Curr Diab Rep (2014) 14:495
DOI 10.1007/s11892-014-0495-z

OBESITY (J MCCAFFERY, SECTION EDITOR)

The Negative Effects of Obesity and Poor Glycemic Control on Cognitive Function: A Proposed Model for Possible Mechanisms

Michael L. Alosco · John Gunstad

Published online: 22 April 2014

Abstract Obesity has reached epidemic proportions and is a contributor to many adverse health outcomes, including increased risk for dementia and adverse structural and functional brain changes. Milder forms of cognitive impairment in multiple domains can also be found in obese individuals of all ages that are believed to stem from brain abnormalities long prior to onset of neurologic conditions such as dementia. However, the mechanisms for adverse brain changes and subsequent cognitive dysfunction in obesity are complex and poorly understood. This paper proposes a possible etiologic model for obesity associated cognitive impairment with emphasis on the role of poor glycemic control and conditions like type 2 diabetes mellitus. Clinical implications associated with treatment of obesity in persons with cognitive deficits in addition to the cognitive promoting effects of weight loss surgery are also discussed.

Keywords Obesity · Type 2 diabetes mellitus · Cognitive function · Brain mechanisms · Glycemic control

Introduction

Approximately 80 million American adults are obese [1], and it is estimated that obesity rates will exceed 44 % within every state over the next 20 years [2]. This pattern is concerning as obesity is a source of societal and economic hardship and is projected to account for up to 18 % of healthcare costs by the year 2030 [1]. Indeed, obesity is associated with increased risk of morbidity and mortality and many poor physical health outcomes, including hypertension and type 2 diabetes mellitus (T2DM) [3].

Rapidly growing evidence also shows that obesity is associated with poor neurocognitive outcomes. Specifically, obesity is linked with elevated risk for Alzheimer's disease (AD), vascular dementia, and abnormalities on neuroimaging [4••, 5]. Obesity is also associated with mild deficits on cognitive testing, including on tasks assessing global cognition, attention, executive function, and memory [6, 7•, 8••]. Such deficits are particularly pronounced in severely obese individuals [6]. Although cognitive dysfunction is common in obese middle aged and older adults [6, 7•], obesity-related cognitive deficits are not limited to specific age cohorts. For instance, higher BMI is correlated with cognitive dysfunction in multiple domains in children, adolescent individuals, and young adults [8••, 9–11].

Higher BMI is also associated with reduced cognitive function in otherwise healthy adult samples [12–14]. Indeed, Gunstad et al (2006) [15] found prominent memory deficits in obese young and middle-aged healthy adults. These findings in healthy samples suggest that the presence of adiposity alone may negatively impact neurocognitive function.

Despite these findings, the mechanisms of cognitive deficits in obesity are poorly understood. The purpose of this paper is to propose a possible etiologic model for obesity associated cognitive impairment with emphasis on the role of T2DM and related conditions (eg, impaired glucose tolerance prior to T2DM onset). We chose to focus on the role of T2DM because of its high prevalence in obese individuals and strong association with poor neurocognitive outcomes independent of obesity. As an example, T2DM has been shown to nearly double the risk of dementia among >6000 elderly subjects [16].

This article is part of the Topical Collection on *Obesity*

M. L. Alosco · J. Gunstad (✉)
Department of Psychology, Kent State University, 238 Kent Hall Addition, Kent, OH 44242, USA
e-mail: jgunstad@kent.edu

