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Review article

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Effects of obesity on brain health and cognition

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Abstract

Obesity is a global health issue, and cognitive impairment and elevated risk of dementia are emerging as important consequences. Clinical studies have documented that obesity over the life course is associated with cognitive decline, with midlife obesity carrying a particularly high risk. Evidence from both preclinical and clinical studies suggests that obesity has multiple pathophysiological effects on the brain, including hypothalamic dysregulation and disruptions in biological processes that affect the hippocampus and prefrontal cortex, such as metabolic, inflammatory and vascular dysfunction. In this Review, we summarize the global epidemiology of obesity and examine its clinical relevance as a risk factor for cognitive impairment and dementia. We also discuss the peripheral and central mechanisms through which obesity affects brain function and review obesity-related interventions that have been shown to improve cognition. We conclude by identifying crucial gaps in the existing clinical, translational and intervention-focused literature that warrant future investigation.

Sections

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Key points

- Obesity is a global issue and is emerging as a key factor in impaired brain health and as a possible driver of dementia.
- Midlife obesity is associated with cognitive impairment and elevated dementia risk, even after weight loss in later life.
- Morphological and structural changes in the brain in individuals with midlife obesity are linked to cognitive decline.
- Obesity acts as a feed-forward mechanism driving hypothalamic dysfunction, thereby exacerbating loss of appetite control and worsening obesity.
- Obesity impairs neuronal, microglial, metabolic and cerebrovascular function in the hippocampus, prefrontal cortex, white matter and other regions that are crucial for cognition, mirroring changes observed in ageing and dementia.
- Lifestyle, surgical and pharmacological interventions targeting obesity offer potential strategies to mitigate obesity-related cognitive impairment and dementia risk.

Introduction

Over the past two decades, the global population of individuals with obesity has doubled, and almost 900 million people are currently classified as obese[1]. The World Health Organization (WHO) defines obesity as the accumulation of excess fat that impairs overall health[2]. Although genetic predisposition can increase the risk of obesity, the rising prevalence is largely driven by factors that promote an obesogenic lifestyle, such as calorie-dense and ultraprocessed foods, low levels of physical activity and prolonged sedentary behaviour[3]. Importantly, obesity increases the risk of numerous diseases and outcomes, including cardiovascular disease, hypertension, stroke, type 2 diabetes (T2D), cancer and mortality[3].

Obesity is emerging as a key factor in impaired brain health and as a driver of elevated dementia risk. The brain is particularly vulnerable to common pathophysiological features of obesity, such as hyperglycaemia, dyslipidaemia, hypertension, systemic inflammation and vascular dysfunction. These insults lead to overall neurological dysfunction that results in cognitive impairment[4–6] and ultimately increases the likelihood of developing dementia[7]. Importantly, rates of dementia are projected to nearly triple by 2050[8], and rising obesity rates are a contributing force behind these projections. Together, the converging trajectories for obesity and dementia pose an immediate threat to the global healthcare system.

Here, we review the current global epidemiology of obesity and describe the clinical relevance of obesity over the life course as a risk factor for cognitive impairment and dementia. We also highlight the pathophysiological effects of obesity on the brain, arising both from the periphery and from within the brain, and consider currently available obesity-related interventions that improve cognitive function. We conclude by summarizing the existing gaps in the literature relating to translational and clinical research, as well as gaps in current methods of therapy development and prevention.

Global epidemiology of obesity

Obesity is a global health challenge, with prevalence increasing markedly over recent decades. Obesity is defined by a body mass index (BMI) ≥30 kg/m^2 for adults or ≥2 s.d. above the WHO Child Growth Standards median for children[2] (Box 1). Other diagnostic measures have been proposed, including central adiposity, low-grade inflammation and impairments in daily living activities, but their inclusion in clinical diagnosis remains controversial[9]. Obesity frequently coexists with hypertension, dyslipidaemia and hyperglycaemia, which collectively define metabolic syndrome (MetS)[10]. Obesity is also linked to a spectrum of diseases, including cardiovascular disease, T2D, psychiatric disorders and neurodegenerative diseases[3,11].

In 1990, obesity was observed predominantly in North, South and Central American, European and Middle Eastern countries[1]. Now, however, rates of obesity are growing globally, with prevalence also rising in African and Asian countries[1]. Women[1,12] and middle-aged adults[12] are exhibiting particularly high incidences of obesity, and trends in children increasingly mirror those observed in adults[1]. The economic impact of obesity is substantial, incurring both direct and indirect medical costs[13,14]. The WHO estimates that, if current trends continue, annual global obesity-related costs could reach US$18 trillion by 2060[15].

Obesity arises from a complex interplay of lifestyle (for example, diet and activity levels), genetic, psychological and social factors. Specifically, western and other pro-inflammatory diets[16,17], alcohol use[18] and sedentary behaviour[3,18] are linked to an elevated risk of obesity in adults. Similar risk factors apply to childhood obesity, with poor diets and reduced physical activity having central roles[19,20]. Certain Indigenous populations, such as the Samoans and Pima Native Americans, are predisposed to elevated rates of obesity, and heritable genetic differences account for the majority of BMI variation in these populations[21]. Polygenic risk scores based on obesity-specific polymorphisms can be used to assess individual obesity risk[22,23], which is exaggerated further by poor lifestyle factors[24]. A decompression analysis of UK Biobank participants concluded that lifestyle factors accounted for 42.8% of the association between genetic predisposition and obesity-related phenotypes[25], supporting the idea that genetic risk factors for obesity do not act in isolation.

Obesity risk increases with age, probably owing to changes in body composition and a transition to a more sedentary lifestyle[26]. Psychiatric disorders such as depression, anxiety and some eating disorders promote overeating, thereby contributing to obesity[3], although the precise relationship between mental health conditions and elevated BMI is unclear[27]. Prevalent antidepressant use linked to weight gain might also contribute to rising obesity rates[28]. Socioeconomic factors such as poverty further influence the likelihood of developing obesity by limiting access to healthy foods and opportunities for physical activity[29]. In summary, the causes of obesity are multifactorial; however, many contributory factors are modifiable and could be targeted to counteract the rising prevalence of this condition.

Obesity and cognitive impairment

A growing number of longitudinal and highly adjusted studies provide evidence that obesity is linked to cognitive impairment (Supplementary Table 1), which is defined as a decline in cognition, including but not limited to memory, attention and problem solving (Box 2). Cognitive impairment ranges from minor changes that do not interfere with most daily functions, commonly termed mild cognitive impairment (MCI)[30], to more severe global cognitive changes that interfere with functional abilities, as seen in conditions such as Alzheimer disease and related

Box 1 | Obesity definitions and assessments

The full diagnostic criteria for clinical obesity are beyond the scope of this Review (see Rubino et al.[9] for adult criteria and Jebeile et al.[19] and Lister et al.[20] for childhood criteria).

Obesity in adults

Generalized obesity

Generalized obesity is usually measured by BMI, calculated from the weight divided by the height squared (kg/m^2). The World Health Organization (WHO) obesity classifications for men and women are as follows:

- Overweight: 25.0 to <30.0.
- Moderate class 1 obesity: 30.0 to <35.0.
- Severe class 2 obesity: 35.0 to <40.0.
- Very severe/morbid class 3 obesity: ≥40.0.

BMI cutoffs depend on ancestry: the above cutoffs are applicable to European and African populations[51], but the cutoffs for people of Asian descent are 23.0–27.5 for overweight and ≥27.5 for obese.

Central obesity

Central obesity is a measure of visceral adiposity that is linked to cardiovascular risk. Waist circumference is a frequent measure and criterion for central obesity in the context of metabolic syndrome[216]. According to the American Heart Association–National Heart, Lung, and Blood Institute Scientific Statement, elevated waist circumference is ≥88 cm in women and ≥102 cm in men. Cutoffs vary by ancestry and issuing organization[217]:

- European: ≥80 cm for women and ≥94 cm for men (International Diabetes Federation (IDF)–WHO criteria).
- Asian: ≥80 cm for women and ≥90 cm for men (IDF–WHO criteria).
- Japanese: ≥90 cm for women and ≥85 cm for men (Japanese Obesity Society criteria).
- Chinese: ≥80 cm for women and ≥85 cm for men (Cooperative Task Force criteria).
- Middle Eastern, Mediterranean and sub-Saharan African: ≥80 cm for women and ≥94 cm for men (IDF criteria).
- Ethnic Central and South American: ≥80 cm for women and ≥90 cm for men (IDF criteria).

Waist-to-hip ratio is another widely used measure of central obesity that is increasingly used in obesity research[9], with specific cutoffs for sex and race and ethnicity.

Body fat composition

Body fat composition refers to total and regional percent fat mass, lean mass and water mass, measured using dual X-ray absorptiometry, computed tomography, magnetic resonance imaging and bioimpedance analysis[51].

Obesity in children

Generalized obesity

Generalized obesity in children is usually measured by BMI relative to sex and age-adjusted population growth classifications[19,20]:

- 0–5 years (or 0–2 years in the USA): WHO 2006 growth standard is recommended[218].
- 5–19 years: WHO 2007 growth standard, defining overweight as BMI ≥1 s.d. and obesity as BMI ≥2 s.d. above the median for age and sex.
- 2–18 years: International Obesity Task Force curves based on international data aligning with adult BMI cutoffs for overweight (25.0) and obesity (30.0) at age 18 years, used for epidemiological purposes[219].
- 2–20 years: US Centers for Disease Control and Prevention growth references, defining underweight as <5th, normal as 5th to 84th, overweight as 85th to 94th, and obesity as ≥95th percentiles[220].

Central obesity

Central obesity in children is determined by age-adjusted and sex-adjusted waist circumference based on international[221] or regional[222] growth references. A waist-to-height ratio of >0.5 does not require growth references[223].

dementias. The relationship between obesity and cognitive impairment is complex, and is influenced by age, fat distribution and metabolic comorbidities.

Even in childhood, obesity[31] (Box 1) with or without MetS[32] is associated with cognitive impairment and brain structural changes[33], potentially setting young people on the path to later-life dementia. Most of the early studies were cross-sectional[34,35], but longitudinal studies, including the large, prospective US population-based Adolescent Brain Cognitive Development (ABCD) study, are beginning to emerge. The ABCD study found that higher baseline BMI was linked to worsening psychopathology but not to cognitive impairment at 2-year follow-up[36]. However, poorer cognition and higher rates of psychopathology at baseline were linked to increased BMI at 2-year follow-up, suggesting that early cognitive deficits could trigger subsequent obesity — an assertion that was corroborated in an independent longitudinal, community-based study[37]. Alternatively, the link between cognitive impairment[38] and eating behaviours[34] could be bidirectionally linked to adiposity. It is crucial to understand how cognitive impairment and eating behaviours relate to obesity, as initiating events and trajectories might be targeted to mitigate weight gain. Individual structural and functional variations in the prefrontal cortex (PFC) are thought to predispose to overeating, thereby promoting obesity and, in turn, triggering PFC changes in a feed-forward loop[35]. Importantly, in the context of interpreting brain morphological changes in adult obesity, co-analysis of ABCD with adult UK Biobank data indicated that early-life changes in head size, rather than smaller brain sizes per se, could underlie neuroimaging traits that have been attributed to obesity-related atrophy in later life[39].

Besides childhood obesity, midlife obesity and trajectories over the life course are additional crucial factors in the relationship with cognitive impairment and dementia. The Lancet Commission on dementia prevention, intervention and care now formally recognizes midlife obesity as a dementia risk factor[7], validating seminal early work in the field[40]. The Northern Manhattan Study found that midlife but not late-life obesity, assessed by waist-to-hip ratio (WHR) measurements of central adiposity, correlated negatively with global cognition based

Box 2 | Cognitive impairment: definitions and assessments

Cognitive impairment is defined as a deficit in cognition, including but not limited to memory, attention problem solving, processing speed, and speech and language. It ranges from minor deficits (for example, mild cognitive impairment[30]) to more severe dysfunction, as seen in dementias including Alzheimer disease and related dementias. Diagnosis of cognitive impairment commonly involves tests measuring cognition (for example, memory, executive function and attention), which can be complemented by other diagnostic tools, such as neuroimaging (for example, magnetic resonance imaging, computed tomography or positron emission tomography) and plasma and cerebrospinal fluid biomarkers. A full diagnostic work-up for cognitive impairment is outlined by Bradfield et al.[224]. Below, we describe some of the assessment tools that are commonly used to screen for obesity-related cognitive impairment in the clinic.

Mini-Cog
A short 3-min test using word recall and a clock-drawing test to assess cognitive deficits. Cognitive impairment is defined by a failed test (≤2 points out of 5).

Montreal Cognitive Assessment
A cognitive test assessing memory, executive function, language, attention, orientation and visuospatial skills, commonly used to screen for cognitive deficits. Cognitive impairment is defined by a score of ≤25 out of 30.

Mini-Mental State Examination
A cognitive assessment involving questions related to attention, orientation, memory, language and ability to follow simple commands. This test is scored out of 30 points:
- ≥24 points: cognitively normal.
- 19–23 points: mild cognitive impairment.
- 10–18 points: moderate cognitive impairment.
- ≤9 points: severe cognitive impairment.

NIH Toolbox Cognitive Battery
A comprehensive assessment of multiple cognitive domains, including memory, processing speed, comprehension and problem solving. Composite cognitive scores are generated to assess overall cognitive function, in addition to scores for individual cognitive domains. All scores are standardized to enable comparison across studies. The NIH Toolbox also includes cognitive tests that are specific to children (for example, ages 3–6 years). Normative data are available that span age ranges and languages of administration[225–227].

on episodic and semantic memory, executive function and processing speed domains, even after adjusting for vascular factors[41]. In the Trøndelag Health Study, which used BMI and waist circumference as measures of obesity, midlife obesity was associated with increased dementia risk whereas being overweight in later life was linked to decreased dementia risk[42]. A similar phenomenon has been reported for incident dementia in elderly Chinese adults[43] and for cognitive impairment risk in various cognitive domains in elderly US adults[44]. The observation that midlife obesity raises whereas later-life obesity lowers dementia risk is termed the dementia obesity paradox. To address this paradox, Cannon et al. assessed incident dementia in the Atherosclerosis Risk in Communities study, stratified by late-life BMI status and BMI change over 8 years[45]. Only participants whose midlife BMI decreased in late life were at elevated dementia risk, regardless of whether their late-life BMI was low, normal or high. These findings suggest that BMI trajectories from midlife to late life are more important than late-life BMI per se in determining the risk of dementia[45].

In addition to obesity trajectories, fat distribution is a key factor in the correlation between obesity and cognitive impairment. A prominent risk factor that has been identified across diverse populations is visceral adipose tissue[46] — an important driver of central obesity that is measured by waist circumference, WHR, waist-to-height ratio and fat mass[43,47–49]. A global meta-analysis involving 5,060,687 participants across 21 studies from 10 countries (the USA, Sweden, France, Italy, Australia, Chile, Singapore, China, the UK and the Republic of Korea) reported that central obesity significantly increased the risk of cognitive impairment and dementia, emphasizing the importance of fat distribution over BMI, regardless of age[6]. Although the findings regarding the effects of elevated visceral adipose tissue on cognitive impairment and dementia risk are well established, with few inconsistencies, the role of other fat depots is less clear[46], with subcutaneous fat being shown to pose a risk in some studies[46,49] but not in others[46]. A study involving 793 participants in China measured 27 body composition variables that were condensed into six factors, one of which, central obesity, increased the risk of cognitive impairment, whereas two others, muscle mass and leg-dominant fat distribution, lowered the risk[50]. This study suggests that central fat accumulation could be more detrimental than limb fat accumulation, but further research is warranted.

Fat distribution varies by race[51] and sex, which might influence the relationship between obesity and cognitive impairment. Race-specific BMI and waist circumference cutoffs have been developed (Box 1), which are crucial for studies to adopt. Lack of race-specific cutoffs for some metrics could affect study findings, leading to inconsistent results. Future investigations should establish whether results that differ by race arise from inherent differences in body fat distribution and the relationship with cognitive impairment or from differences in study design. Besides the influence of race or ethnicity on body fat distribution, we also need to consider the cutoffs that define MCI, which, if not properly defined, could overclassify non-white individuals as showing impairment[52].

