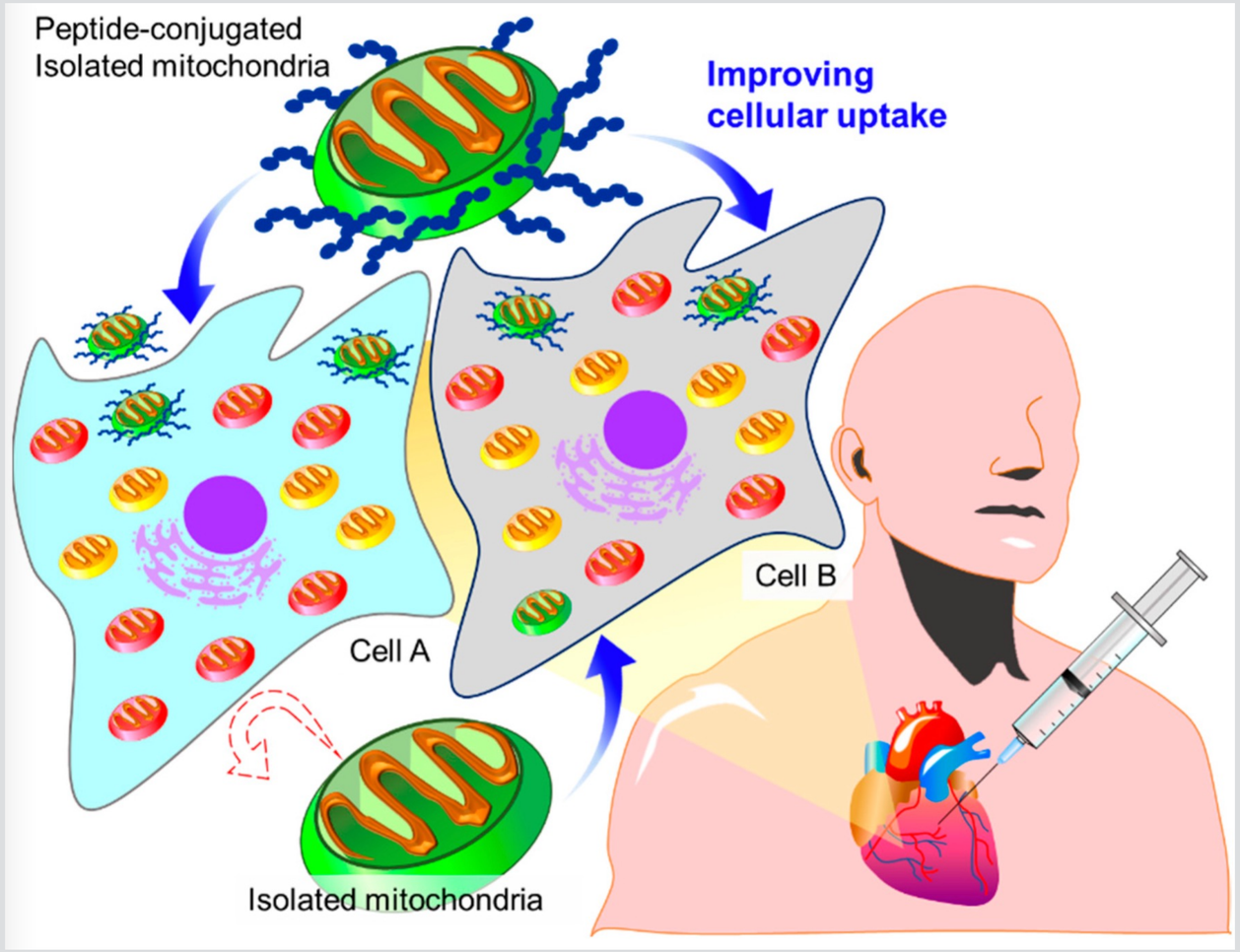
Wesselink E, Koekkoek K, ...Van Zanten AR, Clin Nutr 2018

Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy



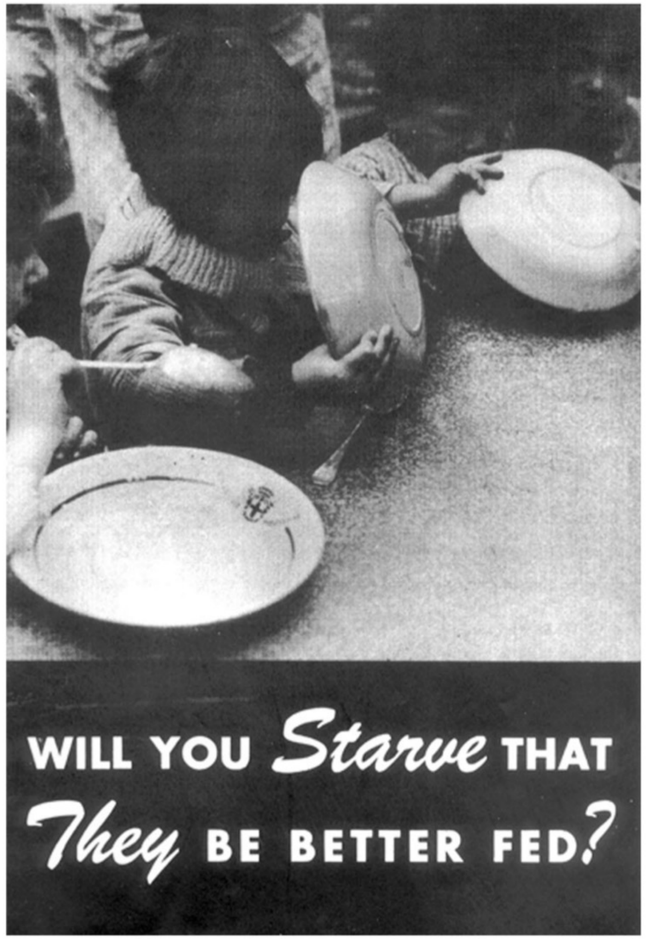
Rocheteau P, et al. Nat Commun. 2015 Dec 15;6:10145.

Mitochondrial Transplantation Therapy

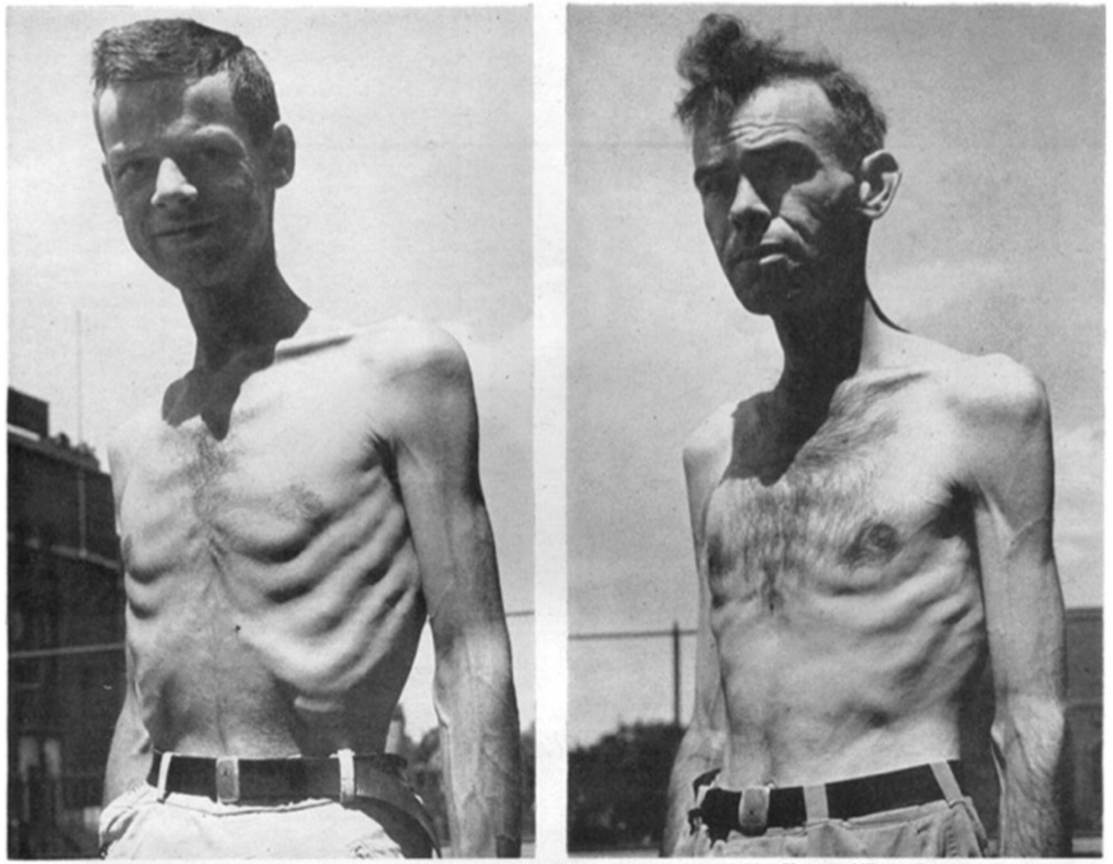


Yamada Y, et al. Int. J. Mol. Sci. 2020, 21(17), 6365

How much food is necessary to recover from starvation?



