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.

PAST 2 WEEKS

Daily avg. eaten: 2292 burned: 2913

4k

3k

2k

1k

0k

May 20 – May 26

May 27 – Jun 02

BURNED  EATEN
Weight: 97.7 kg

Recent:
- Weight: 97.7 kg
- BMI: 28.55

Past Month:
- Weight on May 30: 97.7 kg
Biscuit, “hagelslag”, espresso, milk

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<th>content</th>
<th>Amount (g)</th>
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<td>Carbohydrate</td>
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T(max) 45 min
C(max) 5,7 mM
My “metabolism” is a system

Nakatsuji, Metabolism 2009
For optimal “phenotypic flexibility”, each process needs to function optimally

PHYSIOLOGY IS A SHOCK ABSORBER!
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

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

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

Pancreas
- Systemic insulin sensitivity
- b-cell failure

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

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

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

Kidney
- (re)absorption
- Urea cycle
- Tissue injury

Diagnosis assay: quantify the stress response (OGTT, OLTT, etc)
320 metabolites and 1270 proteins quantified after a "standard meal"
<table>
<thead>
<tr>
<th>Important processes in T2D</th>
<th>Diagnosis</th>
<th>Potential interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Pancreatic β-cell function (impaired insulin secretion)</strong></td>
<td><em>OGTT: I/ΔG and DI(0)</em>&lt;br&gt;*PYY, Arg, His, Phe, Val, Leu</td>
<td>Lifestyle; β-cell protective nutrients (MUFA/isoflavonoids); β-cell protective medication (TZDs, GLP-1 analogs, DPP4-inhibitors)</td>
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<td><strong>2. Muscle insulin resistance (decreased glucose uptake)</strong></td>
<td><em>OGTT: Muscle insulin resistance index, Insulin secretion/insulin resistance index</em>&lt;br&gt;<em>Val, Ile, Leu, Gamma-glutamyl-derivatives, Tyr, Phe, Met</em></td>
<td>PUFA/SFA balance; Physical activity; Weight loss; TZDs (e.g. PPARγ)</td>
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<tr>
<td><strong>3. Hepatic insulin resistance (decreased glucose uptake and increased hepatic glucose production-HGP)</strong></td>
<td><em>Hepatic insulin resistance index</em>&lt;br&gt;OGTT: Hepatic insulin sensitivity index&lt;br&gt;<em>ALAT, ASAT, bilirubine, GGT, ALP, ck-18 fragments, lactate, α-hydroxybutyrate, β-hydroxybutyrate</em></td>
<td>Decrease SFA and n-6 PUFA, and increase n-3 PUFA; Weight loss; Metformin; TZDs; Exenatide (GLP-1 analog); DPP4 inhibitors</td>
</tr>
<tr>
<td><strong>4. Adipocyte insulin resistance and lipotoxicity</strong></td>
<td><em>basal adipocyte insulin resistance index</em>&lt;br&gt;<em>FFA platform, glycerol</em></td>
<td>α-lipoic acid; PUFA/SFA balance; Omega 3 fatty acids; Chitosan/plant sterols; TZDs; Acipimox</td>
</tr>
<tr>
<td><strong>5. GI tract (incretin deficiency/resistance)</strong></td>
<td><em>ivGTT vs OGTT</em>&lt;br&gt;<em>GLP-1, GIP, glucagon, galzuren</em></td>
<td>MUFA; Dietary fibre (pasta/rye bread); Exenatide</td>
</tr>
<tr>
<td><strong>6. Pancreatic α-cell (hyperglucagononemia)</strong></td>
<td><em>fasting plasma glucagon</em></td>
<td>Glucagon receptor antagonists; Exenatide; DPP4 inhibitors</td>
</tr>
<tr>
<td><strong>7A. Chronic low-grade inflammation in pancreas, muscle, liver, adipose tissue, hypothalamus</strong></td>
<td><em>CRP, total leucocytes</em>&lt;br&gt;<em>V-CAM, I-CAM, Oxylipids, cytokines</em></td>
<td>Fish oil/n-3 fatty acids; Vit. C/Vit. E/Carotenoids; Salicylates; TNF-α inhibitors and others</td>
</tr>
<tr>
<td><strong>7B. Vascular inflammation</strong></td>
<td><em>CRP, total leucocytes</em>&lt;br&gt;<em>V-CAM, I-CAM, Oxylipids, cytokines</em></td>
<td>Fish oil/n-3 fatty acids; Vit. C/Vit. E/Carotenoids; Salicylates; TNF-α inhibitors and others</td>
</tr>
</tbody>
</table>
The 5-year efficacy of diabetes type 2 treatment

Kahn, NEJM 2006
Positive proof of global warming.

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-ll-blockers, beta-blockers, tumor angiogenesis-blockers, interleukin-5-blockers, etc.

adapted after Ton Nicolai
Systems flexibility is the key!

