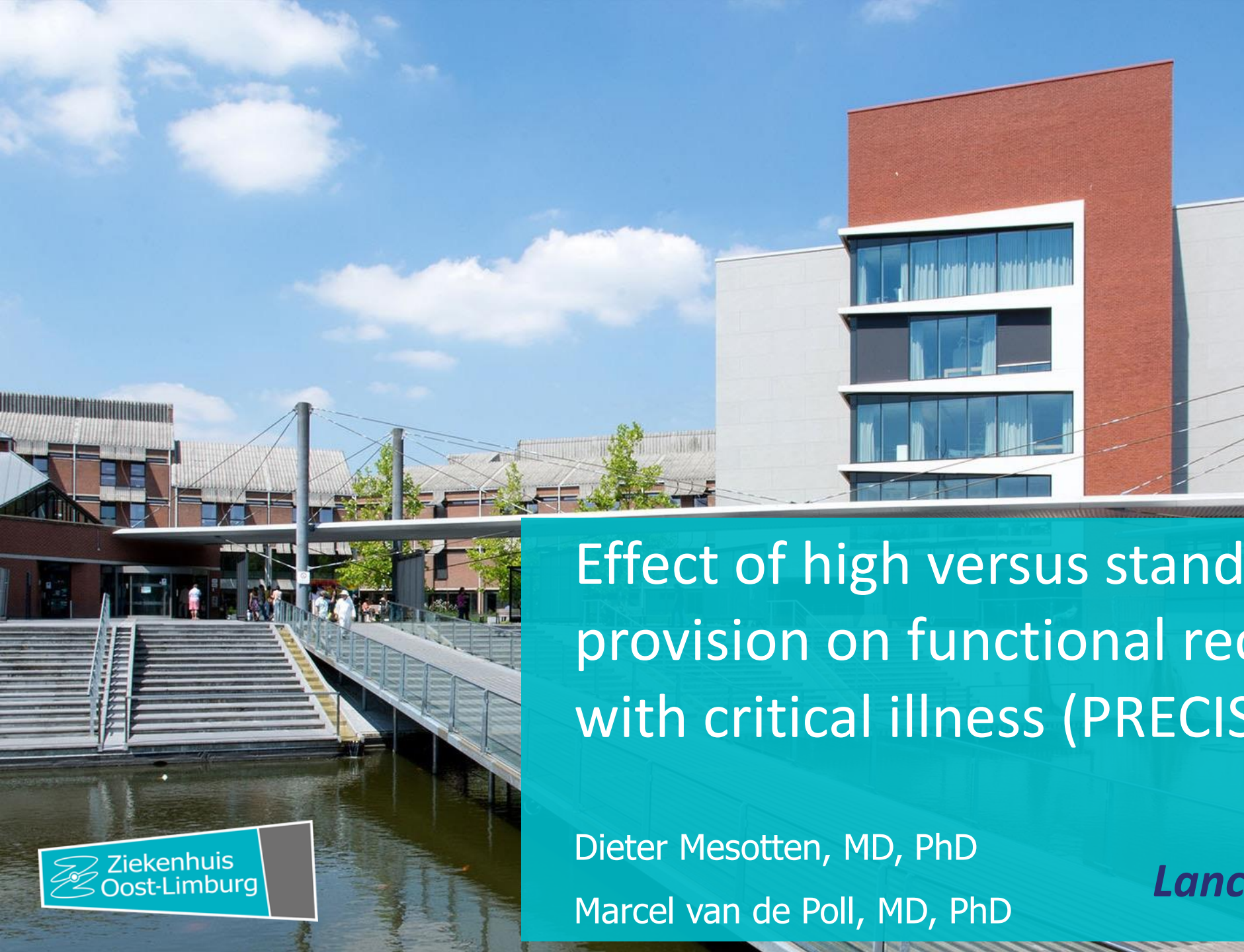




Effect of high versus standard protein provision on functional recovery in people with critical illness (PRECISE)