Several studies have used stratified analyses to assess whether the influence of obesity on cognitive impairment and dementia varies according to sex. However, the findings so far are mixed, with different studies showing that obesity confers a higher[53–55] or a similar risk[42,56] of cognitive impairment in women compared with men. A meta-analysis and systematic review concluded that waist circumference had no effect on the risk of cognitive impairment and dementia in men but showed a positive correlation with the risk in women[6]. Thus, women with obesity might be at higher risk of cognitive impairment than their

male counterparts, but the findings need to be confirmed in studies that adjust for covariates that differ by sex. More research is urgently needed to better understand the complex interrelationships between adiposity, race, sex, age and brain health, especially in developing countries (Fig. 1). Given the growing prevalence of obesity worldwide, a full understanding of how obesity influences cognition is crucial for public health. The current data suggest that interventions targeting midlife weight will be particularly important, and the WHO advocates for the development of global public health strategies to preserve cognition over the lifespan and reduce dementia risk[57].

The proposed studies must also address factors beyond race, sex and age. For example, sarcopenic obesity, a condition characterized by low muscle mass and high fat mass, was found to be associated with impaired cognition and reduced functional independence in cohorts of older frail adults[6]. Another important confounding factor is MetS, as T2D, dyslipidaemia and hypertension are also dementia risk factors[7]. In addition, obesity is frequently comorbid with other conditions, such as depression and sleep disorders, that also influence cognition, underscoring the need for studies to comprehensively adjust for confounders.

Pathophysiological effects of obesity on the brain

Under physiological conditions, metabolic, endocrine, neurological and immune processes systemically function in a coordinated manner to maintain energy homeostasis and support brain health. In obesity, chronic caloric excess disrupts this balance, driving widespread peripheral pathophysiological changes that directly and indirectly affect the central nervous system[58].

Adipose tissue has a central role in obesity[59]. Under physiological conditions, this tissue functions as a tightly regulated metabolic and endocrine organ that stores excess energy and releases free fatty acids (FFAs) during periods of increased energy demand[59,60]. In obesity, adipose tissue expands through adipocyte hypertrophy (increased cell size) and hyperplasia (increased cell number), predominantly within visceral depots. Visceral adipose tissue is particularly susceptible to hypoxia and oxidative stress and, when inflamed, releases increased amounts of inflammatory circulating cytokines and adipokines (for example, leptin), thereby promoting the development of systemic low-grade, chronic inflammation[59]. This dysfunctional state is characterized by impaired insulin responsiveness, altered secretory adipokine profiles and increased basal lipolysis, which contributes to dyslipidaemia characterized by increased circulating FFAs and triglyceride-rich lipoproteins[61] and might drive cognitive impairment[62,63]. In addition, chronic low-grade inflammation associated with obesity, potentially mediated by adipokines and adipose tissue-resident immune cells, contributes to an increased risk of dementia[64]. Together, the robust physiological changes induced by obesity drive systemic metabolic disruption that targets the brain and increases the risk of dementia[65,66].

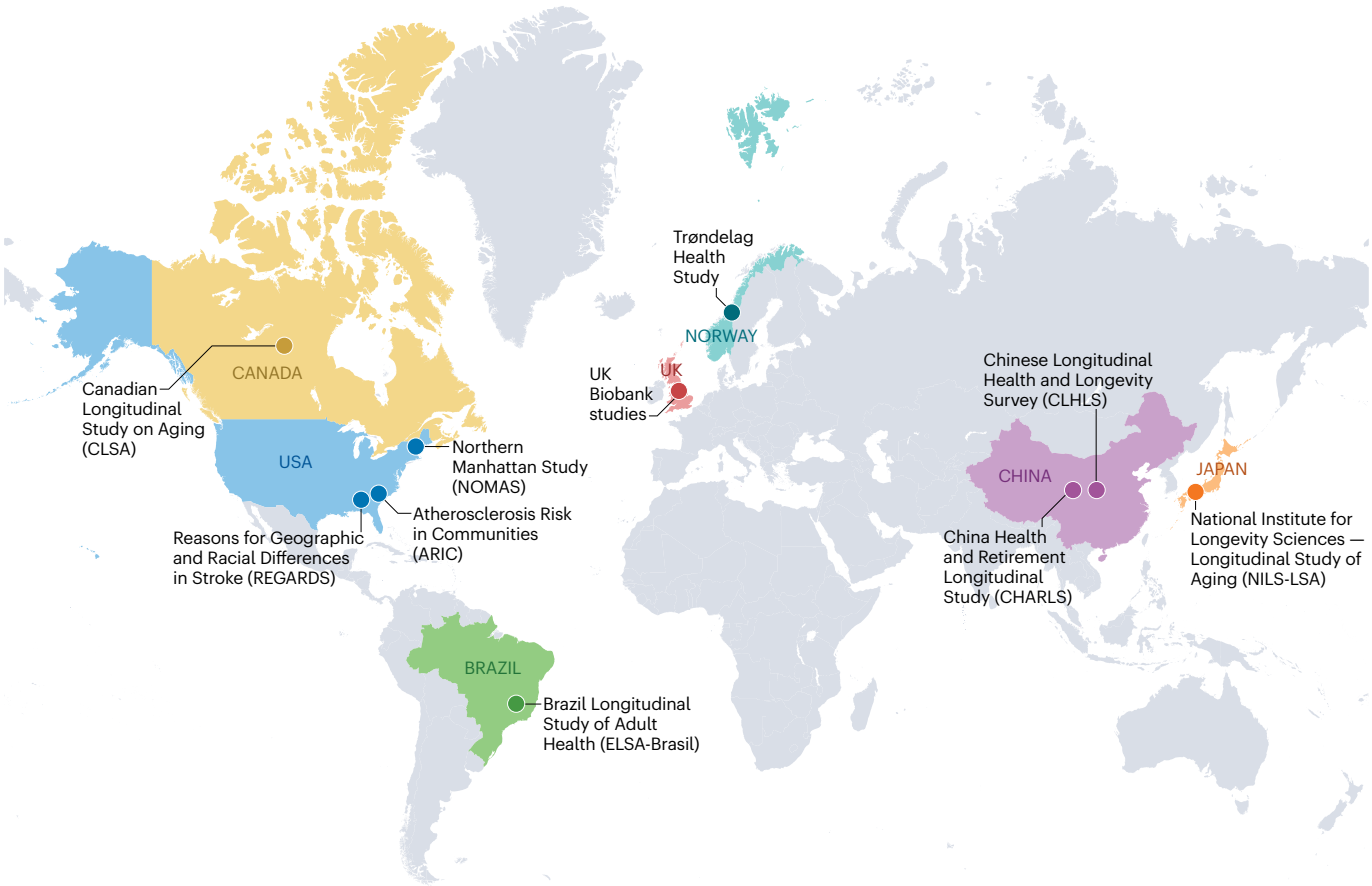
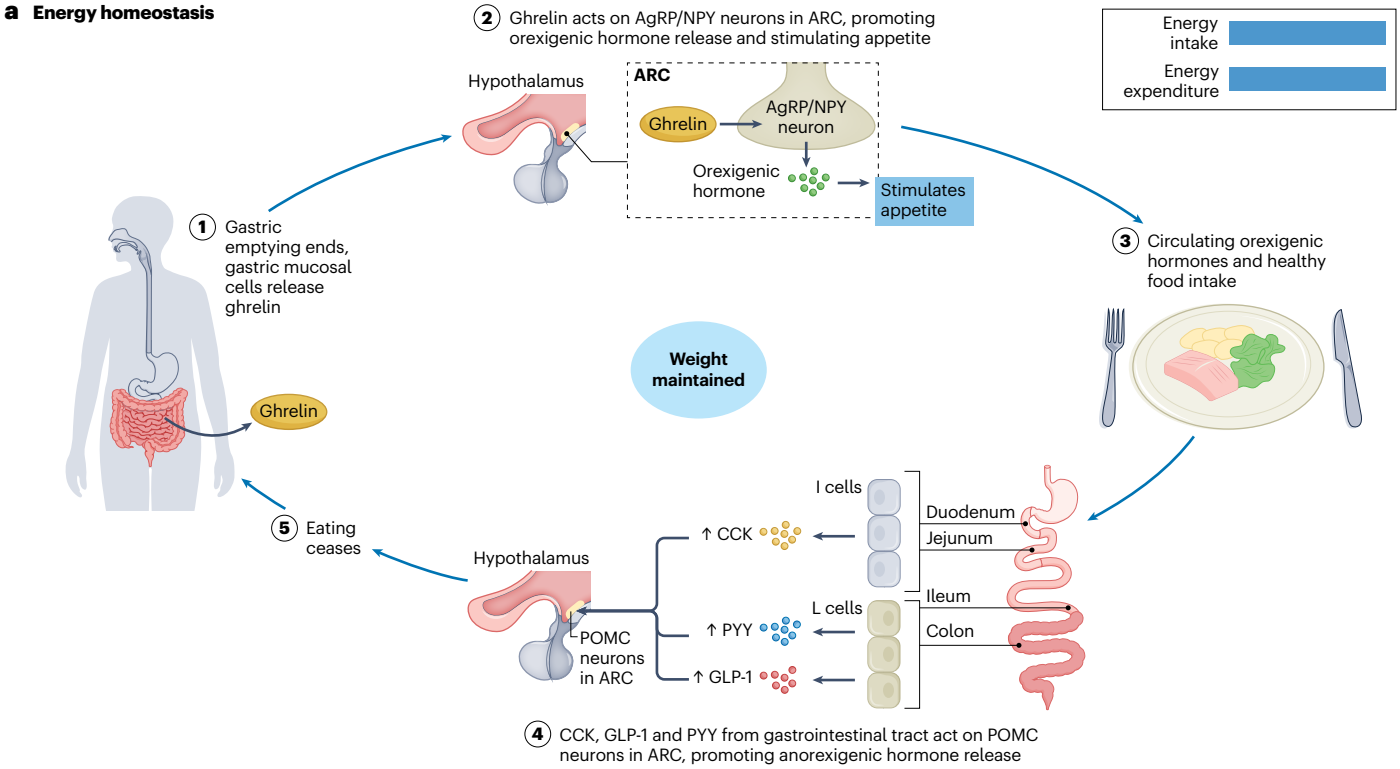


Fig. 1 | Clinical studies investigating obesity-related cognitive impairment. The figure indicates the locations of recent studies investigating obesity-related cognitive impairment.


a Energy homeostasis
2 Ghrelin acts on AgRP/NPY neurons in ARC, promoting orexigenic hormone release and stimulating appetite
Hypothalamus
ARC
Ghrelin
AgRP/NPY neuron
Orexigenic hormone
Stimulates appetite
Energy intake
Energy expenditure
1 Gastric emptying ends, gastric mucosal cells release ghrelin
Ghrelin
3 Circulating orexigenic hormones and healthy food intake
Weight maintained
5 Eating ceases
Hypothalamus
POMC neurons in ARC
↑ CCK
↑ PYY
↑ GLP-1
I cells
L cells
Duodenum
Jejunum
Ileum
Colon
4 CCK, GLP-1 and PYY from gastrointestinal tract act on POMC neurons in ARC, promoting anorexigenic hormone release

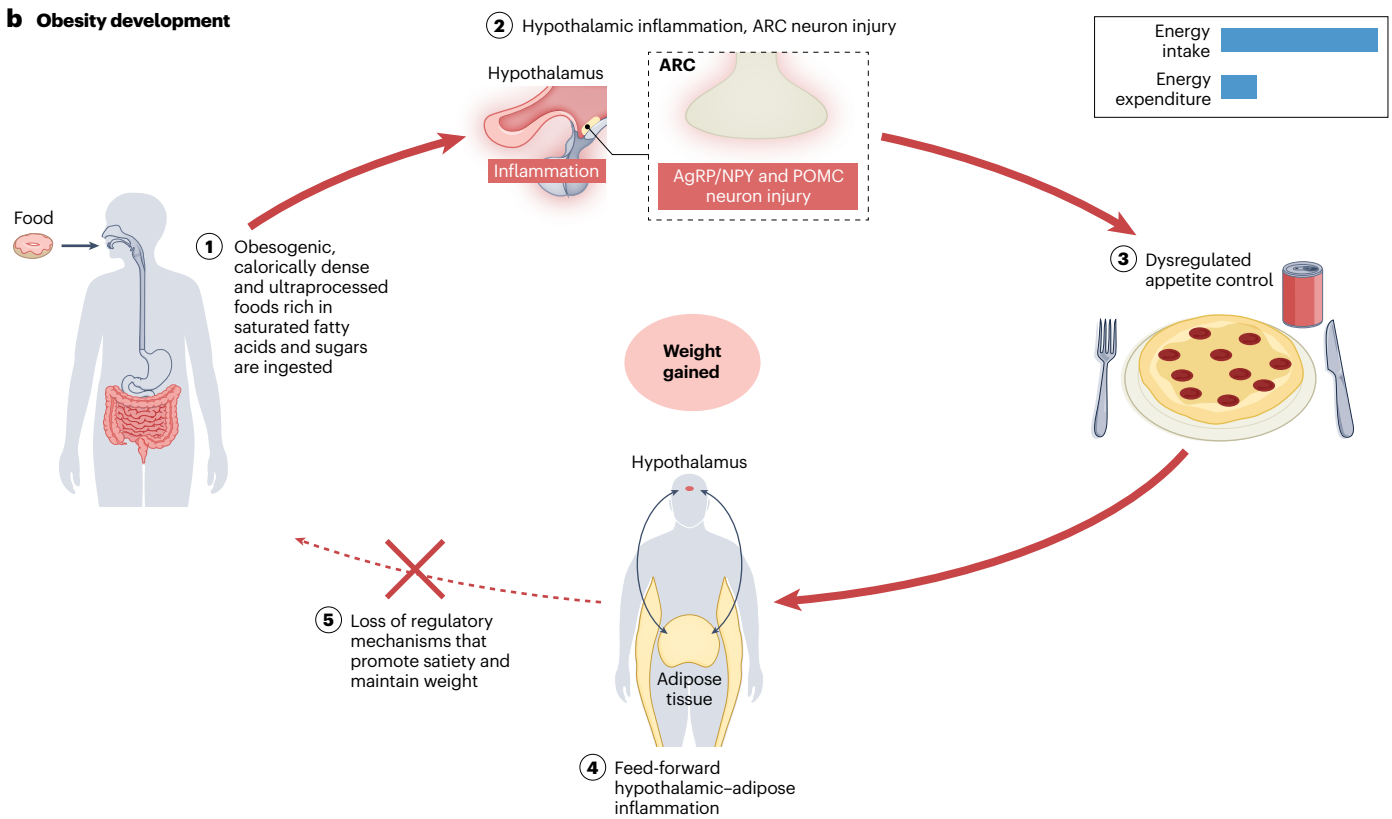

b Obesity development
2 Hypothalamic inflammation, ARC neuron injury
Hypothalamus
ARC
Inflammation
AgRP/NPY and POMC neuron injury
Energy intake
Energy expenditure
Food
1 Obesogenic, calorically dense and ultraprocessed foods rich in saturated fatty acids and sugars are ingested
3 Dysregulated appetite control
Weight gained
Hypothalamus
5 Loss of regulatory mechanisms that promote satiety and maintain weight
Adipose tissue
4 Feed-forward hypothalamic–adipose inflammation

Fig. 2 | Pathophysiological effects of obesity on the hypothalamus. **a**, Homeostatic conditions. After a meal is fully digested in the gastrointestinal tract and gastric emptying ends, gastric mucosal cells are signalled to release ghrelin (1). Ghrelin is an orexigenic hormone that acts on agouti-related peptide and neuropeptide Y (AgRP/NPY)-expressing neurons in the hypothalamic arcuate nucleus (ARC), promoting further orexigenic hormone release, which stimulates hunger (2). Triggering of appetite promotes food intake, which, in people of healthy weight, generally consists of a healthy meal of moderate portion size. Eating (3) promotes release of cholecystokinin (CCK) from I cells of the proximal duodenum and jejunum and glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) from L cells in the ileum and colon (4). Eating also stimulates release of insulin from β-cells of the pancreas and leptin from adipocytes. GLP-1, CCK and PYY are anorexigenic hormones that act on the pro-opiomelanocortin (POMC)-expressing neurons of the hypothalamic ARC, promoting further anorexigenic hormone release, which stimulates satiety. Triggering of satiety promotes food intake cessation (5) and healthy weight. This cycle repeats to balance energy intake with energy expenditure to maintain weight. **b**, Pathological conditions of obesity. Ingestion of obesogenic, calorically dense and ultraprocessed foods rich in saturated fatty acids and sugars (1) triggers hypothalamic inflammation, thereby injuring ARC neurons (2). ARC neuron dysfunction leads to dysregulated appetite control (3). Hyperphagia expands adipose tissues through adipocyte hypertrophy (increased cell size) and hyperplasia (increased cell number), predominantly within visceral depots (4). The expanded adipose tissue becomes hypoxic and inflamed and releases pro-inflammatory cytokines and adipokines, thereby exacerbating hypothalamic inflammation in a feed-forward mechanism (4). Rising insulin and leptin resistance in the hypothalamus further drives appetite dysregulation (5). For full reviews on these mechanisms, see refs. 83 and 71.

