Ernährungs-Assessment und Therapie des Internistischen Patienten

DAPEN Meeting 2021

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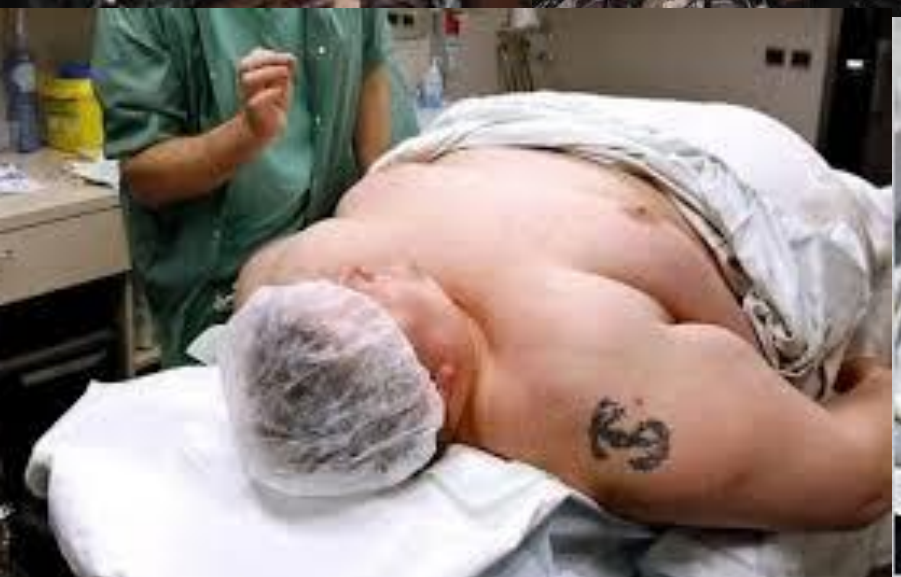
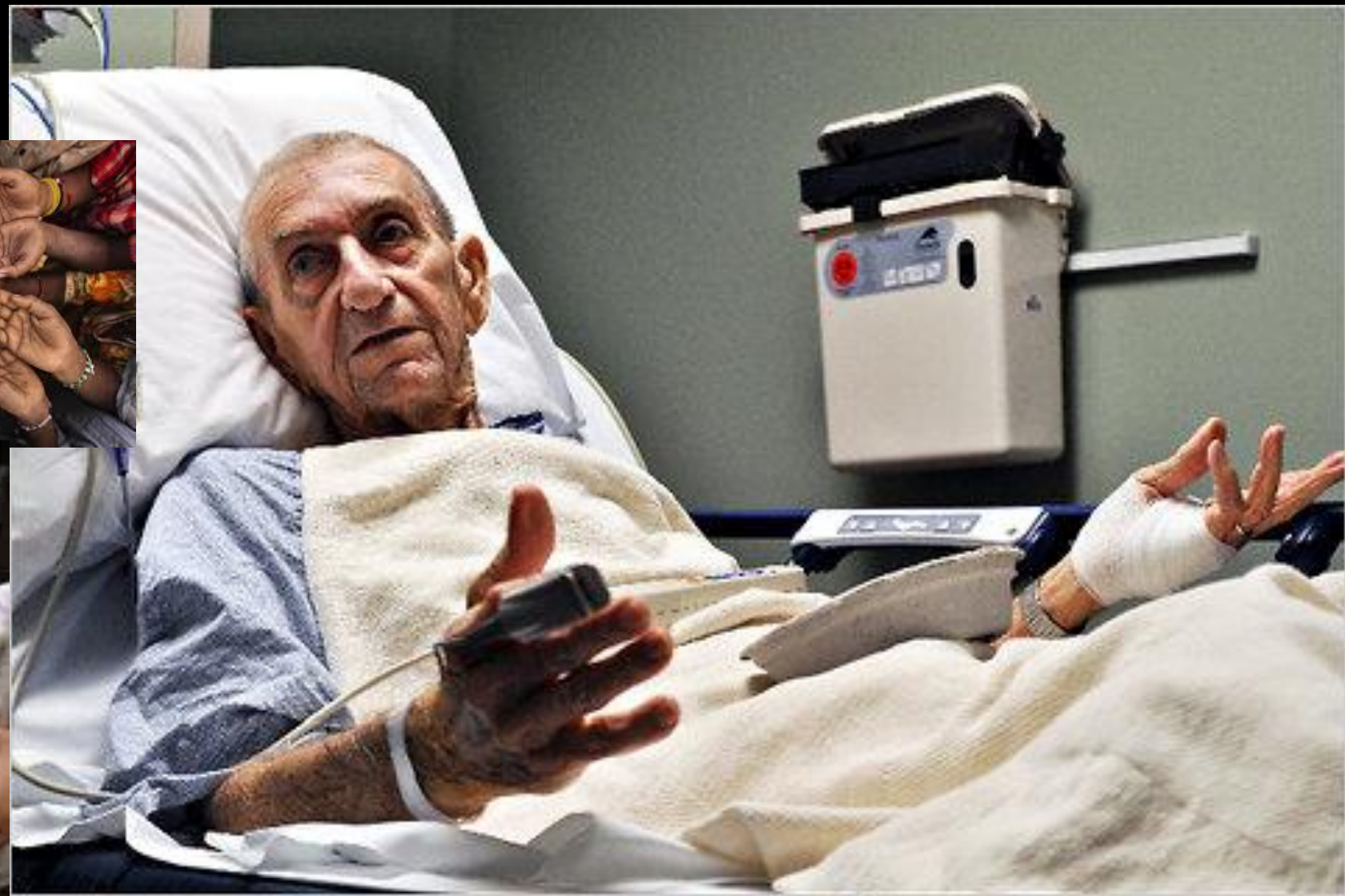
BIDMC & HSPH, Boston

Kantonsspital Aarau

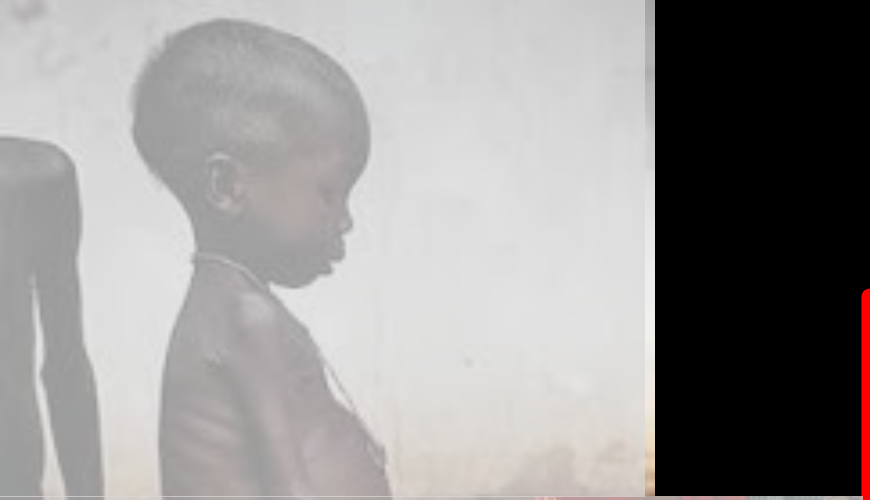
University Hospital Basel

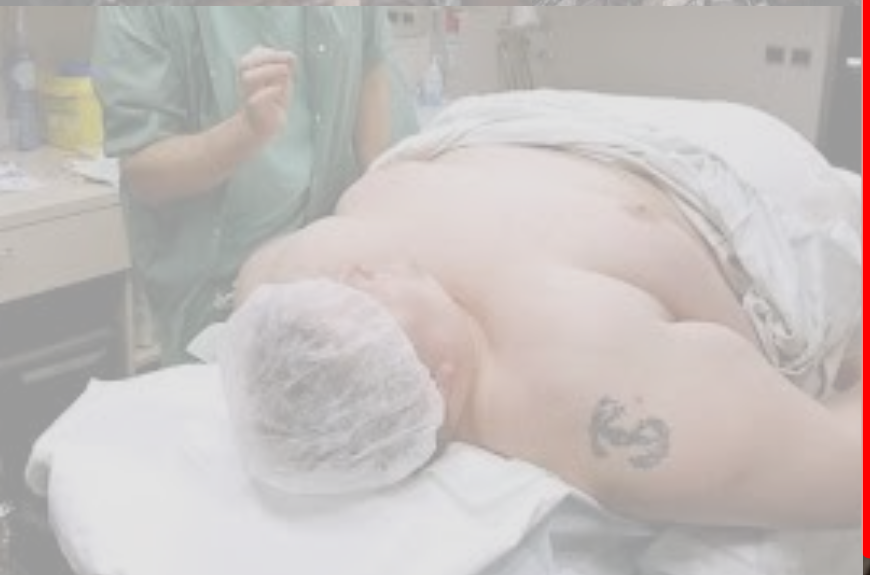
…but it has many different faces and pathophysiologies



