International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 5 | Issue: 5 | Sep – Oct 2024 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v5i5.11

The Interplay Between Genetic, Environmental, and Microbiome Factors in the Development of Obesity: A Comprehensive Literature Review

Dzaky Ramadhan Hidayat[1,2], Fatita Rachma Laudira[1], Anggie Dewi Pitaloka[1], Fesli Fadhila Ramadhani Saputro[1], Sintia Wahyu Arifah[1]

[1]Faculty of Medicine, University of Muhammadiyah Malang, Indonesia

[2]General Practitioner, Melati Husada Hospital, Malang, Indonesia

ABSTRACT

Obesity is a multifactorial condition that primarily occurs due to genetic, environmental, and microbiome-related factors. This broad-based review attempts to deliberate on how these varying aspects come together and determine the risk and the case of obesity. It has been shown that genetic predisposition leads to obesity outcomes. Environmental factors including dietary habits, exercise, and lifestyle are engaging with the genes, either being a persuasor or a deterrent to obesity. Emerging research highlights the critical role of the gut microbiome in modulating metabolism, inflammation, and energy balance, further complicating the obesity landscape. Studies demonstrate that microbial dysbiosis can drive increased fat storage and insulin resistance, often in conjunction with genetic and dietary factors. This review integrates evidence from genetic, environmental, and microbiomic attention with inseparable relationships of the factors. On top of this, we discuss possible treatment approaches that utilize modulation of the microbiome and individualized strategies aimed at the gene-environment-microbiome interplay. The review highlights the importance of integrative, multi-dimensional approaches to understanding and managing obesity, offering insights into future research and personalized treatment strategies.

Keywords: obesity; gut microbiome; genetics; environmental factors; personalized medicine; metabolic disease.

INTRODUCTION

Obesity has emerged as a significant global health concern, characterized by excessive body fat accumulation that poses health risks. The prevalence of obesity has reached alarming levels globally. According to the WHO, in 2014, more than 1.9 billion adults, aged 18 years and older, were overweight, and of these, over 600 million were classified as obese. The trend continues to rise, with projections indicating that by 2030, approximately 38% of the world's adult population will be overweight, and 20% will be obese [1]. The increase in obesity rates is not uniform; it varies significantly across different regions and demographics. For instance, the prevalence of obesity is particularly high in North America, where approximately 34% of adults are classified as obese, compared to lower rates in parts of Asia and Africa. Several epidemiological studies have documented the rising prevalence of obesity across various populations. In the United States, the prevalence of obesity has more than doubled since the 1970s, with significant increases observed in all age groups, ethnicities, and socio-economic statuses [2]. Similarly, countries in Europe and the Middle East have reported substantial increases in obesity rates, with some regions experiencing rates exceeding 30% among adults [3]. In low- and middle-income countries, rapid urbanization and the adoption of Western dietary patterns have contributed to rising obesity rates, leading to a dual burden of malnutrition and obesity [4].

The prevalence of obesity in Indonesia has been steadily increasing over the past few decades. According to recent studies, the proportion of overweight and obese individuals has risen significantly, particularly in urban areas. A narrative review indicated that the incidence of overweight and obesity is higher in urban populations compared to rural ones, driven by lifestyle changes associated with urbanization, such as increased consumption of high-calorie foods and reduced physical activity. The Indonesian National Health Survey (RISKESDAS) reported that the prevalence of obesity among adults increased from 14% in 2007 to 21.8% in 2018, highlighting the urgency of addressing this public health challenge [5]. Cultural perceptions of body image can influence dietary habits and obesity prevalence. In some Indonesian communities, larger body size is often associated with wealth and prosperity, which can lead to overconsumption and increased obesity rates [5]. The double burden of malnutrition, where undernutrition coexists with overnutrition, is also prevalent in Indonesia, complicating the public health landscape [5,6]. Obesity is associated with numerous health complications, including type 2 diabetes, cardiovascular diseases, certain cancers, and musculoskeletal disorders [7]. Epidemiological studies have shown that obesity significantly increases the risk of developing chronic diseases, with over 85% of individuals with type 2 diabetes being overweight or obese [8].

Obesity represents a major public health challenge worldwide, with its prevalence continuing to rise at alarming rates. The interplay of genetic, environmental, and lifestyle factors contributes to this complex condition, necessitating comprehensive strategies for prevention and management.

GENETIC FACTORS IN OBESITY

Genetics can contribute to causing increased body weight by influencing metabolic pathways, neural networks, and appetite control centers. For example, the interaction of multiple genes, such as genes encoding peptides targeted to transmit hunger and satiety signals, genes involved in adipocyte growth and differentiation, and genes involved in energy expenditure control. These can lead to several metabolic disorders such as insulin resistance, dyslipidemia, inflammation, hypertension, and ectopic fat deposition-especially in the liver, which are the markers of obesity [9]. Genetics is also related to the hypothalamic system in the control of energy balance, which includes the leptin-melanocortin system. The result of this mutation leads to changes in the activity of hormones, enzymes, and receptors, which causes hyperphagia with the onset of obesity [10]. The genome-wide association studies (GWAS) and next-generation sequencing (NGS) discovery of genetic associations and awareness of monogenic and polygenic causes of obesity are put in non-syndromic obesity classification. Furthermore, the genetics of obesity could be classified into syndromic and non-syndromic obesity [11]. Syndromic obesity is caused by chromosomal rearrangements. Chromosomal defects can lead to other clinical manifestations. It is associated with other signs of a developmental disorder and may or not be accompanied by a congenital malformation syndrome. Congenital malformation is marked by dysmorphic features and organ abnormalities. Some examples of syndromes are Prader-Willi syndrome, WAGR syndrome, SIM1 syndrome, and pleiotropic syndromes, including Bardet-Biedl syndrome, Fragile X syndrome, Cohen syndrome, and PCOS [12,13]. Non-syndromic obesity is associated with genes. The amount of body fat is affected by many different factors, including how efficiently the digestive system extracts nutrients from food, how easily nutrients are stored as fat or burned as fuel, and how hungry we feel. Each of these factors is influenced by hundreds of genes. The contribution of each of these genes is not defined. While there are some genetic variants that greatly increase the risk of obesity, these are rare. Even people with a similar risk of obesity may have different genetic reasons for that risk [14]. Monogenic obesity is caused by a single gene mutation that affects the increased input of food and reduces energy use. Defects in at least 15 genes are the cause of monogenic obesity cases, resulting mostly from mutations in the melanocortin-4 receptor (*MC4R*) gene in the leptin-melanocortin signaling pathway. This is related to variation in genes associated with hyperphagia. Meanwhile, leptin is involved with appetite. People with a lack of leptin are not obese. On the other hand, people who are obese have hyperleptinemia.

