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Sugar Consumption and Cognitive Aging in the Swedish Adoption/Twin Study of Aging

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by

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Dedication

To my dad, who picked me up and carried me on his shoulders one more time. To my mom, who never stopped believing in me and, most importantly, never let me stop believing in myself. To my wife for her love and patience; this would not have been possible without her support. To my sister who was always there with kind words, encouragement, and laughter when I needed it the most. To my entire immediate and extended family, both living and passed; without their blessings, I would not be here. To God; He is the true author.

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Abstract

Consumption of foods high in sugar content has been linked with the development of metabolic abnormalities such as cardiovascular disease and type II diabetes, major sources of global health concerns. Although the detrimental consequences of high intake of sugar on abnormal metabolic processes are established, it is not known how this association affects (or accelerates) cognitive aging.

The current project was based on data from the Swedish Adoption/Twin Study of Aging (SATSA) to test the hypothesis that high refined sugar intake contributes to accelerated trajectories of cognitive decline assessed longitudinally. Trajectories of cognitive change were assessed as a function of age, thereby allowing for the observation of changes in cognitive performance across the entire age distribution of the sample. Analyses also accounted for the influences of clinically relevant factors such as cardiovascular health and clinical depression on the relationship between high sugar intake and cognitive aging.

Results showed that high sugar consumption was significantly related to lower overall cognitive performance on tests of verbal ability, spatial ability, memory, and perceptual speed compared to low consumption, but there were no significant differences with respect to cognitive change over time. Findings provide unique insight into the potential for dietary sugar to produce decrements in cognitive functioning in older adults.

Chapter 1: Introduction

As indicated by the United States Department of Agriculture, Americans have increased their ingestion of sugars over the past several decades. In turn, this increased consumption of (Gross, Li, Ford & Liu, 2004) has been related to the development of development of insulin resistance syndrome, type II diabetes (T2D), and cardiovascular disease (CVD) (Montmayeur & le Coutre, 2010; Kopp, 2006; Morse, 2008). In addition to contributing to poor metabolic health, accumulating evidence suggests that the consumption of sugar-rich foods may produce impairments in brain functioning and cognition (Molteni, Barnard, Ying, Roberts, & Gomez-Pinilla, 2002). Gaining knowledge in this area is important in the development of strategies that may not only help to prevent metabolic abnormalities, but also protect against cognitive deficits in the aging population.

Forms of carbohydrates distinguishable by their structure have been shown to confer varying effects on physiology. Understanding these differences forms the basis for examining the influence of refined sugars on the brain and behavior. Findings from animal research, therefore, provide a theoretical framework by which results of human studies can be based by providing insight into brain mechanisms underlying sugar-induced cognitive deficits. Examining human literature regarding the effects of dietary sugar-related disorders, such as CVD elucidates the importance of studying the effects of dietary sugars on cognitive aging.

Carbohydrates/Sugar

Carbohydrates have different physical and chemical structures. They can be classified according to three principal groups: sugars, oligosaccharides and polysaccharaides. In turn, each of these sub-classifications can be further divided according to their monosaccharide chemical composition. The term *sugars* refers to moncosaccharides (glucose, galactose, fructose), dissacharides (sucrose, lactose, trehalose) and polyols (sorbitol, mannitol), which are considered to be *simple or refined*. The effects of dietary carbohydrates on physiological responses have been studied for decades and seem to differ depending on, in part, the type of carbohydrate and rates of digestibility (Montmayeur & le Coutre, 2010).

A major source of carbohydrates in the human diet is starch, a complex energy source found in many plants and can be beneficial for health (Montmayeur & le Coutre, 2010). The consumption of simple sugars has been related to the development of various diseases, such as CVD (Kopp, 2006), a major source of global health concern (Popkin & Nielsen, 2003). A commonly utilized measure to predict the physiological effects of various forms of carbohydrates is the glycemix index (GI) (Montmayeur & le Coutre, 2010). The GI is used to illustrate the relative rate of glucose absorption from foods and, hence, the rate at which glucose appears in the blood stream. For this reason, plasma glucose is often referred to as "blood sugar." Simple sugars are indexed by a higher GI value compared to more complex carbohydrates, although glycemic load (GL) is increasing in usage since it takes into account the amount of carbohydrates ingested in addition to its potency in elevating plasma glucose (Morse, 2008). Evidence indicates that people replacing low GI/GL foods (i.e. simple carbohydrates/refined sugars) for high GI/GL foods

(i.e. complex carbohydrates/less refined sugars) demonstrated decreases in glucose and insulin elevations, which have been used as dietary treatments for glucose intolerance (Liu, Willett, Stampfer, Hu, et al., 2000). Evidence from animal models provides insight into the potential for dietary sugars to facilitate impairments in brain and cognitive processes.

Effects of High Sugar Diets on the Brain and Behavior: Animal Research

In recent years, there has been an increased emphasis on research focused on examining the effects of dietary factors on the brain and behavior. Specifically, an increasing body of evidence has shown that animals maintained on high refined sugar diets exhibit neurobiological and behavioral changes indicative of cognitive impairment. Such studies are useful in that dietary factors can be experimentally manipulated. This allows for the causal assessment of the specific effects of dietary factors on brain changes and behavioral measures of cognitive abilities. Thus, understanding findings from animal research provides a basis for understanding sugar-induced cognitive impairments observed in humans.

High Sugar Intake & Brain Health. Accumulating evidence indicates that diets high in refined sugars produce brain changes indicative of impaired cognition. Findings showed that rats maintained on high refined sugar diets exhibited significant reductions in brain-derived neurotropic factor (BDNF) and cyclic-amp response element binding protein (CREB) levels in the hippocampus (Molteni, et al., 2002**;**Molteni, Wu, Vaynman, Ying, et al., 2004**;**Wu, Molteni, Ying, & Gomez-Pinilla, 2003), a medial temporal lobe structure critical in the formation of spatial/declarative memories (Eichenbaum, 2004). Both BDNF and CREB have been identified as being crucial mediator of neuronal function, synaptic

plasticity and learning and memory processes (Bramham & Messaoudi, 2005;Tao, Finkbeiner, Arnold, Shaywitz, & Greenberg, 1998). Sugar fed rats also exhibited significant reductions in levels of neurogenesis (Lindqvist, Mohapel, Bouter, Frielingsdorf, et al., 2006), established as a neurobiological marker of hippocampus-dependent memory (Snyder, Hong, McDonald, & Wojtowicz, 2005).

High Sugar Intake & Behavioral Measures of Cognition. In addition to inhibitions in brain parameters, research has shown that animals maintained on high sugar diets demonstrate impairments on behavioral measures of cognitive abilities. A majority of the research in this area has assessed spatial memory performance in rodents. A recent study, for instance, examined the influence of dietary sugar on memory performance on the Morris water maze (MWM), a commonly utilized apparatus to test spatial learning abilities in rodents (Morris, 1984). Results revealed that, relative to controls, sucrose fed animals showed impaired learning and long-term memory retrieval abilities (Jurdak, Lichtenstein, & Kanarek, 2008). In similar findings, rats maintained on a high fructose diet demonstrated impaired spatial capabilities (Jurdak & Kanarek, 2009).

An effective method of assessing declarative memory in animals is through the use of novel object recognition (NOR) (Broadbent, Squire, & Clark, 2004). Rats supplemented with sucrose show impaired performance on an NOR task, (Jurdak & Kanarek, 2009), as well as significantly more working and reference memory errors (Kanoski & Davidson, 2010), all suggestive of impaired spatial performance. Other than evidence based on memory tests, work has shown that, compared to those fed sugar free (complex vegetable starch) or refined sucrose diets, rats supplemented with honey had less behavioral signs of anxiety in addition to lower spatial impairment (Chepulis, Starkey, Waas, & Molan, 2009).

It is possible that ingesting honey, a less refined sugar rich in antioxidant properties, alleviated anxiety and memory deficits compared to the ingestion of a more refined sugar. Animal research provides insight into the potential detrimental effects of dietary sugar on the brain and behavior. Additionally, the literature in this area provides insight into underlying biological processes, such as oxidative stress which may explain the source of these impairments.

Oxidative Stress. Oxidative stress refers to an imbalance between normal free radical production and an inability of cells to buffer against them, which can contribute to cellular damage (Baynes, 1991). A molecular sign of oxidative stress is the presence of reactive oxygen species (ROS) (Touyz, 2004). In addition to impairments in synaptic plasticity, findings showed that high sugar diets produced significant increases in protein oxidation, suggestive of protein damage, (Molteni, et al., 2004;Wu, Ying, & Gomez-Pinilla, 2004), as well as hippocampal levels of ROS (Molteni, et al., 2004). These results suggest that high sugar diet-induced impairments in plasticity may be modulated by oxidative stress. In turn, research suggests that elevations in blood sugar may play a critical role in the oxidative stress response.

High Blood Sugar. Elevations in plasma glucose are a main source of free radical production, a biomarker of oxidative stress (Souza, Moreira, Siqueira, Pereira, et al., 2007). Elevations in blood sugar, which can be the result of high sugar diets, have been related to impaired memory. Sucrose supplemented animals, along with elevations in plasma glucose, showed impairments in spatial learning (Jurdak, et al., 2008) and declarative memory (Jurdak & Kanarek, 2009) performance compared with control diet rats. Other work found that rats fed high fructose corn syrup (HFCS), exhibited significant reductions in

hippocampal dendritic spines, BDNF and long-term potentiation (LTP) compared to controls (Stranahan, Norman, Lee, Cutler, et al., 2008). Furthermore, HFCS fed animals had impaired spatial memory performance which was accompanied by significant elevations in blood glucose (Stranahan, et al., 2008).

Chronic elevations in plasma glucose produced by high sugar diets have been posited to produce disturbances in intracellular secondary messenger systems and elevations in ROS, all implicated in contributing substantially to neuronal loss and cognitive impairment (Stephan, Wells, Brayne, Albanese, & Siervo, 2010). Here, elevations in blood sugar may have contributed to increased oxidative damage and, as a result, produced cellular damage underlying observed behavioral impairments.

Insulin Resistance. Insulin stimulates the uptake of glucose into cells for energy. Insulin resistance arises when cells become resistant to the actions of insulin. The pancreas, in an attempt to overcome this resistance, secretes more insulin and, therefore, can result in an overproduction of insulin (i.e. hypersinsulinemia). Hyperinsulinemia and insulin resistance can arise as a result of chronic elevations in plasma glucose, which may be produced by the ingestion of foods high in refined sugar (Montmayeur & le Coutre, 2010). Accumulating evidence suggests that insulin resistance may, not only be detrimental to metabolic activity, but may also contribute to impairments in neurobiological functioning.

A growing body of research suggests that insulin resistance may be a crucial mediator in the relationship between high sugar diet and cognitive/ brain impairments by affecting synaptic plasticity in the hippocampus. To this point, animals genetically depleted of insulin receptors exhibited significant reductions in phosphorylated Akt and GSK3β, two of the main downstream targets of growth and neurotropic factors (Schubert, Gautam, Surjo, Ueki, et al., 2004).

Some findings have suggested that normalizing insulin signaling may protect against neurobiological impairments. For instance, animals injected with streptozotocin (STZ; (a pharmacological agent which depletes insulin, insulin receptor and insulin-like growth factor activity) showed significant reductions in insulin binding, as well as insulin receptor and insulin-like growth factor receptor expression in the hippocampus, thereby mimicking an insulin resistant state (de la Monte, Tong, Lester-Coll, Plater, & Wands, 2006). Additionally, STZ animals were impaired on spatial memory performance relative to controls. Importantly, STZ-induced impairments were prevented with administration of an insulin sensitizing agent. Here, normalizing insulin signaling protected against impairments in brain and behavioral assessments of memory impairment elevations in ROS (de la Monte, et al., 2006). Limiting the ingestion of refined sugars, therefore, may protect against insulin-induced decrements in the brain and cognitive abilities. These findings suggest that insulin signaling may modulate free radical production and, in turn, contribute to oxidative stress-induced brain impairments governing cognitive functioning. This provides insight into mechanisms by which sugar consumption may contribute to various aspects of cognitive impairment.

Sugar Consumption & Cognition

Accumulating evidence indicates that individuals consuming high levels of sugar demonstrate impaired cognitive performance across various measures. In addition, there are indications that elevated plasma glucose, insulin resistance and T2D are related to impaired cognition in human studies. Studies indicate that individuals ingesting high refined sugar foods demonstrated impaired verbal recall (Benton, Ruffin, Lassel, Nabb, et al., 2003; Nabb & Benton, 2006), recognition memory (Ingwersen, Defeyter, Kennedy, Wesnes, & Scholey, 2007) and reaction time (Lloyd, Green, & Rogers, 1994) compared to those eating complex carbohydrates. Additionally, research shows that sugar consumption may be particularly harmful to those with T2D (Greenwood, Kaplan, Hebblethwaite, & Jenkins, 2003). In this fashion, sugar consumption, in combination with T2D, may exacerbate cognitive deficits.

Type II Diabetes & Cognitive Performance

Experimental studies indicate that T2D patients assigned to high GI diets scored significantly worse on immediate (Greenwood, et al., 2003) and delayed (Papanikolaou, Palmer, Binns, Jenkins, & Greenwood, 2006) word recall compared to control and low GI diet groups. Interestingly, findings also showed significant correlations between increased levels of plasma glucose and impaired memory performance (Greenwood, et al., 2003; Papanikolaou, et al., 2006). T2D patients also show impairments in performance on executive functioning, immediate verbal recall, information processing speed and reaction time tests (Awad, Gagnon, & Messier, 2004;van Harten, Oosterman, Muslimovic, van Loon, et al., 2007).

In case control and large population-based studies, there are robust findings indicating a relationship between T2D and impaired immediate and delayed verbal/visuospatial recall, verbal fluency, mental flexibility, psychomotor speed and semantic memory performance (Stewart & Liolitsa, 1999). It is important to note, however, that conclusions based on case control studies should be treated with caution since, typically, T2D participants are part of outpatient groups and, therefore, findings may not generalize to other populations. Additionally, inconsistencies across studies may arise due to the lack of control of comorbidities such as hypertension and depression which are independently related to impaired cognition (Messier, 2005;Stewart & Liolitsa, 1999). There is a lack of research examining the influence of refined sugar diets on long-term cognitive functioning. Existing evidence does indicate, however, a relationship between T2D and cognitive decline with age (e.g. Messier, 2005). This body of literature, in turn, provides some insight into the potential harmful effects of dietary sugars, which may lead to T2D (Gross, Li, Ford, & Liu, 2004), on cognitive aging.

Type II Diabetes & Cognitive Aging

Findings suggest that T2D may facilitate longitudinal cognitive declines in verbal fluency (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004), executive functioning, verbal recall memory, mental speed, motor speed (van Harten, et al., 2007), information processing and executive functioning (Manschot, Brands, van der Grond, Kessels, et al., 2006). Additionally, T2D patients were impaired on organization, attention (Knopman, Boland, Mosley, Howard, et al., 2001), as well as planning and sequencing (Gregg, Yaffe, Cauley, Rolka, et al., 2000), which may also target executive processes. Importantly, these

decrements were present after controlling for hypertension, which is a significant risk factor for cerebrovascular injury (Johnston, O'Meara, Manolio, Lefkowitz, et al., 2004) and stroke (Elias, Sullivan, D'Agostino, Elias, et al., 2004), both which can potentiate cognitive decline. Additional findings have shown that T2D diagnosis at mid-life increases the risk for dementia, and related cognitive declines, assessed later in life (Xu, Qiu, Gatz, Pedersen, et al., 2009). Interestingly, those that reported a 15 year or more duration of T2D demonstrated accelerated cognitive decline compared to those having the disease for a shorter amount of time (Gregg, et al., 2000), suggesting that high sugar intake contributing to the development of T2D may exert harmful effects on cognition in a compounding fashion over time.

Type II Diabetes & Brain Impairment. A cause of cognitive decline associated with T2D may be due to impaired functioning of cortical and subcortical structures. For instance, findings showed that T2D was associated with atrophy in the hippocampus (Xu, et al., 2009) and amygdala (den Heijer, Vermeer, van Dijk, Prins, et al., 2003), as well as white matter injury (den Heijer, et al., 2003), both potential causes of cellular injury and declines in cognitive performance. Importantly, these associations were shown to be independent of cerebrovascular injury.

A recently proposed model suggests that chronic elevations in plasma glucose can produce an increase in both oxidative stress and uric acid (UA) (Stephan, et al., Previous studies showed that UA was associated with cognitive decline in (Schretlen, Inscore, Jinnah, Rao, et al., 2007). Additionally, UA has been found to result in an inhibition of nitric oxide (NO) through inflammatory pathways, contributing to the development of T2D (Johnson, Perez-Pozo, Sautin, Manitius, et al., 2009).

Importantly, NO has also been shown to be integral in synaptic efficacy and memory (Matsumoto, Unoki, Aonuma, & Mizunami, 2006).

Dietary Sugar & CVD

Accumulating evidence provides support for the notion that CVD may mediate the relationship between sugar consumption and cognitive impairment. To address this, it is important to understand research assessing the impact of dietary sugars on the development of CVD. A key biological process in the progression of CVD is the development of atherosclerotic plaques. Atherosclerotic plaques are the result of, in part, the proliferation and migration of monocytes, lymphocytes and smooth muscle cells into the arterial wall after injury to the endothelium on the surface of the arterial wall. Accumulating substances in the arterial wall can produce an atheroma (i.e. "bulge") which can eventually rupture resulting in a cardiac event (Ross, 1999). Under normal metabolic conditions, the endothelium (surface lining of arteries) maintains a non-adhesive, smooth surface, which acts to inhibit abnormal growth of SMCs and damage may compromise this protective state (Ross, 1999). Accumulating research suggests that hyperinsulinemia and insulin resistance contributes to damage to the endothelial surface, abnormal SMC growth and, in turn, to atherosclerosis.

