

NUTRIOME

# NUTRIOME workshop1

Nutrigenomics and personalized nutrition  
Maastricht, May 27, 2024  
Stine M. Ulven, coordinator



Funded by  
the European Union



GAP-101119497



NUTRIOME

# Nutrition and gene regulation

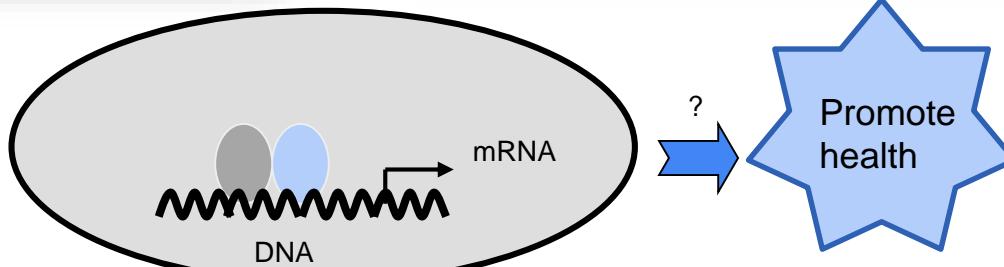


From: "Babette's Feast" by Karen Blixen



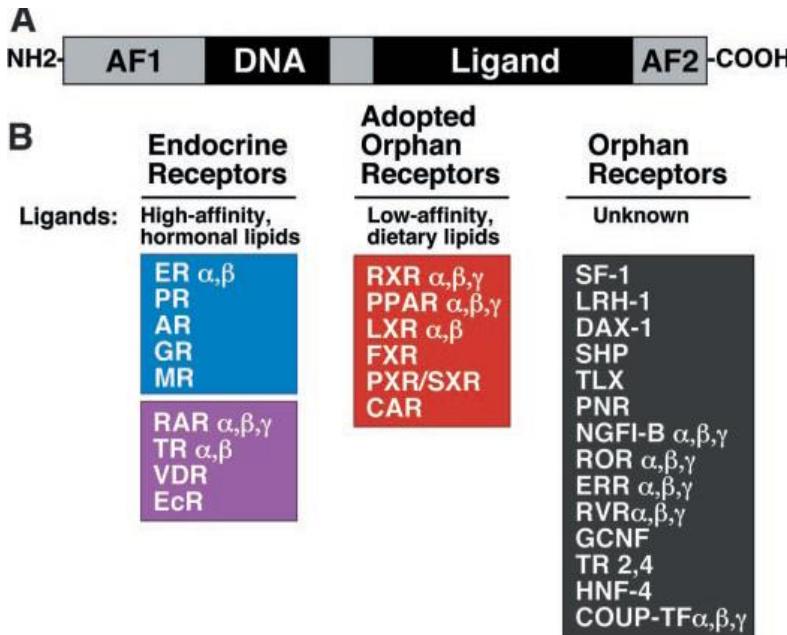
Nutrient	Compound	Transcription factor
<b>Macronutrients</b>		
Fats	Fatty acids Cholesterol	PPARs, SREBPs, LXR, HNF4, ChREBP SREBPs, LXRs, FXR
Carbohydrates	Glucose	USFs, SREBPs, ChREBP
Proteins	Amino acids	C/EBPs
<b>Micronutrients</b>		
Vitamins	Vitamin A Vitamin D Vitamin E	RAR, RXR VDR PXR
Minerals	Calcium Iron Zinc	Calcineurin/NF-ATs IRP1, IRP2 MTF1
<b>Other food components</b>		
	Flavonoids Xenobiotics	ER, NF $\kappa$ B, AP1 CAR, PXR

Müller and Kersten, Nature Genetic, vol 4, 2003





# Non-steroid nuclear receptors

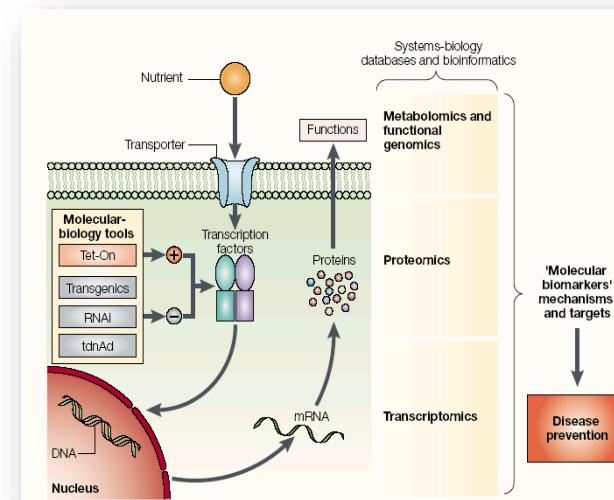




# Definition of nutrigenomics

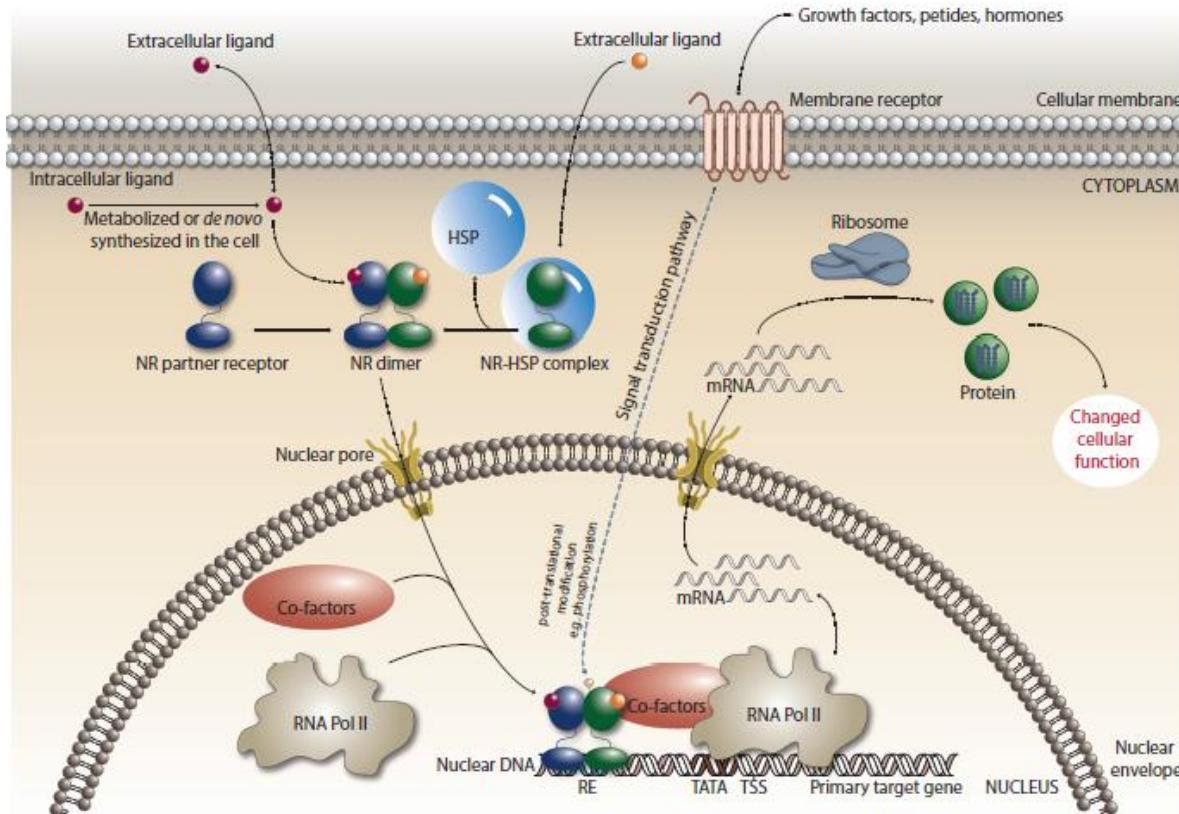
Nutrigenomics aims to understand how changes in gene expression and protein function by nutrients can affect human health

- Nutrigenomics
  - explores the effects of nutrients on the genome, transcriptome, proteome and metabolome
- Nutrigenetics
  - elucidate the effect of genetic variation on the interaction between diet and disease





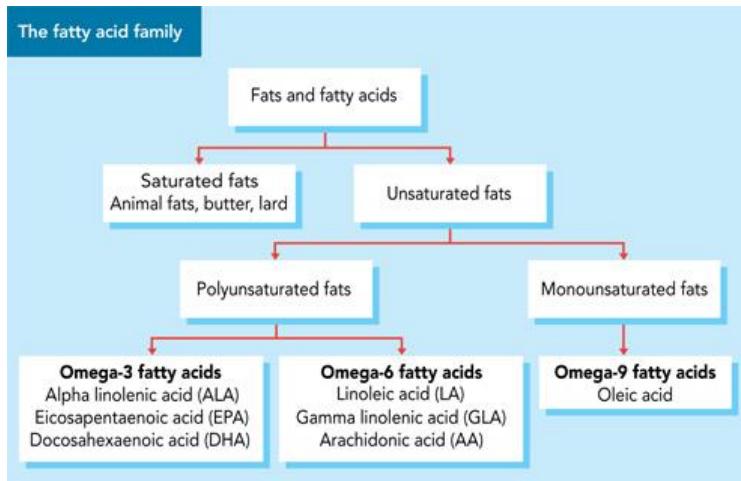
# Nutrient sensing via nuclear receptors



