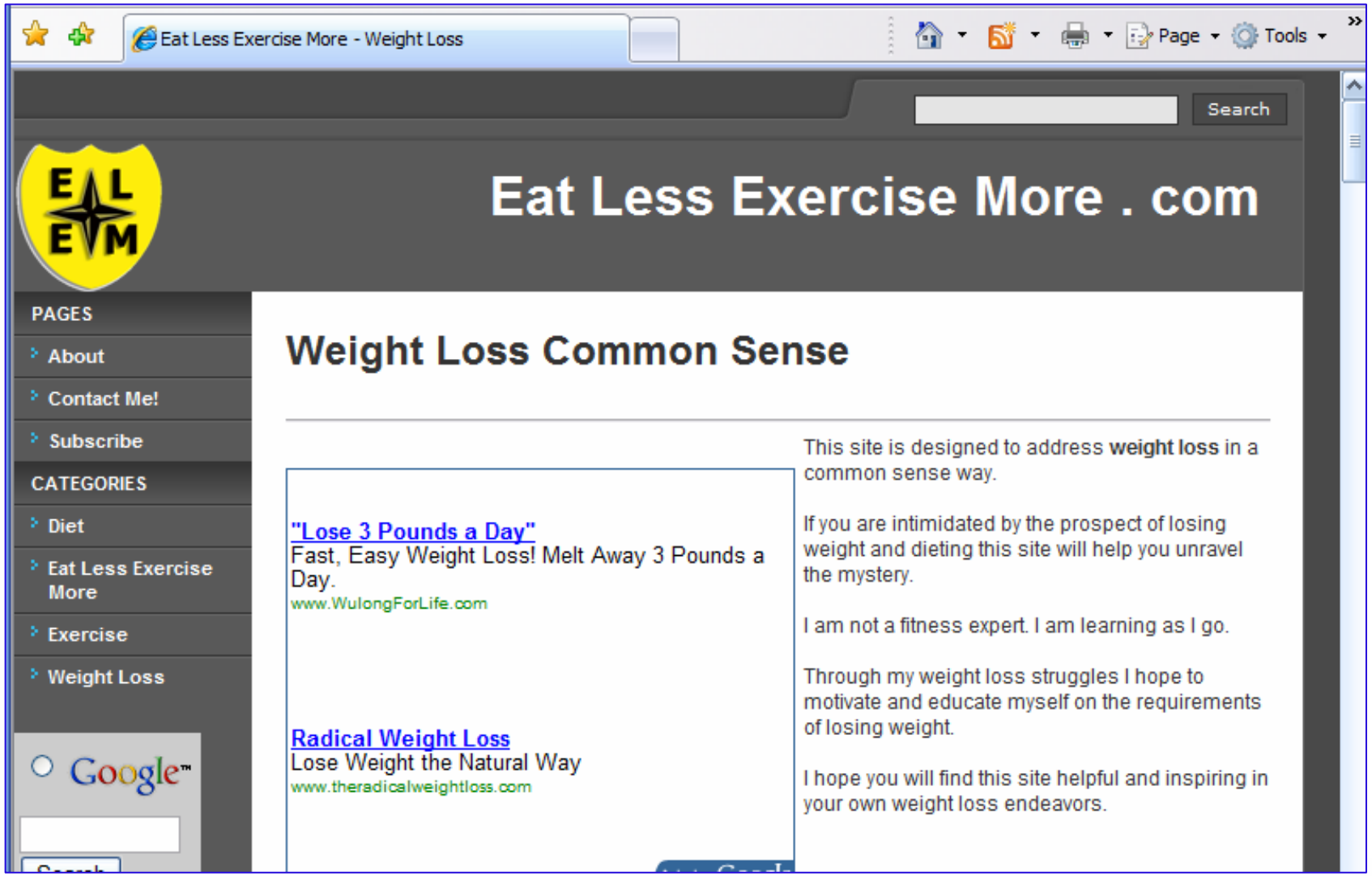
Can nutrigenomics lead us to prevention of obesity?

Ben van Ommen

TNO | Knowledge for business

Stupid question, of course not!



Eat less, exercise more, Bush tells ailing Sharon

Associated Press in Jerusalem
Wednesday December 21, 2005
The Guardian

President George Bush told Ariel Sharon yesterday to eat less, work less and exercise more after the Israeli prime minister was released from hospital following treatment for a stroke, according to an Israeli government statement.

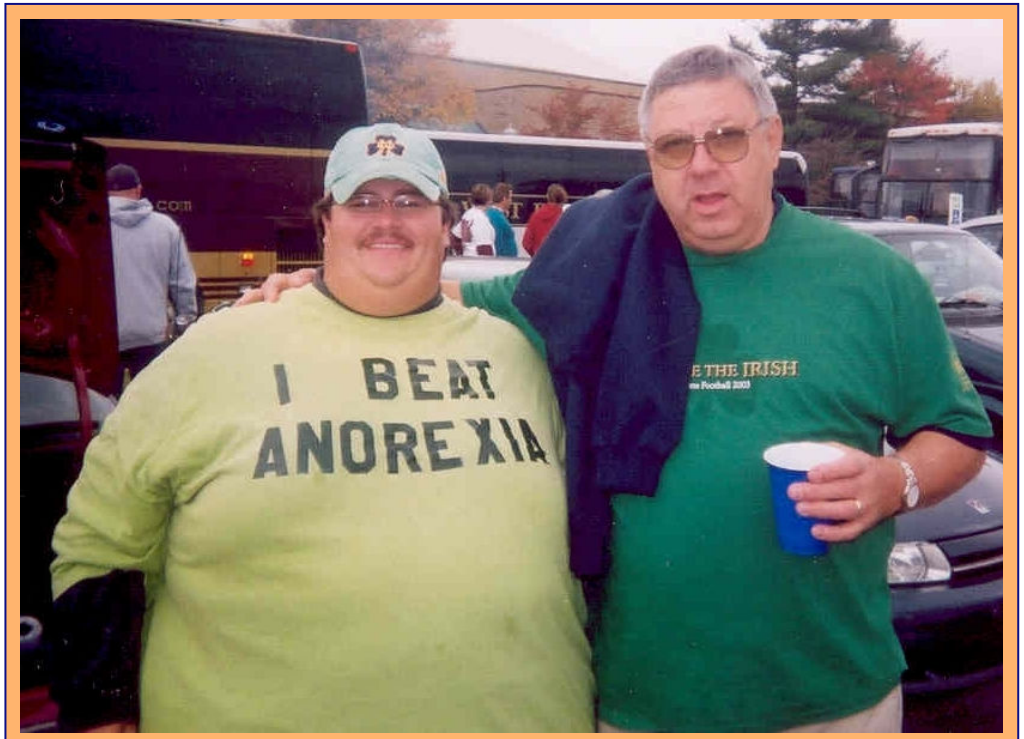
Mr Bush reportedly said: "Be careful, my friend." He was quoted as saying that if they were to be partners in the struggle against terrorism, Mr Sharon had to stay out of hospital. Mr Sharon, 77, told Mr Bush he would rest for a few days. President Hosni Mubarak of Egypt also advised Mr Sharon to take care of his health and reduce his workload, Mr Sharon's office said.

Having said this, and being lazy, what can we do about the diet?

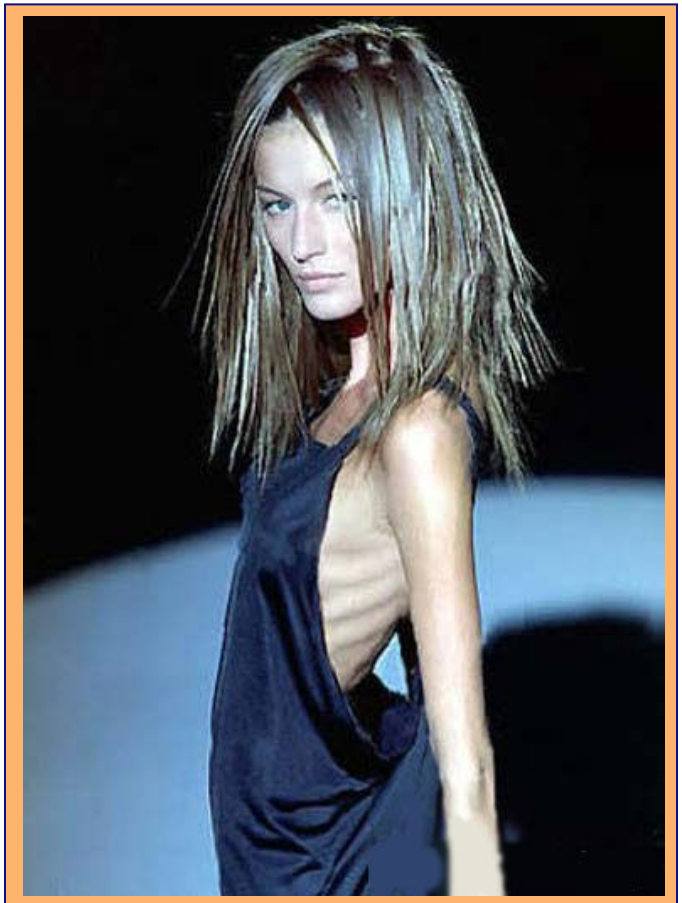
Dietary advice can be done in many ways …

“Can we determine nutrient needs based on phenotypic observations?”

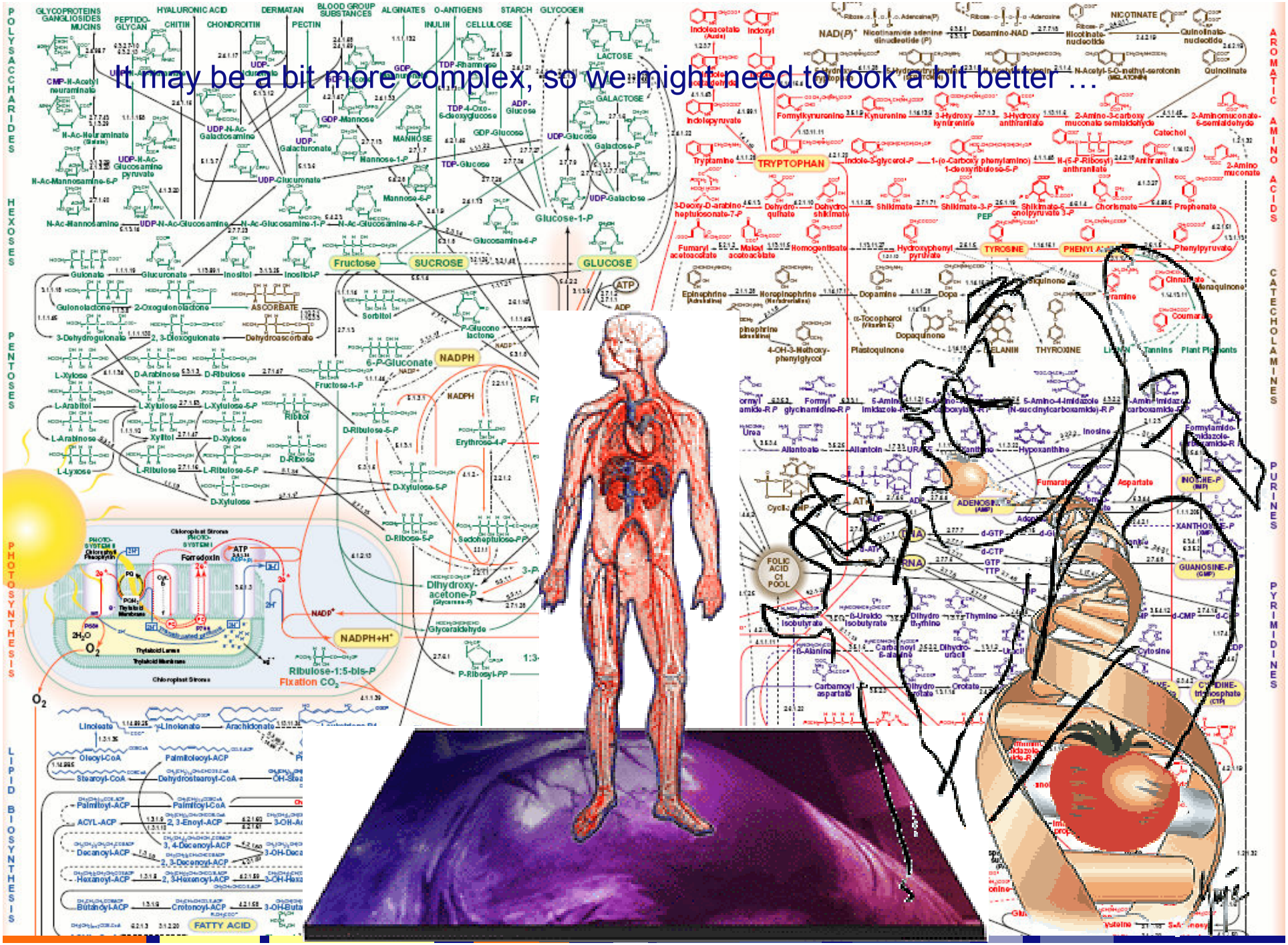
How would that work? - example



Need less food

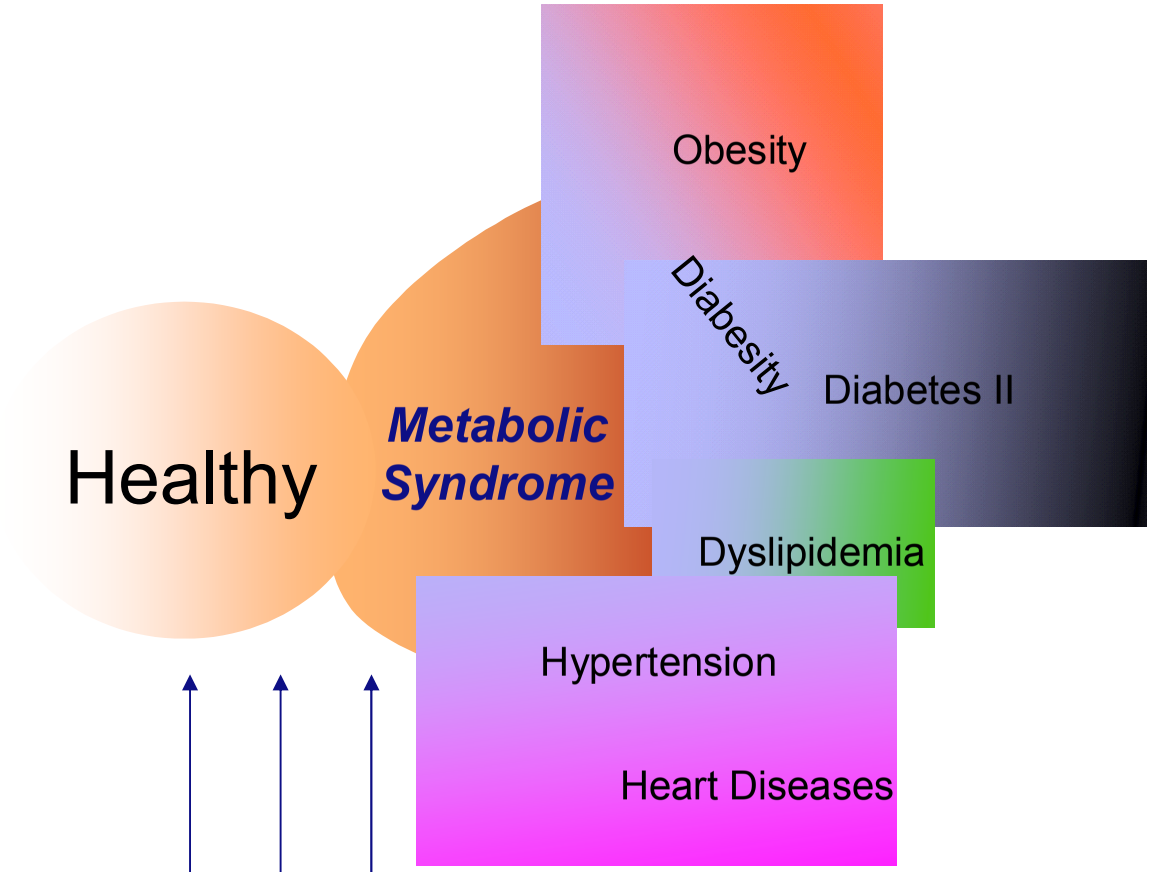


Needs more food


It may be a bit more complex, so we might need to look a bit better …
POLYSACCHARIDES
HEXOSES
PENTOSES
PHOTOSYNTHESIS
LIPID BIOSYNTHESIS
AROMATIC AMINO ACIDS
CATECHOLAMINES
PURINES
PYRIMIDINES
GLUCOSE
SUCROSE
TRYPTOPHAN
TYROSINE
PHENYL ALA
FATTY ACID
FOLIC ACID C1 POOL

