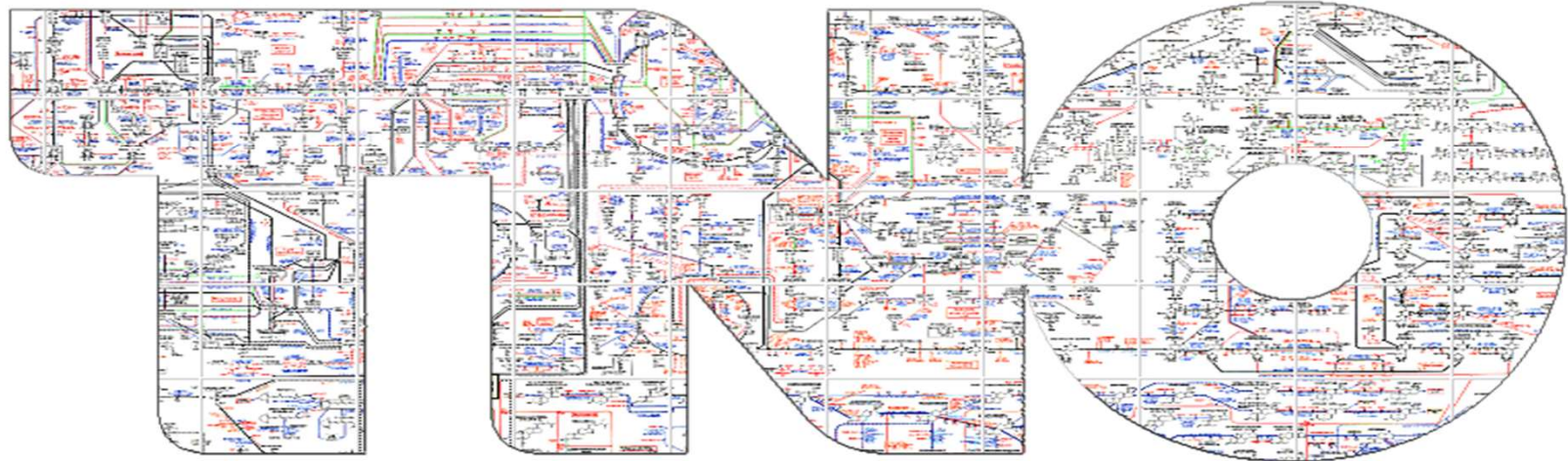


Systems approaches needed

Ben van Ommen

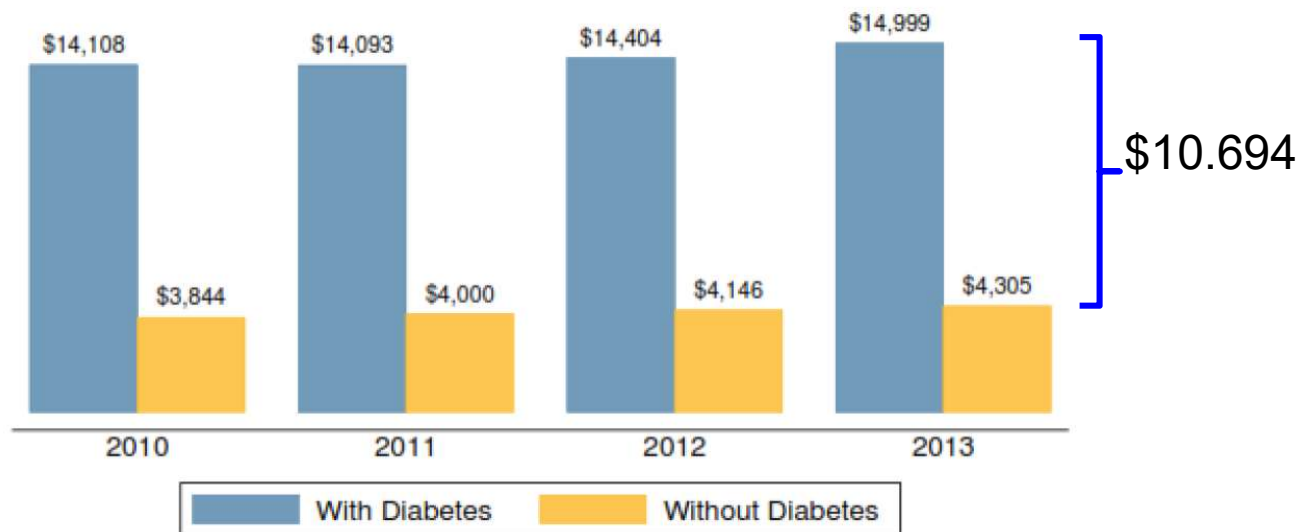


Health & Science

People with diabetes are facing rising prices for lifesaving drugs

By Michelle Andrews August 24

Figure 1
Total Per Capita Expenditures for Insureds,
With and Without Diabetes: 2010-2013



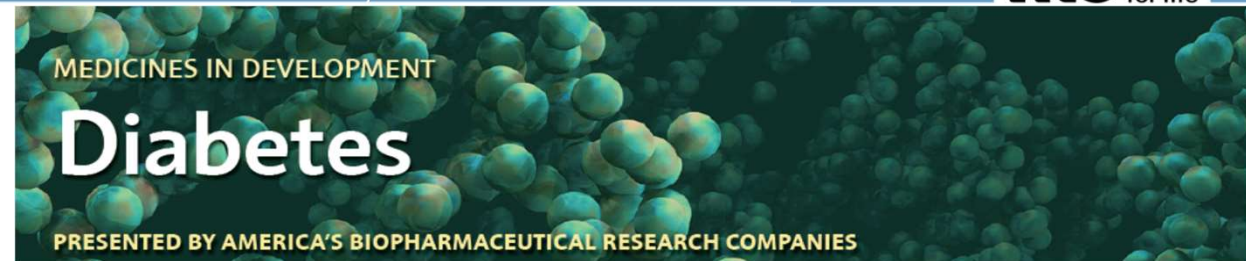
Source: HCCI, 2015.
Notes: All data weighted to reflect the national, younger than 65 ESI population.
Data from 2012 and 2013 actuarially completed.

JAMA | Original Investigation

US Spending on Personal Health Care and Public Health, 1996-2013

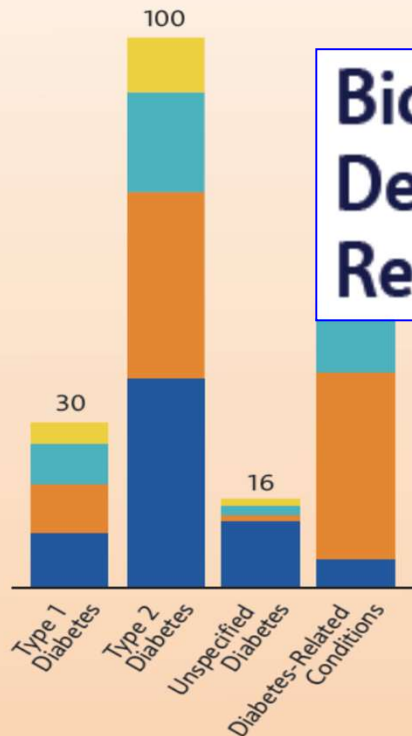
RESULTS From 1996 through 2013, \$30.1 trillion of personal health care spending was disaggregated by 155 conditions, age and sex group, and type of care. Among these 155 conditions, diabetes had the highest health care spending in 2013, with an estimated \$101.4 billion (uncertainty interval [UI], \$96.7 billion-\$106.5 billion) in spending, including 57.6% (UI, 53.8%-62.1%) spent on pharmaceuticals and 23.5% (UI, 21.7%-25.7%) spent on ambulatory care. Ischemic heart disease accounted for the second-highest amount of health care spending in 2013, with estimated spending of \$88.1 billion

JAMA. 2016;316(24):2627-2646.



Medicines in Development For Diabetes

- Application Submitted
- Phase III
- Phase II
- Phase I



Biopharmaceutical Research Companies Are Developing 180 Medicines to Treat Diabetes and Related Conditions

... and NONE of them aims at CURING the disease ...!

Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study

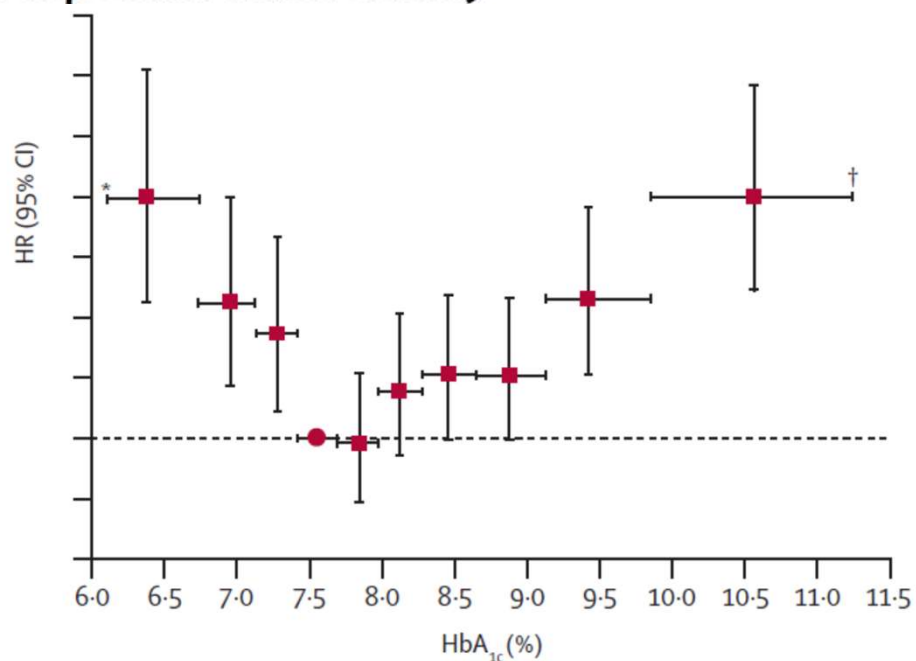
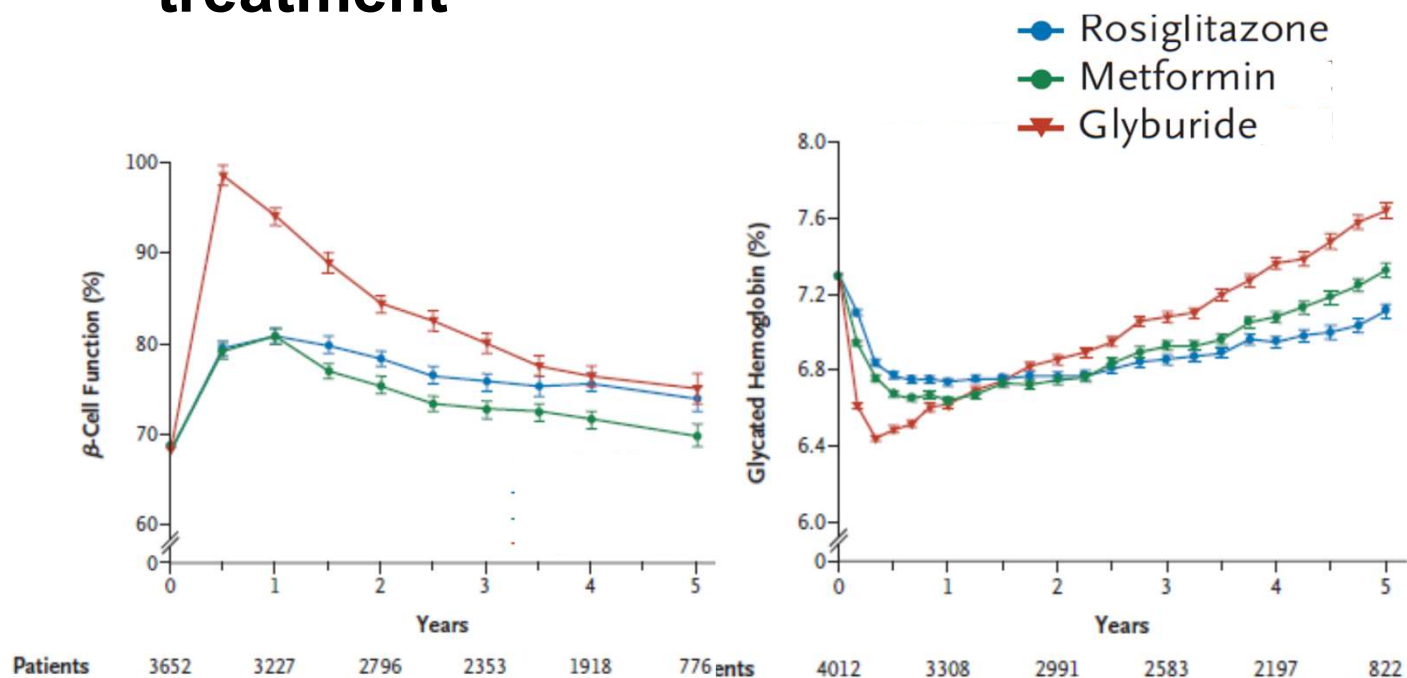


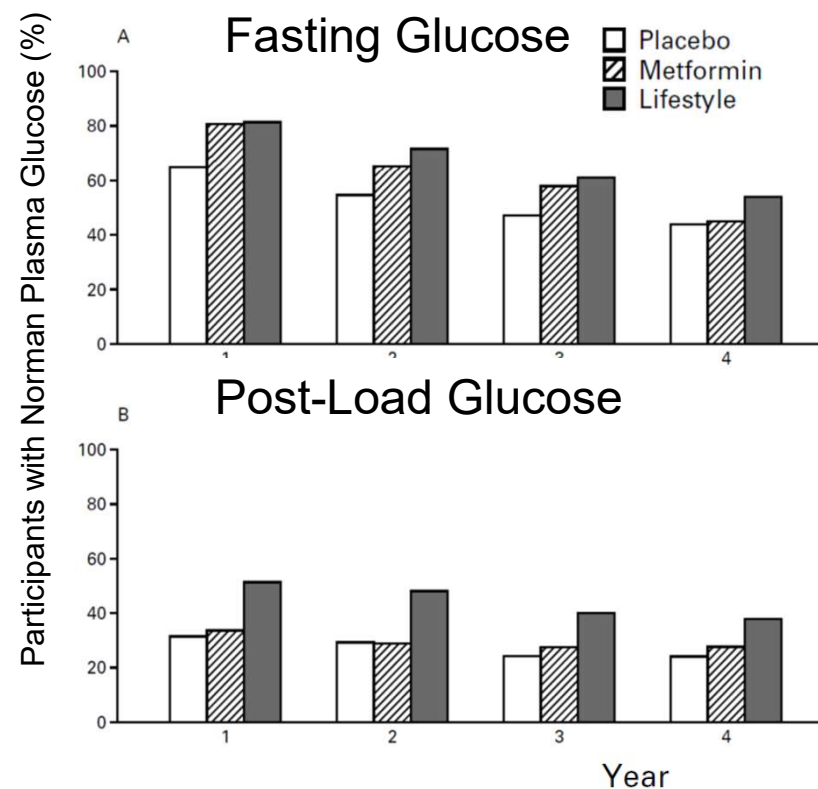
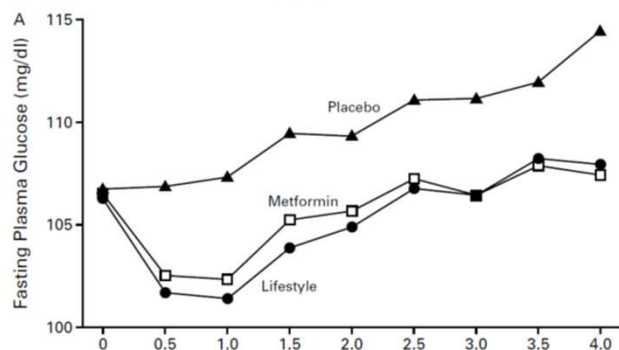
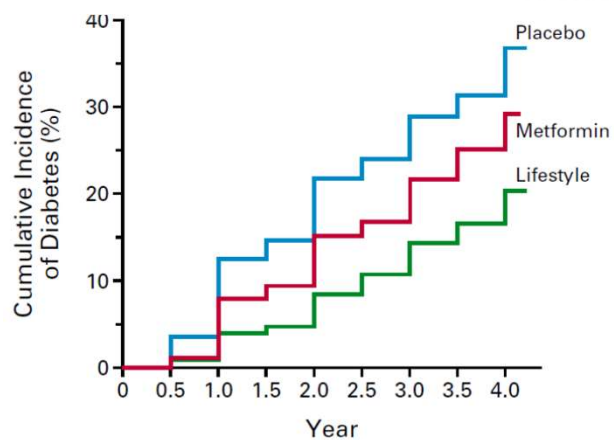
Figure 1: Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies
 Cox proportional hazards models were used, with the HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range. Red circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

