HHS Public Access

Author manuscript

Behav Brain Res. Author manuscript; available in PMC 2016 February 01.

Published in final edited form as:

Behav Brain Res. 2015 February 1; 278: 342–347. doi:10.1016/j.bbr.2014.10.010.

Brain structure and cognitive correlates of body mass index in healthy older adults

Jacob D. Bolzenius[a], **David H. Laidlaw**[b], **Ryan P. Cabeen**[b], **Thomas E. Conturo**[c], **Amanda R. McMichael**[c], **Elizabeth M. Lane**[d], **Jodi M. Heaps**[a], **Lauren E. Salminen**[a], **Laurie M. Baker**[a], **Staci E. Scott**[a], **Sarah A. Cooley**[a], **John Gunstad**[e], and **Robert H. Paul**[a]

[a]University of Missouri – Saint Louis, One University Boulevard, Stadler Hall 443, Saint Louis, MO 63121, United States

[b]Brown University, Computer Science Department, 115 Waterman St., 4th Floor, Providence, RI 02912, United States

[c]Washington University School of Medicine, Mallinckrodt Institute of Radiology, 510 S. Kingshighway, Saint Louis, MO 63110, United States

[d]Vanderbilt University Medical Center, 1211 Medical Center Drive, Nashville, TN 37232, United States

[e]Kent State University, Department of Psychology, 221 Kent Hall Addition, Kent, OH 44242, United States

Abstract

Obesity, commonly measured with body mass index (BMI), is associated with numerous deleterious health conditions including alterations in brain integrity related to advanced age. Prior research has suggested that white matter integrity observed using diffusion tensor imaging (DTI) is altered in relation to high BMI, but the integrity of specific white matter tracts remains poorly understood. Additionally, no studies have examined white matter tract integrity in conjunction with neuropsychological evaluation associated with BMI among older adults. The present study examined white matter tract integrity using DTI and cognitive performance associated with BMI in 62 healthy older adults (20 males, 42 females) aged 51 to 81. Results revealed that elevated BMI was associated with lower fractional anisotropy (FA) in the uncinate fasciculus, though there was no evidence of an age by BMI interaction relating to FA in this tract. No relationships were observed between BMI and other white matter tracts or cognition after controlling for demographic variables. Findings suggest that elevated BMI is associated with lower structural integrity in a brain region connecting frontal and temporal lobes and this alteration precedes cognitive dysfunction. Future studies should examine biological mechanisms that mediate the

Corresponding Author: +1(636) 541-1249, Fax: (314) 516-5392, jdbdgf@umsl.edu.

Disclosure Statement

The authors declare that they have no conflict of interest.

relationships between BMI and white matter tract integrity, as well as the evolution of these abnormalities utilizing longitudinal designs.

Keywords

BMI; Tractography; DTI; Cognition; White Matter; Aging

1. Introduction

Obesity has become an increasingly prevalent health concern in recent decades, especially in the United States and other Western cultures (Baskin, Ard, Franklin, & Allison, 2005; Flegal, Carroll, Ogden, & Curtin, 2010). Recent estimates indicate that nearly one third of adults in the United States are classified as obese (Flegal et al., 2010). High body weight, commonly quantified by body mass index (BMI), is associated with increased risk for chronic health conditions such as diabetes, cardiovascular disease, and late life dementia (Malnick & Knobler, 2006; Whitmer et al., 2008). If uncorrected, these obesity-related consequences can contribute to decreased quality of life, increased cost of health care, and increased mortality (Sturm, 2002).

Elevated BMI has also been associated with alterations in brain structure and function. A recent meta-analysis suggested that high BMI is related to poor cognitive performance, especially in domains of executive function, processing speed, and memory (van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Other studies have demonstrated poor cognitive performance in relation to high BMI after controlling for demographics and cardiovascular comorbidities (Cournot et al., 2006; Gunstad et al., 2007; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009). In addition, neuroimaging methodologies incorporating structural magnetic resonance imaging (MRI) have reported smaller volumes of gray and white matter in obese individuals compared to normal-weight individuals, especially in frontal and temporal structures (Gunstad et al., 2008; Ho et al., 2011; Raji et al., 2010; Ward et al., 2005). Though these volumetric approaches are valuable for assessing the amount of regional tissue composition in the brain, they are unable to provide information regarding the microstructural integrity of brain tissue.