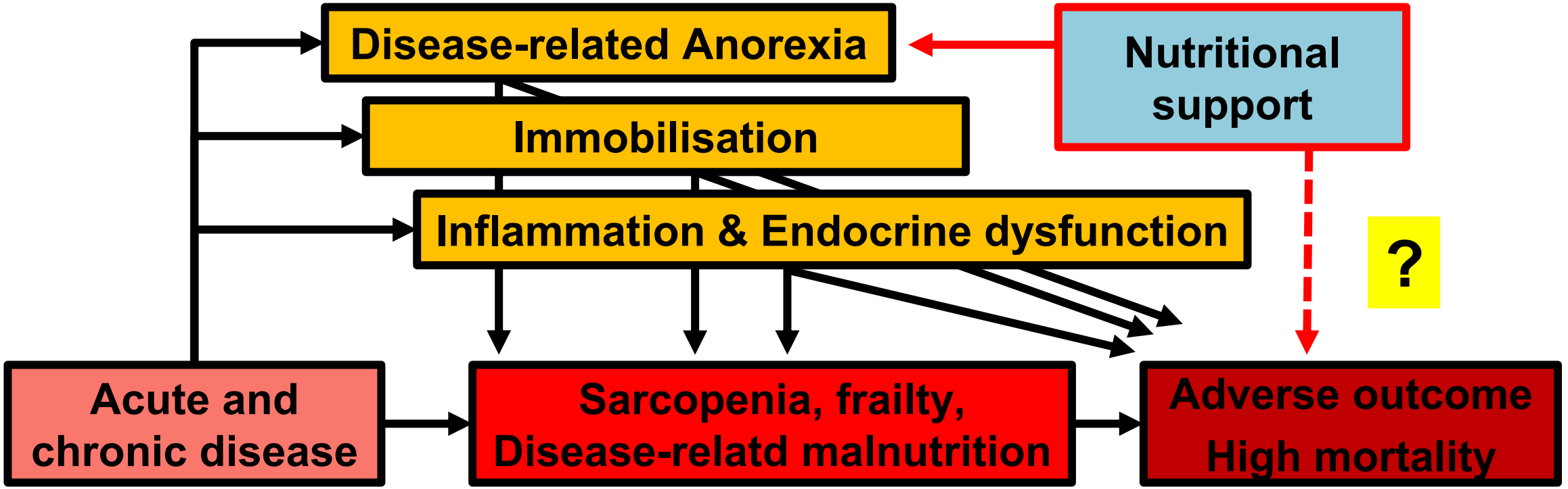


Disease-related malnutrition
In the hospital



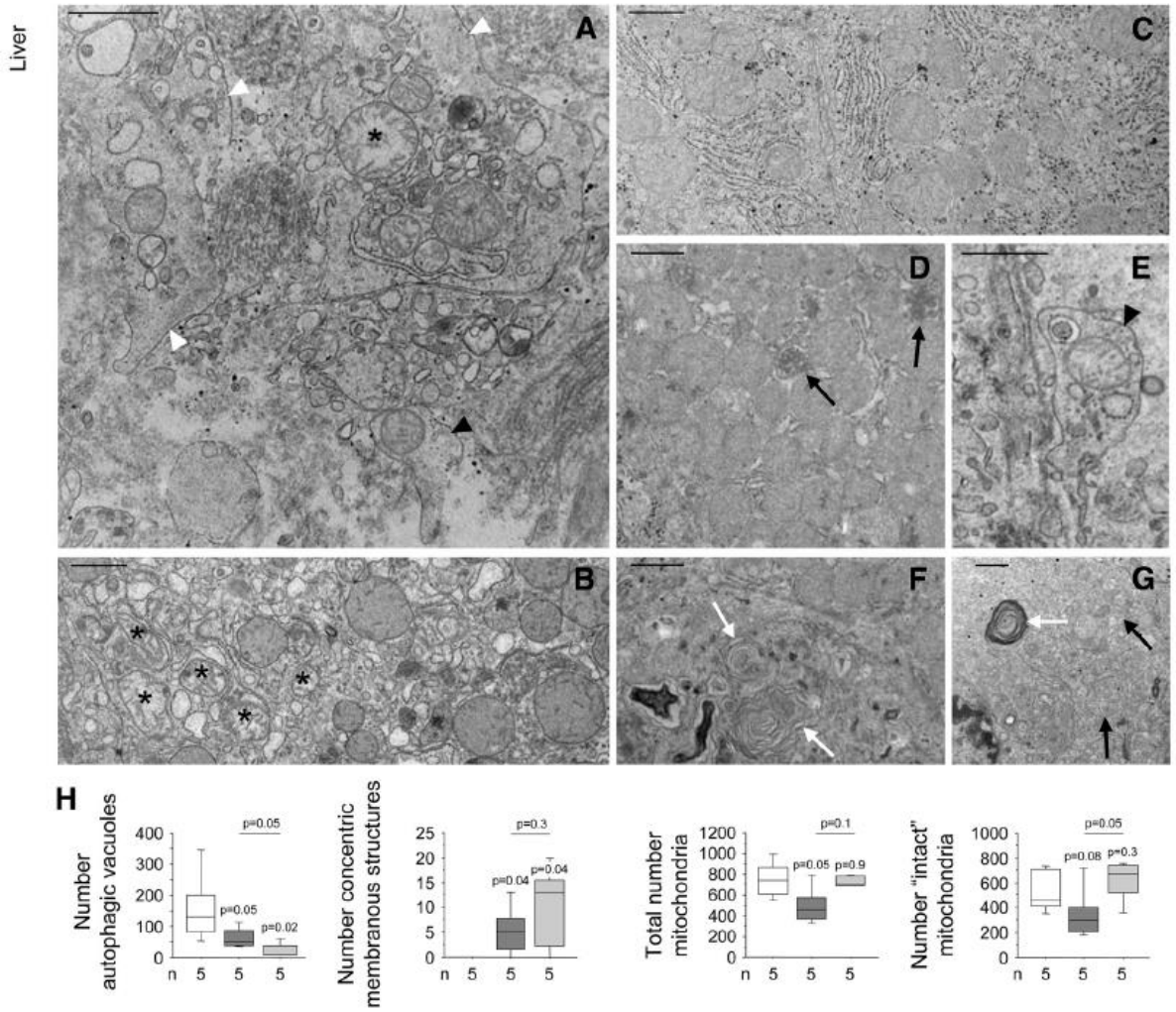


Pathophysiology of Malnutrition:
Our current concept



Could loss of appetite and low nutritional intake be protective during acute disease?

Over-nutrition impairs Autophagy in critically ill patients



Electron microscopy

- intact/swollen mitochondria
- autophagic vacuoles

Histochemistry

- eosin staining
- ubiquitin

Protein analysis

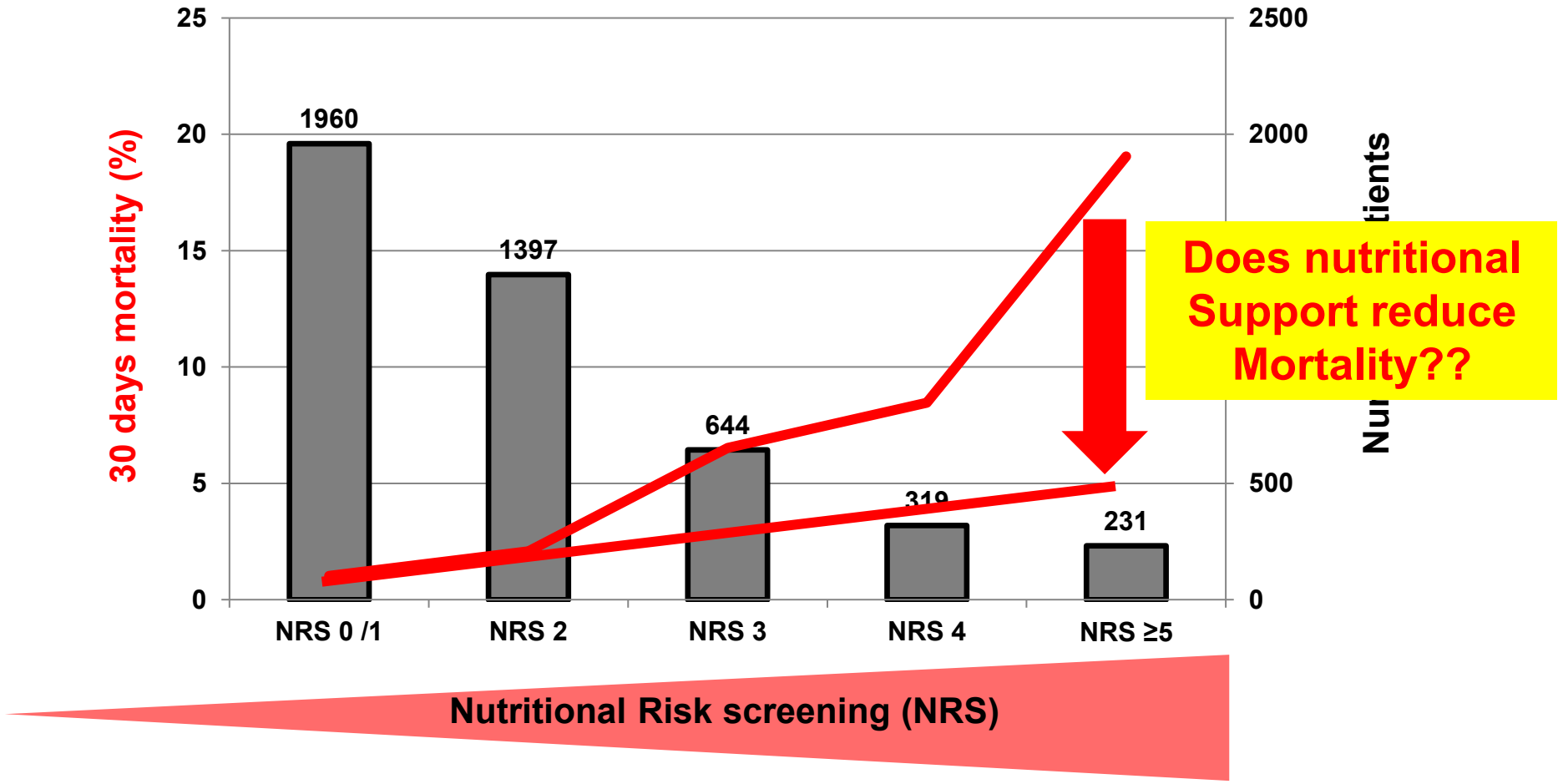
- phosphoinositide-3-kinase (PI3K) class III,
- sirtuin-1,
- protein disulfide isomerase
- glucose-related protein 78
- inositol-requiring enzyme-1
- AMP-activated protein kinase (AMPK),

Vanhorebeek et al, J Clin Endocrinol Metab 96: E633–E645, 2011

Is this mechanism still
protective in the chronically-ill polymorbid patient?

Malnutrition and Mortality

Kantonsspital Aarau,
6 month observation (04/2013-10/2013)
4000 patients, ~ 30% at risk for malnutrition (NRS≥3 points)



Schuetz P et al, Schuetz P et al, SMW (2014)

THE LANCET

Articles

Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial EFFORT Trial

Philipp Schuetz, Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Filomena Gomes, Alexander Kutz, Pascal Tribolet, Thomas Bregenzer, Nina Braun, Claus Hoess, Vojtech Pavlicek, Sarah Schmid, Stefan Bilz, Sarah Sigrist, Michael Brändle, Carmen Benz, Christoph Henzen, Silvia Mattmann, Robert Thomann, Claudia Brand, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi, Jacques Donzé, Zeno Stanga, Beat Mueller**

Summary

Background Guidelines recommend the use of nutritional support during hospital stays for medical patients (patients not critically ill and not undergoing surgical procedures) at risk of malnutrition. However, the supporting evidence for this recommendation is insufficient, and there is growing concern about the possible negative effects of nutritional therapy during acute illness on recovery and clinical outcomes. Our aim was thus to test the hypothesis that protocol-

