

Ionomics, Microbial metabolome, Nutrikinetics

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Ionome refers to the mineral nutrient and trace element composition of an organism, representing the inorganic component of cellular and organismal systems

Ionomics is the study of elemental accumulation in living systems using high-throughput elemental profiling

Extensively applied in plants, recently extended to soybean, mouse and human cell lines.

BRIEFINGS IN FUNCTIONAL GENOMICS, VOL 9, NO 2, 149-156

Ionomics: The functional genomics of elements

Ivan Baxter

Advance Access publication date 16 January 2010

Ionome

Exposome (environmental exposures, nutrition)

Phenome

Organic molecules
(DNA, RNA, proteins, metabolites)

Metallo-molecules
(proteins, metabolites)

Elements & ion complexes

Genomics, proteomics,
metabolomics

Metallo-
proteomics/metabolomics

Ionomics

Genome/Proteome/Metabolome-element interactions

Nutritional status

Element-element interactions

Occupational health

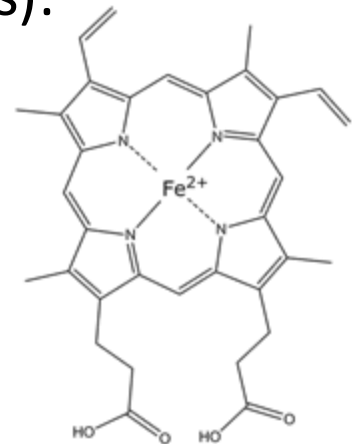
Minerals and elements are involved in numerous essential biological functions, e.g.

- ... signal transduction (**Na, K**),
- ... serve as electrolytes (**Na, Cl**),
- ... key components of proteins, DNA and RNA (**S, P, Mg**),
- ... structural and enzymatic function in proteins (**Fe, Zn**)

More than one-third of all proteins are metalloproteins

In many enzymes, metals are essential to maintain catalytic function (cofactors):

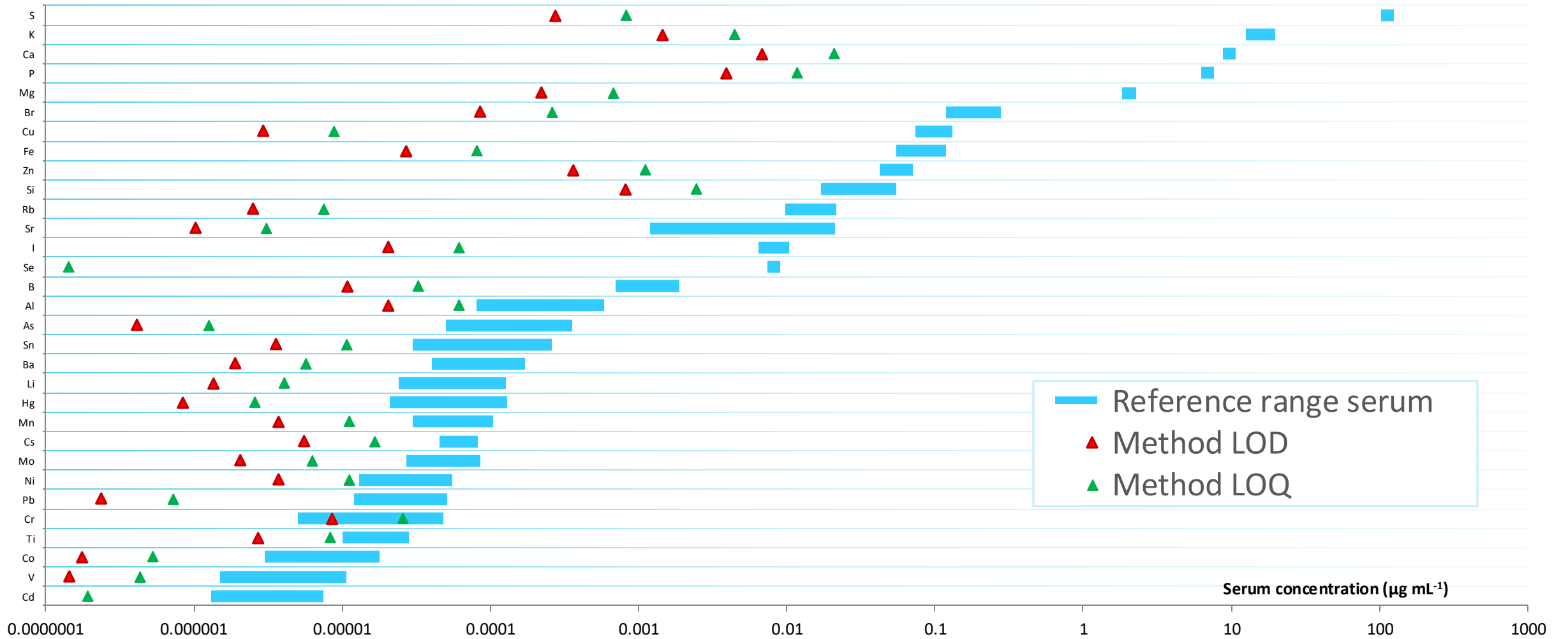
- ... hemoglobin (**Fe**),
- ... RNA- DNA polymerase (**Zn**),
- ... superoxide dismutase (**Mn, Zn, Cu**),
- ... xanthine oxidoreductase (**Mo**),
- ... glutathion peroxidase (**Se**)





SWISS NUTRITION & HEALTH FOUNDATION

From ultra trace analysis to major elements



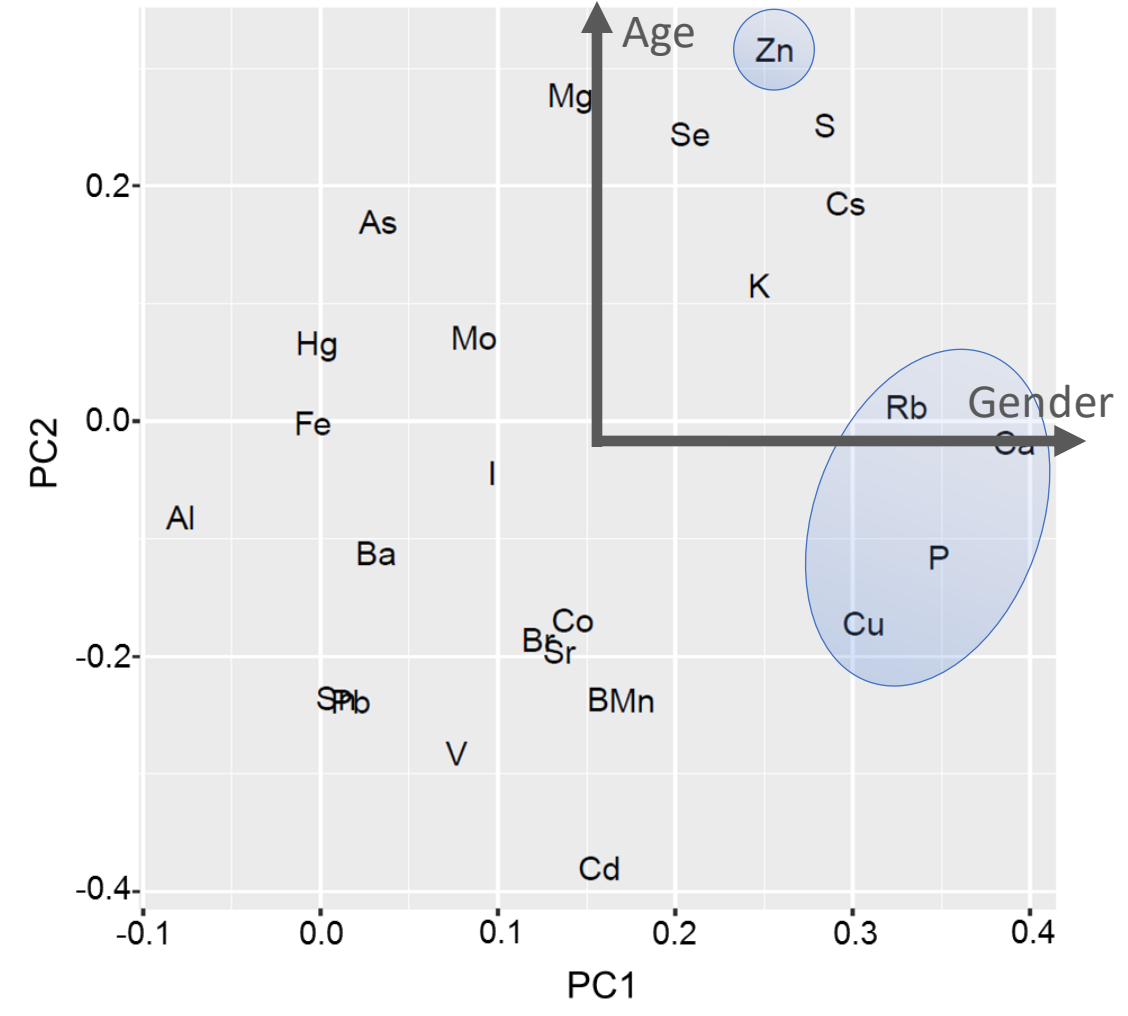
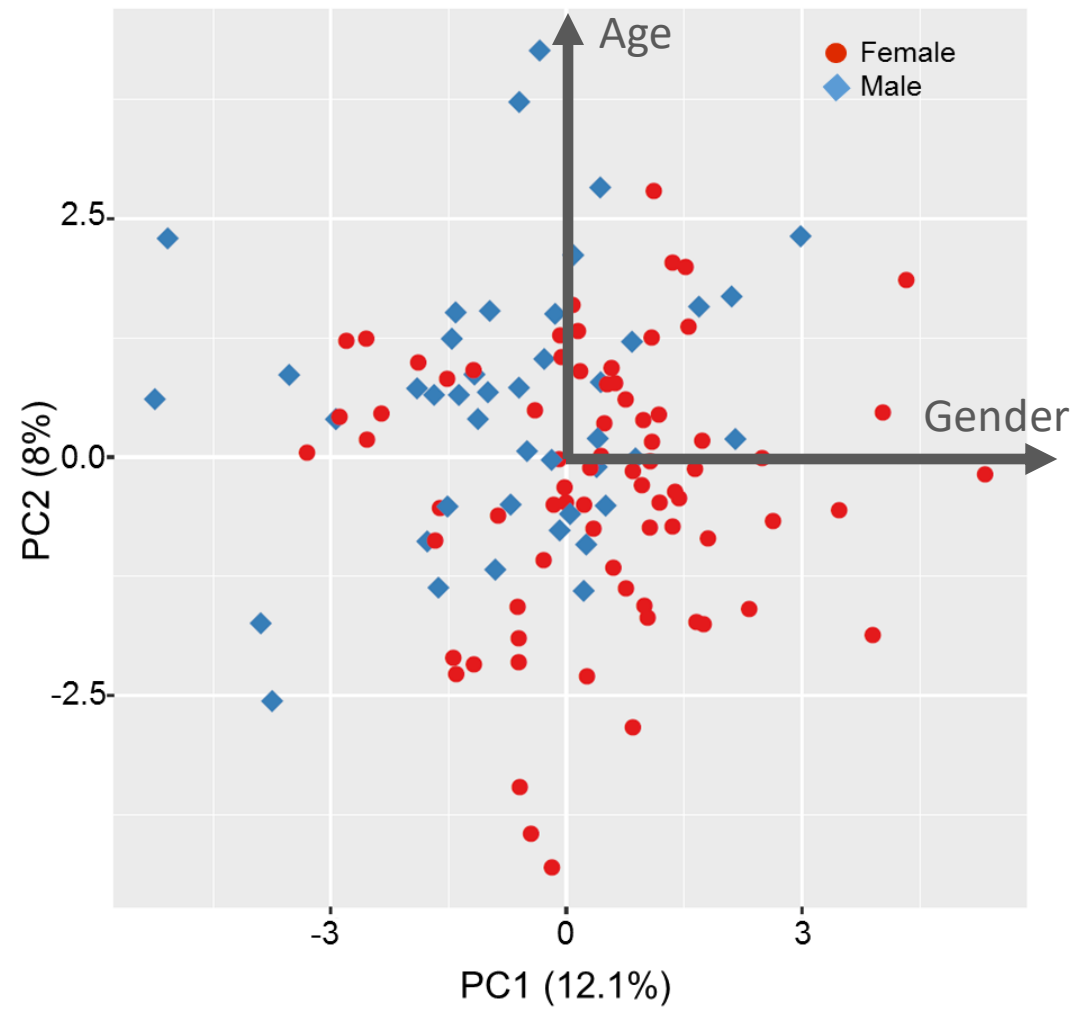
— Reference range serum
▲ Method LOD
▲ Method LOQ

