Current Obesity Reports (2025) 14:62
https://doi.org/10.1007/s13679-025-00652-w

REVIEW

The Role of Adipokines and Gene Polymorphisms in the Development of Obesity- Induced Depression

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Accepted: 8 July 2025

Abstract

Purpose of Review This review examines the role of adipokines and gene polymorphisms in the development of depression and obesity. It is of great importance to understand the mechanisms that may be effective in the development of obesity and depression as their incidence increases.

Recent Findings Adipokines are released from adipose tissues and primarily regulate the connection between the metabolic and inflammatory effects of obesity and the brain cells and adipose tissue. Adipokines may potentially contribute to the pathophysiology of depression by influencing the HPA axis and neurotransmitters. According to some estimates, the genetic overlap between obesity and depression is as high as 12 percent. Furthermore, these genes may be linked to significant interconnected signaling networks that have a role in the etiology of both disorders.

Summary Obesity and depression are both on the rise globally, and it is thought that there is a bidirectional relationship between these two conditions. Obesity and obesity-induced depression seriously limit the psychosocial functionality of individuals and impair their quality of life. Having a high body mass index (BMI) raises the likelihood of developing depression. On the other hand, as the BMI elevates in people suffering from depression, the possibility of developing obesity also rises.

Keywords Body Mass Index (BMI) · Leptin · Asprosin · FTO Gene; MC4R Gene

Abbreviations

5-HTT	Serotonin Transporter
ACTH	Adrenocorticotropic Hormone
ARC	Arcuate Nucleus
BMI	Body Mass Index
CRH	Corticotropin-Releasing Hormone
FTO	Fat Mass and Obesity-Associated
GWAS	Genome-Wide Association Studies
HPA	Hypothalamus-Pituitary-Adrenal
IL	Interleukin
MC4R	Melanocortin 4 Receptor
NPY	Neuropeptide Y
SERT	Serotonin Transporters
SNP	Single Nucleotide Polymorphism
TNF-α	Tumor Necrosis Factor Alpha

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Introduction

Obesity is characterized by a high level of adipose tissue in the body, which poses a significant threat to health. Obesity is an important global health concern and can lead to an increased risk of chronic diseases such as type 2 diabetes and heart disease [1]. Overgrowth of fat cells alters nutrient signals associated with obesity [2]. In addition, genetic, epigenetic, and other environmental factors may affect the etiology of obesity [3]. The prevalence of non-communicable diseases such as metabolic syndrome, diabetes, hypertension, cardiovascular diseases, cancer, depression, and obstructive sleep apnea rises with a higher BMI [4]. Easily accessing foods that are rewarding and have a high energy content is also effective in rapidly increasing obesity [5]. Genetic predisposition to obesity, which may result from strong links between homeostatic circuits and brain reward systems, can affect people with these traits. Obesity can also

Published online: 28 July 2025

result from the accumulation of lipid metabolites, inflammatory signals, or other factors that affect hypothalamic neurons [6]. Addictive eating behaviors also have a significant role in the development of obesity along with the obesogenic environment [7]. Although environmental conditions lead to a rise in body weight, genetic factors also significantly influence its increase. BMI in a population including the full range of BMI values accounts for 40%–50% of its variance, adjusted for age and sex [8]. Results of twin and family studies have indicated that genetic variables account for 40–70% of the variation in obesity [9]. Many obesity-related genes are known to be involved in pathways that control energy metabolism. A single gene mutation or changes in multiple genes can be the genetic causes of obesity. Individuals with these genes experience excessive weight gain. These genes may cause their high energy intake, high level of hunger, inability to control overeating, lack of feeling of fullness, increased tendency for the body to store fat, and increased inactivity [10, 11]. Dietary control and substance abuse often share the same behavioral and neural systems [12–14]. High-fat and high-sugar diets can activate the reward center of the brain, similar to addictive drugs. Thus, addictive foods can cause excessive energy intake, resulting in increased body fat and obesity [15].

Depression is an illness that severely limits the psychosocial functionality of individuals and impairs their quality of life [16], and 5% of the adult population suffers from this illness. Depressed individuals experience unusual mood swings and altered short-term emotional responses to difficulties in their daily lives. Recurrent or moderate-severe depression can cause serious health problems [17]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V, major depression criteria are; the symptoms of depression include weight/appetite changes, psychomotor slowdown, melancholy, lack of motivation, fatigue, sleep/circadian disruption, and suicidal ideation [18]. Changes in appetite according to the types of depressive disorders affect body weight. In melancholic depression, there is a decrease in appetite and body weight, while in atypical depression, on the contrary, body weight and BMI increase with an increase in appetite [19, 20].

There is a neurophysiological relationship between consumption of comfort food and stress. Chronic stress throws off the hypothalamus–pituitary–adrenal (HPA) axis' negative feedback inhibition. Increased consumption of comfort foods has been shown to occur during periods of emotional distress due to the ability of sugar and fat to suppress the HPA axis stress response by reducing glucocorticoid sensitivity. It thus may act as a coping mechanism for depressed mood. This leads people to eat more comfort foods which are high in fat, simple sugar, and calories, as glucocorticoids affect the brain's reward center and make the stomach store fat [20–22]. Consuming comfort foods temporarily reduces feelings of stress and depression, but this repetitive behavior triggers weight gain and the development of obesity [23]. Physiological, psychological, and genetic factors influence food intake and preferences [24]. This review was planned to examine the association between adipokines and gene polymorphisms in the development of obesity and depression.

