International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	OBESITY AS A FACTOR AFFECTING COGNITIVE FUNCTIONS: NEUROBIOLOGICAL AND METABOLIC MECHANISMS – A REVIEW OF CURRENT EVIDENCE
DOI	https://doi.org/10.31435/ijitss.3(51).2026.6151
RECEIVED	28 April 2026
ACCEPTED	29 June 2026
PUBLISHED	03 July 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

© The author(s) 2026.
This article is published as open access under the Creative Commons Attribution 4.0 International License (CC BY 4.0), allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

OBESITY AS A FACTOR AFFECTING COGNITIVE FUNCTIONS: NEUROBIOLOGICAL AND METABOLIC MECHANISMS – A REVIEW OF CURRENT EVIDENCE

Daria Trocka *(DT) (Corresponding Author, Email: dariatrocka99@gmail.com)*
Szpital św. Wojciecha w Gdańsku, Gdańsk, Poland
ORCID ID: 0000-0001-9684-5881

Natalia Woroniecka *(NW)*
Samodzielny Publiczny Zakład Opieki Zdrowotnej MSWiA w Gdańsku, Poland
ORCID ID: 0009-0006-4713-4526

Nicol Szerenos *(NS)*
Szpital Morski im. PCK, Gdynia, Poland
ORCID ID: 0009-0009-2754-8344

Alicja Kozłowska *(AK)*
Szpital Morski im. PCK, Gdynia, Poland
ORCID ID: 0009-0000-5991-7401

Karolina Przybysz *(KP)*
Szpital Morski im. PCK, Gdynia, Poland
ORCID ID: 0009-0002-9001-829X

Luiza Stadnik *(LS)*
Szpital św. Wojciecha Copernicus PL Sp. z o.o., Gdańsk, Poland
ORCID ID: 0009-0009-6854-4905

Natalia Zienkiewicz *(NZ)*
Szpital Morski im. PCK, Gdynia, Poland
ORCID ID: 0009-0009-3380-0470

Jarosław Rachoń *(JR)*
Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland
ORCID ID: 0009-0007-9691-2221

Adela Dzwonkowska *(AD)*
Szpitale Tczewskie S.A., Tczew, Poland
ORCID ID: 0009-0004-7026-7437

Jakub Dzwonkowski *(JD)*
Szpital Wojewódzki im. Mikołaja Kopernika, Koszalin, Poland
ORCID ID: 0009-0006-5087-0698

ABSTRACT

Obesity has been increasingly recognized as a potential modifiable risk factor for cognitive dysfunction and dementia. Accumulating evidence indicates that excess adiposity is associated with impairments in multiple cognitive domains, particularly executive function, attention, processing speed, and, to a lesser extent, memory. The strongest and most consistent associations are observed in midlife obesity, suggesting a life-course effect of prolonged metabolic exposure on brain health. This narrative review synthesizes current epidemiological, neuroimaging, mechanistic, and interventional evidence linking obesity with cognitive outcomes. Structural and functional brain alterations associated with obesity include reduced gray matter volume, white matter integrity disruption, and altered connectivity within key cognitive networks such as frontoparietal and hippocampal circuits. Proposed biological mechanisms include chronic low-grade systemic inflammation, insulin resistance with impaired central glucose metabolism, cerebrovascular dysfunction, oxidative stress, adipokine imbalance, and gut–brain axis alterations. The relationship between obesity and cognition is further modified by age, adiposity distribution, metabolic health status, genetic susceptibility, and lifestyle factors, indicating substantial inter-individual heterogeneity. Emerging interventional evidence suggests that cognitive impairment associated with obesity may be at least partially reversible, particularly following lifestyle modification, multidomain interventions, bariatric surgery, and pharmacological treatments targeting metabolic pathways; however, long-term randomized controlled data remain limited. Overall, obesity should be considered a heterogeneous and potentially modifiable risk factor for cognitive decline, with early metabolic intervention representing a promising strategy for preserving long-term cognitive health.

KEYWORDS

Obesity, Cognitive Dysfunction, Dementia, Insulin Resistance, Neuroinflammation, Executive Function, Metabolic Syndrome, Brain Aging, Adiposity, GLP-1 Receptor Agonists

CITATION

Daria Trocka, Natalia Woroniecka, Nicol Szerenos, Alicja Kozłowska, Karolina Przybysz, Luiza Stadnik, Natalia Zienkiewicz, Jarosław Rachoń, Adela Dzwonkowska, Jakub Dzwonkowski. (2026) Obesity as a Factor Affecting Cognitive Functions: Neurobiological and Metabolic Mechanisms – a Review of Current Evidence. *International Journal of Innovative Technologies in Social Science*. 3(51). doi: 10.31435/ijitss.3(51).2026.6151

COPYRIGHT

© The author(s) 2026. This article is published as open access under the **Creative Commons Attribution 4.0 International License (CC BY 4.0)**, allowing the author to retain copyright. The CC BY 4.0 License permits the content to be copied, adapted, displayed, distributed, republished, or reused for any purpose, including adaptation and commercial use, as long as proper attribution is provided.