The 5-year efficacy of diabetes type 2 treatment

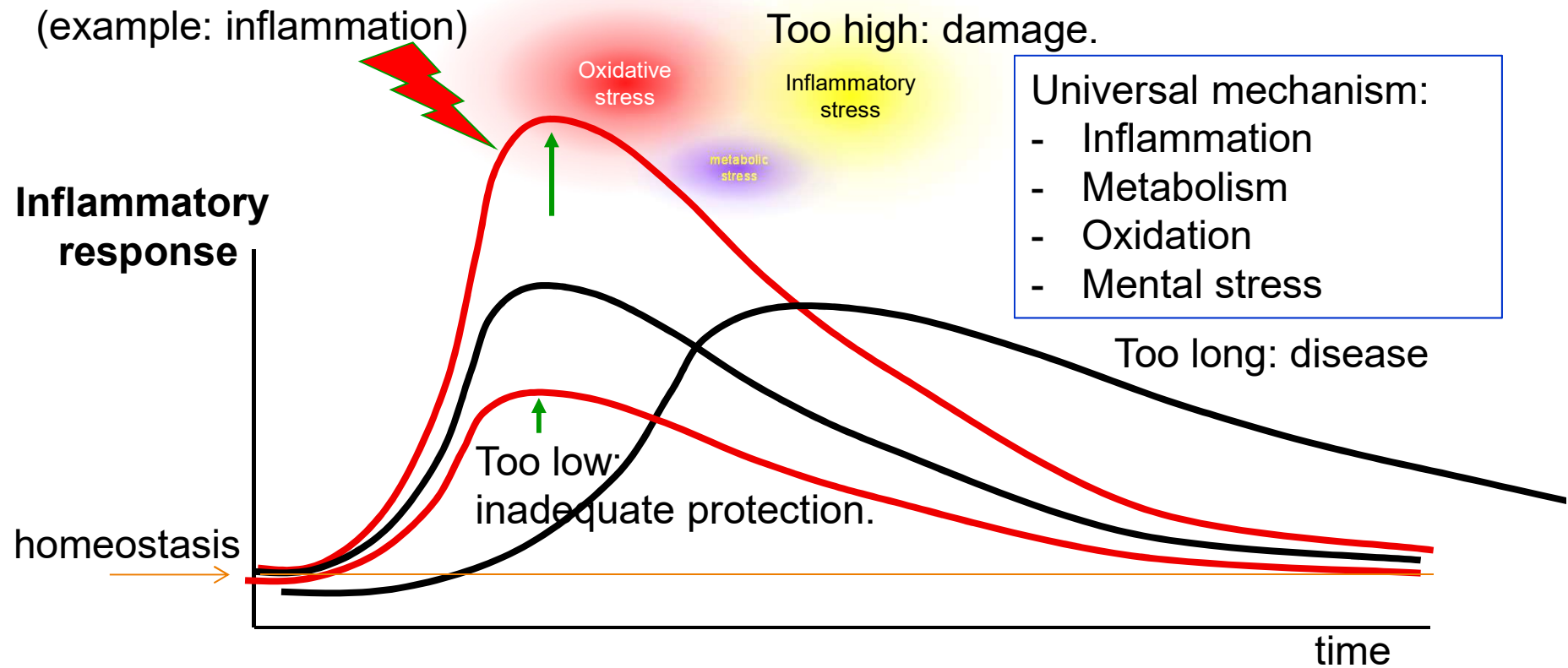


Kahn, NEJM 2006

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

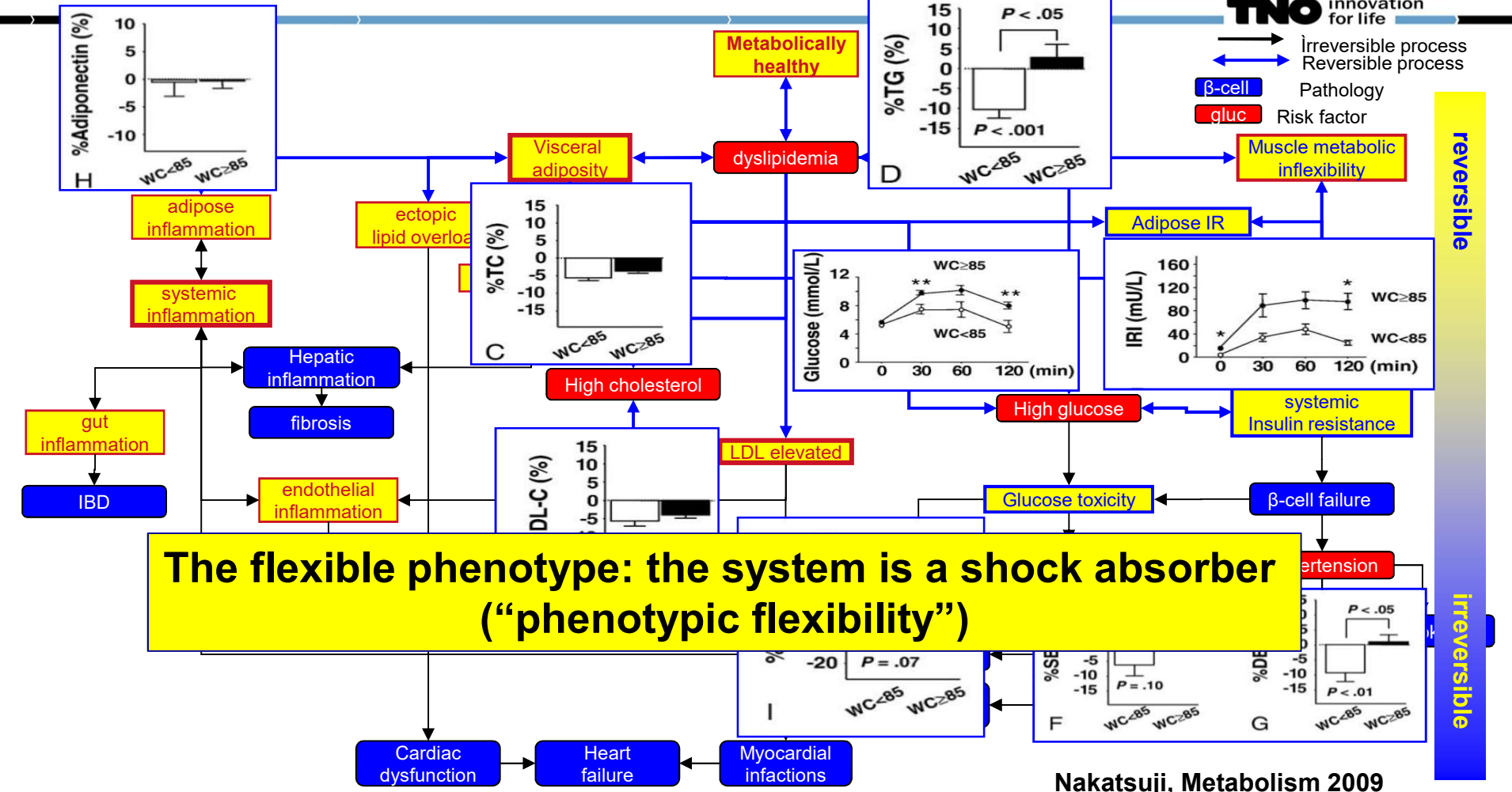


Health and disease are characterized by flexibility, i.e. the capacity to regain homeostasis upon a challenge.

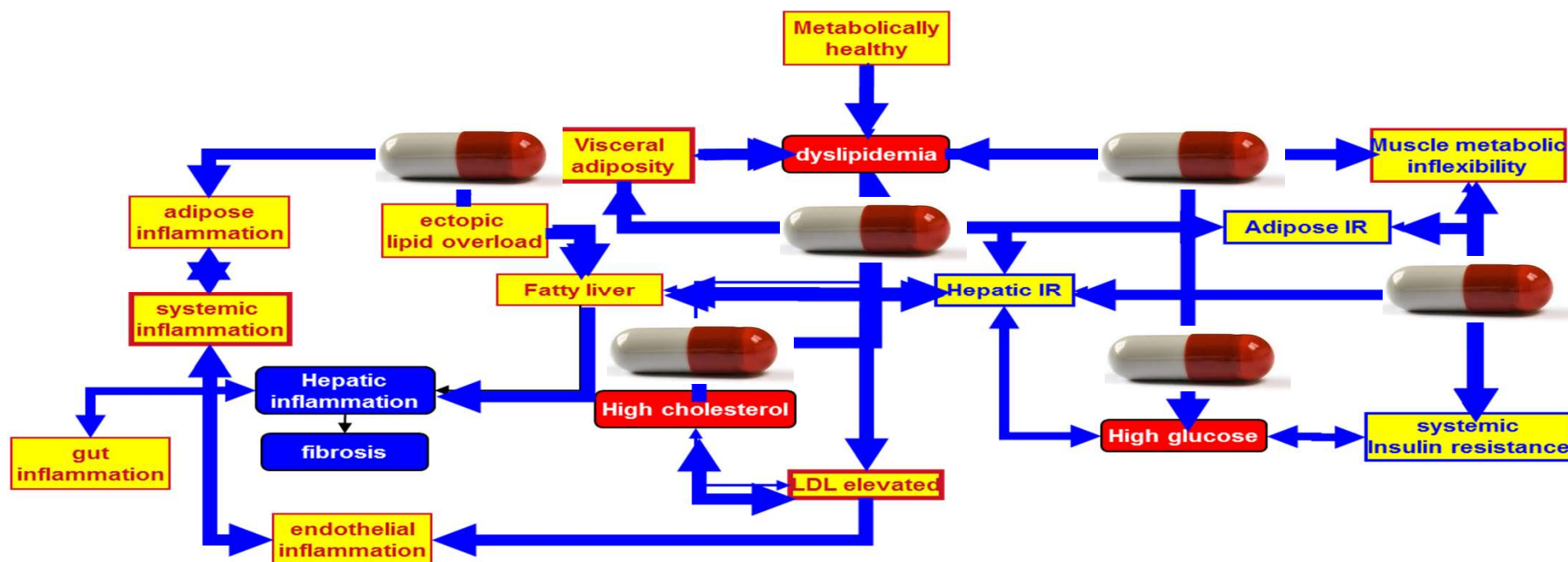


75 g Glucose

TNO innovation for life



Even precision medicine will not cure type 2 diabetes



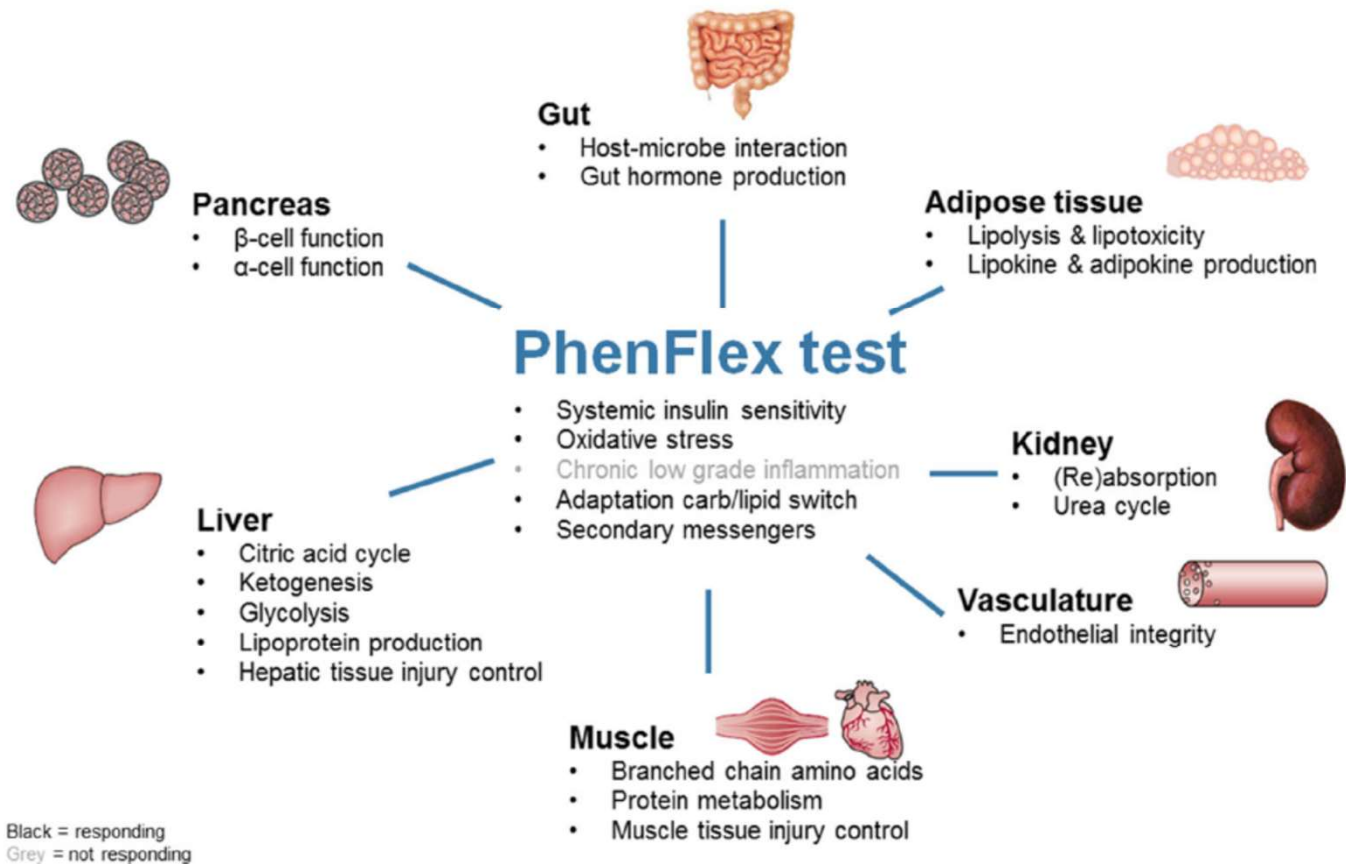


Fig. 2 Overview of processes that are modulated by the PhenFlex test based on biomarker response in $n = 20$ healthy male subjects. Black: modulated by PFT; gray: not responding

