Review

Neuroscience

A Comprehensive Review on the Role of Obesity in Functional Cognition (Part II)

Cognition Impairment and Underlying Mechanisms, and Development of Neurodegenerative Diseases

Ronnie Callaghan*
University of Central Oklahoma, 100 N University Dr, Edmond, OK 73034, USA
*: All correspondence should be sent to: Dr. Ronnie Callaghan.
Author's Contact: Ronnie Callaghan, Ph.D., E-mail: roncallaghan@yahoo.com
DOI: https://doi.org/10.15354/si.23.re701
Funding: No funding source declared.
COI: The author declares no competing interest.

Epidemiological and neuroimaging studies have accumulated evidence of a significant relationship between obesity and cognitive impairment. The mechanisms underlying the connection between these two ostensibly unrelated domains are complex and multifactorial. First, obesity is frequently accompanied by comorbidities, such as Type 2 Diabetes and hypertension, which can contribute to cerebrovascular alterations and neuronal dysfunction, resulting in cognitive deficits. Second, chronic low-grade inflammation activates proinflammatory cytokines that may impair cognitive processes by affecting neuronal plasticity and synaptic function. In addition, obesity-related hormonal imbalances, such as insulin resistance and dysregulation of adipokines, may disrupt neuroendocrine pathways that are essential for cognitive health. The gut-brain axis, which influences inflammation, metabolic signaling, and the synthesis of neuroactive compounds, has also been linked to cognitive decline in obese individuals with altered gut microbiota composition. Changes in the structure of the brain, such as a reduction in hippocampal volume and a disruption in the integrity of the white matter, have also been observed in obese individuals, further implicating the negative effects of obesity on cognition. In addition, lifestyle factors such as sedentary behavior and unfavorable dietary patterns associated with obesity can contribute independently to cognitive dysfunction.

Keywords: Obesity; Cognition; Neuronal Plasticity; Neuroinflammation; Outcomes

Science Insights, 2023 September 30; Vol. 43, No. 3, pp.1049-1057.

© 2023 Insights Publisher. All rights reserved.
Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed by the Insights Publisher.

THE CONDITION of obesity is a significant worldwide health issue that has wide-ranging implications, including its notable influence on cognitive abilities. An increasing amount of scholarly research has shed light on a strong correlation between obesity and cognitive impairment, which includes deficiencies in memory, attention, executive functions, and overall cognitive abilities (1). The association between these factors is of particular concern due to the escalating global prevalence of obesity. Gaining insight into the fundamental mechanisms that establish a connection between obesity and cognitive dysfunction holds significant importance in terms of both clinical intervention and the formulation of public health strategies.

The complex nature of the association between obesity and cognition involves various sophisticated systems. A key element pertains to the metabolic dysregulation frequently observed in obesity, encompassing insulin resistance and hyperglycemia. The occurrence of metabolic disturbances has been associated with cerebral insulin resistance and decreased glucose consumption in the brain, resulting in the disruption of neuronal function and synaptic plasticity (2). As a result, this metabolic imbalance has the potential to impede cognitive processes, namely in the brain regions associated with memory and executive functions, such as the hippocampus and prefrontal cortex. Furthermore, metabolic abnormalities associated with obesity might result in the buildup of advanced glycation end products (AGEs) and oxidative stress, hence exacerbating neuroinflammation and cognitive deterioration.

Chronic low-grade inflammation is an additional crucial factor within the obesity-cognition connection. The adipose tissue, namely the visceral fat, serves as an endocrine organ by releasing proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) (3). The ability of these cytokines to cross the blood-brain barrier and begin neuroinflammatory processes has been associated with synaptic dysfunction and neuronal injury. Moreover, the activation of microglia, which is a characteristic feature of neuroinflammation, can result in the production of cytotoxic substances and hinder the process of synaptic pruning and plasticity. This, in turn, worsens cognitive impairments.

In addition, obesity frequently correlates with comorbidities such as hypertension and dyslipidemia, which have the potential to contribute to cerebrovascular dysfunction. Hypertension, specifically, has the potential to cause microvascular impairment and small vessel pathology in the brain, resulting in diminished cerebral perfusion and oxygenation (4). The aforementioned vascular alterations have the potential to give rise to lesions in the white matter of the brain, thereby compromising the interconnectedness of neural pathways. Consequently, this can have a detrimental impact on the speed and effectiveness of cognitive processing. Moreover, dyslipidemia associated with obesity has the potential to cause the buildup of lipids that are conducive to atherosclerosis, hence intensifying vascular impairment and undermining cognitive well-being.

In the context of degenerative neurological disorders, the adverse impact of obesity on cognitive function assumes heightened importance. Alzheimer's disease (AD) is distinguished by the presence of beta-amyloid plaques and tau protein tangles in the brain. The potential impact of obesity on the development of AD pathology may be attributed to the worsening of pathogenic mechanisms such as insulin resistance, neuroinflammation, and changes in adipokine signaling (5). Moreover, vascular dysfunction associated with obesity can potentially impair the flow of blood to the brain, hence exacerbating neuropathological changes connected to Alzheimer's disease.