The Relationship Between Obesity and Depression

It has often been stated that there is an interactive relationship between depression and obesity. In addition to depression causing body weight gain and obesity, individuals suffering from obesity may also develop depression in later periods [25]. Biological, psychological, and behavioral factors may affect the relationship between depression and obesity [26]. Depression can lead to decreased or increased appetite. When appetite increases, negative emotions can decrease along with increased food intake. Emotional eating is characterized by the consumption of high-calorie, palatable foods in response to negative emotions and may lead to weight gain over time. A previous study reported that emotional eating was associated with higher waist circumference and BMI in depressed people. One behavioral mechanism that associates depression with the development of obesity is emotional eating [27]. Both homeostatic and hedonic processes regulate nutritional intake, and physiological, psychological, and social conditions all have an impact on these processes. While energy balance is regulated in homeostatic processes, pleasure, reward, and taste are effective in hedonic processes [28]. A study conducted on middle-aged adults revealed that emotional eating was a significant factor in a bidirectional relationship. In women, the development of depression-induced obesity was mediated by emotional eating, physical degradation, and social dysfunction. Likewise, physical deterioration and the tendency to eat for emotional reasons had a role in the progression of depression resulting from obesity [29]. A meta-analysis reported that the prevalence of depression symptoms was higher in children and adolescents suffering from obesity [30]. Silva et al. (2020) found a bidirectional relationship between depression and obesity in their meta-analysis [31].

In stress situations, corticotropin-releasing hormone (CRH) secreted from the hypothalamus stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland, encouraging the adrenal glands to secrete cortisol. Cortisol helps cope with stress by increasing blood glucose and strengthening metabolism. As cortisol levels rise, negative feedback gradually decreases cortisol levels. With effective management of this balance, which is disrupted during chronic stress, the HPA axis can improve and allow the body to return to its pre-stress state. The HPA

axis governs the release of cortisol, affecting various bodily functions, including metabolic, psychological, and immunological processes. These mechanisms enable stress to affect memory functions, reward systems, immune responses, metabolism, and disease susceptibility. Depressive disorders are characterized by dysregulation of the HPA axis, leading to elevated cortisol levels and triggering activation of acetylcholine [32, 33]. Long-term exposure to cortisol due to overactivity of the HPA axis, which controls cortisol release, can lead to neuronal damage and loss in the hippocampus and amygdala, brain regions linked to stress and depression. It has also been reported that long-term cortisol exposure causes people to prefer high-energy-dense foods and may lead them to suffer from obesity via a variety of mechanisms. These include increased appetite, stimulation of hypertrophy and adipogenesis, particularly in visceral fat, as well as decreased thermogenesis in brown fat, leading to lower energy expenditure [26].

The Effect of Adipokines and Gene Polymorphisms on Obesity-Induced Depression

Adipokines

Adipokines regulate the metabolic and inflammatory effects of obesity and some obesity-induced diseases. While leptin, adiponectin, and ghrelin have known links to obesity, resistin, omentin, chemerin, and visfatin are thought to affect obesity significantly [34]. Adipose tissue is an endocrine organ that secretes adipokines and shows metabolic activity in addition to being a tissue that stores fat. Obesity may contribute to pathophysiology beyond cardiometabolic conditions, as adipokines play a crucial role in mediating the interaction between adipose tissue and the brain. Depression may be induced by adipokines because of their effects on the HPA axis and neurotransmitters [26, 35]. The main adipokines released by adipose tissues include leptin, ghrelin, adiponectin, resistin, asprosin, and vaspin.

Leptin

The leptin molecule is 16 kDa in size, comprises 167 amino acids, and is mainly produced by adipocytes [36]. A study conducted on obese mice reported that leptin was produced by the obese (ob) gene [37]. Leptin controls the amount of food consumed, body weight, and reproductive function, and is crucial for fetal growth, angiogenesis, lipolysis, and pro-inflammatory immune responses. The discovery of the leptin gene revealed its role in controlling appetite and metabolism through the suppression of neuropeptide Y (NPY) production and release in the arcuate nucleus (ARC) [38]. Circulating leptin concentration decreases during fasting and energy restriction and increases during refeeding and overfeeding [39]. Leptin can inhibit the neuronal pathways that appetite stimulants (orexigenics) activate to consume fewer calories and activate the neural pathways that anorexigenics target to make you eat less [40]. In people suffering from obesity adipose tissues, leptin gene expression increases. The rate of body fat is positively correlated with leptin levels [39]. Jayachandran et al. (2017) found that overweight adolescents and adult women had higher salivary leptin levels compared to normal-weight individuals [41]. Another study on overweight and obese children indicated that their salivary levels of leptin were much higher than those of normal-weight children [42]. The HPA axis is linked to several biomarkers related to stress [43]. A meta-analysis reported that leptin was a stress biomarker that decreased after acute stress. Researchers found that normal-weight ones reacted more strongly, supporting the idea that stress, obesity, and leptin resistance are all correlated. Furthermore, the higher change in leptin levels following acute stress in women suggests that leptin might exert a gender-specific effect on the onset of obesity in reaction to stress [44].

Ghrelin

Ghrelin is a hormone that stimulates appetite and is secreted by endocrine X/A-like cells in the stomach. Its main function is to increase appetite and food intake. It plays a role in regulating the release of insulin and growth hormone, as well as glucose metabolism. Additionally, it affects heart rate, blood pressure, gastrointestinal motility, neurogenesis, and lipid metabolism [45, 46]. Additionally, it regulates several activities of the central nervous system, such as stress-related behavioral functions. Stress exposure changes the levels of ghrelin, which in turn has a major effect on neuro-endocrinological parameters. Ghrelin increases the production rate of serotonin, which subsequently regulates ghrelin signaling to affect anxiety-related behaviors [47]. Bouillon-Minois et al. (2021) indicate in their meta-analysis that ghrelin may be a stress biomarker due to its elevated levels after acute stress. Stress can cause eating behavior disorders and lead to obesity. People suffering from obesity exhibit a greater and longer-term response, highlighting the connection between obesity and stress. Administering ghrelin to humans or animals can have an antidepressant effect when it comes to depression [48]. On the other hand, after taking anti-depressants, ghrelin levels often lowered. The results of this study suggest that the severity of depression may be associated with ghrelin levels [49].

