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Central and peripheral neurological complications of obesity

Abstract

Obesity is a clinical and metabolic condition characterized by a pathological increase in the percentage of body fat with the potential to cause damage to health, in the last 35 years the number of obese people in the world has doubled. This literature review aims to clarify the mechanisms responsible for the neurological disorders related to excess body fat and to gather up-to-date information on the subject. A narrative review of the literature in Medline databases from 2010 to 2022 was performed on neurological disorders, obesity, overweight, neurology and central obesity. In Medline, 154 articles were found by the Mesh descriptor "(neurological disorder AND obesity AND overweight AND neurology AND central obesity)", of which 59 were selected after the first set of criteria. Exclusion of titles that did not address the topic "obesity and/or neurological disorders", articles not included in English and gray literature were excluded. As classically in the physiology of the cardiovascular system, it is now also evident that obesity has negative impacts on the brain. Likewise, it was exposed that the increase in BMI is directly related to the presence of attention deficits, poor executive function, impaired ability to make decisions and decreased verbal learning and memory. In addition, studies show that obesity is strongly associated with neurological dementia disorders such as Alzheimer's disease, which has a doubled risk if developed in these patients. Therefore, although the neurological mechanisms of obesity are not completely elucidated, it is a fact that a high-fat diet and increased BMI have correlations with the release of inflammatory mediators that lead to aggression of the nervous system - central and peripheral - through numerous mechanisms.

Keywords: inflammation, alzheimer, disturbances, cheers

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Júlio César Claudino dos Santos,[1,2,3,5] Alan Bessa Aguiar,[1] Gabriel Romão Mesquita do Nascimento,[1] Isabella Araujo Duarte,[1] José de Ribamar Barroso Jucá Neto,[1] Rafaella Lughetti da Costa,[1] Leandro Freitas Oliveira,[2,3] Gabriel Moreira de Araújo,[5] Marilia Porto Oliveira Nunes,[5,6] Júlio César Chaves Nunes Filho[4,5]

[1]Faculty of Medicine, Christus University Center, Brazil
[2] Federal University of São Paulo, Brazil
[3]Department of Neurology and Neurosurgery, Federal University of São Paulo, Brazil
[4]Department of Clinical Medicine at the Federal University of Ceará, Brazil
[5]Nutrition Course, Christus University Center, Brazil
[6] Nutrition Course, University of Fortaleza, Brazil

Correspondence: Júlio César Claudino dos Santos, Departamento de Neurologia e Neurocirurgia, Universidade Federal de São Paulo, Rua Sena Madureira, 1500, Vila Clementino (SP), Brasil, CEP 04021-001, Tel 55-19-98450666, Email cesar.claudino@unifesp.br

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Introduction

Obesity is a clinical and metabolic condition characterized by the pathological increase in the body fat percentage with potential of causing damages to health.[1–3] In fact, the adult individual that has obesity should be stratified in the BMI scale, which represents a triage scale from the individual´s mass in kilograms divided by its height in meters, comparatively in children, the weight percentile scale is utilized, and the diagnosis is confirmed when the result is above 95%.[4]

In the last 35 years the number of obese people in the world doubled, highlighting that in 2014 the percentage of obese people in the world (above 18 years old) was 11% of men and 15% of women, of which 0,64% and 1,6%, respectively, have morbid obesity (BMI ≥40 kg/m²).[5] In North America, the most important numbers are from the United States that have approximately 38,3% of the female population and 34,3% of the male population with obesity, highlighting the hispanic ethnicity, which represents the biggest portion of this characterized context, due to variables, such as behavior, risk factors and social determinants, which are target of clinical and social interventions to reduce this expressive number.[4]

Obesity affects almost all of the systems in the human organism, a fact that can be unleashed by various mechanisms.[6,7] In fact, frequent metabolic alterations present in this condition, such as hyperglycemia, chronic inflammation, hyperleptinemia and endothelial dysfunction, favor the oxidative stress process, that is related with the development of numerous pathologic events, for example, diabetes, cardiovascular complications, asthma and infertility, Besides, it is known that obesity generates dysfunction in the metabolism of the adipose tissue, in a way that dysregulates the secretion of adipokines, substances that, between other functions, participate in the metabolism of glucose, in inflammation and in the regulation of the blood pressure, which has been associated with the pathogenesis of multiple diseases related with obesity.[8–11] Furthermore, the mechanical effects of the increase in body mass also contribute to the development of comorbidities.[6,12]

