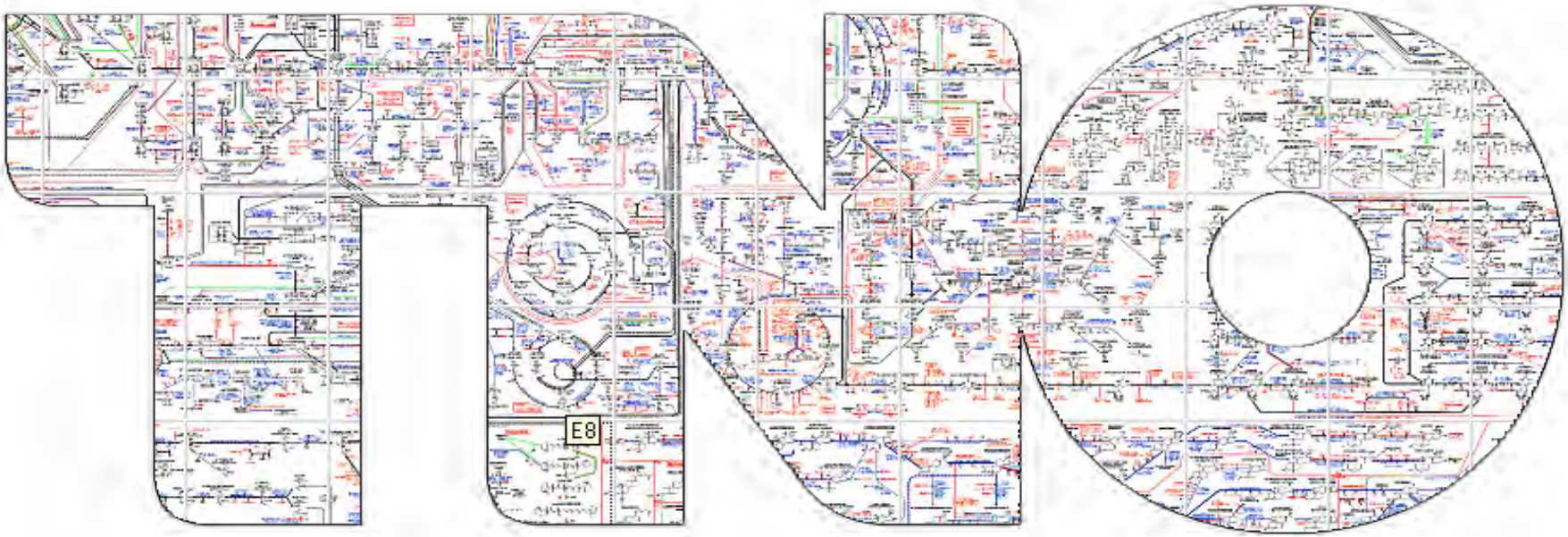
Nutrition and Health

Challenges and gaps in research methodology

Ben van Ommen



What is a healthy diet?

Calories In V. Out

THIS WEEK DAILY AVG.

MON	TUE	WED	THU	FRI	SAT	SUN
IN THE ZONE	UNDER	UNDER	UNDER			

PAST 2 WEEKS

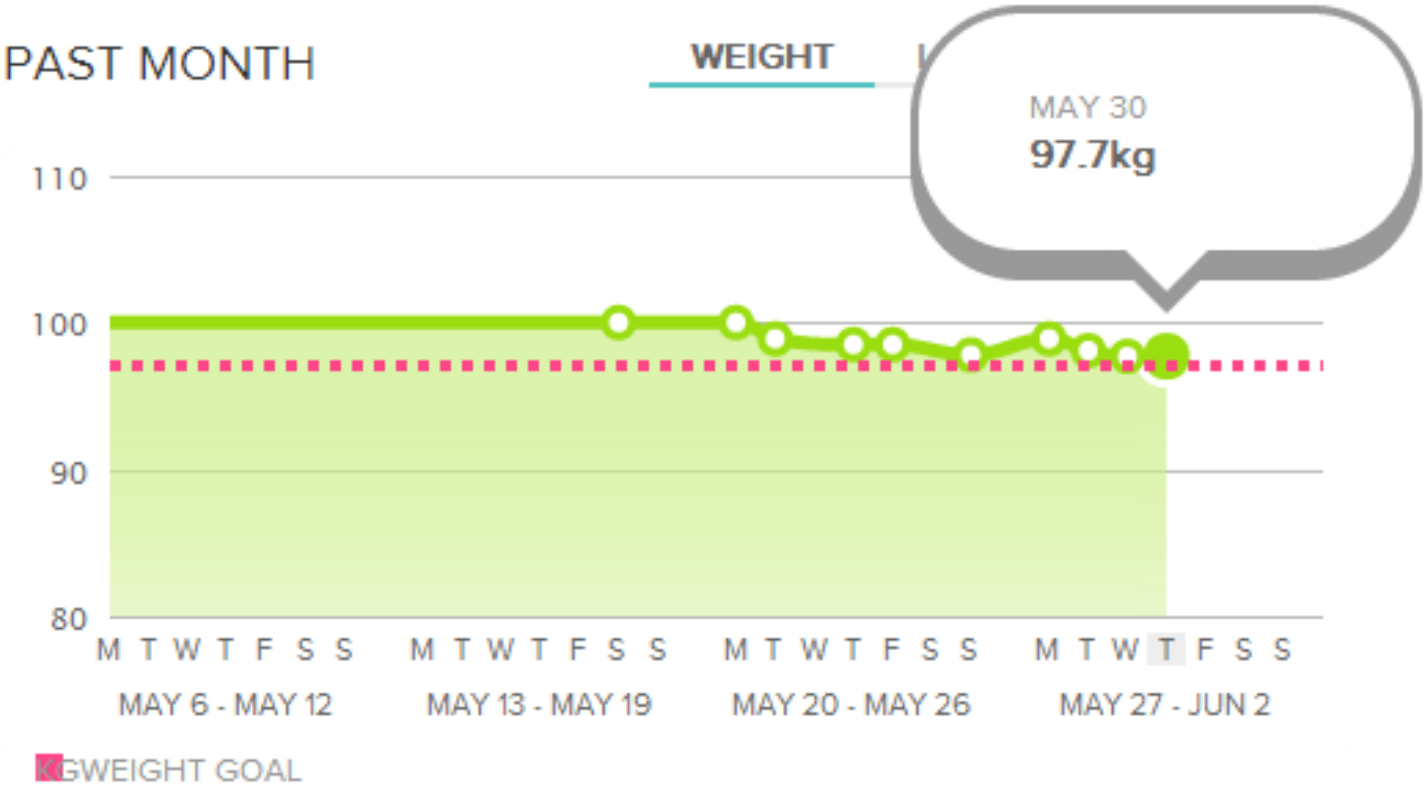
Daily avg. eaten: 2292 burned: 2913

Weight / kg

RECENT

WEIGHT **97.7**kg**0**kg (0% fat)BMI **28.55**

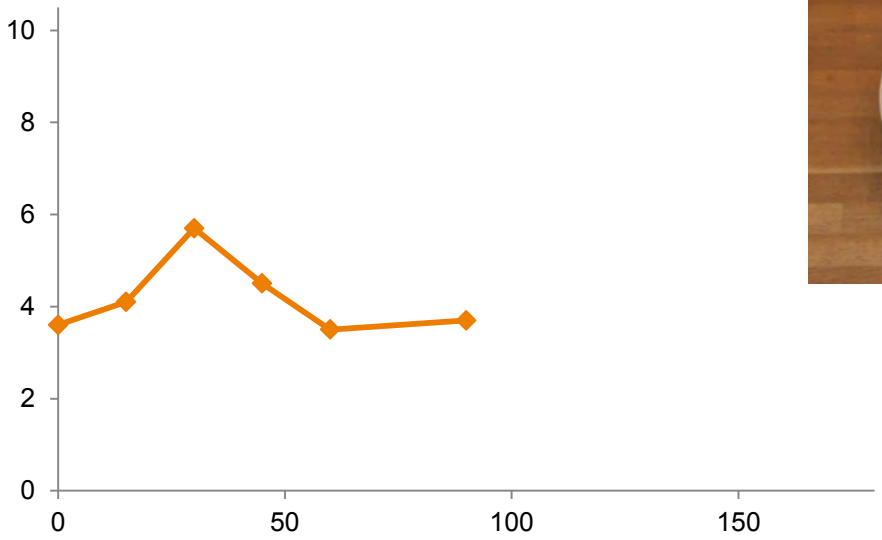
PAST MONTH




COFFEE

My normal breakfast

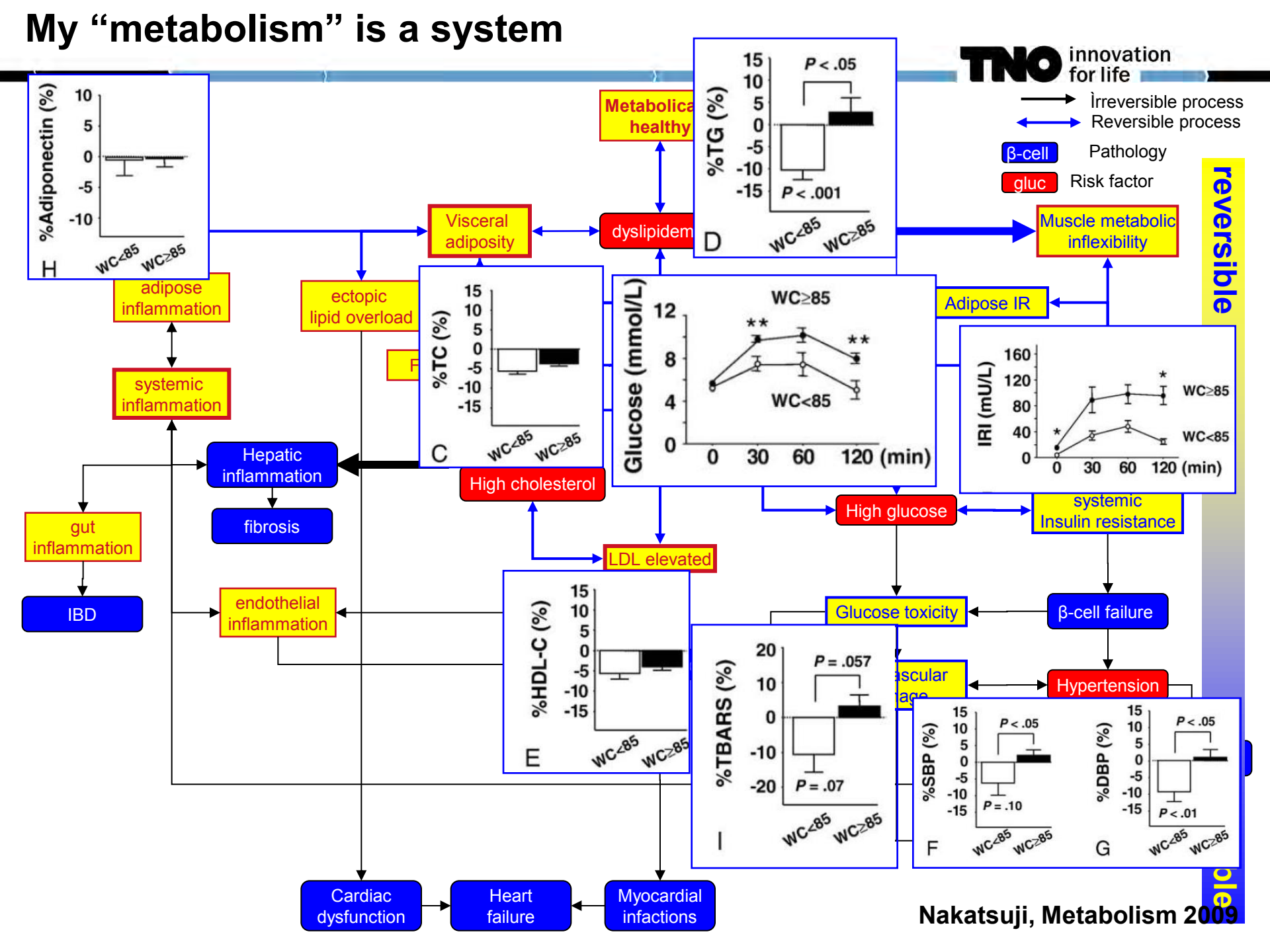
Biscuit, “hagelslag”, espresso, milk



content	Amount (g)
Carbohydrate	
glucose	
Lipids	
SFA	
MUFA	
PUFA	
Protein	
Energy	

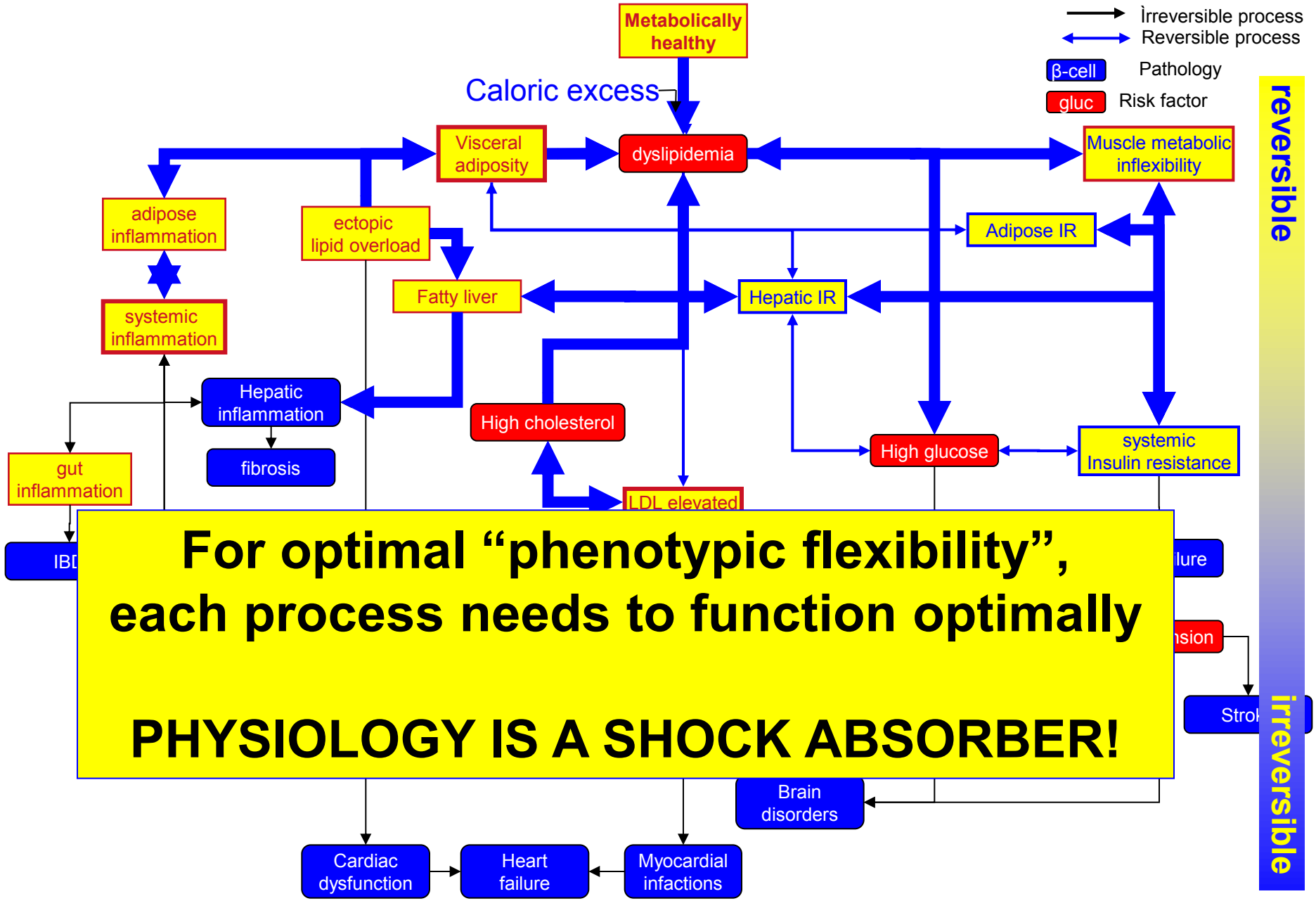
T(max) 45 min
C(max) 5,7 mM

My “metabolism” is a system



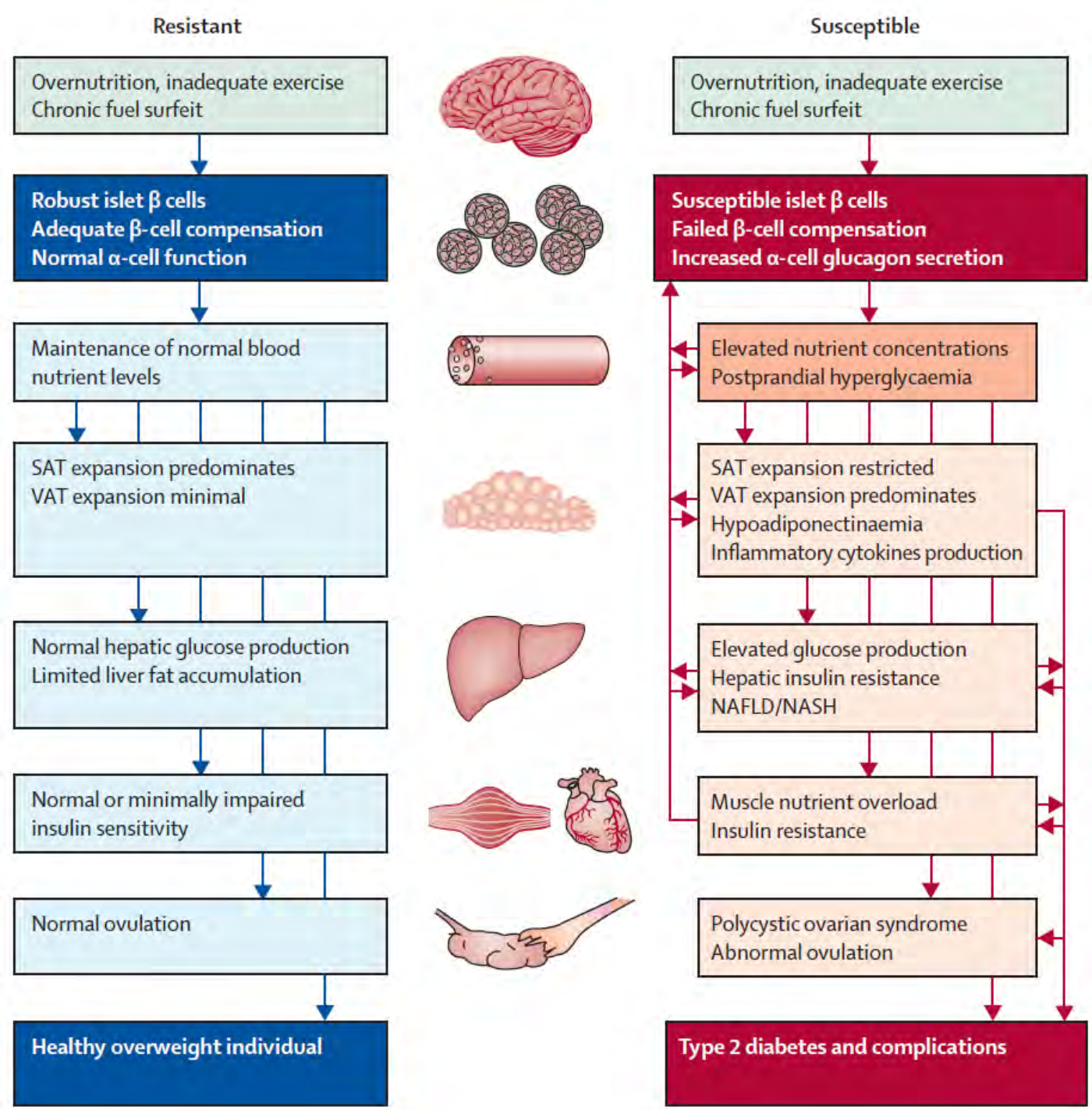
Nakatsuji, Metabolism 2009

Systems flexibility is the key!



