THE IMPACT OF GLUCOSE ON COGNITION IN NEURODEGENERATIVE DISEASE

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Abstract

Glucose dysregulation has been associated with poorer cognitive functioning in healthy adults with and without diabetes, as well as in individuals with neurodegenerative disease. In addition to cognitive changes, hyperglycemia has also been associated with brain atrophy, and this is especially true for those with the apolipoprotein E (ApoE) ε4 genotype. However, most of these studies rely on cognitive screening measures of dementia with vast variations in how cognition is assessed. This precludes the ability to make conclusive inferences from findings that have not assessed cognition consistently nor comprehensively.

In the present study, the effects of glucose on cognition were examined across healthy aging, and two neurodegenerative diseases, namely Alzheimer's (AD) and Parkinson's disease (PD), with the goal of assessing cognition in a detailed and standardized manner across cohorts. Data from the Ontario Neurodegenerative Disease Research Initiative was used to assess three cohorts of healthy adults and individuals with AD and PD. The primary interest was to analyze the effects of elevated glucose levels on cognition after controlling for related covariates of triglycerides, hypertension, and smoking. Secondary analyses examined the roles of genetics, and brain volume with glucose.

Higher glucose levels were differentially related to disease status and cognitive abilities after controlling for the effects of triglycerides, hypertension, and smoking. In healthy adults and those with PD, glucose levels were associated with poorer cognition, but not in those with AD. Among healthy adults, this effect was due to worse language and visuospatial abilities whereas widespread cognitive changes over domain-specific impairment was observed in those with PD. In AD, glucose levels were not associated with cognition. No significant interaction emerged between ApoE-ε4 carriers and glucose in neurodegenerative disease. An interaction between

lower brain volume and poorer cognition was observed among those with higher glucose levels in the healthy adult group but not in the PD or AD groups.

Hyperglycemia appears to have a different relationship in those with and without neurodegenerative disease. In healthy adults, it may be possible that even glucose levels within the normal range may be exerting deleterious effects that manifest clinically, affecting both cognition and brain volume. In neurodegenerative disease, more research is needed to understand the complex relationship between hyperglycemia and specific disease pathology. With the consistent increase in both diabetes and dementia, close monitoring of glucose levels may be a potential modifiable risk factor that contributes to optimal brain health to reduce the risk of a dementia diagnosis.

Dedication

This work is dedicated to my parents who have been the backbone of all of my achievements.

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The prevalence of cognitive impairment and dementia among middle-aged and elderly adults is on the rise. Currently, there are 50 million people worldwide living with dementia, and that number is projected to increase to 80 million in the next 10 years (World Health Organization, 2017). By 2050, it is expected to increase by 200%, to 152 million. Among individuals living with dementia, over 90% have additional underlying health conditions, of which diabetes, hypertension, and stroke are among the highest reported comorbidities (Browne et al., 2017; Bunn et al., 2016). In a recent report, half of the top modifiable risk factors to prevent dementia onset identified by the Lancet Commission (Livingston et al., 2020) were related to vascular health (hypertension, diabetes, obesity, smoking, and alcohol consumption). However, the exact mechanisms of how these vascular factors contribute to cerebral structural changes and the progression to cognitive deficits that lead to a dementia diagnosis remain unclear.

Abnormal glucose levels have been identified as a contributing mechanism in several of these vascular conditions (Burns et al., 2013; Chait & Bornfeldt, 2009; Crane et al., 2013). Poorly regulated glucose levels have been linked to numerous mechanisms that contribute to cognitive changes seen in neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases. The underlying mechanisms that contribute to cognitive changes include atrophy in brain structures, alterations in cerebral blood flow, and neuronal dysfunction (Buysschaert et al., 2015; Kerti et al., 2013; Sima et al., 2004). However, these changes are not consistently demonstrated in studies that have explored cognitive changes due to glucose dysregulation. In a population that is predicted to double in dementia prevalence across the next 20 years, the need

to better understand underlying contributing mechanisms of dementia risk factors is urgent, as the culpable factors may be treatable, and thus their damage may be reversible.

Hyperglycemia refers to chronically elevated glucose levels in the blood. It contributes to various deleterious processes that affect brain health including increased oxidative stress, inflammation, and neuronal death (Mergenthaler et al., 2013). The human brain depends on glucose as its main source of energy supply, and the adult human brain consumes approximately 20% of glucose-derived energy, making it the highest glucose consumer within the human body (Lam et al., 2009; Mergenthaler et al., 2013). Glucose metabolism provides the fuel for physiological function through the generation of adenosine triphosphate and helps with both neuronal and cellular maintenance. This process is tightly regulated, as optimal glucose levels and metabolism within the brain are critical for healthy brain functioning. Disturbances to glucose metabolism underlie several cerebrovascular and neurodegenerative diseases that impact brain health at both structural and functional levels.

In this introduction, I outline recent research advances in understanding the role of hyperglycemia in brain health and how it affects cognitive functioning, implicated brain structures, and the possible contributions of the apolipoprotein gene in this process. Studies conducted with healthy adults and those with neurodegenerative disease, namely Alzheimer's (AD) and Parkinson's diseases (PD), are reviewed.

Function of Glucose in the Brain

Glucose is involved in several important functions to help maintain optimal brain functioning. Neurons rely almost exclusively on glucose as their main source of energy for the generation of action potentials and synaptic activity, which is required for information processing and signalling by the neurons (Lam et al., 2009; Mergenthaler et al., 2013).

In addition, glucose provides the energy for biosynthesis of neurotransmitters and plays a role in learning and memory formation by producing the end-product lactate (Grayson et al., 2013). Although the mechanisms of this relationship are not clear, it is believed that lactate receptors may play a role in linking brain energy metabolism and neurotransmission, which enhance learning and memory (Grayson et al., 2013). There are specialized neuronal networks in the hypothalamus and hindbrain, as well as glucose transporter cells throughout the brain, that mediate and maintain glucose metabolic signalling (Grayson et al., 2013; Mergenthaler et al., 2013). This process also involves the hormone insulin, which is released by the pancreas and allows cells to use glucose as energy. Insulin is closely involved in regulating glucose levels by signaling the oxidation and storage of excess glucose as glycogen in the muscles, liver, and fat cells, which prevents hyperglycemia (Taouis, & Torres-Aleman, 2019). Thus, there is a complex interplay of several brain structures, receptor and transporter cells, and hormones at work to maintain and regulate brain blood glucose levels. Disturbances in this regulation process are associated with several metabolic disorders such as obesity and Type 2 diabetes mellitus (T2DM) that are increasingly recognized as contributing risk factors of neurodegenerative disease and dementia (Kapogiannis & Mattson, 2011; Scheen, 2010).

Mechanisms of Hyperglycemia

Chronic high glucose levels can directly affect brain structures through the accumulation of abnormal metabolites, increased oxidative stress, and the depletion of metabolic cofactors that give rise to neuronal dysfunction and cell death (Biessels et al., 2006; Sima et al., 2004). Prolonged hyperglycemia can further damage the cellular membranes and integrity of capillary walls, which leads to altered cerebral blood flow (Chait & Bornfeldt., 2009), and it has also been associated with increased systemic inflammation as well as increased coagulation activity (Levi

& Van der Poll, 2010; Vaidyula et al., 2006). Systemic inflammation has been shown to be associated with cerebral atrophy, particularly in the hippocampus (Cherbuin et al., 2012; Das & Basu, 2008; Esposito, 2002), whereas coagulation can potentiate inflammatory processes, which together increase the risk of thrombosis, microemboli, and stroke (Levi & Van der Poll, 2010). Thus, inflammation and coagulation are insidious processes that result from hyperglycemia and decrease the integrity of brain functioning.

Evidence from an experimental study demonstrated that induced hyperglycemia in healthy adults was associated with an increase in procoagulant activity, prothrombic factors, and platelet activation (Vaidyula et al., 2006), thereby suggesting that chronic high glucose levels irrespective of underlying diseases such as T2DM can lead to coagulation. Inflammation and coagulation have a bidirectional relationship in which inflammatory pathways lead to coagulation, and coagulation also considerably affects inflammatory activity (Levi & Van der Poll, 2010). These processes are likely to further amplify the effects of high glucose levels. Overall, chronically elevated glucose levels can lead to a cascade of cerebrovascular risk factors attributed to compromised cerebral integrity and associated cognitive changes.

Glucose and Incidence of Dementia

The association of increased glucose levels and dementia risk has been consistently reported among individuals with T2DM (Geijselears et al., 2015), and some studies have also demonstrated this relationship among nondiabetic individuals (Benn et al., 2020; Chatterjee et al., 2016; Crane et al., 2013). Crane and colleagues (2013) examined incidence of dementia in a large longitudinal study among individuals with and without diabetes. Even among participants without diabetes, higher average glucose levels (6.4 compared to 5.5 mmol/L) across 5 years were associated with an increased risk of dementia (i.e., 26% of participants without diabetes had

developed dementia by the end of the study period; Crane et al., 2013). They also found that 20% of their sample had probable Alzheimer's dementia, and another 3% presented with vascular dementia (VaD; Crane et al., 2013). These findings suggest that incremental increases in blood glucose levels across a prolonged period that are within normal limits may increase the risk of dementia in otherwise healthy individuals.

Another longitudinal study with over 100,000 participants (Benn et al., 2020) reported similar findings. However, increased glucose levels were associated only with increased risk of unspecified dementia (dementia due to unknown causes), and not with AD or VaD. Interestingly, individuals with unspecified dementia had higher glucose levels compared to the AD and VaD groups. They also found that individuals with diabetes who progressed to unspecified dementia were less likely to be treated with glucose-lowering drugs than those with AD or VaD. This suggests that poor glycemic management in individuals with diabetes is related to increased dementia risk. Specifically, a 1 mmol/L increase in blood glucose levels was associated with a significant hazard ratio of 1.04 for unspecified dementia after controlling for confounding variables (age, sex, smoking, alcohol intake, and hypertension).

In a recent longitudinal study, the effects of glucose were examined in relation to reversion from MCI to normal cognition (Makino et al., 2021). Individuals with and without diabetes who had elevated glucose levels were less likely to revert to normal cognition from MCI across 4 years, in comparison to those with lower glucose levels. These findings provide support for the idea that hyperglycemia may accelerate processes that cause irreversible neurodegenerative changes and result in permanent cognitive decline.

In sum, findings suggest that poor glycemic control may contribute directly to dementia risk and cognitive decline, although the exact mechanisms and specific dementia profiles are

variable. This is an important finding as it suggests that dementia risk may be modifiable, and careful management and adequate control of glucose levels may reduce or slow the progression to dementia, or even reverse cognitive decline.

Glucose and Cognitive Domain Changes

Relatively little is known about specific cognitive changes that may occur with elevated glucose levels and which may go on to result in a dementia diagnosis. Among studies that have examined glucose and cognitive domains in nondiabetic individuals, only a few studies have examined specific cognitive abilities that may be affected by increased glucose levels. Below is a review of studies that have examined specific cognitive domains.

Kerti and colleagues (2013) examined the effect of glucose on memory performance in healthy, nondiabetic individuals. They found that higher levels of both short-term (fasting blood glucose) and long-term (HbA1c) glucose levels were associated with poorer memory performance on measures of delayed recall, learning across trials, and consolidation, and these findings were accompanied by structural changes in the hippocampus. Although these findings suggest that the deleterious effects of glucose may impact some cognitive abilities, this hypothesis needs further examination to understand how other cognitive abilities are impacted, as only memory was examined in this study. Earlier evidence comes from Dahle et al. (2009) who hypothesized that abilities most affected by the aging process would show further deterioration with higher levels of glucose in otherwise healthy, nondiabetic individuals. They examined the cognitive domains of memory, working memory, executive functions, and psychomotor speed. There was a significant inverse relationship between glucose levels and delayed memory across participants. In other cognitive domains, the relationship between cognitive performance and glucose interacted with sex. Higher glucose levels were associated

with reduced working memory accuracy only in women and with slower processing speed only in men (Dahle et al., 2009). These findings suggest that the effect of glucose on cognitive abilities is complex and may be influenced by additional biological mechanisms.

Similar relationships between glucose and cognition have been shown among healthy younger adults (Repple et al., 2021). A recent study that examined specific cognitive abilities in relation to glucose levels among healthy young adults found that long-term higher glucose levels, even when these were within normal range (HbA1c $\leq$ 5.7 mmol/L), were associated with poorer vocabulary knowledge, working memory, and executive functions and with reduced white matter microstructural integrity (Repple et al., 2021). Messier et al. (2011) examined attention, executive functions, verbal memory, and psychomotor speed in young, nondiabetic adults and found that higher glucose was associated with reduced verbal memory but not with cognitive performance in other domains (Messier et al., 2011). They found that indices of invoked glucose levels (glucose ingestion during the study) were most associated with reduced verbal memory.

Taken together, these findings provide evidence for an association of reductions in cognitive abilities with increased glucose levels in healthy adults without diabetes. It is suggested that glucose may affect some cognitive abilities more than others, and its impact across cognitive abilities is variable.

In contrast, not all studies have found a clear association between glucose and cognition. For example, evidence from a prospective study with over 8,000 participants demonstrated that only a single test of processing speed was significantly associated with glucose levels across 6 years, and even that was seen only in individuals with a diagnosis of diabetes and not in nondiabetic individuals (Christman et al., 2011). Euser et al. (2010) also found no significant cognitive changes in relation to glucose levels in nondiabetic individuals across 5 years, which

suggests that hyperglycemia alone may not be a significant determinant of the elevated risk of cognitive impairment seen in diabetes. It is also important to note that in a meta-analysis with individuals with T2DM (Geijsealer et al., 2015), out of the 32 studies that examined cognitive domains, most (53%) did not report a significant effect of glucose levels on cognitive functioning. Of the studies that did find an association, it tended to be weak (i.e., accounting for less than 10% of the variance in cognitive abilities).

When considered with findings from the studies reported earlier, these findings suggest that the link between elevated glucose levels and cognition is inconsistent. Even among studies that assessed individual cognitive domains, most assessed fewer than five distinct domains or used only one neuropsychological test per domain. This results in an incomplete assessment of cognitive functions and limits our ability to understand whether higher glucose levels differentially affect some cognitive abilities over others.

Structural and Biological Changes in the Brain

It is well understood that chronic hyperglycemia has a strong impact on neuronal activity, which in turn affects the integrity of different brain structures. Brain atrophy is defined as low brain volume that is not related to specific focal injury (e.g., trauma or infarction; Wardlaw et al. 2013). Broadly, there is firm evidence that metabolic disorders such as T2DM are associated with brain atrophy (Biessels & Reijmar, 2014). This consists of widespread changes of white matter connectivity as well as gray matter reductions (Biessels & Reijmar, 2014; Espeland et al. 2013; Moran et al., 2017). These reductions in brain volume in turn are related to cognitive impairment (Biessels & Reijmar, 2014; Moran et al., 2017). Evidence shows that individuals with T2DM have an increased burden of cerebrovascular lesions, especially lacunes, whereas large artery infarcts or microinfarcts are less common (Abner et al., 2016; Pruzin et al., 2017).

Furthermore, specific brain structures have been reported in several studies to be affected by mechanisms of hyperglycemia.

In particular, the hippocampus is especially affected by dysregulation of glucose homeostasis. The hippocampus is one of the few areas where neurogenesis continues throughout adulthood, which supports learning and memory in addition to potentially contributing to brain repair (Mainardi et al., 2015). It has been shown that animals with lower levels of plasma glucose and insulin exhibit increased neurogenesis in the hippocampus, particularly in the dentate gyrus (Lee et al., 2002). Studies in healthy adults found long-term hyperglycemia was associated with volume reductions in the hippocampus (Cherbuin et al., 2012; Convit et al., 2003; Kerti et al., 2013). Reduced hippocampal volume and microstructural changes were found with elevated glucose levels (Convit et al., 2003; Kerti et al., 2013) and at long-term follow up (4 years; Cherbuin et al., 2012). These reductions in hippocampal volume are also consistently found in individuals with T2DM (Gold et al., 2007).

Additional structural brain changes have been noted. Hyperinsulinemia in the brain may be associated with increased amyloid-β (Aβ) deposition, a protein that is elevated in AD (Wang et al., 2017). This may be due to competition for the main clearance mechanism, the insulin-degrading enzyme, which clears the brain of toxic metabolites (Qiu & Folstein, 2006). Similar reasoning has led to the idea that AD may be a third type of diabetes, based on the evidence for insulin resistance and impaired insulin-response pathways in individuals with AD (De la Monte, 2014; De la Monte & Wands, 2008). Given that similar pathways have been linked in AD and T2DM, elevated glucose levels have been explored as a possible contributor in the pathology associated with neurodegenerative disease.