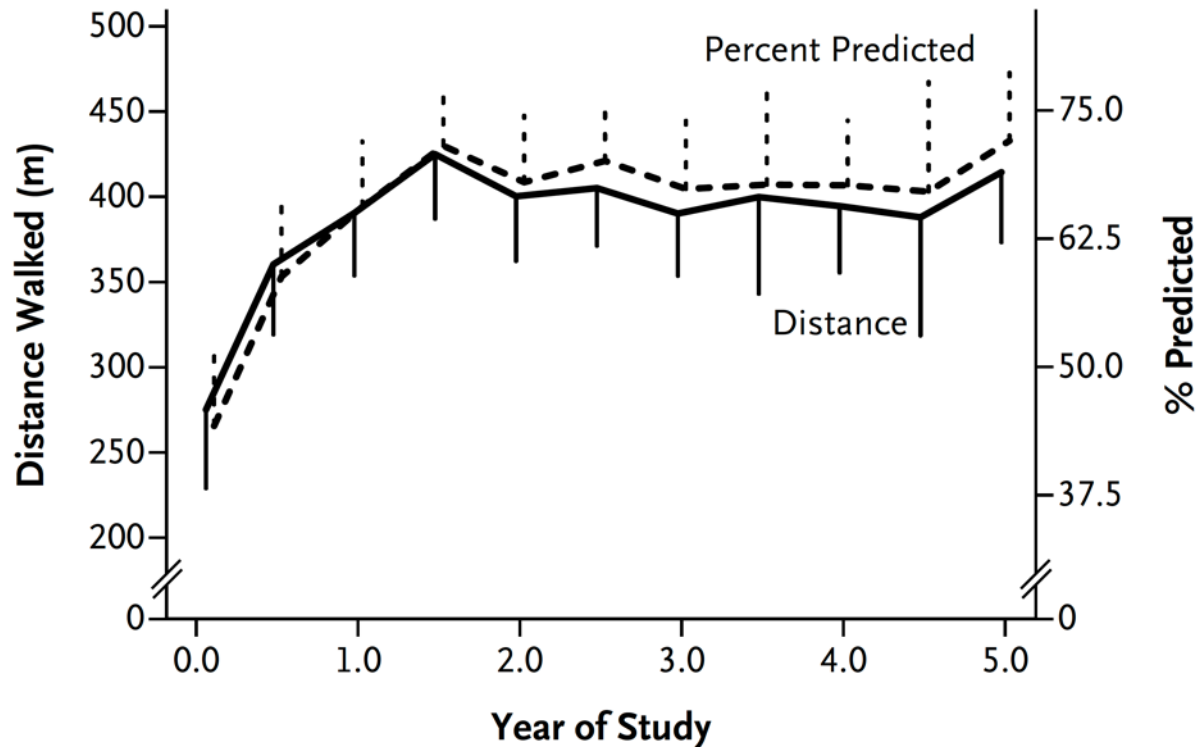
Dieter Mesotten, MD, PhD

Marcel van de Poll, MD, PhD

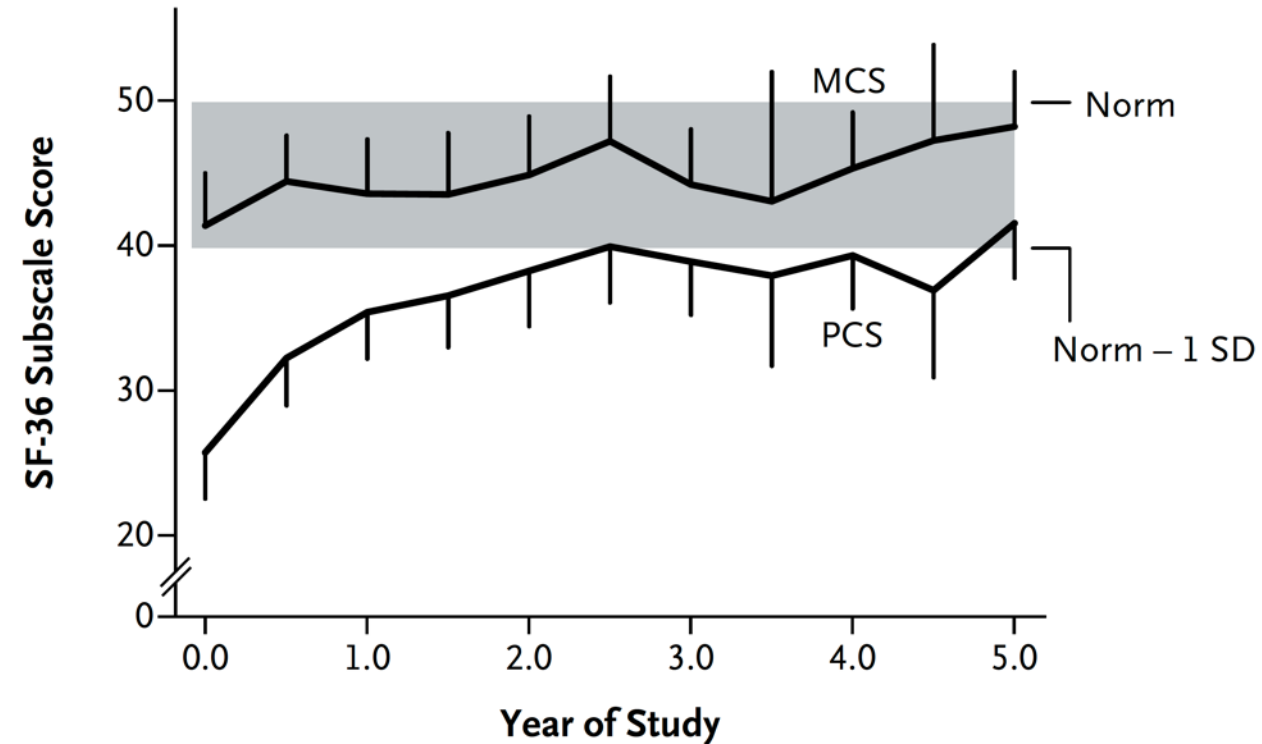
Lancet 2024;404:659-69

Functional disability after ICU admission

Functional disability

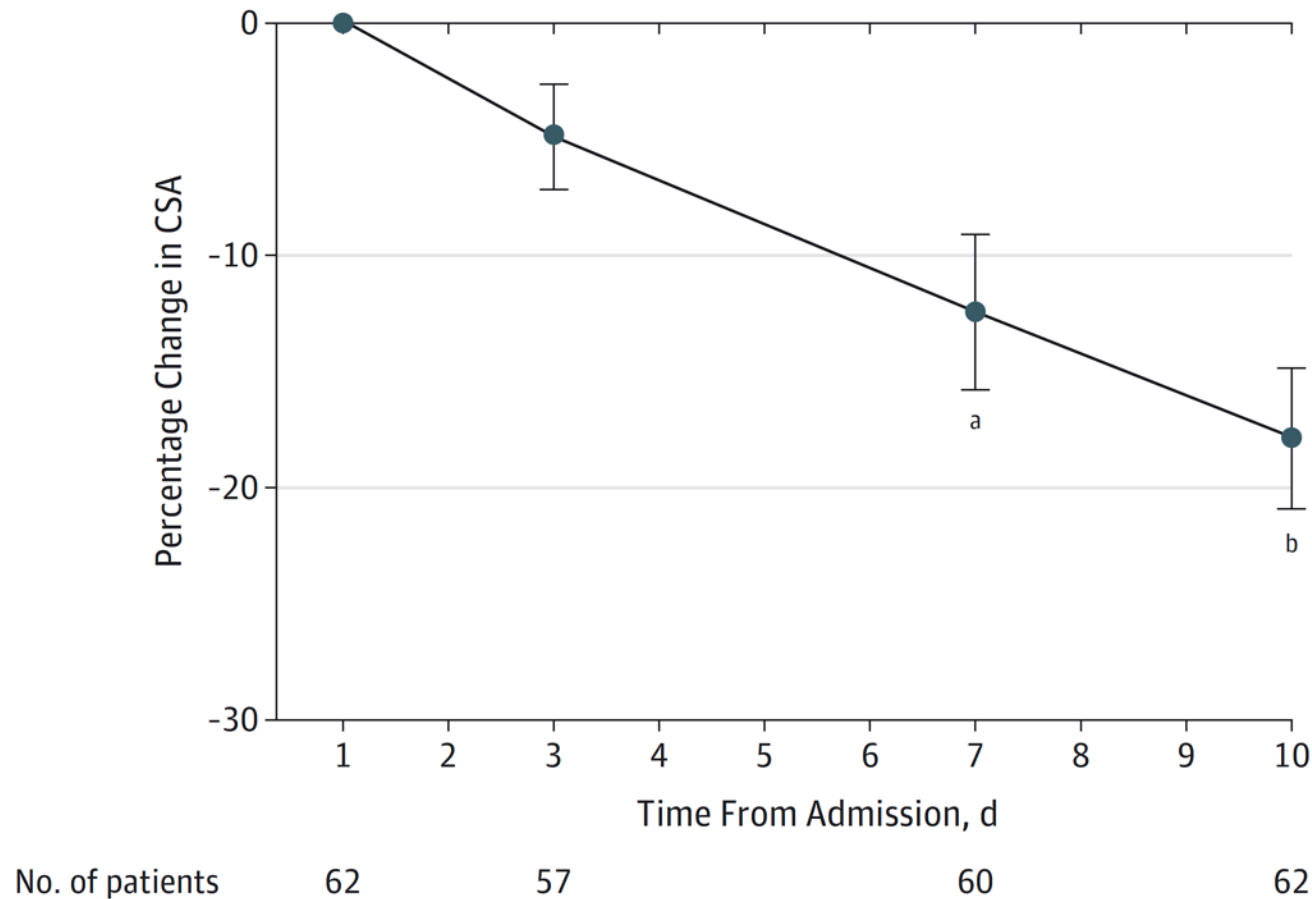


Health-related Quality of Life



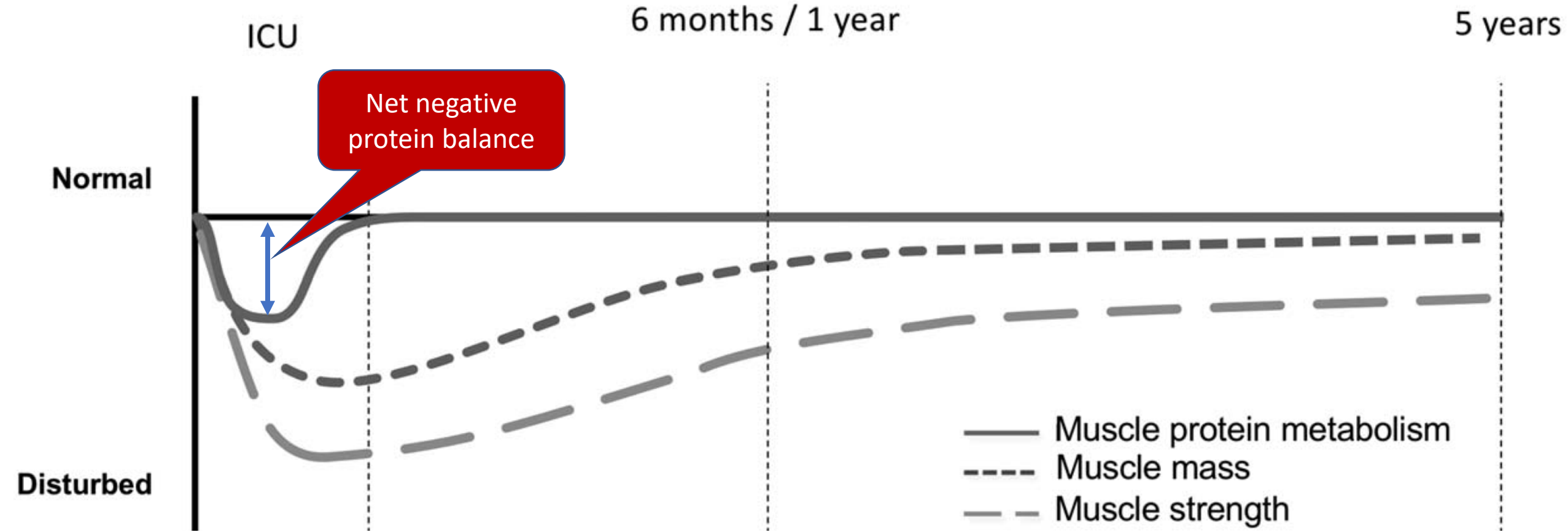
Muscle wasting during ICU admission

A Change in rectus femoris (RF) cross-sectional area (CSA) over 10 d

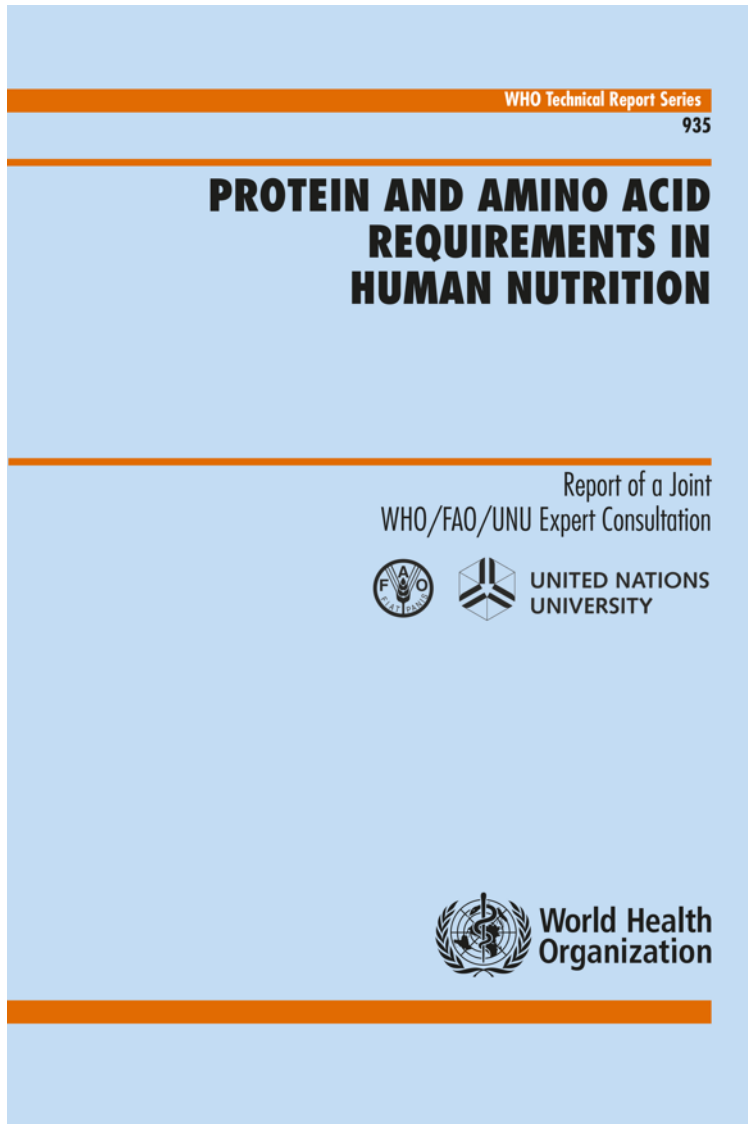


Puthuchearry et al. JAMA 2013;310:1591-600

Protein metabolism, muscle wasting and functional recovery



Recommended Dietary Allowance (WHO)



0.83 g/kg/day

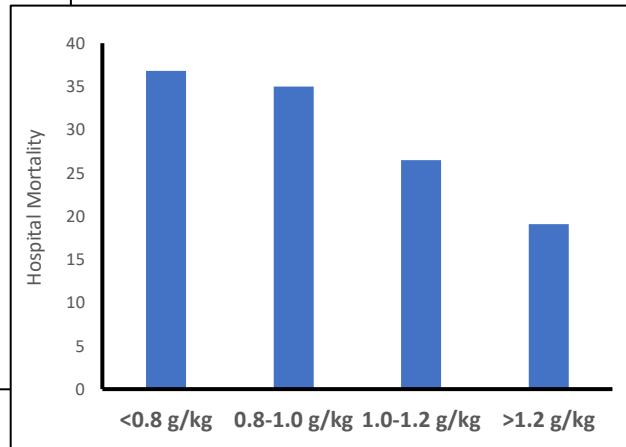
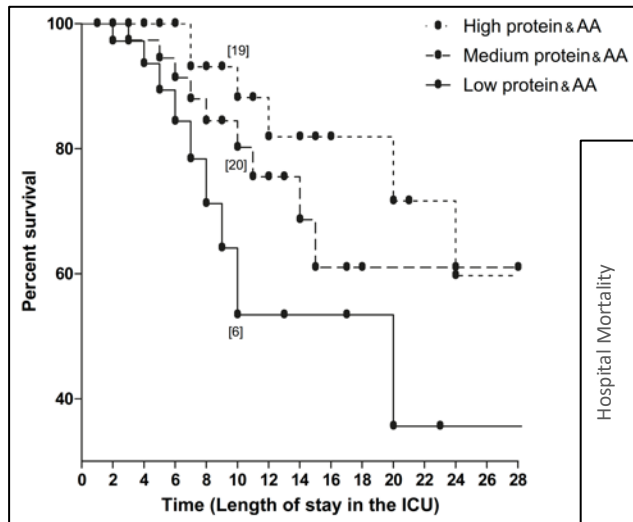
<https://iris.who.int/handle/10665/43411>