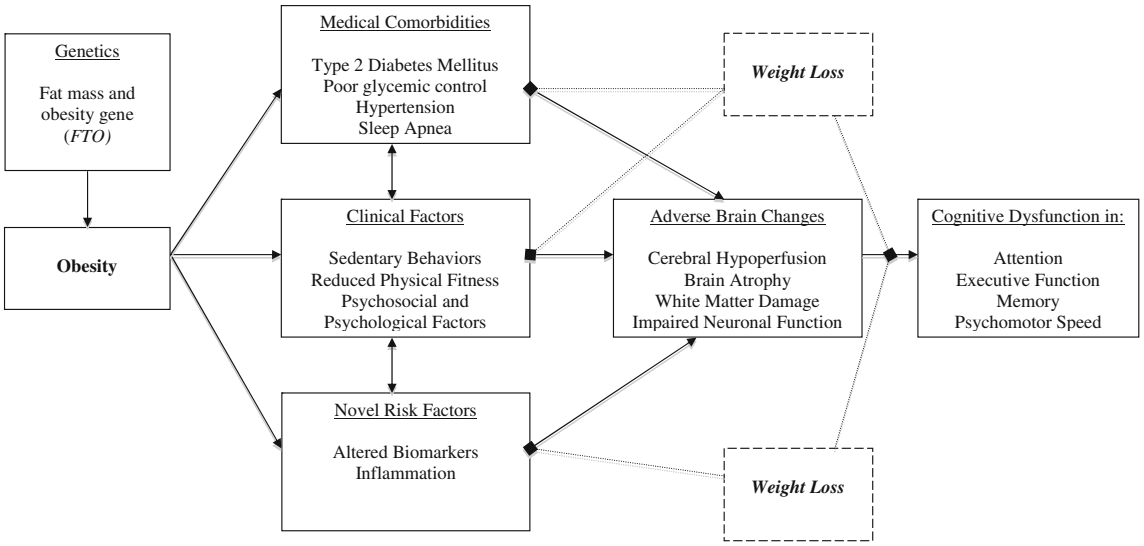

Fig. 1 Proposed model for mechanisms of obesity associated cognitive impairments. The displayed medical, clinical comorbidities, and novel risk factors represent the most common factors in obese individuals. Weight loss may attenuate cognitive dysfunction in obesity via resolution of comorbid medical and clinical conditions, and improvements in novel risk factors stemming from substantial adiposity loss. Of note, although other genetic markers have been linked with obesity, only the FTO is displayed given evidence of it being one of the strongest genetic risk factors for obesity and its close link with cognitive outcomes. Altered biomarkers refer to disturbed levels of adipokines and appetite hormones such as leptin and ghrelin

Proposed Mechanisms for Cognitive Impairment in Obese Persons

Please see Fig. 1 for the proposed model of possible mechanistic pathways for the negative effects of obesity on neurocognitive outcomes. It hypothesizes that obesity-related cognitive impairment results from the adverse effects of comorbid conditions and novel risk factors on brain structure and function.

Adverse Brain Changes

Extant evidence documents the adverse effects of obesity on the brain. Consequently, we propose that adverse brain changes in obese persons directly precede manifestations of cognitive deficits.

Cerebral Hypoperfusion

Obesity is independently associated with reduced cerebral perfusion and metabolic activity among healthy adults, including to brain regions critical for attention, reasoning, and executive function abilities [13, 17]. Reduced cerebral perfusion is a significant contributor to the pathogenesis of dementia [18–20]. Altered cerebral hemodynamics is also directly linked with brain insult, including ischemic-related injuries (eg, white matter hyperintensities) [21]. Indeed, recent work shows that higher BMI interacts with cerebral hypoperfusion in cardiovascular disease patients to exacerbate cognitive impairment, particularly in attention/executive function [6].

Brain Structure and Function

Relative to controls, obese persons exhibit higher levels of AD-related pathology, including tau and amyloid beta protein expression [22]. Obesity has also been linked with smaller regional and total brain volume in neurologic and healthy adult samples [23–25]. White matter hyperintensities (WMH) and axonal injury are also common in obese individuals [26], with a 1 kg/m^2 increase in BMI associated with a 2-fold increased risk of white matter lesions in elderly individuals [26, 27]. Decreased fractional anisotropy of the splenium, genu, and fornix also correlates with BMI among samples of healthy adults [28–30]. Unfortunately, no study has examined the association between structural and functional brain integrity with cognitive test performance in obesity and future studies are needed to clarify the impact of brain injury in obesity on cognitive function.

Contributors to Adverse Brain Changes

We propose that adverse brain changes and resulting cognitive deficits in obesity largely stem from the independent and interactive effects of multiple comorbid conditions, particularly T2DM. However, long prior to the diagnosis of these medical conditions, subclinical pathology (eg, poor glycemic control) may contribute to adverse brain changes and cognitive deficits in obese persons. Alternatively, risk factors

unique to adiposity may also play a key role and future studies are needed to confirm their effects on cognition.

Type 2 Diabetes Mellitus

It is estimated that by the year 2050 nearly 1 out of every 3 American adults could have diabetes [31]. This pattern may largely be attributed to the rapidly rising rates of obesity in the United States. Obesity is recognized as a primary cause of T2DM because of its effects on skeletal muscle insulin resistance and pancreatic beta cell failure [32, 33]. Obesity is associated with a ×40 relative risk for T2DM, making it one of the most common comorbidities in obese individuals [34, 35]. Subclinical elevations in glucose are also prevalent in obese persons and can be found in approximately 33 % of U.S. adults [36, 37].