Likewise, there exists a correlation between obesity and the onset as well as advancement of Parkinson's disease (PD), a neurodegenerative condition distinguished by the degeneration of dopaminergic neurons in the substantia nigra. The potential influence of obesity on PD can be attributed to many processes, such as heightened oxidative stress, neuroinflammation, and modifications in the makeup of gut microbiota (6). The relationship between the gut and the brain, known as the gut-brain axis, is of significant importance in the development of PD. This axis is affected by various factors associated with obesity, including changes in the composition of gut bacteria and inflammation. These factors have the potential to worsen the process of neurodegeneration in PD.

Obesity and Cognitive Functions

Memory Impairment in Obesity

Memory impairment in obesity has emerged as a noteworthy research area with implications for both cognitive neuroscience and public health. While the primary focus of obesity-related research has traditionally been on its metabolic and cardiovascular consequences, recent investigations have unveiled a complex interplay between excess body fat and cognitive function, particularly memory. Memory, a fundamental cognitive process, is essential for daily functioning and quality of life. However, there is mounting evidence that obesity is associated with various forms of memory impairment, ranging from episodic memory deficits (related to the recall of specific events or experiences) to alterations in working memory (responsible for temporary storage and manipulation of information) and spatial memory (associated with navigation and orientation) (7). These memory impairments have been linked to structural and functional brain alterations, including hippocampal atrophy and altered connectivity within the brain's memory-related networks.

Working Memory

Working memory is responsible for the temporary storage and manipulation of information necessary for various cognitive tasks, including problem-solving, decision-making, and language comprehension. Recent studies have increasingly demonstrated a connection between obesity and impairments in working memory. Individuals with obesity often exhibit deficits in tasks that require maintaining and manipulating information over short periods (8). These alterations in working memory have important implications for daily functioning, academic and occupational performance, and overall quality of life.

The mechanisms underlying working memory alterations in obesity are complex and multifaceted. One key factor is the chronic inflammation associated with excess adiposity. Obesity is characterized by a state of chronic low-grade inflammation, with elevated levels of proinflammatory cytokines. These in-

flammatory molecules can disrupt neural networks and synaptic plasticity in brain regions critical for working memory, such as the prefrontal cortex. Additionally, insulin resistance, commonly observed in individuals with obesity, may also contribute to working memory deficits. Insulin resistance can impair glucose metabolism in the brain, which is crucial for energy-intensive cognitive processes like working memory. Furthermore, the obesogenic environment, characterized by easy access to calorie-dense, nutrient-poor foods and sedentary lifestyles, may contribute to working memory alterations. Poor dietary choices and physical inactivity can exacerbate obesity-related metabolic and inflammatory disturbances, further compromising cognitive function. Psychosocial factors, including stress and depression, which are more prevalent among individuals with obesity, may also play a role in working memory deficits.

The consequences of working memory alterations in obesity extend beyond individual cognitive impairments. Impaired working memory can impact an individual's ability to make healthy dietary choices, plan and execute physical activity, and adhere to weight management strategies (9). Additionally, it may affect academic and professional performance, potentially leading to reduced educational attainment and career opportunities for individuals with obesity. Consequently, understanding the mechanisms of working memory impairment in obesity and developing targeted interventions to address these deficits are critical for improving cognitive health and overall well-being in this population.

Therefore, these alterations are linked to chronic inflammation, insulin resistance, and obesogenic lifestyles, highlighting the interconnectedness of metabolic and cognitive health. Recognizing the impact of obesity on working memory underscores the need for comprehensive approaches that address both physical and cognitive aspects of this global public health challenge.

Episodic Memory

The exploration of episodic memory alteration in obesity is an increasingly important and developing field of study in the realms of cognitive neuroscience and public health. Episodic memory, an essential component of declarative memory, is accountable for the processes of encoding, storing, and retrieving individual experiences and events within distinct contextual frameworks. Recent studies have revealed a complex association between obesity and deficits in episodic memory (10). Obese individuals often demonstrate impairments in tasks involving the retrieval of previous events, resulting in difficulties in recalling precise episodic details such as personal experiences, names, dates, and contextual information. Memory modifications can have a substantial impact on various aspects of daily living, such as academic and occupational performance, interpersonal connections, and general quality of life. The etiology of episodic memory alterations in individuals with obesity is complex, encompassing various components such as chronic inflammation, metabolic dysregulation, lifestyle elements, and psychosocial determinants (11). The acknowledgement of the ramifications associated with changes in episodic memory in individuals with obesity highlights the necessity for comprehensive strategies that tackle the physical and cognitive dimensions of this worldwide public health issue.

Attention and Concentration Deficits

The investigation of attention and concentration problems in individuals with obesity has garnered increasing attention within the fields of cognitive neuroscience and public health. The influence of obesity on cognitive functions, which are crucial for efficient information processing and task execution, is progressively gaining recognition. Recent studies have revealed a noteworthy correlation between obesity and deficits in attention and concentration. Individuals who are obese frequently demonstrate a reduced ability to keep attention, an increased vulnerability to distraction, and difficulties in sustaining cognitive effort (12). Attentional deficiencies can result in significant effects that extend to various aspects of an individual's life, including their academic and vocational productivity, decision-making skills, and overall cognitive efficiency (13). The complex nature of these deficiencies in obesity encompasses various aspects, including persistent inflammation, impaired insulin response, individual choices in lifestyle, and psychosocial elements. Together, these issues underscore the deep relationship between metabolic and cognitive well-being. The significance of understanding and acknowledging the consequences of attention and concentration deficiencies in relation to obesity highlights the necessity of implementing holistic approaches that tackle the physical and cognitive aspects of this widespread public health concern.