Many studies have explored the pathophysiology of the brain in the obese state in preclinical animal models. Genetic mouse models of obesity commonly involve disruption of leptin signalling, leading to increased fat mass and the development of other comorbid metabolic diseases, such as T2D[67]. However, obesity can also be induced through a high-fat diet (HFD)[67], which mirrors the western diet — a key driver of obesity in humans. Animals that are fed this diet have increased body weight and adiposity[67]. Both leptin-based and HFD models can also develop insulin resistance, hyperglycaemia, dyslipidaemia[67] and even vascular disease[68]. These features of MetS are also present in the low-density lipoprotein receptor knockout mouse, in which dyslipidaemia coupled with chronic vascular inflammation drives cerebrovascular dysfunction associated with dementia[69]. Together, these models can be used to evaluate the neurological consequences of obesity, including disruptions to metabolic, vascular and cellular mechanisms that promote cognitive impairment.

Current translational evidence suggests that obesity targets the hypothalamus and hippocampus–PFC axis through intrinsic and peripheral mechanisms, which lead to neuronal dysfunction, glial activation, elevated metabolic and oxidative stress, cerebrovascular dysfunction and chronic inflammation and induce learning and memory deficits and anxiety (Box 2). Dysfunction of these pathways disrupts the neurobiology of the brain, leading to cognitive impairment, and could increase the risk of dementia. In the sections that follow, we describe the neurobiological changes in preclinical models of obesity, complemented with evidence from humans, and consider how they correspond to changes in overall cognition.

Effects on the hypothalamus

The hypothalamus is the brain's command centre for energy regulation, operating through complex circuitry that controls energy intake and expenditure. Under homeostatic conditions, the hypothalamic arcuate nucleus (ARC) maintains balance through careful orchestration of agouti-related peptide/neuropeptide Y (AgRP/NPY)-expressing neurons, which signal hunger, thereby stimulating food intake, and pro-opiomelanocortin-expressing neurons, which signal satiety, thereby reducing food intake. These effects are mediated through interactions with paraventricular nucleus (PVN) neurons[70] (Fig. 2a).

The ARC coordinates its activity with the median eminence, a circumventricular organ unprotected by the blood–brain barrier (BBB) that senses circulating hormones and nutrient levels and relays signalling cues to the ARC. Adipose-derived hormones, such as leptin, together with gastrointestinal hormones, such as glucagon-like peptide 1 (GLP-1) and peptide YY (PYY), activate ARC signalling pathways to regulate appetite[71]. In obesity, despite elevated circulating leptin levels, central leptin resistance blunts appetite suppression[72]. Similarly, insulin resistance[73], along with impaired GLP-1 and PYY signalling, disrupts hypothalamic control of energy balance and might influence brain regions involved in reward processing and cognition, while orexigenic signals such as ghrelin further destabilize feeding regulation. Brain-derived neurotrophic factor (BDNF)-expressing neurons in the ventromedial hypothalamus integrate interoceptive inputs to motor centres that regulate food consumption and jaw movements, ultimately linking hypothalamic activity to the physical action of eating[74].

Finer mapping of the hypothalamic circuitry can identify the most susceptible regions or pinpoint neuronal populations that could be targeted to better control appetite and curb obesity. Spatial transcriptomic analysis of the hypothalamus identified the infundibular nucleus and PVN as the regions most susceptible to metabolic-induced dysfunction[75]. Acute pro-opiomelanocortin neuronal activation only marginally affects appetite, hinting at as-yet undiscovered leptin-responsive neuronal populations. Indeed, leptin-activated basonuclin 2 (BNC2)-expressing neurons that acutely promote satiety by directly inhibiting AgRP/NPY neurons have been identified in the ARC[76]. Knockout of the leptin receptor from BNC2-expressing neurons promotes hyperphagia and obesity, mimicking knockout of the leptin receptor from AgRP/NPY neurons. Leptin-controlled hypothalamic GABAergic neurons within the ARC that express prepronociceptin and NPY also control feeding and are activated by palatable food consumption, thereby promoting hyperphagia[77,78]. Conversely, ventromedial hypothalamus BDNF-expressing neurons normally inhibit overfeeding and obesity in animals fed a highly palatable or chow diet[74]. Within the PVN, dopaminergic neurons extend the food intake phase[79], whereas oxytocin-expressing neurons suppress weight gain, food intake and plasma triglyceride and leptin levels[80]. Besides regulation of energy intake, hypothalamic GABAergic neurons expressing cellular retinoic acid-binding protein 1 regulate energy expenditure by promoting physical activity, as well as increasing body temperature and adaptive thermogenesis, thereby helping to prevent obesity[81]. These specialized neuronal populations potentially unlock new therapeutic avenues through appetite suppression[82] (see 'Novel pharmacological interventions' section below).

Through the elevation of saturated FFAs and hyperglycaemia, obesity dysregulates hypothalamic activity by promoting inflammation, with microgliosis, astrogliosis and pro-inflammatory cytokine release, often before the onset of substantial weight gain[83] (Fig. 2b). Circulating

FFAs differentially influence hypothalamic activation depending on their saturation level and double-bond position[84]. In obesity, hypothalamic inflammation is accompanied by increased expression of neurodegenerative pathways[85], reduced numbers of dendritic spines on neurons in the medial basal hypothalamus[86] and loss of satiety, with consequent increased peripheral adiposity. Adipose-derived inflammation further drives hypothalamic impairment, creating a feed-forward mechanism that worsens obesity. Besides hypothalamic inflammation, obesity affects downstream metabolic and cardiometabolic parameters. Hypothalamic glial inflammation, involving astrocytes[87] and microglia[88], influences glucose levels and glucose tolerance. Obesity-related hyperleptinaemia induces hypertension via hypothalamic astrocytes and expanded micro-angioarchitecture[89]. Obesity also promotes iron overload in AgRP/NPY-expressing neurons, with consequent overeating, adiposity, insulin and leptin resistance, and oxidative and endoplasmic reticulum stress[90]. In addition, obesity drives ARC neurofibrosis and extracellular matrix remodelling, thereby promoting insulin resistance and metabolic dysfunction[91].

Effects on the hippocampus and prefrontal cortex

The hippocampus and PFC are fundamental to the architecture of human cognition. The hippocampus is essential for memory consolidation, specifically for spatial, temporal and contextual information[92]. Conversely, the PFC is the primary seat of executive functions, managing working memory, behavioural flexibility and sustained attention[93]. These regions do not operate in isolation: hippocampal neurons project to the medial PFC[94], and both regions receive cholinergic innervation from the basal forebrain[95]. Together, these structures have central roles in cognition, making them prime targets of obesity-related insults.

Growing evidence suggests that obesity induces pathological changes in these brain regions (Fig. 3). The relationship between excess adiposity and grey matter atrophy in the hippocampus and PFC has been reviewed previously[96]. A prospective cohort study of UK Biobank participants reported that midlife central obesity and elevated WHR were associated with reduced grey matter and total brain volumes[5]. Trajectory analyses, also of UK Biobank participants, found that transitioning to obesity was associated with acceleration of brain morphology changes (for example, cortical thinning) and cognitive decline[97]. Dyslipidaemia has also been linked to reduced cortical thickness and whole-brain volume, in addition to cognitive impairment[4,98], and adipokines have been linked to reduced hippocampal volume[63]. Cross-sectional studies indicate that grey matter volume in the hippocampus and PFC is reduced in individuals with high BMI[99], central obesity[100] and elevated body fat percentage[101], and obesity-related reductions in PFC grey matter volume have been linked to cognitive impairment[99]. In addition, obesity is associated with alterations in brain white matter. White matter hyperintensities are increased in individuals with obesity[5], indicating potential tissue damage, and white matter volume is reduced in individuals with high BMI[102], suggesting that communication between brain regions — that is, the hippocampus–PFC axis — is compromised. Hippocampal atrophy is a common characteristic of ageing and dementia[103], supporting the idea that obesity accelerates brain ageing and increases dementia risk.

Impaired neuronal activity is a key consequence of reduced brain volume. Activity within the hippocampus–PFC circuit, characterized by long-term potentiation (LTP), facilitates successful learning and memory[104]. Obesity is associated with impaired neuronal function within this circuit — a feature that is also a hallmark of ageing and dementia[105]. For example, mice fed an HFD exhibit impairments in synaptic plasticity and LTP, leading to dysfunction of spatial working memory and recognition memory[106]. Hippocampal neuronal morphology is altered in obesity, including reductions in dendritic length and spine density[107], as well as changes in perineural nets in the dentate gyrus[108].

The drivers of neuronal dysfunction in obesity remain unclear, although one study in a mouse model of obesity indicated that impaired synaptic plasticity was mediated by dysregulated microRNA expression[109]. Preclinical studies support the idea that obesity induces oxidative stress, arising from either the endoplasmic reticulum[110] or mitochondrial dysfunction[111], leading to the accumulation of reactive oxygen species[112]. Interestingly, obesity and its related cognitive impairment can be induced by deletion of lipoprotein receptor-related protein 1 in GABAergic neurons in rodent models[113], suggesting possible intrinsic neurological mechanisms that drive obesity. However, further studies are needed to elucidate these mechanisms and their drivers.

Brain insulin resistance, potentially affecting diverse cell types, is a hallmark of obesity and contributes to cognitive impairment[114]. Elevated levels of phosphorylated insulin receptor 1, a marker of insulin resistance, are observed in the hippocampus in HFD-fed mice and are associated with reduced markers of synaptic function and increased cognitive impairment[115]. Hippocampal insulin resistance in obesity might be driven in part by impaired microvascular function[116]. Importantly, hippocampal insulin resistance could promote unhealthy decisions around food[117], further contributing to worsening obesity. In humans, obesity and peripheral insulin resistance were found to be associated with reduced hippocampal activity during episodic memory recall, which coincided with impairments in memory performance[118]. However, direct measurements of insulin signalling in the brain remain challenging. An observational study in 71 older adults with obesity but without T2D found no association between neuron-specific insulin resistance and cognitive impairment[119]. Of note, however, this study relied on indirect assessment of brain-specific insulin signalling by measuring circulating neuron-derived extracellular vesicles containing insulin signalling-related proteins[119], highlighting the challenges of disentangling peripheral from brain-specific insulin resistance and emphasizing the need for novel measures.

Another hallmark of obesity-associated neuropathophysiology is the chronic activation of microglia[120], which could drive synaptic dysfunction through impaired neuron–microglia communication. Activated hippocampal microglia contribute to cognitive impairment by internalizing synaptosomes, leading to a measurable reduction in dendritic spine density and to impaired LTP[121]. Both acute[122] and long-term[120] HFD induce microglial activation. Obesity also leads to intracellular lipid accumulation within microglia[107], resulting in increased mitochondrial reactive oxygen species production and defective phagocytosis[123]. However, the composition of these lipids and whether they reflect circulating lipid species remains unclear. Importantly, evidence suggests that obesity-related cognitive impairment could be prevented by abrogating microglial activation through CX3C chemokine receptor 1 knockout or minocycline treatment[121].

Studies conducted over the past few years have identified a molecular hub that mediates microglial dysfunction, with pleiotrophin, a cytokine regulator of energy homeostasis, emerging as a central player. Deletion of the pleiotrophin gene in HFD models attenuates microglial activation and confers protection against cognitive decline[108]. In addition, the cGAS–STING pathway, an innate immune sensor of cytosolic double-stranded DNA, serves as a crucial link between metabolic dysfunction and neuroinflammation[124,125]. Although activation of this

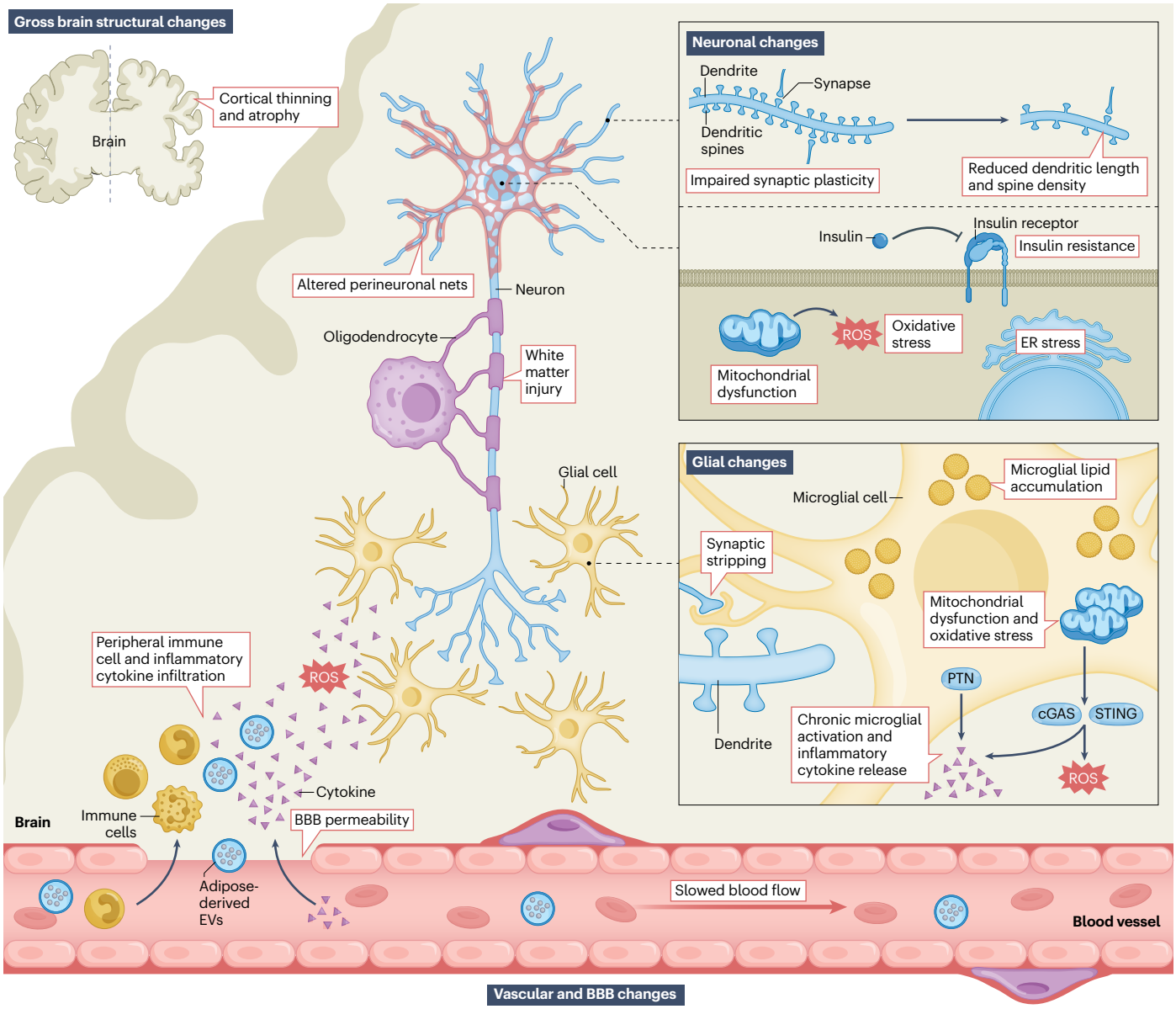


Fig. 3 | Pathophysiological effects of obesity on the hippocampus and prefrontal cortex. Obesity is associated with wide-ranging pathology in the brain, involving the hippocampus and prefrontal cortex. On the larger scale, obesity is linked to gross brain structural changes, including grey matter atrophy, white matter hyperintensities and reduced blood flow. Cellular changes in neurons and glia also occur: neurons exhibit reduced synaptic plasticity and dendritic spines, and microglia become chronically activated. Astrogliosis and myelin thinning are also present. Insulin resistance (shown in this figure in neurons but potentially also affecting other cell types), mitochondrial dysfunction, inflammation and oxidative and endoplasmic reticulum (ER) stress are key features. In addition, breakdown of the blood–brain barrier (BBB) facilitates infiltration into the brain of peripheral immune cells, inflammatory factors and extracellular vesicles (EVs), further aggravating inflammation and oxidative stress. PTN, pleiotrophin; ROS, reactive oxygen species.

pathway is a recognized hallmark of neurodegenerative diseases in general[126], HFD models specifically implicate cGAS–STING signalling in driving the microglia-mediated cognitive impairment that is observed in obesity[122]. Other glial cells besides microglia also contribute to obesity-related cognitive impairment[127], as described in Box 3.

