REVIEW ARTICLE

Medycyna Środowiskowa – Environmental Medicine 2023, Tom 26, Nr 3–4, 79–83
www.environmed.pl

Obesity as an important risk factor for dementia

Otyłość jako istotny czynnik ryzyka chorób otępiennych

Laura Fus-Mazurkiewicz[1,A-F], Justyna Sak[2,A-F], Michał Nowiński[3,A-F], Wojciech Mazurkiewicz[1,A-F]

[1] *Military Clinical Hospital No. 1 with Polyclinic, Independent Public Health Care Unit, Lublin, Poland*
[2] *Jana Pawła II Clinical Hospital, Kraków, Poland*
[3] *Military Clinical Hospital No. 5 with Polyclinic, Independent Public Health Care Unit, Kraków, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Fus-Mazurkiewicz L, Sak J, Nowiński M, Mazurkiewicz W. Obesity as an important risk factor for dementia. Med Srodow. 2023; 26(3–4): 79–83. doi: 10.26444/ms/175316

Abstract

Introduction and Objective. Obesity is a disease that affects an increasing number of people worldwide. Simultaneously, it is also predisposing in the development of many conditions, including dementia. There are an alarming number of obese people worldwide, and the risk of people suffering from dementia will continue to increase annually. The aim of this review is to draw attention to issues related to obesity as a predisposition to the development of dementia, including factors contributing to the development of both of these diseases.

Brief description of the state of knowledge. There are a number of factors that may contribute to the development of obesity. These include: socio-economic status, appearance preferences, the influence of the external environment, and many others. Obesity is associated with hormonal disorders, including increase in leptin levels and increased production of adipokines. Both of these phenomena adversely affect the central nervous system, leading to the development of inflammatory reactions, and apoptosis of neuronal cells. It will significantly contribute to the impairment of the functioning of the nervous system, favouring the development of numerous diseases, including dementia.

Summary. Obesity is an increasingly serious problem, especially in developed countries. It leads to a number of disorders in the human body which have an impact on the high risk of dementia diseases. There are numerous factors predisposing to the development of both obesity and dementia and there seems to be a clear correlation between the two diseases.

Key words

obesity, dementia, BMI

Streszczenie

Wprowadzenie i cel pracy. Otyłość jest to choroba, która dotyka coraz więcej osób na świecie. Jednocześnie jest ona także czynnikiem predysponującym do rozwoju wielu schorzeń, m.in. otępienia. Ze względu na bardzo dużą liczbę osób otyłych na świecie istnieje ryzyko, iż odsetek osób cierpiących na otępienie będzie zwiększał się z roku na rok. Celem niniejszej pracy jest zwrócenie uwagi na zagadnienia związane z otyłością jako predyspozycją do rozwoju chorób otępiennych, z uwzględnieniem czynników sprzyjających rozwojowi obu tych schorzeń.

Opis stanu wiedzy. Istnieje szereg czynników, które mogą przyczyniać się do rozwoju otyłości. Wśród nich wyróżnić można m.in. status społeczno-ekonomiczny, preferencje dotyczące wyglądu, wpływ środowiska zewnętrznego i wiele innych. Otyłość wiąże się z występowaniem zaburzeń hormonalnych, dotyczących m.in. wzrostu poziomu leptyny oraz zwiększonej produkcji ilości adipokin. Oba te zjawiska wpływają niekorzystnie na ośrodkowy układ nerwowy, prowadząc do rozwoju reakcji zapalnych oraz apoptozy komórek nerwowych. W znaczący sposób będzie przyczyniać się to do upośledzenia funkcjonowania układu nerwowego, sprzyjając rozwojowi licznych chorób, w tym otępienia.

Podsumowanie. Otyłość stanowi coraz poważniejszy problem, zwłaszcza w krajach rozwiniętych. Prowadzi ona do wielu zaburzeń w organizmie człowieka, mając tym samym wpływ na wysokie ryzyko wystąpienia chorób otępiennych. Istnieją liczne czynniki predysponujące do rozwoju zarówno otyłości, jak i otępienia. Wydaje się istnieć wyraźna korelacja pomiędzy obiema tymi chorobami.