Diffusion tensor imaging (DTI) provides detail regarding the integrity of neural microstructure in the brain. The advantage of DTI over other neuroimaging sequences is the opportunity to quantify microstructural characteristics of white matter not captured by standard magnetic resonance imaging (Basser & Pierpaoli, 1996). Several studies have demonstrated that the integrity of white matter is adversely affected in individuals with high BMI (Bettcher et al., 2013; Stanek et al., 2011; Xu, Li, Lin, Sinha, & Potenza, 2011). White matter regions such as the corpus callosum, cingulate portion of the cingulum bundle, and fornix are shown to exhibit lower fractional anisotropy (FA) associated with high BMI, indicating that the directionality of water diffusion within these areas is reduced in individuals with elevated BMI (Bettcher et al., 2013; Xu et al., 2011; Verstynen et al., 2012). Few studies, however, have examined BMI as it relates to FA in white matter tracts connecting to frontal and temporal lobes given volumetric evidence for this relationship.

Assessment of these tracts may provide insight into early disruptions in white matter microstructure that lead to cortical atrophy and cognitive dysfunction associated with high BMI.

While many studies suggest that high BMI relates to lower white matter integrity and cognitive performance (Gunstad et al., 2006; Gunstad et al., 2007; Sabia et al., 2009; Stanek et al., 2011), few studies have examined these measures in a healthy older adult sample. Evidence suggests that elevated body mass may have a compounding effect on the cascade of biological process related to aging, which may be a key factor related to aging brain variability (Doherty, 2003). Activation of age-related physiological processes, including oxidative stress, vascular inflammation, and endothelial cell dysfunction, may be partially modified by obesity, potentially resulting in increased risk of ischemic stroke and white matter damage (Malnick & Knobler, 2006; Sierra, Coca, & Schiffrin, 2011; Ungvari et al., 2010). Increased quantities of adipocytes seen in obese individuals may exacerbate the cellular inflammatory response, which have a detrimental impact on the cellular integrity of brain tissue, particularly oligodendrocytes that comprise white matter (Griffin, 2006; Roth, Ramírez, Alarcón, & Von Bernhardi, 2005). Some studies have demonstrated an interactive effect of advanced age and high BMI affecting white matter integrity (Stanek et al., 2011), yet many of these studies have focused exclusively on corpus callosum integrity rather than inclusion of cortical association tracts (Mueller et al., 2011; Stanek et al., 2011). Investigating the integrity of these tracts in relation to high BMI is important for identifying disruption to white matter microstructure that may contribute to later cognitive dysfunction.

In the present study we examined FA in the superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), cingulate portion of the cingulum bundle, and posterior sections of the corpus callosum associated with BMI. We also investigated the impact of high BMI on cognitive performance on tests of executive function, processing speed, and memory, which represent cognitive domains associated with the specific tracts of interest (Fujie et al., 2008; Turken et al., 2008; Voineskos et al., 2012). We hypothesized that while age would relate to DTI and cognitive measures, elevated BMI would be independently associated with lower white matter tract integrity and cognitive performance.

2. Method

2.1 Participants

A total of 62 individuals between the ages of 51 and 81 were included in the study. Participants were recruited from the local community in addition to the Research Participant Registry of the Washington University Institute of Clinical and Translational Sciences. Demographics and health history were obtained as part of cognitive assessment procedures within one month of MRI acquisition. All participants were required to be fluent English speakers to participate in the study protocol. Individuals with a self-reported history of medical conditions with potential to impact cognitive function (e.g., thyroid disease) were excluded. Also, individuals with a history of neurological disease (e.g., dementia, multiple sclerosis, Parkinson's disease), diabetes, significant head injury (defined as loss of consciousness greater than five minutes), alcohol or drug abuse, or MRI contraindication (e.g., claustrophobia) were not considered for inclusion. Individuals were excluded if they

reported a current diagnosis of a DSM Axis I psychiatric condition (e.g., schizophrenia) with the exception of treated depression. The Mini-Mental State Examination (MMSE) was used to screen for current symptoms of dementia, excluding individuals with scores below 24. Trained experimenters measured each individual's height and weight. All study participants provided informed consent and were provided compensation for their participation in the study. Approval was obtained from the local university Institutional Review Boards and all participants provided informed consent according to Institutional Review Board guidelines for participation in all study procedures.