Obesity-related metabolic stress induces systemic vascular dysfunction[128] and, consequently, directly affects the brain's cerebrovascular system and cognitive function. A mediation analysis of more than 20,000 UK Biobank participants demonstrated that hypertension mediated the relationship between obesity and cerebrovascular disease, which was associated with cognitive impairment and altered brain morphology, including reduced cortical thickness and volume[4]. These findings were supported by a cross-sectional study in which individuals with obesity and metabolic dysfunction (for example, hypertension, hyperglycaemia, high triglycerides, hypoalphalipoproteinaemia and reduced kidney function) had an elevated risk of cerebrovascular

Box 3 | Effects of obesity on astrocytes and oligodendrocytes

Neuronal function is aided by glia, including microglia, astrocytes and oligodendrocytes[127]. Consequently, the mechanisms underlying obesity-related cognitive impairment are non-cell-autonomous, with a breakdown in function of both neuronal and glial cells. Microglial contributions are discussed in the main text, and here we briefly describe astrocyte and oligodendrocyte dysfunction in obesity-related cognitive impairment.

Astrocytes

Under homeostatic conditions, astrocytes support neurons by recycling neurotransmitters through the glutamate–glutamine shuttle and maintaining the integrity of the blood–brain barrier[127]. However, obesity adversely affects hippocampal astrocytes, increasing their reactivity[228,229], altering their morphology[230] and promoting apoptosis[231], all of which are linked to cognitive impairment. Deficient astrocyte metabolism — for example, through impaired leptin signalling — compromises neuronal synaptic transmission by reducing glutamate neurotransmission in the hippocampus[232]. Under conditions of obesity, astrocytes also release extracellular vesicles, which induce synaptic dysfunction and cognitive impairment[233], and exhibit altered transcriptomic profiles[136].

Oligodendrocytes

Under homeostatic conditions, oligodendrocytes contribute to neuronal activity by generating myelin, which facilitates saltatory signal transmission[127]. In addition, oligodendrocytes perform metabolic functions by transferring energy substrates, such as lactate, to neurons, thereby supplementing energy production and activity. However, obesity in or outside the context of type 2 diabetes alters lipid content in myelin[234], diminishes the number of oligodendrocyte progenitor cells and inhibits their differentiation into mature oligodendrocytes[111], and reduces myelination[235–237], potentially contributing to white matter atrophy and cognitive impairment[238]. Modelling of obesity in vitro by increasing palmitate levels impairs oligodendrocyte mitochondrial activity[111] and promotes the release of extracellular vesicles that induce insulin resistance in neurons[239].

disease[129], suggesting that cerebrovascular pathology could underlie obesity-related cognitive impairment. In translational models, middle cerebral artery blood flow is reduced in HFD-fed mice, and both cognitive and vascular function correlate negatively with increasing visceral adiposity[130]. Furthermore, cerebral small vessel disease can be induced in mice with impaired leptin signalling or low-density lipoprotein receptor deficiency when fed an HFD, as indicated by reduced hippocampal cerebral blood flow[131]. However, some of these effects could be mediated by sex differences[132], which warrant further investigation.

Peripheral mediators of obesity also directly affect the cerebrovasculature by compromising the integrity of the BBB[133], similar to processes that occur in natural ageing and dementia. Preclinical studies demonstrate that even short-term (for example, 3-day) exposure to an HFD can induce hippocampal BBB permeability, potentially mediated by obesity-associated increases in tumour necrosis factor levels[134]. Single-nucleus RNA sequencing studies in obese T2D animal models revealed disruption of biological signalling pathways in hippocampal neurovascular cells, including those involved in angiogenesis, metabolic signalling and inflammation[135,136]. Increased BBB permeability might also result from disruptions in tight junction proteins, as observed in a transgenic mouse model of Alzheimer disease fed a western diet[137]. Consequently, peripheral inflammatory insults could promote neuroinflammation and oxidative damage, which inflict deleterious effects on brain regions that are essential for cognition, such as the hippocampus[138]. In addition, obesity-related BBB dysfunction might facilitate the infiltration of peripheral immune cells into the brain[139], as well as enhancing transport of adipose-derived extracellular vesicles[140], which preferentially accumulate in hippocampal neurons and induce synaptic loss and cognitive impairment through their microRNA cargo[140].

Overall, obesity induces a robust neuroinflammatory response, which affects multiple cell types in the hippocampus and PFC. However, whether obesity-related neuroinflammation is a result of systemic inflammatory activation or develops independently in parallel is uncertain. Furthermore, even acute HFD (≤10 days) elevates Alzheimer disease-linked biomarkers, such as amyloid-β and phosphorylated tau, and the expression of Alzheimer disease-related genes[141], further supporting obesity as a risk factor for dementia. The pathophysiological effects of obesity on the hippocampus and PFC mirror the natural ageing process. Evidence from the hippocampal transcriptome of HFD-fed mice suggests that they experience premature ageing and inflammation, accompanied by impairments in fear and contextual memory[142]. However, additional studies are necessary to fully substantiate this hypothesis.

Effects of obesity-related interventions on cognitive impairment

Given the adverse effects of obesity on brain health, weight-loss-promoting interventions could mitigate the risk of cognitive impairment[143]. These interventions might exert indirect effects (for example, through systemic improvements in insulin resistance, dyslipidaemia or inflammation) or direct effects (for example, activation of neuroprotective pathways or receptor binding) on the brain. In this section, we review the efficacy of lifestyle, surgical and pharmacological interventions (Fig. 4 and Supplementary Table 2), drawing primarily on clinical studies, supplemented with relevant preclinical evidence.

Lifestyle interventions

Diet. Various dietary interventions have been explored in obesity-associated cognitive impairment (Box 4). Most studies focus on calorie restriction, either alone or combined with other diets, such as the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diet or the ketogenic diet. Besides diet composition, some studies also examined the timing of food intake, such as intermittent fasting (Box 4). Adherence to these diets was found to improve systemic metabolism, including obesity, lipid profiles, glucose and insulin sensitivity, and glycated haemoglobin (HbA1c) levels[144]; however, studies evaluating their efficacy for improving obesity-related cognitive impairment remain sparse. Some studies suggest that calorie restriction[145–148], with or without the MIND diet[146–148], might improve cognition (for example, working memory) in obese individuals, although the added benefit of

the MIND diet over calorie restriction remains unclear[146,147]. However, some studies noted no benefit from either calorie restriction or the MIND diet[149]. The ketogenic diet, with[148] or without[150] calorie restriction, might also improve cognition, but the evidence is limited.

Intermittent fasting[151] by restricting eating hours can also serve as a form of calorie restriction, thereby potentially improving memory. One study found that intermittent fasting promoted weight loss to a greater extent than isocaloric calorie restriction but did not produce additional improvements in processing speed and attention[145]. By contrast, a study including calorie restriction and intermittent fasting arms with similar calorie intake found that intermittent fasting was associated with superior cognition in multiple domains[148]. Therefore, the relative efficacies of intermittent fasting versus calorie restriction, with or without other dietary modifications, remain unclear. An ongoing Spanish clinical trial (NCT05880095) is assessing the effects on cognition of an unrestricted Mediterranean diet compared with calorie-restricted and calorie-unrestricted intermittent fasting Mediterranean diets. The results are expected by the end of 2026.

Besides clinical studies, preclinical research in HFD-fed rodents has demonstrated calorie restriction-related[152,153], intermittent fasting-related[154] and ketogenic diet-related[155] improvements in cognitive function in tandem with beneficial effects on neurogenesis, synaptic function, mitochondrial health, BBB function, neuroinflammation and Alzheimer disease pathology. These preclinical studies further support the nascent clinical evidence that weight-loss-promoting dietary interventions can potentially enhance cognitive function.

Exercise. Various exercise modalities have also been evaluated for improving cognition in obese individuals (Box 4). A meta-analysis[156] and a systematic review[157], based on cumulative evidence, suggested that diverse exercise modalities, alone[156] and combined with diets[157], had beneficial effects on executive function[156] and working memory[157] in overweight or obese participants. A meta-analysis of overweight or obese children concluded that aerobic exercise improved executive function compared with other exercise regimens[158]. Primary studies have also demonstrated the benefits of various exercise modalities. For example, a physical–cognitive exercise routine – that is, dual training simultaneously involving exercise and cognitive activity – improved memory in overweight or obese postmenopausal women, although it was outperformed by physical–cognitive exercise combined with intermittent fasting, which improved both memory and executive function[159]. However, contrary to some of the literature[145,148,151], the study found no effects from intermittent fasting alone[159]. In overweight or obese adolescents, REVERIE, a virtual reality table tennis or soccer sports system, seemed to outperform physical table tennis or sports in terms of enhancing cognition, although both approaches produced similar improvements in metabolic and fitness parameters[160]. The investigators leveraged plasma multiomics to gain mechanistic insights into the response to REVERIE, and they identified distinct lipid, metabolite and protein signatures that were associated with the intervention.

This approach builds on previous studies, such as ActiveBrains[161], which also molecularly profiled the response to exercise in obese adolescents, as well as smaller studies demonstrating that exercise-mediated improvements in brain[162] and peripheral[163] insulin sensitivity and cerebrovascular function[164,165] were associated with improved cognition. Studies in HFD-fed rodents highlighted further exercise-related brain changes, including beneficial alterations in neurotrophic factors, mitochondrial health, neuroinflammation and Alzheimer disease pathology[166]. Combining diet and exercise might enhance cognition[167], although some of the data are contradictory[155], and further investigation is warranted.

Overall, the available data point towards exercise as a viable option to target obesity-related cognitive impairment. However, the high heterogeneity and low methodological quality of the few studies that have been conducted so far limit the conclusions that can be drawn[156,157]. In addition, some studies lacked information on exercise duration

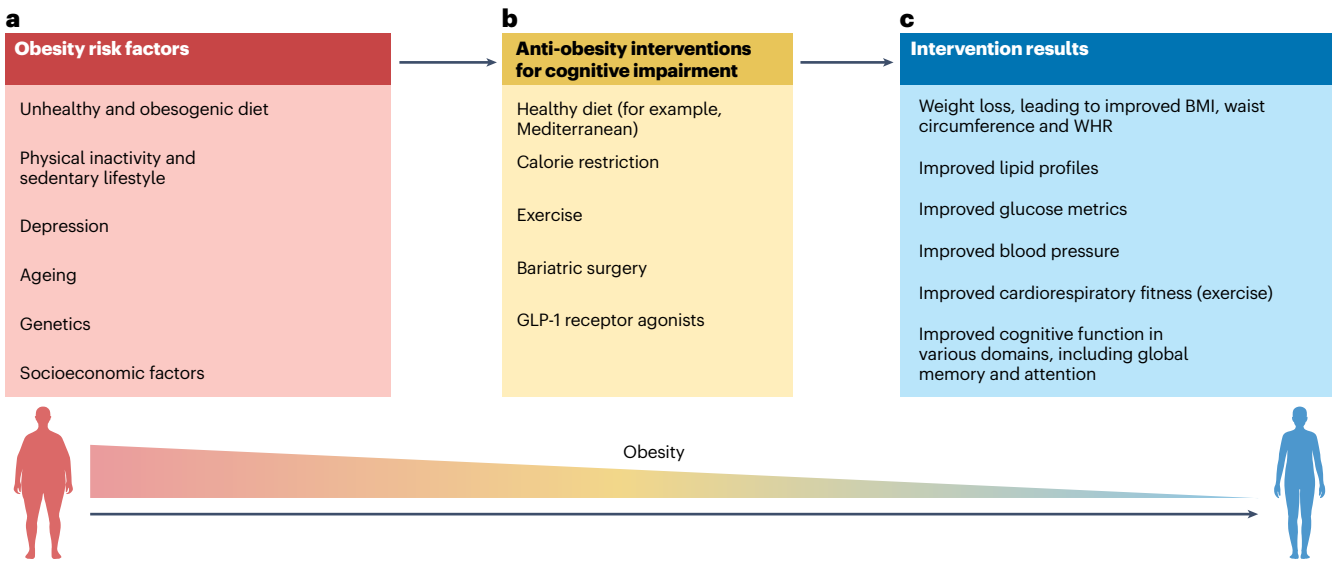


Fig. 4 | Risk factors for obesity and related cognitive impairment, and intervention strategies. a, Risk factors for obesity (see 'Global epidemiology of obesity' section). Obesity is a risk factor for cognitive impairment. **b**, Anti-obesity interventions could improve cognition indirectly (for example, through systemic improvements in weight, insulin resistance, dyslipidaemia or inflammation) or directly through effects on the brain (for example, activation of neuroprotective pathways or receptor binding). **c**, Anti-obesity interventions improve systemic metabolism, cognition and brain structure. BMI, body mass index; GLP-1, glucagon-like peptide 1; WHR, waist-to-hip ratio.

Box 4 | Dietary regimens and bariatric surgical procedures

Dietary regimens

Caloric restriction
A diet that limits calorie intake compared with unrestricted eating.

Intermittent fasting
An umbrella term for eating patterns that alternate between fasting and eating. Once glucose and glycogen stores since the last meal are depleted, intermittent fasting promotes ketosis — that is, ketone body production — by switching to fat as an alternative fuel in the liver. Ketosis onset occurs after ~8–24 h of fasting depending on prior glycogen store levels, carbohydrate content of the diet, activity levels and metabolic health. Several intermittent fasting regimens have been devised:

- Time-restricted eating: a daily form of intermittent fasting that limits eating to specific time windows, for example, an 18-h fasting and 6-h eating schedule.
- Alternate day fasting: a 'fast day' with 0–500 kcal intake, alternating with ad libitum food intake on 'feast days'.
- 5:2 diet: an eating pattern that consists of 2 fasting days and 5 feasting days per week.

Ketogenic diet
A high-fat, low-carbohydrate and moderate-protein regimen that promotes ketosis.

MIND diet
The Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diet is a hybrid of the Mediterranean diet and the DASH (Dietary Approaches to Stop Hypertension) diet, modified to include foods putatively linked to reduced dementia risk.

