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Can Bariatric Surgery Reduce Risk of Alzheimer's Disease?

Kelly Stanek, Ph.D.^a and John Gunstad, Ph.D.^b

^aDepartment of Psychology, University of Alabama, Box 870348, Tuscaloosa, AL, 35487

^bDepartment of Psychology, Kent State University, Kent, OH, 44242

Abstract

Recent studies demonstrate that obesity is independently associated with poor neurocognitive outcomes, including cognitive impairment, increased risk for dementia, and regional alterations in brain structure. Bariatric surgery is an effective treatment for obesity and initial findings suggest that it may result in cognitive improvements. The current paper reviews and integrates recent research in this area, with a focus on potential mediators and moderators of neuropsychological outcome in bariatric surgery patients, including anesthetic and nutritional complications and proposes novel avenues for continued study in this area.

Keywords

obesity; Alzheimer's disease; bariatric surgery; cognitive function

1. Introduction

While obesity continues to spread to pandemic proportions, healthcare providers and researchers are challenged with the task of identifying and targeting the mechanisms responsible for functional decline in obese individuals. Rapidly accumulating evidence associates excess body fat with an array of metabolic, cardiovascular, and psychological sequelae, including a direct increase in risk for dementia, specific cognitive impairment, and corresponding neurological alterations across the lifespan (e.g., Fergenbaum et al., 2009; Kopelman, 2000; Raji et al., 2010; Whitmer et al., 2007). Weight loss surgery has been identified as an effective treatment for obesity and related metabolic and cardiovascular comorbidities (e.g., Buchwald et al., 2004). The effects of bariatric surgical interventions on the neuropsychological sequelae of obesity are currently under investigation and many questions remain unanswered. Can the substantial weight loss achieved thru a successful surgical intervention result in sustained improvement in cognitive abilities and reduced risk for future dementia? Will such neuropsychological improvements mitigate any concurrent risk for perioperative complications in morbidly obese patients and/or anesthetic related postoperative cognitive decline? While ongoing work in our lab offers provocative evidence for cognitive benefits of weight loss surgery in young adults (Gunstad et al., 2011), more work is needed to elucidate underlying mechanisms and to elaborate on the above-mentioned areas of inquiry. The goal of the present paper is to review these and other recent

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Address correspondence to: Kelly Stanek, Ph.D. Department of Psychology, Box 870348, University of Alabama, Tuscaloosa, AL 35487-0348, Phone: (205) 348-6362, Fax: (205) 348-8648, kstanek@mac.com.

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research findings in an attempt to integrate current knowledge regarding the neuropsychology of obesity and weight loss surgery and to propose novel avenues for continued study.

2. Obesity, Cognitive Impairment, and Dementia

2.1. Obesity-Related Cognitive Impairment

A growing body of literature indicates that increases in body fat and body mass index (BMI) are associated with deficits in multiple cognitive domains in children and adults (e.g., Cserjési et al., 2007; Gunstad et al., 2010; Fergenbaum et al., 2009; Maayan et al., 2010). Moreover, these relationships exist independent of age and comorbid medical conditions known to directly impact cognition (e.g., diabetes mellitus, hypertension, sleep apnea). Specific abilities impacted by adiposity across the lifespan in otherwise healthy individuals include memory (Gunstad et al., 2010; 2006), executive function (Fergenbaum et al., 2009; Gunstad et al., 2007), and complex attention and psychomotor processing speed (Cournot et al., 2006). Studies such as these, which control for potentially confounding medical comorbidities in individuals across the lifespan, suggest to us that pathophysiological mechanisms directly related to elevated adiposity may be underlying these relationships.

