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Review Article

Dietary biomarkers – an update on their validity and applicability in nutritional epidemiology

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A R T I C L E I N F O

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A B S T R A C T

Accurate assessment of dietary intake remains a fundamental challenge in nutritional epidemiology. Conventional self-reported instruments, including food-frequency questionnaires and dietary recalls, are vulnerable to systematic and random measurement error, potentially attenuating associations between diet and chronic disease outcomes. Dietary biomarkers-objective molecular indicators measured in biological specimens-offer a promising strategy to enhance exposure assessment. Advances in metabolomics and high-resolution analytical platforms have facilitated the identification and validation of candidate biomarkers across major food groups, including dairy, meat, fish, cereals, fruits, and vegetables. Validation frameworks emphasize biological plausibility, food specificity, biospecimen selection, analytical robustness, correlation with habitual intake, pharmacokinetic characterization, reproducibility over time, and dose–response relationships. Among established biomarkers, plasma odd-chain fatty acids reflect dairy fat intake; acetylcarnitine and 3-methylhistidine are associated with meat consumption eicosapentaenoic acid and docosahexaenoic acid robustly indicate fish intake alkylresorcinols serve as reliable markers of whole-grain wheat and rye and proline betaine and carotenoids reflect citrus and vegetable consumption, respectively. Nevertheless, many biomarkers lack complete specificity, and concentrations may be influenced by interindividual metabolic variability, gut microbiota composition, renal function, and genetic factors. Emerging multi-biomarker panels and systems-based approaches integrating metabolomics and machine learning offer opportunities to improve dietary pattern assessment and reduce exposure misclassification. Integration of objective biomarkers with traditional dietary instruments may substantially strengthen causal inference and advance precision nutrition research.

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INTRODUCTION

Precise quantification of dietary intake remains one of the most persistent methodological challenges in nutritional science [1,7]. For more than half a century, epidemiologic investigations have relied primarily on self-reported instruments—food-frequency questionnaires (FFQs), 24-hour recalls, and dietary records—to estimate habitual intake and evaluate associations between diet and chronic disease [7,8]. These tools, though indispensable for large-scale population studies, are inherently vulnerable to both systematic and random error [8]. Recall bias, social desirability bias, underreporting of socially undesirable foods, portion-size misestimation, and food misclassification introduce distortions that may attenuate effect estimates, obscure dose–response relationships, and weaken causal inference [7,8].

Measurement error in dietary assessment is not trivial [8]. Unlike many biomedical exposures that can be directly quantified (e.g., blood pressure or serum cholesterol), diet is complex, multidimensional, and dynamic [7]. Individuals consume combinations of foods whose nutrient composition varies by preparation method, season, and geography [7]. Moreover, dietary intake fluctuates daily and seasonally [7]. These factors collectively contribute to within-person variability and between-person misclassification [8]. Statistical correction methods, such as regression calibration, have improved analytical approaches, yet they depend on the availability of objective reference measures [8].

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In this context, dietary biomarkers have emerged as promising objective indicators capable of strengthening exposure assessment [1,2]. A dietary biomarker is a measurable compound—either a parent food constituent or a metabolite—detected in biological specimens such as plasma, urine, erythrocytes, hair, nails, or adipose tissue that reflects recent or habitual intake [2,7]. Biomarkers may represent direct intake markers, recovery biomarkers, predictive biomarkers, or concentration biomarkers [2,8]. Unlike self-report instruments, biomarkers are independent of memory and reporting behavior, providing a biologically grounded metric of exposure.

The rapid advancement of metabolomics, lipidomics, and proteomics has expanded the repertoire of candidate biomarkers [14,15]. High-resolution analytical techniques—including liquid chromatography–mass spectrometry (LC-MS), gas chromatography–mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy—permit detection of thousands of small molecules in biological matrices [14]. These technologies have transformed nutritional epidemiology from reliance on single-nutrient indicators to a molecular systems-based discipline capable of capturing dietary complexity [14,15].

However, enthusiasm for dietary biomarkers must be tempered by rigorous validation standards [3,25]. Not all measurable compounds are suitable as exposure indicators [3]. The interpretation of biomarker concentrations requires understanding of pharmacokinetics, metabolic pathways, tissue distribution, elimination dynamics, and non-dietary determinants. Consequently, a structured validation framework is essential [25].

