Systematic Review

Association Between Diet and Metabolome in Childhood and Adolescence: A Systematic Review

Mariona Gispert-Llaurado [1,2]; Irina Gheorghita [1,2]; Lara Vehovec [3]; Natàlia Ferré [1,2]; Noelia Ramírez [2]; Jeannie Horak [4,5]; Hans Demmelmair [4,5]; Bernadeta Patro-Golab [4,5]; Veit Grote [4,5]; Berthold Koletzko [4,5]; Gabi Kastenmüller [3]; Klaus Kratochwill [6,7]; Elvira Verduci [8,9]; Dariusz Gruszfeld [10]; Joaquin Escribano [1,2,*]; Veronica Luque [1,2,*]

[1]Pediatrics, Nutrition and Development Research Unit, Universitat Rovira i Virgili (URV), Reus, 43201, Spain; [2]Pediatrics, Nutrition and Development Research Unit, Institut de Recerca Biomèdica Catalunya Sud (IRBCatSud), Reus, 43201, Spain; [3]Institute of Computational Biology, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, 85764, Germany; [4]Department of Pediatrics, Dr von Hauner Children's Hospital, LMU Munich, Munich, 80337, Germany; [5]German Center for Child and Adolescent Health, Munich, 80337, Germany; [6]Core Facility Proteomics, Medical University of Vienna, Vienna, 1090, Austria; [7]Division of Pediatric Nephrology and Gastroenterology, Department of Pediatrics and Adolescent Medicine, Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, 1090, Austria; [8]Department of Pediatrics, Vittore Buzzi Children's Hospital, Metabolic Disease Unit, University of Milan, Milan, 20154, Italy; [9]Department of Health Sciences, University of Milan, Milan, 20142, Italy; [10]Neonatal Department, Children's Memorial Health Institute, Warsaw, 04-730, Poland

*Corresponding Authors: Veronica Luque, Pediatrics, Nutrition and Development Research Unit, Universitat Rovira i Virgili, IISPV, Sant Llorenç 21, 43201 Reus, Spain (Veronica.luque@urv.cat); and Joaquín Escribano, Pediatrics, Nutrition and Development Research Unit, Universitat Rovira i Virgili, IISPV, Sant Llorenç 21, 43201 Reus, Spain (joaquin.escribano@urv.cat).

Context: *Accurately assessing dietary intake in children and adolescents is challenging due to the limitations of traditional self-reported methods. Metabolomics has emerged as a valuable tool for assessing the body's biochemical response to specific foods, food groups, or dietary patterns, thereby improving the evaluation of diet–health relationships. However, evidence on how diet influences metabolomic profiles in pediatric populations remains limited.*

Objective: *To evaluate the evidence on the relationship between nutritional interventions or habitual dietary intake and metabolites measured in blood or urine among children and adolescents.*

Data Sources: *A systematic search was conducted in PubMed, Cochrane, and Embase databases up to September 2024*

Data Extraction: *This systematic review was conducted in accordance with the principles of the Cochrane Collaboration, and PRISMA guidelines were followed. Randomized clinical trials and observational studies in children and adolescents were included.*

Data Analysis: *From 659 records, 8 studies met the inclusion criteria, involving 5992 participants across 12 countries. The included studies reported associations across 3 dietary categories: dietary patterns, food groups, and specific food ingredients. Both targeted and untargeted metabolomic analyses were used to identify diet-related biomarkers in blood and urine. Positive associations were observed between higher adherence to the Mediterranean diet and greater fruit and vegetable consumption with metabolites such as hippurate, trigonelline, and proline betaine. In contrast, higher intake of ultra-processed foods and adherence to vegan*

https://doi.org/10.1093/nutrit/nuaf305

diets were inversely associated with branched-chain amino acids and aromatic amino acids such as tyrosine and docosahexaenoic acid.

Conclusion: *This review identifies several metabolites consistently associated with specific dietary components across different studies in children and adolescents. These findings support the potential of metabolomics for validating dietary biomarkers and improving the accuracy of dietary assessment in pediatric populations. Although metabolomic markers reflect actual dietary intake, their implications for health outcomes remain to be explored.*

Systematic Review Registration: *PROSPERO registration no. CRD42024506437.*

Key words: children, adolescents, diet, metabolomics, biomarkers.

INTRODUCTION

Unhealthy dietary habits contribute to approximately 11 million deaths annually.[1] However, accurate evaluation of individual dietary intake remains a challenge. Traditional methods, such as food-frequency questionnaires, 24-hour dietary recalls, and food diaries are commonly used, but are associated with several limitations, including underreporting, recall errors, and difficulty in accurate assessment of portion sizes.[2] Even more important, food consumption affects individuals differently due to other relevant factors, including metabolism, physical activity, exposure to environmental toxins, and genetic predisposition. Although assessing dietary intake and other lifestyle factors provides valuable insights, conventional assessments provide only a partial understanding of the complex interactions between diet and health.

Metabolomic analyses detect and quantify a wide range of metabolites in cells, tissues, organs, or biological fluids.[3] While many of these metabolites are of low molecular weight (<1500 Da), metabolomics also captures larger molecules such as certain lipids and lipoproteins. Unlike traditional compound-specific methods, metabolomics enables the parallel measurement of numerous metabolites, providing a more comprehensive picture of the biochemical state of an organism, which is influenced by multiple factors, including diet, disease, environmental factors, and genetic background.[4] Metabolomics has emerged as a crucial method for evaluating and identifying an individual's response to specific foods, food groups, or dietary patterns, thereby determining the most effective diet or lifestyle interventions to promote health benefits.[5]

Diet-related metabolomic studies in adults have predominantly focused on analyzing the effects of specific food or food group intakes on metabolite alterations.[6–8] Recently, research on the association between dietary patterns and metabolite profiles has gained attention, particularly in exploring how different dietary patterns, and specifically, the Mediterranean diet, impact metabolite concentrations.[9,10] Key metabolites associated with these dietary patterns include lipids such as docosahexaenoic acid (DHA); eicosapentaenoic acid (EPA); certain lysophospholipids, phosphatidylcholines (PCs), and acylcarnitines; as well as organic acids and derivatives, including pipecolate, homostachydrine, and hippurate.[10–13] Several systematic reviews have already summarized findings from diet-related metabolomic studies in adults.[14,15]

In comparison to the wealth of studies on the relationship between dietary intake and metabolomic profiles in adults, most dietary studies in children have focused on early-life nutrition, such as the effects of infant feeding practices (eg, breastfeeding or formula feeding) or on dietary supplements, rather than on habitual food intake beyond infancy and its metabolic impact.[16,17] Interest in how habitual dietary intake during childhood and adolescence influences metabolic profiles has been increasing, as these developmental periods are widely recognized as critical windows for the prevention of metabolic diseases.[18] Although some studies have begun to explore these associations, comprehensive evidence remains limited. Further research is needed to identify valid dietary biomarkers in pediatric populations, and integrating of 'omics techniques could enhance our understanding of diet-related metabolic processes.[19]

To our knowledge, no systematic review has yet compiled the available evidence on how nutritional interventions or habitual dietary intake influence metabolomic profiles in children and adolescents. This systematic review aims to fill that gap by evaluating existing studies on diet-related blood and urine metabolites in this population and exploring their potential implications for metabolic pathways and health outcomes.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the principles of the Cochrane Collaboration.[20]

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed for reporting.[21] The protocol for this systematic review was registered in PROSPERO (registration ID: CRD42024506437).

Research Question

The research question for this review was as follows: How does dietary intake influence metabolite levels during childhood and adolescence? Is there a relationship between the consumption of specific foods, food groups, or dietary patterns and the metabolomic signatures observed in urine or blood?

Eligibility Criteria

The inclusion of studies was determined according to the Population, Intervention, Comparison, Outcomes, and Study design (PICOS) framework (**Table 1**). Eligible studies included children and adolescents from birth to 18 years, whether healthy or with specific conditions that did not require dietary modifications. Studies were excluded if participants had diseases or medical conditions requiring specific therapeutic diets (eg, gluten-free diet or ketogenic diet). However, studies were considered eligible if no individualized diet had been prescribed and any dietary recommendations were intended only to promote general healthy eating. Interventions could encompass any types of dietary or nutritional interventions. Observational studies examining habitual or current dietary intake were also eligible. However, interventions involving supplements, formula feeding, or breastfeeding were excluded. Additionally, studies focusing on habitual or current dietary intake related to nutrient intake were not included. The comparison varied depending on the type of study: in intervention studies, it could refer either to a group that does not receive the dietary intervention (usual diet) or to a comparison between 2 different interventions. In observational studies, although there is no formal control group, comparisons can be made across categories of exposure. Studies were required to evaluate at least 1 of the following outcomes: the correlation between food intake and blood or urine metabolites or the relationship between the consumption of specific foods and variations in the concentration of certain metabolite groups, either as differences in changes compared with baseline (in intervention studies) or as differences between groups with different levels of intake (in observational studies). Case reports, protocols, reviews, or systematic reviews were not considered for inclusion in this systematic review. Only studies published in English were considered eligible.

Search Strategy

A comprehensive literature search was conducted in PubMed, Embase, and The Cochrane Library on November 13, 2023. The search strategy included both free-text terms and medical subject heading (MeSH) terms, combined to retrieve studies on metabolomics related to the outcomes of interest. The complete search strategy is detailed in **Table S1**. To ensure the review included the most recent evidence, an updated search was performed covering the literature up to September 2, 2024.

Study Selection and Data Extraction

The studies retrieved from the search results were imported into Rayyan software (Rayyan Systems, Inc.,

Table 1. PICOS Criteria for Inclusion of Studies

Parameter	Criteria
Population	Children or adolescents from birth to 18 y old. Healthy individuals and those with certain conditions who do not require dietary modifications other than adherence to a healthy, age-appropriate diet. Participants already following a prescribed or restrictive diet at baseline were excluded.
Intervention/exposure	Dietary or nutritional interventions evaluating the impact of foods, food groups, or dietary patterns on metabolomic outcomes. Exposure to habitual or current dietary intake of dietary patterns, food groups, or specific food items and their association with metabolomic profiles.
Comparison	In dietary or nutritional intervention studies, comparisons could involve a group that does not receive the dietary intervention (usual diet) or a second dietary intervention. In observational studies, comparisons could be made across categories of exposure.
Outcome	Associations between dietary intake and individual metabolites or groups of metabolites measured in blood or urine. Studies using both targeted and untargeted metabolomic analyses were included. Eligible analytical techniques comprised LC-MS/MS and NMR-based metabolomics.
Study design	Randomized clinical trials (RCTs), nonrandomized intervention studies, and observational studies.

