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Decoding the Depression Obesity Axis: Genetics Inflammation and Artificial Intelligence Applications

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Abstract

Depression and obesity are among the most prevalent and disabling health conditions worldwide, imposing a substantial burden on healthcare systems and society. Increasing evidence suggests a bidirectional relationship between these disorders, supported by common biological, genetic, metabolic, inflammatory, and psychosocial mechanisms. Obesity contributes significantly to the development of numerous chronic diseases, including cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, sleep disorders, and neurodegenerative conditions, all of which may further exacerbate depressive symptomatology. Recent advances in artificial intelligence (AI) have created new opportunities for identifying, predicting, and treating obesity-related depression through machine learning, deep learning, digital phenotyping, and precision medicine approaches. This narrative review examines the complex relationship between depression and obesity, discusses the major diseases associated with obesity, and explores the current and future role of AI in clinical decision-making, risk prediction, genetic profiling, and personalized therapeutic interventions.

Introduction

Major depressive disorder encompasses a heterogeneous group of affective, cognitive, and behavioral symptoms that significantly interfere with daily functioning, interpersonal relationships, and overall quality of life [1]. Clinical manifestations commonly include persistent low mood, anhedonia, cognitive impairment, sleep disruption, and reduced psychosocial performance. The etiology of depression is multifactorial, but no specific mechanism has yet been identified to explain all aspects of the disease. In the case of major depression, neuroimaging studies have revealed reduced volumes of the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, medial temporal lobe (hippocampus and amygdala), and basal ganglia structures. These structural brain changes have been associated with increased volume of the lateral and third ventricles. Along with anatomical brain changes, functional changes such as abnormalities in cerebral blood flow (and/or metabolism) in the prefrontal cortex (orbitofrontal, dorsolateral, and dorsomedial cortex), anterior cingulate cortex (especially the subgenual region), amygdala, thalamus, and basal ganglia have also been identified in major depression [2]. Over time, depression has been linked to craniomandibular disorder severity, neuropathic chronic pain, celiac disease or social media addiction [3].

According to the World Health Organization, depression remains one of the leading causes of disability worldwide and contributes substantially to the global burden of disease [4]. At the same time, obesity has reached epidemic proportions, affecting individuals across all age groups and socioeconomic backgrounds. The growing prevalence of obesity has been attributed to complex interactions among genetic predisposition, environmental influences, dietary habits, sedentary lifestyles, and socioeconomic factors [5].

Historically, depression and obesity were regarded as separate clinical entities. However, contemporary research increasingly supports the existence of a bidirectional relationship between these disorders. Individuals with obesity demonstrate a significantly higher risk of developing depressive symptoms, while patients with depression frequently exhibit weight gain, altered eating behaviors,

and metabolic abnormalities that predispose them to obesity [6]. The coexistence of both conditions creates a vicious cycle in which psychological distress contributes to unhealthy lifestyle behaviors, while obesity-related physiological changes further worsen mood regulation.

Several biological mechanisms have been proposed to explain this association, including chronic low-grade inflammation, hypothalamic-pituitary-adrenal axis dysregulation, insulin resistance, gut microbiota alterations, neurotransmitter dysfunction, and shared genetic susceptibility [7]. Furthermore, advances in artificial intelligence have ,introduced novel opportunities to investigate these mechanisms and develop personalized approaches for prevention, diagnosis, and treatment.

Material and Methods

This study was conducted as a narrative literature review aimed at examining the relationship between depression and obesity, obesity-associated diseases, and the role of artificial intelligence in the identification, prediction, and treatment of these conditions. Particular emphasis was placed on shared biological mechanisms, genetic susceptibility, inflammatory pathways, metabolic dysfunction, and AI-driven precision medicine approaches.

A comprehensive literature search was performed using the PubMed and Google Scholar databases. These databases were selected because of their broad coverage of biomedical, psychiatric, metabolic, and artificial intelligence-related research. The search strategy incorporated combinations of Boolean operators and keywords as follows: “depression” AND “obesity”, “depression” AND “obesity” AND “artificial intelligence,” “depression” AND “obesity” AND “genetics” AND “precision medicine”, “machine learning” AND “depression diagnosis”, “machine learning” and “obesity prediction”, “deep learning” AND “obesity” AND “depression”.

The initial search identified approximately 312 potentially relevant articles. Following the removal of duplicate records and screening of titles and abstracts, 74 studies were selected for full-text evaluation. After detailed assessment of methodological quality, scientific relevance, and alignment with the objectives of the review, 25 articles were included in the final analysis. Preference was given to systematic reviews, meta-analyses, large cohort studies, genome-wide association studies, and recent investigations published between 2015 and 2025. Older publications were included when considered essential for understanding the biological and clinical relationship between depression and obesity.

Results

The Bidirectional Relationship Between Depression and Obesity

The relationship between depression and obesity is increasingly recognized as bidirectional and multifaceted. Individuals with obesity frequently experience psychological distress related to body image dissatisfaction, social stigma, discrimination, reduced self-esteem, and impaired quality of life. These factors may contribute directly to the development of depressive symptoms. Simultaneously, depression may promote weight gain through emotional eating, reduced physical activity, altered sleep patterns, endocrine dysfunction, and adverse effects associated with psychopharmacological treatment.

