Invloed van voeding op het zelf-herstellend vermogen

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The bamboo that bends is stronger than the oak that resists

Invloed van voeding op zelfherstellend vermogen

Outline

- Resilience (veerkracht)
- Metabolic resilience and allostasis
  - Function tests (OGGT)
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  - Selenium and infection
- Conclusions

Charles Robert Darwin, (1809-1882)

***On the Origin of Species,* 1859**

"Adaptation to the conditions of existence"

In the long run (species) we adapt by **mutation/selection.**

In the intermediate (several generations) and short run (individual) we adapt by **epigenetics**.

In the short run (individual) we adapt through **sensors**, e.g. receptor/transcription activators/repressors like PRR, PPARs, NFkB, nrf2, etc

Muskiet, Adaptation to the conditions of existence, NTKC 2006

Definitie van Gezondheid
Louis Bolk Instituut, Machteld Huber, 2011

Het vermogen om zich aan te passen en zichzelf te redden

(Geïnspireerd door milieuwetenschappers die de gezondheid van de aarde beschrijven als 'het vermogen van een complex systeem om binnen een relatief smal bereik een stabiele omgeving te handhaven')

How should we define health_Huber BMJ 2011

Veerkracht
(weerstand, resilience)

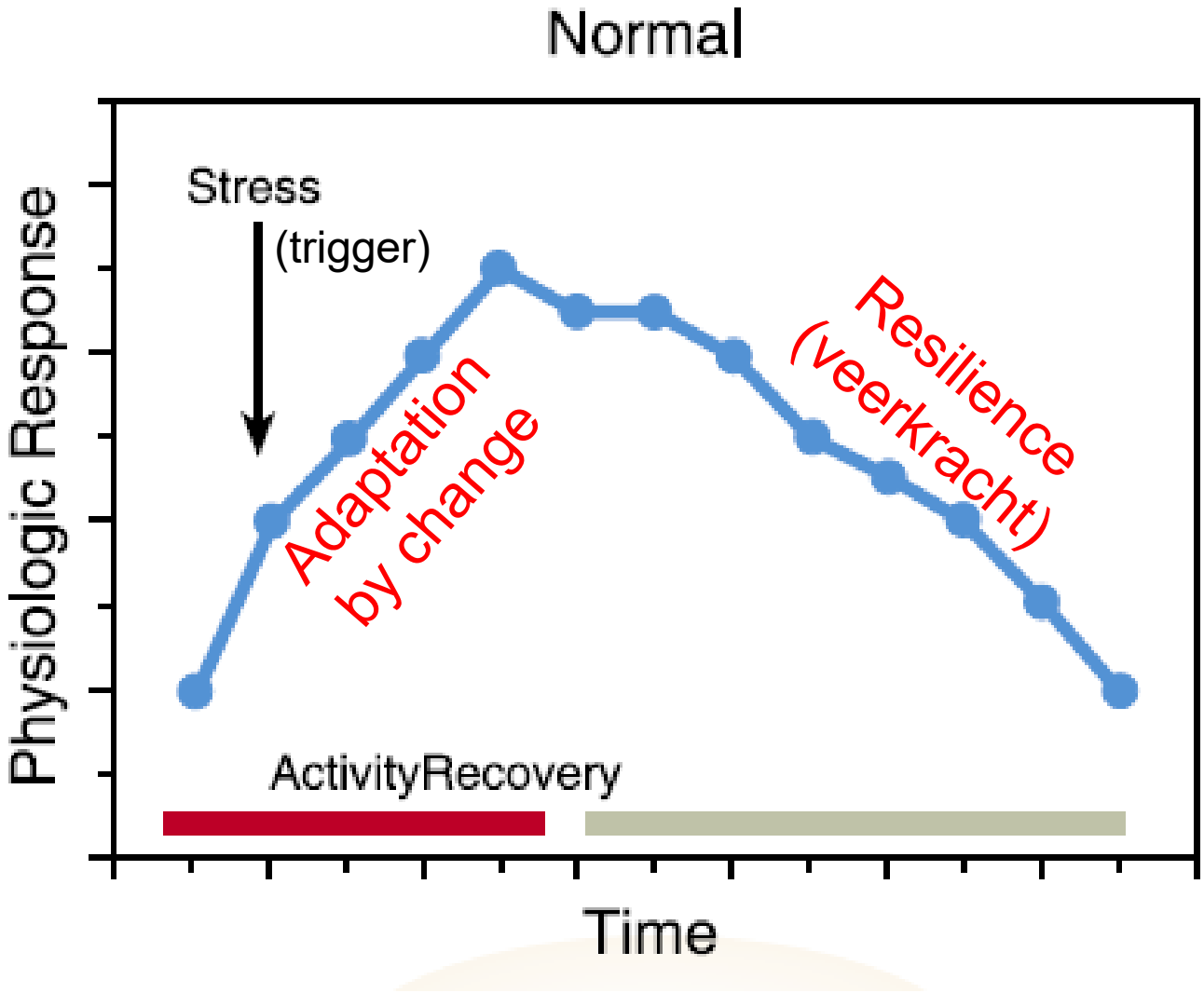
Komt uit de psychologie.
Het vermogen van een persoon om zich adequaat aan te passen aan tegenspoed (een stressfactor)

McEwen, Ann Acad Sci 2004; Wingfield, Animal Behav 2003

Homeostase vs. Allostase

- **Homeostase** houdt in dat een organisme binnen een bepaald bereik van fysiologische parameters blijft om een stabiele functie te behouden

- **Allostase** houdt in dat een organisme zich aanpast na een (patho)fysiologische stressor om een stabiele functie te behouden



A normal allostatic response

The response is initiated by a stressor/trigger, sustained for an appropriate interval, and then turned off

McEwen, Physiol Rev 2007

Allostatische Belasting

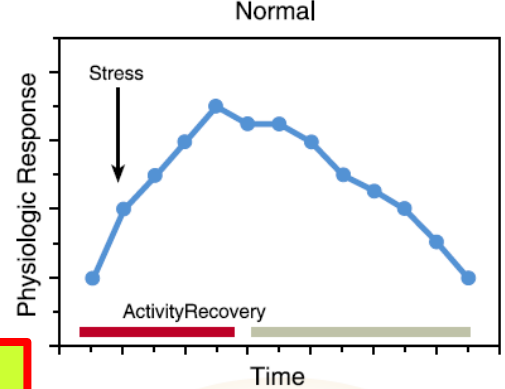
Na een trigger is aanpassing via allostase nodig om te overleven

Op de lange termijn brengt allostase kosten met zich mee die ziekteprocessen kunnen versnellen

‘Allostatische belasting’ is de prijs die het lichaam betaalt om zich aan te passen

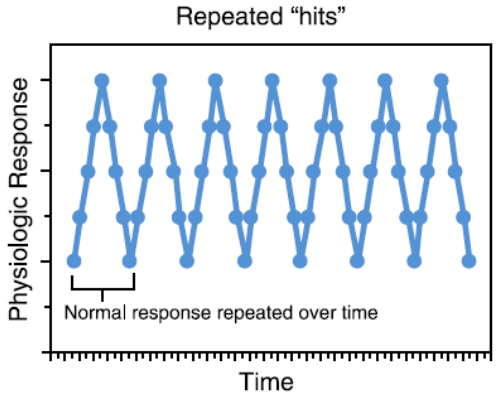
McEwen, Neuropsychopharmacol 2000

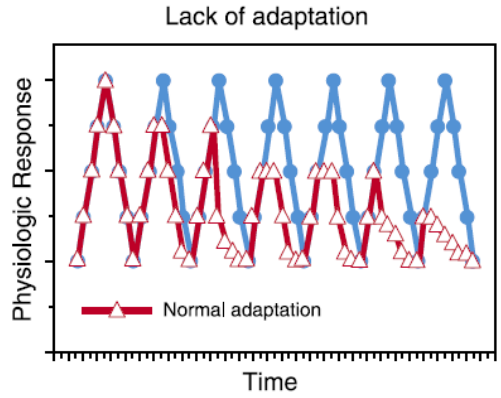
Four conditions leading to an allostatic load



Allostatic load

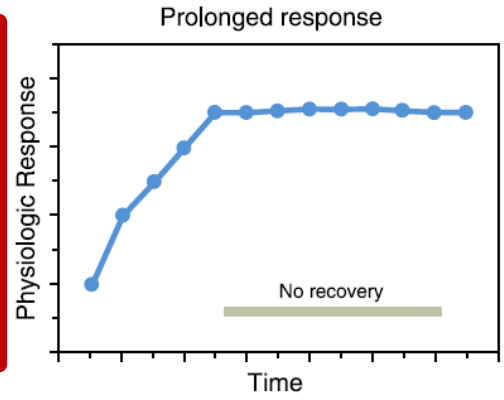
Repeated "hits" from multiple stressors

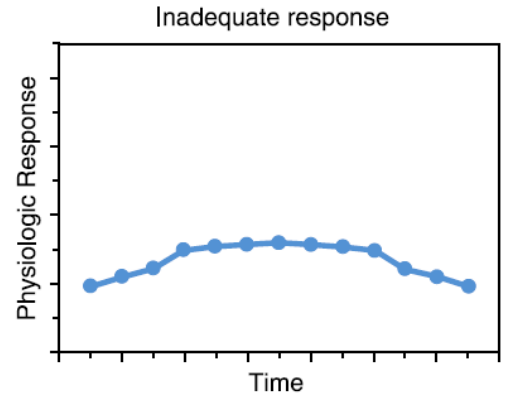




Lack of adaptation

Prolonged response due to delayed shut down





Inadequate response leading to compensatory hyperactivity of other mediators

(e.g. inadequate secretion of glucocorticoids resulting in increased levels of cytokines that are normally counter-regulated by glucocorticoids)

McEwen, Physiol Rev 2007

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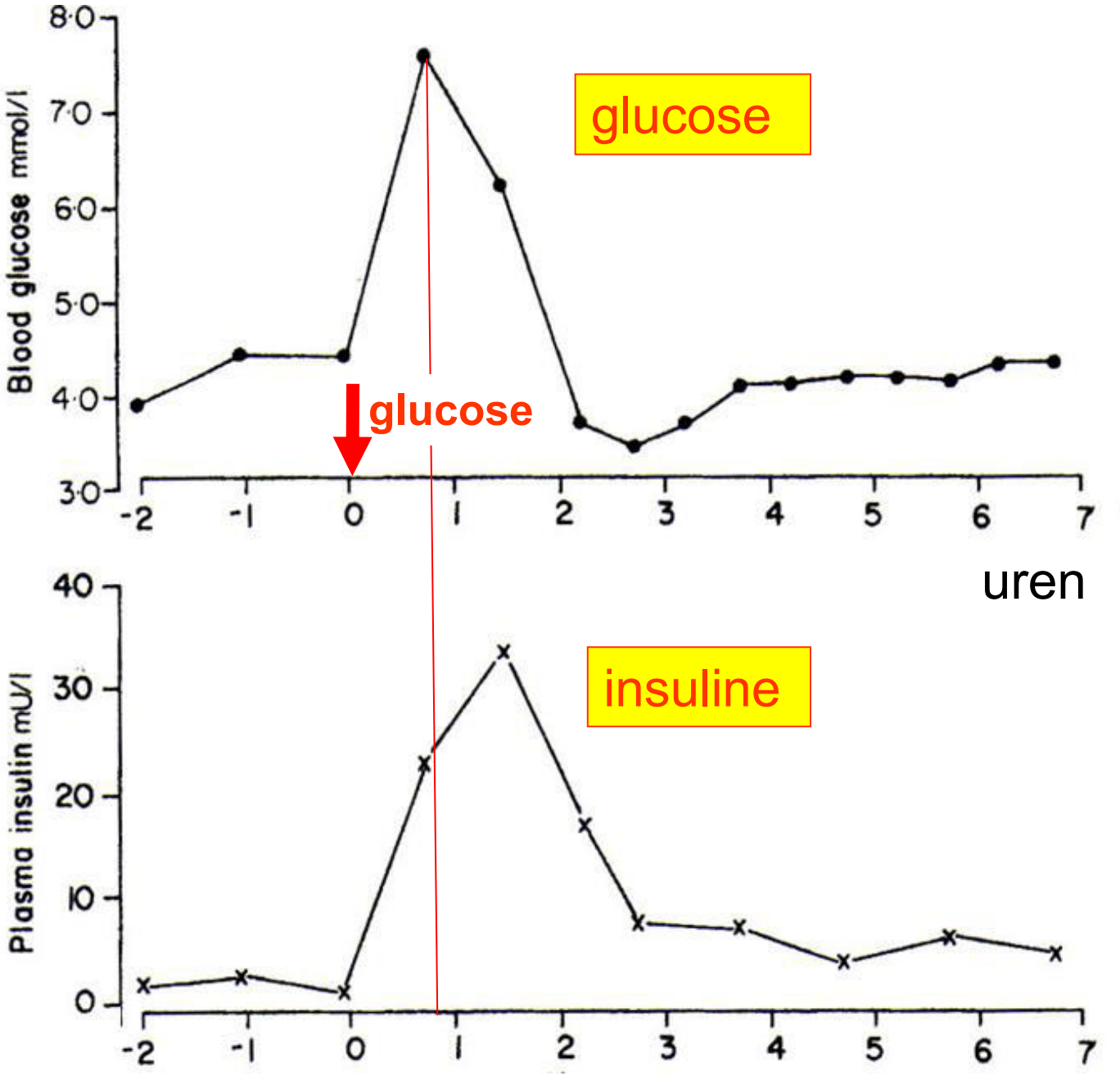
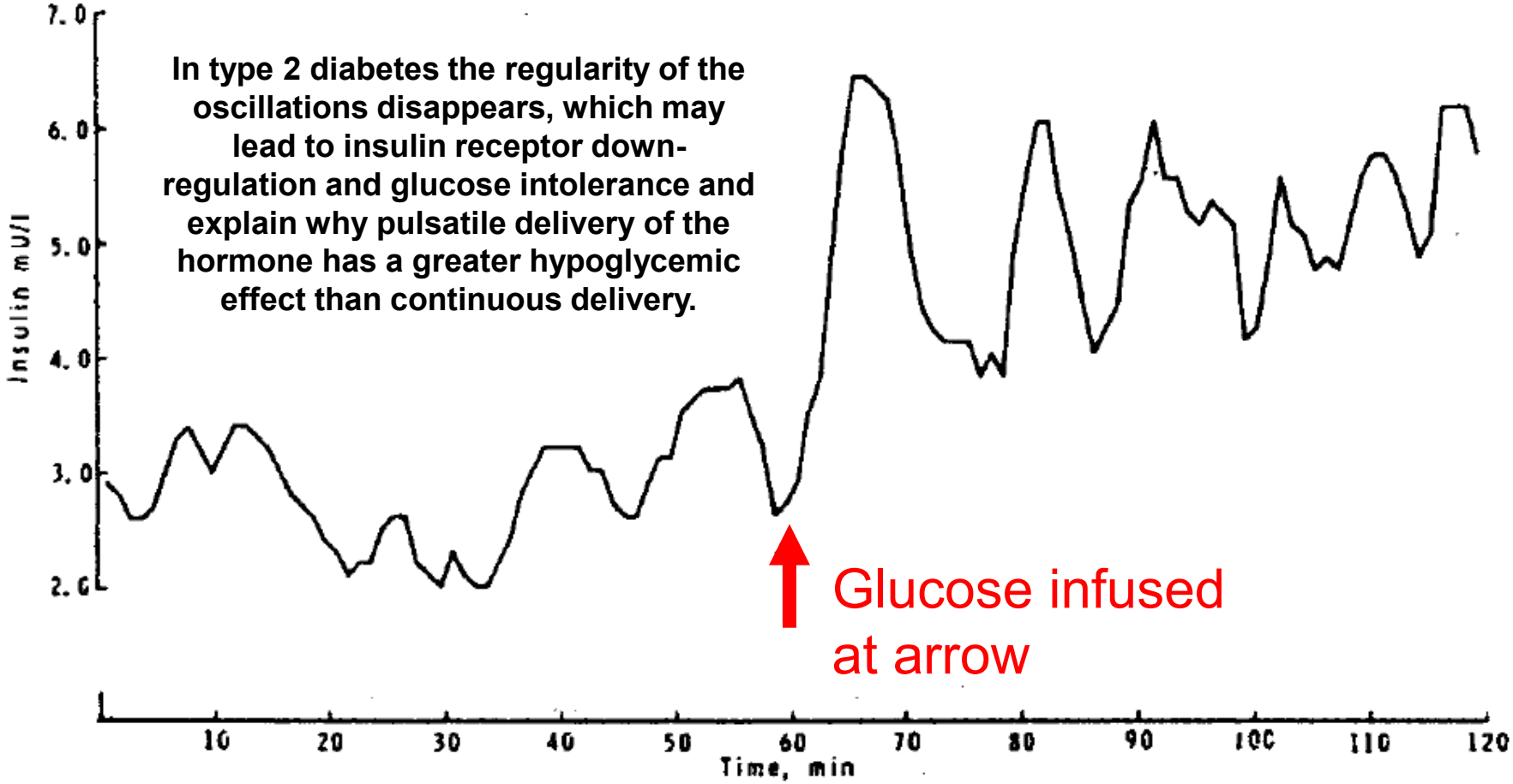


Reactie op 75 g glucose oraal

Pulsatile secretion of insulin (healthy subject)

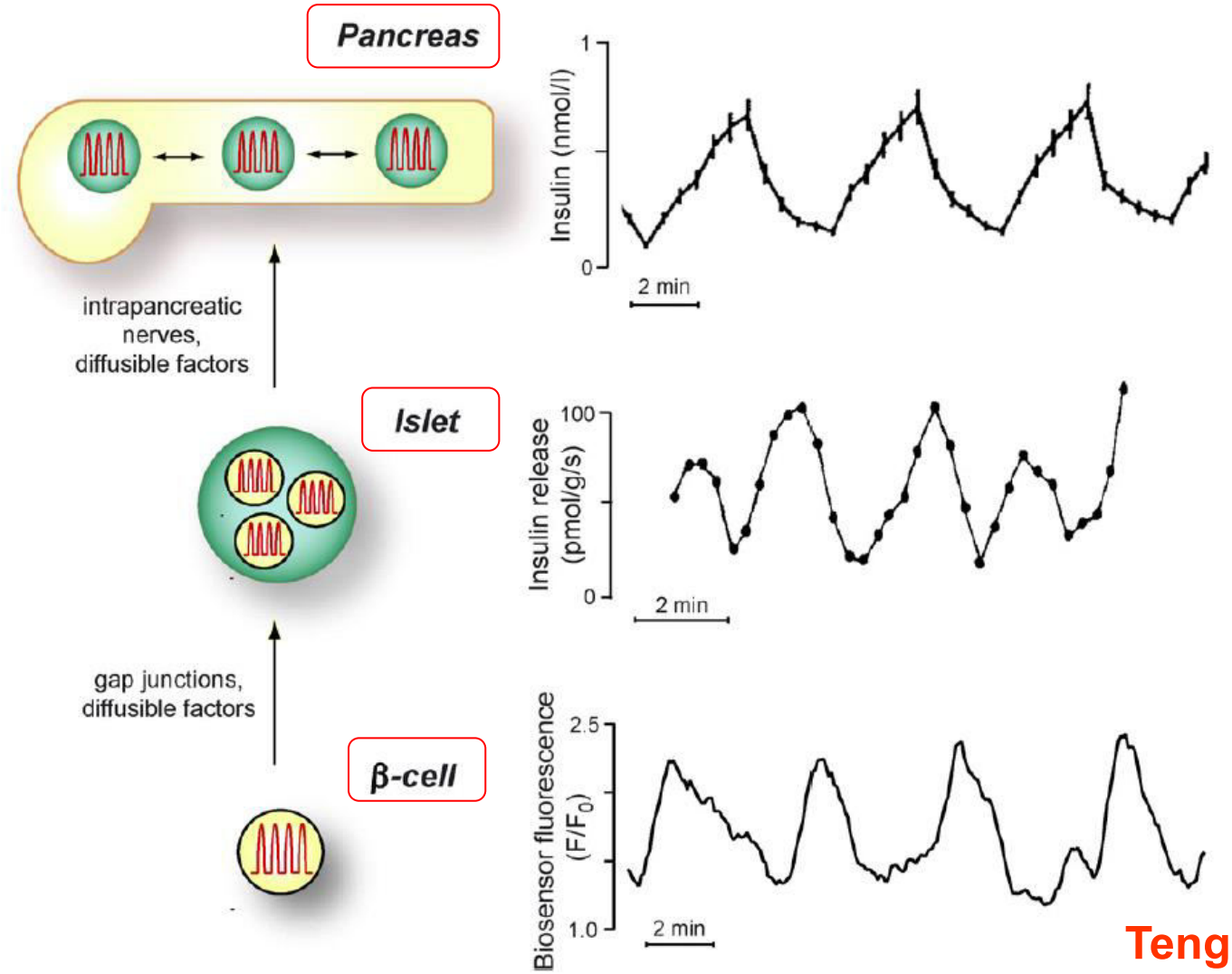
Plasma insulin displays 5±10 min oscillations

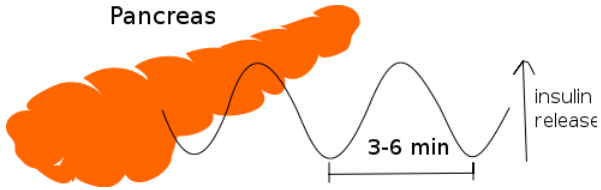
In type 2 diabetes the regularity of the oscillations disappears, which may lead to insulin receptor down-regulation and glucose intolerance and explain why pulsatile delivery of the hormone has a greater hypoglycemic effect than continuous delivery.