Abbreviations: LC-MS/MS, liquid chromatography–tandem mass spectrometry; NMR, nuclear magnetic resonance.

Cambridge, MA, USA) for screening and management.[22] Duplicate records were removed prior to screening.

Subsequently, 2 reviewers (M.G.-L. and I.G.) independently screened titles and abstracts to assess their eligibility. For studies considered potentially relevant, full-text articles were retrieved and assessed independently by 2 reviewers. Any discrepancies between reviewers were resolved through consensus with a third reviewer (V.L.). All excluded articles were categorized according to the reason for their exclusion, which is detailed in Figure 1.

A standardized template, implemented within a Microsoft Excel spreadsheet (Microsoft Office, version 1808 [10351.20054]; Microsoft Corporation, Redmond, WA, USA), was used to analyze and extract data from the included articles. Study characteristics collected included author name and year of publication, type of study, population, country, sample size, nutritional intervention/exposure, methodology used for dietary data collection, urine or blood sample, fasting status, targeted or untargeted metabolic analyses, analytical technique, food/food group/dietary pattern metabolite associations, statistical analyses, confounders, and adjustments. Data extraction was conducted in duplicate and in parallel by 2 reviewers to ensure consistency and accuracy.

Risk-of-Bias and Study Quality Assessment

The methodological quality of the included studies was evaluated using the RoB2 assessment tool[23] for

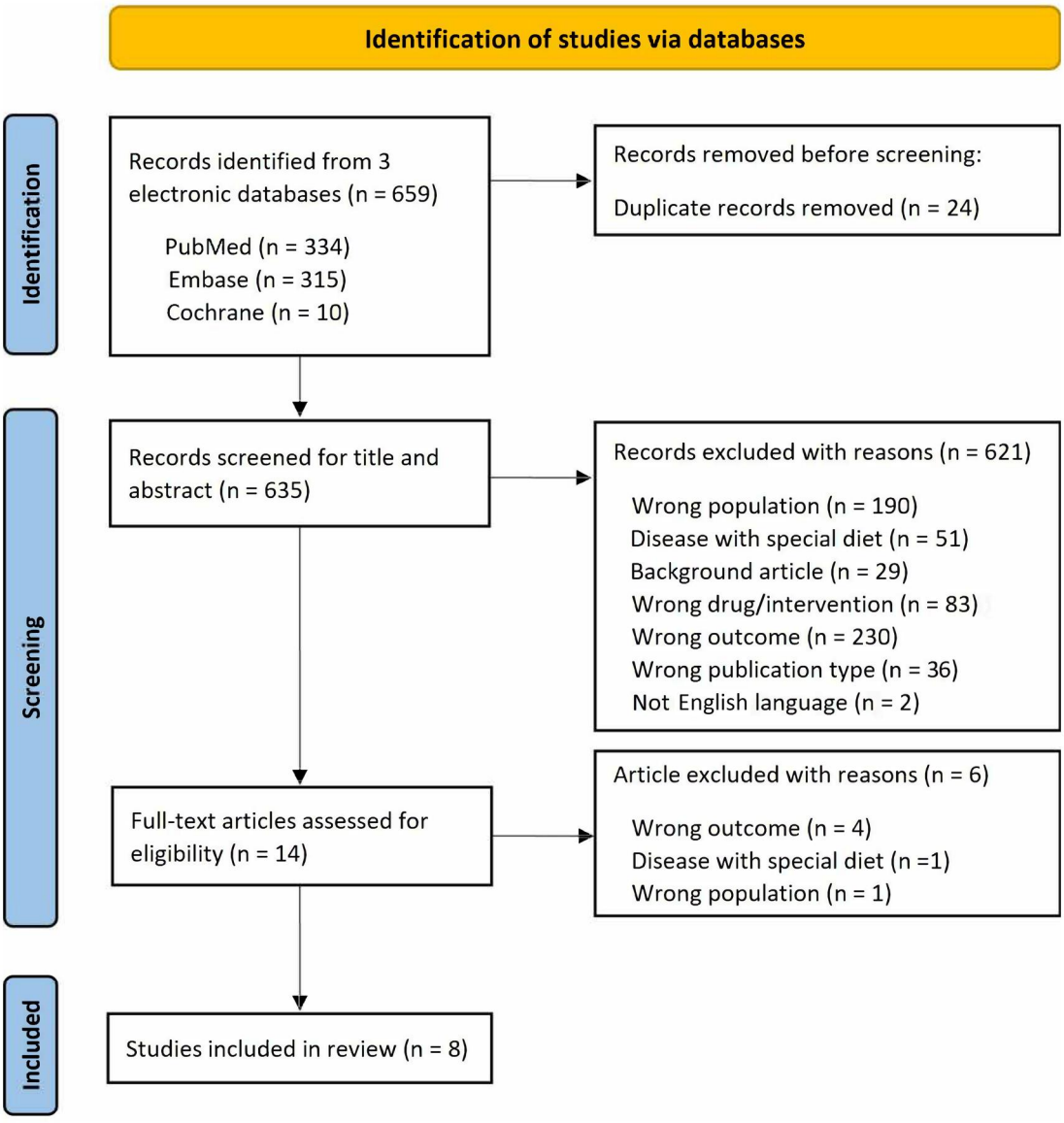

Figure 1. Flow Chart of the Study Selection Process

randomized clinical trials (RCTs) and the National Institutes of Health (NIH) quality assessment tool[24] for observational studies. Specifically, the NIH tool for cross-sectional studies was applied to studies with that design and the NIH tool for case-control studies was used for the 1 case-control study included. For the RoB2 tool, the evaluation focused on the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall risk of bias. Each domain, as well as each study overall, was rated as having low, some, or high risk of bias. The NIH quality assessment tool examined key methodological aspects, including the research question or objective, study population, participation rate, inclusion and exclusion criteria, sample size, exposure(s), association exposure–outcome, levels of the exposure as related to the outcome, exposure measures, exposure(s) assessed, outcome measures, assessors blinded, loss to follow-up, and confounding variables. For this tool, each criterion was categorized as low, fair, or high risk of bias.

Given the metabolomic focus of this systematic review, the Biomarker-based Cross-sectional Studies (BIOCROSS) tool was also applied to assess the quality of biomarker measurement and data modeling.[25] This tool complements the above assessments by specifically evaluating key aspects of biomarker reliability in cross-sectional studies, including sample collection, processing, storage, analytical procedures, and statistical interpretation.

With regard to the substantial methodological variability inherent in metabolomic studies, the BIOCROSS tool allowed us to critically appraise if these factors were adequately reported and controlled for each study. Particular attention was given to how quantification was performed, as these parameters can substantially affect metabolite concentration results and their comparability across studies.

Each selected article was independently assessed by 2 authors and subsequently discussed in a meeting involving all authors engaged in the quality assessment process. The synthesis of the risk-of-bias assessment was conducted using the Risk-of-bias Visualization (ROBVIS) tool.[26]

Synthesis of Results

Due to the heterogeneity in study design, populations, and types of interventions, a meta-analysis was not conducted. Therefore, the results were synthesized narratively and summarized based on study characteristics and outcome measures.

RESULTS

The search process identified 659 records, of which 635 remained after the removal of duplicates. Following title and abstract screening, 621 studies were excluded. The full texts of the remaining 14 articles were assessed for eligibility, and 6 were excluded for the following reasons: wrong outcomes ($n = 4$), involvement of children with diseases requiring special diets ($n = 1$), or wrong population ($n = 1$). Finally, 8 eligible studies, involving a total of 5992 children and adolescents from 12 countries, were included in the final analysis (**Figure 1**). A list of excluded full-text studies, including citations and reasons for exclusion, is provided in **Table S2**. The 8 eligible studies reported a total of 9 associations: 3 on dietary patterns, 3 on food groups, and 3 on food ingredients, as 1 study contributed to 2 different categories.

Study Characteristics

Among the 8 studies included in this review, 3 were RCTs[27–29] and 5 were observational studies.[30–34] **Tables 2** and **3** summarize the key characteristics of these included studies.

The studies were published between 2018 and 2023, with participant ages ranging from 5 months to 17 years. Most studies involved healthy children, with only 2 studies including participants with specific health conditions, such as abnormal lipid profiles[28] and hypertension.[33] These studies were included because no specific therapeutic diets were implemented, and dietary recommendations were focused on general improvements in dietary quality.

Among the RCTs, the interventions extended between 4 weeks and 7 months. They assessed the effects of a meat-based vs dairy-based complementary diet,[27] rice-bran supplementation compared with a control group,[29] and rice bran, navy bean, and combined rice bran plus navy bean supplementation compared with each other and with a control group[28] on metabolomic outcomes (**Table 2**). These ingredients were selected due to their nutritional profile: rice bran is rich in fiber and bioactive compounds, such as γ-oryzanol, and navy beans provide protein, fiber, and polyphenols, all of which have been associated with metabolic health benefits.

The only case-control study compared hypertensive and healthy children, assessing the impact of nut consumption on metabolite profiles.[33] Nuts are rich in unsaturated fats, fiber, and phytosterols, which may influence lipid metabolism and cardiovascular health.

