Cancer cachexia

Frits A.J. Muskiet

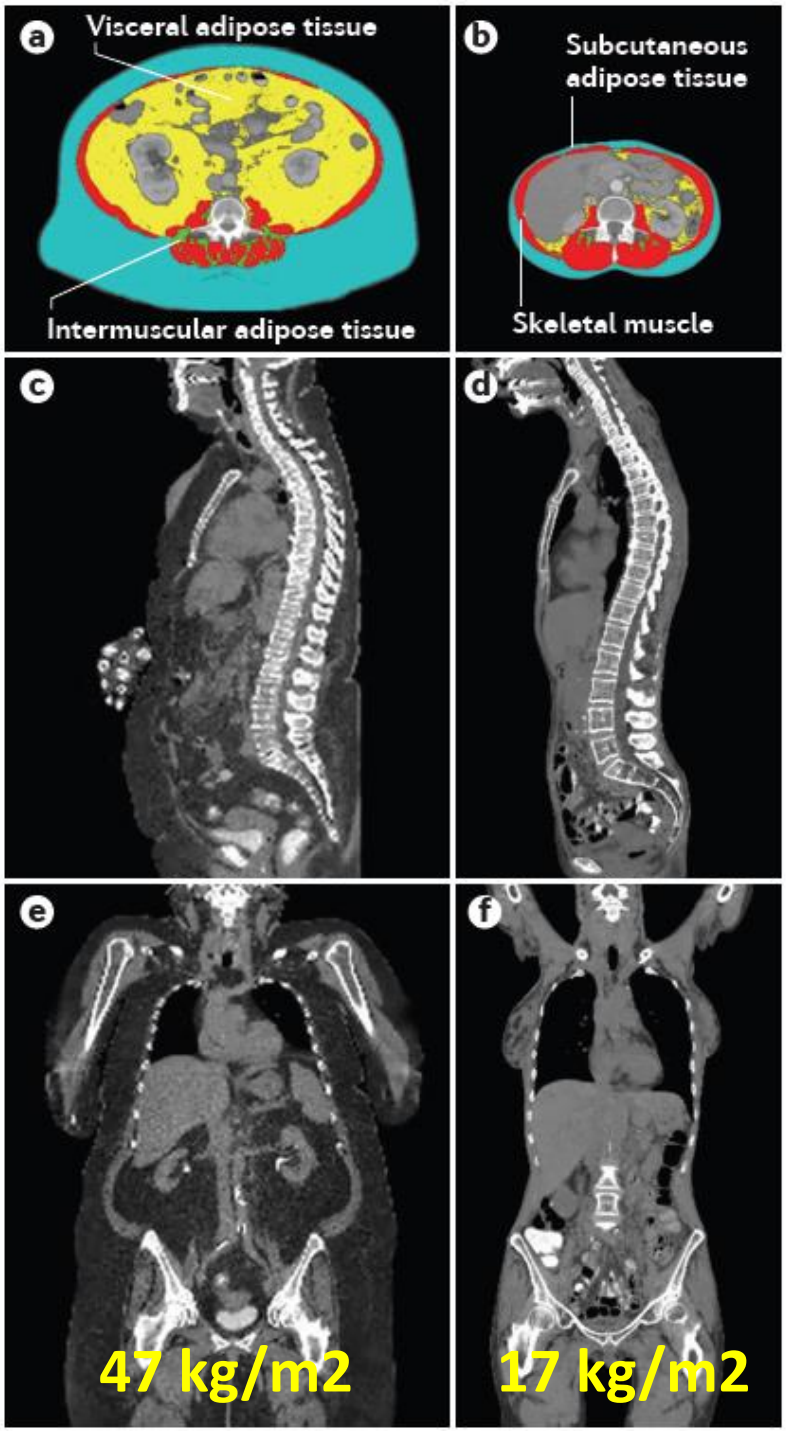
Laboratory Medicine
UMCG, Netherlands

Cachexie

- Een hyperkatabole toestand gedefinieerd als een versneld verlies van skeletspieren in de context van een chronische ontstekingsreactie, die kan optreden bij gevorderde kanker, maar ook bij chronische infectie, AIDS, hartfalen, reumatoïde artritis en chronische obstructieve longziekte

- Bij deze ziektes zijn de veranderingen in de lichaamssamenstelling niet gelijk

Pathogenesis, clinical features, and assessment of cancer cachexia - UpToDate april 2022



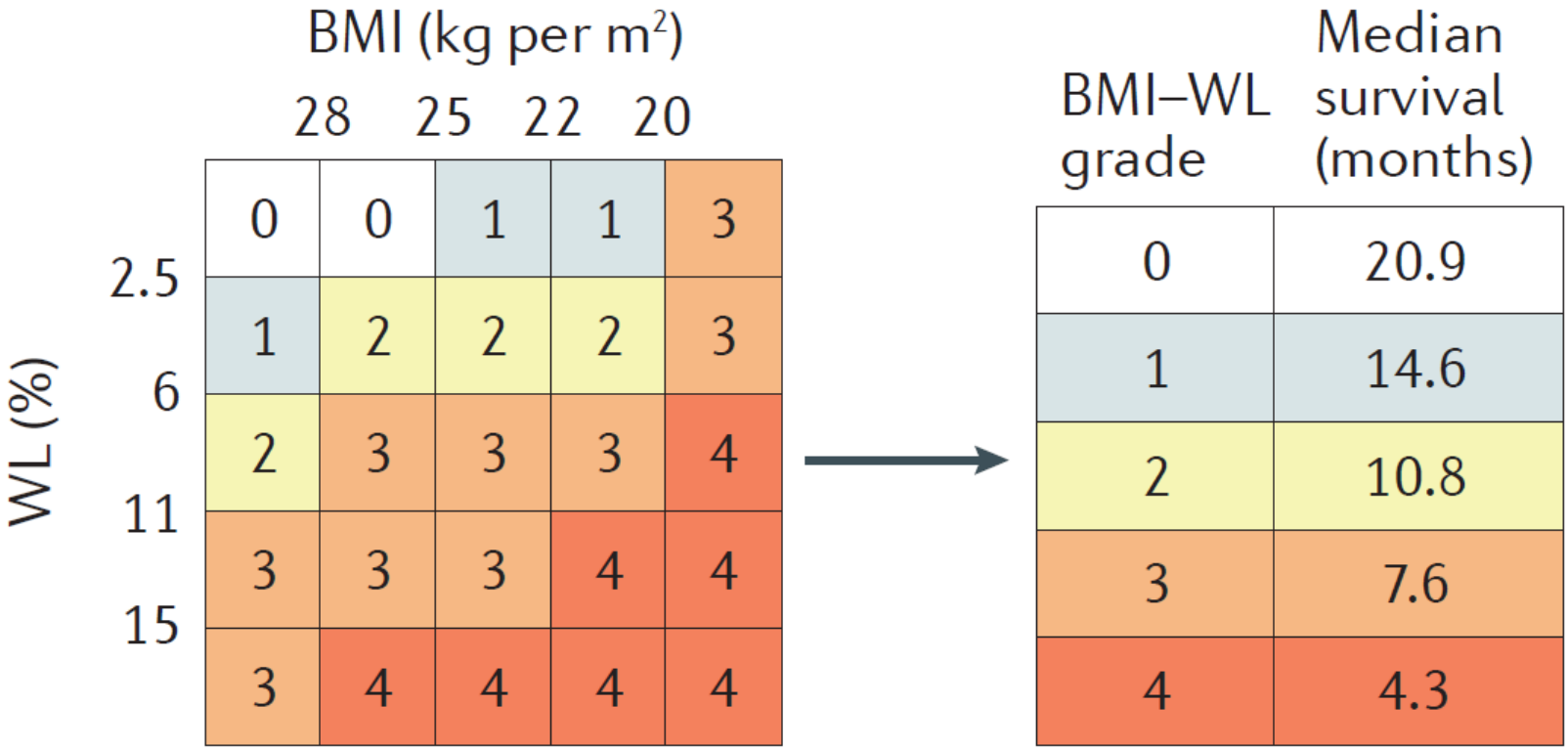
Severe muscle depletion could have occurred in patients with both low and high actual BMI

CT images from two female patients with sarcopenia are shown; the images on the left (parts **a**, **c**, **e**) correspond to a woman with a body mass index (BMI) of **47 kg/m2**, and the images on the right (parts **b**, **d**, **f**) correspond to a woman with a BMI of **17 kg/m2**. Sarcopenia is occult in the woman on the left but obvious in the woman on the right.

The axial plane (parts **a**, **b**), the sagittal plane (parts **c**, **d**) and the coronal plane (parts **e**, **f**) are shown.

Baracos Nat Rev Dis Primers. 2018

Grading scheme for Weight Loss on the basis of risk of mortality in patients with advanced-stage cancer

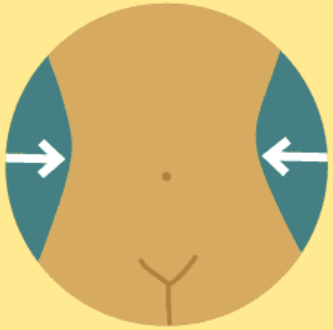


BMI–WL grade	Median survival (months)
0	20.9
1	14.6
2	10.8
3	7.6
4	4.3

The grading scheme was developed based on groupings of body mass index (BMI) and weight loss (WL), showing distinct median survival durations. The analysis was laid out in a 5 × 5 matrix representing 5 different WL categories within each of the 5 different BMI categories, producing 25 possible combinations of WL and BMI. A multivariate survival model was adjusted for age, sex, cancer site, cancer stage and performance status. Grade 0 was assigned to the subgroups in the matrix with the lowest risk (longest survival), and grades 1–4 were assigned to the subgroups according to decreasing survival. Grades were developed based on 8,160 patients and an external validation cohort of 2,683 patients.

Baracos Nat Rev Dis Primers. 2018

Symptoms of Cachexia



unintentional weight loss

skeletal muscle wasting

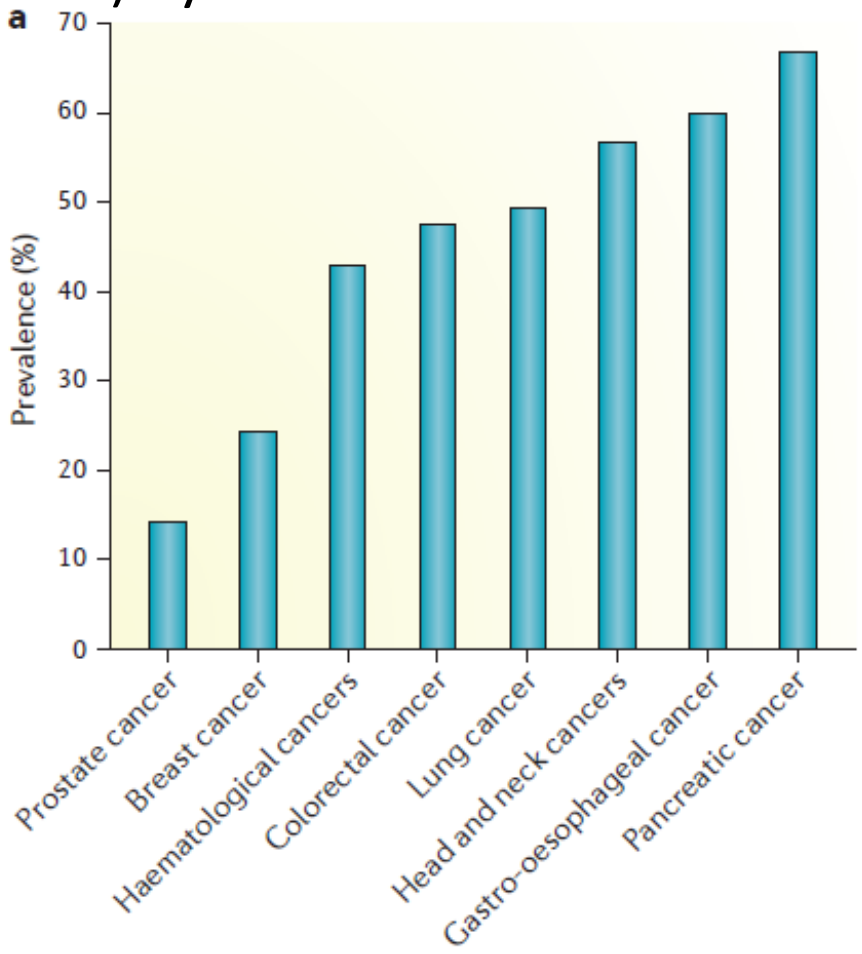
anorexia/loss of appetite

lowered quality of life

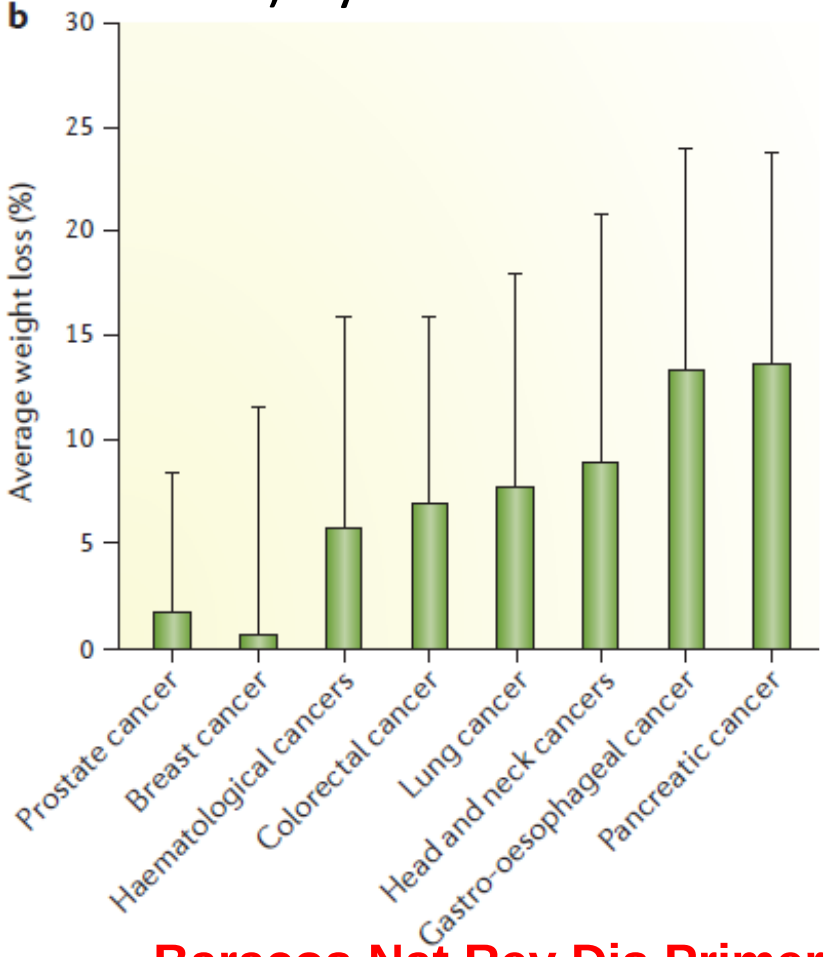
Cancer cachexia by tumor site

Some cancers are more prominently related to cachexia

The prevalence of cachexia (defined as >5% weight loss in the previous 6 months) by cancer site