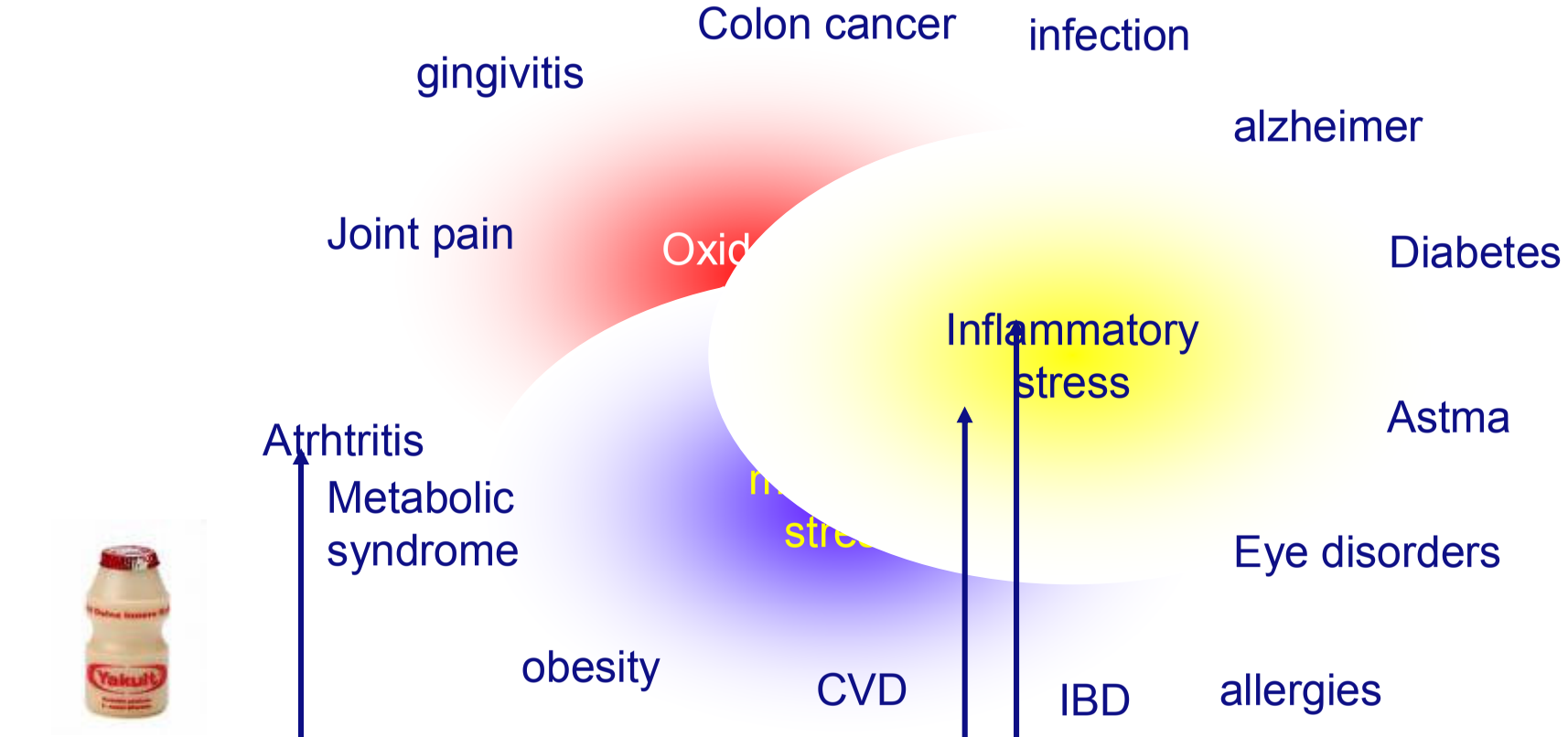
So, what are the bottleneck in obtaining real health claims and good dietary advice?

Many chronic nutrition related diseases originate from metabolic imbalance.



What is happening here? Can we identify, quantify and modulate these processes?

Nutrition relates to health optimizing, so needs to target the homeostasis of overarching processes instead of the disease process.



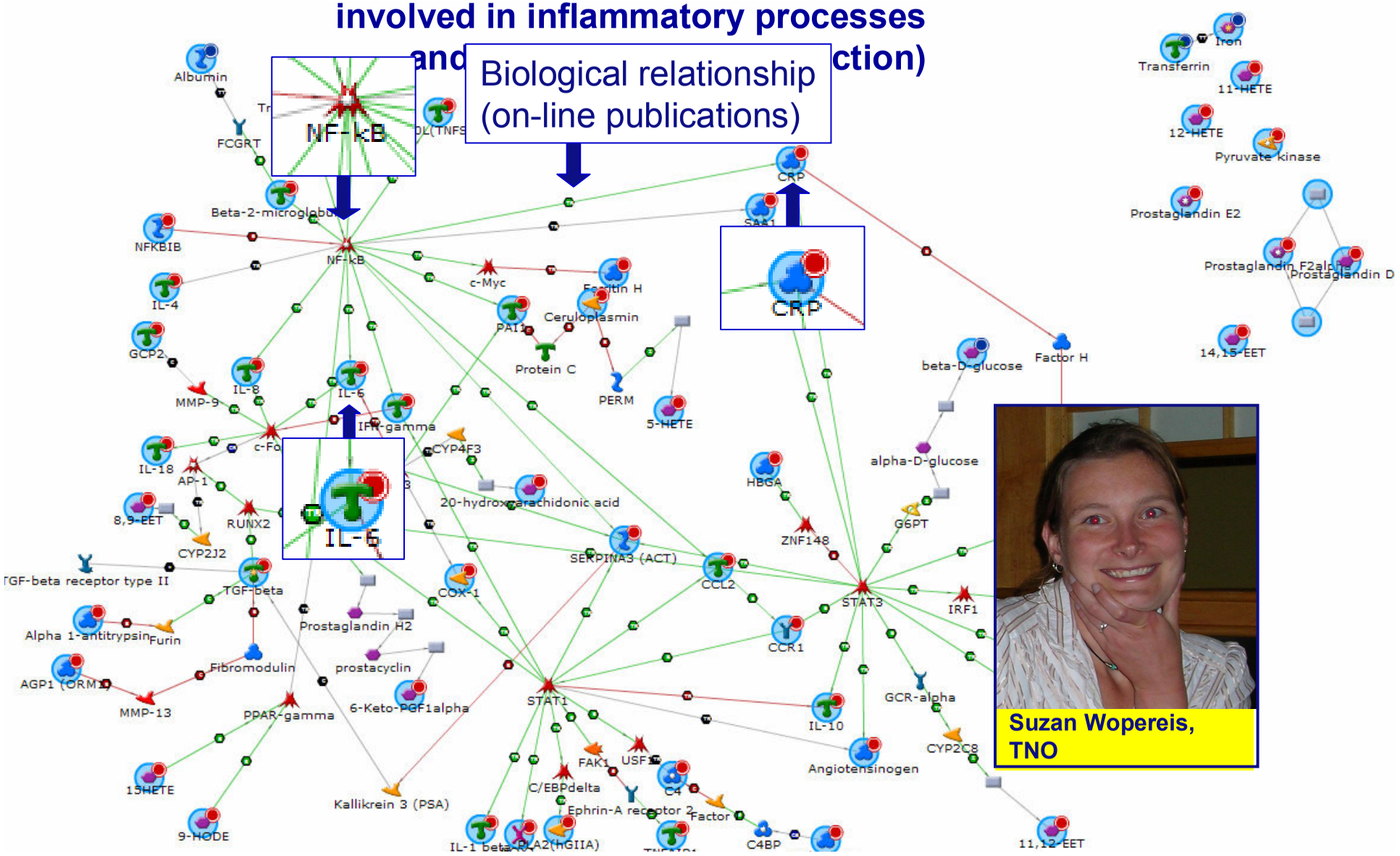
What are the targets of functional foods?

Is this the reason why we have so few real functional foods?

probiotics

Human Plasma Inflammation Interactome

(proteins and metabolites in plasma involved in inflammatory processes and [illegible]ction)



So, what is needed?
Quantification of health status


Jose Ordovas, Tufts

The basic algorithm of nutrition and health

$$\text{health status} = \int_{\text{conception}}^{\text{now}} \text{exposure} \times \text{genome}$$

↑ Mortality?
Disease?
Early disease biomarkers?
Physiological changes?
Health?

↑ Diet
Exercise
Toxins
Pharma
"Environment"

↑ "stable"

In nutrition research, we need to quantify all three parts of the equation.
So, how are we doing?

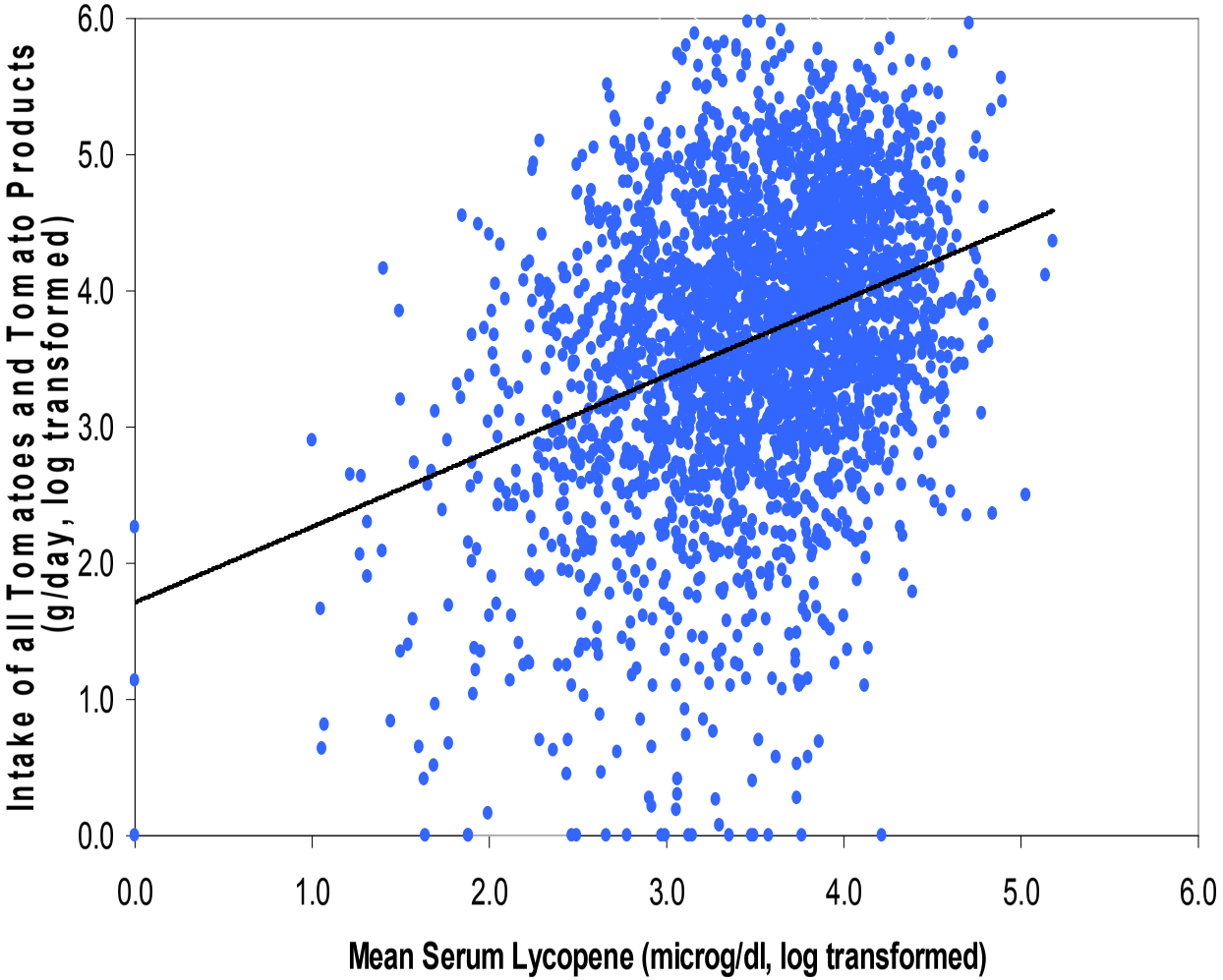
↑ worse than lousy

↑ lousy

↑ OK

Individual Consumption of All Tomatoes and Tomato Products and Serum Lycopene Levels

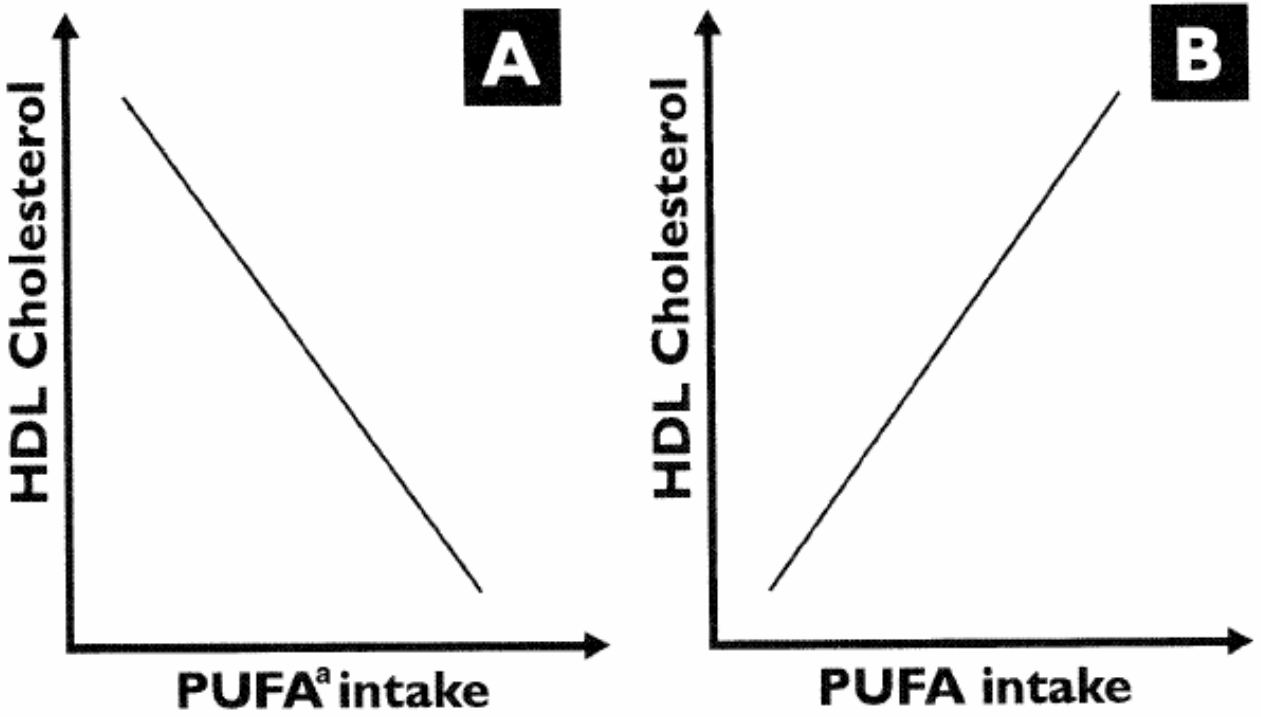
(EPIC Cross-sectional Study in 3000 subjects)



Corr = 0.23

Jenab et al.
J. Nutr. 135:2032, 2005

the genetic part



Jose Ordovas

Figure 2. Effect of polyunsaturated fatty acid intake on high-density lipoprotein (HDL) cholesterol blood levels. Panel A depicts conventional wisdom as reflected in women with the –75 GG genotype at the *APOA1* gene (G allele frequency=0.835). Panel B illustrates a new understanding of gene–diet interaction, as reflected in women with the –75 G/A and A/A genotypes at the *APOA1* gene (A allele frequency=0.165). [a]PUFA=polyunsaturated fatty acid.