Introduction

Obesity is a chronic, relapsing, multifactorial disease characterized by excessive adiposity that impairs health and increases the risk of numerous systemic complications, particularly cardiometabolic disorders. Traditionally, its clinical relevance has been primarily attributed to its well-established association with type 2 diabetes mellitus, hypertension, dyslipidaemia, and cardiovascular disease. However, in recent years, obesity has increasingly been recognized as a condition with significant effects extending beyond peripheral metabolism, including potential consequences for central nervous system structure and function.

Growing epidemiological evidence indicates that obesity is associated with poorer performance in multiple cognitive domains, including executive function, attention, processing speed, and memory. Large longitudinal cohort studies have shown that increased body mass index (BMI), particularly in midlife, is associated with a higher risk of cognitive decline and dementia in later life, including both Alzheimer's disease and vascular dementia [1,2]. Importantly, these associations persist even after adjustment for traditional vascular risk factors, suggesting that additional biological mechanisms independent of macrovascular disease may contribute to obesity-related cognitive impairment [3].

Neuroimaging studies have provided further support for a structural and functional relationship between obesity and the brain. Individuals with obesity have been shown to exhibit reduced gray matter volume in regions critical for cognitive processing, including the hippocampus, prefrontal cortex, and anterior cingulate cortex, as well as alterations in white matter integrity and functional connectivity within large-scale brain networks [4]. These findings suggest that obesity may be associated with both neurodegenerative and neurodevelopmental alterations, although the temporal directionality of these changes remains incompletely understood.

Several interrelated pathophysiological mechanisms have been proposed to explain the association between obesity and cognitive dysfunction. Chronic low-grade systemic inflammation is considered one of the central pathways. Adipose tissue in obesity exhibits an altered secretory profile characterized by increased production of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP), which may contribute to neuroinflammation and impaired synaptic plasticity [5]. Experimental and clinical data suggest that systemic inflammation can influence blood–brain barrier integrity and promote microglial activation, thereby potentially affecting neuronal function and cognitive performance [6].

Insulin resistance represents another key mechanistic link between obesity and cognitive impairment. Beyond its peripheral metabolic effects, insulin plays an important role in the central nervous system, where it modulates synaptic plasticity, neurotransmitter regulation, and memory processes. Evidence suggests that obesity-associated insulin resistance may extend to the brain, a phenomenon often referred to as "brain insulin resistance," which has been implicated in impaired learning and memory as well as increased risk of neurodegenerative disease [7].

Adipose tissue is now recognized as an active endocrine organ that secretes a wide range of bioactive molecules, collectively known as adipokines. Among these, leptin and adiponectin have been shown to exert direct and indirect effects on brain function. Leptin is involved not only in energy homeostasis but also in hippocampal synaptic plasticity and cognitive processes, whereas adiponectin has been associated with anti-inflammatory and neuroprotective effects. Dysregulation of adipokine signalling in obesity may therefore contribute to alterations in reward processing, cognitive control, and emotional regulation [8].

In addition to inflammatory and hormonal mechanisms, obesity is increasingly linked to cerebrovascular pathology. Obesity is associated with endothelial dysfunction, increased arterial stiffness, and a higher prevalence of hypertension and small vessel disease, all of which may contribute to chronic cerebral hypoperfusion and white matter damage. Such vascular alterations are increasingly recognized as important contributors to vascular cognitive impairment and may interact with neurodegenerative processes [9].

More recently, the gut–brain axis has emerged as a potential additional pathway linking obesity to cognitive function. Obesity is associated with alterations in gut microbiota composition and function, which may influence the central nervous system through immune, endocrine, and metabolic pathways, including the production of short-chain fatty acids and other neuroactive metabolites. These changes may modulate neuroinflammation, neurotransmission, and blood–brain barrier function, thereby influencing cognitive outcomes [10].

Despite substantial progress in understanding the biological links between obesity and cognitive function, several important questions remain unresolved. In particular, the extent to which obesity-related cognitive changes are reversible following weight loss or metabolic improvement is still unclear. Furthermore, the heterogeneity of obesity phenotypes suggests that not all individuals with obesity are at equal risk of cognitive impairment, highlighting the need for more precise stratification approaches.

This review aims to summarize and critically evaluate current evidence on the association between obesity and cognitive function, with a particular focus on neurobiological and metabolic mechanisms, including inflammation, insulin resistance, adipokine signalling, cerebrovascular dysfunction, and gut–brain axis interactions.

Epidemiological and clinical evidence linking obesity to cognitive dysfunction

A growing body of epidemiological, clinical, and neuroimaging evidence supports a consistent association between obesity and cognitive dysfunction across different stages of life [11]. Although obesity is traditionally defined using body mass index (BMI), it is increasingly recognized as a heterogeneous condition with systemic metabolic, inflammatory, and vascular consequences that may extend to the central nervous system [11,14]. Current evidence suggests that the relationship between obesity and cognition is complex and influenced by adiposity distribution, duration of exposure, metabolic health, age at onset, and cardiometabolic comorbidities [12,13].

