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Obesity-induced cognitive impairment: Underlying mechanisms and therapeutic prospects

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ABSTRACT

The prevalence of obesity continues to rise worldwide. Obesity is not only a core risk factor for chronic metabolic diseases, but also significantly associated with the risk of cognitive impairment. Obesity in middle age can cause aprosexia, cognitive disorder, dementia, hypomnesis, and increase the risk of execution decline, depression and anxiety. The underlying mechanisms involve multiple pathological pathways such as neuroinflammation, imbalance of gut microbiota-gut-brain axis, metabolic abnormalities, and imbalance of adipokines. Obesity induced chronic inflammation impairs neuroprotection by activating microglia, exacerbating β-amyloid deposition and neurodegeneration. Intestinal flora disorder impairs neuroprotection by reducing the production of short-chain fatty acids. Metabolic syndrome has synergistic damage to cerebral vascular and white matter microstructure. Genetic factors, comorbidities and ethnic differences clearly moderated the association between obesity and cognition. Among the interventions, bariatric surgery can improve executive function and memory, while lifestyle modification and drug intervention have protective effects by reducing inflammation and metabolic disorders. In the future, we need to focus on precise intervention strategies, such as developing multidimensional biomarkers, and optimizing obesity assessment indicators to overcome the limitations of existing studies, so as to provide a basis for phased and individualized prevention and treatment.

1. Introduction

Obesity has become a global public health crisis, and its prevalence has increased exponentially over the past four decades. By 2022, 800 million people are already with obesity, and the number continues to rise, especially in developing countries and regions with rapid urbanization [1,2]. Obesity directly increases the risk of diabetes, hypertension, dyslipidemia and cardiovascular disease by 2–3 times, and is closely related to non-alcoholic fatty liver disease, cancer, sarcopenia and other diseases (Fig. 1) [3–5]. Around 13 % of deaths globally are linked to overweight/obesity, and obesity was directly responsible for 4.7 million premature deaths in 2017 [6]. These data underscore the urgency of the prevention and control of obesity and its far-reaching impact on the achievement of global health goals. Overweight and obesity may be associated with a lower risk of cognitive impairment in the elderly, presenting an “obesity paradox” phenomenon, while obesity in young and middle-aged people is associated with an increased risk of dementia [7–9]. The association of body mass index (BMI)-genetic risk score (PRS) with cognitive impairment was found to be independent of actual BMI level, suggesting the influence of gene environment interaction [10]. Dynamic changes in the trajectory of obesity are more predictive than static BMI, and either persistent obesity or weight loss may accelerate cognitive decline through different mechanisms [11,12]. Cognitive impairment and dementia have become a major challenge in the global public health field. As the population ages, the prevalence of dementia continues to rise, with the number of people affected worldwide expected to increase from 50 million today to more than 150 million by 2050, placing a huge strain on healthcare systems and social support systems [13]. Such diseases not only lead to severe degradation of patients' memory, thinking and social ability, but also are closely related to higher mortality, disability rates and long-term care needs, which directly aggravates the social and economic burden [14]. The

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synergistic effect of obesity related metabolic disorders and dementia further adds to the challenge [15]. Women with obesity have a higher risk of cognitive impairment, which may be related to the differences in hormone levels and fat distribution [16]. In addition, obesity may affect the function of gut-brain axis by changing the structure of gut microbiota, thereby aggravating cognitive decline [17]. New intervention targets such as the time window effect of obesity on cognition, the gene environment interaction mechanism, and the regulation of the gut-brain axis are the core issues to be solved urgently [18,19]. Therefore, this article explores the role of obesity in cognitive impairment from multiple perspectives in order to provide a more comprehensive assessment and analysis (Table 1).

2. Association of obesity with cognitive function

Obesity in middle age can cause aprosexia, cognitive disorder, dementia, hypomnesis, and increase the risk of execution decline, depression and anxiety (Fig. 2). Elevated BMI or central obesity are independent risk factors for accelerated cognitive decline [20,21]. Midlife obesity may promote β-amyloid (Aβ) deposition and neurodegeneration through insulin resistance, chronic inflammation, vascular endothelial dysfunction and other pathways, thereby increasing the risk of Alzheimer's disease (AD) and other types of dementia [22]. People with obesity in midlife have 20–40 % higher odds of developing mild cognitive impairment (MCI) and dementia later in life than those who are of normal weight, and risk for cognitive impairment increases the longer they are with obesity [23]. Weight control in midlife may improve cognitive outcomes, and dietary modifications or increased physical activity may reduce obesit related neuroinflammatory responses and slow the progression of cognitive decline [24,25]. Maintaining a healthy BMI in midlife reduces dementia risk by 30 % [26].

The association between BMI and cognitive impairment showed an inverse J-shaped or U-shaped dose response curve. Risk for cognitive impairment was lowest in the normal weight range, whereas underweight (BMI <18.5 kg/m2) and obesity (BMI ≥30 kg/m2) both increased risk. Measures of abdominal obesity (e.g., WHR, waist circumference) were significantly and positively associated with cognitive decline without protective thresholds. Among people with diabetes, each 0.1 unit increase in Waist-to-Hip Ratio adjusted for Body Mass Index (WHRadjBMI) was associated with a 35 % higher risk for cognitive impairment [27]. Individuals with a waist-to-hip ratio (WHR) > 0.9 were 1.6 times more likely to have cognitive decline than those with a normal ratio [28]. The effect of abdominal obesity on cognition was more remarkable in women, with an 18 % increased risk of cognitive impairment for each 1 standard deviation increase in WHRadjBMI in women, but only 7 % in men, which may be related to sex differences in estrogen metabolism and visceral fat distribution [29].