In the observational studies, different methods were used to collect dietary intake data, including food-

Table 2. Summary of Characteristics of Included Randomized Clinical Trial Studies

First author, year	Type of study	Country	Participants	Age range	Duration	Diet intervention (dietary pattern/food group/food ingredient) (No. of participants) (sex: M/F)
Tang, 2021[27]	Randomized clinical trial	United States	Healthy	5-12 mo	7 mo	• Dietary pattern: meat-based complementary diet ($n = 26$) (NR) vs dairy-based complementary diet ($n = 25$) (NR)
Baxter, 2022[28]	Randomized clinical trial	United States	Children at risk of CVD due to abnormal lipids	8-13 y	4 wk	• Food ingredient: rice-bran supplementation ($n = 9$) (4/5) vs navy bean supplementation ($n = 10$) (5/5) vs navy bean + rice-bran supplementation ($n = 10$) (5/5) vs control group ($n = 9$) (5/4)
Pfluger, 2022[29]	Randomized clinical trial	Mali	Healthy	6-12 mo	6 mo	• Food ingredient: rice-bran supplementation ($n = 24$) (12/12) vs control group ($n = 24$) (12/12)

Abbreviations: CVD, cardiovascular disease; F, female; M, male; NR, not reported.

frequency questionnaires (FFQs), the KIDMED questionnaire (Mediterranean Diet Quality Index for children and adolescents) for assessing the adherence to the Mediterranean diet, the NOVA classification for ultra-processed food (UPF) intake, and 3- to 4-day dietary records.

Seven studies conducted metabolomic analyses on blood samples, with 3 also analyzing metabolites in urine, and only 1 study focusing exclusively on urine metabolites. **Tables 4** and **5** summarize the analytical techniques used across the studies. The most commonly used analytical techniques were liquid chromatography–tandem mass spectrometry (LC–MS/MS), including both high-performance liquid chromatography (HPLC) and ultra-high-performance liquid chromatography (UHPLC) systems, and proton nuclear magnetic resonance (1H NMR) spectroscopy. The overall risk-of-bias assessment for the included studies is summarized in **Figure 2**. On average, the overall risk of bias was evaluated as ranging from low to moderate.

Associations Between Dietary Intake and Metabolites

Tables 4 and **5** summarize associations between metabolites and dietary intake reported across the included studies that were considered both statistically significant ($P < .05$). The findings are categorized according to whether the metabolites were associated with dietary patterns, food groups, or specific food ingredients. For a comprehensive overview, all significant positive and negative associations between dietary patterns, food groups, food ingredients, and the identified metabolites are detailed in **Table S3**.

Associations Between Dietary Patterns and Metabolites

Three studies (1 RCT and 2 observational) investigated the associations between adherence to specific dietary patterns and metabolite profiles.[27,31,34] An RCT comparing meat-based and dairy-based complementary diets assessed their effects on metabolomic profiles in infants.[27] Significant increases in essential amino acids, including isoleucine, valine, and phenylalanine, and a significant decrease in threonine compared with baseline were observed in both study groups from 5 to 12 months ($P < .005$ for all), along with an increase in concentration levels of certain acylcarnitines over the same period. However, no significant differences were found between intervention groups for these metabolites. In contrast, trimethylamine N-oxide (TMAO) levels increased significantly only in the meat-based group from 5 to 12 months ($P = .043$), but no significant differences were observed between the diet groups over time (**Table 4**).

According to the findings from Stratakis et al,[31] higher adherence to the Mediterranean diet, measured using the KIDMED index, was associated with higher urinary levels of tyrosine, pantothenic acid, p-hydroxyphenylacetate, urea, acetate, hippurate, p-cresol sulfate, trimethylamine, and N-methylnicotinic acid ($P < .05$ for all) (**Table 5**).

Hovinen et al[34] reported that vegan participants had significantly higher levels of unconjugated primary bile acids and a lower taurine-to-glycine conjugation ratio of bile acids compared with omnivores. Furthermore, circulating levels of essential amino acids, such as isoleucine,

Table 3. Summary of Characteristics of Included Observational Studies

First author, year	Type of study (project)	Country	Participants	Age range, y	No. of participants	Sex, M/F	Dietary intake collection	Diet exposure (dietary pattern/food group/ food ingredient)
Lau, 2018[30]	Cross-sectional study (HELIX Project)	France, Greece, Spain, Lithuania, Norway, and United Kingdom	Healthy	6-11	1192 (157, 199, 207, 201, 229, 199)[a]	651/541	FFQ	• Food groups: cereal, meat, fish, dairy, lipids, potatoes, vegetables, fruits, sweets, bakery products, and beverages
Stratakis, 2022[31]	Cross-sectional study (HELIX Project)	France, Greece, Spain, Lithuania, Norway, and United Kingdom	Healthy	6-11	1147 (149, 192, 202, 194, 221, 189)[a]	626/521	FFQ; KIDMED; NOVA classification	• Dietary pattern: Mediterranean diet • Food group: UPFs
Handakas, 2022[32]	Cross-sectional study (ALSPAC cohort)	United Kingdom	Healthy	7 and 13-17	4528 and 3086[b]	2361/2167 and 1509/1577	3-d dietary records	• Food group: UPFs
Qin, 2023[33]	Case-control (Chongqing cohort)	China	Hypertension and healthy	10-13	96	45/51	FFQ	• Food ingredient: nuts
Hovinen, 2021[34]	Cross-sectional study	Finland	Healthy	1-7	40	19/21	4-d dietary records	• Dietary pattern: vegan, vegetarian, and omnivore diet

Abbreviations: F, female; FFQ, food-frequency questionnaire; KIDMED, Mediterranean Diet Quality Index for children and adolescents; M, male; UPF, ultra-processed food.
[a]Numbers in parentheses indicate the distribution of participants per country in the order listed.
[b]Participants at 7 and 13–17 y, respectively.

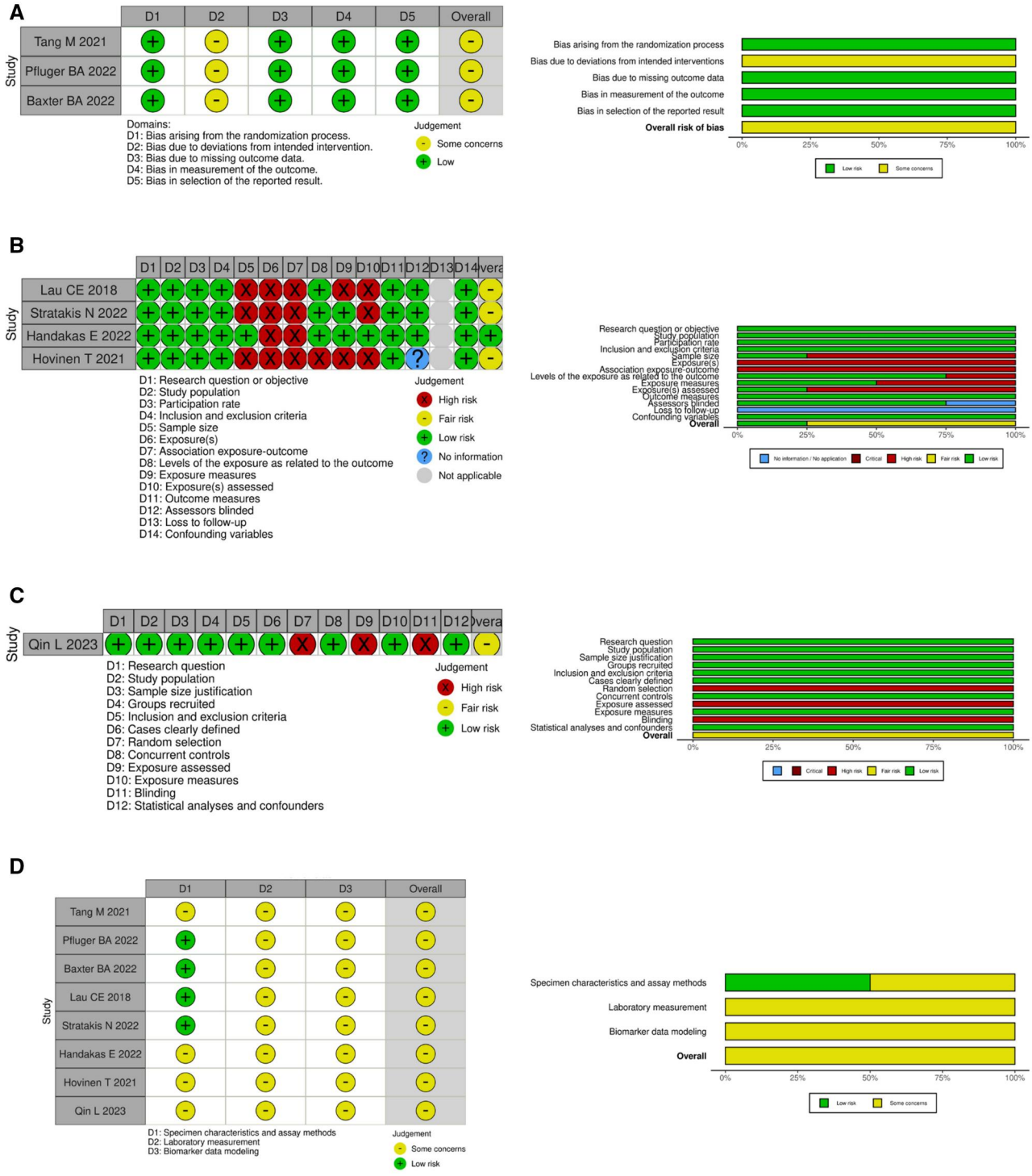

Figure 2. Traffic Light Plots (Left) and Summary Plots (Right) Illustrating the Risk of Bias Within the Randomized Clinical Trials Using the RoB2 tool (A), Cross-sectional Studies Evaluated With the NIH Quality Assessment Tool (B), Case-Control Study Assessed Using the NIH Quality Assessment Tool for Case-Control Studies (C), and Quality of Biomarker Measurements Using the BIOCROSS tool (D)

Abbreviations: BIOCROSS, Biomarker-based Cross-sectional Studies; NIH, National Institutes of Health.

valine, and taurine, were also significantly lower in vegans ($P < .05$ for all). Additionally, vegans showed reduced levels of docosahexaenoic acid (DHA) ($P < .001$) and increased levels of long-chain fatty acid carnitine esters and lysophosphatidylcholine (Lyso-PC) 18:1 compared with omnivorous participants (Table 5).