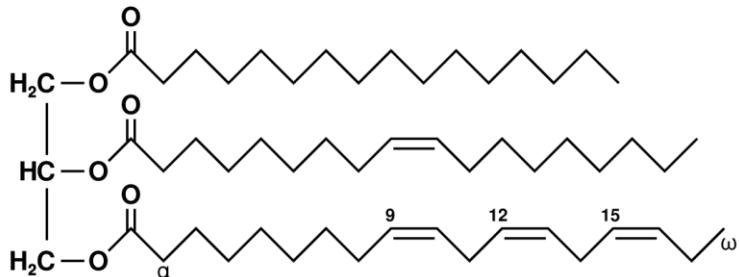


# Fatty acids and diet

FA



TG



	NNR 2024
Total fat (E%)	25-40
SFA (E%)	<10
MUFA (E%)	10-20
PUFA (E %)	5-10



# Peroxisome proliferator-activated receptors (PPARs) and lipid metabolism

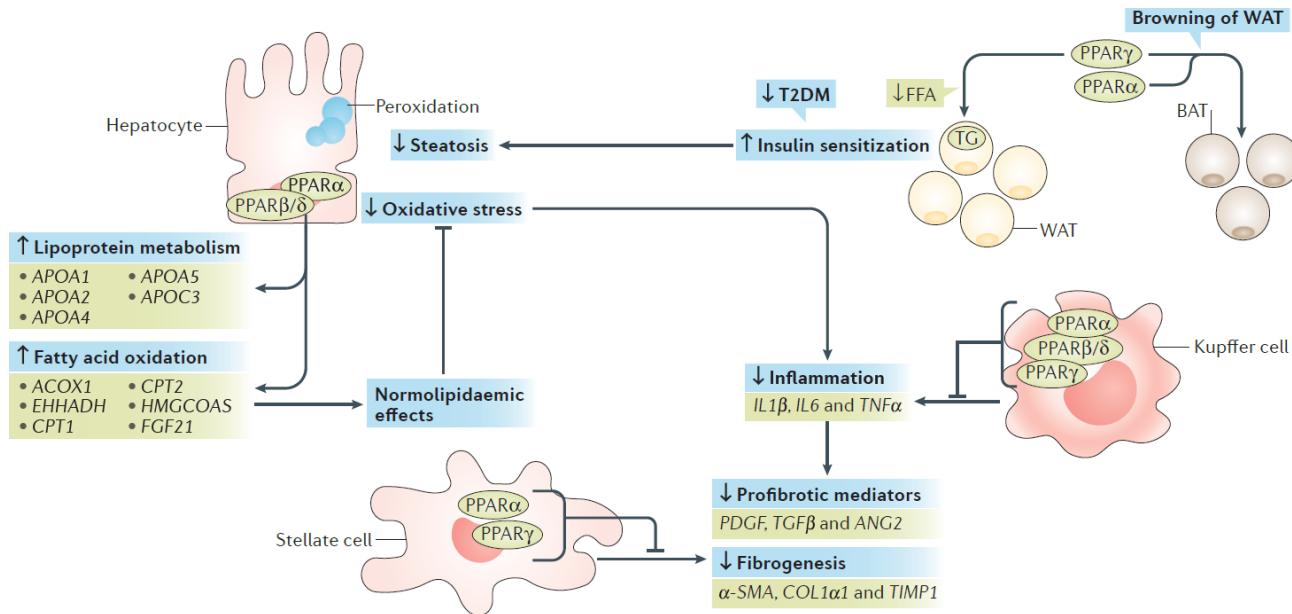




Table 1 | PPAR expression, ligands, function and therapeutic potential for metabolic diseases

Isotype	Tissues of highest expression	Natural ligands	Synthetic ligands	Functions regulated	Potential therapeutic use
PPAR $\alpha$	BAT, liver, kidney, heart, skeletal muscle	<ul style="list-style-type: none"> <li>Unsaturated fatty acids</li> <li>Phospholipids</li> <li>Leukotriene B4</li> <li>8(S)-hydroxyeicosatetraenoic acid</li> </ul>	<ul style="list-style-type: none"> <li>Fibrates (generically marketed such as clofibrate, fenofibrate, bezafibrate, gemfibrozil)</li> <li>Pemafibrate (K-877, Kowa, phase III)</li> <li>LY518674 (Eli Lilly, phase II)</li> </ul>	<ul style="list-style-type: none"> <li>Mitochondrial <math>\beta</math>-oxidation</li> <li>Peroxisomal <math>\beta</math>-oxidation</li> <li>Microsomal <math>\omega</math>-oxidation</li> <li>Fatty acid binding</li> <li>Fatty acid transport</li> <li>Thermogenesis</li> <li>Lipoprotein metabolism</li> <li>Inflammation</li> <li>Oxidative stress</li> <li>Adipokine secretion and uptake</li> <li>Fibrosis</li> </ul>	<ul style="list-style-type: none"> <li>Hypertriglyceridaemia</li> <li>Atherogenic dyslipidaemia</li> <li>NAFLD</li> </ul>
PPAR $\beta/\delta$	Gastrointestinal tract, skin, heart, kidney, BAT, WAT, skeletal muscle	<ul style="list-style-type: none"> <li>Unsaturated fatty acids</li> <li>Component of VLDL</li> <li>Prostacyclin I<sub>2</sub></li> <li>13-S-hydroxy-ostadecadienoic acid</li> </ul>	<ul style="list-style-type: none"> <li>GW501516 (GlaxoSmithKline, phase II, discontinued) and its analogue GW610742 (GlaxoSmithKline, preclinical)</li> <li>L-165041 (Merck, preclinical)</li> <li>MBX-8025 (Cymabay, phase II)</li> </ul>	<ul style="list-style-type: none"> <li>Mitochondrial <math>\beta</math>-oxidation</li> <li>Fatty acid binding</li> <li>Fatty acid transport</li> <li>Lipoprotein metabolism</li> <li>Thermogenesis</li> <li>Preadipocyte differentiation</li> <li>Oxidative metabolism</li> <li>Inflammation</li> <li>Oxidative stress</li> <li>Glucose utilization</li> <li>Muscle fibre switch</li> <li>ER stress</li> </ul>	<ul style="list-style-type: none"> <li>Atherogenic dyslipidaemia</li> <li>Insulin resistance/T2DM</li> <li>Obesity</li> <li>NAFLD</li> </ul>
PPAR $\gamma$	BAT, WAT, colon, immune cells	<ul style="list-style-type: none"> <li>Unsaturated fatty acids</li> <li>15-hydroxyeicosatetraenoic acid</li> <li>9-S-hydroxy-ostadecadienoic acid and 13-S-hydroxy-ostadecadienoic acid</li> <li>15-deoxy-D12,14-prostaglandin J2 (15d-PGJ<sub>2</sub>)</li> </ul>	Thiazolidinediones (pioglitazone and rosiglitazone)	<ul style="list-style-type: none"> <li>BAT and WAT differentiation</li> <li>Thermogenesis</li> <li>Lipogenesis</li> <li>Triglyceride hydrolysis</li> <li>Lipolysis</li> <li>Fatty acid uptake</li> <li>Glucose uptake and insulin signalling</li> <li>Adipokine secretion</li> <li>Inflammation</li> <li>Oxidative stress</li> <li>ER stress</li> <li>Fibrosis</li> </ul>	Insulin resistance/T2DM

BAT, brown adipose tissue; ER, endoplasmic reticulum; NAFLD, nonalcoholic fatty liver disease; PPAR, peroxisome proliferator-activated receptors; T2DM, type 2 diabetes mellitus; WAT, white adipose tissue.



# Nutrigenomics and personalized nutrition

2008

**Health maintenance**  
Generalised diet and other lifestyle approaches



**Diagnosis**  
Clinical evidence of disease  
Risk biomarkers



Often generalised therapy

20..?



Predisposition

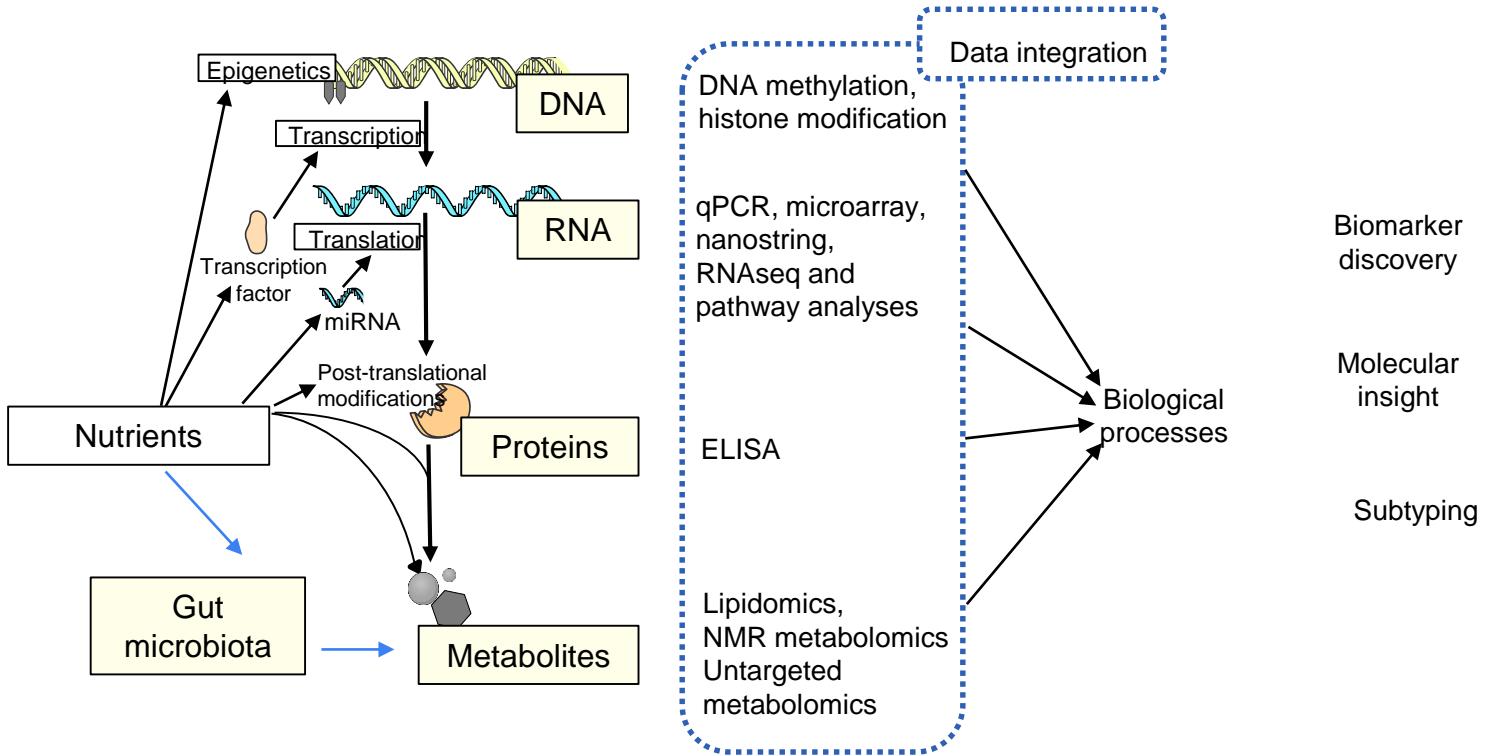
Early detection

Personalised earlier more effective prevention strategies or therapies

Genetic profile

Based on classical and new biomarkers

# Nutrigenomics in controlled dietary intervention studies



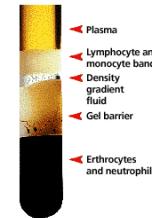


# Peripheral blood mononuclear cells (PBMCs)

- Plasma 55%
- Cellular elements 45%
  - Blood platelets (Thrombocytes) 3%
  - White blood cells (Leukocytes) 1%
    - Granulocytes (polymorfonuclear)
      - Neutrophils 62%
      - Basophils 0.4%
      - Eosinophils 3.3%
    - Mononuclear cells
      - Monocytes 5.3%
      - Lymphocytes 30%
  - Red Blood cells (erythrocytes) 96%