For optimal "phenotypic flexibility", each process needs to function optimally

PHYSIOLOGY IS A SHOCK ABSORBER!



TNO innovation for life

Each organ has its own characteristics in maintaining / loosing flexibility and this determines health→diabetes transition

Nolan, Lancet 2011

Gut
- Host-microbe interaction
- Absorption, intestinal integrity, barrier function
- Gut-mediated inflammation control
- Chylomicron production

Kidney
•(re)absorptionn
•urea cycle
•Tissue injury

Brain
•Gut-Brain axis
•Endocrine responses
•HPA axis

Liver
•Adaptation carb/lipid switch
•Oxidative stress
•ER stress
•Tissue injury
•Fibrosis
•Toxicity
•Insulin sensitivity

Diagnosis assay: quantify the stress response

(OGTT, OLTT, etc)

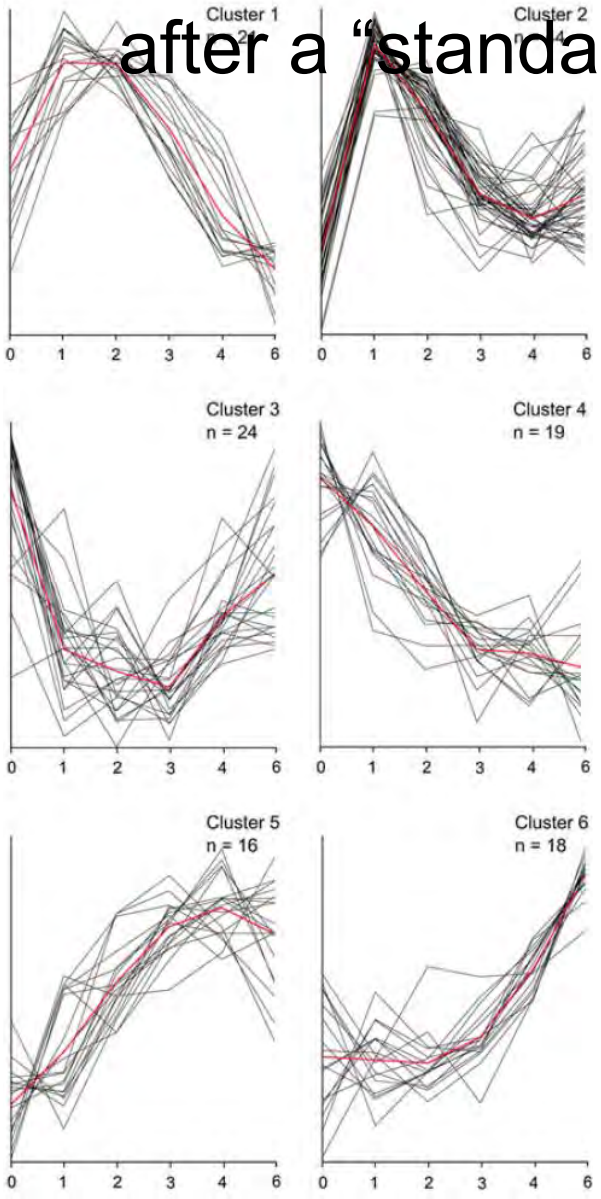
Adipose tissue
•Lipoprotein metabolism
•Lipid metabolism
•Energy metabolism
•Macrophage infiltration
•NEFA
•Expandibility
•Lipokine/Adipokine production
•Insulin sensitivity

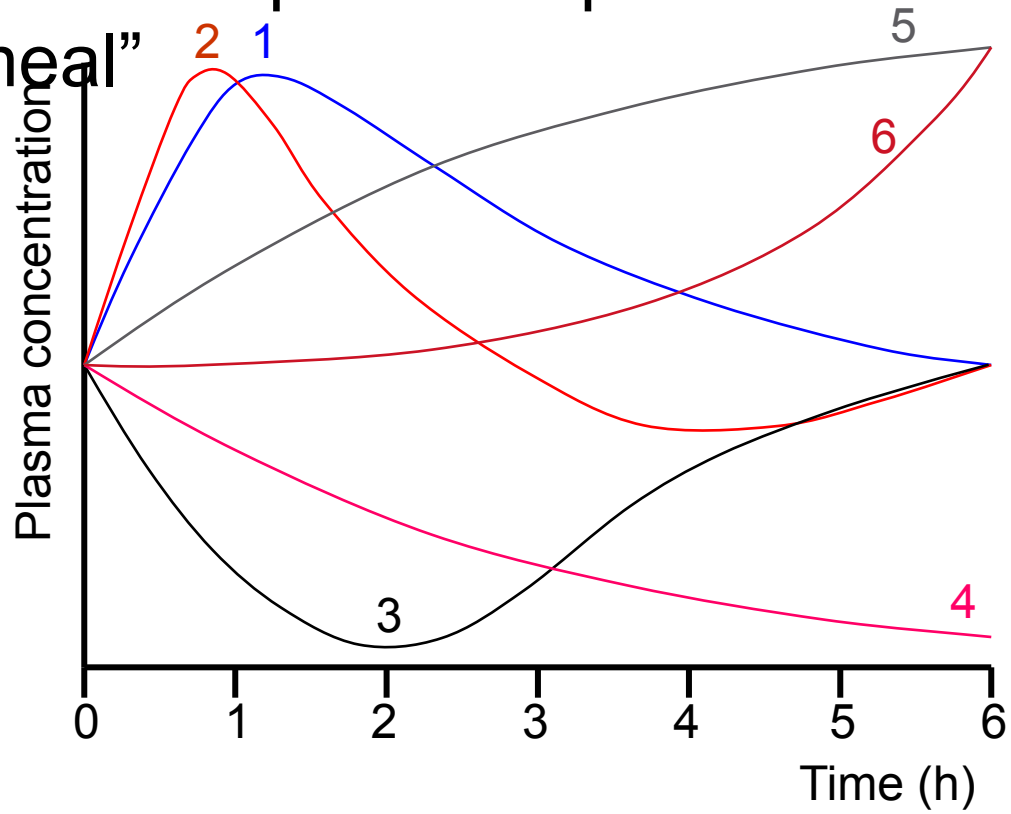
Muscle
•Protein metabolism
•Oxidative stress
•ER stress
•Tissue injury
•Energy metabolism
•Insulin sensitivity

Vasculature
•NO metabolism
•chronic low-grade inflammation
•Endothelial flexibility/integrity
•Reversibility of inflammation
•Microvascular damage
•Lipid droplet formation
•Arterial stiffness

Pancreas
•Systemic insulin sensitivity
•b-cell failure

320 metabolites and 1270 proteins quantified after a "standard meal"





Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status

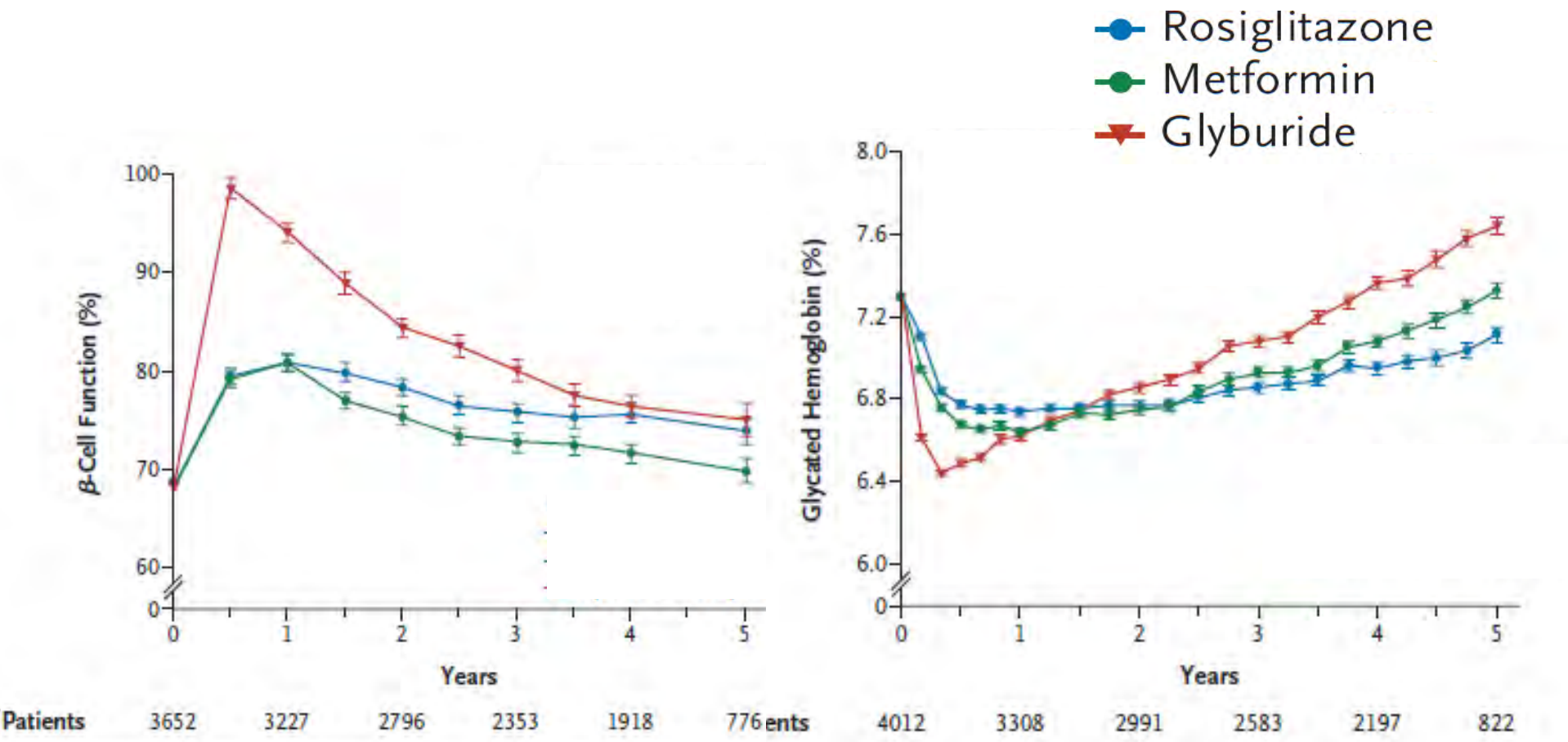
Linette Pellis · Marjan J. van Erk · Ben van Ommen · Gertruud C. M. Bakker · Henk F. J. Hendriks · Nicole H. P. Cnubben · Robert Kleemann · Eugene P. van Someren · Ivana Bobeldijk · Carina M. Rubingh · Suzan Wopereis

Metabolomics

Received: 31 March 2011 / Accepted: 12 May 2011

Important processes in T2D	Diagnosis	Potential interventions
1.Pancreatic β-cell function (impaired insulin secretion)	*OGTT: I/ΔG and DI(0) *PYY, Arg, His, Phe, Val, Leu	Lifestyle; β-cell protective nutrients (MUFA/isoflavonoids); β -cell protective medication (TZDs, GLP-1 analogs, DPP4-inhibitors)
2.Muscle insulin resistance (decreased glucose uptake)	*OGTT: Muscle insulin resistance index, Insulin secretion/insulin resistance index *Val, Ile, Leu, Gamma-glutamylderivates, Tyr, Phe, Met	PUFA/SFA balance; Physical activity; Weight loss; TZDs (e.g.PPARγ)
3.Hepatic insulin resistance (decreased glucose uptake and increased hepatic glucose production-HGP)	*Hepatic insulin resistance index *OGTT: Hepatic insulin sensitivity index *ALAT, ASAT, bilirubine, GGT, ALP, ck-18 fragments, lactate, α-hydroxybutyrate, β-hydroxybutyrate	Decrease SFA and n-6 PUFA, and increase n-3 PUFA; Weight loss; Metformin; TZDs; Exenatide (GLP-1 analog); DPP4 inhibitors
4. Adipocyte insulin resistance and lipotoxicity	*basal adipocyte insulin resistance index *FFA platform, glycerol	α-lipoic acid; PUFA/SFA balance; Omega 3 fatty acids; Chitosan/plantsterols; TZDs; Acipimox
5. GI tract (incretin deficiency/resistance)	*ivGTT vs OGTT *GLP-1, GIP, glucagon, galzuren	MUFA; Dietary fibre (pasta/rye bread); Exenatide
6. Pancreatic α-cell (hyperglucagonemia)	*fasting plasma glucagon	Glucagon receptor antagonists; Exenatide; DPP4 inhibitors
7A.Chronic low-grade inflammation in pancreas, muscle, liver, adipose tissue, hypothalamus 7B. Vascular inflammation	*CRP, total leucocytes * V-CAM, I-CAM, Oxylipids, cytokines	Fish oil/n-3 fatty acids; Vit. C/Vit. E/Carotenoids; Salicylates; TNF-α inhibitors and others

The 5-year efficacy of diabetes type 2 treatment



Kahn, NEJM 2006

The power of observational science …

Current disease management model of thinking

disease = the war against

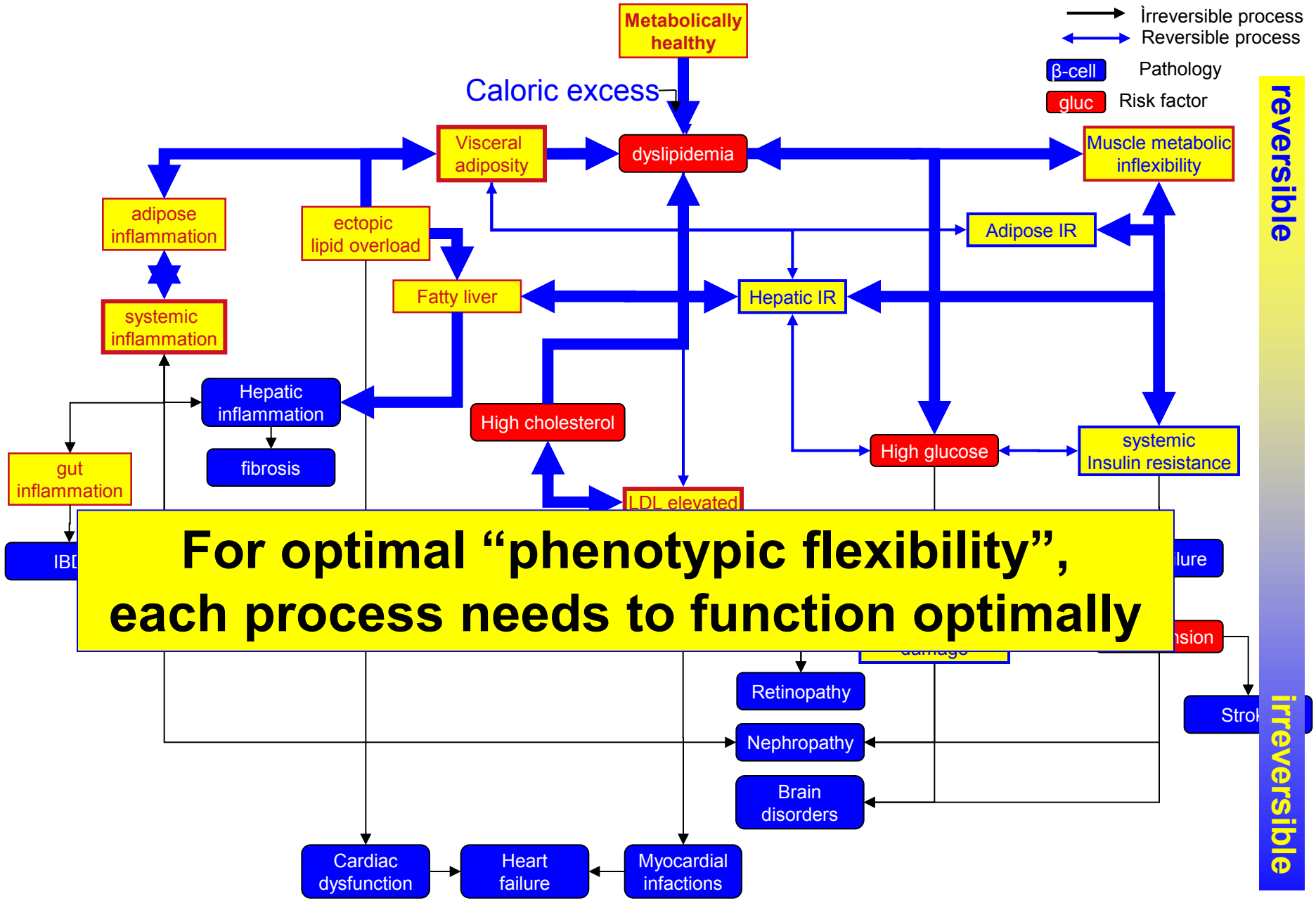
- anti-hypertensive's, anti-inflammatory agents, anti-biotic's, anti-viral agents, anti-cholinergic's, anti-epileptics, anti-mycotic's, anti-psychotics

- proton pump-inhibitors, ACE--inhibitors, TNF-alpha--inhibitors, selective-serotonin-reuptake--inhibitors, prostaglandin-synthetase-inhibitors, alfa-1-proteinase--inhibitors

- angiotensin-II-blockers, beta-blockers, tumor angiogenesis-blockers, interleukin-5-blockers, etc.

adapted after Ton Nicolai

Systems flexibility is the key!