2.2 Neuroimaging Acquisition

MRI scan acquisitions were obtained using a head-only Magnetom Allegra 3T MRI scanner located at Washington University in St. Louis. During the duration of data acquisition, all hardware, software, acquisition protocols, and pulse sequences remained unchanged to ensure quality assurance of neuroimaging data. High-performance gradients with a maximum strength of 40 mT/m in a 100-microsecond rise time and maximum slew rate of 400 T/m/s (simultaneously on all 3 axes) were used to limit scan times. Every scan session was initiated by a scout scan surveying three orthogonal planes to ensure correct head position. Structural MRI data were obtained utilizing T1-weighted magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence, T2-weighted turbo spin echo (TSE), and T2-weighted fluid-attenuated inversion recovery (FLAIR). An initial pilot sample from the same parent study was used to establish slice coverage and field of view parameters. Total scan time was limited to less than one hour.

2.3 DTI Acquisition and Analysis

To obtain diffusion weighted images, a custom single-shot multislice echo-planar tensor-encoded pulse sequence was used, with 31 non-collinear diffusion gradient directions comprising the 24 main direction used for data processing (diffusion weighting of b = 996 s/mm^2) and 5 baseline I_0 acquisition sequences (b = 0 s/mm^2). To ensure whole brain coverage, acquisition parameters (TE = 86.2 ms, TR = 7.82 s) were optimized across 64 contiguous 2.0 mm slices for each contrast. Additional imaging parameters included a 128 × 128 acquisition matrix with 256 × 256 mm field of view (isotropic 2.0 × 2.0 × 2.0 mm voxels). Scan data were averaged with two scan repeats (total of 72 acquisitions). Raw (k-space) data were saved, stored, then reconstructed floating-point diffusion weighted images using a custom method of image reconstruction. Each of the participants' diffusion weighted images and diffusion-encoding vectors were registered via affine registration to the first I_0 volume with the mutual information metric of FSL FLIRT to correct for motion in the scanner and eddy current artifacts (Jenkinson, Bannister, Brady, & Smith, 2002). Brain tissue was extracted with the FSL Brain Extraction Tool. Diffusion tensors and their associated FA were estimated using linear least squares. To identify specific white matter tracts, the Johns Hopkins University (JHU) DTI atlas was mapped to each participant through affine registration to the FA image with mutual information (Wakana et al., 2007). The corpus callosum was segmented into five different subsections – of which the two most posterior sections are examined in this study – based on established anatomical connections to distinct cortical areas (Rosas et al., 2010). Tracts of interest (SLF, UF, cingulate, midposterior corpus callosum (mpCC), and posterior corpus callosum (pCC)) were

segmented from whole brain streamline tractography with the principal tensor eigenvector and the following parameters: one random seed per voxel, second-order Runge-Kutta integration, an angle threshold of 35°, an FA termination threshold of 0.15, and a minimum length threshold of 10 mm. For each tract of interest, streamline curves were included if the JHU atlas region contained at least 80% of its arc length. Weighted FA (raw FA weighted by length of streamline; see Correia et al., 2008) for cortical association tracts (i.e. SLF, UF, and cingulate) was recorded and computed from the diffusion tensor and used in statistical analyses.

2.4 Neuropsychological Evaluation

A battery of cognitive tests focusing on domains of executive function, processing speed, and memory was administered to all participants, as these constructs are thought to be most commonly affected in relation to high BMI (van den Berg et al., 2009). Trained research assistants using standardized procedures administered tests.

2.4.1 Executive Function

Trails B from the Trail Making Test (TMT; AITB, 1944), Trial 4 of the Color-Word Interference Test (CWIT) of the Delis-Kaplan Executive Function System (D-KEFS; Delis, 2001), and Letter Number Sequencing (LNS) from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) were administered to assess executive function. Trails B requires participants to draw lines connecting alternating numbers and letters in a sequential order. Trial 4 of the CWIT is an advanced task of response inhibition and set shifting requiring participants to name the color of ink in which a word is printed (i.e. the word “blue” depicted in red ink). A subset of these words are printed within a box, and participants must read the word if contained inside a box but name the ink color if not contained inside a box. LNS requires participants to listen to a string of both letters and numbers, then mentally sequence numbers in order first followed by letters in alphabetical order. The task sequences lengthen as participants answer correctly, and the difficulty of responding correctly rises accordingly. Time to completion was the outcome measure for Trails B and CWIT Trial 4, and total number correct was the outcome measure for LNS.