The atherosclerotic process involves the transition of SMCs from a static to a dynamic state, where they can proliferate, migrate and accumulate inside the arterial wall, contributing to the atherosclerotic process. This process seems to be governed, in part, by insulin and insulin-like growth factors. Monocytes and macrophages which proliferate in the arterial wall have been shown to secrete insulin-like growth factor-I (IGF-I). These

elevations, in turn, interact with surrounding SMCs thereby modulating their accumulation and, in turn, contribute to the atherosclerotic plaque (Arnqvist, Bornfeldt, Chen, & Lindstrom, 1995). To support the premise underlying this biological process, reports indicate that IGF-I is a potent chemo-attractant to SMCs and facilitate SMC hypertrophy (Zhu, Zhao, Witte, Hui, & Fagin, 2001). Studies also show that elevated insulin levels are associated with the proliferation of SMCs (Kopp, 2006). Hyperinsulinemia facilitates the growth and migration of SMCs, in part, by activating the renin-angiotensin system and, specifically, angiotensin- II (ang-II;Kopp, 2006) through an increased ang-II enzymes (Kamide, Rakugi, Nagai, Takiuchi, et al., 2004). Ang-II, in turn, facilitates the production of ROS, an inflammatory biomarker key in the atherosclerotic process (Brasier, Recinos, & Eledrisi, 2002; Kopp, 2006). ROS further inhibits the synthesis of NO, a potent vasodilator (Kopp, 2006). Therefore, activation of ang-II under hyperinsulinemic conditions may act as a vasoconstrictor, thereby restricting blood flow and increasing the risk of CVD, and cardiac events through inflammatory-mediated processes, as well as by increasing indices of coagulation (Ginsberg, 2000). The relationship between insulin resistance and CVD has also been illustrated in epidemiological studies. One study, which directly measured insulin resistance and atherosclerosis, directly found significant negative relationship between insulin sensitivity and intima-media thickness (Howard, O'Leary, Zaccaro, Haffner, et al., 1996), suggesting that this specific marker of atherosclerosis was directly related to insulin resistance.

CVD & Brain Aging

Although dementia will not be a direct focus of analysis in the present study, an analysis of the literature provides evidence for mechanisms by which CVD may potentiate neuronal changes underlying cognitive decline with age. This sheds light on how CVD may contribute to cognitive aging and mediate the relationship between sugar intake and cognitive decline. Neurobiological abnormalities have been found in the normal aging process, but seem to be more pronounced in cases of dementia, such as Alzheimer's Disease (AD), indicative of accelerated brain aging (Swaab, 1991).

Dementia is characterized by multiple deficits in neurological and cognitive functioning. The most common forms of dementia are primary dementias (e.g. AD; Alzheimer's disease, VaD; vascular dementia). AD, the most prevalent dementia, is most often characterized by memory loss, language difficulties, impaired judgement, disorientation and difficulties retaining new information (Saxon, Etten & Perkins, 2010). Studies indicate that AD brains show cortical atrophy, reduced total brain weight, and neuronal loss, especially in the cerebral cortex and hippocampus (Saxon et al., 2010). Amyloid plaques (cells around an abnormal brain protein called amyloid) are a hallmark of the disease, and are found most primarily in the amygdala, hippocampus, and cerebral cortex (Saxon et al., 2010). Additionally, neurofibrillary tangles (tangled filaments or abnormal collections of the tau protein) have been found in the cerebral cortex, hippocampus, amygdala, and brain stem nuclei (Saxon et al., 2010).

In contrast to more neurodegenerative processes involved in AD, vascular dementia is typically thought to be caused by damage to brain tissue as the result of successive small or moderate strokes. The cognitive deficits in VaD patients are similar to those observed in

AD, although there is increased evidence supporting the notion that these two disorders should not be classified as separate entities (Kalaria & Ballard, 1999). CVD, stroke, and hypertension have all been related to the risk of both AD and VaD (Meyer, Rauch, Rauch, Haque, & Crawford, 2000).

CVD, Cognitive Decline & Dementia.

Findings based on large prospective studies have found that previous myocardial infarction (MI) served to shift population scores of cognitive functioning lower compared to those without MI or CVD (Breteler, Claus, Grobbee, & Hofman, 1994). A more recent study indicated a significant relationship between CVD and cognitive decline in studies with an average follow-up period of, approximately, 8 years (Anstey & Christensen, 2000). In a related study, CVD, independent of stroke, increased the risk of AD, VaD, as well as "mixed" dementia, where both cerebrovascular and neurodegenerative processes were present (Newman, Fitzpatrick, Lopez, Jackson, et al., 2005). Further, AD and VaD were found to be significantly associated with atherosclerosis severity (Hofman, Ott, Breteler, Bots, et al., 1997). These findings suggest that CVD may potentiate the onset of dementia and related neurobiological and cognitive impairments.

CVD may facilitate cognitive decline through the formation of spontaneous cerebral emboli (SCEs). CVD can increase the chances of SCE as a result of blood vessels breaking loose, traveling through the blood stream and blocking vessels (Stampfer, 2006).

SCE production, in turn, increases the risk of stroke or transient ischemic attacks (TIAs), and leukoaroasis (changes in cerebral white matter resulting from multiple microvessel infarcts), contributing to neuronal loss and cellular injury, which are common in dementia, especially VaD (Stampfer, 2006).

The development of age-related cognitive decline, are the results of complex cascades of interacting mechanisms. Chronic elevations in blood sugar produced, for instance, increases the chances of glycation (the irreversible binding of glucose to proteins resulting in their ineffectiveness). Glycation increases the production of advanced glycation end products (AGEs), which have been found in both plaques and tangles in AD brains, and found to facilitate plaque aggregation *in vitr*o (Martins, Hone, Foster, Sunram-Lea, et al., 2006).

Depression & Cognitive Aging

In addition to cardiovascular abnormalities, evidence suggests that clinical depression, and related symptoms, contribute to cognitive impairment. It is important, therefore, to gain an understanding of the effects of depression on the brain and cognitive abilities in order to study diet effects on cognitive aging. There is evidence that a significant relationship exists between symptoms of depression and poorer performance on various cognitive abilities, such as memory, perceptual speed, verbal capabilities, and visuospatial performance (Jorm, 2000**)**. Depressive symptoms also seem to be an important factor in cognitive aging in older adulthood (Burt, Zembar, & Niederehe, 1995; Jorm, 2000).

Prolonged exposure to stress, which may be reflected in higher depressive symptoms scores (Pace, Mletzko, Alagbe, Musselman, et al., 2006), may lead to sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis, chronically elevated glucocorticoids (e.g., cortisol), and increased proinflammatory cytokines (e.g., IL-6) (Sapolsky, 2001). In turn, chronic stress may lead to neural degeneration (Radley & Morrison, 2005; Sapolsky, 1996). Elderly participants were found to have significant elevations in stress-induced cortisol and greater sympathetic activity (e.g. blood pressure) compared to younger depressed patients, which was related to impaired cognitive performance (Gotthardt, Schweiger, Fahrenberg, Lauer, et al., 1995). Additionally, there is evidence indicating that depressive symptoms are a significant risk factor for age-related cognitive disorders such as AD (Wilson, Barnes, Mendes de Leon, Aggarwal, et al., 2002) and mild cognitive impairment (Geda, Knopman, Mrazek, Jicha, et al., 2006). In fact, retrospective analyses show significant relationships between history of clinical depression and AD (Jorm, van Duijn, Chandra, Fratiglioni, et al., 1991). Together, these findings suggest that depression may affect cognition and, therefore, need to be considered in the study of cognitive change.

Depression & Brain Functioning. There is a general consensus in the literature that depression detrimentally affects cognitive processing in older adults on, for instance, tests of memory (Austin, Mitchell, & Goodwin, 2001), attention (Trichard, Martinot, Alagille, Masure, et al., 1995), and executive functioning (Veiel, 1997), and that these changes may be the result of inhibitions in various brain processes. One clinically controlled trial, for instance, found a significant reduction in serum BDNF extracted from patients diagnosed with major depressive disorder. Additionally, these decreases were prevented with

antidepressant treatment (Huang et al., 2007). These findings suggest that clinical depression may produce impairments in brain plasticity which may underlie impairments in cognitive processes, such as memory. In addition, research suggests that depression may result in cognitive decline through enhancement of glucocorticoid-induced neurotoxicity, and hippocampal volume loss (Sheline, Gado, & Kraemer, 2003). In brain imaging analyses, findings showed that depressed elderly patients exhibited significantly smaller hippocampal volumes relative to healthy control participants (Bell-McGinty, Butters, Meltzer, Greer, et al., 2002), suggestive of impaired memory processing. Other work indicates impairment in brain structures controlling movement, automatic processing, and executive functioning, indicated by smaller volumes of caudate nuclei (Krishnan, Tupler, Ritchie, McDonald, et al., 1996), pre-frontal cortices (Kumar, Bilker, Jin, & Udupa, 2000), and lower pre-frontal cerebal blood flow (Nobler, Roose, Prohovnik, Moeller, et al., 2000), again, indicating poorer executive functioning in elderly individuals with depressive symptoms (Alexopoulos, Meyers, Young, Kalayam, et al., 2000).

Dietary Sugar & Depression

In addition to influencing cognitive changes, clinical depression and related symptoms may alter food intake. For instance, a cross-national study showed a significant relationship between per capita sugar intake across 6 countries and major depression (Westover & Marangell, 2002). Some research supports the notion that clinical depression may increase individuals' preference for sugar (Kazes, Danion, Grange, Pradignac, & Schlienger, 1993). Sugar has also been linked with lower self reports in mood and increased levels of tiredness and tension assessed 60 minutes post-ingestion (Thayer,

1987). Increased oxidative stress may be one pathway through which sugar intake interacts with depression to influence cognitive functioning (Westover & Marangell, 2002). In fact, a growing body of research has linked major depressive disorder with oxidative stress in humans (Bilici, Efe, Koroglu, Uydu, et al., 2001). In summary, depressive symptoms may have an influence on sugar intake as well as cognitive outcomes. Therefore, depressive symptoms are important factors that need to be accounted for when examining relationships between sugar consumption and cognitive aging.

Other Potential Confounders

Age. Age is among the most reliable correlates of cognitive performance. Age is related to decrements in various cognitive abilities, such as speed of processing, reasoning, episodic memory (Verhaeghen & Salthouse, 1997), possibly the result of age-related declines in functioning of pre-frontal and medial-temporal lobe structures related to executive functioning (West, 1996).

Additionally, there has been increasing interest in the speed of processing hypothesis, which suggests that age-related decrements in cognitive abilities are globally explained by decreases in the speed by which individuals process information (Salthouse, 1996).

Age may influence changes in dietary patterns. Research, for instance, suggests that changes in dietary patterns, including an overall decrease in appetite, may be the result of declines in chemosensory systems. Specifically, there are indications that age is accompanied by declines in taste perception and olfactory dysfunction. Sensory deficits, in turn, facilitate a diminishment in the ability to respond to smells and tastes of food (Rolls, 1999). Although there are no clear patterns, some findings indicate that elderly individuals

have a preference for higher sugar levels (Murphy & Withee, 1986), possibly due to their decreased taste sensitivity. On average, elderly adults also needed higher levels of sugar in their food to perceive the same sweetness intensity compared to younger adults (Murphy & Withee, 1986). Additionally, those with olfactory dysfunction showed higher intake of sugary foods compared to controls (Madeira & Goldman, 1988). Age may influence changes in various aspects of cognitive abilities and, potentially, may alter sugar intake patterns. Therefore, age is an important variable to account for in the study of sugar effects on cognitive aging.

Gender. With regards to cognitive abilities, gender differences in domains such as verbal ability, quantitative ability, and visual-spatial ability, although with small effect sizes, have been reported (Hyde & Plant, 1995). Some evidence suggests, however, that males outperform females on spatial cognition and arithmetic reasoning tests (Geary, Saults, Liu, & Hoard, 2000), Findings have also shown women to outperform men on verbal production (Herlitz, Airaksinen, & Nordstrom, 1999), and facial recognition tasks (Guillem & Mograss, 2005) but men scored better on mental rotation tasks (Herlitz, et al., 1999), although there were no substantial gender differences on semantic memory in a sample of adults ranging from 35-80 years old (Herlitz, Nilsson, & Backman, 1997).

Gender seems to have an influence on food choice. In general, evidence indicates that women tend to be more focused on healthy eating and weight control compared to men (Wardle, Haase, Steptoe, Nillapun, et al., 2004), which may lead to differences in sugar consumption. Some have indicated that men, in fact, ate higher levels of sugary foods compared to women in a study of diet records among 500 adults (Milligan, Burke, Beilin, Dunbar, et al., 1998).

However, there are also indications that women may ingest high sugar levels after undergoing laboratory stressors (Epel, McEwen, Seeman, Matthews, et al., 2000), suggesting a relationship between gender and emotional eating.

Education. Research suggests that lower education is significantly associated with cognitive decline. For instance, a meta-analysis indicated that education was negatively related to cognitive decline across 34 different studies with an average follow-up of 8 years (Anstey & Christensen, 2000). In addition, lower education levels were related to cognitive impairment with age, but only across certain cognitive domains, such as verbal performance, but not executive functioning (Ardila, Ostrosky-Solis, Rosselli, & Gomez, 2000). Higher education levels may protect against age-related cognitive decline due to greater cognitive reserve, a topic which is of increasing focus among investigators in this area (Whalley, Deary, Appleton, & Starr, 2004). It is important to note that the influence of lower education on cognitive impairment may be the result of environmental factors, such as low socioeconomic status (SES), which may also lead to decrements in cognitive abilities (Ardila, et al., 2000).

Education itself may also be related to changes in sugar intake. There is some evidence indicating that lower education is related to higher sugar consumption (Galobardes, Morabia, & Bernstein, 2001), including, for example, soda intake (Elfhag, Tynelius, & Rasmussen, 2007). Additionally, in a study of over 13000 adults, findings indicated that low SES was associated with higher intake of soda, and lower ingestion of healthy foods, such as vegetables, fruits, and protein (Hulshof, Brussaard, Kruizinga, Telman, & Lowik, 2003).

Education may influence cognitive abilities, as well as dietary sugar patterns, and needs to be accounted for when examining relationships between sugar intake and cognitive change.

Analysis of Cognitive Aging: Random Effects Growth Modeling

The investigation of how people change over time has been the focus of empirical researchers for generations. Over the past several years, methodologists have developed and refined a class of statistical models known as random effects growth models. Growth models have become increasingly prevalent in the assessment of longitudinal cognitive change. Investigators have utilized random effects models across a variety of studies to examine how biological, psychological and social predictors relate to longitudinal change (Hertzog & Nesselroade, 2003)**.** These models allow for the simultaneous estimation of overall fixed effects (i.e. average groups effects), as well as random effects which reflect individual deviation from the fixed effect (i.e. deviations from the slopes and intercepts). Additionally, a description of the covariation between the slopes and intercepts is provided. This procedure, therefore, allows for the effective depiction of the nature of change over time (Raudenbush & Bryk, 2002). In this study, random effects were calculated using an unstructured covariance matrix and included baseline cognitive performance across each domain (i.e. intercept), and rate of decline (i.e. slope). Estimates of slopes and intercept depict relationships between predictors, initial status, rates of change, as well as variability contained within slopes and intercepts (Raudenbush & Bryk, 2002). The models utilized in this study statistically adjusted for age and education (both centered at the mean), gender, depressive symptoms, and CVD.

Growth Model Advantages

In contrast to other common analytical tools for assessing longitudinal, repeated measures, types of data, random effects models provide greater utility and flexibility regarding interpretation of inter-individual and intra-individual change. It is useful to provide an overview on the advantages of these types of models over some of these other statistical procedures in order to gain insight into their appropriateness of use in the current study.

Repeated Measures Analysis of Variance (rANOVA). In contrast to more traditional statistical techniques of conducting repeated measures analyses (e.g., rANOVA), random effects models provide more flexibility regarding the treatment of time, enable the use of all data across measurements, and properly account for correlations between repeated measurements on the same subject (Gueorguieva & Krystal, 2004). Methodologists have pointed out that one of the biggest drawbacks associated with the use of rANOVA is its lack of flexibility in accounting for missing observations. Researchers using this method often eliminate subjects from the analysis, even if they are only missing a single measurement time point. This omission may produce biased results, as the sample analyzed may not be representative of the true population of study (Gueorguieva & Krystal, 2004). One of the main advantages of growth models, in turn, is the ability to take into account missing data by giving more weight to individuals with the more number of measurement time points, but retaining individuals with missing data points by estimating their expected trajectory based on all available data. In addition, random variance across measurement occasions is accounted for, thereby reducing biases attributable to differences in baseline

performance and correlations between cognitive scores across measurement occasions (Singer & Willett, 2003). Another disadvantage of rANOVA is the requirement that observations made on all individuals need to be conducted at the same time points, whereas growth modeling techniques are more flexible in this regard since repeated observations are treated as being nested within the person rather than being treated as fixed for all individuals (Raudenbush & Bryk, 2002). This is especially an advantage in longitudinal studies where attrition may be present. Further, in contrast to rANOVA, growth models are robust to violations of the sphericity assumption (i.e. equal variability of measurements at each time point) (Jacobs, Small, Booth-Jones, Jacobsen, & Fields, 2007).

Regression Analysis. Random effects modeling allows for the specific study of individual change. The application of traditional regression techniques has been used in the past, but the model of individual growth is not specifically addressed in these methods (Bryk & Raudenbush, 1987; 2002). Studies of change using traditional regression analyses discriminate among individuals at a fixed point in time, but fail to provide information regarding *rates* of change over time (Bauer, 2011). Modeling individual change using traditional regression methods is only able to provide results based on differences between two time points (e.g. pretest-posttest) (Bryk & Raudenbush, 1987). Generally speaking, change across two time points is inadequate to accurately represent change in a longitudinal context. Even in instances where data have been measured across multiple time points, researchers have analyzed these data using separate equations for each pair of time points (Bryk & Raudenbush, 1987).

Therefore, random effects models have been increasing in use by researchers attempting to study individual change (Gueorguieva & Krystal, 2004) because of their ability to take an integrated and more accurate approach to the study of growth patterns (Bryk & Raudenbush, 1987; 2002).

