Ionomics, Microbial metabolome, Nutrikinetics

November 12 2024

Serge Rezzi, PhD
CEO Swiss Nutrition and Health foundation
serge.rezzi@nutritionhealthfoundation.ch
https://nutritionhealthfoundation.ch/

Tel. +41 21 65326 50 – Fax +41 21 653 26 52
Route de la Corniche 3B
CH-1066 EPALINGES

EPFL 2024

SWISS NUTRITION & HEALTH FOUNDATION

IONOMICS
Exploring the mammalian ionome

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

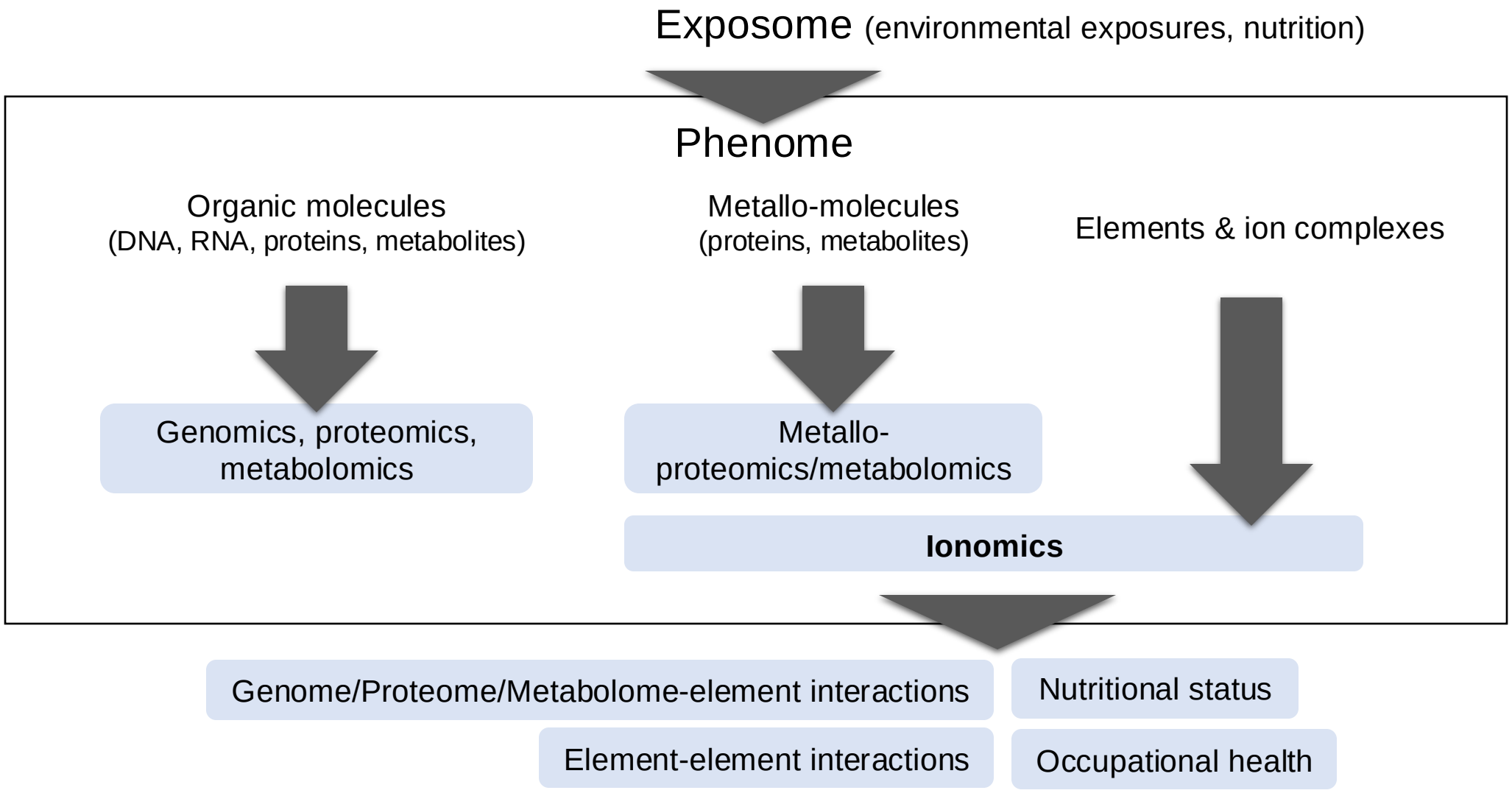
Ivan Baxter

Advance Access publication date 16 January 2010

D.E. Salt et al.; AnnuRevPlantBiol 59 (2008) 709-733

SWISS NUTRITION & HEALTH FOUNDATION

Ionome



Konz T. *et al*. J. Proteome Res. 2017, 16, 2080−2090

SWISS NUTRITION & HEALTH FOUNDATION

Essential Role of Minerals and Elements in Humans

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):

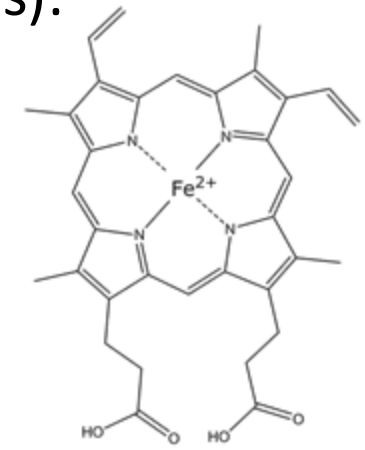
… hemoglobin (**Fe**),

… RNA- DNA polymerase (**Zn**),

… superoxide dismutase (**Mn**, **Zn**, **Cu**),

… xanthine oxidoreductase (**Mo**),

… glutathion peroxidase (**Se**)



SWISS NUTRITION & HEALTH FOUNDATION

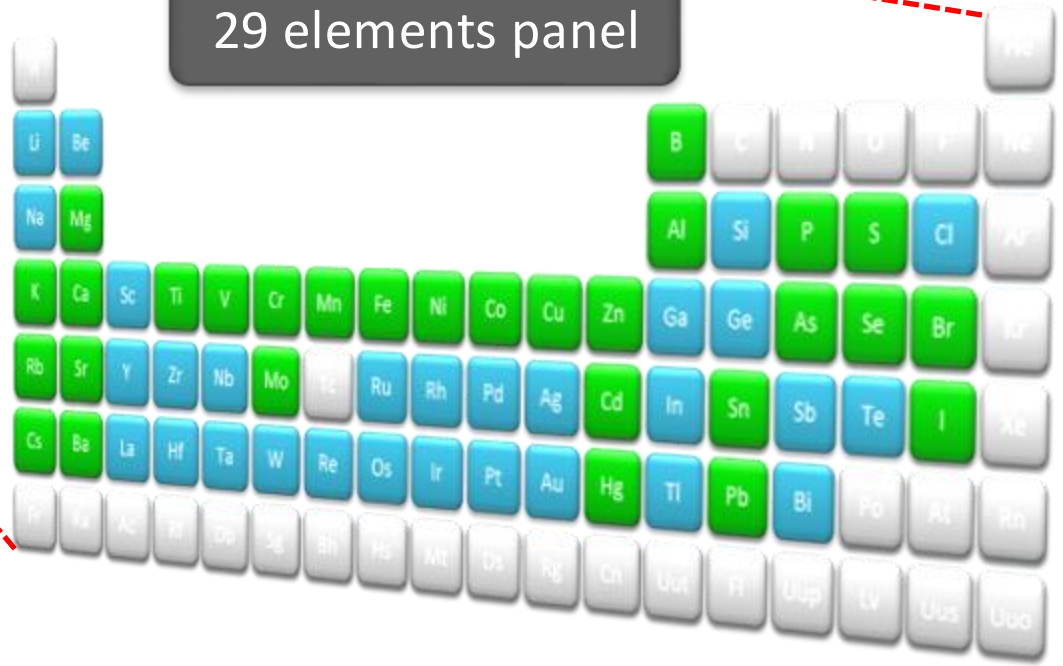
ICP-MS as elemental detector

Graphic from: Agilent Technologies

Liquid samples:

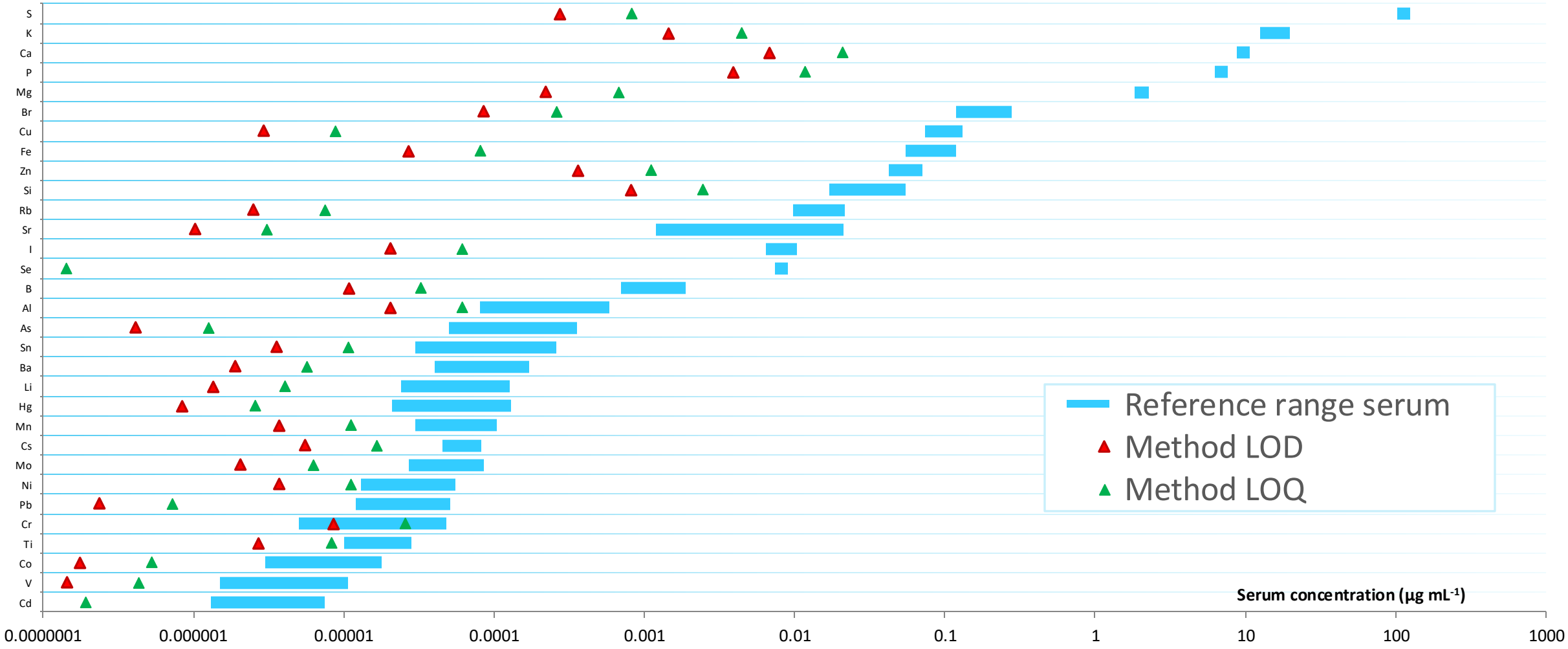
- Whole blood
- Serum / Plasma
- CSF
- Urine
- Lysed cells
- Mineralized tissues (e.g. skin, liver, muscle)

