The impact of obesity on dementia

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Abstract

Introduction
Dementia is a syndrome characterized by a gradual deterioration of cognitive functions,
including memory, thinking, orientation, attention span, perception, judgment, and language abilities. Obesity influences its development.

**Materials and methods**
The following review of studies is based on recent scientific articles available in PubMed and Google Scholar databases. The most searched phrases included: "dementia", "obesity", "midlife", and "the relationship between obesity and the risk of dementia".

**Results**
Literature review indicates the existence of a relationship between midlife obesity and later dementia. It has also been pointed out that the forecasts for the onset of obesity and dementia are alarmingly rising worldwide. It is estimated that by the year 2050, we can expect a threefold increase in dementia cases.

**Conclusion**
The results of the cited studies indicate that further research into the occurrence of obesity and its later association with dementia is necessary. Midlife obesity likely plays a significant role in the etiopathogenesis of dementia.

**Key words:** "dementia"; "obesity"; "the relationship between obesity and the risk of dementia"; "midlife"

**Introduction:**
The word "dementia" comes from the Latin words "de" (out of) and "mens" (mind). Dementia is a clinical syndrome characterized by severe impairments in cognitive function, negatively impacting daily life activities. [1] It's a condition associated with age, posing a global public health challenge, especially given the aging population. The majority of dementia cases are diagnosed in older individuals, with over 90% occurring after the age of 60, and 32% affecting individuals aged 85 and older. [2]

Dementia is a condition that currently has no known cure. Forecasts suggest a rapid increase in the number of dementia cases as the population ages. [3]

In 2015, the global population of people with dementia was around 50 million. It is estimated that by 2050, the number of affected individuals could reach 131 million. [4]
I. Types of dementia include
There are many types of dementia, with Alzheimer's disease being the most common. The next most common group is vascular dementia, followed by dementia with Lewy bodies. Mixed dementia is also common, which may include features of more than one type of dementia. Less common are cases of frontotemporal degeneration and dementia related to brain injury, infections, or alcohol abuse.[5] In this paper, by referring to "dementia," we will encompass all the types mentioned.

II. Factors influencing the development of dementia include
Modifiable factors influencing the development of dementia include: hypertension, diabetes, lack of access to education, smoking, hearing impairment, lack of physical activity, alcoholism, air pollution, traumatic brain injury, social isolation, and obesity. [6]

III. The relationship between obesity and dementia
Excess adipose tissue, particularly when centrally distributed, can impact cognitive function, leading to its deterioration. [7] Speculation suggests that obesity may influence by increasing the risk of dementia through the release of signaling proteins by adipose tissue and its negative impact on overall body function, as well as the development of cardiometabolic diseases.[8] These changes form the basis of many cases of dementia in older age and can be precisely observed using brain imaging techniques and image analysis, which provide information about brain tissue volume and the presence of small and large vascular lesions, both focal and diffuse. [7] This mean sthat high BMI in midlife is associated with a great risk of dementia. However, research on older individuals shows that there is a reverse relationship between high BMI and dementia. [9] However, not all studies are consistent, and not all have shown the same associations. [10]

IV. Obesity as a public health issue.
Obesity itself constitutes a primary public health concern. Since the 1980s, the prevalence of overweight and obesity in adults, as determined by body mass index (BMI), has been steadily increasing worldwide. Over the course of 33 years of data recording, there has been no successful decline in these indicators in any country. [4] It is largely genetically determined, although environmental factors also play a significant role. Across the globe, rates of overweight and obesity continue to rise, reaching levels comparable to an epidemic. Typically, the highest rates occur in middle age. [11]
V. The genetic predisposition to obesity.

A change in a single base pair in the single nucleotide polymorphism (SNP) rs9939609, located in the FTO (fat mass and obesity-associated gene), is associated with obesity and higher body mass. FTO is a gene encoding a protein associated with DNA N6-methyladenosine demethylation via 2-oxoglutarate. It is located on chromosome 16q12.2 in humans and consists of 9 exons and 8 introns.

