Ziekenhuis Gelderse Vallei

Masterclass Voeding 2019

How to reach protein targets without overfeeding?

Arthur R.H. van Zanten, MD PhD, Internist-intensivist

Head of ICU & Research
Gelderse Vallei Hospital,
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Dr. van Zanten has received honoraria for advisory board meetings, lectures, research and travel expenses from:

- Astellas
- Baxter
- BBraun
- Cardinal Health
- Fresenius Kabi
- Gilead
- Lyric
- Mermaid
- MSD
- Nestlé-Novartis
- Nutricia-Danone
- Pfizer

Other COI:

- ESPEN guidelines committee Critical Care Nutrition for Adults
- ESICM Working Group Gastrointestinal Failure
- NESPEN Executive Team
- Chair Netherlands Sepsis Guideline Working Group Dutch Working Party on Antibiotic Policy Guideline Committee for the Management of Fungal Infections

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Content

- Rationale for high protein delivery in critical illness
- Are proteins always good?
- Results of the Protinvent Study
- Why do we need higher protein to energy ratio enteral feeds?
- Results of the Protill Study
- Practical recommendations for proteins during the patient journey

Clinical Nutrition 38 (2019) 48–79

Contents lists available at ScienceDirect

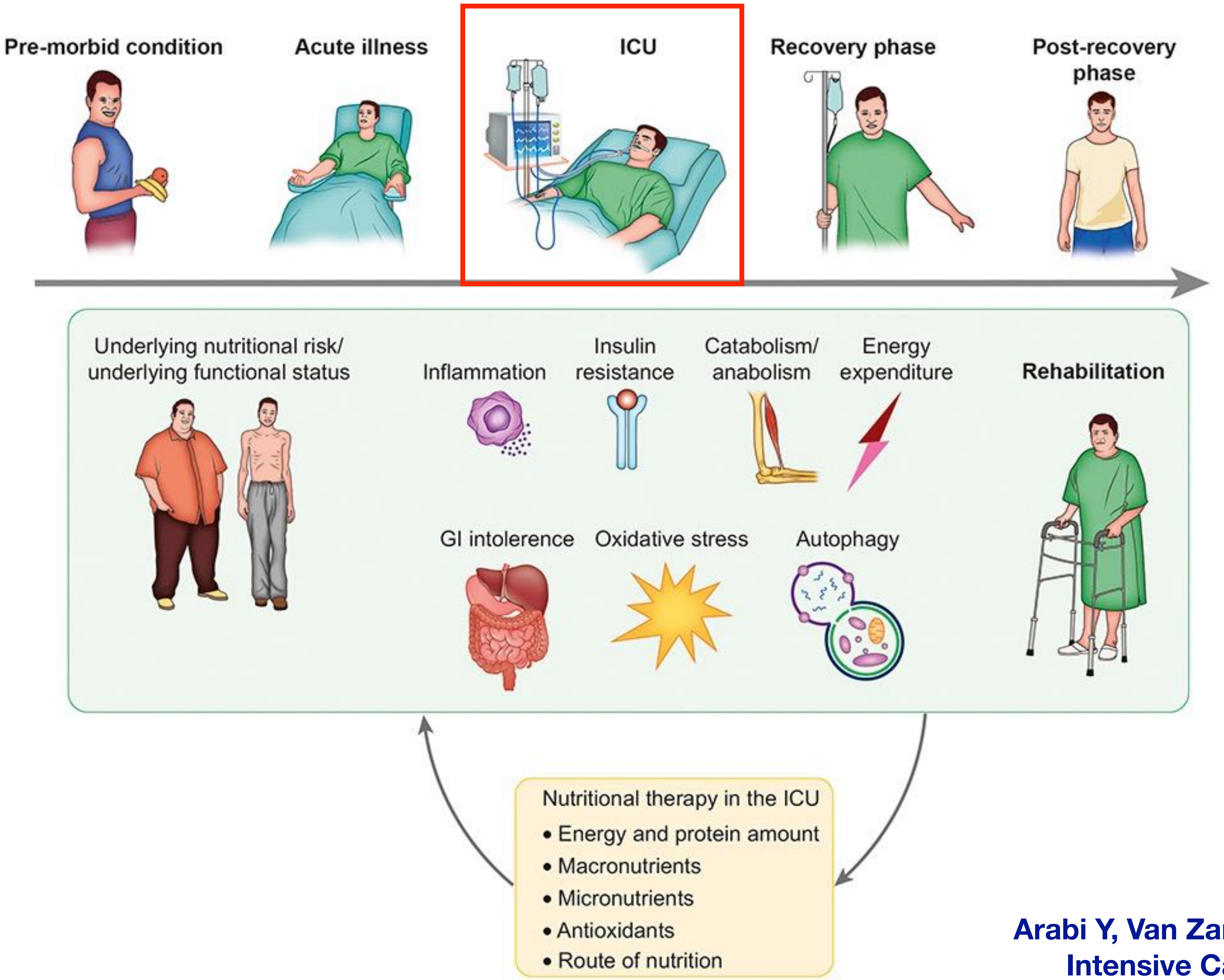
Clinical Nutrition

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

ESPEN Guideline

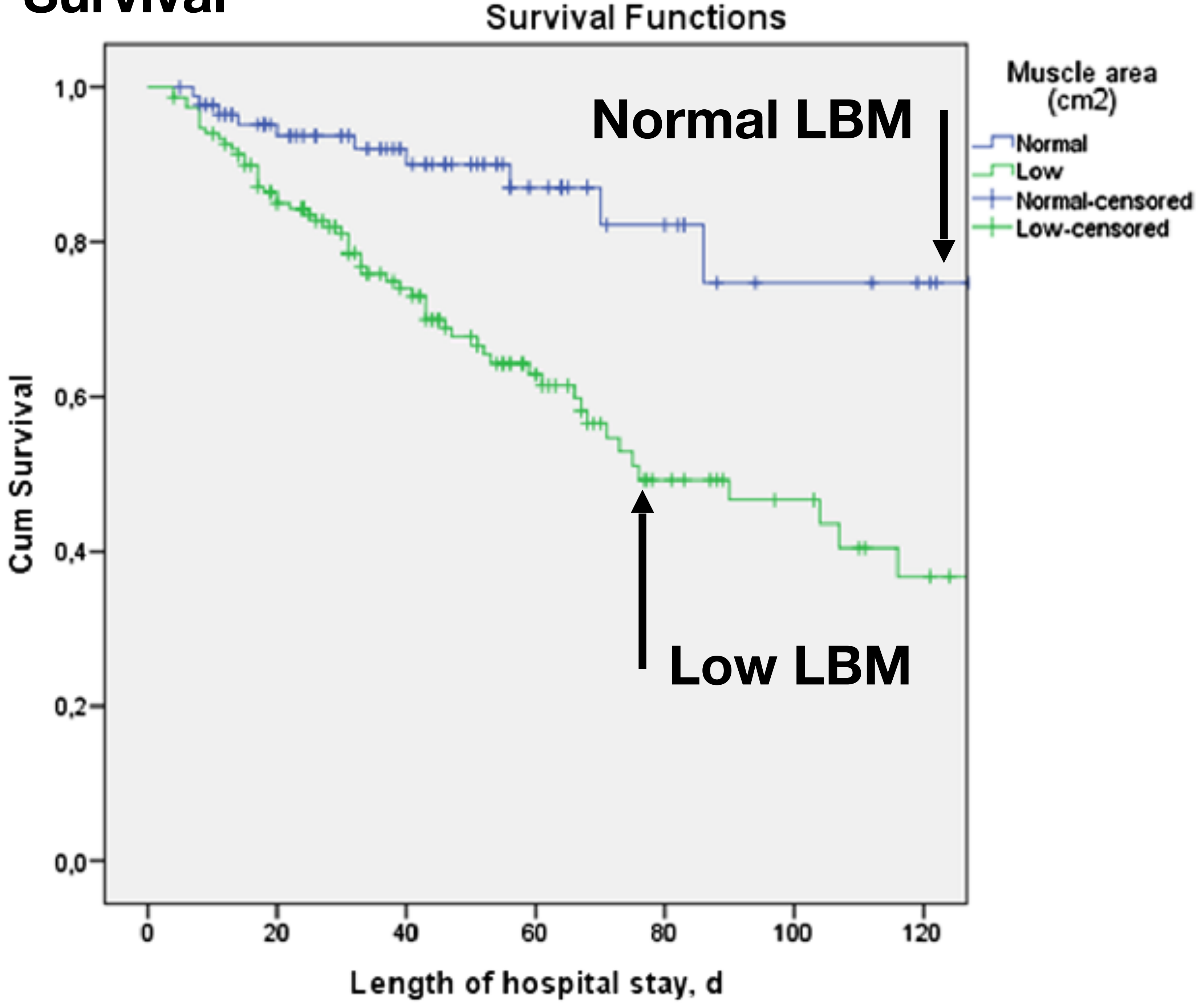
ESPEN guideline on clinical nutrition in the intensive care unit

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]

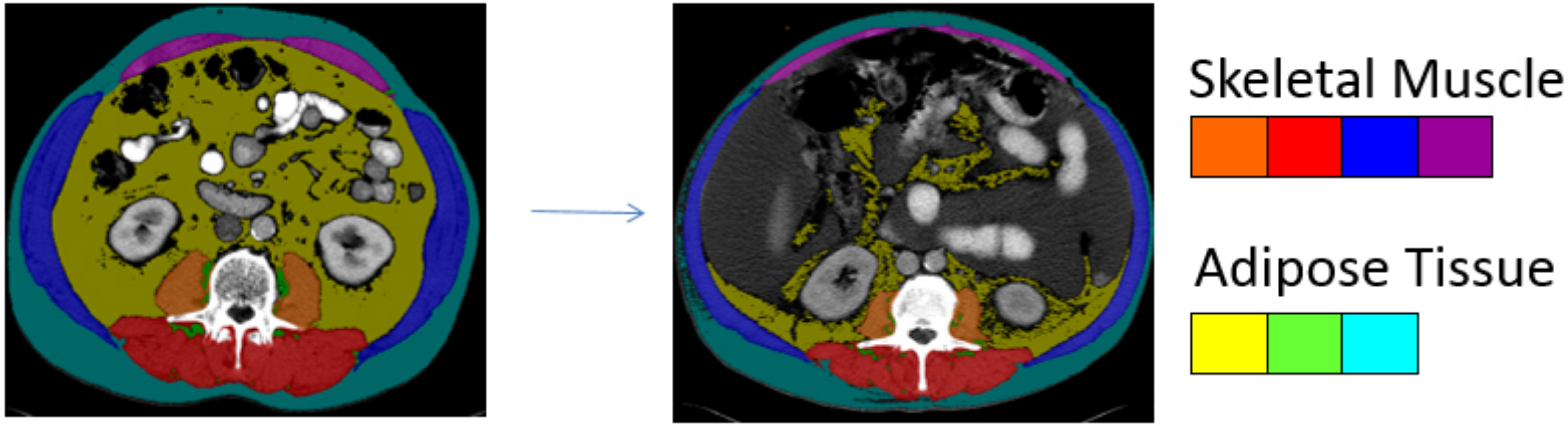


Arabi Y, Van Zanten AR et al: Intensive Care Med 2017

Survival

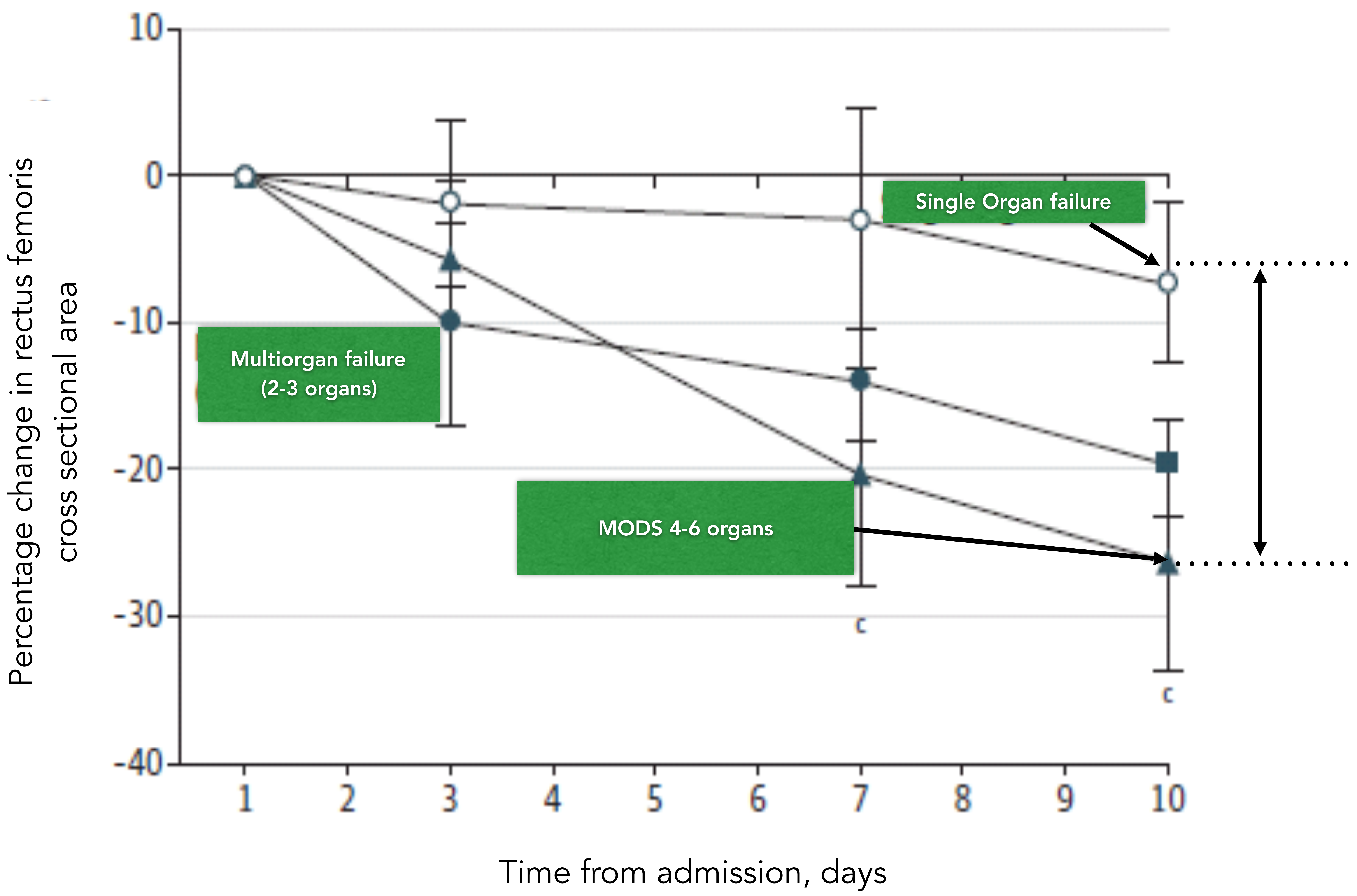


- Patients with a high BMI have better survival odds in the ICU: "obesity paradox"
- BMI is not an independent predictor of mortality when muscle area is accounted for.



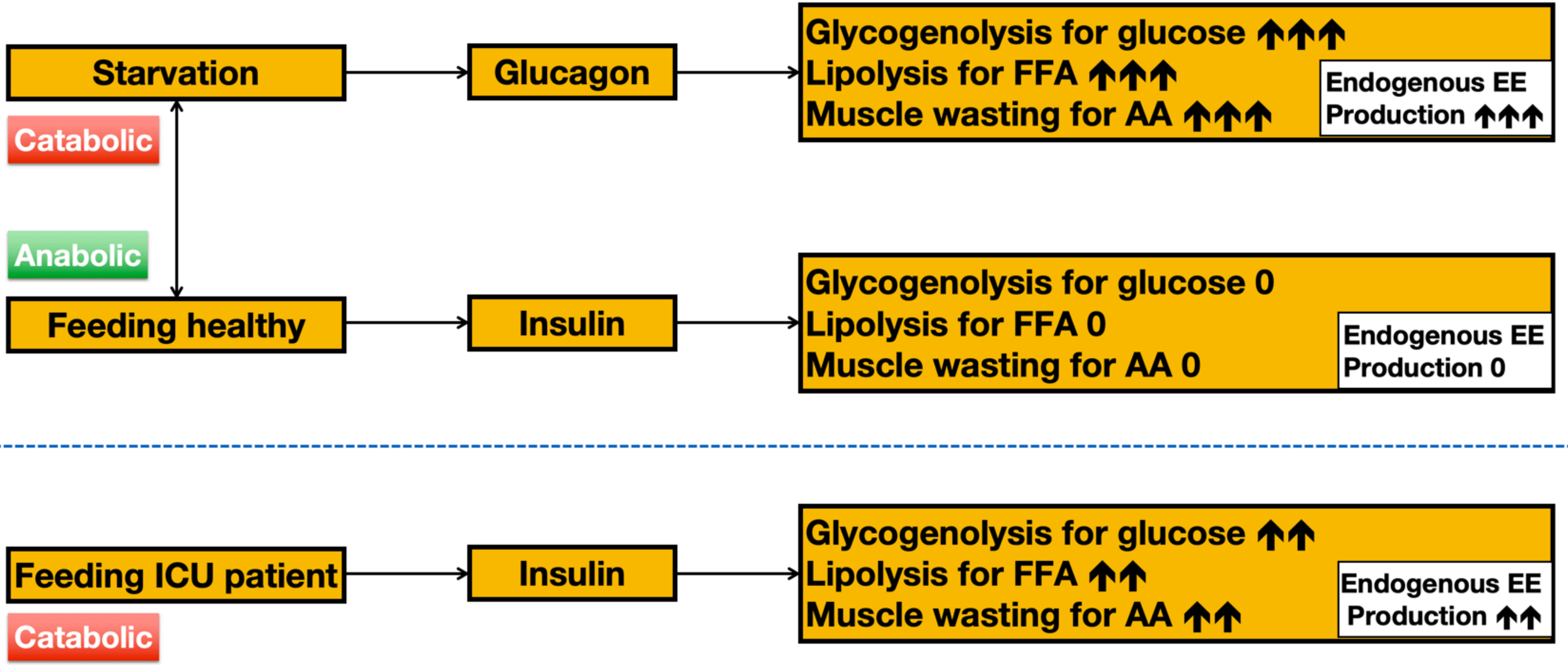
Weijs et al. Critical Care 2014 18:R12

In MODS: Muscle mass loss 1 kg per day

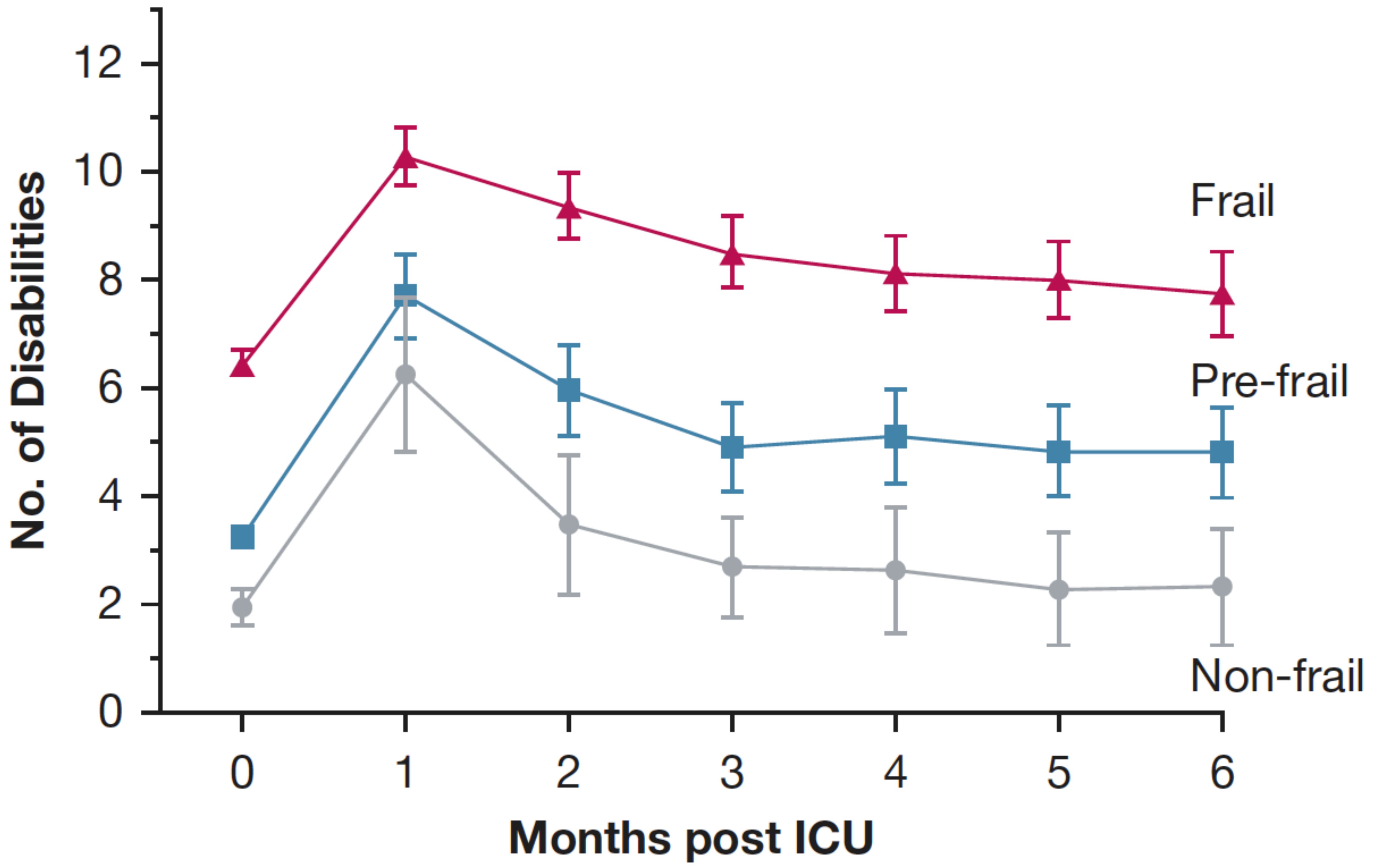


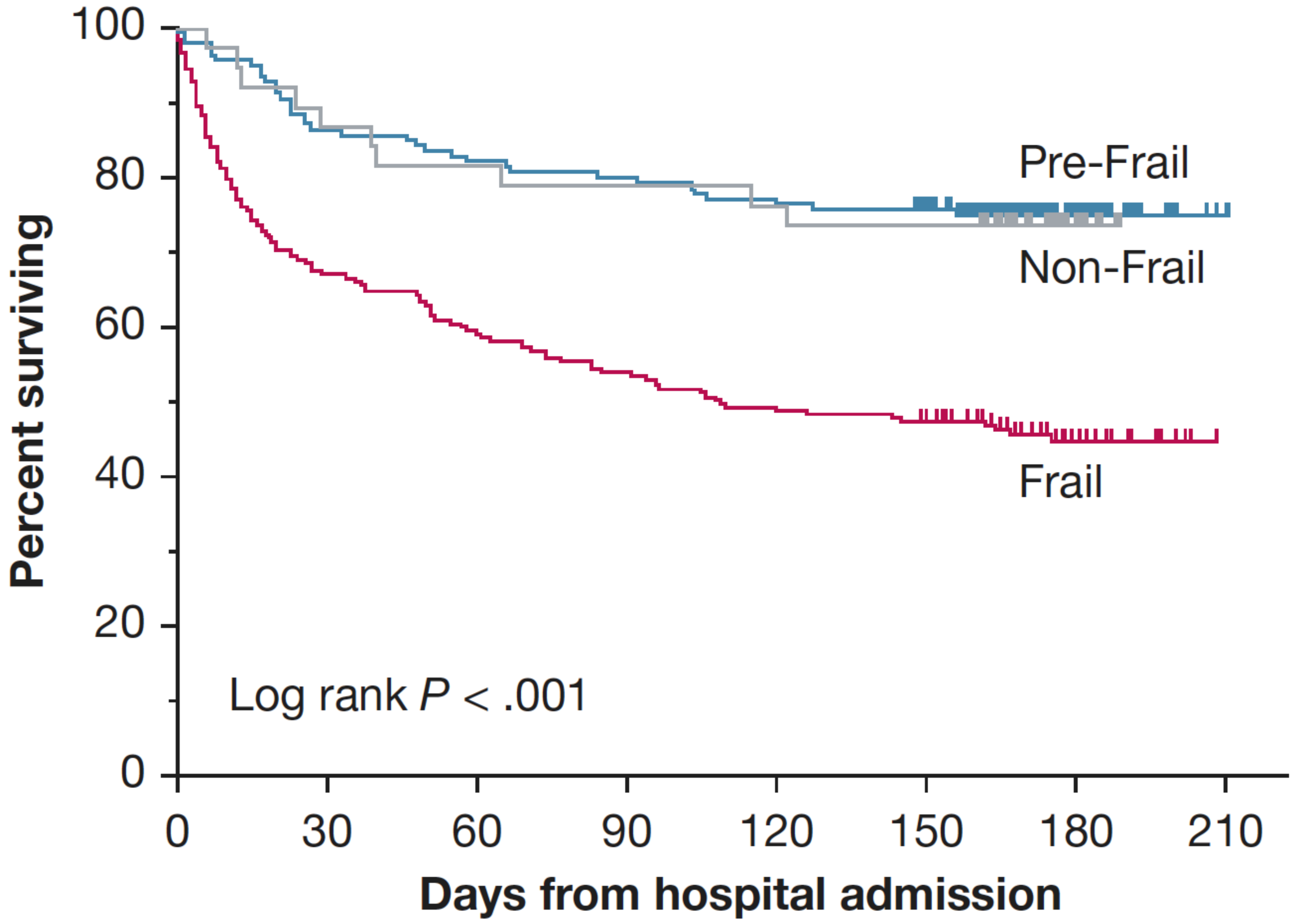
Puthucheary ZA et al., JAMA 2013

Differences feeding in health and during critical illness



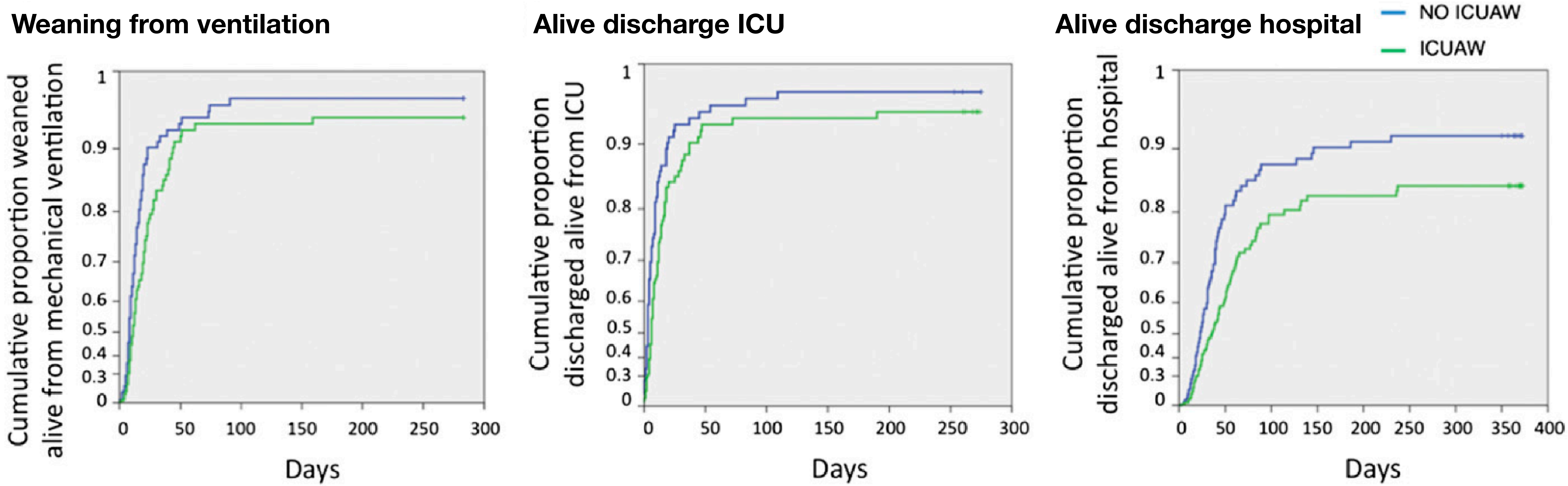
What is essential for the (elderly) ICU patient?





