HHS Public Access

Author manuscript

Ageing Res Rev. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Ageing Res Rev. 2015 March ; 20: 86–97. doi:10.1016/j.arr.2014.03.007.

Does the brain shrink as the waist expands?

Auriel A. Willette[1] and **Dimitrios Kapogiannis**[1,*]

[1]Laboratory of Neurosciences, National Institute on Aging, 3001 S. Hanover St, NM531, Baltimore, MD, 21225, U.S.A

Abstract

Recent studies suggest that being overweight or obese is related to worse cognitive performance, particularly executive function. Obesity may also increase the risk of Alzheimer's disease. Consequently, there has been increasing interest in whether adiposity is related to gray or white matter (GM, WM) atrophy. In this review, we identified and critically evaluated studies assessing obesity and GM or WM volumes either globally or in specific regions of interest (ROIs). Across all ages, higher adiposity was consistently associated with frontal GM atrophy, particularly in prefrontal cortex. In children and adults < 40 years of age, most studies found no relationship between adiposity and occipital or parietal GM volumes, whereas findings for temporal lobe were mixed. In middle-aged and aged adults, a majority of studies found that higher adiposity is associated with parietal and temporal GM atrophy, whereas results for precuneus, posterior cingulate, and hippocampus were mixed. Higher adiposity had no clear association with global or regional WM in any age group. We conclude that higher adiposity may be associated with frontal GM atrophy across all ages and parietal and temporal GM atrophy in middle and old age.

Keywords

Obesity; adiposity; brain atrophy; gray matter; white matter; body mass index; MRI; MRS; frontal lobe; cognition

1.0. Introduction

One-third of adults and 17% of children and adolescents in the United States are currently obese, where the prevalence of obesity continues to rise among boys and men and remains high for girls and women (Ogden et al., 2012a, b). It has been well established that obesity increases the risk for cardiovascular disease (Whitlock et al., 2009; Friedemann et al., 2012), type 2 diabetes (Haslam and James, 2005), various cancers (Vucenik and Stains, 2012), and overall mortality in children and adolescents (Flegal et al., 2007) as well as adults (Whitlock et al., 2009). Several studies have shown a negative association between anthropometric measures of obesity, such as body weight, body mass index (BMI), or waist circumference

*Please, send correspondence to: Dimitrios Kapogiannis, M.D., Laboratory of Neurosciences, National Institute on Aging, 3001 S. Hanover St, NM531, Baltimore, MD, 21225, U.S.A.; Phone: +1-410-350-3953; Fax: +1-410-350-7308; kapogiannisd@mail.nih.gov.

(WC), and cognitive performance (Elias et al., 2012), in particular worse executive function (Gunstad et al., 2007). However, other studies have found no such association with cognition (van Boxtel et al., 2007) or even small positive associations (Kuo et al., 2006).

Regarding children and adolescents, recent reviews (Liang et al., 2013; Reinert et al., 2013) indicate that higher adiposity (i.e., being overweight or obese) is consistently associated with poorer executive function, inhibitory control, and attention, as well as worse academic achievement. It has been speculated that these deficits reflect dysregulation of brain networks mediating these higher cognitive functions, as well as regulating appetitive drive. These networks include medial parietal areas, insula, hippocampus, prefrontal cortex (PFC), and cingulate cortex (Del Parigi et al., 2002; Martin et al., 2010; Mehta et al., 2012; Brooks et al., 2013b). By contrast, only half of the studies in that literature find an association with worse learning and memory performance.

Toward the other end of the lifespan, increased midlife adiposity has been linked to worse cognitive performance and higher risk for Alzheimer's disease (AD) (Elias et al., 2012), although sex effects and other factors appear to modify this risk. For example, for women but not men at age 70, every 1-point increase in BMI corresponded to a 36% increase in AD risk over a 10 to 18 years time span (Gustafson et al., 2003). A recent meta-analysis (Beydoun et al., 2008) found that increased AD risk was attributable to obesity (BMI > 30) but not being overweight (BMI 25-30), although Huang and Yu reanalyzed the same data and contest the distinction (2008). Obesity may increase AD risk not as an isolated factor, but as a component of the Metabolic Syndrome, which refers to the constellation of impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol, and is progressively being recognized as a major mechanism underlying age-related cognitive decline and development of AD (Frisardi et al., 2010; Craft et al., 2012).

Based in part on the association between excess adiposity and AD risk, Gustafson and colleagues published one of the first papers examining excess adiposity and lobar brain volume (Gustafson et al., 2004). Specifically, in Swedish women, higher BMI measured at some point between midlife and old age predicted a small but significantly higher likelihood of atrophy (OR 1.11-1.14) in temporal gray matter (GM) volume based on Likert scale ratings by expert radiologists. No relationship was found for frontal, parietal, or occipital lobes. Since this seminal report, many cross-sectional and a few longitudinal studies have examined anthropometric or quantitative measures of adiposity and brain structure using magnetic resonance imaging (MRI), microstructure using diffusion tensor imaging (DTI), and various magnetic resonance spectroscopy (MRS) techniques. Akin to the obesity literature in younger cohorts, these studies have also focused on hippocampus, PFC, precuneus and posterior cingulate cortex, and to a lesser extent insula, due in part to their relationship with late life cognitive decline and atrophy seen in AD (Whitwell et al., 2007; McDonald et al., 2009; Risacher et al., 2010).

Despite the remarkable number of recent publications addressing adiposity in relation to brain atrophy in these areas and others, there has been no systematic, critical review of this literature in younger or older age groups. It is important to distinguish between these age

groups because the pathophysiology underlying excess adiposity and brain may differ across the lifespan. For example, aging is related to low-grade chronic expression of peripheral proinflammatory cytokines and chemokines, in part due to increased abdominal adiposity (Michaud et al., 2013). Peripheral proinflammatory cytokines and chemokines predict brain atrophy cross-sectionally in aged rhesus monkeys (Willette et al., 2010) and aged humans (Satizabal et al., 2012), as well as longitudinally in middle-aged adults at risk for AD (Willette et al., 2013a). Furthermore, comorbidities such as insulin resistance (IR), cardiovascular disease, hypertension, and hyperlipidemia preferentially affect older age groups (Michaud et al., 2013). Finally, the loss of lean muscle mass with ageing (i.e., sarcopenia) complicates direct age group comparisons based on BMI. Indeed, BMI is the most common adiposity index used in this literature, and this metric does not distinguish between non-fat mass and fat mass.

This review first focuses on defining brain atrophy and various measures of adiposity. After detailing search criteria and the analytic strategy, we summarize the literature in younger and then older cohorts, followed by a discussion of those studies and then potential underlying mechanisms and interventions.

1.1. Defining atrophy

In the context of pathology, atrophy is characterized by reduction of brain tissue volume and cortical thickness over time or compared to normal brains, due to various combinations of reduced synaptic density, dendritic arborization, corpuscular volume of neurons and glia, and cell death (Donkelaar, 2011). Given the paucity of neuroimaging studies longitudinally assessing brain volume and adiposity (Haltia et al., 2007; Debette et al., 2011; Bobb et al., 2012; Driscoll et al., 2012), the term “atrophy” has been mainly used to characterize lower GM or white matter (WM) volumes relative to various control groups (Yaffe et al., 2004). This usage presupposes established norms for regional GM and WM and that the various control groups represent the population distribution. This assumption becomes problematic for smaller studies, or newer methodologies where norms have not been well established (e.g., DTI, MRS). In neuroimaging studies, all available methodologies for tissue segmentation used to generate GM and WM maps remove voxels containing CSF (albeit with variable success). Therefore, reported associations refer to brain tissue volume free of CSF.

1.2. Defining adiposity using BMI

Various metrics have been devised to reflect central adiposity (i.e., fat tissue surrounding viscera in the peritoneum), subcutaneous adiposity (i.e., fat tissue underlying the skin), or total body adiposity. Body mass index, or BMI, is a simple anthropometric surrogate of total body fat and is calculated by dividing kilograms of body weight by squared meters in height. The World Health Organization has created standardized BMI groups (2000) including lean (18.5-24.99), overweight (25-29.99), obese class I and II or obese (30-39.99), and obese class III or morbidly obese (≥40.00). As detailed in many other reports (e.g., Dalton et al., 2003), BMI does not distinguish between visceral and subcutaneous fat, as well as non-fat mass, and has major limitations as a disease biomarker, since it can be affected by non-fat mass loss, which typically occurs in old age (i.e., sarcopenia). Waist circumference (WC) is

assessed by circumference around the umbilicus after breath release, while waist-to-hip ratio (WHR) utilizes both waist and hip circumference measurements. These measures preferentially reflect central adiposity and are more accurate predictors of type 2 diabetes and cardiovascular disease than BMI (Luchsinger et al., 2012). Given their greater relevance to metabolism, WC and WHR may also better reflect associations between adiposity and brain health across the lifespan.

2.0. Methods

2.1. Search criteria

Articles from 2004 to 2013 were reviewed. Searches prior to 2004 did not return any results that met criteria. The last search occurred in August 2013. Searches were performed in PubMed/Medline using combinations of the following terms: brain; atrophy; gray matter; white matter; obesity; fat; high fat diet; neurons; brain volume; magnetic resonance imaging; magnetic resonance spectroscopy; body mass index; waist circumference; waist to hip ratio; cortical density; body weight; histopathology. Human studies were included if they had: 1) been published in English; 2) included at least one brain scan; 3) examined global, lobar, regional brain volumes or measured metabolites that reflect brain tissue integrity using MRS; 4) included at least one anthropometric or quantitative assessment of central or global adiposity, such as body weight, BMI, WC or abdominal girth, WHR, visceral adipose tissue (VAT) and/or subcutaneous adipose tissue (SAT), percentage body fat (% body fat), and similar indices; and 5) focused on the weight spectrum from normal to class III obesity, which did not include studies on being underweight such as anorexia nervosa. An alternative criterion was a genetic predisposition toward obesity, such as Praeder-Willi syndrome (Cassidy, 1997) or risk alleles for the fat mass and obesity associated (FTO) gene (Dina et al., 2007) when combined with an adiposity measure. While important, it was beyond the scope of this review to include articles examining adiposity and fMRI activation, brain metabolism, brain vascular pathology (e.g., white matter hyperintensities), or autopsy studies that only considered brain weight instead of composition.

2.2. Evaluation and Organization of studies

First, we developed a set of criteria to critically evaluate studies for scientific and statistical rigor. Studies were considered optimal if they had: 1) large sample sizes, with balanced sampling of different weight groups, if applicable; 2) indices of adipose tissue (SAT, VAT) over anthropometric measures like BMI; 3) a clear study design, where hypotheses were clearly stated and based on pre-existing literature, the methodology and analytic strategy were rigorous and a priori driven, and the results confirmed at least some of the hypotheses; 4) stringent exclusion criteria including type 2 diabetes and related comorbidities, cardiovascular disease, psychiatric disorders, and central nervous system disorders, all of which may be independently associated with both obesity and brain volume and, therefore, are potential confounders; 5) adjustment for type 1 error; and 6) an intervention, were longitudinal, or otherwise novel.