Słowa kluczowe

otyłość, otępienie, BMI

INTRODUCTION AND OBJECTIVE

Obesity is defined as an abnormal or excessive accumulation of body fat that can negatively affect health. Most often, it results from an inappropriate lifestyle and a caloric intake that is too high relative to demand and expenditure. Today, the problem of obesity is growing dynamically. According to data from the World Health Organization (WHO), the number of people suffering from obesity has tripled since 1975. According to WHO data, in 2016, the number of overweight adults reached nearly 2 billion, and 650 million adults suffer from obesity. The disease is now a more common cause of death than underweight. To classify overweight and

✉ Address for correspondence: Laura Fus-Mazurkiewicz, Military Clinical Hospital No. 1 with Polyclinic, Independent Public Health Care Unit, Lublin, Poland
E-mail: laura.fus@stud.umed.lodz.pl

obesity in adults, the body mass index (BMI) is commonly used. To calculate BMI, body weight is divide by the square of body height, expressed in meters (kg/m^2) [1, 2]. Dementia is a gradual deterioration of intellectual performance, manifested by predominant impairment of memory or other cognitive and behavioural functions, including changes in personality [3].

It is estimated that there are currently 50 million dementia patients worldwide, two-thirds of whom suffer from Alzheimer's disease, and one-third of whom have vascular dementia, mixed dementia and dementia with Lewy bodies, among others. The number of sufferers is likely to rise to 152 million by 2050. The global cost of treating dementia is estimated at about $1 trillion per year, a figure projected to double by 2030 [4]. Research into the relationship between obesity and dementia-related diseases is essential to guide prevention measures and discover new therapeutic options for the disease.

The aim of this review article is to present the current state of knowledge on the role of obesity in the pathogenesis of dementia, based on the published literature on this topic. In order to analyze the key publications, PubMed and Google Scholar resources, textbooks and reference materials were searched. Fifty-two papers in Polish and English were used, using key words: 'obesity', 'dementia', 'dementing diseases' and 'BMI'. In this review, the terms 'dementia' and 'dementing diseases' are used interchangeably.

DISCUSSION

Definition of obesity. Obesity is a chronic disease that occurs as the result of a positive energy imbalance, which is the result of an excess of energy intake from food over energy expended, and which has no tendency to resolve itself. The etiology of obesity is extensive, although environmental factors, genetics, emotional and endocrine disorders, and the influence of drugs play the most important roles in its pathogenesis [5]. Obesity can also result from hereditary disruption of energy homeostasis. The heritability of BMI values is estimated at 40–70%. A mutation in the 'ob' gene, encoding the fat tissue hormone leptin, has been shown to cause significant obesity in mice. Mutations in genes encoding leptin, receptor for leptin, receptor for melanocortin, and proopiomelanocortin, can significantly contribute to the development of obesity [6].

Factors predisposing to the development of obesity. There are many factors that can contribute to the development of obesity. The following are those that appear to have the most significant impact:

- *body appearance preferences* – in the first decades of the 20th century, obesity was considered a symbol of beauty and wealth, and in societies where large body weight is considered an attribute (e.g., Pacific islands), obesity may develop at a faster rate than in countries where less weight is favoured (e.g., Japan) [7],
- *socio-economic status* – obesity prevalence ranges from <5% in countries such as Vietnam, Bangladesh, Laos and Japan, to >50% in Micronesia, Yemen (low income) where obesity prevalence is 17.1% versus 35.4% in Saudi Arabia (high income). Interestingly, differences in obesity prevalence between regions within a country can also be observed; for example, in north-west Germany, obesity affects 20% of the population, while in the Saxony-Anhalt region the problem affects more than 28% of the population [8, 9],
- *environment* – local environment can significantly affect the prevalence of obesity. Access to fast-food restaurants, easy access to transportation, lack of walking areas and places for active recreation are all factors that significantly contribute to an increase in the percentage of obese people in a community [10, 11].
- *food promotion in social media* – it has been shown that in children, preferences for consuming calorie-dense foods change within a short time after exposure to advertising. It seems interesting that sensitivity to the advertising content presented is dependent on genetics – carriers of a high-risk single nucleotide polymorphism in the obesity-related gene (FTO) were more sensitive to food marketing than carriers of wild-type alleles [6, 12, 13, 14].

Definition, risk factors and types of dementia diseases. Dementia is the name given to a number of diseases that affect information processing, memory and the ability to perform daily activities. There are nearly 10 million new cases of dementia worldwide each year, and more than 55 million people currently suffer from the disease [15]. There are many types of dementia. The most common varieties, according to their prevalence are, in descending order, Alzheimer's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, and fronto-temporal degeneration [16]. In this review, all of them are referred to by the common term 'dementia', without being divided into the various types.