- Study: “Comprehensive biomarker analysis of serum/plasma and CSF”
- Clinical trial aiming to identify new biomarkers of cognitive health that are more easily accessible and non-invasive.
- Determination of **serum ionome** and **clinical routine parameters**

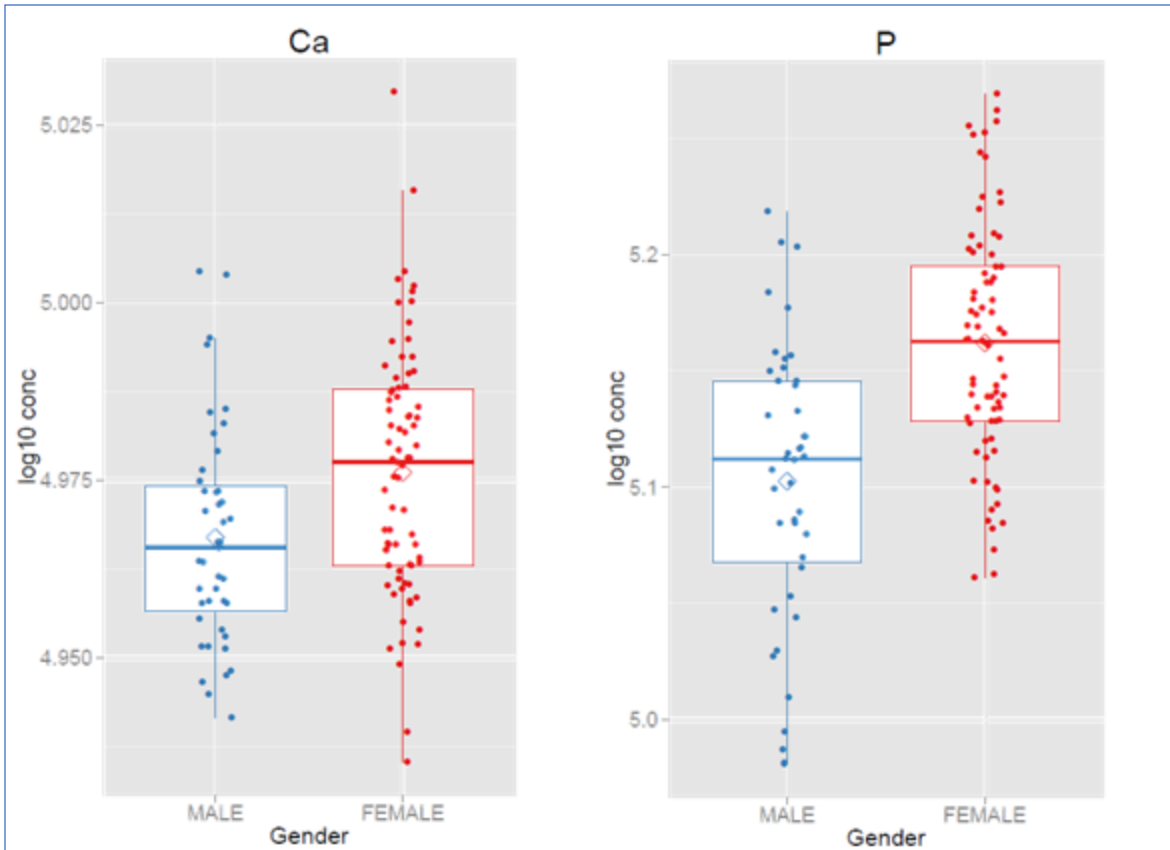
Study population:

- 120 Serum samples from 120 community dwelling older adults
- Mean age of 70.4 years (standard deviation SD = 7.9)
- 43 males and 77 females
- Sample collection after overnight fasting

Principal component analysis of the human Serum Ionome

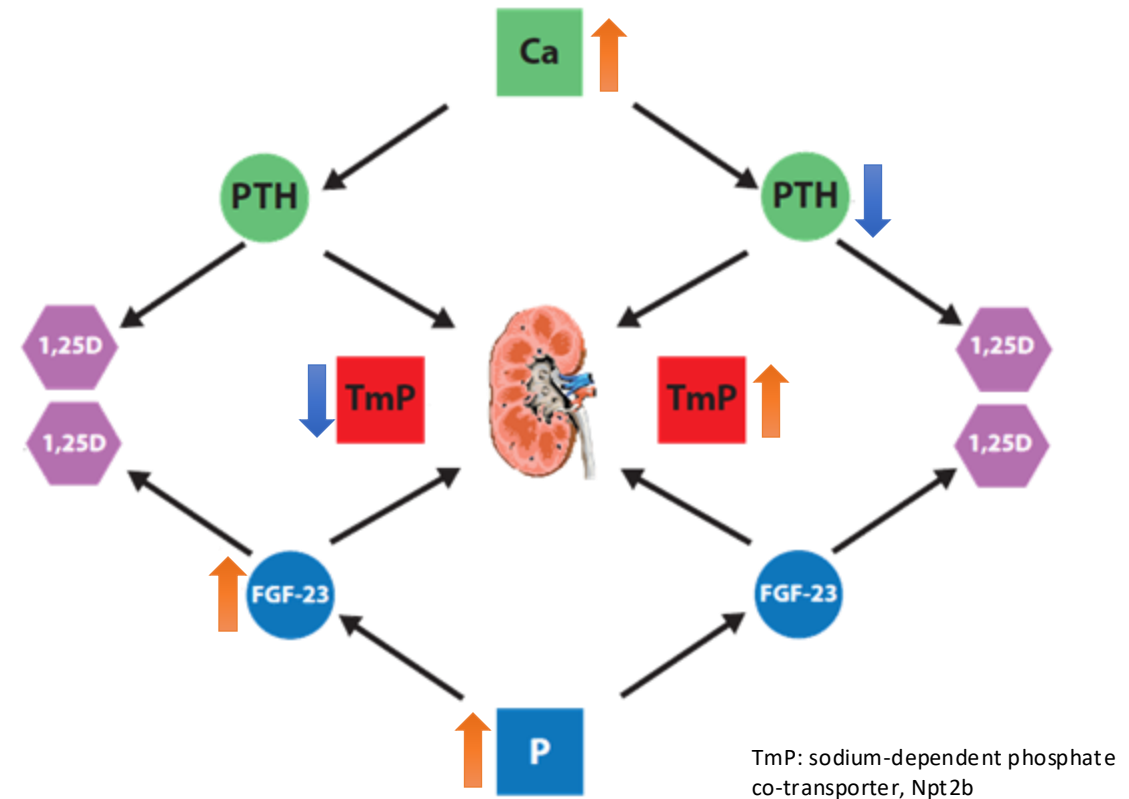


Calcium and phosphate homeostasis



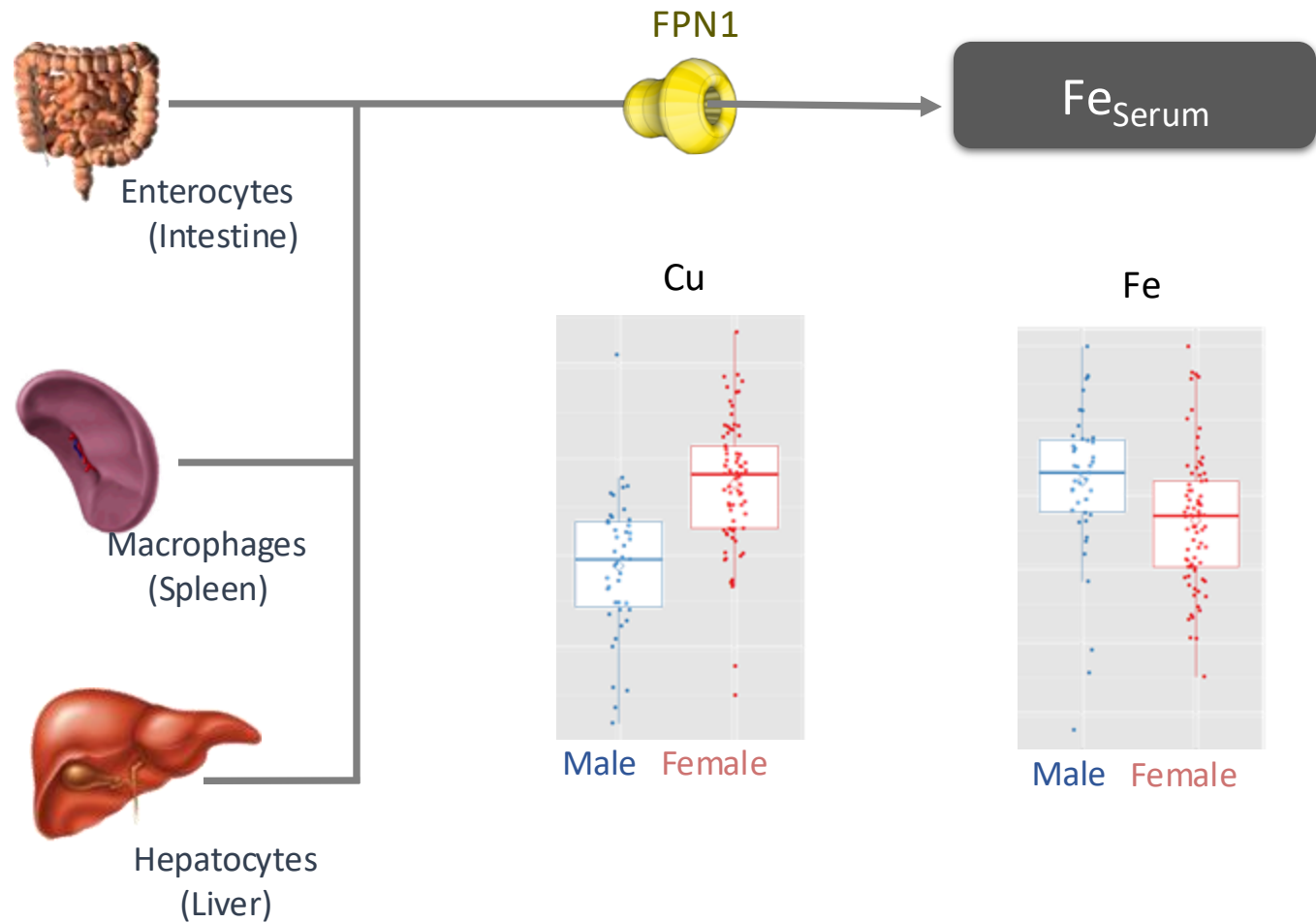
T. Konz, *et al.* ICP-MS/MS-based Ionomics. J. Proteome Res. 2017

- Increased levels of Ca and P in females could be explained by gender-specific bone-remodeling with slightly bone resorption rate in females