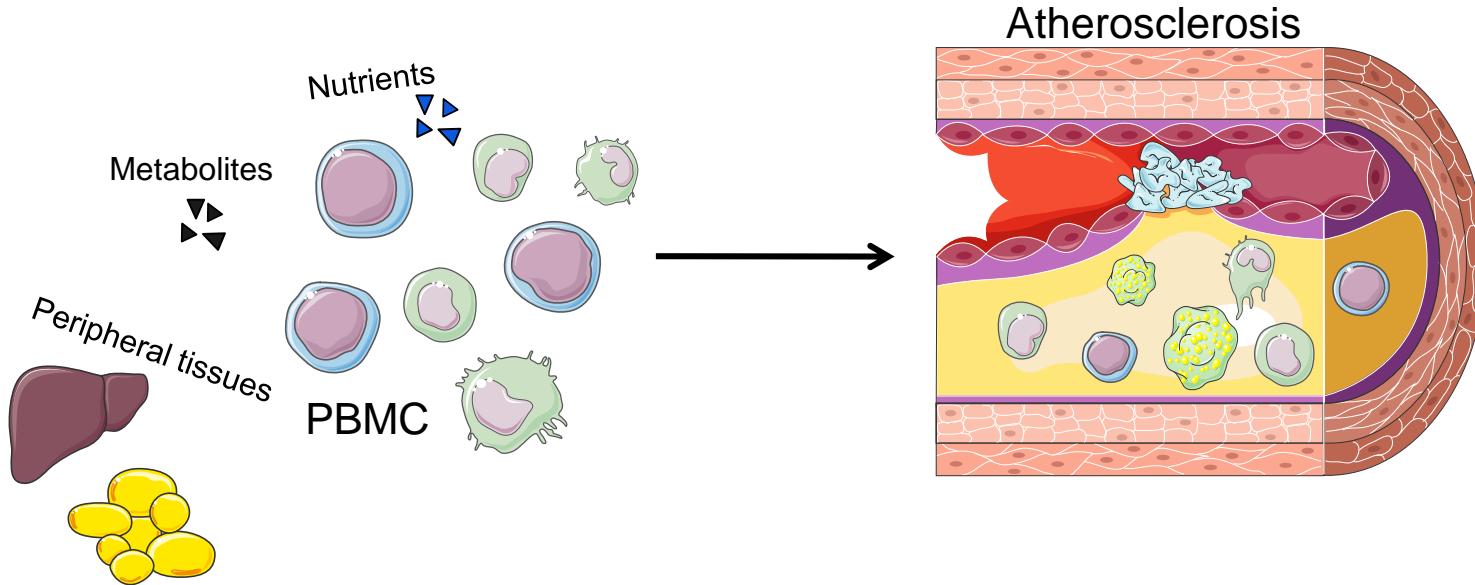
PBMCs

- Monocytes
- Lymphocytes
  - B-cells
  - T-cells
  - NK-cells



- Represent important cells of the innate and adaptive immune system
- Produces cytokines and endothelial adhesion molecules
- Important in the process of atherosclerosis and insulin resistance

# PBMC gene expression can serve as a model system in nutrition science



de Mello VD et al. *Mol Nutr Food Res* 2012  
Bouwens M et al. *Am J Clin Nutr* 2007  
O'Grada CM et al. *Mol Nutr Food Res* 2014

# Fasting induces changes in peripheral blood mononuclear cell gene expression profiles related to increases in fatty acid $\beta$ -oxidation: functional role of peroxisome proliferator-activated receptor $\alpha$ in human peripheral blood mononuclear cells<sup>1–3</sup>

Mark Bouwens, Lydia A Afman, and Michael Müller

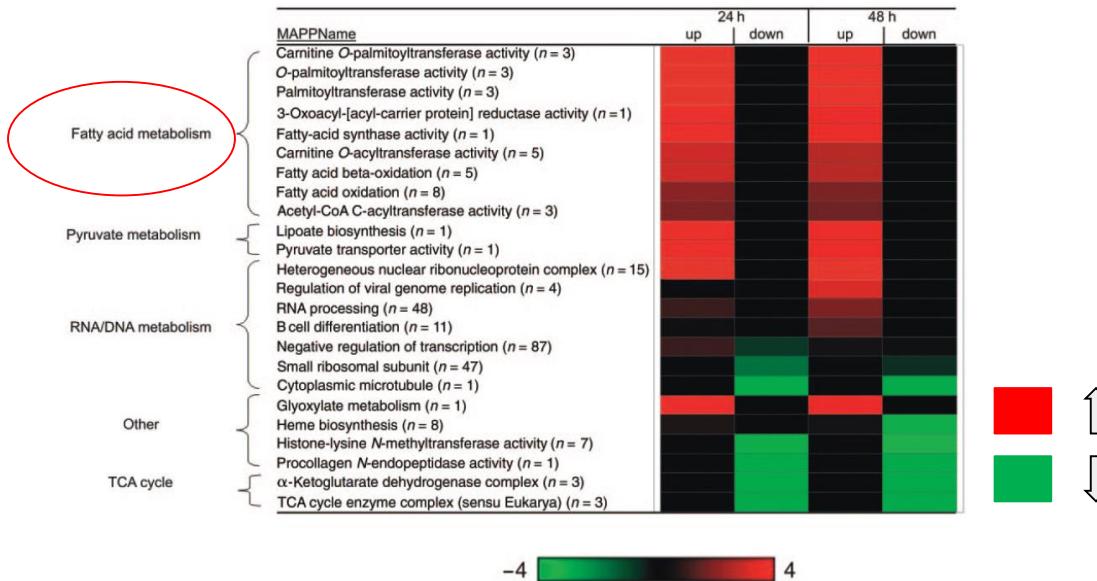
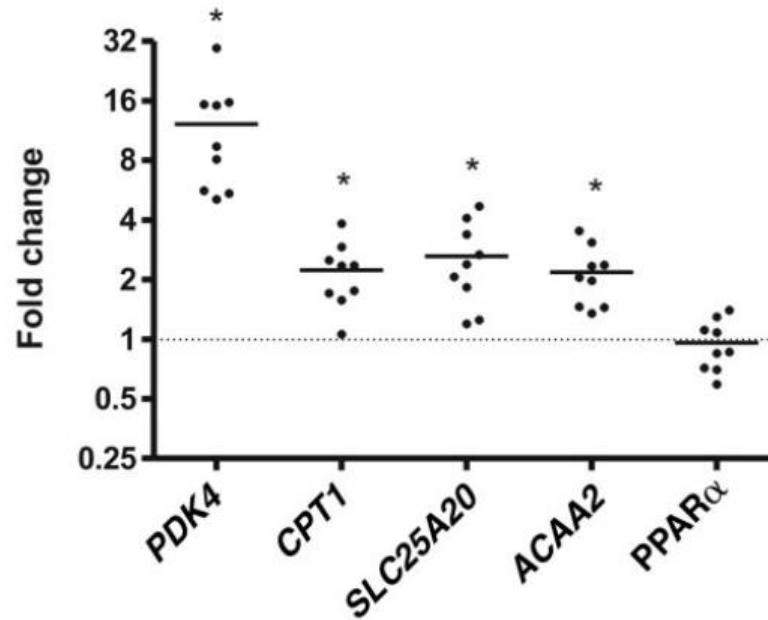


FIGURE 3. Heat map of changed pathways after 24 and 48 h of fasting in peripheral blood mononuclear cells ranked by z scores (GENMAPP 2.0). Only pathways with z scores > 1 at either 24 or 48 h were included. The z scores for down-regulated pathways were inverted. Red indicates up-regulated, green indicates down-regulated. CoA, coenzym A; TCA, tricarboxylic acid.

# PPAR $\alpha$ agonist (Wy14643) induces lipid gene expression in PBMCs



PDK4: Pyruvate dehydrogenase kinase isoform 4

CPT1: carnitine palmitoyltransferase 1

SLC25A20: solute carrier family 25(carnitine/acylcarnitine translocase), member 20

ACAA2: acetyl-coenzyme A acyltransferase 2

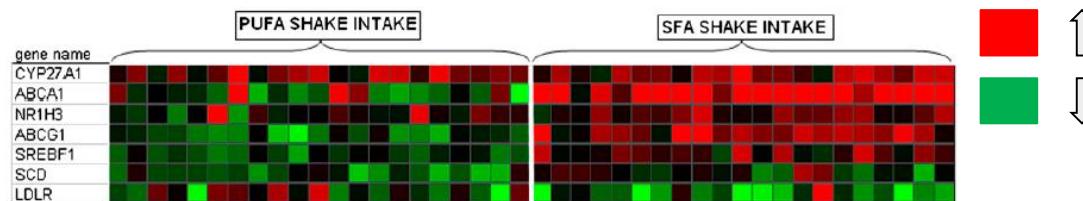
# Postprandial dietary lipid-specific effects on human PBMC gene expression profiles

TABLE 2

Percentages of fatty acids as measured by gas-liquid chromatography<sup>1</sup>

	PUFAs	SFAs	MUFAs
Total fat (% of energy)	71.5	71.5	71.5
SFAs (% of total fat)	18.51	70.73	7.63
MUFAs (% of total fat)	15.04	25.46	84.62
PUFAs (% of total fat)	65.77	2.39	7.75
n-6 PUFAs (% of total fat)	6.77	1.35	7.75
n-3 PUFAs (% of total fat)	59.00	1.04	0.00
Docosahexaenoic acid (% of total fat)	48.54	0.00	0.00
Eicosapentaenoic acid (% of total fat)	7.24	0.00	0.00

Fatty acid composition of three different «shakes»  
21 healthy male  
PBMC gene expression 0h and 6h after intake



**FIGURE 5.** Heat map of genes changed after consumption of the shakes enriched in polyunsaturated fatty acids (PUFAs) or saturated fatty acids (SFAs) within the process liver X receptor signaling, with a false discovery rate  $Q$  value  $<0.05$ , in all 21 subjects. Red indicates up-regulation, green indicates down-regulation, and black indicates no change.



