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Microbiome and Metabolomics in Obesity: Advances in Understanding and Interventions Across the Lifespan

Ioanna Panagiota Kalafati[1,2] | David Krongauz[3,4] | Alice Bosco[5] | Antonio Noto[6] | Cristina Piras[6] | Maria Kafyra[1] | Angelica Dessì[5] | Matteo Mauri[5] | Luigi Atzori[6] | Adina Weinberger[3,4] | Vassilios Fanos[5] | George V. Dedoussis[1] | on behalf of the BETTER4U consortium

[1]Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University of Athens, Athens, Greece | [2]Department of Nutrition and Dietetics, School of Physical Education, Sport Science and Dietetics, University of Thessaly, Trikala, Greece | [3]Department of Computer Science and Applied Mathematics, Weizmann Institute of Science, Rehovot, Israel | [4]Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel | [5]Department of Surgical Sciences, University of Cagliari, Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy | [6]Department of Biomedical Sciences, Metabolomic Laboratory, University of Cagliari, Cittadella Universitaria di Monserrato, Monserrato, Cagliari, Italy

Correspondence: Ioanna Panagiota Kalafati (kalafati@hua.gr)

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ABSTRACT

Obesity arises from intertwined and reciprocal diet-microbiome-host pathways that reshape energy balance, insulin sensitivity, and inflammation. This review synthesizes mechanistic links between microbial functions and metabolic control, charts lifestyle-related lifecourse dynamics from birth to older age, examines how GLP-1-based therapies may perturb gut ecology and metabolite output and surveys AI/ML frameworks for multi-omics integration. Plant-based, fiber-rich dietary patterns generally enrich saccharolytic guilds, boost SCFAs production, and modulate bile acid signaling, whereas Westernized patterns favor bile-tolerant, amino acid-fermenting consortia and proinflammatory metabolites. Preclinical data suggest that incretin-based therapies remodel the microbiome-metabolome axis, but human causal mediation remains unproven and observed changes may partly reflect weight loss or metabolic improvement. Function-centered metrics outperform phylum-level ratios for translation. Harmonized longitudinal cohorts and explainable ML-derived microbial and metabolomic signatures are now pivotal to identify responder subtypes and actionable microbe-metabolite targets, enabling precision nutrition alongside pharmacotherapy across the lifespan.

1 | Introduction

The global burden of obesity continues to rise at an alarming pace. It is estimated that 890 million adults were living with obesity in 2022, meaning roughly one in eight people worldwide now meet clinical criteria for the disease [1, 2]. This trend is projected to accelerate through the remainder of the decade, underscoring the need to move beyond a simple energy-balance framework and toward a deeper understanding of the biological systems that govern body-weight regulation.

Abbreviations: ACTH, adrenocorticotropic hormone; ARC, arcuate nucleus; BAs, bile acids; BAT, brown adipose tissue; BBB, blood–brain barrier; BCAAs, branched-chain amino acids; BMI, body mass index; CART, cocaine- and amphetamine-regulated transcript; CCK, cholecystokinin; CNS, central nervous system; EECs, enteroendocrine cells; ENS, enteric nervous system; fMRI, functional magnetic resonance imaging; FMT, fecal microbiota transplantation; GABA, gamma-aminobutyric acid; GBA, gut-brain axis; GLP-1, glucagon-like peptide-1; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HPA, hypothalamic–pituitary–adrenal axis; LPS, lipopolysaccharide; MWAS, metagenome-wide association studies; MS, mass spectrometry; NMR, nuclear magnetic resonance; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; POMC, proopiomelanocortin; PVN, paraventricular nucleus; PYY, peptide YY; SCFAs, short-chain fatty acids; SVM, support vector machine.

Studies using germ-free mice provided early evidence that the gut microbiome can modulate host adiposity. In a landmark gnotobiotic experiment, fecal microbiota from human twin pairs discordant for obesity were transplanted into germ-free mice, resulting in the transmission of the donor's metabolic phenotype. Mice receiving microbiota from obese donors gained more weight and accumulated greater fat mass compared to those colonized with microbiota from their lean co-twins, implicating microbe-derived functions in energy harvest and storage [3]. In humans, a controlled dietary crossover study demonstrated that switching from a plant-based to an animal-based diet for just 5 days was sufficient to reshape the taxonomic composition, gene expression, and metabolite output of the gut microbiome [4]. These rapid diet-induced changes highlight the remarkable plasticity of the gut ecosystem and its responsiveness to environmental inputs. Together, these findings established the microbiome as a dynamic regulator of host metabolism and supported earlier conceptual models linking nutrient sensing, enteroendocrine signaling, and the gut-brain axis to energy balance and appetite control [5, 6].

A central unresolved question is whether gut microbiome dysbiosis is a driver of obesity, a consequence of the obese state, or both. Current evidence supports a bidirectional model. Experimental studies in germ-free and microbiota-transplantation systems indicate that obesity-associated microbial communities can contribute to increased adiposity and impaired metabolic regulation, supporting a causal role for the microbiome in obesity development [3, 6]. At the same time, the gut microbiome is highly responsive to host diet and physiological state, and obesity-related changes in nutrient exposure, inflammation, and gut environment can themselves reshape microbial composition [4, 7]. Thus, rather than a simple cause-versus-consequence relationship, obesity is increasingly viewed as involving a reciprocal host-microbiome interaction in which microbial dysbiosis may both promote and reflect disease progression [7].

Metabolomics offers functional resolution that complements taxonomic surveys by capturing the chemical language through which microbes communicate with the host. Short-chain fatty acids, secondary bile acids, branched-chain amino acids, indoles, and phenolic metabolites form an extended endocrine network that can influence appetite, insulin sensitivity, and low-grade inflammation [8]. Integrated microbiome-metabolome analyses therefore reveal mechanisms that remain invisible when each layer is examined in isolation [9, 10].

Microbiome-metabolome interactions are dynamic and undergo nonlinear transitions across the human lifespan. Multi-omics profiling of over 1000 European children identified distinct clusters of microbial, epigenomic, proteomic, and metabolomic features associated with differential obesity risk, emphasizing the need for age-specific prevention strategies [11]. In adults, longitudinal data from population-scale cohorts reveal marked shifts in microbial composition and circulating metabolites from adolescence through late adulthood, with key inflection points around midlife [12]. These age-related transitions are accompanied by a decline in beneficial microbial cross-feeding and reduced host-microbe co-metabolism, as shown by both human time-series data and metabolic modeling in aged mice [13]. Together with earlier findings on neonatal colonization patterns [14] these observations underscore the importance of tailoring metabolic interventions to different stages of life.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as liraglutide, semaglutide, and tirzepatide have transformed pharmacotherapy for both diabetes and obesity. A 2025 systematic review covering 38 animal and human studies concluded that GLP-1 RAs consistently reshape gut microbial composition, raise microbiota diversity, and enrich taxa linked to improved metabolic outcomes [15]. Metabolomic profiling in treated subjects further suggests that part of the clinical benefit may derive from shifts in amino acid and bile acid pathways, although causal links remain to be established.

The explosion of high-throughput sequencing and mass-spectrometry data has opened the door for artificial-intelligence and machine-learning frameworks that integrate multiple omics layers. Recent studies demonstrate that multi-omics factor analysis and graph neural networks can identify biomarker panels predicting weight-loss trajectories and drug response more accurately than conventional statistics [16–18]. These tools promise to accelerate the move toward precision nutrition and personalized obesity therapeutics.

This review synthesizes current knowledge on microbiome-metabolome interactions in obesity. We begin with mechanistic links between microbial ecology, metabolite production and host energy balance; trace these interactions from infancy through senescence; evaluate how glucagon-like peptide-1 receptor agonists (GLP-1 RAs) perturb the axis; and survey emerging AI-driven strategies for multi-omics integration. Throughout, we focus on studies that profile the microbiome together with at least one additional omics modality, aiming to outline a path toward precision prevention and treatment of obesity across the lifespan.

2 | Microbiome and Metabolomics in Obesity: Mechanistic Links

2.1 | The Gut Microbiome as a Metabolic Regulator

A central component in metabolic regulation and energy homeostasis involves the gastrointestinal (GI) system. Central to this is the activation of the bidirectional gut-brain axis (GBA), which triggers a cascade of biological events influencing metabolic pathways, macronutrient synthesis and degradation, and inflammatory responses [19, 20]. After meal intake, the subsequent presence of nutrients stimulates secretion of various hormones from endocrine cells located throughout the GI tract. These hormones act on the enteric nervous system (ENS) and, subsequently, on the autonomic and central nervous systems via both endocrine and paracrine signaling from enteroendocrine cells (EECs) to vagal afferents within the GI epithelium. This signaling simultaneously activates metabolic pathways in multiple visceral organs [21, 22]. These neural and hormonal signals project to brain regions including the nucleus tractus solitarius (NTS), which in turn influences the hypothalamus, arcuate nucleus (ARC), and paraventricular nucleus (PVN), effectively integrating peripheral and central

metabolism-regulatory mechanisms aligned with current food availability [23].