TNO innovation for life

...h organ has its ...rocesses ...olic

GUT

Relev
- Enter "meta
- Gut-b regula barrie
- Gut-m
- Chylo

Relev
- Bile a
- Barrie camp
- Gut m (aceta
- 'Incre Ghrel
- Lipop
- LPS i
- Meta

LIVER

Releva
- Rever
- Insulin contro
- Energ
- Inflam
- Adipo
- Toxici

Relev
- Core oxidat metab plasm
- Lipop partic sterol
- Acute fibrinc
- ALAT,
- CLAM

ADIPOSE

Relevant
- Reversibil
- Expandab hypertrophl
- Inflammat
- Insulin ser
- Lipokine p
- Pediatric (

Relevant
- Free fatty activity in
- adiponect plasma
- Crown like enzyme a tissue biop
- Cytokine a adipose ti
- CLAMP a
- Body com

MUSCLE

Relevant
- Lipotoxic ceramide insulin)
- Protein r
- Metaboli muscle r oxidative
- Heart mu

Relevan
- Cerami
- Creatin
- Branch
- Carnitir
- Glycoge
- Muscle
- Extrace plasma
- CLAMF

VASCULAR SYSTEM

Releva
- Revers
- Oxidati damag
- Choles atheros
- Lipopro
- Endoth

Releva
- Lipopro
- Plaque
- E-sele
- Blood
- ROS fo sulfoxi
- comple
- coagul
- kinin sy
- MMPs
- glycosy
- BNP (b

SYSTEMIC INFLAMMATION

Relevar
- Lipotoxi
- Macrop
- Inflamm
- Resilien
- Chronic
- Resolut
- Nutrient

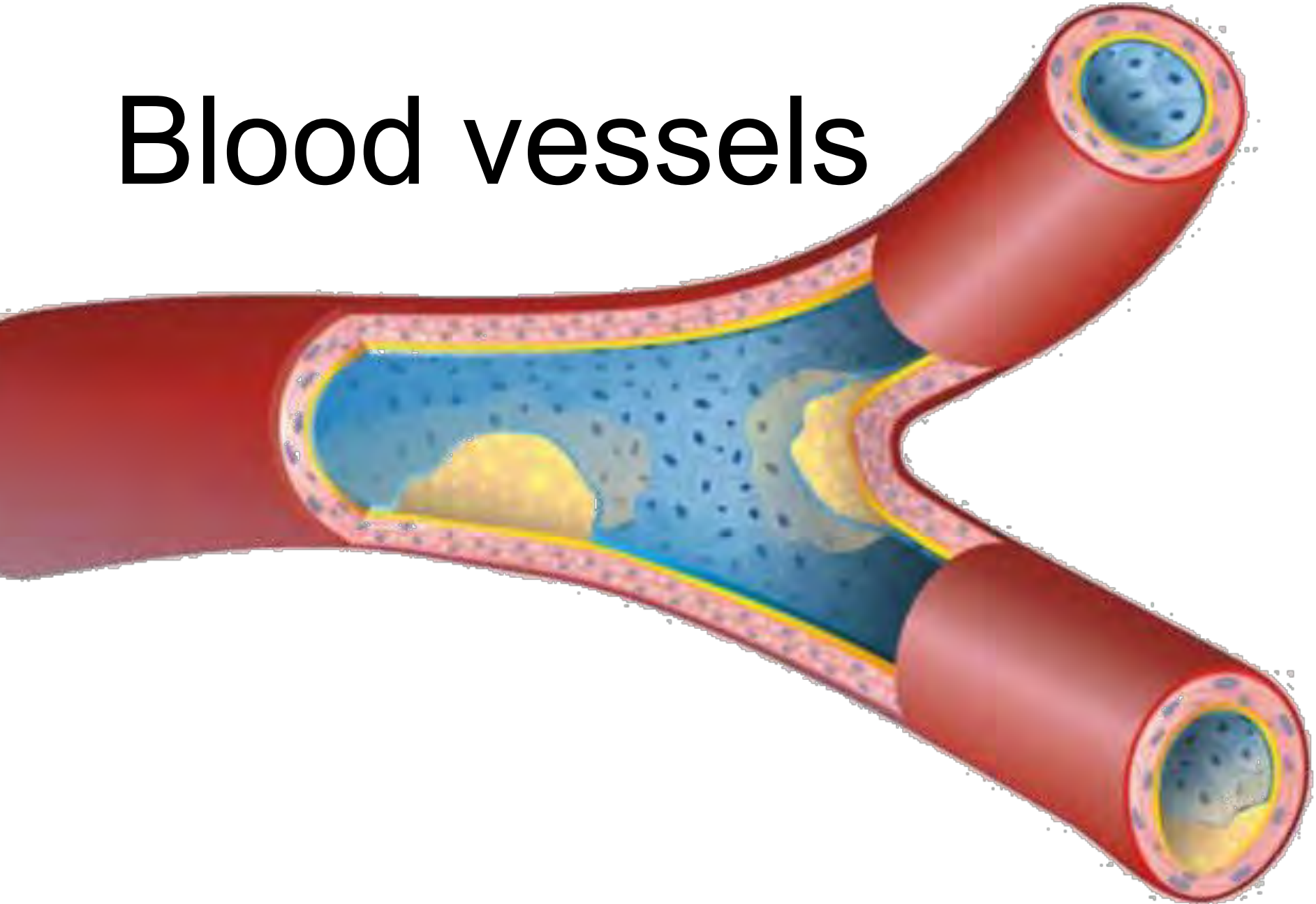
Relevar
- Bile aci
- Barrier campes
- Gut mic (acetate
- 'Incretin Ghrelin
- Lipopro
- LPS in
- Metage

SYSTEMIC PROCESSES

Relevant processes
- Signalling in metabolic adaptive control
- Gut-Brain axis
- HPA axis
- Endocrine & pancreas response
- Lipid metabolism
- Inflammation in acute&chronic phase
- Metabolic flexibility

Relevant analysis
- Lipid enzyme activities in plasma
- Oxylipids, cytokines and chemokines in plasma challenge test response
- Endocannabinoid, lipokines & 'incretins'
- Cytokines & Chemokines
- Carb vs fat oxidation switch
- Activity hypothalamus (scan)
- Parasympatic activity (HRV)
- OGTT with metabolic profiling

Blood vessels



In human studies, we quantify ~120 plasma inflammation related proteins

Monocytes
- MMP9

Macrophages
- TNFα
- IL1ß
- platelet derived growth factor
- IFNγ
- MMP1
- MMP8
- MMP13
- Myeloid Related Protein14
- CD40
- CD40L
- tissue factor

Foam cells
- IL18
- IL18Rα/ß

Endothelial cells
- P-selectin
- VCAM1
- ICAM1
- MCP1/CCL2
- platelet derived growth factor
- CSF1
- NO
- CD40
- CD40L
- tissue factor
- PAI1
- NFκB
- adenine dinucleotide phosphate oxidase
- Cathepsin S

Smooth muscle cells
- collagen
- IFNγ
- IL6
- CD40
- CD40L
- tissue factor
- MCP1/CCL2

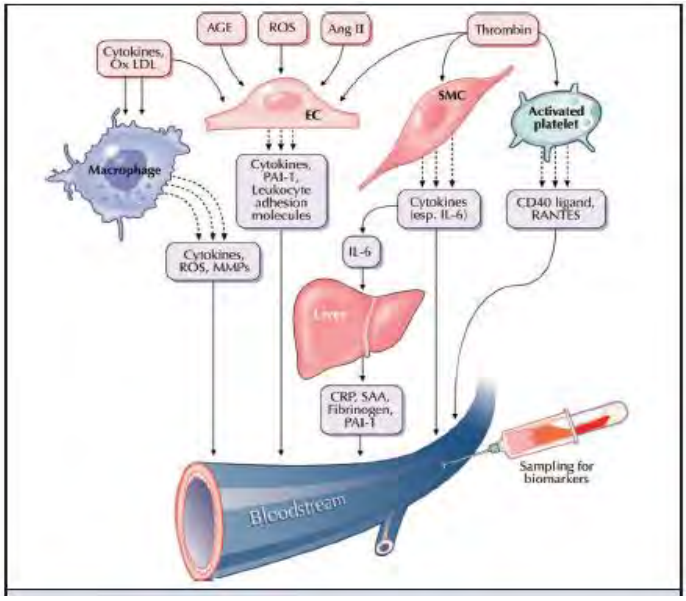
Platelets
- CD40L
- Myeloid Related Protein8
- Myeloid Related Protein14
- platelet derived growth factor
- CD40

T helper 1 cells
- IL1
- sCD40L
- INFγ
- RANTES
- MIF
- CD40

Adipose tissue
- adiponectin
- IL18
- PAI1

HDL
LDL
oxLDL
Thrombin
Factor VII
paraoxonase 1
Angiotensin II
Lipoprotein lipase
Hepatic lipase
MPO
Lipoprotein associated phospholipase A2

Liver
- CRP
- PAI1
- fibrinogen



effect of healthy diet components

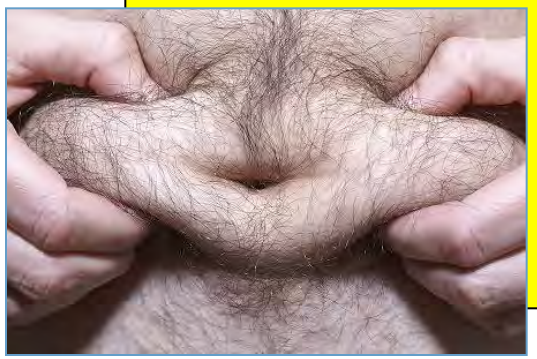
- Supplement mix: based on mediterranean diet, contains resveratrol, vitamin E, vitamin C, tomato extract, green tea extract, fish oil

- Designed to exert effect on different **metabolism, oxidation** and **inflammaton** pathways (based on literature)

- Test in homogeneous group of 35 men at the level of metabolite, protein and transcripts

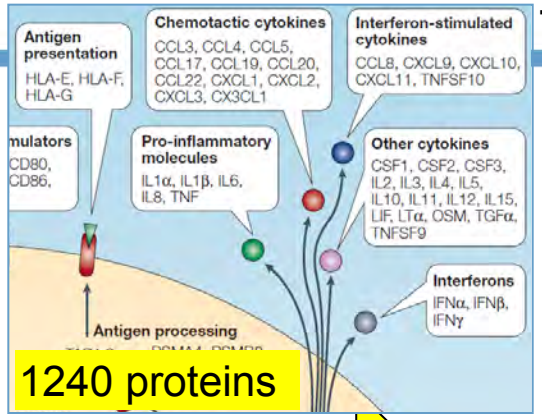
Bakker G, Pellis L, van Erk et al. AJCN 2010

Extensive phenotyping



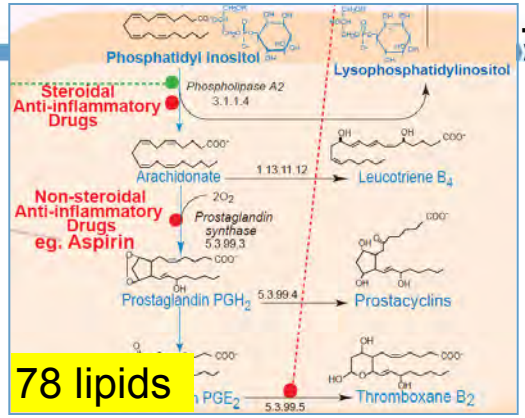
‘omics’ analysis allows quantification of enormous # of parameters

proteome



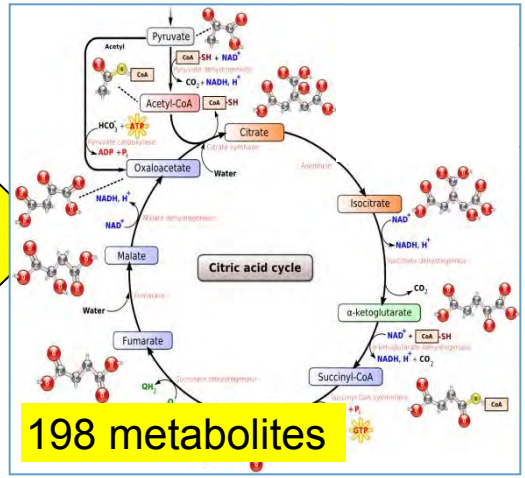
1240 proteins

lipidome



78 lipids

metabolome



198 metabolites

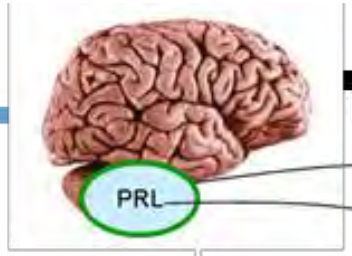
clinical chemistry

~ 30 parameters

transcriptome

11.000 genes

TNO innovation for life



Eicosanoid related inflammation
(but no effect PGE2)

endothelial inflammatory factors

fish oil
↑PUFA

plaque formation / coagulation

ICAM1
VCAM1
TNFR2
VEGFB
PEAR1
F7
MYOM1
IGHV3-47
B2M
IL18BP
IGHD
IL18
IL4R
CCL21
IL12A
inosine
CCL22
PF4
PTGIS
PGDS
HPGD
TLR7
DPP4
PTGFRN
SELP
THBD
IL10RA
SMOC2
ANGPTL5
SOCS3
IL8RB
IL7R
KLRG1
TESC
HBB
NKTR
HBM
Adiponectin
PPBP
F10
PROCR
NAPG
ALAS2
IL15
FGF10
EDG2
PPARγ

Protective against atherosclerosis ?

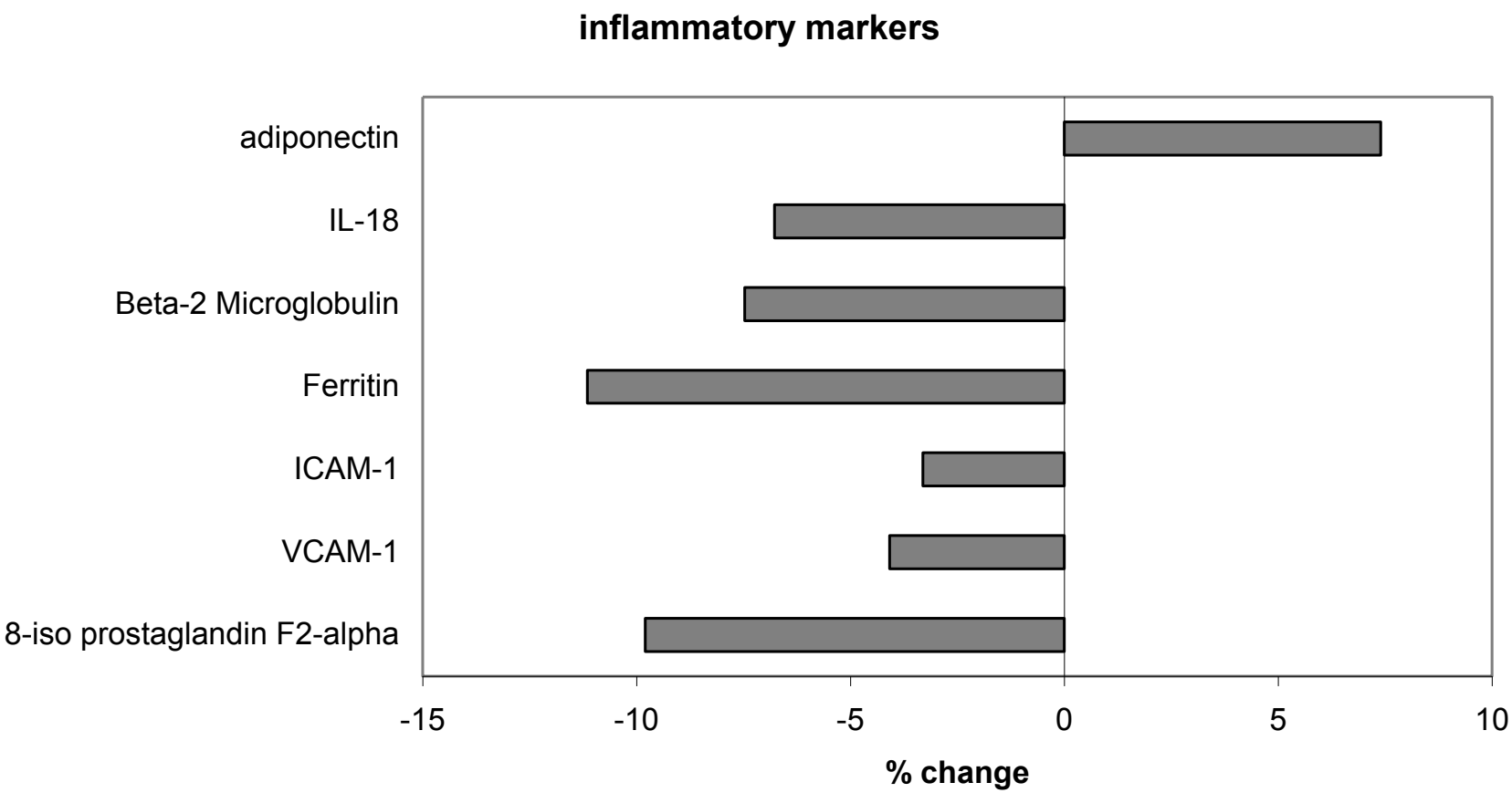
Pro-inflammatory
Anti-inflammatory
Anti-atherogenic
coagulation
blood cell differentiation
stimulate
inhibit
up
down
receptor
enzyme