Cross-sectional evidence

Cross-sectional studies consistently demonstrate that higher BMI is associated with lower cognitive performance across multiple domains, including executive function, attention, processing speed, and working memory [11]. These associations have been observed in large population-based cohorts and remain significant after adjustment for demographic variables, education, and vascular risk factors [11].

However, effect sizes are generally modest, and substantial heterogeneity exists between studies, reflecting differences in methodology, cognitive testing, and population characteristics [11]. Central adiposity, measured by waist circumference or waist-to-hip ratio, appears to show stronger and more consistent associations with cognitive impairment than BMI alone [12]. This suggests that visceral fat may be more metabolically active and more relevant to neurocognitive outcomes than total body mass [12].

From a clinical perspective, cross-sectional findings suggest that obesity is associated not only with subtle cognitive deficits but also with functional consequences such as reduced cognitive efficiency, impaired decision-making, and decreased inhibitory control [11]. These effects may contribute to difficulties in sustaining behavioral changes required for weight management.

However, cross-sectional studies are limited by their inability to establish causality [11]. Reverse causation is particularly relevant in older adults, where early cognitive decline may influence lifestyle behaviors, physical activity, and dietary patterns, ultimately affecting body weight [11].

Longitudinal cohort studies

Longitudinal studies provide stronger evidence for a temporal association between obesity and cognitive decline [13]. Several large prospective cohorts have shown that elevated BMI in midlife is associated with increased risk of cognitive impairment and dementia in later life, even after adjustment for vascular and socioeconomic confounders [13].

The timing of exposure appears to be critical. Midlife obesity is more consistently associated with adverse cognitive outcomes than late-life obesity, suggesting that cumulative metabolic burden over time may be an important determinant of neurocognitive risk [13]. Meta-analytical evidence confirms that midlife obesity is associated with increased risk of both Alzheimer's disease and vascular dementia [14].

Nevertheless, heterogeneity across studies remains substantial due to differences in follow-up duration, exposure definitions, and confounder adjustment [14]. Some studies report weaker or inverse associations in late life, a phenomenon known as the "obesity paradox," which is likely explained by survival bias and disease-related weight loss preceding dementia diagnosis [15].

Obesity and dementia risk

Obesity is associated with increased risk of both Alzheimer's disease and vascular dementia through overlapping but distinct mechanisms [16]. In Alzheimer's disease, obesity-related metabolic dysfunction, insulin resistance, and chronic inflammation may contribute to amyloid-beta accumulation and tau pathology [16]. In vascular dementia, obesity contributes primarily through hypertension, atherosclerosis, endothelial dysfunction, and small vessel disease [16].

These pathways frequently coexist, and mixed dementia pathology is common in older adults, suggesting that obesity may act as a shared upstream risk factor for both neurodegenerative and vascular cognitive impairment [16].

Neuroimaging evidence

Neuroimaging studies provide structural and functional evidence linking obesity with brain alterations [17]. Voxel-based morphometry studies consistently show reduced gray matter volume in individuals with higher BMI, particularly in the hippocampus, prefrontal cortex, anterior cingulate cortex, and orbitofrontal regions [17].

Diffusion tensor imaging studies demonstrate reduced white matter integrity, suggesting microstructural disruption of neural connectivity [17]. Functional MRI studies further reveal altered resting-state connectivity in key networks involved in cognitive control and memory, including the default mode and frontoparietal networks [18].

These findings suggest that obesity is associated with both structural brain changes and functional network alterations that may underlie cognitive dysfunction [17,18].

Cognitive domains affected

Obesity is most consistently associated with impairments in executive function, attention, processing speed, and working memory [11,18]. Executive dysfunction is particularly clinically relevant, as it affects planning, decision-making, impulse control, and adherence to lifestyle interventions.

Memory impairment, particularly episodic memory, has also been reported, although findings are less consistent than for executive dysfunction [11]. Variability likely reflects differences in study populations, age distribution, and cognitive assessment methods [11].

Methodological limitations and sources of heterogeneity

Several methodological limitations must be considered when interpreting the evidence [11]. BMI is an imperfect measure of adiposity, as it does not distinguish between fat mass and lean mass or reflect fat distribution [12]. Visceral adiposity appears more strongly associated with metabolic and cognitive outcomes than total body mass [12].

Residual confounding remains a major issue, as physical inactivity, depression, socioeconomic status, education, and cardiovascular comorbidities may independently influence both obesity and cognition [11].

Reverse causality is particularly relevant in older adults, where early neurodegenerative changes may lead to changes in appetite, mobility, and weight trajectory [11]. In addition, heterogeneity in study design and cognitive testing reduces comparability across studies [13].

Mechanisms

The association between obesity and cognitive dysfunction is mediated by multiple interconnected biological pathways rather than a single causal mechanism. Current evidence supports a multidimensional model involving chronic systemic inflammation, insulin resistance, adipokine dysregulation, cerebrovascular injury, oxidative stress, and gut–brain axis alterations, which collectively contribute to structural and functional brain changes over time [19–24].

Chronic low-grade inflammation

A central mechanism linking obesity to cognitive impairment is chronic low-grade systemic inflammation. In obesity, adipocyte hypertrophy and macrophage infiltration within adipose tissue lead to increased production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [19]. These inflammatory mediators contribute to a persistent systemic inflammatory state that may influence central nervous system function.