# Effect of fatty acids on PBMC gene expression

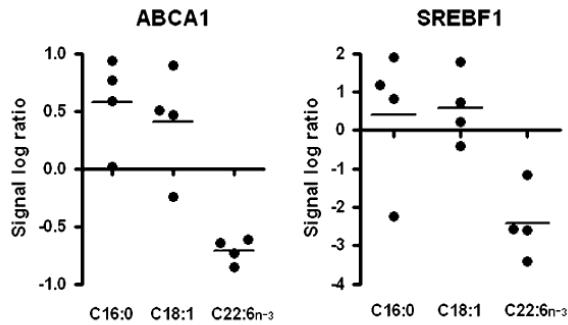
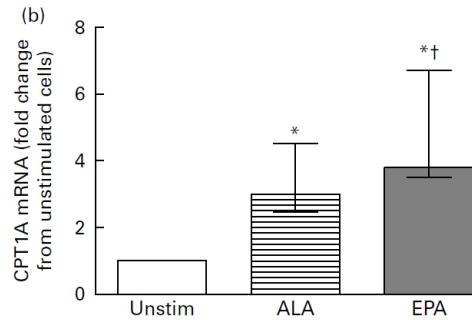


FIGURE 7. Effects of incubation of peripheral blood mononuclear cells from 4 donors with 3 different fatty acids, which represent the main fatty acid types in the experimental shakes, on expression of *ABCA1* (ATP-binding cassette A1) and *SREBF1* (sterol regulatory element binding protein-1). Dots represent subjects, and lines represent means. C16:0, palmitic acid; C18:1, oleic acid; C22:6n-3, docosahexaenoic acid.

Bouwens M et al, Am J Clin Nutr 2010



Myhrstad M et al, Br J Nutr 2011



NUTRIOME

# Large differences in response to food

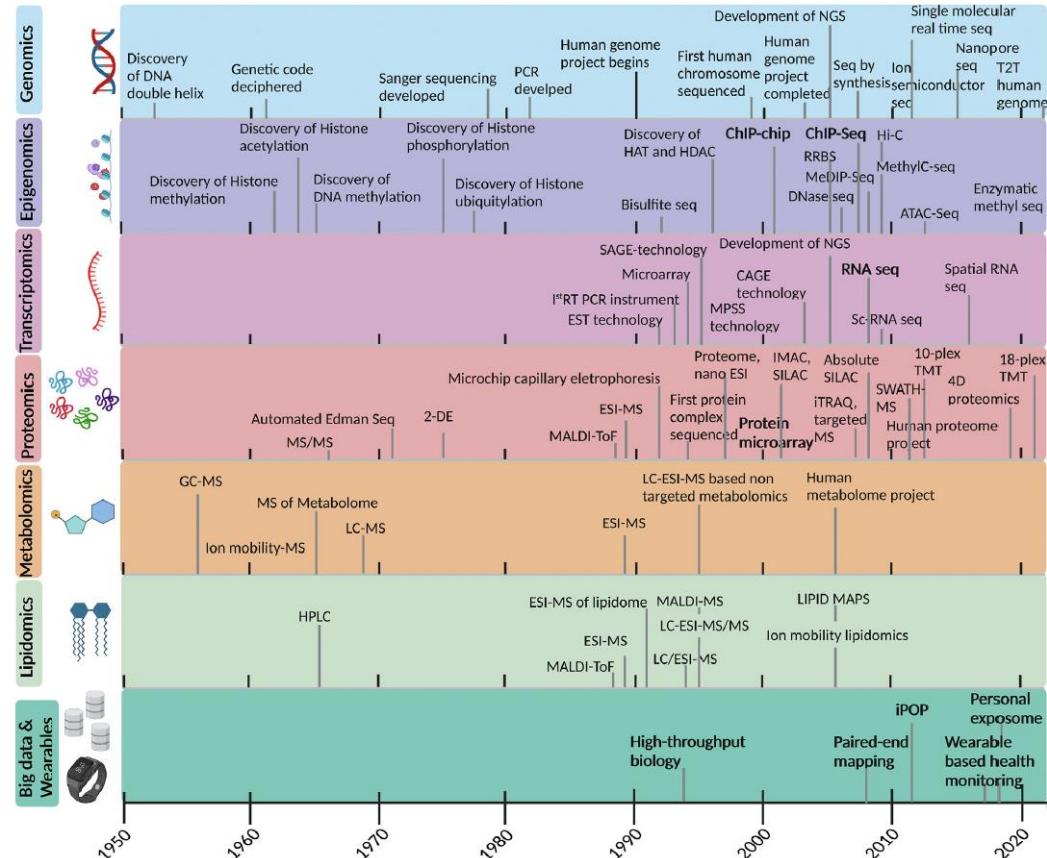


Moving from  
“one-diet-fits-all”  
to  
“the right diet for the right person at the right time”

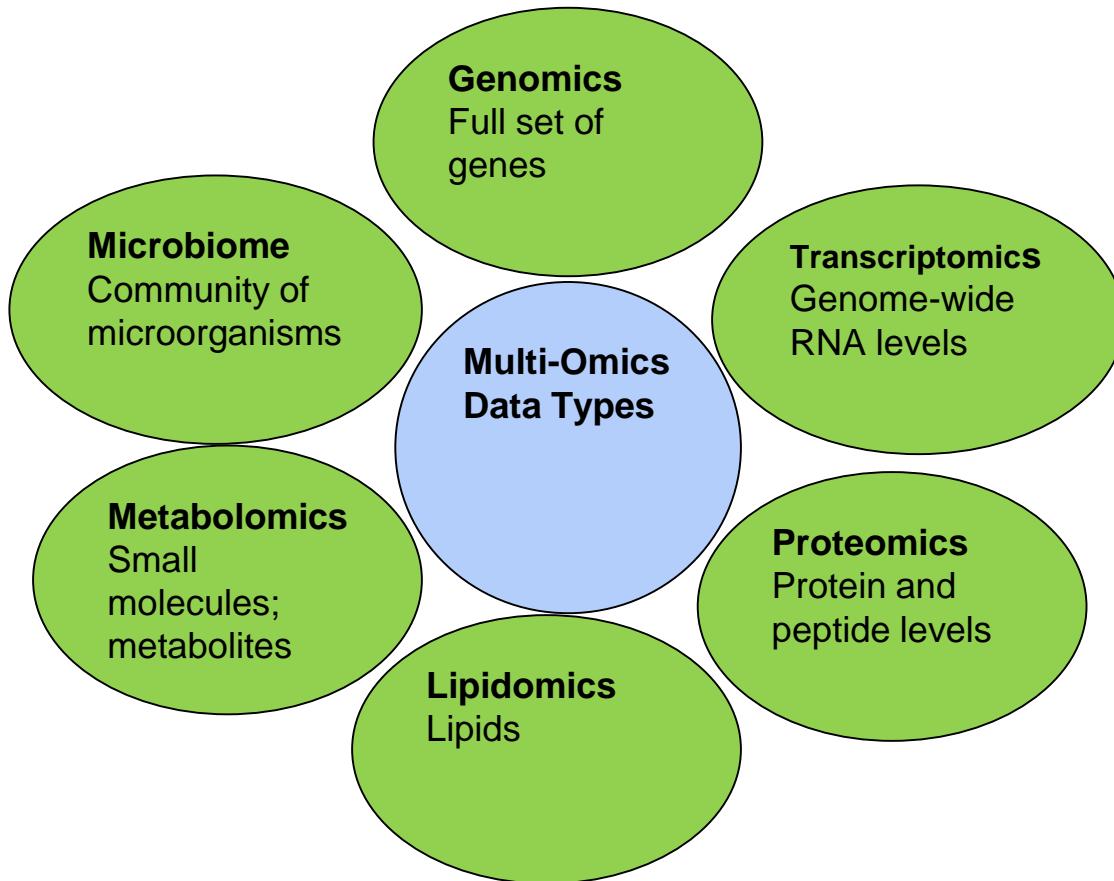
Personalized nutrition/precision nutrition



# Major technological developments in Omics analysis



# Nutrigenomics and multi-omics approaches



# Diet and health in the exposome era

## Ecosystems

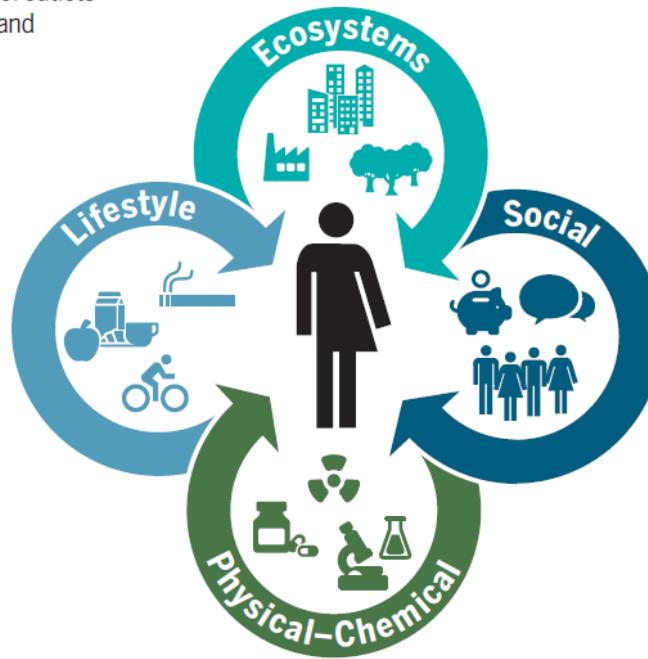
Food outlets, alcohol outlets  
 Built environment and urban land uses  
 Population density  
 Walkability  
 Green/blue space

## Lifestyle

Physical activity  
 Sleep behavior  
 Diet  
 Drug use  
 Smoking  
 Alcohol use

## Social

Household income  
 Inequality  
 Social capital  
 Social networks  
 Cultural norms  
 Cultural capital  
 Psychological and mental stress

