PHENOTYPIC FLEXIBILITY: A NEW WAY TO QUANTIFY EFFECTS OF NUTRITION ON HEALTH

Suzan Wopereis
TNO: founded in a time of crisis (1932)

*Mission*
TNO aligns knowledge and people to create innovations to enhance the competitive power of industry and to increase well being in a sustainable society.
Scope: Cardiometabolic diseases

Diabetes + comorbidities

TNO helps to develop:
• healthy foods/nutrients
• innovative lifestyle concepts
• improve pharmacotherapy

Source: International Diabetes Federation
Extensive phenotyping by ‘omics’ analysis

Technology: high throughput, multi organ, multi level

High-end data mining and warehousing
WHO definition of Health
Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.
ability to adapt and self-manage in the face of social, physical and emotional challenges

How should we define health?

The WHO definition of health as complete wellbeing is no longer fit for purpose given the rise of chronic disease. Machteld Huber and colleagues propose changing the emphasis towards the ability to adapt and self-manage in the face of social, physical, and emotional challenges.

Machteld Huber senior researcher, J André Knottnerus president, Scientific Council for Government Policy, Lawrence Green editor in chief, Oxford Bibliographies Online—public health, Henriëtte van der Horst head, Alejandro R Jadad professor, Daan Kromhout vice president, Health Council of the Netherlands, Brian Leonard professor, Kate Lorig professor, Maria Isabel Loureiro coordinator for health promotion and protection, Jos W M van der Meer professor, Paul Schnabel director, Richard Smith director, Chris van Weel head, Henk Smid director.
How do we react to external changes and challenges?

Is our physiology capable of properly maintaining homeostasis?
The challenge concept:  
Study and quantification of the stress response curve
Health is maintained by a complex interaction of processes, each maintaining “homeostasis”, elasticity and robustness

= phenotypic flexibility
Overall scheme of metabolic health & disease related processes

**Caloric excess**

- Adiponectin (% Adipocyte)
- LDL elevated
- Glucose toxicity
- HDL-C (%)
- Fibrosis
- Gastrointestinal inflammation
- Endothelial inflammation
- Cardiac dysfunction
- Heart failure
- Myocardial infarctions

**Visceral adiposity**

- Adipose inflammation
- Ectopic lipid overload
- Hepatic inflammation

**Dyslipidemia**

- %TC (%)
- %TG (%)
- %HDL-C (%)
- %LDL-C (%)
- %TLD (%)
- %SBP (%)
- %DBP (%)

**Insulin resistance**

- Adipose IR
- Hepatic IR
- Muscle metabolic inflexibility

**Pathologies resulting from the ‘metabolic syndrome’**

- Brain disorders
- Nephropathy
- Atherosclerosis
- Stroke
- Retinopathy

**Risk factors of the ‘metabolic syndrome’**

- High cholesterol
- High glucose
- Hypertension

**Nakatsuji, Metabolism 2009**
From “healthy” to “at risk” to “diseased”: derailing biomarkers

Van der Greef (2005)
Effect of interventions on a challenged healthy system

Challenge test response

Intervention effect

Amplitude and duration of the challenge can change by intervention.
Challenge test as tool to test the capacity of the shock absorber
Phenotypic Flexibility as a measure of health

Can help nutritional research to tackle its challenges and needs

Current challenge in nutritional health research:

- Design and perform science-based nutritional interventions that allow evaluation of health improvement in apparently healthy consumers

Need for:

- New biomarkers of health
- Acceptance of new approach and new biomarkers of health by regulatory bodies (EFSA)
PhenFlex

Innovative scientific approach that aims to develop standardised research methods and tools in nutrition science to substantiate subtle effects of food and nutrition on health

An approach that measures health instead of disease

Based on:

1. New definition of health
2. System biology based biomarkers
3. Challenge test to determine resilience
The standardized PhenFlex challenge test

- 320 ml tap water
- 60 grams palm oleine
- 75 grams of glucose
- 20 grams of Protifar
- 0.5 gram / 20 droplets of artificial aroma
A HIGH-FAT, HIGH-CALORIC DRINK AS STANDARD TO PERTURB HOMEOSTASIS:
THE PHENFLEX CHALLENGE

Suzan Wopereis, Herman van Wijstmarshen, Annelies Dijis-Strewee, Gertrud Bukker, Bas Kremer, Ben van Ommen, Annette Stafleu, Marjan van Erk

