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Effects of Adiposity and Metabolic Dysfunction on Cognition: A Review

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Abstract

Obesity and metabolic dysfunction are both correlated with increased rates of cognitive decline. However, because these two conditions often co-occur, it remains unclear whether their cognitive consequences are independent. In this review, we carefully consider literature examining the effects of metabolic dysfunction and increased adiposity on cognition across the lifespan, including only well-controlled studies that attempt to dissociate their effects. We found a total of 36 studies, 17 examining metabolic dysfunction and 19 examining the effects of adiposity. We found evidence from the literature suggesting that increased adiposity and metabolic dysfunction may contribute to deficits in executive function, memory, and medial temporal lobe structures largely independent of one another. These deficits are thought to arise principally from physiological changes associated with inflammation, vascularization, and oxidative stress, among others. Such processes may result from excess adipose tissue and insulin resistance that occur independently and can further exacerbate when the two conditions co-occur. However, we also find it likely that impaired cognition plays a role in behavioral and lifestyle choices that lead to increased adiposity and metabolic dysfunction, which can then perpetuate and augment cognitive decline. We recommend additional prospective and longitudinal studies to examine whether impaired cognition is a cause and/or consequence of these factors.

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Supplementary data
Supplementary material

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INTRODUCTION

Human obesity and type 2 diabetes (T2D) are associated with impaired cognition and dementia (van den Berg et al., 2009; Profenno et al., 2010). Rates of cognitive decline in individuals with T2D are increased by approximately 1.5-fold to 2.0-fold compared to those without diabetes (Jan Biessels et al., 2008). These changes principally manifest as psychomotor, executive function, and learning and memory deficits (Jan Biessels et al., 2008). Recent estimates suggest that the combined overall relative risk for Alzheimer's disease is 46% higher in those with T2D compared to those without (Cheng et al., 2012). Individuals with Alzheimer's disease and T2D furthermore show similar pathogenic mechanisms including inflammation, insulin resistance, and mitochondrial dysfunction (Pugazhenthi et al., 2017). Likewise, obesity is associated with similar decrements in cognition. Meta-analyses conclude that obesity results in a 42% increase in the risk for dementia in adults (Beydoun et al., 2008). Children and adolescents with obesity are similarly at increased risk for deficits in executive function, including poorer performance on inhibitory control tasks and decreased reward sensitivity (Reinert et al., 2013; Gunstad et al., 2007). Epidemiological studies suggest that these same individuals may have a predisposition to developing a diagnosis of ADHD due to the two conditions' shared genetic and neurobiological dysfunctions (Cortese and Vincensi, 2011). Obesity and T2D are highly comorbid conditions and their association has been shown consistently and is pervasive even among diverse populations with high and low rates of diabetes (Khaodiar et al., 1999). Therefore, they are difficult to dissociate with few studies examining effects of metabolic dysfunction while controlling for adiposity or examining effects of adiposity while controlling for metabolic health. Whether there are independent effects of metabolic dysfunction and adiposity on human cognition is unknown and is an important avenue for future research.

In contrast, in animal studies, where it is possible to manipulate adiposity and metabolism independently, there are a variety of results that support independent effects of adiposity and metabolic disease on cognition. Adiposity can alter brain structure and function in rodents even when metabolic function is uncompromised, leading to loss of synapses, reduced number of dendritic spines, altered microglia morphology, and poor performance on cognitive tasks (Bocarsly et al., 2015). Before the onset of diabetes, dietary-induced obesity can further impair hippocampal-dependent memory and long-term potentiation (LTP) primarily through increased synaptic stripping by microglia (Hao et al., 2016). In parallel, insulin resistance in the rodent hypothalamus can result from acute exposure to high fat diet before changes in adiposity are observed (Clegg et al., 2011). Brief exposure to high fat/sugar diets are also associated with impaired performance on hippocampal-dependent tasks, such as the radial arm maze (Kanoski and Davidson, 2010).

Whether such effects occur directly as a result of nutrition or indirectly from acute metabolic dysfunction is unclear. A recent study found that mice fed a high fat diet exhibited glucose intolerance, impairments in working memory, and increased anxiety and depressive-like behaviors (Almeida-Suhett et al., 2017). Importantly, these effects were unmitigated in mice that did not gain excessive weight indicating that diet and/or metabolic dysfunction can impact cognition independent of obesity.

Published studies in humans have historically failed to consider these separable effects. A prospective study examining the impact of obesity on cognition found that a variety of obesity indices were associated with poorer performance on tests of memory and verbal fluency (Gunstad et al., 2010). However, this study did not consider the potential influence of diabetes and furthermore did not exclude participants for this disease. A separate analysis of the effects of glucose intolerance in this dataset found a negative impact of this variable on memory function. In a resting state fMRI study, experimenters concluded that individuals with T2D exhibit reduced functional connectivity compared to controls within the default mode network, a group of brain regions that are more active at rest than during cognitive tasks (Musen et al., 2012). They conclude that this disruption in functional connectivity could result from insulin resistance, but did not control for BMI, which was 4 kg/m^2 higher on average in T2D patients than controls. Finally, another fMRI study found that individuals with obesity exhibit reduced responses in medial frontal, middle cingulate, and dorsal caudate nuclei during appetite control compared to healthy weight individuals (Tuulari et al., 2015). However, blood glucose and insulin levels were not measured in these individuals, and it is unclear whether metabolic dysfunction drives these findings.

In summary, animal studies suggest independent effects of adiposity and metabolic impairment on cognition, while findings in humans are often unclear. The aim of this review is to consider the literature surrounding the effects of metabolic dysfunction and adiposity on cognition to provide exposition and summary of studies that attempt to dissociate their effects. Finally, we structure this review based on studies with participants along various points of the developmental trajectory, from children and adolescents to adults and the elderly. Not only is this a self-organizing principle of the literature, but in doing so we hope to elucidate the complex roles of obesity and T2D in potential changes in cognition during the vulnerable period of adolescence and in the onset of cognitive decline and dementia.

METHODS

We considered both PubMed and Google Scholar to identify studies relevant to this review. All publications included human subjects and had, at a minimum, to control for the effects of adiposity or metabolic dysfunction. For instance, studies examining the effects of adiposity on cognition had to either exclude patients with a diagnosis of T2D or had to control for the effects of blood glucose, insulin, or HOMA-IR. Publications examining the effects of metabolic dysfunction on cognition had to either exclude participants with obesity or control for one of the many anthropometric features of adiposity, including body weight, BMI, body fat %, waist/hip ratio, and waist circumference. We define ‘metabolic dysfunction’ in this review as, at a minimum, evidence of impaired glucose tolerance or insulin resistance. The term ‘diabetes’ as commonly used reflects a diagnosis of diabetes

mellitus type 2, rather than type 1, gestational or insipidus diabetes. Our search included the initial terms “cognition and obesity,” and “cognition and glycemia (or diabetes)” on both Google Scholar and PubMed. After identifying five studies meeting inclusion criteria for each type, metabolism and adiposity, we expanded our search terms using the Yale MeSH Analyzer (Grossetta Nardini and Wang, 2018). In brief, the Yale MeSH Analyzer takes PubMed identifiers (PMIDs) as an input and creates a list of medical subject headings (MeSH) that allow users to enhance their search strategies by identifying new and relevant keywords (Hocking 2017). The Yale MeSH Analyzer allowed us to use the ten studies previously mentioned to identify new keywords, including “body mass index,” “adolescent,” “child,” “elderly,” “executive function,” “insulin resistance,” “MRI,” “NGT,” and “IGT.” We used these new terms in various combinations to identify an additional 14 articles for adiposity and 12 articles for diabetes, for a total of 36 articles (Table 1). Using packages in RStudio (v.1.0.153) we also summarize the cognitive constructs and brain regions most often mentioned as being affected by metabolic dysfunction and increased adiposity (Fig. S1–2).

RESULTS

ADIPOSITY – Children

Approximately one third of U.S. children are classified as overweight or obese, weighing on average 5 kg more than they did three decades ago (Lobstein et al., 2015). While childhood obesity was considered a disease of wealthy nations, rates have risen rapidly in low and middle-income countries, particularly in Latin America and the Caribbean (Jaacks et al., 2015; Lobstein et al., 2015). Today, the rise in obesity persists in children worldwide and is part of the reason it has become a pandemic (Frank, 2016; Wallace et al., 2016; Meldrum et al., 2017; Regestein, 2018). The relative contribution of adiposity to changes in cognition in children has been explored, but these results have not been reviewed to yield a coherent narrative.

Analysis of approximately 12,000 children 3–5 years of age from the Millennium Cohort Study (MCS) determined the extent to which weight status affects visuospatial, expressive language, and reasoning skills (Martin et al., 2016). These tests were acquired from the British Ability Scales II battery and comprised pattern construction, vocabulary, and picture similarity subtests, respectively. Though prevalence is increasing, T2D is rarer in children this young. Therefore the effects of adiposity on cognition could be studied with less concern for the confounding effects of metabolic disease. In boys, obesity at 3 years of age was associated with worse performance on the pattern construction subtest at age 5. Girls with obesity performed worse on both pattern construction and vocabulary compared to those with healthy weight, but these effects were not significant when adjusting for general cognitive ability at 3 years. From 3 to 5 years of age, transitioning from obesity to a healthy weight was associated with higher scores on the picture similarity test but only explained approximately 6.6% of the variance in improvement. These findings on the whole reflect a rather modest association between increased adiposity and lower cognitive abilities. This study did not include any markers of metabolic function (e.g. fasting glucose/insulin, HOMA-IR, HbA1C) as covariates, which is an inherent weakness; however, given the very young age of these children, severe metabolic dysfunction is not as likely.

ADIPOSITY – Children and Adolescents

A similar study examined the effects of BMI on cognition in children, but included adolescent participants as well (Bozkurt et al., 2016). Cognitive function is thought to operate suboptimally during adolescence, a period marked by increased incidence of sexually transmitted disease, unintended pregnancy, substance abuse, and violence, among others (Casey et al., 2008). If adiposity impairs cognition during such a critical period of development, it may compound already poor health outcomes. Bozkurt et al. are the only group included to endeavor to examine the effects of adiposity on cognition in both children and adolescents, while also adequately controlling for metabolic dysfunction. 92 participants from 8 to 16 years of age with overweight and obesity were recruited from a Turkish hospital and assessed on a neurocognitive test battery, the Central Nervous System Vital Signs (CNSVS). This test generates seven domain scores that reflect abilities of memory, psychomotor speed, processing speed, reaction time, complex attention, executive function, and cognitive flexibility. To reduce the potential for a confounding effect of metabolic dysfunction on cognition, all participants were free from a diagnosis of T2D, metabolic syndrome, hypertension, and nonalcoholic fatty liver disease. Strikingly, children and adolescents with obesity demonstrated poorer performance on all seven cognitive domains of the CNSVS compared to age and gender-matched controls, a result characterized by a very large effect size (Cohen's $d = 1.29–1.63$) (Sawilowsky, 2009). While a large effect size is rather impactful, this study notably did not control for an effect of socioeconomic status or education, which may impact cognition independent of adiposity. Furthermore, while participants did not have metabolic syndrome, it is unclear whether this was simply a diagnosis of metabolic syndrome or whether markers of metabolic function were actually assessed. If the former is the case, it is possible that some participants were in fact insulin resistant, which could confound these results. The authors note that sleep apnea may play a role in the observed effects, though it is a matter of debate whether or not sleep apnea directly results from increased adiposity and is thus part of the overweight and obese phenotype.

ADIPOSITY –Adolescents

Directly assessing metabolic function is possibly the best method to differentiate the effects of adiposity on cognition from those of metabolic disease. A study of 63 Spanish adolescents from 12–17 did exactly this, obtaining measurements of fasting insulin, basal glucose, triglycerides, HDL, and total cholesterol (Delgado-Rico et al., 2012). Participants with overweight, obesity, and healthy weight were only included in this study if these measures were within-normal levels. Metabolic variables were not included as subsequent covariates in their analyses, however, which constitutes a major weakness of this study as those with excess weight had significantly higher fasting insulin, triglyceride, and HDL levels. Neurocognitive indices derived from tests of impulsivity (UPPS-P), response inhibition, and switching (Color Word Interference Test). These indices did not significantly correlate with any of the aforementioned metabolic measures, suggesting a lack of an effect of fasting insulin on cognition in this sample, though HOMA-IR was not assessed. Increases in BMI were found to positively predict emotion-driven impulsivity and cognitive inflexibility associated with response switching, but were not significantly correlated with response inhibition.