Still, some of the most compelling evidence for obesity-related cognitive deficits emerges from investigations of morbidly obese individuals, including candidates for weight loss surgery. Several recent studies have compared the pre-surgical cognitive performance of morbidly obese patients with normative data. In one study, significant deficits in specific executive functions, including planning, problem solving, and cognitive flexibility, were found in morbidly obese surgical candidates (Lokken et al., 2010). In a prospective study of candidates for bariatric surgery, up to 24% of patients demonstrated baseline impairments in learning and memory (Gunstad et al., 2011). Other studies have compared severely obese individuals to non-obese counterparts, providing evidence for reduced psychomotor speed and sustained attention (Cserjési et al., 2009), as well as both behavioral (i.e., impulsivity; Davis et al., 2010) and cognitive (i.e., cognitive response inhibition; Cserjési et al., 2009) aspects of executive control in obese women. Interestingly, this research has been extended to include both extremely obese adolescents and older adults (Elias et al., 2003; Lokken et al., 2009; Walther et al., 2010) with similar findings of executive dysfunction in each population.

In sum, observational studies of obesity and specific cognitive abilities provides fairly consistent evidence that midlife adiposity is related to specific cognitive deficits, including memory difficulties, psychomotor slowing, and a range of executive dysfunction. While it may be easy to imagine how the impact of obesity-related cognitive deficits might and hinder one's ability to effectively engage in certain weight-loss strategies and lead to chronic obesity, it has also been proposed that these relationships are more likely to be complex and cyclical in nature (e.g., Smith et al., 2011; Stanek-Sellbom & Gunstad, 2012). Accumulating evidence for cognitive and brain abnormalities in obese children and adolescents leads us to speculate on the potential developmental nature of underlying mechanisms, however, longitudinal research is needed before conclusions can be drawn.

2.2. Obesity as Risk Factor for Dementia

Consistent with cross sectional work, prospective data also indicate that obesity may produce longer-term neurocognitive consequences and may even serve to accelerate normal cognitive aging processes. For instance, a large literature demonstrates that obesity in midlife, particularly abdominal adiposity, confers a substantially increased risk of both Alzheimer's disease and vascular dementia in older adulthood (Hassing et al., 2009; Kivipelto et al., 2005; Whitmer et al., 2005, 2007, 2008). While medical conditions

associated with obesity and metabolic syndrome, including type 2 diabetes and hypertension, have long been shown to relate to neurocognitive changes, elevated body composition indices have also been independently associated with longitudinal decline in cognitive performance of older adults in studies that controlled for the presence of these medical conditions (e.g., Elias et al., 2003, 2005; Sabia et al., 2009; Wolf et al., 2007). These findings suggest the possibility of a relatively independent neuropathology for adiposity related neurocognitive changes that may lead to dementia in adults. In older adults, however, current obesity levels have been inversely associated with dementia conversion (Atti et al., 2008; Fitzpatrick et al., 2009; Hughes et al., 2009; West & Hahn, 2009), perhaps highlighting an “obesity paradox” (e.g., Fitzpatrick et al., 2009), in which late-life weight-loss may represent an incipient marker of dementia (e.g., Atti et al., 2008; Hughes et al., 2009).

In light of these combined findings, work from our lab and others has begun to look more specifically at potential interactive relationships among obesity, ageing, and cognitive functioning. For example, recent results from the cross-sectional Baltimore Longitudinal Study of Aging demonstrated an age by body composition interaction for memory, attention, and executive function that was independent of the influence of coexisting medical conditions (e.g., diabetes, hypertension; Gunstad et al., 2010). While the precise nature and mechanisms of these interactions are not fully understood, this preliminary evidence in combination with findings from prospective studies of dementia risk suggest that adiposity-related pathophysiological processes may have longstanding, direct, and cumulative actions on the aging brain. Longitudinal studies are needed to clarify how patterns of weight gain and loss throughout the lifespan may correspond to neurocognitive outcomes such as Alzheimer’s disease.

2.3. Mechanisms for Cognitive Decline in Obesity

Structural and functional brain abnormalities corresponding to cognitive dysfunction and decline have been found in obese individuals and recent research has identified several biomarkers that are implicated in these relationships (for reviews see Carnel et al., 2012; Michaelides et al., 2011; Stanek, Smith, & Gunstad, 2011); however, the neuropathological mechanisms underlying these changes are not yet clear. Multiple hypotheses have been proposed and it seems increasingly likely that the mechanisms involved in obesity-related cognitive decline are complex, varied, and interactive with aging, as well as processes more directly related to the many medical comorbidities of obesity (see Stanek-Sellbom & Gunstad, 2012 for a preliminary model of obesity-related cognitive decline and Bruce-Keller, Keller, & Morrison, 2009; Jagust, 2007; Smith et al., 2011 for additional reviews of this area).

