



Blood metabolite profiles linking dietary patterns with health—Toward precision nutrition

Downloaded from: <https://research.chalmers.se>, 2026-04-06 11:15 UTC

Citation for the original published paper (version of record):

Noerman, S., Landberg, R. (2023). Blood metabolite profiles linking dietary patterns with health—Toward precision nutrition. *Journal of Internal Medicine*, 293(4): 408-432.
<http://dx.doi.org/10.1111/joim.13596>

N.B. When citing this work, cite the original published paper.

Blood metabolite profiles linking dietary patterns with health—Toward precision nutrition

■ Stefania Noerman & Rikard Landberg

Department of Biology and Biological Engineering, Division of Food and Nutrition Science, Chalmers University of Technology, Gothenburg, Sweden

Abstract. Noerman S, Landberg R. Blood metabolite profiles linking dietary patterns with health—Toward precision nutrition. *J Intern Med.* 2023;**293**:408–432.

Diet is one of the most important exposures that may affect health throughout life span. Investigations on dietary patterns rather than single food components are gaining in popularity because they take the complexity of the whole dietary context into account. Adherence to such dietary patterns can be measured by using metabolomics, which allows measurements of thousands of molecules simultaneously. Derived metabolite signatures of dietary patterns may reflect the consumption of specific groups of foods or their constituents originating from the dietary pattern per se, or the physiological response toward the food-derived metabolites, their interaction with endogenous metabolism, and exogenous factors such as gut microbiota. Here, we review and discuss blood metabolite fingerprints of healthy dietary patterns. The plasma concentration of several food-derived metabolites—such as betaines from whole

grains and $n - 3$ polyunsaturated fatty acids and furan fatty acids from fish—seems to consistently reflect the intake of common foods of several healthy dietary patterns. The metabolites reflecting shared features of different healthy food indices form biomarker panels for which specific, targeted assays could be developed. The specificity of such biomarker panels would need to be validated, and proof-of-concept feeding trials are needed to evaluate to what extent the panels may mediate the effects of dietary patterns on disease risk indicators or if they are merely food intake biomarkers. Metabolites mediating health effects may represent novel targets for precision prevention strategies of clinical relevance to be verified in future studies.

Keywords: biomarkers, healthy dietary patterns, metabolomics, plasma, serum

List of abbreviations: DASH, Dietary Approaches to Stop Hypertension; HDI, Healthy Diet Indicator; HEI, Healthy Eating Index; PUFA, polyunsaturated fatty acids

Introduction

Noncommunicable diseases are responsible for over 70% of total deaths worldwide [1], and cardiometabolic diseases—that is, coronary heart disease, stroke, type 2 diabetes, and their preconditions—are the main causes of morbidity and mortality. Cardiometabolic diseases are to a great extent preventable through lifestyle modification, and eating a healthy diet, staying physically active, and avoiding alcohol, stress, and smoking are encouraged for the prevention and improved quality of life [2–4]. Traditionally, studies on the health effects attributed to diet have focused on individual food items, nutrients, or bioactive compounds [5–7]. However, foods are consumed as

complex meals that constitute a diet where many dietary components interact and are highly correlated. Most evidence-based dietary guidelines on a population level promote complex healthy eating patterns, particularly for the long-term reduction of cardiometabolic risk [8–11].

Several “prudent” dietary patterns, such as Dietary Approaches to Stop Hypertension (DASH), the Mediterranean diet, and the Nordic diet have been repeatedly associated with lower weight gain, body mass index, blood pressure, cholesterol levels, oxidative stress, and inflammation markers, as well as lowered risk of metabolic diseases in observational studies [12–21] and in

randomized controlled trials [22–25]. However, a detailed understanding of the mechanisms underlying the observed unique or shared health effects across dietary patterns remains elusive. Many of the prudent dietary patterns are rich in whole grains, fruits, berries, and vegetables and are, therefore, naturally rich in unsaturated fatty acids, minerals, vitamins, dietary fiber, and bioactive compounds. At the same time, they are relatively low in sodium, added sugar, and saturated fat. In contrast, the “Western” diet high in saturated fat, salt, and red and processed meat has been associated with higher oxidative stress, inflammation markers, and increased risk of metabolic syndrome across different locations [16, 26].

In both observational and intervention studies, dietary assessment represents a major challenge. It relies on self-reports that are subject to large measurement errors inherent to, for example, recall bias, error in estimation of portion size, misreporting of dietary intake, and bias toward socially desirable answers [27–29]. To overcome this challenge, dietary biomarkers have been suggested as a tool to objectively reflect specific intakes and complement traditional dietary assessment.

Metabolomics has been proven to be a useful technology to discover food intake biomarkers and to capture perturbation in metabolic systems, which may aid in understanding the molecular mechanism of disease etiology and prediction of disease risk. Metabolomics also enables profiling of individual metabolic phenotypes (metabotypes), which may cause differential responses to diet and subsequent altered risk to metabolic diseases [30]. Discovery of metabolite mediators of disease risk at an early stage may enable early intervention or lifestyle changes to slow down or reverse disease progression. Metabolomics refers to a technique used to profile small molecules (metabolites) in a sample at a given timepoint, enabled by the chosen analytical platform. In untargeted metabolomics, the aim is to profile as many molecules as possible. With a broad detection of metabolites from body fluids, discovered biomarkers and metabolite profiles can thus reflect either one or a combination of dietary exposures, that is, both individual foods (food intake biomarkers), and entire dietary patterns [31–35]. These profiles may also reflect the interaction between dietary exposure and endogenous metabolism shaped by individual susceptibility or host factors, such as age, sex, and genetic factors [36]; surrounding lifestyle exposures

(physical activity, sleep, stress); and gut microbiome, as well as the physiological effects of such metabolites (Fig. 1). This complexity hinders the interpretation of what these metabolites exactly reflect.

Here we summarize and discuss how metabolomics has been used to profile blood metabolites associated with adherence to healthy dietary patterns, and their implications for health and future clinical applications. We reviewed the literature, summarized the current findings, and interpreted whether metabolites reflect a specific food item or a whole dietary pattern, whether they are shared across several dietary patterns, and the implications of how they can be used to further understand the relationship between diet and health. We chose to focus on blood metabolites because they reflect the interaction with other individual and environmental exposures, endogenous metabolism, and co-metabolism by gut microbiota [37]. We also focused on MS instead of NMR because MS captures a broader range of metabolites than NMR, with robust specificity on lipoprotein subfractions [38, 39].

Healthy dietary patterns

Dietary patterns can be defined by two fundamental approaches: data-driven methods, where dietary patterns emerge from the data by statistical methods [21, 40], or by hypothesis-defined patterns [41, 42]. Here we focus on a priori -defined healthy dietary patterns, as they were formulated for dietary guidelines or public health recommendations based on previously established knowledge on the health benefits of included food items (Table 1).

In the United States, the DASH diet was specifically designed to lower blood pressure [43], which has been verified in randomized controlled trials [44]. Since then, DASH has been associated with a lower risk of cardiovascular diseases, stroke, cancer, type 2 diabetes, and inflammatory markers C reactive protein and interleukin 6 [45, 46]. Besides being rich in fruits and vegetables, DASH encourages the consumption of low-fat dairy products and low intake of saturated and total fat [43].

The Healthy Eating Index (HEI) was developed as a measure of the adherence to the Dietary Guidelines for Americans, and it has been updated several times [47, 48]. The version updated in 2015

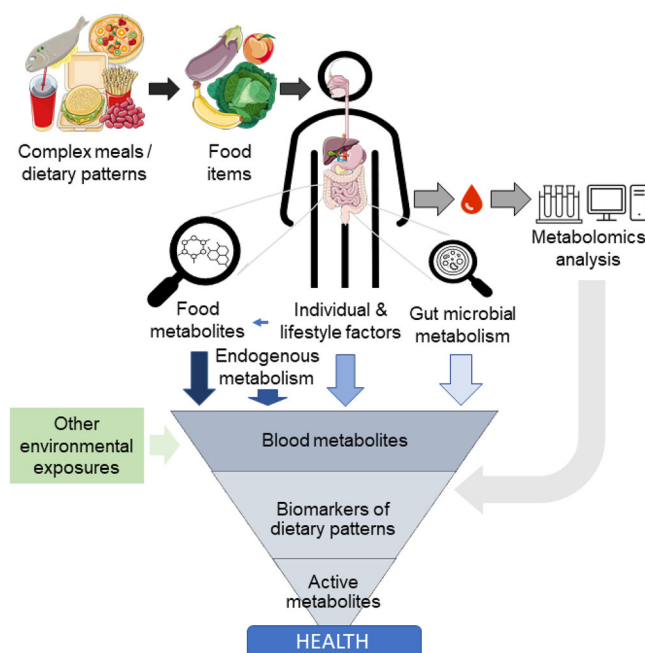


Fig. 1 Various metabolites in the metabolome reflecting a range of processes from dietary exposure, metabolism of intake related molecules, physiological responses thereof, to molecular fingerprints of progression of metabolic diseases. Individual and lifestyle factors (e.g., body composition, stress, physical activity), as well as other environmental factors (e.g., exposures to pollutants) may affect blood metabolomes, which may later also carry health implications. Metabolomics captures this pool of metabolites but does not discern from which processes they are derived. Biomarkers of dietary patterns were a small subset of these metabolites that indicate specific dietary pattern(s) or consistently shared across different dietary patterns. Further studies are required to investigate if such biomarkers are causally linked to health.

encourages consumption of whole fruits ($\geq 50\%$ of the total fruit intake), greens and beans/legumes ($\geq 20\%$ of the total vegetable intake), whole grains, dairy, seafood, and plant proteins ($\geq 30\%$ of the total protein food intake), and a ratio of unsaturated fatty acids to saturated fatty acids ≥ 2.5 [48]. The consumption of refined grains, sodium, added sugars, and saturated fats is conversely discouraged [48].

In Europe, two healthy dietary patterns are the Nordic and Mediterranean diets. In the Nordic diet, consumption of fish, shellfish, root vegetables (such as cabbage and carrots), stone fruits (such as apples and pears), berries, rapeseed oil, whole grain rye, and oats is encouraged. Emphasis is put on foods that are abundant in the Nordic region. Slight differences occur among dietary indices and countries in Northern Europe. For example, the Baltic Sea Diet Score developed in Finland encourages the consumption of low-fat dairy products [49], whereas New Nordic Diet formulated in Denmark did not include dairy in their recommendation [50]. Similarly, in the Mediterranean diet, the high consumption of fresh fruits, vegetables, nuts, fish, whole grain wheat, and the abundantly available olive oil is encouraged. Some variations on the Mediterranean diet also exist, for example, moderate consumption of red wine in some cultures but not in others, as well as

variation in carbohydrate sources (couscous in North Africa or pasta, rice, and potatoes in Southern Europe) [51]. The reliance of both dietary patterns on local and seasonal plant-based foods hence makes them more environmentally sustainable and socially acceptable by the local communities [52, 53], which promotes better adoption and adherence.