Nutritional Genomics in Practice: Where Do We Begin?

RUTH M. DEBUSK, PhD, RD; COLLEEN P. FOGARTY, MS, RD; JOSÉ M. ORDOVAS, PhD; KENNETH S. KORNMAN, PhD, DDS

Your genetic passport is important, but don`t blame your genes …

Financial Times UK, 2000

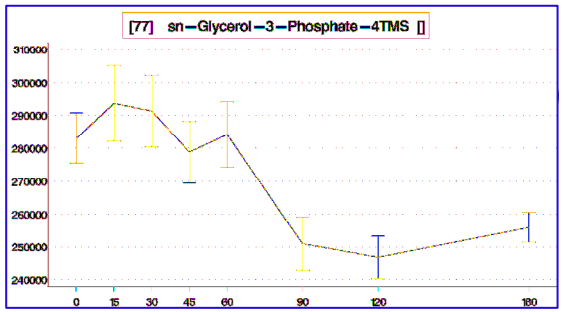
So, how good are we in studying subtle changes in our healthy phenotype?

The relationship between metabolic status and inflammatory status

Characterization of 19 mildly obese males (BMI 28):

- Transcriptome analysis of Peripheral Blood Mononuclear Cells
- Proteome analysis of 80 selected inflammation and metabolism related proteins
- Oral Glucose Tolerance Test with plasma sampling at t=0, 15, 30, 45, 60, 90 , 120, 180 minutes
  - Lipidome analysis at all time points
    - Free Fatty Acids
    - Inflammation related lipids
    - All TG, LPC, PC, Cholesterol esters, SPM
  - Metabolome analysis at all time points

ens wi ?


[77] sn−Glycerol−3−Phosphate−4TMS []
310000
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290000
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240000
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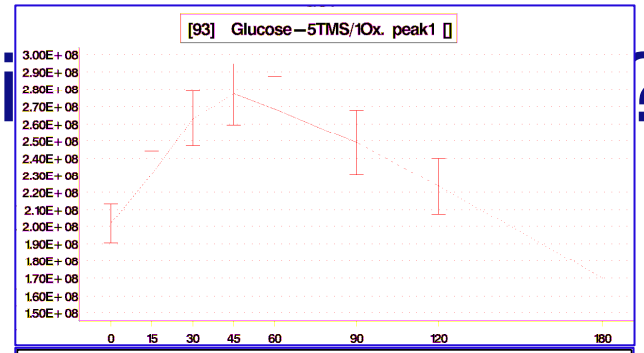
[93] Glucose−5TMS/1Ox. peak1 []
3.00E+08
2.90E+08
2.80E+08
2.70E+08
2.60E+08
2.50E+08
2.40E+08
2.30E+08
2.20E+08
2.10E+08
2.00E+08
1.90E+08
1.80E+08
1.70E+08
1.60E+08
1.50E+08
0
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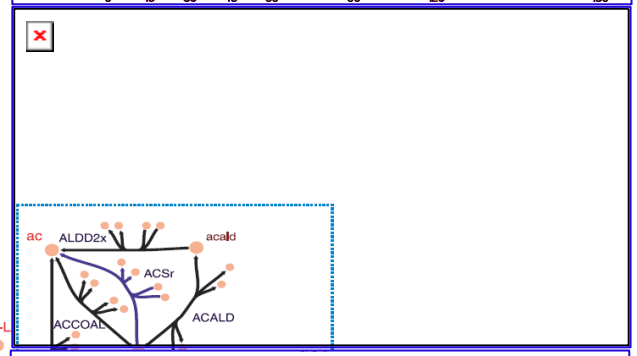
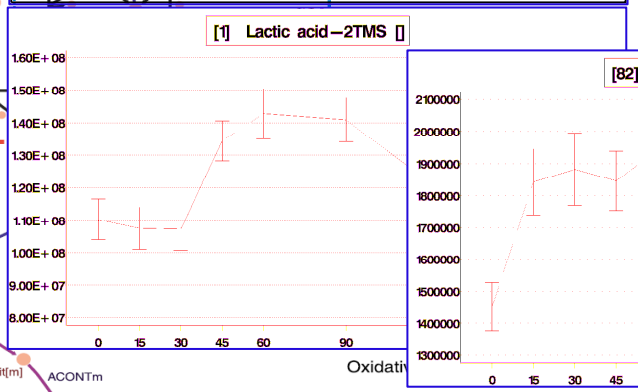

ac
ALDD2x
acald
ACSr
ACCOAL
ACALD


[1] Lactic acid−2TMS []
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
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15
30
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60
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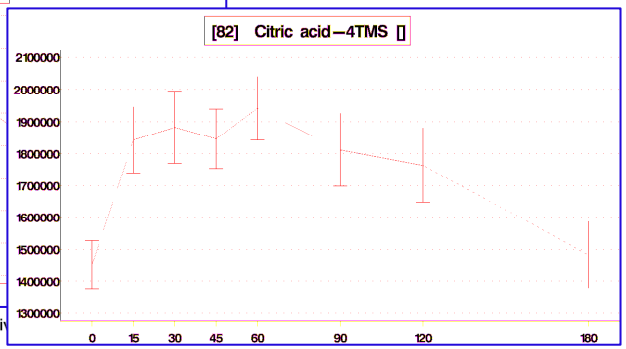
[82] Citric acid−4TMS []
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2000000
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1800000
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1400000
1300000
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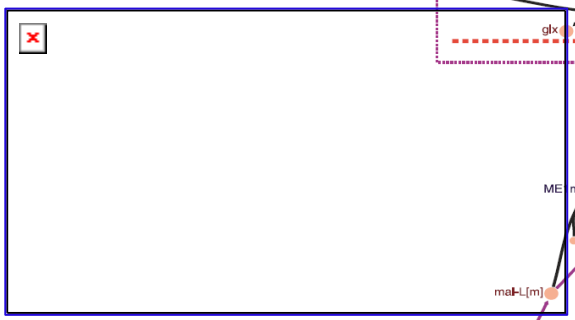

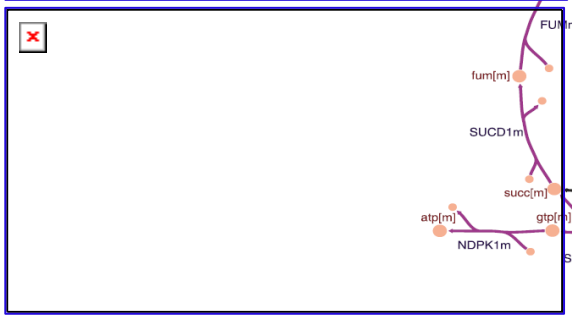

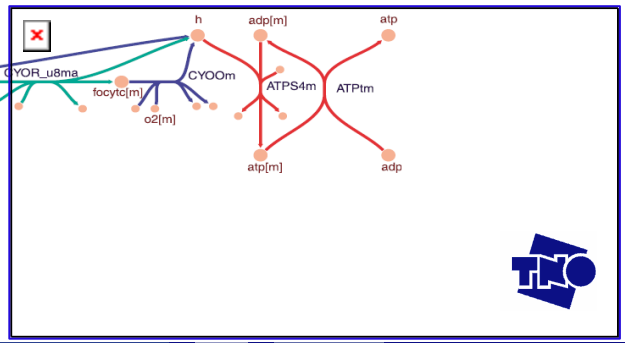
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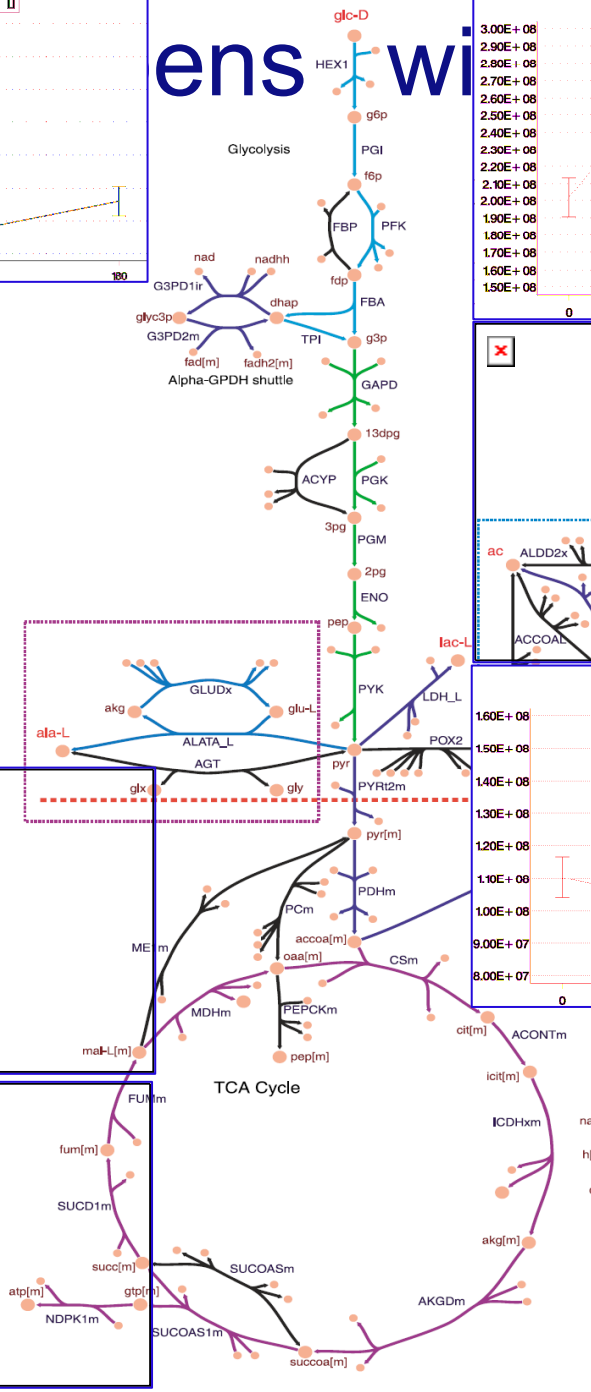
adp[m]
atp
CYOR_u8ma
CYOOm
ATPS4m
ATPtm
focytc[m]
o2[m]
atp[m]
adp


glc-D
HEX1
g6p
Glycolysis
PGI
f6p
FBP
PFK
fdp
nad
nadhh
G3PD1ir
dhap
FBA
glyc3p
G3PD2m
TPI
g3p
fad[m]
fadh2[m]
Alpha-GPDH shuttle
GAPD
13dpg
ACYP
PGK
3pg
PGM
2pg
ENO
pep
lac-L
PYK
LDH_L
GLUDx
akg
glu-L
ala-L
ALATA_L
POX2
AGT
pyr
glx
gly
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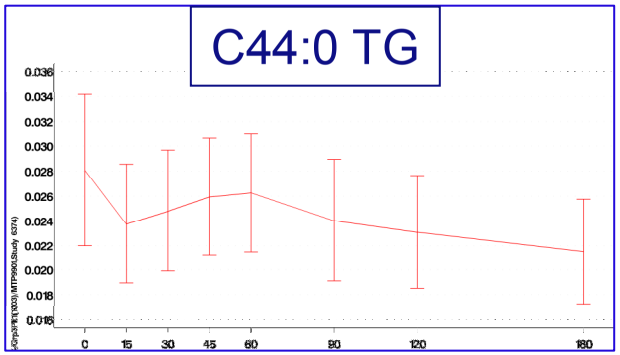
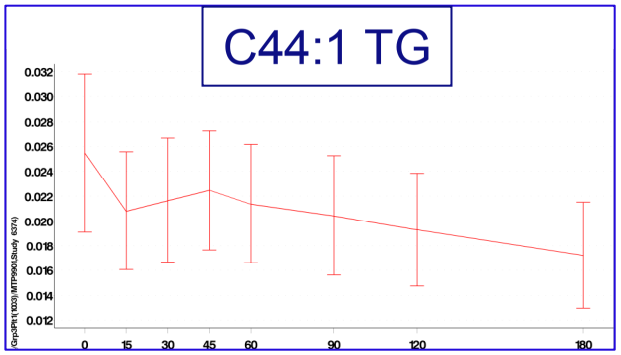
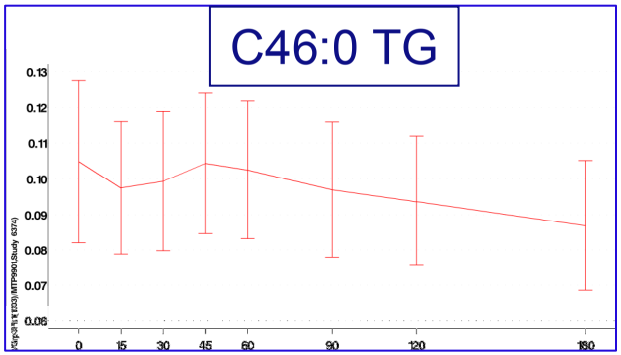
nad[m]
nadh[m]
NADH21m
q8h2[m]
h[m]
SUCD3-u8m
q8[m]

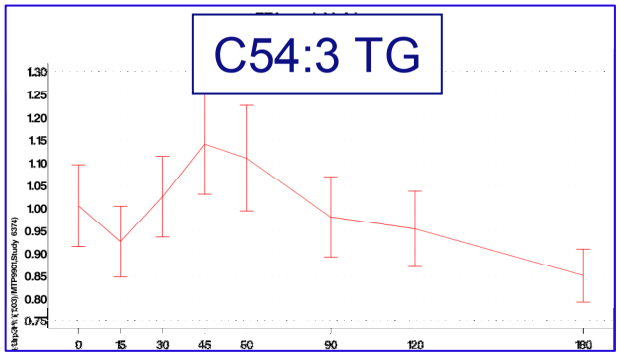
Short chain triglycerides are insensitive to glucose / insluin

