### PAPER DETAILS

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PAGES: 346-351

ORIGINAL PDF URL: https://dergipark.org.tr/tr/download/article-file/3838427

## Obesity's cognitive consequences: leptin's influence on dementia

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Cite this article as: Kara E, Işıklı Ş. Obesity's cognitive consequences: leptin's influence on dementia. J Health Sci Med. 2024;7(3):346-351.

Received: 01.04.2024	•	Accepted: 15.05.2024	•	Published: 27.05.2024

### ABSTRACT

Dementia is characterized by progressive cognitive decline and is increasingly associated with obesity. Obesity is identified by a number of pathological features, including excess fat accumulation, insulin resistance, gut dysbiosis, oxidative stress, inflammatory activation and systemic inflammation. These pathological factors trigger neuroinflammation and brain damage, making the complex relationship between metabolic health and cognitive function more salient. The amount of leptin in the bloodstream is correlated with the proportion of body fat and regulates cognitive processes as well as metabolic functions through its effects on the central nervous system. However, obesity can lead to leptin resistance, which may contribute to the development of neurodegenerative disorders such as dementia by impairing leptin's ability to maintain cognitive functions. This article discusses the gut-brain axis as a critical mediator of the effects of obesity on cognitive health and highlights the impact of gut dysbiosis on cognitive decline as a result of neuroinflammation. Obesity-specific systemic inflammation exacerbates neurodegeneration, increasing the need for integrated approaches to manage obesity and its cognitive repercussions. Addressing the pathological features of obesity by optimizing leptin signaling may offer promising strategies to prevent or slow the progression of cognitive decline associated with obesity and metabolic syndrome.

Keywords: Obesity, dementia, cognitive decline, leptin

### INTRODUCTION

Dementia covers a range of conditions marked by severe and/or persistent cognitive decline, which significantly affects an individual's daily functioning and quality of life. This cognitive decline is manifested through deficits in one or more of six cognitive domains: language, memory, attention, social/emotional behavior, executive functioning, and visuospatial abilities. As a multifaceted disorder, dementia's etiology is affected by various factors, including aging, genetics, cardiovascular health, and metabolic conditions. With the global aging population, the prevalence of dementia is alarmingly projected to increase from roughly 57 million cases in 2019 to over 150 million by 2050, highlighting a growing public health concern.<sup>1</sup>

This dire projection emphasizes the critical necessity for a deeper understanding of dementia's pathophysiology and contributing risk factors to spur the development of effective treatments. Currently, the therapeutic landscape for dementia remains starkly limited, leaving many patients without effective options to manage their condition.

Obesity, rapidly emerging as a major contributing factor for dementia, presents a complex challenge in understanding and mitigating cognitive decline. Defined commonly through the body mass index (BMI), obesity reflects excessive adipose tissue accumulation, contributing to a myriad of health issues beyond cognitive health, including cardiovascular diseases and diabetes. Approximately 1.2 billion people worldwide are classified as overweight, with 650 million suffering from obesity, indicating a global health epidemic.<sup>2</sup> The link between obesity and dementia is multifaceted, encompassing various pathological features beyond simple nutrient storage. Chronic, low-grade inflammation, a hallmark of obesity, along with adipose tissue hypertrophy, stimulates the release of pro-inflammatory mediators leading to oxidative stress and end-organ damage. These pathological features not only have systemic effects but also specifically impact brain health by compromising neurovascular connectivity, essential for delivering oxygen and nutrients to active neurons, thereby fostering conditions conducive to cognitive impairment and dementia.<sup>3</sup>

Moreover, obesity's impact on dementia risk varies across different life stages, with mid to late adulthood identified as critical periods for increased risk. This variability suggests that the timing and duration of obesity exposure may influence the trajectory of cognitive decline, highlighting the importance of early intervention and sustained health management across the lifespan.<sup>4</sup>

The gut-brain axis emerges as a critical pathway through which obesity may influence dementia risk. Altered gut microbiota, or dysbiosis, has been linked to increased neuroinflammation, a recognized characteristic of dementia.<sup>5</sup> The dynamic relationship between the gut and brain, mediated by neural, endocrine, metabolic, and immune pathways, offers potential therapeutic targets for mitigating cognitive decline through interventions aimed at restoring gut health balance.<sup>6</sup>