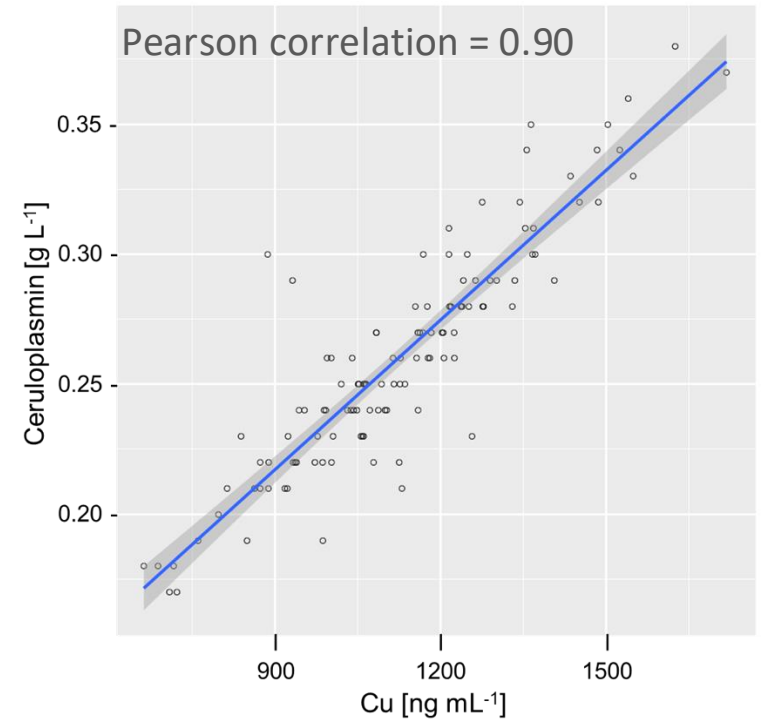


TmP: sodium-dependent phosphate co-transporter, Npt2b

Gender-specific ionome signature of Cu and Fe



Fe-stocks



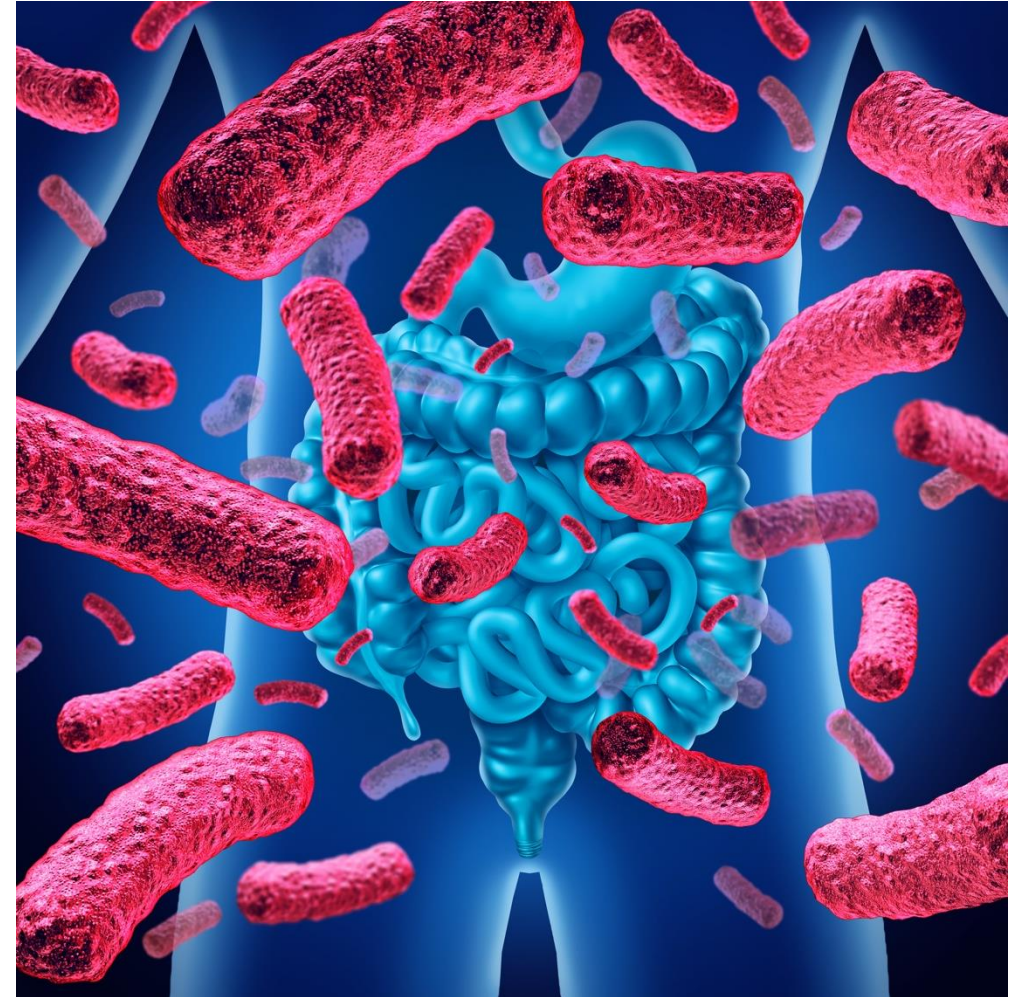
Zinc shows age-related Ionic Variance

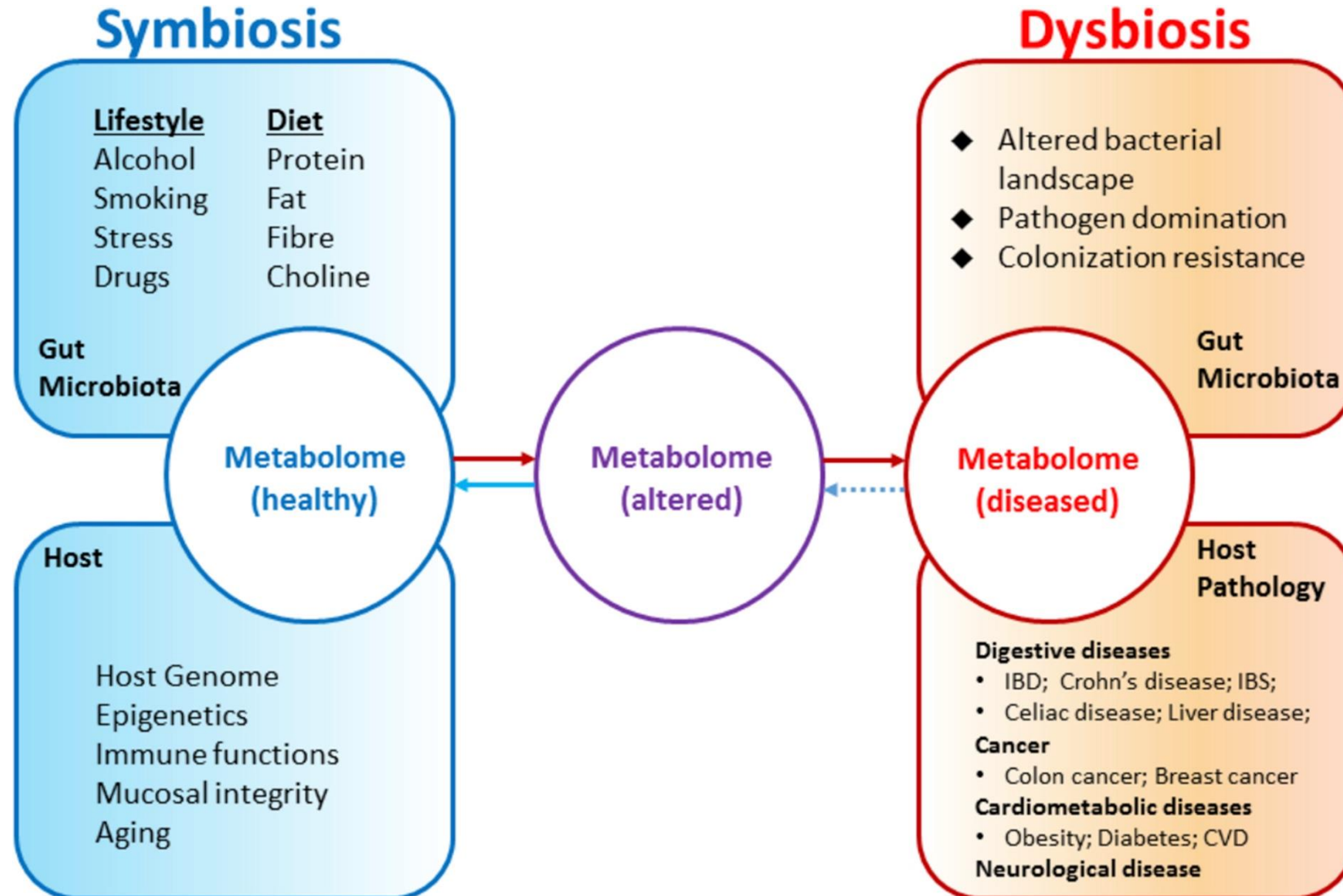
- Negative correlation with age might be related to lower intake/absorption or altered compartmentalization.
- **Cu/Zn ratio:**
$$\text{Cu/Zn}_{\text{Females}} = 1.55$$
$$\text{Cu/Zn}_{\text{Males}} = 1.27$$
- Potential biomarker of inflammatory and/or nutritional biomarker of mortality in elderly*.
- Driven by Cu compartmentalization related to aging-associated inflammatory status.



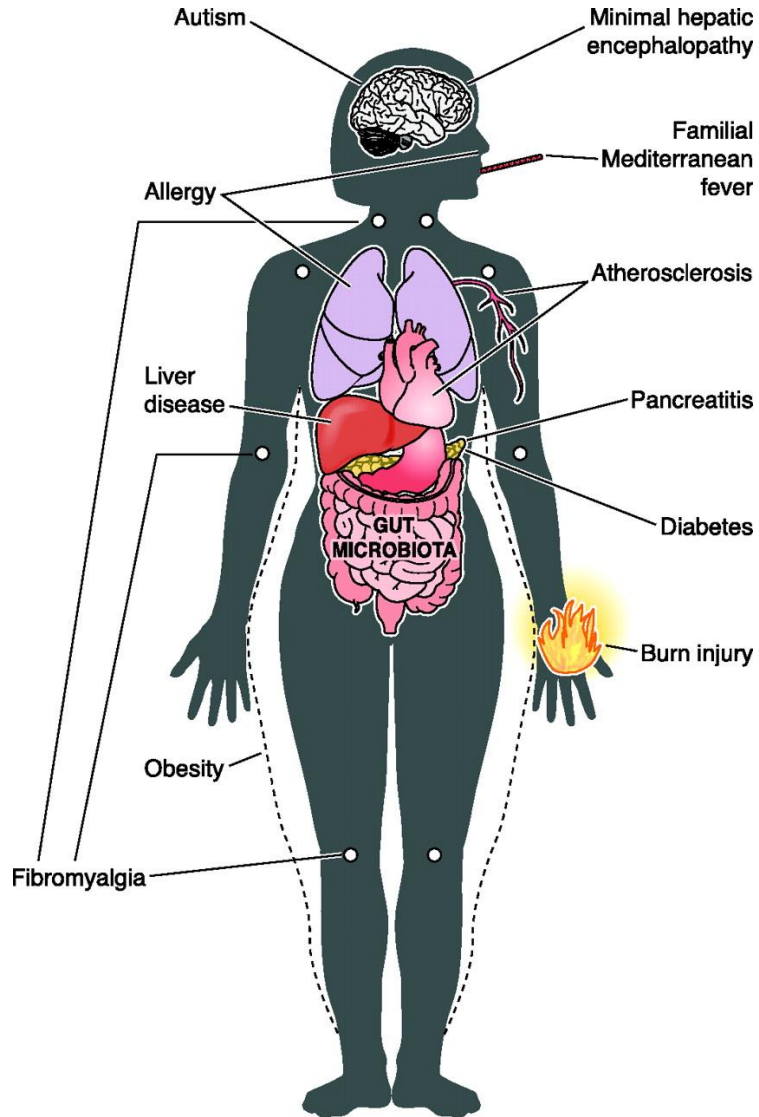
Why measuring microbial metabolome?