increased expr prostaglandin metabolism genes in adipose tissue

anti-inflammatory effects in adipose tissue: adiponectin, IL10RA, SOCS3

Bakker, AJCN 2010

Effect on inflammation: part of the Inflammatory profile in plasma

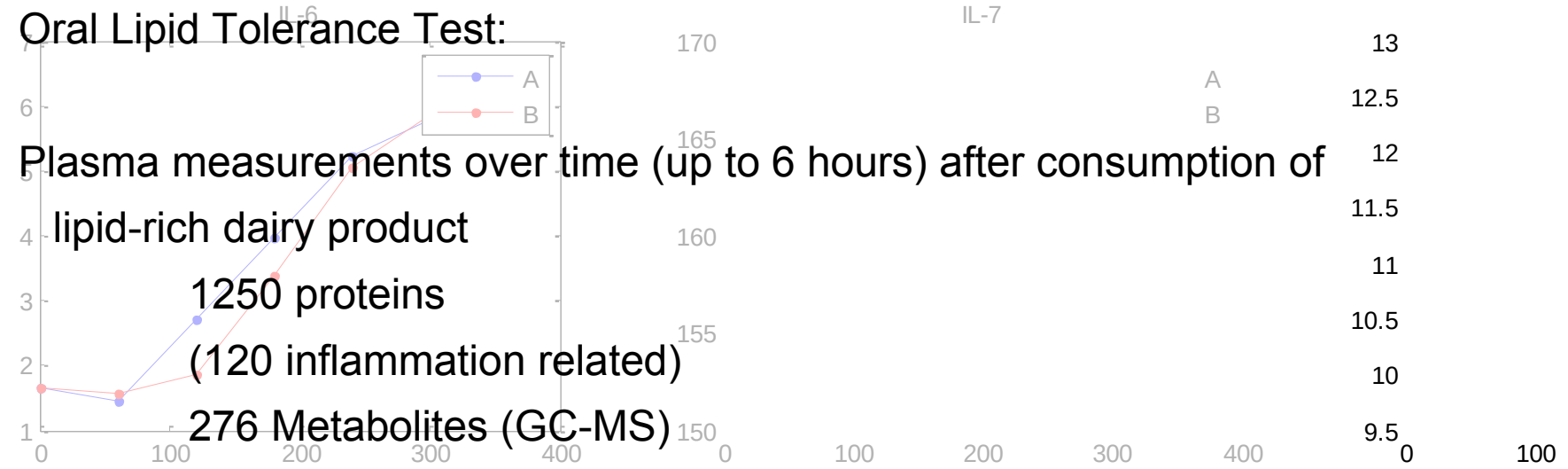


Anti-inflammatory effects of supplement mix
Postprandial challenge

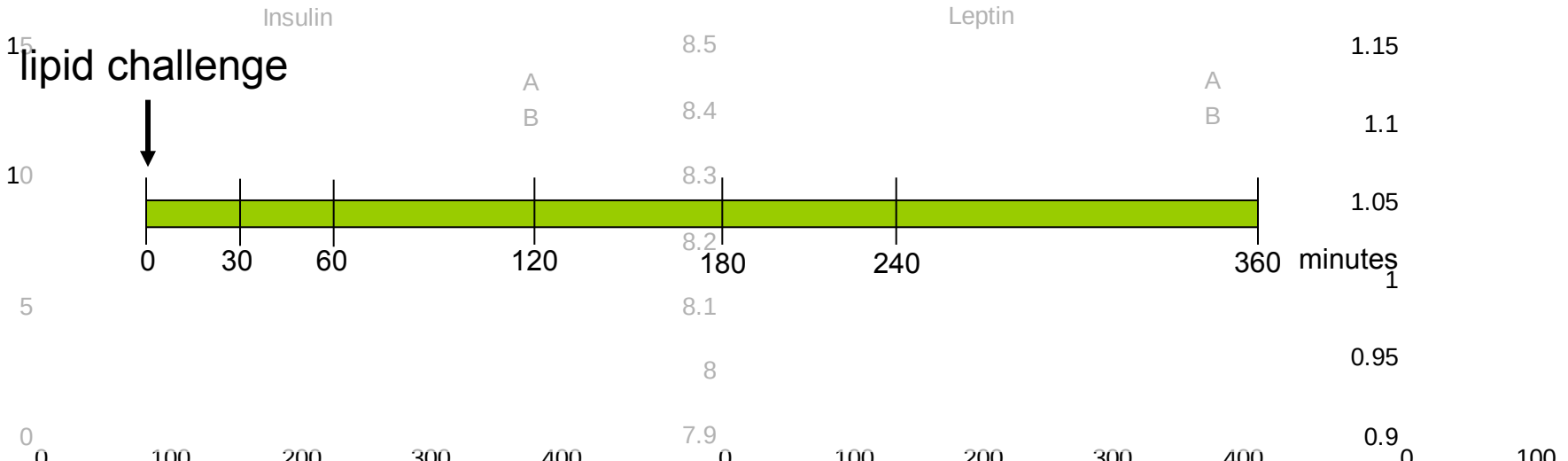
Oral Lipid Tolerance Test:

Plasma measurements over time (up to 6 hours) after consumption of lipid-rich dairy product

- 1250 proteins
- (120 inflammation related)
- 276 Metabolites (GC-MS)

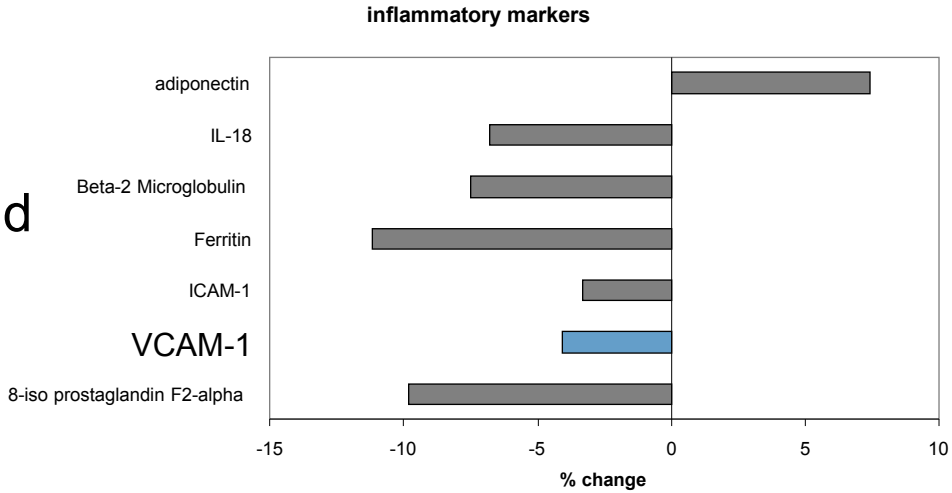


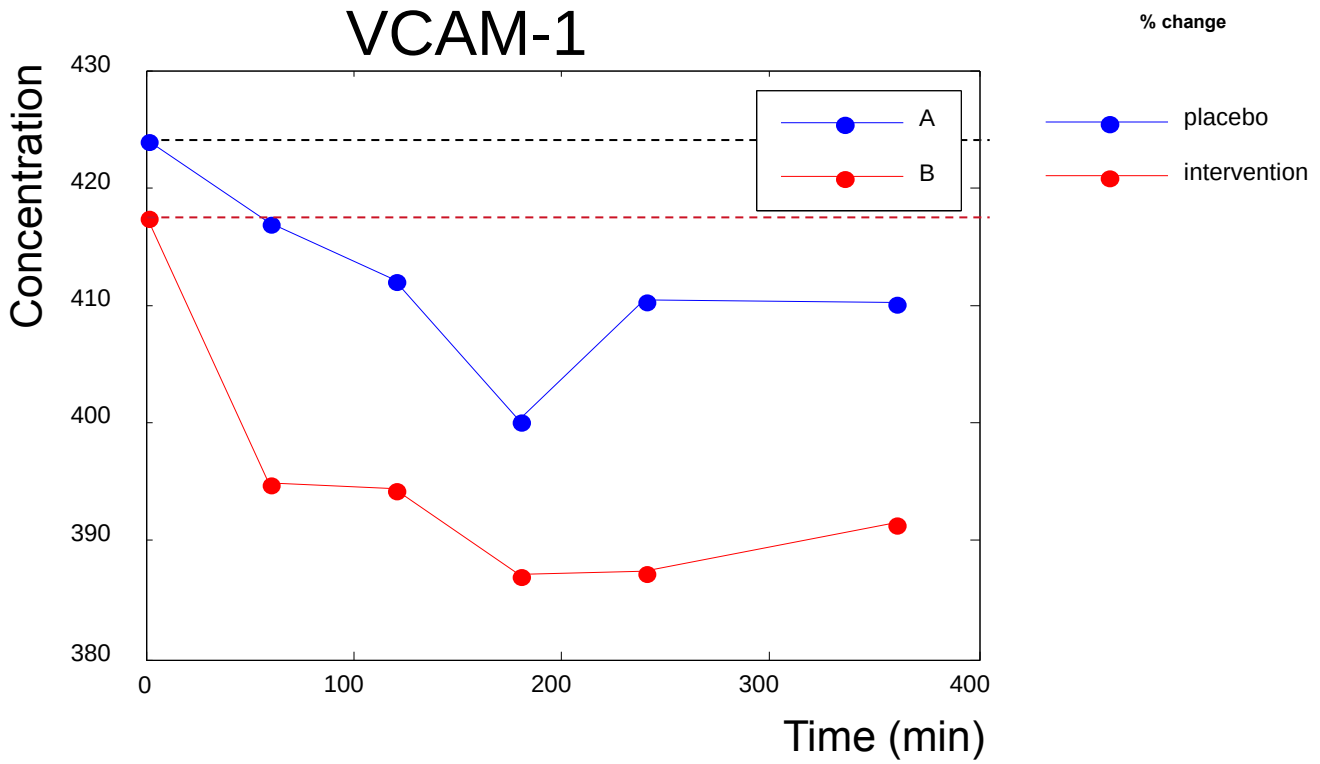
lipid challenge

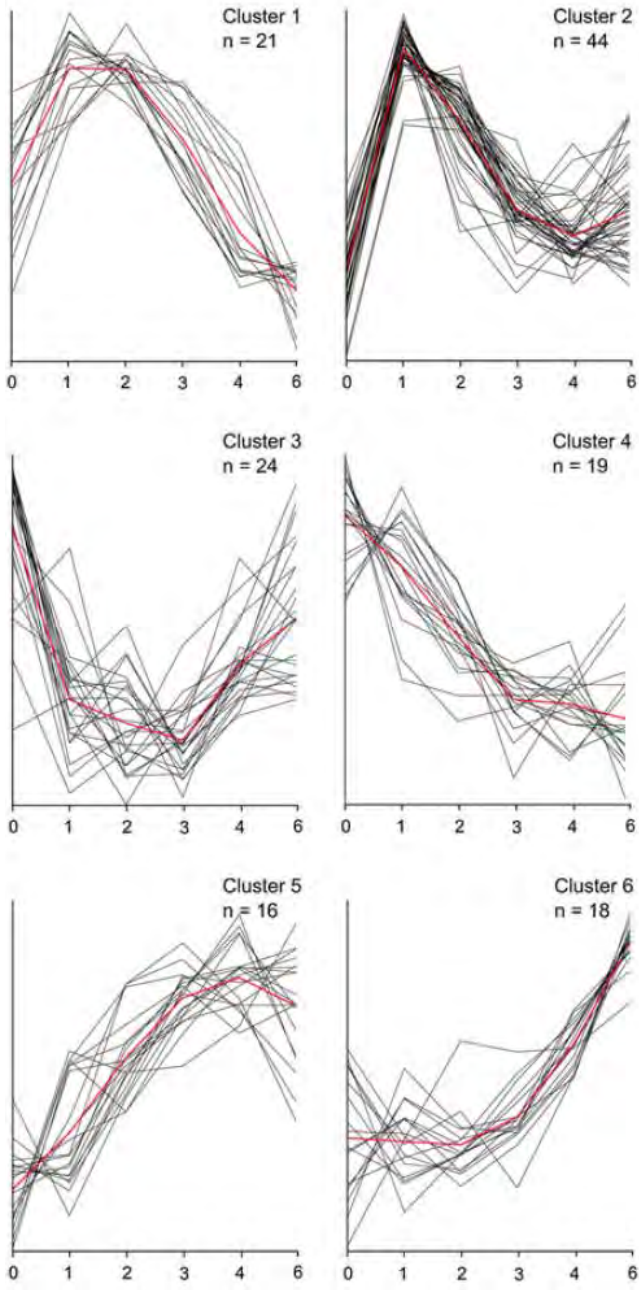


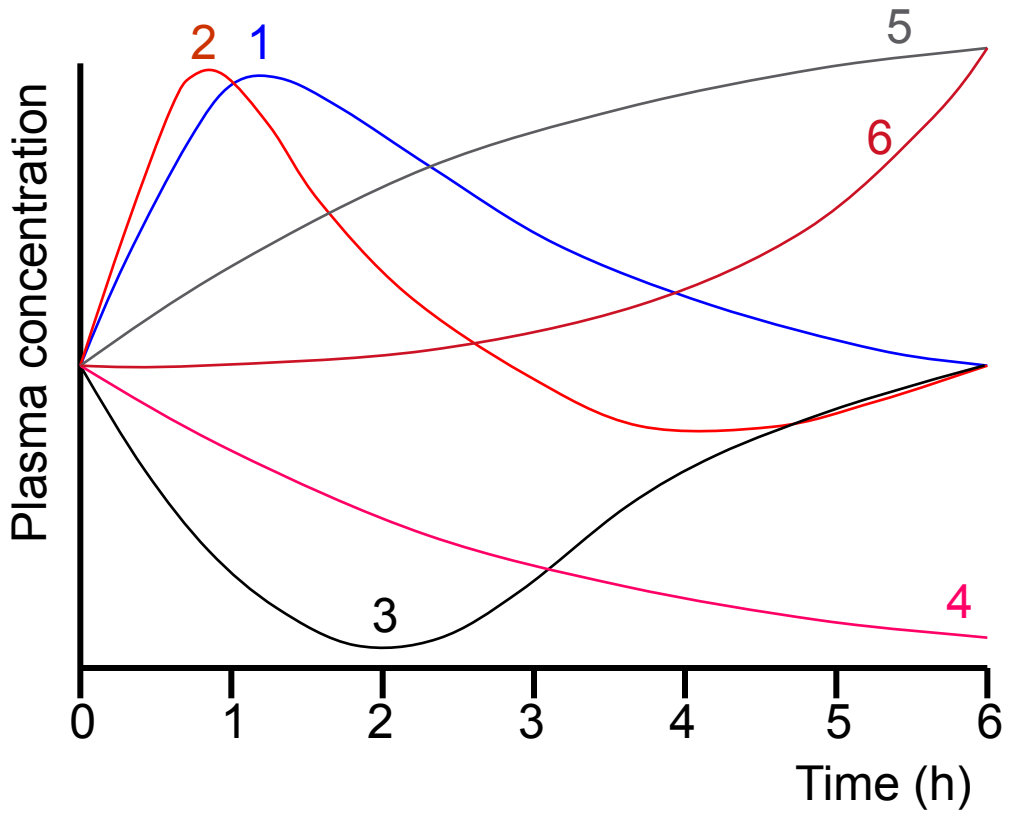
Homeostasis versus perturbation

Inflammation markers at baseline and during an oral lipid tolerance test









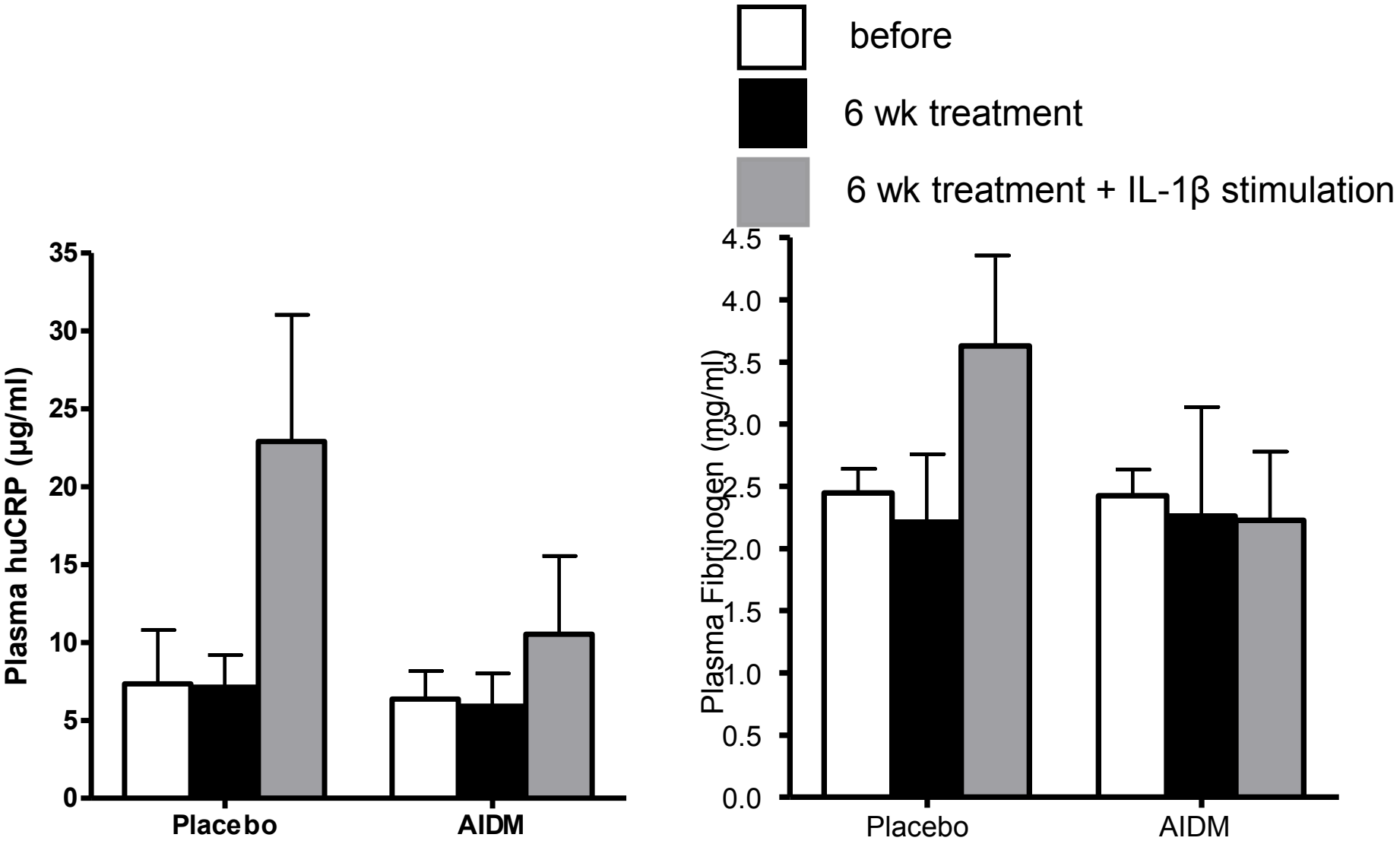
Plasma metabolomics and proteomics profiling after a postprandial challenge reveal subtle diet effects on human metabolic status

Linette Pellis · Marjan J. van Erk · Ben van Ommen · Gertruud C. M. Bakker · Henk F. J. Hendriks · Nicole H. P. Cnubben · Robert Kleemann · Eugene P. van Someren · Ivana Bobeldijk · Carina M. Rubingh · Suzan Wopereis