Bergsten, Diabetes Metab Res Rev 2000

Pulsatiele secretie van insuline op het niveau van de pancreas, eilandje van Langerhans en individuele pancreas beta-cel: synchroon om de 3-6 minuten





Insulin release from the pancreas oscillates with a period of 3-6 minutes (100-800 pmol/L): this mechanism may avoid downregulation of the insulin receptor (Wikipedia)

Tengholm, Mol Endocrinol 2009

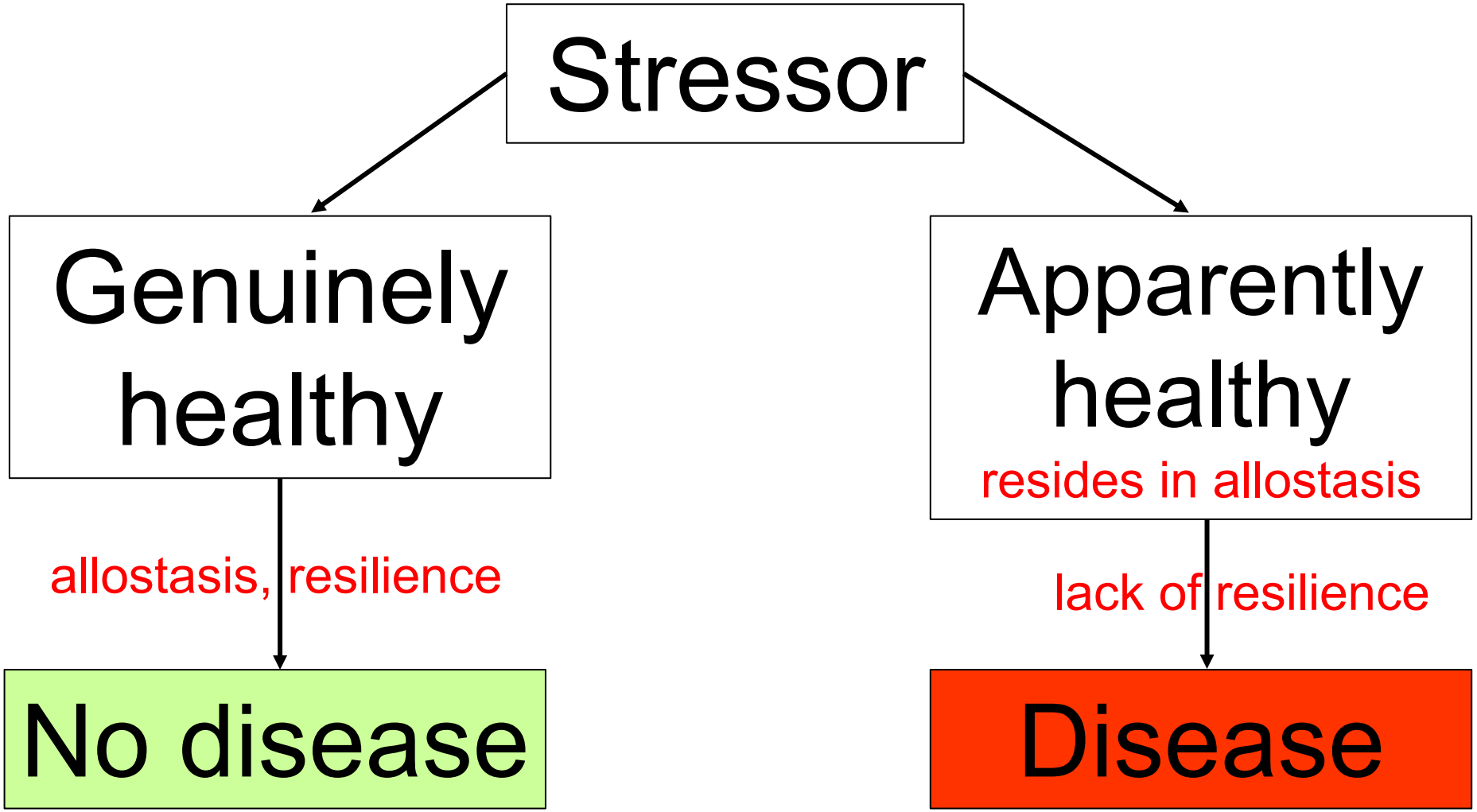
Pulsatiele secretie van insuline op het niveau van de pancreas, eilandje van Langerhans en individuele pancreas beta-cel: synchroon en minuten

De scheidslijn tussen homeostase en allostase is klein. Eigenlijk bestaat homeostase niet. Zelfs “rust” is dynamisch

Tengholm, Mol Endocrinol 2009

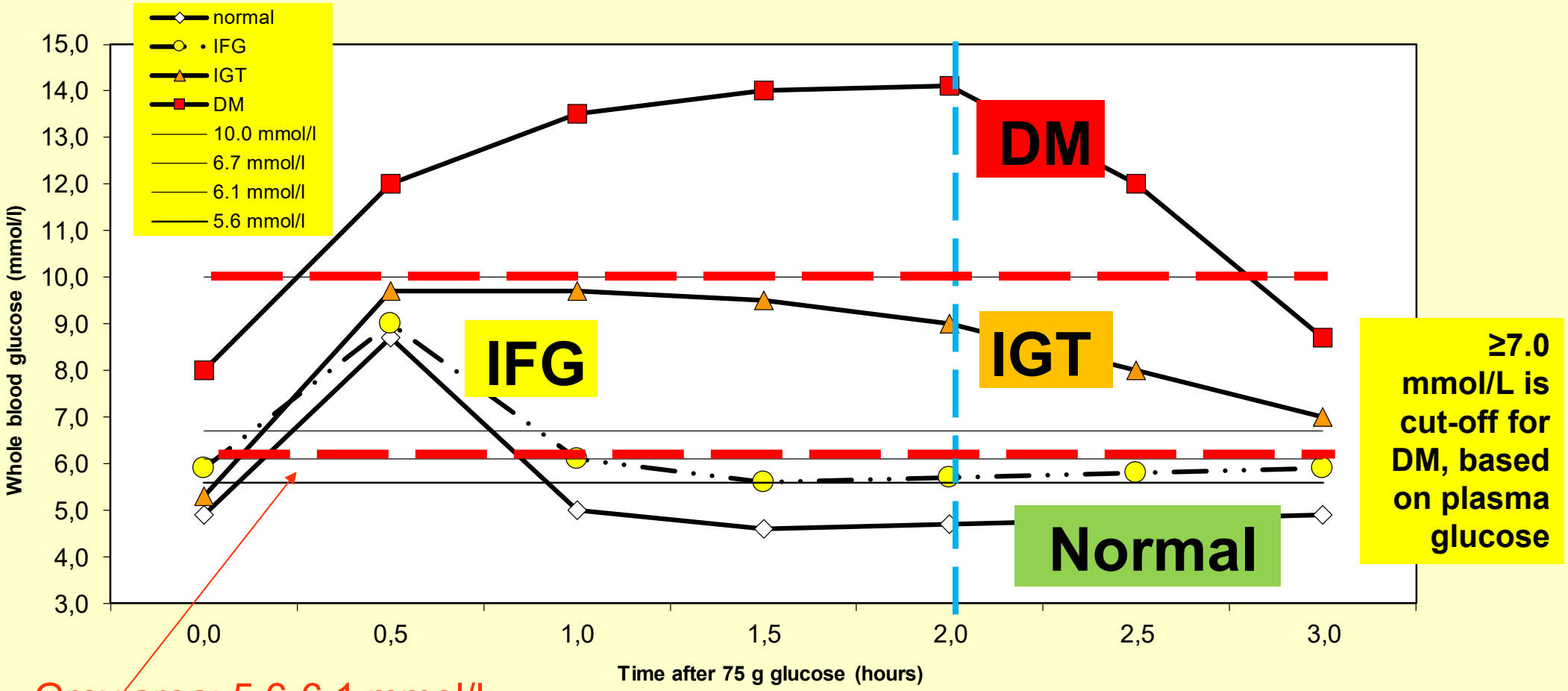
Many people are apparently healthy

Vulnerability shows when stressed



Abnormalities become notably apparent when the body is stressed

Whole blood OGGT for normal, IFG, IGT and DM2



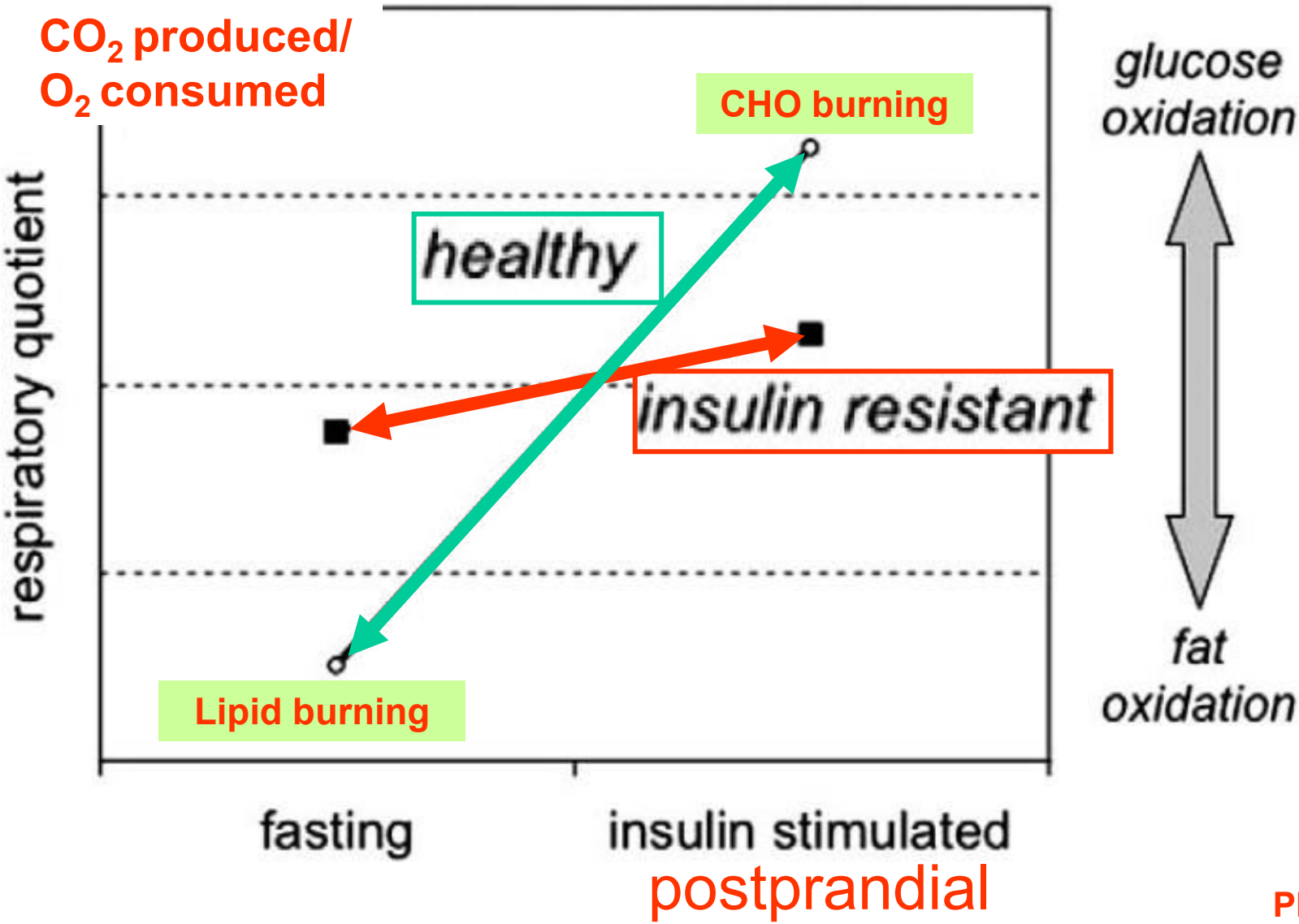
≥7.0 mmol/L is cut-off for DM, based on plasma glucose

Grey area: 5.6-6.1 mmol/L
(= above reference cut-off)
Diabetes positive: ≥ 6.1 mmol/L

OGTT positive: ≥ 6.7 mmol/L after 2 h
kidney threshold: ± 10 mmol/L

Metabolic (in)flexibility

RQ =
CO_2 produced/
O_2 consumed



Healthy subjects (green line) display metabolic flexibility, i.e. heavily rely on lipid as source for substrate oxidation during fasting (low respiratory quotient, RQ) and rapidly switch to glucose oxidation upon insulin-stimulation (high RQ). In contrast, insulin-resistant – metabolic inflexible – subjects (red line) display a lower rate of lipid oxidation under fasting conditions (increased RQ), and do hardly increase glucose oxidation upon insulin-stimulation (lower RQ) compared to healthy individuals

Phielix, Physiol Behav 2008

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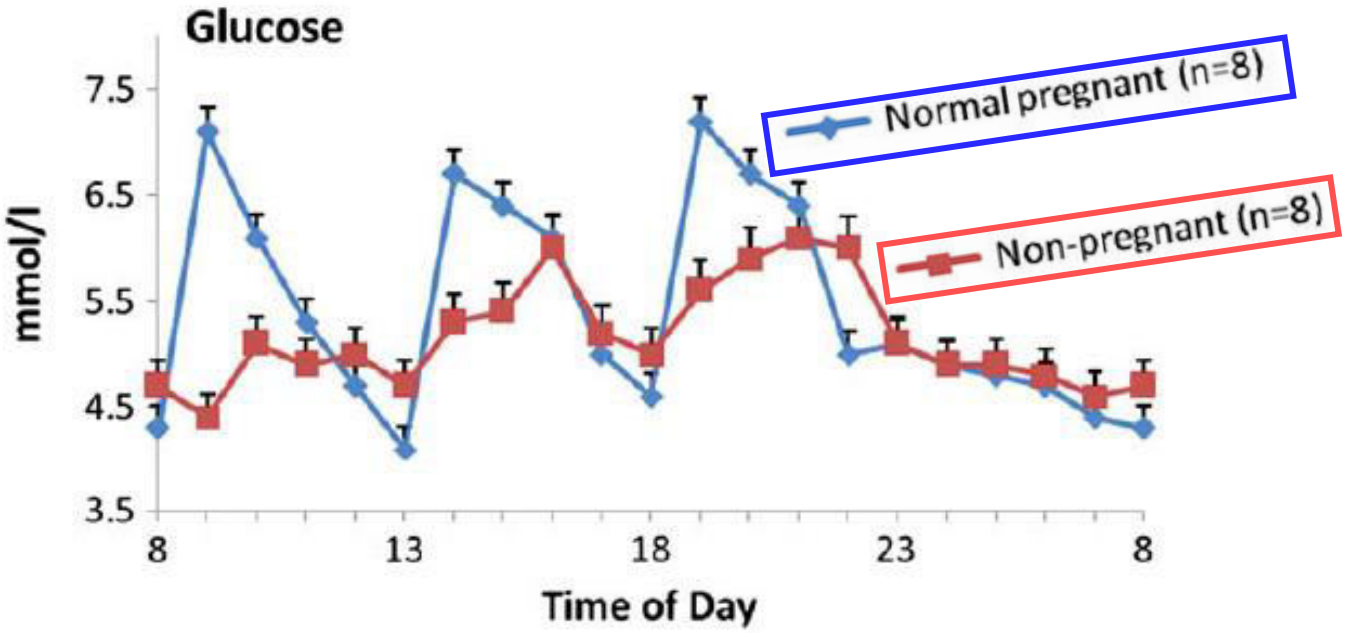
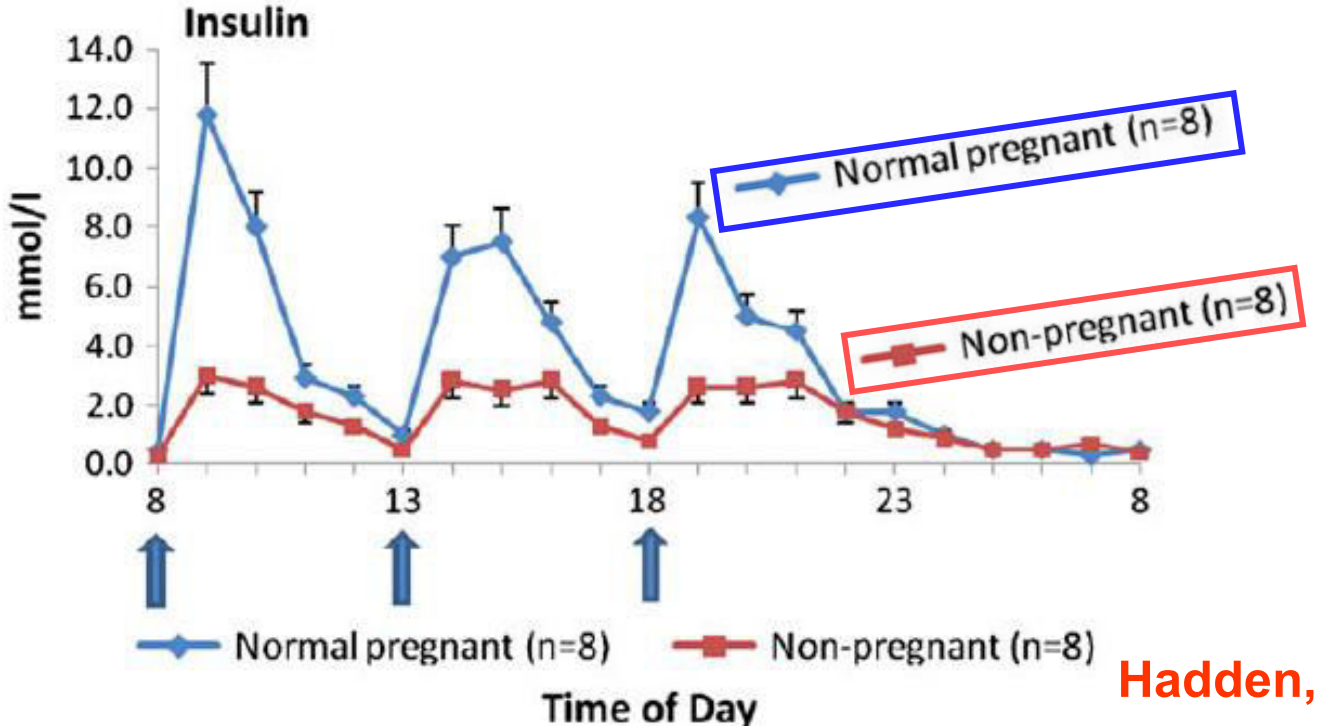




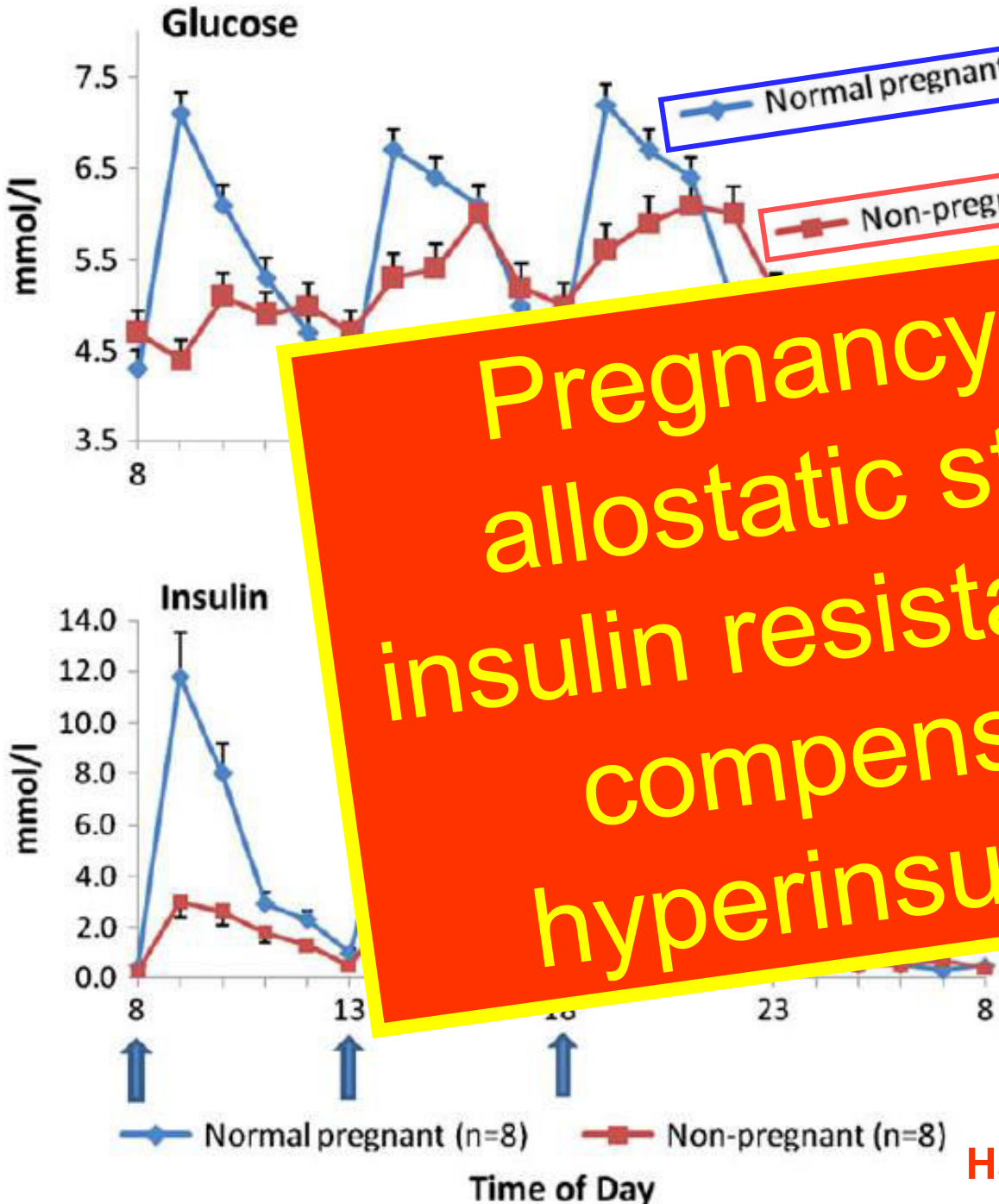
The effect of normal late pregnancy on the diurnal changes in:

(a) plasma glucose

and

(b) insulin

Hadden, Semin Fetal Neonatal Med 2009



Pregnancy is an allostatic state of insulin resistance and compensatory hyperinsulinemia

The effect of
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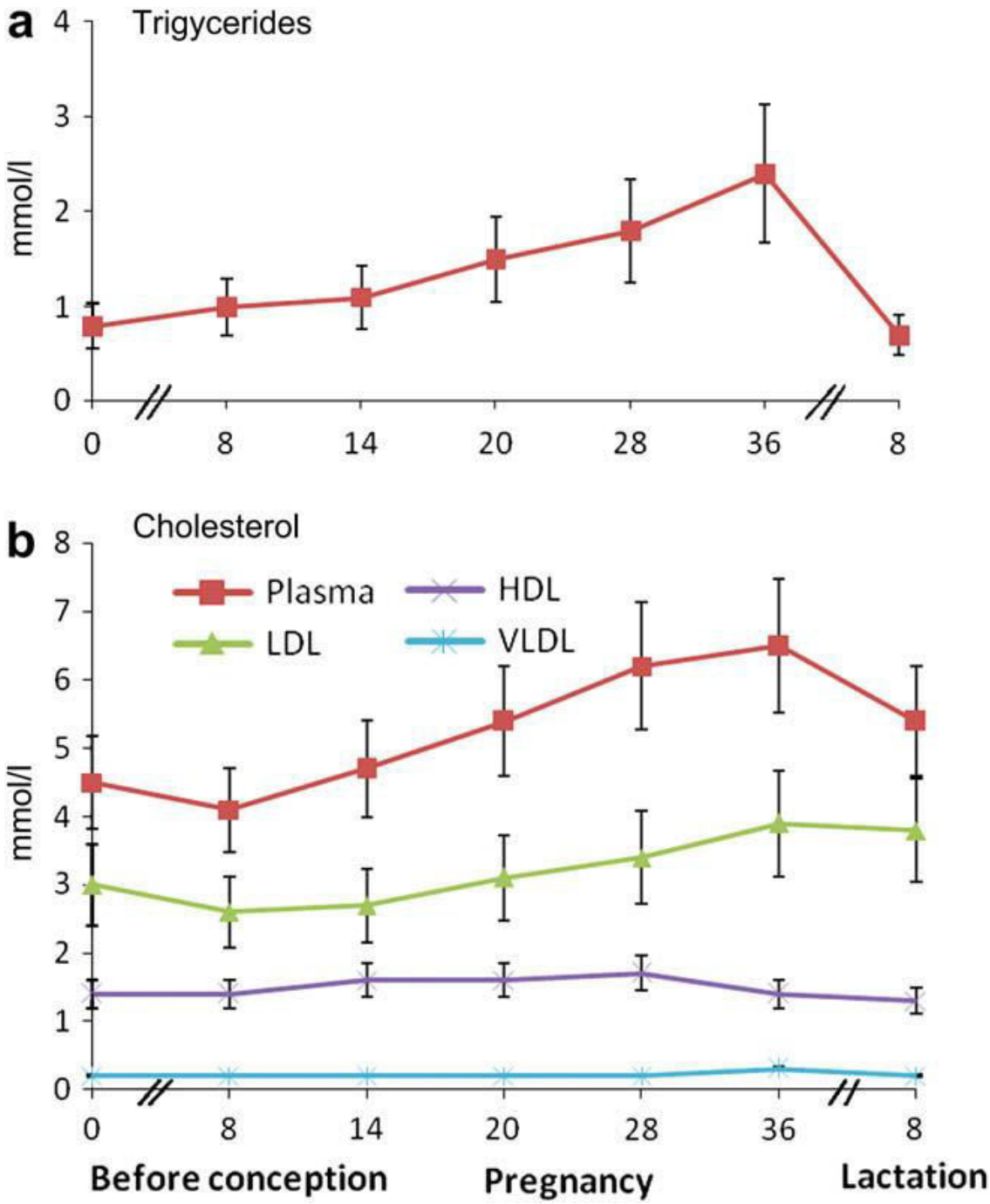
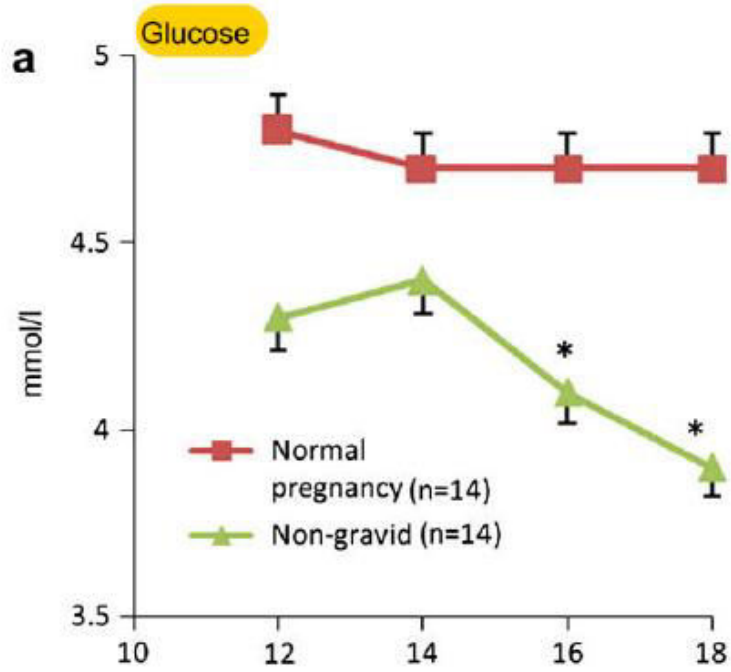
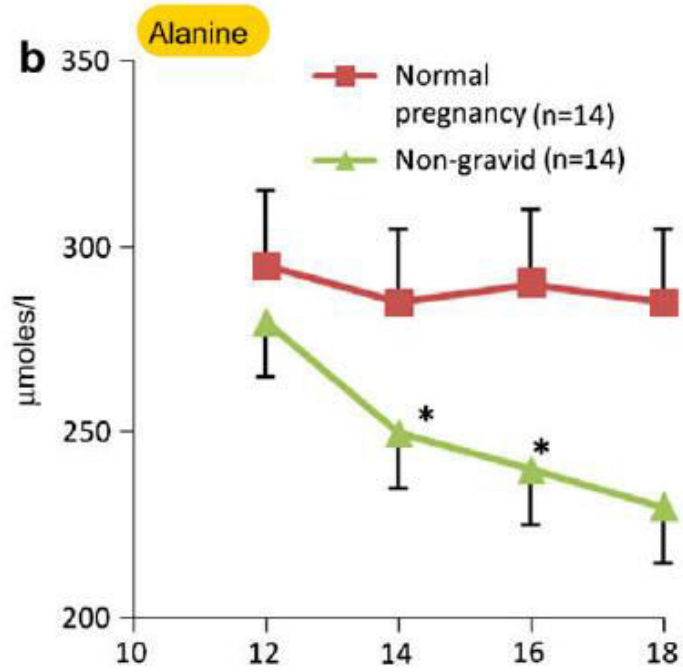
Hadden, Semin Fetal Neonatal Med 2009