The Healthy Diet Indicator (HDI) was developed by the World Health Organization to provide a more generalizable dietary pattern across cultural and geographical differences. The focus is more on the nutrients than food items to ensure its applicability across the globe. This pattern requires adequate intake (6%–10% of total energy) of polyunsaturated fatty acids (PUFA) and at least 400 g/day of fruits and vegetables to ensure >25 g/day of total dietary fiber. Conversely, the consumption of trans fats and free sugars is limited to $<1\%$ and $<10\%$ of daily energy intake, respectively [54].

All these dietary patterns share some common features, that is, they encourage a high consumption of whole grains, fruits, vegetables, legumes, nuts, fish, and plant-based oils, which are rich sources of PUFA. At the same time, they all urge a limited consumption of alcohol, salt, added sugar, red and processed meat, and saturated fat.

Table 1. Studies on associations between selected dietary patterns and health outcomes

Dietary patterns	Regions	Key food items	Associated health outcomes	References
Mediterranean	Mediterranean	Cereals, fruits, vegetables, legumes, nuts and seeds, fish and seafood, mono- and unsaturated fatty acids (olive oil), low intake of red and processed meats, ethanol 5–25 g/day	Lower blood pressure, oxidative stress, inflammatory markers, and risk of CVD	16, 44, 100
Nordic	Northern Europe	Rapeseed oil, fruits (apples, pears, berries), (root) vegetables, whole grains (rye and oats), fish and seafood, low-fat dairy	Lower blood pressure, body weight	19, 44
Dietary Approaches to Stop Hypertension (DASH)	United States	Rich in fruit, vegetables, and low-fat dairy products; moderate in meat, fish, poultry, nuts, and beans; and low in sugar-sweetened beverages, sweets, and red meat	Lower blood pressure, adiposity (body weight, BMI, waist circumference), total and LDL cholesterol, oxidative stress and inflammatory markers, risk of kidney disease, CVD, cancers, T2D, and stroke	12, 16, 43–46, 101, 102
Healthy Eating Index (HEI)		High intakes of fruits, vegetables, wholegrains, dairy, protein (fish and seafood), unsaturated fatty acids, low sodium, alcohol, solid fat, and added sugars	Lower oxidative stress and inflammatory markers, lower mortality, lower risk of CVD, coronary heart disease, stroke, cancers, and T2D	16, 46, 100, 103
Healthy Diet Indicator (HDI)		High intake of fruits and vegetables (>400 g/day), PUFA (6–10%E), fiber (>25 g), adequate protein (10–15%E), low intake of sugar (<10%E), SFA (<10%E), cholesterol (<300 mg)	Inversely associated with CVD risk markers (aortic pulse wave velocity, C-reactive protein), stroke, CVD- and all-cause mortality and increased life expectancy	102, 104, 105

Abbreviations: BMI, body mass index; CVD, cardiovascular diseases; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; T2D, type 2 diabetes.

Biomarkers of specific healthy dietary patterns

With the growing application of metabolomics in nutrition science, studies have attempted to discover biomarkers of healthy dietary patterns. We compiled information from such studies and present a comprehensive list of metabolites shown to reflect dietary patterns (Table S1). Among them, some metabolites were associated only with one dietary pattern, which may suggest their

potential as biomarkers of specific dietary patterns (Table 2).

For example, alkylresorcinols uniquely reflect consumption of whole grain cereals that are notable foods in a Nordic diet (Table 2). Thus, they are also indicative of high adherence to a Nordic diet [55, 56]. Medium-chain acylcarnitines with an odd number of carbon atoms also seemed to indicate high adherence to a Nordic diet,

Table 2. Putative metabolites biomarkers^b of specific diet patterns^a

Metabolite groups	NOR	DASH	HEI	MED	HDI
Acylcarnitines	Acylcarnitine C8:1	Acylcarnitine C3:0	Acylcarnitine C12:0	Acylcarnitine C14:2	Acylcarnitine C18:1
	Acylcarnitine C10:3		Acylcarnitine C12:1		
	Acylcarnitine C13:0				
	Acylcarnitine C13:1				
Alkylresorcinols	Alkylresorcinol C19:0				
	glucuronide				
	Alkylresorcinol C21:0				
	glucuronide				
Benzoic acids and derivatives	Alkylresorcinol C21:1				
	glucuronide				
	Dihydroxybenzoic acid				
	Loliolide				
Amino acids and derivatives	3,4,5,6-Tetrahydrohippurate				
	2-Hydroxybenzoic acid				
	3,4,5-Trimethoxycinnamic acid				
	Aspartic acid	2-Methylserine	3-Methylhistidine		S-Methylcysteine
Indoles	<i>N</i> -Acetylaspartic acid	Ornithine	Creatine		
	Prolyl-hydroxyproline	<i>S</i> -Allylcysteine	<i>N</i> -Acetyl-3-methylhistidine		
	(2-Oxo-2,3-dihydro-1 <i>H</i> -indol-3-yl)acetic acid				Hypaphorine
					Indoleacetate
Purines and purine derivatives					
Organic acids	3-(2,5-Dimethoxyphenyl)propionic acid	3-Phenylpropionate (hydrocinnamate)	<i>N</i> -Methylmalonic acid (NMMA)		4-Guanidinobutanoate
	Methylimidazoleacetic acid		Xylonate		
Phenyl sulfates		4-Allylphenol sulfate			
Sugars alcohols	Xylitol				
	Erythritol				

(Continued)

Table 2. (Continued)

Metabolite groups	NOR	DASH	HEI	MED	HDI
Sugar conjugates	Hydroquinone glucuronide		Ethyl glucuronide		
Inorganic compounds	Pyrophosphate				
Vitamin derivatives	CEHC Tocopherol glucuronide		Pantothenate α -CEHC glucuronide α -CEHC sulfate		
Sterols and sterol esters			Campesterol CE(18:3)		
Bile acids			γ -Muricholate	Lithocholic acid	
Fatty acids	Palmitoleic acid (16:1)		Stearidonate (18:4n - 3) Adrenate (22:4n - 6) Dihomo-linoleate (20:2n - 6) Docosadienoate (22:2n - 6) DPA (22:5n - 3) α -Hydroxyisovalerate		
Hydroxy fatty acids	2,3-Dihydroxybutanoic acid Hydroxydecanoic acid		3- Hydroxyisobutyrate		
Sterols	3-Hydroxybutanoic acid				
Fatty acid amides	Linoleamide				
Fatty acid esters	Dibutyl adipate				
Furan fatty acids	CMPentylF CPF				
MG				MG(16:0)	
DG	DG(16:0/18:4) DG(18:1(18:2) DG(18:2/18:2) DG(18:4/18:1)/DG(36:5)	DG(18:2/18:3) DG(18:2/22:6)	DG(16:0/18:1)		
TG	TG(34:2) TG(36:3)		TG(48:0) TG(54:3)		
PE	LPE(22:6)		PE(36:2)	PE(18:2/16:0) /PE(34:2)	
PI	PE(22:6/P-18:1)				
SM	SM(34:2)		LPI(18:1) SM(22:1)	SM(24:1)	

(Continued)

Table 2. (Continued)

Metabolite groups	NOR	DASH	HEI	MED	HDI
PC	LPC(16:0)	LPC(19:0)		LPC(14:0)	
	PC(16:0/HODE)			LPC(24:0)	
	PC(18:0/22:4)			PC(18:2/14:0)	
	/PC(40:4)			/PC(32:2)	
	PC(40:7)			PC(20:4/14:0)	
	PC(40:9)			/PC(34:4)	
				PC(36:0)	
				PC(36:6)	
				PC(38:0)	
				PC(38:1)	
PC plasmalogens	LPC(O-20:2)			PC(40:1)	
	LPC(O-22:2)			PC(40:2)	
				PC(42:0)	
				PC(42:4)	
				PC(O-38:0)	
				PC(O-38:6)	
				PC(O-40:1)	
				PC(O-40:6)	
				PC(O-42:0)	
				PC(O-42:4)	
			PC(O-44:6)		
	PC(P-36:5)				
	PC(P-38:6)				
				PC(P-16:0/18:1)	

^aMetabolites were associated with only one dietary pattern. NOR: Nordic diet, including New Nordic Diet (NND) based in Denmark, Baltic Sea Diet Score (BSDS) in Finland, and Healthy Nordic Food Index (HNFI) [32, 34, 56, 59, 106–110]. DASH: Dietary Approaches to Stop Hypertension [13, 31, 32, 35]. HEI: Healthy Eating Index, including Alternate HEI (AHEI) [31–33, 111, 112]. MED: Mediterranean diet, including Alternate Mediterranean Diet Score (aMED) [31–33, 64, 81, 113]. HDI: Healthy Diet Indicator [32].

^bCE: cholesterol ester; CEHC: carboxyethyl hydrochroman; CMPF: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate; DG: diglyceride; DPA: docosapentaenoic acid; (L)PC: (lyso)phosphatidylcholine; (L)PE: (lyso)phosphatidylethanolamine; (L)PI: (lyso)phosphatidylinositol; MG: monoglyceride; PUFA: polyunsaturated fatty acids, SM: sphingomyelin; TG: triglyceride.

together with aspartic acid and its acetylated form (*N*-acetylaspartic acid), pyrophosphate, two sugar alcohols (xylitol and erythritol), hydroquinone glucuronide, two organic acids (3-(2,5-dimethoxyphenyl) propionic acid and methylimidazoleacetic acid), three hydroxy fatty acids (3-hydroxybutanoic acid, 2,3-dihydroxybutanoic acid, hydroxydecanoic acid), linoleamide, and dibutyl adipate (Table 2).

On the other hand, acylcarnitines with 12 carbon atoms were reported among individuals with high adherence to HEI diet. The breakdown products of animal proteins—that is, creatine, 3-methylhistidine, and *N*-acetyl-3-methylhistidine [57]—also appeared as signatures of high adherence to HEI (Table 2). Bile acid γ -muricholate was also associated with HEI, together with 1,7-dimethylurate, *N*-methylmalonic acid, xylonate, ethyl glucuronide, pantothenic acid (vitamin B5) and two metabolites of vitamin E, two hydroxy fatty acids (2-hydroxyisovalerate and 3-hydroxyisobutyrate), and some PUFAs (Table 2).