3. Potential biological mechanisms of cognitive impairment caused by obesity

3.1. Neuroinflammation and immune dysregulation

There is a complex interaction mechanism between obesity induced systemic inflammation and neuroinflammation in the brain (Fig. 3). In people with obesity state, adipose tissue dysfunction triggers systemic chronic low-grade inflammation, which is characterized by persistent elevation of proinflammatory cytokines (such as IL-1β, IL-18, and TNF-α) and abnormal activation of immune cells (such as macrophages) [30,

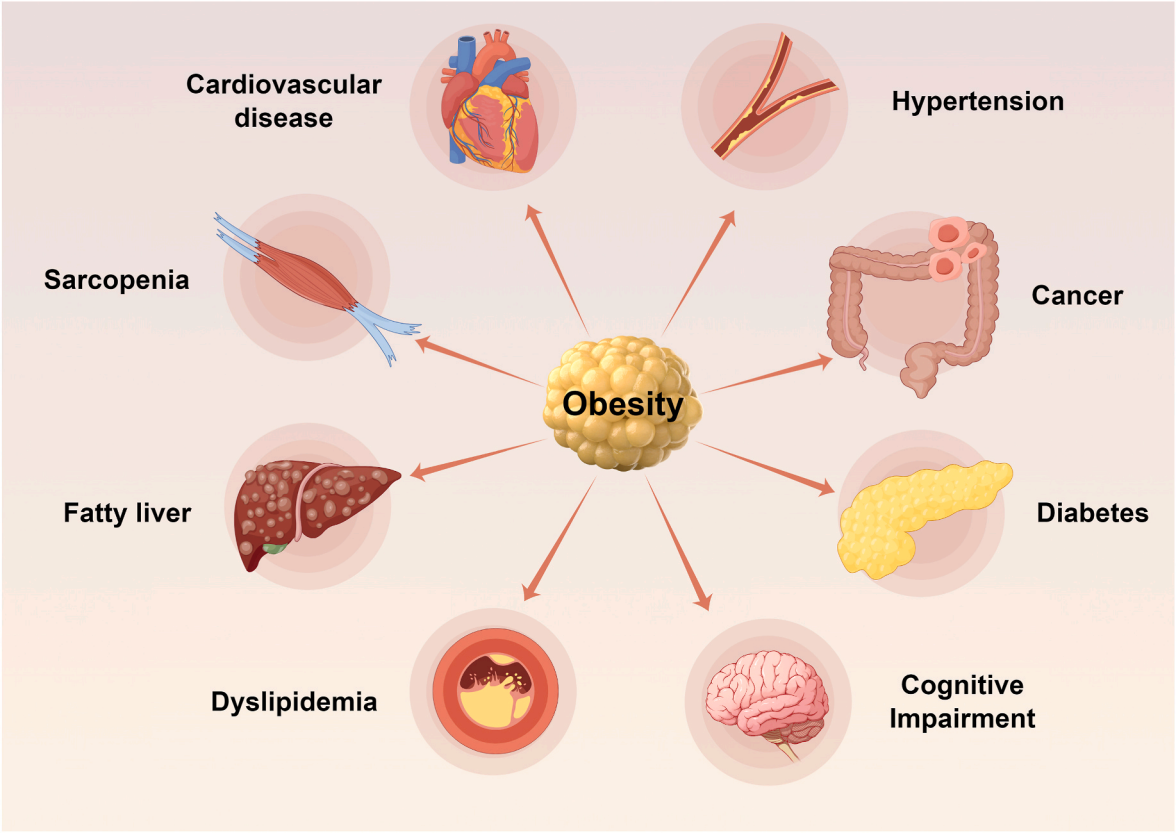

Fig. 1. Obesity can lead to a variety of comorbidities. As a global epidemic, obesity directly increases the risk of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases (e.g., coronary heart disease, myocardial infarction, stroke). It is also closely related to non-alcoholic fatty liver disease, a variety of cancers (such as breast cancer, liver cancer, colorectal cancer, etc.), sarcopenia, and other diseases (such as metabolic syndrome, polycystic ovary syndrome, obstructive sleep apnea, osteoarthritis, depression).

Table 1
Basic information of included studies.