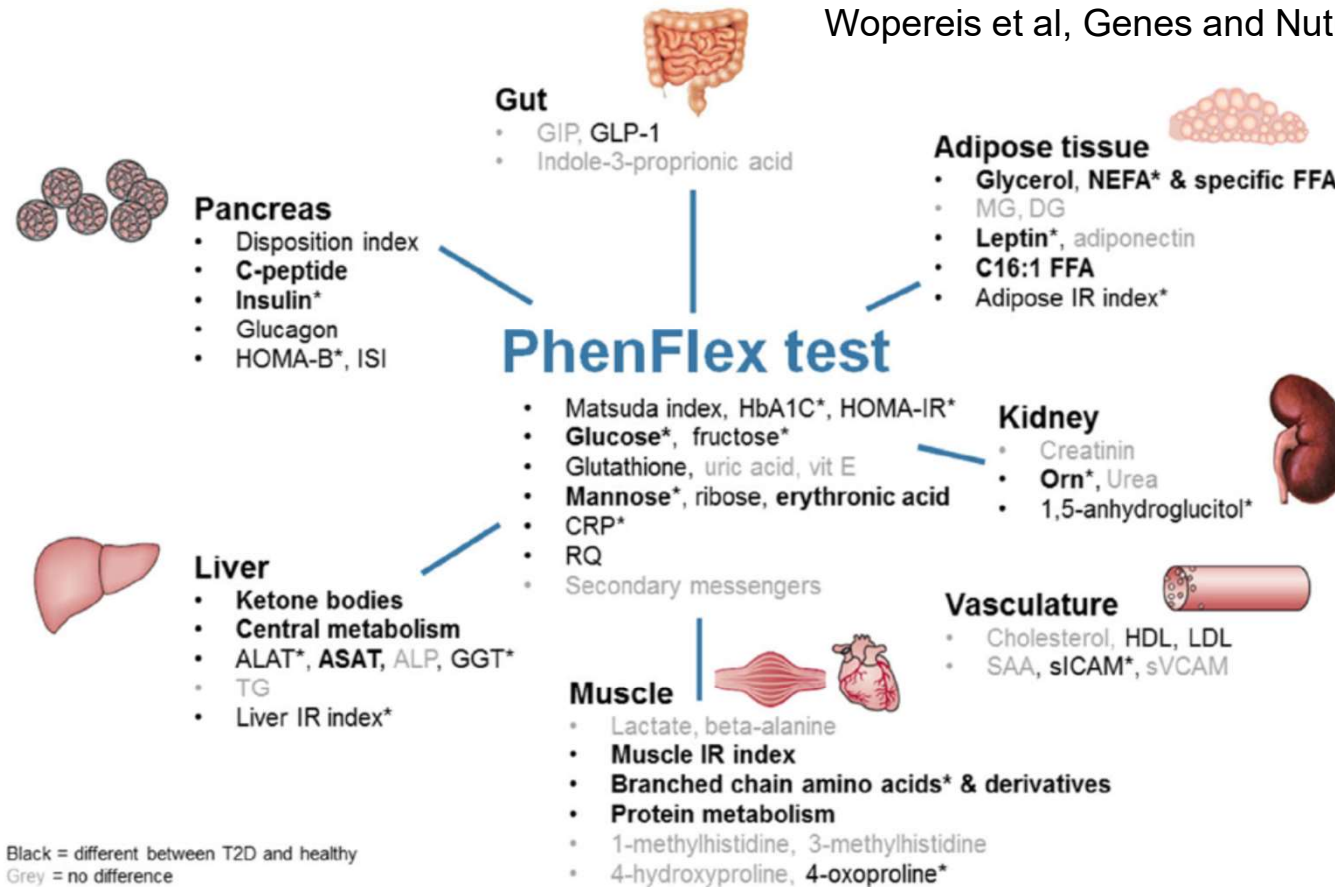
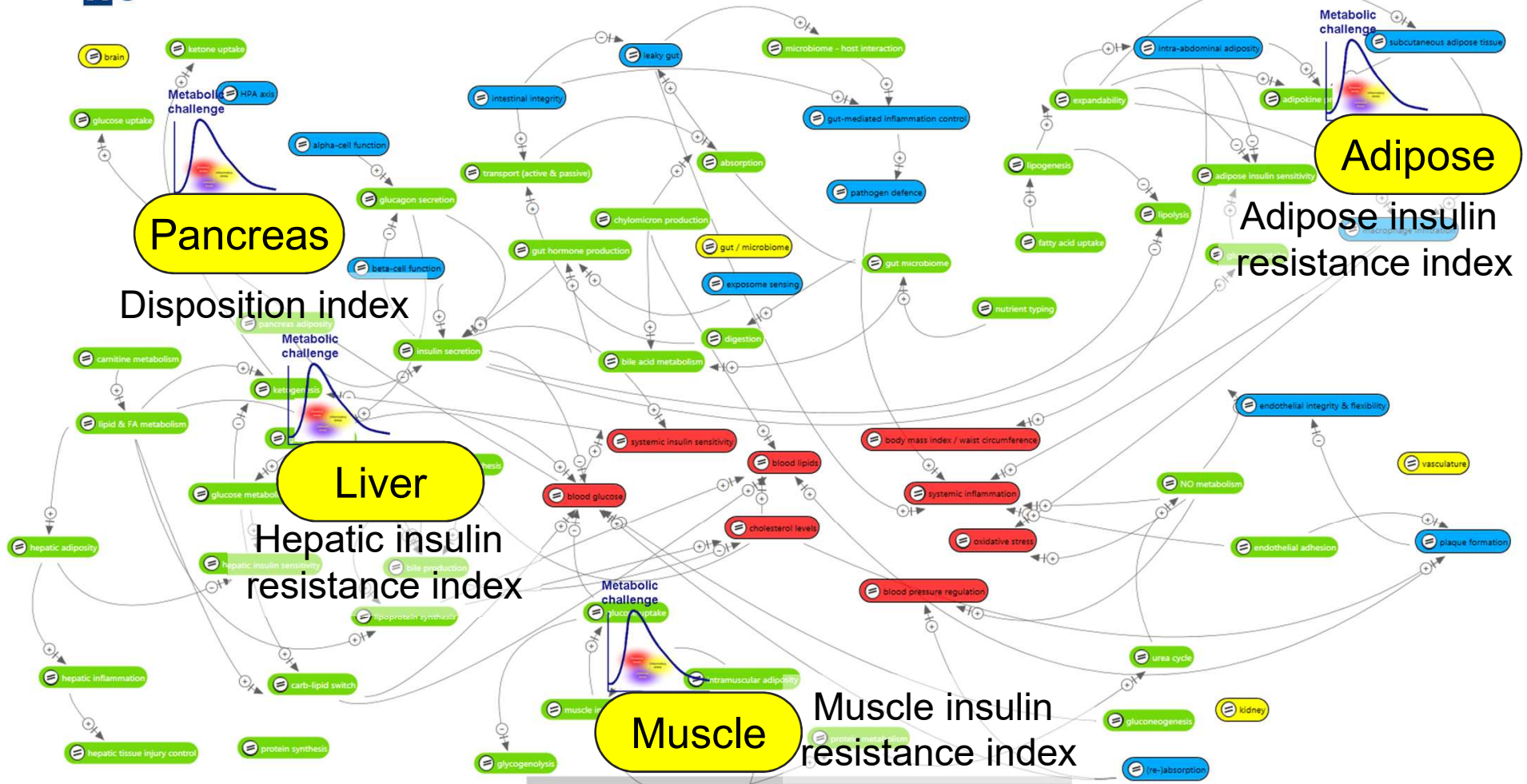
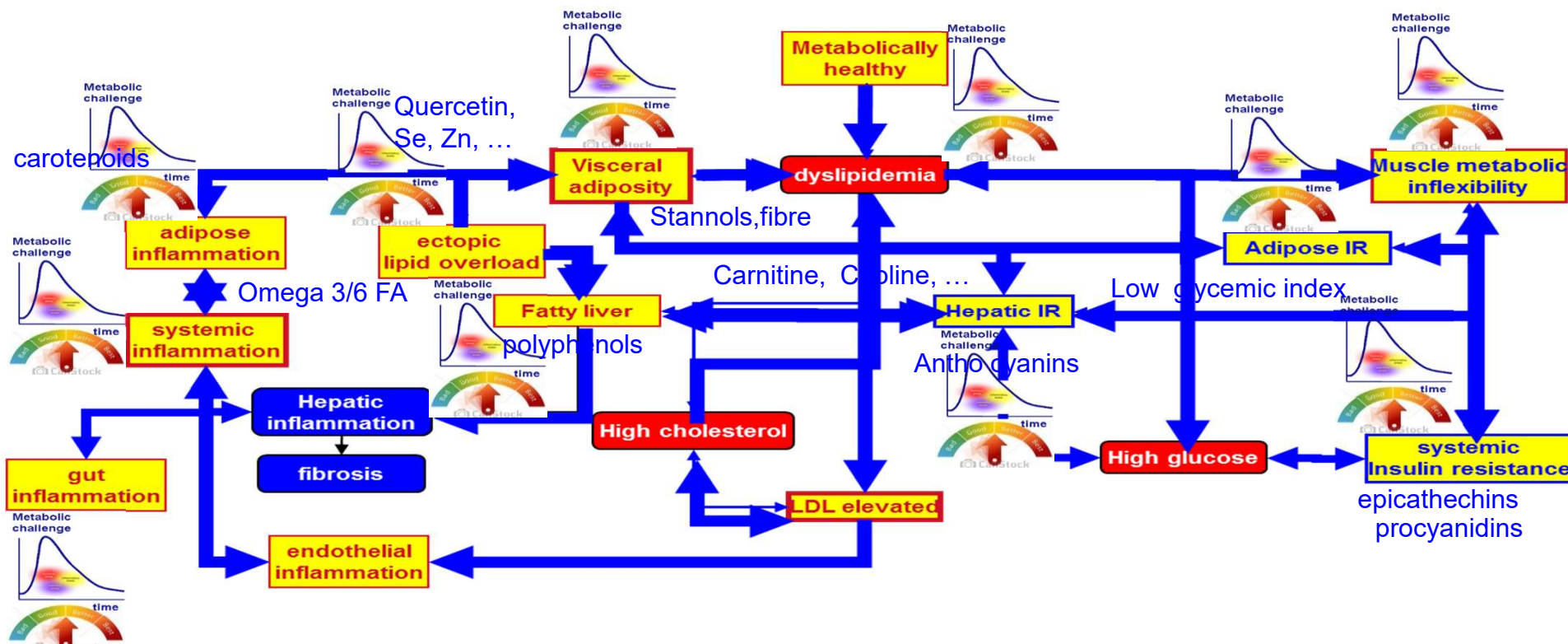


Fig. 4 Overview of markers that have a different PhenFlex test response between 20 healthy male and 20 male type 2 diabetic patients. Gray = no significant differences between T2D and healthy subjects; black = significant different postprandial levels between healthy and diabetic subjects; bold black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



The processes that orchestrate phenotypic flexibility depend on calories and nutrients...



Type 2 diabetes subgroups react differently on different diets

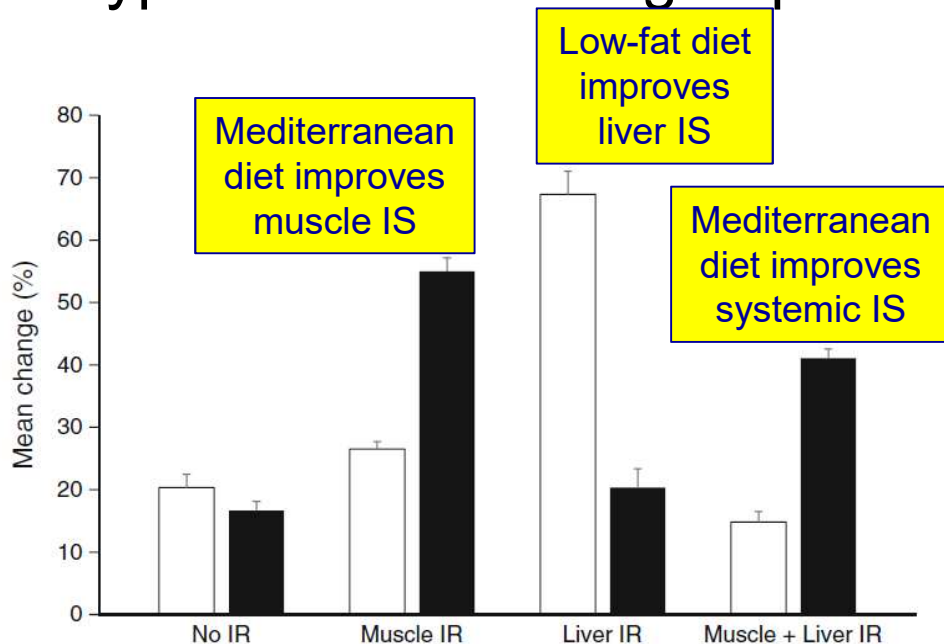
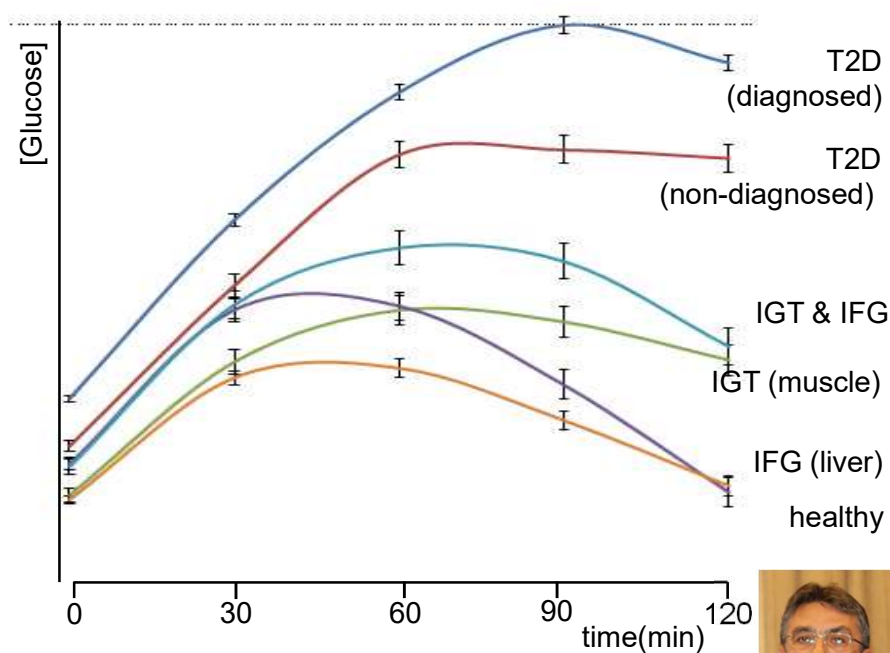


Fig. 1 Mean percentage change in values of disposition index between baseline and after 2 years of follow-up by IR phenotype. * $p < 0.05$ between low-fat diet (white bars) and Mediterranean diet (black bars) in each IR subgroup analysed using a univariate model adjusted for age, sex, baseline BMI and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

T2D subgroup glucose response to Oral Glucose Tolerance Test



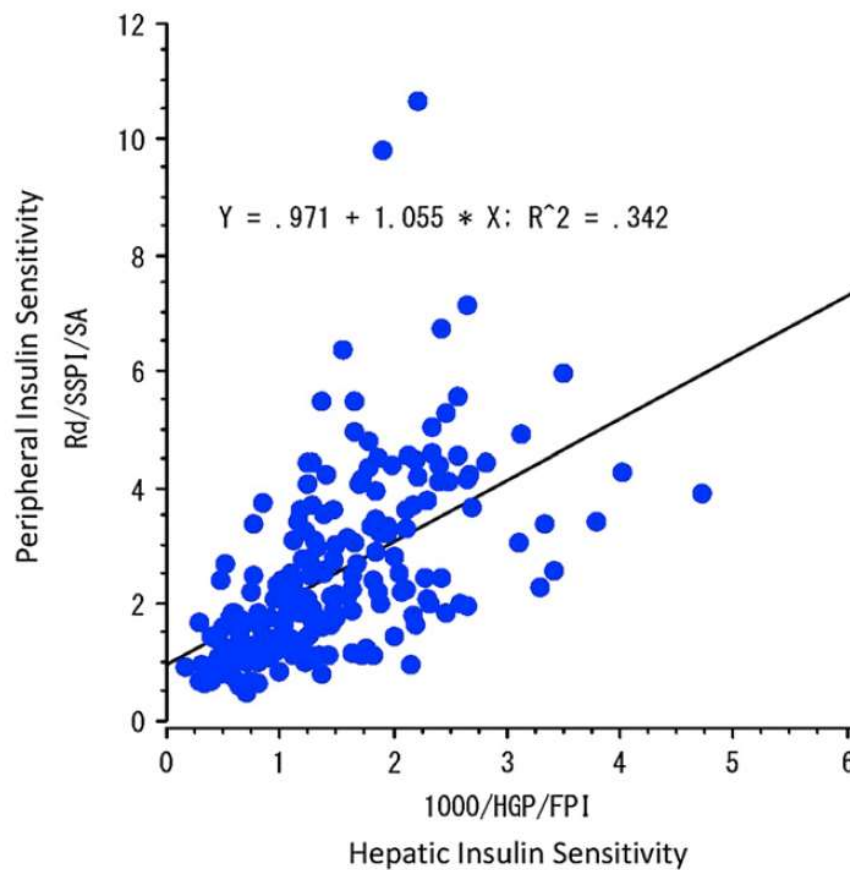
Blanco-Rojo, Diabetologia, Oct 2015



José Lopez-Miranda



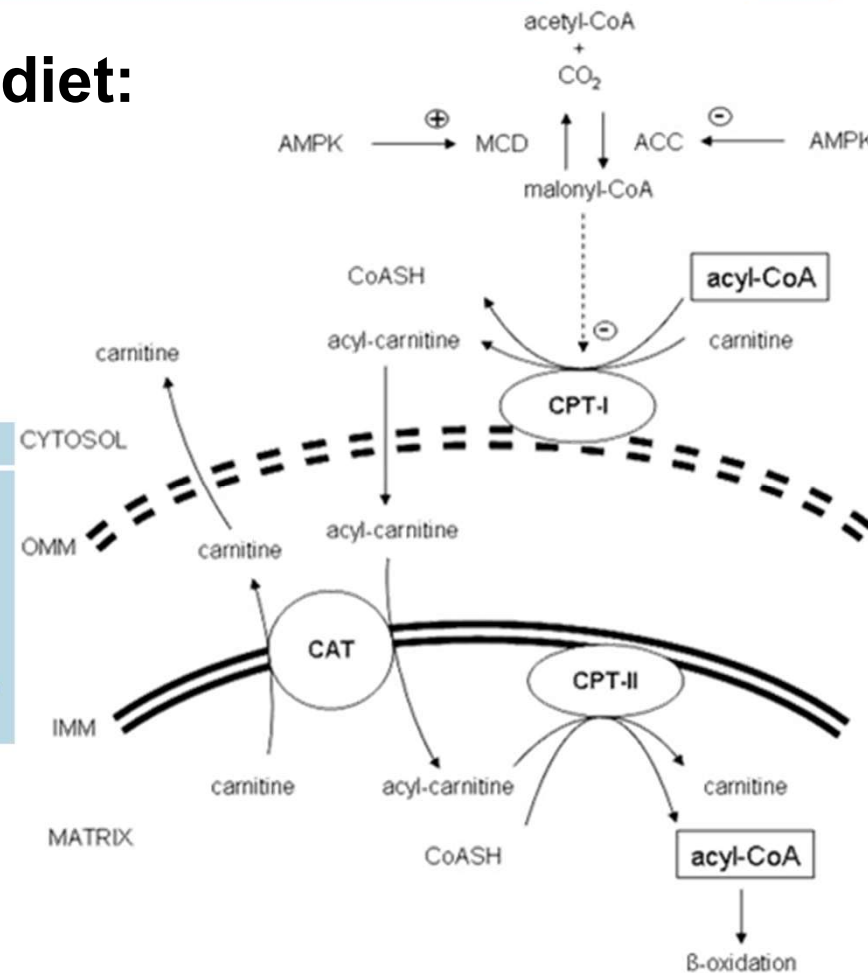
Hepatic insulin sensitivity and peripheral insulin sensitivity