Study Analyses & Parameters

For this study, a linear individual growth model was utilized to examine the influence of dietary sugar intake on cognitive aging, based on tests of performance across 4 cognitive domains (Verbal, Spatial, Memory, Speed). Here, sugar predictor variables (Total Sugar, Dessert, Sweetened Beverages & Bread, Sugar in Coffee) were estimated to examine their influence on trajectories of cognitive change over time. Additionally, the models were adjusted for covariates which had the potential to exert confounding influences on cognitive change, which included gender, education, depressive symptoms and CVD. The models across each cognitive domain were specified which adjusted for gender, as well as mean centered age and education. Then, covariates representing depressive symptoms and cardiovascular health were added to the models in a sequential fashion in order to assess their specific influence on trajectories of cognitive change over the study duration.

Mediation

Mediation analyses allows for the statistical examination of whether a proposed relationship between given independent and dependent variables are driven by a separate variable (i.e. an indirect effect). This type of analysis allows for a more precise assessment

of a theoretical mechanism underlying a given outcome. A common methodology for conducting mediation analysis follows a procedure popularized by Baron & Kenny (Baron & Kenny, 1986). In the Baron & Kenny method, there are 4 criteria that need to be fulfilled in order to satisfy mediation conditions. First, there must be a significant direct effect (i.e. direct relationship between the IV and DV). Secondly, there must be a significant effect of the IV on the proposed mediator. Thirdly, the effect of the mediator on the DV, controlling for the IV must be significant. Lastly, the direct effect of the IV on the DV, controlling for the mediator must be smaller than the total effect of the IV on the DV. With respect to these criteria, Baron & Kenny suggest that if the effect of the IV on the DV reaches zero in the presence of the proposed mediator, this is an indication of perfect mediation, or a fully mediated model. Furthermore, if the direct effect remains significant, but is simply reduced in the presence of the mediator, this is an indication of partial mediation (Baron & Kenny, 1986;Fritz & Mackinnon, 2007).

The Baron & Kenny method provides a strong foundation for mediation analyses. However, discussions regarding drawbacks to their method have been increasing in recent years (Preacher & Hayes, 2004). Some researchers have suggested that the Baron & Kenny method may not be the most accurate procedure to test for mediation due to its lack of testing for the indirect effect (Hayes, 2009)**.** Additionally, the Baron & Kenny method has low power to detect statistically significant differences and, therefore, is conservative in terms of detecting mediation (i.e., increases the likelihood of type II errors; Hayes, 2009). A more advanced method of conducting mediation analyses is through bootstrapping, which involves the repeated and random resampling from a data set with replacement to generate estimates of indirect effects (Preacher & Hayes, 2004). This

method is suggested to be superior to other common methods, such as the Sobel Test, since it does not require the sampling distribution of the indirect effect to be normally distributed and allows for assessing all mediation-related pathways simultaneously (Hayes, 2009). In addition, the bootstrapping procedure provides a clear estimate of the indirect effect with a 95% confidence interval, as well as limiting the likelihood of type I and type II errors (Hayes, 2009). Further, literature suggests that bootstrapping requires a sample size of 405 or larger in order to reach .8 power, a common threshold indicative of sufficient power, whereas studies utilizing the Baron & Kenny required very large sample sizes to reach .8 power (at least 20,886) (Fritz & Mackinnon, 2007). Therefore, a bootstrapping procedure was utilized in this study to assess mediation due to its enhanced power capabilities and utility as a valid analytic tool.

Study Hypotheses

This study tested the hypothesis that: 1) High sugar consumption, defined as above standardized median intake, would be significantly associated with worse overall cognitive performance when compared to low total sugar consumption, after adjusting for the potentially confounding influences of age, gender, education, depressive symptoms and CVD, 2) High sugar consumption would be related to significantly steeper trajectories (i.e. higher rates) of cognitive decline with age compared to low sugar consumption in fully adjusted models, 3) CVD would mediate the relationships between high sugar consumption and cognitive performance and decline. A secondary set of hypotheses tested that high levels of dessert, sweetened beverages & bread and added sugar in coffee consumption would be significantly related to poorer overall cognitive functioning and steeper

trajectories of cognitive decline in fully adjusted models. Again, CVD was hypothesized to mediate the relationships. It was expected that high sugar consumption would exert a particularly detrimental influence on predominantly hippocampus-dependent tasks characteristic of memory and spatial performance. Both verbal and perceptual speed performance were also examined, since they require some level of memory/hippocampus processing, and because previous work has indicated decrements across these measures related to T2D (Stewart & Liolitsa, 1999; Kanaya, et al., 2004; van Harten, et al., 2007). Findings of this study can shed light on the influence of dietary sugar on long-term cognitive health, a topic which has not been extensively studied.

Chapter 2: Methods

Participants & Data Collection

This study utilized a subset of twins from the population-based Swedish Twin Registry (Lichtenstein, De Faire, Floderus, Svartengren, et al., 2002) known as the Swedish Adoption/Twin Study of Aging (SATSA). The SATSA (Pedersen, McClearn, Plomin, Nesselroade, et al., 1991) is a longitudinal research program that was initiated in order to study genetic and environmental influences on individual change over time. It consists of all pairs of twins from the Swedish Twin Registry who were separated prior to age 11 and a sample of twins reared together matched on gender, date, and county of birth in Sweden.

Testing Procedures

Questionnaire Phase. The SATSA, initiated in 1984, began with mailing an initial questionnaire (Q1) containing sections on health, lifestyle and environment. The questionnaire was designed to represent issues related to aging by including scales used in other aging studies available at that time, such as the Older Americans Resources and Services (OARS) study (Fillenbaum & Smyer, 1981) and the H-70 study of aging (Rinder, Roupe, Steen, & Svanborg, 1975). A second questionnaire (Q2) was mailed out 3 years after Q1 (i.e. 1987), Q3 was sent out in 1990, and Q4 in 1993. Table 1 displays participation in the questionnaires across the waves of questionnaire data collection.

Table 1: *Participation in Questionnaires*

	Participation by wave				Participation by multiple waves			
	Q1	Q2	Q3	Q4	1Qs	2Qs	3Qs	4Qs
N	2019	1637	1496	1450	394	341	370	1104

Note. Q= Questionnaire. 2 Qs= Any 2 Qs. 3 Qs= Any 3 Qs. 4 Qs= All 4 Qs

In-Person Testing. Non-demented twin pairs who responded to Q1 (response rate 70.7%), and were aged 50 years or older, were invited to participate in the in-person testing (IPT) procedure aimed at assessing health and cognitive abilities. At the onset of the SATSA, the first testing session (IPT1) was conducted in a location convenient for participants (e.g. district nurses' office, health-care schools, long-term clinics) during a single 4-hr consultation. The second testing session (IPT2) was conducted 3 years after the initial session, and the third session (IPT3) was carried out after another 3 years. The next wave of testing (IPT4) occurred 7 years after IPT3. Finally, the last testing session (IPT5) was conducted 3 years later.

Each testing session was performed by a registered nurse who was specifically trained to administer the IPT measures. Cognitive tests were followed with a health examination during each IPT (Pedersen, et al., 1991). For the current study, data from 553 participants with both sugar intake and cognitive scores were available for assessment. The average age across the study was 69.7 years, and approximately 62% of the participants were female.

Individuals were enrolled on a continuous basis for the duration of the study period, as long as they were at least 50 years of age at the time of the testing session. A depiction of participation across each wave, and longitudinal participation, is provided in Table 2.

Table 2: *Description of Study Sample (N=553)*

Testing Wave	Years	Sample N	Mean Age, in Years (SD)
IPT1	1986-1988	531	66.2 (7.5)
IPT2	1989-1991	392	67.5 (7.0)
IPT3	1992-1994	367	70.1 (7.3)
IPT4	1999-2001	272	73.1 (6.7)
IPT5	2002-2004	215	77.2 (7.0)
Only 1 IPT	-	105	-
Any 2 IPTs	-	83	-
Any 3 IPTs	-	120	-
Any 4 IPTs	-	79	-
All 5 IPTs	-	166	-

Note. IPT= In Person Testing.

*Cognitive Measures***.** The cognitive battery employed in the SATSA was selected to test crystallized intelligence, fluid intelligence, and memory (Nesselroade, Pedersen, McClearn, Plomin, & Bergeman, 1988;Pedersen, et al., 1991). The battery included all tests used in the H-70 study of aging in Göteborg, Sweden (Berg, 1980). Subsequently, tests of spatial ability and perceptual speed were included to tap into cognitive areas commonly tested in quantitative behavioral research.

The SATSA cognitive battery includes 13 tests (Pedersen, et al., 1991) designed to represent specific cognitive abilities (Nesselroade, et al., 1988). A principal components analysis was conducted in order to represent a measure of general cognitive ability. Here, individuals' scores on the first principal component of the 13 tests at each testing point were obtained. Except for the Forward Digit Span Test, all measures loaded higher than .50 on this principal component, accounting for between 42% and 45% of the total variance during each testing period (Pedersen, Plomin, Nesselroade & McClearn, 1992).

In addition to general cognitive ability assessment, the analysis yielded latent measures from the individual tests of 4 cognitive domains representing verbal abilities, spatial capabilities, memory and perceptual speed (Pedersen et al., 1992). The factor analysis producing latent factors from the individual tests in each domain were created based on data gathered at IPT1. This factor structure was not found to significantly vary across age or time (i.e. waves of testing), validating the structure across time points (Hertzog & Nesselroade, 2003). The cognitive measures assessed after the initial wave were standardized relative to the means and variances at IPT1. The factor loadings at IPT1, in turn, were utilized to construct the verbal, spatial, and memory components (Finkel, Reynolds, McArdle, & Pedersen, 2005). Assessments of perceptual speed were combined

into a speed component with unit weighing. To standardize values across domains, and enhance interpretation of the results, all component scores were translated to *T* scores using means and variances from IPT1 (Finkel, Andel, Gatz, & Pedersen, 2009).

The domain *Verbal Ability* included Information (questions of general knowledge), Synonyms (participants were asked to find a synonym among five alternatives that matched a target word) and Analogies (Austin, Deary, Whiteman, Fiwkes, Pedersen, Rabbitt et al., 2002; Jonsson & Molander, 1964). *Spatial abilities* were tapped by Figure Logic (identification of one figure out of five in a row that is of different concept compared to the others;), Block Design (reproduction of pattern shown on cards using blocks; Dureman, Kebben & Osterberg, 1971), and Card Rotation (test of spatial mental rotation; Pertusic, Varro, & Jamieson, 1978). *Memory* was constructed utilizing Forward and Backward Digit Span (recall of orally presented digits in the correct order; Wechsler, 1991), Picture Memory (non-verbal recognition of 28 pictures among 3 distractors; Johansson, Hofer, Allaire, Maldonado-Molina, et al., 2004), as well as immediate and delayed recall of Names & Faces (Defries, Plomin, Vandenberg & Kuse, 1981). Finally, *Perceptual Speed* was measured by Digit Symbol (verbal response indicating what digits match symbols within a 90 second period; Wechsler, 1991) and Figure Identification (Dureman, Kebbon & Osterberg, 1971) performance. The sources of the tests and corresponding reliability information are provided in Table 3 (Pedersen, 1992).

For loadings of each test onto the verbal, spatial and perceptual latent domain constructs, loadings ranged from .78 to .92 and were found to explain 74%, 67% and 85% of the variance among the individual measures. For the memory component, loadings ranged from .64 to .78 and explained 53% of the variance among the measures (Pedersen et

al., 1992). These latent components representing the 4 specific cognitive domains (verbal, spatial, memory, perceptual) have been taken as a comprehensive index of cognitive abilities and have been used in multiple studies of cognitive aging using the SATSA (See Table 3) (Pedersen et al., 1992; Finkel, et al., 2005; Finkel, et al., 2009)

Table 3: *Cognitive Tests & Domains*

Test	Cognitive Domain	Resource	Reliability
Information	Verbal Ability	[c]CVB (Modified WAIS)	.89
Synonyms	Verbal Ability	[b]DS Battery	.95
Analogies	Verbal Ability	[d]WIT-III	.82
Figure Logic	Spatial Ability	DS Battery	.87
Kohs Block Design	Spatial Ability	DS Battery	.91
Card Rotations	Spatial Ability	[e]Educational Testing Service	.88
Forward & Backward Digit Span	Memory	CVB (Modified WAIS)	.92
Picture Memory	Memory	DS Battery	.82
Names and Faces (Immediate & Delayed)	Memory	[f]Colorado Adoption Project	.93
Digit Symbol	Perceptual Speed	[a]WAIS	.92
Figure Identification	Perceptual Speed	DS Battery	.96

Note. *[a]Wechsler Adult Intelligence Scale (Wechsler, 1991), [b]Dureman-Salde Battery (Dureman et al,1971),[c]Johnsson & Molander,1964, [d]Westrin, 1967, [e]Ekstrom et al, 1976,[f]DeFries et al, 1981. Adapted with permission from Pedersen et al., 1992**:** Sage Publishing.

Sugar Consumption. The SATSA includes a set of questionnaires which focused on dietary habits gathered from participants during Q1 of the questionnaire phase prior to entrance into the testing phase of the study. For the purposes of this study, consumption of dietary simple carbohydrates/refined sugars was examined. Specifically, consumption of white bread, sweetened beverages, ice cream and cake was the focus as shown in Tables 4 and 5. To assess white bread consumption, participants were asked; "How many slices of white bread per day do you eat?" For sweetened beverages, participants responded to "How many glasses of soft drinks, nectar and sweetened juices do you drink per day?" Both ice cream and cake/biscuit consumption were assessed by asking participants to rate their normal consumption of these foods during a given year. They responded by checking boxes corresponding to "More than 4 times/week," "1-4 times/week," "1-3 times/month," "Less than once/month," or "Never." An example of the questionnaire given to participants is provided in the appendix.

Table 4

Sugar Consumption: Quantity Assessment

Consumption	Soft Drinks[a]	White Bread[b]	Added Sugar[c] in Coffee
0	321 (50.2)	262 (42.5)	351 (57.9)
1	73 (11.1)	157 (26.0)	110 (18.2)
2	141 (22.0)	129 (21.4)	125 (20.6)
3	32 (5.0)	30 (5.0)	16 (2.6)
4	39 (6.1)	16 (2.7)	2 (0.3)
5	3 (0.5)	5 (0.8)	2 (0.3)
6	17 (2.7)	4 (0.7)	-
7	2 (.31)	-	-
8	8 (1.3)	-	-
9	-	-	-
10	3 (.47)	-	-
11	1 (.16)	-	-
N	640	603	606

Note. [a]Assessed as glasses/day
[b]Assessed as slices/day
[c]Measured in terms of lumps/teaspoons per cup. Values are expressed as frequency (% sample).

Table 5: *Sugar Consumption: Frequency Assessment*

Consumption	Ice Cream	Coffee Cake & Biscuits	Pastries
>4times/wk	15 (2.4)	212 (33.4)	6 (1.0)
1-4 times/wk	89 (14.0)	245 (38.6)	20 (3.2)
1-3 times/mo	267 (41.9)	108 (17.0)	171 (27.2)
< once/mo	214 (33.5)	48 (7.6)	361 (57.5)
Never	53 (8.3)	22 (7.6)	70 (11.2)
N	638	635	628

Note. Values are expressed as frequency (% sample).

Covariates. A set of covariates were taken into account in order to adjust for their potentially confounding influences on cognitive functioning and sugar intake. *Cardiovascular Disease* (CVD) was specified based on self-reported incidences of angina pectoris, myocardial infarction according to the Rose questionnaire (Rose, McCartney, & Reid, 1977**;**Svardh, Isacson, & Pedersen, 1998), which were coded as absence or presence at least once during the study. Additionally, the CVD index included presence or absence of heart attack, claudication, high blood pressure, stroke, or any other cardiovascular dysfunction (e.g. thrombosis, tachycardia, circulation problems, heart operation, heart valve problems, phlebitis) occurring at least once during measurement occasions.

Participants were further classified by *Age* (in years), *Education*, dichotomized into Elementary School and High School or above, *Gender* (male or female), as well as *Depressive Symptoms*, measured using the 20-item Center for Epidemiologic Studies Depression Scale (Radloff, 1977) and scaled from 0 to 5, where 0 represented no symptoms while 5 represented high depressive symptoms, which was then dichotomized.

Statistical Analyses

All analyses were conducted utilizing SAS 9.2 statistical software (SAS Institute, Cary, NC.) with significance level set at the two-tailed < .05 level. A total sugar composite variable was constructed in order to examine the influence of sugar consumption on cognitive aging. Additionally, a principal components analysis revealed 3 latent factors to describe sugar intake. Correlation matrices were generated to further investigate relationships among all the variables in this study, including between the covariates and the sugar variables. In addition, differences in the covariates between high and low sugar consumption groups were assessed using χ^2 statistics.

Random effects growth models (Singer, 1998; Singer & Willett, 2003) were utilized to describe the influence of sugar consumption on cognitive performance and trajectories of cognitive change, adjusting for covariates including gender, age, education, depressive symptoms, and cardiovascular health. A mediation analysis (Hayes, 2009) was conducted in order to test the hypothesis that cardiovascular health would mediate the relationship between sugar intake and cognitive decline. Each of the analytical procedures is detailed in the below sections.

Correlation Matrices

Correlation matrices were generated to depict the relationships between all of the covariates, outcomes, and the sugar consumption variables that were specified (i.e. total sugar, and resulting sugar variables from the factor analysis). This was accomplished utilizing the SAS procedure CORR, outputting Pearson correlation coefficients (default).

Total Sugar Consumption

In order to assess total sugar consumption across all of the observed intake variables, a single composite sugar intake variable was constructed by taking the summation of the z-score values for each individual intake measure. This single variable representing total sugar consumption was then dichotomized at the median into "low intake" and "high intake." A χ^2 analysis was conducted to assess differences between high and low consumption across all of the covariates of interest utilizing the SAS procedure FREQ with a chisq specification.