Study	Year	Country	Study design	Patients analysed (n)	Mean age (years)	Relative research results	Sex (Male/ Female)
Liang et al. [9]	2011–2018	China	Prospectivestudy	9765	80.7	A reverse J-shaped association was observed between BMI and cognitive impairment. Obese had a decreased risk of cognitive impairment. Lower PDI, lower hPDI, and higher uPDI were associated with an increased risk of cognitive impairment.	2425/7340
Wang et al. [10]	2010–2023	N/A	Cross-sectional study	1005	63.6	BMI among females, the risk of cognitive impairment increases for both groups with BMI ≥30 kg/m2, with a strong association between BMI and cognitive impairment in females.	627/378
Liu et al. [11]	2014	United States	Prospectivestudy	10798	58.3	Higher PRS for BMI was associated with an increased risk. A favourable lifestyle was associated with a low risk of cognitive impairment.	4443/6355
Gong et al. [13]	1999–2014	United States	Retrospective study	5809	72.9	In comparison with participants who remained at non-obese, those moving from the non-obese to obese weightchange pattern from young (25 years of age) to middle adulthood showed lower DSST scores.	N/A
Grapsa et al. [15]	2011	Greek	HELIAD Study	1076	N/A	BMI ≥25 kg/m^2 was related to greater reduction in the visuospatial composite score over time. Aged >75 years and BMI ≥30 kg/m^2 contributed to a slower rate of decline in the memory composite score over time.	434/642
Shang et al. [22]	2014–2015	China	Cross-sectional study	1792	55.53	The relationships among BMI, WHR, and CI were significant. A low BMI or high WHR was positively associated with CI	726/1066
González et al. [23]	2015–2019	Mexico	Prospective study	8197	66	The prevalence of cognitive impairment was higher in women than in men.	2565/5632
Tashiro et al. [30]	2006–2016	Japan	Prospective study	37414	48.8	Increased dementia risk was observed with obesity at baseline.	17550/19864
Bohn et al. [36]	2020	Canada	Longitudinal study	869	71.75	Higher BMI predicted less decline in EF, neurocognitive speed, and memory.	296/573
Talaei et al. [37]	2014–2016	Singapore	Prospective study	14691	72.9	Obesity was associated with a higher risk of cognitive impairment.	6148/8543
Chen et al. [43]	2018–2022	China	Cross-sectional study	1154	61.9	WHRadjBMI was positively correlated with MoCA scores.	625/529
Zhang et al. [74]	N/A	China	Cross-sectional study	112	30.18	Except for working memory and visual cognition, and degree of cognitive impairment in SOB group was more than that in OB group.	50/62
Kim et al. [109]	2010–2018	Korea	Longitudinal study	4889	63.19	The risk of obesity (BMI ≥25) on cognitive decline.	N/A
Sakib et al. [120]	2022–2023	Canada	Cross-sectional study	30097	N/A	Reliable associations exist between cognitive function and adiposity in middle-aged and older adults.	14940/15157
Järvholm et al. [125]	2015	Sweden	Randomized controlled trial	46	15.8	Accompanying significant weight loss with overall greater improvement in executive functions and memory in adolescents over two years compared with a non-surgical group without weight loss.	12/34
Keawtep et al. [137]	2014–2015	Iran	Randomized controlled trial	92	52.8	Combined physical-cognitive exercise and dietary intervention are promising interventions to improve cognition.	Postmenopa-usal obesity women
Johar et al. [175]	2013–2015	Germany	Prospective study	1583	30.4	Pre-pregnancy obesity were significantly positively associated with the odds of developing PPD.	Pre-pregnancy women

BMI, body mass index; PDI, plant-based diet index; hPDI, healthful plant-based diet index; uPDI, unhealthful plant-based diet index; PRS, polygenic risk score; DSST, digit symbol substitution test; WHR, waist-to-hip ratio; CI, cognitive Impairment; WHRadjBMI, waist-to-hip ratio adjusted for body mass index; MoCA, montreal cognitive assessment; OB, obesity; SOB, severe obesity; PPD, postpartum depression.

31]. Systemic inflammation can affect the central nervous system through a variety of ways, such as the infiltration of inflammatory mediators through the blood-brain barrier, vagus nerve signaling or the activation of immune cells in the brain to affect the central nervous system, triggering neuroinflammation, which is manifested as the activation of microglia, astrogliosis and the activation of NLRP3 inflammasome [32–34]. The hypothalamus and hippocampus are the main target areas for obesity related neuroinflammation. Hypothalamic inflammation directly affects the energy metabolism regulatory centers, leading to appetite disorders and metabolic disorders, while hippocampal inflammation is closely related to synaptic plasticity impairment, neuronal apoptosis, and memory dysfunction, which manifest as spatial memory impairment and cognitive flexibility decline [35]. This neuroinflammation may gradually damage the nerve through mechanisms such as oxidative stress and mitochondrial dysfunction, ultimately increasing the risk of neurodegenerative diseases [36]. Obesity related systemic inflammation and neuroinflammation form a vicious cycle [37, 38].

3.2. Regulation of gut microbiota-gut-brain axis

The elevated Firmicutes/Bacteroidetes ratio (F/B) in the gut microbiota of individuals with obesity is not only a marker of obesity, but also closely related to cognitive decline and neurodegenerative diseases (Fig. 3) [39,40]. The excessive proliferation of firmicutes may aggravate the metabolic burden of obesity by increasing the efficiency of energy absorption, reduce the production of beneficial metabolites such as short-chain fatty acids (SCFAs), and weaken their neuroprotective and anti-inflammatory effects [41]. The high F/B ratio associated with obesity can aggravate intestinal permeability, promote the release of proinflammatory factors such as lipopolysaccharide (LPS) into the circulation, trigger systemic low-grade inflammation and insulin resistance, and then cross the blood-brain barrier to damage the hippocampus and other regions [42,43]. Enteric dysbacteriosis leads to

