TARGETING RESILIENCE FOR LIFESTYLE (AND) MEDICINE
The example of type 2 diabetes

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https://resilientcities2019.iclei.org/

THE OBESITY GLOBAL SYNDEMIC

Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health

More than 1.9 billion adults were overweight in 2016, and 650 million obese

39 million children <5 years were overweight or obese in 2020

Overweight & obesity are linked to more deaths worldwide than underweight

Once associated with high income countries, obesity is now prevalent in low- and middle-income countries

Eating a healthy diet can help prevent obesity

Regular physical activity helps maintain a healthy body

Curbing the obesity pandemic requires a population-based multisectoral, multi-disciplinary and culturally relevant approach

AMBITION: "ADDING HEALTH TO LIFE"

GOING FROM LIFESPAN TO HEALTHSPAN BY BRINGING EVIDENCE BASED LIFESTYLE SOLUTIONS TO THE PUBLIC

Life Expectancy (LE):	1981	2019
♂	73 jr	80 jr
♀	79 jr	84 jr

LE WITHOUT CHRONIC DISEASE:	1981	2019
♂	55 jr (18)	46 jr (34)
♀	54 jr (25)	41 jr (43)

CBS

We live longer (+ 6 years of life expectancy),
but with less healthy years (+17 years of life expectancy <u>with</u> chronic disease)
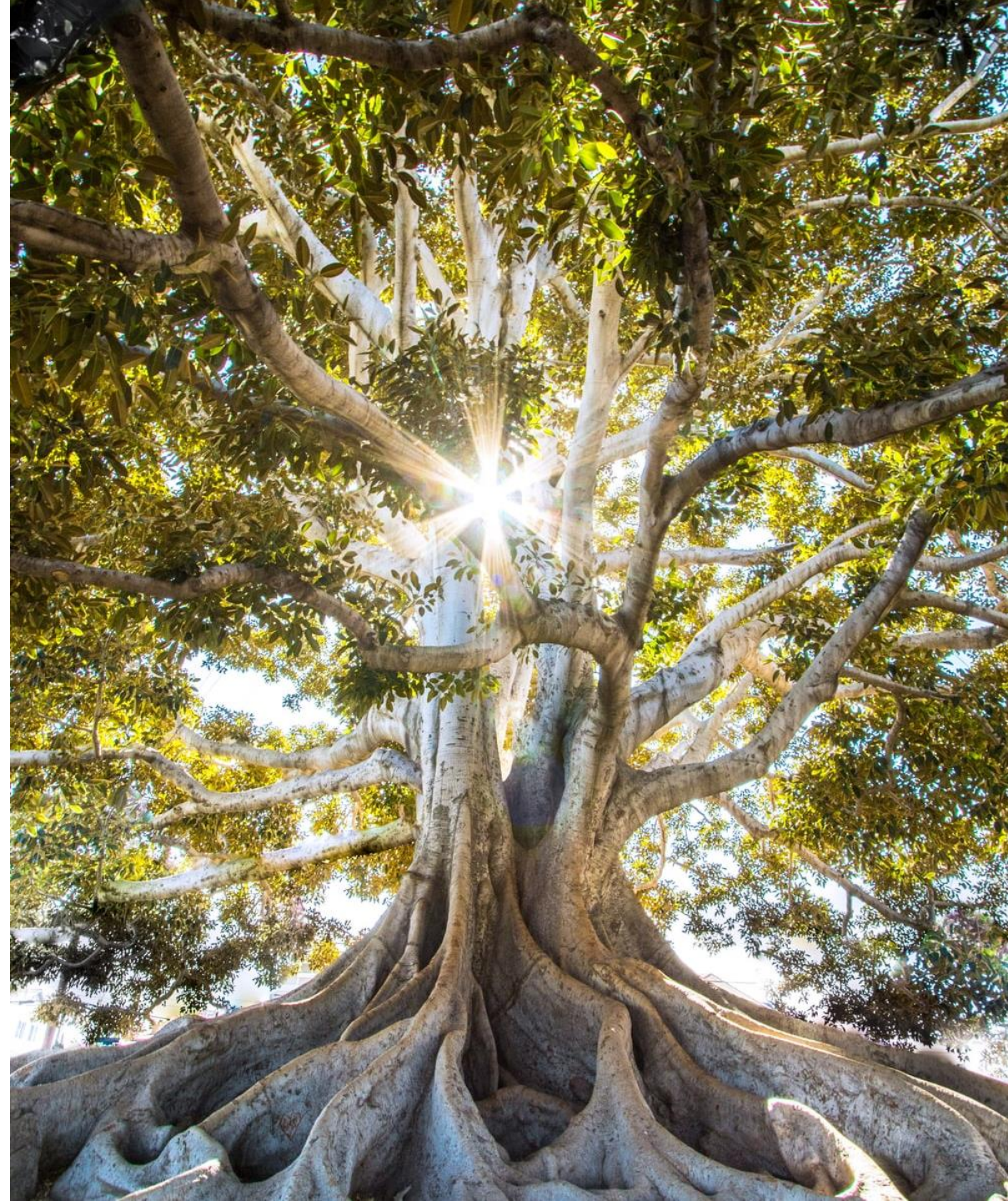
NUTRITION & LIFESTYLE AND DISEASE: STATUS QUO