Starvation period: 1800 kcal/dag



AFTER FIVE MONTHS OF STARVATION DIET CONSCIENTIOUS OBJECTORS SAMUEL LEGG (LEFT) AND EDWARD COWLES HAVE LOST 35 AND 30 POUNDS RESPECTIVELY

MEN STARVE IN MINNESOTA

CONSCIENTIOUS OBJECTORS VOLUNTEER FOR STRICT HUNGER TESTS TO STUDY EUROPE'S FOOD PROBLEM

Wischmeyer Critical Care 2017, 21(Suppl 3):316

Minnesota starvation project vs. ICU and hospital starvation

Minnesota starvation regimen: 1800 kcal/day for several months

Refeeding program

Proteins
During 1 year:
2-2.5 g/kg/day (3x normal)

Energy:
During 1 year:
4000-4500 kcal/day (2-3x normal)

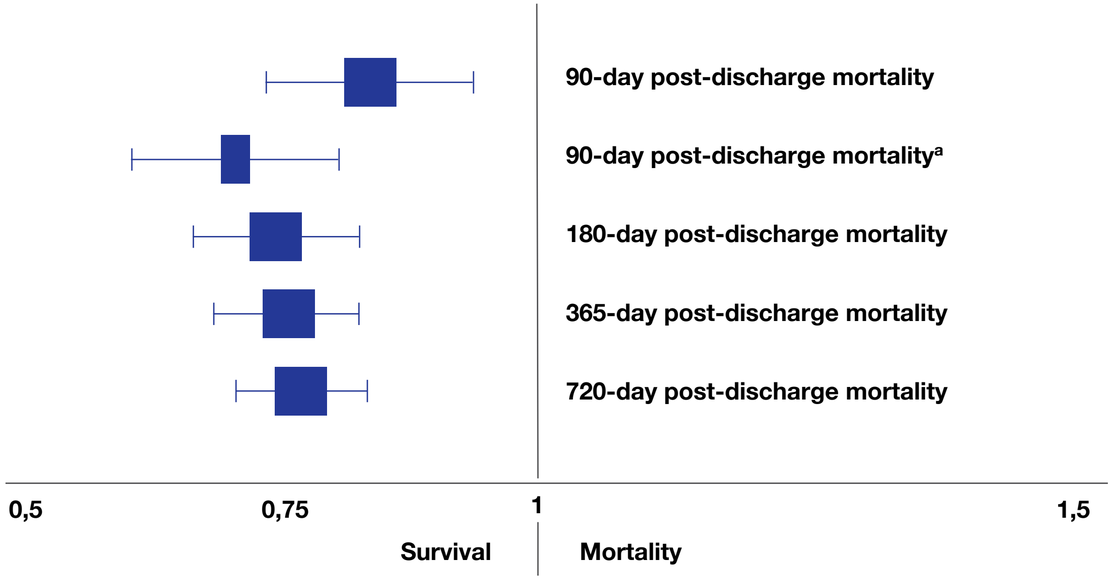
Most ICU patient get less!

Wischmeyer Critical Care 2017, 21(Suppl 3):316

Current status of patients after ICU discharge

Higher daily protein delivery during hospitalization is associated with decreased mortality following hospital discharge

Discharge mortality associated for each 1g/kg/day increase in protein delivery.



[a] Restricted to patients diagnosed with Malnutrition

Cohort Study (n=801)
ICU survivors
(2004-2012)

90-day post-discharge mortality was 13.9%.

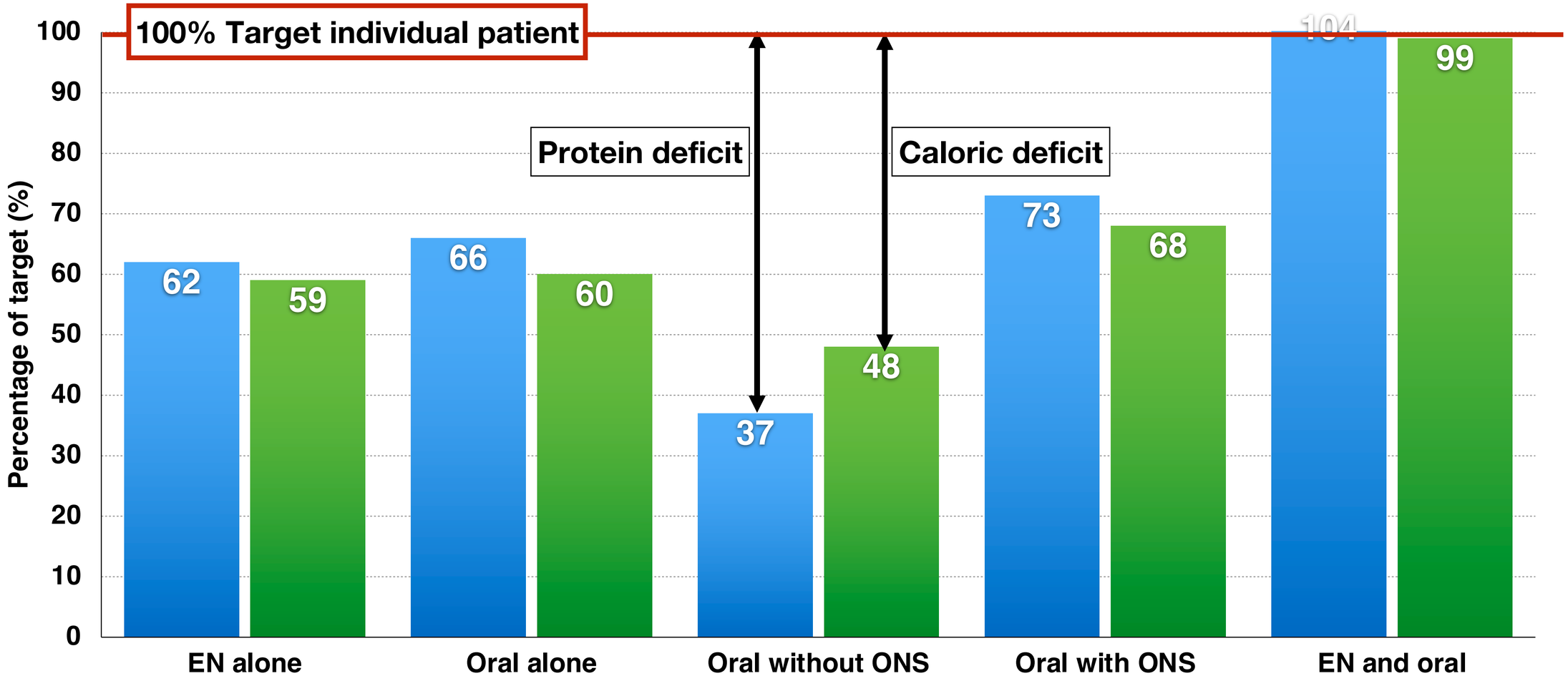
Mean nutrition delivery days 15 days.

