Nutritional metabolomics: Recent developments and future needs

(article starts on next page)

Nutritional metabolomics: Recent developments and future needs

Maaria Kortesniemi[1], Stefania Noerman[2], Anna Kårlund[1], Jasmin Raita[1], Topi Meuronen[1], Ville Koistinen[1,3], Rikard Landberg[2] and Kati Hanhineva[1,3]

Abstract

Metabolomics has rapidly been adopted as one of the key methods in nutrition research. This review focuses on the recent developments and updates in the field, including the analytical methodologies that encompass improved instrument sensitivity, sampling techniques and data integration (multiomics). Metabolomics has advanced the discovery and validation of dietary biomarkers and their implementation in health research. Metabolomics has come to play an important role in the understanding of the role of small molecules resulting from the diet—microbiota interactions when gut microbiota research has shifted towards improving the understanding of the activity and functionality of gut microbiota rather than composition alone. Currently, metabolomics plays an emerging role in precision nutrition and the recent developments therein are discussed.

Addresses
[1] Food Sciences Unit, Department of Life Technologies, University of Turku, FI-20014 Turun yliopisto, Finland
[2] Division of Food and Nutrition Science, Department of Life Sciences, Chalmers University of Technology, SE-412 96 Gothenburg, Sweden
[3] Institute of Public Health and Clinical Nutrition, School of Medicine, University of Eastern Finland, FI-70211 Kuopio, Finland

Corresponding author: Kortesniemi, Maaria (mkkort@utu.fi)

Keywords:
Metabolomics, Nutrition, Biomarker, Dietary pattern, Endogenous metabolite, Gut microbiota, Precision prevention.

Introduction

Metabolomics has become a key methodological approach in nutrition research. It allows the characterization of the molecular phenotypes of individuals, their metabolic responsiveness to various foods and diets, and comprehensive assessment of their mechanistic and predictive role in health. Ultimately, this may pave the way for the development of novel precision prevention approaches [1]. The use of metabolomics in nutritional research also helps to gain a mechanistic understanding of the role of dietary compounds in nutritional status and metabolism, provides a read-out from gut microbiota composition and function, and may reflect other external exposures and their interactions with the host with implications for human health. Metabolomics may also provide novel, objective biomarkers that reflect specific dietary and lifestyle exposures. Single metabolites or metabolite profiles reflecting specific exposures could be used to assess individual responses to dietary interventions eventually enabling improved disease risk prediction. In precision nutrition, metabolomics is emerging as an important technique to assess the impact of foods and diets on an individual level [1] and to determine metabotypes, *i.e.*, subgroups of individuals with a similar metabolic response to diet [2]. Self-sampling and the use of non-invasive sample materials are emerging and could further enhance practical applications for precision nutrition and precision medicine, where frequent sampling is warranted, but comprehensive metabolomics techniques integrated and validated with the self-sampling techniques are yet lacking [3]. Advances in instrumentation, spectral databases, and computational tools have promoted the understanding of the complexity related to nutrition due to the wealth of biochemicals derived from foods, especially those produced from whole plants, although this "dark matter" of food remains mostly unresolved and poorly acknowledged [4*,5]. In this review, we highlight the most recent developments and challenges in nutritional metabolomics including methodological aspects and their application in nutrition research to reflect dietary and life-style exposures, molecular responses, diet—microbiota interactions, eventually offering possibilities for tailored precision nutrition.

Methodological advancements and challenges

The primary analytical techniques used in nutritional metabolomics are MS- and NMR-based methods.

Coupled with UHPLC, and more recently with ion mobility, the MS techniques provide broad metabolite coverage and high sensitivity [6,7]. Although ion mobility greatly enhances the separation and identification of metabolite and lipid isomers by providing an additional dimension to the measurements, its utilization in nutritional research has thus far been limited [8]. In NMR-based metabolomics, increased sensitivity of probes, optimized NMR excitation pulse schemes, hybrid NMR approaches and faster spectra preprocessing are important recent developments [9].

The main methodological advantages during the past few years have come from merging the metabolomics data with other omics, clinical, and dietary data alongside with developments of tools and pipelines for the purpose [10—13*,14**,15—21]. Since the plasma metabolome represents a snap-shot read-out modified by the host genetics, gut microbiota, diet and the exposome, recent research is increasingly focused on elucidating their interactions [11,22]. The most widely used multiomics approaches in current nutritional studies include combining metabolomics data and metagenomics data on gut microbial composition with a variety of available computational methods, such as metabolic networks, Spearman's correlation networks, and Sparse Generalized Canonical Correlation Analysis (SGCCA) [10—12,16,18—20]. Eventually, multiomics and data integration will help to unravel interactions between diet, gut microbiota and health [14**]. To promote this, novel multiomics databases are being introduced [14**,23]. Furthermore, the use of new sampling techniques, such as dried blood spot by finger-prick lancet [24], allowing for the first time quantitative measurement of metabolites in small volume samples [25], as well as alternative biofluids, including saliva [26], sweat [27], and breast milk [12], broaden the possibilities of metabolomics in human nutritional studies because of their non-invasive and less labor-intensive nature, allowing the samples to be collected at home. So far, these applications have been only used to a limited extent in nutritional studies. The variation of the reported metabolites in different biological matrices and the question of their representativeness of the food intake are challenging the field.

One of the biggest challenges in metabolomics is also to comprehensively characterize and annotate the vast number of compounds measured. This is particularly challenging in the case of nutritional metabolomics, as the immense pool of compounds gained from foods adds a level of complexity that needs to be addressed [4*,28]. In the case of lipidomics, essential improvements within the analytical methods as well as identification of lipids have been accomplished recently [29,30]. Besides the advancements in analytical technology, both open-access and commercial spectral databases are continuously expanding, and software utilizing machine learning and molecular networking have emerged to assist with the laborious process of metabolite identification [14**,15,17,31]. To fully understand the nutritional and eventually health properties of foods and diets, remarkable advancements are still required in our capacity to identify the individual metabolites to track down their metabolism and effects in the body. Randomized controlled trials represent the gold standard for establishing a causal relationship between food/diets and the metabolome of the collected sample material. Considering the inter- and intra-individual variability is vital and identifying responders and non-responders and their underlying determinants (*i.e.*, metabotypes) will provide new possibilities to tailored diets to improve the efficacy of interventions [1,32*].

