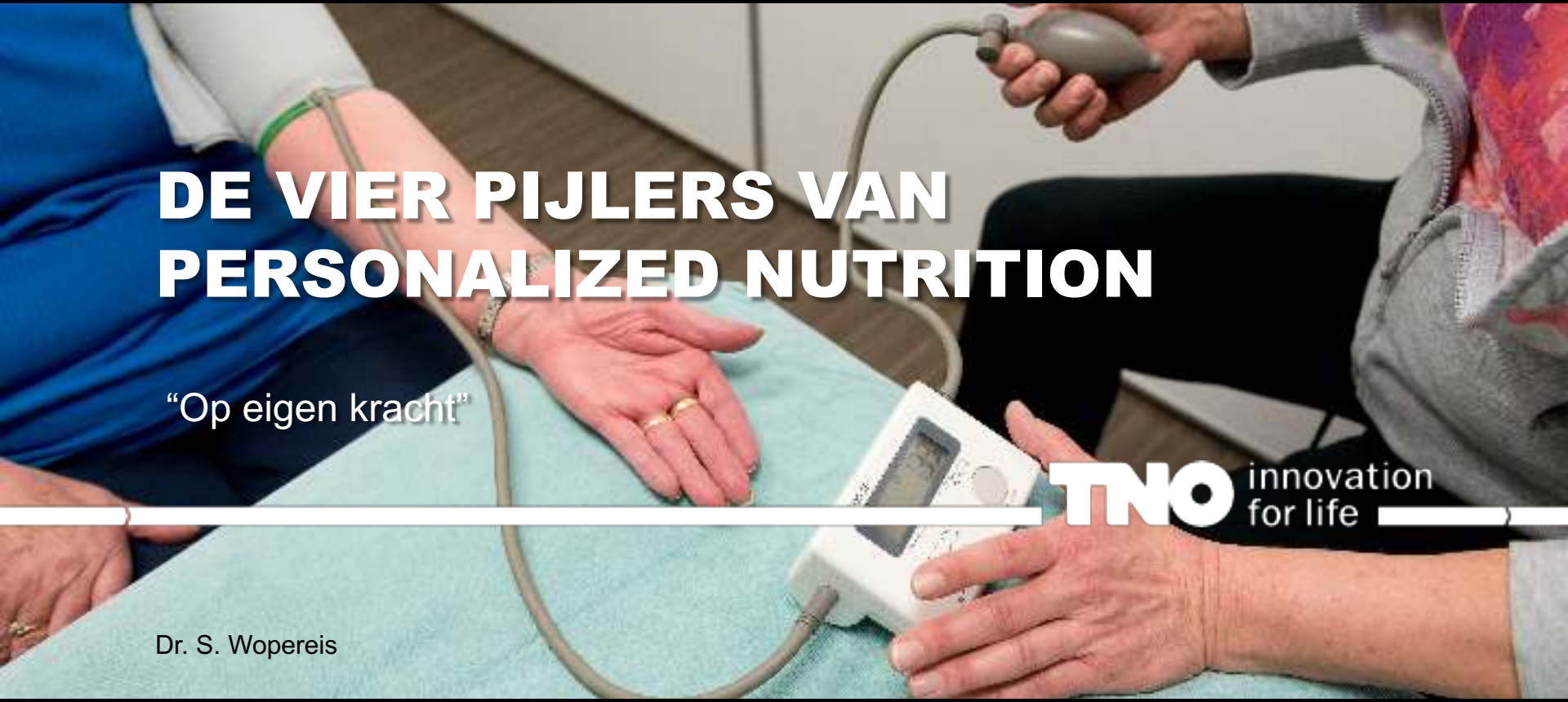


DE VIER PIJLERS VAN PERSONALIZED NUTRITION

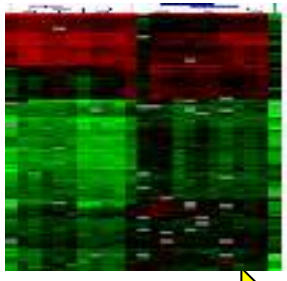
"Op eigen kracht"