L-Carnitine supplementation to diet: a new tool in treatment of non- alcoholic steatohepatitis

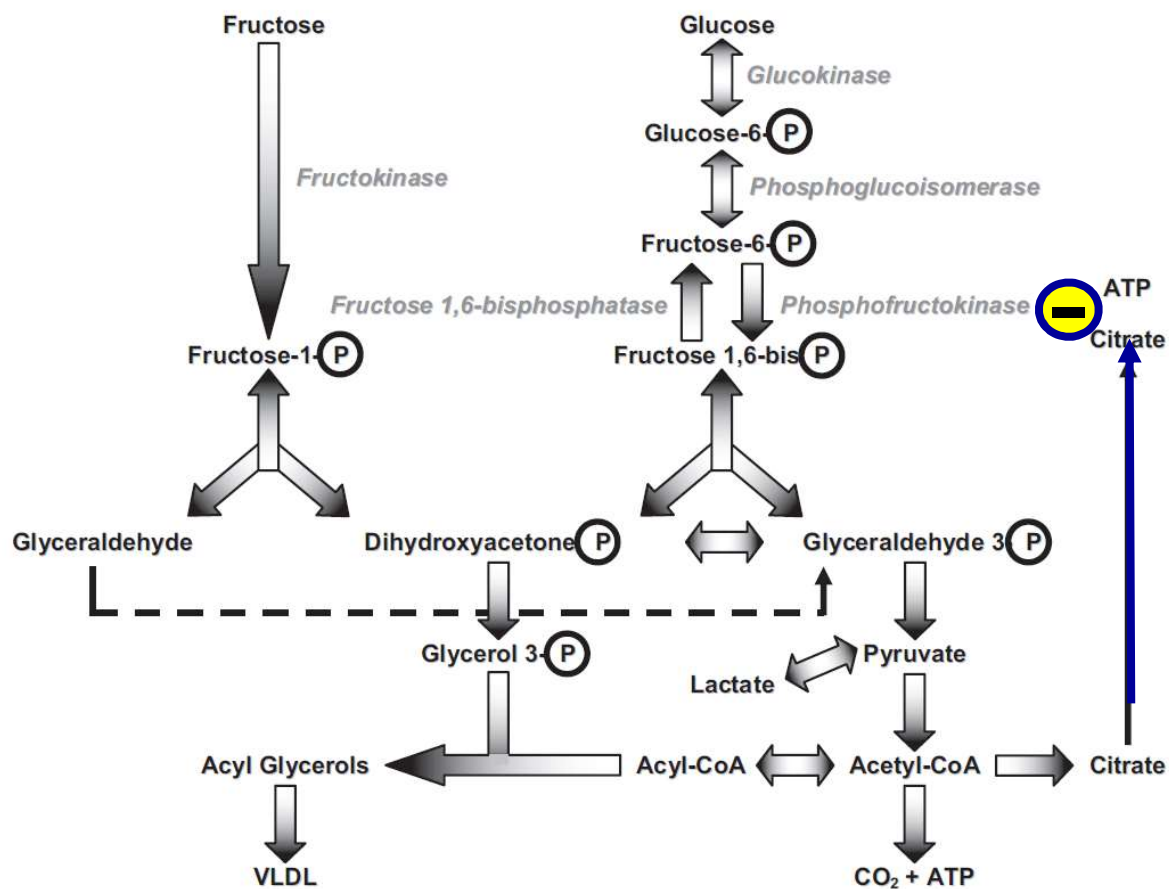
WHAT IS NEW HERE

- ✓ L-carnitine is effective in reducing total cholesterol, oxidized low-density lipoprotein cholesterol, and triglycerides, and in improving insulin resistance.
- ✓ L-carnitine treatment and lifestyle changes, including weight loss and exercise, can represent therapeutic options in NASH.

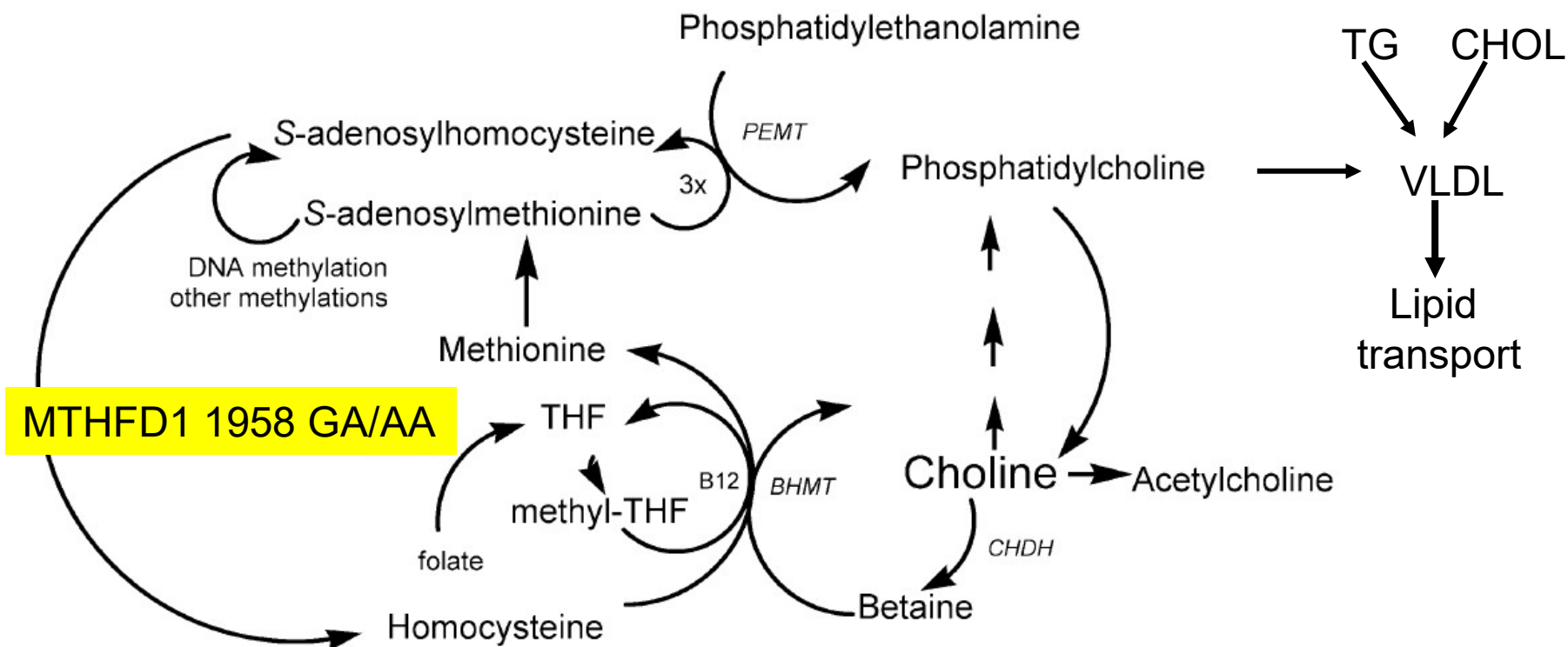


Malaguenera, Am J Gastroent 2010

Why does fructose produce a fatty liver?



Metabolic pathway of Choline



Choline: an essential nutrient for public health

Steven H Zeisel and Kerry-Ann da Costa *Nutrition Reviews*® Vol. 67(11):615–623

High intensity intermittent exercise improves cardiac structure and function and reduces liver fat in patients with type 2 diabetes: a randomised controlled trial

Table 3 The effect of HIIT on body composition, blood variables and metabolic control

Parameter	Control			HIIT			Adjusted between-group <i>p</i> value ^b
	Pre	Post	Within-group <i>p</i> value ^a	Pre	Post	Within-group <i>p</i> value ^a	
Body composition							
Weight (kg)	90±9	91±10	0.06	90±15	89±15	0.09	0.02 [†]
Fat mass (kg)	35.6±10.9	36.0±11.3	0.36	31.9±9.3	30.8±10.2	0.09	0.08
Fat free mass (kg)	54.3±5.9	54.7±5.7	0.28	57.7±9.0	58.2±8.9	0.34	0.72
Visceral adipose tissue (cm ²)	159±58	156±49	0.21	201±80	181±72	0.04*	0.08
Liver fat (%)	7.1±6.8	7.7±6.9	0.12	6.9±6.9	4.2±3.6	0.06	0.01 ^{††}

High-carbohydrate, high-fiber diets for insulin-treated men with diabetes mellitus^{1, 2}

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

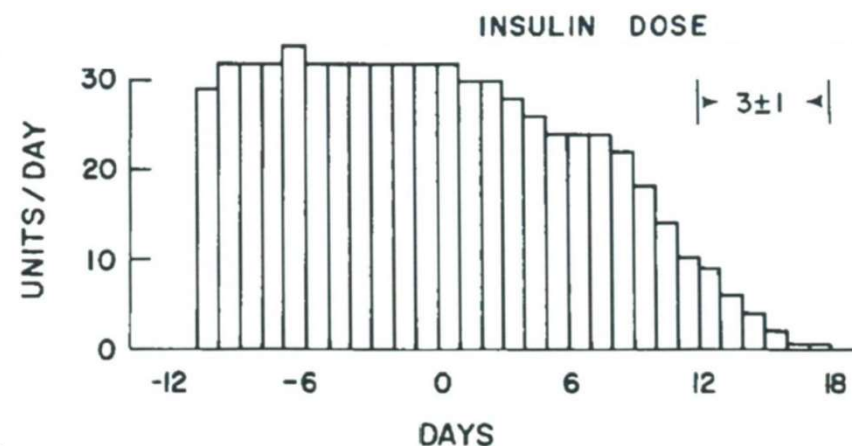


TABLE 2
Composition of diets^a

	Control diet		HCF diet	
	g/day	% kcal	g/day	% kcal
Protein	92	20	98	21
Carbohydrate, total ^b	191	43	314	70
Simple	79		91	
Complex	112		223	
Fat, total	74	37	18	9
Saturated	26		5	
Monosaturated	39		5	
Polyunsaturated fatty acids	9		8	
Cholesterol	0.48		0.065	
Plant fiber, total	26		65	
Insoluble	16		53	
Soluble	10		12	

^a Values are given for representative 1800-kcal diets. ^b Total carbohydrate refers to available carbohydrate and does not include plant fiber (24).

Reversal of type 2 diabetes: normalisation of beta cell function in association with decrease pancreas and liver triacylglycerol

Lim and Taylor, Diabetologia 2011

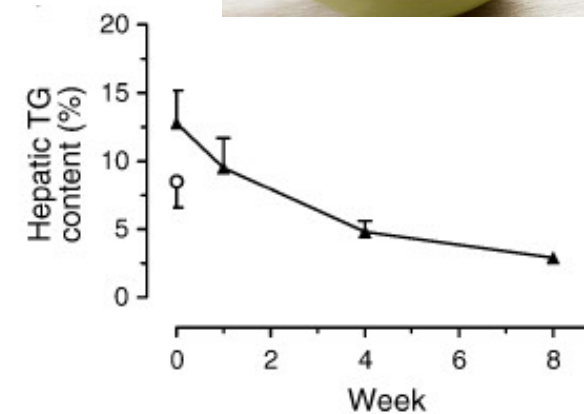
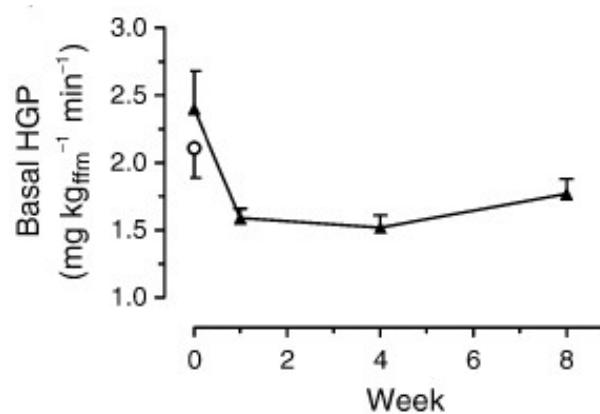
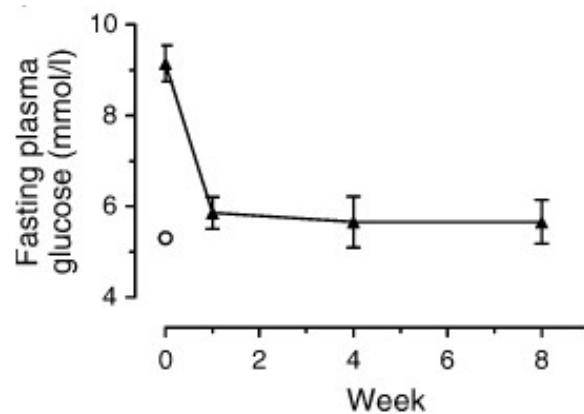
Nestlé Optifast
(46% carb, 33% protein and
20% fat, micronutrients)



3 portions of non starchy
vegetables



8 weeks 600 Kcal diet



Population response to information on reversibility of Type 2 diabetes

Information on the Counterpoint Study (reversibility of Type 2 diabetes using a very low energy diet) triggered 77 subjects to report their “self-experimentation results” to the authors:

	before “study”	after “study”
Body weight (kg)	96.7 +/- 17.5	81.9 +/- 14.8
Fasting blood glucose (mM)	8.3 (5.9-33.0)	5.5 (4.0-10.0)
T2D occurrence	100%	39%

Conclusion:

These data demonstrate that intentional weight loss achieved at home by health-motivated individuals can reverse Type 2 diabetes.

Diabetes reversal should be a goal in the management of Type 2 diabetes.