Other melanocortin pathway, such as POMC (pro-opiomelanocortin) and PCSK1 (proprotein convertase subtilisin/kexin type 1) also have contributed to obesity. In patients with congenital POMC deficiency, there is now a pharmacologic alternative that counteracts hyperphagia and obesity. Studies on patients with severe obesity identified a mutation in the *PCSK1* gene. Most of those patients have early-onset obesity and hyperphagia [15]. Another gene of interest is the *NPY* (neuropeptide Y). It is a potent hypothalamic orexigenic peptide. NYP can cause increased food intake and obesity. Neuropeptide Y neurons inhibit POMC neurons that decrease appetite, and they activate orexin- and melanin-concentrating hormones, which are appetite-inducing peptides [16]. The most important recognized gene is the FTO (fat mass and obesity-associated) gene. FTO is the first obesity-susceptibility found through GWAS in European diabetes type 2 patients. This gene is significantly associated with BMI (body mass index). In studies, when patients control their weight or BMI, there is no significant association between these two. Thereby indicating that the association between FTO and type 2 diabetes was mediated through the effect of FTO on BMI [17]. Polygenic obesity is complex and multifactorial. It is found in 95% of cases of obesity and many related genes cause this type of obesity while they are also influenced by environmental factors such as the obesogenic environment. Various number of polymorphism (SNPs) identified as susceptibility genomic biomarkers for obesity are indeed found in obesity as increased BMI, lipid metabolism, insulin secretion, and genes involved in neural circuits of appetite and satiety, such as BDNF, NEGR, IRS1, and INSIG2. Certain individuals can be susceptible to variations in obesity-causing genes through various pathways such as appetite control (NPY, POMC, MC4R), energy expenditure (uncoupling protein/ UCP), or inflammatory (adiponectin/ ADIPOQ, tumor necrosis factor-α/TNFα, interleukin-6/IL6, Resistin/RETN [10,14]. In a study, a significant relationship was found between the immune system and microbiota. In another study showed a significant relationship between the immune system and genetics. Furthermore, it can be hypothesized that immune genome variation may help explain the differential representation of the gut microbiota that is unique to each individual. This variability may be directly related to inflammatory diseases (intestinal and non-intestinal). Inflammation also plays a role in obesity [18].

ENVIRONMENTAL INFLUENCES ON OBESITY

Environment and culture are the main combined causes of obesity. According to recent research, these are visible in people's lifestyles and influence health-related behaviors, such as food diet, and physical activity [19]. Adolescents often have poor diets and physical inactivity, which can lead to overweight and obesity. Important elements that influence this include dietary changes, affordability and easy access to unhealthy foods, a plethora of entertainment options that do not require active movement, and attractive advertisements [20].

In the United States, obesity rates are known to be higher in rural areas than in metropolitan areas [21]. Factors that influence this include lack of physical activity and easy access to nutritious food. In addition, this is also due to local infrastructure as well as variations in the income and education levels of people living in these places. An increase in the prevalence of obesity can be attributed to the difficulty of obtaining healthy food. Price and distance to food sources such as shops are also factoring making it difficult to get the food needed. In addition, the availability of unhealthy food, such as in fast food restaurants, can also increase the chance of obesity [22]. The COVID-19 pandemic and all the regulations imposed by many countries to prevent transmission, such as social distancing and lockdowns, are affecting people's diets and activity patterns. In many cases, people are spending more time in front of screens and the duration of sleep is increasing while the level of physical activity is decreasing. The amount of food consumed has also increased. Processed foods that can be stored for long periods of time are being preferred and consumed by many people. As a result, people find it more difficult to manage their weight [23]. In pandemic conditions, people buy processed foods that have a longer shelf life in large quantities, and they consume them instead of fresh, nutritious, and healthy foods, which are less accessible during lockdown [22]. Food processing has undergone significant changes with the increasing availability and consumption of ultra-processed foods (UPFs). UPFs are industrial formulations that use food extracts from original sources, usually containing five or more ingredients. These foods comprise packaged snacks, soft drinks, and cereals. The amount of UPFs consumed worldwide is huge and has grown rapidly in recent years. Clinical data show an association between higher caloric intake and weight gain with UPFs, and observational data show a positive correlation between UPFs, weight gain, and obesity. The mechanism by which UPF promotes obesity is not entirely clear. Larger portions and eating faster are two other characteristics that can lead to obesity due to higher calorie consumption [22]. The risk of weight gain is increased by consuming sugary drinks containing sugar and artificial sweeteners [24]. Urbanization has significantly transformed dietary patterns in Indonesia, leading to increased consumption of ultra-processed foods, which are often high in sugars and unhealthy fats. This shift is particularly pronounced in urban areas like Jakarta, where the prevalence of obesity is notably higher [25].

According to the research findings, children and adolescents in China are more likely to be overweight or obese as their family's socioeconomic status improves. In developing countries such as Nigeria and India, families with better socioeconomic levels are also more likely to have overweight or obese children and adolescents. The main reason for this phenomenon is that people's lifestyles and eating habits have changed significantly as a result of China's rapid economic growth and abundant food supply, but parents' awareness of a balanced diet and their knowledge of nutrition have not kept up. There are gender differences in the prevalence of overweight and obesity with boys having a higher prevalence than girls. The following factors may play a role in explaining why boys are more likely to be overweight or obese than girls: First, the difference in the food given to boys and girls is due to the tendency of parents in China to recognize their children's physical growth. Boys are fed more, which increases the prevalence of overweight and obesity higher than that of girls; second, most boys' food intake is much higher than that of girls, and boys prefer meat and potato foods, which are associated with overweight and obesity; third, from living behaviors, the 2005 Adolescent Risk Behavior Monitoring Report shows that 29.1% of boys play computer games more than 2 hours a day, twice as much as girls [26]. Studies indicate that higher socioeconomic status (SES) is associated with increased rates of obesity in Indonesia, contrary to trends observed in many high-income countries where lower SES is often linked to higher obesity rates [27,28]. This phenomenon can be attributed to better access to resources, including food and healthcare, which allows wealthier individuals to afford higher-calorie diets and engage in less physically demanding occupations. Additionally, the role of education and awareness regarding nutrition and health is significant, as individuals with higher education levels tend to have better health outcomes and dietary choices [29]. Furthermore, cultural factors and social norms surrounding body image and health can influence dietary choices and physical activity levels. In some Indonesian communities, higher body weight is often perceived as a sign of wealth and health, which can discourage weight management efforts [30]. This cultural perception, combined with the marketing of unhealthy food options, exacerbates the obesity crisis.

