Chapter

Dietary Determinants of Metabolic Syndrome: Focus on the Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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Abstract

Metabolic syndrome, a cluster of conditions including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol levels, significantly heightens the risk of cardiovascular disease, diabetes, obesity, and fatty liver disease. With the adoption of a Western-style diet characterized by a high intake of corn sugar, saturated fats, and ultra-processed foods, these metabolic disorders have reached pandemic proportions globally. This chapter addresses the rising rates of obesity and MASLD, stressing the critical impact of dietary habits on these issues. It highlights how a healthy diet can mitigate risks, pointing out the detrimental effects of poor nutrition. The text examines the complex relationship between diet, adiposity, and liver health, analyzing the role of macronutrient composition, calorie intake, and processed foods in metabolic dysregulation. It proposes comprehensive nutritional strategies and public health policies, including the adoption of an inverted food pyramid, to tackle metabolic syndrome, obesity, and MASLD effectively, advocating for a holistic approach to dietary changes.

Keywords: metabolic syndrome, obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), diet, saturated trans fats, corn fructose, western-style diet, inverted food pyramid, healthy lifestyle

1. Introduction

In recent decades, the prevalence of obesity and its associated comorbidity, metabolic dysfunction-associated steatotic liver disease (MASLD; previously known as non-alcoholic fatty liver disease, NAFLD) and its severe form metabolic dysfunction-associated steatohepatitis (MASH; previously known as non-alcoholic steatohepatitis (NASH), has escalated to pandemic levels, posing a challenging

situation to global health systems [1, 2]. The escalating incidence of these disorders is not an isolated trend but rather a component of the broader constellation of metabolic syndrome. This syndrome is a collection of interrelated metabolic risk factors that augments the probability of developing type 2 diabetes (T2D), cardiovascular disease (CVDs), chronic kidney disease (CKD), and various forms of liver pathology [3–5].

The pathophysiology underlying obesity and MASLD is intrinsically complex and multifactorial, involving genetic predisposition, dietary habits, lifestyle choices, and environmental exposures. The hallmark of these diseases is the excessive accumulation and storage of lipids in adipose tissue and the liver, driven by an energy surplus (**Figure 1**) [6]. This lipid overload leads to a cascade of metabolic disruptions, primarily insulin resistance, which is a central feature of obesity and metabolic syndrome. Insulin resistance facilitates the progression of hepatic steatosis to more severe liver injury, characterized by inflammation and fibrosis in MASH [7]. The interplay between obesity, MASLD, and metabolic syndrome represents a critical nexus in the pathogenesis of these conditions. Excessive adipose tissue, particularly visceral fat (adiposopathy), is not only a passive reservoir for excess energy but also an active endocrine organ that secretes a myriad of bioactive molecules, such as adipokines, cytokines, and free fatty acids [8]. These molecules have systemic effects that influence insulin sensitivity, energy metabolism, inflammatory pathways, and liver function. The consequence is a self-perpetuating cycle of metabolic dysfunction that exacerbates the risk of further health complications [9].

In this context, the global escalation of obesity and MASLD reflects an intersection of societal, behavioral, and biological factors that have merged to create an

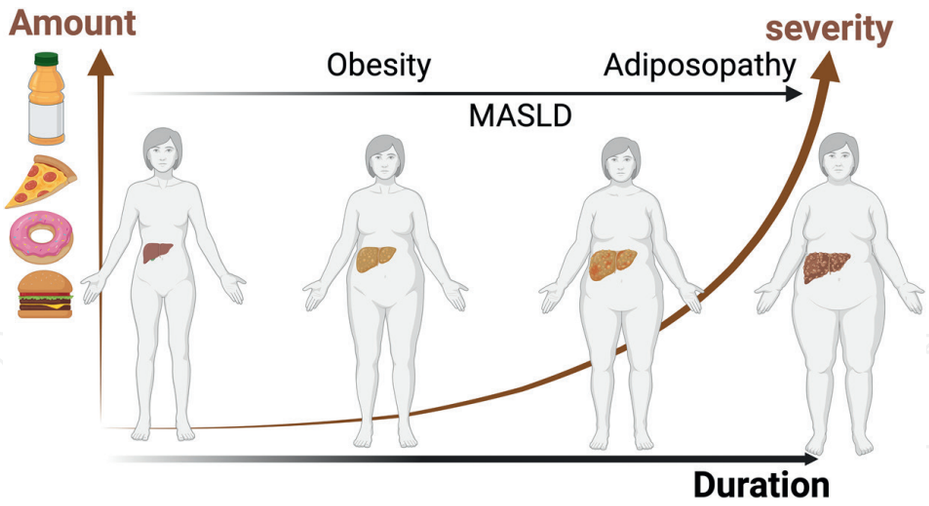

Figure 1.
Progression model of obesity and its advancement into metabolic dysfunction-associated fatty liver disease (MASLD) and adiposopathy: The illustration represents the correlation between the amount and duration of excessive caloric intake from unhealthy food choices (symbolized by foods commonly associated with high energy content) and the severity of disease states. While vertical axis suggests that as the consumption of high-calorie foods increases, there is a corresponding escalation in the severity of metabolic conditions, horizontal axis indicates the progression over time, illustrating that prolonged exposure to unhealthy dietary habits exacerbates the severity of metabolic disorders. Indicative stages of progression; (i) obesity: The first figure symbolizes the initial stage of weight gain, where increased adiposity is mostly localized in the abdominal (visceral) area, (ii) MASLD: As time and unhealthy eating continue, the second figure shows the progression to MASLD where liver involvement begins due to excess fat deposition, (iii) Adiposopathy with MASH: The final figure depicts adiposopathy, where adipose tissue dysfunction is at its peak, and the liver is heavily laden with fat and inflammation (MASH), indicating a high risk or presence of serious liver disease. Note: This illustration is designed to represent the progression of obesity and related metabolic conditions without gender specificity, indicating that the depicted pathophysiology applies broadly across different genders. Illustration was created in BioRender.com.

environment favorable to metabolic dysregulation. This introduction sets the stage for an in-depth exploration of the etiological underpinnings of these conditions, their epidemiological significance, and the interdependent metabolic pathways that facilitate their progression. Through this lens, we will scrutinize the evidence linking dietary patterns to the pathogenesis of metabolic syndrome, obesity, and fatty liver disease, thereby underscoring the imperative for strategic public health interventions aimed at curtailing this escalating crisis.

