Roles of our gut microbes in metabolic disorders and fatty liver

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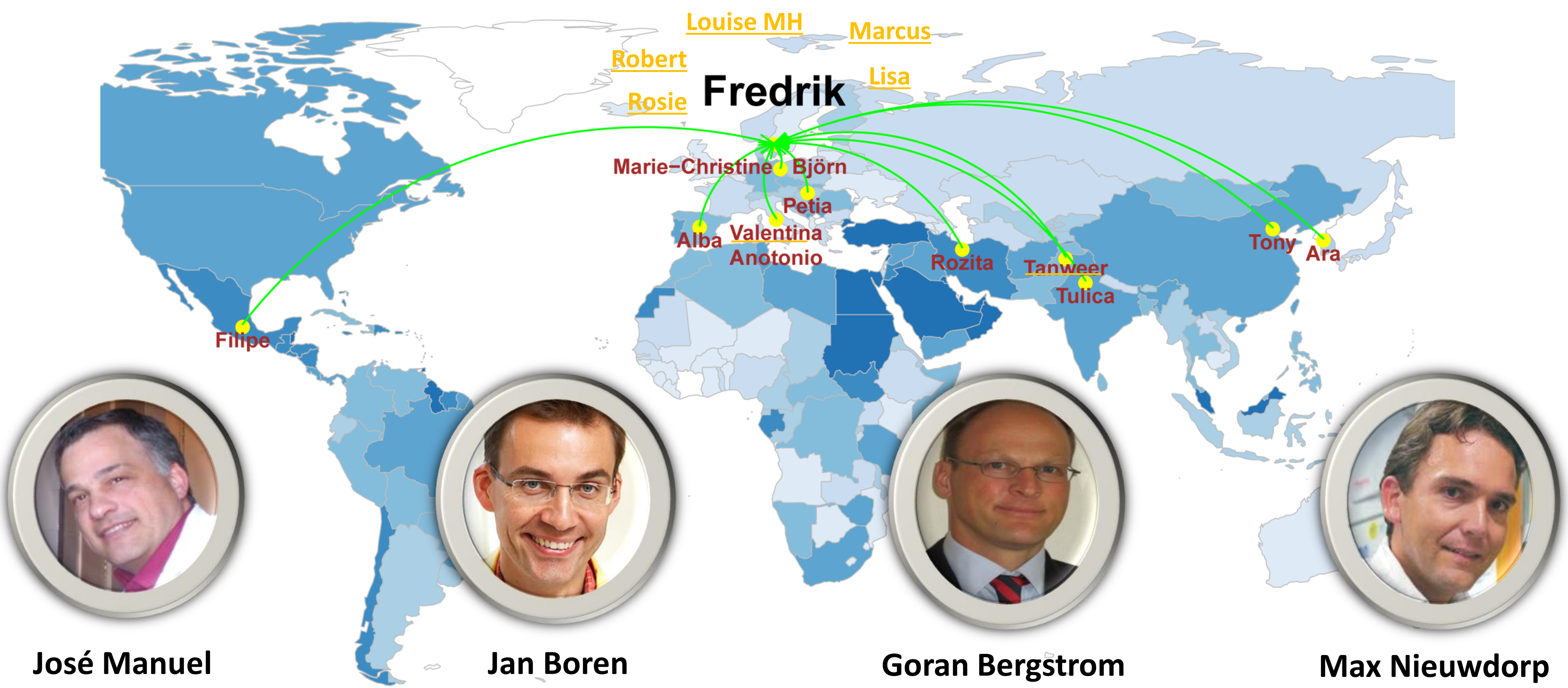
Acknowledgement

One World, One Aim



José Manuel

The metformin study
(2017, nature medicine)