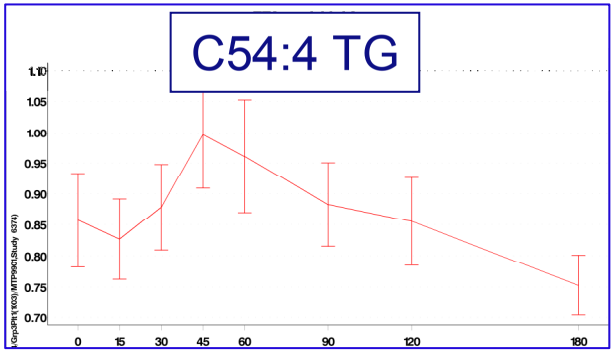


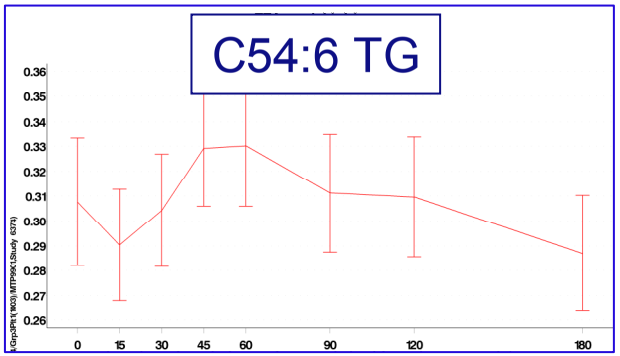


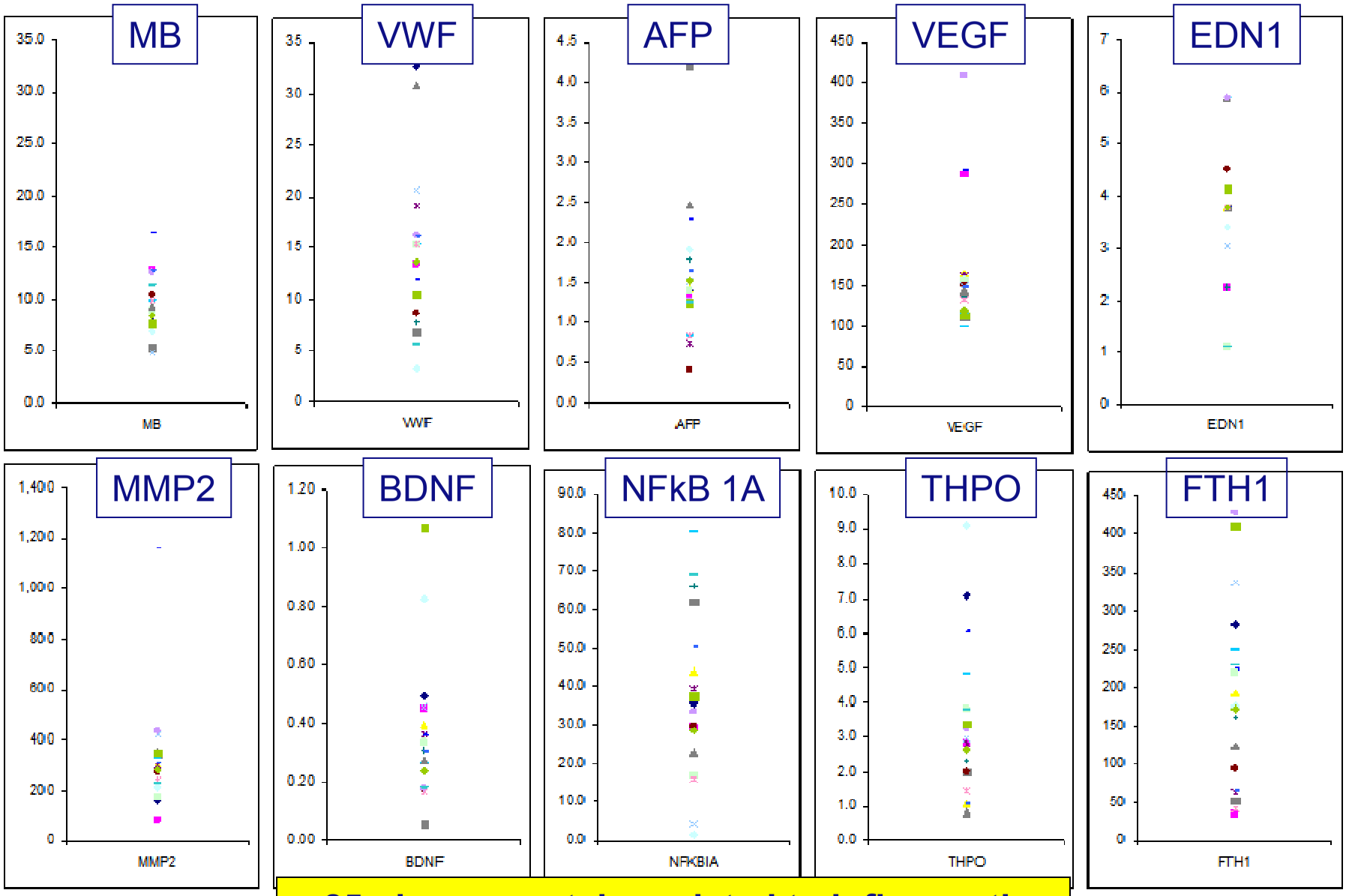


Long chain triglycerides are sensitive to glucose / insulin



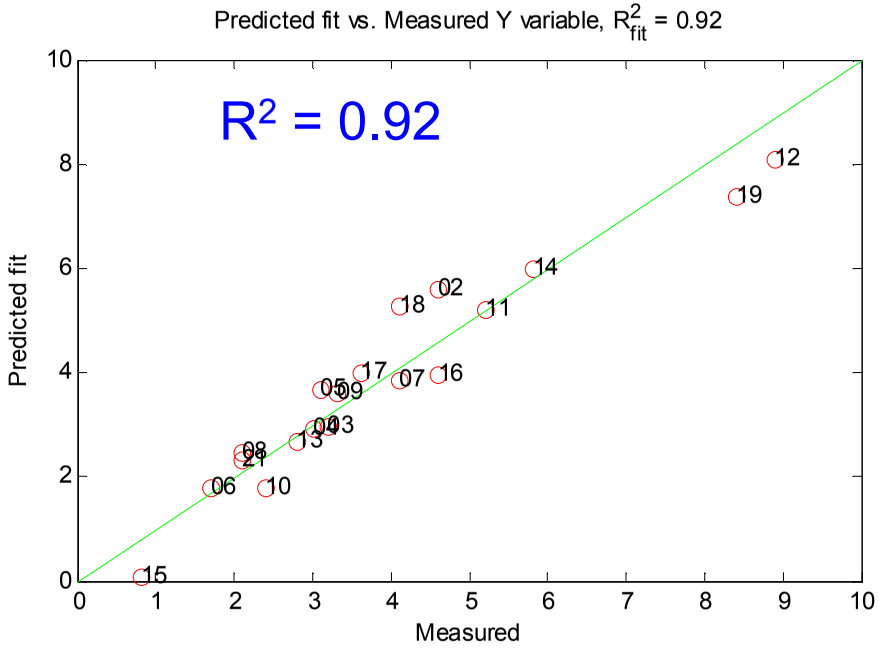


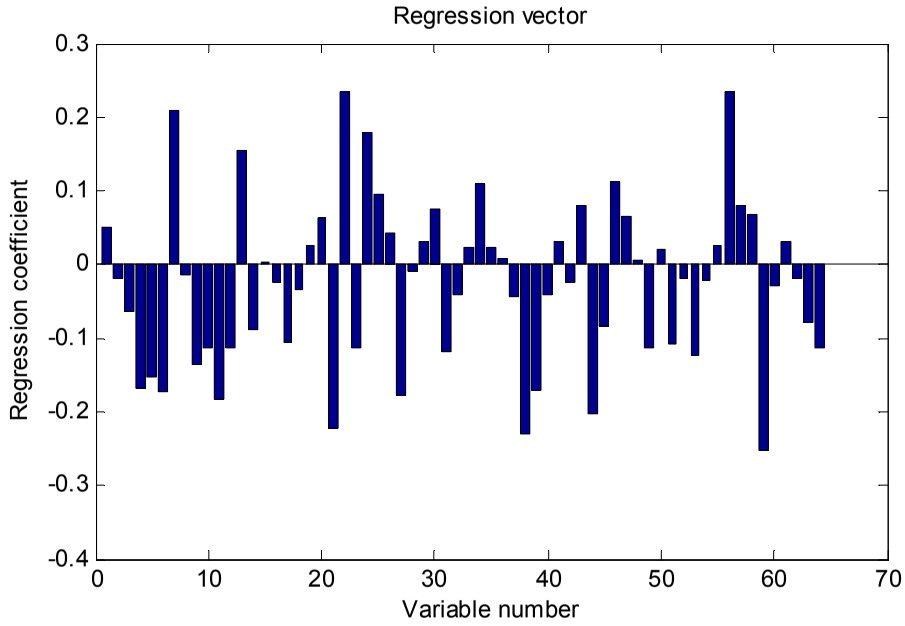




~ 85 plasma proteins related to inflammation analysed by RBM

PLS correlation between plasma inflammation proteome and Insulin Resistance

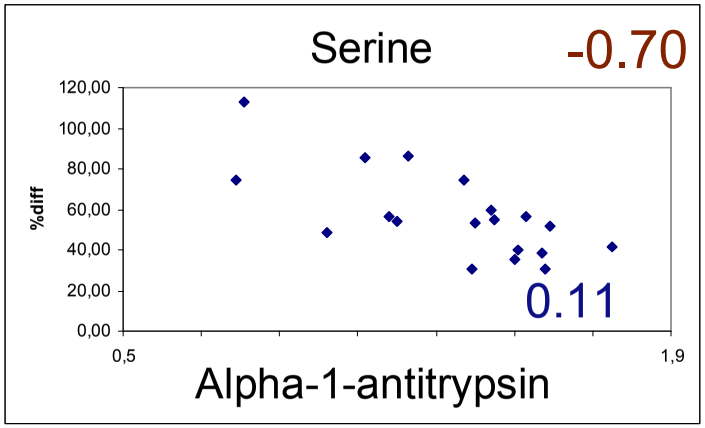


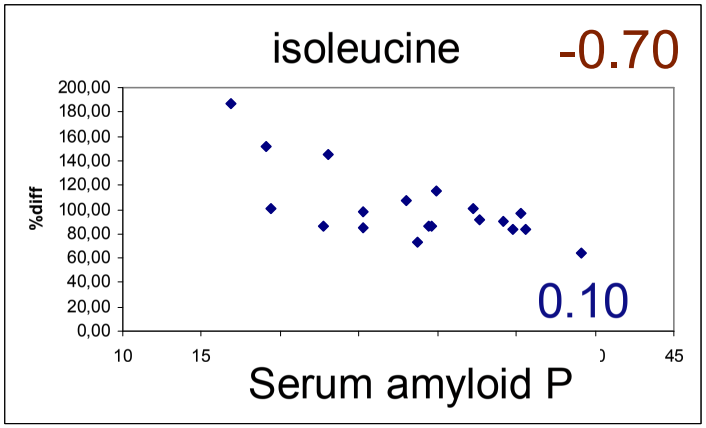


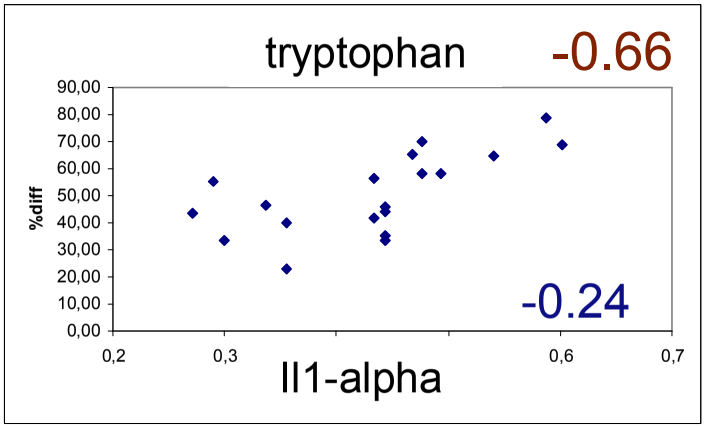
"Insulin resistance" determined by Oral Glucose Tolerance Test (ISIcomp)

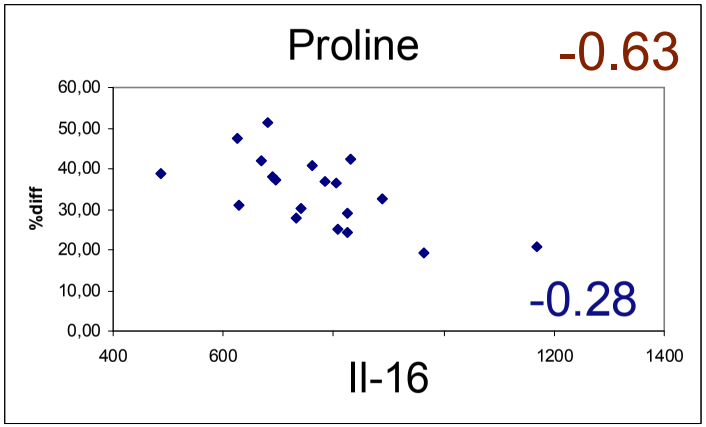
Strong correlation between insulin resistance and plasma "inflammation proteome, with many proteins involved