Metabolomics

Received: 31 March 2011 / Accepted: 12 May 2011

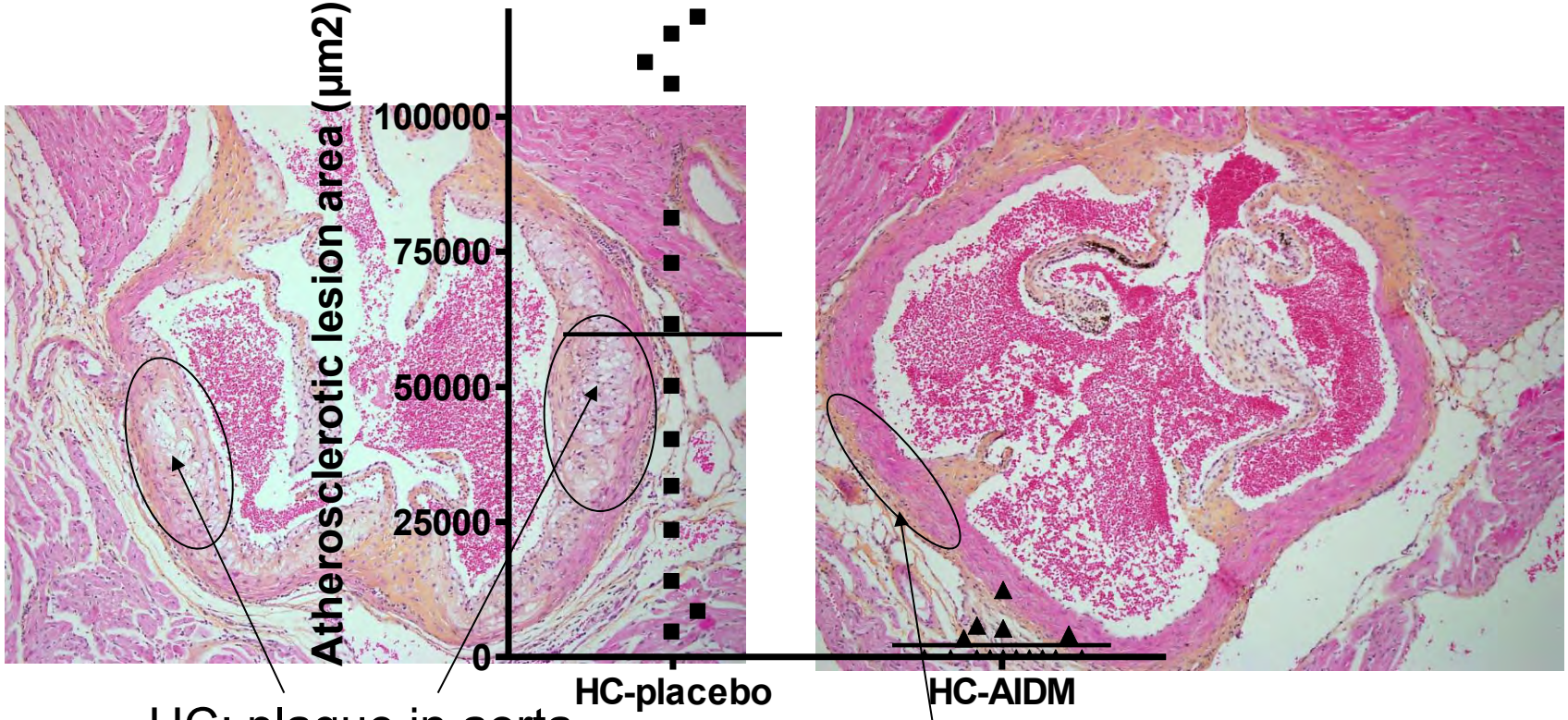
Effect of anti inflammatory diet on inflammation in mice



Verschuren, J Nutr 2011

Effect of anti inflammatory diet on inflammation in mice

- ApoE3L mice on high cholesterol diet develop atherosclerosis
- Supplementation with food mix inhibits atherosclerosis development

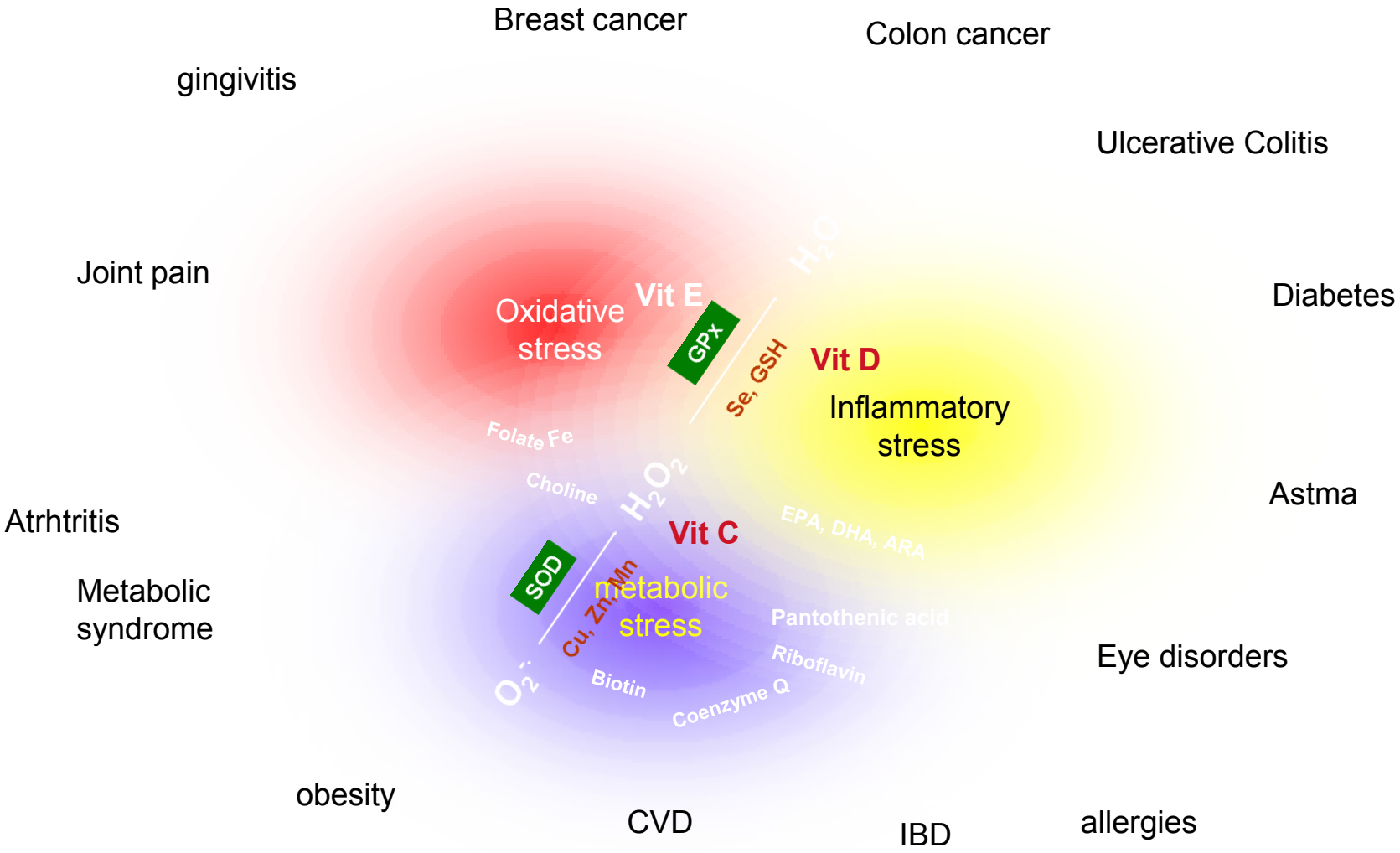


HC: plaque in aorta

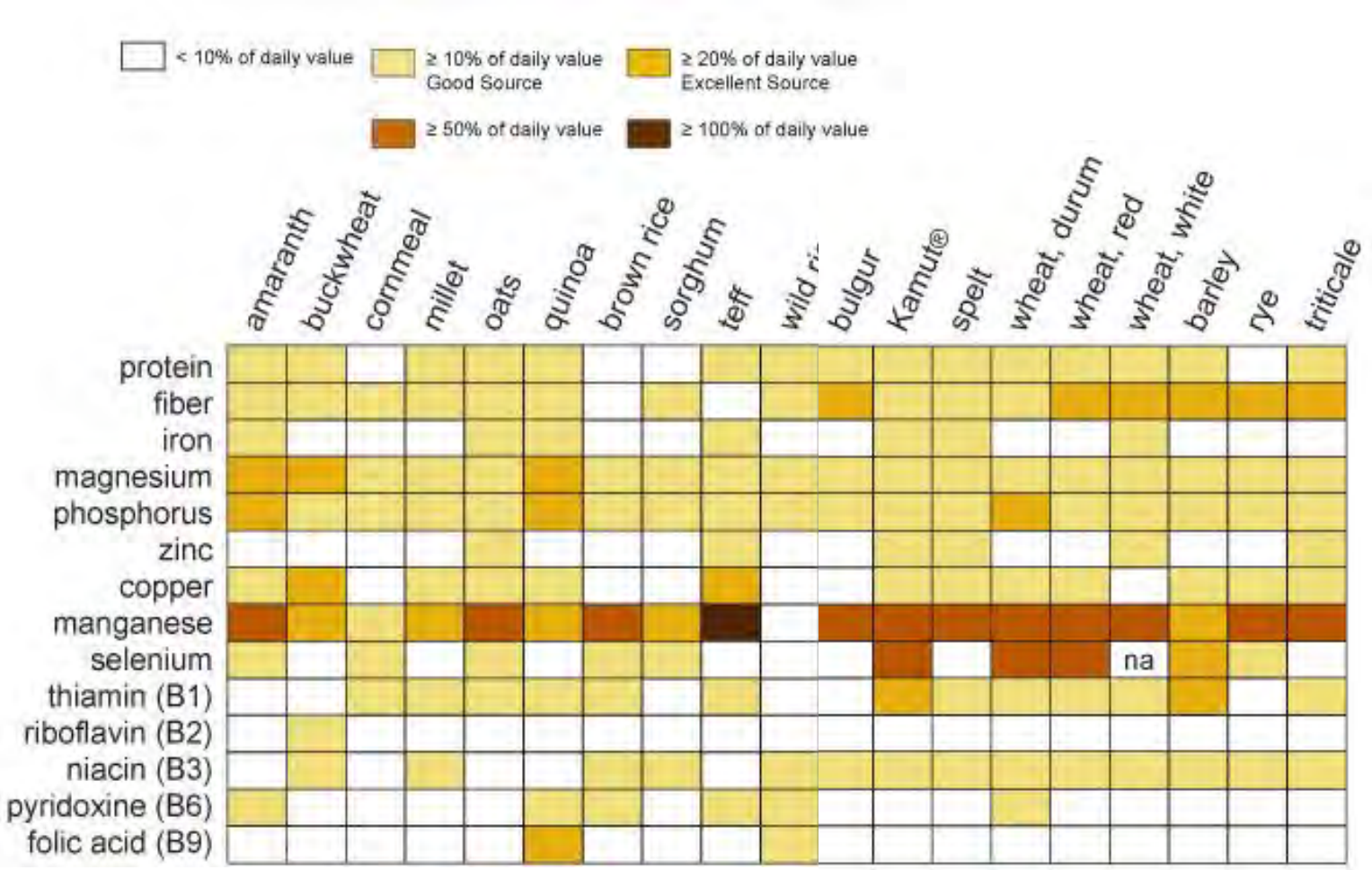
HC + food mix: no plaque in aorta

Verschuren, J Nutr 2011

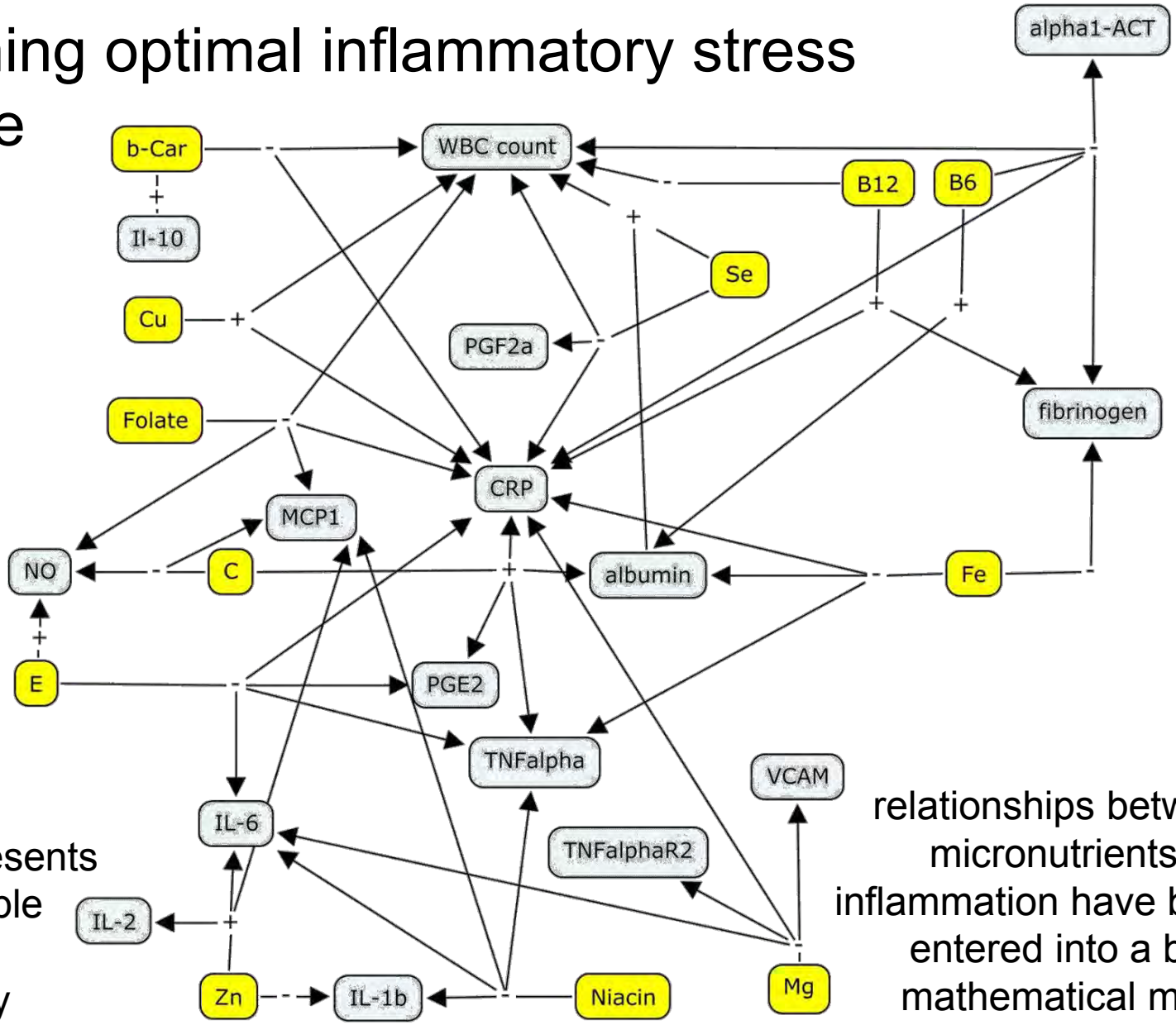
Many (essential) nutrients primarily serve to optimize the performance and resilience of overarching processes.



nutrients in 45g dry grain



Multiple micronutrients are involved in maintaining optimal inflammatory stress response

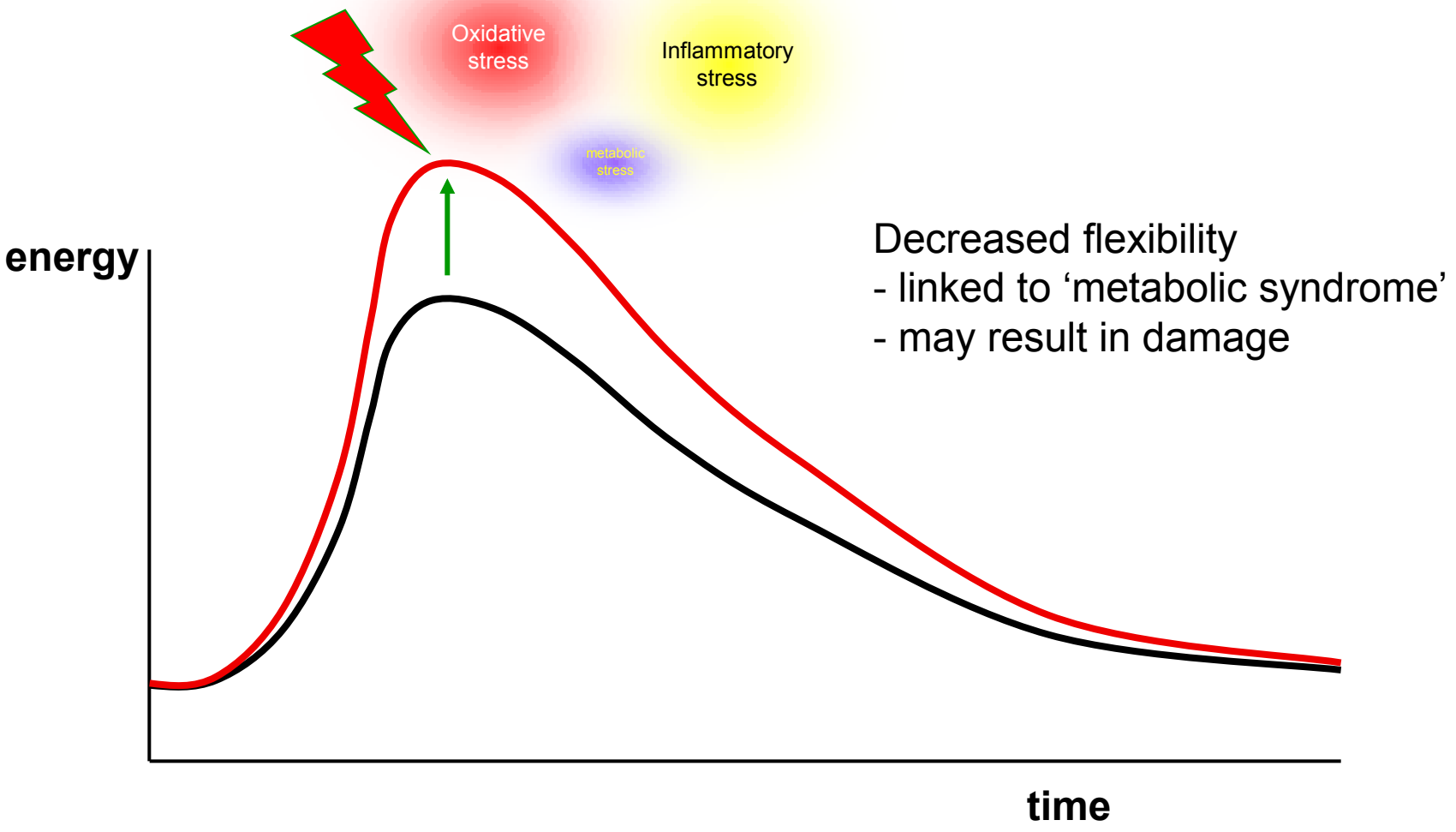


Each arrow represents at least one reliable published human intervention study

relationships between micronutrients and inflammation have been entered into a basic mathematical model

Nutrition and maintaining robustness?

