DEVELOPING STANDARDISED RESEARCH METHODS IN NUTRITIONAL SCIENCE

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

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

Metabolically healthy

Irreversible process

Reversible process

β-cell

Pathology

gluc

Risk factor

Muscle metabolic inflexibility

The ‘metabolic syndrome’

Risk factors of the ‘metabolic syndrome’

Pathologies resulting from the ‘metabolic syndrome’

Hypertension

Atherosclerosis

Nephropathy

Retinopathy

IBD

Fatty liver

Gut inflammation

Endothelial inflammation

Adipose inflammation

Ectopic lipid overload

Visceral adiposity

High cholesterol

High glucose

LDL elevated

Glucose toxicity

β-cell failure

Vascular damage

Hypertension

Myocardial infarctions

Heart failure

Cardiac dysfunction

Hepatic inflammation

IBD

Fibrosis

Systemic inflammation

Gut inflammation

Systemic inflammation

High adiponectin

Nakatsuji, Metabolism 2009

Caloric excess
For optimal “phenotypic flexibility”, each process needs to function optimally
From “healthy” to “at risk” to “diseased”: derailing biomarkers

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

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 PHENFFLEX CHALLENGE

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

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

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

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

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

orange = responding; green = not responding; black = not determined
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%
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
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!
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