ADIPOSITY –Adolescents and Adults

To better determine the effects of adiposity on cognition, Maayan et al. assessed 37 healthy weight and 54 individuals with obesity from 14–21 years of age, examining fasting glucose, insulin, lipid, and inflammatory markers before performing neurocognitive testing (2011). Participants were thoroughly matched on variables that could influence cognition, including age, education, gender, socioeconomic status, and IQ. Diagnoses of T2D or evidence of insulin resistance were included as exclusion criteria, making this one of the most well-controlled studies to include adolescents to date. Neurocognitive assessments were thorough, including measures of response inhibition (Stroop), attention (Trail Making Task A: TMT-A), cognitive flexibility (Trail Making Task B: TMT-B), verbal fluency (Controlled Oral Word Association Test: COWAT), working memory (Wide Range Assessment of Memory and Learning: WRAML), and attention and concentration (WRAML). Structural MRI analyses were then implemented to determine the effect of adiposity on grey matter volume within frontal lobe regions of the brain. While adolescents with obesity performed worse on all cognitive tests compared to healthy controls, these results did not control for the aforementioned metabolic markers. However, this study excluded individuals who were insulin resistant, and therefore it is likely that much of the variance in cognitive performance could result from increased adiposity. With regard to brain measures, adolescents with obesity had lower grey matter volume in orbitofrontal cortex compared to lean adolescents after covarying for age, systolic blood pressure, and insulin resistance. These results suggest that adiposity may be a cause or consequence of reduced grey matter volume in a region of the brain that plays a pivotal role in executive function (Elliott et al., 2000).

Similar to Maayan et al. (2011), a more recent study (Sweat et al., 2017) sought to examine the relationship between obesity and potential cognitive and structural deficits associated with frontal lobe function. In this study, 162 adolescents and young adults (mean age: 19.39, SD: 1.52) were assessed on an array of neurocognitive tests. Tests assessed frontal lobe function, (COWAT, Stroop, TMT, Digit Symbol Substitution Test: DSST, and the Letter Number Sequencing subtest from the Wechsler Memory Scale-III), executive function (Tower of London, Category Test), sustained attention (Digit Vigilance Test: DVT) and effort (Medical Symptom Validity Test, Non-Verbal Medical Symptom Validity Test). Compared to participants with normal weight, those with obesity performed worse on single components of the DSST, Stroop, COWAT, and DVT, all of which reflected measures of processing speed. The authors hypothesize that, because processing speed reflects interhemispheric communication within the brain, obesity may compromise corpus collosum integrity. Indeed, the rostrum of the corpus callosum was significantly smaller in participants with obesity compared to healthy controls. Finally, while 32.4% of participants with obesity met criteria for metabolic syndrome, none of the metabolic measures collected were associated with either cognitive function or structural MR measures. While the experimenters did not explicitly control for metabolic measures, the inability of metabolic dysfunction to predict cognition in this sample suggests that adiposity contributes to the bulk of the variance in cognition.

The only publication included that found no relationship between BMI and cognition came from Gunstad et al. (2008), who examined a large cohort of 478 children and adolescents

ages 6–19 without a diagnosis of T2D. Participants completed measures of attention (digit span), executive function (switching of attention), memory (verbal recall), and language (animal fluency), and motor ability (finger tapping). In no instance did this study find evidence for an effect of increased adiposity on cognition, though lower BMI was predictive of poorer memory in females. The discrepancy between this publication and the bulk of studies conducted on the association between adiposity and cognition in this population may arise from the neurocognitive battery administered, which was initially designed for use in EEG and ERP experiments.

ADIPOSITY – Adults

While increased adiposity in children and adolescents may predispose them to health issues, excess adipose tissue in adults is likely to result in more proximal health incidents, including increased risk for heart attack, stroke, and dementia (Wilson et al., 2002; Fitzpatrick et al., 2009; Lavie et al., 2009). Like children and adolescents, however, increased adiposity in adults has been associated with changes in cognition. For example, a study of 50 total adults with healthy weight, overweight, and obesity from 18–35 years of age examined the relationship between BMI and performance on a what-where-when (WWW) episodic memory task (Cheke et al., 2016). Individuals with higher BMI performed worse on the WWW task, with higher total errors compared to leaner participants. Individuals with T2D were excluded from participation, but it is possible that changes in metabolic function contributed to these behavioral deficits as metabolic markers were not measured.

A study conducted in a slightly older age group (19–40) of adults with healthy weight and obesity assessed the relationship between BMI and cognition and its interaction with both DRD2/ANKK1-Taq1A and DRD4 VNTR 7R polymorphism carrier status. (Ariza et al., 2012). Carriers of the A1 allele of the Taq1A polymorphism have reduced D2 receptor density in the striatum (Jönsson et al., 1999), which has been correlated with addictive behaviors such as alcoholism and cannabinoid dependence (Munafo et al., 2007; Nacak et al., 2012). The 7R variant of the DRD4 gene reduces dopamine receptor binding and similarly plays a role in the pathophysiology of diseases characterized by impulsive behavior, such as pathological gambling and ADHD (Ashgari et al., 1995; Comings et al., 1999). Participants were assessed on neurocognitive tests of processing speed and working memory (Letters and Numbers: LN), visual scanning, tracking, and motor speed (Symbol Digit Modalities Test), attention and mental flexibility (TMT), verbal fluency (COWAT), and cognitive flexibility and set shifting (Wisconsin Card Sorting Test: WCST). There was a significant group x carrier status interaction such that A1 allele carriers with obesity performed worse on the LN than both controls and non-carriers with obesity. A comparable interaction exists for the DRD4 allele such that carriers of the 7R polymorphism with obesity performed worse on the TMT than both non-carriers with obesity and carriers with healthy weight. This evidence suggests that excess adiposity interacts with dopamine polymorphism status to negatively impact cognition. However, similar to the previous study, participants were only excluded for a diagnosis of T2D or hypertension and thus there is no way to confirm that metabolic dysfunction did not influence these findings.

Boeka et al. (2008) specifically assessed whether cognitive performance differed between adults with obesity that were with or without diabetes, hypertension, and sleep apnea. Participants consisted of 68 patients with extreme obesity (BMI ≥ 40) ages 20–57 who were seeking surgical treatment for their condition. Neurocognitive assessments were included to measure reading ability (Wide Range Achievement Test: WRAT-3), general intelligence (Wechsler Adult Intelligence Scale: WAIS-III), perceptual and organizational skills (Rey Complex Figure Test: CFT), processing speed and cognitive flexibility (TMT), problem-solving and set shifting (WCST), verbal fluency (COWAT), and verbal learning and memory (California Verbal Learning Test: CVLT-II and Logical Memory). Participants performed worse on the CFT and WCST, but better on the COWAT. Analyses demonstrated no significant differences in performance on these cognitive tasks between individuals with and without the aforementioned comorbidities. Individuals with extreme obesity that were with or without comorbid conditions also did not differ on any demographic variables. This study is unique in its comparison of individuals with obesity that are with or without metabolic dysfunction and in its finding that adiposity is associated with improved performance on the TMT. A particular weakness of this publication is the self-reported nature of the medical comorbidities, though the authors note that participants had recent medical examinations at the time of assessment.

In contrast to Boeka et al. (2008), a study conducted in a Canadian First Nations population of 190 adults (age ≥ 18) ranging in BMI from underweight to obese found the opposite association between adiposity and TMT performance (Fergenbaum et al., 2009). In this case, however, TMT-A and TMT-B were combined into a total score, TMT-exec, to capture general executive function. Participants with a TMT-exec score indicating lowered cognitive performance were classified as cases, while those with no evidence of impaired performance were classified as controls. TMT cases were more likely to have higher BMI, increased waist circumference, and higher systolic blood pressure than controls. Among participants without diabetes in this sample, obesity was associated with a significantly increased risk of lowered cognition, but insulin resistance, dyslipidemia, cardiovascular disease, and hypertension were not. Metabolic syndrome in these participants was defined as having elevated waist circumference, triglycerides, hypertension, and fasting blood glucose as well as lower high-density lipoprotein. While having more than one symptom of metabolic syndrome was associated with significantly increased risk for lowered cognition, it is unclear which of the aforementioned measures were principally driving this effect. This study demonstrates that adiposity independent of multiple metabolic markers can contribute to deficits in executive function, though it is possible that elevated fasting blood glucose or lowered high density lipoprotein were contributing the most variance in TMT-exec scores.

A robust study of approximately 2,000 middle-aged (32–62) French participants of the VISAT cohort examined the association between adiposity across the BMI spectrum and cognition (Cournot et al., 2006). Participants were free of dementia at the time of participation, but included individuals with a diagnosis of diabetes, coronary artery disease, hypertriglyceridemia, thyroid disease, and prior history of stroke. Participants were administered neurocognitive tests to determine age-related learning differences (word-list learning test), information processing speed (WAIS-DSST), and selective attention (Selective attention test). BMI at baseline and scores on word-list learning and WAIS-DSST

at a 5-year follow-up were significantly associated, such that higher BMI predicted lower cognitive scores. This association persisted after correcting for diabetes, systolic blood pressure, perceived health, age, sex, and education level. Like previous studies, this publication demonstrates that adiposity independent of diabetes is associated with cognitive decline. However, it remains unclear whether this relationship would change if specific metabolic measures, such as insulin resistance (e.g. HOMA-IR), were included as covariates in their analysis.

ADIPOSITY – Adults and Elderly

The relationship between adiposity and the onset of cognitive decline and dementia in the elderly is poorly understood. Epidemiological evidence suggests that obesity in mid to late life may predispose an individual to cognitive decline and dementia, while being underweight preceding a diagnosis may hasten the onset of dementia (Gustafson, 2012; Whitmer, 2007). To better understand this relationship, a prospective examination of approximately 1,400 men and women ages 55–88 examined how various risk factors, including BMI, were associated with cognition assessed 4–24 years later (Elias et al., 2005). Potential participants were excluded for a diagnosis of dementia, stroke, and cardiovascular disease. Neurocognitive assessments included various subtests taken from the WAIS, the Wechsler memory scale, and the multilingual aphasia examination and included logical memory-immediate recall, visual reproductions, paired associate learning, word fluency, similarities, digit span, and delayed recall. For men and women, obesity was predictive of poorer cognitive performance after covarying for age, although this association was not significant on the paired associate learning task in men. After including education, occupation, English as a native language, age, and risk factors (hypertension, diabetes, BMI, total cholesterol, and cigarette smoking) to their statistical model, the association between obesity and lower cognition in females became non-significant. In males, this association remained for visual reproductions and digit span backward. These results demonstrate that obesity, independent of diabetes, is associated with poor cognition on tests of visual and short-term memory in an elderly cohort.

Examining a broad range of ages allows for a better understanding of how cognition changes across the lifespan, not just at a single time point or range of points. A study of 408 adults from the Brain Resource International Database ranging in age from 20–82 years accomplished exactly this, examining how cognition interacts with adiposity from early to late adulthood (Gunstad et al., 2007). Potential participants were excluded for a history of psychiatric diagnoses that may affect cognition as well as for several medical conditions, including hypertension, diabetes, cardiac disease, thyroid disease, and sleep apnea. Eligible participants were administered tests designed to gauge intellectual functioning (spot-the-word), attention (digit span forward; choice reaction time; modified TMT-A; modified spatial span), and executive function (modified Stroop test; modified TMT-B; Austin Maze). Across the lifespan, BMI was associated with poorer performance on all cognitive variables assessed, though BMI could only maximally account for about 4% of the variance in performance on any given test. While increases in age were also associated with poorer cognitive performance, there were no BMI × Age interactions on any tests. Finally, a main

effect of BMI on performance was only evident for tests of executive function after adjusting for confounds.