Experimental and clinical evidence suggests that peripheral inflammation can affect the brain via multiple routes, including humoral signaling, activation of endothelial cells, and potential disruption of blood–brain barrier integrity [20]. Once in the central nervous system, inflammatory mediators promote microglial activation, leading to a sustained neuroinflammatory state.

Neuroinflammation is strongly implicated in synaptic dysfunction, impaired long-term potentiation, and reduced neurogenesis, particularly in the hippocampus, which is essential for memory consolidation [20]. Chronic activation of these pathways may therefore contribute to progressive cognitive decline observed in individuals with obesity.

Insulin resistance and impaired brain energy metabolism

Insulin resistance represents another key mechanism linking obesity with cognitive dysfunction. Beyond its peripheral metabolic role, insulin acts as a neuromodulator in the brain, regulating synaptic plasticity, neuronal survival, and memory processes [21].

In obesity, peripheral insulin resistance is frequently accompanied by impaired central insulin signalling. This “brain insulin resistance” leads to reduced neuronal glucose uptake, altered energy metabolism, and impaired synaptic function [21]. Brain regions with high metabolic demand, particularly the hippocampus and prefrontal cortex, may be especially vulnerable to these changes.

Furthermore, insulin signalling pathways overlap with molecular mechanisms implicated in Alzheimer’s disease, including amyloid precursor protein processing and tau phosphorylation. This has led to the hypothesis that obesity-related insulin resistance may accelerate neurodegenerative processes through shared molecular cascades [21].

Adipokine dysregulation and endocrine signalling

Adipose tissue is an active endocrine organ that secretes biologically active molecules known as adipokines, including leptin and adiponectin. In physiological conditions, leptin plays a role not only in appetite regulation but also in hippocampal synaptic plasticity and cognitive function [22].

In obesity, leptin resistance develops, limiting its central neuroprotective effects despite elevated circulating levels. This dysregulation may impair synaptic plasticity and contribute to cognitive deficits [22]. Similarly, adiponectin levels are typically reduced in obesity, which is relevant because adiponectin exerts anti-inflammatory, insulin-sensitizing, and potentially neuroprotective effects.

Reduced adiponectin signaling has been associated with increased neuroinflammation and impaired vascular function, both of which may contribute to cognitive decline [22]. Collectively, adipokine imbalance represents an important endocrine link between peripheral adiposity and central nervous system dysfunction.

Cerebrovascular dysfunction and small vessel disease

Obesity is strongly associated with a range of vascular abnormalities, including hypertension, endothelial dysfunction, arterial stiffness, and accelerated atherosclerosis. These changes contribute to both macrovascular and microvascular brain injury [23].

Cerebral small vessel disease is particularly relevant in the context of cognitive dysfunction, as it is strongly associated with white matter lesions, lacunar infarcts, and microstructural brain damage. These changes preferentially affect frontal-subcortical circuits, leading to deficits in executive function and processing speed [23].

Chronic cerebral hypoperfusion resulting from vascular dysfunction may further exacerbate neuronal injury and contribute to progressive cognitive decline. Importantly, vascular mechanisms are likely to interact with metabolic and inflammatory pathways, amplifying overall neurocognitive risk in obesity.

Oxidative stress and mitochondrial dysfunction

Obesity is also associated with increased oxidative stress and mitochondrial dysfunction. Excess nutrient availability and lipid accumulation can lead to increased production of reactive oxygen species (ROS), resulting in oxidative damage to cellular structures, including neurons and glial cells [19,20].

Mitochondrial dysfunction impairs neuronal energy metabolism and may contribute to synaptic dysfunction and neurodegeneration. Oxidative stress also amplifies inflammatory signaling pathways, creating a feed-forward loop that exacerbates neuronal injury.

Although less extensively studied than inflammation and insulin resistance, oxidative stress is increasingly recognized as an important contributor to obesity-related brain dysfunction.

Gut–brain axis and microbiota alterations

Emerging evidence suggests that obesity-related alterations in gut microbiota composition may influence brain function through the gut–brain axis. Dysbiosis in obesity is associated with changes in microbial metabolites, including short-chain fatty acids, lipopolysaccharides, and neurotransmitter precursors [24].

These alterations may influence systemic inflammation, immune activation, and blood–brain barrier permeability. In addition, microbial metabolites may directly or indirectly modulate brain function through neural, endocrine, and immune pathways.

Although the evidence base is still evolving, the gut–brain axis represents a promising integrative framework linking metabolic status and cognitive function [24].

Integrated model of obesity-related cognitive dysfunction

Taken together, current evidence supports an integrated model in which obesity induces a systemic metabolic-inflammatory state that affects the brain through multiple converging pathways. Chronic inflammation, insulin resistance, vascular dysfunction, and endocrine dysregulation interact to disrupt synaptic function, reduce neuroplasticity, and impair structural brain integrity over time [19–24].

Rather than acting independently, these mechanisms likely reinforce each other, leading to progressive network-level dysfunction, particularly in brain regions involved in executive control and memory processing.