Factor Analysis

Since the sugar intake variables were measured on different scales, each sugar intake value was transformed into a standardized z-score. Based on the standardized values, a principal components analysis, was conducted in order to assess if specific latent variables could be identified, thereby reducing the number variables related to sugar consumption and, in turn, the number of analyses. In general, a principal components analysis allows for the representation of the maximum amount of variance present in the original set of variables with a minimum amount of latent variables. Essentially, this

method allows for the reduction and summarization of many variables into a smaller number of representative factors (Costello & Osborne, 2005; Rao, 1964**;**Vyas & Kumaranayake, 2006). The factor analysis was conducted utilizing the SAS procedure FACTOR with a Varimax rotation method, which strengthens the uniqueness of individual factor scores due to the specification of the factors as orthogonal (i.e. completely uncorrelated). Significant factor loadings were taken at values greater than or equal to .40, a common threshold utilized in principal components analysis (Costello & Osborne, 2005). Each factor resulting from the analysis was then dichotomized into "low intake" and "high intake" at the standardized median for the purposes of further analysis.

Random Effects Models

Preliminary analysis revealed that scores for variables representing sugar consumption were not normally distributed, showing substantial negative skewedness (>|1|). In addition, the aim was to provide a clinically useful representation of the influence of sugar consumption on cognitive aging. Therefore, all of the sugar consumption variables were dichotomized at the median into "high" and "low" consumption and entered into the tested models.

The influence of sugar consumption on cognitive performance and trajectories of cognitive change was assessed utilizing random effects growth models in SAS procedure MIXED. For this study, 4 models were specified to test for relationships between each sugar factor (Total Sugar, Dessert, Sweetened Beverage & Bread, Sugar in Coffee) and the cognitive domains (Verbal, Spatial, Memory, Perceptual Speed). Model 1 included gender, as well as mean centered age and education as covariates. In Model 2, depressive

symptoms were added as a covariate. In Model 3, depressive symptoms were removed and cardiovascular health was added as a covariate. Lastly, Model 4 included both CVD and depressive symptoms as covariates to define a fully adjusted model. This project was focused on the examination of participants as individuals. Therefore, the models employed to test cognitive change were adjusted for twin dependence and in this fashion, both the intra-individual and intra-twin pair variance was accounted for.

Covariance Structures. One of the main strengths of random effects modeling is the ability to compare difference structures for error covariance matrices. By comparing goodness-of-fit parameters between models utilizing different structures, the user can determine which structure is most appropriate for the data (Singer, 1998; Liu, Rovine, & Molenaar, 2012). The random effects produced by the models reflect the natural variability in a sample, both in the estimates of slopes and intercepts. In model specification, there are various covariance structures that can be utilized in order to account for length of study, number of repeated measurements and to account for design-specific situations, such as multiple repeated measurements taken on the same experimental unit at a certain time point, a single measurement assessed on the same experimental unit multiple times, or a combination of these (Wolfinger, 1996).

The most commonly used covariance structures are Autoregressive, noted as AR(1), Compound Symmetry (CS), and Unstructured (UN) (Singer, 1998). AR(1) covariance structures are typically specified when assuming that measurement points made in close temporal distance are more correlated compared to measurements that are farther apart in time, which are less related. Compound symmetry structures assume that separate measurements are correlated, regardless of their temporal proximity to each other.

Unstructured specifications are the most liberal, placing no restrictions on the variance-covariance matrix, and are found to be most appropriate for small waves of data (Singer, 1998; Singer & Willet, 2003**;** Wolfinger, 1996), and typically provide better fit to the data. Additionally, UN specifications typically provide ease of model convergence (Singer & Willet, 2003), and tend to be particularly useful when analyzing data with inherent dependencies, such as in the analysis of twins (Finkel, Reynolds, McArdle, Gatz, & Pedersen, 2003;Pedersen, Ripatti, Berg, Reynolds, et al., 2003).

The commonly utilized covariance structures (AR, CS, UN) were employed to test model fit in fully adjusted models. Goodness-of-fit indices are shown in Table 6 where lower indices are reflective of better fit to the data (Singer & Willet, 2003). As depicted in the table, the unstructured (UN) specification provided the best overall fit to the data, indicated by smaller AIC and BIC levels across all of the cognitive domains compared to the other covariance structures. Therefore, in order to reach the most parsimonious model findings, the TYPE=UNR specification was set in the MIXED procedure to estimate the fixed and random parameters.

Table 6: *Model Fit Based on Covariance Structure Specification*

Assumption	Cognitive Domain	AIC	BIC
AR(1)	Verbal	11629.5	11676.9
	Spatial	11467.2	11536.7
	Memory	11885.4	11932.9
	Perceptual Speed	11974.4	12021.9
CS	Verbal	11629.4	11676.9
	Spatial	11489.2	11536.7
	Memory	11885.4	11932.9
	Perceptual Speed	11974.4	12021.9
UN	Verbal	10201.4	10253.2
	Spatial	10489.3	10536.8
	Memory	11108.6	11160.4
	Perceptual Speed	10990.2	11042.0

Note. AR(1)= Autoregressive, CS= Compound Symmetry, UN= Unstructured

Mediation Analyses

Analyses were performed to assess whether associations between sugar intake and cognitive outcomes would be significantly mediated by cardiovascular health. The mediation analyses utilized a bootstrapping-based mediation procedure developed by Preacher and Hayes (Preacher & Hayes, 2004), which extends upon the work by Baron and Kenny (Baron & Kenny, 1986). The analyses were conducted with a SAS macro, which provides estimations of all three hypothesized pathways in the mediation structure (predictor to outcome; predictor to mediator and mediator to outcome) simultaneously, thereby providing a more reliable estimation of the indirect effect compared to the Baron and Kenny method (Preacher & Hayes, 2004), partly due to the use of a bootstrapping technique, which also reduces sample size demands (Fritz & Mackinnon, 2007).

Mediation testing was conducted for all significant and non-significant relationships between sugar consumption and cognitive performance, since it is possible for a significant mediator to exist even in the absence of an association between the predictor and the outcome (Hayes, 2009). Significant mediation was concluded if the estimate of the proposed mediator generated by the bootstrap procedure was significantly different from zero with 95% confidence. In other words, if zero was not included in the 95% confidence interval, this was taken as an indication of significant mediation.

Chapter 3: Results

Factor Analysis

A description of the components and factor loadings from the analysis are outlined in Table 7. Factor loadings were considered significant at the >.40 level. Results indicated that the sugar consumption variables were best described by 3 latent components, which were labeled Dessert (ice cream, cakes, pastries), Sweetened Beverages & Bread (sweetened beverages, white bread) and Sugar in Coffee (added sugar in coffee). The factor loadings accounted for approximately 63% of the total variance, suggesting a good solution.

Table 7: *Factor Loadings for Principle Components Analysis*

Sugar Variable	Dessert	Sweetened Beverages & Bread	Sugar in Coffee
Sweetened Beverages	-.12	.72*	.01
White Bread	.06	.75*	.09
Ice Cream	.65*	-.27	.29
Coffee Cakes & Biscuits	.76*	.09	-12
Pastries & Gateaux	.78*	-.03	-.14
Added Sugar in Coffee	-.01	.12	.94*

Note. *Factor Loadings > .40

Correlations between Covariates & Sugar Consumption Specified as Continuous Variables

As depicted in Table 8, *Total Sugar* consumption was positively correlated with age, having CVD, and negatively correlated with gender, suggesting higher total sugar consumption in men. Additionally, total sugar consumption was related to worse performance on all of the cognitive outcomes (verbal, spatial, memory, perceptual speed). *Dessert* consumption was positively correlated with age, total sugar, and negatively correlated with perceptual speed. *Sweetened Beverages & Bread* was negatively correlated with gender, suggesting high consumption in men. It was also negatively related to memory and perceptual speed performance and positively related to total sugar.

Finally, *Sugar in Coffee* was positively correlated with age and total sugar, and negatively with being a female, memory scores, and perceptual speed scores. Interestingly, the 3 latent sugar consumption factors did not correlate with each other at a significant level.

Correlations Between Covariates & Dichotomized Sugar Consumption

As shown in Table 9, *Total Sugar* was positively related to age, depressive symptoms, and higher CVD prevalence. Additionally, total sugar was significantly related to male prevalence, and lower scores on all of the cognitive outcomes (verbal, spatial, memory and perceptual speed). *Dessert* was positively correlated with age, depressive symptoms, CVD incidence, and total sugar. It was also significantly related to poorer verbal, spatial, and perceptual speed performance. *Sweetened Beverages & Bread was* negatively related to gender, indicative of male prevalence ,and positively associated with total sugar. It was also negatively related to verbal, memory, and perceptual speed performance. *Sugar in Coffee* was positively associated with age, and negatively correlated with gender being male. Additionally, sugar in coffee consumption was negatively correlated with memory and perceptual speed performance.

Table 8: *Correlation Matrix of all Study Variables: Sugar Consumption as Continuous Variables*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	-												
2. Gender	.07	-											
3. Education	-.13**	-.14**	-										
4. Depressive Symptoms	.10*	.29***	-.12**	-									
5. CVD	.13**	.04	-.05	.17***	-								
6. Total Sugar	.15**	-.16**	-.03	.05	.10*	-							
7. Dessert	.11**	.01	-.06	.04	.04	.76***	-						
8. Sweetened Beverages & Bread	.02	-.13**	.05	.03	.10*	.50***	.01	-					
9. Sugar in Coffee	.13**	-.27***	-.004	-.02	.05	.42***	.01	.01	-				
10. Verbal	-.30***	-.18***	.48***	-.14**	-.15**	-.10*	-.07	-.07	-.01	-			
11. Spatial	-.44***	-.21***	.30***	-.20***	-.08*	-.11**	-.08	-.04	-.07	.55***	-		
12. Memory	-.34***	.10*	.31***	-.08	-.07	-.14**	-.04	-.10*	-.13**	.55***	.50***	-	
13. Perceptual Speed	-.54***	.01	.30***	-.14**	-.12**	-.18***	-.09*	-.10*	-.16**	.54***	.73***	.57***	-

Note. ***p<.001; **p<.01; *p<.05. CVD= Cardiovascular Disease.

Table 9: *Correlation Matrix of all Study Variables: Sugar Intake as Dichotomous Variables*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	-												
2. Gender	.07	-											
3. Education	-.13**	-.14**	-										
4. Depressive Symptoms	.10*	.29***	-.11**	-									
5. CVD	.13**	.04	-.05	.17***	-								
6. Total Sugar	.20**	-.11**	-.06	.09*	.16**	-							
7. Dessert	.09*	.05	-.04	.13**	.10*	.52***	-						
8. Sweetened Beverages & Bread	.05	-.13**	-.01	.01	.05	.40***	.08*	-					
9. Sugar in Coffee	.17**	-.28***	-.02	-.08	.04	.32***	-.05	.06	-				
10. Verbal	-.30***	-.18***	.48***	-.14**	-.15**	-.14**	-.08*	-.09*	-.002	-			
11. Spatial	-.44***	-.21***	.30***	-.20***	-.08*	-.12**	-.09*	-.07	-.08	.55***	-		
12. Memory	-.34***	.10*	.31***	-.08*	-.07	-.15**	-.06	-.09*	-.12**	.55***	.50***	-	
13. Perceptual Speed	-.54***	.01	.30***	-.14**	-.12**	-.20***	-.09*	-.13**	-.17**	.54***	.73***	.57***	-

Note. ***p<.001; **p<.01; *p<.05. CVD= Cardiovascular Disease

Covariates Based on Low and High Sugar Consumption

In order to assess specific differences between low and high consumption of each sugar variable across the covariates, a χ^2 analysis was conducted. Sugar consumption data were available for a total of 553 participants across each of the covariates. As shown in Table 10, there was a significant relationship between *Total Sugar* and gender, $\chi^2(1,553)=6.27$, $p<.05$. Here, it was found that, overall, there were more males in the high consumption group compared to males in the low consumption group, and more females in the low consumption versus high consumption group. There were more females compared to males in both high and low consumption groups. Those consuming high amounts were also more likely to have cardiovascular problems, $\chi^2(1,553)=14.26$, $p<.05$. Additionally, high sugar individuals were less educated, $\chi^2(1,553)=10.65$, $p<.05$. There were no significant differences between high and low sugar consumption individuals on depressive symptoms, $\chi^2(1,553)=0.01$, $p>.05$.

Table 10: *Covariates Based on Total Sugar*

Covariate	% Low Consumption (N=305)	% High Consumption (N=248)	*p*
Gender			
Male	35.1	45.6	.012
Female	64.9	54.4	
Education			
Elementary School	60.2	73.7	.001
High School or Higher	39.8	26.3	
Depressive Symptoms			
Low	90.2	89.9	.92
High	9.8	10.1	
CVD			
Absence	81.3	67.3	<.001
Presence	18.7	32.7	

Note. CVD = Cardiovascular Disease.

For *Dessert* consumption, as depicted in Table 11, results showed no significant relationship between gender, χ^2 (1,553)= 1.96, level of education, χ^2(1,553)= 2.27 and level of Dessert consumption (*p*'s > .05). However, there was a significant relationship between CVD status and consumption level, such that there was a higher presence of CVD among High Consumption individuals compared to Low Consumption counterparts, χ^2(1,553)= 5.49, $p < .05$. There were no significant differences between high and low consumption with regards to gender, χ^2 (1,553)= 1.52, education, χ^2 (1,553)= 2.27, or depressive symptoms, χ^2 (1,553)= 3.17 (*p*'s > .05).

Table 11: *Covariates Based on Dessert*

Covariate	% Low Consumption (N=304)	% High Consumption (N=249)	*p*
Gender			
Male	42.1	37.0	.218
Female	57.9	63.0	
Education			
Elementary School	63.3	69.4	.132
High School or Higher	36.7	30.6	
Depressive Symptoms			
Low	92.1	87.6	.075
High	7.9	12.4	
CVD			
Absence	79.0	70.3	.019
Presence	21.0	29.7	

Note. CVD = Cardiovascular Disease.

As shown in Table 12, for *Sweetened Beverages & Bread* consumption, results did show a significant relationship between gender and level of Sweetened Beverages & Bread consumption, where there were more males in the High Consumption category compared to males, $\chi^2(1,553)= 9.89$, $p < .05$. There were no significant relationship between education, $\chi^2(1,553)= 0.40$, CVD, $\chi^2(1,553)= 1.39$, depressive symptoms, $\chi^2(1,553)= 0.56$, and level of consumption on this sugar factor (p's > .05).

Table 12: *Covariates Based on Sweetened Beverages & Bread*

Covariate	% Low Consumption (N=336)	% High Consumption (N=217)	*p*
Gender			
Male	34.5	47.9	.002
Female	65.5	52.1	
Education			
Elementary School	65.0	67.6	.526
High School or Higher	35.0	32.4	
Depressive Symptoms			
Low	89.3	91.2	.250
High	10.7	8.8	
CVD			
Absence	76.8	72.4	.239
Presence	23.2	27.6	

Note. CVD = Cardiovascular Disease.

As shown in Table 13, for the *Sugar in Coffee* factor, results of the χ^2 analysis showed significant relationships between level of Added Sugar in Coffee consumption and gender, $\chi^2(1,553)= 44.61$, as well as education, $\chi^2(1,553)= 7.43$ (p's $< .05$). Results of the analysis revealed significantly more males in the High Consumption group compared to Low Consumption counterparts. Further, individuals in the high consumption group had lower depressive symptoms, $\chi^2(1,553)= 6.93$, and were less educated, $\chi^2(1,553)= 7.43$ (p's $< .05$), There were no significant relationship between CVD, $\chi^2(1,553)= 0.85$, $p > .05$, and level of consumption on this sugar factor.

Table 13: *Covariates Based on Sugar in Coffee*

Covariate	% Low Consumption (N=331)	% High Consumption (N=222)	*p*
Gender			
Male	28.4	56.8	<.001
Female	71.6	43.2	
Education			
Elementary School	61.5	72.7	.006
High School or Higher	38.5	27.3	
Depressive Symptoms			
Low	87.3	94.1	.009
High	12.7	5.9	
CVD			
Absence	76.4	73.0	.356
Presence	23.6	27.0	

Note. CVD= Cardiovascular Disease.

Model Outcomes: Fixed and Random Effect Parameter Estimates

Random effects growth models generate estimations of intercepts (estimates of average outcome values) and slopes (rate of change over time points), as well as random effects (variability around the intercepts and slopes; Singer, 1998).

As depicted in Table 14 and Figure 1A-D, there was a negative association between *Total Sugar* and average cognitive performance for all examined domains, suggesting that, on average, high sugar intake was associated with significantly lower cognitive performance relative to low total sugar intake, reflected by a significant negative estimate for the fixed effect corresponding to "sugar" in all of the models. For verbal, spatial, and speed domains, these associations were not explained by depressive

symptoms and/or cardiovascular health (since estimates remained significant after adjusting for these covariates). For the memory domain, controlling for depressive symptoms (Model 2), and depressive symptoms plus cardiovascular abnormalities (Model 4), reduced the association between total sugar intake and lower memory scores to non-significance. There were no significant age x sugar interaction terms, suggesting that low and high consumption individuals did not substantially differ in terms of age-related cognitive change.

Estimations of the random effects showed significant variability around the intercepts and slopes for each model across all of the cognitive domains, reflected by significant estimates of varI and varS in the tested models. These suggest the presence of additional variability around the average cognitive scores across people at initial testing, as well as in the average group differences between high and low sugar consumption individuals on cognitive performance, which could be accounted for by variables not included in the tested models. There were no significant estimates depicting the correlation between slopes and intercepts (i.e. Ris) in any of the tested models, suggesting no substantial relationship between mean cognitive performance and rates of cognitive change. Results also indicated significant estimates of the residual (i.e. Res) in all of the tested models, suggestive of additional overall variance not accounted for in the current models. For purposes of clarity of result presentation, only the fixed effects results for the remaining sugar variables are explicitly discussed below. However, both fixed and random effects data for the remaining sugar factors are shown in their respective tables.

As shown in Table 15 and Figure 2A-D, *Dessert* was negatively related to mean perceptual speed performance. This estimate was reduced to non-significance when depressive symptoms (Model 2) or both depressive symptoms and CVD (Model 4) were controlled for. All other cross-sectional associations between dessert consumption and cognitive performance were not significant. There was a significant age x sugar interaction in the Verbal domain. This finding indicates that high dessert consumption was related to improved performance with age compared with low consumption individuals, an estimate which was not explained by depressive symptoms and/or CVD.