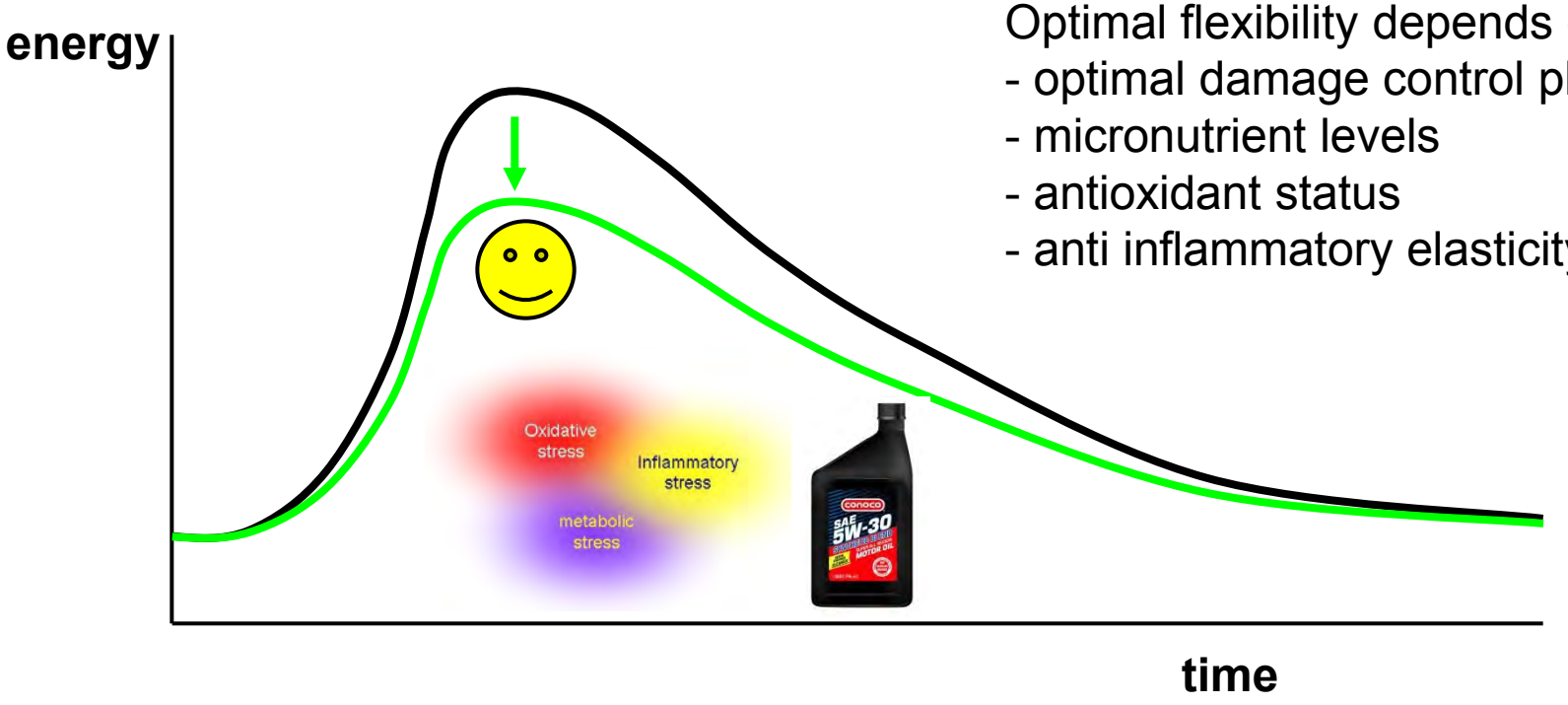
The energy pulse and the control mechanisms



Decreased flexibility
- linked to ‘metabolic syndrome’
- may result in damage

Nutrition and maintaining robustness?

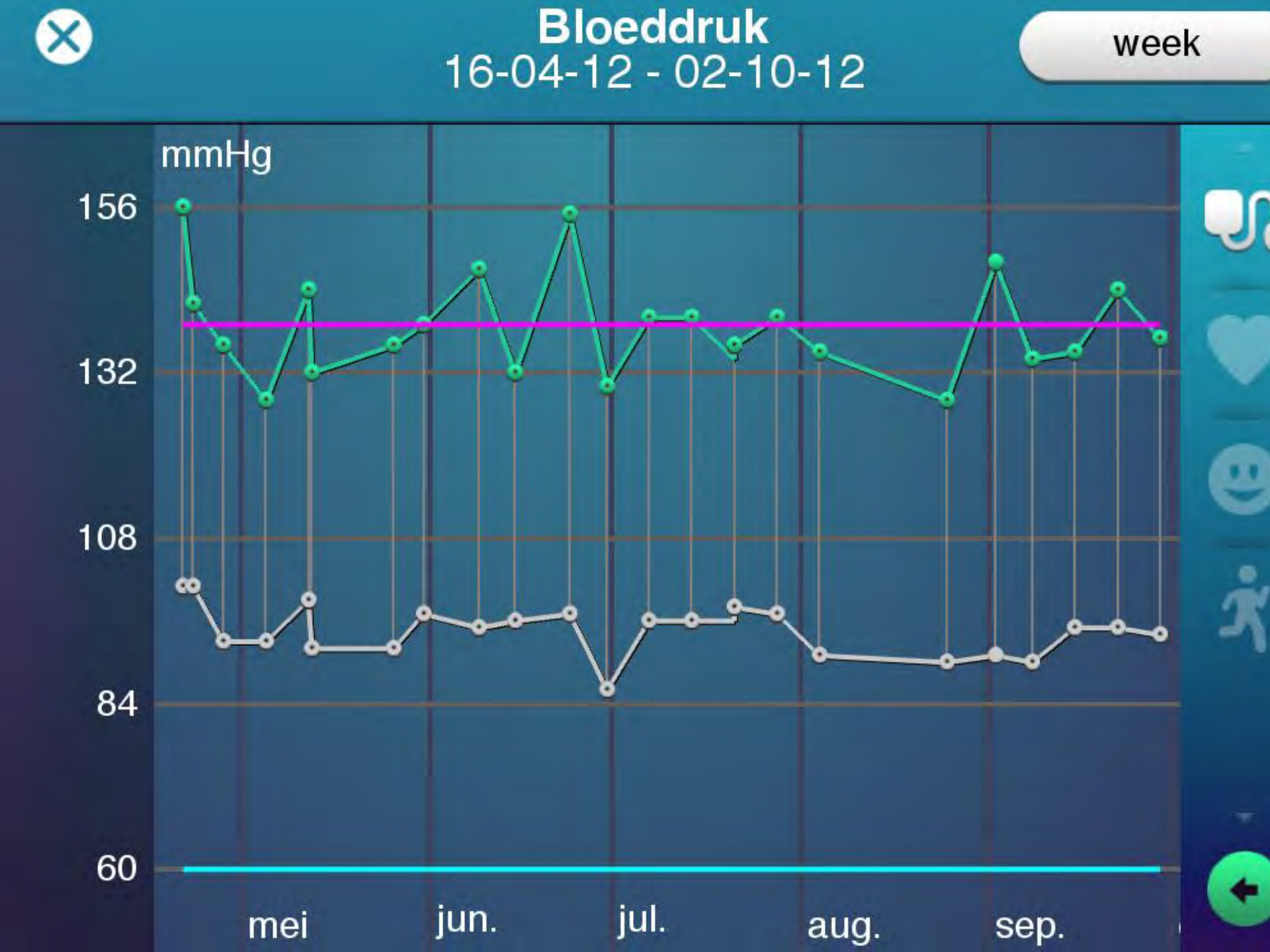
The energy pulse and the control mechanisms

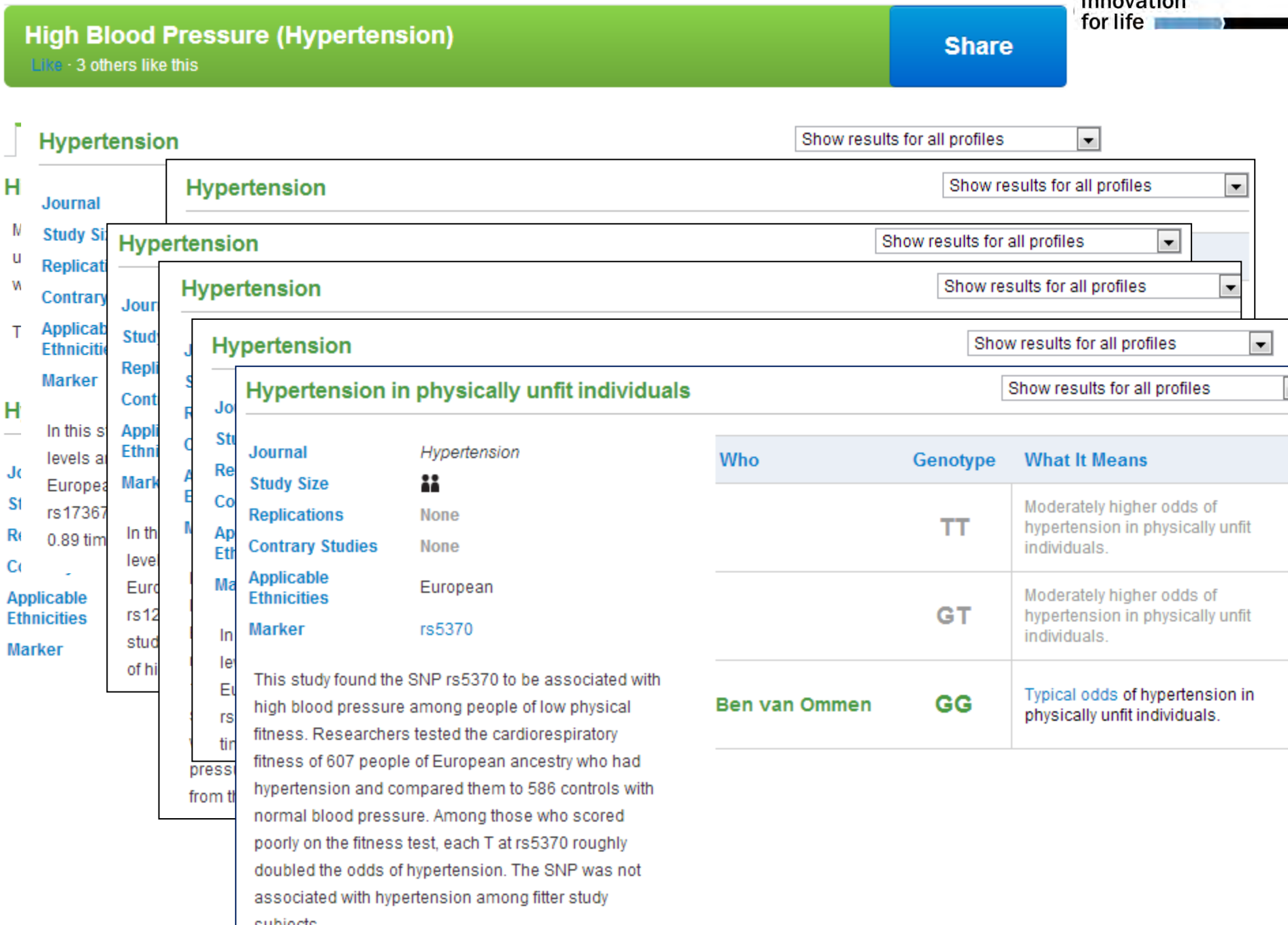


Optimal flexibility depends on
- optimal damage control phenotype
- micronutrient levels
- antioxidant status
- anti inflammatory elasticity

This is me – my clinical chemistry values? Can I now make healthy dietary choices based on my genotype and phenotype?

Parameter	unit	My value	min	max
Cholesterol	mmol/l	**5.3**	3.0	6.5
HDL-chol	mmol/l	**1.2**	>0.9	
LDL-chol	mmol/l	**3.6**		4.0
Triglycerides	mmol/l	**1.2**	0.4	3.6
Glucose (fasting)	mmol/l	**4.9**	4.0	6.0
TSH	mIU/l	**1.0**	0.25	5.6
HbA1c	%	**5.2**		5.8
ALAT	IU/l	**19**	5	45
gammaGT	IU/l	**22**	5	45
Creatinine	µmol/l	**106**	62	115
Sodium	mmol/l	**141**	135	145
Potassium	mmol/l	**3.9**	3.5	5.1
Blood Press sys	mm Hg	**141**		140
Blood Press dia	mm Hg	**90**		90
Pulse rate	b/min	**73**		


Bloeddruk
16-04-12 - 02-10-12
week
mmHg
156
132
108
84
60
mei
jun.
jul.
aug.
sep.


High Blood Pressure (Hypertension)
Like · 3 others like this
Share
innovation for life
Hypertension
Show results for all profiles
Hypertension in physically unfit individuals
Journal
Hypertension
Study Size
Replications
None
Contrary Studies
None
Applicable Ethnicities
European
Marker
rs5370
This study found the SNP rs5370 to be associated with high blood pressure among people of low physical fitness. Researchers tested the cardiorespiratory fitness of 607 people of European ancestry who had hypertension and compared them to 586 controls with normal blood pressure. Among those who scored poorly on the fitness test, each T at rs5370 roughly doubled the odds of hypertension. The SNP was not associated with hypertension among fitter study
Who
Genotype
What It Means
TT
Moderately higher odds of hypertension in physically unfit individuals.
GT
Moderately higher odds of hypertension in physically unfit individuals.
Ben van Ommen
GG
Typical odds of hypertension in physically unfit individuals.

Dietary advice based on genetics?

CYP1A2 genotype modifies the association between coffee intake and the risk of hypertension

Paolo Palatini[a], Giulio Ceolotto[a], Fabio Ragazzo[a], Francesca Dorigatti[a], Francesca Saladini[a], Italia Papparella[a], Lucio Mos[b], Giuseppe Zanata[c] and Massimo Santonastaso[d]

Conclusion These data show that the risk of hypertension associated with coffee intake varies according to CYP1A2 genotype. Carriers of slow ∗1F allele are at increased risk and should thus abstain from coffee, whereas individuals with ∗1A/∗1A genotype can safely drink coffee..

Journal of Hypertension 2009, Vol 27 No 00

Caffeine Metabolism ★★★

share this

Preliminary Research report on 1 reported marker.

Your Data

Next ▸
Clopidogrel (Plavix®) ...

About Caffeine Metabolism

Printable Version

Some people get jumpy after drinking a single cup of coffee, while others can gulp down a Venti Americano without feeling a thing. Part of that variability is due to the development of tolerance by regular coffee drinkers; but there are genetic differences in how people metabolize caffeine as well.

Caffeine metabolism and heart attack

Show results for all profiles

Journal	*JAMA*
Study Size	●●●●
Replications	None
Contrary Studies	None
Applicable Ethnicities	European
Marker	rs762551

Caffeine is primarily metabolized by the liver enzyme cytochrome P450 1A2 (CYP1A2). The form of the SNP rs762551 a person has determines how fast CYP1A2 metabolizes caffeine. In this study, people with the slower version of the CYP1A2 enzyme who also drank at least two to three cups of coffee per day had a significantly increased risk of a non-fatal heart attack. The study

Who	Genotype	What It Means
Ben van Ommen	AA	Fast caffeine metabolizer: drinking coffee didn't increase subjects' heart attack risk
	AC	Slow caffeine metabolizer: drinking coffee increased subjects' heart attack risk.
	CC	Slow caffeine metabolizer: drinking coffee increased subjects' heart attack risk.

Is it that simple?

- 1000+ compounds
- Many of them with bioactivity
- Effects on insulin resistance and glycemix index (cholorogenic acid?)
- Effect on LDL-cholesterol (kafestol)
- Effects on colon cancer, calcium absorption, stomach, endurance, blood pressure, CVD, iron, bone health…?

BMJ

BMJ 2012;345:e551

"We've long known that almost all benefit from treating severe hypertension comes with lowering BP [blood pressure] just a little. On the other hand, efforts to lower BP to 'normal,' typically requiring multiple drugs, are not only **usually unsuccessful** but produce **more harm than good**, since adverse effects of intensive treatment outweigh the minimal marginal benefit of a little more BP 'control.'

Cochra
treatme

Jeanne Lenze

Drug treatment of mild hypertension, like intensive treatment of severe hypertension, may be of great value to drug makers, but it was almost predictable that it would **provide little or no benefit** for patients."