Studies in children to young adults were evaluated and are presented separately from those in middle-aged to aged age groups. For the young adult or middle-aged to aged groups, we

present findings for lobar GM posteriorly to anteriorly (i.e., from occipital to frontal lobe), as well as four regions of interest (ROI). Finally, findings for global and regional WM are discussed. The four GM ROIs we focus on are: precuneus or posterior cingulate cortex, hippocampus, insula, and any sub-region of PFC. These brain regions were selected because they are AD-sensitive areas (Whitwell et al., 2007; McDonald et al., 2009; Risacher et al., 2010), and the hippocampus, insula, and ventral PFC are also involved in appetitive drive and inhibitory control. Many of these regions are also important for declarative memory and executive function (Del Parigi et al., 2002; Martin et al., 2010; Mehta et al., 2012; Brooks et al., 2013b), processes that are thought to be dysregulated in obese participants.

3. Results

3.1. Adiposity and Brain: Search Results

We found 44 articles that directly or indirectly addressed the possible link between adiposity and brain volume or metabolites reflecting tissue composition. Supplementary Table 1 summarizes the findings of these studies in detail and allows for direct comparisons. The table includes the publication date, sample size, brain modality, neuroimaging modality (structural MRI vs. MRS), whether categorical or continuous measures of adiposity were used, age group, and a color-coded chart indicating if and in what direction adiposity was associated with brain volumes and/or MRS metabolites. DTI findings from 5 studies that will be referenced in the discussion are also included. Table 1 highlights eight methodologically rigorous reports that either typify overall findings in the literature or present noteworthy findings.

BMI was the most common adiposity index in this literature, with 33 of the 44 studies reviewed exclusively using continuous BMI or BMI groups for associations with brain volume indices. WC, WHR, or equivalent measures were used separately or in concert with BMI in 7 of the 44 studies reviewed. Lastly, 3 studies (Anan et al., 2010; Debette et al., 2010; Weise et al., 2013) directly measured adipose tissue in whole or in the separate subcutaneous and peritoneal compartments. Twenty-eight of the 44 studies used an anatomically defined region of interest approach to acquire volumetric measures for lobar volumes and/or the 4 ROIs. Eighteen of the 44 studies used voxel-wise statistics (Ashburner and Friston, 2000). Lastly, 2 of the 44 studies used Likert scale ratings of brain volume to qualitatively assess brain volumes. Most of the 44 studies included age or age and sex as covariates. Furthermore, many reports in older cohorts with large sample sizes assessed models that additionally covaried components of the metabolic syndrome, such as dyslipedemia and hypertension indices.

3.2. Adiposity and Brain Atrophy: Children and Younger Adults (< 40 years of age)

Fifteen studies have examined the association of global or regional brain volumes and adiposity in participants less than 40 years of age (Pannacciulli et al., 2006; Haltia et al., 2007; Miller et al., 2007; Miller et al., 2009; Maayan et al., 2011; Ogura et al., 2011; Brain Development Cooperative Group, 2012; Maudsley et al., 2012; Mueller et al., 2012; Smucny et al., 2012; Ursache et al., 2012; Yokum et al., 2012; Alosco et al., 2013; Melka et al., 2013; Weise et al., 2013). Thirteen of these 15 studies used BMI as a continuous variable or

BMI groups, while one study used a quantitative index of fat mass and non-fat mass (Weise et al., 2013). See Supplemental Table 1 for more details.

Six of these studies were deemed optimal based on our criteria. Weise and colleagues (2013) conducted a study in 76 healthy participants (mean age = 32.1 ± 8.8 years), where they examined fat-free mass index (FFMI) or fat mass index (FMI) and gray matter volume using voxel-wise regression. While higher FMI predicted less GM in superior temporal and prefrontal areas, these effects became non-significant after covarying FFMI; therefore, the authors suggest that overall body mass instead of adiposity may underlie brain associations. The Brain Development Cooperative Group (2012) studied a large cohort of 325 children and adolescents (~70% normal BMI) from 4.5-18 years of age and examined total brain, lobar, and ventricular ROI volumes. They found small to moderate correlations between higher BMI and lower global GM volume and GM volume in occipital, parietal, and temporal but not frontal lobes, whereas higher BMI predicted higher WM volume. In a comparably aged cohort, Alosco and colleagues (2013) used an ROI approach to examine if higher BMI predicted less GM in 120 children and adolescents (mean age = 13.5 ± 2.9 years). Higher BMI was associated with less GM in frontal lobe, as well as a “limbic lobe” ROI that included the hippocampus, parahippocampus, amygdala, cingulate, and cerebellum. Pannacciulli and co-workers (2006) examined regional WM and GM differences between 24 morbidly obese and 36 lean participants (mean age = 32.5 ± 8.5 years). Obese participants had less GM in parietal, temporal, and middle prefrontal areas, but also had more GM in occipital and inferior prefrontal regions, as well as more WM. A more recent study (Yokum et al., 2012) that considered the full BMI range, by including 17 obese, 36 overweight, and 31 lean adolescent females (mean age = 18.4 ± 2.8 years), found no volumetric differences between overweight participants and other groups. However, they did note medium to large effect sizes when comparing obese versus lean, where obese participants had less occipital GM and global WM, but more regional WM in inferior and temporal areas, as well as in rolandic operculum and dorsal striatum. Finally, Haltia et al. (2007) compared 30 obese and 16 lean participants (mean age = 37 ± 16.5 years) at baseline and after a 6-week very low calorie diet in the obese group. At baseline, regional WM volume was higher in obese participants. After the intervention, WM volumes did not significantly differ between the once obese participants who had become lean versus the always-lean participants. No GM differences were noted at either time-point.

3.2.1. Summary of Findings in Children and Younger Adults (< 40 years of age)—Although these studies and the others produce several conflicting or non-replicable findings, some trends are clear. Two of the 4 studies that assessed total brain volume (Ogura et al., 2011; Melka et al., 2013) found negative associations with more adiposity. Three of 5 studies that assessed global GM (Brain Development CooperativeOgura et al., 2011; Group, 2012; Yokum et al., 2012) also found that more adiposity predicted lower volume.

Two of 11 studies that examined occipital lobes reported more (Brain Development Cooperative Group, 2012; Yokum et al., 2012) atrophy associated with more adiposity, but one study showed the opposite association (Pannacciulli et al., 2006). Three of 11 studies that examined parietal lobes also found an association between less atrophy and more adiposity (Brain Development Research Pannacciulli et al., 2006; Ogura et al., 2011; Group,

2012). Of 8 reports examining precuneus or posterior cingulate, only one study by Alosco et al. (2013) shows a relationship between more adiposity and less volume in a 'limbic lobe' incorporating these areas.

Results for temporal lobe GM are mixed (i.e., no clear consensus among reports about the presence and direction of an association). Three of the 6 optimal studies to examine temporal lobes (Pannacciulli et al., 2006; Brain Development Cooperative Group, 2012; Weise et al., 2013) and 2 of 3 other studies to examine temporal lobes (Mueller et al., 2011; Ogura et al., 2011) reported more atrophy with adiposity. Furthermore, only 2 of 9 studies that used a hippocampus ROI (Mueller et al., 2012; Alosco et al., 2013) found such an association between more adiposity and lower volumes. These findings parallel the mixed results noted between obesity and learning and memory (Liang et al., 2013). Similarly, only 3 of 7 reports examining the insula showed an association between more atrophy and either higher BMI or more fat mass (Pannacciulli et al., 2006; Smucny et al., 2012; Weise et al., 2013).

Five of 11 studies examining frontal lobes (Pannacciulli et al., 2006; Ogura et al., 2011; Smucny et al., 2012; Alosco et al., 2013; Weise et al., 2013) noted an association between higher BMI and lower GM, also suggesting mixed results. Interestingly, 6 of 9 reports specifically assessing PFC (Pannacciulli et al., 2006; Maayan et al., 2011; Ogura et al., 2011; Smucny et al., 2012; Ursache et al., 2012; Weise et al., 2013) found that higher BMI or fat mass predicted less GM volume. Furthermore, Maayan and colleagues (2011), found that obese participants performed markedly worse than lean controls on executive tasks, particularly on a Stroop task, and linked lower frontal volumes with worse executive performance. These findings may reflect the generally consistent relationship between more adiposity and worse executive performance in children and adolescents (Liang et al., 2013).

Finally, 4 of 7 reports examining global or regional WM (Pannacciulli et al., 2006; Haltia et al., 2007; Brain Development Cooperative Group, 2012; Yokum et al., 2012) found that more WM was related to more adiposity, whereas 2 of 7 reports examining global or regional WM (Ogura et al., 2011; Yokum et al., 2012) found that more adiposity was associated with less WM volume. Similar studies examining WM microstructure using DTI clarify these findings and will be discussed later in the review.

3.3. Adiposity and Brain Atrophy: Middle-Aged to Aged Adults (> 40 years of age)

Many studies have been motivated by the link between obesity and AD risk (Gustafson et al., 2003; Beydoun et al., 2008; Elias et al., 2012) to examine associations between adiposity and regional brain volumes or metabolite concentrations in older cohorts. Twenty-nine studies have been published as of August 2013 in middle-aged (Ward et al., 2005; Gazdzinski et al., 2008; Gunstad et al., 2008; Taki et al., 2008; Bruehl et al., 2009; Debette et al., 2010; Debette et al., 2011; Gonzales et al., 2012; Hassenstab et al., 2012; Haley et al., 2013; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013) or aged participants (Gustafson et al., 2004; Jagust et al., 2005; Soreca et al., 2009; Anan et al., 2010; Gazdzinski et al., 2010; Ho et al., 2010a; Ho et al., 2010b; Raji et al., 2010; Walther et al., 2010; Ho et al., 2011a; Ho et al., 2011b; Widya et al., 2011; Bobb et al., 2012; Driscoll et al., 2012; Brooks et al., 2013a; Metzler-Baddeley et al., 2013). Twenty-one reports used BMI

continuously or used it to define subgroups from lean to morbidly obese categories, whereas the remainder used BMI and one or more other anthropometric indices (5), WHR quartiles (1), SAT and VAT with anthropometric indices (1), or VAT alone (1). Thirteen of these studies met our criteria for being optimal and will be briefly detailed before summarizing findings from the literature. We note that the Cardiovascular Health Study Cognition Study sample used by Raji et al. (2010) was likely used in a subsequent paper (Ho et al., 2011a), after more CHS-CS participants had been added to the analysis. We therefore highlight the Raji paper for its technical merits, but do not include it in our tallies below.