Glucose Metabolism in Neurodegenerative Diseases

Alzheimer's Disease

Clinically, dementia due to AD is characterized by severe memory loss and global cognitive dysfunction with impairment in daily functioning (Smith, 1998). In the brain, AD neuropathology consists of deposition of amyloid-β that initiates a pathological cascade of events including formation of neurofibrillary tangles, gliosis, inflammatory changes, synaptic damage, and neurotransmitter loss (Hillen, 2019). A study examining Aβ clearance and deposition in AD patients showed that Aβ production was normal in AD as compared to healthy controls, but Aβ clearance was significantly decreased (Mawuenyega et al., 2010). Decreased Aβ clearance leading to its increased deposition in the brain is central to AD pathology.

Another frequently noted biomarker of AD is decreased glucose metabolism which was noted as one of the earliest brain changes and a distinct characteristic of the disease (Mosconi, 2005; Patil et al., 2012). This was found even in individuals with mild cognitive impairment (MCI) who subsequently developed Alzheimer's dementia (Hunt et al., 2007). The uptake of glucose into the brain is a saturable process, meaning there is a limit to how much glucose can be absorbed. In order to increase the uptake of glucose in the brain, it would require the upregulation of insulin receptors as well. But when this receptor activity is compromised, it could lead to functional hypoglycemia, which reduces the glucose metabolic rate in the brain (Mittal & Katare, 2016). This reduced uptake of glucose and in turn reduced glucose metabolism is an early biomarker consistently seen in AD, which suggests that glucose dysregulation may be an underlying mechanism of the disease.

Both glucose utilization and adenosine triphosphate formation in the brain are significantly lower in AD compared to healthy controls (Hoyer, 1991; Karran & De Strooper

2016), and reductions in glucose metabolism in AD correlate with disease severity (Alam et al., 2016; Munch et al., 1998). Glucose metabolic changes have also been documented well before clinical manifestations of the disease begin in individuals who are genetically predisposed to AD (Gibson, 2002), and these reductions have been observed at the MCI stage (Hunt et al., 2007). Reductions and alterations in glucose metabolism may be a prodromal mechanism to other pathological changes in AD, in particular affecting the clearance of Aβ, which leads to increased Aβ in the brain.

Both T2DM and increased fasting blood glucose levels occur more often in AD patients than healthy controls (Janson et al., 2004). However, AD pathology (e.g., Aβ depositions) is not always greater in AD patients with T2DM than in nondiabetic individuals with AD. Thus, T2DM might exacerbate the progression of AD, but alone it is not necessarily sufficient to cause AD pathology, as there are many individuals with T2DM who do not progress to AD (Janson et al., 2004). Overall, although there have been strong links between T2DM, insulin dysregulation and AD, the underlying mechanisms are still not well understood.

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease characterized by degeneration of the substantia nigra, reduced dopamine production, and abnormal aggregation of alpha-synuclein protein (Poewe et al., 2017; Trost et al., 2019). Clinically, the disease causes impaired motor movements, including bradykinesia, rigidity, resting tremor, and cognitive impairment (Schapira, 2017). Cognitive decline is one of the most debilitating nonmotor symptoms of PD (Aarsland, 2017), and almost 80% of PD patients go on to develop dementia within 20 years of diagnosis (Reid et al., 2011). Cognitive changes are observed in several domains, with changes in planning, working memory and executive functions most commonly reported (dysexecutive

syndrome; Gratwicke et al., 2015; Kehagia et al., 2013). This is attributed to a disruption of the fronto-striatal dopamine network caused by depletion of dopamine transmission rather than by primary frontal dysfunction. Some PD patients also experience deficits in visuospatial functioning and semantic fluency which are attributed to posterior temporal lobe dysfunction (Gratwicke et al., 2015; Kehagia et al., 2013). This posterior pattern of cognitive impairment is more predictive than the frontal dysexecutive pattern of progression to dementia (Alves et al., 2006).

The link between vascular factors and cognitive impairment in PD is less studied than in AD and not well established. The few areas of related vascular research in PD are reviewed below.

Hypometabolism. Changes in brain glucose metabolism in PD have been well documented, and like in AD, impaired glucose metabolism precedes brain atrophy (Gonzales-Redondo et al., 2014). These metabolic changes are more commonly reported than structural changes (Albrecht et al., 2019). More recent literature on glucose metabolism in PD has focused on cognitive decline in specific stages of PD. For example, individuals with mild cognitive impairment in PD (PD-MCI) show regional glucose hypometabolism in the temporo-parieto-occipital regions compared to healthy controls (Hu et al., 2000; Lyoo et al., 2010). Studies examining the progression of cognitive decline show that extensive parietal and occipital hypometabolic changes can predict the development of cognitive decline in PD-MCI patients (Baba et al., 2017; Bohnen et al., 2011) and also in PD patients with normal cognition (Shoji et al., 2014). These findings suggest that early metabolic changes in glucose can be useful in predicting cognitive changes at various stages of disease severity.

Other Vascular Contributors. In addition to dysregulation of brain glucose metabolism, several other shared vascular mechanisms among diabetes and neurodegenerative disease have been suggested to contribute to the development of PD and subsequent cognitive impairment. A recent study examined progression and baseline predictors of cognitive and motor symptoms in PD across 4 years (Mollenhauer et al., 2019). Decreased hippocampal volume and several vascular risk factors, including dysregulated blood glucose levels, heavy alcohol use, and elevated HDL cholesterol were significant predictors of cognitive but not motor decline. Notably, both fasting blood glucose levels as well as hyperglycemia were significant predictors of cognitive decline and were specific to PD patients in comparison to healthy controls (Mollenhauer et al., 2019). When controlling for diabetes in the PD group, only fasting blood glucose remained a significant predictor of cognitive decline.

Glycation of alpha synuclein could promote abnormal aggregation of the protein and brain neurodegeneration (Vincente et al., 2016). These disturbances in metabolic factors should be further studied, as diabetes has been described as a risk factor for PD with a 38% higher risk of developing PD among individuals with T2DM compared to nondiabetic individuals (Yue et al., 2016). In a recent finding among individuals with PD and diabetes, higher glucose levels were associated with poorer cognition. However, after controlling for other vascular factors, this relationship was no longer significant (Uyar et al., 2022). Although dysregulated glucose levels may be involved in progression of cognitive decline, it should be noted that global cognitive measures such as the Mini-Mental Status Examination (Folstein, Robins, & Helzer, 1983) and Montreal Cognitive Assessment (Nasreddine et al., 2005) were used to assess cognitive decline in most studies, and these measures do not detect subtle and specific cognitive changes. A more

comprehensive neuropsychological battery would likely be better able to detect subtle cognitive changes that may be present in early stages of the disease.

Apolipoprotein E4 Gene

The apolipoprotein gene makes the protein apolipoprotein E (ApoE). This protein combines with fats (lipids) in the body to form molecules called lipoproteins (Farmer et al., 2019; Liu et al., 2013). ApoE is primarily synthesized in the liver and brain; it is responsible for the homeostasis of cholesterol and metabolism of lipids and aids in carrying them through the bloodstream (Eid, 2019). Maintaining normal levels of lipids is essential for the prevention of disorders that affect the brain, heart and central nervous system (Irie et al., 2008; Jellinger, 2008)

The ApoE gene exists as three polymorphic alleles (epsilon 2, epsilon 3, and epsilon 4). Each individual inherits two alleles of the gene, which can be either homozygous (e.g., ε2/ε2), or heterozygous (e.g., ε2/ε3; Eid et al. 2019). These variations in allelic forms alter the structure and function of the protein, which, in turn, also differentially affect Aβ aggregation and clearance. The ε2 allele has been considered protective against AD as it is more efficient in metabolizing lipids, whereas the ε4 allele, which is less efficient at clearing lipids, is considered a risk factor for AD (Harold et al. 2009; Lambert et al., 2009). The ε3 allele is considered to harbour neutral risk for the development of AD. The prevalence of the ε2 allele is quite low, with a worldwide frequency of only 5%, whereas the ε3 allele has a 75% prevalence rate, and the ε4 allele is intermediate, with a prevalence of 15-20% (Angelopoulou et al., 2021; Davignon, 1988).

In individuals with AD, the frequency of the ε4 allele is dramatically increased relative to the general population, with a prevalence of ~60% (Lanfranco, 2020). The ε4 allele further increases the risk of developing AD at an earlier age of onset in a gene dose-dependent manner. A meta-analysis demonstrated that compared with individuals with an ε3/ε3 genotype, risk of

AD was increased in individuals with one copy of the ε4 allele with an odds ratio (OR) of 2.6-3.2, and those with two copies of the ε4 allele jumped to an OR of 14.9 (Farrer et al. 1997). The ε4 allele is also associated with increased prevalence of AD and earlier age at onset (Corder et al., 1993; Farrer et al. 1997; Rebeck et al., 1993). The frequency of AD and mean age at onset are 91% and 68 years of age in ε4 homozygotes, 47% and 76 years of age in ε4 heterozygotes, and 20% and 84 years in those without an ε4 allele (Corder et al., 1993; Rebeck et al., 1993). These studies demonstrate the dose-dependent relationship with ε4 alleles, as ε4 carriers develop AD at an earlier age and are at greater risk of AD compared to those without an ε4 allele.

ApoE and Glucose in Alzheimer's Disease

In comparison to other variants of ApoE, the ε4 genotype is associated with increased deposition of Aβ, is less protective against oxidative stress, and is associated with cholinergic dysfunction (Hunsberger, 2019; Kanekiyo et al., 2014). The precise mechanism by which elevated blood glucose and ApoE ε4 genotype interact to increase AD neuropathology is not as well understood. One theory is that the mechanisms of advanced glycation end-products (AGE) interact with ApoE ε4 to increase pathology in neurodegenerative diseases (Sasaki et al., 1998). Indeed, ApoE ε4 genotype is associated with three-fold greater AGE-binding activity compared to the ApoE ε3 genotype. Li and Dickson (1997) found that AGE by ApoE ε4 interactions may contribute to the formation of dense amyloid deposits as well as neurofibrillary tangles.

In support of this theory, Bangen et al. (2016) found that midlife elevated blood glucose predicted the later development of AD tangle pathology in individuals with the ApoE ε4 genotype. Presence of the ApoE ε4 allele significantly modified the association between elevated blood glucose and AD tangle pathology independently of other known risk factors for AD, including age, history of smoking, midlife obesity, hypertension, and high cholesterol (Bangen et

al., 2016). Interestingly, results did not change when adjusting for presence of late-life diabetes, suggesting that genetic risk may interact with elevated glucose to cause AD pathology (Bangen et al., 2016). These results suggest that higher levels of blood glucose, even among nondiabetics, may exert deleterious effects on the aging brain especially among those at genetic risk for AD.

However, the interaction of ApoE ε4 with glucose has not been consistently demonstrated. A review examining the association between diabetes and the ApoE gene reported that although having an ε4 allele increases chances of developing AD, overall, individuals with AD who are ε4 carriers tend to have normal insulin and glucose levels (Messier, 2003; Ravona-Springer et al., 2012). This suggests that the ε4 allele may not dysregulate glucose but instead may interact with glucose with additional mechanisms in play to increase AD pathology. Individuals who have both an ApoE ε4 allele and diabetes have more than double the risk of developing Alzheimer's disease compared to people with an ApoE ε4 allele but no diabetes (Messier, 2003; Peila et al., 2002). Individuals with diabetes and an ε4 allele who developed AD were found to have an increase of neuritic plaques in the hippocampus, an increase in cerebral neurofibrillary tangles, and increased cerebral amyloid angiopathy at autopsy examination compared to individuals with AD, without diabetes or an ε4 allele (Peila et al., 2002). In sum, these studies suggest that glycemic mechanisms interact with the ApoE gene to increase AD pathology; however, the exact mechanisms underlying this interaction warrant further examination. Understanding these factors may be highly beneficial in lowering the risk between diabetes and developing dementia, especially among individuals who have an increased genetic risk of developing AD.

Parkinson's Disease and the ApoE Gene

The role of ApoE ε4 in Parkinson's disease is less consistently demonstrated than in AD, and only a few studies have examined the relationship of the gene with cognitive impairment and dementia onset in PD. A few large cohort studies have demonstrated an increased prevalence of the ε4 allele in PD patients with dementia (PDD) relative to PD patients without dementia (Pankratz et al., 2006; Parsian et al., 2002), whereas other studies failed to find such an ε4 allele effect (Ezquerra et al., 2008; Federoff et al., 2012; Ryu & Kwon, 2010). Additionally, where studies supported the high rates of ApoE ε4 in PDD versus PD without dementia (Williams-Gray et al., 2009), the effect is modest, with an OR of 1.74. This is much smaller than seen in AD (OR of 15.5; Nalbantoglu et al, 1994; Rasmussen et al., 2020).

Recent findings from a large cohort study examining PD and other neurodegenerative diseases found that having an ApoE ε4 allele contributed to cognitive decline in AD but not in PD (Dilliott et al., 2021). Reconciliation of these conflicting data may lie in the findings of a longitudinal study. Individuals with PD who were also ApoE-ε4 allele carriers had a faster rate of cognitive decline (Moreley et al., 2012) compared to any other variants of the gene. This suggests that having an ε4 allele does contribute to cognitive decline in PD but may not always lead to a diagnosis of dementia. Nonetheless, the ε4 variant differentially affects individuals with PD compared to AD, which underscores the need for a better understanding of its role in the relationship between glucose metabolism and neurodegenerative disease.

Summary and Rationale of Proposed Studies

The literature reviewed above demonstrates that glucose dysregulation is linked to cognitive impairment even among nondiabetic healthy individuals, as well as in neurodegenerative disease and in diabetes. Firstly, as previously reviewed, reduced glucose

metabolism is consistently reported as an early biomarker of both AD and PD (Hu et al., 2000; Patil et al., 2012). Metabolic changes resulting from chronically elevated glucose levels precede structural brain changes, which suggests that glucose dysregulation may be part of early subtle changes that do not manifest clinically until later stages of disease severity.

In regard to cognition, most studies that have examined cognitive impairment with elevated glucose levels have used global cognitive screening measures (e.g., Mini-Mental State Examination or Montreal Cognitive Assessment). Among studies that have examined specific cognitive abilities, only one study with healthy adults used at least two neuropsychological tests per domain to examine cognitive functioning (Dahle et al., 2009). Using at least two tests per domain is important to conduct a comprehensive examination of each cognitive domain; using a single test per domain is not as robust or stable as when performance is consistently impaired or unimpaired on multiple measures. Thus, using multiple measures to assess one domain provides more validity, reliability and confidence in the findings than using a single measure.

Studies that did examine specific cognitive domains more often reported reductions in memory and no other cognitive domains with elevations in glucose levels (Kerti et al., 2013; Messier et al., 2011). Although memory is not consistently related to glucose levels across studies, it is examined more frequently than other cognitive domains. Studies of other cognitive domains, including executive dysfunction, slowed processing speed, and reduced attention abilities have all been reported across separate studies, never within the same participant groups. This variation in findings highlights the need to further characterize cognitive changes that may occur in concert with chronically elevated glucose levels in order to potentially identify a modifiable risk factor.

Cognitive changes that have been reported have been linked to changes in neural correlates, namely, global atrophy with reductions in gray and white matter volume and reduced volume and microstructural changes in the hippocampus (Repple et al., 2021). Conflicting findings have been noted in AD. Some studies report increased amyloid-β deposits and plaques in individuals with reduced glucose metabolism and elevated plasma glucose levels, whereas other studies have not found these links. In PD, changes in glucose metabolism are more reliably reported than structural changes. Lastly, the ApoE ε4 gene is associated with increased risk of developing AD and cognitive decline in AD, especially among those who have diabetes, whereas it is less consistently associated with increased risk of developing cognitive decline in individuals with PD.

Study Aims and Hypotheses

In this dissertation, I examine the relationship between higher glucose levels and cognition in healthy adults and in individuals with neurodegenerative disease, namely AD and PD. The primary aim of this project was to understand the association of elevated blood glucose levels in neurodegenerative disease from a neuropsychological perspective. Using a comprehensive neuropsychological battery was intended to facilitate not only detection of more subtle cognitive changes that occur early in disease progression, but also a better understanding of which cognitive abilities may be more susceptible to the early harmful effects of chronically elevated glucose levels so as to potentially identify a modifiable risk factor. The use of a detailed neuropsychological battery, as opposed to a global cognitive measure, allows for examination of

specific cognitive abilities with changes in structural correlates and relation to genetic risk factors. As such, the study objectives and hypotheses were as follows:

1. To understand which distinct cognitive domains are affected by elevated glucose levels among healthy individuals through a comprehensive examination of cognitive abilities. As reported in previous studies, memory was expected to be most implicated relative to other cognitive domains.
2. To understand whether cognitive performance is affected by elevated glucose levels in neurodegenerative disease. Given that reduced glucose metabolism is an early biomarker in AD and PD, elevated glucose levels were expected to exacerbate cognitive disturbances in comparison to lower glucose levels among those with AD and PD.
3. To explore whether the relationship between elevated glucose levels and cognitive deficits interacts with changes in cerebral gray and white matter and hippocampal volumes in neurodegenerative disease. Based on previous findings, it was expected that structural changes in the hippocampus would moderate the relationship between memory decline and elevated glucose levels, especially in the AD population. Global volume reductions were expected to be associated with elevated glucose levels in both AD and PD populations as an indicator of more global and widespread changes that were expected with elevated glucose levels.
4. To examine whether the ApoE ε4 genotype is associated with additional cognitive impairment in individuals with elevated glucose levels in comparison to those with the ApoE ε3/3 genotype. It was expected that among individuals with AD or PD, the ApoE ε4 genotype would interact with glucose levels to exhibit greater cognitive impairment.