T2DM and Cognitive Function

The well-known effects of T2DM and prediabetes on the brain are theorized to play a major role in obesity associated cognitive impairments. T2DM has been suggested to be a significant contributor to the development of mild cognitive impairment (MCI) and accelerate progression from MCI to dementia [38]. Neuropsychological testing reveals that persons with T2DM most commonly exhibit deficits on tasks of verbal memory and processing speed [39]. Prediabetic individuals also perform poorly on formal cognitive testing and are at a 2-fold increased risk for cognitive decline relative to individuals with normal fasting glucose levels [40]. Not surprisingly, when compared with obese controls, obese persons with T2DM demonstrate greater cognitive deficits including in memory and psychomotor speed [41].

T2DM and Adverse Brain Changes

T2DM and related conditions likely impact the brain to exacerbate cognitive deficits in obese persons. Most notably, T2DM is an established risk factor for stroke and brain infarcts [42•]. However, T2DM is also linked with brain atrophy [43] in addition to greater postmortem AD neuropathology such as increased hippocampal neuritic plaques, neurofibrillary tangles in the cortex and hippocampus, and higher risk of cerebral amyloid angiopathy [44]. Persons with T2DM also exhibit functional brain impairments. For instance, diabetes is associated with neuronal injury and [45] negatively impacts cerebral circulation to contribute to the development of WMH [46]. Resting state fMRI studies show that T2DM patients exhibit impaired neuronal activity in among many lobar structures, notably in middle temporal lobe regions, and these impairments predicted poor neurocognitive performances [47]. Taken together, obese individuals with T2DM are at significant risk for accelerated brain insult, including atrophy and impaired neuronal function among structures implicated in AD (eg, hippocampus) [48, 49].

Physiological Mechanisms of T2DM

The synergistic effects of T2DM and obesity on shared abnormal physiological processes likely produce additive effects on the brain and cognition. Specifically, macrovascular risk factors (eg, hypertension, atherosclerosis, elevated cholesterol) and microvascular disease (eg, endothelial dysfunction) are prevalent in both obese and T2DM patients and associated with cognitive impairment and development of AD [50, 51]. Alternatively, inflammatory markers are also elevated in obese [52] and T2DM populations [51] and may produce additive brain and cognitive deficits in obese individuals with T2DM [51, 53, 54].

T2DM further introduces several unique mechanisms in obese persons to negatively impact neurocognitive function. Advanced glycation end products (AGE) are elevated in patients with T2DM and linked with microvascular complications [55, 56], AD-related pathology, as well as impaired neuronal function, oxidative stress, and glucose hypometabolism [51, 57]. Hyperinsulinemia is also a likely mechanism of poor neurocognitive outcomes in T2DM, including increased risk for AD. Insulin plays a key role in the brain with receptor sites located in the hippocampus and entorhinal cortex—brain structures [58] affected by AD [59]. Impaired insulin function accelerates cognitive decline [60] and affects amyloid beta clearance in the brain [61]. Chronic hyperglycemia in obese persons with T2DM may also accelerate cognitive decline via cerebral hypoperfusion [62] and its adverse effects on central glucose utilization [63, 64]. Last, lipoprotein related proteins (LRP) are diminished in T2DM patients and are another possible mechanism for risk of AD in this population, particularly in light of its role in amyloid beta clearance [43, 65].

Impaired Glucose Tolerance

Obese persons commonly exhibit impairments in glycemic control before the onset of T2DM. Such abnormalities also likely contribute to cognitive dysfunction in obese persons. Recent work in nondiabetic elderly shows that increases in HbA1c predicts cognitive decline over time [66]. Other work also demonstrates the negative effects of glucose intolerance on neurocognitive outcomes, including increased risk for MCI and dementia in nondiabetic individuals [67]. Poor glycemic control further appears to adversely impact the integrity of the brain. For instance, high HbA1c levels have been linked with reduced hippocampal volume, and possibly vascular related brain pathology such as cerebral hypoperfusion [68, 69]. Future work is needed to clarify the effects of poor glycemic

control on the brain and cognitive function in obese individuals prior to the development of T2DM.