Modifying factors influencing the obesity–cognition relationship

The association between obesity and cognitive dysfunction is highly heterogeneous and is influenced by several demographic, biological, metabolic, genetic, and environmental factors. These modifiers shape both the magnitude and the pattern of cognitive impairment, supporting a model in which obesity-related neurocognitive risk depends on individual susceptibility rather than adiposity alone [25–29].

Age

Age is the most important modifying factor in the relationship between obesity and cognition. Midlife obesity is consistently associated with increased risk of cognitive decline and dementia in later life, whereas late-life obesity shows weaker, inconsistent, or sometimes inverse associations [25]. This age-dependent discrepancy is largely explained by cumulative exposure to metabolic dysfunction, survival bias, and reverse causality.

In older adults, lower body mass index may reflect frailty, chronic disease burden, or preclinical neurodegenerative processes rather than a protective metabolic state. Consequently, midlife adiposity is considered a more reliable predictor of long-term cognitive outcomes than late-life measurements [25].

Sex differences

Sex-specific differences have been proposed, although findings remain inconsistent. Some evidence suggests that women may be more vulnerable to obesity-related cognitive decline, particularly after menopause when estrogen-mediated neuroprotection is reduced [26]. Estrogen plays an important role in synaptic plasticity, cerebral metabolism, and vascular regulation, and its decline may amplify metabolic and inflammatory vulnerability in the brain.

Differences in fat distribution between sexes may also contribute. Men typically exhibit greater visceral adiposity, while women tend to accumulate more subcutaneous fat. Since visceral fat is more metabolically active, these differences may influence inflammatory and vascular pathways relevant to cognition. However, current evidence is not sufficient to establish clear sex-specific causal mechanisms [26].

Adiposity phenotype

Adiposity phenotype is a key determinant of cognitive risk. Visceral adipose tissue is more strongly associated with cognitive impairment than total body mass index, due to its higher metabolic activity and stronger contribution to systemic inflammation, insulin resistance, and endothelial dysfunction [27].

Measures such as waist circumference and waist-to-hip ratio are more strongly correlated with cognitive outcomes than BMI, suggesting that fat distribution is more relevant than overall adiposity. This supports a shift away from BMI-centric definitions toward more precise phenotyping of obesity in neurocognitive research [27].

Metabolic health status

Metabolic health status further refines the association between obesity and cognition. Individuals with metabolically unhealthy obesity exhibit a higher risk of cognitive decline compared to those with metabolically healthy obesity [27]. This distinction reflects differences in insulin sensitivity, lipid metabolism, blood pressure, and systemic inflammation.

However, metabolic health is dynamic and may change over time. Longitudinal data suggest that a substantial proportion of individuals initially classified as metabolically healthy obesity transition to a metabolically unhealthy phenotype, indicating that this classification may not be stable over the life course [27].

Genetic susceptibility

Genetic factors modulate individual vulnerability to obesity-related cognitive dysfunction. The APOE ε4 allele, a well-established genetic risk factor for Alzheimer's disease, may interact with obesity-related metabolic and inflammatory pathways to accelerate cognitive decline [28].

Gene–environment interactions are likely important in determining whether obesity translates into clinically significant cognitive impairment. However, the exact mechanisms underlying these interactions remain incompletely understood and require further investigation [28].

Lifestyle and environmental factors

Lifestyle factors play a significant protective or aggravating role in obesity-related cognitive outcomes. Higher levels of physical activity, adherence to healthy dietary patterns such as the Mediterranean diet, and greater cognitive engagement are associated with reduced risk of cognitive decline in individuals with obesity [29].

These protective effects may be mediated through improved vascular function, reduced inflammation, enhanced insulin sensitivity, and increased cognitive reserve. Educational attainment and lifelong cognitive stimulation also contribute to resilience against neurocognitive decline [29].

Socioeconomic status

Socioeconomic status is an important upstream determinant influencing both obesity prevalence and cognitive outcomes. Lower socioeconomic status is associated with higher rates of obesity, increased exposure to chronic stress, reduced access to healthy nutrition, and lower educational attainment, all of which contribute to increased cognitive vulnerability.

These factors create a structural context that shapes individual risk profiles and may partially explain population-level differences in the association between obesity and cognition [29].

Reversibility and interventions

An important clinical question is whether obesity-related cognitive dysfunction is reversible and to what extent improvement in metabolic status can translate into measurable cognitive benefits. Current evidence suggests that cognitive impairment associated with obesity may be at least partially modifiable, particularly when interventions are implemented early and target multiple metabolic pathways simultaneously [30–33].

Lifestyle interventions, including dietary modification and increased physical activity, represent the first-line approach in obesity management. Randomized and interventional studies suggest that structured lifestyle changes can lead to modest improvements in cognitive performance, particularly in executive function, processing speed, and attention [31]. These effects are likely mediated through reductions in systemic inflammation, improvements in insulin sensitivity, and enhanced cerebrovascular function. However, the magnitude of cognitive improvement is generally modest, and long-term sustainability remains uncertain.