Executive Function Impairments

Executive functions encompass a collection of cognitive processes at a higher level that are accountable for activities such as planning, decision-making, inhibitory control, and goal-oriented behavior. Recent studies have shed light on a significant correlation between obesity and impairments in executive processes. Obese individuals frequently demonstrate challenges in cognitive flexibility, impulse control, and adaptive behavior, which are essential for successfully completing activities that involve adjusting to new situations (14). The presence of executive function deficits can significantly impact multiple facets of everyday life, such as the ability to regulate one's diet, adhere to weight management measures, and make well-informed decisions on health. The multifaceted origins of these deficiencies in obesity involve various aspects including persistent inflammation, resistance to insulin, decisions regarding lifestyle, and psychosocial components. The acknowledgement and comprehension of the consequences of executive function deficits in relation to obesity highlights the importance of implementing holistic strategies that tackle the physical and cognitive aspects of this widespread public health issue.

Emotional and Psychological Aspects of Cognition

The emotional aspects of obesity frequently become apparent through the utilization of maladaptive coping strategies, such as engaging in emotional eating, which is motivated by the desire to reduce negative emotions such as stress, anxiety, or grief. The observed phenomenon of emotional eating highlights the complex interaction between cognitive regulation and emotional

urges, which plays a role in the onset and persistence of obesity (15). Moreover, the reciprocal association between obesity and depression serves to underscore the complex emotional dynamics inherent in this condition. Obesity in individuals has been found to be associated with an increased vulnerability to depression, which can be attributed to several variables like social stigma and diminished self-esteem. Conversely, depression has been observed to potentially worsen obesity by promoting heightened engagement in emotional eating behaviors (16). The interplay of emotional elements and cognitive processes results in the impairment of executive function, decision-making, and impulse control. Consequently, this has a direct effect on an individual's capacity to make sound decisions and exhibit self-control in relation to overeating. In addition, the cognitive ramifications of obesity, including memory deficits, diminished cognitive adaptability, and challenges in maintaining attention, emphasize the cognitive aspects associated with obesity (17). In order to effectively address the emotional and psychological dimensions of cognition in individuals with obesity, it is imperative to adopt a comprehensive and interdisciplinary strategy that integrates cognitive-behavioral therapy, mindfulness-based interventions, and pharmaceutical treatments. This approach not only focuses on the physiological components of obesity, but also acknowledges the psychological and cognitive elements that contribute to its multifaceted nature, therefore enhancing the holistic welfare of those affected by obesity.

Mechanisms Underlying Obesity-Related Cognitive Impairment

Insulin and Glucose Dysregulation

The complicated association between obesity and cognitive impairment is primarily driven by the dysregulation of insulin and glucose pathways. Obesity is a condition defined by the presence of persistent low-grade inflammation and excessive adipose tissue. This condition frequently results in insulin resistance and hyperinsulinemia, which refers to a diminished responsiveness of the body's cells to the hormone insulin. Insulin resistance not only contributes to the perpetuation of obesity but also plays a pivotal role in the emergence of cognitive impairments (18). Insulin, a hormone primarily linked to the regulation of glucose metabolism, has significant impacts on the central nervous system by modulating synaptic plasticity, maintaining neurotransmitter equilibrium, and promoting neuronal viability. In the context of obesity, insulin resistance hampers the capacity of insulin to effectively carry out these crucial neuroregulatory activities. As a result, the presence of neuronal insulin resistance has the potential to interfere with synaptic plasticity, hinder the consolidation of memory, and diminish the brain's ability to adapt to evolving cognitive requirements (19). Additionally, it is worth noting that hyperinsulinemia, which is caused by an excessive consumption of calories, has the potential to stimulate neuroinflammation and oxidative stress. These factors can have a detrimental impact on neuronal function and cognitive functions. Simultaneously, the presence of glucose dysregulation, a common occurrence in adults with obesity, can result in episodes of hyperglycemia and hypoglycemia, both of which can have adverse effects on cognitive functioning. Episodes of hyperglycemia have the potential to induce neurotoxicity and hinder the transport of glucose into the brain (20). Conversely, hypoglycemia can give rise to cognitive impairments as a consequence of inadequate energy provision to neurons. In brief, the dysregulation of insulin and glucose serves as crucial mechanistic connections between obesity and cognitive impairment, emphasizing the significance of holistic therapies that address metabolic health in addition to cognitive well-being when managing cognitive deficits associated with obesity.

Inflammatory Pathways

In recent times, there has been a growing emphasis in scientific investigations on comprehending the involvement of inflammatory pathways in facilitating the cognitive deficits linked to obesity. Obesity is distinguished by the presence of persistent low-level inflammation, in which adipose tissue releases pro-inflammatory cytokines, including TNF-α and IL-6. The presence of these inflammatory chemicals can exert significant impacts on the central nervous system, hence playing a role in the progression of cognitive impairment. The relationship between systemic inflammation and neuroinflammation has been widely recognized, wherein the activation of microglia and subsequent release of inflammatory mediators within the brain are key features (21). The neuroinflammatory response has the potential to disturb the intricate equilibrium of neurotransmitters, hinder synaptic development, and induce oxidative stress. These pathways have been linked to cognitive impairment.