Table 4. Summary of Biological Sample, Metabolomic Technique, and Metabolite Associations of Included Randomized Clinical Trial Studies

First author, year	Biological sample and time point	Analytical technique	Dietary pattern/food group/food ingredient and metabolite association
Tang, 2021[27]	Blood 5, 12 and, 24 mo of age	Untargeted and targeted: UHPLC–MS/MS	Untargeted metabolomics: 151 metabolites annotated Essential amino acids: ↓ threonine ($P_{FDR} = .004$) and ↑ valine ($P_{FDR} = .021$) from 5 to 12 mo with no differences between diet groups Acylcarnitines: ↑ acylcarnitine C5 ($P_{FDR} = .021$) and ↑ acylcarnitine C5:1 ($P_{FDR} = .001$) from 5 to 12 mos in both diet groups Targeted metabolomics: Essential amino acids: ↑ isoleucine ($P_{FDR} = .047$), ↑ valine ($P_{FDR} = .001$), ↑ phenylalanine ($P_{FDR} = .002$), ↓ threonine ($P_{FDR} = .010$) from 5 to 12 mo in all participants. No significant differences from 12 to 24 mo or between meat- and dairy-based complementary diet groups over time. Acylcarnitines: ↑ acylcarnitine C4 ($P_{FDR} = .047$), ↑ acylcarnitine C5 ($P_{FDR} = .013$), and ↑ acylcarnitine C5:1 ($P_{FDR} = .04$) from 5 to 12 mo. A decrease in acylcarnitine C4 from 12 to 24 mo ($P_{FDR} = .005$) after the intervention ended. No significant differences between diet groups. TMAO: No significant differences between diet groups over time. ↑ TMAO from 5 to 12 mo only in the meat group ($P_{FDR} = .043$).
Baxter, 2022[28]	Blood At baseline and at week 4	Untargeted and targeted: UPLC–MS/MS	Untargeted metabolomics: From the 138 – 175 metabolites modulated by diet according to untargeted analyses, 11 were targeted for quantification: pyridoxal, salicylurate (2-hydroxyhippurate), apigenin, xanthurenate, myoinositol, pipecolate, *S*-methylcysteine, *S*-methylcysteine sulfoxide, trigonelline, N-methylpipecolate, and salicylate. Targeted metabolomics: ↑ Trigonelline ($P = .04$) and ↑ pipecolate ($P = .04$) after 4 wk in navy bean group compared with baseline and the control group ($P < .05$ for both) ↑ Trigonelline ($P = .04$) after 4 wk in the rice-bran group compared with baseline and the control group ($P < .05$) ↑ Xanthurenate ($P = .01$) in the rice-bran group after 4 wk compared with baseline ↓ N-Methylpipecolate ($P = .04$) in the rice-bran group after 4 wk compared with baseline Navy bean + rice-bran group showed no significant associations.
Pfluger, 2022[29]	Dried blood spots From 7-12 mo	Untargeted: RP/UPLC–MS/MS	Untargeted metabolomics: A total of 796 metabolites identified, with 94 showing significant differences in 2-way ANOVA with repeated measures. Amino acids and related metabolites: ↑ glutamate ($P = .029$), ↑ cysteinylglycine ($P < .01$), ↑ glycine ($P = .016$), ↑ tryptophan betaine ($P = .026$), ↓ glutamine ($P = .020$), ↓ nicotinamide adenine dinucleotide (NAD+) ($P = .031$),

(continued)

Table 4. Continued

First author, year	Biological sample and time point	Analytical technique	Dietary pattern/food group/food ingredient and metabolite association
			and ↓ salicylate ($P = .035$) in rice-bran supplementation compared with the control group Fatty acids: ↑ stearate (18:0) ($P < .05$), ↓ acetylcarnitine (C2) ($P = .005$) Glycerophospholipids: ↓ 1-stearoyl-2-docosahexaenoyl-GPC (18:0/22:6) ($P \leq .01$), ↓ 1-palmitoyl-2-docosahexaenoyl-GPC (16:0/22:6) ($P = .011$), and ↓ 1-stearoyl-2-oleoyl-GPC (18:0/18:1) ($P = .023$) in rice-bran–fed infants compared with the control group Sphingoid bases: ↑ sphingosine ($P = .005$) and ↑ sphinganine ($P = .012$) in rice-bran–supplemented infants

Abbreviations: ANOVA, analysis of variance; FDR, false discovery rate; GPC, glycero-phosphocholine; RP/UPLC–MS/MS, ultra-high-performance liquid chromatography (reverse-phase)–tandem mass spectrometry; TMAO, trimethylamine N-oxide; UHPLC–MS/MS, ultra-high-performance liquid chromatography–tandem mass spectrometry; UPLC-MS/MS, ultra-performance liquid chromatography–tandem mass spectrometry.

Associations Between Food Groups and Metabolites

Three studies investigated the associations between the consumption of specific food groups and metabolite profiles.[30–32] Of these, 2 studies focused on the impact of UPF intake on metabolite levels.[31,32]

Stratakis et al[31] reported negative associations between UPF intake and levels of branched-chain amino acids (BCAAs), specifically valine and leucine as well as other amino acids and organic acids, including taurine, tyrosine, 4-deoxythreonic acid, urea, 3-hydroxyisovalerate, hippurate, 2-hydroxyisobutyrate, and N-methylnicotinic acid ($P < .05$ for all).

Similarly, Handakas et al[32] found inverse associations between UPF intake and BCAAs, such as valine, isoleucine, and leucine, consistent with Stratakis et al's findings ($P < .05$ for all). They also observed that higher UPF consumption was related to lower levels of acetate, cholines, phosphoglycerides, sphingomyelins, and PCs ($P < .05$ for all). Furthermore, total, free, and esterified cholesterol, along with total saturated and polyunsaturated fatty acids (PUFAs), including conjugated linoleic acid and DHA, were also reduced with greater UPF intake ($P < .05$ for all). In contrast, positive associations were observed between UPF consumption and metabolites such as glutamine, citrate, and creatinine in blood ($P < .05$ for all) (**Table 5**).

The study by Lau et al[30] examined the relationship between the consumption of various food groups, such as cereals, meat, fish, dairy, potatoes, vegetables, fruits, sweets, bakery products, and beverages, and specific metabolite profiles. In blood, fish consumption was significantly associated with increased levels of several PC species, including PC aa C36:6, PC aa C38:0, PC ae C38:6, and PC aa C38:6 (aa: suggested diacyl [acyl–acyl] structure; ae: suggested acyl–alkyl [ether] structure) ($P < .001$ for all). In contrast, the consumption of bakery products was associated with decreased levels of these same PC species ($P < .001$ for all). Meat intake was positively associated with PC ae C36:3, PC ae C36:4, PC ae C36:5, and PC ae C38:5 ($P < .001$ for all). Additionally, the consumption of beverages, particularly soft and fizzy drinks, was associated with decreased levels of 2 acylcarnitines (C5:1, C6:1) and a sphingolipid (SM [OH] C16:1) ($P < .001$) (26) (**Table 5**). In the same study, urine metabolite analyses revealed significant associations with various food groups. Meat intake was associated with higher creatine levels ($P < .001$), while fruit and vegetable consumption correlated with higher hippurate levels ($P < .001$ for both). Fruit intake was also positively associated with proline betaine, N-methylnicotinic acid, and scyllo-inositol ($P < .001$ for all), and negatively associated with amino acids such as glutamine, alanine, and leucine ($P < .001$ for all). Dairy intake was positively associated with pantothenate levels ($P < .001$), and beverage consumption was inversely associated with 3-hydroxybutyrate/3-aminoisobutyrate ($P < .001$)[30] (**Table 5**).

Associations Between Food Ingredients and Metabolites

Three studies examined the relationships between the intake of specific food ingredients and metabolite profiles.[28,29,33] In the study by Baxter et al,[28] navy bean supplementation led to increased blood levels of trigonelline and pipecolate ($P = .04$ for both), while rice-bran supplementation was associated with elevated levels of trigonelline ($P < .05$) and xanthurenate ($P = .01$). However, the combination of navy bean and rice bran did not show any significant association with metabolite levels (**Table 4**).

Table 5. Summary of Biological Samples, Metabolomic Technique, and Metabolite Associations of Included Observational Studies

First author, year	Biological sample and time point	Analytical technique	Dietary pattern/food group/food ingredient and metabolite association
Lau, 2018[30]	Blood and urine 6-11 y	Blood/targeted: LC-MS/MS and FIA-MS/MS Urine: 1H NMR spectroscopy	Blood metabolites ↑ PC aa C36:0, PC aa C36:5, PC aa C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:1, PC aa C42:2, PC ae C38:0, PC ae C38:6, and PC ae C40:6 with fish consumption ($P < .001$) ↓ PC aa C36:6, PC aa C38:0, PC aa C38:6, PC aa C40:6, PC ae C38:0, PC ae C38:6, PC ae C40:2, PC ae C40:6, and 2 sphingolipids (SM [OH] C14:1, SM [OH] C16:1) with bakery products intake ($P < .001$) ↑ PC ae C36:3, PC ae C36:4, PC ae C36:5, PC ae 38:5 with meat consumption ($P < .001$) ↓ PC aa C38:0, PC aa C38:6, PC ae C38:5, PC ae 38:6, PC ae C40:6 with sweets consumption ($P < .001$) ↑ Acetylornithine with fruit intake ($P < .001$) ↓ 2 Acylcarnitines (C5:1, C6:1) and 1 sphingolipid (SM [OH] C16:1) with beverage consumption (soft and fizzy drinks) ($P < .001$) ↑ PC aa C28:1, PC aa/ae C30:0, SM (OH) C14:1, and ↓ PC aa C38:0, PC ae C38:6 with dairy consumption ($P < .001$) ↓ PC ae C30:0, PC ae C34:0, SM (OH) C14:1 with potatoes intake Urine metabolites ↑ Creatine with meat intake ($P < .001$) ↑ Hippurate with both fruit ($P < .001$) and vegetable ($P < .001$) intake ↑ Proline betaine, N-methylnicotinic acid, and scyllo-inositol with fruit consumption ($P < .001$) ↑ Pantothenate with dairy intake ($P < .001$) ↑ Acetate with potato intake ($P < .001$) ↓ Glutamine, alanine, and leucine with fruit intake ($P < .001$) ↓ 3-Hydroxybutyrate/3-aminoisobutyrate with beverage consumption ($P < .001$)
Stratakis, 2022[31]	Urine 6-11 y	1H NMR spectroscopy	Urine metabolites Higher adherence to KIDMED: ↑ Pantothenic acid, ↑ p-hydroxyphenylacetate, ↑ urea, ↑ acetate, ↑ hippurate, ↑ p-cresol sulfate, ↑ tyrosine, ↑ trimethylamine and ↑ N-methylnicotinic acid ($P < .05$ for all) Higher consumption of UPFs: ↓ 4-Deoxythreonic acid, ↓ taurine, ↓ urea, ↓ 3-hydroxyisovalerate, ↓ hippurate, ↓ valine, ↓ tyrosine, ↓ leucine, ↓ 2-hydroxyisobutyrate, and ↓ N-methylnicotinic acid ($P < .05$ for all)
Handakas, 2022[32]	Blood Cross-sectional at 7 y Prospective at 13 y	1H NMR spectroscopy	Cross-sectional analyses UPF: ↓ Tyrosine, ↓ phenylalanine, ↓ acetate, ↓ isoleucine, ↓ leucine, ↓ valine, ↓ cholines, ↓ phosphoglycerides, ↓ sphingomyelin, and ↓ phosphatidylcholines ↓ Conjugated linoleic acid and ↓ DHA ($P < .05$ for all after Bonferroni correction) ↑ Glutamine, ↑ citrate, and ↑ creatinine ($P < .05$ for all after Bonferroni correction) Prospective analyses ↓ Ratios of DHA to total fatty acids, ↓ ratios of omega-3 fatty acids to total fatty acids, ↓ very large HDL, ↓ ratio of free and total cholesterol to total lipids in medium and large HDL and IDL ($P < .05$ after Bonferroni correction for all)