Acylcarnitine C3:0, interestingly, was associated only with the DASH diet and not with other patterns. Other metabolites uniquely associated with high adherence to the DASH diet were 2-methylserine, ornithine, 3-phenylpropionate, 4-allylphenol sulfate, and *S*-allylcysteine (Table 2). *S*-Allylcysteine has been suggested as a potential biomarker for garlic consumption [58].

Based on the included articles, only two metabolites were uniquely associated with high adherence to HDI, that is, *S*-methylcysteine and 4-guanidinobutanoate. On the other hand, acylcarnitines C14:2 and C18:1, hypaphorine, indoleacetate, and lithocholic acid reflected high adherence to a Mediterranean diet (Table 2).

Metabolite biomarkers common to several healthy dietary patterns

Due to a large diversity of the metabolites associated with the healthy dietary patterns, similar compounds were collapsed into representative compound classes and summarized per dietary pattern (Table 3). Interestingly, some blood metabolites reflected adherence to several healthy dietary patterns irrespective of geographic locations and variations of the dietary patterns. Considering the compound groups, betaines, methylated amino acids, organic acids, and sugar alcohols showed

consistent associations across the healthy dietary patterns (Table 3).

Some individual compounds—such as threonate, galactonate, glycerate, *N*-methylproline, and γ -carboxyethyl hydrochroman (γ -CEHC)—were consistently associated with at least two dietary patterns (Table 4). Some lipids also showed consistent associations with these dietary patterns, including medium-chain acylcarnitines, PUFA (linolenate [C18:3], EPA [C20:5], or DHA [C22:6]), either as free fatty acids or incorporated as (phospho)lipids, furan fatty acids (3-carboxy-4-methyl-5-propyl-2-furanpropanoate [CMPF] and its metabolites) (Table 3). Some phospholipids and acylglycerols (diglycerides and triglycerides) were also associated with healthy diets (Table 3), but because they consist of a vast variation of acyl side chains that often were not clearly distinguished in the included reports, the interpretation is difficult. This inadequate information and inconsistent nomenclature—such as plasmalogens with unclear descriptions of alkyl or alkenyl side chains—did not allow for combining such information. Moreover, studies often report unknown metabolites, and metabolite annotation is a huge hurdle in metabolomics analysis. We hence listed only known metabolites with their synonyms in Table S1.

What do biomarkers of healthy diets reflect?

Some of the metabolites consistently associated with healthy dietary patterns were derived from the food components included in healthy dietary patterns and, thus, reflect their intake per se. For example, furan fatty acids and PUFA were associated with high adherence to Nordic and Mediterranean diets (Table 4) because these compounds are mainly derived from fish [57, 59, 60]. Betaines and sugar alcohol were associated with (almost) all mentioned dietary patterns and are derived from the consumption of whole grains [61, 62] and fruits [63], thus most likely reflecting the intake of such foods that are core elements in several of the dietary patterns. Other metabolites—for example, CEHC glucuronide associated with HEI as well as phospholipids containing EPA and DHA associated with adherence to Nordic and Mediterranean diets (Table 4)—may reflect the interaction between individual food-derived metabolites and human endogenous metabolism. Moreover, some metabolites that are produced by gut microbiota were present in samples from

Table 3. Groups of metabolites associated with or responding to different dietary patterns^a

Metabolites ^b	NOR	DASH	HEI	MED	HDI
Acylcarnitines					
Short-chain (<10C) acylcarnitines	~	~	~	~	
Medium-chain (10–18C) acylcarnitines	+		+	+	+
Saturated medium-chain (10–18C) acylcarnitines (Deoxy)carnitine			–	–	
Acylglycerols					
Medium SFA-monoglycerides			–	+	
Medium unsaturated fatty acid monoglycerides			~		
Long PUFA-monoglycerides			+	+	
Diglycerides	+	+	+		
Triglycerides	+	+	~	~	
Fatty acids and derivatives					
Short branched odd-chain fatty acids (OCFA)	~		+		
Medium (7, 11, 17, 19C) OCFA	–		–		
Branched-chain fatty acids (e.g., phytanate)	–		–	–	
Long PUFA	+		+	+	
Medium (10–18C) SFA			–	–	
Medium unsaturated (10–18C) fatty acids	+		+	+	+
Eicosanoids	–				
Hydroxy fatty acids	~		~	–	
Fatty acid esters	+				
Fatty acid amides	+				
Phospholipids					
LPC-medium-chain unsaturated fatty acids	+		~	~	
LPC-medium OCFA		+	–		
LPC-PUFA	~	+	+	~	
LPC-SFA	~			~	
LPC-O	+				
PC-PUFA	+	+	+	~	
PC-MUFA	~	–	–	–	
PC(O)-PUFA				+	
PC(O)-AA	–			–	
PC(O)-other	–			~	
PC-SFA				+	
PC-oxylipins (e.g., PC(16:0/HODE))	+				

(Continued)

Table 3. (Continued)

Metabolites ^b	NOR	DASH	HEI	MED	HDI
Other PCs	–		~	~	
PC(P)	+		+		
LPE-DHA	+				
LPE-AA			–		
LPE-medium-chain unsaturated fatty acids			~	+	
Other PEs	+		~	+	
LPI-medium-chain unsaturated fatty acids	–		~		+
Sphingomyelins					
SM-medium chain(s)		–	–	–	
SM-long chain	+		+	+	
SM-odd-chain				–	
Alkylresorcinols (glucuronide)	+				
Steroids, sterols, and derivatives					
Steroid (androsteroid monosulfate 1)			–		
Sterols and sterol esters		+	+	+	
Cholesterol	–				
Bile acids			+	+	
Furan fatty acids	+	+	+	+	
Amino acids and derivatives					
Branched-chain amino acids (Leu, Ile, Val) and derivatives			–	–	
Aromatic amino acids (Phe, Trp, pyroglutamine, dihydroorotate)	–	–	–	~	
Acidic amino acids (Asp, Glu)	+			–	
Aliphatic amino acids (Pro, Ala, Gly, Cys) and derivatives (citrulline, creatine, creatinine, ornithine)	~	~	+	–	
Hydroxy amino acids (Thr, methoxy-Tyr)	–		–	–	
Histidine and derivatives			+	+	
Methylated amino acids (Pro, Ser, Cys)		+	+	+	+
Acetylated amino acids	+	+	~	~	
Proline dipeptides	~			~	
Indoles	~			~	
Betaines	+	+	+	+	+
Organic acids					
Hydroxy acids (xylonate, threonate, galactonate, glycerate)	+	+	+	+	

(Continued)

Table 3. (Continued)

Metabolites ^b	NOR	DASH	HEI	MED	HDI
TCA cycle intermediates (citric acid, isocitrate, lactic acid) and isomers (aconitate)	–	–	–	–	
Phenylpropanoic acids	+	~	–		
Carboxylic acids and derivatives (<i>N</i> -methylmalonic acid, methylimidazoleacetic acid, oxalic acid)	~	+	+	+	+
Purines and purine derivatives					
Purine nucleosides (N ⁶ -carbamoylthreonyladenosine)		–	–		
Xanthines (methylxanthines, (di)methylurates, theobromine)	–	–	~	–	
Pyrimidine nucleosides		+	+	–	
Benzoic acids and derivatives					
Hydroxybenzoic acids	+				
Cinnamic acids	+	+			
Hippuric acids	+	+	+	+	
Benzoic acid esters	–				
Benzofuran	+				
Naphthalenes (e.g., 2,6-diisopropyl-naphthalene)	–				
Phenyl sulfates		+	+		+
Vitamins derivatives					
Vitamin A derivatives		+	+		
Vitamin B derivatives		+	+		
Vitamin E derivatives	~	–	~	~	+
Sugar conjugates					
Sugars alcohols	+	+	+	+	
Glucuronides (ethyl glucuronide, hydroquinone glucuronide)	+		+		
Methyl glucopyranoside		+	+		
Inorganic compounds					
Pyrophosphate	+				

^aPositive sign (+) indicates a positive association or increment after dietary patterns, negative sign (–) indicates an inverse association, “~” indicates inconsistent findings across studies. NOR: Nordic diet, including New Nordic Diet (NND) based in Denmark, Baltic Sea Diet Score (BSDS) in Finland, and Healthy Nordic Food Index (HNFI) [32, 34, 56, 59, 106–110]. DASH: Dietary Approaches to Stop Hypertension [13, 31, 32, 35]. HEI: Healthy Eating Index, including Alternate HEI (AHEI) [31–33, 111, 112]. MED: Mediterranean diet, including Alternate Mediterranean Diet Score (aMED) [31–33, 64, 81, 113]. HDI: Healthy Diet Indicator [32].

^bAA: arachidonic acid (20:4); CE: cholesterol ester; CEHC: carboxyethyl hydrochroman; CMPF: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate; DG: diglyceride; DHA: docosahexaenoic acid (22:6); DPA: docosapentaenoic acid (22:5); EPA: eicosapentaenoic acid (20:5); (L)PC: (lyso)phosphatidylcholine; (L)PE: (lyso)phosphatidylethanolamine; (L)PI: (lyso)phosphatidylinositol; MG: monoglyceride; PUFA: polyunsaturated fatty acids, SFA: saturated fatty acids; SM: sphingomyelin; TG: triglyceride.