1.1 Obesity: an epidemic of excessive weight gain

Obesity, characterized by an abnormal or excessive accumulation of adipose tissue, becomes pathologically significant as adiposopathy when it detrimentally impacts health, posing a significant global health challenge [10, 11]. Clinically, obesity is demarcated by a body mass index (BMI) exceeding 30 kg/m^2, but this metric belies the complex, heterogeneous nature of the condition. The pathogenesis of obesity is a multifaceted interplay between genetic predisposition, epigenetic modifications, metabolic programming, and environmental factors, including diet, physical activity, and even microbial flora of the gut [9, 12]. At the cellular level, obesity is the consequence of adipocyte hypertrophy and hyperplasia precipitated by chronic energy surplus. The primary etiological factor is an energy imbalance, caloric intake surpasses metabolic demands, leading to the storage of excess calories as triglycerides within adipose tissue. This simplistic caloric surplus model is influenced by neuroendocrine signals, such as leptin and ghrelin, and the central regulatory pathways in the hypothalamus [13–15].

Moreover, obesity's pathophysiological impact extends beyond mere energy storage. Adipose tissue, particularly in visceral deposits, operates as an active endocrine organ, orchestrating a myriad of pathological processes through the dysregulated secretion of adipokines, pro-inflammatory cytokines, and non-esterified fatty acids [8, 9]. These adipocyte-derived factors cause systemic insulin resistance, a cornerstone of metabolic syndrome, and incite a chronic, low-grade inflammatory state, which is implicated in the pathogenesis of a spectrum of non-communicable diseases [12]. The epidemiology of obesity reveals its pandemic spread, driven by the sedentarization of lifestyles and a global dietary transition toward energy-dense, nutrient-poor foods rich in saturated fats, trans fats, refined sugars, and salt. This nutritional shift, emblematic of the Western diet, combined with increased portion sizes and the ubiquity of processed food, has fueled a surge in obesity rates. Concurrently, urbanization and economic development have facilitated a sedentary lifestyle, characterized by decreased physical activity, further exacerbating the prevalence of obesity.

The consequences of obesity are far-reaching, including an augmented risk of CVDs, T2D, various cancers, musculoskeletal disorders, and psychological disturbances. Thus, obesity represents not only a personal health crisis but also a substantial burden on public health infrastructure and economies globally. Addressing the obesity epidemic necessitates a holistic approach that encompasses dietary modifications, physical activity promotion, behavioral changes, and, where appropriate, pharmacological or surgical interventions. It also calls for a concerted public health strategy to reshape the obesogenic environment that currently prevails in many societies.

1.2 MASLD: a growing concern

MASLD, a condition characterized by excessive hepatic triglyceride accumulation, is rapidly becoming the most prevalent form of chronic liver disease

globally. This hepatic steatosis, in the absence of significant alcohol consumption, encompasses a pathological spectrum ranging from simple steatosis to the more aggressive MASH, which may progress to fibrosis, cirrhosis, and even hepatocellular carcinoma [1, 6]. The pathobiology of MASLD is intrinsically linked to insulin resistance, the hallmark of metabolic syndrome, and a key pathological mechanism of obesity. The term 'hepatic steatosis' reflects lipid infiltration of hepatocytes, typically resulting from an imbalance between lipid acquisition (uptake and synthesis) and lipid disposal (oxidation and export). In the milieu of insulin resistance, the suppression of lipolysis is impaired, leading to an increased influx of free fatty acids into the liver. Concurrently, hyperinsulinemia stimulates lipogenic enzymes, further exacerbating hepatic fat accumulation [7]. The disease's progression to MASH is mediated through a 'multiple-hit' process that goes beyond simple steatosis induced by insulin resistance. The additional 'hits' may include oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, altered gut microbiota, and the activation of inflammatory pathways. The lipid peroxidation and subsequent generation of reactive oxygen species initiate hepatocellular injury, inflammation, and fibrogenesis [16].

The increasing prevalence of MASLD parallels the rising tide of obesity, reflecting a shift in global dietary patterns toward high-calorie, high-fat, and high-fructose diets, coupled with sedentary lifestyles. The epidemiological trajectory of MASLD is alarming, with an estimated one-quarter of the global population affected, making it a formidable public health challenge [17]. MASLD's natural history is heterogeneous, with a variable risk of progression to end-stage liver disease. It significantly contributes to the burden of liver-related morbidity and mortality, but it also represents an independent cardiovascular risk factor, adding to the disease's complexity and clinical management. The economic impact of MASLD is substantial, encompassing direct healthcare costs from the management of advanced liver disease and indirect costs from loss of work productivity.

Current therapeutic strategies focus on lifestyle modification as the primary intervention, with an emphasis on diet and physical activity to induce weight loss and improve insulin sensitivity. Pharmacological treatments are limited and primarily aimed at those with NASH and fibrosis. Advances in understanding the molecular mechanisms underlying NAFLD are paving the way for the development of targeted therapies, which are urgently needed to address this silent epidemic.

2. Pathogenesis of obesity and MASLD

The pathogenesis of obesity and MASLD interconnects complex physiological processes, where excessive accumulation of adipose tissue and systemic insulin resistance lay the groundwork for a cascade of metabolic dysfunctions. Central to this interplay is the role of adipose tissue not only as an energy storage site but also as an active participant in metabolic regulation, secreting various adipokines that influence insulin sensitivity and inflammatory pathways. Concurrently, the liver, overwhelmed by the influx of free fatty acids and compounded by insulin resistance, undergoes a pathological transformation, first into steatosis and potentially advancing to steatohepatitis, fibrosis, or cirrhosis. This narrative encapsulates the multifaceted nature of these conditions, highlighting the critical intersection of dietary habits, lifestyle factors, and genetic predispositions in their evolution.

2.1 Adipose tissue expansion and insulin resistance

The development of obesity is intrinsically linked to the expansion of adipose tissue and the onset of insulin resistance. Adipose tissue expansion, a hallmark of obesity, occurs through two primary mechanisms: hypertrophy (increase in adipocyte size) and hyperplasia (increase in adipocyte number) [18]. This expansion is not merely a result of energy surplus but also involves complex interactions among genetic factors, dietary intake, physical activity levels, and hormonal signals. Adipose tissue, especially when excessively expanded, functions not just as an energy storage site but also as an active endocrine organ. It secretes a wide array of bioactive substances, including adipokines (leptin, adiponectin), cytokines (TNF-α, IL-1β, IL-6, etc), and other molecules that play pivotal roles in metabolic regulation [8]. In obesity, the altered secretion pattern of these adipokines contributes to the development of insulin resistance, a condition where cells fail to respond adequately to insulin. The process of insulin resistance is further exacerbated by chronic low-grade inflammation, a characteristic feature of obesity. Adipose tissue expansion leads to hypoxia, necrosis, and the infiltration of immune cells, which in turn secrete pro-inflammatory cytokines [11]. These cytokines impair insulin signaling pathways, leading to systemic insulin resistance. Moreover, the excess free fatty acids released by hypertrophic adipocytes can accumulate in non-adipose tissues, including the liver and muscle, causing lipotoxicity and further contributing to insulin resistance.