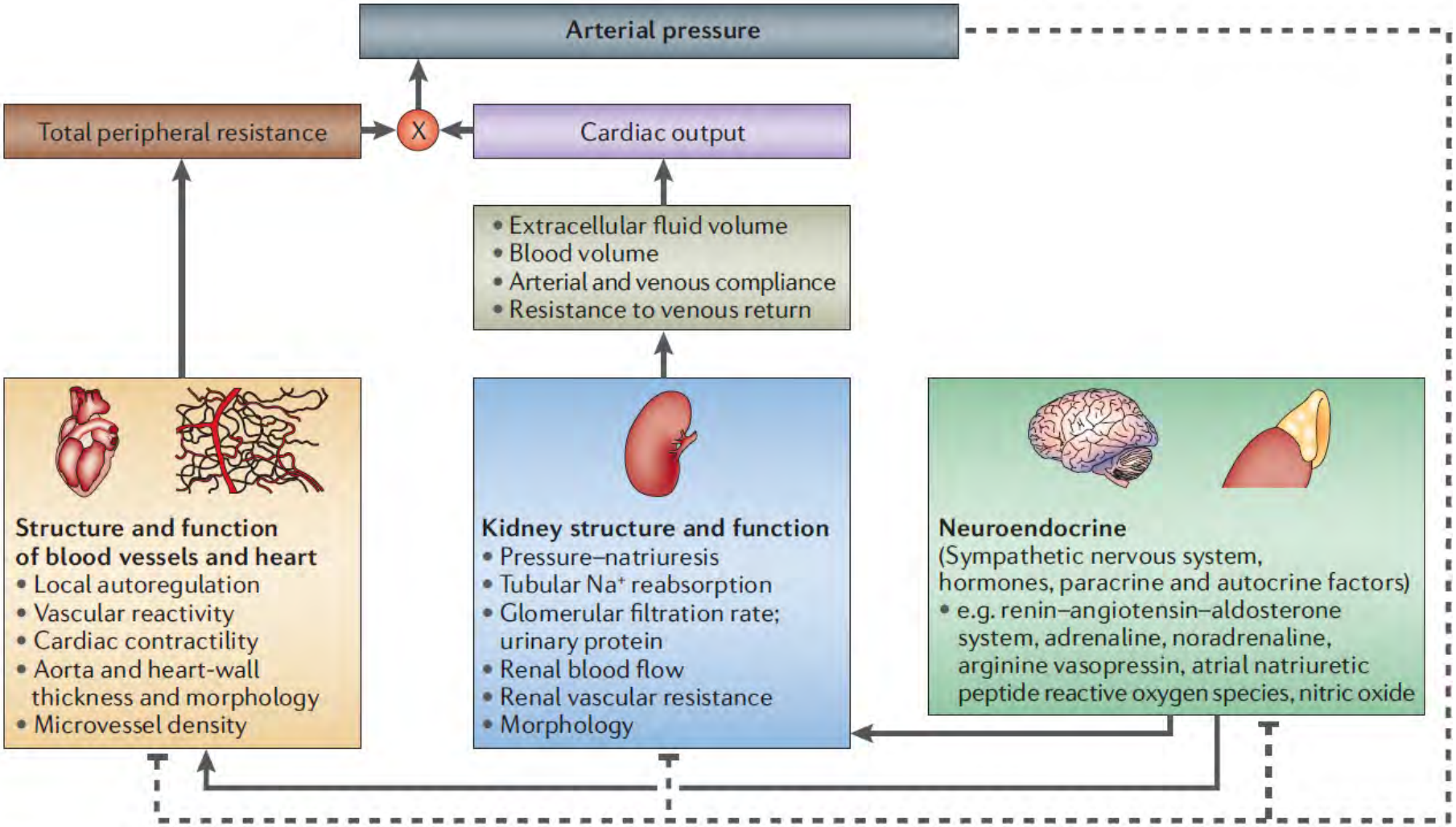
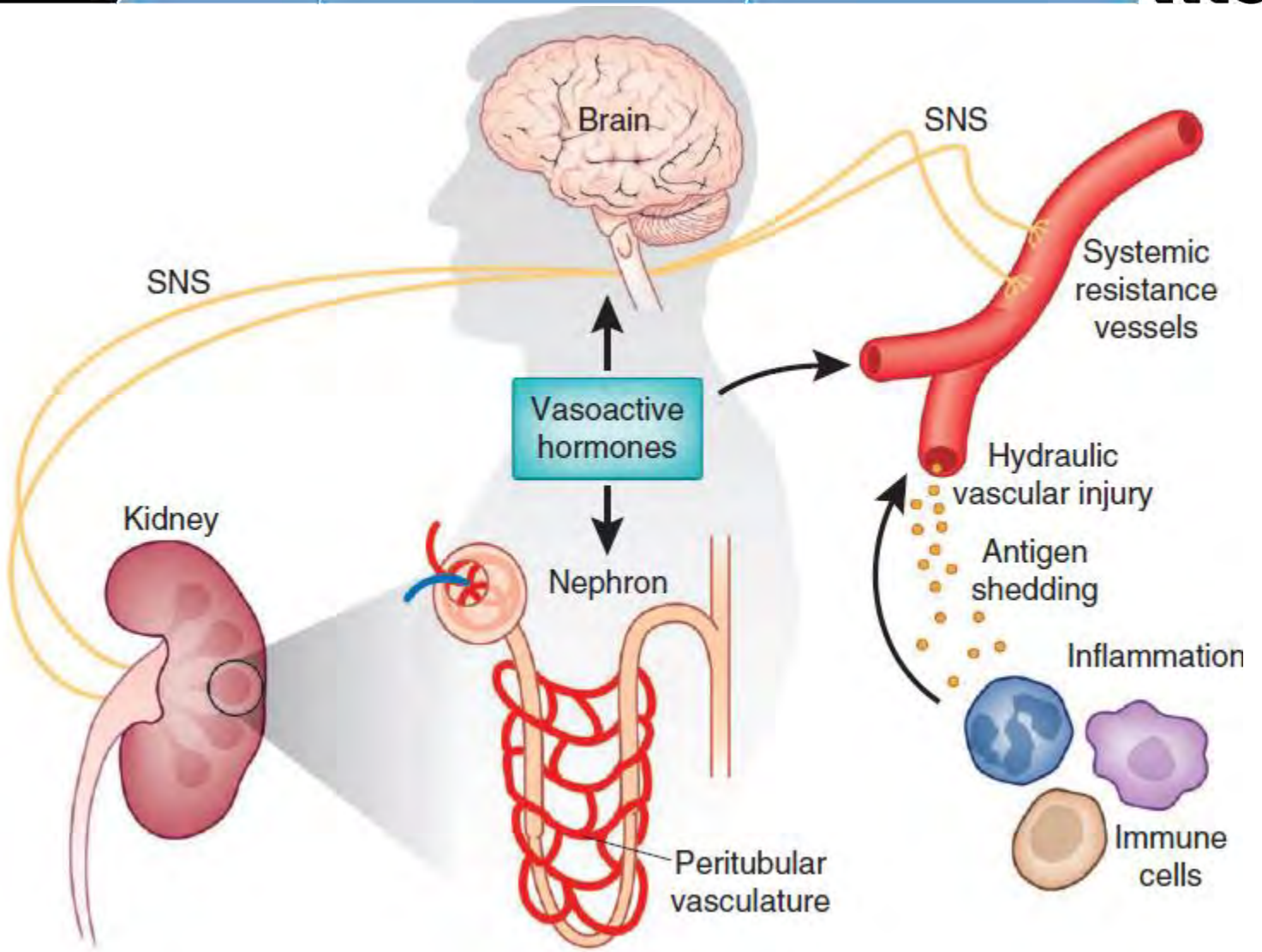


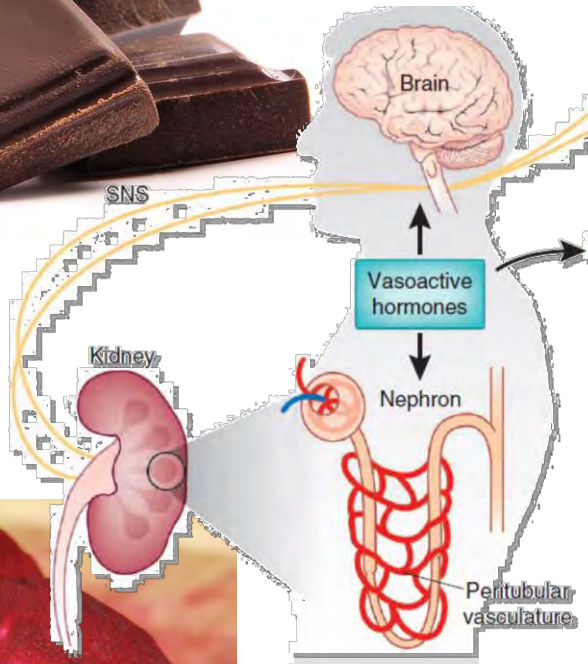
Figure 1 | **Mechanisms of arterial blood pressure regulation.** Arterial pressure is highly dynamic. At any moment it

Cowley, Nature Reviews Genetics 2006



Regulatory mechanisms for blood pressure are targets for therapy in hypertension.

Coffman, Nature Medicine 2011


Brain
SNS
SNS
Vasoactive hormones
Kidney
Nephron
Peritubular vasculature
Systemic resistance vessels
Hydraulic vascular injury
Antigen shedding
Inflammatic
Immun cells

Potassium supplementation for the management of primary hypertension in adults (Review)

Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2010.02338.x

Fish oil, selenium and mercury in relation to incidence of hypertension: a 20-year follow-up study

P. Xun[1,2], N.

Effect of cocoa on blood pressure (Review)

Our finding ith
incidence

Ried K, Sullivan TR, Fakler P, Frank OR, Stocks NP

Short term studies effective (2 weeks)
Long term studies not effective (8 weeks)

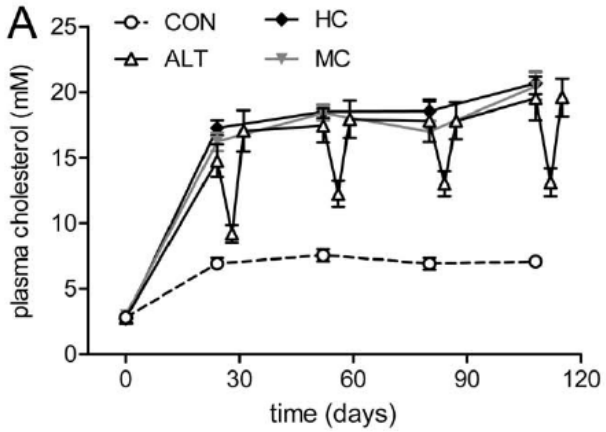
OPEN ACCESS Freely available online

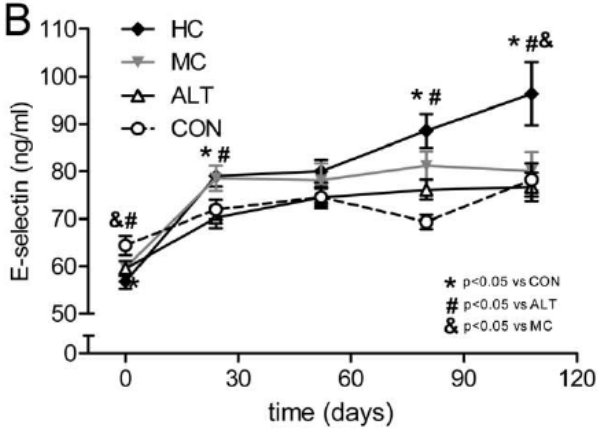
PLoS one

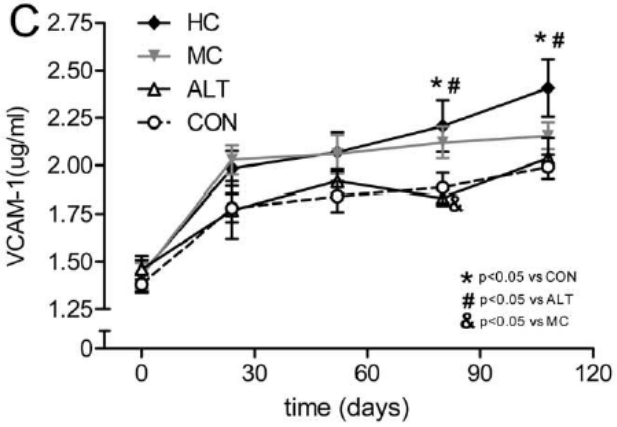
Beneficial Effects of Alternate Dietary Regimen on Liver Inflammation, Atherosclerosis and Renal Activation

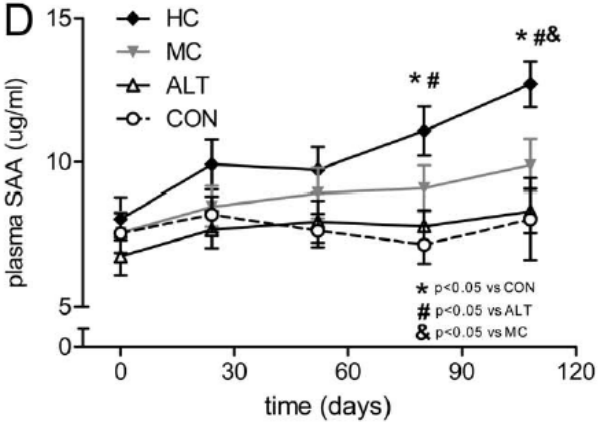
Peter Y. Wielinga[1,3]*, Gopala K. Yakala[2,3], Peter Heeringa[2,3], Robert Kleemann[1,3], Teake Kooistra[1]

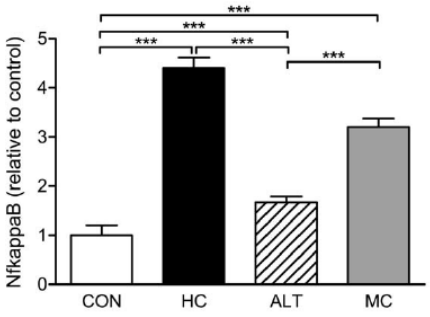
1 TNO-Metabolic Health Research, Leiden, The Netherlands, 2 Medical Biology Section, Department of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands, 3 Top Institute Food and Nutrition, Wageningen, The Netherlands

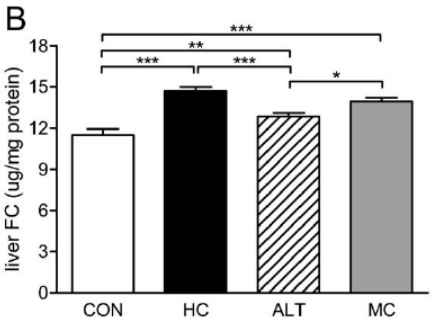


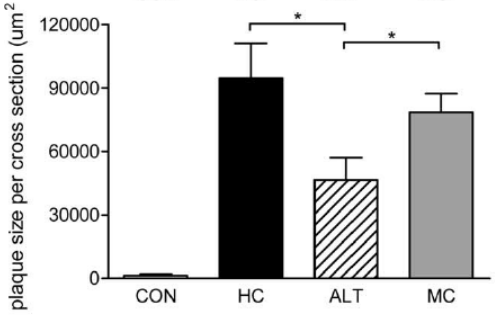


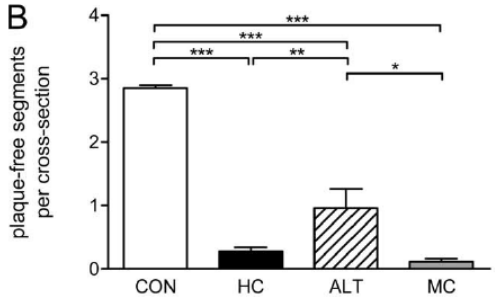












They always change their food. First they eat flesh, then fish, then vegetables, then afterward they go back to flesh, and nature is never incommoded or weakened.

Hanno però distinto li cibi utili dalli disutili, e secondo la medicina si serveno; una fiata mangiano carne, una pesce ed una erbe, e poi tornano alla carne per circolo, per non gravare né estenuare la natura.

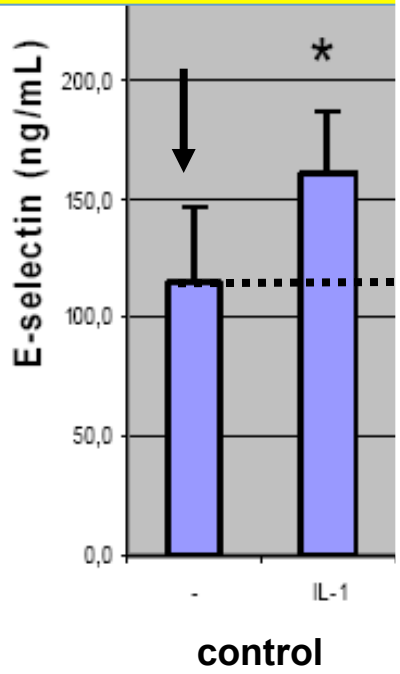
Tommaso Campanella
-
La Cittá del Sole
(The City of the Sun)
1623

Low dose or high dose?

Salicilate stimulates the inflammatory response at low concentration

Salicilate inhibits the inflammatory response at high concentration

Salicilate does no homeostatic inflam status



Interleukin-1 triggers an E-selectin (= “inflammatory) response in mice

Anti-inflammatory foods?
Pro-inflammatory foods?

No!

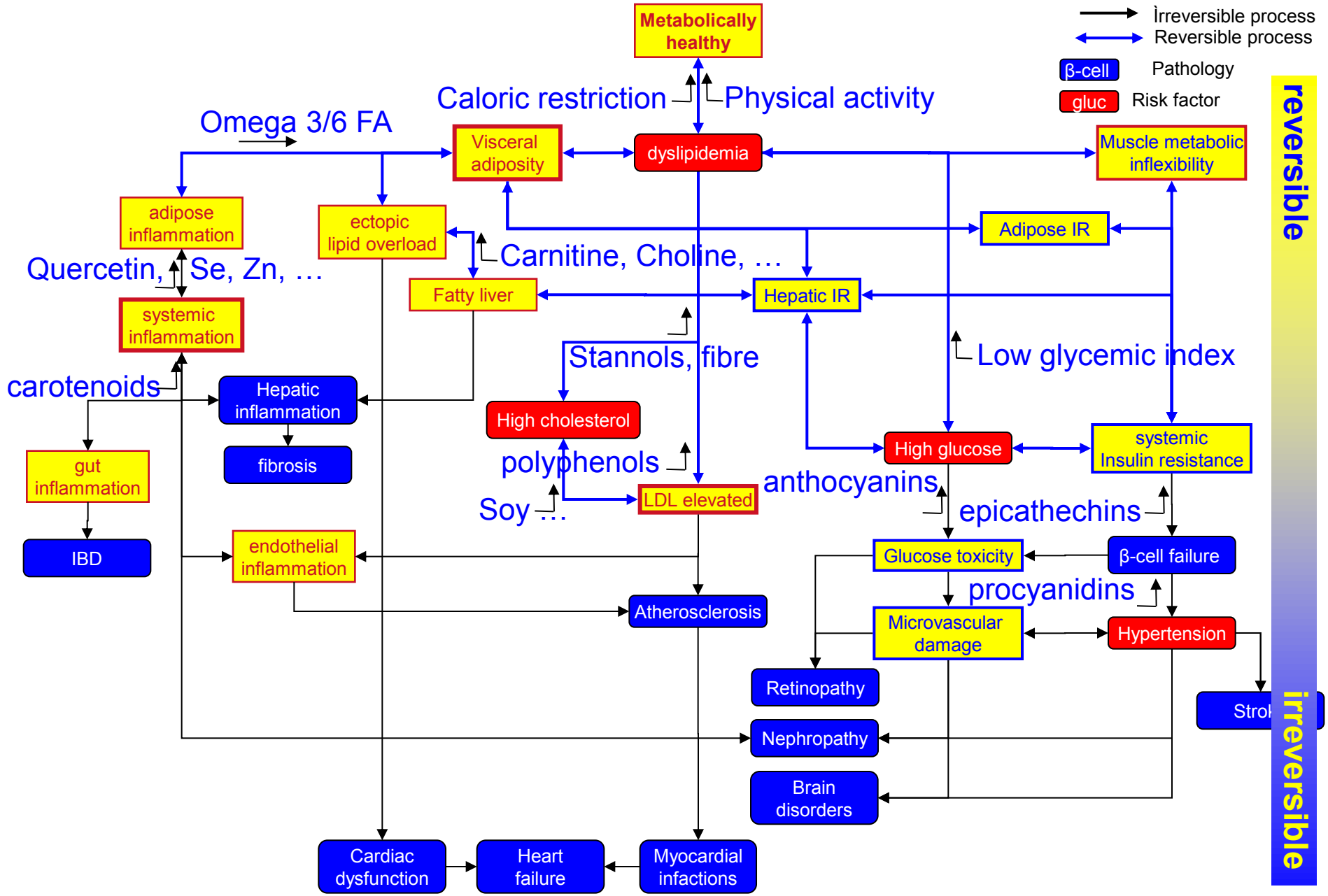
Foods that optimally facilitate the inflammation physiology

(same for "anti-oxidant foods")

