High-fat diet and cognitive dysfunction: Mechanistic insights into diet-induced neurodegeneration (Review)

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Abstract. Cognitive impairment encompasses a spectrum of neurological deficits affecting memory, attention, executive function and other higher-order cognitive processes. Increasing attention has been paid to modifiable lifestyle factors that influence its onset and progression. Among these, chronic high-fat diet (HFD) consumption has emerged as a significant and potentially reversible risk factor for cognitive decline. Both epidemiological and experimental studies have consistently linked HFD-particularly diets rich in saturated fatty acids-to impairments in memory, attention and executive functions. Mechanistically, HFD induces neuroinflammation, oxidative stress, insulin resistance and gut microbiota dysbiosis, which collectively disrupt synaptic plasticity and neuronal survival. Individual susceptibility factors such as age, sex and the presence of the apolipoprotein E ε4 allele may further exacerbate these pathological effects. This review also highlights promising intervention strategies, including adherence to Mediterranean or Dietary Approaches to Stop Hypertension dietary patterns, regular physical exercise, pharmacological approaches and gut microbiota modulation. A comprehensive understanding of these multifactorial pathways is essential for developing targeted preventive and therapeutic interventions to mitigate HFD-associated neurodegeneration.

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1. Introduction

Cognitive impairment encompasses a continuum of conditions characterized by deficits in memory, attention, executive function, language and visuospatial abilities, ranging from mild cognitive impairment (MCI) to more severe forms such as dementia, including Alzheimer's disease (AD), vascular dementia and other neurodegenerative disorders (1). These cognitive deficits significantly compromise individual autonomy, reduce quality of life and impose growing burdens on caregivers and healthcare systems (2). As the global population ages, the prevalence of cognitive disorders is projected to rise dramatically, amplifying their public health and socioeconomic impact. Despite advances in pharmacological and behavioral interventions, current treatment options remain limited in efficacy, particularly for dementia, underscoring the urgent need to identify modifiable risk factors and implement preventive strategies at earlier stages of disease progression.

One such modifiable factor that has gained increasing attention is diet-particularly the role of high-fat diets (HFDs) in the development and progression of cognitive dysfunction. An HFD is typically defined as one in which total energy intake from fats exceeds 35-40%, with a disproportionate enrichment in saturated fatty acids (SFAs) and trans fats, often coupled with insufficient intake of carbohydrates, essential amino acids, dietary fiber and micronutrients (3). Over the past several decades, the global spread of Western dietary patterns-marked by increased consumption of processed foods, sugary beverages and high-fat fast food-has contributed to the widespread adoption of HFDs across both developed and developing nations (4). As a result, the incidence of metabolic disorders linked to high-fat consumption, such as

obesity, type 2 diabetes, dyslipidemia and non-alcoholic fatty liver disease, has escalated to epidemic proportions (5-7).

Emerging research suggests that chronic exposure to HFDs may not only impair systemic metabolic homeostasis but also exert deleterious effects on brain health (3,8,9). Epidemiological studies have demonstrated that individuals with high dietary fat intake, particularly SFAs, have a significantly increased risk of developing MCI and dementia (10,11). For instance, longitudinal cohort studies have revealed that older adults adhering to diets rich in saturated fats experience accelerated cognitive decline and exhibit higher incidences of AD compared to those following diets high in polyunsaturated or monounsaturated fats (12). Conversely, adherence to dietary patterns rich in unsaturated fatty acids-such as the Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diets-has been associated with reduced cognitive decline and improved neurological outcomes, supporting the notion that the type and quality of dietary fat play a critical role in modulating cognitive health (13,14).

HFD-induced cognitive impairment is driven by a multifactorial network of neuropathological processes, including neuroinflammation, oxidative stress, mitochondrial dysfunction, insulin resistance and gut microbiota dysbiosis (15). These mechanisms collectively disrupt synaptic plasticity, impair neurogenesis and compromise neuronal survival, particularly in hippocampal regions critical for learning and memory. Individual susceptibility-such as advanced age, female sex and genetic predispositions like the apolipoprotein E ε4 (APOE-ε4) allele-can amplify these deleterious effects.

Given the rising global prevalence of both HFD consumption and dementia-related disorders, elucidating the mechanistic links between diet and neurodegeneration has become a pressing public health priority. Importantly, the modifiable nature of diet offers a compelling avenue for early intervention. Emerging strategies-including adherence to Mediterranean or DASH dietary patterns, regular physical exercise, insulin-sensitizing or anti-inflammatory pharmacotherapy, and microbiota-targeted interventions such as probiotics-show promise in mitigating HFD-associated cognitive decline. A more comprehensive understanding of how dietary fats interact with neuroimmune, metabolic and microbial pathways may pave the way for personalized, mechanism-based prevention and treatment strategies aimed at preserving cognitive function across the lifespan.

2. Association between HFD and cognitive function

Epidemiological and experimental evidence of cognitive impairment induced by HFDs. A substantial body of epidemiological research has identified a significant association between chronic HFD consumption and increased risk of cognitive decline, MCI and dementia (Table I) (8,16-21). Prospective cohort studies in diverse populations have consistently shown that long-term adherence to HFD-particularly those rich in SFAs-is linked to poorer cognitive outcomes and a higher incidence of AD (10,11). For instance, a longitudinal study involving ~6,000 older adults reported that individuals in the highest quartile of SFA intake experienced markedly faster cognitive decline and a >2-fold increased risk of developing AD compared to those in the lowest quartile (22,23). Similar trends of accelerated cognitive deterioration have been observed in other population-based studies, further supporting the link between high SFA intake and impaired cognitive outcomes (8,24). Complementary findings from animal studies further substantiate this association: Rodents exposed to chronic SFA-enriched diets exhibit impairments in spatial learning and memory, along with pathological features characteristic of AD, such as enhanced β-amyloid deposition and tau hyperphosphorylation (25). Early manifestations of cognitive impairment in HFD models include disrupted circadian rhythms and diminished semantic fluency, with clinical symptoms predominantly affecting memory, executive function, learning ability and other early cognitive domains associated with neurodegeneration. Experimental evidence indicates that HFD impairs spatial memory, as reflected by increased escape latency in the Morris water maze, indicative of hippocampal dysfunction (26). In humans, elevated serum free fatty acids (FFAs) are associated with impaired delayed recall, particularly in individuals with reduced hippocampal volume (27,28). High intake of SFAs has been consistently linked to memory decline in older adults. A longitudinal study involving >2,500 elderly participants found that those with the highest SFA intake had more than double the risk of developing AD compared to those with the lowest intake (24). A meta-analysis of four independent cohorts revealed that individuals in the highest SFA quartile had a 39% higher risk of AD and a 105% higher risk of all-cause dementia compared to the lowest quartile (29). Dose-response analysis indicated that each additional 4 grams per day of SFA intake were associated with a 15% increased risk of AD. Furthermore, excessive SFA intake has been linked to accelerated episodic and prospective memory loss, particularly in older women, who exhibited a 40% slower recall rate and prolonged task completion times in neuropsychological assessments such as the Trail Making Test (30).

Beyond memory, executive dysfunction is another hallmark of HFD-induced impairment. Clinically, this manifests as reduced cognitive flexibility and impaired decision-making, while in rodent models, this has been demonstrated by increased error rates in reversal learning tasks, attributed to disrupted synaptic plasticity in the prefrontal cortex (PFC). Impulse control deficits are also evident, as shown by decreased inhibition performance in Go/No-Go tasks, potentially linked to downregulation of striatal dopamine D2 receptors (31).

Learning processes are likewise compromised: Mice on an HFD exhibit reduced exploration of novel objects, suggesting deficits in novelty recognition, and extinction of conditioned fear memory is delayed, likely due to amygdala-PFC circuit disruptions that contribute to anxiety-related cognitive rigidity. These impairments are associated with altered expression of synaptic proteins such as synaptophysin and postsynaptic density protein 95 (PSD-95), as well as reduced levels of bone-derived neurotrophic factor (BDNF), all of which are critical for synaptic plasticity (32). Chronic HFD has been shown to downregulate these proteins in the hippocampus and cortex, impairing neuronal communication and long-term potentiation (LTP) (33).

Taken together, current epidemiological and experimental evidence suggest that long-term HFD, particularly SFA-rich diets, exert a detrimental effect on multiple cognitive

Table I. Effects of HFD on cognitive function: Evidence from animal and human studies.

Subjects	Study design	Diet used	Main findings	(Refs.)
6-month-old male C57BL/6 mice (aged model)	1, 2 and 4-month randomized controlled feeding (HFD vs. normal diet)	HFD: 60 kcal% fat; normal diet: 10 kcal% fat	↓ Object place recognition; ↑ Tau hyperphosphorylation, microglial activation, IL-6 in hippocampus	(16)
Transgenic AD mice (tauopathy model)	30-week HFD feeding starting at 2 months of age	HFD: 23.5% fat; Control diet: 4.8% fat	↑ Depression-like behavior; ↓ cognition; ↑ Tau pathology and metabolic disorders	(17)
Juvenile/adolescent rodents (mice and rats)	Various durations (short to long term) HFD feeding	High-fat/high-sugar diets (varied fat content)	↓ Spatial and relational memory; altered neurotransmission; ↓ neurogenesis; ↑ hippocampal inflammation	(18)
Control and triple transgenic Alzheimer's (3xTg-AD; triple-transgenic) mice	Long-term HFD vs. normal diet, with chronic intranasal insulin intervention	HFD vs. normal diet (exact fat % not specified)	↓ Cognition; ↑ brain insulin resistance; ↓ brain mass and dentate gyrus size; intranasal insulin improved outcomes	(19)
Humans (review of multiple studies) and rodents	Review of acute and chronic exposure studies	High-energy diets high in fat and/or sugar (varied fat types)	↑ Memory impairment before weight gain; ↑ inflammation; ↓ BDNF; potential benefits from omega-3 and curcumin supplementation	(20)
Healthy male adults (22±1 years) (n=16)	Randomized crossover design; 5 days of high-fat, low-carbohydrate diet vs. standard diet, 2-week washout; cardiac and cognitive assessments	High-fat (75% of calories), low-carbohydrate diet for 5 days	↑ Plasma free fatty acids; ↓ cardiac PCr/ATP; ↓ attention, speed and mood	(21)

HFD, high-fat diet; BDNF, bone-derived neurotrophic factor; ATP, adenosine triphosphate; PCr, phosphocreatine.

domains, including memory, executive function and learning. However, it is important to acknowledge the inherent limitations of observational studies, including potential residual confounding and lack of causal inference. Therefore, further well-designed randomized controlled trials (RCTs) are necessary to validate these associations and inform evidence-based dietary guidelines for cognitive health promotion.

Modifiers of HFD-induced cognitive impairment. The adverse cognitive effects of HFDs do not occur in isolation but are significantly modulated by individual-level factors such as age, sex, and genetic predisposition.

Age is a well-established modifier of HFD-induced cognitive outcomes. Numerous studies have shown that older individuals are more susceptible to the detrimental neurological effects of chronic HFD exposure compared to younger populations. Aging is associated with increased vulnerability to HFD-induced neuroinflammation, oxidative stress and insulin resistance-key mechanisms contributing to accelerated cognitive decline and heightened dementia risk (34,35). Animal studies corroborate these findings, demonstrating that aged rodents exhibit more severe cognitive impairments and neuropathological changes in response to prolonged HFD intake than younger counterparts (36-38). Epidemiological data in humans further support these age-related interactions, indicating more pronounced cognitive deficits among older adults consuming an SFA-rich diet (8,39).

Sex differences also influence HFD-related cognitive vulnerability. Both clinical and preclinical evidence suggests that females may be more sensitive to cognitive impairments associated with high dietary fat intake. Population-based studies report stronger associations between HFD and cognitive decline in women than in men (40). Similarly, animal models show enhanced diet-induced insulin resistance, neuroinflammation and hippocampal dysfunction in female subjects, potentially due to hormonal fluctuations and the loss of estrogen-mediated neuroprotection with ageing (26,41,42).