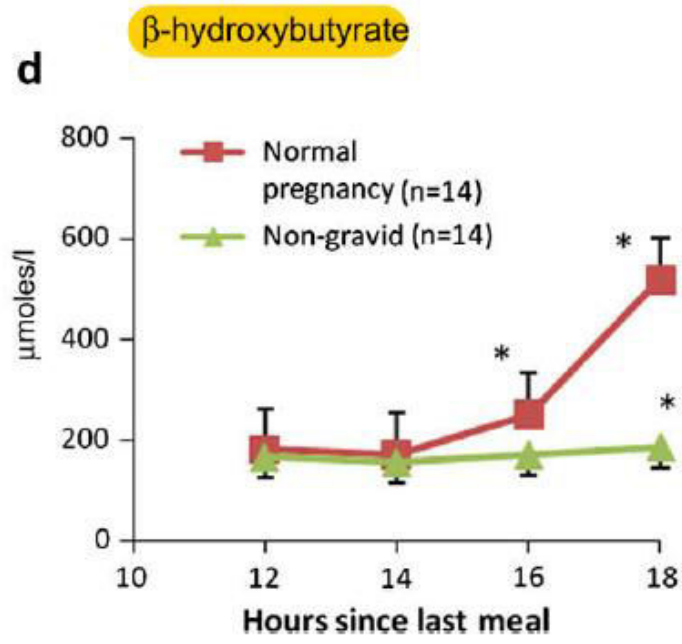


Triglycerides and cholesterol in plasma and in lipoprotein fractions before, during and after **normal pregnancy**

Hadden, Semin Fetal Neonatal Med 2009





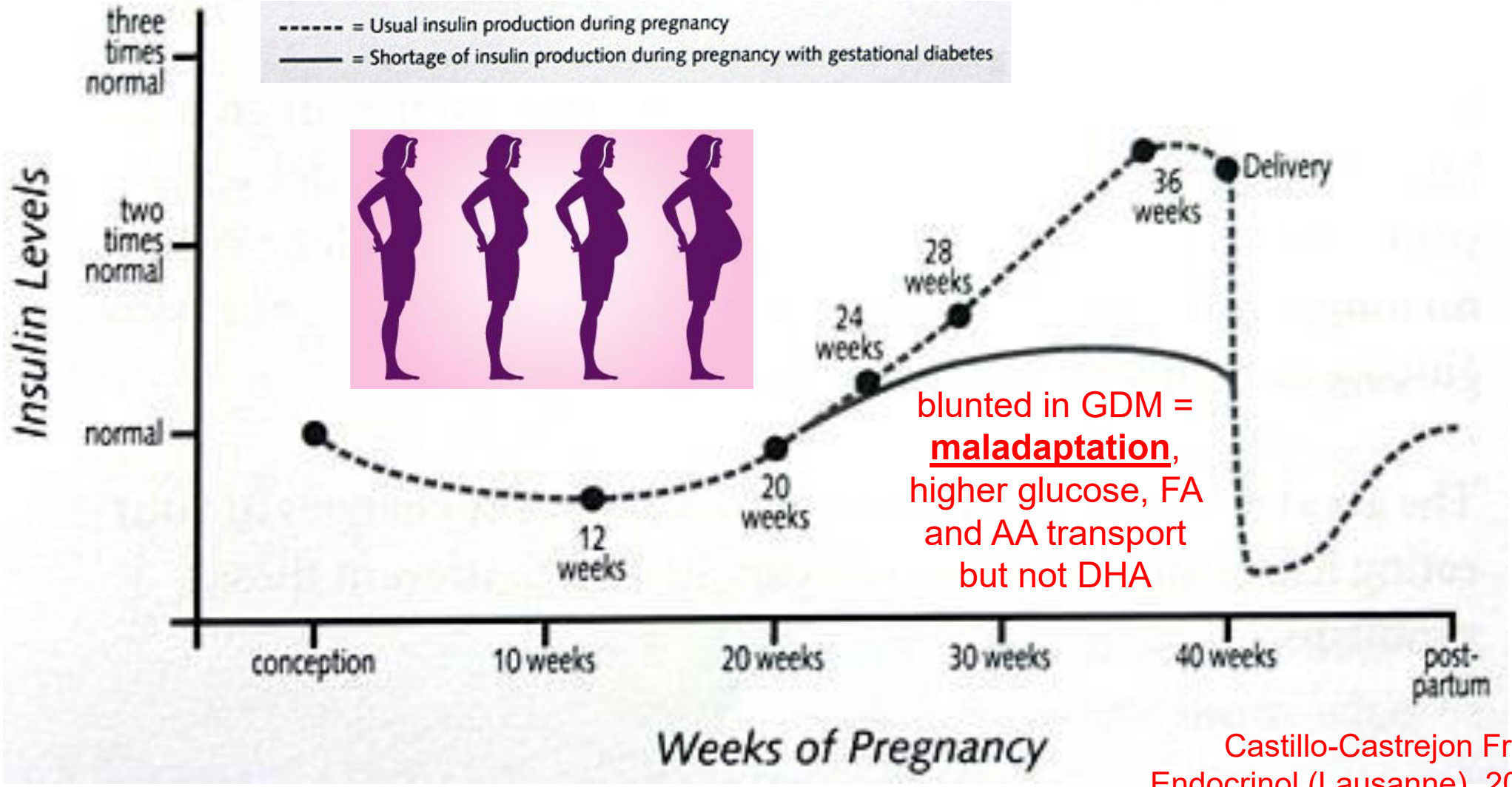


Facilitated starvation in late pregnancy:

Changes in plasma concentrations of (a) glucose, (b) alanine, (c) free fatty acids (d) beta-hydroxybutyrate in non-pregnant and pregnant women between 12 h fasting and 18 h fasting during the 3rd trimester

Hadden, Semin Fetal Neonatal Med 2009

Insulin in pregnancy: the placenta starts an inflammatory reaction (TNFa), causing progressive loss of insulin sensitivity and thereby increasing nutrient transfer to the fetus



Castillo-Castrejon Front Endocrinol (Lausanne). 2017

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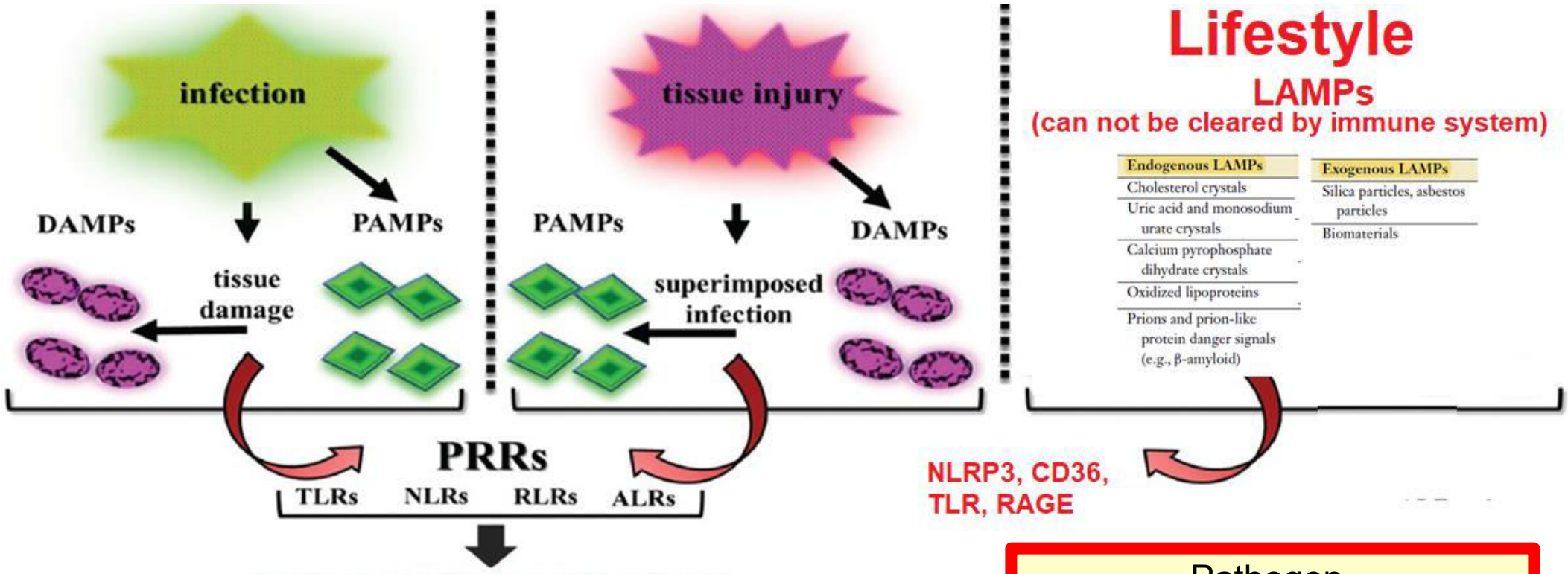
PAMPs, DAMPs and LAMPs

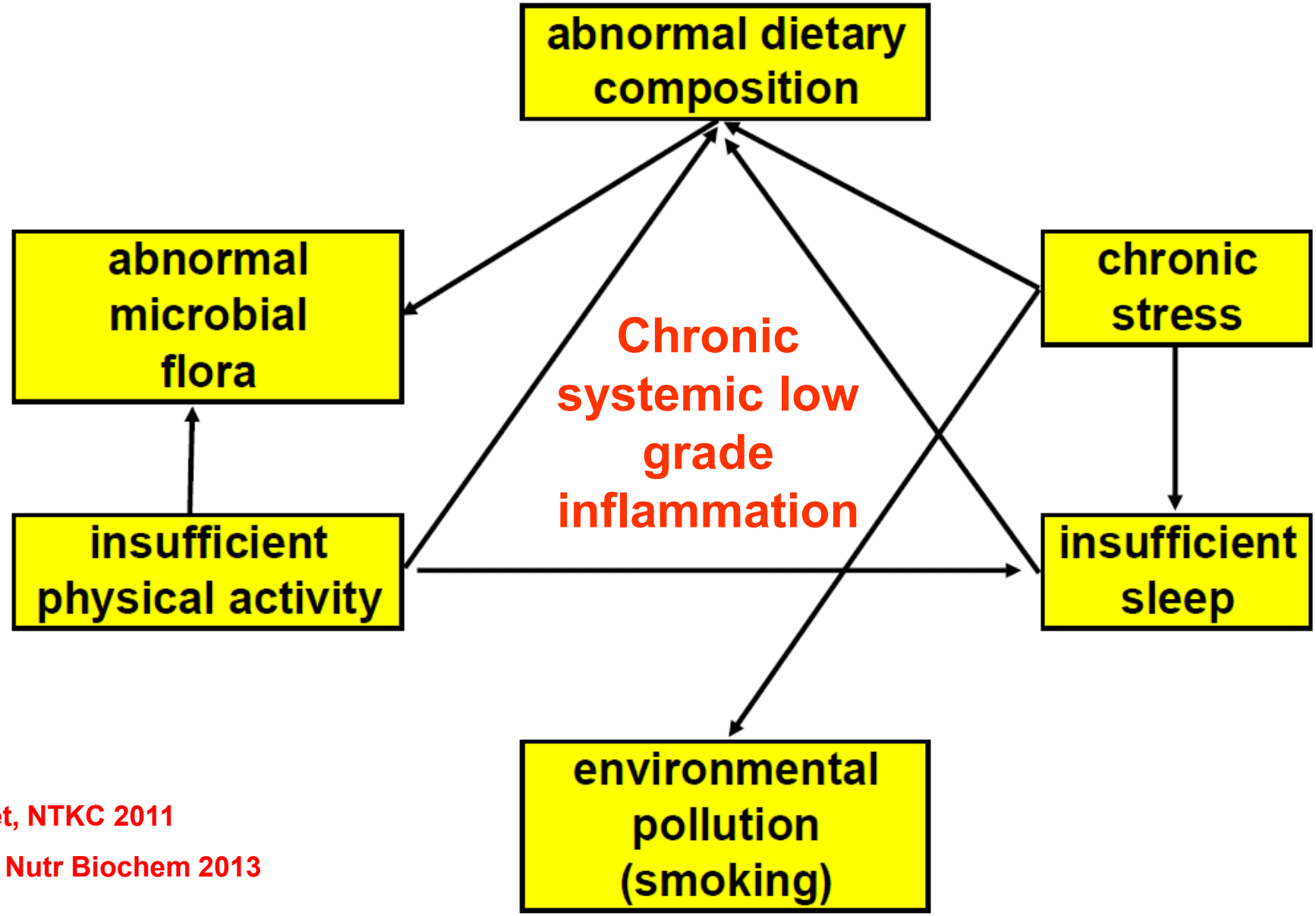
Three sources of danger signals/inflammation



Pathogen-
Damage-
Lifestyle-
Associated Molecular Patterns

Zindel Annu Rev Pathol. 2020

Lifestyle factors exhibit interaction



Muskiet, NTKC 2011

Ruiz, J Nutr Biochem 2013

Western people reside in a pro-inflammatory state

Constituent	Adjusted score
Energy	−0.0549
Energy*	−0.23
Garlic	0.27
Ginger	0.18
Saffron	0.18
Turmeric	0.774
Tea	0.552
Caffeine	0.035
Wine	0.48
Beer	0.2
Liquor	0.1
Alcohol	0.534
Carbohydrate	−0.346
Fiber	0.52
Fat	−0.323
(n-3) Fatty acids	0.384
(n-6) Fatty acids	−0.016
MUFA	−0.05
Saturated fat	−0.25
Protein	0.05
Cholesterol	−0.21

Constituent	Adjusted score
Vitamin A	0.58
Thiamin	0.05
Riboflavin	0.16
Niacin	0.26
Vitamin B-6	0.286
Folic Acid	0.214
Vitamin B-12	−0.09
Vitamin C	0.367
Vitamin D	0.342
Vitamin E	0.401
β-carotene	0.725
Magnesium	0.905
Zinc	0.316
Iron	0.029
Selenium	0.021
Quercetin	0.49
Luteolin	0.43
Genistein	0.68
Daidzein	0.17
Cyanidin	0.13
Epicatechin	0.12

The 42 nutrients in the dietary 'inflammatory index' of the University of North Carolina

Based on the ability to predict hs-CRP

Cavicchia, J Nutr 2009

Lifestyle related pro- and anti-inflammatory factors

Pro-inflammatory	Anti-inflammatory
Lifestyle	
Exercise	Exercise/physical activity/fitness
Too little (inactivity)	'Healthy' obesity
Too much	Intensive lifestyle change
Nutrition	Nutrition
Alcohol (excessive)	Alcohol
Excessive energy intake	Capsaicin
'Fast food'/western style diet	Cocoa/chocolate (dark)
Fat	Dairy calcium
Saturated	Eggs
Trans fatty acids	Energy intake (restricted)
High-fat diet	Fish/fish oils
High N6 : N3 ratio	Fibre (high intake)
Fibre (low intake)	Garlic
Fructose	Grapes/raisons
Glucose	Herbs and spices
High glucose/GI foods	Lean game meats
Glycaemic load	Low GI foods
Glycaemic status	Low N6 : N3 ratio
Meat (domesticated)	Mediterranean diet
Salt	Fruits/vegetables
Sugar-sweetened drinks	Mono-unsaturated fats
Starvation	Nuts
Obesity/weight gain	Olive oil
Smoking	Soy protein
Sleep deprivation	Tea/green tea
Stress/anxiety/depression/ 'burn out'	Vinegar
'Unhealthy' lifestyle	Smoking cessation
	Weight loss

Egger, Obes Rev 2010

Components of the

Dietary Inflammation Score (DIS) and Lifestyle Inflammation Score (LIS)

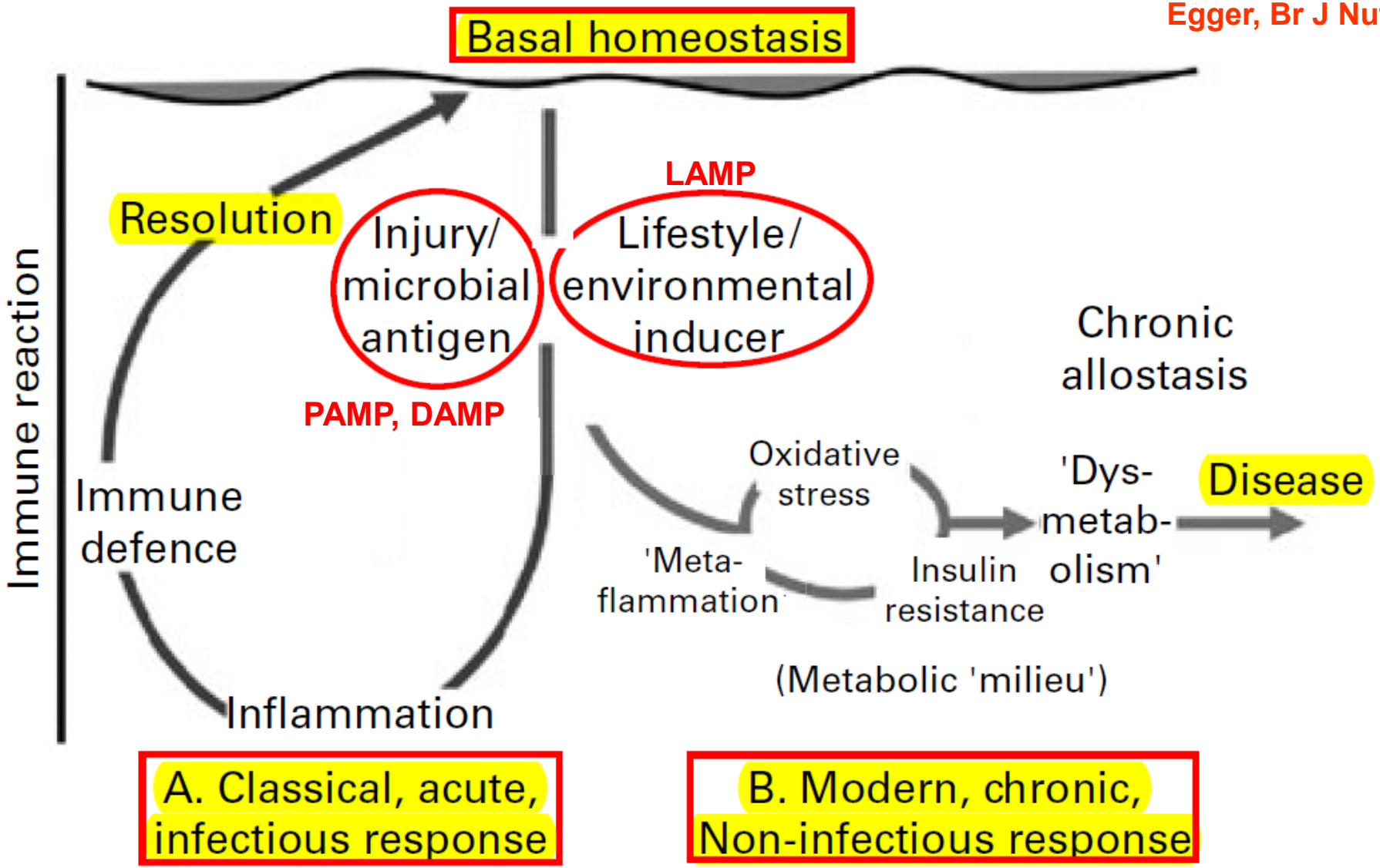
descriptions, rationales for inclusion, and assigned weights

Components	Rationales for inclusion	General descriptions	Weights[2]
DIS components[3]			
Leafy greens and cruciferous vegetables	Kale, spinach, lettuce (iceberg, head, romaine, or leaf), broccoli, Brussels sprouts, cabbage, cauliflower, parsley, watercress	Contain a variety of potent antioxidants (e.g., β-carotene, folacin, magnesium, calcium, glucosinolates, isothiocyanates, lutein, and indoles); contain flavonoids and polyphenols, which activate the transcription factor, Nrf2, which plays a key role in cellular protection against oxidative stress and inflammation (29–31, 50, 61, 72, 80–83)	−0.14
Tomatoes	Tomatoes, tomato juice, tomato sauce, salsa	Contain β-carotene, vitamin C, and lycopene, the latter of which is a potent singlet oxygen quencher and one of the most powerful antioxidants among the natural carotenoids (32–35)	−0.78
Apples and berries	Fresh apples, pears, apple juice or cider, strawberries, blueberries, raspberries, cherries	Contain flavonoids (e.g., anthocyanins, quercetin, and phenolic acids) that suppress proinflammatory cytokine production and are powerful antioxidants; potentially increase postprandial plasma antioxidant capacity (36–38)	−0.65
Deep yellow or orange vegetables and fruit	Cantaloupe, peaches, carrots, dark yellow or orange squash, figs	Contain provitamin A carotenoids (e.g., β-carotene and α-carotene), which have a conjugated double-bond structure making them strong antioxidants (40)	−0.57
Other fruits and real fruit juices	Fresh fruits other than those listed above (e.g., pineapples, honeydew, grapes, kiwi, watermelon, lemon, grapefruit, and oranges), orange juice, grapefruit juice, grape juice, and other real fruit juice	Contain antioxidants (e.g., flavonoids, such as hesperidin, naringenin, neohesperidin, limonene, vitamin C, β-cryptoxanthin, plant sterols, salicylates, naringin, nobelitin, and narirutin) with similar mechanisms to those described above (41–48, 72)	−0.16
Other vegetables	Vegetables other than those listed above (e.g., okra, green peppers, onions, zucchini, and eggplant)	Contain antioxidants and polyphenols with similar mechanisms to those described above	−0.16
Legumes	String beans, peas, lima beans, lentils, and other beans (excluding soybeans)	Contain folacin, iron, isoflavones, protein, vitamin B6, and have a high antioxidant capacity; rich in fiber, which is associated with beneficial alterations to the gut microbiota, reducing immune response in the gut (49, 51, 61)	−0.04
Fish	Tuna fish, salmon, other light and dark meat fish, breaded fish cakes or fish sticks	Contain Ω-3 fatty acids, which compete with proinflammatory Ω-6 fatty acids by synthesizing eicosanoids and suppress the capacity of monocytes to synthesize IL-1β and TNF-α (52–54)	−0.08

Byrd J Nutr. 2019

The difference between classical inflammation initiated by a microbial antigen or injury, and metaflammation caused by lifestyle or environmental inducers