29 elements panel



SWISS NUTRITION & HEALTH FOUNDATION

From ultra trace analysis to major elements



SWISS NUTRITION & HEALTH FOUNDATION

Biological Variability of the Human Ionome

- 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**

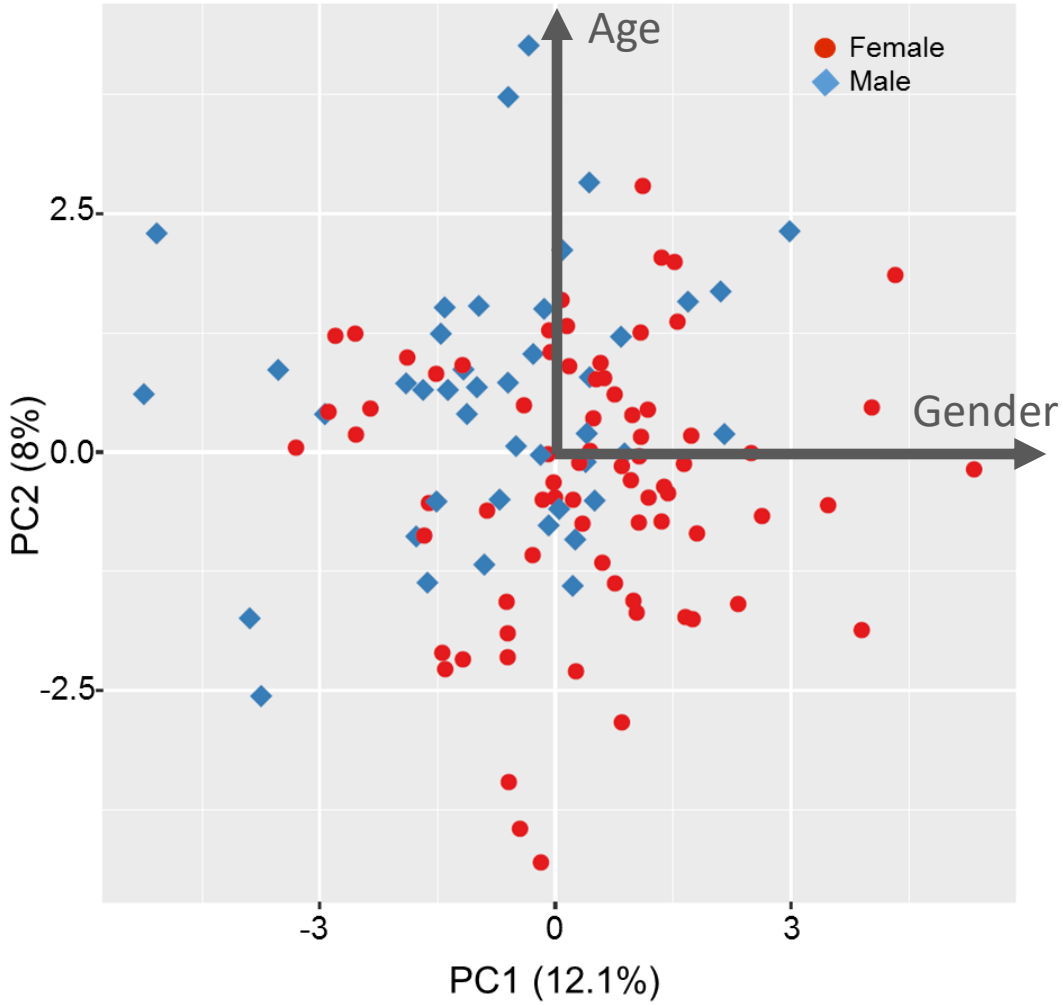
Study population:

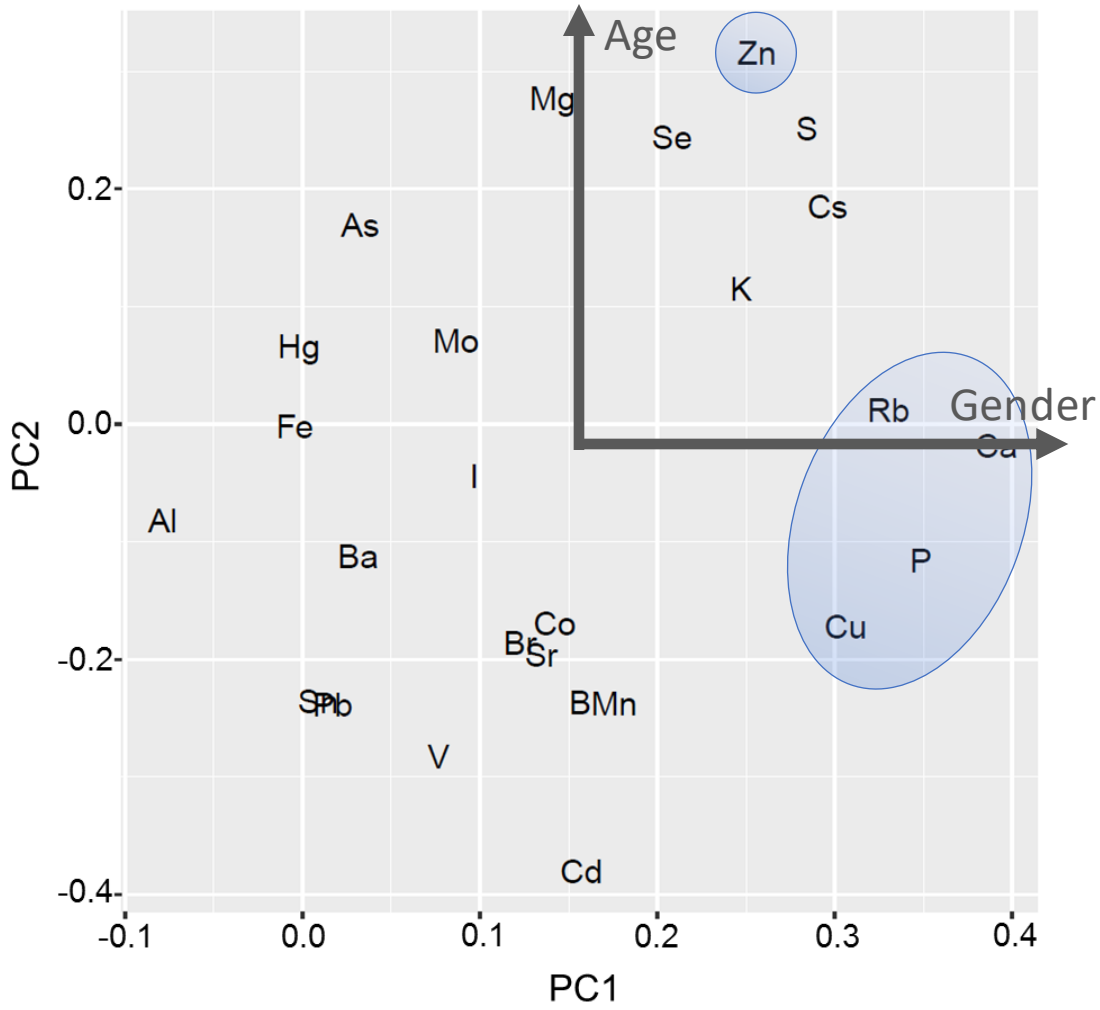
- 120 Serum samples from 120 community dwelling older adults
- Mean age of 70.4 years (standard deviation SD = 7.9)
- 43 males and 77 females
- Sample collection after overnight fasting

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

SWISS NUTRITION & HEALTH FOUNDATION

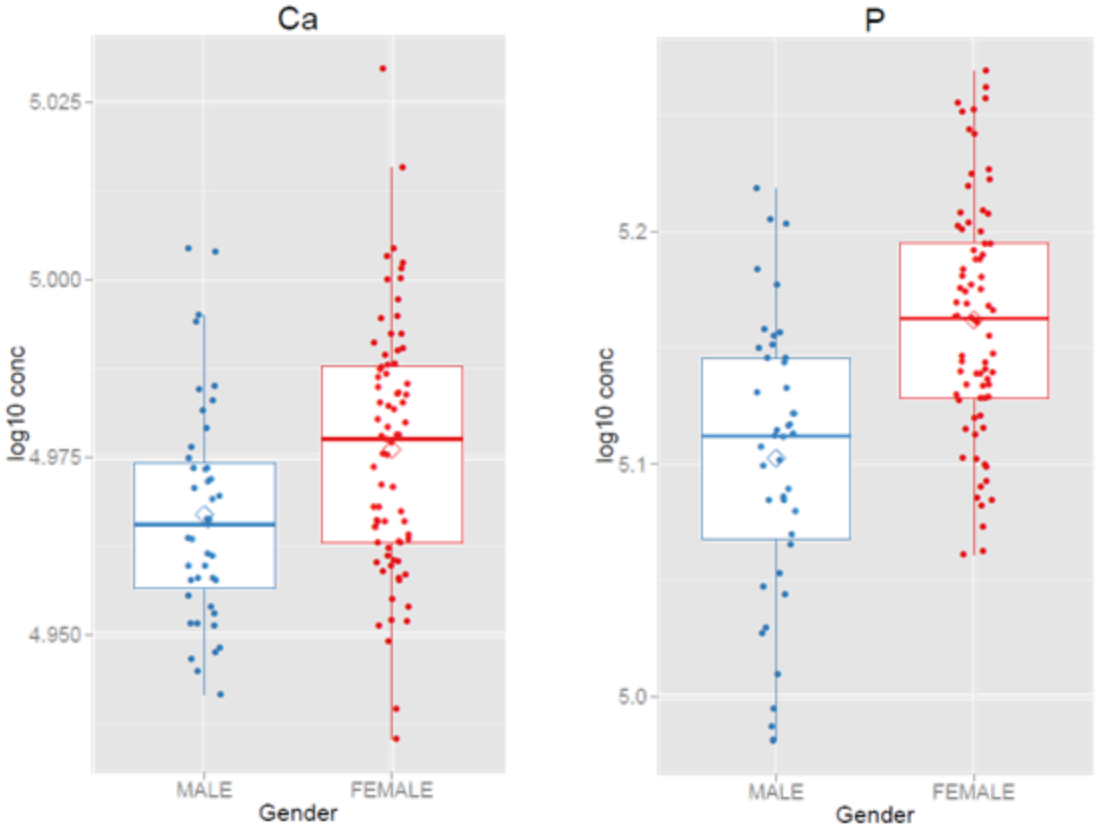
Principal component analysis of the human Serum Ionome