TNO innovation for life

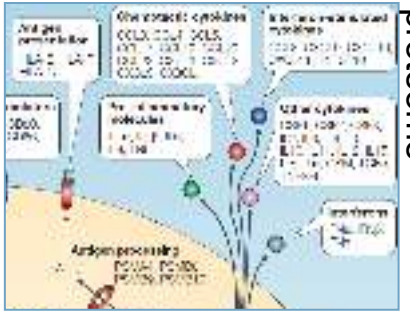
Dr. S. Wopereis

Extensive phenotyping by ‘omics’ analysis

clinical chemistry



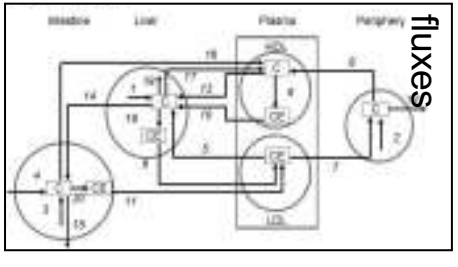
microbiome



proteome

Technology: high throughput, multi organ, multi level

High-end data mining and warehousing, artificial intelligence



fluxes

metabolome

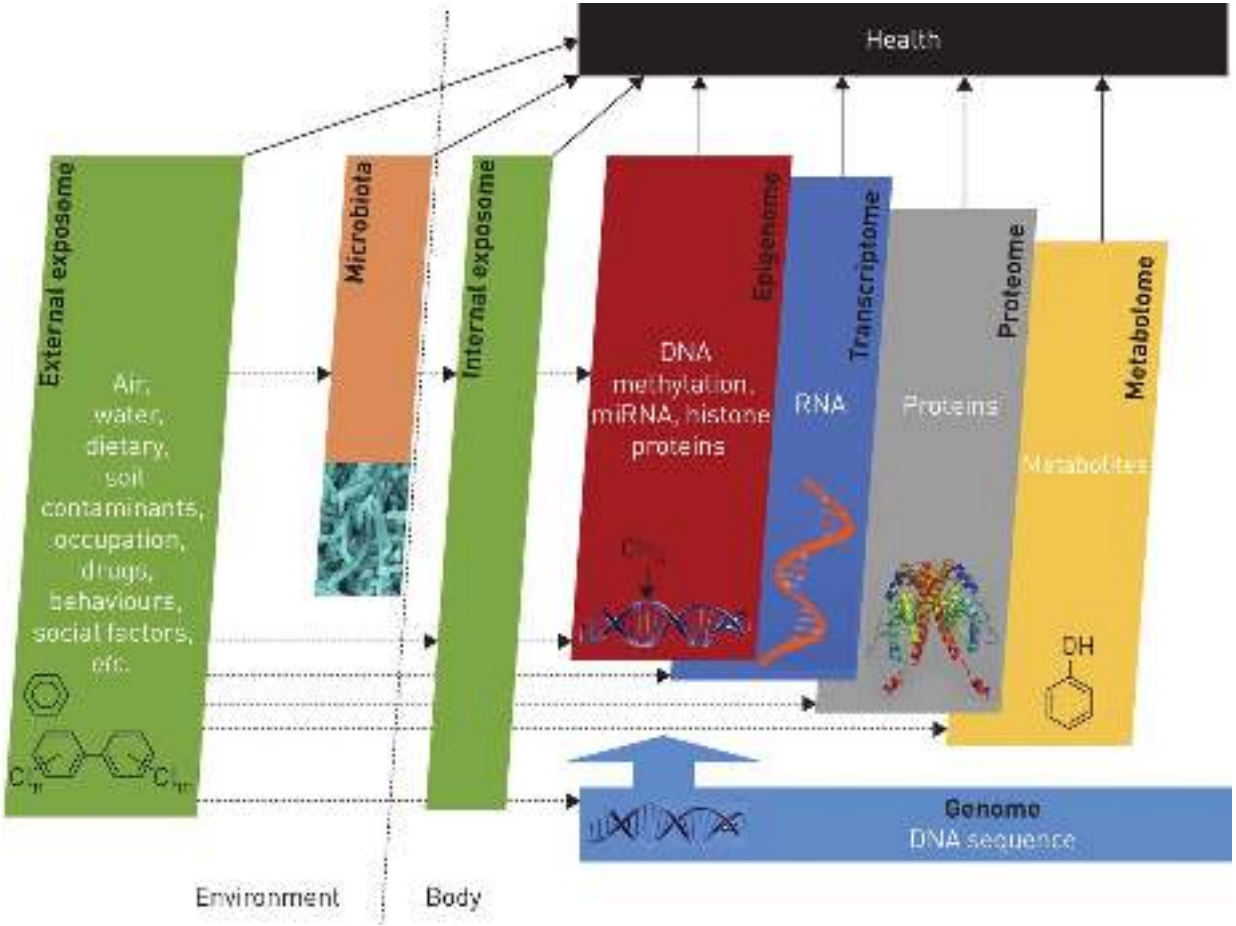
transcriptome

Definition for personalized nutrition

TNO innovation for life

"Personalised nutrition uses individual-specific information, is founded in evidence-based science and has the goal to empower consumers and promote a positive, sustainable dietary behavioural change. This may then result in measurable benefits for personal goals like health improvement and maintenance, or disease specific benefits."

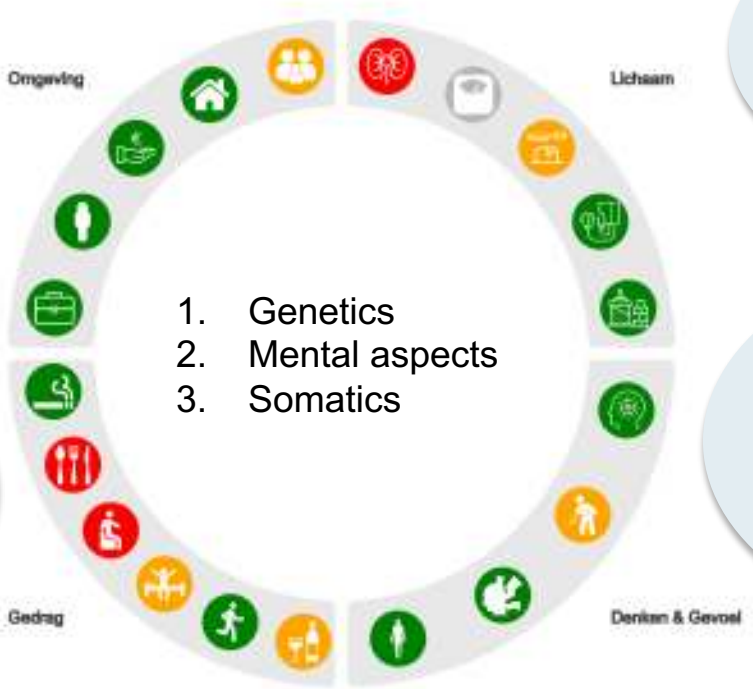
Position paper personalised nutrition
Van der Horst et al. FoodValley NL



The four pillars of personalized nutrition

3. **Environment** or socio-economic situation, family & culture

1. **Body** or biomedical information

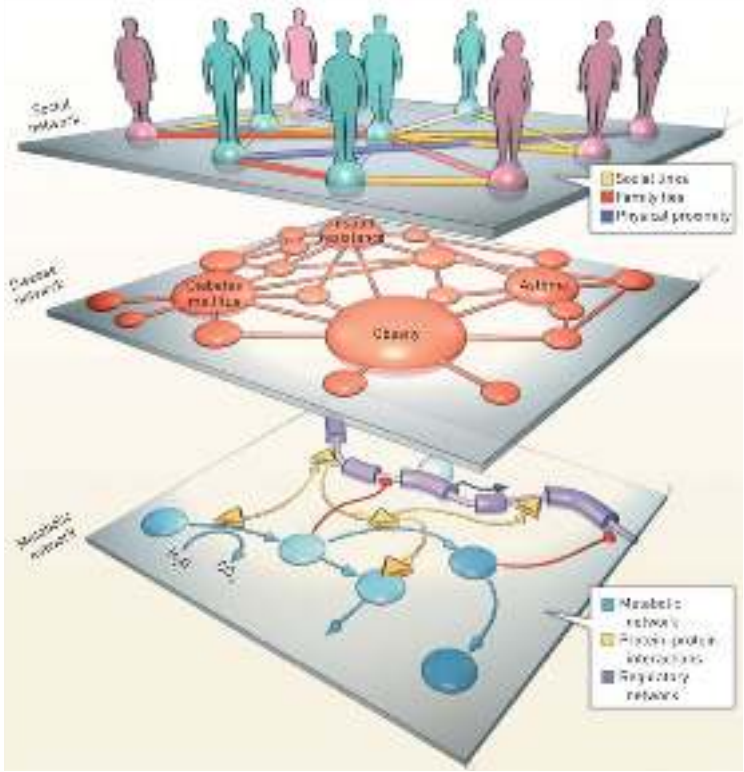


4. **Lifestyle behaviour**, e.g. nutrition, physical activity, sleep, smoking etc.

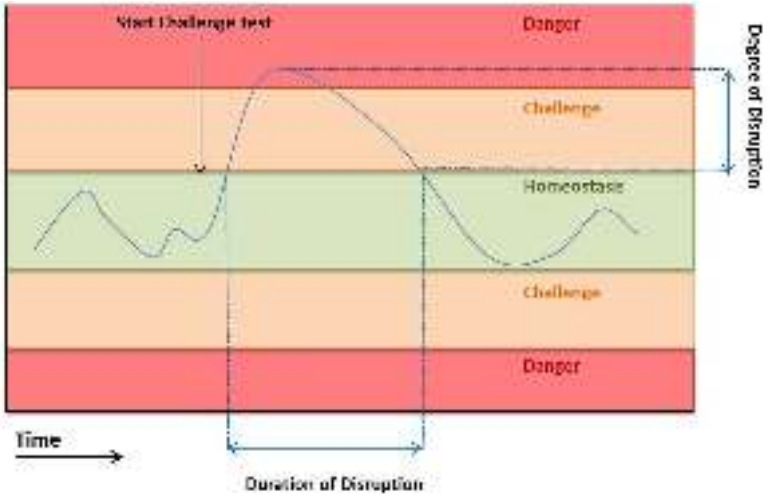
2. **Thinking & feeling** or personal believes, experience and/or preferences

The two TNO pillars: systems & flexibility

1 – HEALTH IS A SYSTEM



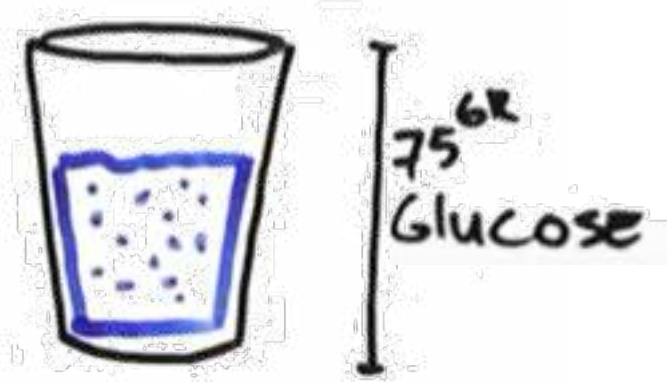
2 – HEALTH IS RESILIENCE



Health / disease = the (in)capacity to regain homeostasis upon a challenge

Types of challenge test used in context of personalized health

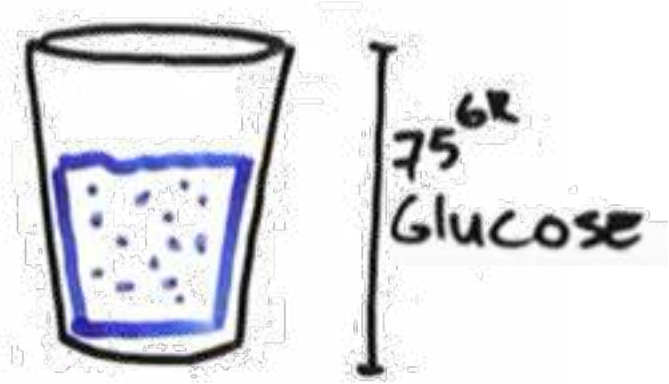
Preventive setting;
“lifestyle to prevent disease”



