CECOT, Jakub, ZARZECKI, Konrad, MANDRYK, Miłosz, JERCZYŃSKI, Paweł, DZIK, Dominika and PIASTA, Małgorzata. Obesity as a risk factor for dementia and cognitive impairment - a systematic review. Journal of Education, Health and Sport. 2024;67:55063. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.67.55063
https://apcz.umk.pl/JEHS/article/view/55063

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 10.08.2024. Revised: 10.09.2024. Accepted: 11.09.2024. Published: 13.09.2024.

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Abstract

Obesity, affecting One in eight people, poses significant health risks, including an increased risk of cognitive impairment and dementia. This article is exploring the complex and multifaceted relationship between obesity and cognitive function, highlighting several mechanisms that may contribute to cognitive decline in obese individuals. Research reveals that obesity in middle age is associated with a higher risk of cognitive decline, while in older adults, it might provide some protection against rapid cognitive deterioration. In adolescents, obesity is linked to lower scores on cognitive tests, indicating damaging effects on cognitive abilities from an early age. Key mechanisms discussed include neuroinflammation, mitochondrial dysfunction, and insulin resistance. Neuroinflammation involves elevated levels of pro-inflammatory cytokines leading to increased blood-brain barrier permeability and potential neuronal damage. Mitochondrial dysfunction in obesity results in impaired neuronal function due to disrupted mitochondrial processes. Insulin resistance, a common feature of obesity, affects brain regions critical for memory and executive functions. Additionally, the impact of weight loss on cognitive function is examined, with evidence suggesting that weight reduction through bariatric surgery, lifestyle interventions, or pharmacological treatments can improve cognitive abilities. However, further research is needed to establish definitive causal relationships and to understand the underlying biological changes.

Introduction

Obesity is one of the most commonly occurring diseases in modern societies, affecting 1 in 8 persons in the world [1]. Despite significant advances in treatments for the condition, it continues to place a significant burden on health systems around the world. While it may be sometimes overlooked, obesity is dangerous due to the numerous complications it causes. Obesity increases the risk of type two diabetes, non-alcoholic fatty liver disease, hypertension, cardiovascular incidents, stroke, obstructive sleep apnea, cancer, among others [2]. One of the complications recently tied to obesity is dementia. It is a clinical syndrome defined by a group of symptoms that include memory problems, language and cognitive function impairments,

behavioural changes, and difficulties in performing daily activities. It encompasses a variety of neurological disorders marked by memory loss and cognitive decline. With an ageing population, the prevalence of dementia is on the rise [3]. Worldwide, around 46.8 million people have been diagnosed with this condition. This number is expected to increase to 74.7 million by 2030 and 131.5 million by 2050 [4], pointing to a crisis ahead. For this reason, contemporary research is paying increasing attention to the pathogenesis and risk factors of dementia in order to combat it more effectively. Numerous publications point to the association of obesity with dementia and reduced cognitive abilities, the results of which we would like to present in this review.

Aim of the work

Obesity is currently one of the most commonly encountered health problems, particularly dangerous because of the numerous complications affecting virtually every organ and system within the human body. The primary aim of this review article is to systematically synthesise existing research on the relationship between obesity and cognitive functions across different age groups. Additionally, the review will explore the underlying biological and physiological mechanisms through which obesity may impact cognitive functions. Furthermore, we included information regarding the efficiency of weight loss in mitigating these consequences. In conclusion, the review will identify gaps in the current literature and propose directions for future research to better understand and address the cognitive impacts of obesity.

Methodology

This article is a literature review based on publications on PubMed using key words: obesity; dementia; cognitive impairment; brain insulin resistance;. The search was limited to articles published between the years 2010-2024. We focused particularly on high-quality meta-analyses with a large study sample, and ones that included different age groups in their observations.

Results

Impact of obesity on dementia and cognitive functions

The connection between obesity and future cognitive decline is not well understood. Increasing evidence suggests that higher levels of obesity, measured by Body Mass Index (BMI) and central obesity, during middle age are risk factors for later cognitive decline and are recognized as modifiable risk factors for cognitive deterioration. However, in later life, obesity seems to offer some protection against cognitive decline, with certain studies indicating that obese

individuals experience slower cognitive decline compared to those of normal weight. [5] To trace the relationship between obesity and dementia, we analysed recently published meta-analyses.