Genetic predisposition further modulates the impact of HFD on cognitive function. The APOE-ε4 allele-an established genetic risk factor for AD-has been shown to amplify the neurocognitive consequences of chronic HFD exposure. Carriers of the APOE-ε4 allele demonstrate faster cognitive decline and greater vulnerability to HFD-related neurodegeneration than non-carriers (43,44). Additionally, polymorphisms in genes involved in inflammatory and metabolic pathways may exacerbate HFD-induced disruptions in lipid metabolism,

neuroimmune responses and cerebral insulin signaling, thereby potentiating cognitive dysfunction (45,46).

In summary, the cognitive impact of HFDs is strongly modulated by host-specific factors such as age, sex and genetic background. These interactions underscore the multifaceted nature of HFD-induced cognitive impairment. A comprehensive understanding of how HFD synergizes with individual risk factors is essential for developing effective strategies to mitigate cognitive decline.

3. Potential mechanisms

HFDs, particularly those rich in SFAs, have consistently been associated with adverse cognitive outcomes. Evidence from both preclinical models and clinical studies indicates that excessive SFA intake induces a cascade of deleterious pathophysiological processes, including microglia-mediated neuroinflammation, increased oxidative stress, impaired insulin signaling, gut microbiota dysbiosis and disruption of the blood-brain barrier (BBB) integrity. These interrelated mechanisms converge to impair neuronal function and accelerate cognitive decline (47-50).

Neuroinflammation. Neuroinflammation is recognized as a central mechanism through which HFDs contribute to cognitive impairment. Chronic HFD consumption activates microglia-the principal immune effector cells in the central nervous system (CNS)-prompting a shift from a homeostatic surveillance state toward a pro-inflammatory M1 phenotype (46,51). Under physiological conditions, microglia play key roles in maintaining synaptic plasticity, clearing cellular debris, and supporting adult neurogenesis. However, diets rich in SFAs-such as palmitic acid, lauric acid and stearic acid-trigger aberrant microglial activation. SFAs bind to Toll-like receptor 4 (TLR4) on microglial surfaces, activating MyD88-dependent signaling pathways and serving as potent inducers of nuclear factor κB and c-Jun N-terminal kinase signaling cascades. These pathways, together with endoplasmic reticulum stress responses, initiate and amplify pro-inflammatory signaling (52). Consequently, activated microglia release large quantities of inflammatory cytokines (TNF-α, IL-1β, IL-6, C-C motif chemokine ligand 2) and reactive oxygen species (ROS), leading to synaptic loss, neuronal injury, and impaired hippocampal function (53,54). Furthermore, SFAs may act synergistically with advanced glycation end products derived from processed lipids to exacerbate neuroinflammation. These cytokines amplify local neuroinflammatory cascades and directly disrupt neuronal integrity by impairing synaptic transmission, reducing synaptic plasticity, and promoting neuronal apoptosis.

Notably, HFD-induced neuroinflammation can occur within days of dietary exposure, preceding systemic metabolic disturbances. This inflammatory response often begins in the mediobasal hypothalamus (MBH)-a region highly sensitive to circulating lipid signals due to its specialized median eminence BBB and tanycyte-mediated transport. HFDs also promote the recruitment of bone marrow-derived myeloid cells to the MBH and hippocampus, where they differentiate into microglia-like pro-inflammatory cells, reinforcing the inflammatory milieu and enhancing M1 polarization (55). Importantly, this neuroinflammatory response occurs independently of body weight gain, suggesting a direct impact of dietary fat on central immune activation. Prolonged HFD exposure further propagates glial activation to other brain regions, including the hippocampus and prefrontal cortex, contributing to spatial memory deficits and depression-like behaviors (16).

Prolonged HFD exposure further propagates glial activation to other brain regions, including the hippocampus and prefrontal cortex, contributing to spatial memory deficits and depression-like behaviors (56-58). For instance, Sobesky *et al* (59) demonstrated that mice maintained on an HFD exhibited marked microglial activation in the hippocampus, elevated IL-1β expression and significant spatial memory deficits in the Morris water maze. Similarly, Spencer *et al* (60) reported that prolonged consumption of SFAs in rodents increased microglial activation and TNF-α expression, resulting in decreased synaptic density and impaired hippocampal-dependent learning tasks. Notably, pharmacological inhibition of microglial activation attenuated these cognitive impairments, highlighting a causal role for neuroinflammation (16,51,61).

Mitochondrial dysfunction and oxidative stress. Mitochondrial dysfunction is a pivotal mechanism by which HFD consumption contributes to cognitive impairment, often accompanied by energy dysregulation and enhanced oxidative stress (Fig. 1). HFD induces a disruption of mitochondrial dynamics, favoring pathological fragmentation. Fatty acids enter cells via fatty acid transport proteins and are directed toward either mitochondrial β-oxidation (for 2-18 carbon chains) or peroxisomal metabolism (for ≥26 carbon chains via ATP binding cassette transporters). In mitochondria, fatty acid oxidation is carnitine-dependent and contributes to ATP production. However, chronic exposure to high levels of saturated SFAs impairs mitochondrial dynamics. Specifically, SFA-rich diets markedly upregulate dynamin-related protein 1 (Drp1), particularly its phosphorylation at Ser616, promoting Drp1 translocation from the cytosol to the outer mitochondrial membrane, where it oligomerizes to drive mitochondrial fission. Concurrently, the expression of fusion-related proteins-including mitofusins 1/2 and optic atrophy 1-is significantly reduced, impairing mitochondrial fusion capacity. This imbalance leads to mitochondrial network fragmentation, structural disruption and functional decline. Notably, such metabolic impairment extends beyond the central nervous system. Bone marrow-derived monocytes exposed to an HFD exhibit similar mitochondrial fragmentation, lactate accumulation and bioenergetic inefficiency, suggesting a systemic mitochondrial reprogramming that may amplify the neuroenergetic imbalance through peripheral-to-central metabolic cross-talk (62,63).

Furthermore, excessive SFAs stimulate mitochondrial fatty acid β-oxidation, enhancing electron flux through complexes I and III of the electron transport chain. Additionally, peroxisomal β-oxidation does not generate ATP directly. Instead, it transfers electrons directly to molecular oxygen. This process increases electron leakage, leading to overproduction of ROS, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (·OH) (9,64-67). These ROS species damage mitochondrial DNA, respiratory enzymes and phospholipid membranes, further exacerbating mitochondrial

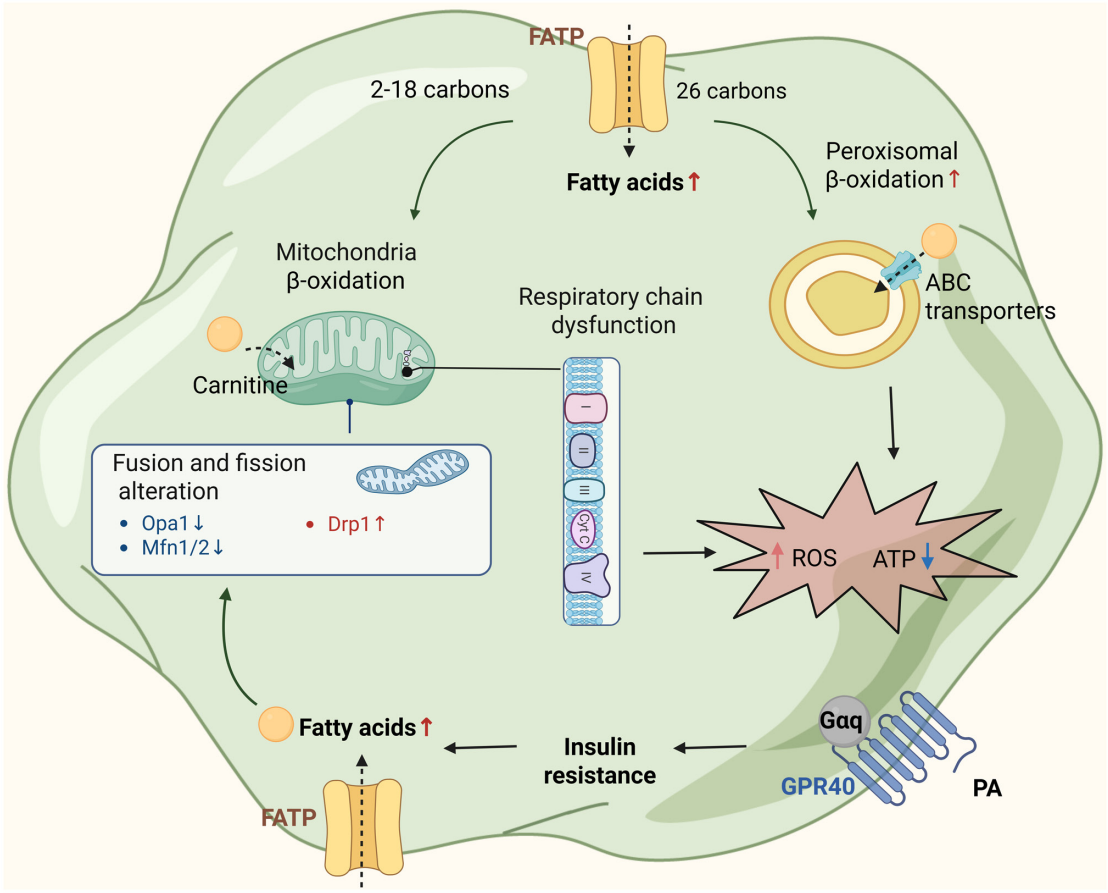

Figure 1. Mechanism of mitochondrial dysfunction induced by HFD. HFD increases circulating FFAs, which are taken up via FATPs and directed to mitochondrial and peroxisomal β-oxidation. Insulin resistance promotes excessive FFA influx, overwhelming mitochondrial capacity. Impaired mitochondrial dynamics (↓Opa1, ↓Mfn1/2, ↑Drp1) and respiratory chain dysfunction lead to reduced ATP production and elevated ROS levels. These alterations contribute to cellular energy failure and oxidative stress, exacerbating cognitive decline. ABC, ATP binding cassette; HFD, high-fat diet; FATPs, fatty acid transport proteins; FFAs, free fatty acids; ROS, reactive oxygen species; ATP, adenosine triphosphate; OPA1, optic atrophy protein 1; Mfn1/2, mitofusin 1/2; Drp1, dynamin-related protein 1; Cyt c, cytochrome c; PA, phosphatidic acid; GPR, G protein-coupled receptor; Gαq, guanine nucleotide-binding protein α q subunit.

dysfunction (68-70). Excess ROS accumulation causes oxidative damage via lipid peroxidation, protein oxidation and DNA fragmentation. Lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), are particularly toxic to neurons. Elevated levels of MDA and 4-HNE have been detected in the hippocampus and cortex of HFD-fed animals and are closely associated with impairments in spatial memory, working memory and executive function (71,72). For instance, Liu *et al* (73) demonstrated that long-term HFD exposure in mice led to significantly increased hippocampal MDA levels, reduced antioxidant enzyme activities [e.g., superoxide dismutase (SOD) and glutathione peroxidase], and worsened spatial learning in the Morris water maze.

Insulin resistance. Insulin signaling is essential for maintaining neuronal glucose metabolism, mitochondrial bioenergetics, synaptic plasticity and neuronal survival-all of which are fundamental to cognitive function. In the CNS, insulin binds to its receptor, triggering the phosphorylation of insulin receptor substrates (IRS), which in turn activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway (45,74,75). This cascade not only promotes neuronal glucose uptake via glucose transporters (GLUT), i.e., GLUT3 and GLUT4, and supports mitochondrial function, but also plays key roles in neurogenesis, synaptic remodeling and cell viability.

