Nutrition for the malnourished patient: what's the role of Inflammation?

DAPEN Meeting May 2023

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BIDMC & HSPH, Boston

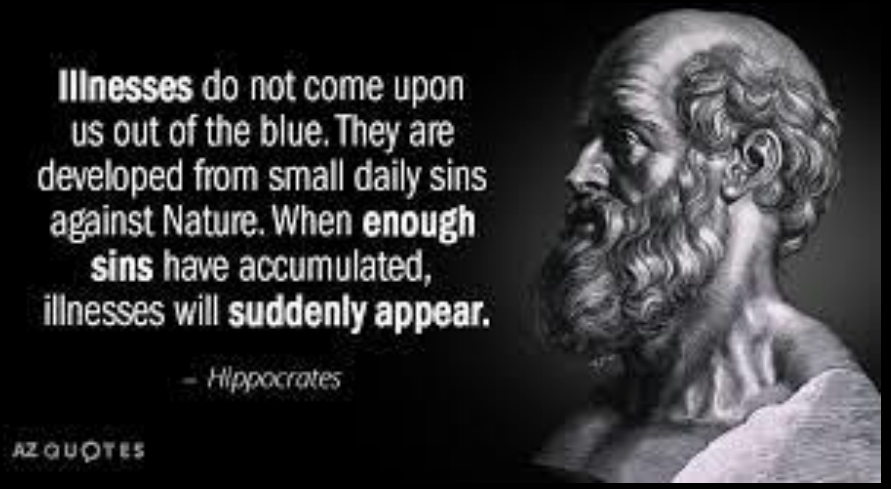
Kantonsspital Aarau

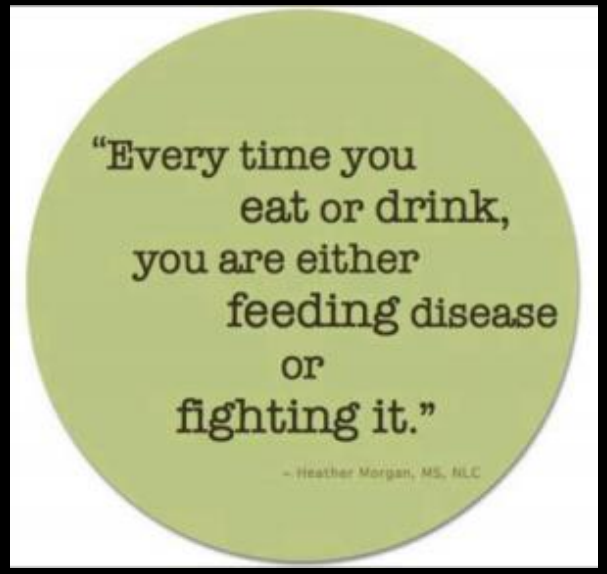
University Hospital Basel

25% of hospitalised patients are «at risk of malnutrition»

But … what are we doing about? How effective is treatment? What treatment is most effective ? Are all malnourished patients the same? …

In Times before «evidence-based medicine»



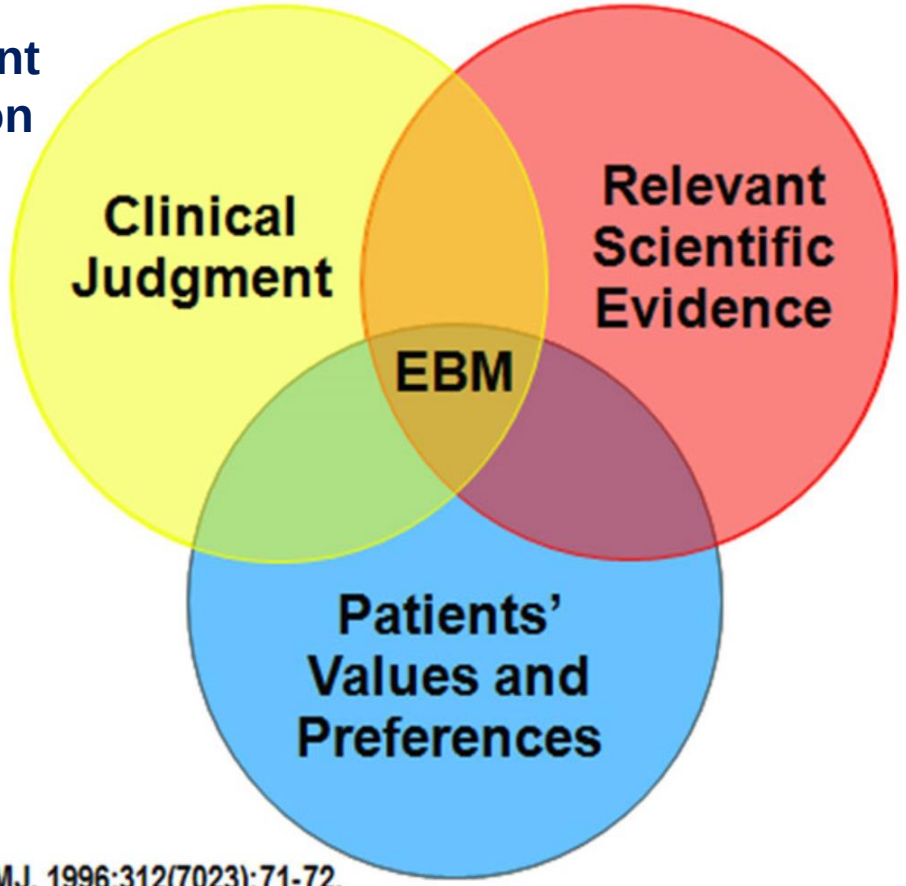


From Evidence based medicine (EBM) to Evidence-based nutrition (EBN)!

Pathophysiology?

Is it really «disease-related malnutrition»?

Did we exclude relevant diseases or medication side effects?



. BMJ. 1996;312(7023):71-72.

The pathophysiology of malnutrition is complex and includes different pathophysiological pathways

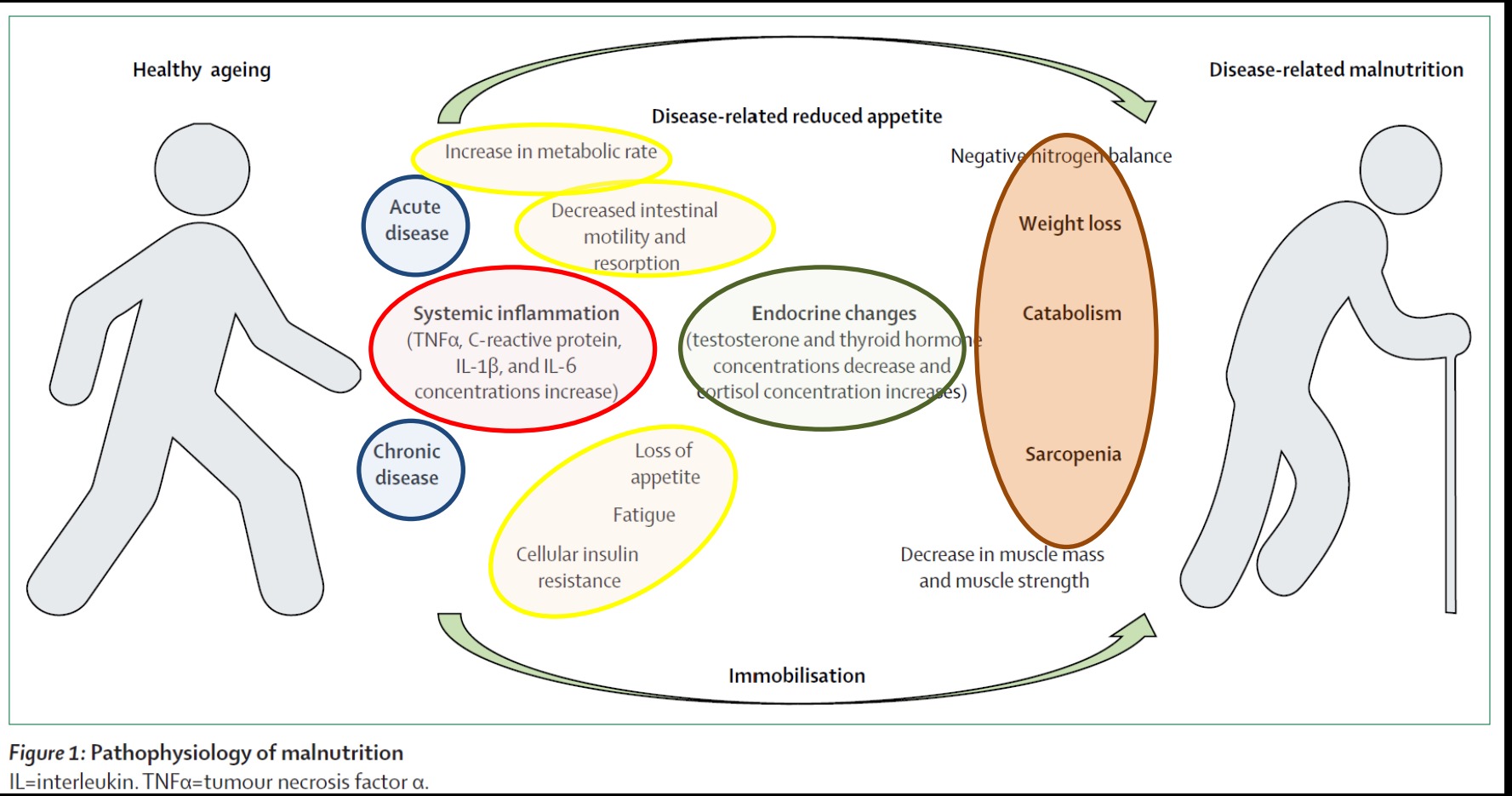


Figure 1: **Pathophysiology of malnutrition**
IL=interleukin. TNFα=tumour necrosis factor α.

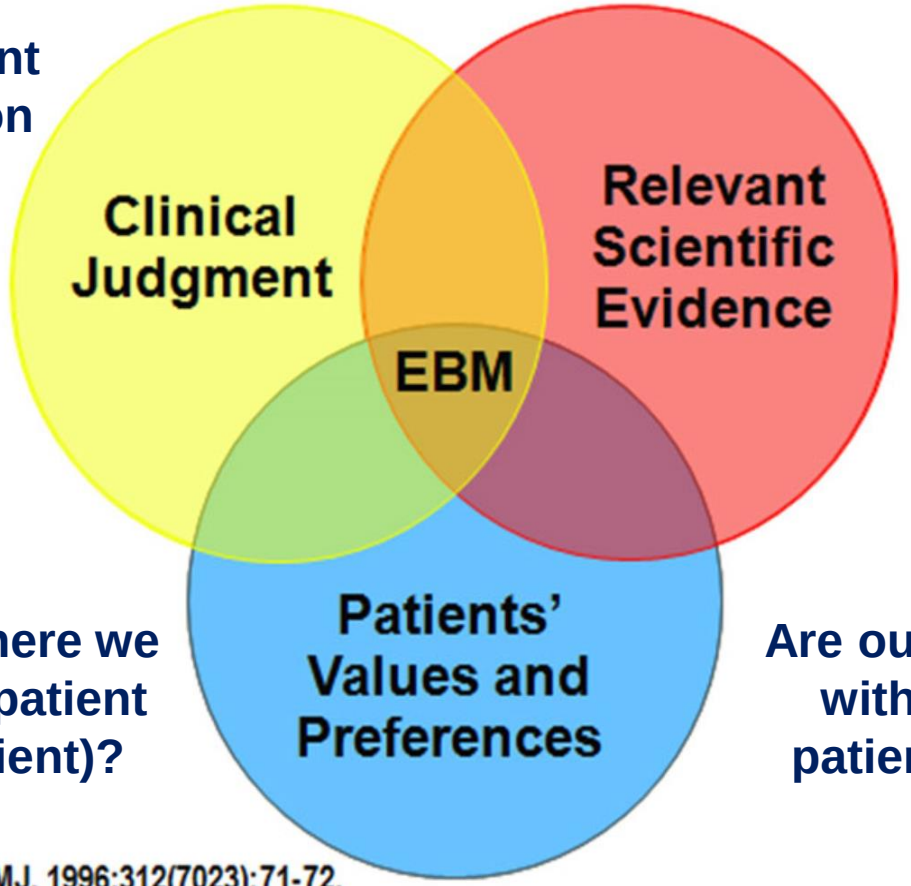
Schuetz P et al, Lancet. 2021 Nov 20;398(10314):1927-1938.

From Evidence based medicine (EBM) to Evidence-based nutrition (EBN)!

Is it really «disease-related malnutrition»?

Did we exclude relevant diseases or medication side effects?

Do we have evidence that Nutritional support improves clincial outcomes for this patient?



Is it a situation where we want to treat the patient (e.g., cancer patient)?

Are our goals aligned with goals of the patient and family?

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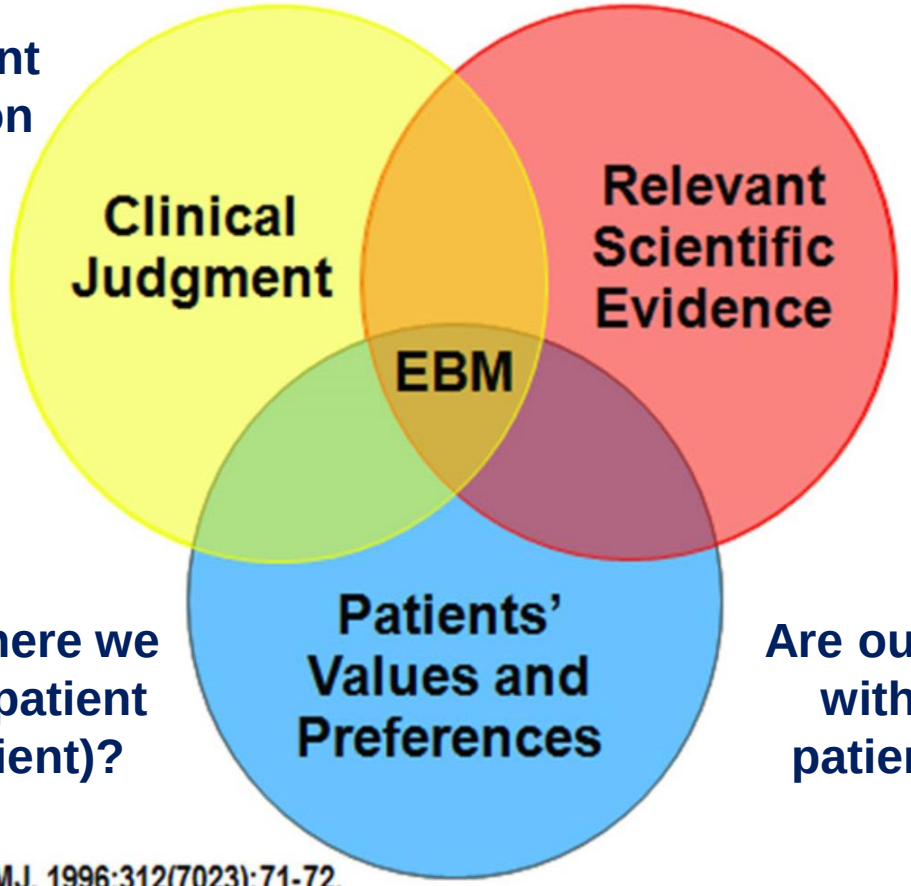


Is it a situation where we want to treat the patient (e.g., cancer patient)?

Are our goals aligned with goals of the patient and family?

. BMJ. 1996;312(7023):71-72.

Lets look back 10 year … how effective was nutrition by then?

Research

JAMA Internal Medicine 2016

Original Investigation

Nutritional Support and Outcomes in Malnourished Medical Inpatients

A Systematic Review and Meta-analysis

Martina R. Bally, MD; Prisca Z. Blaser Yildirim, MD; Lisa Bounoure, PhD; Viktoria L. Gloy, PhD; Beat Mueller, MD; Matthias Briel, MD, MSc; Philipp Schuetz, MD, MPH

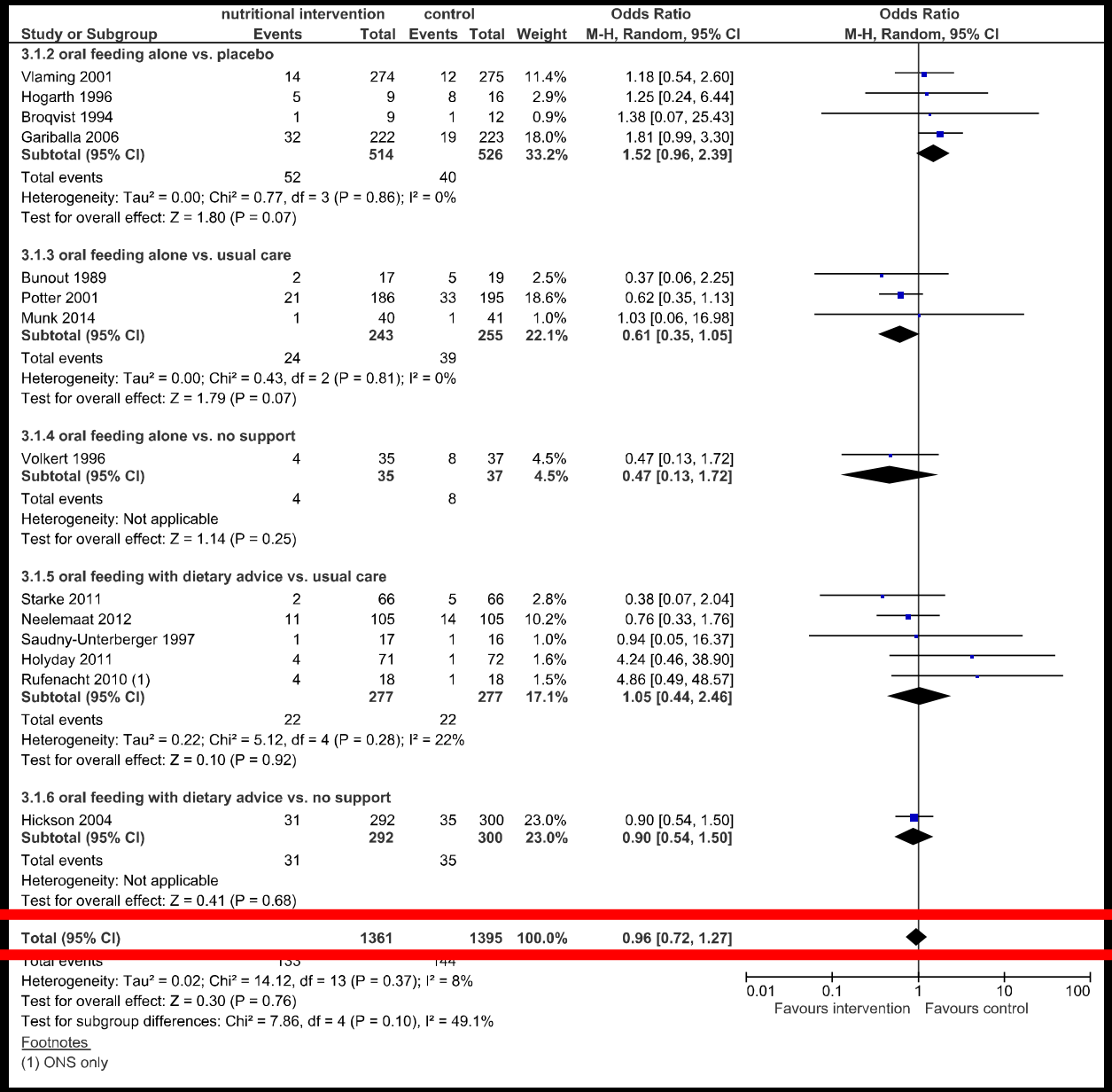
IMPORTANCE During acute illness, nutritional therapy is widely used for medical inpatients with malnutrition or at risk for malnutrition. Yet, to our knowledge, no comprehensive trial has demonstrated that this approach is effective and beneficial for patients.

OBJECTIVE To assess the effects of nutritional support on outcomes of medical inpatients with malnutrition or at risk for malnutrition in a systematic review of randomized clinical trials (RCTs).