Biomarkers of food intake and dietary patterns

Dietary biomarkers are metabolites objectively depicting the intake of certain foods or dietary patterns. Biomarkers can be classified based on the level of evidence [33**]. Recently, biomarker development and validation frameworks have been advanced [34] and the most promising biomarkers across important foods categories have been recently comprehensively reviewed [35**]. There are currently few validated food intake biomarkers, such as alkylresorcinols for whole grain wheat and rye intake, proline betaine for citrus fruits, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) for fish [33**,34,36*]. The search of novel biomarkers brings constantly emerging candidates for various food categories as summarized for the past 2—3 years in Table 1. For example, a study conducted by following the protocols of the Food Biomarker Alliance (FoodBAll) project aiming for the systematic coverage and validation of food biomarkers, shows promise for novel volatile biomarkers for dairy, cheese and soy-based drink intake [37]. Sex-specific differences in metabolic outcomes portray as one important aspect of biomarker discovery. Langenau et al. [38], for example, have reported differential biomarkers between men and women for coffee and fish.

In addition to individual foods, various studies have suggested biomarker candidates also for dietary patterns, as summarized for the past 2—3 years in Table 2. Mediterranean and Nordic diets are frequently referred as healthy dietary patterns with *e.g.* fish and whole-grain consumption as common elements. For example, Gürdeniz et al. [36*] reported urinary DHBA-glycine, CMPF and CMPF-glucuronide being significant metabolites associated with Healthy Nordic Diet. To accommodate both human and planetary health, plant-rich diets are increasingly important, which also shows in the recent research (Table 2).

Table 1

Most recently suggested biomarkers of food intake (reported in 2020−2023).

Food	Biomarker	HMDB ID	Sample; method	Reference
Almond	*alpha*-Tocopherol	HMDB0001893	Feces; GC−MS	[39]
	5-Hydroxyindoleacetic acid (5-HIAA)	HMDB0000763		
Beer	ʟ-Cysteine	HMDB0000574	Plasma; GC−MS	[40]
	ᴅ-Lactose	HMDB0041627	Urine; GC−MS	
	ᴅ-Psicose	HMDB0250793		
Bell pepper	Six capsanthin- and capsorubin-derived glucuronides (see ref. for exact structures)	n/a	Urine; LC-MS, structural elucidation with NMR	[41]
Butter	Undecylenic acid (11:1*n*–1)	HMDB0033724	Serum; LC-MS/MS	[38]
Cheese	2-Heptanone	HMDB0003671	Plasma; GC−MS	[37]
	2-Undecanone	HMDB0033713		
Coffee	Glutamic acid	HMDB0000148	Plasma; GC−MS	[38,40]
	Quinic acid	HMDB0003072	Serum; LC-MS/MS	
	Paraxanthine (in men)	HMDB0001860	Urine; GC−MS	
	Catechol	HMDB0000957		
	Dimethyluric acid	HMDB0001857		
	Methyluric acid	HMDB0003099		
	Niacin	HMDB0001488		
	ᴅ-Psicose	HMDB0250793		
Dairy	3,5-Dimethyloctan-2-one	n/a	Plasma; GC−MS	[37]
Fish	EPA (20:5*n*–3) (in men)	HMDB0001999	Serum; LC-MS/MS	[38]
Milk	3-Ethylphenol	HMDB0059873	Urine; GC−MS	[37]
Poultry	3-Methylhistidine	HMDB0000479	Serum; LC-MS/MS	[38]
Spinach	Des-aminoarginine pentenol ester*	n/a	Urine; LC-MS	[42]
	ᴅ/ʟ-Malic acid-*p*-coumarate	HMDB0303755		
Walnut	5-HIAA	HMDB0000763	Feces; GC−MS	[39]
	Uric acid	HMDB0000289		
White bread	Dodecanoic acid	HMDB0000638	Plasma; GC−MS	[40]
Whole-grain (wheat/rye)	5-Aminovaleric acid betaine (5-AVAB)	HMDB0240732	Serum; LC-MS	[43,44**]
	Pipecolic acid betaine	HMDB0304559		
	Tetradecanedioic acid	HMDB0000872		
Wine	Erythritol	HMDB0002994	Plasma; GC−MS	[40]
	Xylitol	HMDB0242149	Urine; GC−MS	
	Cinnamoylglycine	HMDB0011621		
	Citramalate	HMDB0000426		
	Erythritol	HMDB0002994		
	ᴅ-Gluconic acid	HMDB0000625		
	Tartaric acid	HMDB0000956		

* Tentative identification, novel structure not verified

Table 2

Examples of biomarker candidates of dietary patterns (reported in 2021–2022). Most of the biomarkers remain to be validated.

Food intake pattern	Associated foods	Associated metabolites	HMDB ID	Reference
Dietary approaches to stop hypertension (DASH)	Rich in fruits, vegetables, low-fat dairy products; moderate in meat, fish, poultry, nuts, and beans; low in sugar and red meat	2-Methylserine	n/a	[45–47]
		4-Allylphenol sulfate	HMDB0170765	
		beta-Cryptoxanthine	HMDB0033844	
		CAR 3:0	HMDB0000824	
		DG 18:2/18:3	HMDB0007249	
		DG 18:2/22:6	HMDB0007266	
		N-Methylproline	HMDB0094696	
		Ornithine	HMDB0000214	
		Panthotenate	HMDB0000210	
		Proline betaine	HMDB0004827	
		S-Allylcysteine	HMDB0034323	
		Threonate	HMDB0245425	
Healthy Nordic diet	Berries, fish, fruits, low/non-fat dairy, vegetables, whole-grain	3,5-Dihydroxybenzoic acid (3,5-DHBA)	HMDB0013677	[36*,48]
		3,5-DHBA-glycine	n/a	
		CEHC	n/a	
		3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF)	HMDB0061112	
		CMPF-glucuronide	n/a	
		CAR 8:1	n/a	
		CAR 10:3	n/a	
		(Glycine) betaine	HMDB0000043	
		Hippuric acid	HMDB0000714	
		Indole-3-propionic acid	HMDB0002302	
		Linoleamide	HMDB0062656	
		Loliolide	HMDB0302428	
		Methylimidazoleacetic acid	HMDB0002820	
		Phenylalanine	HMDB0000159	
		Proline betaine	HMDB0004827	
Healthy plant-based diet (hPDI)	Coffee, fruits, legumes, nuts, plant protein, tea, vegetables, whole-grain	1-Methylnicotinamide	HMDB0000699	[49,50]
		1-Methyluric acid	HMDB0003099	
		3-Hydroxypyridine sulfate	HMDB0240652	
		4-Pyridoxic acid	HMDB0000017	
		4-Vinylphenol sulfate	HMDB0062775	
		Glyceric acid	HMDB0000139	
		Hippuric acid	HMDB0000714	
		Hydrocinnamic acid (3-phenylpropionic acid)	HMDB0000764	
		Indole-3-propionic acid	HMDB0002302	
		Lenticin (tryptophan betaine)	HMDB0061115	
		myo-Inositol	HMDB0000211	
		N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	
		N-Acetylornithine	n/a	
		O-methoxycatechol-O-sulfate	HMDB0060013	
		Pantothenic acid	HMDB0000210	
		Pipecolic acid	HMDB0000070	
		Pyrocatechol sulfate	HMDB0059724	
		Quinic acid	HMDB0003072	
		Threitol	HMDB0004136	