A first example concerns the anorexigenic hormone cholecystokinin (CCK), secreted by the intestine. CCK levels rise postprandially and act as a satiety signal to reduce further food intake. CCK exerts effects both directly, via central receptors, and indirectly, by activating vagal afferents that relay signals to the NTS. In addition to inducing satiety, CCK suppresses hepatic glucose production in the postprandial state [19, 24]. Another key pillar is the glucagon-like peptide-1 (GLP-1), which is released early after nutrient ingestion and is hence a major anorexigenic hormone. GLP-1 binds to the receptors on the vagal afferent neurons that traverse the GI tract, causing satiety by mediating glycemic responses [19, 24]. Additionally, although the exact role of peptide YY (PYY) in GBA signaling remains to be fully elucidated, current evidence suggests that PYY produced in the intestine leads to long-term satiety by activating the anorexigenic pro-opiomelanocortin (POMC) and inhibiting neuropeptide Y (NPY) via vagal afferents [19, 24]. Interestingly, the stimulation mechanisms for hormonal secretion can be quite different, depending on which macronutrients are being metabolized. For example, CCK or GLP-1 release induced by glucose by intestinal cells is different from the one elicited by long-chain fatty acids (LCFAs) [19]. Bearing that in mind, mixed macronutrients are present in most meals, and we can expect these pathways to function in tandem to induce satiety and inhibit further intake.

It is worth noting that the well-known directionality of signaling between microbial or host-derived metabolites and enteroendocrine hormone secretion is becoming increasingly elucidated based on current findings. The majority of the microbial metabolites' activity occurs upstream of EECs, where it can affect the release of hormones, including GLP-1 and PYY. Dietary fibers are fermented by intestinal bacteria into short-chain fatty acids (SCFAs), which stimulate EECs directly by acting upon G-protein-coupled receptors such as free fatty acid receptor 2 (FFAR2) and FFAR3 to enhance the secretion of both GLP-1 and PYY [25, 26]. Concurrent with this, the gut microbiota transforms bile acids (BAs) to secondary bile acids which act as crucial signaling molecules that integrate microbial activity into host endocrine responses. A direct mechanistic connection between secondary bile acids and GLP-1 secretion has recently been shown to be mediated through the activation of the G-protein-coupled bile acid receptor 1 (TGR5), which is expressed on enteroendocrine L-cells. Inducers of TGR5 signaling include secondary bile acids including lithocholic acid (LCA) and deoxycholic acid (DCA), which are potent agonists of this pathway by activating the intracellular cyclic AMP (cAMP) signaling cascade, resulting in stimulating GLP-1 secretion [27, 28]. Emerging evidence would indicate that similar mechanisms may be involved in the release of PYY, though this relationship is less well characterized. Taken together, these results are consistent with a model in which gut microbiota-derived metabolites act as regulators of EEC function, whilst host hormonal outputs act distally through the GBA to regulate appetite, glucose homeostasis and energy balance [29].

Additionally, nutrient stimulation of hormonal secretion is mediated by the chemoreceptors throughout the GI tract that are being dynamically influenced by the gut microbiome. The relationship between host and gut microbiota forms a dynamic environment where nutrient influx shapes the microbiome composition, which in turn affects metabolic and immune pathways [19]. The GBA is affected by many microbiota-dependent processes, and each can influence the other, such as: (i) modulation or production of metabolites such as SCFAs, tryptophan-derived molecules, gamma-aminobutyric acid (GABA), catecholamines and bile acids (BAs), which influence diverse metabolic and physiological pathways; (ii) modulation of serotonin (5-hydroxytryptamine) synthesis from enterochromaffin cells by metabolites such as BAs and SCFAs that activate either the ENS or vagal afferents; (iii) inhibition of the ENS functioning through lipopolysaccharide (LPS) production from Gram-negative gut bacteria; and iv) indirect activation of the hypothalamus-pituitary–adrenal (HPA) axis mediated by microbial metabolites [19, 23].

2.2 | Gut Microbiota-Derived Metabolites and Their Role in Obesity

Metabolite modulation stands at the very core of gut-mediated activation of metabolic signaling pathways. BAs can bind to respective receptors on EECs like TGR5, and in doing so, activation of the transcription factors which regulate GLP-1 production may also be enhanced [30]. Similarly, the fermentation of complex carbohydrates by the microbiome can promote the SCFAs to act on EEC or vagal receptors [31]. Consequently, these interactions modulate glucose metabolism and signal metabolic hormone secretion, including GLP-1 and PYY [24].

More specifically, production of SCFAs is one of the cornerstones on which the gut microbiome-derived metabolites exert their influence in metabolism. Acetate, propionate, and butyrate are the main SCFAs examples, produced from the microbial fermentation of dietary fibers in the colon. They can then enact endocrine and paracrine functions through their receptor bindings, namely on GPR41 and GPR43 with expression on EECs, vagal afferents, and various peripheral tissues, thus affecting glucose homeostasis, gut hormone release, and inflammatory responses [31]. Propionate, especially, supports hepatic gluconeogenesis alongside regulating appetite, whereas butyrate enhances the gut barrier mechanism, and acetate enters the circulation, crosses the blood–brain barrier, and influences central pathways in energy homeostasis. SCFAs, along with the stimulation of GLP-1 and PYY release, influence appetite and insulin sensitivity [31]. Furthermore, gut bacteria can transform BAs into secondary BAs that interact with several host receptors, including the G protein-coupled bile acid receptor TGR5. These receptors are expressed on EECs, as well as other metabolic tissues, and regulate lipid metabolism, insulin signaling, and energy expenditure. Activation of TGR5 has been shown to increase the transcription of genes responsible for GLP-1 secretion, which, in turn, improves glycemic control and intensifies satiety signaling [30].

Neuroendocrine modulation may be ascribed to the microbiota by the release of neurotransmitters or neuromodulatory compounds. Perhaps most importantly, GABA produced by the *Bifidobacterium* and *Lactobacillus* species crosses the

blood–brain barrier (BBB) and influences central neural circuits that regulate stress, hunger, and energy homeostasis [32]. Besides these functions, through tryptophan degradation, microbes regulate serotonin synthesis in the gut, thereby influencing intestinal motility and feedback to the CNS through vagal and enteric mechanisms [33].

Apart from hormonal and neural control, microbial metabolites are also likely to modulate host metabolism through immune-mediated pathways. LPS from the outer membrane of Gram-negative bacteria are able to access systemic circulation whereas intestinal permeability is increased. These LPS are then recognized by both the immune cells and the ENS, with inflammatory cascades initiated through the release of cytokines as well as signaling through toll-like receptor pathways [34]. This LPS-induced low-grade chronic inflammation increase is believed to be seen in obesity and insulin resistance. In addition, heightened levels of LPS and other pro-inflammatory stimuli are likely to stimulate the HPA axis to produce elevated secretion of a stress hormone called adrenocorticotropic hormone (ACTH). These impacts can be exacerbated by other environmental stressors like high-fat diets or psychological stress, thus deranging the normal body metabolism [34].

More specifically, emerging evidence has identified specific gut microbes and metabolites that are causally associated with obesity risk and metabolic protection. Recent research studies show that the decreased abundance of *Akkermansia muciniphila* has been linked to both obesity and metabolic dysfunction and adiposity, in both animals and humans, whereas restoring *A. muciniphila* levels appears to result in better insulin sensitivity and weight loss [35–37]. Moreover, the presence of SCFAs-producing bacterial genera such as *Faecalibacterium prausnitzii* and certain *Bifidobacterium* species appears to protect against both obesity and inflammation through their ability to produce SCFAs and thus strengthen the gut barrier functions and minimize intestinal endotoxin absorption [38].

Furthermore, gut microbiome controls the production of host serotonin (5-HT) through their ability to metabolize tryptophan and communicate with enterochromaffin cells producing a cascade of reactions [39, 40]. The first effect concerns regulating intestinal motility and hormone release, while also exerting systemic effects on energy storage, glucose homeostasis, and appetite regulation. This obesity-related dysbiosis has been shown to create changes in the serotonin pathways whereas interventions that restore healthy 5-HT production are associated with improved metabolic phenotypes. Additionally, the dysbiotic microbiota produce high amounts of branched-chain amino acids (BCAAs) and other metabolites which come from aromatic amino acids, implicated in insulin resistance and weight gain [41]. On the other hand, a microbiota enriched in SCFAs-producing bacteria and capable of generating secondary bile acids supports TGR5 signaling, enhancing energy expenditure, improving glucose tolerance, and promoting reduced body fat [42]. Overall, current research shows that gut microbes and their derived metabolites determine how body metabolism functions through their effects on hormonal systems, brain functions and immune responses which create different levels of obesity protection and risk.

2.3 | Methodological Differences in Microbiome and Metabolomics Studies

Research in microbiome and metabolomics constitutes two distinct but interrelated and complementary views of the biological processes underlying obesity, the methodological divergence of which needs to be meticulously considered. Findings in both fields are tied very intimately to one another via metabolite generation and determination, such as SCFAs and other biochemical compounds. Its functional traits to produce these metabolites provide the direct impact on metabolomic profiles measured in biofluids or tissues [43]. Recent studies also demonstrate that specific metabolite ratios in circulation reflect obesity-related metabolic disturbances, thus providing reasonable ground for the need to link microbial activity directly to host metabolic phenotypes and highlight the value of integrating metabolomics with microbiome analyses [44]. However, this connection pertains to significant differences, given that microbiome studies look toward the microbial composition and its dependencies with gene expression, whereas metabolomics embraces the chemical signatures produced by both the microbiome and the host organism [43, 45].