Jan Boren

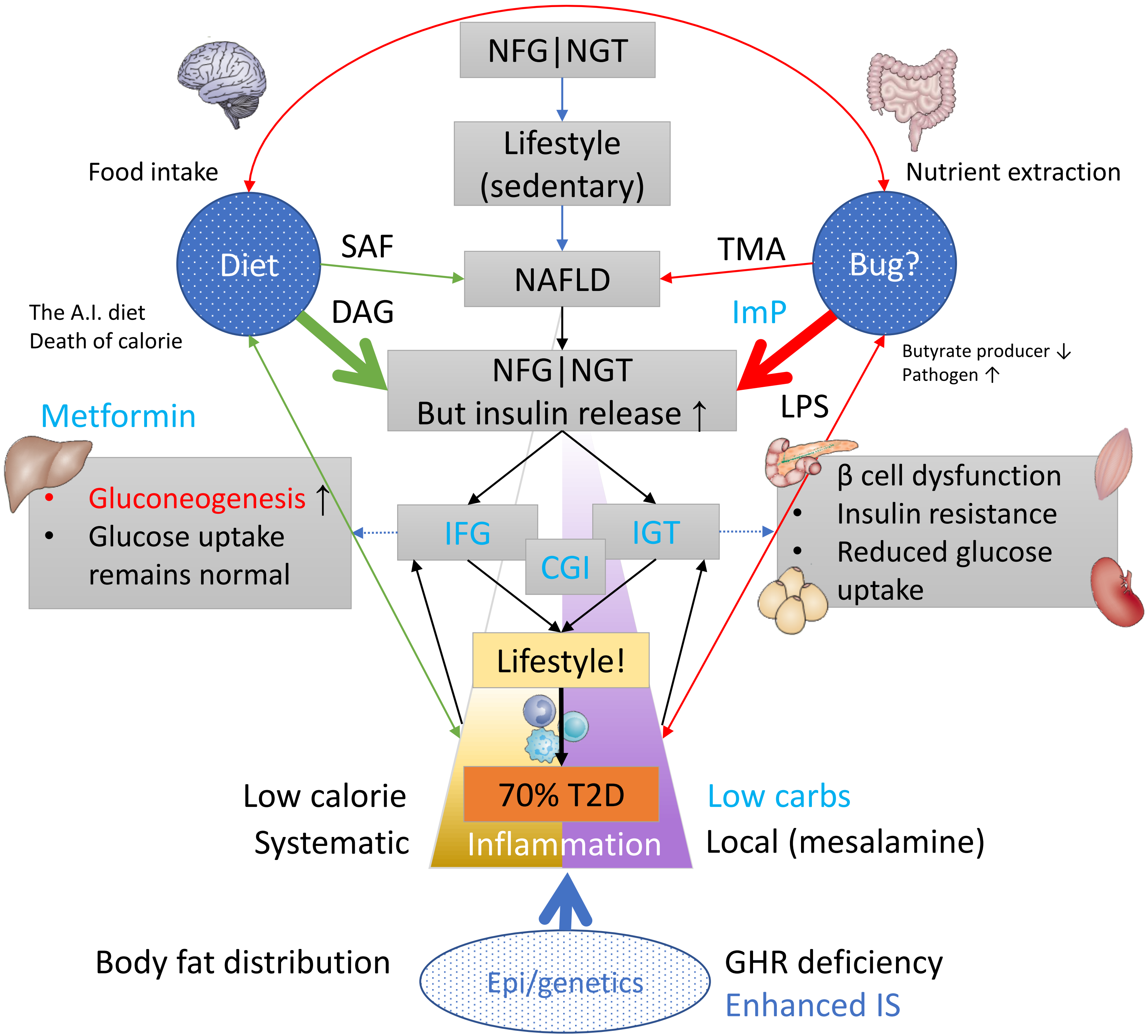
The NAFLD study
(2018, cell metabolism)

Goran Bergstrom

The IGT study
(2019, submitted)

Max Nieuwdorp

The ImP study
(2019, Cell)


NFG|NGT
Lifestyle (sedentary)
Food intake
Nutrient extraction
Diet
SAF
NAFLD
TMA
Bug?
DAG
ImP
The A.I. diet
Death of calorie
NFG|NGT
But insulin release ↑
Butyrate producer ↓
Pathogen ↑
LPS
Metformin
Gluconeogenesis ↑
Glucose uptake remains normal
IFG
CGI
IGT
β cell dysfunction
Insulin resistance
Reduced glucose uptake
Lifestyle!
70% T2D
Inflammation
Low calorie
Systematic
Low carbs
Local (mesalamine)
Body fat distribution
Epi/genetics
GHR deficiency
Enhanced IS

BACKGROUND (1)

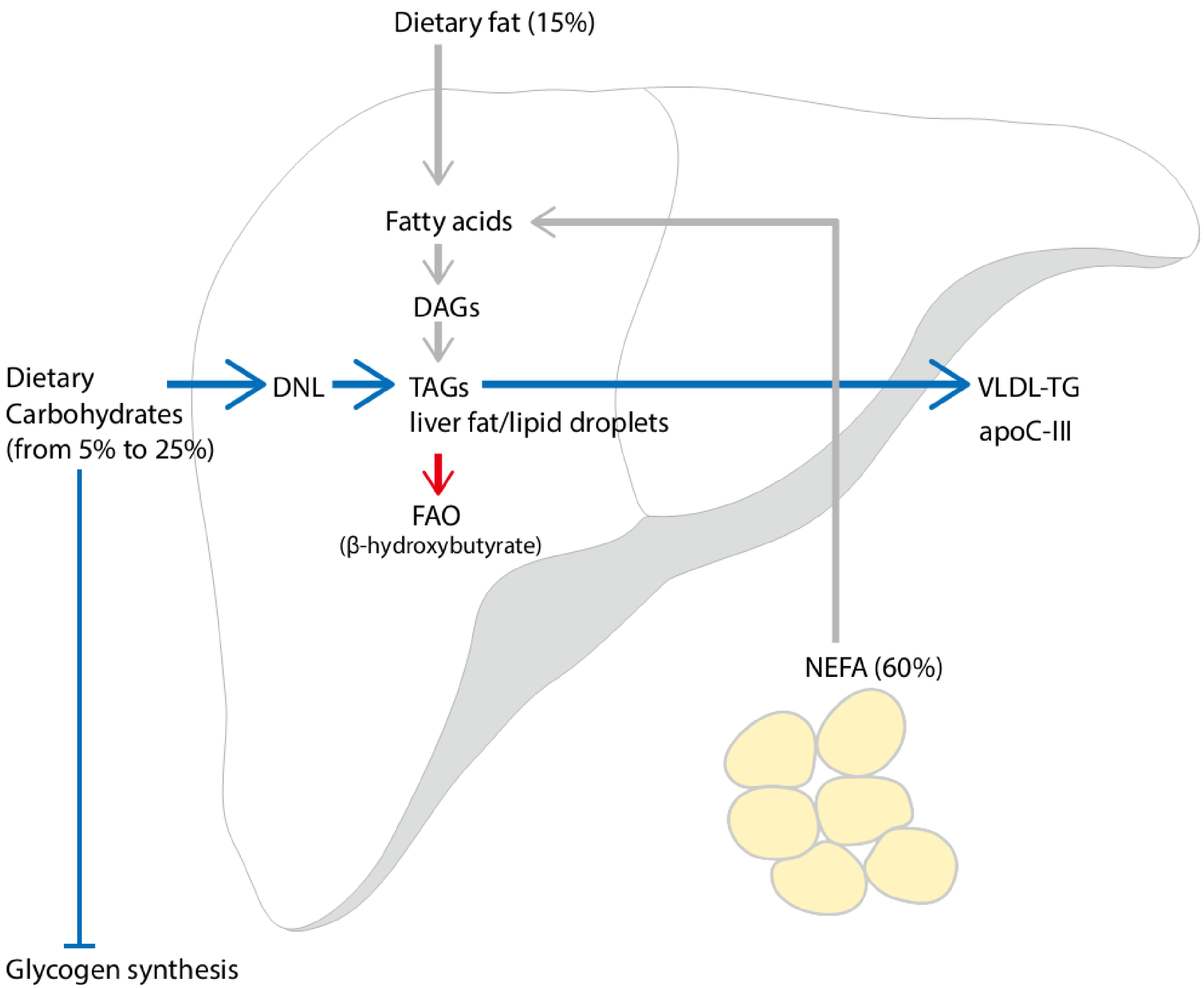
Hepatic lipid accumulation:

- Non-esterified fatty acids (60%)

- Dietary fat (15%)

- Dietary carbs: 5% in healthy but 25% in subjects with NAFLD, one potential reason is that insulin resistance common to NAFLD re-routes glycogen synthesis to DNL

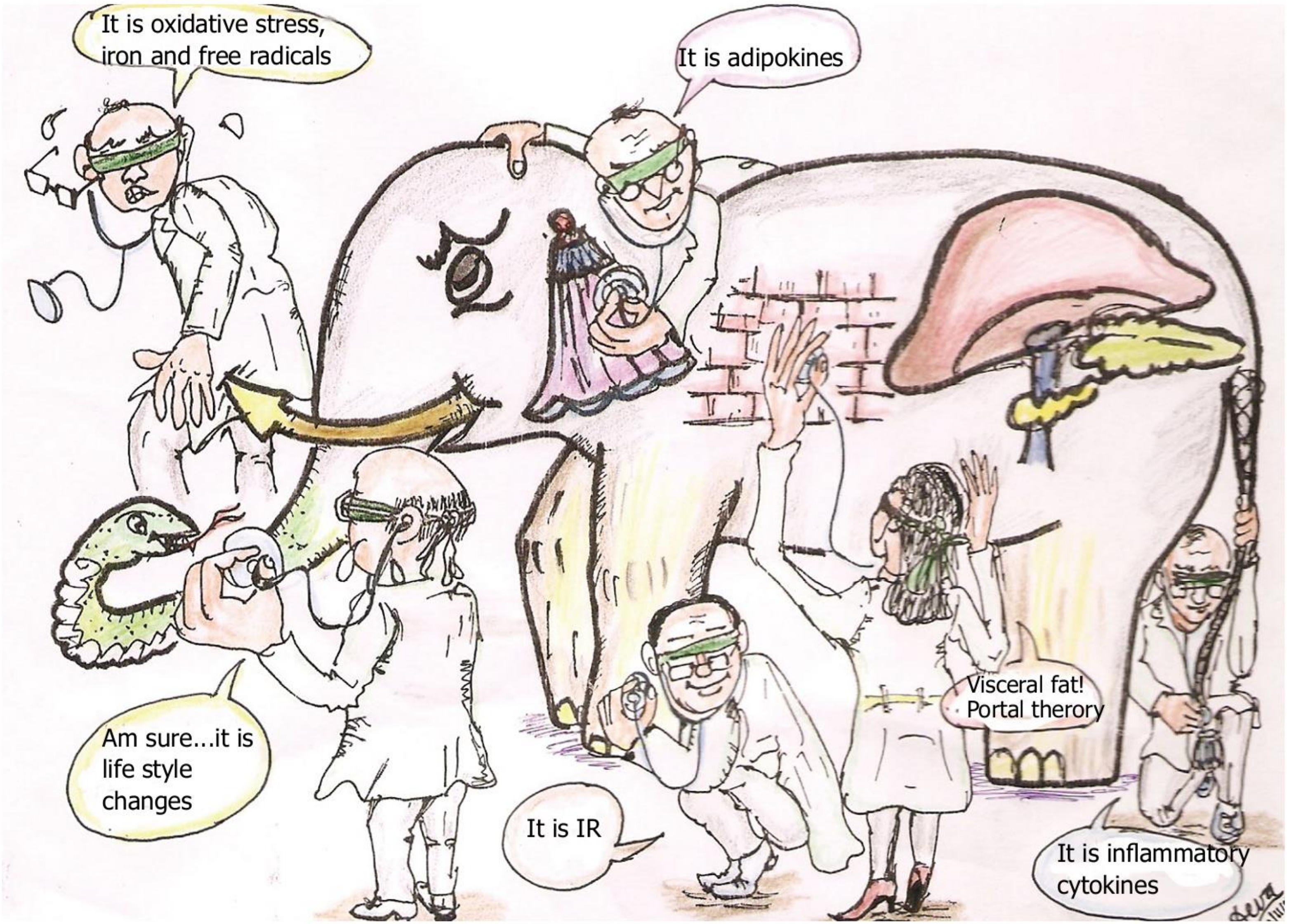
- Without interventions: NAFLD to NASH, cirrhosis, liver failure, and hepatocellular carcinoma