Taki et al. (2008) were the first group to examine BMI and voxel-wise GM associations with a very large cohort of 1,428 middle-aged Japanese participants. In men but not women, higher BMI corresponded to less global GM, as well as less regional GM in inferior and medial temporal, precuneus, anterior cerebellar, prefrontal, and midbrain regions. Unlike most groups using voxel-wise analyses, they also conversely tested if higher BMI corresponded to more GM and found significant clusters in frontal and temporal areas, thalamus, caudate, and posterior cerebellum. Soreca and colleagues (2009) examined baseline BMI and BMI change over a 15-20 year period from 1983-1984 (the time of initial evaluation) to 2005-2006 (when MRI was acquired) in 48 healthy, postmenopausal women (mean age at MRI = 67.1 ± 1.3). BMI increase of over time predicted less global GM volume, whereas no relationship was found for global WM. Walther and co-workers (2010) compared cognitive performance and regional GM and WM using voxel-wise analysis in 53 lean, 22 overweight, and 20 obese older women (mean age = 69.3 ± 9.3 years). Obese participants had worse executive function. Higher BMI corresponded to lower GM in frontal, inferior and medial temporal but not hippocampal, inferior parietal, and occipital areas, as well as cerebellum. Less GM in orbital frontal cortex was associated with poorer executive performance. In addition, BMI predicted less WM volume in all 4 lobes. Widya and coworkers (2011) tested if 140 lean, 256 overweight, and 75 obese, non-demented participants (mean age = 74.3 ± 3.1 years) varied in 7 sub-cortical volumes. Obese versus lean participants had significantly larger bilateral amygdala and left hippocampus, even after type 1 error and covariate correction. Gonzales et al. (2012) used MRS in occipitoparietal junction to examine brain tissue metabolites, cognition, and continuous BMI in 54 middle-aged participants (mean age = 50.7 ± 6.3 years). Higher BMI predicted higher Myoinositol/Creatine, a ratio thought to represent glial tissue content, but not N-Acetyl-Aspartate/Choline (NAA:Choline), a ratio thought to reflect neuronal density. Using structural equation modeling, higher values of Myoinositol/Creatine significantly mediated lower scores on a global cognitive index comprised of several memory, executive function, and general intelligence measures. Gazdzinski and colleagues (2008), in 50 middle-aged adults (mean age = 43.1 ± 8.03 years), in part examined associations between higher BMI and NAA metabolite concentrations in frontal, parietal, temporal, and occipital lobes. After Bonferroni correction, higher BMI was related to less NAA in frontal GM, as well as frontal, temporal, and parietal WM.

Hassenstab and colleagues (2012) examined 17 obese, 19 always-lean participants, and 17 successful weight loss maintainers who were once obese but had been lean for at least 3 years (mean age = 46.6 ± 9.1 years). An ROI approach was used to compare cortical thickness in anterior insula, dorsal anterior cingulate, dorsal PFC, and posterior parietal

cortex including precuneus. Obese versus always-lean participants had less GM in anterior insula, dorsal anterior cingulate, and posterior parietal cortex. Importantly, weight loss maintainers had brain volumes between obese and lean groups and did not significantly differ from either of them. This result suggests that GM atrophy associated with obesity might be ameliorated with weight loss, but prospective interventional studies are needed to confirm this finding.

Several consistent findings have emerged in findings from large cohorts such as the Alzheimer's Disease NeuroImaging Initiative (ADNI) and/or CHS-CS cohorts. Raji et al. (2010) initially compared GM volume between 29 lean, 51 overweight, and 14 obese participants (mean age = 77.2 ± 3.1 years), or across groups using continuous BMI, with tensor-based morphometry (TBM). These participants had remained cognitively stable for at least 5 years after the brain scan, which minimized any potential atrophy due to dementia.Across participants, there were small to moderate correlations between higher BMI and lower GM in medial temporal lobe including hippocampus, frontal lobe, sub-cortical midline areas, anterior cingulate, and subcortical WM volume. Similarly, obese participants showed less GM volume in these regions versus lean participants. Ho and colleagues (Ho et al., 2010b) extended this work by examining not only continuous BMI and TBM in 206 ADNI participants (mean age = 76.2 ± 5 years), but also non-risk (n=78) versus risk (n=128) genotype groups for the FTO gene, which has been associated with increased fat mass and higher obesity prevalence (Dina et al., 2007). Higher BMI predicted lower volume predominantly in deep WM, and frontal and occipital GM, but not hippocampus unlike Raji and colleagues. Higher BMI also predicted higher GM in precuneus. Interestingly, FTO risk carriers showed less GM in occipital and frontal areas that overlapped with areas associated with BMI. Another noteworthy study (Ho et al., 2010a) examined BMI and TBM in 476 Mild Cognitive Impairment (MCI) and 224 AD participants. Each BMI point increase was related to a 0.5-1.5% decrease in WM volume in brainstem and cerebellum, as well as medial PFC, occipital lobe, globus pallidus, cerebellum, and brain stem GM. Relative increases were found in anterior cingulate, precuneus, occipital lobe, and dorsal PFC GM. One of the clusters partially covered the hippocampus, but it is unclear to us whether that coverage genuinely reflects contraction in hippocampus, or is due to the strength of the association between higher BMI and volume contraction within nearby WM.

Finally, the Framingham Heart Study has also produced several reports on obesity and brain. Debette et al. (2010) cross-sectionally assessed 733 middle-aged participants (mean age = 60 ± 9 years) using standardized ROIs of total brain volume and temporal horn volume. Temporal horn volume is a CSF measure that increases as hippocampal volume decreases. Adiposity was measured using BMI, WC, and WHR, as well as SAT and VAT. Higher values for any adiposity measure predicted less TBV, especially VAT. In addition, WHR predicted increased temporal horn volume, suggesting relatively smaller hippocampi. Later, in a larger middle-aged cohort of 1,352 participants (Debette et al., 2011) (mean age = 54 ± 9 years), annual changes from baseline to roughly 7 years later were assessed for TBV, temporal horn volume, and cognition. Across all participants, no relationships between BMI, WHR, or WC were found with annual changes in MRI or cognition, although the authors note an unusually strong cross-sectional association between higher WHR and lower TBV

(10.81 Odds Ratio) in those participants in the top quartile of change in brain or cognitive indices. Finally, Zade et al. (2013) examined TBV, lateral ventricle volume, frontal brain volume, and temporal horn volume in 494 middle-aged participants. The fourth quartile of WHR was used to represent central obesity. Fourth Quartile WHR was significantly associated with lower TBV, frontal volume, higher CSF volume in lateral ventricle and temporal horn, and worse performance on executive function and memory tasks. The inclusion of frontal volume and moderating effects of ApoE Genotype (see Supplemental Table 1) distinguish this analysis from Debette et al. (2010).

3.3.1. Summary of Findings for Middle-Aged to Aged Participants (> 40 years of age)—For participants aged 40 years or older, 5 of the 8 reports that assessed total brain volume (Ward et al., 2005; Gunstad et al., 2008; Debette et al., 2010; Debette et al., 2011; Zade et al., 2013) found a negative association with more adiposity. Three of 6 reports assessing global GM also found that more adiposity predicted less volume (Gunstad et al., 2008; Taki et al., 2008; Soreca et al., 2009). Seven of 14 studies examining occipital lobes report negative associations with more adiposity and brain volume (Ho et al., 2010a; Ho et al., 2010b; Walther et al., 2010; Ho et al., 2011a; Bobb et al., 2012; Karlsson et al., 2013; Kurth et al., 2013). While the Ho and Raji studies consistently noted this association (Ho et al., 2010b; Raji et al., 2010; Ho et al., 2011a; Ho et al., 2011b), studies with larger cohorts (Taki et al., 2008) have not found this relationship. Longitudinal studies examining occipital atrophy and adiposity are also mixed as either not finding (Bobb et al., 2012; Driscoll et al., 2012) or finding (Walther et al., 2010) a link.

Seven of 13 studies examining parietal lobes report negative associations between lower volume and more adiposity (Taki et al., 2008; Ho et al., 2010a; Ho et al., 2010b; Walther et al., 2010; Ho et al., 2011a; Karlsson et al., 2013; Kurth et al., 2013). Three of these 13 studies using ADNI and/or CHS-CS data from different sub-samples simultaneously showed a positive association with posterior-medial parietal volume (Ho et al., 2010a; Ho et al., 2010b; Ho et al., 2011a). Four of 14 studies examining precuneus and posterior cingulate volume (Taki et al., 2008; Driscoll et al., 2012; Hassenstab et al., 2012; Karlsson et al., 2013) report negative associations with more adiposity, whereas 3 of 14 studies examining precuneus and posterior cingulate volume (Ho et al., 2010a; Ho et al., 2010b; Ho et al., 2011a) report positive associations with more adiposity.

Nine of 13 studies examining temporal lobe (Jagust et al., 2005; Taki et al., 2008; Ho et al., 2010a; Ho et al., 2010b; Walther et al., 2010; Ho et al., 2011a; Bobb et al., 2012; Karlsson et al., 2013; Kurth et al., 2013) report negative associations with temporal lobe GM volumes and more adiposity, whereas Taki and colleagues (2008) report a positive relationship. While hippocampus has been the central focus of this literature, only 9 of 19 reports examining hippocampal volume (Jagust et al., 2005; Taki et al., 2008; Bruehl et al., 2009; Anan et al., 2010; Debette et al., 2010; Ho et al., 2010a; Ho et al., 2010b; Ho et al., 2011a; Kurth et al., 2013) found the expected relationship between greater hippocampal atrophy and more adiposity, while Widya et al. (2011) and Bobb et al. (2012) showed that more adiposity predicted less atrophy. Effect sizes or correlations were generally small. Five of 10 reports examining the insula (Ho et al., 2010a; Ho et al., 2010b; Raji et al., 2010; Ho et al., 2011a; Hassenstab et al., 2012; Kurth et al., 2013) found a negative association between

lower GM volume and more adiposity, whereas Taki et al. (2008) showed more adiposity predicted more insula volume.

Ten of 14 studies examining frontal lobe volume found that more adiposity corresponded to greater atrophy (Gazdzinski et al., 2008; Taki et al., 2008; Ho et al., 2010a; Ho et al., 2010b; Walther et al., 2010; Ho et al., 2011a; Brooks et al., 2013b; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013). Two of these 15 studies examining frontal lobe volume showed that higher adiposity predicted higher GM volume (Taki et al., 2008; Ho et al., 2010a). Eleven of 14 studies examining PFC found that more adiposity was related to less GM volume (Taki et al., 2008; Gazdzinski et al., 2010; Ho et al., 2010a; Ho et al., 2010b; Walther et al., 2010; Ho et al., 2011a; Hassenstab et al., 2012; Brooks et al., 2013a; Karlsson et al., 2013; Kurth et al., 2013; Zade et al., 2013). Among the 14 studies assessing PFC, Taki and colleagues (2008) conversely found that more adiposity predicted more GM in PFC.