		Threonic acid	HMDB0000943	
		Trigonelline	HMDB0000875	
Mediterranean diet	Fruits, legumes, olive oil, red wine, seafood, vegetables, whole-grain	5-Hydroxyindole	HMDB0059805	[10,51,52]
		Deoxycholic acid glucuronide	HMDB0002596	
		Hydroxyperoxyeicosapentaenoic acid	n/a	
		L-Aspartylphenylalanine	HMDB0000706	
		PC 35:1	n/a	
		PC 40:6	n/a	
		Succinic acid	HMDB0000254	
		TMA	HMDB0000906	
Plant-based diet (overall PDI)	Plant foods in general	4-Vinylphenol sulfate	HMDB0062775	[49,50]
		gamma-CEHC	HMDB0001931	
		gamma-Glutamyl peptides	n/a	
		(Glycine) betaine	HMDB0000043	
		Cinnamoylglycine	HMDB0011621	
		Glutamine	HMDB0000641	
		Glycerate	HMDB0000139	
		Glycine	HMDB0000123	
		Hippuric acid	HMDB0000714	
		Indole-3-propionic acid	HMDB0002302	
		Lenticin	HMDB0061115	
		myo-Inositol	HMDB0000211	
		N-Acetylornithine	n/a	
		N-Methylproline	HMDB0094696	
		O-methoxycatechol-O-sulfate	HMDB0060013	
		Paraxanthine	HMDB0001860	
		Pipecolic acid	HMDB0000070	
		Proline betaine	HMDB0004827	
		Pyrocatechol sulfate	HMDB0059724	
		scyllo-Inositol	HMDB0006088	
		Threonic acid	HMDB0000943	
		Trigonelline	HMDB0000875	
Sugar-rich diet	E.g. sugar-sweetened beverages	Chenodeoxycholic acid	HMDB0000518	[53]
		Glycocholic acid	HMDB0000138	
		Glutamic acid	HMDB0000148	
		Lithocholic acid	HMDB0000761	
		Phenylglycine	HMDB0002210	
		Tyrosine	HMDB0000158	
Unhealthy plant-based diet (uPDI)	Desserts, fruit juices, potatoes, refined grains, sugar-sweetened and artificially sweetened beverages, sweets	1,5-Anhydrosorbitol (1,5-anhydroglucitol)	HMDB0002712	[49]
		3-Methyl-2-oxovaleric acid	HMDB0000491	
		gamma-CEHC	HMDB0001931	
		Bilirubin (Z,Z)	HMDB0000054	
		Bradykinin	HMDB0004246	
		Hydroxyphenyllactic acid	HMDB0000755	
		N2,N2-Dimethylguanosine	HMDB0004824	
		Proline	HMDB0000162	
		S−N-Methylcysteine	HMDB0302211	
Ultra-processed foods	Industrially processed meat-containing products, instant noodles,	3-Methyl-2-oxovaleric acid	HMDB0000491	[54,55]
		4-Methylsyringol sulfate	n/a	
		Bradykinin	HMDB0004246	
		Elaidic acid	HMDB0000573	

(*continued on next page*)

Table 2. (continued)

Food intake pattern	Associated foods	Associated metabolites	HMDB ID	Reference
Vegan diet	confectionery, margarine Fruits, legumes, vegetables, whole-grain	N2,N2-Dimethylguanosine Saccharin 4-Acetylphenyl sulfate 4-Allylpyrocatechol sulfate 4-Ethylphenyl sulfate beta-Cryptoxanthin alpha-Linolenic acid Butyric acid Folic acid Glycohyocholic acid Indole-3-propionic acid N-Methylproline Proline betaine S-Methylmethionine	HMDB0004824 HMDB0029723 n/a HMDB0304934 HMDB0062551 HMDB0033844 HMDB0001388 HMDB0000039 HMDB0000121 HMDB0240607 HMDB0002302 HMDB0094696 HMDB0004827 HMDB0038670	[56,57]

Abbreviations: CAR, acylcarnitine; CEHC, carboxyethyl hydroxychroman; TMA, trimethylamine; PC, phosphatidylcholine.

Host and gut metabolites reflecting diet

Gut microbiota is an essential modulator of the metabolic response to diet and resulting health effects [10,53,58**,59,60]. Indeed, gut microbiota has been shown to contribute to approx. 13% of the total variation in plasma metabolites [58**]. The importance of microbiota is evidenced by the recent cataloguing of the metabolites related to diet—microbiota interactions [14**,59]. Indolepropionic acid is a microbial conversion product from dietary tryptophan linked with better insulin as well as lower risk of type 2 diabetes (T2D) and metabolic syndrome [61*], while indolelactic acid is associated with obesity, insulin resistance, and higher T2D risk [62]. Indolepropionic acid levels in blood were associated with a lower intake of animal-based food and a higher intake of fiber-rich plant-based foods [62], and partially explained by indolepropionic acid-associated gut bacteria, such as *Firmicutes* and *Bifidobacterium*. The interaction between diet, gut microbiota, and metabolite profiles was particularly shown by the association between higher milk intake, higher levels of bifidobacteria and serum indolepropionic acid (detected only among lactase non-persistent individuals) [62].

Among the most recently emerged compounds related to diet, gut microbiota and health is 5-aminovaleric acid betaine (5-AVAB) [44**,63,64]. It can be directly absorbed from its dietary sources, such as whole-grain cereals (Table 1), or conversion of other compounds with trimethyl groups potentially mediated by gut microbiota. Despite its anti-inflammatory, anticancer, and antioxidant properties, associations with fatty liver disease and cognitive decline have been reported, calling for further studies to disentangle if the association between 5-AVAB and health outcomes is depending on certain constraints or individual factors [44**].

Another controversial metabolite in terms of health relevance is trimethylamine *N*-oxide (TMAO), that has been linked with a higher risk of cardiovascular disease [65—67]. TMAO can enter circulation either directly from dietary sources such as fish, or *via* the activity of gut bacteria and liver metabolism from dietary precursors such as carnitine and choline rich in for example red meat [66,68,69]. Interestingly, females seem to have a higher abundance of bacteria producing trimethylamine, despite generally higher consumption of meat in males [68]. Even when TMAO levels can be associated with foods such as fish, whole-grains, poultry and eggs, these dietary items *per se* are not linked with adverse health outcomes, but merely the opposite, which highlights the fact that we have not yet fully understood the metabolic role of TMAO [66,67,70].