Another publication examining the effect of BMI on cognition in younger versus older adults also sought to determine whether cognitive reserve exerts a protective effect on this relationship (Kirton and Dotson, 2016). Cognitive reserve refers to a feature of an individual that allows them to sustain more brain damage before exhibiting functional deficits. The idea is that individuals with more cognitive reserve are able to process tasks in a more efficient manner, and thus have brains that require fewer resources to operate effectively (Stern, 2002). Participants in this study were younger (mean age 21.10) and older (mean age 65.72) community-dwelling volunteers 18–81 years of age and free of neurological conditions, MRI contraindications, narcotic use, and comorbid medical conditions. Neurocognitive measures included tests of processing speed (Stroop – Word Reading, Color Naming), executive function (Stroop – Interference, TMT-B), and working memory (WAIS-III – Letter Number Sequencing, Digit Backwards). Years of education was used as a proxy for cognitive reserve. A vascular risk score, created to capture diagnosis of diabetes, hypertension, and hypercholesterolemia, was initially used as a covariate but was later dropped after failing to account for significant variance in any analysis. Executive function varied significantly as a function of age, with older adults performing worse than their younger counterparts. In older adults, cognitive reserve, as quantified by years of education, was not protective of BMI-related deficits in executive function. However, only younger adults with low levels of education were susceptible to BMI-related deficits in cognition. These findings demonstrate that adiposity, independent of diabetes, hypertension and hypercholesterolemia, contributes to age-related cognitive decline and that cognitive reserve (or education) is particularly protective of adiposity's effects in younger adults.

ADIPOSITY – Elderly

Benito-León et al. were among the first and only to examine the relationship between adiposity and cognition in a wholly elderly sample while also controlling for metabolic deficits (2013). Their analyses of a central Spanish population of approximately 2,000 community-dwelling elderly participants ages ≥ 65 again found a negative association between BMI and cognition. Neurocognitive tests included assessments of global cognitive performance, psychomotor speed, verbal fluency, and memory. Covariates included demographic variables (including age) as well as medications with CNS effects, diabetes, heart disease, hypertension, dementia, stroke, smoking/drinking, depressive symptoms/antidepressant use, and waist circumference. Participants with a normal-range BMI performed significantly better than participants with overweight and obesity on all tests. However, after adjusting for the aforementioned covariates, obesity was significantly associated with the lower quartiles of cognitive performance on 6 of 11 tests, namely immediate logical memory, delayed free recall, TMT-A, verbal fluency, 37-Mini Mental State Examination (MMSE), and pre-morbid intelligence. Overweight exhibited a similar relationship but in only 4 of 11 tests, excluding verbal fluency and TMT-A. Strengths of this investigation include adjustment for a multitude of variables that may indirectly impact cognitive function such as antidepressants and other medications with effects on the CNS. Furthermore, in adjusting for waist circumference, the authors argue they are accounting for

the increase in adipose tissue without subsequent weight gain that often accompanies the ageing process.

An assessment of approximately 2,700 elderly participants ages 65–94 participating in the ACTIVE trial, in contrast, found the opposite association between obesity and cognitive performance (Kuo et al., 2006). Here, participants were assessed on four cognitive domains that included global cognition, memory, reasoning, and processing speed. On the Useful Field of View task, designed to assess visual attention and processing speed, participants with overweight and obesity performed better than their healthy weight counterparts after correcting for demographic variables as well as smoking status, blood pressure, history of diabetes, heart attack, stroke, and hypercholesterolemia (Ball and Owsley, 1993). Effect sizes, however, were small (Cohen's $d = 0.13$) and there were no other significant differences in cognitive performance after adjusting for the aforementioned variables.

ADIPOSITY – Evidence from Magnetic Resonance Imaging

MRI has yielded unique insights into the relationship between changes in brain structure and increased adiposity. For example, Pannacciuli et al. (2006) recruited 34 participants with obesity and 36 participants with healthy weight that were free of T2D, hypertension, and cardiovascular disease. Then, they used structural MRI to examine their brain anatomy. Participants with obesity relative to their healthy-weight counterparts exhibited lower grey matter density in a variety of brain regions, including cerebellum, motor cortex, frontal operculum, putamen, and bilateral middle frontal gyrus. Increased grey matter volume, however, was also found in multiple regions of occipital cortex and inferior frontal gyri. White matter volume was notably increased in the striatum of participants with obesity. While this study did exclude for a diagnosis of T2D, it is notable that participants with obesity had significantly higher fasting insulin and fasting glucose levels compared to those with healthy weight, which were not controlled for in these analyses. It is therefore likely that metabolic dysfunction confounds these results to some extent. A subsequent investigation of a cohort of 1,428 healthy Japanese subjects from the Aoba Brain Imaging Project used volumetric and voxel-based morphometric analyses and related these measures to BMI (Taki et al., 2008). These analyses included covariates for age, diagnosis of T2D, and hypertension. There was a significant correlation between BMI and grey matter ratio in men, but not in women, which manifested in multiple brain regions. These regions, including medial temporal lobe, frontal lobe, and striatum, decreased in grey matter volume as BMI increased. The opposite pattern was found in regions such as cerebellum, inferior frontal gyrus, thalamus, and caudate. Such results demonstrate that BMI independent of a diagnosis of diabetes may predict decrements in core regions responsible for executive function (frontal lobe) and memory (medial temporal lobe). Increased grey matter volume as a function of BMI could comprise a marker of resiliency. Last, a more recent diffusion tensor imaging analysis of 103 adults varying in BMI found a negative correlation between BMI and fractional anisotropy (FA) of the corpus callosum, an indicator of white matter health in this region (Stanek et al., 2011). FA in the corpus callosum was also significantly lower in subjects with obesity compared to those with healthy weight. These results were obtained in a cohort free from a diagnosis of T2D, which suggests that these changes occur independent of metabolic dysfunction. However, a significant weakness is that none of the

aforementioned MRI studies explicitly rule out an effect of prediabetes on these brain indices.

METABOLISM – Children and Adolescents

While diabetes is typically thought to affect adults, T2D rates are increasing rapidly within the child and adolescent population (Mayer-Davis et al., 2017). Strikingly, before the mid-1990's T2D diagnoses comprised only 1–2% of all diabetes diagnoses but now comprises about 25–45% of all cases (Pulgaron and Delamater, 2014). Estimates suggest that the incidence of T2D in children and adolescents currently ranges from 1–51/1000 (Pulgaron and Delamater, 2014). Comorbid with T2D are retinopathy, neuropathy, nephropathy, and cardiovascular disease. This not only contributes to an increased risk for mortality and additional morbidity, but also increases the economic burden of diabetes which was approximated at $327 billion in 2017 (American Diabetes Association, 2018). T2D is known to negatively impact cognitive function; however, whether these deficits emerge independent of increased adiposity is unclear. Even less clear is whether these deficits emerge in children and adolescents who are now at increased risk for developing T2D.

A study examining whether cognitive dysfunction is a cause or consequence of T2D did so in a large cohort of 9,000 British children born in the late 1950's (National Child Development Study; Olsson et al., 2008). BMI was measured at 7 years of age and cognitive assessments of general intellectual ability and reading comprehension were obtained at 11 years. Diagnosis of T2D was assessed at multiple time points after 16 years of age. Poorer test scores at 11 years old were significantly associated with the development of T2D after age 16, even after adjusting for BMI. The authors argue that cognitive deficits that emerge early in life may play a large role in poor lifestyle choices that lead to T2D. A subsequent publication demonstrates a similar relationship between impaired cognition and future metabolic dysfunction in approximately 17,000 Israeli adolescents participating in the Metabolic, Lifestyle and Nutrition Assessment (MELANY) cohort (Cukierman-Yaffe et al., 2015). Participants were assessed for their General Intelligence Score (GIS) at 17 years of age and were brought back about 7 years later to determine whether or not they had impaired fasting glucose (IFG), a form of prediabetes. Those with higher GIS scores had a lower incidence of IFG, even after adjusting for demographic variables and BMI. Analyses covarying for the same variables determined that, for every one point lost in GIS, a participant was 11% more likely to develop IFG. In total, these results suggest that metabolic dysfunction in the form of T2D and IFG, independent of adiposity, may result from impaired cognition in childhood and adolescence.

A third publication in children and adolescents examined the relationship between metabolic syndrome and performance on various neurocognitive assessments in approximately 2,000 individuals ages 12–16 participating in the U.S. National Health and Nutrition Examination Survey (NHANES-III) (Rubens et al., 2016). Metabolic syndrome in these participants was defined as having low HDL-C as well as high waist circumference, triglycerides, systolic blood pressure, and fasting glucose. Neurocognitive assessments included the WRAT-R, which comprised mathematics and reading tests, and the Revised Wechsler Intelligence Scale for Children, which included the block design and digit-span subtests. After adjusting

for BMI, individuals diagnosed with metabolic syndrome performed worse than their healthy counterparts on both digit span and reading examination tests. Of note is the definition of metabolic syndrome used in this publication, which includes waist circumference, a measure of adiposity. However, when specifically examining metabolic markers of systolic blood pressure and fasting glucose, participants with elevated levels of these variables performed worse on digit span and reading examination tests, respectively. This investigation provided the first evidence that specific components of metabolic dysfunction in children and adolescents could correlate with specific negative changes in cognition.

METABOLISM –Adolescents

If the aforementioned decrements in cognition associated with metabolic dysfunction do indeed exist, it follows that these changes should manifest in the brain at a structural and/or functional level. Yau et al. (2010) offered the first report demonstrating changes in brain structure as a function of metabolic disease in adolescents. Here, 18 adolescents with obesity and T2D and 18 controls with obesity only matched for demographic variables, BMI, and waist circumference performed several neurocognitive assessments and underwent structural MRI. Adolescents with obesity and T2D performed worse on all cognitive tests, which included measures of intellectual capacity and academic achievement (Wechsler Abbreviated Scale for Intelligence FSIQ, WRAT), memory (WRAML), attention and psychomotor efficiency (DSST, Digit vigilance, WRAML), and executive function (WCST, Tower of London, COWAT). Notably, these differences were associated with an average medium to large effect size (mean Cohen's $d = 0.48$). Because participants were matched on both BMI and waist circumference and because sleep apnea did not correlate with cognition in this sample, it is likely that a decline in cognition was influenced by metabolic dysfunction rather than adiposity. Structural MRI demonstrated that, compared to controls with obesity, the brains of adolescents with T2D and obesity had significantly smaller white matter volume and significantly larger CSF volume. White matter diffusion abnormalities were observed in right cingulate, left cerebral peduncle, and left temporal stem of adolescents with T2D, while grey matter abnormalities were found in right superior temporal gyrus, left prefrontal cortex, and right prefrontal cortex.

A study similar in design to that of Yau et al. (2010) found further alterations in structure in particular regions of the brain responsible for executive function and memory, the frontal lobe and hippocampus, respectively (Bruehl et al., 2011). 18 participants with concurrent T2D and obesity and 18 controls with obesity only were matched on BMI, waist circumference, self-reported sleep apnea, and demographic variables. While neurocognitive tests were not administered, participants underwent structural MRI to determine whether deficits emerge in the brains of those diagnosed with T2D. Indeed, hippocampal and prefrontal volumes in those with T2D were significantly smaller when compared to individuals with obesity but not T2D. HbA1c, a measure of the average level of blood sugar in the past 2–3 months, was negatively correlated with prefrontal volume and positively correlated with global cerebral atrophy in those with T2D. In total, these investigations of adolescent populations suggest that, not only are changes in metabolic function associated

with declines in cognition, but they also correlate with atrophy of brain regions that are principally responsible for important cognitive functions, such as learning and memory.

METABOLISM – Adolescents and Adults

The prevalence of diabetes among U.S. adults has increased from 5.1% some thirty years ago to approximately 14% today (Harris et al., 1998; Menke et al., 2015). Rates of metabolic dysfunction are even higher, with an estimated 38% of adults classified as prediabetic (Menke et al., 2015). An increased incidence of metabolic dysfunction in the form of diabetes and prediabetes has consequences for the cognitive abilities of those diagnosed. Indeed, meta-analyses suggest that adults with T2D have clear negative changes in motor function, executive function, processing speed, verbal memory, and visual memory (Palta et al., 2014). Similar to children and adolescents, it is unknown to what extent metabolic dysfunction in adults contributes to cognitive deficits independent of the effects of increased adiposity. The first and only study to examine effects of metabolic dysfunction in young adulthood did so in a large cohort of 111 individuals from the New York City metropolitan area. Yau et al. (2012) found that those participants with metabolic syndrome had poorer spelling and arithmetic performance, as well as lower measures of attention and mental flexibility than healthy controls. These findings again manifested as differences in brain structure, as insulin resistance among participants with metabolic syndrome was significantly associated with smaller hippocampal volumes after adjusting for BMI, age, and gender. This result suggests that metabolic dysfunction independent of adiposity correlates with lower hippocampal volumes even in young adulthood, a particularly vulnerable period during development. Such changes in brain structure may predispose affected these individuals to even more adverse outcomes later in life.