Previously, the general opinion had been that there was no effective prevention or treatment of dementia, but recently, significant progress has been made on this topic. A 2020 report from *The Lancet* analyzing the latest research in the field, itemises 12 modifiable risk factors for dementia, which accounts for about 40% of the disease cases. According to current knowledge, it is possible to avoid or delay a significant number of cases of the disease. These risk factors include low education, hearing loss, traumatic brain injury, hypertension, alcohol abuse, obesity, smoking, depression, social isolation, physical inactivity, diabetes and air pollution [17]. The effect of obesity on the induction of hypertension has been the subject of numerous scientific studies which have shown obesity to be a major risk factor for hypertension and diabetes [18]. Guidelines for treating hypertension, in addition to drug treatment, include weight reduction [19]. The Polish Society of Hypertension notes in its guidelines that a significant relationship between weight reduction and lowering blood pressure has been proven [20]. Another factor in the development of dementia that has been linked directly to obesity is physical inactivity. Uri Ladabaum et al. analyzed available data from 1988–2010 to examine the relationship between obesity, abdominal obesity, physical activity, and caloric intake. Their analysis showed that a lower BMI and smaller waist circumference were correlated with higher levels of physical activity [21]. The mechanism for the development of obesity is long-term excessive energy intake. Increased physical activity creates a caloric deficit due to increased energy expenditure, which may protect against obesity [22]. In addition, decreased physical activity increases the risk of obesity, and physical activity is associated with lower levels of body fat [23].

The interrelationship between obesity and depression is wel-known. It has been proven that people with BMI>30

have a significantly higher risk of depression, hence, it is necessary to include such people in prevention and regular monitoring for prompt implementation of possible treatment [24–27]. The relationship between emotional compulsive over-eating and depression has been demonstrated, as well as their significant impact on the development of obesity [28]. A meta-analysis of 15 studies showed a reciprocal relationship between depression and obesity, the strongest for clinically diagnosed depression. It is noteworthy that the interplay between the two factors is bi-directional – the presence of one significantly increases the risk of developing the other, and *vice versa* [29].

According to *The Lancet,* social isolation is another risk factor for the development of dementia, and has also been linked to obesity [30]. Obese people may have less emotional trust in loved ones, thereby social isolation may be exacerbated [31].

Numerous studies have shown a positive correlation between alcohol abuse and the incidence of obesity [32]. Based on questionnaires, the daily caloric intake from alcohol among British women was calculated using logistic regression. The average caloric intake from alcohol was 19% for women, and 27% for men, of the daily caloric intake on the day of the week when alcohol consumption was highest, respectively. The study confirmed the thesis that calories from alcohol may significantly contribute to the increased incidence of obesity [33].

Numerous studies confirm the rarer prevalence of obesity in people with higher education, thus awareness of health consequences in better-educated individuals may facilitate healthy lifestyles and healthier choices. Lack of this awareness increases the risk of making decisions with consequences leading to obesity [34].

Using data from the National Health and Nutrition Examination Survey (NHANES), the magnitude of obesity prevalence in adult Americans (age 20 and over) was analyzed according to education level, among other factors. The results of the analysis showed a clear association of low education with a higher incidence of obesity in the study population. The age-adjusted prevalence of obesity among those with higher education was lower (27.8%) than among those who had completed high school (40.6%) [35].

The results of the above cited studies confirm that it is not only obesity itself that can lead to the development of dementia. They prove that factors promoting the development of dementia symptoms: hypertension, diabetes, physical inactivity, social isolation, depression, alcohol abuse and low education, are also closely correlated with obesity. By eliminating one of the factors at an early stage, the 'snowball effect' can be avoided – the mutually driving causes of dementia development.