Egger, Br J Nutr 2009



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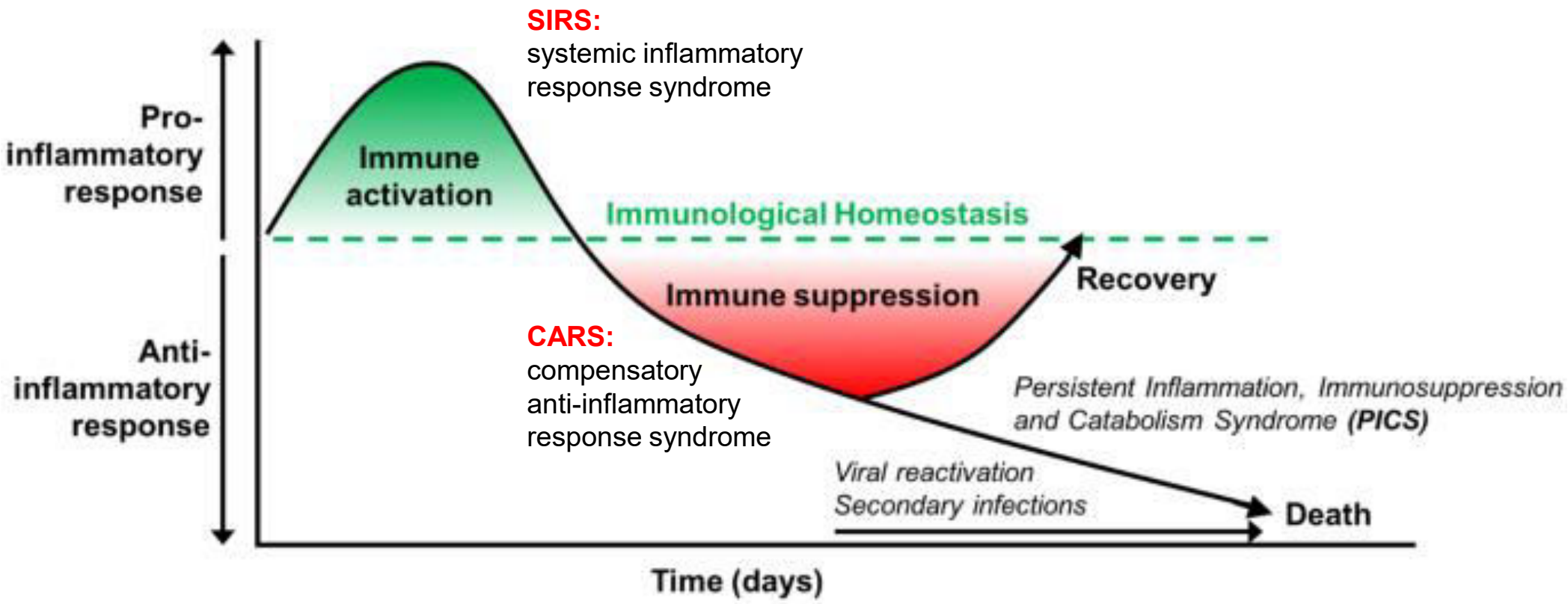
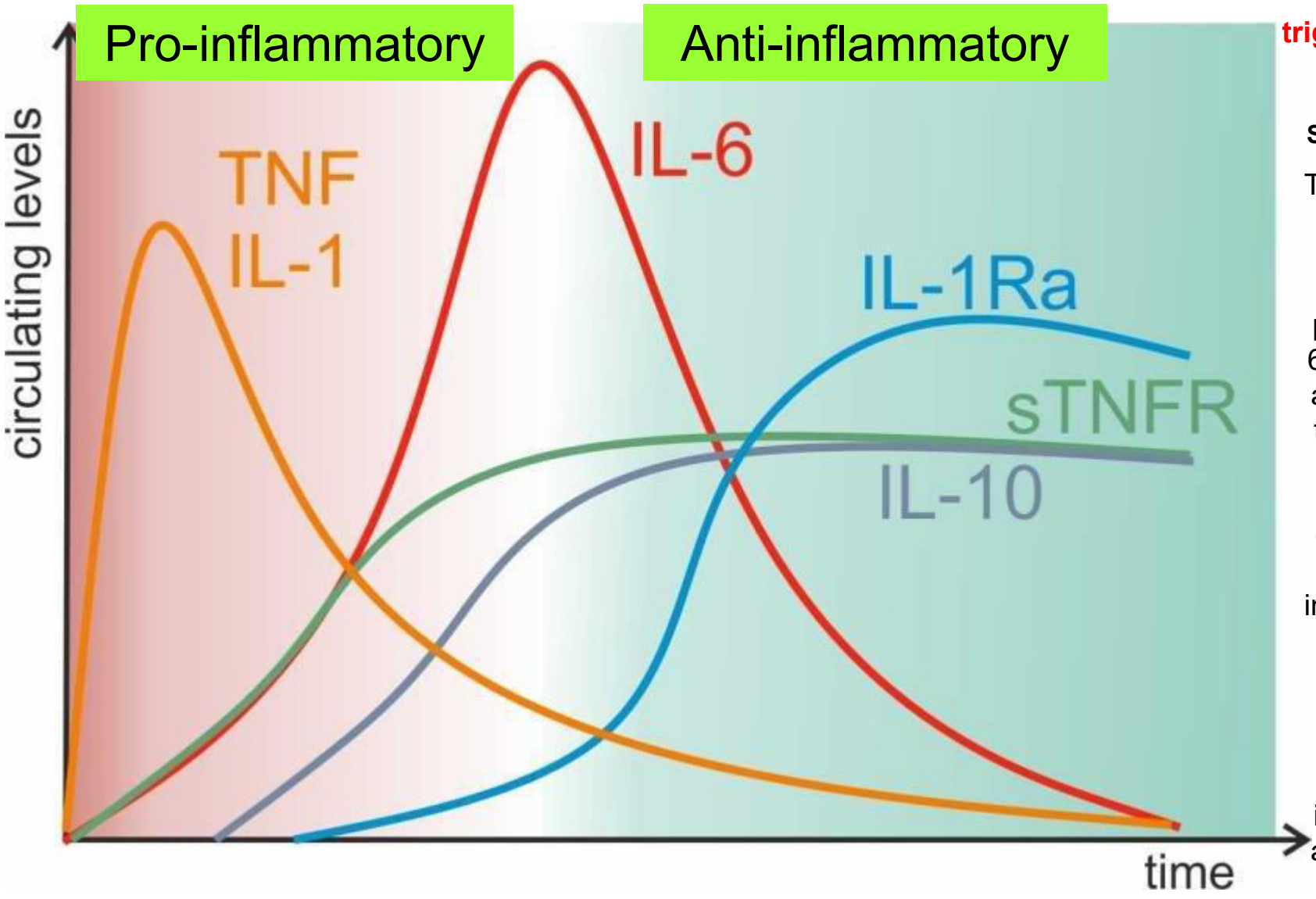
The immunological response following infection:

PAMP/DAMP detection by PRR→ SIRS→CARS→recovery/death/PICS



Cytokine kinetics in sepsis



Steeland Int J Mol Sci 2018

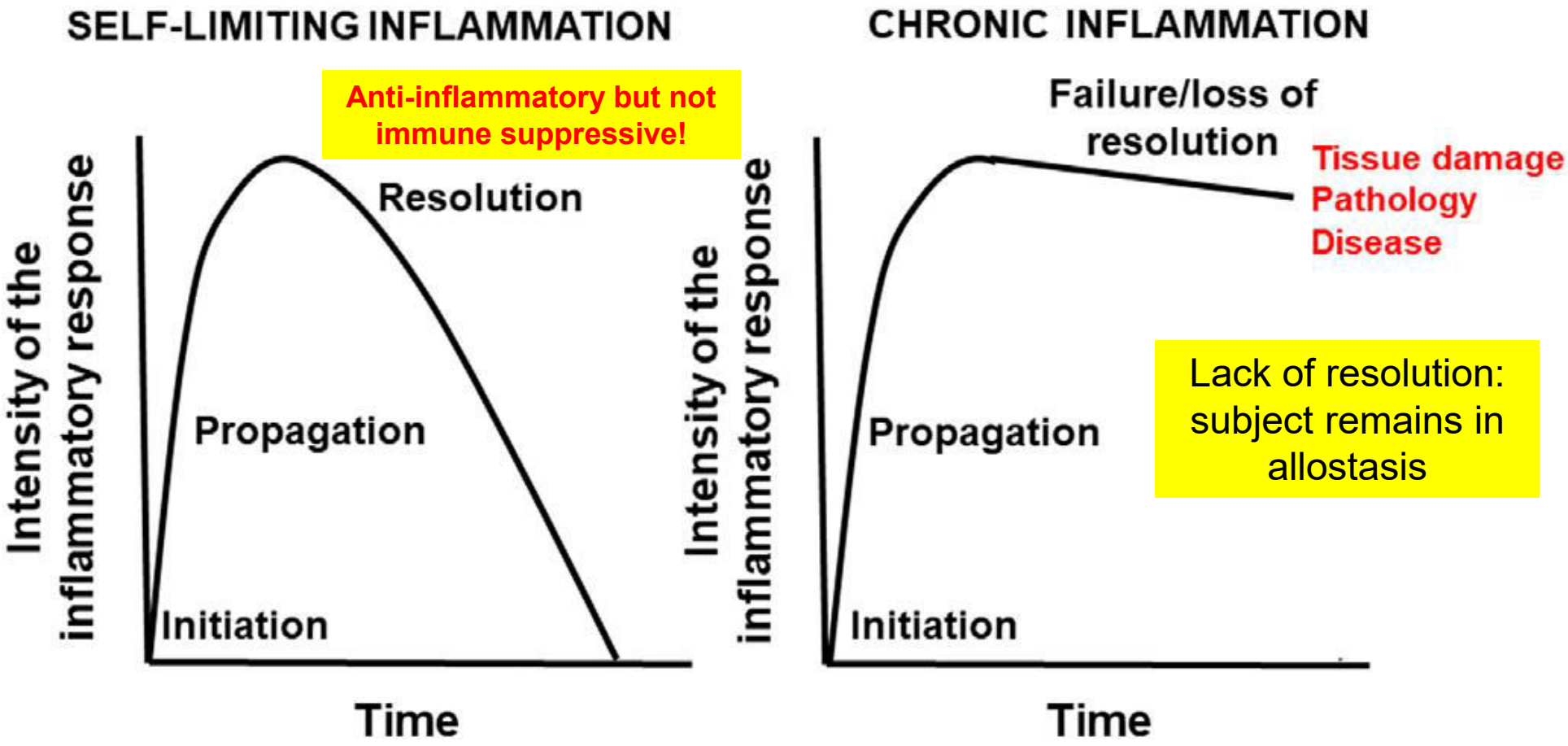
Both, IL-1β and TNF-α trigger an anti-inflammatory cascade resulting in the production of IL-10.
Sugimoto Front Immunol 2016

Tumor necrosis factor (TNF) and interleukin (IL-)1 are the first cytokines to be released in sepsis and promote the secretion of IL-6. Together, these cytokines are the orchestrators during the pro-inflammatory phase in sepsis.

After some time, compensation mechanisms arise to dampen the pro-inflammatory response such as IL-10, IL-1 receptor antagonist (IL-1Ra) and soluble TNF receptor (sTNFR).

Interleukin 6 (IL-6) is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine.

Self-limiting vs. chronic inflammation



Calder Biochimie. 2020

Endogenous biochemical pathways that become jointly activated during a defense reaction can counter-regulate inflammation and promote resolution

Resolution is an active rather than a passive process

Serhan FASEB journal 2007

Many mediators regulate the pro- and anti- inflammatory responses

Mediator class	Pro-inflammatory	Anti-inflammatory
Amines	Histamine, bradykinin	Adrenaline, noradrenaline
Lipid mediators	PGE_2, PGI_2, LTB_4, LTC_4	PGJ_2, $PGA_{1/2}$, lipoxins
Complement	C3a, C5a	C1q receptor
Cyclic nucleotides	cGMP	cAMP
Adhesion molecules	E-selectin, P-selectin, ICAM1, VCAM1	$\alpha_v\beta_3$ integrin, TSP receptor, PS receptor
Cytokines	TNF, IL-1β, IL-6	TGF-β1, IL-10
Chemokines	IL-8 (CCL8), GRO/KC, MIP1α (CCL3), MCP1 (CCL2)	-
Steroid hormones	-	Glucocorticoids

SPMs

Cross-talk

cAMP, cyclic adenosine 3,5 monophosphate; cGMP, cyclic guanosine 3,5 monophosphate; ICAM1, intercellular adhesion molecule 1; IL, interleukin; LT, leukotriene; MCP1, monocyte chemotactic protein 1; MIP1α, macrophage inflammatory protein 1α; PG, prostaglandin; PS, phosphatidylserine; TGF-β1, transforming growth factor-β1; TNF, tumour-necrosis factor; TSP, thrombospondin; VCAM1, vascular cell adhesion molecule 1.

Lawrence Nat Rev Immunol 2002

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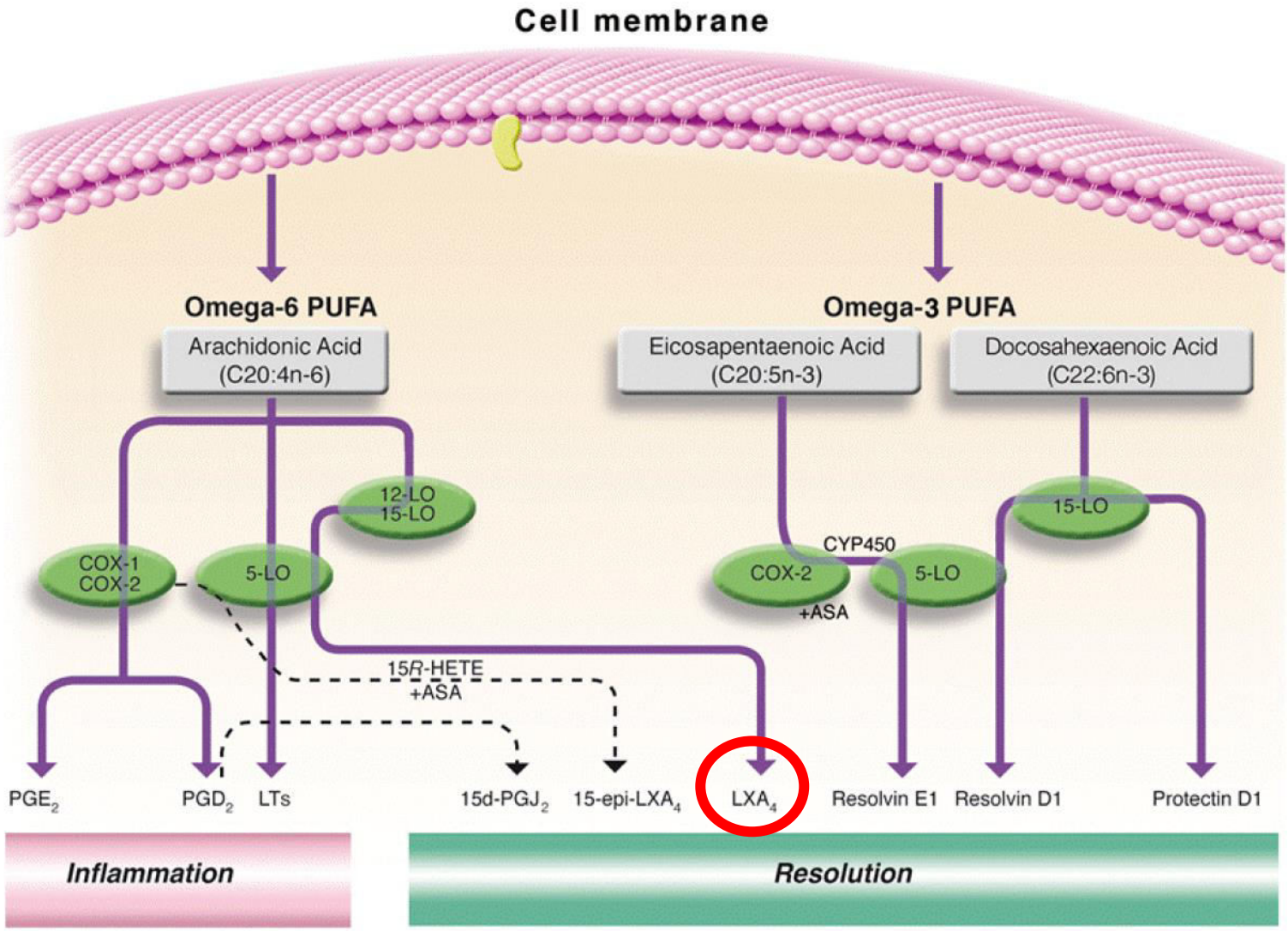
- Metabolic resilience and allostasis
  - Function tests (OGGT)
  - Pregnancy
  - Metabolic syndrome
- **Inflammation and resolution**
  - SIRS/CARS
  - **Specialized pro-resolving mediators (SPMs)**
  - LCPω3 and disease
  - Selenium and infection
- Conclusions

Protective ω-6 and ω-3 derived circuits in inflammation

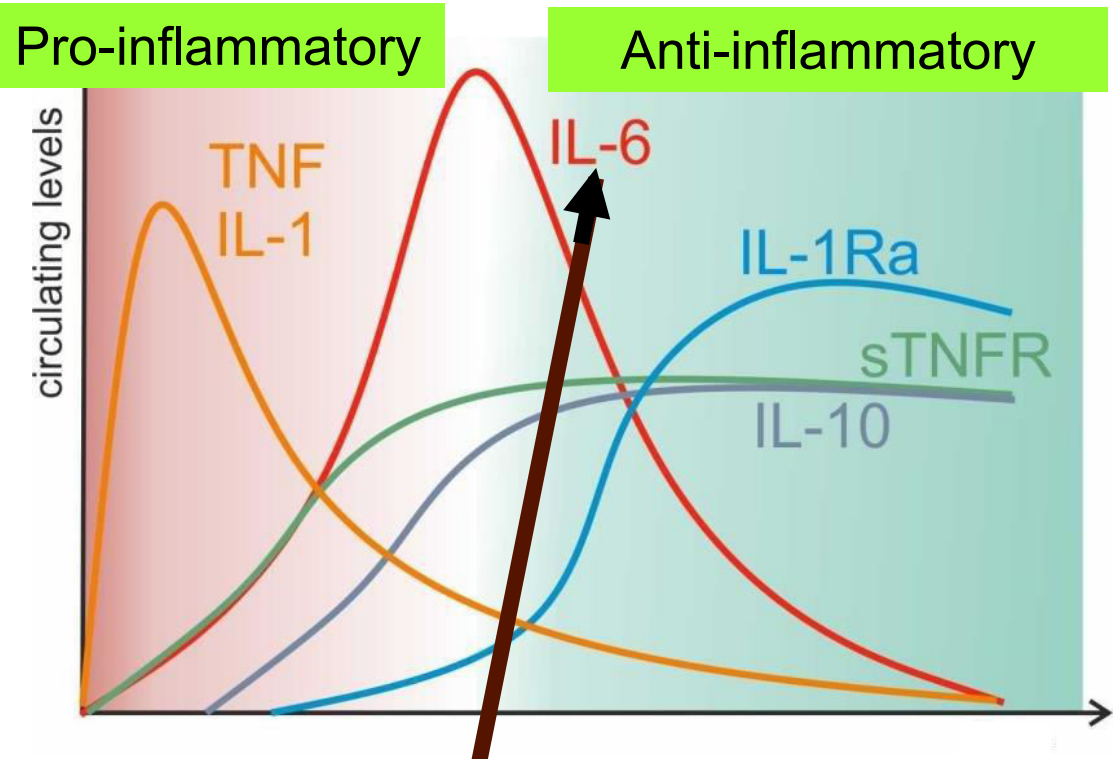


The ω-6 PUFA arachidonic acid is released from phospholipids and metabolized by COX or 5-LO to form inflammatory mediators, such as PGs and LTs. During the process of resolution, there is a —class switch from the biosynthesis of these inflammatory mediators to the formation of lipid autacoids with anti-inflammatory and proresolving properties, including the LXs and the cyclopentenone PGs of the D series (15d-PGJ_2). In addition, during the resolution of inflammation, ω-3 PUFAs such as EPA and docosahexaenoic acid (DHA) are converted to potent anti-inflammatory and proresolving lipid mediators, including resolvin E1, resolvin D1, and protectin D1. ASA: aspirin, CYP450: cytochrome P450.

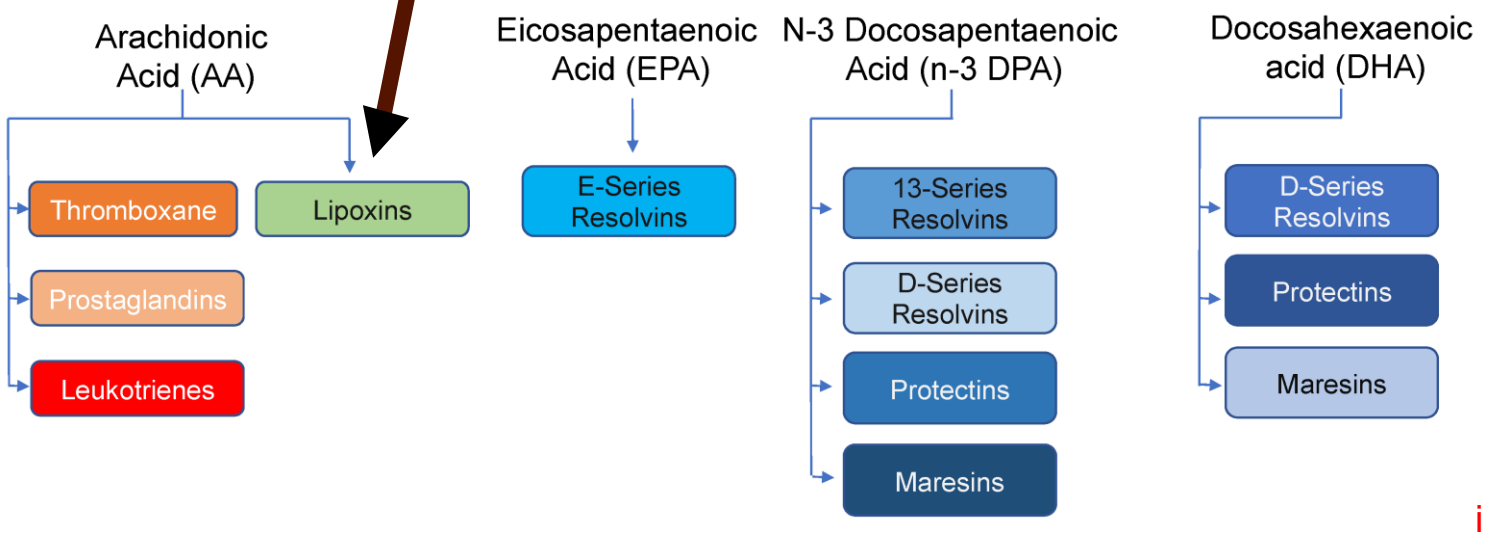
Lipoxin A2

Gonzalez-Periz, ScientificWorldJournal 2010

Cytokine and Lipid mediators that regulate the acute inflammatory response



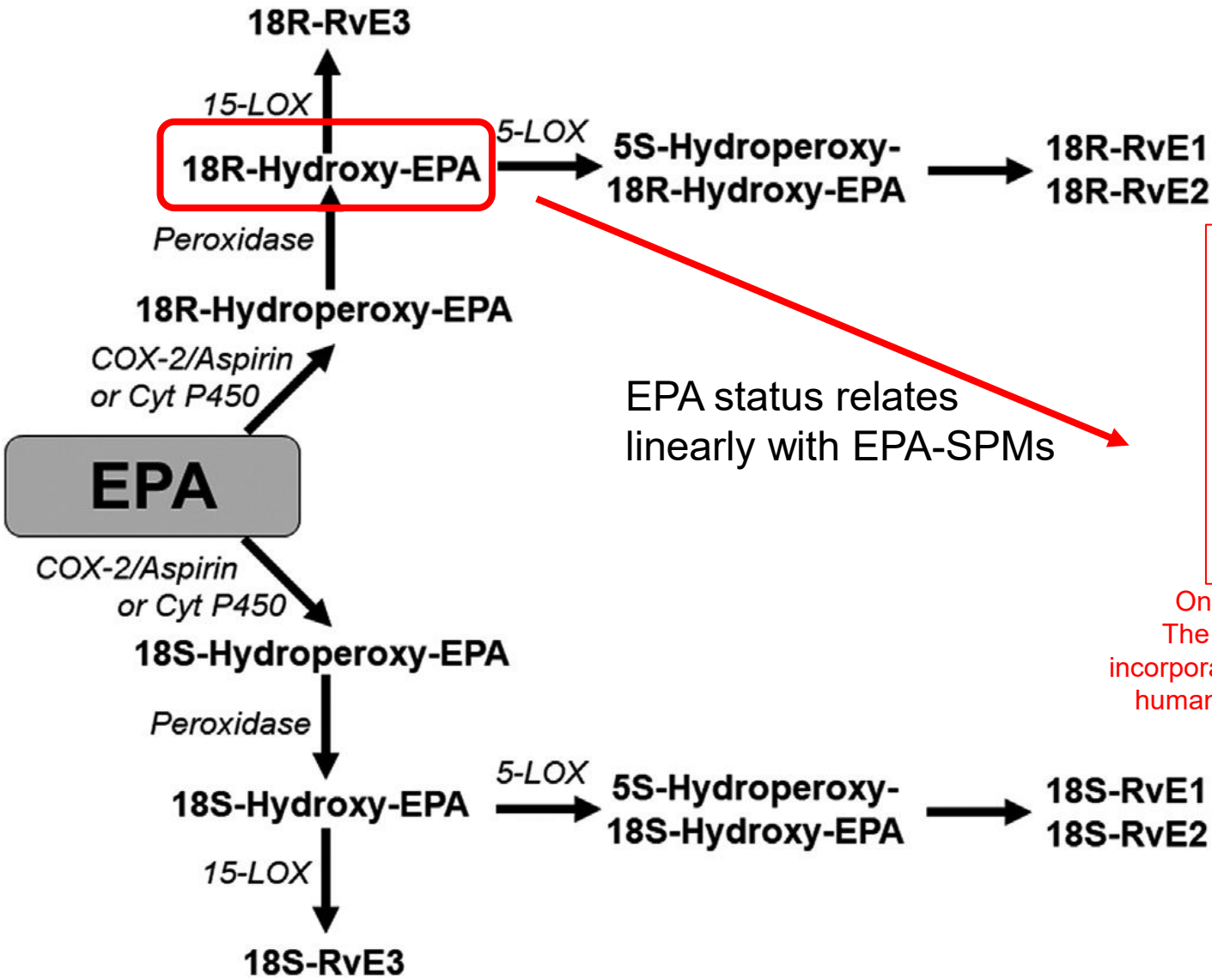
Steeland Int J Mol Sci 2018



Cytokine SPM cross talk: Serhan J Clin Invest. 2018

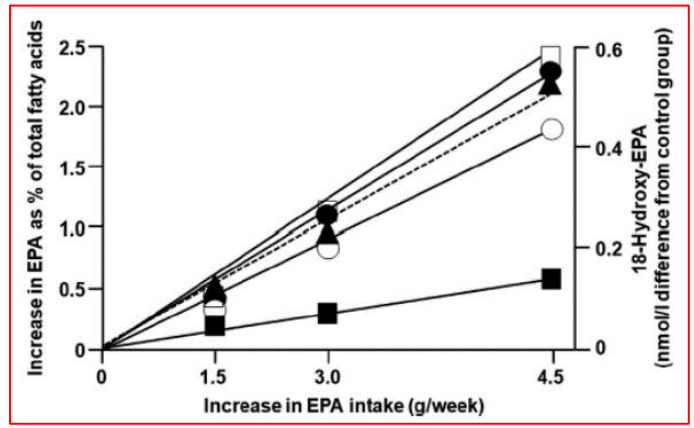
Role of lipid mediators in the initiation and resolution of inflammation; Dalli Biomolecules. 2022