Bariatric surgical procedures

Sleeve gastrectomy
This procedure involves removing 80% of the stomach, resulting in a tube-like organ, the 'sleeve'. Substantially reducing the size of the stomach limits the amount of food that an individual can ingest and decreases the amount of ghrelin that the stomach releases, thereby lowering appetite and cravings. Overall, sleeve gastrectomy promotes weight loss and improved metabolic profiles.

Roux-en-Y gastric bypass
This procedure involves reducing the stomach to a small pouch and connecting it to the mid-jejunum. Substantially reducing the size of the stomach limits the amount of food that a patient can ingest, and bypassing part of the small intestine additionally decreases macronutrient absorption. Unfortunately, Roux-en-Y gastric bypass also prevents micronutrient absorption in the small intestine, thereby predisposing individuals to nutrient deficiencies to a greater extent than sleeve gastrectomy. Nevertheless, overall, Roux-en-Y gastric bypass promotes weight loss and improved metabolic profiles.

and intensity, thereby precluding analysis of dose–response relationships and necessitating more comprehensive studies to inform health recommendations for minimal and optimal exercise doses.

Bariatric surgery

Bariatric surgery is a feasible option for treating class 2 and 3 obesity in eligible patients[168] (Box 4), producing improvements in BMI[169–173], waist circumference[169,171,172], triglyceride[169] and high-density lipoprotein levels[169], blood pressure[171,172] and glucose metrics (for example, HbA1c[169]). A 2021 review suggested that bariatric surgery improved cognition in obese patients but recommended further investigation[174]. Since then, additional primary cohort studies have reported improved or stable cognitive function in various domains, including memory and executive function, 1 year[170], 2 years[169,172] and 3 years[171] after bariatric surgery. The intervention could produce long-term benefits: in a large retrospective, single-centre analysis, obese individuals who underwent bariatric surgery were at lower risk of developing MCI and Alzheimer disease compared with matched control participants who did not undergo the procedure[175]. In this study, patients who received bariatric surgery lost more weight than control individuals, which might have contributed to their reduced risk of cognitive impairment[175]. However, the benefits might be limited to patients without a family history of Alzheimer disease[176].

Not all studies support beneficial effects of bariatric surgery on cognition. In the long-running Teen-Longitudinal Assessment of Bariatric Surgery cohort study, surgery did not prevent the development of cognitive impairment in young adults, although, notably, the participants remained obese despite weight loss[173]. Meta-analyses suggested salutary benefits from bariatric surgery in various cognitive domains[177,178], but concluded that high-powered studies are still needed[178].

Data on the relative effects of different bariatric surgical procedures on cognitive impairment are sparse and inconsistent[173,175,178], and as sleeve gastrectomy is overtaking Roux-en-Y gastric bypass as the surgery of choice[168], this issue warrants investigation. Although bariatric surgery outperforms lifestyle interventions with regard to metabolic improvement[168,179,180], it is not without risks, which include acid reflux and internal hernia[168]. In addition, whether bariatric surgery outperforms other interventions for improving cognitive impairment in people with obesity remains uncertain. The Adolescent Morbid Obesity Surgery 2 randomized controlled trial noted that bariatric surgery with tandem substantial weight loss did not confer additional benefits on most cognitive tests versus a non-surgical group without weight loss at 2-year follow-up[180]. The investigators noted a possible lack of statistical power, however, as cognition was an exploratory outcome of the trial, and they advocated further studies[180]. A meta-analysis concluded that bariatric surgery does not outperform non-surgical interventions for most cognitive outcomes, although the certainty was generally low to very low, and additional high-quality studies are needed[181].

Novel pharmacological interventions

Lifestyle or surgical interventions can be combined with pharmacological treatments to reduce body fat and mitigate obesity-related cognitive impairment. In the sections that follow, we describe novel pharmacological strategies that are being used to treat obesity and highlight their possible effects on cognition (Table 1 and Supplementary Table 2).

GLP-1 receptor agonists. GLP-1 receptor agonists (GLP-1RAs) mimic the endogenous peptides to activate the GLP-1 receptor, thereby reducing appetite, lowering energy intake and promoting weight loss[182] (see the 'Effects on the hypothalamus' section above). Although originally developed as an antidiabetic medication to improve hyperglycaemia[183], these synthetic peptides were also shown to provide cognitive benefits in individuals with T2D[184]. GLP-1RAs are now widely used to treat obesity[185], and they might offer the same neurocognitive benefits in people with obesity-related cognitive impairment. Current GLP-1RAs vary slightly with regard to parameters such as dosing frequency and efficacy, but they all target the same pathway, so for this Review we assessed the literature regarding all GLP-1RAs.

In the brain, GLP-1RAs regulate satiety by acting on hypothalamic neurons[82,186] and surrounding microglia[86]. In preclinical models, these peptides improve obesity-related cognitive impairment induced by an HFD[187–189] or genetic mutations[190]. In humans, GLP-1RAs reduce cognitive impairment[191], and their cognitive benefits seem to be independent of weight loss, as they were not observed in individuals who achieved comparable weight loss with lifestyle interventions such as dietary counselling and exercise[192]. Some evidence suggests that longer exposure to GLP-1RAs results in greater improvement in memory[192]; however, this observation might not translate to all GLP-1RA medications[191], and short-term interventions have yet to be investigated. In addition, as obesity and T2D are often comorbid, few studies have examined changes in cognitive impairment following GLP-1RA treatment in obese populations without T2D. An ongoing clinical trial (NCT06072963) is addressing this gap by assessing cognitive function as a primary outcome of GLP-1RA treatment in people with isolated obesity or MetS, excluding those with diabetes.

Global studies encompassing all individuals who have been treated with GLP-1RAs, including for obesity, report a reduced incidence of dementia in this patient population[193–195]. Many of the cohorts included patients with additional conditions, such as diabetes, but the findings suggest potential neuroprotective effects of GLP-1RAs across diverse clinical populations. These observations have prompted clinical trials evaluating GLP-1RAs in individuals with MCI or Alzheimer disease (NCT04777396, NCT04777409 and NCT01843075)[196,197], although the early findings suggest little to no effect on dementia[198,199]. The potential mechanisms of these therapeutics were recently discussed at the National Academies Workshop 'Examining Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists for Central Nervous System Disorders'[200] in 2025 and are a major focus of ongoing research[201].

Other GLP-1RA-like peptides. Gastric inhibitory polypeptide (GIP)/GLP-1 dual agonists contain synthetic forms of the endogenous GIP and GLP-1 peptides, and, like GLP-1RAs, they reduce appetite and promote weight loss[202]. GIP/GLP-1 dual agonists are relatively new, so studies examining their effects on obesity-related cognitive impairment are limited. Nevertheless, a retrospective analysis indicated that individuals treated with GIP/GLP-1 dual agonists exhibited reduced rates of dementia[195]. Further research is needed to determine whether these medications protect against cognitive impairment, and ultimately dementia, in people with obesity, but the available data suggest that they show promise as a therapeutic strategy in this context.

A novel *N*-methyl-D-aspartate receptor antagonist has been developed that uses GLP-1RA-like delivery to minimize adverse effects and facilitate weight loss by upregulating genes related to synaptic activity within the hypothalamus[203]; however, it remains in preclinical development, and its influence on cognitive impairment has yet to be investigated. Other peptide hormones, such as bone morphogenic protein/retinoic acid-inducible neural-specific 2-related peptides[204], show promise for the treatment obesity, but their direct cognitive effects and clinical translatability remain unknown.

Table 1 | Studies of GLP-1RAs in people with or without obesity and/or T2D

Study	Participant numbers and age	Location	Intervention and duration	Cognitive tests or study tools	Main findings
Cukierman-Yaffe et al.[191]	8,828 people with T2D aged ≥50 years	Global	At least 6 months of dulaglutide or placebo	Montreal Cognitive Assessment, Digit Symbol Substitution Test	Reduced cognitive impairment in the dulaglutide group
Lin et al.[195]	60,860 people with T2D and obesity) aged ≥40 years	USA	Retrospective study of semaglutide and tirzepatide versus other antidiabetic drugs with variable follow-up duration	NA; risk incidence	Reduced incidence of dementia in people treated with GLP-1RAs compared with other antidiabetic drugs
Nassar et al.[194]	230,782 people with T2D or obesity aged ≥18 years	Global	Retrospective study of unspecified GLP-1RAs with 5-year follow-up	NA; risk incidence	Reduced incidence of dementia and AD
Siddeeque et al.[193]	205,870 people with obesity aged ≥18 years	Global	Retrospective study of individuals treated semaglutide, dulaglutide or liraglutide versus control individuals with variable follow-up duration	NA; risk incidence	Reduced incidence of dementia (Alzheimer disease, Lewy body dementia or vascular dementia) in GLP1-RA-treated participants
Vadini et al.[192]	40 people with obesity and prediabetes or early T2D aged 49–64 years	Italy	3–12 months (depending on achievement of target weight) of liraglutide versus lifestyle counselling	Trail-Making Test A, Trail-Making Test B, visual search matrices, forward digit span, ROCF direct copying, ROCF-recall delayed reproduction trial, phonemic verbal fluency task	After losing the same weight, liraglutide was more effective at improving memory than the lifestyle invention; more time on drug correlated with better memory function

GLP-1RA, glucagon-like peptide 1 receptor agonist; NA, not applicable; ROCF, Rey–Osterrieth complex figure; T2D, type 2 diabetes.

Box 5 | From research to real-world benefits

Obesity rates are rising globally, with a parallel increase in the number of individuals affected by obesity-related cognitive impairment and eventual dementia. These issues warrant further investigation into brain health in obese populations to mitigate the future burden of dementia. Clinical research is needed to better clarify the relationship between obesity and cognitive impairment, while basic and translational research should improve our understanding of the mechanisms underlying obesity-related cognitive impairment.

From the clinical research perspective, large population-based, longitudinal prospective studies will be required to comprehensively examine obesity and cognitive impairment trajectories and fully account for potential confounding from factors that are frequently comorbid with obesity. As obesity is increasingly affecting younger populations, studies must emphasize the impact of obesity on brain health across the life course. Moreover, as obesity is a global issue, studies should include ethnically and socioeconomically diverse populations.

Regarding the underlying mechanisms, cognitive impairment secondary to obesity has a complex and multifactorial pathophysiology, spanning neuronal dysfunction, glial activation, metabolic stress, vascular dysfunction and chronic inflammation. An urgent need exists to disentangle the pathways that drive obesity-related cognitive impairment and to identify specific causal mechanisms that could be amenable to therapeutic intervention. Leveraging advances in preclinical models combined with multiomic approaches will be essential to identify key drivers of obesity-related cognitive impairment and enable the development of targeted therapies.

In the clinical care sphere, emerging interventional studies on anti-obesity approaches suggest that obesity-related cognitive impairment marks an early and potentially reversible stage before severe neurodegeneration occurs. Weight-loss interventions spanning lifestyle, surgical and pharmacological approaches, including GLP-1RAs, are being explored for their therapeutic potential, with possible translation to future clinical care. A key future challenge will be to identify personalized therapeutic strategies for cognitive impairment, probably involving a combination of lifestyle, surgical and pharmacological interventions tailored to individual patients.

Knowledge gaps and future directions

Despite considerable progress, additional work is necessary to clarify the clinical and translational mechanisms underlying obesity-related cognitive impairment and to identify effective interventions.

Clinical research

Clinical studies so far support a relationship between obesity and cognitive impairment. However, fully elucidating the effects of obesity on cognition is challenging owing to the presence of many confounding variables, such as sex; obesity-related cardiometabolic comorbidities (for example, MetS and MetS components, including T2D, hypertension, dyslipidaemia and inflammation); comorbid medical conditions (for example, depression and sleep disorders such as sleep apnoea); lifestyle factors (for example, sedentary behaviour, physical inactivity, dietary habits, smoking and alcohol intake); and socioeconomic factors (for example, education, income and social disadvantage). Although studies have adjusted for many of these factors to varying extents, comprehensively accounting for them to determine the direct effects of obesity on cognition is difficult. Studies should adopt a longitudinal design to account for BMI trajectories throughout the life course, with a special emphasis on childhood as well as midlife to late-life BMI transitions, as cognitive impairment secondary to obesity might occur early and influence the risk of dementia in later life. Longitudinal studies will also facilitate evaluation of the bidirectional relationship between cognitive issues and obesity.

Dementia is around 1.3 times more prevalent in women than in men[205], partly owing to the longer life expectancy of women[8] but possibly also because of biological factors such as menopause. Menopause induces hormonal changes that promote weight gain and central adiposity[206], which, as risk factors for cognitive impairment, might predispose post-menopausal women to dementia. Moreover, oestrogen exerts numerous neuroprotective effects[207], and levels of this hormone diminish during menopause. Although findings are mixed regarding dementia in older women compared with men across various obesity metrics and dementia subtypes[6,42,54–56], some studies in post-menopausal women report that obesity and prior menopause symptoms[208] correlate with an elevated risk of cognitive impairment, potentially driven by interactions between menopause and vascular risk factors[209]. Overall, the evidence points towards an elevated risk of obesity-related cognitive impairment in post-menopausal women, but studies are sparse and additional research is necessary to fully understand the relationship.

Trajectory-based analyses of obesity over the life course represent an important direction for future research. In adults, BMI trajectories from midlife to late life seem to be crucial; however, some of the data are conflicting (see the 'Obesity and cognitive impairment' section). Whether similar trajectories exist in childhood obesity and whether they predict obesity and cognitive impairment in adulthood is currently unclear. More research is needed across the lifespan in both sexes and in different racial and ethnic groups to fully define the relationship. Regardless, obesity prevention should remain a central priority, with a particular emphasis on targeting children and young adults.

Preclinical and translational research

The neurobiological impact of obesity is highly dependent on biological context, with age and sex having crucial roles. In aged rodents, an HFD exacerbates microglial reactivity and dysregulates the hippocampal cytokine balance, resulting in more severe learning deficits and anxiety compared with younger animals[106,210]. In addition, young and aged HFD-fed male mice exhibit deficits in fear conditioning, whereas young female mice seem to be relatively resilient to these specific cognitive impairments[85]. More research is needed to disentangle the effects of ageing and sex on obesity-related cognitive impairment. Preclinical studies must also determine the mechanistic drivers of obesity-related cognitive impairment, both within and outside the brain, while addressing the differences between lifestyle (for example, HFD) and genetic (for example, leptin-based) models of obesity and obesity with comorbid T2D and how they translate to the clinic. These preclinical models might not accurately replicate human obesity and its related comorbidities[67,211]. In addition, genetically homogenous rodent models do not reflect the heterogeneity of the human population. Therefore, future studies should explore the use of multiple preclinical models of obesity, including outbred models, to explore the translatability of preclinical findings.

Therapy development and prevention

Measures to prevent obesity are an important priority, as obese individuals are at increased risk of dementia irrespective of weight loss. Nevertheless, for individuals who have already developed obesity, weight-loss interventions could help to mitigate obesity-related cognitive impairment. Many interventional studies so far have been short in duration, ranging from a few weeks[145,151] to several months[149], and, therefore, provide limited insight into long-term benefits or sustained effects. Longitudinal studies are required to assess both the long-term efficacy and potential adverse effects of these interventions. In addition, improved reporting of obesity-related comorbidities will enhance translatability to the general population (see the 'Clinical research' section above), as many individuals present with multiple comorbid conditions in addition to obesity.

Weight-loss interventions need to be explored across the lifespan. Many current studies focus on older adults (>65 years)[147,149,191] with progressive obesity (BMI ≥35 kg/m^2; class 2 and above)[148–150,192,195]. Although studies in childhood obesity have generated promising results, investigations in young or middle-aged adults have been limited by small sample sizes (n < 50)[150]. In addition, examining individuals with less severe obesity might help us to determine whether earlier intervention is more effective. Furthermore, whether early-life interventions provide greater protection than later-life interventions against obesity-related cognitive impairment and dementia remains to be determined.