Table 4. Blood metabolites associated with at least two dietary patterns in fulfilling the validation criteria of food intake biomarkers

Metabolite groups ^a	Dietary patterns ^b					Validation criteria ^c					Analytical performance	Reproducibility	
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	Robustness	Reliability	Stability				
Acetylated amino acids	Acetylornithine	+	+	+	+	U	U	U	U	U	U	U	Y
Acetylated amino acids	<i>N</i> -Acetylalanine	-	-	-	-	N	U	Y	U	U	U	U	Y
Aliphatic amino acids and derivatives	Glycine	+	+	+	+	N	U	Y	U	U	U	U	Y
Aliphatic amino acids and derivatives	Hydroxyproline	-	-	-	-	U	U	Y	U	U	U	U	Y
Aliphatic amino acids and derivatives	Proline	-	-	-	-	U	U	Y	U	U	U	U	Y
Betaines	Glycine betaine	+	+	+	+	Y	U	Y	U	U	U	U	Y
Betaines	Pipecolic acid betaine (homostachydrine)	+	+	+	+	Y	U	Y	U	U	U	U	Y
Betaines	Stachydrine (proline betaine)	~	+	+	+	Y	U	Y	U	U	U	U	N
Betaines	Tryptophan betaine	+	+	+	+	Y	U	Y	U	U	U	U	Y
Betaines	Trimethylamine <i>N</i> -oxide (TMAO)	+	+	+	+	Y	U	Y	U	U	U	U	Y
Branched-chain amino acids and derivatives	Isoleucine	-	-	-	-	N	U	Y	U	U	U	U	Y
Branched-chain fatty acids	Methyl palmitate	-	-	-	-	U	U	Y	U	U	U	U	Y
Branched-chain fatty acids	Phytanate	-	-	-	-	U	U	Y	U	U	U	U	Y
Carboxylic acids and derivatives	Oxalic acid	-	+	+	+	U	U	Y	U	U	U	U	Y

(Continued)

Table 4. (Continued)

Metabolite groups ^a	Dietary patterns ^b					Validation criteria ^c					Analytical performance	Reproducibility	
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	Robustness	Reliability	Stability	Stability			
Furan fatty acids	CMHPF (hydroxy-CMPF)	+	+	+	+	Y	U	U	U	U	U	U	Y
Furan fatty acids	CMPF	+	+	+	+	Y	U	U	U	Y	Y	Y	Y
Hippuric acids	Hippurate	+	+	+	+	Y	U	U	U	U	U	U	Y
Histidine and derivatives	Ergothioneine	+	+	+	+	U	U	U	U	U	U	U	Y
Hydroxy acids	Threonate	+	+	+	+	U	U	U	U	U	U	U	Y
Hydroxy acids	Galactonate	+	+	+	+	U	U	U	U	U	U	U	Y
Hydroxy acids	Glycerate	+	+	+	+	U	U	U	U	U	U	U	Y
Hydroxy amino acids (Thr, methoxy-Tyr)	Threonine	-	-	-	-	U	U	U	U	U	U	U	Y
Hydroxy fatty acids	3-Hydroxy-2-ethylpropionate	-	-	-	-	U	U	U	U	U	U	U	Y
Indoles	Indolepropionate	+	+	+	+	Y	U	U	U	U	U	U	N
Long polyunsaturated acid (PUFA)-monoglycerides	MG(22:6)	+	+	+	+	Y	U	U	U	U	U	U	Y
Long PUFA	DHA (22:6n - 3)	+	+	+	+	Y	U	U	U	U	U	U	Y
Long PUFA	DHA-choline	+	+	+	+	Y	U	U	U	U	U	U	N
Long PUFA	EPA	+	+	+	+	Y	U	U	U	Y	Y	Y	Y
Long PUFA	EPA-choline	+	+	+	+	Y	U	U	U	U	U	U	Y
Long PUFA	Mead acid (20:3n - 9)	-	-	-	-	U	U	U	U	U	U	U	Y
LPC-medium-chain unsaturated fatty acids	LPC(14:1)	-	-	-	-	U	U	U	U	U	U	U	Y
LPC-PUFA	LPC(20:5)	+	+	+	+	Y	U	U	U	U	U	U	Y
LPC-PUFA	LPC(22:6)	+	+	+	+	Y	U	U	U	U	U	U	Y
LPE-medium-chain unsaturated fatty acids	LPE(18:1)	+	+	+	+	N	U	U	U	U	U	U	Y

(Continued)

Table 4. (Continued)

Metabolite groups ^a	Dietary patterns ^b				Validation criteria ^c				Analytical performance	Reproducibility		
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	response	Time-response			Robustness	Reliability
LPI-medium-chain unsaturated fatty acids	LPI(16:1)	-	-	N	N	U	U	Y	U	U	U	Y
LPI-medium-chain unsaturated fatty acids	LPI(18:2)	+	+	N	N	U	U	Y	U	U	U	Y
Medium unsaturated (10-18C) fatty acids	Linoleate (18:2n - 6)	+	+	+	Y	U	U	Y	U	U	U	Y
Medium unsaturated (18:3n - 3 or 18:3n - 6) fatty acids	Linolenate (18:3n - 3 or 18:3n - 6)	+	+	+	Y	U	U	Y	U	U	U	Y
Medium unsaturated fatty acid monoglycerides	MG(18:2)	+	+	+	Y	U	U	Y	U	U	U	Y
Medium-chain acylcarnitines	Acylcarnitine C10:1 (cis-4-decenoylcarnitine)	+	+	+	U	U	U	Y	U	U	U	Y
Medium-chain acylcarnitines	Acylcarnitine C18:2	+	+	+	U	U	U	Y	U	U	U	Y
Methyl glucopyranoside	Methyl glucopyranoside	+	+	U	U	U	U	Y	U	U	U	Y
Methylated amino acids	N-Methylproline	+	+	+	U	U	U	Y	U	U	U	Y
PC(P)	PC(P-18:1/20:3)/PC(P-38:4)	+	+	+	Y	U	U	Y	U	U	U	Y
PC-MUFA	PC(16:0/16:1)/PC(32:1)	+	-	-	N	U	U	Y	U	U	U	N
PC-MUFA	PC(16:0/18:1)/PC(34:1)	-	-	-	N	U	U	Y	U	U	U	N

(Continued)

Table 4. (Continued)

Metabolite groups ^a	Dietary patterns ^b					Validation criteria ^c					Analytical performance	Reproducibility
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	Robustness	Stability	Reliability	Time-response		
PC-PUFA	PC(16:0/20:5)/PC(36:5)	+	+	+	N	U	Y	U	U	U	U	Y
PC-PUFA	PC(18:0/20:3)/PC(38:3)	-	-	-	N	U	Y	U	U	U	U	Y
PC-PUFA	PC(18:0/22:5)/PC(40:5)	-	-	-	N	U	Y	U	U	U	U	Y
PC-PUFA	PC(18:0/22:6)/PC(40:6)	+	+	+	Y	U	Y	U	U	U	U	Y
PC-PUFA	PC(18:2/20:4)/PC(38:6)	+	+	+	Y	U	Y	U	U	U	U	Y
Phenyl sulfates	2-Aminophenol sulfate	+	+	+	U	U	Y	U	U	U	U	Y
Phenylpropanoic acids	3-(4-Hydroxyphenyl) lactate	-	-	-	U	U	Y	U	U	U	U	Y
Purine nucleosides	N6-carbamoylthreonyladenine	-	-	-	U	U	Y	U	U	U	U	Y
Pyrimidine nucleosides	Uridine	+	+	+	U	U	Y	U	U	U	U	Y
Short branched odd-chain fatty acids (OCFA)	10-Undecenoate (11:1n - 1)	-	-	-	U	U	Y	U	U	U	Y	N
Short-chain acylcarnitines	Acylcarnitine C4:0	-	-	-	U	U	Y	U	U	U	U	N
Short-chain acylcarnitines	Acylcarnitine C6 (adipoylcarnitine)	-	-	-	U	U	Y	U	U	U	U	Y
SM-medium chain(s)	SM(18:0)	-	-	-	U	U	Y	U	U	U	U	Y
SM-medium chain(s)	SM(18:1)	-	-	-	U	U	Y	U	U	U	U	Y
SM-medium chain(s)	SM(d18:2/18:1)	-	-	-	U	U	Y	U	U	U	U	Y
Sterols and sterol esters	CE(22:6)	+	+	+	U	U	Y	U	U	U	U	Y

(Continued)

Table 4. (Continued)

Metabolite groups ^a	Dietary patterns ^b					Validation criteria ^c					Analytical performance	Reproducibility		
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	response	Dose-response	Time-response	Robustness			Reliability	Stability
Sugars alcohols	Chiro-inositol	+	+	+	U	U	U	U	Y	U	U	U	U	Y
Sugars alcohols	Myoinositol	-	~	-	U	U	U	U	Y	U	U	U	U	N
Sugars alcohols	Scyllo-inositol	+	+	+	U	U	U	U	Y	U	U	U	U	Y
Sugars alcohols	Threitol	+	+	+	U	U	U	U	Y	U	U	U	U	Y
TCA cycle intermediates	Aconitate	-	-	-	U	U	U	U	Y	U	U	U	U	Y
TCA cycle intermediates	Isocitrate	-	-	-	N	U	U	U	Y	U	U	U	U	Y
TCA cycle intermediates	Lactic acid	-	-	-	N	U	U	U	Y	U	U	U	U	Y
Triglycerides	TG(56:7)	+	+	+	N	U	U	U	Y	U	U	U	U	Y
Triglycerides	TG(56:8)	+	~	+	N	U	U	U	Y	U	U	U	U	N
Triglycerides	TG(58:10)	+	+	+	N	U	U	U	Y	U	U	U	U	Y
Triglycerides	TG(58:8)	+	+	+	N	U	U	U	Y	U	U	U	U	Y
Triglycerides	TG(58:9)	+	+	+	N	U	U	U	Y	U	U	U	U	Y
Vitamin A derivatives	Carotenediol	+	+	+	Y	U	U	U	Y	U	U	U	U	Y
Vitamin A derivatives	β -Cryptoxanthin	+	+	+	Y	U	U	U	Y	U	U	U	U	Y
Vitamin B derivatives	Pyridoxate	+	+	+	Y	U	U	U	Y	U	U	U	U	Y
Vitamin E derivatives	α -Tocopherol	+	+	+	Y	U	U	U	Y	U	U	U	U	Y
Vitamin E derivatives	β -Tocopherol/ γ -tocopherol	-	~	-	Y	U	U	U	Y	U	U	U	U	N
Vitamin E derivatives	γ -CEHC	+	+	+	Y	U	U	U	Y	U	U	U	U	Y

(Continued)

Table 4. (Continued)

Metabolite groups ^a	Dietary patterns ^b					Validation criteria ^c							
	Metabolites ^a	NORDASH	HEI	MED	HDI	Plausibility	Dose-response	Time-response	Robustness	Reliability	Stability	Analytical performance	Reproducibility
Xanthines	Theobromine	-	-	-	Y	Y	U	U	Y	U	U	U	Y
Xanthines	3-Methylxanthine	-	-	-	U	U	U	U	Y	U	U	U	Y
Xanthines	7-Methylurate	-	-	-	U	U	U	U	Y	U	U	U	Y

^aAA: arachidonic acid (20:4); CE: cholesterol ester; CEHC: carboxyethyl hydrochroman; CMPF: 3-carboxy-4-methyl-5-propyl-2-furanpropanoate; DG: diglyceride; DHA: docosahexaenoic acid (22:6); DPA: docosapentaenoic acid (22:5); EPA: eicosapentaenoic acid (20:5); (L)PC: (lysophosphatidyl)choline; (L)PE: (lysophosphatidyl)ethanolamine; (L)PI: (lysophosphatidyl)inositol; MG: monoglyceride; PUFA: polyunsaturated fatty acids, SFA: saturated fatty acids; SM: sphingomyelin; TG: triglyceride.