Other Medical and Clinical Comorbid Conditions

Obesity is associated with many other comorbid conditions that negatively impact neurocognitive function and increase risk for AD. Most notably, obese persons exhibit reduced cardiac function and present with conditions such as hypertension and sleep apnea. Obese individuals also demonstrate higher rates of sedentary behaviors, poorer physical fitness, and are at greater risk for psychological disorders such as depression [70, 71]. A vast literature supports the negative effects of these medical comorbidities and clinical factors on reduced neurocognitive function and increased risk for AD and dementia related processes [72–74]. Past work shows that obesity interacts with many of these conditions such as hypertension and reduced physical fitness to exacerbate neurocognitive impairments [75, 76].

Novel Risk Factors

The extant literature linking obesity with cognitive deficits in healthy samples suggests that the presence of adiposity may introduce unique mechanisms to adversely impact neurocognitive outcomes. Much attention has been paid to the role of genetic factors and biomarker concentrations in cognitive function among obese individuals. Specifically, the fat mass and obesity associated gene (*FTO*) is associated with obesity [77] and carriers of the *FTO* risk allele exhibit poorer neurocognitive outcomes [78]. APOE ∈4 is also involved in lipid regulation and may interact with vascular risk factors to accelerate cognitive decline and risk of AD [79].

Obese individuals also exhibit elevated inflammatory markers [52] and abnormal concentrations of circulating biomarkers, including appetitive neurohormones (eg, leptin, ghrelin), brain derived neurotrophic factor (BDNF), and amyloid beta [80–83]. Increased inflammatory markers accelerate cognitive decline in medical and elderly populations and are also a hallmark of AD, suggesting a possible role for inflammation in obesity associated cognitive deficits [84, 85]. Similarly, adipokines and appetite hormones (eg, ghrelin, leptin) have important neurotrophic and neuroprotective roles [86, 87] and disturbed levels of these biomarkers may contribute to the pathogenesis of AD and reduced cognitive function [86–88]. Interestingly, weight loss surgery and behavioral weight loss interventions may correspond to better cognitive function via their effects on concentrations of many of these biomarkers, appetite hormones (eg, leptin, ghrelin, amyloid beta) [89–91], as well as insulin levels [92] and prospective studies should test this possibility.

Discussion

Obesity has reached epidemic proportions and is a significant contributor to poor health outcomes. Obesity is now also a recognized risk factor for reduced neurocognitive outcomes, including increased risk for dementia (eg, AD and vascular dementia). Obese individuals of all ages also exhibit deficits on formal cognitive testing that may stem from the impact of obesity on the brain. The etiology of adverse brain changes and cognitive dysfunction in obese persons likely involves multiple physiological processes subsequent to the effects of medical and clinical comorbidities as well as excess adiposity.

T2DM is one of the most common comorbid medical conditions in obesity and obese persons with significant impairments in glucose tolerance may be at greatest risk for cognitive impairment and dementia. Indeed, T2DM is associated with abnormalities on neuroimaging, cognitive decline, AD, and interacts with BMI to exacerbate poor neurocognitive outcomes [42•]. Although it is plausible that tightly controlled glucose in obese individuals may attenuate cognitive impairment [93], the literature is not entirely consistent on this approach. For instance, past work has shown that better glycemic control is not related to improved cognitive function [94]. The exact reason for the discrepancy in these findings is unclear, but suggests other factors associated with T2DM (eg, advanced glycation end products) may contribute to cognitive dysfunction. Future work in obese individuals is much needed to determine other recently theorized mechanisms (eg, epigenetics) [95] and medical and clinical factors by which T2DM may exacerbate cognitive deficits in obesity. Future work should also explore whether sustained treatment of obesity and its accompanying medical conditions (eg, T2DM) translates to improved cognitive function in obese individuals.

Cognitive impairment in obesity has significant clinical implications. Obese individuals are asked to adhere to complex treatment regimens to manage their many medical comorbidities and promote weight loss. Recent work shows that poorer cognitive function is strongly predictive of worse adherence behaviors among cardiovascular disease patients and persons with T2DM [96, 97]. Interestingly, cognitive deficits in severely obese individuals undergoing bariatric surgery may interfere with adherence to postoperative treatment recommendations and result in decreased ability to lose or maintain weight loss [98]. Specific impairments in executive function seem most likely to preclude obese persons cognitive ability to plan ahead, multi-task self-care behaviors, organize medications, implement routine exercise regimens, and monitor symptoms, among many other adherence behaviors. Poor adherence likely becomes particularly problematic in obese patients with

T2DM, as cognitive impairment is exacerbated and the treatment regimens become more complicated. Future studies are needed to determine the benefits of cognitive screening in obese individuals to help determine those patients at greatest risk for treatment nonadherence, particularly among patients undergoing weight loss surgery.