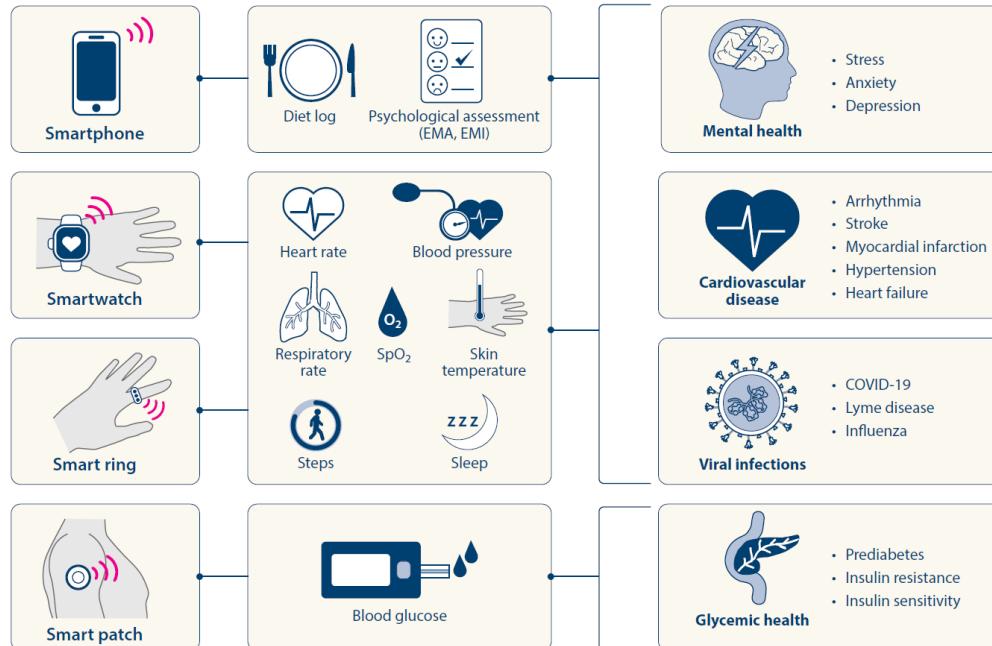


## Physical-Chemical

Temperature/humidity  
 Electromagnetic fields  
 Ambient light  
 Odor and noise  
 Point, line sources, e.g., factories, ports  
 Outdoor and indoor air pollution  
 Agricultural activities, livestock  
 Pollen/mold/fungus  
 Pesticides  
 Fragrance products  
 Flame retardants (PBDEs)  
 Persistent organic pollutants  
 Plastic and plasticizers  
 Food contaminants  
 Soil contaminants  
 Drinking water contamination  
 Groundwater contamination  
 Surface water contamination  
 Occupational exposures



# Wearable devices enable physiological monitoring of health





NUTRIOME

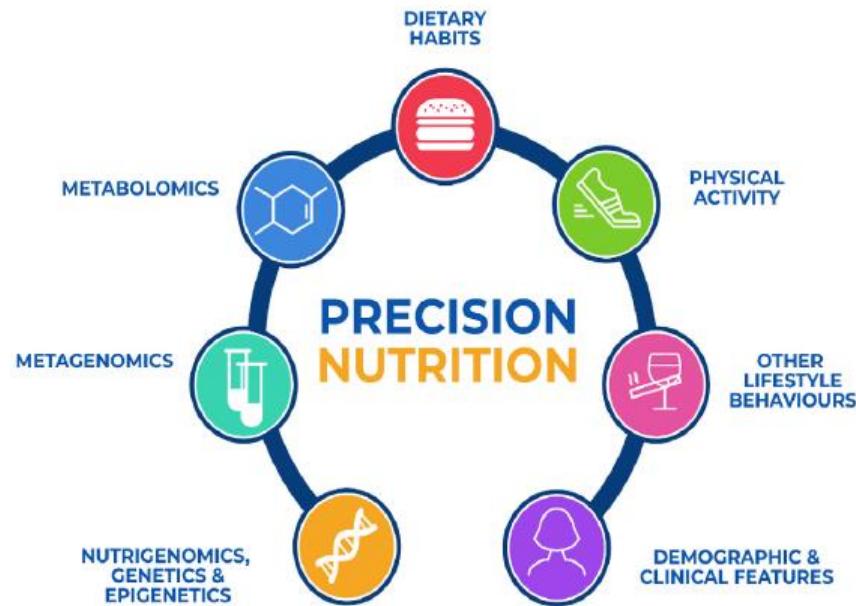
# **What is precision nutrition for you?**



NUTRIOME

# No agreed definition on the definition of personalized nutrition

- Stratified nutrition
  - Group individuals with shared characteristics
- Personalized nutrition
  - Provision of dietary advice based on genotype
- Precision nutrition
  - An approach that uses information on individual characteristics to develop targeted nutritional advice





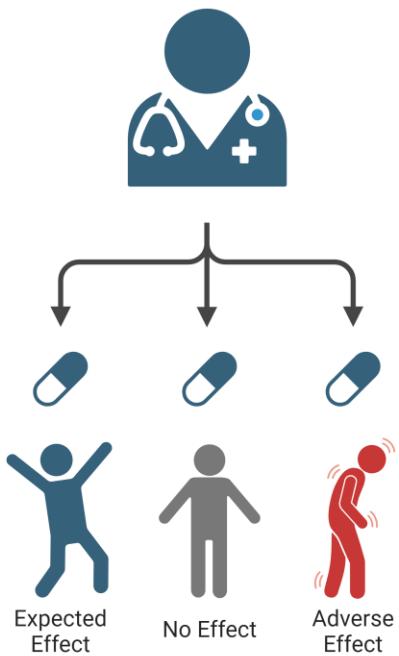
# The goal of precision nutrition

- Improve health using genetic; phenotypic, medical, nutritional, and other relevant information about individuals to deliver more specific healthy eating guidance
- Can be used for patients and healthy people in order to prevent diseases
  - More effective interventions for improving public health
- Maximizing the benefits and reducing the adverse effects of dietary changes

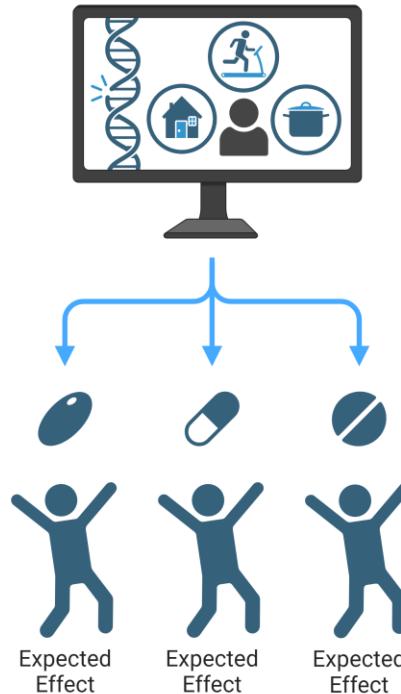


NUTRIOME

## Healthcare Professional One-Fits-All Treatment



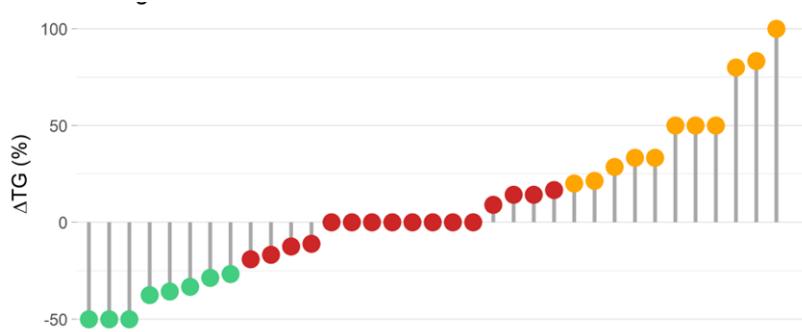
## AI-assisted personalized treatment



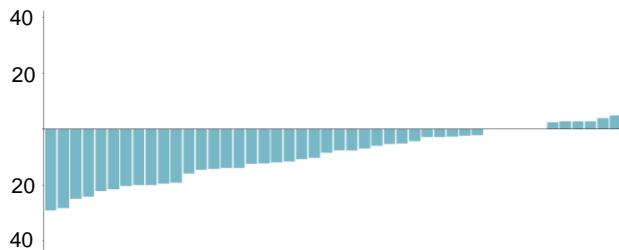


# Large variation in response despite good compliance

- Individual change in TG (in %) in FO-group in LA study

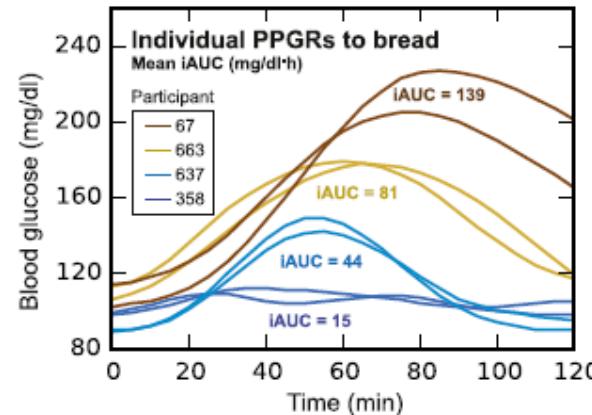
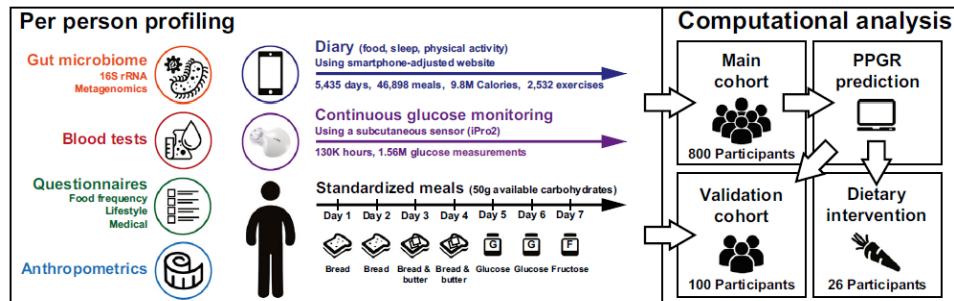
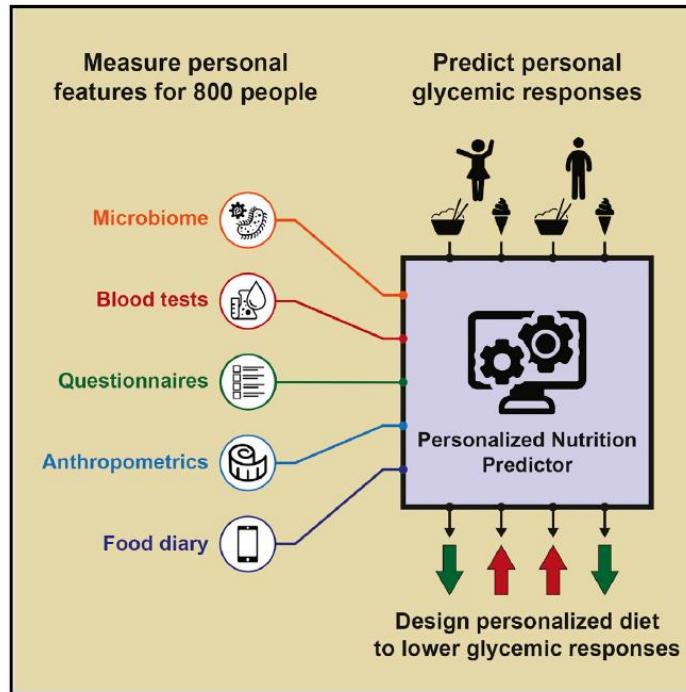