Curative setting;
“lifestyle as medicine”

Types of challenge test used in context of personalized health

Preventive setting;
“lifestyle to prevent disease”



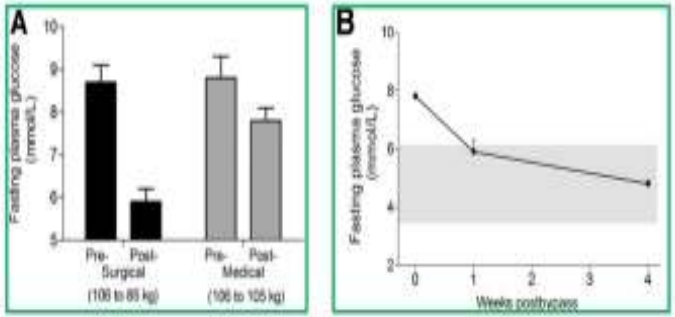
Curative setting;
“lifestyle as medicine”

Starting with Type 2 diabetes

Lifestyle may bring diabetes type 2 into remission

TNO innovation for life

Gastric Banding cures Diabetes



A: Fasting plasma glucose and weight change 2 years after randomization either to gastric banding or to intensive medical therapy for weight loss and glucose control.

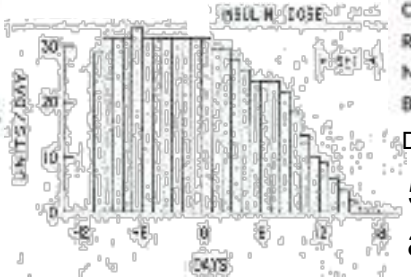
Adjustable gastric banding and conventional therapy for type 2 diabetes JAMA 2008;299:316-232

Dixon JB et al. JAMA. 2008

High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus[1, 2]

James W. Anderson, M.D. and Kyleen Ward, R.D.

Am J Clin Nutr. 1979.



Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

(very) low-calorie diet ≥ 15 kg weight loss (4-5 months program)

Lean et al. Diabetes Endocrinol. 2019

ORIGINAL ARTICLE

Type 2 diabetes remission 1 year after an intensive lifestyle intervention: A secondary analysis of a randomized clinical trial

Mathias Ried-Larsen PhD[1] | Mette Y. Johansen MSc[1] | Christopher S. MacDonald MSc[1,2] | Katrine B. Hansen PhD[1] | Robin Christensen PhD[3,4] | Anne-Sophie Wedell-Neergaard MD[1] | Nanna Skytt Pilmark MD[1] | Henning Langberg DMSc[2] | Allan A. Vaag PhD[5] | Bente K. Pedersen DMSc[1] | Kristian Karstoft PhD[1,6]

Diabetes Obes. Metab. 2019

5-6 weekly 30-60 minutes aerobic and strength training (1 yr program)

T2D remission is not achievable for every patient!

TNO innovation for life

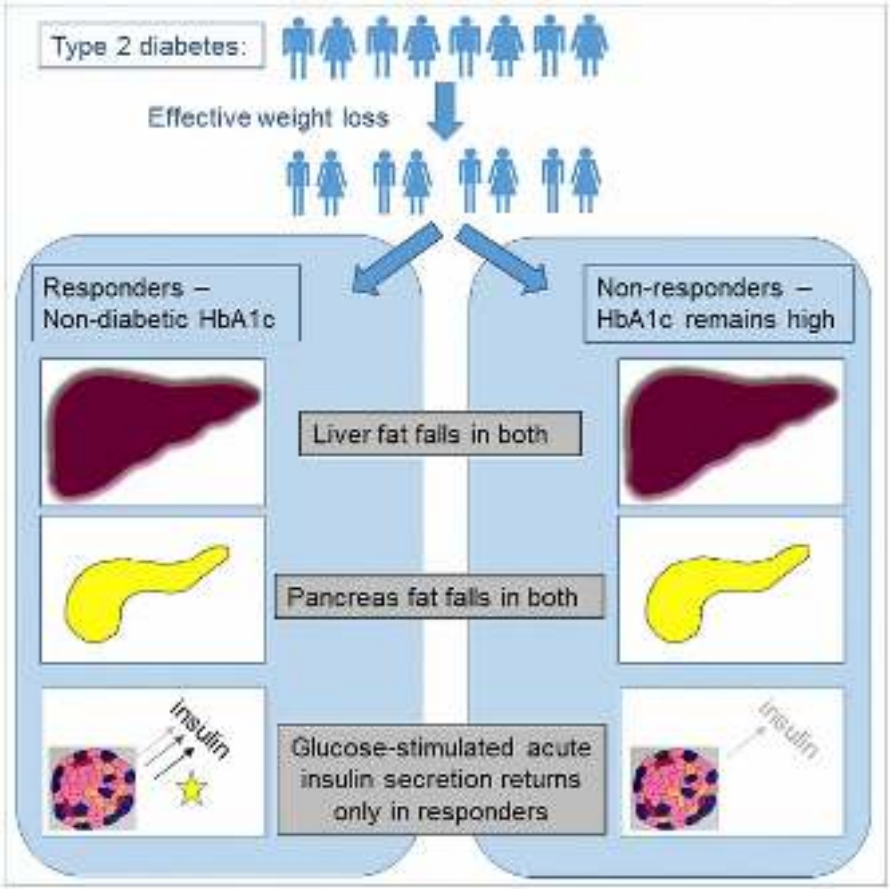
Cell Metabolism

Volume 28, Issue 4, 2 October 2018, Pages 547-556.e3

Clinical and Translational Report

Remission of Human Type 2 Diabetes Requires Decrease in Liver and Pancreas Fat Content but Is Dependent upon Capacity for β Cell Recovery

Roy Taylor [1,2,3,*], Ahmad Al-Mrabeh [1], Svitlana Zhyzhneuskaya [1], Carl Peters [1], Alison C. Barnes [2], Benjamin S. Aribisala [4], Kieren G. Hollingsworth [1], John C. Mathers [4], Naveed Sattar [5], Michael E.J. Lean [6]