The primary aim of these studies was to explore the links between glucose levels and the presence and severity of cognitive complications in neurodegenerative disease. Considering that individual glucose levels in general are a modifiable risk factor, understanding their contributions to cognitive decline, especially in underlying neurodegenerative disease, has important consequences for future dementia preventive efforts.

Methods

Participants

Data from the Ontario Neurodegenerative Disease Research Initiative (ONDRI) were used for this study. ONDRI is a longitudinal cohort study investigating four neurodegenerative diseases and cerebrovascular disease using rigorous evaluations across multiple assessment platforms (Farhan et al., 2017). In addition, ONDRI has a control cohort of 45 healthy older adults without neurodegenerative disease. The assessments include genomics, neuroimaging, comprehensive hematological tests, ocular function, retinal imaging, gait and balance, and neuropsychological assessment. Approximately 600 participants were recruited across Ontario, Canada and were followed annually up to 3 years. This large cohort study provides a unique opportunity to examine cognitive functioning across different diseases in a harmonious and standard fashion.

For the present study, data from the healthy aging, Alzheimer's disease, and Parkinson's disease cohorts were used. Participant characteristics are outlined in Table 1 for all three cohorts. Baseline data from the clinical, neuropsychological, genetic and neuroimaging platforms were obtained. Genetic data for the healthy aging group were not available and was obtained for the neurodegenerative groups only. All participants were required to meet extensive inclusion and exclusion criteria for the larger ONDRI study, as well as specific criteria for individual disease

cohorts and specific assessment platforms. Below is an outline of the general study criteria as well as specific inclusion and exclusion criteria for each of the cohorts.

General Inclusion and Exclusion Criteria

Inclusion Criteria. Participants had to identify as male or post-menopausal female (minimum of one year since the last menstrual period) and be between the ages of 45-90 years. They were required to be (a) proficient in speaking and understanding spoken English, (b) have at least 8 years of formal education, (c) be capable of cooperating for the duration of the study procedures and assessments, (d) be willing to undergo study procedures and remain unaware of the results (unless there were findings that were deemed of clinical significance), (e) have sufficient vision and hearing to participate in cognitive testing, (f) have good venous access for phlebotomy to be performed, and (g) be able to walk with or without an assistive aid (e.g., cane, walker).

All participants were also required to have a reliable study partner. The study partner must have regular interaction with the participant (i.e., have contact with the participant at least once per month over the phone, email, or face-to-face) and know the participant well enough to answer questions about their cognitive abilities, communication skills, mood, and daily functioning (i.e., have known the participant for at least 2 years).

Exclusion Criteria. The general exclusion criteria consisted of not having any underlying conditions (other than the disease being studied) that may interfere with participation in the study or the study results. These included (a) unstable cardiac, pulmonary, renal, hepatic, endocrine or hematologic disease; (b) active malignancy or infectious disease; (c) significant psychiatric illness, including life-long depressive illness; (d) history of significant learning disability; (e) other significant neurologic disease; (f) cognitive complications of cancer; (g)

symptomatic stroke within the past 6 months; (h) substance abuse within the past year or history of alcohol or drug abuse; (i) history of significant head trauma or recurrent concussions requiring hospitalization followed by persistent neurologic defaults or known structural brain abnormalities; (j) pain or sleep disorder that could interfere with cognitive testing; or (k) any disability that would limit the ability to perform study assessments.

For three of the five recruiting sites (Toronto, London, Ottawa) participants were excluded if they had poorly controlled diabetes, defined by HbA1c levels of 7.5 mmol/L or higher. Lastly, participants were excluded if they were enrolled in a disease-modifying therapeutic trial that could potentially compromise study results.

Assessment Platform Criteria. Participants were also excluded if they had any significant ocular conditions, including previous retinal laser therapy for diabetic retinopathy, clinical diagnosis of glaucoma, taking eye drops for glaucoma, previous surgery (including laser) for glaucoma, history of optic neuritis, or any other serious eye disease or treatment or eye surgery.

Reasons for exclusion also included brain imaging abnormalities detected on CT or MRI, including evidence of infection or focal compressive mass lesions (tumours, subdural hematomas, malformations, etc.), contraindications to 3T MRI (e.g., metal implant), or inability to tolerate the MRI environment (e.g., due to physical size and/or claustrophobia).

For the neuropsychology platform, all participants were required to complete at least 75% of the test battery, which must include the hearing and vision screening measures, in order to be included. As such, potential participants who were nonverbal and/or had severe dysarthria at screening were excluded from neuropsychological assessment.

Cohort Criteria.

Healthy Aging. Participants had to be cognitively normal and functionally independent in prescreening history and score within normal limits on the Montreal Cognitive Assessment (MoCA score ≥ 26) and Toronto Cognitive Assessment (TorCA score > 28; Freedman et al., 2018).

Alzheimer's Disease. Participants had to be between the ages of 45-90 years and meet the National Institute on Aging-Alzheimer's Association core clinical criteria for probable AD dementia or amnestic single or multiple domain Mild Cognitive Impairment (McKhann et al., 2011). Participants with a nonamnestic presentation (e.g., language, visuospatial, or executive function) of AD or MCI were excluded from the study. Participants were also required to score ≥ 18 on the MoCA.

Parkinson's Disease. Participants had to be between the ages of 55-85 years and be diagnosed with idiopathic Parkinson's disease based on the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hughes, Daniel, Kilford, & Lee, 1992) including acceptable and sustained response to dopaminergic drugs. Participants had to be diagnosed with PD within the last 8 years, be in Stage 2 or 3 of the Hoehn & Yahr Scale (Hoehn & Yahr, 1967) and score ≥ 18 on the MoCA.

Study Procedures

All participants and study partners were required to provide written informed consent. Data used for this study were from the baseline screening visit for all three cohorts. Participants were required to complete all baseline measures and testing within an 8-week window from the day the consent form was signed. All cognitive testing was conducted in the "ON" state for the

Parkinson's disease cohort and all participants were required to fast for 8-10 hours prior to their blood tests for biomarkers and genetic testing.

Study Variables

Neuropsychological Battery

Rigorously trained study coordinators administered the neuropsychological tests, and extensive quality assurance and quality control protocols were completed on all neuropsychological data for the larger ONDRI study (McLaughlin, 2020; Sunderland, 2019). For the current study, the neuropsychological battery was divided into five cognitive domains. Recommendations by the ONDRI Neuropsychology platform team were followed to create composite scores for each cognitive domain (McLaughlin et al., 2021). These recommendations and steps are based on conventions in clinical neuropsychology (Lezak et al., 2004), and follow the Movement Disorder Society Task Force's framework for characterizing and diagnosing cognitive impairment in Parkinson's disease (Litvan et al., 2012). This procedure consisted of using raw test scores that were adjusted for age, sex and education, mean centered, and converted to z-scores for each cohort. Standardized test scores (*z*-scores) were then averaged across measures within each domain to generate a composite score. The composite scores were calculated separately for each of the cohorts; thus, the standardized scores represent scores that are relative to each cohort and not the combined sample of all three cohorts. Five cognitive domains were assessed, including attention and working memory, executive functions, language,

memory and visuospatial abilities. The list of specific tests that comprised each cognitive domain are provided in Appendix A.

Glucose and Covariates

HbA1c. The primary measure of blood glucose used in the study was glycated hemoglobin A1c (HbA1c). This measure represents the average blood sugar levels, or the concentration of glucose in the blood, over the past 2-3 months and is measured as millimole per liter (mmol/L). The American Diabetes Association (2020) recommends that HbA1c levels of 5.6 mmol/L or lower are healthy, 5.7-6.4 mmol/L are characterized as prediabetic or at risk of developing diabetes, and HbA1c levels higher than 6.4 mmol/L are diagnostic of diabetes (American Diabetes Association, 2020). The measure of HbA1c is more commonly used than fasting blood glucose and has shown more robust findings of deleterious effects in relation to cognition (Kirvalidze et al., 2022.). In comparison, fasting blood glucose has shown both deleterious and advantageous outcomes for cognitive performance, and it is less consistently reported in the glucose and cognition literature (Kirvalidze et al., 2022; Riby et al., 2004). For these reasons, only HbA1c was used as the primary measure for glucose in the secondary analyses with the genetic and brain volume variables.

Fasting Blood Glucose. Fasting blood sugar test is the secondary glucose measure in the study. This provides a measure of short-term glucose in the blood (based on approximately the last 24 hours) and measures the free glucose molecules in the blood. This test requires a minimum 8-hour fast prior to the test. Fasting blood glucose guidelines suggest that less than 5.5 mmol/L is normal, 5.5-6.9 mmol/L is considered prediabetic, and 7.0 mmol/L or greater is diagnostic of diabetes (American Diabetes Association, 2020).

Triglycerides. Triglyceride blood levels were measured as part of a lipid profile. Participants were required to fast for a minimum of 8 hours prior to the test. Triglyceride test results less than 1.7 mmol/L are categorized as normal, 1.7-2.2 mmol/L as borderline, and greater than 2.3 mmol/L as high.

Hypertension. Presence of hypertension was assessed by self-report of a diagnosis that must have been received by the participant's medical health professional. This was a yes or no question that was part of an extensive health history questionnaire.

Smoking. Smoking was assessed by self-reported number of years smoked. Smoking history was assessed as part of an extensive health history questionnaire.

Genotyping

Genomic DNA was isolated from whole blood and sequenced using ONDRISeq, a custom-designed next-generation sequencing gene panel that targets 80 genes previously associated with the disease cohorts in ONDRI (Dilliott et al., 2018; Farhan et al., 2016). For the present study, ApoE genotypes were used to categorize participants into three groups based on carrier status: ε2 carriers (ε2/2, ε3/2); ε3 carriers (ε3/3); and ε4 carriers (ε4/3, ε4/4). Participants harbouring an ε4/2 genotype were excluded from the study. Genotype analyses were conducted for the disease groups using only ε3 and ε4 carriers.

MRI

3D T1-weighted neuroimages were acquired for each participant. Prior to image processing, MRI images were reviewed by a neuroradiologist for incidental findings and by a medical biophysics scientist for imaging quality. The structural neuroimaging pipeline used in ONDRI is a component-based algorithm commonly referred to as Semi-Automatic Brain Region Extraction Lesion Explorer (SABRE-LE; Ramirez, 2020). This method separates the brain into

26 regions of interest. Each imaging analyst was required to achieve an intraclass correlation coefficient (ICC) > 0.90 in order to work on ONDRI patient imaging analysis. For the present study, three volumetric regions of interest were used: normal appearing gray matter, normal appearing white matter, and total hippocampal volume.

Missing Data

Two methods were used to correct for missing data for the neuropsychological dataset. If data were missing due to a cognitive or behavioural impairment, then the assumption was that these individuals would have obtained the worst possible score had they completed the measure. For these data points the lowest possible score for the test was imputed. Correction for cognitive or behaviour impairment was very infrequent, occurring for none of the 1150 data points in the healthy aging group, 12 of 3150 (0.4%) data points in the AD group and 3 of 3500 (0.09%) data points in the PD group.

The remaining reasons for missing data included administration errors, verbal refusal by participant or other (participant not wearing hearing aids, auditory screening not administered, test session discontinued due to time constraints). Corrections using mean imputation were also very infrequent occurring for 5 out of a possible 1150 (0.4%) data points in the healthy aging group, 50 of 3150 (1.6%) data points in the AD group, and 14 of 3500 (0.4%) data points in the PD group.

Missing data for any of the clinical, genetic, and MRI measures were not corrected. Only 3 individuals were missing glucose data across all three cohorts and no individuals were missing genetic and MRI data. As previously mentioned, genetic data were not available for the healthy aging group.

Approach to Data Analyses

Primary Analyses: Multivariate Regression

Multivariate multiple regression analysis was used as the primary multivariate approach to understand the combined influence of multiple adverse variables that affect cognition. Specifically, this approach allowed examination of whether glucose levels predict various cognitive domains while controlling for the effect of related covariates using one model. Multivariate multiple regression analysis is considered an effective technique to analyze the relationship between multiple predictor variables and multiple outcome variables (Hartung & Knapp, 2005), which in this case is a set of vascular-related factors and a set of cognitive abilities.

The selection of covariates for the model was based on a-priori hypotheses after extensive review of the literature on glucose and cognition. The final model consisted of two predictor variables of glucose levels (short-term fasting blood glucose and long-term HbA1c levels), three related vascular covariates (triglycerides, smoking, and hypertension) and five variables that represented each cognitive domain for the outcome variables (attention and working memory, executive functions, language, memory, and visuospatial abilities). This model was conducted first with the healthy aging group, then with each of the disease groups separately. Wilk's lambda was used to assess the significance of the multivariate model, in other words, to determine whether the glucose variables significantly predict cognition after controlling for the vascular covariates. Here, significance indicated that predictor contribution was non-zero for at least one of the five cognitive domain variables. For those multivariate models that were significant, individual coefficients were examined in order to determine which of the five cognitive domain variables were predicted.

Secondary Analyses: Interaction Effects

As secondary analyses, the relationships between genotype, brain volumes, glucose levels, and cognition were further explored. Interaction analyses were used to examine whether genotype and brain volumes affected the strength of the relationship between glucose levels and each of the five cognitive domains.

For the genetic analysis, a one-way multivariate analysis of variance (MANOVA) was conducted to examine group differences and determine whether ApoE-ε4 carriers differed on cognitive abilities compared to ApoE-ε3/3 carriers. The significant MANOVA model was followed by one-way ANOVA tests to examine which of the five cognitive domains differed between the two groups. Next, interaction effects of genotype and glucose levels (HbA1c) on each of the five cognitive domains were examined using a multivariate regression model, which allowed for all five dependent variables to be examined in one model. Genetic analyses were conducted for the disease groups only.

Similarly, interaction effects of total white matter volume (WM), total gray matter volume (GM), and long-term glucose levels (HbA1c) were examined for each of the five cognitive domains using a separate multivariate model. A total of five terms were entered into one model: total gray volume, total white matter volume, HbA1c levels, and two interactions terms (GM*HbA1c and WM*HbA1c), and there were five outcome measures of cognitive performance. For only the memory domain, the interaction effect of total hippocampal volume and HbA1c levels was also examined separately.

As in the primary analyses, all interaction analyses were conducted in the control group and two disease groups separately. All statistical analyses were performed using SPSS version 28.0.

Results

Healthy Aging

Genetics data were not collected for this cohort; consequently, analyses examined only glucose and brain volumes.

Multivariate Regression with Glucose and Covariates

After excluding three individuals with missing lab data, 42 individuals from the healthy adult cohort were included in the analyses. A Wilk's Lambda test on the multivariate multiple regression revealed a large significant contribution of HbA1c levels, $\Lambda = .65$, $F(1,36) = 3.40$, $p = .01$, partial $\eta^2 = .35$, but not fasting blood glucose, $\Lambda = .77$, $F(1,36) = 1.90$, $p = .12$, partial $\eta^2 = .23$, to cognitive abilities when controlling for triglycerides, smoking, and hypertension. When examining univariate coefficients, higher HbA1c levels significantly predicted lower language performance, $b = -1.04$, $p = .01$, and lower visuospatial abilities, $b = -.91$, $p = .01$. Given that the multivariate model was not significant for fasting blood glucose, individual coefficients for each cognitive domain for this variable were not examined.

Analyses of Brain Volume and Glucose

Interactions for Gray and White Matter Volume and Glucose. Next, the main effects of total gray matter volume, total white matter volume, and their interaction with HbA1c on cognitive performance were examined using a separate multivariate multiple regression model. A Wilk's Lambda test on the multivariate multiple regression revealed large significant contributions of the interaction of total gray matter volume and HbA1c levels, $\Lambda = .66$, $F(1,37) = 3.47$, $p = .01$, partial $\eta^2 = .34$, and the interaction of total white matter volume and HbA1c levels, $\Lambda = .71$, $F(1,37) = 2.73$, $p = .04$, partial $\eta^2 = .29$, but their main effects did not reach significance Λs $> .04$, $Fs(1,37) < 1.34$, ps $> .25$, partial η^2 s $< .18$. However, examination of individual

coefficients with univariate analyses did not reach significance for any of the five cognitive domains for the interaction of gray or white matter volume with HbA1c levels, *b*s < .34, *p*s > .09.