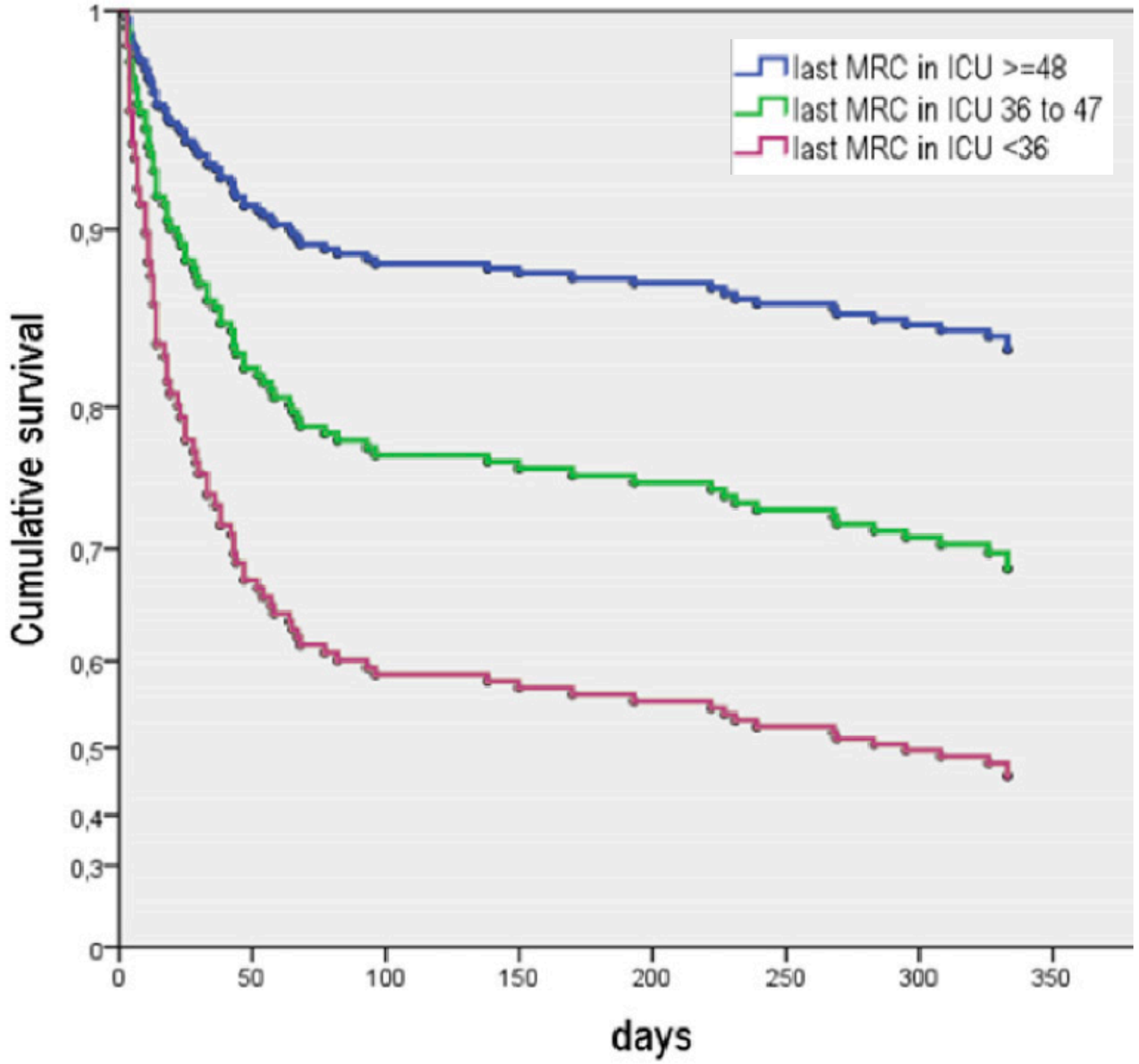
Ferrante LE et al. Chest. 2018 Jun;153(6):1378-1386.

Consequences of ICU Acquired Weakness y/n



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

Consequences of ICU Acquired Weakness y/n



Last MRC sum score recorded in the ICU

MRC sum score

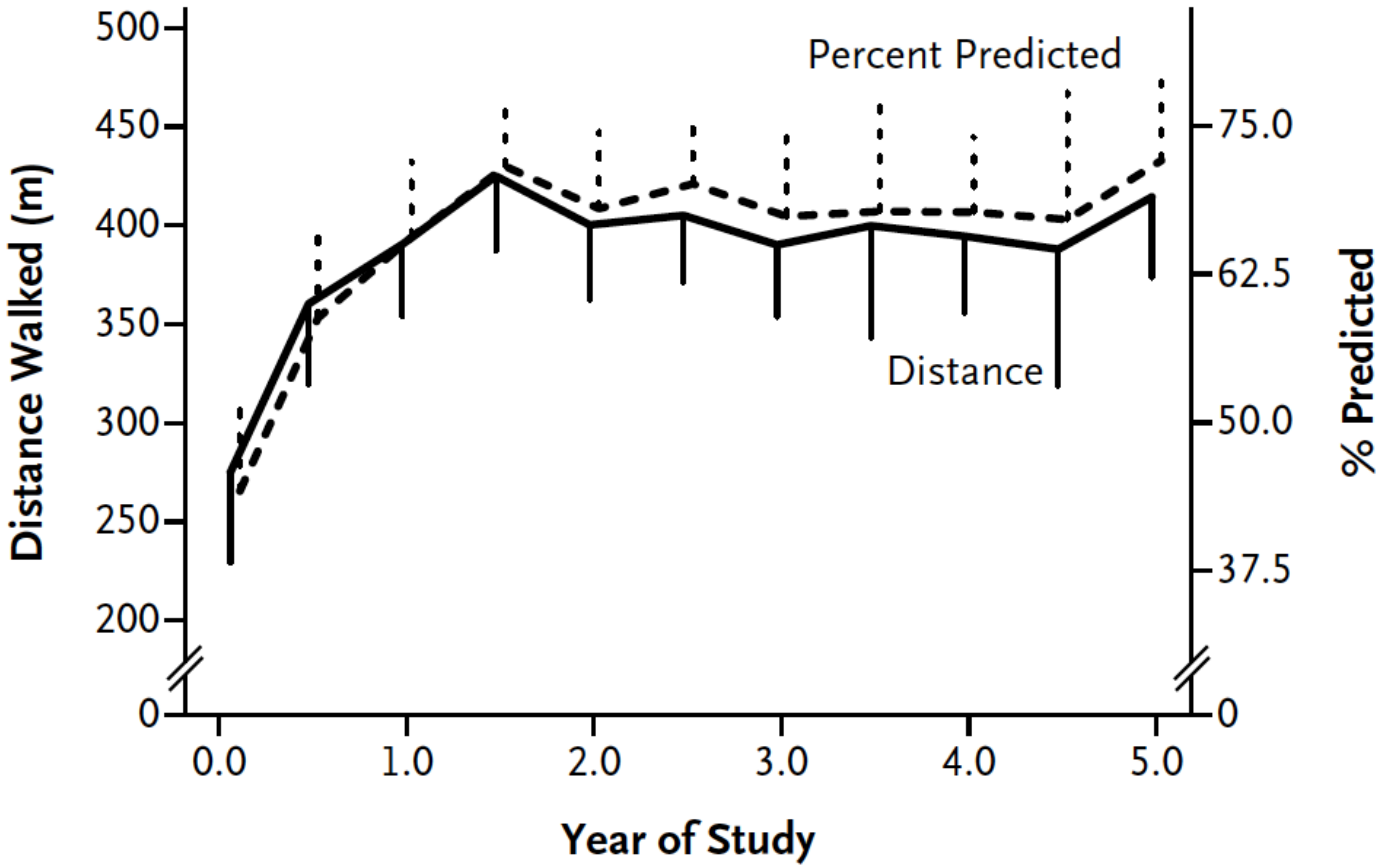
- Involves the assessment of muscle power from 3 movements of each limb:
  - Shoulder abduction
  - Elbow flexion
  - Wrist extension
  - Hip flexion
  - Knee extension and
  - Ankle dorsiflexion.
- Maximal power graded according to MRC scale.
- Total score =60

- 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

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



Herridge MS et al NEJM 2011

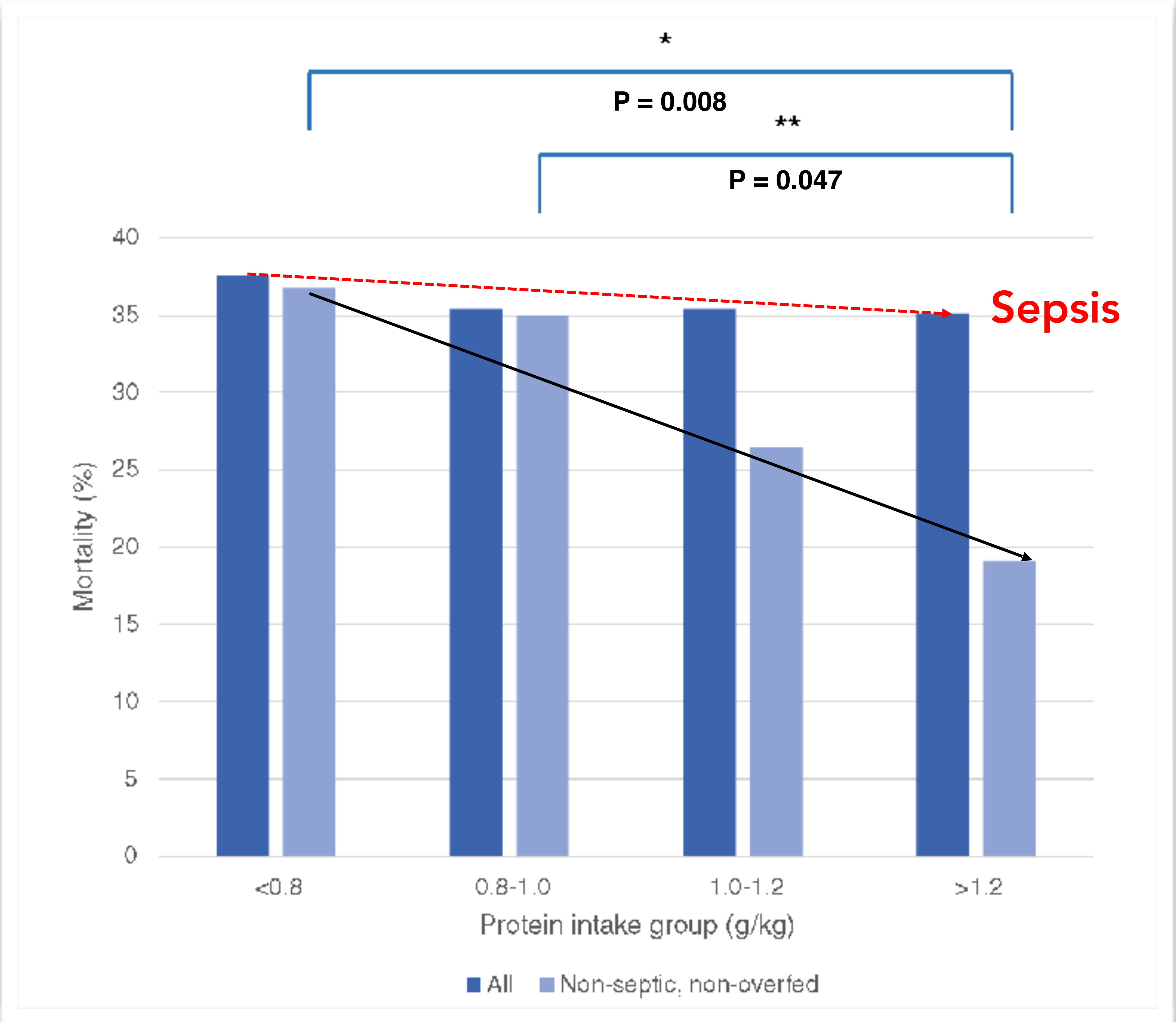
More Protein and Energy Associated With Lower Mortality in Higher Risk Patients

Outcome	Protein Intake (per 10% of Goal): Low NUTRIC Score	Protein Intake (per 10% of Goal): High NUTRIC Score	Energy Intake (per 10% of Goal): Low NUTRIC Score	Energy Intake (per 10% of Goal): High NUTRIC Score
Sample in ICU ≥ 4 d				
	(*n* = 1,217)	(*n* = 1,636)	(*n* = 1,217)	(*n* = 1,636)
Mortality[a,b]	0.952 (0.895–1.011)	0.930 (0.892–0.969)[c]	0.962 (0.904–1.023)	0.927 (0.893–0.962)[c]
Adjusted[d]	0.998 (0.936–1.064)	0.934 (0.894–0.975)[c]	1.011 (0.946–1.079)	0.929 (0.893–0.966)[c]
TDA[f,g]	0.970 (0.936–1.006)	1.004 (0.967–1.043)	0.956 (0.921–0.992)[c]	0.995 (0.959–1.032)[c]
Adjusted[d]	1.013 (0.975–1.052)	1.051 (1.012–1.091)[c]	0.998 (0.958–1.039)	1.045 (1.007–1.085)[c]
Sample in ICU ≥ 12 d	Protein Intake (per 10% of Goal)[h]: Low NUTRIC Score	Protein Intake (per 10% of Goal)[h]: High NUTRIC Score	Energy Intake (per 10% of Goal)[h]: Low NUTRIC Score	Energy Intake (per 10% of Goal)[h]: High NUTRIC Score
Outcome	(*n* = 711)	(*n* = 891)	(*n* = 711)	(*n* = 891)
Mortality[a,b]	1.059 (0.964–1.165)	0.913 (0.853–0.977)[e]	1.069 (0.975–1.173)	0.909 (0.854–0.967)[e]
Adjusted[d]	1.052 (0.954–1.156)	0.899 (0.84–0.963)[e]	1.067 (0.967–1.178)	0.884 (0.829–0.941)[c]
TDA [f,g]	0.963 (0.913–1.016)	1.062 (1.002–1.126)[e]	0.937 (0.888–0.989)[e]	1.048 (0.990–1.109)
Adjusted[d]	0.999 (0.946–1.056)	1.092 (1.032–1.155)[e]	0.981 (0.925–1.040)	1.091 (1.032–1.155)[e]

Compher C et al. Crit Care Med 2017; 45:156–163

Hospital mortality per protein intake group

More protein intake is associated with lower in-hospital mortality



0.8 g/kg per day

1.2 g/kg per day

Weijs P. Crit Care 2014;18:701

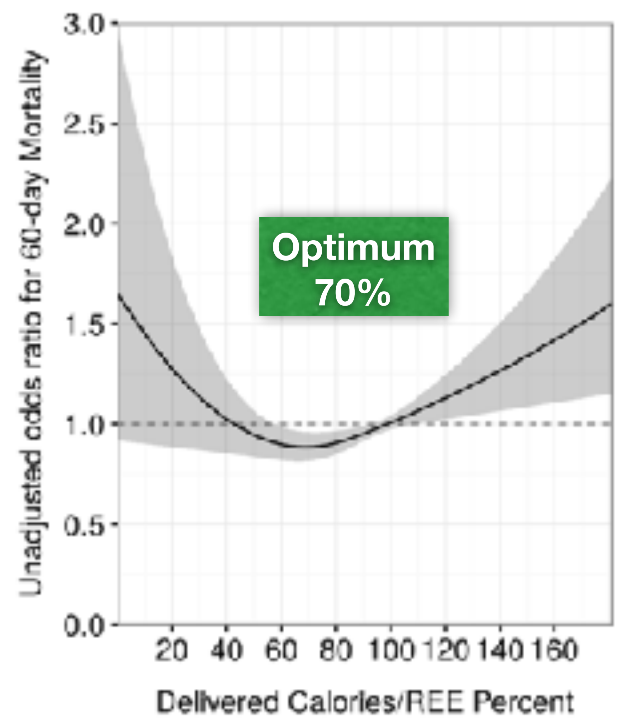
Why early aggressive nutrition may be a metabolic challenge?

Hyperglycemia

Calories

Calories

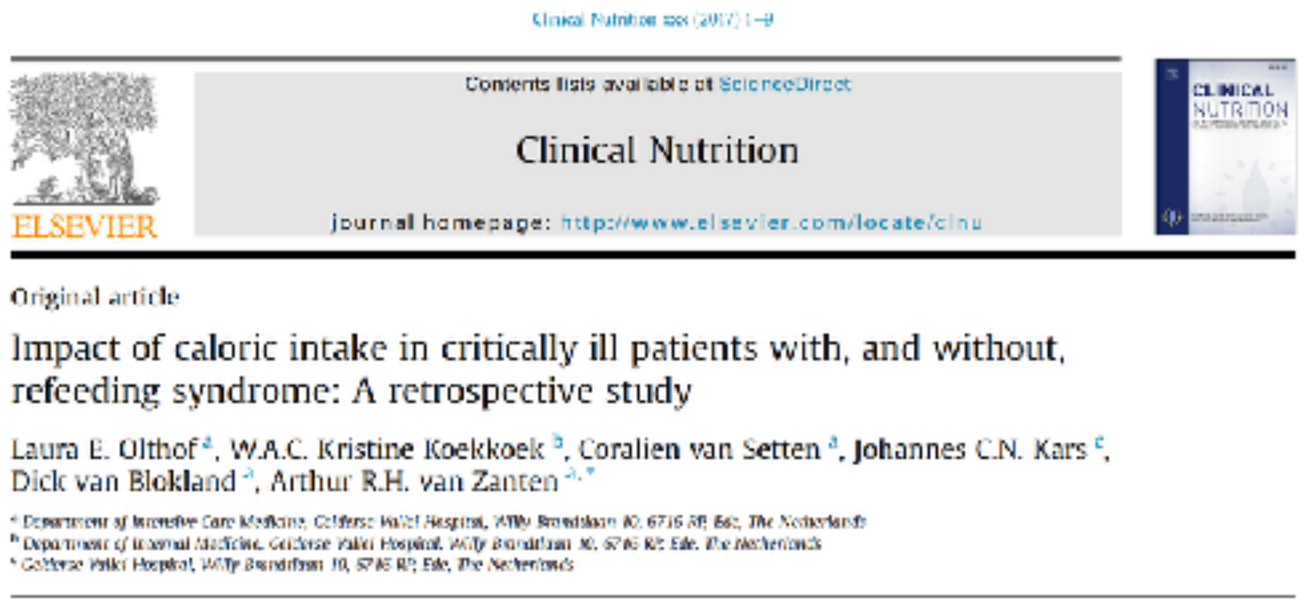
Overfeeding



Refeeding syndrome

Calories

Autophagy deficiency



Clinical Nutrition xxx (2017) 1–9

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

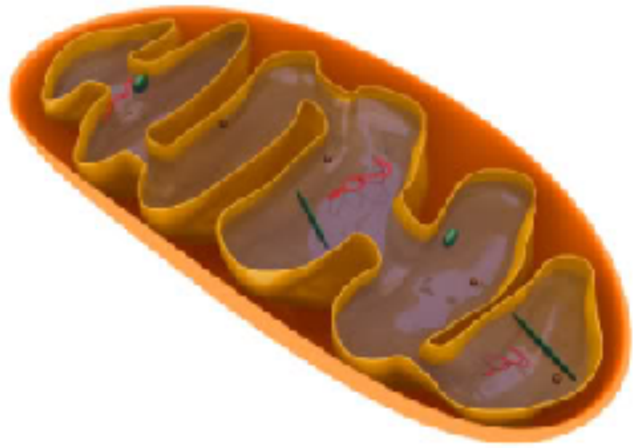
ELSEVIER

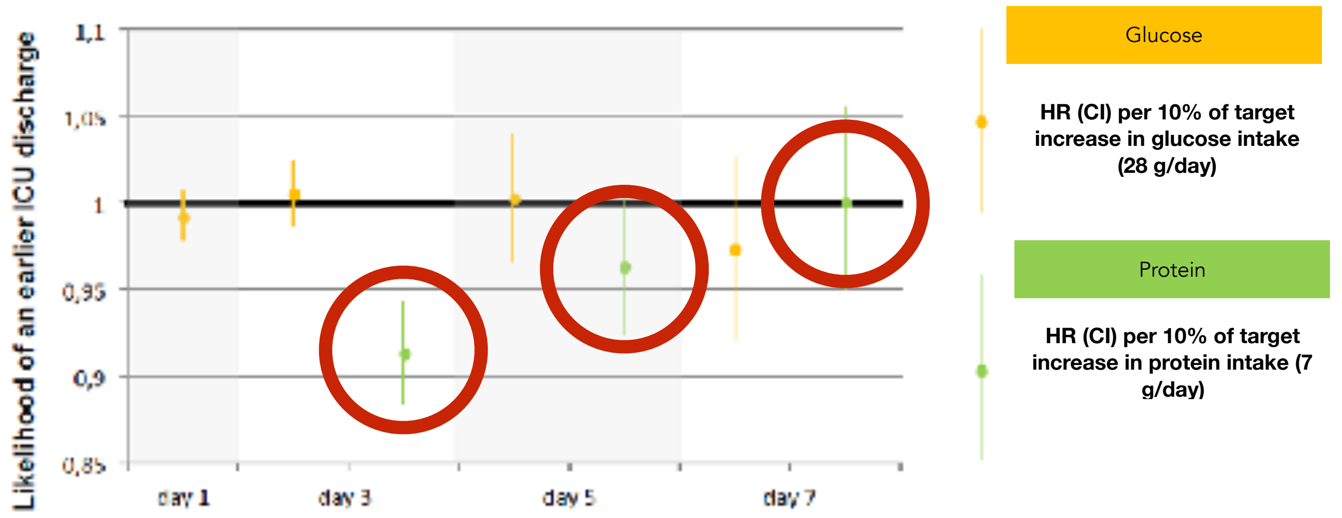
Original article

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

Mitochondrial dysfunction

Proteins

The NEW ENGLAND JOURNAL of MEDICINE

Ziekenhuis Gelderse Vallei

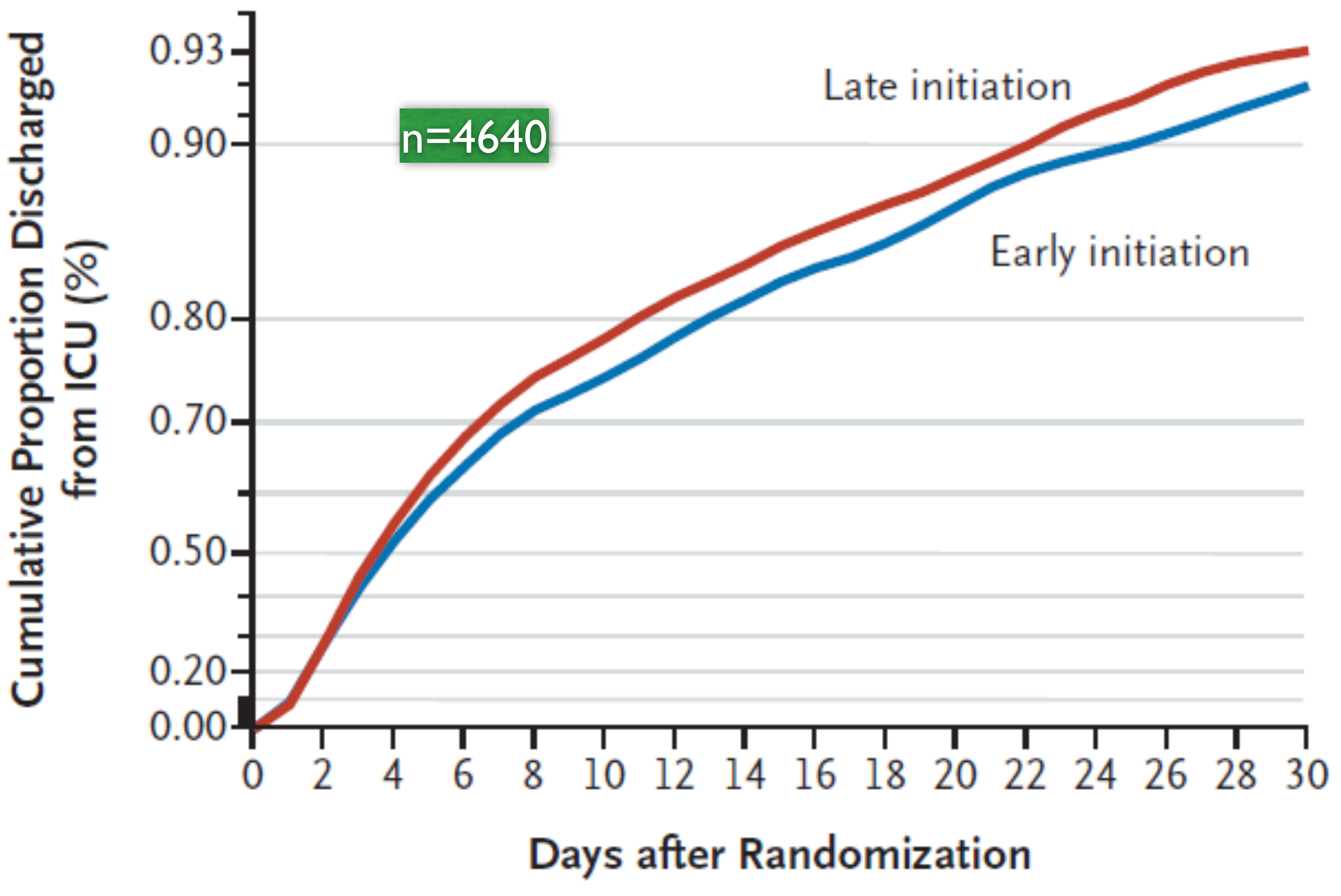
ORIGINAL ARTICLE

Early versus Late Parenteral Nutrition in Critically Ill Adults

Michael P. Casaer, M.D., Dieter Mesotten, M.D., Ph.D., Greet Hermans, M.D., Ph.D., Pieter J. Wouters, R.N., M.Sc., Miet Schetz, M.D., Ph.D., Geert Meyfroidt, M.D., Ph.D., Sophie Van Cromphaut, M.D., Ph.D., Catherine Ingels, M.D., Philippe Meersseman, M.D., Jan Muller, M.D., Dirk Vlasselaers, M.D., Ph.D., Yves Debaveye, M.D., Ph.D., Lars Desmet, M.D., Jasperina Dubois, M.D., Aime Van Assche, M.D., Simon Vanderheyden, B.Sc., Alexander Wilmer, M.D., Ph.D., and Greet Van den Berghe, M.D., Ph.D.*

Casaer M et al. N Engl J Med 2011; 365: 506-517

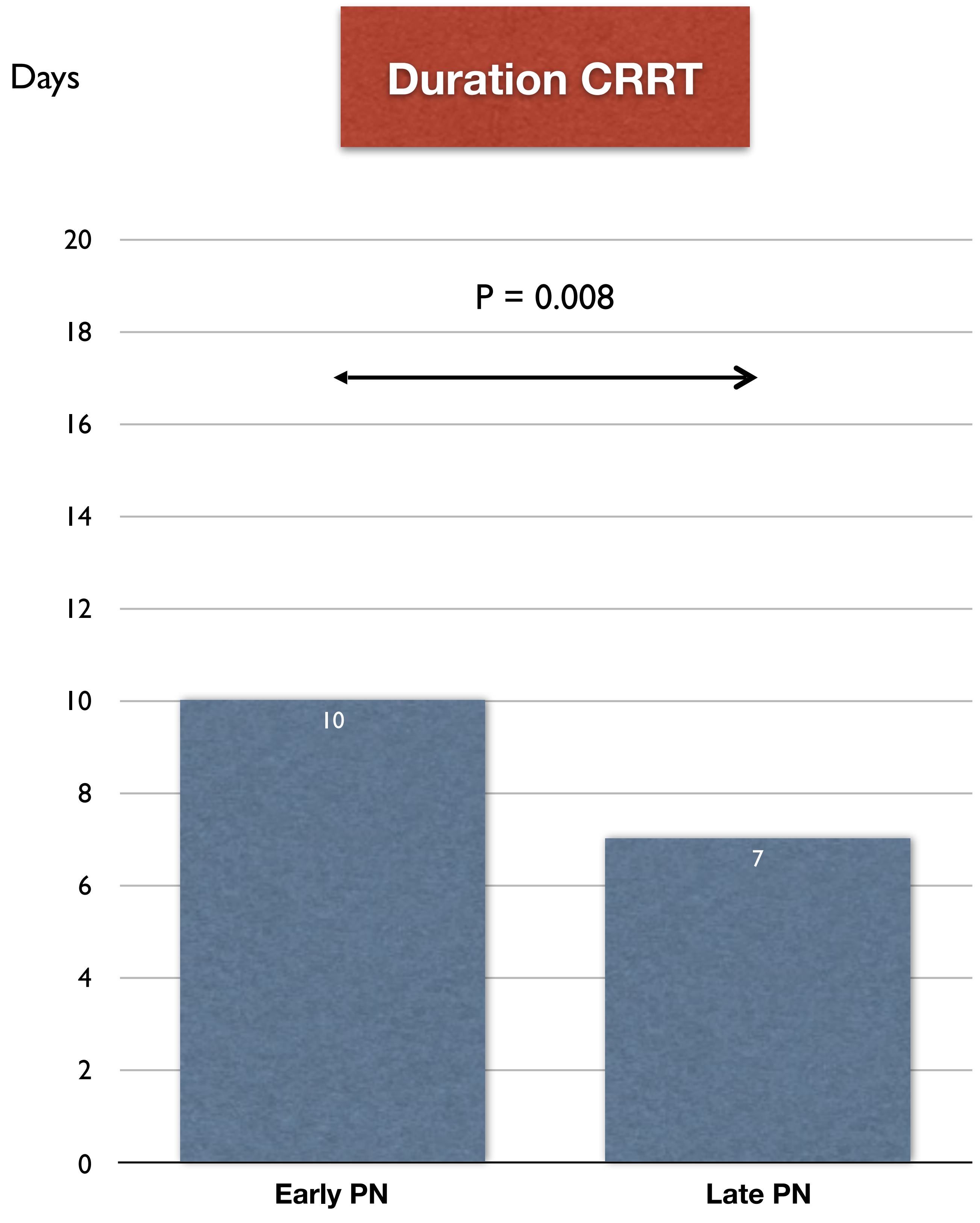
EPaNIC trial: primary end point and some secondary endpoints