The first study involved a cohort of 5,060,687 participants. Results indicated that a high waist circumference (WC) was linked to an elevated risk of cognitive impairment and dementia. The combined hazard ratio (HR) for the association between high WC and the risk of cognitive impairment and dementia was 1.10 (95% CI: 1.05–1.15) when compared to low WC, despite variations in cut-off values across different studies. The adverse effect of high WC on cognitive impairment and dementia remained significant in individuals over 65 years old (HR = 1.13, 95% CI: 1.08–1.19), whereas the association was not significant in those younger than 65 years (HR = 1.04, 95% CI: 0.93–1.16). These results did not apply to waist-to-hip ratio (WHR), as no clear link was found between WHR and the increased risk of dementia or cognitive decline [6].

Another meta-analysis investigated the relationship between BMI, waist WC, and the annual percentage change in body weight with the risk of dementia and its subtypes. This analysis combined data from 19 prospective cohort studies and four clinical trials. The study included 2,790,753 participants, with 57,294 reported cases of dementia from all causes over an average follow-up period of 9.6 years. The average age of participants at the beginning of the study ranged from 36 to 87. Regarding the risk of all-cause dementia, particularly its major subtype of non-vascular dementia, there was no evidence linking excessive body weight to a higher risk. However, for vascular dementia, only the highest levels of BMI and WC were associated with a 50% increased risk compared to lower normal BMI and the lowest quintile of WC [7].

As suggested by the authors Tang X, et al., the discrepancies in results may stem from the broader age range in the study by Lee CM, et al. To obtain more precise results, the authors propose the use of more sensitive measurement methods. Further research is needed to thoroughly explore these risks [6].

A recent study considered 4,839 Chinese citizens. It tested the associations of obesity and grip strength with cognitive function in the elderly. Average age of individuals participating in the study was approximately 68.6 years. Cognitive function was assessed face-to face by the Telephone Interview for Cognitive Status (TICS). The TICS assesses: orientation, concentration, short-term memory, language, and mathematical skills. This study discovered that being overweight is significantly linked to a reduced rate of lower cognitive function (OR: 0.82; 95% CI: 0.71–0.94), compared to normal weight adults. However, no such link was noted

in obese individuals.The authors conclude that this is due to the likely protective effect of excessive body weight in the elderly population [8].

The study by Meo SA, et al. monitored the potential impact of obesity (expressed in BMI) on specific cognitive functions such as perception, attention, recognition, memory, and executive functions. The study group consisted of male students (n=400) aged 12-15 years. A significant relationship was found between high BMI (≥30) and reduced abilities in memory, concentration, and recognition. The results of the study indicate that adolescents with obesity have worse results in tests of cognitive functions compared to their peers with normal BMI. Particularly marked differences were noted in the speed of response to stimuli (5.74% slower), response to incongruent stimuli (6.75% slower), number of correct trials (7.37% less) and number of errors made (26.29% more) [9].

The Baltimore Longitudinal Study of Aging also found an association between obesity and cognitive decline. The results were divided into categories: global cognitive function, attention and executive function, memory, language and visuospatial. The study included 1,703 individuals aged 19-93 years. Participants were followed up periodically. Higher rates of obesity were associated with worse scores on tests assessing global cognitive functioning, such as the Mini-Mental State Examination (MMSE) and the Blessed Information-Memory-Concentration (IMC) test. Higher BMI was associated with poorer performance in prospective memory tasks, letter and categorical verbal fluency tests. Higher WC was associated with poorer performance on prospective memory tasks, The Benton Visual Retention Test, and the letter fluency test. In the visual-spatial domain, analyses showed that higher WC was associated with better performance on Card Rotations Test, but there was no association with higher BMI or WHR. Higher WHR were associated with poorer performance on: The Benton Visual Retention Test, categorical verbal fluency tests. In cross-sectional analyses, higher BMI, WC and WHR were associated with faster performance on the Trail Making Test A, which could indicate better processing speed [10].