Short-chain fatty acids (SCFAs; formate, acetate, propionate, and butyrate) have been shown to benefit gut health *e.g.* by protecting epithelial integrity and

suppressing pro-inflammatory pathways [71]. SCFAs have also been shown to play roles in the regulation of intestinal hormones, appetite, and blood pressure, as well as glucose and lipid homeostasis [52]. Consumption of fiber-rich foods has been shown to increase SCFA levels, *e.g.* in vegan and Mediterranean diets [10,16]. Other determinants of SCFAs are intestinal gases, iron abundance, and colonic pH, all connected to both diet and gut microbial composition and activity [72]. Recent studies have suggested that plasma SCFA concentrations are of greater importance than fecal SCFA concerning metabolic risk factors and diseases [73–75].

Glycerophospholipids have been suggested to provide a pool of early biomarker candidates for metabolic syndrome, cardiometabolic diseases [13*,76,77*,78] and adherence to healthy eating patterns [36*]. Lysophosphatidylcholine (LPC) species may be the most interesting group of glycerophospholipids regarding the discovery of dietary biomarkers for metabolic health. For example, decreased LPC 18:2 levels have been suggested to indicate metabolic syndrome risk [13*,76] whereas a positive association has been found between LPC 18:1 and LPC 18:2 and adherence to dietary recommendations of The World Cancer Research Fund and American Institute for Cancer Research (WCRF/AICR) [79]. As LPC 18:2 may play a role as a robust biomarker for healthy dietary patterns and metabolic health, acyl-carnitine (CAR) with an 18:2 fatty acid tail has been found to correlate positively with the intake of linoleic acid (18:2), as well as with circulating ornithine and male sex [80]. In general, circulating acylcarnitines are often suggested as markers of impaired lipid and/or glucose metabolism [80].

Besides phospholipids, two other interesting categories to mention are bile acids and ceramides. Sex-based differences in fecal levels of bile acids have been observed [81]. Adherence to certain dietary patterns, such as vegan, Mediterranean or sugar-rich diet, has been shown to modulate such bile acids profiles and metabolic risk markers [10,16,52,53]. Fecal chenodeoxycholic acid, glycocholic acid, cholic acid, and hyodeoxycholic acid have been shown to be associated with higher circulating glucose, insulin, triglycerides, and LDL, especially in individuals with metabolic syndrome [13*]. Ceramides (Cer) seem to associate with either a higher or lower risk of T2D depending on the acyl chain length. For example, Cer 16:0, Cer 18:0 and dihydroceramide dhCer 20:0 were associated with higher risk, whereas Cer 20:0, dhCer 22:2 and dhCer 26:1 were associated with lower T2D risk [82]. These ceramides were also suggested to partly mediate the previously reported adverse effect of high red meat consumption on T2D risk. Similarly, Cer 22:2 was suggested to mediate the positive effect of coffee consumption on T2D risk. Ceramides may exemplify how metabolites may mediate the interaction between diet and cardiometabolic health [82].

Towards precision nutrition and prevention with metabolomics

It is well established that people vary in response to diet [83], which makes it important to find metabolites indicating or responsible for such variations in metabolic phenotypes (metabotypes) [84]. Thus, profiling such metabolites is promising in predicting dietary responses and stratifying the individuals based on their predicted responses. Once the metabolites are well characterized, further attempts can be made to trace the dietary sources or other factors responsible for such metabolites. This knowledge will aid in precision prevention, either using specific dietary components or lifestyle intervention to target the alteration of such metabolites to achieve the desired metabolite profiles. On the other hand, a precision intervention strategy specifically targeted to responders [47] will help improve the efficacy rate of the intervention [85]. For example, giving dietary intervention according to tissue-specific metabotypes has been shown to enhance improvement in cardiometabolic health markers in targeted participants [86]. The PERSonalized Glucose Optimization Through Nutritional Intervention (PERSON) study was one of the first randomized clinical trials to test effects of a personalized dietary intervention based on metabolism related phenotypes [87*]. Also in the PREVENTOMICS platform individuals are classified into clusters for personalized dietary plans [32*]. Although a personalized diet plan did not show significant improvement in the endpoint markers compared to a generic healthy diet, the PREVENTOMICS study may work as a pioneer study to further investigate the use of metabolomics together with other omics in biomarker-guided dietary interventions [32*].

Concluding remarks

Metabolomics holds the potential for wider utilization in all aspects related to nutrition as discussed in this review, as long as the computational methods to process, mine, and visualize the complex metabolomics data, including the identification of the metabolites, continue to be developed to provide reliable results and informative interpretations of the data. This is also the prerequisite in order to fully exploit the latest technological advancements and to have them more widely adopted. Metabolomics-based frameworks keep accelerating the discovery and validation of dietary biomarkers. Examples mentioned here raise the importance of the examination of metabolome profiles in investigating the links between diet, gut microbiota and metabolic health outcomes. Metabolomics has a key role in defining more detailed and personalized nutritional recommendations and dividing foods into more health-relevant categories.

Author contributions

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Kati Hanhineva reports a relationship with Afekta Technologies that includes: board membership, employment, and equity or stocks. Ville Koistinen reports a relationship with Afekta Technologies that includes: board membership, employment, and equity or stocks. Topi Meuronen reports a relationship with Afekta Technologies that includes: consulting or advisory and paid expert testimony.

Data availability

No data was used for the research described in the article.

Acknowledgments

References

Papers of particular interest, published within the period of review, have been highlighted as:

   * of special interest
  ** of outstanding interest

1.   LeVatte M, Keshteli AH, Zarei P, Wishart DS: **Applications of metabolomics to precision nutrition**. *Lifestyle Genom* 2022, **15**: 1−9.

2.   Hillesheim E, Brennan L: **Metabotyping and its role in nutrition research**. *Nutr Res Rev* 2020, **33**:33−42.

3.   Lichtenberg S, Trifonova OP, Maslov DL, Balashova EE, Lokhov PG: **Metabolomic laboratory-developed tests: current status and perspectives**. *Metabolites* 2021, **11**:423.

4.   Barabási A-L, Menichetti G, Loscalzo J: **The unmapped chemi-**
 * **cal complexity of our diet**. *Nat Food* 2020, **1**:33−37.
The article presents new perspectives and tools for understanding the complexity of chemical components in our food.

5.   Jacobs DM, van den Berg MA, Hall RD: **Towards superior plant-based foods using metabolomics**. *Curr Opin Biotechnol* 2021, **70**:23−28.

6.   Delvaux A, Rathahao-Paris E, Alves S: **Different ion mobility-mass spectrometry coupling techniques to promote metab-olomics**. *Mass Spectrom Rev* 2022, **41**:695−721.