Invited Commentary

Supplemental content at jamainternalmedicine.com

Very few randomized-controlled studies
No significant effect of nutrition on mortality



Study or Subgroup	nutritional intervention Events	Total	control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.2 oral feeding alone vs. placebo						
Vlaming 2001	14	274	12	275	11.4%	1.18 [0.54, 2.60]
Hogarth 1996	5	9	8	16	2.9%	1.25 [0.24, 6.44]
Broqvist 1994	1	9	1	12	0.9%	1.38 [0.07, 25.43]
Gariballa 2006	32	222	19	223	18.0%	1.81 [0.99, 3.30]
Subtotal (95% CI)		**514**		**526**	**33.2%**	**1.52 [0.96, 2.39]**
Total events	52		40			
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
3.1.3 oral feeding alone vs. usual care						
Bunout 1989	2	17	5	19	2.5%	0.37 [0.06, 2.25]
Potter 2001	21	186	33	195	18.6%	0.62 [0.35, 1.13]
Munk 2014	1	40	1	41	1.0%	1.03 [0.06, 16.98]
Subtotal (95% CI)		**243**		**255**	**22.1%**	**0.61 [0.35, 1.05]**
Total events	24		39			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
3.1.4 oral feeding alone vs. no support						
Volkert 1996	4	35	8	37	4.5%	0.47 [0.13, 1.72]
Subtotal (95% CI)		**35**		**37**	**4.5%**	**0.47 [0.13, 1.72]**
Total events	4		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.14 (P = 0.25)						
3.1.5 oral feeding with dietary advice vs. usual care						
Starke 2011	2	66	5	66	2.8%	0.38 [0.07, 2.04]
Neelemaat 2012	11	105	14	105	10.2%	0.76 [0.33, 1.76]
Saudny-Unterberger 1997	1	17	1	16	1.0%	0.94 [0.05, 16.37]
Holyday 2011	4	71	1	72	1.6%	4.24 [0.46, 38.90]
Rufenacht 2010 (1)	4	18	1	18	1.5%	4.86 [0.49, 48.57]
Subtotal (95% CI)		**277**		**277**	**17.1%**	**1.05 [0.44, 2.46]**
Total events	22		22			
Heterogeneity: Tau² = 0.22; Chi² = 5.12, df = 4 (P = 0.28); I² = 22%						
Test for overall effect: Z = 0.10 (P = 0.92)						
3.1.6 oral feeding with dietary advice vs. no support						
Hickson 2004	31	292	35	300	23.0%	0.90 [0.54, 1.50]
Subtotal (95% CI)		**292**		**300**	**23.0%**	**0.90 [0.54, 1.50]**
Total events	31		35			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Total (95% CI)		**1361**		**1395**	**100.0%**	**0.96 [0.72, 1.27]**
Total events	133		144			
Heterogeneity: Tau² = 0.02; Chi² = 14.12, df = 13 (P = 0.37); I² = 8%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Test for subgroup differences: Chi² = 7.86, df = 4 (P = 0.10), I² = 49.1%						

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours intervention Favours control

Footnotes

(1) ONS only

Cochrane

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Feeding support in hospitalised adults at risk of undernourishment

Published:
19 May 2017

Authors:
Feinberg J, Nielsen E, Korang S, Halberg Engell K, Nielsen M, Zhang K, Didriksen M, Lund L, Lindahl N, Hallum S, Liang N, Xiong W, Yang X, Brunsgaard P, Garioud A, Safi S, Lindschou J, Kondrup J, luud C, Jakobsen JC

Primary Review Group:
Hepato-Biliary Group

Review question

We reviewed the benefits and harms
hospital at risk of undernourishment
the formally-validated to 'according t

Background

People who are malnourished when t
increased risk of death or are more lik
Delivering feeding support might help
be associated with a severe underlyin
interventions aimed at improving the
would not be the poor nutritional sta
death or of experiencing a serious ha

Authors' conclusions:

There is low-quality evidence for the effects of nutrition support on mortality and serious adverse events. Based on the results of our review, it does not appear to lead to a risk ratio reduction of approximately 10% or more in either all-cause mortality or serious adverse events at short-term and long-term follow-up.

There is very low-quality evidence for an increase in weight with nutrition support at the end of treatment in hospitalised adults determined to be at nutritional risk. The effects of nutrition support on all remaining outcomes are unclear.

Despite the clinically heterogenous population and the high risk of bias of all included trials, our analyses showed limited signs of statistical heterogeneity. Further trials may be warranted, assessing enteral nutrition (tube-feeding) for different patient groups. Future trials ought to be conducted with low risks of systematic errors and low risks of random errors, and they also ought to assess health-related quality of life.

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JAMA Internal Medicine | Review LESS IS MORE

2017 Update on Medical Overuse
A Systematic Review

Daniel J. Morgan, MD, MS; Sanket S. Dhruva, MD; Eric R. Coon, MD; Scott M. Wright, MD; Debora

IMPORTANCE Overuse of medical care is a well-recogni

OBJECTIVE To identify and highlight origi re most relevant to understanding medica

EVIDENCE REVIEW A es on PubMed published in 2016 coupled gh-impact journals to identify article ticles were appraised for their i

2252 articles, 1224 of which addressed medical overuse. Of most relevant based on originality, methodologic quality, and potentially affected. The 10 most influential articles were selected by ensus. Select findings from the studies include the lack of benefit of esophageal echocardiography in the workup of cryptogenic stroke, increasing use of computed tomography in the emergency department from 2.2% to 9.4% from 2001 to 2010, and carotid ultrasonography and revascularization being performed for uncertain or inappropriate indications with 95% frequency. Likewise, services for which harms are likely to outweigh benefits include treatment for early-stage prostate cancer, which provides no mortality benefit but increases absolute risk of erectile dysfunction by 10% to 30%, oxygen for patients with moderate chronic obstructive pulmonary disease, surgery for meniscal tear with mechanical symptoms, and nutritional interventions for inpatients with malnutrition.

Author Affiliations: Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore (Morgan); Department of Hospital Epidemiology, Veterans Affairs Maryland Health Care System, Baltimore (Morgan); Robert Wood Johnson Foundation Clinical Scholars Program, Yale University School of Medicine, New Haven, Connecticut (Dhruva); Department of Veterans Affairs, West Haven, Connecticut (Dhruva); Department of Pediatrics, University of Utah School of Medicine, Salt Lake City (Coon);

We have to do the randomized trials!

EFFORT: effect of early nutritional therapy on frailty, functional outcomes and recovery of malnourished medical inpatients trial

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**

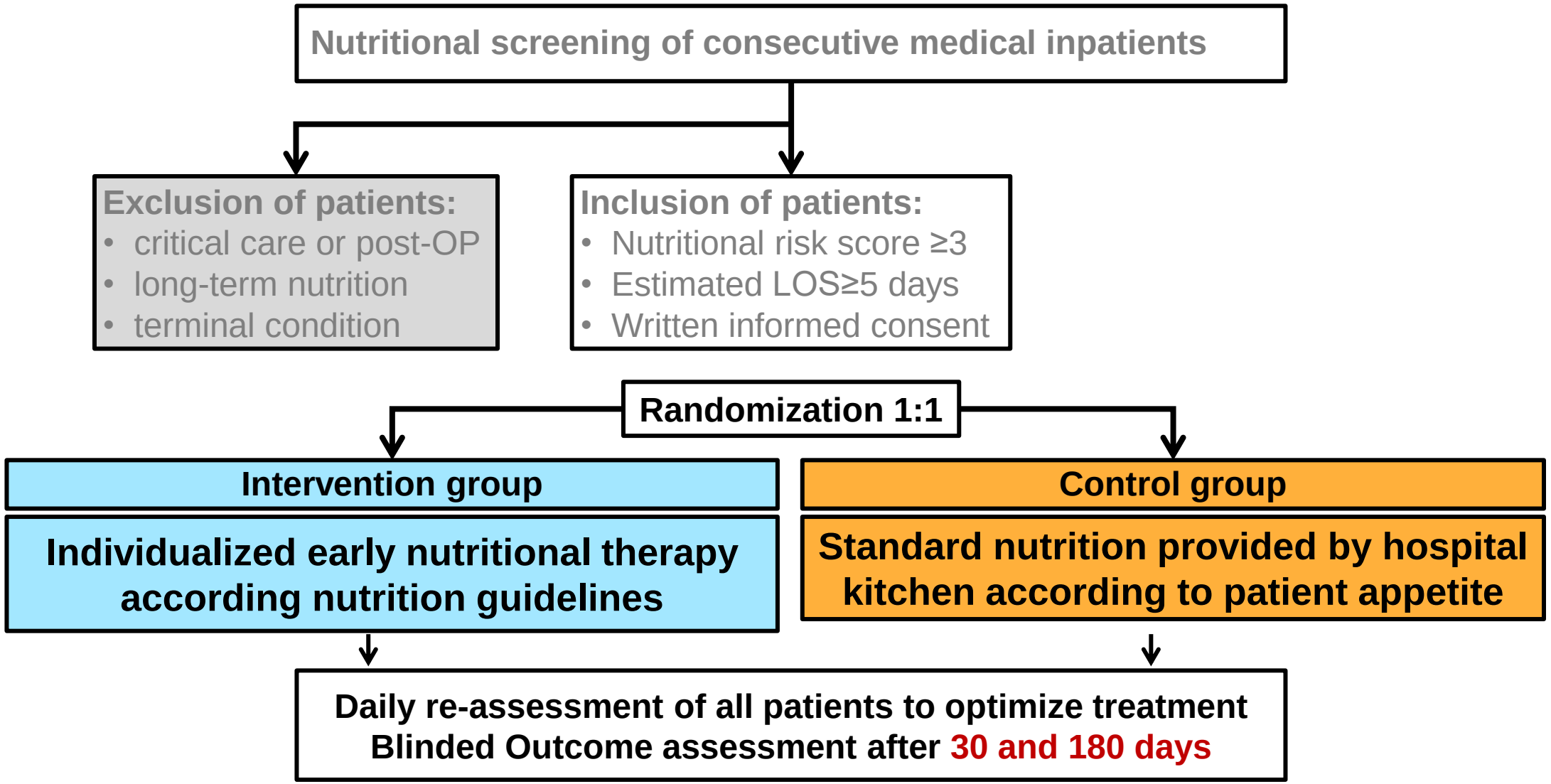
Summary

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-

Published Online
April 25, 2019
http://dx.doi.org/10.1016/S0140-6736(18)32776-4

See Online/Comment

The EFFORT trial - study flow diagram



Nutritional algorithm used during the trial

Nutrition risk screening (NRS 2002) within 48 h of hospital admission in all patients

If increased risk for malnutrition → individual assessment of the patient → if risk for malnutrition is present and nutritional therapy is not contraindicated → establish a strategy to achieve individual nutritional targets

Individual nutrition targets

Caloric requirements	**Protein requirements**	**Micronutrient requirements**	**Specific targets**
Harris-Benedict equation with adjusted bodyweight or indirect calorimetry	1·2–1·5 g/kg bodyweight per day (0·8 g/kg of bodyweight per day in patients with renal failure with no dialysis)	Multivitamin use; other micronutrients according to specific laboratory results	Disease-specific adaptations (eg, medium-chain triglycerides, low potassium in patients with renal failure)

Schuetz P et al, Lancet. 2019 Jun 8;393(10188):2312-2321.

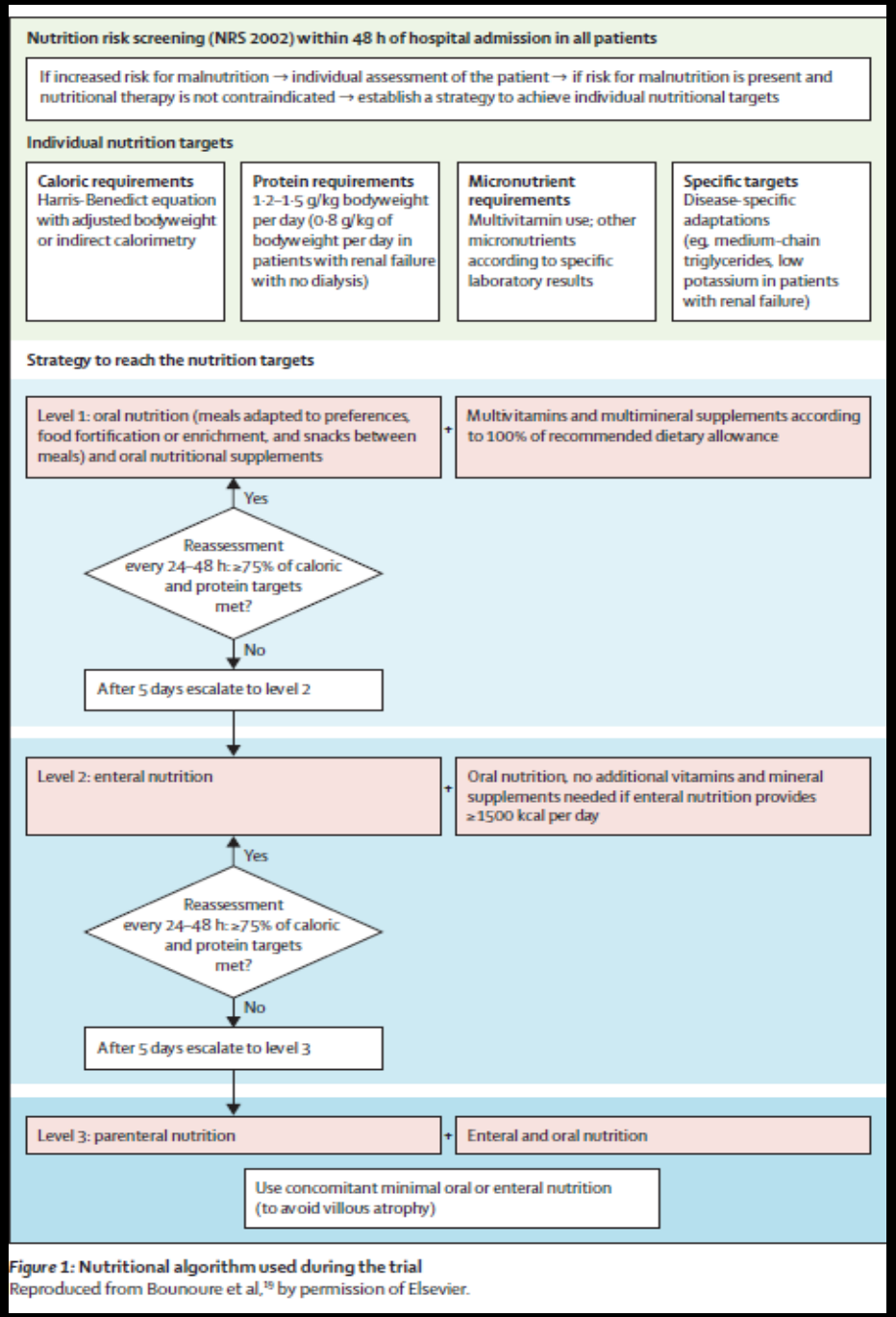


Figure 1: **Nutritional algorithm used during the trial**
Reproduced from Bounoure et al,[19] by permission of Elsevier.

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.

Principals results

Results-Hospital Stay

Intervention group

Nutritional Support prescribed= 939 patients

- **Food adjustment, food fortification, oral nutritional supplements and individualised input from a specialist dietitian: 91% patients**
- Enteral nutrition was used: 8 patients
- Parenteral nutrition were used: 12 patients

Daily caloric intake: **1501 kcal/d**

Daily protein intake: **57 g/d**

Control group

Nutritional Support prescribed= 122 patients

- Usual care hospital food

Daily caloric intake: **1211 kcal/d**

Daily protein intake: **47 g/d**

Intervention group had significantly higher mean daily caloric and protein intake

- Difference **290 kcal per day** [95% CI 240–340])
- Difference **10 g protein per day** [8–12]

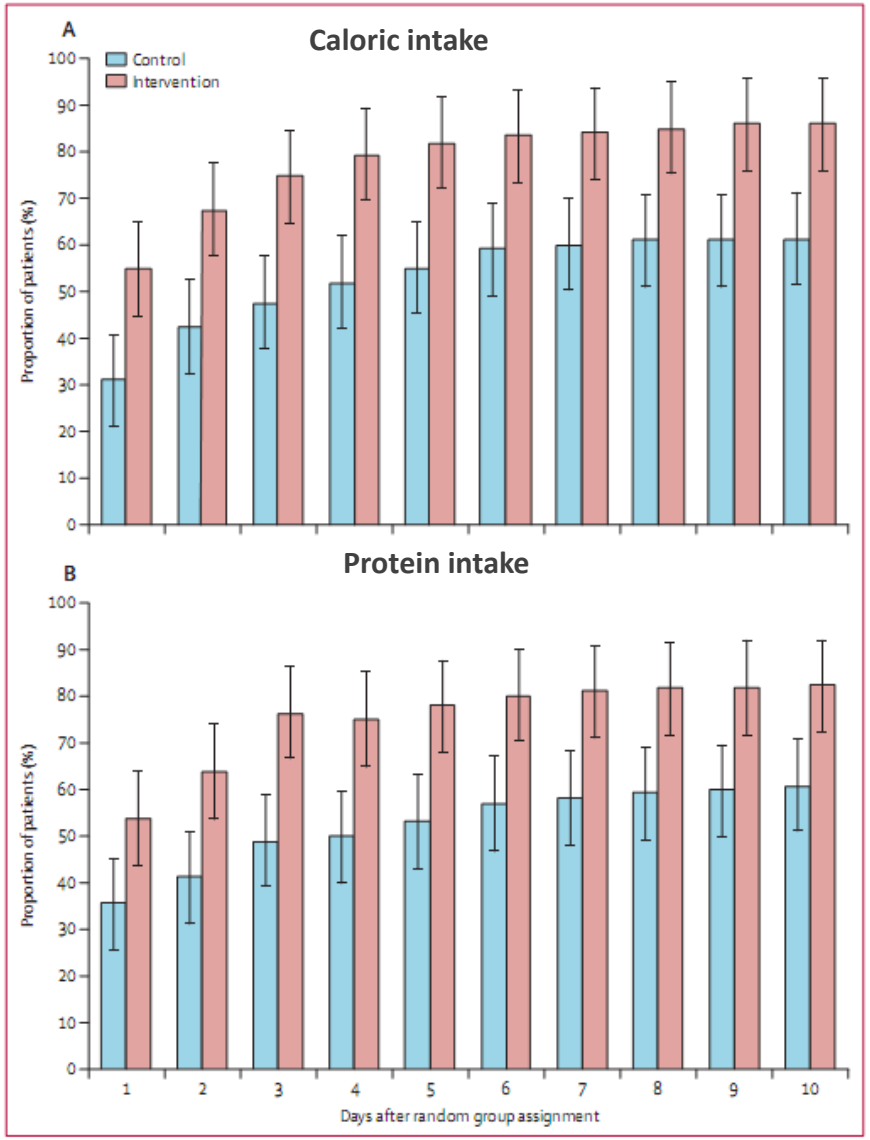


Figure 3: Proportion of patients reaching caloric (A) and protein (B) requirements during the first 10 days after random group assignment

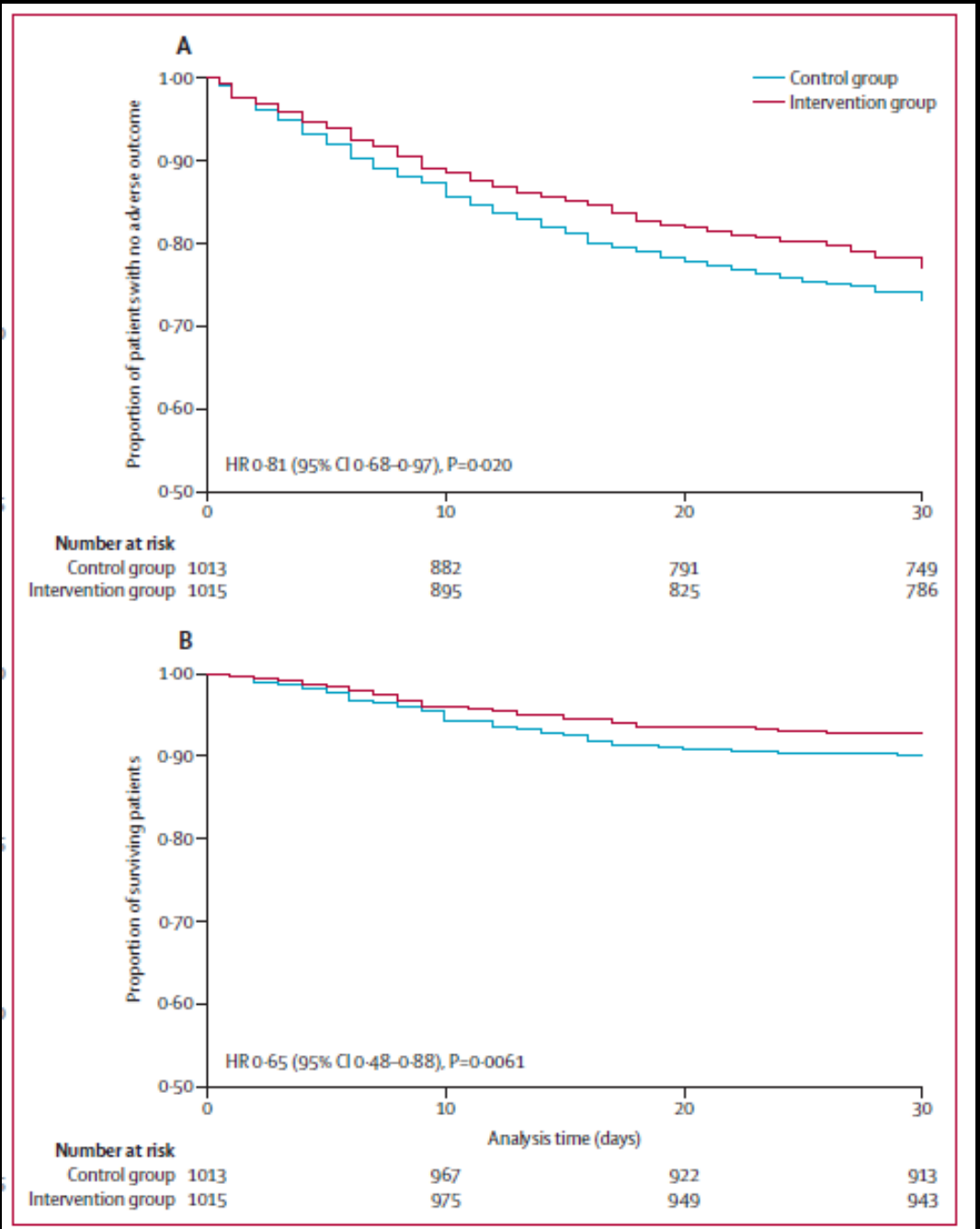


Figure 4: Kaplan-Meier estimates of the cumulative incidence of the primary endpoint and all-cause mortality
(A) Time to the first event of the composite primary endpoint (log-rank p value=0·035). (B) Time to death (log-rank p value=0·031).