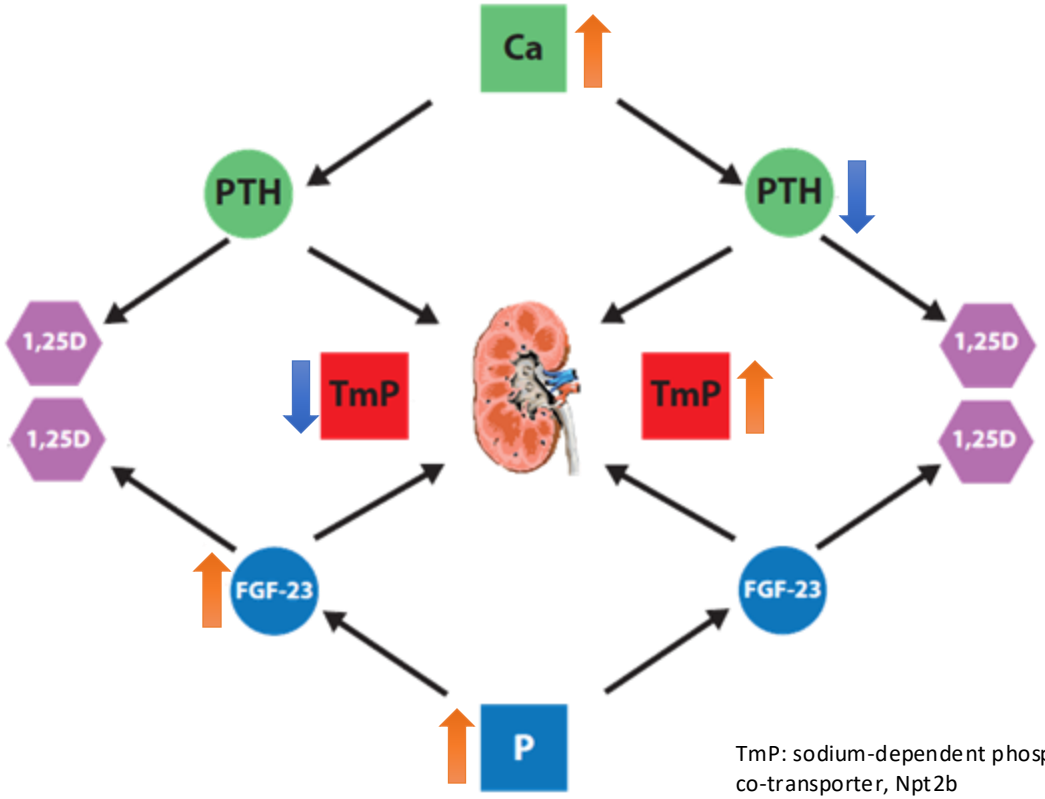
T. Konz, *et al.* ICP-MS/MS-based Ionomics. *J. Proteome Res.* 2017