Average percentage of weight loss and its variation (error bars) by cancer site



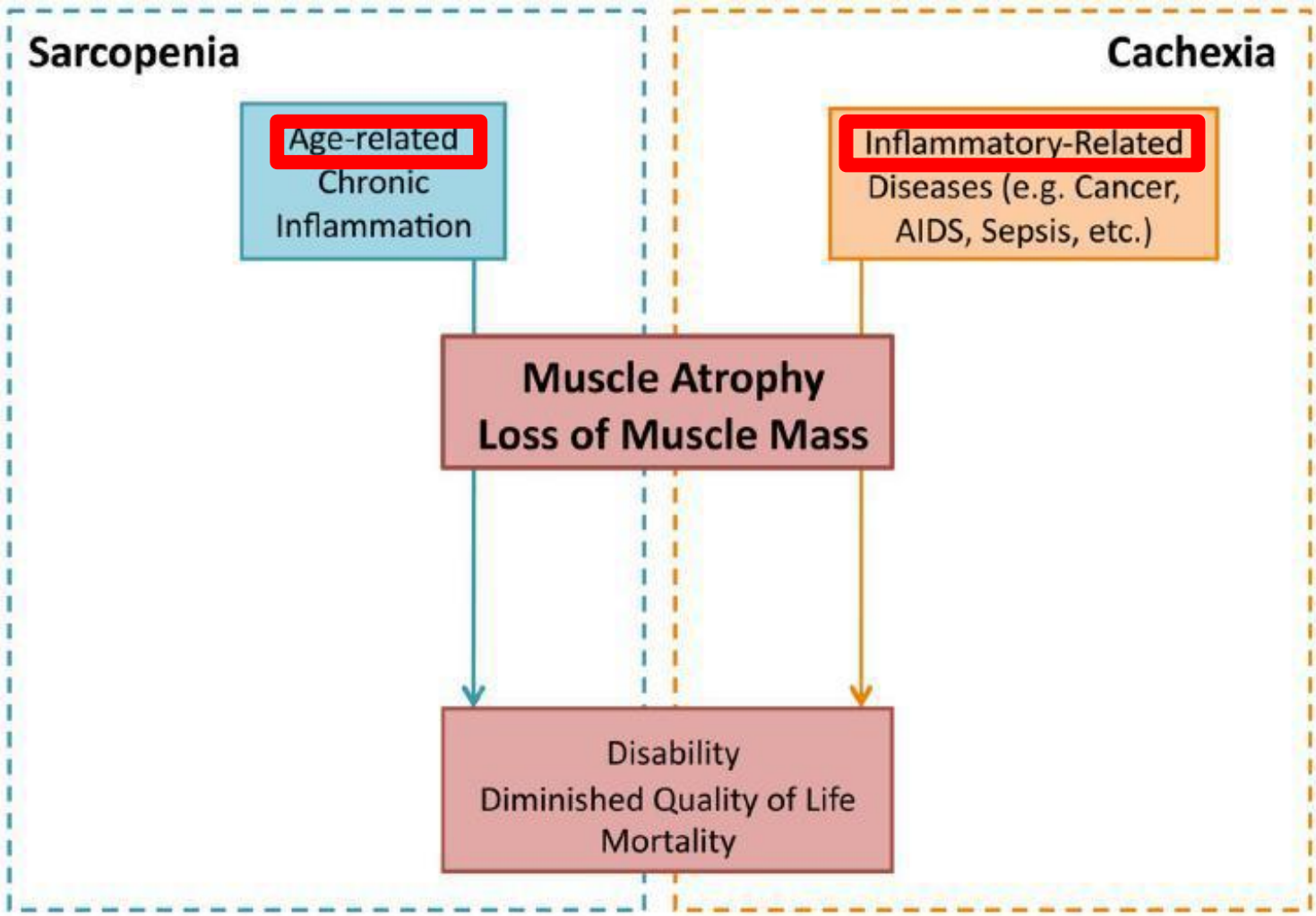
Baracos Nat Rev Dis Primers. 2018

Factors contributing to the variable prevalence of cachexia

- Cancer type
- More-advanced cancer stage
- Sex (men are more susceptible than women)
- Advanced age
- Genetic risk factors
- Comorbidities (~30% of patients have concurrent cardiac disorders with risk of cardiac cachexia)
- Treatment-related catabolic effects (sorafenib, a tyrosine kinase inhibitor, or in palliation of cancer symptoms, such as glucocorticoids)

Baracos Nat Rev Dis Primers. 2018

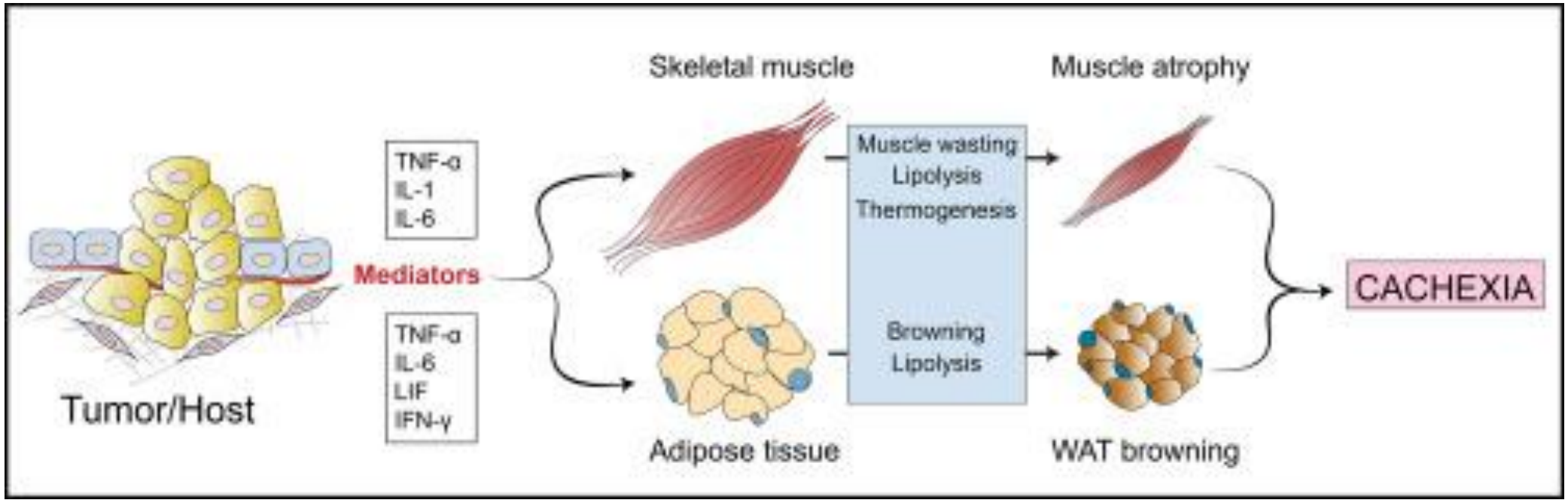
Inflammatory-induced sarcopenia vs. age-related cachexia



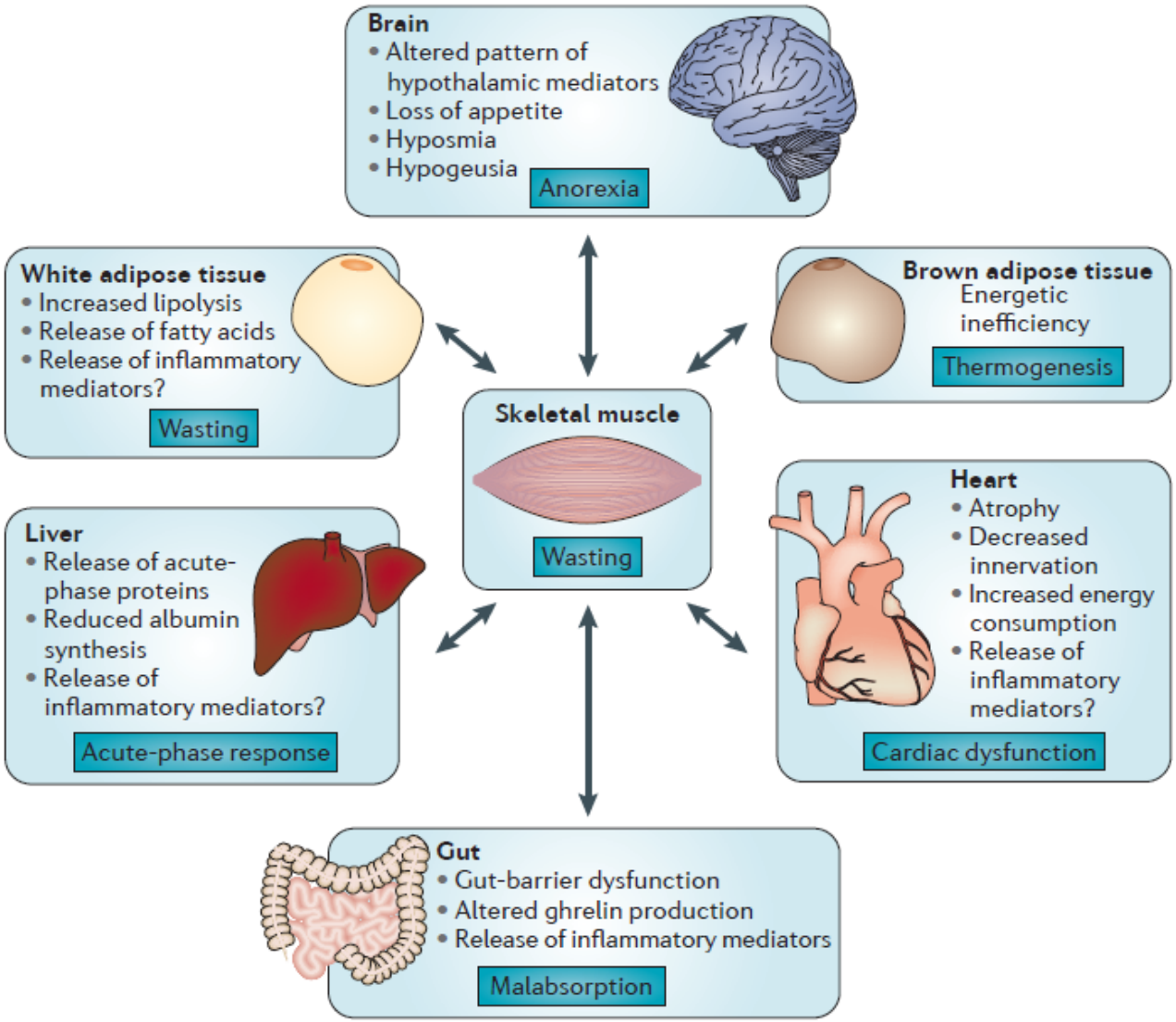
Hall Aging (Albany NY). 2011

Sarcopenia and cachexia represent two distinct diseased states, though both can result from an imbalance in the body's inflammatory mechanisms. Whereas sarcopenia (blue) results from chronic inflammation associated with age, cachexia (orange) results from inflammation associated with a primary disease (e.g. cancer, AIDS, and sepsis). Although resulting from different overlying conditions, both sarcopenia and cachexia result in muscle atrophy and loss. The dramatic loss of skeletal muscle tissue, occurring gradually in sarcopenia and acutely in cachexia, leads to disability and increased mortality.

Pathophysiology of cachexia: inflammatory cytokines



Cachexia as a multi-organ syndrome

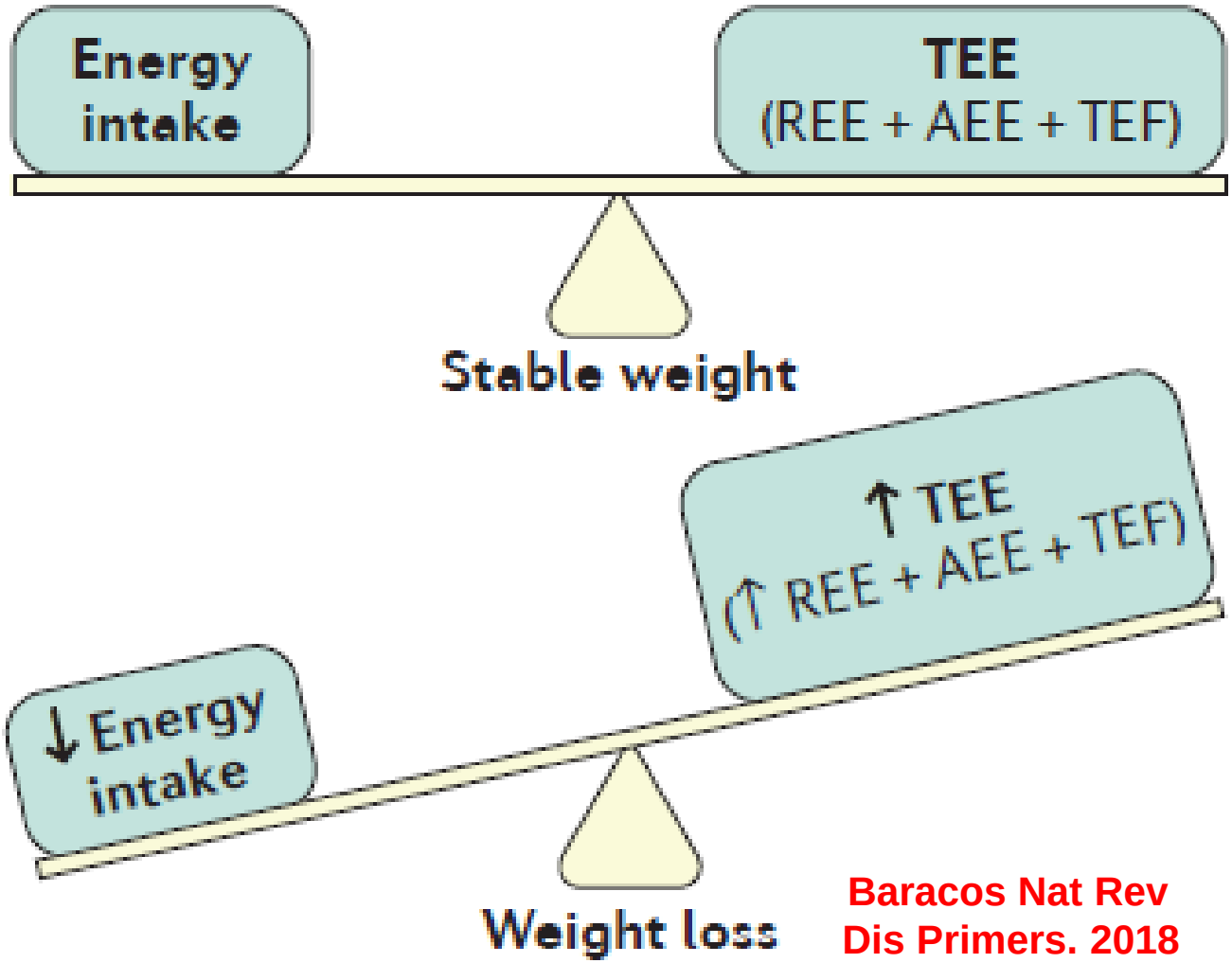


In addition to skeletal muscle and adipose tissue, other organs are affected by the cachectic process. In fact, the wasting that takes place in muscle could well be dependent on alterations in other organs or tissues, such as white adipose tissue. Abnormalities in heart function, alterations in liver protein synthesis, changes in hypothalamic mediators and activation of brown adipose tissue are also involved in the cachectic syndrome.