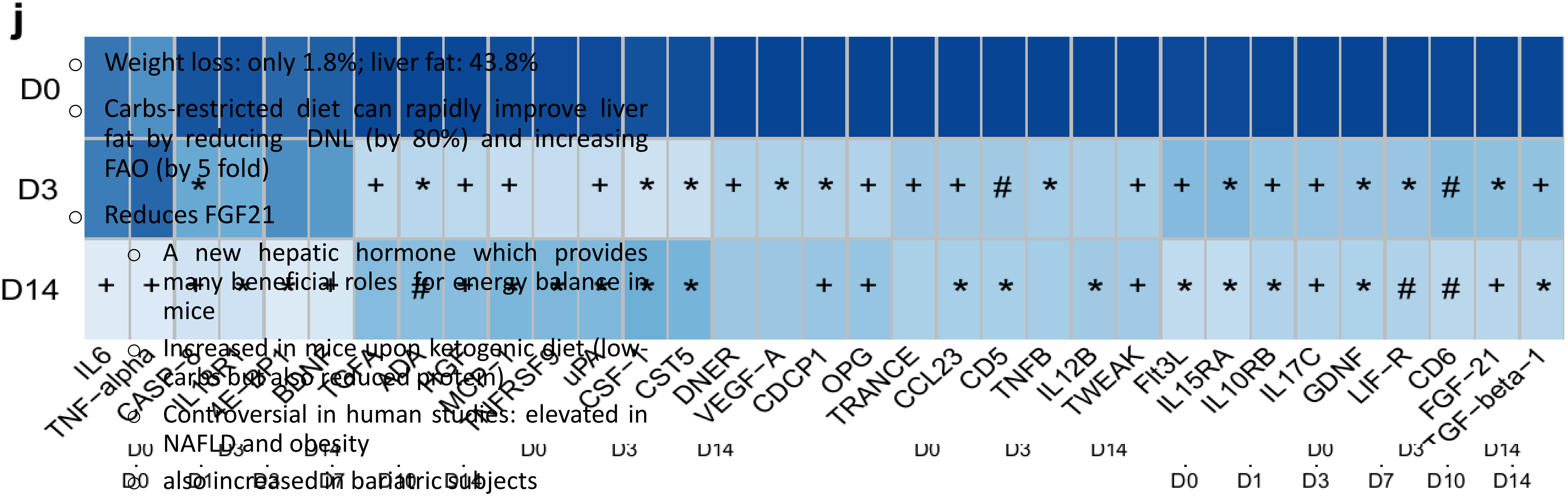
BACKGROUND (2)

Pathogenesis of NAFLD:

- From two hits (1998) to multiple hits: but best characterized by 'the blind men and the elephant' story
- Recently the microbiota also joined this ally and interestingly, microbial shifts have been linked with all these contributing factors.
- How do we get a systematic perspective or a global picture?



Carbs reduction improves liver lipid metabolism & reduces inflammation



- Weight loss: only 1.8%; liver fat: 43.8%
- Carbs-restricted diet can rapidly improve liver fat by reducing DNL (by 80%) and increasing FAO (by 5 fold)
- Reduces FGF21
  - A new hepatic hormone which provides many beneficial roles for energy balance in mice
  - Increased in mice upon ketogenic diet (low-carbs but also reduced protein)
  - Controversial in human studies: elevated in NAFLD and obesity
  - also increased in bariatric subjects