1. Framework for Biomarker Validation

The validation of dietary biomarkers has been formalized through the FoodBAll (Food Biomarkers Alliance) framework and related methodological criteria [25,26]. In epidemiologic applications, key validation domains include biological plausibility and specificity, appropriate biospecimen selection, analytical robustness, correlation with habitual intake, characterization of time-response kinetics, reproducibility over time, and demonstration of dose–response relationships [3,25].

Validation Criteria

Table - 1. Validation Criteria

Criterion	Description	Reference
Plausibility/Specificity	Parent compound or metabolite; food-specificity.	3, 4
Biospecimen	Plasma, urine, adipose.	2
Analytical Method	LC-MS, GC-MS, NMR.	4
Habitual Intake Correlation	r with FFQ (weak <0.2, moderate 0.2–0.5, strong >0.5).	2, 3
Time Response	Half-life pharmacokinetics.	4
Reproducibility Over Time	ICC (poor <0.4, fair 0.4–0.6, good 0.6–0.75, excellent >0.75).	1
Dose Response	Concentration change with intake levels.	1, 3

These criteria adapt the 8-step FoodBAll framework for epidemiology, excluding stability and interlab reproducibility due to data gaps.

2.1 Biological Plausibility and Specificity

A valid biomarker must have a plausible mechanistic link to the food of interest. Ideally, the compound should be a unique constituent of the food or a metabolite formed specifically after its ingestion . Specificity is critical: biomarkers that originate from multiple dietary sources or endogenous metabolism risk misclassification [3]. For example, odd-chain fatty acids such as pentadecanoic acid (15:0) are enriched in dairy fat but also present in certain meats, limiting absolute specificity [31,33].

2.2 Biospecimen Considerations

The choice of biospecimen—plasma, serum, erythrocytes, urine, adipose tissue, or hair—determines the temporal window of exposure captured [2,7]. Urinary metabolites often reflect short-term intake over hours to days [7]. Plasma phospholipid fatty acids may represent intake over weeks [13]. Adipose tissue fatty acids can integrate exposure over months to years [11].

2.3 Analytical Robustness

High-resolution analytical platforms are necessary to ensure sensitivity, specificity, and reproducibility. LC-MS and GC-MS provide quantitative accuracy for targeted compounds, whereas untargeted metabolomics enables discovery of novel candidate biomarkers [14]. Analytical validation includes calibration curves, limits of detection, interassay and intraassay variability, and quality-control procedures. Without standardized protocols, biomarker comparability across cohorts is compromised.

2.4 Correlation with Habitual Intake

Biomarker validity is often quantified by correlation coefficients between biomarker concentrations and self-reported intake. Correlations are typically categorized as weak (<0.2), moderate (0.2–0.5), or strong (>0.5). Importantly, modest correlations may still be meaningful, given the known measurement error inherent in dietary questionnaires.

2.5 Time Response and Pharmacokinetics

Biomarker kinetics determine responsiveness to changes in intake (3).Short-lived compounds, such as proline betaine following citrus consumption, peak within hours and decline rapidly. Long-lived compounds incorporated into lipid pools display slower turnover. Characterizing half-life and steady-state kinetics is crucial for interpreting single-time-point measurements.

2.6 Reproducibility Over Time

Reproducibility is commonly assessed using intraclass correlation coefficients (ICCs), with thresholds of poor (<0.4), fair (0.4–0.6), good (0.6–0.75), and excellent (>0.75). High ICCs indicate stability of biomarker concentrations over time, a desirable property for prospective cohort studies.

2.7 Dose–Response Relationship

Demonstration of a monotonic, preferably linear, increase in biomarker concentration with increasing intake strengthens causal inferenceControlled feeding studies provide the most robust evidence for dose–response validation [3,25] .Collectively, these criteria offer a rigorous foundation for evaluating candidate dietary biomarkers. Nonetheless, few biomarkers meet all domains with high performance.

2. Dairy Biomarkers

Dairy intake has been implicated in cardiometabolic outcomes. Among candidate biomarkers, odd-chain saturated fatty acids—particularly pentadecanoic acid (15:0) and trans-palmitoleic acid (trans-16:1n-7)—have received substantial attention [31–34].

