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

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

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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
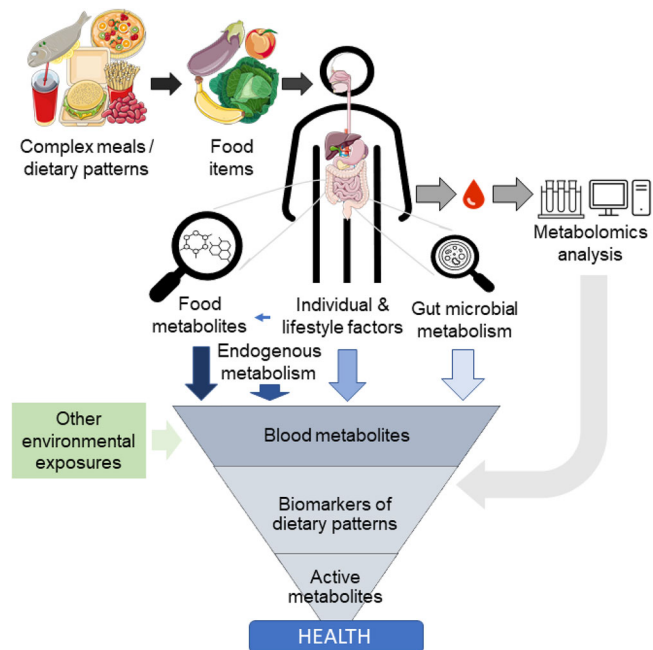
Fig. 1 *Various metabolites in the metabolome reflecting a range of processes from dietary exposure, metabolism of intake related molecules, physiological responses thereof, to molecular fingerprints of progression of metabolic diseases. Individual and lifestyle factors (e.g., body composition, stress, 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 $\geq$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 cholesterols, 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 C10:3 Acylcarnitine C13:0 Acylcarnitine C13:1	Acylcarnitine C3:0	Acylcarnitine C12:0 Acylcarnitine C12:1	Acylcarnitine C14:2 Acylcarnitine C18:1	
Alkylresorcinols	Alkylresorcinol C19:0 glucuronide Alkylresorcinol C21:0 glucuronide Alkylresorcinol C21:1 glucuronide				
Benzoic acids and derivatives	Dihydroxybenzoic acid Loliolide 3,4,5,6-Tetrahydrohippurate 2-Hydroxybenzoic acid 3,4,5-Trimethoxycinnamic acid				
Amino acids and derivatives	Aspartic acid N-Acetylaspartic acid Prolyl-hydroxyproline	2-Methylserine Ornithine S-Allylcysteine	3-Methylhistidine Creatine N-Acetyl-3-methylhistidine		S-Methylcysteine
Indoles	(2-Oxo-2,3-dihydro-1H-indol-3-yl)acetic acid			Hypaphorine Indoleacetate	
Purines and purine derivatives			1,7-Dimethylurate		
Organic acids	3-(2,5-Dimethoxyphenyl)propionic acid	3-Phenylpropionate (hydrocinnamate)	N-Methylmalonamic acid (NMMA) Xylonate		4-Guanidinobutanoate
Phenyl sulfates	Methylimidazoleacetic acid	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)		
Hydroxy fatty acids	2,3-Dihydroxybutanoic acid Hydroxydecanoic acid 3-Hydroxybutanoic acid		α-Hydroxyisovalerate 3-Hydroxyisobutyrate		
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(22:6/P-18:1)		PE(36:2)	PE(18:2/16:0)/PE(34:2)	
PI			LPI(18:1)		
SM	SM(34:2)		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)	
				LPC(24:0)	
	PC(16:0/HODE)			PC(18:2/14:0) /PC(32:2)	
	PC(18:0/22:4) /PC(40:4)			PC(20:4/14:0) /PC(34:4)	
	PC(40:7)			PC(36:0)	
	PC(40:9)			PC(36:6)	
				PC(38:0)	
				PC(38:1)	
				PC(40:1)	
				PC(40:2)	
				PC(42:0)	
				PC(42:4)	
PC plasmalogens	LPC(O-20:2)			PC(O-38:0)	
	LPC(O-22:2)			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-16:0/18:1)		
	PC(P-38:6)				

[a]Metabolites 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].

[b]CE: 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: (lysophosphatidylinositol; 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*-methylmalonamic 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 (*N*-methylmalonamic acid, methylimidazoleacetic acid, oxalic acid)	∼	+	+	+	+
Purines and purine derivatives					
Purine nucleosides (N6-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-diisopropylnaphthalene)	−				
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	+				

[a]Positive 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].