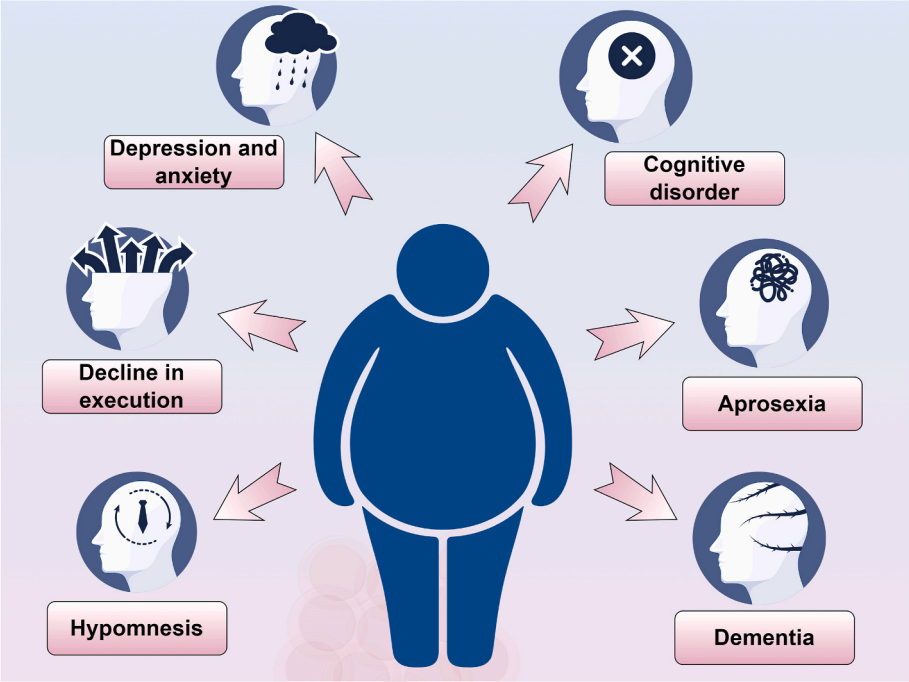

Fig. 2. People with midlife obesity are at higher risk of aprosexia, cognitive disorder, dementia, hypomnesis, execution decline, depression and anxiety. Obesity in midlife can accelerate the progression of aprosexia, cognitive disorder and dementia. Obesity performed worse in core cognitive domains such as executive function and memory. Depression and anxiety symptoms are more common in people with obesity, which can further aggravate cognitive impairment through mechanisms such as hypothalamic-pituitary-adrenal axis dysfunction.

a reduction in the production of SCFAs, and butyrate can enhance the expression of brain-derived neurotrophic factor by inhibiting histone deacetylase, thereby impairing synaptic function and memory formation [19]. Depletion of probiotics (e.g., clostridium butyricum) impairs immune and neuroendocrine communication between the gut and the brain, and aggravate obesity related anxiety behavior and spatial memory impairment. *Clostridium butyricum* intervention can alleviate obesity related cognitive impairment and delay the process of neurodegeneration. Its mechanism involves multi-target regulation of gut microbiota-gut-brain axis, inhibition of Aβ deposition, reduction of tau protein hyperphosphorylation, and inhibition of microglia over activation [44]. Randomized controlled trials in AD or mild cognitive impairment have found that specific probiotic combinations (e.g., Bifidobacterium and Lactobacillus) can improve cognitive scores, especially in early cognitive decline [45,46].

3.3. Metabolic abnormalities and vascular injury

Abnormal cortisol metabolism under chronic stress may play a key mediating role in obesity related cognitive impairment (Fig. 3). The over activation of hypothalamic-pituitary-adrenal axis (HPA axis), which is common in people with obesity, can lead to continuous increase of circulating glucocorticoid levels, it directly acts on cognitive related brain areas such as hippocampus and prefrontal cortex through glucocorticoid receptors, and eventually leads to functional defects such as spatial memory, language learning and social cognition [47]. In a high-fat diet induced obese mouse model, hyperactivation of the HPA axis is related to an increase in plasma corticosterone levels, and inhibition of glucocorticoid synthesis improved cognitive dysfunction. The impairting effects of cortisol on cognition may exist independently of BMI, especially in complex cognitive domains such as proactive interference and working memory [48]. This pathological process is particularly prominent in adolescents with obesity, as their HPA axis and limbic system are at a critical stage of development. Elevated cortisol may interfere with hippocampal neurogenesis and amygdala function maturation, leading to long-lasting cognitive and emotional abnormalities [49]. These findings collectively reveal the therapeutic potential of targeting cortisol metabolic pathways in improving obesity related cognitive impairment.

Cognitive function is markedly impaired in people with metabolic syndrome (MetS), as indicated by decreased memory, executive function, and speed of information processing. It may be mediated through abnormal white matter microstructure and neural network dysfunction [50]. The burden of white matter hyperintensities (WMHs) is clearly increased in MetS compared to healthy individuals, especially in the deep and periventricular white matter areas, which are strongly associated with microvascular dysfunction, disruption of the blood-brain barrier, and chronic hypoperfusion [51,52]. MetS have abnormal white matter microstructure, suggesting impaired axonal integrity and demyelination, which may become early neuroimaging markers of cognitive impairment and dementia [53].

3.4. Adipokines and pathological changes of neurodegeneration

Leptin and adiponectin exhibit complex bidirectional interactions, and their dysfunction may exacerbate disease progression through metabolic disorders, inflammatory responses, and neurotoxicity (Fig. 3). Leptin has an inhibitory effect on hippocampal synaptic damage induced by β-amyloid (Aβ) and can improve memory function [54]. In addition, there is bidirectional regulation between leptin and Aβ, and Aβ oligomers can directly interfere with leptin receptor signaling, while disorders of the leptin system can promote Aβ deposition, forming A vicious cycle [55]. The abnormal increase of adiponectin in patients with non-obese AD may reflect the compensatory mechanism of adipose tissue dysfunction [56]. Leptin may inhibit tau hyperphosphorylation through GSK-3β, while adiponectin may enhance dephosphorylation by activating PP2A. This imbalance may accelerate the formation of neurofibrillary tangles [57,58]. At the metabolic level, they jointly regulate the function of the HPA axis, and their synergistic disorders lead to abnormal glucose and lipid metabolism, which causes insulin