- World-wide, 20% deaths due to poor nutrition, or 11,000,000 people annually
  (Global Burden of Disease Report, Lancet, 2019)

- 50% of cardiovascular morbidity & mortality preventable by "better" nutrition;
  80% can be prevented by controlling BP, diabetes and cholesterol *(AHA, Circulation, 2019)*

- "What we're not eating is killing us"—diets low in fibers, whole grains, fruits, nuts,
  legumes; high in refined foods, sugars, trans fats *(Global Burden of Disease Report, Lancet, 2019)*

- An anti-inflammatory diet reduces all cause cancer & cardiovascular morbidity &
  mortality significantly *(Kaluza, J Internal Medicine, 2018)*

- In type 2 diabetes dietary interventions can remit in about 40% of patients
  (Lean, Lancet, 2018; Lean, Lancet Diabetes Endocrinol. 2019)

- Dementia, which is predicted to be the nr. 1 disease with highest patient burden in
  2040, can be prevented in 40% of the cases based on 12 modifiable lifestyle related
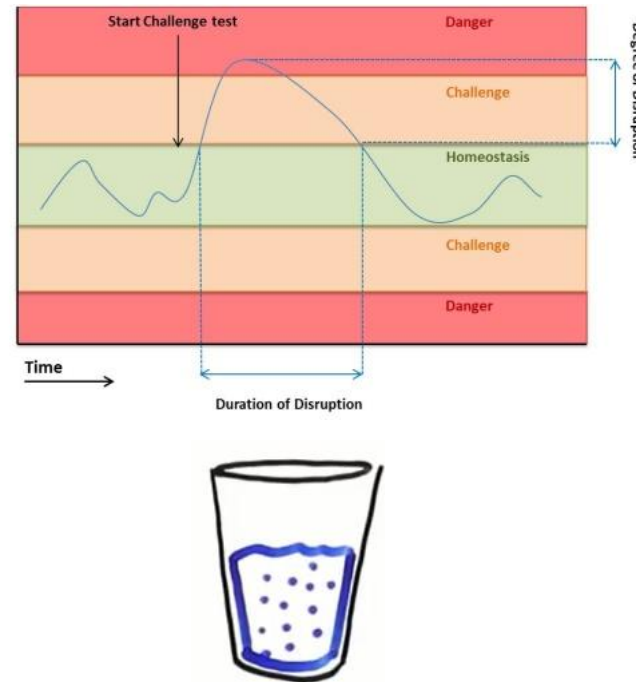 risk factors *(Livingston, Lancet, 2020)*

