Çelik *et al. Journal of Translational Medicine* (2026) 24:363
https://doi.org/10.1186/s12967-026-07836-5

Journal of Translational Medicine

REVIEW Open Access

Multiomics: the intersection of personalized nutrition in cardiometabolic diseases

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Abstract

Background Cardiometabolic diseases are among the leading causes of increasing morbidity and mortality worldwide. However, current population-based dietary recommendations do not sufficiently account for biological differences between individuals and therefore do not have the same effect on everyone. The multiomic approach, which incorporates genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiome data, facilitates more accurate classification of disease risk and selection of appropriate nutritional interventions by mapping food-disease relationships across different biological layers.

Methods Through a narrative synthesis of the current literature, we focused on evidence from multiomic studies to assess their ability to guide personalized nutrition strategies based on individual genetic, metabolic, and microbiome characteristics in cardiometabolic diseases.

Results Recent evidence indicates that metabolomic markers have been reported to provide predictive value in addition to classic risk indicators and to increase the predictive power of models when combined with genetic data. Microbiome research shows that glycemic and lipemic responses can be predicted using algorithms based on gut microbiota. Recent clinical studies show that personalized nutrition plans, which evaluate the microbiome and clinical characteristics together, improve continuous glucose monitoring-based glycemic control, glycated hemoglobin levels, and triglycerides more than the classic Mediterranean diet.

Conclusion This review summarizes the current multiomic evidence, discusses the methodological and practical challenges in this field, and highlights future priorities. The integration of digital biomarkers obtained from wearable technologies with multiomic systems and artificial intelligence-supported models, when developed in accordance with ethical and equitable access principles, has the potential to support the transition from the discovery phase to patient-centered clinical applications.

Keywords Multiomics, Obesity, Type 2 diabetes, Cardiometabolic disease, Personalized nutrition

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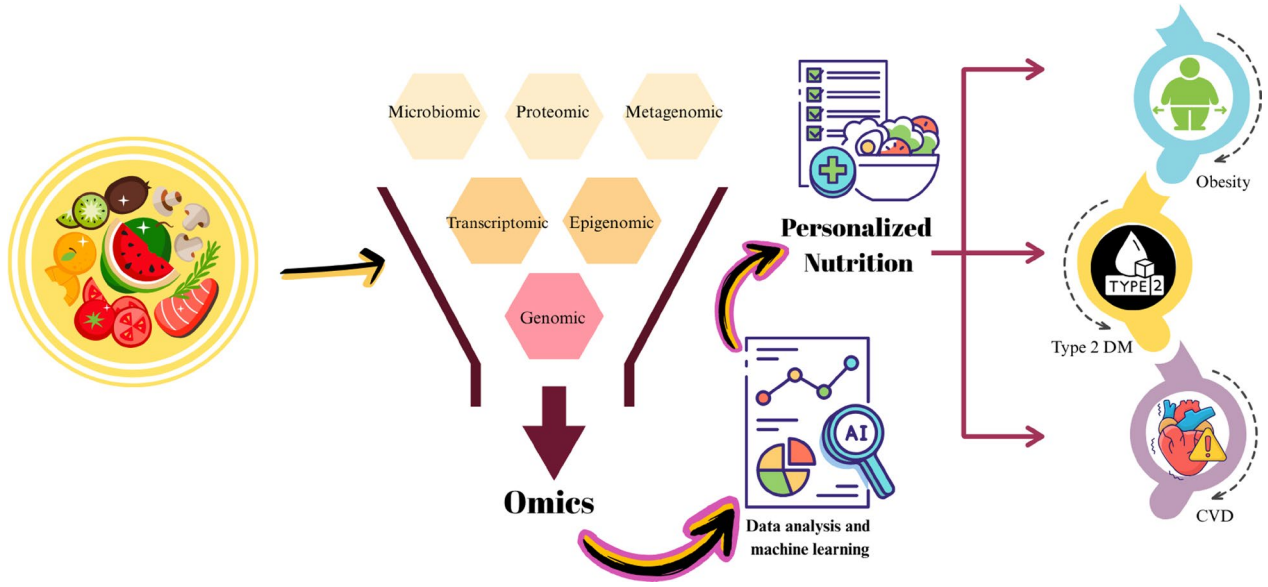
Graphical Abstract



Background

Cardiometabolic diseases (CMDs), including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and associated metabolic disorders, represent a significant and growing worldwide health challenge [1]. In 2022, the age-standardized prevalence of CVD varied between around 5881 and 11343 cases per 100000 individuals across different areas, and mortality rates ranged from approximately 73.6 to over 432 deaths per 100000, contingent upon geographic location [2]. In the United States, an analysis of nearly 4 million adults demonstrates significant variability in the prevalence of chronic CMDs: T2DM rates among Asian subgroups varied from 6.3% in Vietnamese adults to 15.2% in Filipino adults, whereas angina or coronary heart disease rates among Hispanic/Latino subgroups ranged from 3.1% in Cubans to 6.3% in Puerto Ricans [3]. The emergence of these trends highlights the insufficiency of conventional, general preventative efforts and underscores the pressing necessity for more targeted, individualized ways to alleviate the rising burden of CMDs worldwide.

Growing research indicates significant inter-individual variability in metabolic responses to identical meals: the PREDICT program quantified considerable person-to-person heterogeneity in postprandial glycemia, lipemia, and insulinemia—even among identical twins—and demonstrated that machine-learning models utilizing multidimensional phenotyping can forecast these responses [4]. This variability elucidates why average outcomes from dietary experiments sometimes obscure responders and non-responders, and it offers a scientific justification for personalized nutrition.

The advancement of multiomics—comprising genomes, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics—has revolutionized our ability to delineate pathways connecting food to chronic metabolic disease risk and to predict individual responses to specific dietary interventions. Population-scale studies demonstrate that baseline plasma metabolite fingerprints forecast the incidence of several prevalent illnesses, such as T2DM and atherosclerosis incidents, frequently enhancing risk discriminating beyond traditional determinants [5, 6]. Metabolomic risk scores exhibited a stronger correlation with future disease onset than polygenic scores for the majority of endpoints, whereas integrated models (metabolomics + genetics) demonstrated superior performance—underscoring a complementary, multi-faceted approach to risk stratification pertinent to dietary personalization [6]. Concurrent progress has been the establishment and verification of objective food consumption biomarkers. Self-reporting techniques (e.g., food frequency questionnaires, recalls) are susceptible to misclassification; in contrast, both targeted and untargeted metabolomics can accurately quantify exogenous and endogenous compounds indicative of specific food, nutrient, and dietary pattern consumption, facilitating a less biased assessment of exposure in nutrition-disease research and N-of-1 guidance [7]. As these indicators are developed and standardized, they offer essential contributions to algorithmic customization processes, such as verifying adherence and parameterizing dose–response curves for specific diets.

Importantly, multiomic-enabled customization holds therapeutic significance [8]. Simultaneously, significant

public initiatives like the National Institutes of Health (NIH) Nutrition for Precision Health consortium were producing standardized, multiomic datasets (genome, microbiome, metabolome, continuous phenotyping) to develop and assess predictive models that allocate the appropriate dietary pattern to the suitable individual [9].

These advancements positioned multiomics at the forefront of personalized nutrition (PN) in the context of CMD prevention, as metabolomic and microbiome profiles offered objective biomarkers, polygenic and molecular scores refined risk assessment and stratification, and integrated predictive models enabled optimized dietary prescriptions alongside improved adherence monitoring. In this review, recent multiomic evidence linking diet to CMD phenotypes was synthesized, methodological and implementation challenges were evaluated, and translational priorities were outlined to support the progression from discovery to equitable, patient-centered nutrition care.

Methodology of literature selection

The literature review concentrated on studies released in the past ten years to highlight recent methodological innovations and translational progress, while key earlier studies were incorporated as needed to establish a foundational context. Emphasis was placed on extensive human cohort studies, randomized controlled trials, systematic reviews, meta-analyses, and global clinical practice guidelines that focused on nutrition-related outcomes or clinical significance. Selective inclusion of animal and mechanistic studies was employed to bolster biological plausibility in instances where human evidence was scarce. The chosen literature was organized thematically based on distinct omics layers and their significance in personalized nutrition approaches for the prevention and management of CMDs.

The promise of multiomics in healthcare

The combined analysis of multi-omic data supports early diagnosis, more accurate risk assessment, and the development of targeted interventions for complex diseases [10, 11] (Fig. 1).

Genomics

Genomics is the most oldest and extensively utilized application within omics technology [12]. The HPG has revolutionized studies to comprehend human biology, disease conditions, and associated therapies. The emphasis on the significance of the systems biology approach in biomedical research has necessitated the elucidation of intricate connections inside the body [11, 13]. Variations in nucleotide sequences at a certain gene locus might alter the epigenetic control of the gene, impacting both gene expression and the resultant protein, hence influencing the organism's metabolic activities. In addition, differences in genetic sequences can change the degree of response of the individual to toxicity and affect the development of disease in the organism. Moreover, variations in genetic sequences might alter an individual's

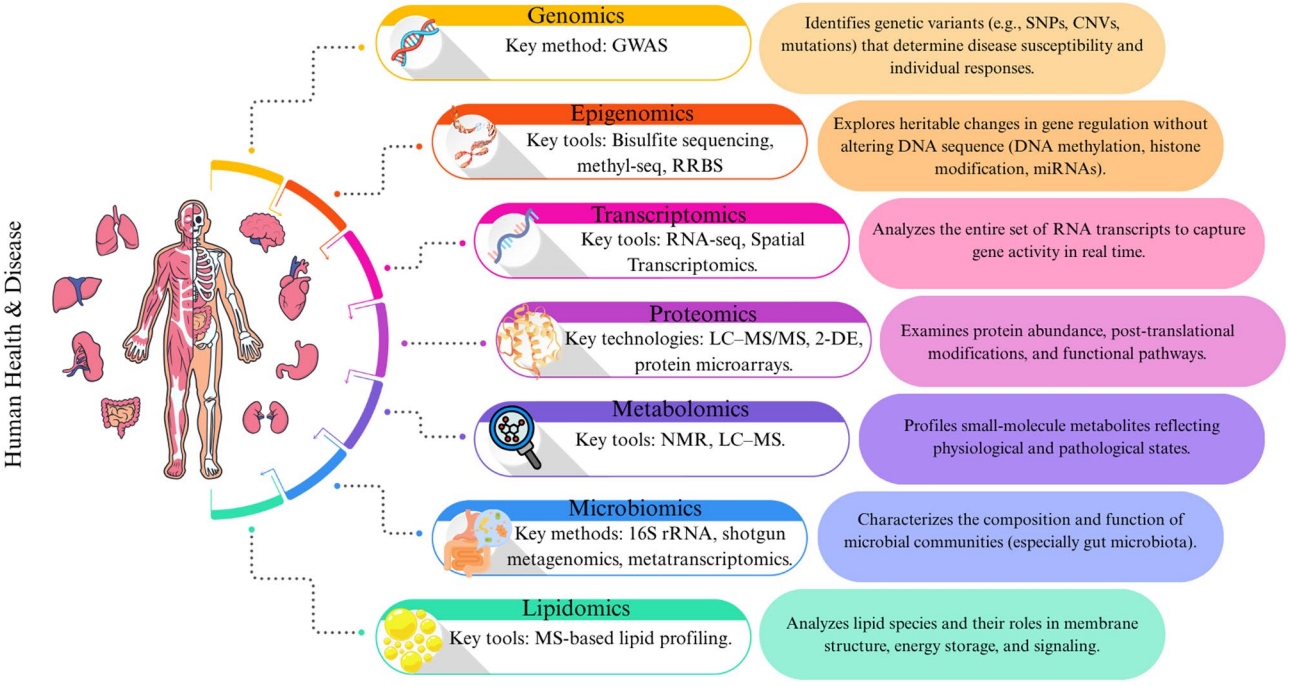


Fig. 1 Layers of omics: Tools and applications in biomedical research

susceptibility to toxicity and influence disease progression within the organism [14, 15].