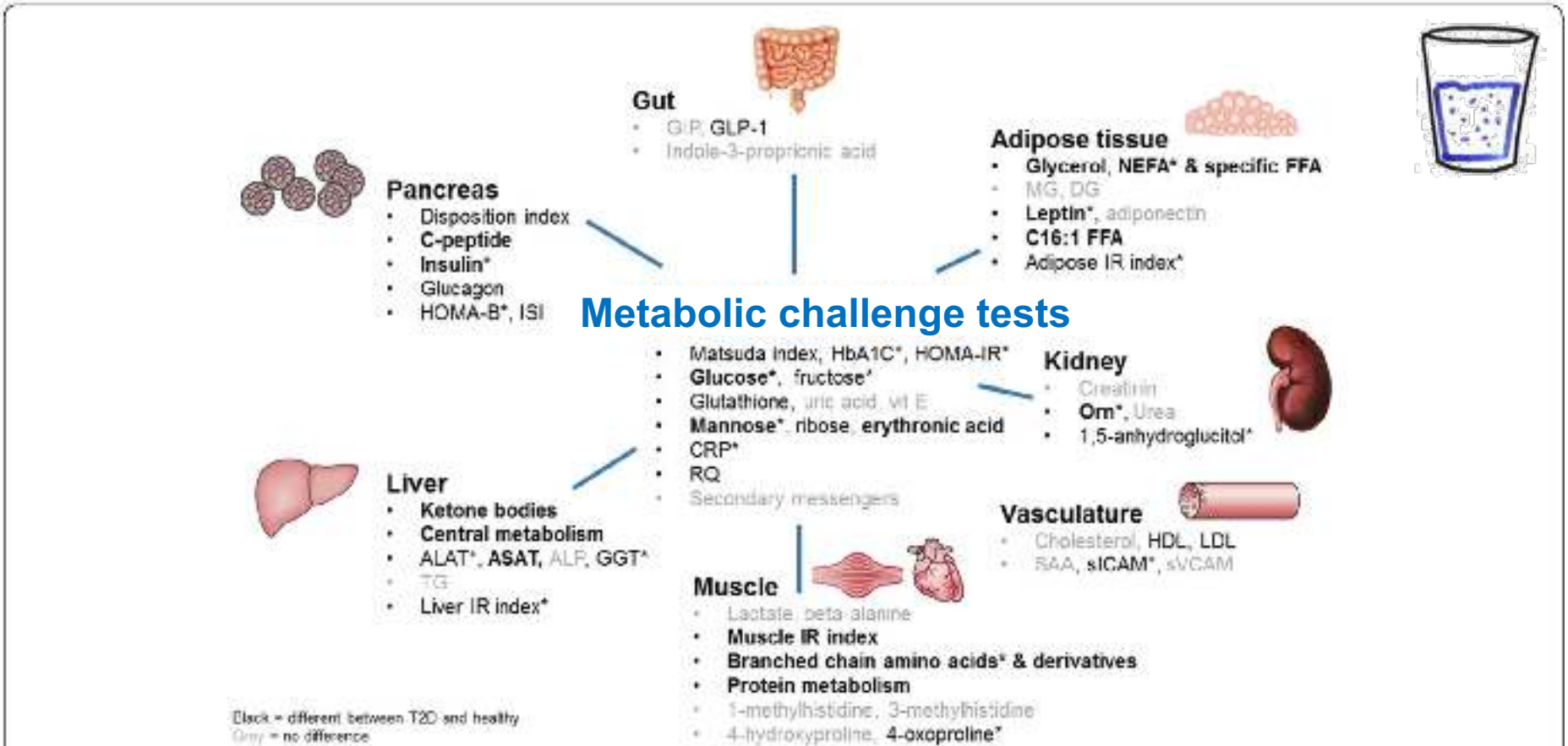
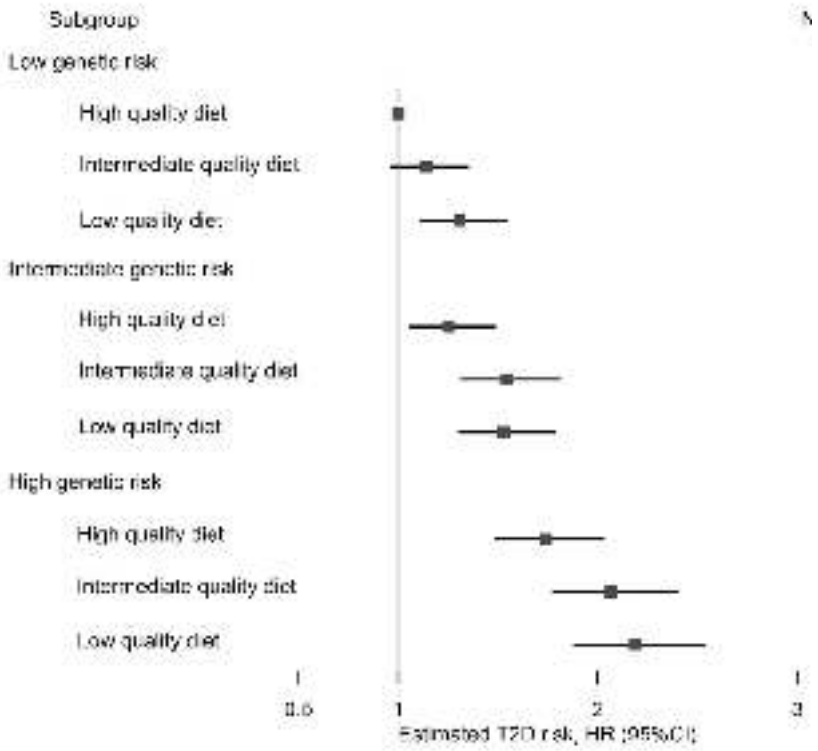
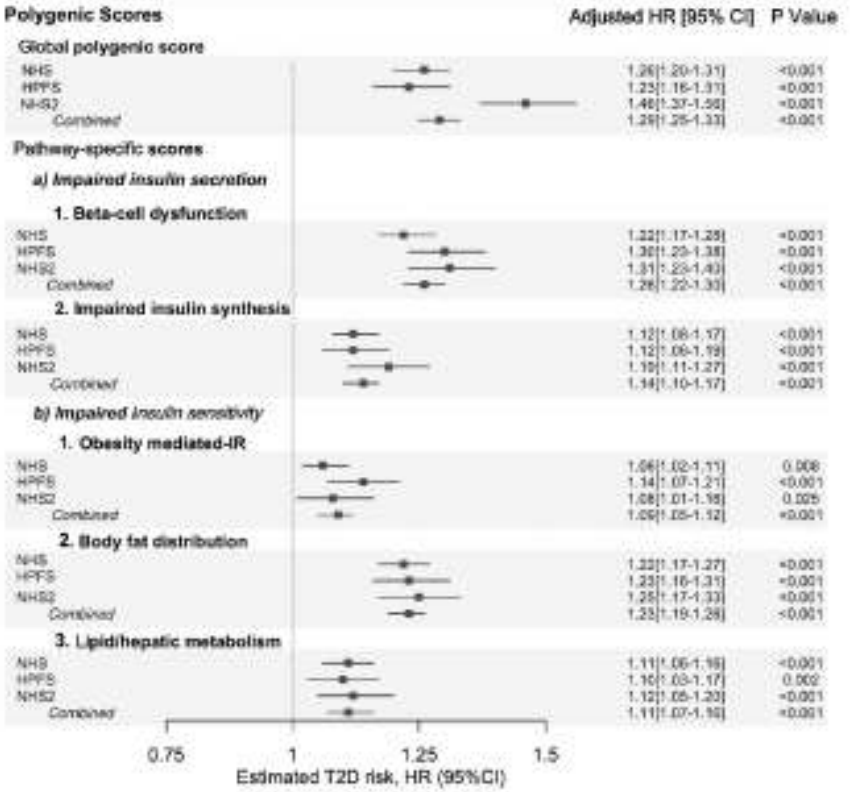


Fig. 4 Overview of markers that have a different PhenFlex test response between 20 healthy male and 20 male type 2 diabetic patients. Gray = no significant differences between T2D and healthy subjects; black = significant different postprandial levels between healthy and diabetic subjects; bold black = significantly different responses to PhenFlex challenge between healthy and type 2 diabetics; asterisk = significant different fasting levels

Wopereis et al, Genes and Nutrition, 2017

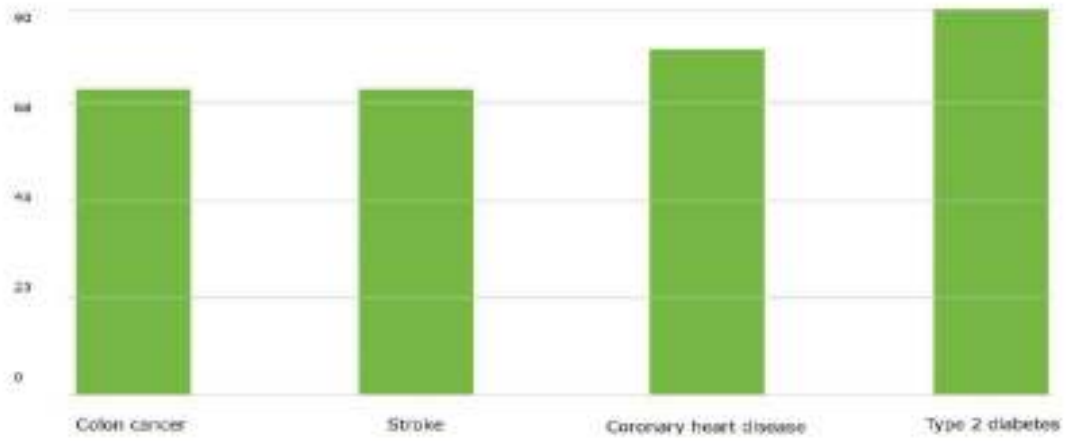
What about genetics vs diet quality in development of type 2 diabetes?