GUT MICROBIOME AND OBESITY

In recent years, the gut microbiota has become a subject of great interest because it is a component that has a direct impact on human health. The gut microbiota is the group of bacteria, archaea, fungi, and viruses that live in the gut. This microbial assemblage is host-dependent but can be altered by endogenous and exogenous events [31,32]. Approximately 3.8 × 1013 bacterial cells are present in and on the human body, and 3.0×10^{13} human cells. In a healthy individual, there are about 195 bacterial strains of 101 species, some of which are found in the fecal microbiota. The gut microbiota is about 1 kg of total body weight, so it varies with each individual. In addition, the number of genes in the human microbiome is at least a hundred times greater than the number of genes in the human genome. In the human body, there are four dominant bacterial phyla: Firmicutes, Bacteoidetes, Proteobacteria, and Actinobacteria [33,34]. About 90% of the total bacterial species are Firmicutes and Bacteroidetes [31]. The diversity of gut microbiota is decreased in obese people due to different diets, such as those containing a lot of sugar, fat, and animal protein.

Compared to normal-weight people, obese adults usually have larger Firmicutes and Proteobacteria phyla. Research results also show that obese patients have higher numbers of Bacteroidetes and Actinobacteria compared to normal-weight patients [34,35]. The analysis also showed that there was no difference in microbial diversity in the upper gastrointestinal tract between obese and normal-weight people. One reason why no variation was found in the upper gastrointestinal tract is that the number of bacteria in the proximal area is very small [31]. The microbial communities that inhabit the gut have recently been considered to play an important role in obesity and related metabolic problems. Firmicutes and Bacteroidetes are the two microbiota types most commonly associated with these events [36]. The gut microbiota is symbiotic and plays an important role in various physiological processes, including performing its function in metabolism. This is because microbiota have the ability to increase energy production from food and are involved in regulating fatty acid tissue composition [31]. Short-chain fatty acids (SCFAs) are the result of the fermentation of poorly digested carbohydrates, which are then absorbed by the gut or excreted in the feces. SCFAs consist of acetate, propionate, and butyrate, which have the ability to add about 10% additional energy daily, making them very important in the regulation of energy homeostasis.

Additionally, SCFAs are responsible for the release of satiety hormones [36,37]. SCFAs bind to G protein-coupled receptors, such as GPCR41 and GPCR43. Acetate mainly binds to GPCR43, propionate binds to GPCR41 and GPCR43, and butyrate binds to GPCR41. GPCR41 and GPCR43 receptors function in the intestinal epithelium and adipose tissue. If GPCRs are found in adipose tissue, it suggests that this tissue is a prime target for metabolites produced by the gut microbiota. SCFAs increase the expression of PPARs, which are important mediators of adipose formation. SCFA bound to GPCR41 increases leptin expression in adipocytes, and SCFA bound to GPCR43 promotes adipogenesis.

Therefore, the resulting fatty acid profile is associated with the appearance of obesity [38]. Through endocrine, immune, and neural pathways, the gut microbiota and the brain can communicate with each other. The gut microbiota influences food intake by regulating brain function in several ways, one of which is by regulating gut hormones secreted by enteroendocrine cells such as Peptide YY (PYY), pancreatic polypeptide, and glucagon-like peptide-1 (GLP-1), which can decrease glucagon levels and affect gastrointestinal function. Processes related to propionate production by the gut microbiota lead to decreased appetite due to increased concentrations of PYY and GLP-1. The research found that obese patients had higher food intake as their PYY and GLP-1 levels decreased significantly [37,38]. Under healthy conditions, the gut microbiota is in “eubiosis” or a state of balance. However, when a person is sick, the gut microbiota undergoes dysbiosis (altered composition of the gut microbiota). Much evidence in recent years suggests that dysbiosis is a cause of obesity [39,40].

Gut microbiota dysbiosis causes chronic low-grade inflammation and increases lipopolysaccharide (LPS), which is an endotoxin in the host's circulatory system. LPS contains lipid A, which can cross the intestinal mucosa with the help of chylomicrons or by tight binding [38,41]. TNF-α mRNA expression in adipose tissue increases as a result of the increase of LPS in the circulation, which promotes endotoxemia [42,43]. In addition to inflammation, feeding rhythms are thought to regulate circadian and gut microbiota. Studies show that time-restricted feeding reduces the harmful effects of a high-fat diet by regulating circadian gut microbiota. Not only does disruption of the feeding rhythm disrupt the gut microbiota, leading to glucose intolerance and obesity, but sleep deprivation can also disrupt the circadian rhythm, thus affecting the gut microbiota and causing obesity. Thus, the gut microbiota has many links to obesity, including affecting appetite, energy absorption, fat storage, circadian rhythms, and low levels of chronic inflammation [37].

INTERACTION BETWEEN GENES, ENVIRONMENT, AND GUT MICROBIOME

The interaction between genetic factors, environmental influences, and the gut microbiome is a critical area of research in understanding obesity. This multifaceted relationship highlights how these elements collectively contribute to the development and progression of obesity, emphasizing the need for a comprehensive approach to prevention and treatment. Genetic predispositions play a significant role in obesity, with numerous studies identifying specific genes associated with increased body mass index (BMI) and obesity risk. For instance, the FTO gene has been extensively studied and shown to influence appetite regulation and energy expenditure, where certain variants are linked to higher BMI and obesity [44,45]. But this does not mean that these genetic factors are bound to occur and will not be affected by various factors such as diet and lifestyle. have been able to proven that in the human gut microbiome is largely influenced by the surrounding environment than by hereditary factors, which further shows that the microbial community is more sensitive to what people consume than their genes [45].