As shown in Table 16 and Figure 3A-D, results showed that *Sweetened Beverages & Bread* was significantly related to worse average performance across the Verbal, Spatial, and Perceptual Speed domains (but not the memory domain), which were not explained by depressive symptoms and/or cardiovascular health. No significant interaction emerged, suggesting similar change in cognitive performance for participants with low and high intake of sweetened beverages and bread.

As shown in Table 17 and Figure 4A-D, *Sugar in Coffee* was related to poorer average spatial, memory and perceptual speed performance. These estimates remained significant after adjusting for depressive symptoms (Model 2) or both depressive symptoms and CVD (Model 4), suggesting that these covariates did not substantially contribute to the relationship. Controlling for just CVD (Model 3), however, reduced the association between sugar in coffee consumption and lower memory performance to non-significance.

Table 14: *Total Sugar Consumption and Cognitive Aging*

	Parameter Estimates							
	Fixed Effect (SE)				Random Effect (SE)[b]			
Cognitive Domain[a]	Intercept	Age	Sugar	Age*Sugar	varI	varS	Ris	Residual
Verbal								
Model 1	55.32(1.26)***	-0.12(0.02)***	-2.14(0.70)**	-0.02(0.04)	59.11(3.92)***	0.03(0.01)**	0.10(0.11)	10.72(0.50)***
Model 2	55.46(1.26)***	-0.12(0.02)***	-1.97(0.70)**	-0.02(0.04)	58.55(3.88)***	0.03(0.01)***	0.08(0.11)	10.72(0.51)***
Model 3	55.53(1.25)***	-0.12(0.02)***	-1.81(0.70)*	-0.02(0.04)	58.14(3.87)***	0.02(0.01)**	0.06(0.12)	10.72(0.51)***
Model 4	55.62(1.25)***	-0.12(0.02)***	-1.70(0.70)*	-0.02(0.04)	57.76(3.84)***	0.03(0.01)**	0.05(0.11)	10.73(0.51)***
Spatial								
Model 1	55.13(1.28)***	-0.40(0.03)***	-1.92(0.71)**	-0.02(0.05)	56.54(3.96)***	0.00(0.00)	-.001(0.00)	19.68(0.84)***
Model 2	55.45(1.27)***	-0.40(0.03)***	-1.64(0.71)**	-0.02(0.05)	55.15(3.91)***	0.02(0.01)	0.07(0.18)	19.14(0.92)***
Model 3	55.25(1.28)***	-0.40(0.03)***	-1.94(0.72)**	-0.02(0.72)	56.63(4.01)***	0.02(0.01)	0.13(0.18)	19.11 (0.92)***
Model 4	55.34(1.27)***	-0.40(0.03)***	-1.68(0.71)*	-0.01(0.71)	55.15(3.87)***	0.00(0.00)	-.002(0.00)	19.68(0.84)***
Memory								
Model 1	45.14(1.33)***	-0.26(0.03)***	-1.73(0.73)**	0.02(0.06)	58.88(4.34)***	0.03(0.02)**	-0.23(0.16)	26.16(1.23)***
Model 2	45.32(1.32)***	-0.26(0.03)***	-1.42(0.73)	0.03(0.06)	57.32(4.24)***	0.03(0.02)*	-0.29(0.16)	26.23(1.23)***
Model 3	45.26(1.33)***	-0.26(0.03)***	-1.55(0.74)*	0.02(0.06)	58.59(4.32)***	0.03(0.02)*	-0.25(0.16)	26.17(1.23)***
Model 4	45.40(1.32)***	-0.26(0.03)***	-1.31(0.74)	0.03(0.06)	57.19(4.23)***	0.03(0.02)*	-0.30(0.17)	26.23(1.23)***
Speed								
Model 1	46.59(1.22)***	-0.63(0.03)***	-2.40(0.68)**	-0.04(0.04)	51.07(3.73)***	0.05(0.02)***	0.19(0.11)	18.69(0.89)***
Model 2	46.87(1.20)***	-0.62(0.03)***	-2.11(0.67)**	-0.04(0.05)	49.43(3.63)***	0.05(0.02)***	0.16(0.11)	18.72(0.89)***
Model 3	46.64(1.22)***	-0.62(0.03)***	-2.34(0.68)**	-0.04(0.05)	51.02(3.73)***	0.05(0.02)**	0.19(0.11)	18.70(0.89)***
Model 4	46.88(1.21)***	-0.62(0.03)***	-2.11(0.68)**	-0.04(0.05)	49.43(3.63)***	0.05(0.02)***	0.16(0.11)	18.72(0.89)***

Note. ***p<.001; **p<.01; *p<.05

[a]Model 1 reflects an unconditional model, Model 2 adjusted for depressive symptoms, Model 3 adjusted for CVD, Model 4 adjusted for depressive symptoms and CVD. All models were adjusted for baseline age, gender and education.

[b]varI=variance around the intercept, varS= variance around age, Ris=covariance between intercept and time, and Residual indicates residual variance.

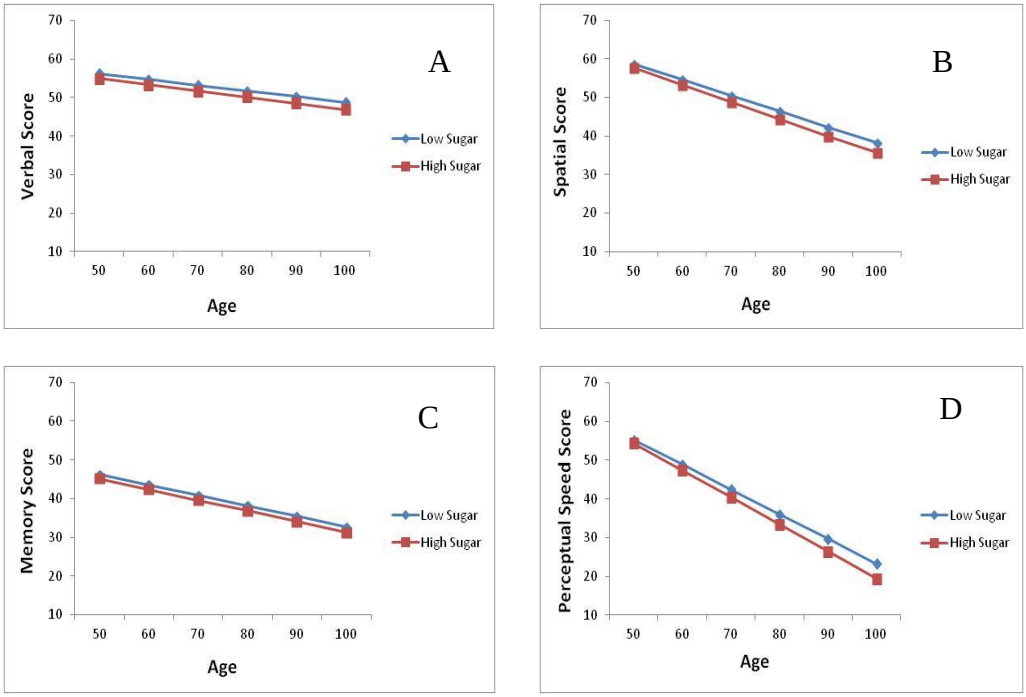

Figure 1: Total Sugar Consumption & Cognitive Performance

Table 15: *Dessert Consumption and Cognitive Aging*

	Parameter Estimates							
	Fixed Effect (SE)				Random Effect (SE)[b]			
Cognitive Domain[a]	Intercept	Age	Sugar	Age*Sugar	varI	var5	Ris	Residual
Verbal								
Model 1	54.26(1.21)***	-0.15(0.02)***	-0.90(0.70)	0.08(0.03)*	60.32(3.94)***	0.00(0.00)	-0.03(0.00)	11.52(0.48)***
Model 2	54.56(1.21)***	-0.16(0.02)***	-0.76(0.70)	0.08(0.04)*	58.93(3.90)***	0.02(0.01)**	0.10(0.12)	10.75(0.51)***
Model 3	54.70(1.21)***	-0.15(0.02)***	-0.69(0.69)	0.08(0.03)*	59.11(3.87)***	0.00(0.00)	-0.02(0.00)	11.52(0.48)***
Model 4	54.87(1.20)***	-0.16(0.02)***	-0.60(0.69)	0.08(0.04)*	57.96(3.85)***	0.02(0.01)**	0.06(0.12)	10.75(0.51)***
Spatial								
Model 1	54.48(1.22)***	-0.42(0.03)***	-1.30(0.71)	0.02(0.05)	56.95(4.03)***	0.02(0.01)	0.14(0.18)	19.12(0.92)***
Model 2	54.71(1.21)***	-0.41(0.03)***	-1.00(0.70)	0.02(0.04)	55.39(3.89)***	0.00(0.00)	-.001(0.00)	19.69(0.84)***
Model 3	54.39(1.23)***	-0.41(0.03)***	-1.25(0.71)	0.02(0.04)	56.85(3.98)***	0.00(0.00)	-.001(0.00)	19.70(0.84)***
Model 4	54.68(1.22)***	-0.41(0.03)***	-1.01(0.70)	0.02(0.04)	55.38(3.89)***	0.00(0.00)	-.001(0.00)	19.70(0.84)***
Memory								
Model 1	44.24(1.28)***	-0.27(0.03)***	-0.28(0.73)	0.03(0.05)	59.44(4.37)***	0.03(0.02)*	-0.24(0.16)	26.17(1.23)***
Model 2	44.54(1.27)***	-0.27(0.03)***	-0.29(0.72)	0.03(0.05)	57.69(4.26)***	0.03(0.02)*	-0.30(0.17)	26.23(1.23)***
Model 3	44.48(1.28)***	-0.26(0.03)***	-0.27(0.73)	0.03(0.05)	59.04(4.35)***	0.03(0.02)*	-0.25(0.16)	26.18(1.23)***
Model 4	44.69(1.27)***	-0.26(0.03)***	-0.23(0.73)	0.03(0.05)	57.51(4.29)***	0.03(0.02)*	-0.31(0.17)	26.25(1.23)***
Speed								
Model 1	45.57(1.17)***	-0.62(0.03)***	-1.44(0.68)*	-0.05(0.05)	51.87(3.79)***	0.05(0.02)**	0.19(0.11)	18.66(0.89)***
Model 2	45.97(1.16)***	-0.62(0.03)***	-1.16(0.68)	-0.05(0.05)	50.07(3.68)***	0.05(0.02)**	0.16(0.11)	18.69(0.89)***
Model 3	45.71(1.17)***	-0.62(0.03)***	-1.38(0.68)*	-0.05(0.04)	51.74(3.78)***	0.05(0.02)**	0.19(0.11)	18.67(0.89)***
Model 4	46.01(1.16)***	-0.62(0.03)***	-1.14(0.67)	-0.05(0.05)	50.04(3.67)***	0.05(0.02)***	0.15(0.11)	18.69(0.89)***

Note. ***p<.001; **p<.01; *p<.05

[a]Model 1 reflects an unconditional model, Model 2 adjusted for depressive symptoms, Model 3 adjusted for CVD, Model 4 adjusted for depressive symptoms and CVD. All models were adjusted for baseline age, gender and education.

[b]varI=variance around the intercept, varS= variance around age, Ris=covariance between intercept and time, and Residual indicates residual variance.

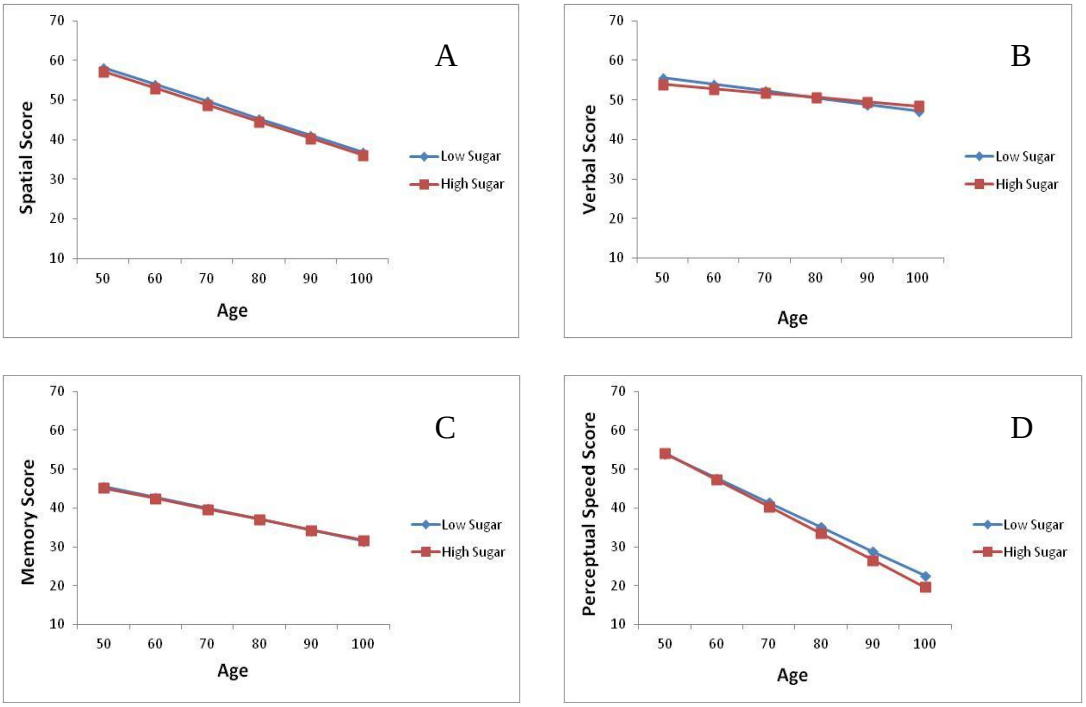

Figure 2: Dessert Consumption & Cognitive Performance

Table 16: *Sweetened Beverages & Bread Consumption and Cognitive Aging*

	Parameter Estimates							
	Fixed Effect (SE)				Random Effect (SE)[b]			
Cognitive Domain[a]	Intercept	Age	Sugar	Age*Sugar	varI	var5	Ris	Residual
Verbal								
Model 1	55.13(1.26)***	-0.13(0.02)***	-2.00(0.71)**	0.01(0.03)	59.95(3.92)***	0.05(0.01)***	0.07(0.08)	9.28(0.45)***
Model 2	55.44(1.25)***	-0.13(0.02)***	-1.93(0.71) **	0.01(0.04)	57.12(3.83)***	0.05(0.01)***	0.05(0.08)	9.28(0.45)***
Model 3	55.60(1.25)***	-0.13(0.02)***	-1.87(0.71)**	0.01(0.04)	56.32(3.78)***	0.06(0.01)***	0.03(0.08)	9.27(0.45)***
Model 4	55.73(1.87)***	-0.13(0.02)***	-1.82(0.70)**	0.01(0.04)	56.05(3.77)***	0.06(0.01)***	0.02(0.08)	9.26(0.45)***
Spatial								
Model 1	54.94(1.28)***	-0.40(0.03)***	-1.67(0.72)*	-0.01(0.04)	56.93(3.98)***	0.00(0.00)	-0.01(0.00)	18.55(0.80)***
Model 2	55.40(1.88)***	-0.41(0.03)***	-1.56(0.72) *	-0.01(0.05)	55.65(3.89)***	0.00(0.00)	-0.01(0.00)	18.54(0.80)***
Model 3	54.98(1.28)***	-0.40(0.03)***	-1.66(0.72)*	.0001(0.04)	56.92(3.98)***	0.00(0.00)	-0.01(0.00)	18.54(0.80)***
Model 4	55.30(1.27)***	-0.40(0.03)***	--1.58(0.72)*	-.004(0.04)	55.64(3.90)***	0.00(0.00)	-0.01(0.00)	18.54(0.80)***
Memory								
Model 1	44.69(1.33)***	-0.27(0.03)***	-1.01(0.74)	0.05(0.06)	59.13(4.38)***	0.04(0.02)*	-0.15(0.13)	25.46(1.22)***
Model 2	45.00(1.32)***	-0.27(0.03)***	-0.88(0.74)	0.05(0.05)	57.73(4.29)***	0.04(0.02)*	-0.21(0.13)	25.53(1.22)***
Model 3	44.91(1.33)***	-0.26(0.03)***	-0.92(0.75)	0.05(0.05)	58.66(4.35)***	0.04(0.02)*	-0.17(0.13)	25.51(1.22)***
Model 4	45.14(1.32)***	-0.26(0.03)***	-0.83(0.74)	0.05(0.05)	57.47(4.27)***	0.04(0.02)*	-0.22(0.13)	25.52(1.22)***
Speed								
Model 1	46.42(1.22)***	-0.67(0.03)***	-2.02(0.69)**	0.08(0.05)	52.66(3.79)***	0.07(0.02)***	0.18(0.09)*	15.31(0.77)***
Model 2	46.85(1.20)***	-0.67(0.03)***	-1.92(0.68)**	0.07(0.05)	51.23(3.70)***	0.07(0.02)***	0.15(0.09)	15.32(0.77)***
Model 3	46.55(1.22)***	-0.67(0.03)***	-1.98(0.69)**	0.08(0.05)	52.51(3.78)***	0.07(0.02)***	0.18(0.08)	15.34(0.77)***
Model 4	46.89(1.20)***	-0.67(0.03)***	-1.91(0.68)**	0.08(0.05)	51.20(3.70)***	0.07(0.02)***	0.15(0.09)	15.33(0.77)***

Note. ***p<.001; **p<.01; *p<.05

[a]Model 1 reflects an unconditional model, Model 2 adjusted for depressive symptoms, Model 3 adjusted for CVD, Model 4 adjusted for depressive symptoms and CVD. All models were adjusted for baseline age, gender and education.

[b]varI=variance around the intercept, varS= variance around age, Ris=covariance between intercept and time, and Residual indicates residual variance.