Merino J et al. PLoS Med. 2022

Nutrition and lifestyle contribute up to 90% in the development of chronic non-communicable diseases



Source: Willett WC, Science 2002

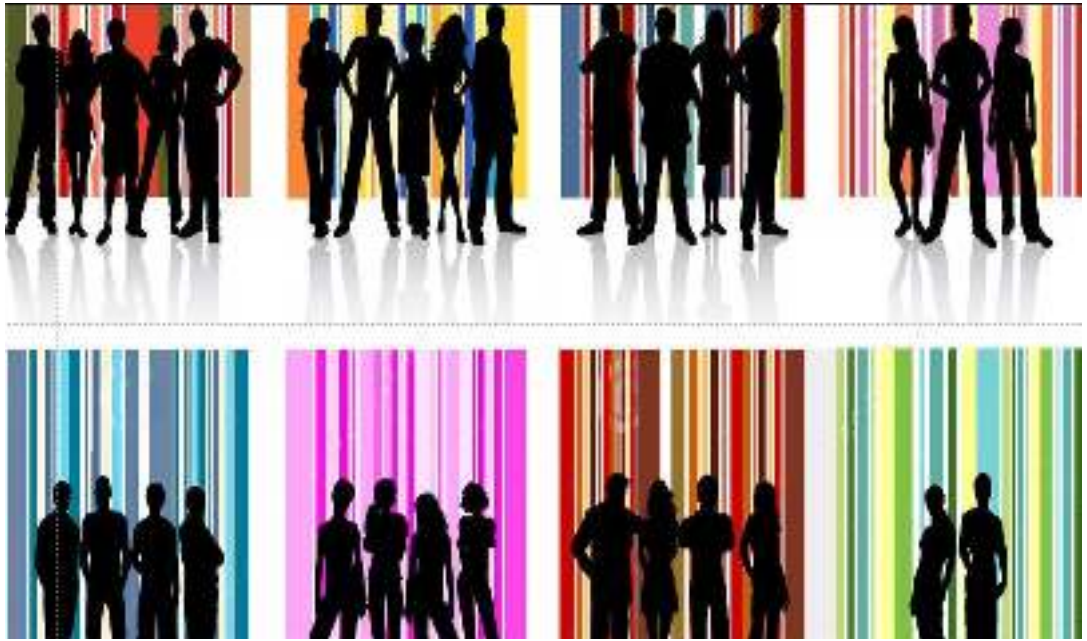
Summary of T2D and lifestyle as 'treatment'

- Type 2 diabetes is a systems disease, which for 90% is caused by the environment of a person. The genetic background of a person makes a person more susceptible for T2D, but is not the only cause of the disease.
- Remission of type 2 diabetes is possible with lifestyle; percentages of ~ 25 – 40% have been reported
- However, responders and non-responders are described and often participants could not achieve the proposed lifestyle goal (e.g. Lean et al. Lancet 2018)
- Sustained lifestyle change is an important topic to address: how to achieve that?

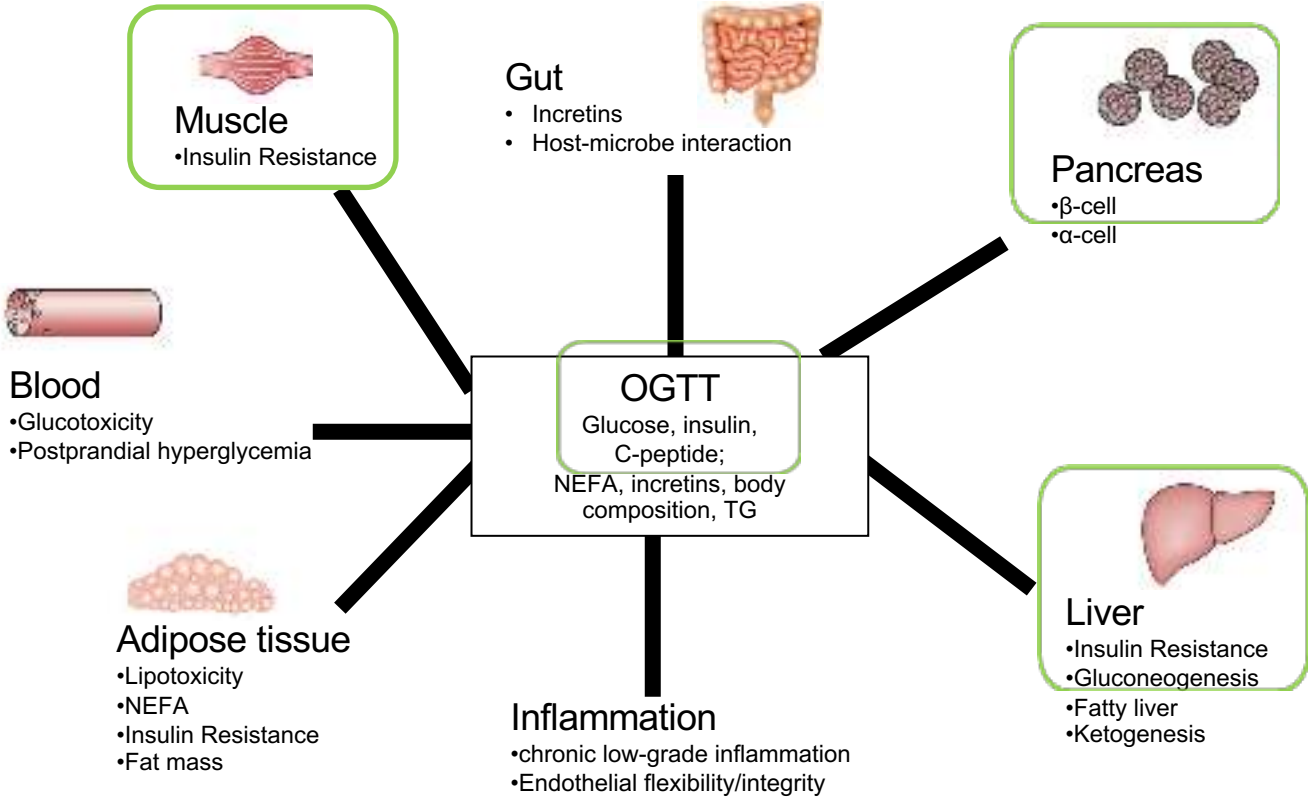
Aim: Develop a personalized approach for sustained behaviour change to reduce the number of persons with type 2 diabetes as well as to further reduce cardiometabolic complications