Pathway of synthesis of specialised pro-resolving mediators from eicosapentaenoic acid (EPA)



EPA status relates linearly with EPA-SPMs

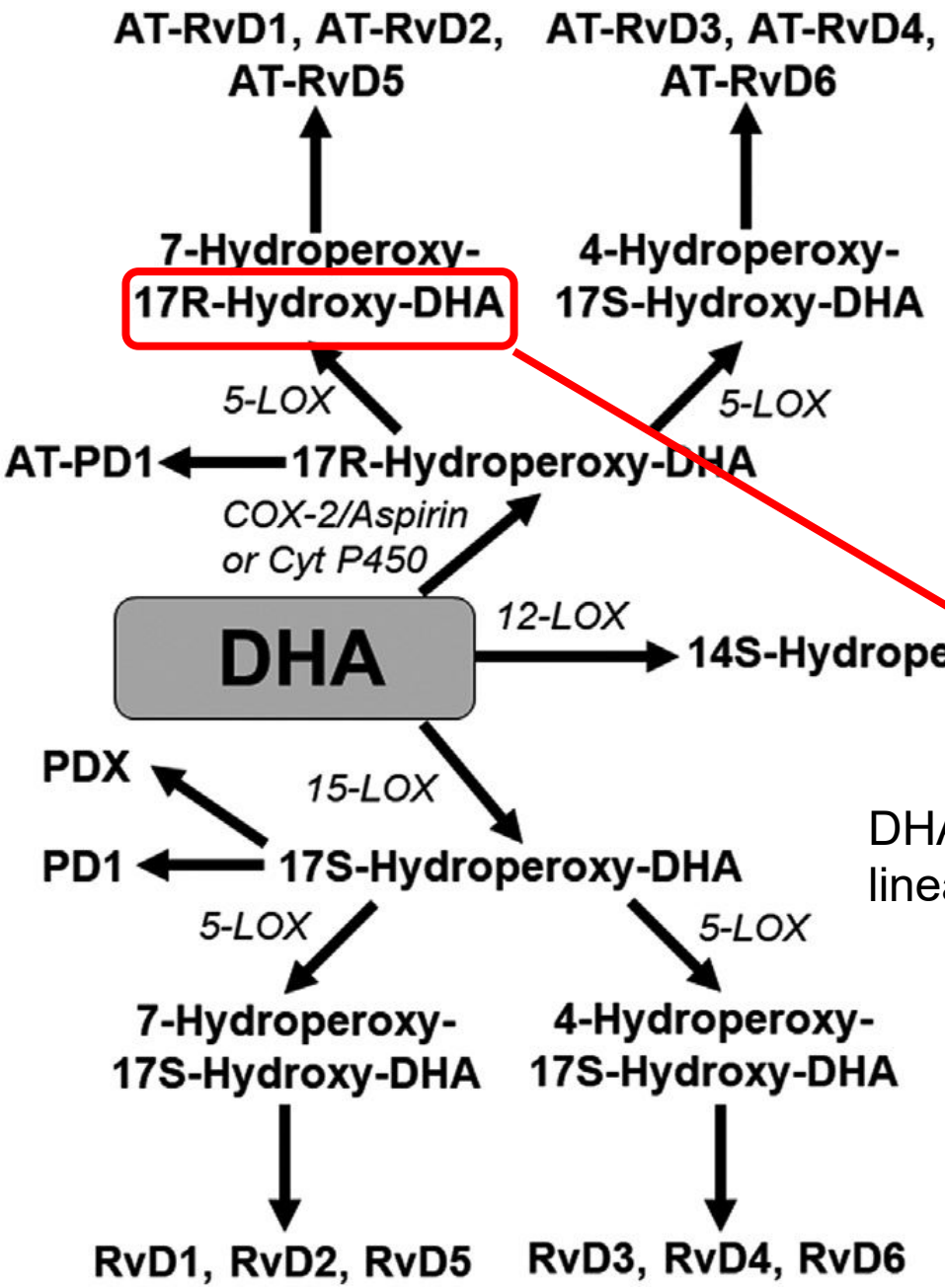
Plasma phosphatidylcholine (closed circles), plasma non-esterified fatty acids (closed squares), mononuclear cells (open circles) and platelets (open squares)
Plasma 18-hydroxy-EPA concentrations (closed triangles)



One year supplementation study, healthy subjects. The relationship between increased EPA intake, the incorporation of EPA into different blood pools in healthy humans and the increase in plasma 18- hydroxy-EPA.

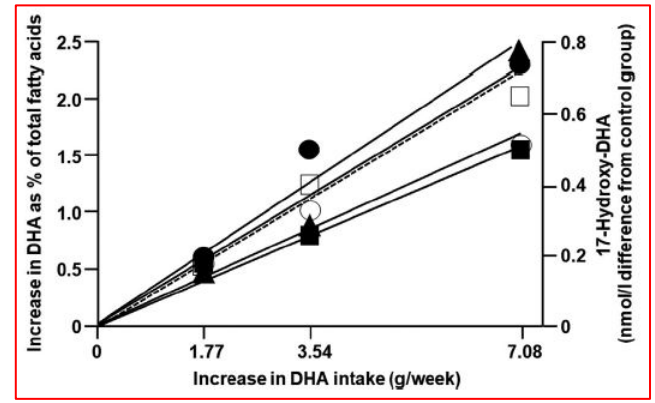
Calder Biochimie. 2020

Pathway of synthesis of specialised pro-resolving mediators from docosahexaenoic acid (DHA)



DHA status relates linearly with DHA-SPMs

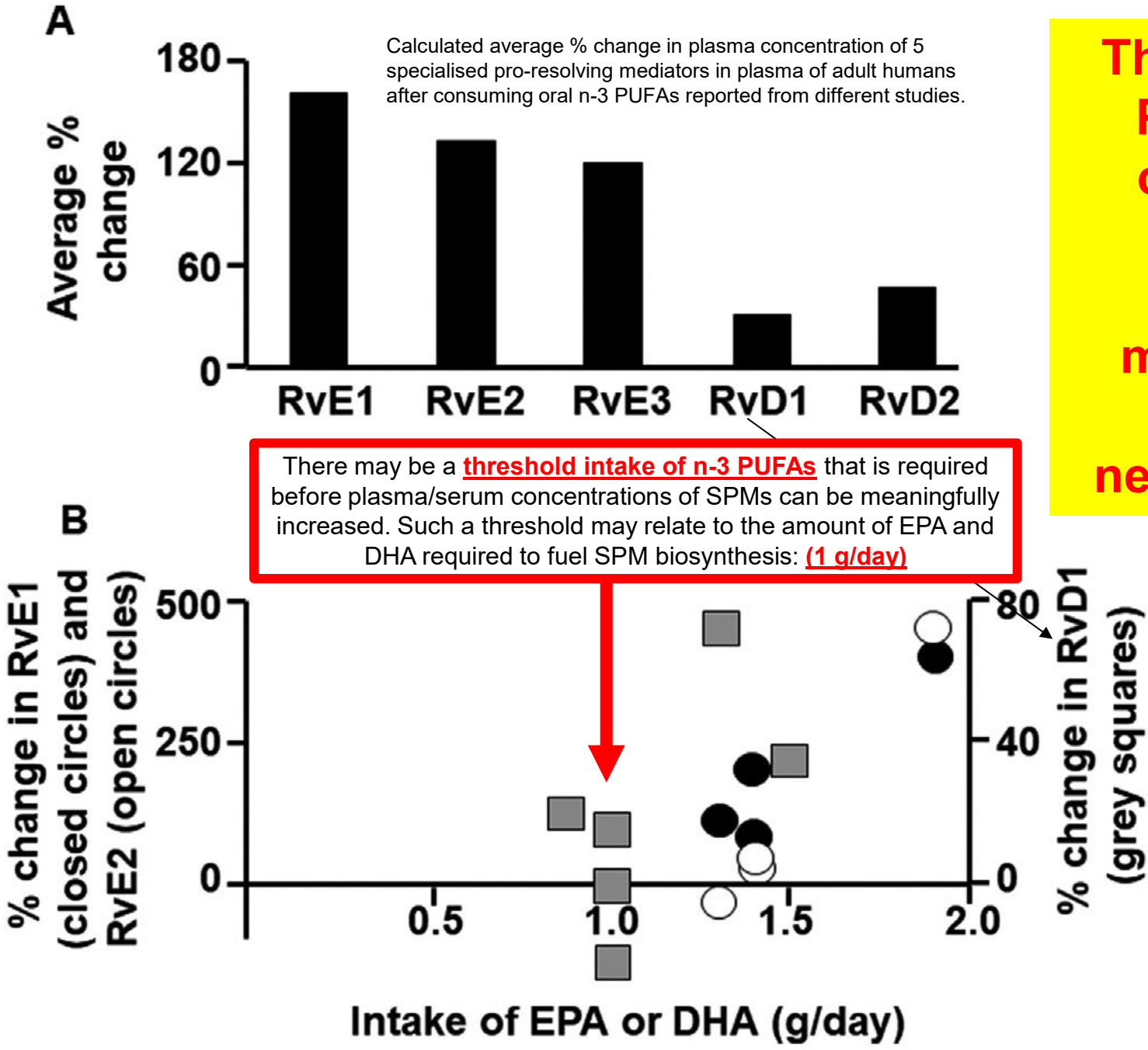
DHA content of plasma phosphatidylcholine (closed circles), plasma non-esterified fatty acids (closed squares), mononuclear cells (open circles) and platelets (open squares) Plasma 17-hydroxy-DHA concentrations (closed triangles)



One year supplementation study, healthy subjects. The relationship between increased DHA intake, the incorporation of DHA into different blood pools in healthy humans and the increase in plasma 17- hydroxy-DHA.

Calder Biochimie. 2020

The effect of oral n-3 PUFAs on plasma concentrations of specialized pro-resolving mediators (SPM) in adult humans: need >1 g LCPω3/day



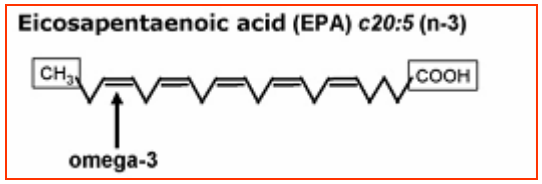
Calculated average % change in plasma concentration of 5 specialised pro-resolving mediators in plasma of adult humans after consuming oral n-3 PUFAs reported from different studies.

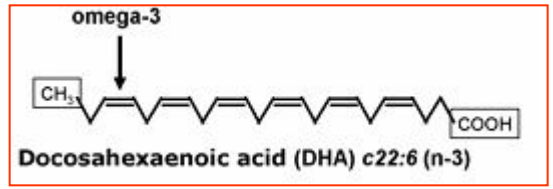
There may be a **threshold intake of n-3 PUFAs** that is required before plasma/serum concentrations of SPMs can be meaningfully increased. Such a threshold may relate to the amount of EPA and DHA required to fuel SPM biosynthesis: **(1 g/day)**

Data are calculated as % difference between group average after and before n-3 PUFAs or, where before n-3 PUFA data were not available, between after n-3 PUFAs and values in the control group

Calder Biochimie. 2020

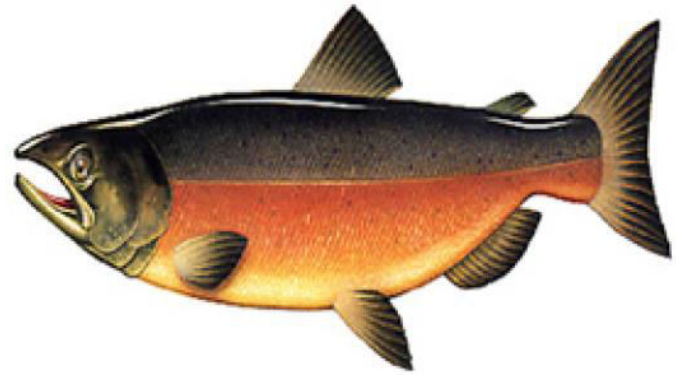
EPA and DHA per 100 g fish



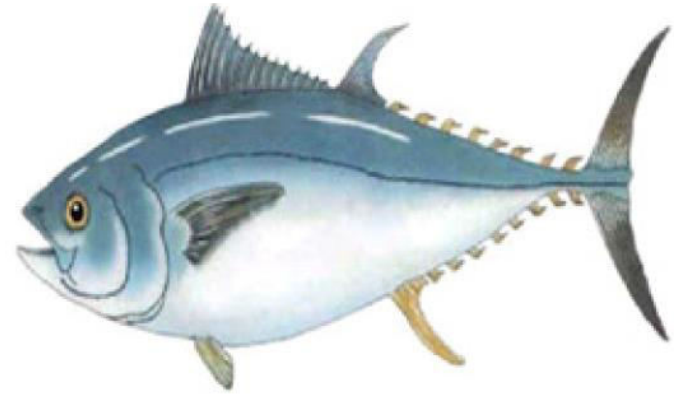


'fatty' fish: 1-1.5 g/100 g

Mackerel - 1 810 mg



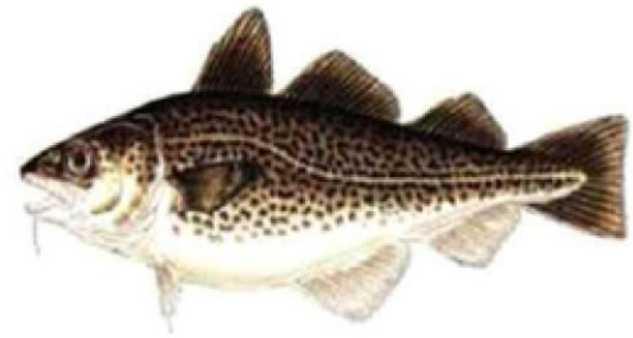
Salmon - 1 800 mg



Tuna - 1 500 mg

Haring - 1 200 mg

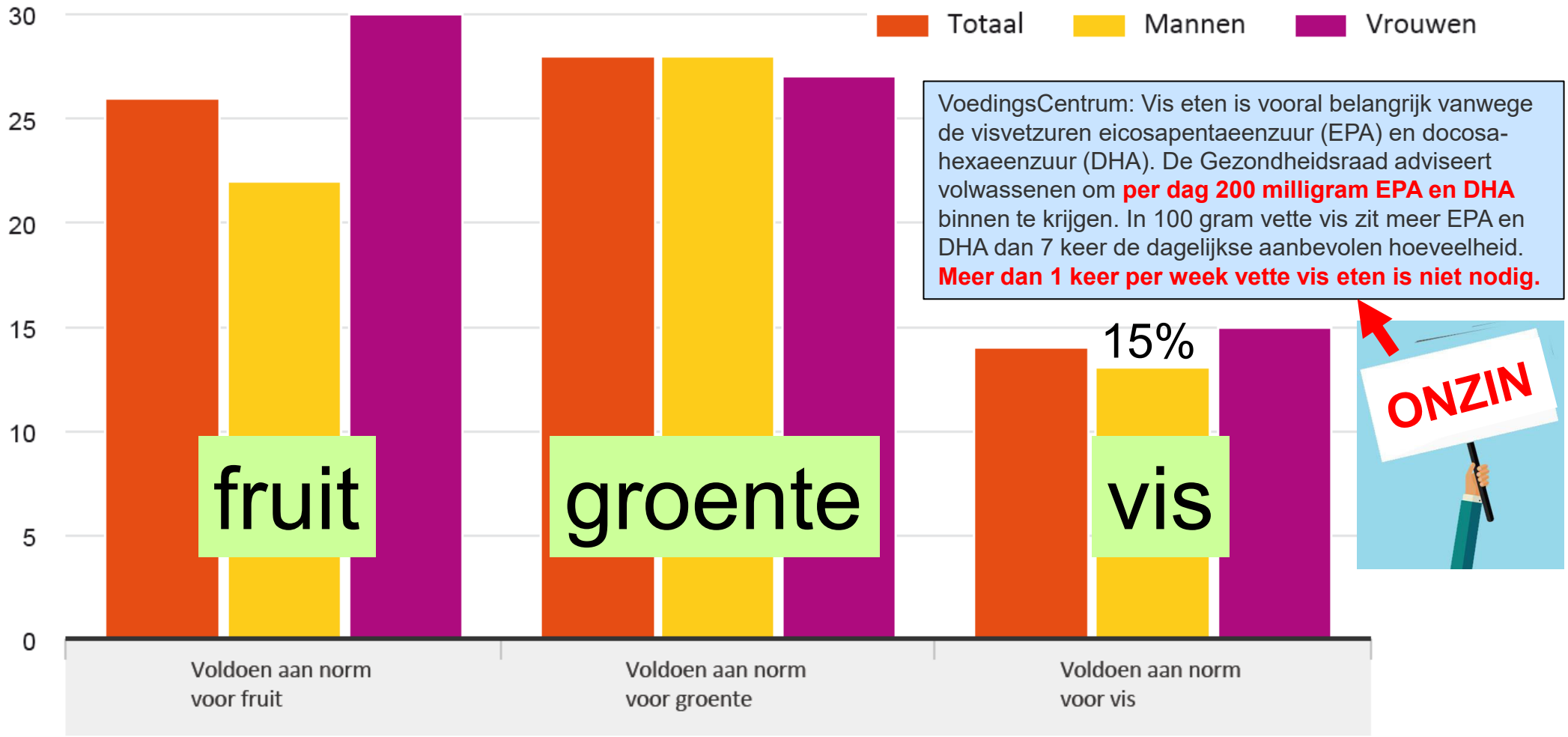
Salmon trout - 1 060 mg



Codfish - 240 mg

Fedacko Pathophysiology 2007

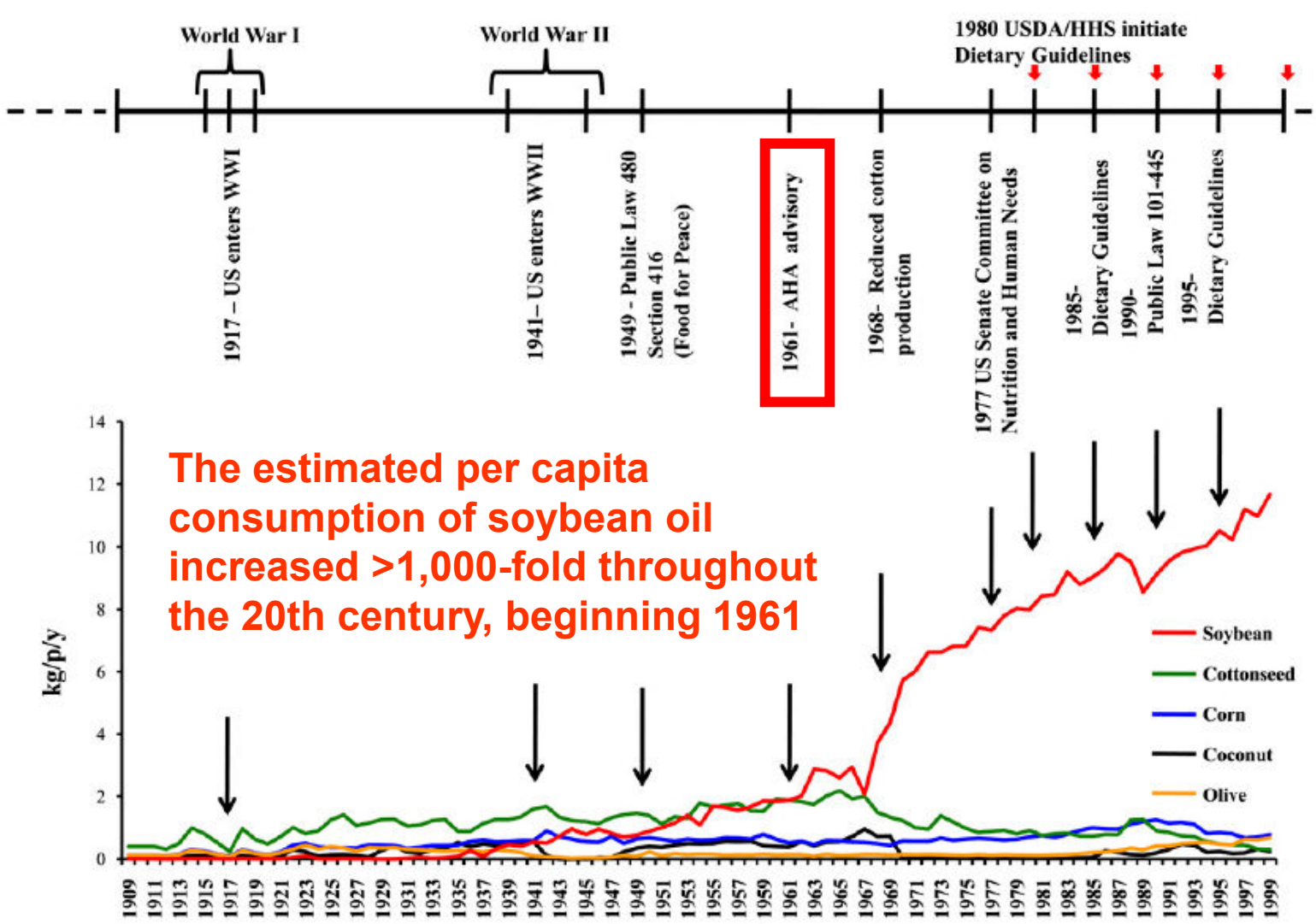
Voldoen aan de richtlijnen voor fruit, groente en vis vanaf 4 jaar naar geslacht, 2014



VoedingsCentrum: Vis eten is vooral belangrijk vanwege de visvetzuren eicosapentaeenzuur (EPA) en docosahexaeenzuur (DHA). De Gezondheidsraad adviseert volwassenen om **per dag 200 milligram EPA en DHA** binnen te krijgen. In 100 gram vette vis zit meer EPA en DHA dan 7 keer de dagelijkse aanbevolen hoeveelheid. **Meer dan 1 keer per week vette vis eten is niet nodig.**

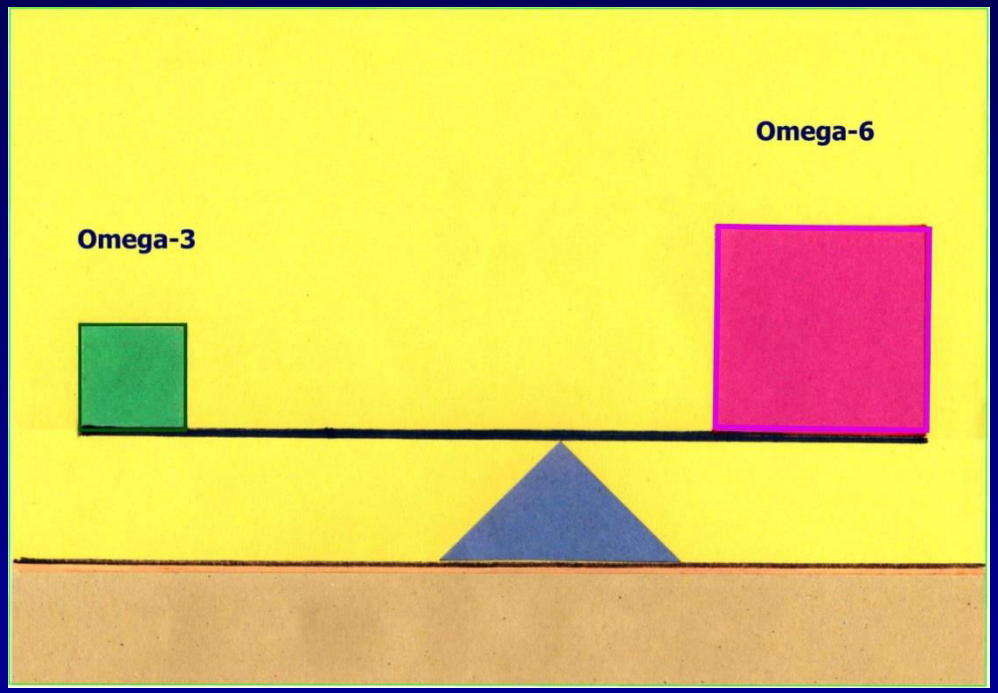
CBS, Nederland eet onvoldoende groente, fruit en vis, 23 april 2015

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.