Argiles Nat Rev Cancer. 2014

Energy intake and energy expenditure imbalance in cancer-associated cachexia

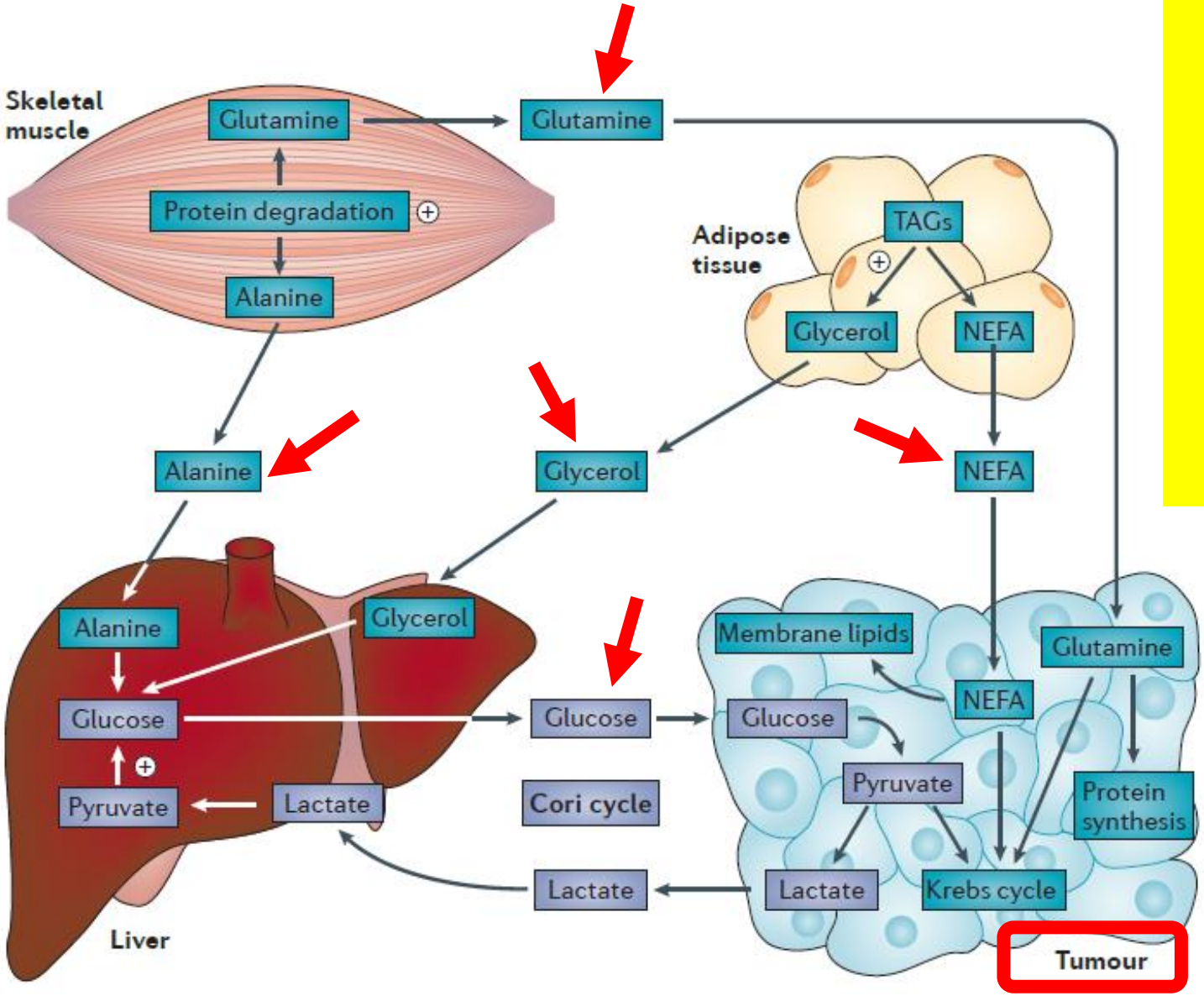
energy intake < energy expenditure (= REE + AEE + TEF)



Baracos Nat Rev Dis Primers. 2018

Body weight remains stable when there is balance between energy intake (that is, calories provided via oral, enteral or parenteral routes) and the **total energy expenditure (TEE)** by the body (see the illustration). Body weight loss occurs when there is a negative energy balance, a state in which TEE exceeds energy intake. TEE is the sum of **resting energy expenditure (REE)**, **activity-related energy expenditure (AEE)** and the **thermic effect of food (TEF)**. REE is the amount of energy expended by the body at rest and is the largest contributor to TEE. Accordingly, as TEE is difficult to measure clinically in free-living individuals, REE is typically assumed to represent energy metabolism. REE can be accurately measured using indirect calorimetry or estimated using various equations, which have many limitations. Tumour metabolism and inflammation might increase REE and simultaneously decrease energy intake (through, for example, loss of appetite), shifting the scale towards negative energy balance[187,188]. Additionally, cancer treatments also influence energy balance; for example, energy intake may fall by >50% (~1,200 kcal per day) during chemoradiotherapy for cancers of the head and neck[25]. These factors contribute to the negative energy balance in cancer-associated cachexia.

Gln, Ala, glycerol, glucose and FFA are extracted

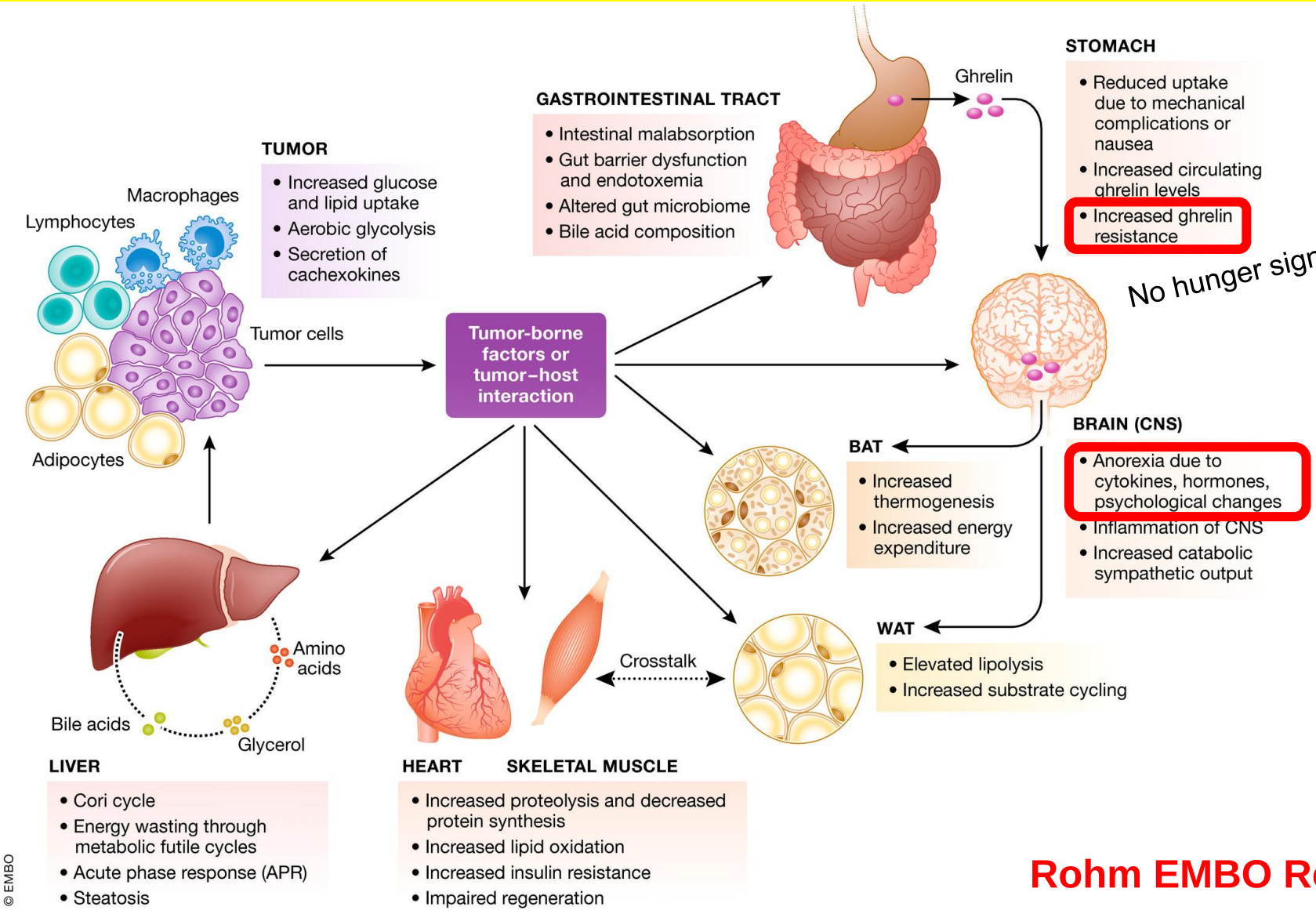


Main metabolic adaptations associated with tumour burden

The selfish tumor, 'eats' the other organs

Argiles Nat Rev Cancer. 2014

Overview of energy consuming processes in cachexia: the ‘cachexokines’



Tumor-secreted factors or tumor/host interactions reduce energy uptake and activate energy-wasting processes in different organ systems, acting on brain/CNS, adipose tissues, gastrointestinal system, liver, and muscles.

Rohm EMBO Rep. 2019

Markers of Cachexia Used in the Clinic

4 categories:

1) cytokines (“inflammation”)
2) lean muscle mass (“muscle wasting”)
3) markers of biological activity and metabolism (“altered metabolism”)
4) other humoral factors

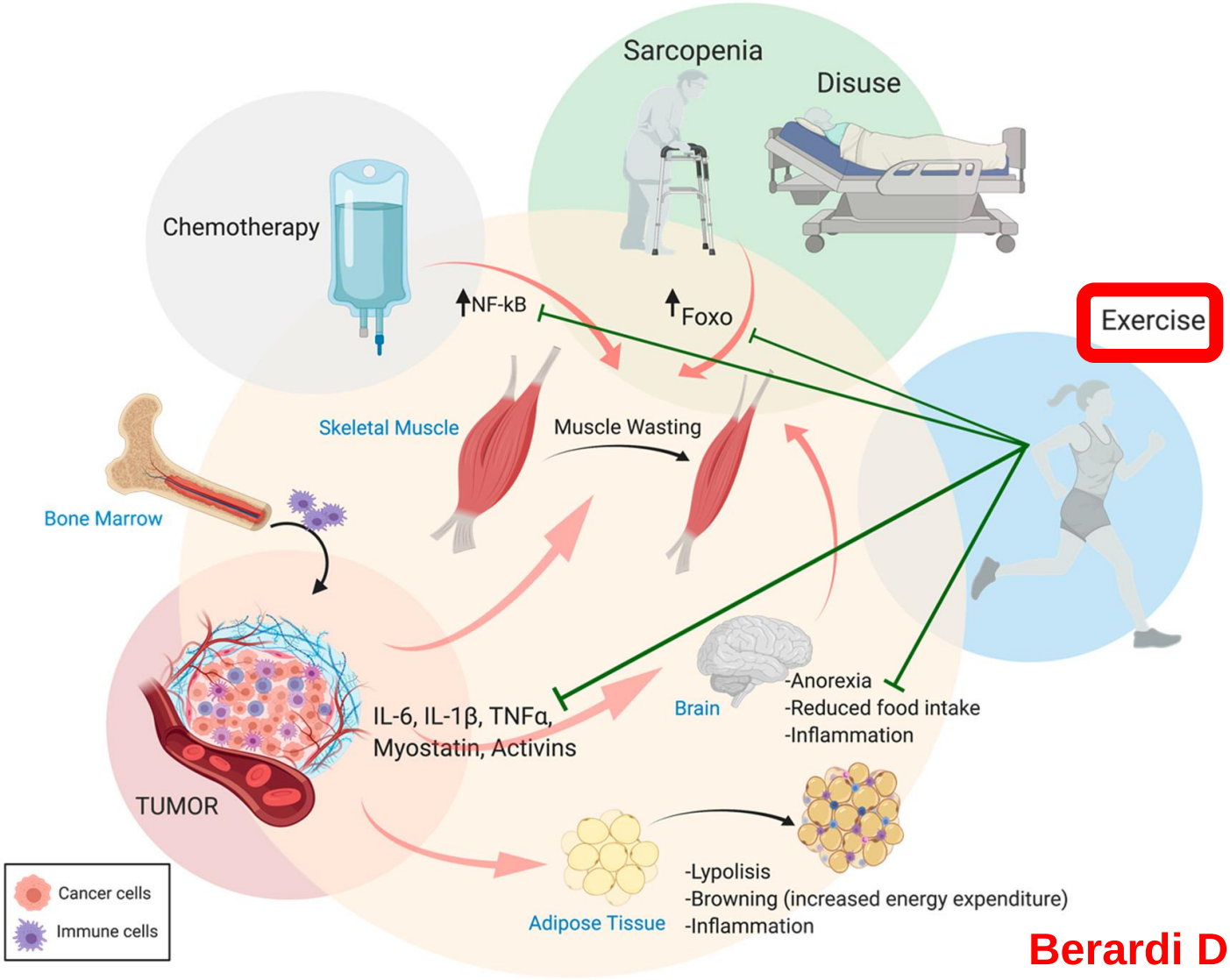
Assessment in any patient to diagnose cachexia independently from underlying disease:

1) Unintentional weight loss
2) Elevated blood levels of CRP (half life 19 h),
   IL- (15.5 h), IL-1 (21 min), TNFα (18.2 min)
3) Muscle function decline

Berardi Diagnostics (Basel). 2021

Exercise training

seems to be a promising strategy to counteract cachexia, even in the presence of chemotherapy

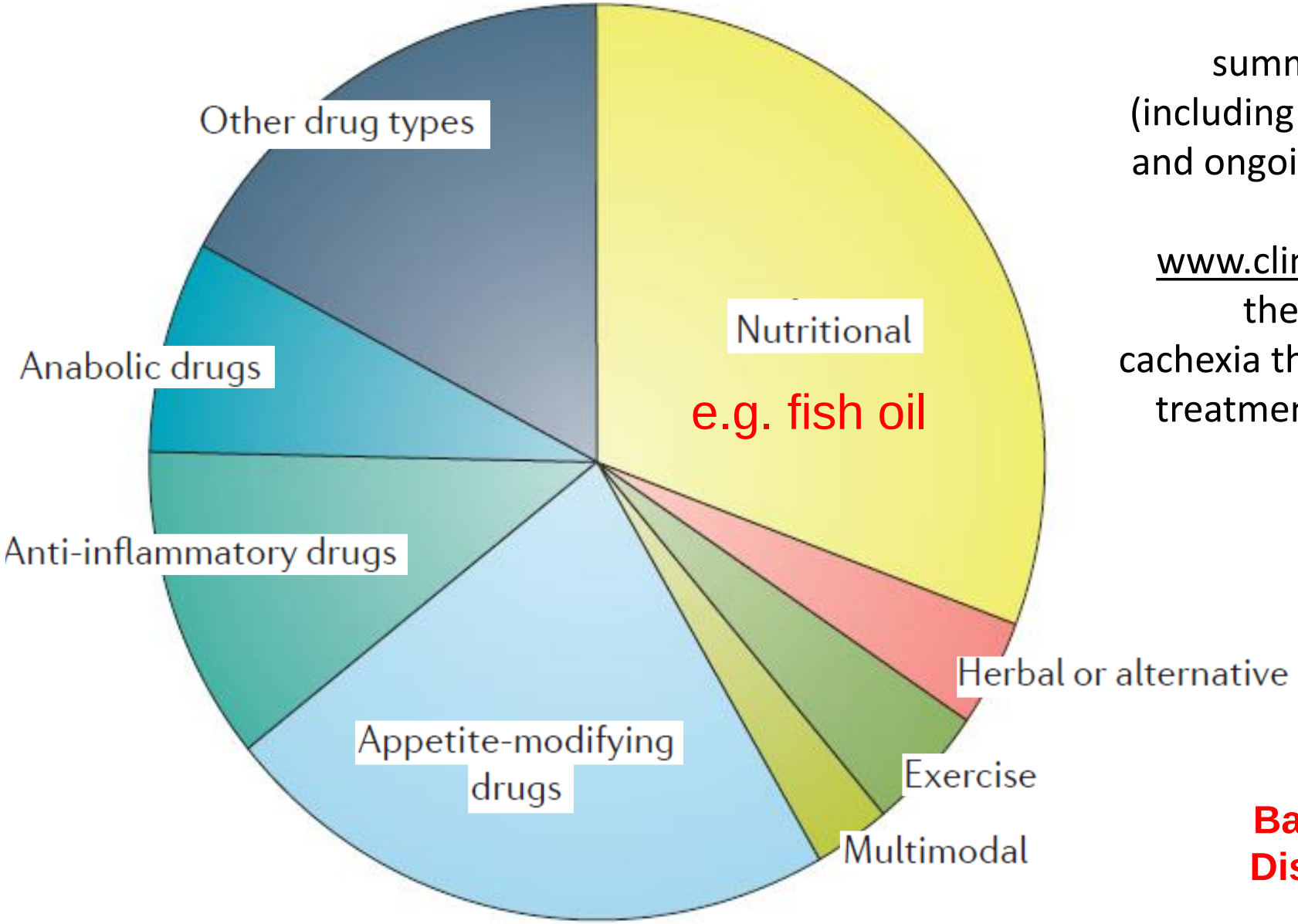


It is now well established that muscle activity (i.e., physical activity and exercise training) protects against cancer-related muscle wasting and promotes the maintenance of muscle mass [20–24] (Figure 1).

Proinflammatory cytokines produced by immune and tumor cells (i.e., in cancer-related cachexia) and other circulating molecules trigger catabolic events in skeletal muscle tissue, adipose tissue, and the central nervous system (CNS). Chemotherapy, sarcopenia, and disuse aggravate cachexia outcomes during physical activity ameliorates prognosis by counteracting muscle wasting and the inflammatory condition.

Berardi Diagnostics (Basel). 2021

Proportional distribution of therapeutic approaches in clinical trials of cancer-associated cachexia therapy



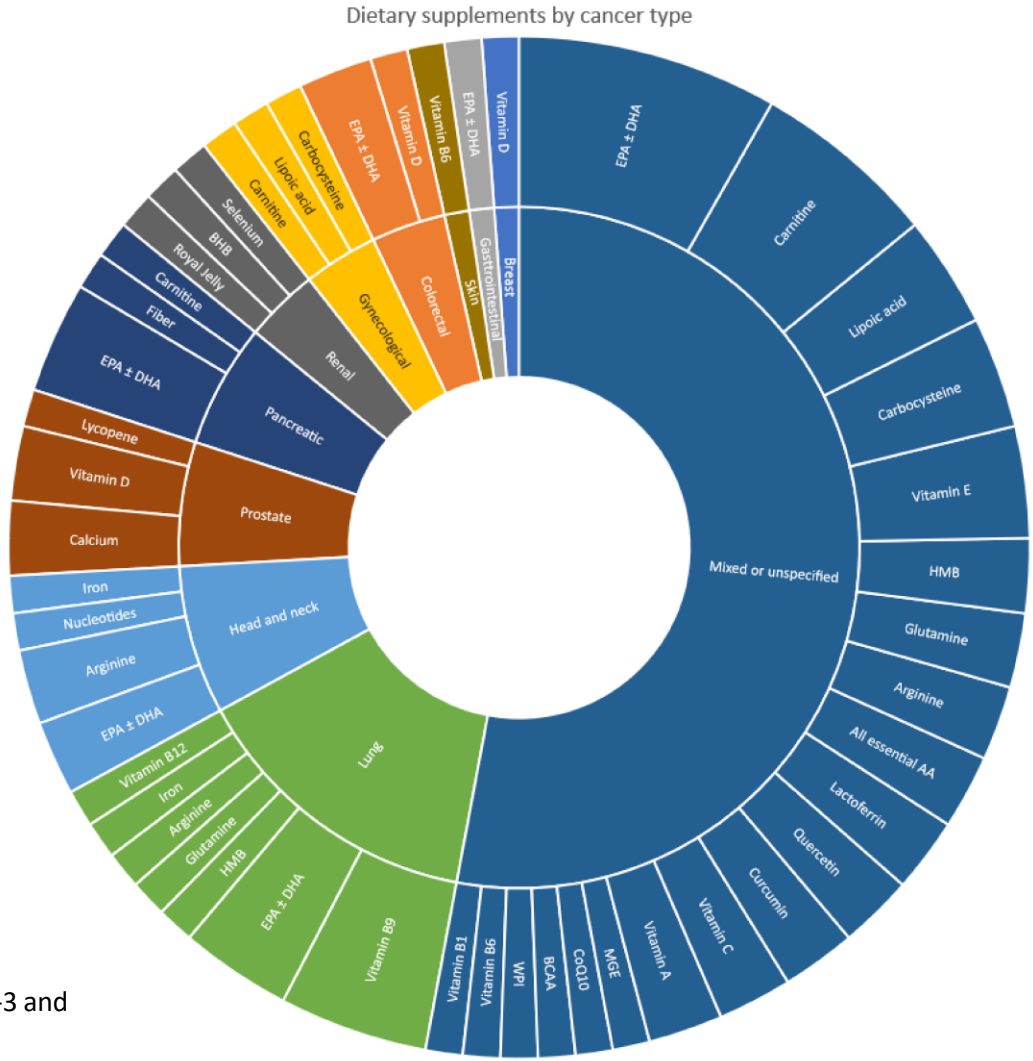
summary of 134 trials (including published works and ongoing investigations reported in www.clinicaltrials.gov) of the major classes of cachexia therapies includes treatments in phase II–IV clinical trials.

Baracos Nat Rev Dis Primers. 2018

Types of dietary supplements included in studies, according to cancer type

Vitamin A	Lactoferrin
Vitamin B1	Whey protein isolate
Vitamin B6	Essential amino acids
Vitamin B9	Arginine
Vitamin B12	BCAA
Vitamin C	Carnitine
Vitamin D	Glutamine
Vitamin E	HMB
Calcium	EPA ± DHA
Iron	Fiber
Selenium	BHB
Carbocysteine	Coenzyme Q10
Curcumin	Muscadine Grape Extract
Lipoic acid	Nucleotides
Lycopene	Royal Jelly
Quercetin	

End points
Weight loss
Anemia
Cachexia
Weight loss
NS
Anorexia, weight loss
Malnutrition, weight loss
NS
Cachexia



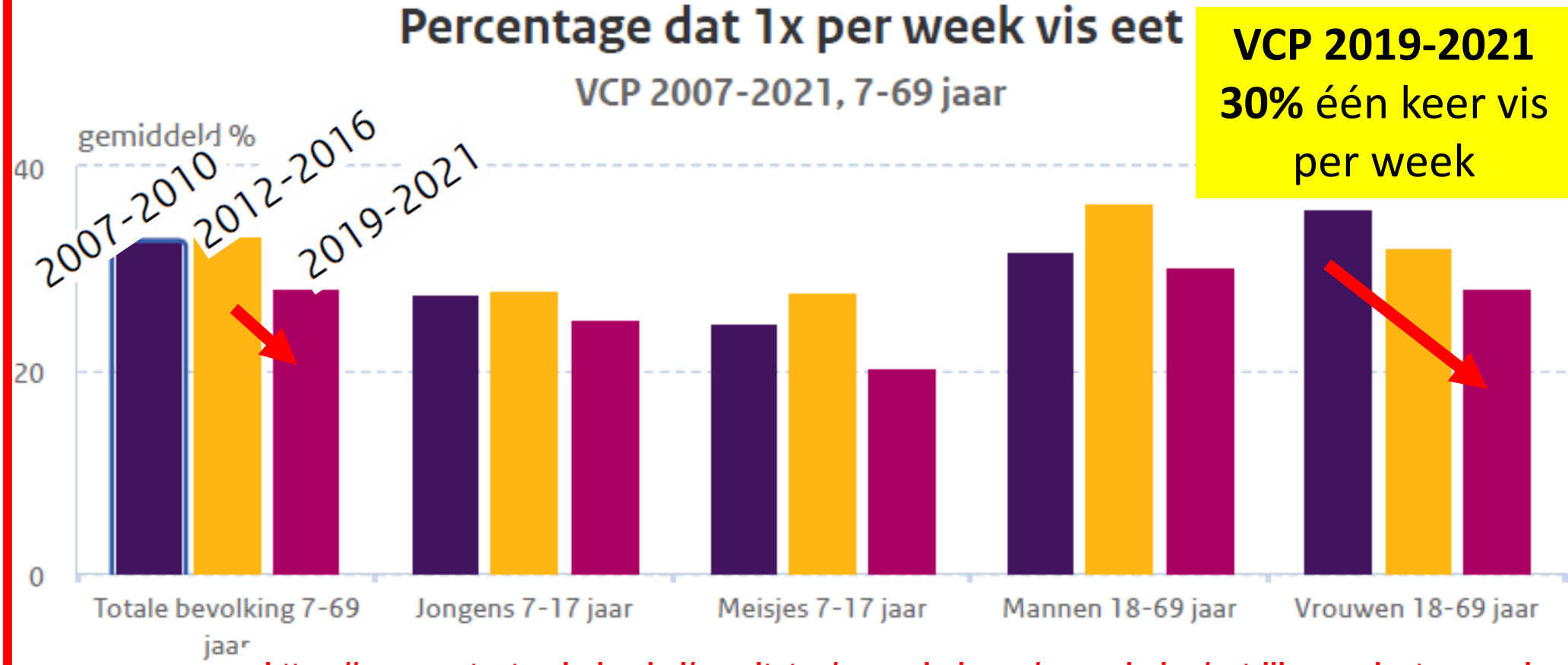
While the types of dietary supplements included varied across cancer types, omega-3 and carnitine were investigated most often. Proposed relevant attributes of dietary supplements included their antioxidant, anti-inflammatory, anti-cancer, and immunomodulatory properties. Overall, there was a paucity of interventional studies, and more randomized controlled trials are warranted.

Johal Nutrients. 2022

Vis: VCP 2007-2021

Richtlijn: Eet één keer per week vis, bij voorkeur vette vis

Het percentage 7-69 jarigen dat 1 keer per week vis eet is de afgelopen jaren eerst vrijwel gelijk gebleven en daarna gedaald. In 2007-2010 was dit 32%, in 2012-2016 was dit 33% en in 2019-2021 was dit 28%.