^bPositive sign (+) indicates a positive association or increment after dietary patterns, negative sign (-) indicates the inverse one, “~” indicates inconsistent findings across studies. NOR: Nordic diet, including New Nordic Diet (NND) based in Denmark, Baltic Sea Diet Score (BSDS) in Finland, and Healthy Nordic Food Index (HINFI) [32, 34, 56, 59, 106–110]. DASH: Dietary Approaches to Stop Hypertension [13, 31, 32, 35]. HEI: Healthy Eating Index, including Alternate HEI (AHEI) [31–33, 111, 112]. MED: Mediterranean diet, including Alternate Mediterranean Diet Score (aMED) [31–33, 64, 81, 113]. HDI: Healthy Diet Indicator [32].

^cValidation criteria was set by Food and Biomarkers Alliance. Y: yes (fulfilled the criteria), N: no (did not fulfill the criteria), U: unknown, or no evidence was found. Please refer to their publication for explanation of each criteria [88].

individuals reporting a high adherence to Nordic and Mediterranean dietary patterns. These metabolites include hippuric acid (a conversion product of glycine and benzoic acid) and indolepropionic acid as a conversion product of tryptophan (Table 4).

The blood metabolome provides rich information on many different biological processes, reflecting the intake of particular food items, dietary patterns, human endogenous metabolism, and their interaction with food-derived molecules, as well as gut microbiota (Fig. 1). It is therefore difficult to classify blood metabolites or blood metabolite profiles associated with healthy eating patterns into groups of biomarkers of food intake, intermediate biomarkers reflecting the interaction between diet and metabolism, gut microbial metabolism, or biomarkers of their physiological effects [36].

Associations between biomarkers/metabolite profiles of dietary patterns and health

Some metabolites associated with a high adherence to a Mediterranean or Nordic diet—including carnitines, sphingomyelins, and phospholipids (including plasmalogens)—are derived from the endogenous metabolism. They have previously been associated with risk markers of cardiometabolic health, such as blood pressure, markers of hyperlipidemia, and insulin resistance [59, 64]. Some endogenous metabolites have been previously shown to mediate the link between red meat and the risk of type 2 diabetes [65], which may suggest the potential of endogenous metabolites to, at least partially, mediate the physiological effects of the mentioned dietary patterns.

Another interesting group of metabolites is microbial metabolites. One of the examples is hippuric acid, which has been associated with higher consumption of coffee, fruits, and whole grains with better glucose control and reduced risk of hypertension and metabolic syndrome [66–68]. Another is indolepropionic acid—which increased after the consumption of the dietary fiber-rich stone fruit and berry Nordic diet—and was associated with a lower concentration of inflammatory marker C reactive protein, better insulin secretion, and lower risk of type 2 diabetes [60, 63, 69, 70]. The roles of the gut microbiome or microbial metabolites associated with healthy eating patterns are yet unclear because they may either merely be proxies

of the food intake pattern, mediate the relationship between diet and health outcome, or a combination of the two.

Factors affecting blood metabolites associated with dietary patterns

Variation in metabolite levels related to healthy dietary patterns is affected by several factors other than intake or direct biological effects of the dietary pattern. This may include effects of environmental exposures, other lifestyle factors, endogenous metabolism, and gut microbiome. Because many of these factors are interconnected and overlap with each other, disentangling underlying processes and the causal role of specific metabolites in health outcomes is challenging. Organic acids and derivatives of amino acids are good examples of this. For example, 3-hydroxyisobutyric acid is a catabolism product of branched-chain amino acid valine that leads to the production of propionyl-CoA, the first building block in the production of odd-chain fatty acids [71]. These compounds are also directly associated with HEI (Table 3), but it is yet unknown to what extent they are derived from specific dietary components or if they are confounded by other lifestyle factors coexisting with such diets. It is unknown at what proportion they are metabolized by the host or by the gut microbiota, and if they at all convey a specific physiological role [72]. Investigations beyond metabolite profiling of samples derived from observational studies are needed to clarify physiological effects related to health and to establish the underlying causal mechanisms. The importance of individual factors for dietary pattern-related metabolites is briefly described below.

Gut microbiota

Almost half (46%) of the blood metabolites have been reported to be associated with the gut microbiome [73], and around 25% of the variation is explained by microbiota, especially for xenobiotics and unknown compounds [74]. Diet is largely responsible for gut microbial population across the life span [74], besides many other factors, such as hygiene, urbanization, and medical treatment [75]. These factors—either directly or indirectly via gut microbiota—are associated with a wide range of blood metabolites, from lipids, amino acids, and bile acids, to xenobiotics [76, 77]. Blood metabolites have also been shown to reflect the diversity of the gut microbiome. Higher diversity of gut microbiota has been associated

with higher levels of circulating hippuric acid, 3-phenylpropionate, indolepropionic acid [67, 78], and lower levels of alanine, isoleucine, and lactate [79].

In particular, habitual dietary patterns have been reported to correlate ($r = 0.31$ – 0.42) with gut microbial composition [80]. Some microbial metabolites—such as indoles, hippuric acids, and bile acids—were directly associated with most of the healthy dietary patterns included in this article (Table 3). The gut microbiome also seems to adapt immediately after an acute change of dietary patterns. A study showed how the composition of the gut microbiome changed after 4 days on a Mediterranean diet, compared to a Western diet rich in fat and salt, although the overall diversity was not much affected [81]. The same study also showed increased levels of some indoles (indoleacetic acid, indolepropionic acid, and indolelactic acid) after acute change to a Mediterranean diet [81].

The composition of the gut microbiota has also been linked with metabolic health, such as markers of glucose and lipid metabolism [80]. Therefore, gut microbiota—either directly or mediated by the metabolites—have the potential to interact with host genetic make-up, metabolic processes, and markers of metabolic health [73, 77, 82, 83]. The gut microbiome has been even previously suggested to mediate the impact of diet or lifestyle factors on metabolic health [67, 84], but the causal mechanisms remain unclear and deserve further investigations.

It is worth noting that current studies on gut microbiota rely heavily on 16S rDNA-based classification to respective operational taxonomic units (OTUs), which are close to the genus/species level. This information, however, may not explain the metabolic capacities of these bacteria with immense variation even within the same OTUs, including their complex interactions with human hosts [34] and their health implications [84]. Furthermore, blood metabolites were more strongly associated with microbial metabolic pathways than with species [73], which emphasizes the importance of focusing on metabolic capacity and biological activities instead of the microbial taxonomy. Thorough investigations are required to disentangle the link between health outcomes and metabolic activity of gut microbiota affected by lifestyle exposures.

Individual and lifestyle factors

Besides gut microbiota, genetic factors, anthropometric measures, age, and biochemical and clinical parameters, as well as lifestyle factors such as physical activity, may also influence the blood metabolome related to healthy eating patterns [30, 85]. For example, men were reported to have higher levels of creatinine, amino acids, and acylcarnitines [86]. Some amino acids have been associated with physical activity and cardiorespiratory fitness [87]. Several sugars, acylcarnitines, and phospholipids were associated with obesity [87]. All of these factors hence may increase the variations, promote inconsistent findings across studies [85], and confound the associations between the blood metabolome and healthy dietary patterns. Current evidence on the effects of individual factors on metabolites associated with healthy dietary patterns is still limited. Further investigations are hence required to investigate to what extent the serum metabolites associated with healthy dietary patterns are affected by individual factors and to discover biomarkers of healthy dietary patterns independent of individual factors and other potential confounders.

Assessing the validity of potential biomarkers of dietary patterns

We assessed to what extent metabolites associated with at least two dietary patterns met the validation scheme of food intake biomarkers outlined by the Food and Biomarkers Alliance (FoodBALL) consortium [88] (Table 4). Validation has been undertaken for biomarkers reflecting the intake of specific foods, for example, TMAO, CMPF, EPA, and DHA for fish [57], alkylresorcinols for wholegrain wheat and rye [89], threitol for fruits [63, 90], α -tocopherol and linolenic acid for nuts [91], acetylcarnitine for legumes [92], and S-allylcysteine for allium vegetables [58]. However, specific criteria developed and tested for assessing the validity of adherence to dietary patterns are still lacking (Table 4). Thus, further work is needed to establish validation criteria for dietary pattern-related metabolites. This will improve the understanding of what they reflect and how they are linked to health outcomes.

Future perspectives

Several healthy dietary patterns mentioned above include similar food items, nutrients, or bioactive compound classes. These similarities are reflected

in the presence of some common metabolites that are shared across these dietary patterns, such as betaines from whole grains, and $n - 3$ PUFA and furan fatty acids from fish. Because the blood biomarkers reflecting the common dietary aspects of several healthy dietary patterns can be analyzed, they open exciting new routes toward precision prevention. It remains to be understood if such biomarkers mediate disease risk or if they are just reflecting specific food intakes common to these dietary patterns, or both. If they mediate disease risk, they could possibly be included in specific biomarker panel assays as a novel target for precision prevention to guide personalized dietary advice. Down the road, this could be adopted by consumers through commercial solutions and/or by health care.

However, the evidence is far from sufficient for translation to such services or clinical applications. First, the current blood biomarkers of healthy dietary patterns have so far emerged from a limited number of observational studies. Hence, there is a need to validate the metabolite panel across different cohorts or participant groups to ensure its robustness and reproducibility. Using observational studies, mediation analysis between the dietary patterns as the exposure, the risk of metabolic disease as the outcome, and the panels or patterns of metabolites as the mediators could be used to gain further insights into to what extent identified metabolites are mediators of associations observed with health outcomes. A positive result can serve as a decision point to undertake subsequent proof-of-concept feeding trials to (i) establish a dose–response relationship between the consumption of common foods shared across the healthy dietary patterns and increased concentrations of metabolites at stake and (ii) establish a cause-and-effect relationship between alteration in metabolite concentrations and effects on established disease risk markers. Information derived from such studies would be critical to evaluate the feasibility and the cost-effectiveness of metabolite-panel-guided precision prevention of chronic diseases.

Moreover, feeding trials could provide valuable insights into participants' responses to the specific dietary pattern intervention both in terms of identifying individuals who are “producers” and “non-producers” of specific metabolites of interest as well as “responders” and “nonresponders” of the effects on clinical markers of such metabolites.