HFD exposure impairs both peripheral and central insulin signaling, contributing to systemic insulin resistance. Peripherally, an HFD may diminish insulin's anti-lipolytic function, resulting in excessive FFA release from adipose tissue. These circulating FFAs accumulate in metabolic organs-including liver, skeletal muscle, brain and astrocytes-overloading oxidative pathways and increasing mitochondrial and peroxisomal β-oxidation (Fig. 1). Notably, palmitic acid (a major SFA in HFDs) reduces GLUT1 expression at the BBB, thereby limiting glucose delivery to the brain, diminished glucose uptake and compromised neuronal energy homeostasis (76-78).

In the CNS, insulin resistance particularly affects the hippocampus and prefrontal cortex-regions crucial for memory encoding and executive function (36,45,79). Dysfunctional insulin signaling reduces Akt activation and downregulates BDNF, contributing to synaptic degeneration, reduced dendritic spine density and impaired LTP, which are key substrates of cognitive performance (80,81). For instance, Arnold *et al* (48) reported that HFD-fed mice showed reduced insulin receptor activity, lower Akt phosphorylation and impaired hippocampal synaptic plasticity, as well as spatial learning and memory deficits. Similarly,

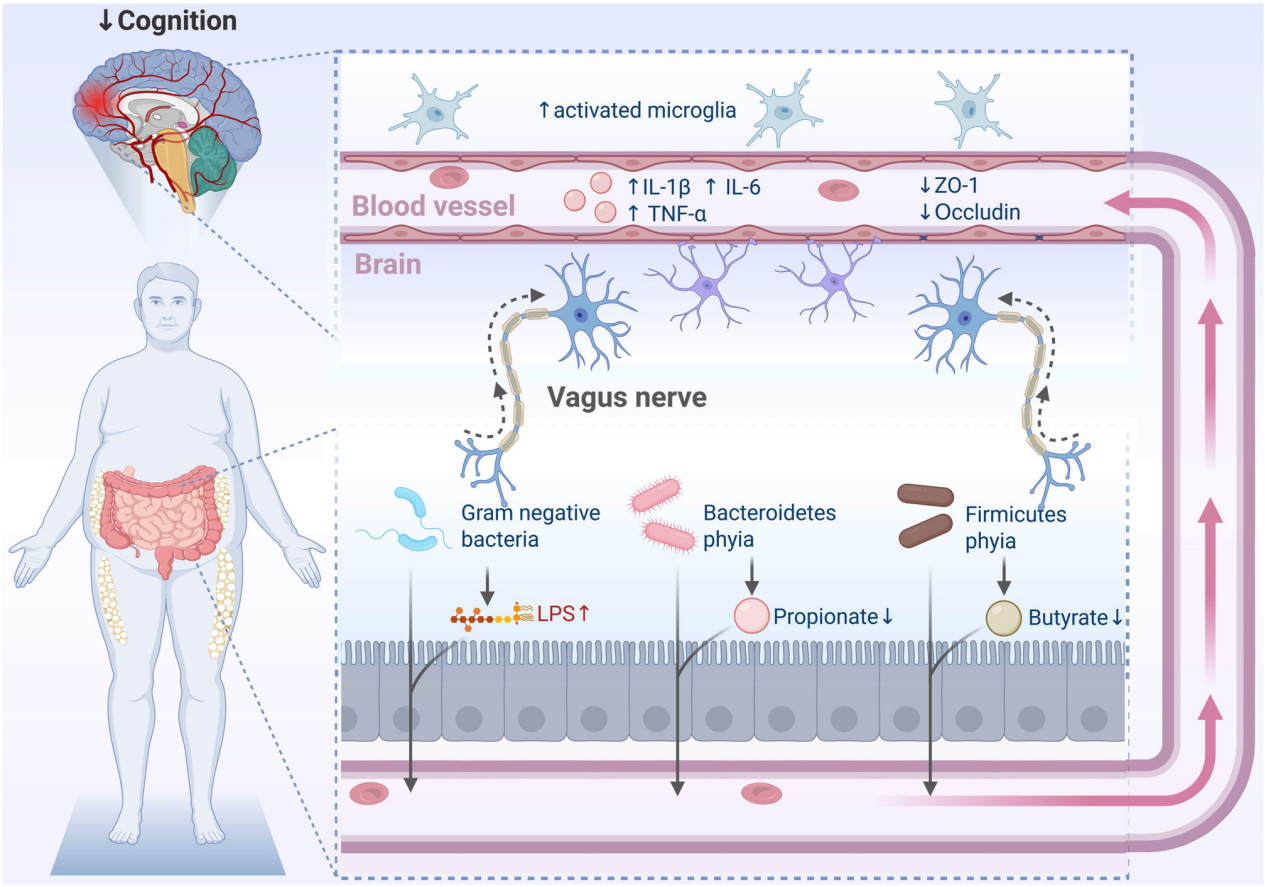

Figure 2. Gut-brain axis disruption in HFD-induced cognitive impairment. HFD induces gut microbiota dysbiosis, characterized by an increased *Firmicutes-to-Bacteroidetes* ratio and elevated levels of Gram-negative Proteobacteria. This leads to elevated LPS and reduced SCFAs, such as propionate and butyrate. These changes compromise intestinal barrier integrity, allowing microbial products to enter circulation and activate neuroinflammatory pathways via the vagus nerve or systemic cytokines. Consequent microglial activation, elevated IL-1β, IL-6 and TNF-α, and reduced tight junction proteins (ZO-1, occludin), contribute to blood-brain barrier disruption and cognitive decline. HFD, high-fat diet; LPS, lipopolysaccharides; SCFAs, short-chain fatty acids; IL, interleukin; TNF, tumor necrosis factor; ZO-1, zonula occludens-1.

Kothari *et al* (36) demonstrated that chronic HFD exposure suppressed BDNF expression and reduced dendritic complexity in the hippocampus, correlating with cognitive decline. Furthermore, HFD-induced insulin resistance may promote AD-like neuropathology via multiple mechanisms. It activates downstream kinases such as glycogen synthase kinase-3β, inducing pathological tau hyperphosphorylation at Ser396/404 and facilitating neurofibrillary tangle formation. It also suppresses insulin-degrading enzyme, reducing Aβ clearance and accelerating amyloid plaque accumulation. Additionally, impaired insulin signaling inhibits the proliferation and differentiation of neural progenitor cells, thereby limiting adult hippocampal neurogenesis and reducing cognitive flexibility and plasticity (82).

Gut microbiota dysbiosis. The gut microbiota-comprising trillions of bacteria, archaea, viruses and fungi-plays a pivotal role in regulating host metabolism, immune responses and CNS function via the gut-brain axis (83-85) (Fig. 2). Human studies have shown that individuals consuming Western-style high-fat diets HFDs exhibit distinct gut microbial profiles associated with impaired memory and executive function (86). These profiles are typically characterized by a reduction in beneficial genera such as *Bifidobacterium* and *Lactobacillus*, and an overrepresentation of pro-inflammatory taxa including members of the *Firmicutes*, *Proteobacteria* and *Desulfobacterota* phyla (87-90).

Animal models have validated these associations: Fecal microbiota transplantation from HFD-fed mice into germ-free recipients reproduces spatial learning deficits and neuroinflammation (91). By contrast, microbiota-targeted interventions-including probiotics (*Bifidobacterium*, *Lactobacillus*), prebiotics (e.g., inulin, fructooligosaccharides) and polyphenol-rich diets-have demonstrated the ability to restore gut microbial homeostasis, enhance short-chain fatty acid (SCFA) production, suppress systemic inflammation and improve cognitive outcomes in HFD-fed animal (92,93).

HFD-induced dysbiosis alters gut-brain axis communication through multiple pathways, including neural (e.g., vagus nerve), humoral, and immune mechanisms (94). One of the most significant consequences is the dysregulation of microbial metabolite production. HFD significantly reduces SCFAs such as acetate, propionate, and butyrate-metabolites essential for maintaining gut barrier integrity, regulating immune responses, and exerting anti-inflammatory and neuroprotective functions. Concurrently, HFD increases the production of harmful metabolites such as lipopolysaccharide (LPS), trimethylamine-N-oxide and secondary bile acids (86,95,96).

Depletion of SCFAs impairs the expression of antimicrobial peptides, particularly regenerating islet-derived protein 3γ, further weakening the gut epithelial barrier and increasing intestinal permeability. This allows microbial products like LPS to enter systemic circulation, where they activate TLR4 and trigger inflammatory cascades that elevate circulating pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 (97,98). These cytokines subsequently exacerbate BBB permeability, promote microglial activation and initiate CNS neuroinflammation (99).

Other potential mechanisms. In addition to inflammation, oxidative stress, insulin resistance, and gut dysbiosis, HFD consumption contributes to cognitive deterioration through several additional mechanisms, including BBB disruption, epigenetic modifications, and neurotransmitter imbalance.

One critical pathway involves the breakdown of BBB integrity. Chronic HFD exposure significantly increases BBB permeability, as evidenced by enhanced Evans blue dye extravasation and increased infiltration of peripheral immune cells into the brain parenchyma-findings closely correlated with impaired spatial memory performance (100). This compromised barrier allows peripheral inflammatory mediators, ROS and LPS to enter the CNS, thereby promoting microglial activation, neuroinflammation and cerebral Aβ deposition. Studies have shown that saturated fat-enriched diets exacerbate BBB disruption and facilitate plasma-derived Aβ accumulation in the brain, aggravating AD-like neuropathology (101). Additionally, oxidized cholesterol produced during high-temperature cooking, along with excess SFAs, directly damages cerebrovascular endothelial cells, reduces cerebral perfusion and promotes the development of white matter hyperintensities-radiological markers strongly linked to executive dysfunction and cognitive decline (102).

Epigenetic dysregulation is another significant contributor. Chronic HFD intake has been shown to reduce histone acetylation and increase DNA methylation at the promoter region of BDNF, leading to reduced BDNF expression. This downregulation impairs synaptic plasticity and neurogenesis-both essential for learning and memory (103). HFD also disrupts the expression of core circadian clock genes such as *Bmal1* and *Clock*, causing neuronal metabolic desynchronization and cognitive dysfunction. These epigenetic changes further perpetuate neuroinflammation and oxidative stress, creating a maladaptive neurochemical environment that exacerbates cognitive decline (104).

HFD also induces widespread alterations in neurotransmitter homeostasis. Animal studies have reported elevated dopamine release alongside disruptions in multiple neurotransmitter systems, including glutamate, acetylcholine, γ-aminobutyric acid, serotonin and dopamine. Impaired glutamate reuptake results in extracellular glutamate accumulation, contributing to excitotoxicity, neuronal injury and impaired synaptic plasticity (105). Cholinergic dysfunction, characterized by reduced synthesis and release of acetylcholine, impairs attention and learning capabilities (106). Furthermore, an HFD decreases the expression of neurotensin, a neuropeptide involved in dopaminergic reward regulation, further disrupting reward pathways and contributing to compulsive overeating, metabolic dysregulation and cognitive deficits.

4. Intervention strategies

Given the multifactorial mechanisms underlying HFD-induced cognitive impairment, a variety of intervention strategies have been explored to improve cognitive function by targeting different pathological pathways (Table II) (22,88,93,107-120).

Dietary interventions. Dietary modification is among the most accessible and effective strategies for mitigating cognitive impairment associated with chronic HFD exposure. Nutritional patterns emphasizing balanced macronutrient intake-such as the Mediterranean diet and DASH diet-have been consistently linked to reduced risks of cognitive decline and dementia (121).