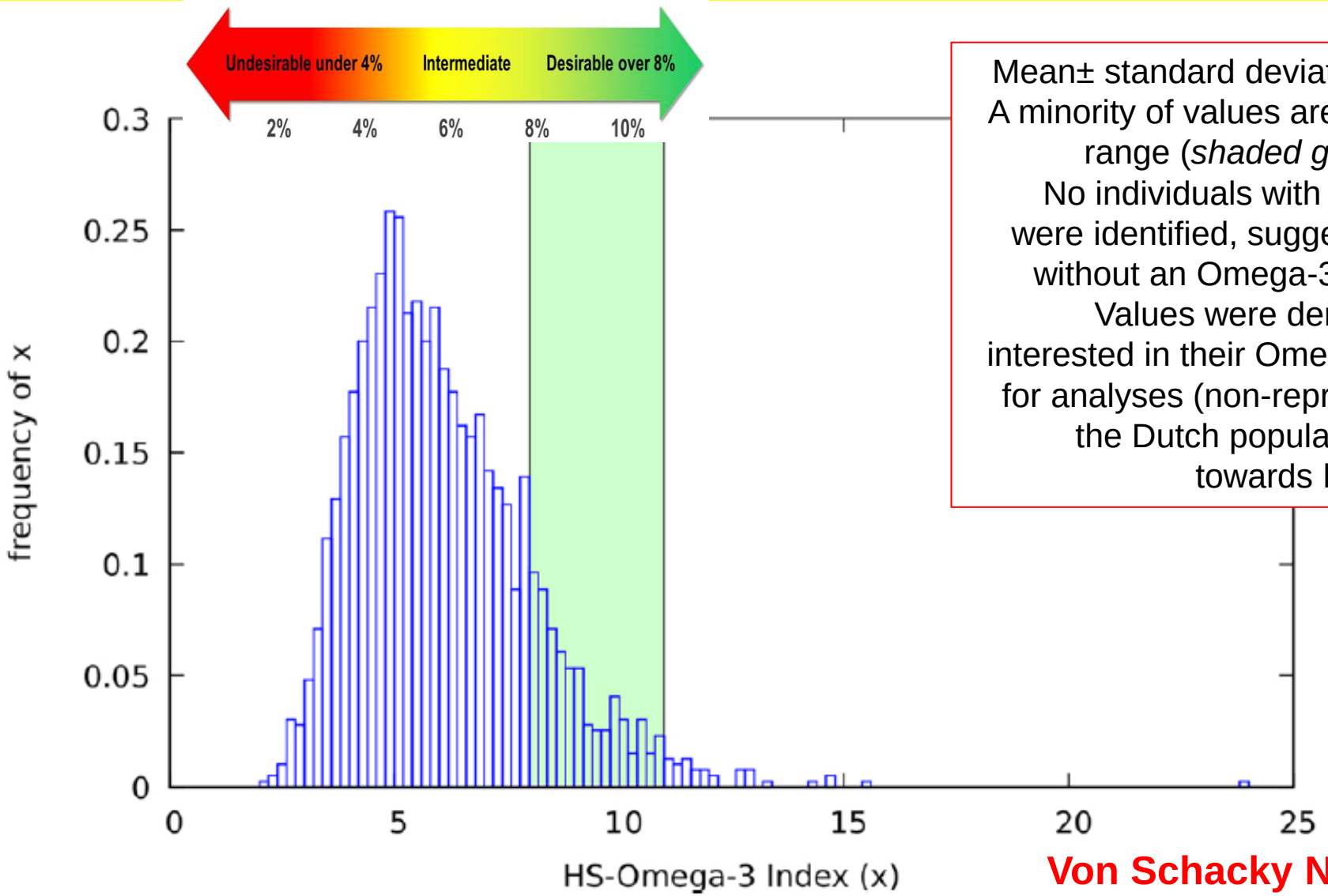


VCP 2019-2021
30% één keer vis per week

https://www.wateetnederland.nl/resultaten/veranderingen/verandering/vetrijke-producten-en-vis

https://www.wateetnederland.nl/resultaten/veranderingen

Histogram of HS-Omega-3 Index based on data from 1974 inhabitants of the Netherlands (only first-time measurements shown).

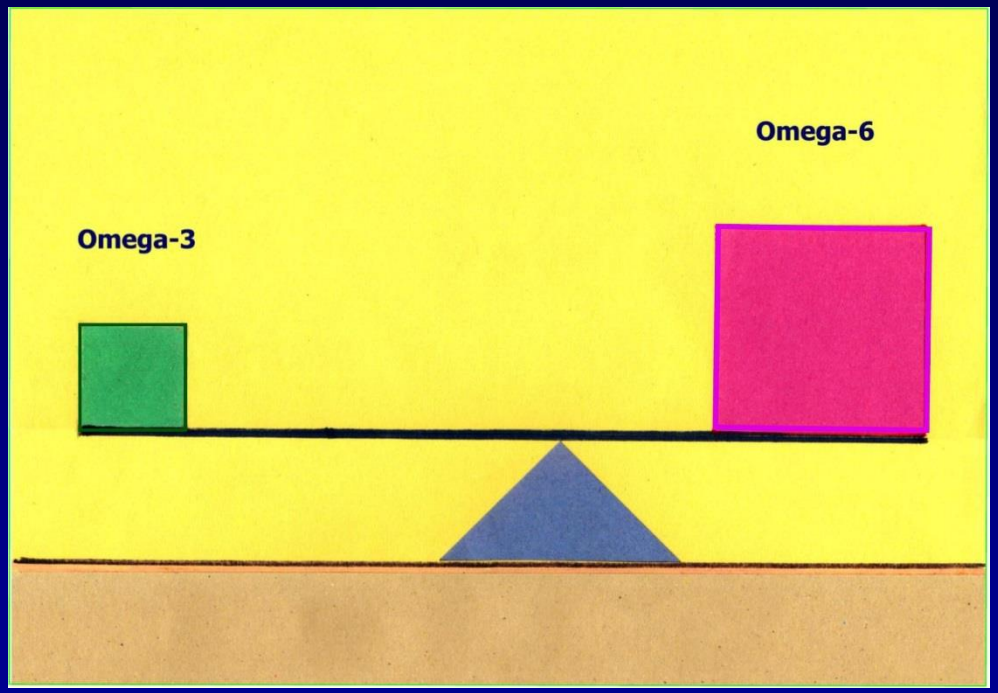


Mean± standard deviation is 6.06%±1.95%. A minority of values are within 8–11% target range (*shaded green*); few are >11%. No individuals with Omega-3 Index <2% were identified, suggesting that human life without an Omega-3 Index is impossible. Values were derived from individuals interested in their Omega-3 Index, who paid for analyses (non-representative sample of the Dutch population). Therefore, bias towards higher values is likely

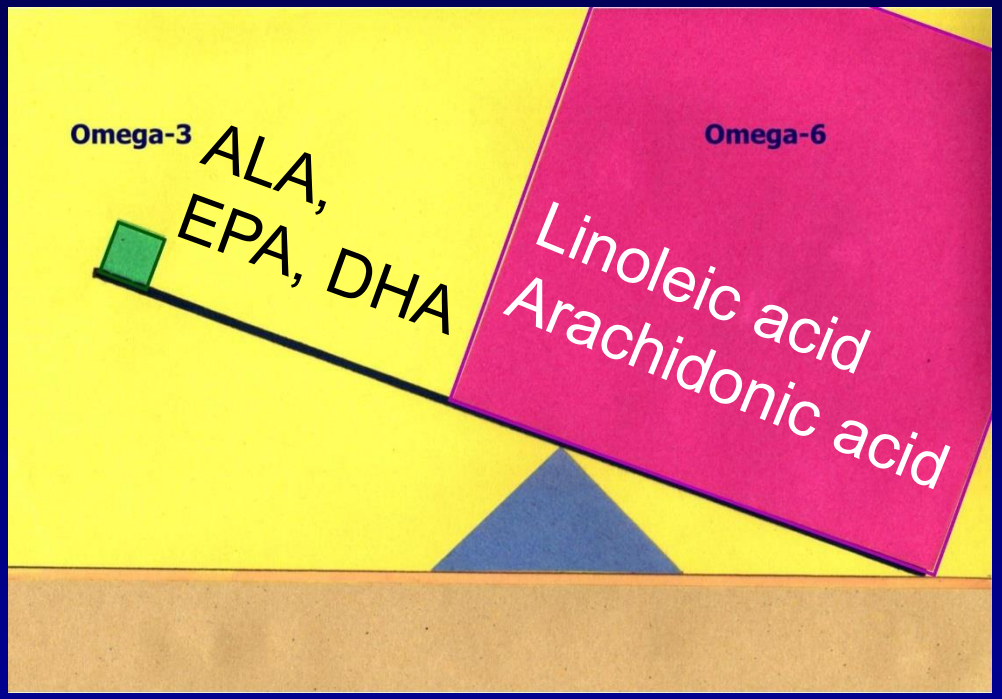
Von Schacky Neth Heart J 2023

MMV Voedingsmiddelenkaart 01-2021

Omega 3/6 balance

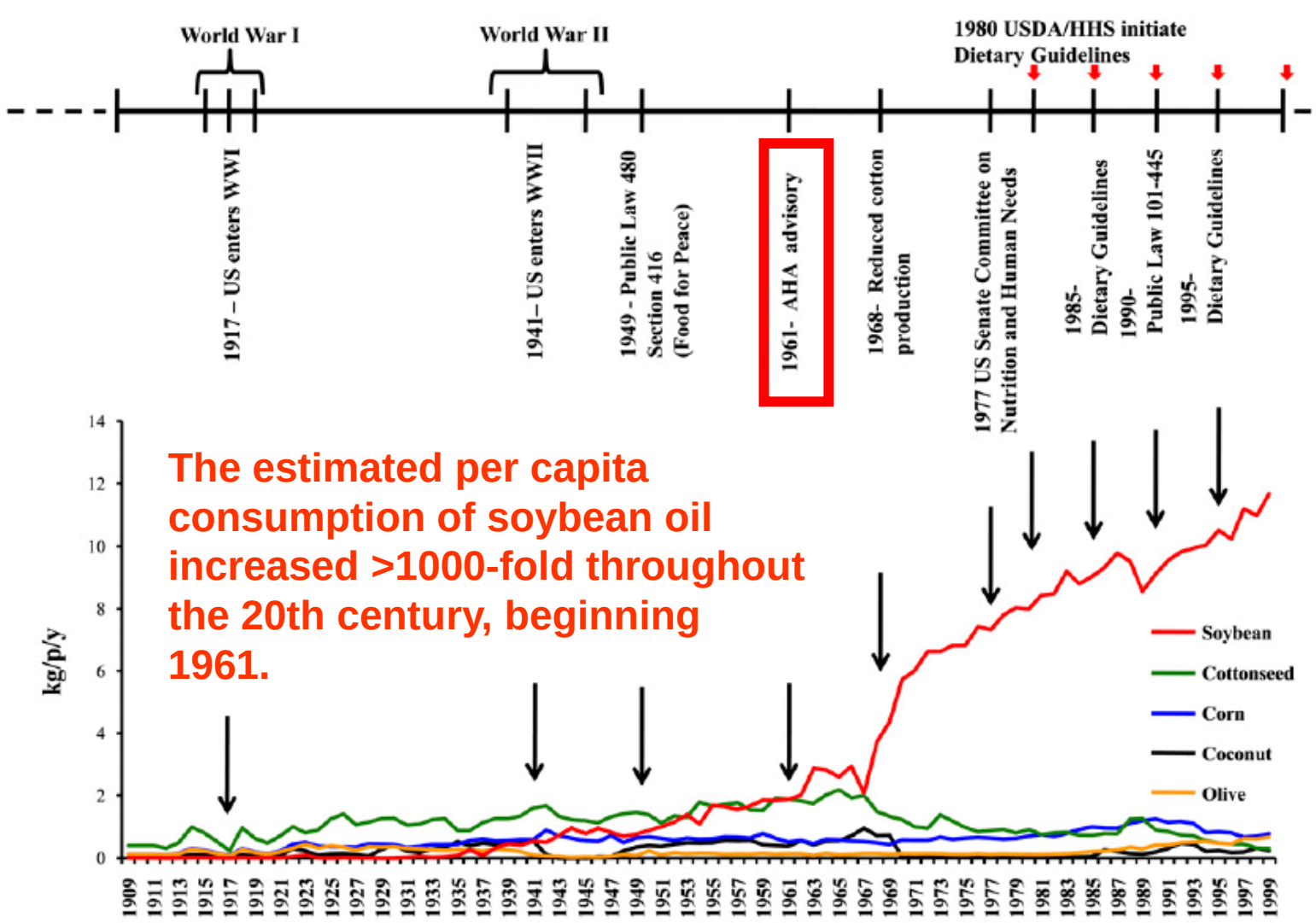


Ancient diet



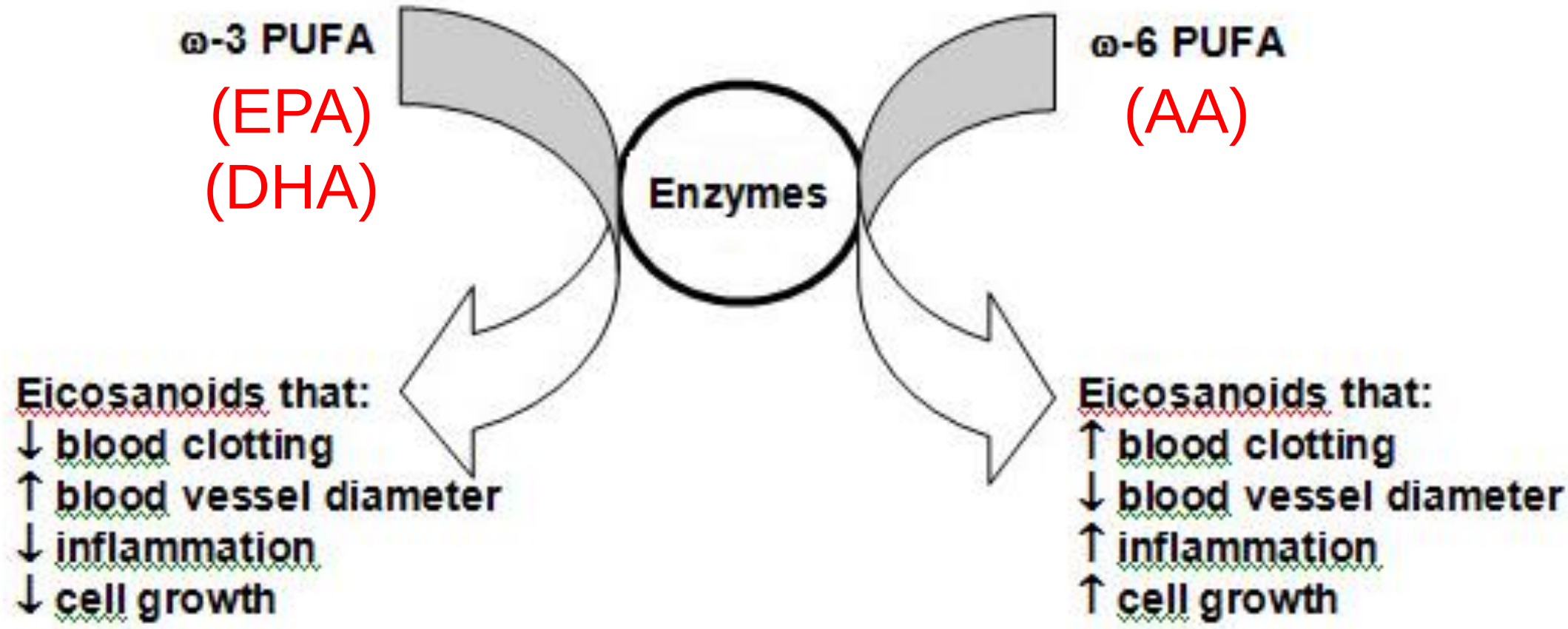
Current diet

The historical event immediately preceding the largest increase in apparent consumption of soy oil in the United States was the 1961 American Heart Association (AHA) Central Committee Advisory Statement that advised Americans to replace their saturated fat intake with polyunsaturated fats.