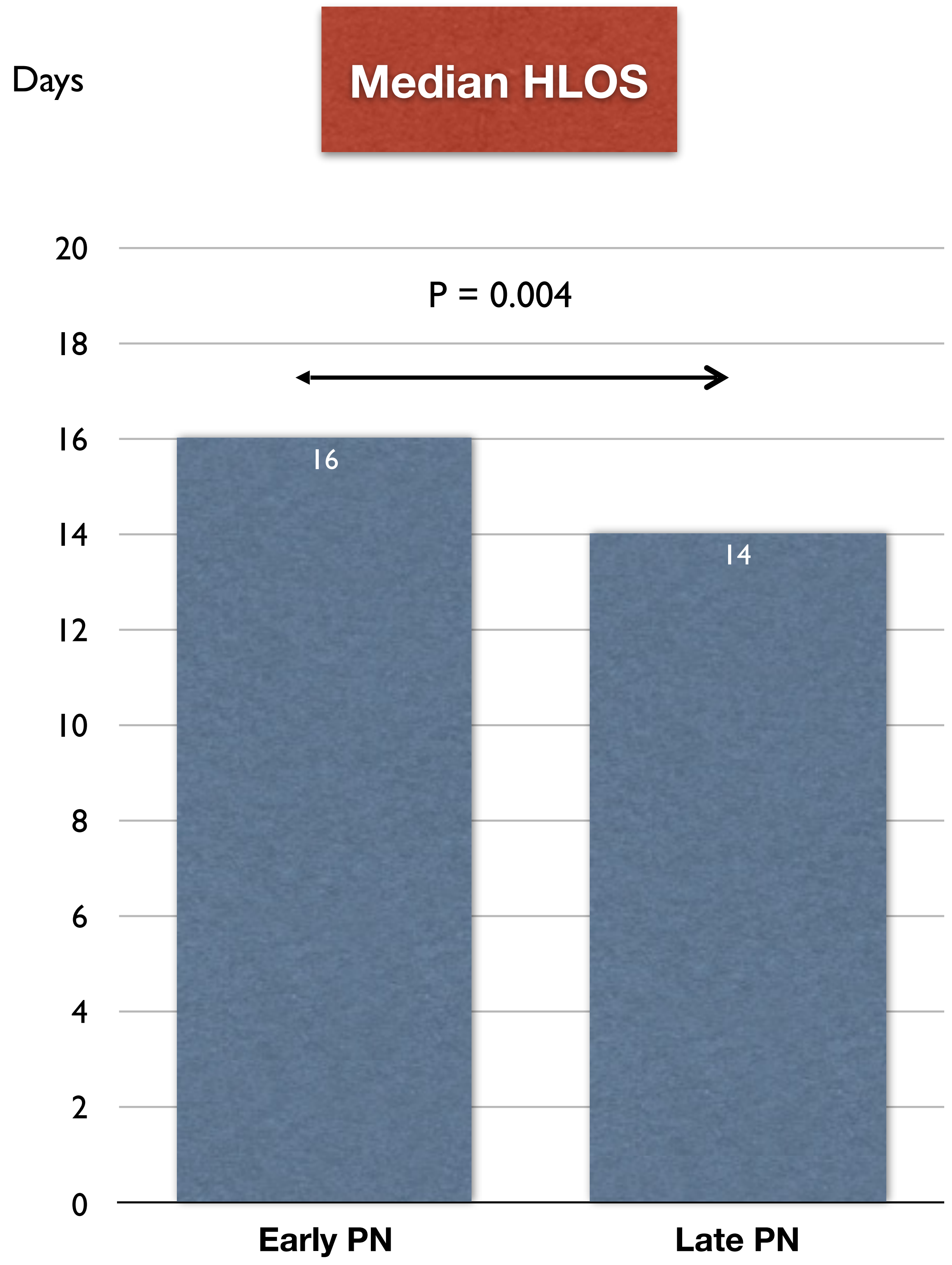


No. at Risk

Late initiation	2328	574	291	122
Early initiation	2312	646	342	147

Hazard ratio (95% CI) for time to discharge alive from ICU 1.06 (1.00–1.13)





Casaer M et al. N Engl J Med 2011; 365: 506-517

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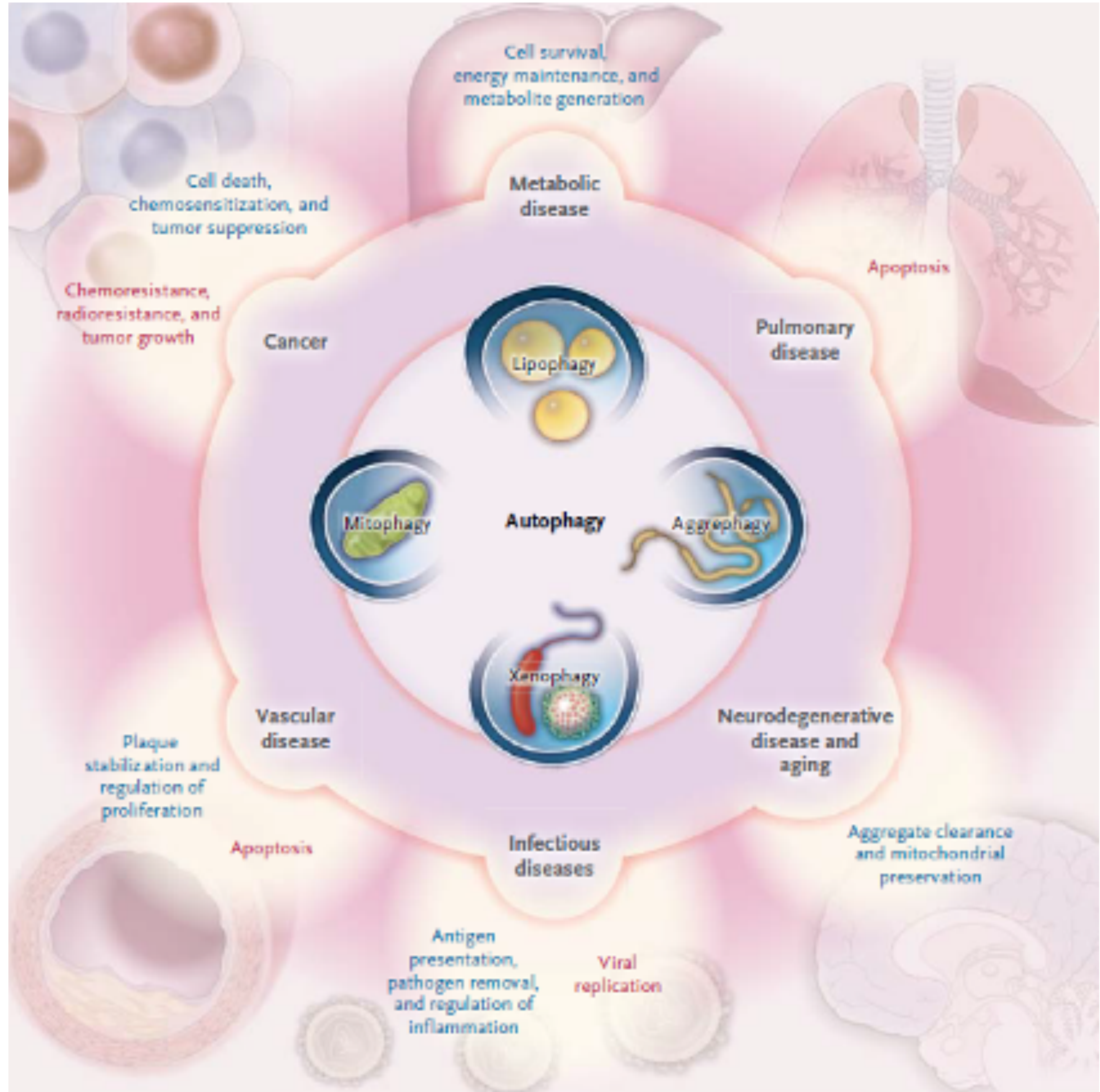
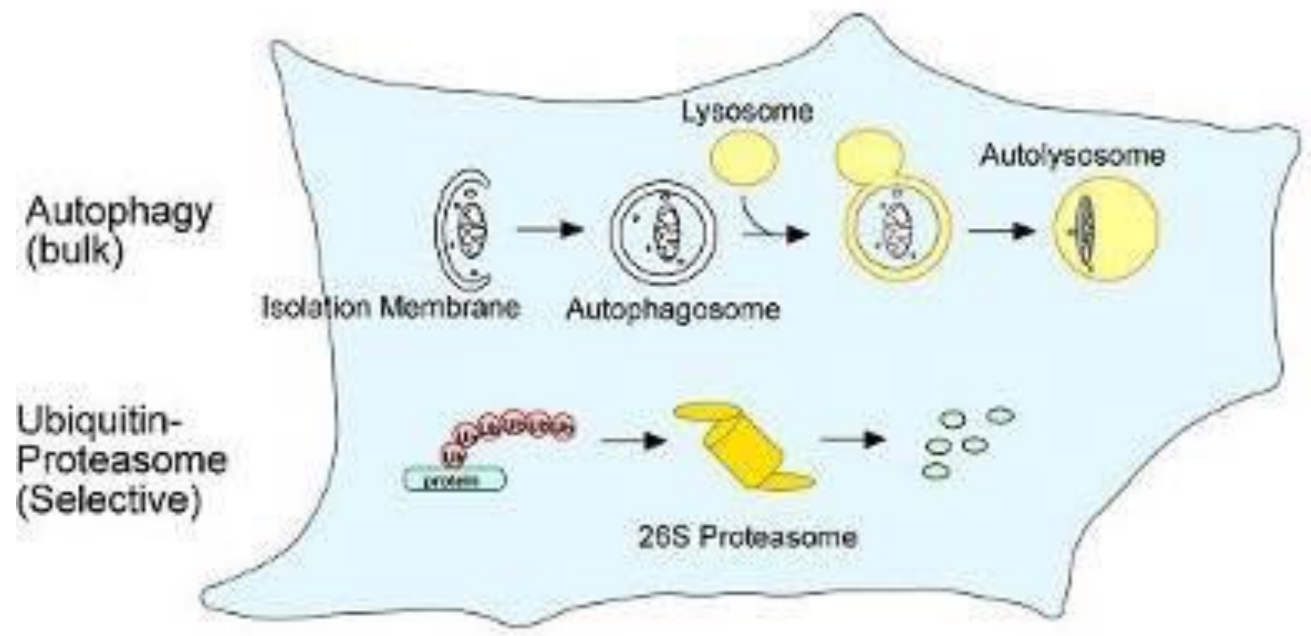
Proteins and Autophagy



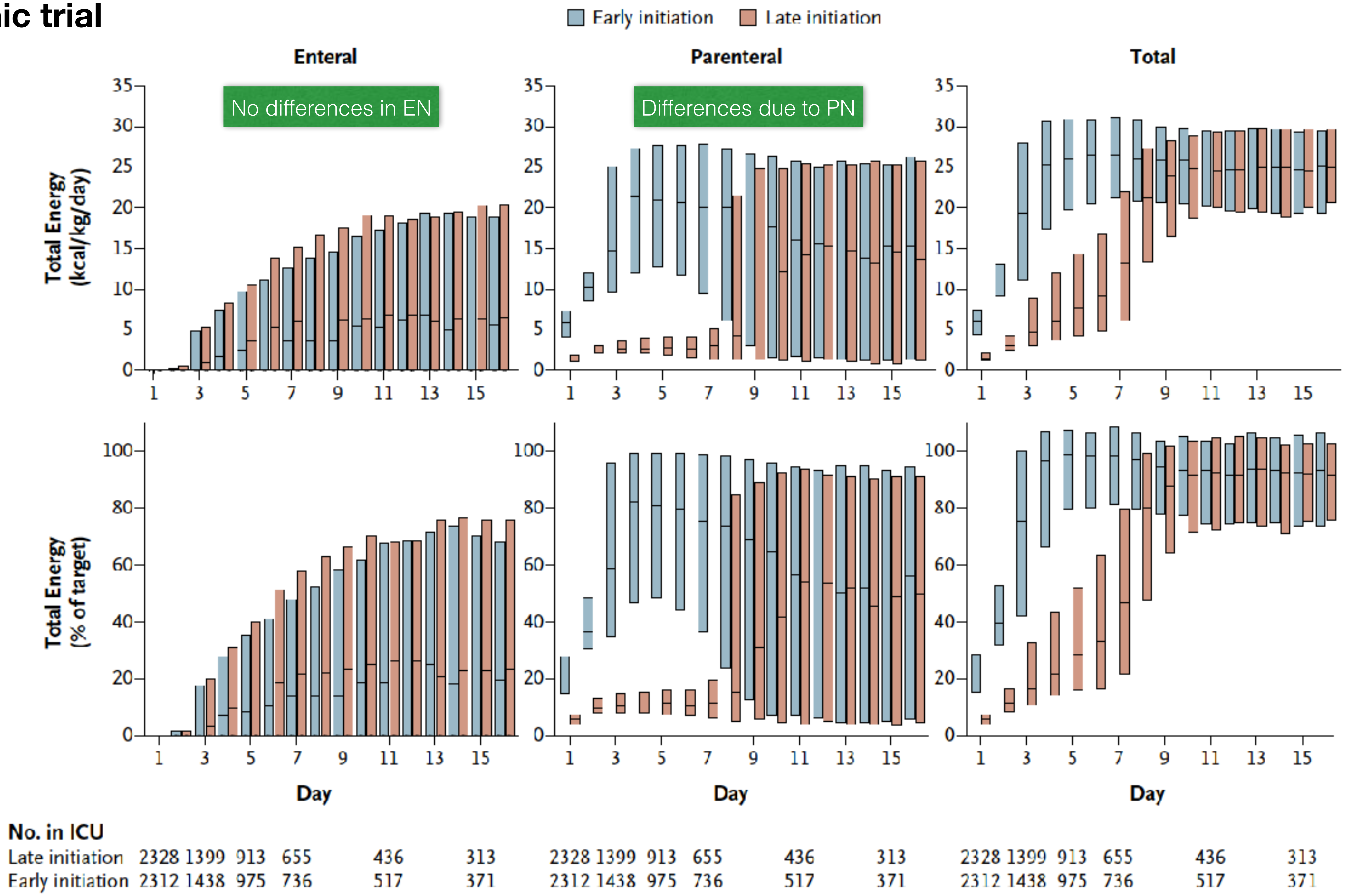


- **Method eukaryotic cells dispose damaged organelles or protein aggregates too large for proteasome ubiquitin system**
- **Involves lysosomal system for removing unfolded proteins, virus, bacteria, fat/carb, organelles**
- **Autophagy role in immunity, inflammation, infection, cancer, aging, pulmonary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

AMK Choi et al NEJM 2013;368:651

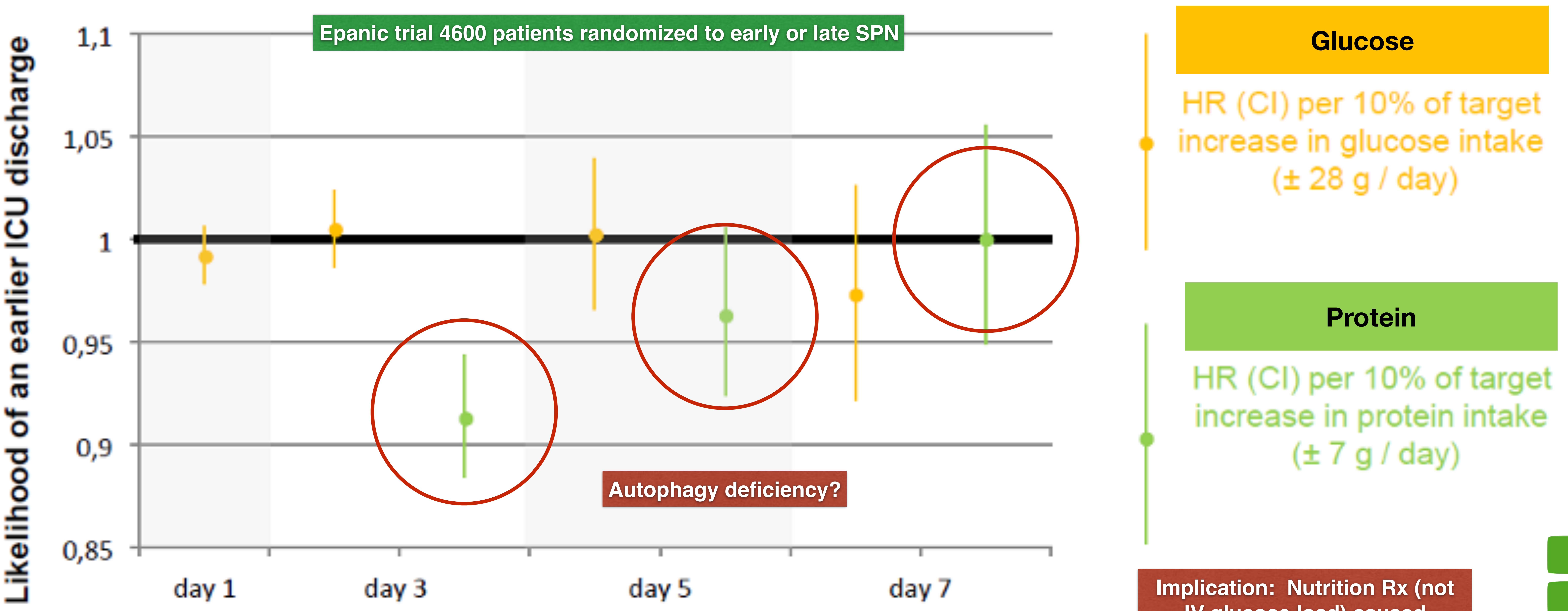
Early Parenteral Nutrition but not Enteral Nutrition induced an Autophagy Deficiency Phenotype

Data from the Epanic trial



Casaer MP, Van Den Berghe G. NEJM 2011;365:506

Epanic trial: Early Protein administration induced Deleterious Effects, Not Glucose: Autophagy suppression?



Implication: Nutrition Rx (not IV glucose load) caused adverse outcome

Casaer MP. Am J Respir Crit Care Med 2013;187:247-55.

Role of timing protein intake

Clinical Nutrition xxx (2018) 1–8

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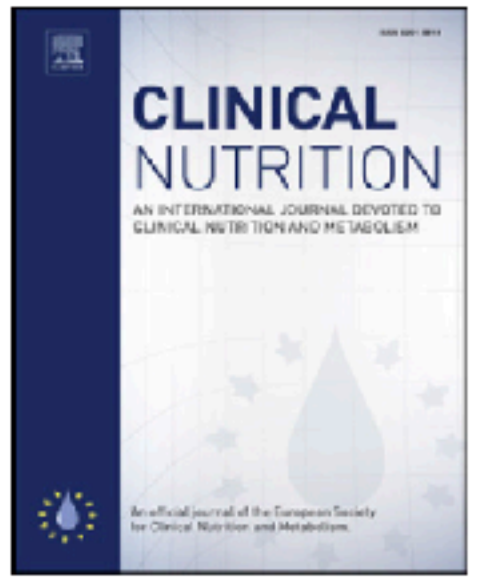
journal homepage: http://www.elsevier.com/locate/clnu



Original article

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

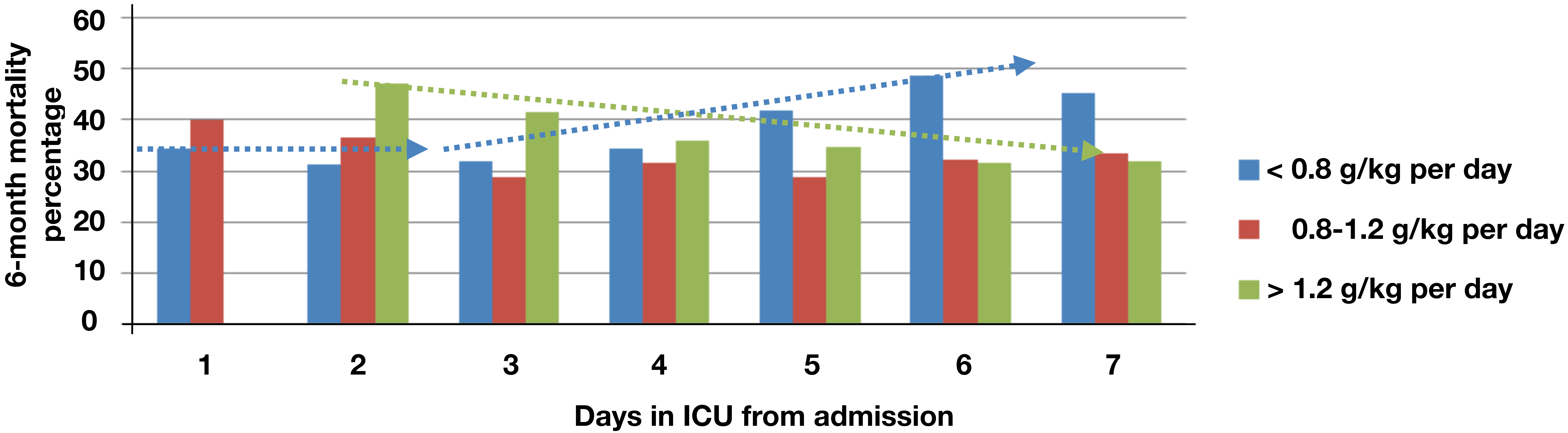
W.A.C. (Kristine) Koekkoek [a, 1], C.H. (Coralien) van Setten [a, 1], Laura E. Olthof [a], J.C.N. (Hans) Kars [b], Arthur R.H. van Zanten [a, *]

[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

Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17. pii: S0261-5614(18)30075-X.

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

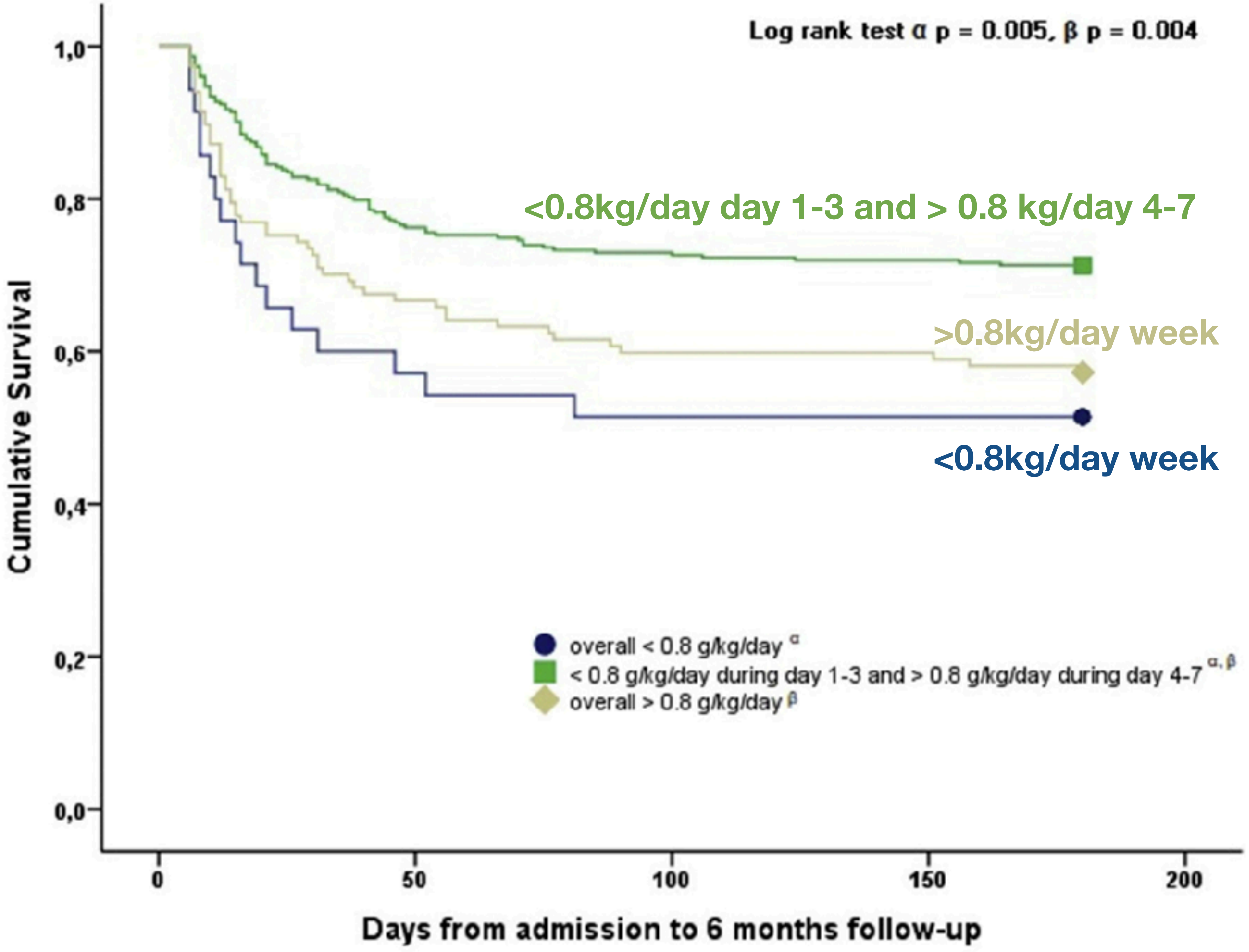
PROTein INtake and clinical outcome in adult critically ill patients on prolonged mechanical VENTilation: n=456; 2011-2015, Mechanical Ventilation > 7 days; Primary endpoint 6 month mortality



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?

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



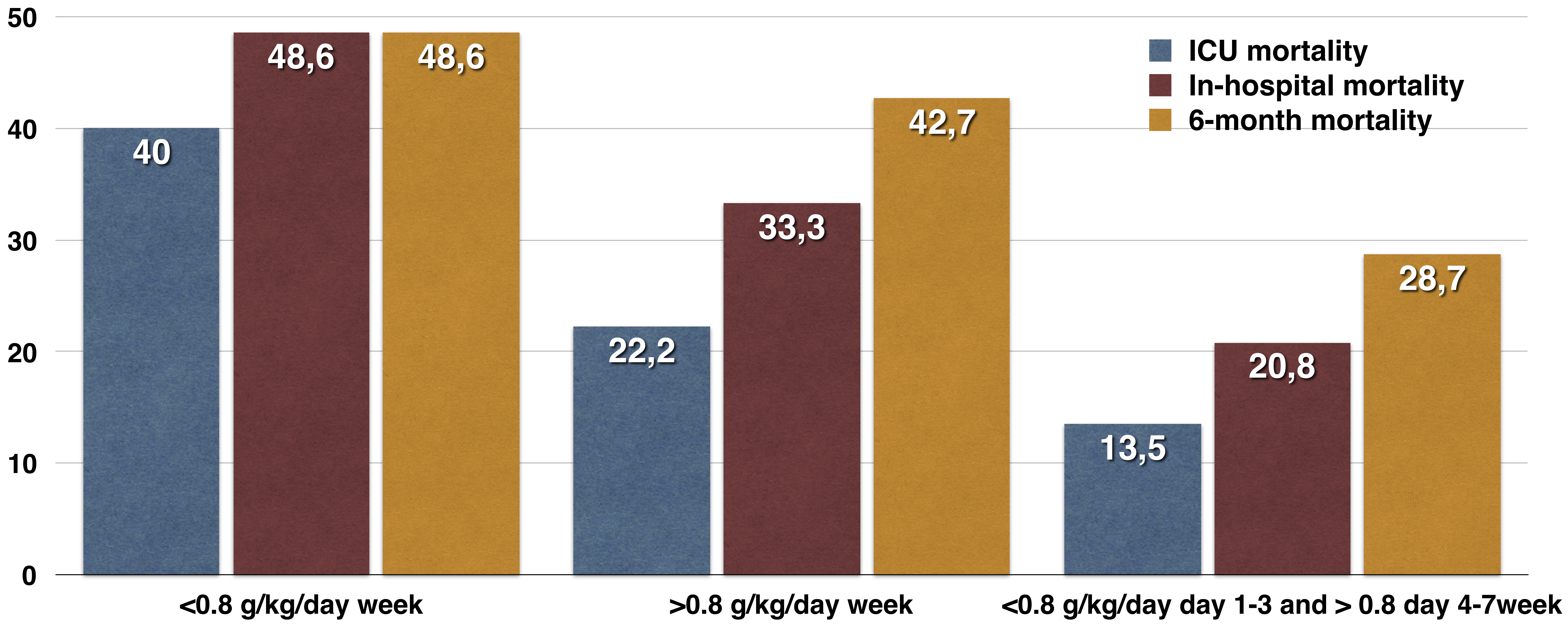
A time-dependent effect of protein intake in critically ill patients is observed.

A gradual increase from low protein intake during the 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.

In addition, overall low protein intake is associated with the highest 6-month, ICU and hospital mortality and should be avoided.

Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17. pii: S0261-5614(18)30075-X.

Effect of Protein intake (day 1-3) and (day 4-7) on ICU, in-hospital and 6-month mortality rates



Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17. pii: S0261-5614(18)30075-X.

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Conclusions PROTINVENT study

- Time-dependent effect of protein intake during critical illness
- Gradual increase from low protein intake during the first 2 days to intermediate on day 3-5 and high protein intake from day 6 is associated with lower 6-month mortality.
- Overall low protein intake is associated with the highest 6-month, ICU and hospital mortality and should be avoided.
- Suggested targets:

  Day 1-2: < 0.8 g/kg/day,

  Day 3-5: 0.8 – 1.2 g/kg/day,

  Day 5 =>: >1.2 g/kg/day

Koekkoek WA, Van Setten C, Van Zanten AR. Clin Nutr. 2018 Feb 17. pii: S0261-5614(18)30075-X.