The Mediterranean diet is characterized by high consumption of fruits, vegetables, whole grains, legumes, fish, nuts and olive oil, with moderate intake of dairy products and red wine. Epidemiological and interventional studies have demonstrated significant cognitive benefits associated with this dietary pattern (122). For instance, the large-scale PREDIMED RCT reported that older adults adhering to a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts exhibited substantial improvements in memory and executive function compared to those following a low-fat control diet (123). Similarly, the DASH diet-emphasizing fruits, vegetables, lean protein sources such as skinless poultry, fish and legumes, and low-fat dairy products while limiting saturated fat intake-has been shown to benefit cognitive function (108,124,125). Older adults adhering to the DASH diet demonstrate superior performance on executive function and memory tasks relative to control groups (108).

These neuroprotective effects are largely attributed to high intake of polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which enhance neuronal membrane fluidity, reduce neuroinflammation, promote neurogenesis and support synaptic plasticity (109,126-128). Observational studies have consistently linked greater omega-3 PUFA consumption, particularly from fatty fish and nuts, with improved cognitive outcomes and a reduced risk of dementia. These findings are corroborated by clinical trials demonstrating that omega-3 supplementation improves memory and executive performance in older adults (129-131). Likewise, monounsaturated fatty acids, such as oleic acid-abundant in olive oil-have shown cognitive benefits by reducing oxidative stress, improving brain insulin sensitivity and enhancing cerebrovascular function (123).

Meal timing also plays a pivotal role in metabolic regulation and cognitive health. Time-restricted eating, which confines caloric intake to defined daily windows, has been shown to restore circadian rhythmicity by normalizing clock gene expression [e.g., brain and muscle ARNT-like 1 (Bmal1)] and reducing hippocampal oxidative stress in HFD-fed models (132,133). Additionally, dietary supplementation with antioxidants-including vitamins E and C, and polyphenols, such as resveratrol, quercetin and curcumin-has demonstrated efficacy in attenuating oxidative stress, preserving mitochondrial function and improving cognitive outcomes. Resveratrol, in particular, enhances mitochondrial biogenesis, lowers oxidative burden and maintains synaptic integrity in

Table II. Nutritional and therapeutic strategies to combat cognitive decline.

Intervention type	Main intake/substances or strains	Key components and mechanisms	Cognitive improvement and research findings	(Refs.)
MIND diet	Leafy greens (e.g., spinach, kale) Berries (e.g., blueberries, strawberries) Nuts Fish Whole grains Poultry Legumes Olive oil	↑ Antioxidants (vitamins E, C, polyphenols, lavonoids) ↑ Omega-3 fatty acids ↑ Dietary fiber ↓ Inflammation Promotes antioxidant and anti-inflammatory protection of brain cells	↓ Alzheimer's disease risk (up to 53%) ↓ Cognitive decline rate (equivalent to being cognitively '7.5 years younger') ↑ Memory, executive function and language abilities	(22,107,108)
Mediterranean diet	Fresh fruits and vegetables Whole grains Fish and seafood Olive oil (main fat source) Nuts Moderate red wine Legumes	↑ Monounsaturated fatty acids (olive oil) ↑ Omega-3 fatty acids ↑ Antioxidants (vitamins E, C, polyphenols) ↓ Inflammation and oxidative stress Improves cerebrovascular health	↓ Mild cognitive impairment and dementia risk ↑ Memory and language function ↑ Brain vascular health ↓ Neuroinflammation and oxidative stress	(109,110)
Antidiabetic drugs	Metformin	Metformin: ↑ AMPK activity, improves energy metabolism, modulates gut microbiota, ↓ inflammation and oxidative stress	↓ Cognitive decline rate and significantly reduced dementia risk ↑ Memory and language functions	(111,112)
	Intranasal insulin	Intranasal insulin: ↑ Brain insulin receptor activation, improves neuronal glucose uptake and synaptic plasticity		(113,114)
Anti-inflammatory drugs	Various anti-inflammatory agents (research ongoing)	↓ Release of pro-inflammatory cytokines in the brain ↓ Oxidative stress and neuronal damage ↓ Neuroinflammation	↓ Rate of cognitive decline, especially in inflammation-related cognitive impairment Still under clinical research	(115,116)
Probiotics	*Lactobacillus rhamnosus*	Modulates gut microbiota balance ↓ Pro-inflammatory cytokines, ↓ neuroinflammation Influences neurotransmitters (dopamine, serotonin) and brain signaling	↓ Beta-amyloid deposition ↑ Spatial memory ↑ Attention and language learning abilities (clinical trials)	(93,117,118)
	Bifidobacterium longum	↑ Gut barrier function ↑ Short-chain fatty acid production, anti-inflammatory effects Regulates neuroendocrine and immune responses	↑ Cognitive function (especially combined with omega-3 supplementation) -↑ Mood and sleep quality, indirectly promoting cognitive health	(88,119,120)

AMPK, adenosine monophosphate-activated protein kinase; MIND diet, Mediterranean-DASH Intervention for Neurodegenerative Delay diet (a hybrid dietary pattern combining the Mediterranean and DASH diets, designed to promote brain health and delay cognitive decline).

HFD-exposed rodents, ultimately improving learning and memory performance (134). Similarly, curcumin has been shown to reduce lipid peroxidation, normalize antioxidant enzyme activity and mitigate memory deficits in diet-induced obesity models (135).

Importantly, dietary interventions achieve greater efficacy when combined with structured physical exercise. Evidence from both preclinical and clinical studies suggests that synergistic effects arise from this integration: While diet optimizes nutrient intake, reduces oxidative stress and restores metabolic balance, exercise further enhances neurotrophic support, insulin sensitivity and cerebral blood flow (136,137). For instance, overweight individuals adhering to Mediterranean or DASH dietary patterns alongside regular aerobic training exhibited more pronounced improvements in executive function and memory performance compared to those receiving either intervention alone (138).

Exercise interventions. Regular physical exercise represents a potent intervention to counteract cognitive decline associated with chronic HFD exposure, particularly in the context of HFD-induced insulin resistance (139,140).

In preclinical studies, voluntary aerobic exercise markedly increases BDNF expression and promotes hippocampal neurogenesis, thereby reversing HFD-induced deficits in memory performance (141). Exercise also upregulates other neurotrophic mediators, including nerve growth factor and insulin-like growth factor-1, which collectively enhance neuronal survival, dendritic branching and synaptogenesis (142). For instance, rats undergoing aerobic training after chronic HFD exposure exhibited increased expression of synaptic proteins, such as synaptophysin and PSD-95, correlating with improved spatial learning and memory performance (143).

These animal findings are mirrored in clinical studies. In older adults, aerobic exercise has been shown to increase hippocampal volume, elevate serum BDNF levels and enhance spatial memory, supporting the translational relevance of animal data (139). Furthermore, overweight or obese individuals engaging in structured aerobic training-particularly when combined with dietary modifications-exhibited significant improvements in executive function, processing speed and attentional control when compared to sedentary controls (144).

From a metabolic perspective, aerobic exercise improves systemic and cerebral glucose homeostasis by upregulating GLUT4 expression in skeletal muscle and brain tissues (145). In HFD-fed rodents, treadmill exercise restored hippocampal insulin signaling pathways, including IRS-1 phosphorylation and PI3K/Akt activity, thereby reversing HFD-induced cognitive decline (146). Exercise also exerts potent anti-inflammatory effects in the CNS. It reduces the expression of pro-inflammatory cytokines such as IL-1β and TNF-α, and attenuates microglial activation within the hippocampus and cortex. For instance, in AD models, treadmill training ameliorated memory deficits by downregulating IL-1β and phosphodiesterase-5 expression and restoring phosphorylated cAMP response element-binding protein signaling (140,147). Similarly, voluntary wheel running reversed HFD-induced microglial activation and rescued memory consolidation processes (148). In addition, regular physical activity combats oxidative stress by enhancing the activity of endogenous antioxidant enzymes-including SOD, catalase and glutathione peroxidase-while preserving mitochondrial integrity and reducing ROS accumulation in brain tissue (149).

Microbiota-targeted interventions. Microbiota-targeted therapies-including probiotics, prebiotics and next-generation bacterial strains-have emerged as promising strategies to modulate the gut-brain axis and ameliorate cognitive impairment associated with HFD exposure.

Probiotics, defined as live beneficial microorganisms (e.g., *Lactobacillus* and *Bifidobacterium* species), and prebiotics, which are non-digestible fibers such as inulin and fructooligosaccharides (FOS) that selectively promote the growth of commensal microbes, have demonstrated consistent neuroprotective effects in preclinical models. For example, oral administration of *Lactobacillus plantarum* in HFD-fed mice restored gut microbial diversity, reduced systemic and hippocampal inflammation, upregulated synaptic proteins such as synaptophysin and PSD-95, and reversed deficits in learning and memory (117). Similarly, supplementation with Bifidobacterium-containing probiotic formulations normalized microbial composition, enhanced hippocampal BDNF expression and alleviated HFD-induced spatial memory deficits and anxiety-like behaviors (150).

Clinical trials further support the cognitive benefits of microbiota modulation. In an RCT, elderly individuals with MCI receiving a multispecies probiotic mixture (*L. acidophilus, L. casei, B. bifidum*) exhibited significant improvements in cognitive performance, reduced circulating proinflammatory cytokines and enhanced antioxidant enzyme activity compared to placebo (151). Similarly, prebiotic interventions with inulin or FOS have been shown to increase the abundance of SCFA-producing bacteria, strengthen intestinal barrier integrity, suppress systemic inflammation and subsequently improve cognitive outcomes in populations with metabolic syndrome or cognitive decline.

Pharmacological interventions. Pharmacological interventions targeting HFD-induced cognitive impairment primarily aim to modulate neuroinflammation, oxidative stress, insulin resistance, and disrupted neuroplasticity signaling. A range of agents-including anti-inflammatory drugs, insulin sensitizers, and neurotrophic modulators-have demonstrated cognitive benefits in both preclinical and clinical studies.

Anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors have shown promise in preclinical models. For instance, celecoxib effectively attenuates microglial activation, reduces pro-inflammatory cytokines including IL-1β and TNF-α, and improves hippocampal-dependent memory performance in HFD-fed rodents (102,152). Minocycline, a tetracycline derivative with central anti-inflammatory and neuroprotective properties, similarly reduces hippocampal inflammation, preserves synaptic architecture, and enhances spatial learning and memory (153,154).

Insulin sensitizers, including metformin and thiazolidinediones (e.g., rosiglitazone, pioglitazone), exert neuroprotective effects by restoring central insulin signaling, reducing neuroinflammation and mitigating oxidative stress (155). Metformin improves hippocampal IRS phosphorylation and downstream

PI3K/Akt signaling, enhancing synaptic plasticity and memory function in metabolic dysfunction models (156,157). Peroxisome proliferator-activated receptor γ agonists further promote adult neurogenesis and synaptic remodeling, contributing to cognitive improvements in HFD-fed animals (158). In addition, glucagon-like peptide-1 receptor agonists (e.g., liraglutide, exenatide) represent a novel class of therapeutics with dual metabolic and neuroprotective actions (159). These agents enhance insulin signaling in the brain, reduce hippocampal inflammation and oxidative stress, stimulate neurogenesis, and improve learning and memory performance in HFD-exposed rodents. Clinical trials in obese and diabetic patients have also demonstrated cognitive benefits, suggesting translational potential for diet-associated neurocognitive disorders (160,161). Neuroplasticity-targeted therapies offer additional avenues. Pharmacological agents that enhance BDNF signaling-such as selective serotonin reuptake inhibitors (SSRIs), PDE inhibitors and histone deacetylase inhibitors-have been shown to restore synaptic plasticity and cognitive function. For instance, fluoxetine, a commonly used SSRI, upregulates hippocampal BDNF expression and reverses cognitive deficits in HFD-fed rodents (162,163).

5. Limitations and future perspectives

Limitations. Despite substantial evidence linking chronic HFD intake to cognitive impairment, several limitations remain in current research, which hinder the establishment of definitive causal relationships (26,55).