In addition, it should be noted that the presence of chronic inflammation in individuals with obesity might potentially result in the development of insulin resistance. As previously discussed, this condition can have adverse consequences for cognitive function. The impairment of insulin signaling pathways in the brain due to insulin resistance can have detrimental effects on neuronal survival, synaptic plasticity, and neurotransmitter modulation, all of which are essential processes (22). As a result, cognitive processes such as the creation of memory, learning, and executive functions may experience impairments.

Recent studies have additionally emphasized the significance of the gut-brain axis in cognitive impairment associated with obesity. The gut microbiota has the ability to impact systemic inflammation by generating metabolites and signaling molecules. Dysbiosis, an imbalance in the makeup of the gut microbiota frequently observed in individuals with obesity, has the potential to lead to heightened gut permeability and the subsequent translocation of bacterial products into the bloodstream (23). Bacterial compounds, such as lipopolysaccharides, have the ability to initiate immunological responses and induce inflammation, hence intensifying the inflammatory environment linked to obesity.

Leptin and Ghrelin Hormones

Leptin and ghrelin, which are two pivotal hormones responsible for regulating hunger and maintaining energy balance, have garnered significant interest within the area of cognitive impairment associated with obesity.

Leptin, an endocrine hormone predominantly synthesized by adipose tissue, exerts a crucial influence on the control of hunger and energy expenditure through modulating the hypo-

thalamus (24). Nevertheless, the impact of leptin goes beyond regulating metabolism, given that leptin receptors are extensively dispersed throughout the central nervous system (CNS). Leptin has been associated with synaptic plasticity, neuronal development, and neuroprotection (25). In the context of obesity, it is common for individuals to display hyperleptinemia as a result of leptin resistance, which is defined by a diminished responsiveness to the effects of leptin. The presence of leptin resistance has the potential to disrupt the normal functioning of leptin signaling in the CNS, thereby leading to cognitive impairments, namely in memory and executive function. Research conducted on animals has shown that improving the sensitivity of the CNS to leptin can improve cognitive deficits that are linked to obesity (26). This highlights the significance of leptin in the cognitive dysfunction that is associated with obesity.

In contrast, ghrelin, which is predominantly produced in the gastric region, is a hormone that elicits hunger and facilitates the consumption of food. Ghrelin has receptor presence not just in the hypothalamus but also in various other brain areas, encompassing those implicated in cognitive function. The complex involvement of ghrelin in obesity has prompted inquiries into its potential effects on cognitive function, given its capacity to traverse the blood-brain barrier and regulate neuronal activity. Recent research findings indicate that ghrelin exhibits potential neuroprotective properties and may also enhance cognitive function (27). For example, previous studies have demonstrated that ghrelin exerts a protective effect against neurodegenerative disorders and promotes the generation of new neurons in the hippocampus (28). Paradoxically, it has been observed that persons who are obese frequently exhibit reduced levels of circulating ghrelin, which may be attributed to the desensitization of ghrelin receptors. The insufficiency described here could potentially play a role in the cognitive decline found in individuals with obesity, as the neuroprotective and cognitive-enhancing effects of ghrelin are reduced.

The complicated and incompletely understood nature of the connection between leptin and ghrelin in cognitive impairment associated with obesity is evident. Leptin resistance, a prevalent occurrence in individuals with obesity, has the potential to disturb the equilibrium between these two hormones, resulting in dysregulated appetite, modified energy expenditure, and cognitive impairment. Moreover, it is worth noting that both hormones have the potential to influence same brain regions that are implicated in cognitive functions, including the hippocampus and prefrontal cortex. The potential dysregulation of these specific regions could potentially play a role in the development of cognitive impairment associated with obesity. The examination of the interaction between leptin and ghrelin, along with their subsequent signaling pathways, is of utmost importance in order to get a thorough comprehension of the mechanisms that contribute to cognitive impairments in individuals affected by obesity.

Adipokines and Their Impact on the Brain

Adipose tissue serves as more than just a passive depot for energy storage; it functions as a metabolically active organ that releases various bioactive chemicals, such as adipokines. These molecules have the ability to influence a diverse array of physiological processes, such as inflammation, insulin sensitivity, and vascular function. Recent research has brought attention to the influence of adipokines, specifically adiponectin and leptin, on the regulation of cognitive function. One example of a molecule with notable characteristics is adiponectin, which exhibits anti-inflammatory qualities and enhances insulin sensitivity. Moreover, elevated levels of adiponectin in the bloodstream have been linked to improved cognitive performance. On the other hand, the dysregulation of adiponectin in individuals with obesity may potentially lead to cognitive impairment through affecting inflammation and insulin resistance. Leptin, an additional adipokine, is involved in the control of hunger and energy balance, while also exerting notable influences on neuronal growth and synaptic plasticity. Leptin resistance, a prevalent phenomenon observed in individuals with obesity, has the potential to interfere with the neuroprotective mechanisms, hence resulting in cognitive impairments.