- Assess the microbiome dynamics (functional ecology) in health and disease conditions
- Identify and/or quantify microbiome-specific metabolite(s)
- Study the mechanism of the role of gut microbiota in:
 - Pathophysiological processes
 - Developmental biology
 - Nutritional intervention





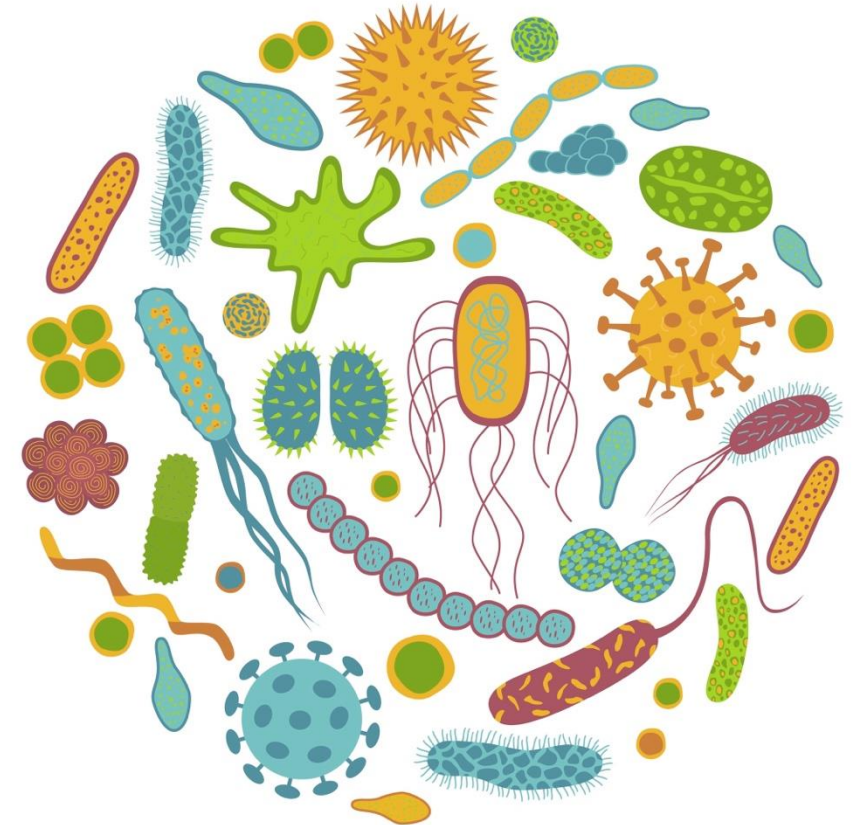
Association of microbiota with pathophysiological processes



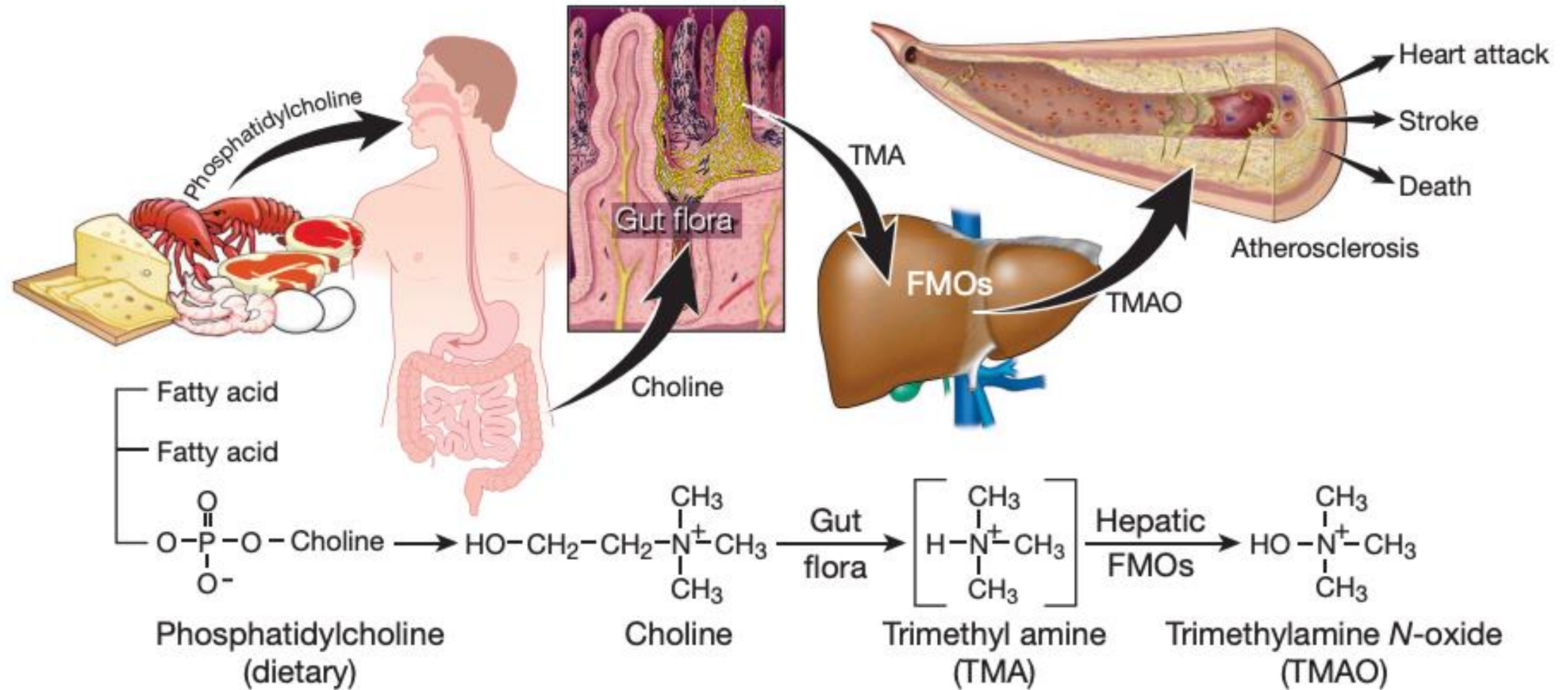
- **Brain** (autism,..)
- **Immune system** (allergies, virus/bacterial infections...)
- **Cardiovascular** (atherosclerosis, blood pressure)
- **Gastrointestinal** (pancreatitis, non alcoholic steatohepatitis, non alcoholic fatty liver, inflammatory bowel disease)
- **Metabolic health** (insulin resistance, type 2 diabetes, obesity)

...and more to be discovered !

- Short chain fatty acids (propionate, butyrate...)
- Organic acids (benzoate, hippurate...)
- Vitamins (B9, B2, B12, K2...)
- Bile acids (taurodeoxycholate...)
- Hydroxycinnamic acids... from polyphenols
- 1,3-propanediol from lipids (glycerol...)
- Phenols, indoles (amino acids)
- Biogenic amines (amino acids)