2.4.2 Processing

Speed Tests administered to assess processing speed included Trails A from the TMT, Trial 1 from the CWIT, and Coding from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998). Trails A requires participants to draw lines that sequentially connect circles numbered 1 through 25 as quickly as possible. Trial 1 of the CWIT requires participants to name patches of ink color as quickly as possible. Coding presents participants with rows of boxes. In the top half of each box is a number, and participants must fill in the bottom half of each box with the corresponding symbol according to a given key. Time to completion served as the outcome measure for Trails A and Trial 1 of the CWIT, and total number of correct responses within 90 seconds served as the outcome measure for Coding.

2.4.3 Memory

Immediate and delayed memory were assessed using subtests of the RBANS. Immediate memory consisted of List Learning and Story Memory subtests, and delayed memory consisted of List Recall and Story Recall. The List Learning subtest presents participants with a list of ten semantically unrelated words, repeated across four separate trials, each trial followed by immediate recall. List Recall occurs approximately 20 minutes after initial presentation, at which time participants are instructed to freely recall as many words as possible in the original list. Story Memory involves a story being presented twice to participants, both followed by immediate recall, followed by Story Recall that requires participants to freely recall the story after a delay of approximately 20 minutes. Number correct served as the outcome measure for each of the RBANS subtests.

2.5 Statistical Analyses

Prior to statistical computation, data were screened for outliers by computing standardized z-scores for all dependent variables. Outliers were identified at $|z| \geq 3$ and removed in a pairwise fashion from analyses. White matter indices were collapsed across hemispheres. Cognitive test raw scores served as outcome variables for neuropsychological evaluation analyses. Statistical significance was determined using a cutoff of $\alpha = .05$.

Primary analyses were calculated in two main steps. First, demographic variables significantly associated with white matter integrity or cognitive performance were identified using Pearson's correlation coefficients (i.e., age, years of education) and independent samples t-tests were used to examine if outcome variables differed between males and females. Next, a series of hierarchical linear regressions were computed among each outcome variable. Demographic variables identified in the preliminary step were entered in the first step of a hierarchical linear regression model, with FA for each tract or cognitive raw score as the dependent variables. In the second step of the regression, BMI was entered to determine its association with outcome measures independent of significant covariates. To test for interactive effects, age and BMI variables were mean-centered and factored to create an interaction term, and these were utilized to test for an interaction between age and BMI on outcome variables exhibiting significant main effects of BMI.

3. Results

See Table 1 for full characterization statistics regarding demographic/health status. Preliminary demographic analyses revealed that age was strongly associated with most cognitive scores ($p < .05$) but not tract FA. Significant associations were observed between FA in the cingulate and sex ($t(59) = 3.703$, $p < .001$) and between FA of the pCC and years of education ($r(53) = .294$, $p < .05$).

After controlling for these associations, regression analyses revealed significant alterations in FA in the UF related to BMI. Specifically, higher BMI was associated with lower FA in the UF ($F(1, 60) = 6.981$, $p = .01$, $\beta = -.323$), which explained 10.4% of the variance. The test for an interaction between age and BMI in FA was not significant ($F(1, 58) = 2.653$, $p \geq .05$), suggesting no interactive effect of age and BMI relating to FA of the UF (Table 2).

No significant associations between BMI and cognitive performance were observed after controlling for the influence of age (Table 3).

4. Discussion

This study provides one of the first examinations of white matter tract integrity and neuropsychological performance in relation to BMI in a healthy older adult sample. Results of initial analyses suggested that age was strongly related to cognitive performance. By contrast, age was not significantly related to tract-based FA in this sample. After controlling for these confounding influences, elevated BMI was associated with lower FA in the UF. Contrary to hypotheses, there was no evidence of an interaction between age and BMI relating to FA in this tract. Additionally, no significant relationships were observed between BMI and cognition after controlling for potential confounds. These results indicate that the integrity of white matter tracts is compromised in older individuals with high BMI in the absence of cognitive dysfunction.