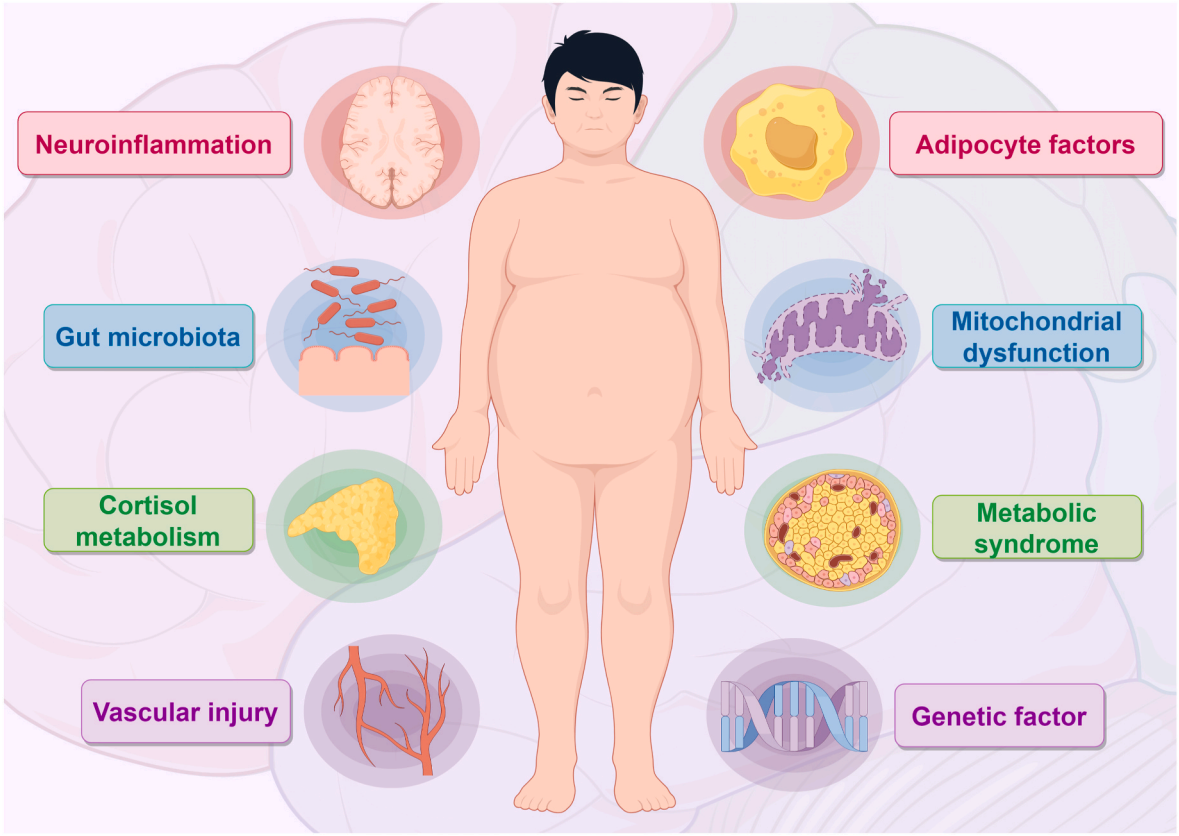

Fig. 3. Potential mechanisms of obesity-induced cognitive impairment. Obesity induces inflammatory mediators that affect the central nervous system through blood-brain barrier penetration, vagus nerve signaling, or immune cell activation in the brain, causing neuroinflammation and displaying spatial memory impairment. Cognitive impairment in MetS or elevated cortisol is mainly manifested in complex cognitive aspects such as spatial memory and information processing. Enteric dysbacteriosis leads to reduced production of short-chain fatty acids, which impairs synaptic function and memory formation. Adipokine dysfunction can exacerbate disease progression through metabolic disorders, inflammation, and neurotoxicity. Obesity are more likely to have intracerebral vascular injury, which leads to an increased risk of cortical microinfarcts and intracerebral hemorrhage, and such lesions are often accompanied by cognitive decline. Mitochondrial dysfunction leads to impaired synaptic plasticity in neurons by activating inflammatory pathways through oxidative stress. The APOE genotype may modulate the effects of obesity on cognition through metabolic synergy, neurovascular impairment and pathological deposition.

resistance and mitochondrial dysfunction in the brain and then promotes the pathological process of cognitive impairment [59].

3.5. Other pathological mechanisms

Mitochondrial dysfunction and oxidative stress play key roles in obesity-related cognitive impairment (Fig. 3). Excessive production of reactive oxygen species (ROS) in obesity triggers oxidative stress and destroys mitochondrial function [60,61]. Its dysfunction will further exacerbate the accumulation of ROS, creating a vicious cycle of oxidative damage and insufficient energy supply to neurons. There are decreased mitochondrial respiratory chain complex activity, abnormal mitochondrial membrane potential and decreased ATP synthesis in the brain tissue of people with obesity, and these changes are closely related to cognitive decline [62]. Oxidative stress can also aggravate neuronal synaptic plasticity and neurodegeneration by activating inflammatory pathways and inhibiting mitophagy [63]. Obesity-related insulin resistance may further amplify the damage of oxidative stress in the hippocampus and prefrontal cortex, brain regions critical for memory and executive functions, possibly by inhibiting mitochondrial biosynthesis in the brain (e.g., by reducing PGC-1α expression) [64].