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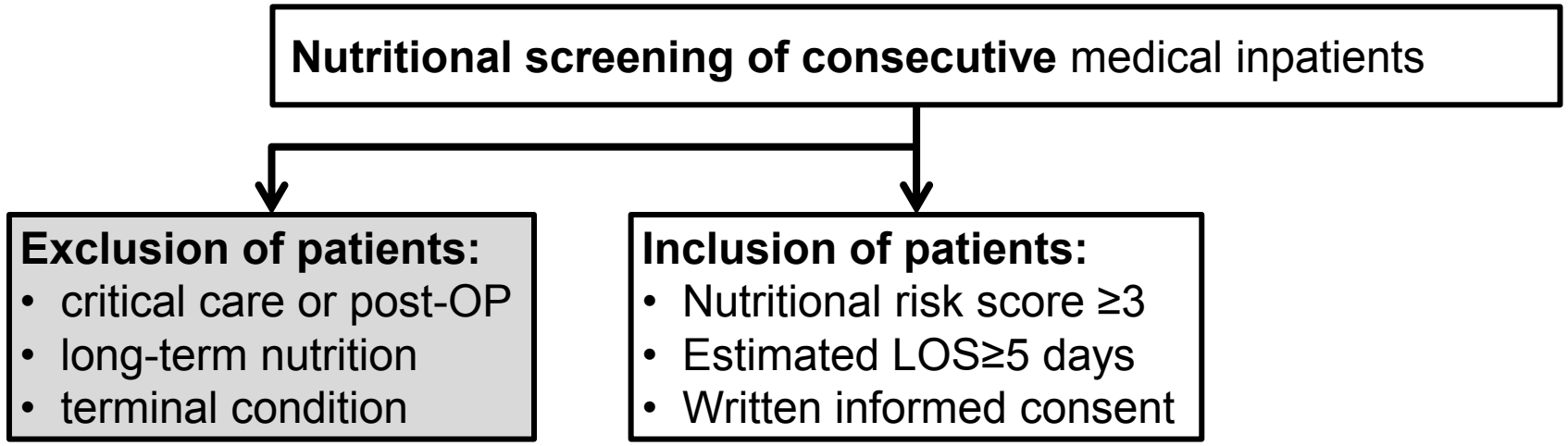
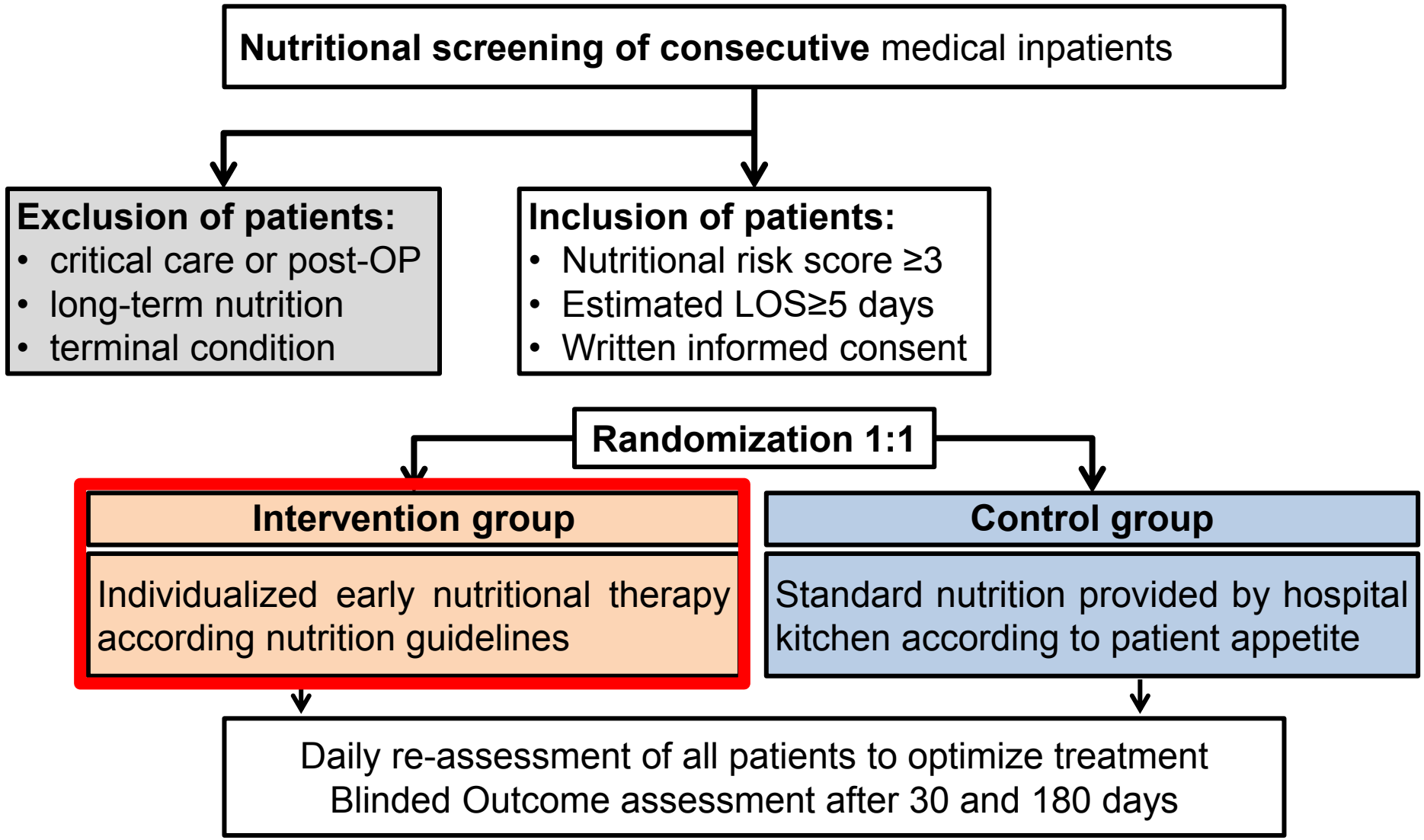
See Online/Comment

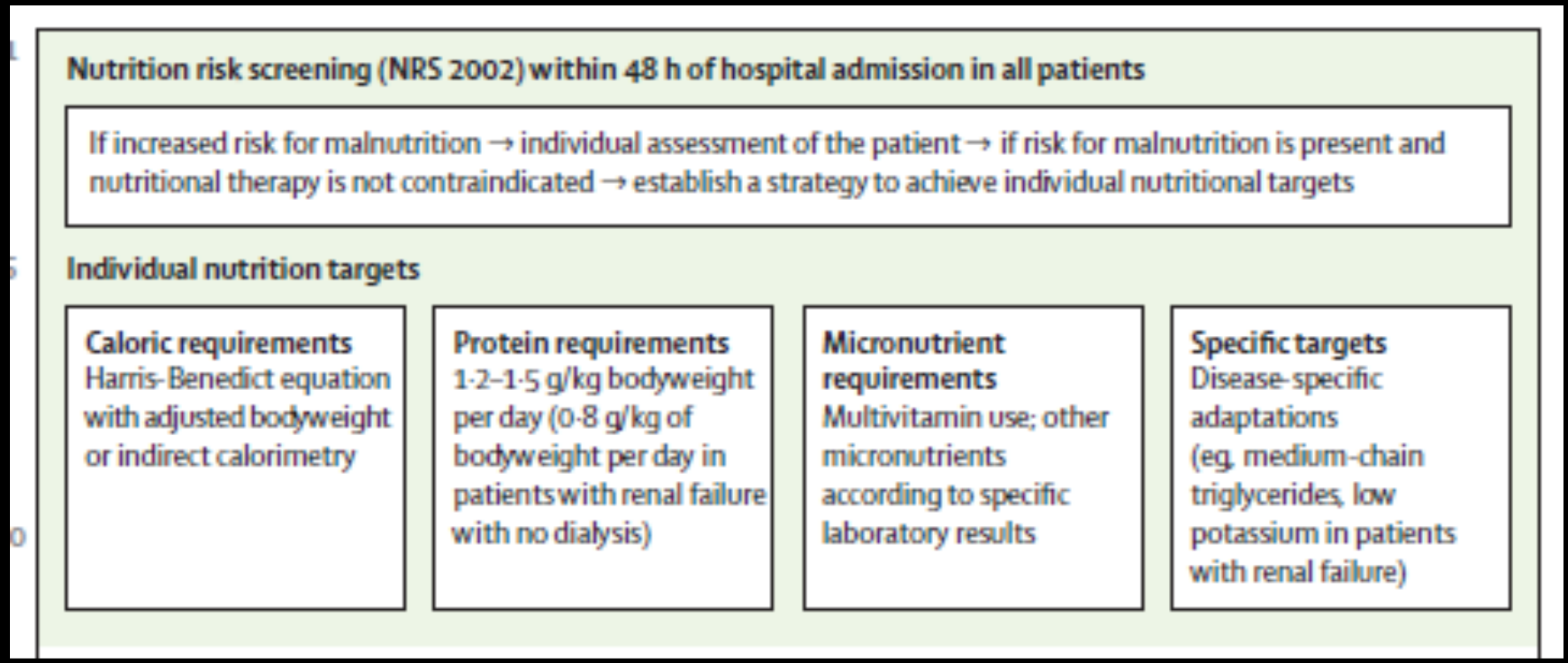
The EFFORT trial - study flow diagram (1/2)



The EFFORT trial - study flow diagram (2/2)



Step 1: Screening and Assessment



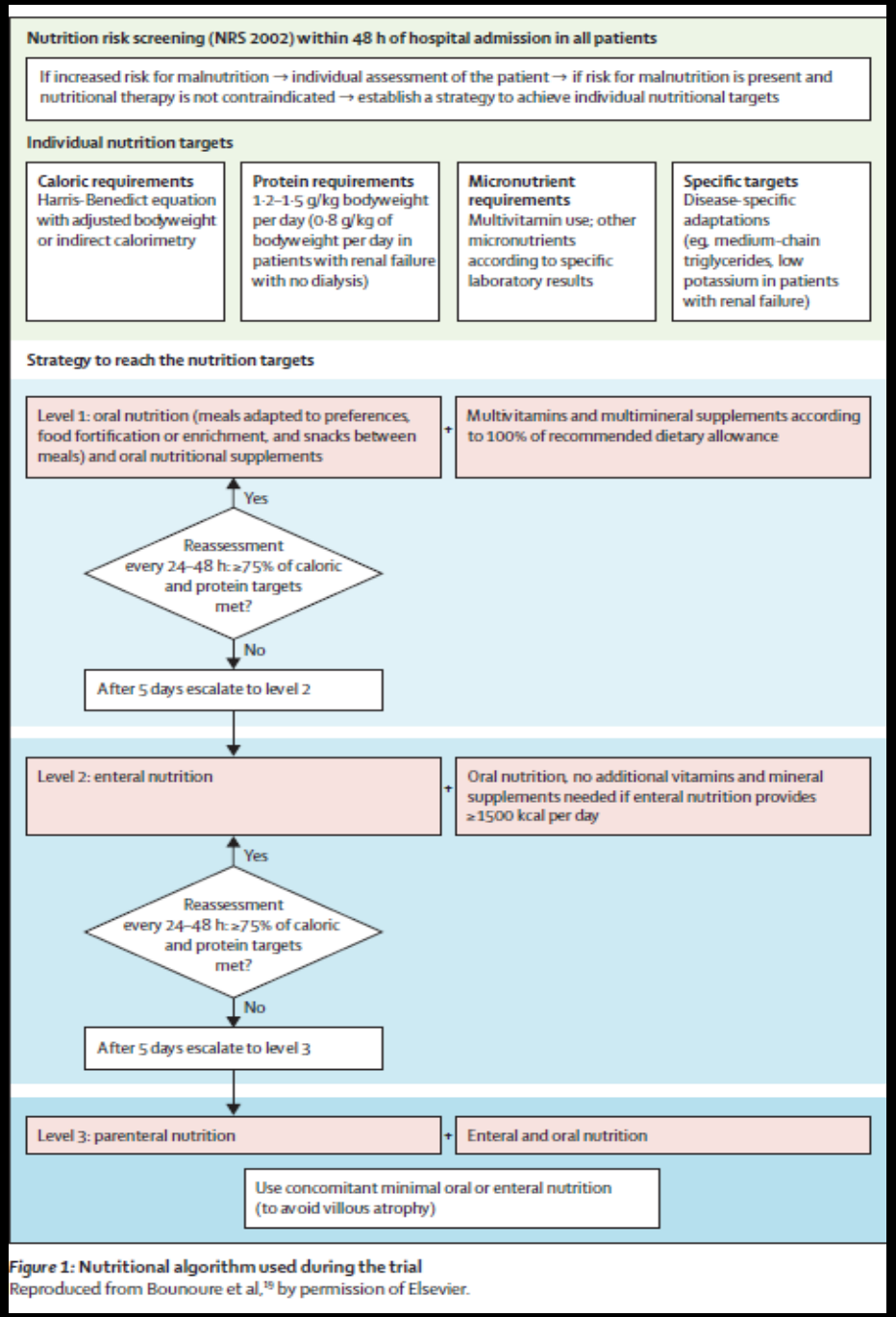


Figure 1: **Nutritional algorithm used during the trial**
Reproduced from Bounoure et al,[15] by permission of Elsevier.

1. Malnutrition screening (NRS 2002)

2. Definition of individual nutritional goals

3. Individual nutritional intervention to reach goals

Oral

↓

enteral

↓

parenteral

Schuetz P, et al. *Lancet*. 2019;393(10188):2312-2321.