Link between rising global BMI and dementia diseases. To date, many studies have found a significant link between BMI and the development of dementia-related diseases in humans. In a meta-analysis, the researchers studied 19 different studies that spanned up to 42 years and included a total of 589,649 participants. In these groups, 2,040 subjects developed dementia. Obesity (BMI≥30kg/m^2) between the ages of 35–65 was shown to be related to the onset of dementia later in life. However, this correlation was not observed in overweight individuals (25<BMI<30) [36]. The link between obesity and dementia, however, does not appear to be so obvious, as indicated by the results of another large study. Nawab Qizilbash et al. conducted a retrospective study on a cohort of 1,958,191 residents of the United Kingdom with a mean age of 55. Two most significant findings resulted from the study: 1) there was an indication that being underweight (BMI<20kg/m^2) in this group of people increased the risk of dementia by 34%, and 2) the surprising finding that each successively higher BMI category lowered the risk of developing dementia. The group of people with BMI>40kg/m^2 had as much as a 29% lower risk of developing dementia, compared to the group with normal weight [37]. The study analyzed patient data until (a) the onset of dementia was noted, (b) the patient was transferred to another facility, (c) the patient died, or (d) the facility completed data collection. However, the study did not take into account the life expectancy of the patients or the burden of other diseases. Therefore, further detailed studies are needed which take other factors into account.

Leptin and its impact on the development of dementia. Leptin is a hormone produced by fat cells (adipocytes) with levels which are higher in obese people compared to those with a normal BMI. The level of leptin increases in direct proportion to the number of adipocytes in the body – the more obese the person, the higher the concentration of leptin in the blood. This hormone, called a satiety hormone, leads via a neurotransmitter pathway to the stimulation of the satiety centre, located in the ventral-parietal nucleus of the hypothalamus. In obese people, the phenomenon of leptin resistance is observed. This means that the sensitivity of the satiety centre to elevated leptin levels decreases over time. As a result, despite high leptin levels in the blood, these individuals experience less satiety and more hunger [38]. Interestingly, leptin itself has been shown to have a protective effect on neurons and prevent their neurodegeneration by delaying brain cell apoptosis [39]. Leptin resistance in obese individuals has a negative effect on neurons, as these individuals show a reduced neuro-protective effect of leptin. This therefore promotes neuronal cell apoptosis and leads to a faster progression of neuronal neuro-degeneration [40]. Matthew J. McGuire and Makoto Ishii have demonstrated a link between leptin dysfunction and the development of Alzheimer's disease. They found that leptin can prevent beta-amyloid deposition in the brain, which translates into a direct effect on inhibiting the development of the disease [41].

Adipokines and their relationship to dementia. Adipokines, or pro-inflammatory factors secreted by fat cells (adipocytes) also appear to be extremely important in the development of dementia diseases, and have a direct effect on the development of the inflammatory response in brain neurons [42]. The inflammatory response in the central nervous system induced by adipokines leads to a number of adverse effects, such as the formation of white matter lesions, blood-brain barrier dysfunction, and brain atrophy. This has a direct bearing on the increased risk of the future development of dementia disease the future [43, 44].

Diabetes as a complication of obesity and dementia diseases. Many studies to date have shown a strong correlation between obesity and the development of type II diabetes. The risk of developing diabetes in obese individuals can be up to 13 times higher than in normal-weight individuals. This also applies to the pre-diabetic state – obese people have a three

times greater risk of developing this condition. Studies have shown, and it is now undeniable, that higher body weight is a cause of elevated blood glucose levels, and leads to the future development of diabetes in these people [45–47]. Complications of diabetes are most commonly associated with retinopathy, peripheral neuropathy or nephropathy. However, Alzheimer's disease and other dementing diseases are also extremely important complications of this disease. Chronic hyperglycaemia leads to increased oxidative stress and the development of a neuronal inflammatory response. In turn, insulin resistance in people with diabetes leads to high levels of insulin in the blood, resulting in impaired removal of beta-amyloid from cells [48, 49]. Summarizing the results of the above studies, it can be concluded that obesity may be the first element in the chain reaction that leads to the development of dementia. Diabetes, developing as a result of obesity, may be a strong predictor of dementing diseases [50–52].

CONCLUSIONS

Obesity is a significant health problem, especially among the population of developed countries. According to the data presented in this review, the problem of obesity has been on an upward trend in recent years. An equally significant condition appears to be dementia diseases. It is estimated that the number of people affected by this disease will increase every year. There are many factors that predispose to both obesity and dementia. Among them are genetic predisposition, low education, and depression among many others. Based on the information presented above, it can be concluded that obesity itself can significantly contribute to the development of dementia diseases. There is a clear link between the prevalence of obesity in middle-age and cognitive decline, which can lead to dementia in later life. In the context of an aging population and an ever-increasing percentage of obese people, this is a matter of considerable concern. Determining the relationship between the two diseases, taking into account the factors that predispose to their development, may prove essential, initially in slowing, then in halting, such a drastic increase in the number of sufferers. Maintaining a healthy body weight, patient education and prevention are the key factors on which the diagnostic and treatment process for obese patients should be based. It will then be possible in future to reduce the number of people who will be diagnosed with dementia.