4. Influencing factors and moderating factors in clinical research

4.1. The moderating role of genetic factors

APOE genotype may modulate the effect of obesity on cognition through metabolic synergy, neurovascular injury and pathological deposition (Fig. 3). APOEε4 carriers are more likely to have cognitive impairment when they are with obesity, which may be related to the enhancement of metabolic disorders induced by high-fat diet by APOEε4. APOEε4 mice showed more severe synaptic damage and abnormal brain region specific gene expression under high-fat diet induction, while polyunsaturated fatty acid supplementation could partially alleviate the damage [65]. Middle-aged overweight or APOEε4 carriers with obesity show abnormal functional connectivity in prefrontal and parietal brain regions, alterations in neural activity that may accelerate cognitive decline [66,67]. APOEε4 may lead to cognitive impairment by aggravating obesity-related abnormal cerebral blood flow regulation (such as hypoperfusion in the posterior cingulate cortex and precuneus area) and promoting the invasion of peripheral inflammatory factors into the central nervous system [68].

The BMI related genetic risk score is associated with cognitive function, and this association may be driven by genetic factors. Studies have found that loci (such as FTO and MC4R) are associated with elevated BMI and cognitive decline, suggesting that these genes may affect brain health by regulating metabolic or neuroinflammatory

pathways [69]. People with higher BMI-PRS showed cognitive decline, especially in those with BMI≥25, the impairment of executive function and attention was more obvious [70]. A healthy lifestyle may partially offset the negative impact of high BMI-PRS on cognition [71]. APOE genotyping and genetic risk associated with BMI both have important clinical implications for the formulation of obesity-related cognitive intervention strategies [72,73].

4.2. The impact of comorbidities

Comorbidities such as obesity, diabetes, and hypertension have shown clear synergistic effects in causing cognitive impairment. When obesity coexists with type 2 diabetes, the risk of memory and language impairment is markedly increased. In particular, the synergistic effect of abdominal obesity and diabetes increased the risk of cognitive impairment by 2.4–2.5 times [74]. This synergistic mechanism may involve multiple pathophysiological processes of metabolic syndrome, including insulin resistance, chronic inflammation, oxidative stress, and vascular endothelial dysfunction [75,76]. Common factors aggravate structural damage and functional decline in the central nervous system [77,78]. Obesity with hypertension and diabetes showed more severe impairments in attention, delayed memory and executive function [79]. In the elderly population, the rate of cognitive decline is 30 % faster than those with single risk factor, and the degree of executive function impairment shows a dose-response relationship [80].

5. Interventions and treatments

5.1. Cognitive benefits of bariatric surgery

Bariatric surgery improves cognitive function in people with class II/III obesity (Fig. 4). People with grade II/III obesity undergoing gastric bypass surgery have improvements in executive function and global cognitive scores within 6 months after surgery, and improvement in executive function is positively correlated with weight loss [81]. Long-term observations at six months after surgery revealed significant improvements in memory, attention, and information processing speed, which may be related to fat loss and improved insulin sensitivity [82]. Among adults with severe obesity, the prevalence of MCI was reduced from 25 % at baseline to 12 % at 12 months after gastric bypass [83]. Ten-year follow-up data on adolescent demonstrated that the surgical group consistently outperformed the non-surgical controls in terms of visuospatial ability and working memory [84]. Long-term studies also found that some patients had a temporary decline in memory function within 2 years after surgery, which may be related to changes in nutrient absorption, but most patients could recover to the baseline level within 5 years [85,86]. The improvement mechanism may involve multiple pathways: (1) weight loss directly reduces central neuroinflammation and improves hippocampal function by reducing proinflammatory cytokines [87]; (2) metabolic improvement restores brain glucose utilization efficiency, and the increased brain glucose uptake after surgery is related to the activation of GLP-1 signaling pathway [88]; (3) regulation of adipokines, normalization of leptin and adiponectin levels, and