- Individual change in LDL-C (%) in Ex-diet group in NOMA study

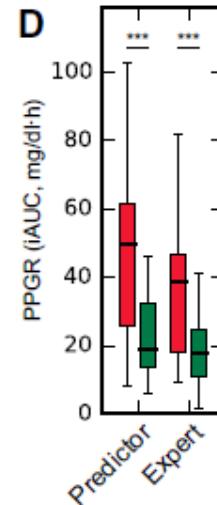
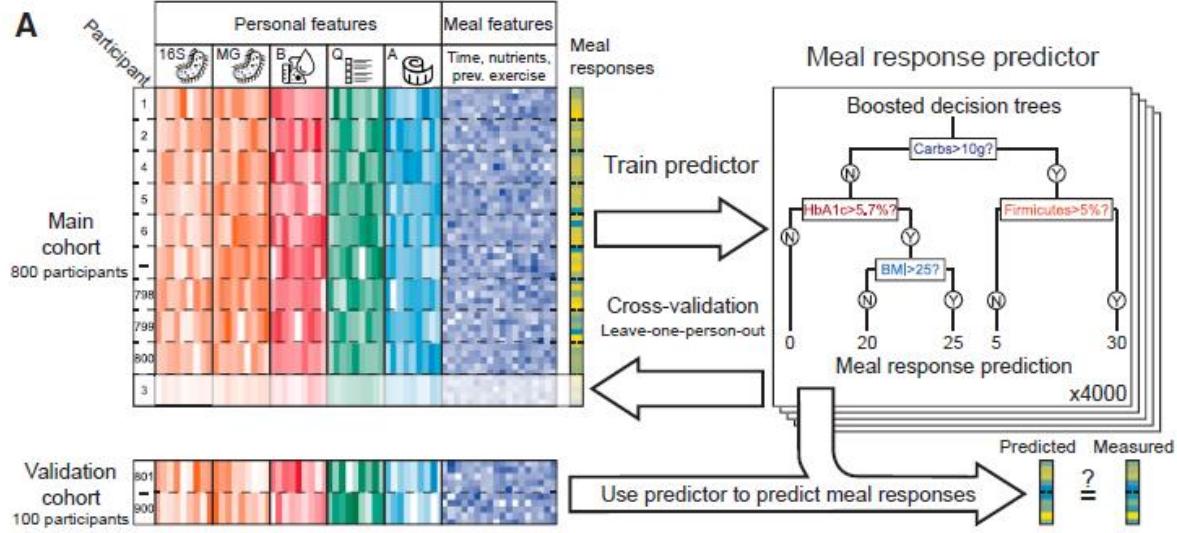




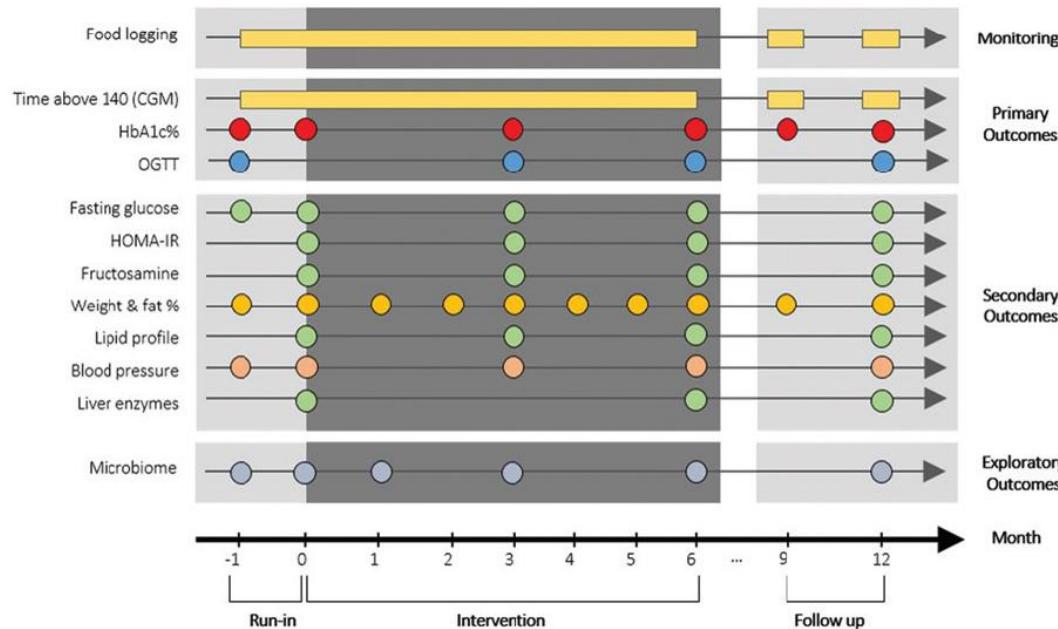
# Personalized nutrition by prediction of glycemic responses



# Accurate predictions and personally tailored dietary interventions improve postprandial glycemic responses



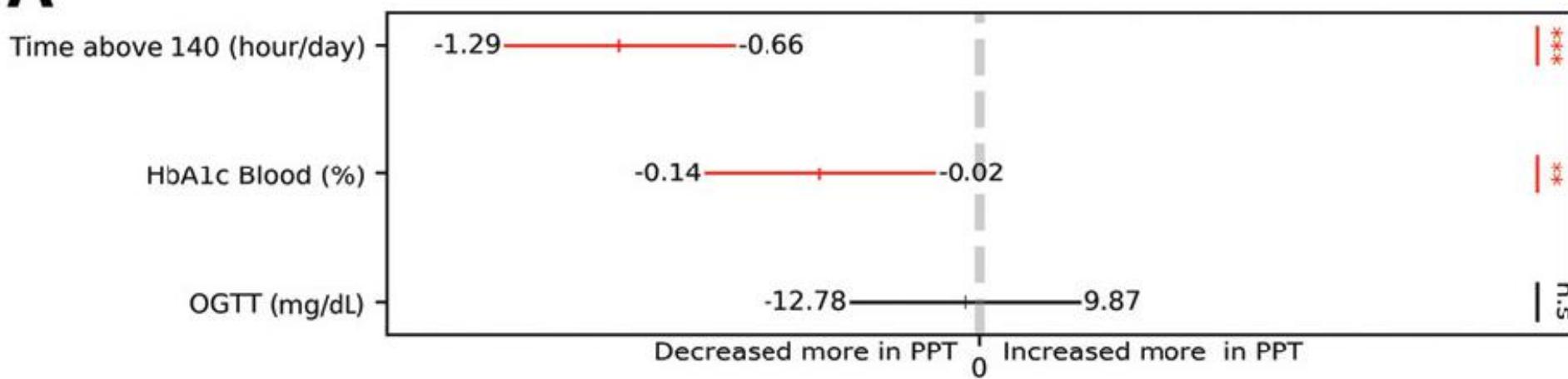
# Personalized postprandial glucose response-targeting diet versus Mediterranean diet



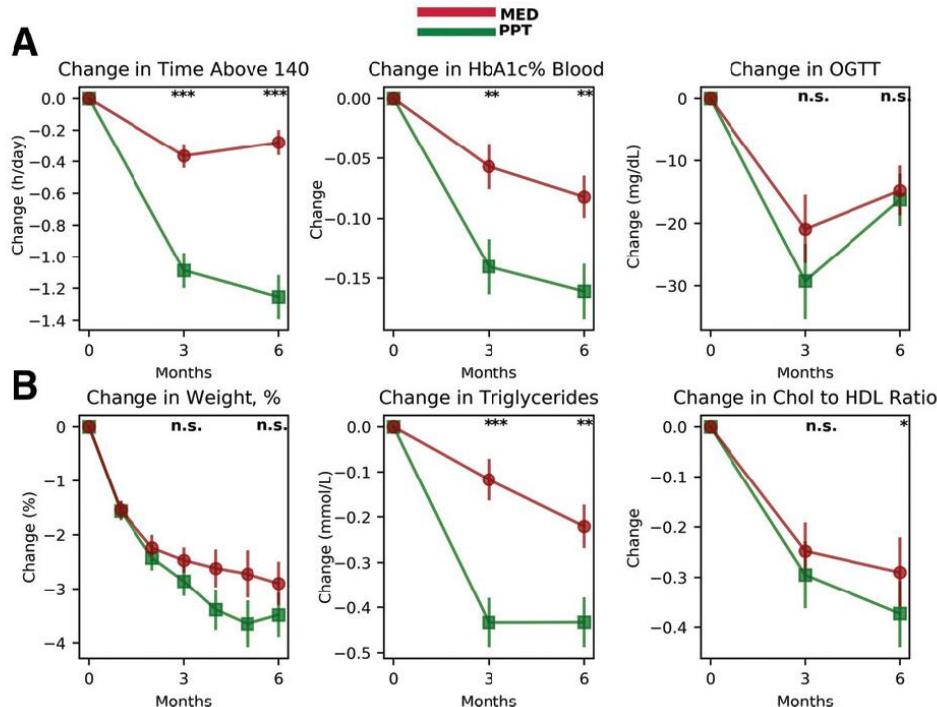
# Decrease in hour/day of glucose > 140 mg/dl (7.8 mmol/L) and HbaA1c

**A**

## Primary Outcomes



# Changes in primary and secondary outcomes during the intervention





## PREDICT 1

# Human postprandial responses to food and potential for precision nutrition

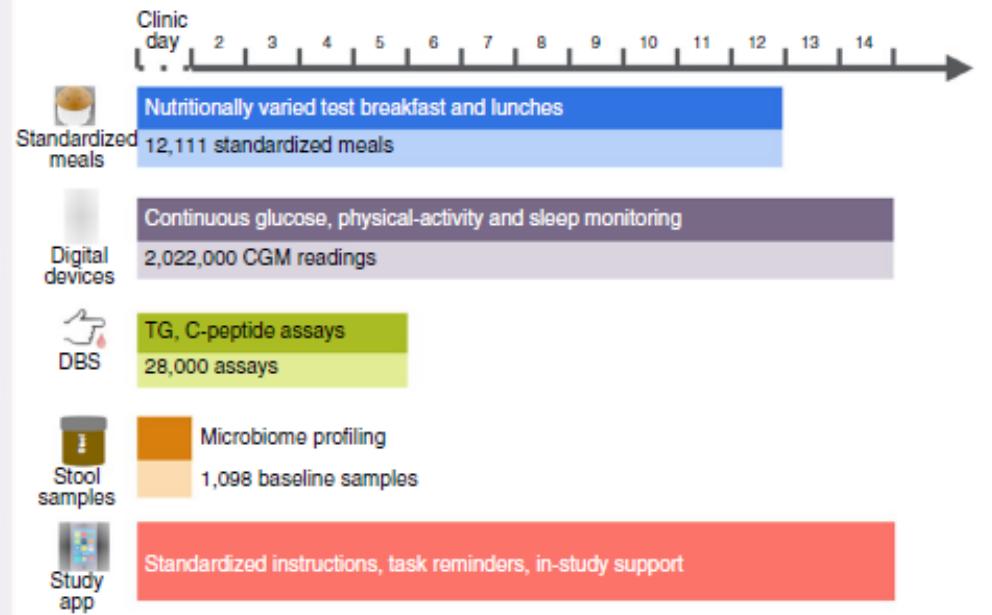
## Study design

## Baseline clinic visit (day 1)

Controlled time (min)