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

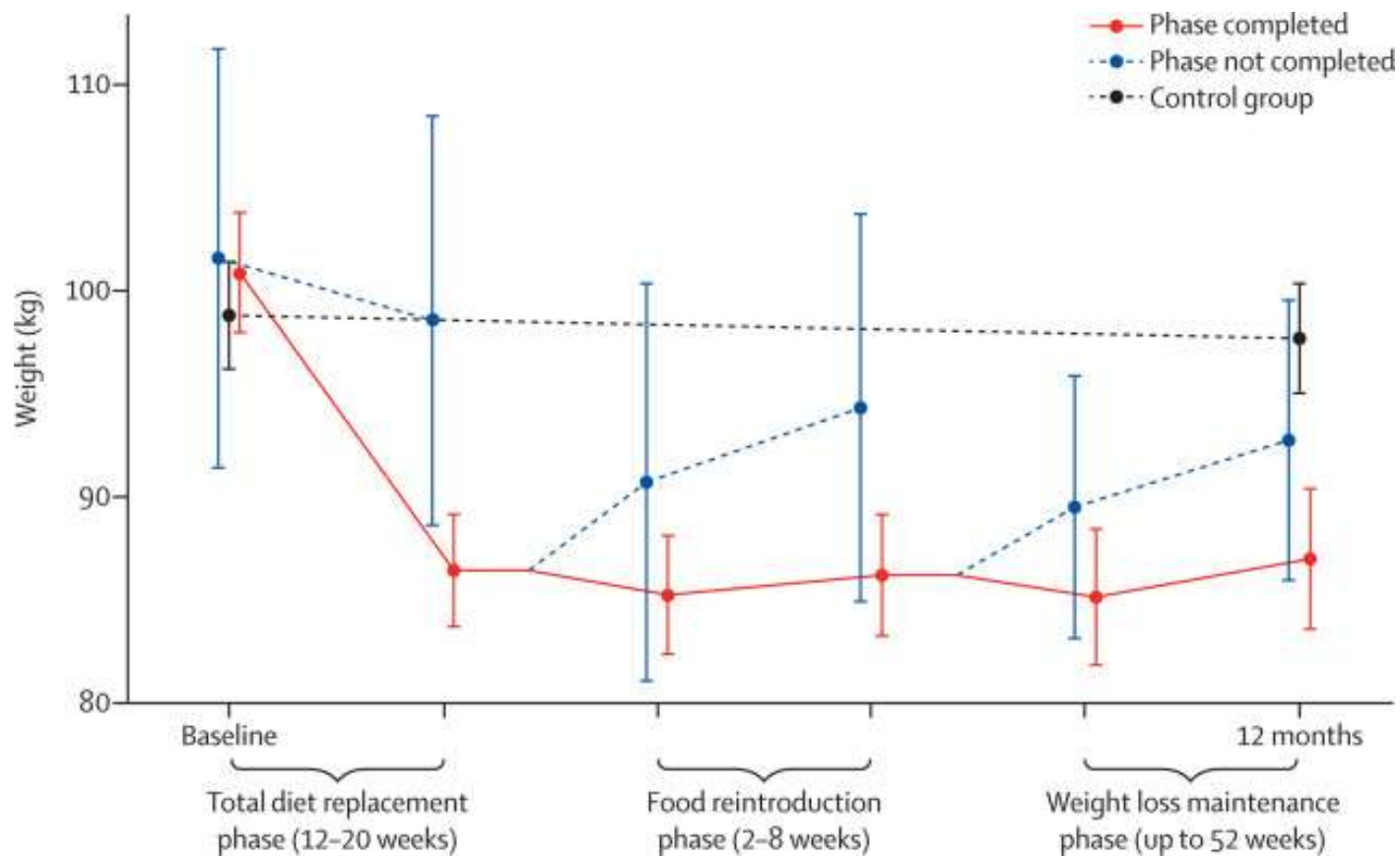
Michael EJ Lean, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Renae Stefanetti, Michael Trenell, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Naveed Sattar, Roy Taylor**

Remission of type 2 diabetes: mission not impossible

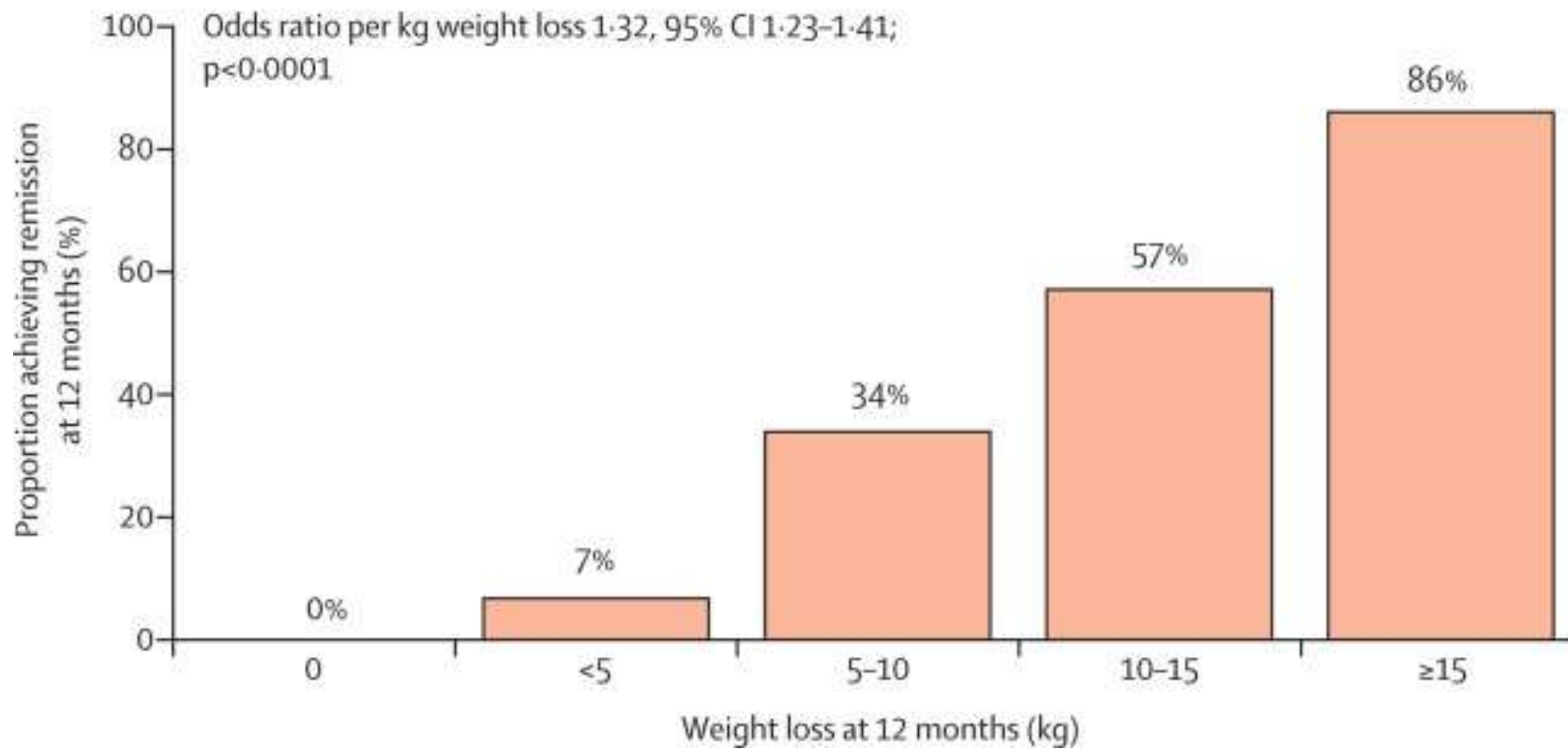
Type 2 diabetes is a heterogeneous disease with a rapidly increasing prevalence worldwide. The main risk factors are weight gain and obesity, sedentary lifestyle, and unhealthy dietary pattern—all of which

These results are impressive and strongly support the view that type 2 diabetes is tightly associated with excessive fat mass in the body. Interest to take part in the study was high, and 128 (86%) participants in

www.thelancet.com Published online December 5, 2017



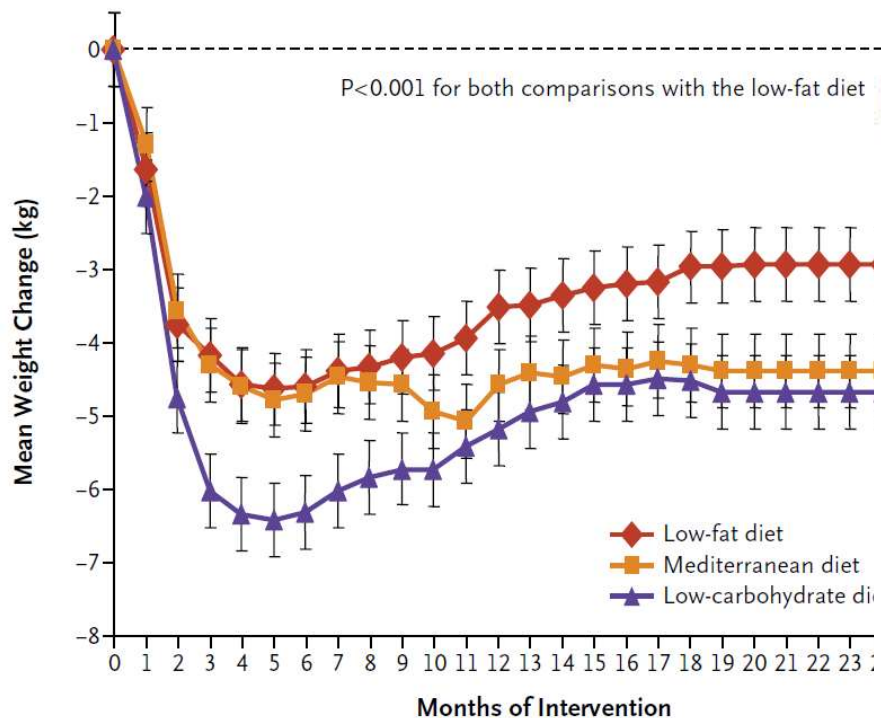
Lean et al, Lancet, 2017



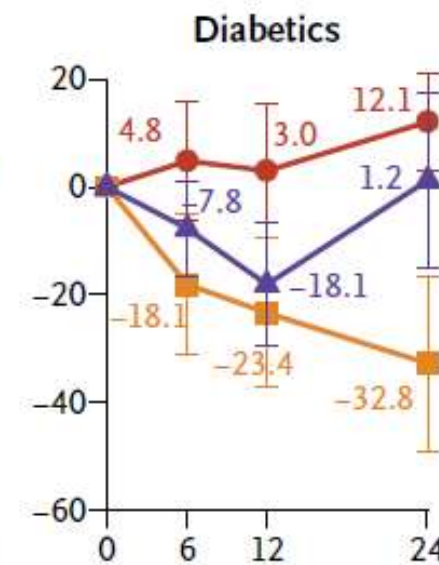
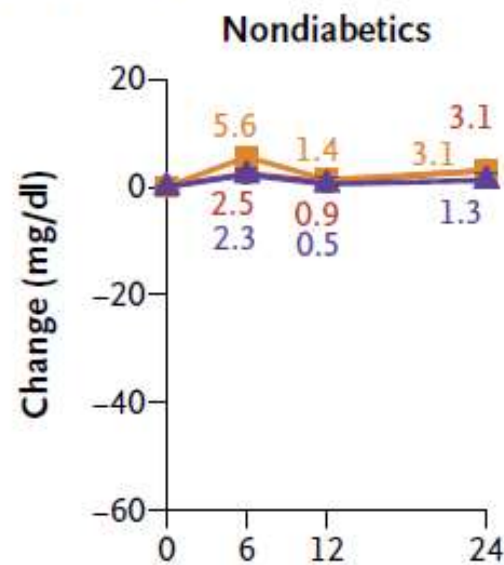
Lean et al, Lancet, 2017

Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet

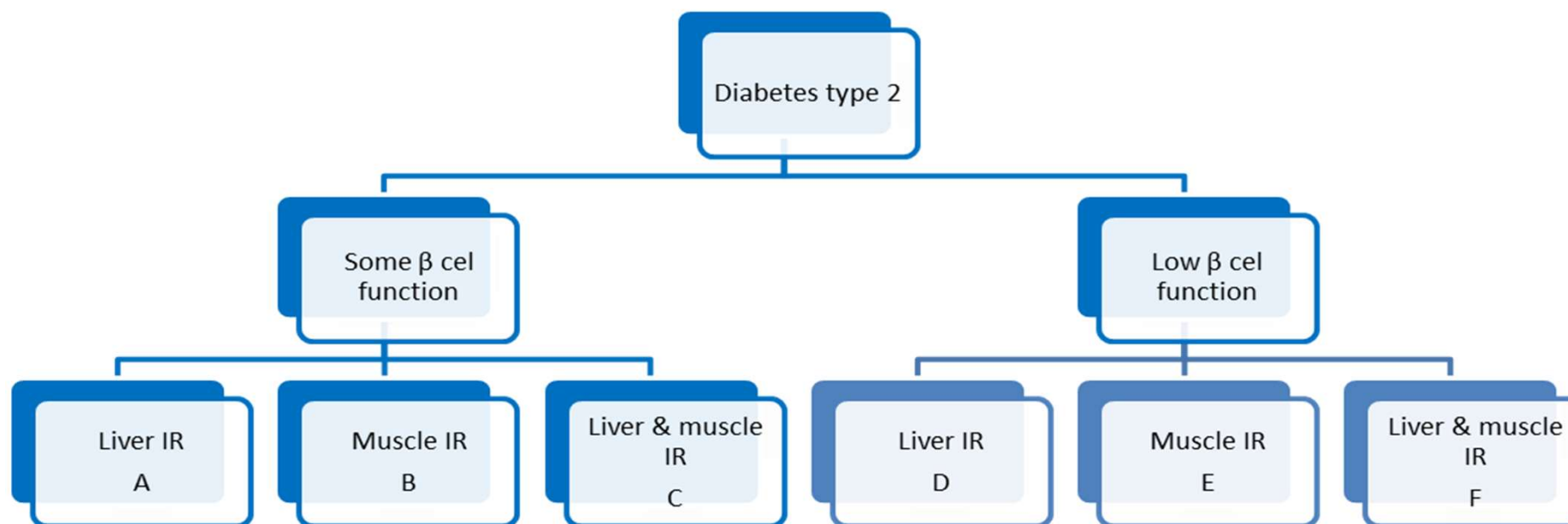
Shai, NEJM 359 (2008)



Fasting Glucose



Decision tree used to determine type 2 diabetes subgroups



A. Liver insulin resistance and moderately impaired β -cell function

Week 1: VLCD, intensifying exercise regime

Week 2-12: LCD, Exercise emphasizing aerobic training

B Muscle insulin resistance and moderately impaired β -cell function

Week 1-12: LCD. Exercise mixing aerobic training and resistance training

C. Liver and muscle insulin resistance and moderately impaired β -cell function

Week 1: VLCD, intensifying exercise regime

Week 2-12: LCD, Exercise emphasizing aerobic training

D. Insufficient β -cell function and liver insulin resistance

Week 1-12: LCD, emphasis on low glycemic index. Low intensity exercise

E. Insufficient β -cell function and muscle insulin resistance

Week 1-12: LCD, emphasis on low glycemic index. Low intensity exercise including resistance training

F. Insufficient β -cell function and liver and muscle insulin resistance

Week 1-12: LCD, emphasis on low glycemic index. Low intensity exercise including resistance training

LCD: 500 kcal lower than isocaloric needs

Intensive lifestyle coaching with advanced type 2 diabetes patients

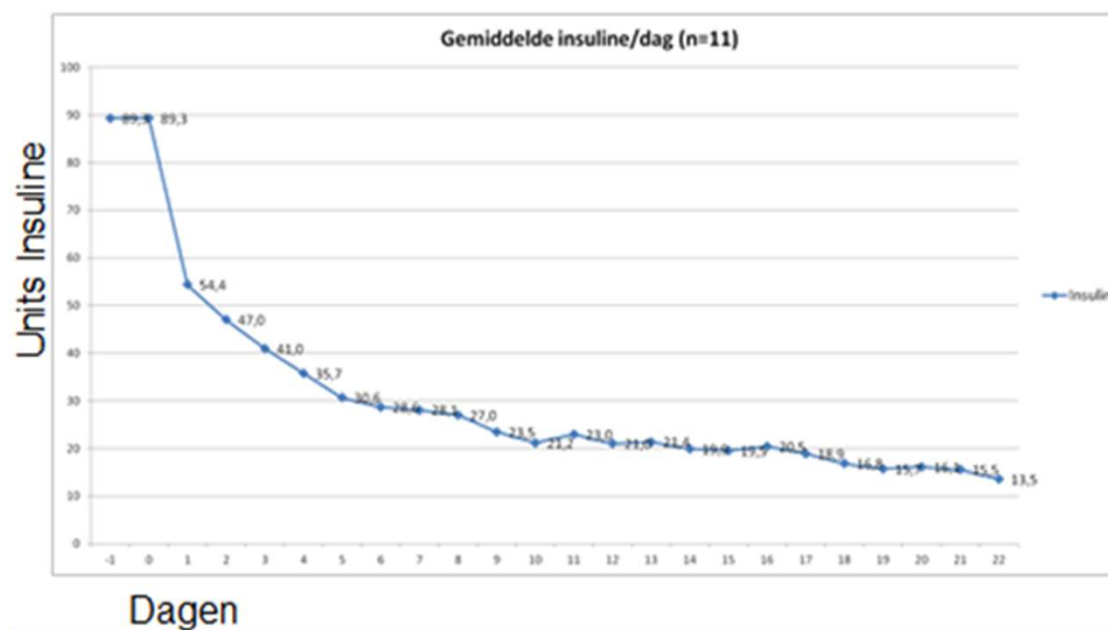
11 type 2 diabetic patients in advanced disease state entered into an intensive program of lifestyle coaching:

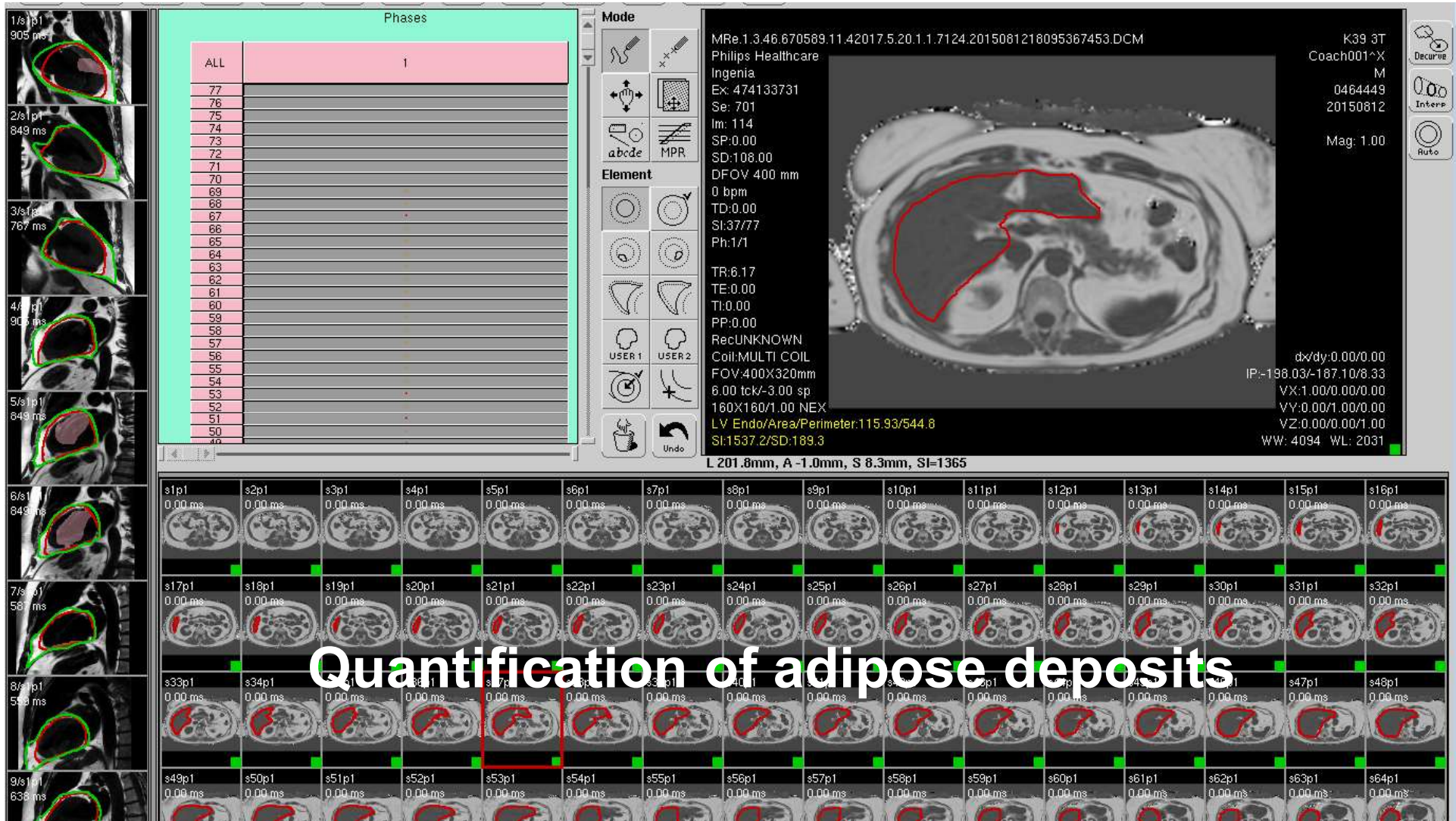
- Motivational coaching
- Physical activity
- Healthy diet

Insulin dosing was reduced with 80% in 3 weeks.

After three months, 10 out of 11 patients did not use insulin anymore.

Average Insulin trend



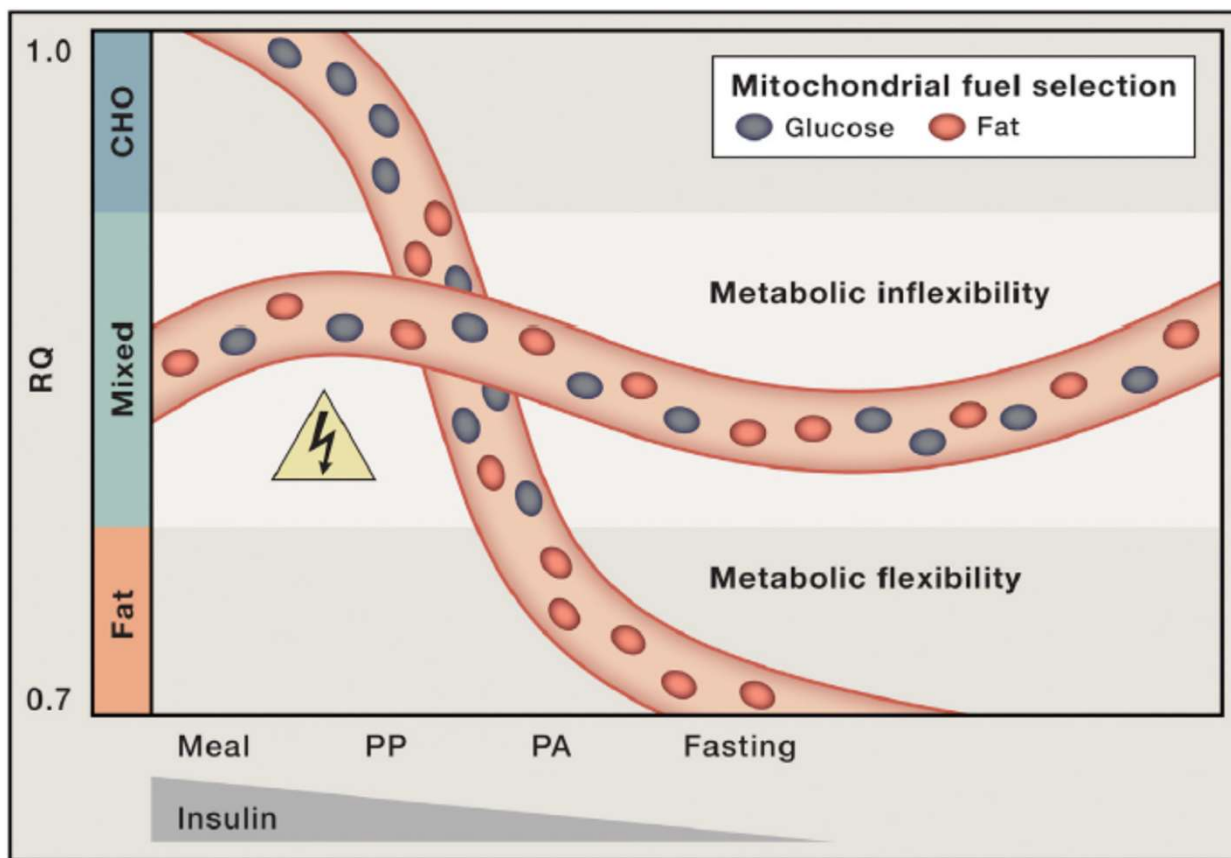


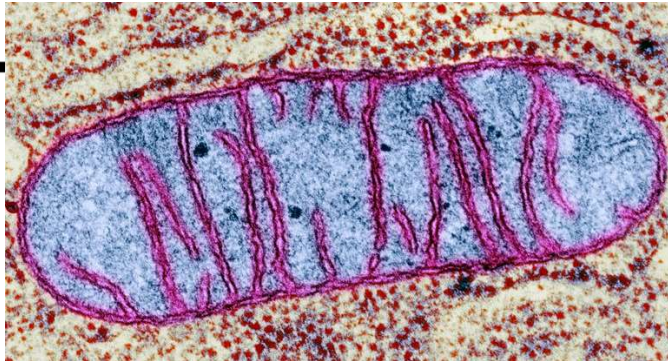
2 stages in cure:

1 – reversal : Proper glucose control (easy if I hardly consume glucose)

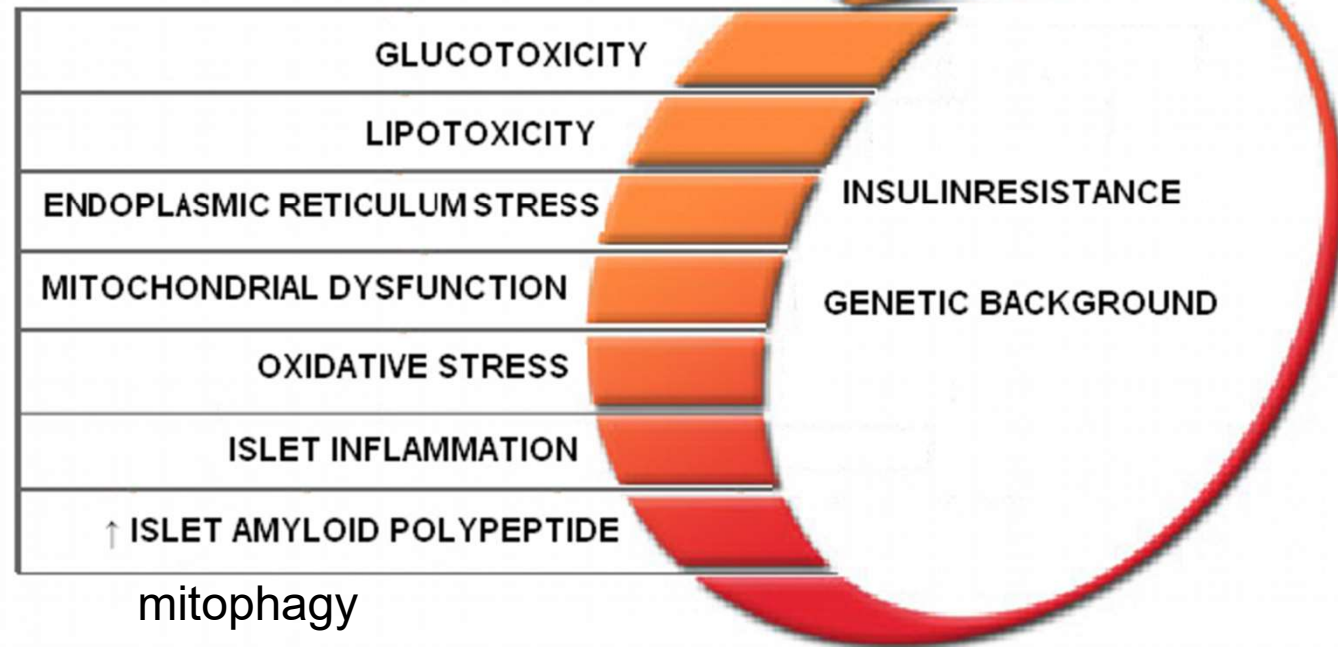
2 – cure: Organ flexibility (= insulin sensitivity restored)

But what if I do not produce insulin anymore (beta-cell failure)?





β-CELL FAILURE



Fasting Mimicking Diet and beta-cell regeneration

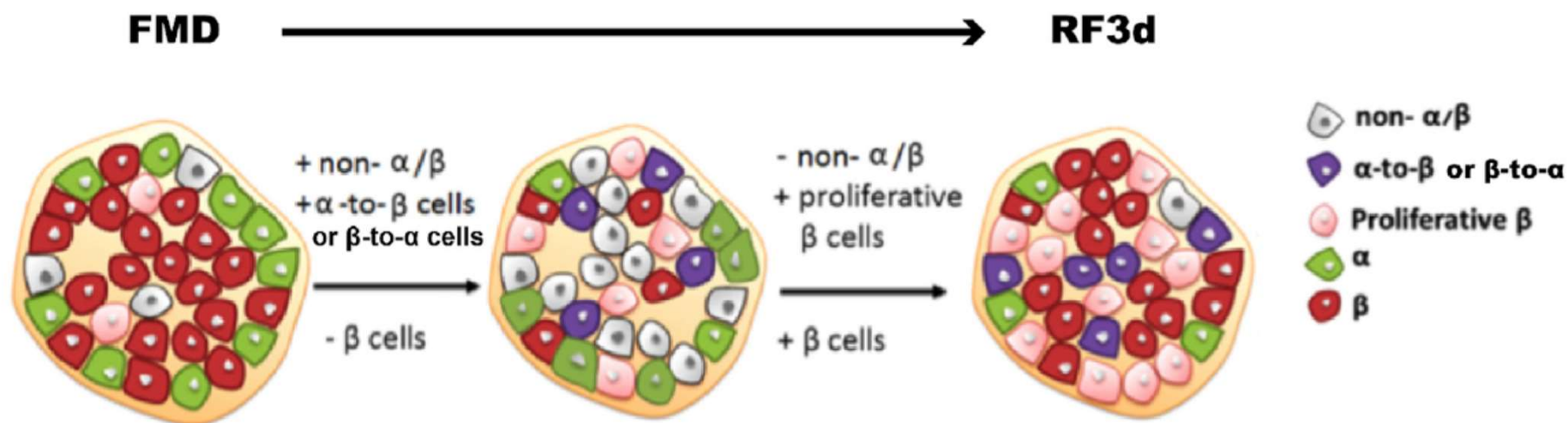


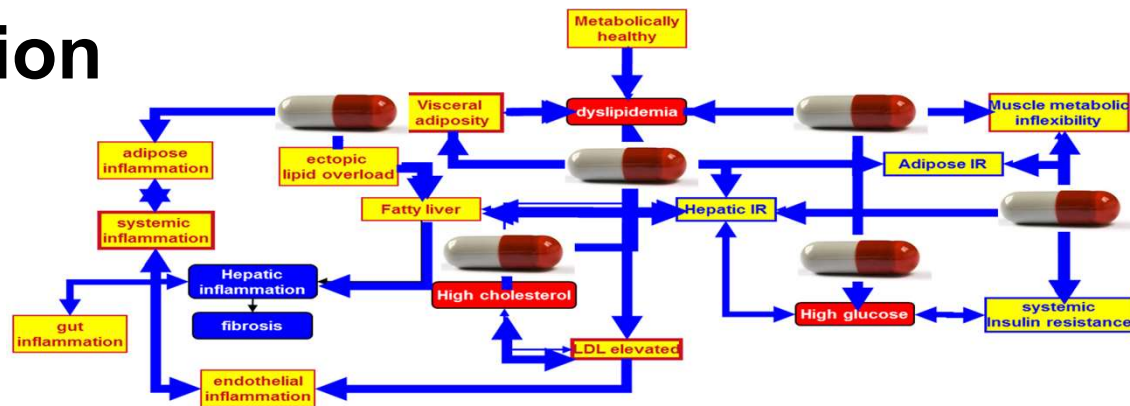
Figure 3. FMD and Post-FMD Refeeding Promote β -Cell Proliferation and Regeneration

(A) Size and number of pancreatic islets per pancreatic section.

(B) Proportion of PCNA+ proliferating β cells and of total β cells per islet.

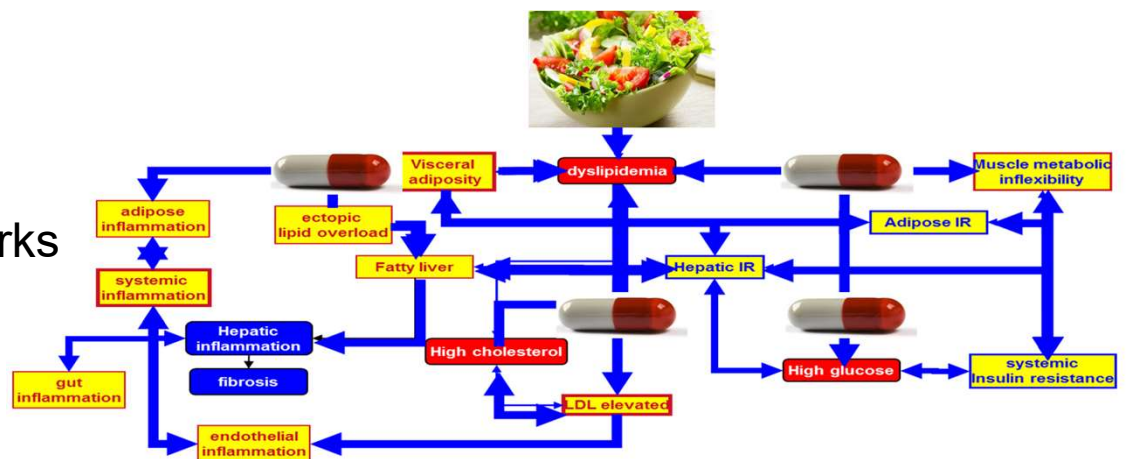
(C) Representative images of pancreatic islets with insulin, glucagon, and PCNA immuno-staining. Scale bar, 50 μ m.