Nonetheless, obesity is a modifiable risk factor and cognitive impairment in this population may be reversible. A growing literature shows that bariatric surgery is associated with improved acute and long-term cognitive function across several domains, particularly in memory abilities [7•, 99]. A likely mechanism for these findings involves resolution of medical comorbidities such as T2DM (Fig. 1). For example, bariatric surgery has been shown to improve glycemic control and result in long-term improvements and/or remission of T2DM and other metabolic risk factors [100]. In fact, recent attention has been paid to surgical intervention as an alternate treatment for T2DM vs lifestyle modifications [101••]. Improvements in inflammation and circulating biomarkers after bariatric surgery may also lead to better cognitive outcomes [89, 90]. Prospective studies are needed to clarify the mechanisms of improved cognitive function after weight loss surgery and whether surgical intervention can reduce the risk of cognitive decline and/or dementia in obese individuals. Although behavioral strategies (eg, diet and exercise) are less successful for long-term weight loss, such interventions have been shown to improve cognitive function [102] and prospective studies should examine the neuroprotective effects of lifestyle modifications in obesity, particularly relative to weight loss surgery.

Conclusions

In brief summary, obese individuals are at risk for cognitive impairment via comorbid conditions and novel risk factors associated with adiposity. Clinicians working with obese individuals should be mindful of the possible presence of cognitive dysfunction and establish procedures for screening and/or referring for formal neuropsychological evaluation. Such screening methods may help to determine those patients at risk for reduced treatment adherence. Randomized control trials that follow obese individuals throughout the lifespan are needed to confirm the effects of obesity on the brain and identify the nature of cognitive decline in this population.

Compliance with Ethics Guidelines

Conflict of Interest Michael L. Alosco and John Gunstad declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation. 2013;127:e6–e245.
2. Levi J, Segal LM, Laurent R, et al. F as in Fat: how obesity threatens Americas future. Trust for Americas Health. 2012.
3. Lenz M, Richter T, Muhlhauser I. The morbidity and mortality associated with overweight and obesity in adulthood. Dtsch Arztebl Int. 2009;106:641–8.
4.•• Luchsinger JA. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Arch Neurol. 2009;66:336–42. *This study shows that mid-life obesity is associated with increased risk for dementia.*
5. Karlsson HK, Tuulari JJ, Hirvonen J, et al. Obesity is associated with white matter atrophy: a combined diffusion tensor imaging and voxel-based morphometric study. Obesity. 2013;21:2530–7.
6. Alosco ML, Spitznagel MB, Raz N, et al. Obesity interacts with cerebral hypoperfusion to exacerbate cognitive impairment in older adults with heart failure. Cerebrovasc Dis Extra. 2012;2:88–98.
7.• Gunstad J, Strain G, Devlin MJ, et al. Improved memory function 12 weeks after bariatric surgery. Surg Obes Relat Dis. 2011;7:465–72. *The results from this study show that bariatric surgery patients exhibit significant cognitive impairments that improved 12-weeks postoperatively relative to obese controls.*
8.•• Benito-Leon J, Mitchell AJ, Hernandez-Gallego J, et al. Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES). Eur J Neurol. 2013;20:899–906. *This study documents the adverse effects of obesity on cognitive function in >1500 persons.*
9. Mond JM, Stich H, Hay PJ. Associations between obesity and development functioning in pre-school children: a population-based study. Int J Obes. 2007;31:1068–73.
10. Lokken KL, Boeka AG, Austin AM, et al. Evidence of executive dysfunction in extremely obese adolescents: a pilot study. Surg Obes Relat Dis. 2009;5:547–52.
11. Fedor A, Gunstad J. Higher BMI is associated with reduced cognitive performance in division I athletes. Obes Facts. 2013;6:185–92.
12. Gunstad J, Paul RH, Cohen RA, et al. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr Psychiatry. 2007;48:57–61.
13. Volkow ND, Wang GJ, Telang G, et al. Inverse association between BMI and prefrontal metabolic activity in healthy adults. Obesity. 2009;17:60–5.
14. Cournot M, Marqui JC, Ansiau D, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006;67:1208–14.
15. Gunstad J, Paul RH, Cohen RA, et al. Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disor. 2006;11:e15–9.
16. Ott A, Stolk RP, van Harksamp F, et al. Diabetes mellitus and the risk of dementia. The Rotterdam Study. Neurology. 1999;53:1937.
17. Willeumier K, Taylor D, Amen D. Elevated BMI is associated with decreased blood flow in the prefrontal cortex using SPECT imaging in healthy adults. Obesity. 2011;19:1095–7.