2.2 Role of lipid metabolism in fatty liver development

The development of MASLD intricately ties into the dysregulation of lipid metabolism during obesity due to fatty, sugary, and inflammatory diets [19, 20]. Mechanistically, this process is rooted in the disruption of normal lipid homeostasis, leading to an excessive accumulation of lipids in the liver.

2.2.1 Insulin resistance and lipolysis

In a healthy metabolic state, insulin regulates lipolysis, the process by which triglycerides stored in adipose tissue are broken down into free fatty acids (FFAs) and glycerol, ensuring a balanced release of FFAs into circulation. However, insulin resistance impairs this regulatory mechanism, resulting in uncontrolled lipolysis and a surge of FFAs into the bloodstream. These excess FFAs are then transported to the liver, imposing a metabolic burden that exceeds the liver's capacity for lipid oxidation and VLDL secretion, thereby fostering hepatic lipid accumulation or steatosis.

2.2.2 Hepatic de novo lipogenesis

Concurrently, insulin resistance alters hepatic lipid metabolism by promoting *de novo* lipogenesis (DNL), the process of synthesizing fatty acids from non-lipid precursors, such as carbohydrates [21]. This paradoxical increase in DNL, despite insulin resistance, is mediated through the upregulation of lipogenic transcription factors like SREBP-1c (sterol regulatory element-binding protein-1c) and ChREBP (carbohydrate-responsive element-binding protein). These transcription factors are activated not only by insulin but also by dietary intake, especially from simple carbohydrates and fructose, further exacerbating hepatic fat accumulation.

2.2.3 From steatosis to steatohepatitis

While the initial stages of hepatic steatosis serve as a buffer against lipotoxicity by sequestering FFAs in the form of triglycerides, the liver's capacity to mitigate lipotoxic effects diminishes with continuous metabolic stress. Persistent insulin resistance, alongside dietary excesses, perpetuates a state of oxidative stress and inflammation within the liver. These conditions, coupled with mitochondrial dysfunction and endoplasmic reticulum stress, initiate hepatocellular injury [20, 22, 23]. The liver's response to injury involves inflammation and fibrogenesis, marking the progression from simple steatosis to MASH.

2.2.4 Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction plays a pivotal role in the pathogenesis of NASH by impairing fatty acid β-oxidation, leading to an accumulation of toxic lipid intermediates. These intermediates, alongside reactive oxygen species (ROS) generated from dysfunctional mitochondria, inflict oxidative damage and further exacerbate inflammation and fibrosis [23, 24].

2.2.5 Endoplasmic reticulum stress and gut microbiota alterations

The unfolded protein response, activated by endoplasmic reticulum stress, contributes to the inflammatory milieu of NASH. Additionally, alterations in gut microbiota can influence the progression of NAFLD through mechanisms involving gut-liver axis interactions, including the modulation of bile acid metabolism and the systemic inflammatory response [22, 25].

The transition from MASLD to MASH and potentially to cirrhosis and hepatocellular carcinoma encapsulates a multifaceted interplay of metabolic disturbances, driven by insulin resistance and compounded by dietary factors, oxidative stress, mitochondrial and endoplasmic reticulum dysfunction, and changes in gut microbiota. This complex pathophysiology highlights the need for a multidimensional approach to the prevention and management of fatty liver disease.

3. Dietary factors contributing to obesity and fatty liver

The interplay between diet and the development of obesity and MASLD is a focal point of metabolic health research, emphasizing the profound impact of dietary choices on the pathogenesis of metabolic syndrome including these conditions. The composition and quantity of food consumed not only influence body weight and adiposity but also have direct and indirect effects on liver health. Factors such as excessive caloric intake, imbalance in macronutrient composition, high consumption of added sugars and high-fructose corn syrup, along the intake of processed and ultra-processed foods, collectively contribute to the metabolic derangements underlying these diseases. Conversely, dietary components like fiber play a protective role, modulating gut microbiota and promoting metabolic health. Understanding these dietary factors offers insights into the mechanisms by which nutrition influences the risk and progression of obesity and fatty liver, highlighting the potential for dietary interventions in prevention and management strategies.

3.1 Caloric intake and energy balance

The fundamental principle underlying obesity and MASLD is an imbalance between caloric intake and energy expenditure (**Figure 2**) [26]. Energy homeostasis is orchestrated by a complex network of hormonal signals, nutrient sensors, and neurobehavioral responses that regulate appetite, food intake, and the metabolic rate. Caloric excess, particularly from hypercaloric diets, provides substrates for adipogenesis, leading to the expansion of adipose tissue through the accrual of triglycerides in adipocytes [27].

Mechanistically, when the energy consumed surpasses the body's metabolic demands, the surplus is stored in adipose tissue as triglycerides, a process facilitated by insulin, a hormone that promotes glucose uptake and lipid storage. Over time, chronic overnutrition and insufficient physical activity tilt the scales of this balance, resulting in sustained positive energy balance and weight gain. The storage capacity of adipose tissue may become overwhelmed, leading to ectopic fat deposition in non-adipose tissues, such as the liver, contributing to the pathophysiology of MASLD.

The accumulation of ectopic fat, particularly in the liver, disrupts normal hepatic metabolism and insulin signaling, creating a state of hepatic insulin resistance. Insulin resistance further exacerbates energy imbalance by impairing the suppression of hepatic glucose production and compromising the ability of insulin to inhibit adipose tissue lipolysis. The result is a paradoxical situation where insulin levels are high, yet their regulatory effects are diminished, leading to hyperglycemia and the continued