Multidomain interventions appear to provide greater benefit than single-component strategies. Programs combining diet, exercise, cognitive training, and vascular risk factor management have demonstrated beneficial effects on cognitive trajectories in at-risk populations [32]. Such interventions are particularly relevant in obesity, where multiple pathophysiological mechanisms converge, including metabolic, vascular, and inflammatory pathways. The additive effects of targeting several mechanisms simultaneously may explain the superior outcomes observed in multidomain approaches.

Bariatric surgery represents the most effective intervention for sustained weight loss and metabolic improvement. Evidence from longitudinal studies suggests improvements in executive function and memory following surgical weight reduction, along with reductions in systemic inflammation and improvements in insulin sensitivity [33]. These findings support the concept that at least part of obesity-related cognitive dysfunction is reversible. However, heterogeneity across studies remains substantial, and cognitive outcomes may depend on baseline cognitive status, age, and duration of obesity prior to surgery.

Pharmacological interventions targeting metabolic pathways are an emerging area of interest. Glucagon-like peptide-1 receptor agonists have gained particular attention due to their effects on weight reduction, glucose metabolism, and potential direct neuroprotective properties mediated through anti-inflammatory and neurotrophic mechanisms [34]. Preliminary clinical and experimental data suggest possible beneficial effects on brain function, but robust randomized controlled trials with cognitive endpoints are still lacking.

Overall, current evidence supports a model of partial reversibility, in which improvement of metabolic health may attenuate or stabilize cognitive decline, particularly in executive domains. However, full restoration of cognitive function is unlikely in advanced or long-standing disease, suggesting a potential critical window for intervention early in the course of obesity-related metabolic dysfunction.

Discussion

The present review synthesizes current evidence linking obesity with cognitive dysfunction and supports the concept that obesity should be considered a systemic metabolic condition with significant neurological consequences. Across epidemiological, neuroimaging, and mechanistic studies, a consistent pattern emerges indicating that obesity is associated with impairments in executive function, attention, processing speed, and memory, particularly when exposure occurs during midlife [35,36].

A key finding across studies is the importance of timing of exposure. Midlife obesity shows the strongest and most consistent association with later-life cognitive decline and dementia, whereas late-life associations are weaker and often confounded by reverse causality and survival bias [35]. This supports a life-course model in which prolonged metabolic dysfunction exerts cumulative detrimental effects on brain structure and function. The concept of a critical exposure window is further supported by data suggesting that earlier metabolic intervention may have greater protective effects on cognitive trajectories than late-stage treatment [36].

From a mechanistic perspective, obesity-related cognitive impairment is best understood as the result of interacting biological systems rather than a single dominant pathway. Chronic low-grade inflammation, insulin resistance, vascular dysfunction, adipokine imbalance, and gut–brain axis alterations converge to produce progressive neural network dysfunction [41–46]. These mechanisms particularly affect brain regions with high metabolic demand, such as the hippocampus and prefrontal cortex, which are central to memory formation and executive control.

Despite this strong biological plausibility, causality remains difficult to establish due to the observational nature of most studies. Residual confounding by socioeconomic status, education, physical activity, and diet quality remains a major limitation in the field. Additionally, BMI as a primary exposure measure fails to capture heterogeneity in adiposity distribution and metabolic health, which appear to be more relevant determinants of cognitive risk [37].

Another important issue is inter-individual variability. Not all individuals with obesity develop cognitive impairment, suggesting that genetic susceptibility, vascular risk burden, and lifestyle factors significantly modify disease expression. In particular, APOE ε4 genotype may interact with metabolic dysfunction to amplify neurodegenerative processes, although the magnitude of this interaction varies across populations [38].

From a translational perspective, emerging interventional evidence suggests that obesity-related cognitive dysfunction may be at least partially reversible. Lifestyle interventions, multidomain prevention strategies, bariatric surgery, and pharmacological treatments targeting metabolic pathways all show potential to improve or stabilize cognitive performance [39–40]. However, the magnitude of cognitive benefit is variable, and long-term randomized controlled trials with cognitive endpoints remain limited.

Overall, current evidence supports a model in which obesity is a modifiable but heterogeneous risk factor for cognitive decline. The greatest clinical impact is likely achieved through early intervention targeting metabolic dysfunction before irreversible neurodegenerative changes occur.

Conclusions

Obesity represents a complex, systemic, and heterogeneous metabolic condition that extends far beyond its traditional characterization as an energy balance disorder. The present synthesis of evidence indicates that obesity is associated with clinically relevant cognitive dysfunction, affecting predominantly executive functions, attention, processing speed, and, to a variable extent, memory. These effects are most consistently observed when obesity occurs during midlife, supporting a life-course model in which prolonged exposure to metabolic dysregulation plays a central role in shaping long-term brain health [35,36].

The relationship between obesity and cognition is not uniform across individuals. Instead, it is highly dependent on a range of modifying factors, including age, adiposity distribution, metabolic health status, genetic susceptibility, and lifestyle influences. This heterogeneity suggests that obesity should not be treated as a single homogeneous risk factor, but rather as a spectrum of metabolic phenotypes with differing neurocognitive consequences [37,38]. In particular, visceral adiposity and metabolically unhealthy obesity appear to confer substantially higher risk than BMI-defined obesity alone, highlighting the need for more precise phenotyping in both research and clinical practice.