In adults, increased BMI has been directly associated with cortical atrophy and metabolic alterations, particularly in prefrontal brain regions (Gunstad et al., 2008; Pannacciulli et al., 2006; Taki et al., 2008; Volkow et al., 2009; Ward et al., 2005), as well as reduced connectivity in white matter tracts (Stanek et al., 2010). In older adults, obesity has been shown to be directly associated with disturbances of temporal, frontal, and subcortical brain regions (Gustafson et al., 2004; Gustafson, Steen, Skoog, 2004; Jagust et al., 2005). While there is currently limited published data concerning brain abnormalities in obese individuals under the age of 18, an ongoing project in our lab shows preliminary evidence for similar relationships between BMI and regional gray matter volume in healthy children and adolescents (Stanek et al., under review). In this study, magnetic resonance and diffusion tensor imaging indices were examined in relation to BMI in 120 individuals ranging from 6–18 years of age. Controlling for age and other relevant variables, Bonferroni-corrected analyses revealed significant inverse associations between BMI and grey matter in frontal and limbic brain regions. No significant associations were found between BMI and white

matter fractional anisotropy indices. While these changes may be at least partly related to a preclinical expression of the neuropathological processes underlying hypertension, type-2 diabetes, hyperlipidemia, and sleep apnea (among other obesity-related medical conditions), it is also possible that adiposity exerts more direct effects on the brain throughout the lifespan. For instance, much recent work has focused on the potential role of adipokine (e.g., leptin, ghrelin) alterations in obesity, which is thought to be a function of excess secretion of such chemicals via the excess adipose tissue present in obese individuals (Gunstad, Spitznagel et al., 2008; Pannacciulli et al., 2007; Scharf & Ahima, 2004; Spitznagel et al., 2010). Additional biomarkers related to adiposity, insulin resistance, and physical activity are under investigation (e.g., van Dijk et al., 2010), as are similar adiposity-related pro-inflammatory mechanisms (Bastard et al., 2006; Sweat et al., 2008). A recent meta-analysis found that both diabetes and obesity (assessed by BMI) were independently associated with increased risk of Alzheimer's disease (Profenno, Porsteinsson, & Faraone, 2010), and the pooled effect size for Alzheimer's disease risk was higher when combining studies that examined obesity and diabetes, as well as abnormal glucose and insulin levels participants. Such findings encourage continued investigation of both independent and interactive or cumulative mechanisms for cognitive decline in obese populations, as etiology is likely both complex and multifactorial. Other studies have explored a more direct pathophysiological connection between obesity and adverse neurocognitive outcomes, including as Alzheimer's disease. For instance, post-mortem studies have shown increased expression of Alzheimer's disease-related markers, including tau protein, amyloid precursor protein, and amyloid-peptide in obese older adults compared to controls (Mrak, 2009), while circulating levels of A β have also been positively associated with body fat in healthy individuals (Balakrishnan et al., 2005).

It is generally agreed that much more research is needed to elucidate the complex mechanisms linking obesity and poor neurocognitive outcomes. Another intriguing new area of research seeks to help elucidate these mechanisms via investigation of the neuropsychological outcomes of weight-loss treatment.