7.   Yuliana ND, Hunaefi D, Goto M, Ishikawa YT, Verpoorte R: **Measuring the health effects of food by metabolomics**. *Crit Rev Food Sci Nutr* 2022, **62**:6359−6373.

8.   Lacalle-Bergeron L, Portolés T, López FJ, Sancho JV, Ortega-Azorín C, Asensio EM, Coltell O, Corella D: **Ultra-performance liquid chromatography-ion mobility separation-quadruple time-of-flight MS (UHPLC-IMS-QTOF MS) metabolomics for short-term biomarker discovery of orange intake: a random-ized, controlled crossover study**. *Nutrients* 2020, **12**:1916.

9.   He W, Bertram HC: **NMR-based metabolomics to decipher the molecular mechanisms in the action of gut-modulating foods**. *Foods* 2022, **11**:2707.

10. Galié S, García-Gavilán J, Papandreou C, Camacho-Barcía L, Arcelin P, Palau-Galindo A, Rabassa A, Bulló M: **Effects of Mediterranean Diet on plasma metabolites and their rela-tionship with insulin resistance and gut microbiota compo-sition in a crossover randomized clinical trial**. *Clin Nutr* 2021, **40**:3798−3806.

11. Galié S, Papandreou C, Arçelin P, Garcia D, Palau-Galindo A, Gutiérrez-Tordera L, Folch À, Bulló M: **Examining the interac-tion of the gut microbiome with host metabolism and cardi-ometabolic health in metabolic syndrome**. *Nutrients* 2021, **13**: 4318.

12. Olshan KL, Zomorrodi AR, Pujolassos M, Troisi J, Khan N, Fanelli B, Kenyon V, Fasano A, Leonard MM: **Microbiota and metabolomic patterns in the breast milk of subjects with celiac disease on a gluten-free diet**. *Nutrients* 2021, **13**:2243.

13. Comte B, Monnerie S, Brandolini-Bunlon M, Canlet C, Castelli F,
 * Chu-Van E, Colsch B, Fenaille F, Joly C, Jourdan F, *et al.*: **Multiplatform metabolomics for an integrative exploration of metabolic syndrome in older men**. *EBioMedicine* 2021, **69**, 103440.
Multiomics platform combining non-targeted metabolomics and lipido-mics is utilized for deep phenotyping in order to define the molecular signature for metabolic syndrome in a longitudinal cohort.

14. Wishart DS, Oler E, Peters H, Guo A, Girod S, Han S, Saha S,
** Lui VW, LeVatte M, Gautam V, *et al.*: **MiMeDB: the human mi-crobial metabolome database**. *Nucleic Acids Res* 2023, **51**: D611−D620.
New multiomics database aiming to advance the understanding of the human microbiome, the human microbial metabolome and the human exposome in respect to human health and disease.

15. Schmid R, Heuckeroth S, Korf A, Smirnov A, Myers O, Dyrlund TS, Bushuiev R, Murray KJ, Hoffmann N, Lu M, *et al.*: **Integrative analysis of multimodal mass spectrometry data in MZmine**. *Nat Biotechnol* 2023:447−449.

16. Prochazkova M, Budinska E, Kuzma M, Pelantova H, Hradecky J, Heczkova M, Daskova N, Bratova M, Modos I, Videnska P, *et al.*: **Vegan diet is associated with favorable effects on the meta-bolic performance of intestinal microbiota: a cross-sectional multi-omics study**. *Front Nutr* 2022, **8**, 783302.

17. Ni Z, Wölk M, Jukes G, Mendivelso Espinosa K, Ahrends R, Aimo L, Alvarez-Jarreta J, Andrews S, Andrews R, Bridge A, *et al.*: **Guiding the choice of informatics software and tools for lipidomics research applications**. *Nat Methods* 2023, **20**: 193−204.

18. Bao R, Hesser LA, He Z, Zhou X, Nadeau KC, Nagler CR: **Fecal microbiome and metabolome differ in healthy and food-allergic twins**. *J Clin Invest* 2021, **131**, e141935.

19. Taylor BC, Lejzerowicz F, Poirel M, Shaffer JP, Jiang L, Aksenov A, Litwin N, Humphrey G, Martino C, Miller-Montgomery S, *et al.*: **Consumption of fermented foods is associated with systematic differences in the gut microbiome and metabolome**. *mSystems* 2020, **5**, e00901−e00919.

20. Wang B, Zhang B, Zhou L, Li S, Li Z, Luo H: **Multi-omics reveals diet-induced metabolic disorders and liver inflammation via microbiota-gut-liver axis**. *J Nutr Biochem* 2023, **111**, 109183.

21. Marabita F, James T, Karhu A, Virtanen H, Kettunen K, Stenlund H, Boulund F, Hellström C, Neiman M, Mills R, *et al.*: **Multiomics and digital monitoring during lifestyle changes reveal independent dimensions of human biology and health**. *Cell Sys* 2022, **13**:241−255.e7.

22. Zhang P, Carlsten C, Chaleckis R, Hanhineva K, Huang M, Isobe T, Koistinen VM, Meister I, Papazian S, Sdougkou K, *et al.*: **Defining the scope of exposome studies and research needs from a multidisciplinary perspective**. *Environ Sci Technol Lett* 2021, **8**:839−852.

23. Rakusanova S, Fiehn O, Cajka T: **Toward building mass spectrometry-based metabolomics and lipidomics atlases for biological and clinical research**. *TrAC Trends Anal Chem* 2023, **158**, 116825.

24. McNairn M, Brito A, Dillard K, Heath H, Pantaleon M, Fanter R, Pilolla K, Amin S, La Frano MR: **Postprandial dried blood spot-based nutritional metabolomic analysis discriminates a high-fat, high-protein meat-based diet from a high carbohydrate vegan diet: a randomized controlled crossover trial**. *J Acad Nutr Diet* 2021, **121**:931−941.e2.

25. Deprez S, Van Uytfanghe K, Stove CP: **Liquid chromatography-tandem mass spectrometry for therapeutic drug monitoring of immunosuppressants and creatinine from a single dried blood spot using the Capitainer® qDBS device**. *Anal Chim Acta* 2023, **1242**, 340797.

26. Gardner A, Carpenter G, So P-W: **Salivary metabolomics: from diagnostic biomarker discovery to investigating biological function**. *Metabolites* 2020, **10**:47.

27. Delgado-Povedano MM, Castillo-Peinado LS, Calderón-Santiago M, Luque de Castro MD, Priego-Capote F: **Dry sweat as sample for metabolomics analysis**. *Talanta* 2020, **208**, 120428.

28. *FooDB*. 2023. https://foodb.ca/. Accessed 8 February 2023.