TNO innovation for life

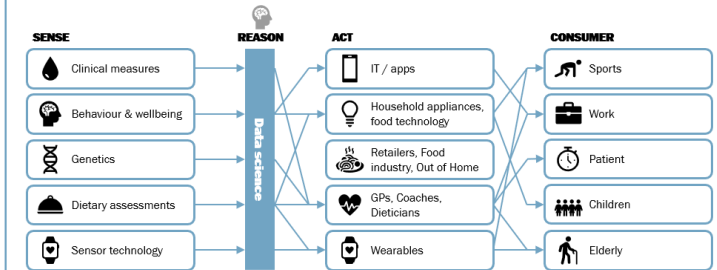# FOR A HEALTHY SOCIETY WE FOCUS ON SYSTEMS FLEXIBILITY

1 – health is a system
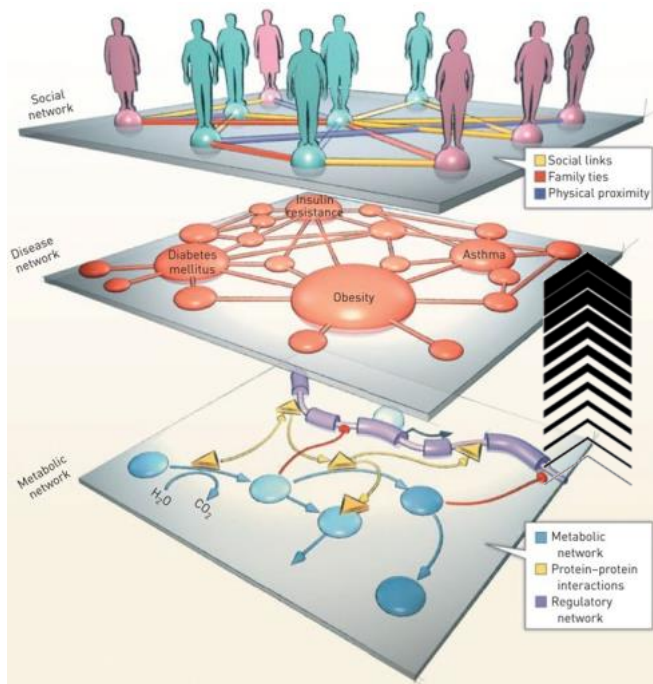
2 – health is resilience

3 – health becomes digital

› **From care to cure: reversible diseases**

› **Prevention & wellbeing: maintenance and optimization of health**

Lifestyle to prevent disease

(de Hoogh, Nutrients, 2021)

Late biomakers of disease/effect

Early biomarkers of disease/effect

"healthy" homeostasis

Pharma

Personalized medicine

Public lifestyle (i.e. regulatory guidelines)