Plasma and adipose concentrations of 15:0 demonstrate moderate correlations with reported dairy intake and fair to good reproducibility [31,33]. Trans-16:1n-7 shows similar though slightly weaker correlations [34]. These fatty acids are incorporated into phospholipid and adipose fractions, providing medium- to long-term exposure windows.

Galactonate, a metabolite derived from lactose metabolism, has emerged as a complementary marker, particularly in high-dairy-consuming populations. Plasma or urinary galactonate concentrations correlate moderately with dairy intake and demonstrate promising reproducibility. Despite these strengths, specificity remains imperfect. Meat consumption contributes to circulating odd-chain fatty acids, and endogenous synthesis via gut microbiota may influence levels. Furthermore, metabolic conditions such as insulin resistance may alter fatty acid profiles independent of intake. Thus, while dairy fat biomarkers enhance exposure assessment, they should be interpreted within a broader metabolic context.

Table 2. Dairy Biomarkers

Biomarker	Biospecimen	Correlation (r)	ICC	Method	Reference
15:0 (pentadecanoic acid)	Plasma/adipose	0.3–0.5	0.52–0.72	GC-MS	1
trans-16:1n-7	Plasma	0.2–0.4	0.52–0.72	GC-MS	1
Galactonate	Plasma/urine	0.2–0.5	Good (0.65)	LC-MS	1

3. Meat Biomarkers

Red and processed meat consumption has been associated with colorectal cancer, cardiovascular disease, and mortality [10,19,29] in observational studies. Objective biomarkers could clarify these associations.

Acetylcarnitine and 4-hydroxyproline are linked to total meat intake [1,10]. Acetylcarnitine reflects fatty acid oxidation processes influenced by carnitine-rich animal foods. 4-Hydroxyproline derives from collagen degradation and is elevated after meat consumption. Correlations with intake are moderate, and reproducibility ranges from poor to moderate (ICC 0.17–0.55).

3-Methylhistidine exhibits stronger specificity for poultry intake, reflecting muscle protein turnover after ingestion. However, its short half-life and variability limit long-term assessment utility.

Trimethylamine-N-oxide (TMAO), produced via gut microbial metabolism of carnitine and choline, rises after red meat and fish intake [19]. Because fish independently elevates TMAO, specificity for meat is limited. Moreover, gut microbiota composition, renal function, and genetic polymorphisms substantially influence TMAO concentrations.

Emerging markers such as piperine (processed sausage) and syringolsulfate (smoked meat) illustrate the potential of metabolomics for identifying processing-specific indicators. However, large-scale validation is pending.

Table 3. Meat Biomarkers

Biomarker	Food	Biospecimen	Correlation (r)	ICC	Reference
Acetylcarnitine	Total meat	Plasma/urine	Moderate-strong	0.34–0.55	1
3-Methylhistidine	Poultry	Plasma/urine	>0.5	0.07–0.66	1
4-Hydroxyproline	Total meat	Plasma	Moderate	0.17–0.51	1

5. Fish/Seafood Biomarkers

Among dietary exposures, fish intake possesses some of the most robust biomarkers [13,20]. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) concentrations in plasma phospholipids or erythrocyte membranes demonstrate strong correlations with reported intake [13,20] and good to excellent reproducibility (ICC >0.6). Their incorporation into cell membranes provides a biologically meaningful integration of intake over weeks to months.

3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF)is a metabolite strongly associated with fish consumption [1], exhibiting high specificity and dose responsiveness. TMAO increases dose-dependently with fatty fish intake, though, as noted, it lacks exclusive specificity.

The robustness of fish biomarkers underscores the feasibility of accurate dietary exposure measurement when biochemical uniqueness and stable incorporation are present.

Table 4. Fish/Seafood Biomarkers

Biomarker	Biospecimen	Correlation (r)	ICC	Dose Response	Reference
CMPF	Plasma	Strong	0.55–0.99	Yes	1
EPA/DHA	Plasma	>0.5	>0.6	Linear	1
TMAO	Urine/plasma	Moderate	0.55–0.99	Yes (fish)	1

6. Cereal Biomarkers

Whole-grain intake has been associated with reduced risk of colorectal cancer and cardiometabolic disease [18,21]. Alkylresorcinols serve as specific biomarkers of whole-grain consumption [11,18]. Plasma AR concentrations correlate moderately to strongly (r = 0.4–0.7) with habitual intake and demonstrate linear dose–response relationships.