A landmark meta-analysis conducted by Luppino and colleagues demonstrated that obesity increases the risk of future depression by approximately 55%, whereas depression increases the risk of developing obesity by nearly 58% [6]. These findings highlight the dynamic interaction between mental health and metabolic status and emphasize the importance of addressing both conditions simultaneously.

Biological Mechanisms Linking Depression and Obesity

Several biological pathways contribute to the association between depression and obesity. Chronic low-grade inflammation represents one of the most extensively investigated mechanisms. Adipose tissue functions as an active endocrine organ capable of producing pro-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-6, and C-reactive protein. Elevated concentrations of these inflammatory mediators may influence neurotransmitter metabolism, neuroplasticity, and neural network function, thereby contributing to depressive symptomatology [8].

Another important mechanism involves dysregulation of the hypothalamic-pituitary-adrenal axis. Chronic psychological stress results in prolonged cortisol secretion, which promotes visceral adiposity, insulin resistance, and metabolic dysfunction. Hyperactivation of the stress response system has also been consistently observed in individuals with major depressive disorder [7].

Emerging evidence additionally supports the involvement of the gut-brain axis. Alterations in gut microbiota composition may increase intestinal permeability and systemic inflammation while influencing neurotransmitter production and immune signaling pathways. These changes have been implicated in both obesity and depression, suggesting a common microbiome-mediated mechanism [9][7].

Obesity-Related Diseases

Obesity contributes significantly to the development of numerous chronic diseases. Cardiovascular disease remains one of the most important obesity-related complications, with excess adiposity promoting hypertension, endothelial dysfunction, dyslipidemia, atherosclerosis, and increased cardiovascular mortality. Similarly, obesity is a major risk factor for type 2 diabetes mellitus through mechanisms involving insulin resistance and pancreatic beta-cell dysfunction [5][10].

Metabolic syndrome represents another critical consequence of obesity and is characterized by the coexistence of abdominal obesity, hypertension, hyperglycemia, and dyslipidemia. This syndrome substantially increases the risk of cardiovascular disease and has also been associated with higher rates of depression [5][11].

Additional obesity-related diseases include non-alcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, several forms of cancer, and neurodegenerative disorders such as Alzheimer's disease. Importantly, many of these conditions contribute independently to psychological distress and may further worsen depressive symptoms, thereby reinforcing the reciprocal relationship between physical and mental illness [5][12].

Artificial Intelligence in the Identification and Treatment of Depression and Obesity

Artificial intelligence has emerged as one of the most transformative technologies in modern healthcare. Machine learning algorithms can analyze large volumes of clinical, behavioral, laboratory, imaging, and genetic data to identify patterns associated with disease development and progression. These approaches have demonstrated significant potential in improving diagnostic accuracy and predicting

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clinical outcomes in both psychiatric and metabolic disorders [13,14].

AI-powered systems can utilize information obtained from electronic health records, wearable devices, smartphone applications, and patient-reported outcomes to identify individuals at elevated risk of depression or obesity. Continuous monitoring of sleep quality, physical activity, heart rate variability, and behavioral changes allows for earlier detection of clinical deterioration and more timely intervention [13].

Furthermore, natural language processing technologies can analyze speech patterns, linguistic characteristics, and social media activity to detect subtle indicators of depressive symptomatology. Such tools may enhance early screening efforts and improve access to mental health services, particularly in underserved populations [15].

Artificial Intelligence and Shared Genetic Predisposition Between Depression and Obesity

Artificial intelligence (AI) has become an increasingly valuable tool for investigating the complex genetic relationship between depression and obesity. Recent advances in machine learning, deep learning, and multi-omics analysis have enabled researchers to identify shared genetic variants and biological pathways that contribute to both conditions.

Large-scale genomic datasets generated through genome-wide association studies (GWAS) contain millions of genetic markers, making conventional statistical approaches insufficient for detecting complex interactions. AI algorithms can analyze these vast datasets and uncover subtle patterns linking depression-related genes with obesity-associated genetic loci. For example, machine learning models have identified overlapping genetic influences involving genes that regulate inflammation, hypothalamic-pituitary-adrenal (HPA) axis activity, dopamine signaling, leptin and insulin pathways, and appetite regulation [16-18].

Polygenic risk score (PRS) models enhanced by AI can estimate an individual's inherited susceptibility to obesity among patients diagnosed with depression and, conversely, predict depression risk among individuals with obesity. Deep learning systems can further integrate genomic information with neuroimaging, metabolomic profiles, electronic health records, lifestyle factors, and behavioral data to create highly personalized risk assessments. These approaches may reveal that a patient presenting with depressive symptoms carries a genetic profile associated with future obesity development, even before significant weight gain occurs [16,17].