Personalized lifestyle

Lifespan
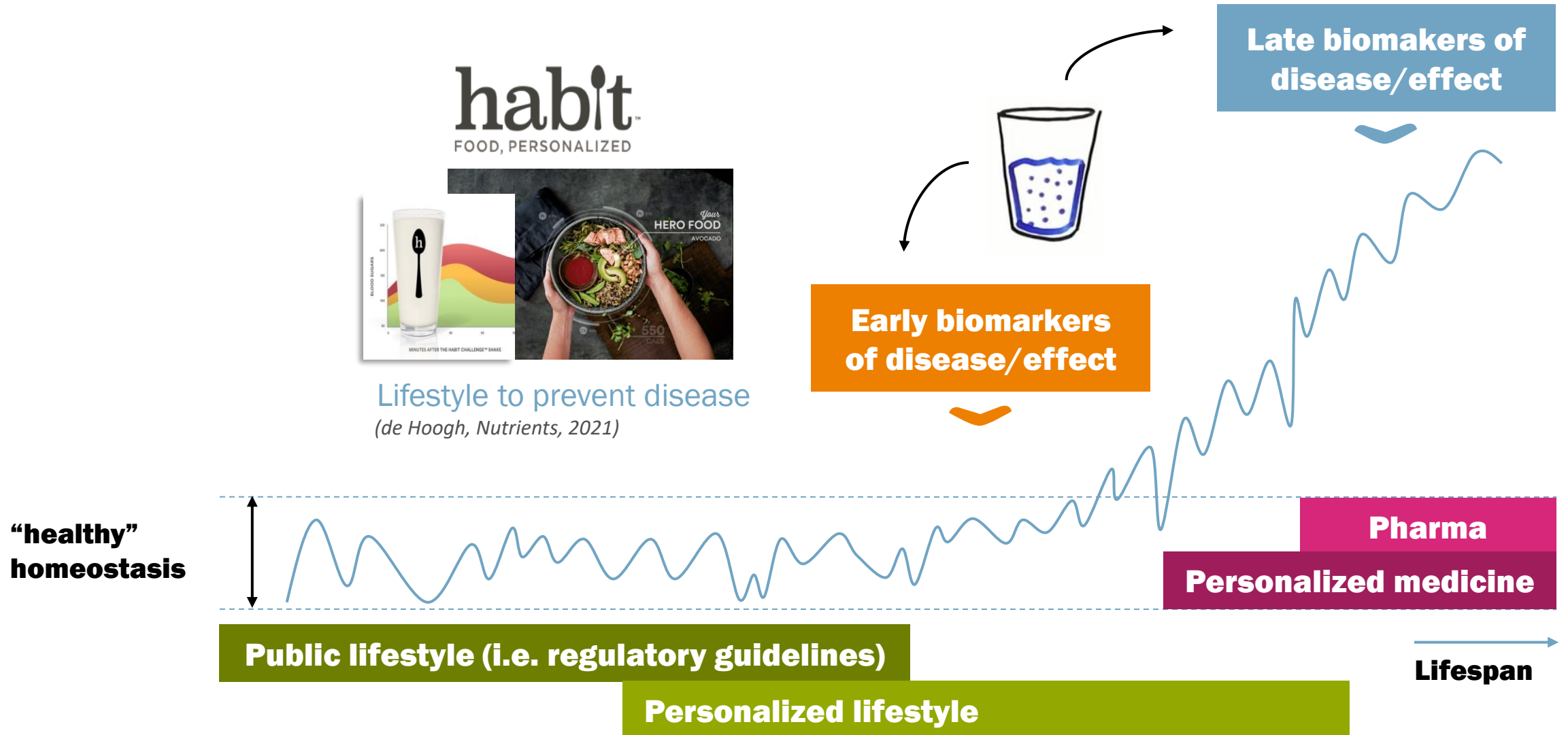
Systems view on processes in glucose control and T2D