Metabolic profiles disrupted by obesity or henceforth weight gain depict altered metabolite levels in some of the major biochemical pathways. These major biochemical pathways would usually implicate BCAAs, SCFAs metabolism, and general disruption to pathways mediating the onset and resolution phases of inflammation, immune regulation, and mitochondrial function [46]. Obesity, therefore, drives a reciprocal cascade of metabolic disturbances, whereby increases in certain metabolites perturb the presence of several others [46, 47]. This very complex network of interactions is the fundamental reason for the value and the difficulty in using both microbiome and metabolomics data to untangle the various layers of obesity-related pathophysiology [45, 47].

Although metabolomics can unravel such intricacies of biochemical shifts, microbiome research addresses the very changes that relate to the structure and functional mechanisms of the gut microbial ecosystem. Though the common ends of both aim for describing biological processes, the broad methodology of conducting microbiome and metabolomics studies is far different—from sample processing and data generation, to their analysis and interpretation [48]. In microbiome studies, sample handling requires the immediate freezing of stool samples to preserve the integrity of microbial DNA and RNA. On the other hand, metabolomics requires that biofluids or tissue extracts be rapidly stabilized to minimize metabolite degradation [43, 48]. Analytical techniques are also different with microbiome studies primarily using 16S rRNA gene sequencing to characterize bacterial taxa or whole-metagenome sequencing to characterize functional gene content. Metabolomics employs mass spectrometry (MS) or nuclear magnetic resonance (NMR) to detect and quantify metabolites [43].

Data structures between the two approaches also vary with microbiome data being sparse and compositional, whereas metabolomics data often high-dimensional and skewed [17]. Furthermore, biological classification can be complicated because many metabolites can be produced by varying microbial

species or they can be influenced by host genetics, diet, medications, or other environmental factors [45, 49]. These factors complicate the process of attributing cause from specific microbial taxa to metabolic outputs. Although various integration schemes have been proposed, including correlation matrices, multivariate regression, and machine learning models, very few associations have indeed been reproduced in different cohorts [46, 49]. Further complexity arises from microbiome and metabolomics profiles being highly sensitive to lifestyle, geographic, and demographic factors. Although this responsiveness reflects biology, it can generate variability that limits cross-study comparability [49]. Hence, the need for harmonized protocols in sample collection, processing, and analysis becomes all the more urgent. In the absence of such standardization, studies will find it hard to reproduce one another's findings or translate them into clinical or public health practice [45, 48].

3 | Microbiome -Metabolome Interactions Across the Lifespan

The symbiotic relationship between the host and gut microbiota ensures the proper development of the human metabolic system [49, 50]. Besides, the metabolome, the complete set of small-molecule chemicals found within a biological sample offers a dynamic representation of metabolic activities influenced by both host and microbial processes. Understanding the interplay between the microbiome and metabolome at various stages of life offers valuable insights into developmental biology, disease progression, and potential therapeutic interventions. Key representative bacterial taxa and their metabolites, together with their directionality in obesity across the lifespan, are summarized in Table 1, whereas Figure 1 illustrates how lifestyle drivers across the lifespan shape gut microbial functions and metabolites and link to clinical outcomes.

3.1 | Early Life: Birth and Infancy

The infant gut microbiome is highly dynamic and shaped by delivery mode, maternal microbiota, antibiotics, feeding practices, maternal metabolic status, the hospital environment, and other early exposures [51]. The early postnatal period represents a neonatal “window of opportunity” during which microbial signals influence long-term immune and metabolic homeostasis [14]. Vaginally delivered infants initially acquire communities resembling the maternal vaginal microbiota, whereas cesarean-delivered infants show skin-associated profiles and reduced transmission of beneficial taxa such as Bifidobacterium and Bacteroides. Notably, Bacteroides species are strong modulators of early immune development, contributing to regulatory T-cell expansion and tolerogenic mucosal priming [51]; both inadequate colonization and aberrant timing of their establishment during the neonatal “window of opportunity” have been proposed to affect later immune calibration and susceptibility to allergic and metabolic disease, although the precise developmental thresholds remain an active area of investigation. Because C-section rates remain high worldwide and are projected to increase further, this disruption of vertical transmission is clinically relevant [52, 53]. Cesarean-associated dysbiosis is linked to lower microbial diversity, delayed colonization, altered SCFAs, BAs, and amino acid metabolism, and increased pro-inflammatory metabolites, with potential consequences for gut barrier maturation, immune development, and later obesity risk [14, 54–56]. Although some deficits normalize over time, others may persist, especially with formula feeding, antibiotic exposure, and limited environmental microbial diversity [57, 58].

Once born, the newborn's nutrition becomes tremendously crucial. Breast milk is much more than just food for the infant. Before the 2000s, it was widely believed that breast milk was free from bacterial colonization, which was considered one of the advantages of breastfeeding [59]. However, in 2003, the presence of bacteria in breast milk was first described. Today, it is known that breast milk contains a significant amount of bacteria, a microbiota composed of 50 genera and 200 species called MOM (milk-oriented microbiota), which plays a crucial and multifaceted role in shaping the neonatal microbiome and metabolome during the earliest stages of life. Human breast milk is not only a source of essential nutrients but also acts as a bioactive fluid rich in immunological and microbial modulators [60–62].

One of the key components of breast milk is human milk oligosaccharides (HMOs). These complex carbohydrates are indigestible by the infant but selectively utilized by beneficial gut bacteria, particularly *Bifidobacterium* species. This selective fermentation fosters a microbiome dominated by health-promoting bacteria, which supports immune maturation, gut barrier integrity, and protection against pathogens [63].

From a metabolomic perspective, the microbial fermentation of HMOs leads to the production of SCFAs such as acetate and lactate. These metabolites have systemic effects, including anti-inflammatory properties, energy supplements to colonocytes, and modulation of glucose and lipid metabolism [64, 65]. Furthermore, breast milk contains a spectrum of bioactive lipids, amino acids, cytokines, and maternal microbes, all of which contribute to a personalized metabolic and microbial environment in the infant [66]. These interactions help program the infant's metabolic pathways and immune responses, with long-term implications for disease susceptibility, such as allergies, obesity, and autoimmune conditions [67].

Studies have shown that breastfed infants exhibit distinct fecal and urinary metabolomic profiles compared to formula-fed infants, reflecting the unique biochemical inputs of human milk and the associated microbial activity [56, 68, 69]. These profiles often include the absence or lower levels of potentially harmful metabolites (referred to as alien metabolites, which are present only in formula milk) and higher concentrations of anti-inflammatory and neuroprotective compounds. In summary, breastfeeding acts as a natural modulator of both microbiome and metabolome, promoting early-life homeostasis and potentially reducing the risk of metabolic and immunological diseases later in life [70].

3.2 | Childhood and Adolescence

Childhood and adolescence represent critical periods of physiological, immunological, and neurological development, during which microbiome and metabolome undergo dynamic changes.

TABLE 1 | Key gut bacterial taxa, their metabolites and directionality in obesity across the lifespan.

Taxon	Metabolites	Life stage	Trend in obesity	Functions	References
Bifidobacterium spp.	Acetate, lactate; GABA	Infancy	↓	Human milk oligosaccharides utilization; immune training; barrier support; neuroendocrine signaling	73,84
Bacteroides spp.	SCFAs; BAs-related metabolites	Infancy	↓	Immune tolerance programming; bile acid/SCFAs metabolism	51
Akkermansia muciniphila	SCFAs	Childhood–adulthood	↓	Mucus layer maintenance; barrier integrity; metabolic inflammation	84,94
Faecalibacterium spp.	Butyrate	Childhood–older age	↓	SCFAs production; gut barrier; anti-inflammatory signaling	84,94
Roseburia spp.	Butyrate	Childhood–older age	↓	SCFAs production; gut barrier; anti-inflammatory signaling	84,94
Anaerobutyricum spp.	Butyrate	Childhood–older age	↓	SCFAs production; gut barrier; anti-inflammatory signaling	84
Bacteroides finegoldii	TMA/TMAO	Adulthood	↑	Hepatic flavin monooxygenase 3 axis; vascular and renal risk markers	98
Bacteroides uniformis	TMA/TMAO	Adulthood	↑	Hepatic flavin monooxygenase 3 axis; vascular and renal risk markers	98

Note: Genus-level groups are indicated as Genus spp.; species-level taxa are indicated by binomial names.
Abbreviations: BAs: bile acids; GABA: gamma-aminobutyric acid; SCFAs: short-chain fatty acids; spp.: species, indicating multiple species within the same genus; TMA: trimethylamine; TMAO: trimethylamine N-oxide.