A study of a Taiwanese population involving 28,486 participants showed deterioration of global cognitive function in individuals with abdominal obesity and obesity-related indices. Cognitive function was assessed using the MMSE. The participants were divided into two groups according to their MMSE score. Among the group with a lower score <24 points, there was a higher prevalence of metabolic syndrome, abdominal obesity, low HDL-cholesterol, hyperglycemia, high blood pressure, and higher levels of all obesity-related indices, including BMI, WHR and others [11].

Reversibility of cognitive impairment as a result of weight reduction

The unclear causal relationship between obesity and cognitive functions encourages researchers to conduct studies aimed at demonstrating the impact of weight reduction on cognitive functions, which would provide evidence of a more specific relationship than just correlation. In 2024, a meta-analysis was published that considered studies involving patients with a BMI > 35 kg/m² who underwent bariatric surgery followed by weight loss and neuropsychological testing. Improvements in attention, memory, and executive functions were observed 12 weeks and 12 months after surgery. The results were compared to those obtained from the same participants before undergoing surgery. No impact on language abilities was proven [12]. An older but larger meta-analysis conducted by Veronese at al. (2017) yielded similar findings. Besides patients with obesity, it also included those with overweight defined as a BMI > 25 kg/m², and it considered interventions other than bariatric surgery, such as dietary changes and increased physical activity. However, it highlighted the difficulties in definitively determining whether the improvement in cognitive functions was due to weight loss itself or the other effects of the interventions conducted [13].

The impact of intentional weight loss through reduced caloric intake was also studied in individuals over the age of 60 with mild cognitive impairment. All participants had a BMI > 30 kg/m² and experienced an average weight loss of 1.7 kg/m² during the study. This was associated with improvements in verbal memory tests, language, executive functions, and global cognition [14]. A similar association between weight loss and improved cognitive functions was observed in a study involving middle-aged and older adults without mild cognitive impairment [15]. The studies conducted among children and adolescents with obesity and overweight provide less substantial evidence. An analysis of 18 studies involving 2,384 participants considered various interventions aimed at weight loss, used either as standalone methods or in combination with two methods, such as increased physical activity, healthy lifestyle education, and dietary changes. Overall, it was demonstrated that treating obesity in children and adolescents can positively impact academic achievements and cognitive abilities. However, the authors emphasise that despite the large number of studies analysed, further research is required to provide better evidence, as the quality of those from the current studies is moderate to low [16].

The observed correlation between weight loss and improved cognitive functions encourages further research to establish objective changes in the human body that could be the reason behind these results. Important data has been provided by a literature review that includes studies on functional and structural brain imaging in obese individuals both before and after

interventions leading to weight loss. Among other things, it has been shown that bariatric surgery leads to improved functional and structural connectivity in prefrontal regions, resulting in increased cognitive control and contributing to further weight loss. These changes are secondary to alterations in hormonal regulation, with reduced ghrelin levels playing a leading role by reducing cravings for high-calorie foods. The recovery of brain grey matter volume is attributed to decreased levels of pro-inflammatory cytokines, while increases in brain white matter volume are linked to remyelination. Lifestyle interventions have also made their mark. A 12-month diet and increased physical activity program led to increased blood flow in extensive brain regions, including the frontoparietal cortex and subcortical areas, as well as numerous other detailed changes described in the study. Regarding pharmacological treatment, it has been demonstrated that liraglutide and dapagliflozin therapy led to reduced brain activity in the reward processing region, in structures such as the caudate, putamen, and insula [17]. The impact of weight loss on brain neuroimaging changes is established, but translating these changes into improved cognitive function requires further research. Researchers in a study from 2023 sought a different mechanism of how obesity affects cognitive functions. They demonstrated that treating obese mice with semaglutide and empagliflozin improved obesity-induced spatial learning and memory impairments in these animals. The proposed mechanism of this phenomenon was the increased phosphorylation of proteins CACNA1D, CACNA1A, and CACNA1B in hippocampal cells, as shown in the study. These proteins are involved in biological processes such as synaptic plasticity, neuronal projection development, and axonogenesis. Additionally, it was found that a high-calorie diet led to reduced phosphorylation of these proteins [18].

Possible mechanisms linking obesity with dementia and cognitive impairment

The relationship between obesity and cognitive impairment is complex and multifaceted, involving various physiological, metabolic, and psychological mechanisms. We want to present the three most studied potential mechanisms linking obesity to reduced cognitive function. Other mechanisms mentioned in the literature include disturbances in microbiota composition, behavioural abnormalities or epigenetic factors, however they are not sufficiently understood and studied to unequivocally attribute a role in neurodegeneration to them.