29. Criscuolo A, Nepachalovich P, Garcia-del Rio DF, Lange M, Ni Z, Baroni M, Cruciani G, Goracci L, Blüher M, Fedorova M: **Analytical and computational workflow for in-depth analysis of oxidized complex lipids in blood plasma**. *Nat Commun* 2022, **13**:6547.

30. Medina J, Borreggine R, Teav T, Gao L, Ji S, Carrard J, Jones C, Blomberg N, Jech M, Atkins A, *et al.*: **Omic-scale quantitative HILIC-MS/MS approach for circulatory lipid phenotyping in clinical research**. *Anal Chem* 2023, **95**:3168−3179.

31. Bach E, Schymanski EL, Rousu J: **Joint structural annotation of small molecules using liquid chromatography retention order and tandem mass spectrometry data**. *Nat Mach Intell* 2022, **4**:1224−1237.

32. Aldubayan MA, Pigsborg K, Gormsen SMO, Serra F, Palou M,
* Galmés S, Palou-March A, Favari C, Wetzels M, Calleja A, *et al.*: **A double-blinded, randomized, parallel intervention to evaluate biomarker-based nutrition plans for weight loss: the PREVENTOMICS study**. *Clin Nutr* 2022, **41**:1834−1844.
Pioneering study where metabolomic and genetic information was used to classify individuals into different metabolic clusters to create personalized dietary plans.

33. Rafiq T, Azab SM, Teo KK, Thabane L, Anand SS, Morrison KM,
** de Souza RJ, Britz-McKibbin P: **Nutritional metabolomics and the classification of dietary biomarker candidates: a critical review**. *Adv Nutr* 2021, **12**:2333−2357.
Classification of dietary biomarker candidates by a scoring system based on replicated reports in interventional and observational studies.

34. Dragsted LO, Gao Q, Scalbert A, Vergères G, Kolehmainen M, Manach C, Brennan L, Afman LA, Wishart DS, Andres Lacueva C, *et al.*: **Validation of biomarkers of food intake—critical assessment of candidate biomarkers**. *Genes Nutr* 2018, **13**:14.

35. Landberg R, Karra P, Hoobler R, Loftfield E, Huybrechts I,
** Rattner JI, Noerman S, Claeys L, Neveu V, Vidkjaer NH, *et al.*: **Dietary biomarkers - an update on their validity and applicability in epidemiological studies**. *Nutr Rev* 2023, https://doi.org/10.1093/nutrit/nuad119.
Recent update on the validity and applicability of dietary biomarkers in epidemiological studies.

36. Gürdeniz G, Uusitupa M, Hermansen K, Savolainen MJ,
* Schwab U, Kolehmainen M, Brader L, Cloetens L, Herzig K-H, Hukkanen J, *et al.*: **Analysis of the SYSDIET Healthy Nordic Diet randomized trial based on metabolic profiling reveal beneficial effects on glucose metabolism and blood lipids**. *Clin Nutr* 2022, **41**:441−451.
Study presents a novel way to re-analyse dietary intervention studies.

37. Fuchsmann P, Tena Stern M, Münger LH, Pimentel G, Burton KJ, Vionnet N, Vergères G: **Nutrivolatilomics of urinary and plasma samples to identify candidate biomarkers after cheese, milk, and soy-based drink intake in healthy humans**. *J Proteome Res* 2020, **19**:4019−4033.

38. Langenau J, Oluwagbemigun K, Brachem C, Lieb W, di Giuseppe R, Artati A, Kastenmüller G, Weinhold L, Schmid M, Nöthlings U: **Blood metabolomic profiling confirms and identifies biomarkers of food intake**. *Metabolites* 2020, **10**:468.

39. Shinn LM, Mansharamani A, Baer DJ, Novotny JA, Charron CS, Khan NA, Zhu R, Holscher HD: **Fecal metabolites as biomarkers for predicting food intake by healthy adults**. *J Nutr* 2022, **152**:2956−2965.

40. Li KJ, Burton-Pimentel KJ, Brouwer-Brolsma EM, Blaser C, Badertscher R, Pimentel G, Portmann R, Feskens EJM, Vergères G: **Identifying plasma and urinary biomarkers of fermented food intake and their associations with cardiometabolic health in a Dutch observational cohort**. *J Agric Food Chem* 2023, **71**:4426−4439.

41. Schulz M, Hövelmann Y, Hübner F, Humpf H-U: **Identification of potential urinary biomarkers for bell pepper intake by HPLC−HRMS-based metabolomics and structure elucidation by NMR**. *J Agric Food Chem* 2021, **69**:13644−13656.

42. Xi M, La Barbera G, Eriksen JN, Prahm AP, Jeppesen PB, Dragsted LO: **Discovery of urinary biomarkers of spinach consumption using untargeted LC-MS metabolomics in a human intervention trial**. *Mol Nutr Food Res* 2022, **66**, 2100260.

43. Noerman S, Virtanen JK, Lehtonen M, Brunius C, Hanhineva K: **Serum metabolites associated with wholegrain consumption using nontargeted metabolic profiling: a discovery and reproducibility study**. *Eur J Nutr* 2023, **62**:713−726.

44. Haikonen R, Kärkkäinen O, Koistinen V, Hanhineva K: **Diet- and
** microbiota-related metabolite, 5-aminovaleric acid betaine (5-AVAB), in health and disease**. *Trends Endocrinol Metabol* 2022, **33**:463−480.
Review on 5-aminovaleric acid betaine (5-AVAB) and its role in human physiology and pathology.

45. Louca P, Nogal A, Mompeo O, Christofidou P, Gibson R, Spector TD, Berry SE, Valdes AM, Mangino M, Menni C: **Body mass index mediates the effect of the DASH diet on hypertension: common metabolites underlying the association**. *J Hum Nutr Diet* 2022, **35**:214−222.

46. Kim H, Rebholz CM: **Metabolomic biomarkers of healthy dietary patterns and cardiovascular outcomes**. *Curr Atheroscler Rep* 2021, **23**:26.

47. Noerman S, Landberg R: **Blood metabolite profiles linking dietary patterns with health – toward precision nutrition**. *J Intern Med* 2023, **239**:408−432.

48. Noerman S, Kokla M, Koistinen VM, Lehtonen M, Tuomainen T-P, Brunius C, Virtanen JK, Hanhineva K: **Associations of the serum metabolite profile with a healthy Nordic diet and risk of coronary artery disease**. *Clin Nutr* 2021, **40**:3250−3262.

49. Kim H, Yu B, Li X, Wong KE, Boerwinkle E, Seidelmann SB, Levey AS, Rhee EP, Coresh J, Rebholz CM: **Serum metabolomic signatures of plant-based diets and incident chronic kidney disease**. *Am J Clin Nutr* 2022, **116**:151−164.