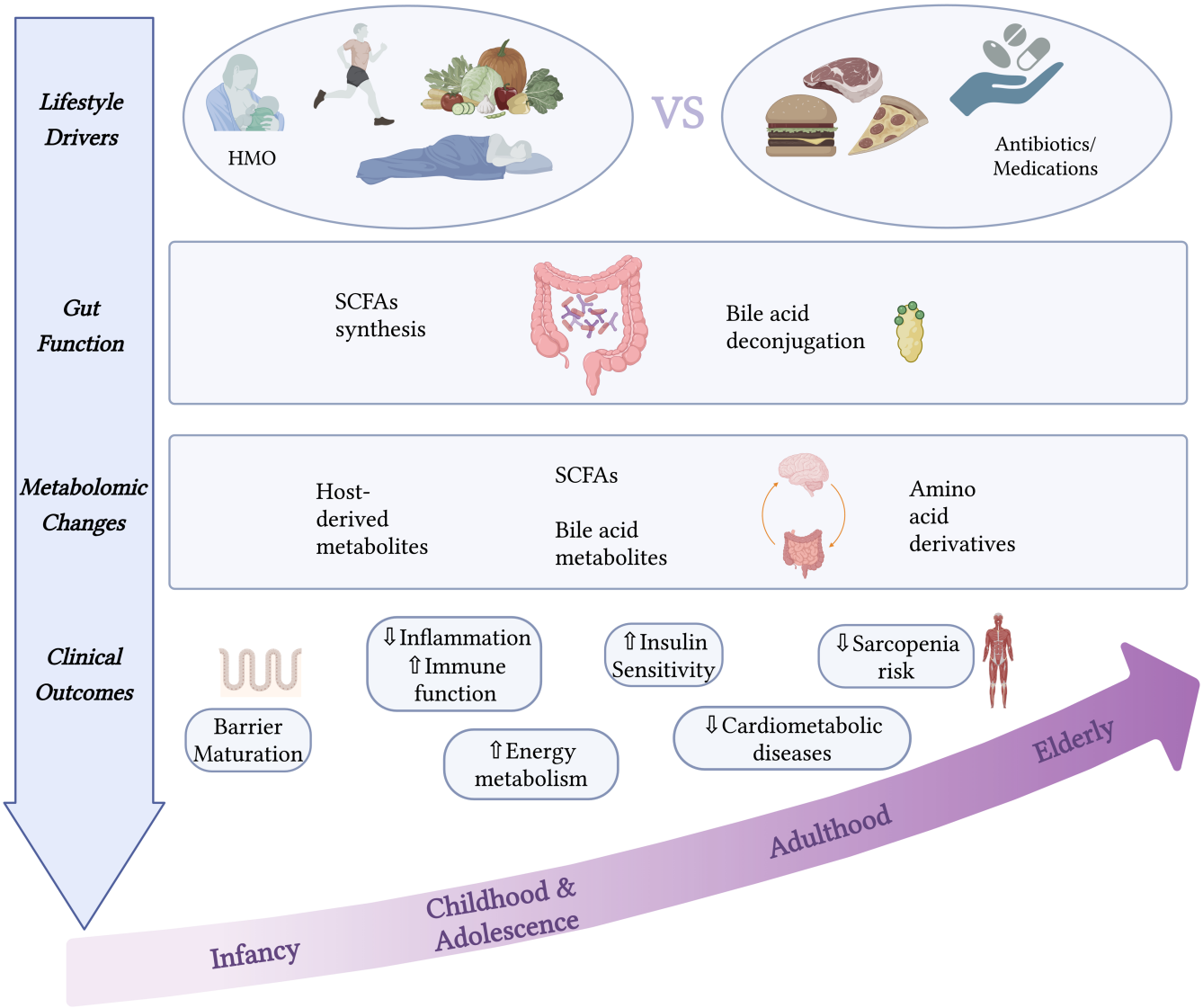

FIGURE 1 | Lifecourse trajectory from lifestyle choices to microbial functions and metabolites; links with clinical outcomes. This figure summarizes how lifestyle drivers across the lifespan shape gut functions, generate metabolomic changes, and how these alterations are linked to various clinical outcomes. Breastfeeding, plant-based dietary patterns, physical activity and good quality of sleep steer functional guilds toward SCFAs synthesis and modulate bile acid deconjugation, influencing downstream metabolite pools. Key metabolite classes highlighted herein include host-derived metabolites, SCFAs, bile acid and amino acid derivatives. These metabolomic shifts have been associated with barrier maturation and improvements in inflammatory markers, immune function and energy metabolism from early life, with greater insulin sensitivity and lower cardiometabolic disease risk in later stages and reduced sarcopenia risk in elderly individuals. Abbreviations: HMO: Human milk oligosaccharides; SCFAs: Short-chain fatty acids. Created in BioRender. Kalafati, I. (2026) https://BioRender.com/85uzzum.

The interplay between these two systems reflects ongoing maturation and adaptation to environmental, dietary, and hormonal influences.

After initial colonization, the gut microbiome continues to evolve throughout childhood [71]. By about 3 years of age, it becomes more diverse and adult-like, but it remains sensitive to diet, antibiotics, lifestyle, and infections [72]. During this phase, *Firmicutes* and *Bacteroidetes* predominate. Beneficial genera such as *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Roseburia* contribute to health maintenance [73–75]. As the microbiome matures, it shapes the host metabolome by producing bioactive molecules such as:

- SCFAs, including acetate, propionate, and butyrate, play a crucial role in supporting gut integrity, regulating the immune system, and facilitating energy metabolism [76].
- Amino acid derivatives, such as tryptophan metabolites (such as indoles and kynurenines), influence gut-brain signaling [77].
- Bile acid metabolites facilitate lipid digestion and regulate metabolic and immune functions [78].

The urinary and fecal metabolomic profiles of children reflect these changes, showing increasing complexity and alignment with adult patterns as dietary variety expands [79].

The onset of puberty introduces significant hormonal changes, including surges in sex steroids (estrogen, testosterone), which influence both the host and the microbial environment [80]. These hormones can alter the composition of the gut microbiota (as an example increasing *Clostridia* and *Bacteroides*) and influence the production of microbial metabolites that may impact mood, metabolism, and inflammation [81].

Moreover, adolescent behaviors such as dietary choices, sleep patterns, and physical activity further shape the microbiome–metabolome interface. For example, diets high in sugar and fat may lead to dysbiosis and the production of pro-inflammatory metabolites, whereas fiber-rich diets support SCFAs production and microbial diversity [4, 82].

The childhood and adolescent periods are marked by rapid and dynamic changes in both the microbiome and metabolome, shaped by environmental exposures, lifestyle factors, and physiological development. These systems interact closely to support growth, immune function, and neurodevelopment. Significantly, perturbations during these windows of plasticity may predispose individuals to chronic diseases later in life, underscoring the value of early-life interventions to support microbial and metabolic health [83]. Among these conditions, pediatric obesity has emerged as a particularly relevant example of microbiome-metabolome dysregulation. It is commonly associated with lower microbial diversity, reduced abundance of taxa involved in mucin turnover and butyrate production, and enrichment of pathways consistent with increased energy harvest and low-grade inflammation [84]. Across studies, one of the more reproducible findings is the depletion of *A. muciniphila* and several butyrate-producing genera, such as *Faecalibacterium* and *Roseburia*, together with shifts in carbohydrate and amino acid related metabolic pathways. At the metabolite level, pediatric obesity has also been associated with altered SCFAs profiles, bile acid pools, and aromatic amino acid metabolites, suggesting broader disturbances in microbial fermentation and host metabolic regulation.

3.3 | Adulthood (25–65 Years)

Adulthood is often characterized as a period of microbiome stability, during which microbial communities reach a relatively stable and homeostatic state in healthy individuals [85]. However, this stability is dynamically sensitive to lifestyle, environmental exposures, and host physiological changes [86]. The adult metabolome, shaped mainly by microbial activity, reflects these interactions and serves as a functional readout of both microbial and host metabolism [9]. In adults, the gut microbiome exhibits high taxonomic diversity and functional redundancy, providing resilience against perturbations. The dominant bacterial phyla include *Firmicutes* (commonly reported genera: *Faecalibacterium*, *Clostridium*, *Lactobacillus*), *Bacteroidetes* (commonly reported genera: *Bacteroides*, *Prevotella)*, *Actinobacteria* (commonly reported genera: *Bifidobacterium)*, and *Proteobacteria* (in smaller proportions under healthy conditions) [87]. This microbial ecosystem contributes to critical physiological processes, including fermentation of dietary fibers into SCFAs like acetate, propionate, and butyrate, vitamin biosynthesis (B-vitamins, vitamin K), regulation of bile acid metabolism and modulation of host immune responses, and maintenance of gut barrier integrity. During adulthood, the gut-brain axis becomes particularly relevant, as microbial products can influence mood, stress responsiveness, and cognitive function by producing neurotransmitter precursors and bioactive metabolites, including GABA and serotonin-related compounds derived from tryptophan metabolism. In parallel, meta-analytic studies integrating multi-country datasets suggest that obesity is consistently associated with reduced overall microbial diversity and depletion of taxa involved in barrier maintenance and SCFAs production, although specific taxonomic associations may vary across populations and datasets [88].