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Additionally, the role of adipokines, particularly leptin, in modulating cognitive health offers further insight into the obesity-dementia link. Leptin, known for its role in energy homeostasis and body weight regulation, also influences cognitive functions. However, obesity can lead to leptin resistance, undermining its protective effects on the brain and potentially contributing to the onset of neurodegenerative diseases like Alzheimer's disease (AD).<sup>78</sup>

The increasing amount of research associating obesity to chronic conditions like diabetes further complicates the relationship between metabolic health and cognitive function. Type 2 diabetes, often a consequence of obesity, has been closely linked to a higher risk of developing dementia, including AD. This association emphasizes the intertwined nature of metabolic and cognitive health, underscoring the need for integrated approaches to treatment and prevention.<sup>9,10</sup>

In light of these challenges, current research efforts are focused on identifying early markers of dementia, elucidating the mechanisms by which obesity contributes to cognitive decline, and exploring potential interventions. Addressing obesity through lifestyle modifications, targeted therapies, and interventions aimed at improving gut health could have a considerable impact on reducing dementia risk.<sup>11</sup>

In conclusion, the intersection of obesity, metabolic health, and dementia presents a complex challenge requiring a multifaceted approach to research, treatment, and prevention. Understanding the intricate pathways linking these conditions is crucial for developing effective strategies to alleviate the increasing burden of dementia. As the global population ages and obesity prevalence rises, the need for concerted efforts to address these interconnected health issues becomes increasingly urgent. Future research should proceed to explore the gut-brain axis, adipokine modulation, and the potential for lifestyle and therapeutic measures to prevent or invert the cognitive decline linked to obesity and metabolic syndrome, offering hope for those affected by dementia.

### **OBESITY AND DEMENTIA LINK**

Obesity's link to dementia is increasingly evident, underscoring a complex interplay between excessive adipose tissue accumulation and cognitive decline. This condition, marked by chronic, low-grade inflammation and metabolic dysregulation, poses significant risks for both physical health and cognitive functions, contributing to the pathogenesis of dementia, including AD and vascular dementia.<sup>12,13</sup>

Recent research highlights the critical period of middle age as a major risk factor for the subsequent development of dementia. Studies indicate that a BMI exceeding 25 during this phase is related to an increased probability of cognitive decline in subsequent years.<sup>14</sup> Conversely, weight loss in later life, potentially due to malnutrition, also correlates with heightened dementia risk, suggesting the timing of obesity's impact plays a crucial role in cognitive outcomes.<sup>15</sup>

The pathological features of obesity, such as adipose tissue hypertrophy and the resultant systemic inflammation, compromise neurovascular connectivity, crucial for neuron function and health.<sup>16</sup> This impairment can initiate

or exacerbate neuronal dysfunction, leading to cognitive impairments seen in various dementia forms. Notably, obesity in mid-life appears to set the stage for long-term brain damage, with the effects potentially becoming apparent only as dementia in later life.<sup>17-19</sup>

Obesity's role as a dementia risk factor is further complicated by its contribution to other neurodegenerative diseases, such as Parkinson's<sup>20,21</sup> and Huntington's diseases.<sup>21,22</sup> The mechanisms include alterations in brain structure, evidenced by reduced grey matter volume, and functional changes, such as impaired insulin signaling in the brain, which are central to obesity's impact on cognitive health.<sup>23</sup>

The measurement of adiposity through BMI, although widely used, has its limitations, prompting the use of other indices like waist circumference and waist-to-hip ratio (WHR) to assess fat accumulation.<sup>23</sup> These measures have shown that obesity's metabolic profile, including its association with grey matter volume reductions, could contribute to decreased cognitive functions.<sup>23,24</sup> Nevertheless, the association between obesity and dementia remains complex, with studies suggesting a possible U-shaped curve, where both low and high adiposity levels are linked with cognitive impairment.<sup>25-31</sup>