Diagnosis of subpopulations in diabetes patients

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



An extension of the oral glucose tolerance test



Subgroup specific efficacy of lifestyle

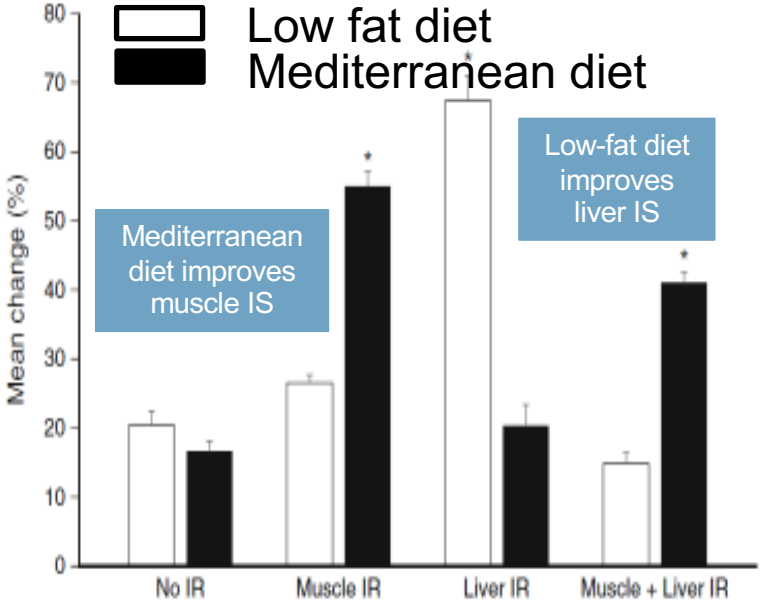
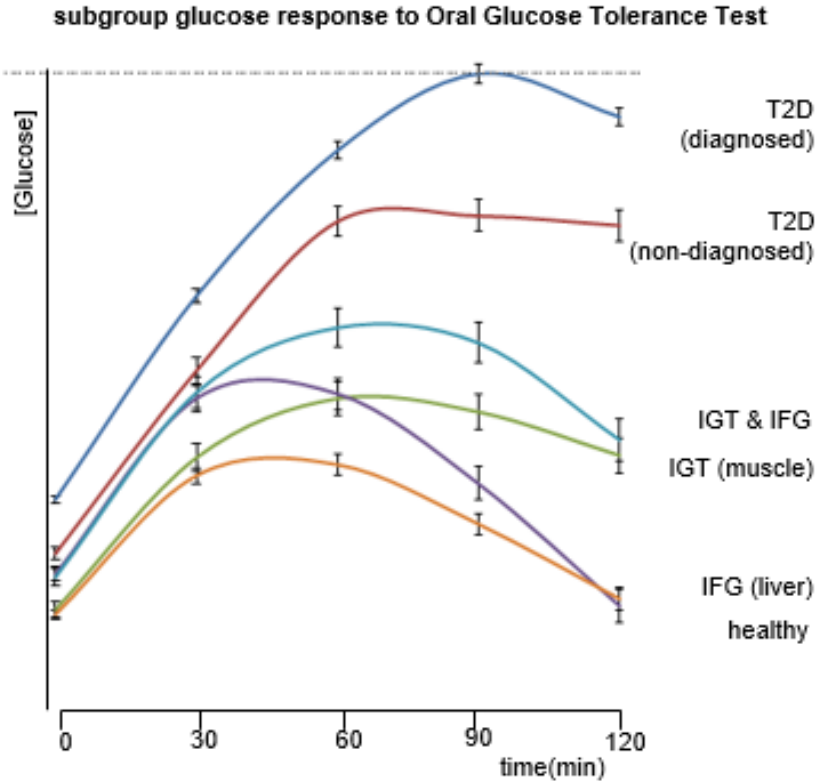


Fig. 1 Mean percentage change in values of disposition index between baseline and after 2 years of follow-up by IR phenotype. *$p<0.05$ between low-fat diet (white bars) and Mediterranean diet (black bars) in each IR subgroup analysed using a univariate model adjusted for age, sex, baseline BMI and change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



Blanco-Rojo, Diabetologia, 2015

Prospective Diabetes Field lab in Hillegom

Aim:

reduce diabetes incidence and complications

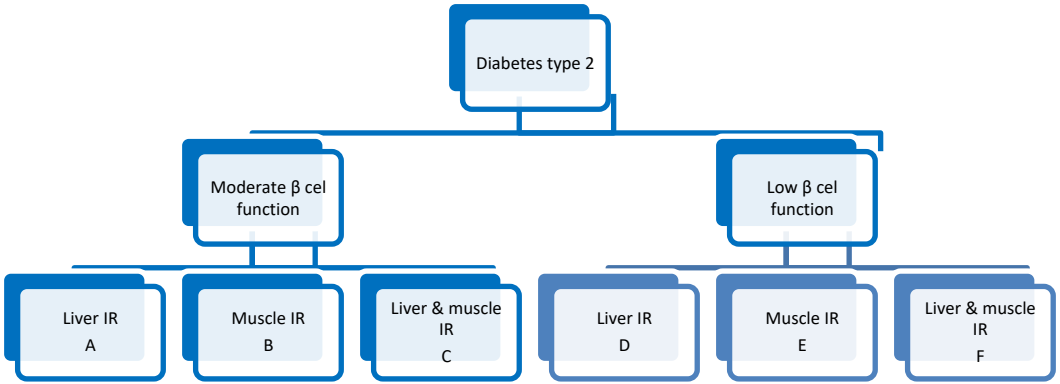
Approach:

tackle newly diagnosed diabetes type 2 with lifestyle changes

Method:

personalized diagnosis and advice

use OGTT (oral glucose tolerance test) to stratify



De Hoogh et al. Biomedicines 2022, 10, 643

Diagnosis lifestyle treatment combinations

Hepatic IR

Muscle IR

Poor beta

Hepatic & Muscle IR

Poor beta – Hepatic IR

Poor beta – Muscle IR

Poor beta – Hepatic & Muscle IR

Treatments

Muscle IR → Exercise (resistance training 3*60 min per wk)
Liver IR → Caloric restriction (1 wk VLCD 500 kcal; 12 wk LCD 1000 kcal)
Pancreas → 13 wk LCD with poor pancreas; VLCD&LCD with moderate pancreas
Multiple IR → Combinations of treatments (exercise and diet)

De Hoogh et al. Biomedicines 2022, 10, 643

Effect of usual care *vs* intervention

Variable	Usual care	Intervention	p-value (group*time)
Body weight (kg)			
Baseline	90.4 (15.1)	96.3 (16.1)	
13 weeks	91.2 (15.7)	88.1 (16.9)‡	<0.0001
1 year	90.3 (15.5)	89.3 (16.6)†	
2 years	87.8 (14.0)‡	88.9 (13.8)‡	
Fasting glucose (mmol/)			
Baseline	8.3 (4.0)	7.0 (1.5)	
13 weeks	7.4 (1.6)	6.2 (0.9)	0.2595
1 year	7.6 (1.8)	6.4 (1.0)	
2 years	7.4 (1.6)	6.5 (1.4)	
HbA1c (mmol/mol)			
Baseline	49.7 (13.9)	42.6 (7.4)	
13 weeks	48.1 (9.8)	38.6 (4.9)†	0.0009
1 year	48.3 (10.8)	39.1 (6.7)‡	
2 years	48.6 (10.8)	41.4 (8.9)*	

*Data are mean ± standard deviation. HbA1c = glycated hemoglobin. * = p<0.05, † = p<0.01 and ‡ = p<0.001 as compared to baseline.*

Higher degree of weight loss and improvement of glycemic control in the intervention group that is sustained

De Hoogh et al. Biomedicines 2022, 10, 643

Remission data for Hillegom field lab

	Usual care (n=41)	Intervention (n=25)
13 weeks	22.0%	75.0% (n=15)
52 weeks	-	52.4%
104 weeks	-	28.6%