**BRAIN**
- gut-brain signaling
- endocrine responses

**GUT**
- host-microbe interaction
- absorption & barrier function
- inflammation control
- chylomicron production
- gut hormone production

**ADIPOSE TISSUE**
- energy metabolism
- lipoprotein metabolism
- insulin sensitivity
- macrophage infiltration
- expandability
- lipokine & adipokine production

**PANCREAS**
- systemic insulin sensitivity
- β-cell function

**LIVER**
- adaptation carb/lipid switch
- core metabolism
- lipoprotein production
- bile production
- insulin sensitivity
- fibrosis & inflammation
- oxidative stress
- ER stress
- tissue injury control

**MUSCLE**
- adaptation carb/lipid switch
- energy metabolism
- protein metabolism
- insulin sensitivity
- oxidative stress
- ER stress
- tissue injury control

**KIDNEY**
- (re)absorption
- urea cycle
- tissue injury control

**VASCUŁATURE**
- systemic insulin sensitivity
- chronic low-grade inflammation
- reversibility of inflammation
- endothelial integrity
- blood pressure regulation
- arterial stiffness
- oxidative stress
- tissue injury control

*orange = responding; green = not responding; black = not determined*
Phenotypic flexibility as a measure of health: the optimal nutritional stress response test

Johanna H. M. Stroeve¹ · Herman van Wietmarschen¹ · Bas H. A. Kremer¹ · Ben van Ommen¹ · Suzan Wopereis¹

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Abstract Nutrition research is struggling to demonstrate beneficial health effects, since nutritional effects are often subtle and long term. Health has been redefined as the ability to adapt to stressors while preserving intactness. This paradigm shift necessitates biomarkers that detect the conditions of metabolic homeostasis disturbances and point to possible vulnerabilities. This study aimed at studying the feasibility of identifying such biomarkers related to this subset of processes to the different challenge tests. Based on the obtained insights, we propose a nutritional stress test composed of a high-fat meal and a standardized exercise protocol to probe the effects of the feeding and physical energy expenditure on phenotypic flexibility.
Extensive analyses

Time course studies:
Blood sampling at multiple time points after challenge, up to 10 hours

Aim: to monitor response of multiple biological processes
Resilience markers of health:

- Variation in response within 100 healthy subjects with different phenotypic flexibility

→ Healthy ranges study
Variation in phenotypic flexibility in healthy subjects

Based on ~160 markers
Variation in phenotypic flexibility in healthy subjects

Age 30-59
LOW FAT%

Based on ~160 markers
Variation in phenotypic flexibility in healthy subjects

Age 30-59
LOW FAT%
NORMAL FAT%

Based on ~160 markers
Variation in phenotypic flexibility in healthy subjects

Age 30-59
LOW FAT%
NORMAL FAT%
HIGH FAT%

Based on ~160 markers
Variation in phenotypic flexibility in healthy and diabetic subjects

Age 30-59
LOW FAT%
NORMAL FAT%
HIGH FAT%
Healthy 30-59 N
Diabetes type 2
From Phase 1….

Biomarkers of health:
- Challenge response
- Difference healthy vs T2D

Reduced adaptability study

Biomarkers of health:
- Variation in response within 100 healthy subjects with different phenotypic flexibility

Healthy ranges study

…..into Phase 2

INTERVENTION STUDY

Proof of concept that new biomarkers of health are useful to substantiate beneficial health effects in a dietary intervention study

New partners welcome to join!
Improved resilience after micronutrient intervention

Metabolism

Oxidation

Inflammation

Average health

Improved health
Reduced resilience after hypercaloric intervention

- Day 1: Healthy, n=10
- Day 29: MetS, n=9

High-fat challenge
Blood sampling
Comparisons

4 weeks + 1300 kcal
High-fat diet induced host-gut microbiota interactions

Day 1
healthy

n=10

Gut microbial composition
Metabolic functioning

Day 29

4 weeks + 1300 kcal

Take home message

› For substantiation of health benefits of nutrition we need resilience markers of health rather than biomarkers of disease

› These are “multi-biomarker” panels representing defined and accepted health-related processes

› In combination with the new PhenFlex challenge test most defined health related processes are modulated

› The PhenFlex challenge discriminates between different states of health

› In this way we can measure health effects of nutrition
THANK YOU FOR YOUR ATTENTION