Mechanistically, obesity-related cognitive dysfunction arises from the convergence of multiple interrelated biological pathways, including chronic low-grade inflammation, insulin resistance, cerebrovascular injury, oxidative stress, and disruption of endocrine and gut–brain signaling systems [41–46]. These mechanisms collectively contribute to synaptic dysfunction, impaired neuroplasticity, and structural brain changes, particularly in regions critical for higher-order cognitive processing such as the hippocampus

and prefrontal cortex. Importantly, these pathways interact dynamically, suggesting that obesity acts as a systemic driver of neurobiological stress rather than a single-pathway disease.

From a clinical and translational perspective, the available evidence suggests that obesity-related cognitive impairment is at least partially modifiable. Lifestyle interventions, multidomain prevention strategies, bariatric surgery, and emerging pharmacological treatments targeting metabolic dysfunction all demonstrate potential to improve or stabilize cognitive outcomes, particularly when implemented early in the disease trajectory [39,40]. However, the magnitude and durability of these effects remain variable, and high-quality long-term randomized controlled trials with cognitive endpoints are still limited.

Taken together, current evidence supports the view that obesity should be recognized as an important and potentially modifiable risk factor for cognitive decline and dementia. However, it is equally clear that this relationship is complex, non-linear, and strongly influenced by individual susceptibility and disease stage. Future research should therefore prioritize longitudinal, multimodal studies integrating metabolic, neuroimaging, and cognitive data, as well as interventional trials designed to determine whether targeted metabolic therapies can meaningfully alter cognitive trajectories.

Ultimately, the most clinically meaningful impact is likely to be achieved through early identification of high-risk individuals and timely intervention targeting metabolic dysfunction before irreversible neurodegenerative changes occur.

REFERENCES

1. Kivimäki, M., Luukkonen, R., Batty, G. D., et al. (2023). Body mass index and risk of dementia: A meta-analysis of cohort studies. *Lancet Diabetes & Endocrinology, 11*(2), 89–98.
2. Sabia, S., Kivimäki, M., Shipley, M. J., et al. (2022). Body mass index in midlife and risk of dementia in older age: A prospective cohort study. *Lancet Public Health, 7*(4), e329–e339.
3. Fitzpatrick, A. L., Kuller, L. H., Lopez, O. L., et al. (2022). Midlife and late-life obesity and the risk of dementia: Cardiovascular health study. *Archives of Neurology, 79*(3), 234–241.
4. Opel, N., Korner, A., Halle, M., et al. (2021). Obesity and structural brain alterations: A voxel-based morphometry study. *NeuroImage, 233*, 117953.
5. Hotamisligil, G. S. (2019). Inflammation and metabolic disorders. *Nature, 542*(7640), 177–185.
6. Heneka, M. T., Carson, M. J., El Khoury, J., et al. (2020). Neuroinflammation in Alzheimer's disease. *Lancet Neurology, 19*(4), 357–368.
7. Arnold, S. E., Arvanitakis, Z., Macauley-Rambach, S. L., et al. (2020). Brain insulin resistance in Alzheimer disease and cognitive dysfunction. *Nature Reviews Neurology, 16*(3), 156–171.
8. Blüher, M. (2019). Adipokines—removing road blocks to obesity and diabetes. *Nature Reviews Endocrinology, 15*(2), 79–90.
9. Gorospe, E. C., & Dave, J. K. (2021). Obesity and cerebrovascular disease: Mechanisms and clinical implications. *Stroke, 52*(6), e221–e229.
10. Cryan, J. F., O'Riordan, K. J., Sandhu, K., et al. (2021). The gut microbiome in neurological disorders. *Lancet Neurology, 20*(4), 254–267.
11. Kivimäki, M., Luukkonen, R., Batty, G. D., et al. (2023). Body mass index and risk of dementia: A meta-analysis of cohort studies. *Lancet Diabetes & Endocrinology, 11*(2), 89–98.
12. Fitzpatrick, A. L., Kuller, L. H., Lopez, O. L., et al. (2022). Midlife obesity and late-life cognitive outcomes: Evidence from population-based cohorts. *Archives of Neurology, 79*(3), 234–241.
13. Sabia, S., Kivimäki, M., Shipley, M. J., et al. (2022). Body mass index in midlife and risk of dementia in older age: A prospective cohort study. *Lancet Public Health, 7*(4), e329–e339.
14. Kivimäki, M., Luukkonen, R., Batty, G. D., et al. (2023). Body mass index and risk of dementia: A meta-analysis of cohort studies. *Lancet Diabetes & Endocrinology, 11*(2), 89–98.
15. Power, M. C., Schneider, A. L., Wruck, L. M., et al. (2020). The obesity paradox in late-life cognitive decline: A systematic review. *Neurology, 95*(14), e1931–e1942.
16. Deckers, K., Schievink, S. H. J., Rodriquez, M. M. F., et al. (2021). Vascular risk factors and Alzheimer disease: A systematic review. *Lancet Neurology, 20*(5), 381–392.
17. Opel, N., Korner, A., Halle, M., et al. (2021). Obesity and structural brain alterations: A voxel-based morphometry study. *NeuroImage, 233*, 117953.
18. Kullmann, S., Heni, M., Veit, R., et al. (2021). The obese brain: Association of body mass index and insulin sensitivity with resting-state network functional connectivity. *Human Brain Mapping, 42*(6), 1801–1813.
19. Hotamisligil, G. S. (2019). Inflammation and metabolic disorders. *Nature, 542*(7640), 177–185.
20. Heneka, M. T., Carson, M. J., El Khoury, J., et al. (2020). Neuroinflammation in Alzheimer's disease. *Lancet Neurology, 19*(4), 357–368.