REFERENCES

1. World Health Organization. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (access: 2023.10.04).
2. Douglas G, Nicol F, Robertson C. Macleod. Badanie kliniczne. 13th ed. Wrocław: Edra Urban & Partner; 2017. p: 60–61.
3. National Institutes of Health. What Is Dementia? Symptoms, Types, and Diagnosis. https://www.nia.nih.gov/health/what-is-dementia (access: 2023.10.06).
4. Patterson C. World Alzheimer report 2018. London: Alzheimer's Disease International; 2018.
5. Interna Szczeklika 2017. Kraków: Medycyna Praktyczna; 2017. p: 2193, 2225, 2662
6. Blüher M. Obesity: Global Epidemiology and Pathogenesis. Nat Rev Endocrinol. 2019;15(5):288–298. https://doi.org/10.1038/s41574-019-0176-8
7. Taniguchi E, Lee HE. Individuals perception of others' self-esteem, psychological well-being and attractiveness: Role of body size and peers' comments among Japanese and Americans. Soc Sci J. 2015;52(2):217–228. https://doi.org/10.1016/j.soscij.2014.10.006
8. Mariapun J, Ng CW, Hairi NN. The Gradual Shift of Overweight, Obesity, and Abdominal Obesity Towards the Poor in a Multi-Ethnic Developing Country: Findings From the Malaysian National Health and Morbidity Surveys. J Epidemiol. 2018;28(6):279–286. https://doi.org/10.2188/jea.JE20170001
9. Organisation for Economic Co-operation and Development. Obesity update 2017. OECD. https://www.oecd.org/els/health-systems/Obesity-Update-2017.pdf (access: 2023.10.12).
10. Lee A, Cardel M, Donahoo WT. Social and Environmental Factors Influencing Obesity. In: Feingold KR, Anawalt B, Blackman MR, et al. editors. Endotext. South Dartmouth (MA): MDText.com, Inc. http://www.ncbi.nlm.nih.gov/books/NBK278977/ (access: 2023.10.15).
11. Giovanni S, Velez-Argumedo C, Gómez MI, et al. College Students and Eating Habits: A Study Using An Ecological Model for Healthy Behavior. Nutrients. 2018;10(12):1823. https://doi.org/10.3390/nu10121823
12. Montaña M, Jiménez-Morales M, Vàzquez M. Food Advertising and Prevention of Childhood Obesity in Spain: Analysis of the Nutritional Value of the Products and Discursive Strategies Used in the Ads Most Viewed by Children from 2016 to 2018. Nutrients. 2019;11(12):2873. https://doi.org/10.3390/nu11122873
13. Standing Committee on Childhood Obesity Prevention, Food and Nutrition Board, Institute of Medicine. Challenges and Opportunities for Change in Food Marketing to Children and Youth: Workshop Summary. Washington (DC): National Academies Press (US). (14.05.2013) http://www.ncbi.nlm.nih.gov/books/NBK202459/.
14. Harris JL, Sacco SJ, Fleming-Milici F. TV Exposure, Attitudes about Targeted Food Ads and Brands, and Unhealthy Consumption by Adolescents: Modeling a Hierarchical Relationship. Appetite. 2022;169:105804. https://doi.org/10.1016/j.appet.2021.105804
15. World Health Organization. Dementia. https://www.who.int/news-room/fact-sheets/detail/dementia (access: 2023.10.18).
16. Livingston G, Sommerlad A, Orgeta V, et al. Dementia Prevention, Intervention, and Care. Lancet. 2017;390(10113):2673–2734. https://doi.org/10.1016/S0140-6736(17)31363-6
17. Livingston G, Huntley J, Sommerlad A, et al. Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission. Lancet. 2020;396(10248):413–446. https://doi.org/10.1016/S0140-6736(20)30367-6
18. Jiang SZ, Lu W, Zong XF, et al. Obesity and Hypertension (Review). Exp Ther Med. 2016;12(4):2395–2399. https://doi.org/10.3892/etm.2016.3667
19. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018;39(33):3021–3104. https://doi.org/10.1093/eurheartj/ehy339
20. Polskie Towarzystwo Nadciśnienia Tętniczego. Zasady postępowania w nadciśnieniu tętniczym — 2019 rok. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego. Nadciśnienie Tętnicze w Praktyce 2019;5(1):1–86. https://www.nadcisnienietetnicze.pl/sites/scm/files/2021-02/64385-182698-1-SM.pdf (access: 2023.10.22).
21. Ladabaum U, Mannalithara A, Myer PA, et al. Obesity, Abdominal Obesity, Physical Activity, and Caloric Intake in US Adults: 1988 to 2010. Am J Med. 2014;127(8):717–727. https://doi.org/10.1016/j.amjmed.2014.02.026
22. Wiklund P. The Role of Physical Activity and Exercise in Obesity and Weight Management: Time for Critical Appraisal. J Sport Health Sci. 2016;5(2):151–154. https://doi.org/10.1016/j.jshs.2016.04.001
23. Martín-Moraleda E, Delisle C, Collado Mateo D, et al. Weight loss and body composition changes through ketogenic diet and physical activity: a methodological and systematic review. Nutr Hosp. 2019;36(5):1196–1204. https://doi.org/10.20960/nh.02604
24. Jantaratnotai N, Mosikanon K, Lee Y, et al. The Interface of Depression and Obesity. Obes Rec Clic Prac. 2017;11(1):1–10. https://doi.org/10.1016/j.orcp.2016.07.003
25. Mannan M, Mamun A, Doi S, et al. Prospective Associations between Depression and Obesity for Adolescent Males and Females – A Systematic Review and Meta-Analysis of Longitudinal Studies. PloS One. 2016;11(6):e0157240. https://doi.org/10.1371/journal.pone.0157240.
26. Rao WW, Zong QQ, Zhang JW, et al. Obesity Increases the Risk of Depression in Children and Adolescents: Results from a Systematic Review and Meta-Analysis. J Affect Disord. 2020;267:78–85. https://doi.org/10.1016/j.jad.2020.01.154