ICC values are generally categorized as good, indicating stability over time. Urinary metabolites such as 3,5-dihydroxybenzoic acid provide short-term exposure assessment.

Avenanthramides have been proposed as oat-specific markers, though validation remains limited. The cereal biomarker field exemplifies successful translation of food chemistry into epidemiologic application.

Table 5. Cereal Biomarkers

Biomarker	Cereal Type	Biospecimen	r (Habitual)	ICC	Reference
ARs (total)	WG wheat/rye	Plasma	0.4–0.7	Good	4
3,5-DHBA	WG rye	Urine	Moderate	Fair-good	4
Avenanthramides	Oats	Plasma	Moderate	N/A	4

7. Fruit/Vegetable Biomarkers

Proline betaine is a highly specific marker of citrus intake [4], demonstrating moderate to strong correlations in plasma and urine. However, its short half-life (<8 hours) restricts utility to recent intake unless repeated measures are obtained.

Lycopene concentrations reflect tomato intake [30] and exhibit good reproducibility. α-Carotene serves as a broader vegetable intake indicator but may be confounded by fruit sources. Carotenoids generally display excellent reproducibility (30)(ICC >0.8), making them useful long-term markers of plant-based diets.

Dopamine sulfate has been proposed as a biomarker of banana intake, illustrating the expanding frontier of metabolomics-driven discovery.

Table 6. Fruit/Vegetable Biomarkers

Biomarker	Food	Biospecimen	r	ICC	Half-life	Reference
Proline betaine	Citrus	Urine/plasma	0.4–0.7	0.35–0.50	Short	4
Lycopene	Tomato	Plasma	>0.5	Good	Medium	4
α-Carotene	Vegetables	Plasma	0.3–0.5	0.83	N/A	4

8. Challenges and Methodological Considerations

Despite progress, significant challenges remain. Many biomarkers lack comprehensive dose–response validation in controlled feeding studiesMany biomarkers lack comprehensive dose–response validation [3,25]. Interindividual variability in metabolism, absorption, gut microbiota composition, renal clearance, and genetic polymorphisms introduces heterogeneity unrelated to intake [7,15]. Reverse causation and disease-related metabolic alterations may also influence biomarker concentrations in prospective studies.

Temporal variability poses additional complexity. Single measurements may not capture long-term patterns, especially for short-lived metabolites. Serial sampling, though costly, may improve reliability.

Standardization across laboratories is limited. Harmonized analytical platforms and reference materials are necessary for cross-cohort comparability. Integration of multi-omics data requires advanced statistical modeling to prevent overfitting and spurious associations.

9. Future Directions

The future of dietary assessment lies in multi-biomarker panels capable of capturing dietary patterns rather than isolated foods [5,15,17]. Systems biology approaches integrating metabolomics, lipidomics, proteomics, and microbiome data may provide composite signatures reflecting overall dietary quality [15]. Machine learning algorithms offer opportunities to derive predictive dietary scores from high-dimensional biomarker data.

Collaborative initiatives, including international consortia dedicated to biomarker discovery and validation, are advancing methodological rigor and translational application. Ultimately, integrating objective biomarkers with traditional dietary instruments may substantially reduce exposure misclassification, refine effect estimates, and enhance our understanding of the relationship between diet and human disease.

10. Conclusion

Dietary biomarkers represent a transformative advancement in nutritional epidemiology, providing objective, biologically grounded measures of food intake that complement traditional self-reported instruments. While substantial progress has been achieved in identifying validated biomarkers for specific food groups-particularly fish, whole grains, citrus, and dairy-important limitations persist. Many candidate markers demonstrate moderate correlations with intake but incomplete specificity, limited reproducibility data, or insufficient dose-response validation. Furthermore, interindividual metabolic variation and microbiome-dependent pathways introduce complexity in interpreting biomarker concentrations.

Future research should prioritize standardized validation protocols, controlled feeding studies to establish pharmacokinetics and dose–response relationships, and harmonized analytical methodologies across laboratories. The development of multi-biomarker panels capable of capturing dietary patterns rather than single foods is likely to represent the next major advance. Integrating objective biomarkers with traditional dietary assessment tools will enhance exposure measurement precision, reduce misclassification bias, and strengthen the evidence base linking diet to chronic disease prevention and management. Ultimately, such integration is essential for advancing precision nutrition and informing evidence-based dietary guidelines.

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