These findings are consistent with results of previous DTI studies exhibiting significant alterations in white matter microstructure associated with elevated BMI (Bettcher et al., 2013; Bolzenius et al., 2013; Stanek et al., 2011; Verstynen et al., 2012; Xu et al., 2011). These results did not reveal an interaction between age and BMI with regard to FA in the UF, despite some studies reporting an age by BMI interaction on FA in white matter tracts (Stanek et al., 2011). Significantly lower FA in the UF associated with high BMI is a novel finding, as very few studies have examined the UF in relation to BMI. The UF connects the orbital gyrus region of the frontal lobe to the anterior temporal lobe, and is shown to be involved in memory performance (Fujie et al., 2008; Sasson et al., 2012). This finding is consistent with prior research revealing lower white matter integrity in the temporal lobe associated with elevated BMI (Bolzenius et al., 2013; Verstynen et al., 2012).

While other studies have suggested that sections of the corpus callosum exhibit lower FA with high BMI (Bettcher et al., 2013; Mueller et al., 2011, Stanek et al., 2011), no associations between BMI and posterior corpus callosum integrity were observed in this study. While the reason for this discrepancy is unclear, Xu et al. (2011) indicated that additional DTI metrics of axial, radial, and mean diffusivity, but not FA, within the corpus callosum are altered in association with elevated BMI. These diffusivity metrics may reveal alterations specific to axonal and myelin integrity that lead to “pseudonormalized” FA values, as FA assesses the overall shape of the diffusion ellipsoid rather than integrity of specific neuronal components (Xu et al., 2011). This hypothesis is supported by a recent spectroscopy study demonstrating that axonal membranes and myelin were compromised in relation to high BMI (Gazdzinski, Kornak, Weiner, & Meyerhoff, 2008). However, future studies are needed to assess DTI diffusivity metrics and evaluate underlying characteristics of neuronal integrity in relation to BMI.

Despite these observed differences in UF integrity, no relationships between BMI and cognition were observed in this study after controlling for age. A recent meta-analysis suggested that a relationship exists between BMI and cognition, particularly in tests of executive function, processing speed, and memory (van den Berg et al., 2009). Other studies

suggest BMI is negatively related to cognition in older adults (Elias et al., 2003; Waldstein & Katzel, 2006). While we did not observe cognitive dysfunction in the present study associated with high BMI and DTI alterations, it is possible that cognitive disruption in the current sample would develop with time, as alterations to white matter microstructure precede cognitive changes (Brickman et al., 2006; Medina et al., 2006). Future longitudinal studies are needed to identify BMI-related alterations in brain integrity and to determine if these alterations persist or exacerbate over time.

The mechanism by which high BMI leads to white matter disruption likely involves multiple mechanisms. Evidence suggests that obesity may modify the severity of vascular aging expression, affecting overall brain health (Ungvari et al., 2010). Researchers theorize that obesity has independent effects on several aging processes, potentially exacerbating age-related disruption of endothelial cell function, hypertension, and development of cerebrovascular disease (Malnick & Knobler, 2006; Sierra, Coca, & Schiffrin, 2011). Higher quantities of adipocytes in higher weight individuals likely have an important role in this physiological cascade leading to altered white matter integrity. Leptin, a key neuromodulator involved in feeding behavior, is released by adipocytes (Harvey, Shanley, O'Malley, & Irving, 2005; Wisse, 2004). It is thought that in obesity, a chronic state of elevated leptin release and insufficient leptin recognition by the brain, the release of pro-inflammatory cytokines regulated by leptin is disrupted (Considine et al., 1996; Harvey et al., 2005; Wisse, 2004). These cytokines have been linked to dystrophic neurite growth, which is shown to trigger synthesis of β-amyloid precursor protein (APP). Consistently heightened feedback between APP and pro-inflammatory interleukin (IL-1 and IL-6) and S100β cytokines leads to alterations in intracellular calcium concentrations, potentially resulting in astrogliosis and apoptosis (Griffin, 2006; Mrak, Sheng, & Griffin, 1996). Together, these changes in cellular physiology have been linked to oligodendrocyte dysfunction and subsequent white matter alterations (Roth et al., 2005), thereby serving as a potential mechanism for altered white matter integrity in this study.