(continued)

Table 5. Continued

First author, year	Biological sample and time point	Analytical technique	Dietary pattern/food group/food ingredient and metabolite association
Qin, 2023[33]	Blood 10-13 y	Targeted: LC-MS/MS	↑ Phosphatidylglycerol (43:6) ($P = .052$), ↑ phosphatidylcholine (18:0/20:3) ($P < .05$), and ↑ phosphatidylethanolamine (P-22:0/18:2) ($P < .05$) with nut intake
Hovinen, 2021[34]	Blood and urine 1-7 y	Blood/targeted: GLC and HPLC-MS/MS Blood/untargeted: flow injection–TOF MS Urine/targeted: IPC-MS	Blood untargeted metabolites 872 Metabolites were identified, 136 showed significant differences between vegan and omnivore diet ↓ Isoleucine, valine, and taurine ($P < .05$ for all) in vegans Blood targeted metabolites ↑ Unconjugated primary bile acids ($P = .047$) and ↓ taurine to glycine conjugation ratio of bile acids ($P = .047$) in vegans than in omnivores ↑ Folate, ↓vitamin A, vitamin D_2, and vitamin D_3 in vegans compared with omnivore participants ($P < .05$ for all associations) ↓ DHA ($P < .001$), total cholesterol ($P < .001$), LDL cholesterol ($P < .001$), and HDL cholesterol ($P < .05$) in vegans compared with omnivores ↑ Long-chain fatty acid carnitines 18:4 ($P < .001$) and ↑ lysophosphatidylcholine (Lyso-PC) 18:1 ($P < .05$) in vegans compared with omnivores Urine targeted metabolites No significant differences in creatinine levels between diet groups

Abbreviations: aa, a diacyl (acyl–acyl) structure; ae, acyl–alkyl (ether) structure; DHA, docosahexaenoic acid; FIA-MS/MS, flow-injection-analysis mass spectrometry; GLC, gas–liquid chromatography; HDL, high-density lipoprotein; HPLC-MS/MS, high-performance liquid chromatography–mass spectrometry; IDL, intermediate-density lipoprotein; IPC-MS, ion pair chromatography-mass spectrometry; KIDMED, Mediterranean Diet Quality Index for children and adolescents; LC-MS/MS, liquid chromatography tandem mass spectrometry; LDL, low-density lipoprotein; PC, phosphatidylcholine; TOF MS, time-of-flight mass spectrometry; UPF, ultra-processed food; 1H NMR, proton nuclear magnetic resonance.

Pfluger et al[29] reported that rice-bran supplementation significantly increased levels of several amino acids and related metabolites, including glutamate, glycine, cysteinylglycine, and tryptophan betaine, compared with the control group ($P < .05$ for all). In contrast, nicotinamide adenine dinucleotide (NAD+), salicylate, and glutamine levels were significantly higher in the control group ($P < .05$ for all). Additionally, participants receiving rice-bran supplementation showed significant increases in several phosphatidylcholines ($P < .05$ for all) and in acylcarnitine C2 ($P = .005$) compared with controls[29] (**Table 4**).

The case-control study, which investigated the associations of nut consumption with metabolite profile in hypertensive compared with healthy children, found positive associations between nut intake and increased levels of several phospholipids, including phosphatidylglycerol (PG) (43:6) ($P = .052$), PC (18:0/20:3) ($P < .05$), and phosphatidylethanolamine (PE) (P-22:0/18:2) ($P < .05$) (**Table 5**). All analyses were conducted in the full study population, including both hypertensive (cases) and normotensive (controls) children. Mediation analysis indicated that PG (43:6) had a significant mediating effect on the association between nut intake and systolic blood pressure (SBP), acting as a negative regulator ($B = -0.023$; 95% CI: −0.055, −0.006; $P = .049$). Phosphatidylcholine (18:0/20:3) also showed a potential lowering effect on SBP, although its indirect effect was not significant in the final path model. The total effect of nut consumption on SBP approached statistical significance ($B = -0.047$; 95% CI: −0.097 to 0.002; $P = .064$), suggesting that the influence of nuts on blood pressure may be mediated primarily through lipid metabolites such as PG (43:6).[33]

Metabolites Associated With Multiple Dietary Components

Several key metabolites, such us BCAAs, tyrosine, trigonelline/N-methylnicotinic acid, 1-palmitoyl-2-docosahexaenoyl-glycero-phosphocholine (GPC (16:0/22:6)), and hippurate were consistently associated with various dietary components across the reviewed studies. For consistency, metabolite names are presented as reported in the original studies. In some cases, different annotations refer to the same or similar analytes—for example, LysoPC a C18:1, as identified using flow-injection-analysis mass spectrometry (FIA-MS/MS) in Biocrates kits, corresponds to Lysophosphatidylcholine 18:1 (LPC (18:1)), and GPC (16:0/22:6) is the major

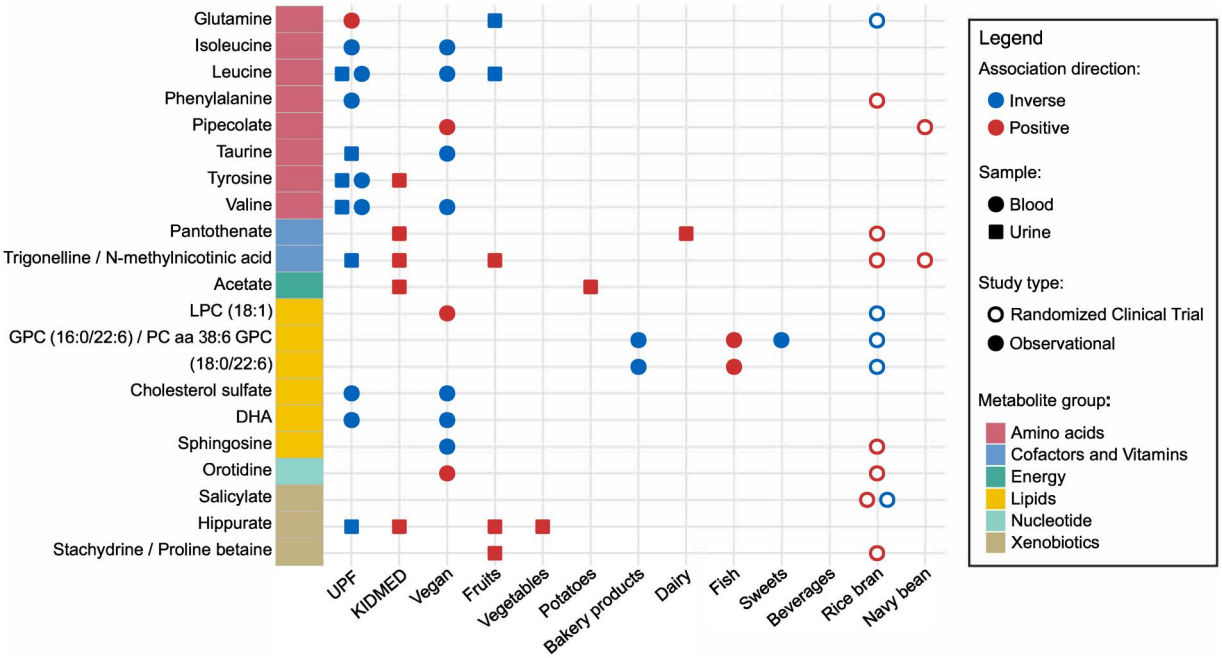

Figure 3. Metabolites Associated With Dietary Components Across the Reviewed Studies

Abbreviations: DHA, docosahexaenic acid; GPC, glycero-phosphocholine; GPC (16:0/22:6), 1-palmitoyl-2-docosahexaenoyl-GPC (16:0/22:6)/PC aa C38:6; GPC (18:0/22:6), 1-stearoyl-2-docosahexaenoyl-GPC (18:0/22:6); KIDMED, Mediterranean Diet Quality Index for children and adolescents; LPC (18:1), 1-oleoyl-GPC (18:1)/LysoPC a C18:1; UPF, ultra-processed food.