Guideline recommendations ICU patients



(2016/2022)

1.2 – 2.0 g/kg



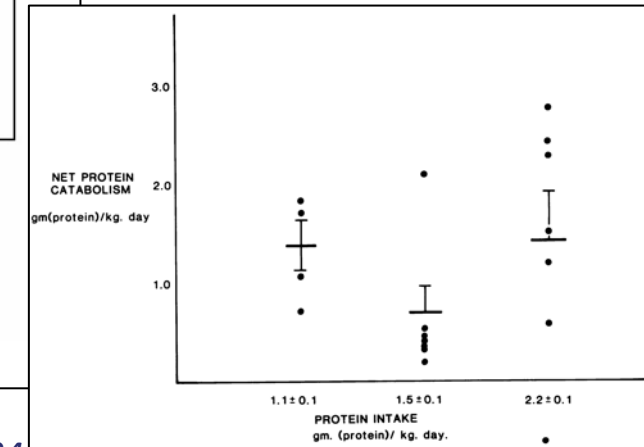
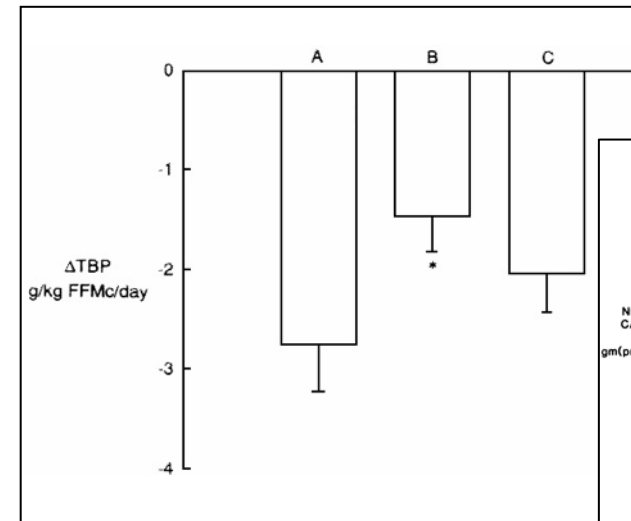
Allingstrup et al. Clin Nutr 2012;31:462-8
Weijs et al. Crit Care 2014;18:701



(2019/2023)

1.3 g/kg

(1.5 – 2.0 g/kg in trauma patients)

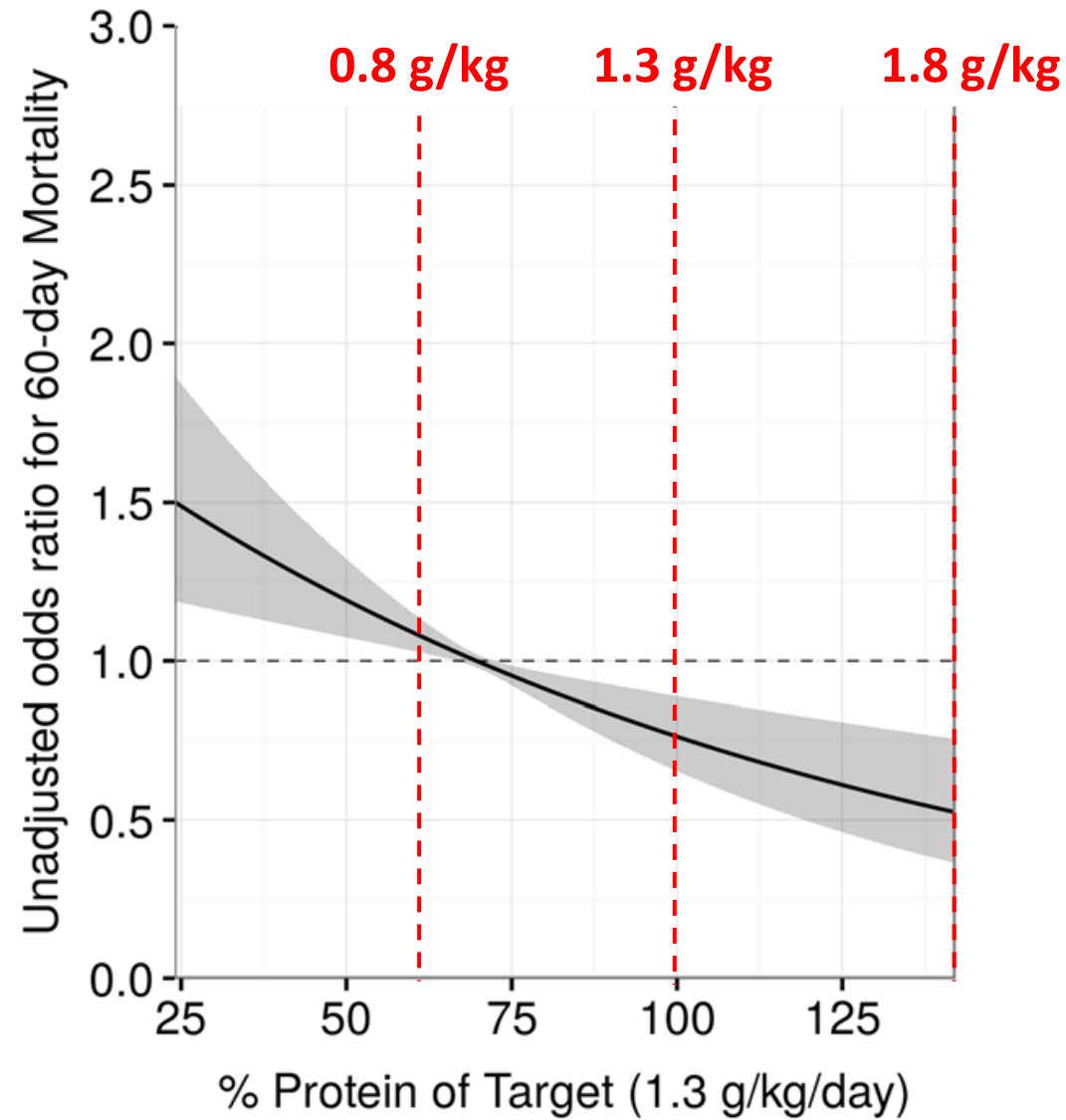


Shaw et al. Ann Surg 1987;205:288-94

Ishibashi et al. Crit Care Med 1998;26:1529-35

Larsson et al. Acta Chir Scand 1981;147:317-24

Association between protein intake and outcome



Zusman et al. Crit Care 2016;20:367

Summary background

- 1.2-1.3 g/kg protein current standard recommendation in ICU
 - *(However, no solid evidence base)*
- Observational data suggest even higher targets associated with better outcome

Protein targets in critically ill		
Low	Standard	High
0.8 g/kg/day	1.2-1.3 g/kg/day	2.0 g/kg/day
RDA (WHO)	ASPEN (low end)/ESPEN	ASPEN (high end)

Intensive care medicine research agenda in nutrition and metabolism

What is the optimal protein dose to facilitate recovery

in general and nutritionally high-risk patients in particular (mortality and physical function) and does it need to be combined with some sort of muscle use/exercise?

Table 4 Selecting the top 10 trials critical care nutrition and metabolism

Topic #	Candidate research topic	Average score
1	Effects of high vs low protein dose on (mortality and) recovery during the acute phase of critical illness	

PRotEin provision in Critical IllneSs (PRECISE)

trial

Aim

To assess whether high protein provision improves health-related quality of life and functional outcome in critical illness

- Randomised controlled

Patients

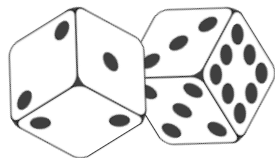
- High risk for functional disabilities
- Sufficient exposure to intervention to exert potential effect

Key inclusion criteria

- Unplanned ICU admission
- Intubation <24 hours
- Expected invasive ventilation >72 hours
- Start EN <48 hours

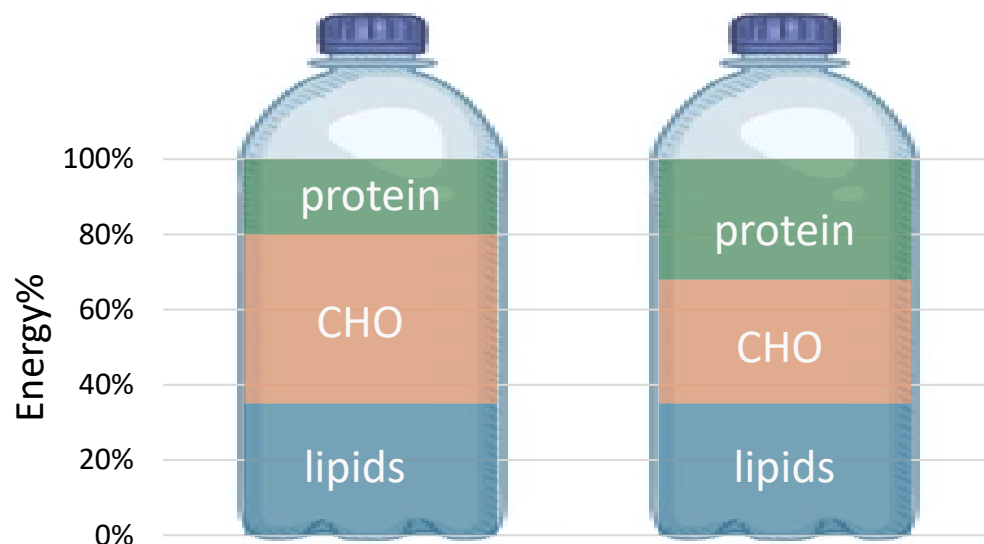
Table S2. Overview of all inclusion and exclusion criteria	
Inclusion criteria	Exclusion criteria
• Adult (18 years or above) patient admitted to ICU • Unplanned ICU admission • Invasive, mechanical ventilation initiated < 24 hours following ICU admission • Expected ICU stay on ventilator support of three days or more	• Contraindication to enteral nutrition • Moribund or withholding of treatment • Kidney failure AND a no dialysis code on ICU admission • Hepatic encephalopathy (West Haven grade 3–4) • Body-mass index < 18 kg/m²