18. Luchsinger JA, Cheng D, Tang MX, et al. Central obesity in the elderly is related to late-onset Alzheimer disease. Alzheimer Dis Assoc Disord. 2012;26:101–5.
19. Qiu C, Winblad B, Marengoni A, et al. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med. 2006;166:1003–8.
20. Ruitenberg A, den Heijer T, Bakker SL, et al. Cerebral hypoperfusion and clinical onset of dementia: the Rotterdam Study. Ann Neurol. 2005;57:789–94.
21. Alosco ML, Brickman AM, Spitznagel MB, et al. Cerebral perfusion is associated with white matter hyperintensities in older adults with heart failure. Congest Heart Fail. 2013;19:E29–34.
22. Mrak RE. Alzheimer-type neuropathological changes in morbidly obese individuals. Clin Neuropathol. 2009;28:40–5.
23. Ho AJ, Raji CA, Becker JT, et al. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiol Aging. 2010;31:1326–39.
24. Yokum S, Ng J, Stice E. Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. Int J Obes. 2012;36:656–64.
25. Gunstad J, Paul RH, Cohen RA, et al. Relationship between body mass index and brain volume in healthy adults. Int J Neurosci. 2008;118:1582–93.
26. Gustafson DR, Steen B, Skoog I. Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. Int Psychogeriatr. 2004;16:327–36.
27. Jagust W, Harvey D, Mungas D, et al. Central obesity and the aging brain. Arch Neurol. 2005;62:1545–8.
28. Kurth F, Levitt JG, Phillips OR, et al. Relationships between gray matter, body mass index, and waist circumference in healthy adults. Hum Brain Mapp 2013;34:1737–46
29. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2010;341:c3666.
30. Stanek KM, Grieve SM, Brickman AM, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity. 2011;19:500–4.
31. Boyle JP, Thompson TJ, Gregg EW, et al. Projection of the year 2050 burden of diabetes in the U.S. adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metrics. 2010;8:29.
32. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A collusion responsible for NIDDM [review]. Diabetes. 1988;37:667–87.
33. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000;106:171–6.
34. Chan JM, Rimm EB, Colditz GA, et al. Obesity., fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care. 1994;17:961–9.
35. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol. 1990;132:501–13.
36. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and prediabetes in the U.S. population in 1988–1994 and 2005–2006. Diabetes Care. 2011;32:287–94.
37. Geiss LS, James C, Gregg EW, et al. Diabetes risk reduction behaviors among U.S. adults with prediabetes. Am J Prev Med. 2010;38:403–9.
38. Xu W, Caracciolo B, Wang HX, et al. Accelerated progression from mild cognitive impairment to dementia in people with diabetes. Diabetes. 2010;59:2928–35.
39. Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J Clin Exp Neuropsychol. 2004;26:1044–80.
40. Yaffe K, Blackwell T, Kanaya AM, et al. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology. 2004;63:658–63.
41. Yau PL, Javier DC, Ryan CM, et al. Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia. 2010;53:2298–306.
42.• Luchsinger JA. Type 2 diabetes and cognitive impairment: linking mechanisms. J Alzheimers Dis. 2012;30:S185–98. *This is a recent review paper highlighting the common mechanisms of cognitive impairment in type 2 diabetes mellitus*.
43. Schmidt R, Launer LJ, Nilsson LG, et al. Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) Study. Diabetes. 2004;53:687–92.
44. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia Aging Study. Diabetes. 2002;51:1256–62.
45. Li ZG, Zhang W, Grunberger G, et al. Hippocampal neuronal apoptosis in type 1 diabetes. Brain Res. 2002;946:221–31.
46. Novak V, Last D, Alsop DC, et al. Cerebral blood flow velocity and periventricular white matter hyperintensities in type 2 diabetes. Diabetes Care. 2006;29:1529–34.
47. Xia W, Wang S, Sun Z, et al. Altered baseline brain activity in type 2 diabetes: a resting-state fMRI study. Psychoneuroendocrinology. 2013;38:2493–501.
48. Bruehl H, Sweat V, Tirsi A, Shah B, et al. Obese adolescents with type 2 diabetes mellitus have hippocampal and frontal lobe volume reductions. Neurosci Med. 2011;2:34–42.
49. Toda N. Age-related changes in endothelial function and blood flow regulation. Pharmacol Ther. 2012;133:159–76.
50. Whitmer RA, Gunderson EP, Quesenberry CP, et al. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res. 2007;4:103–9.
51. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. Diabetes Res Clin Prac. 2005;69:29–35.
52. Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline: MacArthur studies of successful aging. Neurology. 2002;59:371–8.
53. Yaffe K, Lindquist K, Penninx BW, et al. Inflammatory markers and cognition in well-functioning African-American and White elders. Neurology. 2003;61:76–80.
54. Vlassara H, Striker LJ, Teichberg S, et al. Advanced glycation end products induce glomerular sclerosis and albuminuria in normal rats. Proc Natl Acad Sci U S A. 1994;91:11704–8.
55. Stitt AW. Advanced glycation: an important pathological event in diabetic and age related ocular disease. Br J Ophthalmol. 2001;85:746–53.
56. Brownlee M. Advanced protein glycosylation in diabetes and aging. Annu Rev Med. 1995;46:223–34.
57. Frolich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm. 1998;105:423–38.
58. Small SA, Perera GM, DeLaPaz R, et al. Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol. 1999;45:466–72.
59. Vanhanen M, Soininen H. Glucose intolerance, cognitive impairment and Alzheimer's disease. Curr Opin Neurol. 1998;11:673–7.
60. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res. 2007;4:147–52.
61. Wakisaka M, Nagamachi S, Inoue K, et al. Reduced regional cerebral blood flow in aged noninsulin-dependent diabetic patients with not history of cerebrovascular disease: evaluation by N-isopropyl-123I-p-iodoamphetamine with single-photon emission computed tomography. J Diabet Complicat. 1990;4:170–4.
62. Jakobsen J, Nedergaard M, Aarsle-jensen M, et al. Regional brain glucose metabolism and blood flow in streptozocin-induced diabetic rats. Diabetes. 1990;39:437–40.