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

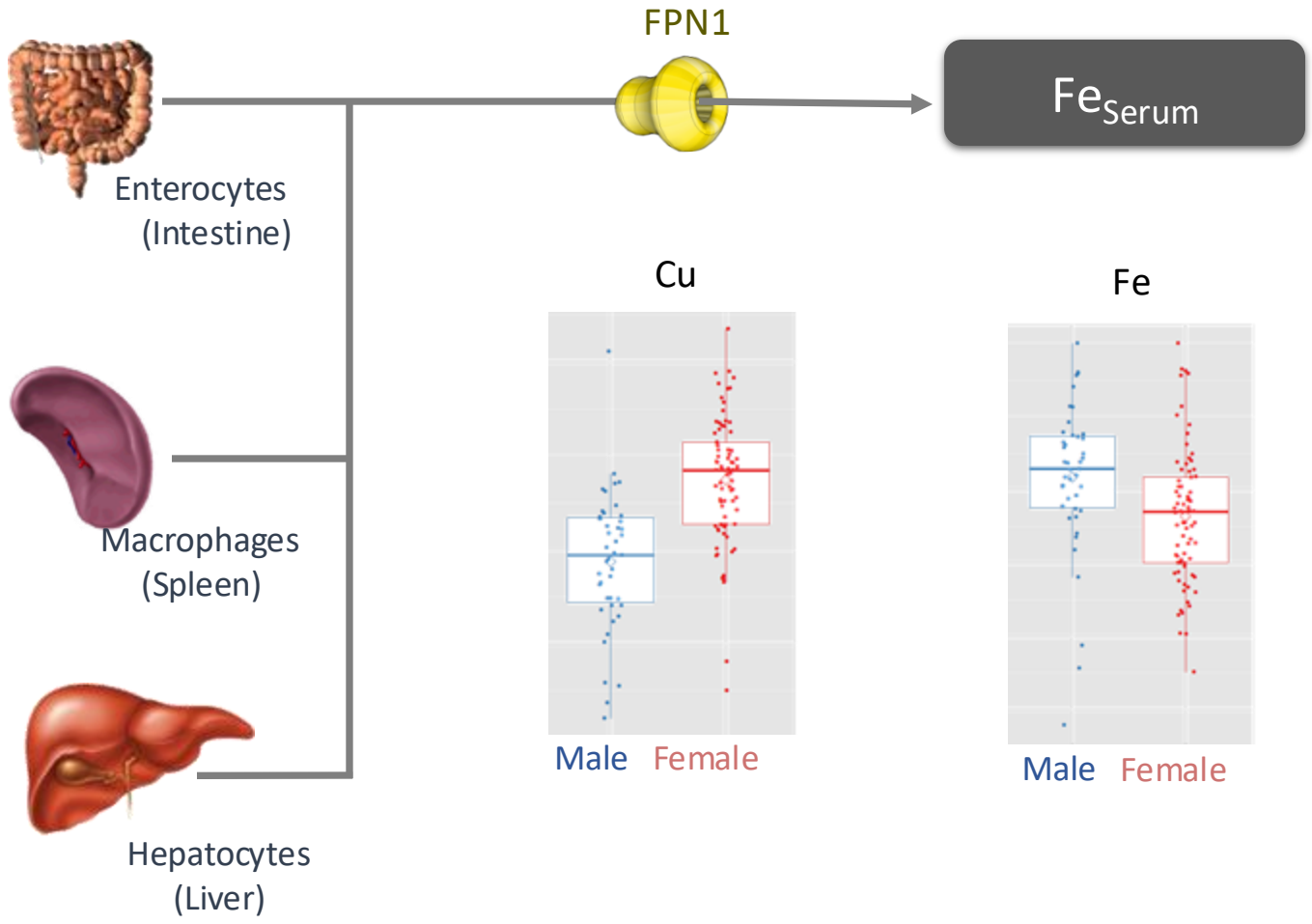


TmP: sodium-dependent phosphate co-transporter, Npt2b

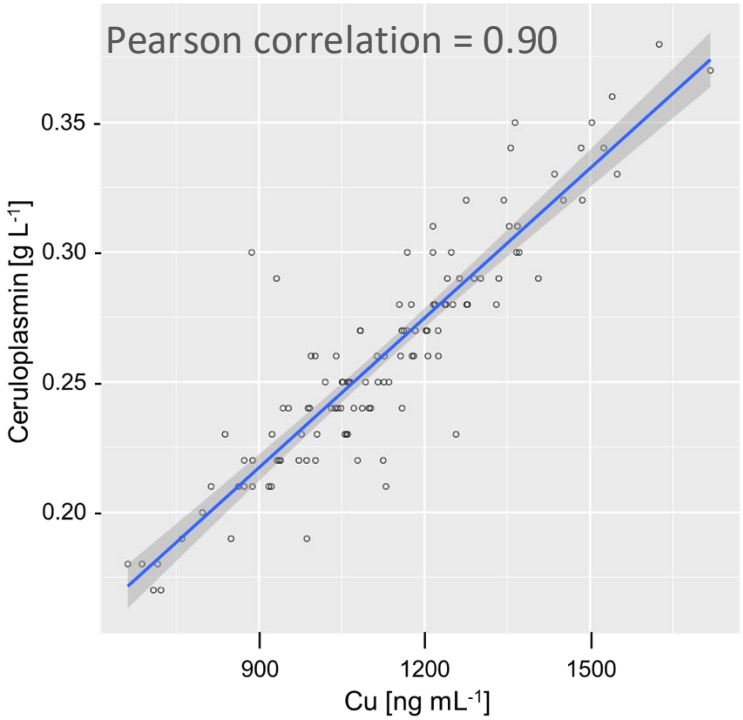
Peacock M, Clin J Am Soc Nephrol 2010

SWISS NUTRITION & HEALTH FOUNDATION

Gender-specific ionome signature of Cu and Fe



Fe-stocks



Konz T. *et al*. J. Proteome Res. 2017, 16, 2080−2090

SWISS NUTRITION & HEALTH FOUNDATION

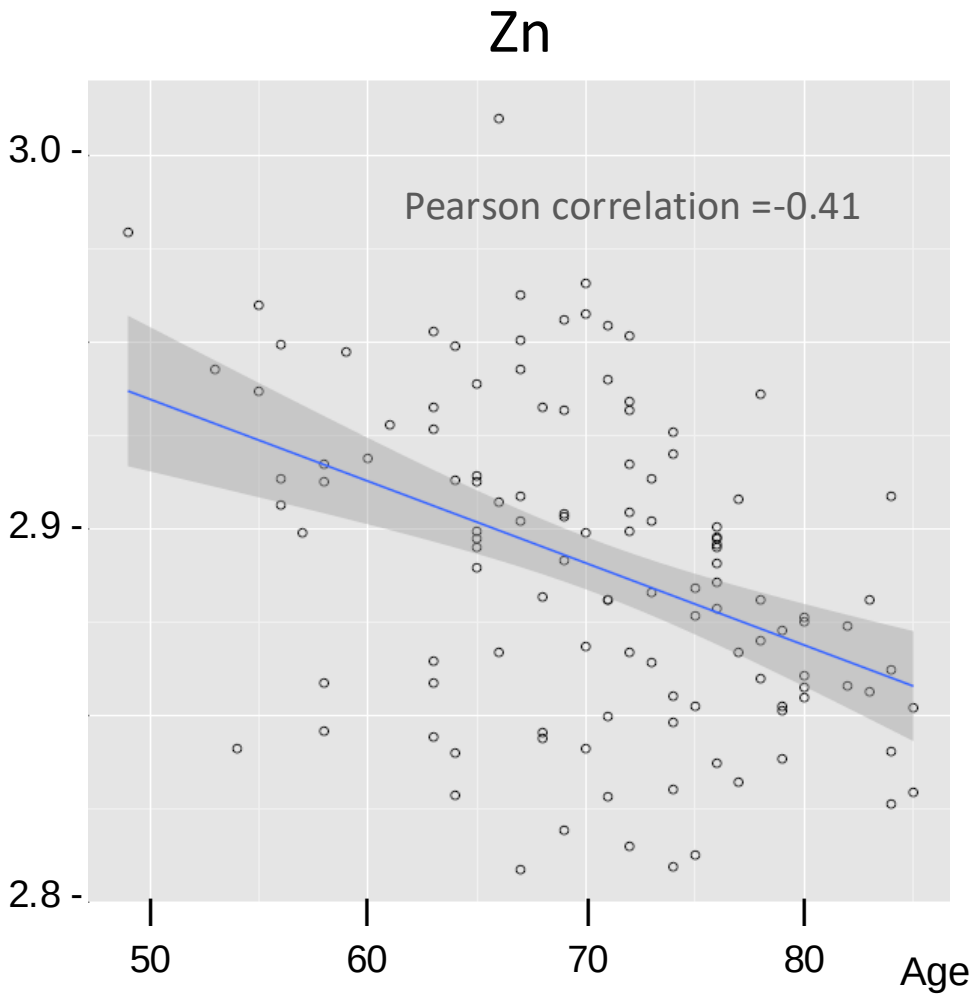
Zinc shows age-related Ionomic Variance

- Negative correlation with age might be related to lower intake/absorption of altered compartmentalization.
- **Cu/Zn ratio:**

$$Cu/Zn_{Females} = 1.55$$

$$Cu/Zn_{Males} = 1.27$$

- Potential biomarker of inflammatory and/or nutritional biomarker of mortality in elderly*.
- Driven by Cu compartmentalization related to aging-associated inflammatory status.



M. Malavolta et al.; Mech. Ageing Dev. 151 (2015) 93-100

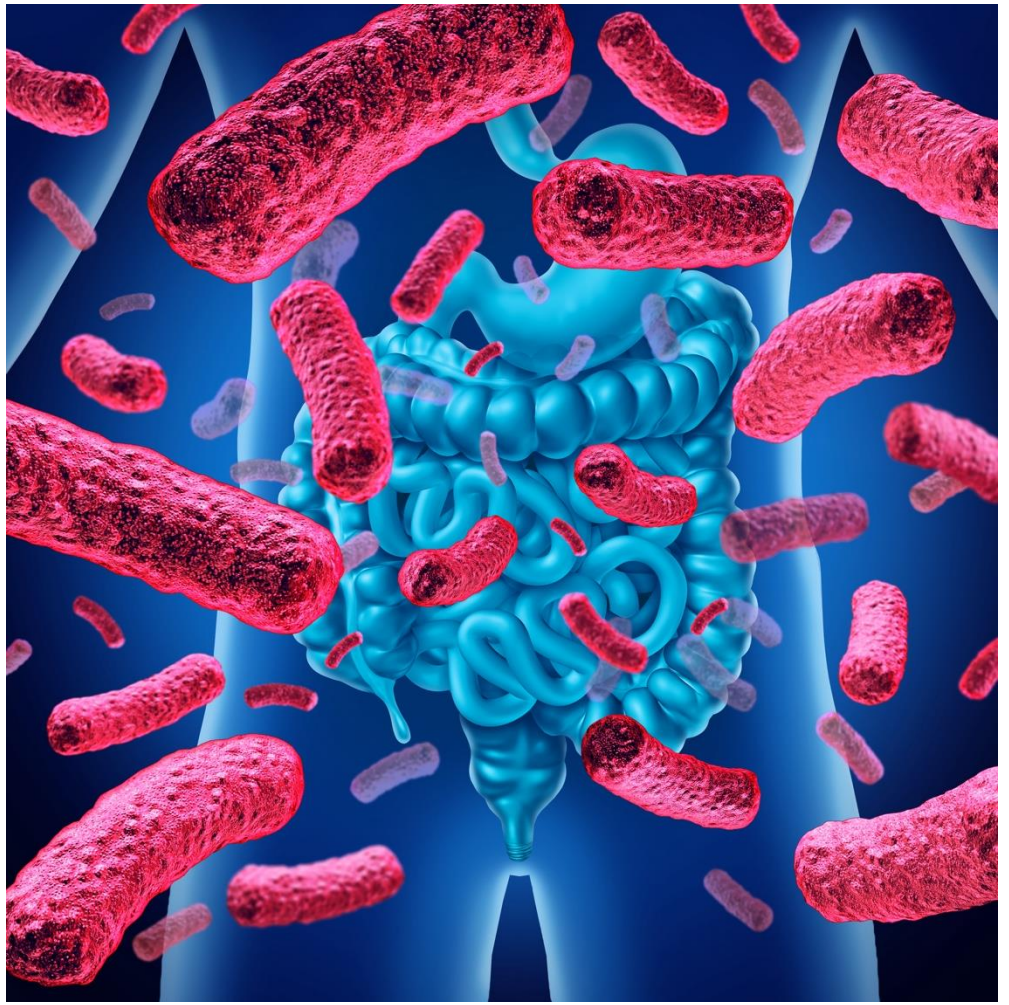
Konz T. *et al*. J. Proteome Res. 2017, 16, 2080−2090

SWISS NUTRITION & HEALTH FOUNDATION

Microbial metabolome

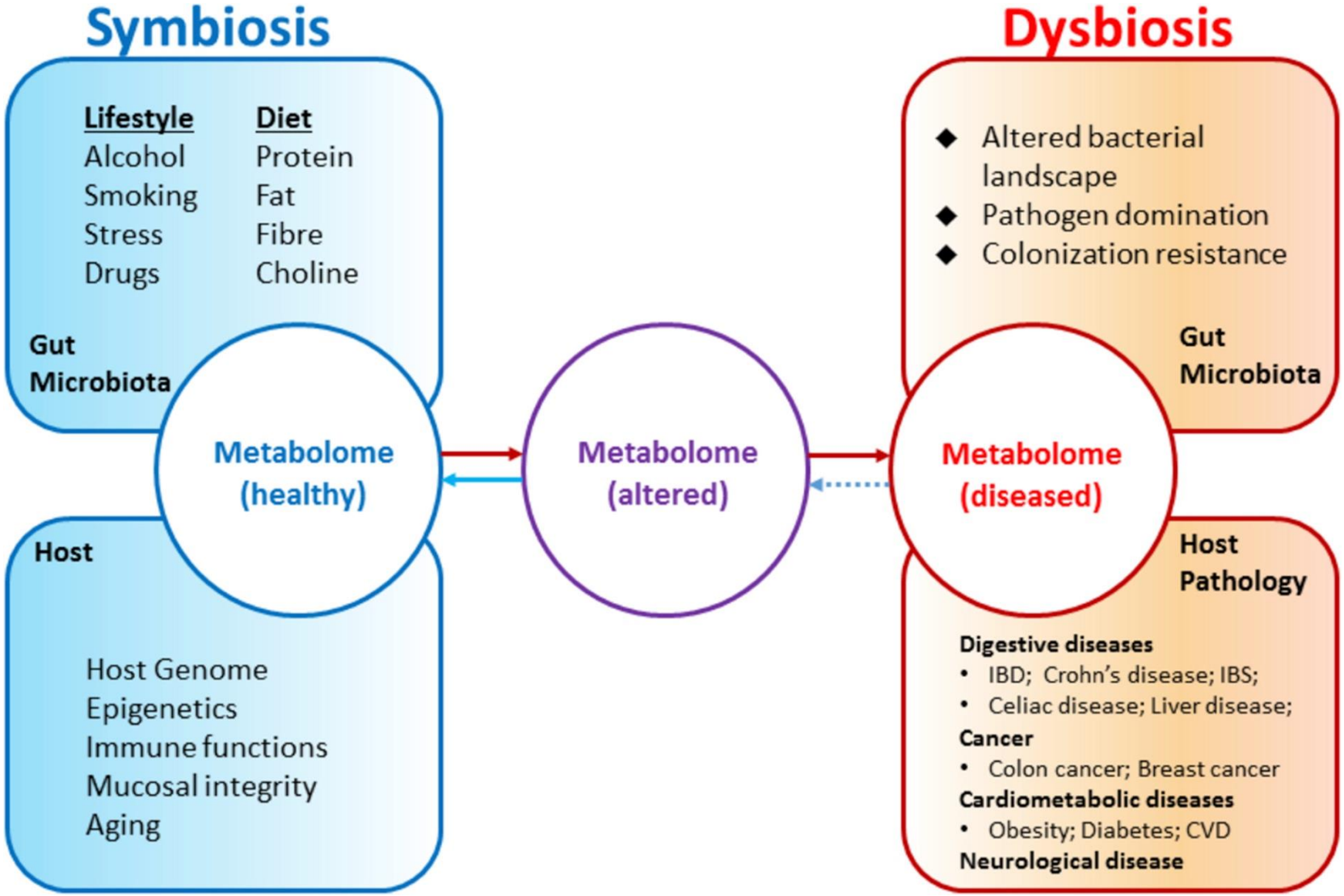
Why measuring microbial metabolome?