Procedures



Standard Protein

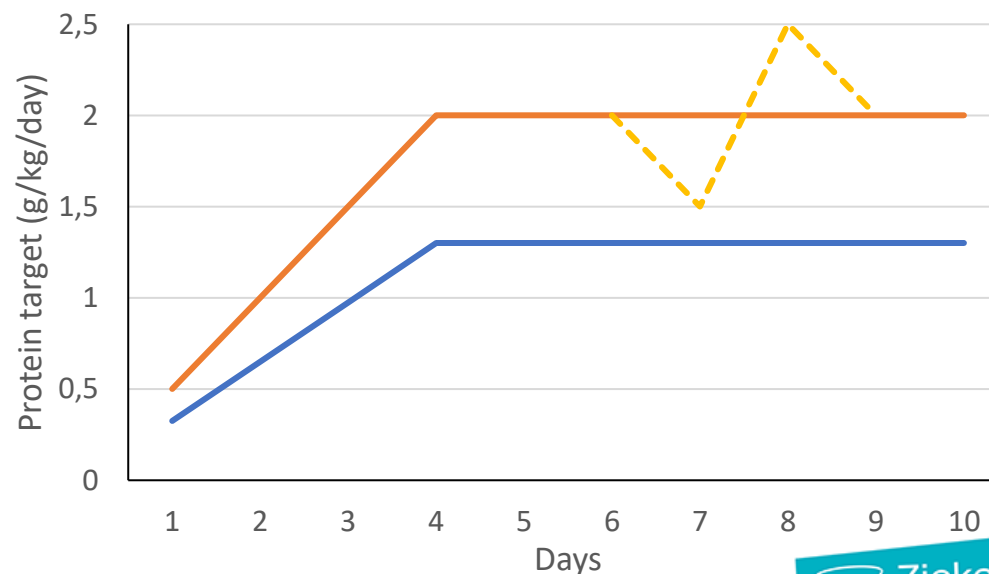
High Protein



- Blinded isocaloric enteral feeds

- **Volume based protocol**

- 25 kcal/kg/day
- 1.3 vs. 2.0 g/kg protein/day
- Progressive dosing (100% from day 4 onwards)
- Until cessation of enteral feeding within ICU (max 90 days)
- “Catch up feeding”



Outcomes

- **Primary**

- Health related quality of life over 180 days (30, 90, 180 days)
 - EuroQoL-5D-5L Health Utility Score

- **Secondary (a.o.)**

- Overall survival over 180 days
- Physical function
 - Handgrip strength
 - MRC-SUM score
 - 6 minute walking test

- **Tertiary (a.o.)**

- Time-to-discharge alive

ORIGINAL ARTICLE

Core Outcome Measures for Clinical Research in Acute Respiratory Failure Survivors

An International Modified Delphi Consensus Study

Dale M. Needham^{1,2,3}, Kristin A. Sepulveda^{1,2}, Victor D. Dinglas^{1,2}, Caroline M. Chessare^{1,2}, Lisa Aronson Friedman^{1,2}, Clifton O. Bingham III^{4,5}, and Alison E. Turnbull^{1,2,6}

¹Outcomes After Critical Illness and Surgery Group, ²Division of Pulmonary and Critical Care Medicine, School of Medicine, ³Department of Physical Medicine and Rehabilitation, School of Medicine, ⁴Division of Rheumatology, School of Medicine, ⁵Division of Allergy and Clinical Immunology, School of Medicine, and ⁶Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland

Needham et al. AJRCCM 2017;196:1122–30

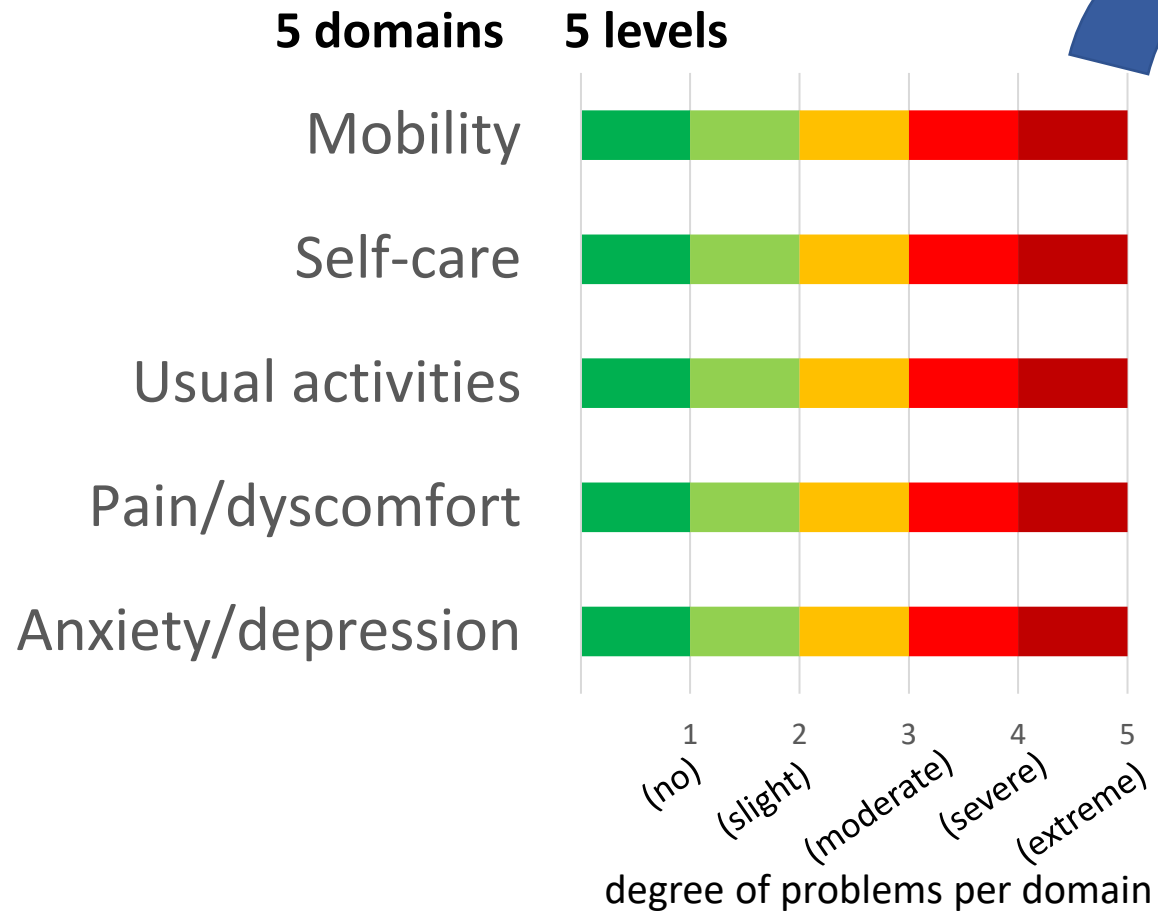


The effect of higher protein dosing in critically ill patients with high nutritional risk (EFFORT Protein): an international, multicentre, pragmatic, registry-based randomised trial

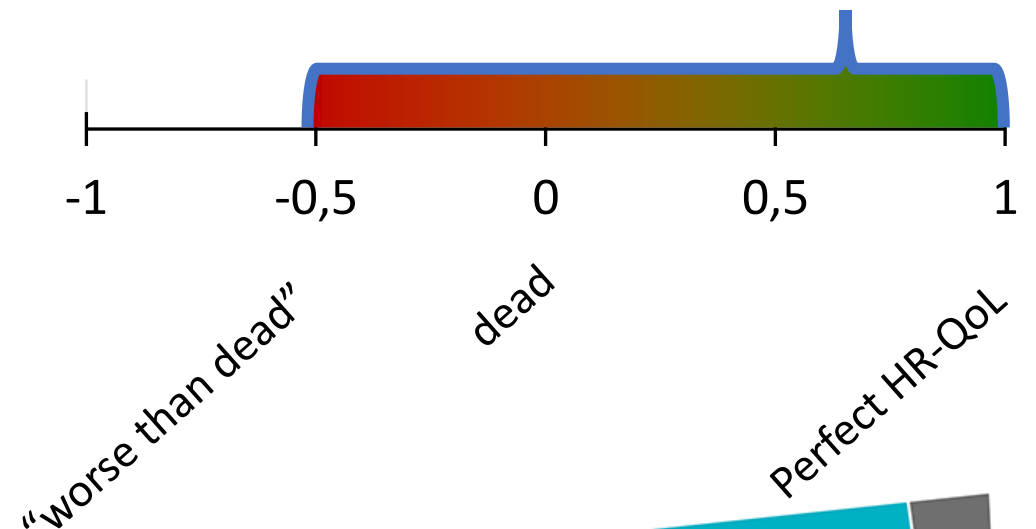
Daren K Heyland, Jayshil Patel, Charlene Compher, Todd W Rice, Danielle E Bear, Zheng-Yii Lee, Victoria C González, Kevin O'Reilly, Raquel Regala, Courtney Wedemire, Miguel Ibarra-Estrada, Christian Stoppe, Luis Ortiz-Reyes, Xuran Jiang, Andrew G Day, on behalf of the EFFORT Protein Trial team