Genomic studies indicated that genetic variation in pathways associated with glucose and lipid metabolism influenced individual variability in metabolic responses to dietary patterns [16, 17]. The interplay between genetic risk scores and food quality affected glycemic characteristics and cardiometabolic outcomes, suggesting that dietary impacts varied among genotypes [18]. Systematic reviews of randomized trials demonstrated that specific nutrition interventions more consistently enhanced eating patterns compared to generic dietary recommendations, whereas their impacts on physical activity and clinical health outcomes were small and varied [19]. Clinical practice guidelines for CMDs highlighted the necessity of individualized nutrition therapy, indicating that standardized dietary recommendations were inadequate to tackle the variability in metabolic risk. Conversely, evidence from randomized trials of PN primarily demonstrated enhancements in dietary behaviors rather than consistent clinical outcomes [20, 21].

Epigenomics

Epigenomics refers to the alteration of deoxyribonucleic acid (DNA) and histones, as well as the regulatory mechanisms influencing the expression of genes, particularly the process of DNA methylation [22]. Next Generation Sequencing (NGS) techniques like bisulfite sequencing, methyl-seq, methylated DNA immunoprecipitation, reduced representation bisulfite sequencing, and enzymatic methyl sequencing have facilitated precise visualization of genome-wide methylation trends and various epigenetic markers that affect gene regulation [23, 24].

Epigenetic regulation is crucial in modulating gene expression and cellular functions. Cells normally express their genes according to their unique programming [25]. Nevertheless, it may be affected by external or genetic factors, resulting in aberrant gene expression, causing enduring and hereditary medical conditions and disorders. Numerous studies have indicated that epigenetic alterations are linked to various illnesses, including T2DM [26], CVD [27], and cancer [28].

Numerous human cohort studies revealed that epigenome-wide DNA methylation patterns in peripheral tissues and blood were associated with significant cardiometabolic traits, such as body mass index, IR, and glucose homeostasis, indicating that epigenetic variation partially mediated the relationship between environmental exposures and susceptibility to CMDs [29–31]. Significantly, evidence suggested that lifestyle and nutritional factors—such as diet quality, energy balance, and fat composition—affected epigenetic regulation in pathways pertinent to cardiometabolic health, reinforcing the notion that epigenomic markers may aid in risk stratification and guide preventive, nutrition-centered strategies within the CMDs continuum [32].

Transcriptomics

The transcriptome is defined as the whole collection of RNA transcripts, encompassing both protein-encoding (mRNA) and non-protein-coding RNA (such as rRNA, tRNA, lncRNA, and pri-miRNA) molecules generated by the genome of a living organism [33]. Transcriptomics pertains to the examination of genome expression on the level of transcription, yielding insights into gene organization, expression, control, and the functional products of genes, therefore enhancing the comprehension of genome processes [34, 35].

Initially, transcriptome research was conducted via DNA microarrays, enabling the concurrent assessment of hundreds of transcripts. Nevertheless, microarrays are constrained by hybridization-dependent detection and probe formulation. The advent of high levels of throughput RNA sequencing (RNA-seq) has transformed the discipline, enabling unbiased, extremely sensitive, and quantitative investigation of transcriptomes in many species [34, 36]. The advancement of single-cell sequencing of RNA has enhanced transcriptomics by elucidating gene expression variability among different cells inside tissues. This has yielded discoveries about processes of development, immunological responses, and cancer environments [37].

Tisssue-specific gene expression signatures linked to obesity, T2DM, and CVD were found in transcriptome studies across CMDs, especially in pathways involving inflammation, insulin signaling, mitochondrial function, and lipid metabolism. Numerous studies involving large human cohorts and RNA-sequencing meta-analyses have revealed consistent changes in gene expression in peripheral blood and metabolically active tissues. These changes correlate with IR, body fat, and cardiometabolic risk, highlighting the importance of transcriptomic profiles as intermediate molecular markers that connect environmental and dietary factors to cardiometabolic characteristics [38–40].

Proteomics

Proteomics has developed as a formidable technique in contemporary life sciences, sometimes termed a "post-genomic" subject [41]. Genomics offers insights into the whole collection of genes inside an organism, whereas proteomics emphasizes the thorough examination of proteins, the functional molecules that predominantly drive biological activities. The proteome exhibits significant dynamism and is influenced by various contexts, showcasing alterations linked to developmental phases, environmental factors, disease states, and cell-based micro-environments. Consequently, proteomics provides

a more profound understanding of phenotype compared to genomics by itself [41, 42].

The proteome is significantly larger and more complex, undergoing continuous and substantial alterations from post-transcriptional processes (including glycosylation, the processes of methylation and ubiquitination, and phosphorylation oxidation). Consequently, advanced proteomics technologies have been devised to isolate, measure, identify, and define each protein found within a sample [36]. Mass spectrometry (MS) has emerged as the fundamental technology for identifying proteins and measurement, providing exceptional sensitivity and precision. Methods like the use of liquid chromatography combined with tandem MS (LC–MS/MS) have transformed the identification of intricate protein mixes. Two-dimensional gel electrophoresis was among the initial methodologies in proteomics, facilitating the separation of proteins based on the isoelectric point and molecular mass, although it is now complemented by more sophisticated gel-free techniques. Moreover, protein microarrays provide the systematic examination of protein interactions with other protein chains, nucleic acids, or tiny molecules, therefore permitting extensive functional assessments [43, 44].

Proteomics has a broad range with important applications. By identifying possible targets for therapy and using proteome-wide analysis to assess medication effectiveness as well as safety, proteomics aids in drug development in the chemical industry. In addition to medical, proteomics is utilized in nutrition along with agriculture for the analysis of dietary proteins, the identification of allergies, and the enhancement of crop resistance [45, 46].

Proteomic analyses revealed circulating protein patterns associated with cardiometabolic risk, highlighting significant roles of inflammatory pathways, insulin signaling, lipid transport, and vascular biology. Multimarker analyses demonstrated that composite protein panels improved risk discrimination beyond standard clinical indicators and indicated metabolic responses to lifestyle and dietary factors, underscoring the translational significance of proteomics for personalized risk stratification and the assessment of nutrition-related interventions [47–49].

Metabolomics

The metabolome comprises many metabolites, including endogenous metabolites, microbiome-derived metabolites, xenobiotics, and dietary components [50]. In the field of metabolomics, researchers typically utilize both an untargeted and targeted strategy. The untargeted technique aims to identify and measure a wide array of metabolites to uncover phenotypic patterns, which in turn aid in the discovery of biomarkers. In contrast, focused metabolomics concentrates on specific metabolites or groups of metabolites, for instance lipids or metabolites of the tricarboxylic acid cycle. Metabolomics typically entails the examination of intricate biological systems, such as blood, urine, or tissue extracts, necessitating meticulous sample preparation and resilient analytical methodologies to guarantee precise and thorough metabolite identification, notwithstanding their significant physicochemical variability. The metabolomics approach generally encompasses metabolite the extraction, chromatographic separation, identification using MS or nuclear magnetic resonance (NMR) and further intricate processing of data and statistical analysis [51, 52].

Metabolomics has improved cardiovascular risk assessment in persons with type 2 diabetes within clinical studies. A study revealed that the inclusion of particular metabolite indicators in prediction models substantially enhanced cardiovascular incident stratification. Another study fully covered metabolomics approaches in the research of disease mechanisms, emphasizing its applicability in cancer, neurological diseases, and biomarker development [50, 53].

Metabolomic profiling revealed that circulating metabolites suggested systemic changes in energy metabolism, insulin sensitivity (IS), and cholesterol management in CMDs. In human studies, metabolite patterns were viewed as comprehensive indicators of metabolic state rather than just dietary influences, establishing metabolomics as a descriptive method for delineating disease-associated metabolic disturbances rather than an independent decision-making tool [54].

Microbiomics

The microbiota is community of microorganisms, including numerous bacteria, archaea, fungi, and eukaryotic viruses that coexist on human surfaces. The totality of all gut microbial genes (microbiome) within an individual represents a genetic repertoire containing more genes than the human genome [55]. A key driver of metabolic disorders and CMD is alteration in intestinal environment (dysbiosis) causing chronic low-grade inflammation. With increasing evidence showing the relationship between microbial dysbiosis and susceptibility to various diseases, the use of microbiome profiling has gained importance in identifying individuals at high risk of disease [56]. The gut microbiome modifies host chromatin, induces differential splicing, transforms the epigenetic landscape, and directly disrupts host signaling pathways [57]. There is an interaction between the host and microbiome, which can be measured across omics layers. Multiomics approaches to the microbiome allow us to understand host-microbiome interactions

and understand disease mechanisms based on the diet-microbiome-host relationship [58].

Research on the microbiome revealed that differences in gut microbial makeup and function among individuals greatly affected metabolic responses to diet and cardiometabolic risk profiles [55]. The use of microbiomics in stratified nutritional treatments rather than homogeneous dietary advice was supported by large human studies that demonstrated that microbiome-derived features allowed the identification of dietary response phenotypes [59]. Moreover, integrative models that combine gut microbiome profiles with dietary intake data enhanced the prediction of postprandial glycemic and metabolic responses, demonstrating a proof-of-concept for clinical nutrition tools that can inform personalized dietary counseling and nutrition-related decision-making in the prevention and management of CMDs [55, 59]. Microbiomics has shown new possibilities in therapeutic development. Probiotics, prebiotics, synbiotics, and nutritional therapies are being formulated to reestablish an optimal microbial homeostasis. Emerging personalized microbiome-based therapeutics utilize microbial patterns to provide customized nutritional recommendations and predict reactions to pharmaceuticals, particularly immunotherapies against cancer [60, 61].

Lipidomics

Lipidomics, a subfield of metabolomics, is the extensive investigation of the systems, directions, and roles of cell membrane lipids in the functioning of life [62]. Lipids are crucial for membrane shape, storage of energy, and communication; hence, lipidomics has emerged as a potent method for elucidating physiological and pathological processes at the molecular level. Modern bioinformatics and MS have completely changed the game when it comes to lipidomic profiling, allowing for in-depth examination of different types of lipids, their species, and how they change in both well-being and disease. Lipidomics has rapidly become an integral part of personalized medicine, biological systems, and medical research [63, 64].

Lipidomic research has identified unique lipid profiles in metabolic diseases such obesity, T2DM, and non-alcoholic fatty liver diseases that provide light on the processes behind elevated insulin levels and dyslipidemia. Comparably, plasma lipidomics has discovered certain ceramide and sphingolipid species that function as trustworthy indicators for atherosclerosis and coronary artery disease in CVD [65].