Some important limitations of the current study should be mentioned. The physiological nature of the relationship between elevated BMI and lower FA in the UF was not examined in the present study. Further, the range of BMI values of the current sample may not have been fully representative of the older adult population, given the underrepresentation of individuals in the obese BMI classification (i.e. BMI ≥ 30.0, $n = 7$). This is likely an artifact of study inclusion due to MRI incompatibility, but as a result, the generalizability of current study findings to a population more inclusive of obese individuals is limited. Overall, the healthy nature of this sample may have led to lower expression of medical comorbidities in this study which are suggested to account for a significant portion of the variance in cognitive performance (Elias et al., 2003).

4.1 Conclusions

Overall, this is one of the first studies to combine both DTI measurement and cognitive performance in relation to BMI in healthy older adults. Results indicate that high BMI is related to lower tract integrity but not cognitive performance in this sample. Future studies are needed to investigate the relationship between BMI and brain tissue integrity, and how

this relates to changes in cognitive performance over time. Examination of additional white matter structures, particularly frontal and temporal structures such as the anterior thalamic radiation, forceps minor, and hippocampus, and collecting blood markers of inflammatory factors related to obesity would help clarify these relationships.

Acknowledgements

Study Funding: Supported by National Institutes of Health/National Institute of Neurological Disorders and Stroke grant number R01 NS052470 and R01 NS039538, and National Institutes of Health/National Institute of Mental Health grant R21 MH090494. Recruitment database searches were supported in part by National Institutes of Health/National Center for Research Resources grant UL1 TR000448.

References

Army Individual Test Battery (AITB). Manual of Directions and Scoring. War Department, Adjutant General's Office; Washington, DC: 1944.

Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the United States. Obesity Reviews. 2005; 6(1):5–7. [PubMed: 15655032]

Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. Journal of Magnetic Resonance. Series B. 1996; 111(3):209–19. [PubMed: 8661285]

Bettcher BM, Walsh CM, Watson C, Miller JW, Green R, Patel N, et al. Body mass and white matter integrity: the influence of vascular and inflammatory markers. PloS one. 2013; 8(10):e77741. [PubMed: 24147070]

Bolzenius JD, Laidlaw DH, Cabeen RP, Conturo TE, McMichael AR, Lane EM, et al. Impact of body mass index on neuronal fiber bundle lengths among healthy older adults. Brain Imaging and Behavior. 2013; 7(3):300–6. [PubMed: 23564371]

Brickman AM, Zimmerman ME, Paul RH, Grieve SM, Tate DF, Cohen RA, et al. Regional white matter and neuropsychological functioning across the adult lifespan. Biological Psychiatry. 2006; 60(5):444–53. [PubMed: 16616725]

Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. New England Journal of Medicine. 1996; 334(5):292–5. [PubMed: 8532024]

Correia S, Lee SY, Voorn T, Tate DF, Paul RH, Zhang S, et al. Quantitative tractography metrics of white matter integrity in diffusion-tensor MRI. NeuroImage. 2008; 42(2):568. [PubMed: 18617421]

Cournot M, Marquié JC, Ansiau D, Martinaud C, Fonds H, Ferrières, et al. Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology. 2006; 67:1208–14. [PubMed: 17030754]

Delis, DC. Delis-Kaplan Executive Function System: D-KEFS. Psychological Corporation; Orlando, FL: 2001.

Doherty TJ. Invited review: aging and sarcopenia. Journal of Applied Physiology. 2003; 95(4):1717–27. [PubMed: 12970377]

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. 2003; 27(2):260–8. [PubMed: 12587008]

Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA: The Journal of the American Medical Association. 2010; 303(3):235–41.