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REVIEW

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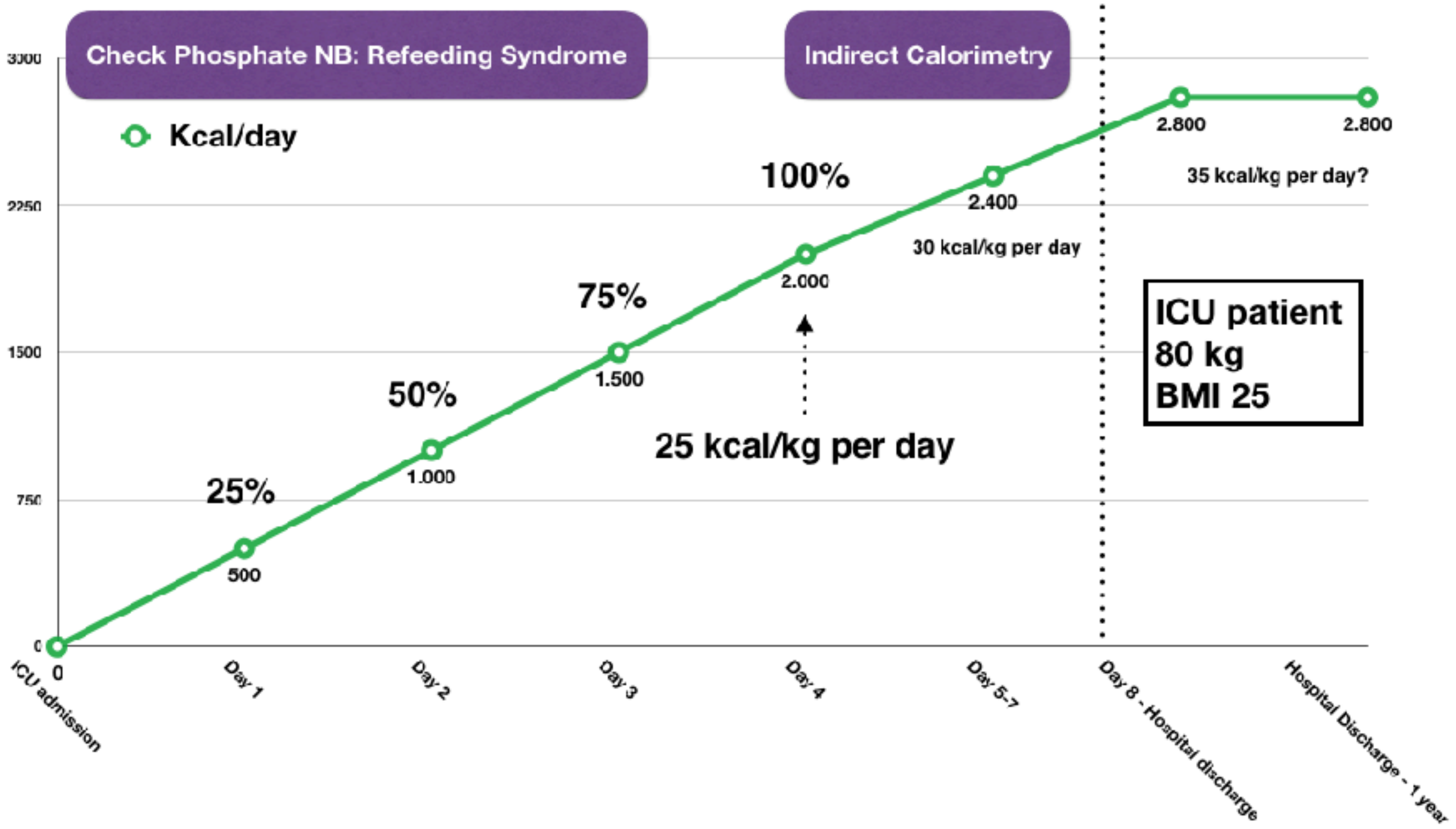
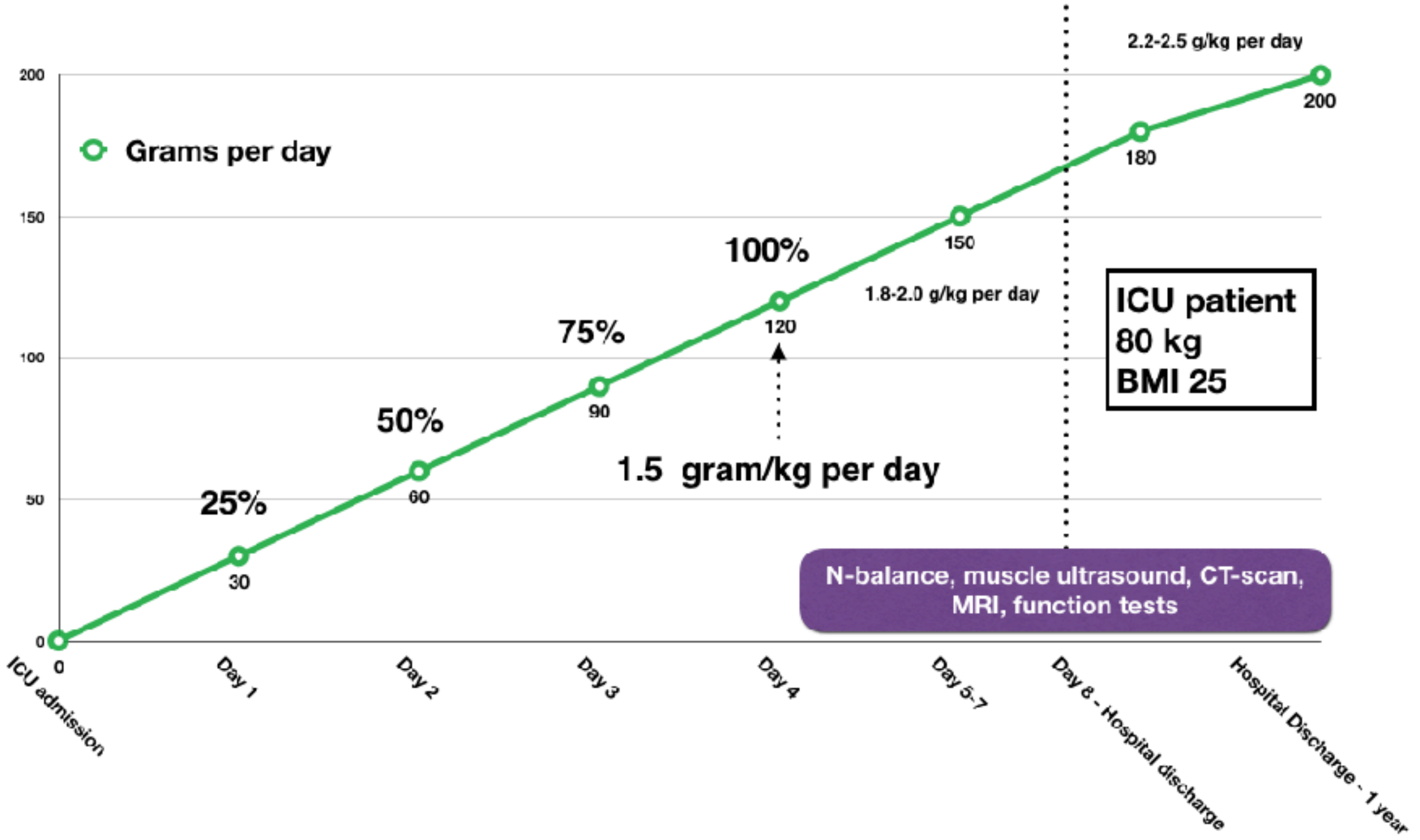
Nutrition in the ICU: new trends versus old-fashioned standard enteral feeding?

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

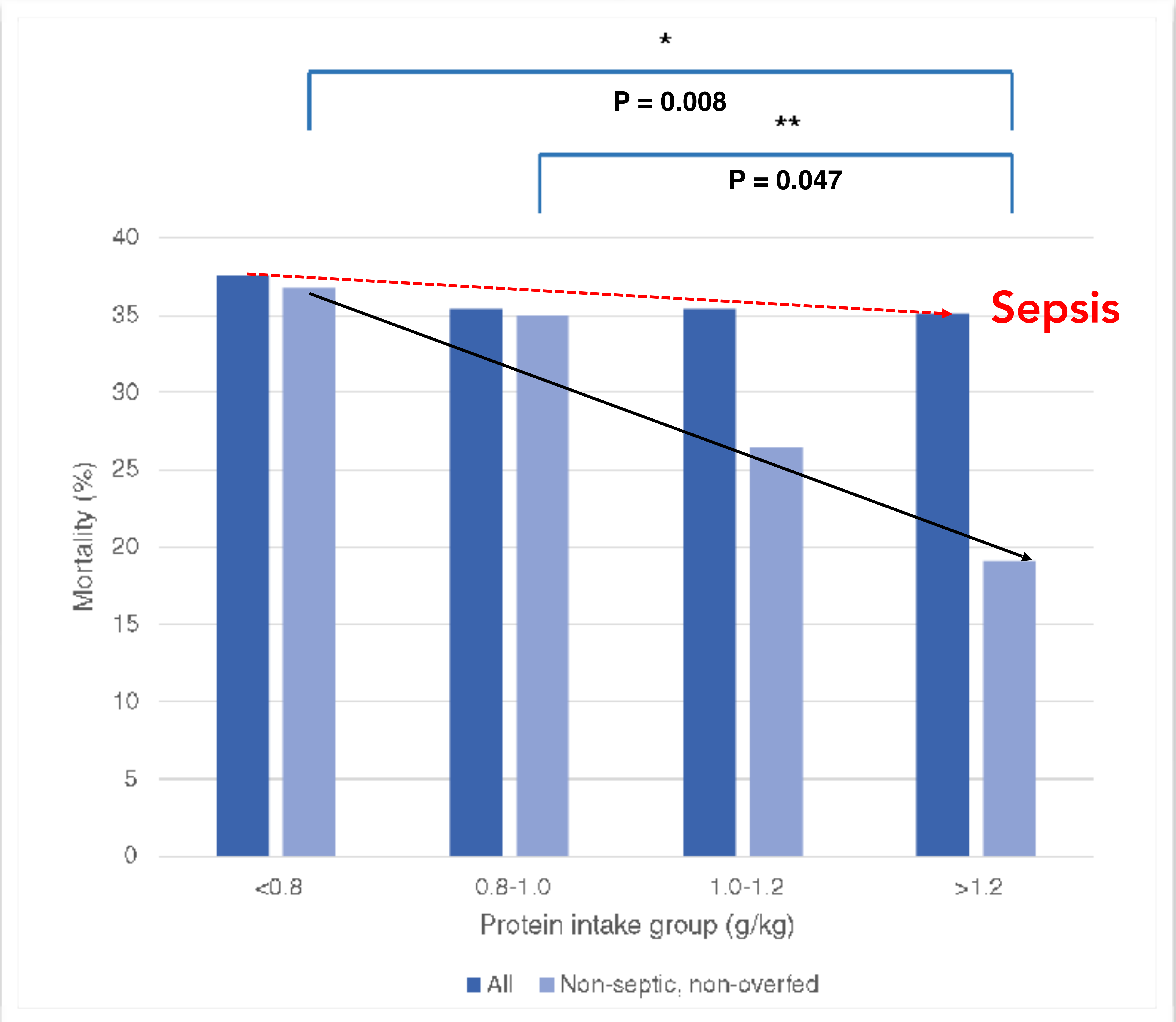




Koekkoek WAC, Van Zanten AR. Curr Opin Anesthesiol 2018, 31:136–143

Hospital mortality per protein intake group

More protein intake is associated with lower in-hospital mortality



0.8 g/kg per day

1.2 g/kg per day

Weijs P. Crit Care 2014;18:701

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Original Communication

Journal of Parenteral and Enteral Nutrition
Volume 0 Number 0
xxx 2019 1–10

DOI: 10.1002/jpen.1663
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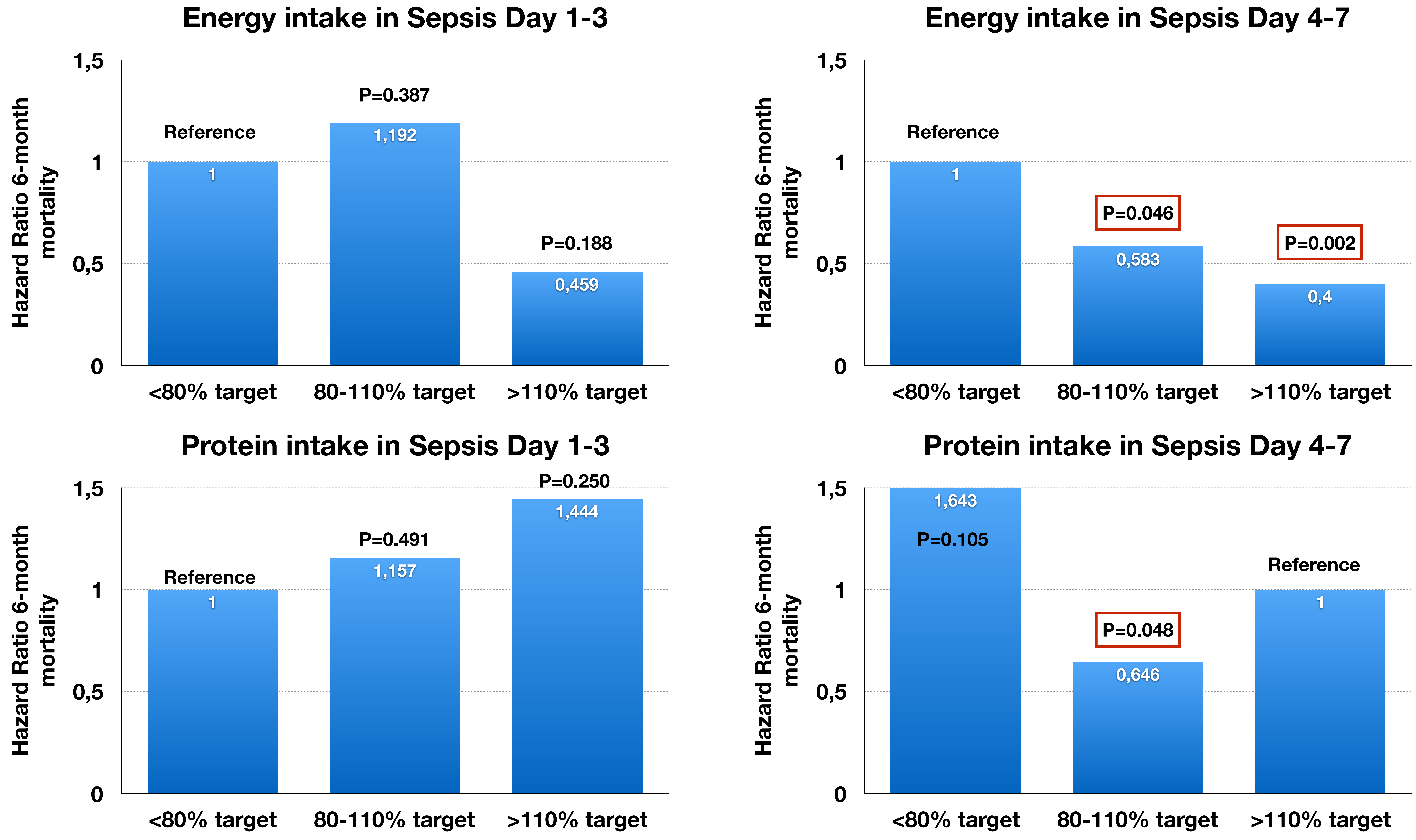
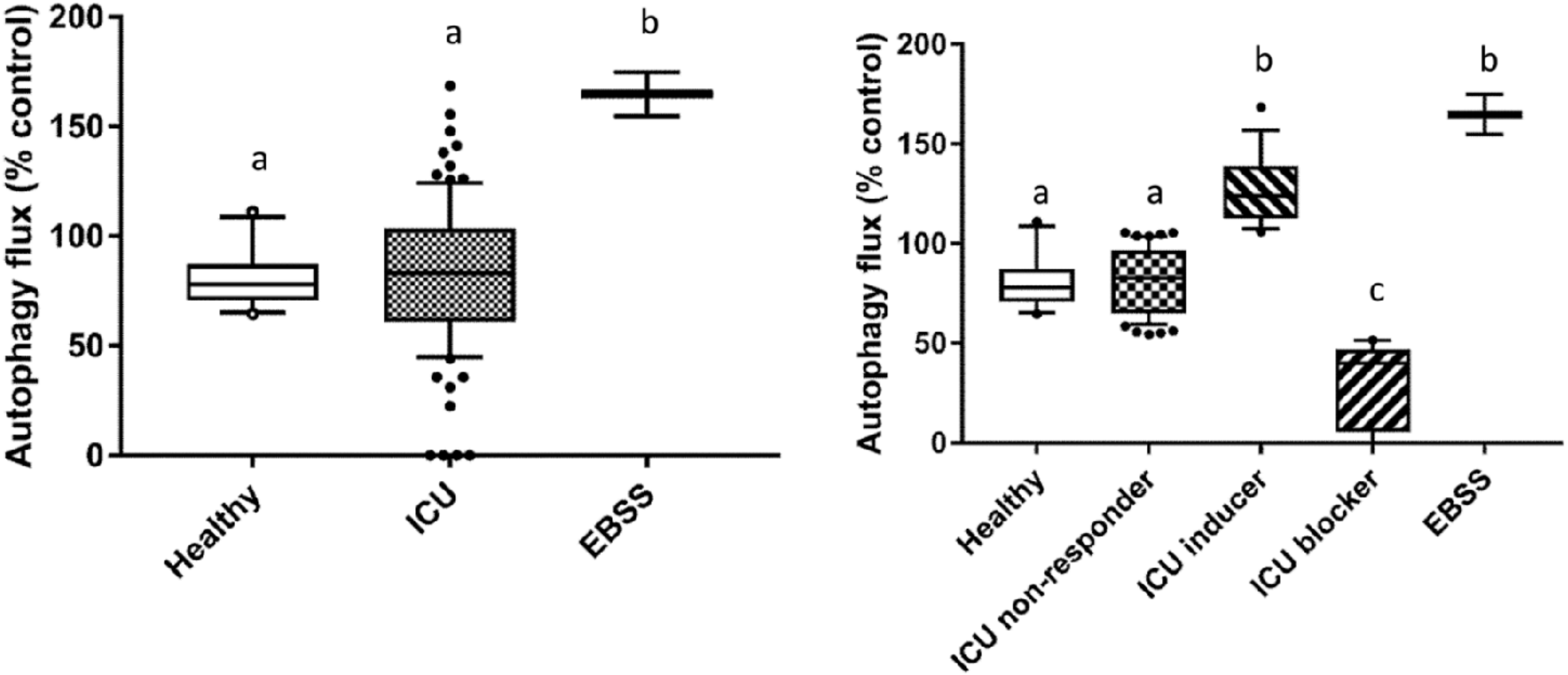
Association of PROtein and CAloric Intake and Clinical Outcomes in Adult SEPTic and Non-Septic ICU Patients on Prolonged Mechanical Ventilation: The PROCASEPT Retrospective Study

Marie-Sophie Louise Yvonne de Koning, MD[1]; Wilhelmina Aria Christina (Kristine) Koekkoek, MD[2]; Johannes Cornelis Nicolaas (Hans) Kars, MSc[3]; and Arthur Raymond Hubert van Zanten, MD, PhD[1]


Energy intake in Sepsis Day 1-3
Hazard Ratio 6-month mortality
1,5
1
0,5
0
Reference
1
P=0.387
1,192
P=0.188
0,459
<80% target
80-110% target
>110% target
Energy intake in Sepsis Day 4-7
Hazard Ratio 6-month mortality
1,5
1
0,5
0
Reference
1
P=0.046
0,583
P=0.002
0,4
<80% target
80-110% target
>110% target
Protein intake in Sepsis Day 1-3
Hazard Ratio 6-month mortality
1,5
1
0,5
0
Reference
1
P=0.491
1,157
P=0.250
1,444
<80% target
80-110% target
>110% target
Protein intake in Sepsis Day 4-7
Hazard Ratio 6-month mortality
1,5
1
0,5
0
1,643
P=0.105
P=0.048
0,646
Reference
1
<80% target
80-110% target
>110% target

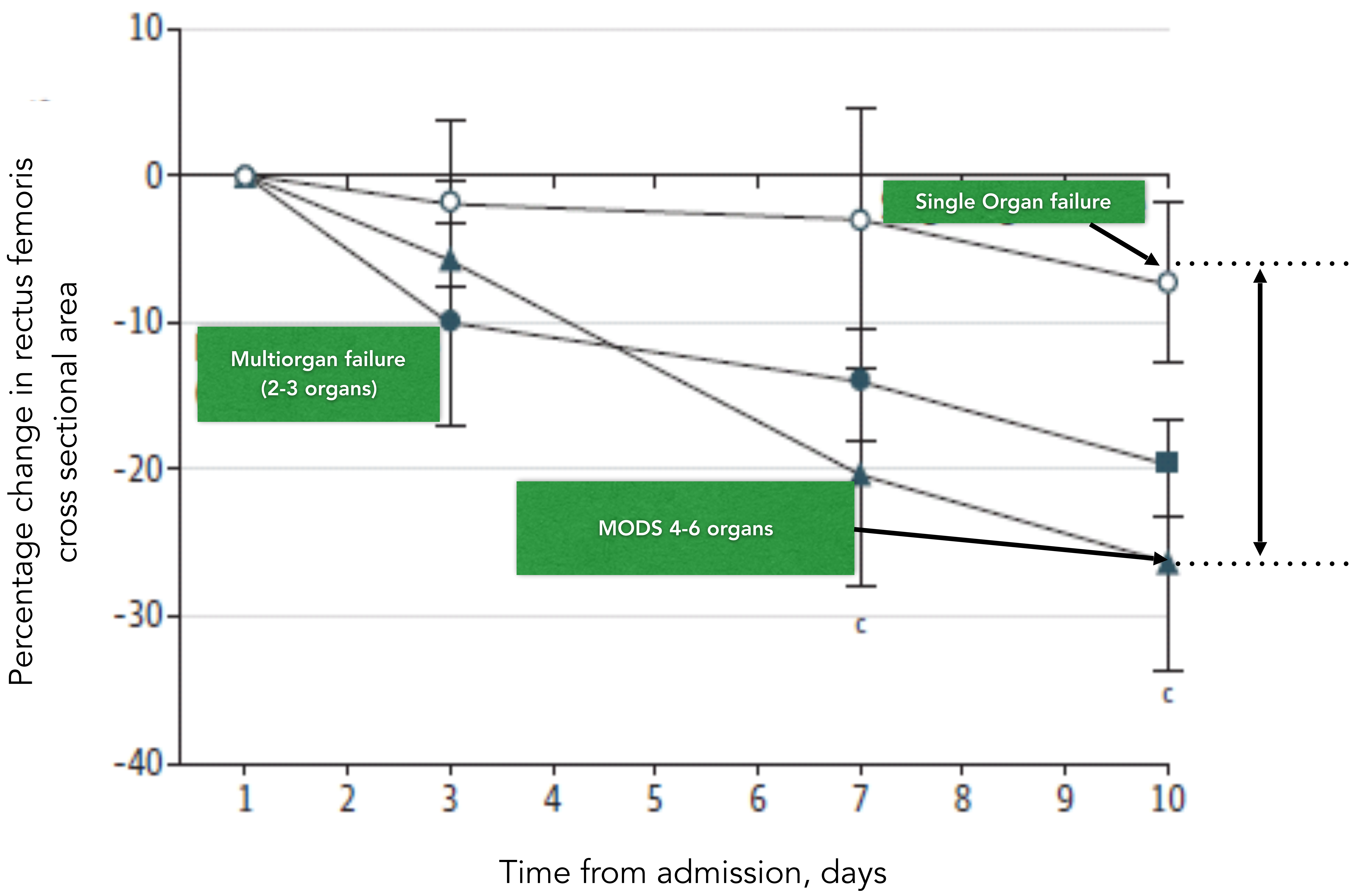
Divergent autophagy response in critical illness



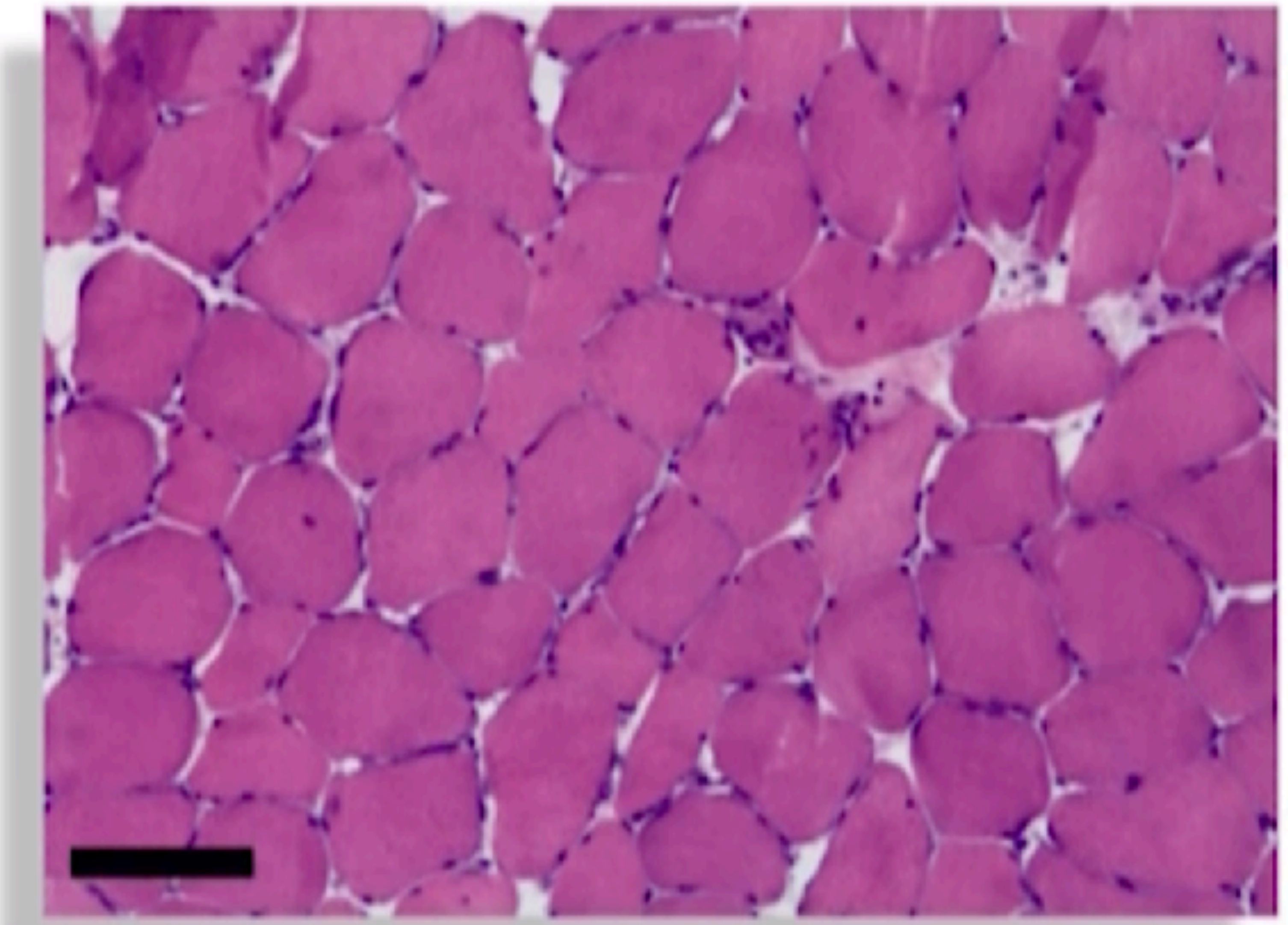
block was related to an accumulation of autophagosomes/autolysosomes, which indicates an impairment in the last steps of the autophagy process.