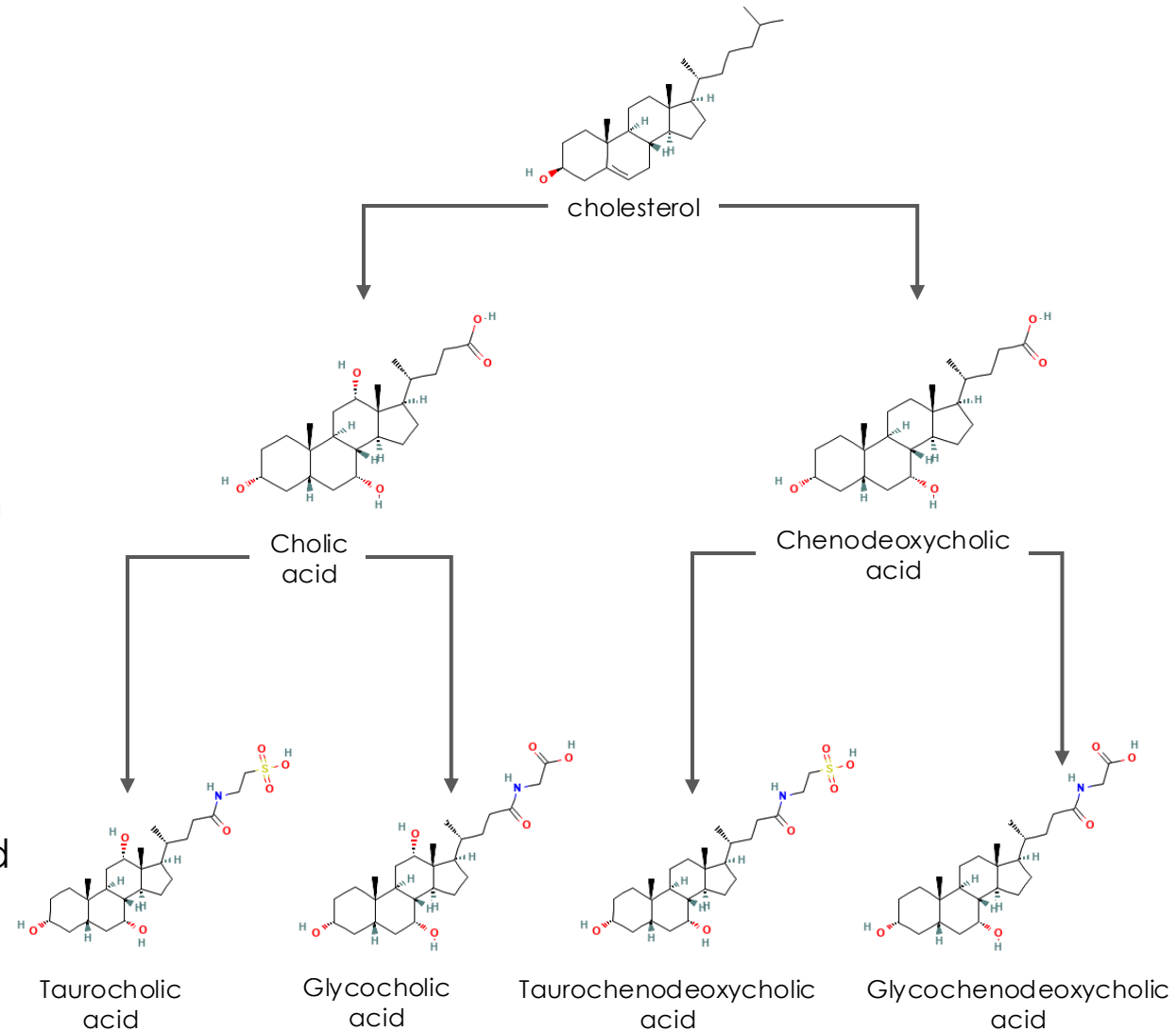


Host-microbiome nutrient co-metabolism



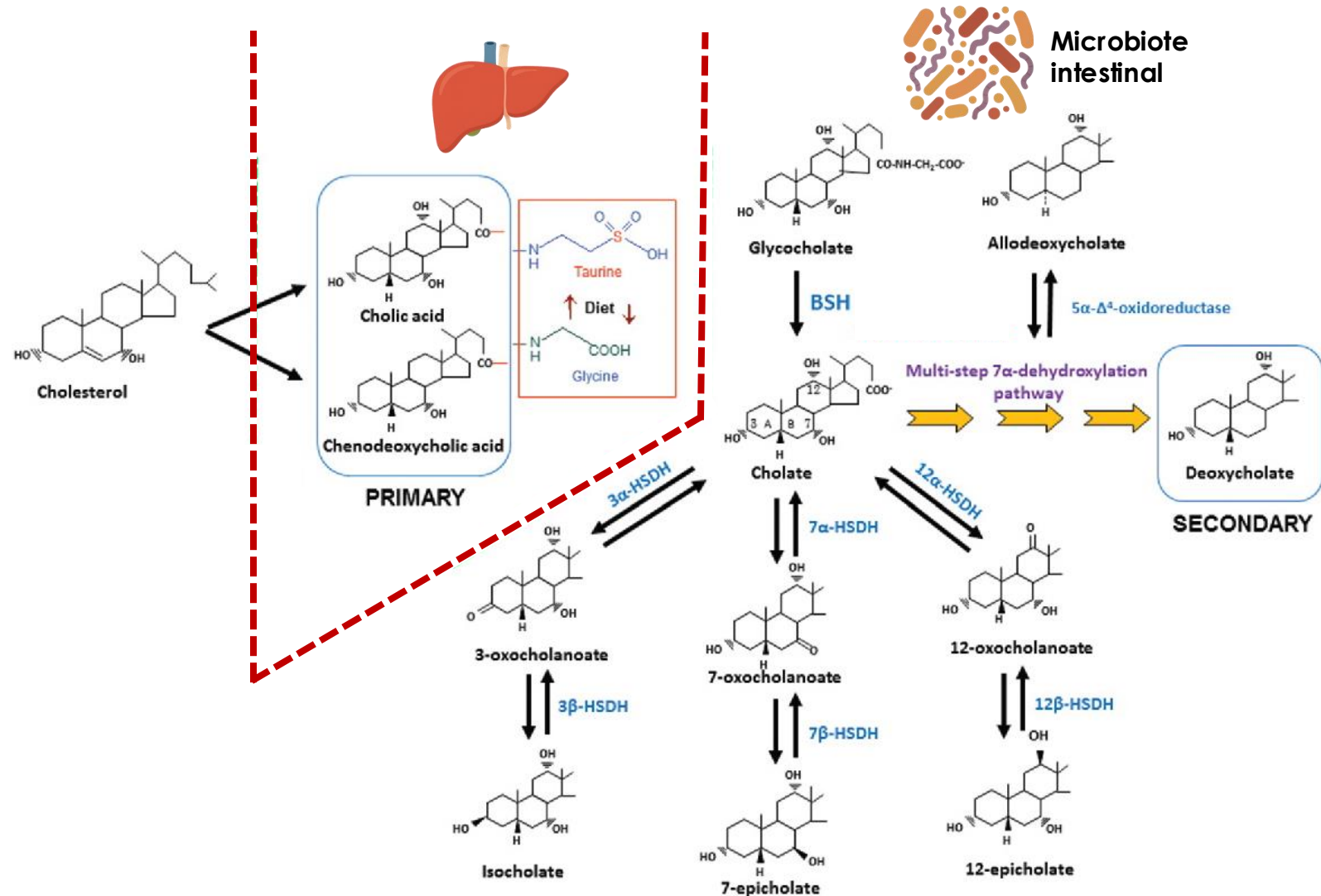
Primary bile acids/salts

- Synthesized in the liver from cholesterol and conjugated to taurine and glycine (primary salts)
- Bile salts are amphiphilic molecules:
 - Hydrophilic side (hydroxyl groups, glycine/taurine conjugated carboxyl)
 - Hydrophobic face (steroidal core)
- Ensure the emulsification of fat droplets in the small intestine (→ decrease in the surface interfacial tension of lipid droplets)
- Emulsification:
 - Increases the exchange surface between pancreatic lipase and fats (→ promotes lipolysis)
 - Promote the integration of lipolysis products and fat-soluble nutrients (vitamins A, E, D, K) into mixed micelles (→ allowing their transport from the intestinal lumen through the intestinal mucosa to the enterocytes)



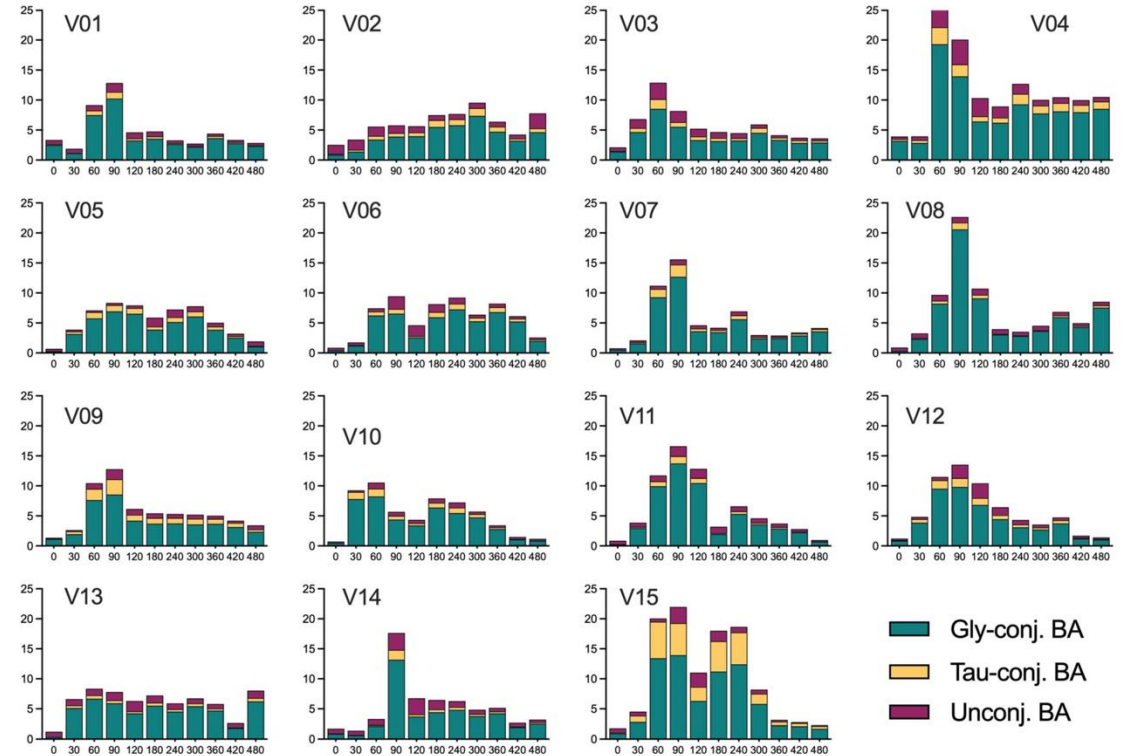
Secondary bile acids

- Synthesis of primary bile acids in the liver and biotransformations of bile acids carried out by intestinal bacteria.
- The main quantitative and irreversible reactions carried out by gut bacteria include:
 - Hydrolysis via the microbial hydrolysis of Bile Salt Hydrolase (BSH) of conjugated bile acids
 - 7 α -dehydroxylation of cholic acid and chenodeoxycholic acid
 - More than 20 bile acid metabolites can be produced from primary bile acids by the gut microbiota



Inter-individual variability of bile acids

- Study on 15 healthy men subjected to three challenges: 36-hour fasting; OGTT, OLTT (emulsion containing 50 g of long-chain triglycerides per 100 ml)
- Plasma bile acid analyses
- During OLTT: increased bile acids conjugated to glycine and taurine
- Bile acid profiles vary greatly from individual to individual, depending on genetic and metabolic factors.
- The gut microbiota is an important determinant of inter-individual variability through its role in changes in primary bile acids (deconjugation, etc.).



Fiamoncini J et al. Front Nutr. 2022;9:932937.
doi:10.3389/fnut.2022.932937

Changes in bile acids by the microbiota can affect the formation of mixed micelles, thus the process of digestion of fats and fat soluble nutrients

These modifications also modulate various metabolic processes (gluconeogenesis, lipogenesis, inflammation) via their interaction with receptors such as TGR5 and FXR.

Metabolomics pipeline for gut microbiome

Metabolic profiles of 178 microorganisms

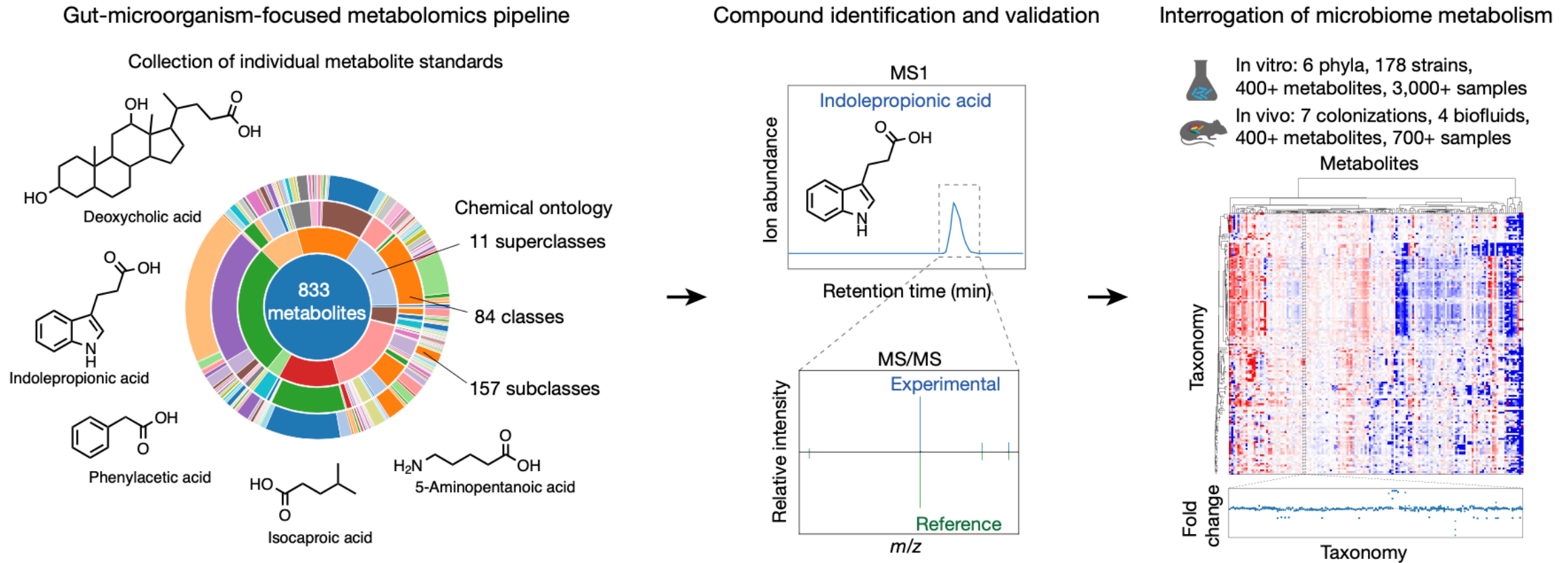
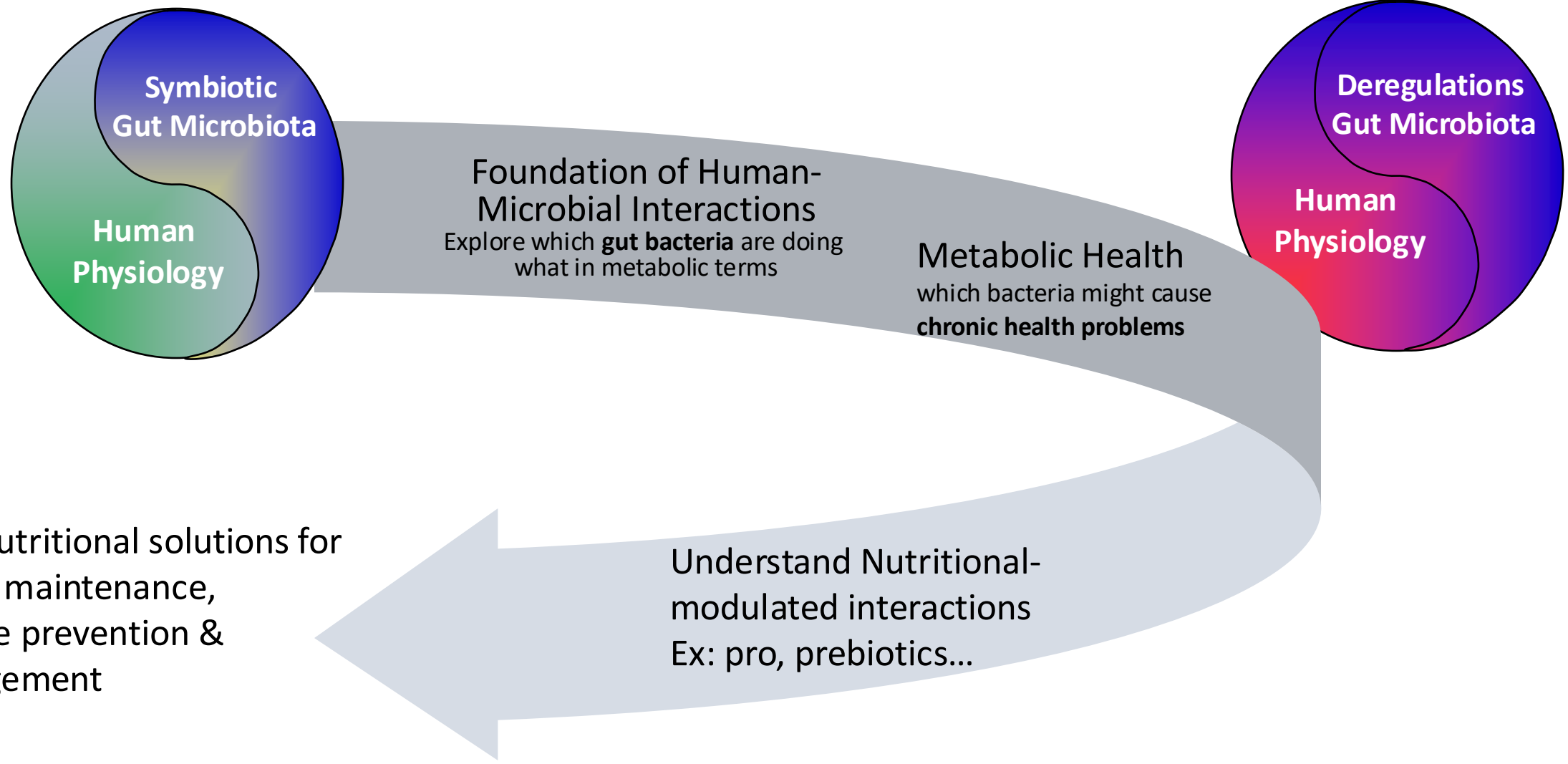