METABOLISM – Adults

Structural MRI methods have thus far been used to successfully demonstrate relationships among adiposity, metabolism, and neural architecture. In contrast to structural MRI, functional MRI (or fMRI) studies typically use cognitive tasks within the MR environment to correlate the blood-oxygen-level-dependent (or BOLD) response of the brain with overt behavior. In adults, these studies have successfully examined whether metabolic dysfunction can impact brain activity. For instance, a study conducted on 32 participants ages 40–60 examined brain response to an n-back working memory paradigm as a function of insulin sensitivity (Gonzales et al., 2010). While performance among participants with normal weight, overweight, and obesity did not differ in terms of reaction time or accuracy, there was a difference in brain response among BMI groups. Participants with obesity had significantly lower activation in right parietal cortex compared to normal weight and overweight participants in response to increased working memory load. Furthermore, higher accuracy in this region of right parietal cortex was associated with greater task accuracy. Insulin sensitivity fully mediated the relationship between BMI and right parietal cortex activation, suggesting that insulin insensitivity is detrimental to the proper function of a working memory-related region of the brain.

While imaging studies clearly demonstrate a relationship between metabolic dysfunction and poorer structural and functional integrity of the brain, this does not provide definitive

evidence of a relationship between metabolism and behavior. To examine this, cognitive ability was assessed in a group of 70 young adults (Mean Age = 20.8 ± 2.4) and related to fasting blood glucose (Hawkins et al., 2016). Cognitive function was measured using the Automated Neuropsychological Assessment Metrics-4, which consists of tests designed to ascertain inhibitory control, working memory, and sustained attention. While none of the participants had a diagnosis of T2D, higher fasting glucose in this sample was predictive of poorer inhibitory control as evidenced by more commission errors on a Go-No-Go task. When directly comparing participants with prediabetes to healthy participants, this effect was both statistically significant and characterized by a large effect size (Cohen's $d = 1.22$). A trend existed for a relationship between sustained attention and metabolic dysfunction, as more errors of omission were committed on a Standard Continuous Performance Task the higher a participants' fasting blood glucose. All analyses in this study were adjusted for BMI along with several demographic variables.

METABOLISM – Adults and Elderly

The transition from early to late adulthood is associated with an increase in glucose intolerance and insulin resistance. Indeed, elderly individuals are more likely to experience loss of mobility, physical inactivity, changes in body fat distribution, and poor dietary choices that may all contribute to these changes (Schleen, 2005). Including elderly individuals therefore can inform us on how such deleterious metabolic changes, independent of adiposity, affect brain architecture and cognition as we age. Notably, a publication examining approximately 1,300 German adults from early to late adulthood (i.e. ages 21–81) found a significant negative relationship between whole-brain grey matter volume and both fasting glucose and 2-hour post-load glucose after adjusting for several potential confounds, including weight (Markus et al., 2017). Each 1mmol/l increase in fasting glucose and 2-hour post-load glucose was associated with grey matter volume reductions of 7.02ml and 1.97ml, respectively. Further, individuals classified as either having isolated impaired fasting glucose and unknown T2D exhibited significantly lower mean grey matter volume compared to those with normal glucose tolerance. The cross-sectional nature of this study makes it impossible to determine whether these features are a cause or consequence of prediabetes. However, these findings do lend strong evidence to the notion that metabolic dysfunction independent of adiposity in these adults is associated with changes in brain architecture that may in turn affect cognition. Additional evidence for a deleterious effect of metabolic dysfunction is replicated in a cohort of approximately 3,000 Swedish adults ages 60 years and older (SNAC-C cohort) (Marseglia et al., 2018). After controlling for BMI and demographic variables, prediabetes compared to diabetes-free status was associated with lower white matter volume and higher white matter hyperintensity volume in a subsample of 455 participants. Over a nine-year period, diabetes was significantly associated with a faster increase in volume of white matter hyperintensities as well as with qualitatively lower white matter volume. General cognition, as assessed using the MMSE, was also significantly associated with metabolic dysfunction. After adjusting for covariates, both prediabetes and diabetes status were associated with cognitive decline, with affected participants losing up to a maximum of three points on the MMSE over the nine-year period. Hyperglycemia and higher HbA1C levels were similarly associated with cognitive decline over this time period.

Additional evidence for an effect of insulin resistance on brain atrophy is supported by a study conducted on 372 individuals from 40–65 years of age participating in the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort (Willette et al., 2013). Participants were given structural MRI scans, genotyped for APOE, assessed for fasting glucose and insulin levels (HOMA-IR was then calculated), and administered the Rey Auditory Verbal Learning Test (RAVLT) at baseline. Approximately four years later, 121 of these participants were scanned again with structural MRI. Increased baseline HOMA-IR was significantly associated with baseline grey matter deficits in medial temporal lobe structures such as the hippocampus, parahippocampus, and amygdala. Only hippocampal and parahippocampal deficits emerged as significant after covarying for BMI, though these were not correlated with RAVLT scores. Further analyses determined that higher baseline HOMA-IR predicted reduced grey matter volume in prefrontal gyri, hippocampus and parahippocampus, and much of the cingulate cortex in the follow-up cohort four years later. An ROI analysis of hippocampus and parahippocampus determined that atrophy in these regions correlated with HOMA-IR and that this in turn mediated lower RAVLT scores after adjusting for covariates. These results provide evidence that insulin resistance predicts reduced volume of brain structures responsible for the formation and retrieval of memory that in turn mediates poorer performance on tasks designed to ascertain these abilities. Of note, morphological changes in medial temporal lobe structures often accompany dementia and Alzheimer's disease. Thus, the development of insulin resistance independent of increased adiposity may represent a risk factor for these illnesses.

A subsequent study by the same research group examined the relationship between insulin resistance and amyloid deposition in 186 members of the WRAP cohort with either a positive or negative family history of Alzheimer's disease. Amyloid plaques are formed by β-amyloid, a 39 to 43 amino acid peptide that is neurotoxic and whose deposition has previously been associated with aberrant medial temporal lobe function (Hensley et al., 1994; Marks et al., 2017). Here, higher insulin resistance in normoglycemic participants after adjusting for BMI was associated with greater amyloid deposition in frontal and temporal ROIs as measured by PET. These results demonstrate that insulin resistance, independent of adiposity, predicts amyloid deposition in key regions of the brain that mediate executive function and memory. Notably, the authors caution against inferring directionality or causality with regard to these findings, especially since these participants are not cognitively impaired. Further, a general weakness of this study is the failure to determine whether amyloid deposition and insulin resistance interact to predict neurocognitive outcomes.

In contrast to cross-sectional studies, longitudinal studies allow researchers to determine how changes in metabolic function affect cognition over time. Cognitive ability, assessed using the CVLT, the Spot-the-Word test, Symbol-Digit Modalities test, and MMSE, was measured longitudinally in a group of approximately 4,500 adult (ages 25–85) Australians of the AusDiab cohort and related to metabolic markers (Anstey et al., 2015). A diagnosis of diabetes at baseline and at a 5-year follow-up period across all participants was predictive of slower processing speed 12 years after baseline. Younger males (ages 25–59) with higher HbA1c at the 5-year follow-up time point were significantly more likely to have poor memory, with a trend existing between high blood glucose in this group and worse memory,

verbal ability, and processing speed. Over the course of the 12-year period, high, stable patterns of HbA1c levels in males younger than 60 predicted significantly worse verbal ability than those with normal, stable HbA1c levels. In females younger than 60, a similar relationship existed between high, stable fasting plasma glucose and lower episodic memory over the 12-year period. Additional latent class analyses demonstrate that increasing HbA1c levels relative to normal, stable HbA1c predict lower scores on measures of global cognitive function. All results were adjusted for BMI and several demographic variables, suggesting that these relationships exist independent of adiposity.

A comparable longitudinal study of the Finnish Diabetes Prevention Study (DPS) examined the relationship between impaired glucose tolerance, subsequent development of T2D, and a variety of cognitive outcomes (Lehtisalo et al., 2016). Participants consisted of 364 individuals ages 45–65 with impaired glucose tolerance at baseline. These participants were randomized into two intervention groups, individualized dietary and exercise counseling or general health advice, which lasted for a mean duration of 4 years. At a 9-year time point, participants were given neurocognitive assessments which included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-TS) battery and the TMT-A. These assessments were administered twice within a 2-year period, though only 282 participants had both CERAD time points and 277 had both TMT-A time points. While mean CERAD-TS scores improved over time in non-diabetics and short-term diabetics, performance declined in long-term diabetes (duration > 7.5 years). After adjusting for BMI, individuals with diabetic glucose concentrations performed significantly worse on the TMT-A with a trend toward worse performance on the CERAD-TS compared to those with normal glucose levels. Further, increases in HbA1c over the course of the study were associated with lower CERAD-TS scores, but not TMT-A scores, after adjusting for BMI. A trend existed for the same relationship between increases in fasting glucose and 2-h glucose and cognition.

Finally, evidence suggests that insulin resistance itself, even in the absence of a diagnosis of T2D, may correlate with lower cognitive functioning independent of increased adiposity. Bruehl et al. (2010) compared cognitive function in 92 middle-aged and older volunteers who were either healthy or insulin resistant without a diagnosis of T2D (i.e. fasting glucose < 126 mg/dl). Participants were assessed on measures of declarative memory, working memory, executive function, attention, and general intellectual functioning. Participants with insulin resistance performed worse on all measures of cognitive functioning in comparison to healthy controls, with a significant effect in the domains of executive function and declarative memory. After adjusting for BMI, however, only the effect on declarative memory remained significant. In parallel to Anstey et al. (2015), this study found that HbA1c levels predicted poorer cognition, but this effect was specific to the domain of executive function.

METABOLISM – Evidence from Hispanic and Latino Americans

Previous studies have found that diabetes prevalence is much higher in Hispanic-Americans than among white non-Hispanics (Schneiderman et al., 2014). A study of incidence rates in four major U.S. metropolitan areas found that approximately 18.3% of Mexican Americans ages 18–74 had diabetes, compared to 11.3% for adult non-Hispanic whites (Menke et al.,

2015). It is therefore particularly important to examine the influence of metabolic dysfunction on cognition in these populations, as they share a disproportionate amount of the burden. To accomplish this, a study examined the relationship between cognitive function and glycemic control among participants of the Hispanic Community Health Study (HCHS), a cohort comprised ultimately of 1794 Hispanic adults 45–76 years of age following subject exclusion (Strizich et al., 2016). Neurocognitive tests included the previously-described DSST, Spanish English Verbal Learning Test, and word fluency test. A global cognitive measure was created out of the sum of each test score. Analyses were adjusted for demographic variables as well as history of cardiovascular disease and BMI. Experimenters found that the odds of uncontrolled diabetes (i.e. HbA1c ≥ 7%) were higher for individuals with lower DSST scores. No such relationship was found with the other tests. A similar study of a larger, slightly older cohort of Hispanic participants found additional correlations between metabolic dysfunction and cognitive outcomes independent of adiposity. Here, 600 participants ages 55 to 64 from the Northern Manhattan Study of Metabolism and Mind were assessed for metabolic measures and administered a neurocognitive battery (Luchsinger et al., 2015). This battery consisted of tests of memory and executive function, and included the Color Trails Test (memory), verbal fluency (memory), and the Selective Reminding Test (SRT) (executive function). After covarying for BMI, demographic variables, and vascular risk factors, experimenters found that individuals with high HbA1c had lower SRT total recall and delayed recall scores, but no effect was observed on recognition scores. Diabetes status was significantly associated with lower scores in total recall, but not for delayed recall or recognition. Further, prediabetes status was associated with lower performance on both Color Trails 1 and 2, but no effect was found for verbal fluency. Finally, experimenters related composite Z-scores of executive function, memory, and global cognition to their metabolic parameters of interest. A trend existed for an anticorrelated relationship between executive function z-scores and HbA1c, as well as for global cognition z-scores and diabetes status. A significant association after adjusting for covariates was only found between executive function z-scores and prediabetes status. These results demonstrate a clear relationship between metabolic dysfunction and cognitive decline in an adult Hispanic population independent of adiposity.

DISCUSSION

Evidence from the literature suggests that both adiposity independent of metabolic dysfunction and metabolic dysfunction independent of adiposity can adversely impact cognition throughout the lifespan. In this review we have found consistent evidence for these effects on performance on tasks of attention, intelligence, memory, cognitive flexibility, processing speed, and general executive function, as well as structural brain abnormalities in frontal and medial temporal lobe regions (see Table 1 and Fig. S1–2). The biological bases of these effects are likely bidirectional and certainly reflect multiple pathophysiological mechanisms.