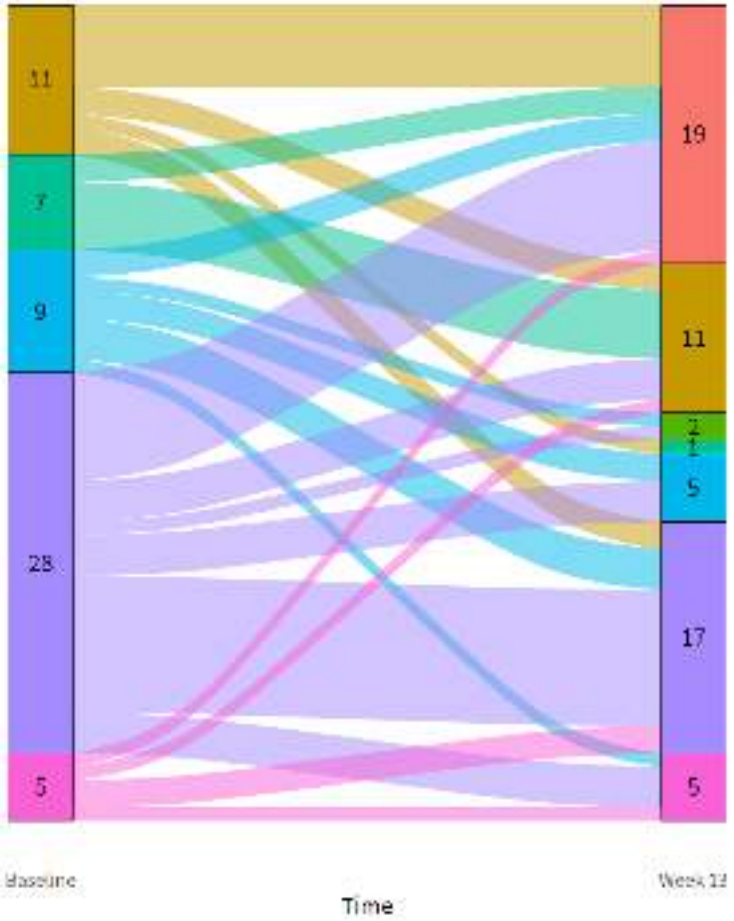
Remained prediabetic	Progressed towards T2D
89%	11%

Remission:
HbA1C ≤ 48 mmol/mol (≤ 6.5 %) and fasting glucose ≤6.9 mmol/L.
NB. medication use unknown in usual care

Only 28% were classified as 'healthy' with diabetyping methodology → still underlying pathology in ~70% of patients that achieved 'remission'

De Hoogh et al. Biomedicines 2022, 10, 643

Flow of T2D subtypes baseline – wk 13



n=7 with remission;
n=11 prediabetic;
n=1 T2D with FPG 7.0

n=6 T2D

n=3 T2D

Severity of T2D

Phenotype

- H
- HIR
- MIR
- CIR
- PB
- PB-HIR
- PB-CIR

De Hoogh et al. Biomedicines 2022, 10, 643

Long-term subgroup specific effects

Table 4. Changes in body weight, FPG, and HbA1c from baseline (week 0) to the end of the intervention (week 13) and to the one- and two-year follow-ups (weeks 52 and 104) for the type 2 diabetes subtypes.

	HIR (n = 11)	CIR (n = 7)	PB (n = 9)	PB-HIR (n = 28)	PB-CIR (n = 5)
Bodyweight (kg)					
Weeks 0–13	−10.2 ***	−13.1 ***	−5.6 **	−8.8 ***	−5.7 *
Weeks 0–52	−9.1 ***	−7.3 **	−4.8 ***	−6.0 ***	2.0
Weeks 0–104	−8.4 ***	−7.1 **	−2.3 *	−6.0 ***	3.3 *
Fasting glucose (mmol/L)					
Weeks 0–13	−1.1 ***	−0.3	0.3	−1.1 ***	−0.5
Weeks 0–52	−1.3 ***	−0.2	0.0	−0.7 ***	0.4
Weeks 0–104	−1.0 ***	−0.2	0.4	−0.7 ***	−0.3
HbA1c (mmol/mol)					
Weeks 0–13	−3.4 ***	−3.3 *	0.0	−6.2 ***	−2.2
Weeks 0–52	−4.3 **	−1.3	−1.3	−4.9 ***	−1.5
Weeks 0–104	−2.4 *	−0.4	1.8	−2.5 **	−1.3

The data are deltas comparing baseline to week 13 (end of intervention), week 52 (one year follow-up), and week 104 (two years follow-up). HIR = moderate BCF and liver IR; CIR = moderate BCF and combined IR; PB = low BCF and no IR; PB-HIR = low BCF and liver IR; PB-CIR = low BCF and combined IR. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ compared with baseline.

PPG was significantly improved at 3 months!

De Hoogh et al. Biomedicines 2022, 10, 643

Conclusions

- The personalized/subgroup lifestyle treatment of three months resulted in reduced body weight, and improved glycemic control (HbA1C) as compared to standard care

- Although 75.0% versus 22.0% (netto 53.0 %) of persons with T2D was in remission, only 28% of patients was fully normalized after 13 weeks of lifestyle intervention

- Long-term follow-up showed that the beneficial effects of the 13 week intervention was still present at two years, especially in persons with liver insulin resistance with or without reduced beta-cell function. Persons with combined insulin resistance, or only reduced beta-cell function did not show long-term improved glycemic control

De Hoogh et al, Nutrients, 2021

nutrients

MDPI

TNO innovation for life

Article

The Effect of a Lifestyle Intervention on Type 2 Diabetes Pathophysiology and Remission: The Stevenshof Pilot Study

Iris M. de Hoogh [1,*], Johanneke E. Oosterman [1], Wilma Otten [2], Anne-Margreeth Krijger [3], Susanne Berbée-Zadelaar [4], Wilrike J. Pasman [1], Ben van Ommen [1], Hanno Pijl [5] and Suzan Wopereis [1]

[1] Research Group Microbiology & Systems Biology, TNO, Netherlands Organization for Applied Scientific Research, 3708 AJ Zeist, The Netherlands; [illegible] (J.E.O.); Wilrike [illegible] (W.J.P.); ben [illegible] (B.v.O.); suzan [illegible] (S.W.)

[2] Research Group Child Health, TNO, Netherlands Organization for Applied Scientific Research, 2301 DA Leiden, The Netherlands; [illegible]

[3] Academic Pharmacy Stevenshof and SIR Institute for Pharmacy Practice and Policy, 2331 JE Leiden, The Netherlands; [illegible]

[4] Susanne Berbée, Diëtist, Partnership with Primary Care Centre Stevenshof, Diabetes, 2331 JE Leiden, The Netherlands; [illegible]

[5] Department of Internal Medicine, Leiden University Medical Center (LUMC), 2300 RC Leiden, The Netherlands; H.Pijl [illegible]

* Correspondence: [illegible]

Abstract: Although lifestyle interventions can lead to diabetes remission, it is unclear to what extent type 2 diabetes (T2D) remission alters or improves the underlying pathophysiology of the disease. Here, we assess the effects of a lifestyle intervention on T2D reversal or remission and the effects on the underlying pathology. In a Dutch primary care setting, 15 adults with an average T2D duration of 13.4 years who were (pharmacologically) treated for T2D received a diabetes subtyping ("diabetyping") lifestyle intervention (DLI) for six months, aiming for T2D remission. T2D subtype was determined based on an OGTT, insulin and sulphonylurea (SU) derivative treatment could be

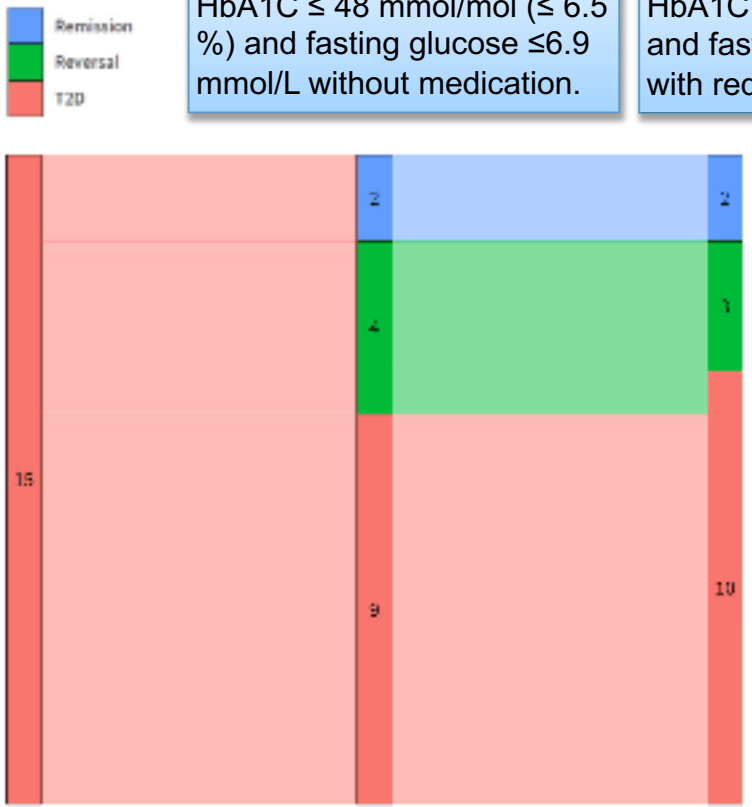
Citation: de Hoogh, I.M.; Oosterman, J.E.; Otten, W.; Krijger, A.-M.; Berbée-Zadelaar, S.; [illegible]; Pasman, W.J.; van Ommen, B.; Pijl, H.; Wopereis, S. The Effect of a Lifestyle

N=15 T2D patients with an average T2D duration of 13.4 years

Remission data for Stevenshof field lab

Remission:
HbA1C ≤ 48 mmol/mol (≤ 6.5 %) and fasting glucose ≤6.9 mmol/L without medication.