Fig. 1 | A microbiome-focused metabolomics pipeline enables the mechanistic interrogation of microbiome metabolism. Schematic of our metabolomics workflow, consisting of mass-spectrometry reference library construction and validation, producing in vitro and in vivo metabolomic

profiles across diverse sample types. Our entire dataset is publicly accessible through a web-based, interactive Metabolomics Data Explorer (https://sonnenburglab.github.io/Metabolomics_Data_Explorer).

Scientific approaches to deciphering function of gut microbiome

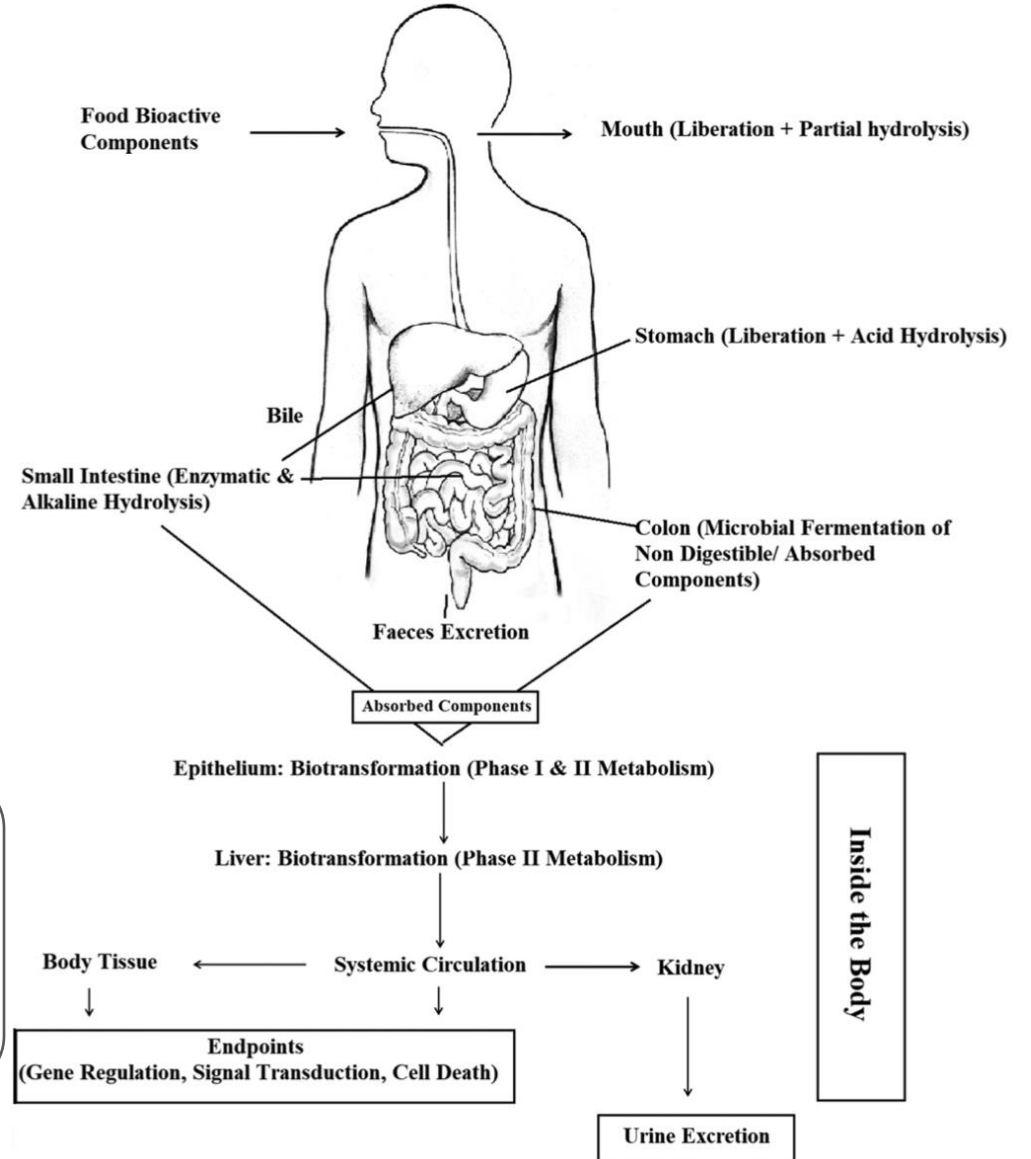


New nutritional solutions for health maintenance, disease prevention & management

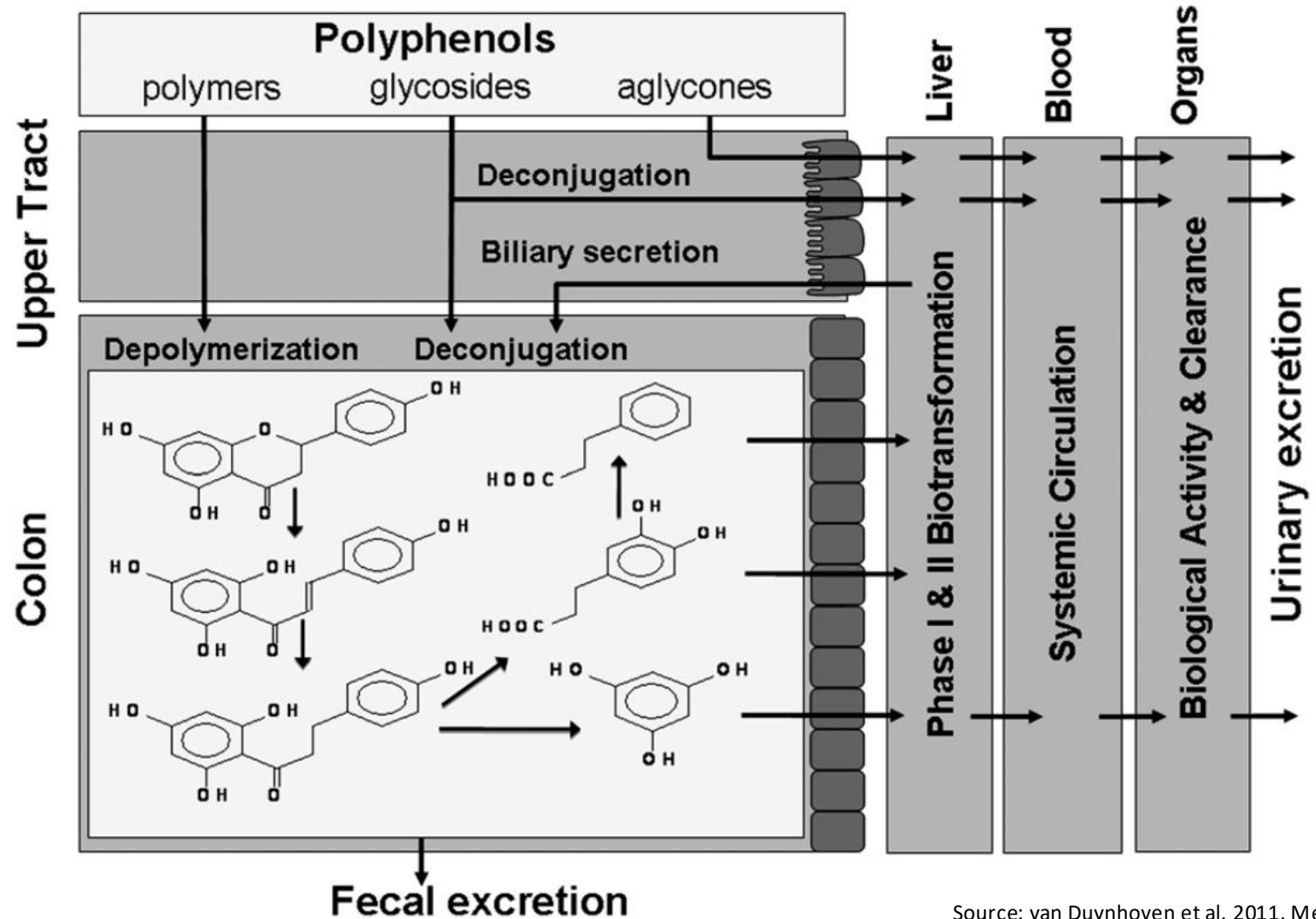
Nutrikinetics Time-dependant analysis of nutrient