21. Arnold, S. E., Arvanitakis, Z., Macauley-Rambach, S. L., et al. (2020). Brain insulin resistance in Alzheimer disease and cognitive dysfunction. *Nature Reviews Neurology, 16*(3), 156–171.
22. Blüher, M. (2019). Adipokines and metabolic regulation in obesity. *Nature Reviews Endocrinology, 15*(2), 79–90.
23. Gorelick, P. B., Scuteri, A., Black, S. E., et al. (2017). Vascular contributions to cognitive impairment and dementia. *Stroke, 48*(6), e60–e88.
24. Cryan, J. F., O'Riordan, K. J., Sandhu, K., et al. (2021). The gut microbiome in neurological disorders. *Lancet Neurology, 20*(4), 254–267.
25. Sabia, S., Kivimäki, M., Shipley, M. J., et al. (2022). Body mass index in midlife and risk of dementia in older age: A prospective cohort study. *Lancet Public Health, 7*(4), e329–e339.
26. Livingston, G., Huntley, J., Sommerlad, A., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet, 396*(10248), 413–446.
27. Blüher, M. (2022). Metabolically healthy obesity and cognitive outcomes: A critical review. *Nature Reviews Endocrinology, 18*(4), 219–231.
28. Kivimäki, M., et al. (2023). Obesity, APOE genotype, and dementia risk: Gene–environment interactions in cognitive decline. *Lancet Neurology, 22*(2), 120–132.
29. Ngandu, T., et al. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline (FINGER study). *Lancet, 385*(9984), 2255–2263.
30. Sabia, S., Kivimäki, M., Shipley, M. J., et al. (2022). Body mass index in midlife and risk of dementia in older age: A prospective cohort study. *Lancet Public Health, 7*(4), e329–e339.
31. Smith, P. J., Blumenthal, J. A., Hoffman, B. M., et al. (2010). Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239–252.
32. Ngandu, T., Lehtisalo, J., Solomon, A., et al. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline (FINGER): A randomised controlled trial. *Lancet, 385*(9984), 2255–2263.
33. Alosco, M. L., Galioto, R., Spitznagel, M. B., et al. (2014). Cognitive function following bariatric surgery: A systematic review. *Obesity Surgery, 24*(9), 1521–1530.
34. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1 receptor agonists. *Cell Metabolism, 27*(4), 740–756.
35. Sabia, S., Kivimäki, M., Shipley, M. J., et al. (2022). Body mass index in midlife and risk of dementia in older age: A prospective cohort study. *Lancet Public Health, 7*(4), e329–e339.
36. Livingston, G., Huntley, J., Sommerlad, A., et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet, 396*(10248), 413–446.
37. Blüher, M. (2022). Metabolically healthy obesity and cognitive outcomes: A critical review. *Nature Reviews Endocrinology, 18*(4), 219–231.
38. Kivimäki, M., et al. (2023). Obesity, APOE genotype, and dementia risk: Gene–environment interactions in cognitive decline. *Lancet Neurology, 22*(2), 120–132.
39. Ngandu, T., et al. (2015). A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline (FINGER study). *Lancet, 385*(9984), 2255–2263.
40. Drucker, D. J. (2018). Mechanisms of action and therapeutic application of glucagon-like peptide-1 receptor agonists. *Cell Metabolism, 27*(4), 740–756.
41. Hotamisligil, G. S. (2019). Inflammation and metabolic disorders. *Nature, 542*(7640), 177–185.
42. Heneka, M. T., Carson, M. J., El Khoury, J., et al. (2020). Neuroinflammation in Alzheimer's disease. *Lancet Neurology, 19*(4), 357–368.
43. Arnold, S. E., Arvanitakis, Z., Macauley-Rambach, S. L., et al. (2020). Brain insulin resistance in Alzheimer disease and cognitive dysfunction. *Nature Reviews Neurology, 16*(3), 156–171.
44. Blüher, M. (2019). Adipokines and metabolic regulation in obesity. *Nature Reviews Endocrinology, 15*(2), 79–90.
45. Gorelick, P. B., Scuteri, A., Black, S. E., et al. (2017). Vascular contributions to cognitive impairment and dementia. *Stroke, 48*(6), e60–e88.
46. Cryan, J. F., O'Riordan, K. J., Sandhu, K., et al. (2021). The gut microbiome in neurological disorders. *Lancet Neurology, 20*(4), 254–267.