Correlation of Amino Acids OGTT-time curve with protein inflammation markers

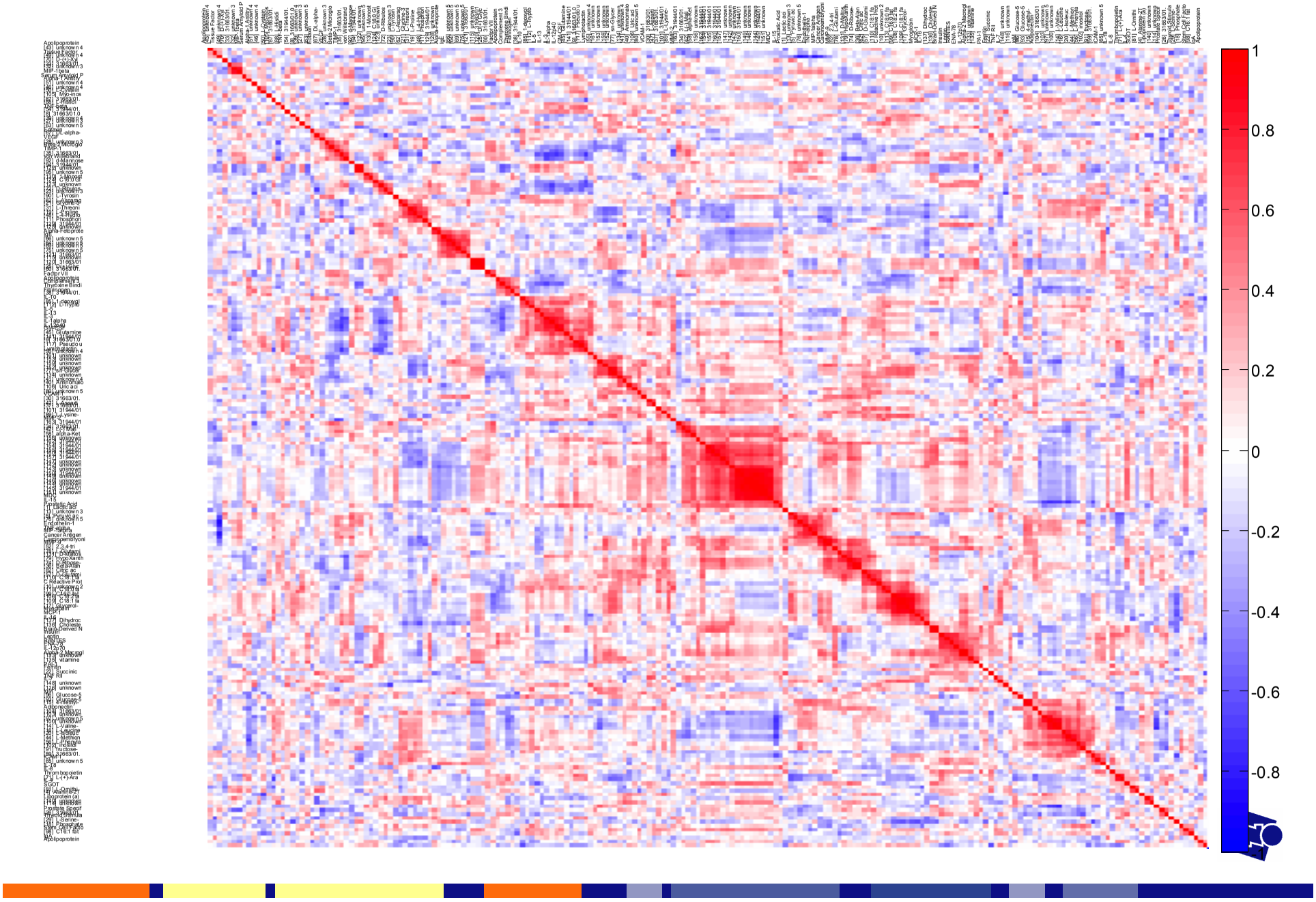




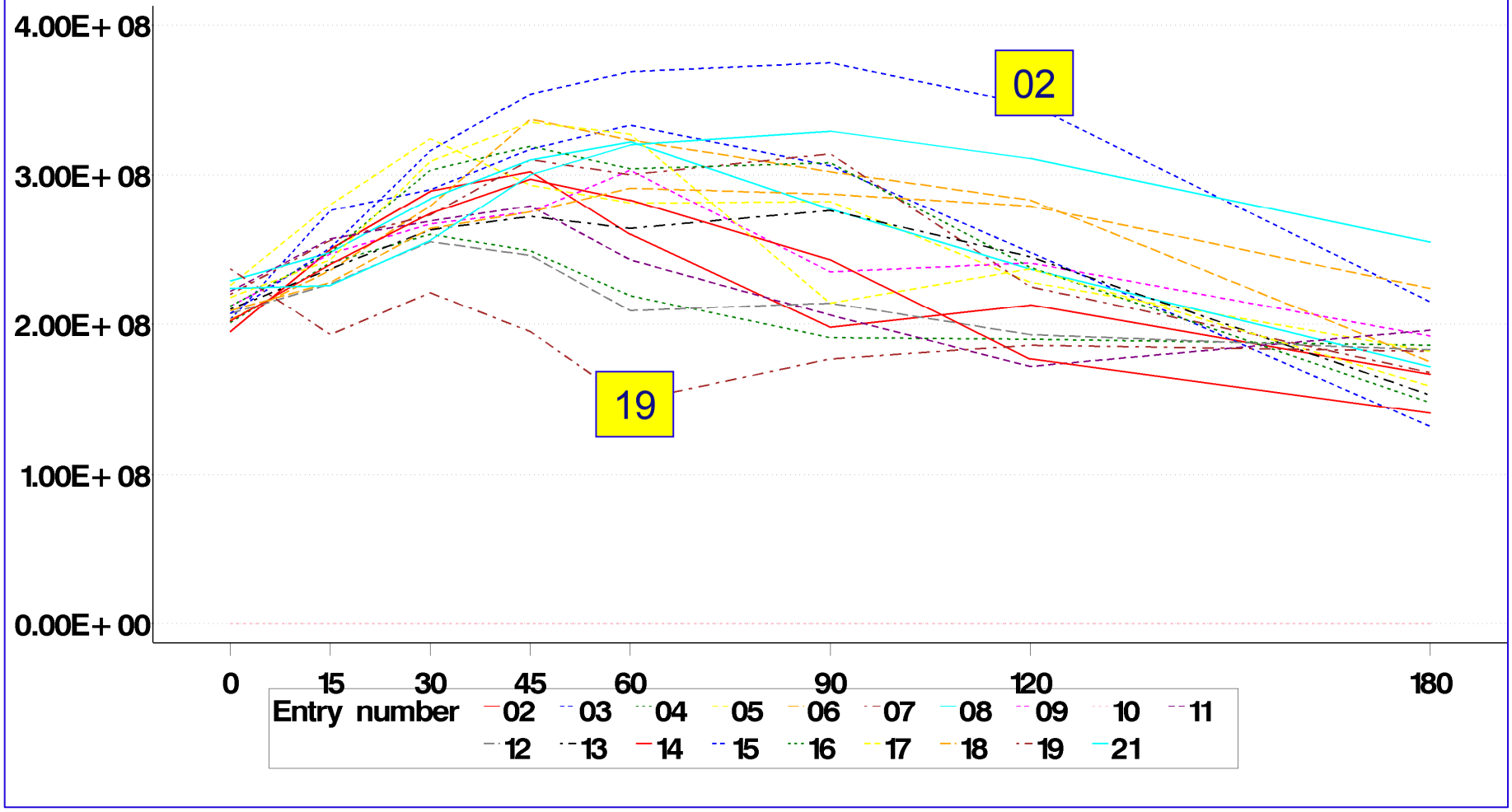




GC+RBM Correlation Map, Variables Regrouped by Similarity

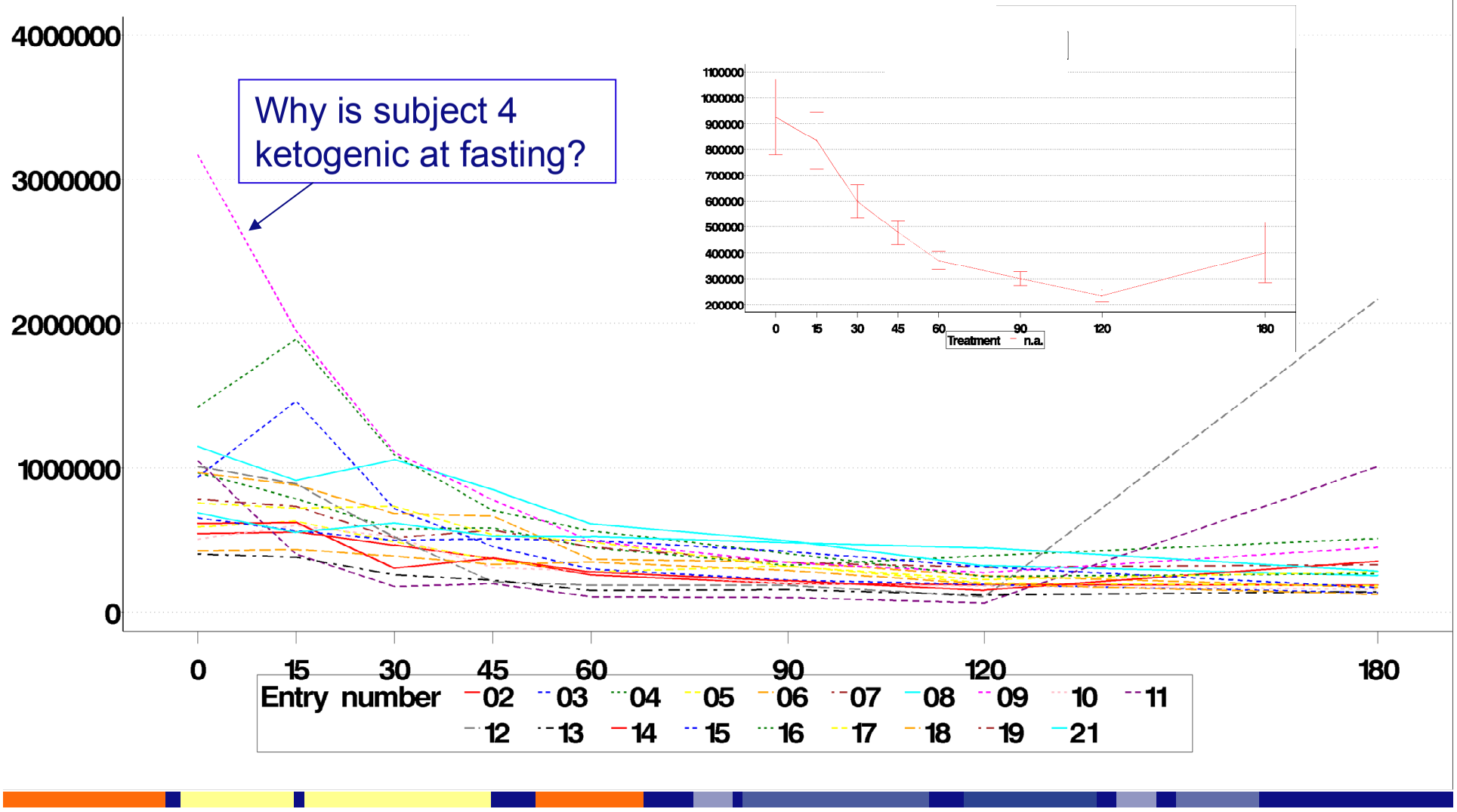


Individual glucose curves of 19 subjects: large interindividual differences

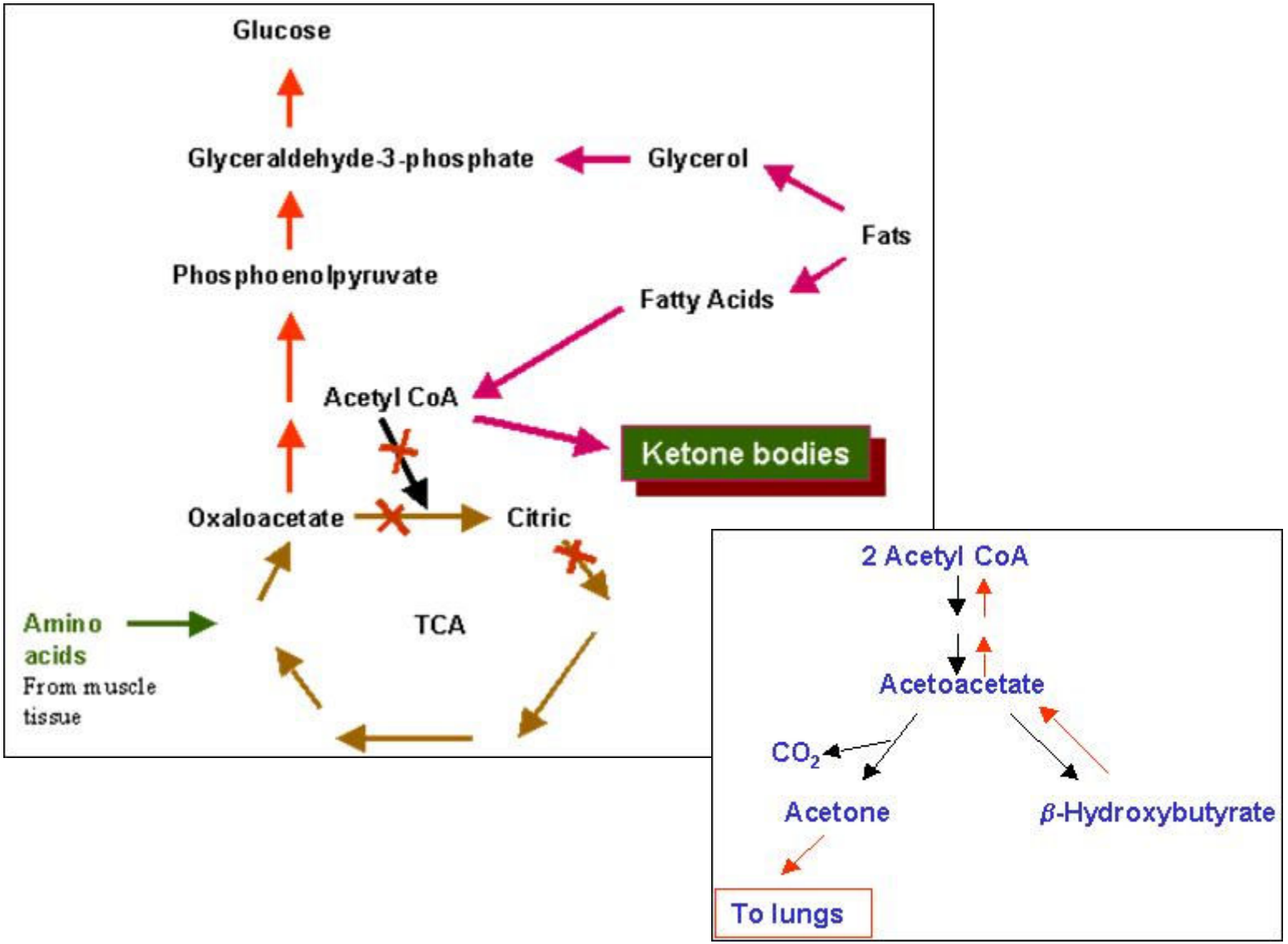


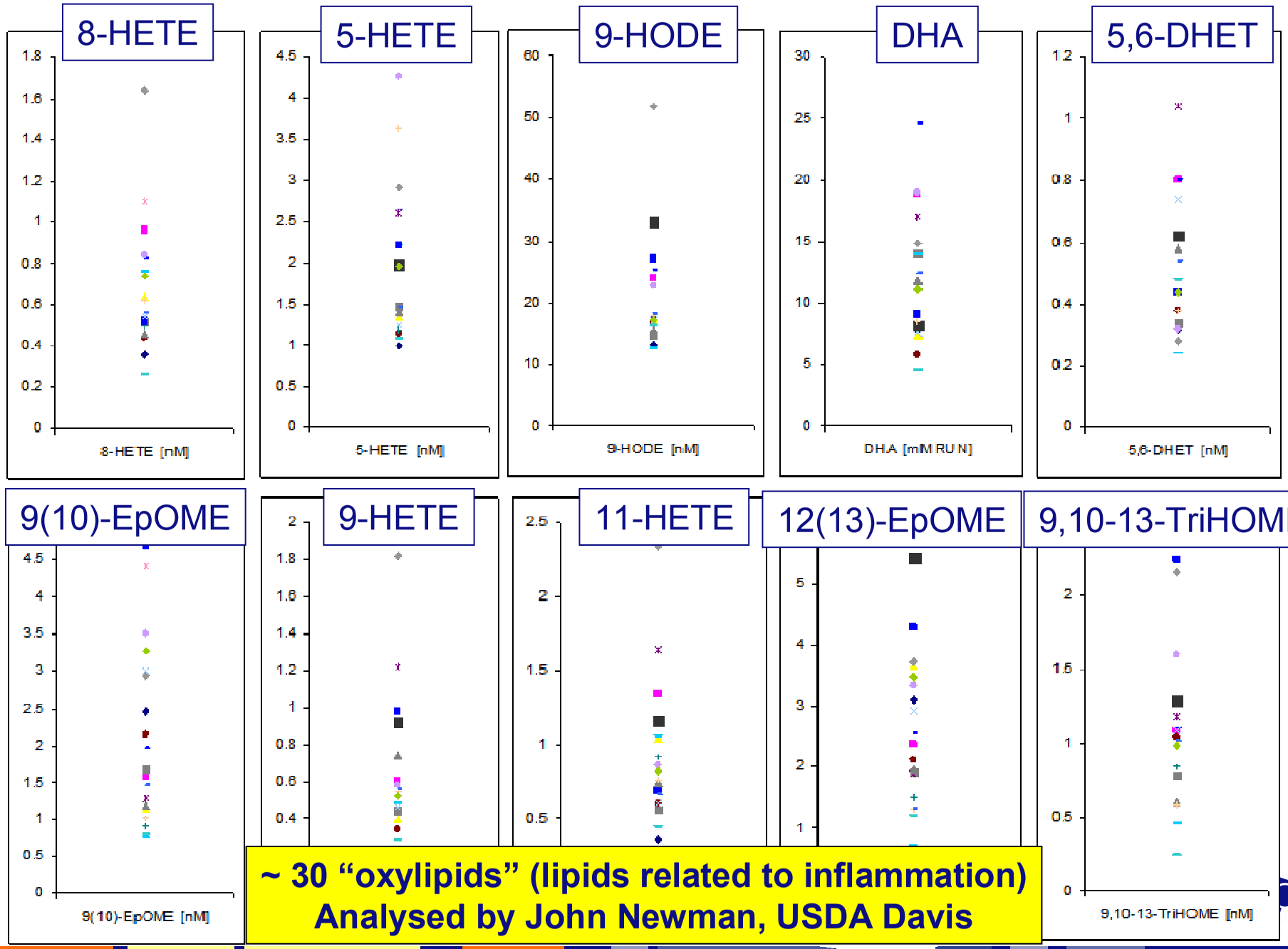
Metabolites added after identification

3-hydroxy butyrate



3-hydroxybutyrate is produced in excess of Acetyl CoA, either due to shortage of oxaloacetate (diabetes or fasting) or excess of fatty acids.