About the central nervous system, it is viewed that obesity and a diet rich in fats have negative roles,[13] leading to systemic inflammation, mediated by cytokines, and the excess of free fatty acids circulating, which reaches the brain at a hypothalamic level.[14] The local inflammation causes neurodegeneration of the hypothalamus and synaptic remodeling, which provokes alterations of internal circuits and of other cerebral regions. Therefore, there is, in regions of the hippocampus, amygdala and reward processing centers, an interruption of cognition, of the satiety signals and of the perception of excesses. Some studies in humans suggest that obesity can accelerate the degenerative processes of the cerebral function related to age.[13]

Obesity is related to neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. This association occurs because the fat excess, due to metabolic alterations, can cause a decrease of the brain´s integrity, which results in changes of the synaptic plasticity and death by cellular necrosis or apoptosis.[15,16] Besides, in an american study, it was evidenced that many obese patients presented a decrease in the volume of the hyppocampus. This structure, which is also attacked in Alzheimer's disease, is essential for learning and for memory.[17] Furthermore, as a consequence of modifications in the metabolism of the adipose tissue present in obesity, the development of pathologies such as migraine and pseudotumor cerebri can also be observed as a result of the weight excess.[6,18–23]

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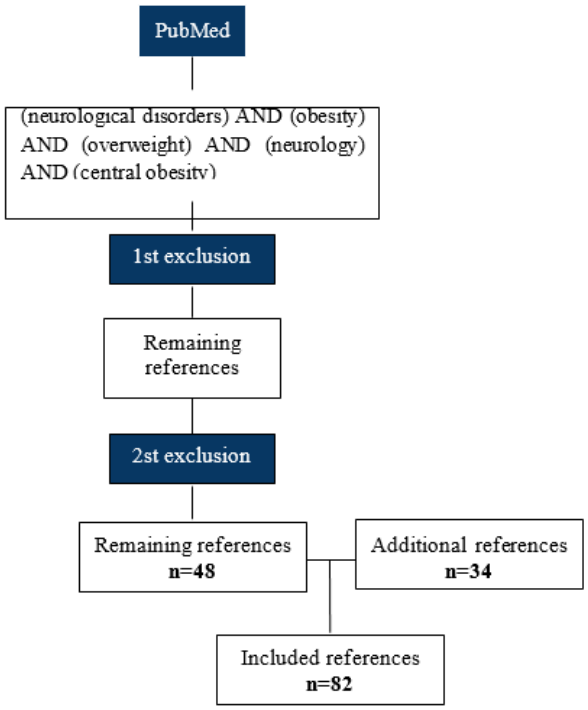
According with the informations exposed, this literature review aims to enlighten the mechanisms responsible for the neurologic disturbances related with the excess of body fat and gather updated information about the subject, considering the increase in the prevalence of obese people in the world.[5]

Methods

A narrative literature review was conducted in the Medline Databases, from 2010 to 2022, on neurological disorders, obesity, overweight, neurology and central obesity. In the Medline, 154 articles were found by the Mesh descriptor "(neurological disorders AND obesity AND overweight AND neurology AND central obesity)", of which 59 were selected, after the first set of criteria — exclusion of titles not addressing to the topic "obesity and/or neurological disorders", articles not included in the search period 2010-2022, as well as non-English articles. The second set of criteria — exclusion of the abstracts not addressed to obesity or neurological disorders and of those in which the neurological disorder was the cause of obesity — was applied, by which 11 articles were excluded. Other articles that did not contemplate these conditions were excluded. To ensure content saturation, the authors checked the included research references and related reviews on topics to identify missing publications. Furthermore, 34 articles from the Medline Database were manually screened and added according to their relevance in the qualitative evidence synthesis. Of the total, 82 original articles remained.