Adiposity can have dramatic consequences on body physiology, including systemic inflammation, reduced cardiac fitness, and vascular changes, which can impact cognition (Gunstad et al., 2007). Evidence suggests that obesity can induce chronic low-grade inflammation that directly harms neurons independent of its effects on metabolism

(Spyridaki et al., 2016). This process occurs as adipocytes increase in size leading to a systemic pro-inflammatory response that causes adverse changes to neuronal circuitry, metabolism, endocrine response, and can even harm hippocampal neurogenesis (Spyridaki et al., 2016). Recent evidence has found that inflammation in humans predicts poorer performance on tests of memory and executive function as well as reduced brain grey matter and white matter volume, which is directly correlated with BMI (Marsland et al., 2015). Additional analyses found that associations between BMI, cognitive function, white matter volume, and grey matter volume were directly mediated by a composite of inflammatory markers plasma interleukin-6 (IL-6) and C-reactive protein (CRP) (Marsland et al., 2015).

Adiposity may directly impact cognition through its effects on cardiovascular fitness. Hypertension resulting from increased peripheral adipose tissue can harm the integrity of cerebral vasculature, leading to ischemic damage of brain white matter (Iadecola et al., 2016). Further, hypertension and cardiovascular disease predict increased incidences of silent infarcts that in turn predict significantly poorer performance on tests of memory and attention (Fanning et al., 2014; Squarzoni et al., 2017). Increased fat deposition in the tongue and increased tongue volume has been found in sleep apneics with obesity compared to controls (Kim et al., 2010; Chi et al., 2011). Sleep apnea's deleterious effects on cognitive function are extensive, and have been observed in the domains of memory, executive function, and psychomotor speed (Gagnon et al., 2014). Increased body fat, even in the tongue, can cause downstream effects on cognition that exist independent of any relationship between body fat and metabolism.

Metabolic dysfunction and insulin resistance in particular are known to have, among other effects, damaging impacts on brain vasculature, inflammatory processes, and mitochondrial function, which can alter cognition. In the brain, mitochondrial dysfunction leading to elevated Reactive Oxidative Species (ROS) has been linked to early brain ageing (De Felice and Ferreira, 2014). Insulin is known to exert protective effects against oxidative stress in the brain, and thus central insulin resistance can act in concert with mitochondrial dysfunction to promote cognitive decline (De Felice and Ferreira, 2014; Ramalingayya et al., 2017). Hyperglycemia itself can alter polylol and hexosamine pathways and increase glycation end products, which could alter cognition via enhanced oxidative stress, tissue damage, and cellular dysfunction (Pennathur and Heinecke, 2007; Kodl and Seaquist, 2008; Yaffe et al., 2012).

Insulin resistance also plays a role in the pathophysiology of neurodegenerative diseases, such as Alzheimer's disease (AD) and vascular dementia (Craft and Watson, 2004). In particular, insulin resistance in AD potentiates brain amyloidosis and alters clearance of amyloid beta, which can have direct effects on memory (Craft and Watson, 2004). Animal models demonstrate that insulin binding sites are highly concentrated in hippocampus, and thus impaired insulin signaling in this region may directly affect learning and memory separate from its role in AD pathology (Dore et al., 1997; Bruehl et al., 2009). Similarly, elevated blood glucose has been found to predict hippocampal and amygdalar atrophy, accounting for 6–10% of volume change in these brain regions (Cherbuin et al., 2012).

Insulin plays additional roles in altering brain structure and function. In the periphery, insulin signaling in endothelial cells plays a pivotal role in glucose uptake and vasodilation within muscle, which can be negatively impacted by insulin resistance (Kubota et al., 2011; Steinberg et al., 1996). Similar dysfunction in endothelial cells comprising the blood brain barrier could theoretically impair cognitive processes as well. While adipose tissue can induce a systemic inflammatory response leading to poorer cognition, insulin resistance itself can also lead to inflammation. For example, evidence suggests that increased mean fasting insulin and HOMA-IR significantly predicts elevated serum CRP, a marker of systemic inflammation, independent of BMI (Gelaye et al., 2010). Higher IL-6 has also been found to correlate with IFG/IGT status independent of adiposity (de Rekeneire et al., 2006). Again, both of these markers are inversely correlated with cognition (Wright et al., 2006; Sweat et al., 2008).

Evidence suggests that metabolic dysfunction and adiposity may both affect cognition independent of one another. However, obesity-related cognitive decline is likely not just a consequence of the downstream effects of excess adipose tissue and insulin resistance, but a cause as well. Lower childhood IQ is predictive of adult BMI, suggesting that individuals of lower IQ may make poorer food choices and engage in a less healthy lifestyle that ultimately leads to obesity (Chandola et al., 2006). This results in a “vicious cycle” where lower cognitive abilities perpetuate obesity and insulin resistance, which in turn perpetuate cognitive decline through the lifespan. This cycle is best evidenced by rodent models, in which excessive intake of a western diet directly causes hippocampal dysfunction and subsequent impaired memory inhibition, which leads to increased responding to appetitive food cues (Kanoski and Davidson, 2011). If an organism is ‘pushed’ into this cycle by a predilection to make poorer food choices due to lower IQ or pre-existing impairment in executive function, they will be stuck in this cycle.

CONCLUSIONS

In conclusion, we have found evidence from the literature suggesting that increased adiposity and metabolic dysfunction associated with obesity may affect cognition independent of one another. Memory, executive function, and medial temporal lobe structures seem particularly affected by these processes. These changes may likely occur due to both distinct and overlapping physiological changes, such as increased central inflammation, oxidative stress, sleep apnea, decreased neurogenesis, and silent infarcts, which can directly impact brain function. We recommend more prospective and longitudinal studies, particularly ones that seek to determine whether potential deficits in cognition are a cause or consequence (or both) of insulin resistance and adiposity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Almeida-Suhett CP, Graham A, Chen Y, & Deuster P (2017). Behavioral changes in male mice fed a high-fat diet are associated with IL-1β expression in specific brain regions. Physiology & behavior, 169, 130–140. [PubMed: 27876639]

American Diabetes Association. (2018). Economic Costs of Diabetes in the US in 2017. Diabetes care, 41(5), 917. [PubMed: 29567642]

Anstey KJ, Sargent-Cox K, Eramudugolla R, Magliano DJ, & Shaw JE (2015). Association of cognitive function with glucose tolerance and trajectories of glucose tolerance over 12 years in the AusDiab study. Alzheimer's research & therapy, 7(1), 48.

Ariza M, Garolera M, Jurado MA, Garcia-Garcia I, Hernan I, Sanchez-Garre C, Vernet-Vernet M, Sender-Palacios MJ, Marques-Iturria I, Pueyo R, Segura B, & Narberhaus A (2012). Dopamine genes (DRD2/ANKK1-TaqA1 and DRD4–7R) and executive function: their interaction with obesity. PLoS One, 7(7), e41482. [PubMed: 22848508]

Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, & Van Tol HH (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. Journal of neurochemistry, 65(3), 1157–1165. [PubMed: 7643093]

Ball K, & Owsley C (1993). The useful field of view test: a new technique for evaluating age-related declines in visual function. Journal of the American Optometric Association, 64(1), 71–79. [PubMed: 8454831]

Benito-León J, Mitchell AJ, Hernández-Gallego J, & Bermejo-Pareja F (2013). Obesity and impaired cognitive functioning in the elderly: a population-based cross-sectional study (NEDICES). European Journal of Neurology, 20(6), 899–e77. [PubMed: 23323838]

Beydoun MA, Beydoun HA, & Wang Y (2008). Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obesity reviews, 9(3), 204–218. [PubMed: 18331422]

Biessels GJ, Deary IJ, & Ryan CM (2008). Cognition and diabetes: a lifespan perspective. The Lancet Neurology, 7(2), 184–190. [PubMed: 18207116]

Bocarsly ME, Fasolino M, Kane GA, LaMarca EA, Kirschen GW, Karatsoreos IN, McEwen BS, & Gould E (2015). Obesity diminishes synaptic markers, alters microglial morphology, and impairs cognitive function. Proceedings of the National Academy of Sciences, 112(51), 15731–15736.

Boeka AG, & Lokken KL (2008). Neuropsychological performance of a clinical sample of extremely obese individuals. Archives of Clinical Neuropsychology, 23(4), 467–474. [PubMed: 18448310]

Bozkurt H, Özer S, Yílmaz R, Sönmezgöz E, Kazancí Ö, Erbaş O, & Demir O (2017). Assessment of neurocognitive functions in children and adolescents with obesity. Applied Neuropsychology: Child, 6(4), 262–268. [PubMed: 27183151]

Bruehl H, Sweat V, Hassenstab J, Polyakov V, & Convit A (2010). Cognitive impairment in nondiabetic middle-aged and older adults is associated with insulin resistance. Journal of clinical and experimental neuropsychology, 32(5), 487–493. [PubMed: 20524222]

Bruehl H, Sweat V, Tirsi A, Shah B, & Convit A (2011). Obese adolescents with type 2 diabetes mellitus have hippocampal and frontal lobe volume reductions. Neuroscience and medicine, 2(1), 34. [PubMed: 21691448]

Casey BJ, Jones RM, & Hare TA (2008). The adolescent brain. Annals of the New York Academy of Sciences, 1124(1), 111–126. [PubMed: 18400927]

Chandola T, Deary IJ, Blane D, & Batty GD (2006). Childhood IQ in relation to obesity and weight gain in adult life: the National Child Development (1958) Study. International journal of obesity, 30(9), 1422. [PubMed: 16520812]

Cheke LG, Simons JS, & Clayton NS (2016). Higher body mass index is associated with episodic memory deficits in young adults. The Quarterly Journal of Experimental Psychology, 69(11), 2305–2316. [PubMed: 26447832]

Cheng G, Huang C, Deng H, & Wang H (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. Internal medicine journal, 42(5), 484–491. [PubMed: 22372522]

Cherbuin N, Sachdev P, & Anstey KJ (2012). Higher normal fasting plasma glucose is associated with hippocampal atrophy: The PATH Study. Neurology, 79(10), 1019–1026. [PubMed: 22946113]

Chi L, Comyn FL, Mitra N, Reilly MP, Wan F, Maislin G, ... & Schwab RJ (2011). Identification of craniofacial risk factors for obstructive sleep apnoea using three-dimensional MRI. European Respiratory Journal, erj01192–2010.

Clegg DJ, Gotoh K, Kemp C, Wortman MD, Benoit SC, Brown LM, ... & Woods SC (2011). Consumption of a high-fat diet induces central insulin resistance independent of adiposity. Physiology & behavior, 103(1), 10–16. [PubMed: 21241723]

Comings DE, Gonzalez N, Wu S, Gade R, Muhleman D, Saucier G, ... & Rugle LJ (1999). Studies of the 48 bp repeat polymorphism of the DRD4 gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. American journal of medical genetics, 88(4), 358–368. [PubMed: 10402503]

Cortese S, & Vincenzi B (2011). Obesity and ADHD: clinical and neurobiological implications In Behavioral neuroscience of attention deficit hyperactivity disorder and its treatment (pp. 199–218). Springer, Berlin, Heidelberg.

Cournot MCMJ, Marquie JC, Ansiau D, Martinaud C, Fonds H, Ferrieres J, & Ruidavets JB (2006). Relation between body mass index and cognitive function in healthy middle-aged men and women. Neurology, 67(7), 1208–1214. [PubMed: 17030754]

Craft S, & Watson GS (2004). Insulin and neurodegenerative disease: shared and specific mechanisms. The lancet neurology, 3(3), 169–178. [PubMed: 14980532]

Cukierman-Yaffe T, Kasher-Meron M, Fruchter E, Gerstein HC, Afek A, Derazne E, Tzur D, Karasik A, & Twig G (2015). Cognitive performance at late adolescence and the risk for impaired fasting glucose among young adults. The Journal of Clinical Endocrinology & Metabolism, 100(12), 4409–4416. [PubMed: 26431506]

De Felice FG, & Ferreira ST (2014). Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes, DB_131954.