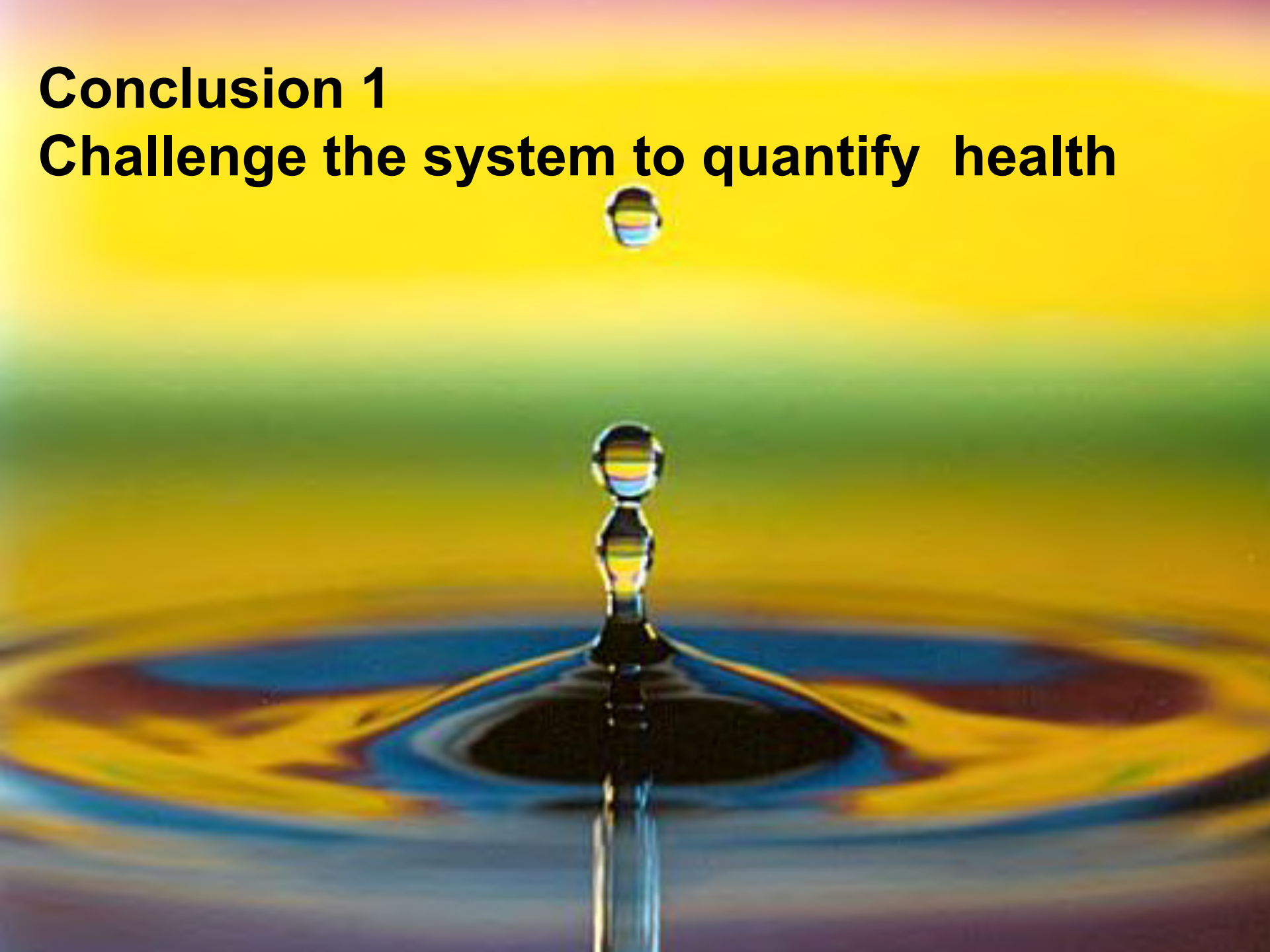
mechanism? (my private hypothesis):

"training" of primary reactions (intestinal TLRs and downstream cascades), thus keeping the inflammatory system alert when it is really needed…

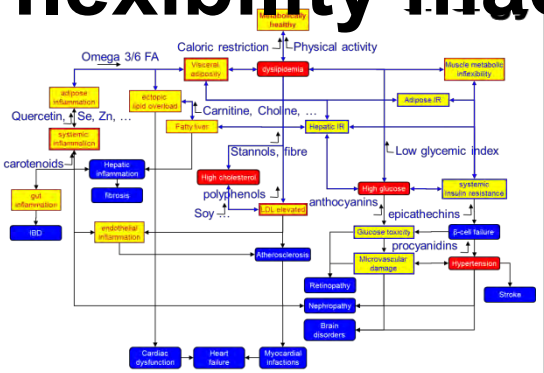
Many dietary ingredients optimize these processes

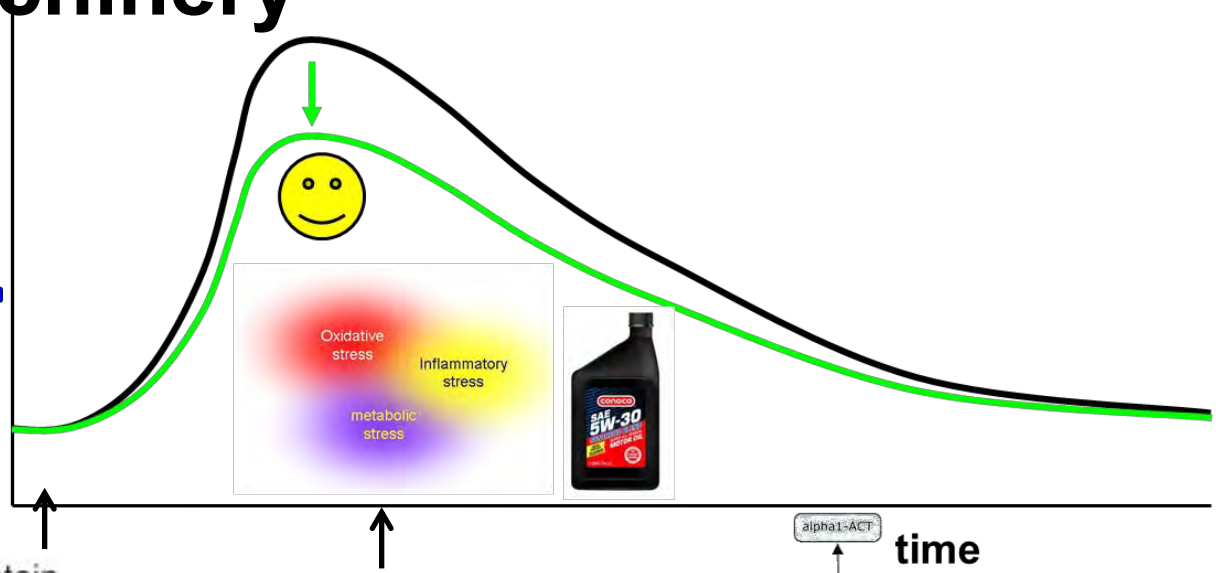


Conclusion 1
Challenge the system to quantify health

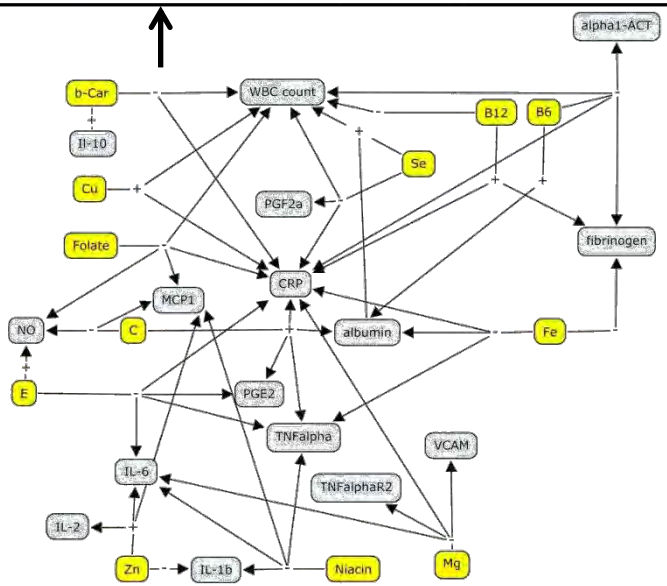


Conclusion 2: Food components “oil” the flexibility machinery

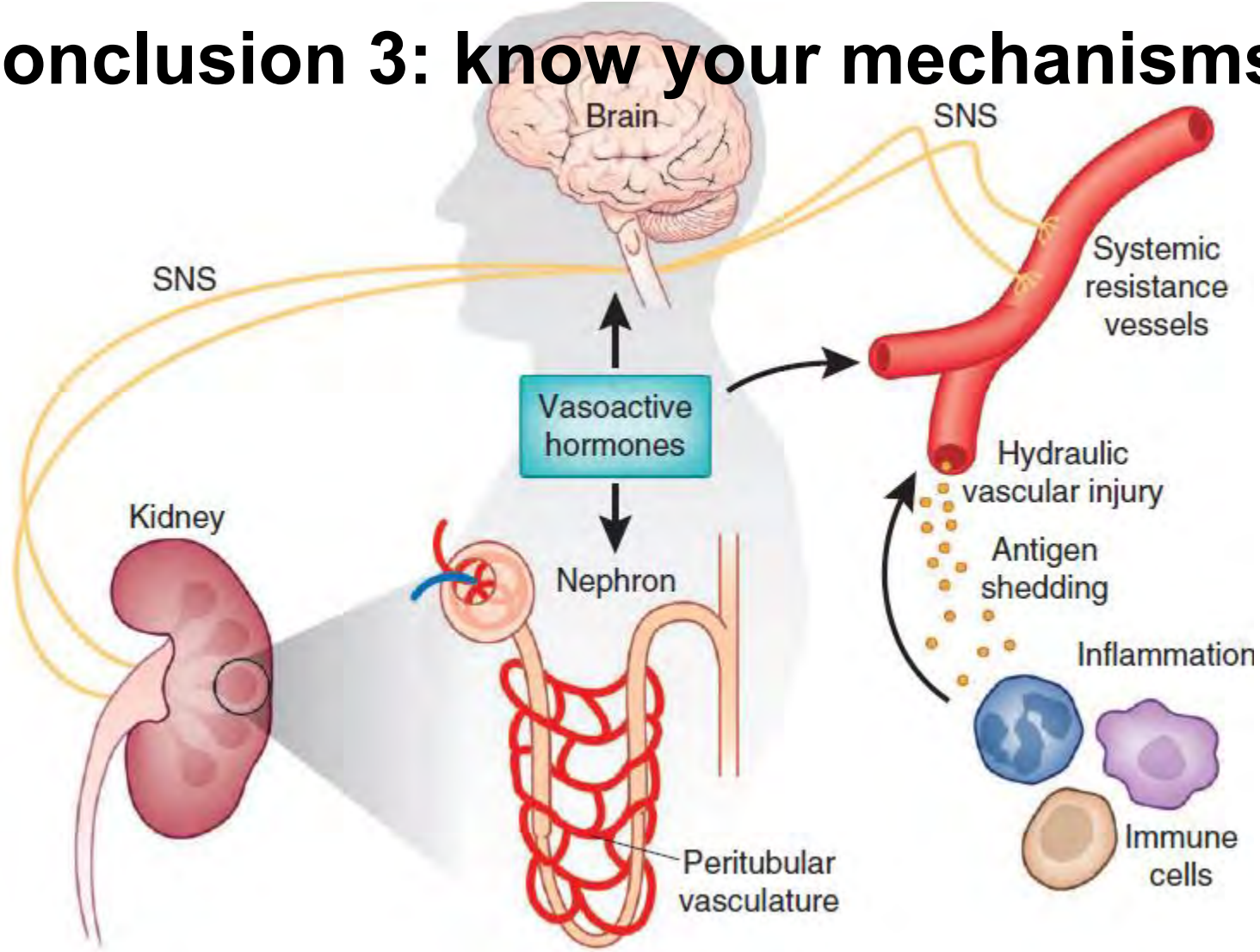




protein
fiber
iron
magnesium
phosphorus
zinc
copper
manganese
selenium
thiamin (B1)
riboflavin (B2)
niacin (B3)
pyridoxine (B6)
folic acid (B9)



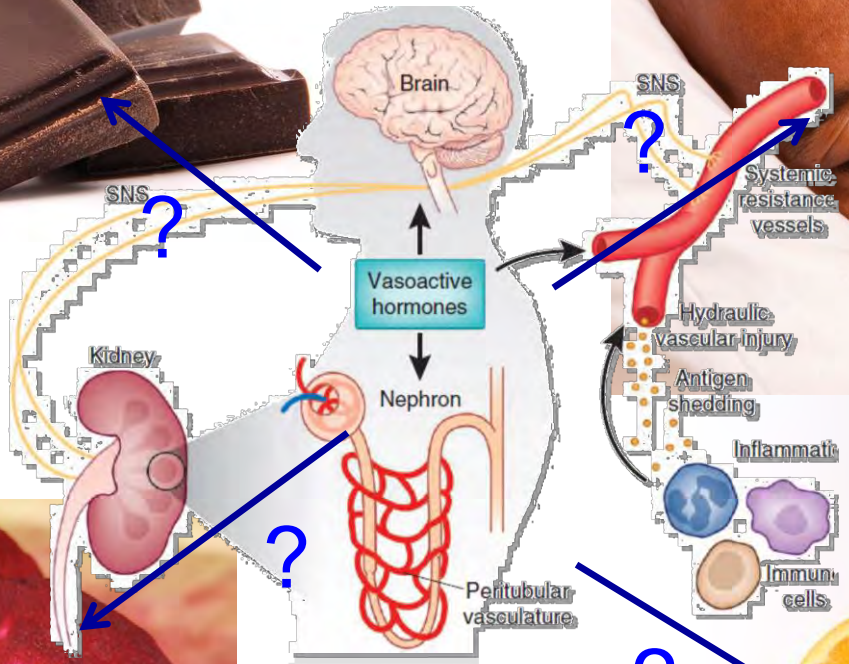
Conclusion 3: know your mechanisms



Regulatory mechanisms for blood pressure are targets for therapy in hypertension.

Coffman, Nature Medicine 2011

Conclusion 4: go personalized, also in research?!



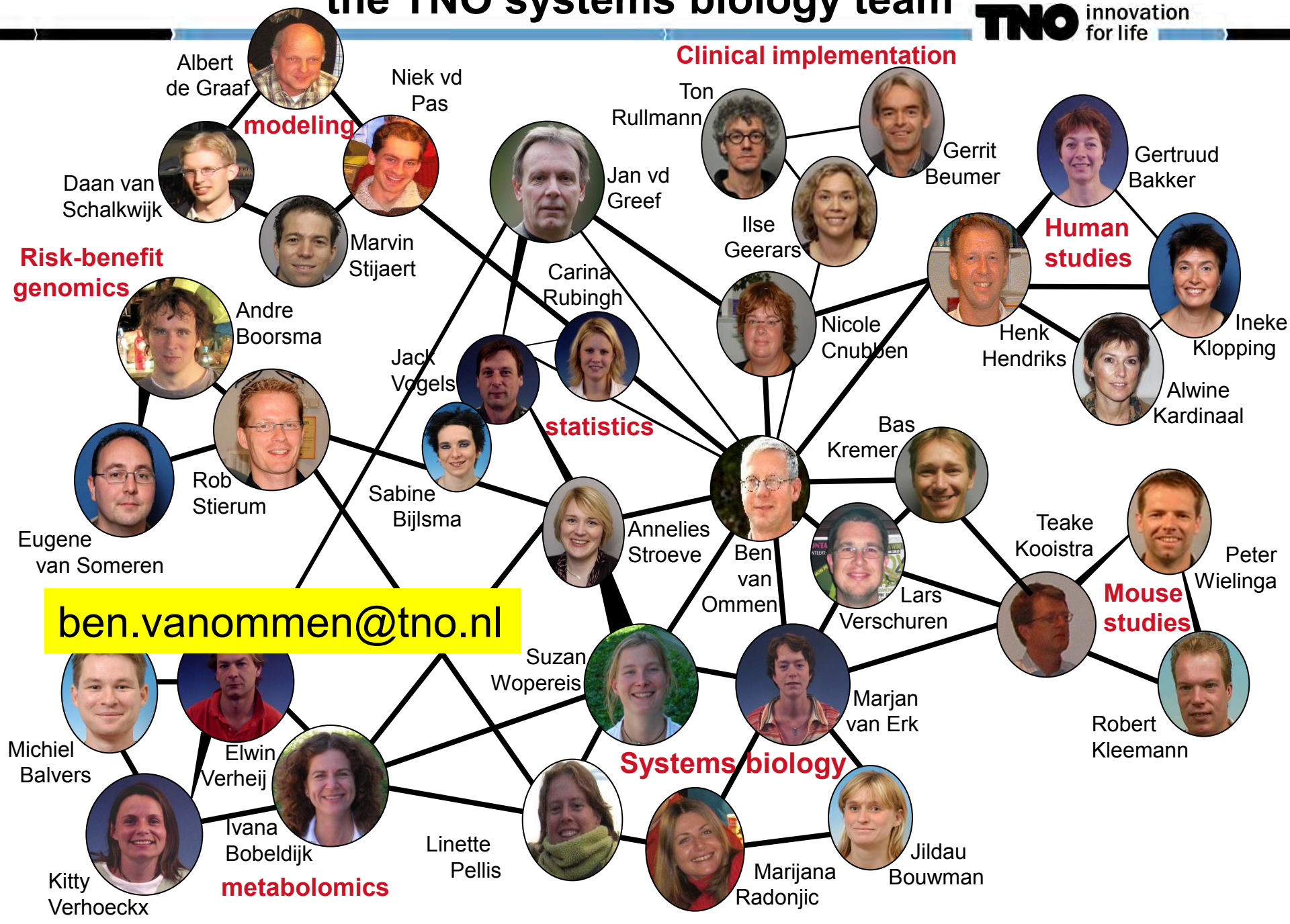
Conclusion 5 and 6: Train the system

…by an alternating diet

… by providing low doses

the TNO systems biology team

TNO innovation for life



NuGO
Nutrigenomics Organisation

NuGOweek 2013

REGISTRATION IS OPEN

NuGO week 2013, a joint symposium of NuGO and the German Nutrition Society, will be held from 9-12 September 2013 at the Technische Universität München, Campus Weihenstephan, Freising, Germany

Under the title Nutrigenomics & More, NuGO week will cover all aspects of Nutrigenomics research but will have a strong focus on genetics in the context of diet and food by addressing aging, sensory sciences but also obesity, type-2 diabetes and cancers. The presentations will provide state of the art coverage, will critically assess what GWAS have delivered and discuss the road ahead.

NuGOweek 2013 is organised in collaboration with DGE, TUM and ZIEL

Technische Universität München

DGE

ZIEL
Research Center for Nutrition and Food Sciences