The modulation of inflammation inside the CNS is a significant method through which adipokines exert their influence on cognitive performance. Obesity is distinguished by the presence of persistent low-grade inflammation, commonly known as "metaflammation," which has the potential to result in neuronal impairment and cognitive deterioration (29). Adipokines, such as adiponectin, have the ability to elicit either anti-inflammatory or pro-inflammatory responses in the brain, contingent upon their concentrations and communication mechanisms. Adiponectin, due to its anti-inflammatory characteristics, has the potential to provide protection against neuroinflammation and the resulting cognitive impairment (30). On the other hand, the presence of leptin resistance, which is frequently detected in individuals with obesity, has the potential to worsen central nervous system inflammation, hence potentially playing a role in the development of cognitive impairments. Additionally, the disparity in levels of pro-inflammatory and anti-inflammatory adipokines may exacerbate cognitive impairment in those who are obese.

Besides their involvement in the inflammatory process, adipokines also exert an influence on neurovascular function, which is of paramount importance in the preservation of cognitive well-being. Previous studies have demonstrated that adiponectin possesses the ability to augment cerebral blood flow and safeguard against endothelial dysfunction, hence facilitating the sufficient transportation of oxygen and nutrients to the brain (31). The potential cognitive outcomes may be improved due to the vascular benefits associated with adiponectin. The dysregulation of adipokine signaling in individuals with obesity has the potential to disturb the process of neurovascular coupling. This disruption can compromise the regulation of cerebral blood flow, leading to a worsening of cognitive impairment.

Obesity, Cognitive Decline, and Neurodegenerative Diseases

Association between Obesity and Alzheimer's Disease

The issue of obesity has become a significant global health concern in recent years, with its prevalence reaching epidemic levels. This condition has a widespread impact, impacting individ-

uals across many age groups. Concurrently, Alzheimer's disease has emerged as a significant public health concern, manifesting as a progressive neurodegenerative condition marked by cognitive deterioration and memory dysfunction. Recent research findings have provided insights into a plausible correlation between obesity and Alzheimer's disease, indicating the possibility of shared underlying pathogenic pathways between these two illnesses (32). This scholarly discourse explores the complex correlation between obesity and Alzheimer's disease, providing a comprehensive analysis of the various causes and mechanisms that establish a connection between these seemingly disparate health conditions.

The correlation between obesity and Alzheimer's disease is based on a complex network of interconnected variables, encompassing metabolic dysfunction, inflammation, and vascular impairments. Obesity is defined as the excessive buildup of adipose tissue, leading to the disruption of adipokines, including leptin and adiponectin, as well as insulin resistance. The metabolic changes discussed are not solely associated with obesity, but also demonstrate a significant involvement in the development of Alzheimer's disease. One example of a physiological condition that hinders the normal functioning of glucose metabolism in the brain is insulin resistance (33). This disruption in glucose metabolism has detrimental effects on neuronal activity and plays a role in the formation of beta-amyloid plaques, which are a prominent pathological characteristic associated with Alzheimer's disease. Moreover, the onset of adipose tissue-induced inflammation in obesity elicits a persistent condition of mild inflammation across various bodily systems, including the CNS. The presence of this inflammatory condition has the potential to expedite the neuroinflammatory mechanisms that are commonly identified in individuals with Alzheimer's disease, so intensifying the deterioration in cognitive function and damage to neurons.

In conjunction with metabolic and inflammatory processes, obesity has been linked to cerebrovascular dysfunction, hence potentially intensifying the susceptibility to Alzheimer's disease. The occurrence of obesity has a strong association with the onset of atherosclerosis and hypertension, both of which have the potential to negatively impact cerebral blood flow and contribute to the development of vascular cognitive impairment (34). The compromised circulation of blood can result in a condition known as hypoxia, which refers to a deficiency of oxygen, as well as inadequate supply of essential nutrients to the brain. This, in turn, can expedite the progression of neurodegenerative mechanisms. In addition, vascular dysfunction associated with obesity has the potential to compromise the integrity of the blood-brain barrier, so facilitating the entry of inflammatory chemicals and toxins into the brain. This process may contribute to the acceleration of neurodegenerative processes.

There is a mounting amount of epidemiological evidence that substantiates the correlation between obesity and a heightened susceptibility to Alzheimer's disease. Numerous longitudinal studies have provided evidence supporting a positive correlation between BMI and the likelihood of getting Alzheimer's disease in the future. Moreover, there exists a notable correlation between obesity and Alzheimer's disease, particularly throughout the middle stages of life. This implies that interventions aimed at addressing obesity during this crucial period may hold promise in reducing the likelihood of cognitive decline in later years. Nevertheless, it is crucial to acknowledge that the correlation between obesity and Alzheimer's disease is intricate, as it involves various elements such as genetic predisposition, lifestyle choices, and environmental influences that collectively contribute to the overall susceptibility.