Regarding the adult metabolome, profiling of fecal, plasma, and urinary samples reveals biomarkers associated with dietary patterns, inflammation, and disease risk, offering opportunities for personalized health assessment [48]. Microbial and host interactions produce a complex mixture of host-derived metabolites (such as hormones, amino acids, and lipids), microbial metabolites (such as SCFAs, indoles, and phenolic compounds), and co-metabolites (produced through shared pathways between the host and microbes) [89]. Again, the presence of SCFAs may be related to maintaining gut health, influencing energy homeostasis, and having systemic anti-inflammatory effects. Tryptophan derivatives are shown to influence the central nervous system, immune responses, and intestinal homeostasis [90]. However, despite general stability, the adult microbiome-metabolome axis remains highly plastic, responding to:

a. diet: a high-fiber, plant-based diet promotes beneficial metabolic profiles, whereas Western diets (high fat, high sugar) are associated with dysbiosis, increased endotoxin production, and inflammatory metabolites [67];

b. antibiotics and medications can induce transient or long-term alterations in microbial diversity and metabolite output [91];

c. physical activity is associated with increased microbial diversity and beneficial metabolite production, including higher levels of butyrate and anti-inflammatory markers [92];

d. chronic stress and disrupted sleep patterns can alter microbial composition and reduce microbial metabolite diversity, particularly those affecting mood and immune responses [93].

3.4 | Aging and Obesity in the Elderly (> 65 Years)

Dysbiosis and metabolic imbalance may contribute to the development of several disorders that become more common with aging [94]. Metabolic diseases, including obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease, have been associated with alterations in gut microbiota composition and reduced production of SCFAs. In addition, increased circulating levels of trimethylamine N-oxide (TMAO) and BCAAs have been linked to insulin resistance and higher cardiovascular risk. However, current evidence suggests that

elevated BCAAs levels may primarily reflect impaired catabolic capacity across multiple tissues rather than act as direct mediators of diabetes risk, a view further supported by bidirectional Mendelian randomization studies [95–97]. Likewise, TMAO levels are strongly influenced by dietary intake and kidney function, which makes causal interpretation more complex. Gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease also show distinct microbiome and metabolome profiles, typically characterized by reduced abundance of butyrate-producing bacteria and increased levels of pro-inflammatory metabolites.

4 | The Role of GLP-1 Receptor Agonists in Microbiome and Metabolomics in Obesity

4.1 | Mechanisms of GLP-1 Agonists in Obesity Treatment

GLP-1 RAs are among the most promising obesity therapies to date due to their combination of central, metabolic and gastrointestinal effects [98]. This class includes liraglutide and semaglutide, which are pure receptor agonists and tirzepatide, which is a dual agonist of the GLP-1 and the glucose-dependent insulinotropic polypeptide (GIP) receptors [99, 100]. Studies with GLP-1 RAs (liraglutide 1.8 mg/3.0 mg vs. placebo) in adults with obesity showed decreased hunger and food cravings, increased satiety and decreased caloric intake during an ad libitum meal [101]. GLP-1 RAs act mainly on the central nervous system (CNS) through anorexigenic and satiety-stimulating actions that affect the hypothalamus, specifically the ARC and PVN [102, 103] as well as areas involved in the reward system, including the insula, orbitofrontal cortex and nucleus accumbens (NA) [102, 103]. Specifically with regard to satiety and the homeostatic regulation of hunger, studies using a mouse model with GLP-1 receptor agonists (liraglutide) showed activation of the GLP-1 receptor in ARC neurons. This results in the inhibition of neuropeptide Y (NPY) and agouti-related peptide (AgRP), which are responsible for orexigenic action, as well as the stimulation of cocaine- and amphetamine-regulated transcript (CART) and proopiomelanocortin (POMC), which are anorexigenic neuropeptides [102]. Additionally, other animal model studies have demonstrated the involvement of the PVN through action on corticotropin-releasing hormone (CRH+) neurons [103]. Given the centrality of the PVN to the hypothalamic–pituitary–adrenal (HPA) axis, this involvement suggests the integration of metabolic and neuroendocrine signals. This integration is potentially responsible for not only homeostatic appetite control but also the response to stressogenic conditions [103]. Regarding the effects of GLP-1 RAs on the reward system, thus on hedonic hunger, studies conducted with functional magnetic resonance imaging (fMRI) have demonstrated reduced activation of the bilateral insula and orbitofrontal cortex in response to food imagery [104, 105]. The anorexigenic effect, especially in the early stages of treatment with GLP-1 RAs is also enhanced by a direct action on the cells of the gastric musculature and enteric nervous system, where it inhibits their motility [101, 106, 107]. This is compounded by the action of GLP-1 RAs on vagal afferents, where they are responsible for pancreatic vagal stimulation that anticipates and increases the efficiency of insulin secretion [108], the detection of mechanical distension and thus the perception of satiety [109] and the delay of gastric emptying that influences the regulation of caloric intake [108]. A further contribution of GLP-1 RAs in counteracting obesity could be explained through stimulation of thermogenesis in brown adipose tissue (BAT). Animal studies have shown that this action occurs through the involvement of the ARC. In fact, stimuli to sympathetic neurons that project to the BAT induce the expression of uncoupling protein 1 (UCP1) deputed to heat production at the mitochondrial level resulting in increased resting energy expenditure, independent of physical activity, thus emerging as a promising preclinical hypothesis [102, 110].

However, a greater efficacy of pure GLP-1 agonists in tackling obesity has been observed with the use of dual agonists, such as tirzepatide, which is responsible for average weight declines of more than 20 percent [99, 100]. This is due to the expression of GIP in numerous metabolically relevant tissues such as pancreas, adipose tissue and gastrointestinal tract but also in the CNS, resulting in synergistic and complementary effects. The impact of this unimolecular dual incretin, obtained from a mixed sequence of GLP-1 and GIP, showed both a more effective reduction of fat mass and a greater antihyperglycemic and insulinotropic action than selective GLP-1 agonists in animal models of obesity and diabetes [111]. In the mouse model, relevant central actions were also observed given the expression of GIP at the hypothalamic level (ARC and PVN) and in the NTS, especially in the context of co-agonism with GLP-1 RAs. Indeed, GIP activation, when concurrent with GLP-1, inhibits orexigenic circuits while amplifying anorexigenic signaling [112]. In the animal model, increased hypothalamic sensitivity to leptin was also found due to an enhanced response of POMC neurons [113] and an action on GABAergic neurons responsible for decreased body weight and food intake [114], attributable to GIP receptor activation, even in the absence of co-agonism with GLP-1.

4.2 | Safety Profile and Durability of Response to GLP-1-Based Therapies

Despite their well-established efficacy in weight reduction, GLP-1 RAs are associated with a range of adverse effects that primarily involve the gastrointestinal system and reflect their mechanisms of action on gastric motility and central appetite pathways [100, 115]. The most frequently reported adverse events with GLP-1 RAs and dual incretin agonists are gastrointestinal, including nausea, diarrhea, vomiting, constipation, and abdominal discomfort. These events are usually transient, mild to moderate in severity, occur predominantly during dose escalation, and tend to decrease over time. Treatment discontinuation due to these adverse events occurs in approximately 4%–7% of participants [100, 115]. An emerging concern, although still under investigation as the available evidence is still inconclusive, relates to severe impairment of gastrointestinal motility. In fact, GLP-1 RAs can delay gastric emptying to levels indicative of gastroparesis, raising concerns about the risk of intestinal obstruction [116].

Hepatobiliary adverse events have also been reported: gallbladder-related disorders, mainly cholelithiasis, were documented more frequently with semaglutide than with placebo (2.6% vs. 1.2%). In contrast, with tirzepatide, no difference

in the incidence of cholelithiasis was observed between the treated and placebo groups, although cholecystitis occurred more frequently among participants receiving tirzepatide [100, 115]. It is important to note, however, that an increased incidence of gallbladder-related events has also been reported in individuals experiencing substantial weight loss with other obesity therapies participants [100, 115, 117]. Concerning pancreatic safety, both semaglutide and dual agonists have reported rare episodes of pancreatitis, with tirzepatide showing comparable results between the treated group and the placebo group. With respect to neoplastic risk, randomized controlled trials (RCT) have not shown differences in cancer incidence between patients treated with GLP-1 receptor agonists or dual agonists (semaglutide or tirzepatide) and those receiving placebo [100, 115]. However, the relatively short duration of most RCT limits the ability to adequately assess long-term oncologic outcomes [116]. At the same time, emerging safety concerns have been raised regarding potential neuropsychiatric effects, including suicidal ideation, as well as ocular complications, particularly diabetic retinopathy. However, current evidence remains inconclusive, and further longitudinal studies are required before specific recommendations can be established for individuals potentially susceptible to these adverse outcomes [116].