50. Wang F, Baden MY, Guasch-Ferré M, Wittenbecher C, Li J, Li Y, Wan Y, Bhupathiraju SN, Tobias DK, Clish CB, *et al.*: **Plasma metabolite profiles related to plant-based diets and the risk of type 2 diabetes**. *Diabetologia* 2022, **65**:1119−1132.

51. Barber C, Mego M, Sabater C, Vallejo F, Bendezu RA, Masihy M, Guarner F, Espín JC, Margolles A, Azpiroz F: **Differential effects of Western and Mediterranean-type diets on gut microbiota: a metagenomics and metabolomics approach**. *Nutrients* 2021, **13**:2638.

52. Galié S, García-Gavilán J, Camacho-Barcía L, Atzeni A, Muralidharan J, Papandreou C, Arcelin P, Palau-Galindo A, Garcia D, Basora J, *et al.*: **Effects of the Mediterranean diet or nut consumption on gut microbiota composition and fecal metabolites and their relationship with cardiometabolic risk factors**. *Mol Nutr Food Res* 2021, **65**, 2000982.

53. Yan T, Shi L, Xu K, Bai J, Wen R, Liao X, Dai X, Wu Q, Zeng L, Peng W, *et al.*: **Habitual intakes of sugar-sweetened**

beverages associated with gut microbiota-related metabolites and metabolic health outcomes in young Chinese adults. *Nutr Metabol Cardiovasc Dis* 2022, **33**:359−368.

54. Huybrechts I, Rauber F, Nicolas G, Casagrande C, Kliemann N, Wedekind R, Biessy C, Scalbert A, Touvier M, Aleksandrova K, *et al.*: **Characterization of the degree of food processing in the European Prospective Investigation into Cancer and Nutrition: application of the Nova classification and validation using selected biomarkers of food processing**. *Front Nutr* 2022, **9**, 1035580.

55. Su D, Chen J, Du S, Kim H, Yu B, Wong KE, Boerwinkle E, Rebholz CM: **Metabolomic markers of ultra-processed food and incident CKD**. *Clin J Am Soc Nephrol* 2023, **18**:327−336.

56. Hovinen T, Korkalo L, Freese R, Skaffari E, Isohanni P, Niemi M, Nevalainen J, Gylling H, Zamboni N, Erkkola M, Suomalainen A: **Vegan diet in young children remodels metabolism and challenges the statuses of essential nutrients**. *EMBO Mol Med* 2021, **13**, e13492.

57. Miles FL, Orlich MJ, Mashchak A, Chandler PD, Lampe JW, Duerksen-Hughes P, Fraser GE: **The biology of veganism: plasma metabolomics analysis reveals distinct profiles of vegans and non-vegetarians in the Adventist Health Study-2 cohort**. *Nutrients* 2022, **14**:709.

58. Chen L, Zhernakova DV, Kurilshikov A, Andreu-Sánchez S,
** Wang D, Augustijn HE, Vich Vila A, Weersma RK, Medema MH, Netea MG, *et al.*: **Influence of the microbiome, diet and genetics on inter-individual variation in the human plasma metabolome**. *Nat Med* 2022, **28**:2333−2343.
Extensive investigation of inter-individual variation in the plasma metabolome in association with diet, the gut microbiome and genetics.

59. Dekkers KF, Sayols-Baixeras S, Baldanzi G, Nowak C, Hammar U, Nguyen D, Varotsis G, Brunkwall L, Nielsen N, Eklund AC, *et al.*: **An online atlas of human plasma metabolite signatures of gut microbiome composition**. *Nat Commun* 2022, **13**:5370.

60. Tang L, Li L, Bu L, Guo S, He Y, Liu L, Xing Y, Lou F, Zhang F, Wang S, *et al.*: **Bigu-style fasting affects metabolic health by modulating taurine, glucose, and cholesterol homeostasis in healthy young adults**. *J Nutr* 2021, **151**:2175−2187.

61. Sehgal R, de Mello VD, Männistö V, Lindström J, Tuomilehto J,
* Pihlajamäki J, Uusitupa M: **Indolepropionic acid, a gut bacteria-produced tryptophan metabolite and the risk of type 2 diabetes and non-alcoholic fatty liver disease**. *Nutrients* 2022, **14**: 4695.
The role of indolepropionic acid as a marker of metabolic disorders is comprehehensively discussed in this review.

62. Qi Q, Li J, Yu B, Moon J-Y, Chai JC, Merino J, Hu J, Ruiz-Canela M, Rebholz C, Wang Z, *et al.*: **Host and gut microbial tryptophan metabolism and type 2 diabetes: an integrative analysis of host genetics, diet, gut microbiome and circulating metabolites in cohort studies**. *Gut* 2022, **71**:1095−1105.

63. Koistinen VM, Kärkkäinen O, Borewicz K, Zarei I, Jokkala J, Micard V, Rosa-Sibakov N, Auriola S, Aura A-M, Smidt H, Hanhineva K: **Contribution of gut microbiota to metabolism of dietary glycine betaine in mice and in vitro colonic fermentation**. *Microbiome* 2019, **7**:103.

64. Zhao M, Zhao L, Xiong X, He Y, Huang W, Liu Z, Ji L, Pan B, Guo X, Wang L, *et al.*: **TMAVA, a metabolite of intestinal microbes, is increased in plasma from patients with liver steatosis, inhibits γ-butyrobetaine hydroxylase, and exacerbates fatty liver in mice**. *Gastroenterology* 2020, **158**: 2266−2281.e27.

65. Mei Z, Chen G-C, Wang Z, Usyk M, Yu B, Baeza YV, Humphrey G, Benitez RS, Li J, Williams-Nguyen JS, *et al.*: **Dietary factors, gut microbiota, and serum trimethylamine-N-oxide associated with cardiovascular disease in the Hispanic Community Health Study/Study of Latinos**. *Am J Clin Nutr* 2021, **113**:1503−1514.

66. Wang M, Wang Z, Lee Y, Lai HTM, de Oliveira Otto MC, Lemaitre RN, Fretts A, Sotoodehnia N, Budoff M, DiDonato JA, *et al.*: **Dietary meat, trimethylamine N-oxide-related metabolites, and incident cardiovascular disease among older adults: the cardiovascular health study**. *Arterioscler Thromb Vasc Biol* 2022, **42**:e273−e288.

67. Li J, Li Y, Ivey KL, Wang DD, Wilkinson JE, Franke A, Lee KH, Chan A, Huttenhower C, Hu FB, *et al.*: **Interplay between diet and gut microbiome, and circulating concentrations of trimethylamine *N*-oxide: findings from a longitudinal cohort of US men**. *Gut* 2022, **71**:724−733.