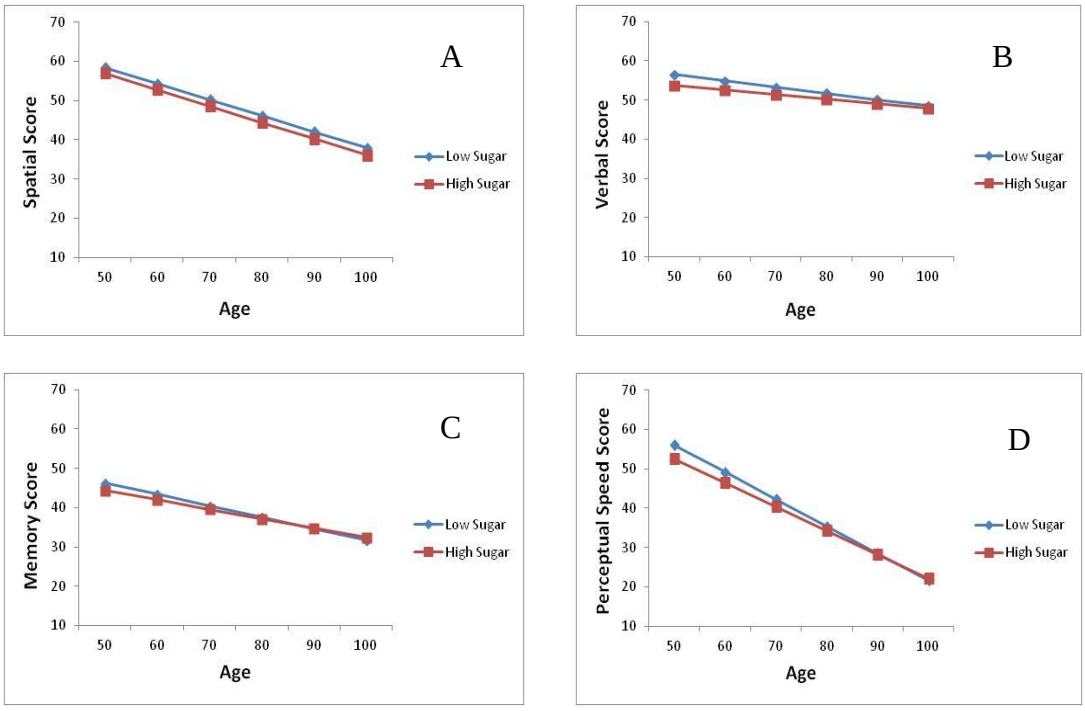

Figure 3: Sweetened Beverages & Bread Consumption and Cognitive Performance

Table 17: *Sugar in Coffee Consumption and Cognitive Aging*

	Parameter Estimates							
	Fixed Effect (SE)				Random Effect (SE)[b]			
Cognitive Domain[a]	Intercept	Age	Sugar	Age*Sugar	varI	var5	Ris	Residual
Verbal								
Model 1	54.28(1.35)***	-0.11(0.02)***	-0.45(0.74)	-0.03(0.03)	58.61(3.92)***	0.06(0.01)***	0.05(0.08)	9.28(0.45)***
Model 2	54.64(1.91)***	-0.12(0.02)***	-0.47(0.74)	-0.03(0.04)	58.05(3.89)***	0.06(0.01)***	0.04(0.08)	9.28(0.45)***
Model 3	54.71(1.35)***	-0.11(0.02)***	-0.34(0.73)	-0.03(0.03)	57.21(3.84)***	0.06(0.01)***	0.02(0.08)	9.27(0.45)***
Model 4	54.93(1.34)***	-0.12(0.02)***	-0.37(0.73)	-0.03(0.04)	56.91(3.82)***	0.06(0.01)***	0.01(0.08)	9.27(0.45)***
Spatial								
Model 1	55.47(1.36)***	-0.40(0.03)***	-1.80(0.74)*	-0.01(0.05)	56.96(3.98)***	0.00(0.00)	-0.01(0.00)	18.52(0.80)***
Model 2	55.96(1.35)***	-0.40(0.03)***	-1.82(0.73) *	-.004(0.05)	55.62(3.90)***	0.00(0.00)	-0.01(0.00)	18.52(0.80)***
Model 3	55.51(1.37)***	-0.40(0.03)***	-1.79(0.74)*	-0.01(0.05)	56.97(3.98)***	0.00(0.00)	-0.01(0.00)	18.51(0.80)***
Model 4	56.00(1.36)***	-0.40(0.03)***	-1.82(0.74)*	-0.01(0.05)	55.61(3.89)***	0.00(0.00)	-0.01(0.00)	18.52(0.80)***
Memory								
Model 1	45.38(1.42)***	-0.23(0.03)***	-1.52(0.77)*	-0.06(0.06)	59.10(4.37)***	0.04(0.02)*	-0.19(0.13)	25.47(1.22)***
Model 2	45.80(1.41)***	-0.23(0.03)***	-1.53(0.76)*	-0.05(0.06)	57.66(4.28)***	0.04(0.02)*	-0.24(0.14)	25.53(1.22)***
Model 3	45.61(1.42)***	-0.22(0.03)***	-1.46(0.77)	-0.06(0.06)	58.67(4.34)***	0.04(0.02)*	-0.21(0.14)	25.50(1.22)***
Model 4	45.94(1.41)***	-0.23(0.03)***	-1.49(0.76)^	-0.08(0.05)	57.41(4.27)***	0.04(0.02)*	-0.25(0.14)	25.52(1.22)***
Speed								
Model 1	46.43(1.30)***	-0.63(0.03)***	-1.57(0.72)*	-0.03(0.05)	53.12(3.82)***	0.08(0.02)***	0.15(0.09)	15.24(0.76)***
Model 2	47.00(1.29)***	-0.63(0.03)***	-1.61(0.71)*	-0.01(0.05)	51.57(3.73)***	0.08(0.02)***	0.12(0.09)	15.25(0.76)***
Model 3	46.57(1.31)***	-0.63(0.03)***	-1.54(0.72)*	-0.03(0.05)	52.98(3.81)***	0.08(0.02)***	0.15(0.09)	15.26(0.76)***
Model 4	47.05(1.30)***	-0.63(0.03)***	-1.60(0.71)*	-0.02(0.05)	51.54(3.73)***	0.08(0.02)***	0.12(0.09)	15.25(0.76)***

Note. ***p<.001; **p<.01; *p<.05, p=.05

[a]Model 1 reflects an unconditional model, Model 2 adjusted for depressive symptoms, Model 3 adjusted for CVD, Model 4 adjusted for depressive symptoms and CVD. All models were adjusted for baseline age, gender and education.

[b]varI=variance around the intercept, varS= variance around age, Ris=covariance between intercept and time, and Residual indicates residual variance.

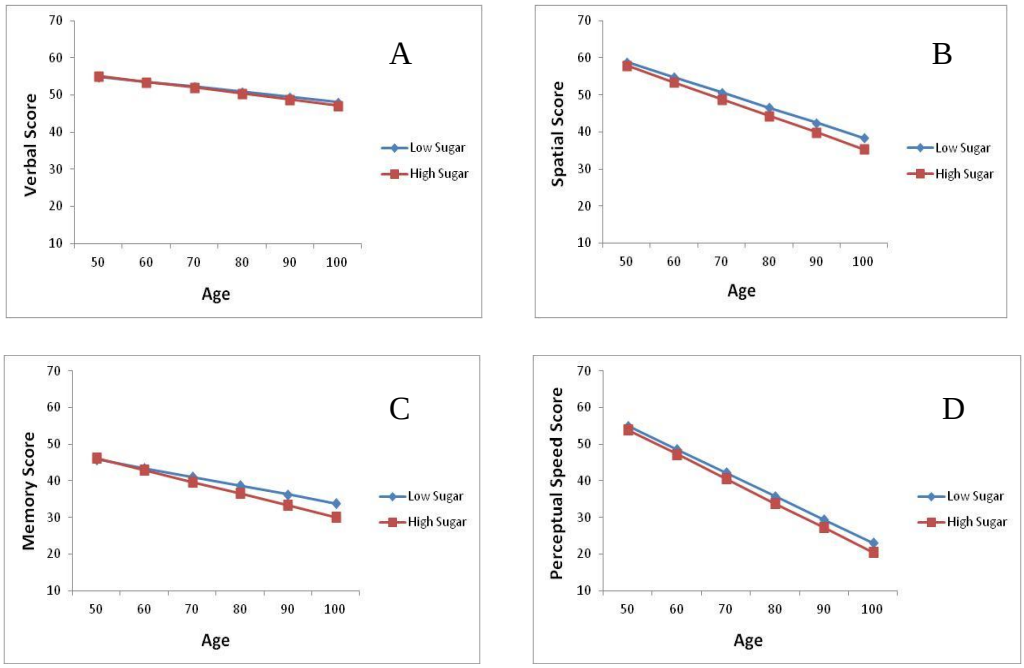

Figure 4: Sugar in Coffee Consumption and Cognitive Performance

Mediation

As shown in Table 18, results of the mediation analyses showed that CVD mediated the relationship between *Total Sugar* and verbal performance, as the bootstrap estimate was significantly different from zero with 95% confidence. However, there was no mediating effect of CVD in the relationship between high total sugar and spatial, memory and perceptual speed performance.

Table 18: *Mediation of CVD in Total Sugar Influence on Cognitive Performance*

	Cognitive Domain			
	Verbal	Spatial	Memory	Perceptual Speed
Bootstrap Estimate	-0.37	-0.16	-0.17	-0.21
95% CI [LL,UL]	[-0.77, -.08]	[-0.50, 0.13]	[-0.51, 0.11]	[-0.56, 0.05]
Mediation by CVD?	Yes	No	No	No

Note. CI= Confidence Interval. CVD= Cardiovascular Disease. LL= lower limit. UL= upper limit.

As indicated in Table 19, results of the analyses showed that CVD mediated the relationship between *Dessert* and verbal impairment. However, CVD was not found to mediate the effect of high dessert consumption on lower spatial, memory, and perceptual speed performance.

Table 19: *Mediation of CVD in Dessert Influence on Cognitive Performance*

	Cognitive Domain			
	Verbal	Spatial	Memory	Perceptual Speed
Bootstrap Estimate	-0.26	-0.11	-0.14	-0.18
95% CI [LL,UL]	[-0.58, -.03]	[-0.38, 0.06]	[-0.43, 0.03]	[-0.45, 0.02]
Mediation by CVD?	Yes	No	No	No

Note. CI= Confidence Interval. CVD= Cardiovascular Disease. LL= lower limit. UL= upper limit.

In Table 20, *Sweetened Beverages & Bread* results showed that CVD did not mediate any of the relationships between consumption on this factor and cognitive performance. Similarly, Table 21 shows that CVD was not a significant mediator in the relationship between *Sugar in Coffee* and performance across any of the cognitive measures.

Table 20: *Mediation of CVD in Sweetened Beverages & Bread Influence on Cognitive Performance*

	Cognitive Domain			
	Verbal	Spatial	Memory	Perceptual Speed
Bootstrap Estimate	-0.13	-0.06	-0.08	-0.08
95% CI [LL,UL]	[-0.42, 0.09]	[-0.27, 0.06]	[-0.28, 0.05]	[-0.31, 0.08]
Mediation by CVD?	No	No	No	No

Note. CI= Confidence Interval. CVD= Cardiovascular Disease. LL= lower limit. UL= upper limit.

Table 21

Mediation of CVD in Sugar in Coffee Effect on Cognitive Performance

	Cognitive Domain			
	Verbal	Spatial	Memory	Perceptual Speed
Bootstrap Estimate	-0.10	-0.05	-0.41	-0.08
95% CI [LL,UL]	[-0.39, 0.12]	[-0.22, 0.07]	[-0.22, 0.10]	[-0.29, 0.07]
Mediation by CVD?	No	No	No	No

Note. CI= Confidence Interval. CVD= Cardiovascular Disease. LL= lower limit. UL= upper limit

Chapter 4: Discussion

There has been increased focus on the detrimental effects of dietary sugar on promoting physical disorders such as CVD and related risk factors, such as type II diabetes (Popkin & Nielsen, 2003). In recent years, there has also been a growing interest in examining the relationship between sugar consumption, physiological abnormalities and cognitive health (Awad, et al., 2004; Benton, et al., 2003; Molteni, et al., 2004; Newman, et al., 2005;). However, there is a lack of research investigating the specific influence of dietary sugar on longitudinal cognitive change, which is important in the study of aging populations.

The main hypothesis of this study was that high sugar consumption would be significantly related to poorer cognitive performance, as well as steeper trajectories of cognitive decline relative to low consumption, over a 16 year period in a population of Swedish adults ranging from 50 to 96 years old at baseline assessment. Sugar consumption was assessed with a composite *Total Sugar* variable, which was used as the main independent variable. In addition, sugar intake was measured using 3 other latent factors: *Dessert* (ice cream, cake, pastries), *Sweetened Beverages & Bread* (sweetened juice, white bread), and *Sugar in Coffee* (added sugar in coffee). Cognitive performance was measured across four cognitive domains: Verbal (general knowledge, synonyms, analogies), Spatial (Figure Logic, Block Design, Card Rotation), Memory (Digit Span, Picture Recognition, Visual Recall) and Perceptual Speed (Digit Symbol, Figure Identification).

A secondary hypothesis was that high consumption measured by the four sugar factors would be specifically related to poorer performance and decline on hippocampus-dependent tasks (Spatial, Memory), although performance across the other two cognitive domains (Verbal, Perceptual Speed) were also examined. Additionally, it was expected that relationships between high sugar consumption and cognitive deficits would be mediated by CVD.

Total Sugar

The results indicated that high (i.e., above median) total sugar consumption was significantly related to poorer overall verbal, spatial, memory, and perceptual speed performance, controlling for age, gender, education, depressive symptoms and CVD . However, there were no significant differences in rates of cognitive decline between high and low consumption. Therefore, findings confirmed the hypothesis in showing that sugar consumption was related to poorer cognitive abilities controlling for several potentially important covariates, whereas they offered no support for the expectation that total sugar consumption would accelerate cognitive decline into older adulthood.

The lack of significant associations between total sugar and age-related cognitive decline may be a reflection of how and when the data were collected. One possibility is that the testing of the participants may have begun at a point superseding substantial cognitive decline. Dietary habits tend to be established early in life. Those with high consumption of sugar rich foods may have been experiencing accelerated cognitive aging for years or even decades prior to their 50^{th} year—the first year participants were eligible for cognitive assessment. It may be that if baseline cognitive performance were

established somewhat earlier in life, higher rate of cognitive decline may have been observed in those with high sugar consumption. The cross-sectional analyses, which were adjusted for several important covariates, provide some, albeit tentative, evidence for this notion. Future studies should consider baseline cognitive assessment prior to 50 years of age. Additionally, diet was only assessed at a single time point, prior to the initiation of in-person testing. Although the questions were intended to capture long-term dietary habits, it is possible that changes in patterns of dietary sugar took place during the testing phase of the study, which may have affected cognitive performance in subsequent waves of data collection. However, this is unlikely during the stages of life considered here, since dietary habits tend to be well established in young adulthood (Mikkila, Rasanen, Raitakari, Pietinen, & Viikari, 2005). One possibility is that diminishing sugar consumption with age may have led to a reduced variability in sugar consumption after baseline.

The results indicating relationships between high total sugar consumption and poorer overall cognitive performance support work indicating that diets high in refined sugars may impair performance across various cognitive outcomes in both humans (Benton, et al., 2003; Ingwersen, et al., 2007; Lloyd, et al., 1994; Nabb & Benton, 2006), and animals (Jurdak, et al., 2008; Jurdak & Kanarek, 2009; Kanoski & Davidson, 2010). High sugar intake has also been shown to impair brain processes governing cognitive processes, such as declarative memory (Bramham & Messaoudi, 2005; Lindqvist, et al., 2006;Molteni, et al., 2002**;**Molteni, et al., 2004**;** Tao, et al., 1998;Wu, et al., 2003), which are supported by results of the current study.

It is possible that high sugar consumption, likely reflecting lifelong dietary habits, may have adversely affected cognitive performance through chronic elevations in blood sugar, insulin resistance and oxidative stress responses, which have all been shown to inhibit synaptic plasticity (Molteni, et al., 2004; Stranahan, et al., 2008; Schubert, et al., 2004;Wu, et al., 2004). Additionally, it is possible that the development of AGEs, which have been found in AD brains (Martins, et al., 2006) could have been an underlying process involved in the observed relation between total sugar intake and cognitive deficits. Even though dementia-related changes were not a focus of this specific study, the development of AGEs may have still influenced poorer cognition through neurotoxicity (Takeuchi, Bucala, Suzuki, Ohkubo, et al., 2000).

The results confirmed the hypothesis that high sugar consumption would be associated with worse performance specifically in the Spatial and Memory domains, which were thought to be predominantly hippocampus-mediate tasks, although these tests require several forms of processing. The findings also showed significant associations between high total sugar intake and poorer verbal and perceptual speed performance compared to low consumption . These findings are not surprising since verbal abilities were based on tests of general knowledge-based memory, and identification of synonyms, which require individuals to utilize some memory processes. Additionally, Figure Identification, a test contained in the perceptual speed domain, also requires individuals to utilize memory. Therefore, these findings contribute to previous research indicating that dietary sugar inhibit hippocampus-dependent processing (Ingwersen et al., 2007; Jurdak & Kanarek, 2009; Stranahan et al., 2008), although, again, these observed deficits may also be indicative of poor general cognitive abilities. Dietary sugar has also

been found to produce deficits in reaction time in health individuals (Lloyd, et al., 1994) and deficits on tests of verbal (Kanaya, et al., 2004) and processing speed capabilities (Manschot, et al., 2006) in type II diabetics, results which are supported by the current findings.