	Intervention group (n=1015)	Control group (n=1013)
Sociodemographics		
Mean age (years)	72·4 (14·1)	72·8 (14·1)
Age group		
<65 years	177 (17%)	178 (18%)
65–75 years	349 (34%)	322 (32%)
>75 years	489 (48%)	513 (51%)
Male sex	525 (52%)	539 (53%)
Nutritional assessment		
Mean body-mass index (kg/m²)*	24·9 (5·4)	24·7 (5·3)
Mean bodyweight (kg)	70·9 (16·4)	70·9 (16·4)
NRS 2002 score (%)†		
3 points	310 (31%)	314 (31%)
4 points	391 (39%)	384 (38%)
5 points	263 (26%)	261 (26%)
>5 points	51 (5%)	54 (5%)
Admission diagnosis		
Infection	298 (29%)	315 (31%)
Cancer	201 (20%)	173 (17%)
Cardiovascular disease	92 (9%)	113 (11%)
Failure to thrive	99 (10%)	95 (9%)
Lung disease	50 (5%)	75 (7%)
Gastrointestinal disease	96 (9%)	68 (7%)
Neurological disease	42 (4%)	53 (5%)
Renal disease	34 (3%)	34 (3%)
Metabolic disease‡	30 (3%)	32 (3%)
Other	30 (3%)	25 (2%)
Comorbidity		
Hypertension	557 (55%)	552 (54%)
Malignant disease	338 (33%)	329 (32%)
Chronic kidney disease	323 (32%)	318 (31%)
Coronary heart disease	287 (28%)	279 (28%)
Diabetes	215 (21%)	213 (21%)
Congestive heart failure	174 (17%)	179 (18%)
Chronic obstructive pulmonary disease	147 (14%)	156 (15%)
Peripheral arterial disease	80 (8%)	106 (10%)
Cerebrovascular disease	75 (7%)	87 (9%)
Dementia	39 (4%)	36 (4%)

Data are number of participants (%) or mean (SD). There were no significant differences between the groups at baseline, except for admission diagnosis of gastrointestinal disease and lung disease, and comorbidity of peripheral arterial disease.*The body-mass index is the weight in kilograms divided by the square of the height in metres. †Scores on nutritional risk screening range from 0 to 7, with a score of 3 or more identifying patients at nutritional risk and higher scores indicating increased risk. ‡Metabolic disease included, but was not limited to, hypoglycaemia, hyperglycaemia, ketoacidosis, electrolyte disturbances including hyponatraemia and hypernatraemia, hypokalaemia, and hyperkalaemia. NRS 2002=nutritional risk screening 2002.

Table 1: **Characteristics of the patients at trial entry**

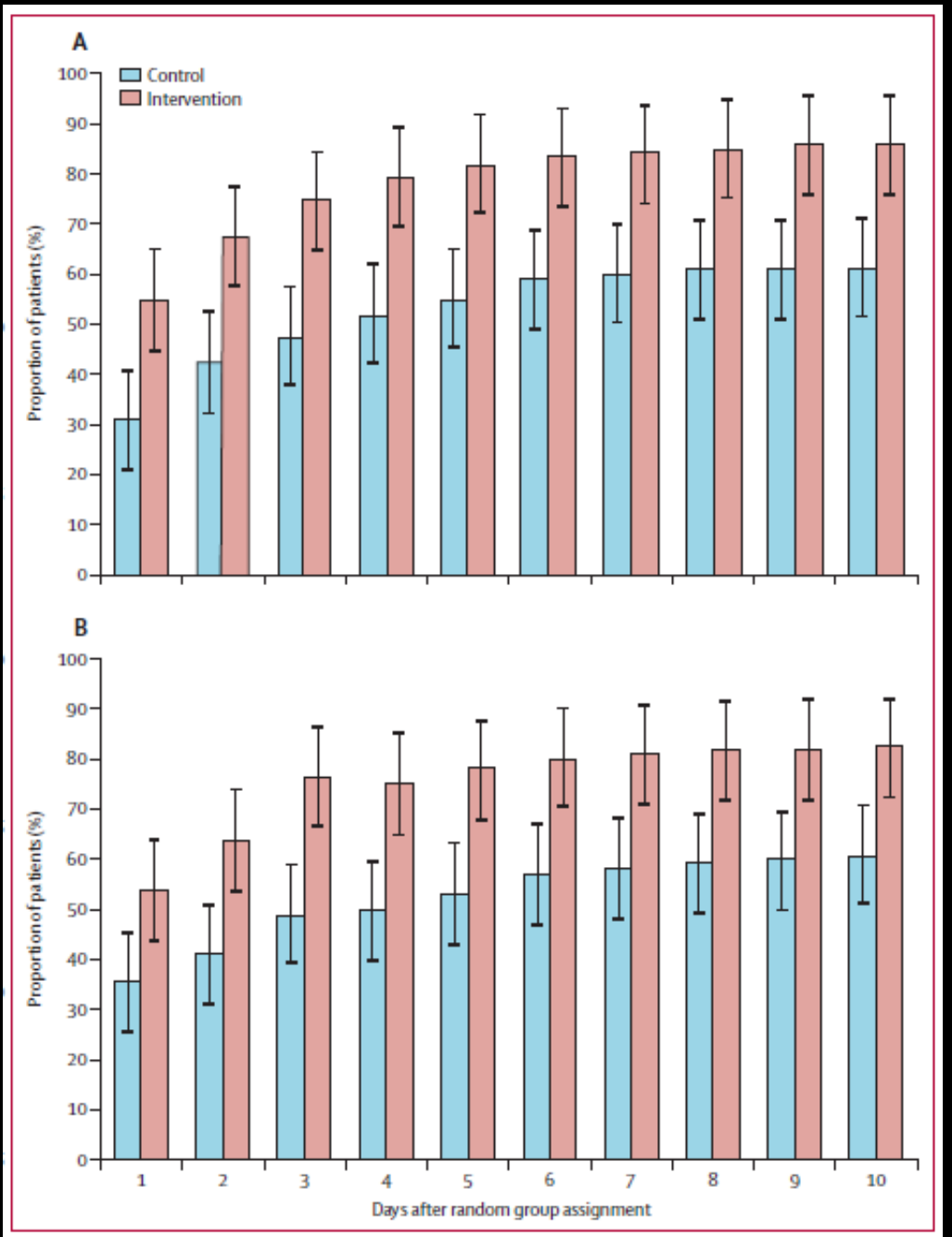


Figure 3: **Proportion of patients reaching caloric (A) and protein (B) requirements during the first 10 days after random group assignment**

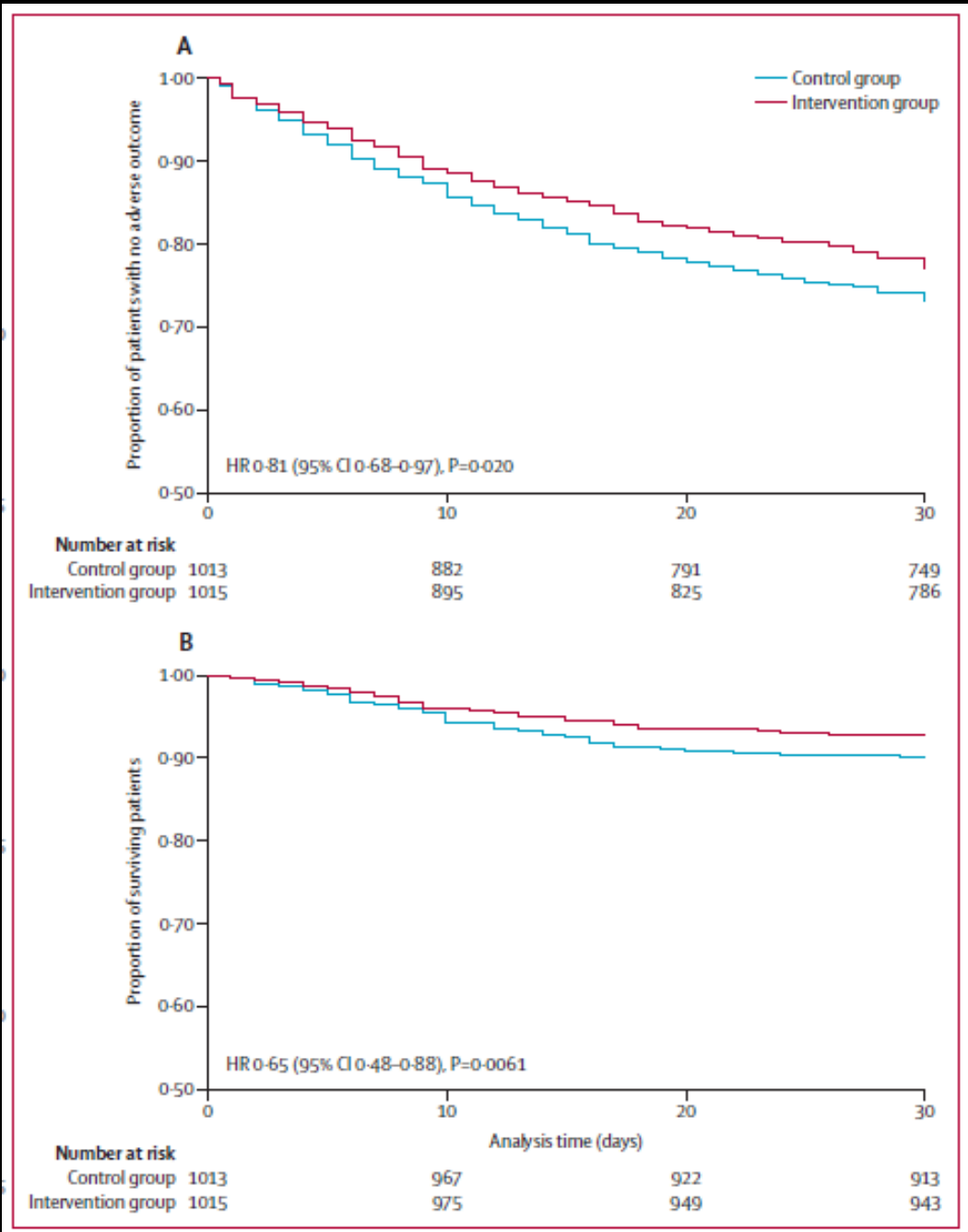


Figure 4: Kaplan-Meier estimates of the cumulative incidence of the primary endpoint and all-cause mortality
(A) Time to the first event of the composite primary endpoint (log-rank p value=0·035). (B) Time to death (log-rank p value=0·031).

Complications

26.9% (Controls) vs 22.9% (Intervention)
Number needed to treat (NNT): 25

Mortality

9.9% (Controls) vs 7.2% (Intervention)
Number needed to treat (NNT): 37

	Intervention group (n=1015)	Control group (n=1013)	Odds ratio or coefficient (95% CI)	p value
Outcomes				
Primary outcome				
Adverse outcome within 30 days	232 (23%)	272 (27%)	0·79 (0·64 to 0·97)	0·023
Single components of primary outcome				
All-cause mortality	73 (7%)	100 (10%)	0·65 (0·47 to 0·91)	0·011
Admission to the intensive care unit	23 (2%)	26 (3%)	0·85 (0·48 to 1·51)	0·58
Non-elective hospital readmission	89 (9%)	91 (9%)	0·99 (0·73 to 1·35)	0·96
Major complications				
Any major complication	74 (7%)	76 (8%)	0·95 (0·68 to 1·34)	0·79
Nosocomial infection	40 (4%)	39 (4%)	1·01 (0·63 to 1·59)	0·98
Respiratory failure	14 (1%)	13 (1%)	1·06 (0·49 to 2·28)	0·89
Major cardiovascular event	8 (1%)	7 (1%)	1·11 (0·40 to 3·11)	0·84
Acute kidney failure	32 (3%)	31 (3%)	1·01 (0·61 to 1·69)	0·96
Gastrointestinal events	9 (1%)	15 (1%)	0·57 (0·25 to 1·31)	0·19
Decline in functional status of ≥10%*	35 (4%) of 942	55 (6%) of 913	0·62 (0·40 to 0·96)	0·034
Additional secondary outcomes				
Mean length of stay (days)	9·5 (7·0)	9·6 (6·1)	−0·21 (−0·76 to 0·35)	0·46
Mean Barthel score (points)*	88 (26)	85 (30)	3·26 (0·93 to 5·60)	0·006
Mean EQ-5D VAS (points)†	59 (26)	56 (29)	3·06 (0·53 to 5·59)	<0·0001
Mean EQ-5D index (points)	0·75 (0·32)	0·73 (0·34)	0·13 (0·09 to 0·17)	0·018
Side-effects from nutritional support				
All side-effects	162 (16%)	145 (14%)	1·16 (0·90 to 1·51)	0·26
Gastrointestinal side-effects	43 (4%)	40 (4%)	1·12 (0·68 to 1·83)	0·66
Complications due to enteral feeding or parenteral nutrition	5 (<1%)	3 (<1%)	1·63 (0·38 to 6·95)	0·51
Liver or gall bladder dysfunction	4 (<1%)	7 (1%)	0·54 (0·15 to 1·91)	0·34
Severe hyperglycaemia	48 (5%)	46 (5%)	1·06 (0·69 to 1·61)	0·80
Refeeding syndrome	86 (8%)	73 (7%)	1·21 (0·86 to 1·70)	0·27

Data are number of events (%), unless otherwise stated. All odds ratios were calculated with a logistic regression for binary data and linear regression for continuous data. Models were adjusted for predefined prognostic factors (initial nutritional risk screening score and baseline Barthel index) and study centre. *To estimate decline in functional status, we used the Barthel index (scores range from 0 to 100, with higher scores indicating better functional status) and compared initial scores on admission with scores at day 30; only surviving patients were included in this analysis. †To estimate quality of life we used the European Quality of Life 5 Dimensions index (EQ-5D; values range from −0·205 to 1, with higher scores indicating better quality of life) including the visual-analogue scale (EQ-5D VAS; scores range from 0 to 100, with higher scores indicating better health status).