Heyland et al. Lancet 2023;401:568–76

Primary outcome: EuroQoL-5D-5L

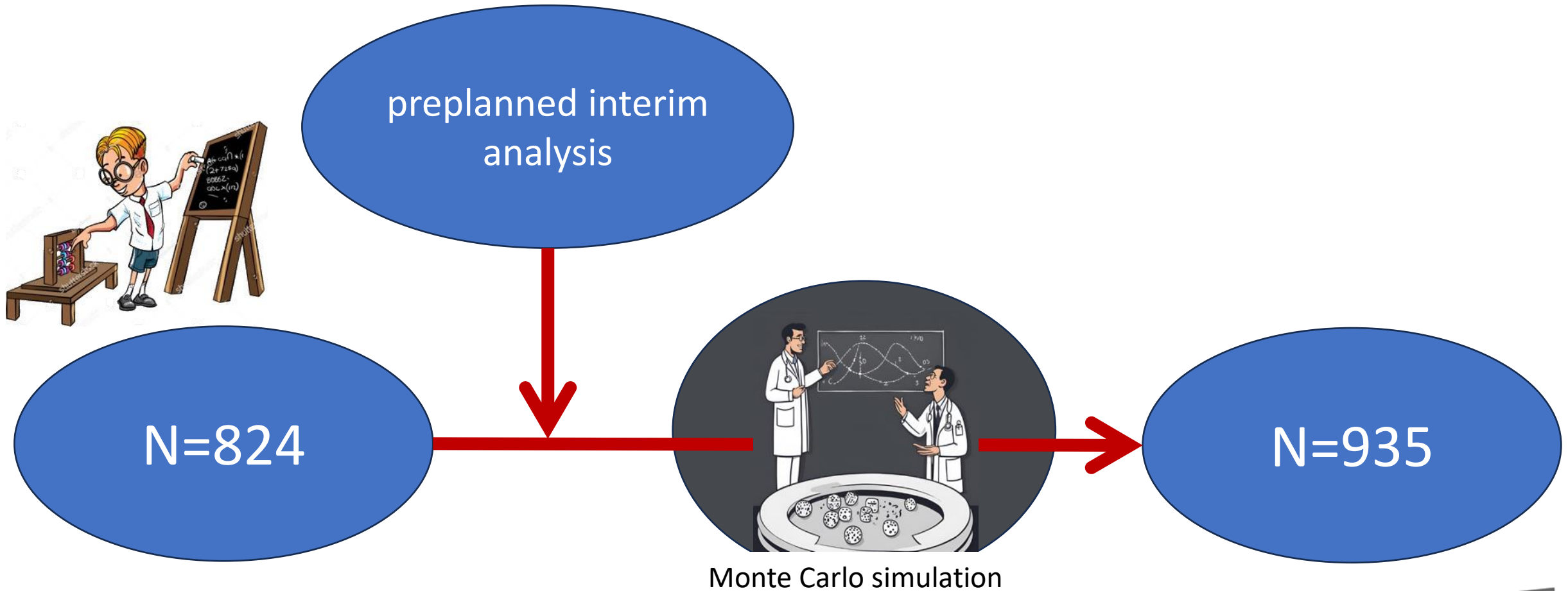


EQ-5D-5L Health Utility Score



Sample size calculation

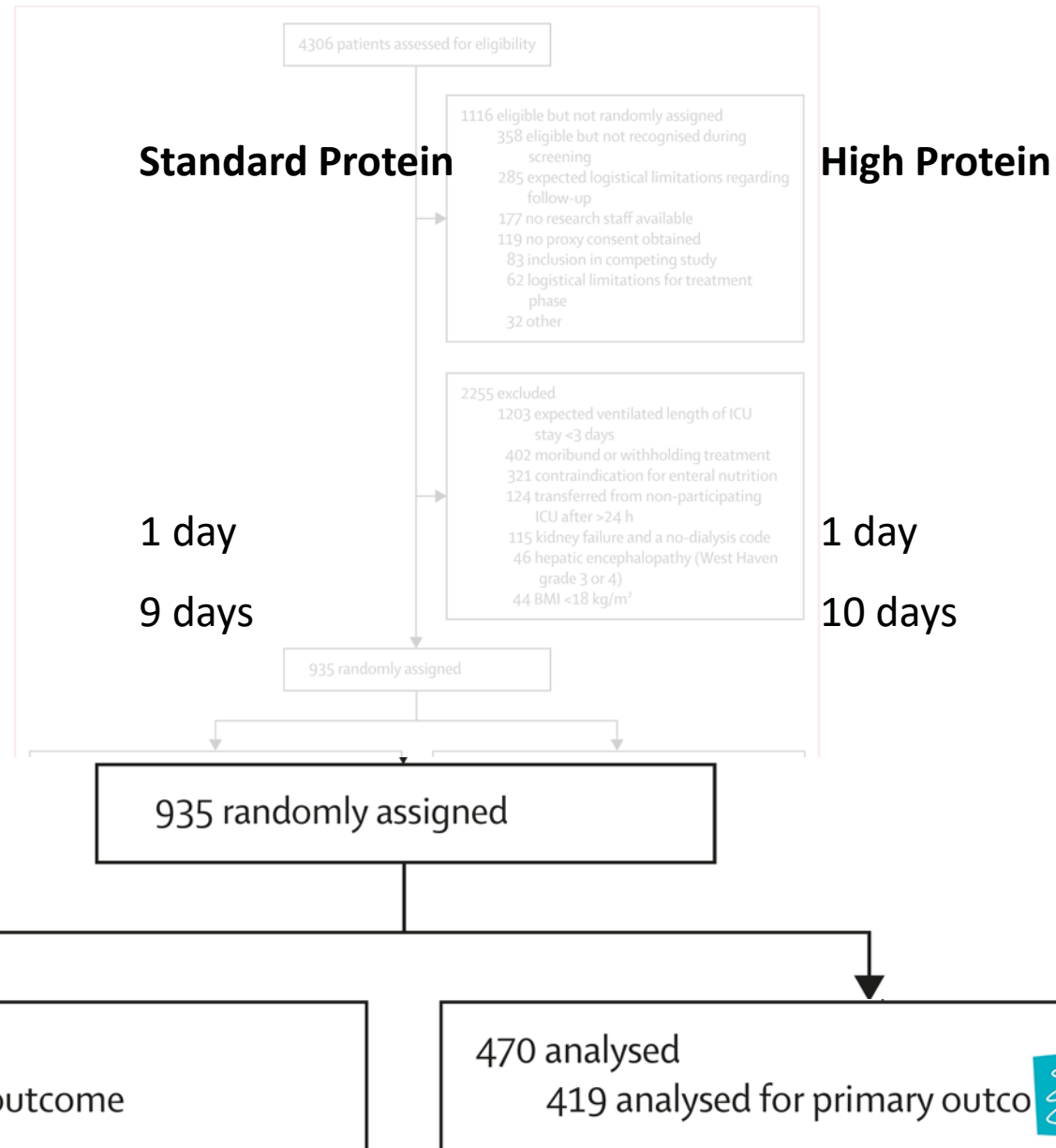
- Clinically important difference EQ-5D-5L Health Utility Score ≈ 0.06



Trial profile

Admission to intervention (median)

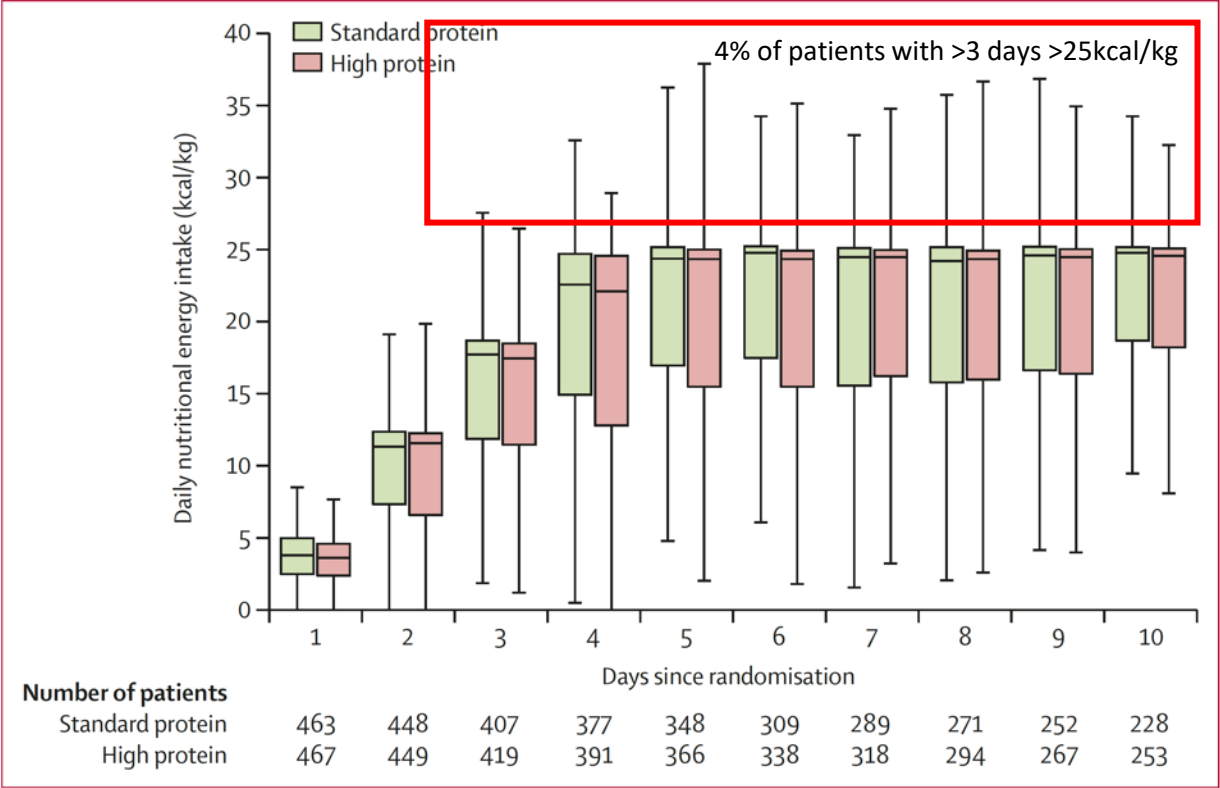
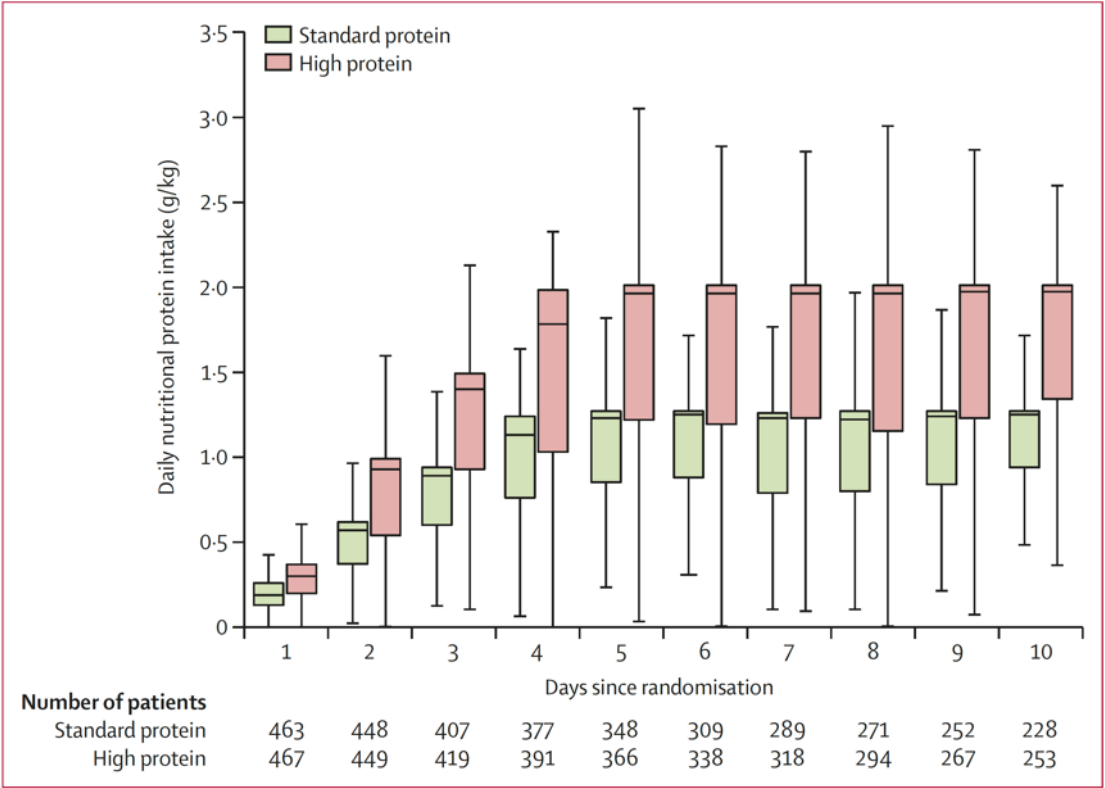
Duration of intervention (median)