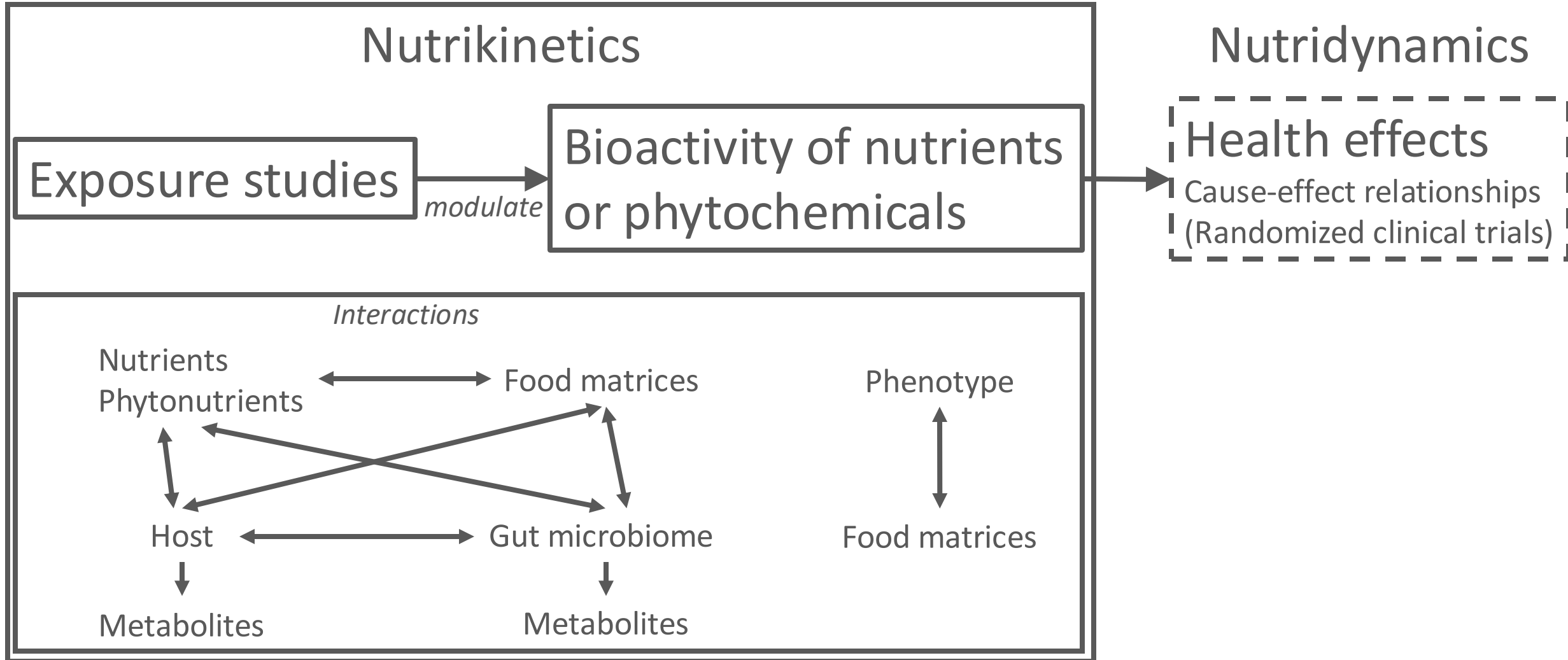
Phytonutrients



Polyphenol absorption journey



Source: van Duynhoven et al. 2011. Metabolic fate of polyphenols in the human superorganism. Proceedings of the National Academy of Sciences of the United States of America, 108, 4531e4538.

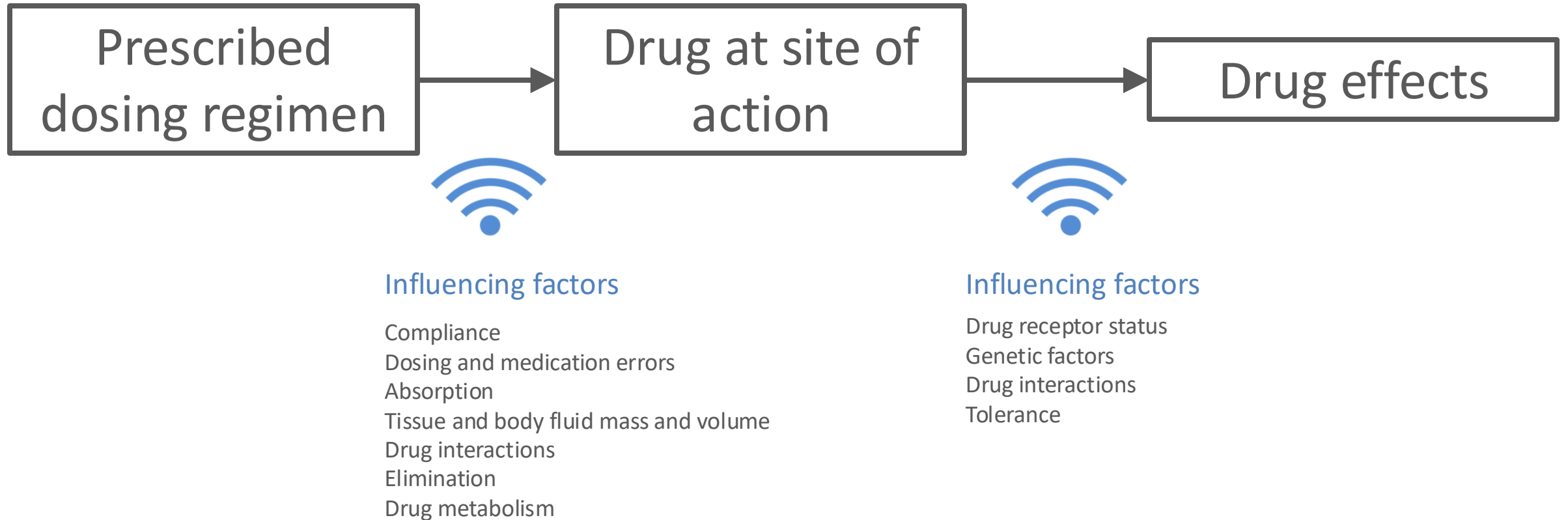


“Nutrikinetics is an extension of the classical pharmacokinetic concept with explicit model adaptations. The concept relies on integrated deployment of metabolic profiling, multi-level data analysis and population-based single component modelling.”

“Application area of pharmacokinetics that studies the absorption, distribution, metabolism and excretion (ADME) of food compounds or dietary supplements within the human superorganism, including the interactions between the host metabolome and the gut microbiome. It considers the compositional complexity of dietary ingredients, background diet and inter-individual variation and integrates study design, metabolic profiling, variable selection and NLMEM.”

Pharmacokinetics

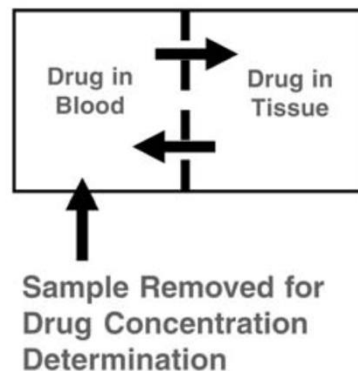
Pharmacodynamics



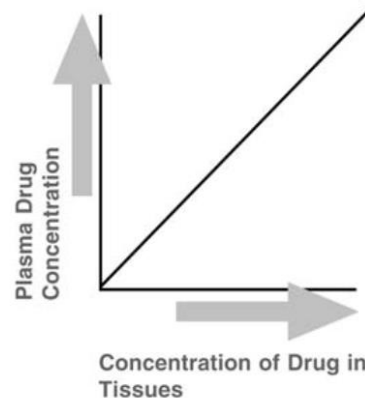
The study of the time course of drug and metabolite levels in different fluids, tissues, and excreta of the body, and of the mathematical relationships to develop models to interpret such data

Gibaldi, M., & Perrier, D. (2007), *Pharmacokinetics*, (2 ed.) Vol. 15 New York: Informa Healthcare.

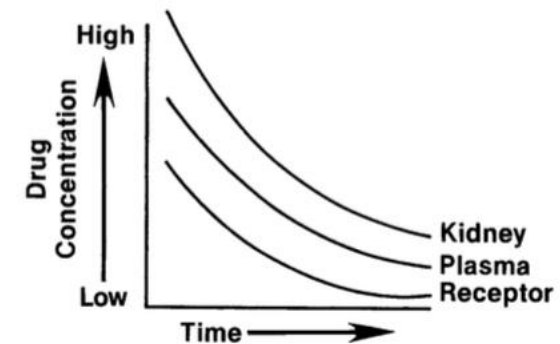
Kinetic homogeneity: describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect



Blood is the fluid most often sampled for drug concentration determination



Relationship of plasma to tissue drug concentrations

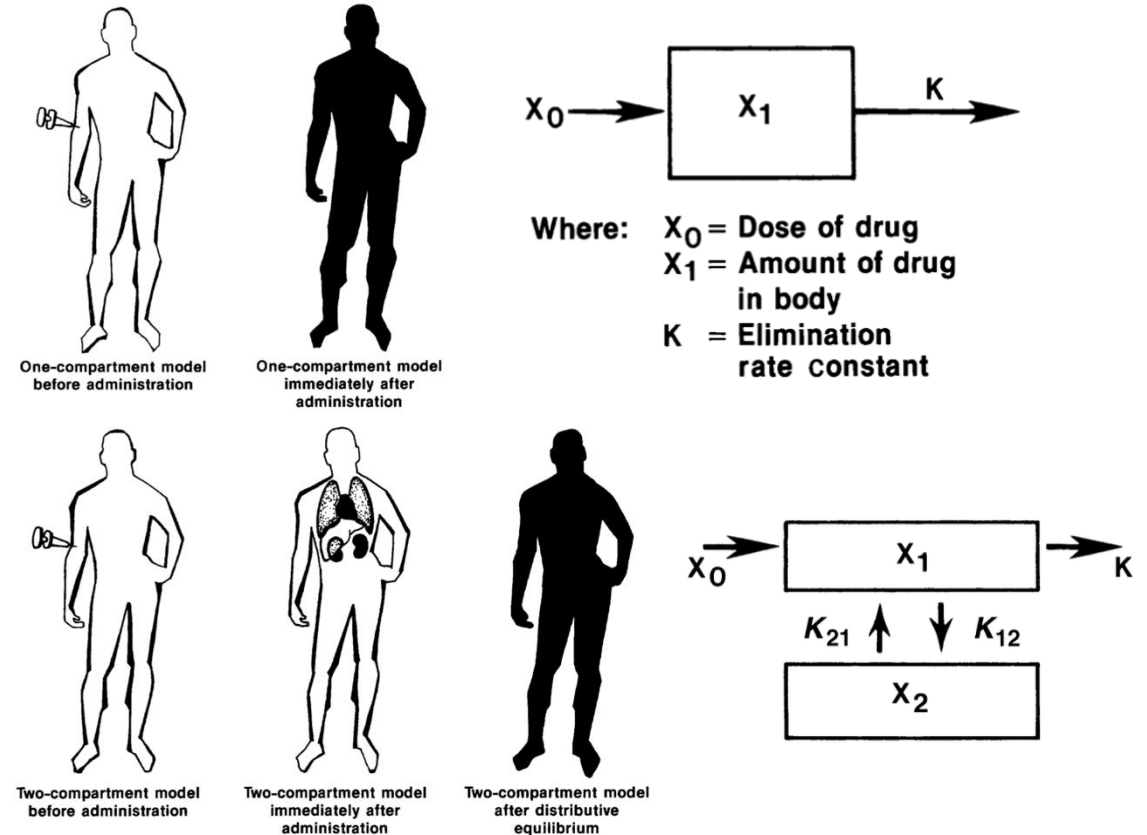
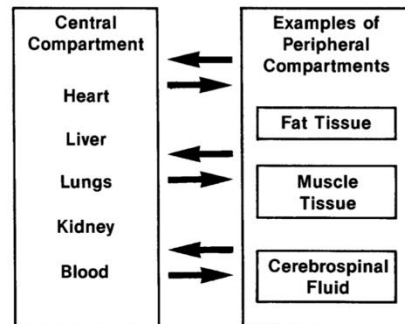


Simplified plot of the drug concentration versus time profile after an intravenous drug dose