A major limitation lies in the predominant reliance on observational epidemiological studies and preclinical animal models. While these approaches have elucidated critical mechanistic insights, their applicability to human physiology remains limited due to species-specific metabolic, neuroimmune and behavioral differences (164). Notably, numerous rodent studies utilize acute or supra-physiological doses of dietary fat, which fail to recapitulate the chronic, moderate exposures and complex eating patterns typical of human dietary habits-including meal timing, social eating behaviors and food processing. Furthermore, substantial heterogeneity across studies-including variations in dietary fat composition (e.g., saturated vs. unsaturated), intervention durations, cognitive assessment tools and demographic characteristics complicates cross-study comparisons and undermines the generalizability of findings (165).

The bidirectional relationship between metabolic dysfunction and gut microbiota dysbiosis poses another unresolved challenge. It remains elusive whether microbial alterations serve as a causal antecedent or secondary consequence of HFD-induced metabolic changes (16). Similarly, while microglial activation is frequently implicated in cognitive decline, conflicting data persist. For instance, inhibition of microglial activation via Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) deletion has been shown to mitigate cognitive deficits in HFD-fed mice, suggesting a pathogenic role (166). Conversely, other models of neuroinflammation do not consistently produce cognitive impairments, indicating that additional mechanisms-such as BBB disruption, mitochondrial dysfunction and oxidative stress-likely contribute to cognitive decline in a context-dependent manner (167).

Genetic and epigenetic heterogeneity in human populations adds further complexity. Polymorphisms in genes such as TLR4, or variations in neuroimmune and metabolic regulatory pathways, may modulate individual vulnerability to HFD-related cognitive impairment and influence response to microbiota-targeted interventions (168). Furthermore, neuromodulatory strategies-such as vagus nerve stimulation-while efficacious in preclinical settings, have shown inconsistent cognitive benefits in human trials, underscoring the challenges of translational fidelity (169).

Future perspectives. Given the multifaceted and interconnected mechanisms by which chronic HFD contributes to cognitive decline, future research must adopt a more integrative and mechanistically grounded approach to uncover effective preventive and therapeutic strategies. While preclinical studies have yielded extensive insights, their translational relevance remains limited (121,170,171). Robust clinical validation through well-powered, longitudinal RCTs is urgently needed to establish causal links between dietary fat subtypes and cognitive outcomes, particularly across genetically and metabolically diverse populations. Such trials should incorporate long-term exposure assessments and harmonized cognitive endpoints to improve comparability and external validity (172).

At the mechanistic level, the field is poised to benefit from emerging tools such as single-cell multi-omics, spatial transcriptomics and metabolic flux analysis. These approaches allow for high-resolution dissection of how HFD alters brain homeostasis at cellular and molecular levels-uncovering how neuronal, glial, immune and vascular cell types interact in spatially distinct and temporally dynamic ways (173). Integrating these datasets may clarify unresolved questions, such as whether microbiota dysbiosis precedes metabolic dysfunction or merely reflects it, and how the gut-brain axis mediates diet-induced neuroinflammation and synaptic degeneration.

Importantly, the pronounced heterogeneity in individual responses to HFD highlights the necessity of personalized interventions. Moving beyond 'one-size-fits-all' recommendations, future strategies should be tailored to individual characteristics such as APOE genotype, insulin sensitivity, microbiome enterotype and sex-specific vulnerabilities. Precision nutrition-guided by validated biomarkers such as plasma ceramides or microbial metabolites-holds particular promise for early risk stratification and targeted intervention (174). Furthermore, there is growing recognition that single-modality interventions are unlikely to fully reverse or prevent HFD-induced cognitive dysfunction. Future studies should prioritize multimodal strategies that combine dietary modification, structured physical activity, pharmacologic agents targeting neuroinflammation or insulin resistance, microbiota-targeted therapies (e.g., *Akkermansia muciniphila* supplementation) and neuromodulation techniques (e.g., transcranial direct current stimulation). Such integrative approaches are better positioned to tackle the complex neurobiological cascades underlying metabolic-cognitive deterioration.

6. Conclusions

HFD consumption accelerates cognitive decline through converging mechanisms such as neuroinflammation, oxidative stress, insulin resistance, gut dysbiosis and synaptic dysfunction. These effects are further modulated by genetic

and demographic factors, including APOE genotype, age and sex. Current evidence supports the efficacy of integrative interventions-such as Mediterranean-style diets, physical exercise, metabolic modulators and microbiota-targeted therapies-in mitigating HFD-induced neurodegeneration. Future research should focus on validating these strategies in diverse populations via large-scale trials and leveraging multi-omics technologies to guide precision prevention.

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Availability of data and materials

Not applicable.

Authors' contributions

MY was involved in the conceptualization of the study, drafted the manuscript, writing-review & editing and visualization. FW contributed to the conceptualization of the study and writing-review & editing. FX, XH and HW were responsible for writing-review & editing. MY and FW performed the literature search and selection. LZ and HZ contributed to writing-review & editing acquired funding and supervised the study. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Roberts R and Knopman DS: Classification and epidemiology of MCI. Clin Geriatr Med 29: 753-772, 2013.
2. Wimo A, Guerchet M, Ali GC, Wu YT, Prina AM, Winblad B, Jönsson L, Liu Z and Prince M: The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimers Dement 13: 1-7, 2017.
3. Yi W, Chen F, Yuan M, Wang C, Wang S, Wen J, Zou Q, Pu Y and Cai Z: High-fat diet induces cognitive impairment through repression of SIRT1/AMPK-mediated autophagy. Exp Neurol 371: 114591, 2024.
4. GBD 2019 Dementia Forecasting Collaborators: Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the global burden of disease study 2019. Lancet Public Health 7: e105-e125, 2022.
5. Frazier K, Kambal A, Zale EA, Pierre JF, Hubert N, Miyoshi S, Miyoshi J, Ringus DL, Harris D, Yang K, *et al*: High-fat diet disrupts REG3γ and gut microbial rhythms promoting metabolic dysfunction. Cell Host Microbe 30: 809-823, 2022.
6. Wang X, Song R, Clinchamps M and Dutheil F: New insights into high-fat diet with chronic diseases. Nutrients 15: 4031, 2023.
7. Jones-Muhammad M and Warrington JP: When high-fat diet plus hypertension does not equal vascular dysfunction. Am J Physiol Heart Circ Physiol 321: H128-H130, 2021.
8. Cao GY, Li M, Han L, Tayie F, Yao SS, Huang Z, Ai P, Liu YZ, Hu YH and Xu B: Dietary fat intake and cognitive function among older populations: A systematic review and meta-analysis. J Prev Alzheimers Dis 6: 204-211, 2019.
9. Song M, Bai Y and Song F: High-fat diet and neuroinflammation: The role of mitochondria. Pharmacol Res 212: 107615, 2025.
10. Roberts RO, Roberts LA, Geda YE, Cha RH, Pankratz VS, O'Connor HM, Knopman DS and Petersen RC: Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia. J Alzheimers Dis 32: 329-339, 2012.
11. Valentin-Escalera J, Leclerc M and Calon F: High-Fat diets in animal models of Alzheimer's disease: How can eating too much fat increase Alzheimer's disease Risk? J Alzheimers Dis 97: 977-1005, 2024.
12. Hoscheidt S, Sanderlin AH, Baker LD, Jung Y, Lockhart S, Kellar D, Whitlow CT, Hanson AJ, Friedman S, Register T, *et al*: Mediterranean and western diet effects on Alzheimer's disease biomarkers, cerebral perfusion, and cognition in mid-life: A randomized trial. Alzheimers Dement 18: 457-468, 2022.
13. Yanai H: Effects of N-3 polyunsaturated fatty acids on dementia. J Clin Med Res 9: 1-9, 2017.
14. Román GC, Jackson RE, Gadhia R, Román AN and Reis J: Mediterranean diet: The role of long-chain ω-3 fatty acids in fish; polyphenols in fruits, vegetables, cereals, coffee, tea, cacao and wine; probiotics and vitamins in prevention of stroke, age-related cognitive decline, and Alzheimer disease. Rev Neurol (Paris) 175: 724-741, 2019.
15. Di Meco A and Praticò D: Early-life exposure to high-fat diet influences brain health in aging mice. Aging Cell 18: e13040, 2019.
16. de Paula GC, Brunetta HS, Engel DF, Gaspar JM, Velloso LA, Engblom D, de Oliveira J and de Bem AF: Hippocampal function is impaired by a short-term high-fat diet in mice: Increased blood-brain barrier permeability and neuroinflammation as triggering events. Front Neurosci 15: 734158, 2021.
17. Xiong J, Deng I, Kelliny S, Lin L, Bobrovskaya L and Zhou X: Long term high fat diet induces metabolic disorders and aggravates behavioral disorders and cognitive deficits in MAPT P301L transgenic mice. Metab Brain Dis 37: 1941-1957, 2022.
18. Boitard C, Cavaroc A, Sauvant J, Aubert A, Castanon N, Layé S and Ferreira G: Impairment of hippocampal-dependent memory induced by juvenile high-fat diet intake is associated with enhanced hippocampal inflammation in rats. Brain Behav Immun 40: 9-17, 2014.
19. Sanguinetti E, Guzzardi MA, Panetta D, Tripodi M, De Sena V, Quaglierini M, Burchielli S, Salvadori PA and Iozzo P: Combined effect of fatty diet and cognitive decline on brain metabolism, food intake, body weight, and counteraction by intranasal insulin therapy in 3xTg mice. Front Cell Neurosci 13: 188, 2019.
20. Attuquayefio T, Stevenson RJ, Boakes RA, Oaten MJ, Yeomans MR, Mahmut M and Francis HM: A high-fat high-sugar diet predicts poorer hippocampal-related memory and a reduced ability to suppress wanting under satiety. J Exp Psychol Anim Learn Cogn 42: 415-428, 2016.
21. Holloway CJ, Cochlin LE, Emmanuel Y, Murray A, Codreanu I, Edwards LM, Szmigielski C, Tyler DJ, Knight NS, Saxby BK, *et al*: A high-fat diet impairs cardiac high-energy phosphate metabolism and cognitive function in healthy human subjects. Am J Clin Nutr 93: 748-755, 2011.
22. Morris MC, Tangney CC, Wang Y, Sacks FM, Barnes LL, Bennett DA and Aggarwal NT: MIND diet slows cognitive decline with aging. Alzheimers Dement 11: 1015-1022, 2015.
23. Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J and Wilson RS: Dietary fats and the risk of incident Alzheimer disease. Arch Neurol 60: 194-200, 2003.
24. Morris MC, Evans DA, Bienias JL, Tangney CC and Wilson RS: Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 62: 1573-1579, 2004.