Baseline characteristics

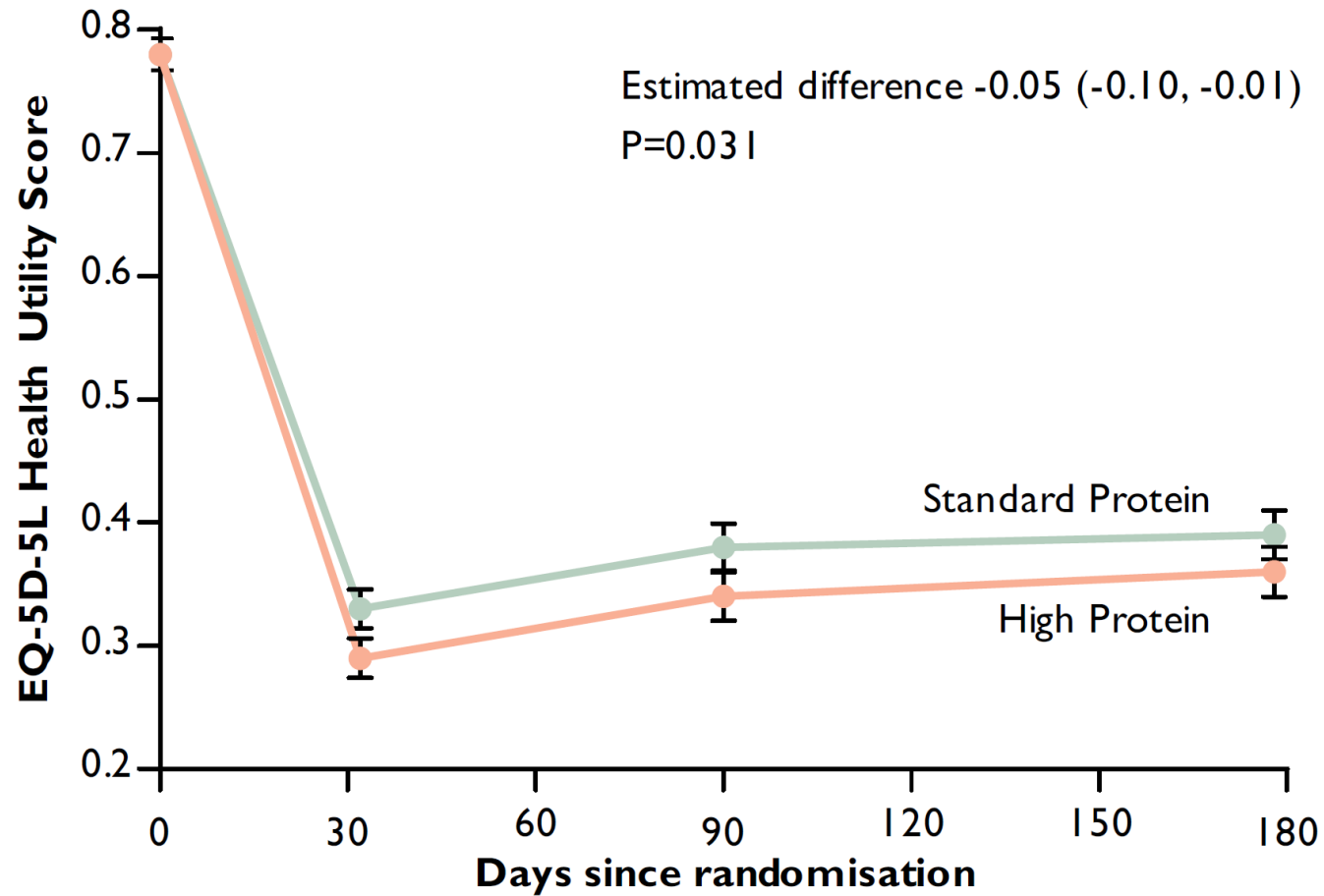
	Standard protein (n=465)	High protein (n=470)
Age, years	63 (14)	62 (14)
Sex		
Female	156 (34%)	179 (38%)
Male	309 (67%)	291 (62%)
BMI	27 (5)	28 (6)
Type of admission		
Medical	341 (73%)	308 (66%)
Surgical	124 (27%)	162 (35%)
Emergency surgery	107/124 (86%)	138/162 (85%)
Complications of elective surgery	17/124 (14%)	24/162 (15%)
COVID-19 infection	73 (16%)	71 (15%)
Acute kidney injury†	97 (21%)	105 (22%)
Sepsis	229 (49%)	230 (49%)
APACHE IV score‡	83 (26)	81 (26)

Nutritional intake



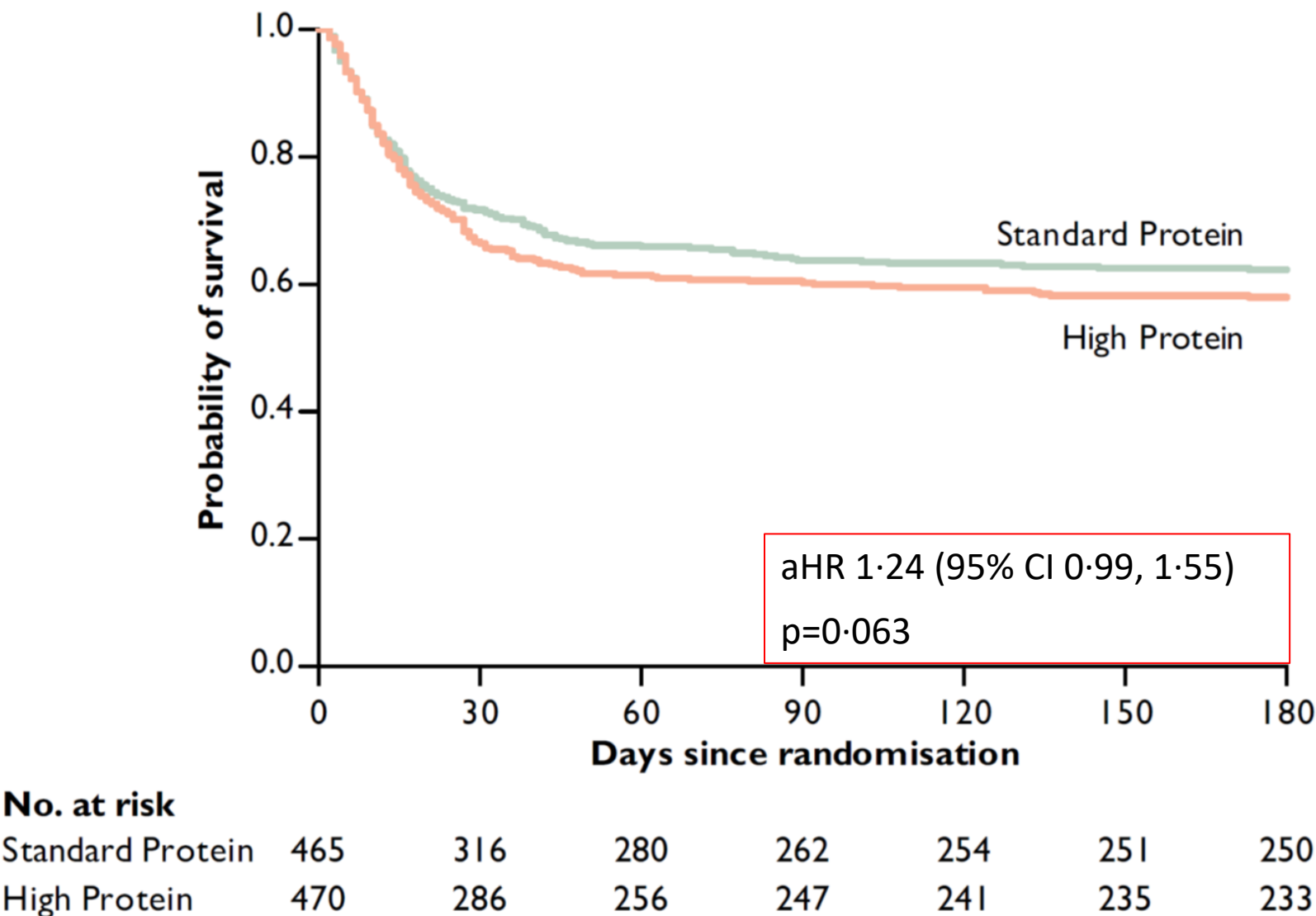
Daily protein intake during the intervention period (g/kg)		
	Standard Protein	High Protein
Mean (SD)	0.95 (0.44)	1.48 (0.70)
Median (IQR)	1.19 (0.63;1.26)	1.87 (0.96;2.00)