Discussion

Pathophysiology of obesity

Obesity has an important evolutive component, considering that, in the beginning of evolution, the species suffered a selective pressure to adapt in a hostile environment and with little nutritional resources.[5] Therefore, humans and their ancestors needed to survive in long periods of malnutrition, a situation that selected the genotype that had the capacity to store more energy in adipose tissue,[24] with low energy expenditure and physical inactivity. However, it is known that, nowadays, the supernutrition has become extremely problematic to the species, because, according to WHO,[25] the mortality due to excess weight has been becoming greater than death because of low weight. This condition negatively affects the individuals and contributes to the development of numerous enfermities, highlighting the neurological disorders (Figure 1).[24]

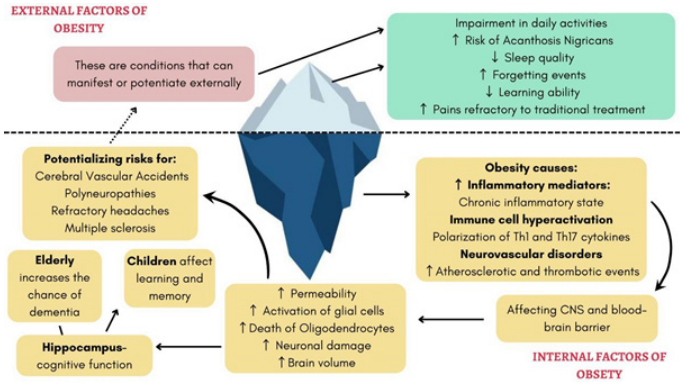


Figure 1 Risk factors for obesity: external and internal.

Furthermore, many researches have been made to understand the gut-brain axis, and how the adipose tissue dysfunctions can lead to intestinal and hepatic hormonal dysregulations, and affect the transmission of information, such as satiety and appetite for the hypothalamus.[5,26] In this context, it is expected that this correlation will be useful in the comprehension of how the brain of obese individuals processes the desire for food, and in the therapeutic interventions for obesity.

About pathogenesis, the pro-inflammatory systemic component of obesity is well established (Figure 2). The diet rich in grease leads to the increase in the profile of pro-inflammatory cytokines (as TNF-alpha), through numerous mechanisms,[13] from which stand out the stimulation of the free fatty acids and lipopolysaccharides (LPS) receptors and toll like receptor 4 (TLR4), the increased infiltration of macrophages, apoptosis of adipocytes and the reduction of the vascularization of the white adipose tissue,[27] contributing to the inflammatory cascade.

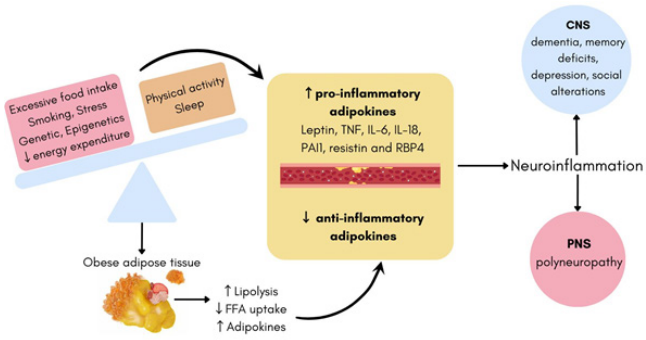


Figure 2 Pathophysiology of obesity and neuroinflammation.

These events have hepatic and muscular consequences that can favor the systemic resistance to insulin[28]. Besides, some hypothalamic pathways can be interrupted by neuroinflammation, such as the leptin pathway, an anorexigen hormone, responsible for satiety, which could complicate the control of obesity and the interruption of a diet rich in fats.[13,27]

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Obesity effects in the central nervous system

Just as classically in the physiology of the cardiovascular system, now it is also evident that obesity has negative impacts in the brain.[13,29–37] Numerous studies have shown a link between a higher BMI - and other measurements of central obesity, such as waist circumference and waist-hip ratio[14] - with the damage of the cognitive function, independently of its relation with cardiovascular and cerebrovascular diseases.[17,38–42] In the same way, it was exposed that an increased BMI is directly related to the presence of attention deficits, bad executive function, impaired capacity to make decisions, and decrease in verbal learning and in memory.[43] Besides, studies show that obesity is strongly associated with dementia neurological disturbances,[44] such as Alzheimer's disease, which has doubled risk if developed in these patients.[45–51]