For optimal “phenotypic flexibility”, each process needs to function optimally.
Each organ has its specific processes related to metabolic health, and analytical methods to study/diagnose these processes.

**Relevant processes**

- Enterotypin, host-microbe interaction – "metabolic destiny"
- Gut-brain axis, energy expenditure regulation
- Absorption, intestinal integrity, barrier
- Gut-mediated inflammation control
- Chylomicron production

**Relevant analysis**

- Bile acids in plasma & faeces
- Barrier function / lactoluse, mannitol, campesterol, sitosterol
- Gut microbiota products in plasma (acetate, propionate, butyrate, IPA)
- 'Incretin' plasma proteins (GLP-1, PYY, Ghrelin, CCK-1)
- Lipoproteins in plasma (chylomicrons)
- LPS in plasma
- Metagenomics in faeces

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**Relevant processes**

- Reversible steatosis (lipoprotein, FA-ox)
- Insulin sensitivity (glucose homeostasis & control mechanisms)
- Energy metabolism (e.g. by FGF21)
- Inflammation / fibrosis
- Adipocyte production
- Toxicity, liver functioning, liver injury

**Relevant analysis**

- Core metabolism (citric acid cycle, beta-oxidation, glycogen cycle, PPP, amino acid metabolism, glucose metabolism etc) in plasma
- Lipoprotein production (VLDL, HDL particles), carnitines, cholesterol and other sterols, bile acids in plasma
- Acute phase proteins (CRP, SAA, fibrinogen etc) in plasma
- ALAT, ASAT, etc in plasma
- CLAMP analysis
- Body composition (Inbody, dexa, MRI)

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**Relevant processes**

- Reversibility (localisation, "jo-jo")
- Expandability (hyperplasia vs. hypertrophy, ECM modifications)
- Inflammation (macrophage infiltration)
- Insulin sensitivity (glucose hom, lipolysis)
- Lipokine production
- Pediatric (non invasive)

**Relevant analysis**

- Free fatty acid and estimated SCD activity in plasma
- Adiponectin, C16:1, leptin, resistin in plasma
- Crown like structure staining Lipid & enzyme activity measurements in adipose tissue biopsies
- Cytokine and chemokine measurements in adipose tissue biopsies
- CLAMP analysis
- Body composition (Inbody, dexa, MRI)

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**Relevant processes**

- Lipotoxicity (cellular accumulation of ceramides & diglycerides → altered insulin)
- Protein metabolism
- Metabolic flexibility – capacity to adapt muscle metabolism to carb/lipid switch, oxidative stress
- Heart muscle (Diabetes)

**Relevant analysis**

- Ceramides, DG in plasma
- Creatine/creatinine in plasma
- Branched chain amino acids in plasma
- Carnitines in plasma
- Glycogen in plasma
- Muscle biopsy measurements
- Extracellular matrix components in plasma
- CLAMP analysis

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**Relevant processes**

- Lipotoxicity
- Macrophage infiltration
- Inflammatory stress response
- Resilience of inflammatory homeostasis
- Chronic low-grade inflammation
- Resolution of inflammation
- Nutrient sensing - inflammation control

**Relevant analysis**

- Bile acids in plasma & faeces
- Barrier function / lactoluse, mannitol, campesterol, sitosterol
- Gut microbiota products in plasma (acetate, propionate, butyrate, IPA)
- 'Incretin' plasma proteins (GLP-1, PYY, Ghrelin, CCK-1)
- Lipoproteins in plasma (chylomicrons)
- LPS in plasma
- Metagenomics in faeces

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**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)
- OGGT with metabolic profiling
Blood vessels
In human studies, we quantify ~120 plasma inflammation related proteins

**Macrophages**
- TNFα
- IL1β
- platelet derived growth factor
- IFNγ
- MMP1
- MMP8
- MMP13
- Myeloid Related Protein14
- CD40
- CD40L
- tissue factor

**Monocytes**
- MMP9

**Endothelial cells**
- P-selectin
- VCAM1
- ICAM1
- MCP1/CCL2
- platelet derived growth factor
- CSF1
- NO
- CD40
- CD40L
- tissue factor
- CD40L

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

**Foam cells**
- IL18
- IL18Rα/β

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

**Adipose tissue**
- adiponectin
- IL18
- PAI1

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

**Endothelial cells**
- P-selectin
- VCAM1
- ICAM1
- MCP1/CCL2
- platelet derived growth factor
- CSF1
- NO
- CD40
- CD40L
- tissue factor
- CD40L

**Macrophages**
- TNFα
- IL1β
- platelet derived growth factor
- IFNγ
- MMP1
- MMP8
- MMP13
- Myeloid Related Protein14
- CD40
- CD40L
- tissue factor

**Liver**
- CRP
- PAI1
- fibrinogen

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

**HDL**
- LDL
- oxLDL
- Thrombin
- Factor VII
- paraoxonase 1
- Angiotensin II
- Lipoprotein lipase
- Hepatic lipase
- MPO
- Lipoprotein associated phospholipase A2
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 inflammation 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 allows quantification of enormous # of parameters.

