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# Diet patterns, gut microbiota and metabolic disorders: Perspectives and challenges

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ABSTRACT

The worldwide surge in obesity and associated metabolic disorders is emerging as a significant public health issue for societies and healthcare systems. Available evidence has shown that alterations in the gut microbiota could be implicated in the pathogenesis of obesity and associated disorders. A healthy gut microbiome is characterized by richness and high microbial diversity. Gut microbiota affect how the host responds to diet, and conversely, the host may modify the gut microbiota through changes in dietary habits. Diet can impact and alter the composition, diversity, and species richness of the gut microbiota over time. An unhealthy diet, high in fat and sugar, may lead to decreased microbial diversity, reduced synthesis of metabolites that maintain gut permeability, damage to the mucus layer, increased bacterial translocation and lipopolyssacharide which can trigger endotoxemia, chronic subclinical inflammation and metabolic disorders. Currently, the impact of diet on gut microbial composition and its involvement in the pathogenic mechanisms underlying metabolic disorders is one of the most promising areas of research in nutrition. This special issue has gathered original research articles in topics related to diet patterns, gut microbiota, obesity and associated metabolic disorders as well as brief reports, reviews and perspectives in the wider field of translational and clinical metabolic research. In particular, the aim of this Special Issue was to present evidence connecting gut microbiota with metabolic disorders, explore the underlying mechanisms of this association, and examine how diet patterns may influence this relationship.

## 1. Diet patterns, gut microbiota and metabolic disorders

The worldwide surge in obesity, often termed "globesity," is emerging as a significant public health crisis for societies and healthcare systems. Acknowledging the severe impacts of the growing obesity rates globally, the World Health Organization (WHO) officially classified obesity as an epidemic in 1997 [1]. The World Obesity Atlas 2023 report indicates that 38 % of the world's population is now either overweight or obese, with a body mass index (BMI) exceeding 25 kg/m$^2$ [2]. By 2035, it is anticipated that 51 % of the global population will fall into these categories, with the South Pacific Islands being particularly affected by the obesity epidemic. Notably, projections for the United States suggest that by 2030, 78 % of American adults will have excess body weight [2,3]. The global rise in disorders related to obesity, such as type 2 diabetes mellitus (T2DM), metabolic syndrome (Mets), cardiovascular disorders and metabolic dysfunction-associated fatty liver disease (MAFLD), is becoming increasingly significant [4,5]. Notably, the prevalence of Mets is often higher in urban areas of developing countries compared to developed nations. Among American adults, the prevalence of Mets increased from 28 % to 37 % between 1999 and 2018, primarily due to higher rates of fasting hyperglycemia and obesity [3,6].

Currently available evidence suggests that alterations in the gut microbiota could be implicated in the pathogenesis of obesity and associated disorders [7,8]. The majority of microorganisms in the human body are located in the gastrointestinal (GI) tract and are collectively known as the gut microbiota, with up to 100 trillion ($10^{14}$) microbes residing in the colon. The gut microbiota influences human physiology and pathology by regulating nutrition and energy harvest. Other functions include the synthesis of vitamins, such as vitamin K, riboflavin, cobalamin, folate and biotin, and amino acids, the fermentation of indigestible substrates such as dietary fiber and gut mucus, the synthesis of short-chain fatty acids (SCFA), the metabolism of dietary toxins, several xenobiotics including drugs and carcinogens, the conversion of cholesterol and bile acids, the maintenance of intestinal epithelial homeostasis, the maturation of the immune system, and the immunity against pathogens [7–11]. SCFAs, of which the most abundant are acetate, propionate and butyrate in an analogy of 3:1:1 approximately, serve as a crucial energy source for intestinal epithelial cells, aiding in gut barrier integrity as well as the growth and maintenance of microbiota in the anaerobic environment of the gut. In particular, butyrate is a key energy provider for colonocytes and supports intestinal homeostasis through its anti-inflammatory properties. Meanwhile, acetate and propionate are vital for the interconnected networks involved in macronutrient metabolism [11,12]. A healthy gut microbiome is characterized by richness and high microbial diversity with a wide range of species present. Greater species diversity or richness in gut microbiota is considered beneficial, whereas dysbiosis, as indicated by 16S rRNA gene sequencing data, is linked to metabolic dysfunction in the host, leading to the development and progression of various diseases [7–12]. Accumulating data have indicated that the human gut microbiota is primarily composed of *Firmicutes* and *Bacteroidetes*, with *Actinobacteria* and *Proteobacteria* present in smaller proportions. The ratio of *Firmicutes* to

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*Bacteroidetes* (F/B) is crucial for maintaining normal intestinal homeostasis being influenced by various genetic and environmental parameters, including mode of birth delivery, breastfeeding, dietary habits, drugs (especially antibiotics), hygiene, exposure to toxins, and physical activity [11–14]. An imbalance in this ratio, whether elevated or decreased, is considered dysbiosis, with a higher F/B ratio often associated with obesity and susceptibility to obesity as observed in studies with genetically obese ob/ob mice, diet-induced obese mice as well as in humans with excess body weight [10–12,15]. A reversed pattern was observed in individuals following one-year diet treatment and gut bypass as well as weight-loss diets [12,16]. Interestingly, the ability to harvest energy can be transferred by transplanting microbiota from obese individuals into healthy, lean recipients [16,17].