Table 2: **Endpoints and adverse events**

How about real world data?

(Propensity-mached Analysis with all Swiss hospitalisations in 2013 – 2018 with >100`000 Patients at risk for malnutrition [NRS ≥3])

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Evaluation of Nutritional Support and In-Hospital Mortality in Patients With Malnutrition

Nina Kaegi-Braun, MD; Marlena Mueller; Philipp Schuetz, MD, MPH; Beat Mueller, MD; Alexander Kutz, MD, MSc

Abstract

IMPORTANCE Malnutrition affects a considerable proportion of patients in the hospital and is associated with adverse clinical outcomes. Recent trials found a survival benefit among patients receiving nutritional support.

OBJECTIVE To investigate whether there is an association of nutritional support with in-hospital mortality in routine clinical practice.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted from April 2013 to December 2018 among a population of patients from Swiss administrative claims data. From 114 264 hospitalizations of medical patients with malnutrition, 34 967 patients (30.6%) receiving nutritional support were 1:1 propensity score matched to patients with malnutrition in the hospital who were not receiving nutritional support. Patients in intensive care units were excluded. Data were analyzed from February 2020 to November 2020.

EXPOSURES Receiving nutritional support, including dietary advice, oral nutritional supplementation, or enteral and parenteral nutrition.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause in-hospital mortality. Secondary outcomes were 30-day all-cause hospital readmission and discharge to a postacute care facility. Poisson and logistic regressions were used to estimate incidence rate ratios (IRRs) and odds ratios (ORs) of outcomes.

RESULTS After matching, the study identified 69 934 hospitalizations of patients coded as having malnutrition in the cohort (mean [SD] age, 73.8 [14.5] years; 36 776 [52.6%] women). Patients receiving nutritional support, compared with those not receiving nutritional support, had a lower

Key Points

Question Is nutritional support as prescribed in clinical practice associated with a mortality benefit among patients with malnutrition?

Findings In this cohort study of 69 934 patients with malnutrition in a nationwide Swiss claims database, the in-hospital mortality rate was significantly lower among patients receiving nutritional support compared with those not receiving nutritional support.

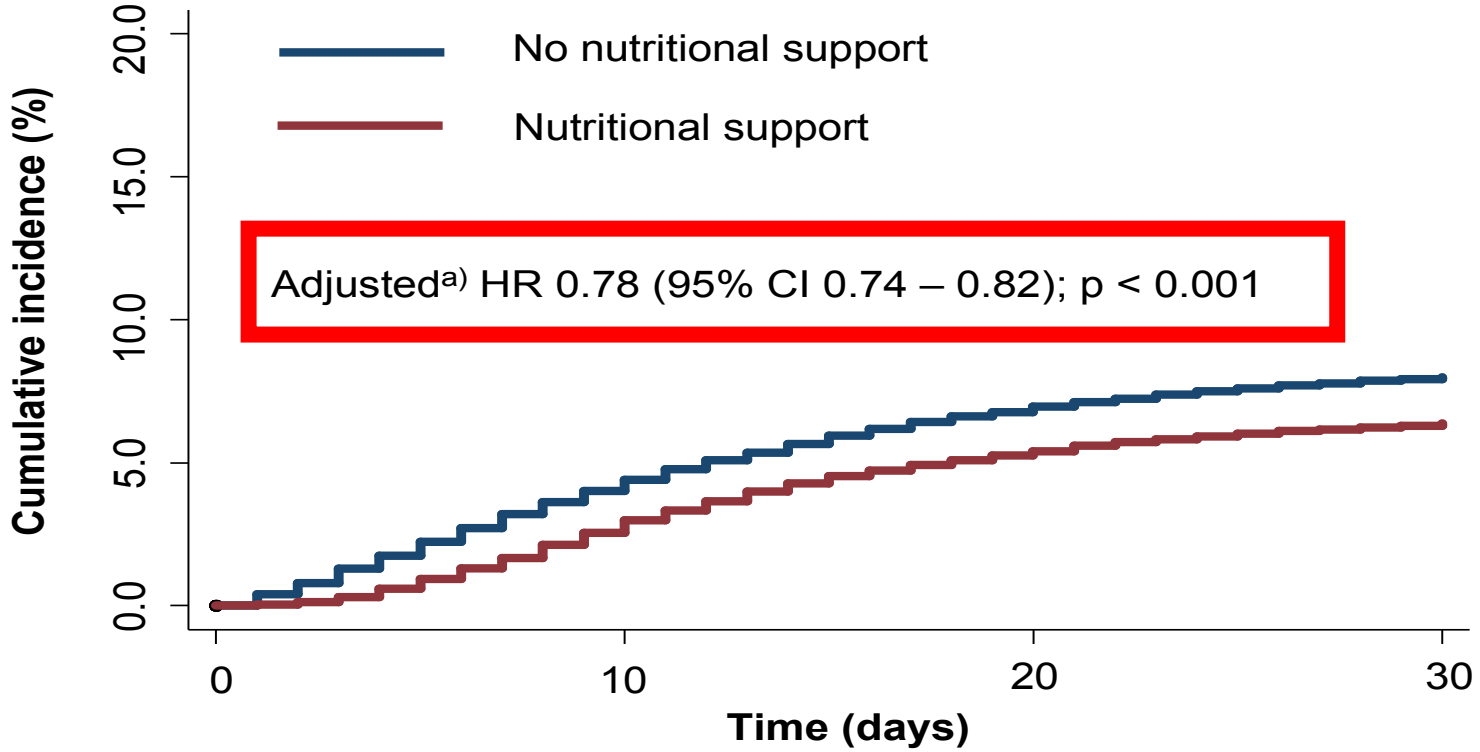
Meaning This study found that nutritional support was associated with a mortality benefit, highlighting the importance of nutritional support for patients in the hospital with malnutrition.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

BFS Bundesamt für Statistik



Number at risk, n

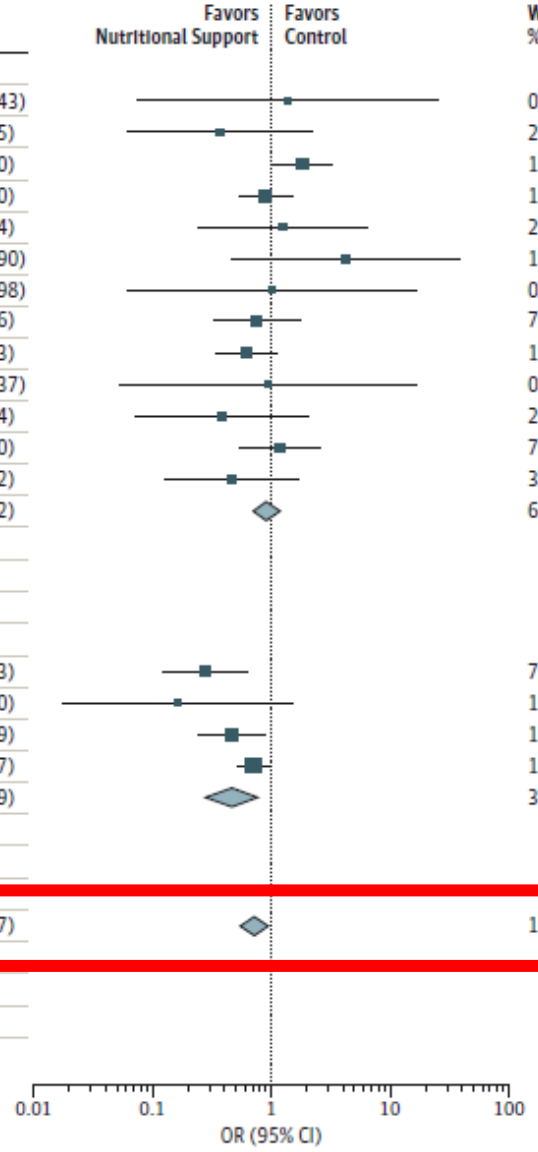
No nutritional support	34 967	33 563	32 600	32 195
Nutritional support	34 967	34 074	33 132	32 767

Nina Kaegi-Braun; Marlena Mueller; Philipp Schuetz at al, Association of nutritional support with in-hospital mortality in malnourished medical patients, JAMA Open, 2021

How are the data form EFFORT compared to other randomized trial data?

Figure 1. Forest Plot Comparing Nutritional Intervention vs Control for Mortality, Stratified by Publication Year