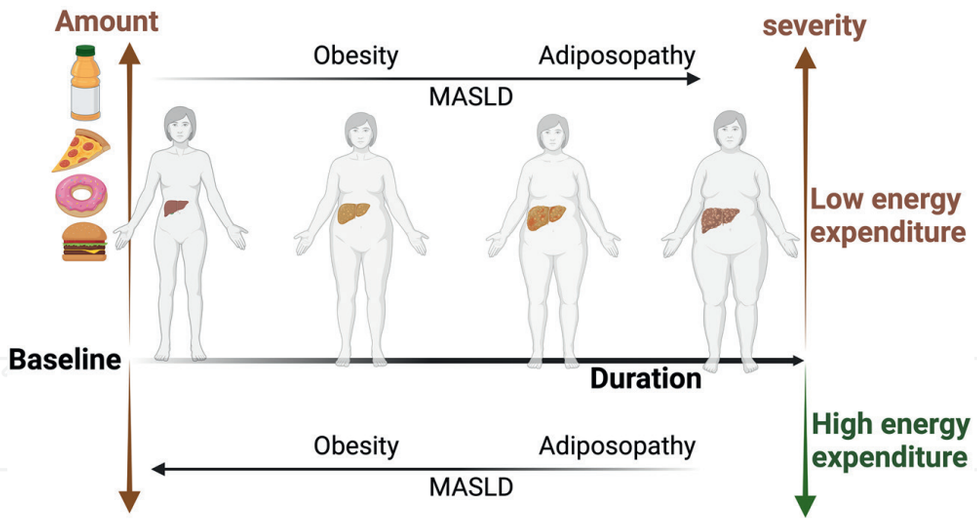

Figure 2.
Conceptual model of the progression of obesity and its complications over time and varying energy balances: Vertical Axis (on left) indicates the volume of high-calorie food intake, with higher positions representing greater consumption levels, contributing to increased body fat and the risk of obesity and MASLD conditions. Left side at horizontal axis represents 'baseline', the starting point of normal metabolic health before the onset of obesity and MASLD. Horizontal axis toward the right shows the timeline over which an individual progresses from a healthy state through obesity, then MASLD, and finally to adiposopathy and MASH, which are pathogenic states of adipose and liver tissues. Vertical axis on the right shows 'severity' that correlates with the progression of disease and the worsening of metabolic health, as evidenced by the accumulation of fat in the liver and other tissues. Low energy expenditure (represented by brown upward arrow on the right) suggests that decreased physical activity or metabolic rate exacerbates the severity, while high energy expenditure (represented by green downward arrow on the right) implies that increased physical activity or metabolic rate can potentially mitigate the severity or progression of obesity, adiposopathy, MASLD, and MASH. Note: This illustration is gender-neutral and represents a process that can occur in any individual exposed to the risk factors of high caloric intake and low energy expenditure over time. Illustration was created in BioRender.com.

release of free fatty acids from adipose tissue. The liver, facing an influx of free fatty acids and glucose, responds by increasing DNL while simultaneously experiencing an impaired capacity for fatty acid oxidation and VLDL-triglyceride export.

The imbalance between caloric intake and energy expenditure is the fundamental driver of obesity and NAFLD, with far-reaching metabolic consequences. This disequilibrium, rooted in dietary excess and sedentary lifestyle, initiates a series of metabolic derangements that not only lead to the expansion of adipose tissue but also disrupt lipid homeostasis within the liver, setting a pathogenic trajectory toward metabolic disease.

3.2 Macronutrient composition: the influence of fat, carbohydrates, and protein

The composition of the diet, particularly the types and amounts of macronutrients consumed, plays a significant role in the development of obesity and MASLD. Diets high in saturated fats and trans fats contribute to the accumulation of visceral fat and promote hepatic steatosis by increasing the influx of free fatty acids into the liver. Conversely, diets rich in carbohydrates, especially refined carbohydrates and simple sugars, stimulate insulin secretion and can lead to insulin resistance. Overconsumption of these macronutrients also promotes DNL in the liver, exacerbating fat accumulation. Proteins have a more complex role, generally promoting satiety and having a thermogenic effect, yet excessive intake, particularly from red and processed meats, may also contribute to metabolic dysfunction.

3.2.1 Fats

Saturated and trans fats have been implicated in the development of obesity and MASLD due to their propensity to induce adipose tissue expansion, liver fat accumulation, inflammation, and lipotoxicity [28]. Mechanistically, saturated fats can activate toll-like receptor 4 (TLR4), triggering inflammatory pathways and promoting insulin resistance. When excessive dietary fats are consumed, they increase the plasma concentration of free fatty acids (FFAs). These FFAs are taken up by the liver and can overwhelm mitochondrial beta-oxidation, leading to their incorporation into triglycerides and subsequent steatosis. Trans fats, similarly, can interfere with lipid metabolism and have been associated with an increased risk of NAFLD due to their deleterious effect on lipoprotein profiles and inflammatory status [29].

3.2.2 Carbohydrates (added sugars and high-fructose corn syrup)

High-carbohydrate diets, particularly those rich in refined sugars, have a profound impact on insulin dynamics. Further, the consumption of added sugars, particularly high-fructose corn syrup (HFCS), has been linked to an increased risk of obesity and MASLD [30]. HFCS consumption can lead to metabolic dysregulation and changes in dopamine signaling even without the presence of obesity [31]. Simple sugars, like glucose and fructose, rapidly elevate blood glucose levels, prompting a sharp insulin response. Chronic consumption of high-carb diets can lead to sustained hyperinsulinemia, contributing to insulin resistance [32]. Unlike glucose, fructose metabolism bypasses the rate-limiting step of glycolysis regulated by phosphofructokinase. This allows fructose to enter the glycolytic pathway downstream, leading to an unregulated supply of acetyl-CoA, the substrate for DNL [33], and subsequent triglyceride synthesis in the liver. The excess triglycerides can accumulate as lipid droplets in hepatocytes, contributing to steatosis.

Mechanistically, fructose is metabolized primarily in the liver, where it rapidly depletes intracellular adenosine triphosphate (ATP) as it is converted to fructose-1-phosphate by fructokinase. The resulting drop in ATP leads to the formation of uric acid, which can induce oxidative stress and trigger the production of pro-inflammatory cytokines. Moreover, fructose can directly increase intestinal permeability, allowing translocation of bacterial endotoxins into the portal circulation. These endotoxins can activate Kupffer cells, the resident macrophages in the liver, leading to the secretion of additional pro-inflammatory cytokines such as TNF-α and IL-6, which exacerbate hepatic inflammation and can further impair insulin signaling. Thus, fructose consumption was also linked to inflammation, particularly in the context of MASLD and metabolic syndrome [32].

Chronic consumption of high levels of fructose can initiate and perpetuate a cycle of inflammation and metabolic disturbance that not only contributes to the development of MASLD but also propagates systemic inflammation, insulin resistance, and the clustering of metabolic syndrome features. This inflammatory cascade underscores the importance of moderating dietary fructose, particularly from sources like high-fructose corn syrup, to maintain metabolic health and mitigate the risk of associated chronic diseases.