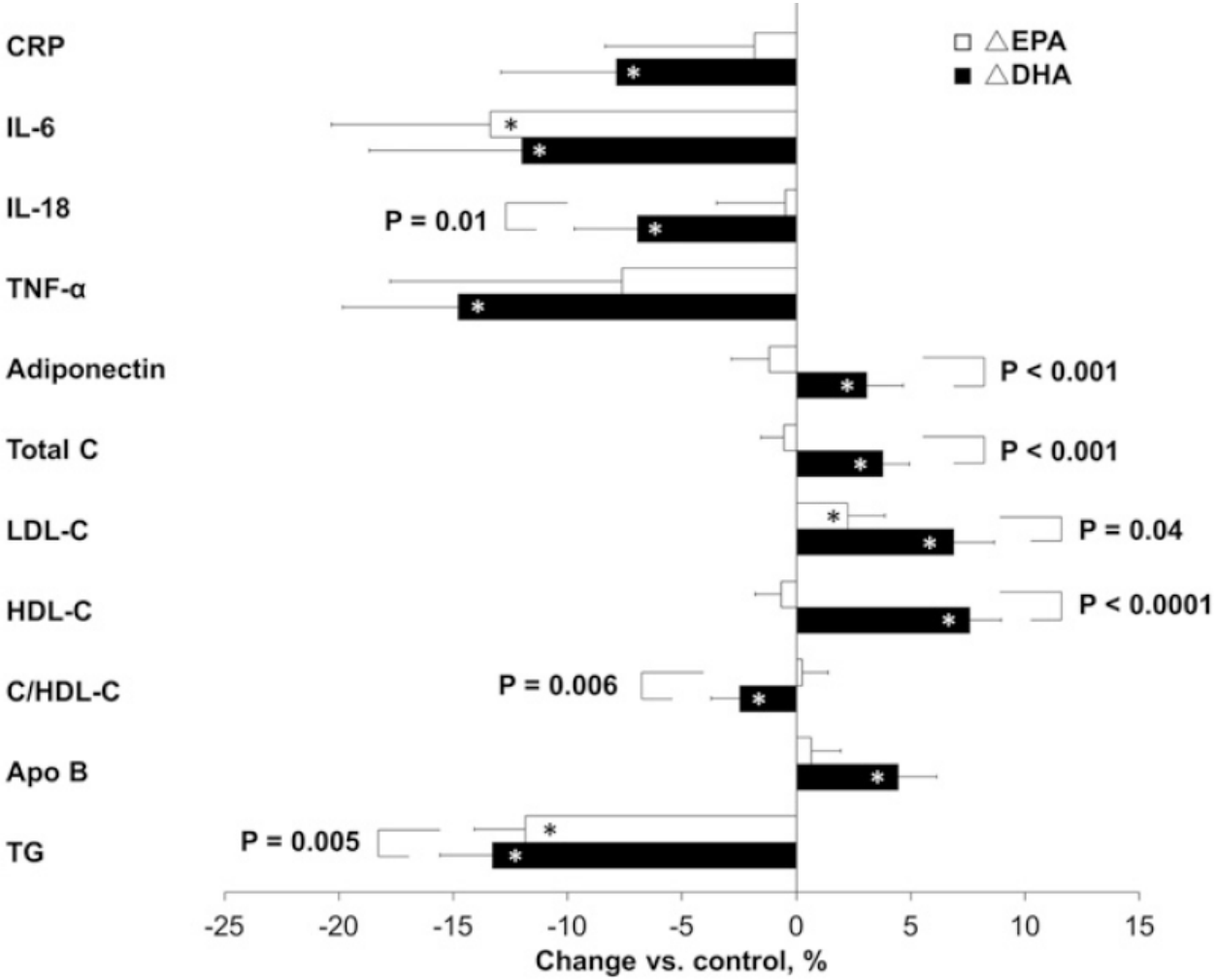


Blasbalg, Ramsden AJCN 2011

Eicosanoids from LCPω6 and LCPω3 often have opposing functions



RCT: influence of 2.7 g/d EPA and 2.7 g/d DHA on inflammation markers and blood lipids inflammation vs metabolism



Characteristics at screening of subjects randomly assigned into the study (n = 154)[1]

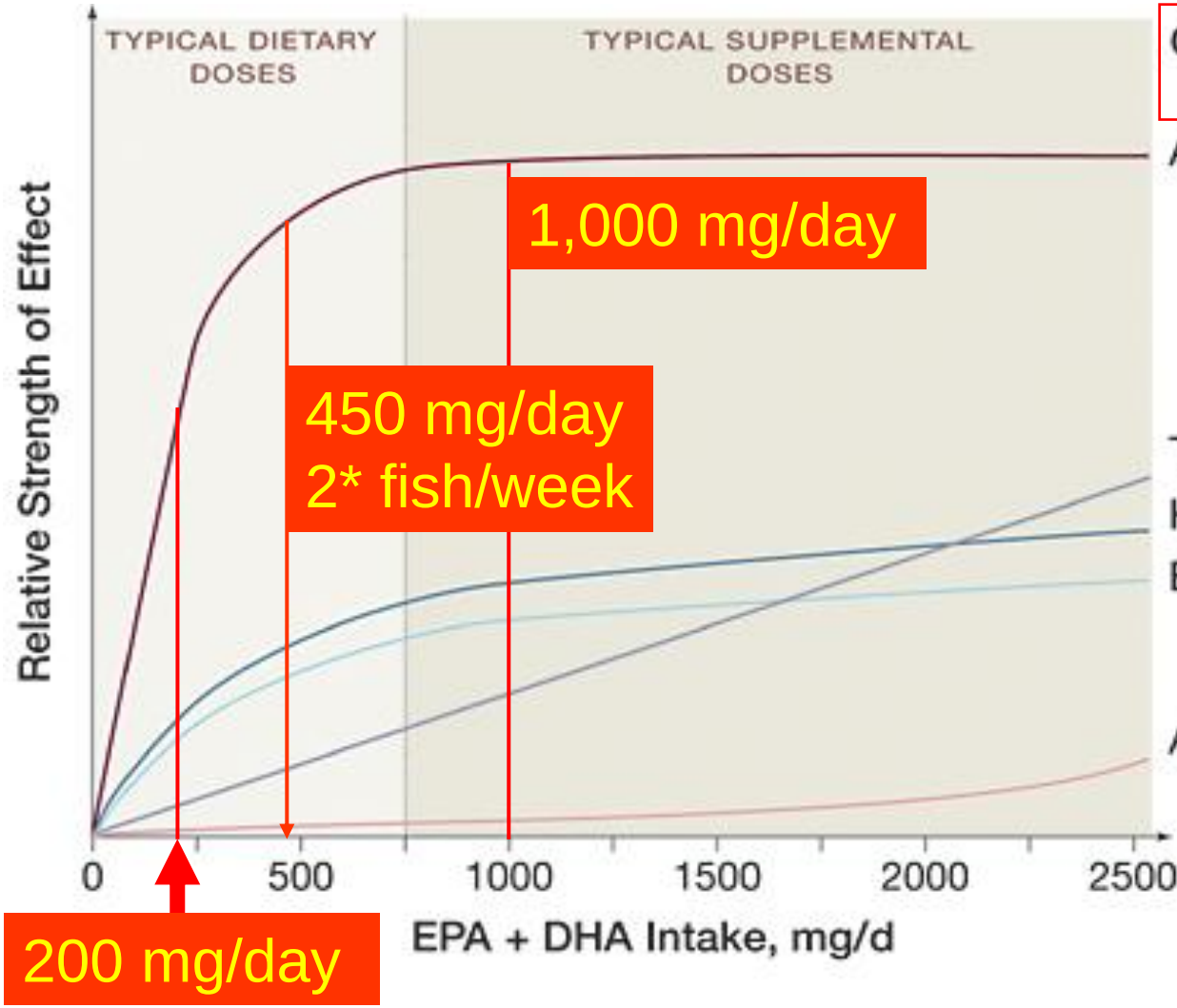
	Men (n = 48)	Women (n = 106)
Age, y	57 ± 12[2]	50 ± 16
BMI, kg/m^2	30 ± 4	29 ± 4
Waist circumference, cm	107 ± 10	98 ± 9
SBP, mm Hg	119 ± 13	111 ± 12
DBP, mm Hg	78 ± 9	71 ± 8
Total cholesterol, mmol/L	4.9 ± 0.7	5.5 ± 0.9
LDL cholesterol,[3] mmol/L	3.0 ± 0.7	3.2 ± 0.8
HDL cholesterol, mmol/L	1.3 ± 0.3	1.7 ± 0.4
Cholesterol:HDL-cholesterol ratio	4.0 ± 0.9	3.5 ± 1.0
Triglycerides, mmol/L	1.5 ± 0.8	1.4 ± 0.7
CRP, mg/L	2.8 ± 1.8	3.7 ± 2.4
Fasting glucose, mmol/L	5.5 ± 0.9	5.2 ± 0.7
Subjects with MetS, n (%)	25 (12)	17 (19)

In a double-blind, randomized, crossover, controlled study, healthy men (n = 48) and women (n = 106) with abdominal obesity and low-grade systemic inflammation consumed 3 g/d of the following supplements for periods of 10 wk: 1) EPA (2.7 g/d), 2) DHA (2.7 g/d), and 3) corn oil as a control with each supplementation separated by a 9-wk washout period.

Indicated are mean±SEM percent changes compared with control

Allaire Am J Clin Nutr. 2016

Effect of Supplemental Time Course and Dose to reach a Clinical Effect and an alter Clinical Events of Fish Oil Intake



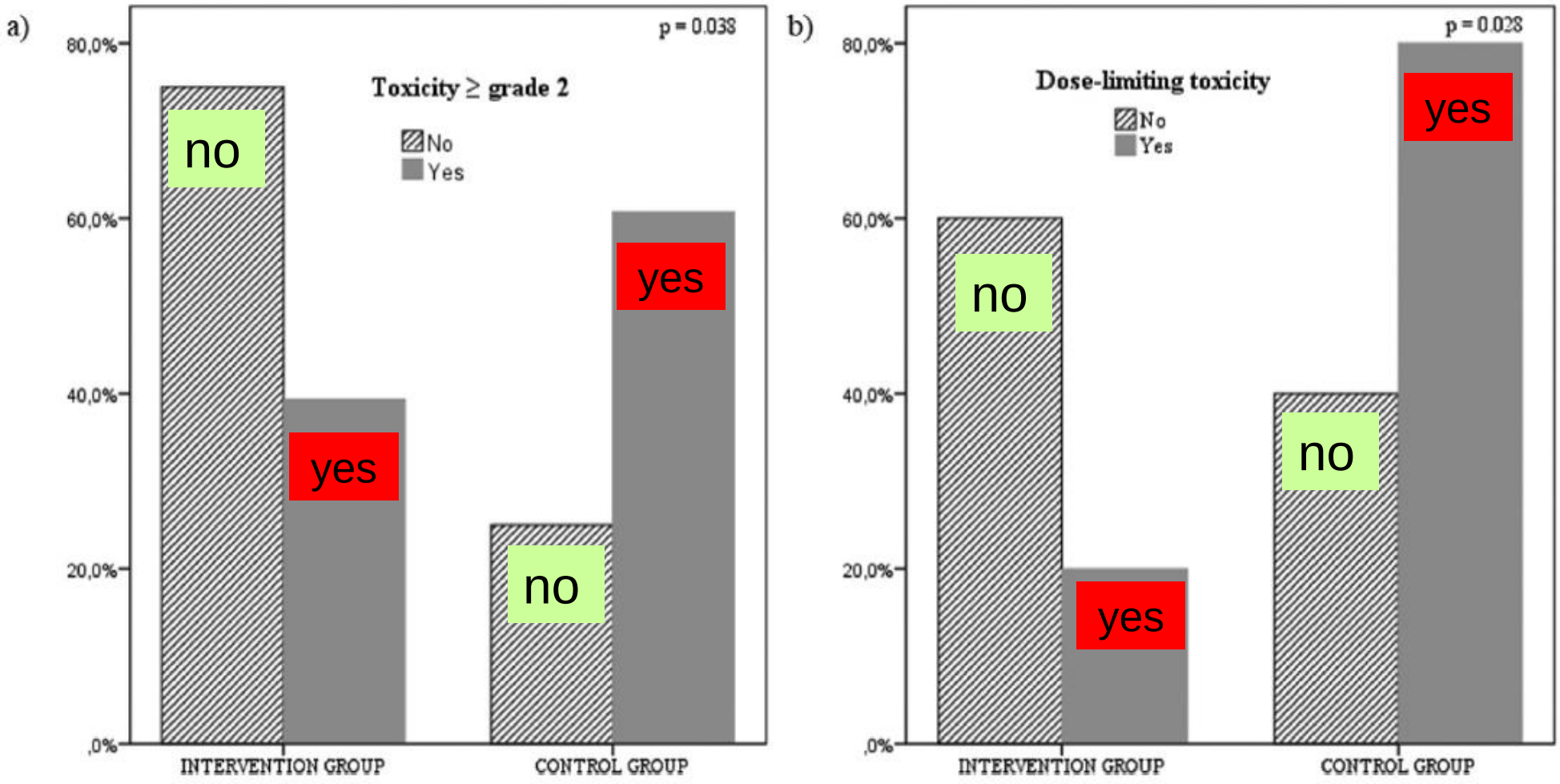
Clinical Effect	Time Course To Alter Clinical Events
Antiarrhythmia	Weeks
Triglyceride-Lowering	Months to Years
Heart Rate–Lowering	Months
BP–Lowering	Months to Years
Antithrombosis	Weeks

Brain DHA half life = 2.5 y
Umhau J Lipid Res 2009;
Rapoport PLEFA 2009

Mozaffarian, D. et al. JAMA 2006;296:1885-1899.