Interaction of Hippocampal Volume and Glucose for Memory. Lastly, the main effects of total hippocampal volume, HbA1c, and their interaction for the memory domain were examined using a separate multiple linear regression. There was no significant main effect of hippocampal volume or HbA1c level, nor an interaction effect of hippocampal volume and HbA1c levels on memory performance, $F(3,39) = 0.36$, $p = .78$, $R^2 = .03$.

Alzheimer's Disease

Multivariate Regression with Glucose and Covariates

After excluding one participant with missing glucose data, 125 individuals from the Alzheimer's Disease cohort were included in the analyses. A Wilk's Lambda test on the multivariate multiple regression did not reveal a significant contribution of fasting blood glucose, $\Lambda = .94$, $F(1,119) = 1.63$, $p = .16$, partial $\eta^2 = .07$ or HbA1c levels, $\Lambda = .93$, $F(1, 119) = 1.84$, $p = .11$, partial $\eta^2 = .07$ to cognitive abilities when controlling for triglycerides, smoking, and hypertension. Given that the multivariate model was not significant, individual coefficients for each cognitive domain were not examined.

Analyses with Genotype and Glucose

Genotype Group Differences. For the genetics analyses, 120 individuals who were ApoE-ε3/3 or ε4 carriers were included. A one-way MANOVA revealed that there was a large, significant difference in cognitive performance based on genotype, $\Lambda = .85$, $F(1, 118) = 4.19$, $p = .002$, partial $\eta^2 = .16$. Examining individual cognitive domains using an ANOVA revealed medium significant mean differences on the memory domain in favour of the ApoE ε3/3 group, $F(1, 118) = 13.23$, $p < .001$, partial $\eta^2 = .10$. No other cognitive domains showed statistically

significant mean differences between ε3/3 and ε4 carriers, $Fs(1, 118) < 1.32$, $ps > .25$, partial $\eta^2 s < .01$. Means for each cognitive domain by ApoE genotype are presented in Table 2.

Interactions for Genotype and Glucose. To examine the interaction effect of genotype and HbA1c on cognitive performance, a separate multivariate multiple regression model was conducted. A Wilk's Lambda test on the multivariate multiple regression revealed a medium significant main contribution of genotype, $\Lambda = .85$, $F(1,115) = 4.08$, $p = .002$, partial $\eta^2 = .16$, but no main effect of HbA1c, $\Lambda = .94$, $F(1,115) = 1.46$, $p = .21$, partial $\eta^2 = .06$. The interaction of HbA1c and genotype also did not reach significance, $\Lambda = .91$, $F(1,115) = 2.21$, $p = .06$, partial $\eta^2 = .09$. As in the previously reported MANOVA, examining individual coefficients of the regression analysis revealed a medium significant main effect of genotype on memory performance, in which ε4 carriers performed 0.26 standard deviations lower on memory measures ($M = -.29$) than ε3/3 carriers ($M = .24$), $b = -.26$, $p < .001$, $R^2 = .10$. No other significant main effect or interactions were noted for any of the five cognitive domains. Fasting blood glucose and HbA1c means by ApoE genotype are presented in Table 2.

Analyses of Brain Volume and Glucose

Interactions for Gray and White Matter Volume and Glucose. Next, the main effects of total gray matter volume, total white matter volume, and their interaction with HbA1c on cognitive performance were examined using a separate multivariate multiple regression model. A Wilk's Lambda test on the multivariate multiple regression did not reach significance for total gray or white matter volumes, and no interaction terms reached significance, $\Lambda s > .91$, $Fs(1,119) < 2.24$, $ps > .06$, partial $\eta^2 s < .08$.

Interaction of Hippocampal Volume and Glucose for Memory. Lastly, the main effects of total hippocampal volume, HbA1c, and their interaction for the memory domain was

examined using a separate multiple linear regression. The model was significant, $F(3,121) = 5.29$, $p = .002$, $R^2 = .12$, due to a medium, significant main effect of hippocampal volume, with greater hippocampal volume predicting better memory performance, $b = .27$, $p < .001$. There was no significant main effect of HbA1c, $b = .05$, $p = .52$, or an interaction effect of hippocampal volume and HbA1c, $b = -.06$, $p = .45$,

Parkinson's Disease

Multivariate Regression with Glucose and Covariates

All 140 individuals from the Parkinson's disease cohort were included in the analyses. A Wilk's Lambda test on the multivariate multiple regression revealed a medium significant contribution of HbA1c levels, $\Lambda = .92$, $F(1,134) = 2.38$, $p = .04$, partial $\eta^2 = .08$, but not fasting blood glucose, $\Lambda = .94$, $F(1,134) = 1.72$, $p = .13$, partial $\eta^2 = .06$, to cognitive abilities when controlling for triglycerides, smoking, and hypertension. However, when examining univariate coefficients, HbA1c levels were not significant for any of the five cognitive domains, bs < .06, ps > .08, partial η^2s < .02.

Analyses Involving Genotype and Glucose

Genotype Group Differences. For the genetics analyses, 116 individuals who were ApoE-ε3/3 or ε4 carriers were included. A one-way MANOVA revealed that there was a large significant difference in cognitive performance between individuals with these two genotypes, $\Lambda = .88$, $F(1, 114) = 3.13$, $p = .01$, partial $\eta^2 = .13$. Examining individual cognitive domains using univariate ANOVAs revealed large, significant mean differences on the visuospatial abilities domain in favour of the ApoE ε3/3 group, $F(1, 114) = 14.79$, $p < .001$, partial $\eta^2 = .12$. No other cognitive domains showed statistically significant mean differences between ε3/3 and ε4 carriers,

Fs(1, 114) < 3.19, *ps* > .08, partial $\eta^2 s$ < .03. Means for each cognitive domain by ApoE genotype are presented in Table 2.

Interactions for Genotype and Glucose. To examine the interaction effect of genotype and HbA1c on cognitive performance, a separate multivariate multiple regression model was conducted. A Wilk's Lambda test on the multivariate multiple regression revealed a significant main contribution of genotype, $\Lambda = .87$, $F(1,112) = 3.17$, $p = .01$, partial $\eta^2 = .13$, but no main effect of HbA1c levels, $\Lambda = .96$, $F(1,112) = 0.96$, $p = .45$, partial $\eta^2 = .04$. The interaction of HbA1c and genotype also did not reach significance, $\Lambda = .96$, $F(1,112) = .86$, $p = .51$, partial $\eta^2 = .04$. As in the previously reported MANOVA, examining individual coefficients of the regression analysis revealed a medium, significant main effect of genotype on visuospatial abilities, in which ε4 carriers performed 0.22 standard deviations lower on visuospatial abilities measures ($M = -.37$) than ApoE ε3/3 carriers ($M = .12$), $b = -.22$, $p < .001$, $R^2 = .12$. No other significant main effect or interactions were noted for any of the five cognitive domains *b*s < -.11 *p*s > .14, partial η^2s < .02. Fasting blood glucose and HbA1c means by ApoE genotype are presented in Table 2.

Analyses of Brain Volume and Glucose

Interactions for Brain Volume and Glucose. Next, the main effects of total gray matter volume, total white matter volume, and their interaction with HbA1c on cognitive performance were examined using a separate multivariate multiple regression model. A Wilk's Lambda test on the multivariate multiple regression revealed a large significant main contribution of total gray matter volume, $\Lambda = .83$, $F(1,134) = 5.19$, $p < .001$, partial $\eta^2 = .17$ and a medium significant main contribution total white matter volume, $\Lambda = .91$, $F(1,134) = 2.70$, $p = .02$, partial $\eta^2 = .09$, but not their interactions with HbA1c, Λs > .96, *Fs*(1,134) < 0.97, *p*s > .44 , partial η^2 s < .04.

Examination of individual coefficients revealed that greater total gray matter volume predicted better performance for attention and working memory, $b = .25$, $p = .007$, language, $b = .31$, $p = .002$, memory, $b = .36$, $p < .001$, and visuospatial abilities, $b = .20$, $p = .02$. Greater white matter volume predicted better memory, $b = .27$, $p = .008$, and visuospatial abilities, $b = .19$, $p = .02$. No other significant main effect or interactions were noted for any of the five cognitive domains.

Interaction of Hippocampal Volume and Glucose for Memory. Lastly, the main effects of total hippocampal volume, HbA1c and their interaction for the memory domain was examined using a separate multiple linear regression. There was no significant main effect of hippocampal volume, or HbA1c level, nor an interaction effect of hippocampal volume and HbA1c levels on memory performance, $F(3,136) = 0.76$, $p = .52$, $R^2 = .02$.

The results from all three cohorts are summarized in Table 3. Figures 1.1, 1.2, and 1.3 present a visualization of the relevant analyses and the key findings for each of the cohorts.

Discussion

The present study tested the relationship between glucose levels and cognitive abilities among healthy aging and neurodegenerative disease. The results suggested that higher glucose levels are differentially related to disease status and cognitive abilities after controlling for the effects of related covariates of triglycerides, hypertension, and smoking. The following is a summary of the present findings, how they contribute to previous research, the clinical

implications of the results, and the strengths and limitations of the study. This section ends with brief suggestions for future directions for research.

Healthy Aging

Summary of Findings

Among the healthy aging group, higher glucose levels, specifically HbA1c, was associated with poorer cognition compared to lower levels of glucose when controlling for triglycerides, hypertension, and smoking. This relationship was demonstrated across language and visuospatial abilities, but performance in the domains of memory, executive functions, and attention and working memory was unrelated to glucose levels. Fasting blood glucose levels were not related to cognitive performance in any domain. Additionally, a significant interaction emerged in which lower brain volumes were related to poorer cognitive performance in those who exhibited higher levels of glucose (HbA1c), relative to those with lower levels of glucose. This interaction was significant for both whole brain gray and white matter volumes. This pattern was not observed when examining hippocampal volume and the memory domain alone. As previously mentioned, genetic analyses were not conducted for the healthy aging group.

Relation to Previous Research

A large systematic review summarized the existing literature on the association between markers of poor glycemic control, cognitive function, and progression to dementia in nondiabetic individuals (Kirvalidze et al., 2022). No definitive conclusions for an association between poor glycemic control and worse cognitive functions were made, however there was evidence that poor glycemic control is associated with brain abnormalities on MRI (Kirvalidze et al., 2022). A recent study examined HbA1c levels and specific cognitive domains using a detailed cognitive battery rather than global cognitive measures and reported evidence for a negative association

between HbA1c levels and vocabulary knowledge, working memory, and executive functions and with white matter microstructural integrity in healthy young adults (Repple et al., 2021). However, this study did not include older adults and used fewer than two cognitive measures to represent each cognitive domain.

The present findings build upon this literature by examining specific cognitive abilities with a comprehensive assessment of five distinct cognitive domains, with a minimum of three neuropsychological tests to represent a specific cognitive domain. Using a comprehensive battery of tests revealed that the effects of higher glucose levels are not observed consistently across all cognitive abilities and affect verbal and visuospatial abilities more than other cognitive domains. Importantly, the domain of memory, which is more frequently assessed in the literature than other domains, was not associated with glucose levels (Convit et al., 2003; Kerti et al., 2013). Moreover, there was no significant interaction of hippocampal volume and glucose levels with memory performance. There was, however, an interaction with global gray and white matter brain volume and glucose, which suggests that higher glucose levels may lead to more widespread changes rather than targeting specific brain structures. It may be that widespread changes occur prior to changes in specific brain structures. These findings support the hypothesis that glucose may differentially affect healthy adults compared to those with neurodegenerative disease where additional biological abnormalities may already be occurring.

Neurodegenerative Disease

Summary of Findings

Alzheimer's Disease. With the AD cohort, glucose levels were not associated with cognition for either HbA1c levels or for fasting blood glucose after controlling for covariates. Genetic analyses revealed that ApoE-ε4 carriers performed worse on the memory domain, but no

other cognitive differences emerged between ApoE ε3/3 and ε4 carriers. There was also no interaction effect of glucose levels and ApoE with cognition. Lastly, there was no interaction of gray and white matter volumes or of hippocampal volume with glucose and cognition.

Parkinson's Disease. Within the PD cohort, there was an association of higher glucose levels, specifically with HbA1c and not fasting blood glucose, with cognition when all cognitive domains were combined. However, when individual cognitive domains were examined, no specific domain revealed a significant association. Genetic analyses revealed that ApoE-ε4 carriers performed worse on the visuospatial domain compared to the ApoE-ε3/3 carriers, and no other cognitive domain differences emerged between the two ApoE groups. Lastly, while there was an association between gray and white matter volumes and cognitive abilities, no significant interaction emerged between glucose levels and brain volume. Greater total gray matter volume predicted better performance on the attention and working memory, language, and memory domains, whereas greater white matter volume predicted better memory and visuospatial abilities. No significant association or interactions emerged when examining hippocampal volume and glucose with memory.

Relation to Previous Research

Past research has shown decreased glucose metabolism as one of the earliest brain changes to occur in AD (Mosconi, 2005; Patil et al., 2012). For example, individuals with mild cognitive impairment (MCI) who subsequently develop AD show disturbances in glucose metabolism (Hunt et al., 2007). Some research has also shown this relationship directly with

decreased cognitive performance with higher levels of HbA1c in individuals with MCI or AD but not with healthy adults (Pappas et al., 2019).

The current findings were not consistent with previous research. Here, glucose levels were not associated with cognition in the AD group, nor did a significant interaction of ApoE or brain volume with glucose emerge. Our findings are consistent with other research that concluded that higher glucose levels may have a causal effect on the risk of unspecified dementia, but not on the risk of AD (Benn et al., 2020; Larsson et al., 2017; Ostergaard et al., 2015). One hypothesis put forth in the literature that may explain these findings suggests that key features of AD, such as deposits of amyloid-β and aggregates of hyperphosphorylated tau, are not more common in AD individuals with diabetes in comparison to AD individuals without diabetes (Benn et al., 2020; Arvanitakis et al., 2006). This supports the suggestion that high glucose concentrations or poor glycemic control do not directly contribute to the underlying pathology seen in Alzheimer's disease.

An additional explanation for the lack of observation between glucose and cognition may be that insulin resistance has greater impact than glucose on cognition. Insulin resistance is a key feature of both diabetes and AD (Abner et al., 2016) and has shown associations with cognition (Craft & Watson., 2004). Improvements to memory following the administration of intranasal insulin point to the importance of this hormone in cognitive functioning (Claxton et al., 2015) and thus may be an important vascular index to examine in neurodegenerative disease. Although information on insulin resistance was not available, it would be interesting to study its impact upon the cognitive domains assessed in the present study in neurodegenerative disease.

Interestingly, the mechanisms of hyperglycemia on cognition differentially affected those with PD relative to AD. The findings of the current study with the PD cohort were in line with

recent research concluding that higher glucose levels are negatively associated with cognition in PD (Huxford et al., 2022; Mollenhauer et al., 2019; Uyar et al., 2022), although these studies assessed cognition using only global cognitive measures (MMSE and MoCA). Higher glucose levels in individuals with PD have been associated with greater progression of cognitive decline, more severe motor impairment, and greater neuroaxonal damage (Uyar et al., 2022).

The results of the present study build upon these previous findings by reporting that higher glucose is associated with poorer cognitive abilities in PD while controlling for related covariates and using a comprehensive neuropsychological battery. The present results further suggest that elevated glucose levels in PD may lead to more widespread cognitive changes rather than altering specific cognitive abilities, as no single cognitive domain was significantly associated with glucose. Previous research suggests that diabetes is a risk factor for PD, and glycation of the alpha-synuclein protein could promote the aggregation of the protein, leading to altered glucose signaling pathways, which in turn may cause neurodegeneration (Cereda et al., 2013; Culberson, 2017; Mollenhauer et al., 2019). Although an interaction between brain volume, glucose, and cognition did not emerge in the present study, lower brain volumes were associated with poorer cognition. One explanation may be that the structural changes seen from glycation which can be detected by MRI may occur in the later stages of disease progression, whereas the current sample was relatively recently diagnosed (M = 4.7 years since PD diagnosis).

It may be possible that glucose metabolism was dysregulated in the disease cohorts, as higher HbA1c levels were observed among the neurodegenerative disease groups (M = 5.9% in AD, and 5.7% in PD) compared to the healthy aging cohort (M = 5.5%). However, these higher levels of HbA1c did not demonstrate the same association with cognition in the disease groups

that was observed in the healthy aging group. One explanation for this difference may lie in the possibility that greater brain pathology in those with neurodegenerative disease (increased amyloid-β or alpha-synuclein protein, neurofibrillary tangles, inflammatory changes, or decreased dopamine production) may be causing greater damage and accounting for greater variance than the processes caused by glucodysregulation. Thus, increased HbA1c levels may indeed be similarly harmful in neurodegenerative disease as in healthy aging, but when examined in isolation of other pathological processes may not be sufficient to reach statistical significance. This explanation is supported by the finding in the PD cohort in which higher HbA1c levels were associated with poorer cognition when examined in aggregate, but no individual cognitive domain reached statistical significance in isolation.