3.2.3 Proteins

Proteins generally play a protective role in metabolic health due to their effects on satiety and their higher thermic effect compared to carbohydrates and fats [34, 35]. This means that the metabolism of proteins requires more energy, which can contribute to a higher resting metabolic rate. However, the source and type of protein are critical, as excessive intake of certain proteins, particularly those from red and processed meats, has been linked to an increased risk of metabolic syndrome and MASLD. This association may be due to the presence of heme iron, saturated fat, and sodium in these foods, along with certain additives used in processing meats, which can contribute to oxidative stress and inflammation, two key factors in the pathogenesis of NAFLD.

Thus, the interplay between the types and amounts of dietary macronutrients can either predispose to or protect against metabolic derangements leading to obesity and MASLD. The dietary pattern that emphasizes a balanced intake of macronutrients, favoring unsaturated fats, complex carbohydrates, and high-quality protein sources, is likely to be beneficial in preventing and managing these conditions.

3.3 Processed and ultra-processed foods in obesity and MASLD

Processed and ultra-processed foods, characterized by high levels of added sugars, fats, and sodium/salt, along with a plethora of food additives, play a pivotal role in the obesity epidemic and the pathogenesis of MASLD. These foods are designed for palatability and overconsumption, often at the expense of nutritional quality. The high caloric density and low satiety index of these foods promote excessive caloric intake, while their nutrient-poor composition contributes to metabolic dysregulation, insulin resistance, and hepatic steatosis.

3.3.1 Caloric density and satiety

The high caloric density of processed foods means that they provide a large number of calories in small volumes, which can lead to overeating before the body's

natural satiety mechanisms signal fullness. Additionally, the rapid digestion of these foods leads to swift and significant postprandial glucose and insulin spikes, contributing to a shorter duration of satiety and a quicker return of hunger signals [36].

3.3.2 Nutrient composition and metabolic regulation

The nutrient composition of ultra-processed foods is often poor, lacking essential vitamins, minerals, and dietary fiber. This deficiency can disrupt the gut microbiota and impair normal digestive and absorptive processes, leading to alterations in energy homeostasis [36]. Moreover, the high sugar and fat content can lead to an imbalance in the gut-brain axis, influencing reward pathways and potentially leading to addictive eating behaviors [37].

3.3.3 Insulin resistance and lipid accumulation linked to processed food

Processed foods high in refined carbohydrates and added sugars can contribute to systemic insulin resistance [38]. The mechanism involves the overstimulation of the pancreas to release insulin in response to rapid glucose uptake, eventually leading to the pancreas' inability to produce sufficient insulin and the body's reduced responsiveness to insulin. This condition is a significant risk factor for the development of T2D and is closely associated with the accumulation of ectopic fat, particularly in the liver.

3.3.4 Processed food and endoplasmic reticulum stress

Processed foods, particularly those high in trans fats and refined sugars, can instigate endoplasmic reticulum (ER) stress in hepatocytes [39]. The ER is responsible for the proper folding and maturation of proteins. When overloaded with an excess of nutrients, the ER's capacity can be overwhelmed, leading to the accumulation of misfolded proteins, a condition known as ER stress. In response, the cell initiates the unfolded protein response (UPR) to restore normal function, but chronic ER stress can lead to apoptosis, inflammation, and further exacerbation of insulin resistance.

3.3.5 Processed food and inflammation

Inflammation is a fundamental component of adiposopathy and MASLD, and the consumption of processed foods significantly contributes to this phenomenon. The high content of trans fats, often present in processed foods, is implicated in the pathogenesis of liver inflammation [40]. Trans fats are known to alter the composition of cell membranes, affecting their fluidity and function, and they can disrupt lipid metabolism, leading to an increase in the synthesis of inflammatory mediators. One such pathway is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, a central mediator of the inflammatory response [41]. Activation of NF-κB leads to the transcription of various inflammatory cytokines, chemokines, and adhesion molecules, which can perpetuate a local inflammatory response. Moreover, the c-Jun N-terminal kinase (JNK) pathway is another critical mediator of inflammation induced by dietary stress. It is activated by various stress signals, including ER stress and cytokines [42]. Activation of the JNK pathway has been associated with insulin resistance and the promotion of inflammatory gene expression, further linking processed food consumption to metabolic dysfunction.

3.3.6 Food additives in processed food

Food additives commonly found in processed foods, such as emulsifiers, preservatives, and artificial sweeteners, have been implicated in the disruption of adipose tissues and hepatic metabolism. Emulsifiers can disrupt gut integrity, leading to a leaky gut syndrome which allows for the translocation of pro-inflammatory molecules into the portal circulation, contributing to systemic inflammation that is associated with obesity and the initiation and progression of MASLD [43, 44]. Preservatives can alter hepatic enzyme function and disrupt normal lipid metabolism, potentially leading to the accumulation of fat in adipose tissue and the liver, hallmark features of obesity and MASLD [45, 46]. Artificial sweeteners may affect the gut microbiome and metabolic signaling and have been linked to altered glucose handling and a predisposition to insulin resistance [47, 48]. Moreover, these additives can impact bile acid metabolism, crucial for fat digestion and absorption, and they can modulate metabolic pathways that contribute to the pathophysiology of adiposopathy and MASLD. Moreover, altering immune responses via food additives can lead to a pro-inflammatory state, affecting lipid metabolism in ways that promote the accumulation of lipids in the liver, thus driving the progression of MASLD in the context of obesity [36, 39, 48].

Thus, the consumption of processed and ultra-processed foods is closely linked to detrimental effects on metabolic health, driving the epidemics of obesity and fatty liver disease. These foods disrupt energy balance, interfere with insulin signaling, promote inflammation, and can contribute to addictive eating patterns, all of which can precipitate the development of metabolic syndrome and its hepatic manifestations.

3.4 Dietary fiber and microbiota

Dietary fiber plays a protective role against obesity and MASLD through various mechanisms [38, 49, 50]. High-fiber diets enhance feelings of fullness, reducing overall caloric intake. Furthermore, soluble fibers are fermented by gut microbiota, producing short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate, which have been shown to exert anti-inflammatory effects, improve gut barrier function, and regulate liver fat metabolism [43, 51]. The composition of the gut microbiota itself is influenced by dietary patterns, with high-fiber diets promoting a more diverse and beneficial microbial community. Dysbiosis, or the imbalance of gut microbiota, has been associated with metabolic endotoxemia, inflammation, and the development of insulin resistance, linking the gut-liver axis directly to the pathogenesis of obesity and NAFLD.

3.4.1 Satiety and caloric intake

Dietary fibers, especially soluble fibers, have the capacity to absorb water and form viscous gels in the digestive tract, slowing gastric emptying and enhancing feelings of fullness. This delayed gastric emptying, coupled with fiber's minimal caloric content, contributes to reduced caloric intake and, over time, weight management. By moderating appetite and reducing the likelihood of overeating, high-fiber diets can play a critical role in preventing and managing obesity.