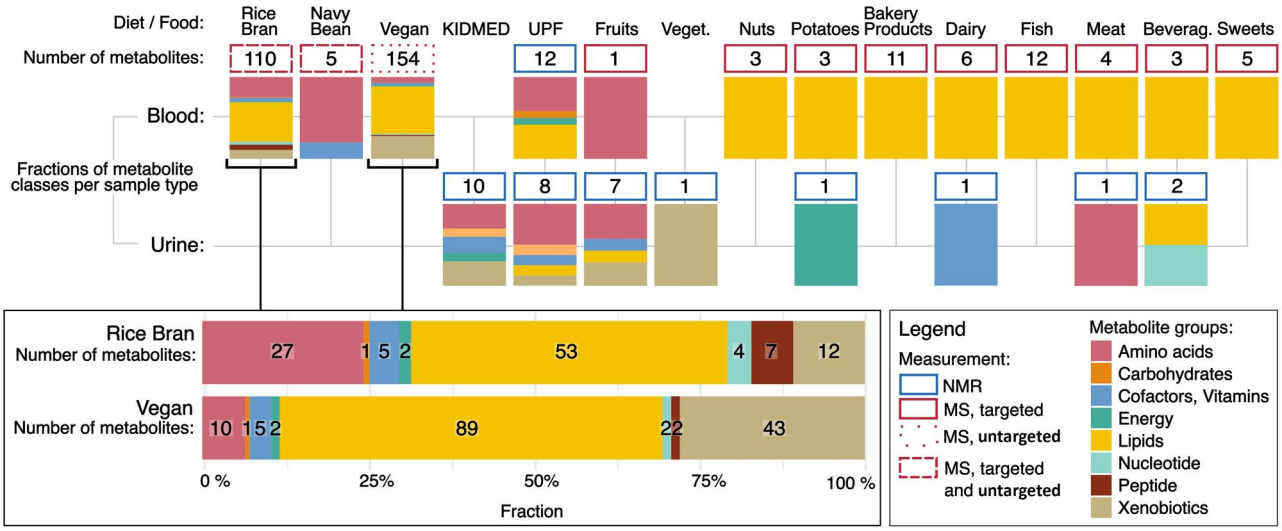

Figure 4. Number and Distribution of Significant Associations Between Dietary Intake Components and Metabolites by Sample Type and Metabolite Group

Abbreviations: Beverag., beverages; KIDMED, Mediterranean Diet Quality Index for children and adolescents; MS, mass spectrometry; NMR, nuclear magnetic resonance; UPF, ultra-processed food; Veget., vegetables.

component of PC aa C38:6 in human plasma.[35] Figure 3 illustrates these key metabolites and their associations with multiple dietary components.

Figure 4 illustrates the number of significant associations with dietary components based on sample type, measurement method, and predominant metabolite groups identified. In blood samples, significant associations were primarily observed with metabolites from the lipid group, as well as amino acids. In contrast, urine samples predominantly showed significant associations with amino acids, cofactors and vitamins, and xenobiotics.

DISCUSSION

This systematic review summarizes the evidence on the associations between dietary patterns, specific food groups, and food ingredients intake with metabolite profiles in children and adolescents. Adherence to healthy dietary patterns, such as the Mediterranean diet, along with the inclusion of nutrient-rich foods, was linked to particular metabolomic profiles. Conversely, frequent consumption of UPFs was consistently associated with distinct metabolite patterns, including lower levels of several essential amino acids and lipid metabolites.

These findings align with previous hypothesis-driven studies that have reported associations between healthy dietary patterns, food groups, or specific food ingredients and markers of metabolic status.[19] Metabolomics offers an opportunity to further characterize these associations by exploring the molecular pathways involved and the potential interactions between dietary components.

To our knowledge, this is the first systematic review specifically focusing on the relationship between nutritional interventions or habitual dietary intake and biomarkers obtained through metabolite profiling using LC-MS/MS, FIA-MS/MS, and proton nuclear magnetic resonance (^{1}H-NMR) in blood and urine samples of children and adolescents. Children and adolescents differ from adults not only due to growth demands but also because of age-specific differences in metabolism, dietary patterns, gut microbiota composition, and hormonal regulation. These factors can shape metabolic responses to diet, requiring a specifically tailored approach to metabolomic research in the pediatric population. Although a systematic review published in 2022 included both adults and children and investigated similar associations between diet and metabolomic profiles, only 2 of the 35 included studies were conducted in children or adolescents, and these studies assessed outcomes that differed from those defined in our protocol.[36] This highlights the limited evidence available in the pediatric population and underscores the novelty and relevance of our structured approach.

Interpretation of Results

Two of the included studies found that higher levels of hippurate were associated with greater adherence to the Mediterranean dietary pattern, higher fruit and vegetable intake, and lower consumption of UPFs.[30,31] These associations likely reflect the Mediterranean diet's abundance in fruits, vegetables, and fish, which are rich in bioactive compounds with anti-inflammatory and antioxidant properties, thereby supporting overall metabolic health.[37] In adults, hippurate levels have been shown to increase following a Mediterranean diet intervention[13] and the consumption of polyphenol-rich diets that include fruits, vegetables, berries, fatty fish, and coffee,[14,38–41] all of which are key components of the Mediterranean diet. While polyphenols in adults are predominantly derived from non-fruit and non-vegetable sources, such as coffee, tea, and cocoa, children and adolescents typically consume less of these beverages. As a result, the urinary excretion of hippuric acid likely primarily reflects their fruit and vegetable intake. Hypothesis-driven research from the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) study demonstrated that urinary hippuric acid may serve as a valuable biomarker for fruit and vegetable intake in children using traditional analytical methods.[42,43] Similarly, a systematic review further supported the potential of hippuric acid as a promising candidate biomarker for fruit and vegetable consumption during childhood and adolescence, although only one of the included studies used high-precision metabolomic techniques.[19]

With regard to UPFs, 2 studies included in this systematic review found a negative association between their consumption and levels of tyrosine[31,32] and BCAAs, including leucine,[31,32] valine,[31,32] and isoleucine.[32] This negative association may be explained by the low nutrient quality of UPFs, which are typically low in high-quality proteins. Furthermore, the intake of these foods may displace nutrient-dense, protein-rich whole foods from the diet, leading to a reduction in protein intake and consequently lower plasma BCAA levels.

In adults, a recent study identified a negative association between UPF intake and circulating valine concentrations, supporting the idea that high-UPF diets may be linked to lower levels of certain BCAAs across age groups.[44] In children, elevated plasma BCAA levels have also been associated with worse metabolic outcomes, including obesity and insulin resistance.[45]

Although BCAAs have been widely studied in adults for their association with insulin resistance in individuals with obesity and type 2 diabetes, the exact underlying mechanism remains unclear.[46,47] Elevated plasma BCAA levels have also been linked to inflammation and alterations in the gut microbiota, which may impair amino acid absorption and metabolism. A study by Pedersen et al[48] found that a gut microbiome with a higher capacity for BCAA biosynthesis and a reduced number of bacterial transporters for this BCAA metabolism was associated with increased plasma BCAA levels. However, this should not be interpreted as a protective effect of UPF consumption. BCAAs are essential amino acids, particularly important for growth during childhood.

Furthermore, Hovinen et al[34] also found that circulating levels of essential amino acids, including

isoleucine, valine, and taurine, were significantly lower in the vegan dietary pattern. In contrast, Tang et al[27] did not observe significant differences in amino acids or blood metabolite levels between meat-based and dairy-based complementary diets in infants under 1 year of age. One possible explanation for this finding is that this last RCT involved infants from 5 months of age, and all were fed with the same cow-milk–based formula as their primary food source (and primary source of essential amino acids). The only difference between groups was the complementary foods introduced. Since both meat and dairy are considered high-quality protein sources according to the World Health Organization (WHO) Digestible Indispensable Amino Acid Score (DIAAS),[49] consuming similar amounts of dairy resulted in similar amino acid blood profiles, regardless of differences in the amino acids provided in the still-limited intake of complementary food at that age.

Continuing with the vegan dietary pattern, a study included in this review found significantly higher levels of unconjugated primary bile acids and a higher glycine-to-taurine conjugation ratio of bile acids compared with the omnivorous dietary pattern.[34] This suggests that bile acid biosynthesis is the pathway most significantly affected by these diet patterns. These results are consistent with those observed in adults, where primary and glycine-conjugated bile acids were also found to be higher in vegans than in omnivores.[50] Additionally, vegans showed lower levels of DHA, low-density-lipoprotein (LDL), and high-density-lipoprotein (HDL) cholesterol. This could be explained by the absence of animal-based foods, which are primary sources of DHA. Furthermore, a plant-based diet is typically low in saturated fats, which may contribute to reduced LDL cholesterol, while lower HDL levels may reflect the absence of specific nutrients found in animal fats. DHA plays a critical role in brain and visual development during childhood. Low DHA levels have been associated with poorer cognitive performance and attention, highlighting the need for adequate intake during growth periods.[51,52]

Three studies have identified associations between trigonelline and N-methylnicotinic acid (a secondary metabolite of trigonelline) and various food ingredients, food groups, and dietary patterns.[28,30,31] Specifically, a significant inverse association was found with the intake of UPFs,[31] whereas positive associations were observed with adherence to the Mediterranean diet[31] and with fruit consumption.[30] Additionally, in the study by Baxter et al[28] trigonelline levels were higher in participants receiving navy bean or rice-bran supplementation compared with the control group without supplementation. The observed associations may be attributed to the natural presence of trigonelline in foods such as coffee, legumes, cereals, fruits, and vegetables, which are common in Mediterranean diets. In contrast, the inverse association observed in infants with diets rich in UPFs may reflect displacement of natural foods by other types of processed foods. Several reviews have reported that trigonelline shows multiple beneficial effects, including neuroprotection, antioxidant activity, and improved glucose metabolism. It also enhances lipid regulation, reduces adipose tissue accumulation, and decreases tumor cell invasiveness by modulating oxidative stress and cancer-related pathways, as shown in animal models.[53,54] While evidence in humans remains limited,[55] preliminary data of in vitro studies have demonstrated the antioxidant property of trigonelline.[56] Additionally, in adults, a correlation has been found between urinary trigonelline levels and a reduction in glycated hemoglobin (HbA1c).[57]

The case-control study included in this review identified positive associations between nut intake and specific phospholipids, particularly PG (43:6), which showed a significant mediating effect on SBP.[33] These findings suggest that lipid metabolites could partly mediate the cardiometabolic benefits of nuts and highlight their potential role in the cardioprotective effects of nut consumption in the pediatric population. While previous studies in adults have reported associations between nut intake and various beneficial lipid metabolites,[58,59] the association with PG (43:6) has not, to our knowledge, been previously reported and may represent a novel finding in children.

All of these findings highlight the potential of metabolomics to support more personalized and targeted nutritional approaches in children by providing insights into specific metabolic pathways influenced by diet. This approach may contribute to more effective strategies for preventing and managing metabolic disorders in pediatric populations. Furthermore, the identification of specific metabolites that are responsive to dietary interventions opens the door for the development of noninvasive biomarkers, providing a promising tool for monitoring and assessing nutritional status and metabolic health in this population.