Finally, 7 of 12 studies examining global or regional WM (Gazdzinski et al., 2008; Ho et al., 2010a; Ho et al., 2010b; Ho et al., 2011a; Driscoll et al., 2012; Karlsson et al., 2013; Metzler-Baddeley et al., 2013) found a negative association between WM volume and more adiposity, while two other groups (Walther et al., 2010; Bobb et al., 2012) noted the opposite relationship.

4.0. Discussion

4.1. Overall Findings

The most consistent finding of studies in both younger and older cohorts is that more adiposity is related to GM atrophy in frontal lobe and PFC. In middle-aged and aged adults, more adiposity is associated with temporal GM atrophy and to a lesser degree parietal GM atrophy. Adiposity is not consistently related to global and regional WM volume in any age group. The different findings for older and younger cohorts may be due to methodology. For instance, almost all of the reviewed studies in younger cohorts used BMI as an index of adiposity instead of WC, WHR, or direct measures of fat mass. Alternatively, younger people may not be affected by certain adiposity-related mechanisms of brain atrophy. For example, vascular disease requires chronicity, and secretion of proinflammatory cytokines from adipose tissue, increases with age (Michaud et al., 2013). Finally, younger brains show greater plasticity in response to stressors and, which may partially or wholly mitigate any deleterious effects of adiposity (McEwen and Morrison, 2013).

For occipital lobe, most studies find no relationship with adiposity regardless of age. The few reported occipital associations come almost exclusively from voxel-wise analyses, often as part of a larger cluster that includes cerebellum. For parietal lobe, adiposity is associated with GM volume in older adults but not children and young adult cohorts. Generally, these associations are found within superior and to a lesser extent inferior parietal areas.

The temporal lobe has received an immense amount of attention for its role in AD (Beydoun et al., 2008) and learning and memory (Liang et al., 2013; Reinert et al., 2013). Reported associations with adiposity are more consistent for the temporal lobe as a whole than for hippocampus. Although no consistent pattern was apparent in young cohorts, almost all

methodologically rigorous studies in older participants showed temporal atrophy with more adiposity (Taki et al., 2008; Ho et al., 2010a; Ho et al., 2010b; Raji et al., 2010; Walther et al., 2010). Importantly, when higher visceral fat, a specific measure for central adiposity, was studied in young (Weise et al., 2013) and aged (Anan et al., 2010) adults, it also predicted lower temporal volume. In general, adiposity had no associations with hippocampus in younger cohorts. Among middle-aged and aged adults, on the one hand, none of the studies examining hippocampal atrophy longitudinally found any association with adiposity (Debette et al., 2011; Bobb et al., 2012; Driscoll et al., 2012). Most null findings studies used categorical BMI comparisons, typically obese versus lean, and used voxel-wise analysis. On the other hand, most of the rigorous cross-sectional studies meeting our criteria did find a negative association between more adiposity and lower hippocampal volume (Taki et al., 2008; Debette et al., 2010; Ho et al., 2010a; Raji et al., 2010; Zade et al., 2013), while a report from Widya and colleagues (2011) found a positive association with left hippocampal volume.

More adiposity predicting lower frontal GM, and in particular PFC volume, has by far been the most consistent finding in the literature. Among studies of younger cohorts that met our criteria, roughly half found a frontal relationship (Pannacciulli et al., 2006; Alosco et al., 2013; Weise et al., 2013) and half did not (Brain Development Cooperative Haltia et al., 2007; Group, 2012; Yokum et al., 2012). However, we note that the Haltia and Yokum reports found non-significant associations in frontal areas. The Brain Development Cooperative Group sample was also relatively lean (mean ± SD BMI = 19.24 ± 4.3), which may explain the lack of association between BMI and frontal GM. Among middle-aged and aged participants, studies that did not find an association with regard to frontal GM (Gustafson et al., 2004; Gunstad et al., 2008; Driscoll et al., 2012) either used overly stringent error correction, or a qualitative index of atrophy, or suffered from not including important covariates.

For global or regional WM, adiposity was related to variation in volume, but the directionality varied greatly, especially in participants less than 40 years of age. In the study by Haltia et al. (2007), six weeks of a very low calorie diet reduced WM volume, such that once obese participants no longer had more WM volume than lean controls (Haltia et al., 2007), suggesting a dynamic modulation of WM volume by obesity. Using DTI, which assesses the microstructural integrity of WM axons and myelin using fractional anisotropy or mean diffusivity of water (Song et al., 2002), several groups have found that more adiposity consistently predicted lower WM microsctructural integrity among younger (Mueller et al., 2011; Xu et al., 2013), middle-aged (Alkan et al., 2008; Stanek et al., 2011; Karlsson et al., 2013), and aged (Marks et al., 2011; Metzler-Baddeley et al., 2013) participants. This consistency in DTI findings may be contrasted with the inconsistent associations found between BMI and WM volume, particularly in younger cohorts. In general, WM volumetric and DTI studies offer complementary information, since aging or insults of variable intensity may decrease WM microstructural integrity without decreasing (or even while increasing) WM volume (Kou et al., 2013; Tseng et al., 2013). Collectively, these DTI results suggest that WM, regardless of age, may be less intact as adiposity increases.

4.2. Adiposity and Brain Atrophy: Potential Mechanisms

4.2.1. Inflammation—It is now well established that adipose tissue is not inert, but rather actively produces proinflammatory cytokines and chemokines primarily via macrophage activation (Johnson et al., 2012). Inflammatory activity in the gut and brain is highly integrated and bidirectional due to vagal innervation (Dantzer, 2004). Obesity can induce gliosis and damage in the hypothalamus in rodents and humans (Thaler et al., 2012), while a 5 month high-fat diet in male rodents leads to increased expression of prostaglandin E_2, cyclooxygenases, and reactive oxygen species in rat cortex, suggesting increased neuroinflammation and oxidative stress (Zhang et al., 2005). Neuroinflammation is generally thought to contribute to brain atrophy and worse cognitive performance (Wilson et al., 2002). Given their ease of acquisition, peripheral cytokines reflecting systemic, and to some degree brain, inflammation are often used in combined biomarkers-neuroimaging studies. Higher concentrations of peripheral interleukin-6, a proinflammatory cytokine, are associated with less hippocampal volume cross-sectionally in middle-aged (Marsland et al., 2008) and aged (Satizabal et al., 2012) adults. It is also relevant to highlight recent voxel-wise studies in aged rhesus macaques on an ad libitum enriched diet or long-term calorie restriction (CR; see 4.3.1.). Higher peripheral levels of the proinflammatory cytokine IL-6 predicted less GM volume or tissue density in temporal, frontal, and parietal regions (Willette et al., 2010). Conversely, higher peripheral concentrations of the anti-inflammatory cytokine IL-10 among CR but not control monkeys was associated with more volume or greater microstructural integrity in similar regions, particularly dorsal PFC (Dantzer, 2004). Higher levels of the proinflammatory chemokine IL-8 have also been related to lower volume exclusively in bilateral hippocampus for control but not CR monkeys (Dantzer, 2004). Central IL-8 is predominantly released by microglia in brain, particularly in hippocampus and hypothalamus in at least rodents (Licinio et al., 1992), where IL-8 can have neurotoxic actions through secondary mediators like amyloid-beta (Franciosi et al., 2005; Liu et al., 2010).

4.2.2. Vascular Risk Factors—Cardiovascular risk factors, such as dyslipidemia (Launer, 2002), midlife hypertension (Fillit et al., 2008), and other components of the metabolic syndrome (Yaffe, 2007) can affect the brain vasculature and may additively contribute to increased AD risk. However, risk factors examined individually show complex or inconsistent results with respect to brain volume and cognition. For example, high-density but not low-density lipoprotein or total cholesterol concentrations have been associated with lower hippocampal volume and higher AD risk (Wolf et al., 2004), whereas hypercholesterolemia in cognitively normal elders either does not show this relationship (Debette et al., 2011) or predicts higher total cerebral volume, as suggested by the Rotterdam study (Hoogendam et al., 2012). Treatment with statins may decrease neurofibrillary tau pathology (Li et al., 2007) but not GM atrophy over time (ten Dam et al., 2005).

Midlife systolic hypertension predicts declines in executive function over roughly a decade later, but no changes in total brain or temporal horn volumes (Debette et al., 2011). Annualized medial temporal atrophy over 2.4 years, however, is significantly associated with higher systolic and diastolic blood pressure but not lipoproteins in elders (de Jong et al.,

2014). Biomarkers of vascular stiffness induced by impaired nitric oxide production may contribute to the development of small vessel disease, which is associated with brain atrophy in normally aging but not cognitively impaired participants (Barnes et al., 2013). Indeed, a peripheral biomarker of impaired nitric oxide synthase, asymmetrical dimethylarginine, predicts greater prevalence of stroke and subclinical vascular injury manifested as WM hyperintensities (Pikula et al., 2009).

4.2.3. Insulin Resistance—In the brain, insulin normally facilitates microvascular blood flow, glucose uptake, and glucose oxidation for ATP generation (Cersosimo and DeFronzo, 2006). IR is defined broadly as reduced cellular responsiveness to insulin (Goldstein, 2002), and is characterized by higher insulin levels needed to maintain glucose levels in the periphery and brain. Critically, IR develops in up to 40% of late middle-aged adults who are overweight or obese (Matsuzawa et al., 2011). IR is found in AD patient brains (Giordano et al., 2007). For example, hippocampal tissue from AD patients versus cognitively normal controls shows impaired insulin signaling, reflecting brain IR, which strongly predicted worse antemortem cognitive performance (Talbot et al., 2012). IR may also increase AD risk (Craft and Watson, 2004; Schrijvers et al., 2010).

Higher IR also predicts less brain volume in AD-sensitive regions in primates. In aged rhesus macaques, long-term calorie restriction increased insulin sensitivity (i.e., lowered IR) derived from a glucose tolerance test. Higher insulin sensitivity in CR but not control monkeys was related to more volume in ventral PFC and bilateral hippocampus (Willette et al., 2012a). Higher baseline IR in middle-aged adults at risk for AD corresponded to less GM volume over 4 years, and IR was a mediator of worse memory performance (Willette et al., 2013a). Although there are many pathophysiological processes that may underlie these associations, Bomfim and colleagues (2012) found that amyloid beta oligomers injected into the brains of cynomologus monkeys lead to neuron-specific increases in c-Jun N-terminal kinase (JNK) activity induced by tumor necrosis factor-alpha signaling, subsequent serine phosphorylation of insulin receptor substrate-1 (IRS-1) in hippocampus, and axonal transport dysfunction. These results suggest that complex interactions between amyloid, inflammation, and insulin resistance may disrupt tissue function and could eventually lead to tissue atrophy.