Lipidomic analyses found that specific lipid species, notably ceramides and other sphingolipids, were consistently linked to insulin resistance, atherosclerotic load, and detrimental cardiometabolic outcomes, irrespective of traditional lipid metrics [66]. Studies demonstrated that these lipid signatures represented qualitative facets of lipid metabolism and were responsive to metabolic conditions affected by dietary fat composition, hence serving as molecular indicators pertinent to nutrition-related risk assessment [67]. The identification of high-risk lipidomic profiles points out the potential of lipidomics to guide stratified nutritional strategies, including the customization of dietary fat quality and the intensity of dietary interventions, thereby aiding in the creation of clinical nutrition tools designed to enhance cardiometabolic risk management beyond conventional lipid panels [66, 67].

Multiomics in understanding for certain cardiometabolic diseases

Obesity

Obesity is not only the result of an imbalance between energy intake and expenditure, but also a condition associated with many factors, including genetic predisposition, epigenetic regulation, transcriptional changes, metabolic status, and the complex interaction of the gut microbiota [68–73]. Therefore, it is important to examine different omics structures together in order to understand the molecular causes of obesity and to reveal the development process of the disease in a much more comprehensive manner [74].

At the genomic level, large-scale genome-wide association study (GWAS) have identified numerous gene variants associated with obesity. In particular, polymorphisms in the fat mass and *FTO* (rs1421085, rs9939609, rs3751812), *MC4R* (rs17782313, rs12970134), *TMEM18* (rs7561317), *NEGR1* (rs2815752), *CLOCK* (rs1801260), *FLJ33534*, and *CARTPT* have been strongly linked to obesity-related factors such as body mass index (BMI), waist circumference, waist-hip ratio, body fat distribution, and energy homeostasis [75–81]. In the study conducted by Egorova et al., the calculated genetic risk explained 8.3% of the variance in BMI, emphasizing the role of genetic predisposition in obesity risk. Lifestyle factors (including diet, sleep, and physical activity) accounted for 7.8% of the variance, indicating that environmental influences are similarly important. When genetic and lifestyle factors were combined, they explained 15% of the variance in BMI, with *ADCY3*, *FTO*, and *SLC22A3* variants showing significant associations with BMI [82].

Several genes with epigenetic influence and associated with obesity—such as *ADIPOQ*, *LEP*, *MC4R*, *POMC*, *GLUT4*, *UCP1*, *CLOCK*, and other metabolism-regulating genes—are modulated at the epigenetic level, thereby affecting energy balance and obesity risk [83].

Multiple histone deacetylase (HDAC) isoforms, including HDAC3, HDAC9, and HDAC11, have been implicated in obesity pathogenesis by regulating adipogenesis, energy metabolism, and IS, thereby establishing histone deacetylases as potential therapeutic targets for

metabolic disease [84]. Specifically, methylation changes in the promoter regions of the *PPARγ*, *LEP*, and *ADIPOQ* genes are associated with adipocyte differentiation and IS [85–87]. miRNAs have been reported to significantly influence adipocyte formation, fat metabolism, and insulin production by regulating the expression of numerous genes [87, 88]. It has been found that the expression levels of miR-532-5p, miR-423-5p, miR-520c-3p, miR-146a, miR-15a, miR-155, and miR-499a are decreased, while those of miR-142-3p, miR-140-5p, miR-222, miR-143, and miR-130 are increased in obese individuals [89, 90]. Gallardo et al. reported epigenetic alterations associated with obesity, and similarly, our study found significant DNA methylation changes in *LPL*, *LEP*, *RXRα*, *LXR*, *SCD*, and *SREBF1* genes, which are linked to lipid metabolism and inflammation. These modifications may underline the metabolic improvements observed following lifestyle intervention in the prepubertal population [91].

At the transcriptomic level, RNA-seq studies conducted in adipose tissue, liver, peripheral blood mononuclear cells, and skeletal muscle have shown differential expression profiles in genes related to energy metabolism, inflammation, and immune response in obesity [92–98]. For example, the excessive expression of proinflammatory cytokines such as TNF-α, IL-1β and IL-6 supports the low-grade inflammatory state accompanying obesity [99].

Proteomic analyses have revealed distinct protein profiles in plasma and adipose tissue in obesity [100]. Changes in proteins involved in insulin signaling pathways and dysregulation of adipokines such as leptin and adiponectin provide critical insights into the metabolic consequences of obesity [101–104]. In obese individuals, adiponectin secretion from adipose tissue is reduced, while leptin secretion is increased [105].

Metabolomic studies show that there are significant changes in glucose, amino acid, and fatty acid metabolism in obese individuals [106–111]. The primary metabolomic markers of obesity include elevated levels of essential and non-essential amino acids (e.g., branched-chain amino acids-BCAA) associated with protein breakdown and inadequate amino acid utilization [112–118]; changed serum fatty acids and metabolites (glycerol) [112, 117, 119–121]; increased acylcarnitines, indicating mitochondrial dysfunction and deficient fatty acid oxidation [106, 122–124]; and changes in lipid metabolites such as lysophosphatidylcholines, reflecting impaired cell membrane integrity and lipid transport [112]. Tulipani et al. found that acetylated lysophosphatidylcholine species with long-chain fatty acids (C17:0, C18:1, and C18:2) have the most specific metabolic relationship with morbid obesity. Lyso-phosphatidylcholine levels showed a strong negative correlation with morbid obesity; as BMI and body weight increased, the serum levels of this specific lyso-phosphatidylcholine decreased [112]. In addition, various metabolic products such as energy metabolites (e.g., pyruvate, citrate, acetaldehyde, glucose, TCA) [118, 121, 125, 126], uric acid, and carnitine [113], as well as gut microbiota metabolites (phenylacetamide, phenylacetylglutamine, Trimethylamine N-oxide (TMAO), indole-3-acetic acid etc.) indicating alterations in gut microbiota metabolism [127–129], are among the key metabolic signatures of obesity. It has been demonstrated that IR developing in obesity is closely related to increased levels of BCAA in the blood [114–116]. BCAA accumulation reduces insulin sensitivity by altering protein synthesis through excessive activation of the rapamycin-sensitive complex 1 (mTORC1) pathway, contributes to insulin resistance by suppressing insulin signaling through S6K1 activation, and is associated with obesity and high metabolic risk due to the accompanying increase in acylcarnitines, diacylglycerols, and steroid hormones [110, 130, 131]. However, since most of these metabolic profiles were obtained from observational studies, it is not clear whether they reflect direct causal mechanisms in obesity or whether they arise because of metabolic dysfunction.

Microbiomic data indicates that gut microbiota plays an important role in obesity [132]. The increase in the *Firmicutes/Bacteroidetes* ratio [133], *Bacteroides* and *Escherichia-Shigella* levels [134], increase gut permeability [135], alterations in short-chain fatty acid production [136–139], and the effects of microbial metabolites (e.g., TMAO, indole derivatives) [140–142] on host metabolism explain the basis of obesity and related metabolic disorders. In mice with obesity induced by a high-sugar and high-fat diet, the relative abundance of the phyla *Firmicutes* and *Actinobacteria* increased, whereas the abundance of the phylum *Bacteroidetes* decreased, leading to an elevated *Firmicutes/Bacteroidetes* ratio. At the genus level, *Blautia*, *Lachnoclostridium*, *Parvibacter*, *Bifidobacterium*, and *Ruminiclostridium* increased, while the *Lactobacillus* genus, known for its anti-obesity effects, decreased [143]. Changes in the gut microbiome associated with obesity are linked to impaired gut barrier integrity, increased inflammation, and impaired glucose metabolism. Specifically, certain bacterial profiles are associated with genes and related miRNAs that negatively affect the inflammatory response and insulin sensitivity, while beneficial bacteria are associated with genetic and epigenetic profiles that support lipid metabolism and IS [135, 144–146]. Systematic reviews have revealed that bacterial groups such as *Bacteroidetes*, *Firmicutes*, and *Verrucomicrobiota*, along with miRNA-34a, miRNA-21, miRNA-122, and miRNA-378a, play a key role in regulating inflammation, intestinal barrier function, and lipid-glucose metabolism [144].

Genomic, epigenomic, transcriptomic, proteomic, metabolomic, and microbiomic changes contributing to the development of obesity and metabolic disorders are summarized in Fig. 2.

Omics studies on obesity reveal significant relationships between epigenetic changes, gene expression, and metabolic markers. However, most of these studies are limited to establishing correlations, and causality must also be evaluated. Genetic variants identified in GWAS explain a certain portion of the variables associated with BMI. In contrast, metabolomic and lipidomic findings evaluate the relationship with processes associated with obesity, such as insulin resistance, mitochondrial dysfunction, and chronic inflammation. However, conflicting results from some gut microbiota-derived metabolites and BCAAs across different populations prevent the generalization of these markers. In conclusion, rather than focusing solely on genomic or metabolomic approaches in understanding and treating obesity, conducting a comprehensive assessment will enable both a deeper understanding of the pathophysiology of obesity and the development of personalized medicine and nutrition strategies.

Type 2 diabetes mellitus

T2DM is a multifaceted, complex condition that now impacts hundreds of millions globally and is increasingly prevalent, resulting in significant morbidity, mortality, and healthcare expenditures [147]. Recent worldwide evaluations by international agencies emphasize the magnitude and progression of the global epidemic, underscoring the necessity for earlier identification, enhanced risk classification, and tailored preventive and treatment approaches [148, 149].

An international consensus in 2023 advocated for "precision diabetic therapy" based on integrated molecular profiling, while extensive multi-ancestry genomic investigations have started to delineate unique processes and probable endotypes within T2DM [150, 151]. Given this, multiomics—which includes the fields of genomics, epigenomics, transcriptomics, proteomics, metabolomics/lipidomics, and the gut microbiome—offers a systems perspective that can relate genetic susceptibility to circulating biomarkers and cell-type-specific regulation, which in turn can lead to clinical manifestations.

Extensive prospective studies indicate that targeted protein panels significantly enhance the prediction of T2DM risk beyond traditional clinical models. Additionally, multiomic signatures that incorporate proteins, metabolism products, and polygenic assessments can further improve discrimination, especially in individuals not identified by standard screening methods [152, 153]. Lipidomic analysis has consistently highlighted the role of sphingolipid pathways, particularly specific ceramide and dihydroceramide species (e.g., Cer18:0, Cer22:0, dhCer20:0) that were prospectively linked to the