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

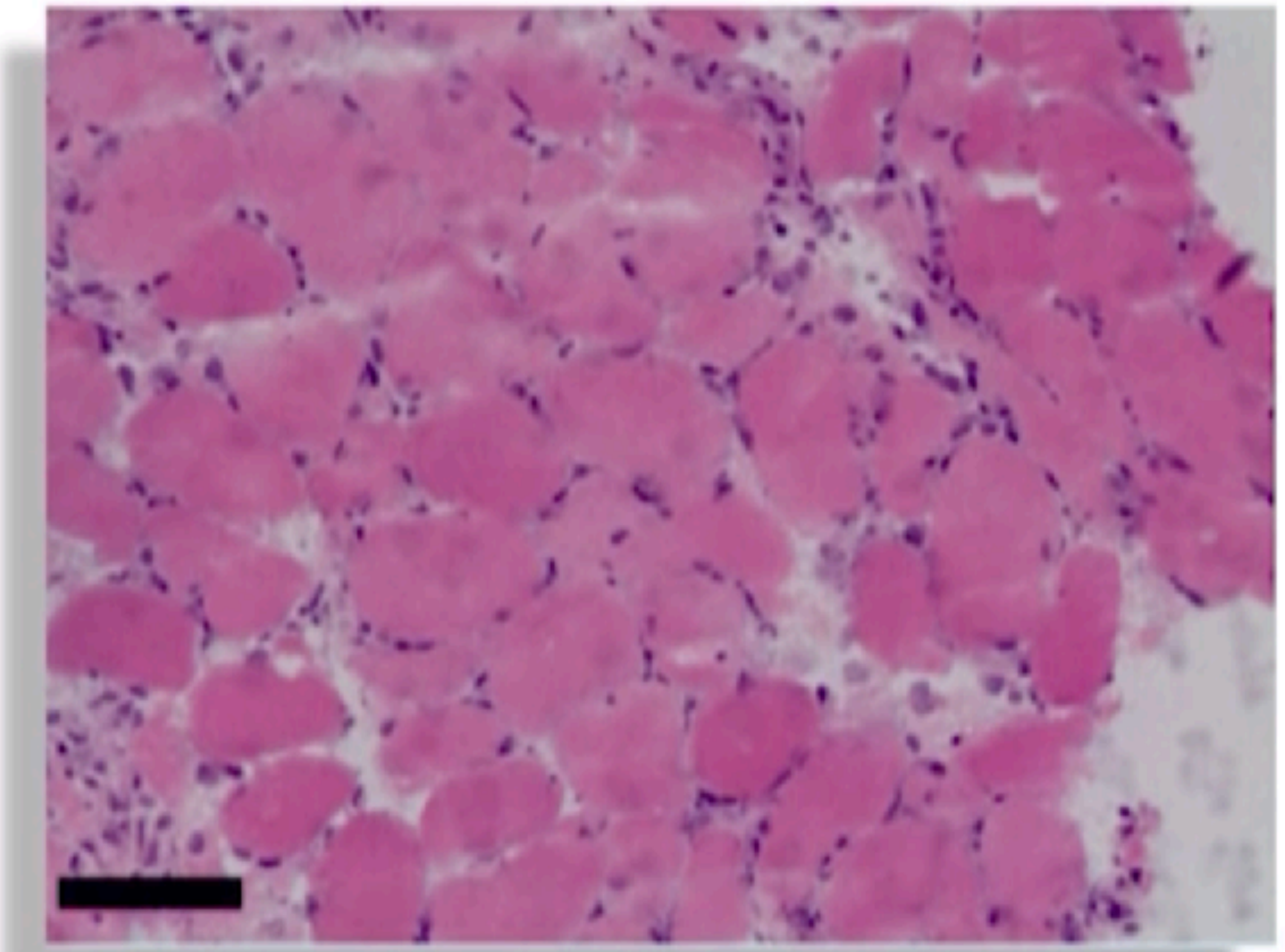
In MODS: Muscle mass loss 1 kg per day



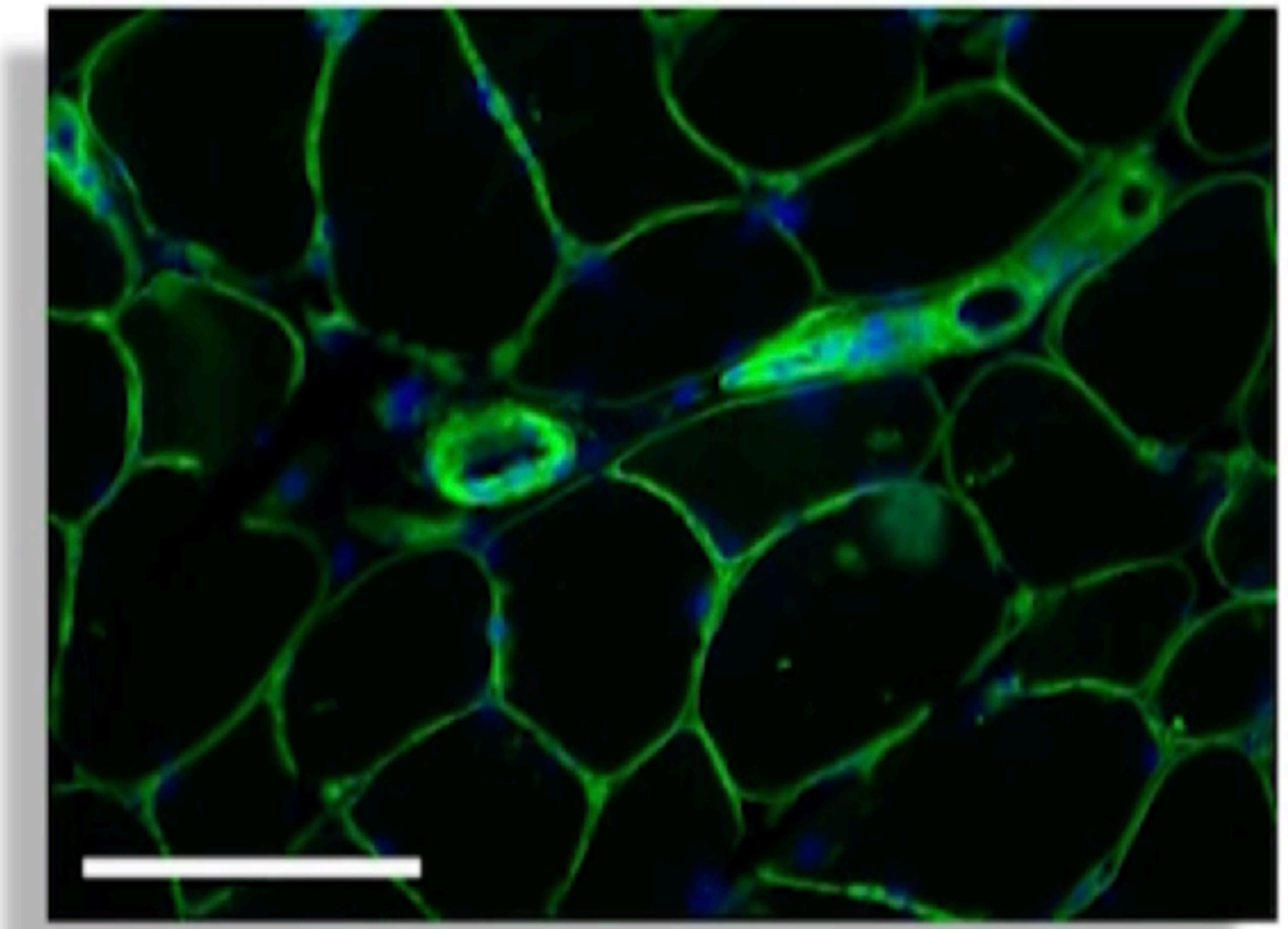
Puthucheary ZA et al., JAMA 2013



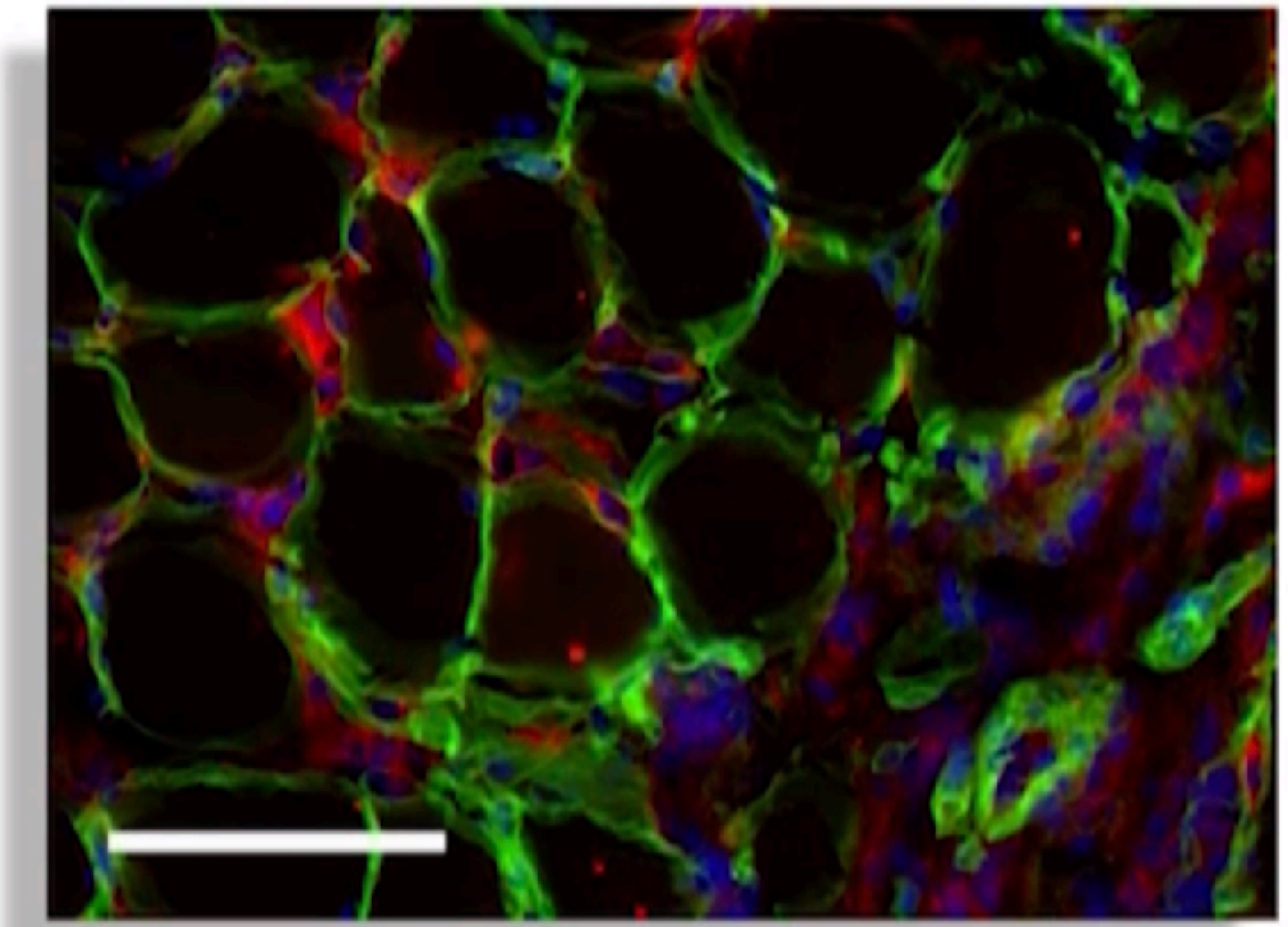
d1-d7

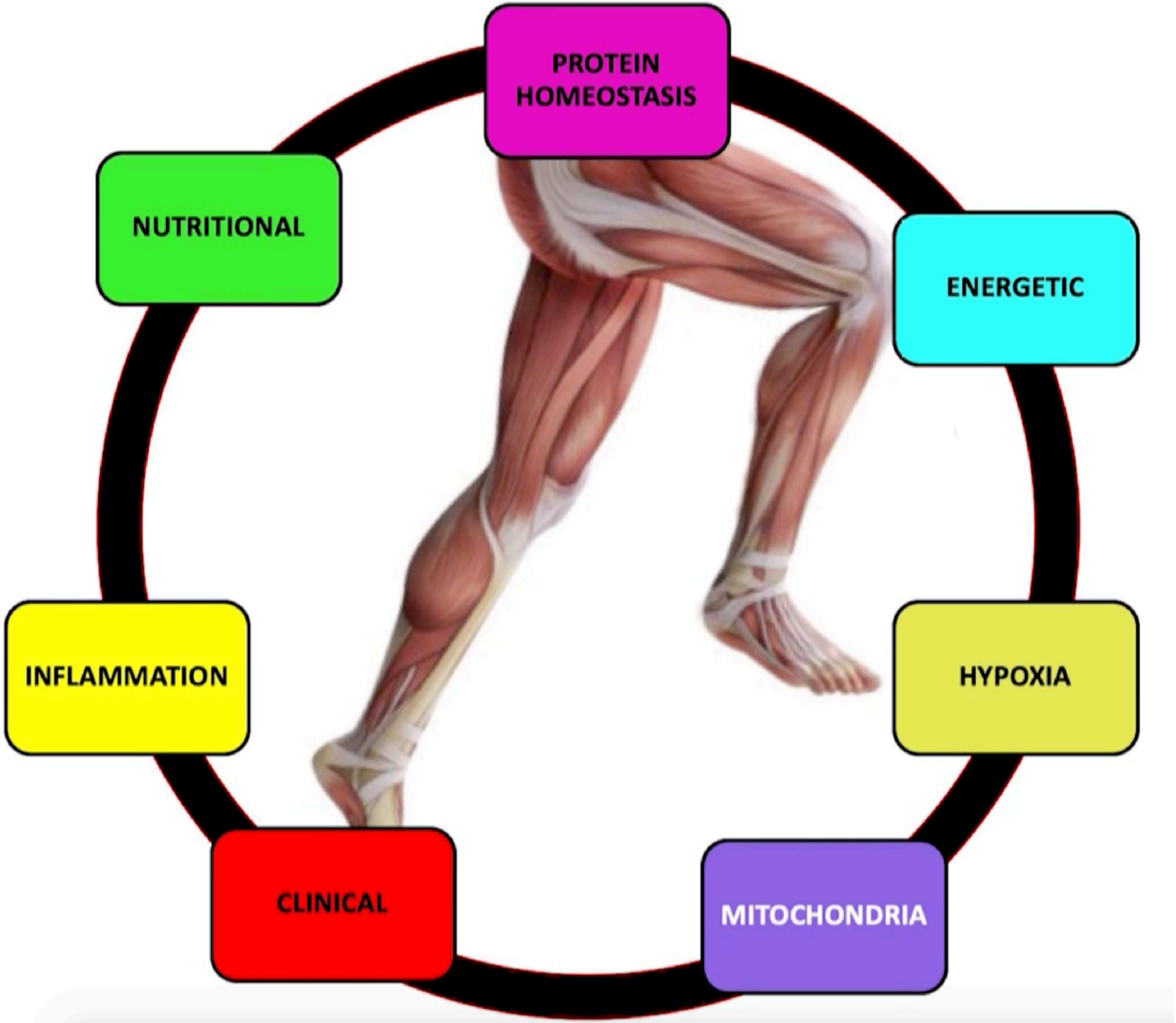


Myonecrosis and inflammation: Myositis



d1-d7





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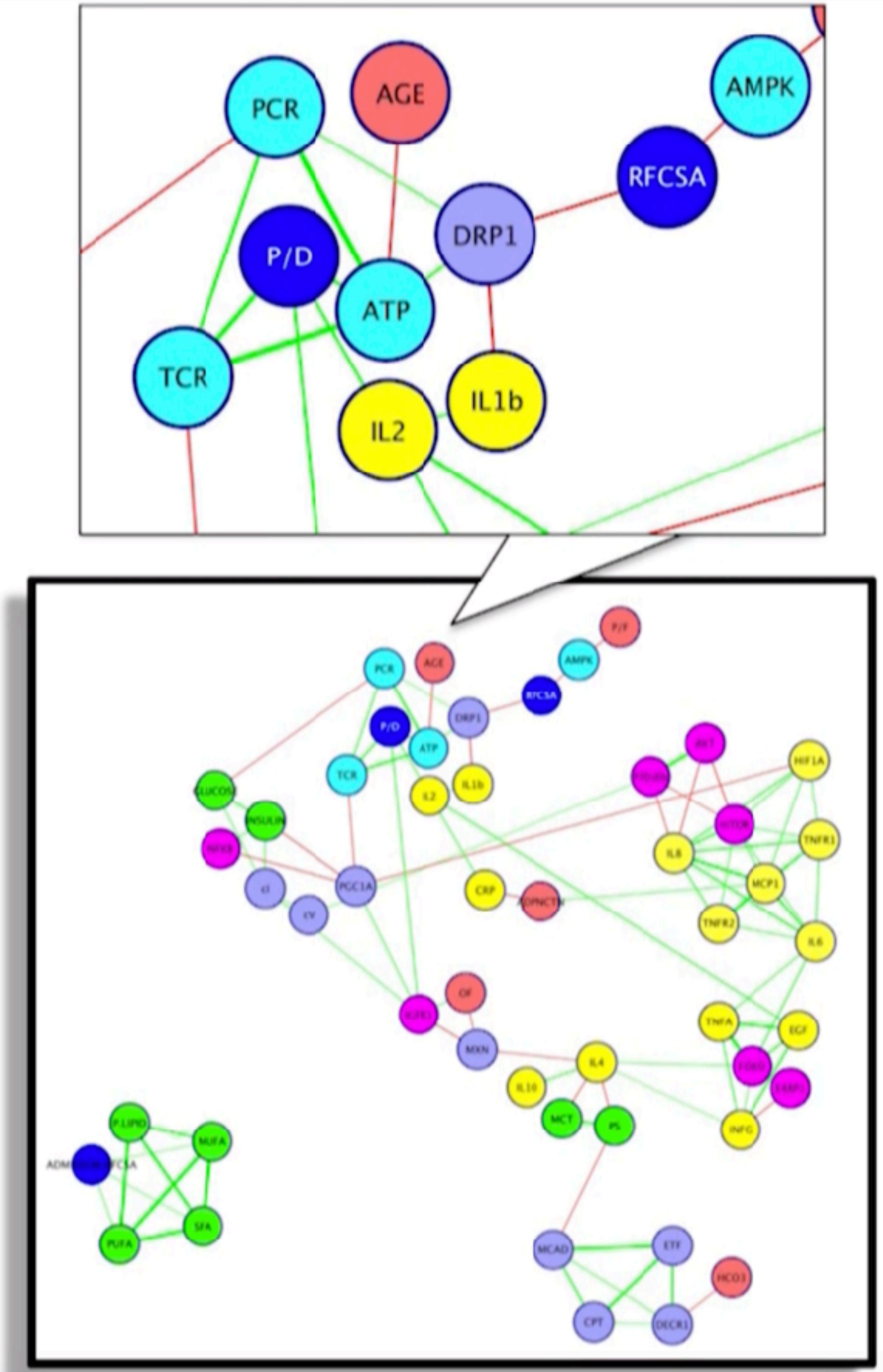
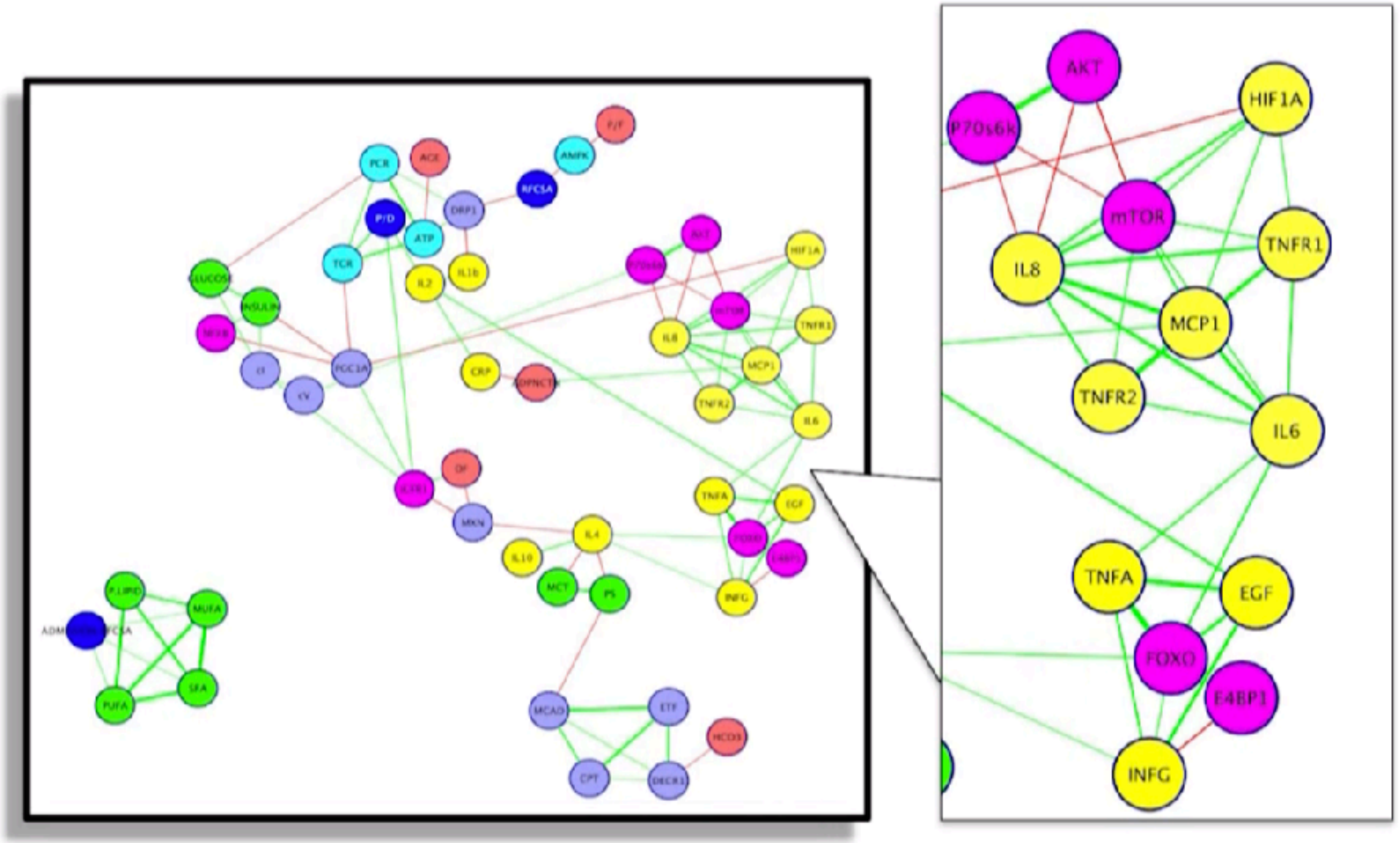
Protein synthesis, muscle mass, ultrasound are strongly associated with energy (ATP)



Without solving the energy problem the loss in muscle mass cannot be prevented



Anabolic signalling and inflammation are strongly associated

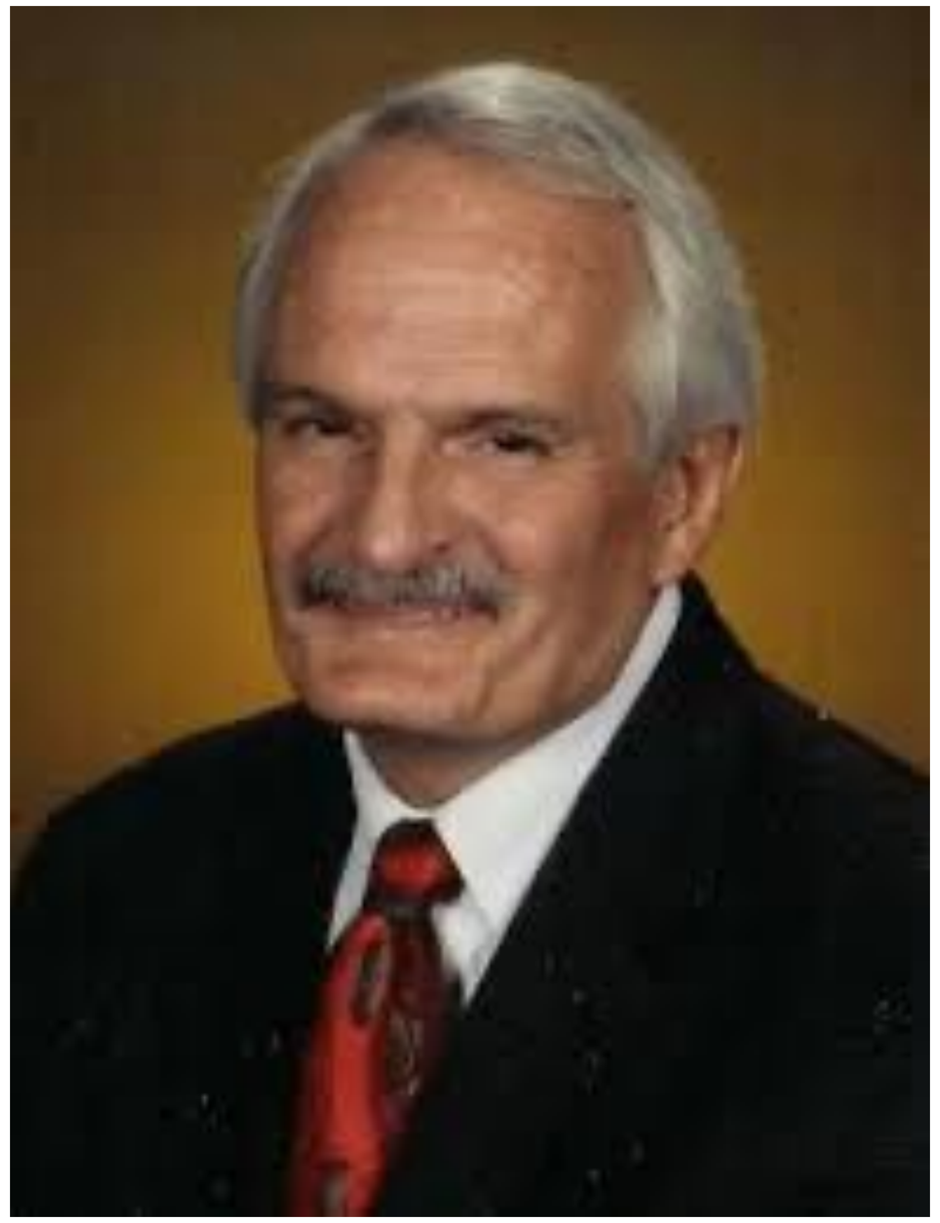
Without solving the inflammation muscle mass loss cannot be prevented

Not proteins or calories provided, but cellular energy is king

Zudin Puthucheary

Arthur van Zanten

Bob Martindale



Steve McClave

In muscles deficient of ATP, exercise may induce more necrosis & inflammation, as exercise is a catabolic metabolic event, we have to search for alternative routes to provide energy without the cost of ATP production

Alternatives

Parenteral Amino Acid Supplementation	Enteral Protein Supplementation	Very High Protein Enteral Feeds
Bioavailability	Costs	No overfeeding
Costs Infection No splanchnic first pass Workload Discarded volume Additional volume	Opening closed feeding system Contamination Workload Additional volume	Costs? Limited experience GI-intolerance for hydrolyzed formulations

Why do we need higher protein to energy ratio feeds?

	Standard high intact- protein * (SHPF)	
	Per 100 ml	% of energy
Energy	125 kcal	
Protein**	6.3 g	20 %
Carbohydrate	14.2 g	45 %
Fat	4.9 g	35%

Patient 100 kg

Target calories 20 kcal/kg per day = 2000 kcal

Protein target 1.5 g/kg per day = 150 g proteins

Energy strategy

2000 kcal/ 1,25 mL = 1600 mL

150 g proteins/ 0,063 mL = 2381 mL

Protein strategy

Energy strategy → 101 g protein deficit 49 g/day

Protein strategy → 976 kcal/day overfeeding

Why do we need higher protein to energy ratio feeds?

- 70-80% of energy target is optimum
- Overfeeding >110% of REE is associated with increased mortality
- >1.3 g/kg per days of protein intake achieved is target (ESPEN guideline 2018)
- Enteral feeding products should have protein content of >30% to prevent overfeeding while achieving the protein target.
- NB: more intake of a low protein/energy ratio product will lead to overfeeding when the protein target should be achieved

van Zanten *et al. Critical Care* (2018) 22:156
https://doi.org/10.1186/s13054-018-2070-5

Critical Care

RESEARCH

Open Access

Very high intact-protein formula successfully provides protein intake according to nutritional recommendations in overweight critically ill patients: a double-blind randomized trial

Arthur R. H. van Zanten[1*], Laurent Petit[2], Jan De Waele[3], Hans Kieft[4], Janneke de Wilde[5], Peter van Horssen[5], Marianne Klebach[5] and Zandrie Hofman[5]

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Van Zanten et al AR Crit Care 2018; 22: 156.