Incidence of chemotherapy toxicity in control and intervention: (a) toxicity grade 2 and (b) dose-limiting toxicity

Omega-3- supplementation is effective in maintaining nutritional status, skeletal muscle quality, and reduced symptoms of chemoradiotherapy among women with cervical cancer



Aredes Nutrition. 2019

Visolie-aanbeveling van The European Society of Clinical Nutrition and Metabolism, ESPEN, mei 2021 (2 meta-analyses)

Bij patiënten met gevorderde kanker die chemotherapie ondergaan en met het risico op gewichtsverlies of ondervoeding, raden we suppletie aan met langketenige n-3-vetzuren of visolie om te stabiliseren of te verbeteren de:

De eetlust

De voedingsinname

De vetvrije massa

Het lichaamsgewicht

Aanbeveling B5-7;

Sterkte van aanbeveling zwak,

Niveau van bewijskracht laag

Sterke overeenstemming

Muscaritoli Clin Nutr. 2021

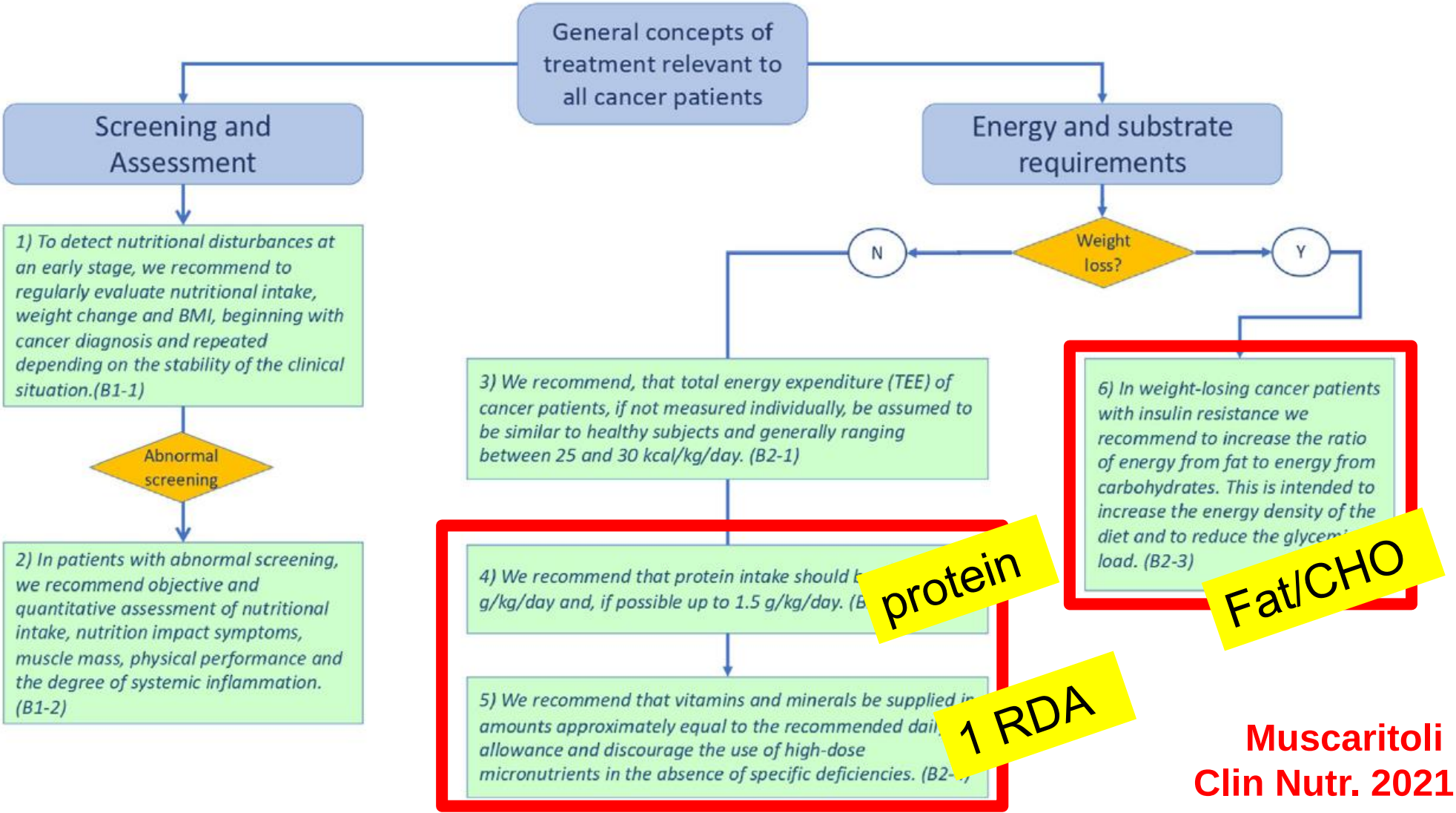
Visolie-aanbeveling van The European Society of Clinical Nutrition and Metabolism, ESPEN, mei 2021 (2 meta-analyses)

- Twee recente reviews tonen aan dat lange ketenvetzuren verbeterde: de eetlust, het lichaamsgewicht, de postoperatieve morbiditeit en de kwaliteit van leven bij kankerpatiënten die gewicht verliezen
- Er zijn verschillende studies over de beschermende effecten van visolie op de door de chemotherapie-veroorzaakte toxiciteit, zoals perifere neuropathie
- De gebruikelijke doses visolie en n-3 lange ketenvetzuren worden meestal goed verdragen.
- Er zijn mogelijk milde gastro-intestinale effecten en de naleving wordt belemmert door smaak, visachtige nasmaak en het oprispen van vis
- De zwakke aanbeveling voor het gebruik van visolie en lange-keten n-3-vetzuren zijn gebaseerd op verschillende positieve onderzoeken in de afgelopen jaren, de plausibele biologische rationale, slechts milde bijeffecten en geen overtuigende ernstige veiligheidskwesties

Muscaritoli Clin Nutr. 2021

General concepts of treatment relevant to all cancer patients: screening and assessment; energy and substrate requirements.

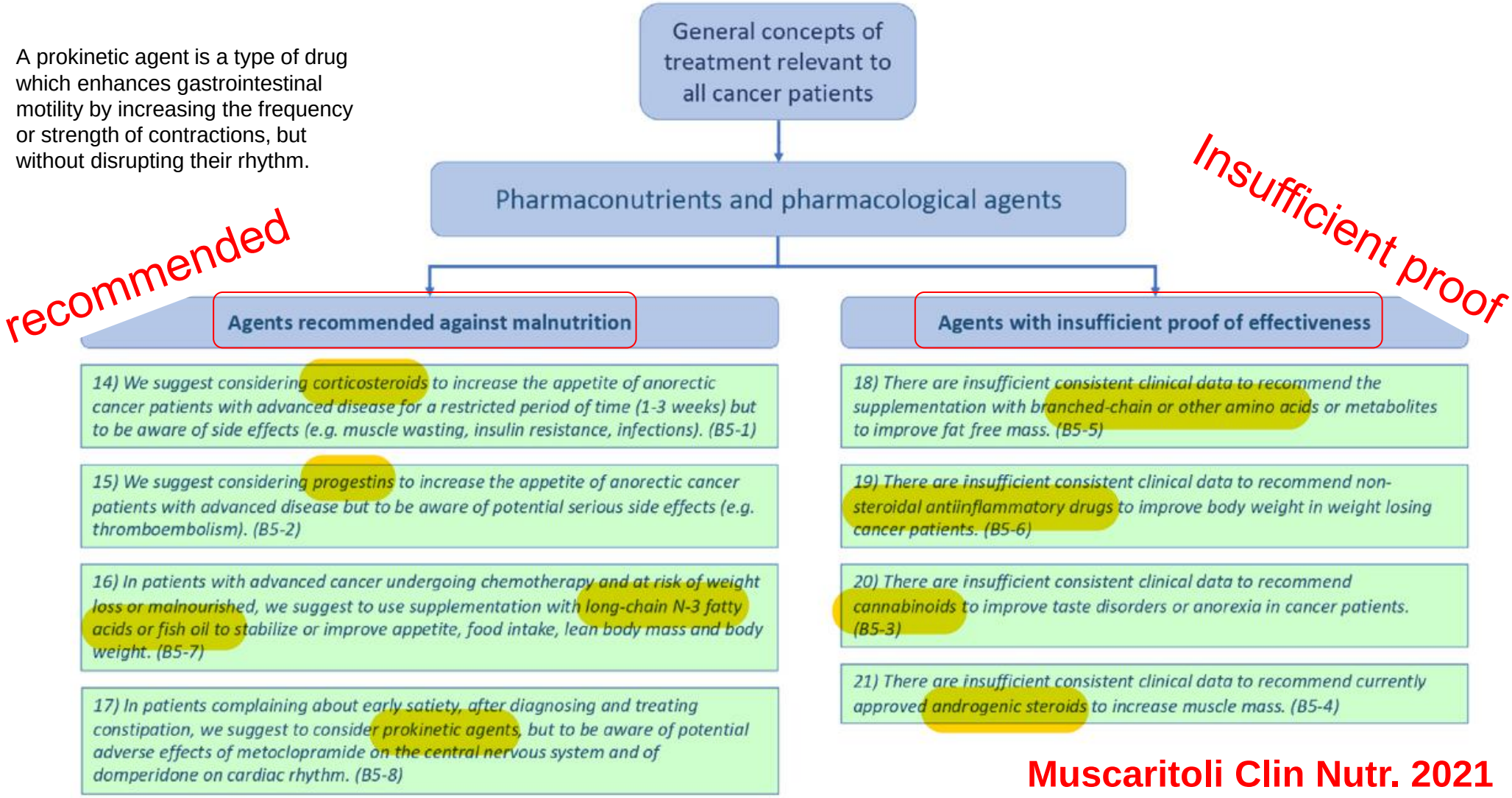
Note: protein 1 g/kg/day, 1 RDA micronutrients and increase fat/CHO ratio to increase energy density and reduce glycemic load



Muscaritoli
Clin Nutr. 2021

General concepts of treatment relevant to all cancer patients: pharmaco-nutrients and pharmacological agents against malnutrition, ESPEN, May 2021

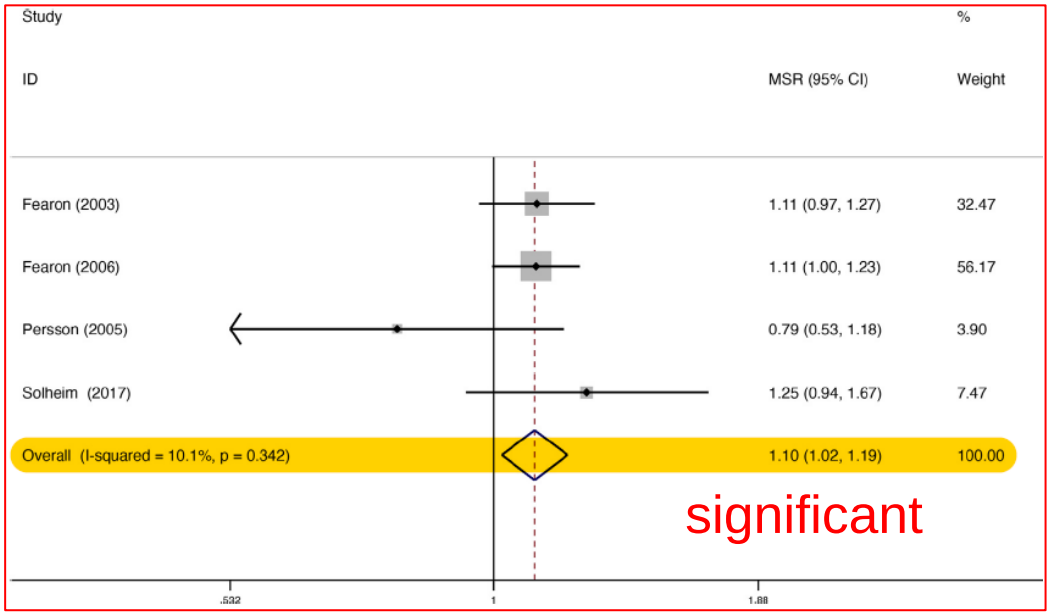
A prokinetic agent is a type of drug which enhances gastrointestinal motility by increasing the frequency or strength of contractions, but without disrupting their rhythm.



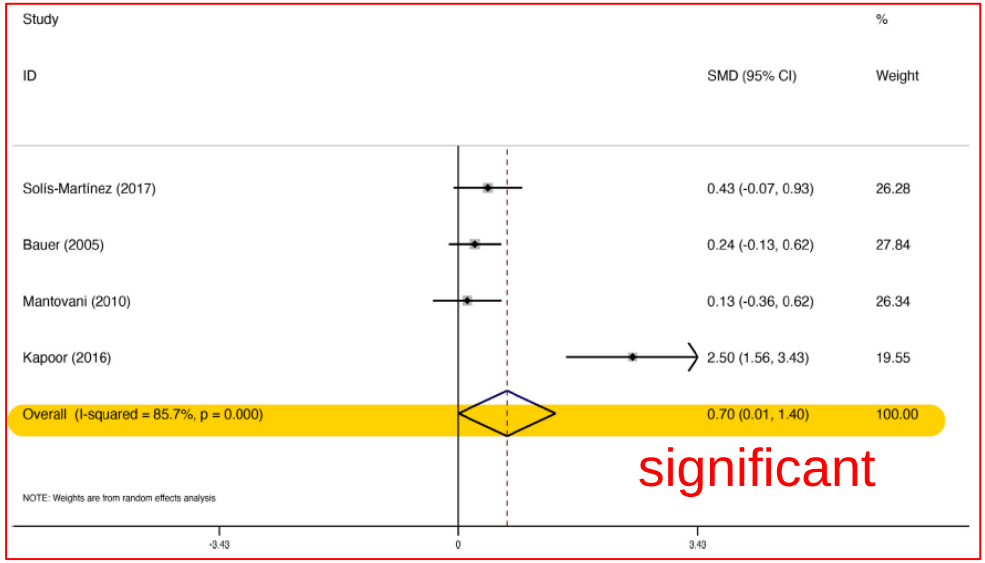
Muscaritoli Clin Nutr. 2021

Omega-3 polyunsaterated fatty acids improve quality of life and survival, but not body weight in cancer cachexia
A systematic review and meta-analysis of controlled trials

Forest plots of the meta-analysis of the effect of n-3 PUFAs on the median duration of survival



Forest plots of the meta-analysis of the effect of n-3 PUFAs on quality of life



The use of n-3 PUFAs was associated with a significant improvement in quality of life (SMD, 0.70; 95% CI, 0.01-1.40; *P* = .048) and median duration of survival (median survival ratio, 1.10; 95% CI, 1.02-1.19; *P* = .014). For patients with cancer cachexia, our meta-analysis indicated that n-3 PUFAs improved quality of life and survival, but not body weight.

Jin Nutr Res. 2022

According to the GRADE methodology, no positive recommendation for these nutritional supplements could be expressed

Four randomized clinical trials showed a significant body weight (BW) increase in patients treated with eicosapentaenoic acid (EPA), beta-hydroxy-beta-methyl butyrate (beta-HMB), arginine, and glutamine or marine phospholipids (MPL). An upward BW trend was observed in patients treated with L-carnitine, an Ethanwell/Ethanzyme (EE) regimen enriched with omega-3 fatty acids, micronutrients, probiotics, fish oil, a leucine-rich supplement, or total parental nutrition (TPN) with a high dose of a branched-chain amino acid (BCAA).