25. Galloway S, Takechi R, Nesbit M, Pallebage-Gamarallage MM, Lam V and Mamo JCL: The differential effects of fatty acids on enterocytic abundance of amyloid-beta. Lipids Health Dis 18: 209, 2019.
26. Evans AK, Saw NL, Woods CE, Vidano LM, Blumenfeld SE, Lam RK, Chu EK, Reading C and Shamloo M: Impact of high-fat diet on cognitive behavior and central and systemic inflammation with aging and sex differences in mice. Brain Behav Immun 118: 334-354, 2024.
27. Boraxbekk CJ, Stomby A, Ryberg M, Lindahl B, Larsson C, Nyberg L and Olsson T: diet-induced weight loss alters functional brain responses during an episodic memory task. Obes Facts 8: 261-272, 2015.
28. Yao X, Yang C, Jia X, Yu Z, Wang C, Zhao J, Chen Y, Xie B, Zhuang H, Sun C, *et al*: High-fat diet consumption promotes adolescent neurobehavioral abnormalities and hippocampal structural alterations via microglial overactivation accompanied by an elevated serum free fatty acid concentration. Brain Behav Immun 119: 236-250, 2024.
29. Ruan Y, Tang J, Guo X, Li K and Li D: Dietary fat intake and risk of Alzheimer's disease and dementia: A meta-analysis of cohort studies. Curr Alzheimer Res 15: 869-876, 2018.
30. You SC, Geschwind MD, Sha SJ, Apple A, Satris G, Wood KA, Johnson ET, Gooblar J, Feuerstein JS, Finkbeiner S, *et al*: Executive functions in premanifest Huntington's disease. Mov Disord 29: 405-409, 2014.
31. Klaus K, Vaht M, Pennington K and Harro J: Interactive effects of DRD2 rs6277 polymorphism, environment and sex on impulsivity in a population-representative study. Behav Brain Res 403: 113131, 2021.
32. Nieto-Estévez V, Defterali Ç and Vicario C: Distinct effects of BDNF and NT-3 on the dendrites and presynaptic boutons of developing olfactory bulb GABAergic interneurons in vitro. Cell Mol Neurobiol 42: 1399-1417, 2022.
33. McLean FH, Grant C, Morris AC, Horgan GW, Polanski AJ, Allan K, Campbell FM, Langston RF and Williams LM: Rapid and reversible impairment of episodic memory by a high-fat diet in mice. Sci Rep 8: 11976, 2018.
34. Zhang Y, Peng Y, Deng W, Xiang Q, Zhang W and Liu M: Association between dietary inflammatory index and cognitive impairment among American elderly: A cross-sectional study. Front Aging Neurosci 16: 1371873, 2024.
35. Valcarcel-Ares MN, Tucsek Z, Kiss T, Giles CB, Tarantini S, Yabluchanskiy A, Balasubramanian P, Gautam T, Galvan V, Ballabh P, *et al*: Obesity in aging exacerbates neuroinflammation, dysregulating synaptic function-related genes and altering eicosanoid synthesis in the mouse hippocampus: Potential role in impaired synaptic plasticity and cognitive decline. J Gerontol A Biol Sci Med Sci 74: 290-298, 2019.
36. Kothari V, Luo Y, Tornabene T, O'Neill AM, Greene MW, Geetha T and Babu JR: High fat diet induces brain insulin resistance and cognitive impairment in mice. Biochim Biophys Acta Mol Basis Dis 1863: 499-508, 2017.
37. Julien C, Tremblay C, Phivilay A, Berthiaume L, Emond V, Julien P and Calon F: High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. Neurobiol Aging 31: 1516-1531, 2010.
38. Henn RE, Elzinga SE, Glass E, Parent R, Guo K, Allouch AM, Mendelson FE, Hayes J, Webber-Davis I, Murphy GG, *et al*: Obesity-induced neuroinflammation and cognitive impairment in young adult versus middle-aged mice. Immun Ageing 19: 67, 2022.
39. Morris MC, Evans DA, Tangney CC, Bienias JL, Schneider JA, Wilson RS and Scherr PA: Dietary copper and high saturated and trans fat intakes associated with cognitive decline. Arch Neurol 63: 1085-1088, 2006.
40. Chatterjee S, Peters SA, Woodward M, Arango SM, Batty GD, Beckett N, Beiser A, Borenstein AR, Crane PK, Haan M, *et al*: Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. Diabetes Care 39: 300-307, 2016.
41. Sanz-Martos AB, Roca M, Plaza A, Merino B, Ruiz-Gayo M and Olmo ND: Long-term saturated fat-enriched diets impair hippocampal learning and memory processes in a sex-dependent manner. Neuropharmacology 259: 110108, 2024.
42. Muscat SM, Butler MJ, Mackey-Alfonso SE and Barrientos RM: Young adult and aged female rats are vulnerable to amygdala-dependent, but not hippocampus-dependent, memory impairment following short-term high-fat diet. Brain Res Bull 195: 145-156, 2023.
43. Armstrong NM, An Y, Beason-Held L, Doshi J, Erus G, Ferrucci L, Davatzikos C and Resnick SM: Predictors of neurodegeneration differ between cognitively normal and subsequently impaired older adults. Neurobiol Aging 75: 178-186, 2019.
44. Laitinen MH, Ngandu T, Rovio S, Helkala EL, Uusitalo U, Viitanen M, Nissinen A, Tuomilehto J, Soininen H and Kivipelto M: Fat intake at midlife and risk of dementia and Alzheimer's disease: A population-based study. Dement Geriatr Cogn Disord 22 (2006).
45. Kleinridders A, Ferris HA, Cai W and Kahn CR: Insulin action in brain regulates systemic metabolism and brain function. Diabetes 63: 2232-2243, 2014.
46. Martiskainen H, Helisalmi S, Viswanathan J, Kurki M, Hall A, Herukka SK, Sarajärvi T, Natunen T, Kurkinen KM, Huovinen J, *et al*: Effects of Alzheimer's disease-associated risk loci on cerebrospinal fluid biomarkers and disease progression: A polygenic risk score approach. J Alzheimers Dis 43: 565-573, 2015.
47. Fan L, Borenstein AR, Wang S, Nho K, Zhu X, Wen W, Huang X, Mortimer JA, Shrubsole MJ and Dai Q; Alzheimer's Disease Neuroimaging Initiative: Associations of circulating saturated long-chain fatty acids with risk of mild cognitive impairment and Alzheimer's disease in the Alzheimer's disease neuroimaging initiative (ADNI) cohort. EBioMedicine 97: 104818, 2023.
48. Arnold SE, Lucki I, Brookshire BR, Carlson GC, Browne CA, Kazi H, Bang S, Choi BR, Chen Y, McMullen MF and Kim SF: High fat diet produces brain insulin resistance, synaptodendritic abnormalities and altered behavior in mice. Neurobiol Dis 67: 79-87, 2014.
49. Li C, Shi L, Wang Y, Peng C, Wu L, Zhang Y and Du Z: High-fat diet exacerbates lead-induced blood-brain barrier disruption by disrupting tight junction integrity. Environ Toxicol 36: 1412-1421, 2021.
50. Meza-Miranda ER, Camargo A, Rangel-Zuñiga OA, Delgado-Lista J, Garcia-Rios A, Perez-Martinez P, Tasset-Cuevas I, Tunez I, Tinahones FJ, Perez-Jimenez F and Lopez-Miranda J: Postprandial oxidative stress is modulated by dietary fat in adipose tissue from elderly people. Age (Dordr) 36: 507-517, 2014.
51. Valdearcos M, Douglass JD, Robblee MM, Dorfman MD, Stifler DR, Bennett ML, Gerritse I, Fasnacht R, Barres BA, Thaler JP and Koliwad SK: Microglial inflammatory signaling orchestrates the hypothalamic immune response to dietary excess and mediates obesity susceptibility. Cell Metab 26: 185-197, 2017.
52. Yanguas-Casás N, Crespo-Castrillo A, de Ceballos ML, Chowen JA, Azcoitia I, Arevalo MA and Garcia-Segura LM: Sex differences in the phagocytic and migratory activity of microglia and their impairment by palmitic acid. Glia 66: 522-537, 2018.
53. Block ML, Zecca L and Hong JS: Microglia-mediated neurotoxicity: Uncovering the molecular mechanisms. Nat Rev Neurosci 8: 57-69, 2007.
54. Ransohoff RM: How neuroinflammation contributes to neurodegeneration. Science 353: 777-783, 2016.
55. Liang Z, Gong X, Ye R, Zhao Y, Yu J, Zhao Y and Bao J: Long-Term high-fat diet consumption induces cognitive decline accompanied by tau hyper-phosphorylation and microglial activation in aging. Nutrients 15: 250, 2023.
56. Kipnis J, Cohen H, Cardon M, Ziv Y and Schwartz M: T cell deficiency leads to cognitive dysfunction: Implications for therapeutic vaccination for schizophrenia and other psychiatric conditions. Proc Natl Acad Sci USA 101: 8180-8185, 2004.
57. Yirmiya R and Goshen I: Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav Immun 25: 181-213, 2011.
58. Toyama K, Koibuchi N, Hasegawa Y, Uekawa K, Yasuda O, Sueta D, Nakagawa T, Ma M, Kusaka H, Lin B, *et al*: ASK1 is involved in cognitive impairment caused by long-term high-fat diet feeding in mice. Sci Rep 5: 10844, 2015.
59. Sobesky JL, Barrientos RM, De May HS, Thompson BM, Weber MD, Watkins LR and Maier SF: High-fat diet consumption disrupts memory and primes elevations in hippocampal IL-1β, an effect that can be prevented with dietary reversal or IL-1 receptor antagonism. Brain Behav Immun 42: 22-32, 2014.
60. Spencer SJ, Korosi A, Layé S, Shukitt-Hale B and Barrientos RM: Food for thought: how nutrition impacts cognition and emotion. NPJ Sci Food 1: 7, 2017.
61. Crupi R, Marino A and Cuzzocrea S: n-3 fatty acids: Role in neurogenesis and neuroplasticity. Curr Med Chem 20: 2953-2963, 2013.