Along with the effect on cognitive performance, it is also known that obesity influences aspects of the cerebral morphology, leading, more precisely, to a brain atrophy,[52–58] which can be enhanced in males.[59] Studies have reported that there is a decrease, mainly in the frontal and temporal lobes (including the hippocampus), of the gray matter´s focal volume[52] and an increase of the orbitofrontal white matter associated with axonal and/or myelinic abnormalities, which can reflect the loss of neurons.[60,61] Thus, once a larger hippocampus is closely linked to good cognitive function,[62] and that frontal regions of the brain are important for executive functions,[13] it is conceivable that such brain atrophy can contribute to cognitive damage in obese individuals.[14,15]

Therefore, it was demonstrated that a hyperlipidic diet increases the expression of pro-inflammatory cytokines in the hypothalamic region,[17,63,64] and that this inflammation can interrupt the normal signalization related to nutrition, favoring the weight gain and maintaining an increased body weight.[13] Another subject concerning this inflammatory process is that many studies with animal models have shown that this is an initial step in a vicious cycle of dysfunction of the CNS, in ultimate analysis, to the cognitive decline.[65]

Obesity effects on the peripheral and autonomic nervous system

The peripheral nervous system has two divisions, the autonomic nervous system, which is subdivided in sympathetic and parasympathetic, and the somatic nervous system, which is subdivided in sensitive and motor peripheral nerves. In this division, there are regions that are not protected by the blood-brain barrier, differentiating from the regions of the CNS, for example, the autonomic nervous system and the sensorial ganglia, along with the non myelinated fibers and the terminations of the synapses of the PNS, therefore are vulnerable locations and exposed to the aggressive factors of the inflammatory pathophysiology of the adipose tissue.[17,66–68]

Therefore, these locals more sensitive to lipidic inflammation present increase of the sympathetic flow in neuro-adipose junctions, stimulating the lipolysis via β, which results in triglyceride hydrolysis, and consequently in an increase of long chain fatty acids (LCFAs).[69–74] This sympathetic flow, besides the damages to the PNS, also causes chronic stimulation of angiotensinogen in the adipose tissue, besides acting on the musculoskeletal system causing insulin resistance, in the pancreas with insulin release and in the liver with gluconeogenesis and glycogenolysis.[68,75–77]

Similarly to the blood-brain barrier, the blood-nerve barrier exists in the PNS, which is formed by microvessels of the endoneurium and perineurium, but, anatomically, the dorsal root, the ganglionar neurons and the peripheral sensory receptors are unprotected.[17,69,78] Therefore, a chronic dysfunction secondary to the inflammation caused by obesity can happen, affecting the nervous structures and its subjacent components, through the increase in inflammatory interleukins, such as TNFα, IL-1β and immune cells, such as macrophages and lymphocytes.[68,70,78,79]

Additionally, it is possible to evidence the increase of free fatty acids and LCFAs that alter the operation neurophysiology of the PNS, through dysfunction of the Schwann cells, axonal degeneration and polyneuropathies.[68,78,80,81] This lesion caused by LCFAs occurs because these fatty acids cause the stress of the endoplasmic reticulum, mitochondrial depolarization and generation of reactive oxygen species, interrupting, finally, the ATP production by the mitochondria and damaging the PNS profoundly.[17,68,78]

Clinical implications and future perspectives

The increase of the visceral adiposity is a risk factor for the development of numerous neurological conditions, but, currently, an ideal intervention to prevent the cognitive damage is still unknown.[8,17] Until this moment, few controlled prospective studies have evaluated the comparative efficiency of the medical, pharmacological, surgical and lifestyle interventions. Furthermore, just as the comparison of the efficiency of the interventions, it is necessary to evaluate the benefit-cost ratio between them. Future studies are necessary to determine a potential role for the neuroinflammation in the cognitive damage related to obesity.[17,82] Given the available evidences until this moment, doctors should advise obese individuals, especially those that present precocious evidences of lesions in the CNS and PNS.