Gut microbiota affect how the host responds to diet, and conversely, the host may modify the gut microbiota through changes in dietary habits. Diet can impact and alter the composition, diversity, and species richness of the gut microbiota over time. The Western-style diet has become a major factor in promoting gut microbial imbalance, chronic inflammation, and various chronic diseases, particularly impacting the cardiovascular system, systemic metabolism, and the digestive tract. For example, in mice, a shift from a diet rich in plant polysaccharides and low in fat to a diet high in fat and sugar may alter intestinal microbiota within a single day [12,18]. Research in humans has shown significant changes in gut microbiota within 24 hours of switching from a high-fat, low-fiber diet to a low-fat, high-fiber diet [19]. Consequently, an unhealthy diet leads to decreased microbial diversity, reduced synthesis of metabolites that maintain gut permeability, damage to the mucus layer, increased bacterial translocation and lipopolyssacharide (LPS) which can trigger endotoxemia, chronic low-grade inflammation and metabolic disorders. On the contrary, a healthy diet enhances gut barrier function and mucus production, lowers luminal pH, and diminishes microbial translocation, resulting in an improved insulin sensitivity and an elevation of anti-inflammatory molecules. Moreover, an increase in SCFA is associated with the release of anorectic gut hormones, such as PYY and glucagon-like peptide (GLP-1), which play a significant role in regulating satiety, hunger, energy expenditure, insulin sensitivity, and lipolysis [20,21].

Obesity constitutes a persistent state of low-grade inflammation, which differs significantly from acute classical inflammation [22–28]. It is characterized by a mild increase in pro-inflammatory cytokines and adipocytokines like tumor necrosis factor (TNF)-alpha, IL (interleukin)-1beta, IL-6, C-C Motif Chemokine Ligand 2, leptin, resistin, visfatin, chemerin, etc along with a reduction of anti-inflammatory cytokines such as adiponectin and omentin-1, and elevated levels of mast cells, T cells, and macrophages [29–36].

Currently, the impact of diet on intestinal microbial composition and its involvement in the pathogenic mechanisms underlying metabolic disorders is one of the most promising areas of research in nutrition [12, 37,38]. Therefore, the goal of this Special Issue is to present evidence connecting gut microbiota with metabolic disorders, explore the underlying mechanisms of this association, and examine how diet patterns influence this relationship.

## 2. Special issue on diet patterns, gut microbiota and metabolic disorders

This special issue has collected original research articles in topics related to diet patterns, gut microbiota, obesity and associated metabolic disorders as well as brief reports, reviews and perspectives in the wider field of translational and clinical metabolic research.

Obesity is a major global health issue being associated with a wide array of metabolic disorders, cancers at 13 anatomic sites and infections [39–48]. Despite the increasing rates of obesity among adolescents, there is limited understanding of their perspectives on this condition. Batzios et al. aimed at exploring adolescent's perceptions in association with various aspects of obesity in a prospective cohort study [49]. Their findings affirm that adolescents are fully capable of expressing their opinions regarding obesity. Therefore, their perspectives should be carefully considered when designing intervention programs for managing adolescent obesity [49].

The Mediterranean Diet (MedDiet) is widely acknowledged as one of the healthiest and most sustainable dietary patterns globally, rooted in the traditional eating habits of those living in the Mediterranean region [50,51]. MedDiet refers to a dietary pattern that emphasizes plant-based foods such as fruits, vegetables, minimally processed cereals, legumes, nuts, and seeds. It includes moderate consumption of dairy products, primarily in the form of fermented items like cheese and yogurt, as well as modest amounts of fish and poultry. Red meat is consumed sparingly, and meals are often accompanied by wine [52]. An umbrella review of meta-analyses, encompassing observational studies and randomized clinical trials with data from over 12,800,000 participants, strongly supports the protective link between adherence to the MedDiet and various health outcomes, such as reduced mortality from any cause, diabetes, cardiovascular diseases, cancer and neurodegenerative diseases [53]. In their review, Tsigalou et al. aimed at exploring holistically the interplay between diet and gut microbiota and the potential beneficial effects of MedDiet on metabolic disorders such as obesity and its associated disorders focusing on useful perspectives and potential therapeutic targets [54]. Research on the influence of gene-diet interactions on the development of gestational diabetes mellitus (GDM) is limited. Recent studies have indicated that adherence to MedDiet in the late first trimester is linked to a decreased risk of GDM. Barabash et al. aimed to explore whether this effect is influenced by the TCF7L2 rs7903146 polymorphism [55]. They found that women with the rs7903146 T-allele who follow a MedDiet closely early in pregnancy have a reduced risk of developing gestational GDM compared to those with the CC genotype. This highlights the significance of recognizing patients at a higher risk of GDM who may benefit more from dietary interventions tailored to their genetic profiles [55].