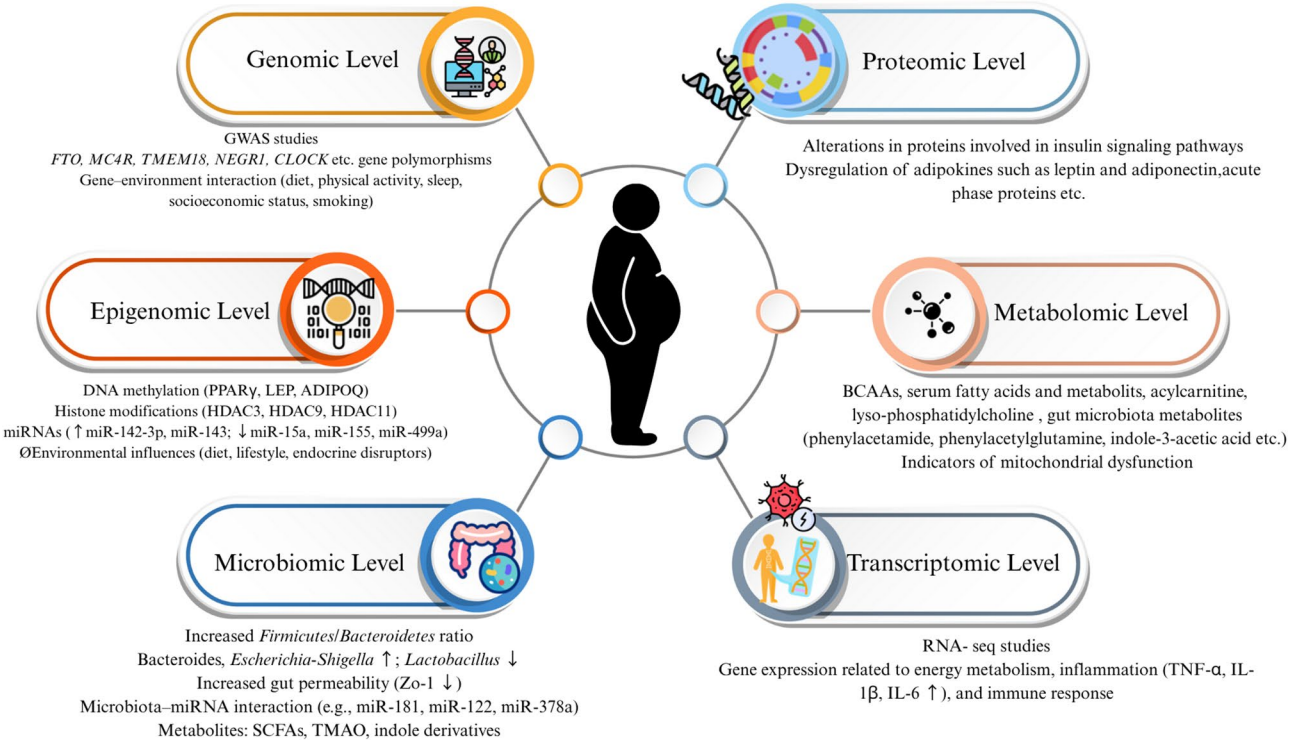


Fig. 2 Multiomics landscape of obesity

onset of T2DM and corroborated by genetic instruments. Additionally, independent cohorts reveal more extensive sphingolipid signatures that differentiate diabetes risk [154, 155]. These findings demonstrate how types of metabolites might transition from associative markers to potential mediators and therapeutic targets. Cause-and-effect research utilizing biobank-scale genetics has clarified enduring observations; for instance, BCAAs exhibit metabolite-specific, occasionally contradictory, effects on diabetes-related outcomes, highlighting the necessity of separating associated exposures in multiomics epidemiological studies [156].

Investigations at both the tissue and single-cell levels are elucidating the regulatory mechanisms within pancreatic islets and how these are disrupted under stress conditions. Multiple-layer datasets that combine chromatin state, DNA methylation, and transcriptomics illustrate changes specific to cell types that are pertinent to beta-cell dysfunction. Moreover, experimental perturbations demonstrate unique responses of islet cells to endoplasmic-reticulum stress, which have major consequences for glucose homeostasis [157]. Concurrent research at the host–microbiome interface indicates that gut microbial and metabolomic patterns were closely associated with glycemic regulation and may reflect the development and remission of T2DM; long-term multiomics cohorts now connect microbial pathways, circulating substances, and glucose phenotypes between individuals [158].

Alongside advancements in molecular classification, global clinical guidelines continually highlighted nutrition as a fundamental element in the prevention and management of T2DM. The American Diabetes Association (ADA) Standards of Care and the joint consensus report by the European Association for the Study of Diabetes (EASD) emphasized that personalized medical nutrition therapy—rather than a uniform dietary prescription—can markedly enhance glycemic control, lipid profiles, and cardiometabolic risk factors in individuals with T2DM, with documented reductions in HbA1c comparable to those attained through glucose-lowering pharmacotherapy [159]. Dietary patterns like the Mediterranean, plant-based, and low-carb diets were supported by both the ADA and EASD guidelines. This highlighted the translational relevance of PN strategies in routine clinical care, especially when customized to individual preferences, metabolic phenotypes, and comorbidities [160]. Recent studies also showed that dietary interventions high in fermented foods, unsaturated fats, and dietary fiber altered the composition of the gut microbiota and metabolic outputs, improving IS and glycemic control—mechanisms that were increasingly acknowledged in modern clinical guidelines as an adjunct to pharmacological therapy [161, 162]. In this context, the integration of dietary intake assessment with metabolomic and microbiome-derived indicators coincides with guideline-supported objectives of precision care, providing a means to enhance risk stratification and optimize nutrition-based therapies throughout the T2DM care spectrum [163].

In addition to discovery, integrative analytic frameworks are converting multiomics into therapeutically pertinent models. Deep-learning-powered variational autoencoders and related techniques can amalgamate heterogeneous omics, clinical, and chemical exposure data to elucidate drug-omics relationships and drug metabolism profiles in individuals with T2DM, therefore prioritizing possible pathways and guiding personalized therapy [164]. These advancements collectively demonstrate that multiomics can: (i) enhance risk prediction and early detection through protein, metabolite, and lipid panels; (ii) elucidate tissue- and cell-type-specific mechanisms connecting genetic risk to beta-cell dysfunction; (iii) elucidate the microbiome-host metabolic axis pertinent to glycemic control; and (iv) facilitate precision therapeutics via drug-omics signatures. The subsequent phase will depend on longitudinal, ancestrally varied populations, standardized assays and analytics, causal frameworks, and pragmatic trials to evaluate omics-guided therapies along the T2DM care spectrum [150, 153, 165]. A comprehensive summary of the major omics technologies contributing to the molecular understanding of CMDs is presented in Table 1.

Cardiovascular disease

Cardiovascular diseases, encompassing a broad spectrum including coronary artery disease, cerebrovascular disease, peripheral artery disease, and congenital heart disease, are one of the leading causes of death worldwide. According to estimates, CVD caused the deaths of 19.8 million people in 2022, accounting for approximately one-third of global deaths [176]. Underlying CVD is the complex interplay of environmental and genetic factors [177]. However, to fully explain inter-individual heterogeneity, multiomic approaches are important for the comprehensive analysis of individual biological information, enabling the development of PN and health strategies.

Genetic variants that contribute to CVD risk and revealed gene-diet interactions that differentiate individuals' responses to nutrition [178, 179]. Genes associated with cardiovascular diseases are usually caused by variations in genes related to lipid metabolism, blood pressure regulation, inflammation, clotting, and vascular structure. The *APOE* gene encodes the APOE protein, a common lipid transporter that binds to various lipid types such as cholesterol, phospholipids, and TG, and genetic variations are considered an important risk

Table 1 Summary of major omics technologies and their significance in cardiometabolic diseases

Omics Type	Definition	Key Technologies	Advantages/ Limitations	Relevance in CMD	References
Genomics	Study of DNA sequence variation and inherited risk.	WGS, SNP arrays	Adv: stable, predictive; Lim: lacks env. info	Risk stratification; polygenic scores for diabetes/CVD	[166, 167]
Epigenomics	Heritable, reversible gene regulation changes.	Methylation arrays, ChIP-seq, ATAC-seq	Adv: gene–env. link; Lim: tissue-specific, dynamic	DNA methylation QTLs reveal pathways linked to cardiovascular disease	[168, 169]
Transcriptomics	Profiling of RNA transcripts (gene expression).	RNA-seq, microarrays	Adv: reflects gene activity; Lim: highly dynamic	Inflammatory, metabolic pathways in CMD	[170, 171]
Proteomics	Study of protein abundance and modifications.	Mass spectrometry, protein arrays	Adv: functional readout; Lim: complex, costly	Biomarkers (CRP, troponins) for CMD outcomes	[172, 173]
Metabolomics	Profiling of small-molecule metabolites.	NMR, LC-MS/MS	Adv: real-time metabolic status; Lim: variable	Prediction of diabetes, obesity; dietary biomarkers	[5, 174]
Microbiomics	Study of gut microbial communities.	16S rRNA sequencing, metagenomics	Adv: diet–host insights; Lim: variable, causality issues	Gut microbiota links to obesity, glycemia, lipids	[59, 175]
Phenotyping	Quantitative assessment of traits (clinical, digital).	CGM, imaging, wearables	Adv: bridges omics–clinic; Lim: longitudinal need	Postprandial responses; CMD trajectories	[3, 4]

CGM: continuous glucose monitoring, CMD: cardiometabolic diseases, CVD: cardiovascular disease, LC-MS: liquid chromatography–mass spectrometry, NMR: nuclear magnetic resonance, SNP: single nucleotide polymorphism, WGS: whole-genome sequencing

determinant for CMD. The *APOE* gene has three main alleles (ε2, ε3, and ε4). Combinations of these alleles differentiate lipoprotein profiles and susceptibility to CVD [180–185]. In particular, the ε4 allele has been associated with increased LDL cholesterol (LDL-c) levels, impaired lipid profile, and the development of atherosclerosis [186–188]. In contrast, the ε2 allele has been associated with a lower risk of atherosclerosis at normal TG levels and independently of LDL-c levels. It has been stated that anti-inflammatory pathways are activated in ε2 carriers, erythrocyte homeostasis, coagulation and complement systems are modulated, and ε2 plays a cardioprotective role through these biological pathways [189].

The *LDLR* gene encodes the low-density lipoprotein receptor, and its mutations cause familial hypercholesterolemia [184, 190–192]. The *PCSK9* gene increases the degradation of LDL receptors, thereby raising LDL-c levels, and thus plays an important role in CVD [191, 192]. The *APOB* gene is involved in the structure of LDL particles, and mutations in this gene can lead to hypercholesterolemia [184, 191, 192]. The *CETP* gene regulates HDL metabolism, and variants in this gene cause changes in HDL-cholesterol (HDL-c) levels, affecting cardiovascular health [193, 194]. In Chinese adults, although some variants in the *CETP* gene alter HDL metabolism, they have not lowered LDL-c levels and have not shown a significant association with CVD risk [193]. Four variants (V6D, L168P, L278R, A291D) that inhibit CETP secretion cause autosomal dominant hyperalphalipoproteinemia. Five variants (A291G, L313Q, Y378C, E443K, D459G) significantly reduce CETP secretion, causing mild hyperalphalipoproteinemia [194].

The renin-angiotensin system plays a critical role in regulating blood pressure [195]. Polymorphism in the *ACE* gene may affect the risk of hypertension [196–199]. Variations in the *AGT* gene have been associated with hypertension. Furthermore, changes in the *AGTR1* gene are associated with hypertension [200–203]. In hypertensive patients, the C-allele of the *AGTR1* gene (rs5186) is linked to elevated blood pressure [200]. Al-Eitan found that the rs10739150 genotype of the *PTPRD* gene increases the risk of hypertension, and the G allele is strongly associated with the development of the disease [204]. The *REN* gene is directly involved in blood pressure regulation, and renin-angiotensin-aldosterone system activity. It has been determined that the *REN* rs6676670 allele is associated with plasma aldosterone levels, while the *REN* rs2887284 variant is associated with basal plasma renin activity and changes in renin and angiotensin II levels in response to treatment [205].