The associations between high total sugar consumption and poor cognitive performance remained significant after adjusting for age, gender, education, depressive symptoms and CVD, which can all independently contribute to cognitive impairment (Anstey & Christensen, 2000; Ardila, et al., 2000; Hyde & Plant, 1995; Wilson, et al., 2002;Verhaeghen & Salthouse, 1997), and alter sugar intake (Epel, et al., 2000; Galobardes, et al., 2001; Rolls, 1999; Kazes, et al., 1993). There were more females among high total sugar consumption individuals in this sample compared to low consumption counterparts. Additionally, high consumption individuals were less educated, and had greater occurrence of CVD. Further, there were significant correlations between high total sugar intake and age, more depressive symptoms, and more CVD incidences. Therefore, the fact that relationships were still present in fully adjusted models allows for a more valid conclusion that sugar intake was specifically related to cognitive deficits independent of these potentially confounding variables. There was, however, no observed correlation between high total sugar consumption and education levels. This may have been driven by the lack of normality when examining the distribution of the total sugar variable. This being said, lower education levels in the high consumption compared to the low consumption group in the χ^2 analysis, where the sugar variable was dichotomized, point to the importance of including education as a covariate in the models.

The association between total sugar consumption and memory deficits was eliminated in the model where depressive symptoms were added as a covariate in the statistical model (i.e. Model 2, Table 14), as well as when both CVD and depressive symptoms were controlled for (i.e. Model 4, Table 14). These findings suggest that depressive symptoms may have played a role in influencing the relationship between sugar intake and memory performance supporting research showing depressive symptoms to alter patterns of sugar consumption (Kazes, et al., 1993**;**Rogers, 1995**)**, and be related to memory deficits (Burt, et al., 1995; Wilson, et al., 2002)**.** Therefore, depressive symptoms, which were correlated with total sugar in the sample, may explain the association between high total sugar intake and low cognitive performance.

Dessert

High dessert consumption was significantly related to poorer overall perceptual speed performance, These findings support research indicating that refined sugar consumption relates to deficits in reaction time (Lloyd, et al., 1994). Even though there is limited work examining how dietary sugar affects perceptual speed, existing evidence indicates that type II diabetics demonstrate cognitive deficits across tests of processing speed and reaction time (Awad, et al., 2004; Manschot, et al., 2006). The association between high dessert consumption and poorer perceptual speed scores may be the result of inhibitions of pre-frontal cortex (PFC) activity, which plays an important role in executive functioning (Floresco & Jentsch, 2011; Koechlin & Summerfield, 2007;). Deficits in executive functioning capabilities may, in turn, help to explain poor processing speed performance (Albinet, Boucard, Bouquet, & Audiffren, 2012). This

notion supports work indicating that type II diabetics demonstrate poorer performance on tests of executive functioning (Stewart & Liolitsa, 1999; van Harten, et al., 2007). Additionally, animals maintained on high refined sugar diets exhibits significant increases in oxidative stress in the PFC (Souza, et al., 2007), changes which can lead to cellular damage (Baynes, 1991).

The results also indicated that depressive symptoms may have played some role in either influencing perceptual speed performance, or altering sugar consumption, since the association between dessert and perceptual speed effect was eliminated when depressive symptoms (Model 2, Table 15), or depressive symptoms along with CVD (Model 4, Table 15) were controlled for. Other unmeasured environmental factors may have also played a role. The interrelation of dessert consumption and depressive symptoms in relation to cognition should be further examined in future research. The effect remained significant after adjusting for CVD (Model 3: Table 15), suggesting that this factor did not play a substantial role in cognitive differences observed in relation to dessert consumption.

Results showed no significant relationships between high dessert consumption and cognitive performance across the verbal, spatial, and memory domains. This could perhaps be explained by differential performance across short-term or working versus long-term memory tasks. For instance, the Memory domain included a Digit Span test (reproduction of digits in a correct sequential order), and spatial testing included Figure Logic (identification of a figure different from a target figure), which may be considered short-term or working memory tasks. Therefore, it is possible that high sugar plays a more important role in long-term compared to short-term or working memory tasks. This

idea is supported by work indicating that high sugar diets may impair predominantly hippocampus-dependent tasks shown in the animal literature (Stranahan et al., 2008). To this points, researchers suggest that short-term tasks may not require as much hippocampus involvement compared to long-term memory tasks (Cave & Squire, 1992), although this requires further investigation utilizing more tests of both short-term, working, and long-term memory tests in each domain.

The lack of significant associations between dessert consumption and verbal, spatial, and memory performance may also have been the result of the nature in which Dessert was specified as a latent factor comprised of ice cream and cake consumption. To this point, a recent epidemiological study showed that ice cream consumption was associated with greater levels of global cognitive decline at a 13 year follow-up test, an effect not produced by cake and pastry consumption (Vercambre, Boutron-Ruault, Ritchie, Clavel-Chapelon, & Berr, 2009). Additionally, previous research showed that cake consumption produced greater insulin and plasma glucose responses compared with eating ice cream (Crapo, Scarlett, Kolterman, Sanders, et al., 1982), possibly due to differences between sucrose and fructose-induced responses (Akgun & Ertel, 1985;Lee & Wolever, 1998). In fact, investigators showed that ice cream and cake made with sucrose produced significant elevations in plasma glucose compared with these foods made with fructose (Vercambre, et al., 2009). Elevations in blood sugar, in turn, may contribute to oxidative stress responses (Souza, et al., 2007) and cognitive deficits (Stephan, et al., 2010). Therefore, it is possible that cake consumption, analyzed separately from ice cream, may have produced differences in verbal, spatial, or memory performance when comparing high versus low consumption.

However, It must be noted that previous investigators only utilized one assessment of global cognition (Vercambre, et al., 2009). Therefore, conclusions may not generalize across studies due to methodological differences.

High dessert consumption was significantly related to a *slower* rate of decline in verbal performance compared to low consumption in all of the tested statistical models. Though this finding may seem counterintuitive, it may be explained by the attenuation of psychological stress by dessert consumption. Depressive symptoms, which was positively related to dessert consumption, are often accompanied by chronic psychological stress (Cohen, Kamarck, & Mermelstein, 1983;Pruessner, Hellhammer, Pruessner, & Lupien, 2003). Chronic stress has been shown to impair performance across several cognitive domains, including memory in both humans (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996;Kuhlmann, Piel, & Wolf, 2005) and animals (Conrad, Galea, Kuroda, & McEwen, 1996;Park, Campbell, & Diamond, 2001), as well as inhibit hippocampal plasticity (McEwen, 1999). In the current study, people may have utilized dessert consumption as a source of "comfort food" (Dallman, Pecoraro, Akana, La Fleur, et al., 2003; Wansink, Cheney, & Chan, 2003) to reduce stress-induced responses. This notion is supported by studies indicating that consumption of sugar-laden "comfort food" was effective in ameliorating stress-induced responses (Dube, LeBel, & Lu, 2005; Dallman, Pecoraro, & la Fleur, 2005; Ortolani, Oyama, Ferrari, Melo, & Spadari-Bratfisch, 2011; Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004). Therefore, high dessert consumption may have contributed to an attenuation of stress-induced declines in verbal performance due to an enhanced "comfort food" effect and, hence, produced the observed attenuation of declines in verbal scores.

Sweetened Beverages & Bread

Sweetened Beverages & Bread was specified as a latent factor comprised of juice, soda, and white bread. Results showed that high consumption was related to poorer overall performance across the verbal, spatial, and perceptual speed domains which, again, confirmed the study hypothesis and supported findings indicating that dietary sugar is related to deficits in these domains (Nabb & Benton, 2006; Stewart & Liolitsa, 1999). Some assessments of verbal (e.g. general knowledge, analogies) and spatial (e.g. Block Design) capabilities can be viewed as tapping into long-term recall and spatial reproduction abilities. These deficits may also be explained by the observed deficiencies in perceptual speed capabilities. Salthouse's seminal paper introducing the speed of processing hypothesis suggests that declines in processing speed may explain all cognitive deficits, especially in older adults (Salthouse, 1996). In fact, reports indicate that controlling for processing speed produces substantial reductions, or even eliminations of deficits across tests of, for instance, memory (Clarys, Isingrini, & Gana, 2002) and spatial capabilities (Finkel, Reynolds, McArdle, & Pedersen, 2007). These findings provide support for the theory that the slowing of processing speed capabilities may be the most important factor in explaining cognitive deficits, especially in the context of aging populations (Albinet, et al., 2012). Therefore, observed deficits in perceptual speed may, in fact, serve to be an explanation for poorer performance in the other cognitive domains.

The observed deficits in relation to high sweetened beverage & bread consumption may be strongly influenced by the presence of high fructose corn syrup. Cognitive impairment, associated with the ingestion of high fructose corn syrup, often present in soda (Bray, Nielsen, & Popkin, 2004; Hu & Malik, 2010;Popkin & Nielsen, 2003), has been found to detrimentally affect hippocampus-dependent tasks (Jurdak & Kanarek, 2009;Ross, Bartness, Mielke, & Parent, 2009). In addition, soda can produce high plasma glucose and insulin responses, based on its high glycemic load (Willett, Manson & Liu, 2002). High GL foods, in turn, have been related to memory impairment (Greenwood, et al., 2003), as well as increases in oxidative stress (Ceriello, Bortolotti, Motz, Pieri, et al., 1999;Hu, Block, Norkus, Morrow, et al., 2006**)**, which could have contributed to the observed deficits through disruptions in cellular activity.

Unexpectedly, the results failed to show a significant influence of sweetened beverage and bread consumption on the Memory domain. This may have been due to the nature of memory testing employed in the study. As mentioned earlier, for memory testing, participants were tested on their ability to orally recall presented digits in a correct order (Digit Span), recognize pictures presented to them (Picture Memory), and to recall name and faces, all of which were short-term memory tests. It is possible that short-term memory was not sufficiently affected by sweetened beverages and bread consumption, since some evidence suggests that short-term processing is less hippocampus-dependent (Cave & Squire, 1992; Kim, Rison, & Fanselow, 1993).

Therefore, the results could be suggestive of high sweetened beverage and bread intake relating to deficits in long-term memory (e.g. Verbal), but failing to show any influence on short-term memory (e.g. Memory). Again, future studies should aim to employ direct tests of both short-term and long-term memory.

Deficits in verbal, spatial, and perceptual speed performance produced by Sweetened Beverages & Bread were not observed with Dessert. Sweetened Beverages & Bread was assessed as consumption in terms of glasses/day or slices/day. The variables comprising Dessert, on the other hand, were assessed in terms of frequency of ingestion (e.g. frequency of eating ice cream/week, frequency of eating/month). Based on how the questions were phrased to participants, it is unclear as to the *quantity* of dessert consumption. For instance, an individual could eat a small portion of ice cream daily, but still have been categorized into the high consumption group based on their high frequency of consumption. On the other hand, a person may eat very large ice cream portions, but only consume it 3 days a month, which would lead to them being miss-classified as low consumers based on their low frequency of consumption. Therefore, frequency may not have been the best measure of high and low consumption. Since high and low consumption of dessert consumption was perhaps not well-defined, this could have contributed to the lack of relation between high dessert intake and performance across the verbal, spatial and perceptual speed domains. In fact, there is some evidence suggesting that high frequency carbohydrate snacking may be beneficial in terms of weight gain (Kirk, 2000), which is a risk factor for physiological disorders, such as T2D (Mokdad, Ford, Bowman, Dietz, et al., 2003), which can, in turn, relate to cognitive dysfunction (Gregg, et al., 2000).

The interrelationships between the frequency and quantity of consumption of refined sugars and cognitive performance, however, require further study. It is important for future investigations to aim for consistency in terms of the nature of questions assessing consumption to better compare differences between types of foods consumed in relation to cognitive performance.

Added Sugar in Coffee

High consumption of sugar in coffee was significantly related to poorer overall spatial, memory, and perceptual speed performance compared to low consumption. The effect observed in the memory domain was no longer significant when CVD (i.e. Model 3: Table 16) or both CVD and depressive symptoms (i.e. Model 4: Table 16) were adjusted for. Here, it is possible that CVD mediated the relationship between sugar consumption and memory deficits. This was directly tested utilizing advanced statistical techniques discussed in the following section. When examining relationships between added sugar in coffee and cognitive performance, the possible influence of caffeine intake needs to be considered. Caffeine is related to deficits in some aspects of declarative (Childs & de Wit, 2006; Erikson, Hager, Houseworth, Dungan, et al., 1985) and spatial (Jarvis, 1993;Sansone, Battaglia, & Castellano, 1994) memory performance. However, others have shown limited effects of caffeine on learning and memory performance (Loke, Hinrichs, & Ghoneim, 1985; Mednick, Cai, Kanady, & Drummond, 2008), while other findings even indicated recovery of memory impairment with caffeine in both animals (Prediger, Pamplona, Fernandes, & Takahashi, 2005) and humans (Reidel

et al., 1995). Additionally, caffeine can improves reaction time performance (Frewer & Lader, 1991) and speed of processing (Rees, Allen, & Lader, 1999; Smith, Brice, Nash, Rich, & Nutt, 2003) capabilities. The cognitive deficits observed in the current study were most likely due to the sugar added in coffee and not caffeine, although this requires further investigation.

There was no significant influence of added sugar in coffee on verbal performance. As discussed earlier, the Verbal domain can be, in part, considered as testing long-term memory. There are several factors which may have played a role in influencing this result. Compared to low consumption individuals, high consumption people showed significantly lower occurrence of depressive symptoms (Table11). Even though this factor was adjusted for in the models, depressive symptoms may be related to higher levels of psychological stress. Stress, in turn, may produce deficits in verbal capabilities by detrimentally affecting long-term memory retrieval, as assessed by some tests comprising the verbal domain, due to impaired hippocampus plasticity, supporting previous research (McEwen, 1999). However, since depressive symptoms were *lower* in high consumption individuals, this may be an indication of lower stress levels in these people, perhaps through the influence of sugar in coffee as a comfort food, shown to reduce stress and anxiety-related responses (Dallman, et al., 2005), which have been related to depressive symptoms (Cohen, et al., 1983; Pruessner, et al., 2003).

Mediation Analyses

It was expected that CVD (an index of cardiovascular health comprised of self-reported data of angina pectoris, myocardial infarction, claudication, or any other cardiovascular abnormality (Svardh, et al., 1998;Rose, et al., 1977) would significantly mediate the relationship between sugar consumption and cognitive functioning. Therefore, mediation analyses were conducted in the fully adjusted models. CVD was found to be a significant mediator for the relationship between total sugar and dessert consumption with overall poorer verbal scores. This finding confirms the hypothesis that CVD may be a mechanism by which high sugar dietary lifestyles may influence poor cognitive functioning. These findings support the notion that diets high in sugar may contribute to the development of CVD (Arnqvist, et al., 1995; Kopp, 2006; Zhu, et al., 2001) which, in turn, can contribute to accelerated brain aging (Martins, et al., 2006;Stampfer, 2006) and cognitive impairment (Anstey & Christensen, 2000; Awad, et al., 2004;Breteler, et al., 1994; Papanikolaou, et al., 2006). Although T2D, an indicator of poor cardiovascular health (Lehto, Ronnemaa, Pyorala, & Laakso, 2000), was not assessed in the current analysis, the significant relation between high total sugar consumption and poorer verbal performance goes along with work demonstrating that T2D is related to poor verbal fluency (Kanaya, et al., 2004), and long-term memory (van Harten, et al., 2007). Additionally, T2D patients show increased cortical and subcortical atrophy, deep white matter lesions (Manschot, et al., 2006) and lower hippocampal volumes (den Heijer, et al., 2003), which could underlie the observed deficits in verbal performance.

CVD was not found to significantly mediate the relationship between Total Sugar or Dessert and lower spatial, memory, and perceptual speed performance. This may be explained by the development of neurodegenerative processes independent of CVD. Brain microglia function similarly to peripheral macrophages, which underlie the atherosclerotic process in CVD (Arnqvist, et al., 1995) by increasing inflammatory responses and coagulation factors in the brain vasculature (McGeer & McGeer, 1995). To this point, high sugar consumption and accompanying changes, such as elevated plasma glucose (Stephan, et al., 2010) and insulin resistance (de la Monte, et al., 2006), contribute to brain inflammation (Molteni, et al., 2004; Souza, et al., 2007). Animal studies show that inflammatory responses impair synaptic plasticity (Stranahan, et al., 2008; Schubert, et al., 2004), and are related to impairments in behavioral assessments of memory (Jurdak, et al., 2008; Stephan, et al., 2010**)**. Therefore, enhanced brain inflammation produced by high total sugar and dessert consumption could have produced cognitive deficits independent of the influence of CVD.

Even though the current study used participants free of dementia at baseline, it is possible that AD-related changes were present in a subset of people as they aged. In fact, evidence indicates that senile plaques and neurofibrillary tangles, which are main biomarkers of AD and can lead to neuronal death (Selkoe, 2001), were seen in brains of individuals 40-50 years prior to the onset of dementia, even extending into adolescence (Ohm, Muller, Braak, & Bohl, 1995). High sugar consumption has been found to increase glycation and the production of AGEs, which have been found in AD plaques and tangles (Martins, et al., 2006). Further, the glycation of Aβ (the main constituent of plaques) increases plaque aggregation *in vitro* (Takeuchi, et al., 2000). Additionally,

hyperinsulinemia has been found to increase plaque deposition in humans (Martins, et al., 2006) and that inflammatory biomarkers (e.g. C-reactive protein) in middle age increased the risk of AD 25 years later. Importantly, this result was independent of cardiovascular abnormalities (Schmidt, Schmidt, Curb, Masaki, et al., 2002). These findings are support the possibility that cognitive deficits observed in the current study could have been produced by enhanced inflammatory processes, vascular injury, and AD-like brain changes by high sugar consumption outside of the influence of peripheral CVD. Future studies should examine whether the presence of cognitive deficits may precede the onset of CVD due to sugar intake. That is, whether cognitive performance would mediate the relation between sugar intake and CVD. Such finding would support reports indicating that vascular inflammation can enhance the atherogenic process (Brasier, et al., 2002). Results failed to show any significant mediating effects of CVD on the relationship between consumption of high sweetened beverages & bread or sugar in coffee and any of the estimates indicating poorer cognitive scores relative to low consumption. Again, this lack of effect may be the result of sugar-induced vascular inflammation, leading to neurodegeneration independent of CVD. Additionally, the type of sugars contained in the foods assessed could have also influenced results. Soda, for instance, typically contains high amounts of high fructose corn syrup (Montmayeur & le Coutre, 2010). Fructose, unlike sugars such as glucose, does not stimulate the pancreas to release insulin (Bray, et al., 2004**;** Montmayeur & le Coutre, 2010), although it does produce elevations in blood sugar (Basciano, Federico, & Adeli, 2005). Therefore, high fructose corn syrup may have directly influenced deficits in cognitive functioning (Stranahan, et al., 2008) through elevations in substances such as uric acid, which have been found to contribute to

cognitive decline (Schretlen, et al., 2007) independent of CVD. Uric acid inhibits nitric oxide (Johnson, et al., 2009), shown to be important in synaptic efficacy (Matsumoto, et al., 2006). This being said, high fructose corn syrup has been related to the development of T2D (Hu & Malik, 2010; Schulze, Manson, Ludwig, Colditz, et al., 2004) and obesity (Bocarsly, Powell, Avena, & Hoebel, 2010; Forshee, Storey, Allison, Glinsmann, et al., 2007; Tordoff & Alleva, 1990), both risk factors for CVD (Carr & Brunzell, 2004;Hu & Malik, 2010). More work is needed to address whether different forms of sugar influence cognitive deficits through CVD or independently of it.