3. Weight Loss Surgery and Cognitive Functioning

As alluded to above, weight loss surgery has been identified as an efficacious treatment for obesity and associated conditions including hypertension and type-2 diabetes (Buchwald et al., 2004), and there is existing evidence from other patient populations to suggest that successful treatment of hypertension, type-2 diabetes, and poor cardiovascular fitness may alleviate some of the cognitive dysfunction associated with these conditions (Ahmad et al., 2004; Amenta et al., 2002). Post surgical weight loss may also be efficacious in addressing some of the mechanisms believed to underlie the more direct relationships between excess body fat and neuropsychological dysfunction (e.g., adipokine alterations, insulin resistance, inflammation; Cummings et al., 2002; Plum et al., 2011; Vázquez et al., 2005). Moreover, longitudinal research has indicated that post-surgical gains in terms of weight-loss and reduction of medical comorbidities can be maintained at long-term follow-up (Sjöström et al., 2004), which is particularly important given that weight loss is often rapid during the first 6 months post-operatively and continues until 24 months, where weight loss often plateaus or starts to regress after bariatric surgery (O'Brien et al., 2004). Cumulatively, these data lead to the hypothesis that weight-loss surgery may be cognitively beneficial to extremely obese individuals - a topic of current investigation in our lab. Initial results have supported this hypothesis and follow-up analyses are currently underway.

In our initial study, 109 bariatric surgery patients were compared to 41 obese control subjects who did not elect to undergo surgery on measures of neurocognitive functioning, both prior to weight loss surgery and at 12-week follow-up. Although exploratory

mechanistic analyses suggested that change in weight loss and medical status (e.g. hypertension, type 2 diabetes) were largely unrelated to cognitive changes, the results of this study demonstrated improvements in memory performance for the bariatric surgery candidates, while the obese control subjects showed a decline in memory performance over the same time period (Gunstad et al., 2011).

We've continued to follow this cohort and found continued improvement in memory at 12-month follow-up in the bariatric surgery patients (Miller et al., under review). As above, neither BMI nor conditions such as hypertension or type-2 diabetes account for the continued gains in neuropsychological test performance. Analyses of longer-term follow-up data (i.e., 24 months, 36 months) are needed to more fully explain these initial results and identify mechanisms of change, especially examination of possible cognitive changes following weight re-gain.

While these data support the idea that successful bariatric surgery may provide important cognitive benefits, questions surrounding other short and long-term risks and benefits to weight loss surgery must still be addressed. For instance, major surgery of any kind is associated with risk of perioperative complications and morbidity (Dijkstra et al., 1998, as well as more specific risk for post-operative cognitive impairment related to general anesthesia (Monk et al., 2008). Furthermore, extremely obese individuals may pose unique challenges to anesthetic management, including risk for operative tracheal intubation difficulties, atelectasis and reduced oxygenation, as well as thromboembolic and cardiac complications (O'Neill & Allam, 2010). Although recent meta-analyses have reported relatively low risk for perioperative complications and mortality in bariatric surgery patients (Buchwald et al., 2007; Flum et al., 2009), more research is needed to identify any long-term neurological ramifications of weight loss surgery in obese individuals.

For instance, one recent study reported evidence for post-surgical focal thalamic atrophy in bariatric surgery candidates relative to both a pre-surgical-BMI-matched comparison group and another age-matched group of healthy adults (Graff-Radford et al., 2011). While a brief neurocognitive test battery failed to reveal objective impairments in memory and executive function, the bariatric patients involved in this small study had reported subjective cognitive complaints at a median interval of 4 years after surgery, at which time they had achieved a median weight loss of 53 kg. This study was methodologically limited in several ways, including the retrospective design and lack of longitudinal cognitive evaluation, as well as reported variation in perioperative complications and history of medical comorbidities; however, these findings highlight the need for further research.

Importantly, studies of postoperative cognitive dysfunction after major surgery have identified preoperative cognitive impairment as specific risk factor for postoperative cognitive decline, particularly in the domains of attention and speeded processing (Silverstein et al., 2007). While an initial study demonstrated that bariatric surgery patients were no more likely to exhibit cognitive decline at 12-week follow-up than an obese control group (Gunstad et al., 2011), additional prospective cognitive outcome data is needed in light of what we know about cognitive dysfunction in obese individuals prior to weight loss. Of course, the question of whether the cognitive benefits of bariatric surgery might mitigate concurrent risk for perioperative complications in morbidly obese patients and/or postoperative cognitive decline will also need to be directly addressed.