The 90-day post-discharge mortality rate was 17% lower (95% CI: 6 26) for each 1 g/kg increase in daily protein delivery (OR = 0.83 (95% CI 0.74–0.94; p = 0.002)).

*Oral, enteral and parenteral sources

Weijs PJM, et al. J Clin Med. 2019;8(1):E43.

Post-ICU nutrition: percentage of target achieved

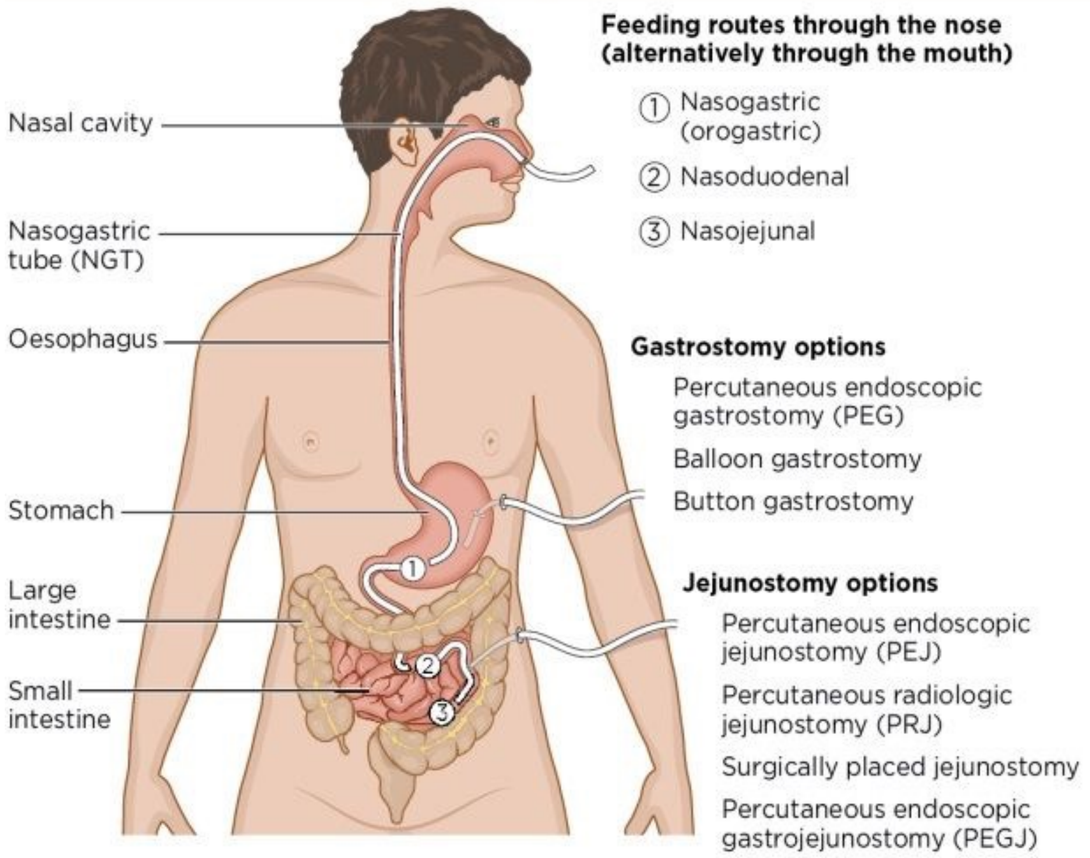


Ridley EJ, et al. JPEN J Parenter Enteral Nutr. 2019 Jan;43(1):88-95.