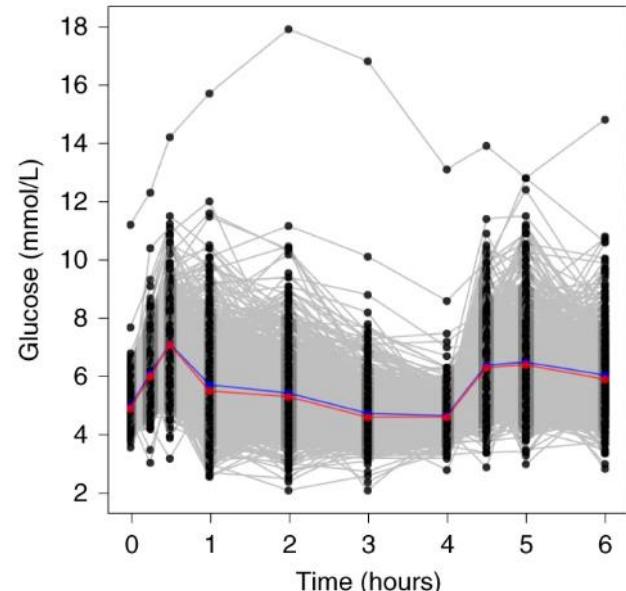
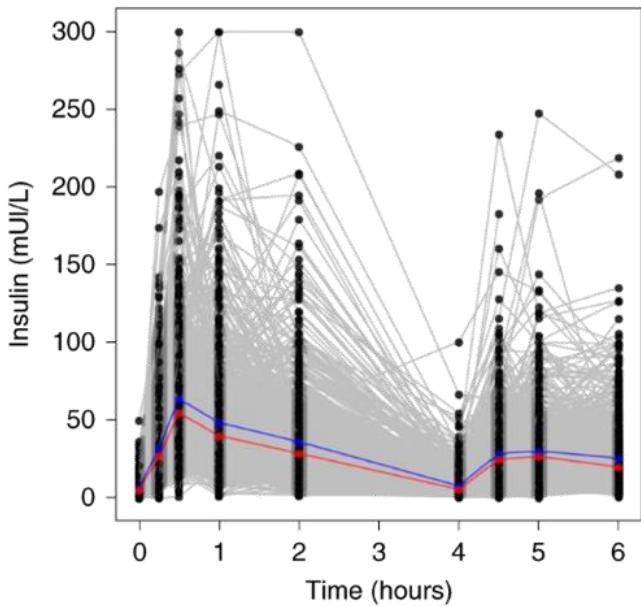
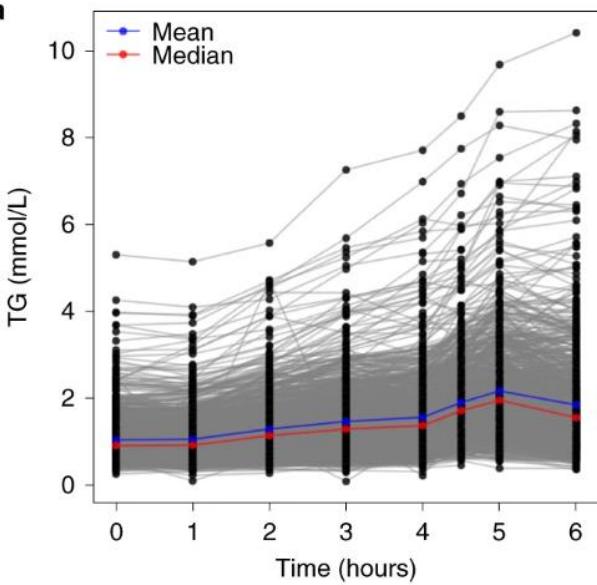