63. Moll L, Schubert M. The role of insulin and insulin-like growth factor-1/FoxO-Mediated transcription for the pathogenesis of obesity-associated dementia. Curr Gerontol Geriatr Res. 2012;2012:384094.
64. Sagare A, Deane R, Bell RD, Johnson B, et al. Clearance of amyloid-beta by circulating lipoprotein receptors. Nat Med. 2007;13:1029–31.
65. Ravona-Springer R, Moshier E, et al. Changes in glycemic control are associated with changes in cognition in nondiabetic elderly. J Alzheimers Dis. 2012;30:299–309.
66. Yaffe K, Blackwell T, Whitmer RA, et al. Glycosated hemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging. 2006;10:293–5.
67. Jorgensen L, Jenssen T, Joakimsen O, et al. Glycated hemoglobin level is strongly related to the prevalence of carotid artery plaques with high echogenicity in nondiabetic individuals: the Tromoso study. Circulation. 2004;110:466–70.
68. Duckrow RB, Beard DC, Brennan RW. Regional cerebral blood flow decreases during chronic and acute hyperglycemia. Stroke. 1987;18:52–8.
69. Enzinger C, Fazekas F, Matthews PM, et al. Risk factors for progression of brain atrophy in aging: 6 year follow-up of normal subjects. Neurology. 2005;64:1704–11.
70. Cameron AJ, Welborn TA, Zimmel PZ, et al. Overweight and obesity in Australia: the 1999-2000 Australian diabetes, obesity and lifestyle study (AusDiab). Med J Aust. 2003;178:427–32.
71. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67:220–9.
72. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001;56:42–8.
73. Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. Arch Med Res. 2012;43:615–21.
74. Alosco ML, Spitznagel MB, Raz N, et al. The interactive effects of cerebral perfusion and depression on cognitive function in older adults with heart failure. Psychosom Med. 2013;75:632–9.
75. Wolf PA, Beiser A, Elias MF, et al. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Curr Alzheimer Res. 2007;4:111–6.
76. Marks BL, Katz LM, Styner M, et al. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. Br J Sport Med. 2011;45:1208–15.
77. Peng S, Zhu Y, Xu F, et al. FTO gene polymorphisms and obesity risk: a meta-analysis. BMC Med. 2011;9:71.
78. Ho AJ, Stein JL, Hua X, et al. A commonly carried allele of the obesity-related gene is associated with reduced brain volume in the healthy elderly. Proc Natl Acad Sci U S A. 2010;107:8404–9.
79. Mielke MM, Leoutsakos JM, Tschanz JT, et al. Interaction between vascular factors and the APOE ε4 allele in predicting rate of progression in Alzheimer's disease. J Alzheimer Dis. 2011;26:127–34.
80. Wren AM, Seal LJ, Cohen MA, et al. Ghrelin enhances appetite and increases food intake in humans. J Clin Endocrinol Metab. 2001;86:5992–5.
81. Xu B, Goulding EH, Zang K, et al. Brain-derived neurotrophic factor regulates energy balance downstream of menacortin-4 receptor. Nat Neurosci. 2003;6:736–42.
82. Sorensen T, Echwald SM, Holm J. Leptin in obesity. BMJ. 1996;313:953–4.
83. Lee Y, Martin JM, Maple RL, et al. Plasma Amyloid-beta peptide levels correlate with adipocyte amyloid precursor protein gene expression in obese individuals. Neuroendocrinology. 2009;90:383–90.