Removal feeding tube post-ICU

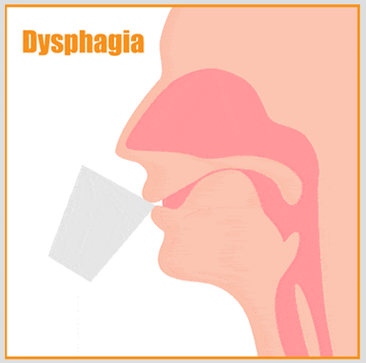
- 44.1% lower energy intake
- 50.9% lower protein intake
- We should continue the tube feeding longer post-ICU

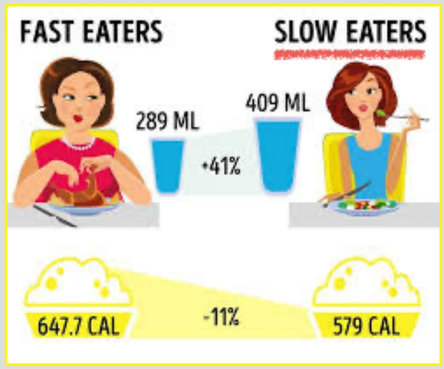
PROSPECT I study

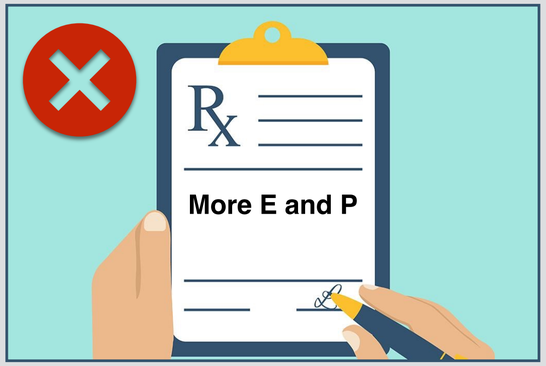


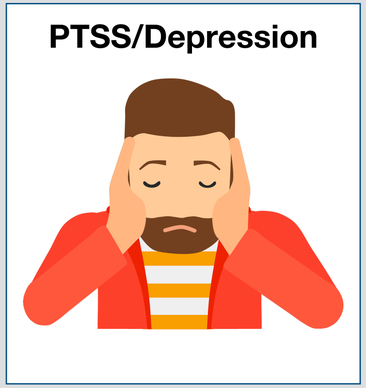
In preparation: Slingerland-Boot R, van der Heiden I, de Vries J, van Zanten AR.

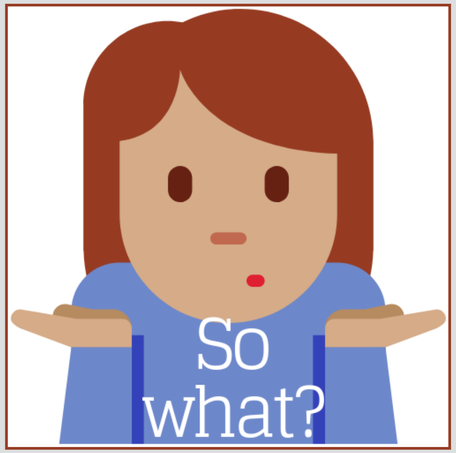
9 reasons for low food intake in post ICU patients











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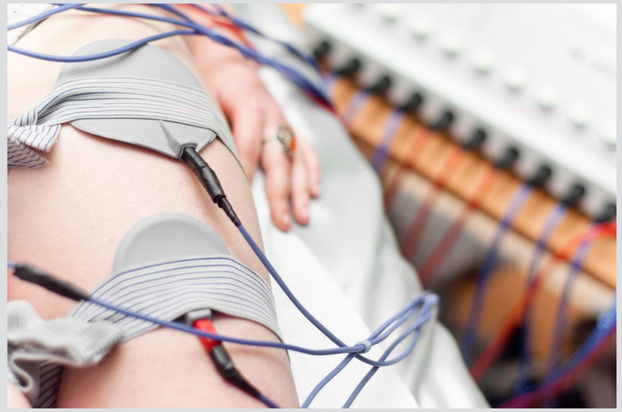
Exercise in ICU patients: bed cycling and electrostimulation



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Journal of Critical Care 50 (2019) 287–295

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Interventions for the management and prevention of sarcopenia in the critically ill: A systematic review

Samuel P. Trethewey [a], Nicholas Brown [b], Fang Gao [a,c], Alice M. Turner [a,d,*]

[a] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.
[b] University of Birmingham, Birmingham, UK.
[c] Birmingham Acute Care Research Group, University of Birmingham, Birmingham, UK.
[d] Institute of Applied Health Research, University of Birmingham, Birmingham, UK.

NMES and exercise-based interventions may preserve muscle mass and function in patients with critical illness. There is a lack of consistency seen in the effects of these interventions. Further, large, high quality RCTs are required.