Similarly, AI can identify obese individuals with genetic and neurobiological signatures suggesting elevated vulnerability to major depressive disorder. Such predictive capabilities support precision medicine by enabling early preventive interventions, personalized nutritional strategies, targeted psychotherapy, optimized pharmacological treatment, and continuous monitoring of high-risk individuals.

As AI technologies continue to evolve, they are expected to play a central role in elucidating the shared genetic architecture of depression and obesity, ultimately improving diagnostic accuracy and individualized patient care [7,13,16,17,14].

Discussion

The findings of the present review highlight the complex and bidirectional relationship between depression and obesity. Contemporary evidence suggests that these disorders should no longer be considered independent clinical entities but rather interconnected conditions that share multiple biological, psychological, and environmental determinants [6,7]. The reviewed literature consistently demonstrates that obesity increases the risk of developing depressive symptoms, whereas depression contributes to behavioral and physiological changes that facilitate weight gain and metabolic dysfunction. Furthermore, growing evidence suggests that psychiatric symptoms may also reflect underlying neurological dysfunction. Neuropsychiatric manifestations including depression, anxiety, cognitive impairment, and personality changes, may represent early clinical indicators of underlying neurological pathology, emphasizing the complex interaction between brain function and psychiatric symptomatology [19].

Several mechanisms appear to explain this association. Chronic low-grade inflammation, hypothalamic-pituitary-adrenal axis dysregulation, insulin resistance, and alterations in the gut-brain axis have been repeatedly implicated in both depression and obesity [8,9,7]. Furthermore, psychosocial factors such as weight stigma, social isolation, reduced self-esteem, and impaired quality of life contribute substantially to the development and persistence of depressive symptoms among individuals with obesity [20]. The interaction between these biological and psychosocial mechanisms creates a self-perpetuating cycle that may complicate treatment outcomes and increase the overall burden of disease.

The present review also emphasizes the broad spectrum of obesity-related comorbidities. Cardiovascular disease, type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, obstructive sleep apnea, and neurodegenerative disorders represent major health consequences associated with excessive adiposity [5,10]. Importantly, these chronic conditions may independently contribute to psychological distress and reduced quality of life, thereby exacerbating depressive symptomatology and further reinforcing the reciprocal relationship between physical and mental illness.

One of the most significant developments identified in the literature is the growing role of artificial intelligence in healthcare. Machine learning algorithms, deep learning systems, digital phenotyping approaches, and predictive analytics are increasingly being utilized to identify individuals at risk for depression and obesity, often before clinical manifestations become evident [13,14]. The integration of electronic health records, wearable sensor data, neuroimaging findings, and behavioral information enables earlier disease detection and facilitates more individualized therapeutic interventions.

Particularly promising is the application of artificial intelligence to genomic and precision medicine research. AI-based models are capable of analyzing complex genomic datasets and identifying shared genetic pathways involved in both depression and obesity [16,17]. Through the incorporation of polygenic risk scores, metabolomic data, and clinical characteristics, these systems may facilitate personalized prevention strategies and optimize treatment selection according to an individual's unique biological profile [13,14]. Such approaches represent an important step toward precision psychiatry and personalized metabolic medicine.

Despite these advances, several limitations remain. Much of the available evidence is observational, which limits the ability to establish causal relationships between depression and obesity [6]. Furthermore, artificial intelligence systems are dependent upon the quality, diversity, and representativeness of training datasets and may be affected by algorithmic bias [21]. Ethical concerns regarding data privacy, cybersecurity, transparency, and equitable access to AI-driven healthcare solutions must also be carefully addressed before widespread implementation.

Future research should focus on longitudinal investigations examining the temporal relationship between depression and obesity, as well as studies integrating genomic, neuroimaging, metabolomic,

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and behavioral datasets within artificial intelligence frameworks. Such efforts may contribute to a more comprehensive understanding of the shared pathophysiology underlying these disorders and support the development of highly individualized therapeutic strategies capable of improving both psychiatric and metabolic outcomes.

Future Perspectives

Future developments in artificial intelligence are expected to further transform the management of obesity-related depression. The integration of genomics, metabolomics, neuroimaging, wearable sensor data, and electronic health records will enable increasingly sophisticated predictive models capable of supporting truly personalized medicine. Continued collaboration among clinicians, neuroscientists, geneticists, bioinformaticians, and computer scientists will be essential to ensure the safe and ethical implementation of these technologies [14,21].

Conclusion

Current evidence suggests that depression and obesity should be viewed as overlapping clinical conditions characterized by substantial convergence across neurobiological, metabolic, inflammatory, genetic, and psychosocial pathways. Their coexistence contributes significantly to psychological distress, reduced quality of life, and increased healthcare utilization.Obesity-related diseases, including cardiovascular disease, diabetes mellitus, metabolic syndrome, sleep disorders, and neurodegenerative conditions further complicate clinical management and may exacerbate depressive symptoms. Artificial intelligence offers unprecedented opportunities for understanding the intricate relationship between these disorders, identifying shared genetic predispositions, predicting disease risk, and delivering personalized therapeutic interventions. As AI technologies continue to evolve, they are likely to play a central role in advancing precision psychiatry and metabolic medicine.

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