Conclusion

Therefore, despite the neurologic mechanisms of obesity not being completely elucidated, it is a fact that a hyperlipidic diet and an increased BMI have correlations with the release of inflammatory mediators that lead to the aggression of the nervous system - central and peripheral - through numerous mechanisms. The neuroinflammation stands out, which affects the hypothalamic pathway that controls satiety, the cognitive function since childhood until senescence and the peripheral synapsis, leading to sociofunctional related damages, respectively, with the maintenance of a greasy diet, difficulty in learning and in memory and polyneuropathies. Furthermore, it is also known that obesity leads to morphological and structural alterations of the nervous system and that this can also be associated to the cognitive decline in the obese individuals. Finally, even before the analyzed knowledge, it is necessary that there are scientific deepenings in the investigation of pharmacological, surgical and social lifestyle intervention mechanisms, aiming to better approach the control of the damaging effects of obesity.

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Medical School and Nutrition Course University Center Christus, UNICHRISTUS, Fortaleza, CE, Brazil.

Conflict of interest

The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

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References

1. Chooi YC, Ding C, Magkos F. The epidemiology of obesity. *Metabolism*. 2019;92:6–10.
2. Mollan SP, Grech O, Alimajstorovic Z, et al. New horizons for idiopathic intracranial hypertension: advances and challenges. *Br Med Bull*. 2020;136(1):118–126.
3. Hesse S, Becker GA, Rullmann M, et al. Central noradrenaline transporter availability in highly obese, non–depressed individuals. Eur *J Nucl Med Mol Imaging*. 2017;44(6):1056–1064.
4. Arroyo–Johnson C, Mincey KD. Obesity Epidemiology Worldwide. *Gastroenterol Clin North Am*. 2016;45(4):571–579.
5. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288–298.
6. Tsai AG, Bessesen DH. Obesity. *Ann Intern Med*. 2019;170(5):ITC33–ITC48.
7. Fitzgerald KC, Salter A, Tyry T, et al. Measures of general and abdominal obesity and disability severity in a large population of people with multiple sclerosis. *Mult Scler*. 2020;26(8):976–986.
8. Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. *Metab Syndr Relat Disord*. 2015;13(10):423–444.
9. Bas DF, Ozdemir AO. The effect of metabolic syndrome and obesity on outcomes of acute ischemic stroke patients treated with systemic thrombolysis. *J Neurol Sci.* 2017;383:1–4.
10. Kim JH, Choi KH, Kang KW, et al. Impact of Visceral Adipose Tissue on Clinical Outcomes After Acute Ischemic Stroke. *Stroke*. 2019;50(2):448–454.
11. Li P, Quan W, Lu D, et al. Association between Metabolic Syndrome and Cognitive Impairment after Acute Ischemic Stroke: A Cross–Sectional Study in a Chinese Population. *PLoS One*. 2016;11(12):e0167327.
12. McCutchan JA, Marquie–Beck JA, Fitzsimons CA, et al. Role of obesity, metabolic variables, and diabetes in HIV–associated neurocognitive disorder. *Neurology*. 2012;78(7):485–492.
13. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun*. 2014;42:10–21.
14. Bruce–Keller AJ, Keller JN, Morrison CD. Obesity and vulnerability of the CNS. *Biochim Biophys Acta*. 2009;1792(5):395–400.
15. Flores–Dorantes MT, Díaz–López YE, Gutiérrez–Aguilar R. Environment and Gene Association With Obesity and Their Impact on Neurodegenerative and Neurodevelopmental Diseases. *Front Neurosci*. 2020;14:863.
16. Wang YL, Wang YT, Li JF, et al. Body Mass Index and Risk of Parkinson's Disease: A Dose–Response Meta–Analysis of Prospective Studies. *PLoS One*. 2015;10(6):e0131778.
17. O'Brien PD, Hinder LM, Callaghan BC, et al. Neurological consequences of obesity. *Lancet Neurol*. 2017;16(6):465–477.
18. Chai NC, Bond DS, Moghekar A, et al. Obesity and headache: Part II—potential mechanism and treatment considerations. *Headache*. 2014;54(3):459–471.