62. Butler MJ, Mackey-Alfonso SE, Massa N, Baskin KK and Barrientos RM: Dietary fatty acids differentially impact phagocytosis, inflammatory gene expression, and mitochondrial respiration in microglial and neuronal cell models. Front Cell Neurosci 17: 1227241, 2023.
63. Alkan I, Altunkaynak BZ, Gültekin Gİ and Bayçu C: Hippocampal neural cell loss in high-fat diet-induced obese rats-exploring the protein networks, ultrastructure, biochemical and bioinformatical markers. J Chem Neuroanat 114: 101947, 2021.
64. Lin MT and Beal MF: Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature 443: 787-795, 2006.
65. Kelty TJ, Taylor CL, Wieschhaus NE, Thorne PK, Amin AR, Mueller CM, Olver TD, Tharp DL, Emter CA, Caulk AW and Rector RS: Western diet-induced obesity results in brain mitochondrial dysfunction in female Ossabaw swine. Front Mol Neurosci 16: 1320879, 2023.
66. Grel H, Woznica D, Ratajczak K, Kalwarczyk E, Anchimowicz J, Switlik W, Olejnik P, Zielonka P, Stobiecka M and Jakiela S: Mitochondrial dynamics in neurodegenerative diseases: Unraveling the role of fusion and fission processes. Int J Mol Sci 24: 13033, 2023.
67. Madreiter-Sokolowski CT, Hiden U, Krstic J, Panzitt K, Wagner M, Enzinger C, Khalil M, Abdellatif M, Malle E, Madl T, *et al*: Targeting organ-specific mitochondrial dysfunction to improve biological aging. Pharmacol Ther 262: 108710, 2024.
68. Haack F, Lemcke H, Ewald R, Rharass T and Uhrmacher AM: Spatio-temporal model of endogenous ROS and raft-dependent WNT/beta-catenin signaling driving cell fate commitment in human neural progenitor cells. PLoS Comput Biol 11: e1004106, 2015.
69. Ghosh P, Fontanella RA, Scisciola L, Pesapane A, Taktaz F, Franzese M, Puocci A, Ceriello A, Prattichizzo F, Rizzo MR, *et al*: Targeting redox imbalance in neurodegeneration: Characterizing the role of GLP-1 receptor agonists. Theranostics 13: 4872-4884, 2023.
70. Bórquez DA, Urrutia PJ, Wilson C, van Zundert B, Núñez MT and González-Billault C: Dissecting the role of redox signaling in neuronal development. J Neurochem 137: 506-517, 2016.
71. Morrison CD, Pistell PJ, Ingram DK, Johnson WD, Liu Y, Fernandez-Kim SO, White CL and Purpera MN: High fat diet increases hippocampal oxidative stress and cognitive impairment in aged mice: Implications for decreased Nrf2 signaling. J Neurochem 114: 1581-1589, 2010.
72. Iqbal G and Ahmed T: Co-exposure of metals and high fat diet causes aging like neuropathological changes in non-aged mice brain. Brain Res Bull 147: 148-158, 2019.
73. Liu Y, Fu X, Lan N, Li S, Zhang J, Wang S, Li C, Shang Y, Huang T and Zhang L: Luteolin protects against high fat diet-induced cognitive deficits in obesity mice. Behav Brain Res 267: 178-188, 2014.
74. Könner AC, Janoschek R, Plum L, Jordan SD, Rother E, Ma X, Xu C, Enriori P, Hampel B, Barsh GS, *et al*: Insulin action in AgRP-expressing neurons is required for suppression of hepatic glucose production. Cell Metab 5: 438-449, 2007.
75. Huang CC, Lee CC and Hsu KS: An investigation into signal transduction mechanisms involved in insulin-induced long-term depression in the CA1 region of the hippocampus. J Neurochem 89: 217-231, 2004.
76. Pearson-Leary J and McNay EC: Novel roles for the insulin-regulated glucose transporter-4 in hippocampally dependent memory. J Neurosci 36: 11851-11864, 2016.
77. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, Xu XJ, Wands JR and de la Monte SM: Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease-is this type 3 diabetes? J Alzheimers Dis 7: 63-80, 2005.
78. Denver P, Gault VA and McClean PL: Sustained high-fat diet modulates inflammation, insulin signalling and cognition in mice and a modified xenin peptide ameliorates neuropathology in a chronic high-fat model. Diabetes Obes Metab 20: 1166-1175, 2018
79. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, Koenig AM, Wang HY, Ahima RS, Craft S, Gandy S, Buettner C, Stoeckel LE, *et al*: Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. Nat Rev Neurol 14: 168-181, 2018.
80. Ehtewish H, Arredouani A and El-Agnaf O: Diagnostic, prognostic, and mechanistic biomarkers of diabetes mellitus-associated cognitive decline. Int J Mol Sci 23: 6144, 2022.
81. Zhang H, Liang JL, Wu QY, Li JX, Liu Y, Wu LW, Huang JL, Wu XW, Wang MH and Chen N: Swimming suppresses cognitive decline of HFD-induced obese mice through reversing hippocampal inflammation, insulin resistance, and BDNF level. Nutrients 14: 2432, 2022.
82. Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, Silverman MA, Kazi H, Melo HM, McClean P, *et al*: An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Aβ oligomers. J Clin Invest 122: 1339-1353, 2012.
83. Socała K, Doboszewska U, Szopa A, Serefko A, Włodarczyk M, Zielińska A, Poleszak E, Fichna J and Wlaź P: The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res 172: 105840, 2021.
84. Sharon G, Sampson TR, Geschwind DH and Mazmanian SK: The central nervous system and the gut microbiome. Cell 167: 915-932, 2016.
85. Carabotti M, Scirocco A, Maselli MA and Severi C: The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28: 203-209, 2015.
86. Fasina OB, Wang J, Mo J, Osada H, Ohno H, Pan W, Xiang L and Qi J: Gastrodin from gastrodia elata enhances cognitive function and neuroprotection of AD mice via the regulation of gut microbiota composition and inhibition of neuron inflammation. Front Pharmacol 13: 814271, 2022.
87. Schneeberger M, Everard A, Gómez-Valadés AG, Matamoros S, Ramírez S, Delzenne NM, Gomis R, Claret M and Cani PD: Akkermansia muciniphila inversely correlates with the onset of inflammation, altered adipose tissue metabolism and metabolic disorders during obesity in mice. Sci Rep 5: 16643, 2015.
88. Zhang B, Qiu J, Qu Z, Xiao R, Wang L, Tian P, Zhang H, Chen W and Wang G: Bifidobacterium adolescentis FJSSZ23M10 modulates gut microbiota and metabolism to alleviate obesity through strain-specific genomic features. Food Funct 16: 2415-2431, 2025.
89. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R and Gordon JI: The effect of diet on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic mice. Sci Transl Med 1: 6ra14, 2009.
90. Wan Y, Wang F, Yuan J, Li J, Jiang D, Zhang J, Li H, Wang R, Tang J, Huang T, *et al*: Effects of dietary fat on gut microbiota and faecal metabolites, and their relationship with cardiometabolic risk factors: A 6-month randomised controlled-feeding trial. Gut 68: 1417-1429, 2019.
91. Bruce-Keller AJ, Salbaum JM, Luo M, Blanchard E IV, Taylor CM, Welsh DA and Berthoud HR: Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. Biol Psychiatry 77: 607-615, 2015.
92. Zheng M, Ye H, Yang X, Shen L, Dang X, Liu X, Gong Y, Wu Q, Wang L, Ge X, *et al*: Probiotic Clostridium butyricum ameliorates cognitive impairment in obesity via the microbiota-gut-brain axis. Brain Behav Immun 115: 565-587, 2024.
93. Krüger JF, Hillesheim E, Pereira ACSN, Camargo CQ and Rabito EI: Probiotics for dementia: A systematic review and meta-analysis of randomized controlled trials. Nutr Rev 79: 160-170, 2021.
94. Fung TC, Olson CA and Hsiao EY: Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci 20: 145-155, , 2017.
95. Visekruna A and Luu M: The role of short-chain fatty acids and bile acids in intestinal and liver function, inflammation, and carcinogenesis. Front Cell Dev Biol 9: 703218, 2021.
96. Lin H, An Y, Hao F, Wang Y and Tang H: Correlations of fecal metabonomic and microbiomic changes induced by high-fat diet in the pre-obesity state. Sci Rep 6: 21618, 2016.
97. Koh A, De Vadder F, Kovatcheva-Datchary P and Bäckhed F: From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. Cell 165: 1332-1345, 2016.
98. Stilling RM, van de Wouw M, Clarke G, Stanton C, Dinan TG and Cryan JF: The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis? Neurochem Int 99: 110-132, 2016.
99. Stephenson J, Nutma E, van der Valk P and Amor S: Inflammation in CNS neurodegenerative diseases. Immunology 154: 204-219, 2018.
100. Hargrave SL, Davidson TL, Zheng W and Kinzig KP: Western diets induce blood-brain barrier leakage and alter spatial strategies in rats. Behav Neurosci 130: 123-135, 2016.

101. Takechi R, Galloway S, Pallebage-Gamarallage MM, Lam V, Dhaliwal SS and Mamo JC: Probucol prevents blood-brain barrier dysfunction in wild-type mice induced by saturated fat or cholesterol feeding. Clin Exp Pharmacol Physiol 40: 45-52, 2013.
102. Tan BL and Norhaizan ME: Effect of high-fat diets on oxidative stress, cellular inflammatory response and cognitive function. Nutrients 11: 2579, 2019.
103. Heyward FD, Walton RG, Carle MS, Coleman MA, Garvey WT and Sweatt JD: Adult mice maintained on a high-fat diet exhibit object location memory deficits and reduced hippocampal SIRT1 gene expression. Neurobiol Learn Mem 98: 25-32, 2012.
104. Finnerup NB, Kuner R and Jensen TS: Neuropathic pain: From mechanisms to treatment. Physiol Rev 101: 259-301, 2021.
105. Hardingham GE and Bading H: Synaptic versus extrasynaptic NMDA receptor signalling: Implications for neurodegenerative disorders. Nat Rev Neurosci 11: 682-696, 2010.
106. Martinelli I, Tayebati SK, Roy P, Di Bonaventura MV, Moruzzi M, Cifani C, Amenta F and Tomassoni D: Obesity-Related brain cholinergic system impairment in high-fat-diet-fed rats. Nutrients 14: 1243, 2022.
107. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA and Aggarwal NT: MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 11: 1007-1014, 2015.
108. Barnes LL, Dhana K, Liu X, Carey VJ, Ventrelle J, Johnson K, Hollings CS, Bishop L, Laranjo N, Stubbs BJ, *et al*: Trial of the MIND diet for prevention of cognitive decline in older persons. N Engl J Med 389: 602-611, 2023.
109. Franco GA, Interdonato L, Cordaro M, Cuzzocrea S and Di Paola R: Bioactive compounds of the mediterranean diet as nutritional support to fight neurodegenerative disease. Int J Mol Sci 24: 7318, 2023.
110. Martínez-Lapiscina EH, Clavero P, Toledo E, Estruch R, Salas-Salvadó J, San Julián B, Sanchez-Tainta A, Ros E, Valls-Pedret C and Martinez-Gonzalez MÁ: Mediterranean diet improves cognition: The PREDIMED-NAVARRA randomised trial. J Neurol Neurosurg Psychiatry 84: 1318-1325, 2013.
111. Ng TP, Feng L, Yap KB, Lee TS, Tan CH and Winblad B: Long-term metformin usage and cognitive function among older adults with diabetes. J Alzheimers Dis 41: 61-68, 2014.
112. Zhu X, Shen J, Feng S, Huang C, Wang H, Huo F and Liu H: Akkermansia muciniphila, which is enriched in the gut microbiota by metformin, improves cognitive function in aged mice by reducing the proinflammatory cytokine interleukin-6. Microbiome 11: 120, 2023.
113. Lochhead JJ, Kellohen KL, Ronaldson PT and Davis TP: Distribution of insulin in trigeminal nerve and brain after intranasal administration. Sci Rep 9: 2621, 2019.
114. Stranahan AM, Norman ED, Lee K, Cutler RG, Telljohann RS, Egan JM and Mattson MP: Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. Hippocampus 18: 1085-1088, 2008.
115. Kaelber S, Pantcheva P and Borlongan CV: Drug- and cell-based therapies for targeting neuroinflammation in traumatic brain injury. Neural Regen Res 11: 1575-1576, 2016.
116. Fielder E, Tweedy C, Wilson C, Oakley F, LeBeau FEN, Passos JF, Mann DA, von Zglinicki T and Jurk D: Anti-inflammatory treatment rescues memory deficits during aging in nfkb1-/- mice. Aging Cell 19: e13188, 2020.
117. Wang QJ, Shen YE, Wang X, Fu S, Zhang X, Zhang YN and Wang RT: Concomitant memantine and Lactobacillus plantarum treatment attenuates cognitive impairments in APP/PS1 mice. Aging (Albany NY) 12: 628-649, 2020.
118. Li X, Zheng P, Cao W, Cao Y, She X, Yang H, Ma K, Wu F, Gao X, Fu Y, *et al*: Lactobacillus rhamnosus GG ameliorates noise-induced cognitive deficits and systemic inflammation in rats by modulating the gut-brain axis. Front Cell Infect Microbiol 13: 1067367, 2023.
119. Dong J, Ping L, Cao T, Sun L, Liu D, Wang S, Huo G and Li B: Immunomodulatory effects of the Bifidobacterium longum BL-10 on lipopolysaccharide-induced intestinal mucosal immune injury. Front Immunol 13: 947755, 2022.
120. Mandelbaum N, Zhang L, Carasso S, Ziv T, Lifshiz-Simon S, Davidovich I, Luz I, Berinstein E, Gefen T, Cooks T, *et al*: Extracellular vesicles of the Gram-positive gut symbiont Bifidobacterium longum induce immune-modulatory, anti-inflammatory effects. NPJ Biofilms Microbiomes 9: 30, 2023.
121. Smith PJ and Blumenthal JA: Dietary factors and cognitive decline. J Prev Alzheimers Dis 3: 53-64, 2016.
122. Petersson SD and Philippou E: Mediterranean diet, cognitive function, and dementia: A systematic review of the evidence. Adv Nutr 7: 889-904, 2016.
123. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martínez-González MÁ, Martínez-Lapiscina EH, Fitó M, Pérez-Heras A, Salas-Salvadó J, *et al*: Mediterranean diet and age-related cognitive decline: A randomized clinical trial. JAMA Intern Med 175: 1094-1103, 2015.
124. Liu X, Morris MC, Dhana K, Ventrelle J, Johnson K, Bishop L, Hollings CS, Boulin A, Laranjo N, Stubbs BJ, *et al*: Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) study: Rationale, design and baseline characteristics of a randomized control trial of the MIND diet on cognitive decline. Contemp Clin Trials 102: 106270, 2021.
125. Jiwani R, Robbins R, Neri A, Renero J, Lopez E and Serra MC: Effect of dietary intake through whole foods on cognitive function: Review of randomized controlled trials. Curr Nutr Rep 11: 146-160, 2022.
126. Bazinet RP and Layé S: Polyunsaturated fatty acids and their metabolites in brain function and disease. Nat Rev Neurosci 15: 771-785, 2014.
127. Dyall SC: Long-chain omega-3 fatty acids and the brain: A review of the independent and shared effects of EPA, DPA and DHA. Front Aging Neurosci 7: 52, 2015.
128. Calon F and Cole G: Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: Evidence from animal studies. Prostaglandins Leukot Essent Fatty Acids 77: 287-293, 2007.
129. Külzow N, Witte AV, Kerti L, Grittner U, Schuchardt JP, Hahn A and Flöel A: Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. J Alzheimers Dis 51: 713-725, 2016.
130. Danthiir V, Hosking DE, Nettelbeck T, Vincent AD, Wilson C, O'Callaghan N, Calvaresi E, Clifton P and Wittert GA: An 18-mo randomized, double-blind, placebo-controlled trial of DHA-rich fish oil to prevent age-related cognitive decline in cognitively normal older adults. Am J Clin Nutr 107: 754-762, 2018.
131. Power R, Nolan JM, Prado-Cabrero A, Roche W, Coen R, Power T and Mulcahy R: Omega-3 fatty acid, carotenoid and vitamin E supplementation improves working memory in older adults: A randomised clinical trial. Clin Nutr 41: 405-414, 2022.
132. Engin A: Misalignment of circadian rhythms in diet-induced obesity. Adv Exp Med Biol 1460: 27-71, 2024.
133. Altaha B, Heddes M, Pilorz V, Niu Y, Gorbunova E, Gigl M, Kleigrewe K, Oster H, Haller D and Kiessling S: Genetic and environmental circadian disruption induce weight gain through changes in the gut microbiome. Mol Metab 66: 101628, 2022.
134. Su X, Li Q, Yang M, Zhang W, Liu X, Ba Y, Deng Q, Zhang Y, Han L and Huang H: Resveratrol protects against a high-fat diet-induced neuroinflammation by suppressing mitochondrial fission via targeting SIRT1/PGC-1α. Exp Neurol 380: 114899, 2024.
135. Pivari F, Mingione A, Piazzini G, Ceccarani C, Ottaviano E, Brasacchio C, Dei Cas M, Vischi M, Cozzolino MG, Fogagnolo P, *et al*: Curcumin supplementation (Meriva®) modulates inflammation, lipid peroxidation and gut microbiota composition in chronic kidney disease. Nutrients 14: 231, 2022.
136. Alghadir A, Gabr SA and Iqbal A: Enhancing cognitive performance and mitigating dyslipidemia: The impact of moderate aerobic training on sedentary older adults. BMC Geriatr 24: 678, 2024.
137. Blumenthal JA, Smith PJ, Mabe S, Hinderliter A, Lin PH, Liao L, Welsh-Bohmer KA, Browndyke JN, Kraus WE, Doraiswamy PM, *et al*: Lifestyle and neurocognition in older adults with cognitive impairments: A randomized trial. Neurology 92: e212-e223, 2019.
138. Saslow LR, Jones LM, Sen A, Wolfson JA, Diez HL, O'Brien A, Leung CW, Bayandorian H, Daubenmier J, Missel AL and Richardson C: Comparing very low-carbohydrate vs DASH diets for overweight or obese adults with hypertension and prediabetes or type 2 diabetes: A randomized trial. Ann Fam Med 21: 256-263, 2023.
139. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, *et al*: Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 108: 3017-3022, 2011.
140. Sabouri M, Kordi M, Shabkhiz F, Taghibeikzadehbadr P and Geramian ZS: Moderate treadmill exercise improves spatial learning and memory deficits possibly via changing PDE-5, IL-1 β and pCREB expression. Exp Gerontol 139: 111056, 2020.