Moreover, the gut microbiome itself is a rapidly growing topic of interest in the context of obesity. It plays the role of the environmental factor that affects both genes and life conditions. For example, they highlighted that the gut microbiota can act like a polygenic trait that is influenced by several factors in the environment and host genetics and shown that the composition of microbiota can affect fat deposition and immune modulation [46]. Also, a certain microbial profile was identified as a risk factor for obesity such as Firmicutes and vice versa Bacteroidetes for thin typing [47]. This suggests that the balance of these microbial populations may play a crucial role in energy metabolism and obesity risk. Environmental exposures, such as dietary patterns and chemical pollutants, can also induce changes in the gut microbiome that contribute to obesity.

Discussed how environmental chemical exposures can lead to gut dysbiosis, which may further exacerbate obesity and related metabolic disorders [44]. Also, provided that genetic control underlies host-gut microbiota interactions showing that the microbiome in obesity is a combination of genetic and environmental factors [48]. Even more complicating is the ability of a gut microbiome to adapt quickly to the changes in its diet, whereas, the genetic factors involved in response differ at a much slower pace. Due to this dynamic nature of the microbiome, there could be a reduction of the genetic susceptibility factors to obesity through diet and behavior alterations [49]. For instance, prebiotic and probiotic supplementation has been suggested as a strategy to improve metabolic health and reduce obesity risk, particularly during critical periods such as pregnancy [50,51].

THERAPEUTIC APPROACHES AND INTERVENTIONS

Obesity is a chronic, relapsing, multifactorial disease. Similar to other chronic conditions, obesity requires therapeutic interventions and appropriate treatment strategies on a long-term basis [52]. Screening and diagnosing obesity in routine care should be mainly based on BMI. Apart from its use for the diagnosis of obesity, BMI cut-offs guide obesity treatment recommendations in most obesity guidelines in Europe and North America [53]. Several strategies are currently used for weight management in obesity, these can be divided into three groups the pillars of obesity management such as lifestyle modifications, pharmacotherapies, and bariatric surgery [52,54,55]. Lifestyle modification included recommendations on diets, physical activity, and behavioral interventions. Weight reduction is recommended for people with a BMI greater than or equal to 30 kg/m2 or a BMI greater than or equal to 25 kg/m2 and weight-related complications (eg, diabetes mellitus type 2, hypertension). This change took place at least six to twelve months. For people who are overweight but do not have any weight-related health issues, guidance and information on behavior modification to adopt a healthier diet and up their physical activity levels should be given [53].

The majority of international standards suggest a daily caloric deficit of at least 500 kcal in order to achieve clinically significant weight loss [52]. Along with meal replacements, portion control, and structured meal plans, a specific dietary plan that takes into account the patient's cultural and personal preferences as well as altering the unhealthy components should be used [56]. A diet's macronutrient composition is unimportant as long as it is well-balanced and wholesome. A more recent meta-analysis discovered that, as compared to control diets, weight loss is achievable at six months with low-carb and low-fat diets; however, these benefits prove temporary after a year [57]. A weekly exercise goal of at least 150 minutes of cumulative moderate-intensity endurance activity, combined with strength training, should be the foundation of any weight loss effort. After a successful weight loss, changing one's lifestyle to maintain weight for the long term requires increasing exercise to 300 minutes a week of moderate-intensity activity, which is unsustainable for many obese people. Additional recommendations include decreasing sedentary behavior (such as watching television or using computers) and increasing daily activities (such as walking, cycling, climbing stairs, and gardening) in addition to customizing the exercise goals to the individual's physical capabilities and preferences [52].

In addition to weight loss, physical activity is known to have other health benefits, such as reducing the risk of CV and type 2 diabetes [58]. According to international guidelines, every adult participating in a weight management program should be offered the option of behavioral intervention in the form of individual or group sessions. Regular weighing, stimulus control, modifying existing dietary and fitness habits, and setting reasonable and individualized weight loss targets are examples of behavioral strategies. Antiobesity medications (AOMs) combined with lifestyle modification is advised if behavioral interventions are not sufficiently effective after six months in helping the patient reach their specific weight loss or health-related goals, or if they have a higher BMI in addition to an obesity-related complication [53]. Optimally, AOMs are prescribed in adjunct to lifestyle modification. Patients with a BMI of 27 kg/m2 or above who are obese (BMI of 30 kg/m2) are clinically appropriate for AOMs. There are five approved AOMs: phentermine, phentermine/topiramate extended-release, orlistat, liraglutide (3.0 mg), and naltrexone/bupropion sustained-release, excluding Lorcaserin, which was pulled in early 2020 due to a large post-marketing trial showing a higher incidence of cancer compared to placebo. The latter 4 are approved for long-term use [59]. According to guidelines, a 12-week prescription for phentermine should be given. Concerns concerning phentermine's potentially harmful long-term effects on CVD persist because no RCTs have examined the drug's long-term safety and effectiveness as monotherapy.

In addition, phentermine causes psychotic symptoms. Initially in 1968, a study (n = 108) promoted the use of phentermine in conjunction with a 1000-kcal diet. The results showed that after 36 weeks, individuals who used phentermine intermittently or continuously dropped 13 kg or 12.2 kg, respectively, in comparison to the placebo group, which lost 4.8 kg [59,60]. Orlistat was studied for up to 4 years in the XENical in the Prevention of Diabetes in Obese Subjects study. In addition to lifestyle change, 3305 volunteers with an obese diagnosis received either orlistat or placebo in this randomized controlled study (RCT); patients showed normal (79%) or impaired (21%) glucose tolerance. The weight loss after four years was 3.0 kg for the placebo group and 5.8 kg for the orlistat group [59,61]. Liraglutide, a drug that is frequently recommended for type 2 diabetes, is also licensed to help with weight loss; 3.0 mg/day can be taken for weight loss in addition to the maximum 1.8 mg/day for T2D for about 56 weeks in duration (Kenisher et al., 2021).