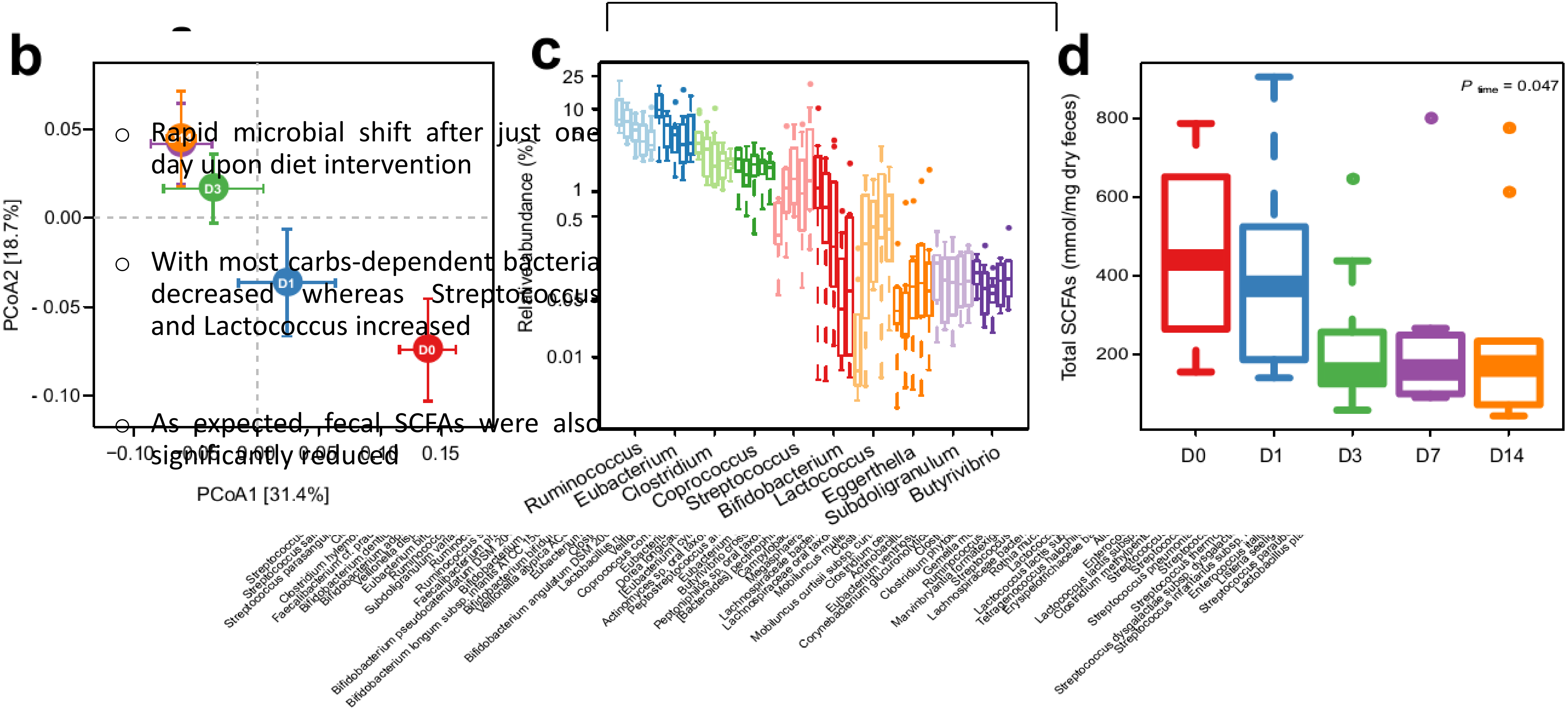
Mardinoglu* and Wu* et al. 2018. Cell Metabolism