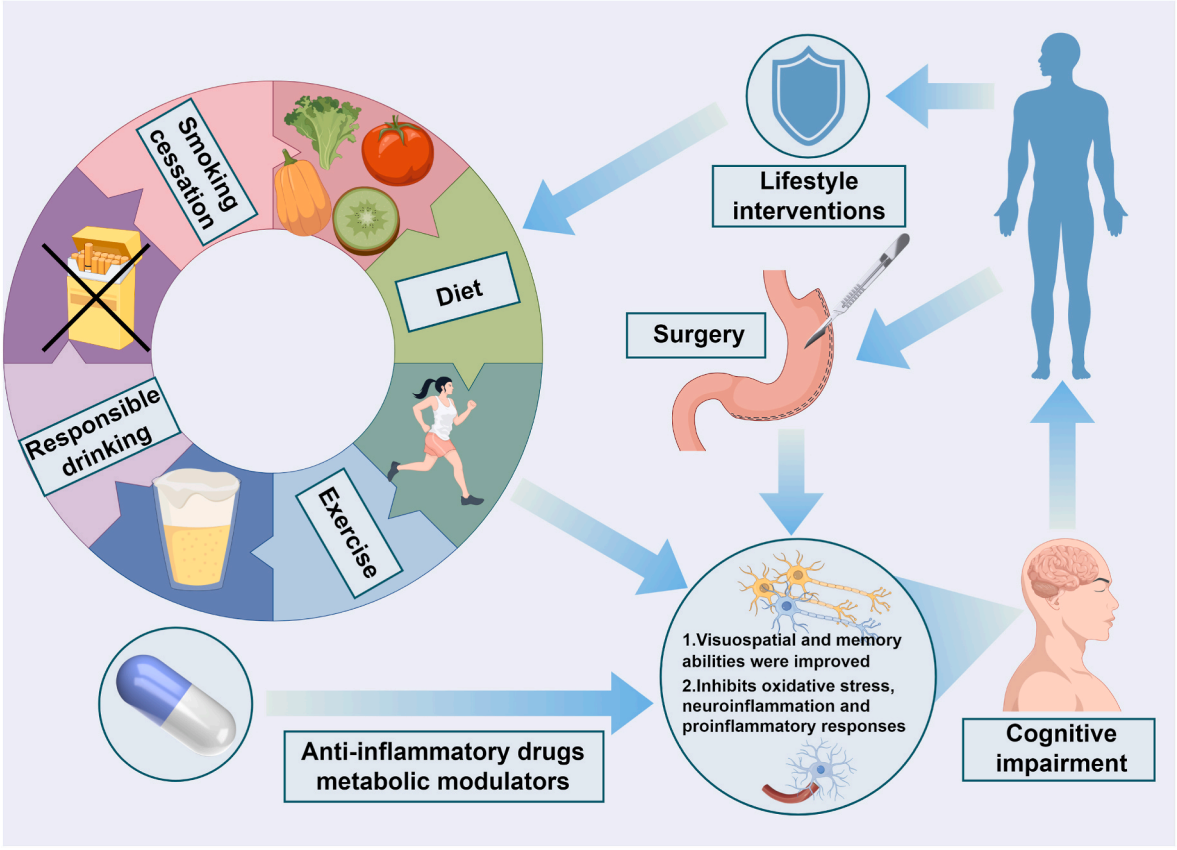

Fig. 4. Approaches to alleviating obesity-induced cognitive impairment. Healthy lifestyle including smoking cessation, moderate alcohol consumption, reasonable dietary pattern and regular exercise showed independent protective effects on obesity-related cognitive impairment. It can improve metabolic indexes, enhance cerebral blood flow and neuroplasticity, and significantly improve multi-dimensional cognitive performance such as executive function and memory. Anti-inflammatory drugs and metabolic modulators have shown multi-target intervention potential in improving obesity-related cognitive impairment. Anti-inflammatory drugs can reduce cognitive impairment caused by obesity by inhibiting neuroinflammatory pathways, and metabolic modulators work by improving glucose and lipid metabolism disorders and insulin resistance. In addition, plant extracts can inhibit oxidative stress, neuroinflammation and proinflammatory responses to improve cognitive impairment. Bariatric surgery can improve cognitive function in in people with class II/III obesity.

improvement of blood-brain barrier affect the activity of brain regions related to cognition [89].

5.2. Lifestyle interventions

Smoking cessation, moderate drinking and regular exercise in healthy lifestyle showed special independent protective effects on obesity-induced cognitive impairment (Fig. 4). First, smoking cessation has been shown to independently reduce the risk of cognitive impairment. Never smokers had a lower risk of cognitive impairment compared to frequent smokers, and the higher the amount and duration of smoking, the faster the rate of cognitive decline [90,91]. Long-term abstinence from alcohol (especially lasting >9 years) was associated with lower risk for cognitive impairment, while moderate drinking (e.g., 1–3 times per month) showed a protective trend compared with no alcohol consumption or heavy drinking, and heavy drinking (≥4 times per week) increased risk for cognitive impairment [92,93]. The protective effect of regular exercise is particularly prominent. Exercise can offset obesity-related brain structural abnormalities and cognitive decline, and its mechanism involves improving metabolic indicators, enhancing cerebral blood flow and neuroplasticity [94,95]. Exercise combined with diet control not only leads to effective weight loss, but also dramatically improves multidimensional cognitive performance such as executive function and memory [96]. More importantly, these health behaviors had independent and synergistic protective effects. When there is a genetic predisposition to obesity or low BMI, even non-smoking, moderate alcohol consumption and regular exercise can still reduce the risk of cognitive impairment by 34 %–53 % [10].

The combination of dietary control and exercise interventions had a synergistic effect on cognitive function improvement (Fig. 4). Combining a Mediterranean diet with regular exercise improved executive function, memory and global cognitive performance. The Mediterranean diet is characterized by olive oil, nuts, and deep-sea fish, which provide abundant ω-3 fatty acids and polyphenols, together with the aerobic exercise induced increase in the secretion of brain derived neurotrophic factor to promote the improvement of hippocampal neural and synaptic plasticity [97,98]. The response of the combined intervention group in the stroop test was 15 % shorter than that of the intervention group, and the error rate was 22 % lower than that of the intervention group, and the cognitive gain effect was maintained for more than 6 months after the intervention [99,100]. The combination of a low-fat/low-sugar diet and resistance exercise demonstrated a unique metabolic cognitive coupling mechanism. An intervention in type 2 diabetes found that a 30 % reduction in daily carbohydrate intake combined with resistance training three times weekly resulted in a 1.2 % reduction in glycated hemoglobin and an 18 % improvement in accuracy on a working memory task [101].

5.3. Pharmacological and nutritional interventions

Anti-inflammatory drugs and metabolic modulators have shown the potential for multi-target interventions to improve cognitive impairment associated with obesity (Fig. 4). Anti-inflammatory drugs can alleviate obesity-induced cognitive impairment by inhibiting neuroinflammatory pathways. Long-term use of non-steroidal anti-inflammatory drugs may reduce the risk of Alzheimer's disease by inhibiting systemic inflammation [102,103]. Metabolic modulators work by improving glucose and lipid metabolism disorders and insulin resistance. They can markedly improve cognitive impairment induced by a high-fat diet by modulating glucose tolerance and insulin sensitivity, while inhibiting proinflammatory responses [104]. Some natural metabolic modulators, such as tea saponin, can alleviate obesity-related neuroinflammation and synaptic damage by remodeling gut microbiota and reducing levels of proinflammatory factors [105]. Neuregulin not only improves metabolic abnormalities, but also repairs synaptic plasticity in the hippocampus and delays the progression of cognitive impairment by activating NTR1 receptor [106]. The mechanism of action of these drugs is to reduce synaptic phagocytosis by anti-inflammation and inhibit abnormal activation of microglia, while metabolic modulators can improve the vicious cycle of neuroinflammation-metabolic disorders associated with obesity by restoring energy metabolism balance and neurotransmitter homeostasis in the brain.