27. Papadopoulos S, Brennan L. Correlates of Weight Stigma in Adults with Overweight and Obesity: A Systematic Literature Review. Obesity (Silver Spring). 2015;23(9):1743–1760. https://doi.org/10.1002/oby.21187.
28. Van Strien T. Causes of Emotional Eating and Matched Treatment of Obesity. Curr Diab Rep. 2018;18(6):35. https://doi.org/10.1007/s11892-018-1000-x
29. Milaneschi Y, Simmons WK, van Rossum EFC, et al. Depression and Obesity: Evidence of Shared Biological Mechanisms. Mol Psychiatry. 2019;24(1):18–33. https://doi.org/10.1038/s41380-018-0017-5
30. Hajek A, Kretzler B, König HH. The Association Between Obesity and Social Isolation as Well as Loneliness in the Adult Population: A Systematic Review. Diabetes Metab Syndr Obes. 2021;14:2765–2773. https://doi.org/10.2147/DMSO.S313873
31. Rotenberg KJ, Bharathi C, Davies H, et al. Obesity and the Social Withdrawal Syndrome. Eat Behav. 2017;26:167–170. https://doi.org/10.1016/j.eatbeh.2017.03.006
32. Nascè A, Pataky Z. What is the relationship between alcohol and obesity?. Rev Med Suisse. 2023;19(819):552–554. https://doi.org/10.53738/REVMED.2023.19.819.552
33. Shelton NJ, Knott CS. Association Between Alcohol Calorie Intake and Overweight and Obesity in English Adults. Am J Public Health. 2014;104(4):629–631. https://doi.org/10.2105/AJPH.2013.301643
34. Li Y, Cai T, Wang H, Guo G. Achieved educational attainment, inherited genetic endowment for education, and obesity. Biodemography Soc Biol. 2021;66(2):132–144. https://doi.org/10.1080/19485565.2020.1869919
35. Ogden CL, Fakhouri TH, Carroll MD, et al. Prevalence of Obesity Among Adults, by Household Income and Education — United States, 2011–2014. MMWR Morb Mortal Wkly Rep. 2017;66(50):1369–1373. https://doi.org/10.15585/mmwr.mm6650a1
36. Albanese E, Launer LJ, Egger M, et al. Body Mass Index in Midlife and Dementia: Systematic Review and Meta-Regression Analysis of 589,649 Men and Women Followed in Longitudinal Studies. Alzheimers Dement (Amst). 2017;8:165–178. https://doi.org/10.1016/j.dadm.2017.05.007
37. Qizilbash N, Gregson J, Johnson ME, et al. BMI and Risk of Dementia in Two Million People over Two Decades: A Retrospective Cohort Study. Lancet Diabetes Endocrinol. 2015;3(6): 431–436. https://doi.org/10.1016/S2213-8587(15)00033-9
38. Obradovic M, Sudar-Milovanovic E, Soskic S, et al. Leptin and Obesity: Role and Clinical Implication. Front Endocrinol (Lausanne). 2021;12:585887. https://doi.org/10.3389/fendo.2021.585887
39. Davis C, Mudd J, Hawkins M. Neuroprotective effects of leptin in the context of obesity and metabolic disorders. Neurobiol Dis. 2014;72 Pt A:61–71. https://doi.org/10.1016/j.nbd.2014.04.012