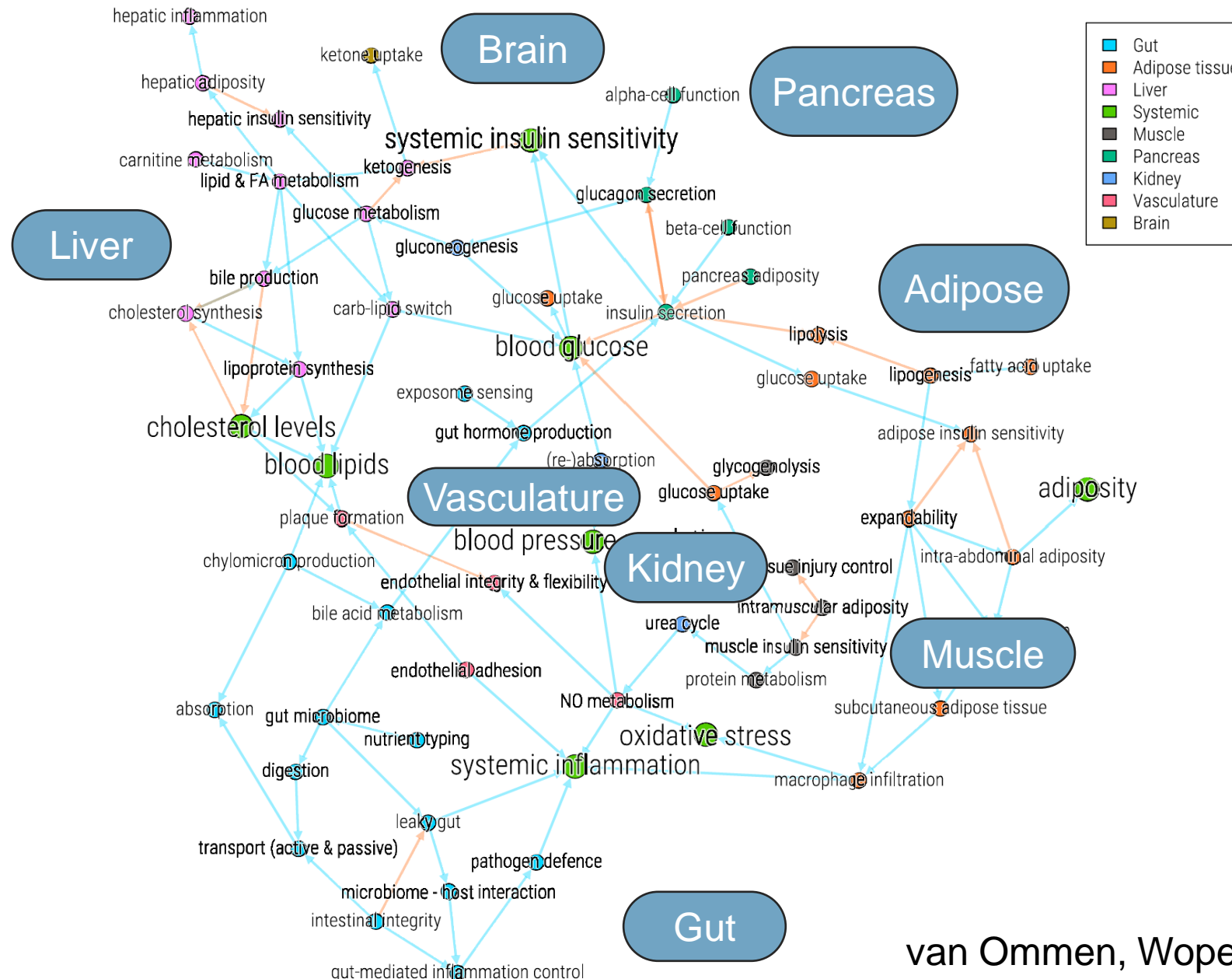
The flexible phenotype: the system functions as a shock absorber