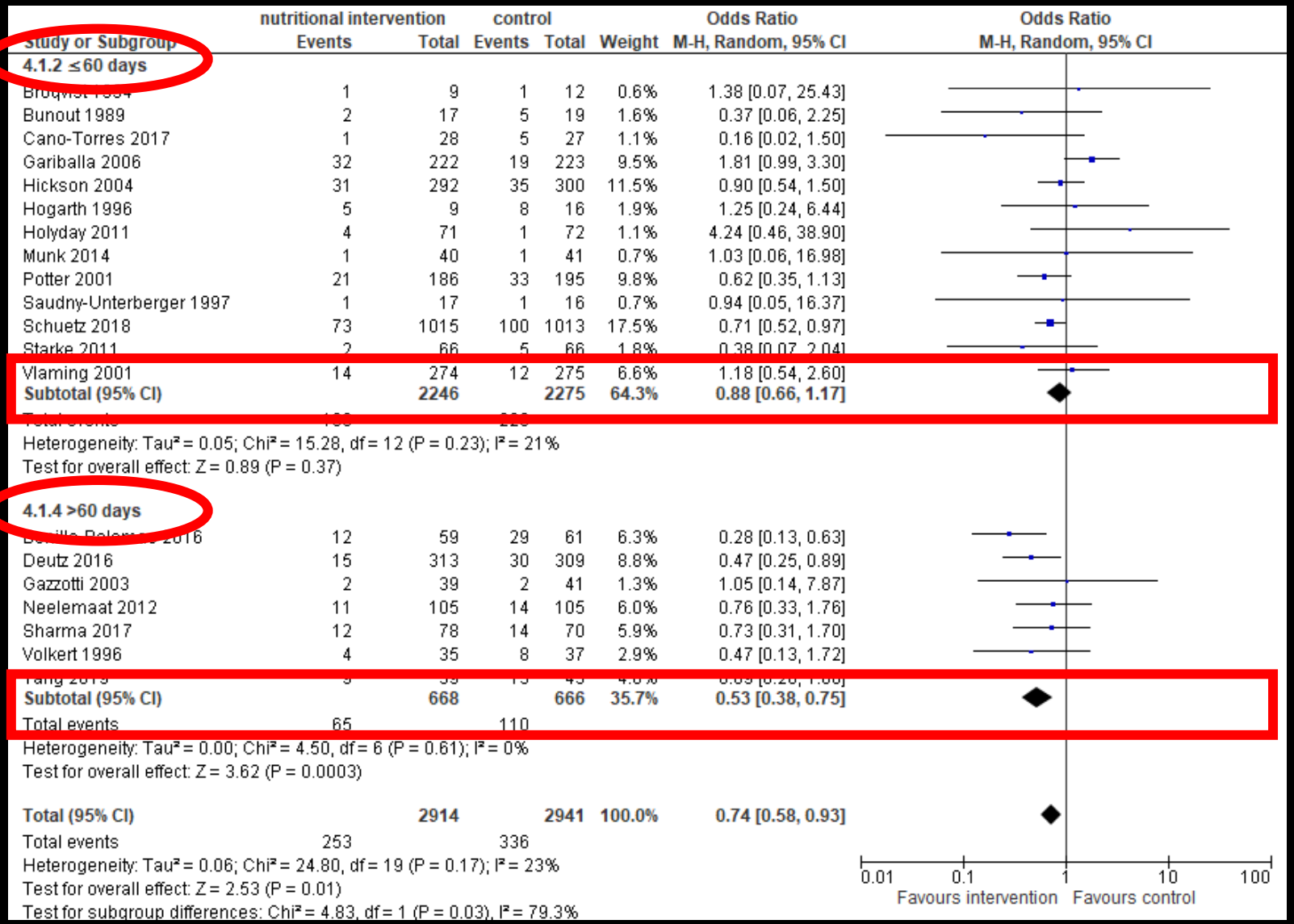
Study or Subgroup	Nutritional Support Events	Nutritional Support Total	Control Events	Control Total	OR (95% CI)	Weight, %
6.1.1 ≤2014						
Broqvist et al,[14] 1994	1	9	1	12	1.38 (0.07-25.43)	0.9
Bunout et al,[15] 1989	2	17	5	19	0.37 (0.06-2.25)	2.2
Gariballa et al,[16] 2006	32	222	19	223	1.81 (0.99-3.30)	10.7
Hickson et al,[18] 2004	31	292	35	300	0.90 (0.54-1.50)	12.4
Hogarth et al,[19] 1996	5	9	8	16	1.25 (0.24-6.44)	2.5
Holyday et al,[20] 2012	4	71	1	72	4.24 (0.46-38.90)	1.5
Munk et al,[23] 2014	1	40	1	41	1.03 (0.06-16.98)	0.9
Neelemaat et al,[24] 2012	11	105	14	105	0.76 (0.33-1.76)	7.2
Potter et al,[26] 2001	21	186	33	195	0.62 (0.35-1.13)	10.9
Saudny-Unterberger et al,[30] 1997	1	17	1	16	0.94 (0.05-16.37)	0.9
Starke et al,[40] 2011	2	66	5	66	0.38 (0.07-2.04)	2.4
Vlaming et al,[32] 2001	14	274	12	275	1.18 (0.54-2.60)	7.8
Volkert et al,[41] 1996	4	35	8	37	0.47 (0.13-1.72)	3.8
Subtotal (95% CI)		1343		1377	0.94 (0.72-1.22)	64.1
Total events	129		143			
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 12.19$, df = 12 ($P = .43$), $I^2 = 2\%$						
Test for overall effect: $z = 0.47$ ($P = .64$)						
6.1.2 ≤2015						
Bonilla-Palomas et al,[34] 2016	12	59	29	61	0.28 (0.13-0.63)	7.6
Cano-Torres et al,[35] 2017	1	28	5	27	0.16 (0.02-1.50)	1.5
Deutz et al,[36] 2016	15	313	30	309	0.47 (0.25-0.89)	10.0
Schuetz et al,[38] 2019	73	1015	100	1013	0.71 (0.52-0.97)	16.8
Subtotal (95% CI)		1415		1410	0.47 (0.28-0.79)	35.9
Total events	101		164			
Heterogeneity: $\tau^2 = 0.13$, $\chi^2 = 6.28$, df = 3 ($P = .10$), $I^2 = 52\%$						
[illegible]						
Total (95% CI)		2758		2787	0.73 (0.56-0.97)	100
Total events	230		307			
Heterogeneity: $\tau^2 = 0.09$, $\chi^2 = 24.67$, df = 16 ($P = .08$), $I^2 = 35\%$						
Test for overall effect: $z = 2.18$ ($P = .03$)						
Test for subgroup differences: $\chi^2 = 5.34$, df = 1 ($P = .02$), $I^2 = 81.3\%$						



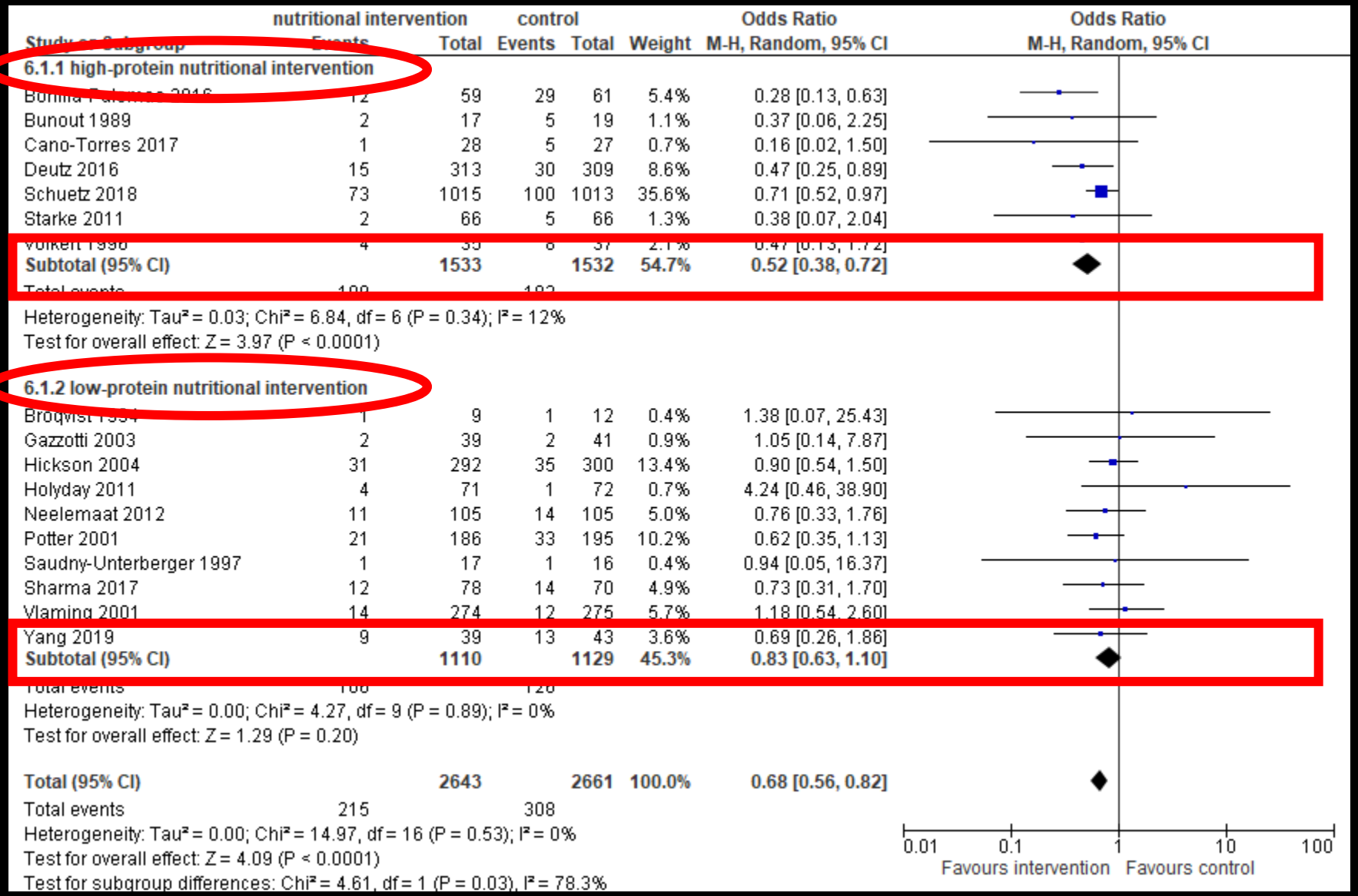
A Mantel-Haenszel random-effects model was used. Squares indicate mean values, with the size of squares reflecting the weight and the lines indicating 95% CIs. Diamonds indicate pooled estimates, with horizontal points of the diamonds indicating 95% CIs. OR indicates odds ratio.

Gomes F. et al. *JAMA Open. 2019*

Mortality: short (≤60d) vs. Long (>60d) intervention



Mortality: high-protein vs. low-protein intervention



Is there a legacy effect inhospital nutrition after long term follow-up?

Clinical Nutrition xxx (xxxx) xxx

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Randomized Control Trials

Six-month outcomes after individualized nutritional support during the hospital stay in medical patients at nutritional risk: Secondary analysis of a prospective randomized trial

Nina Kaegi-Braun [a], Pascal Tribolet [a, b], Filomena Gomes [a, c], Rebecca Fehr [a], Valerie Baechli [a], Martina Geiser [a], Manuela Deiss [a], Alexander Kutz [a], Thomas Bregenzer [d], Claus Hoess [e], Vojtech Pavlicek [e], Sarah Schmid [e], Stefan Bilz [f], Sarah Sigrist [f], Michael Brändle [f], Carmen Benz [f], Christoph Henzen [g], Silvia Mattmann [g], Robert Thomann [h], Jonas Rutishauser [i], Drahomir Aujesky [j], Nicolas Rodondi [j, k], Jacques Donzé [j, l], Zeno Stanga [m], Beat Mueller [a, n], Philipp Schuetz [a, n, *]