Adiponectin

Adiponectin is a 244-amino acid protein secreted mainly by the adipose tissue, first described in the mid-1990s [50, 51]. Adiponectin exhibits anti-atherogenic, anti-diabetic,

insulin-sensitizing, and anti-inflammatory properties [52]. Lower levels of adiponectin in the bloodstream are associated with chronic inflammation in people with type 2 diabetes, obesity, and metabolic disorders, including atherosclerosis [51, 53]. Adiponectin, unlike other adipokines, exhibits an inverse relationship with BMI, central obesity, and waist/hip ratio [54]. Compared to normal-weight ones, people suffering from obesity may have decreased levels of salivary adiponectin. A study reported that adult women's BMI was negatively correlated with salivary adiponectin levels [55]. Adiponectin can traverse the blood–brain barrier and attach to receptors present in several regions of the brain, including hypothalamus, cortical neurons, endothelial cells, and brainstem [56]. Both normal-weight and obese mice treated with exogenous adiponectin demonstrated antidepressant-like effects [57]. A meta-analysis demonstrated a correlation between depression and lowered adiponectin levels [58].

Resistin

In the family of cysteine-rich proteins with hormone-like functions that initiate inflammatory processes, human resistin is the precursor of resistin-like molecules [59]. Resistin primarily functions to regulate inflammatory, immunological, and auto-immune responses at a physiological level [60]. It is thought that resistin plays a major role in stress biology and can be used as a biomarker to determine the degree of illness and the efficacy of some treatments [61]. A meta-analysis revealed that circulating resistin levels was correlated with both obesity and type 2 diabetes [62]. In their study, [63] reported that salivary resistin levels were higher in people having a BMI of >30 kg/m^2. In another study, BMI was statistically significantly correlated with salivary resistin levels. Salivary resistin levels were found to be higher in obese diabetics and obese non-diabetics compared to the control group (Control group included those with BMI of <30 kg/m^2 and non-diabetics) [64]. A previous study conducted on children revealed that resistin levels in saliva were significantly higher in overweight and obese children (2.4 times higher) compared to normal-weight ones [65]. Resistin can induce the expression of several cytokines since it is a pro-inflammatory adipocyte [66]. Cytokines, on the other hand, inhibit the central nervous system's hypothalamus from a synthesis of dopamine and noradrenaline. This may lower levels of intra-synaptic monoamine and cause depression symptoms [67, 68]. Rahman et al. (2022) showed that depressed individuals have higher levels of resistin than healthy control [69].

Asprosin

Asprosin is present in the plasma at nanomolar concentrations. It is synthesized by the Fibrillin 1 (FBN1) gene and is secreted by white adipose tissue and taken up by the liver via the activation of the G protein-cAMP-PKA pathway. This pathway leads to a rapid release of glucose into the bloodstream. Insulin resistance in humans and mice is characterized by pathologically increased plasma asprosin and decreased hepatic glucose production related to immunological or genetic loss of function, which lowers insulin and glucose levels [70, 71]. People suffering from obesity exhibit higher levels of asprosin in their serum [72]. A study indicated that while the lowest levels of asprosin in serum and saliva were observed in underweight individuals, asprosin levels were associated with obesity as they increased due to increasing BMI [73]. Asprosin acts as an orexigenic peptide by stimulating AgRP neurons in the hypothalamus when it passes through the blood–brain barrier. Therefore, asprosin is very important for maintaining homeostasis in the body's energy systems. There is a pathological increase in asprosin levels in obesity and related illnesses [74]. A previous study on patients with bulimia nervosa reported that the higher the asprosin concentration, the higher frequency of overeating and loss of eating control. Moreover, an increase in asprosin levels and more severe depression have been linked to a greater loss of eating control [75].

Vaspin (Serpin A12)

Vaspin (serpin A12), initially detected in the visceral adipose tissue of obese and type 2 diabetic rats, is another marker that can be utilized to diagnose obesity [76]. It is classified as a serine protease inhibitor belonging to the serpin family. In the human body, it is synthesized in adipose tissue, pancreas, liver, skeletal muscle, and skin. Vaspin has the ability to decrease food consumption and help lowering pro-inflammatory adipokines by blocking inflammatory pathways, which can enhance insulin sensitivity. Compared to healthy individuals, individuals suffering from obesity have elevated serum vaspin levels. On the other hand, weight loss lowers serum vaspin levels [77]. A previous study reported that salivary vaspin levels of individuals suffering from obesity without comorbidities were significantly higher than those of overweight and normal-weight individuals [63]. In another study, it was observed that serum vaspin concentrations displayed diurnal variation that was associated with meals. While vaspin levels elevated before meals, they lowered after meals. The daily variation in serum vaspin levels was associated with the patterns of insulin and glucose. It is thought that increased insulin and/or glucose plasma concentrations, or the energy intake itself, maybe the cause of the postprandial drop in serum vaspin levels [78]. A previous study including both healthy and participants suffering from obesity reported that serum vaspin concentrations were positively correlated with body fat mass [79].

Other Adipokines

Tumor necrosis factor alpha (TNF-α) It regulates numerous biological processes like cell differentiation, the immune system, apoptosis, and energy metabolism. It is one of the initial adipokines associated with diseases such as obesity, insulin resistance, and diabetes. It not only promotes lipolysis but also affects other adipokines with its pro-inflammatory properties [80, 81]. Since TNF-α is expressed in adipose tissue, it is excessively secreted in case of obesity [82]. It also affects neurological functions by regulating the production and secretion of neurotransmitters and can make the blood–brain barrier more permeable, which is often seen in people exhibiting depressive behaviors [83]. TNF-α stimulates indoleamine 2,3-dioxygenase, which increases the conversion of tryptophan to kynurenine and reduces its conversion to serotonin, thus resulting in serotonin depletion. However, TNF-α reduces serotonin in the synaptic cleft by increasing serotonin reabsorption through the activation of serotonin transporters (SERT). It also plays a role in depression by over activating the HPA axis [84].