3.4.2 Fermentation and SCFA production

In the colon, soluble fibers are fermented by the gut microbiota, resulting in the production of SCFAs such as acetate, propionate, and butyrate. SCFAs serve as

energy sources for colonocytes and have systemic effects. Butyrate, for example, is crucial for maintaining colonic barrier integrity and has anti-inflammatory properties. SCFAs also act on the liver, modulating gluconeogenesis and lipid metabolism, and have been shown to reduce hepatic steatosis. Furthermore, SCFAs can influence energy homeostasis and insulin sensitivity by acting on G-protein-coupled receptors (GPCRs), such as GPR41 and GPR43, which are expressed in adipose tissue, the gut, and the liver.

3.4.3 Gut microbiota and metabolic health

The composition of the gut microbiota is significantly influenced by dietary fiber intake. High-fiber diets promote a more diverse and resilient microbial ecosystem, enhancing the production of beneficial metabolites like SCFAs and reducing the abundance of pathogenic bacteria. Conversely, diets low in fiber can lead to dysbiosis, characterized by reduced microbial diversity and an imbalance in microbial populations. Dysbiosis has been linked to metabolic endotoxemia, wherein increased gut permeability allows bacterial endotoxins to enter the circulation, triggering systemic inflammation and insulin resistance, pivotal factors in the pathogenesis of obesity and MASLD [52–54].

Dietary fiber plays a crucial protective role against obesity and MASLD through mechanisms that enhance satiety, modulate gut microbiota and SCFA production, improve gut barrier function, and regulate metabolic pathways involved in inflammation and insulin sensitivity. These findings highlight the importance of dietary fiber in maintaining metabolic health and mitigating the risk of obesity-related liver diseases.

4. Fast food and beverage consumption patterns

Modern dietary habits, particularly the consumption of fast food, sugar-sweetened beverages, and the trends toward larger portion sizes and increased eating frequency, significantly influence the prevalence and progression of metabolic diseases such as obesity and MASLD [55]. These food and beverage consumption patterns, hallmarks of a rapidly globalizing food environment, contribute to an excess caloric intake and poor nutritional quality, setting the stage for a host of metabolic dysfunctions [56].

4.1 Fast food and restaurant meals

The consumption of fast food and restaurant meals significantly impacts metabolic health through various mechanisms. These meals often contain high levels of saturated fats, trans fats, refined carbohydrates, and sodium, which can contribute to an increased risk of obesity, insulin resistance, and MASLD.

4.2 Sugar-sweetened beverages and sweet fruit juices

Sugar-sweetened beverages (SSBs) and fruit juices represent a major source of added sugars in the diet, primarily in the form of sucrose or high-fructose corn syrup. The consumption of these beverages leads to a rapid increase in fructose and glucose intake, overloading the liver's capacity to metabolize fructose efficiently.

4.3 Role of portion sizes and eating frequency

Increasing portion sizes and frequent eating or snacking can disrupt normal eating patterns and satiety cues, leading to a sustained positive energy balance and weight gain. Large portion sizes can cause individuals to consume more calories than they need, contributing to adipose tissue expansion and the subsequent development of obesity and insulin resistance. Frequent eating, especially if it involves high-calorie, nutrient-poor foods, can maintain insulin levels in a perpetually high state, hindering the body's ability to efficiently metabolize fats and leading to increased fat storage in the liver and adipose tissue. This pattern of eating can also disrupt the natural fasting state necessary for the body to perform metabolic housekeeping processes, such as autophagy, which can help maintain cellular health and prevent disease [57].

Thus, modern food and beverage consumption patterns, characterized by high intakes of fast food, sugar-sweetened beverages, large portion sizes, and frequent eating, play a significant role in the pathogenesis of metabolic diseases. These dietary habits contribute mechanistically to the disruption of metabolic processes, leading to obesity, insulin resistance, inflammation, and the development of fatty liver disease.

5. Nutritional interventions for obesity and MASLD

Nutritional interventions stand at the forefront of strategies to combat obesity and MASLD, representing a spectrum of approaches that target the metabolic dysfunctions underlying these conditions. From caloric restriction and weight loss to the adoption of specific dietary patterns such as the Mediterranean and plant-based diets, and the strategic reduction of carbohydrate intake through low-carb and ketogenic diets, these nutritional strategies offer a path to mitigate the adverse effects of these diseases [58]. Coupled with the incorporation of dietary fiber and prebiotics to harness the beneficial effects of the gut microbiome, and the emphasis on personalized dietary plans, these interventions encapsulate a holistic approach to managing and potentially reversing obesity and fatty liver disease. This section delves into the scientific mechanisms by which these dietary interventions exert their effects, highlighting their importance in the broader context of metabolic health and disease management.

5.1 Caloric restriction, intermittent fasting, and weight loss

Caloric restriction and intermittent fasting is a fundamental approach for managing obesity and MASLD, primarily through the reduction of energy intake below daily energy expenditure to induce weight loss [58]. Mechanistically, caloric restriction diminishes the influx of dietary fatty acids to the liver, reducing substrate availability for triglyceride synthesis and accumulation. Weight loss achieved through caloric restriction also improves insulin sensitivity, lowering the hepatic and adipose tissue insulin resistance that contributes to obesity and MASLD. Furthermore, caloric restriction and intermittent fasting can modulate adipokine profiles, reducing the secretion of pro-inflammatory cytokines and enhancing the release of anti-inflammatory adipokines, which play roles in ameliorating systemic inflammation and metabolic dysfunction.

5.2 Mediterranean diet and plant-based diets

The Mediterranean diet, rich in fruits, vegetables, whole grains, legumes, nuts, olive oil, and fish, and plant-based diets emphasize the consumption of foods with anti-inflammatory properties and high antioxidant content [59, 60]. These diets are associated with reduced risks of obesity and NAFLD due to their high contents of dietary fiber, polyunsaturated and monounsaturated fatty acids, and phytochemicals. These components can improve insulin sensitivity, reduce hepatic fat accumulation, and modulate gut microbiota composition, promoting the growth of beneficial bacteria and the production of SCFA that have protective effects against obesity and MASLD.

5.3 Low carbohydrate and ketogenic diets

Low carbohydrate and ketogenic diets reduce carbohydrate intake, limiting glucose availability and forcing the body to use fatty acids as the primary energy source [61, 62]. This metabolic shift enhances lipid oxidation and ketone body production, which can reduce hepatic fat content and improve markers of metabolic health. Additionally, these diets can lower postprandial glucose and insulin levels, further contributing to improved insulin sensitivity, obesity, and reduced risk of MASLD.