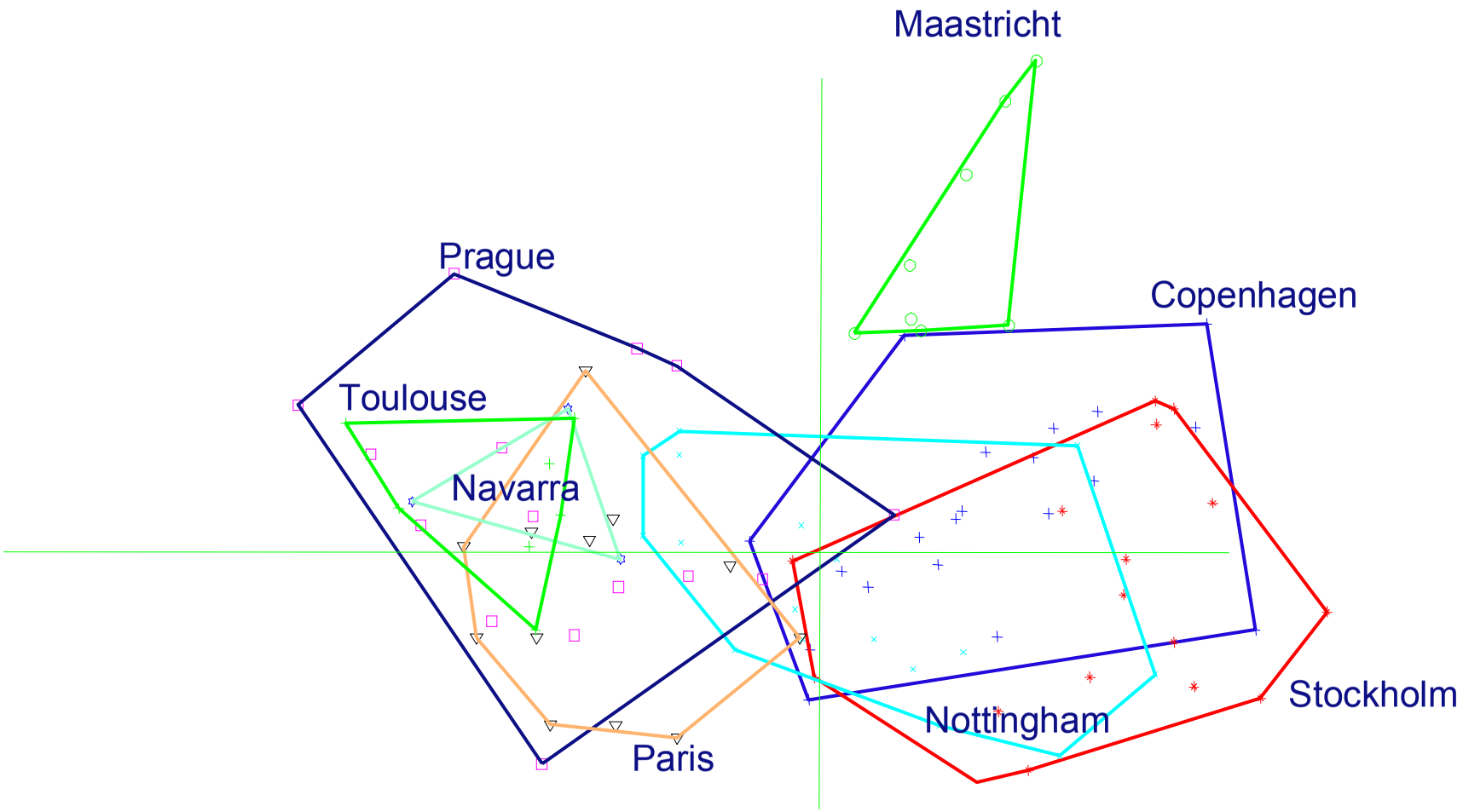


~ 30 "oxylipids" (lipids related to inflammation)
Analysed by John Newman, USDA Davis

Conclusion

As everybody is different, don`t “calculate away” the confounders but exploit differences to come to a personalised conclusion

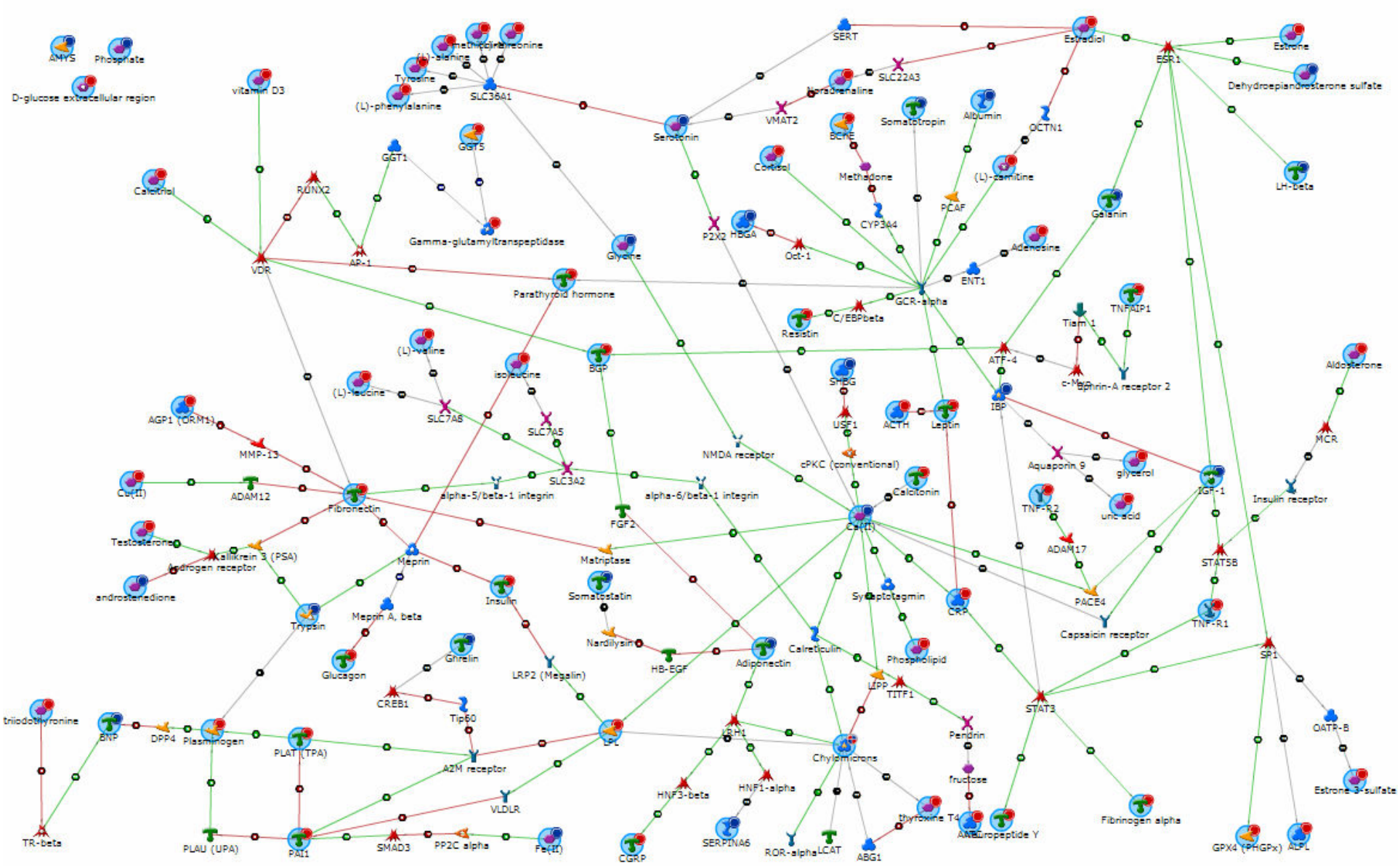
Differences between study center subcohorts in the Nugenob intervention study: fasting lipidome (~ 100 quantified lipids in plasma) before lipid intervention



(Nestlé–Nugenob–TNO data)

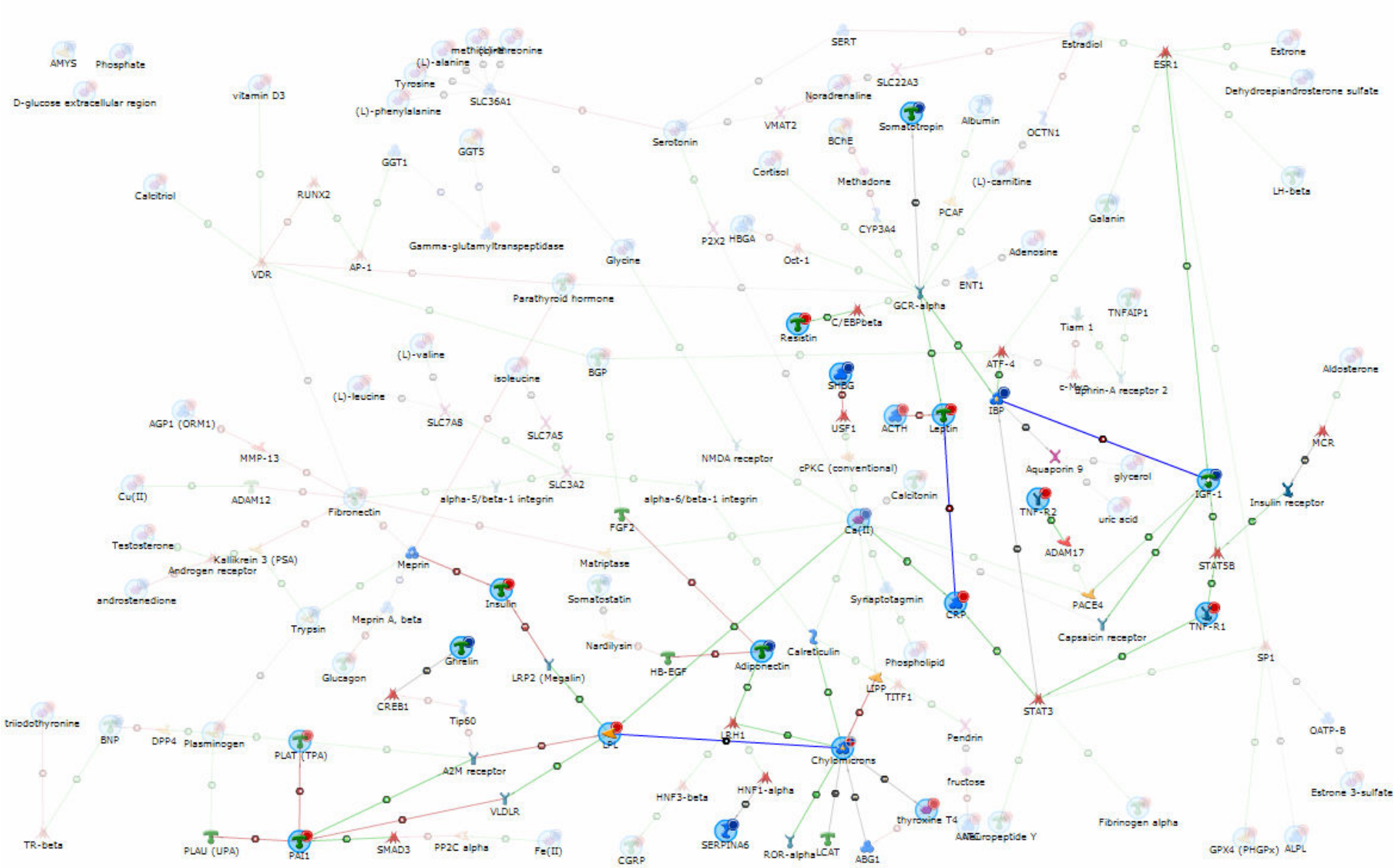
Obesity human plasma interactome

(proteins and metabolites in plasma involved in inflammatory processes and their biological interaction)

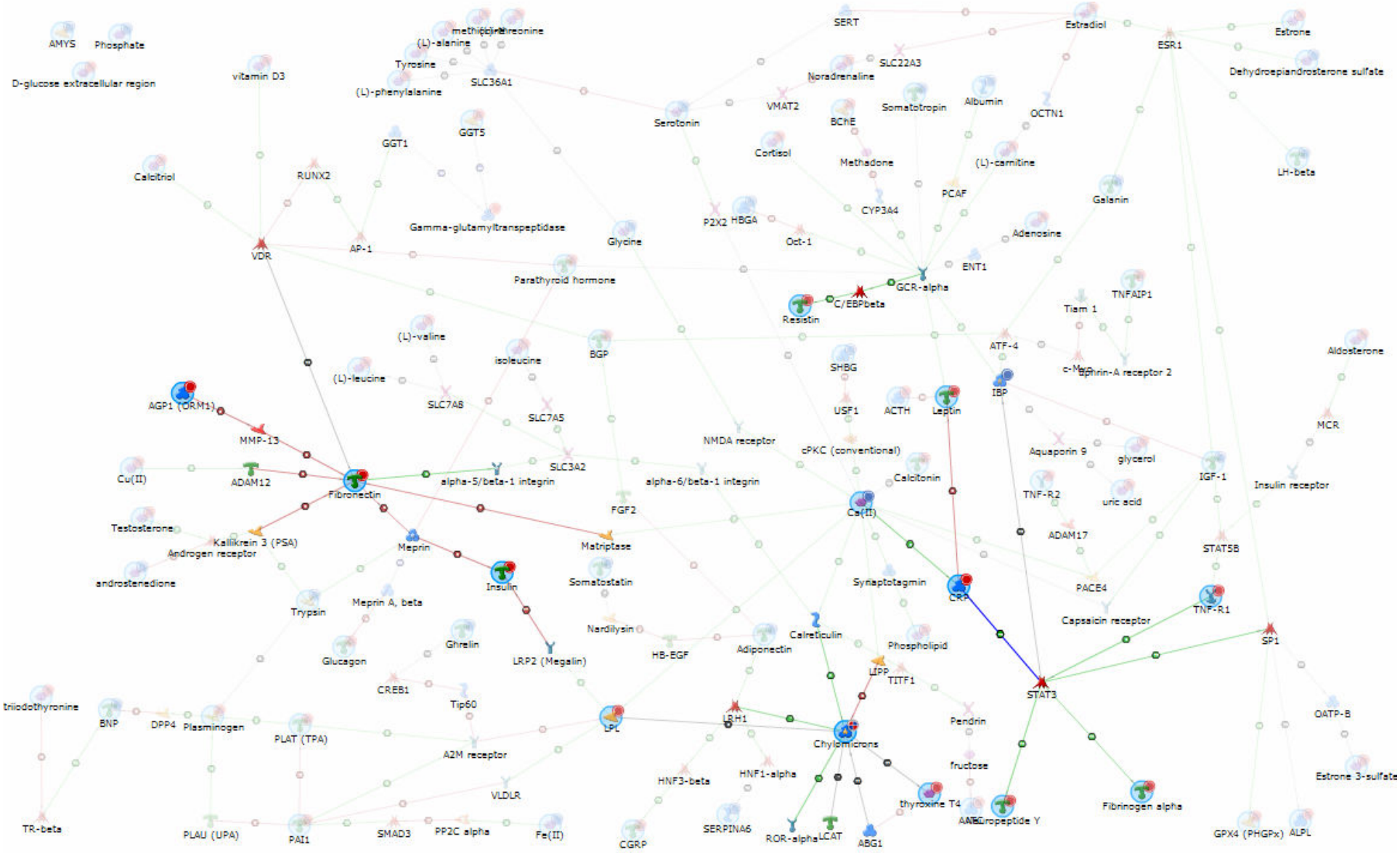


Components involved in insulin resistance

highlighted in human plasma obesity interactome



Components involved in acute phase response
highlighted in human plasma obesity interactome



The issue of low dose and hormesis

The time and dose factor …

This phenotype is too late …

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

Systematic Review and Meta-analysis

Goran Bjelakovic

JAMA, February 28, 2007—Vol 297, No. 8

nutrients usually do not have acute effects on health, so how to quantify the exposure → status → health effect relationship?