IL-6, IL-10, IL-1 Beta Interleukins regulate the immune system by ensuring the proliferation and differentiation of immune cells [85]. Systemic and chronic inflammation of adipose tissue is the primary cause of issues associated with obesity. IL-6, IL-10, and IL-1β are among the inflammatory cytokines produced by obesity-induced adipose tissue [86]. One meta-analysis study revealed that depressed subjects had greater levels of IL-6 and IL-10 than healthy controls, although IL-1 β did not significantly differ between the two groups [87].

Chemerin It regulates the synthesis of GLUT4, triglycerides, and the levels of leptin and adiponectin, hence influencing the functions and differentiation of adipocytes [88]. Chemerin levels were reported to be high in individuals suffering from obesity [89]. Deyama et al. (2018) indicated that intracerebral administration of chemerin to mice had antidepressant effects [90].

Omentin It is encoded by omentin-1 and omentin-2 genes. It has anti-inflammatory and antioxidant properties [91]. It is inversely proportional to BMI and waist circumference, and its levels lower in individuals suffering from obesity [92]. In a mouse study, lower levels of omentin-1 signified that anxiety and depression-like behaviors increased. Furthermore, there was a notable increase in proinflammatory cytokines, namely IL-1B, IL-6, and TNF-α [93].

Table 1 shows the findings of studies reviewing the association of adipokines with obesity and depression.

Gene Polymorphisms Associated with Depression and Obesity

Genome-wide association studies (GWAS) have associated more than two hundred loci in the genome with BMI, obesity status, and the distribution of fat, which are the genetic components of obesity [112]. Over 50 genetic loci associated with depression symptoms have been reported [113, 114]. Brain regions associated with hunger and energy balance (pituitary and hypothalamus) and mood regulation (hippocampus and limbic system) are significantly prevalent in genes close to BMI-related loci [26]. Genetic variants in GWAS have shown strong correlations with obesity in a variety of populations, particularly in the FTO and MC4R genes [115] (Table 2). Additionally, the existence of overlapping of common genetic variants between both conditions has been demonstrated. Obesity accounts for up to 12% of the genetic factor of depression [116]. Additionally, these genes are associated with dopamine signaling and serotonin receptors, axonal guidance, leptin, AMPK, and corticotropin-releasing hormone. Both diseases may have their origins in these highly interrelated signaling pathways [26, 117].

Fat Mass and Obesity-Associated (FTO) Gene

FTO gene exhibits the most compelling evidence in the human population when it comes to its relationship with obesity and BMI. This gene is the first to be identified with higher BMI in GWAS [136, 137]. A single nucleotide polymorphism (SNP) located in the first intron of the FTO gene increases the likelihood of developing obesity by 1.20 times and elevates the body mass index (BMI) by 0.39 kg/m^2 for each copy of the allele [138]. The s9939609 FTO polymorphism is the most extensively researched SNP in this gene. An increased rate of obesity and weight gain are associated with the existence of the risky 'A' allele of polymorphisms, which is found in the first intron. Moreover, this genotype has been linked to mechanisms associated with raised BMI, such as heightened energy intake or reduced satiety [139]. A meta-analysis showed a strong bidirectional association between depression and obesity. In other words, while BMI increases the risk of developing depression, high BMI increases the risk of individuals with depression [140, 141]. A study reported that adults who had higher genetic predisposition to obesity with the rs1421085, rs1121980, rs17817449, rs8050136, rs9939973, and rs3751812 FTO polymorphisms were more vulnerable to the negative consequences of an unhealthy Western diet [120]. A meta-analysis revealed that the polymorphism most closely associated with obesity was the rs9939609 FTO polymorphism and FTO gene polymorphisms were strongly associated with obesity [142]. In their systematic review, Zarza-Rebollo et al. (2021) did not reach a conclusive conclusion about the involvement of FTO in the comorbidity of depression-obesity [139]. However, the brain 's high FTO expression increased the possibility of an association with the development of depression. In a study, mice lacking the FTO gene displayed a reduced body weight, as well as depression and

Table 1 Some studies on adipokines related to obesity and depression

Adipokines	Population	Sample type	Results	Reference
Leptin Adiponectin Vaspin Resistin	19 obese women 25 normal-weight women	Saliva	Vaspin and resistin levels were found to be significantly higher in the obese group, and no significant difference was found between leptin and adiponectin levels	[63]
Leptin Adiponectin	262 middle-aged women (42–52 years old)	Blood serum	It has been shown that there is a strong association between depressive symptoms and low adiponectin concentrations, but not leptin, in middle-aged women over a 5-year follow-up period	[94]
Leptin	17 overweight/obese children 5 children of normal weight	Saliva	It was found to be significantly higher in overweight/obese children compared to normal weight children (40.4 ng/mL ± 28.8; 9.58 ng/mL ± 3.1, respectively)	[42]
Adiponectin	90 women aged 18–35 (30 normal-weight women; 30 overweight women; 30 obese women)	Saliva	A negative correlation was found between salivary adiponectin levels and BMI ($r = -0.28$, $p < 0.05$)	[55]
Resistin	76 children aged 6–10 (40 normal weight; 36 overweight/obese)	Saliva	It has been shown to be significantly 2.4 times higher in overweight and obese children compared to normal-weight children	[65]
Leptin	500 participants (250 with depression and 250 without depression)	Blood serum	The number of depressed people in obese BMI groups was three times higher than that of non-depressed people. Depression was associated with a decrease in serum leptin in low-weight BMI groups	[95]
Asprosin	116 participants (8 underweight, 44 normal, 19 overweight, 10 grade I obese, 13 grade II obese, and 22 grade III obese)	Blood serum and Saliva	While the lowest asprosin level was observed in thin individuals, asprosin level increased with increasing BMI and a positive significant relationship was shown between asprosin level and BMI (Saliva $r = +0.612$, $p < 0.01$; serum $r = +0.677$, $p < 0.01$)	[73]
Leptin	32-year-old woman with major depression 49 elderly women (≥60 years) without depression	Blood serum	There was no statistically significant difference in fasting serum leptin level between patients with depression (3.04 ± 1.79 ng/mL) and the control group (2.46 ± 1.70 ng/mL) ($p = 0.14$)	[96]
Leptin Adiponectin	194 young adults with depressive symptoms 57 healthy controls (18–25 years old)	Blood serum	While a significant increase was observed in leptin levels in both men and women with depressive symptoms, no such change was observed in adiponectin. BMI and waist-hip ratio show a positive correlation with leptin in both men and women, while adiponectin shows an inverse correlation in women ($p < 0.01$)	[97]
Asprosin	47 obese children 40 normal weight healthy children	Blood serum	Asprosin concentrations were lower in obese children (9.24 ± 4.11 ng/mL) than in normal weight controls (12.33 ± 4.18 ng/mL, $p < 0.001$)	[98]
Ghrelin	15 obese (BMI > 35 kg/m^2) 15 healthy controls (BMI < 30 kg/m^2)	Blood serum	Serum ghrelin levels were found to be significantly lower in the obese group (375.2 ± 47.6 pg/mL, 811.6 ± 87.8 pg/mL; $p < 0.001$, respectively)	[99]
Resistin	25 normal weight controls 58 obese	Blood serum	Resistin levels of healthy controls were found to be significantly lower compared to obese patients [14.0 ng/mL, 11.8 ng/mL, respectively; $p = 0.041$]. Resistin level in obese individuals is related to body weight ($r = 0.335$, $p = 0.012$], BMI ($r = 0.272$, $p = 0.048$), waist ($r = 0.335$, $p = 0.016$) and hip circumference ($r = 0.389$, $p = 0.004$) was found to be related	[100]