Given that the pathophysiological effects of obesity often parallel those of ageing, senotherapeutic strategies could hold promise for mitigating obesity-related cognitive impairment[212]. Although the cognitive outcomes were mixed, preclinical studies using senolytics in mouse models of obesity demonstrated clearance of senescent glial cells and improvements in anxiety-like behaviour[213]. Moreover, senomorphic drugs, which modify senescent cells to reduce their harmful effects, were shown to rescue cognitive function in HFD-fed rats[214]. Collectively, these findings suggest that senotherapeutics have potential for alleviating the cognitive consequences of obesity, although further investigation is required to fully understand their impact on obesity-related cognitive impairment.

The comparative and combinatorial effects of different interventions on cognitive impairment in individuals with obesity remain poorly understood. Few studies have directly compared approaches (for example, diet versus exercise[159] or exercise versus bariatric surgery[153]); thus, the optimal regimen has not been established. Combined interventions could have additive or synergistic effects on obesity-related cognitive impairment. For example, healthy dietary strategies and exercise are commonly recommended alongside GLP-1RA treatment[215]. However, financial or social barriers faced by lower-income individuals impose challenges to adopting lifestyle interventions, such as diet and exercise, and development of accessible strategies that are applicable to the entire global population should be prioritized.

Conclusion

Collectively, the clinical and preclinical evidence that we have summarized in this Review supports a direct relationship between obesity and cognitive impairment. Obesity is a global epidemic, and obesity-related cognitive dysfunction represents a key consequence. Furthermore, obesity increases the risk of dementia. Children could be at risk of obesity-related cognitive impairment in later life if their obesity is not addressed, although further studies are required to fully understand the factors and mechanisms that drive these risks. Longitudinal studies will be vital to assess the effects of BMI trajectories throughout the life course on cognitive function, with a particular emphasis on midlife to late-life BMI transitions. Strategies to target obesity, such as lifestyle, surgical and pharmacological interventions, might help to mitigate cognitive impairment. Bridging the research gaps that we have identified in this Review will advance the field of obesity, brain health and cognition, with the aim of curbing the anticipated future global burden of dementia (Box 5).

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References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *Lancet* **403**, 1027–1050 (2024).
2. Obesity and overweight. *World Health Organization* https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2025).
3. Lingvay, I., Cohen, R. V., Roux, C. W. L. & Sumithran, P. Obesity in adults. *Lancet* **404**, 972–987 (2024).
4. Morys, F., Dadar, M. & Dagher, A. Association between midlife obesity and its metabolic consequences, cerebrovascular disease, and cognitive decline. *J. Clin. Endocrinol. Metab.* **106**, e4260–e4274 (2021).
5. Zhang, L. et al. Association of birth weight, midlife obesity, and transition patterns with mild cognitive impairment and brain MRI indices: a prospective population-based study. *J. Affect. Disord.* **380**, 384–393 (2025).
6. Tang, X. et al. Relationship between central obesity and the incidence of cognitive impairment and dementia from cohort studies involving 5,060,687 participants. *Neurosci. Biobehav. Rev.* **130**, 301–313 (2021).
7. Livingston, G. et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet* **404**, 572–628 (2024).
8. 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).
9. Rubino, F. et al. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol.* **13**, 221–262 (2025).
10. Neeland, I. J. et al. Metabolic syndrome. *Nat. Rev. Dis. Primers* **10**, 77 (2024).
11. Neto, A., Fernandes, A. & Barateiro, A. The complex relationship between obesity and neurodegenerative diseases: an updated review. *Front. Cell Neurosci.* **17**, 1294420 (2023).
12. GBD 2021 Adult BMI Collaborators. Global, regional, and national prevalence of adult overweight and obesity, 1990–2021, with forecasts to 2050: a forecasting study for the Global Burden of Disease Study 2021. *Lancet* **405**, 813–838 (2025).
13. Nagi, M. A. et al. Economic costs of obesity: a systematic review. *Int. J. Obes.* **48**, 33–43 (2024).
14. Fatoye, F. et al. The clinical and economic burden of obesity in low- and middle-income countries: a systematic review. *Int. J. Obes.* **49**, 2453–2461 (2025).
15. Okunogbe, A. et al. Economic impacts of overweight and obesity: current and future estimates for 161 countries. *BMJ Glob. Health* **7**, e009773 (2022).
16. Adolph, T. E. & Tilg, H. Western diets and chronic diseases. *Nat. Med.* **30**, 2133–2147 (2024).
17. Wang, Y. B. et al. Association between dietary inflammatory index, dietary patterns, plant-based dietary index and the risk of obesity. *Nutrients* **13**, 1536 (2021).
18. Sun, Z. et al. Using interpretable machine learning methods to identify the relative importance of lifestyle factors for overweight and obesity in adults: pooled evidence from CHNS and NHANES. *BMC Public Health* **24**, 3034 (2024).
19. Jebeile, H., Kelly, A. S., O'Malley, G. & Baur, L. A. Obesity in children and adolescents: epidemiology, causes, assessment, and management. *Lancet Diabetes Endocrinol.* **10**, 351–365 (2022).
20. Lister, N. B. et al. Child and adolescent obesity. *Nat. Rev. Dis. Primers* **9**, 24 (2023).
21. Stryjecki, C., Alyass, A. & Meyre, D. Ethnic and population differences in the genetic predisposition to human obesity. *Obes. Rev.* **19**, 62–80 (2018).
22. Smit, R. A. J. et al. Polygenic prediction of body mass index and obesity through the life course and across ancestries. *Nat. Med.* **31**, 3151–3168 (2025).
23. Damavandi, N., Soleymaniniya, A., Bahrami Zadegan, S., Samiee Aref, M. H. & Zeinali, S. Development of a genetic risk score for obesity predisposition evaluation. *Mol. Genet. Genomics* **297**, 1495–1503 (2022).
24. Kim, M. S. et al. Association of genetic risk, lifestyle, and their interaction with obesity and obesity-related morbidities. *Cell Metab.* **36**, 1494–1503.e1493 (2024).
25. Zhang, M. et al. How do lifestyle factors modify the association between genetic predisposition and obesity-related phenotypes? A 4-way decomposition analysis using UK Biobank. *BMC Med.* **22**, 230 (2024).
26. Malandrino, N., Bhat, S. Z., Alfaraidhy, M., Grewal, R. S. & Kalyani, R. R. Obesity and aging. *Endocrinol. Metab. Clin. North. Am.* **52**, 317–339 (2023).
27. Rindler, G. A., Gries, A. & Freidl, W. Associations between overweight, obesity, and mental health: a retrospective study among European adults aged 50. *Front. Public Health* **11**, 1206283 (2023).
28. Moss, L., Laudenslager, M., Steffen, K. J., Sockalingam, S. & Coughlin, J. W. Antidepressants and weight gain: an update on the evidence and clinical implications. *Curr. Obes. Rep.* **14**, 2 (2025).

29. Anekwe, C. V. et al. Socioeconomics of obesity. *Curr. Obes. Rep.* **9**, 272–279 (2020).
30. Petersen, R. C. et al. Current concepts in mild cognitive impairment. *Arch. Neurol.* **58**, 1985–1992 (2001).
31. Liang, J., Matheson, B. E., Kaye, W. H. & Boutelle, K. N. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. *Int. J. Obes.* **38**, 494–506 (2014).
32. Sadler, J. R. et al. Paediatric obesity and metabolic syndrome associations with cognition and the brain in youth: current evidence and future directions. *Pediatr. Obes.* **18**, e13042 (2023).
33. Jiang, F. et al. Obesity is associated with decreased gray matter volume in children: a longitudinal study. *Cereb. Cortex* **33**, 3674–3682 (2023).
34. Kulisch, L. K., Arumäe, K., Briley, D. A. & Vainik, U. Triangulating causality between childhood obesity and neurobehavior: behavioral genetic and longitudinal evidence. *Dev. Sci.* **26**, e13392 (2023).
35. Lowe, C. J., Reichelt, A. C. & Hall, P. A. The prefrontal cortex and obesity: a health neuroscience perspective. *Trends Cogn. Sci.* **23**, 349–361 (2019).
36. Li, Z. A., Ray, M. K., Gu, Y., Barch, D. M. & Hershey, T. Weight indices, cognition, and mental health from childhood to early adolescence. *JAMA Pediatr.* **178**, 830–833 (2024).
37. Tomaso, C. C., James, T., Nelson, J. M., Espy, K. A. & Nelson, T. D. Longitudinal associations between executive control and body mass index across childhood. *Pediatr. Obes.* **17**, e12866 (2022).
38. Sakib, M. N., Best, J. R. & Hall, P. A. Bidirectional associations between adiposity and cognitive function and mediation by brain morphology in the ABCD Study. *JAMA Netw. Open.* **6**, e2255631 (2023).
39. Chiesa, S. T. et al. Childhood adiposity underlies numerous adult brain traits commonly attributed to midlife obesity. *Brain* **148**, 133–142 (2025).
40. Whitmer, R. A. et al. Central obesity and increased risk of dementia more than three decades later. *Neurology* **71**, 1057–1064 (2008).
41. Gardener, H. et al. Obesity measures in relation to cognition in the northern manhattan study. *J. Alzheimers Dis.* **78**, 1653–1660 (2020).
42. Zotcheva, E. et al. Sex differences in body mass index and waist circumference trajectories and dementia risk: the HUNT4 70+ study. *Geroscience* **48**, 405–419 (2025).
43. Zeng, M. et al. Adiposity and dementia among Chinese adults: longitudinal study in the China Health and Retirement Longitudinal Study (CHARLS). *Int. J. Obes.* **49**, 706–714 (2025).
44. Zhu, W. et al. Changes in adiposity and cognitive function in older adults: the REGARDS study. *J. Gerontol. B* **79**, gbad184 (2024).
45. Cannon, E. J. et al. Association of body mass index in late life, and change from midlife to late life, with incident dementia in the ARIC study participants. *Neurology* **104**, e213534 (2025).
46. Boccara, E., Golan, S. & Beeri, M. S. The association between regional adiposity, cognitive function, and dementia-related brain changes: a systematic review. *Front. Med.* **10**, 1160426 (2023).
47. Lazzaris Coelho, P. H. et al. Association of adiposity evaluated by anthropometric and bioelectrical impedance analysis measures with cognitive performance in the ELSA-Brasil study. *Int. J. Obes.* **49**, 1382–1389 (2025).
48. Sakib, M. N., Ramezan, R., Thompson, M. E., Best, J. R. & Hall, P. A. Cognitive function is associated with multiple indices of adiposity in the Canadian Longitudinal Study on Aging: a cross-sectional analysis. *Psychosom. Med.* **84**, 773–784 (2022).
49. Uchida, K. et al. Association between abdominal adiposity and cognitive decline in older adults: a 10-year community-based study. *J. Nutr. Health Aging* **28**, 100175 (2024).
50. Wang, L. et al. Body composition and cognitive function in Chinese rural adults: an exploratory factor analysis and network analysis. *Front. Aging Neurosci.* **17**, 1722050 (2025).
51. Sweatt, K., Garvey, W. T. & Martins, C. Strengths and limitations of BMI in the diagnosis of obesity: what is the path forward? *Curr. Obes. Rep.* **13**, 584–595 (2024).
52. Milani, S. A., Marsiske, M., Cottler, L. B., Chen, X. & Striley, C. W. Optimal cutoffs for the Montreal Cognitive Assessment vary by race and ethnicity. *Alzheimers Dement.* **10**, 773–781 (2018).
53. Chen, S. et al. Impact of visceral adiposity index on cognitive impairment and cognitive trajectories in Chinese middle-aged and older adults. *Front. Public. Health* **13**, 1612801 (2025).
54. Guo, D. et al. Sex differences in the association between obesity and cognitive impairment in a low-income elderly population in rural china: a population-based cross-sectional study. *Front. Neurol.* **12**, 669174 (2021).
55. Zakharova, A. et al. Sex differences in the association between body mass index and dementia risk in community-dwelling Japanese people aged 40–74 years. *J. Alzheimers Dis.* **94**, 949–959 (2023).
56. Lee, C. M. et al. Association of anthropometry and weight change with risk of dementia and its major subtypes: a meta-analysis consisting 2.8 million adults with 57 294 cases of dementia. *Obes. Rev.* **21**, e12989 (2020).
57. The debate on how to protect and restore brain health. *Lancet Neurol.* **21**, 857 (2022).
58. Gómez-Apo, E., Mondragón-Maya, A., Ferrari-Díaz, M. & Silva-Pereyra, J. Structural brain changes associated with overweight and obesity. *J. Obes.* **2021**, 6613385 (2021).
59. Kawai, T., Autieri, M. V. & Scalia, R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am. J. Physiol. Cell Physiol* **320**, C375–C391 (2021).
60. Luo, L. & Liu, M. Adipose tissue in control of metabolism. *J. Endocrinol.* **231**, R77–R99 (2016).
61. Kerr, A. G., Andersson, D. P., Dahlman, I., Ryden, M. & Arner, P. Adipose insulin resistance associates with dyslipidemia independent of liver resistance and involves early hormone signaling. *Arterioscler. Thromb. Vasc. Biol.* **43**, 1054–1065 (2023).
62. Gong, M. et al. Causal links between obesity, lipids, adipokines, and cognition: a bidirectional Mendelian-randomization analysis. *Front. Endocrinol.* **16**, 1439341 (2025).
63. Ha, J. et al. Relationship between adipokines, cognition, and brain structures in old age depending on obesity. *J. Gerontol. A* **78**, 120–128 (2023).
64. Weijie, Z. et al. Obesity-induced chronic low-grade inflammation in adipose tissue: a pathway to Alzheimer's disease. *Ageing Res. Rev.* **99**, 102402 (2024).
65. Dhurandhar, Y. et al. Chronic inflammation in obesity and neurodegenerative diseases: exploring the link in disease onset and progression. *Mol. Biol. Rep.* **52**, 424 (2025).
66. Le Thuc, O. & García-Cáceres, C. Obesity-induced inflammation: connecting the periphery to the brain. *Nat. Metab.* **6**, 1237–1252 (2024).
67. Kleinert, M. et al. Animal models of obesity and diabetes mellitus. *Nat. Rev. Endocrinol.* **14**, 140–162 (2018).
68. Tran, V. et al. The vascular consequences of metabolic syndrome: rodent models, endothelial dysfunction, and current therapies. *Front. Pharmacol.* **11**, 148 (2020).
69. van den Hoek, A. M. et al. A translational mouse model for NASH with advanced fibrosis and atherosclerosis expressing key pathways of human pathology. *Cells* **9**, 2014 (2020).
70. Vohra, M. S., Benchoula, K., Serpell, C. J. & Hwa, W. E. AgRP/NPY and POMC neurons in the arcuate nucleus and their potential role in treatment of obesity. *Eur. J. Pharmacol.* **915**, 174611 (2022).
71. Holliday, A., Horner, K., Johnson, K. O., Dagbasi, A. & Crabtree, D. R. Appetite-related gut hormone responses to feeding across the life course. *J. Endocr. Soc.* **9**, bvae223 (2025).
72. Obradovic, M. et al. Leptin and obesity: role and clinical implication. *Front. Endocrinol.* **12**, 585887 (2021).
73. Kullmann, S. et al. Selective insulin resistance in homeostatic and cognitive control brain areas in overweight and obese adults. *Diabetes Care* **38**, 1044–1050 (2015).
74. Kosse, C., Ivanov, J., Knight, Z., Pellegrino, K. & Friedman, J. A subcortical feeding circuit linking an interoceptive node to jaw movement. *Nature* **636**, 151–161 (2024).
75. Lei, Y. et al. Region-specific transcriptomic responses to obesity and diabetes in macaque hypothalamus. *Cell Metab.* **36**, 438–453 (2024).
76. Tan, H. L. et al. Leptin-activated hypothalamic BNC2 neurons acutely suppress food intake. *Nature* **636**, 198–205 (2024).
77. Jais, A. et al. PNOC(ARC) neurons promote hyperphagia and obesity upon high-fat-diet feeding. *Neuron* **106**, 1009–1025 (2020).
78. Solheim, M. H. et al. Hypothalamic PNOC/NPY neurons constitute mediators of leptin-controlled energy homeostasis. *Cell* **188**, 3550–3566 (2025).
79. Ariyani, W. et al. Dopaminergic neurons in the paraventricular hypothalamus extend the food consumption phase. *Proc. Natl Acad. Sci. USA* **122**, e2411069122 (2025).
80. Inada, K., Tsujimoto, K., Yoshida, M., Nishimori, K. & Miyamichi, K. Oxytocin signaling in the posterior hypothalamus prevents hyperphagic obesity in mice. *eLife* **11**, e75718 (2022).
81. Wang, T. et al. Identification of a neural basis for energy expenditure in the mouse arcuate hypothalamus. *Neuron* **113**, 3813–3833 (2025).
82. Webster, A. N. et al. Molecular connectomics reveals a glucagon-like peptide 1-sensitive neural circuit for satiety. *Nat. Metab.* **6**, 2354–2373 (2024).
83. Sonnefeld, L., Rohmann, N., Geisler, C. & Laudes, M. Is human obesity an inflammatory disease of the hypothalamus? *Eur. J. Endocrinol.* **188**, R37–R45 (2023).
84. Sanchez, C. et al. Dietary fatty acid composition drives neuroinflammation and impaired behavior in obesity. *Brain Behav. Immun.* **117**, 330–346 (2024).
85. Evans, A. K. et al. 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).
86. Rong, X. et al. Microglial activation and hypothalamic structural plasticity in HFD obesity: insights from semaglutide and minocycline. *J. Lipid Res.* **66**, 100736 (2025).
87. Herrera Moro Chao, D. et al. Hypothalamic astrocytes control systemic glucose metabolism and energy balance. *Cell Metab.* **34**, 1532–1547 (2022).
88. Douglass, J. D. et al. Obesity-associated microglial inflammatory activation paradoxically improves glucose tolerance. *Cell Metab.* **35**, 1613–1629 (2023).
89. Gruber, T. et al. Obesity-associated hyperleptinemia alters the gliovascular interface of the hypothalamus to promote hypertension. *Cell Metab.* **33**, 1155–1170 (2021).
90. Zhang, Y. et al. Iron overload in hypothalamic AgRP neurons contributes to obesity and related metabolic disorders. *Cell Rep.* **43**, 113900 (2024).
91. Beddows, C. A. et al. Pathogenic hypothalamic extracellular matrix promotes metabolic disease. *Nature* **633**, 914–922 (2024).
92. Danieli, K., Guyon, A. & Bethus, I. Episodic memory formation: a review of complex hippocampus input pathways. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **126**, 110757 (2023).
93. Chafee, M. V. & Heilbronner, S. R. Prefrontal cortex. *Curr. Biol.* **32**, R346–R351 (2022).
94. Morici, J. F., Weisstaub, N. V. & Zold, C. L. Hippocampal-medial prefrontal cortex network dynamics predict performance during retrieval in a context-guided object memory task. *Proc. Natl Acad. Sci. USA* **119**, e2203024119 (2022).
95. Okada, K., Hashimoto, K. & Kobayashi, K. Cholinergic regulation of object recognition memory. *Front. Behav. Neurosci.* **16**, 996089 (2022).
96. Willette, A. A. & Kapogiannis, D. Does the brain shrink as the waist expands? *Ageing Res. Rev.* **20**, 86–97 (2015).
97. Zhang, D. et al. Long-term obesity impacts brain morphology, functional connectivity and cognition in adults. *Nat. Ment. Health* **3**, 466–478 (2025).