4. Future Directions

One related area of great importance for future studies is the investigation of both short- and long-term neurological and cognitive consequences of bariatric surgery in children/adolescents and in older adults. Not only do we need prospective data to determine whether

successful weight loss surgery in younger adulthood can reduce the risk for future dementia in obese adults, but we will also need to explore the long-term neuropsychological impact of bariatric surgery in severely obese children and adolescents who undergo this procedure prior to adulthood, as well as the potential risks and benefits associated with bariatric surgery for obese elderly individuals. Neuropsychological outcome within both age groups may be impacted by the vulnerability of each group's brain state (i.e., distinct periods of brain maturation and deterioration, respectively). As increasing numbers of obese children and older adults are recommended for surgical treatment, it is imperative that begin to develop answers to these and other important questions regarding surgical interventions for weight loss in specific and/or vulnerable populations.

Future research should also investigate specific risks and possible benefits to functional abilities, including post-surgical self-care, in elderly bariatric surgery patients. Prospective studies in obese older adults are needed to directly address whether even substantial weight-loss via successful bariatric surgery will be enough to reverse whatever pathophysiological processes have developed over time in these individuals and, if not, at least delay or moderate cognitive and functional outcomes in previously obese individuals who are still likely to develop dementia.

Prospective studies are also needed to investigate the potential acute and long-term impact of anesthesia-related post-operative cognitive impairment on bariatric surgery patients of all ages. Similarly, specific investigation of the potential impact of post-operative nutritional deficiencies on neurocognitive function in bariatric surgery patients is needed. Micronutrient and mineral deficiencies are possible and common following weight-loss surgery, particularly malabsorptive procedures (Bloomberg et al., 2005), and such deficiencies have been linked to cognitive impairments, particularly in children and older adults (Black, 2003; Goodwin, Goodwin & Garry, 1983). Future studies are needed to evaluate the impact of post-operative nutrition status on cognitive functioning in bariatric surgery patients.

5. Conclusion

Recent studies have provided substantial evidence that obesity is associated with both specific cognitive impairments and increased risk for dementia and provocative new evidence suggests that bariatric surgery may help alleviate some of that cognitive dysfunction in adults. Many important questions remain regarding potential mediators and moderators of post-surgical cognitive change in this population, as well as in specific vulnerable populations, such as obese children and older adults. While longitudinal research is needed to evaluate the long-term clinical significance of these findings, bariatric surgery appears to be a viable and promising option for reducing obesity-related cognitive impairment.

Abbreviations

BMI Body Mass Index

References

- Amenta F, Mignini F, Rabbia F, et al. Protective effect of anti-hypertensive treatment on cognitive function in essential hypertension: analysis of published clinical data. *Journal of the Neurological Sciences*. 2002;203–204. 147–151.
- Atti AR, Palmer K, Volpato S, Winblad B, De Ronchi D, Fratiglioni L. Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *Journal of the American Geriatric Society*. 2008; 56(1):111–116.