Table 1 (continued)

Adipokines	Population	Sample type	Results	Reference
Asprosin	44 obese children 54 overweight children 60 normal weight children	Blood serum	Serum asprosin levels showed significant differences between groups as 70.903 ± 17.49 ng/mL, 79.744 ± 29.54 ng/mL and 106.293 ± 122.69 ng/mL in normal weight, overweight and obese children, respectively. Post-hoc analysis revealed that asprosin level was significantly higher in obese children compared to normal weight children ($P = 0.009$). Additionally, asprosin was found to be a predictor of obesity in multiple regression analysis	[101]
Leptin Asprosin	48 sedentary male university students 48 male college students exercising	Blood serum	Serum leptin and asprosin levels were found to be significantly higher in obese individuals in the sedentary and exercise group compared to normal and overweight individuals	[102]
Asprosin	38 young male participants (19–25 years old) (20 controls; 18 obese)	Blood serum	Compared with the normal group, serum asprosin levels in the obese group were significantly higher ($p < 0.01$). In addition, diet and exercise were applied to the obese group (n = 14) for 14 weeks and serum asprosin levels were shown to decrease significantly compared to the beginning ($p < 0.01$)	[103]
Resistin	252 participants (126 major depression patients; 126 healthy controls)	Blood serum	Significantly higher resistin levels were shown in individuals with depression compared to healthy controls (13.82 ng/mL ± 1.24; 6.35 ng/mL ± 0.51 $p < 0.001$, respectively)	[69]
Asprosin Adiponectin Leptin Resistin	291 participants (89 controls, 105 Type 2 diabetes/obese, and 97 obese)	Blood serum	Asprosin level was found to be significantly higher in the obese group than the other groups, and adiponectin level was found to be significantly higher in the control group than the other groups. No significant difference was found between groups in leptin and resistein levels. Serum asprosin levels show a significant positive correlation with BMI (r = 0.22, $p < 0.01$)	[104]
Leptin Adiponectin IL-6, IL-10 TNF-α	94 adolescent participants (47 major depression patients; 47 healthy controls)	Blood serum	Significantly higher BMI was shown in individuals with depression compared to healthy controls, also increased adiposity measures, including total fat ($p = 0.016$), trunk fat ($p = 0.016$), and trunk/total fat ratio ($p = 0.021$). Significantly higher leptin, IL-6, and TNF-α levels were shown in individuals with depression compared to healthy controls. Adiponectin levels were significantly lower in depressed individuals than in healthy controls	[105]
Leptin	189 elderly diabetics people (age > 65 years; 57 depressive symptoms, 132 controls)	Blood serum	Leptin concentrations were significantly higher in type 2 diabetes patients with depressive symptoms compared to controls ($p < 0.01$). Additionally, increased BMI and leptin levels were found to be a predictive capacity of depressive symptoms in univariate logistic regression models	[106]
Vaspin	60 participants (40 obese, 20 controls)	Blood serum	Vaspin concentrations in the obese group were significantly higher than in the control group (0.82 ± 0.62 ng/mL vs. 0.43 ± 0.59 ng/mL; $p < 0.001$)	[107]
Omentin	88 participants (51 obese, 37 controls)	Blood serum	Omentin-1 concentrations were significantly lower in obese individuals compared to those control groups (234.36 ± 104.06 ng/mL vs. 286.97 ± 113.23 ng/mL; $p = 0.027$)	[108]

Table 1 (continued)

Adipokines	Population	Sample type	Results	Reference
Asprosin	109 children and adolescents (62 obese, 47 control) (age mean:9.6 years)	Blood plasma	Obese invididuals had higher plasma asprosin levels than healthy invididuals (mean 87.6 ± 26.2 vs. 69.3 ± 16.3 ng/mL; $p = 0.001$)	[109]
Ghrelin	155 participants (90 MDD patients, 65 healthy controls) (age: 18–50 years)	Blood plasma	Ghrelin levels were higher in the MDD (MDD patients 1368.99 ng/L, healthy controls 1157.08 ng/L; $p < 0.001$) Analysis of covariance with gender, age, and BMI as covariates to correct the p-value, still showed significant differences ($p = 0.047$)	[110]
Leptin Ghrelin Adiponectin	120 children and adolescents (60 obese and 60 healthy controls) (age: 7–17 years)	Blood serum	Obese individuals have higher leptin and ghrelin levels than the normal weight group (Leptin 377.8 ± 24.96 pg/mL vs. 256.4 ± 48.86 pg/mL, Ghrelin 2.52 ± 0.66 ng/mL vs. 1.62 ± 0.52 ng/mL; $p < 0.001$) Adiponectin levels are he normal weight group higher than those of obese individuals (2.56 ± 1.24 ng/mL vs. 1.47 ± 1.02 ng/mL; $p < 0.001$)	[111]

anxiety-like behaviors [143]. Another study revealed that those who possess the A allele in the FTO gene rs9939609 polymorphism obtained a higher Beck Depression Score. In multivariate regression models, the presence of the A allele in the FTO rs9939609 polymorphism was positively correlated with depression [124].