The US Food and Drug Administration authorized bupropion/naltrexone sustained release in 2014. The combination medications' effect on weight loss compare favorably to other AOMs. In particular, a 78-week randomized controlled trial (naltrexone [32 mgs]/bupropion [360 mgs]) saw a nearly 10% decrease in body weight percentage. After 56 weeks, two more RCTs with comparable doses reported percentage reductions in body weight of 6.1% and 9.3% [59,62,63]. Barriers to the general adoption of AOMs remain since they are linked to a variety of adverse effects; liraglutide, for instance, is more frequently stopped because of side symptoms than placebo (odds ratio: 2.95). Despite being certified in obesity medicine, physicians may still be hesitant to recommend AOMs because insurance companies might not be able to pay for such expensive treatments [59]. Due to its high efficacy in terms of weight loss, duration of effectiveness, and improvement of obesity-related complications, bariatric surgery is regarded as the "gold standard" treatment for severe obesity [64]. Gastric banding, sleeve gastrectomy, and Roux-en-Y gastric bypass are common surgical procedures that result in 15.9%, 29.5%, and 31.9 percent weight loss, respectively [65].

After ten years, the weight loss that was attained is essentially maintained [66]. Bariatric surgery-induced sustained weight loss is linked to numerous advantages, most notably in relation to cardiometabolic disorders [67]. However, there are still significant drawbacks to this treatment strategy, such as the possibility of surgical complications, the requirement for lifetime nutritional monitoring and supplements, and nutritional inadequacies. It is advised to have multidisciplinary follow-up for at least two years following the surgical procedure [53]. The gut microbiota is a complex ecosystem made up of over a thousand different strains of bacteria, and its prokaryotic population is an order of magnitude larger than all of the human body's cells [68]. The complex relationships between the microbiome and human health particularly when it comes to host metabolism—have only lately started to be studied [69]. The germ-free (GF) mice used in the original research to show a causal link between the microbiome and an obese phenotype were found to be resistant to diet-induced obesity even when fed a high-fat (HF) diet [70].

Additionally, these animals might acquire an obese phenotype by fecal transplants from genetically or Western diet-fed obese mice, which resulted in a higher weight increase than the inoculation with wild-type bacteria. Motivated by these results, other microbial survey investigations have endeavored to delineate the components of an "obese" microbiome and identify the particular strains that facilitate the emergence of obesity and associated metabolic abnormalities. These studies have led to the general conclusion that a lean phenotype is linked to a higher Bacteriodetes: Firmicutes ratio, while the reverse is true for obese people [69]. According to a recent study, there is little correlation between the Bacteriodetes: Firmicutes ratio and obesity status in analytical investigations. These early findings were probably confused by high levels of experimental "noise," which included interpersonal variance and a small sample size. This implies that notable variations in pathology-related microbiota may arise at a more specific phylogenetic level than the general divisions mentioned above, along with other inconsistencies in the research [71]. Probiotics and prebiotics have a long history of beneficial benefits on digestive health [69]. Prebiotics have been shown in numerous experimental investigations to be beneficial in the fight against obesity and metabolic disorders, with different modes of action. Among other things, there is mounting evidence that prebiotic-based treatment reduces systemic inflammation linked to obesity. Obese mice treated with oligofructose (OFS) had an increase in intestinal Bifidobacteria. This alteration in the microbiota's composition was connected adversely with both fat mass and inflammatory tone (as determined by metabolic endotoxemia and plasma cytokines) [69]. Dewulf et al. conducted human studies wherein obese women receiving inulin/oligofructose prebiotics showed increased Bifidobacterium and Faecalibacterium proportions.

This result was correlated with a decrease in fat mass and serum LPS [72]. It has been demonstrated that supplementing people with fructans-type prebiotics (16 g/d) increases plasma PYY/GLP1, reduces appetite, and attenuates the glycemic response. In a similar vein, a regimen that added 21 g/d of inulin-type fructans to the diets of obese patients resulted in elevated plasma PYY and decreased ghrelin production, markers that correlated with decreased food intake, fat mass, and weight gain [69]. Oral administration of viable bacterial strains (probiotics), which can be incorporated into the gut environment, is an alternative strategy for reorganizing the gut microbiota. To maintain their growth and function, probiotic bacteria can also be combined with prebiotic fibers and added to food products. This combinatorial strategy, known as "synbiotics," may help to amplify the positive benefits of probiotics [69].

Probiotic treatments developed from this list have been shown to be beneficial for treating and preventing obesity in animals, where weight loss is frequently accompanied by improvements in a variety of metabolic parameters. Additional human clinical trials have produced equally encouraging results, consistently showing that probiotic administration has a favorable effect on body weight, body composition, and a variety of metabolic indicators. When compared to control patients, children who took a probiotic blend supplement for four months had a significantly lower BMI, higher GLP-1 levels, and improved liver adiposity [73].

Additionally, compared to placebo controls, an 8-week synbiotic supplementation regimen significantly reduced body weight, total cholesterol, and plasma triglycerides in a cohort of adult patients who were overweight or obese [74]. Overall, probiotic supplementation with different species of Bifidobacterium, Lactobacillus, and other selected taxa, either in isolation or as blended probiotics,

elicits positive effects on obesity and associated metabolic pathophysiology, as shown by these and other human clinical trials in children and adults. But as was already indicated, the strains being studied, the dosage, and the length of the intervention all have a significant impact on these outcomes [75,76,77].

CONCLUSION

Obesity is a multifactorial condition mediated through genetic, environmental, and microbial factors. Although some people may be born with tendencies concerning metabolism and fat deposition, habits affecting lifestyles and eating patterns sway these risks. The gut microbiome also plays a significant role, with imbalances in microbial populations linked to increased fat accumulation and metabolic dysfunction. Understanding these interactions is crucial for developing personalized obesity prevention and treatment strategies.

CONFLICTS OF INTEREST

No competing interests declared.

FUNDING

This research received no specific grant from any funding agency.

REFERENCE

[1] Gérard, C. and Vidal, H. (2019) "Impact of gut Microbiota on host glycemic control," *Frontiers in endocrinology*, 10. doi: 10.3389/fendo.2019.00029.

[2] Inoue, Y. *et al.* (2018) "Epidemiology of obesity in adults: Latest trends," *Current obesity reports*, 7(4), pp. 276–288. doi: 10.1007/s13679-018-0317-8.