Delgado-Rico E, Río-Valle JS, González-Jiménez E, Campoy C, & Verdejo-García A (2012). BMI predicts emotion-driven impulsivity and cognitive inflexibility in adolescents with excess weight. Obesity, 20(8), 1604–1610. [PubMed: 22421897]

De Rekeneire N, Peila R, Ding J, Colbert LH, Visser M, Shorr RI, ... & Vellas B (2006). Diabetes, hyperglycemia, and inflammation in older individuals: the health, aging and body composition study. Diabetes care, 29(8), 1902–1908. [PubMed: 16873800]

Dore S, Kar S, Rowe W, & Quirion R (1997). Distribution and levels of [125I] IGF-I,[125I] IGF-II and [125I] insulin receptor binding sites in the hippocampus of aged memory-unimpaired and-impaired rats. Neuroscience, 80(4), 1033–1040. [PubMed: 9284058]

Elias MF, Elias PK, Sullivan LM, Wolf PA, & D'Agostino RB (2005). Obesity, diabetes and cognitive deficit: the Framingham Heart Study. Neurobiology of aging, 26(1), 11–16. [PubMed: 16223549]

Elliott R, Dolan RJ, & Frith CD (2000). Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cerebral cortex, 10(3), 308–317. [PubMed: 10731225]

Fanning JP, Wong AA, & Fraser JF (2014). The epidemiology of silent brain infarction: a systematic review of population-based cohorts. BMC medicine, 12(1), 119. [PubMed: 25012298]

Fergenbaum JH, Bruce S, Lou W, Hanley AJ, Greenwood C, & Young TK (2009). Obesity and lowered cognitive performance in a Canadian First Nations population. Obesity, 17(10), 1957–1963. [PubMed: 19478788]

Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, & Luchsinger JA (2009). Midlife and late-life obesity and the risk of dementia: cardiovascular health study. Archives of neurology, 66(3), 336–342. [PubMed: 19273752]

Frank J (2016). Origins of the obesity pandemic can be analysed: statistical and biological methods are available to probe why the prevalence of obesity has risen more in some countries than in others. Nature, 532(7598), 149–150. [PubMed: 27075060]

Gagnon K, Baril AA, Gagnon JF, Fortin M, Decary A, Lafond C, ... & Gosselin N (2014). Cognitive impairment in obstructive sleep apnea. Pathologie Biologie, 62(5), 233–240. [PubMed: 25070768]

Gelaye B, Revilla L, Lopez T, Suarez L, Sanchez SE, Hevner K, ... & Williams MA (2010). Association between insulin resistance and c-reactive protein among Peruvian adults. Diabetology & metabolic syndrome, 2(1), 30. [PubMed: 20482756]

Gonzales MM, Tarumi T, Miles SC, Tanaka H, Shah F, & Haley AP (2010). Insulin sensitivity as a mediator of the relationship between BMI and working memory-related brain activation. Obesity, 18(11), 2131–2137. [PubMed: 20814415]

Grossetta Nardini HK, & Wang L (2018). The Yale MeSH Analyzer. Retrieved from http://mesh.med.yale.edu/

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, & Gordon E (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Comprehensive psychiatry, 48(1), 57–61. [PubMed: 17145283]

Gunstad J, Spitznagel MB, Paul RH, Cohen RA, Kohn M, Luyster FS, Clark R, Williams LM, & Gordon E (2008). Body mass index and neuropsychological function in healthy children and adolescents. Appetite, 50(2–3), 246–251. [PubMed: 17761359]

Gunstad J, Lhotsky A, Wendell CR, Ferrucci L, & Zonderman AB (2010). Longitudinal examination of obesity and cognitive function: results from the Baltimore longitudinal study of aging. Neuroepidemiology, 34(4), 222–229. [PubMed: 20299802]

Gustafson DR (2012). Adiposity and cognitive decline: underlying mechanisms. Journal of Alzheimer's Disease, 30(s2), S97–S112.

Hao S, Dey A, Yu X, & Stranahan AM (2016). Dietary obesity reversibly induces synaptic stripping by microglia and impairs hippocampal plasticity. Brain, behavior, and immunity, 51, 230–239.

Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, ... & Byrd-Holt DD (1998). Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988–1994. Diabetes care, 21(4), 518–524. [PubMed: 9571335]

Hawkins MA, Gunstad J, Calvo D, & Spitznagel MB (2016). Higher fasting glucose is associated with poorer cognition among healthy young adults. Health Psychology, 35(2), 199. [PubMed: 26523354]

Hensley K, Carney JM, Mattson MP, Aksenova M, Harris M, Wu JF, ... & Butterfield DA (1994). A model for beta-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer disease. Proceedings of the National Academy of Sciences, 91(8), 3270–3274.

Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, ... & Saczynski JS (2016). Impact of hypertension on cognitive function: a scientific statement from the American Heart Association. Hypertension, 68(6), e67–e94. [PubMed: 27977393]

Jaacks LM, Slining MM, & Popkin BM (2015). Recent trends in the prevalence of under- and overweight among adolescent girls in low-and middle-income countries. Pediatric obesity, 10(6), 428–435. [PubMed: 25558987]

Jönsson EG, Nöthen MM, Grünhage F, Farde L, Nakashima Y, Propping P, & Sedvall GC (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. Molecular psychiatry, 4(3), 290. [PubMed: 10395223]

Kanoski SE, & Davidson TL (2011). Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiology & behavior, 103(1), 59–68. [PubMed: 21167850]

Khaodhiar L, McCowen KC, & Blackburn GL (1999). Obesity and its comorbid conditions. Clinical cornerstone, 2(3), 17–31. [PubMed: 10696282]

Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, ... & Schwab RJ (2014). Tongue fat and its relationship to obstructive sleep apnea. Sleep, 37(10), 1639–1648. [PubMed: 25197815]

Kirton JW, & Dotson VM (2016). The interactive effects of age, education, and BMI on cognitive functioning. Aging, Neuropsychology, and Cognition, 23(2), 253–262.

Kodl CT, & Seaquist ER (2008). Cognitive dysfunction and diabetes mellitus. Endocrine reviews, 29(4), 494–511. [PubMed: 18436709]

Kubota T, Kubota N, Kumagai H, Yamaguchi S, Kozono H, Takahashi T, ... & Kumagai K (2011). Impaired insulin signaling in endothelial cells reduces insulin-induced glucose uptake by skeletal muscle. Cell metabolism, 13(3), 294–307. [PubMed: 21356519]

Kuo HK, Jones RN, Milberg WP, Tennstedt S, Talbot L, Morris JN, & Lipsitz LA (2006). 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, 54(1), 97–103. [PubMed: 16420204]

Lavie CJ, Milani RV, & Ventura HO (2009). Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. Journal of the American College of Cardiology, 53(21), 1925–1932. [PubMed: 19460605]

Lehtisalo J, Lindström J, Ngandu T, Kivipelto M, Ahtiluoto S, Ilanne-Parikka P, Keinanen-Kiukaanniemi A, Eriksson JG, Uusitupa M, Tuomilehto J, & Luchsinger JA (2016). Diabetes, glycaemia, and cognition—a secondary analysis of the Finnish Diabetes Prevention Study. Diabetes/metabolism research and reviews, 32(1), 102–110. [PubMed: 26172529]

Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA, ... & McPherson K (2015). Child and adolescent obesity: part of a bigger picture. The Lancet, 385(9986), 2510–2520.

Luchsinger JA, Cabral R, Eimicke JP, Manly JJ, & Teresi J (2015). Glycemia, diabetes status, and cognition in middle aged Hispanics. Psychosomatic medicine, 77(6), 653. [PubMed: 26163818]

Maayan L, Hoogendoorn C, Sweat V, & Convit A (2011). Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. Obesity, 19(7), 1382–1387. [PubMed: 21350433]

Marks SM, Lockhart SN, Baker SL, & Jagust WJ (2017). Tau and β-amyloid are associated with medial temporal lobe structure, function and memory encoding in normal aging. Journal of Neuroscience, 3769–16.

Markus MRP, Ittermann T, Wittfeld K, Schipf S, Siewert-Markus U, Bahls M, Bulow R, Werner N, Janowitz D, Baumeister SE, Felix SB, Dorr M, Rathmann W, Volzke H, & Grabe HJ (2017). Prediabetes is associated with lower brain gray matter volume in the general population. The Study of Health in Pomerania (SHIP). Nutrition, Metabolism and Cardiovascular Diseases, 27(12), 1114–1122.

Marseglia A, Fratiglioni L, Kalpouzos G, Wang R, Bäckman L, & Xu W (2018). Prediabetes and diabetes accelerate cognitive decline and predict microvascular lesions: A population-based cohort study. Alzheimer's & Dementia.

Marsland AL, Gianaros PJ, Kuan DCH, Sheu LK, Krajina K, & Manuck SB (2015). Brain morphology links systemic inflammation to cognitive function in midlife adults. Brain, behavior, and immunity, 48, 195–204.

Martin A, Booth JN, Young D, Revie M, Boyter AC, Johnston B, Tomporowski PB, & Reilly JJ (2016). Associations between obesity and cognition in the pre-school years. Obesity, 24(1), 207–214. [PubMed: 26638123]

Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, ... & Pihoker C (2017). Incidence trends of type 1 and type 2 diabetes among youths, 2002–2012. New England Journal of Medicine, 376(15), 1419–1429. [PubMed: 28402773]

McFall GP, Geall BP, Fischer AL, Dolcos S, & Dixon RA (2010). Testing covariates of type 2 diabetes-cognition associations in older adults: Moderating or mediating effects?. Neuropsychology, 24(5), 547. [PubMed: 20804243]

Meldrum DR, Morris MA, & Gambone JC (2017). Obesity pandemic: causes, consequences, and solutions—but do we have the will?. Fertility and sterility, 107(4), 833–839. [PubMed: 28292617]

Menke A, Casagrande S, Geiss L, & Cowie CC (2015). Prevalence of and trends in diabetes among adults in the United States, 1988–2012. Jama, 314(10), 1021–1029. [PubMed: 26348752]

Munafo MR, Matheson IJ, & Flint J (2007). Association of the DRD2 gene Taq1A polymorphism and alcoholism: a meta-analysis of case–control studies and evidence of publication bias. Molecular psychiatry, 12(5), 454. [PubMed: 17453061]

Musen G, Jacobson AM, Bolo NR, Simonson DC, Shenton ME, McCartney RL, ... & Hoogenboom WS (2012). Resting-state brain functional connectivity is altered in type 2 diabetes. Diabetes, 61(9), 2375–2379. [PubMed: 22664957]

Nacak M, Isir AB, Balci SO, Pehlivan S, Benlier N, & Aynacioglu S (2012). Analysis of dopamine D2 receptor (DRD2) gene polymorphisms in cannabinoid addicts. Journal of forensic sciences, 57(6), 1621–1624. [PubMed: 22536882]

Olsson GM, Hulting AL, & Montgomery SM (2008). Cognitive function in children and subsequent type 2 diabetes. Diabetes Care, 31(3), 514–516. [PubMed: 18083794]

Pannacciulli N, Del Parigi A, Chen K, Le DSN, Reiman EM, & Tataranni PA (2006). Brain abnormalities in human obesity: a voxel-based morphometric study. Neuroimage, 31(4), 1419–1425. [PubMed: 16545583]

Palta P, Schneider AL, Biessels GJ, Touradji P, & Hill-Briggs F (2014). Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. Journal of the International Neuropsychological Society, 20(3), 278–291. [PubMed: 24555960]

Pennathur S, & Heinecke JW (2007). Oxidative stress and endothelial dysfunction in vascular disease. Current diabetes reports, 7(4), 257–264. [PubMed: 17686400]

Profenno LA, Porsteinsson AP, & Faraone SV (2010). Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. Biological psychiatry, 67(6), 505–512. [PubMed: 19358976]

Pugazhenthi S, Qin L, & Reddy PH (2017). Common neurodegenerative pathways in obesity, diabetes, and Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1863(5), 1037–1045. [PubMed: 27156888]

Pulgaron ER, & Delamater AM (2014). Obesity and type 2 diabetes in children: epidemiology and treatment. Current diabetes reports, 14(8), 508. [PubMed: 24919749]

Ramalingayya GV, Sonawane V, Cheruku SP, Kishore A, Nayak PG, Kumar N, ... & Nandakumar K (2017). Insulin protects against brain oxidative stress with an apparent effect on episodic memory in doxorubicin-induced cognitive dysfunction in wistar rats. Journal of Environmental Pathology, Toxicology and Oncology, 36(2).