Identification of the determinants of response or nonresponse and their biomarkers will be critical to improving precision in tailoring diets for the promotion of cardiometabolic health or disease prevention. This information would also be important to improving the efficacy of the metabolite-guided prevention approach by identifying individuals who are receptive to the different specific diet component(s) and the subsequent effects on established disease risk factors. Such metabolite panels will be needed for the development and validation of the concept. It will also aid in the subsequent translation of the metabolite panel into a tool to guide individuals toward healthier eating patterns in clinical practice.

However, there are many challenges to overcome. Attempts to find common metabolites that may reflect or mediate health effects shared across the dietary patterns are hampered due to variations in analytical platforms and study settings, which may skew the findings toward certain metabolites. These differences may also add a challenge in absolute quantification and achieving consensus of the biomarker panel related to both diets and health outcomes. More harmonized workflows and protocols in metabolomics are needed and are currently underway [93–95]. Similarly, inconsistent naming systems and challenges in metabolite annotation may hinder merging information from various datasets and research groups. This calls for studies of healthy dietary patterns using similar methodological platforms in large populations to properly find specific biomarkers or a biomarker profile panel that may represent common aspects of different healthy dietary patterns that mediate their effects on disease risks. Understanding determinants of individual variation in dietary responses and modeling such variations is challenging but could also improve the understanding of how specific foods affect key metabolites and their effects on disease risk factors. Important steps have already been taken [96–99] and more are currently ongoing. Interdisciplinary collaborations between experts in nutrition, medicine, and bioinformatics incorporating various omics and computational modeling—for example, machine learning and analysis of big data—are necessary to accomplish this task.

Conclusion

We found that some metabolites previously reported in the literature were consistently

associated with one or more healthy dietary patterns. Still unclear is whether they are derived from specific food items or dietary components in the dietary patterns; their interaction with other environmental exposures, individual or lifestyle factors, human endogenous metabolism, or gut microbiota; or if they reflect metabolic effects with health implications of the diet. Further attempts are hence needed to validate, characterize, and quantify these biomarkers in rapid and reliable analytical platforms. Next, we need to understand their variation between individuals and identify the determinants of such variation. This understanding would be important to establishing the dose-response relationship between the dietary patterns and the plasma levels of the metabolites, and how the variations of the blood levels may relate to health outcomes. If these metabolites mediate the effect of the dietary patterns on health, subsequent follow-up in intervention studies would be necessary to validate the effects of plasma concentration of the metabolites on health and to establish the causal relationship. This could pave the way for tailored dietary prevention strategies and more precise nutrition recommendations guided by metabolite profile signatures.

Acknowledgments

This work was supported by funding from the Swedish Research Council (2019-01264), Formas (Dnr: 2019-02201) under the umbrella of the European Joint Programming Initiative “A Healthy Diet for a Healthy Life” (JPI HDHL) and of the ERA-NET Cofund HDHL INTIMIC (GA No. 727565 of the EU Horizon 2020 Research and Innovation Programme). The funders had no contribution in study design, data collection, data analysis, preparation of the manuscript, or decision to publish.

Conflicts of interest

Both authors declare no conflicts of interest.

Author contributions

Stefania Noerman and Rikard Landberg developed the concept of the manuscript. Stefania Noerman drafted the manuscript. Rikard Landberg edited, revised, provided scientific input to the manuscript, and had primary responsibility for the final content. Both authors read, critically reviewed, and approved the final manuscript.

References

- 1 World Health Organization (WHO). The top 10 causes of death. In: *Global health estimates*. Washington: World Health Organization; 2020.
- 2 Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;**344**:1343–50.
- 3 Uusitupa M, Khan TA, Vigiouliouk E, Kahleova H, Rivellese AA, Hermansen K, et al. Prevention of type 2 diabetes by lifestyle changes: a systematic review and meta-analysis. *Nutrients*. 2019;**11**:2611.
- 4 Pérez-Martínez P, Mikhailidis DP, Athyros VG, Bullo M, Couture P, Covas M-AI, et al. Lifestyle recommendations for the prevention and management of metabolic syndrome: an international panel recommendation. *Nutr Rev*. 2017;**75**:307–26.
- 5 Mortensen MW, Spagner C, Cuparencu CTL, Astrup A, Raben A, Dragsted LO. Sea buckthorn decreases and delays insulin response and improves glycaemic profile following a sucrose-containing berry meal: a randomised, controlled, crossover study of Danish sea buckthorn and strawberries in overweight and obese male subjects. *Eur J Nutr*. 2018;**57**:2827–37.
- 6 Tosh SM, Bordenave N. Emerging science on benefits of whole grain oat and barley and their soluble dietary fibers for heart health, glycemic response, and gut microbiota. *Nutr Rev*. 2020;**78**:13–20.
- 7 Hanhineva K, Lankinen MA, Pedret A, Schwab U, Kolehmainen M, Paananen J, et al. Nontargeted metabolite profiling discriminates diet-specific biomarkers for consumption of whole grains, fatty fish, and bilberries in a randomized controlled trial. *J Nutr*. 2015;**145**:7–17.
- 8 Tapsell LC, Neale EP, Satija A, Hu FB. Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. *Adv Nutr*. 2016;**7**:445–54.
- 9 Brink E, Van Rossum C, Postma-Smeets A, Stafleu A, Wolvers D, Van Dooren C, et al. Development of healthy and sustainable food-based dietary guidelines for the Netherlands. *Public Health Nutr*. 2019;**22**:2419–35.
- 10 Cespedes EM, Hu FB. Dietary patterns: from nutritional epidemiologic analysis to national guidelines. *Am J Clin Nutr*. 2015;**101**:899–900.
- 11 Cena H, Calder PC. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. *Nutrients*. 2020;**12**:334.
- 12 Lari A, Sohoulí MH, Fatahi S, Cerqueira HS, Santos HO, Pourrajab B, et al. The effects of the Dietary Approaches to Stop Hypertension (DASH) diet on metabolic risk factors in patients with chronic disease: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2021;**31**:2766–78.
- 13 Louca P, Notal A, Mompeo O, Christofidou P, Gibson R, Spector TD, et al. Body mass index mediates the effect of the DASH diet on hypertension: common metabolites underlying the association. *J Hum Nutr Diet*. 2022;**35**: 214–22.
- 14 Cowell OR, Mistry N, Deighton K, Matu J, Griffiths A, Minihane AM, et al. Effects of a Mediterranean diet on blood pressure: a systematic review and meta-analysis of

- randomized controlled trials and observational studies. *J Hypertens.* 2021;**39**:729–39.
- 15 Wu P-Y, Chen K-M, Tsai W-C. The Mediterranean dietary pattern and inflammation in older adults: a systematic review and meta-analysis. *Adv Nutr.* 2021;**12**:363–73.
 - 16 Aleksandrova K, Koelman L, Rodrigues CE. Dietary patterns and biomarkers of oxidative stress and inflammation: a systematic review of observational and intervention studies. *Redox Biol.* 2021;**42**:101869.
 - 17 Fung TT, Li Y, Bromage S, Bhupathiraju SN, Batis C, Fawzi W, et al. Higher global diet quality score is associated with less 4-year weight gain in US women. *J Nutr.* 2021;**151**:162S–7S.
 - 18 Critselis E, Kontogianni MD, Georgousopoulou E, Chrysohoou C, Tousoulis D, Pitsavos C, et al. Comparison of the Mediterranean diet and the Dietary Approach Stop Hypertension in reducing the risk of 10-year fatal and non-fatal CVD events in healthy adults: the ATTICA Study (2002–2012). *Public Health Nutr.* 2021;**24**:2746–57.
 - 19 Ramezani-Jolfaie N, Mohammadi M, Salehi-Abargouei A. The effect of healthy Nordic diet on cardio-metabolic markers: a systematic review and meta-analysis of randomized controlled clinical trials. *Eur J Nutr.* 2019;**58**:2159–74.
 - 20 Galbete C, Kröger J, Jannasch F, Iqbal K, Schwingshackl L, Schwedhelm C, et al. Nordic diet, Mediterranean diet, and the risk of chronic diseases: the EPIC-Potsdam study. *BMC Med.* 2018;**16**:99.
 - 21 Smith E, Ericson U, Hellstrand S, Orho-Melander M, Nilsson PM, Fernandez CL, et al. A healthy dietary metabolic signature is associated with a lower risk for type 2 diabetes and coronary artery disease. *BMC Med.* 2022;**20**:1–10.
 - 22 Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. *N Engl J Med.* 2018;**378**:e34.
 - 23 Adamsson V, Reumark A, Fredriksson I-B, Hammarström E, Vessby B, Johansson G, et al. Effects of a healthy Nordic diet on cardiovascular risk factors in hypercholesterolaemic subjects: a randomized controlled trial (NORDIET). *J Intern Med.* 2011;**269**:150–9.
 - 24 Brader L, Uusitupa M, Dragsted LO, Hermansen K. Effects of an isocaloric healthy Nordic diet on ambulatory blood pressure in metabolic syndrome: a randomized SYSDIET sub-study. *Eur J Clin Nutr.* 2014;**68**:57–63.
 - 25 Poulsen SK, Due A, Jordy AB, Kiens B, Stark KD, Stender S, et al. Health effect of the New Nordic Diet in adults with increased waist circumference: a 6-mo randomized controlled trial. *Am J Clin Nutr.* 2014;**99**:35–45.
 - 26 Fabiani R, Naldini G, Chiavarini M. Dietary patterns and metabolic syndrome in adult subjects: a systematic review and meta-analysis. *Nutrients.* 2019;**11**:2056.
 - 27 Kirkpatrick SI, Baranowski T, Subar AF, Toozé JA, Frongillo EA. Best practices for conducting and interpreting studies to validate self-report dietary assessment methods. *J Acad Nutr Diet.* 2019;**119**:1801–16.
 - 28 de la Hunty A, Buttriss J, Draper J, Roche H, Levey G, Florescu A, et al. UK Nutrition Research Partnership (NRP) workshop: forum on advancing dietary intake assessment. *Nutr Bull.* 2021;**46**(2):228–37.
 - 29 Hellstrand S, Ottosson F, Smith E, Brunkwall L, Ramne S, Sonestedt E, et al. Dietary data in the Malmö Offspring Study—reproducibility, method comparison and validation against objective biomarkers. *Nutrients.* 2021;**13**:1579.
 - 30 Palmnäs M, Brunius C, Shi L, Rostgaard-Hansen A, Torres NE, González-Domínguez R, et al. Perspective: metabotyping—a potential personalized nutrition strategy for precision prevention of cardiometabolic disease. *Adv Nutr.* 2020;**11**:524–32.
 - 31 Kim H, Rebholz CM. Metabolomic biomarkers of healthy dietary patterns and cardiovascular outcomes. *Curr Atheroscler Rep.* 2021;**23**:26.
 - 32 Playdon MC, Moore SC, Derkach A, Reedy J, Subar AF, Sampson JN, et al. Identifying biomarkers of dietary patterns by using metabolomics. *Am J Clin Nutr.* 2017;**105**:450–65.
 - 33 McCullough ML, Maliniak ML, Stevens VL, Carter BD, Hodge RA, Wang Y. Metabolomic markers of healthy dietary patterns in US postmenopausal women. *Am J Clin Nutr.* 2019;**109**:1439–51.
 - 34 Landberg R, Hanhineva K. Biomarkers of a healthy Nordic diet—from dietary exposure biomarkers to microbiota signatures in the metabolome. *Nutrients.* 2020;**12**:27.
 - 35 Rebholz CM, Lichtenstein AH, Zheng Z, Appel LJ, Coresh J. Serum untargeted metabolomic profile of the Dietary Approaches to Stop Hypertension (DASH) dietary pattern. *Am J Clin Nutr.* 2018;**108**:243–55.
 - 36 Gao Q, Praticò G, Scalbert A, Vergères G, Kolehmainen M, Manach C, et al. A scheme for a flexible classification of dietary and health biomarkers. *Genes Nutr.* 2017;**12**:34.
 - 37 Wishart DS. Metabolomics for investigating physiological and pathophysiological processes. *Physiol Rev.* 2019;**99**:1819–75.
 - 38 Rankin NJ, Preiss D, Welsh P, Burgess KEV, Nelson SM, Lawlor DA, et al. The emergence of proton nuclear magnetic resonance metabolomics in the cardiovascular arena as viewed from a clinical perspective. *Atherosclerosis.* 2014;**237**:287–300.
 - 39 Drenos F. Systems epidemiology of metabolomics measures reveals new relationships between lipoproteins and other small molecules. *Metabolomics.* 2021;**18**:1.
 - 40 Zhao J, Li Z, Gao Q, Zhao H, Chen S, Huang L, et al. A review of statistical methods for dietary pattern analysis. *Nutr J.* 2021;**20**:1–18.
 - 41 Sharma I, Roebötham B, Zhu Y, Woodrow J, Parfrey PS, McLaughlin JR, et al. Hypothesis and data-driven dietary patterns and colorectal Cancer survival: findings from Newfoundland and Labrador colorectal Cancer cohort. *Nutr J.* 2018;**17**:55.
 - 42 Kowalkowska J, Wadolowska L, Czarnocinska J, Galinski G, Dlugosz A, Loboda D, et al. Data-driven dietary patterns and diet quality scores: reproducibility and consistency in sex and age subgroups of poles aged 15–65 years. *Nutrients.* 2020;**12**:3598.
 - 43 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;**336**:1117–24.
 - 44 Gibbs J, Gaskin E, Ji C, Miller MA, Cappuccio FP. The effect of plant-based dietary patterns on blood pressure: a systematic review and meta-analysis of controlled intervention trials. *J Hypertens.* 2021;**39**:23–37.
 - 45 Fung TT. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med.* 2008;**168**:713–20.