Animal studies have confirmed obesity's link with cognitive dysfunctions, demonstrating that diets rich in saturated fats can impair hippocampal-dependent learning and memory functions.<sup>32,33</sup> Furthermore, obesity-induced inflammation and insulin resistance are crucial factors that exacerbate neurodegeneration, underscoring the necessity of addressing obesity as part of dementia prevention and management strategies.<sup>34</sup>

In summary, the connection between obesity and dementia is multifaceted, involving direct impacts on brain health through systemic inflammation, metabolic dysfunction, and alterations in brain structure and function. As obesity remains to be a significant public health challenge, understanding its role in dementia is essential for developing preventive measures and therapeutic interventions aimed at mitigating cognitive decline associated with excessive adiposity.

### PATHOLOGICAL FEATURES OF OBESITY

Obesity's pathological landscape is marked by several detrimental features, notably insulin resistance,<sup>35</sup> gut dysbiosis,<sup>36</sup> oxidative stress,<sup>37</sup> inflammatory activation,<sup>38</sup> and systemic inflammation.<sup>16</sup> Each plays a crucial role in the cascade leading to neuroinflammation and brain damage. Insulin resistance, a hallmark of obesity, exacerbates metabolic dysregulation and has been shown to contribute directly to neuroinflammation, setting the stage for neurodegeneration and cognitive dysfunction.<sup>35</sup> Clinical evidence suggests an association between insulin and leptin resistance and cognitive impairment and neuropsychiatric conditions. Interestingly, these studies suggest that deficits in neuroplasticity associated with these conditions may potentially be reversed by restoring insulin and leptin sensitivity.<sup>39</sup> This metabolic anomaly impacts the brain's insulin signaling, which is essential for cognitive function and neuronal health. There is evidence that leptin may be involved in AD. The decline in plasma leptin levels with age has been associated with an increased risk of cognitive decline and the potential onset of this condition.<sup>40</sup>

A recent study comparing leptin levels in lesions from psoriasis patients with and without multiple sclerosis (MS) found that leptin levels in psoriatic lesions were significantly higher in psoriasis patients with MS than in those without MS. This finding suggests that leptin may be a key molecule responsible for the poor response of psoriasis associated with MS.<sup>41</sup>

Gut dysbiosis in obesity further complicates this picture by disrupting equilibrium between beneficial and harmful bacteria in the gastrointestinal tract. This imbalance promotes a state of chronic inflammation and oxidative stress-conditions known to negatively impact brain health.<sup>5</sup> Elevated levels of hippocampal glutathione, a marker of oxidative stress, have been closely linked to increased risks for developing dementia, showcasing the direct impact of metabolic health on cognitive function.<sup>42</sup>

### **GUT-BRAIN AXIS**

The gut-brain axis offers a critical pathway through which obesity influences cognitive health. This bidirectional communication network between the gut microbiota, the enteric nervous system (ENS), and the central nervous system (CNS) highlights the profound effect of gut-derived factors on brain function.<sup>5</sup> Dysbiosis, characterized by an imbalance in gut microbiota composition, triggers oxidative stress, thereby promoting neuroinflammation and paving the way for cognitive impairment.<sup>43</sup> The interplay between the gut and the brain during dysbiosis involves complex neural, endocrine, metabolic, and immune pathways, emphasizing the potential cognitive decline stemming from compromised gut health.<sup>6</sup> Furthermore, bacterial endotoxins can affect behavior and cognitive function by sending sensory inputs to the CNS via vagal afferent fibers, showcasing a direct link between gut health and brain function.44 In addition, the gastrointestinal-brain axis releases several anorexigenic signals, including uroguanylin, glucagon-like peptide-1, amylin and cholecystokinin, which may mitigate resistance to the effects of leptin.45