Regestein QR (2018). The big, bad obesity pandemic. Menopause, 25(2), 129–132. [PubMed: 29315131]

Reinert KRS, Po'e EK, & Barkin SL (2013). The relationship between executive function and obesity in children and adolescents: a systematic literature review. Journal of obesity, 2013.

Rubens M, Ramamoorthy V, Saxena A, George F, Shehadeh N, Attonito J, McCoy V, & Beck-Sagué CM (2016). Relationship between metabolic syndrome and cognitive abilities in US adolescents. Metabolic syndrome and related disorders, 14(8), 397–403. [PubMed: 27529580]

Sawilowsky SS (2009). New effect size rules of thumb.

Scheen AJ (2005). Diabetes mellitus in the elderly: Insulin resistance and/or impaired insulin secretion?. Diabetes & Metabolism, 31, 5S27–5S34. [PubMed: 16415763]

Schneiderman N, Llabre M, Cowie CC, Barnhart J, Carnethon M, Gallo LC, ... & Teng Y (2014). Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic community health study/study of Latinos (HCHS/SOL). Diabetes Care, 37(8), 2233–2239. [PubMed: 25061138]

Spyridaki EC, Avgoustinaki PD, & Margioris AN (2016). Obesity, inflammation and cognition. Current Opinion in Behavioral Sciences, 9, 169–175.

Squarzoni P, Tamashiro-Duran JH, Duran FL, Leite CC, Wajngarten M, Scazufca M, ... & Busatto GF (2017). High frequency of silent brain infarcts associated with cognitive deficits in an economically disadvantaged population. Clinics, 72(8), 474–480. [PubMed: 28954006]

Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, & Gunstad JJ (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. Obesity, 19(3), 500–504. [PubMed: 21183934]

Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, & Baron AD (1996). Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. The Journal of clinical investigation, 97(11), 2601–2610. [PubMed: 8647954]

Stern Y (2002). What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society, 8(3), 448–460. [PubMed: 11939702]

Strizich G, Kaplan RC, González HM, Daviglus ML, Giachello AL, Teng Y, Lipton RB, & Grober E (2016). Glycemic control, cognitive function, and family support among middle-aged and older Hispanics with diabetes: The Hispanic Community Health Study/Study of Latinos. Diabetes research and clinical practice, 117, 64–73. [PubMed: 27329024]

Sweat V, Yates KF, Migliaccio R, & Convit A (2017). Obese adolescents show reduced cognitive processing speed compared with healthy weight peers. Childhood Obesity, 13(3), 190–196. [PubMed: 28256922]

Sweat V, Starr V, Bruehl H, Arentoft A, Tirsi A, Javier E, & Convit A (2008). C-reactive protein is linked to lower cognitive performance in overweight and obese women. Inflammation, 31(3), 198–207. [PubMed: 18347963]

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

Tuulari JJ, Karlsson HK, Hirvonen J, Salminen P, Nuutila P, & Nummenmaa L (2015). Neural circuits for cognitive appetite control in healthy and obese individuals: an fMRI study. PLoS One, 10(2), e0116640. [PubMed: 25658479]

Van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ, & Biessels GJ (2009). Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: a systematic comparison of their impact on cognition. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1792(5), 470–481. [PubMed: 18848880]

Wallace R, & Wallace D (2016). Gene Expression and Its Discontents: the Social Production of Chronic Disease, Cham, Switzerland: Springer International Publishing CrossRef Google Scholar.

Whitmer RA (2007). The epidemiology of adiposity and dementia. Current Alzheimer Research, 4(2), 117–122. [PubMed: 17430233]

Willette AA, Xu G, Johnson SC, Birdsill AC, Jonaitis EM, Sager MA, Hermann BP, La Rue A, Asthana S, & Bendlin BB (2013). Insulin resistance, brain atrophy, and cognitive performance in late middle–aged adults. Diabetes care, 36(2), 443–449. [PubMed: 23069842]

Willette AA, Johnson SC, Birdsill AC, Sager MA, Christian B, Baker LD, Craft S, Oh J, Statz E, Hermann BP, Jonaitis EM, Koscik RL, La Rue A, Asthana S, & Bendlin BB (2015). Insulin resistance predicts brain amyloid deposition in late middle-aged adults. Alzheimer's & dementia, 11(5), 504–510.

Wilson PW, D'agostino RB, Sullivan L, Parise H, & Kannel WB (2002). Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Archives of internal medicine, 162(16), 1867–1872. [PubMed: 12196085]

Wright CB, Sacco RL, Rundek TR, Delman JB, Rabbani LE, & Elkind MS (2006). Interleukin-6 is associated with cognitive function: the Northern Manhattan Study. Journal of Stroke and Cerebrovascular Diseases, 15(1), 34–38. [PubMed: 16501663]

Yaffe K, Falvey C, Hamilton N, Schwartz AV, Simonsick EM, Satterfield S, ... & Harris TB (2012). Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. Archives of neurology, 69(9), 1170–1175. [PubMed: 22710333]

Yau PL, Javier DC, Ryan CM, Tsui WH, Ardekani BA, Ten S, & Convit A (2010). Preliminary evidence for brain complications in obese adolescents with type 2 diabetes mellitus. Diabetologia, 53(11), 2298–2306. [PubMed: 20668831]

Yau PL, Mary Grace Castro BS, Tagani A, Tsui WH, & Convit A (2012). Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics, peds-2012.

Highlights

- Adiposity and metabolic dysfunction may independently and adversely alter cognition
- Effects have been found on attention, memory, and executive function, among others
- Structural and functional changes occur in frontal and medial temporal brain regions
- Additional longitudinal studies are needed to resolve cause versus consequence

Table 1.

Characteristics and Results of Included Studies

Publication	Design	N	Population	Mean Age	Relevant Covariates or Exclusions	Tests Administered	Main Findings
Adiposity							
Ariza et al.	Case/Control	42 Obese, 42 Lean	People living near three public medical centers	Obese = 31.81 Lean = 29.67	Excl: presence of diabetes or hypertension	LN, SDMT, TMT-A, TMT-B, COWA-T, Stroop, WCST	Ob TaqA1 carriers worse on LN; Ob non-carriers of D4.7 worse on TMT B-A than lean non-carriers, opposite true for carriers
BenitoLeon et al.	Case/Control	507 Lean, 850 Overweight, 592 Obese	Elderly participants living in three Spanish communities	Lean = 76.9 Overweight = 75.7 Obese = 74.9	Cov: diabetes, hypertension, heart disease, dementia, stroke	MMSE, attention task, visual order task, construction task, TMT-A, Verbal fluency, Six objects test, Story recall, Word accentuation test	Ob/Ow status assoc. with lowest quartiles on MMSE, TMT-A, VF, SOT (delayed recall and immediate logical memory), WAT; Ob worse than Ow
Boeka et al.	Cross-sectional	68 Obese	Patients seeking surgical treatment for obesity	Obese = 41	No differences in performance on neuropsychological tests between participants with and without diabetes or hypertension	WRAT-3, WAIS-III, CTF, TMT-A, TMT-B, WCST, COWA-T, CVLT, Logical memory subtest of WMS	Ob performed worse compared to normative data on CFT Copy, WCST, and did better on COWA-T
Bozkurt et al.	Case/Control	92 Obese, 55 Lean	Children and Adolescents referred to a Turkish hospital	Obese = 11.85 Lean = 11.90	Excl: T2D, metabolic syndrome, hypertension, NAFLD	CNSVS (verbal memory, visual memory, finger tapping, single digit coding, Stroop, shifting attention, and continuous performance tests)	Ob group performed worse on all cognitive indices with large effect size (d = 1.29–1.63)
Cheke et al.	Case/Control	26 Lean, 24 Overweight and Obese	Adults recruited via advertisements	Full sample = 24.62	Excl: Diagnosis of diabetes	“Treasure Hunt Task” – encoding, WWW, where, what, and when	Negative effect of increased BMI on performance of all tasks
Cournot et al.	Longitudinal	2,223 participants across BMI ranges	Current and former salaried workers of VISAT study	Range: 32–62 at baseline	Excl: Vascular disease, dementia; Cov: diabetes, blood pressure, hypertriglyceri demia	word list learning + free recall + delayed free recall, WAIS DigitSymbol substitution subtest, selective attention test	Baseline: Cognitive performan ce lower w/ higher BMI; BMI at baseline associated with lower scores at follow up on word list learning, delayed recall, DSST, and selective attention (women only); Longitudi nal: Negative associatio n between BMI and changes in cognition for word-list learning
Delgado-Rico et al.	Case/Control	26 Obese, 16 Overweight, 21 Lean	Adolescents recruited through educational centers and national health services to participate in later interventio n for excess weight	Lean = 14.14 Overwei ght and Obese = 14.19	Excl: Non-normal insulin, basal glucose, triglycerides, HDL, total cholesterol	Delis–Kaplan Executive Function System (D-KEFS) Color-Word Interference Test Stroop (CWIT Stroop)	BMI negatively predicts Stroop switching performance
Elias et al.	Longitudinal	1,423 participants across BMI ranges	Participants recruited through the Framingha m Heart Study	Men = 65.7 Women = 67.2 Mean = 67	Excl: Stroke, dementia, CVD Cov: Ever diabetic, diabetes years	Logical memory-immediate recall, Visual Reproductions, Paired Associates Learning, Digit Span Forward, Digit Span Backward, Word Fluency (Controlled Oral Word Associations), Similarities, Logical memory- delayed recall, global composite	Obesity status in men, not women, associated with worse performance on visual reproductions, digit span backward, and global composite. Diabetes and diabetes years did not interact with obesity

Publication	Design	N	Population	Mean Age	Relevant Covariates or Exclusions	Tests Administered	Main Findings
Fergenbaum et al.	Cross-sectional	207 participants w/ CDT data, 109 w/ TMT data	Adults in a First Nations community of southern Manitoba, Canada	Range: 19–65 Median: 39 for CDT participants	Excl: Diabetes, fasting glucose ≥ 7 mmol/l	CDT, TMT-A, TMT-B, TMTexec (TMT-A+TMT-B)	Poor TMT-exec performance associated with obese status independent of diabetes, an effect stronger in younger (<39) than older (≥39)
Gunstad et al (1)	Cross-sectional	408 participants across BMI ranges	Data extracted from the Brain Resource International Database	Younger lean = 31.56 Younger Ov/Ob = 32.4 Older lean = 58.34 Older Ov/Ob = 60.4	Excl: Hypertension, diabetes, cardiac disease, sleep apnea	Spot-the-word, digit span forward, choice reaction time, switching of attentionnumber, span of visual memory, verbal interference, switching of attention-letter/number, maze errors	Increased BMI predicted poorer performance on all cognitive tasks
Gunstad et al (2)	Cross-sectional	478 participants across BMI ranges	Data from children and adolescents extracted from Brain Resource International Database	Underwe ight = 12.63 Normal = 12.62 At risk = 12.57 Overweight = 10.82	Excl: Cardiovascular disease, diabetes	Spot-the-word, Digit Span Backward, Switching of AttentionLetter/Number, Verbal Recall, Animal Fluency, Finger Tapping	No correlation between BMI and cognitive function, underweig ht females recalled fewer words than other female BMI groups
Kirton et al.	Cross-sectional	56 participants across BMI ranges	Healthy, community dwelling adults in Gainesville, Florida	Mean = 41.02 Older adults = 65.72 Young adults = 21.20	Cov: Vascular risk score (presence of and medication use for hypertension, hypercholester olemia, diabetes	Stroop Word Reading, Stroop Color Naming, TMT-A, WAISletter number, WAIS-digit backward, Stroop Interference, TMT-B, composite score	Age differences in EF increased in individuals w/ higher BMI, older adults showed greater BMI-related deficits; in younger adults, higher BMI associated w/ lower scores in those w/ lower education
Kuo et al.	Cross-sectional	2,684 participants across BMI ranges	Recruited elderly from ACTIVE trial across six field sites in the U.S.	Lean = 74.7 Ov = 74.0 Class I Ob = 72.9 Class II Ob = 71.3	Cov: smoking status, blood pressure, history of diabetes, myocardial infarction, hypercholester olemia, and stroke	MMSE, Hopkins Verbal Learning, Rey Auditory-Verbal Learning, Rivermead Behavioral Memory test, Word Series, Letter Series, Letter Sets, Useful Field of View, Digit Symbol Substitution	Ov performed better on reasoning tasks than normal weight, Ov performed between on UFOV than normal weight, no difference in global cognition
Maayan et al.	Case-control	54 Obese, 37 Lean	Adolescents	Lean = 17.32 Ob = 17.50	Excl: T2D Cov: systolic BP, HOMA-IR only for OFC results	COWA-T, TMT-A, TMT-B, Stroop Task, Attention/Concentration Index of WRAML, Working Memory Index of WRAML	Ob performed worse on all tasks, most pronounced for Stroop and working memory (WRAML); Trend for lower frontal lobe volume in Ob, lower GMV in OFC
Martin et al.	Longitudinal	12,349 participants across BMI ranges	Infants from the U.K. Millennium Cohort Study	Lean = 3.1 Ov = 3.1 Ob = 3.2	None	British Ability Scales II subtests – vocabulary, picture similarity, pattern construction	Negative relationship between obesity in boys at age 3 and pattern construction at age 5, those who became obese at 5 had lower naming vocabulary and pattern construction, persistent obesity in boys related to lower pattern construction; in girls growing out of obesity related to better picture similarity
Pannacciulli et al.	Cross-sectional	24 obese, 36 lean	Volunteers recruited from the greater Phoenix area	Lean = 33 Obese = 32	Excl: T2D, hypertension, CVS diseases	MRI	Obese participants had lower grey matter density in motor cortex, frontal operculum, middle frontal gyrus, and putamen.
Stanek et al.		103 adults across BMI range	Adult participants from the Brain Resource Internation al Database	Lean = 42.64 Overweight = 45.88 Obese = 51.89	Excl: T2D, hypertension, sleep apnea	MRI	BMI negatively correlated with fractional anisotropy (FA) in the corpus callosum. FA was significantly lower in obese compared to overweight and lean participants
Sweat et al.	Cross-sectional	162 participants across BMI ranges	Adolescents recruited from online advertisements	Lean = 19.39 Obese = 19.60	Excl: T2D MetS symptoms not associated with cognition or CC volume	WASI, COWA-T, Stroop, TMT, DSST, Letter-number sequencing, Tower of London, Category Test,	Ob worse on DSST, Stroop, DVT Total Time, and COWA-T; anterior CC volume lower in