98. Angoff, R. et al. Relations of metabolic health and obesity to brain aging in young to middle-aged adults. *J. Am. Heart Assoc.* **11**, e022107 (2022).
99. Kharabian Masouleh, S. et al. Higher body mass index in older adults is associated with lower gray matter volume: implications for memory performance. *Neurobiol. Aging* **40**, 1–10 (2016).
100. Pflanz, C. P. et al. Central obesity is selectively associated with cerebral gray matter atrophy in 15,634 subjects in the UK Biobank. *Int. J. Obes.* **46**, 1059–1067 (2022).
101. Dekkers, I. A., Jansen, P. R. & Lamb, H. J. Obesity, brain volume, and white matter microstructure at MRI: a cross-sectional UK Biobank Study. *Radiology* **291**, 763–771 (2019).
102. Repple, J. et al. Elevated body-mass index is associated with reduced white matter integrity in two large independent cohorts. *Psychoneuroendocrinology* **91**, 179–185 (2018).
103. Dawe, R. J. et al. Late-life cognitive decline is associated with hippocampal volume, above and beyond its associations with traditional neuropathologic indices. *Alzheimers Dement.* **16**, 209–218 (2020).
104. Watanabe, Y., Dezawa, S., Takei, H., Nagasaka, K. & Takashima, I. Hippocampal-prefrontal long-term potentiation-like plasticity with transcranial direct current stimulation in rats. *Neurobiol. Learn. Mem.* **201**, 107750 (2023).
105. Gonzales, M. M. et al. Biological aging processes underlying cognitive decline and neurodegenerative disease. *J. Clin. Invest.* **132**, e158453 (2022).
106. Valcarcel-Ares, M. N. 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* **74**, 290–298 (2019).
107. Zhuang, H. et al. Long-term high-fat diet consumption by mice throughout adulthood induces neurobehavioral alterations and hippocampal neuronal remodeling accompanied by augmented microglial lipid accumulation. *Brain Behav. Immun.* **100**, 155–171 (2022).
108. Cañeque-Rufo, H. et al. Pleiotrophin deletion prevents high-fat diet-induced cognitive impairment, glial responses, and alterations of the perineuronal nets in the hippocampus. *Neurobiol. Dis.* **205**, 106776 (2025).
109. Spinelli, M. et al. High fat diet affects the hippocampal expression of miRNAs targeting brain plasticity-related genes. *Sci. Rep.* **14**, 19651 (2024).
110. Niu, Y. et al. Obese mice induced by high-fat diet have differential expression of circular RNAs involved in endoplasmic reticulum stress and neuronal synaptic plasticity of hippocampus leading to obesity-associated cognitive impairment. *Front. Mol. Neurosci.* **15**, 1000482 (2022).
111. Langley, M. R. et al. High fat diet consumption results in mitochondrial dysfunction, oxidative stress, and oligodendrocyte loss in the central nervous system. *Biochim. Biophys. Acta Mol. Basis Dis.* **1866**, 165630 (2020).
112. Mullins, C. A. et al. Neural underpinnings of obesity: the role of oxidative stress and inflammation in the brain. *Antioxidants* **9**, 1018 (2020).
113. da Cruz Rodrigues, K. C. et al. LRP1 in GABAergic neurons is a key link between obesity and memory function. *Mol. Metab.* **84**, 101941 (2024).
114. Al Haj Ahmad, R. M., Ababneh, N. A. & Al-Domi, H. A. Brain insulin resistance as a mechanistic mediator links peripheral metabolic disorders with declining cognition. *Diabetes Metab. Syndr.* **16**, 102468 (2022).
115. Arnold, S. E. et al. High fat diet produces brain insulin resistance, synaptodendritic abnormalities and altered behavior in mice. *Neurobiol. Dis.* **67**, 79–87 (2014).
116. Fu, Z. et al. Long-term high-fat diet induces hippocampal microvascular insulin resistance and cognitive dysfunction. *Am. J. Physiol. Endocrinol. Metab.* **312**, E89–E97 (2017).
117. Mucellini, A. B., Fonseca, N., Manfro, G. G. & Silveira, P. P. Hippocampal insulin resistance and altered food decision-making as players on obesity risk. *Neurosci. Biobehav. Rev.* **77**, 165–176 (2017).
118. Cheke, L. G., Bonnici, H. M., Clayton, N. S. & Simons, J. S. Obesity and insulin resistance are associated with reduced activity in core memory regions of the brain. *Neuropsychologia* **96**, 137–149 (2017).
119. McIntyre, C. C. et al. Insulin resistance, cognition, and functional brain network topology in older adults with obesity. *Sci. Rep.* **15**, 22612 (2025).
120. Elzinga, S. E. et al. Metabolic stress and age drive inflammation and cognitive decline in mice and humans. *Alzheimers Dement.* **21**, e70060 (2025).
121. Cope, E. C. et al. Microglia play an active role in obesity-associated cognitive decline. *J. Neurosci.* **38**, 8889–8904 (2018).
122. Elzinga, S. E. et al. cGAS/STING and innate brain inflammation following acute high-fat feeding. *Front. Immunol.* **13**, 1012594 (2022).
123. Marschallinger, J. et al. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat. Neurosci.* **23**, 194–208 (2020).
124. Bai, J. et al. DsbA-L prevents obesity-induced inflammation and insulin resistance by suppressing the mtDNA release-activated cGAS-cGAMP-STING pathway. *Proc. Natl Acad. Sci. USA* **114**, 12196–12201 (2017).
125. Yuan, L. et al. Palmitic acid dysregulates the Hippo-YAP pathway and inhibits angiogenesis by inducing mitochondrial damage and activating the cytosolic DNA sensor cGAS–STING–IRF3 signaling mechanism. *J. Biol. Chem.* **292**, 15002–15015 (2017).
126. Gulen, M. F. et al. cGAS–STING drives ageing-related inflammation and neurodegeneration. *Nature* **620**, 374–380 (2023).
127. Henn, R. E. et al. Glial-neuron crosstalk in health and disease: a focus on metabolism, obesity, and cognitive impairment. *Neurobiol. Dis.* **170**, 105766 (2022).
128. Koenen, M., Hill, M. A., Cohen, P. & Sowers, J. R. Obesity, adipose tissue and vascular dysfunction. *Circ. Res.* **128**, 951–968 (2021).
129. Ishida, A. et al. Association of obesity and metabolic health status with cerebral small-vessel disease in stroke-free individuals. *J. Atheroscler. Thromb.* **32**, 1304–1315 (2025).
130. Pétrault, O. et al. Visceral adiposity links cerebrovascular dysfunction to cognitive impairment in middle-aged mice. *Neurobiol. Dis.* **130**, 104536 (2019).
131. Jia, R. et al. Identification and characterization of a translational mouse model for blood-brain barrier leakage in cerebral small vessel disease. *Int. J. Mol. Sci.* **26**, 6706 (2025).
132. Eminhizer, N. N. et al. Sex-dependent effects of a high-fat diet-induced obesity model on cerebrovascular health and brain metabolism. *Exp. Physiol.* https://doi.org/10.1113/EP093187 (2025).
133. Lama, A. et al. Palmitoylethanolamide dampens neuroinflammation and anxiety-like behavior in obese mice. *Brain Behav. Immun.* **102**, 110–123 (2022).
134. de Paula, G. C. et al. 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).
135. Milenkovic, D., Nuthikattu, S., Norman, J. E. & Villablanca, A. C. Single nuclei transcriptomics reveals obesity-induced endothelial and neurovascular dysfunction: implications for cognitive decline. *Int. J. Mol. Sci.* **25**, 11169 (2024).
136. Norman, J. E., Nuthikattu, S., Milenkovic, D. & Villablanca, A. C. Cell- and sex-specificity in the transcriptomic response of the hippocampal neurovascular unit to obesity. *Commun. Biol.* **8**, 1712 (2025).
137. Tyagi, A., Mirita, C., Shah, I., Reddy, P. H. & Pugazhenthi, S. Effects of lipotoxicity in brain microvascular endothelial cells during Sirt3 deficiency-potential role in comorbid Alzheimer's disease. *Front. Aging Neurosci.* **13**, 716616 (2021).
138. Tucsek, Z. et al. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J. Gerontol. A* **69**, 1212–1226 (2014).
139. Buckman, L. B. et al. Obesity induced by a high-fat diet is associated with increased immune cell entry into the central nervous system. *Brain Behav. Immun.* **35**, 33–42 (2014).
140. Wang, J. et al. Extracellular vesicles mediate the communication of adipose tissue with brain and promote cognitive impairment associated with insulin resistance. *Cell Metab.* **34**, 1264–1279 (2022).
141. Nakandakari, S. et al. Short-term high-fat diet modulates several inflammatory, ER stress, and apoptosis markers in the hippocampus of young mice. *Brain Behav. Immun.* **79**, 284–293 (2019).
142. Henn, R. E. et al. Obesity-induced neuroinflammation and cognitive impairment in young adult versus middle-aged mice. *Immun. Ageing* **19**, 67 (2022).
143. Veronese, N. et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* **72**, 87–94 (2017).
144. Dinu, M. et al. Effects of popular diets on anthropometric and cardiometabolic parameters: an umbrella review of meta-analyses of randomized controlled trials. *Adv. Nutr.* **11**, 815–833 (2020).
145. Teong, X. T. et al. Eight weeks of intermittent fasting versus calorie restriction does not alter eating behaviors, mood, sleep quality, quality of life and cognitive performance in women with overweight. *Nutr. Res.* **92**, 32–39 (2021).
146. Barnes, L. L. et al. Trial of the MIND diet for prevention of cognitive decline in older persons. *N. Engl. J. Med.* **389**, 602–611 (2023).
147. Arjmand, G., Abbas-Zadeh, M. & Eftekhari, M. H. Effect of MIND diet intervention on cognitive performance and brain structure in healthy obese women: a randomized controlled trial. *Sci. Rep.* **12**, 2871 (2022).
148. Mela, V. et al. Microbiota fasting-related changes ameliorate cognitive decline in obesity and boost ex vivo microglial function through the gut-brain axis. *Gut* **74**, 1828–1846 (2025).
149. Tussing-Humphreys, L. et al. Effect of Mediterranean diet and Mediterranean diet plus calorie restriction on cognition, lifestyle, and cardiometabolic health: a randomized clinical trial. *Prev. Med. Rep.* **29**, 101955 (2022).
150. Mohorko, N. et al. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. *Nutr. Res.* **62**, 64–77 (2019).
151. Rizvi, Z. A. et al. Effects of intermittent fasting on body composition, clinical health markers and memory status in the adult population: a single-blind randomised controlled trial. *Nutr. J.* **23**, 147 (2024).
152. Liśkiewicz, A. D. et al. Obesity-associated deterioration of the hippocampus is partially restored after weight loss. *Brain Behav. Immun.* **96**, 212–226 (2021).
153. Pantiya, P. et al. Higher untrained fitness exerts a neuroprotection in Independence to caloric restriction or exercise in high-fat diet-induced obesity. *Exp. Neurol.* **365**, 114416 (2023).
154. Lee, J. et al. Intermittent fasting reduces neuroinflammation and cognitive impairment in high-fat diet-fed mice by downregulating lipocalin-2 and galectin-3. *Nutrients* **16**, 159 (2024).
155. Jaisil, P. et al. Dietary and exercise interventions improve cognition and alter hippocampal transcriptomics in a mouse model of the metabolic syndrome. *Exp. Neurol.* **395**, 115483 (2025).