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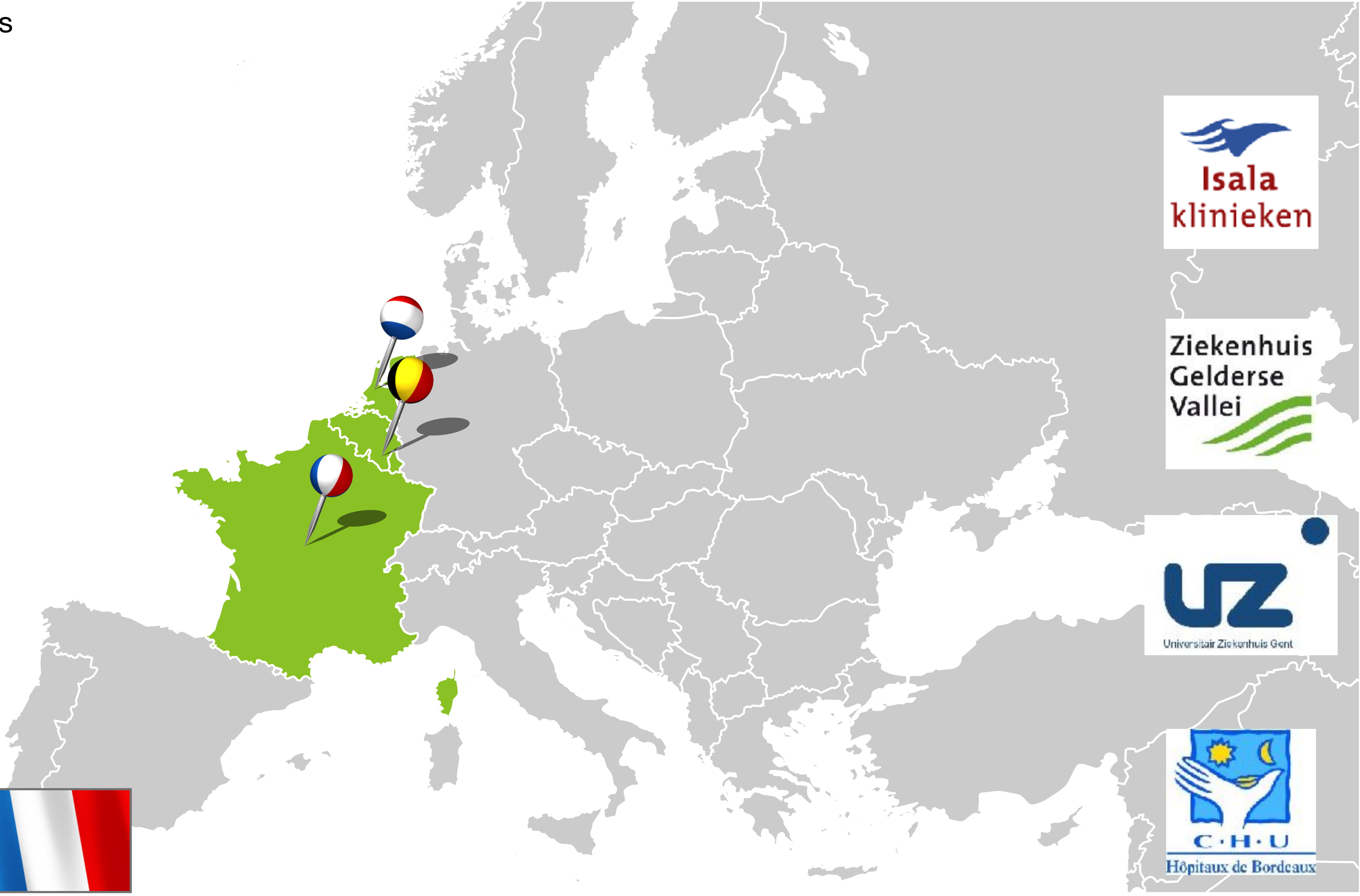


Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

Ziekenhuis Gelderse Vallei

Study products and feeding regimen

	New very high intact- protein (VHPF)		Standard high intact- protein * (SHPF)	
	Per 100 ml	% of energy	Per 100 ml	% of energy
Energy	125 kcal		125 kcal	
Protein**	10 g	32 %	6.3 g	20 %
Carbohydrate	10.3 g	33 %	14.2 g	45 %
Fat	4.9 g	35%	4.9 g	35%

* : Nutrison Protein Plus (Nutricia, Zoetermeer),
** : intact protein sources: 35% whey, 25% casein, 20% soy and 20% pea

Feeding regimen recommended in protocol: Start enteral feeding with 20 ml/hour, Assess Gastric Residual Volume (GRV) and increase enteral feeding with 20 ml/hour every 6 hour, Target 25 kcal/kg bw per day, If BMI > 30 kcal/m^2, the Ideal Body Weight (IBW) was defined: 30 x height^2

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

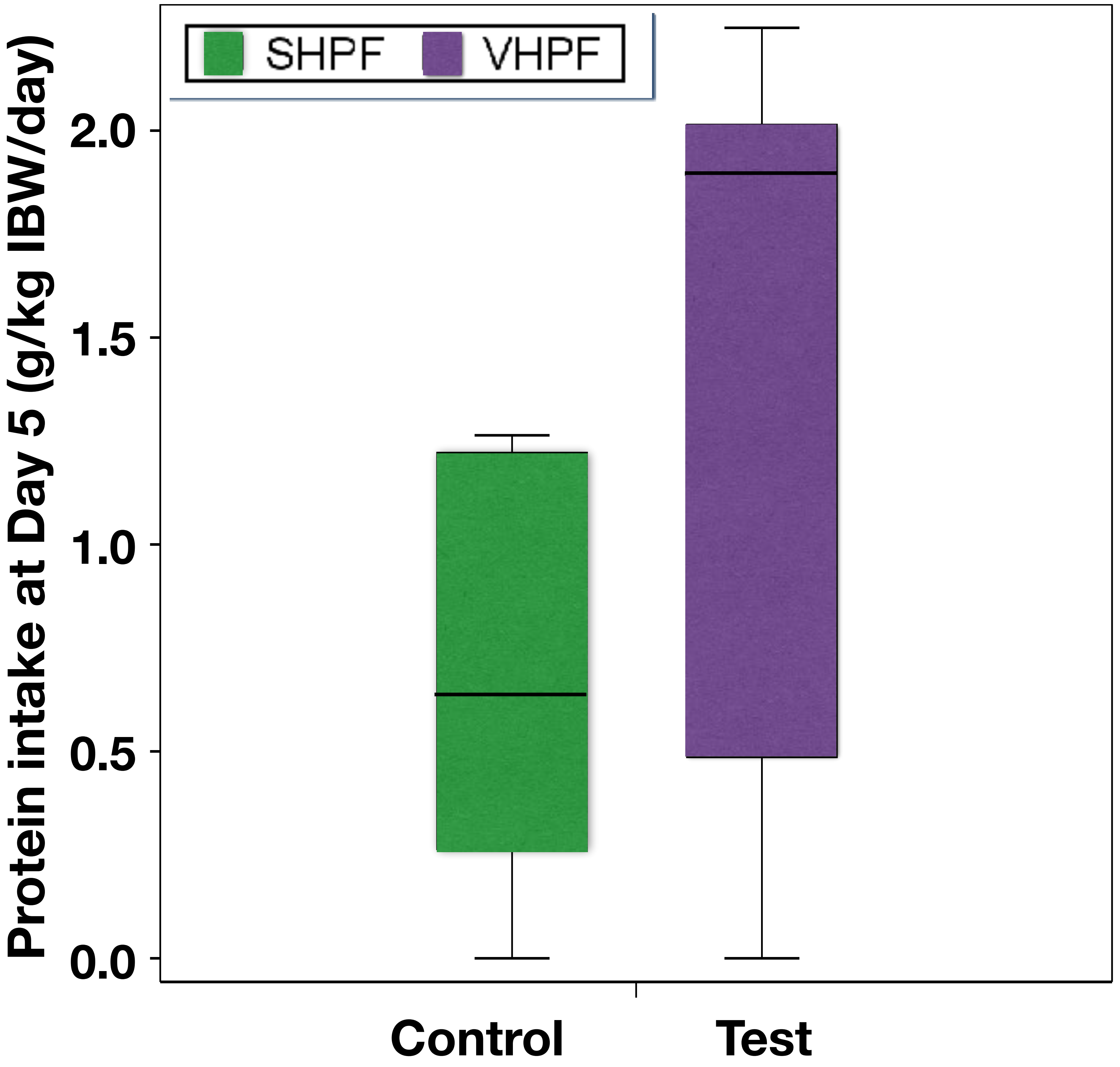
Patient characteristics

		SHPF (standard) (N = 22)	VHPF (new) (N = 22)
Sex (Male) Sex (Female)	n (%) n (%)	13 (59.1%) 9 (40.9%)	9 (40.9%) 13 (59.1%)
Age (years)	Mean (sd)	60.8 (15.2)	63.9 (13.3)
Body weight (kg)	Mean (sd)	91.2 (20.7)	84.9 (18.3)
BMI (kg/m^2)	Mean (sd)	30.7 (8.4)	30.3 (4.1)
Type of patient			
• Medical	n (%)	9 (40.9%)	8 (36.4%)
• Surgical	n (%)	10 (45.5%)	11 (50.0%)
• Surgical non-trauma	n (%)	4 (18.2%)	4 (18.2%)
• Surgical trauma*	n (%)	6 (27.3%)	7 (31.8%)
• Trauma	n (%)	9 (40.9%)	10 (45.5%)
• Trauma non-surgical	n (%)	3 (13.6%)	3 (13.6%)
SOFA score from screening	Median (Q1-Q3)	9 (7-11)	10 (9-11)
APACHE II score at baseline Predicted mortality (%) Adjusted predicted mortality (%)	Median (Q1-Q3) Mean (sd) Mean (sd)	24 (18-27) 48.4 (18.7) 38.7 (19.8)	25 (21-28) 52.6 (17.7) 42.7 (20.3)

*surgical trauma patients were included in both the surgical and trauma subgroup of patients

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

Protein intake at day 5



		SHPF (N = 22)	VHPF (N = 22)	p-value
Protein g/kg ABW	Mean (SD) Median (Q1-Q3)	0.68 (0.47) 0.6 (0.3-1.2)	1.32 (0.80) 1.6 (0.4-2.0)	
	LS mean (95% CI)	**0.76** (0.49, 1.03)	**1.49** (1.21, 1.78)	<0.001
Protein g/kg IBW	Mean (SD) Median (Q1-Q3)	0.72 (0.47) 0.6 (0.3-1.2)	1.37 (0.82) 1.9 (0.5-2.0)	
	LS mean (95% CI)	**0.80** (0.52, 1.07)	**1.54** (1.26, 1.83)	<0.001

VHPF: Statistically significant higher protein intake at day 5

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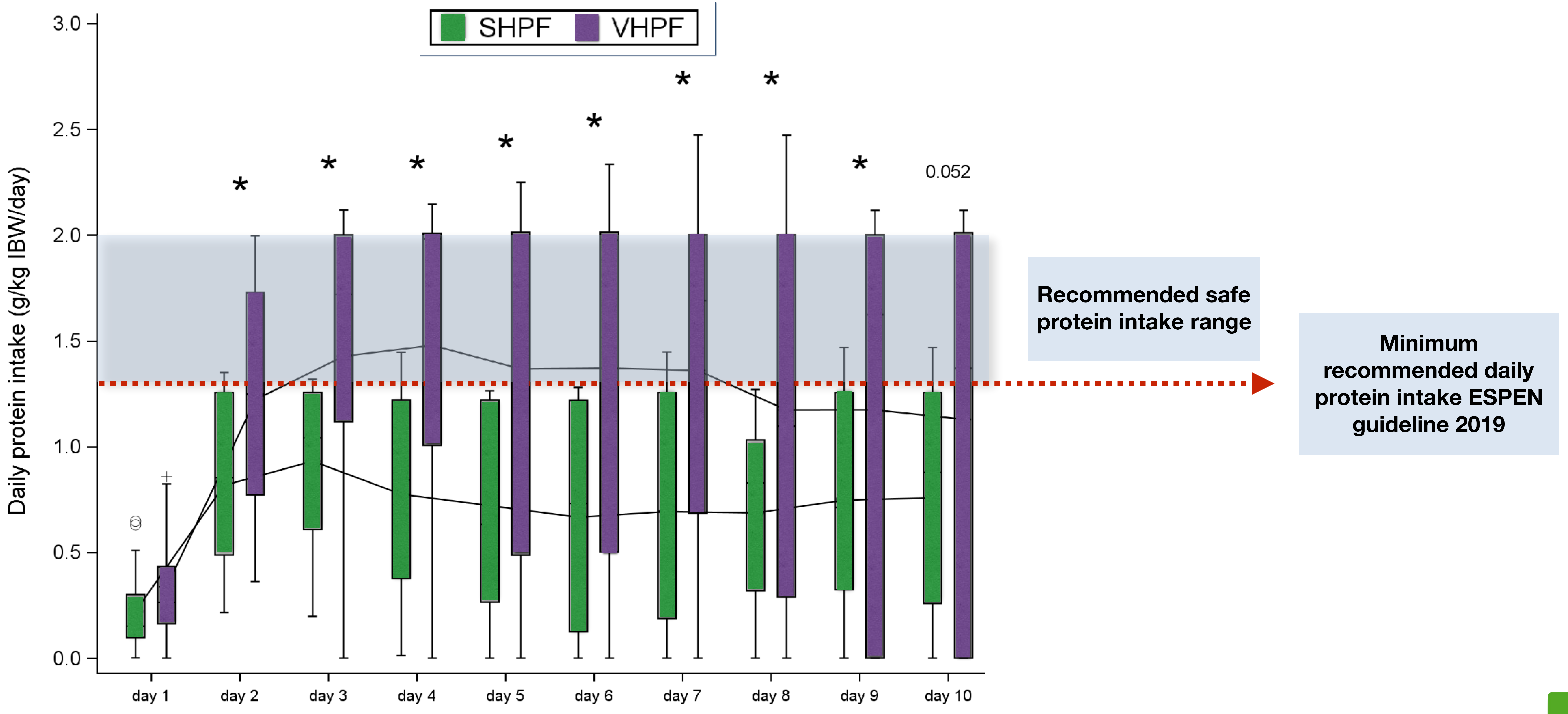
Very high protein feed: Significant higher protein intake day 1-10



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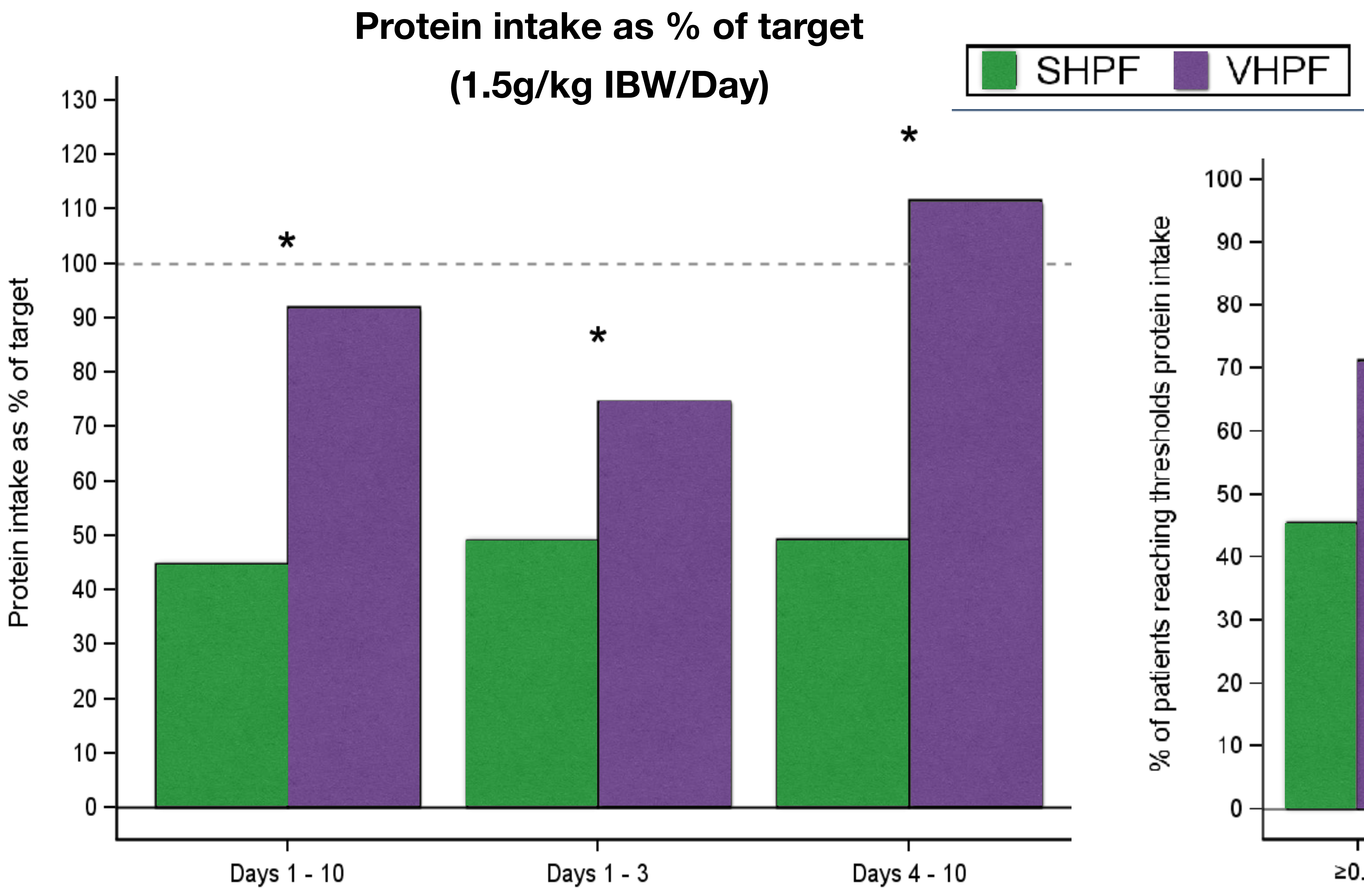
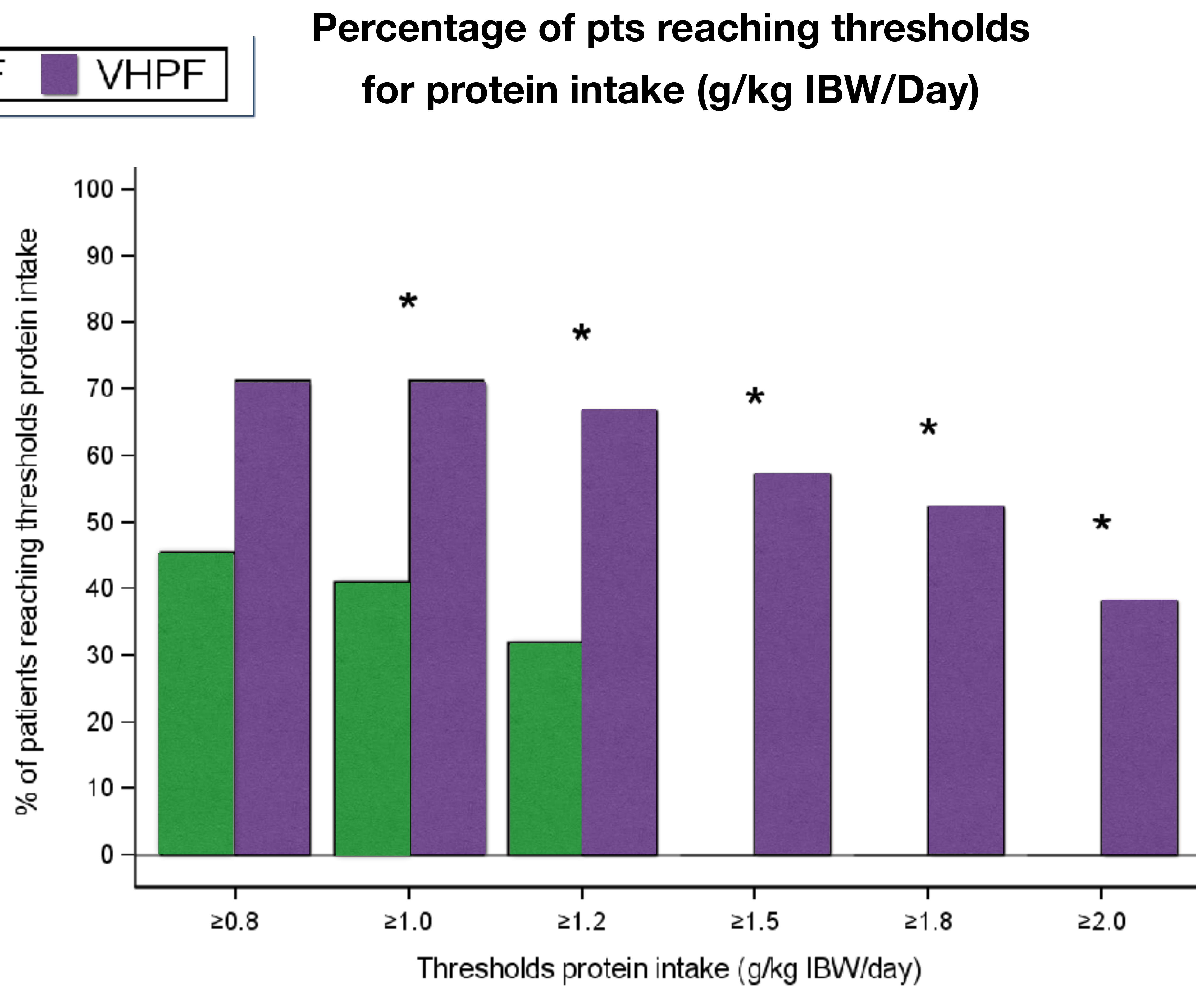
Protein intake relative to target protein intake





* Statistically significant VHPF vs SHPF ($p<0.05$)

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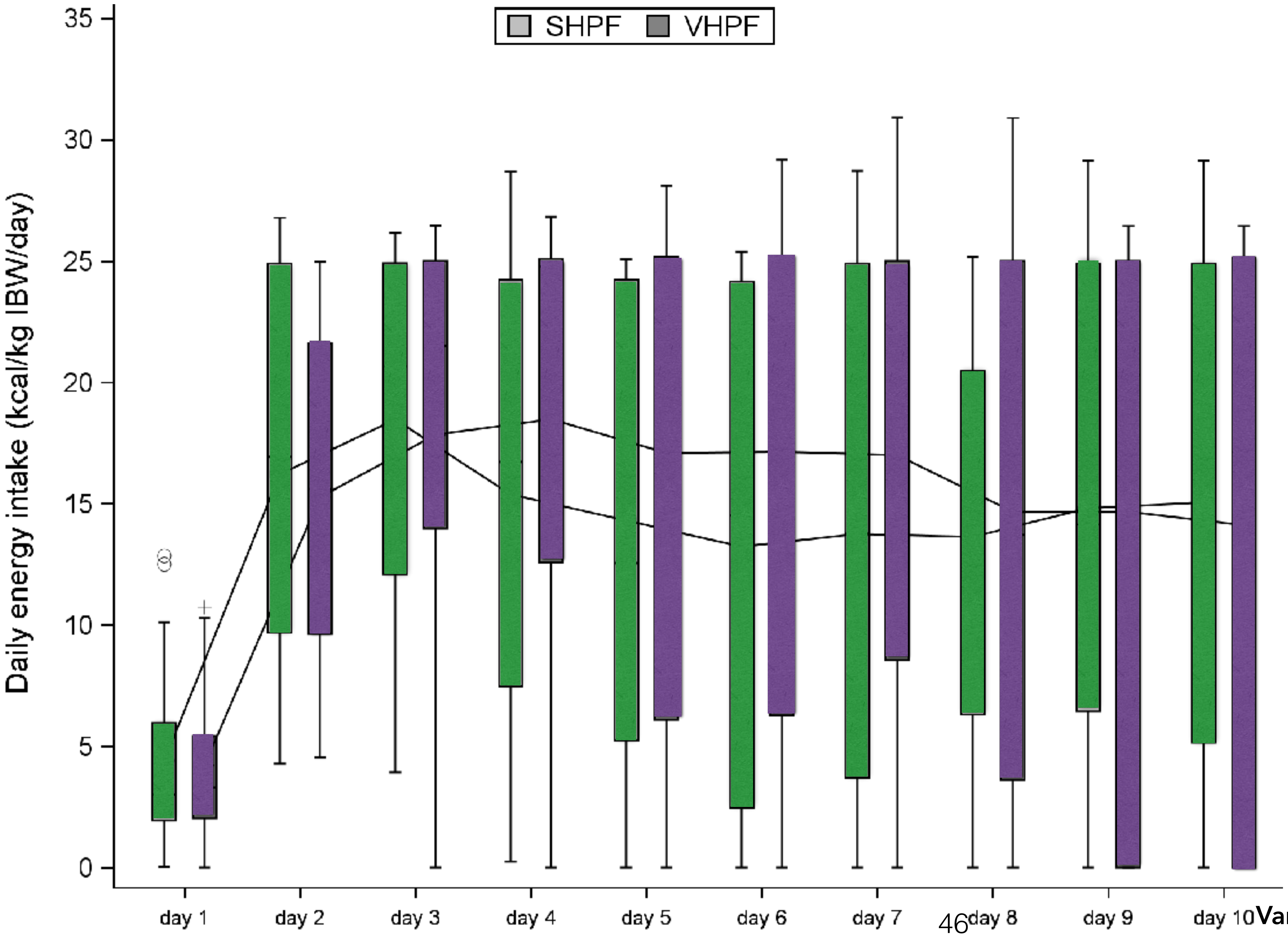
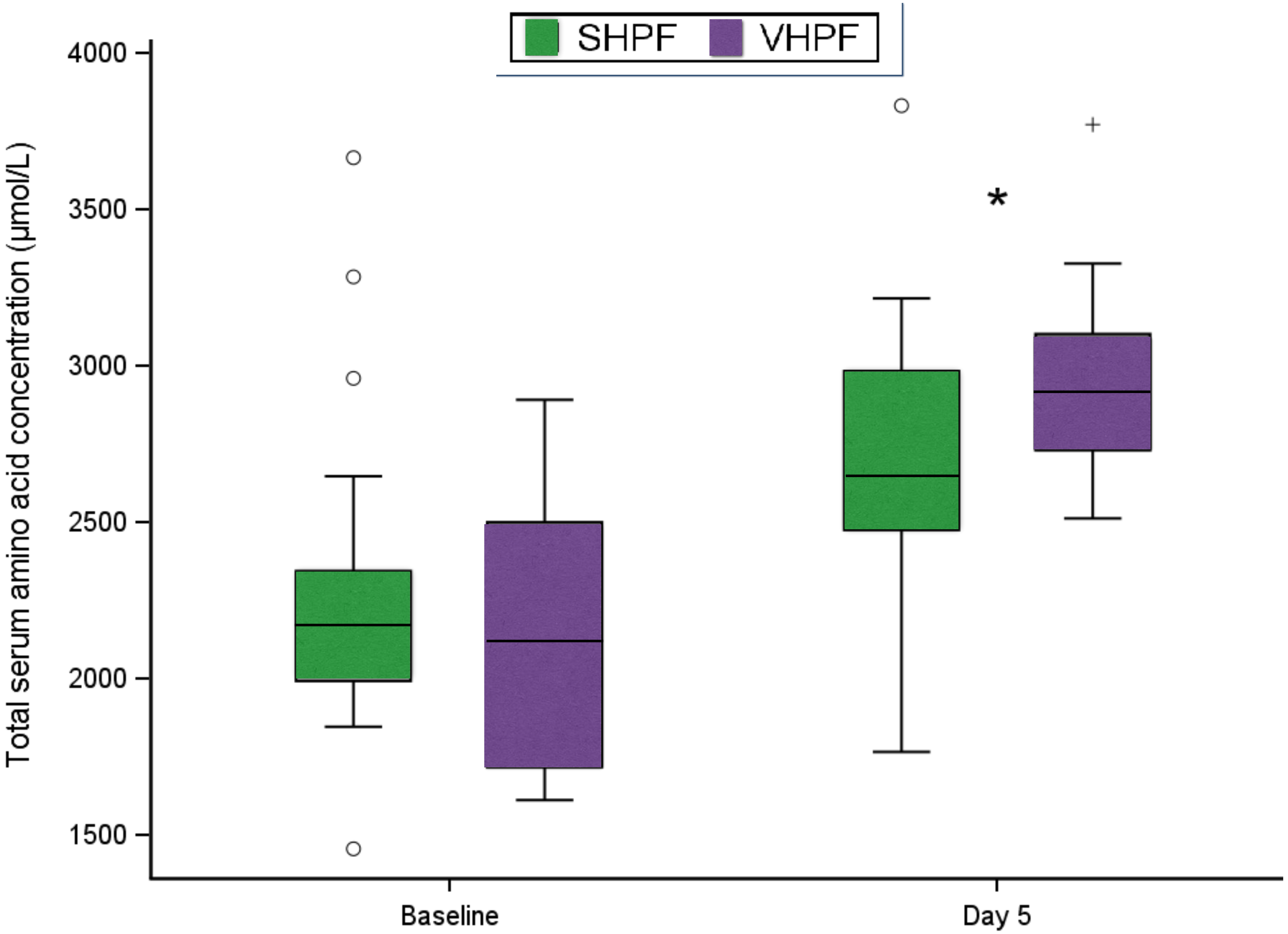
Energy intake day 1 - 10



No statistically significant differences found in energy intake between VHPF and SHPF

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

Plasma amino acid concentrations at baseline and day 5



VHPF: Statistically significant higher concentrations of plasma amino acids

* : Statistically significant higher amino acid concentration at Day 5 (p=0.031)

* : Statistically significant within-group increase from baseline (both p <0.001)

* : Significantly higher increase from baseline compared to control (p=0.031)

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

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Clinical outcome parameters

			SHPF (N = 22)	VHPF (N = 22)	P value
Mortality rates:	**ICU**	n (%)	2 (9.1%)	1 (4.5%)	0.637[6]
	Hospital	n (%)	3 (13.6%)	2 (9.1%)	0.638[6]
	Total 28 days	n (%)	3 (13.6%)	2 (9.1%)	0.560[3]
	Total 42 days	n (%)	3 (13.6%)	3 (13.6%)	0.886[3]
Duration of ICU stay		Mean (SD)	18.3 (12.7)	18.4 (13.4)	
		95% CI	12.7 – 23.9	12.4 – 24.3	0.913[1]
Duration of hospital stay		Mean (SD)	28.2 (13.2)	28.5 (13.3)	
		95% CI	22.4 – 34.1	22.5 – 34.4	0.955[1]
Duration of first ventilation period		Mean (SD)	7.4 (5.4)	10.0 (8.7)	0.234[1]
		95% CI	5.0 – 9.8	6.1 – 13.9	
Sofa Scores :	**Screening**	Median [IQR]	9 [7-11]	10 [9-11]	0.514[4]
	Day 5		6 [4-8]	6 [3-8]	0.647[4]
	Day 10		5 [4-9]	4 [1-7]	0.432[4]
	End of study		2 [1-3]	2 [1-3]	0.608[4]
	Day 28		1 [0-2]	3 [2-3]	0.446[4]

[1]Two-way analysis of variance (ANOVA) with treatment and centre as factors.

[3]Cox proportional hazards regression analysis with study product and stratification factor

[4] Van Elteren test (stratified for centre)

[6]Cochran-Mantel-Haenszel test.

Four subjects were not discharged from the ICU at follow-up (Day 42±3 days). For these subjects ICU stay was limited to day of follow-up.

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

Gastro intestinal tolerance

	SHPF (N=22)	VHPF (N=22)	P value
Incidence of diarrhoea[1], n (%) **95% confidence interval (%)**	11 (50.0) (28.2 - 71.8)	8 (36.4) (17.2 - 59.3)	0.361[4]
Incidence of constipation[2], n (%) **95% confidence interval (%)**	16 (72.7) (49.8 - 89.3)	13 (59.1) (36.4 - 79.3)	0.340[4]
Incidence of vomiting[3], n (%)	6 (27.3%)	5 (22.7%)	1.000[5]
Gastric Residual Volume > 500 ml	5 (22.7%)	4 (18.2%)	0.567[6]

[1]Incidence of diarrhoea was collected during the first 10 days of ICU stay and is defined as DDS > 15 for at least one day and/or a DDS ≥ 6 for at least two consecutive days.
[2]Incidence of constipation was collected during the first 10 days of ICY stay and is defined as no bowel evacuation within 72 hours. [3]Based on recorded Adverse Events (excluding procedural vomiting) collected during ICU stay
[4]P value derived from a Chi-squared Test.
[5]P value derived from a Fischer's Exact Test
[6]Cochran-Mantel-Haenszel test.