An additional issue relates to the possible gradual attenuation of treatment effectiveness over time. In fact, long-term clinical studies have shown that weight loss may plateau rather than continue indefinitely [118, 119]. Specifically, semaglutide treatment induced a progressive reduction in body weight that plateaued after approximately 60 weeks, but this does not reflect a loss of treatment efficacy but the establishment of a new energy balance; indeed weight loss was maintained throughout the 104-week follow-up [118]. Similarly, a comparable trajectory has been reported with tirzepatide, where weight loss progressively declines before stabilizing as patients approach a weight-loss plateau [119]. Several physiological mechanisms may contribute to this phenomenon. Predominantly, weight loss itself triggers compensatory biological responses, including shift in neuroendocrine hormones, reductions in resting energy expenditure and modest decreases in lean body mass, which may contribute to a lower metabolic rate and potentially predispose individuals to weight-loss plateau [119, 120]. Indeed, analyses of body composition indicate that weight loss associated with incretin-based therapies is predominantly driven by reductions in adipose tissue but a reduction in lean mass was observed [115, 116]. For this reason, strategies aimed at preserving lean body mass, particularly regular physical activity, should be considered an essential component of obesity management also during pharmacological treatment. Furthermore, dietary quality may deteriorate if pharmacological therapy is not accompanied by appropriate nutritional guidance. Indeed, reduced appetite does not necessarily translate into optimal food choices, and patients may still consume ultra-processed foods, exhibit an imbalanced macronutrient distribution, like insufficient protein intake, factors that may negatively influence body composition and metabolic outcomes [120].

In this context, a recent systematic review [121] has highlighted that discontinuation of GLP-1 RAs is frequently associated with partial weight regain, largely independent of lifestyle interventions. Consequently, these drugs should be regarded as long-term therapies aimed at maintaining weight reduction and preventing the re-emergence of obesity-related complications. This long-term dependency is largely explained by the pharmacological mechanisms underlying incretin-based therapies. These agents markedly suppress appetite, reduce energy intake and improve satiety through central and peripheral pathways, thereby helping to maintain a negative energy balance. When treatment is interrupted, this pharmacological support is removed, whereas compensatory biological adaptations to weight loss, such as reduced resting energy expenditure, neuroendocrine changes, and lower lean body mass, may persist, favoring weight regain [120, 121].

4.3 | Effects of GLP-1 Agonists on Gut Microbiota

The effects of GLP-1 RAs on the gut microbiota remain somewhat uncertain given the relatively recent commercialization of these molecules [15]. Data from a recent systematic review of the literature [15], which included both animal models and human studies, showed several effects of GLP-1 analog drugs on the composition, richness and/or microbial diversity of the gut microbiota. However, in most of the research conducted, it is not possible to say whether microbial changes are the cause of metabolic improvements or simply a consequence of weight loss or change in metabolic profile. Moreover, the specific microbial changes reported across studies remain heterogeneous and no consistent microbial signature has been identified [15, 122–128]. In addition, treatment duration, metabolic status and the type of model being tested (human vs. animal model) influence the effects of each molecule, necessitating large-scale studies with high-resolution sequencing [15]. Nevertheless, some taxa associated with metabolic health, including *Akkermansia* and SCFAs-producing bacteria such as *Blautia*, have been repeatedly reported among the microbial groups modulated following treatment [15, 122–128].

Specifically, increased abundance of *A. muciniphila* together with a reduction in *Proteobacteria* has been reported in obese rodents treated with liraglutide [122]. In another experimental model, liraglutide treatment significantly altered the overall microbial community structure in high-fat diet rodents and was associated with increased abundance of SCFAs-producing bacteria including the genera *Bacteroides* and *Blautia* [123]. By contrast, Madsen et al. [124]observed that liraglutide induced only modest microbiota alterations in diet-induced obese mice, mainly affecting bacterial taxa with low relative abundance, despite some shifts observed at the phylum level.

These findings highlight the heterogeneity of microbiota responses to liraglutide across experimental models. Therefore, although some studies have shown that treatment with GLP-1 receptor agonists is associated with changes in the composition of the gut microbiota, these findings remain inconsistent and are not supported by clear evidence of causality demonstrating that these effects are independent of weight loss. Consequently, based on the currently available evidence, it remains difficult to determine whether alterations in the microbiota reflect a direct effect of the drug or are secondary to reduced calorie intake, delayed gastric emptying, improved metabolic status, and metabolic adaptations associated with weight loss [15, 122–124].

Human evidence on the interaction between GLP-1 receptor agonists and the gut microbiota remains more limited and largely inconclusive, partly because most available studies have been conducted in populations characterized by the coexistence of obesity and type 2 diabetes [15, 125–128]. Some clinical investigations did not observe significant changes in gut microbial composition following GLP-1-based therapies [125, 126]. In contrast, other studies [127] have reported specific microbial shifts associated with treatment, including an increased abundance of *A. muciniphila*. Interestingly, Tsai et al. [128] highlighted that, in individuals with elevated BMI and type 2 diabetes, the baseline gut microbial composition was associated with the glycemic response to GLP-1 receptor agonists. These findings suggest a third perspective, in which baseline gut microbial signatures may predict responsiveness to GLP-1 RAs, beyond the ongoing debate on whether microbiota changes are directly drug-induced or secondary to treatment-related weight loss.

Semaglutide was also found to influence the composition of the gut microbiota in animal models, based primarily on descriptive associations [15, 129–132]. Indeed, in HFD-induced obese mice, semaglutide partially alleviated diet-induced gut microbial dysbiosis by restoring depleted bacterial taxa and suppressing excessive bacterial abundance [129]. Notably, correlation analyses revealed inverse associations between *Akkermansia* levels and body weight, glycemia, and several obesity-related parameters, suggesting that microbiota modulation may contribute to the metabolic effects of semaglutide [129]. Other experimental studies confirmed that semaglutide treatment significantly reshaped microbial community structure in obese mice and reversed several HFD-associated alterations in bacterial taxa, including *Lactobacillus* and *Akkermansia* [130, 132]. Moreover, the fecal microbiota transplantation experiment suggested that part of these metabolic benefits could be transferred through microbiota [132]. In another study semaglutide remodeled gut microbiota composition especially by promoting the growth of acetate-producing bacteria [131]. These results suggest that semaglutide may partially counteract obesity-associated gut dysbiosis in animal models; however, although these observations support a potential mediating role of gut microbiota, the extent to which these changes reflect direct pharmacological effects of semaglutide or secondary consequences of weight loss and reduced food intake remains to be fully clarified.

Finally, also for tirzepatide, studies confirm correlational-type changes in the microbiota, with a favorable effect in counteracting high-fat diet-induced dysbiosis [133, 134]. Indeed, one study shows that the intervention with tirzepatide facilitated restoration of intestinal microbiota homeostasis and correlation analyses highlight a negative association between *Akkermansia*, *Bacteroides* and *Enterococcus* levels and weight gain, blood glucose levels and other obesity-related indicators [133]. Another study [134] conducted in an ovariectomized female mouse model with obesity and diabetes also confirmed the efficacy of tirzepatide in counteracting obesity-induced intestinal dysbiosis, resulting in a rebalancing of the *Firmicutes/Bacteroidetes* ratio, along with an increase in beneficial bacteria, including *Akkermansia* and SCFAs-producing bacteria.

4.4 | GLP-1 Therapy-Induced Metabolomic Changes

The effects of GLP-1 RAs on the metabolome are also not fully elucidated. Most of the data come from animal models, although there are also initial data from human studies [132, 135–138]. Moreover, the interaction between gut microbiota, metabolome and clinical response to GLP-1 RAs represents an emerging area of research, especially from the perspective of personalized medicine.

Specifically, the effects of liraglutide on a mouse model of obesity and diabetes were studied to analyze changes in the urinary metabolomic profile. This analysis revealed the presence of 11 significant metabolites [135]. These metabolites were involved in nicotinamide adenine dinucleotide (NAD+) metabolism, β-oxidation of fatty acids and changes in the microbiome, evident from the decrease in bacterial-derived compounds, suggesting mitochondrial recalibration and microbiota interaction. Most of the altered metabolites were similar to those previously identified after the administration of other antidiabetics in a similar mouse model, however the changes in creatinine, taurine and trigonelline were specific to liraglutide administration [135]. Another study [136] examined the effect of liraglutide on plasma metabolites in an obese mouse model and in patients with type 2 diabetes (T2DM), with machine learning (ML) approaches. The analysis identified 47 altered metabolites common to both models and among them 42 metabolites were significantly modulated by liraglutide treatment. The metabolic pathways mainly affected by liraglutide were amino acid and carbohydrate metabolism, the citric acid cycle, the pentose phosphate pathway and taurine/hypotaurine metabolism. Using predictive ML models based on the 42 overlapping metabolites, liraglutide appeared to induce common metabolic shifts in both DIO mice and patients with T2DM. Specifically, 20 metabolites were identified as key indicators of treatment response in both species, exhibiting consistent cross-species patterns in correlation plot, thus supporting the presence of conserved metabolomic signatures [136]. However, the study does not clarify whether these metabolomic alterations are directly induced by liraglutide or reflect secondary effects related to weight loss and metabolic improvements [136].

Another study [137] evaluated the change in the renal metabolome in an obese mouse model induced by semaglutide, highlighting the efficacy of the drug in reducing obesity-induced renal lipotoxicity and positive effects at the level of mitochondrial pathways. Precisely, semaglutide reduced toxic renal lipids (fatty acids, cholesterol, phospholipids, triglycerides), a pivotal change in slowing kidney damage. Improvement in mitochondrial and cellular metabolism at the renal level was also observed, with increases NAD^+ and adenosine-related metabolites, essential for mitochondrial respiration and cellular repair, and taurine-related metabolites, known for their osmoprotective and antioxidant properties [137]. Beyond descriptive profiling, this study highlights the potential of metabolomics to identify drug-responsive metabolic pathways linked to obesity-related renal injury, supporting its emerging role in precision medicine to define targeted interventions [137].