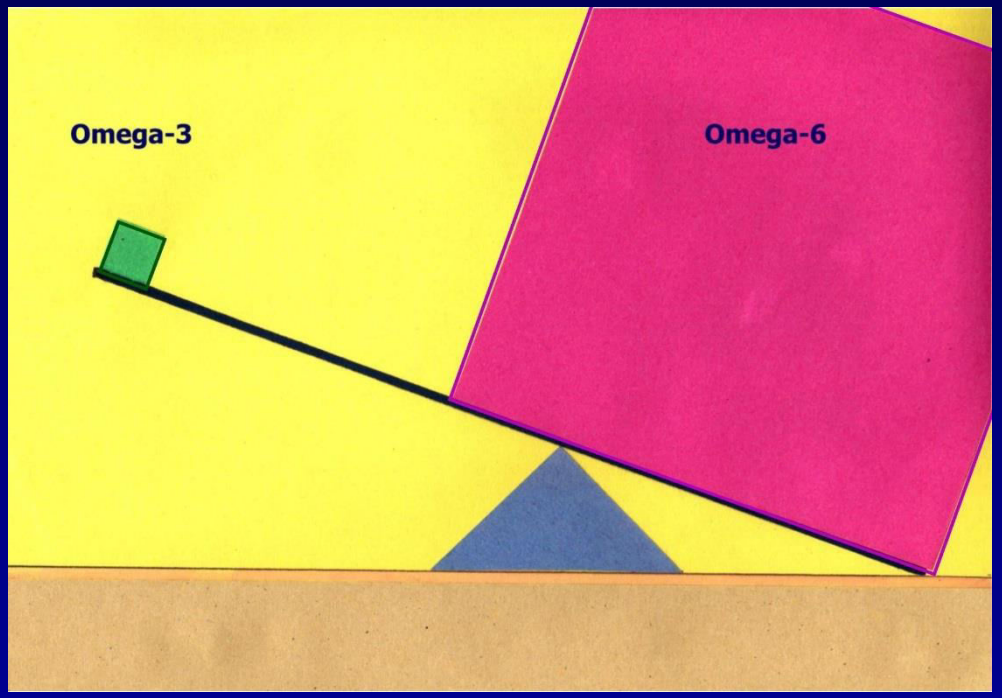


Blasbalg, Ramsden AJCN 2011

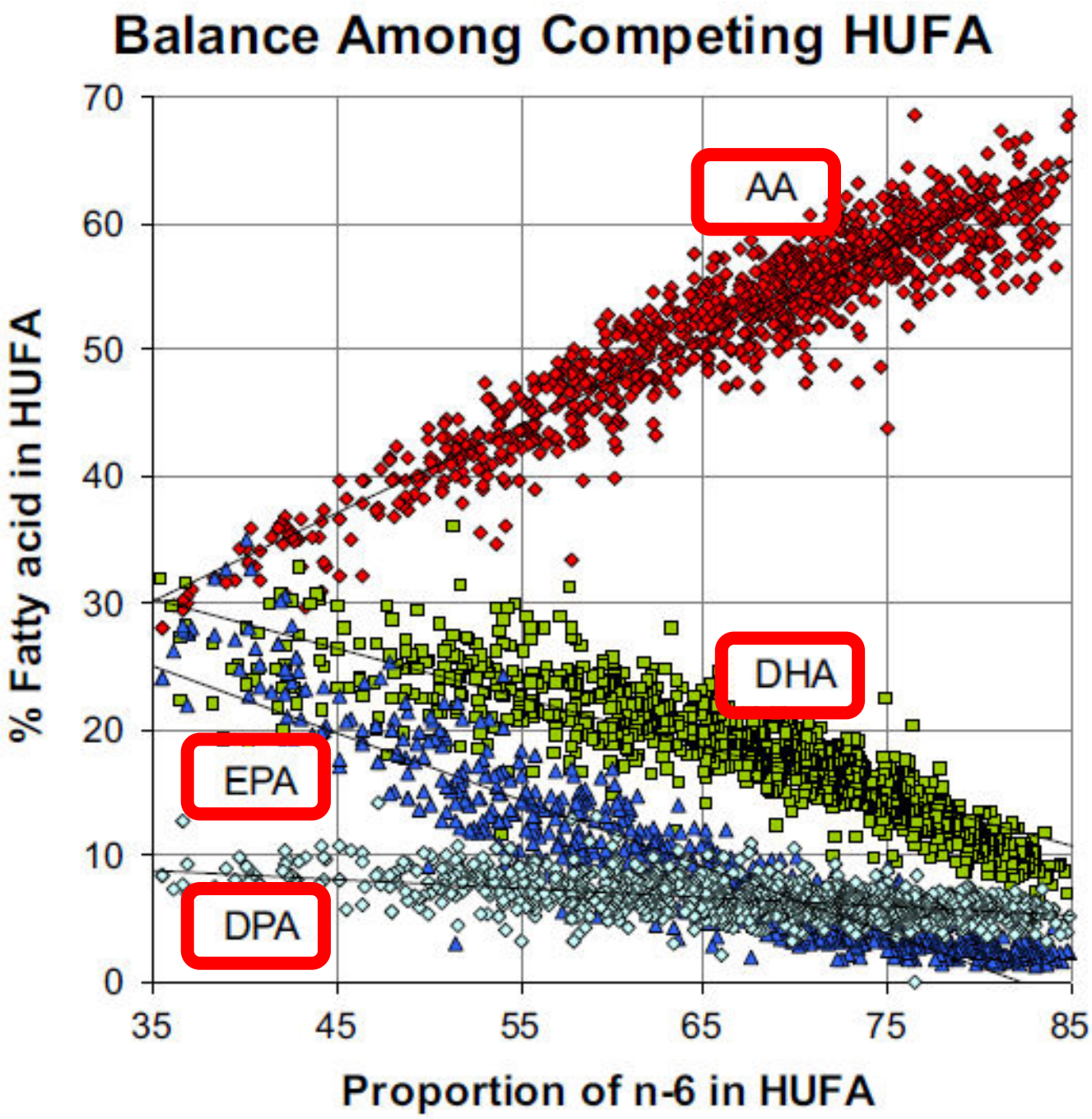
Omega 3/6 balance



Ancient diet



Current diet



Balance among competing n-3 and n-6 HUFA

Analysis of the proportions of individual HUFA among total HUFA in 1015 whole blood samples show lower proportions of 20:4n-6 (AA) when proportions of 20:5n-3 (EPA), 22:5n-3 (DPA) and 22:6n-3 (DHA) are higher.The proportions of 20:3n-6, 22:4n-6, and 22:5n-6 were all less than 10% of HUFA and are not shown.

The dotted lines represent approximate HUFA balances for people in the indicated regional groups with different traditional food habits that cause different %n-6 in HUFA

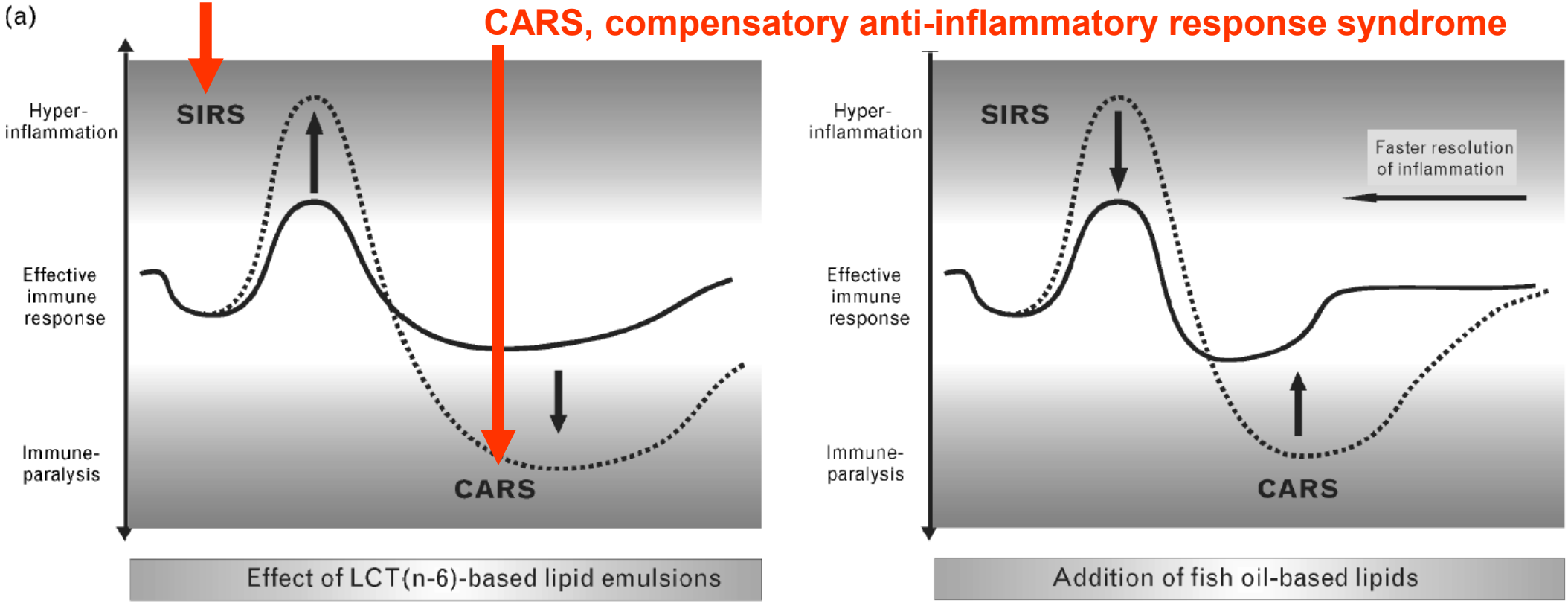
Bilbus Lands 2015

Immune reaction during sepsis

Omega-6 increases and fish oil dampens SIRS/CARS

SIRS, systemic inflammatory response syndrome

CARS, compensatory anti-inflammatory response syndrome



A high LCPω3/LCPω6 ratio dampens both the SIRS and CARS, resulting in a more balanced immune response and preventing hyper-inflammation and immuneparalysis.

Mayer Curr Opin Clin Nutr Metab Care 2006; Ruiz, J Nutr Biochem 2013

Invloed van voeding op zelfherstellend vermogen

Outline

- Resilience (veerkracht)
- Metabolic resilience and allostasis
  - Function tests (OGGT)
  - Pregnancy
  - Metabolic syndrome
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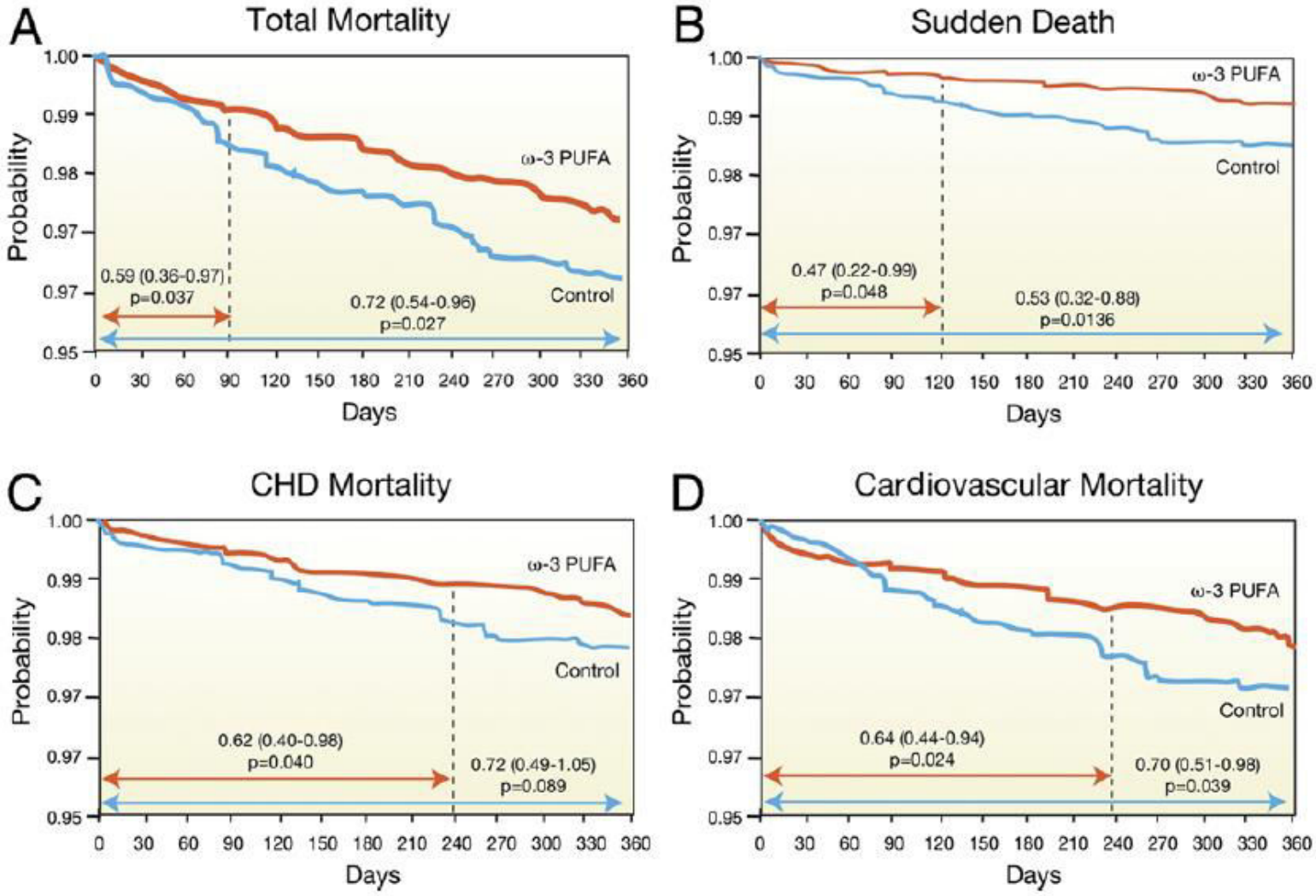
  - Selenium and infection
- Conclusions

Fish oil fatty acids play roles in:

- (Brain) development
- Coronary heart disease
- (Neuro) psychiatric diseases
- Pregnancy complications
- Traumatic brain injury
- Other

GISSI, 1999: 11,323 post-MI patients ω3PUFA (850 mg of EPA/DHA=1.2:1) vs. usual care

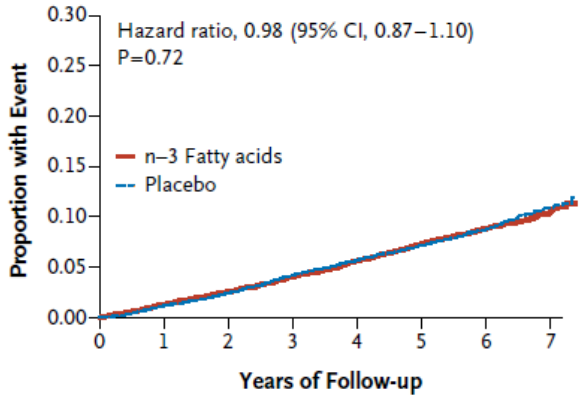


Lavie, J Am Coll Cardiol 2009

ORIGIN trial (international multicenter), 2012

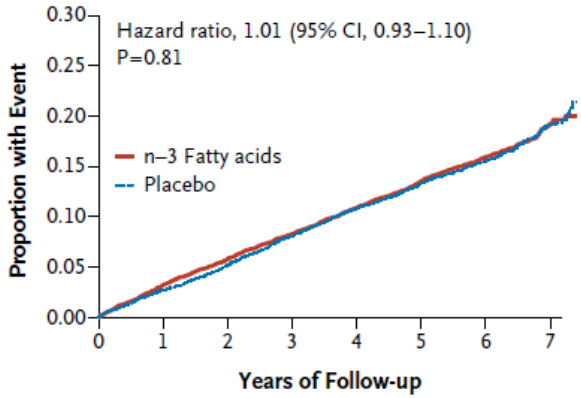
12,536 patients at high risk for CAD events, with impaired fasting glucose, impaired glucose tolerance, or diabetes, 6.2 years at least 900 mg ethyl esters of n–3 fatty acids or placebo

A Death from Cardiovascular Causes



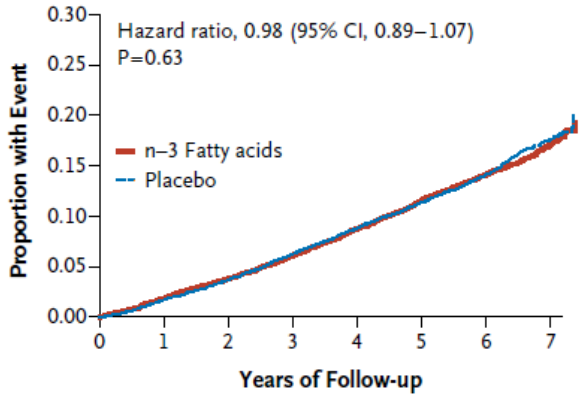
No. at Risk								
n–3 Fatty acids	6281	6161	6034	5882	5706	5503	3896	879
Placebo	6255	6143	6017	5848	5685	5492	3893	837

B Myocardial Infarction, Stroke, or Cardiovascular Death



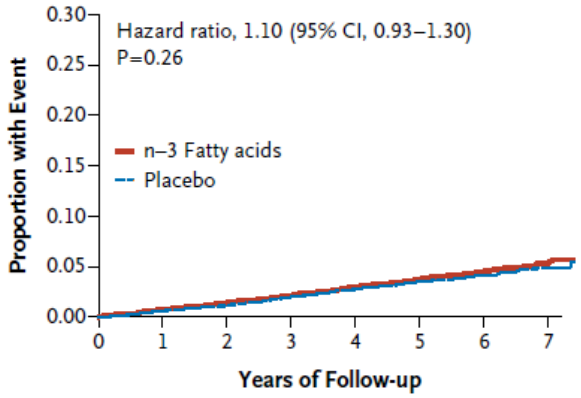
No. at Risk								
n–3 Fatty acids	6281	6044	5843	5630	5403	5154	3601	791
Placebo	6255	6051	5852	5616	5387	5140	3604	766

C Death from Any Cause



No. at Risk								
n–3 Fatty acids	6281	6161	6034	5882	5706	5503	3896	879
Placebo	6255	6143	6017	5848	5685	5492	3893	837

D Death from Arrhythmia

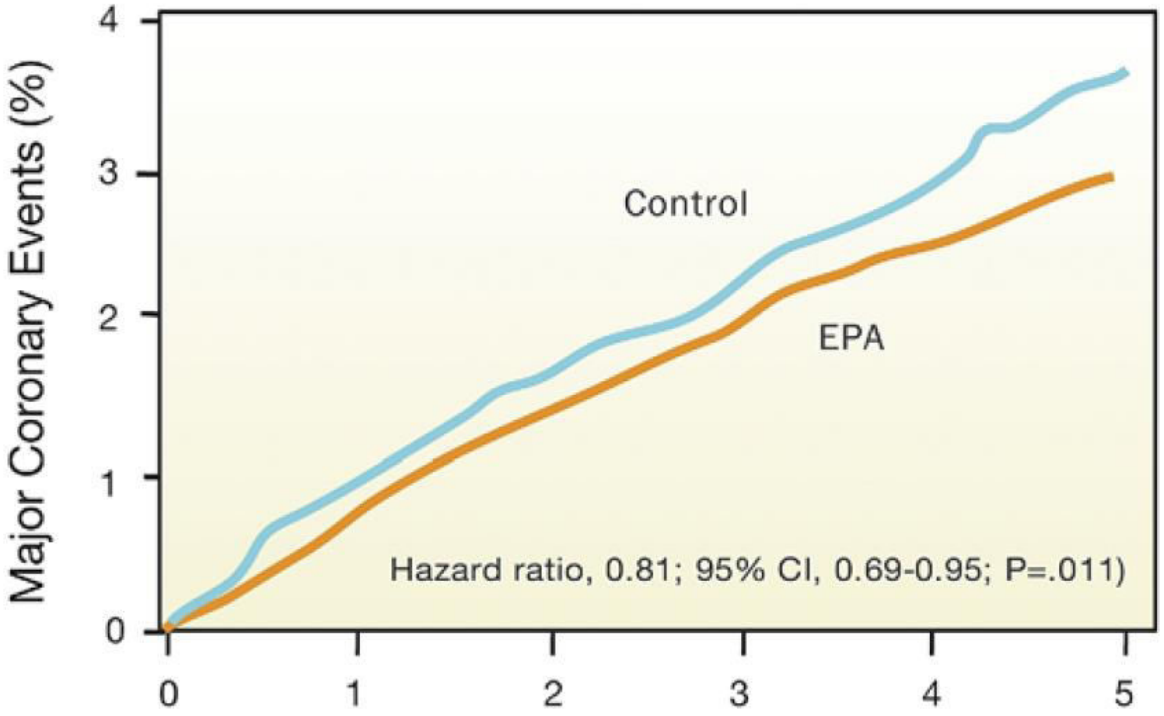


No. at Risk								
n–3 Fatty acids	6281	6161	6034	5882	5706	5503	3896	879
Placebo	6255	6143	6017	5848	5685	5492	3893	837

ORIGIN investigators, Bosch, NEJM 2012

EPA in primary prevention (JELIS)

18,645 patients ≥6.5 mmol/L cholesterol, 1,800 mg EPA with statin or statin-only, 5 years, primary: major coronary event (SCD, (non)fatal MI, unstable angina, angioplasty, stenting, CABG)