- Awad N, Gagnon M, Messier C. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *Journal of Clinical and Experimental Neuropsychology*. 2004; 26:1044–1080. [PubMed: 15590460]
- Balakrishnan K, Verdile G, Mehta PD, Beilby J, Nolan D, Galvão DA, et al. Plasma Abeta42 correlates positively with increased body fat in healthy individuals. *Journal of Alzheimers Disease*. 2005; 8:269–282.
- Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European Cytokine Network*. 2006; 17:4–12. [PubMed: 16613757]
- Black MM. Micronutrient deficiencies and cognitive functioning. *J Nutr*. 2003; 133(11):39275–39315.
- Bloomberg RD, Fleishman A, Nalle JE, Herron DM, Kini S. Nutritional deficiencies following bariatric surgery: What have we learned? *Obesity Surgery*. 2005; 15:145–154. [PubMed: 15802055]
- Bruce-Keller AJ, Keller JN, Morrison CD. Obesity and vulnerability of the CNS. *Biochim Biophys Acta*. 2009; 1792(5):395–400. [PubMed: 18992327]
- Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004; 292(14):1724–1737. [PubMed: 15479938]
- Buchwald H, Estok R, Fahrbach K, Banel D, Sledge I. Trends in mortality in bariatric surgery: a systematic review and meta-analysis. *Surgery*. 2007; 142(4):621–632. [PubMed: 17950357]
- Carnel S, Gibson C, Benson L, Ochner CN, Geliebter A. Neuroimaging and obesity: Current knowledge and future direction. *Obesity Reviews*. 2012; 13:43–56. [PubMed: 21902800]
- Cournot M, Marquie JC, Ansiau D, Martinaud C, Fonds H, Ferrières J, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. *Neurology*. 2006; 67:1208–1214. [PubMed: 17030754]
- Cserjési R, Luminet O, Poncelet AS, László L. Altered executive function in obesity. Exploration of the role of affective states on cognitive abilities. *Appetite*. 2009; 52:535–539. [PubMed: 19260167]
- Cserjési R, Molnár D, Luminet O, Lénárd L. Is there any relationship between obesity and mental flexibility in children? *Appetite*. 2007; 49(3):675–678. [PubMed: 17543417]
- Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma ghrelin levels after diet-induced weight loss or bariatric surgery. *N Engl J Med*. 2002; 346(21):1623–1630. [PubMed: 12023994]
- Davis C, Patte K, Curtis C, Reid C. Immediate pleasures and future consequences. A neuropsychological study of binge eating and obesity. *Appetite*. 2010; 54:208–213. [PubMed: 19896515]
- Dijkstra J, van Boxtel M, Houx P, et al. An operation under general anesthesia as a risk factor for age-related cognitive decline: results from a large cross-sectional population study. *J Am Geriatr Soc*. 1998; 46:1258–1265. [PubMed: 9777908]
- Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *International Journal of Obesity and Related Metabolic Disorders*. 2003; 7:260–268. [PubMed: 12587008]
- Elias MF, Elias PK, Sullivan LM, Wolf PA, D'Agostino RB. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. *Neurobiology of Aging*. 2005; 26(Suppl)(1):11–16. [PubMed: 16223549]
- Fergenbaum JH, Bruce S, Lou W, Hanley AJ, Greenwood C, Young TK. Obesity and lowered cognitive performance in a Canadian first nations population. *Obesity*. 2009; 17:1967–1963.
- Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, et al. Midlife and late-life obesity and the risk of dementia: Cardiovascular Health Study. *Archives of Neurology*. 2009; 66:336–342. [PubMed: 19273752]
- Flum DR, Belle SH, King WC, Wahed AS, Berk P, Chapman W, Pories W, Courcoulas A, McCloskey C, Mitchell J, Patterson E, Pomp A, Staten MA, Yanovski SZ, Thirlby R, Wolfe B. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med*. 2009; 361(5):445–454. [PubMed: 19641201]