## Home phase (days 2–14)



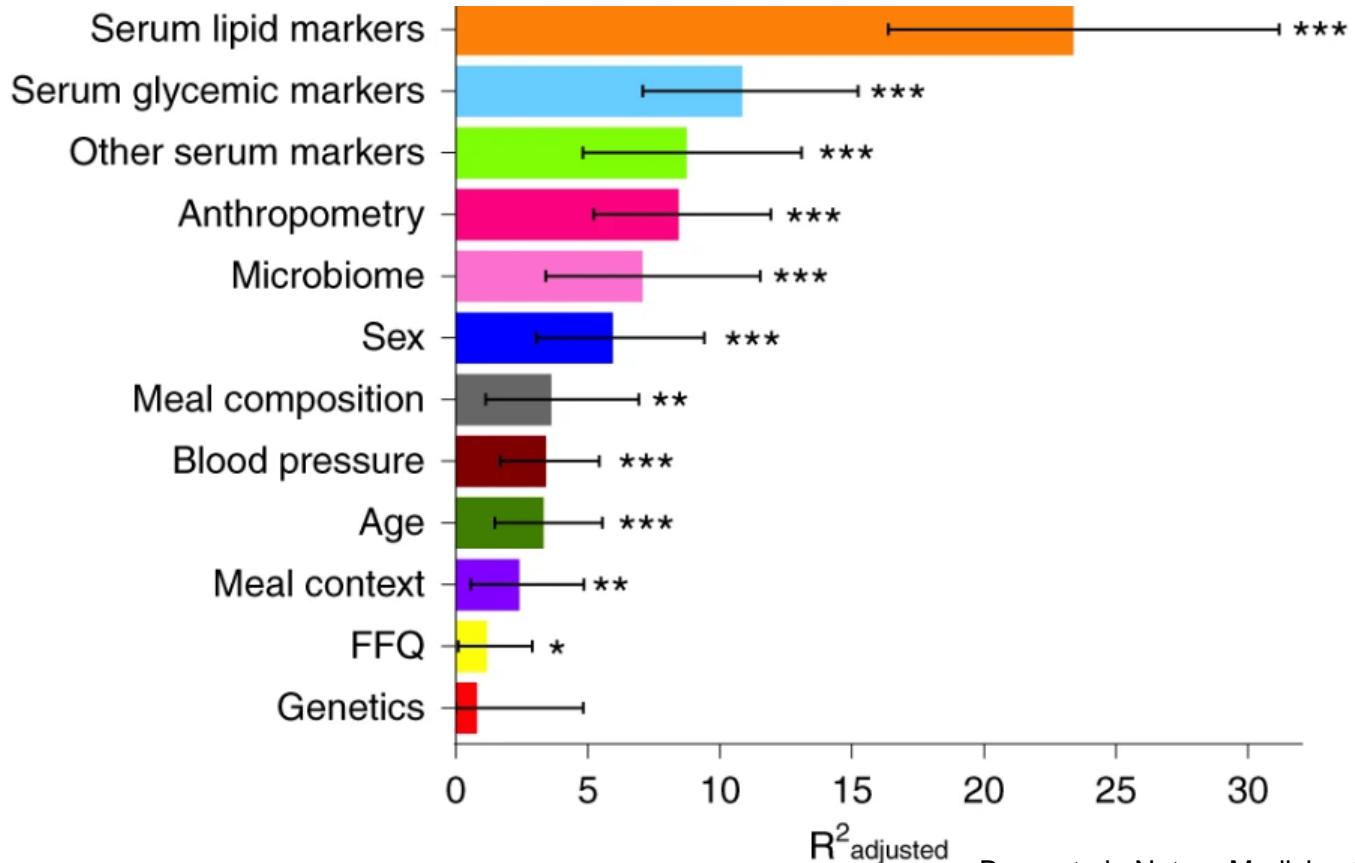


# Large variation in postprandial responses



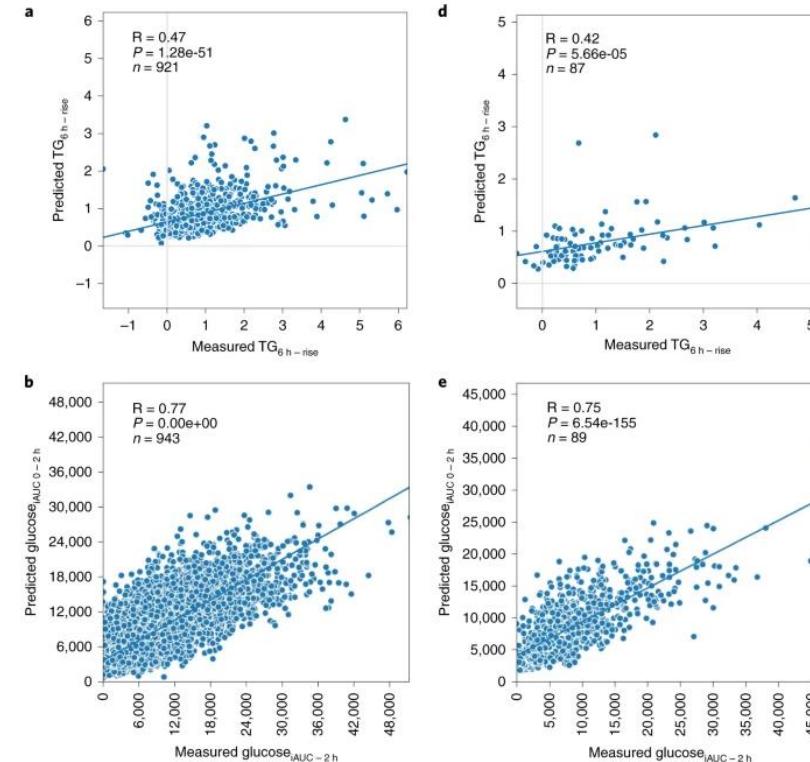


# Variation explained by different variables in predicting postprandial responses of TG



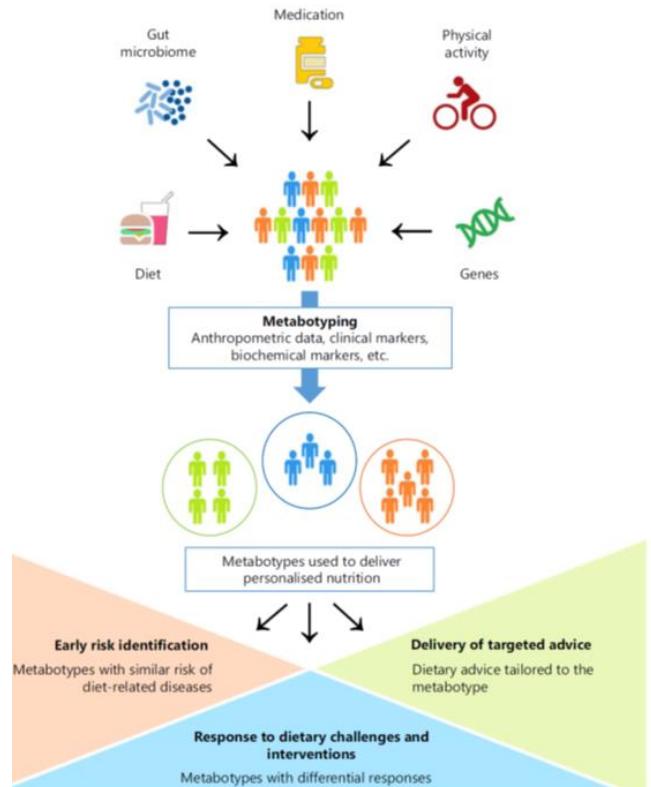
# Developed a ML model that predict TG and glycemic response to food intake

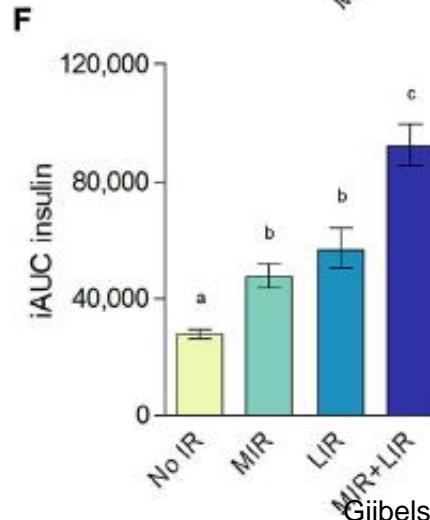
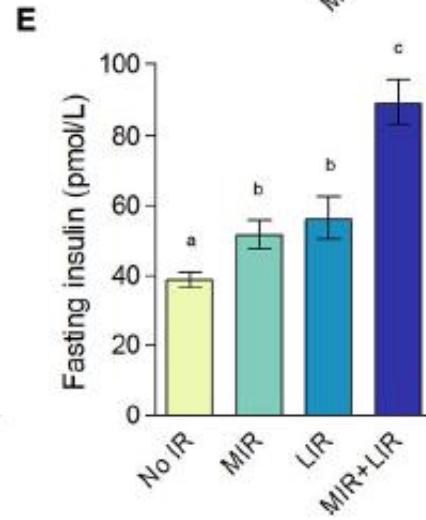
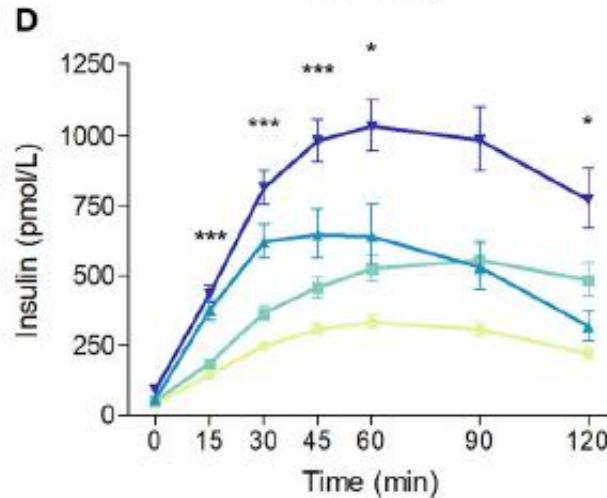
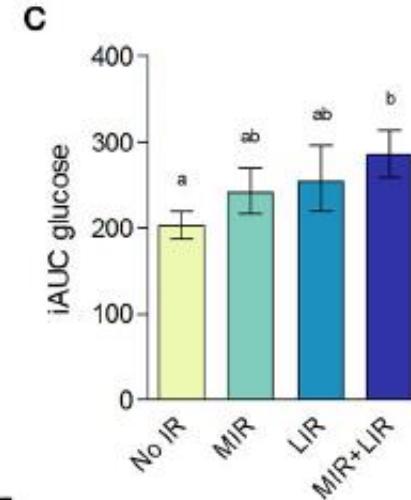
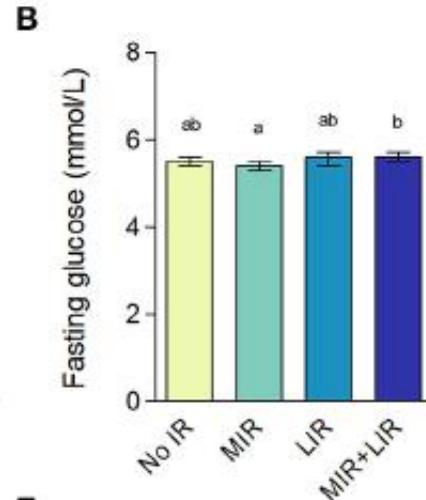
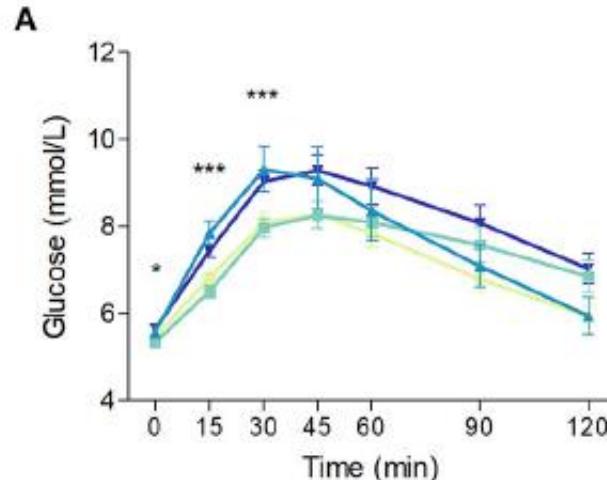
Fig. 4: Machine-learning models fitted to postprandial measures.





# Precision nutrition and possibilities

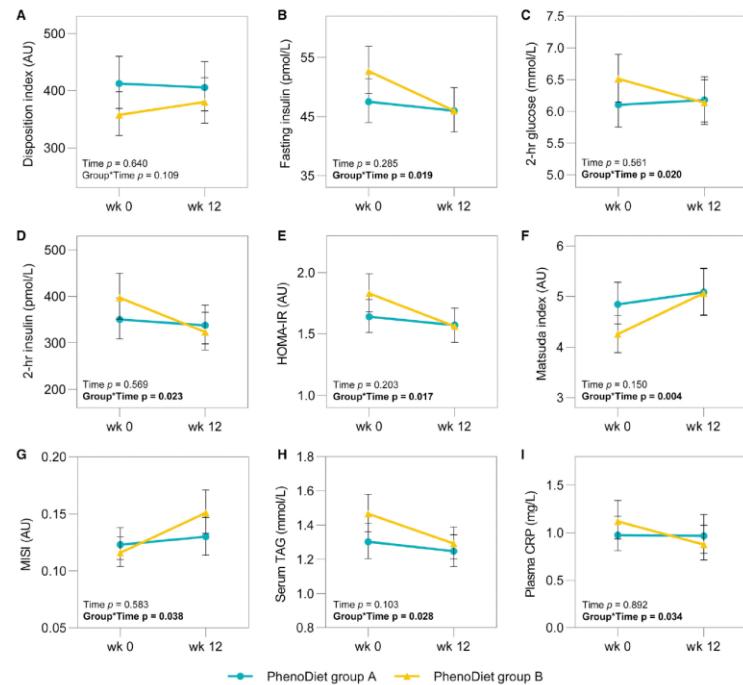
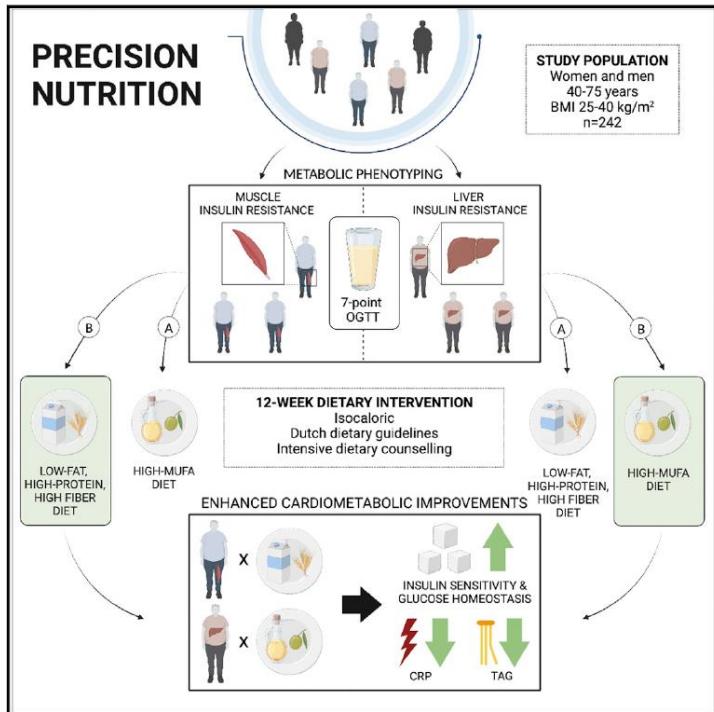






NUTRIOME

# Cardiometabolic health improvements upon dietary intervention are driven by-tissue specific IR phenotype





# Precision nutrition and ultimate goal



- The goal is to provide a more effective ways to prevent and treat disease by providing more accurate and targeted nutrition strategies.
- Precision nutrition assumes that each person may have a different response to specific foods and nutrients, so that the best diet for one individual may look very different than the best diet for another.
  - highlighting the need for better understanding of the determinants of inter-individual differences in response to food
  - Molecular insight
    - Understand the mechanisms behind the different responses

# Increase competence in multi-omics and data-driven precision nutrition for better prevention strategies