19. Westgate CSJ, Israelsen IME, Jensen RH, et al. Understanding the link between obesity and headache– with focus on migraine and idiopathic intracranial hypertension. *J Headache Pain*. 2021;22(1):123.
20. Peterlin BL, Rapoport AM, Kurth T. Migraine and obesity: epidemiology, mechanisms, and implications. *Headache*. 2010;50(4):631–648.
21. Kristoffersen ES, Børte S, Hagen K, et al. Migraine, obesity and body fat distribution – a population–based study. *J Headache Pain*. 202021(1):97.
22. Sergentanis TN, Tsivgoulis G, Perlepe C, et al. Obesity and Risk for Brain/CNS Tumors, Gliomas and Meningiomas: A Meta–Analysis. *PLoS One*. 2015;10(9):e0136974.
23. Peterlin BL, Rosso AL, Rapoport AM, et al. Obesity and migraine: the effect of age, gender and adipose tissue distribution. *Headache*. 2010;50(1):52–62.
24. Yanovski JA. Obesity: Trends in underweight and obesity – scale of the problem. *Nat Rev Endocrinol*. 2018;14(1):5–6.
25. World Health Organization. Obesity and overweight.
26. Contreras–Rodriguez O, Arnoriaga–Rodríguez M, Miranda–Olivos R, et al. Obesity status and obesity–associated gut dysbiosis effects on hypothalamic structural covariance. *Int J Obes (Lond).* 2022;46(1):30–38.
27. Shu CJ, Benoist C, Mathis D. The immune system's involvement in obesity–driven type 2 diabetes. *Semin Immunol*. 2012;24(6):436–442.
28. Thaler JP, Schwartz MW. Minireview: Inflammation and obesity pathogenesis: the hypothalamus heats up. *Endocrinology*. 2010;151(9):4109–4115.
29. Nash MS, Tractenberg RE, Mendez AJ, et al. Cardiometabolic Syndrome in People With Spinal Cord Injury/Disease: Guideline–Derived and Nonguideline Risk Components in a Pooled Sample. *Arch Phys Med Rehabil*. 2016;97(10):1696–705.
30. Li R, Li Q, Cui M, et al. Visceral adiposity index, lipid accumulation product and intracranial atherosclerotic stenosis in middle–aged and elderly Chinese. *Sci Rep*. 2017;7(1):7951.
31. Song Z, Qiu L, Hu Z, et al. Evaluation of the Obesity Genes FTO and MC4R for Contribution to the Risk of Large Artery Atherosclerotic Stroke in a Chinese Population. *Obes Facts*. 2016;9(5):353–362.
32. Chiquete E, Ruiz–Sandoval JL, Murillo–Bonilla L, et al. Central adiposity and mortality after first–ever acute ischemic stroke. *Eur Neurol.* 2013;70(1–2):117–123.
33. Lekoubou A, Ovbiagele B, Markovic D, et al. Age, sex, and race/ethnic temporal trends in metabolic syndrome prevalence among individuals with myocardial infarction or stroke in the United States. *J Neurol Sci.* 2017;376:24–28.
34. Towfighi A, Zheng L, Ovbiagele B. Weight of the obesity epidemic: rising stroke rates among middle–aged women in the United States. *Stroke*. 2010;41(7):1371–1375.
35. Bodenant M, Kuulasmaa K, Wagner A, et al. Measures of abdominal adiposity and the risk of stroke: the MOnica Risk, Genetics, Archiving and Monograph (MORGAM) study. *Stroke*. 2011;42(10):2872–2877.
36. Wang GS, Tong DM, Chen XD, et al. Metabolic Syndrome Is a Strong Risk Factor for Minor Ischemic Stroke and Subsequent Vascular Events. *PLoS One*. 2016;11(8):e0156243.
37. Muuronen AT, Taina M, Hedman M, et al. Increased visceral adipose tissue as a potential risk factor in patients with embolic stroke of undetermined source (ESUS). *PLoS One.* 2015;10(3):e0120598.
38. Gunstad J, Lhotsky A, Wendell CR, et al. Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology*. 2010;34(4):222–229.
39. Marini S, Merino J, Montgomery BE, et al. Mendelian Randomization Study of Obesity and Cerebrovascular Disease. *Ann Neurol*. 2020;87(4):516–524.
40. Kantorová E, Jesenská Ľ, Čierny D, et al. The Intricate Network of Adipokines and Stroke. *Int J Endocrinol*. 2015;2015:967698.
41. Wang J, Li J, Li M, et al. Association between dynamic obesity and mortality in patients with first–ever ischemic stroke: A hospital–based prospective study. *Medicine (Baltimore).* 2020;99(38):e22243.
42. Zou X, Wang L, Xiao L, et al. Deciphering the Irregular Risk of Stroke

Increased by Obesity Classes: A Stratified Mendelian Randomization Study. *Front Endocrinol (Lausanne).* 2021;12:750999.