van Ommen, Wopereis et al. Front Endocrin. 2018

› Can we identify biomarkers for subpopulations of T2D that form the basis for stratified treatment options?

An extension of the oral glucose tolerance test

Muscle
- Insulin Resistance

Gut
- Incretins
- Host-microbe interaction

Pancreas
- β-cell
- α-cell

Blood
- Glucotoxicity
- Postprandial hyperglycemia

OGTT
Glucose, insulin, C-peptide;
NEFA, incretins, body composition, TG

Liver
- Insulin Resistance
- Gluconeogenesis
- Fatty liver
- Ketogenesis

Adipose tissue
- Lipotoxicity
- NEFA
- Insulin Resistance
- Fat mass

Inflammation
- chronic low-grade inflammation
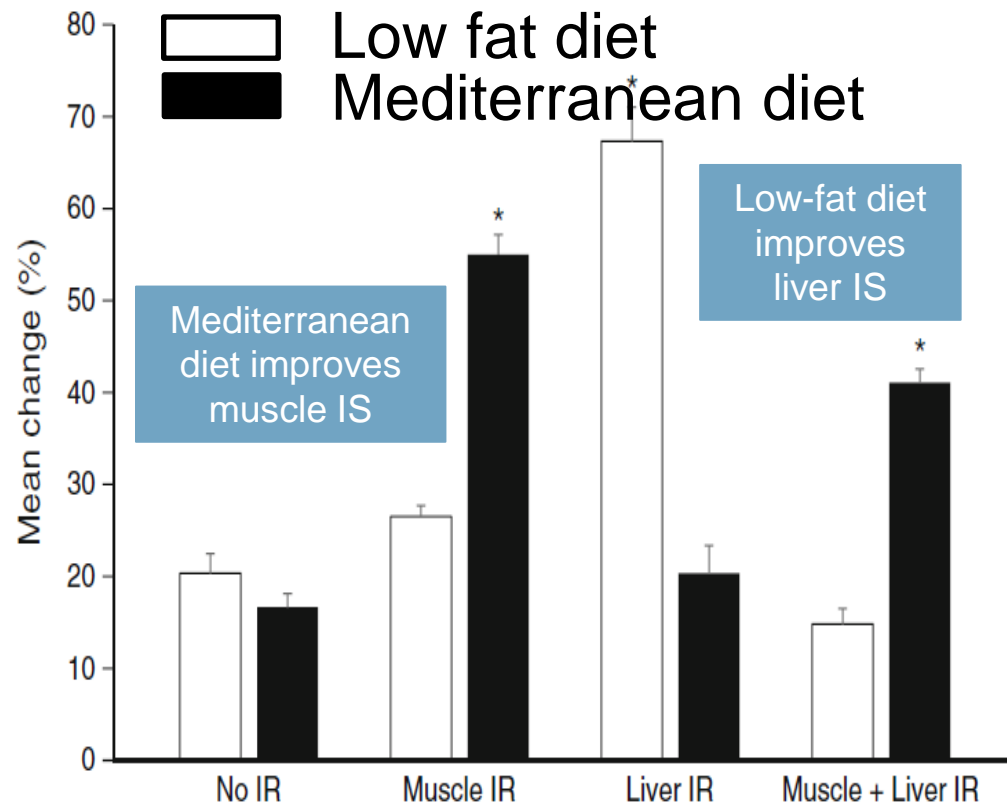- Endothelial flexibility/integrity

Subgroup specific efficacy of lifestyle

Fig. 1 Mean percentage change in values of disposition index between baseline and after 2 years of follow-up by IR phenotype. *p<0.05 between low-fat diet (white bars) and Mediterranean diet (black bars) in each IR subgroup analysed using a univariate model adjusted for age, sex, baseline BMI and change in weight