Alongside genes, miRNAs, which are effective in processes such as endothelial function, lipid metabolism, inflammation, hypertrophy, and fibrosis, are critical regulatory factors in the development of diseases such as atherosclerosis, hypertension, myocardial infarction, and heart failure [206–212]. In a study examining the relationship between plasma miRNA levels and CVD, miR-182-5p was found to be significantly increased in coronary plasma, while miR-5187-5p was decreased [212, 213]. Wang et al. found that miR-208a, which is not normally found in the blood of healthy individuals, rapidly increases in plasma following acute myocardial infarction [210]. miR-3135b and miR-107 have been identified as potential biomarkers for severe hypertension [206]. In another study, miRNA 4516 upregulation and miRNA 145 downregulation were identified as independent predictors of hypertension [207]. miRNAs can be considered as potential biomarkers for diagnosis, prognosis, and treatment, serving as important biological mediators in understanding the molecular mechanisms of cardiovascular diseases.

Proteomic and lipidomic approaches have also gained importance in CVD [214–216]. For example, GDF15 and ADM proteomic markers have been found to be associated with poor cardiovascular health [214]. Tanaka et al. analyzed 1301 proteins that may be related to cardiovascular health and found that 22 of them were positively, and 70 were negatively associated. The proteins showing the strongest negative correlation with cardiovascular health were found to be leptin, fatty acid-binding protein 3, angiopoietin-2, and GDF15. The proteins most strongly associated with CVD and mortality were found to be GDF15, insulin-like growth factor 2, and growth hormone receptor [217]. Environmental factors can affect CVD risk at the proteomic level. Environmental exposures such as diet, social vulnerability, lack of green space, air pollution, and temperature have been shown to be associated with circulating proteins. These proteomic effects have been linked to cardiometabolic phenotypes such as obesity, left ventricular mass increase, lipid profile, and lung function [49]. Certain types of lipids may show a strong association with CVD risk, independent of total cholesterol, HDL-c, and LDL-c [65]. Lipids such as TG, cholesterol esters, lysophosphatidylcholine, phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin are associated with CVD. TG, cholesterol esters, and phosphatidylethanolamine have been identified as the most informative lipid types in terms of CVD risk [218]. Ceramides (d18:1/16:0, d18:1/18:0, and d18:1/24: 1) phospholipids containing saturated and monounsaturated fatty acid (MUFA) chains showed a positive association with CVD outcomes, while phospholipids containing polyunsaturated fatty acid chains (PUFAs) showed an inverse association with CVD outcomes [65].

The gut microbiota can influence cardiovascular risk factors through metabolites such as TMAO, SCFAs, and lipopolysaccharide (LPS) [219]. Additionally, dysbiosis resulting from changes in the composition of the microbiota has also been associated with CVD [220–222]. A study found that the overgrowth of bacteria such as *Prevotella* and *Klebsiella* is associated with disease as a microbial function in both prehypertensive and hypertensive populations [220]. According to the results of the meta-analysis, elevated levels of the *Proteobacteria* phylum were observed in individuals with CVD. In addition to this species, an increase in *Streptococcus* and *Streptococcaceae* levels was observed, while a decrease was observed in *Faecalibacterium* and the *Faecalibacterium prausnitzii* species [222]. Two studies have indicated that individuals with high intima-media thickness values and coronary heart disease have an elevated *Firmicutes/Bacteroidetes* ratio [223, 224]. High levels of *Streptococcus* are associated with coronary atherosclerosis and systemic inflammation [225]. *Faecalibacterium prausnitzii* has been found to be responsible for the production of SCFAs, particularly butyrate, which is believed to benefit cardiovascular health [226–228]. It has been reported that butyrate may improve cardiovascular health by activating phosphorylated-adenosine 5′-monophosphate-activated protein kinase and increasing GLUT4 expression, thereby regulating glucose uptake and energy metabolism in adipose tissue and modulating the immune response [229, 230]. Dietary fiber has improved dysbiosis by positively rebalancing the gut microbiota and promoting the proliferation of SCFA-producing bacteria belonging to the *Prevotella* and *Bifidobacterium* genera. This has resulted in increased fecal and systemic SCFA concentrations [231]. Inadequate intake of prebiotic fiber leads to dysbiosis in the gut microbiota, reducing SCFA production and consequently resulting in cardiovascular risk factors such as inflammation, metabolic imbalance, hypertension, and vascular dysfunction. Furthermore, insufficient activation of receptors that work through SCFA contributes to impaired vascular homeostasis and increased susceptibility to CVD [232].

Trimethylamine N-oxide, a metabolite associated with cardiovascular disease, is primarily produced in the liver through the oxidation of a metabolite produced by the gut microbiota during the breakdown of various dietary precursors, including choline, phosphatidylcholine, betaine, carnitine, dimethylglycine, and ergothioneine, which are converted by the gut microbiota into trimethylamine and then oxidized in the liver [233–235]. Elevated TMAO levels have been reported that exhibits proatherosclerotic effects, and positively associated with CVD, coronary artery disease, peripheral artery disease, and severe artery stenosis [236–241], major adverse cardio- and cerebrovascular events, and all-cause mortality [242], and T2DM [243]. TMAO can trigger inflammation and thrombosis via protein kinase, nuclear factor-κB, nucleotide-binding oligomerization domain-like receptor family pyrin domain-3, and also promotes myocardial hypertrophy, fibrosis, mitochondrial dysfunction, endoplasmic reticulum stress, mitochondrial reactive oxygen species, and glycolysis pathways [239, 244–248]. TMAO has also been reported to be associated with hypertension, which is a risk factor for coronary artery disease [235], increased BMI [249] and systemic inflammation [250].

Recent studies have shown that TMAO can modulate the expression of microRNAs associated with cardiovascular diseases and thus may also play a role in CVD pathogenesis through this pathway [251–253]. TMAO increased the expression of miR-21-5p and miR-30c-5p, which are associated with CVD, in HEPG-2 and THP-1 cells [251]. Liu et al. found that TMAO promotes atherosclerosis development by activating the lncRNA enriched abundant transcript 1/miR-370-3p/signal transducer and activator of transcription 3/ flavin-containing

monooxygenase-3 axis in human aortic endothelial cells. Consequently, TMAO promotes atherosclerosis progression by creating a feedback loop at both the molecular and cellular levels [253]. Dietary TMAO production increases with high consumption of animal-based foods, while plant-based diets and probiotic supplements can lower TMAO levels and reduce the risk of CVD [254]. Therefore, TMAO has been considered both a dietary risk marker and a target molecule playing a significant role in the pathophysiology of cardiovascular diseases.

Nutritional therapies, in addition to molecular factors, significantly contributed to the prevention and management of CVD, serving as a crucial translational application of multiomic research. A systematic review and meta-analysis indicated that dietary strategies focusing on overall dietary patterns and nutrient quality correlated with enhancements in cardiometabolic risk factors, such as lipid profiles, blood pressure, and inflammatory markers, thus aiding in the reduction of CVD risk [255]. Variability among individuals in cardiometabolic reactions to dietary interventions was noted, highlighting the limitations of universal dietary recommendations and underscoring the necessity for more customized nutrition methods in the prevention of CVD. A randomized controlled research demonstrated that personalized diet recommendations tailored to individual biological and metabolic traits led to more significant enhancements in specific cardiometabolic health indicators than traditional population-based dietary recommendations [8]. The complex etiology of CVD necessitates the combined assessment of genetic predisposition, metabolite profile, protein expression, and microbiome structure, and the development of PN strategies based on this assessment. This enables more accurate prediction of cardiovascular risk, prevention, and more effective management of treatment processes.

Personalized nutrition: the intersection of multiomics and health

Obesity, diabetes, dyslipidemia, and hypertension are the main risk factors for CMD. The most important modifiable risk factor is diet for CMD. Despite the publication of national and international nutritional guidelines to prevent and treat diseases, the rate of diet-related diseases is increasing [256]. Therefore, further research and implementation efforts are needed to make current dietary guidelines more effective in improving the health [257]. The effects of health consequences of various diets can differ greatly among individuals due to factors such as age, sex, physiology, health conditions, lifestyle, and environmental factors [258]. The International Society of Nutrigenetics/Nutrigenomics (ISNN) emphasizes that an individual's response to nutrients is shaped by their genetic background, various biological and cultural factors [259].

Additional interindividual variability can be attributed to differences in genomic, epigenomic, transcriptomic, proteomic, lipidomic, metabolomic, and gut microbiome profiles, all of which may interact with dietary, lifestyle, and environmental factors [260, 261]. The differences in omics profiles have led to a population-level approach to nutrition that goes beyond a "one size fits all" approach and underscore more personalized dietary interventions [262].

The American Nutrition Association defines the PN is an approach that leverages human individuality to plan dietary strategies that prevent, and treat disease and optimize health [263]. The ISNN also suggested that PN approaches would be more effective than general recommendations in preventing chronic diseases [259]. GWAS enhances our understanding of gene-diet interactions and their implications for disease risk. The integration of the sequencing of the human genome and human genetic variability have contributed significantly to the emergence and development of PN [264, 265]. Machine learning algorithms play a key role in PN planning by integrating large datasets from omics profiles with personal and clinical measurements, and provide more successful dietary interventions by predicting postprandial glucose, TG, and insulin levels [260].

Metabolomics explains the biochemical effects of specific dietary components on human metabolic processes. This knowledge has facilitated the development of advanced personalized dietary interventions [266]. The application of metabolomics in nutrition science, nutrimetabolomic, investigates how specific nutrients, foods, and overall dietary patterns influence biochemical pathways, gene expression, and physiological functions by integrating principles from nutrition, metabolomics, and systems biology. This approach also provides a means to identify novel biomarkers of food intake, validate dietary assessment tools, and monitor dietary adherence [267, 268].

Many studies have shown that PN created by a complex dataset is effective at the individual level. Metabotyping, grouping individuals based on similarities in their metabolic phenotypes, could provide a strategy for disease prevention at the population level by enabling the development of personalized, yet scalable and cost-effective strategies [257]. There are commonly used phenotypic variables such as BMI, body weight, sex, or age at the macro level. Micro-level metabotyping may incorporate more specific biological markers, including inflammatory biomarkers, IR, or markers of gut barrier function, etc. Molecular metabotyping, utilizing multiomics technologies, offers promising pathway towards greater PN but still in early stages [269, 270].

It has been suggested that disease-associated metabotypes will influence the response to a dietary pattern. The gut microbiota is an important determinant of metabotypes, and therefore the interaction between exogenous factors and host is a key factor in dietary response. The identifying such functional metabotype instead of "clinical biomarker-based" metabotypes may be more effective in optimizing individuals' diets for the prevention of CMD [271]. The metabolites generated through microbial metabolism integrate into the host metabolome, contributing substantially to interindividual variability in metabolomic profiles [272].

Several studies have reported that PN based on metabotypes have positive effects on metabolic health [273–275]. A randomized controlled trial examined the effects of metabotypes (using triacylglycerol, HDL-c, total cholesterol, and glucose) on metabolic parameters in individuals who received PN (increasing legume and dairy intake or limiting added sugar, high-fat foods, and alcohol intake) compared to population-level dietary advice. Both nutritional interventions were reported to improve diet quality, nutrient intake, blood pressure, triacylglycerol, and LDL-c. Correlations were also identified between changes in total cholesterol, LDL-c, triacylglycerol, insulin, HOMA-IR, and lipid metabolites such as sphingomyelins, glycerophosphocholines, lysophosphatidylcholines, and fatty acid carnitines [273]. In a randomized controlled trial, DNA-based PN intervention was reported to reduce fasting plasma glucose and HbA1c levels in individuals with non-diabetic hyperglycemia compared to the standard UK population guideline [274]. The PERSonalized Glucose Optimization Through Nutritional Intervention Study examined the effects of different dietary macronutrients on glucose metabolism and other health outcomes based on tissue-specific IR phenotype (muscle or liver). This study stated that different metabolic phenotypes may respond differently to dietary interventions, thus a more personalized dietary intervention is important to improve metabolic outcomes [275].