The role of medication



Now: suppress glucose:

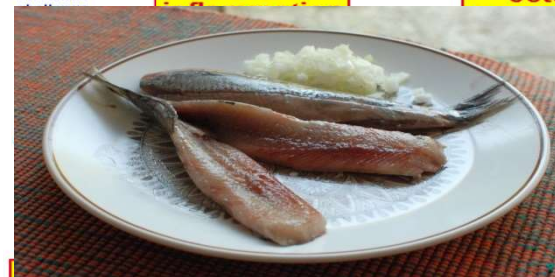
Sometimes: retreat if lifestyle works



Future: personalized medicine & nutrition



carotenoids



gut inflammation



Quercetin, Se, Zn, ...

adipose

ectopic overload

Fatty liver

polyphenols

endothelial inflammation

High cholesterol

LDL elevated

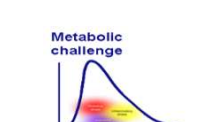
Visceral adiposity

dyslipidemia

Stannols, fibre

Carnitine, Choline, ...

Hepatic IR



Metabolic challenge

time

Adipose IR

Low glycemic index

Anthocyanins

High glucose

systemic insulin resistance

epicatechins procyanidins

Metabolic challenge

time



Metabolic health



Adipose IR

Low glycemic index

High glucose

systemic insulin resistance

epicatechins procyanidins

Metabolic challenge

time

Metabolic challenge

time

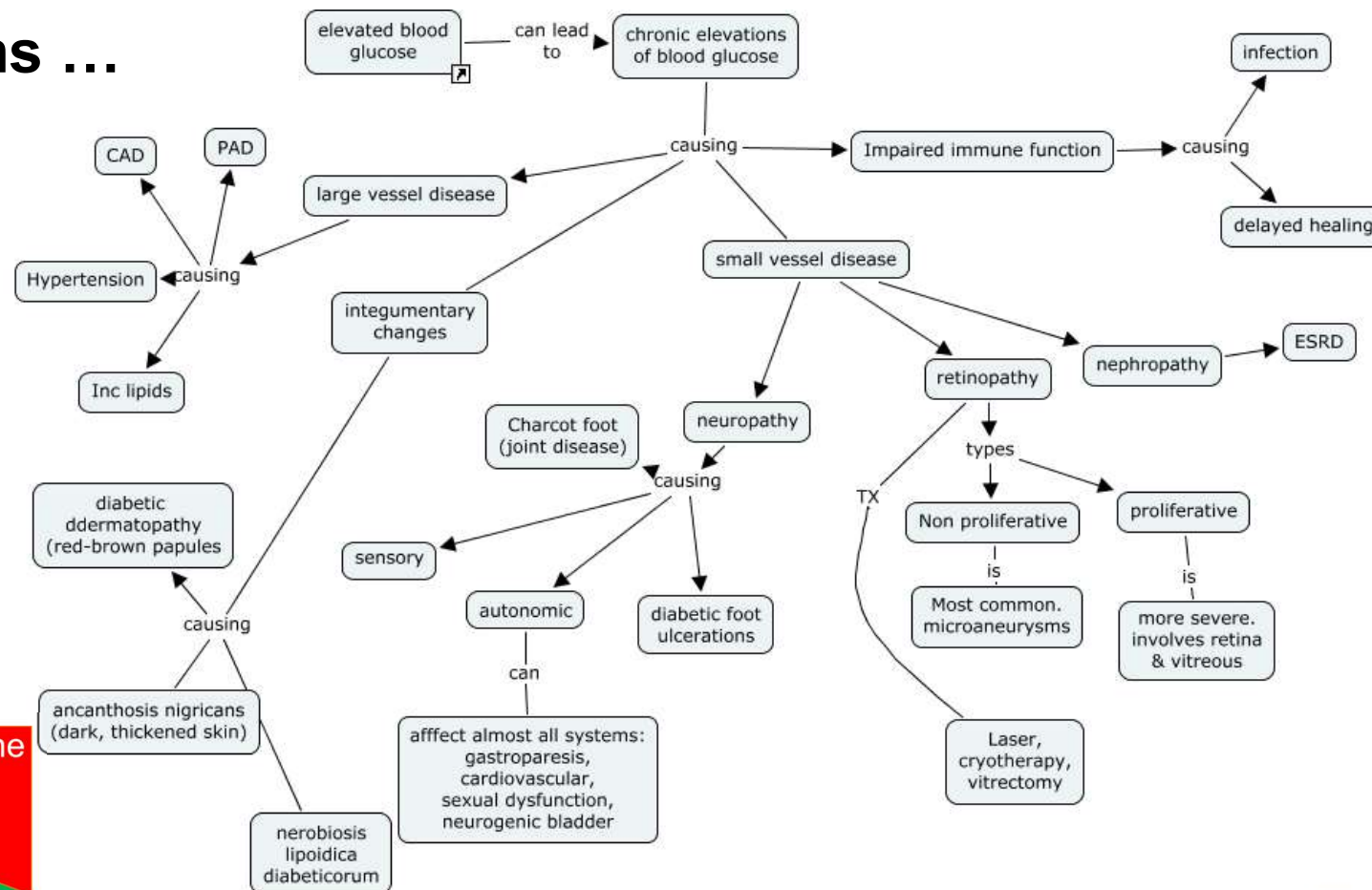
Metabolic challenge

time

Metabolic challenge

time

Complications ...



Social system

Physiological system

Healthcare system

T2 Diabetes is a 'systems disease'

- › Obesogenic environment
- › Limited engagement with health status
- › Social interactions are important for outcome

- › Multiple interacting physiological processes
- › T2 Diabetes initiates when one or more biological processes lose flexibility

- › Conflicting stakeholder interests
- › No focus on prevention
- › Short term financial vision

T2 Diabetes needs a 'systems solution'

- › Optimal coaching, participation and communication
- › Integration of medical, social, economical and mental solutions

- › Diagnosis of all relevant processes and predispositions
- › Goal: regain flexibility in all relevant processes, exploiting diet, lifestyle, medication and genetics where relevant

- › Patient empowerment
- › Implement in regional setting
- › Acceptance by accreditation

OMGEVING

LICHAAM

GEDRAG

DENKEN & GEVOEL



Fundamental research

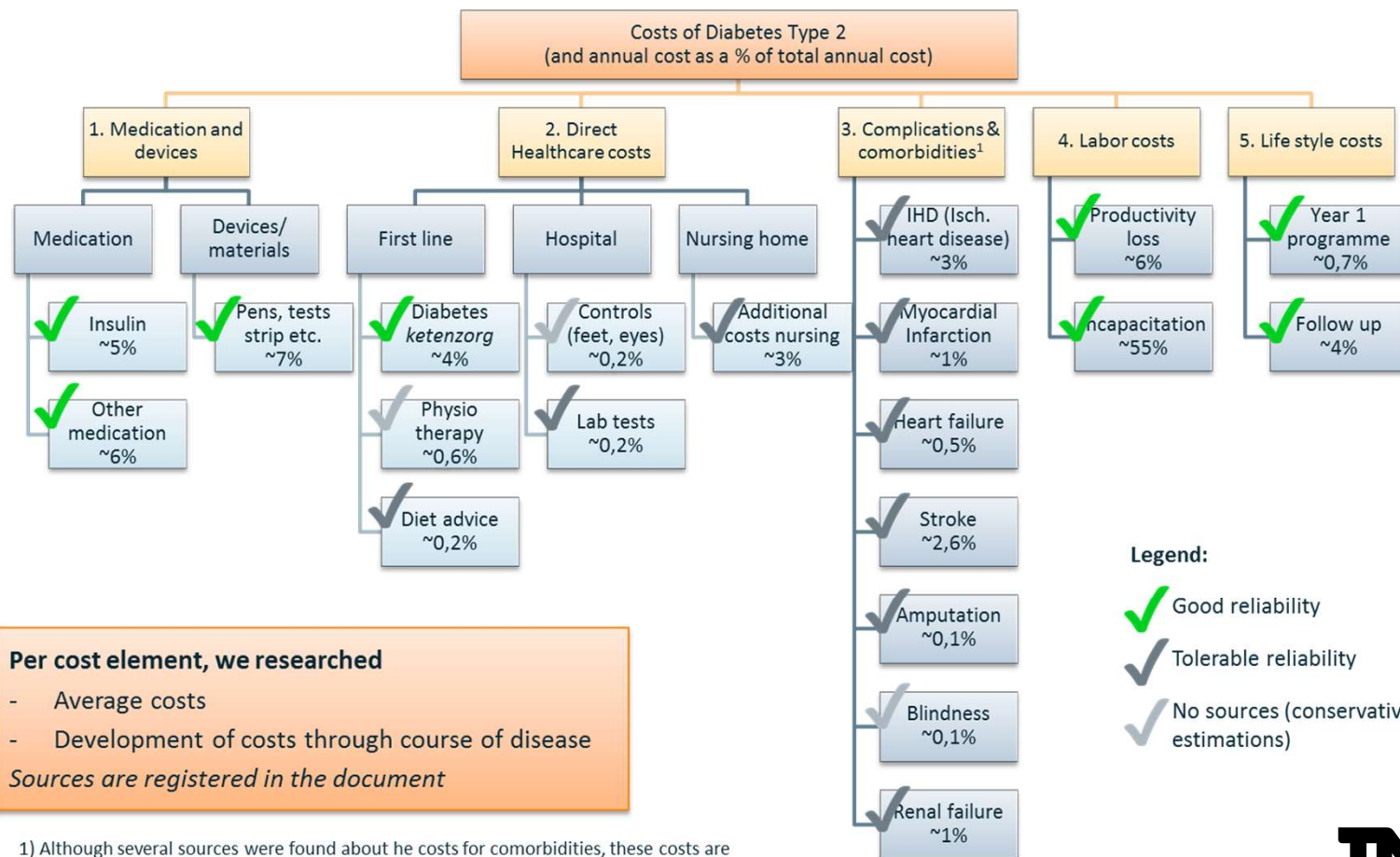
- mechanisms of action
- systems biology
- behavioral change theory
- mathematical models
- artificial intelligence
- Health Data Cooperative

Applied research

- ICT infrastructure
- personal health portal
- intervention strategies
- behavioural applications
- tailored solutions
- connect healthcare and research (n=1)

Implementation (economy & society)

- local new economy
- New services and products
- community involvement
- healthcare party buy-in
- multi-stakeholder consortium
- accreditation
- reimbursement



Per cost element, we researched

- Average costs
- Development of costs through course of disease

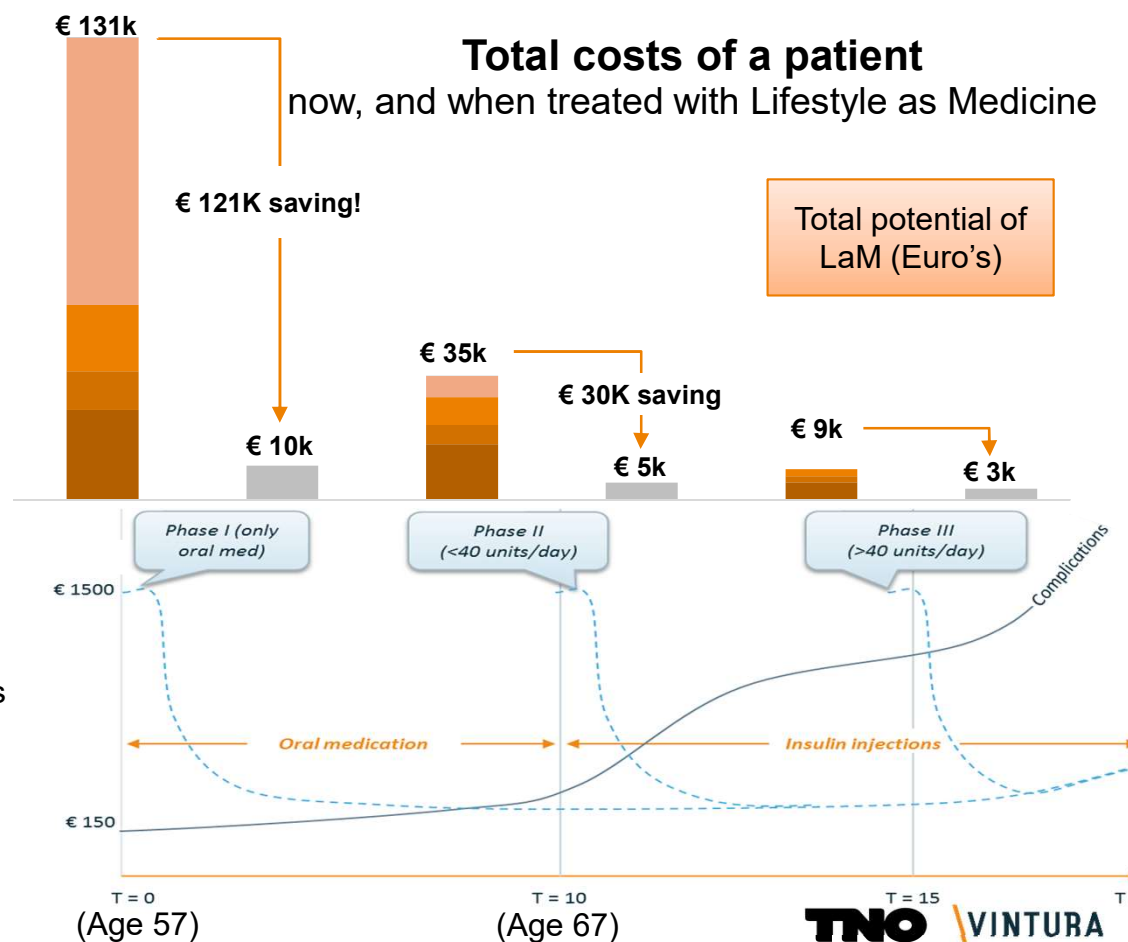
Sources are registered in the document

1) Although several sources were found about the costs for comorbidities, these costs are known to be very difficult to estimate (source: RIVM)

The financial aspects ...

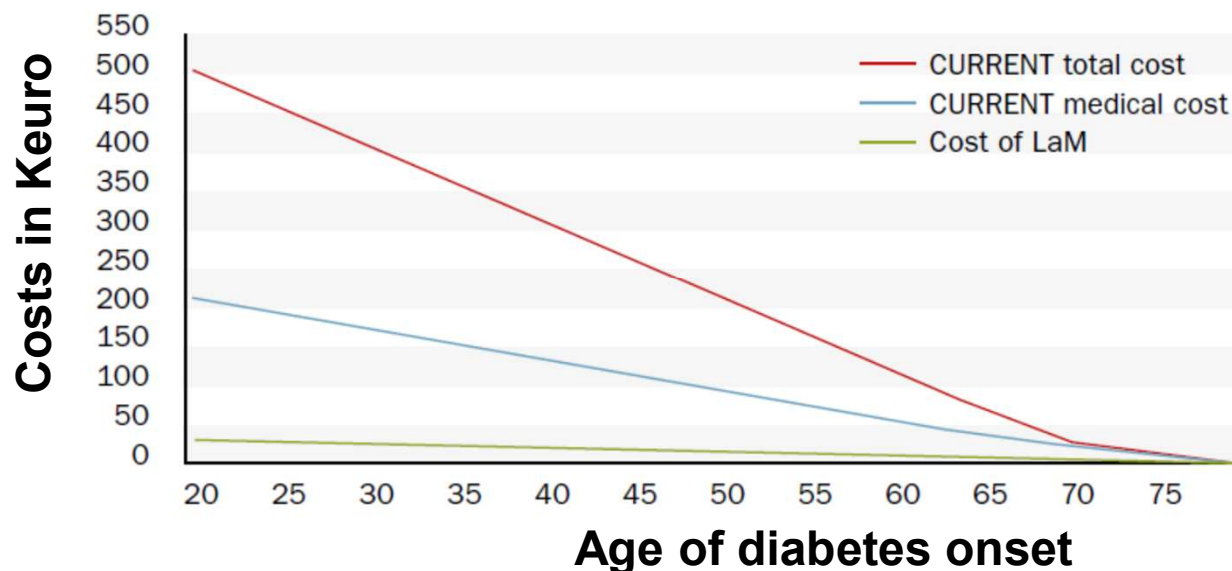
cost are 13x lower than current practice for a patient who is treated with success at the moment of diagnosis.