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

THE LANCET

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"EFFORT has provided 21st century evidence to substantiate the aphorism of Hippocrates: 'The patient ought likewise to be consider'd, whether he is able to hold out with the prescribed diet, even in the height of the disease; for if the diet is not sufficient, the patient will grow too faint, and be overcome by the disease.'"

See Comment page 2278

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Dileep N Lobo
Gastrointestinal Surgery, Nottingham Digestive Diseases Centre, The University of Nottingham, Nottingham NG7 2UH, UK; and MRC Arthritis Research UK Centre for Musculoskeletal Ageing Research, School of Life Sciences, The University of Nottingham, Nottingham, UK
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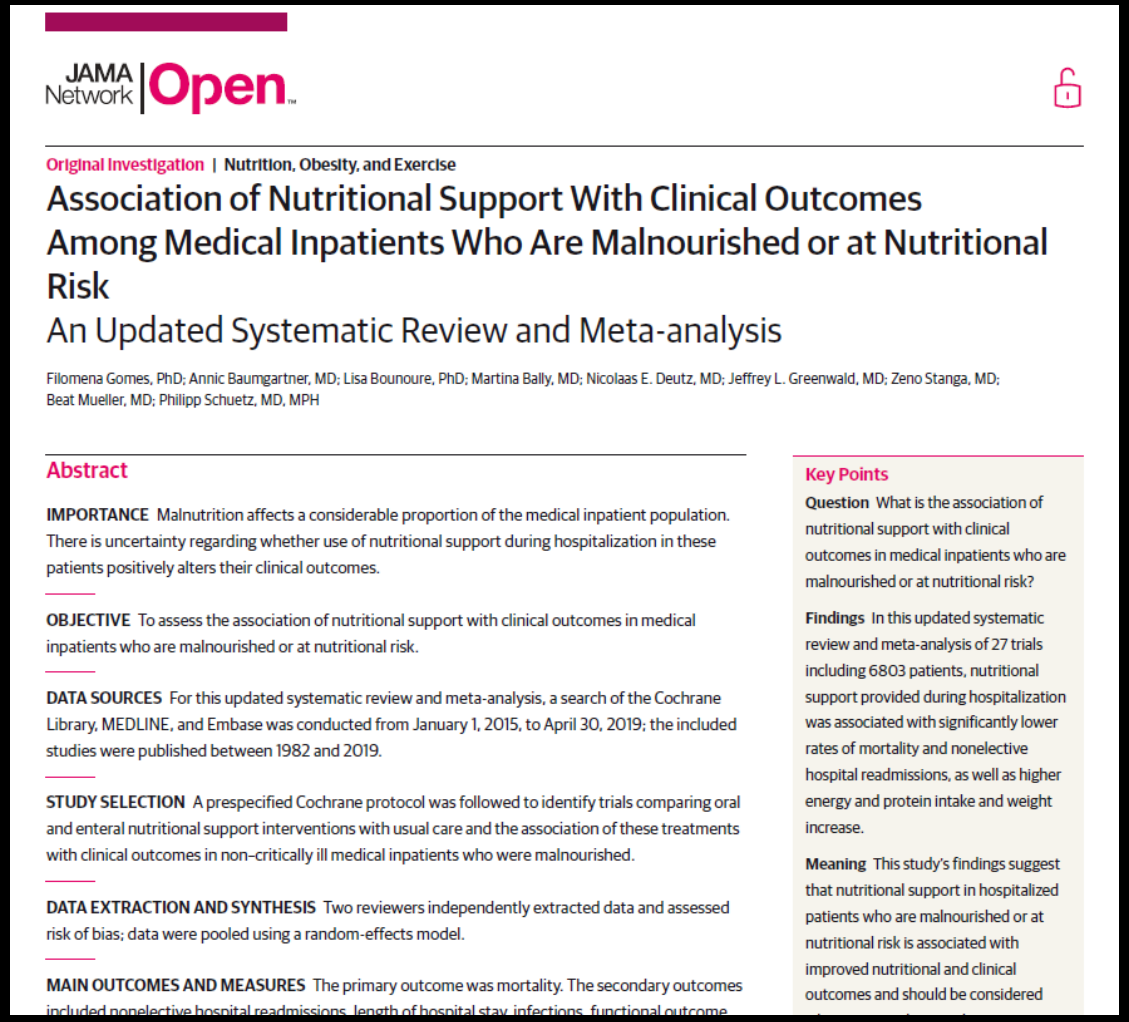
Comment

Improving outcomes with a little EFFORT

Published Online
April 25, 2019
http://dx.doi.org/10.1016/S0140-6736(18)32856-3
See Online/Articles
http://dx.doi.org/10.1016/S0140-6736(18)32776-4

The adverse effect of excessive weight loss on clinical outcomes was documented over 80 years ago when Hiram Studley[1] showed that, in patients undergoing surgery for perforated duodenal ulcer, postoperative mortality was ten times greater in those who had lost more than 20% of their bodyweight preoperatively, compared with those who had lost less. Similarly, less pronounced results were shown in medical (not undergoing surgical treatment) patients. The potential importance of these observations was emphasised by a study from the 1990s showing that 30% of infections, length of stay, and functional improvement,[6] and these findings were also supported by a Cochrane review.[7] A study not included in these analyses showed that although a high-protein oral nutritional supplement containing β-hydroxy-β-methylbutyric acid had no effect on the primary composite endpoint of incidence of death or non-elective readmission up to 90 days after discharge when compared with placebo, it was associated with decreased mortality and improved indices of nutritional status during the period of observation.[8]

Updated metaanalysis regarding effects of nutritional treatment on mortality in medical inpatients



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Original Investigation | Nutrition, Obesity, and Exercise

Association of Nutritional Support With Clinical Outcomes Among Medical Inpatients Who Are Malnourished or at Nutritional Risk

An Updated Systematic Review and Meta-analysis

Filomena Gomes, PhD; Annic Baumgartner, MD; Lisa Bounoure, PhD; Martina Bally, MD; Nicolaas E. Deutz, MD; Jeffrey L. Greenwald, MD; Zeno Stanga, MD; Beat Mueller, MD; Philipp Schuetz, MD, MPH

Abstract

IMPORTANCE Malnutrition affects a considerable proportion of the medical inpatient population. There is uncertainty regarding whether use of nutritional support during hospitalization in these patients positively alters their clinical outcomes.

OBJECTIVE To assess the association of nutritional support with clinical outcomes in medical inpatients who are malnourished or at nutritional risk.

DATA SOURCES For this updated systematic review and meta-analysis, a search of the Cochrane Library, MEDLINE, and Embase was conducted from January 1, 2015, to April 30, 2019; the included studies were published between 1982 and 2019.

STUDY SELECTION A prespecified Cochrane protocol was followed to identify trials comparing oral and enteral nutritional support interventions with usual care and the association of these treatments with clinical outcomes in non–critically ill medical inpatients who were malnourished.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data and assessed risk of bias; data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES The primary outcome was mortality. The secondary outcomes included nonelective hospital readmissions, length of hospital stay, infections, functional outcome

Key Points

Question What is the association of nutritional support with clinical outcomes in medical inpatients who are malnourished or at nutritional risk?

Findings In this updated systematic review and meta-analysis of 27 trials including 6803 patients, nutritional support provided during hospitalization was associated with significantly lower rates of mortality and nonelective hospital readmissions, as well as higher energy and protein intake and weight increase.

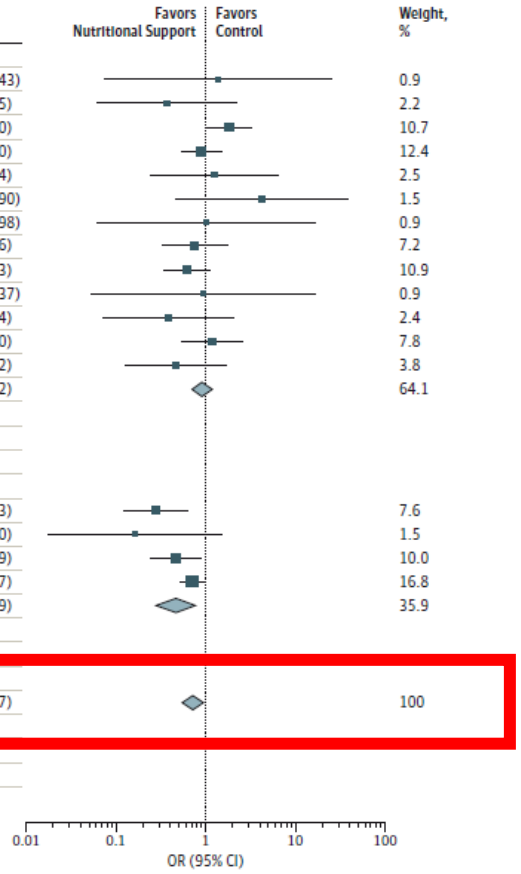
Meaning This study's findings suggest that nutritional support in hospitalized patients who are malnourished or at nutritional risk is associated with improved nutritional and clinical outcomes and should be considered

Gomes F, JAMA Netw Open. 2019 Nov 1;2(11):e1915138.

25% Mortality reduction associated when medical inpatients receive nutritional treatment

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

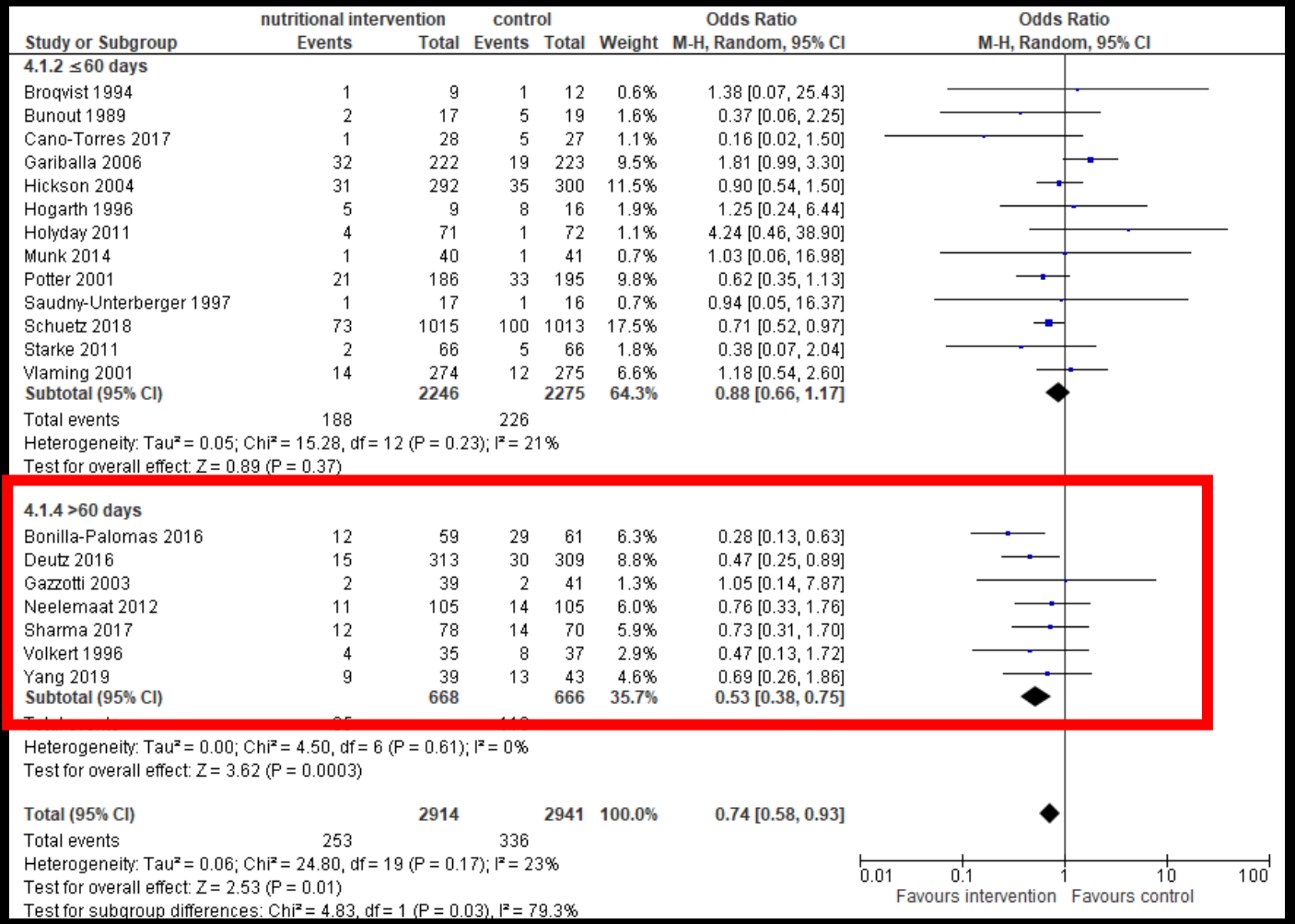
Study or Subgroup	Nutritional Support Events	Nutritional Support Total	Control Events	Control Total	OR (95% CI)	Weight, %
6.1.1 ≤2014						
Broqvist et al,[14] 1994	1	9	1	12	1.38 (0.07-25.43)	0.9
Bunout et al,[15] 1989	2	17	5	19	0.37 (0.06-2.25)	2.2
Gariballa et al,[16] 2006	32	222	19	223	1.81 (0.99-3.30)	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			
Test for overall effect: z = 2.85 ($P = .004$)						
Total (95% CI)		2758		2787	0.73 (0.56-0.97)	100
Total events	230		307			
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, JAMA Netw Open. 2019 Nov 1;2(11):e1915138.

Subanalysis 1:
Long (>60 days) intervention are most effective



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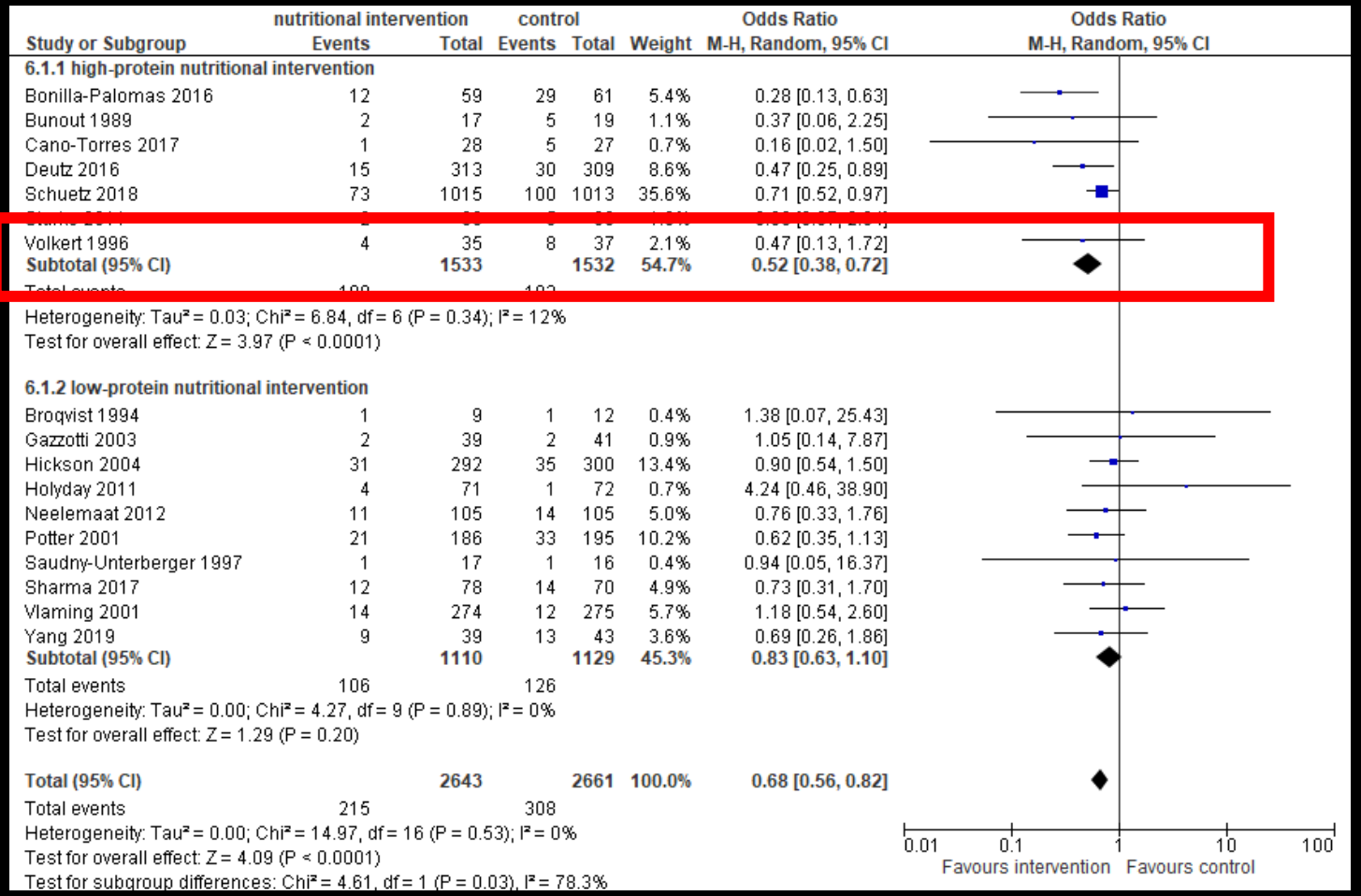
Hickson 2004	31	292	35	300	11.5%	0.90 [0.54, 1.50]
Hogarth 1996	5	9	8	16	1.9%	1.25 [0.24, 6.44]
Holyday 2011	4	71	1	72	1.1%	4.24 [0.46, 38.90]
Munk 2014	1	40	1	41	0.7%	1.03 [0.06, 16.98]
Potter 2001	21	186	33	195	9.8%	0.62 [0.35, 1.13]
Saudny-Unterberger 1997	1	17	1	16	0.7%	0.94 [0.05, 16.37]
Schuetz 2018	73	1015	100	1013	17.5%	0.71 [0.52, 0.97]
Starke 2011	2	66	5	66	1.8%	0.38 [0.07, 2.04]
Vlaming 2001	14	274	12	275	6.6%	1.18 [0.54, 2.60]
Subtotal (95% CI)		**2246**		**2275**	**64.3%**	**0.88 [0.66, 1.17]**
Total events	188		226			
Heterogeneity: Tau² = 0.05; Chi² = 15.28, df = 12 (P = 0.23); I² = 21%						
Test for overall effect: Z = 0.89 (P = 0.37)						
4.1.4 >60 days						
Bonilla-Palomas 2016	12	59	29	61	6.3%	0.28 [0.13, 0.63]
Deutz 2016	15	313	30	309	8.8%	0.47 [0.25, 0.89]
Gazzotti 2003	2	39	2	41	1.3%	1.05 [0.14, 7.87]
Neelemaat 2012	11	105	14	105	6.0%	0.76 [0.33, 1.76]
Sharma 2017	12	78	14	70	5.9%	0.73 [0.31, 1.70]
Volkert 1996	4	35	8	37	2.9%	0.47 [0.13, 1.72]
Yang 2019	9	39	13	43	4.6%	0.69 [0.26, 1.86]
Subtotal (95% CI)		**668**		**666**	**35.7%**	**0.53 [0.38, 0.75]**
Heterogeneity: Tau² = 0.00; Chi² = 4.50, df = 6 (P = 0.61); I² = 0%						
Test for overall effect: Z = 3.62 (P = 0.0003)						
Total (95% CI)		**2914**		**2941**	**100.0%**	**0.74 [0.58, 0.93]**
Total events	253		336			
Heterogeneity: Tau² = 0.06; Chi² = 24.80, df = 19 (P = 0.17); I² = 23%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Chi² = 4.83, df = 1 (P = 0.03), I² = 79.3%						

Kaegi-Braun N, Clin Nutr ESPEN. 2021 Oct;45:45-54.

Subanalysis 2:
High protein interventions are most effective



Kaegi-Braun N, Clin Nutr ESPEN. 2021 Oct;45:45-54.