Fujie S, Namiki C, Nishi H, Yamada M, Miyata J, Sakata D, et al. The role of the uncinate fasciculus in memory and emotional recognition in amnestic mild cognitive impairment. Dementia and Geriatric Cognitive Disorders. 2008; 26(5):432–9. [PubMed: 18957848]

Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Annals of Neurology. 2008; 63(5):652–7. [PubMed: 18409192]

Griffin WST. Inflammation and neurodegenerative diseases. The American Journal of Clinical Nutrition. 2006; 83(2):470S–4S. [PubMed: 16470015]

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: EWD. 2006; 11(1):e15. [PubMed: 16801734]

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(1):57–61. [PubMed: 17145283]

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, et al. Relationship between body mass index and brain volume in healthy adults. International Journal of Neuroscience. 2008; 118(11):1582–93. [PubMed: 18853335]

Harvey J, Shanley LJ, O'Malley D, Irving AJ. Leptin: a potential cognitive enhancer? Biochemical Society Transactions. 2005; 33(Pt 5):1029–32. [PubMed: 16246038]

Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, et al. The effects of physical activity, education, and body mass index on the aging brain. Human Brain Mapping. 2011; 32(9):1371–82. [PubMed: 20715081]

Jacobs HI, Leritz EC, Williams VJ, Van Boxtel MP, Elst WVD, Jolles J, et al. Association between white matter microstructure, executive functions, and processing speed in older adults: the impact of vascular health. Human Brain Mapping. 2013; 34(1):77–95. [PubMed: 21954054]

Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002; 17(2):825–41. [PubMed: 12377157]

Malnick SDH, Knobler H. The medical complications of obesity. QJM. 2006; 99(9):565–79. [PubMed: 16916862]

Marks BL, Katz LM, Styner M, Smith JK. Aerobic fitness and obesity: relationship to cerebral white matter integrity in the brain of active and sedentary older adults. British Journal of Sports Medicine. 2011; 45(15):1208–15. [PubMed: 20558529]

Medina D, deToledo-Morrell L, Urresta F, Gabrieli JD, Moseley M, Fleischman D, et al. White matter changes in mild cognitive impairment and AD: a diffusion tensor imaging study. Neurobiology of Aging. 2006; 27(5):663–72. [PubMed: 16005548]

Mrak RE, Sheng JG, Griffin WST. Correlation of astrocytic S100 [beta] expression with dystrophic neurites in amyloid plaques of Alzheimer's disease. Journal of Neuropathology & Experimental Neurology. 1996; 55(4):273–9. [PubMed: 8786385]

Mueller K, Anwander A, Möller HE, Horstmann A, Lepsien J, Busse F, et al. Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. PloS One. 2011; 6(4):e18544. [PubMed: 21494606]

Ownby RL. Neuroinflammation and cognitive aging. Current Psychiatry Reports. 2010; 12(1):39–45. [PubMed: 20425309]

Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, et al. Brain structure and obesity. Human Brain Mapping. 2010; 31(3):353–64. [PubMed: 19662657]

Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity. Journal of Clinical and Experimental Neuropsychology. 1998; 20(3):310–9. [PubMed: 9845158]

Rosas HD, Lee SY, Bender AC, Zaleta AK, Vangel M, Yu P, et al. Altered white matter microstructure in the corpus callosum in Huntington's disease: implications for cortical "disconnection". Neuroimage. 2010; 49(4):2995–3004. [PubMed: 19850138]

Roth AD, Ramírez G, Alarcón R, Von Bernhardi R. Oligodendrocytes damage in Alzheimer's disease: beta amyloid toxicity and inflammation. Biological Research. 2005; 38(4):381–387. [PubMed: 16579521]

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. The American Journal of Clinical Nutrition. 2009; 89(2):601–7. [PubMed: 19073790]

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y. Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. Brain Structure and Function. 2012; 217(2):503–15. [PubMed: 21909706]

Sierra C, Coca A, Schiffrin EL. Vascular mechanisms in the pathogenesis of stroke. Current Hypertension Reports. 2011; 13:200–7. [PubMed: 21331606]

Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, et al. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity. 2011; 19(3): 500–4. [PubMed: 21183934]

Sturm R. The effects of obesity, smoking, and drinking on medical problems and costs. Health Affairs. 2002; 21(2):245–53. [PubMed: 11900166]

Turken AU, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD. Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage. 2008; 42(2):1032–44. [PubMed: 18602840]

Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csiszar A. Mechanisms of vascular aging: new perspectives. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2010; 65A(10):1028–41.

van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2009; 1792(5):470–81.