[3] Kelishadi, R., Poursafa, P. and Jamshidi, F. (2013) "Role of environmental chemicals in obesity: A systematic review on the current evidence," *Journal of environmental and public health*, 2013, pp. 1–8. doi: 10.1155/2013/896789.

[4] Cui, N., Sun, Q. and Chen, L. (2021) "A meta-analysis of the influence of body mass index on the clinicopathologic progression of papillary thyroid carcinoma," *Medicine*, 100(32), p. e26882. doi: 10.1097/md.0000000000026882.

[5] Mahmudiono, T., Segalita, C. and Rosenkranz, R. R. (2019) "Socio-ecological model of correlates of double burden of malnutrition in developing countries: A narrative review," *International journal of environmental research and public health*, 16(19), p. 3730. doi: 10.3390/ijerph16193730.

[6] Ferreira, M. S. *et al.* (2020) "Lung function in obese children and adolescents without respiratory disease: a systematic review," *BMC pulmonary medicine*, 20(1). doi: 10.1186/s12890-020-01306-4.

[7] Legeay, S. and Faure, S. (2017) "Is bisphenol A an environmental obesogen?," *Fundamental & clinical pharmacology*, 31(6), pp. 594–609. doi: 10.1111/fcp.12300.

[8] Tumminia, A. *et al.* (2019) "Adipose tissue, obesity and adiponectin: Role in endocrine cancer risk," *International journal of molecular sciences*, 20(12), p. 2863. doi: 10.3390/ijms20122863.

[9] Sanghera, D. K. *et al.* (2019) "Obesity genetics and cardiometabolic health: Potential for risk prediction," *Diabetes, obesity & metabolism*, 21(5), pp. 1088–1100. doi: 10.1111/dom.13641.

[10] Hastuti, P. (2022) "Obesity and the role of genetic polymorphism: A review of genes as the risk of obesity," *Berkala ilmu kedokteran*, 54(2). doi: 10.19106/jmedsci005402202209.

[11] Mahmoud, R., Kimonis, V. and Butler, M. G. (2022) "Genetics of obesity in humans: A clinical review," *International journal of molecular sciences*, 23(19), p. 11005. doi: 10.3390/ijms231911005.

[12] Dubern, B. *et al.* (2022) "Rare genetic causes of obesity: Diagnosis and management in clinical care," *Annales d'endocrinologie*, 83(1), pp. 63–72. doi: 10.1016/j.ando.2021.12.003.

[13] Liu, Q. *et al.* (2022) "Genomic correlation, shared loci, and causal relationship between obesity and polycystic ovary syndrome: a large-scale genome-wide cross-trait analysis," *BMC medicine*, 20(1). doi: 10.1186/s12916-022-02238-y.

[14] Novelli, G. *et al.* (2023) "Genetics: A starting point for the prevention and the treatment of obesity," *Nutrients*, 15(12), p. 2782. doi: 10.3390/nu15122782.

[15] Bouchard, C. (2021) "Genetics of obesity: What we have learned over decades of research," *Obesity (Silver Spring, Md.)*, 29(5), pp. 802–820. doi: 10.1002/oby.23116.

[16] Williams, D. M., Nawaz, A. and Evans, M. (2020) "Drug therapy in obesity: A review of current and emerging treatments," *Diabetes therapy: research, treatment and education of diabetes and related disorders*, 11(6), pp. 1199–1216. doi: 10.1007/s13300-020-00816-y.

[17] Masood, B. and Moorthy, M. (2023) "Causes of obesity: a review," *Clinical medicine (London, England)*, 23(4), pp. 284–291. doi: 10.7861/clinmed.2023-0168.

[18] Cuevas-Sierra, A. *et al.* (2019) "Diet, gut Microbiota, and obesity: Links with host genetics and epigenetics and potential applications," *Advances in nutrition (Bethesda, Md.)*, 10(suppl_1), pp. S17–S30. doi: 10.1093/advances/nmy078.

[19] NCD Risk Factor Collaboration (NCD-RisC) (2020) "Height and body-mass index trajectories of school-aged children and adolescents from 1985 to 2019 in 200 countries and territories: a pooled analysis of 2181 population-based studies with 65 million participants," Lancet, 396(10261), pp. 1511–1524. doi: 10.1016/S0140-6736(20)31859-6.

[20] Shams, L., Shafiei, F. and Sadremomtaz, Z. (2024) "The social and environmental factors impacting the motivation of adolescents for weight control, why and how? A qualitative study," BMC nutrition, 10(1), p. 19. doi: 10.1186/s40795-024-00822-4.

[21] Gurka, M. J., Filipp, S. L. and DeBoer, M. D. (2018) "Geographical variation in the prevalence of obesity, metabolic syndrome, and diabetes among US adults," Nutrition & diabetes, 8(1). doi: 10.1038/s41387-018-0024-2.

[22] Wolińska, I. A. et al. (2023) "Environmental factors of obesity before and after COVID-19 pandemic: a review," Frontiers in public health, 11, p. 1213033. doi: 10.3389/fpubh.2023.1213033.

[23] Robinson, E. et al. (2021) "Obesity, eating behavior and physical activity during COVID-19 lockdown: A study of UK adults," Appetite, 156(104853), p. 104853. doi: 10.1016/j.appet.2020.104853.

[24] Nicolaidis, S. (2019) "Environment and obesity," Metabolism: clinical and experimental, 100S(153942), p. 153942. doi: 10.1016/j.metabol.2019.07.006.

[25] Syatira, A. P. and Ekaria, E. (2022) "The effects of price, income, and household characteristics on ultra-processed food consumption in Jakarta, Indonesia," *Jurnal Aplikasi Statistika & Komputasi Statistik*, 14(1), pp. 37–54. doi: 10.34123/jurnalasks.v14i1.386.

[26] Guo, Y. et al. (2021) "Research on environmental influencing factors of overweight and obesity in children and adolescents in China," Nutrients, 14(1), p. 35. doi: 10.3390/nu14010035.

[27] Ayuningtyas, D. *et al.* (2022) "Disparities in obesity rates among adults: Analysis of 514 districts in Indonesia," *Nutrients*, 14(16), p. 3332. doi: 10.3390/nu14163332.