ESPEN Guideline recommendations on polymorbid patients

Clinical Nutrition 37 (2018) 336–353

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

ESPEN guidelines on nutritional support for polymorbid internal medicine patients

Filomena Gomes [a, n, 1], Philipp Schuetz [a, n, *, 1], Lisa Bounoure [a, n], Peter Austin [b], María Ballesteros-Pomar [c], Tommy Cederholm [d], Jane Fletcher [e], Alessandro Laviano [f], Kristina Norman [g], Kalliopi-Anna Poulia [h], Paula Ravasco [i], Stephane M. Schneider [j], Zeno Stanga [k], C. Elizabeth Weekes [l], Stephan C. Bischoff [m]

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[b] Oxford and Southampton University Hospitals, United Kingdom
[c] Complejo Asistencial Universitario de León, Spain
[d] Uppsala University, Sweden
[e] Queen Elizabeth Hospital, Birmingham, United Kingdom
[f] Sapienza University of Rome, Italy
[g] Charité University Medicine Berlin, Germany
[h] Laiko General Hospital of Athens, Greece
[i] University of Lisbon, Portugal
[j] University of Nice Sophia-Antipolis, France
[k] University Hospital and University of Bern, Switzerland
[l] Guy's & St. Thomas' NHS Foundation Trust and King's College London, United Kingdom
[m] Institute of Nutritional Medicine, University of Hohenheim, Stuttgart, Germany
[n] Medical Faculty, University of Basel, Switzerland

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SUMMARY

Background & aims: Polymorbidity (also known as multimorbidity) – defined as the co-occurrence of at least two chronic health conditions – is highly prevalent, particularly in the hospitalized population. Nonetheless, clinical guidelines largely address individual diseases and rarely account for polymorbidity. The aim of this project was to develop guidelines on nutritional support for polymorbid patients hospitalized in medical wards.

Methods: The methodology used for the development of the current project follows the standard operating procedures for ESPEN guidelines. It started with an initial meeting of the Working Group in January 2015, where twelve key clinical questions were developed that encompassed different aspects of nutritional support: indication, route of feeding, energy and protein requirements, micronutrient requirements, disease-specific nutrients, timing, monitoring and procedure of intervention. Systematic literature searches were conducted in three different databases (Medline, Embase and the Cochrane Library), as well as in secondary sources (e.g. published guidelines), until April 2016. Retrieved abstracts were screened to identify relevant studies that were used to develop recommendations, which were followed by submission to Delphi voting rounds.

Results: From a total of 4532 retrieved abstracts, 38 relevant studies were analyzed and used to generate a guideline draft that proposed 22 recommendations and four statements. The results of the first online voting showed a strong consensus (agreement of >90%) in 68% of recommendations and 75% of statements, and consensus (agreement of >75–90%) in 32% of recommendations and 25% of statements.

Abbreviations: BI, Barthel Index; βHMB, β-hydroxy β-methylbutyrate; CG, Control Group; DRM, disease-related malnutrition; EN, enteral nutrition; GEB, Guidelines Editorial Board; IC, indirect calorimetry; IG, Intervention Group; LOS, length of hospital stay; MNA(-sf), Mini Nutritional Assessment (short form); NRS 2002, Nutritional Risk Score 2002; ONS, oral nutritional supplement(s); PICO, population of interest, interventions, comparisons, outcomes; PN, parenteral nutrition; QoL, quality of life; REE, resting energy expenditure; RCT, randomized controlled trial; SGA, Subjective Global Assessment; SIGN, Scottish Intercollegiate Guidelines Network; TEE, total energy expenditure; WG, Working Group.

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E-mail address: philipp.schuetz@unibas.ch (P. Schuetz).
[1] F.G. and P.S. contributed equally to this study.

http://dx.doi.org/10.1016/j.clnu.2017.06.025

- **<u>Screening</u>: In polymorbid medical inpatients, a nutritional screening method using different validated tools should be applied to identify malnutrition risk. In patients at risk, a more detailed assessment should be performed and a treatment plan should be developed, to consent an early adequate nutritional therapy**
  (Grade of recommendation B) e strong consensus (100% agreement)

- **<u>Protein:</u> Polymorbid medical inpatients requiring nutritional support shall receive a minimum of 1.0 g of protein/kg of body weight per day in order to prevent body weight loss, reduce the risk of complications and hospital readmission and improve functional outcome**
  (Grade of recommendation A) e strong consensus (95% agreement)

Main Points

Association Between Malnutrition and Clinical Outcomes

- Patients requiring intensive care unit (ICU) care and diagnosed with malnutrition (using Subjective Global Assessment [SGA]) may have higher hospital mortality compared to well-nourished patients requiring ICU care.
- Patients requiring ICU care and diagnosed with malnutrition (using SGA) are likely to experience prolonged hospital length of stay compared to well-nourished patients requiring ICU care.
- Patients requiring ICU care and diagnosed with malnutrition (using Mini Nutritional Assessment [MNA]) may experience more hospital acquired complications compared to well-nourished patients requiring ICU care.
- Patients hospitalized due to traumatic injury and screened at risk of malnutrition (using Nutritional Risk Screening [NRS]-2002) may experience more hospital acquired conditions compared to well-nourished patients.
- Patients hospitalized with heart failure and diagnosed with malnutrition (using several different measurement tools) may have higher mortality compared to well-nourished patients with heart failure.
- Patients hospitalized with cancer and diagnosed with malnutrition (using SGA) may experience prolonged hospital length of stay compared to well-nourished patients.
- Patients hospitalized with cirrhosis awaiting transplantation and diagnosed with malnutrition (using SGA) may have higher pre-transplant mortality compared to well-nourished patients.

Effectiveness of Screening on Clinical Outcomes

- No studies met inclusion criteria to address effectiveness of screening or diagnostic assessment on clinical outcomes, primarily because studies lacked an appropriate control group.
- This evidence gap underscores the need for future research that addresses the effectiveness of various measurement tools for malnutrition on clinical outcomes. Such research is vital to standardize malnutrition assessment and further understand its downstream implications on patient-relevant outcomes.

Effectiveness of Hospital-Initiated Interventions for Malnutrition

- Hospital-initiated malnutrition interventions (i.e., specialized nutrition care, protein/calorie supplementation) likely decrease mortality compared to usual care.
- Hospital-initiated malnutrition interventions may improve quality of life compared to usual care.

But - what happens once the patient leaves the hospital?

Longterm effects of nutritional support in EFFORT patients (Stopp of treatment after discharge)

Clinical Nutrition 40 (2021) 812–819

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

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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[b] Department of Health Professions, Bern University of Applied Sciences, Bern, Switzerland
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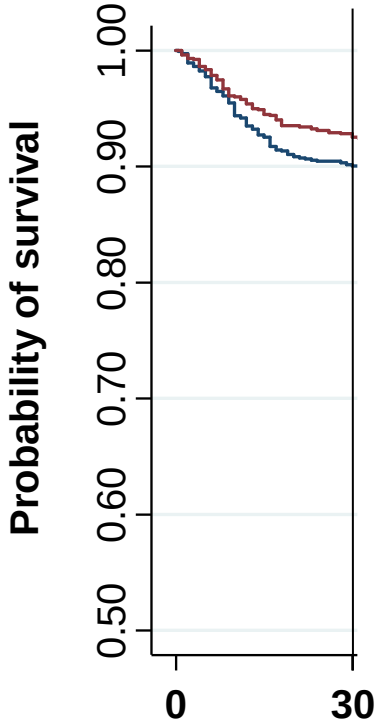
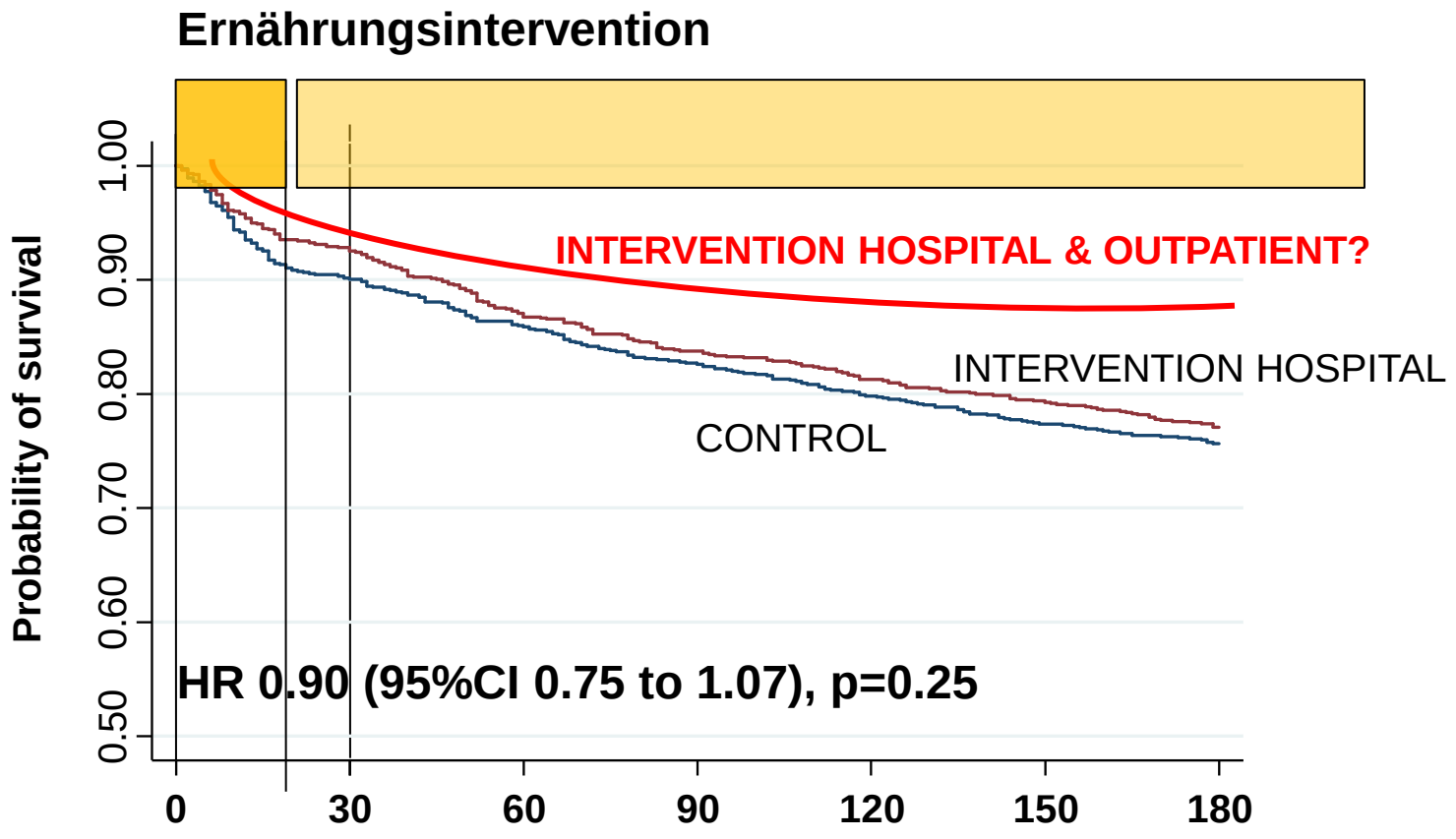
[d] Internal Medicine, Spital Lachen, Switzerland
[e] Internal Medicine, Kantonsspital Münsterlingen, Switzerland
[f] Internal Medicine & Endocrinology/Diabetes, Kantonsspital St.Gallen, Switzerland
[g] Internal Medicine, Kantonsspital Luzern, Switzerland
[h] Internal Medicine, Bürgerspital Solothurn, Switzerland
[i] Internal Medicine, Kantonsspital Baselland, Switzerland
[j] Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland
[k] Institute of Primary Health Care (BIHAM), University of Bern, Switzerland

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

How effective is nutrition in the long-term?

… now recruiting patients!

But - what happens once the patient leaves the hospital?

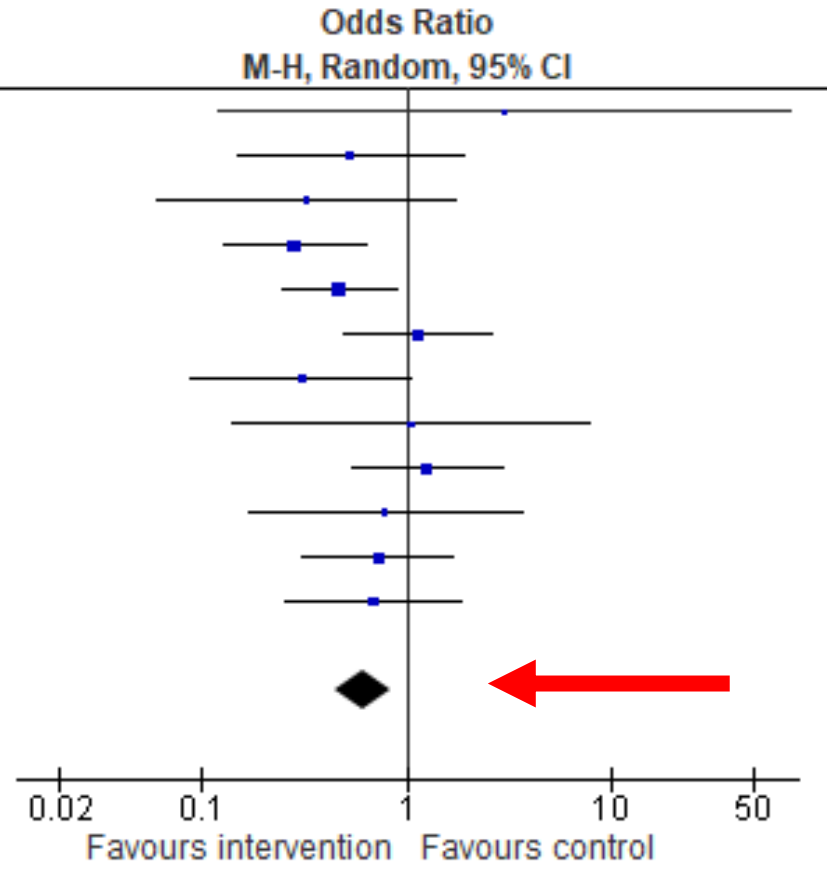
What do other trials tell us?

40%- MORTALITY REDUCTION IN PATIENTS TREATED LONG TERM WITH NUTRITIONAL SUPPORT

Study or Subgroup	nutritional intervention Events	Total	control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Andersson 2017	1	58	0	57	1.0%	3.00 [0.12, 75.19]
Beck 2013	4	63	7	62	5.8%	0.53 [0.15, 1.92]
Beck 2015	2	34	6	37	3.5%	0.32 [0.06, 1.72]
Bonilla-Palomas 2016	12	59	29	61	13.0%	0.28 [0.13, 0.63]
Deutz 2016	15	313	30	309	18.7%	0.47 [0.25, 0.89]
Edington 2004	17	51	15	49	12.2%	1.13 [0.49, 2.63]
Feldblum 2010	3	78	21	181	6.2%	0.30 [0.09, 1.05]
Gazzotti 2003	2	39	2	41	2.5%	1.05 [0.14, 7.87]
Neelemaat 2011	14	89	11	86	11.9%	1.27 [0.54, 2.98]
Price 2005	3	66	4	70	4.1%	0.79 [0.17, 3.65]
Sharma 2017	12	78	14	70	12.0%	0.73 [0.31, 1.70]
Yang 2019	9	39	13	43	9.2%	0.69 [0.26, 1.86]
Total (95% CI)		**967**		**1066**	**100.0%**	**0.62 [0.45, 0.85]**
Total events	94		152			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.47$, $df = 11$ ($P = 0.33$); $I^2 = 12\%$

Test for overall effect: $Z = 2.93$ ($P = 0.003$)



Kaegi-Braun N., Clin Nutr 2022 Nov;41(11):2431-2441.

ESPEN Guideline recommendations on polymorbid patients
Guidelines will be updated in 2023

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[b] Oxford and Southampton University Hospitals, United Kingdom
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[d] Uppsala University, Sweden
[e] Queen Elizabeth Hospital, Birmingham, United Kingdom
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[h] Laiko General Hospital of Athens, Greece
[i] University of Lisbon, Portugal
[j] University of Nice Sophia-Antipolis, France
[k] University Hospital and University of Bern, Switzerland
[l] Guy's & St. Thomas' NHS Foundation Trust and King's College London, United Kingdom
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[n] Medical Faculty, University of Basel, Switzerland

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E-mail address: philipp.schuetz@unibas.ch (P. Schuetz).
[1] F.G. and P.S. contributed equally to this study.

http://dx.doi.org/10.1016/j.clnu.2017.06.025

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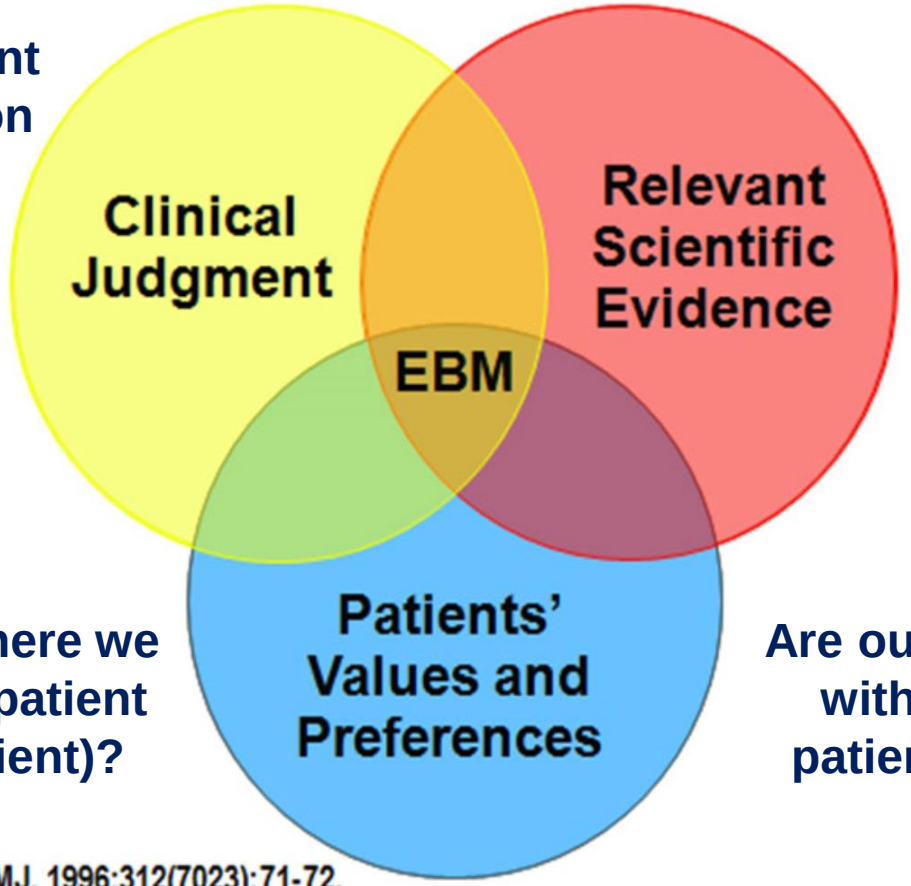
  (Grade of recommendation A) e strong consensus (95% agreement)

- **Timing and continuation: Patients shall be continued after hospital discharge in order to maintain or improve body weight and nutritional status**
  (Grade of recommendation A) e strong consensus (95% agreement)

From Evidence based medicine (EBM) to Evidence-based nutrition (EBN)!

Is it really «disease-related malnutrition»?

Did we exclude relevant diseases or medication side effects?



Do we have evidence that Nutritional support improves clincial outcomes for this patient?

YES!

(for the medical inpatient)

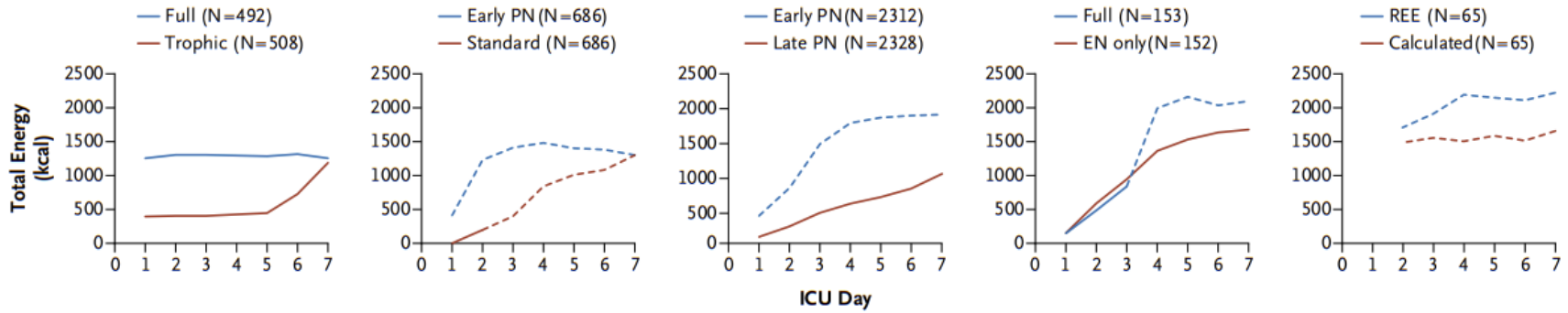
Is it a situation where we want to treat the patient (e.g., cancer patient)?