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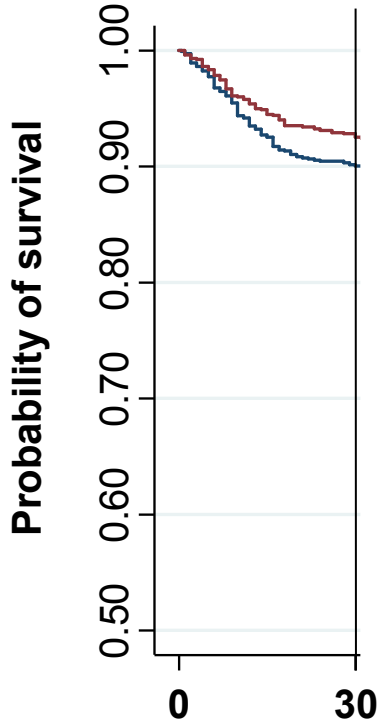
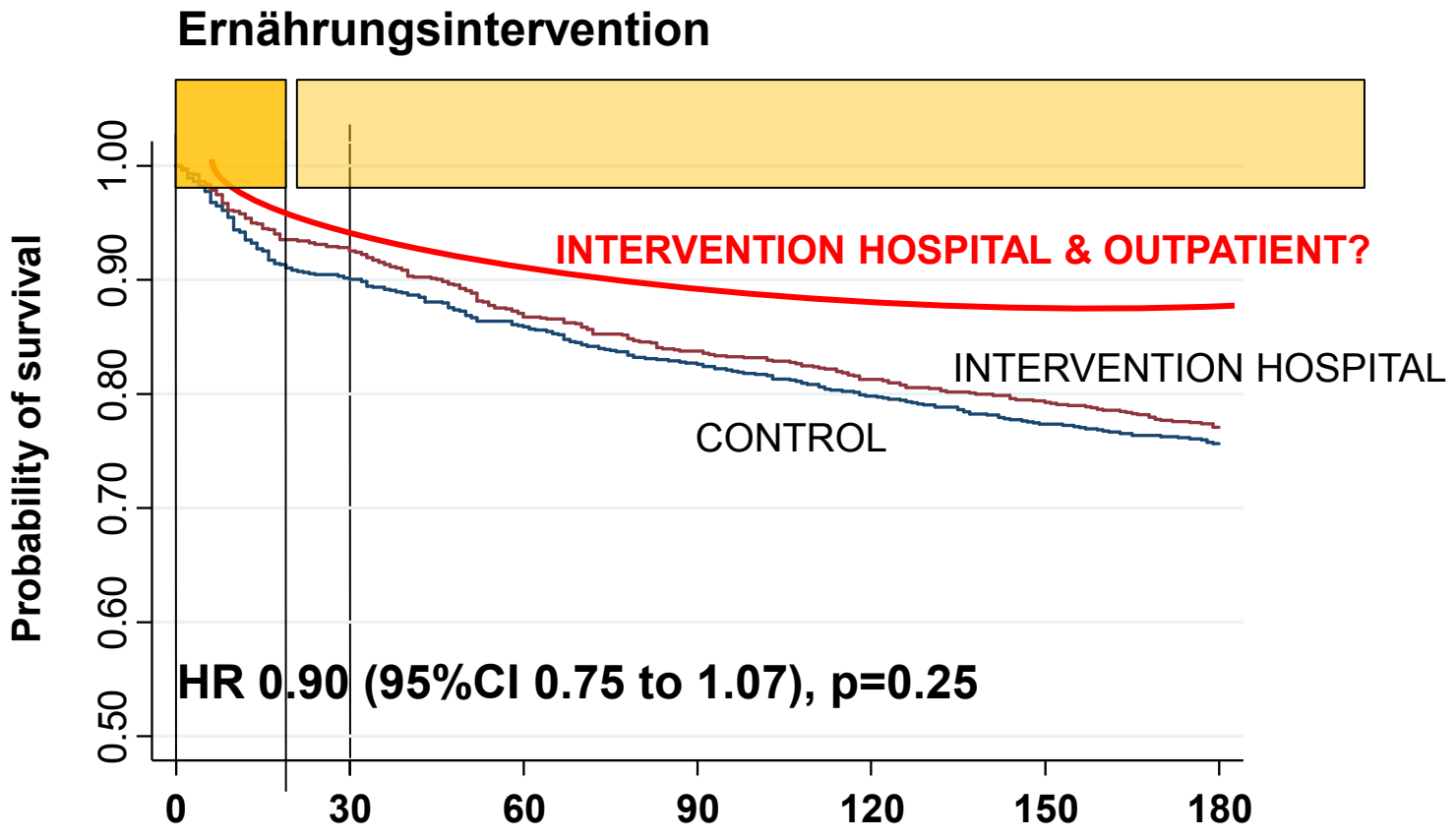
Shortterm - 30-day mortality



Number at risk		
CONTROL	1013	913
INTERVENTION	1015	942

Longterm - 180-day mortality



Number at risk							
CONTROL	1013	913	866	833	804	779	762
INTERVENTION	1015	942	873	840	815	796	773

Should we «individualize» nutritional support according to patient`s comorbidities?

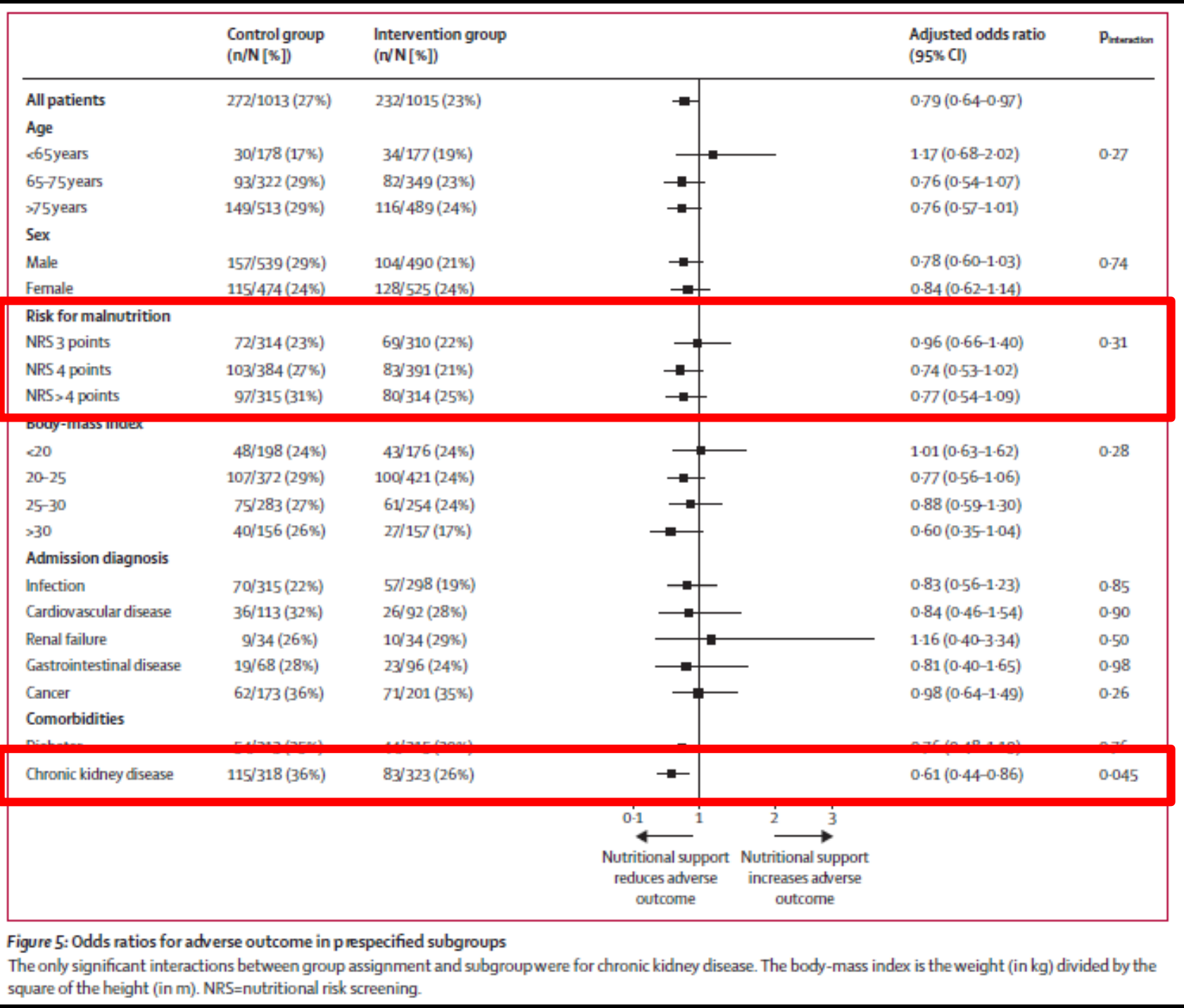


Figure 5: **Odds ratios for adverse outcome in prespecified subgroups**

The only significant interactions between group assignment and subgroup were for chronic kidney disease. The body-mass index is the weight (in kg) divided by the square of the height (in m). NRS=nutritional risk screening.

Schuetz P, et al. *Lancet*. 2019;393(10188):2312-2321.

Should we «individualize» nutritional support according to a patient`s inflammatory response?

JAMA Network Open

Original Investigation | Nutrition, Obesity, and Exercise

Association of Baseline Inflammation With Effectiveness of Nutritional Support Among Patients With Disease-Related Malnutrition

A Secondary Analysis of a Randomized Clinical Trial

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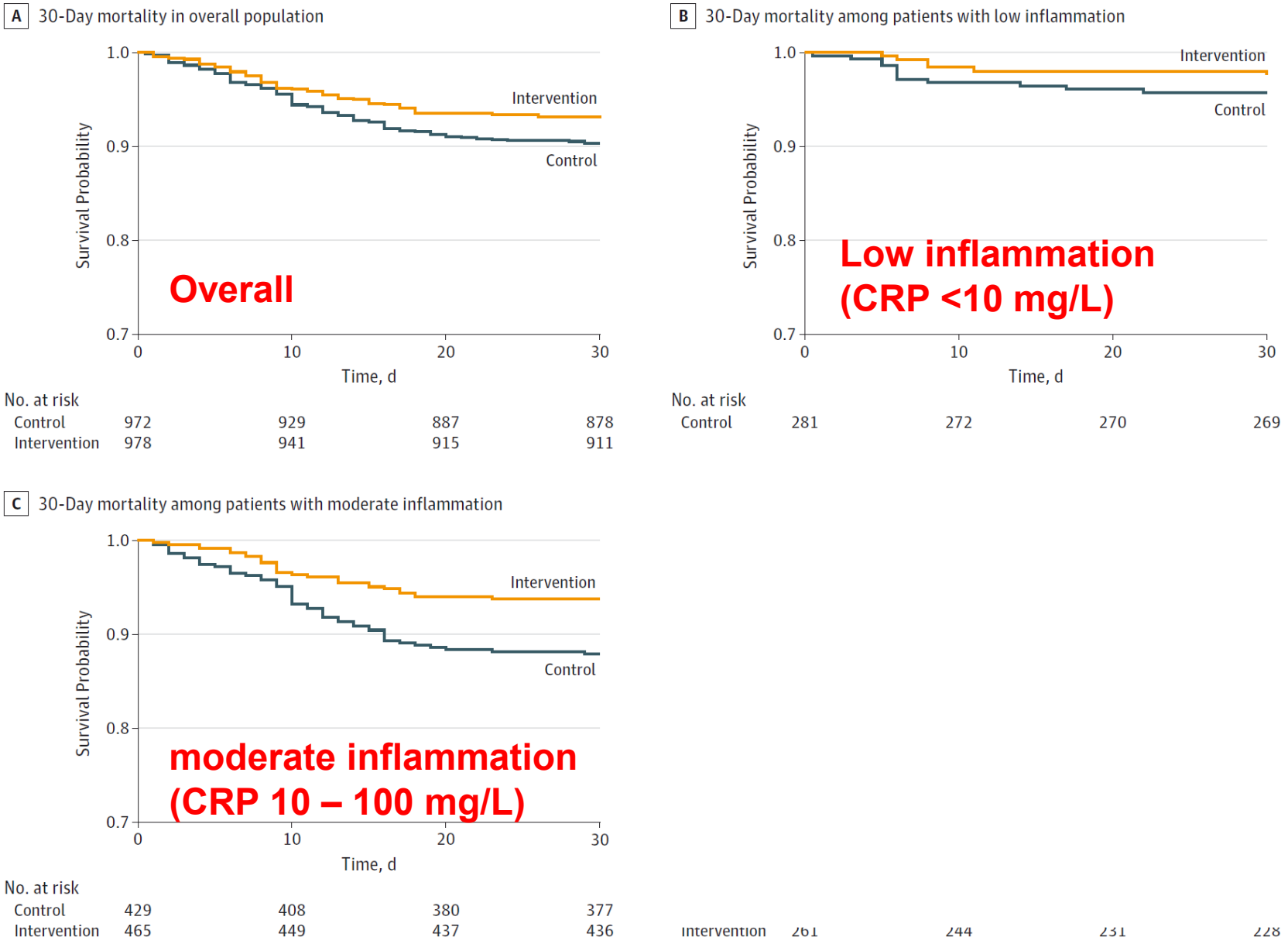
Abstract

IMPORTANCE Inflammation is a key driver of malnutrition during illness and is often accompanied by metabolic effects, including insulin resistance and reduction of appetite. However, it still remains unclear if inflammation influences the response to nutritional support among patients with disease-related malnutrition.

Key Points

Question Does nutritional support have a similar effect on 30-day mortality among patients with high inflammation compared with patients with low or moderate inflammation?