A vegetarian diet is often seen as simply excluding animal-derived foods, but it encompasses a variety of eating patterns. The most prevalent form is the lacto-ovo vegetarian diet, which excludes meat and fish (including mollusks and shellfish) but includes dairy products and eggs. This is the type typically referred to when discussing a vegetarian diet. Other variations include the pesco-vegetarian diet, which allows fish; the lacto-vegetarian diet, which excludes eggs; and the ovo-vegetarian diet, which excludes dairy. Lastly, the vegan diet strictly avoids all animal-derived products, including honey, representing the most restrictive form of vegetarianism [52,56]. The prevalence of restrictive diets, mainly vegetarian and vegan, is markedly increased in Europe and other Western countries whereas the proportion of vegetarians ranges from 4.1 to 11 % depending on the country [56]. Increased adherence to vegetarian diets has been associated with a lower risk of cardiovascular diseases, dyslipidemia, diabetes, certain cancers, and potentially, reduced overall mortality. Various pathways have been implicated, such as metabolic, inflammatory and neurotransmitter pathways, gut microbiota, and genome instability [52]. However, the more restrictive the diet, the greater the risk of various nutrient deficiencies. Vegans are especially prone to vitamin B12 deficiency, as this vitamin is found exclusively in animal-derived foods. Additionally, lower intakes of other nutrients, such as vitamin B2, niacin, iodine, zinc, calcium, potassium, and selenium, have been observed [52,56]. Type 1 diabetes (T1DM) constitutes a chronic autoimmune disorder marked by a complete lack of insulin production [57,58]. The management of T1DM relies on three main components: insulin therapy, a proper diet, and physical activity. Tromba et al. aims to emphasize the role of diet, particularly a vegetarian diet, in order to assess whether this dietary approach can provide the essential nutrients required for growth and effective glycemic control [56]. The authors concluded that vegetarian diet could be suitable for children with T1DM; vegan diet could be too restrictive but with appropriate additions can be followed by these patients [56].

Polycystic Ovary Syndrome (PCOS), a prevalent endocrine disorder among women of reproductive age, affects an estimated 10–15 % of women globally. Its primary clinical features include androgen excess, oligo-anovulatory infertility, polycystic ovaries, insulin resistance, and cardiometabolic manifestations [59,60]. While PCOS is commonly associated with obesity, many patients with PCOS may also be lean. Various dietary patterns have been investigated to manage and improve insulin sensitivity, infertility, and cardiometabolic disturbances in PCOS. Barrea et al. explored the metabolic characteristics and body composition of these patients, and examined the different nutritional strategies employed for women with PCOS based on whether they have a lean or obese phenotype [61].

Intermittent fasting has gained popularity as a more manageable option compared to continuous fasting. It encompasses various regimens that alternate between periods of fasting or restricted eating and periods of normal or unrestricted eating [52]. The circadian rhythm regulates numerous metabolic processes such as sleep-wake cycles, body temperature, hormone secretion, liver function, cellular plasticity, and cytokine release (inflammation), all of which interact dynamically. Evidence has associated various cytokines with the chronic low-grade inflammation and oxidative stress found in obesity [62–64]. Dawn-to-dusk dry fasting (DDDF) may mitigate the negative impacts of obesity by reducing inflammation. Al Lami et al. investigated the effects of DDDF on circulating proinflammatory cytokines in 13 subjects (10 men and 3 women) with a mean age of 32.9 ± 9.7 years and a mean body mass index (BMI) of 32 ± 4.6 kg/m$^2$ [65]. They found that there was a reduction in the levels of multiple proinflammatory cytokines with DDDF, which seems to be an effective and unique approach for decreasing low-grade chronic inflammation associated with obesity and visceral fat. Additional research with longer follow-up periods is needed to explore the long-term anti-inflammatory effects of DDDF in subjects with elevated BMI [65].

Finally, this Special Issue features five studies on some specific nutrients and vitamins and their significance in metabolic disorders and cardiometabolic parameters.