Are our goals aligned with goals of the patient and family?

. BMJ. 1996;312(7023):71-72.


HOUSTON
WE HAVE A
PROBLEM

Have we made progress in the treatment of malnutrition? Why do we not see the same results in critical care trials?



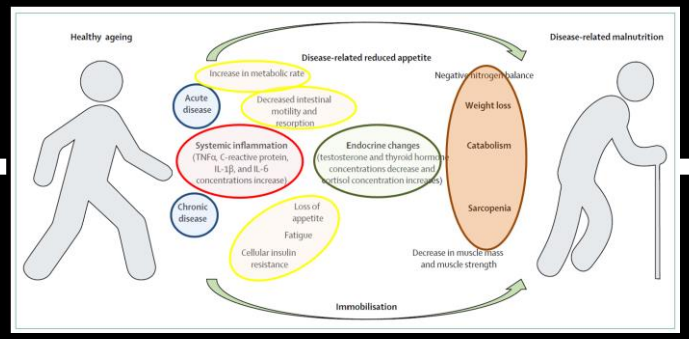
	EDEN Trial (N=1000)	Early PN Trial (N=1372)	EPaNIC Trial (N=4640)	SPN Trial (N=305)	TICACOS (N=130)
Type of Patients	Medical (acute lung injury) Eligible for EN	Mixed medical and surgical EN relatively contraindicated (short term)	Mixed medical and surgical (unselected) With nutritional risk (NRS, ≥3)	Mixed medical and surgical (on day 4) Eligible for EN but <60% target	Mixed medical and surgical
New Infections in ICU	Unaffected	Unaffected	More with early PN	Between day 9 and day 28: less with SPN From randomization to day 28: unaffected	More with REE
Duration of Mechanical Ventilation	Unaffected	Shorter with early PN	Longer with early PN	Unaffected	Longer with REE
Length of Stay in ICU	Unaffected	Unaffected	Longer with early PN	Unaffected	Longer with REE
Mortality in ICU	Unaffected	Unaffected (60-day mortality: unaffected)	Unaffected	Unaffected	Unaffected (trend toward reduced hospital mortality)

Figure 1. Comparison of Macronutrient Intake and Outcomes of Five Randomized, Controlled Trials Evaluating Nutrition during Critical Illness.

Casaer M, N Engl J Med. 2014 Jun 19;370(25):2450-1.

Why do we see such different responses?

Type of nutrition (& control)? patient selection? Acuity and inflammation?



Patient 1

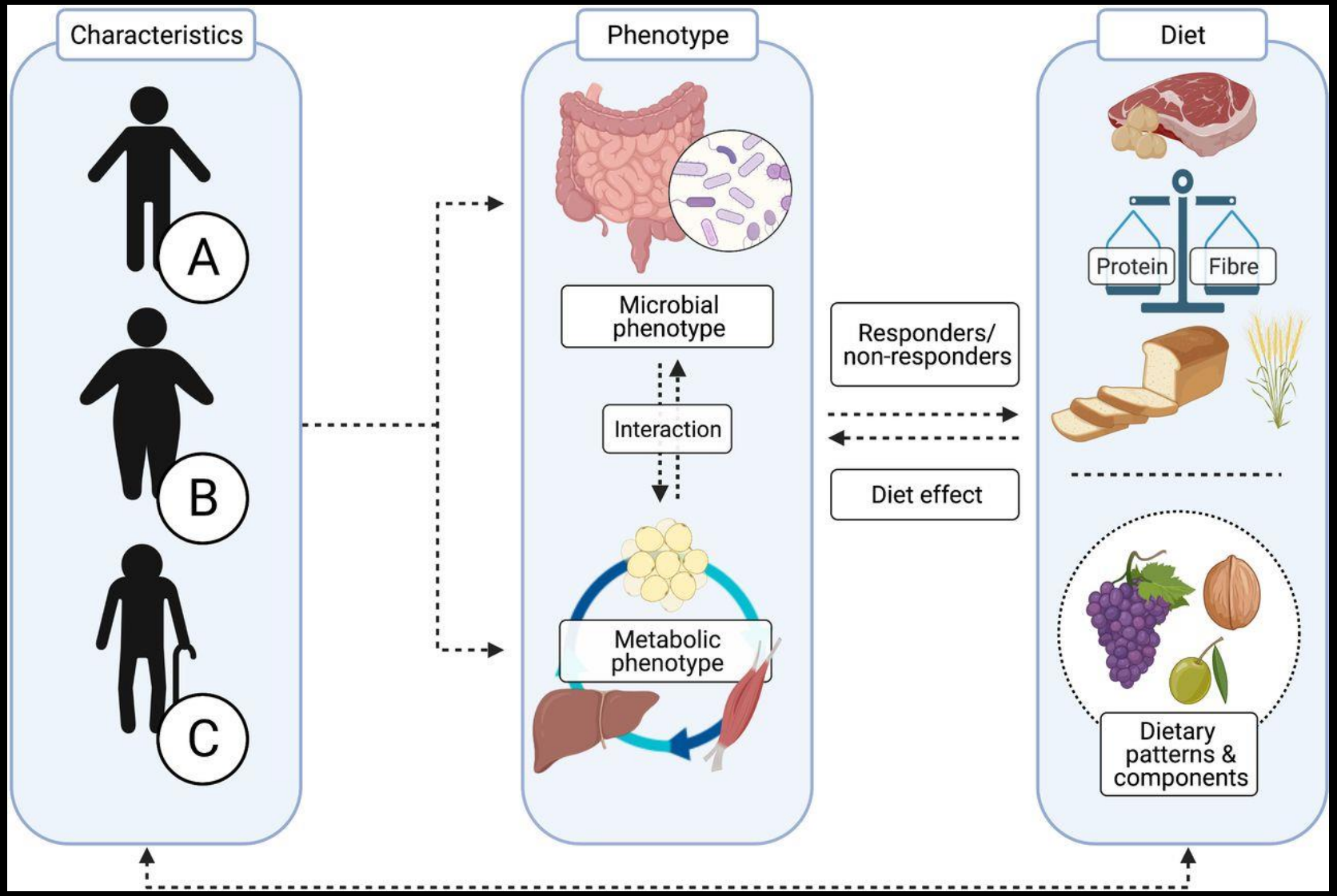
Polymorbid patient from a nursing home that has low appetite and has received low energy and protein feeding over the last 6 month resulting in weight and muscle loss

Patient 2

A catabolic highly inflamed patient with metastatic pancreatic cancer that is receiving appropriate nourishment, but his muscle mass is rapidly declining, and the patient has edema.

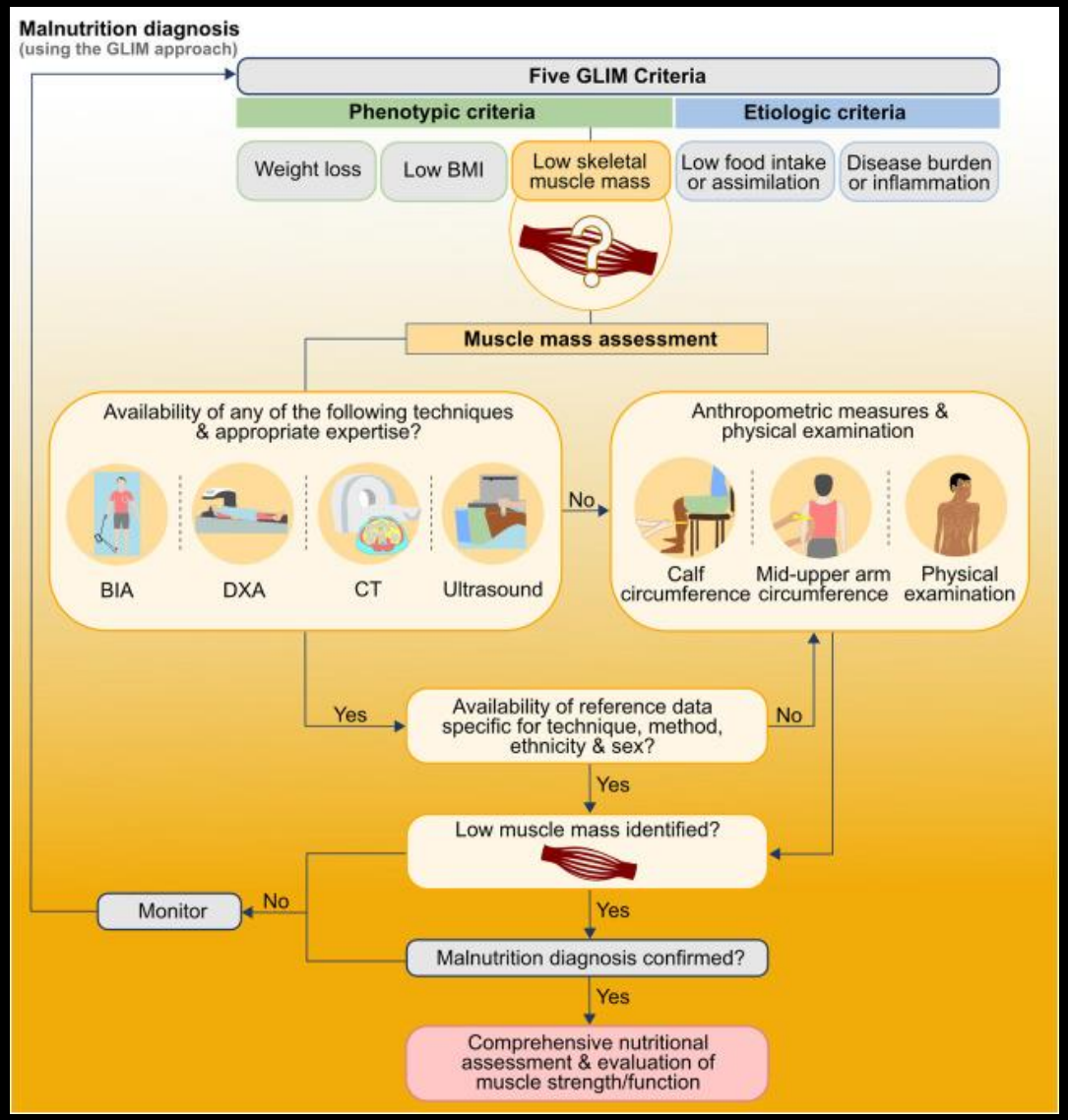
Schuetz P et al, Lancet. 2021 Nov 20;398(10314):1927-1938.

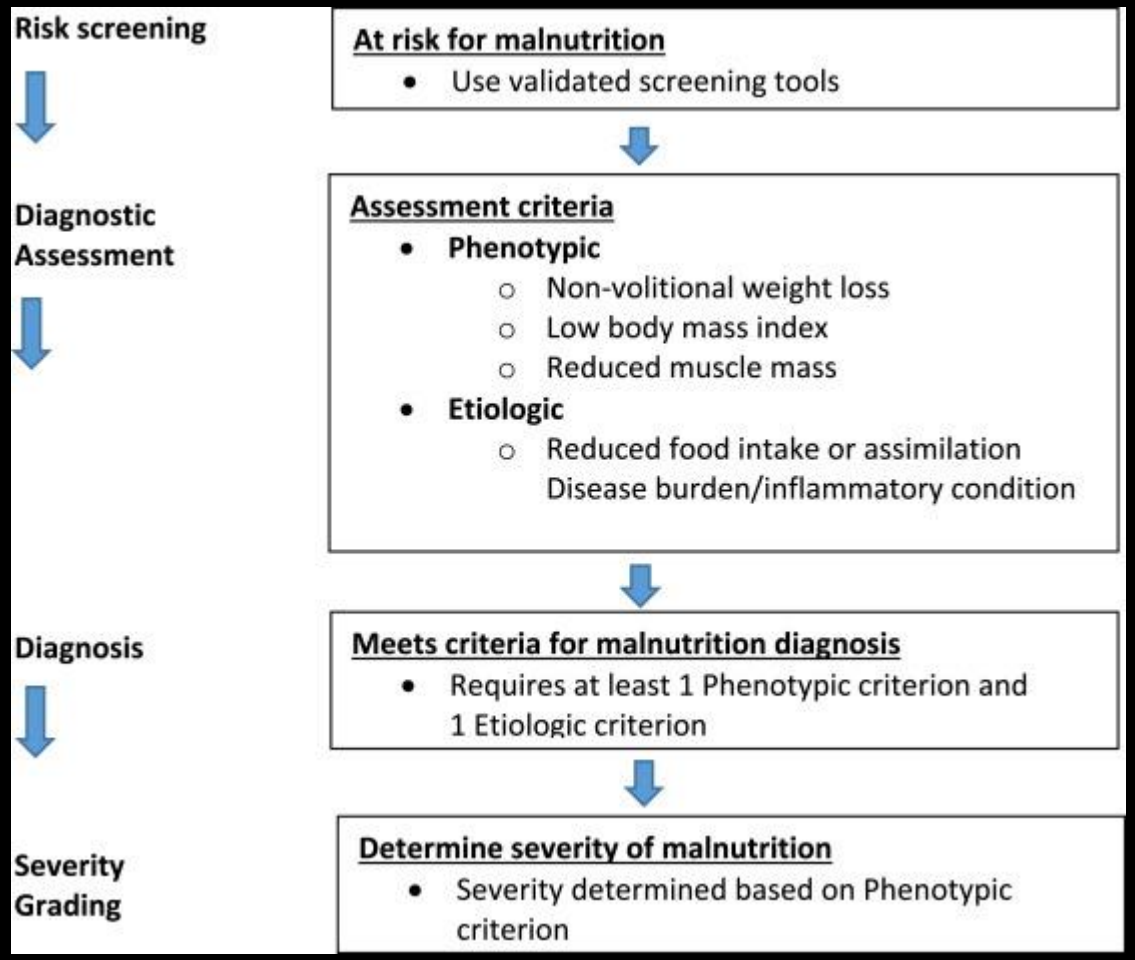
Do we need to better include the patient phenotype ?



Jardon KM, et al. Gut 2022;71:1214–1226.

Patient phenotyping according to GLIM





Barazzoni R., Clin Nutr. 2022 Jun;41(6):1425-1433.

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Type of nutrition (& control)? patient selection? Acuity and inflammation?

Is there a difference between malnutrition (ie, a multi-cause syndrome) and being malnourished (ie, a patient that received inadequate feeding)?

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Polymorbid patient from a nursing home that has low appetite and has received low energy and protein feeding over the last 6 month resulting in weight and muscle loss

Patient 2

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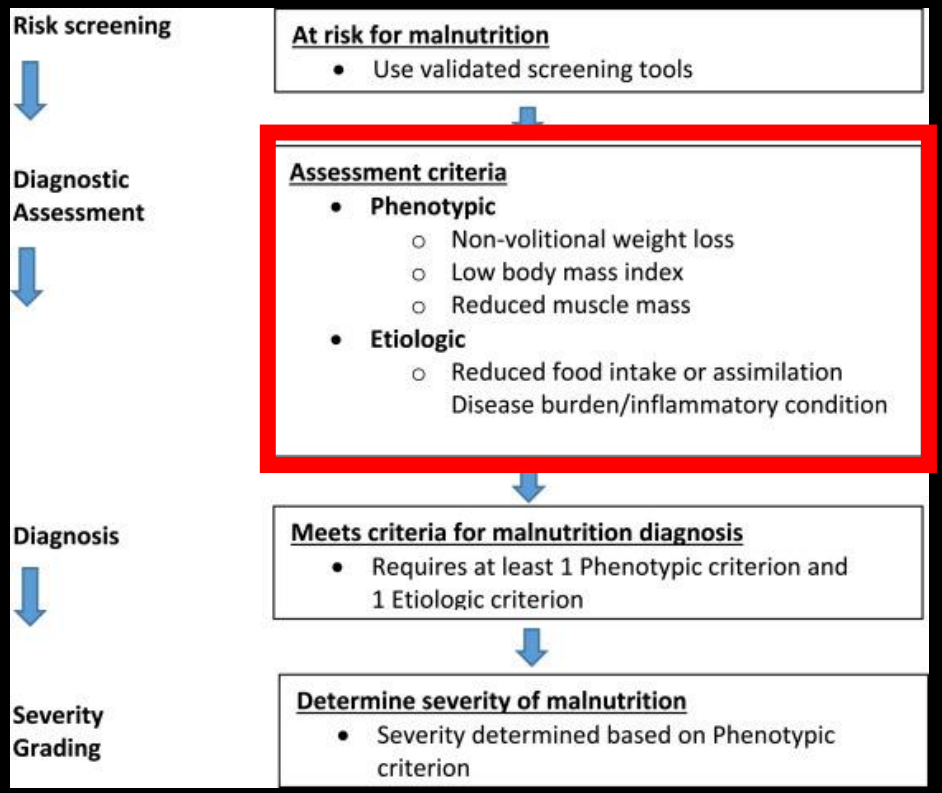
Schuetz P et al, Lancet. 2021 Nov 20;398(10314):1927-1938.

Personlized Nutrition:
a hug opportunity for Medicine (& Industry …?)

Why do we see such different responses?

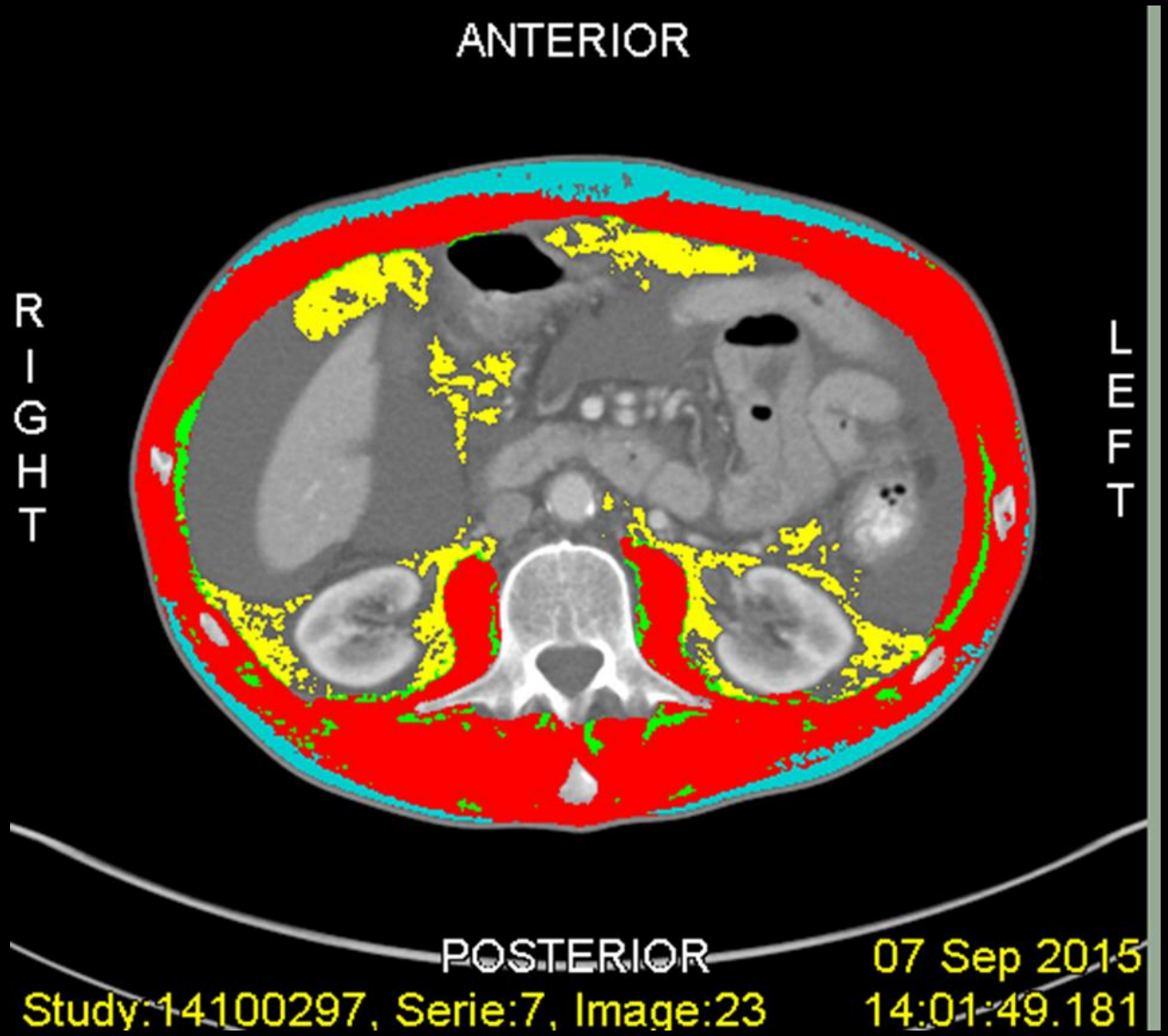
Type of nutrition (& control)? patient selection? Acuity and inflammation?