The expression of this gene is widespread throughout the body but particularly high in the hypothalamus. [12] Individuals who have inherited specific SNP variants may be more susceptible to developing obesity. However, the influence of SNPs on body mass can vary depending on other factors such as lifestyle and environment. [13]

The mechanism of cognitive dysfunction in obese individuals.

Obesity can be interpreted as a result of dysregulation in energy regulation or as a consequence of deficits in mechanisms controlling behaviors and rewards. [14] In imaging studies of overweight and obese individuals, various changes have been observed, such as scattered white matter lesions, focal anomalies in white matter structure, loss of connectivity, and cortical and subcortical gray matter atrophy. [15,16,17] This suggests that the image is similar to that observed in neurodegenerative diseases. Commonly recognized mechanisms of central nervous system dysfunction associated with obesity include inflammation, vascular abnormalities (associated with endothelial dysfunction), as well as, less precisely, energy homeostasis in the brain (resulting from mitochondrial dysfunction) or direct interaction of signals from adipose tissue with the brain. [18,19,20]

In overweight and obese individuals, adipose tissue can initiate a local immune response by activating various cells of the immune system. The increased size of adipocytes may be the first step in attracting macrophages and their activation (transition to the M1 state), leading to local accumulation of immune cells. [21]

Activated immune cells can then interact with cells of the central nervous system immune system or glial cells through various mediators or may circulate and penetrate the blood-brain barrier (BBB), maintaining inflammation at the systemic level. Systemic inflammation may be reflected in the brain, at least partially due to BBB dysfunction and aberrant activation of components of the central nervous system (CNS) and peripheral immune system. Inflammation of the central nervous system (CNS) is associated with functional and structural abnormalities in the brain. [22]
I. The impact of leptin.
Adipose tissue is also a source of signaling molecules that can exert distant effects. It is suspected, though not certain, that cognitive impairment (including Alzheimer's disease) associated with obesity may result from leptin resistance. [23] Leptin, which is a peptide hormone primarily synthesized by white adipose tissue, appears to have a diverse impact on structures of the central nervous system, primarily associated with energy regulation. There are studies suggesting that proper neurological development of brain structures, such as the arcuate nucleus in the hypothalamus, may require specific patterns of leptin action in terms of timing and intensity, which may have potential long-term consequences in case of improper stimulation. [24] In obesity, we observe an increase in serum leptin levels. [25] However, it is not certain whether leptin actually influences the development of dementia. There are studies confirming that high levels of adiponectin are associated with neurodegenerative dementia, while high levels of resistin are associated with vascular dementia, and the level of leptin in healthy patients as well as those with dementia remained similar. [26]

II. Microflora in obese individuals.
Abnormal gut microbiota associated with obesity affects the immune system, leading to its improper activation. Additionally, it is responsible for releasing substances into the circulation that may contribute to pathological interactions with the blood-brain barrier (BBB) and the central nervous system immune system. [27] In one study, associations were observed between the outcomes of all memory domains and altered levels of tryptophan, tyrosine, and phenylalanine, as well as their metabolites in the serum. Changes in tryptophan metabolism associated with memory were observed only in individuals with obesity. Within Bacteroides and Proteobacteria, negative associations between gut microbiota and memory outcomes were identified. [29]

It is worth mentioning that in one study, obesity was shown to be associated with an increase in the Prevotella/Bacteroides ratio, as well as with an increase in the centrality of the semi-lying nucleus and a decrease in the level of tryptophan in feces. [30] Among the substances whose mechanism of action can be linked to immune disorders and cognitive dysfunction, we can also distinguish quinolinic acid, which significantly correlates with BMI and is elevated in this group of patients.
This is a metabolite of tryptophan, which is secreted by macrophages and adipose tissue in the process of inflammation. It is neurotoxic and acts as an agonist of the glutamate receptor. [30,31] The next compounds having a significant impact on the correlation between the microbiome and cognitive impairments are short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, produced by gut bacteria from undigested dietary fiber. They belong to cellular energy sources. They support cellular metabolism and modulate the gut barrier. [32]