The results of an untargeted metabolomic analysis [132] conducted on the murine serum in semaglutide-treated mice showed significant alteration in serum metabolic pathways, particularly those related to amino acids metabolism and biosynthesis, including arginine, proline, phenylalanine, tyrosine, and tryptophan, as well as purine and pyrimidine metabolism. Fecal transplantation was also performed in germ-free mice receiving the microbiota from semaglutide-treated mice following which a partially overlapping metabolomic profile was shown [132].

Only one metabolomics study involved the application of GLP-1 RAs specifically in humans with obesity comparing liraglutide and bariatric surgery [138]. Metabolomic results of the liraglutide-treated group showed significant alterations in metabolites related to energy, oxidative stress and amino acid metabolism. Most liraglutide-induced metabolite changes overlapped with surgery, though surgery had broader effects, but the authors suggest that a substantial proportion of the early metabolomic alterations may primarily reflect weight reduction rather than treatment-specific mechanisms [138]. Indeed, after adjusting for weight loss, most of the metabolomic changes initially observed lost statistical significance. Only a limited number of metabolites, including acetoacetate, β-hydroxybutyrate and citrate, remained differentially modulated in the early post-intervention phase, likely reflecting caloric restriction and dietary changes [138].

Basically, several metabolic pathways identified repeatedly across various studies. Specifically, those relating to energy and redox metabolism (NAD^+-dependent pathways and the citric acid cycle), amino acid metabolism, and taurine-related pathways appear to converge toward common metabolic adaptations induced by GLP-1-based therapies. In line with this model, metabolites such as citrate, β-hydroxybutyrate and acetoacetate were also identified in the human-only study [138]. Nevertheless, the comparison between liraglutide and bariatric surgery revealed a substantial overlap in the metabolomic changes observed between these two interventions, supporting the idea that such alterations are not treatment specific. This interpretation is reinforced by the observation that most of the metabolomic changes lost statistical significance after adjustment for weight loss, collectively suggesting that weight reduction, rather than the pharmacological effect per se, may be the primary driver of the observed metabolic remodelling [138].

Beyond the ongoing debate as to whether microbiota and metabolomic alterations result from direct pharmacological effects of these therapies or arise secondarily from weight loss and metabolic improvements, growing interest has focused on the possibility that microbial and metabolomic signatures may also serve as predictors of treatment responsiveness. In this contest, from pharmacometabolomic studies investigating other antidiabetic therapies, metabolomic profiling in patients with early-stage type 2 diabetes identified baseline metabolites that differed between responders and non-responders to treatment, suggesting that metabolic signatures may help predict therapeutic efficacy [139]. At the same time, metabolomic profiling has already been proposed as a means to identify drug-responsive metabolic pathways associated with disease-specific complications, thereby providing insights into potential therapeutic targets and supporting precision medicine approaches [137].

5 | Role of AI and Machine Learning in Multi-Omics Microbiome Research for Obesity

5.1 | Rationale for AI-Driven Multi-Omics Integration in Obesity Research

High-dimensional and interdependent microbiome, metabolome, transcriptome, and clinical datasets require analytical frameworks capable of reducing dimensionality, handling sparsity, and modeling nonlinear dependencies. Modern machine learning pipelines are increasingly considered essential for addressing these challenges [140]. Multi-omic analyses further demonstrate that "metabolic BMI," an omics-derived proxy of adiposity and metabolic dysfunction, can stratify individuals into heterogeneous health phenotypes that conventional BMI fails to capture. This finding highlights the added value of integrative AI approaches for patient stratification and risk prediction [141]. In children, layered datasets spanning multiple omics domains reveal molecular clusters associated with adiposity and future insulin resistance, emphasizing age-dependent signatures and the importance of life-course aware models [11].

5.2 | Data-Integration Methodologies: From Correlation Networks to Deep Learning

Early integrative efforts relied on unsupervised correlation and co-occurrence network analyses to show that functional microbial guilds, rather than single taxa, better explain obesity-associated metabolite shifts, thereby motivating feature set aggregation and module-level inference in downstream ML models [142]. However, such traditional approaches are often limited to pairwise or approximately linear relationships and therefore may miss the distributed, nonlinear, and interacting signals that characterize host-microbiome-metabolome biology in obesity. In contrast, machine learning can derive composite microbial signatures by integrating many individually modest features across taxa, genes, pathways, and metabolites, thereby capturing functional redundancy, inter-individual heterogeneity, and cross-omic structure more effectively than conventional differential-abundance or correlation-based analyses alone.

Latent-variable approaches such as LOCATE explicitly model microbiome-metabolome interactions as hidden factors and achieve higher phenotype classification accuracy than either omic alone, illustrating the synergistic information captured by joint embeddings [143]. Neural-network frameworks such as MiMeNet further map entire microbiomes to global metabolomes, capturing nonlinear, many-to-many dependencies that standard linear models overlook [144]. In precision-nutrition contexts, deep multi-branch architectures, such as McMLP, predict individual metabolite responses to diet and outperform strong gradient-boosting baselines across multiple dietary interventions, demonstrating the translational utility of deep learning for intervention design [145].

Beyond these, multi-omics disease-signature discovery is increasingly powered by graph-based and probabilistic integration strategies that encode inter-omic relationships directly into the model structure, improving robustness and interpretability for complex phenotypes like obesity [17]. Graph convolutional networks tailored for multi-omics (e.g., MO-GCN) further promise scalable, phenotype-aware embeddings that respect biological network topology [146]. A comprehensive deep-learning review in microbiome science converges on the same conclusion: to reach the clinic, models must fuse modalities, quantify uncertainty, and adopt explainability methods that bridge predictive power with mechanistic insight [147].

5.3 | Predictive Modeling of Obesity Phenotypes and Intervention Response

AI-integrated multi-omics has begun to clarify why patients respond heterogeneously to obesity treatments. Rather than relying on single taxa, isolated metabolites, or simple group-wise comparisons, these approaches derive multifeatured microbial and metabolomic signatures that better capture the distributed biology underlying treatment response. This is especially relevant in obesity, where functional redundancy across microbial communities and substantial inter-individual heterogeneity often limit the explanatory power of traditional analytical methods. By integrating microbial, metabolomic, and clinical variables into predictive models, ML frameworks can move from descriptive association toward clinically useful stratification of responders, non-responders, and remission-prone patients.

In a bariatric-surgery cohort, multi-omic phenotyping (metagenomics, plasma metabolomics, clinical data) pinpointed surgery-specific microbial bile-acid pathways that tracked improvements in glycemic control more accurately than weight loss alone, suggesting mechanistic mediators beyond caloric restriction [148]. Intermittent fasting combined with "protein pacing" produced distinct responder vs. non-responder microbiome-metabolome trajectories that only became evident after integrated ML analysis, emphasizing the value of holistic modeling for stratifying treatment outcomes [149]. Symbolic regression applied to baseline urinary metabolomes identified just two metabolites (adipic and argininic acids) that predicted long-term success on a Nordic diet (AUC $\approx$ 0.80), illustrating how ML can also yield parsimonious and clinically tractable predictive signatures for dietary personalization [150].

Outside nutrition, a multimodal model that merged fecal metabolomics with brain white-matter metrics classified obese vs. overweight adults with 90% accuracy, highlighting systemic axes (gut-brain) that purely microbial models may overlook [151]. Pharmacotherapy is entering the same analytical space: GLP-1 RAs appear to remodel gut ecology and metabolite output, and ML-guided analyses link these shifts to improvements in insulin sensitivity, suggesting a drug-microbiome synergy that could be therapeutically exploited [152]. Even prior to treatment, baseline microbiome configurations can predict sustained diabetes remission after Roux-en-Y gastric bypass, indicating that pre-operative, ML-derived microbial signatures could inform patient selection and counseling [153].

5.4 | Translational Outlook: Toward Precision Nutrition and Mechanism-Driven Therapies

Longitudinal metabolomics demonstrates that bariatric surgery and low-calorie diets elicit divergent bile-acid dynamics; ML modeling nominates taurine-conjugated chenodeoxycholic acid as a putative mediator of surgery-specific metabolic benefits, pointing to bile-acid pathway engineering as an adjunct target [154]. Using machine-learning models that combined gut metagenomes, circulating metabolites, and detailed diet logs from 1098 participants, the study demonstrated that microbiome features markedly enhance the prediction of fasting and post-prandial metabolic biomarkers, delineating diet-responsive "metabotypes" that support algorithm-guided, mechanism-informed dietary personalization [155]. To bring these systems into practice, next-generation graph models that encode inter-omics edges (e.g., gene-metabolite-species networks) are poised to refine disease-signature discovery and enable causal hypothesis generation at scale [17], whereas multi-omics GCNs offer scalable phenotyping across tissues and organ systems [146]. Finally, translation will hinge on explainable AI: transparent, uncertainty-aware models that return testable mechanistic hypotheses and clinician-friendly features, rather than opaque risk scores [156].