Does malnutrition phenotype or sorcopenia matter?



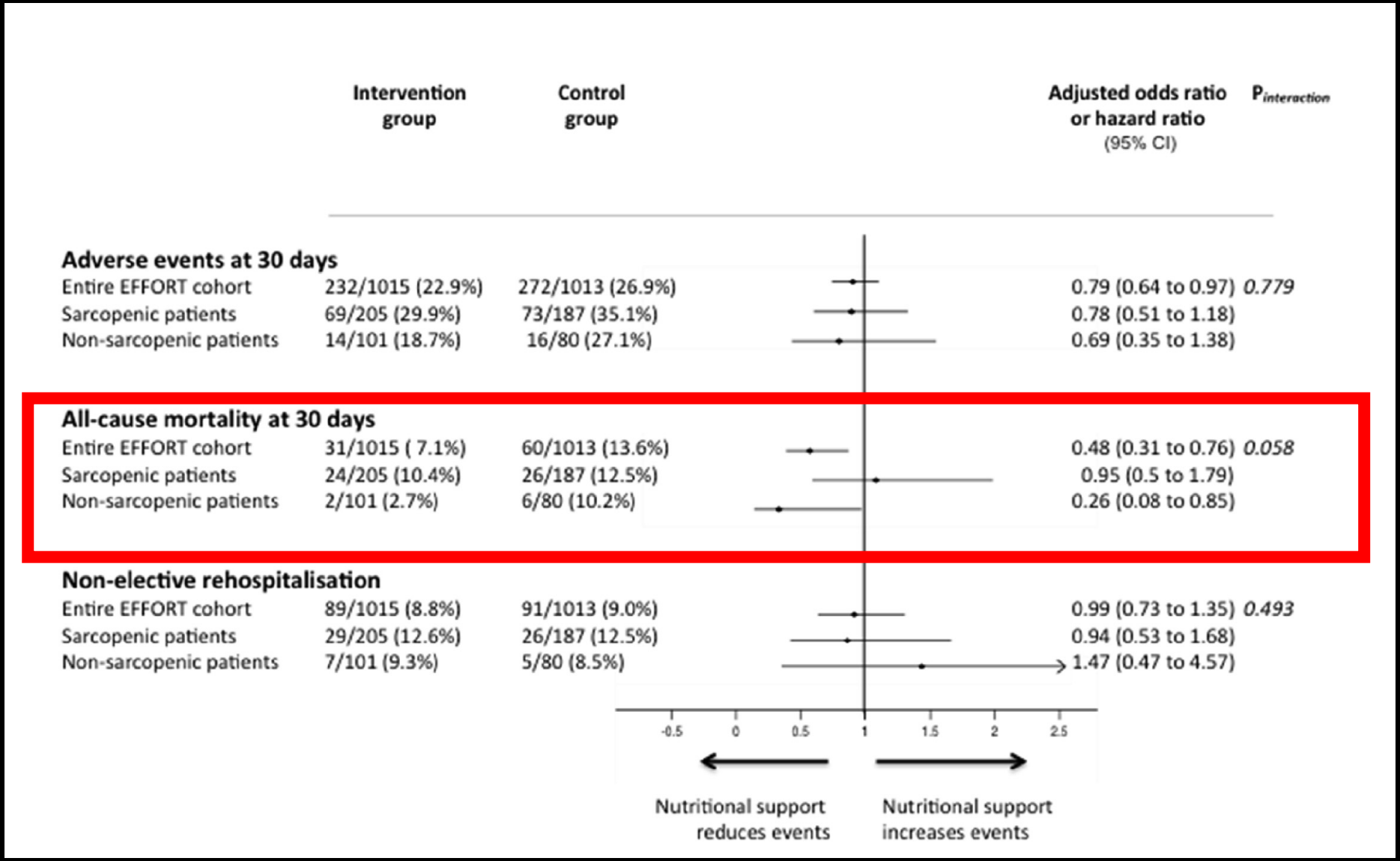
Cederholm T, Barazzoni R, Feb 2017;36(1):49-64. doi:10.1016/j.clnu.2016.09.004

Sarcopenia? Check the routine scans!



Sarcopenic patients have LESS treatment response!

Importance of early recognition of malnutiriton!



Baumgartner A, Clin Nutr. 2023 Feb;42(2):199-207.

The pathophysiology of malnutrition is complex and includes different pathophysiological pathways

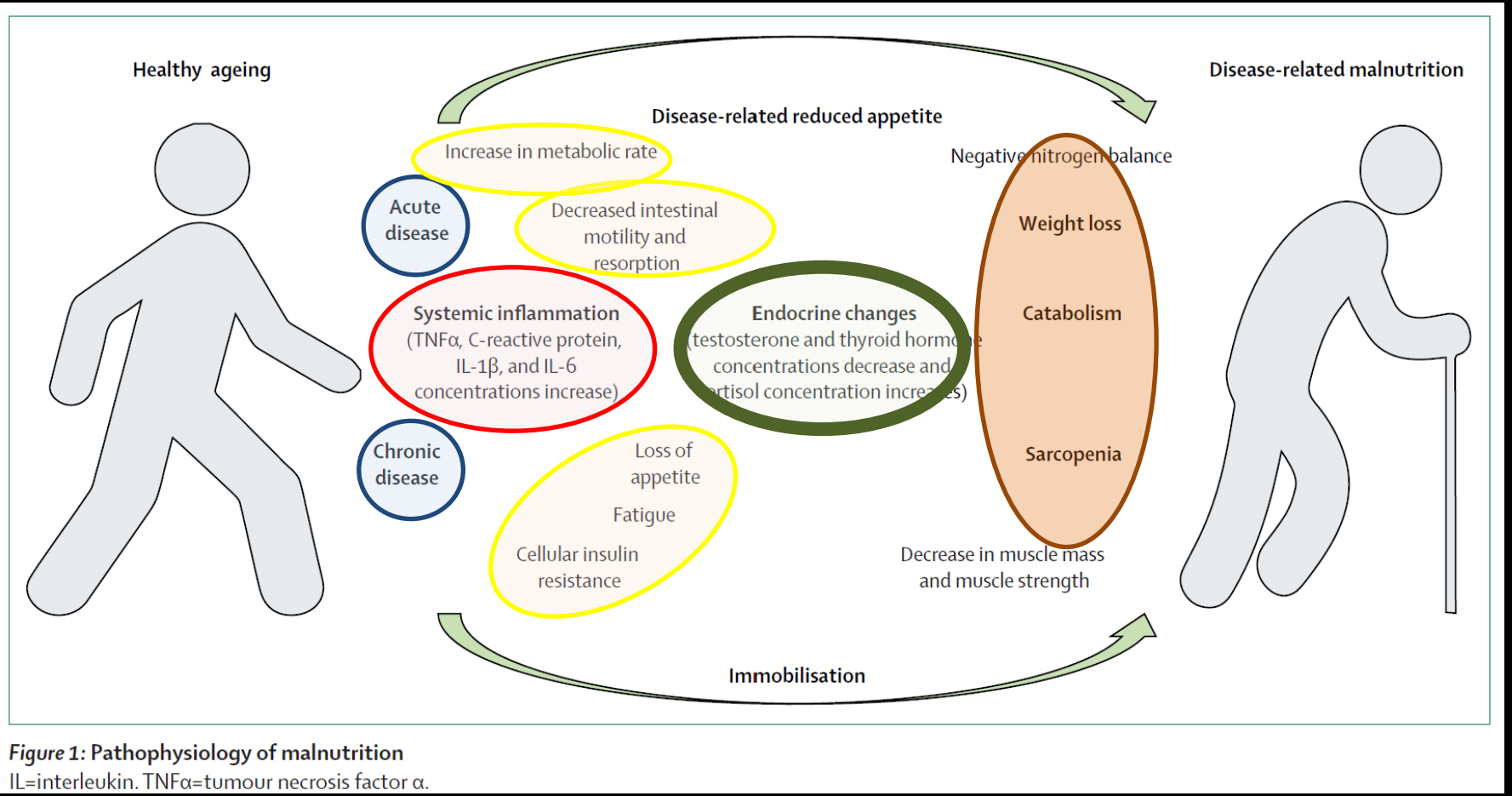
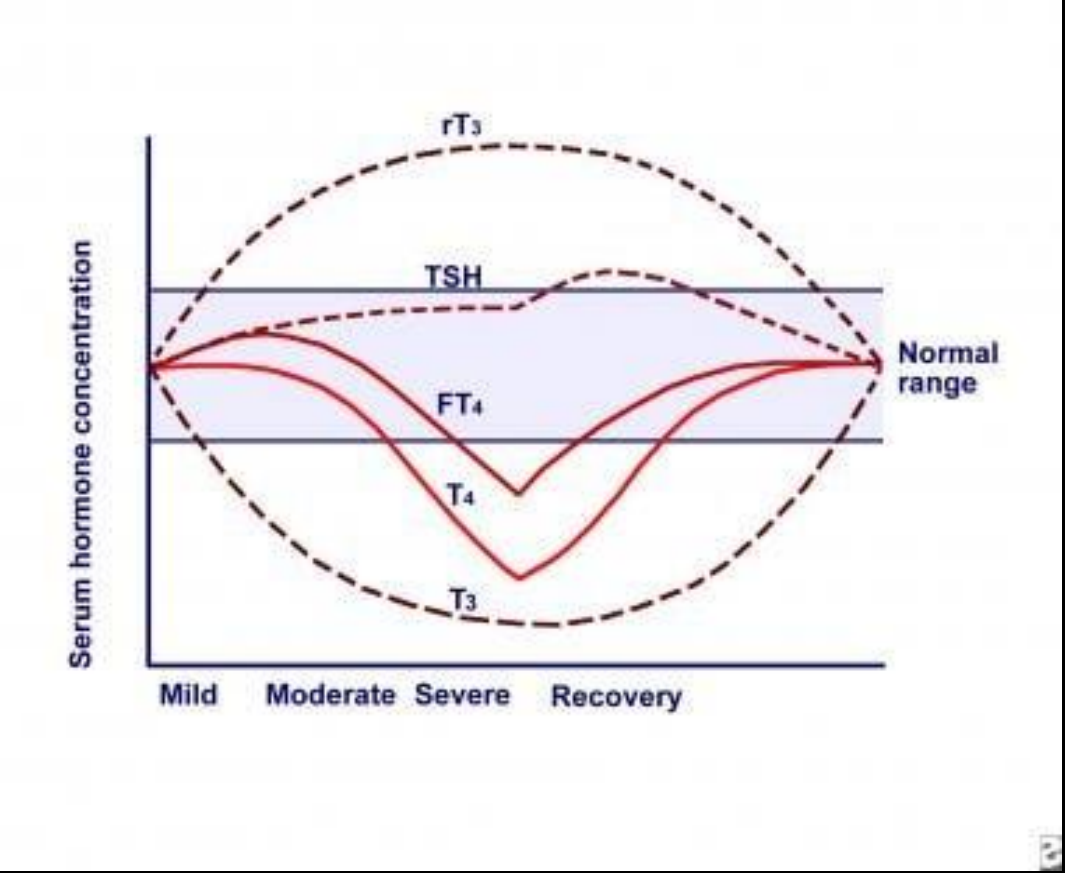


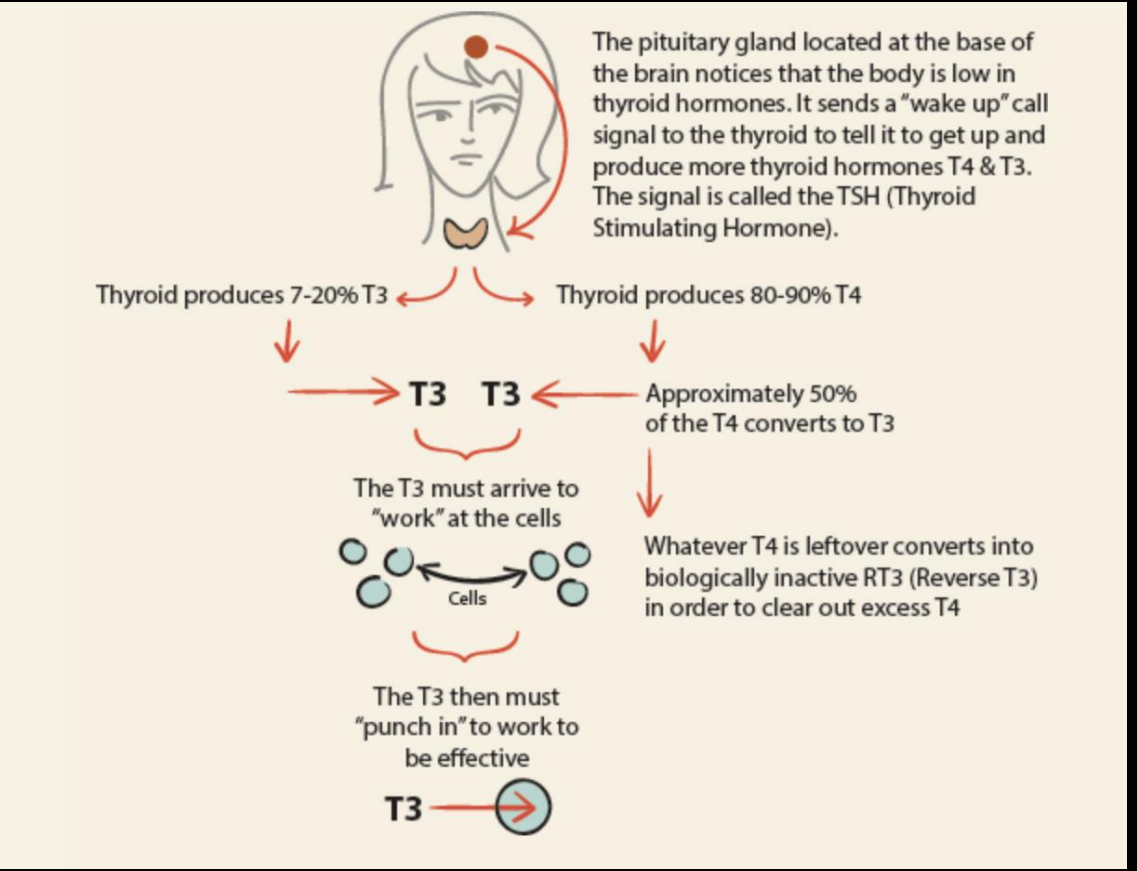
Figure 1: **Pathophysiology of malnutrition**
IL=interleukin. TNFα=tumour necrosis factor α.

Schuetz P et al, Lancet. 2021 Nov 20;398(10314):1927-1938.

Is treatment response dependent on endocrine dysfunction?

Disease causes «low-T syndrome»
Is it relevant for malnutrition?





YES – 60% of patients in EFFORT had low T3 syndrome

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JOURNAL ARTICLE CORRECTED PROOF

Low T3 Syndrome on Admission and Response to Nutritional Support in Malnourished Medical Inpatients

Get access

Natasha Anouschka Müller, Nina Kaegi-Braun, Mirsada Durmisi, Carla Gressies, Pascal Tribolet, Zeno Stanga, Beat Mueller, Philipp Schuetz

The Journal of Clinical Endocrinology & Metabolism, dgac743,
https://doi.org/10.1210/clinem/dgac743

Published: 22 December 2022 **Article history**

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The pathophysiology of malnutrition is complex and includes different pathophysiological pathways

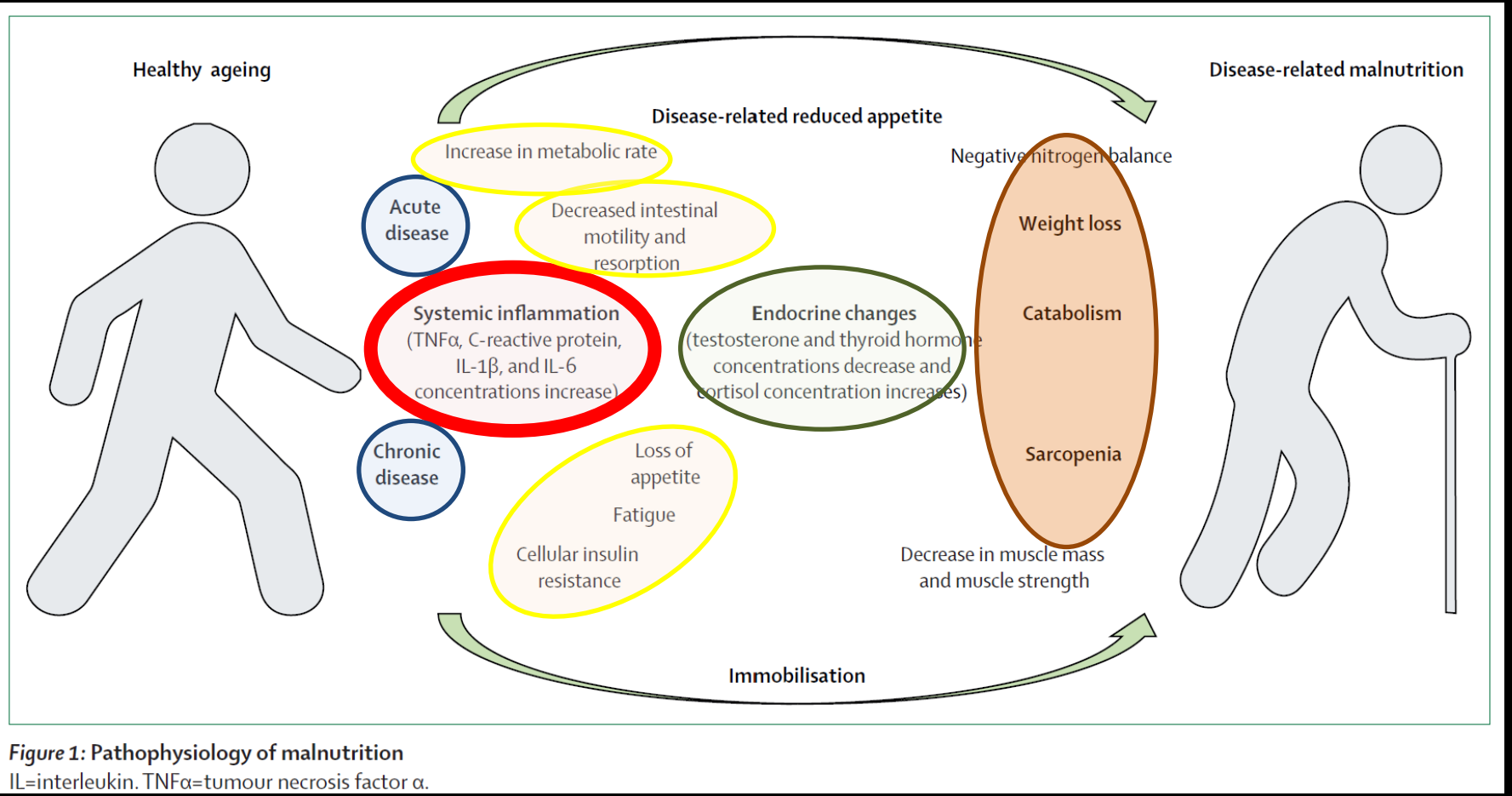
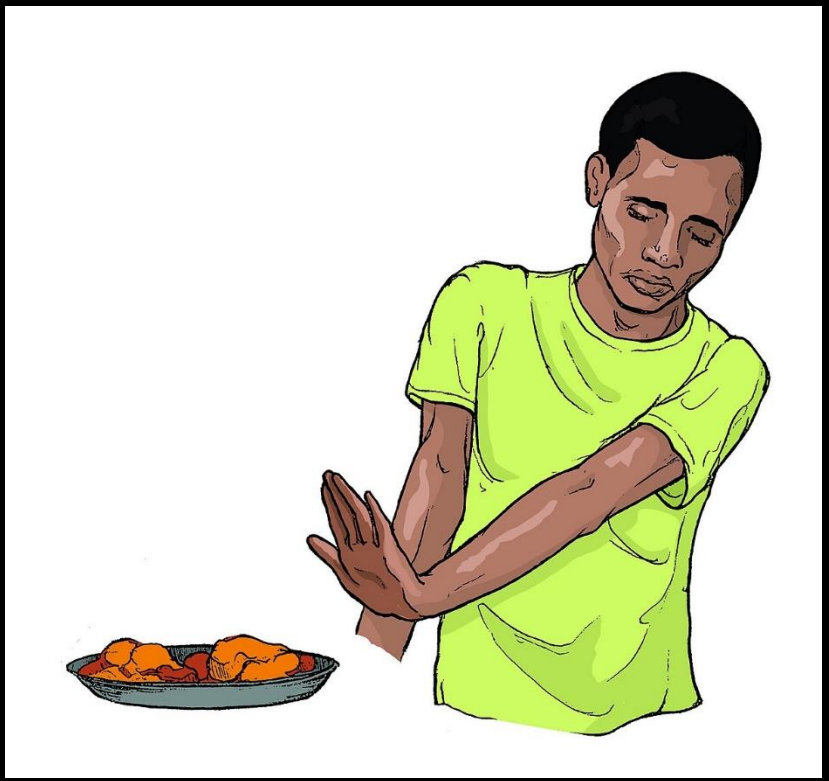


Figure 1: **Pathophysiology of malnutrition**
IL=interleukin. TNFα=tumour necrosis factor α.