Also improved insulin sensitivity

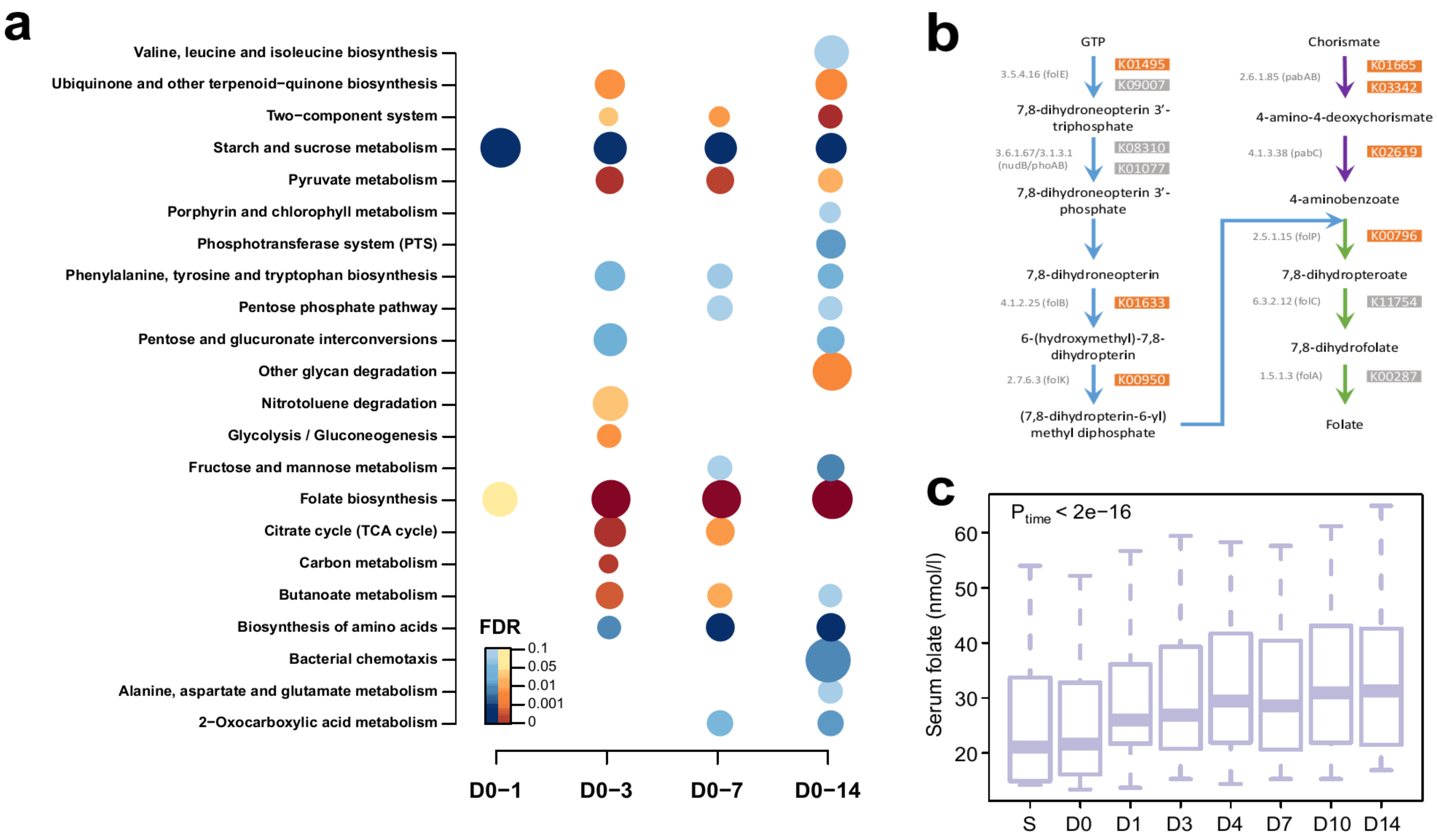
	Discovery cohort						Validation cohort		
	D0	D1	D3	D7	D14	P value	D0	D7	P value
Age (year)	53.7±3.65	NA	NA	NA	NA	NA	48.4±5.6	NA	NA
Gender (male/female)	8/2	NA	NA	NA	NA	NA	5/2	NA	NA
BMI (kg/m²)	34.1±1.2	33.9±1.2	33.7±1.2	33.6±1.2	33.5±1.2	2.03E-10	32.0±1.4	31.7±1.5	0.0007
Weight (kg)	107.2±6.0	106.5±5.9	106.0±5.9	105.6±5.8	105.2±5.8	4.39E-10	98.4±6.6	97.5±6.8	0.1077
Waist (cm)	116.2±5.3	116.0±5.2	115.2±5.0	115.4±5.0	115.2±5.0	0.2114			
Liver fat (%)	16.0±2.3	15.3±2.3	13.8±2.4	12.0±2.4	9.7±1.9	7.41E-15			
Glucose (mmol/L)	6.2±0.2	6.0±0.2	5.9±0.2	6.0±0.2	6.0±0.2	0.3816	6.0±0.1	5.9±0.1	0.0579
P-Insulin (mIE/L)	21.7±5.0	21.8±4.7	16.9±3.0	17.8±4.4	18.8±4.2	0.0183	21.6±3.2	17.2±2.6	0.0313
HOMR-IR	6.0±1.4	5.7±1.2	4.4±0.8	4.8±1.2	5.0±1.1	0.0305	5.8±0.9	4.5±0.7	0.0313
S-Folate (nmol/L)	25.6±4.1	30.0±4.4	31.2±4.4	31.7±4.4	34.5±5.5	6.15E-11	17.6±6.5	22.7±7.1	0.0156
S-ALP (U/L)	55.8±6.0	56.9±6.9	53.7±6.2	48.4±5.4	47.6±5.2	1.83E-07	79.1±6.6	63.5±5.9	0.0223
S-ALT (U/L)	39.7±5.0	39.0±4.8	42.4±5.9	44.1±6.8	37.0±5.0	0.0574	63.8±7.7	61.9±10.2	0.4688
S-AST (U/L)	30.8±2.4	30.8±2.4	35.5±2.6	36.3±2.8	29.7±2.2	0.00015	34.2±2.9	32.7±2.1	0.2969
S-FFA (µmol/L)	524.5±52.1	504.5±42.4	466.4±66.3	431.0±48.1	480.7±63.2	0.4405			
S-Cholesterol (mmol/L)	5.3±0.3	5.5±0.5	5.4±0.4	4.8±0.5	4.4±0.4	2.85E-07	4.6±0.2	4.3±0.2	0.0340
S-Triglycerides (mmol/L)	2.8±0.4	3.7±1.3	1.9±0.4	1.4±0.4	1.4±0.3	0.0113	1.2±0.1	0.7±0.1	0.0156
S-Phospholipids (mmol/L)	228.8±13.5	222.7±22.7	205.3±14.1	182.8±10.1	174.2±9.4	2.65E-06			