Primary outcome – Health Related Quality of Life



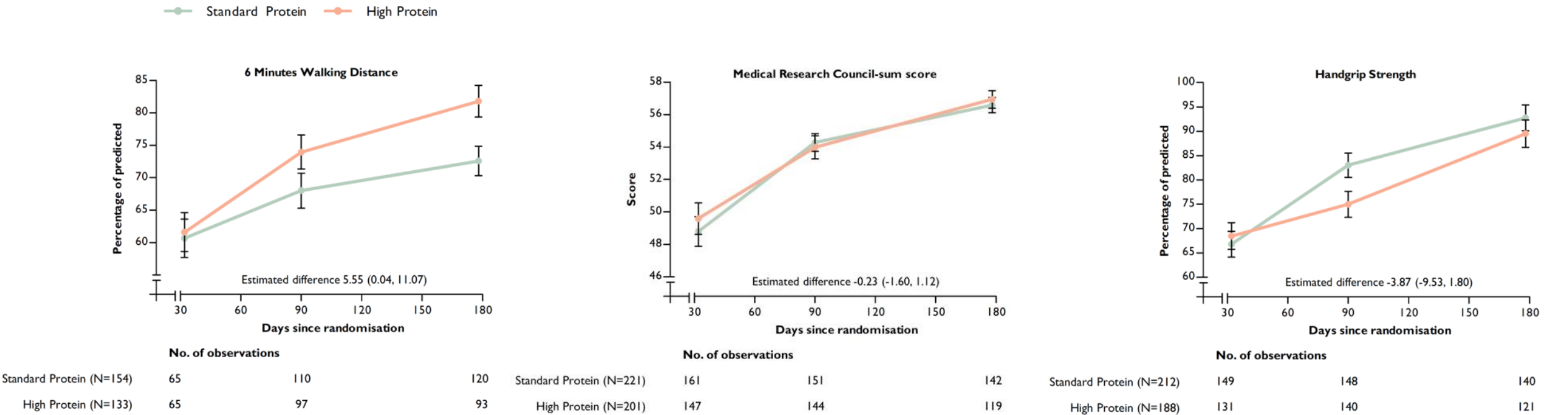
	No. of observations		
Standard Protein (N=430)	407	396	394
High Protein (N=419)	398	386	393

Secondary outcome – Overall survival over 180 days

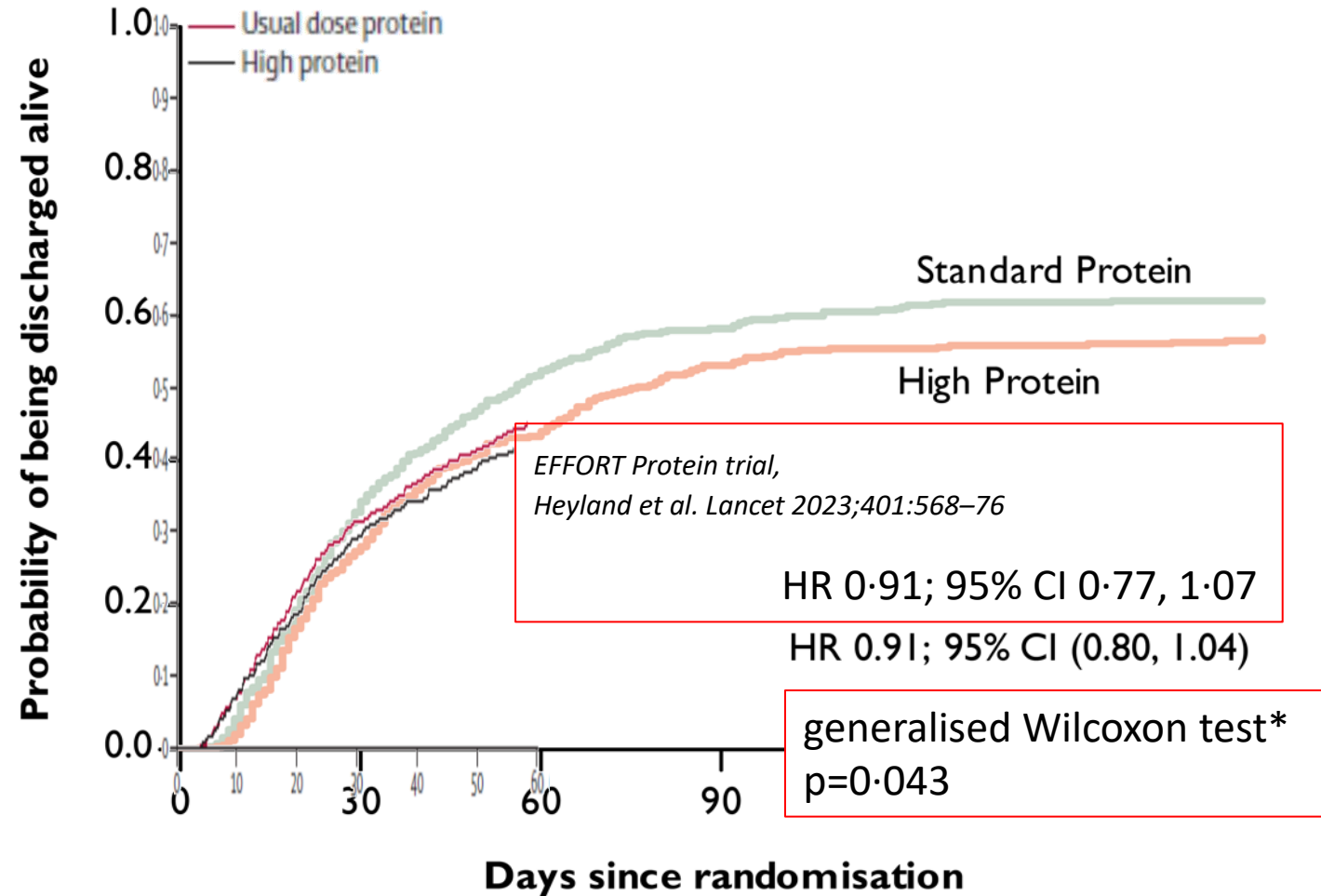


(prescified adjustment for APACHE II score, sex, APACHE IV admission diagnosis, and NRS-2002 score)

Secondary outcome – Physical tests



Tertiary outcome – Time-to-discharge alive



No. at risk

Standard Protein	465	312	224	194	181	177	176
High Protein	470	341	266	220	209	207	204

*Post-hoc test upon request of statistical reviewer

Safety outcomes

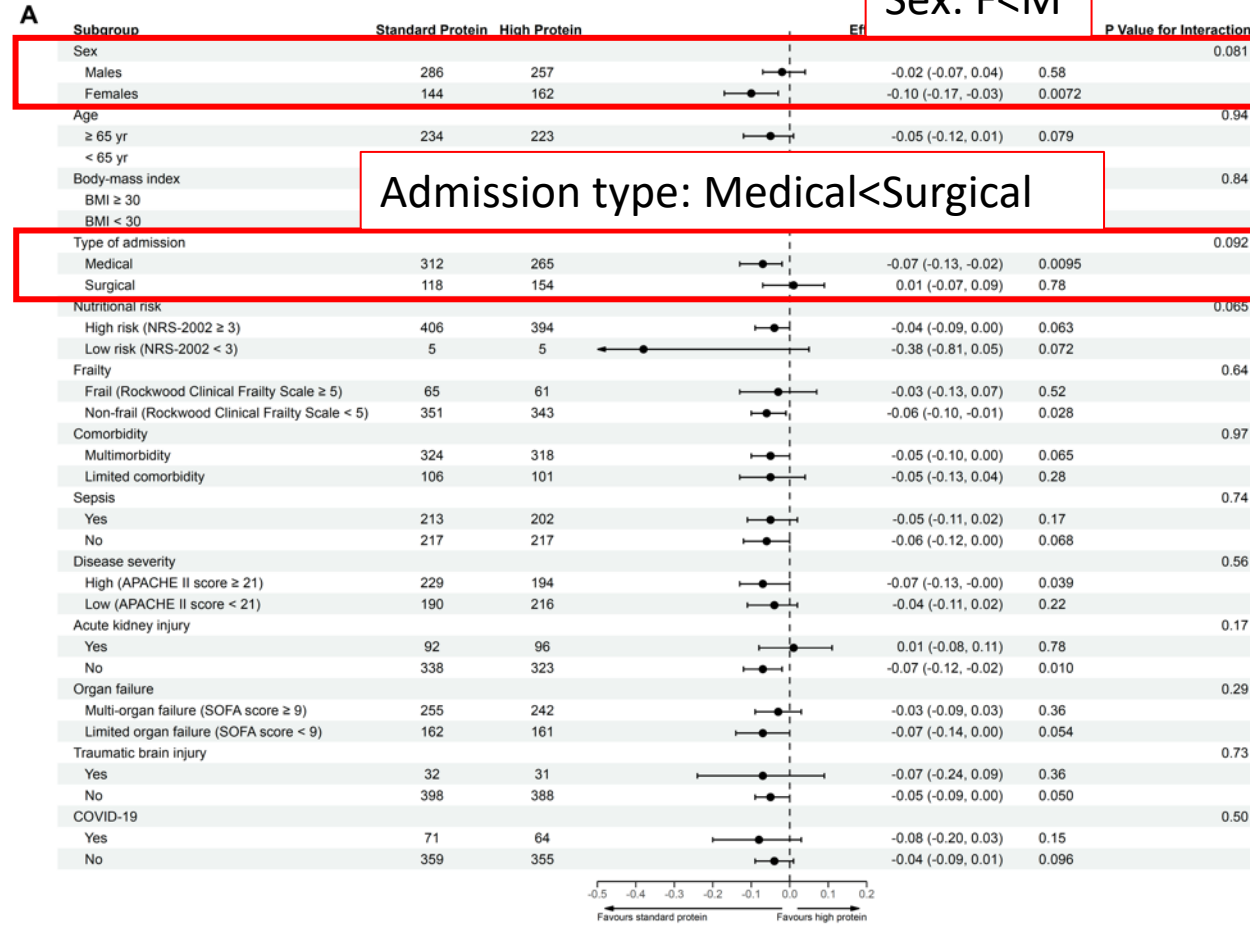
	Standard protein	High protein	
Deaths			
Overall mortality*	0.38 (0.02)	0.42 (0.02)	
Study-emergent serious adverse events†			
Pneumatosis intestinalis	0/465 (<1%)	1/470 (<1%)	
Adverse events of special interest			
ICU-acquired infections	112/465 (24%)	112/469 (24%)	
Ventilator-acquired pneumonia	115/465 (25%)	111/469 (24%)	
Extracorporeal membrane oxygenation	27/465 (6%)	28/469 (6%)	
Acute kidney injury‡	98/465 (21%)	95/469 (20%)	
Refeeding hypophosphataemia§	40/465 (9%)	53/469 (11%)	
Hepatic dysfunction¶	39/465 (8%)	35/469 (8%)	
Gastrointestinal intolerance or symptoms	26/465 (6%)	43/469 (9%)	P=0.030
All-cause mortality after ICU discharge**	36/286 (13%)	35/268 (13%)	
Administration of prokinetics – no./no. (%)	107/465 (23)	140/469 (30)	P=0.015