Blanco-Rojo, Diabetologia, 2015
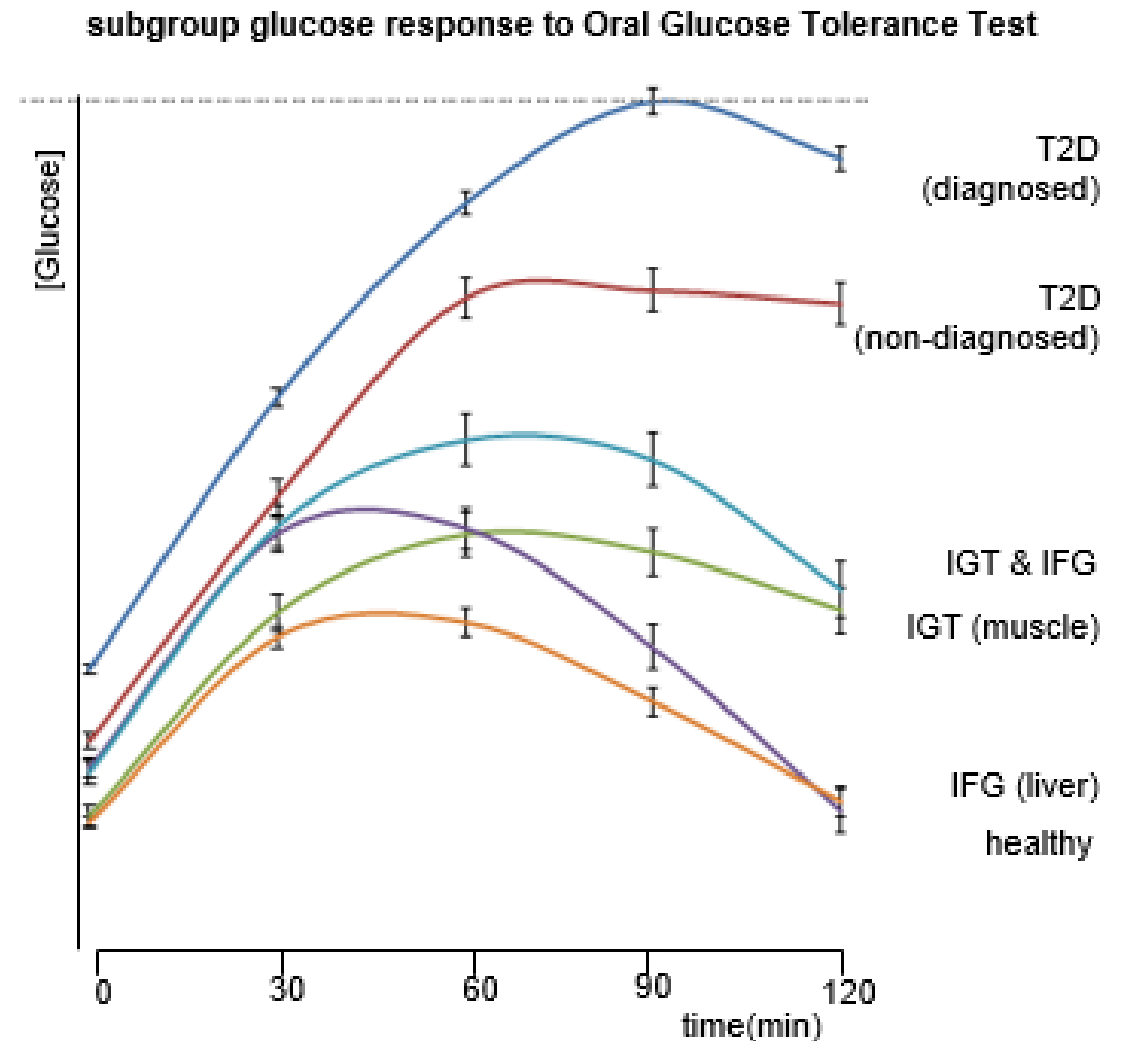
CURATIVE SETTING: DIABETYPING WITH PERSONALIZED LIFESTYLE TREATMENT FOR REMISSION OF TYPE 2 DIABETES

1. Diagnostics

Subtyping based on response to oral glucose tolerance test (OGTT)
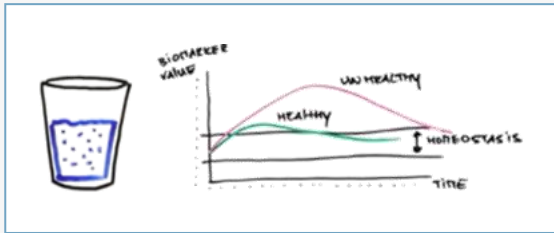
Main cohort
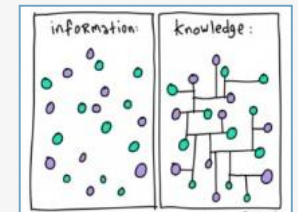800 subjects

Validation cohort
550 subjects

Type 2 diabetes subtyping tool

2. Treatment

Literature Mining & Knowledge Capture

Design personalized lifestyle treatment

3. Application

Piloted in primary care, secondary care and occupational care

4. Validation

Planned: (cost) efficacy study

Blanco-Rojo et al., 2015; Pasman et al. 2020; de Hoogh et al. 2021; de Hoogh et al. 2022

Conclusions

› The personalized/subgroup lifestyle treatment of three months resulted in reduced body weight, and improved glycemic control (HbA1C) as compared to standard care and 75% diabetes remission (vs 22% in historic data) in persons newly diagnosed with type 2 diabetes

› Many T2D patients are being treated with insulin, whereas they are often hyperinsulinemic!