- Proteome: 1240 proteins
- Lipidome: 78 lipids
- Metabolome: 198 metabolites
- Transcriptome: 11,000 genes
- Clinical chemistry: ~30 parameters

'omics' analysis includes:
- Proteins
- Lipids
- Metabolites
- Genes

Image: Antigen presentation, cytokines, interferons, etc., illustrating the complexity of the 'omics' analysis.
Eicosanoid related inflammation (but no effect PGE2)

Increased expression of prostaglandin metabolism genes in adipose tissue

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

Protective against atherosclerosis?
Effect on inflammation: part of the Inflammatory profile in plasma

-15 -10 -5 0 5 10
8-iso prostaglandin F2-alpha
VCAM-1
ICAM-1
Ferritin
Beta-2 Microglobulin
IL-18
adiponectin
% change
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)
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 · Gertruid 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

Plasma huCRP (µg/ml)

- Placebo
- AIDM

Plasma Fibrinogen (mg/ml)

- before
- 6 wk treatment
- 6 wk treatment + IL-1β stimulation

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

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<th>buckwheat</th>
<th>cornmeal</th>
<th>millet</th>
<th>oats</th>
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Key:
- < 10% of daily value
- ≥ 10% of daily value
- ≥ 20% of daily value
  - Good Source
- ≥ 50% of daily value
- ≥ 100% of daily value
  - Excellent Source

na = not applicable
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

Oxidative stress
Inflammatory stress

energy

time
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?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>unit</th>
<th>My value</th>
<th>min</th>
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<tr>
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<td>mmol/l</td>
<td>1.2</td>
<td>&gt;0.9</td>
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<tr>
<td>Potassium</td>
<td>mmol/l</td>
<td>3.9</td>
<td>3.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Blood Press sys</td>
<td>mm Hg</td>
<td>141</td>
<td></td>
<td>140</td>
</tr>
<tr>
<td>Blood Press dia</td>
<td>mm Hg</td>
<td>90</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>b/min</td>
<td>73</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypertension in physically unfit individuals

<table>
<thead>
<tr>
<th>Journal</th>
<th>Genotype</th>
<th>What It Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>TT</td>
<td>Moderately higher odds of hypertension in physically unfit individuals.</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>Moderately higher odds of hypertension in physically unfit individuals.</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>Typical odds of hypertension in physically unfit individuals.</td>
</tr>
</tbody>
</table>

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 subjects.

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, Giulio Ceolotto, Fabio Ragazzo, Francesca Dorigatti, Francesca Saladini, Italia Papparella, Lucio Mos, Giuseppe Zanata and Massimo Santonastaso

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.
Caffeine Metabolism

About Caffeine Metabolism

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

<table>
<thead>
<tr>
<th>Journal</th>
<th>Study Size</th>
<th>Replications</th>
<th>Contrary Studies</th>
<th>Applicable Ethnicities</th>
<th>Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAMA</td>
<td></td>
<td>None</td>
<td>None</td>
<td>European</td>
<td>rs762551</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who</th>
<th>Genotype</th>
<th>What It Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben van Ommen</td>
<td>AA</td>
<td>Fast caffeine metabolizer: drinking coffee didn't increase subjects' heart attack risk</td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td>Slow caffeine metabolizer: drinking coffee increased subjects' heart attack risk</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>Slow caffeine metabolizer: drinking coffee increased subjects' heart attack risk</td>
</tr>
</tbody>
</table>

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 included 12,000 participants, all of whom drank coffee.
Is it that simple?

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

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

Coffman, Nature Medicine 2011
Potassium supplementation for the management of primary hypertension in adults (Review)

Original Article

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

Effect of cocoa on blood pressure (Review)

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

Short term studies effective (2 weeks)
Long term studies not effective (8 weeks)
Beneficial Effects of Alternate Dietary Regimen on Liver Inflammation, Atherosclerosis and Renal Activation

Peter Y. Wielinga¹,²,³, Gopala K. Yakala²,³, Peter Heeringa²,³, Robert Kleemann¹,³, Teake Kooistra¹

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

A) Plasma cholesterol (mM)

- CON
- HC
- ALT
- MC

B) E-selectin (ng/mL)

- HC
- MC
- ALT
- CON

C) VCAM-1 (µg/mL)

- HC
- MC
- ALT
- CON

D) Plasma SAA (µg/mL)

- HC
- MC
- ALT
- CON

Graphs showing changes over time (days) with statistical comparisons indicated by asterisks and hash marks.
They always change their food. First they eat flesh, then fish, then vegetables, then afterward they go back to flesh, and nature is never incommode 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 not affect homeostatic inflammatory 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”)

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

Coffman, Nature Medicine 2011

Conclusion 3: know your mechanisms
Conclusion 4: go personalized, also in research?!
Conclusion 5 and 6: Train the system

...by an alternating diet

...by providing low doses
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.