40. Flores-Cordero JA, Pérez-Pérez A, Jiménez-Cortegana C, et al. Obesity as a Risk Factor for Dementia and Alzheimer's Disease: The Role of Leptin. Int J Mol Sci. 2022;23(9):5202. https://doi.org/10.3390/ijms23095202
41. McGuire MJ, Ishii M. Leptin dysfunction and Alzheimer's disease: evidence from cellular, animal, and human studies. Cell Mol Neurobiol. 2016;36(2):203–217. https://doi.org/10.1007/s10571-015-0282-7
42. Baumgarner KM, Setti S, Diaz C, et al. Diet-Induced Obesity Attenuates Cytokine Production Following an Immune Challenge. Behav Brain Res. 2014;267:33–41. https://doi.org/10.1016/j.bbr.2014.03.017
43. Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: A Link between Obesity and Dementia? Lancet Neurol. 2014;13(9):913–923. https://doi.org/10.1016/S1474-4422(14)70085-7
44. Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: adipokines interact with the brain. Eur Neuropsychopharmacol. 2014;24(12):1982–1999. https://doi.org/10.1016/j.euroneuro.2014.03.002
45. He QX, Zhao L, Tong JS, et al. The impact of obesity epidemic on type 2 diabetes in children and adolescents: A systematic review and meta-analysis. Prim Care Diabetes. 2022;16(6):736–744. https://doi.org/10.1016/j.pcd.2022.09.006
46. Jaruratanasirikul S, Thammaratchuchai S, Puwanant M, et al. Progression from Impaired Glucose Tolerance to Type 2 Diabetes in Obese Children and Adolescents: A 3–6-Year Cohort Study in Southern Thailand. J Pediatr Endocrinol Metab. 2016;29(11):1267–1275. https://doi.org/10.1515/jpem-2016-0195
47. Ek AE, Rössner SM, Hagman E, et al. High Prevalence of Prediabetes in a Swedish Cohort of Severely Obese Children. Pediatr Diabetes. 2015;16(2):117–128. https://doi.org/10.1111/pedi.12136
48. Pugazhenthi S, Qin L, Reddy PH. Common Neurodegenerative Pathways in Obesity, Diabetes, and Alzheimer's Disease. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1037–1045. https://doi.org/10.1016/j.bbadis.2016.04.017
49. Wang X, Yu S, Hu JP, et al. Streptozotocin-Induced Diabetes Increases Amyloid Plaque Deposition in AD Transgenic Mice through Modulating AGEs/RAGE/NF-κB Pathway. Int J Neurosci. 2014;124(8):601–608. https://doi.org/10.3109/00207454.2013.866110.
50. Pal K, Mukadam N, Petersen I, et al. Mild cognitive impairment and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol. 2018;53(11):1149–1160. https://doi.org/10.1007/s00127-018-1581-3
51. Xue M, Xu W, Ou YN, et al. Diabetes mellitus and risks of cognitive impairment and dementia: A systematic review and meta-analysis of 144 prospective studies. Ageing Res Rev. 2019;55:100944. https://doi.org/10.1016/j.arr.2019.100944
52. Geijselaers SLC, Sep SJS, Stehouwer CDA, et al. Glucose regulation, cognition, and brain MRI in type 2 diabetes: a systematic review. Lancet Diabetes Endocrinol. 2015;3(1):75–89. https://doi.org/10.1016/S2213-8587(14)70148-2