Potential Links to Other Neurodegenerative Conditions

Parkinson's disease (PD) is widely recognized as one of the neurodegenerative illnesses that has been extensively investigated in the context of obesity. PD is distinguished by the gradual degeneration of dopaminergic neurons in the substantia nigra area of the brain, resulting in motor manifestations such as tremors and rigidity (35). Recent research findings indicate that there is a growing body of data supporting the notion that obesity might be a contributing factor to an elevated susceptibility to PD (36). The presence of obesity-related insulin resistance and inflammation has the potential to interfere with the typical insulin signaling in the brain, leading to the initiation of neuroinflammatory mechanisms that could contribute to the progression of PD. Furthermore, it is important to note that metabolic dysfunction associated with obesity can worsen mitochondrial dysfunction and oxidative stress, both of which have been identified as contributing factors in the development of PD.

Amyotrophic lateral sclerosis (ALS), a deadly motor neuron disease, is another neurodegenerative ailment that may have possible associations with obesity. Although the specific mechanisms responsible for the development and advancement of ALS are not yet fully understood, there exists evidence indicating a potential involvement of metabolic changes linked to obesity in the beginning and course of the disease. Dysregulated lipid metabolism, mitochondrial dysfunction, and systemic inflammation, which are frequently identified in individuals with obesity, may potentially contribute to the degeneration of motor neurons in ALS (37). Moreover, certain genetic variants, like as the C9orf72 mutation, that are correlated with ALS have been found to be connected with changes in metabolism and obesity (38). This implies the existence of a reciprocal connection between genetics and obesity in the development of ALS.

The correlation between obesity and neurodegenerative illnesses is progressively apparent, necessitating the acknowledgment of its intricate and varied nature. The risk of having these illnesses is influenced by genetic predisposition, lifestyle factors, and environmental variables. Furthermore, the temporal aspects of obesity, including the timing and duration of its occurrence during an individual's lifespan, have the potential to impact the likelihood and advancement of neurodegenerative disorders. The findings from longitudinal research suggest that there exists a significant association between obesity during midlife and an elevated risk of developing certain diseases (39). This underscores the potential significance of implementing early intervention and prevention techniques.

Longitudinal Studies on Obesity and Cognitive Decline

The examination of the association between obesity and cogni-

tive decline through longitudinal studies has uncovered an intricate and multifaceted connection between these two phenomena. Although a complete understanding of the mechanisms responsible for this relationship has not yet been achieved, other possibilities have been put up. One crucial process is centered on the persistent low-grade inflammation linked to obesity, which has the potential to result in neuronal damage and compromised cognitive performance over an extended period. Moreover, it is worth noting that obesity often leads to insulin resistance and dysregulation of glucose metabolism, which can have an adverse effect on cerebral insulin signaling (40). This, in turn, may play a role in the development of cognitive decline. Moreover, it is worth noting that obesity-associated comorbidities, like hypertension and dyslipidemia, have the potential to induce alterations in cerebrovascular function, hence elevating the susceptibility to cognitive impairment.

Longitudinal studies offer substantial evidence supporting the notion that obesity during middle age is a noteworthy risk factor for the development of cognitive decline and dementia during the later stages of life. Whitmer et al. conducted a seminal study which revealed that persons who had obesity throughout midlife exhibited a markedly elevated susceptibility to developing dementia during later stages of life, in contrast to those who maintained a normal weight (41). Furthermore, a clear dose-response connection was observed in this study, indicating that higher levels of obesity were associated with an increased risk of developing dementia. The obesity-cognitive decline correlation has been supported by other research, such as the Framingham Heart Study and the Whitehall II Study, which have provided further evidence of this relationship. These studies have demonstrated the persistent nature of this association across many groups.

Longitudinal studies provide additional emphasis on the influence of aging on the progression of cognitive decline associated with obesity. As persons who are afflicted with obesity advance in age, they tend to experience a more accelerated progression of cognitive deterioration in comparison to individuals who have a lean body composition (42). The observed loss in cognitive function may be ascribed to the cumulative impact of vascular and metabolic alterations associated with obesity that occur gradually over a period of time. De Silva and Faraci conducted a study that provided evidence of a positive correlation between obesity during middle age and an augmented susceptibility to cerebral small vessel disease (43). This, in turn, was found to be connected with cognitive deterioration and a heightened likelihood of developing dementia in later stages of life. The aforementioned findings highlight the significance of implementing early intervention and prevention measures that specifically address obesity in order to minimize its adverse effects on cognitive well-being among older individuals.

Conclusion

The complex correlation between obesity and cognitive function, as well as its possible ramifications in degenerative neurological disorders, poses a complicated obstacle within the realms of neuroscience and public health. Gaining a thorough comprehension of the fundamental mechanisms that link obesity, cognitive impairment, and neurodegenerative disorders is of utmost importance in order to formulate comprehensive approaches for the prevention and intervention of these problems. In light of the escalating incidence of obesity and the growing impact of degenerative neurological disorders, it is imperative to conduct additional research on these intricate interconnections in order to alleviate the enduring effects on cognitive well-being and the general welfare of individuals and communities. The consideration of obesity as a modifiable risk factor shows potential in mitigating the occurrence and intensity of cognitive impairments linked to degenerative neurological disorders.■