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

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(Serious) adverse events

	SHPF (N = 22)	VHPF (N = 22)
Any adverse event, k[1], n (%)[2]	34, 16 (72.7%)	23, 12 (54.5%)
Any related adverse event, k[1], n (%)[2] • **Vomiting** • **Procedural vomiting**	3, 3 (13.6%) 1, 1 (2.3%) 2, 2 (9.1%)	0, 0 (0.0%)
Any serious adverse event, k[1], n (%)[2]	7, 6 (27.3%)	8, 5 (22.7%)
Any related serious adverse event, k[1], n (%)[2]	0, 0 (0.0%)	0, 0 (0.0%)

[1]number of events. [2]number of subjects with one or more events;

No clinically relevant differences as concluded by medical monitor in:

- (Serious) Adverse Events
- Liver function: Alkaline phosphatase, ALAT, ASAT, GGT and ammonia
- Kidney function: Creatinine and BUN

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Conclusions Protill Study

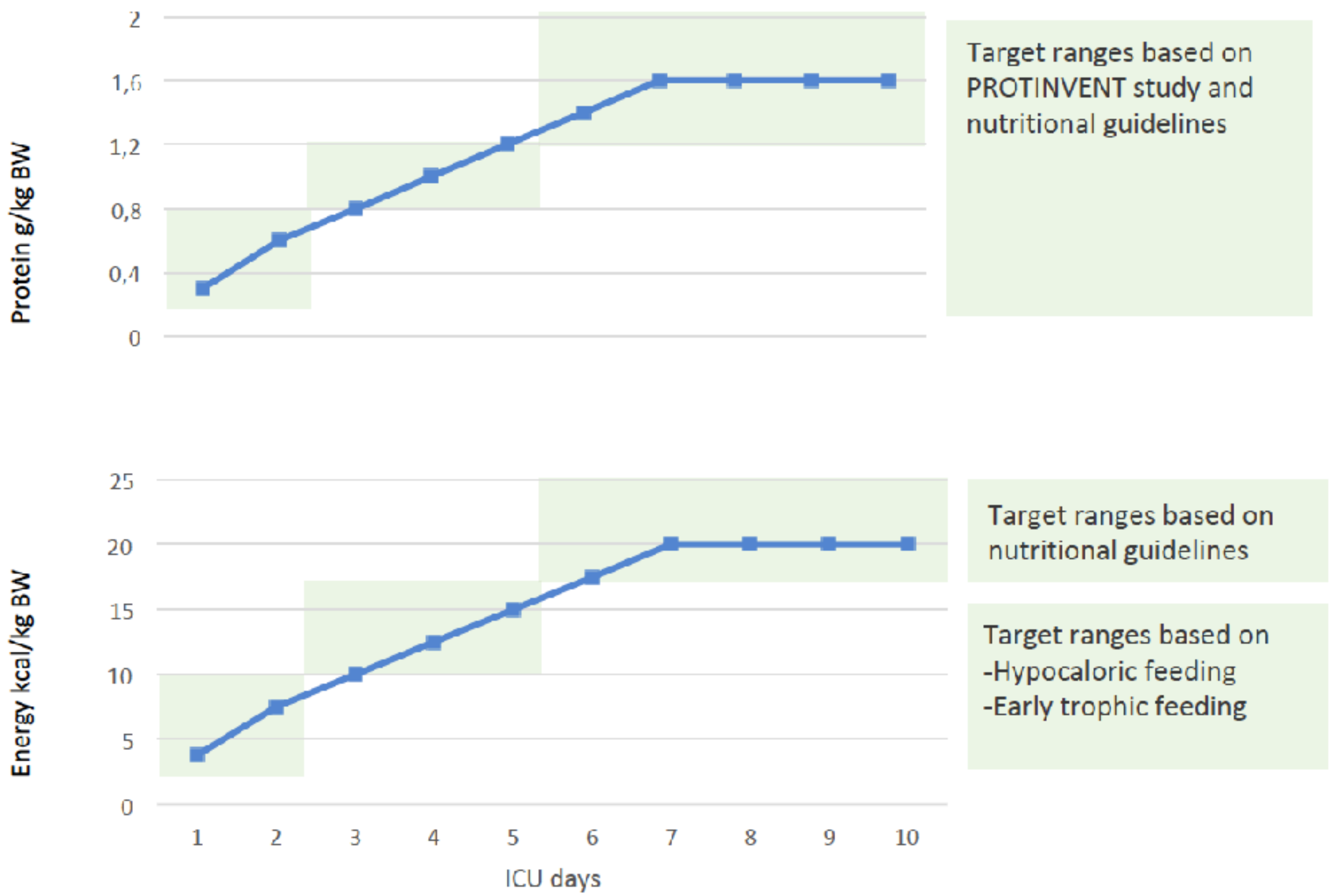
First trial comparing very high protein (8 g/100 ml) with standard high protein enteral formula (5 g/100 ml) based on intact proteins showing:

- Protein provision according to recommendations is feasible with a polymeric enteral nutrition formula
- No signs of increased intolerance or adverse events
- No risk of overfeeding
- Increased amount of protein provided is absorbed and available as substrate for protein synthesis

Van Zanten AR et al Crit Care. 2018 Jun 12;22(1):156.

Feeding regimen with new very high protein product

(1.25 kcal/ml, 8 g protein/100 kcal)



Volume (ml)										
/kg BW	3	6	8	10	12	14	16	16	16	16
75 kg patient	225	450	600	750	900	1050	1200	1200	1200	1200

Feeding protocol

Protein intake target
1.2 – 2.0 g/kg bw: ASPEN

Protein intake target
>1.3 g/kg bw: ESPEN

energy intake target
80 -100 % of 20 – 25 kcal/kg bw

As target achieved during EN is only 80-85% set targets high enough to meet the 1.3 g/kg bw for example 1.5-1.6 g/kg per dag

Van Zanten AR et al 2018 Response letter Critical Care

Ziekenhuis Gelderse Vallei

Muscles protein synthesis and exercise

High-protein diet alone is not enough

X

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Early mobilization in ICU patients

Ziekenhuis Gelderse Vallei

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]

Unable 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.

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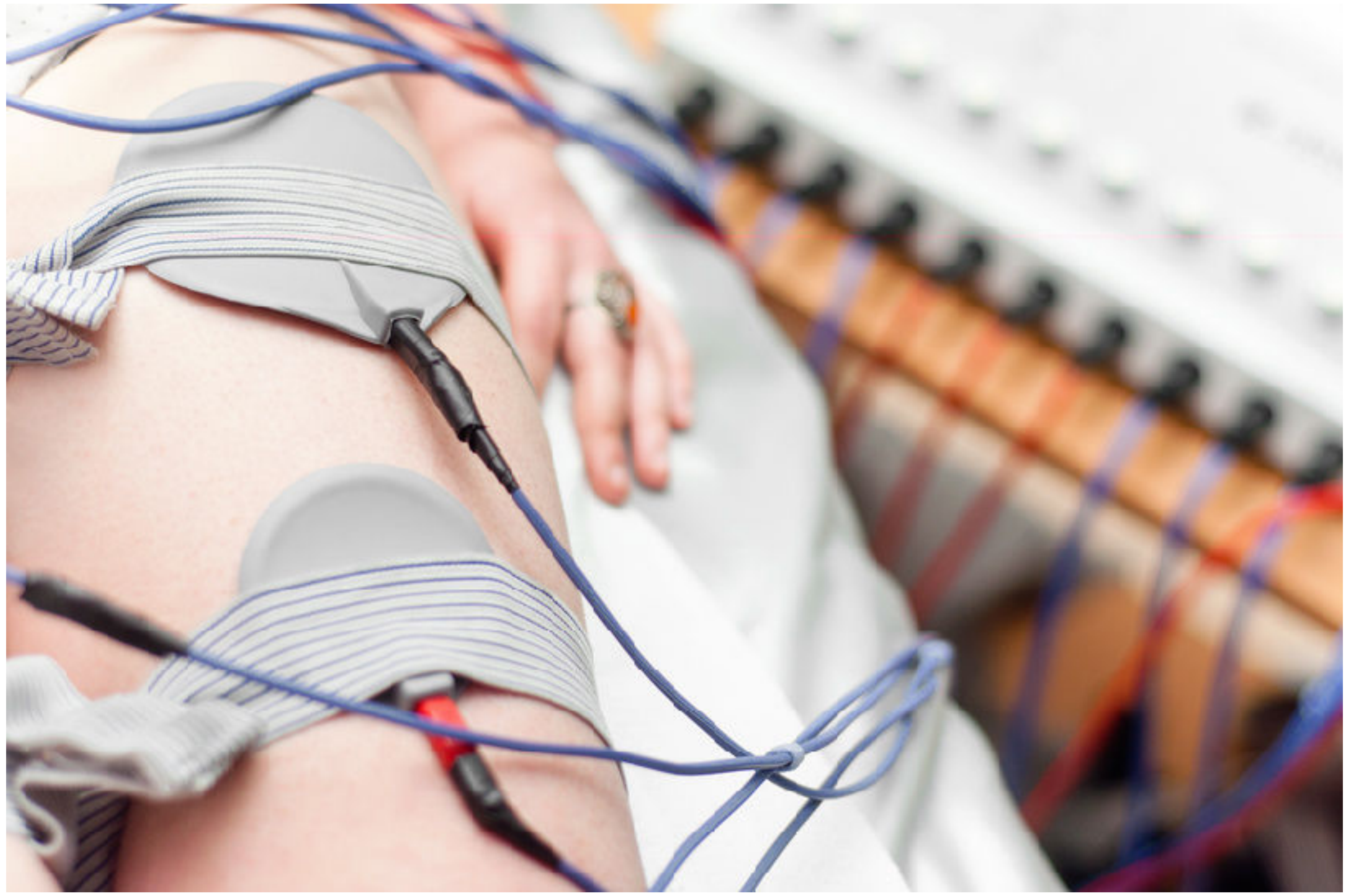
Exercise in ICU patients: bed cycling and electrostimulation



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Journal of Critical Care 50 (2019) 287–295

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

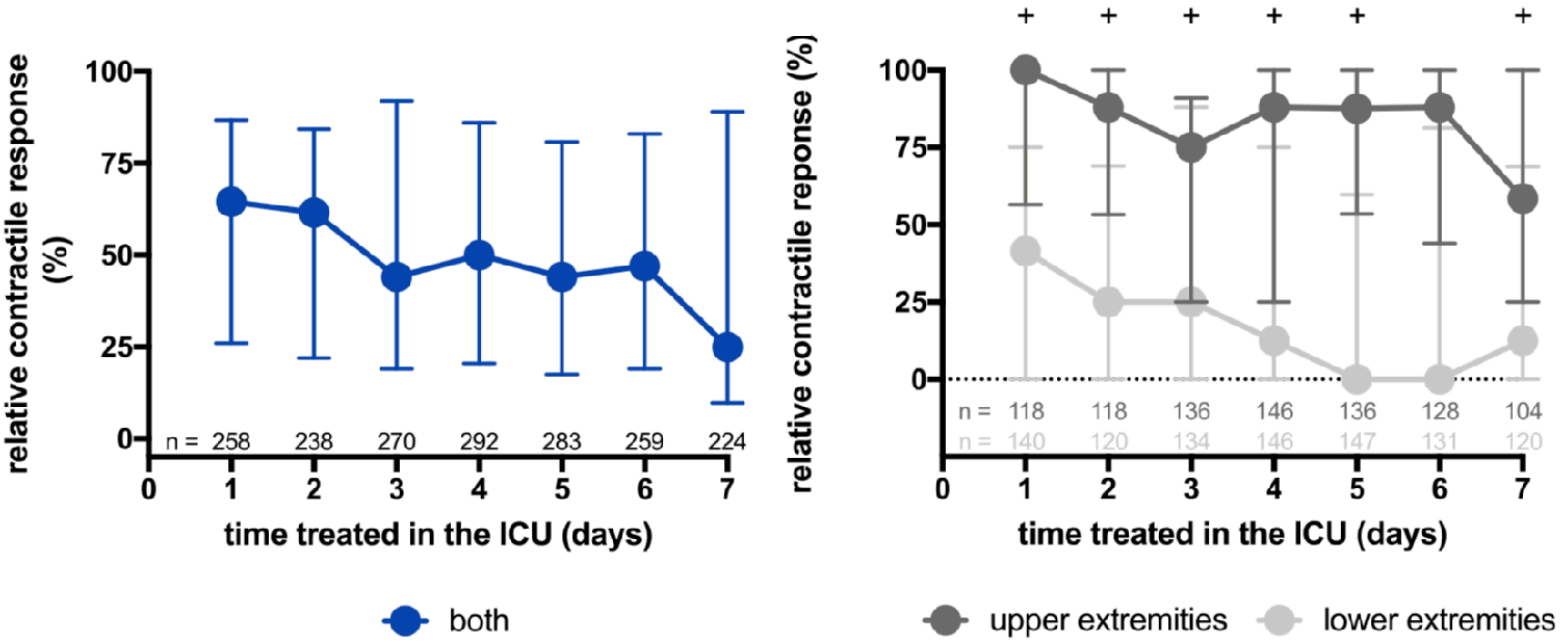
Interventions for the management and prevention of sarcopenia in the critically ill: A systematic review

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.

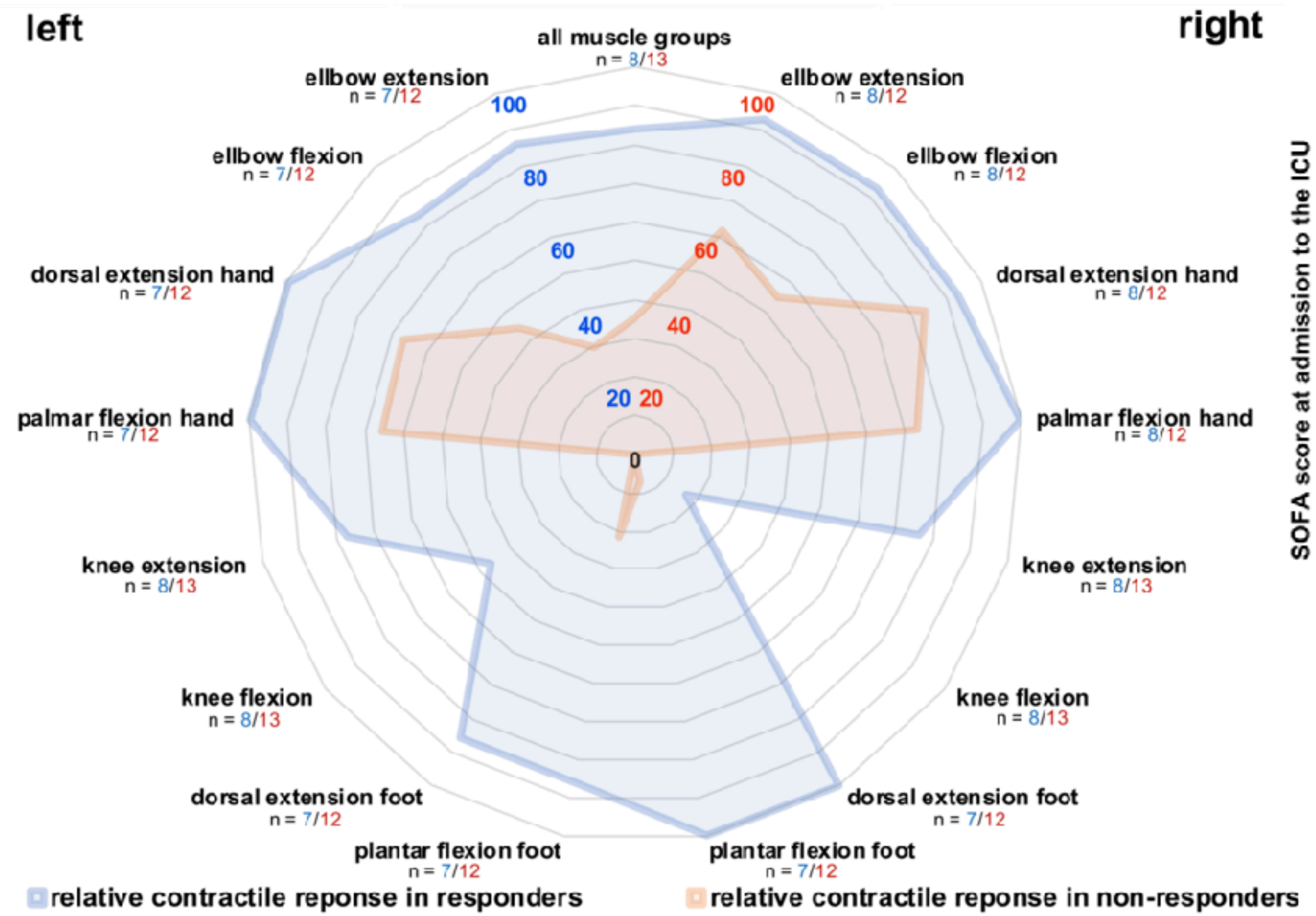
Differential contractile response to NMES in ICU patients



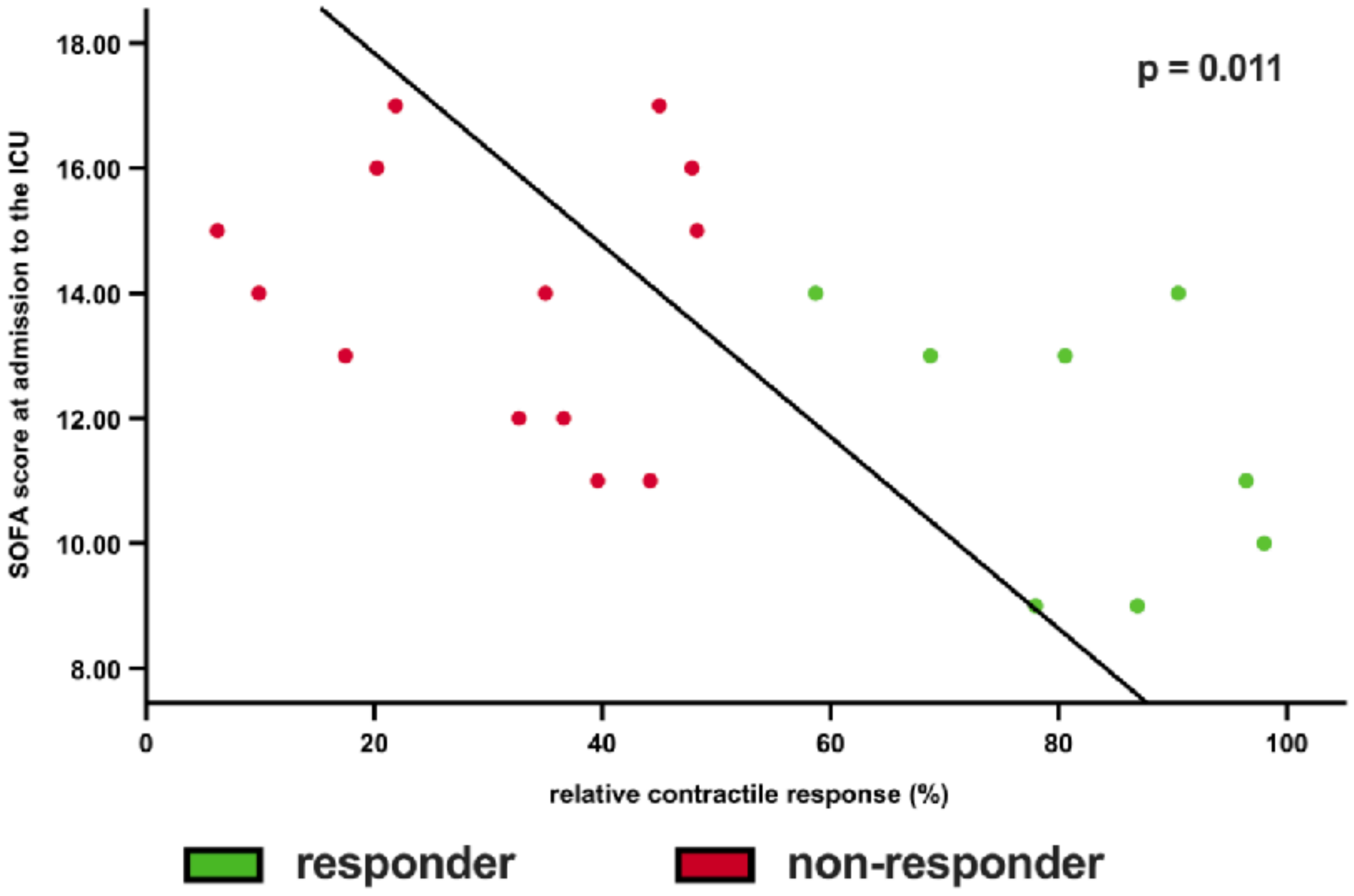
Grunow JJ et al. Crit Care 2019; 23:308

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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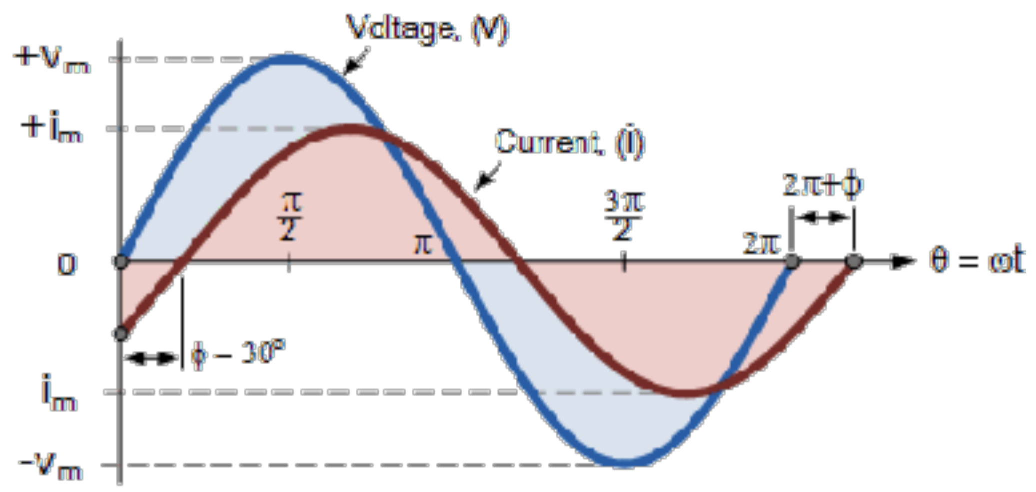
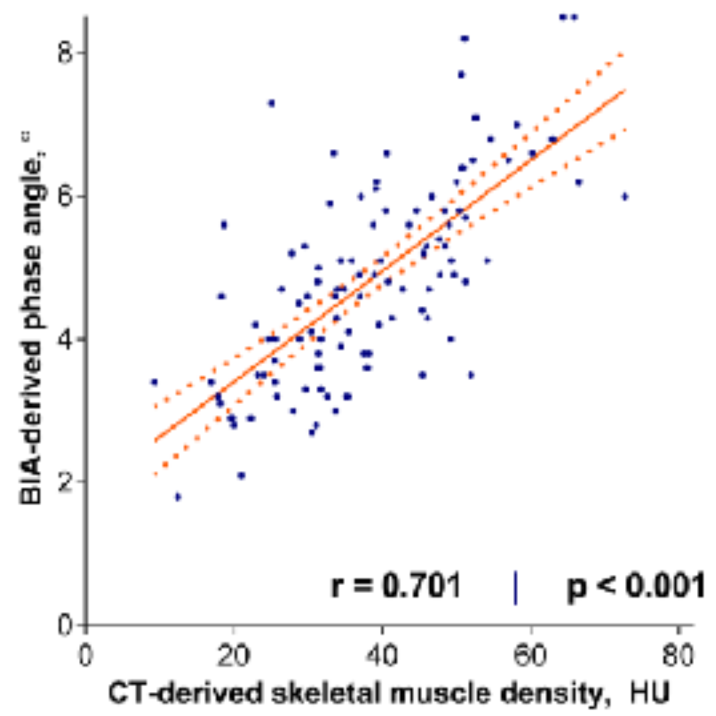
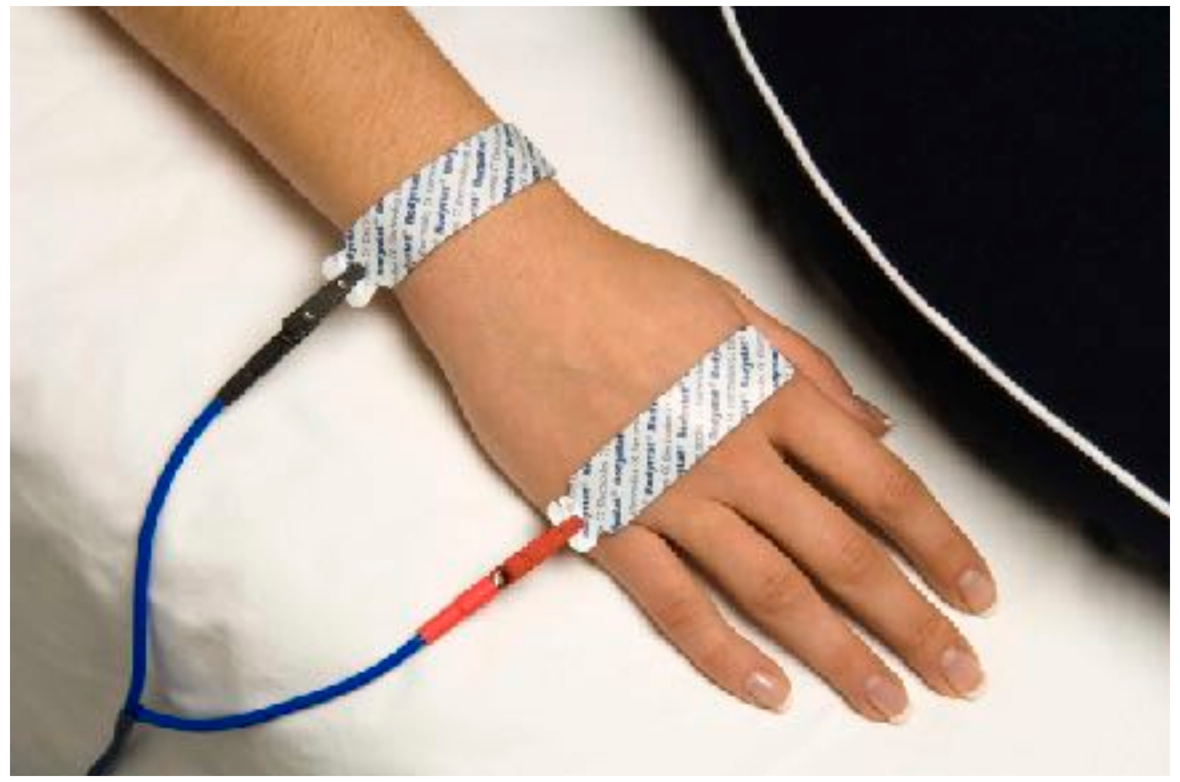
How to monitor the effect of proteins and AA in critical illness?