68. Rath S, Rox K, Kleine Bardenhorst S, Schminke U, Dörr M, Mayerle J, Frost F, Lerch MM, Karch A, Brönstrup M, *et al.*: **Higher trimethylamine-*N*-oxide plasma levels with increasing age are mediated by diet and trimethylamine-forming bacteria**. *mSystems* 2021, **6**, e00945−21.

69. Costabile G, Vetrani C, Bozzetto L, Giacco R, Bresciani L, Del Rio D, Vitale M, Della Pepa G, Brighenti F, Riccardi G, *et al.*: **Plasma TMAO increase after healthy diets: results from 2 randomized controlled trials with dietary fish, polyphenols, and whole-grain cereals**. *Am J Clin Nutr* 2021, **114**:1342−1350.

70. Noerman S, Kärkkäinen O, Mattsson A, Paananen J, Lehtonen M, Nurmi T, Tuomainen T-P, Voutilainen S, Hanhineva K, Virtanen JK: **Metabolic profiling of high egg consumption and the associated lower risk of type 2 diabetes in middle-aged Finnish men**. *Mol Nutr Food Res* 2019, **63**, e1800605.

71. Vasishta S, Ganesh K, Umakanth S, Joshi MB: **Ethnic disparities attributed to the manifestation in and response to type 2 diabetes: insights from metabolomics**. *Metabolomics* 2022, **18**: 45.

72. Deleu S, Machiels K, Raes J, Verbeke K, Vermeire S: **Short chain fatty acids and its producing organisms: an overlooked therapy for IBD?** *EBioMedicine* 2021, **66**, 103293.

73. Yang LL, Stiernborg M, Skott E, Gillberg T, Landberg R, Giacobini M, Lavebratt C: **Lower plasma concentrations of short-chain fatty acids (SCFAs) in patients with ADHD**. *J Psychiatr Res* 2022, **156**:36−43.

74. Xu J, Landberg R, Lavebratt C, Bulik CM, Landén M, Nilsson IAK: **Plasma concentrations of short-chain fatty acids in active and recovered anorexia nervosa**. *Nutrients* 2022, **14**:5247.

75. Müller M, Hernández MAG, Goossens GH, Reijnders D, Holst JJ, Jocken JWE, van Eijk H, Canfora EE, Blaak EE: **Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans**. *Sci Rep* 2019, **9**, 12515.

76. Eichelmann F, Sellem L, Wittenbecher C, Jäger S, Kuxhaus O, Prada M, Cuadrat R, Jackson KG, Lovegrove JA, Schulze MB: **Deep lipidomics in human plasma: cardiometabolic disease risk and effect of dietary fat modulation**. *Circulation* 2022, **146**: 21−35.

77. Calderón-Pérez L, Suárez-García S, Pedret A, Suárez M,
* Llauradó E, Rubió L, del Bas JM, Caimari A, Puiggrós F, Arola L, *et al.*: **Serum lysophospholipidome of dietary origin as a suitable susceptibility/risk biomarker of human hypercholesterolemia: a cross-sectional study**. *Clin Nutr* 2022, **41**: 489−499.
Multiomics platform combining non-targeted metabolomics and lipidomics is utilized for deep phenotyping in order to define the molecular signature for metabolic syndrome in a longitudinal cohort.

78. Chen S, Wu Q, Zhu L, Zong G, Li H, Zheng H, Zeng R, Lin X, Sun L: **Plasma glycerophospholipid profile, erythrocyte n−3 PUFAs, and metabolic syndrome incidence: a prospective study in Chinese men and women**. *Am J Clin Nutr* 2021, **114**: 143−153.

79. Rothwell JA, Murphy N, Bešević J, Kliemann N, Jenab M, Ferrari P, Achaintre D, Gicquiau A, Vozar B, Scalbert A, *et al.*: **Metabolic signatures of healthy lifestyle patterns and colorectal cancer risk in a European cohort**. *Clin Gastroenterol Hepatol* 2022, **20**:e1061−e1082.

80. Wedekind R, Rothwell JA, Viallon V, Keski-Rahkonen P, Schmidt JA, Chajes V, Katzke V, Johnson T, de Magistris MS, Krogh V, *et al.*: **Determinants of blood acylcarnitine concentrations in healthy individuals of the European Prospective Investigation into Cancer and Nutrition**. *Clin Nutr* 2022, **41**: 1735−1745.

81. Liu Y, Chen L, Liu L, Zhao S-S, You J-Q, Zhao X-J, Liu H-X, Xu G-W, Wen D-L: **Interplay between dietary intake, gut microbiota, and metabolic profile in obese adolescents: sex-dependent differential patterns**. *Clin Nutr* 2022, **41**:2706–2719.

82. Wittenbecher C, Cuadrat R, Johnston L, Eichelmann F, Jäger S, Kuxhaus O, Prada M, Del Greco M F, Hicks AA, Hoffman P, *et al.*: **Dihydroceramide- and ceramide-profiling provides insights into human cardiometabolic disease etiology**. *Nat Commun* 2022, **13**:936.

83. Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, Ben-Yacov O, Lador D, Avnit-Sagi T, Lotan-Pompan M, *et al.*: **Personalized nutrition by prediction of glycemic responses**. *Cell* 2015, **163**:1079–1094.

84. Noerman S, Kolehmainen M, Hanhineva K: **Profiling of endogenous and gut microbial metabolites to indicate metabotype-specific dietary responses: a systematic review**. *Adv Nutr* 2020, **11**:1237–1254.

85. Liu Z, de Vries B, Gerritsen J, Smidt H, Zoetendal EG: **Microbiome-based stratification to guide dietary interventions to improve human health**. *Nutr Res* 2020, **82**:1–10.

86. Trouwborst I, Gijbels A, Jardon KM, Siebelink E, Hul GB, Wanders L, Erdos B, Péter S, Singh-Povel CM, de Vogel-van den Bosch J, *et al.*: **Cardiometabolic health improvements upon dietary intervention are driven by tissue-specific insulin resistance phenotype: a precision nutrition trial**. *Cell Metabol* 2023, **35**:71–83.e5.

87. Gijbels A, Trouwborst I, Jardon KM, Hul GB, Siebelink E, Bowser SM, Yildiz D, Wanders L, Erdos B, Thijssen DHJ, *et al.*: **The PERSonalized Glucose Optimization through Nutritional Intervention (PERSON) study: rationale, design and preliminary screening results**. *Front Nutr* 2021, **8**, 694568.
* Among the first randomized clinical trials to test effects of a personalized dietary intervention, which was based on tissue-specific insulin resistance phenotype.