Multiple studies have reported associations between ApoE-ε4 carriers and poorer cognition, specifically for memory performance. These findings have been reported both in individuals with neurodegenerative disease, as well as in healthy adults who were considered cognitively normal for their age (Baxter et al., 2003; Caselli et al., 2009). Dilliott et al. (2021) examined this relationship across five neurodegenerative diseases and observed poorer performance in the verbal memory and visuospatial domains with ApoE-ε4 carriers in comparison to ε3/3 carriers when all disease cohorts were combined. When examining individual diseases, they found that the direction of association with ApoE ε4 was not uniform across diseases. Specifically, only those with AD showed associations between ApoE ε4 and poorer verbal memory performance. These findings suggest that ApoE ε4 may differentially affect neurodegenerative diseases and may interact with various pathology to influence cognition. It has been suggested that ApoE-ε4 carriers are in a prodromal stage of AD, with the ApoE ε4 allele increasing the deposition of amyloid-β and tau (O'Donoghue et al., 2018). The data in the

present study are in concordance with these past findings where an effect of ε4 was observed differentially between the AD and PD cohorts, with AD individuals demonstrating poorer memory performance and the PD individuals performing worse on visuospatial measures when having the ε4 allele.

Clinical Implications

There are a number of important clinical implications for these findings. Firstly, it is important to note that the mean HbA1c level for the healthy aging cohort (M = 5.5 mmol/L) was within the suggested, normal healthy range (< 5.7 mmol/L), well below diabetic (> 6.4 mmol/L) and even prediabetic cut-off levels (5.7-6.4 mmol/L). This suggests that the insidious effects of higher long-term glucose levels may begin to demonstrate subtle clinical changes well before reaching diagnostic levels. Individuals with chronically high glucose levels may be at higher risk for developing cognitive impairment compared to those who consistently maintain lower glucose levels. As such, the use of a diagnostic cutoff score of HbA1c to diagnose diabetes or even prediabetes may not be sufficient to capture the early cognitive changes that may be occurring at the currently suggested normal HbA1c range. In line with previous findings (Repple et al., 2021), the results of the current study suggest that a continuous rather than a categorical application of HbA1c levels with regular monitoring may be a beneficial protective method to mitigate cognitive decline, in healthy aging and in neurodegenerative disease.

Given that higher mean glucose levels were observed in the two disease groups compared to the healthy aging group, it suggests that mechanisms of glucodysregulation may be at play, despite not showing the same effect as seen among the healthy adults. As such, these findings suggest that it may be beneficial to monitor glucose levels throughout disease progression and may be especially important in the early years of disease. Clinically, this may be important in

reducing other disease symptoms that have been linked to higher glucose levels, especially in PD such as motor impairment (Uyar et al., 2022). Early changes to reduce glucose intake through dietary adjustments may be a feasible intervention for patients to help mitigate the severity of disease symptoms, especially cognitive decline.

Secondly, these findings highlight the importance of a comprehensive assessment of cognition when examining potential modifiable risk factors for dementia. Several past studies have examined cognition with global cognitive measures or have focused on only one or two cognitive domains (Arnoriaga et al., 2019; Convit et al., 2003; Kerti et al., 2013), or have used fewer than two measures to assess a specific ability (Repple et al., 2021). The present findings underscore the importance of comprehensive testing when assessing cognition, including the assessment of cognitive domains other than memory, which may have been missed in previous studies simply due to lack of assessment. The present results support the notion that higher glucose levels may differentially affect cognitive domains in healthy older adults. Thus, global cognitive measures may not accurately capture subtle changes that may be occurring in some cognitive abilities over others.

Lastly, these findings are especially important given that they were independent of the influence of other covariates that are likely to covary with either glucose, cognition, or brain volume. The neuropsychological scores were independent of age, sex, and education, and the analyses controlled for additional vascular covariates of triglycerides, hypertension, and smoking. Controlling for these important sources of potential bias reduced the effects of confounding factors that may otherwise interact with the relationship of glucose and cognition.

Strengths and Limitations

There are several strengths of the present study. First, the comprehensive cognitive domains assessed using an extensive neuropsychological battery across all three cohorts allowed for the impact of higher glucose levels on cognition to be studied in a detailed and novel manner. A minimum of at least two tests per domain reduced the likelihood of seeing impairment on a cognitive domain by chance alone or showing single test bias and also increased confidence in the composite score that represented a cognitive domain. Methodological variations involving different assessment methods when testing cognitive performance in this body of literature have precluded conclusive results in previous studies. Our use of a standardized cognitive battery directly addressed this problem and allowed for direct comparisons to be made across all three cohorts. This standardization improved validity of the results when understanding how glucose affects cognition in healthy aging versus neurodegenerative disease and further allowed comparisons among different neurodegenerative diseases (AD vs. PD).

Additionally, the use of multiple modalities of assessment (vascular indices, genetic samples, and neuroimaging data), which were standardized across all three cohorts, allowed for a more complete assessment of additional biological mechanisms that may underlie the complex interplay of glucose and cognition. Lastly, the use of HbA1c as our primary glucose variable rather than fasting blood glucose allowed for a measure of long-term glucose control over two to three months instead of one day. Using HbA1c rather than fasting blood glucose may be advantageous as it provides a reliable measure of glucoregulatory abilities which are less impacted by day-to-day, short term dietary changes.

Some of the limitations of the present study include a small number of individuals with diabetes in all three cohorts and the lack of data on indices of insulin. This limited the ability to

assess glycemic changes in those with and without a diabetes diagnosis or the effects of insulin resistance in relation to glucose and cognition. Additionally, individuals with uncontrolled diabetes, or HbA1c levels higher than 7.5 mmol/L were excluded from recruitment. This reduces the variability of glycemic control in the cohorts and ultimately restricts the range of the observed relationships.

Further, because the study is cross-sectional, it limits the ability to determine conclusively that higher HbA1c leads directly to poorer cognition among healthy adults and those with PD. Longitudinal data are needed to assess the long-term outcomes of chronically elevated glucose levels and whether this effect impacts progression to cognitive impairment or dementia.

Summary, Conclusions, and Future Directions

The current study tested the relationship between glucose levels and cognitive abilities among adults with and without neurodegenerative disease. The results suggested that higher glucose levels are differentially related to disease status and cognitive abilities after controlling for the effects of triglycerides, hypertension, and smoking. In healthy adults and those with PD, higher glucose levels were associated with poorer cognition. Domain-specific impairment with worse language and visuospatial abilities accounted for this effect in the healthy aging group, whereas widespread changes were observed in the PD group. In AD, glucose levels were not associated with cognition. No significant interaction emerged between ApoE-ε4 carriers and glucose in neurodegenerative disease. Lower brain volume and poorer cognition was observed among those with higher glucose levels in the healthy aging group but not in the PD or AD groups.

Future research continuing to understand the complex relationship between

glucodysregulation and cognition is needed among neurodegenerative disease populations, particularly with the interest in identifying protective factors for delaying cognitive impairment and further decline leading to a dementia diagnosis. Longitudinal data is especially needed in understanding the long-term effects of chronic hyperglycemia on cognition. Based on the results of this study, targeting glucoregulatory abilities could be advantageous in preserving cognitive abilities, which in turn may slow down the effects of neurodegenerative disease. The rise in dementia, diabetes and other vascular diseases in recent years highlights the need for targeted lifestyle strategies to promote healthy lifestyle and brain function across the lifespan. Consequently, there is a need for hypothesis-driven, randomized controlled trials that evaluate the role of different glycemic manipulations on cognition. Early-to-midlife interventions aimed at better managing and targeting glycemic control can potentially mitigate or delay early harmful processes that lead to cognitive decline and can yield important healthcare outcomes to manage increasing dementia prevalence.

Table 1

Participant Characteristics

	Healthy aging (*N* = 45)			Alzheimer's disease (*N* = 126)			Parkinson's disease (*N* = 140)		
	M (SD)	Range	*n* (%)	*M (SD)*	Range	*n* (%)	*M (SD)*	Range	n (%)
Age, years	66.7 (6.0)	51-77		71.0 (8.2)	53-87		67.9 (6.3)	55-86	
Education, years	16.3 (2.0)	12-20		15.2 (3.1)	8-20		15.5 (2.7)	8-20	
Sex									
Male			11 (24%)			69 (55%)			109 (78%)
Female			34 (76%)			57 (45%)			31 (22%)
Time since diagnosis, years				1.7 (2.5)	0-19.0		4.7 (1.6)	1.0-8.0	
MoCA Total	28.1 (1.4)	26-30		22.7 (3.0)	15-30		25.8 (2.6)	18-30	
HbA1c, in mmol/L	5.5 (0.4)	4.8-6.9		5.9 (1.0)	4.0-13.0		5.7 (0.8)	4.8-12.4	
Fasting blood glucose, in mmol/L	5.5 (0.7)	4.5-8.1		6.0 (1.8)	4.0-14.0		5.6 (1.4)	3.9-17.4	
Triglycerides, in mmol/L	1.4 (1.4)	0-9.0		1.3 (0.8)	0.5-5.4		1.3 (1.1)	0.43-12.0	
Smoking, years	4.7 (12.5)	0-53		10.8 (14.7)	0-52		7.3 (11.7)	0-46	
Diagnosis of hypertension			15 (33%)			34 (27%)			47 (34%)
Diagnosis of diabetes			3 (7%)			25 (20%)			13 (9%)
APOE									

ε2 carriers					5 (4%)		20 (14%)
ε3 carriers					59 (47%)		86 (61%)
ε4 carriers					61 (48%)		30 (21%)
Gray matter volume, in mm^3	561854 (49619)	471640-678844	533256 (51403)	416442-646058	574693 (47077)	478100-719741	
White matter volume, in mm^3	421417 (53817)	335252-564668	395381 (64321)	260505-556681	446140 (61163)	310887-637969	
Hippocampal volume, in mm^3	819 (199)	408-1307	706 (268)	175-1590	932 (257)	320-1584	

Note. ε2 carriers consisted of individuals with ε2/2 and ε3/2 genotypes; ε3 carriers consisted of individuals with ε3/3; ε4 carriers consisted of ε4/3 and ε4/4 genotypes. All individuals with the ApoE ε4/2 genotype were excluded from all genetic analyses (AD n = 1, PD n = 4). HbA1c = glycated hemoglobin; mmol/L = millimoles per litre; mm^3= cubic millimeter.

Table 2

Group Differences by ApoE Genotype

	Alzheimer's disease (*N*=126)			Parkinson's disease (*N*=140)		
	ε3 carriers *(n = 59)*	ε4 carriers (*n* = 61)		ε3 carriers *(n = 86)*	ε4 carriers (*n* = 30)	
	M (SD)	*M (SD)*	Partial η^2	*M (SD)*	*M (SD)*	Partial η^2
Attention & working memory z-score	0.0 (0.7)	-0.0 (0.7)	.00	0.0 (0.6)	-0.0 (0.7)	.00
Executive functions z-score	-0.0 (0.7)	-0.0 (0.7)	.00	0.1 (0.7)	-0.1 (0.8)	.01
Language z-score	-0.0 (1.1)	-0.1 (0.7)	.00	0.1 (0.6)	-0.2 (0.9)	.03
Memory z-score	0.2 (0.8)	-0.3 (0.8)	.10**	0.1 (0.7)	-0.1 (0.7)	.02
Visuospatial functions z-score	0.1 (0.6)	-0.1 (0.8)	.01	0.1 (0.6)	-0.4 (0.7)	.12**
Fasting blood glucose, in mmol/L	6.2 (1.9)	5.8 (1.4)	.01	5.5 (1.1)	6.0 (2.3)	.02
HbA1c, in mmol/L	6.1 (1.2)	5.7 (.8)	.02	5.7 (.5)	5.9 (1.3)	.01

Note. **$p < .001$

Table 3

Summary of Hypotheses and Relevant Results

Hypotheses	Cohort	Results
Higher glucose levels affect cognition.	Healthy Aging	Significant: HbA1c levels affect cognition, $\Lambda = .65$, $p = .01$, specifically, lower language $b = -1.04$, $p = .01$, and lower visuospatial abilities, $b = -.91$, $p = .01$ with higher HbA1c levels.
	Alzheimer's Disease	No significant relationship, $\Lambda = .94$, $p = .16$.
	Parkinson's Disease	Significant: HbA1c levels affect cognition, $\Lambda = .92$, $p = .04$. Univariate coefficients were not significant for specific cognitive domains, bs < .06, ps > .08.
ApoE interacts with glucose to affect cognition.	Healthy Aging	No genetic analyses conducted.
	Alzheimer's Disease	No significant relationship, $\Lambda = .91$, $p = .06$.
	Parkinson's Disease	No significant relationship, $\Lambda = .96$, $p = .51$.
Brain volume interacts with glucose to affect cognition.	Healthy Aging	Significant: Interaction of total gray matter volume, $\Lambda = .66$, $p = .01$ and interaction of total white matter volume, $\Lambda = .71$, $p = .04$, with HbA1c levels and cognition. No individual cognitive domain was significant. Hippocampal volume and HbA1c interaction was not significant with memory, $F(3,39) = 0.36$, $p = .78$.
	Alzheimer's Disease	No interaction terms reached significance, Λs > .91, ps > .06.
	Parkinson's Disease	No interaction terms reached significance, Λs > .96, ps > .44.

Note. The main hypotheses and corresponding key findings are presented here in summary format to present an overview of the results. Details of the results are presented in the Results section.

Figure 1.1

Visualization of Key Findings for the Healthy Aging Cohort

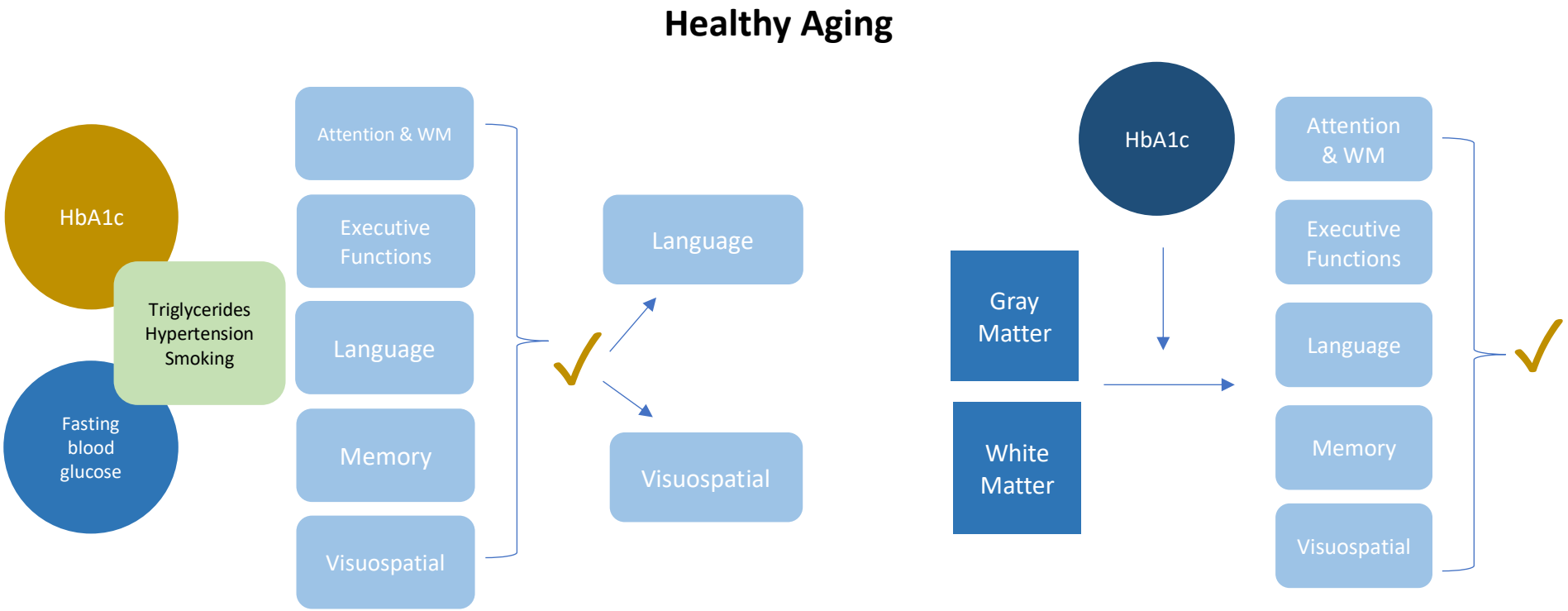

Figure 1.1. Drawing of multivariate multiple regression examining HbA1c levels with cognition and interaction of HbA1c with brain volumes and cognition.