Carbs reduction also rapidly alters gut microbial composition

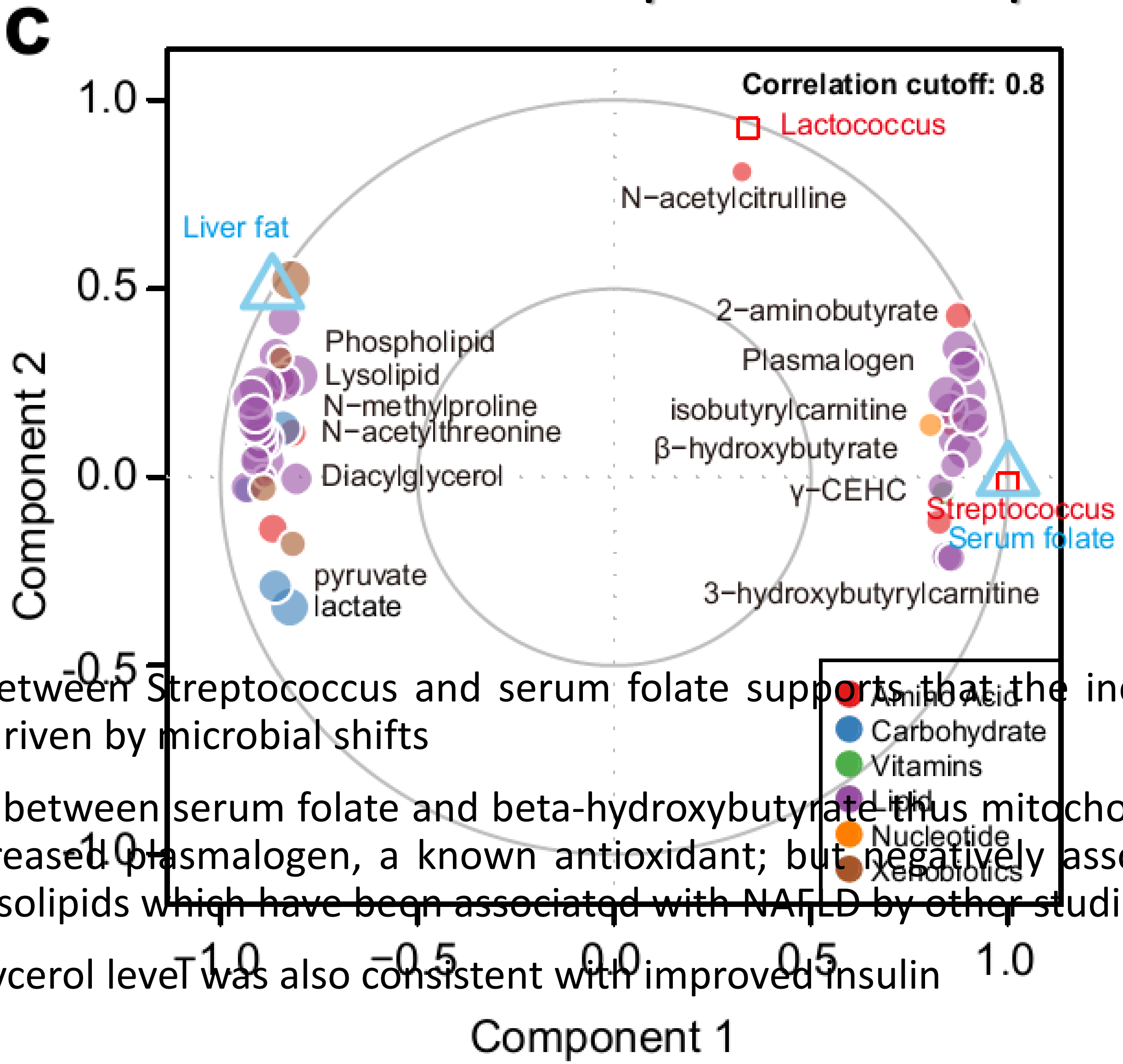
- Rapid microbial shift after just one day upon diet intervention
- With most carbs-dependent bacteria decreased whereas Streptococcus and Lactococcus increased
- As expected, fecal SCFAs were also significantly reduced