Verstynen TD, Weinstein AM, Schneider WW, Jakicic JM, Rofey DL, Erickson KI. Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. Psychosomatic Medicine. 2012; 74(7):682–90. [PubMed: 22879428]

Voineskos AN, Rajji TK, Lobaugh NJ, Miranda D, Shenton ME, Kennedy JL, et al. Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. Neurobiology of Aging. 2012; 33(1):21–34. [PubMed: 20363050]

Wakana S, Caprihan A, Panzenboeck MM, Fallon JH, Perry M, Gollub RL, et al. Reproducibility of quantitative tractography methods applied to cerebral white matter. Neuroimage. 2007; 36(3):630–44. [PubMed: 17481925]

Waldstein SR, Katzel LI. Interactive relations of central versus total obesity and blood pressure to cognitive function. International Journal of Obesity. 2006; 30:201–7. [PubMed: 16231030]

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(1): 23. [PubMed: 16321166]

Wechsler, D. WAIS-III Administration and Scoring Manual. The Psychological Corporation; San Antonio, TX: 1997.

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):1057–164. [PubMed: 18367704]

Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. Journal of the American Society of Nephrology. 2004; 15(11):2792–800. [PubMed: 15504932]

Xu J, Li Y, Lin H, Sinha R, Potenza MN. Body mass index correlates negatively with white matter integrity in the fornix and corpus callosum: a diffusion tensor imaging study. Human Brain Mapping. 2011; 34(5):1044–52. [PubMed: 22139809]

Highlights

- We examine white matter tracts and cognitive performance with BMI in old age
- High BMI was related to low FA in the uncinate fasciculus
- No relationships between BMI and cognition were observed
- BMI-related white matter alterations precede cognitive dysfunction

Table 1

Study sample characteristics

N=62 (20 males, 42 females)				
Variable	**Mean**	**SD**	**Min**	**Max**
Age, years	62.40	8.44	51	81
Education, years	15.23	2.49	12	20
BMI	25.74	3.72	18.60	33.45
MMSE	28.7	1.42	24	30
	Cases (n)			
BMI				
Normal	24			
Overweight	31			
Obese	7			

Table 2

Hierarchical regression results for FA by tract

Superior Longitudinal Fasciculus	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI	−.049	.002	.002	.143	.707
Uncinate Fasciculus	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI*	−.323	.104	.104	6.981	.010
Cingulate	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]Sex	−.439	.189	.189	13.714	<.001
[2]BMI	−.051	.191	.002	.187	.667
Midposterior Corpus Callosum	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]BMI	−.174	.030	.030	1.584	.214
Posterior Corpus Callosum	β	R^2	ΔR^2	ΔF	Sig. ΔF
[1]Education	.292	.086	.086	4.809	.033
[2]BMI	−.066	.091	.005	.241	.626

Superscript denotes the regression step number into which each variable was entered

*BMI significant at $p < .05$

Table 3

Hierarchical regression results for cognitive test scores

Executive Function		β	R^2	ΔR^2	ΔF	Sig. ΔF
Trails B	[1]Age	.318	.095	.095	5.911	018
	[2]BMI	−.070	.100	.005	.296	.588
DKEFS#4	[1]Age	.339	.127	.127	8.127	.006
	[2]BMI	.148	.148	.021	1.396	.243
Letter Number	[1]Age	−.208	.048	.048	2.894	.094
	[2]BMI	−.079	.054	.006	.371	.545
Processing Speed		β	R^2	ΔR^2	ΔF	Sig. ΔF
Coding	[1]Age	−.500	.249	.249	19.536	<.001
	[2]BMI	.009	.249	.000	.006	.941
Trails A	[1]Age	.354	.123	.123	8.136	.006
	[2]BMI	−.032	.124	.001	.064	.801
DKEFS #1	[1]Age	.477	.241	.241	18.466	<.001
	[2]BMI	.097	.251	.010	.692	.409
Memory		β	R^2	ΔR^2	ΔF	Sig. ΔF
List Learning	[1]Age	−.131	.118	.118	3.883	.026
	[1]Sex	.286				
	[2]BMI	−.039	.120	.002	.094	.760
Story Memory	[1]BMI	.045	.002	.002	.118	.732
List Recall	[1]BMI	−.024	.001	.001	.035	.852
Story Recall	[1]BMI	.040	.002	.002	.094	.760

Superscript denotes the regression step number into which each variable was entered