- Goodwin JS, Goodwin JM, Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. *JAMA*. 1983; 249(21):2917–2921. [PubMed: 6842805]
- Graff-Radford J, Whitwell JL, Trenerry MR, Ahlskog JE, Jensen MD, Jack CR, Josephs KA. Focal brain atrophy in gastric bypass patients with cognitive complaints. *Journal of Clinical Neuroscience*. 2011; 18:1671–1676. [PubMed: 22088949]
- Gunstad J, Strain G, Devlin M, Wing R, Cohen R, Paul R, Crosby R, Mitchell J. Improved memory function 12 weeks after bariatric surgery. *Surgery for Obesity and Related Diseases*. 2010
- Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, Zonderman AB. Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. *Neuroepidemiology*. 2010; 34:222–229. [PubMed: 20299802]
- Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E. Obesity is associated with memory deficits in young and middle-aged adults. *Eating and Weight Disorders*. 2006; 11:15–19.
- Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry*. 2007; 48:57–61. [PubMed: 17145283]
- Gunstad J, Paul R, Cohen R, Spitznagel M, Tate D, Grieve S, et al. Relationship Between Body Mass Index and Brain Volume in Healthy Adults. *International Journal of Neuroscience*. 2008; 118:1582–1593. [PubMed: 18853335]
- Gunstad J, Spitznagel M, Keary T, Glickman E, Alexander T, Karrer J, et al. Serum leptin levels are associated with cognitive function in older adults. *Brain Research*. 2008; 1230:233–236. [PubMed: 18675793]
- Gustafson D, Lissner L, Bengtsson C, Bjorkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. *Neurology*. 2004; 63:1990–1991.
- Gustafson DR, Steen B, Skoog I. Body mass index and white matter lesions in elderly women. An 18-year longitudinal study. *International Psychogeriatrics*. 2004; 16:327–336. [PubMed: 15559756]
- Hassing LB, Dahl AK, Thorvaldsson V, Berg S, Gatz M, Pedersen NL, Johansson B. Overweight in midlife and risk of dementia: a 40-year follow-up study. *International Journal of Obesity*. 2009; 33:893–898. [PubMed: 19506566]
- Hughes TF, Borenstein AR, Schofield E, Wu Y, Larson EB. Association between late-life body mass index and dementia: The Kame Project. *Neurology*. 2009; 72:1741–1746. [PubMed: 19451529]
- Jagust W. What can imaging reveal about obesity and the brain? *Current Alzheimer Research*. 2007; 4:135–139. [PubMed: 17430236]
- Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. *Archives of Neurology*. 2005; 62:1545–1548. [PubMed: 16216937]
- Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology*. 2005; 62(10):1556–1560. [PubMed: 16216938]
- Kopelman PG. Obesity as a medical problem. *Nature*. 2000; 404:635–643. [PubMed: 10766250]
- Lokken KL, Boeka AG, Austin HM, Gunstad J, Harmon CM. Evidence of executive dysfunction in extremely obese adolescents: a pilot study. *Surg Obes Relat Dis*. 2009; 5(5):547–552. [PubMed: 19766958]
- Lokken KL, Boeka AG, Yellumhanthi K, Wesley M, Clements RH. Cognitive performance of morbidly obese patients seeking bariatric surgery. *Am Surg*. 2010; 76(1):55–59. [PubMed: 20135940]
- Maayan L, Hoogendoorn C, Sweat V, Convit A. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity*. 2010; 19(7):1382–1387. [PubMed: 21350433]
- Michaelides M, Thanos PK, Volkow ND, Wang GJ. Functional neuroimaging in obesity. *Psychiatric Annals*. 2011; 41(10):496–500.
- Monk TG, Weldon CB, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS. Predictors of Cognitive Dysfunction after Major Noncardiac Surgery. *Anesthesiology*. 2008; 108(1):18–30. [PubMed: 18156878]
- Mrak RE. Alzheimer-type neuropathological changes in morbidly obese individuals. *Clinical Neuropathology*. 2009; 28:40–45. [PubMed: 19216219]