Microbial shifts towards folate production

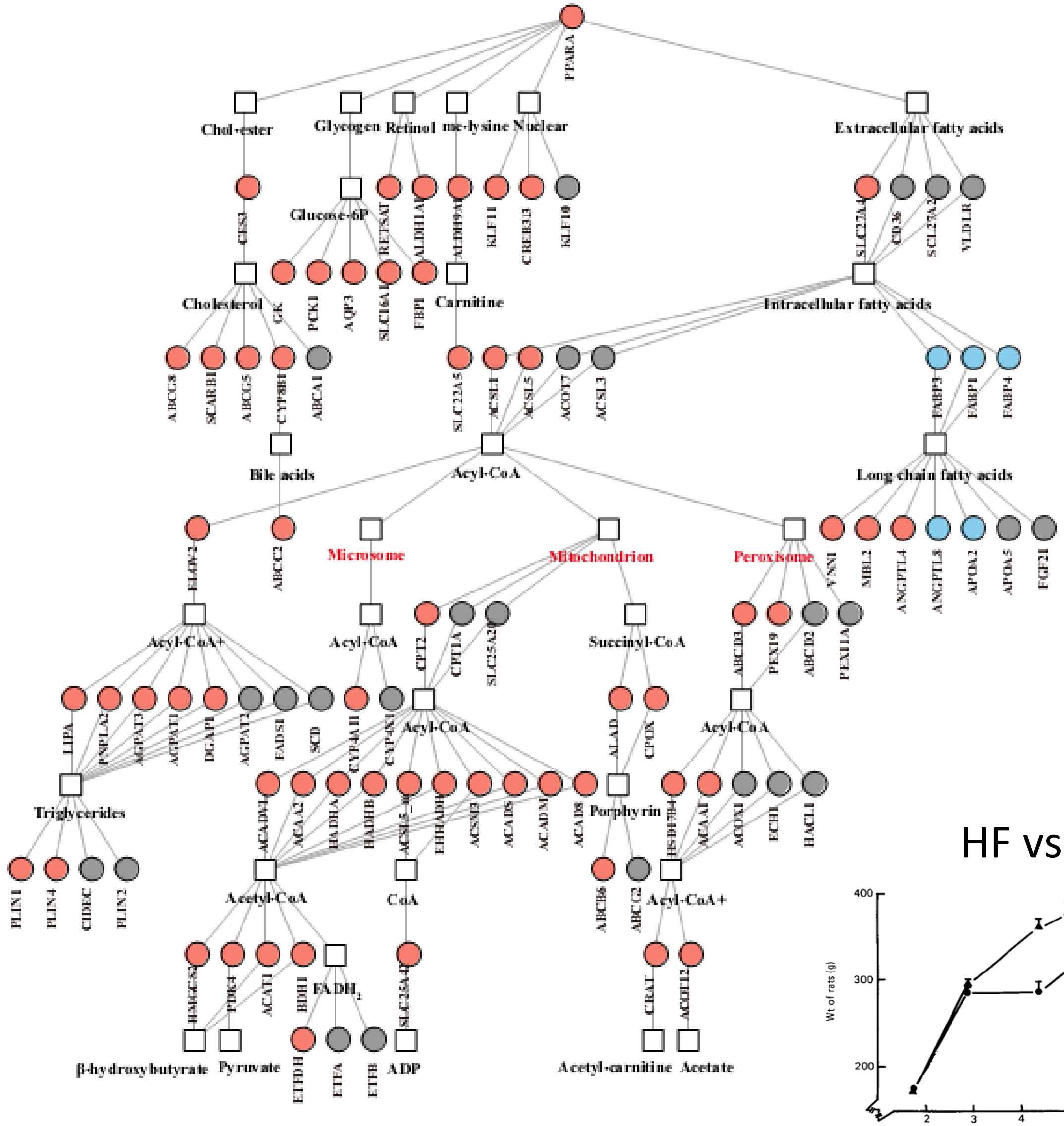


Serum folate is associated with improved liver lipid metabolism

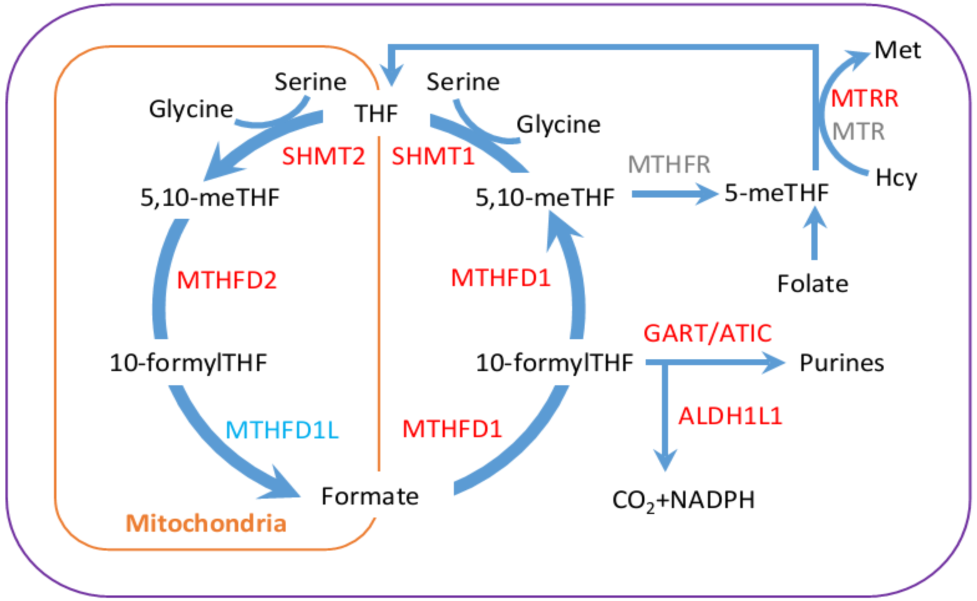


- Strong correlation between Streptococcus and serum folate supports that the increased circulation of folate is potentially driven by microbial shifts
- Positive correlations between serum folate and beta-hydroxybutyrate thus mitochondrial beta oxidation; also linked with increased plasmalogen, a known antioxidant; but negatively associated with liver fat, phospholipids and lysolipids which have been associated with NAFLD by other studies
- Decrease of Diacylglycerol level was also consistent with improved insulin

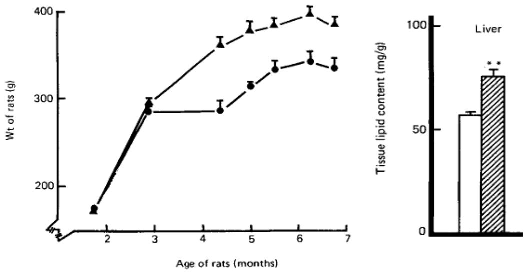
Liver transcriptome changes reflect improved hepatic lipid metabolism



Epigenetics?



HF vs. HF+folate



Supporting evidence

In support of our clinical results, many animal studies have demonstrated that folate supplementation can prevent liver fat accumulation, potentially through PPAR-α and AMPK (Kelley et al., 1950; Akesson et al., 1982; Sid et al., 2017; Sid et al., 2015)

Take home message

- ✓ By taking advantage of integration of multi-Omics datasets, we provided the first clinical evidence showing that specific low carbs diet can shift gut microbes toward folate production.
- ✓ The resulted folate can be further absorbed and utilized by our body to improve lipid metabolism potentially through folate-mediated one carbon metabolism.
- ✓ The low-carbs diet is really beneficial to lipid and glucose metabolism in short term at least.

Hao Wu et al. 2015 Trends in Endocrinology & Metabolism

Welcome to Sweden!