Vitamin D Supplementation and Total Mortality

A Meta-analysis of Randomized Controlled Trials

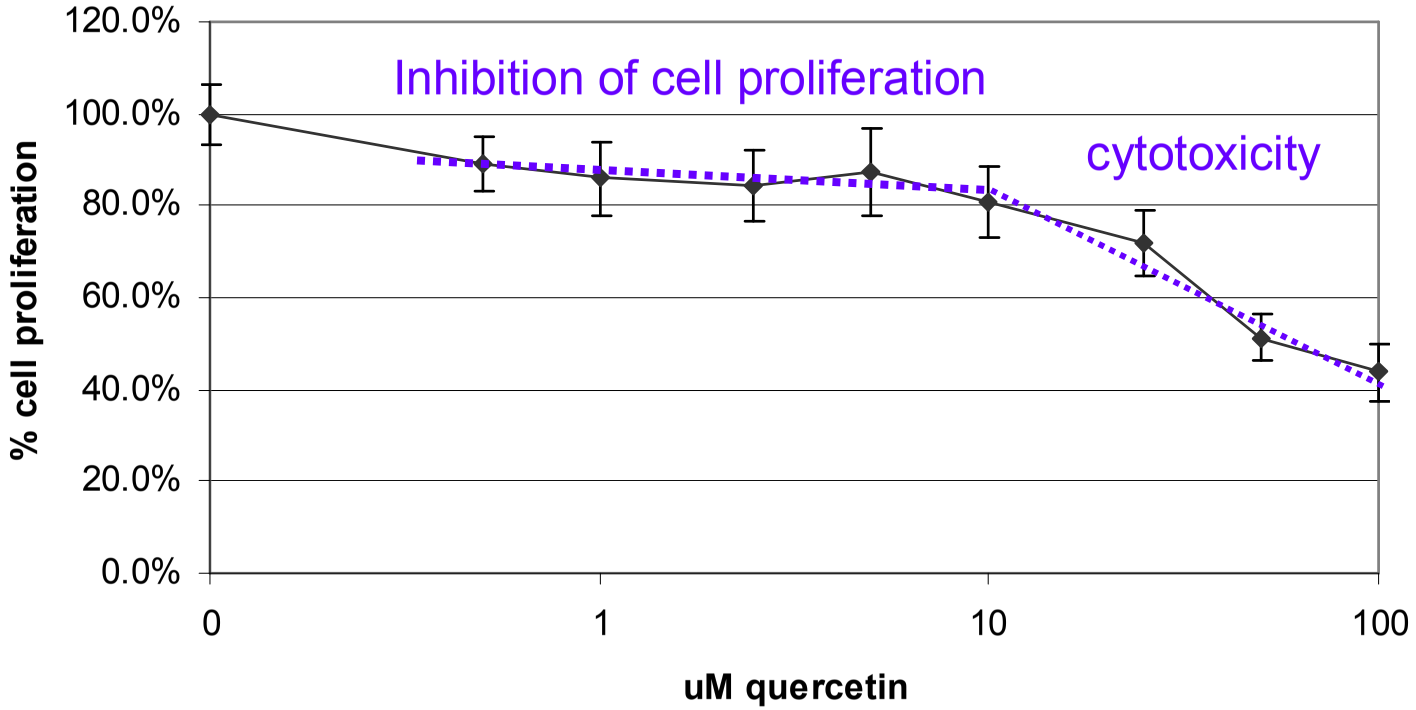
Philippe Autier, MD; Sara Gandini, PhD

Conclusions: Intake of ordinary doses of vitamin D supplements seems to be associated with decreases in total mortality rates. The relationship between baseline vitamin D status, dose of vitamin D supplements, and total mortality rates remains to be investigated. Population-based, placebo-controlled randomized trials with total mortality as the main end point should be organized for confirming these findings.

Arch Intern Med. 2007;167(16):1730-1737

Cell proliferation of Caco-2 cells exposed to quercetin for 48 hours

Concentration dependent biphasic effect

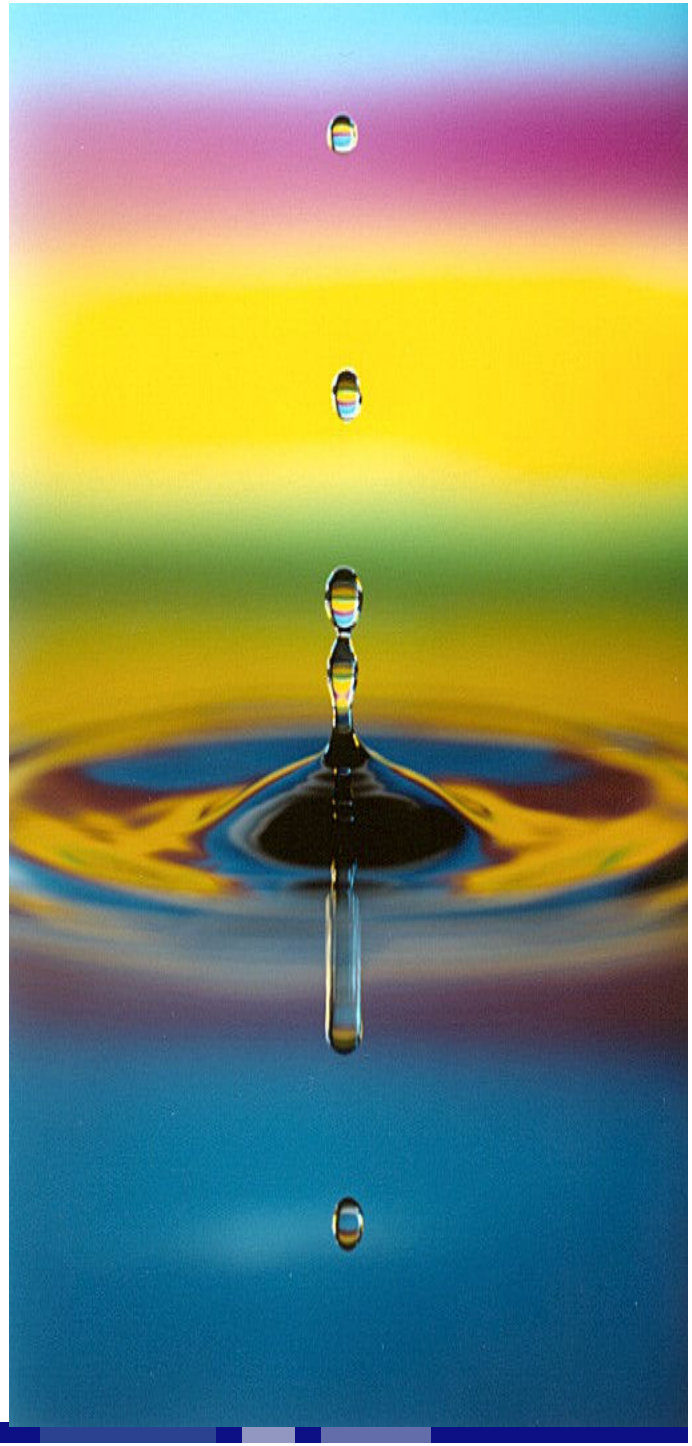


Medium refreshment after 24 hours, measured with BrdU incorporation. Proliferation in cells exposed to solvent control was set to 100%, values are mean ± standard deviation. Observations confirmed by flow cytometry.

Is hormesis a normal process in maintaining optimal health, but has it passed unnoticed because it didn`t fit in our picture?

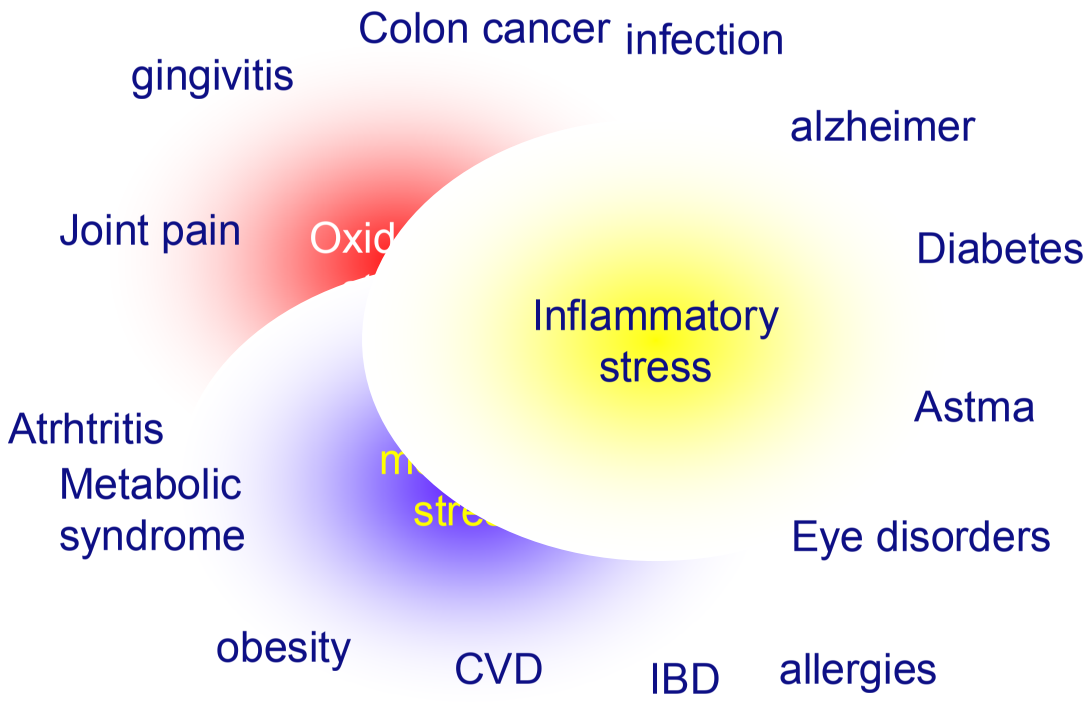
If this is true, many aspects of vitamins and supplements need to be reconsidered.

But this opens new roads for personalization …

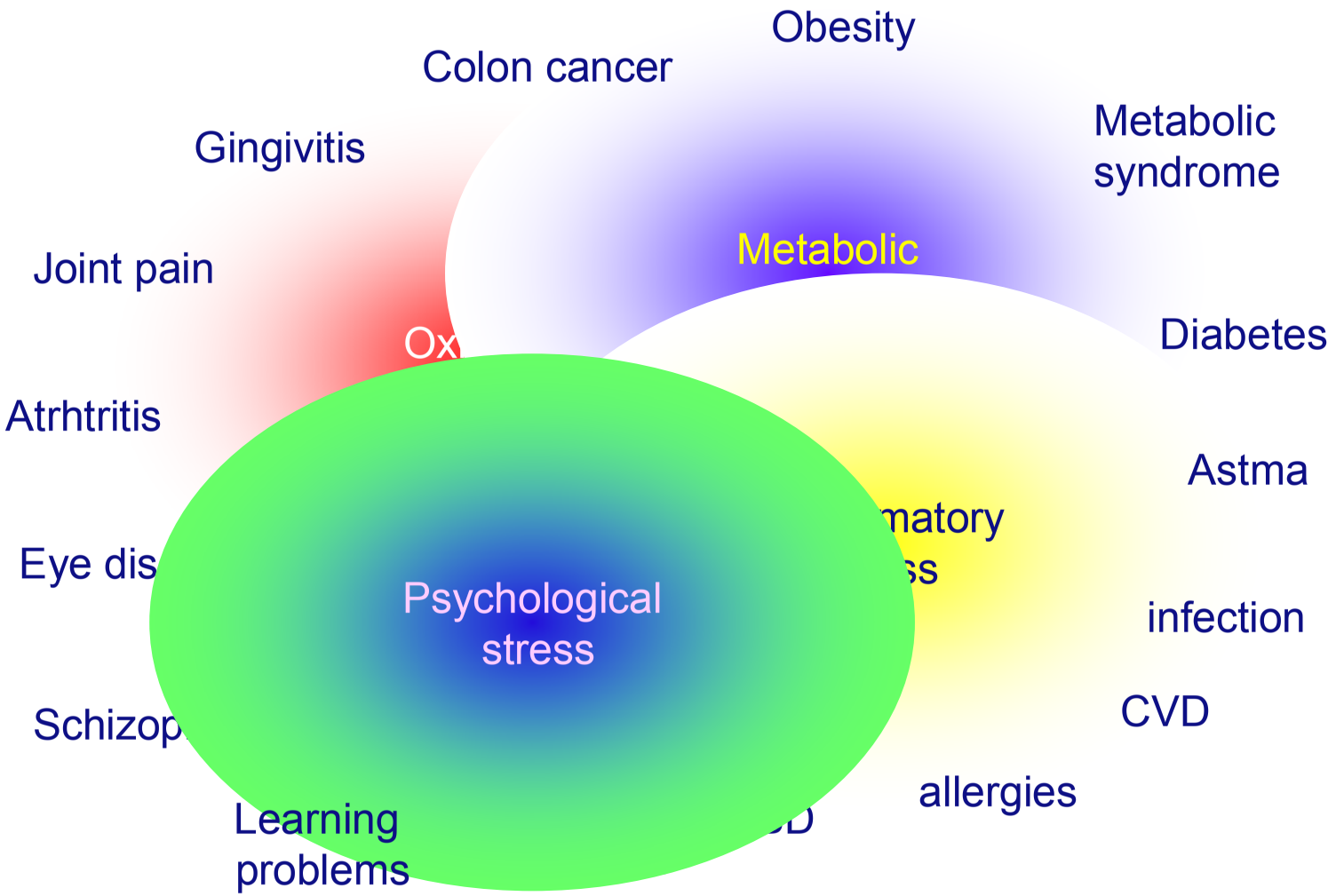


Cause

Health is not the absence of disease but the maintenance of overarching processes controlling health status.



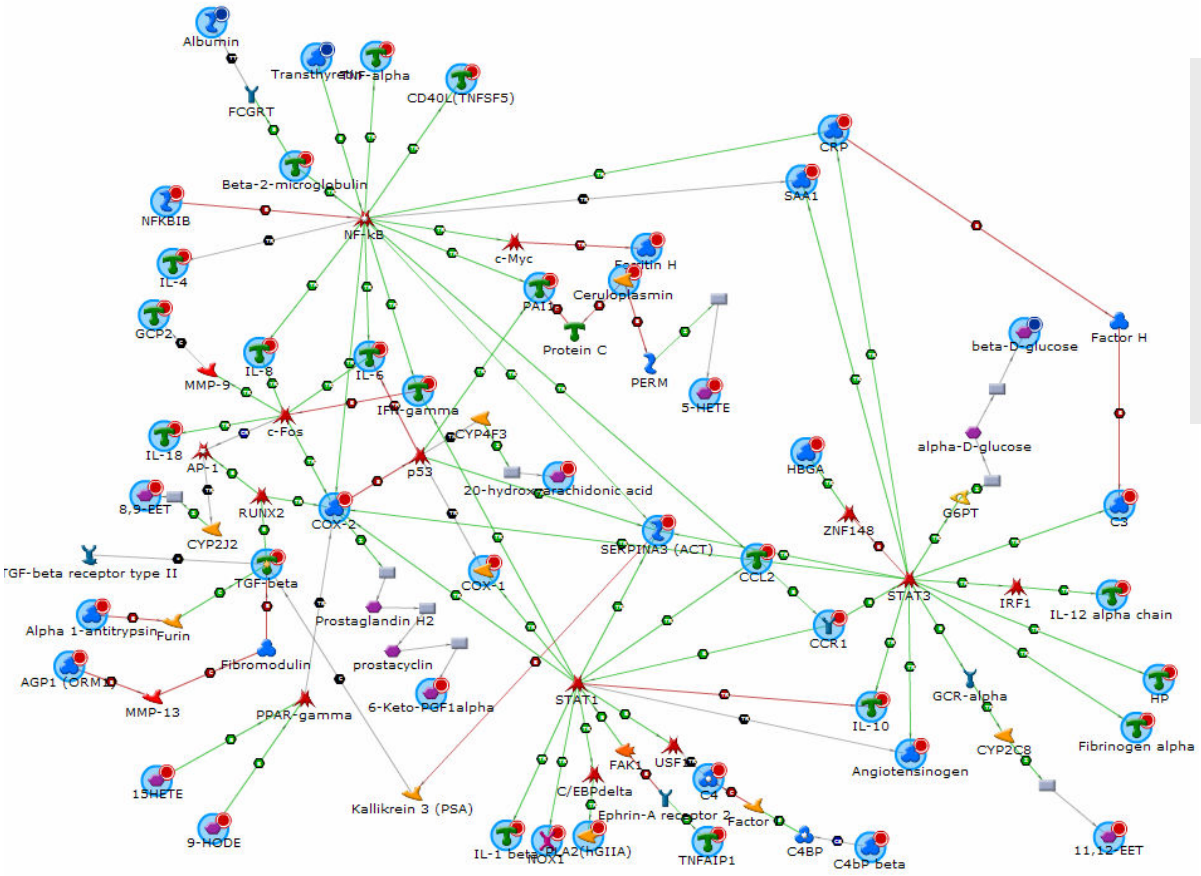
The interaction of metabolic, oxidative and inflammatory processes determines major components of the health status. Related stress causes development of many related diseases.