- 46 Schwingshackl L, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. *J Acad Nutr Diet*. 2015;**115**:780–800.e5.
- 47 Guenther PM, Casavale KO, Reedy J, Kirkpatrick SI, Hiza HAB, Kuczynski KJ, et al. Update of the Healthy Eating Index: HEI-2010. *J Acad Nutr Diet*. 2013;**113**:569–80.
- 48 Krebs-Smith SM, Pannucci TE, Subar AF, Kirkpatrick SI, Lerman JL, Tooze JA, et al. Update of the Healthy Eating Index: HEI-2015. *J Acad Nutr Diet*. 2018;**118**:1591–602.
- 49 Kanerva N, Kaartinen NE, Schwab U, Lahti-Koski M, Männistö S. The Baltic Sea Diet Score: a tool for assessing healthy eating in Nordic countries. *Public Health Nutr*. 2014;**17**:1697–705.
- 50 Mithril C, Dragsted LO, Meyer C, Blauert E, Holt MK, Astrup A. Guidelines for the New Nordic Diet. *Public Health Nutr*. 2012;**15**:1941–7.
- 51 Guasch-Ferré M, Willett WC. The Mediterranean diet and health: a comprehensive overview. *J Intern Med*. 2021;**290**:549–66.
- 52 Krznarić Ž, Karas I, Kelečić D, Vranešić Bender D. The Mediterranean and Nordic diet: a review of differences and similarities of two sustainable, health-promoting dietary patterns. *Front Nutr*. 2021;**8**:683678.
- 53 Bere E, Brug J. Towards health-promoting and environmentally friendly regional diets—a Nordic example. *Public Health Nutr*. 2009;**12**:91–6.
- 54 Nishida C, Uauy R, Kumanyika S, Shetty P. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. *Public Health Nutr*. 2004;**7**:245–50.
- 55 Keski-Rahkonen P, Kolehmainen M, Lappi J, Micard V, Jokkala J, Rosa-Sibakov N, et al. Decreased plasma serotonin and other metabolite changes in healthy adults after consumption of wholegrain rye: an untargeted metabolomics study. *Am J Clin Nutr*. 2019;**109**:1630–9.
- 56 Noerman S, Kokla M, Koistinen VM, Lehtonen M, Tuomainen T-P, Brunius C, et al. Associations of the serum metabolite profile with a healthy Nordic diet and risk of coronary artery disease. *Clin Nutr*. 2021;**40**:3250–62.
- 57 Cuparencu C, Praticó G, Hemeryck LY, Sri Harsha PSC, Noerman S, Rombouts C, et al. Biomarkers of meat and seafood intake: an extensive literature review. *Genes Nutr*. 2019;**14**:1–30.
- 58 Praticó G, Gao Q, Manach C, Dragsted LO. Biomarkers of food intake for Allium vegetables. *Genes Nutr*. 2018;**13**:34.
- 59 Shi L, Brunius C, Johansson I, Bergdahl IA, Lindahl B, Hanhineva K, et al. Plasma metabolites associated with healthy Nordic dietary indexes and risk of type 2 diabetes—a nested case-control study in a Swedish population. *Am J Clin Nutr*. 2018;**108**:564–75.
- 60 Tovar J, De Mello VD, Nilsson A, Johansson M, Paananen J, Lehtonen M, et al. Reduction in cardiometabolic risk factors by a multifunctional diet is mediated via several branches of metabolism as evidenced by nontargeted metabolite profiling approach. *Mol Nutr Food Res*. 2017;**61**:1600552.
- 61 Kärkkäinen O, Lankinen MA, Vitale M, Jokkala J, Leppänen J, Koistinen V, et al. Diets rich in whole grains increase betainized compounds associated with glucose metabolism. *Am J Clin Nutr*. 2018;**108**:971–9.
- 62 Vitale M, Hanhineva K, Koistinen V, Auriola S, Paananen J, Costabile G, et al. Putative metabolites involved in the beneficial effects of wholegrain cereal: nontargeted metabolite profiling approach. *Nutr Metab Cardiovasc Dis*. 2021;**31**:1156–65.
- 63 Ulaszewska M, Vázquez-Manjarrez N, Garcia-Aloy M, Llorach R, Mattivi F, Dragsted LO, et al. Food intake biomarkers for apple, pear, and stone fruit. *Genes Nutr*. 2018;**13**:29.
- 64 Tong TYN, Koulman A, Griffin JL, Wareham NJ, Forouhi NG, Imamura F. A combination of metabolites predicts adherence to the Mediterranean diet pattern and its associations with insulin sensitivity and lipid homeostasis in the general population: the Fenland study, United Kingdom. *J Nutr*. 2020;**150**:568–78.
- 65 Wittenbecher C, Mühlenbruch K, Kröger J, Jacobs S, Kuxhaus O, Floegel A, et al. Amino acids, lipid metabolites, and ferritin as potential mediators linking red meat consumption to type 2 diabetes. *Am J Clin Nutr*. 2015;**101**:1241–50.
- 66 De Mello VD, Lankinen MA, Lindström J, Puupponen-Pimiä R, Laaksonen DE, Pihlajamäki J, et al. Fasting serum hippuric acid is elevated after bilberry (*Vaccinium myrtillus*) consumption and associates with improvement of fasting glucose levels and insulin secretion in persons at high risk of developing type 2 diabetes. *Mol Nutr Food Res*. 2017;**61**:1700019.
- 67 Pallister T, Jackson MA, Martin TC, Zierer J, Jennings A, Mohny RP, et al. Hippurate as a metabolomic marker of gut microbiome diversity: modulation by diet and relationship to metabolic syndrome. *Sci Rep*. 2017;**7**:13670.
- 68 Holmes E, Loo RL, Stalmer J, Bictash M, Yap IKS, Chan Q, et al. Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature*. 2008;**453**:396–400.
- 69 Tuomainen M, Lindström J, Lehtonen M, Auriola S, Pihlajamäki J, Peltonen M, et al. Associations of serum indolepropionic acid, a gut microbiota metabolite, with type 2 diabetes and low-grade inflammation in high-risk individuals. *Nutr Diabetes*. 2018;**8**:1–5.
- 70 De Mello VD, Paananen J, Lindström J, Lankinen MA, Shi L, Kuusisto J, et al. Indolepropionic acid and novel lipid metabolites are associated with a lower risk of type 2 diabetes in the Finnish Diabetes Prevention Study. *Sci Rep*. 2017;**7**:1–12.
- 71 Crown SB, Marze N, Antoniewicz MR. Catabolism of branched chain amino acids contributes significantly to synthesis of odd-chain and even-chain fatty acids in 3T3-L1 adipocytes. *PLoS One*. 2016;**10**:e0145850.
- 72 Hamaya R, Mora S, Lawler PR, Cook NR, Buring JE, Lee IM, et al. Association of modifiable lifestyle factors with plasma branched chain amino acid metabolites in women. *J Nutr*. 2022;**152**:1515–24.
- 73 Visconti A, Le Roy CI, Rosa F, Rossi N, Martin TC, Mohny RP, et al. Interplay between the human gut microbiome and host metabolism. *Nat Commun*. 2019;**10**:1–10.
- 74 Bar N, Korem T, Weissbrod O, Zeevi D, Rothschild D, Leviatan S, et al. A reference map of potential determinants for the human serum metabolome. *Nature*. 2020;**588**:135–40.
- 75 Jacobsen UP, Nielsen HBR, Hildebrand F, Raes J, Sicheritz-Ponten T, Kouskoumvekaki I, et al. The chemical