Schuetz P et al, Lancet. 2021 Nov 20;398(10314):1927-1938.

True or false?



THE LANCET

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SUPPLEMENT | VOLUME 372, SPECIAL ISSUE, S21-S27, DECEMBER 2008

Evolution: medicine's most basic science

Randolph M Nesse

Published: December, 2008 • DOI: https://doi.org/10.1016/S0140-6736(08)61877-2

Further reading

Article info

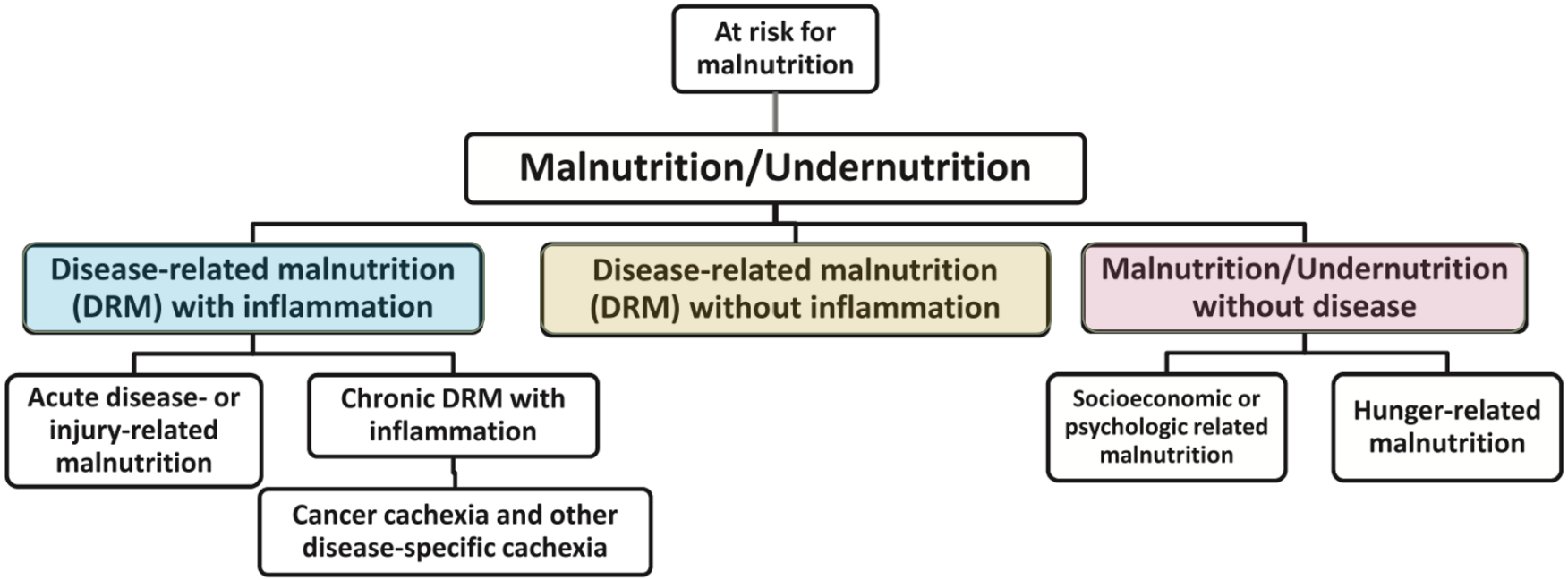
Figures

Brown-throated three-toed sloth, *Bradypus variegates*.

Why do we see such different responses?

Type of nutrition (& control)? patient selection? Acuity and inflammation?

Does inflammation matter?

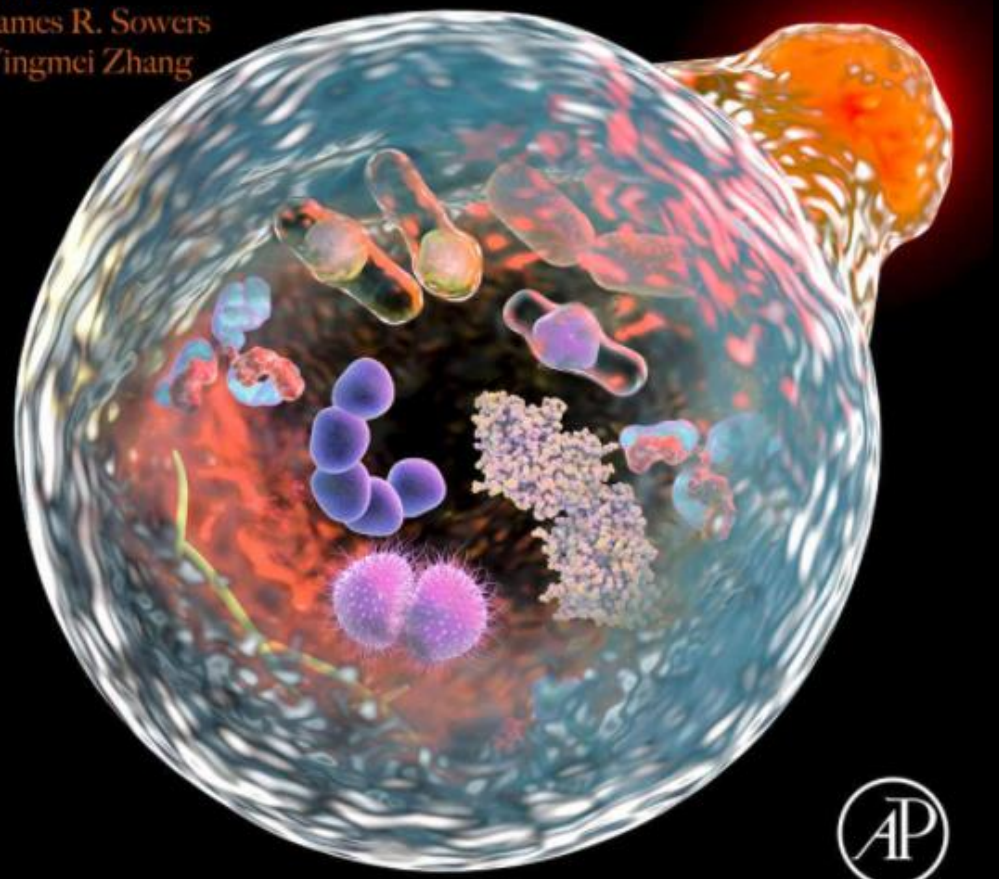


Cederholm T, Barazzoni R, Feb 2017;36(1):49-64. doi:10.1016/j.clnu.2016.09.004

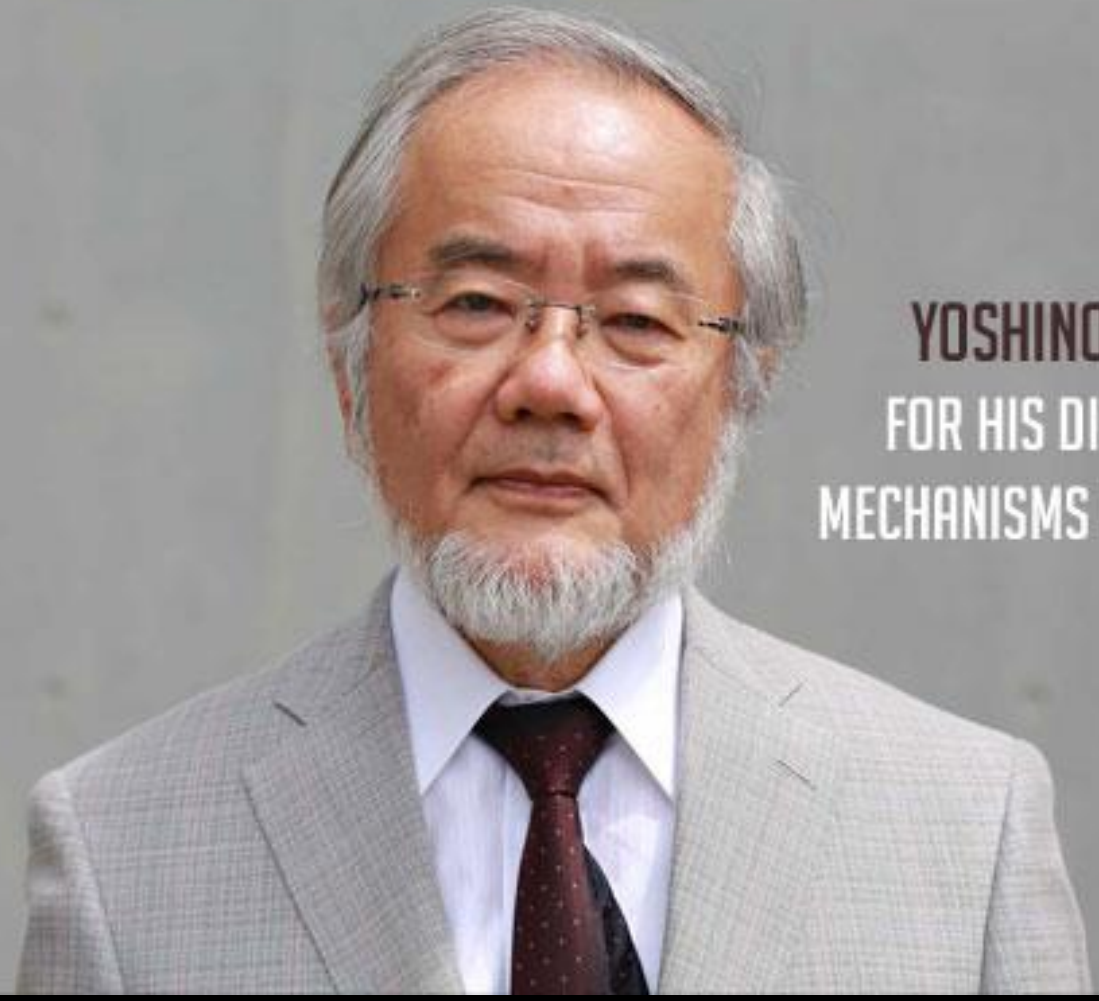
Autophagy and Cardiometabolic Diseases

From Molecular Mechanisms to Translational Medicine

Edited by
Jun Ren
James R. Sowers
Yingmei Zhang



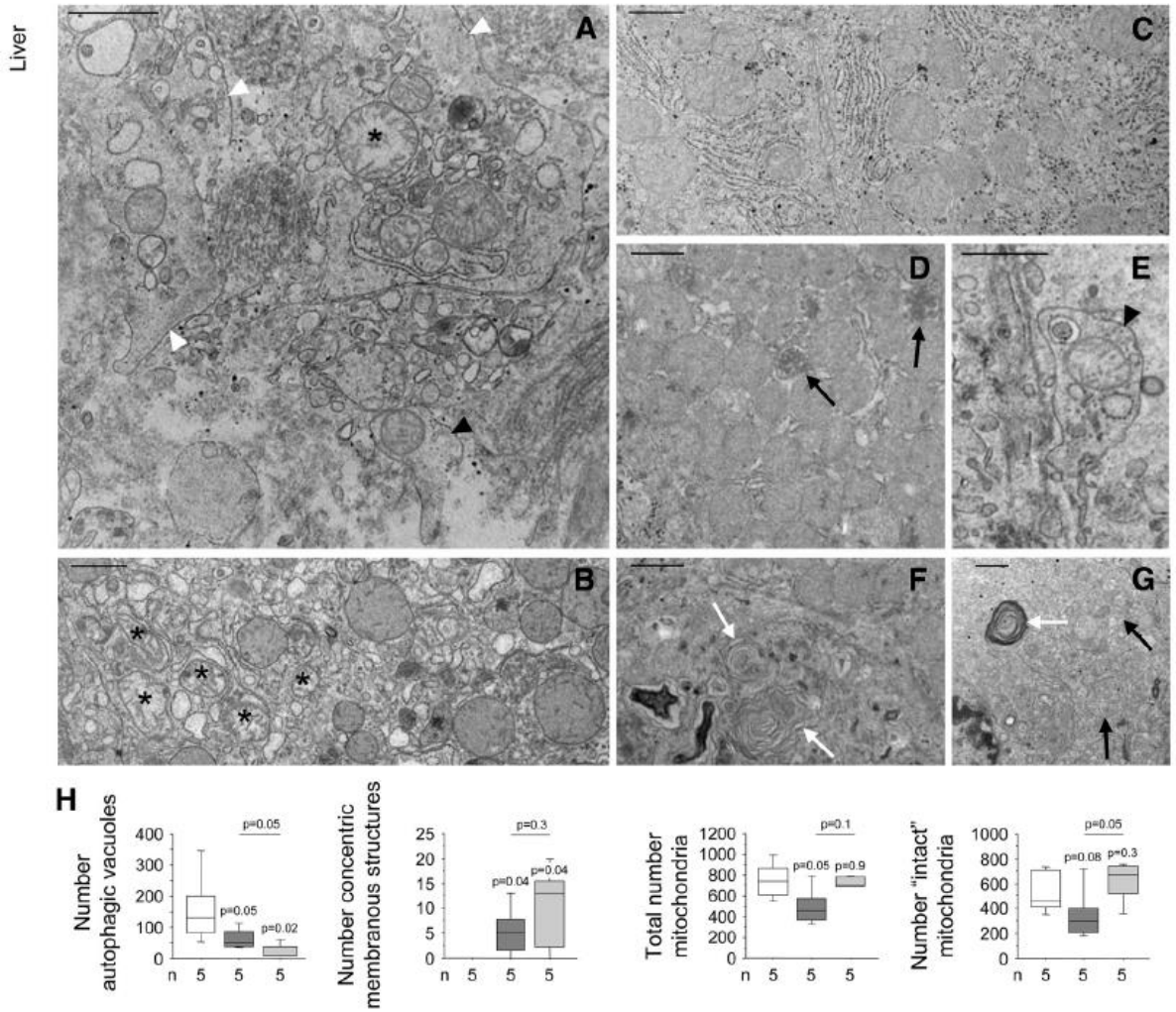
THE 2016 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE



YOSHINORI OHSUMI

FOR HIS DISCOVERIES OF MECHANISMS FOR AUTOPHAGY

Autophagy is impaired when we «overfeed» patients



Electron microscopy

- intact/swollen mitochondria
- autophagic vacuoles

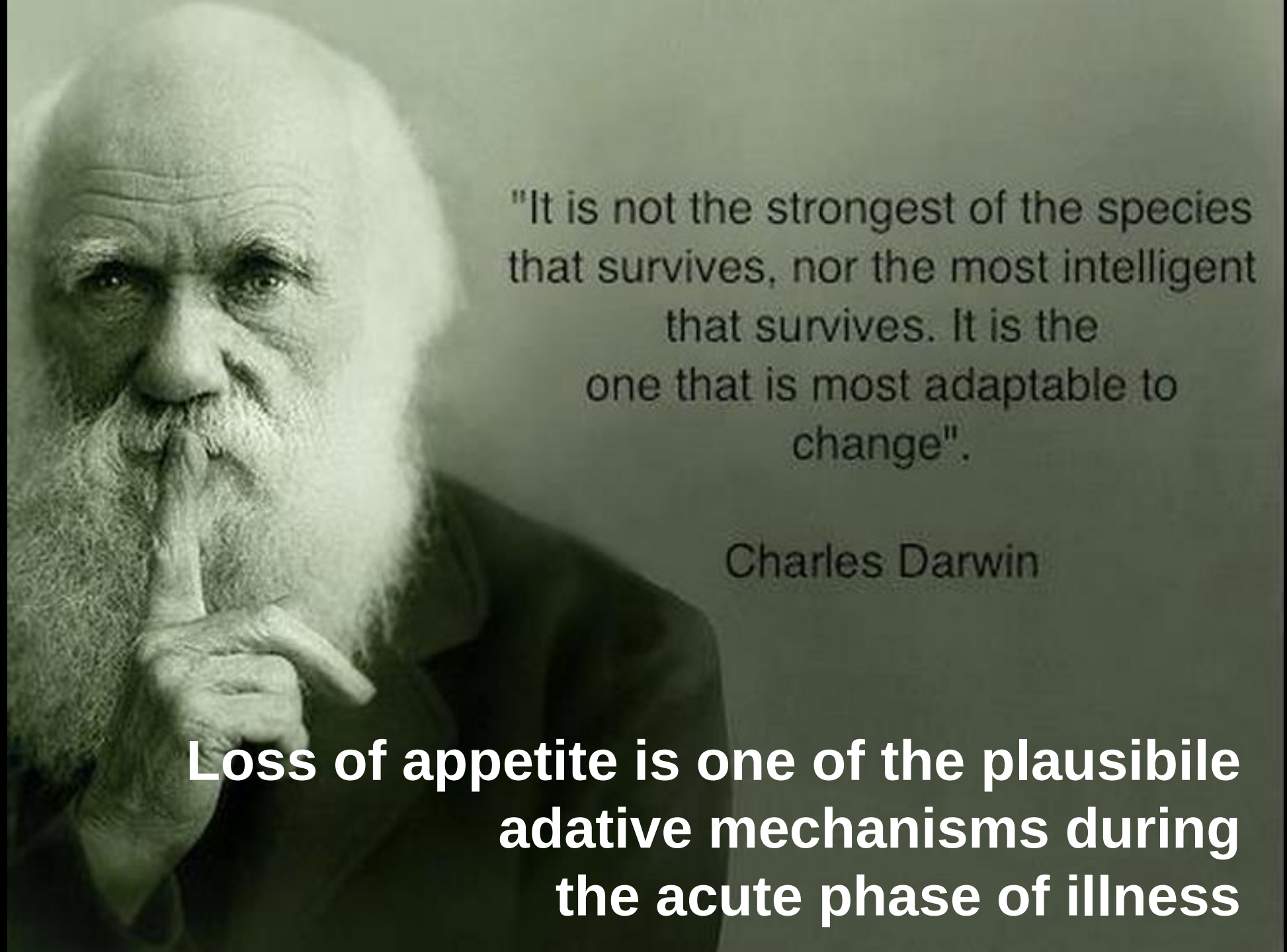
Histochemistry

- 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



Loss of appetite is one of the plausibile adative mechanisms during the acute phase of illness

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

Meret Merker, MD; Martina Felder, BMSc; Louise Gueissaz, BMSc; Rebekka Bolliger, MD; Pascal Tribolet, MSc; Nina Kägi-Braun, MD; Filomena Gomes, PhD; Claus Hoess, MD; Vojtech Pavlicek, MD; Stefan Bilz, MD; Sarah Sigrist, MD; Michael Brändle, MD; Christoph Henzen, MD; Robert Thomann, MD; Jonas Rutishauser, MD; Drahomir Aujesky, MD; Nicolas Rodondi, MD, MAS; Jaques Donzé, MSc; Zeno Stanga, MD; Beat Mueller, MD; Philipp Schuetz, MD, MPH