Obese (OB) Gene

It is determined whether or not individuals will be obese or underweight through mechanisms that balance food consumption and energy expenditure. The obese (ob) gene is one of the components that control the energy balance in rats. The Ob gene consists of three exons and two introns and spans 20 kilobases (kb) of genomic DNA on chromosome 7 in humans. Leptin is encoded by the Ob gene and is involved in a signaling system that controls the amount of body fat stored in adipose tissue [39, 144]. Ob gene mutations lead mice to develop obesity early [40]. The risk for depression is greater among individuals suffering from obesity who suffer from chronic low-grade inflammation. Stress causes neuroinflammation and microglial activation, both of which are crucial in the etiology of depression [145]. Wu et al. (2021) established a depression model by applying mild stress to mice carrying and not carrying the ob/ob gene. Ob/ob mice have been reported to have poor behavioral injury and memory impairment, microglial overactivation, overexpression of pro-inflammatory cytokines and NF-κB, and decreased H3K27me3 levels, as well as decreased adiponectin levels in serum and brain tissues. This was interpreted as the fact that obese mice were more susceptible to depression [146]. A meta-analysis revealed that memory impairments and depressive-like behaviors were present in mice lacking the leptin gene, such as ob/ob mice [147].

Serotonin Transporter (5-HTT) Gene

While the enteric nervous system in the gut contains most (> 90%) of the serotonin (5-HT) in the body, it is located in the central nervous system where this neurotransmitter primarily mediates the behaviors including mood, appetite, aggression, and sociability [148]. The 5-HTT gene encodes those serotonin transporters that help reabsorb serotonin from the synaptic cleft. These transporters are also known as SERT or SLC6A4. After its use, the majority of serotonin is recycled and re-stored in the serotonergic neurons that carry serotonin [149]. The 5-HTT gene contains a 44-bp polymorphism in its promoter region, referred to as 5-HTTLPR, which consists of a variable number of tandem repeats. It is thought to be accountable for changes in the efficiency of transcription. The "short polymorphism" (484 bp) and "long polymorphism" (528 bp) produce the same protein. However, the long allele is linked to a basal activity that is

Table 2 Some studies on FTO and MC4R gene polymorphisms associated with obesity and depression

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[118]	183 individuals with T2DM 74 healthy controls	M:46; F:137 Age:54.10 ± 9.33 years M:51; F:123 Age:48.95 ± 9.65 years	BMI	FTO	rs3751812	Tetra-ARMS-PCR	Case–control	FTO rs3751812 polymorphism with obesity has been associated ($p = 0.003$)
[119]	270 adolescent males	Age: 14.1 ± 1.27 years	W H BMI %BF %BM	FTO	rs9930506 rs9930501 rs9932754	DNA Sequencing	Cross-sectional	A haplotype in the first intron of the FTO gene has a strong association with obesity indices (These polymorphisms are associated with higher weight (OR = 1.32), BMI (OR = 5.36), BM% (OR = 1.46) and lower BM% (OR3.59). was found to be significantly associated with (all $P < 0.001$)
[120]	4292 adults	M: %43.6, F:%56.4 Age: E:42.6 ± 14 years F: 40.4 ± 13 years	GRS WDP BMI WC	FTO	rs1421085 rs1121980 rs17817449 rs8050136 rs9939973 rs3751812	Genotyping	Cohort	It shows that adults with a higher genetic predisposition to obesity are more susceptible to the harmful effects of adherence to WDP, which highlights the need to reduce consumption of unhealthy foods to prevent obesity

Table 2 (continued)

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[121]	198 overweight healthy adults	M: 50, F:148 Age: M: 34.00 ± 6.17 years F: 33.10 ± 6.41 years	BMI WC HC WHR WHtR FFM FM FM% TF	FTO	rs9939609	ARMS-PCR	Cross-sectional	Homozygous carriers of the A allele had significantly higher values for BMI (0.60 kg/m2, $p = 0.026$), WHR (0.04 units, $p = 0.003$) and WHtR (0.02 units, $p = 0.030$) than homozygous carriers of the T-. Individuals with AA allele genotype had more WC (2.66 cm, $p = 0.042$ and 4.03 cm, $p = 0.002$), FM (2.24 kg, $p = 0.004$ and 3.02 kg, $p = 0.001$) and TF (1.53 kg, $p = 0.001$) and 2.08 kg, $p = 0.001$) were higher compared to AT and TT genotypes, respectively. The FTO rs9939609 polymorphism A allele has been shown to be associated with obesity
[122]	196 overweight adults	M: 50, F:146 Between 20–45 years of age	Glucose Leptin Insulin Adiponectin Lipid profile Serum hormones Dietary intake	FTO	rs993960	ARMS-PCR	Cross-sectional	Homozygotes for rs9939609 risk allele A had higher serum leptin $p = 0.005$, F: 5.131) and was associated with lower HDL [$p = 0.001$, F: 7.687) levels
[21]	718 children	M: 356, F:362 Age: M: 8.6 ± 2.1 years, F: 8.6 ± 2.1 years	W H BMI WC	FTO MC4R	rs8050136 rs9939609 rs3751812 rs17700144 rs17782313	RT-PCR	Cohort	FTO (rs8050136, rs9939609) and MC4R (rs17782313) genotypes were also significantly associated with obesity (BMI > 2Z score) in men (OR = 1.89, $P = 0.04$, OR = 3.3, $P = 0.006$ OR = 3.11, $p = 0.04$, respectively)