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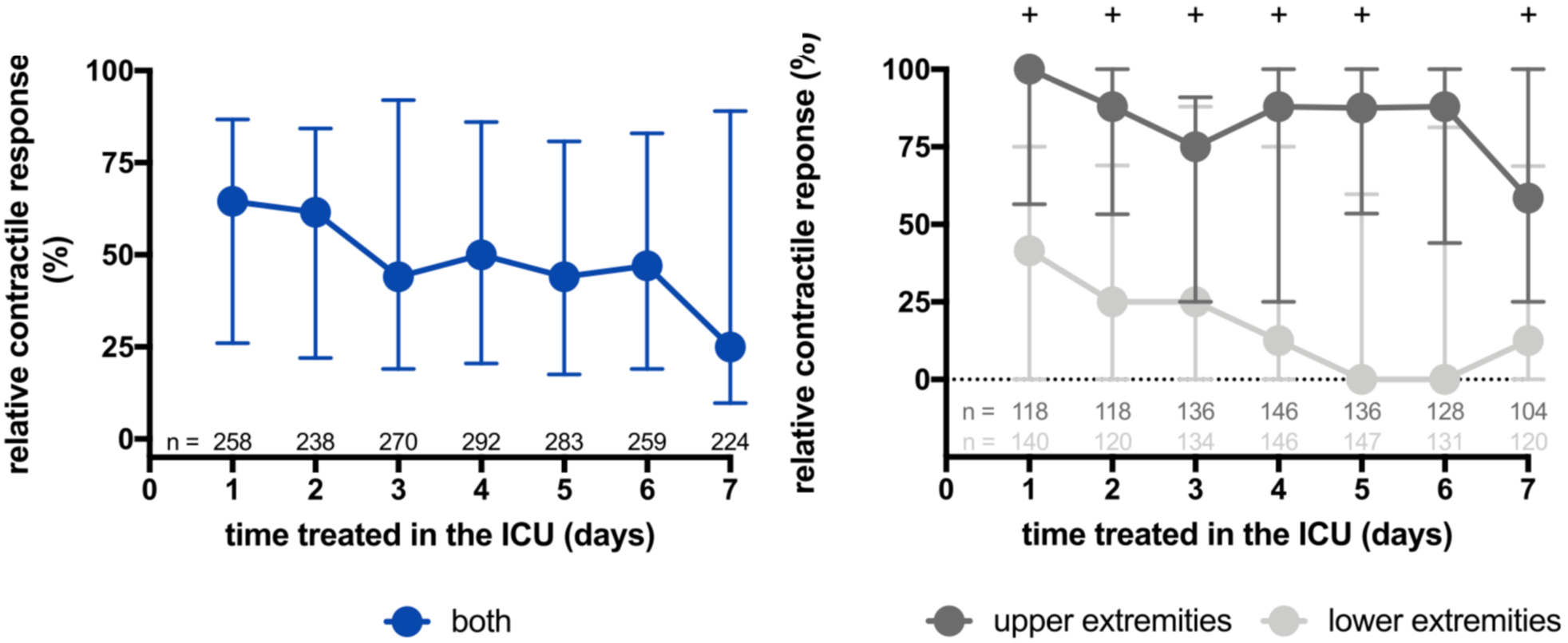
Differential contractile response to NMES in ICU patients