4.2.4. Glucocorticoid and Brain-Derived Neurotrophic Factor Signaling—Obesity can induce higher cortisol secretion through increased hypothalamic-pituitary-adrenocortical axis activity (Bjorntorp, 1996). Many studies, such as in Lupien et al. (1998), have shown that higher cortisol levels may be associated with brain atrophy and worse cognitive performance. In rodents, streptozocin-induced diabetes resulted in deficits in hippocampal synaptic plasticity partly via elevated corticosterone (Stranahan et al., 2008). More recent evidence suggests that obesity per se, in at least adolescents, mediates the relationship between higher waking cortisol response and atrophy in hippocampus and frontal lobe (Ursache et al., 2012). Indeed, mediation of the awakening cortisol secretion response by hippocampus and PFC is dysregulated in obesity (Dedovic et al., 2009).

One potential mechanism underlying the effects of cortisol may be decreased brain-derived neurotrophic factor (BDNF), a key modulator of synaptic activity in hippocampus and other

areas (See Pluchino et al., 2013). Restraint stress in rodents raised peripheral cortisol and lowered BDNF mRNA expression in hippocampus (Walton et al., 2012). Dexamethazone, a synthetic glucocorticoid, lowered rodent BDNF levels in cultured hippocampal neurons (Strle et al., 2004). By contrast, lowering corticosterone levels in diabetic/diabetic (db/db) transgenic mice selectively restored BDNF mRNA expression in hippocampal dentate gyrus (Stranahan et al., 2011). Thus, increased glucocorticoid signaling may have downstream effects via BDNF that may have downstream effects such as reduced synaptic plasticity and induced atrophy.

4.3. Adiposity and Brain Atrophy: Evidence from Interventions

4.3.1. Calorie Restriction and Weight Loss—Calorie restriction, or CR is defined as limiting caloric intake without loss of nutrient content. CR reduces central adiposity in rhesus monkeys (Colman et al., 2009) and humans (Johnson et al., 2007; Harvie et al., 2011; Harvie et al., 2013). In the longitudinal University of Wisconsin-Madison study on 30% long-term, chronic CR in aged rhesus macaques (see Colman et al. (2009) for an overview), long-term CR helped to preserve GM volume bilaterally in temporal and frontal cortices, insula, cingulate cortex, and sub-cortical areas (Colman et al., 2009), as well as WM volume in the centrum semiovale, corpus callosum, and several occipital and parietal tracts (Bendlin et al., 2011).

Furthermore, beneficial effects of CR were noted for peripheral inflammation, vascular factors, insulin sensitivity, and other blood-based parameters that may have indirect ameliorative effects on brain volume, tissue microstructural integrity, and cognition. As noted above, long-term CR reduced IL-6 and IL-8 while increasing concentrations of IL-10 (Dantzer, 2004; Willette et al., 2010; Willette et al., 2013b). CR monkeys showed a weaker or non-significant association with lower PFC and hippocampal volume or microstructure per point increase in IL-6 or IL-8, whereas associations between higher IL-10 and brain indices were significantly stronger. These results suggest an ameliorative effect of CR on brain atrophy via reduced pro-inflammatory and increased anti-inflammatory peripheral interleukins, which to a degree reflect their central concentrations.

In addition CR monkeys showed less WM atrophy and more microstructural density per point higher homocysteine levels primarily in brainstem and cerebellum, as well as less GM atrophy in occipital, hippocampal, caudoputamen, and anterior cingulate areas (Willette et al., 2012b). CR also considerably reduced stress reactivity (Willette et al., 2012c), where aged monkeys on CR showed less corresponding atrophy per point increase in a z-scored stress factor in many WM tracts, as well as similar amelioration in GM volume or microstructural density for orbital PFC and hippocampus. Finally, CR monkeys had many fewer perseverative errors and achieved task criterion in fewer trials for the most complicated Wisconsin Card Sort Test set-shifting tasks (Sridharan et al., 2012). Fewer errors corresponded to more GM in orbital PFC, an area where CR monkeys have more volume.

In regards to human weight loss intervention studies, we have already referred to the study by Haltia et al. (2007) that found that WM, but not GM, volume may change after a 6 week very low calorie diet. This result is inconsistent with the retrospective study by Hassenstab

et al. (Hassenstab et al., 2012) that found that previously obese people who had maintained weight loss for 3 years did not have different GM or WM thickness from either lean or obese groups. More dietary intervention studies are needed to determine whether or not weight loss has any effects on adiposity and brain associations.

4.3.2. Exercise—Non-sedentary adults are less likely to develop AD (Rockwood and Middleton, 2007). Cardiorespiratory fitness in early AD, but not cognitively normal controls, is associated with less whole brain atrophy (Burns et al., 2008). A 24-week moderate-intensity exercise program can modestly reduce cognitive decline in cognitively impaired adults without dementia (Lautenschlager et al., 2008). By extension, moderate aerobic exercise can also have beneficial effects on the brain. Erickson and colleagues (2011) recently found in 60 aged, previously sedentary adults that moderate aerobic exercise (i.e., walking) led to increased anterior hippocampal volume 1 year after baseline by roughly 2%, whereas 60 controls showed age-typical atrophy over 1 year of roughly 1.4%. Nevertheless, cognitive performance on word list recall and ADAS-Cog remained comparable between groups. Curiously, however, 93 aged women who engaged in once- or twice-weekly resistance training showed improved Stroop executive function performance, but not set-shifting or working memory, after 1 year compared to 42 controls (Liu-Ambrose et al., 2010). Curiously, the resistance training group but not the controls showed a modest decrease in total brain volume.

5. Conclusions

Obesity is a common health concern that clearly increases the risk for developing cardiovascular disease, various cancers, and AD. Contrary to many statements that appear in the literature and suggest a strong association between more adiposity and brain atrophy, our systematic review demonstrated that more adiposity has regionally selective and typically modest to moderate associations with brain atrophy. Frontal lobe atrophy, and in particular PFC, is most consistently associated with more adiposity in younger and older cohorts. Associations between more adiposity and lower parietal volumes were seen only in older cohorts, but not in precuneus or posterior cingulate areas, which are of particular interest for their role in AD. Hippocampal atrophy is not consistently linked with adiposity. The association between more adiposity and increased AD risk (Beydoun et al., 2008) may be mediated by factors other than hippocampal atrophy.

To further clarify these associations, it is important for future studies to quantitatively assess visceral fat mass and non-fat mass, and obtain longitudinal measures of brain atrophy. Weise and colleagues (2013), for example, found that associations between higher non-fat mass and brain atrophy were robust, whereas findings with fat mass were rendered non-significant after covarying non-fat mass. Longitudinal TBM has been used to assess modest associations with insulin resistance and brain atrophy using Jacobian determinant maps (Willette et al., 2013a), which may be more sensitive to regional variation than anatomical ROI approaches. Neuroimaging approaches optimized for longitudinal studies could be included in studies that study anti-obesity interventions, such as in calorie restriction, not only to establish associations between brain volume loss over time and adiposity, but also to assess the reversibility of underlying pathophysiological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Alkan A, Sahin I, Keskin L, Cikim AS, Karakas HM, Sigirci A, Erdem G. Diffusion-weighted imaging features of brain in obesity. Magnetic resonance imaging. 2008; 26:446–450. [PubMed: 18063337]

Alosco ML, Stanek KM, Galioto R, Korgaonkar MS, Grieve SM, Brickman AM, Spitznagel MB, Gunstad J. Body mass index and brain structure in healthy children and adolescents. The International journal of neuroscience. 2013

Anan F, Masaki T, Shimomura T, Fujiki M, Umeno Y, Eshima N, Saikawa T, Yoshimatsu H. Abdominal visceral fat accumulation is associated with hippocampus volume in non-dementia patients with type 2 diabetes mellitus. NeuroImage. 2010; 49:57–62. [PubMed: 19683583]

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. NeuroImage. 2000; 11:805–821. [PubMed: 10860804]

Barnes J, Carmichael OT, Leung KK, Schwarz C, Ridgway GR, Bartlett JW, Malone IB, Schott JM, Rossor MN, Biessels GJ, DeCarli C, Fox NC. Vascular and Alzheimer's disease markers independently predict brain atrophy rate in Alzheimer's Disease Neuroimaging Initiative controls. Neurobiology of aging. 2013; 34:1996–2002. [PubMed: 23522844]

Bendlin BB, Canu E, Willette A, Kastman EK, McLaren DG, Kosmatka KJ, Xu G, Field AS, Colman RJ, Coe CL, Weindruch RH, Alexander AL, Johnson SC. Effects of aging and calorie restriction on white matter in rhesus macaques. Neurobiology of aging. 2011; 32:2319 e2311–2311. [PubMed: 20541839]

Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2008; 9:204–218. [PubMed: 18331422]

Bjorntorp P. The regulation of adipose tissue distribution in humans. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1996; 20:291–302.