III. Consequences for obese individuals from a neurological perspective.
There is scientific evidence confirming that obesity is responsible for increasing the risk of early cognitive decline. It turns out, however, that it may have an immediate negative impact on cognitive function. Individuals with high BMI have poorer foreign language learning abilities, reduced working memory performance, and their episodic memory-related task performance is worse compared to individuals with normal body weight. According to Miller's research, a high-fat diet and obesity lead to a systemic inflammatory state, which contributes to synaptic remodeling and neurodegeneration, ultimately leading to impaired brain function and cognitive function. The hippocampus, amygdala, and reward processing centers, disrupted by induced inflammation, impair cognitive function, leading to disrupted satiety signals and causing overeating. Additionally, it has been shown that regardless of age and health status, an increase in BMI leads to a decrease in brain volume, gray matter in the occipital, frontotemporal, and hippocampal cortices. There is also a decrease in blood flow to the prefrontal cortex. In obese individuals, an accelerated aging process of white matter has been observed.[33]

Dementia and BMI
According to the Lancet Commission on Dementia Prevention, about 1% of dementia cases in middle age can be directly attributed to obesity (BMI ≥ 30), while up to 6% of cases can be attributed to obesity-related conditions such as diabetes, hypertension, and low physical activity. It turns out that the data corresponds to the estimated dementia burden attributed to the strongest genetic variant, which is 7% for the E ε4 allele of apolipoprotein E. This indicates that potential modification to a healthy lifestyle in middle age, including weight reduction, could reduce the burden of dementia.
These conjectures are based on observational studies, which are susceptible to systematic errors. Especially the long preclinical period of dementia is a key source of potential systematic errors that can influence whether, when, and to what extent high BMI increases the risk of dementia. [34]

**When does obesity impact dementia?**

There are conflicting estimates regarding when lower BMI or weight loss may be associated with dementia. Most studies suggest a period of 8 to 12 years before the diagnosis of dementia, but some estimates indicate a period extending up to 20 years earlier. [8]

I. The Whitehall II cohort study

In the 28-year Whitehall II cohort study, which included women and men from England, BMI (body mass index) measurements were taken over the course of 28 years (BMI is calculated as weight in kilograms divided by height in meters squared). The study cohort consisted of over 10,308 participants, who were assessed for health status every 5 years. Ultimately, 329 cases of dementia were identified. The studies relied on conducting two sets of analyses: Cox regression to determine the association of obesity indicators at ages 50, 60, and 70 with subsequent dementia, and comparing BMI changes in individuals with dementia to other participants using a retrospective time scale. The results obtained allowed for the association of obesity occurrence at the age of 50 with the onset of dementia, although the relationship was weakened in the case of its occurrence at ages 60 and 70. Another conclusion drawn was that the BMI value decreased in individuals with dementia in the years preceding the diagnosis. [35]

**Dementia in England**

In 2017, dementia accounted for over one-eighth (12.7%) of deaths in England, thus becoming one of the leading causes of death. In the English Longitudinal Study of Aging (ELSA), 6582 participants aged ≥ 50 years were examined for BMI analysis, and 5538 for waist circumference (WC) analysis. The patients were observed for 11 years. At the start of the study, the participants were dementia-free. The study was conducted based on the association between BMI (divided according to standard World Health Organization criteria into normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obesity (≥30 kg/m^2)), and waist circumference (WC) in women > 88 cm and in men > 102 cm, defining
specific parameters as central obesity. Additionally, the analysis included covariates such as gender, age, apolipoprotein E ε4 allele (APOE-ε4) status, education, marital status, smoking habit, physical activity, hypertension, and diabetes. Two confounding factors were identified in the study: marital status and education (due to the suspicion that individuals with formal education over a longer period may have a lower risk of dementia). The observational period lasted 15 years, and Cox proportional hazards models were used.