No. of patients at risk

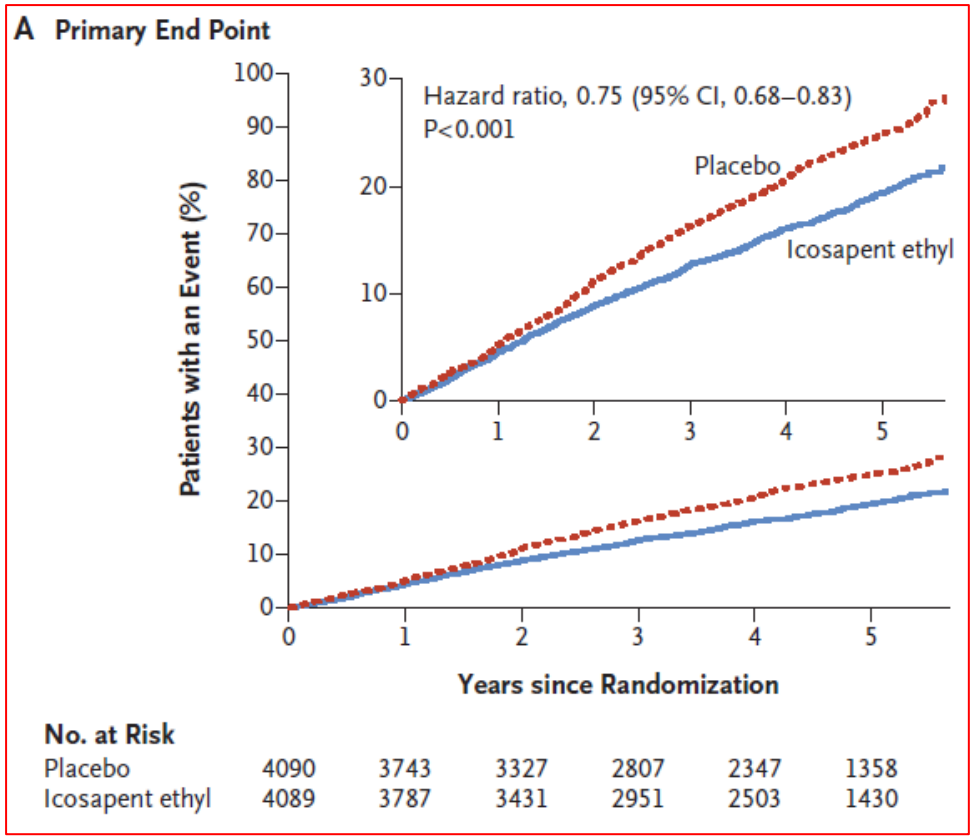
Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

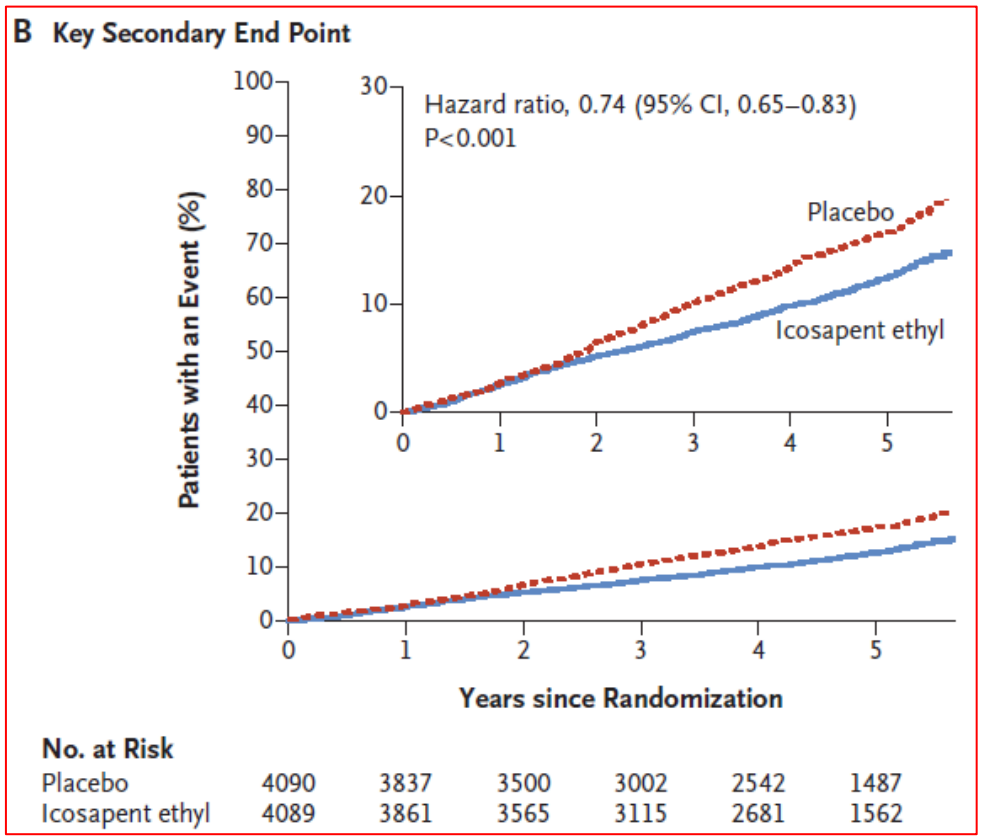
Eicosapentaenoic acid (EPA; 1.8 g/d) reduced the incidence of major adverse coronary events by 19%, in the Japan EPA Lipid Intervention Study (JELIS)

Yokoyama Lancet 2007; Lavie, J Am Coll Cardiol 2009

Among patients with elevated triglyceride levels (despite the use of statins), the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 4 g of icosapent (EPA) ethyl vs placebo (RCT, n=8,179; REDUCE-IT)

Established CAD/diabetes and other risk factors, who had been receiving statin therapy with fasting TG 1.52-5.63 mmol/L and LDLC 1.06-2.59 mmol/L





Primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

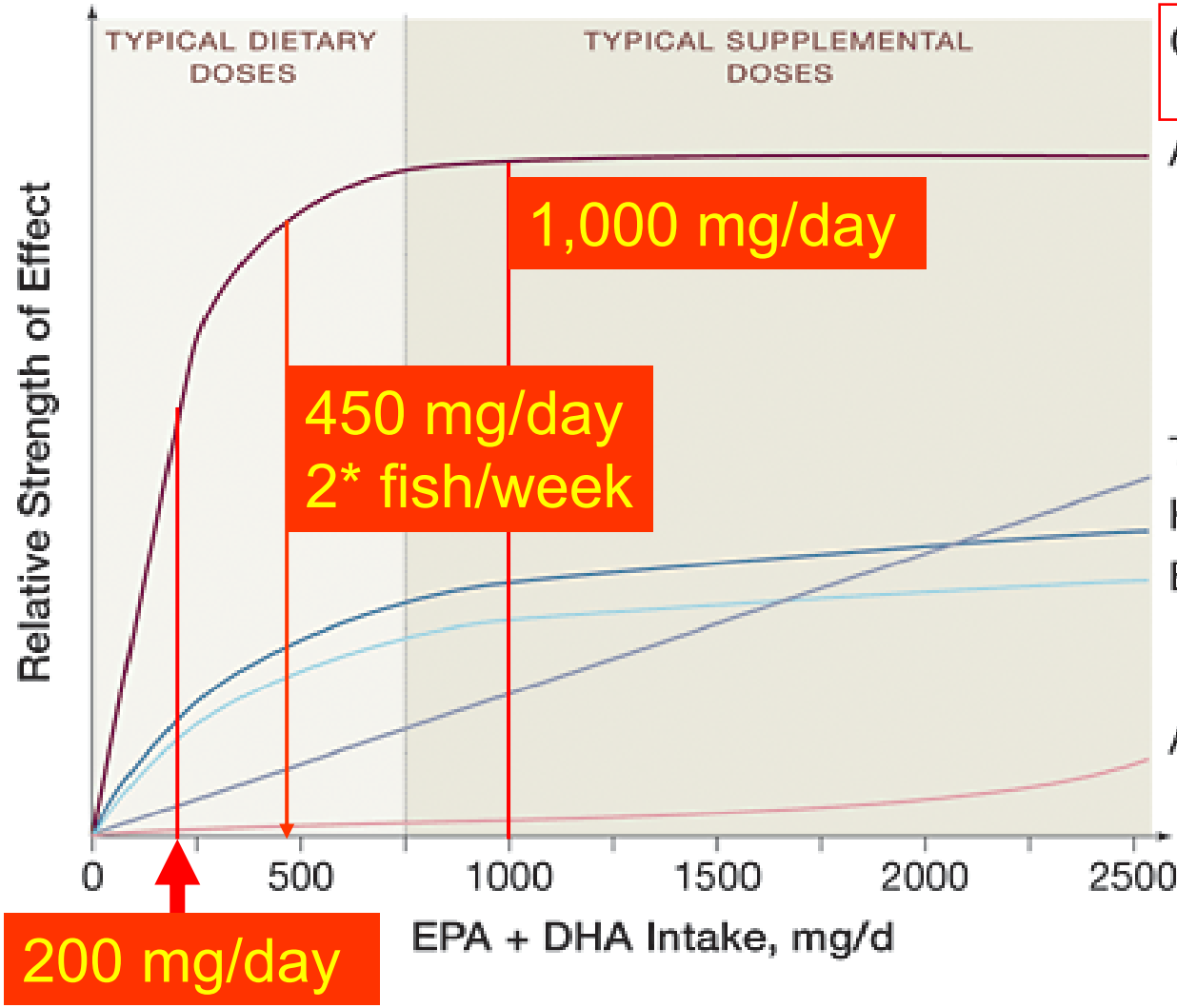
Bhatt NEJM 2019

Why Omega-3 supplementation in secondary prevention does not prevent CVD events

1. Use of an overly strict adjustment for multiple comparisons
2. Failure to stratify by statin use
3. Inclusion of studies with insufficient omega-3 dosing
4. Insufficient consideration of baseline omega-3 status

Pradhan J Steroid Biochem Mol Biol. 2015

Potential Dose Responses and Time Courses for Altering Clinical Events of Physiologic Effects of Fish or Fish Oil Intake

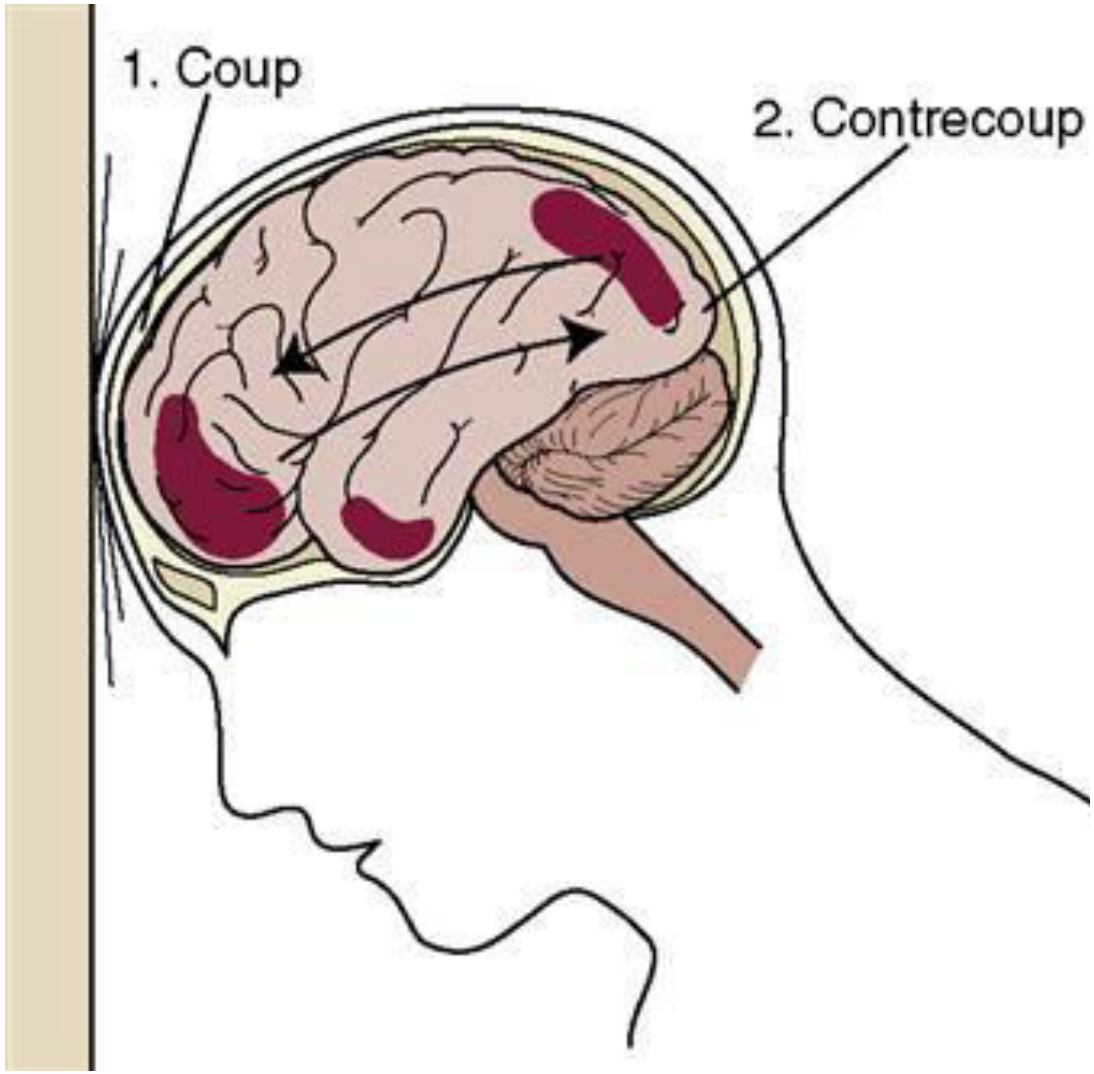


Clinical Effect	Time Course To Alter Clinical Events
Antiarrhythmia	Weeks
Triglyceride-Lowering	Months to Years
Heart Rate–Lowering	Months
BP–Lowering	Months to Years
Antithrombosis	Weeks

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

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

Traumatic Brain Injury (TBI) can lead to neurodegenerative changes

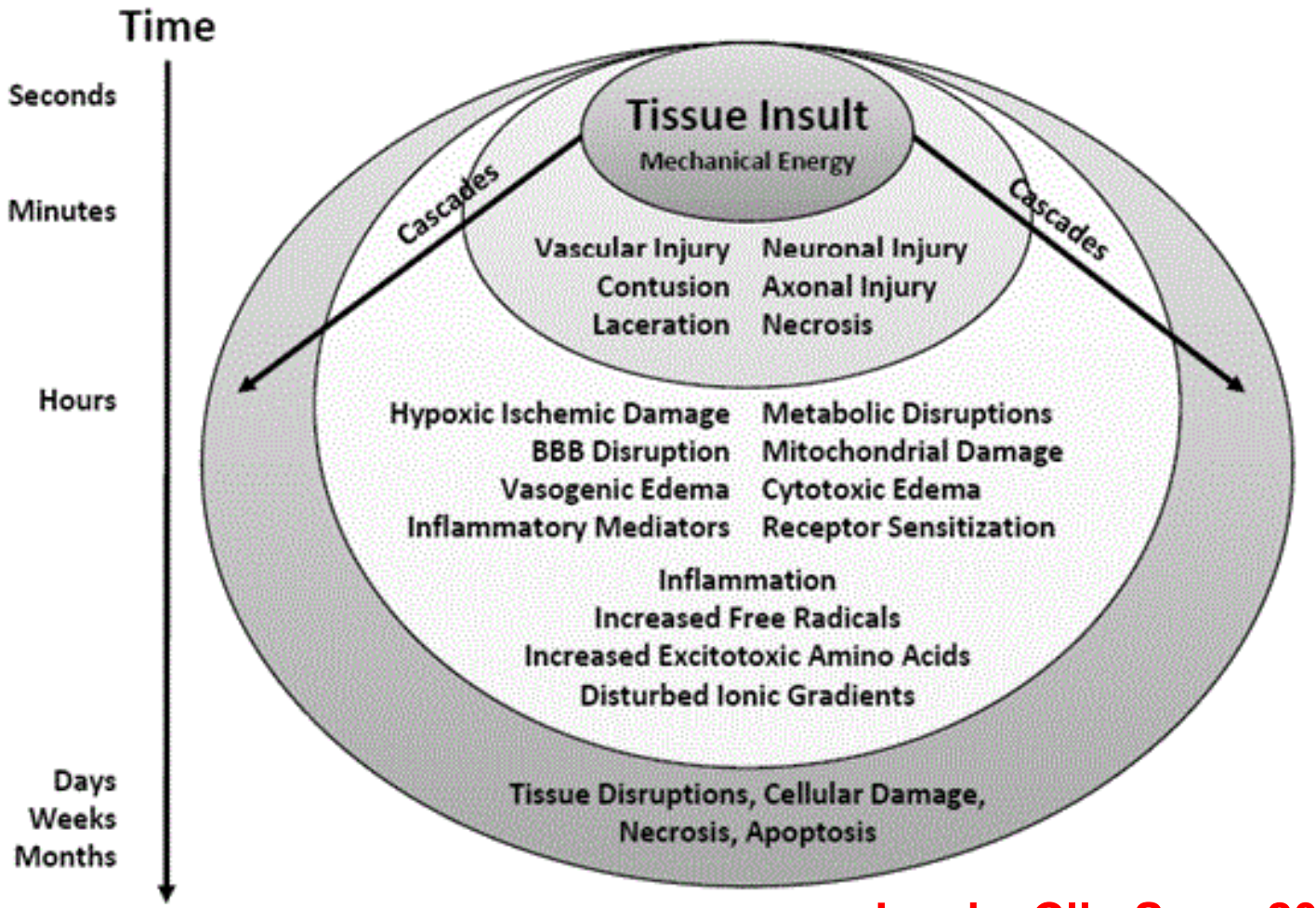


Lewis, Clin Surg. 2017

The brain often strikes both in the direct and opposite plane of motion against the inner bony table. This is the coup-contre-coup pattern, where contusions to the brain are seen at the site of skull impact and 180 degrees opposite the site of impact. Affected individuals often exhibit disordered memory and executive functioning and behavioral and personality disturbances (e.g., apathy, depression, irritability, impulsiveness, and suicidality). Upon autopsy, the presence of hyperphosphorylated tau protein deposition, whether it be in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), or glial tangles (GTs), is a defining feature **of Chronic Traumatic Encephalopathy (CTE)**

The primary injury of TBI is caused by transfer of mechanical injury to brain tissue. This is followed by the secondary injury that occurs over minutes to hours to days and even weeks and months.

It is characterized by numerous metabolic and biochemical cascades that may cause more damage than the initial tissue insult itself



The secondary injury of TBI is a prolonged pathogenic process leading to cell death and worsening damage to the brain far beyond the primary injury. The secondary injury phase of TBI consists of: ischemia, excitotoxicity, and intracellular biochemical cascades; axonal injury; cerebral edema; and inflammation and regeneration.

Lewis, Clin Surg. 2017

"Hersentrauma kan honderdduizenden neuronen doden, maar de secundaire ontstekingsreactie kan miljoenen neuronen en de patiënt doden"

Rogers, J Peridontol 2008

'He's going to be better than he was before'

By **Stephanie Smith**, CNN
January 18, 2014 -- Updated 2109 GMT (0509 HKT)

"That (inflammation) will continue over and over unless there's a second response that turns it off," said Sears, president of theInflammation Research Foundation.

There are seven such cases in the medical literature, according to Sears.

Grant Virgin suffered a traumatic brain injury after being struck by a hit-and-run driver

Weeks before fish oil was even considered, Grant Virgin underwent multiple surgeries, and spent considerable time on a ventilator.

Nine weeks after the accident, as Grant was being transferred from an acute care to a rehabilitation hospital, the Virgin family told doctors at the new facility that he was already on a 20-gram-per-day regimen of fish oil.

Forty-eight hours after receiving high-dose fish oil, Grant Virgin asked a nurse for a cell phone to call his mother, and proceeded to have a conversation with her.

His parents decided to give fish oil a try

The teen surprised his mother by calling her in the middle of the night

His mother calls his recovery "unbelievable"

CNN 18 01 2014

9 TBI patients treated with high dose LCPω3

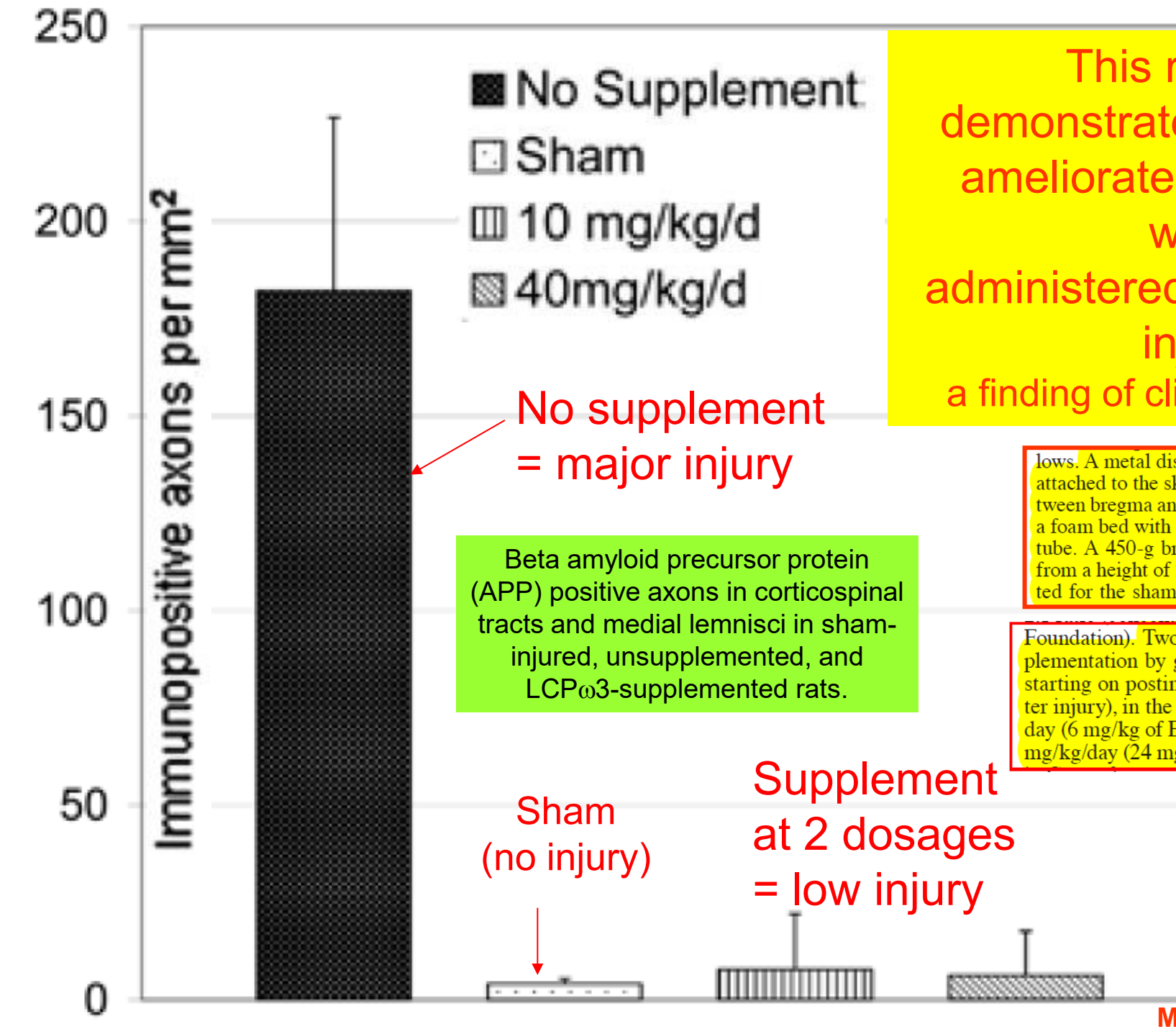
patients presented with severe TBI and traumatically induced coma
treated with 16.2 g/day LCPω3: 10.8 g EPA, 5.4 g DHA
All patients' Glasgow Coma Scale (GCS) scores improved over the course of the study