Reversal:
HbA1C ≤ 53 mmol/mol (≤ 6.5 %) and fasting glucose ≤8.0 mmol/L with reduced medication.



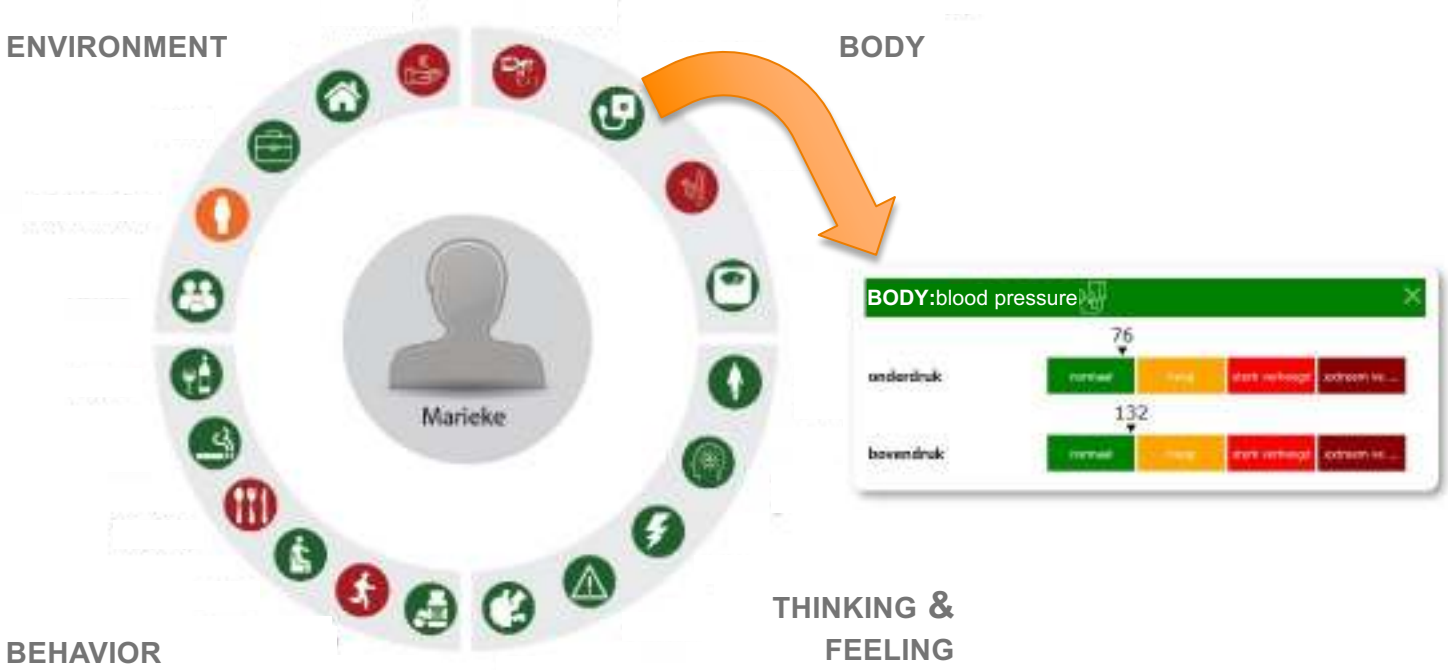
None was 'healthy' according to diabetyping, but BMI, waist circumference, FPG, TG, HDL, HbA1C improved as compared to baseline

Intervention:

1. Hepatic IR by a short, intense, and very low-calorie diet of 1 week vegetables
2. BCF / HIR by a low carb diet (~75 gr per day)
3. MIR / sustainability by MedDiet, vegetables, 100-150 g whole-grains, protein, nuts, dairy, cheese, oil, 3 times a day

De Hoogh et al, Nutrients, 2021

OGTT subtyping integrated in 360º diagnosis



Opinion health care professionals

TNO innovation for life

Valuable to provide persons with T2D a perspective instead of more medication

Collaboration with multiple disciplines works very well: you are complementary to each other.

A different more intensive way of guidance

Shocking to discover that many glucose lowering medication is counterproductive

With this knowledge you will treat T2D patients very differently

Is it still ethically justified to treat T2D patients with insulin without knowing the subtype? .....

PERSONALIZED NUTRITION

TNO innovation for life

T2D subgroups	Potential lifestyle interventions	Supplements
1. Pancreatic β-cell function	Ketogenic diet, low carb diet, plant-based diary	MUFA, leucine, vit K, vit D, Mg, vitB12
2. Muscle IR	Mediterrenean diet, physical activity, diets with a low glycemic index, dairy	Protein supplement, specific types of fibres (beta-glucan, arabinoxylans), leucine, B-vitamins
3. Hepatic IR	Low fat diet, energy restriction, energy restriction on DASH diet, low fructose	Carnitine, choline, fish oil, resveratrol
4. Adipocyte IR and lipotoxicity	Whole grains, energy restriction, fish, decrease SFA	Resveratrol, fish oil, PUFA
5. Gastrointestinal tract	Dietary fiber	Probiotics, prebiotics, symbiotics, fibers
6. Pancreatic α-cell hyperfunction	Ketogenic diet, low carb diet, plant-based dairy	Protein supplement, PUFA
7. Chronic low-grade inflammation	Whole grains, fish, Mediterrenean diet, nuts, fruits & vegetables	Se, vit D, polyphenols, vit C, vit A, fish oil, ECGC, sulforaphane, prebiotics, vit E
8. Cardiovascular dysfunction	DASH diet, low fat diet, low salt	Potassium, plant sterols, Beta-glucan, vitamin B2

Adapted from Van Ommen and Wopereis, 2016

TAKE HOME MESSAGE

- Lifestyle should be the main therapy for treatment of type 2 diabetes! In that case, some persons can remit the disease, otherwise persons can reverse the disease

- However, for a sustained behavioral change a personalized approach leads to a better adherence to the lifestyle therapy. Ideally, the four pillars of personalized nutrition should be considered for that.

- Remission of type 2 diabetes with lifestyle is possible, especially for people with relatively mild type 2 diabetes. For T2D with a longer T2D duration diabetes reversal may be a more realistic goal.

- Our Stevenshof study implies that achieving diabetes remission in individuals with a longer T2D duration is possible, but underlying pathology is only minimally affected, possibly due to an impaired beta-cell function. Thus, even when T2D remission is achieved, patients need to continue adhering to lifestyle therapy

- A personalized lifestyle approach to cure type 2 diabetes is a very promising strategy to increase sustained adherence to the lifestyle advice, especially when people monitor several aspects of health over time, when behavioral aspects are considered (360 degrees feedback) and when realistic (biological) goals are being set and personal preferences can be taken into account!


THANK YOU FOR YOUR ATTENTION
Dr. Suzan Wopereis
Principal Scientist
Microbiology & Systems Biology
TNO innovation for life
T +31 88 866 50 13
M + 31 6 4696 6180
E suzan.wopereis@tno.nl
TNO innovation for life