Dementia developed in 6.9% of the participants in the study. Initially, the risk of dementia was 35% higher compared to participants with normal BMI. It was shown that additional adjustments for education and marital status did not significantly affect the risk of dementia, and no interaction was observed between BMI and APOE, hypertension, or diabetes. However, it was found that in women who had abdominal obesity at the beginning of the study, the risk of developing dementia was increased by 39% compared to women with obesity other than abdominal. This relationship was observed only in the group of women; this observation did not apply to men.

In this study, based on the obtained results, evidence was provided for a positive and independent association between obesity and the risk of dementia. Additionally, it was shown that increased abdominal obesity also indicates a higher incidence of dementia in the group of women. [36]

**Dementia in China and the United States**

In a study that combined prospective studies and meta-analyses of obesity indicators to estimate the prevalence of dementia in the United States and China, it was found that past and current increases in the prevalence of obesity in middle age will significantly contribute to the occurrence of dementia in the future. The selected studies provided information on the relationship between overweight, underweight, or obesity and the risk of dementia or Alzheimer's disease and lasted for a minimum of 12 months. Random-effects DerSimonian and Laird meta-analysis as well as fixed-effects meta-analysis were applied. Population attributable risk (PAR) was calculated, which represents the proportion of individuals suffering from a particular disease in the population. Two measurements were taken, and a time delay between exposure to the risk factor in middle age and the onset of the disease was also considered. A morbidity ratio was applied, corresponding to the population from 25 years ago.
In the study, Pr(E) was calculated, representing the frequency of exposure to the risk factor in the population for the United States in the years 1985, 2000, and 2025. Overweight in midlife was omitted due to lack of data. In the case of China, the impact of overweight and obesity was taken into account.

The results showed that in individuals over 60 years of age, the risk of dementia is lower among those who are overweight compared to those with normal body weight. Additionally, according to the presented forecasts of obesity prevalence, it turns out that the number of future patients will be significantly higher than previously anticipated.

The authors conclude in the findings that obesity in middle age increases the risk of Alzheimer's disease and dementia later in life by almost 100%.

It is predicted that in the United States, the number of patients will increase by 9%, and in China by 19% over the coming years. [37]

**Dementia in Australia**

Australia is a country that is also experiencing an upward trend in the prevalence of obesity. It is predicted that this will contribute to a larger-than-expected dementia epidemic in the country, based on the aging population. The study analyzed and modeled changes among Australians aged 65 and older suffering from dementia, based on past trends in BMI values among older individuals. Projections regarding the population were obtained from the Australian Bureau of Statistics. The average age was set at 50 years old. The participants were divided into four categories based on their BMI values: obesity, overweight, normal range, and underweight, assuming that disease-specific morbidity rates for gender, age, and BMI would remain constant in the future. The results showed that by 2050, the number of dementia cases would be 14% higher than projected based solely on the aging of the population. This will occur due to the increasing prevalence of obesity and a decrease in the prevalence of normal weight. [38]

**Conclusion**

The above study provides information on the impact of obesity on dementia. It confirms that there is a relationship between the risk of dementia and obesity. Obesity occurring in middle-aged individuals can lead to cognitive function impairments in various forms. Additionally, the above study indicates how prevalent the issue of this relationship is worldwide. The gathered data show that the "epidemic" of obesity is present on most continents around the
world. Projections of disease incidence suggest that there will be a significant increase in cases in the coming years, and the occurrence of both diseases represents a serious public health issue.

**Author's contribution**

Conceptualization, Adriana Wojciechowska, Aleksandra Mazurkiewicz and Justyna Marcicka; methodology, Joanna Męczyńska; software, Nazarii Saiuk; check, Joanna Męczyńska, Tomasz Seredyński and Michał Andrzej Kozicz; formal analysis, Magdalena Kołodziej and Wojciech Mądry; investigation, Wojciech Mądry and Weronika Salasa; resources, Magdalena Kołodziej; data curation, Justyna Marcicka; writing - rough preparation, Adriana Wojciechowska; writing - review and editing, Aleksandra Mazurkiewicz and Nazarii Saiuk; visualization, Michał Andrzej Kozicz; supervision, Tomasz Seredyński; project administration, Joanna Męczyńska; receiving funding, Weronika Salasa

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