Table 2 (continued)

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[123]	4480 adults	-	DDS GRS BMI VAI WC Physical activity	FTO	rs1121980 rs14211085 rs805013	Microarray	Cohort	rs1121980 minor allele carriers had lower BMI (Q1: 1.58 ± 0.60 vs Q4: 0.13 ± 0.59) and VAI (Q1: 0.00 ± 0.02 vs Q4) when they had higher DDS: 0.04 ± 0.02) changes are observed ($p < 0.05$)
[124]	197 overweight adults	M:50, F:147 Age: 33.34 ± 6.36 years	Beck depression score Serum vitamin D level	FTO	rs9939609	ARMS-PCR	Cross-sectional	A allele carriers had higher Beck depression score (P = 0.03). Multivariable regression models showed a positive association between the A allele of the FTO rs9939609 polymorphism and depression. Serum vitamin D level had no effect on the relationship between FTO genotype and depression
[125]	819 adults	M:%47.5, F:%52.5 Age: 42.1 ± 14.5 years	BMI VAT SAT WHR	MC4R	rs17782313 rs12970134 rs633265 rs1350341	RT-PCR	Cross-sectional	CC genotype carriers of MC4R rs17782313, those with higher protein intake, have higher VAT content and higher VAT/SAT ratio; AA genotype carriers of MC4R rs12970134 have been reported to have higher BMI, total body fat content, VAT, SAT

Table 2 (continued)

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[126]	303 individuals (208 children, 95 adults)	Children M: 113, F:95 Age: 14.4 ± 1.74 years Adults M: 62, F:33 Age: 20.77 ± 3.18 years	W H BMI WC HC WHR	MC4R	rs17782313	PCR	Cross-sectional	The rs17782313 variant was shown to be moderately associated with increased body weight among children (0.15 ± 0.076 kg, $P = 0.043$), with both populations combined (0.13 ± 0.070, $P = 0.057$). This variant was not found to be associated with any other measure of adiposity
[127]	4084 adults	M: 1133, F: 2951 Age: 40.3 ± 11.3 years	BMI	FTO MC4R	rs9939609 rs17782313	RT-PCR	Case–control	MC4R rs17782313-C was associated with obesity [OR = 1.27, $p = 0.038$). The FTO rs9939609-A allele has been shown to be associated with overweight
[128]	403 overweight/obese adult	M: 212, F:191 Between 20–50 years old	W H BMI WC HC WHR DASS-21 VAS EEQ	MC4R	rs17782313	PCR–RFLP	Cross-sectional	It has been found that adherence to a high-energy and fat diet and a low-protein diet is associated with a higher BMI in individuals with the C allele of MC4R rs17782313. Significant relationships have been observed between food intake, appetite, emotional eating and stress ($p < 0.05$)
[129]	636 adults	M:307, F:329 Age: M: 19.58 ± 3.46 years F: 19.12 ± 1.94 years	W H BMI %BF WC TC Energy intake	FTO	-	Microarray	Cross-sectional	A total of 34 genetic variants were associated with any of the 6 indicators of overweight and obesity, but only 15 showed mean differences using the recessive model after Bonferroni correction

Table 2 (continued)

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[130]	501 adults	M: 240, F:261 Age: 51.62 ± 7.90 years	BMI WC WHR %BF %AFM %GFM	FTO MC4R	rs9939609 rs17782313	PCR	Cross-sectional	It has been shown that those with the rs17782313 CC allele and rs9939609 AA alleles are in the high-risk group for obesity
[131]	280 individuals (140 overweight/obese adult, 140 controls)	Age: Obese and overweight 37.42 ± 14.06 years Healthy controls 29.49 ± 12.74 years	W BMI WHR TC TG HDL-C LDL-C	FTO	rs9939609	ARMS-PCR	Cross-sectional	rs9939609 was strongly associated with the obesity risk factors of increased BMI, TC, TG, and LDL-C
[132]	178 children (80 girls and 98 boys)	Age: 11.8 ± 2.8 years	BMI FMI	MC4R	rs17782313 rs17773430 rs34114122	RT-PCR	Cross-sectional	The minor C allele in the three variants (C–C–C) was significantly associated with anthropometric measures indicative of obesity, such as body mass and fat mass indexes
[133]	289 overweight/obese women (136 overweight and 153 obese)	Age: 36.5 ± 8.3 years	W H BMI WC HC BFI FFM DASS-21 FFQ	MC4R	rs17782313	PCR	Cross-sectional	Unhealthy dietary pattern increases the risk of depression in people with CC alleles of the MC4R gene (OR: 8.77, 95%CI: −0.86–18.40, P: 0.07)
[134]	280 individuals	M:183, F:97 Age: 45.10 ± 9.6 years	BMI WC SBP DBP HbA1C TG HDL	FTO	rs9939609	ARMS-PCR	Cross-sectional	Patients with the AA genotype of the FTO gene variant rs9939609 had increased BMI, WC, SBP, DBP, HbA1C, and TGs and a lower HDL cholesterol level

Table 2 (continued)

Reference	Groups (n)	Gender: M, F; Age: years (X ± SS)	Obesity/ depression diagnostic-criteria	Gene	Polymorphism	Polymorphism detection method	Study type	Results
[135]	319 individuals in case group (BMI ≥ 28 kg/m^2) 319 individuals in control group (BMI < 24 kg/m^2)	Age: 20 to 80 years	BMI	FTO MC4R	rs1121980 rs17817449 rs17782313 rs12970134	RT-PCR	Cross-sectional	MC4R gene polymorphisms were associated with obesity. The SNPs of FTO were not found to be significantly associated with obesity in Tibetan adults

roughly three times higher than that of the shorter variant [150]. Consequently, the long variant generates a considerably higher amount of 5-HTT mRNA and protein. Thus, the long polymorphism causes increased gene expression and higher levels of serotonin transporters on the cell membrane. As a result, higher levels of serotonin are reabsorbed into the presynaptic cell [151, 152]. Genetic variation or polymorphism of the area that includes the serotonin transporter gene (5-HTTLPR) is a contributing factor to the development of depression. Individuals with the short allele are more prone to psychological conditions such as depression due to less serotonin production [153]. A systematic review showed that 5-HTTLPR polymorphism increased the risk of obesity due to the development of depression [154].