[28] Pujilestari, C. U. *et al.* (2017) "Socioeconomic inequality in abdominal obesity among older people in Purworejo District, Central Java, Indonesia – a decomposition analysis approach," *International journal for equity in health*, 16(1). doi: 10.1186/s12939-017-0708-6.

[29] Adisasmito, W. *et al.* (2020) "Geographic and socioeconomic disparity in cardiovascular risk factors in Indonesia: analysis of the Basic Health Research 2018," *BMC public health*, 20(1). doi: 10.1186/s12889-020-09099-1.

[30] Widjaja, N. A. and Prihaningtyas, R. A. (2020) "Determinants of Food Choice in obesity," *The Indonesian Journal of Public Health*, 15(1), p. 122. doi: 10.20473/ijph.v15i1.2020.122-132.

[31] Castaner, O. *et al.* (2018) "The gut microbiome profile in obesity: A systematic review," *International journal of endocrinology*, 2018, pp. 1–9. doi: 10.1155/2018/4095789.

[32] Hughes, R. L. and Holscher, H. D. (2021) "Fueling gut microbes: A review of the interaction between diet, exercise, and the gut Microbiota in athletes," *Advances in nutrition (Bethesda, Md.)*, 12(6), pp. 2190–2215. doi: 10.1093/advances/nmab077.

[33] Geng, J. *et al.* (2022) "The links between gut microbiota and obesity and obesity related diseases," *Biomedecine & pharmacotherapie [Biomedicine & pharmacotherapy]*, 147(112678), p. 112678. doi: 10.1016/j.biopha.2022.112678.

[34] Akagbosu, C. O. *et al.* (2022) "The role of the gut microbiome in pediatric obesity and bariatric surgery," *International journal of molecular sciences*, 23(23), p. 15421. doi: 10.3390/ijms232315421.

[35] Dong, T. S. *et al.* (2020) "A high protein calorie restriction diet alters the gut microbiome in obesity," *Nutrients*, 12(10), p. 3221. doi: 10.3390/nu12103221.

[36] Ejtahed, H.-S. *et al.* (2020) "Gut microbiota-derived metabolites in obesity: a systematic review," *Bioscience of microbiota, food and health*, 39(3), pp. 65–76. doi: 10.12938/bmfh.2019-026.

[37] Liu, B.-N. *et al.* (2021) "Gut microbiota in obesity," *World journal of gastroenterology: WJG*, 27(25), pp. 3837–3850. doi: 10.3748/wjg.v27.i25.3837.

[38] Gomes, A. C., Hoffmann, C. and Mota, J. F. (2018) "The human gut microbiota: Metabolism and perspective in obesity," *Gut microbes*, pp. 1–18. doi: 10.1080/19490976.2018.1465157.

[39] Campbell, C. *et al.* (2023) "Crosstalk between gut Microbiota and host immunity: Impact on inflammation and immunotherapy," *Biomedicines*, 11(2), p. 294. doi: 10.3390/biomedicines11020294.

[40] Li, J. *et al.* (2024) "Association of gastrointestinal microbiome and obesity with gestational diabetes mellitus-an updated globally based review of the high-quality literatures," *Nutrition & diabetes*, 14(1). doi: 10.1038/s41387-024-00291-5.

[41] Gong, J. *et al.* (2022) "Gut Microbiota characteristics of people with obesity by meta-analysis of existing datasets," *Nutrients*, 14(14), p. 2993. doi: 10.3390/nu14142993.

[42] Montenegro, J. *et al.* (2023) "Exploring the influence of gut microbiome on energy metabolism in humans," *Advances in nutrition (Bethesda, Md.)*, 14(4), pp. 840–857. doi: 10.1016/j.advnut.2023.03.015.

[43] Dabke, K., Hendrick, G. and Devkota, S. (2019) "The gut microbiome and metabolic syndrome," *The journal of clinical investigation*, 129(10), pp. 4050–4057. doi: 10.1172/jci129194.

[44] Rosenfeld, C. S. (2017) "Gut dysbiosis in animals due to environmental chemical exposures," *Frontiers in cellular and infection microbiology*, 7. doi: 10.3389/fcimb.2017.00396.

[45] Rothschild, D. *et al.* (2018) "Environment dominates over host genetics in shaping human gut microbiota," *Nature*, 555(7695), pp. 210–215. doi: 10.1038/nature25973.

[46] Benson, A. K. *et al.* (2010) "Individuality in gut microbiota composition is a complex polygenic trait shaped by multiple environmental and host genetic factors," *Proceedings of the National Academy of Sciences of the United States of America*, 107(44), pp. 18933–18938. doi: 10.1073/pnas.1007028107.

[47] Zhai, C. *et al.* (2022) "Comparative analysis of original and replaced gut microbiomes within same individuals identified the intestinal microbes associated with weight gaining," *Microorganisms*, 10(5), p. 1062. doi: 10.3390/microorganisms10051062.

[48] Niska-Blakie, J. *et al.* (2020) "Knockout of the non-essential gene SUGCT creates diet-linked, age-related microbiome disbalance with a diabetes-like metabolic syndrome phenotype," *Cellular and molecular life sciences: CMLS*, 77(17), pp. 3423–3439. doi: 10.1007/s00018-019-03359-z.

[49] Wibowo, M. C. *et al.* (2022) "The impact of multigenerational high-fat diet feeding on the gut microbiome and host metabolism," *bioRxiv*. doi: 10.1101/2022.02.01.478488.

[50] Wiedmer, E. B. and Herter-Aeberli, I. (2022) "The potential of prebiotic and probiotic supplementation during obese pregnancy to improve maternal and offspring's metabolic health and reduce obesity risk—A narrative review," *Frontiers in nutrition*, 9. doi: 10.3389/fnut.2022.819882.

[51] Tamilvanan, J. and Kalpana, C. A. (2023) "Using gut microbiome as A tool in dietary intervention for prevention and management of obesity," *Journal of advanced zoology*, 44(S-5), pp. 1770–1776. doi: 10.17762/jaz.v44is-5.1456.

[52] Blüher, M. *et al.* (2023) "New insights into the treatment of obesity," *Diabetes, obesity & metabolism*, 25(8), pp. 2058–2072. doi: 10.1111/dom.15077.