References

1. Rukadikar C, Shah CJ, Raju A, Popat S, Josekutty R. The influence of obesity on cognitive functioning among healthcare professionals: A comprehensive analysis. Cureus 2023; 15(8):e42926. DOI: https://doi.org/10.7759/cureus.42926
2. Duarte JM. Metabolic alterations associated to brain dysfunction in diabetes. Aging Dis 2015; 6(5):304-321. DOI: https://doi.org/10.14336/AD.2014.1104
3. Chait A, den Hartigh LJ. Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Front Cardiovasc Med 2020; 7:22. DOI: https://doi.org/10.3389/fcvm.2020.00022
4. Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, Csiszar A. Hypertension-induced cognitive impairment: From pathophysiology to public health. Nat Rev Nephrol 2021; 17(10):639-654. DOI: https://doi.org/10.1038/s41581-021-00430-6
5. Flores-Cordero JA, Pérez-Pérez A, Jiménez-Cortegana C, Alba G, Flores-Barragán A, Sánchez-Margalet V. Obesity as a risk factor for dementia and alzheimer's disease: The role of leptin. Int J Mol Sci 2022; 23(9):5202. DOI: https://doi.org/10.3390/ijms23095202
6. Zhu M, Liu X, Ye Y, Yan X, Cheng Y, Zhao L, Chen F, Ling Z. Gut microbiota: A novel therapeutic target for Parkinson's disease. Front Immunol 2022; 13:937555. DOI: https://doi.org/10.3389/fimmu.2022.937555
7. Eichen DM, Kang Sim DE, Appleton-Knapp SL, Strong DR, Boutelle KN. Adults with overweight or obesity use less efficient memory strategies compared to adults with healthy weight on a verbal list learning task modified with food words. Appetite 2023;

181:106402. DOI: https://doi.org/10.1016/j.appet.2022.106402

8. Berbegal M, Tomé M, Sánchez-SanSegundo M, Zaragoza-Martí A, Hurtado-Sánchez JA. Memory function performance in individuals classified as overweight, obese, and normal weight. Front Nutr 2022; 9:932323. DOI: https://doi.org/10.3389/fnut.2022.932323
9. Higgs S, Spetter MS. Cognitive control of eating: The role of memory in appetite and weight gain. Curr Obes Rep 2018; 7(1):50-59. DOI: https://doi.org/10.1007/s13679-018-0296-9
10. Cheke LG, Simons JS, Clayton NS. Higher body mass index is associated with episodic memory deficits in young adults. Q J Exp Psychol (Hove) 2016; 69(11):2305-2316. DOI: https://doi.org/10.1080/17470218.2015.1099163
11. Lin X, Li H. Obesity: Epidemiology, pathophysiology, and therapeutics. Front Endocrinol (Lausanne) 2021; 12:706978. DOI: https://doi.org/10.3389/fendo.2021.706978
12. Martin AA, Davidson TL. Human cognitive function and the obesogenic environment. Physiol Behav 2014; 136:185-193. DOI: https://doi.org/10.1016/j.physbeh.2014.02.062
13. Jangmo A, Stålhandske A, Chang Z, Chen Q, Almqvist C, Feldman I, Bulik CM, Lichtenstein P, D'Onofrio B, Kuja-Halkola R, Larsson H. Attention-deficit/hyperactivity disorder, school performance, and effect of medication. J Am Acad Child Adolesc Psychiatry 2019; 58(4):423-432. DOI: https://doi.org/10.1016/j.jaac.2018.11.014
14. Tronieri JS, Alamuddin N, Wadden TA. Behavioral Approaches to Obesity Management. [Updated 2022 Oct 13]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available at: https://www.ncbi.nlm.nih.gov/books/NBK278952/
15. Dol A, van Gemert-Pijnen L, Schwartz LM, Velthuijsen H, Bode C. Exploring tailored virtual emotion regulation approaches for individuals with emotional eating. J Eat Disord 2023; 11(1):134. DOI: https://doi.org/10.1186/s40337-023-00856-2
16. Dakanalis A, Mentzelou M, Papadopoulou SK, Papandreou D, Spanoudaki M, Vasios GK, Pavlidou E, Mantzorou M, Giaginis C. The association of emotional eating with overweight/obesity, depression, anxiety/stress, and dietary patterns: A review of the current clinical evidence. Nutrients 2023; 15(5):1173. DOI: https://doi.org/10.3390/nu15051173
17. Liang J, Matheson BE, Kaye WH, Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes (Lond) 2014; 38(4):494-506. DOI: https://doi.org/10.1038/ijo.2013.142
18. Sripetchwandee J, Chattipakorn N, Chattipakorn SC. Links between obesity-induced brain insulin resistance, brain mitochondrial dysfunction, and dementia. Front Endocrinol (Lausanne) 2018; 9:496. DOI: https://doi.org/10.3389/fendo.2018.00496
19. Vinuesa A, Pomilio C, Gregosa A, Bentivegna M, Presa J, Bellotto M, Saravia F, Beauquis J. Inflammation and insulin resistance as risk factors and potential therapeutic targets for Alzheimer's Disease. Front Neurosci 2021; 15:653651. DOI: https://doi.org/10.3389/fnins.2021.653651
20. Cacciatore M, Grasso EA, Tripodi R, Chiarelli F. Impact of glucose metabolism on the developing brain. Front Endocrinol (Lausanne) 2022; 13:1047545. DOI: https://doi.org/10.3389/fendo.2022.1047545
21. Kraft AD, Harry GJ. Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. Int J Environ Res Public Health 2011; 8(7):2980-3018. DOI: https://doi.org/10.3390/ijerph8072980
22. Kleinridders A, Ferris HA, Cai W, Kahn CR. Insulin action in brain regulates systemic metabolism and brain function. Diabetes 2014; 63(7):2232-2243. DOI: https://doi.org/10.2337/db14-0568
23. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015; 26:26191. DOI: https://doi.org/10.3402/mehd.v26.26191
24. Picó C, Palou M, Pomar CA, Rodríguez AM, Palou A. Leptin as a key regulator of the adipose organ. Rev Endocr Metab Disord 2022; 23(1):13-30. DOI: https://doi.org/10.1007/s11154-021-09687-5
25. Hamilton K, Harvey J. The neuronal actions of leptin and the implications for treating Alzheimer's disease. Pharmaceuticals (Basel) 2021; 14(1):52. DOI: https://doi.org/10.3390/ph14010052
26. Rezaei MH, Madadizadeh E, Aminaei M, Abbaspoor M, Schierbauer J, Moser O, Khoramipour K, Chamari K. Leptin signaling could mediate hippocampal decumulation of beta-amyloid and tau induced by high-intensity interval training in rats with type 2 diabetes. Cell Mol Neurobiol 2023; 43(7):3465-3478. DOI: https://doi.org/10.1007/s10571-023-01357-1
27. Seminara RS, Jeet C, Biswas S, Kanwal B, Iftikhar W, Sakibuzzaman M, Rutkofsky IH. The neurocognitive effects of ghrelin-induced signaling on the hippocampus: a promising approach to Alzheimer's disease. Cureus 2018; 10(9):e3285. DOI: https://doi.org/10.7759/cureus.3285
28. Kim C, Kim S, Park S. Neurogenic effects of ghrelin on the hippocampus. Int J Mol Sci 2017; 18(3):588. DOI: https://doi.org/10.3390/ijms18030588
29. Litwiniuk A, Bik W, Kalisz M, Baranowska-Bik A. Inflammasome NLRP3 potentially links obesity-associated low-grade systemic inflammation and insulin resistance with Alzheimer's disease. Int J Mol Sci 2021; 22(11):5603. DOI: https://doi.org/10.3390/ijms22115603
30. Rizzo MR, Fasano R, Paolisso G. Adiponectin and cognitive decline. Int J Mol Sci. 2020; 21(6):2010. DOI: https://doi.org/10.3390/ijms21062010
31. Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci 2017; 18(6):1321. DOI: https://doi.org/10.3390/ijms18061321
32. Pugazhenthi S, Qin L, Reddy PH. Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochim Biophys Acta Mol Basis