While pistachios have been found to enhance cardiometabolic biomarkers in both diseased and at-risk populations, there is limited research focusing on young, healthy individuals. Additionally, although some studies suggest that exercise can temporarily improve cardiometabolic markers, the reasons for the variability of outcomes in diverse studies are not well understood. North et al. investigated secondary objectives of a study aimed at evaluating the effects of pistachios on recovery following intense, eccentrically-biased exercise [66]. They found that in healthy young men with normal blood lipid and glucose levels, neither pistachios nor intense exercise had a significant impact on cardiometabolic risk factors. Further research is required to understand how regular dietary intake affects outcomes after an acute exercise session [66]. In another study, Yanni et al. sought to examine how a dietary intervention involving pistachio nuts, which are known for their high content of monounsaturated fatty acids, dietary fibers, and phytochemicals, may affect gut microbiota composition in a rat model of T1DM [67]. They found that a diet including pistachios restored normal gut flora and increased the presence of beneficial microbes in a rat model of streptozotocin-induced diabetes. Specifically, they observed that: 1) the pistachio diet improved the balance of gut microbiota in diabetic rats; 2) fecal counts of *Lactobacilli* and *Bifidobacteria* were higher in rats consuming pistachios; 3) the population of *Firmicutes* increased in healthy rats following a pistachio diet; 4) *Bacteroidetes* levels were lower in healthy rats that were given pistachios; and 5) the genus *Bifidobacterium* was more prevalent in diabetic rats on the pistachio diet [67].

Adhesive transdermal delivery devices, such as patches, represent a recent innovation in administering micronutrients [68]. A significant challenge with this delivery method is overcoming the skin's physical barrier, but microneedle (MN) arrays or skin pretreatment with MNs can improve effectiveness. Evidence from non-randomized human trials suggests that iron delivery through skin patches may be suboptimal, especially since these trials did not utilize MNs. Additionally, patches have shown limited success in addressing micronutrient deficiencies in patients who have undergone bariatric surgery [68,69]. Grammaticopoulou et al. reviewed the sparse human studies and noted the variability in design and methodology in animal research. Consequently, while the approach shows promise, research is still in the early stages, and definitive conclusions about the efficacy of transdermal micronutrient delivery in humans have yet to be established [68].

Zinc is a crucial nutrient for maintaining human health, playing a key role in glucose, lipid, and protein metabolism, as well as in antioxidant networks within biological pathways. Deficiencies in zinc may contribute to various chronic liver conditions [70,71]. NAFLD is a prevalent liver disorder in which zinc deficiency is a significant factor in its development [4,70]. Research in both humans and animals has demonstrated that lower blood zinc levels are linked with both the risk factors for NAFLD (such as insulin resistance, diabetes, dyslipidemia, obesity, and hypertension) and the disease itself [71]. Barbara et al. reviewed the mechanisms connecting zinc deficiency with NAFLD and discussed the potential of zinc in preventing and treating this condition [71].

Recently, incretins have emerged as therapeutic targets for diabetes management [72,73]. GLP-1, an incretin secreted by the gut, plays a significant role in controlling diabetes by reducing pancreatic β-cell apoptosis and improving insulin sensitivity. Pegah et al. investigated the impact of resveratrol and probiotics on insulin resistance, oxidative stress, and GLP-1 levels in diabetic rats [74]. Their findings suggest that both resveratrol and probiotics may be effective in managing T2DM, as they could increase GLP-1 levels and reduce oxidative stress [74].

A complex blend of organic contaminants and metals has been linked to neurologic and fertility disorders, with research indicating that phenolic antioxidants from herbal sources may show beneficial properties. Akintunde et al. investigated the protective effects of phenolic compounds from Croton zambesicus (C-ZAMB) leaves against neurologic and ovarian damage in rats exposed to a chronic mixture of anthropogenic toxicants (EOMABRSL) [75]. They found that both chronic and sub-chronic exposure to EOMABRSL may affect ovarian follicles and lead to increases in biochemical markers associated with neurological disorders. Additionally, these rats showed higher levels of ovarian injury markers and lower fertility biomarkers. The phenolic antioxidants (quercetin, apigenin, caffeic acid, and gallic acid) from C-ZAMB leaves mitigated the effects of chronic EOMABRSL exposure. The treatment improved the condition of cerebral blood vessels and ovarian follicles, enhanced endogenous antioxidant levels, and reduced lipid peroxidation by providing synergistic and additive neuroprotective and ovarioprotective effects. Overall, this study showed that phenolic C-ZAMB compounds may prevent neuro- and ovario-toxicity induced by chronic EOMABRSL exposure in rats [75]. However, further research is needed to explore the molecular mechanisms of each phenolic antioxidant from C-ZAMB leaves.

In summary, we anticipate that this Special Issue, which includes research from our distinguished colleagues, may enhance the understanding of current findings related to dietary patterns, gut microbiota, obesity and associated disorders. We firmly believe that these contributions could be valuable to readers and future researchers, supporting the exploration of new research avenues for identifying and developing diagnostic, prognostic, and predictive biomarkers, as well as novel therapeutic targets.

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**Conflicts of interest**

The authors declare no conflict of interest.

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