- 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



SWISS NUTRITION & HEALTH FOUNDATION

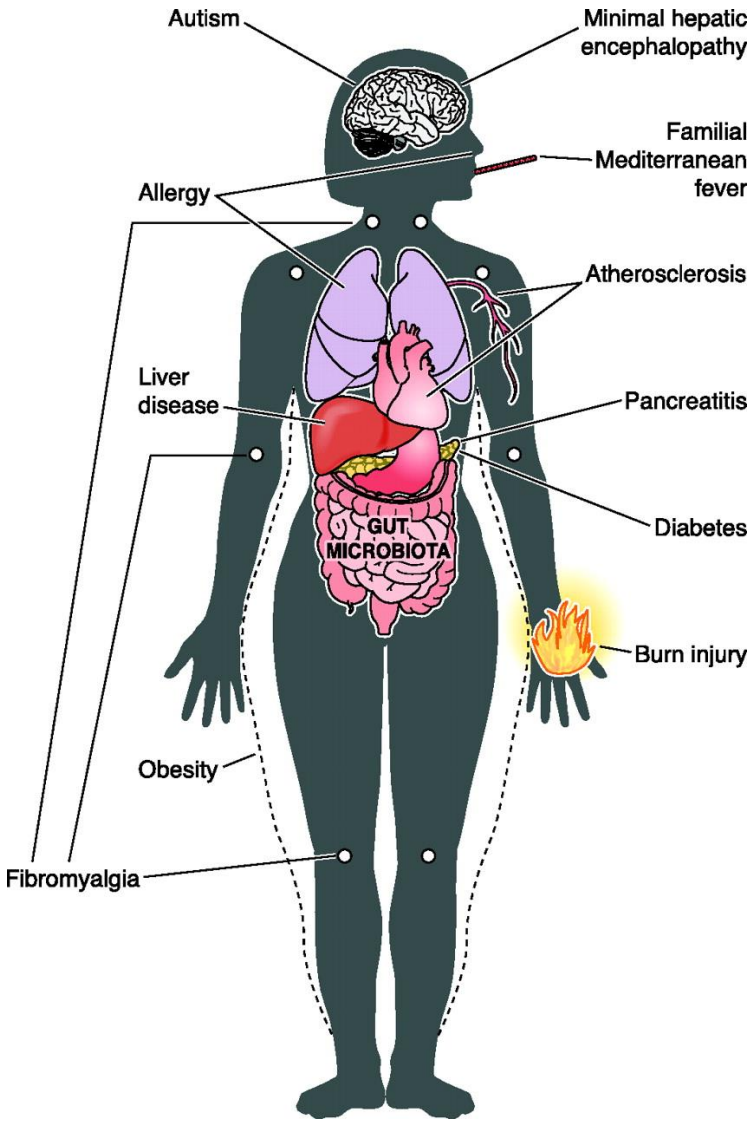
Microbiome-host metabolic interactions



Chen et al. J Formos Med Assoc. 2019 Mar;118 Suppl 1:S10-S22

SWISS NUTRITION & HEALTH FOUNDATION

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)

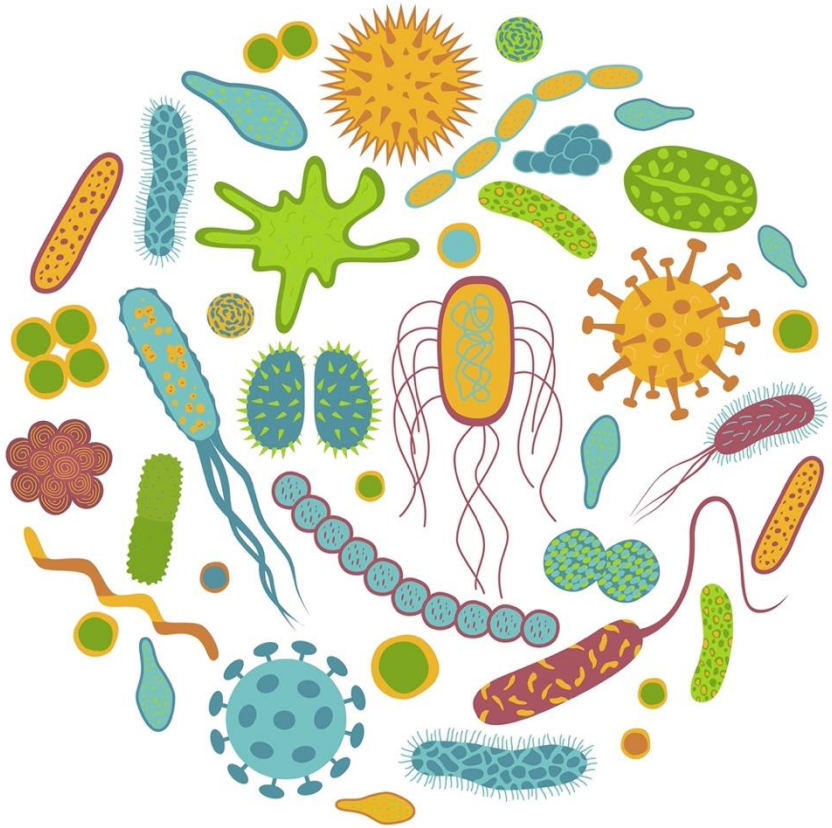
…and more to be discovered !

Sekirov I et al. Physiol Rev 2010;90:859-904

SWISS NUTRITION & HEALTH FOUNDATION

Microbiome metabolites

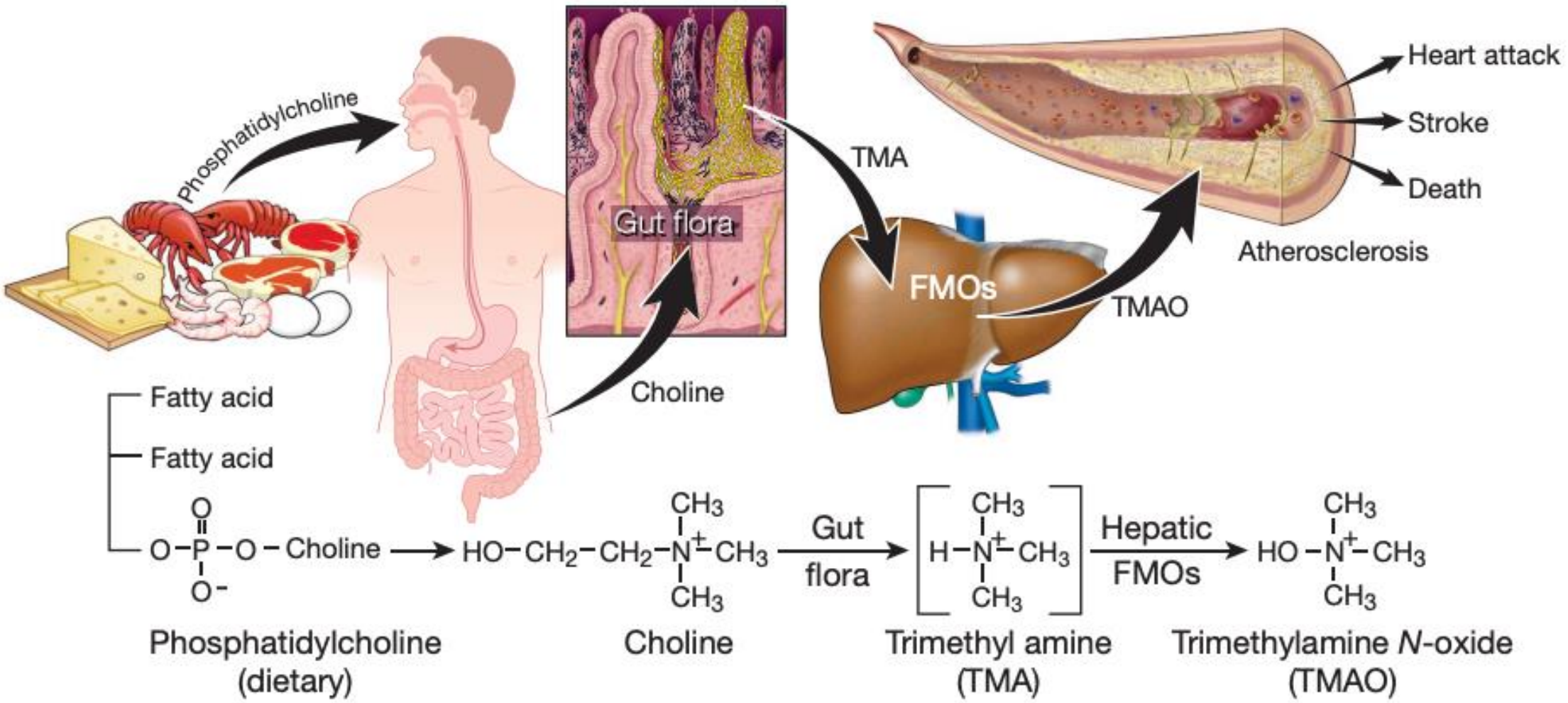
- Short chain fatty acids (propionate, butyrate…)
- Organic acids (benzoate, hippurate…)
- Vitamins (B9, B2, B12, K2…)
- Bile acids (taurodeoxylcholate…)
- Hydroxycinnamic acids… from polyphenols
- 1,3-propanediol from lipids (glycerol…)
- Phenols, indoles (amino acids)
- Biogenic amines (amino acids)



Vernocchi et al. Front Microbiol. 2016 Jul 26;7:1144.