Grunow JJ et al. Crit Care 2019; 23:308

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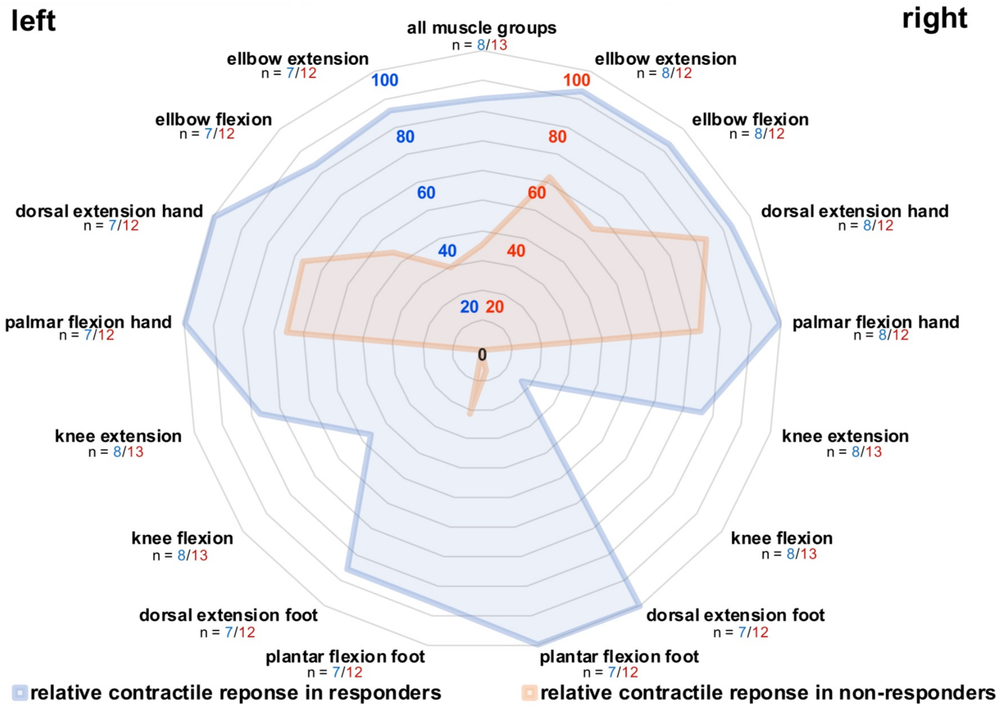
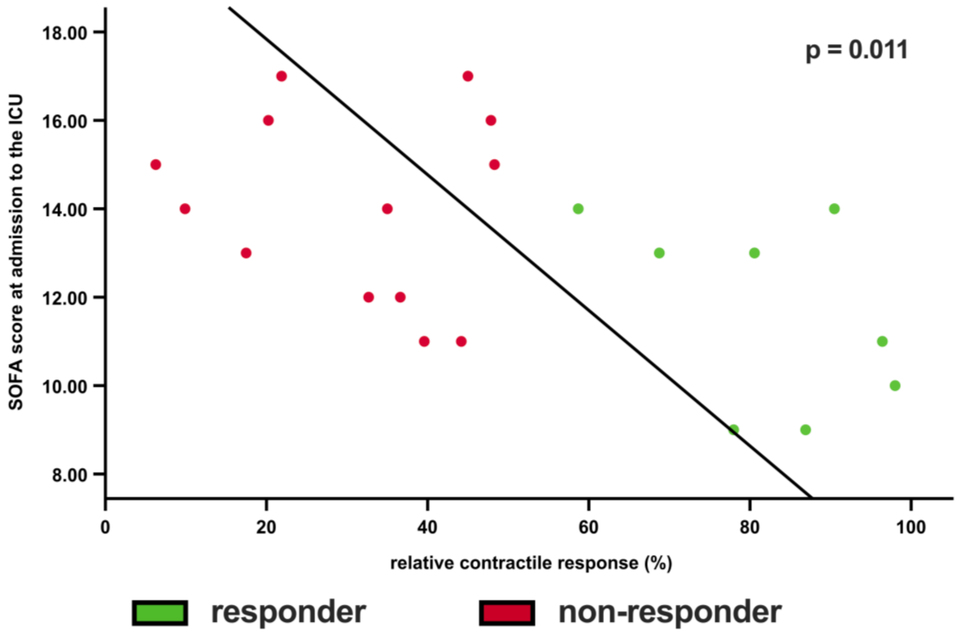
Differential contractile response to NMES in ICU patients

Not all muscles are equal



Higher SOFA lower contractile response



Grunow JJ et al. Crit Care 2019; 23:308

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REVIEW

Journal of Cachexia, Sarcopenia and Muscle (2016)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12146

Exercise rehabilitation following intensive care unit discharge for recovery from critical illness: executive summary of a Cochrane Collaboration systematic review

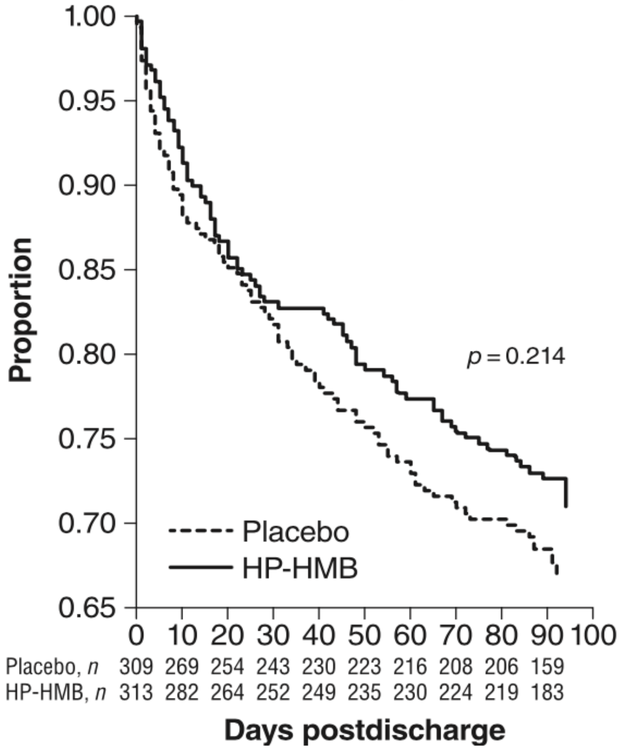
Bronwen Connolly[1,2,3]*, Lisa Salisbury[4], Brenda O'Neill[5], Louise Geneen[6], Abdel Douiri[3,7], Michael P. W. Grocott[8,9,10], Nicholas Hart[1,2,3], Timothy S. Walsh[11] & Bronagh Blackwood[12]

<u>Unable</u> to determine an overall effect on functional exercise capacity or health-related quality of life of interventions initiated after ICU discharge for survivors of critical illness. Findings from ongoing studies are awaited.