Publication	Design	N	Population	Mean Age	Relevant Covariates or Exclusions	Tests Administered	Main Findings
						Digit Vigilance Test, Green's medical symptom delivery test, Non-verbal medical symptom delivery test	Ob; anterior CC volume correlated with COWA-T
Taki et al.	Cross-Sectional	1,428 participants across BMI ranges	Adults from Aoba Brain Imaging Project Cohort	Men = 44.5 Women = 46.4	Cov: Age, Diabetes, Hypertension	MRI	Negative correlation between BMI in men and grey matter ratio. Grey matter volume negatively correlates w/ BMI in medial temporal lobe, frontal lobe, and midbrain. Positively correlated w/ BMI in thalamus, cerebellu m, some parts of frontal and temporal lobes, and caudate
Glycemia							
Anstey et al.	Longitudinal	4,547 participants with varying degrees of GT	Adults taken from the Australian Diabetes, Obesity, and Lifestyle Study cohort	NGT: 47.71 IFG: 51.31 IGT: 53.99 NDM: 56.6 KDM: 56.4	Excl: T1D Cov: BMI	CVLT, STW, SDMT, MMSE	NGT scored higher on all cognitive measures except STW, KDM at baseline and 5 years predicted slower processing speed at 12 years, Higher HbA1c at 5 years predicts poorer memory in males, High, stable HbA1c in males <60 years predicts lower verbal ability, in females <60 years, high, stable FPG predicts lower episodic memory, increasing HbA1c predicted lower MMSE relative to stable
Bruehl et al. (1)	Case-control	38 IR, 54 Controls	Volunteers participating in an associated study or recruited from the web	Controls : 60.71 IR: 62.87	Cov: BMI, Dyslipidemia	Guild Memory Test, CVLT, Logical memory subtest of the WMS-R, Digit span backward (WMS-R), Visual memory span backward (WMS-R), COWA-T, Stroop, TOL, Digit symbol substitution (WAIS), Perceptual speed test, Shipley institute of living scale, WAIS FSIQ	IR participants had significant reductions in declarative memory compared to controls
Bruehl et al. (2)	Case-control	18 Obese w/ T2D, 18 Obese w/ no insulin resistance	Participants referred by endocrinol ogists or responded to advertisem ents on internet	Obese controls: 17.16 Obese w/ T2D: 16.46	Matched on BMI and waist circumference	MRI	Participants with T2D had smaller hippocampal and prefrontal volumes and increased global cerebral atrophy, higher HbA1c associated w/ smaller prefrontal volume and higher global cerebral atrophy
Cukierman-Yaffe et al.	Longitudinal	17,348 normoglycemic adults	Army personnel of the MELANY cohort	Age by General Intelligence Score (GIS) Low GIS: 30.4 Medium GIS: 32.0 High GIS: 32.2 Overall: 31.9	Cov: BMI	General Intelligence Score (GIS), Otis-R, Similarities-R, Arithmetic-R, Raven's Progressive Matrices-R	11% increase in IFG risk for every point decrease in GIS
Gonzales et al.	Cross-sectional	9 Lean, 11 Overweight, 12 Obese	Adults recruited through flyers and newspaper advertisements	Lean: 51.8 Ov: 52.0 Ob: 48.5	Excl: Diabetes, metabolic disorder	MMSE, WASI, CVLT, RCFT, WAIS-digit span, COWA-T, TMT-A, TMT-B, verbal n-back (fMRI paradigm)	Obese group had lower taskrelated activation in right parietal cortex compared to lowerweight groups and this was fully mediated by insulin sensitivity
Hawkins et al.	Case-control	35 Lean, 35 Obese	University students recruited by BMI status	Total sample: 20.8 Normal glucose: 20.8 Prediabetes: 21.0	Excl: Selfreported insulin resistance, cardiovascular disease, diabetes Cov: BMI	Automated Neuropsychological Assessment Metrics-4 (ANAM-4)	Higher fasting glucose predicted poorer performance on inhibitory control, more commission errors; trend for relationship

Publication	Design	N	Population	Mean Age	Relevant Covariates or Exclusions	Tests Administered	Main Findings
						(Go/No-Go, Standard Continuous Performance Test, RMCPT)	between higher fasting glucose and omission errors on SCPT; People with elevated glucose made more commission errors than normal glucose; trend for prediabetic to have more omission errors on SCPT than normal
Lehtisalo et al.	Longitudinal	364 overweight participants w/ impaired glucose tolerance but no diabetes at baseline	Middleaged, overweight or obese participants w/ IGT at baseline recruited to participate in a lifestyle intervention study (Finnish Diabetes Prevention Study)	Age at time of first cognitive assessment Without diabetes: 69.6 With diabetes: 66.9	Cov: BMI	TMT-A, CERAD Battery: Verbal fluency, Modified Boston Naming Test, MMSE, Word List Memory, Constructional praxis, Word List Recall, Word List Recognition, Constructional Praxis recall, Clock drawing, CERAD total score	Cognitive performance did not differ between IGT and those who developed diabetes, diabetes duration was associated with less improvement in CERAD-TS, diabetic glucose concentrations resulted in poor TMT compared to normal, permanent increase in HbA1c predicted poorer CERAD-TS
Luchsinger et al.	Cross-sectional	600 participants w/ varying glucose tolerance	Middleaged Hispanic participants recruited to the Northern Manhattan Study of Metabolism and Mind (NOMEM) cohort	Full sample: 59.3 NGT: 59.1 Prediabe tes: 59.3 Diabetes: 59.4	Cov: BMI, HDL, systolic BP, hsCRP	Color Trails Test, verbal fluency, Selective reminding test, total recall, delayed recall, immediate recall	HbA1c inversely related to total recall and delayed recall of SRT, diabetes status predictive of worse total AND delayed recall of SRT, prediabetes predictive of worse color trails 2, HbA1c associated with worse memory and global Z scores, prediabetes predictive of worse executive z scores
Markus et al.	Cross-sectional	1330 adults w/ varying glucose tolerance	Adults drawn from the central population registry of the German federal state of Mecklenburg-Vorpommern to participate in the Study of Health in Pomerania (SHIP) cohort	NGL: 45 i-IFG: 54 i-IGT: 50 IFG+IGT: 59 UDM: 60	Excl: Diabetes Cov: Weight, Cholesterol	MRI	Inverse association between FG and 2HG; significantly lower mean GMV in iIFG and UDM compared to NGT; no differences in WMV between OGTT groups, no difference between iIGT and IFG+IGT; significant inverse non-linear relationship between insulin and HOMA-IR with GMV
Marseglia et al.	Longitudinal	2746 elderly participants and a 455-person MRI subsample w/ varying glucose tolerance	Elderly participants living at home or in institutions in Stockholm - drawn from populationbased study, the Swedish National study of Aging and Care-Kungshol men (SNAC-K)	Main cohort (2746) Diabetes-Free: 71.3 Prediabetes: 74.6 Diabetes: 74.1	Cov: BMI, hypertension, heart diseases, cerebrovascular diseases, APOE genotype	MMSE, MRI	Prediabetes and diabetes associated w/ faster cognitive decline over 9 years; Higher HbA1C associated w/ faster cognitive decline, hyperglycemia associated w/ steeper cognitive decline; prediabetes predicts smaller TBTV. Diabetes predicts larger WMHV, diabetes predicts faster increase in WMHV
Olsson et al.	Longitudinal	9,113 participants assessed at 7, 11, 16, 33, and 42 years	Participants in National Child Development Study (NCDS), follows individuals born between 3 and 9 March, and living in U.K.	Participants assessed at timepoints of 7, 11, 16, 33, and 42 years of age	Cov: BMI at 7 years Excl: Confirmed or suspected diabetes by 16	School tests for general ability (verbal and nonverbal components)	T2D after 16 had significantly lower scores at age 11
Rubens et al.	Cross-sectional	1,170 adolescents with known metabolic syndrome status	Adolescents recruited as part of the National Health and Nutrition Examination Survey (NHANES) III	Total: 14.1 MetS: 14.0 NonMetS: 14.1	Cov: BMI	WRAT-R, WISC-R	Metabolic syndrome scored lower on reading and digit span, fasting glucose (≥110 mg/dl) scored on average 2.91 points lower on reading examination
Strizich et al.	Cross-sectional	1,794 Hispanic adults with diabetes	Adults recruited for the Hispanic Community Health Study, a population-based study of adults living in 4 urban centers in the U.S.	Range: 45–76	Cov: BMI and history of cardiovascular disease	Spanish English Verbal Learning Test (SEVLT), word fluency test, digit symbol substitution test	Higher odds of uncontrolled diabetes w/ lower DSST scores

Publication	Design	N	Population	Mean Age	Relevant Covariates or Exclusions	Tests Administered	Main Findings
Willette et al. (1)	Longitudinal	372 participants at baseline and 121 at MRI follow up	Middleaged adults in the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort	Baseline: 57.67 Followup: 60.71	Cov: BMI	MRI, RAVLT	Higher HOMA-IR predicts less grey matter in MTL and progressive atrophy; higher HOMA-IR predicted progressive atrophy in MTL, which correlated with worse performance in encoding trials
Willette et al. (2)	Cross-sectional	186 middleaged adults	Middleaged adults in the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort	Mean: 60.37	Cov: diabetes medication, APOE status, BMI, family history of Alzheimer's	MMSE, RAVLT, WAIS, Stroop test, TMT-A, TMT-B	In normoglycemia patients, but not hyperglycemia, higher HOMA-IR was predictive of increased PiB in frontal and temporal brain regions
Yau et al. (1)	Case-Control	18 obese adolescent s w/ T2D and 18 obese controls	Referred by local area pediatric endocrinologists	T2D: 16.46 Controls: 17.16	Matched for BMI and waist circumference	MRI, WASI, WRAT, WRAML, WCST, Digit vigilance test, TOL, COWA-T, DSST	T2D scored lower on all cognitive tests, T2D had smaller WMV and larger CSF space, WM and GM microstructural abnormalities in T2D
Yau et al. (2)	Case-control	49 adolescents with MetS, 62 without MetS	Nondiabetic adolescents recruited and screened for entry	MetS: 17.77 NonMetS: 17.48	Excl: T2D	MRI, WASI, WRAT, WRAML, WCST, TOL, TMT-B, TMT-A, COWA-T, DVT, DSST	QUICKI score predicts lower hippocampal volume and higher CSF volume