› Long-term follow-up showed that the beneficial effects of the 13 week intervention was still present at two years in specific subgroups. However, some subgroups did not achieve improved glycemia at start and after 2 years.

› In patients with more complex type 2 diabetes subtype type 2 diabetes reversal (control of glycemia with less medication) seems a more realistic target. These patients would have lifestyle treatment with medication

References: De Hoogh et al. Biomedicines 2022, 10, 643; De Hoogh et al. Nutrients 2021

TNO innovation for life

T2D subgroups (see fig. 2, based on processes involved)	Diagnosis (i.e. parameters of the P4 biopassport)	Potential interventions
(1) Pancreatic β-cell function (impaired IR)	OGTT: I/ΔG and DI(0), PYY, Arg, His, Phe, Val, Leu	β-cell-protective nutrients (MUFA) and drugs (TZD, GLP-1 analogs, and DPP-4 inhibitors)
(2) Muscle IR (decreased glucose uptake)	OGTT: muscle IR index, insulin secretion/IR index, Val, Ile, Leu, γ-glutamyl derivates, Tyr, Phe, Met	PUFA/SFA balance; physical activity; weight loss; TZD (e.g. PPAR-γ)
(3) Hepatic IR with decreased glucose uptake but increased production and release	Hepatic IR index, OGTT, hepatic IS index, ALAT, ASAT, bilirubin, GGT, ALP, CK-18 fragments, lactate, α/β-hydroxybutyrate	Decrease in SFA and n-6 PUFA, and increase in n-3 PUFA; weight loss; metformin; TZD; exenatide (GLP-1 analog); DPP-4 inhibitors
(4) Adipocyte IR and lipotoxicity	Basal adipocyte IR index, FFA platform, glycerol	α-Lipoic acid; PUFA/SFA balance; n-3 FA; chitosan/plant sterols; TZD; acipimox
(5) Gastrointestinal tract (incretin deficiency/resistance)	i.v. GTT vs. OGTT, GLP-1, GIP, glucagon, bile acids	MUFA; dietary fiber (pasta/rye bread); exenatide
(6) Pancreatic α-cell hyperfunction	Fasting plasma glucagon	Glucagon receptor antagonist; exenatide; DPP-4 inhibitors
(7) Chronic low-grade inflammation	CRP, total leukocytes VCAM, ICAM, oxylipids, cytokines	Fish oil/n-3 fatty acids; vitamin C/E; carotenoids; salicylates; TNF-α inhibitors
Currently, 7 processes involved in T2D are identified, and for each of them a biomarker approach to quantify the process, as well as an intervention strategy to optimize/restore health, is suggested. ALP = Alkaline phosphatase; CK = cytokeratin; CRP = C-reactive protein; DDP-4 = dipeptidylpeptidase-4; DI = disposition index; FA = fatty acids; FFA = free FA; GGT = γ-glutamyltransferase; GIP = glucose-dependent insulinotropic polypeptide; GLP = glucagon-like peptide; IR = insulin resistance; IS = insulin sensitivity; MUFA = monounsaturated FA; OGTT = oral glucose tolerance test; PPAR-γ = peroxisome proliferator-activated receptor-γ; PUFA = polyunsaturated FA; PYY = peptide YY; SFA = saturated FA; TZD = thiazolidinedione.		

Table 1. T2D subgroup (process)-dependent diagnosis/intervention strategies.

Van Ommen and Wopereis, 2016

Lifestyle4Health in numbers:

- Founded in 2018 by TNO, LUMC and Dutch diabetes fund
- €2.7 billion cost savings in medical costs over the next 5 years if 40% of T2D patients would revert their disease through getting a lifestyle treatment
- 25 partners, including 3 pharma companies
- 1 Manifest (2018) signed by >2000 persons & organisations
- 4 publications signed by 47 organisations
- Manifest and 2 publications official handed over to Secretary of State or Minister
- 5000 followers on LinkedIn
- 1500 listeners, n=14 podcasts
- Active website, 200-1000 monthly users
- 5 scientific conferences organised with 150-200 participants

THANK YOU!

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