Subgroup analyses

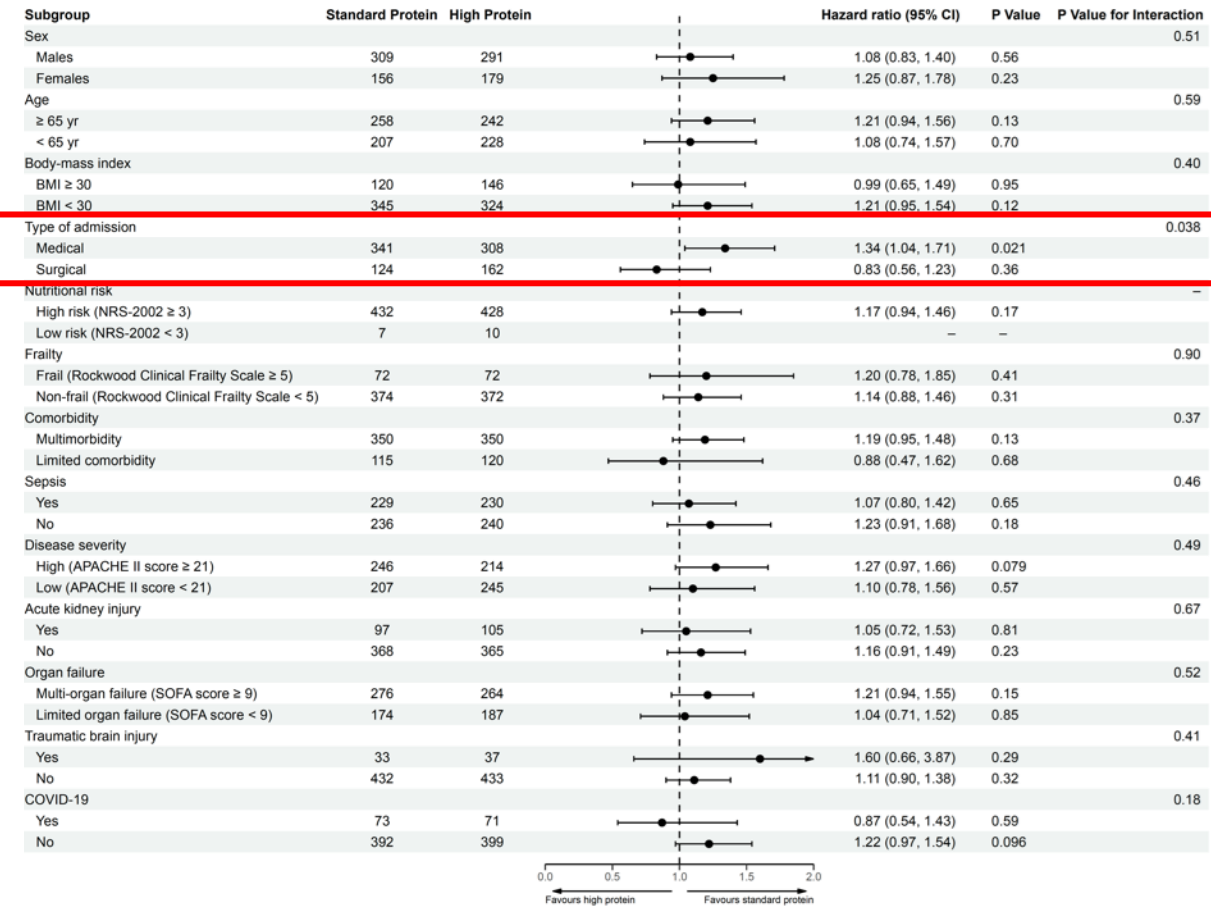
EQ-5D-5L Health utility score

Sex: F<M

Admission type: Medical<Surgical



Overall survival over 180 days

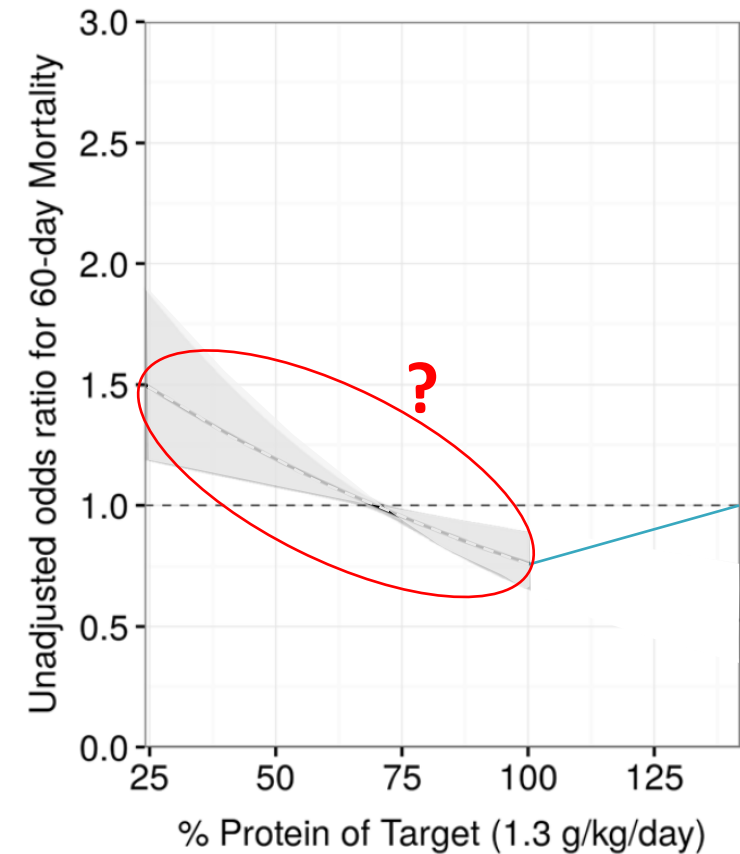


Conclusion

- High (2.0 g/kg) vs. standard (1.3 g/kg) protein target in critical illness:
 - Impairs functional recovery
 - Lower health-related quality of life
 - Longer time-to-discharge alive
 - Increases the incidence of GI intolerance
 - Does not improve physical function in survivors
 - Detrimental effects of high protein most profound in women and medical patients

Discussion

- Only 2nd RCT studying protein targets in ICU, relevant endpoint
- Results are in line with EFFORT Protein trial
 - *but not with prevailing concepts*
- More prospective evidence on protein targets needed



PICO PRECISE-2

- **P**: Adult patients with an unplanned admission to the ICU, who are mechanically ventilated within 48 hours following ICI admission and have an expected duration of mechanical ventilation of at least 3 days. (= **prolonged critically ill patients**)
- **I**: Enteral nutrition with a standard protein content (**0.6 g protein/kg.day**). Dosing of tube feeding is 15 kcal/kg/d nutritional energy. (PRECISE 2 g protein/kg.day)
- **C**: Enteral nutrition with a standard protein content (**1.3 g protein/kg.day**). Dosing of tube feeding is 15 kcal/kg/d nutritional energy. (PRECISE 2 g/kg.day) and identical to intervention group. (= **± control group PRECISE**)
- **O**: - The primary efficacy overall between group-differences in **health-related quality of life** (EQ-5D-5L summary index) at 30 days, 60 days, and 90 days after index ICU admission, corrected for baseline.
- The primary safety outcome measure is **overall survival** at 30, 60 and 90 days after ICU-admission.

Acknowledgments

dieter.mesotten@zol.be

Julia L M Bels, Steven Thiessen, Rob J J van Gassel, Albertus Beishuizen, Ashley De Bie Dekker, Vincent Fraipont, Stoffel Lamote, Didier Ledoux, Clarissa Scheeren, Elisabeth De Waele, Arthur R H van Zanten, Laura Bormans-Russell, Bas C T van Bussel, Marlies M J Dictus, Tom Fivez, Ingeborg Harks, Iwan C C van der Horst, Joop Jonckheer, Hugues Marechal, Paul B Massion, Ingrid Meex, Michelle C Paulus, Martin Rinket, Susanne van Santen, Katrien Tartaglia, Adam M Deane, Frieda Demuydt, Zudin Puthucheary, Lilian C M Vloet, Peter J M Weijs, Sander M J van Kuijk, Marcel C G van de Poll, Dieter Mesotten*, on behalf of the PRECISE study team†*



Julia Bels



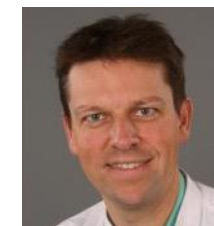
Rob van Gassel



Steven Thiessen



Sander van Kuijk



Marcel van de Poll