Stevia glycosides, as non-nutritive sweetenants extracted from natural stevia plants, have shown improvement effects on cognitive impairment induced by high fat diet. Stevioside can improve cognitive function by inhibiting oxidative stress and neuroinflammation. It can reduce the level of malondialdehyde (MDA), the product of lipid peroxidation in the brain, and increase the activities of superoxide dismutase (SOD) and glutathione (GSH) antioxidant enzymes, and effectively alleviate the oxidative damage of brain tissue induced by high fat diet [107]. Stevioside inhibits the transmission of systemic inflammation to the central nervous system by repairing the integrity of the intestinal barrier and the leakage of LPS from the intestinal lumen to the blood, which plays a role by regulating the gut-brain axis pathway [108]. In addition, its anti-inflammatory properties are also shown to inhibit the activation of microglia and the expression of proinflammatory factors, and may reduce hippocampal neuroinflammation by regulating TLR4/NF-κB signaling pathway [109]. Curcumin can alleviate obesity and related metabolic disorders by inhibiting adipocyte differentiation, reducing the accumulation of white adipose tissue, regulating the activities of lipid metabolism related enzymes (such as lipase and amylase), and improving the balance of intestinal flora [110,111]. Curcumin may also improve obesity-induced cognitive impairment by reducing oxidative stress and neuroinflammation, enhancing central and peripheral insulin sensitivity, and promoting neuroprotection and neurogenesis [112,113]. Curcumin and resveratrol showed synergistic effects when used in combination, such as enhancing antioxidant activity, synergistically inhibiting apoptosis-related proteins and activating Akt survival signaling pathway, thereby more effectively alleviating oxidative damage and neuronal apoptosis [114,115].

6. Research progress in specific populations

The association between obesity and cognitive impairment showed differences among different ethnic groups, especially the contrast between blacks and whites. In the white population, higher BMI was associated with a more pronounced decline in overall cognitive function, particularly in executive function and memory domains, whereas in the black population the correlation is relatively weak or has a different trajectory pattern [116,117].

The study of overweight black groups found that the link between this implicit obesity and mild cognitive impairment may be higher than the white group, and there is a need for more accurate assessment of obesity in different ethnic groups [118]. The negative association of obesity with cognitive function in black populations may be attributed in part to a higher prevalence of metabolic disorders, although race was not found to modify the overall association of BMI with cognitive decline. These differences suggest that the effect of racial specificity on cognitive health should be considered in the formulation of obesity intervention strategies.

Interventions for cognitive impairment in postmenopausal women with obesity need to generate comprehensive strategies based on their unique metabolic and hormonal changes. The precipitous drop in estrogen levels after menopause exacerbates obesity-related cerebrovascular damage, so the timing of intervention is critical. Estrogen deficiency leads to the impairment of estrogen receptor α (ERα) signaling pathway in the central nervous system, deceasing the ability to regulate the neuroprotective effect in the hippocampus and prefrontal cortex [119,120]. Elevated follicle stimulating hormone (FSH) levels have been found to directly promote visceral fat accumulation and lead to abnormal cortisol metabolism by inhibiting the HPA axis regulation [121]. This endocrine disorder was observably associated with reduced

hippocampal volume and decreased executive function. Because obesity in midlife is strongly associated with cognitive decline in later life, and treatment of obesity in early menopause may be more effective [122,123]. For the pathological mechanism of estrogen deficiency, moderate exercise can indirectly improve the function of hippocampal neurons by regulating abnormal lipid metabolism, while estrogen replacement therapy needs to balance its potential risks with neuroprotective benefits [124].

The interplay between postpartum depression and obesity may exacerbate cognitive decline through neuroinflammation and metabolic disturbances, requiring multiple prevention strategies. Pregnancy weight management program is recommended for pregnant women with obesity, and controlling gestational weight gain within a reasonable range (weight loss of 5–9 kg is recommended for those with BMI≥30) can reduce the incidence of postpartum depression by about 40 %, and low glycemic index diet combined with ω-3 fatty acid supplementation can not only improve insulin resistance, but also help with weight control [125,126]. Regular postpartum cognitive behavioral intervention modulates negative thought patterns in pregnant people with obesity after delivery, which may relieve depressive symptoms and improves executive function [127,128].

7. Conclusion

Obesity is closely associated with the risk of cognitive impairment. The pathological mechanism involves chronic neuroinflammation, intestinal gut microbiota-gut-brain axis imbalance and metabolic disorders. In clinical interventions, lifestyle modification and drug intervention can effectively improve cognitive function, and bariatric surgery also significantly reduces the risk of cognitive impairment. In the future, it is necessary to integrate multiple groups of biomarkers and dynamic monitoring systems to optimize the precise prevention and control of obesity-related cognitive impairment.

CRediT authorship contribution statement

Kai Liu: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Shu Liu:** Writing – original draft, Project administration, Methodology, Investigation. **Dong Wang:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources. **Hong Qiao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization.

Contributors

K.L. and S.L. were involved in the concept and design, and D.W. and H.Q. in the analysis and interpretation of the data. K.L. and H.Q. conducted the drafting document and rigorously revised it for intellectual content. All authors reviewed the manuscript to confirm that this is the final approved version for publication, and all authors agree to be responsible for all aspects of the work.

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Conflicts of interest

The authors declare no conflict of interest.

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Figures by figdraw.

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