A meta-analysis evaluated the 24 randomized controlled study investigating the relationship between protein-type intake and metabolomics signatures. It was found that aromatic amino acids, BCAA, short-chain acylcarnitines, glutamate, and TMAO were associated with diets rich in animal protein, while glycine, known to reduce risk, was associated with diets rich in plant protein. Furthermore, urine and serum metabolomic data reported that different protein sources induced differential activity in the gut microbiota, including the involvement of some gut-produced metabolites. The results of this meta-analysis highlighted the importance of nutrimetabolomics in elucidating the interactions between protein sources and health outcomes [276]. The PREDIMED study showed that the Mediterranean diet (MD) with either extra virgin olive oil or nuts affect urinary metabolomic phenotype or metabotype compared to a low-fat diet. Metabolic fingerprinting changed in the MD group compared to baseline and the control group. The most important changes in the MD group were the metabolism of carbohydrates (citrate, 3-hydroxybutyrate, and cis aconitate), creatinine, creatine, amino acids (glycine, proline, N-acetylglutamine, BCAA), lipids (oleic and suberic acids), and microbial metabolites (p-cresol and phenylacetylglutamine). Hippurate, histidine, xanthosine, and TMAO were predominant in individuals with low-fat diet [277].

Lipids sensitive to dietary fat modification may function as biomarkers for the effects of dietary interventions [278]. A study conducted on patients with type T2DM and CVD estimated the correlations between CMD and plasma lipids derived from high-resolution lipidomics. It examined whether the risk-associated lipids were responsive to dietary fat modification (diet rich in saturated fatty acids, rich in MUFA, or rich in mixed unsaturated fatty acids (UFA), including both MUFA and n-6 PUFA). The results suggested that several monoacylglycerols, and FA16:0 and FA18:0 in diacylglycerols were associated with both outcomes; free fatty acids, cholesteryl esters, and sphingolipids were mostly specific for CVD; and several (glycero) phospholipids were specific for T2DM. The MUFA-rich diet decreased diacylglycerol (FA16:0; 18:0; 22:4), triacylglycerol (FA 16:0; FA 18:0), sphingomyelins (14:0; 18:0), phosphatidylethanolamine (FA 16:1), some ceramides, and increased TG (FA 18:2; 22:1), SM (24:1). The mixed UFA-rich diet decreased concentrations of TG (FA18:0), diacylglycerol, sphingomyelin, phosphatidylethanolamine and increased TG and some ceramide [279].

The microbiome and its role in personalized nutrition

The first phase of the NIH Human Microbiome Project (HMP) investigated the composition and diversity of the human microbiome to characterize common patterns of microbial diversity linked to health. Findings from the HMP indicated that the taxonomic composition of the microbiome differed markedly among individuals, suggesting that taxonomic data alone were insufficient to clarify associations with disease [280]. The second phase of the NIH HMP, Integrative HMP, aims to investigate the biology of the microbiome, how it interacts with the host, and how the host responds to its resident microbiota through longitudinal analyses of disease-specific cohorts. This project analyzed the multiple properties of the microbiome, such as phylogenetic composition and associated functional multiomics data (genomic, transcriptomic, proteomic, and metabolomic) for preterm birth, inflammatory bowel disease and onset of T2DM [281]. While the results obtained from the project

revealed new biological findings for all three diseases, the combined effects of shotgun metagenomics, untargeted metabolomics, and immune profiling were reported to be particularly effective in explaining host and microbial characteristics associated with disease. Host-microbiome interactions have been shown to be highly individual-specific, producing both local and systemic effects. It was stated that large-scale, population-wide studies across different races and geographic regions are needed [282].

Creating a global and simultaneous profile of host and microbial molecules in individuals with prediabetes is important to fully understand the molecular mechanism underlying prediabetes and IR, and how these conditions contribute to the development of T2DM. The Integrated Personal' Omics Project reported that IR is also associated with changes in lipid biology, and levels of several long-chain and polyunsaturated fatty acids have been positively correlated with steady-state plasma glucose (SSPG). Indolelactate and hippuric acid, which are inversely correlated with metabolic syndrome and strong indicators of gut microbiome diversity, have been reported to be inversely correlated with IR/IS classification. The genus *Blautia*, which is inversely correlated with hippuric acid, has been shown to be positively correlated with SSPG, while the genera *Odoribacter*, *Oscillibacter*, and *Pseudoflavonifracter* have been shown to be negatively correlated with SSPG. Multiomic associations have been reported to be different in IR and IS individuals. For example, the genus *Barnesiella* was positively correlated with IL-1β only in IS individuals, while the genus *Faecalibacterium* was negatively correlated with TNF-α. Furthermore, the genus *Butyricimonas* was negatively correlated with four lipids only in IR individuals. This situation suggests that IR affects host-microbiome interactions [283].

A study examined individuals during consecutive periods of weight gain and loss using a multiomics strategy found that weight gain was associated with the activation of strong inflammatory and hypertrophic cardiomyopathy signatures in the blood and with changes in the fecal microbiota. Although weight loss reversed some changes, several signatures indicating long-term physiological changes persisted, and some biomolecules were highly individualized. Molecular changes were shown to differ in IR individuals compared to IS individuals. Based on 16S and shotgun metagenomics data, a significant difference in the abundance of the gram-negative *Proteobacterium*, *Oxalobacter formigenes* was found between IR and IS individuals (higher in IS participants). In addition, *Eubacterium hallii*, *Parabacteroides*, *Eubacterium eligens*, and *Bacteroides vulgatus* were shown to exhibit a strong positive correlation in IR participants and a negative correlation in IS individuals. *Proteobacteria* was positively associated with antioxidant 3-indolepropionic acid in the IR subjects. While, in IS participants, N6-trimethyllysine, as a precursor for L-carnitine, was positively associated with the phylum *Proteobacteria*, which increases total energy expenditure, enhances glucose tolerance, and reduces cardiovascular risk [284].

Another study investigating the effects of high fat, high sucrose, and high fat and sucrose diets on cardiometabolic health in mice reported that liver mass and IR were significantly increased in both of the high fat containing diets. In the cluster analysis of the study, 4 groups were created for microbiota and metabolites arranged together in all locations. Cluster 1 contains microbiota and metabolites negatively associated with fat-dependent phenotypes of cardiac diastolic impairment such as fecal butyric acid and propionic acid, aminoadipic acid, cardiac homocysteate and *Lachnospiraceae Roseburia*. In this context, the interaction between these specific metabolites and the gut microbiota suggests a potential fat–microbe feedback mechanism that counter-regulates fat-dependent phenotypes. The cluster 2, comprised liver trans-hydroxyproline and creatine, cecal thiamine and phenylalanine, members of the *Lachnospiraceae* and *Lachnoclostridium* genera, exhibited a positive correlation with these fat-dependent phenotypes. Collectively, these components are likely to act as synergistic potentiators of fat-dependent cardiometabolic disruption. Cluster 3 comprised components driven by high sucrose diet and they were inversely correlated with cardiac contractile function. Components of cluster 4, cecal metabolites such as riboflavin, citrulline, serotonin, and aspartate, and plasma alanine, and the microbiota *Lachnospiraceae Blautia coccoides*, have been reported to be upregulated by high fat and are more strongly associated with these phenotypes than Cluster 2 [285]. A metagenome-wide association study of fecal samples from individuals with CMD indicated increased abundances of *Enterobacteriaceae*, including *Klebsiella* spp., *Escherichia coli*, and *Enterobacter aerogenes* [286] and decreased abundance of *Bacteroides* spp. and anti-inflammatory *Faecalibacterium prausnitzii* in their gut microbiome [287].

Dysbiosis have been shown to correlate with a range of anthropometric and blood-based biomarkers associated with obesity, IS, and hypertension, all of which are recognized risk factors for the development of CMD [288, 289]. Many studies have reported that alterations in the *Firmicutes/Bacteridetes* ratio are particularly associated with disease pathogenesis. Gut microbiota regulates glucose metabolism through SCFAs production, bile acid transformation, incretin secretion, and adipose tissue inflammation [290]. Among SCFAs, in particular butyrate, induces the secretion of the GLP1 from intestinal cells via GPR41 and GPR43, which in turn regulates insulin secretion from pancreatic β-cells. Furthermore, it promotes intestinal gluconeogenesis through transcription

of gluconeogenic genes in enterocytes via cAMP [291]. Primary bile acids are converted into secondary bile acids via gut microbiota, and these bind to Takeda membrane G protein-coupled receptor 5 and stimulate intestinal GLP1 secretion, thus ensuring glucose homeostasis [292].

In addition, gut dysbiosis disrupts the reverse cholesterol transport system, contributing to a condition known as metabolic endotoxemia. Dysbiosis increases intestinal permeability, facilitating the translocation of LPS into the bloodstream. Elevated circulating LPS levels subsequently trigger the expression of pro-inflammatory cytokines and cell adhesion molecules, promoting monocyte adhesion to the endothelial layer. This cascade accelerates the progression of atherosclerosis, enhances systemic inflammation, and leads to the formation of foam cells, which act to clear excess LPS from the circulation [293]. In addition, T2DM and obesity are associated with low grade inflammation stimulated by the LPS. The LPS promotes the phosphorylation of insulin response substrate, caused to decrease in insulin signaling through the stimulation circulating level of the TNF-α [294].

It is widely acknowledged that effective dietary management is essential to the treatment of T2DM and preventing of its complications [258]. However, individual responses to nutrients vary among individuals, causing a single dietary intervention to fail in glycemic control. Implementation of personalized predictive models may facilitate improved management of postprandial glycemic responses by accounting for individual variability in glycemic responses to food [295]. The applicability of microbiome-based PN extends beyond the prevention of T2DM and may also offer potential benefits in managing disorders linked to dysregulated lipid metabolism, including obesity, CVD, and non-alcoholic fatty liver disease [272, 289]. Tily et al. [296] conducted a study on T2DM patients with metatranscriptomic data to assess their glycemic responses and showed that gut microbiome activity made a statistically significant contribution to individual differences in glycemic response. Zeevi et al. used continuous glucose monitoring (CGM), gut microbiome profiling, and machine learning algorithms to tailor dietary interventions. Their study stated that specific microbiome species have been associated with differential predicted postprandial glucose responses. *Eubacterium rectale* has been linked to lower predicted postprandial glucose levels, whereas *Parabacteroides distasonis*, *Bacteroides thetaiotaomicron*, and *Alistipes putredinis* have been associated with higher predicted responses. As a result of the study, PN is effective in glycemic control and enables more accurate decisions to be made in improving nutritional outcomes and treatments [59].

Patients with newly diagnosed T2DM who underwent either a PN integrated with clinical and microbiome characteristics or a MD, were investigated. PN has been reported to have lower CGM-based glycemic measures (postprandial glycemic response-PPGR, mean glucose, glucose levels > 140 mg/dl), HbA1c, blood fructosamine, and TG levels compared to the MD [297]. In another study, it has been reported that a 6-month PN based on a machine learning algorithm integrated with blood parameters, glycemic response, anthropometry, nutritional habits, physical activity and microbiota in individuals with prediabetes improved glycemic (HbA1c, mean CGM glucose, glucose levels > 140 mg/dl, 5 h PPG excursions) and lipemic (TG, HDL) control more than the MD [298]. Additionally, studies have shown that PN motivates individuals to achieve healthy eating and lifestyle behaviour and is more effective in improving diet quality [299–301].