SWISS NUTRITION & HEALTH FOUNDATION

Host-microbiome nutrient co-metabolism



Wang Z et al. Nature. 2011 Apr 7;472(7341):57-63

SWISS NUTRITION & HEALTH FOUNDATION

Metabolomics pipeline for gut microbiome

Metabolic profiles of 178 microorganisms

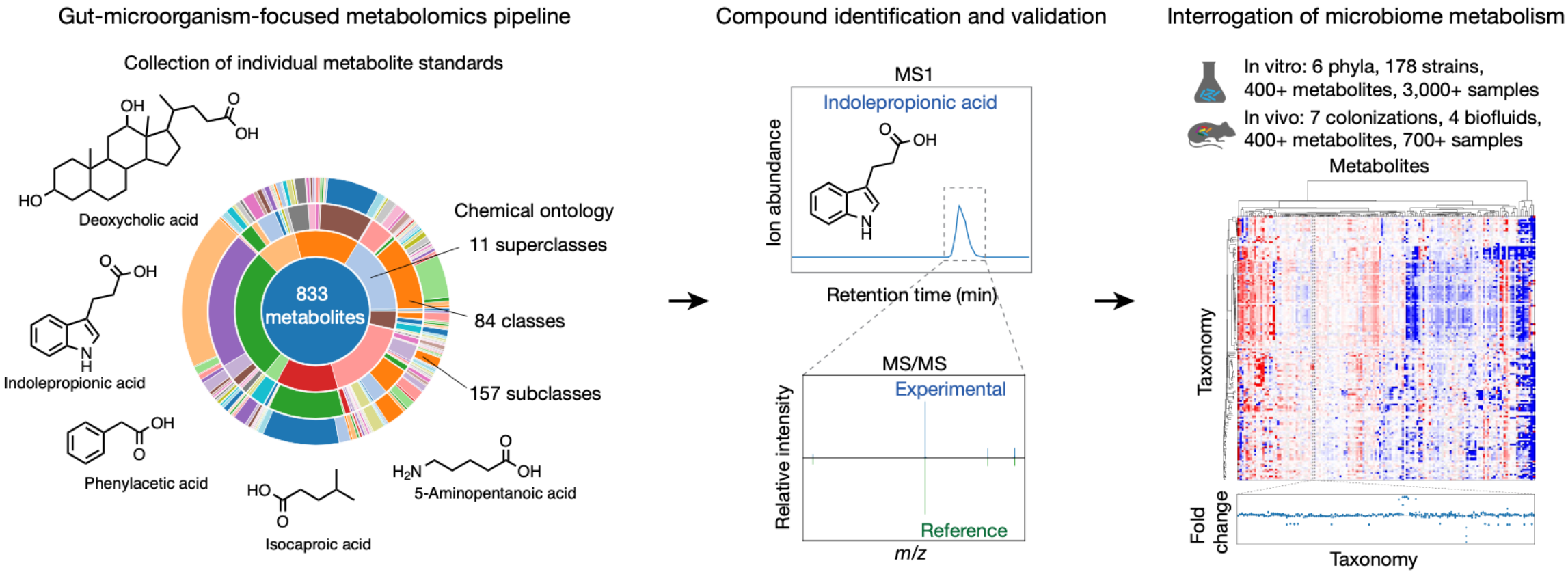
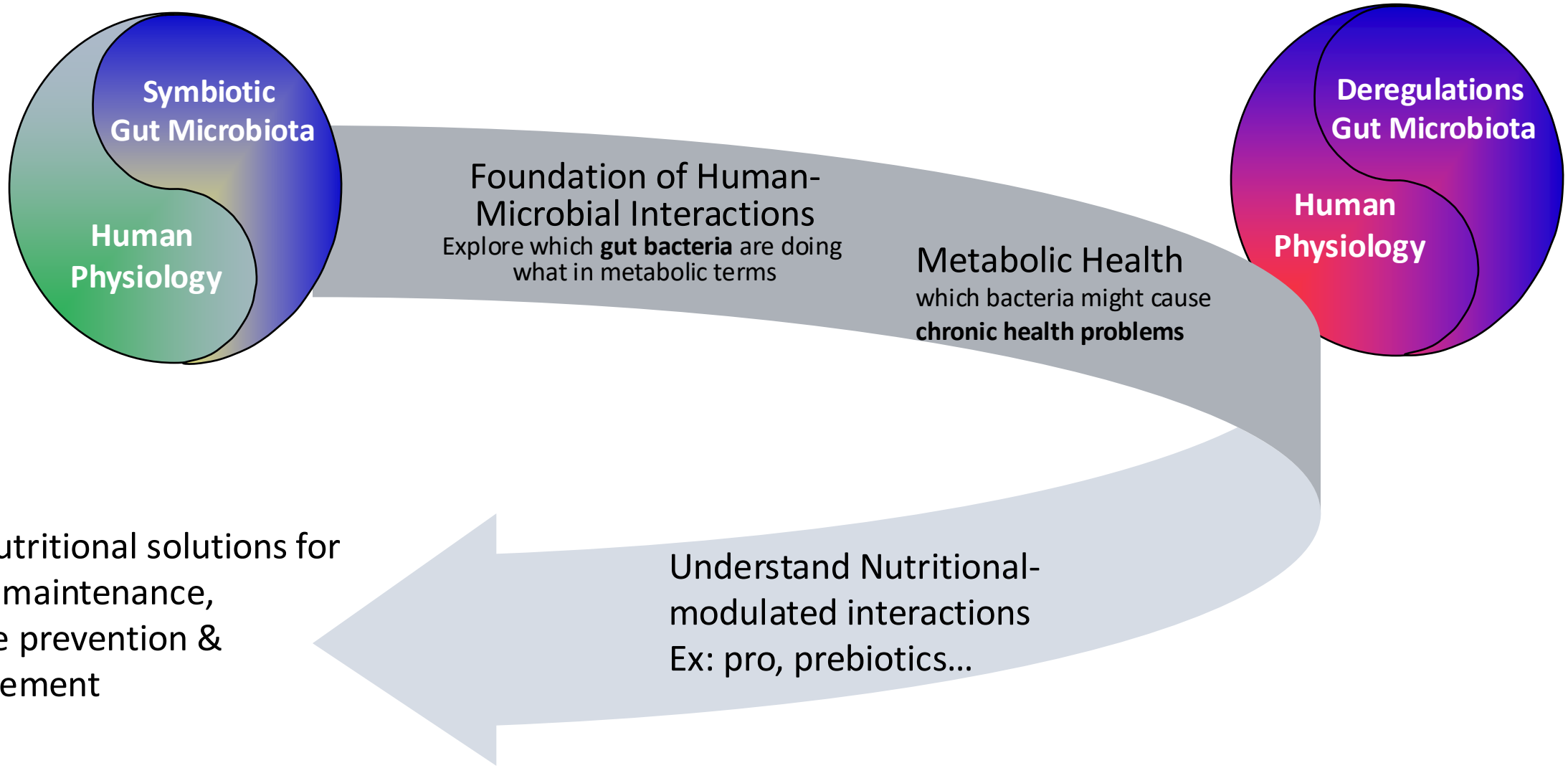


Fig. 1 | A microbiome-focused metabolomics pipeline enables the mechanistic interrogation of microbiome metabolism. Schematic of our metabolomics workflow, consisting of mass-spectrometry reference library construction and validation, producing in vitro and in vivo metabolomic profiles across diverse sample types. Our entire dataset is publicly accessible through a web-based, interactive Metabolomics Data Explorer (https://sonnenburglab.github.io/Metabolomics_Data_Explorer).

Han et al. Nature. 2021 Jul;595(7867):415-420.