5.4 Dietary fiber and prebiotics

Dietary fiber and prebiotics have significant roles in modulating the gut microbiota, enhancing intestinal barrier function, and promoting satiety [63, 64]. The fermentation of dietary fibers by gut microbiota produces short-chain fatty acids, which have been shown to exert beneficial effects on liver metabolism by inhibiting hepatic lipogenesis and promoting fatty acid oxidation. These effects contribute to the reduction of liver fat accumulation and inflammation, thus the management of MASLD.

5.5 Importance of individualized approaches

Individualized nutritional interventions recognize the variability in genetic, environmental, and lifestyle factors among individuals with obesity and MASLD. Tailoring dietary recommendations based on personal preferences, metabolic profiles, and specific health needs can improve adherence and effectiveness. Personalized diets can address unique metabolic dysfunctions, optimize gut microbiota composition, and mitigate specific risk factors associated with obesity and MASLD, thereby enhancing the overall success of nutritional interventions.

Overall, nutritional interventions offer a multifaceted approach to managing obesity and MASLD, with mechanisms ranging from improving insulin sensitivity and modulating lipid metabolism to reducing inflammation and optimizing gut microbiota. These strategies underscore the importance of dietary composition and individualized approaches in the prevention and treatment of metabolic diseases.

6. Future directions: public health strategies and precision medicine

As the global burden of obesity and MASLD continues to escalate, the mission for effective management strategies enters a transformative phase, marked by

the integration of advanced public health initiatives, personalized nutrition, and cutting-edge research on therapeutic targets. This section delves into the pioneering approaches that redefine our combat against these metabolic conditions, encompassing the adoption of an inverted food pyramid in public health strategies, the tailored precision of personalized nutrition, and the exploration of novel therapeutic targets and dietary interventions. These emerging directions not only promise to enhance the precision and effectiveness of obesity and MASLD management but also aim to revolutionize our understanding and approach toward achieving optimal metabolic health. Through a multidisciplinary approach, we explore the potential of these innovations to offer tailored, effective, and sustainable solutions to one of the most pressing health challenges of our time.

6.1 Public health strategies with inverting food pyramid

The traditional food pyramid, which emphasizes high carbohydrate intake at its base, is being reconsidered in light of the obesity epidemic. The concept of an inverted food pyramid suggests a paradigm shift toward a diet higher in healthy fats, moderate in protein, and lower in carbohydrates, particularly refined carbohydrates (**Figure 3**) [65]. This approach aligns with an evolving understanding of macronutrient impacts on satiety, insulin sensitivity, and metabolic health. Public health strategies incorporating this model focus on reducing processed food consumption, encouraging whole food diets rich in vegetables, fruits, nuts, seeds, and quality protein sources, thus readjusting a balanced diet. Implementing these strategies at a population level involves educational campaigns, policy changes to improve access to healthyfoods, and initiatives to reduce the prevalence of high-calorie, nutrient-poor food options in communities.

6.2 Nature and composition of a balanced diet

A balanced diet is key in the prevention and management of metabolic syndrome and necessitates a harmonious blend of macronutrients tailored to individual metabolic needs and health objectives. The composition of a balanced diet is rich in dietary fiber, lean proteins, and a diversity of micronutrients derived from a colorful array of fruits and vegetables, whole grains, and legumes. Emphasis on monounsaturated and polyunsaturated fats, while limiting saturated and trans fats, is crucial for maintaining cardiovascular health and mitigating the risk of insulin resistance. Adequate hydration, mindful portion sizes, and the timing of meals further contribute to the diet's ability to stabilize blood glucose levels, manage body weight, and support liver health. In the public realm, this balanced diet model serves as a blueprint for educational campaigns and health policies that encourage nutritional literacy and accessibility to nutritious foods and has a foundational importance for community-wide efforts in limiting metabolic syndrome.

6.3 Rebalancing daily energy intake by skipping a meal a day and its impact on metabolic health

Skipping a meal a day, often integrated into intermittent fasting regimes, has emerged as a strategy for rebalancing daily energy intake in the context of weight management and metabolic health improvement. This approach aligns with the body's circadian rhythms and can lead to a reduction in overall caloric consumption,