84. Gunstad J, Bausserman L, Paul RH, et al. C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease. J Clin Neurosci. 2006;13:540–6.
85. Finch CE, Morgan TE. Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position Paper. Curr Alzheimer Res. 2007;4:185–9.
86. Lee EB. Obesity, leptin, and Alzheimer's disease. Ann N Y Acad Sci. 2011;1243:15–29.
87. Diano S, Farr SA, Benoit SC, et al. Ghrelin controls hippocampal spine synapse density and memory performance. Nat Neurosci. 2006;9:381–8.
88. Diniz BS, Teizeira AL. Brain-derived neurotrophic factor and Alzheimer's disease: physiopathology and beyond. Neuromol Med. 2011;13:217–22.
89. Gunstad J, Spitznagel M, Keary T, et al. Serum leptin levels are associated with cognitive function in older adults. Brain Res. 2008;1230:233–6.
90. Ghanim H, Monte SV, Sia CL, et al. Reduction in inflammation and the expression of amyloid precursor protein and other proteins related to Alzheimer's disease following gastric bypass surgery. J Clin Endocrinol Metab. 2012;97:E1197–201.
91. Strohacker K, McCaffery JM, Maclean PS, et al. Adaptation of leptin, ghrelin or insulin during weight loss as predictors weight regain: a review of current literature. Int J Obes (London) 2014;38:388–96.
92. Ades PA, Savage PD. Potential benefits of weight loss in coronary heart disease. Prog Cardiovasc Dis. 2014;56:448–56.
93. Terra X, Auguet T, Guiu-Jurado E, et al. Long-term changes in leptin, chemerin, and Ghrelin levels following different bariatric surgery procedures: Roux-en-Y Gastric bypass and sleeve gastrectomy. Obes Surg. 2013;23:1790–8.
94. Luchsinger JA, Palmas W, Teresi JA, et al. Improved diabetes control in the elderly delays global cognitive decline. J Nutr Health Aging. 2011;15:445–9.
95. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomized open-label substudy. Lancet Neurol. 2011;10:969–77.
96. Shaik MM, Hua GS, Kamal MA. Epigenomic approach in understanding Alzheimer's disease and type 2 diabetes mellitus. CNS Neurol Disord Drug Targets. 2014;13(2):283–9.
97. Stilley CS, Bender CM, Dunbar-Jacob J, et al. The impact of cognitive function on medication management: three studies. Health Psychol. 2010;29:50–5.
98. Alosco ML, Spitznagel MB, van Dulmen M, et al. Cognitive function and treatment adherence in older adults with heart failure. Psychosom Med. 2012;74:965–73.
99. Spitznagel MB, Galioto R, Limbach K, et al. Cognitive function is linked to adherence to bariatric postoperative guidelines. Surg Obes Relat Dis. 2013;9:580–5.
100. Alosco ML, Spitznagel MB, Strain G, et al. Improved memory function two years after bariatric surgery. Obesity (Silver Spring). 2014;22:32–8.
101.•• Brethauer SA, Aminian A, Romera-Talamas H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. Ann Surg. 2013;258:628–37. *Bariatric surgery with sustainable remission and improvement in T2DM.*
102. Siervo M, Nasti G, Stephan BC, et al. Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. J Am Coll Nutr. 2012;31:79–86.