Dis 2017; 1863(5):1037-1045. DOI: https://doi.org/10.1016/j.bbadis.2016.04.017

33. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, Holtzman DM, Nathan DM. Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. Nat Rev Neurol 2018; 14(3):168-181. DOI: https://doi.org/10.1038/nrneurol.2017.185
34. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: Role of inflammation and vascular changes. Front Neurosci 2014; 8:375. DOI: https://doi.org/10.3389/fnins.2014.00375
35. Kouli A, Torsney KM, Kuan WL. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects [Internet]. Brisbane (AU): Codon Publications; 2018 Dec 21. Chapter 1. DOI: https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1
36. Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable long-term weight management. J Am Assoc Nurse Pract 2017; 29(S1):S3-S14. DOI: https://doi.org/10.1002/2327-6924.12510
37. Maksimovic K, Youssef M, You J, Sung HK, Park J. Evidence of metabolic dysfunction in amyotrophic lateral sclerosis (ALS) patients and animal models. Biomolecules 2023; 13(5):863. DOI: https://doi.org/10.3390/biom13050863
38. Balendra R, Isaacs AM. C9orf72-mediated ALS and FTD: Multiple pathways to disease. Nat Rev Neurol 2018; 14(9):544-558. DOI: https://doi.org/10.1038/s41582-018-0047-2
39. Xu WL, Atti AR, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. Neurology 2011; 76(18):1568-1574. DOI: https://doi.org/10.1212/WNL.0b013e3182190d09
40. Martyn JA, Kaneki M, Yasuhara S. Obesity-induced insulin resistance and hyperglycemia: Etiologic factors and molecular mechanisms. Anesthesiology 2008; 109(1):137-148. DOI: https://doi.org/10.1097/ALN.0b013e3181799d45
41. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: A 27-year longitudinal population-based study. BMJ 2005; 330(7504):1360. DOI: https://doi.org/10.1136/bmj.38446.466238.E0
42. Bischof GN, Park DC. Obesity and aging: Consequences for cognition, brain structure, and brain function. Psychosom Med 2015; 77(6):697-709. DOI: https://doi.org/10.1097/PSY.0000000000000212
43. De Silva TM, Faraci FM. Contributions of aging to cerebral small vessel disease. Annu Rev Physiol 2020; 82:275-295. DOI: https://doi.org/10.1146/annurev-physiol-021119-034338

Received: June 10, 2023 | Revised: August 12, 2023 | Accepted: August 15, 2023