- O'Brien P, Dixon J, Brown W. Obesity is a surgical disease: Overview of obesity and bariatric surgery. *Australian and New Zealand Journal of Surgery*. 2004; 74:200–204.
- O'Neill T, Allam J. Anaesthetic considerations and management of the obese patient presenting for bariatric surgery. *Current Anaesthesia & Critical Care*. 2010; 21:16–23.
- Pannacciulli N, Del Parigi A, Chen K, Le DNT, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. *NeuroImage*. 2006; 31:1419–1425. [PubMed: 16545583]
- Pannacciulli N, Le DS, Chen K, Reiman EM, Krakoff J. Relationships between plasma leptin concentrations and human brain structure: A voxel-based morphometric study. *Neuroscience Letters*. 2007; 412:248–253. [PubMed: 17123711]
- Plum L, Ahmed L, Febres G, Bessler M, Inabnet W, Kunreuther E, McMahon DJ, Korner J. Comparison of glucostatic parameters after hypocaloric diet or bariatric surgery and equivalent weight loss. *Obesity*. 2011; 19(11):2149–2157. [PubMed: 21593800]
- Profenno LA, Porsteinsson AP, Faraone SV. Meta-Analysis of Alzheimer's Disease Risk with Obesity, Diabetes, and Related Disorders. *Biological Psychiatry*. 2010; 67:505–512. [PubMed: 19358976]
- Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, et al. Brain structure and obesity. *Human Brain Mapping*. 2010; 31:353–364. [PubMed: 19662657]
- Sabia S, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study. *American Journal of Clinical Nutrition*. 2009; 89(2):601–607. [PubMed: 19073790]
- Scharf MT, Ahima RS. Gut peptides and other regulators in obesity. *Seminars in Liver Disease*. 2004; 24:335–347. [PubMed: 15605302]
- Silverstein JH, Steinmetz J, Reichenberg A, Harvey PD, Rasmussen LS. Postoperative cognitive dysfunction in patients with preoperative cognitive impairment: which domains are most vulnerable? *Anesthesiology*. 2007; 106(3):431–435. [PubMed: 17325500]
- Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjöström CD, Sullivan M, Wedel H. Swedish Obese Subjects Study Scientific Group. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med*. 2004; 351(26):2683–2693. [PubMed: 15616203]
- Smith E, Hay P, Campbell L, Troller JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obesity Reviews*. 2011; 12:740–755. [PubMed: 21991597]
- Spitznagel M, Benitez A, Potter V, Alexander T, Glickman E, Gunstad J. Serum ghrelin is inversely associated with cognitive function in a sample of non-demented elderly. *Psychiatry and Clinical Neurosciences*. 2010
- Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul R, Cohen R, Gunstad J. Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity*. 2011; 19:500–504. [PubMed: 21183934]
- Stanek-Sellbom KM, Gunstad J. Cognitive function and decline in obesity. *Journal of Alzheimer's Disease*. (in press).
- Stanek, K.; Smith, J.; Gunstad, J. Structural and functional neuroimaging in obesity. In: Cohen, RA.; Sweet, LH., editors. *Brain imaging in behavioral medicine and clinical neuroscience*. New York: Springer; 2011. p. 193-200.
- Sweat V, Starr V, Bruehl H, Arentoft A, Tirsi A, Javier E, et al. C-reactive protein is linked to lower cognitive performance in overweight and obese women. *Inflammation*. 2008; 31:198–207. [PubMed: 18347963]
- Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, et al. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity*. 2008; 16:119–124. [PubMed: 18223623]
- van Dijk SJ, Feskens EJM, Heidema AG, Bos MB, van de Rest O, et al. Plasma protein profiling reveals protein clusters related to BMI and insulin levels in middle-aged overweight subjects. *PLoS ONE*. 2010; 5(12):e14422. [PubMed: 21203453]
- Vázquez LA, Pazos F, Berrazueta JR, Fernández-Escalante C, García-Unzueta MT, Freijanes J, Amado JA. Effects of changes in body weight and insulin resistance on inflammation and

- endothelial function in morbid obesity after bariatric surgery. *J Clin Endocrinol Metab.* 2005; 90(1):316–322. [PubMed: 15507518]
- Volkow ND, Wang GJ, Telang F, Fowler JS, Goldstein RZ, Alia-Klein N, et al. Inverse association between BMI and prefrontal metabolic activity in healthy adults. *Obesity.* 2009; 17:60–65. [PubMed: 18948965]
- Walther K, Birdsill AC, Glisky EL, Ryan L. Structural brain differences and cognitive functioning related to body mass index in older females. *Human Brain Mapping.* 2009
- Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. The effect of body mass index on global brain volume in middle-aged adults: a cross sectional study. *BMC Neurology.* 2005; 5:23. [PubMed: 16321166]
- West NA, Haan MN. Body adiposity in late life and risk of dementia or cognitive impairment in a longitudinal community-based study. *J Gerontol A Biol Sci Med Sci.* 2009; 64(1):103–109. [PubMed: 19168781]
- Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ.* 2005; 330(7504): 1360. [PubMed: 15863436]
- Whitmer RA, Gunderson EP, Quesenberry CP, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Current Alzheimer Research.* 2007; 4:103–109. [PubMed: 17430231]
- Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology.* 2008; 71(14):1057–1064. [PubMed: 18367704]
- Wolf PA, Beiser A, Elias MF, Au R, Vasan RS, Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. *Current Alzheimer Research.* 2007; 4(2):111–116. [PubMed: 17430232]

Highlights

- Obesity is independently associated with conditions like Alzheimer's disease and vascular dementia
- Obesity is also related to cognitive dysfunction prior to the onset of these conditions
- Bariatric surgery is associated with improved cognitive function in obese adults