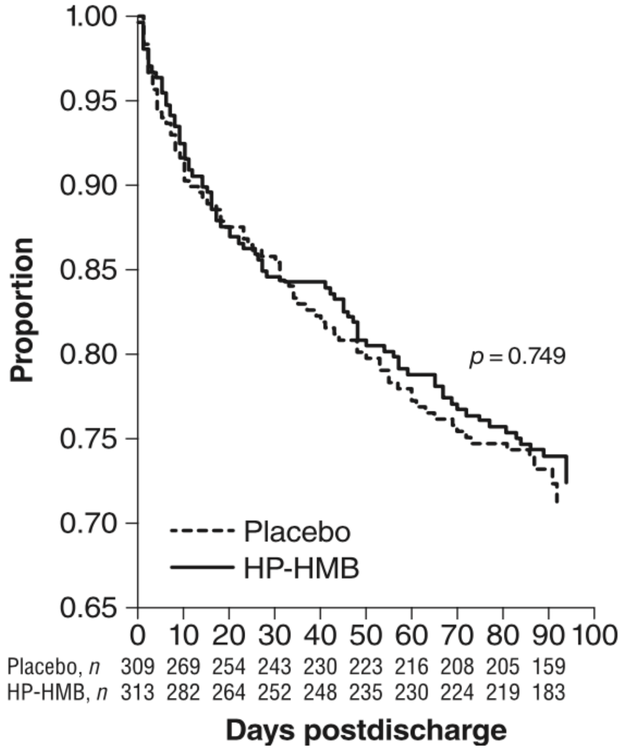
Nourish study: ONS after hospital discharge

Older (≥65 years), malnourished (Subjective Global Assessment [SGA] class B or C) adults hospitalized for congestive heart failure, acute myocardial infarction, pneumonia, or chronic obstructive pulmonary disease. Standard-of-care plus HP-HMB (n = 328) or a placebo supplement (n = 324), 2 servings/day.

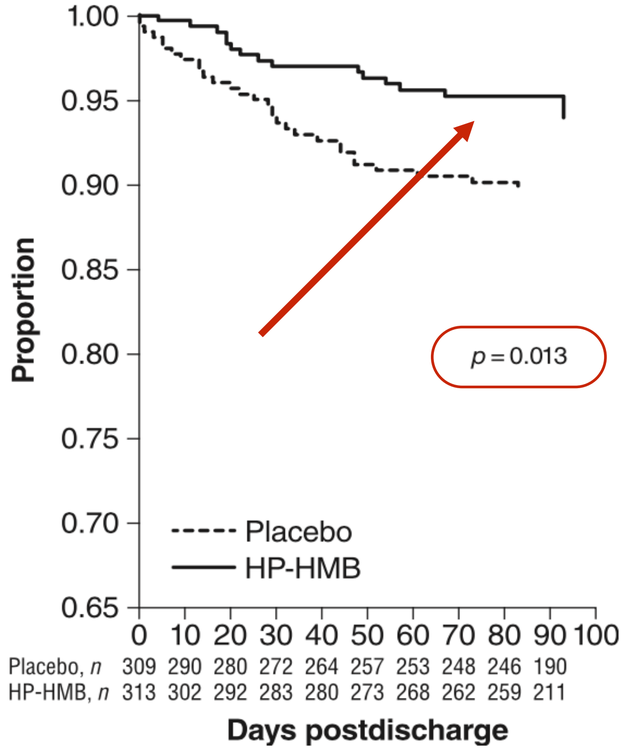
B. Kaplan-Meier Survival Curve: Composite Endpoint of 90-Day Readmission and Mortality



C. Kaplan-Meier Survival Curve: Readmission



D. Kaplan-Meier Survival Curve: Mortality



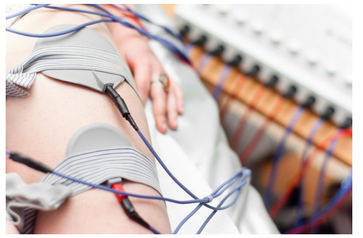
Deutz N et al. Clin Nutr 2016;35:18-26

Multimodal Intervention

Nutrition

Anticatabolic/ Anti-inflammatory Therapies

Exercise



Metabolic Mitochondrial Muscle Resuscitation

Muscles protein synthesis and exercise

High-protein diet alone is not enough

Quality of Life

Conclusions

- Survival is improving
- Disabilities more frequent in survivors
- PICS, long COVID is common: Physical, mental and cognitive problems
- Many do not return to work
- Pathophysiology poorly understood
- Muscle may be more important than the lungs
- Limited therapy options:
- Nutrition, physiotherapy, exercise, psychological support, drugs?

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Sepsis en Daarna Lotgenotendag
Zaterdag 17 september 2022, Zwolle

Post Sepsis
ICU acquired weakness

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