Thanks to Jaap Keijer

Complexity

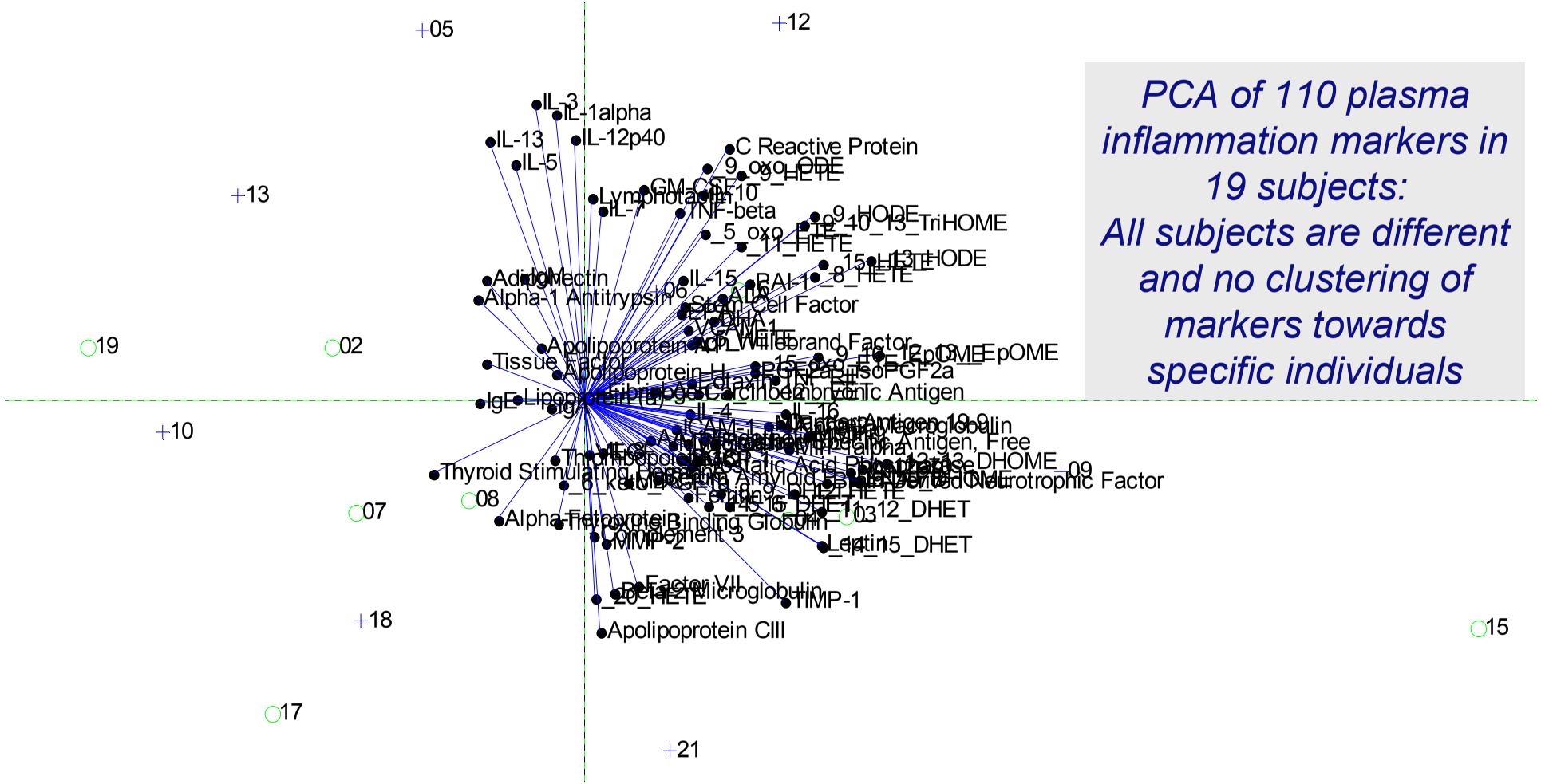
These overarching processes are (by nature) complex as the human organism constantly needs to subtly fine-tune these processes in response to changing environment.



The Human Plasma Inflammation interactome: proteins and metabolites in plasma involved in inflammatory processes and their biological interaction

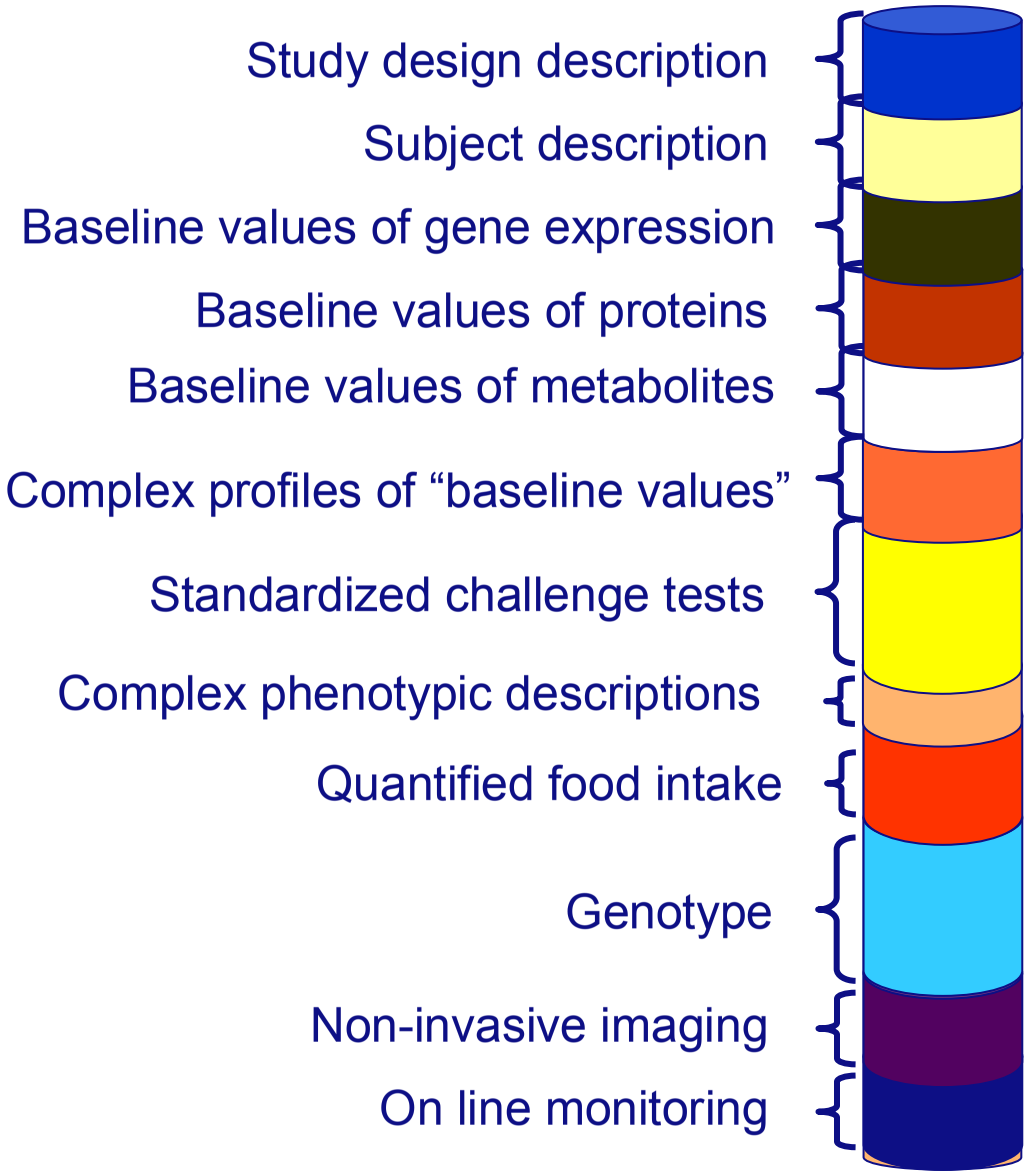
Individuality

The complexity of overarching processes should not be captured by average values but all relevant components should be taken into account in quantification of health status.



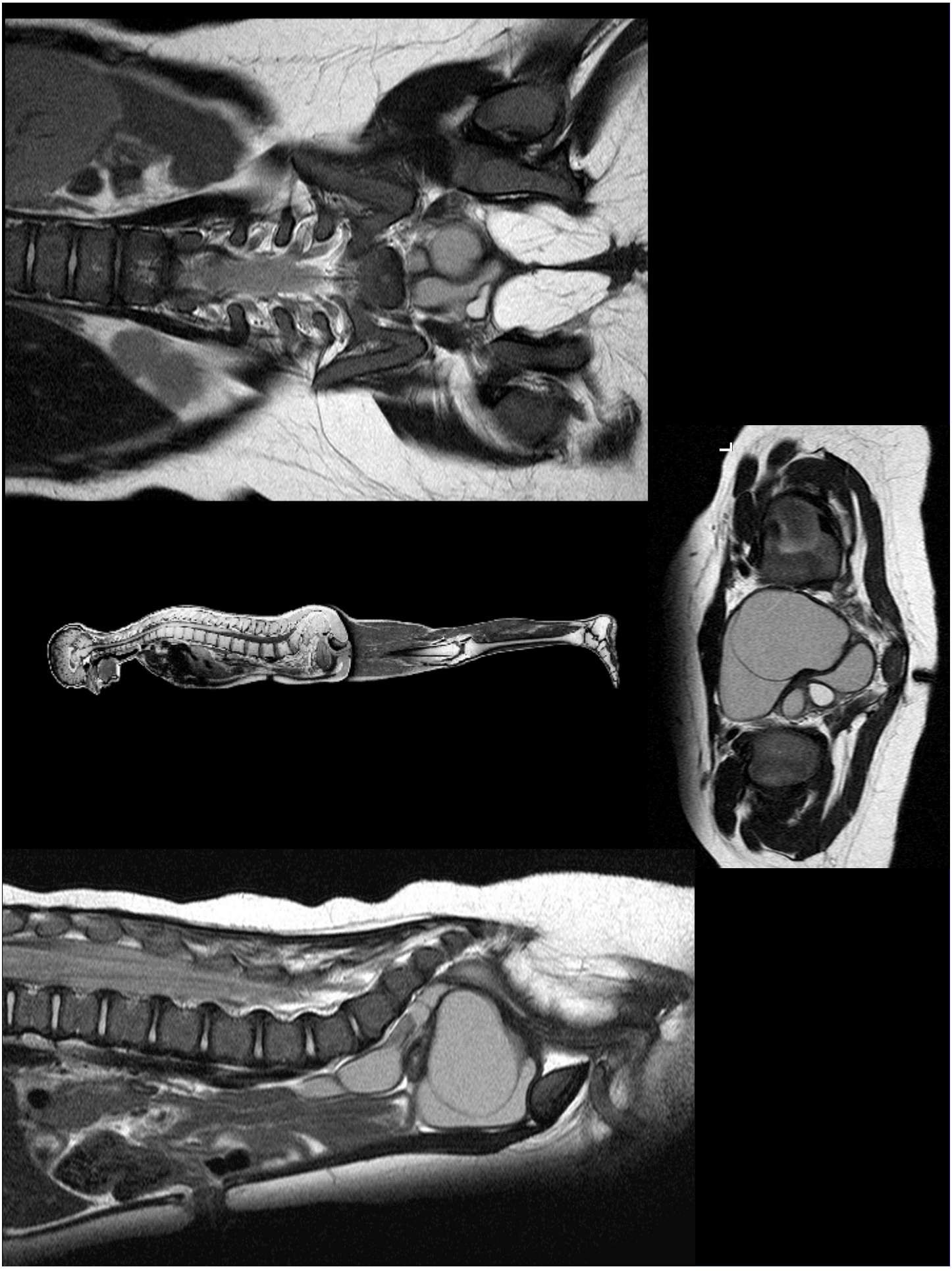
PCA of 110 plasma inflammation markers in 19 subjects:
All subjects are different and no clustering of markers towards specific individuals

How do we quantify “health” in a nutrition context?



The nutritional phenotype database:

An essential research tool relating nutrition to health and personalised dietary advise.



So …

Nutrition research, business and health care will dramatically change if we manage to link the healthy individual phenotype with dietary interventions.

These shifts will lead to new business models where health claims are better appreciated:

- The informed consumer
- Multilevel marketing and sales
- Internet channels
- Personalized nutrition

So …

The optimal personalised health/ nutrition business model will be a full merge of industries in the areas of

- nutrition
- diagnostics
- IT and knowledge management
- healthcare

do you agree … ?

Thanks to

Netherlands Nutrigenomics Consortium
Michael Muller and team

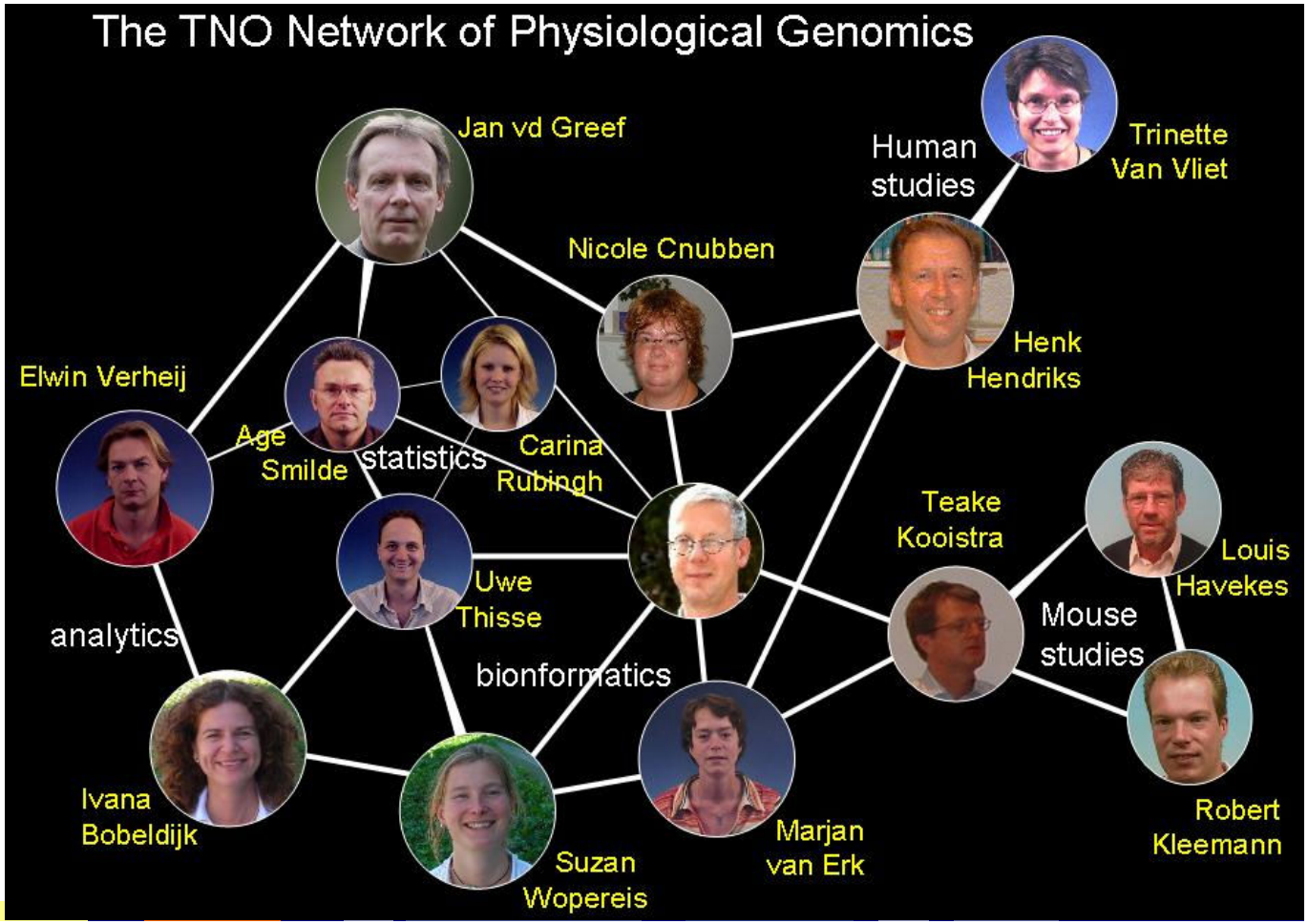
University of Alberta
David Wishart and
Human Metabolome team

Genego
Yuri Nikolsky

USDA Tufts
Jose Ordovas and team

USDA Davis
John Newman and team

Nestlé Research Center
Sunil Kochhar, Laurent Fay, Bruce German *et al*
Nugenob Thorkild Sorensen, Ian MacDonald *et al*



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