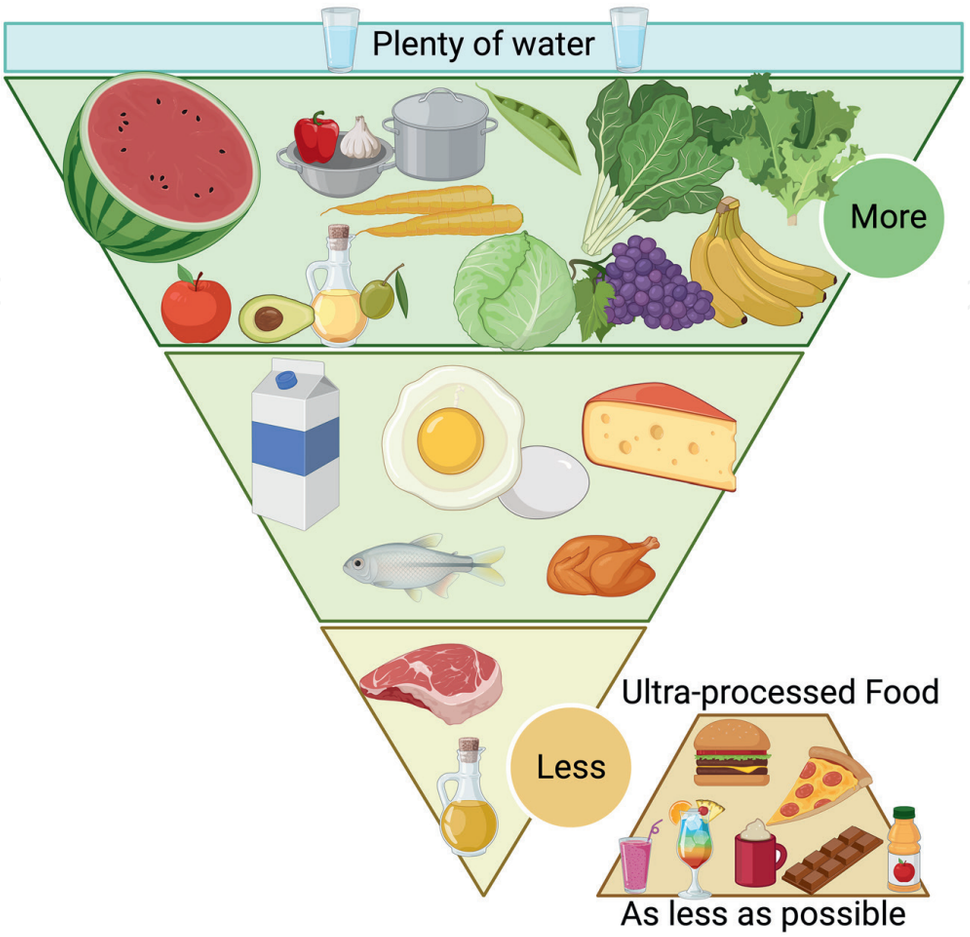

Figure 3.
Inverted food pyramid, an alternative guide for healthy eating: The pyramid emphasizes the consumption of whole foods and minimal intake of processed foods, with different food categories arranged in levels according to recommended consumption frequencies. The top level of the pyramid illustrates that the majority of the diet should consist of water, vegetables, fruits, whole grains, and healthy oils. These nutrient-rich foods are crucial for maintaining optimal health and should be consumed liberally, serving as the primary source of nutrients and hydration. The middle level includes dairy products, eggs, cheese, and lean proteins like fish. These foods provide essential proteins, fats, and other micronutrients. While these provide essential nutrients, they should be consumed in balanced proportions to maintain dietary diversity and metabolic health. The bottom level of the inverted pyramid displays red meats and unhealthy oils such as butter, suggesting that these should be consumed less frequently, in smaller portions due to their higher content of saturated fats and calories. A zone outside the inverted pyramid signifies ultra-processed foods including processed meats, ready-to-eat products and fast foods, alcoholic beverages, and sugary drinks are to be consumed as minimally as possible, indicating their low nutritional value and association with negative health outcomes when consumed in excess. Fall into this category. The model deliberately omits a 'Gray zone,' which comprises foods that have undergone some processing, like salted peanuts, fruit juices, chocolate milk, white bread, and sweetened yogurts. While these items may retain some nutritional benefits, they are less health-promoting compared to their unprocessed or minimally processed counterparts and thus do not feature within the pyramid structure itself. Illustration was created in BioRender.com.

potentially facilitating weight loss and improving insulin sensitivity. By extending the fasting period, meal skipping may enhance metabolic flexibility, allowing the body to switch more efficiently between using glucose and fat as energy sources. However, the consequences of routinely skipping meals can vary widely among individuals and depend on the timing, frequency, and nutritional context of the meals consumed.

From a physiological standpoint, skipping meals can initially induce a temporary state of increased fatty acid oxidation and ketone body production, as the body mobilizes energy reserves. However, chronic meal skipping without appropriate nutrient intake can lead to muscle protein breakdown, decreased basal metabolic

rate, and potential nutrient deficiencies, undermining long-term metabolic health and weight control. Thus, while meal skipping can be a part of a structured dietary approach to reduce energy intake and may confer metabolic benefits, it is crucial to consider individual dietary needs, personalized balanced diet, lifestyle factors, and potential negative outcomes. Nutritional guidance should ensure that overall dietary patterns remain balanced and nutritionally adequate to support bodily functions and metabolic health.

6.4 Personalized nutrition and precision medicine

Personalized nutrition and precision medicine represent a tailored approach to dietary planning and disease management, acknowledging individual variability in genetics, microbiome composition, metabolic status, and lifestyle factors. Advances in genomics, metabolomics, and microbiome research have begun to illuminate how these individual differences can influence responses to specific diets and nutritional interventions. Personalized nutrition aims to optimize health outcomes by customizing dietary recommendations to an individual's unique biological makeup, potentially improving the management of obesity and MASLD. This approach requires robust algorithms that integrate various data types to predict individual responses to dietary interventions, alongside scalable models for delivering personalized nutrition advice.

6.5 Emerging therapeutic targets and novel dietary approaches

Research into the pathophysiology of obesity and MASLD continues to uncover new therapeutic targets, ranging from molecular pathways involved in lipid metabolism and inflammation to gut microbiota-host interactions. These discoveries pave the way for the development of novel dietary approaches and pharmacological interventions aimed at specific molecular targets. For instance, compounds that modulate the activity of nuclear receptors involved in fatty acid oxidation, or agents that alter gut microbiota composition in favor of beneficial species, represent promising areas of investigation. Additionally, the exploration of dietary components that can mimic the effects of pharmacological agents, known as nutraceuticals, offers an intriguing avenue for non-invasive intervention [66, 67]. These emerging strategies highlight the potential for innovative approaches to complement traditional dietary and lifestyle modifications in combating obesity and MASLD.

7. Conclusion

The exploration of dietary determinants and nutritional interventions in the context of obesity and MASLD has ignited the profound impact of food consumption patterns on metabolic health. Through a detailed examination of the roles played by caloric balance, macronutrient composition, processed foods and additives, and the pivotal influence of dietary fibers and gut microbiota, this chapter has underlined the complex connections between diet, metabolic regulation, and the pathogenesis of these metabolic dysfunctions including MASLD. The insights into how various dietary components and habits contribute to or protect against metabolic dysregulation offer valuable guidance for developing effective dietary strategies. Furthermore, the discussion on personalized nutrition and the potential of novel dietary approaches and nutraceuticals-based therapeutic approaches reveals an evolving landscape in the

management and prevention of obesity and MASLD, highlighting the importance of individualized and innovative strategies.

Looking ahead, the integration of personalized nutrition, public health initiatives, and emerging research into therapeutic interventions holds the promise of transforming the management of obesity and MASLD. The shift toward diets that emphasize whole foods, the strategic reduction of processed and ultra-processed food intake, and the incorporation of individual genetic, environmental, and lifestyle factors into dietary planning are poised to offer more targeted and effective solutions. As we move forward, research must continue to unravel the complex mechanisms underlying these conditions, fostering the development of new strategies that can prevent, manage, and potentially reverse obesity and MASLD. The collective efforts in research, public health policy, and clinical practice will be crucial in addressing the global challenge posed by these metabolic diseases, paving the way for healthier futures.

Acknowledgements

The authors are thankful to the Ministry of Health (MOH) and National Medical Research Council (NMRC), Singapore, for financial assistance grant number NMRC/OFYIRG/0002/2016 and MOH-000319 (MOH-OFIRG19may-0002), Khoo Bridge Funding Award (DUKE-NUS-KBRFA/2023/0075), and Duke/Duke-NUS Collaboration Pilot Project award (RECA(Pilot)/2022/0060) to BKS; NMRC/OFYIRG/077/2018 to MT.

Conflict of interest

The authors declare no conflict of interest.

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