In sum, AI/ML-enabled multi-omics is shifting obesity research from association mapping to actionable precision strategies—identifying mechanistic microbe-metabolite axes, predicting who will respond to which intervention, and pointing to tractable microbial or metabolite targets for co-therapy. The next phase will couple these models with prospective, interventional trials to demonstrate that model-guided decisions improve outcomes across the obesity lifespan.

6 | Dietary Interventions and the Microbiome-Metabolome Axis in Obesity

Building on the metabolite pathways described above, diet composition and patterning remodel gut microbial ecology and the chemical outputs that interface with host metabolism. Across human feeding studies and cohorts, plant-forward, fiber-rich, minimally processed diets enrich saccharolytic guilds and cross-feeding networks, increasing SCFAs output and influencing bile acid pools [155, 157, 158]. Westernized patterns high in saturated fat, refined carbohydrates, and ultra-processed foods often depress beneficial fermenters, shift bile acid signaling, and increase endotoxin load and amino acid fermentation products implicated in insulin resistance [4, 10]. These microbiome and metabolome shifts can occur within days and are partially reversible; inter-individual heterogeneity is substantial and is partly explained by baseline microbiome state and habitual diet [4, 155].

From a functional perspective, SCFAs (acetate, propionate, butyrate) bind G-protein-coupled receptors (e.g., FFAR2/3), influence enteroendocrine GLP-1 and PYY secretion, and exert tissue-level effects on insulin sensitivity, adipose inflammation, and gut barrier integrity [130, 131]. Microbial transformations of bile acids (e.g., deconjugation; 7α-dehydroxylation) reshape the FXR/TGR5 axis with consequences for lipid and glucose homeostasis. Aromatic amino acid metabolites (indoles, phenylacetic acid/phenylacetylglutamine) and BCAAs further link microbial

activity to insulin resistance and cardiometabolic risk, often detected by untargeted or targeted liquid chromatography-MS metabolomics [10, 159].

6.1 | The Role of Dietary Patterns in Modulating the Gut Microbiome

Large population studies and controlled trials converge on the conclusion that dietary patterning explains a sizable fraction of microbiome variance compared with host genetics, and that pattern-level choices (Mediterranean-style, fiber-enriched, fermented foods) are more informative than single nutrients [86, 155, 160]. In an intervention among adults with overweight or obesity, a Mediterranean diet shifted the metagenome toward fiber-degrading taxa and pathways, with concordant metabolomic signatures (lower TMAO, altered bile acid and phenolic metabolites) aligned with improved cardiometabolic risk factors [157]. A randomized trial contrasting high-fiber versus fermented-food diets showed that fermented foods increased alpha diversity and reduced multiple inflammatory cytokines, whereas high fiber intake increased the potential to degrade carbohydrates and SCFA-linked improvement in the host-microbe crosstalk [158]. Overall, plant-rich patterns consistently enrich CAZyme capacity and SCFAs output, whereas animal-based, low-fiber patterns push toward bile-tolerant, amino acid fermenting consortia with less favorable metabolite profiles [155, 160].

6.2 | Revisiting the Firmicutes/Bacteroidetes Ratio in Obesity

The Firmicutes/Bacteroidetes ratio, once proposed as an "obesity signature", does not hold as a robust biomarker in humans after accounting for methodology and ecology. Re-analyses and meta-studies report inconsistent directionality and high sensitivity to sequencing platform, region targeted, depth, and covariates such as age, medications, stool consistency, and diet [161, 162]. Given the functional heterogeneity within phyla, contemporary work prioritizes pathway-level readouts (i.e., SCFAs flux, amino acid fermentation, bile acid transformations, LPS biosynthesis) over phylum ratios when linking the microbiome to adiposity and insulin resistance [162, 163].

6.3 | Metagenome-Wide Association Studies (MWAS) in Diet-Microbiome Research

Population-scale metagenome-wide association studies (MWAS) map diet and adiposity to microbial genes and pathways rather than only taxa. The environment, especially dietary habits, tends to dominate over host genetics in shaping gut microbial composition and function, though gene-diet-microbe interactions exist at specific loci [164, 165]. MWAS repeatedly highlight modules for complex-carbohydrate degradation, butyrate synthesis, and bile-salt hydrolases as key mediators between diet and metabolic phenotypes, and microbiome-metabolome integration, then links these modules to circulating or fecal metabolites (SCFAs, indoles, phenolics, bile acid species) with cardiometabolic relevance [48, 86, 155]. Methodologically, best practice includes compositionality-aware statistics, rigorous confounder adjustment (medications, BMI, stool form), multi-cohort replication, and functional validation via metabolomics or gnotobiotic transfer to strengthen causal inference [155, 163].

6.4 | Microbiome-Based Dietary Interventions

6.4.1 | Food-Based Patterns

Mediterranean-style, high-fiber, and fermented food strategies remain first line for steering microbial metabolism toward SCFA-enriched, anti-inflammatory profiles [157, 158]. Benefits on body weight are typically modest but metabolic readouts (insulin sensitivity, inflammation) are more consistently improved.

6.4.2 | Prebiotics

Inulin-type fructans and resistant starch produce context-dependent improvements in insulin sensitivity and post-prandial glycaemia, with heterogeneous effects on adiposity, whereas responses tend to be greater in insulin-resistant phenotypes [166–170]. Gastrointestinal tolerance, stepwise dose increases, dietary habits, and product characteristics (e.g., inulin degree of polymerization and resistant starch type) shape fermentation dynamics and clinical responses.

6.4.3 | Probiotics and Synbiotics

Meta-analyses indicate statistically significant, but clinically modest, reductions in body weight, BMI, and central adiposity in adults, with marked strain- and formulation- specificity [171, 172]. Effects vary by species/strain, dose, duration, delivery matrix (capsule vs. fermented food), and whether the product is a synbiotic (paired with a complementary prebiotic). Proposed mechanisms include enhanced SCFA production and signaling, bile acid deconjugation and altered FXR/TGR5 activity and immunomodulation. However, reproducibility is inconsistent across studies. Response also appears contingent on baseline microbiome structure, dietary context (e.g., fiber intake), and host phenotype (e.g., insulin resistance, central adiposity). Overall, benefits from the use of probiotics/synbiotics are small at the population level (but may be clinically relevant in subsets when the product is mechanistically matched to host and diet), with generally good tolerability and transient gastrointestinal symptoms being the most common adverse events.

6.4.4 | Next-Generation Candidates and FMT

Beyond conventional probiotics and synbiotics, emerging microbiome-directed therapeutics, including pasteurized *A. muciniphila* and fecal microbiota transplantation (FMT) represent interventions that target specific mechanisms and carry distinct regulatory and safety considerations. Pasteurized *A. muciniphila* improved insulin sensitivity and multiple cardiometabolic biomarkers in a proof-of-concept randomized study, suggesting that targeted, mechanism-based microbes

may outperform legacy probiotics for metabolic endpoints [173]. Lean-donor FMT transiently improves peripheral insulin sensitivity in metabolic syndrome, especially among recipients with low baseline diversity, but durable weight-loss effects remain unproven; safety considerations (rare pathogen transmission) restrict clinical use outside *C. difficile* infection [174–176].

7 | Future Directions and Clinical Implications

Future work should move decisively from association to causation and from population averages to personalized care. Methodologically, that means multi-site, longitudinal studies with dense, standardized sampling, randomized dietary perturbations to test mechanism, and functional endpoints that reflect biology, including SCFAs kinetics, bile acid profiles, amino acid catabolites, and host readouts such as insulin sensitivity and inflammation. Integrating metagenomics, metabolomics, transcriptomics, and clinical phenotypes with transparent, well-calibrated machine-learning models will be essential to identify responder subtypes and actionable microbe-metabolite pathways. Clinically, a pragmatic pathway is to pair plant-rich dietary patterns and fermented foods with targeted adjuncts (e.g., prebiotics in insulin-resistant phenotypes, selectively chosen probiotics, or investigational next-generation microbes in trials), whereas monitoring objective biomarkers of response. Pharmacotherapies that alter appetite and metabolism (such as GLP-1-based agents) should be studied alongside diet to define synergistic effects on the microbiome-metabolome axis and to develop predictors of treatment response. To ensure real-world impact, future studies must prioritize diversity (age, medications, ancestry, diet, and geography), adopt harmonized protocols and reporting, and embed implementation outcomes, namely adherence, tolerability, cost, and equity, so that precision nutrition and co-therapies can be delivered safely and effectively across the lifespan.

8 | Conclusion

Diet is the most tractable lever on the microbiome-metabolome axis relevant to obesity, a system increasingly understood as a reciprocal host-microbiome interaction rather than a unidirectional cause-or-consequence relationship. High-quality human evidence shows that Mediterranean-style, fiber-rich, and fermented-food patterns remodel microbial functions in directions consistent with improved insulin sensitivity and dampened inflammation. The Firmicutes/Bacteroidetes ratio lacks robustness as a biomarker, whereas function-centered metrics provide greater mechanistic and translational value. Moving from association to application will depend on standardized methods, causal designs, diverse cohorts, and explainable multi-omics models, enabling precision nutrition strategies that can sit alongside pharmacotherapy across the lifespan.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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