### SYSTEMIC INFLAMMATION

Systemic inflammation stands out as a critical consequence of obesity, significantly contributing to neuroinflammation. The expansion of adipose tissue leads to a hypoxic environment that triggers adipocyte apoptosis and elevates pro-inflammatory cytokines and adipokines such as TNF- $\alpha$ , leptin, and IL-6.<sup>46</sup> These molecules not only foster a systemic inflammatory state but are also recognized as key contributors to cognitive impairment.<sup>17</sup> The dysregulated adipokine release in obesity tips the balance towards a pro-inflammatory state, further exacerbating conditions like leptin resistance and increased blood-brain barrier (BBB) permeability. This pro-inflammatory milieu facilitates cerebral atrophy and compounds the risk of developing dementia.<sup>47</sup>

Understanding obesity's pathological features, the gutbrain axis's role, and the impact of systemic inflammation underscores the intricate relationship between obesity and cognitive decline, including dementia. Addressing obesity's multifaceted pathological impacts is crucial for developing effective strategies to mitigate the risk of dementia, highlighting the need for comprehensive approaches to manage obesity and its widespread effects on cognitive health.

### **OBESITY AND LEPTIN**

Within the framework of obesity and it's association with health complications, leptin plays a pivotal role in maintaining energy homeostasis and body weight by orchestrating a network of signals among peptides secreted by various organs. This hormone, produced by adipocytes, exhibits pleiotropic effects across different tissues, significantly influencing physiological functions. Leptin's primary function in regulating appetite and energy expenditure positions it as a key player in the discussion on obesity and its linkage to dementia.<sup>48,49</sup>

Leptin levels in the bloodstream directly correlate with body fat mass, serving as an adiposity indicator.<sup>50,51</sup> These levels fluctuate due to factors such as gender, BMI, fasting states, and overall energy balance, and are subject to circadian rhythms, peaking between midnight and dawn. The leptin hormone is encoded by the obesity (ob) gene and interacts with class I cytokine receptors, specifically through its various isoforms.<sup>52</sup>

Among these isoforms, the long form (LepRb) is notable for its involvement in the activation of Janus kinase (JAK) and signal transducers and activators of transcription (STAT) signaling pathways, crucial for leptin's systemic effects. Leptin receptors are distributed widely, not only in the CNS across regions integral to hunger and satiety but also throughout the body. Their presence in brain microvessels suggests a role in transporting leptin throughout the BBB, highlighting the complexity of leptin's impact on the brain and its potential contribution to conditions like dementia.<sup>53-57</sup>

Biochemical interaction with the leptin receptor activates JAK2, which subsequently phosphorylates tyrosine residues to initiate several intracellular signaling pathways.<sup>53,58,59</sup> These pathways include the activation of STAT3 via JAK, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, extracellular signal-regulated kinases (ERK), and signal transducer and activator of transcription 5 (STAT5). Through these mechanisms, leptin influences cognition, neurogenesis, neuroprotection, synaptic plasticity, and structural brain changes, underscoring its significant yet complex role in the nexus between obesity and cognitive health.<sup>60,61</sup>

# LEPTIN: COGNITION AND SYNAPTIC FUNCTION RELATIONSHIP

The intricate balance of body weight and energy homeostasis is critically maintained through a network of signals among peptides secreted by various organs, with adipocytes playing a central role through their secretion of adipokines. Among these, leptin stands out for its pivotal role in regulating food consumption and energy expenditure, highlighting its significance in the context of obesity and its potential implications for dementia.<sup>62</sup>

Leptin, proportional to body fat mass, serves as a key indicator

of adiposity, with its plasma levels subject to fluctuations based on gender, BMI, fasting states, and energy balances.<sup>50,51</sup> While leptin and body weight have been tightly controlled in previous studies, the effect of age has been a subject of curiosity. In a mouse study investigating the age-related satiety effect of leptin, exogenous leptin administration was found to have a transient effect in young male mice and to reduce food intake in older mice. Similarly, the lack of changes in leptin clearance from the blood and its transport to the brain suggests that a central resistance to leptin develops in middle age.<sup>63</sup> A study investigating sex differences in leptin found significant species differences in the development of diet-induced obesity between rats and mice; mice exhibited different food preference behaviour, glucose tolerance and energy expenditure compared to rats.<sup>64</sup>