Neuroinflammation

The literature has shown significant links between adipose tissue and the immune system, where one of the most important is the association of the adipokines, leptin and adiponectin, with

stimulation and inhibition of immune responses, respectively. In this context, it is not surprising that obesity includes an inflammatory component, which can be attributed a role in the pathogenesis of its associated complications. Pathologically extended number of fat cells results in systematically elevated concentration of proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 beta (IL-1β), tumour necrosis factor alpha (TNF-α) . Chronic low-grade inflammatory state contributes to an increase in blood-brain barrier permeability, allowing for leukocyte extravasation and enabling entry for potential pathogens and substances toxic to nerve tissue. Microglial cells, which in physiological conditions facilitate neuroprotection through mediation of immune response, in the case of systemic inflammatory processes, can transform into a reactive form, and stimulate an inflammatory response by releasing proinflammatory cytokines [19]. Signalling molecules produced in excess during neuroinflammation mediate pro-apoptotic pathways, suggesting that neuroinflammation may also have a direct influence on neuronal death. [20]. These alterations lead to a vicious circle and a decrease in cognitive abilities due to loss of neurons.

Mitochondrial Dysfunction

Another possible link between obesity and cognitive impairment is mitochondrial dysfunction. Mitochondria are cell organelles preeminently responsible for the production of ATP, but they are also involved in many other processes. They play a major role in cell signalling, such as modulating apoptosis and inflammasome activation. It has been proven that obesity leads to disruption of numerous mitochondrial processes, such as impairment of biogenesis, lowered reactive oxygen species clearance or mitochondrial dynamics changes [21,22]. Because high levels of mitochondrial metabolism are necessary for neuronal function, functional or structural changes to the mitochondria have detrimental effects on neurons. The work of Johnson et al. [23] shows that the aforementioned mitochondrial complications of obesity are clearly correlated with neuronal dysfunction and play a role in the onset and progression of neurodegenerative diseases. Another example of association can be presence of Donut-shaped mitochondria in obese people, an early indicator for mitochondrial stress, which have been identified to negatively correlate with synapse quantity in the brain [24].

Insulin Resistance

Obesity is associated with insulin resistance (IR), a condition that results in long-term systemic hyperinsulinemia by impairing the effects of insulin on important target tissues. It leads to

reduced capacity for intracellular transport and glucose oxidation, glycogen synthesis and lipolysis, contributing to further deterioration of metabolic function. Within the brain, insulin plays a major role in the operation of areas responsible for memory and executive functions. It appears that the prefrontal cortex, fusiform gyrus, striatal areas, and the hypothalamus, due to higher insulin receptors density, are especially susceptible to obesity-related IR. In an article by Willmann et al. [25], researchers revealed that insulin sensitivity was strongly linked to cognitive functions, but no such relationship exists with blood glucose levels, cementing the significant influence of IR. Individual studies have found short-term improvements in memory and associative function after intranasal administration of insulin. The effect of insulin on the phosphorylation of tau protein is also worth mentioning, in the context of the development of Alzheimer's disease, where IR promoted this process, increasing the risk of this condition [26].

Conclusions

Studies indicate a complex relationship between obesity and cognitive function in different age groups. In studies of older adults, being overweight is often associated with worse cognitive test scores than individuals with normal body weight. Although there is a suggestion that obesity in the elderly may offer a protective function against rapid cognitive decline. Among younger people, such as adolescents, obesity is associated with poorer performance on tests of cognitive function, indicating that obesity has negative effects on cognitive ability from a young age. The research also indicates a positive change in cognitive functions following weight reduction. This is especially promising given the recent breakthrough in obesity treatment associated with the introduction of new medications like GLP-1 agonists into treatment. There is a need for further research to better understand the complex relationship between obesity and cognitive function. Attention should be paid to the use of accurate measurement methods and to the variation of results according to age and obesity rates.

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Funding Statement: The study did not receive funding.
Institutional review board statement: Non applicable.
Informed consent statement: Non applicable.
Data availability statement: Non applicable.
Conflict of interest: The authors declare no conflict of interest.

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