Case No.	Age (yrs)/ Sex	MOI	Initial GCS Score	Duration of O3FA Tx (days)	Initial CT Findings	Procedures During Stay	LOS (days)	Discharge	Last Imaging Findings	Last GCS Score	Last Known Follow-Up
1	59/M	Fall, hit by object	7T	35	SDH, SAH	ICP monitor, craniectomy, LD, bone flap removal for infection	54	SNF	Decrease in size of extra-axial collection, improved MLS	11	Sudden death secondary to PE 3 wks postdischarge
2	32/M	MVC	7T	10	tSAH	ICP monitor	10	Inpatient rehab	Normal	15	Discharged to home from SNF
3	39/M	MCC, no helmet	6T	30	EDH, tSAH, SDH	Hemicraniectomy, LD, cranial reimplantation	31	Inpatient rehab	Evolution of postop changes, hemorrhagic contusions	15	Independent living; no focal neurological deficits at 4 mos
4	19/M	MVC, no seatbelt, ejected 30 ft	8T	9	Contusion, SDH, tSAH, EDH, IVH	ICP monitor, craniectomy, TL, SDH evacuation	32	SNF	Temporal & frontal encephalomalacia	11	NA
5	46/M	MCC, no helmet	3T	21	SF, EDH, ICH, spine Fxs	Frontotemporal craniotomy, ICP monitor	29	NA	Postop changes, hypoattenuation of BG, temporal lobe contusion	9	6 mos: lethargy, nonverbal, no spontaneous movements, & spasticity
6	23/F	MCC, w/ helmet	4T	7	ICH, SAH, SDH, DAIs	ICP monitor	14	Inpatient rehab	Bilat ICH w/ vasogenic edema & GWM interface w/ DAI	11	NA
7	22/M	MVC, no seatbelt	6T	12	SF, SDH, ICH	EVD	25	NA	Encephalomalacia, resolving ICH	11	NA
8	26/F	Pedestrian struck by car	5T	23	SFs; cerebral edema MLS; cerebral contusions	Decompressive hemicraniectomy, TL, ICP monitor; craniotomy for EDH evacuation; VPS	35	Inpatient rehab	Resolution of edema; posttraumatic hydrocephalus treated w/ VPS	12	Regained speech in 2 languages, rt-sided spasticity, ambulating w/ cane, returned to university
9	19/F	MCC, no helmet	4T	13	SF, C1 Fx, ICH, tSAH, DAI	ICP monitor	18	Inpatient rehab	Evolving DAI changes	15	2 mos: STM deficits, otherwise normal speech, motor, & ambulation

BG = basal ganglia; DAI = diffuse axonal injury; EDH = epidural hematoma; EVD = external ventricular drain; Fx = fracture; GWM = gray–white matter; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; LD = lumbar drain; LOS = length of hospital stay; MCC = motorcycle collision; MLS = midline shift; MOI = mechanism of injury; MVC = motor vehicle collision; NA = not available; PE = pulmonary embolism; SAH = subarachnoid hemorrhage; SDH = subdural hemorrhage; SF = skull fracture; SNF = skilled nursing facility; STM = short-term memory; TL = temporal lobectomy; tSAH = traumatic SAH; Tx = treatment; VPS = ventriculoperitoneal shunt.

small sample size, open label,
nonrandomized, no placebo arm

Bailes Sears J Neurosurg. 2020



This rat study demonstrates that LCPω3 ameliorate axonal injury when administered 24 h following injury:

a finding of clinical importance

No supplement = major injury

Beta amyloid precursor protein (APP) positive axons in corticospinal tracts and medial lemnisci in sham-injured, unsupplemented, and LCPω3-supplemented rats.

lows. A metal disk 10 mm in diameter and 3-mm thick is attached to the skull with cyanoacrylate and centered between bregma and lambda. The animal is placed prone on a foam bed with the metal disk directly under a Plexiglas tube. A 450-g brass weight is dropped through the tube from a height of 2 m striking the disk. (This step is omitted for the sham-injury group.) The animal is then ven-

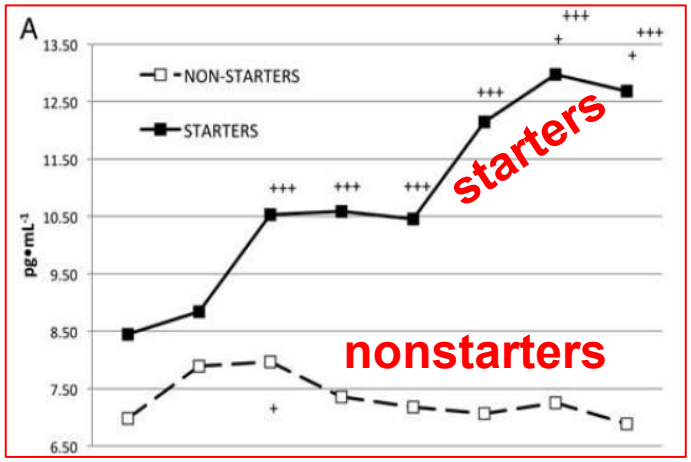
Foundation). Two of the 4 groups received dietary supplementation by gavage with a fish oil concentrate daily, starting on postinjury Day 1 (approximately 24 hours after injury), in the following amounts: Group 1, 10 mg/kg/day (6 mg/kg of EPA and DHA per day); and Group 2, 40 mg/kg/day (24 mg/kg of EPA and DHA per day). The rats

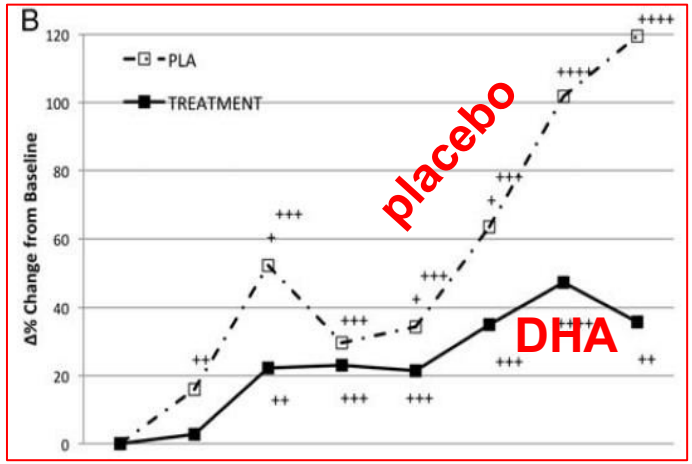
Sham (no injury)

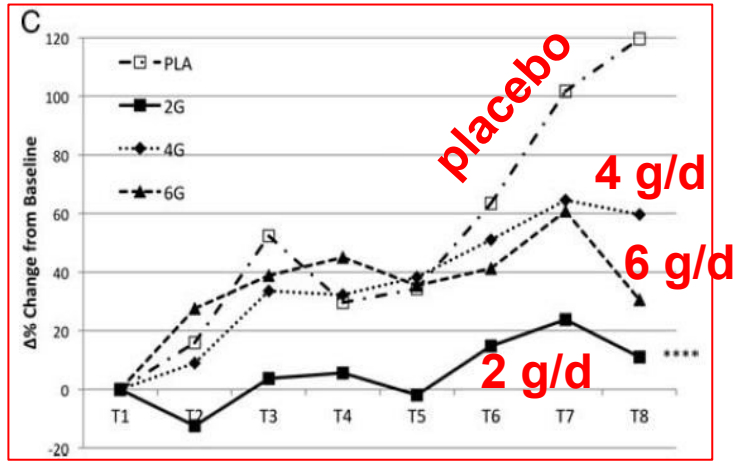
Supplement at 2 dosages = low injury

Mills, Sears, J Neurosurg 2011

A, Changes in serum NFL (pg/mL) over the course of the study in starters (best players, in the starting lineup) and nonstarters (substitutes, bench) B and C, Effect of supplemental DHA on serum neurofilament light (NFL; % change from baseline) over the course of the study in starters, during the season (T1-T8)







2 g/d appeared to produce the most marked reductions in serum NFL.
Conclusions about the differing doses is limited by low study numbers

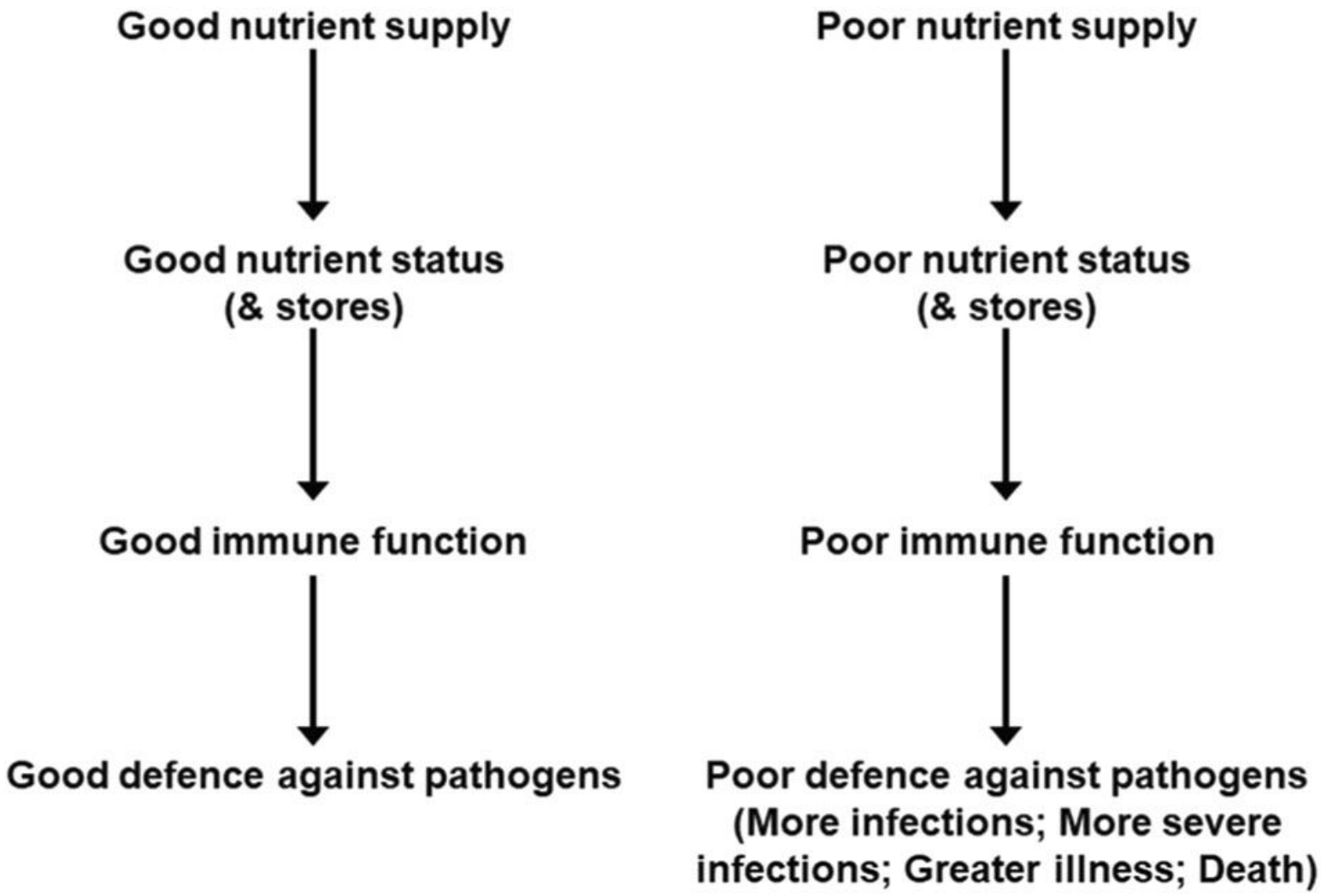
Oliver Med Sci Sports Exerc. 2016

Invloed van voeding op zelfherstellend vermogen

Outline

- Resilience (veerkracht)
- Metabolic resilience and allostasis
  - Function tests (OGGT)
  - Pregnancy
  - Metabolic syndrome
- **Inflammation and resolution**
  - SIRS/CARS
  - Specialized pro-resolving mediators (SPMs)
  - LCPω3 and disease
  - **Selenium and infection**
- Conclusions

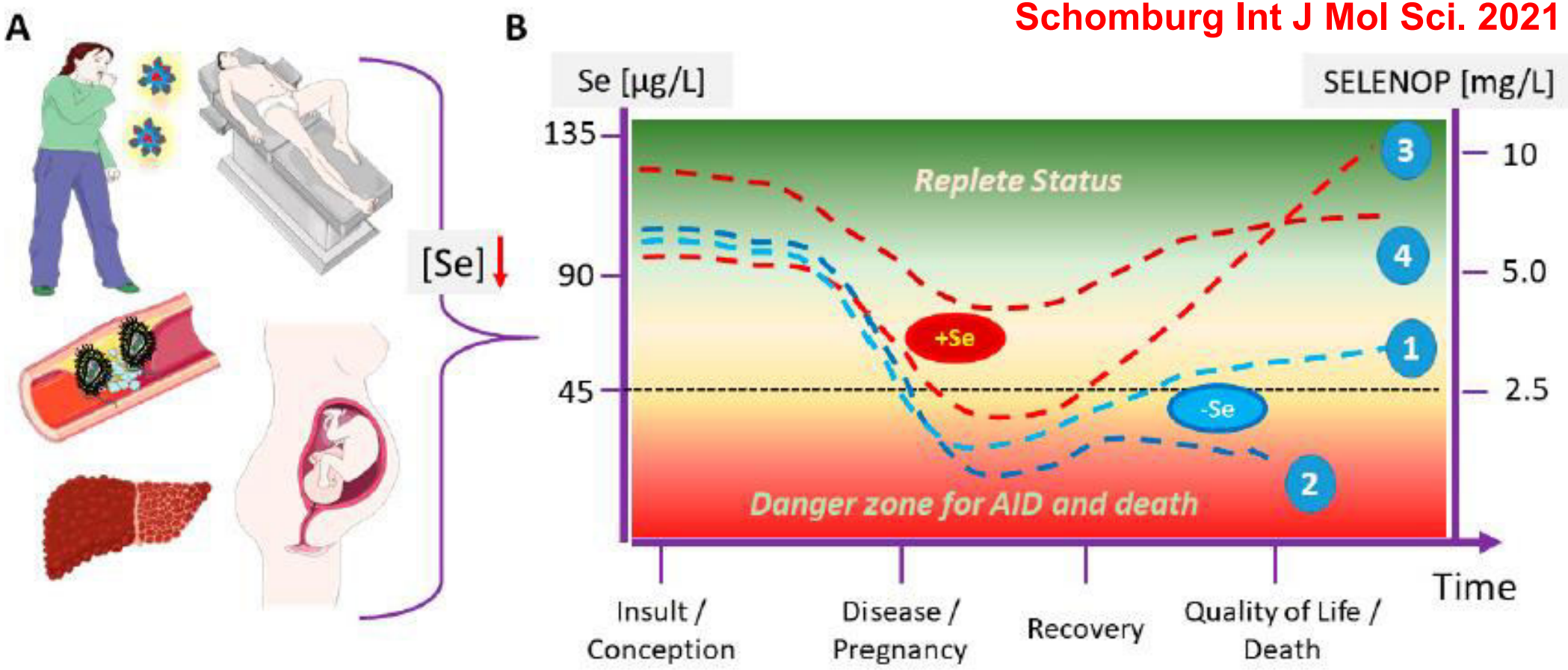
Relationships between good and poor nutrition, immunity and infection.



Calder Nutr Diabetes. 2021

Hypothesis: Se decline into a critical zone as trigger for immune system failure, Autoimmune Disease (AID) or even death

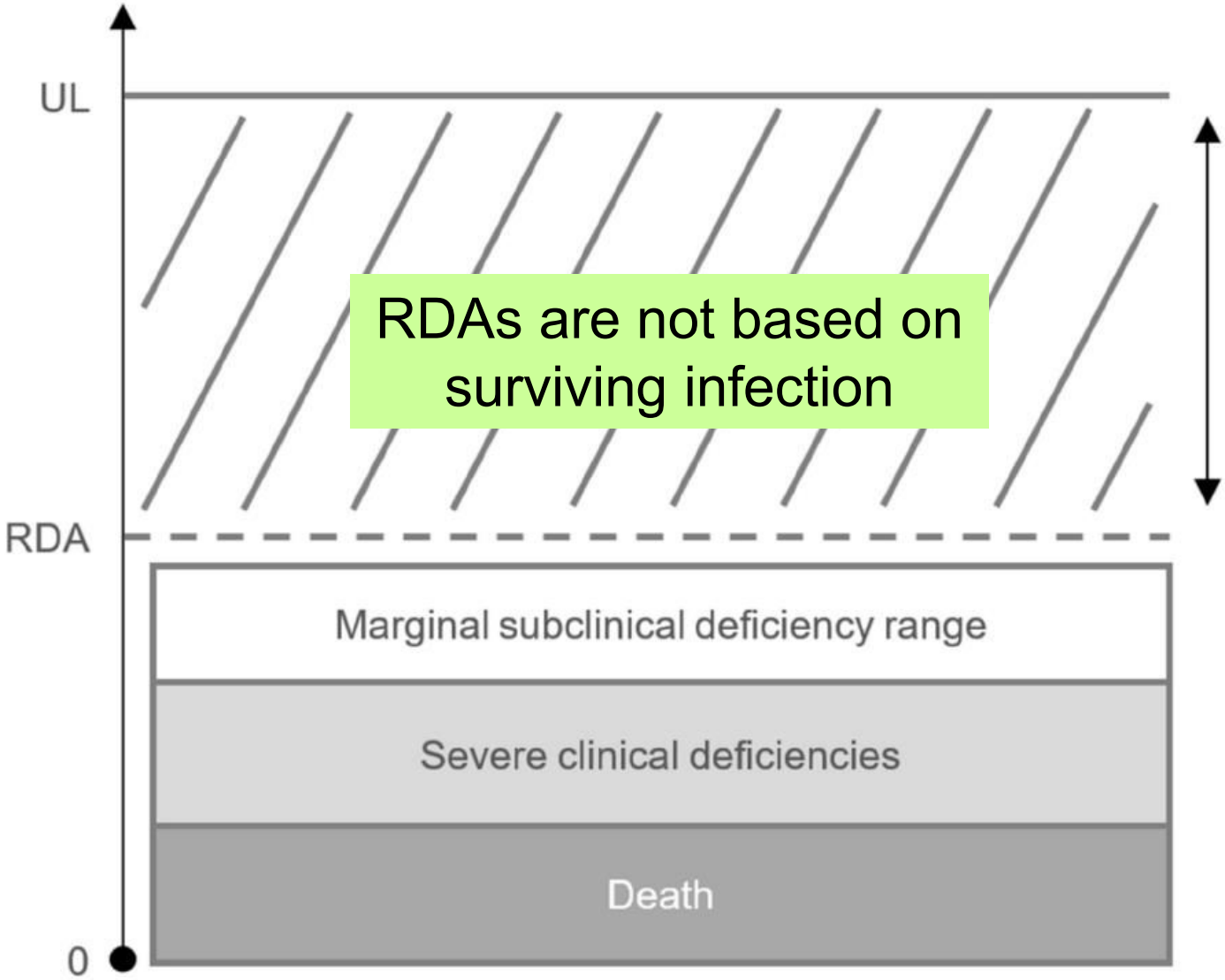
Schomburg Int J Mol Sci. 2021



(A) Bacterial or viral infections, acute or chronic illness, AID, surgery, liver disease, or pregnancy are associated with a vicious cycle of inflammation, increasing cytokine levels and decreasing Se status. During and following to these conditions, AID may develop.

(B) A disease-related drop in Se status below a certain threshold into a critical concentration range ("danger zone") impairs regular immune system function and potentially disrupts self-tolerance, leading to AID. (1) Under regular conditions, disease-associated Se decline is transient, recovering with time. (2) Fatal disease course is associated with strong Se status decline and lack of its recovery. (3) Supplemental Se (+Se) reduces both the Se trough and time spent in severe deficiency, thereby likely improving odds of convalescence. (4) The risk for dropping into the danger zone of severe Se deficiency and immune system failure can be reduced by early Se supplementation, **thereby starting on a sufficiently high status**, ideally in combination with adequate and avoid side effects, i.e., to substitute what is needed without supplementing beyond requirement.

For optimal immune protection and resistance to infection, daily intakes may need to be much higher than the RDAs



Conditions of increased requirements: e.g., infection, stress, and pollution

The immune system needs multiple specific micronutrients, including vitamins A, D, C, E, B6, and B12, folate, zinc, iron, copper, and selenium, which play vital, often synergistic roles at every stage of the immune response.

Gombart Nutrients 2020

Invloed van voeding op zelfherstellend vermogen

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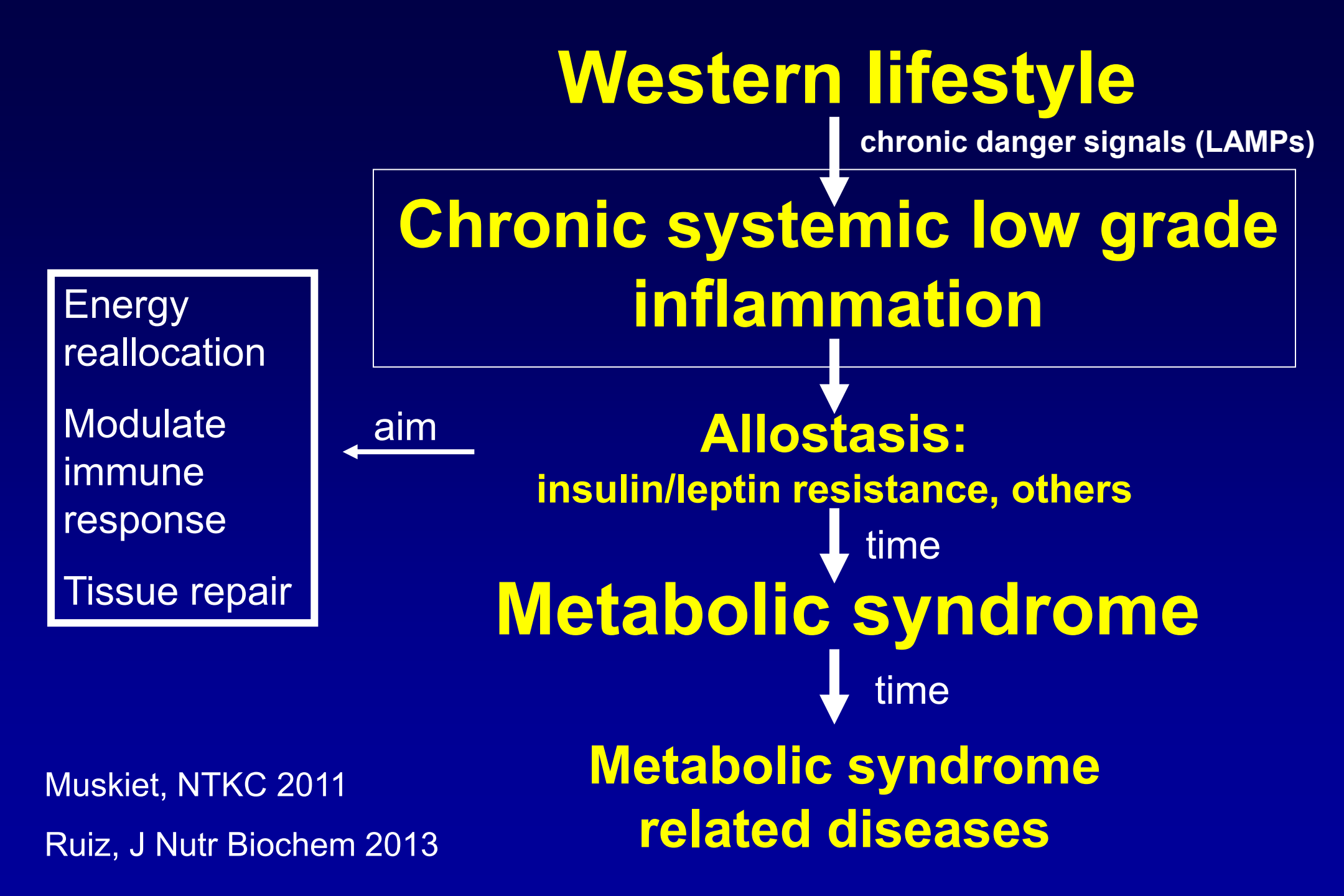
  - LCPω3 and disease
  - Selenium and infection
- **Conclusions**


Western lifestyle
chronic danger signals (LAMPs)
Chronic systemic low grade inflammation
Energy reallocation
Modulate immune response
Tissue repair
aim
Allostasis:
insulin/leptin resistance, others
time
Metabolic syndrome
time
Metabolic syndrome related diseases
Muskiet, NTKC 2011
Ruiz, J Nutr Biochem 2013

Voeding is preventie.
Pas bij een trigger
(infectie, MI, hersentrauma, etc)
worden tekorten duidelijk:
het lichaam kan dan niet adequaat reageren.
Er is dan geen veerkracht

The end