Bobb JF, Schwartz BS, Davatzikos C, Caffo B. Cross-sectional and longitudinal association of body mass index and brain volume. Human brain mapping. 2012

Bomfim TR, Forny-Germano L, Sathler LB, Brito-Moreira J, Houzel JC, Decker H, Silverman MA, Kazi H, Melo HM, McClean PL, Holscher C, Arnold SE, Talbot K, Klein WL, Munoz DP, Ferreira ST, De Felice FG. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers. The Journal of clinical investigation. 2012; 122:1339–1353. [PubMed: 22476196]

Brooks SJ, Benedict C, Burgos J, Kempton MJ, Kullberg J, Nordenskjold R, Kilander L, Nylander R, Larsson EM, Johansson L, Ahlstrom H, Lind L, Schioth HB. Late-life obesity is associated with smaller global and regional gray matter volumes: a voxel-based morphometric study. Int J Obes (Lond). 2013a; 37:230–236. [PubMed: 22290540]

Brooks SJ, Cedernaes J, Schioth HB. Increased prefrontal and parahippocampal activation with reduced dorsolateral prefrontal and insular cortex activation to food images in obesity: a meta-analysis of fMRI studies. PloS one. 2013b; 8:e60393. [PubMed: 23593210]

Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. Brain research. 2009; 1280:186–194. [PubMed: 19463794]

Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM, Swerdlow RH. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. Neurology. 2008; 71:210–216. [PubMed: 18625967]

Cassidy SB. Prader-Willi syndrome. Journal of medical genetics. 1997; 34:917–923. [PubMed: 9391886]

Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. Diabetes/metabolism research and reviews. 2006; 22:423–436. [PubMed: 16506274]

Colman RJ, Anderson RM, Johnson SC, Kastman EK, Kosmatka KJ, Beasley TM, Allison DB, Cruzen C, Simmons HA, Kemnitz JW, Weindruch R. Caloric restriction delays disease onset and mortality in rhesus monkeys. Science. 2009; 325:201–204. [PubMed: 19590001]

Craft S, Foster TC, Landfield PW, Maier SF, Resnick SM, Yaffe K. Session III: Mechanisms of age-related cognitive change and targets for intervention: inflammatory, oxidative, and metabolic processes. J Gerontol A Biol Sci Med Sci. 2012; 67:754–759. [PubMed: 22570133]

Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet neurology. 2004; 3:169–178. [PubMed: 14980532]

Dalton M, Cameron AJ, Zimmet PZ, Shaw JE, Jolley D, Dunstan DW, Welborn TA. Waist circumference, waist-hip ratio and body mass index and their correlation with cardiovascular disease risk factors in Australian adults. Journal of internal medicine. 2003; 254:555–563. [PubMed: 14641796]

Dantzer R. Innate immunity at the forefront of psychoneuroimmunology. Brain, behavior, and immunity. 2004; 18:1–6.

de Jong LW, Forsberg LE, Vidal JS, Sigurdsson S, Zijdenbos AP, Garcia M, Eiriksdottir G, Gudnason V, van Buchem MA, Launer LJ. Different susceptibility of medial temporal lobe and basal ganglia atrophy rates to vascular risk factors. Neurobiology of aging. 2014; 35:72–78. [PubMed: 23992618]

Debette S, Beiser A, Hoffmann U, Decarli C, O'Donnell CJ, Massaro JM, Au R, Himali JJ, Wolf PA, Fox CS, Seshadri S. Visceral fat is associated with lower brain volume in healthy middle-aged adults. Annals of neurology. 2010; 68:136–144. [PubMed: 20695006]

Debette S, Seshadri S, Beiser A, Au R, Himali JJ, Palumbo C, Wolf PA, DeCarli C. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology. 2011; 77:461–468. [PubMed: 21810696]

Dedovic K, Duchesne A, Andrews J, Engert V, Pruessner JC. The brain and the stress axis: the neural correlates of cortisol regulation in response to stress. NeuroImage. 2009; 47:864–871. [PubMed: 19500680]

Del Parigi A, Gautier JF, Chen K, Salbe AD, Ravussin E, Reiman E, Tataranni PA. Neuroimaging and obesity: mapping the brain responses to hunger and satiation in humans using positron emission tomography. Annals of the New York Academy of Sciences. 2002; 967:389–397. [PubMed: 12079866]

Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougneres P, Kovacs P, Marre M, Balkau B, Cauchi S, Chevre JC, Froguel P. Variation in FTO contributes to childhood obesity and severe adult obesity. Nature genetics. 2007; 39:724–726. [PubMed: 17496892]

Donkelaar, HJt. Clinical neuroanatomy : brain circuitry and its disorders. Springer; Heidelberg New York: 2011.

Driscoll I, Beydoun MA, An Y, Davatzikos C, Ferrucci L, Zonderman AB, Resnick SM. Midlife obesity and trajectories of brain volume changes in older adults. Human brain mapping. 2012; 33:2204–2210. [PubMed: 22887828]

Elias MF, Goodell AL, Waldstein SR. Obesity, cognitive functioning and dementia: back to the future. Journal of Alzheimer's disease : JAD. 2012; 30(Suppl 2):S113–125.

Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:3017–3022. [PubMed: 21282661]

Fillit H, Nash DT, Rundek T, Zuckerman A. Cardiovascular risk factors and dementia. The American journal of geriatric pharmacotherapy. 2008; 6:100–118. [PubMed: 18675769]

Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA : the journal of the American Medical Association. 2007; 298:2028–2037. [PubMed: 17986696]

Franciosi S, Choi HB, Kim SU, McLarnon JG. IL-8 enhancement of amyloid-beta (Abeta 1-42)-induced expression and production of pro-inflammatory cytokines and COX-2 in cultured human microglia. Journal of neuroimmunology. 2005; 159:66–74. [PubMed: 15652404]

Friedemann C, Heneghan C, Mahtani K, Thompson M, Perera R, Ward AM. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. BMJ. 2012; 345:e4759. [PubMed: 23015032]

Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, Vendemiale G, Pilotto A, Panza F. Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. Ageing Res Rev. 2010; 9:399–417. [PubMed: 20444434]

Gazdzinski S, Kornak J, Weiner MW, Meyerhoff DJ. Body mass index and magnetic resonance markers of brain integrity in adults. Annals of neurology. 2008; 63:652–657. [PubMed: 18409192]

Gazdzinski S, Millin R, Kaiser LG, Durazzo TC, Mueller SG, Weiner MW, Meyerhoff DJ. BMI and neuronal integrity in healthy, cognitively normal elderly: a proton magnetic resonance spectroscopy study. Obesity (Silver Spring). 2010; 18:743–748. [PubMed: 19816410]

Giordano V, Peluso G, Iannuccelli M, Benatti P, Nicolai R, Calvani M. Systemic and brain metabolic dysfunction as a new paradigm for approaching Alzheimer's dementia. Neurochemical research. 2007; 32:555–567. [PubMed: 16915364]

Goldstein BJ. Insulin resistance as the core defect in type 2 diabetes mellitus. The American journal of cardiology. 2002; 90:3G–10G.

Gonzales MM, Tarumi T, Eagan DE, Tanaka H, Vaghasia M, Haley AP. Indirect effects of elevated body mass index on memory performance through altered cerebral metabolite concentrations. Psychosomatic medicine. 2012; 74:691–698. [PubMed: 22822230]

Brain Development Cooperative Group. Total and regional brain volumes in a population-based normative sample from 4 to 18 years: the NIH MRI Study of Normal Brain Development. Cereb Cortex. 2012; 22:1–12. [PubMed: 21613470]

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 RH, Cohen RA, Tate DF, Spitznagel MB, Grieve S, Gordon E. Relationship between body mass index and brain volume in healthy adults. The International journal of neuroscience. 2008; 118:1582–1593. [PubMed: 18853335]

Gustafson D, Lissner L, Bengtsson C, Bjorkelund C, Skoog I. A 24-year follow-up of body mass index and cerebral atrophy. Neurology. 2004; 63:1876–1881. [PubMed: 15557505]

Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Archives of internal medicine. 2003; 163:1524–1528. [PubMed: 12860573]

Haley AP, Gonzales MM, Tarumi T, Tanaka H. Dyslipidemia links obesity to early cerebral neurochemical alterations. Obesity (Silver Spring). 2013

Haltia LT, Viljanen A, Parkkola R, Kemppainen N, Rinne JO, Nuutila P, Kaasinen V. Brain white matter expansion in human obesity and the recovering effect of dieting. The Journal of clinical endocrinology and metabolism. 2007; 92:3278–3284. [PubMed: 17536002]

Harvie M, Wright C, Pegington M, McMullan D, Mitchell E, Martin B, Cutler RG, Evans G, Whiteside S, Maudsley S, Camandola S, Wang R, Carlson OD, Egan JM, Mattson MP, Howell A. The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss and metabolic disease risk markers in overweight women. The British journal of nutrition. 2013:1–14.

Harvie MN, Pegington M, Mattson MP, Frystyk J, Dillon B, Evans G, Cuzick J, Jebb SA, Martin B, Cutler RG, Son TG, Maudsley S, Carlson OD, Egan JM, Flyvbjerg A, Howell A. The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women. Int J Obes (Lond). 2011; 35:714–727. [PubMed: 20921964]

Haslam DW, James WP. Obesity. Lancet. 2005; 366:1197–1209. [PubMed: 16198769]

Hassenstab JJ, Sweet LH, Del Parigi A, McCaffery JM, Haley AP, Demos KE, Cohen RA, Wing RR. Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: a preliminary MRI study. Psychiatry research. 2012; 202:77–79. [PubMed: 22595506]

Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Lee S, Hibar D, Dinov ID, Stein JL, Jack CR Jr, Weiner MW, Toga AW, Thompson PM. Obesity is linked with lower brain volume in 700 AD and MCI patients. Neurobiology of aging. 2010a; 31:1326–1339. [PubMed: 20570405]

Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, Dinov ID, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN, Corneveaux JJ, Stephan DA, DeCarli CS, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW, Raji CA, Lopez OL, Becker JT, Carmichael OT, Thompson PM. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. Proceedings of the National Academy of Sciences of the United States of America. 2010b; 107:8404–8409. [PubMed: 20404173]

Ho AJ, Raji CA, Becker JT, Lopez OL, Kuller LH, Hua X, Dinov ID, Stein JL, Rosano C, Toga AW, Thompson PM. The effects of physical activity, education, and body mass index on the aging brain. Human brain mapping. 2011a; 32:1371–1382. [PubMed: 20715081]

Ho AJ, Raji CA, Saharan P, DeGiorgio A, Madsen SK, Hibar DP, Stein JL, Becker JT, Lopez OL, Toga AW, Thompson PM. Hippocampal volume is related to body mass index in Alzheimer's disease. Neuroreport. 2011b; 22:10–14. [PubMed: 21539003]

Hoogendam YY, van der Geest JN, van der Lijn F, van der Lugt A, Niessen WJ, Krestin GP, Hofman A, Vernooij MW, Breteler MM, Ikram MA. Determinants of cerebellar and cerebral volume in the general elderly population. Neurobiology of aging. 2012; 33:2774–2781. [PubMed: 22405042]

Huang TL, Yu WW. Weight loss occurs over a decade prior to dementia diagnosis: comment on meta-analysis of obesity as a risk factor for dementia and its subtypes. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2008; 9:631–632. [PubMed: 18801008]

Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. Archives of neurology. 2005; 62:1545–1548. [PubMed: 16216937]

Johnson AR, Milner JJ, Makowski L. The inflammation highway: metabolism accelerates inflammatory traffic in obesity. Immunological reviews. 2012; 249:218–238. [PubMed: 22889225]

Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit VD, Pearson M, Nassar M, Telljohann R, Maudsley S, Carlson O, John S, Laub DR, Mattson MP. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free radical biology & medicine. 2007; 42:665–674. [PubMed: 17291990]

Karlsson HK, Tuulari JJ, Hirvonen J, Lepomaki V, Parkkola R, Hiltunen J, Hannukainen JC, Soinio M, Pham T, Salminen P, Nuutila P, Nummenmaa L. Obesity is associated with white matter atrophy: A combined diffusion tensor imaging and voxel-based morphometric study. Obesity (Silver Spring). 2013