A randomized controlled study investigating the effects of a PN and general dietary advice on cardiometabolic health. The PN was based on food characteristics, food responses, individual postprandial glucose and TG, health history, and microbiome to calculate personalized food scores using an 18-week app-based program. Significant improvements were shown in HbA1c, diet quality, waist circumference, body weight, and microbiota beta diversity, particularly in individuals with high PDP adherence, but no effect was reported on low-density lipoprotein cholesterol. Furthermore, 11 of the 15 selected beneficial species increased in the PN group and 4 in the control group. Species such as *Faecalibacterium prausnitzii*, *Oscillibacter sp.57_20*, and *Eubacterium eligens* were particularly increased in the PN group. Additionally, dietary compliance was 30% higher in PN group than in the control group [8].

PREDICT 1 investigated individual variations in postprandial glucose, TG, and insulin responses. This study obtained genetic, metabolic, microbiomic, and meal composition data. It demonstrated significant differences in postprandial glucose, TG, and insulin responses among individuals, even when they consumed the same meal. Microbiome were found to have a greater impact on postprandial lipemia than the macronutrients of the meal [4]. Similarly, it has been reported that in the Danish population, 48% of the variance in predicting postprandial glycemic responses after a standard meal was due to microbiota and clinical characteristics, with microbiota accounting for 14% of this variance [302]. Other results from the PREDICT-1 study cohort showed that *Prevotella copri* and *Blastocystis* spp. were associated with favorable postprandial glucose metabolism markers, while overall microbiome composition was predictive of a broad panel of cardiometabolic blood markers (fasting and postprandial glycemic, lipemic, and inflammatory markers). Furthermore, gut microbiome alpha diversity was reported to be positively associated with

HDL-c [303]. The Health Professionals Follow-Up Study reported that protective associations between adherence to the MD and CMD risk. This study indicated that protective associations of MD on cardiometabolic health was significantly stronger among participants with decreased abundance of *Prevotella copri* [304].

A recent systematic review examined randomized controlled study in individuals with prediabetes and metabolic syndrome reported that PN generally had consistent improving effects on HbA1c, postprandial glucose, and waist circumference, but results regarding HOMA-IR, blood lipids, and diet were inconsistent (Table 2). Longer and more frequent interventions have been shown to yield greater improvements, particularly in HbA1c and waist circumference. However, few studies have evaluated individual postprandial response, integrating both clinical and gut microbiome and other metabolomic data to provide a PN approach. Advances in multiomics technologies, including genomics and metabolomics, combined with advanced data analysis techniques, have enabled further understanding of the clinical relevance of PN [305].

Challenges of AI- and machine learning–driven multiomic models in personalized nutrition

Digital devices such as phones and apps are now widely available, providing real-time measurements of blood pressure, heart rate, blood glucose, and the application of multiomics technologies in clinical and research [306]. They are strong tools for determining diet and behaviors and are important components in PN. These technologies present several advantages compared to traditional food record methods, including scalability, remote accessibility, real-time feedback, long-term monitoring, or integration with health data platforms. Real-world data are necessary for understanding how individuals interact with and respond to foods and diets. Unlike the controlled conditions of clinical trials and the participation of highly motivated participants, real-world data capture the complexities of actual food choices, reflecting the various factors encapsulated in the socioecological model, such as individual preferences, social norms, local food environments, and health policies [307]. A meta-analysis reported that using mobile dietary apps was more effective in reducing body weight, waist circumference, and energy intake compared to controls without apps [308]. Another study reported that improvements in eating habits, weight loss, glucose control, and physical activity in individuals who underwent a program integrated with wearable (CGM and activity), mobile apps, personalized recommendations, and virtual coaching [309].

Clinical studies are increasingly using integrated data analyses that include metabolomic and microbiota data, allowing for the evaluation of individuals' personalized responses to diet. Nutrimetabolomics also offers a new and effective approach to assessing food intake and is beginning to take its place in nutritional practices. The widespread use of mobile applications and wearable technologies for tracking metabolomic data, particularly for T2DM, facilitates data integration and analysis for this disease [272, 274–276]. However, there are several challenges in the multiomics integration of the microbiome. These include uncertainty in microbiome taxon assignments, the compositional nature and sparsity of microbiome data and the high rate of zero taxon count in many samples, and the high variability of the gut microbiome over time [58].

It remains unclear whether AI-based dietary recommendations are equally valid for everyone such as the lack of large-scale long-term epidemiological studies, challenges in data organization, the high cost of omics analyses, similar socioeconomic and cultural groups, and ethical concerns. Furthermore, differences in data quality,

Table 2 Summary of studies investigating multiomics in personalized nutrition

PN approach	Study design	Key outcomes	Reference
Based combined AI-models	RCT	Reduced HbA1c, TAG, waist circumference, body weight, diet quality andimproved diet quality, microbiota beta diversity, sleep quality and mood	[8]
Based combined AI-models	Observational	Lower PPGR and fluctuations in blood glucose	[59]
Metabolomics-based	RCT	Improved diet quality, blood pressure, TAG, and LDL-C	[273]
DNA-based	RCT	Reduced fasting plasma glucose and HbA1c levels	[274]
Tissue-specific IR phenotype-based	RCT	Reduced fasting insulin, 2-h glucose, HOMA-IR, TAG	[275]
Based on combined AI-models	RCT	Lower CGM-based glycemic measures (PPGR, mean glucose, daily time of glucose levels > 140 mg/dl), HbA1c, blood fructosamine, and TG level	[297]
Based on combined AI-models	RCT	Improved glycemic (HbA1c, mean glucose levels, daily time with glucose levels > 140 mg/dl, 5 h PPG excursions, fructosamine) and lipemic (TG, HDL-c, total c-to-HDL-c ratio) control	[298]
Based on genomics	RCT	Improved diet quality, reduced BMI and body weight	[299]
Based on genomics	RCT	Improved dietary patterns and lifestyle behaviors, reduced BMI, body fat, hip circumference, LDL-c and Total-c	[300]

lack of standardization, and insufficient evidence regarding long-term clinical outcomes limit the use of these approaches in routine practice. Multiomic data includes different data types, high-dimensional data structures, and measurement techniques that vary in nature. This creates technical challenges in applying common analysis, training, and interpretation to the data. Artificial intelligence models may require access to health data such as genetic information and personal health history. This raises significant concerns regarding data privacy and security [310–312]. Healthcare professionals and patients may develop a bias against the use of this technology due to concerns about the reliability and clinical validity of artificial intelligence tools. Furthermore, the fact that different artificial intelligence techniques produce different explanations for the same model reduces confidence in clinical applications and complicates decision-making processes [312].

The system-level understanding of human physiology and individual characteristics associated with metabolic variability are necessary to successful realization of PN, but PN is in its early stage. Because of heterogeneity in effect sizes and the lack of long-term outcome data comparing PN interventions with conventional dietary counseling, more clinical research is needed.

Nutritional genomics: tailoring diet to individual genomes

Genetic variations can significantly influence physiological responses to dietary components and consequently cardiometabolic risk. Genetic variations affecting processes such as lipid metabolism, glucose regulation, and IS interact with dietary factors to shape susceptibility to disease. Variations in genes such as *FTO*, *APOE*, *TCF7L2*, and *PPARγ* may lead to differential metabolic responses to dietary factors such as saturated fat or carbohydrate intake. Such gene-diet interactions play a pivotal role in the development of CMD, including obesity, T2DM, hypertension, and dyslipidemia [313, 314].

The *FTO* gene was first discovered in 2007 in GWAS in association with obesity. Frayling et al. found that a SNP in the *FTO* gene, rs9939609, was strongly associated with increased BMI and obesity risk in both children and adults. This result has led to a more in-depth investigation of the influence of genetic factors on energy balance and dietary behavior [315]. *FTO* gene polymorphisms have significant effects on nutritional habits, body composition and susceptibility to obesity [316]. It has been reported that TC + CC genotypes, especially in the *FTO* rs1421085 variant, are positively associated with increased BMI and higher fat intake [317]. The same variant was found to be associated with abdominal obesity from childhood to young adulthood in males and from adolescence to young adulthood in females, but this association was not mediated by energy or macronutrient intake or physical activity [318]. On the other hand, it has been shown that total body fat in participants with the rs9939609 AA genotype is significantly higher than in participants with the AT and TT genotypes [319]. Melhorn et al. showed that participants with the *FTO* rs9939609 risk genotype (AA) had lower satiety, found high-calorie foods more appealing, and had dietary energy intake approximately 350 kilocalories greater per day [320]. Similarly, Poosri et al. found that participants with rs9939609 and rs1421085 polymorphisms had significantly higher sugar consumption and saturated fat intake [321]. In a randomized controlled study evaluating the interaction between FTO genotype and protein intake, it was determined that high-protein diet was associated with a decrease in appetite and food cravings in participants with rs9939609 A allele [322]. These results suggest that the *FTO* gene may have an effect not only on the predisposition to obesity but also on the predisposition to CMD through altered energy balance and nutritional behaviors.

It has been shown that the responses of individuals to dietary fat and cholesterol content vary depending on the APOE genotype. For example, after dietary intervention in *APOE* ε4 carriers, the diet and genotype interaction was found to be significant. In particular, in the diet where saturated fatty acids were replaced with low glycemic index carbohydrates and total fat intake was reduced, significant decreases in total cholesterol levels were observed in ε4 carriers. On the other hand, replacing saturated fats with MUFA and high glycemic index carbohydrates led to an increase in total cholesterol levels in ε4 carriers. These results indicate that ε4 allele carriers may benefit more from diets, especially low fat, low glycemic index carbohydrate-based diets. It has been shown that *APOE* ε4 carriers are more sensitive to diets rich in saturated fat and high glycemic index carbohydrates, and therefore, such diets may increase cardiometabolic risk in these individuals [187]. Ozen et al. showed that, daily fiber intake in *APOE4* carriers was 4 g higher than in the *APOE2/E3* group, and protein intake in the *APOE3/E3* group was approximately 3% lower in total energy (~ 5 g) than in the *APOE2/E3* group [323]. MacKay et al. showed that plant sterol intervention in mildly hypercholesterolemic adults was associated with greater LDL-c reductions in *APOE* ε4 carriers than in ε3 carriers. This result supports that *APOE* may be not only a determinant of cardiovascular risk but also a determinant of nutrigenetic response [324]. In another study, total and LDL-c levels were found to be lower in individuals with the *APOE ε2* genotype compared to those with the ε3 and ε4 genotypes. Plasma saturated fatty acid ratios were higher in ε2 allele carriers compared to the ε4 group, while omega-6 fatty acids were lower. Adrenic acid and omega-6 docosapentaenoic acid were high in ε2 carriers, while long-chain