Figure 2. Kaplan-Meier Estimate for Time to Death Within 30-Days According to Inflammatory Status



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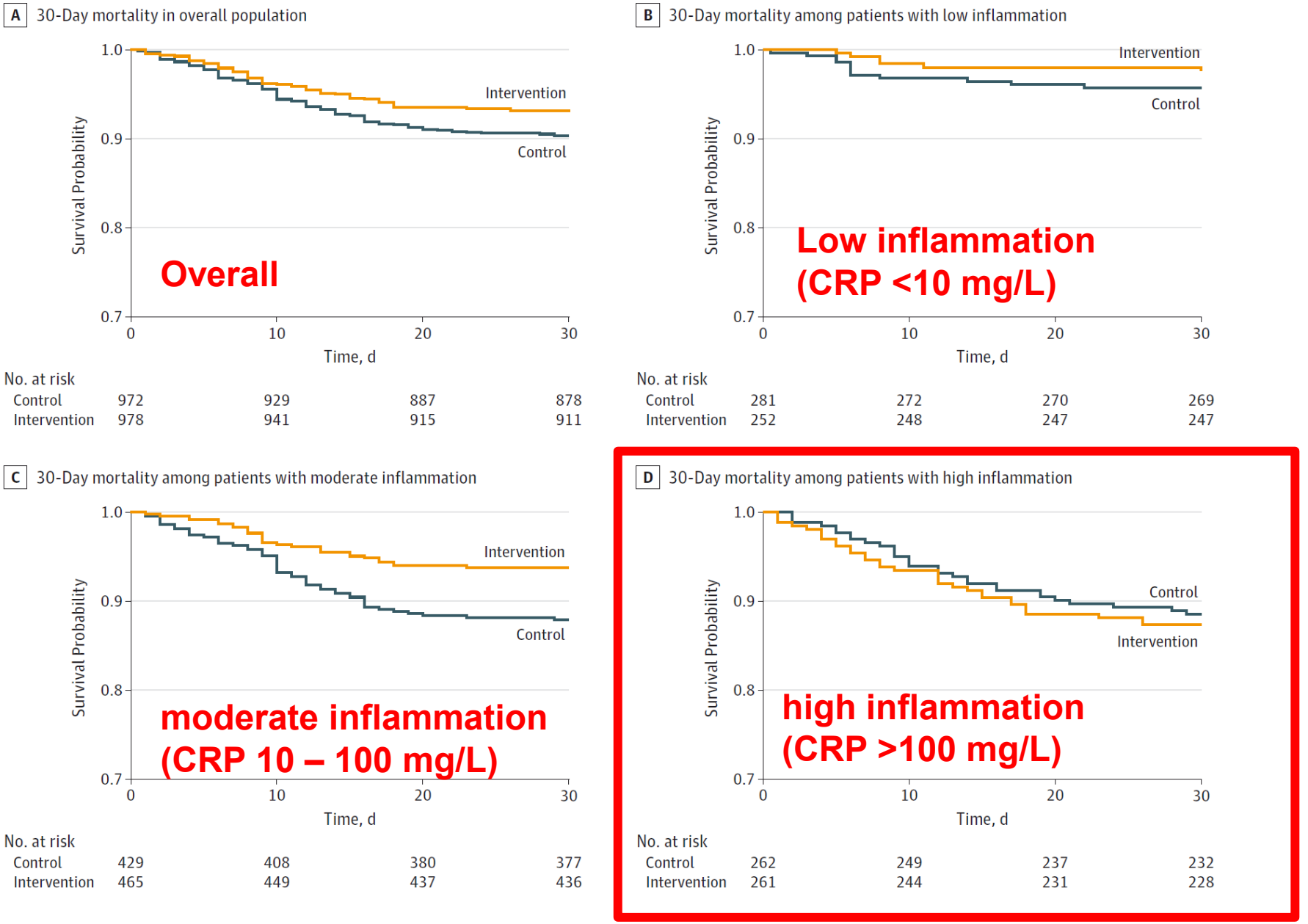


How should we implement these data into clincial routine?

ANNALS FOR HOSPITALISTS

Annals of Internal Medicine

Inpatient Notes: Optimizing Inpatient Nutrition–Why Hospitalists Should Get Involved

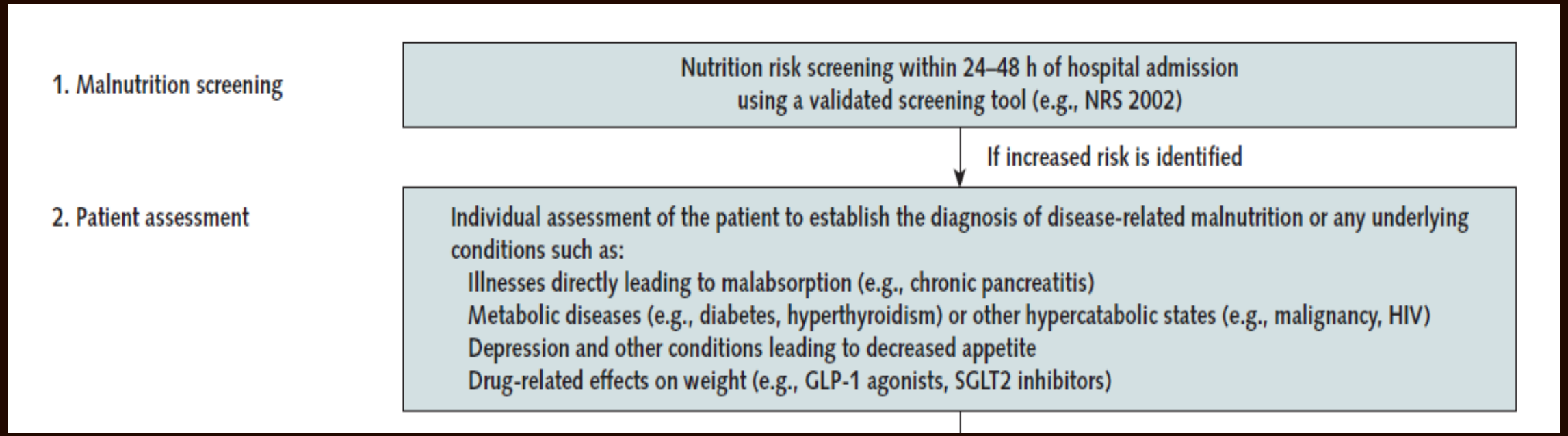
Philipp Schuetz, MD, MPH, and Jeffrey L. Greenwald, MD

Malnutrition is a common condition among newly admitted, medically complex inpatients. Emerging evidence demonstrates that malnutrition directly increases the risk for adverse clinical outcomes, including death, illness, and functional impairments, hospital length of stay, and the risk for hospital readmission (1). Moreover, nutritional status often further deteriorates during the hospital stay because of illness-related loss of appetite, fasting orders for diagnostic studies, or overall suboptimal nutritional management. Data from the United States and Europe show that about 1 in 4

number needed to treat of 25. The trial also found that nutritional support substantially reduced death, with a number needed to treat of 37. A similar positive effect on the risk for death (number needed to treat = 20) was also found in the placebo-controlled, 652-patient NOURISH (Nutrition effect On Unplanned Readmissions and Survival in Hospitalized patients) trial, which studied the effects of using a protein-rich oral supplement on clinical outcomes in malnourished, medical inpatients in the United States (3).

Schuetz P, et al. *Ann Intern Med*. 2020;172(4):HO2-HO3.

NUTRITIONAL SUPPORT ALGORITHM



EFFORT = Effect of early nutritional support on Frailty, Functional Outcomes, and Recovery of malnourished medical inpatients Trial (1); GLP-1 = glucagon-like peptide-1; NRS 2002 = Nutritional Risk Screening 2002 (6); SGLT2 = sodium–glucose cotransporter-2.

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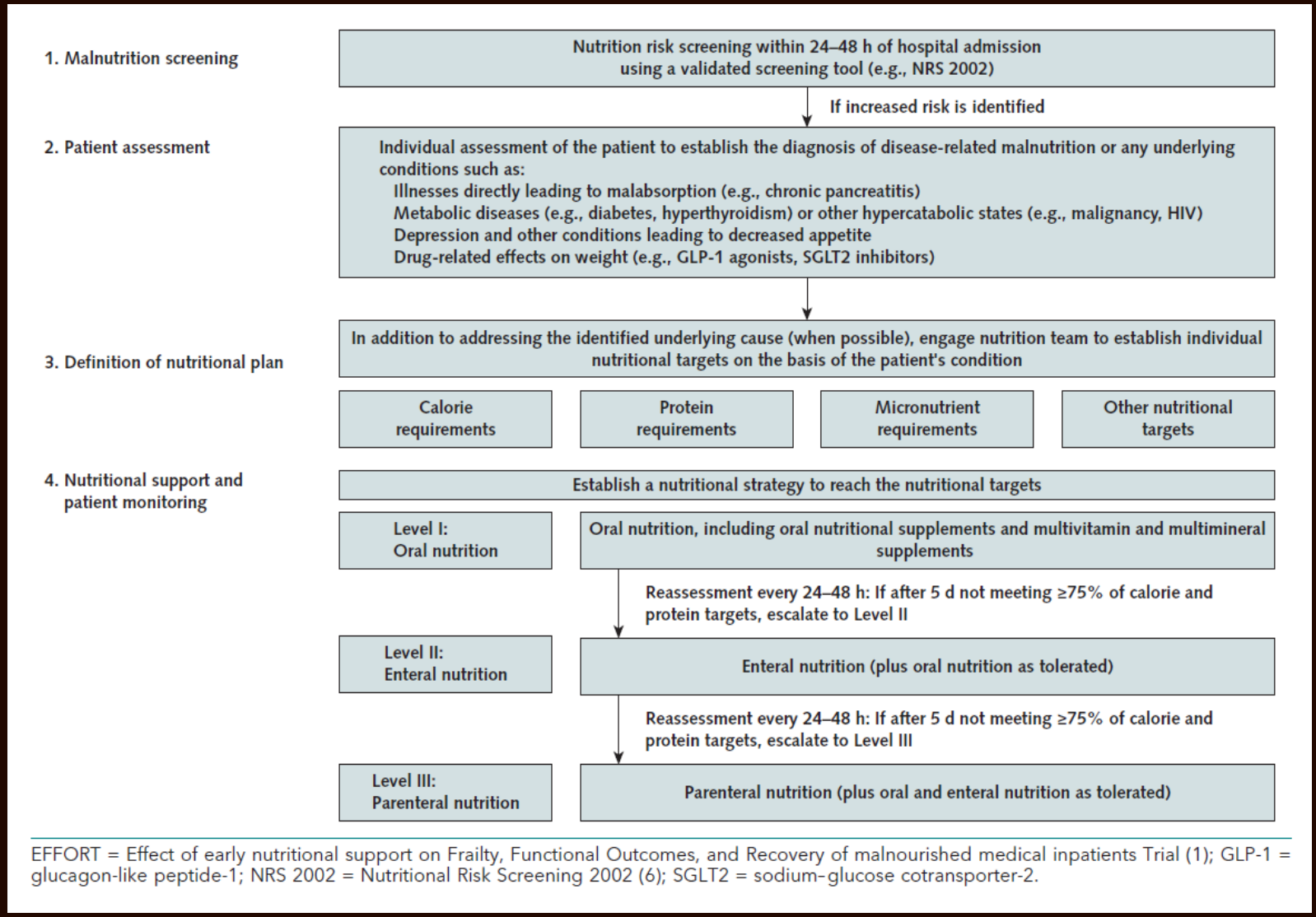

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Summary

- There is increasing evidence that malnutrition is a modifiable risk factor for hospitalized patients with multiple illnesses
- Proactive screening of patients using a validated tool and start of nutritional support protocols should be implemented in the hospital setting to reduce mortality and complications of patients
- In the future, we may need to further individualize nutrition according to the specific situation of our patients including kidney function and inflammatory status
- **Internists should play an active role for early recognition and treatment of disease-related malnutrition**