Melanocortin 4 Receptor (MC4R) Gene

The MC4R gene, consisting of 996 base pairs, is located on chromosome 18q21.3 and is linked to the control of appetite [155]. The melanocortin signaling originating from the hypothalamus induces a reduction in food consumption and a rise in energy expenditure [156]. Severe monogenic forms of obesity that manifest at a very young age are associated with polymorphism in the MC4R gene. Additionally, there is evidence of a relationship between MC4R and BMI [157]. Walia et al. (2021) indicated that there was an important correlation between the MC4R gene rs17782313 polymorphism and body weight [126]. Another study found that individuals suffering from obesity had a higher frequency of the MC4R rs18882313 minor allele. Additionally, people with this variant had an important consumption of fat and processed foods; whereas, their consumption of fruit was importantly lower [158]. Other meta-analyses revealed that the MC4R gene was significantly related to the rs17782313 polymorphism and obesity [159, 160]. MC4R is associated with stress-induced psychological disorders [161]. The MC4R gene increases the amount of MC4R by stimulating stress neuropeptides and thus it may affect eating behaviors [158]. Rahati et al. (2022) reported that a high-energy and high-fat diet and a low-protein diet caused a higher BMI in people with the C allele of MC4R rs17782313. Furthermore, they observed significant correlations between this gene polymorphism and various aspects of eating behavior, including food consumption, appetite, emotional eating, and stress [128]. Another study reported that depressed people had a higher genetic predisposition to having a high BMI than non-depressed people did. This suggested that depression may enhance the expression of a person's natural predisposition to obesity. Depression and obesity are thought to be associated with the MC4R gene, which affects the HPA axis and appetite regulation [162].

Conclusion

Obesity and depression have been increasing rapidly around the world. Genetic, epigenetic and environmental factors are effective in the development of these diseases. It is very difficult to evaluate the impact of genetics on nutrition and obesity. Many genes and numerous environmental factors interact simultaneously with nutrition and obesity. The risk of developing obesity can be reduced by providing healthy eating habits, especially to individuals with a genetic predisposition for obesity or depression. The mechanisms behind the onset of obesity and depression remain unclear, even though adipokines and gene polymorphisms are known to be involved as well.

Understanding the biological mechanisms of these risk factors is crucial for effectively treating and preventing diseases. Therefore, more comprehensive clinical studies on this subject are needed in vivo, in vitro, and on experimental animals and humans.

Suggestions and Future Perspective

While numerous studies have explored the relationship between metabolic and genetic factors in various health conditions, research on their combined effects on mental health remains limited. Given the growing prevalence of both obesity and depression, understanding the underlying biological mechanisms, including the roles of adipokines and gene polymorphisms, is essential. Future studies should focus on how these factors contribute to disease progression across different populations and whether targeted interventions can mitigate their effects.

Additionally, although existing evidence highlights the potential role of adipokines in the bidirectional relationship between obesity and depression, further large-scale, longitudinal, and randomized controlled trials are necessary to establish clearer causal links. Investigating the therapeutic potential of modulating adipokine activity through pharmacological or dietary interventions may provide valuable insights for future treatment strategies.

Moreover, gene polymorphisms associated with both obesity and depression should be examined through advanced genetic and epigenetic studies. Exploring how these genetic variations interact with environmental and lifestyle factors could lead to more personalized prevention and treatment approaches. Future research should also consider the development of novel therapeutic strategies targeting interconnected signaling pathways that influence both metabolic and neuropsychiatric health.

By addressing these gaps, future studies can enhance our understanding of the complex interplay between obesity, depression, adipokines, and genetic factors, ultimately contributing to more effective prevention and treatment strategies for obesity-induced depression.

Limitations

This review is based on an analysis of studies available in the literature, and its limitations are inherently tied to the scope and quality of the reviewed sources. A significant portion of the examined studies consists of observational research, which limits the ability to establish causal relationships between adipokines, gene polymorphisms, and the development of obesity-induced depression. Furthermore, variations in study designs, sample sizes, and measurement methods across different studies may contribute to inconsistencies in findings.

Additionally, while this review highlights the potential role of adipokines and genetic factors in the interplay between obesity and depression, it does not comprehensively address all possible confounding variables, such as environmental influences and lifestyle factors. The lack of large-scale, longitudinal, and interventional studies further restricts our ability to draw definitive conclusions.

Future research should focus on more extensive genetic analyses and controlled trials to evaluate the direct effects of adipokines and gene polymorphisms on the development of depression in individuals with obesity. Moreover, investigating the potential therapeutic implications of targeting adipokines for managing obesity-induced depression remains an important area for further exploration.

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  ○ rs9939609 (FTO) and rs17782313 (MC4R) gene polymorphisms significantly increase the genetic predisposition to the development of obesity in children and adolescents, and these genetic variants are associated with energy balance and appetite regulation.

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  ○ The interaction between the MC4R gene variant (rs17782313) and dietary patterns significantly influences the risk of depression in obese and overweight women, and certain dietary patterns may combine with genetic predisposition to have adverse effects on depression.

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13679-025-00652-w.

Author Contribution "S.N.E. wrote the main manuscript text and prepared figures and tables. N.S. reviewed and revised the manuscript text critically for important intellectual content. Both authors reviewed and approve the manuscript."

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human subjects performed by any of the authors. All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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