Strengths and Limitations

One of the main strengths of this systematic review is the possibility to compile data from almost 6000 children and adolescents derived from both observational studies and clinical trials. This large sample increases the applicability of the findings and provides a robust basis for exploring associations between dietary intake and metabolite profiles. Importantly, despite the heterogeneity in study designs, populations, and analytical techniques, several associations were consistently observed across studies, which strengthens the overall reliability and relevance of the findings.

This systematic review includes studies using untargeted, targeted, or both types of metabolomic analyses. Untargeted approaches allow the identification of a wide range of metabolites, providing a more comprehensive understanding of dietary exposures and their metabolic effects. However, these methods are typically not absolutely quantitative, as they depend on MS/MS spectral library matching and often lack isotopically labeled internal standards (ISTDs) for all detected compounds. In contrast, targeted LC-MS methods quantify a predefined set of metabolites using ISTDs, allowing for more accurate and reproducible measurements. FIA-MS/MS and NMR, used in some of the included studies, are considered relatively quantitative, as they lack chromatographic separation or absolute calibration.

The diversity of analytical techniques may introduce variability in metabolite identification and quantification. Nevertheless, combining data across platforms strengthens the overall synthesis and contributes to a broader understanding of how diet influences metabolic profiles in pediatric populations. Exploring metabolite signatures linked to dietary patterns provides a holistic approach, offering valuable insights into how these profiles may reflect not only food components but also interactions with environmental exposures, lifestyle factors, endogenous metabolism, and gut microbiota. Meanwhile, targeted analyses enable the confirmation of associations previously established in adult populations, providing more precise and focused evidence that supports the reliability of the results. However, it should be noted that, in 1 study, phospholipids and sphingolipids were analyzed using FIA-MS/MS without chromatographic separation, which may have affected the specificity of the measurements. This methodological limitation should be taken into account when interpreting associations involving these lipid species.

This review also has several limitations. The heterogeneity among the included studies, in terms of design, population characteristics, dietary assessment methods, and analytical techniques, presents challenges in interpreting the results and drawing conclusions. Furthermore, most of the studies were observational, which limits the ability to establish causal relationships between dietary intake and metabolite profiles.

Although RCTs provide more robust evidence, they are subject to important ethical constraints, such as the impossibility of assigning children to potentially unhealthy dietary patterns. In this context, observational studies offer valuable complementary evidence for investigating the role of diet in shaping metabolic profiles. However, the small sample sizes of RCTs and their focus on specific supplementation interventions limit the understanding of long-term dietary effects.

Another limitation of this study is the inability to conduct a meta-analysis due to the high methodological variability across the studies, including differences in biological samples and metabolomic techniques. This heterogeneity makes it difficult to synthesize the data and draw more generalized conclusions.

In addition, the included studies were conducted in 12 different countries. Geographical and cultural differences in dietary habits may have influenced the observed metabolic outcomes. Moreover, none of the included studies reported the specific results of interest separately for sex, despite evidence that sex differences may influence metabolomic outcomes. However, most studies adjusted their analyses for sex, which partially addresses this limitation. Finally, the overall risk of bias was rated as low to moderate across the studies, suggesting that, while the findings are generally reliable, some degree of bias, particularly related to sample size, dietary exposure assessment, and laboratory measurements, may still influence the results and limit the ability to draw firm conclusions about the specific effects of dietary intake on metabolite profiles.

CONCLUSION

This systematic review provides a comprehensive synthesis of the evidence on the associations between dietary intake and metabolomic profiles in children and adolescents. The findings show that dietary patterns, food groups, and specific food ingredients are associated with different metabolite signatures, several of which are consistent with findings in adult populations. Metabolites, such as BCAAs, tyrosine, hippurate, trigonelline, N-methylnicotinic acid, and PC aa C38:6, identified in more than 1 study, may serve as potential biomarkers of dietary exposures relevant to metabolic health.

Despite the heterogeneity across studies and analytical methods, the consistency of some associations highlights the potential of metabolomics as a promising tool for evaluating diet-related metabolic profiles in pediatric populations. Future research using longitudinal designs and standardized methodologies is needed to clarify causal pathways, validate dietary biomarkers, and support the development of personalized nutrition strategies for children and adolescents. Although metabolomic markers reflect actual dietary intake, their implications for health outcomes remain to be explored.

Acknowledgments

The authors thank Dr Giulia Fiore for her valuable guidance and logistical support throughout the development of this review. They are also grateful to Camila

Guerrini for generously sharing her knowledge in metabolomics.

Author Contributions. V.L. and J.E. designed the review. M.G.-L. and I.G. performed the literature search and study selection. V.L. contributed to the interpretation of the data and resolved disagreements during study selection. M.G.-L., I.G., and L.V. performed the data extraction. M.G.-L. drafted the manuscript. M.G.-L., I.G., and L.V. prepared the figures and tables. All authors contributed to data interpretation, critically revised the manuscript, and approved the final version for submission.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

Funding. This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the ERA-NET Cofund action number 727565, JPI-HDHL-INTIMIC 2021; Instituto de Salud Carlos III (ISCIII) and Next Generation EU funds for actions of the Recovery, Transformation and Resilience Plan (PRTR) under grant agreement AC21_2/00010 (IISPV); Bundesministerium für Bildung und Forschung (BMBF) under grant agreements 01EA2203A (LMU) and 01EA2203B (HMGU); and Österreichische Forschungsförderungsgesellschaft mbH (FFG), Bundesministerium für Frauen, Wissenschaft und Forschung (BMFWF), and the MissionERA program under grant agreement FO999890543 (MUV). Co-funding was received by the German Ministry of Education and Research, Berlin (01EA2101 and 01EA2203A), and as part of the German Center for Child and Adolescent Health (DZKJ, 01GL2406A). B.K. is the Else Kröner Senior Professor of Pediatrics at LMU—University of Munich, financially supported by the charitable Else Kröner-Fresenius-Foundation, LMU Medical Faculty, and LMU University Hospitals.

Conflicts of Interests

None declared.

Data Availability

Data is available upon reasonable request to project principal investigators.

REFERENCES

1. Afshin A, Sur PJ, Fay KA, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2019;393:1958-1972. https://doi.org/10.1016/S0140-6736(19)30041-8
2. Bingham SA. Biomarkers in nutritional epidemiology. *Public Health Nutr*. 2002;5:821-827. https://doi.org/10.1079/PHN2002368
3. Lindon JC, Nicholson JK. Spectroscopic and statistical techniques for information recovery in metabonomics and metabolomics. *Annu Rev Anal Chem (Palo Alto Calif)*. 2008;1:45-69. https://doi.org/10.1146/ANNUREV.ANCHEM.1.031207.113026
4. Chen L, Zhernakova DV, Kurilshikov A, et al.; Lifelines Cohort Study. Influence of the microbiome, diet and genetics on inter-individual variation in the human plasma metabolome. *Nat Med*. 2022;28:2333-2343. https://doi.org/10.1038/S41591-022-02014-8
5. Sébédio JL. Metabolomics, nutrition, and potential biomarkers of food quality, intake, and health status. *Adv Food Nutr Res*. 2017;82:83-116. https://doi.org/10.1016/BS.AFNR.2017.01.001
6. Gibson R, Lau CHE, Loo RL, et al. The association of fish consumption and its urinary metabolites with cardiovascular risk factors: the International Study of Macro-/Micronutrients and Blood Pressure (INTERMAP). *Am J Clin Nutr*. 2020;111:280-290. https://doi.org/10.1093/AJCN/NQZ293
7. Playdon MC, Sampson JN, Cross AJ, et al. Comparing metabolite profiles of habitual diet in serum and urine. *Am J Clin Nutr*. 2016;104:776-789. https://doi.org/10.3945/AJCN.116.135301
8. Guertin KA, Moore SC, Sampson JN, 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;100:208-217. https://doi.org/10.3945/AJCN.113.078758
9. Garcia-Perez I, Posma JM, Gibson R, et al. Objective assessment of dietary patterns by use of metabolic phenotyping: a randomised, controlled, crossover trial. *Lancet Diabetes Endocrinol*. 2017;5:184-195. https://doi.org/10.1016/S2213-8587(16)30419-3
10. Li J, Guasch-Ferré M, Chung W, et al. The Mediterranean diet, plasma metabolome, and cardiovascular disease risk. *Eur Heart J*. 2020;41:2645-2656. https://doi.org/10.1093/EURHEARTJ/EHAA209
11. Yao Z, Jia X, Chen Z, et al. Dietary patterns, metabolomics and frailty in a large cohort of 120 000 participants. *Food Funct*. 2024;15:3174-3185. https://doi.org/10.1039/D3FO03575A
12. Macias S, Yilmaz A, Kirma J, et al. Non-targeted LC-MS/MS metabolomic profiling of human plasma uncovers a novel Mediterranean diet biomarker panel. *Metabolomics*. 2023;20:3. https://doi.org/10.1007/S11306-023-02058-Y
13. Smith E, Ottosson F, Ericson U, et al. Impact of a short-term Mediterranean diet intervention on plasma metabolites: a pilot study. *Metabolomics*. 2024;20:82. https://doi.org/10.1007/S11306-024-02154-7
14. Rafiq T, Azab SM, Teo KK, et al. Nutritional metabolomics and the classification of dietary biomarker candidates: a critical review. *Adv Nutr*. 2021;12:2333-2357. https://doi.org/10.1093/ADVANCES/NMAB054
15. Jackson MK, Wang B, Rasmussen H, et al. Urinary metabolites as biomarkers of dietary intake: a systematic review. *Front Nutr*. 2025;12:1596543. https://doi.org/10.3389/FNUT.2025.1596543/BIBTEX
16. Abdulkadir B, Nelson A, Skeath T, et al. Routine use of probiotics in preterm infants: longitudinal impact on the microbiome and metabolome. *Neonatology*. 2016;109:239-247. https://doi.org/10.1159/000442936
17. Yu JW, Song MH, Lee JH, et al. Urinary metabolomic differentiation of infants fed on human breastmilk and formulated milk. *Metabolites*. 2024;14:128. https://doi.org/10.3390/METABO14020128/S1
18. Censani M, Cuda S. Metabolomics: a promising tool in the prevention, diagnosis, and treatment of obesity. *J Clin Endocrinol Metab*. 2025;110:e2405-e2406. https://doi.org/10.1210/CLINEM/DGAE634
19. Yuan L, Muli S, Huybrechts I, et al. Assessment of fruit and vegetables intake with biomarkers in children and adolescents and their level of validation: a systematic review. *Metabolites*. 2022;12:126. https://doi.org/10.3390/METABO12020126/S1
20. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane; 2024.
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:N71. https://doi.org/10.1136/BMJ.N71
22. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev*. 2016;5:210. https://doi.org/10.1186/S13643-016-0384-4/FIGURES/6
23. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
24. Musa S, Elyamani R, Dergaa I. COVID-19 and screen-based sedentary behaviour: systematic review of digital screen time and metabolic syndrome in adolescents. *PLoS One*. 2022;17:e0265560. Supplementary file S2 https://doi.org/10.1371/JOURNAL.PONE.0265560.S002
25. Wirsching J, Graßmann S, Eichelmann F, et al. Development and reliability assessment of a new quality appraisal tool for cross-sectional studies using biomarker