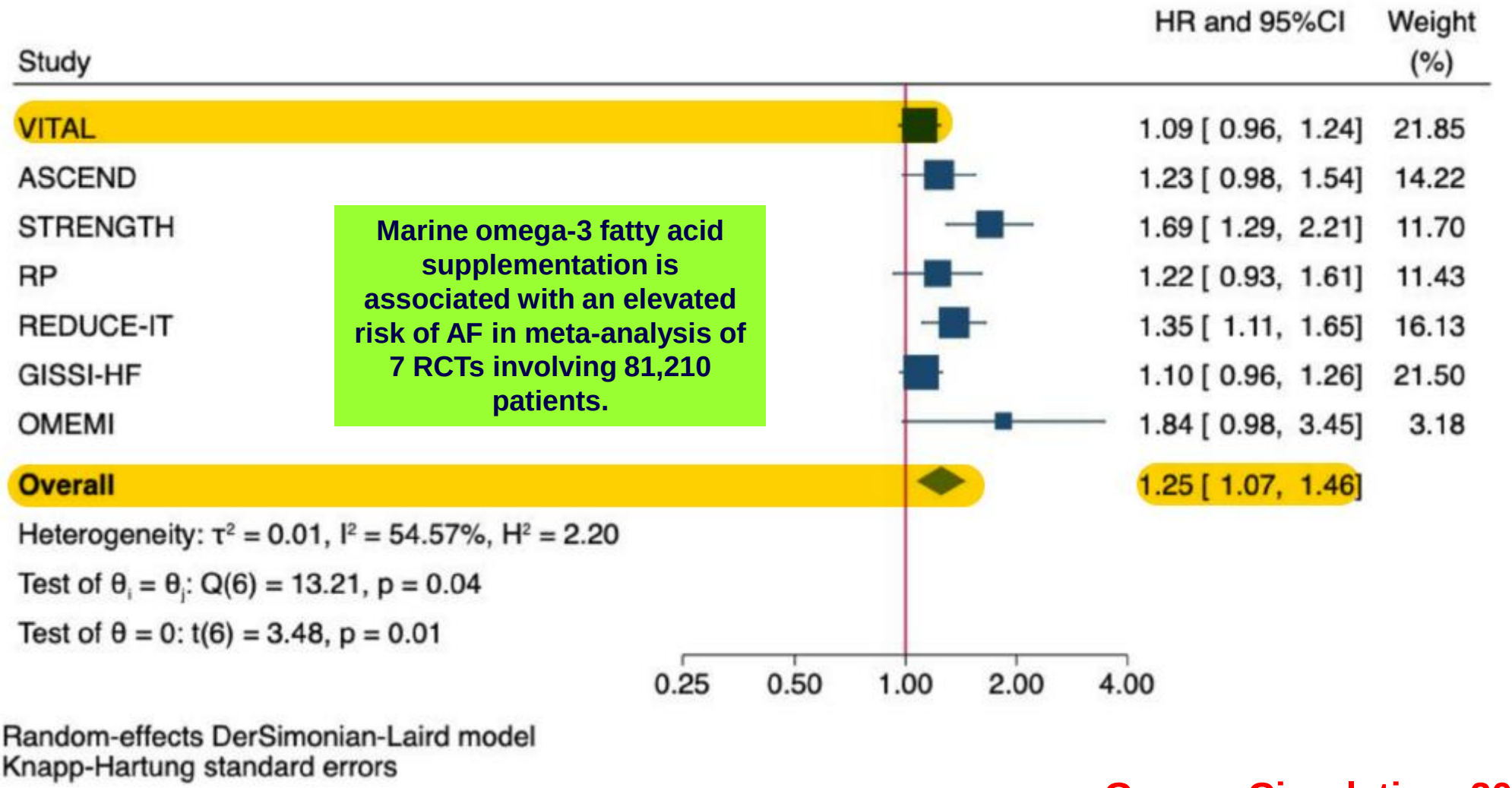
5. Conclusions

Early screening for cancer cachexia risk, and nutritional intervention in cancer patients before aggravating weight loss, may stabilize their weight, preventing cachexia syndrome. According to the GRADE methodology, no positive recommendation for the nutritional supplementation with essential amino acids, L-carnitine, branched-chain amino acid, ω-3 fatty acids, Guarana, cannabinoids, β-hydroxy-beta-methyl butyrate, a combination of HMB, arginine, glutamine and total parenteral nutrition could be expressed. However, no serious adverse effects were reported. Further research is needed to identify the efficacy relating to weight gain and the safety of these supplements in cachectic patients, to provide clear evidence-based recommendations.

Braha Medicina (Kaunas). 2022

Effect of marine omega-3 fatty acids supplements on the risk of Atrial Fibrillation (AF) events

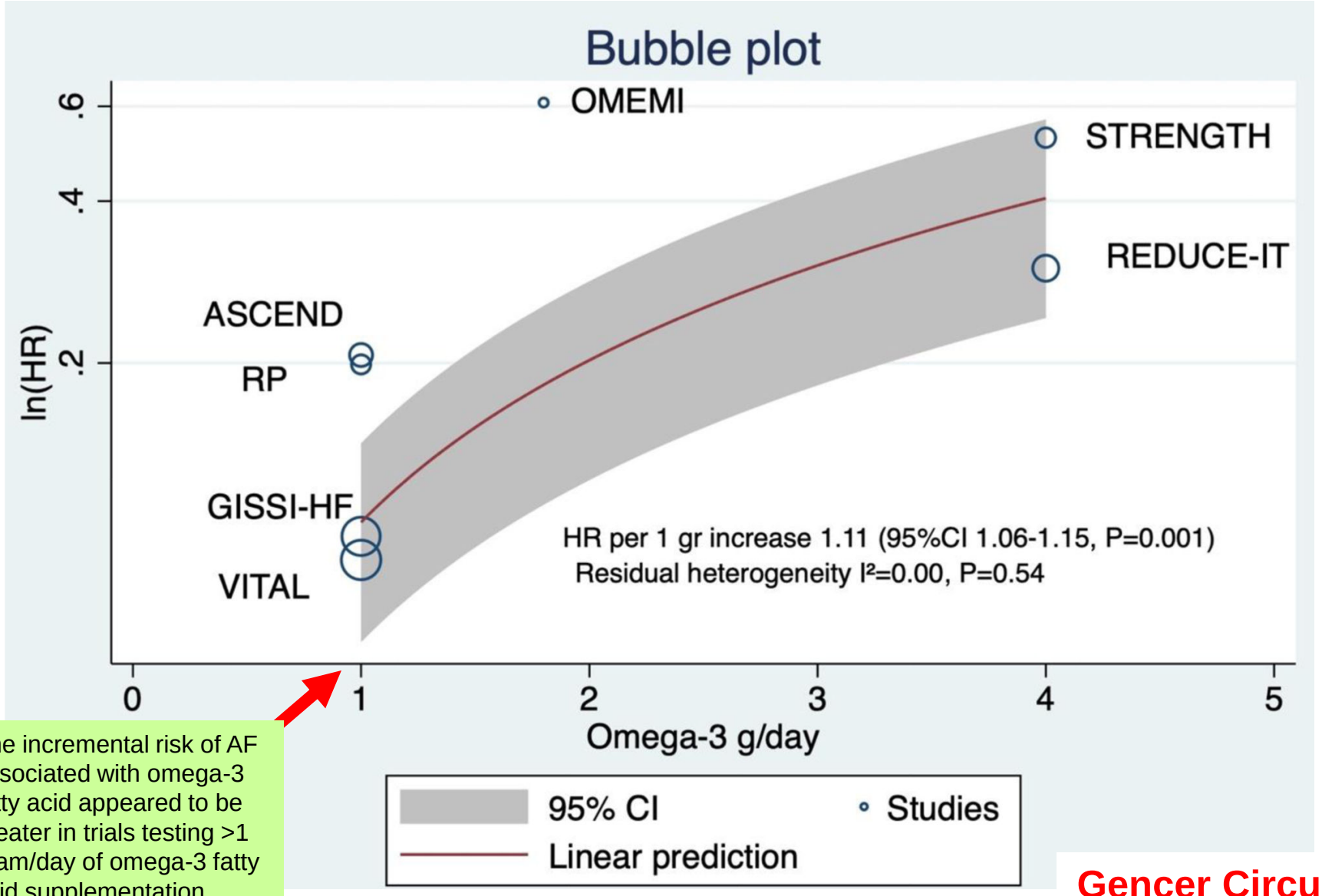
In RCTs examining cardiovascular outcomes, marine omega-3 supplementation was associated with an increased risk of AF. The risk appeared to be greater in trials testing >1g/d.



Marine omega-3 fatty acid supplementation is associated with an elevated risk of AF in meta-analysis of 7 RCTs involving 81,210 patients.

Gencer Circulation. 2021

Omega-3 fatty acid dosage vs. risk for AF events in 7 randomized controlled trials (1.1-5.1 times higher risk)



The incremental risk of AF associated with omega-3 fatty acid appeared to be greater in trials testing >1 gram/day of omega-3 fatty acid supplementation.

Gencer Circulation. 2021

Competing risk bias:
That is an event that precludes the occurrence of the primary event of interest

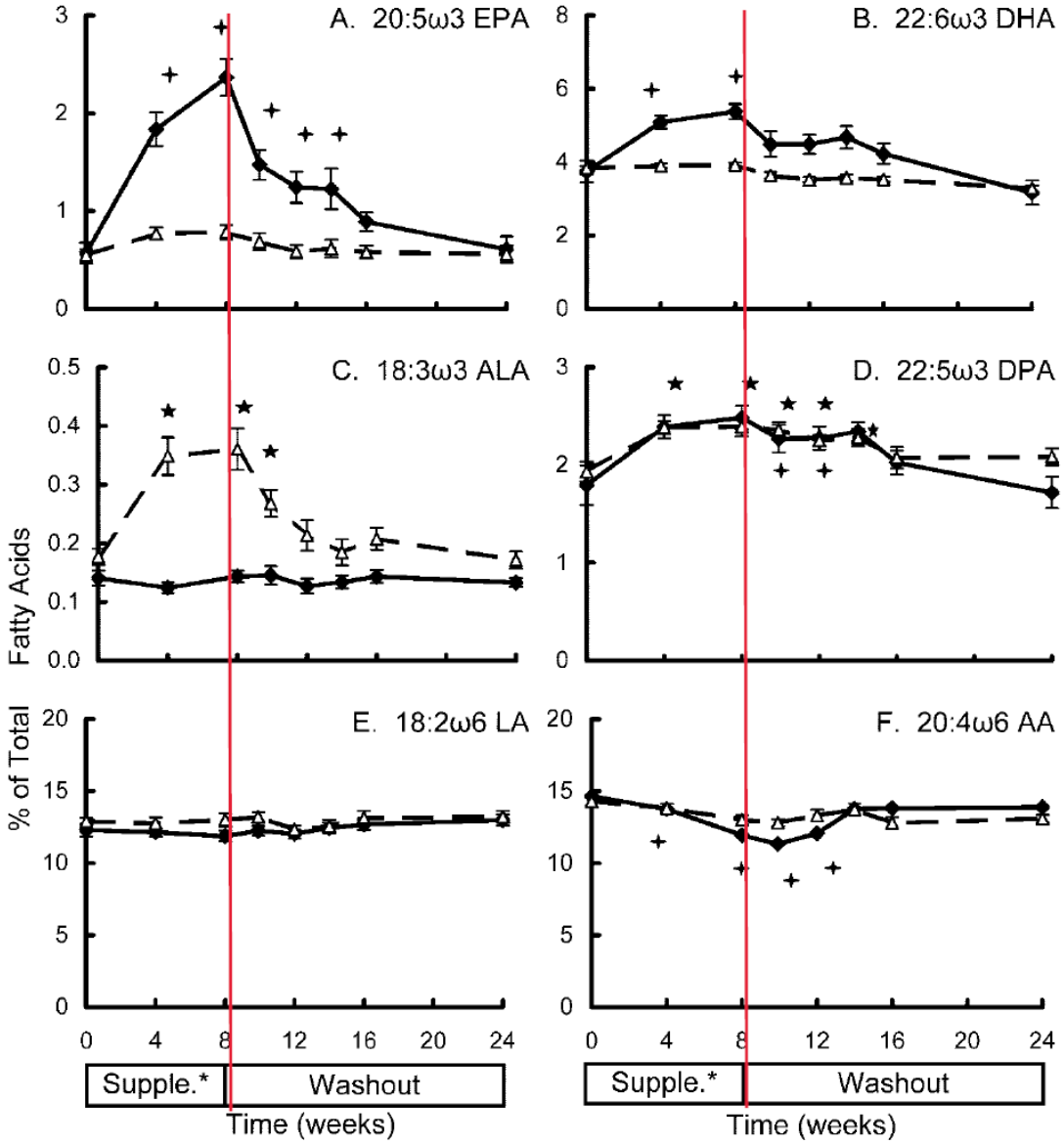
- The primary end points for the RCTs included into the Gencer (Circulation 2021) meta-analysis were a composite of mortality and a specific, cardiovascular event
- Because AF end points were not composite end points with mortality, the competing risk of death needed to be accounted for in the Cox model
- Put simply: if O3FAs reduced the mortality rate or delayed death, the O3FA-treated patients had more person-time or opportunity to acquire AF than controls
- This might have inflated the incidence of AF in the O3FA arm compared with controls and contributed to the observed outcome that links O3FA to higher AF chance
- Accounting for a competing risk in statistical models is especially important when the incidence of the competing event is greater than the incidence of the outcome investigated: which is the case (1-5 times higher AF incidence)

Samuel Circulation. 2021

Other contra-arguments for fish oil causing higher AF risk

- The prevalence of AF in the Greenland general population (1.4%) is comparable to that in other Western countries, indicating that AF is common in Greenland (Albertsen Int J Circumpolar Health. 2022)
- Thrombosis risk from AF might be lower because of fish oil anti-coagulation effect
- AF patients have lower omega-3 index, and RCTs with fish oil in AF patients using AF recurrence as primary end point did not show increased AF risk (Samuel Circulation. 2021)

Kinetics of RBC omega-3 and omega-6 fatty acids during supplementation and wash out: no EPA steady state in 8 weeks



Twenty study participants received supplementation with either fish oil (1296 mg EPA + 864 mg DHA/day) or flaxseed oil (3510 mg alpha-linolenic acid + 900 mg linoleic acid/day) for 8 weeks

A value of 8% is achievable with ingestion of 2 g of EPADHA over a period of 8–20 weeks. For each gram of EPA ingested, there was a mean increase of 1.4% after 8 weeks (range 1.0%–1.8%).

Our results seem to indicate a biphasic decrease of EPA and DHA with a steeper slope in the first 2 weeks postsupplementation, followed by a more gradual decline in the next 6 weeks. After 8 weeks of supplementation, the EPA and DHA concentrations were still marginally higher than baseline, but concentrations returned to baseline when measured 16 weeks postsupplementation.

Cai Clin Chem. 2006

The end