141. Noble EE, Mavanji V, Little MR, Billington CJ, Kotz CM and Wang C: Exercise reduces diet-induced cognitive decline and increases hippocampal brain-derived neurotrophic factor in CA3 neurons. Neurobiol Learn Mem 114: 40-50, 2014.
142. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, Blasco-Lafarga C, Garcia-Dominguez E, Carretero A, Correas A, *et al*: Physical exercise in the prevention and treatment of Alzheimer's disease. J Sport Health Sci 9: 394-404, 2020.
143. Chang YS, Lin CL, Lee CW, Lin HC, Wu YT and Shih YH: Exercise normalized the hippocampal renin-angiotensin system and restored spatial memory function, neurogenesis, and blood-brain barrier permeability in the 2K1C-hypertensive mouse. Int J Mol Sci 23: 5531, 2022.
144. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, Strauman TA and Sherwood A: Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. Hypertension 55: 1331-1338, 2010.
145. Cartee GD, Hepple RT, Bamman MM and Zierath JR: Exercise promotes healthy aging of skeletal muscle. Cell Metab 23: 1034-1047, 2016.
146. Kang EB and Cho JY: Effects of treadmill exercise on brain insulin signaling and β-amyloid in intracerebroventricular streptozotocin induced-memory impairment in rats. J Exerc Nutrition Biochem 18: 89-96, 2014.
147. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS and Nimmo MA: The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 11: 607-615, 2011.
148. Spencer SJ, D'Angelo H, Soch A, Watkins LR, Maier SF and Barrientos RM: High-fat diet and aging interact to produce neuroinflammation and impair hippocampal- and amygdalar-dependent memory. Neurobiol Aging 58: 88-100, 2017.
149. Ionescu-Tucker A and Cotman CW: Emerging roles of oxidative stress in brain aging and Alzheimer's disease. Neurobiol Aging 107: 86-95, 2021.
150. Hadizadeh M, Hamidi GA and Salami M: Probiotic supplementation improves the cognitive function and the anxiety-like behaviors in the stressed rats. Iran J Basic Med Sci 22: 506-514, 2019.
151. Akbari E, Asemi Z, Kakhaki RD, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA and Salami M: Effect of probiotic supplementation on cognitive function and metabolic status in alzheimer's disease: A randomized, double-blind and controlled trial. Front Aging Neurosci 8: 256, 2016.
152. Small GW, Siddarth P, Silverman DH, Ercoli LM, Miller KJ, Lavretsky H, Bookheimer SY, Huang SC, Barrio JR and Phelps ME: Cognitive and cerebral metabolic effects of celecoxib versus placebo in people with age-related memory loss: Randomized controlled study. Am J Geriatr Psychiatry 16: 999-1009, 2008.
153. Kohman RA, Bhattacharya TK, Kilby C, Bucko P and Rhodes JS: Effects of minocycline on spatial learning, hippocampal neurogenesis and microglia in aged and adult mice. Behav Brain Res 242: 17-24, 2013.
154. Leigh SJ, Kaakoush NO, Westbrook RF and Morris MJ: Minocycline-induced microbiome alterations predict cafeteria diet-induced spatial recognition memory impairments in rats. Transl Psychiatry 10: 92, 2020.
155. Craft S and Watson GS: Insulin and neurodegenerative disease: Shared and specific mechanisms. Lancet Neurol 3: 169-178, 2004.
156. Ismail TR, Yap CG, Naidu R and Pamidi N: Environmental enrichment and metformin improve metabolic functions, hippocampal neuron survival, and hippocampal-dependent memory in high-fat/high-sucrose diet-induced type 2 diabetic rats. Biology (Basel) 12: 169-178, 2023.
157. Ameen O, Samaka RM and Abo-Elsoud RAA: Metformin alleviates neurocognitive impairment in aging via activation of AMPK/BDNF/PI3K pathway. Sci Rep 12: 17084, 2022.
158. d'Angelo M, Castelli V, Catanesi M, Antonosante A, Dominguez-Benot R, Ippoliti R, Benedetti E and Cimini A: PPARγ and cognitive performance. Int J Mol Sci 20: 5068, 2019.
159. Chen Z, Deng X, Shi C, Jing H, Tian Y, Zhong J, Chen G, Xu Y, Luo Y and Zhu Y: GLP-1R-positive neurons in the lateral septum mediate the anorectic and weight-lowering effects of liraglutide in mice. J Clin Invest 134: e178239, 2024.
160. Delanogare E, Bullich S, Barbosa LADS, Barros WM, Braga SP, Kraus SI, Kasprowicz JN, Dos Santos GJ, Guiard BP and Moreira ELG: Metformin improves neurobehavioral impairments of streptozotocin-treated and western diet-fed mice: Beyond glucose-lowering effects. Fundam Clin Pharmacol 37: 94-106, 2023.
161. Lennox R, Porter DW, Flatt PR, Holscher C, Irwin N and Gault VA: Comparison of the independent and combined effects of sub-chronic therapy with metformin and a stable GLP-1 receptor agonist on cognitive function, hippocampal synaptic plasticity and metabolic control in high-fat fed mice. Neuropharmacology 86: 22-30, 2014.
162. Leal G, Comprido D and Duarte CB: BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology 76: 639-656, 2014.
163. Zuo X, Zhu Z, Liu M, Zhao Q, Li X, Zhao X and Feng X: Fluoxetine ameliorates cognitive deficits in high-fat diet mice by regulating BDNF expression. ACS Chem Neurosci 15: 4229-4240, 2024.
164. Davidson TL, Jones S, Roy M and Stevenson RJ: the cognitive control of eating and body weight: It's more than what you 'Think'. Front Psychol 10: 62, 2019.
165. Maki KC, Slavin JL, Rains TM and Kris-Etherton PM: Limitations of observational evidence: Implications for evidence-based dietary recommendations. Adv Nutr 5: 7-15, 2014.
166. Wu M, Liao M, Huang R, Chen C, Tian T, Wang H, Li J, Li J, Sun Y, Wu C, *et al*: Hippocampal overexpression of TREM2 ameliorates high fat diet induced cognitive impairment and modulates phenotypic polarization of the microglia. Genes Dis 9: 401-414, 2022.
167. Song T, Song X, Zhu C, Patrick R, Skurla M, Santangelo I, Green M, Harper D, Ren B, Forester BP, *et al*: Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing Res Rev 72: 101503, 2021.
168. Mozhui K, Lu AT, Li CZ, Haghani A, Sandoval-Sierra JV, Wu Y, Williams RW and Horvath S: Genetic loci and metabolic states associated with murine epigenetic aging. Elife 11: e75244, 2022.
169. Kamoga R, Rukundo GZ, Kalungi S, Obungoloch J, Obua C and Ihunwo A: Vagus nerve stimulation in dementia: A scoping review of clinical and pre-clinical studies. AIMS Neurosci 11: 398-420, 2024.
170. Amelianchik A, Sweetland-Martin L and Norris EH: The effect of dietary fat consumption on Alzheimer's disease pathogenesis in mouse models. Transl Psychiatry 12: 293, 2022.
171. Elzinga SE, Guo K, Turfah A, Henn RE, Webber-Davis IF, Hayes JM, Pacut CM, Teener SJ, Carter AD, Rigan DM, *et al*: Metabolic stress and age drive inflammation and cognitive decline in mice and humans. Alzheimers Dement 21: e70060, 2025.
172. Townsend RF, Logan D, O'Neill RF, Prinelli F, Woodside JV and McEvoy CT: Whole dietary patterns, cognitive decline and cognitive disorders: A systematic review of prospective and intervention studies. Nutrients 15: 333, 2023.
173. Yako H, Niimi N, Takaku S and Sango K: Advantages of omics approaches for elucidating metabolic changes in diabetic peripheral neuropathy. Front Endocrinol 14: 1208441, 2023.
174. Zhang R, Zhang M and Wang P: The intricate interplay between dietary habits and cognitive function: Insights from the gut-brain axis. Front Nutr 12: 1539355, 2025.