On the other hand leptin follows a circadian rhythm, peaking at night, and is modulated by other hormonal and cytokine interactions.<sup>52</sup> Originating from the ob gene, leptin acts through its receptors, categorized as class I cytokine receptors, which are extensively present throughout the body, including significant areas within the CNS such as the hypothalamus and the hippocampus.<sup>53,57,60,65-68</sup>

The diversity of leptin receptors, including the long form LepRb crucial for JAK and STAT signaling, underpins the hormone's broad physiological effects. These effects extend beyond metabolic regulation, encompassing roles in cognition, neurogenesis, and synaptic plasticity. The engagement of leptin with hippocampal glutamate receptors underscores its involvement in synaptic transmission, crucial for learning and memory processes. This relationship is evidenced by leptin's ability to enhance long-term potentiation (LTP) and rectify long-term depression (LTD), with deficiencies in leptin signaling leading to cognitive impairments.<sup>55,59,69</sup>

### LEPTIN RESISTANCE: MECHANISMS INVOLVED

Leptin resistance, a paradox of elevated leptin levels without the expected physiological response of satiety in obesity, presents a significant challenge.<sup>69,70</sup> This resistance within the hypothalamus, despite high circulating levels, points to a breakdown in leptin signaling mechanisms.<sup>66</sup> Factors contributing to leptin resistance include genetic predispositions, alterations in BBB transport, receptor desensitization, and a myriad of inflammatory processes that disrupt leptin's signaling pathways. These factors not only perpetuate the cycle of obesity but may also predispose individuals to cognitive decline and dementia by disrupting the homeostatic and cognitive functions regulated by leptin.<sup>58,70</sup>

In the context of dementia, leptin's neuroprotective roles are of particular interest. Based on an in vivo human study, the results suggest that maintaining adequate plasma leptin levels may be protective against the development or progression of AD pathology, including both amyloid-beta (A $\beta$ ) and tau deposition. Therefore, more attention needs to be paid to the role of leptin in the prevention of AD and related cognitive impairment in older adults.<sup>71</sup> Leptin's involvement in neurogenesis, synaptogenesis, and neuronal excitability offers potential pathways through which leptin resistance may contribute to cognitive decline.<sup>62,72</sup> The evidence of leptin enhancing cognitive functions in animal models of AD further supports its potential as a target for therapeutic intervention.

Furthermore, the U-shaped correlation between circulating leptin levels and cognitive performance suggests that both deficiency and excess of leptin could be detrimental to cognitive health. This underscores the need for a balanced leptin signaling mechanism for optimal cognitive functioning.<sup>38,73</sup>

In conclusion, the roles of leptin in energy homeostasis, cognitive functions, and the phenomenon of leptin resistance offer insightful perspectives into the complex interplay between obesity and cognitive health.<sup>48,49,74</sup> Addressing leptin resistance and exploring strategies to optimize leptin signaling could provide promising avenues for mitigating obesity-related cognitive decline and enhancing overall brain health.

### CONCLUSION

The complex relationship between obesity and dementia is marked by intertwined metabolic, inflammatory, and neuroendocrine pathways, which collectively contribute to cognitive decline. Chronic inflammation and metabolic dysregulation, particularly manifesting as leptin resistance, are central to this association, emphasizing the need for multifaceted intervention strategies. The gut-brain axis and systemic inflammation play pivotal roles in linking obesity with neurodegenerative processes, suggesting that targeted interventions in these areas could help mitigate dementia risk.

Understanding the dual role of leptin in energy regulation and cognitive processes offers potential therapeutic targets to counteract obesity-induced cognitive impairments. An integrated approach combining dietary, behavioral, and pharmacological strategies is essential for maintaining metabolic health and cognitive function. Future research should focus on elucidating the underlying mechanisms of the obesity-dementia connection, identifying early disease biomarkers, and developing interventions to address the complex interactions involved.

By advancing our understanding and treatment of obesityrelated cognitive decline, we can aim to lessen the dementia burden, improving life quality and cognitive health for the aging population worldwide.

### ETHICAL DECLARATIONS

### **Referee Evaluation Process**

Externally peer-reviewed.

### **Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

### **Financial Disclosure**

The authors declared that this study has received no financial support.

### **Author Contributions**

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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