Kou Z, Gattu R, Kobeissy F, Welch RD, O'Neil BJ, Woodard JL, Ayaz SI, Kulek A, Kas-Shamoun R, Mika V, Zuk C, Tomasello F, Mondello S. Combining biochemical and imaging markers to improve diagnosis and characterization of mild traumatic brain injury in the acute setting: results from a pilot study. PLoS One. 2013; 8:e80296. [PubMed: 24260364]

Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, Lipsitz LA. Cognitive function in normal-weight, overweight, and obese older adults: an analysis of the Advanced Cognitive Training for Independent and Vital Elderly cohort. Journal of the American Geriatrics Society. 2006; 54:97–103. [PubMed: 16420204]

Kurth F, Levitt JG, Phillips OR, Luders E, Woods RP, Mazziotta JC, Toga AW, Narr KL. Relationships between gray matter, body mass index, and waist circumference in healthy adults. Human brain mapping. 2013; 34:1737–1746. [PubMed: 22419507]

Launer LJ. Demonstrating the case that AD is a vascular disease: epidemiologic evidence. Ageing research reviews. 2002; 1:61–77. [PubMed: 12039449]

Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA : the journal of the American Medical Association. 2008; 300:1027–1037. [PubMed: 18768414]

Li G, Larson EB, Sonnen JA, Shofer JB, Petrie EC, Schantz A, Peskind ER, Raskind MA, Breitner JC, Montine TJ. Statin therapy is associated with reduced neuropathologic changes of Alzheimer disease. Neurology. 2007; 69:878–885. [PubMed: 17724290]

Liang J, Matheson BE, Kaye WH, Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes (Lond). 2013

Licinio J, Wong ML, Gold PW. Neutrophil-activating peptide-1/interleukin-8 mRNA is localized in rat hypothalamus and hippocampus. Neuroreport. 1992; 3:753–756. [PubMed: 1421131]

Liu YJ, Guo DW, Tian L, Shang DS, Zhao WD, Li B, Fang WG, Zhu L, Chen YH. Peripheral T cells derived from Alzheimer's disease patients overexpress CXCR2 contributing to its transendothelial migration, which is microglial TNF-alpha-dependent. Neurobiology of aging. 2010; 31:175–188. [PubMed: 18462836]

Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie BL, Ashe MC, Handy TC. Resistance training and executive functions: a 12-month randomized controlled trial. Archives of internal medicine. 2010; 170:170–178. [PubMed: 20101012]

Luchsinger JA, Cheng D, Tang MX, Schupf N, Mayeux R. Central obesity in the elderly is related to late-onset Alzheimer disease. Alzheimer disease and associated disorders. 2012; 26:101–105. [PubMed: 21666429]

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ. Cortisol levels during human aging predict hippocampal atrophy and memory deficits. Nature neuroscience. 1998; 1:69–73. [PubMed: 10195112]

Maayan L, Hoogendoorn C, Sweat V, Convit A. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. Obesity (Silver Spring). 2011; 19:1382–1387. [PubMed: 21350433]

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; 45:1208–1215. [PubMed: 20558529]

Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. Biological psychiatry. 2008; 64:484–490. [PubMed: 18514163]

Martin LE, Holsen LM, Chambers RJ, Bruce AS, Brooks WM, Zarcone JR, Butler MG, Savage CR. Neural mechanisms associated with food motivation in obese and healthy weight adults. Obesity (Silver Spring). 2010; 18:254–260. [PubMed: 19629052]

Matsuzawa Y, Funahashi T, Nakamura T. The concept of metabolic syndrome: contribution of visceral fat accumulation and its molecular mechanism. Journal of atherosclerosis and thrombosis. 2011; 18:629–639. [PubMed: 21737960]

Maudsley AA, Govind V, Arheart KL. Associations of age, gender and body mass with 1H MR-observed brain metabolites and tissue distributions. NMR in biomedicine. 2012; 25:580–593. [PubMed: 21858879]

McDonald CR, McEvoy LK, Gharapetian L, Fennema-Notestine C, Hagler DJ Jr, Holland D, Koyama A, Brewer JB, Dale AM. Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. Neurology. 2009; 73:457–465. [PubMed: 19667321]

McEwen BS, Morrison JH. The brain on stress: vulnerability and plasticity of the prefrontal cortex over the life course. Neuron. 2013; 79:16–29. [PubMed: 23849196]

Mehta S, Melhorn SJ, Smeraglio A, Tyagi V, Grabowski T, Schwartz MW, Schur EA. Regional brain response to visual food cues is a marker of satiety that predicts food choice. The American journal of clinical nutrition. 2012; 96:989–999. [PubMed: 22990034]

Melka MG, Gillis J, Bernard M, Abrahamowicz M, Chakravarty MM, Leonard GT, Perron M, Richer L, Veillette S, Banaschewski T, Barker GJ, Buchel C, Conrod P, Flor H, Heinz A, Garavan H, Bruhl R, Mann K, Artiges E, Lourdusamy A, Lathrop M, Loth E, Schwartz Y, Frouin V, Rietschel M, Smolka MN, Strohle A, Gallinat J, Struve M, Lattka E, Waldenberger M, Schumann G,

Pavlidis P, Gaudet D, Paus T, Pausova Z. FTO, obesity and the adolescent brain. Human molecular genetics. 2013; 22:1050–1058. [PubMed: 23201753]

Metzler-Baddeley C, Baddeley RJ, Jones DK, Aggleton JP, O'Sullivan MJ. Individual differences in fornix microstructure and body mass index. PloS one. 2013; 8:e59849. [PubMed: 23555805]

Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, Cesari M, Nourhashemi F. Proinflammatory cytokines, aging, and age-related diseases. Journal of the American Medical Directors Association. 2013; 14:877–882. [PubMed: 23792036]

Miller JL, Couch J, Schwenk K, Long M, Towler S, Theriaque DW, He G, Liu Y, Driscoll DJ, Leonard CM. Early childhood obesity is associated with compromised cerebellar development. Developmental neuropsychology. 2009; 34:272–283. [PubMed: 19437203]

Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ. Intracranial abnormalities detected by three-dimensional magnetic resonance imaging in Prader-Willi syndrome. American journal of medical genetics Part A. 2007; 143:476–483. [PubMed: 17103438]

Mueller K, Anwander A, Moller HE, Horstmann A, Lepsien J, Busse F, Mohammadi S, Schroeter ML, Stumvoll M, Villringer A, Pleger B. Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. PloS one. 2011; 6:e18544. [PubMed: 21494606]

Mueller K, Sacher J, Arelin K, Holiga S, Kratzsch J, Villringer A, Schroeter ML. Overweight and obesity are associated with neuronal injury in the human cerebellum and hippocampus in young adults: a combined MRI, serum marker and gene expression study. Translational psychiatry. 2012; 2:e200. [PubMed: 23212584]

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity in the United States, 2009-2010. NCHS data brief. 2012a:1–8.

Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. JAMA : the journal of the American Medical Association. 2012b; 307:483–490. [PubMed: 22253364]

Ogura K, Fujii T, Abe N, Hosokai Y, Shinohara M, Takahashi S, Mori E. Small gray matter volume in orbitofrontal cortex in Prader-Willi syndrome: a voxel-based MRI study. Human brain mapping. 2011; 32:1059–1066. [PubMed: 20669168]

Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA. Brain abnormalities in human obesity: a voxel-based morphometric study. NeuroImage. 2006; 31:1419–1425. [PubMed: 16545583]

Pikula A, Boger RH, Beiser AS, Maas R, DeCarli C, Schwedhelm E, Himali JJ, Schulze F, Au R, Kelly-Hayes M, Kase CS, Vasan RS, Wolf PA, Seshadri S. Association of plasma ADMA levels with MRI markers of vascular brain injury: Framingham offspring study. Stroke; a journal of cerebral circulation. 2009; 40:2959–2964.

Pluchino N, Russo M, Santoro AN, Litta P, Cela V, Genazzani AR. Steroid hormones and BDNF. Neuroscience. 2013; 239:271–279. [PubMed: 23380505]

Raji CA, Ho AJ, Parikshak NN, Becker JT, Lopez OL, Kuller LH, Hua X, Leow AD, Toga AW, Thompson PM. Brain structure and obesity. Human brain mapping. 2010; 31:353–364. [PubMed: 19662657]

Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and adolescents: a systematic literature review. Journal of obesity. 2013; 2013:820956. [PubMed: 23533726]

Risacher SL, Shen L, West JD, Kim S, McDonald BC, Beckett LA, Harvey DJ, Jack CR Jr, Weiner MW, Saykin AJ. Longitudinal MRI atrophy biomarkers: relationship to conversion in the ADNI cohort. Neurobiology of aging. 2010; 31:1401–1418. [PubMed: 20620664]

Rockwood K, Middleton L. Physical activity and the maintenance of cognitive function. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2007; 3:S38–44.

Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. Neurology. 2012; 78:720–727. [PubMed: 22357713]

Schrijvers EM, Witteman JC, Sijbrands EJ, Hofman A, Koudstaal PJ, Breteler MM. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam Study. Neurology. 2010; 75:1982–1987. [PubMed: 21115952]

Smucny J, Cornier MA, Eichman LC, Thomas EA, Bechtell JL, Tregellas JR. Brain structure predicts risk for obesity. Appetite. 2012; 59:859–865. [PubMed: 22963736]

Song SK, Sun SW, Ramsbottom MJ, Chang C, Russell J, Cross AH. Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. NeuroImage. 2002; 17:1429–1436. [PubMed: 12414282]

Soreca I, Rosano C, Jennings JR, Sheu LK, Kuller LH, Matthews KA, Aizenstein HJ, Gianaros PJ. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. Psychosomatic medicine. 2009; 71:485–490. [PubMed: 19483122]

Sridharan A, Willette AA, Bendlin BB, Alexander AL, Coe CL, Voytko ML, Colman RJ, Kemnitz JW, Weindruch RH, Johnson SC. Brain volumetric and microstructural correlates of executive and motor performance in aged rhesus monkeys. Frontiers in aging neuroscience. 2012; 4:31. [PubMed: 23162464]

Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, Gunstad JJ. Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity (Silver Spring). 2011; 19:500–504. [PubMed: 21183934]

Stranahan AM, Arumugam TV, Cutler RG, Lee K, Egan JM, Mattson MP. Diabetes impairs hippocampal function through glucocorticoid-mediated effects on new and mature neurons. Nature neuroscience. 2008; 11:309–317. [PubMed: 18278039]

Stranahan AM, Arumugam TV, Mattson MP. Lowering corticosterone levels reinstates hippocampal brain-derived neurotropic factor and Trkb expression without influencing deficits in hypothalamic brain-derived neurotropic factor expression in leptin receptor-deficient mice. Neuroendocrinology. 2011; 93:58–64. [PubMed: 21160171]

Strle K, Broussard SR, McCusker RH, Shen WH, Johnson RW, Freund GG, Dantzer R, Kelley KW. Proinflammatory cytokine impairment of insulin-like growth factor I-induced protein synthesis in skeletal muscle myoblasts requires ceramide. Endocrinology. 2004; 145:4592–4602. [PubMed: 15256490]

Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R, Fukuda H. Relationship between body mass index and gray matter volume in 1,428 healthy individuals. Obesity (Silver Spring). 2008; 16:119–124. [PubMed: 18223623]

Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. The Journal of clinical investigation. 2012; 122:1316–1338. [PubMed: 22476197]

ten Dam VH, Box FM, de Craen AJ, van den Heuvel DM, Bollen EL, Murray HM, van Buchem MA, Westendorp RG, Blauw GJ. Lack of effect of pravastatin on cerebral blood flow or parenchymal volume loss in elderly at risk for vascular disease. Stroke; a journal of cerebral circulation. 2005; 36:1633–1636.

Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, Zhao X, Sarruf DA, Izgur V, Maravilla KR, Nguyen HT, Fischer JD, Matsen ME, Wisse BE, Morton GJ, Horvath TL, Baskin DG, Tschop MH, Schwartz MW. Obesity is associated with hypothalamic injury in rodents and humans. The Journal of clinical investigation. 2012; 122:153–162. [PubMed: 22201683]

Tseng BY, Gundapuneedi T, Khan MA, Diaz-Arrastia R, Levine BD, Lu H, Huang H, Zhang R. White matter integrity in physically fit older adults. Neuroimage. 2013; 82:510–516. [PubMed: 23769914]

Ursache A, Wedin W, Tirsi A, Convit A. Preliminary evidence for obesity and elevations in fasting insulin mediating associations between cortisol awakening response and hippocampal volumes and frontal atrophy. Psychoneuroendocrinology. 2012; 37:1270–1276. [PubMed: 22265870]

van Boxtel MP, Baars L, Jolles J. Obesity, blood pressure and cognitive function: a reply to Waldstein and Katzel. Int J Obes (Lond). 2007; 31:1186. [PubMed: 17264843]

Vucenik I, Stains JP. Obesity and cancer risk: evidence, mechanisms, and recommendations. Annals of the New York Academy of Sciences. 2012; 1271:37–43. [PubMed: 23050962]

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. 2010; 31:1052–1064. [PubMed: 19998366]

Walton JC, Grier AJ, Weil ZM, Nelson RJ. Photoperiod and stress regulation of corticosteroid receptor, brain-derived neurotrophic factor, and glucose transporter GLUT3 mRNA in the hippocampus of male Siberian hamsters (Phodopus sungorus). Neuroscience. 2012; 213:106–111. [PubMed: 22521589]

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]

Weise CM, Thiyyagura P, Reiman EM, Chen K, Krakoff J. Fat-free body mass but not fat mass is associated with reduced gray matter volume of cortical brain regions implicated in autonomic and homeostatic regulation. NeuroImage. 2013; 64:712–721. [PubMed: 22974975]

Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009; 373:1083–1096. [PubMed: 19299006]

Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr. 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. Brain : a journal of neurology. 2007; 130:1777–1786. [PubMed: 17533169]

Widya RL, de Roos A, Trompet S, de Craen AJ, Westendorp RG, Smit JW, van Buchem MA, van der Grond J. Increased amygdalar and hippocampal volumes in elderly obese individuals with or at risk of cardiovascular disease. The American journal of clinical nutrition. 2011; 93:1190–1195. [PubMed: 21450935]

Willette AA, Bendlin BB, McLaren DG, Canu E, Kastman EK, Kosmatka KJ, Xu G, Field AS, Alexander AL, Colman RJ, Weindruch RH, Coe CL, Johnson SC. Age-related changes in neural volume and microstructure associated with interleukin-6 are ameliorated by a calorie-restricted diet in old rhesus monkeys. NeuroImage. 2010; 51:987–994. [PubMed: 20298794]

Willette AA, Bendlin BB, Colman RJ, Kastman EK, Field AS, Alexander AL, Sridharan A, Allison DB, Anderson R, Voytko ML, Kemnitz JW, Weindruch RH, Johnson SC. Calorie restriction reduces the influence of glucoregulatory dysfunction on regional brain volume in aged rhesus monkeys. Diabetes. 2012a; 61:1036–1042. [PubMed: 22415875]

Willette AA, Gallagher C, Bendlin BB, McLaren DG, Kastman EK, Canu E, Kosmatka KJ, Field AS, Alexander AL, Colman RJ, Voytko ML, Weindruch RH, Coe CL, Johnson SC. Homocysteine, neural atrophy, and the effect of caloric restriction in rhesus monkeys. Neurobiology of aging. 2012b; 33:670–680. [PubMed: 20691506]

Willette AA, Coe CL, Colman RJ, Bendlin BB, Kastman EK, Field AS, Alexander AL, Allison DB, Weindruch RH, Johnson SC. Calorie restriction reduces psychological stress reactivity and its association with brain volume and microstructure in aged rhesus monkeys. Psychoneuroendocrinology. 2012c; 37:903–916. [PubMed: 22119476]

Willette AA, Xu G, Johnson SC, Birdsill AC, Jonaitis EM, Sager MA, Hermann BP, La Rue A, Asthana S, Bendlin BB. Insulin resistance, brain atrophy, and *Manuscript* cognitive performance in late middle-aged adults. Diabetes care. 2013a; 36:443–449. [PubMed: 23069842]

Willette AA, Coe CL, Birdsill AC, Bendlin BB, Colman RJ, Alexander AL, Allison DB, Weindruch RH, Johnson SC. Interleukin-8 and interleukin-10, brain volume and microstructure, and the influence of calorie restriction in old rhesus macaques. Age (Dordr). 2013b

Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition--the case for a head-to-toe inflammatory paradigm. Journal of the American Geriatrics Society. 2002; 50:2041–2056. [PubMed: 12473019]

Wolf H, Hensel A, Arendt T, Kivipelto M, Winblad B, Gertz HJ. Serum lipids and hippocampal volume: the link to Alzheimer's disease? Annals of neurology. 2004; 56:745–748. [PubMed: 15505826]

World Health Organization. Obesity: preventing and managing the global epidemic. 2000

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. 2013; 34:1044–1052. [PubMed: 22139809]

Yaffe K. Metabolic syndrome and cognitive disorders: is the sum greater than its parts? Alzheimer disease and associated disorders. 2007; 21:167–171. [PubMed: 17545744]

Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA : the journal of the American Medical Association. 2004; 292:2237–2242. [PubMed: 15536110]

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 (Lond). 2012; 36:656–664. [PubMed: 21894161]

Zade D, Beiser A, McGlinchey R, Au R, Seshadri S, Palumbo C, Wolf PA, DeCarli C, Milberg W. Apolipoprotein epsilon 4 allele modifies waist-to-hip ratio effects on cognition and brain structure. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013; 22:119–125. [PubMed: 21835633]

Zhang X, Dong F, Ren J, Driscoll MJ, Culver B. High dietary fat induces NADPH oxidase-associated oxidative stress and inflammation in rat cerebral cortex. Experimental neurology. 2005; 191:318–325. [PubMed: 15649487]

Highlights

We reviewed the literature on adiposity and brain atrophy across the lifespan

Adiposity was most consistently related to gray matter atrophy in frontal lobe across all age ranges

Adiposity was not consistently related to global or regional white matter atrophy

Table 1

Examples of Literature Findings

Report	Age Group	N	Neuroimaging Method	Contrast Type	Summary of Findings
Zade et al.	Middle-Aged	494	ROI	WHR Quartiles	Among highest WHR quartile, higher WHR was associated with lower total brain volume, frontal GM volume, temporal horn volume reflective of hippocampus, and ventricular volume.
Taki et al.	Middle-Aged	1,428	VBM Voxel-Wise	Continuous BMI	A BMI * Sex interaction showed no association for women. For men, higher BMI predicted less GM in temporal lobe, anterior cerebellum, fusiform gyrus, frontal lobes, precuneus, and midbrain. Positive associations noted in IFG, posterior cerebellum, frontal and temporal lobes, thalamus, and caudate.
Ho et al. (ADNI + CHS-CS)	Aged	700	TBM Voxel-Wise	Continuous BMI	Higher BMI across AD and MCI participants predicted less GM predominantly in medial PFC, occipital lobe, midline areas, cerebellum, brainstem, and deep WM; slight hippocampal coverage in ADNI cohort. Higher BMI predicted more GM in occipital lobe, posterior and anterior cingulate, and pre-central gyrus.
Walther et al.	Aged	95	VBM Voxel-Wise	Continuous BMI	Higher BMI predicted lower GM in frontal lobe, inferior parietal area, parahippocampus to lingual gyrus, cerebellum, and other regions. Higher BMI predicted more WM predominantly in frontal and temporal areas.
Weise et al.	Young Adult	76	VBM Voxel-Wise	Continuous Fat-Free Mass Index (FFMI) or Fat Mass Index (FMI)	Higher FFMI strongly predicted less GM in insula, temporal gyri, ventral and orbital PFC. Higher FMI was associated with smaller clusters in similar regions. Covarying FFMI rendered FMI associations non-significant.
Haltia et al.	Young Adult	46	VBM Voxel-Wise	Obese (30) vs. Lean (16)	Obese participants showed no significant GM differences after type 1 error correction, but did show more WM near parahippocampus, temporal gyri, brainstem, and cerebellum. After 6 weeks of dieting in obese participants, there was significantly less WM in parahippocampl gyrus and temporal areas
Brain Development Cooperative Group	Children	325	ROI	Continuous BMI	Higher BMI had small to moderate associations with global, parietal, temporal, and occipital GM. No association with frontal lobe GM. Higher BMI predicted small positive correlations with global, frontal, parietal, and temporal WM.
Pannacciulli et al.	Young Adult	60	VBM Voxel-Wise	Morbidly obese (24) vs. lean (36)	Morbidly obese participant had less GM in cerebellum, post-central gyrus, putamen, MFG, and anterior insula. Obese participants also had more GM in occipital areas, cerebellum, and MFG, as well as more WM near striatum.

AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; BMI = Body Mass Index; CHS-CS = Cardiovascular Health Study Cognition Study; GM = Gray Matter; IFG = Inferior Frontal Gyrus; MCI = Mild Cognitive Impairment; MFG = Medial Frontal Gyrus; PFC = Prefrontal Cortex; ROI = Region of Interest; TBM = Tensor-Based Morphometry; VBM = Voxel-Based Morphometry; WHR = Waist to Hip Ratio; WM = White Matter.