Figure 1.2

Visualization of Key Findings for the Alzheimer's Disease Cohort

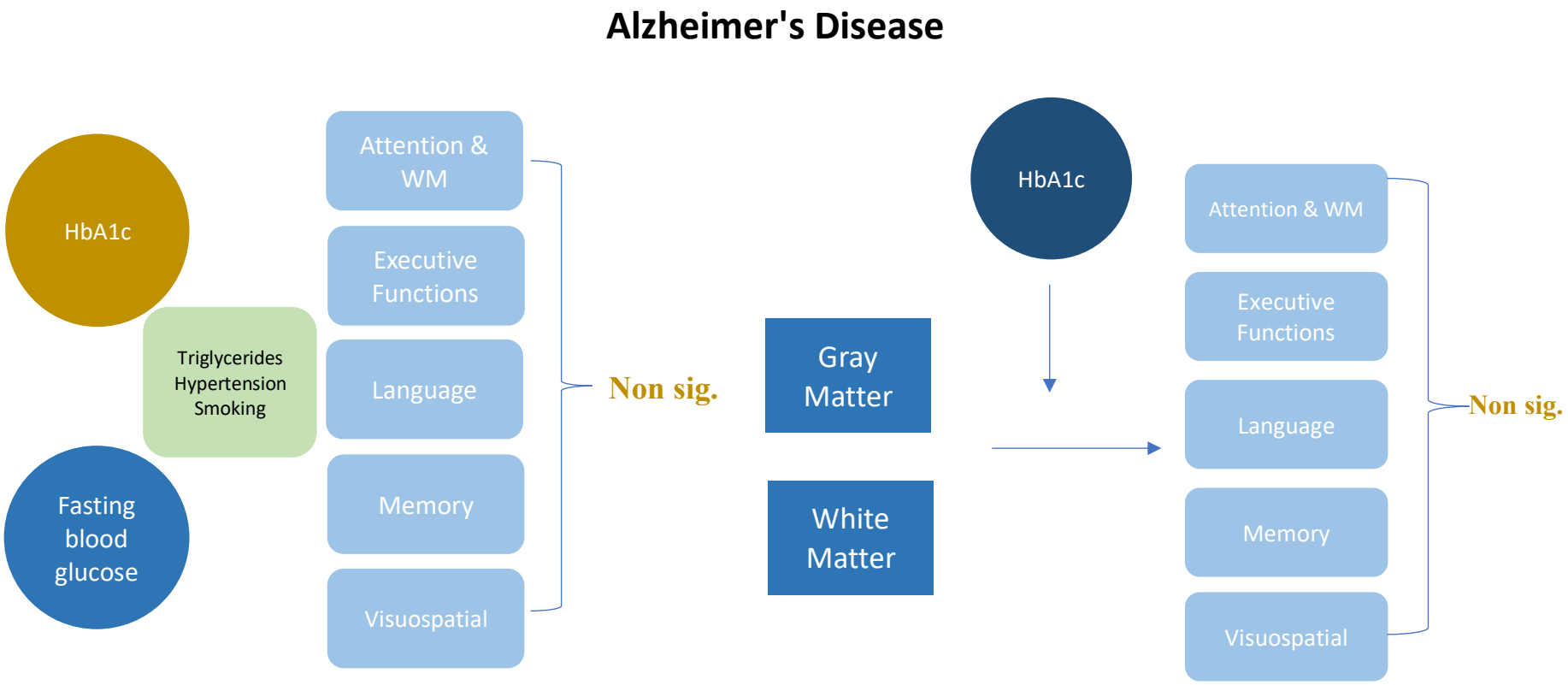

Figure 1.2. Drawing of multivariate multiple regression examining HbA1c levels with cognition and interaction of HbA1c with brain volumes and cognition.

Figure 1.3

Visualization of Key Findings for the Parkinson's Disease Cohort

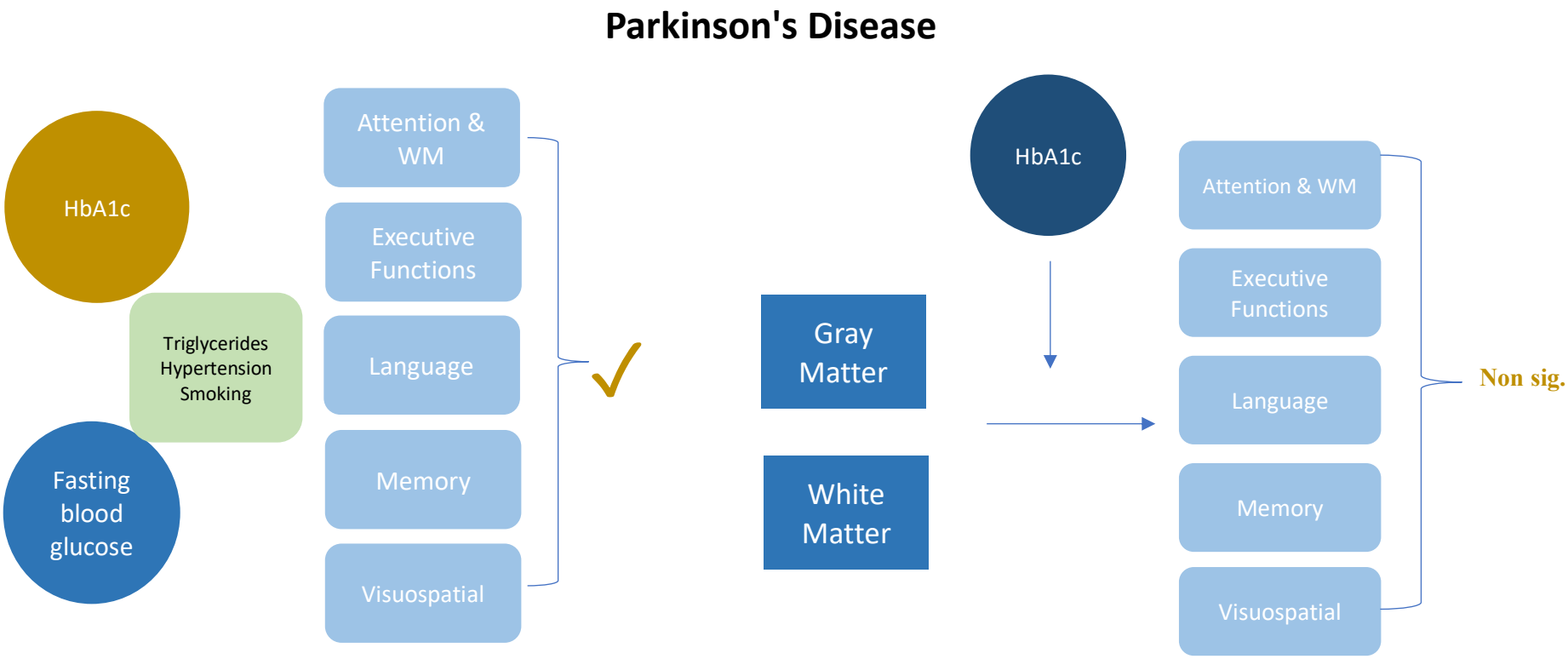

Figure 1.3. Drawing of multivariate multiple regression examining HbA1c levels with cognition and interaction of HbA1c with brain volumes and cognition.

References

Aarsland, D., Creese, B., Politis, M., Chaudhuri, K. R., Weintraub, D., & Ballard, C. (2017). Cognitive decline in Parkinson's disease. *Nature Reviews Neurology*, *13*(4), 217-231. 10.1038/nrneurol.2017.27

Abner, E., Nelson, P., Kryscio, R., Schmitt, F., Fardo, D., Woltjer, R., Cairns, N., Yu, L., Dodge, H., Xiong, C., Masaki, K., Tyas, S., Bennett, D., Schneider, J. & Arvanitakis, Z. (2016). Diabetes is associated with cerebrovascular but not Alzheimer's disease neuropathology. *Alzheimer's & Dementia, 12*(8)*,* 882-889. https://doi.org/10.1016/j.jalz.2015.12.006

Alam, F., Islam, A., Haryo Sasongko, T., & Hua Gan, S. (2016). Type 2 diabetes mellitus and Alzheimer's disease: Bridging the pathophysiology and management. *Current Pharmaceutical Design*, *22*(28), 4430-4442. http://dx.doi.org/10.2174/1381612822666160527160236

Albrecht, F., Ballarini, T., Neumann, J., & Schroeter, M. L. (2019). FDG-PET hypometabolism is more sensitive than MRI atrophy in Parkinson's disease: A whole-brain multimodal imaging meta-analysis. *NeuroImage: Clinical*, *21*, 101594. 10.1016/j.nicl.2018.11.004

Alves, G., Larsen, J. P., Emre, M., Wentzel-Larsen, T., & Aarsland, D. (2006). Changes in motor subtype and risk for incident dementia in Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*, *21*(8), 1123-1130. doi: 10.1002/mds.20897

American Diabetes Association. Classification and diagnosis of diabetes: Standards of medical care in diabetes. (2020). *Diabetes Care,* S14-S31. https://doi.org/10.2337/dc20-s002

Angelopoulou, E., Paudel, Y. N., Papageorgiou, S. G., & Piperi, C. (2021). APOE genotype and Alzheimer's disease: The influence of lifestyle and environmental factors. *ACS chemical neuroscience*, *12*(15), 2749-2764. 10.1021/acschemneuro.1c00295

Arnoriaga Rodriguez, M., Blasco, G., Coll, C., Biarnes, C., Contreras-Rodriguez, O., Garre-Olmo, J., Puig, J., Gich, J., Ricart, W., Ramio-Torrenta, L., & Fernandez-Real, J.M. (2019). Glycated hemoglobin, but not insulin sensitivity, is associated with memory in subjects with obesity. *Obesity*, 27(6), 932–942. https://doi.org/10.1002/oby.22457

Arvanitakis, Z., Schneider, J. A., Wilson, R. S., Li, Y., Arnold, S. E., Wang, Z., & Bennett, D. A. (2006). Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology*, *67*(11), 1960–1965. https://doi.org/10.1212/01.wnl.0000247053.45483.4e

Baba, T., Hosokai, Y., Nishio, Y., Kikuchi, A., Hirayama, K., Suzuki, K., Hasegawa, T., Aoki, M., Takeda, A. & Mori, E. (2017). Longitudinal study of cognitive and cerebral metabolic changes in Parkinson's disease. *Journal of the Neurological Sciences*, *372*, 288-293. https://doi.org/10.1016/j.jns.2016.11.068

Bangen, K., Himali, J., Beiser, A., Nation, D., Libon, D., Fox, C., Seshadri, S., Wolf, P., McKee, A., Au, R. & Delano-Wood, L. (2016). Interaction between midlife blood glucose and APOE genotype predicts later Alzheimer's disease pathology. *Journal of Alzheimer's Disease*, *53*(4), 1553-1562. 10.3233/JAD-160163

Baxter, L. C., Caselli, R. J., Johnson, S. C., Reiman, E., & Osborne, D. (2003). Apolipoprotein E ε4 affects new learning in cognitively normal individuals at risk for Alzheimer's disease. *Neurobiology of Aging*, *24*(7), 947-952. https://doi.org/10.1016/s0197-4580(03)00006-x

Benn, M., Nordestgaard, B. G., Tybjærg-Hansen, A., & Frikke-Schmidt, R. (2020). Impact of glucose on risk of dementia: Mendelian randomisation studies in 115,875 individuals. *Diabetologia*, *63*(6), 1151-1161. https://doi.org/10.1007/s00125-020-05124-5

Biessels, G. J., & Reijmer, Y. D. (2014). Brain changes underlying cognitive dysfunction in diabetes: What can we learn from MRI? *Diabetes*, *63*(7), 2244-2252. https://doi.org/10.2337/db14-0348

Biessels, G. J., Staekenborg, S., Brunner, E., Brayne, C., & Scheltens, P. (2006). Risk of dementia in diabetes mellitus: A systematic review. *The Lancet Neurology*, *5*(1), 64-74. https://doi.org/10.1016/S1474-4422(05)70284-2

Bohnen, N. I., Koeppe, R. A., Minoshima, S., Giordani, B., Albin, R. L., Frey, K. A., & Kuhl, D. E. (2011). Cerebral glucose metabolic features of Parkinson's disease and incident dementia: Longitudinal study. *Journal of Nuclear Medicine*, *52*(6), 848-855. 10.2967/jnumed.111.089946

Browne, J., Edwards, D. A., Rhodes, K. M., Brimicombe, D. J., & Payne, R. A. (2017). Association of comorbidity and health service usage among patients with dementia in the UK: A population-based study. *BMJ Open*, *7*(3), 10.1136/bmjopen-2016-012546

Bunn, F., Burn, A., Goodman, C., Robinson, L., Rait, G., Norton, S., Bennett, H., Poole, M., Schoeman, J. & Brayne, C. (2016). Comorbidity and dementia: A mixed method study on improving healthcare for people with dementia (CoDem). *Health Services and Delivery Research*, *4*(8), 2050-4349. 10.3310/hsdr04080

Burns, C., Chen, K., Kaszniak, A., Lee, W., Alexander, G., Bandy, D., Fleisher, A., Caselli, R. & Reiman, E. (2013). Higher serum glucose levels are associated with cerebral

hypometabolism in Alzheimer regions. *Neurology*, *80*(17), 1557-1564. 10.1212/wnl.0b013e31828f17de

Buysschaert, M., Medina, J. L., Bergman, M., Shah, A., & Lonier, J. (2015). Prediabetes and associated disorders. *Endocrine*, *48*(2), 371-393. https://doi.org/10.1007/s12020-014-0436-2

Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., Baxter, L. C., Rapcsak, S. Z., Shi, J., Woodruff, B. K., Locke, D. E. C., Snyder, C. H., Alexander, G. E., Rademakers, R., & Reiman, E. M. (2009). Longitudinal modeling of age-related memory decline and the ApoE ε4 effect. *New England Journal of Medicine*, *361*(3), 255-263. https://doi.org/10.1056/nejmoa0809437

Chait, A., & Bornfeldt, K. E. (2009). Diabetes and atherosclerosis: Is there a role for hyperglycemia? *Journal of Lipid Research*, *50*, S335-S339. https://doi.org/10.1194/jlr.R800059-JLR200

Chatterjee, S., Peters, S., Woodward, M., Mejia Arango, S., Batty, G., Beckett, N., Beiser, A., Borenstein, A., Crane, P., Haan, M., Hassing, L., Hayden, K., Kiyohara, Y., Larson, E., Li, C., Ninomiya, T., Ohara, T., Peters, R., Russ, T., Seshadri, S., Strand, B., Walker, R., Xu, W. & Huxley, R. (2016). Type 2 diabetes as a risk factor for dementia in women compared with men: A pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care*, 39(2), 300-307. https://doi.org/10.2337/dc15-1588

Cherbuin, N., Sachdev, P., & Anstey, K. J. (2012). Higher normal fasting plasma glucose is associated with hippocampal atrophy: The PATH Study. *Neurology*, *79*(10), 1019-1026. https://doi.org/10.1212/WNL.0b013e31826846de

Christman, A., Matsushita, K., Gottesman, R., Mosley, T., Alonso, A., Coresh, J., Hill-Briggs, F., Sharrett, A. & Selvin, E. (2011). Glycated haemoglobin and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study. *Diabetologia*, *54*(7), 1645-1652. 10.1007/s00125-011-2095-7

Claxton, A., Baker, L. D., Hanson, A., Trittschuh, E. H., Cholerton, B., Morgan, A., Callaghan, M., Arbuckle, M., Behl, C., & Craft, S. (2015). Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. *Journal of Alzheimer's Disease*, *44*(3), 897–906. https://doi.org/10.3233/jad-141791

Convit, A., Wolf, O. T., Tarshish, C., & De Leon, M. J. (2003). Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proceedings of the National Academy of Sciences*, *100*(4), 2019-2022. https://doi.org/10.1073/pnas.0336073100

Corder, E., Saunders, A., Strittmatter, W., Schmechel, D., Gaskell, P., Small, G., Roses, A., Haines, J. & Pericak-Vance, M. (1993). Gene dose of Apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, *261*(5123), 921-923. 10.1126/science.8346443

Craft, S., & Watson, G. S. (2004). Insulin and neurodegenerative disease: Shared and specific mechanisms. *The Lancet Neurology*, *3*(3), 169-178. https://doi.org/10.1016/S1474-4422(04)00681-7

Crane, P., Walker, R., Hubbard, R., Li, G., Nathan, D., Zheng, H., Haneuse, S., Craft, S., Montine, T., Kahn, S., McCormick, W., McCurry, S., Bowen, J. & Larson, E. (2013).