[b]AA: 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]	Metabolites[a]	Dietary patterns[b]				Validation criteria[c]						Analytical	
		NORDASH	HEI	MED	HDI	Plausibility	Dose–response	Time–response	Robustness	Reliability	Stability	performance	Reproducibility
Acetylated amino acids	Acetylornithine	+	+	+		U	U	U	Y	U	U	U	Y
Acetylated amino acids	N-Acetylalanine		−	−		N	U	U	Y	U	U	U	Y
Aliphatic amino acids and derivatives	Glycine	+	+			N	U	U	Y	U	U	U	Y
Aliphatic amino acids and derivatives	Hydroxyproline	−		−		U	U	U	Y	U	U	U	Y
Aliphatic amino acids and derivatives	Proline	−		−		U	U	U	Y	U	U	U	Y
Betaines	Glycine betaine		+	+	+	Y	U	U	Y	U	U	U	Y
Betaines	Pipecolic acid betaine (homostachydrine)	+	+		+	Y	U	U	Y	U	U	U	Y
Betaines	Stachydrine (proline betaine)	~	+	+		Y	U	U	Y	U	U	U	N
Betaines	Tryptophan betaine	+		+		Y	U	U	Y	U	U	U	Y
Betaines	Trimethylamine N-oxide (TMAO)	+	+			Y	U	U	Y	U	U	U	Y
Branched-chain amino acids and derivatives	Isoleucine		−	−		N	U	U	Y	U	U	U	Y
Branched-chain fatty acids	Methyl palmitate		−	−		U	U	U	Y	U	U	U	Y
Branched-chain fatty acids	Phytanate		−	−		U	U	U	Y	U	U	U	Y
Carboxylic acids and derivatives	Oxalic acid	−	+	+		U	U	U	Y	U	U	U	Y

(Continued)

Table 4. *(Continued)*

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

(Continued)

Table 4. *(Continued)*

Metabolite groups[a]	Metabolites[a]	NORDASH	HEI	MED	HDI	Plausibility	Dose–response	Time–response	Robustness	Reliability	Stability	Analytical performance	Reproducibility
LPI-medium-chain unsaturated fatty acids	LPI(16:1)	−	−			N	U	U	Y	U	U	U	Y
LPI-medium-chain unsaturated fatty acids	LPI(18:2)	+		+		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 (10–18C) fatty acids	Linolenate (18:3n − 3 or 18:3n − 6)	+	+	+	+	Y	U	U	Y	U	U	Y	Y
Medium unsaturated fatty acid monoglycerides	MG(18:2)		+	+		Y	U	U	Y	U	U	U	Y
Medium-chain (10–18C) acylcarnitines	Acylcarnitine C10:1 (cis-4-decenoylcarnitine)	+	+	+	+	U	U	U	Y	U	U	U	Y
Medium-chain (10–18C) acylcarnitines	Acylcarnitine C18:2		+	+		U	U	U	Y	U	U	U	Y
Methyl glucopyranoside	Methyl glucopyranoside	+	+			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]	Metabolites[a]	Dietary patterns[b]				Validation criteria[c]							
		NORDASH	HEI	MED	HDI	Plausibility	Dose–response	Time–response	Robustness	Reliability	Stability	Analytical performance	Reproducibility
PC-PUFA	PC(16:0/20:5)/PC(36:5)	+		+		N	U	U	Y	U	U	U	Y
PC-PUFA	PC(18:0/20:3)/PC(38:3)	–	–	–		N	U	U	Y	U	U	U	Y
PC-PUFA	PC(18:0/22:5)/PC(40:5)	–		–		N	U	U	Y	U	U	U	Y
PC-PUFA	PC(18:0/22:6)/PC(40:6)	+	+	+		Y	U	U	Y	U	U	U	Y
PC-PUFA	PC(18:2/20:4)/PC(38:6)	+	+	+		Y	U	U	Y	U	U	U	Y
Phenyl sulfates	2-Aminophenol sulfate		+		+	U	U	U	Y	U	U	U	Y
Phenylpropanoic acids	3-(4-Hydroxyphenyl)lactate	–	–			U	U	U	Y	U	U	U	Y
Purine nucleosides	N6-carbamoylthreonyladenosine	–	–			U	U	U	Y	U	U	U	Y
Pyrimidine nucleosides	Uridine	+	+			U	U	U	Y	U	U	U	Y
Short branched odd-chain fatty acids (OCFA)	10-Undecenoate (11:1$n-1$)	–	–			U	U	U	Y	U	Y	Y	N
Short-chain acylcarnitines	Acylcarnitine C4:0	+		–		U	U	U	Y	U	U	U	N
Short-chain acylcarnitines	Acylcarnitine C6 (adipoylcarnitine)	–	–			U	U	U	Y	U	U	U	Y
SM-medium chain(s)	SM(18:0)	–	–	–		U	U	U	Y	U	U	U	Y
SM-medium chain(s)	SM(18:1)	–	–	–		U	U	U	Y	U	U	U	Y
SM-medium chain(s)	SM(d18:2/18:1)	–	–	–		U	U	U	Y	U	U	U	Y
Sterols and sterol esters	CE(22:6)	+	+	+		U	U	U	Y	U	U	U	Y

(Continued)

Table 4. *(Continued)*

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

(Continued)

Table 4. *(Continued)*

Metabolite groups[a]	Metabolites[a]	NOR	DASH	HEI	MED	HDI	Plausibility	Dose–response	Time–response	Robustness	Reliability	Stability	Analytical performance	Reproducibility
						Dietary patterns[b]				Validation criteria[c]				
Xanthines	Theobromine	–	–				Y	U	Y	U	U	U	U	Y
Xanthines	3-Methylxanthine	–	–				U	U	U	Y	U	U	U	Y
Xanthines	7-Methylurate	–					U	U	U	Y	U	U	U	Y

[a]AA: 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.

[b]Positive 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 (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].

[c]Validation 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], acetylornithine 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.

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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.

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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. ■