- 4. Employability costs
- 3. Complications & comorbidities
- 2. Direct medical costs
- 1. Medication



Lifestyle as Medicine consistently cost effective, regardless of age at start

The costs incurred by newly diagnosed T2D patients throughout the remainder of their lives depend on the age at which the disease manifests itself.



CALCULATING COST SAVINGS

The cost savings per T2D patient are calculated by subtracting the cost of Lifestyle as a Medicine from the current costs.

* Note: The total costs include both medical costs and labour-related expenses.

EXAMPLE

The average age of onset of T2D is 55. The total cost saving that can be achieved throughout the remainder of a 55-year-old patient's life is $€136,329 - €10,385 = €125,944$. This can be derived from the graph by subtracting the data point on the green line (cost of Lifestyle as a Medicine) from the red line (current total cost) at an onset age of 55.

THE 'LIFESTYLE AS MEDICINE' TIMELINE



Aim: cure by lifestyle

Intense personalized lifestyle program

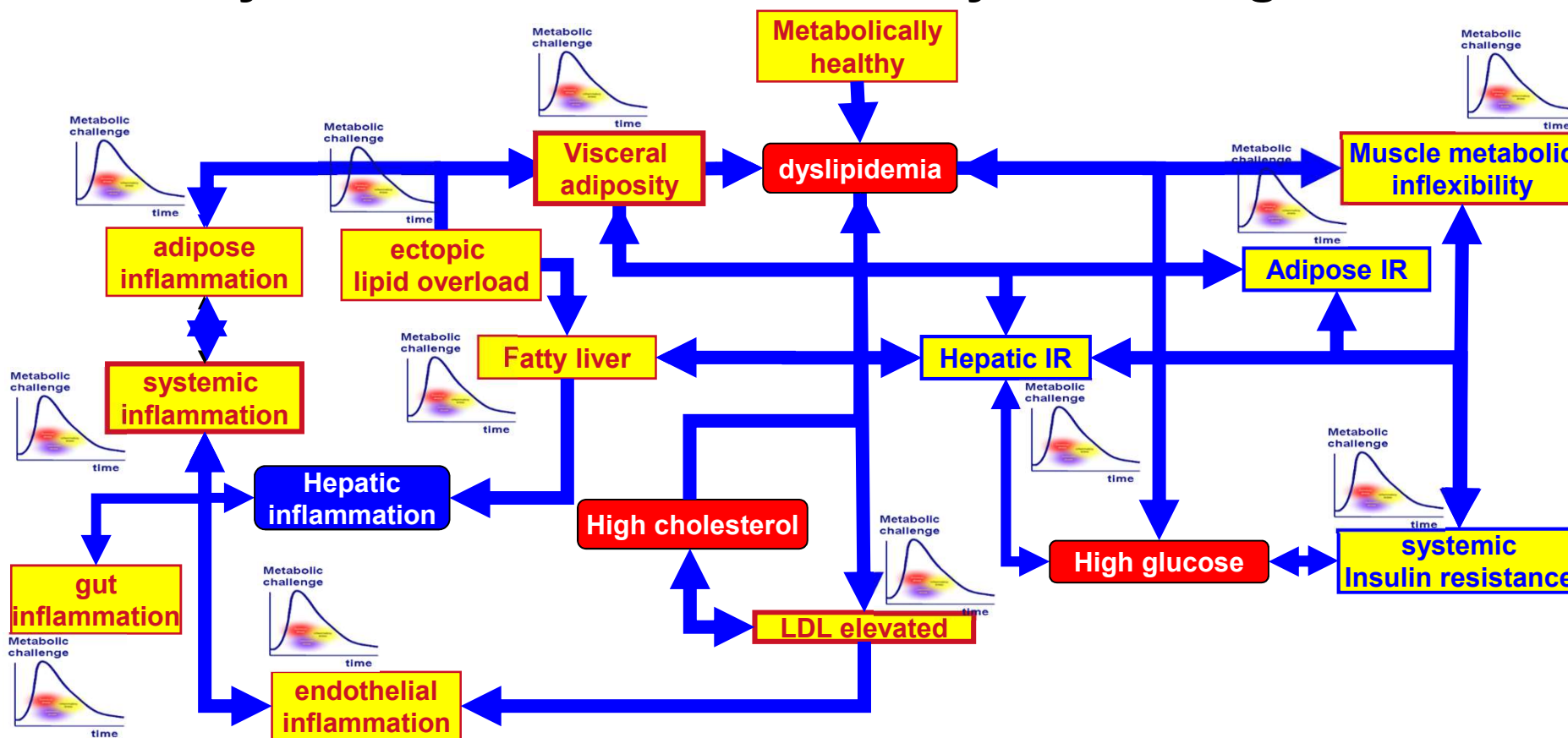
- Start motivational coaching
- Health literacy
- Optimal diet
- Physical activity
- Introduction e-health

Aim: maintain changed lifestyle

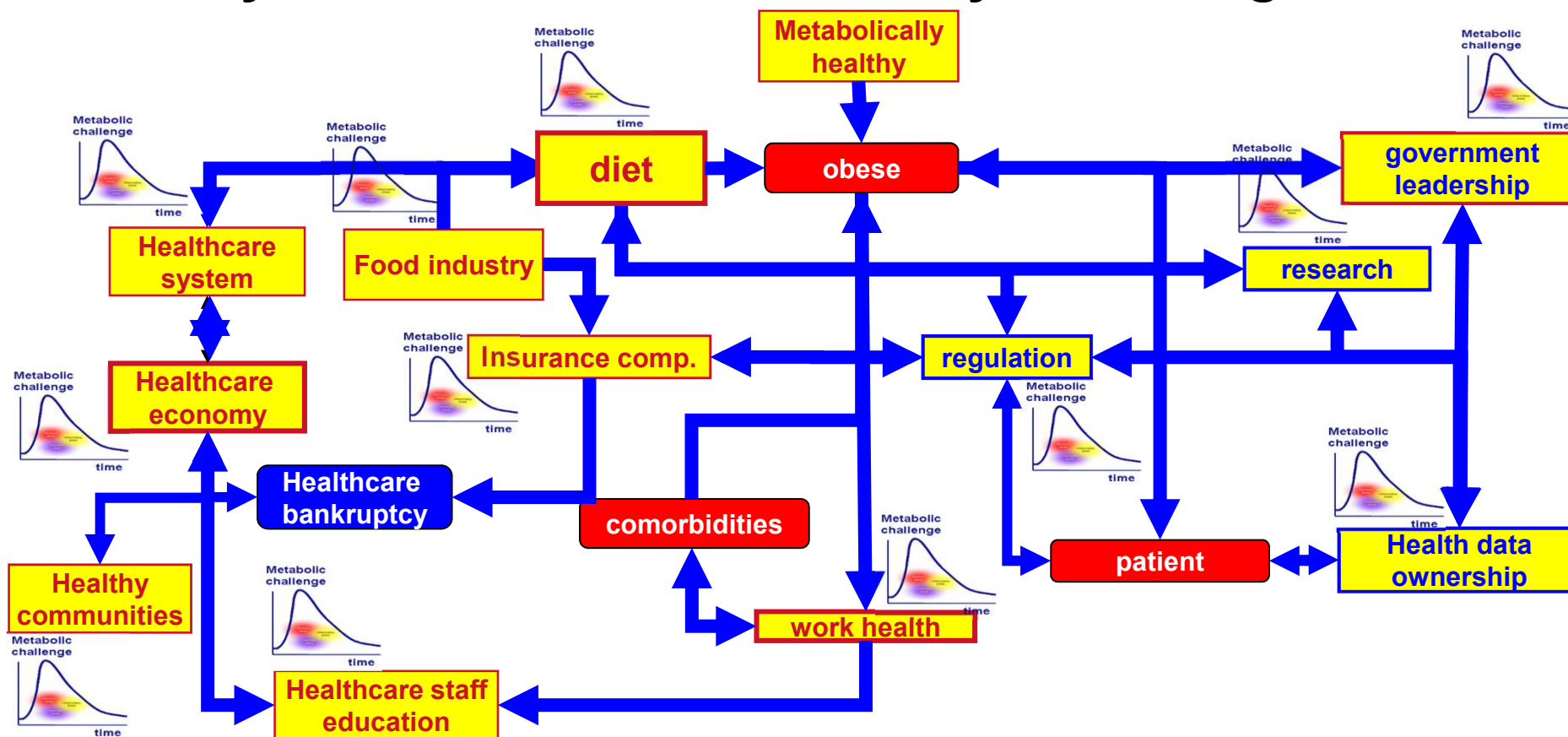
All aspects of new lifestyle have settled into new habits

- All tools are personalized and connected to a sustainable support system
- Connected to one personal health data system (Health Data Cooperative)
- Social, economic and regulatory environment cooperates in habituation

systems interventions need systems diagnosis



systems interventions need systems diagnosis



TNO EN LUMC BUNDELEN KRACHTEN ROND “LEEFSTIJL ALS MEDICIJN”

23 JAN 2017

TNO en het LUMC hebben vandaag in een MoU afgesproken meer samen te werken op het gebied van ‘Leefstijl als medicijn’. Zij doen dit omdat er steeds meer bewijs is dat een aantal ziektes, zoals diabetes type2 of obesitas (en daarmee samenhangende negatieve gezondheidseffecten), met gerichte leefstijlaanpassingen kunnen worden voorkomen en zelfs genezen.

**LEEFSTIJLVERANDERING LEVERT
GROTE VOORDELEN**



Leids Universitair
Medisch Centrum






28

February

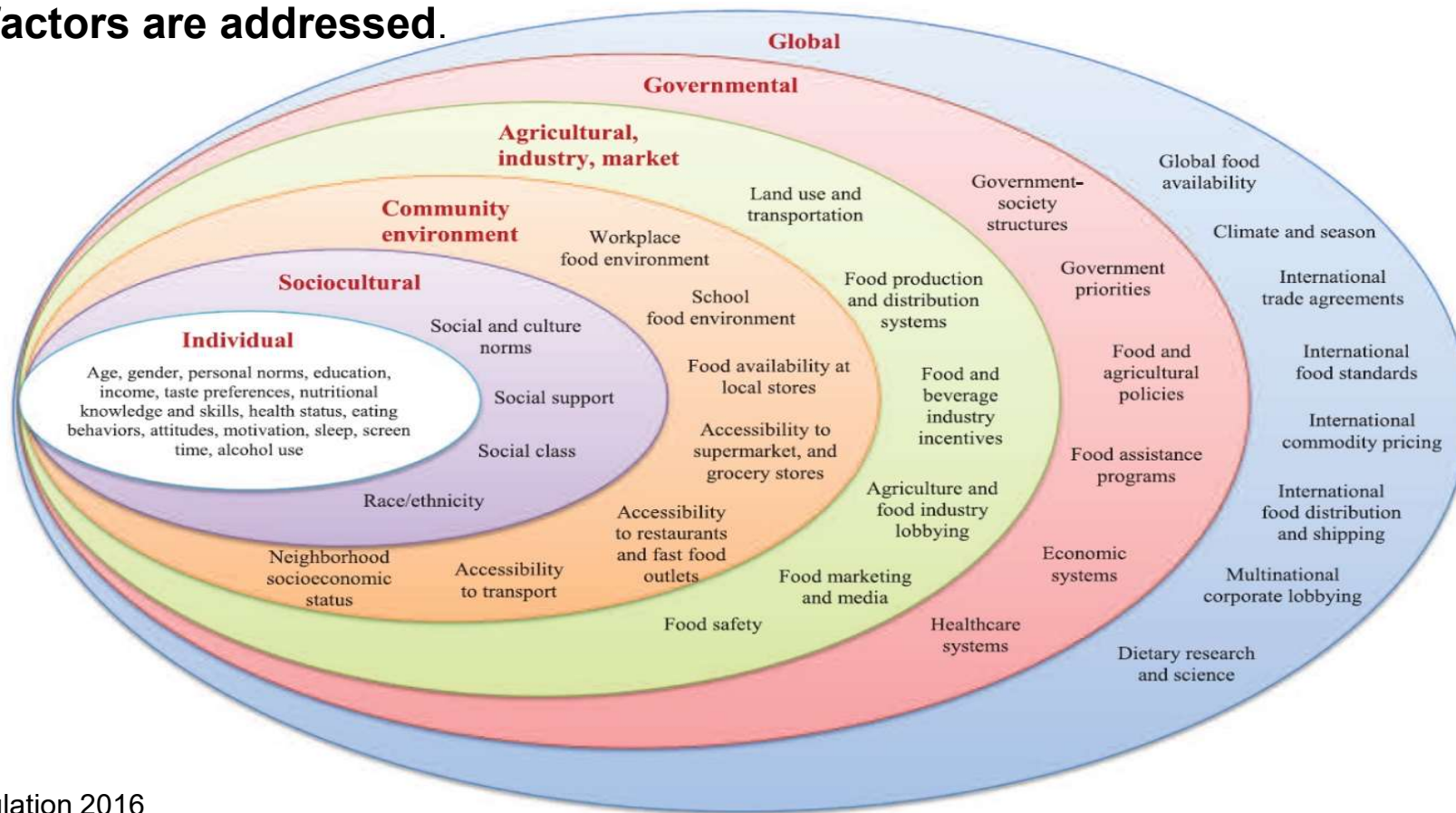
2017

CURING TYPE 2 DIABETES WITH 'LIFESTYLE AS A MEDICINE'

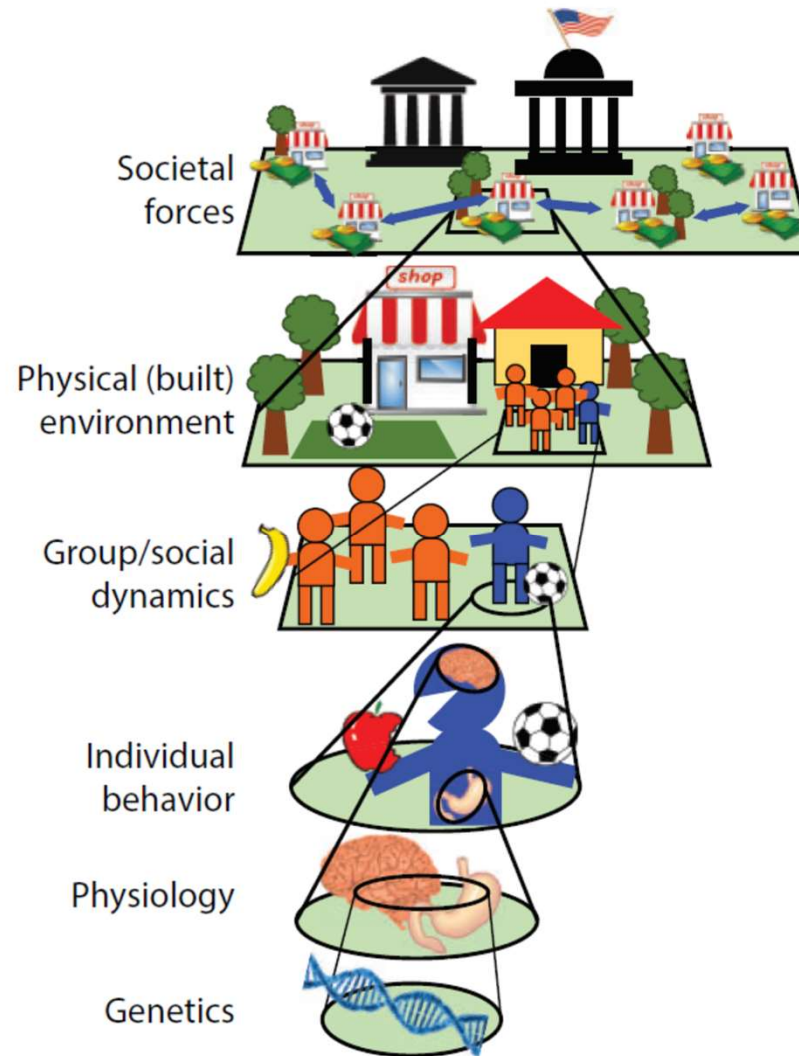
 4 min reading time

About a million people in the Netherlands have adult-onset (type 2) diabetes (T2D). Most of them would not need any medication if they changed their lifestyle. This would lead to savings of something like 2.7 billion euros over a five-year period. TNO and Leiden University Medical Centre (LUMC) signed an agreement at the end of January concerning cooperation aimed at developing the concept of 'Lifestyle as a Medicine'.

Lifestyle related health can only be optimized in a systems approach where all relevant factors are addressed.



systems
change
in health
care



systems
change
in health
economy

Strategy : First implement a systems change in a regional setting



The Netherlands



and the rest ...



If Lifestyle as Medicine works, why do we not use it?



“I want you to find a bold and innovative way to do everything exactly the same way it’s been done for 25 years.”

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