156. Guo, J. et al. The impact of different types of exercise on executive functions in overweight/obese individuals: a systematic review and network meta-analysis. *Behav. Sci.* **14**, 1227 (2024).
157. Cristi-Montero, C. et al. Effectiveness of exercise interventions, alone or in combination with dietary modifications, on working memory in overweight and obese individuals: a systematic review. *Eur. J. Sport. Sci.* **24**, 1350–1364 (2024).
158. Wang, Y., Wang, H. & Zhao, H. Effects of aerobic exercise on executive function among overweight and obese children: a systematic review and meta-analysis. *Front. Psychol.* **15**, 1485610 (2024).
159. Keawtep, P. et al. Effects of combined dietary intervention and physical-cognitive exercise on cognitive function and cardiometabolic health of postmenopausal women with obesity: a randomized controlled trial. *Int. J. Behav. Nutr. Phys. Act.* **21**, 28 (2024).
160. Wang, J. et al. An adaptive AI-based virtual reality sports system for adolescents with excess body weight: a randomized controlled trial. *Nat. Med.* **31**, 2255–2268 (2025).
161. Ortega, F. B. et al. Effects of an exercise program on brain health outcomes for children with overweight or obesity: the activebrains randomized clinical trial. *JAMA Netw. Open.* **5**, e2227893 (2022).
162. Kullmann, S. et al. Exercise restores brain insulin sensitivity in sedentary adults who are overweight and obese. *JCI Insight* **7**, e161498 (2022).
163. Ruegsegger, G. N. et al. Glucose tolerance status associates with improvements in cognitive function following high-intensity exercise in adults with obesity. *Physiol. Behav.* **272**, 114389 (2023).
164. Bliss, E. S., Wong, R. H. X., Howe, P. R. C. & Mills, D. E. The effects of aerobic exercise training on cerebrovascular and cognitive function in sedentary, obese, older adults. *Front. Aging Neurosci.* **14**, 892343 (2022).
165. Knight, S. P. et al. Obesity is associated with reduced cerebral blood flow – modified by physical activity. *Neurobiol. Aging* **105**, 35–47 (2021).
166. De Sousa, R. A. L. et al. Physical exercise consequences on memory in obesity: a systematic review. *Obes. Rev.* **22**, e13298 (2021).
167. Pratchayasakul, W. et al. Combined caloric restriction and exercise provides greater metabolic and neurocognitive benefits than either as a monotherapy in obesity with or without estrogen deprivation. *J. Nutr. Biochem.* **110**, 109125 (2022).
168. Courcoulas, A. P., Daigle, C. R. & Arterburn, D. E. Long term outcomes of metabolic/bariatric surgery in adults. *Bmj* **383**, e071027 (2023).
169. Reynolds, E. L. et al. The effect of surgical weight loss on cognition in individuals with class II/III obesity. *J. Nutr. Health Aging* **27**, 1153–1161 (2023).
170. Smith, K. R. et al. The relationship between weight loss and cognitive function in bariatric surgery. *Surg. Endosc.* **37**, 1976–1984 (2023).
171. Custers, E. et al. Sustained improvement of cognition, mood and plasma markers three years after metabolic bariatric surgery. The BARICO study. *Obes. Surg.* **35**, 3888–3900 (2025).
172. Custers, E. et al. Long-term brain structure and cognition following bariatric surgery. *JAMA Netw. Open.* **7**, e2355380 (2024).
173. Burke, E. et al. Cognitive function 10 years after adolescent bariatric surgery. *Surg. Obes. Relat. Dis.* **20**, 614–620 (2024).
174. Morledge, M. D. & Pories, W. J. Bariatric surgery and cognitive impairment. *Obesity* **29**, 1239–1241 (2021).
175. Chen, Y. et al. Bariatric surgery is associated with reduced incidence of mild cognitive impairment and Alzheimer disease and related dementias: a retrospective cohort study. *Ann. Surg. Open.* **6**, e541 (2025).
176. Alosco, M. L. et al. Family history of Alzheimer's disease limits improvement in cognitive function after bariatric surgery. *SAGE Open. Med.* **2**, 2050312114539477 (2014).
177. Tao, B. et al. Bariatric surgery improves cognition function in the patients with obesity: a meta-analysis. *Obes. Surg.* **34**, 1004–1017 (2024).
178. Hathaway, I. et al. Changes in cognitive function following bariatric surgery: an updated systematic review. *Obes. Surg.* **34**, 2216–2226 (2024).
179. Simonson, D. C. et al. Health-related quality of life and health utility after metabolic/bariatric surgery versus medical/lifestyle intervention in individuals with type 2 diabetes and obesity: the ARMMS-T2D study. *Diabetes Care* **48**, 537–545 (2025).
180. Järvholm, K. et al. Cognitive functioning in adolescents with severe obesity undergoing bariatric surgery or intensive non-surgical treatment in Sweden (AMOS2): a multicentre, open-label, randomised controlled trial. *EClinicalMedicine* **70**, 102505 (2024).
181. van Reekum, E. A. et al. Psychiatric and cognitive functioning after metabolic and bariatric surgery: a systematic review and meta-analysis. *Obes. Rev.* **26**, e13968 (2025).
182. Drucker, D. J. GLP-1-based therapies for diabetes, obesity and beyond. *Nat. Rev. Drug. Discov.* **24**, 631–650 (2025).
183. Liu, Q. K. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Front. Endocrinol.* **15**, 1431292 (2024).
184. Monney, M., Jornayvaz, F. R. & Gariani, K. GLP-1 receptor agonists effect on cognitive function in patients with and without type 2 diabetes. *Diabetes Metab.* **49**, 101470 (2023).
185. Drucker, D. J. Efficacy and safety of GLP-1 medicines for type 2 diabetes and obesity. *Diabetes Care* **47**, 1873–1888 (2024).
186. Kim, K. S. et al. GLP-1 increases preingestive satiation via hypothalamic circuits in mice and humans. *Science* **385**, 438–446 (2024).
187. de Paiva, I. H. R., da Silva, R. S., Mendonça, I. P., de Souza, J. R. B. & Peixoto, C. A. Semaglutide attenuates anxious and depressive-like behaviors and reverses the cognitive impairment in a type 2 diabetes mellitus mouse model via the microbiota–gut–brain axis. *J. Neuroimmune Pharmacol.* **19**, 36 (2024).
188. Lin, M. H. et al. The GLP-1 receptor agonist exenatide ameliorates neuroinflammation, locomotor activity, and anxiety-like behavior in mice with diet-induced obesity through the modulation of microglial M2 polarization and downregulation of SR-A4. *Int. Immunopharmacol.* **115**, 109653 (2023).
189. Estato, V. et al. Semaglutide restores astrocyte–vascular interactions and blood-brain barrier integrity in a model of diet-induced metabolic syndrome. *Diabetol. Metab. Syndr.* **17**, 2 (2025).
190. Kang, X. et al. Exendin-4 ameliorates tau hyperphosphorylation and cognitive impairment in type 2 diabetes through acting on Wnt/β-catenin/NeuroD1 pathway. *Mol. Med.* **29**, 118 (2023).
191. Cukierman-Yaffe, T. et al. Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial. *Lancet Neurol.* **19**, 582–590 (2020).
192. Vadini, F. et al. Liraglutide improves memory in obese patients with prediabetes or early type 2 diabetes: a randomized, controlled study. *Int. J. Obes.* **44**, 1254–1263 (2020).
193. Siddeeque, N. et al. Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative Disorders: a large-scale propensity-matched cohort study. *Int. Immunopharmacol.* **143**, 113537 (2024).
194. Nassar, M., Nassar, O., Abosheaishaa, H. & Misra, A. Comparative outcomes of systemic diseases in people with type 2 diabetes, or obesity alone treated with and without GLP-1 receptor agonists: a retrospective cohort study from the Global Collaborative Network : Author list. *J. Endocrinol. Invest.* **48**, 483–497 (2025).
195. Lin, H. T., Tsai, Y. F., Liao, P. L. & Wei, J. C. Neurodegeneration and stroke after semaglutide and tirzepatide in patients with diabetes and obesity. *JAMA Netw. Open.* **8**, e2521016 (2025).
196. Cummings, J. L. et al. evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease. *Alzheimers Res. Ther.* **17**, 14 (2025).
197. Femminella, G. D. et al. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: study protocol for a randomised controlled trial (ELAD study). *Trials* **20**, 191 (2019).
198. Cummings, J. L. et al. Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): two phase 3, randomised, placebo-controlled trials. *Lancet* **407**, 2167–2179 (2026).
199. Edison, P. et al. Liraglutide in mild to moderate Alzheimer's disease: a phase 2b clinical trial. *Nat. Med.* **32**, 353–361 (2026).
200. National Academies of Sciences, E. et al. Neurodegenerative disorders and other emerging areas. In *Examining Glucagon-Like Peptide-1 Receptor (GLP-1R) Agonists for Central Nervous System Disorders: Proceedings of a Workshop* (eds Norris, S. M. P., Childers, E. & Pool, R.) 51–64 (National Academies Press, 2025).
201. Fang, S., Cui, F. & Drucker, D. J. Glucagon-like peptide-1 medicines in neurological and psychiatric disorders. *Cell Rep. Med.* **6**, 102511 (2025).
202. Jastreboff, A. M. et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* **387**, 205–216 (2022).
203. Petersen, J. et al. GLP-1-directed NMDA receptor antagonism for obesity treatment. *Nature* **629**, 1133–1141 (2024).
204. Coassolo, L. et al. Prohormone cleavage prediction uncovers a non-incretin anti-obesity peptide. *Nature* **641**, 192–201 (2025).
205. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol.* **23**, 344–381 (2024).
206. Hurtado, M. D., Saadedine, M., Kapoor, E., Shufelt, C. L. & Faubion, S. S. Weight gain in midlife women. *Curr. Obes. Rep.* **13**, 352–363 (2024).
207. Ruehr, L. et al. Estrogens and human brain networks: a systematic review of structural and functional neuroimaging studies. *Front. Neuroendocrinol.* **77**, 101174 (2025).
208. Blümel, J. E. et al. Severe obesity and menopause symptoms are associated with cognitive impairment in postmenopausal women from Latin America. *Climacteric* **28**, 579–584 (2025).
209. Wood Alexander, M. et al. Associations between age at menopause, vascular risk, and 3-year cognitive change in the canadian longitudinal study on aging. *Neurology* **102**, e209298 (2024).
210. Butler, M. J. et al. Obesity-associated memory impairment and neuroinflammation precede widespread peripheral perturbations in aged rats. *Immun. Ageing* **22**, 2 (2025).
211. Martins, T. et al. Murine models of obesity. *Obesities* **2**, 127–147 (2022).
212. Chaib, S. et al. Translating cellular senescence research into clinical practice for metabolic disease. *Nat. Rev. Endocrinol.* **22**, 102–115 (2025).
213. Ogrodnik, M. et al. Obesity-induced cellular senescence drives anxiety and impairs neurogenesis. *Cell Metab.* **29**, 1061–1077 (2019).
214. Flores-Torres, R. P. et al. Senotherapy as a multitarget intervention in chronic obesity: modulation of senescence, neuroinflammation, dysbiosis, and synaptic integrity in middle-aged female Wistar rats. *Exp. Neurol.* **392**, 115331 (2025).
215. Sandsdal, R. M. et al. Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity, and inflammation: a randomized controlled trial. *Cardiovasc. Diabetol.* **22**, 41 (2023).
216. Grundy, S. M. et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* **112**, 2735–2752 (2005).
217. Alberti, K. G. et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* **120**, 1640–1645 (2009).

218. Child growth standards. *WHO* https://www.who.int/tools/child-growth-standards (2014).
219. Cole, T. J., Bellizzi, M. C., Flegal, K. M. & Dietz, W. H. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* **320**, 1240–1243 (2000).
220. Growth charts. *CDC* https://www.cdc.gov/growthcharts/index.htm (2024).
221. Xi, B. et al. International waist circumference percentile cutoffs for central obesity in children and adolescents aged 6 to 18 years. *J. Clin. Endocrinol. Metab.* **105**, e1569–e1583 (2020).
222. Nagy, P. et al. Percentile reference values for anthropometric body composition indices in European children from the IDEFICS study. *Int. J. Obes.* **38** (Suppl. 2), S15–S25 (2014).
223. Garnett, S. P., Baur, L. A. & Cowell, C. T. Waist-to-height ratio: a simple option for determining excess central adiposity in young people. *Int. J. Obes.* **32**, 1028–1030 (2008).
224. Bradfield, N. I. Mild cognitive impairment: diagnosis and subtypes. *Clin. EEG Neurosci.* **54**, 4–11 (2023).
225. Akshoomoff, N. et al. The NIH Toolbox Cognition Battery: results from a large normative developmental sample (PING). *Neuropsychology* **28**, 1–10 (2014).
226. Casaletto, K. B. et al. Demographically corrected normative standards for the English version of the NIH Toolbox Cognition Battery. *J. Int. Neuropsychol. Soc.* **21**, 378–391 (2015).
227. Casaletto, K. B. et al. Demographically corrected normative standards for the Spanish language version of the NIH Toolbox Cognition Battery. *J. Int. Neuropsychol. Soc.* **22**, 364–374 (2016).
228. Ding, R. et al. High-fat diet and chronic restraint stress exacerbate anxiety-depressive behaviors via astrocytic A1 phenotype transformation. *Sci. Rep.* **15**, 15031 (2025).
229. Li, Y. et al. High fat diet-induced obesity leads to depressive and anxiety-like behaviors in mice via AMPK/mTOR-mediated autophagy. *Exp. Neurol.* **348**, 113949 (2022).
230. Tsai, S. F. et al. High-fat diet suppresses the astrocytic process arborization and downregulates the glial glutamate transporters in the hippocampus of mice. *Brain Res.* **1700**, 66–77 (2018).
231. Chen, Z. et al. The autophagic degradation of Cav-1 contributes to PA-induced apoptosis and inflammation of astrocytes. *Cell Death Dis.* **9**, 771 (2018).
232. Naranjo, V. et al. Specific deletion of the astrocyte leptin receptor induces changes in hippocampus glutamate metabolism, synaptic transmission and plasticity. *Neuroscience* **447**, 182–190 (2020).
233. Wu, L. et al. Astrocyte-derived extracellular vesicular NFIA mediates obesity-associated cognitive impairment. *J. Neuroinflammation* **22**, 145 (2025).
234. Palavicini, J. P. et al. Early disruption of nerve mitochondrial and myelin lipid homeostasis in obesity-induced diabetes. *JCI Insight* **5**, e137286 (2020).
235. Bouhrara, M. et al. Evidence of association between obesity and lower cerebral myelin content in cognitively unimpaired adults. *Int. J. Obes.* **45**, 850–859 (2021).
236. Wahid, R. M., Samy, W. & El-Sayed, S. F. Cognitive impairment in obese rat model: role of glial cells. *Int. J. Obes.* **45**, 2191–2196 (2021).
237. Graham, L. C. et al. Exercise prevents obesity-induced cognitive decline and white matter damage in mice. *Neurobiol. Aging* **80**, 154–172 (2019).
238. Gong, Z. et al. Lower myelin content is associated with more rapid cognitive decline among cognitively unimpaired individuals. *Alzheimers Dement.* **19**, 3098–3107 (2023).
239. Kim, B. et al. Palmitate and glucose increase amyloid precursor protein in extracellular vesicles: missing link between metabolic syndrome and Alzheimer's disease. *J. Extracell. Vesicles* **12**, e12340 (2023).

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Author contributions

C.M.M., M.G.S. and E.L.F. researched data for the article and contributed substantially to discussion of the article content. C.M.M., M.G.S., M.H.N., S.A.E., W.G. and E.L.F. wrote the article. All authors reviewed and/or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Additional information

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Review criteria Between 14 October 2025 and 5 January 2026, we conducted a search on PubMed for articles in the English language, using the search terms 'obesity' and/or 'cognitive impairment' and/or 'dementia', along with one or more of the following terms: 'aerobic exercise', 'astrocytes', 'atrophy', 'body fat distribution', 'brain', 'bariatric surgery', 'body-mass index', 'cerebrovascular', 'cognition', 'cognitive function', 'caloric restriction', 'childhood obesity', 'dulaglutide', 'exenatide', 'exercise', 'genetic predisposition', 'GLP-1 receptor agonists', 'hippocampus', 'hypothalamus', 'insulin resistance', 'intermittent fasting', 'ketogenic', 'lifestyle factors', 'liraglutide', 'memory', 'menopause', 'meta-analysis', 'metabolism', 'microglial', 'mitochondria', 'modifiable risk factors', 'naltrexone bupropion', 'neuroinflammation', 'neuron', 'neurovascular', 'oligodendrocytes', 'post-menopausal', 'randomized controlled trial', 'semaglutide', 'senescence', 'sex', 'synaptic plasticity', 'tirzepatide', 'trends' and 'youth'. From the search results, we focused on articles that were published from 1 January 2020 to 5 May 2026; however, some recent studies were excluded owing to small sample sizes or substantial study limitations, and important older papers were also included along with articles from the authors' personal reference lists. The authors used their discretion to select articles on the basis of relevance to this Review.