[53] Semlitsch, T. *et al.* (2019) "Management of overweight and obesity in primary care—A systematic overview of international evidence-based guidelines," *Obesity reviews: an official journal of the International Association for the Study of Obesity*, 20(9), pp. 1218–1230. doi: 10.1111/obr.12889.

[54] Eisenberg, D. *et al.* (2022) "2022 American society for metabolic and bariatric surgery (ASMBS) and international federation for the surgery of obesity and metabolic disorders (IFSO): Indications for metabolic and bariatric surgery," *Surgery for obesity and related diseases: official journal of the American Society for Bariatric Surgery*, 18(12), pp. 1345–1356. doi: 10.1016/j.soard.2022.08.013.

[55] Muscogiuri, G. *et al.* (2021) "European guidelines for obesity management in adults with a very low-calorie ketogenic diet: A Systematic Review and meta-analysis," *Obesity facts*, 14(2), pp. 222–245. doi: 10.1159/000515381.

[56] Brown, J. *et al.* (2023) *Canadian Adult Obesity Clinical Practice Guidelines: Medical Nutrition Therapy in Obesity Management*.

[57] Ge, L. *et al.* (2020) "Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials," *BMJ (Clinical research ed.)*, 369, p. m696. doi: 10.1136/bmj.m696.

[58] Bischoff, S. C., & Schweinlin, A. (2020). Obesity therapy. *Clinical nutrition ESPEN*, 38, 9–18. doi : 10.1016/j.clnesp.2020.04.013.

[59] Kheniser, K., Saxon, D. R. and Kashyap, S. R. (2021) "Long-term weight loss strategies for obesity," *The journal of clinical endocrinology and metabolism*, 106(7), pp. 1854–1866. doi: 10.1210/clinem/dgab091.

[60] Munro, J. F. *et al.* (1968) "Comparison of continuous and intermittent anorectic therapy in obesity," *British medical journal*, 1(5588), pp. 352–354. doi: 10.1136/bmj.1.5588.352.

[61] Torgerson, J. S. *et al.* (2004) "XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients," *Diabetes care*, 27(1), pp. 155–161. doi: 10.2337/diacare.27.1.155.

[62] Wadden, T. A. *et al.* (2011) "Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial," *Obesity (Silver Spring, Md.)*, 19(1), pp. 110–120. doi: 10.1038/oby.2010.147.

[63] Greenway, F. L. *et al.* (2010) "Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial," *Lancet*, 376(9741), pp. 595–605. doi: 10.1016/S0140-6736(10)60888-4.

[64] Gadde, K. M. *et al.* (2018) "Obesity: Pathophysiology and management," *Journal of the American College of Cardiology*, 71(1), pp. 69–84. doi: 10.1016/j.jacc.2017.11.011.

[65] van Rijswijk, A.-S. *et al.* (2021) "What is weight loss after bariatric surgery expressed in percentage total weight loss (%TWL)? A systematic review," *Obesity surgery*, 31(8), pp. 3833–3847. doi: 10.1007/s11695-021-05394-x.

[66] O'Brien, P. E. *et al.* (2019) "Long-term outcomes after bariatric surgery: A systematic review and meta-analysis of weight loss at 10 or more years for all bariatric procedures and a single-centre review of 20-year outcomes after adjustable gastric banding," *Obesity surgery*, 29(1), pp. 3–14. doi: 10.1007/s11695-018-3525-0.

[67] Arterburn, D. E. *et al.* (2020) "Benefits and risks of bariatric surgery in adults: A review: A review," *JAMA: the journal of the American Medical Association*, 324(9), pp. 879–887. doi: 10.1001/jama.2020.12567.

[68] Dinan, T. G. and Cryan, J. F. (2017) "Gut-brain axis in 2016: Brain-gut-microbiota axis - mood, metabolism and behaviour," *Nature reviews. Gastroenterology & hepatology*, 14(2), pp. 69–70. doi: 10.1038/nrgastro.2016.200.

[69] Green, M., Arora, K. and Prakash, S. (2020) "Microbial medicine: Prebiotic and probiotic functional foods to target obesity and metabolic syndrome," *International journal of molecular sciences*, 21(8), p. 2890. doi: 10.3390/ijms21082890.

[70] Bäckhed, F. *et al.* (2004) "The gut microbiota as an environmental factor that regulates fat storage," *Proceedings of the National Academy of Sciences of the United States of America*, 101(44), pp. 15718–15723. doi: 10.1073/pnas.0407076101.

[71] Sze, M. A. and Schloss, P. D. (2016) "Looking for a signal in the noise: Revisiting obesity and the microbiome," *mBio*, 7(4). doi: 10.1128/mBio.01018-16.

[72] Dewulf, E. M. *et al.* (2013) "Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women," *Gut*, 62(8), pp. 1112–1121. doi: 10.1136/gutjnl-2012-303304.

[73] Alisi, A. *et al.* (2014) "Randomised clinical trial: the beneficial effects of VSL#3 in obese children with non-alcoholic steatohepatitis," *Alimentary pharmacology & therapeutics*, 39(11), pp. 1276–1285. doi: 10.1111/apt.12758.

[74] Hadi, A. *et al.* (2019) "Clinical and psychological responses to synbiotic supplementation in obese or overweight adults: A randomized clinical trial," *Complementary therapies in medicine*, 47(102216), p. 102216. doi: 10.1016/j.ctim.2019.102216.

[75] Minami, J. *et al.* (2018) "Effects of Bifidobacterium breve B-3 on body fat reductions in pre-obese adults: a randomized, double-blind, placebo-controlled trial," *Bioscience of microbiota, food and health*, 37(3), pp. 67–75. doi: 10.12938/bmfh.18-001.

[76] Pedret, A. *et al.* (2019) "Effects of daily consumption of the probiotic Bifidobacterium animalis subsp. lactis CECT 8145 on anthropometric adiposity biomarkers in abdominally obese subjects: a randomized controlled trial," *International journal of obesity (2005)* , 43(9), pp. 1863–1868. doi: 10.1038/s41366-018-0220-0.

[77] Sanchis-Chordà, J. *et al.* (2018) "Bifidobacterium pseudocatenulatum CECT 7765 supplementation improves inflammatory status in insulin-resistant obese children," *European journal of nutrition*. doi: 10.1007/s00394-018-1828-5.