data (BIOCROSS). *BMC Med Res Methodol*. 2018;18:122. https://doi.org/10.1186/S12874-018-0583-X
26. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (RobVIS): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021;12:55-61. https://doi.org/10.1002/JRSM.1411
27. Tang M, Weaver NE, Berman LM, Brown LD, Hendricks AE, Krebs NF. Different blood metabolomics profiles in infants consuming a meat- or dairy-based complementary diet. *Nutrients*. 2021;13:1-9. https://doi.org/10.3390/NU13020388
28. Baxter BA, Li KJ, Zarei I, Yao L, Rao S, Ryan EP. Nontargeted and targeted metabolomics identifies dietary exposure biomarkers for navy bean and rice bran consumption in children and adults. *J Agric Food Chem*. 2022;70:14531-14543. https://doi.org/10.1021/ACS.JAFC.2C02378
29. Pfluger BA, Smith HV, Weber AM, et al. Non-targeted dried blood spot-based metabolomics analysis showed rice bran supplementation effects multiple metabolic pathways during infant weaning and growth in Mali. *Nutrients*. 2022;14:609. https://doi.org/10.3390/NU14030609/S1
30. Lau CHE, Siskos AP, Maitre L, et al. Determinants of the urinary and serum metabolome in children from six European populations. *BMC Med*. 2018;16:202-219. https://doi.org/10.1186/S12916-018-1190-8
31. Stratakis N, Siskos AP, Papadopoulou E, et al. Urinary metabolic biomarkers of diet quality in European children are associated with metabolic health. *Elife*. 2022;11:e71332. https://doi.org/10.7554/ELIFE.71332
32. Handakas E, Chang K, Khandpur N, et al. Metabolic profiles of ultra-processed food consumption and their role in obesity risk in British children. *Clin Nutr*. 2022;41:2537-2548. https://doi.org/10.1016/J.CLNU.2022.09.002
33. Qin L, Ren Y, Chen L, et al. Nuts consumption and hypertension risks in children: a mediating role of circulating lipid metabolites. *Clin Exp Hypertens*. 2023;45:2243056. https://doi.org/10.1080/10641963.2023.2243056
34. Hovinen T, Korkalo L, Freese R, et al. Vegan diet in young children remodels metabolism and challenges the statuses of essential nutrients. *EMBO Mol Med*. 2021;13:e13492. https://doi.org/10.15252/EMMM.202013492
35. Quell JD, Römisch-Margl W, Haid M, et al. Characterization of bulk phosphatidylcholine compositions in human plasma using side-chain resolving lipidomics. *Metabolites*. 2019;9:109. https://doi.org/10.3390/METABO9060109,
36. Andraos S, Beck KL, Jones MB, Han TL, Conlon CA, De Seymour JV. Characterizing patterns of dietary exposure using metabolomic profiles of human biospecimens: a systematic review. *Nutr Rev*. 2022;80:699-708. https://doi.org/10.1093/NUTRIT/NUAB103.
37. Farias-Pereira R, Zuk JB, Khavaran H. Plant bioactive compounds from Mediterranean diet improve risk factors for metabolic syndrome. *Int J Food Sci Nutr*. 2023;74:403-423. https://doi.org/10.1080/09637486.2023.2232949
38. Hanhineva K, Lankinen MA, Pedret A, 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. https://doi.org/10.3945/JN.114.196840
39. Pallister T, Jackson MA, Martin TC, et al. Hippurate as a metabolomic marker of gut microbiome diversity: modulation by diet and relationship to metabolic syndrome. *Sci Rep*. 2017;7:13670. https://doi.org/10.1038/S41598-017-13722-4
40. Griep LMO, Chekmeneva E, Stamler J, et al. Urinary hippurate and proline betaine relative to fruit intake, blood pressure, and body mass index. *Proc Nutr Soc*. 2016;75:e178. https://doi.org/10.1017/S0029665116001932
41. Brachem C, Oluwagbemigun K, Langenau J, et al. Exploring the association between habitual food intake and the urine and blood metabolome in adolescents and young adults: a cohort study. *Mol Nutr Food Res*. 2022;66:e2200023. https://doi.org/10.1002/MNFR.202200023,
42. Krupp D, Doberstein N, Shi L, Remer T. Hippuric acid in 24-hour urine collections is a potential biomarker for fruit and vegetable consumption in healthy children and adolescents. *J Nutr*. 2012;142:1314-1320. https://doi.org/10.3945/JN.112.159319
43. Penczynski KJ, Krupp D, Bring A, Bolzenius K, Remer T, Buyken AE. Relative validation of 24-h urinary hippuric acid excretion as a biomarker for dietary flavonoid intake from fruit and vegetables in healthy adolescents. *Eur J Nutr*. 2017;56:757-766. https://doi.org/10.1007/S00394-015-1121-9
44. Kityo A, Choi B, Lee JE, Kim C, Lee SA. Association of ultra-processed food-related metabolites with selected biochemical markers in the UK Biobank. *Nutr J*. 2025;24:1-14. https://doi.org/10.1186/S12937-025-01077-W/TABLES/3
45. Mccormack SE, Shaham O, Mccarthy MA, et al. Circulating branched-chain amino acid concentrations are associated with obesity and future insulin resistance in children and adolescents. *Pediatr Obes*. 2013;8:52-61. https://doi.org/10.1111/J.2047-6310.2012.00087.X
46. Vanweert F, Schrauwen P, Phielix E. Role of branched-chain amino acid metabolism in the pathogenesis of obesity and type 2 diabetes-related metabolic disturbances BCAA metabolism in type 2 diabetes. *Nutr Diabetes*. 2022;12:1-13. https://doi.org/10.1038/s41387-022-00213-3
47. Lynch CJ, Adams SH. Branched-chain amino acids in metabolic signalling and insulin resistance. *Nat Rev Endocrinol*. 2014;10:723-736. https://doi.org/10.1038/nrendo.2014.171
48. Pedersen HK, Gudmundsdottir V, Nielsen HB, et al.; MetaHIT Consortium. Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature*. 2016;535:376-381. https://doi.org/10.1038/NATURE18646,
49. Food and Agriculture Organization of the United Nations. Dietary protein quality evaluation in human nutrition: report of an FAO Expert Consultation. *FAO Food Nutr Pap*. 2013;92:1-66.
50. Trefflich I, Marschall HU, Di Giuseppe R, et al. Associations between dietary patterns and bile acids—results from a cross-sectional study in vegans and omnivores. *Nutrients*. 2019;12:47. https://doi.org/10.3390/nu12010047
51. Montgomery P, Burton JR, Sewell RP, Spreckelsen TF, Richardson AJ. Low blood long chain omega-3 fatty acids in UK children are associated with poor cognitive performance and behavior: a cross-sectional analysis from the DOLAB study. *PLoS One*. 2013;8:e66697.https://doi.org/10.1371/JOURNAL.PONE.0066697
52. Sherzai D, Moness R, Sherzai S, Sherzai A. A systematic review of omega-3 fatty acid consumption and cognitive outcomes in neurodevelopment. *Am J Lifestyle Med*. 2023;17:649-685. https://doi.org/10.1177/15598276221116052
53. Mohamadi N, Sharififar F, Pournamdari M, Ansari M. A review on biosynthesis, analytical techniques, and pharmacological activities of trigonelline as a plant alkaloid. *J Diet Suppl*. 2018;15:207-222. https://doi.org/10.1080/19390211.2017.1329244
54. Liang Y, Dai X, Cao Y, et al. The neuroprotective and antidiabetic effects of trigonelline: a review of signaling pathways and molecular mechanisms. *Biochimie*. 2023;206:93-104. https://doi.org/10.1016/J.BIOCHI.2022.10.009
55. Farraj A, Akeredolu TJ, Wijeyesekera A, Mills CE. Coffee and cardiovascular health: a review of literature. *Nutrients*. 2024;16:4257. https://doi.org/10.3390/NU16244257
56. Bakuradze T, Lang R, Hofmann T, et al. Antioxidant effectiveness of coffee extracts and selected constituents in cell-free systems and human colon cell lines. *Mol Nutr Food Res*. 2010;54:1734-1743. https://doi.org/10.1002/MNFR.201000147
57. Friedrich N, Skaaby T, Pietzner M, et al. Identification of urine metabolites associated with 5-year changes in biomarkers of glucose homoeostasis. *Diabetes Metab*. 2018;44:261-268. https://doi.org/10.1016/J.DIABET.2017.05.007
58. Malik VS, Guasch-Ferre M, Hu FB, et al. Identification of plasma lipid metabolites associated with nut consumption in US men and women. *J Nutr*. 2019;149:1215-1221. https://doi.org/10.1093/jn/nxz048
59. Guasch-Ferré M, Hernández-Alonso P, Drouin-Chartier JP, et al. Walnut consumption, plasma metabolomics, and risk of type 2 diabetes and cardiovascular disease. *J Nutr*. 2021;151:303-311. https://doi.org/10.1093/JN/NXAA374

Nutrition Reviews, 2026, 00, 1–18
https://doi.org/10.1093/nutrit/nuaf305
Systematic Review