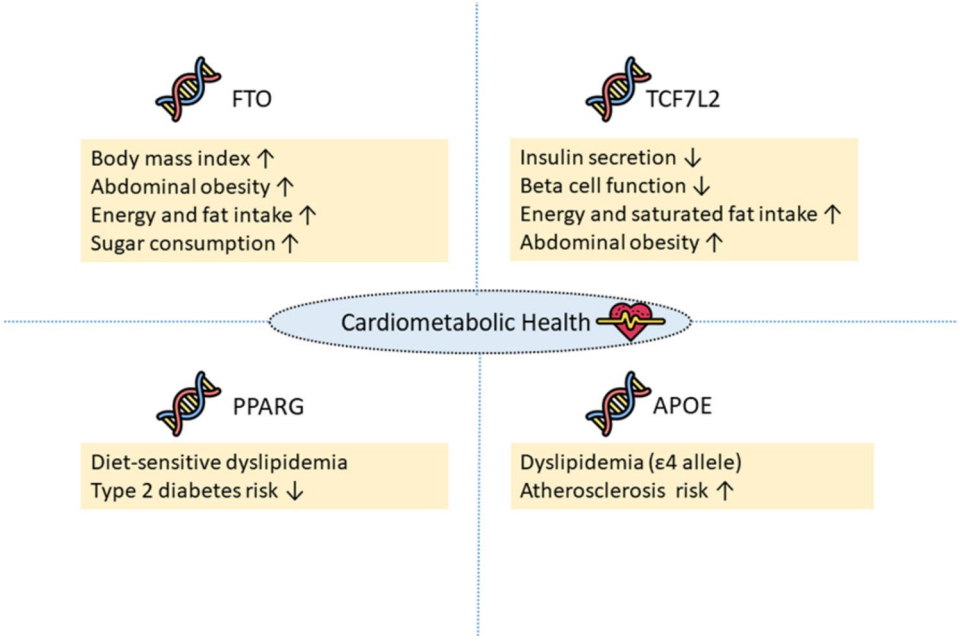


Fig. 3 Genetic variations in cardiometabolic health

omega-3 PUFAs (24:5 n-3 and 24:6 n-3) were low [325]. In this context, developing *APOE* genotype-specific nutritional strategies carries significant potential in the prevention and management of CMD within the scope of PN.

The *TCF7L2* gene encodes a transcription factor that plays a role in Wnt signaling pathways and has decisive effects particularly on glucose metabolism. Some SNP of this gene have been strongly associated with CMD, particularly T2DM. TCF7L2 variants have been shown to negatively affect insulin secretion and beta cell function, leading to impaired glucose tolerance [326–329]. It is reported that TCF7L2 genotypes affect the metabolic responses to dietary macronutrients. It was determined that body weight loss and improvements in IS in TCF7L2 rs7903146 variant T allele carriers were more limited in response to dietary intervention compared to other alleles [330]. In addition, it has been reported that while diets rich in fiber are associated with a decrease in HbA1c levels in participants with the CC and CT genotypes, this protective effect is not observed in individuals with the TCF7L2 rs7903146 TT genotype. This suggests that the effect of fiber intake on the risk of T2DM varies depending on the genotype [329]. It was shown that waist circumference values of rs7903146 TT genotype carriers were higher than other genotypes. This genotype could be associated with abdominal obesity. In addition, it was observed that total energy and saturated fatty acid intakes of TT genotype carriers were significantly higher. This situation indicates that the combination of genetic predisposition and negative nutritional behaviors may increase the risk of CMD [331].

The *PPARγ* gene encodes a nuclear transcription factor that plays a role in the regulation of adipogenesis, IS, and glucose metabolism. The Pro12Ala variant, one of the most common and well-characterized SNP in the *PPARγ* gene, is the focus of nutrigenomic studies due to its association with CMD. AlSaleh et al. showed that plasma total cholesterol and LDL-c levels were significantly higher in Ala12 carriers as the ratio of dietary PUFA to saturated fatty acids decreased. Moreover, significant decreases in plasma total cholesterol and TG levels were observed in Ala12 carriers as the ratio of dietary PUFA to saturated fatty acids increased. This suggests that the Pro12Ala polymorphism may alter the metabolic response to dietary fatty acids [332]. In addition, a significant association was found between Ala12 allele carriers and fasting insulin levels, HOMA-IR and clinical IR in children with high total cholesterol or LDL-c levels. This result suggests that this variant may contribute to metabolic dysfunction even at an early age [333]. On the other hand, a meta-analysis evaluating data from 73 studies found that Ala12 carriers had a statistically significant reduced risk of T2DM. This result is associated with the regulatory role of the *PPARγ* gene on IS and glucose homeostasis [334]. These gene-diet interactions enable the development of PN strategies specific to the PPARγ genotype and highlight the importance of considering genetic factors in the prevention and treatment of CMD (Fig. 3). However, due to bidirectional effects, cardiometabolic risk profiles should be evaluated individually and multidimensionally.

Clinical translation of omics-guided personalized nutrition: opportunities and limitations

Analysis of multilayered biological data sets such as genomics, transcriptomics, proteomics, and metabolomics within the scope of multiomics research plays an important role in understanding health and disease mechanisms. This holistic approach provides the opportunity to deeply understand the molecular mechanisms of diseases, to develop early diagnosis, personalized treatment, and preventive health strategies. However, this holistic approach also raises important ethical, social and economic issues [11, 25].

Although studies supporting the relationship between cardiometabolic risk, nutritional response, and multiomic components are increasing, the routine use of omics-based personalized nutrition in clinical practice remains limited. One of the most important reasons for this is that standard analysis methods and clinically validated biomarkers have not been sufficiently developed across different omics components [335, 336]. Although numerous biomarkers related to cardiometabolic diseases have been identified in the fields of genomics, metabolomics, lipidomics, and microbiomics, differences in how samples are collected, which analytical techniques are used, and how data are evaluated make it difficult to compare studies and interpret results clinically [336–338]. The gut microbiome, in particular, is influenced by many factors and shows significant differences between individuals and populations. This makes it difficult to apply the data obtained clinically to everyone [339, 340].

Furthermore, metabolomic methods enable objective assessment of what an individual consumes and the extent to which they adhere to their diet, thanks to biomarkers specific to certain foods [279, 341]. Instead of evaluating genomic data alone, analyzing it together with metabolomic, proteomic, and microbiome data will enable more accurate interpretation and appropriate interventions [342].

From an ethical perspective, phenotyping and analysis of personal health data in multiomic studies bring with them important ethical issues. Confidentiality of personal data, transparency of informed consent processes and equal access to healthcare are issues that need to be carefully addressed in this area. When genomic, epigenomic, microbiome and metabolomic data are collected, individual disease risk profiles such as T2DM, obesity and hyperlipidemia can emerge. Potential harms such as misuse of such sensitive data by insurance companies and employment problems by employers can create stress in the individual [11]. On the other hand, when using web-based or cloud-based software for the storage and analysis of study data using patient information, data privacy and institutional compliance requirements should be considered. In such cases, institutional platforms that comply with legal regulations should be preferred [343].

From an economic perspective, multiomics analyses are mostly costly [344]. Analyzing large amounts of omics data simultaneously, ensuring comparisons, and conducting studies that require repeated measurements are expensive and have high infrastructure requirements [345]. Additionally, evidence regarding the long-term effects of the results obtained is still limited.

However, it is known that the long-term treatment costs of chronic diseases such as obesity, diabetes, and heart disease are quite high. Early prevention with personalized interventions can provide long-term cost savings for health systems [346]. On the other hand, omic datas are large, complex and multi-layered, so there are difficulties in transferring to clinical applications. Omic data will only become more widely available in clinical applications for health professionals and patients when it is simplified and transformed into meaningful health measures [74]. Although personalized nutrition approaches based on omic data have been shown to improve certain outcomes, the superiority of these approaches over traditional nutrition counseling in terms of preventing disease development in the long term, achieving sustainable behavioral change, and cost-effectiveness has not been clearly established. Furthermore, since individuals respond differently to these interventions, it is important to determine which approach will be more effective for which individual [347, 348].

From a social inequality perspective, it has been shown that metabolic syndrome is associated with differences in microbiome, inflammation and metabolite patterns in individuals with low socioeconomic status. It has also been emphasized that metabolic risk increases in groups with low nutritional quality and low microbiome diversity [349]. It has been shown that CMD such as obesity, hypertension, and T2DM have a higher prevalence in low-income groups with food insecurity. This suggests that both the disease burden is high and access to PN and health services is limited in low socioeconomic groups [350]. Therefore, health inequalities may deepen even further for individuals who cannot access multiomics analyses and professional support for interpreting these analyses.

Conclusion

The multiomic approach enables the transition from "one-size-fits-all" population average strategies to data-driven, dynamic care models based on individual biology by simultaneously revealing the biological diversity of CMD across layers ranging from genomics to the microbiome. Supported by longitudinal and N-of-1 designs rather than static measurements, this framework enables sharper risk classification and targeted

interventions for obesity, T2DM, and CVD through epigenetic reversibility, proteomic/lipidomic early warning panels, and the modulatability of microbiota-metabolite networks. Nutrigenomic interactions (e.g., *FTO*, *APOE*, *TCF7L2*, *PPARγ*) with dietary components, combined with metabotyping and nutrimetabolomic biomarkers, strengthens the scientific basis for PN protocols that predict postprandial glycemic/lipid response and monitor compliance with objective indicators.

Future research should focus on collecting multi-omic data in multi-ethnic and multi-center cohorts that reflect ethnic and geographic diversity, as this is critical for increasing the generalizability of current findings. To accelerate the transition to clinical application, clinically validated biomarker panels must be developed, and artificial intelligence-supported decision support systems must integrate omic data with lifestyle and environmental factors. Combining real-time digital biomarkers obtained from wearable devices with molecular data will enable the dynamic updating of personalized nutrition and treatment approaches. However, the sustainability and inclusivity of these advances depend on the development of application frameworks that uphold ethical principles, ensure data privacy, and support equitable access.

Abbreviations

BCAA	Branched-chain fatty acids
BMI	Body mass index
CMG	Continuous glucose monitoring
CMD	Cardiometabolic disease
CVD	Cardiovascular disease
DNA	Deoxyribonucleic acid
GWAS	Genome-wide association study
HDAC	Histone deacetylase
HDL-c	HDL cholesterol
HMP	Human Microbiome Project
HPG	Human Genome Project
IR	Insulin resistant
IS	Insulin sensitivity
ISNN	International Society of Nutrigenetics/Nutrigenomics
LC-MS/MS	Liquid chromatography combined with tandem mass spectrometry
LDL-c	LDL cholesterol
LPS	Lipopolysaccharide
MD	Mediterranean diet
MS	Mass spectrometry
MUFA	Monounsaturated fatty acid
NGS	Next generation sequencing
NIH	National Institutes of Health
NMR	Nuclear magnetic resonance
PN	Personalized nutrition
PUFA	Polyunsaturated fatty acid
RNA-seq	RNA sequencing
SCFA	Short-chain fatty acid
SNP	Single nucleotide polymorphism
SSPG	Steady-state plasma glucose
ST	Spatial transcriptomics
T2DM	Type 2 diabetes mellitus
TG	Triglyceride
TMAO	Trimethylamine N-oxide
UFA	Unsaturated fatty acids

Acknowledgements
Not applicable.

Author contributions
Conceived and wrote the review: Duygu Ağagündüz, Elif Çelik, Emine Koçyiğit, Feray Gençer Bingöl, Cansu Karaçolak, Özge Cemali, Martina Simonelli, Raffaele Capasso. Prepared the figures: Elif Çelik, Feray Gençer Bingöl. All authors reviewed the manuscript.

Funding
This research received no external funding.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing of interest.

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Received: 19 November 2025 / Accepted: 3 February 2026
Published online: 09 February 2026

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