Glucose levels and risk of dementia. *New England Journal of Medicine*, *369*(6), 540-548. 10.1056/nejmoa1215740

Culberson, J. W. (2017). Clinical aspects of glucose metabolism and chronic disease. *Progress in Molecular Biology and Translational Science*, *146*, 1-11. https://doi.org/10.1016/bs.pmbts.2016.12.011

Cereda, E., Barichella, M., Pedrolli, C., Klersy, C., Cassani, E., Caccialanza, R., & Pezzoli, G. (2011). Diabetes and risk of Parkinson's disease: A systematic review and meta-analysis. *Diabetes Care*, *34*(12), 2614-2623. https://doi.org/10.2337/dc11-1584

Dahle, C. L., Jacobs, B. S., & Raz, N. (2009). Aging, vascular risk, and cognition: Blood glucose, pulse pressure, and cognitive performance in healthy adults. *Psychology and Aging*, *24*(1), 154. https://doi.org/10.1037/a0014283

Das, S., & Basu, A. (2008). Inflammation: A new candidate in modulating adult neurogenesis. *Journal of Neuroscience Research*, *86*(6), 1199-1208. https://doi.org/10.1002/jnr.21585

Davignon, J., Gregg, R. E., & Sing, C. F. (1988). Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis 8*, 1-21, 10.1161/01.ATV.8.1.1

De la Monte, S. M., & Wands, J. R. (2008). Alzheimer's disease is type 3 diabetes – evidence reviewed. *Journal of Diabetes Science and Technology*, *2*(6), 1101-1113. https://doi.org/10.1177/193229680800200619

De la Monte, S. (2014). Type 3 diabetes is sporadic Alzheimer ′s disease: Mini-review. *European Neuropsychopharmacology*, *24*(12), 1954-1960. https://doi.org/10.1016/j.euroneuro.2014.06.008

Dilliott, A. A., Farhan, S. M. K., Ghani, M., Sato, C., Liang, E., Zhang, M., McIntyre, A. D., Cao, H., Racacho, L., Robinson, J. F., Strong, M. J., Masellis, M., Bulman, D. E., Rogaeva, E., Lang, A., Tartaglia, C., Finger, E., Zinman, L., Turnbull, J., … Hegele, R. A. (2018). Targeted next-generation sequencing and bioinformatics pipeline to evaluate genetic determinants of constitutional disease. *Journal of Visualized Experiments*, (134). https://doi.org/10.3791/57266

Dilliott, A. A., Sunderland, K. M., McLaughlin, P. M., Roberts, A. C., Evans, E. C., Abrahao, A., Binns, M. A., Black, S. E., Borrie, M., Casaubon, L. K., Dowlatshahi, D., Finger, E., Fischer, C. E., Frank, A., Freedman, M., Grimes, D., Hassan, A., Jog, M., Kumar, S., … Hegele, R. A. (2021). Association of apolipoprotein E variation with cognitive impairment across multiple neurodegenerative diagnoses. *Neurobiology of Aging*, *105*. https://doi.org/10.1016/j.neurobiolaging.2021.04.011

Eid, A., Mhatre, I., & Richardson, J. R. (2019). Gene-environment interactions in Alzheimer's disease: A potential path to precision medicine. *Pharmacology and Therapeutics. 199*, 173-187, 10.1016/j.pharmthera.2019.03.005

Espeland, M. A., Bryan, R. N., Goveas, J. S., Robinson, J. G., Siddiqui, M. S., Liu, S., Hogan, P. E., Casanova, R., Coker, L. H., Yaffe, K., Masaki, K., Rossom, R., & Resnick, S. M. (2012). Influence of type 2 diabetes on brain volumes and changes in brain volumes. *Diabetes Care*, *36*(1), 90–97. https://doi.org/10.2337/dc12-0555

Esposito, K., Nappo, F., Marfella, R., Giugliano, G., Giugliano, F., Ciotola, M., Quagliaro, L., Ceriello, A. & Giugliano, D. (2002). Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: Role of oxidative stress. *Circulation*, *106*(16), 2067-2072. 10.1161/01.cir.0000034509.14906.ae

Euser, S., Sattar, N., Witteman, J., Bollen, E., Sijbrands, E., Hofman, A., Perry, I., Breteler, M. & Westendorp, R. (2010). A prospective analysis of elevated fasting glucose levels and cognitive function in older people: Results from PROSPER and the Rotterdam Study. *Diabetes*, *59*(7), 1601-1607. 10.2337/db09-0568

Ezquerra, M., Campdelacreu, J., Gaig, C., Compta, Y., Muñoz, E., Martí, M., Valldeoriola, F. & Tolosa, E. (2008). Lack of association of APOE and tau polymorphisms with dementia in Parkinson's disease. *Neuroscience Letters*, *448*(1), 20-23. 10.1016/j.neulet.2008.10.018

Farhan, S. M., Bartha, R., Black, S. E., Corbett, D., Finger, E., Freedman, M., Greenberg, B., Grimes, D. A., Hegele, R. A., Hudson, C., Kleinstiver P. W., Lang, A. E., Masellis, M., McIlroy, W. E., McLaughlin, P. M., Montero-Odasso, M., Munoz, D. G., Munoz, D. P., Strother, S., … ONDRI Investigators. (2017). The Ontario neurodegenerative disease research initiative (ONDRI). *Canadian Journal of Neurological Sciences*, *44*(2), 196-202. https://doi.org/10.1017/cjn.2016.415

Farmer, B. C., Johnson, L. A., & Hanson, A. J. (2019). Effects of apolipoprotein E on nutritional metabolism in dementia. *Current Opinion in Lipidology. 30(1)*, 10-15, 10.1097/MOL.0000000000000566

Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. A., Mayeux, R., Myers, H., Pericak-Vance, M., Risch, N. & Van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease: A meta-analysis. *Jama*, *278*(16), 1349-1356. https://doi.org/10.1001/jama.1997.03550160069041

Federoff, M., Jimenez-Rolando, B., Nalls, M. A., & Singleton, A. B. (2012). A large study reveals no association between APOE and Parkinson's disease. *Neurobiology of Disease*, *46*(2), 389-392. https://doi.org/10.1016/j.nbd.2012.02.002

Folstein, M. F., Robins, L. N., & Helzer, J. E. (1983). The Mini-Mental State Examination. *Archives of General Psychiatry*, *40*(7), 812-812. 10.1001/archpsyc.1983.01790060110016

Freedman, M., Leach, L., Tartaglia, C. M., Stokes, K. A., Goldberg, Y., Spring, R., Nourhaghighi, N., Gee, T., Strother, S. C., Alhaj, M. O., Borrie, M., Darvesh, S., Fernandez, A., Fischer, C. E., Fogarty, J., Greenberg, B. D., Gyenes, M., Herrmann, N., Keren, R., . . . Tang-Wai, D. F. (2018). The Toronto Cognitive Assessment (TorCA): Normative data and validation to detect amnestic mild cognitive impairment. *Alzheimer's Research & Therapy*, *10*(1). 1-18. https://doi.org/10.1186/s13195-018-0382-y

Geijselaers, S. L., Sep, S. J., Stehouwer, C. D., & Biessels, G. J. (2015). Glucose regulation, cognition, and brain MRI in type 2 diabetes: A systematic review. *The Lancet Diabetes & Endocrinology*, *3*(1), 75-89. https://doi.org/10.1016/S2213-8587(14)70148-2

Gibson, G. E. (2002). Interactions of oxidative stress with cellular calcium dynamics and glucose metabolism in Alzheimer's disease. *Free Radical Biology and Medicine*, *32*(11), 1061-1070. https://doi.org/10.1016/S0891-5849(02)00802-X

Gold, S. M., Dziobek, I., Sweat, V., Tirsi, A., Rogers, K., Bruehl, H., Tsui, W., Richardson, S., Javier, E., & Convit, A. (2007). Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*, *50*(4), 711–719. https://doi.org/10.1007/s00125-007-0602-7

González-Redondo, R., García-García, D., Clavero, P., Gasca-Salas, C., García-Eulate, R., Zubieta, J. L., Arbizu, J., Obeso, J. A., & Rodríguez-Oroz, M. C. (2014). Grey matter hypometabolism and atrophy in Parkinson's disease with cognitive impairment: a two-step process. *Brain*, *137*(8), 2356–2367. https://doi.org/10.1093/brain/awu159

Grayson, B. E., Seeley, R. J., & Sandoval, D. A. (2013). Wired on sugar: The role of the CNS in the regulation of glucose homeostasis. *Nature Reviews Neuroscience*, *14*(1), 24-37. https://doi.org/10.1038/nrn3409

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson's disease dementia: A neural networks perspective. *Brain*, *138*(6), 1454-1476. https://doi.org/10.1093/brain/awv104

Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Williams, A., Jones, N., Thomas, C., Stretton, A., Morgan, A., Lovestone, S., Powell, J., Proitsi, P., Lupton, M., K., Brayne, C., ... Williams, J. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nature Genetics*, *41*(10), 1088-1093. 10.1038/ng.440

Hartung, J., & Knapp, G. (2005). Multivariate multiple regression. *Encyclopedia of statistics in behavioral science*. https://doi.org/10.1002/0470013192.bsa432

Hillen, H. (2019). The beta amyloid dysfunction (BAD) hypothesis for Alzheimer's disease. *Frontiers in Neuroscience*, *13*, 1154. https://doi.org/10.3389/fnins.2019.01154

Hoehn, M. M., & Yahr, M. D. (1998). Parkinsonism: Onset, progression, and mortality. *Neurology*, *50*(2), 318-318.

Hoyer S. (1991). Abnormalities of glucose metabolism in Alzheimer's disease. *Annals of the New York Academy of Sciences*. *640*(1), 53-58. 10.1111/j.1749-6632.1991.tb00190.x.

Hu, M. T. M., Taylor-Robinson, S. D., Chaudhuri, K. R., Bell, J. D., Labbe, C., Cunningham, V. J., Koepp, M. J., Hammers, A., Morris, R. G., Turjanski, N., & Brooks, D. J. (2000). Cortical dysfunction in non-demented Parkinson's disease patients: A combined 31P-MRS and 18FDG-PET study. *Brain*, *123*(2), 340-352. https://doi.org/10.1093/brain/123.2.340

Hughes, A. J., Daniel, S. E., Kilford, L., & Lees, A. J. (1992). Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. *Journal of Neurology, Neurosurgery & Psychiatry*, *55*(3), 181-184. http://dx.doi.org/10.1136/jnnp.55.3.181

Hunsberger, H. C., Pinky, P. D., Smith, W., Suppiramaniam, V., & Reed, M. N. (2019). The role of APOE4 in Alzheimer's disease: Strategies for future therapeutic interventions. *Neuronal Signaling*, *3*(2), 1-15. https://doi.org/10.1042/NS20180203

Hunt, A., Schönknecht, P., Henze, M., Seidl, U., Haberkorn, U., & Schröder, J. (2007). Reduced cerebral glucose metabolism in patients at risk for Alzheimer's disease. *Psychiatry Research: Neuroimaging*, *155*(2), 147-154. https://doi.org/10.1016/j.pscychresns.2006.12.003

Huxford, B., Haque, T., Joseph, A. B., Simonet, C., Gallagher, D., Budu, C., Dobson, R., & Noyce, A. (2022). Parkinson's disease and type 2 diabetes: HbA1c is associated with motor and cognitive severity. *Movement Disorders*, *37*(2), 427-428. 10.1002/mds.28829

Irie, F., Fitzpatrick, A. L., Lopez, O. L., Kuller, L. H., Peila, R., Newman, A. B., & Launer, L. J. (2008). Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE ε4: The cardiovascular health study cognition study. *Archives of Neurology*, *65*(1), 89-93. 10.1001/archneurol.2007.29

Janson, J., Laedtke, T., Parisi, J. E., O'Brien, P., Petersen, R. C., & Butler, P. C. (2004). Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*, *53*(2), 474-481. https://doi.org/10.2337/diabetes.53.2.474

Jellinger, K. A. (2008). Morphologic diagnosis of "vascular dementia" — A critical update. *Journal of the Neurological Sciences*, *270*(1-2), 1-12. https://doi.org/10.1016/j.jns.2008.03.006

Kanekiyo, T., Xu, H., & Bu, G. (2014). ApoE and Aβ in Alzheimer's disease: Accidental encounters or partners? *Neuron*, *81*(4), 740-754. https://doi.org/10.1016/j.neuron.2014.01.045

Kapogiannis, D., & Mattson, M. P. (2011). Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease. *The Lancet Neurology*, *10*(2), 187-198. https://doi.org/10.1016/s1474-4422(10)70277-5

Karran, E., & de Strooper, B. (2016). The amyloid cascade hypothesis: Are we poised for success or failure? *Journal of Neurochemistry*, *139*, 237-252. https://doi.org/10.1111/jnc.13632

Kehagia, A. A., Barker, R. A., & Robbins, T. W. (2013). Cognitive impairment in Parkinson's disease: The dual syndrome hypothesis. *Neurodegenerative Diseases*, *11*(2), 79-92. https://doi.org/10.1159/000341998

Kerti, L., Witte, A. V., Winkler, A., Grittner, U., Rujescu, D., & Flöel, A. (2013). Higher glucose levels associated with lower memory and reduced hippocampal microstructure. *Neurology*, *81*(20), 1746-1752. https://doi.org/10.1212/01.wnl.0000435561.00234.ee

Lambert, J. C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O.,Zelenika, D., Bullido, M. J., Tavernier, B., Letenneur, L., Bettens, K., Berr, C., Pasquier, F., Fievet, N., Barberger-Gateau, P., Engerborghs, S., De Deyn, P., Mateo, I., ... Amouyel, P. (2009). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nature genetics*, *41*(10), 1094-1099. 10.1038/ng.439

Lam, C. K., Chari, M., & Lam, T. K. (2009). CNS regulation of glucose homeostasis. *Physiology*, *24*(3), 159-170. https://doi.org/10.1152/physiol.00003.2009

Lanfranco, M. F., Ng, C. A., and Rebeck, G. W. (2020) ApoE lipidation as a therapeutic target in Alzheimer's disease. *International Journal of Molecular Sciences 21*(17), 6336. 10.3390/ijms21176336

Larsson, S. C., Traylor, M., Malik, R., Dichgans, M., Burgess, S., & Markus, H. S. (2017). Modifiable pathways in Alzheimer's disease: Mendelian randomisation analysis. *BMJ*, *359*(1), 5375. 10.1136/bmj.j5375

Lee, J., Seroogy, K. B., & Mattson, M. P. (2002). Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *Journal of Neurochemistry*, *80*(3), 539-547. https://doi.org/10.1046/j.0022-3042.2001.00747.x

Levi, M., & Van der Poll, T. (2010). Inflammation and coagulation. *Critical Care Medicine*, *38*, S26-S34.10.1097/CCM.0b013e3181c98d21

Lezak, M. D., Howieson, D. B., Loring, D. W., & Fischer, J. S. (2004). *Neuropsychological assessment*. Oxford University Press, USA.

Li, Y. M., & Dickson, D. W. (1997). Enhanced binding of advanced glycation endproducts (AGE) by the ApoE4 isoform links the mechanism of plaque deposition in Alzheimer's disease. *Neuroscience Letters*, *226*(3), 155-158.

https://doi.org/10.1016/S0304-3940(97)00266-8

Litvan, I., Goldman, J. G., Tröster, A. I., Schmand, B. A., Weintraub, D., Petersen, R. C., Mollenhauer, B., Adler, C. H., Marder, K., Williams-Gray, C. H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M. C., Burn, D. J., Barker, R. A., & Emre, M. (2012). Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement disorder society task force guidelines. *Movement Disorders*, *27*(3), 349–356. https://doi.org/10.1002/mds.24893

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews Neurology*, *9*(2), 106-118. 10.1038/nrneurol.2012.263

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., . . . Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413-446. https://doi.org/10.1016/s0140-6736(20)30367-6

Lyoo, C. H., Jeong, Y., Ryu, Y. H., Rinne, J. O., & Lee, M. S. (2010). Cerebral glucose metabolism of Parkinson's disease patients with mild cognitive impairment. *European Neurology*, *64*(2), 65-73. https://doi.org/10.1159/000315036

Mainardi, M., Fusco, S., & Grassi, C. (2015). Modulation of hippocampal neural plasticity by glucose-related signaling. *Neural Plasticity*, *2015*. 1-10. https://doi.org/10.1155/2015/657928

Makino, K., Lee, S., Bae, S., Chiba, I., Harada, K., Katayama, O., Shinkai, Y., Makizaki, H., & Shimada, H. (2021). Diabetes and prediabetes inhibit reversion from mild cognitive impairment to normal cognition. *Journal of the American Medical Directors Association*, *22*(9), 1912-1918. 10.1016/j.jamda.2021.02.033

Mawuenyega, K. G., Sigurdson, W., Ovod, V., Munsell, L., Kasten, T., Morris, J. C., Yarasheski, K. E., & Bateman, R. J. (2010). Decreased clearance of CNS β-Amyloid in Alzheimer's disease. *Science*, *330*(6012), 1774. https://doi.org/10.1126/science.1197623

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr, Kawas, C. H.,Klunk, W. E., Koroshetz, W. J., Manly, J. J., Mayeux, R., Mohs, R. C., Morris, J. C.,Rossor, M. N., Scheltens, P., Carrillo, M. C., Thies, B., Weintraub, S., & Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, *7*(3), 263–269. https://doi.org/10.1016/j.jalz.2011.03.005

McLaughlin, P. M., Sunderland, K. M., Beaton, D., Binns, M. A., Kwan, D., Levine, B., Orange, J. B., Peltsch, A. J., Roberts, A. C., Strother, S. C. & Troyer, A. K. (2021). The quality assurance and quality control protocol for neuropsychological data collection and curation in the Ontario Neurodegenerative Disease Research Initiative (ONDRI) study. *Assessment*, *28*(5), 1267-1286. 10.1177/1073191120913933

McLaughlin, P. M., Kwan, D., Sunderland, K., Troyer, A., Roberts, A., Beaton, D., Orange, J. B. & Levine, B. (2021). *Neuropsychology full composite scores*. ONDRI Guidelines.

Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: The role of glucose in physiological and pathological brain function. *Trends in Neurosciences*, *36*(10), 587-597. https://doi.org/10.1016/j.tins.2013.07.001

Messier, C. (2003). Diabetes, Alzheimer's disease and apolipoprotein genotype. *Experimental Gerontology*, *38*(9), 941-946. https://doi.org/10.1016/S0531-5565(03)00153-0

Messier, C., Awad-Shimoon, N., Gagnon, M., Desrochers, A., & Tsiakas, M. (2011). Glucose regulation is associated with cognitive performance in young nondiabetic adults. *Behavioural Brain Research*, *222*(1), 81-88. https://doi.org/10.1016/j.bbr.2011.03.023

Mittal, K., & Katare, D. P. (2016). Shared links between type 2 diabetes mellitus and Alzheimer's disease: A review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*, *10*(2), S144-S149. https://doi.org/10.1016/j.dsx.2016.01.021

Mollenhauer, B., Zimmermann, J., Sixel-Döring, F., Focke, N. K., Wicke, T., Ebentheuer, J., Schaumburg, M., Lang, E., Friede, T., & Trenkwalder, C. (2018). Baseline predictors for progression 4 years after Parkinson's disease diagnosis in the De Novo Parkinson Cohort (DeNoPa). *Movement Disorders*, *34*(1), 67-77. https://doi.org/10.1002/mds.27492

Moran, C., Beare, R., Phan, T., Starkstein, S., Bruce, D., Romina, M., & Srikanth, V. (2017). Neuroimaging and its relevance to understanding pathways linking diabetes and cognitive dysfunction. *Journal of Alzheimer's Disease*, *59*(2), 405-419. 10.3233/JAD-161166

Morley, J. F., Xie, S. X., Hurtig, H. I., Stern, M. B., Colcher, A., Horn, S., Dahodwala, N., Duda, J. E., Weintraub, D., Chen-Plotkin, A. S., van Deerlin, V., Falcone, D., & Siderowf, A. (2012). Genetic influences on cognitive decline in Parkinson's disease. *Movement Disorders*, *27*(4), 512-518. https://doi.org/10.1002/mds.24946

Mosconi, L. (2005). Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. *European Journal of Nuclear Medicine and Molecular Imaging*, *32*(4), 486-510. https://doi.org/10.1007/s00259-005-1762-7

Münch, G., Schinzel, R., Loske, C., Wong, A., Durany, N., Li, J. J., Vlassara, H., Smith, M. A., Perry, G., & Riederer, P. (1998). Alzheimer's disease – synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. *Journal of Neural Transmission*, *105*(4), 439. https://doi.org/10.1007/s007020050069

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L. & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699. 10.1111/j.1532-5415.2005.53221.x

Nalbantoglu, J., Gilfix, B. M., Bertrand, P., Robitaille, Y., Gauthier, S., Rosenblatt, D. S., & Poirier, J. (1994). Predictive value of apolipoprotein E genotyping in Alzheimer's disease: Results of an autopsy series and an analysis of several combined studies. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *36*(6), 889-895. https://doi.org/10.1002/ana.410360614

O'Donoghue, M. C., Murphy, S. E., Zamboni, G., Nobre, A. C., & Mackay, C. E. (2018). APOE genotype and cognition in healthy individuals at risk of Alzheimer's disease: A review. *Cortex*, *104*, 103-123. 10.1016/j.cortex.2018.03.025

Ostergaard, S. D., Mukherjee, S., Sharp, S. J., Proitsi, P., Lotta, L. A., Day, F., Perry, J. R., Boehme, K. L., Walter, S., Kauwe, J. S., Gibbons, L. E., Alzheimer's Disease Genetics Consortium, The GERAD1 Consortium, EPIC-InterAct Consortium, Larson, E., Powell, J. F., Langerberg, C., Crane, P., Wareham, ... Scott, R. A. (2015). Associations between

potentially modifiable risk factors and Alzheimer disease: A Mendelian randomization study. *PLoS Medicine*, *12*(6), e1001841. 10.1371/journal.pmed.1001841

Pankratz, N., Byder, L., Halter, C., Rudolph, A., Shults, C. W., Conneally, P. M., Foroud, T., & Nichols, W. C. (2006). Presence of an APOE4 allele results in significantly earlier onset of Parkinson's disease and a higher risk with dementia. *Movement Disorders*, *21*(1), 45-49. https://doi.org/10.1002/mds.20663

Pappas, C., Small, B. J., Andel, R., Laczó, J., Parizkova, M., Ondrej, L., & Hort, J. (2019). Blood glucose levels may exacerbate executive function deficits in older adults with cognitive impairment. *Journal of Alzheimer's Disease*, *67*(1), 81-89. 10.3233/JAD-180693

Parsian, A., Racette, B., Goldsmith, L. J., & Perlmutter, J. S. (2002). Parkinson's disease and apolipoprotein E: Possible association with dementia but not age at onset. *Genomics*, *79*(3), 458-461. https://doi.org/10.1006/geno.2002.6707

Patil, S. P., Ballard, R., Sanchez, S., Osborn, J., & Santangelo, D. (2012). ApoE: The link between Alzheimer's-related glucose hypometabolism and Aβ deposition? *Medical Hypotheses*, *78*(4), 494-496. https://doi.org/10.1016/j.mehy.2012.01.015

Peila, R., Rodriguez, B. L., & Launer, L. J. (2002). Type 2 Diabetes, APOE Gene, and the risk for dementia and related pathologies. *Diabetes*, *51*(4), 1256–1262. https://doi.org/10.2337/diabetes.51.4.1256

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., Volkmann, J., Schrag, A. E., & Lang, A. E. (2017). Parkinson disease. *Nature Reviews Disease Primers*, *3*(1), 1-21. https://doi.org/10.1038/nrdp.2017.13

Pruzin, J. J., Schneider, J. A., Capuano, A. W., Leurgans, S. E., Barnes, L. L., Ahima, R. S., Arnold, S. E., Bennett, D. A., & Arvanitakis, Z. (2017). Diabetes, hemoglobin A1C, and

regional Alzheimer disease and infarct pathology. *Alzheimer Disease and Associated Disorders*, *31*(1), 41-47. https://doi.org/10.1097/wad.0000000000000172

Qiu, W. Q., & Folstein, M. F. (2006). Insulin, insulin-degrading enzyme and amyloid-β peptide in Alzheimer's disease: Review and hypothesis. *Neurobiology of Aging*, *27*(2), 190-198. https://doi.org/10.1016/j.neurobiolaging.2005.01.004

Ramirez, J., Holmes, M. F., Scott, C. J., Ozzoude, M., Adamo, S., Szilagyi, G. M., Goubran, M., Gao, F., Arnott, S. R., Lawrence-Dewar, J. M., Beaton, D., Strother, S. C., Munoz, D. P., Masellis, M., Swartz, R. H., Bartha, R., Symons, S., & Black, S. E. (2020). Ontario Neurodegenerative Disease Research initiative (ONDRI): Structural MRI methods and outcome measures. *Frontiers in Neurology*, *1, 847*. https://doi.org/10.3389/fneur.2020.00847

Rasmussen, K. L., Tybjærg-Hansen, A., Nordestgaard, B. G., & Frikke-Schmidt, R. (2020). APOE and dementia–resequencing and genotyping in 105,597 individuals. *Alzheimer's & Dementia*, *16*(12), 1624-1637. https://doi.org/10.1002/alz.12165

Ravona-Springer, R., Moshier, E., Schmeidler, J., Godbold, J., Akrivos, J., Rapp, M., Grossman, H. T., Wysocki, M., Silverman, J. M., Haroutunian, V., & Beeri, M. S. (2012). Changes in Glycemic Control are Associated with Changes in Cognition in Non-Diabetic Elderly. *Journal of Alzheimer's Disease*, *30*(2), 299-309. https://doi.org/10.3233/jad-2012-120106

Rebeck, G., Reiter, J. S., Strickland, D. K., & Hyman, B. T. (1993). Apolipoprotein E in sporadic Alzheimer's disease: Allelic variation and receptor interactions. *Neuron*, *11*(4), 575–580. https://doi.org/10.1016/0896-6273(93)90070-8

Reid, W. G. J., Hely, M. A., Morris, J. G. L., Loy, C., & Halliday, G. M. (2011). Dementia in Parkinson's disease: A 20-year neuropsychological study (Sydney Multicentre Study).

Journal of Neurology, Neurosurgery & Psychiatry, *82*(9), 1033–1037. https://doi.org/10.1136/jnnp.2010.232678

Repple, J., Karliczek, G., Meinert, S., Förster, K., Grotegerd, D., Goltermann, J., Redlich, R., Arolt, V., Baune, B. T., Dannlowski, U., & Opel, N. (2019). Variation of hba1c affects cognition and white matter microstructure in healthy, young adults. *Molecular Psychiatry*, *26*(4), 1399–1408. https://doi.org/10.1038/s41380-019-0504-3

Riby, L. M., Meikle, A., & Glover, C. (2004). The effects of age, glucose ingestion and gluco-regulatory control on episodic memory. *Age and Ageing*, *33*(5), 483-487. 10.1093/ageing/afh173

Ryu, H. G., & Kwon, O. D. (2010). Apolipoprotein E epsilon 4 allele is not associated with age at onset or MMSE of Parkinson's disease in a Korean study. *Parkinsonism & Related Disorders*, *16*(9), 615-617. 10.1016/j.parkreldis.2010.06.015

Sasaki, N., Fukatsu, R., Tsuzuki, K., Hayashi, Y., Yoshida, T., Fujii, N., Koike, T., Wakayama, I., Yanagihara, R., Garruto, R., Amano, N., & Makita, Z. (1998). Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. *The American Journal of Pathology*, *153*(4), 1149–1155. https://doi.org/10.1016/s0002-9440(10)65659-3

Schapira, A. H., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nature Reviews Neuroscience*, *18*(7), 435-450. https://doi.org/10.1038/nrn.2017.62

Scheen, A. J. (2010). Central nervous system: A conductor orchestrating metabolic regulations harmed by both hyperglycaemia and hypoglycaemia. *Diabetes & Metabolism*, *36*(3), S31-S38. 10.1016/S1262-3636(10)70464-X

Shoji, Y., Nishio, Y., Baba, T., Uchiyama, M., Yokoi, K., Ishioka, T., Hosokai, Y., Hirayama, K., Fukuda, H., Aoki, M., Hasegawa, T., Takeda, A., & Mori, E. (2014). Neural substrates of cognitive subtypes in Parkinson's disease: A 3-year longitudinal study. *PLoS ONE*, *9*(10), 110-547. https://doi.org/10.1371/journal.pone.0110547

Sima, A. A., Kamiya, H., & Li, Z. G. (2004). Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. *European Journal of Pharmacology*, *490*(1-3), 187-197. 10.1016/j.ejphar.2004.02.056

Smith, M. A. (1998). Alzheimer disease. *International Review of Neurobiology*, *42*, 1-54. 10.1016/S0074-7742(08)60607-8

Sunderland, K. M., Beaton, D., Arnott, S. R., Kleinstiver, P., Kwan, D., Lawrence-Dewar, J. M., Ramirez, J., Tan, B., Bartha, R., Black, S., Borrie, M., Brien, D., Casaubon, L., Coe, B. C., Cornish, B., Dilliott, A., Dowlatshahi, D., Finger, E., Fischer, C., ... Binns, M. (2020). The Ontario Neurodegenerative Disease Research Initiative. *medRxiv*. https://doi.org/10.1101/2020.07.30.20165456

Taouis, M., & Torres-Aleman, I. (2019). Insulin and The Brain. *Frontiers in Endocrinology*, *10*, 299. https://doi.org/10.3389/fendo.2019.00299

Trošt, M., Perovnik, M., & Pirtošek, Z. (2019). Correlations of neuropsychological and metabolic brain changes in Parkinson's disease and other α-synucleinopathies. *Frontiers in Neurology*, *10*, 1204. https://doi.org/10.3389/fneur.2019.01204

Uyar, M., Lezius, S., Buhmann, C., Pötter-Nerger, M., Schulz, R., Meier, S., Gerloff, C., Kuhle, J., & Choe, C. (2022). Diabetes, glycated hemoglobin (hba1c), and neuroaxonal damage in Parkinson's disease (MARK-PD study). *Movement Disorders*, *37*(6), 1299–1304. https://doi.org/10.1002/mds.29009

Vaidyula, V. R., Rao, A. K., Mozzoli, M., Homko, C., Cheung, P., & Boden, G. (2006). Effects of hyperglycemia and hyperinsulinemia on circulating tissue factor procoagulant activity and platelet CD40 ligand. *Diabetes*, *55*(1), 202-208. 10.2337/diabetes.55.01.06.db05-1026

Vicente Miranda, H., El-Agnaf, O. M., & Outeiro, T. F. (2016). Glycation in Parkinson's disease and Alzheimer's disease. *Movement Disorders*, *31*(6), 782-790. https://doi.org/10.1002/mds.26566

Williams-Gray, C. H., Goris, A., Saiki, M., Foltynie, T., Compston, D. A. S., Sawcer, S. J., & Barker, R. A. (2009). Apolipoprotein E genotype as a risk factor for susceptibility to and dementia in Parkinson's disease. *Journal of neurology*, *256*(3), 493-498. https://doi.org/10.1007/s00415-009-0119-8

World Health Organization. (2017). *Global Action Plan on the Public Health Response to Dementia*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/259615/9789241513487-eng.pdf;jsessionid=4DA480FA93471AC53988E52B35F416D8?sequence=1

World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes research and clinical practice. Geneva: World Health Organization; 2011.

Yue, X., Li, H., Yan, H., Zhang, P., Chang, L., & Li, T. (2016). Risk of Parkinson disease in diabetes mellitus: an updated meta-analysis of population-based cohort studies. *Medicine*, *95*(18). 10.1097/MD.0000000000003549

Appendix A

Neuropsychological Battery

Cognitive domain	Neuropsychological tests
Attention & Working Memory	Symbol Digit Modality Test (coding)
	Trail Making Test – Part A (time)
	WAIS-III: Digit Span Forward
	WAIS-III: Digit Span Backward
	WAIS-III: Digit Span Total
	DKEFS: Color naming (time)
	DKEFS: Word reading (time)
Executive Function	Trail Making Test – Part B (time)
	DKEFS: Interference (time)
	DKEFS: Switching (time)
	DKEFS: Letter Fluency
	DKEFS: Category Fluency
	WASI-II: Matrix Reasoning
Language	Boston Naming – 15 Item
	TAWF: Verb Naming
	BDAE: Semantic Probe (raw)
	WASI-II: Vocabulary

Memory	RAVLT: Immediate
	RAVLT: Short-delay
	RAVLT: Long-delay
	BVMT-R: Immediate
	BVMT-R: Delayed
Visuospatial	Judgement of Line Orientation
	VOSP: Incomplete Letters
	BVMT-R: Copy Trial (raw)

Note. BDAE-III = Boston Diagnostic Aphasia Examination–Third edition; BVMT-R = Brief Visuospatial Memory Test–Revised; DKEFS = Delis–Kaplan Executive Function System; RAVLT = Rey Auditory Verbal Learning Task; TAWF = Test of Adolescent/Adult Word Finding; VOSP = Visual Object and Space Perception battery; WAIS-III = Wechsler Adult Intelligence Scale–Third edition; WASI-II = Wechsler Abbreviated Scale of Intelligence–Second edition.

Appendix B

List of Abbreviations

Abbreviation	Definition
Aβ	Amyloid-β (beta-amyloid)
AD	Alzheimer's disease
ApoE	Apolipoprotein E
GM	Gray matter
HbA1c	Glycated hemoglobin
MANOVA	Multivariate analysis of variance
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
PD	Parkinson's disease
T2DM	Type 2 diabetes mellitus
WM	White matter