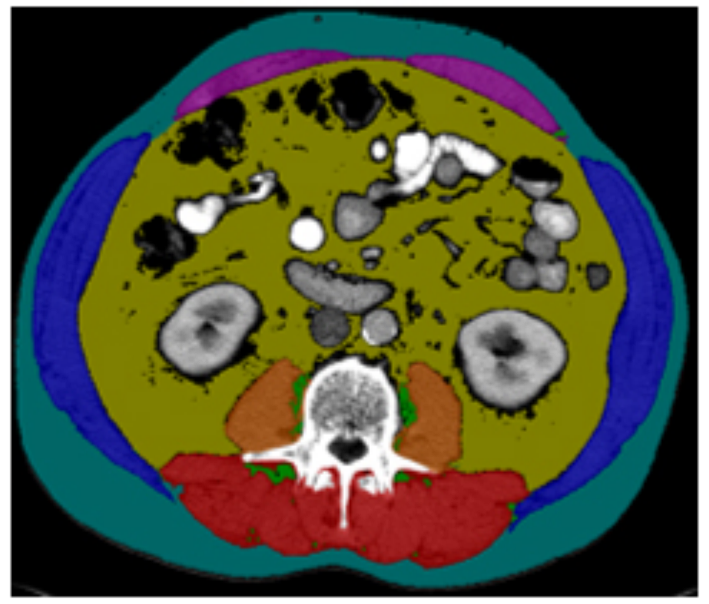




BIA
Phase angle

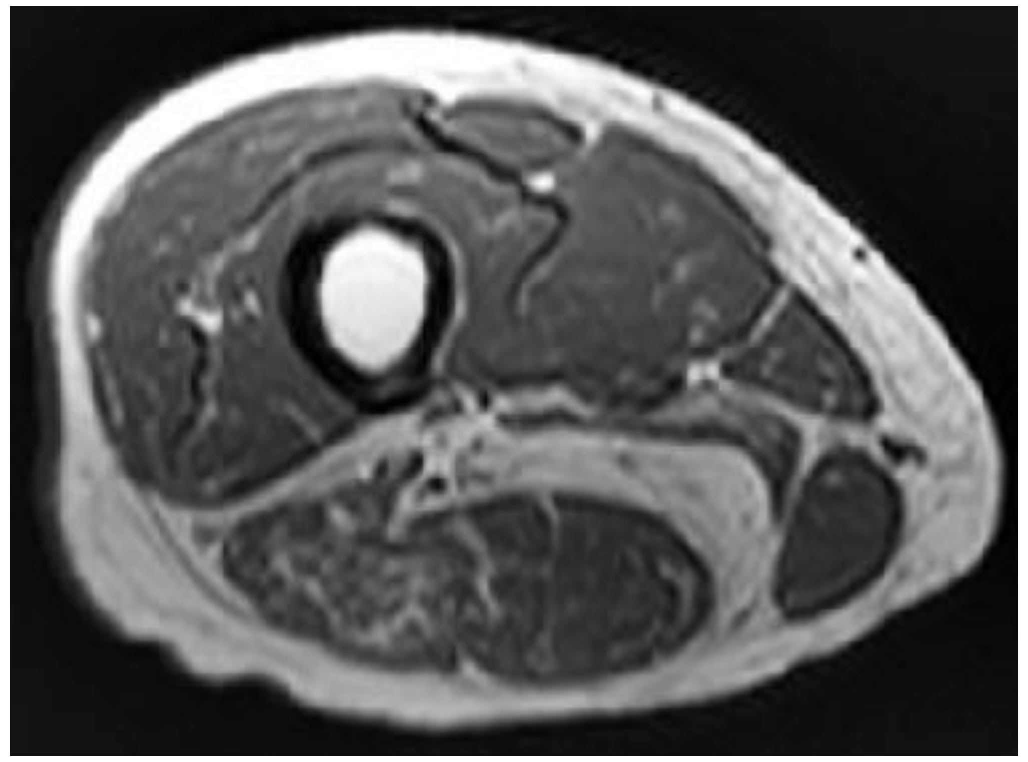


CT scan



N-balance

MRI

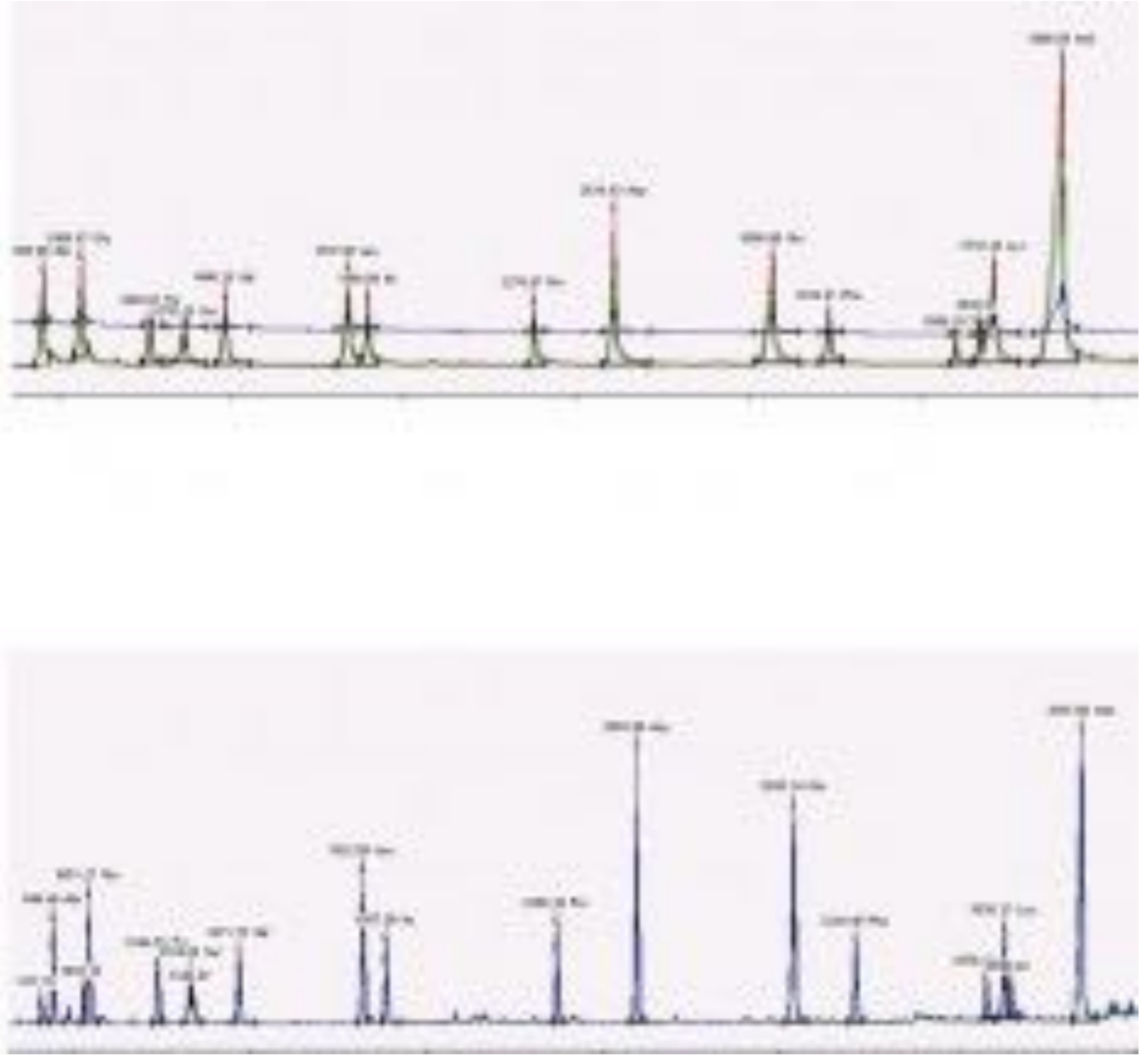


hand grip strength

muscle ultrasound

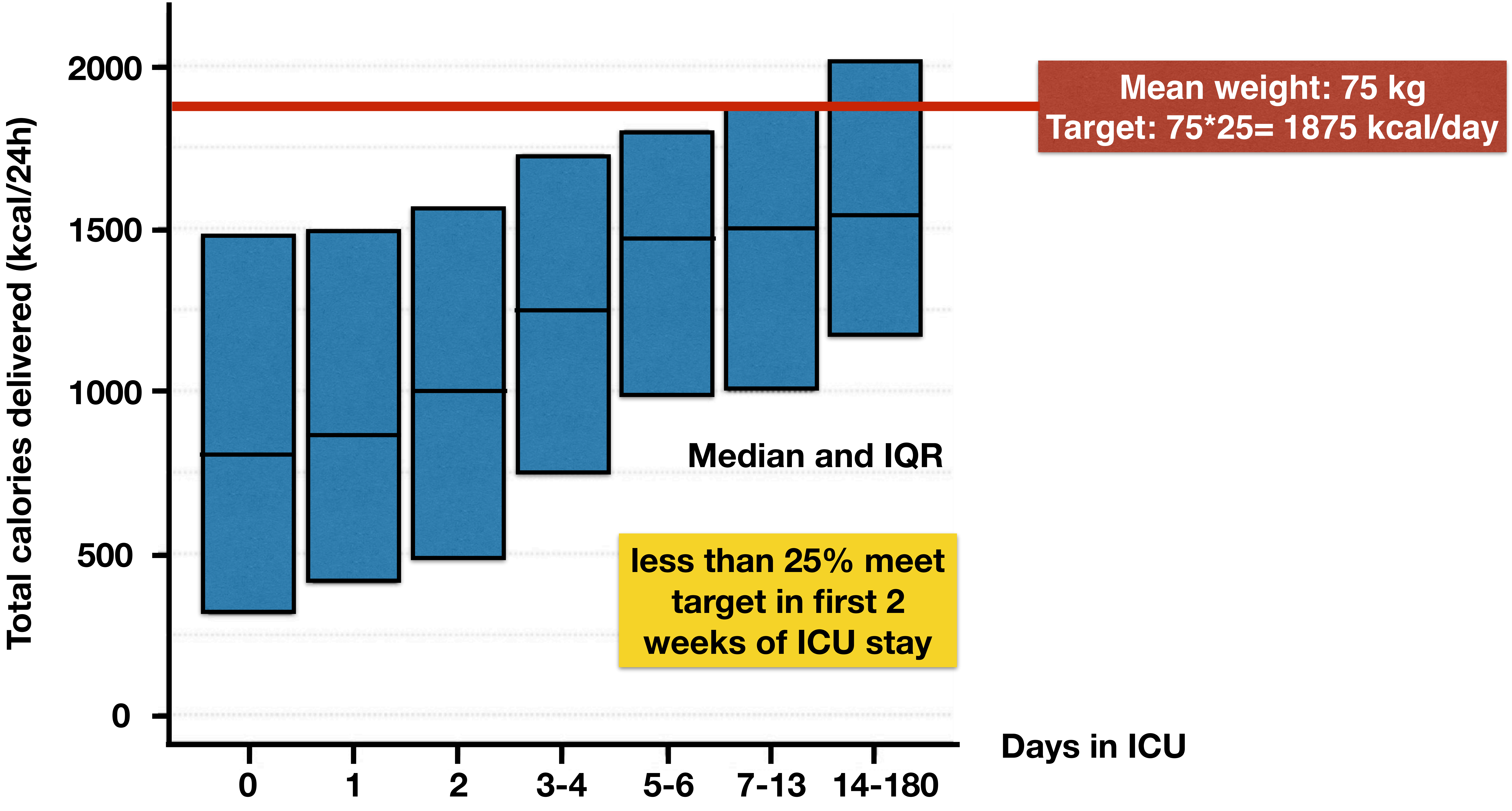
muscle biopsy

Protein turnover studies using stable isotopes



Original article

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



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

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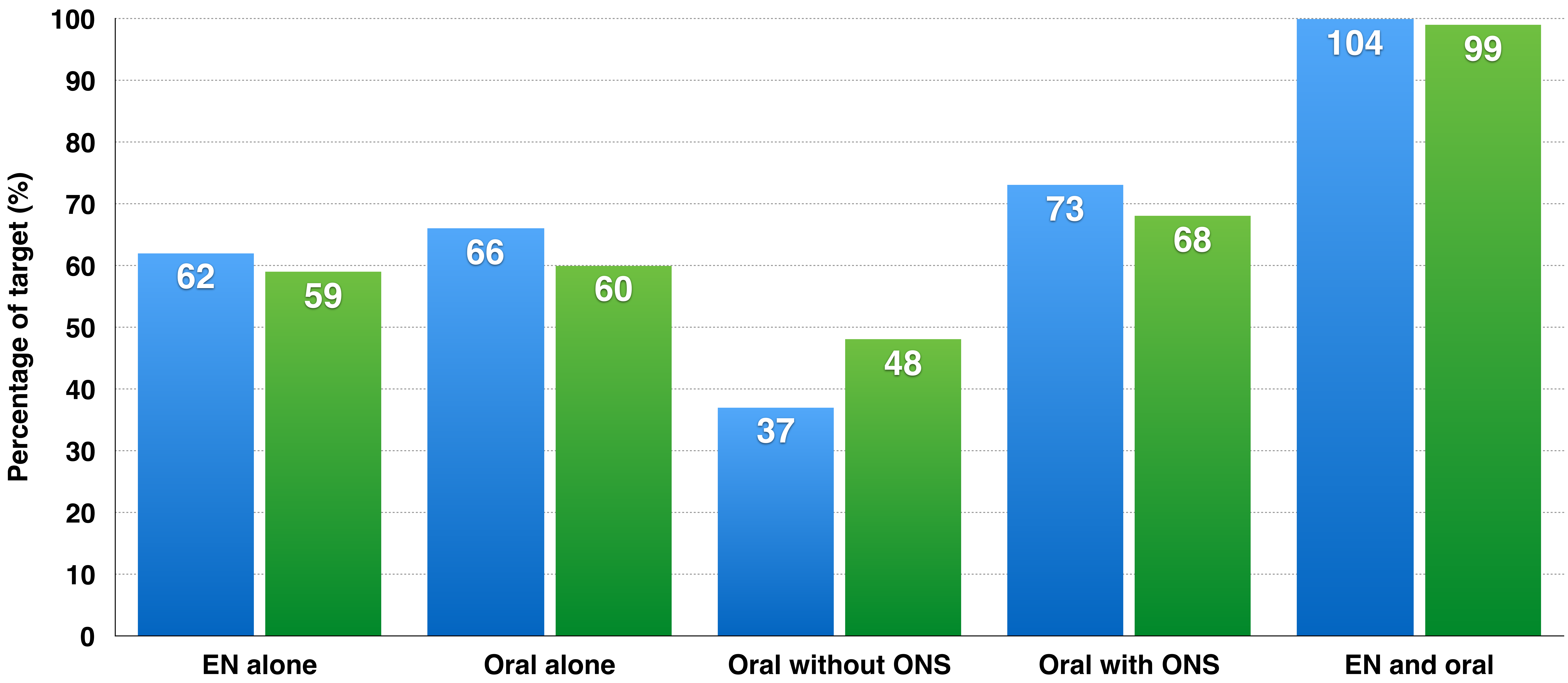
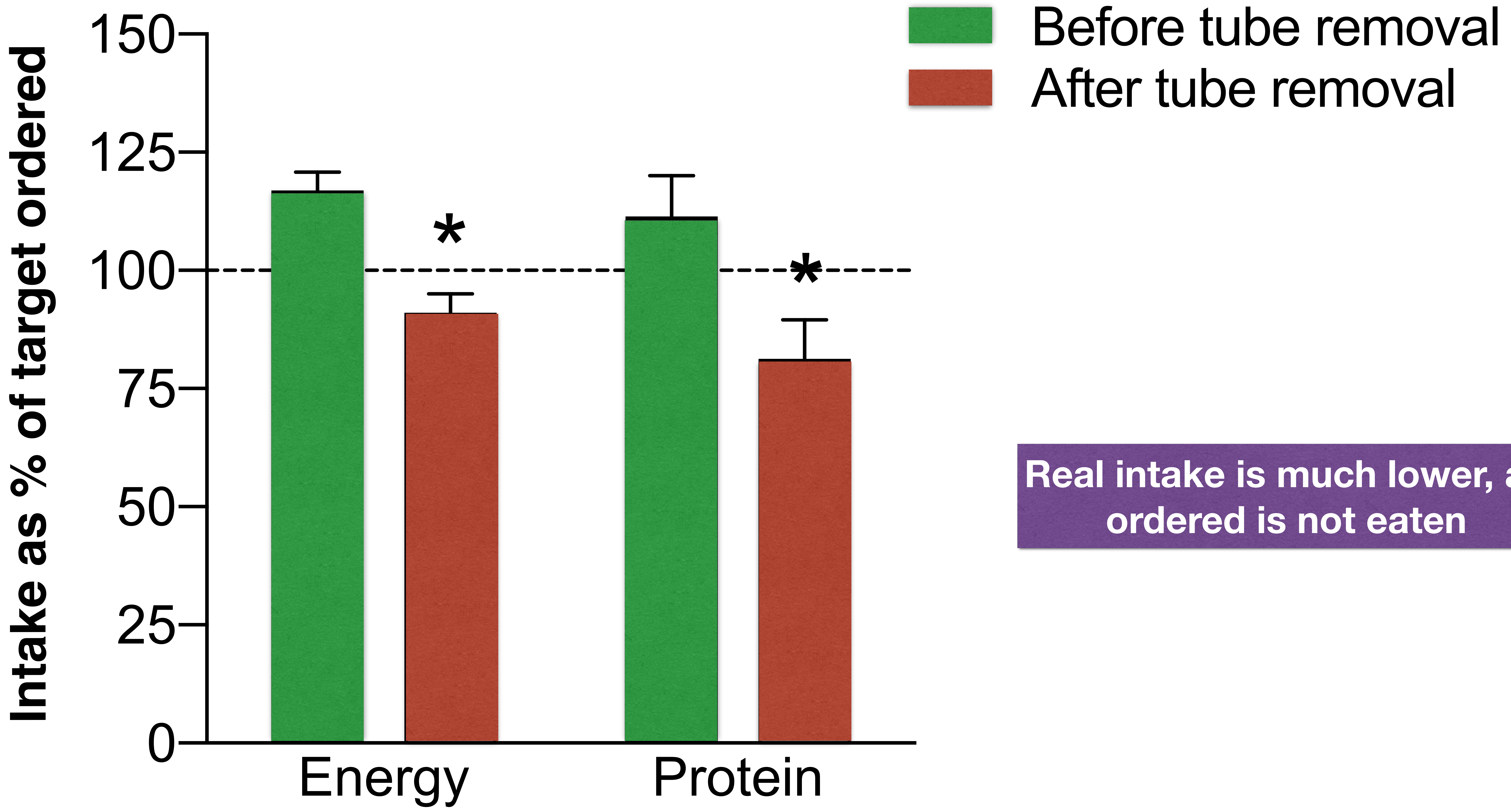
Post-ICU nutrition: percentage of target achieved



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

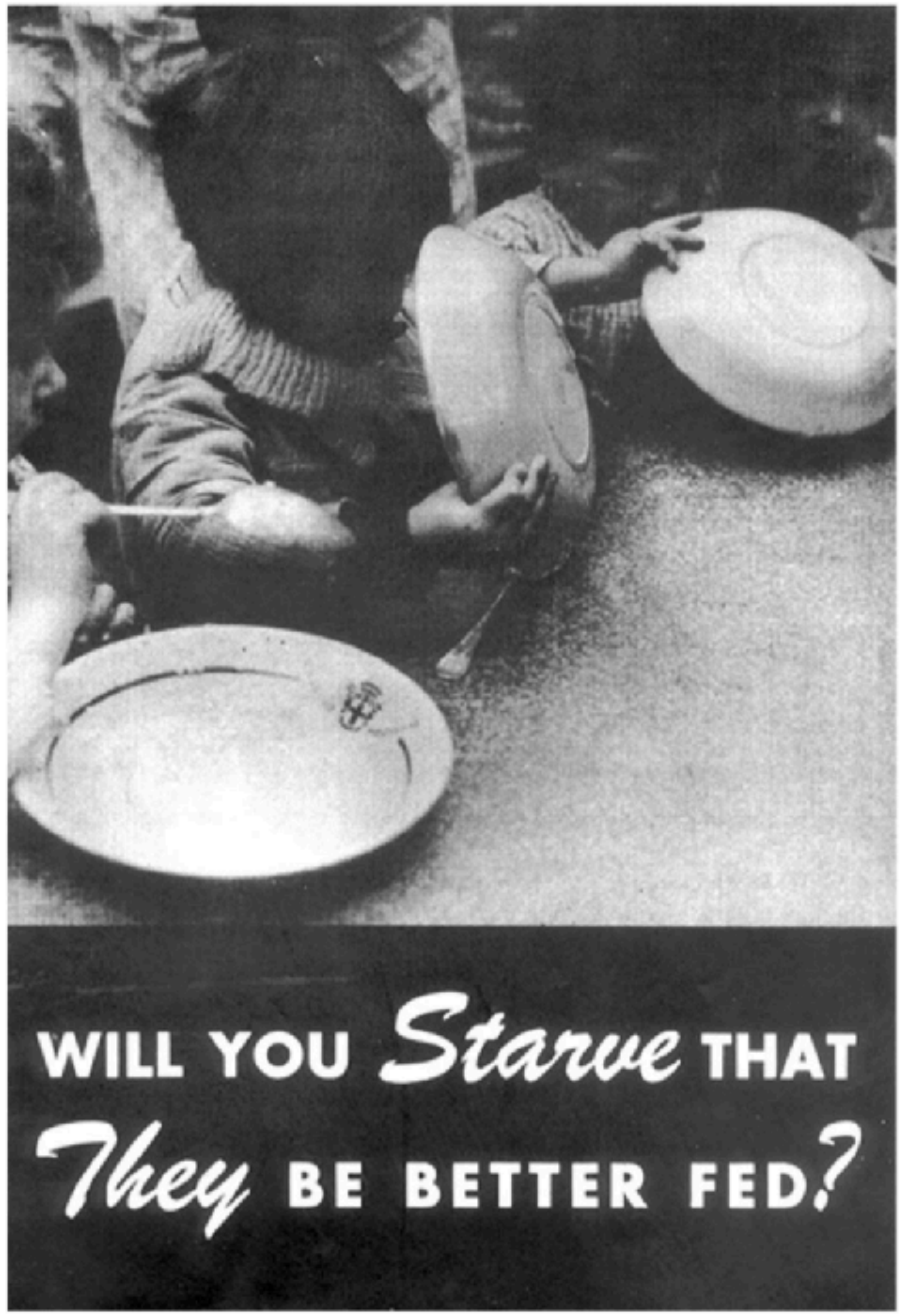
Removal of the feeding tube confers an acute drop in energy and protein intake of around 25-35%/day post-ICU



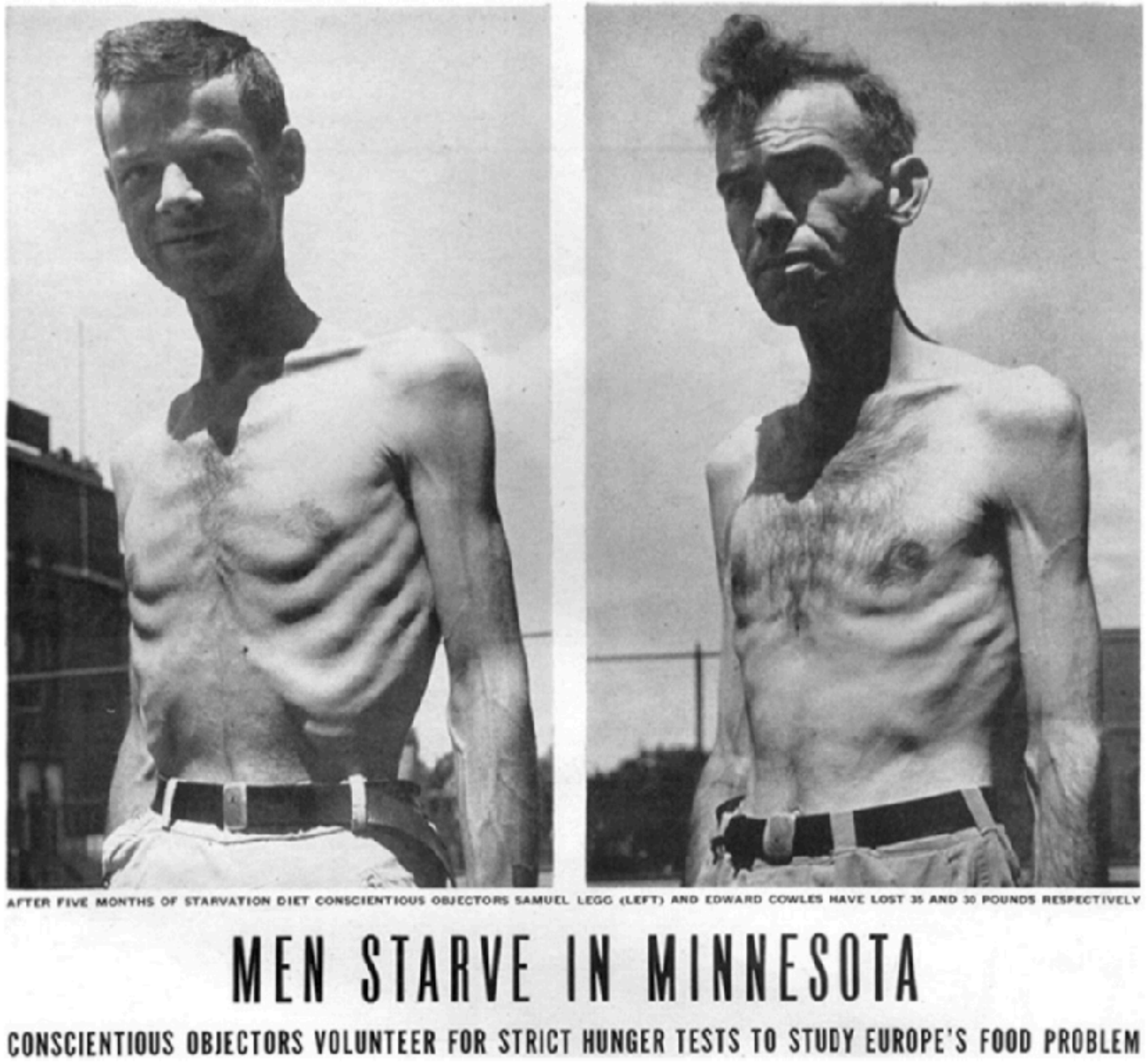
Real intake is much lower, as ordered is not eaten

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

How much food to recover?



Starvation period:
1800 kcal/dag



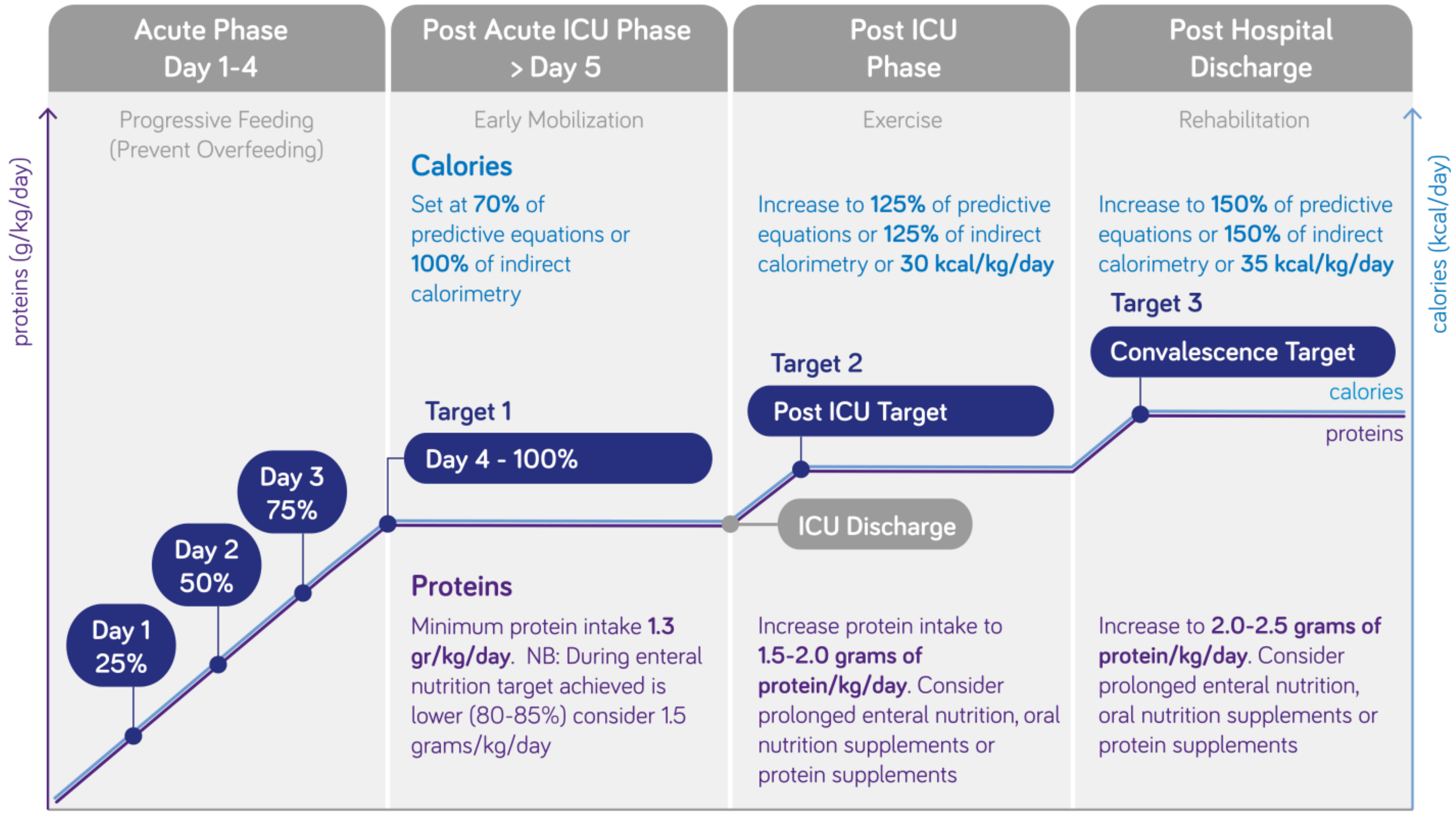
Wischmeyer Critical Care 2017, 21(Suppl 3):316

Minnesota starvation project

Starvation period:
1800 kcal/day

During 1 year:
2-2.5 g/kg/d (3x normal)
4000-4500 kcal/d (2-3x normal)

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



Acute Phase
Day 1-4
Post Acute ICU Phase
> Day 5
Post ICU
Phase
Post Hospital
Discharge
Progressive Feeding
(Prevent Overfeeding)
Early Mobilization
Exercise
Rehabilitation
proteins (g/kg/day)
calories (kcal/day)
Calories
Set at 70% of predictive equations or 100% of indirect calorimetry
Increase to 125% of predictive equations or 125% of indirect calorimetry or 30 kcal/kg/day
Increase to 150% of predictive equations or 150% of indirect calorimetry or 35 kcal/kg/day
Target 3
Convalescence Target
Target 2
Post ICU Target
Target 1
Day 4 - 100%
calories
proteins
Day 3
75%
Day 2
50%
Day 1
25%
ICU Discharge
Proteins
Minimum protein intake 1.3 gr/kg/day. NB: During enteral nutrition target achieved is lower (80-85%) consider 1.5 grams/kg/day
Increase protein intake to 1.5-2.0 grams of protein/kg/day. Consider prolonged enteral nutrition, oral nutrition supplements or protein supplements
Increase to 2.0-2.5 grams of protein/kg/day. Consider prolonged enteral nutrition, oral nutrition supplements or protein supplements

Ziekenhuis Gelderse Vallei

Zanten *et al. Critical Care* (2019) 23:368
https://doi.org/10.1186/s13054-019-2657-5

Critical Care

REVIEW Open Access

Nutrition therapy and critical illness: practical guidance for the ICU, post-ICU, and long-term convalescence phases

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Conclusions

- **Low protein intake during ICU stay and early caloric overfeeding is associated with increased mortality**
- **Early high protein (and caloric) intake is associated with higher 6-month mortality, whereas day 4-7 high protein intake is associated with lower mortality**
- **Protein dose should be increased over time and during the phases of critical illness**

Ziekenhuis Gelderse Vallei

Conclusions

- **ESPEN guideline 2018: Gradual progressing to target over 3-5 days is recommendable both for energy and proteins**
- **ESPEN guideline 2018: after this phase protein intakes >1.3 g/kg/day are essential to improve outcome.**
- **NB: target achieved with EN is 80-85%, aim for 1.5 g/kg/day**
- **New very-high protein enteral and parenteral feeds are available to start, and advance feeding over days, meeting guideline recommendations for protein intake during critical illness, without the risk of overfeeding.**