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

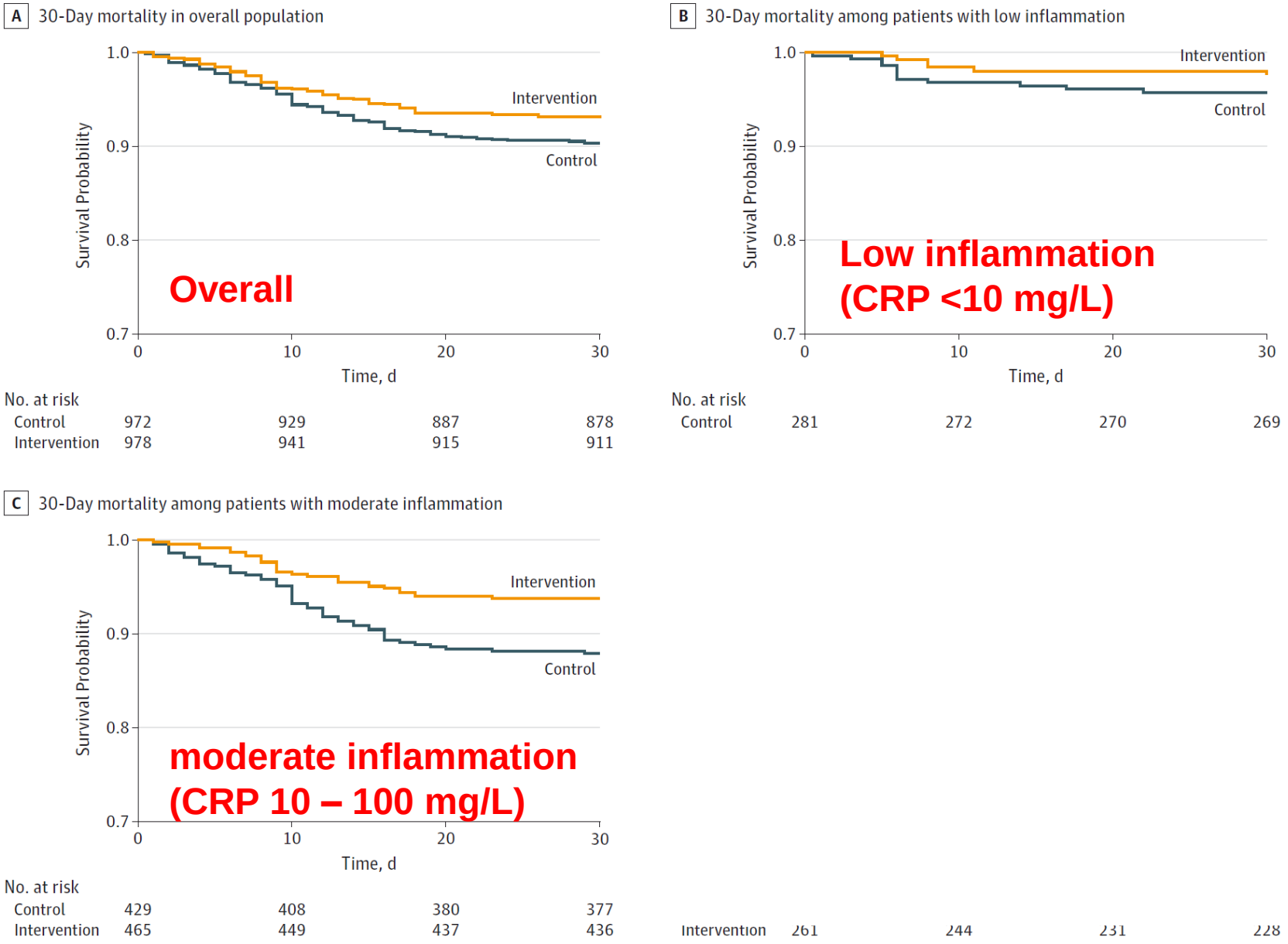
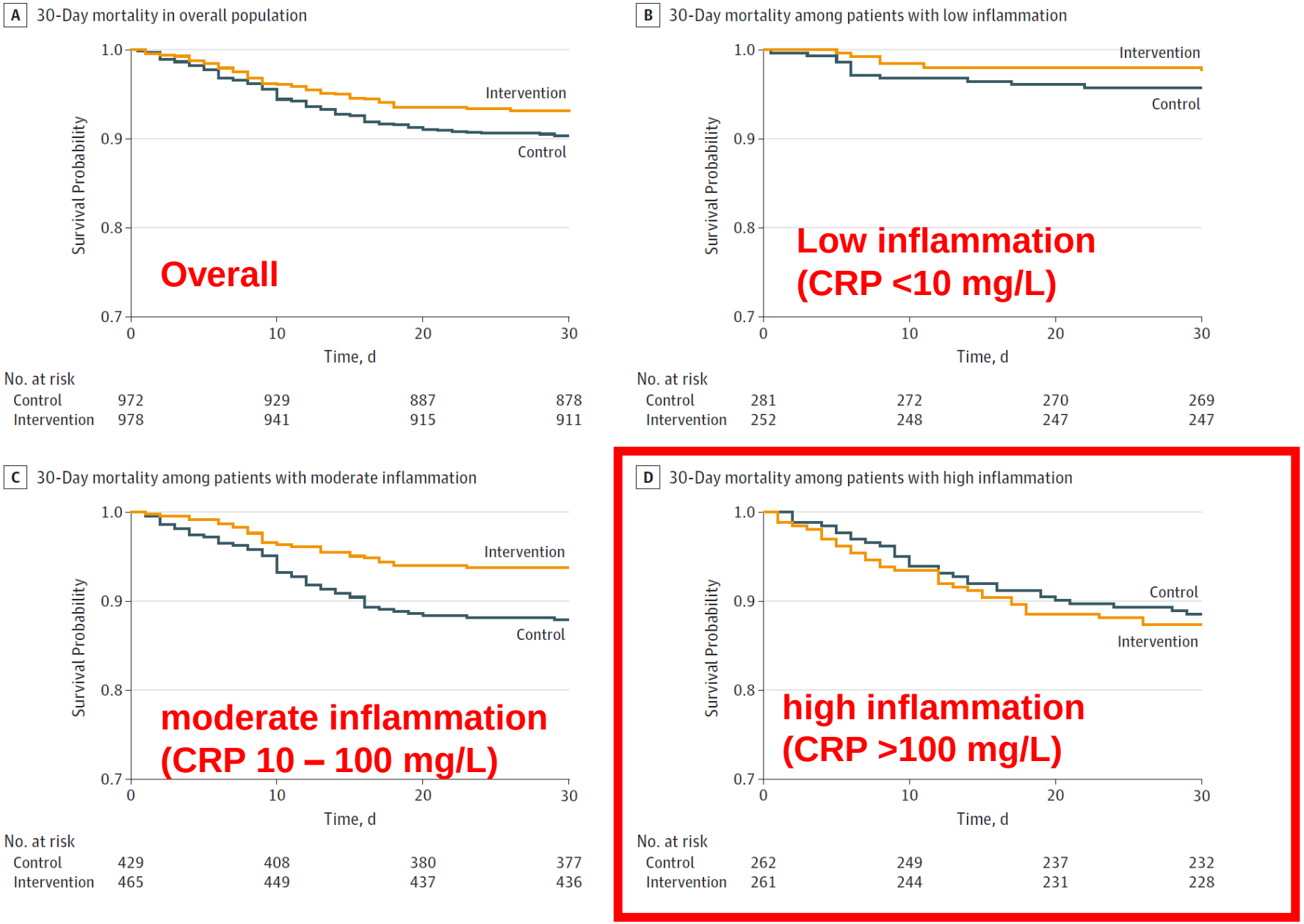


Figure 2. Kaplan-Meier Estimate for Time to Death Within 30-Days According to Inflammatory Status



ANNALS OF ONCOLOGY
driving innovation in oncology

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

LETTER TO THE EDITOR | VOLUME 32, ISSUE 11, P1451-1452, NOVEMBER 01, 2021

Inflammation reduces the effect of nutritional therapy on clinical outcomes in cancer patients

L. Bargetzi • M. Bargetzi • A. Laviano • Z. Stanga • P. Schuetz

Published: August 20, 2021 • DOI: https://doi.org/10.1016/j.annonc.2021.08.1989 •

We agree with the comments of Dr. Arends and colleagues [1] regarding the exploratory nature of our report that was based on a secondary analysis of a randomized trial and needs prospective validation in an independent sample of cancer patients. [2] Herein, we believe that our results may provide a strong rationale for such trials that will be helpful to further improve the understanding of nutritional care in cancer patients. The heterogeneity of patients in our analysis regarding type of cancer, cancer treatments and comorbidities may also be viewed as a strength of the trial, as it allows looking into

Let come back to our patient …

ANNALS FOR HOSPITALISTS

Annals of Internal Medicine

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

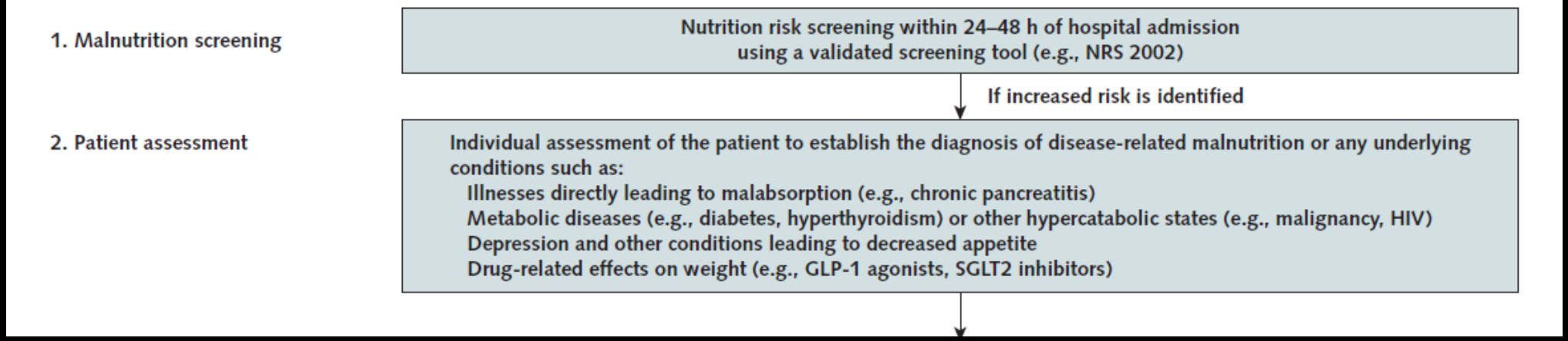
Philipp Schuetz, MD, MPH, and Jeffrey L. Greenwald, MD

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.

Figure. Nutritional support algorithm adapted from EFFORT.



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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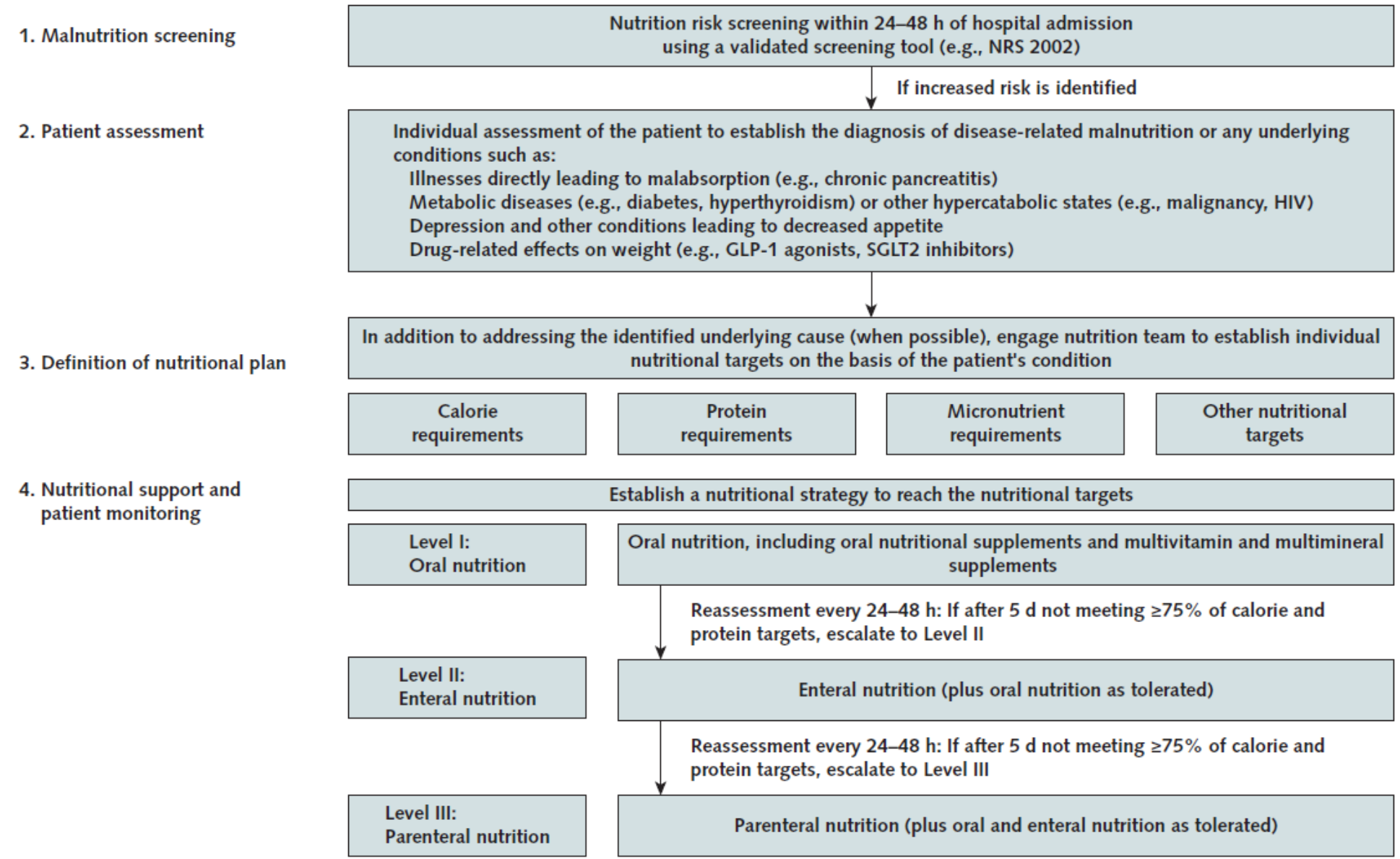

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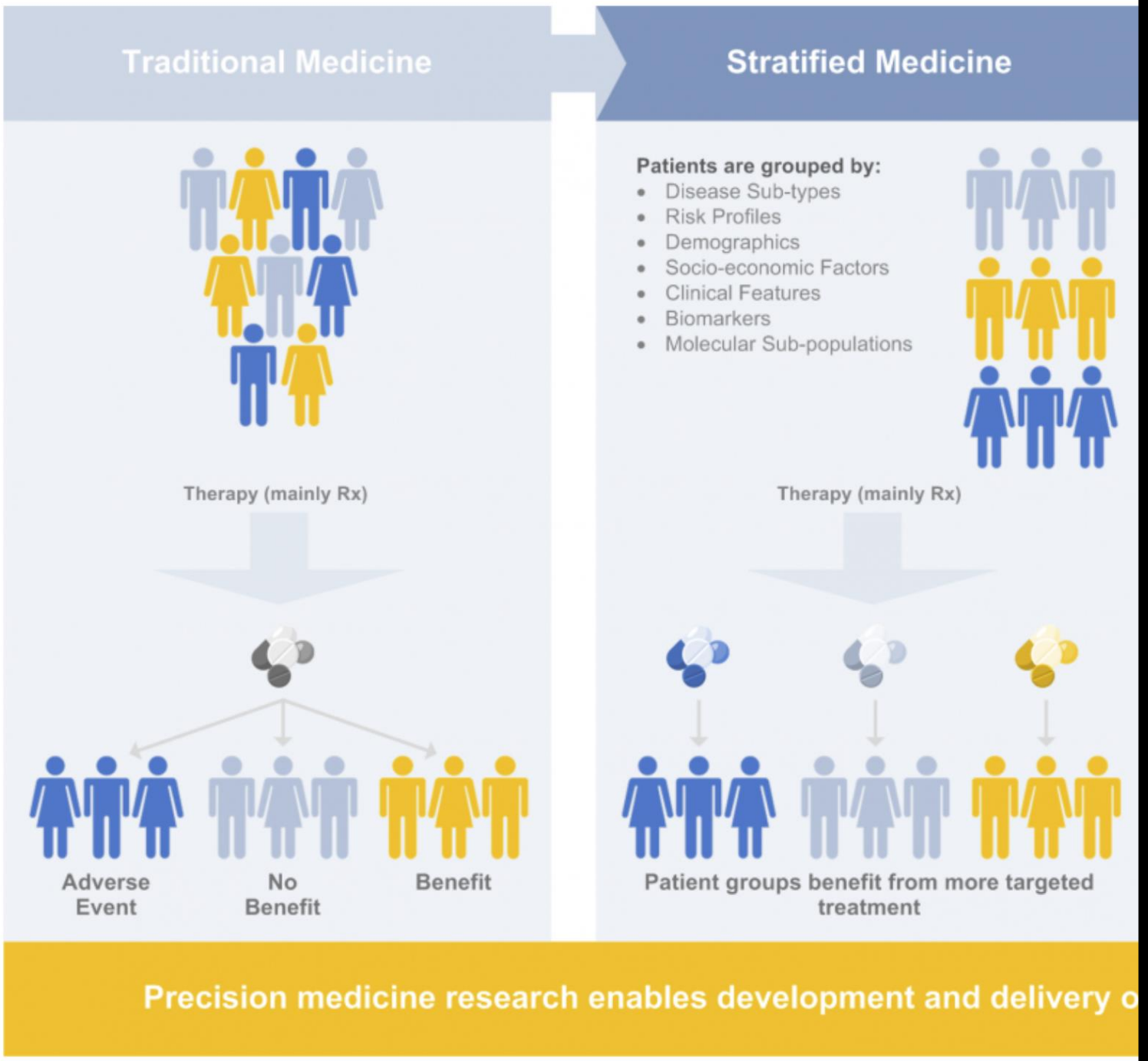
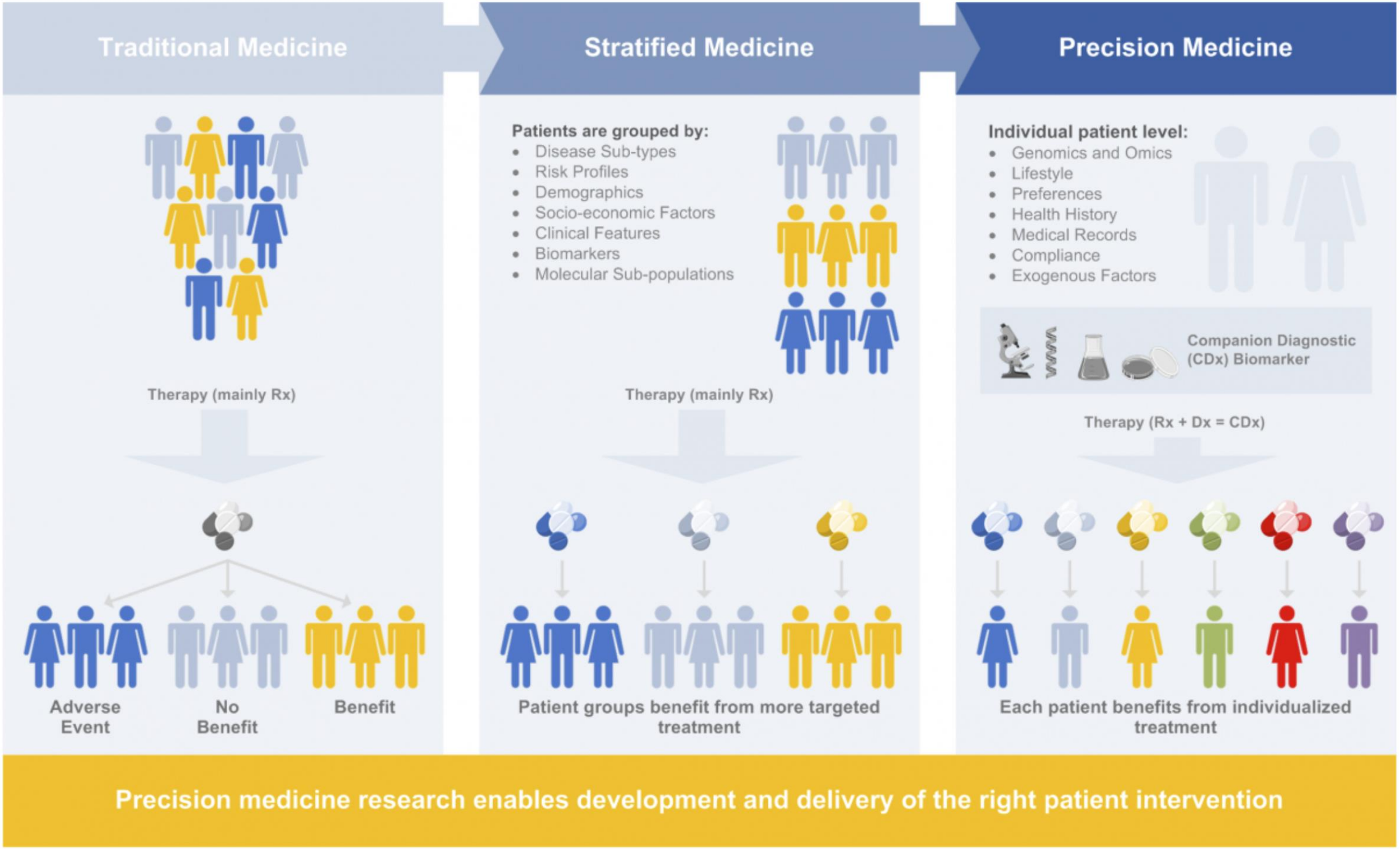
Traditional Medicine

Therapy (mainly Rx)

Adverse Event | No Benefit | Benefit

Precision medicine resear


Traditional Medicine
Stratified Medicine
Patients are grouped by:
Disease Sub-types
Risk Profiles
Demographics
Socio-economic Factors
Clinical Features
Biomarkers
Molecular Sub-populations
Therapy (mainly Rx)
Therapy (mainly Rx)
Adverse Event
No Benefit
Benefit
Patient groups benefit from more targeted treatment
Precision medicine research enables development and delivery o


Traditional Medicine
Stratified Medicine
Precision Medicine
Patients are grouped by:
Disease Sub-types
Risk Profiles
Demographics
Socio-economic Factors
Clinical Features
Biomarkers
Molecular Sub-populations
Individual patient level:
Genomics and Omics
Lifestyle
Preferences
Health History
Medical Records
Compliance
Exogenous Factors
Companion Diagnostic (CDx) Biomarker
Therapy (mainly Rx)
Therapy (mainly Rx)
Therapy (Rx + Dx = CDx)
Adverse Event
No Benefit
Benefit
Patient groups benefit from more targeted treatment
Each patient benefits from individualized treatment
Precision medicine research enables development and delivery of the right patient intervention

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
- **Hospitalists and internists should play an active role for early recognition and treatment of disease-related malnutrition in the hospital setting**


THE FUTURE
OF NUTRITION