Mathematical models are used to simplify complex ADME processes to predict drug behavior in the body

Compartmental models

- The compartments do not represent a specific tissue or fluid but a group of similar tissues or fluids (in terms of drug distribution)
- One-, two- or multicompartments
- They are deterministic (the observed drug concentrations determine the type of compartmental model required to describe the drug pharmacokinetics)
- Highly perfused organs (heart, liver, kidneys) often have similar drug distribution patterns may be considered as one compartment
- Blood (plasma), heart, lungs, liver and kidneys is usually referred to as the central compartment (highly perfused compartment)
- Fat tissue, muscle tissue, cerebrospinal fluid is considered the peripheral compartment



The first step in understanding nutrient causal effect (nutridynamics) on health:

- Absorption
- Distribution
- Metabolism
- Excretion

Relative or absolute Bioavailability Kinetics

Bioavailability:

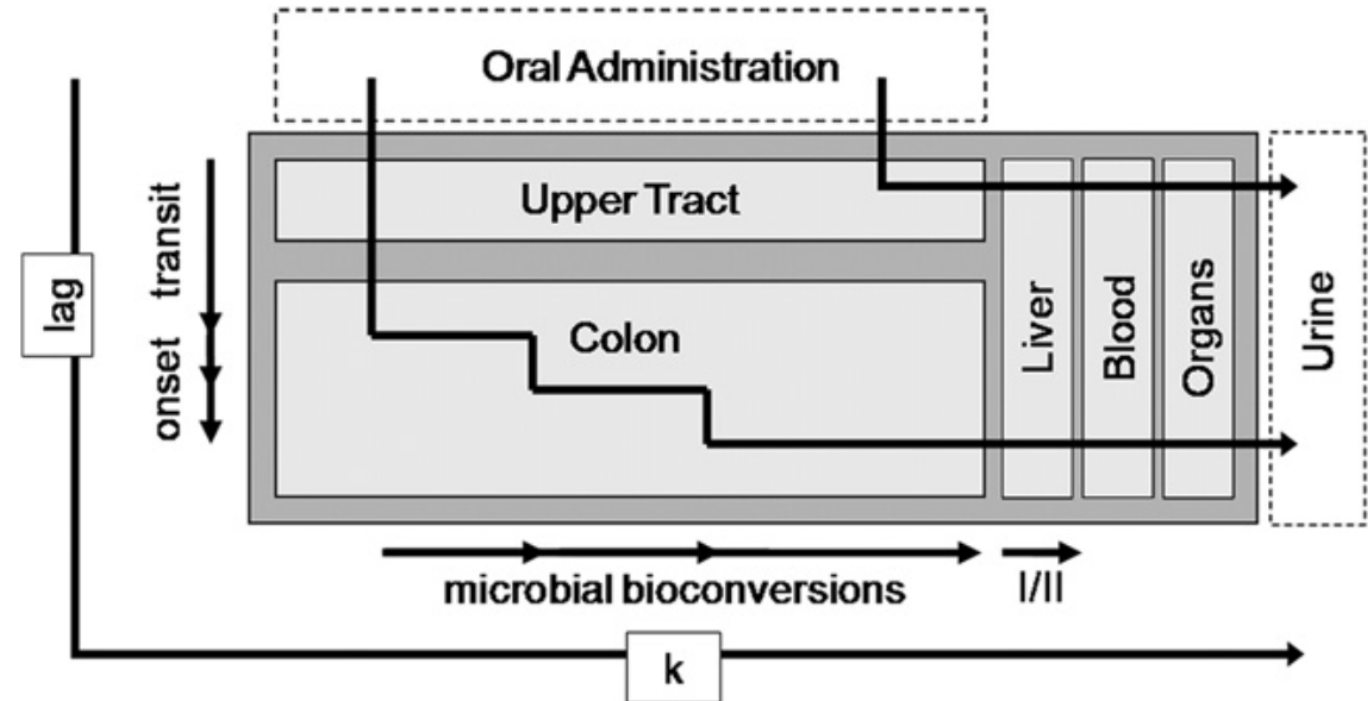
- The fraction of nutrient absorbed as such as the systemic circulation
- The proportion of a substance which enters the circulation when introduced into the body and so is able to have an active effect
- Measured by calculating the area under curve (AUC) of the nutrient concentration time profile

Important challenges vs. pharmacokinetics

- Nutrients are occurring as complex mixtures (foods) vs. single drug compound
- Food/nutrient intakes doesn't mean complete nutrient exposure to the body:
 - Variation in nutrient accessibility: occurrence of antinutrients (phytic acid...) in the food, food matrix-nutrient interaction, digestibility...
 - Variation in nutrient metabolism and bioavailability: intra- and inter-individual variabilities

One-compartmental model:

- Human = one compartment with single nutrient inflow and outflow
- The most used model in nutrikinetics



Lag: finite time taken for a substance to appear in systemic circulation following administration (related to absorption)

K (rate constant): rate at which a drug is removed from the human system

References:

- J.P.M. van Duynhoven et al. Trends in Food Science & Technology 26 (2012) 4-13
- E. J. van Velzen et al. Journal of Proteome Research 8 (2009) 3317e3330

- Determine relevant marker of intake
- Reduction / elimination of confounding factors
 - Factors affecting biological variation
 - Good definition of inclusion and exclusion criteria for subject inclusion in clinical studies
 - Dietary standardization before intervention to assess baseline levels of tested nutrients
 - Standardize timing of intervention (circadian rhythm, seasonal variations...)
 - Assess all possible sources of unrelated variance (due to confounding factors) with variance analysis techniques

- Define the form of nutrient intake and assess food matrix impact on nutrient absorption and variability due to:
 - Gastrointestinal transit time
 - Absorption rate
 - Effect on microbiota on the modulation of
 - nutrient bioavailability
 - production of microbiome-generated nutrient metabolites
 - host metabolism
 - Interactions with other nutrients (antinutrients...)
 - Competition of nutrients with transporter systems and metabolizing enzymes
- Cross over design often recommended for separation of intra- and inter-individual variabilities

Nutrikinetic applications

Vitamins	Reference	Minerals	Reference
Vitamin C	Davis et al., 2016	Iron	Bryszewska et al., 2019 Gandhi et al., 2019
Vitamin D2	Salvia-Trujillo et al., 2017		
Phytonutrients	Reference	Phytonutrients	Reference
Black tea phenolics	Van der Pijl et al., 2015	Pomegranate ellagic acid	Gonzalez-Sarrias et al., 2015
Yerba mate phenolics	Gomez-Juaristi et al., 2018	Cocoa flavanols	Schroeter et al., 2006 Urpi-Sarda et al. 2010
Apple epicatechins	Hollands et al., 2013	Fermented soybean isoflavone metabolites	Lee et al., 2017
Green tea	Renouf et al., 2013 Scholl et al., 2018 Del Rio et al., 2010	Quercetin and metabolites	Chen et al., 2005
Olive oil phenolics	Rubio et al., 2012	Ellagitannins	Cerda et al., 2005
Lignan	Eckhaut et al., 2008	Chlorogenic acids	Gonthier et al., 2003
Carotene	Corte-Real et al., 2018 Gence et al., 2018 Malpelli-Brahm et al., 2019	Phytosterols	Ubeyitogullari et al., 2019
		Methylxanthine	Nugrahini et al., 2019

Single bolus dose of black tea

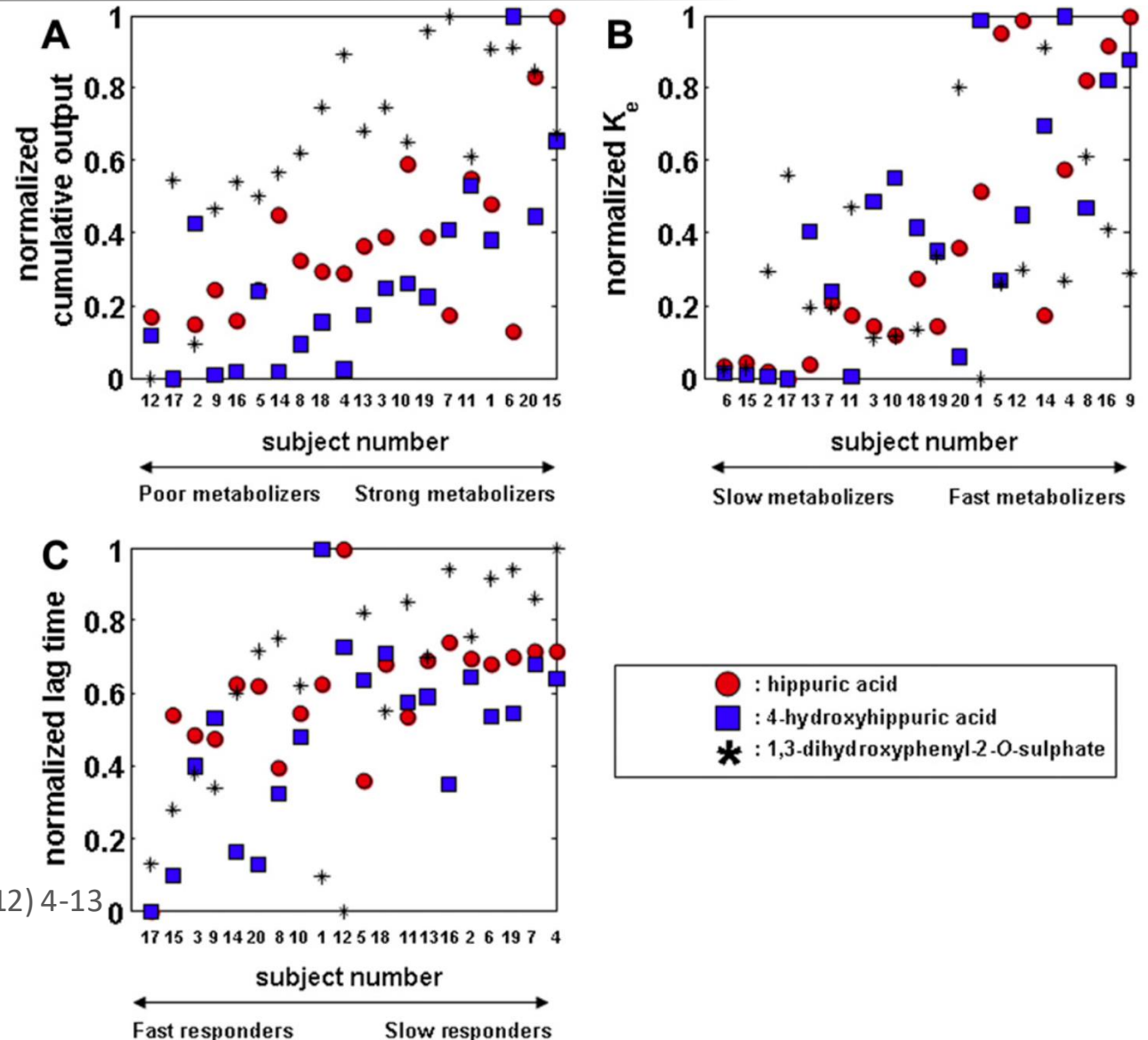
Estimated nutrikinetic quantities of urinary metabolites from 20 volunteers

(A) normalized cumulative (48 h) output

(B) normalized first-order rate constants (k_e)

(C) normalized lag times

Identification of slow and fast responders



References:

- J.P.M. van Duynhoven et al. Trends in Food Science & Technology 26 (2012) 4-13
- E. J. van Velzen et al. Journal of Proteome Research 8 (2009) 3317e3330

- Multicompartmental analysis
- Dynamic simulated Gastrointestinal track model for *in vitro* experiments
- Standardized workflow whenever possible
- Nutrikinetics-Nutridynamics relationships
- Health effects associated with long term exposure