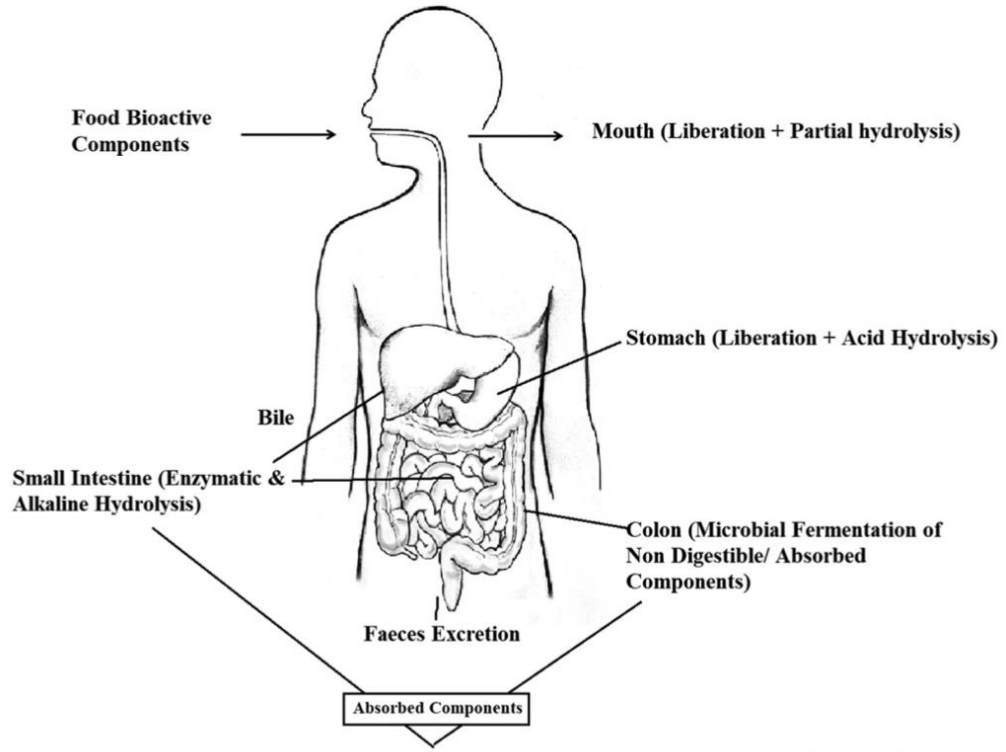
SWISS NUTRITION & HEALTH FOUNDATION

Scientific approaches to deciphering function of gut microbiome



SWISS NUTRITION & HEALTH FOUNDATION

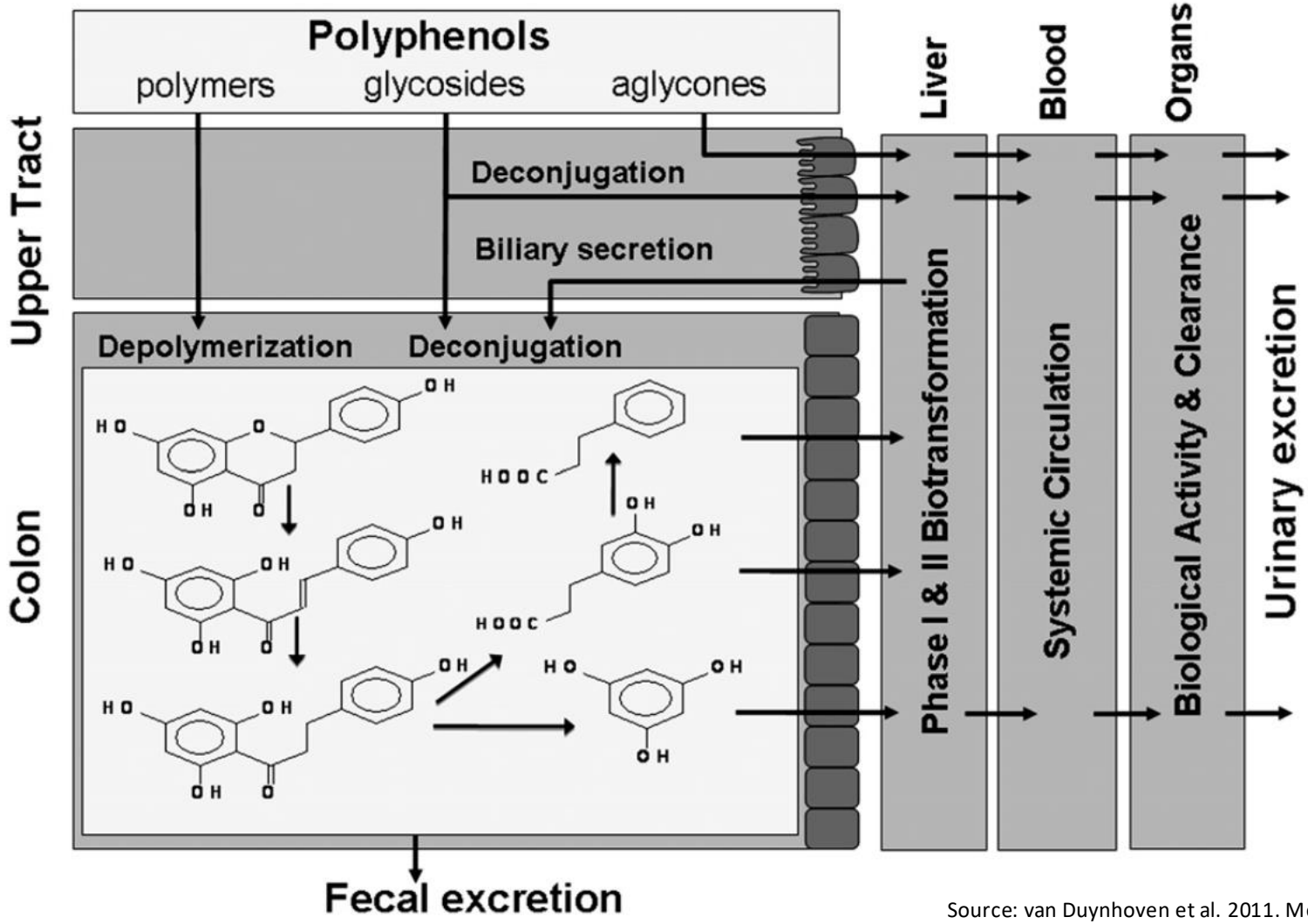
Nutrikinetics
Time-dependant analysis of nutrient



Phytonutients

SWISS NUTRITION & HEALTH FOUNDATION

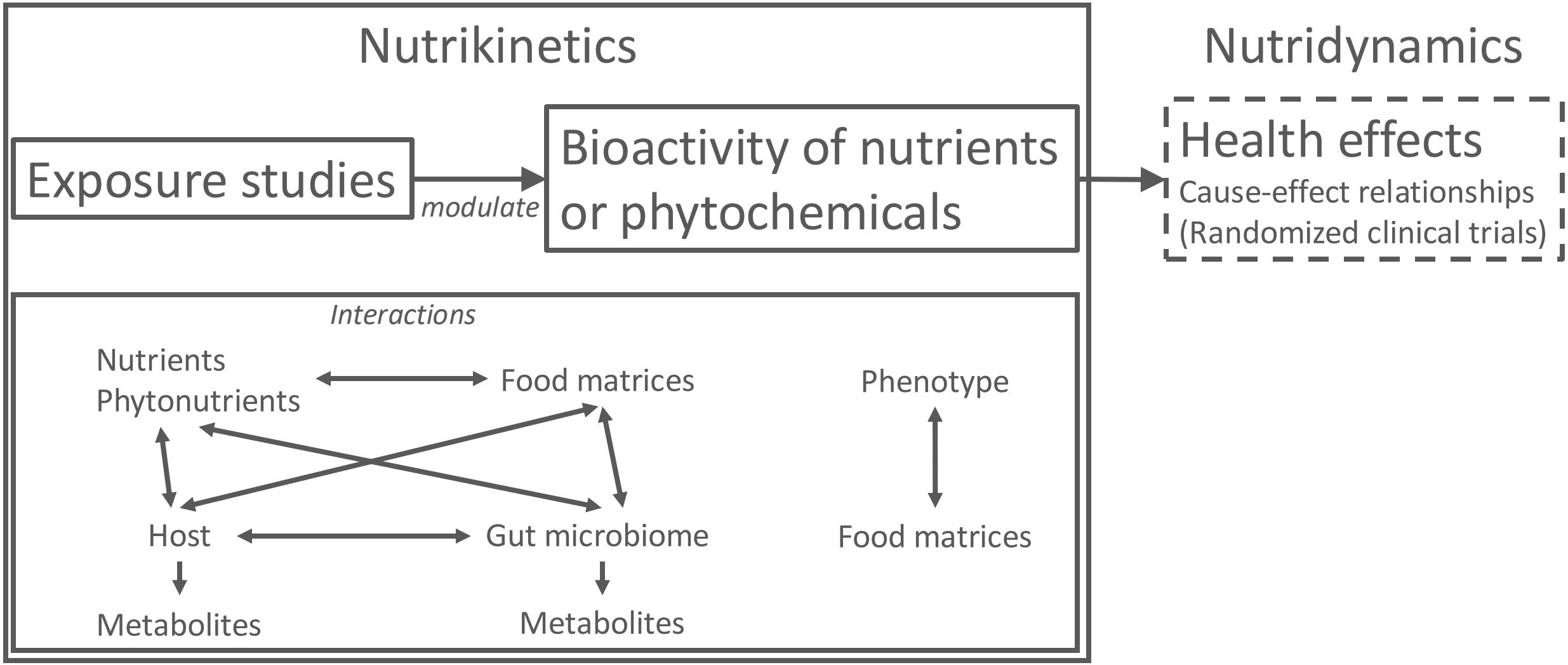
Polyphenol absorption journey



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.

SWISS NUTRITION & HEALTH FOUNDATION

Nutrient pharmacokinetics “Nutrikinetics”



SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics definition

"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."

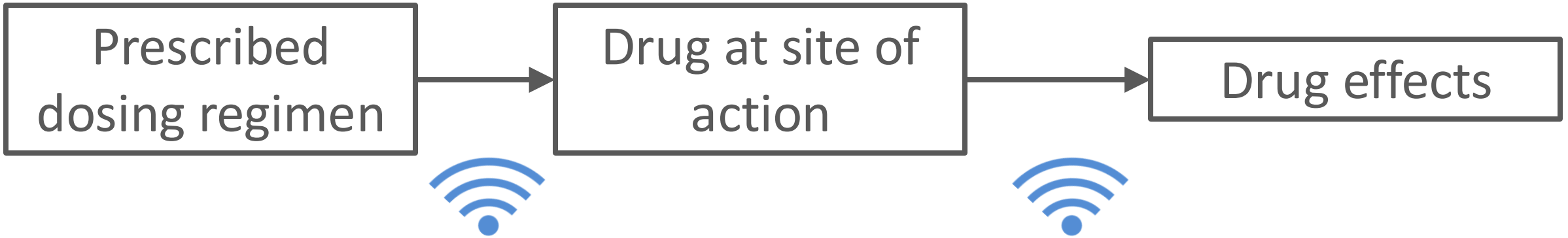
J.P.M. van Duynhoven et al. Trends in Food Science & Technology 26 (2012) 4-13

SWISS NUTRITION & HEALTH FOUNDATION

Basic notions of pharmacokinetics

Pharmacokinetics

Pharmacodynamics



Influencing factors

Compliance
Dosing and medication errors
Absorption
Tissue and body fluid mass and volume
Drug interactions
Elimination
Drug metabolism

Influencing factors

Drug receptor status
Genetic factors
Drug interactions
Tolerance

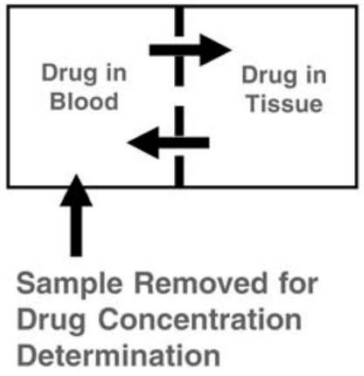
SWISS NUTRITION & HEALTH FOUNDATION

Basic notions of pharmacokinetics

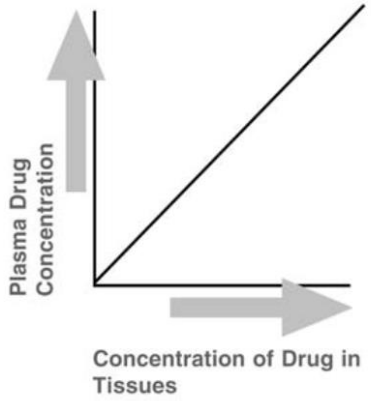
The study of the time course of drug and metabolite levels in different fluids, tissues, and excreta of the body, and of the mathematical relationships to develop models to interpret such data

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

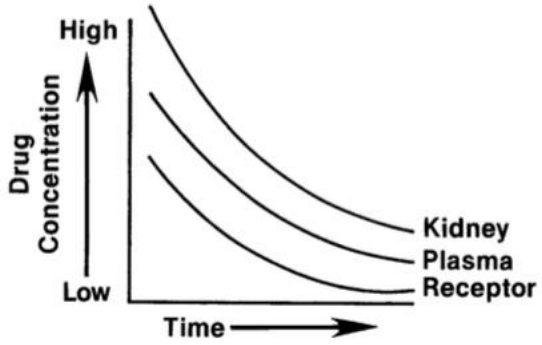
Kinetic homogeneity: describes the predictable relationship between plasma drug concentration and concentration at the receptor site where a given drug produces its therapeutic effect