43. Rochette AD, Spitznagel MB, Sweet LH, et al. Gender Differences in Cognitive Test Performance in Adults With Heart Failure. *The Journal of Cardiovascular Nursing.* 2017;32(3):212–217.
44. Pedditzi E, Peters R, Beckett N. The risk of overweight/obesity in mid–life and late life for the development of dementia: a systematic review and meta–analysis of longitudinal studies. *Age Ageing*. 2016;45(1):14–21.
45. Anstey KJ, Cherbuin N, Budge M, et al. Body mass index in midlife and late–life as a risk factor for dementia: a meta–analysis of prospective studies. *Obes Rev*. 2011;12(5):e426–437.
46. Kiliaan AJ, Arnoldussen IA, Gustafson DR. Adipokines: a link between obesity and dementia? *Lancet Neurol*. 2014;13(9):913–923.
47. Gardener H, Caunca M, Dong C, et al. Obesity Measures in Relation to Cognition in the Northern Manhattan Study. *J Alzheimers Dis.* 2020;78(4):1653–1660.
48. Jiang L, Wang Y, Su L, et al. Donepezil Attenuates Obesity–Associated Oxidative Stress and Central Inflammation and Improves Memory Deficit in Mice Fed a High–Fat Diet. *Dement Geriatr Cogn Disord*. 2019;48(3–4):154–163.
49. Letra L, Rodrigues T, Matafome P, et al. Adiponectin and sporadic Alzheimer's disease: Clinical and molecular links. *Front Neuroendocrinol*. 2019;52:1–11.
50. Gardiner SL, de Mutsert R, Trompet S, et al. Repeat length variations in polyglutamine disease–associated genes affect body mass index. *Int J Obes (Lond)*. 2019;43(3):440–449.
51. Lei Q, Tian H, Xiao Z, et al. Association Between Body Mass Index and Incident Dementia Among Community–Dwelling Older Adults: The Shanghai Aging Study. *J Alzheimers Dis*. 2022;86(2):919–929.
52. Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. *Hum Brain Mapp*. 2010;31(3):353–364.
53. Fotuhi M, Do D, Jack C. Modifiable factors that alter the size of the hippocampus with ageing. *Nat Rev Neurol*. 2012;13;8(4):189–202.
54. Brooks SJ, Benedict C, Burgos J, et al. Late–life obesity is associated with smaller global and regional gray matter volumes: a voxel–based morphometric study. *Int J Obes (Lond).* 2013;37(2):230–236.
55. Marrie RA, Butzkueven H, Ascherio A. Obesity and brain volume loss in multiple sclerosis. *Neurology*. 2018;91(24):1079–1080.
56. Galioto R, Berenholz O, Wang Z, et al. Does obesity exacerbate brain lesion volume and atrophy in patients with multiple sclerosis? *Mult Scler Relat Disord*. 2020;46:102502.
57. Debette S, Wolf C, Lambert JC, et al. Abdominal obesity and lower gray matter volume: a Mendelian randomization study. Neurobiol *Aging*. 2014;35(2):378–386.
58. Rajagopalan P, Toga AW, Jack CR, et al. Alzheimer's Disease Neuroimaging Initiative. Fat–mass–related hormone, plasma leptin, predicts brain volumes in the elderly. *Neuroreport*. 2013;24(2):58–62.
59. Taki Y, Kinomura S, Sato K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity (Silver Spring).* 2008;16(1):119–124.
60. Gazdzinski S, Millin R, Kaiser LG, et al. BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. *Obesity (Silver Spring*). 2010;18(4):743–748.
61. Mueller K, Anwander A, Möller HE, et al. Sex–dependent influences of obesity on cerebral white matter investigated by diffusion–tensor imaging. *PLoS One*. 2011;6(4):e18544.