- interactome space between the human host and the genetically defined gut metabolotypes. *ISME J.* 2013;**7**:730–42.
- 76 Pallister T, Jackson MA, Martin TC, Glastonbury CA, Jennings A, Beaumont M, et al. Untangling the relationship between diet and visceral fat mass through blood metabolomics and gut microbiome profiling. *Int J Obes.* 2017;**41**:1106–13.
 - 77 Shoaie S, Ghaffari P, Kovatcheva-Datchary P, Mardinoglu A, Sen P, Pujos-Guillot E, et al. Quantifying diet-induced metabolic changes of the human gut microbiome. *Cell Metab.* 2015;**22**:320–31.
 - 78 Menni C, Zhu J, Le Roy CI, Mompeo O, Young K, Rebolz CM, et al. Serum metabolites reflecting gut microbiome alpha diversity predict type 2 diabetes. *Gut Microbes.* 2020;**11**:1632–42.
 - 79 Vojinovic D, Radjabzadeh D, Kurilshikov A, Amin N, Wijmenga C, Franke L, et al. Relationship between gut microbiota and circulating metabolites in population-based cohorts. *Nat Commun.* 2019;**10**:5813.
 - 80 Asnicar F, Berry SE, Valdes AM, Nguyen LH, Piccinno G, Drew DA, et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat Med.* 2021;**27**:321–32.
 - 81 Zhu C, Sawrey-Kubicek L, Beals E, Rhodes CH, Houts HE, Sacchi R, et al. Human gut microbiome composition and tryptophan metabolites were changed differently by fast food and Mediterranean diet in 4 days: a pilot study. *Nutr Res.* 2020;**77**:62–72.
 - 82 Fu J, Bonder MJ, Cenit M-AC, Tigchelaar EF, Maatman A, Dekens JAM, et al. The gut microbiome contributes to a substantial proportion of the variation in blood lipids. *Circ Res.* 2015;**117**:817–24.
 - 83 Wilmanski T, Rappaport N, Earls JC, Magis AT, Manor O, Lovejoy J, et al. Blood metabolome predicts gut microbiome α -diversity in humans. *Nat Biotechnol.* 2019;**37**:1217–28.
 - 84 Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol.* 2021;**19**:55–71.
 - 85 Andraos S, Beck KL, Jones MB, Han T-L, Conlon CA, de Seymour JV. Characterizing patterns of dietary exposure using metabolomic profiles of human biospecimens: a systematic review. *Nutr Rev.* 2022;**80**(4):699–708.
 - 86 Verri Hernandez V, Dordevic N, Hantikainen EM, Sigurdsson BB, Vidir Smáráson S, Garcia-Larsen V, et al. Age, sex, body mass index, diet and menopause related metabolites in a large homogeneous alpine cohort. *Metabolites.* 2022;**12**:205.
 - 87 Floegel A, Wientzek A, Bachlechner U, Jacobs S, Drogan D, Prehn C, et al. Linking diet, physical activity, cardiorespiratory fitness and obesity to serum metabolite networks: findings from a population-based study. *Int J Obes.* 2014;**38**:1388–96.
 - 88 Dragsted LO, Gao Q, Scalbert A, Vergères G, Kolehmainen M, Manach C, et al. Validation of biomarkers of food intake—critical assessment of candidate biomarkers. *Genes Nutr.* 2018;**13**:14.
 - 89 Landberg R, Hanhineva K, Tuohy K, Garcia-Aloy M, Biskup I, Llorach R, et al. Biomarkers of cereal food intake. *Genes Nutr.* 2019;**14**:28.
 - 90 Vázquez-Manjarrez N, Ulaszewska M, Garcia-Aloy M, Mattivi F, Praticò G, Dragsted LO, et al. Biomarkers of intake for tropical fruits. *Genes Nutr.* 2020;**15**:11.
 - 91 Garcia-Aloy M, Hulshof PJM, Estruel-Amades S, Osté MCJ, Lankinen M, Geleijnse JM, et al. Biomarkers of food intake for nuts and vegetable oils: an extensive literature search. *Genes Nutr.* 2019;**14**:7.
 - 92 Sri Harsha PSC, Wahab RA, Garcia-Aloy M, Madrid-Gambin F, Estruel-Amades S, Watzl B, et al. Biomarkers of legume intake in human intervention and observational studies: a systematic review. *Genes Nutr.* 2018;**13**:25.
 - 93 Lippa KA, Aristizabal-Henao JJ, Beger RD, Bowden JA, Broeckling C, Beecher C, et al. Reference materials for MS-based untargeted metabolomics and lipidomics: a review by the metabolomics quality assurance and quality control consortium (mQACC). *Metabolomics.* 2022;**18**:24.
 - 94 Evans AM, O'Donovan C, Playdon M, Beecher C, Beger RD, Bowden JA, et al. Dissemination and analysis of the quality assurance (QA) and quality control (QC) practices of LC-MS based untargeted metabolomics practitioners. *Metabolomics.* 2020;**16**:113.
 - 95 Kirwan JA, Gika H, Beger RD, Bearden D, Dunn WB, Goodacre R, et al. Quality assurance and quality control reporting in untargeted metabolic phenotyping: mQACC recommendations for analytical quality management. *Metabolomics.* 2022;**18**:70.
 - 96 Brial FO, Chilloux J, Nielsen T, Vieira-Silva S, Falony G, Andrikopoulos P, et al. Human and preclinical studies of the host-gut microbiome co-metabolite hippurate as a marker and mediator of metabolic health. *Gut.* 2021;**70**:2105–14.
 - 97 Tanaka T, Talegawkar SA, Jin Y, Candia J, Tian Q, Moaddel R, et al. Metabolomic profile of different dietary patterns and their association with frailty index in community-dwelling older men and women. *Nutrients.* 2022;**14**:2237.
 - 98 Hertel J, Fässler D, Heinken A, Weiß FU, Rühlemann M, Bang C, et al. NMR metabolomics reveal urine markers of microbiome diversity and identify benzoate metabolism as a mediator between high microbial alpha diversity and metabolic health. *Metabolism.* 2022;**12**:308.
 - 99 Liu G, Yu Q, Tan B, Ke X, Zhang C, Li H, et al. Gut dysbiosis impairs hippocampal plasticity and behaviors by remodeling serum metabolome. *Gut Microbes.* 2022;**14**:2104089.
 - 100 Shan Z, Li Y, Baden MY, Bhupathiraju SN, Wang DD, Sun Q, et al. Association between healthy eating patterns and risk of cardiovascular disease. *JAMA Intern Med.* 2020;**180**:1090–100.
 - 101 Rebolz CM, Crews DC, Grams ME, Steffen LM, Levey AS, Miller ER, et al. DASH (Dietary Approaches to Stop Hypertension) diet and risk of subsequent kidney disease. *Am J Kidney Dis.* 2016;**68**:853–61.
 - 102 Mertens E, Markey O, Geleijnse JM, Lovegrove JA, Givens DI. Adherence to a healthy diet in relation to cardiovascular incidence and risk markers: evidence from the Caerphilly Prospective Study. *Eur J Nutr.* 2018;**57**:1245–58.
 - 103 Chiuvè SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr.* 2012;**142**:1009–18.
 - 104 Jankovic N, Geelen A, Streppel MT, De Groot LCPGM, Orfanos P, Van Den Hooven EH, et al. Adherence to a healthy diet according to the World Health Organization Guidelines and all-cause mortality in elderly adults from Europe and the United States. *Am J Epidemiol.* 2014;**180**:978–88.
 - 105 Jankovic N, Geelen A, Streppel MT, De Groot LC, Kieftede Jong JC, Orfanos P, et al. WHO guidelines for a healthy diet and mortality from cardiovascular disease in European

- and American elderly: the CHANCES project. *Am J Clin Nutr.* 2015;**102**:745–56.
- 106 Tuomainen M, Kärkkäinen O, Leppänen J, Auriola S, Lehtonen M, Savolainen MJ, et al. Quantitative assessment of betainized compounds and associations with dietary and metabolic biomarkers in the randomized study of the healthy Nordic diet (SYSDIET). *Am J Clin Nutr.* 2019;**110**:1108–11.
- 107 Gürdeniz G, Uusitupa M, Hermansen K, Savolainen MJ, Schwab U, Kolehmainen M, 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**:441–51.
- 108 Khakimov B, Poulsen SK, Savorani F, Acar E, Gürdeniz G, Larsen TM, et al. New Nordic Diet versus average Danish diet: a randomized controlled trial revealed healthy long-term effects of the New Nordic Diet by GC-MS blood plasma metabolomics. *J Proteome Res.* 2016;**15**:1939–54.
- 109 Acar E, Gürdeniz G, Khakimov B, Savorani F, Korndal SK, Larsen TM, et al. Biomarkers of individual foods, and separation of diets using untargeted LC-MS-based plasma metabolomics in a randomized controlled trial. *Mol Nutr Food Res.* 2019;**63**:1800215.
- 110 Andersen M-BS, Rinnan Å, Manach C, Poulsen SK, Pujos-Guillot E, Larsen TM, et al. Untargeted metabolomics as a screening tool for estimating compliance to a dietary pattern. *J Proteome Res.* 2014;**13**:1405–18.
- 111 Bagheri M, Willett W, Townsend MK, Kraft P, Ivey KL, Rimm EB, et al. A lipid-related metabolomic pattern of diet quality. *Am J Clin Nutr.* 2020;**112**:1613–30.
- 112 Guertin KA, Moore SC, Sampson JN, Huang W-Y, Xiao Q, Stolzenberg-Solomon RZ, et al. Metabolomics in nutritional epidemiology: identifying metabolites associated with diet and quantifying their potential to uncover diet-disease relations in populations. *Am J Clin Nutr.* 2014;**100**:208–17.
- 113 Bondia-Pons I, Martinez J, De La Iglesia R, Lopez-Legarrea P, Poutanen K, Hanhineva K, et al. Effects of short- and long-term Mediterranean-based dietary treatment on plasma LC-QTOF/MS metabolic profiling of subjects with metabolic syndrome features: the Metabolic Syndrome Reduction in Navarra (RESMENA) randomized controlled trial. *Mol Nutr Food Res.* 2015;**59**:711–28.

Correspondence: Rikard Landberg, Department of Biology and Biological Engineering, Division of Food and Nutrition Science, Chalmers University of Technology, Gothenburg, Sweden.

Email: rikard.landberg@chalmers.se

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplemental Table 1. Blood metabolites associated with healthy dietary patterns. ■