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

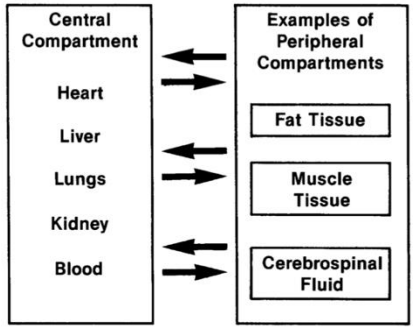
SWISS NUTRITION & HEALTH FOUNDATION

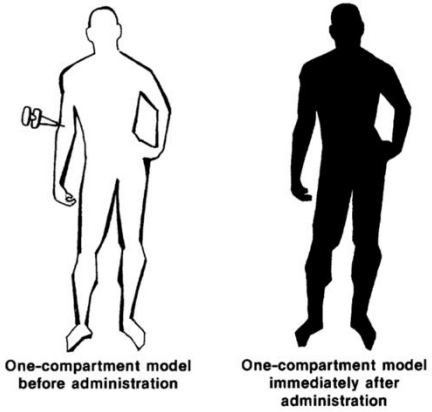
Basic notions of pharmacokinetics

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

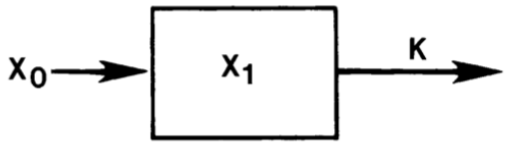
Compartmental models

- 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 peripherical compartment




One-compartment model before administration

One-compartment model immediately after administration

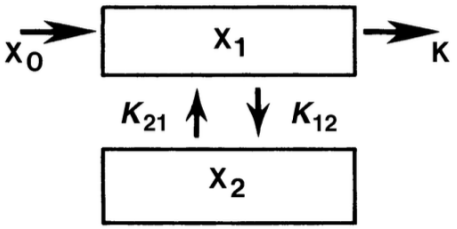


Where: X_0 = Dose of drug
X_1 = Amount of drug in body
K = Elimination rate constant


Two-compartment model before administration


Two-compartment model immediately after administration


Two-compartment model after distributive equilibrium



SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics

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

- Absorption
- Dsitribution
- 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

Nutrikinetics

Important challenges vs. pharmacokinetics

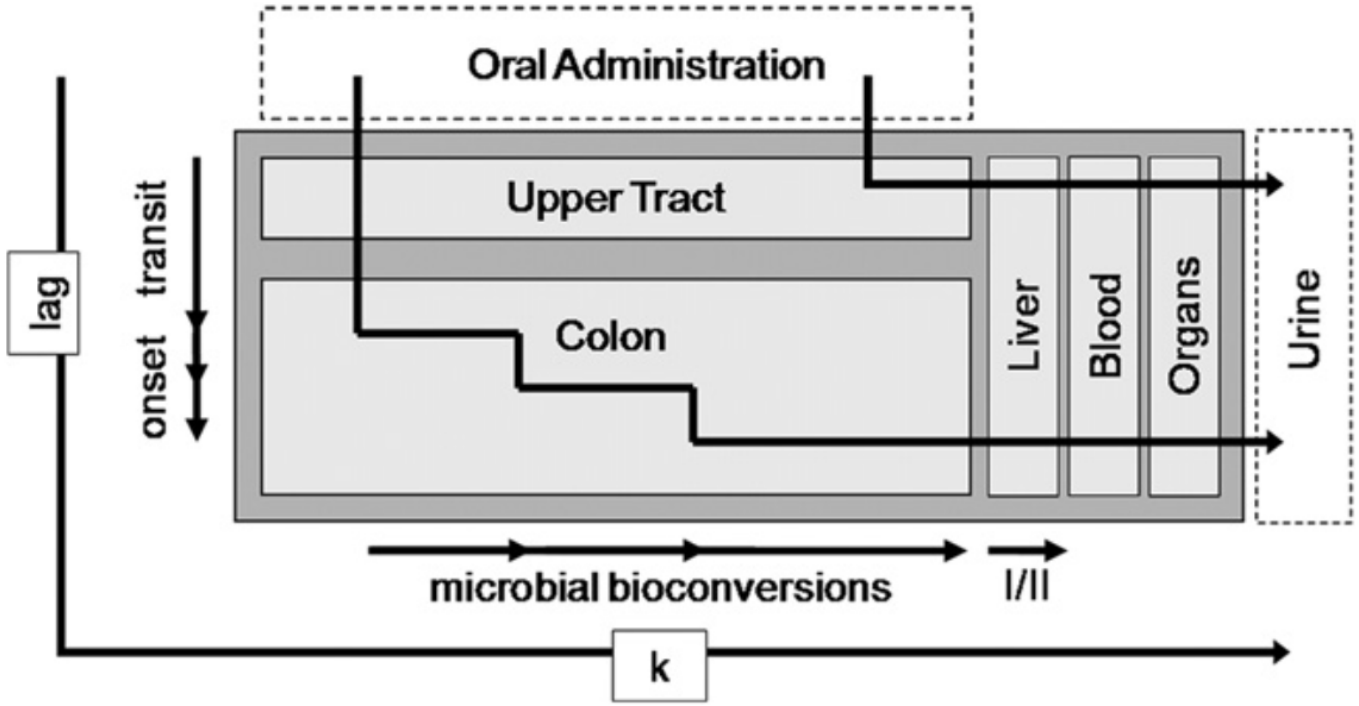
- Nutrients are occurring as complex mixtures (foods) vs. single drug compound
- Food/nutrient intakes doesn't mean complete nutrient exposure to the body:
  - Variation in nutrient accessibility: occurrence of antinutrients (phytic acid…) in the food, food matrix-nutrient interaction, digestibility…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

SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics

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

SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics – Study design ½
Key aspects

- 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

SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics – Study design 2/2
Key aspects

- 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

SWISS NUTRITION & HEALTH FOUNDATION

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	Eeckhaut 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

References available from: H. Riar et al. The conceptual understanding of nutrikinetics: A futuristic approach for designing health foods. Nutrition & Food Science. 2019

SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics application

Single bolus dose of black tea

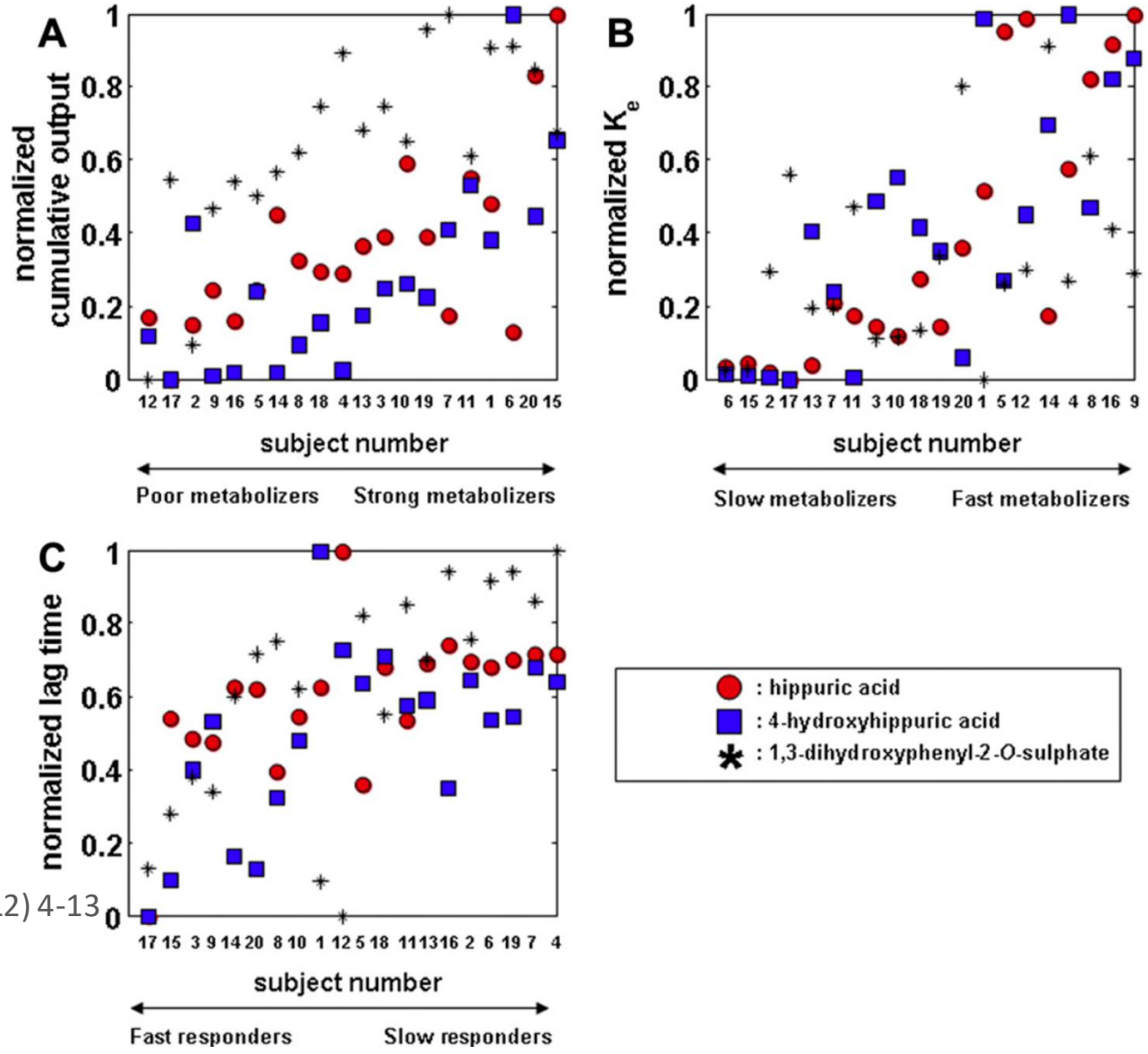
Estimated nutrikinetic quantities of urinary metabolites from 20 volunteers

(A) normalized cumulative (48 h) output

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

(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

SWISS NUTRITION & HEALTH FOUNDATION

Nutrikinetics perspectives

- 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