62. Irving AJ, Harvey J. Leptin regulation of hippocampal synaptic function in health and disease. *Philos Trans R Soc Lond B Biol Sci*. 2013;369(1633):20130155.
63. Maric T, Woodside B, Luheshi GN. The effects of dietary saturated fat on basal hypothalamic neuroinflammation in rats. *Brain Behav Immun*. 2014;36:35–45.
64. Baufeld C, Osterloh A, Prokop S, et al. High–fat diet–induced brain region–specific phenotypic spectrum of CNS resident microglia. *Acta Neuropathol*. 2016;132(3):361–375.
65. Thaler JP, Yi CX, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 2012;122(1):153–162.
66. Thorp AA, Schlaich MP. Relevance of Sympathetic Nervous System Activation in Obesity and Metabolic Syndrome. *J Diabetes Res.* 2015;2015:341583.
67. Kazamel M, Stino AM, Smith AG. Metabolic syndrome and peripheral neuropathy. *Muscle Nerve*. 2021;63(3):285–293.
68. Dimova R, Tankova T, Guergueltcheva V, et al. Risk factors for autonomic and somatic nerve dysfunction in different stages of glucose tolerance. *J Diabetes Complications*. 2017;31(3):537–543.
69. Chiu IM, von Hehn CA, Woolf CJ. Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology. *Nat Neurosci.* 2012;15(8):1063–1067.
70. Bednarska–Makaruk M, Graban A, Wiśniewska A, et al. Association of adiponectin, leptin and resistin with inflammatory markers and obesity in dementia. *Biogerontology*. 2017;18(4):561–580.
71. Ligong Z, Jinjin Q, Chunfu C, et al. Effect of Obesity and Leptin Level on Migraineurs. *Med Sci Monit.* 2015;21:3270–4.
72. Stampanoni Bassi M, Iezzi E, Buttari F, et al. Obesity worsens central inflammation and disability in multiple sclerosis. *Mult Scler*. 2020;26(10):1237–1246.
73. Novo AM, Batista S. Multiple Sclerosis: Implications of Obesity in Neuroinflammation. *Adv Neurobiol*. 2017;19:191–210.
74. Bove R, Musallam A, Xia Z, et al. Longitudinal BMI trajectories in multiple sclerosis: Sex differences in association with disease severity. *Mult Scler Relat Disord*. 2016;8:136–140.
75. Lambert E, Sari CI, Dawood T, et al. Sympathetic nervous system activity is associated with obesity–induced subclinical organ damage in young adults. *Hypertension*. 2010;56(3):351–358.
76. Lohmeier TE, Iliescu R. The sympathetic nervous system in obesity hypertension. *Curr Hypertens Rep.* 2013;15(4):409–416.
77. Kalil GZ, Haynes WG. Sympathetic nervous system in obesity–related hypertension: mechanisms and clinical implications. *Hypertens Res*. 2012;35(1):4–16.
78. Visser NA, Vrancken AF, van der Schouw YT, et al. Chronic idiopathic axonal polyneuropathy is associated with the metabolic syndrome. *Diabetes Care*. 2013;36(4):817–22.
79. Sattler FR, He J, Letendre S, Wilson C, et al. Abdominal obesity contributes to neurocognitive impairment in HIV–infected patients with increased inflammation and immune activation. *J Acquir Immune Defic Syndr*. 2015;68(3):281–288.
80. Jayaraman A, Lent–Schochet D, Pike CJ. Diet–induced obesity and low testosterone increase neuroinflammation and impair neural function. *J Neuroinflammation*. 2014;11:162.
81. Smith AG. Correlation Does Not Imply Causation: Bradford Hill, Causative Inference, and Obesity–Related Neuropathy. *Mayo Clin Proc*. 2020;95(7):1306–1309.
82. Samara A, Murphy T, Strain J, et al. Neuroinflammation and White Matter Alterations in Obesity Assessed by Diffusion Basis Spectrum Imaging. *Front Hum Neurosci.* 2020.