Summary & Conclusions

Findings of this study contribute to existing knowledge indicating that diets high in refined sugar produce cognitive deficits and impairments in brain functioning. Additionally, these results add to research indicating a relationship between metabolic disorders, such as T2D and poor cognitive abilities with age. To our knowledge, however, this study is the first to provide evidence suggesting that dietary sugar detrimentally affects cognitive functioning into older adulthood.

This study confirmed the hypothesis that high total sugar intake would be significantly related to overall lower cognitive performance across the memory and spatial domains, which are mainly hippocampus-dependent. It was also found that high total sugar consumption was related to lower performance across the verbal and perceptual speed domains, suggesting a detrimental influence of dietary sugar on these processes as well. However, the results failed to confirm the study hypothesis that high sugar intake would be associated with steeper trajectories of cognitive decline. High

sweetened beverages and sugar in coffee consumption were found to be related to impaired spatial performance, but dessert consumption was not. It is important for future studies to examine macronutrient content of various sugar-laden foods to assess their potential to differentially affect cognitive changes (e.g. glucose versus sucrose and fructose etc.) Furthermore, future studies should consider assessing individual intake variables that loaded onto the same latent factor to examine their potential to produce varying results (e.g. ice cream versus cake). High dessert consumption was related to less age-related decline in verbal performance relative to low consumption, perhaps due to a stress alleviating effect of dessert consumption leading to attenuated declines.

Results revealed that cardiovascular health mediated the relationship between high total sugar and dessert intake with impaired verbal performance, partially confirming the study hypothesis. However, there were no mediating effects of CVD on the relationship between total sugar and dessert intake on poorer spatial, memory, or perceptual speed scores. Additionally, CVD did not mediate any relation between sweetened beverages and bread or added sugar in coffee consumption and cognitive functioning. These findings are suggestive of another underlying mechanism, such as sugar-induced increases in vascular inflammation leading to cellular injury and, hence, poor cognition which acted independently of CVD. These findings are important in indicating the importance of examining diets high in refined sugar as a risk factor for poor cognitive health with age. In turn, results of this study may be important in the development of dietary treatment strategies for older adults experiencing cognitive difficulties. Furthermore, findings of this study provide some indication that

cardiovascular abnormalities may provide a mechanistic route for sugar-induced cognitive impairment, although this notion requires further investigation.

In summary, these findings provide the first indication that high refined sugar intake is related to cognitive deficits assessed in older adults. These findings shed light on the importance of developing studies to further examine the detrimental influence of dietary sugar on cognitive responses. In this particular study, high sugar was found to be a correlate or marker of poor cognitive performance, and further studies are needed in order to draw causal conclusions.

Study Limitations

There are a few limitations inherent in the study methodology which should be mentioned. Some may have contributed to the finding of a lack of significant estimates of the sugar by age interaction in the majority of the tested models. One possibility is that substantial cognitive decline may have already taken place prior to the initiation of cognitive testing. Additionally, diet was only assessed at a single time point, which did not allow for the examination of possible dietary changes with age which may have affected cognitive performance during later stage waves of testing. Future studies should attempt to assess sugar consumption at multiple time points in order to account for the potential of these changes to affect cognitive functioning. It is also important to note that the items on the diet questionnaire did not include any reliability data. Since the diet questionnaires were given to participants in 1984 (approaching 30 years ago), it was not possible to examine if the original data collectors conducted reliability analyses at the study onset. In other words, based on these data, it is not possible to conclusively state

that the questions posed to participants in the questionnaire accurately measured what they were intended to measure. In future investigations, researchers should aim to provide reliability information to enable for a more clear interpretation of the data.

Even though important covariates such as age, sex, and education were adjusted for in the main models, it may be that other factors may have played a role in relationships between sugar intake and cognitive decline. For instance, it is common for low education to be incorporated into measures of SES, where low education correlates with low SES (Winkleby, Jatulis, Frank, & Fortmann, 1992). Therefore, a variable representing SES may have been a more appropriate factor to adjust for in the models, as lower SES has been shown be an important factor in the study of cognitive deficits (Brayne & Calloway, 1990; Lang, Llewellyn, Langa, Wallace, & Melzer, 2008;)**.** Future studies should examine the influence of SES as a cluster of environmental factors, including education, to see if it has an influence on cognitive change in similar models that were tested in the current study. Further, additional analyses utilizing SES as a potential mediator between sugar intake and cognitive decline, may shed light on the possibility that sugar intake relates to cognitive impairment through low SES (Galobardes, et al., 2001)**.** Future studies should also aim to assess the influence of other possible confounding factors which may affect associations between sugar consumption and cognition, such as dietary fat, cholesterol and environmental factors such as exposure to stress (which was assessed partially here by the inclusion of depressive symptoms), social interaction and exercise. Further, this study did not account for other metabolic and dietary factors which may have influenced the results, such as body mass index (BMI), total fat intake, total cholesterol, or sugar consumption in relation to total caloric

intake. Future studies should aim to control for such factors in order to more clearly draw conclusions regarding relationships between dietary sugar and cognitive responses.

A drawback in the study methodology can be seen from the specification of the latent sugar factors. It is possible that sugar intake measures loaded onto the same latent factor simply because of identical assessment methodologies. For instance, ice cream, cake, and pastries may have loaded onto the same latent factor simply due to the fact that ingestion of these items were assessed using the same questions given to participants. Similarly, soda and white bread consumption may have loaded onto a separate latent factor for the same reason. Future studies should aim for consistency of questions assessing dietary habits to avoid this potential pitfall. Additionally, it may be important for future studies to systematically investigate specific sugar intake variables and their potential to produce different cognitive outcomes (e.g. differences between ice cream and cake). Further, it is important for future studies to consider the macronutrient content of sugar variables to assess the potential for different insulin and plasma glucose responses produced by, for instance, glucose, fructose, and sucrose (Anderson & Woodend, 2003; Kazumi, Vranic, & Steiner, 1986; Lee & Wolever, 1998; Macdonald, Keyser, & Pacy, 1978; Stanhope, Schwarz, Keim, Griffen, et al., 2009)**,** and how these may differentially affect cognitive functioning.

In this study, T2D prevalence was not coded for in the participants. The effect of T2D in the relationship between dietary sugar and cognitive functioning needs additional attention in future studies. The current study did not incorporate an assessment of global cognitive functioning, which may have been more sensitive to detecting cognitive differences compared to testing across specific cognitive domains.

Future Directions: Dietary Sugar & Chemo-Brain

A major adverse effect of cancer treatment that may go untreated is a collection of cognitive deficits experienced by some patients during and following chemotherapy referred to as "chemo-brain" (Staat & Segatore, 2005), which is thought to be the result of neurotoxicity (Taillibert, Voillery, & Bernard-Marty, 2007).

Chemo-brain has been reported in 50% of women undergoing chemotherapy for breast cancer (Paraska & Bender, 2003), where some experience symptoms even 10 years post-treatment (Saykin, Ahles, & McDonald, 2003). Symptoms have also been reported in testicular cancer populations (Tannock, Ahles, Ganz, & Van Dam, 2004) as well as those diagnosed with HIV, hepatitis C, chronic fatigue syndrome, and brain injury (Brem & Kumar; Sweet, Peck, Abramowitz, & Etzweiler, 2002). Therefore, symptoms of chemo-brain can be prevent patients' normal return to pre-diagnostic functioning as symptoms may impair attention, organization, the ability to multi-task (Taillibert, et al., 2007). During and following chemotherapy in cancer survivors, some patients report substantial physical and mental symptoms, such as anxiety, depression, fatigue, difficulty sleeping, worrying, loss of self-esteem, as well as lack of appetite and sexual interest (Kenne Sarenmalm, Ohlen, Jonsson, & Gaston-Johansson, 2007). Additionally, reports indicate variety of specific cognitive deficits, such as weakened speed of information processing, impaired reaction time, as well as declines in memory, concentration, and attention (Ahles, Saykin, Furstenberg, Cole, et al., 2002**;**Brem & Kumar, 2011**;**Meyers, 2000). Research suggests that oxidative damage (Joshi, Hardas, Sultana, St Clair, et al., 2007;Taillibert, et al., 2007) and inflammatory responses (Seigers & Fardell, 2011), which seem to underlie chemo-brain, are similar to those produced by high sugar diets

(Souza, et al., 2007). Additionally, there are similar patterns of impairment when comparing studies examining elevated blood sugar (Greenwood, et al., 2003), type II diabetes (Awad, et al., 2004) and insulin resistance (de la Monte, et al., 2006) with those assessing cognitive performance in cancer survivors treated with chemotherapy (Staat & Segatore, 2005).

Experimental work indicates that, similar to those treated with high sugar diets (Molteni, et al., 2004), rats treated with chemotherapeutic drugs show substantial declines in behavioral assessments of memory, including NOR (ElBeltagy, Mustafa, Umka, Lyons, et al., 2010**;** Mondie, Vandergrift, Wilson, Gulinello, & Weber**,** 2010), MWM (Li, Vijayanathan, Gulinello, & Cole**,** 2009**;** Seigers, Timmermans, van der Horn, de Vries, et al., 2010;Winocur, Binns, & Tannock, 2011), avoidance conditioning (Madhyastha, Somayaji, Rao, Nalini, & Bairy, 2002; Reiriz, Reolon, Preissler, Rosado, et al., 2006), and operant retrieval (Foley, Raffa, & Walker, 2008). Additionally, work has shown chemotherapy drugs to induce inhibitions in markers of hippocampal synaptic plasticity, such as BDNF (Mustafa, Walker, Bennett, & Wigmore, 2008) and neurogenesis (Seigers, Schagen, Beerling, Boogerd, et al., 2008;Yang, Kim, Song, Kim, et al., 2010). Furthermore, animals treated with chemotherapeutic drugs show significant increases in oxidative damage (Joshi, Sultana, Tangpong, Cole, et al., 2005; Rajamani, Muthuvel, Senthilvelan, & Sheeladevi, 2006), white matter damage (Han, Yang, Dietrich, Luebke, et al., 2008; Seigers, et al., 2009), and pro-inflammatory cytokines (Seruga, Zhang, Bernstein, & Tannock, 2008). These findings point to the importance of addressing mechanistic similarities between chemotherapy treatment and metabolic abnormalities accompanying high sugar intake. Controlling plasma glucose levels, for instance, by

limiting the intake of refined sugars may exert a protective influence on the detrimental effects of chemotherapy on cognitive functioning. Also, it may be true that type II diabetics demonstrate enhanced chemo-brain symptoms due to increased oxidative damage and inflammatory responses resulting both from their chronic illness and chemotherapy treatment.

To address this topic, and to extend upon findings of the current study, examining the influence of cancer treatment on longitudinal cognitive functioning would shed light on possible dietary treatment strategies. An analysis of the influence of sugar intake on trajectories of cognitive decline in those treated with chemotherapy may provide insight into the mediating effects of sugar on cognitive decline in cancer survivors, which may be especially important in older individuals. Experimental work in this area would contribute to knowledge regarding the possible synergistic influence of chemotherapy and high sugar diets on cognitive impairment through oxidative stress pathways. Administering low sugar diets, in addition to high antioxidant diets, which, in itself, has been shown to ameliorate oxidative damage produced by chemotherapy (Joshi, et al., 2007), may provide an effective treatment strategy to protect against neurobiological and behavioral impairments underlying chemo-brain symptoms in both humans and animals.

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Appendix A: Diet Questionnaire

ID REGA IDA Name .....

1. How would you describe your normal diet?

	Always	Often	Sometimes	Seldom	Never
	1	2	3	4	5
Do you usually have anything to eat before breakfast? BBREAK	o	o	o	o	o
Do you usually eat breakfast? BREAK	o	o	o	o	o
Do you usually have anything to eat between breakfast and lunch? (e.g. tea, cakes, candy or fruit) AMSNACK	o	o	o	o	o
Do you usually eat lunch? LUNCH	o	o	o	o	o
Do you usually have anything to eat between lunch and supper? (e.g. coffee, tea, cake, candy, fruit) PMSNACK	o	o	o	o	o
Do you usually eat dinner/supper? DINNER	o	o	o	o	o
Do you usually have anything to eat after dinner/supper? EVESNAK	o	o	o	o	o

9 = missing

Take a look at the pictures! They show a small, medium and a large portion of food. Try to judge how much you normally eat. (Please note! If you have changed your diet due to ill health for example, then please describe your diet before you became ill.)

When you have a meal, what size portion do you eat of the following foods:

		0 = VEGETARIAN	1 Small Portion	2 Medium Portion	3 Large Portion
MEATSIZ	Meat		o	o	o
VEGSIZ	Vegetables		o	o	o
FISHSIZ	Fish		o	o	o

How many medium sized potatoes do you normally eat?

Number of medium sized potatoes/meal ____ . POTATNR

How many crispbreads do you normally eat? HSANDNR

Number of crispbreads/day ___.

How many slices of white bread with butter do you normally eat per day?

SSANDNR

Number of slices of white bread and butter/day ___.

How many slices of ordinary bread with butter do you normally eat?

LSANDR

Number of slices of ordinary bread and butter/day ___.

How many slices of whole-meal bread with butter do you normally eat per day?

FSANDR

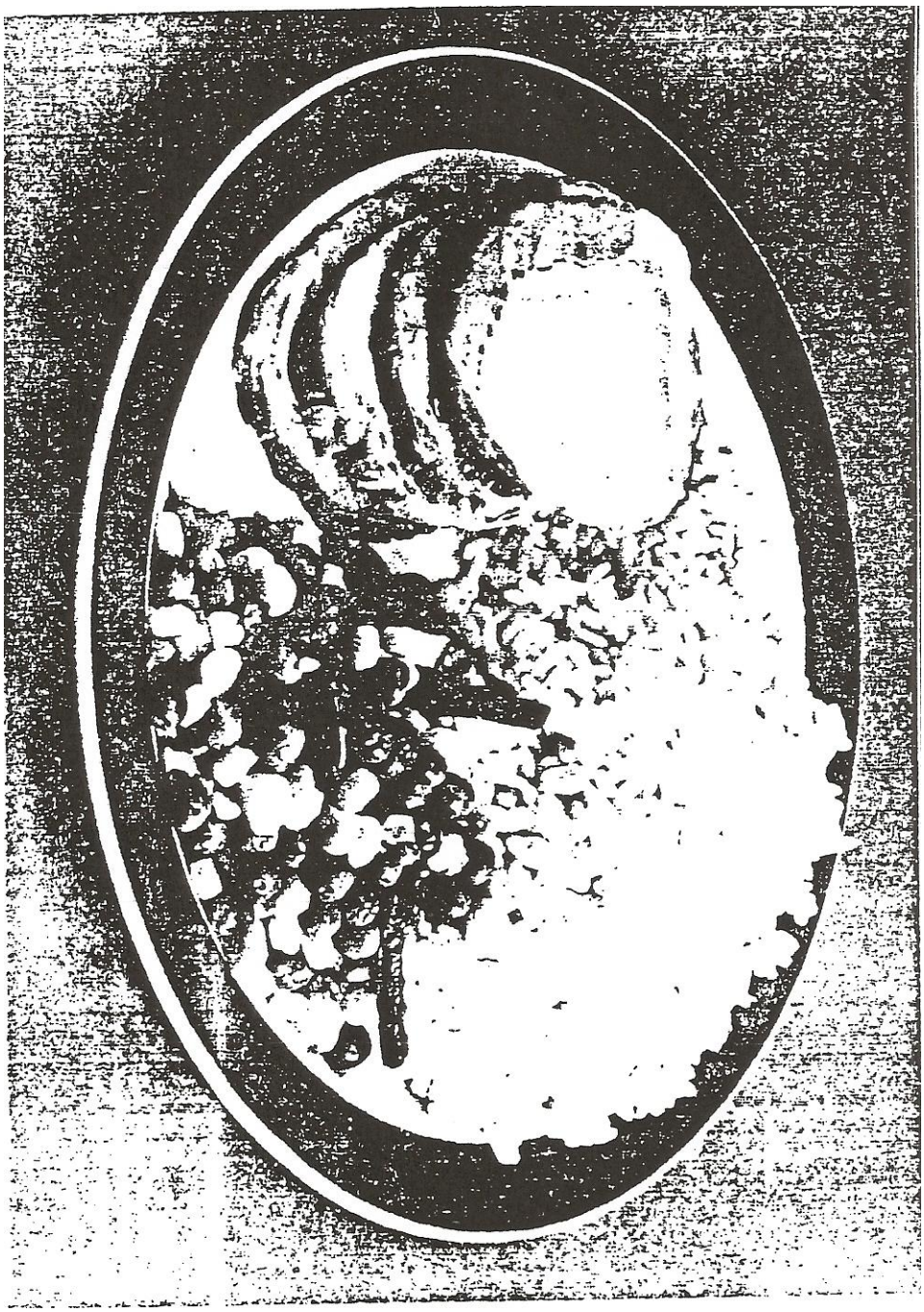
Number of slices of whole-meal bread and butter/day ___.

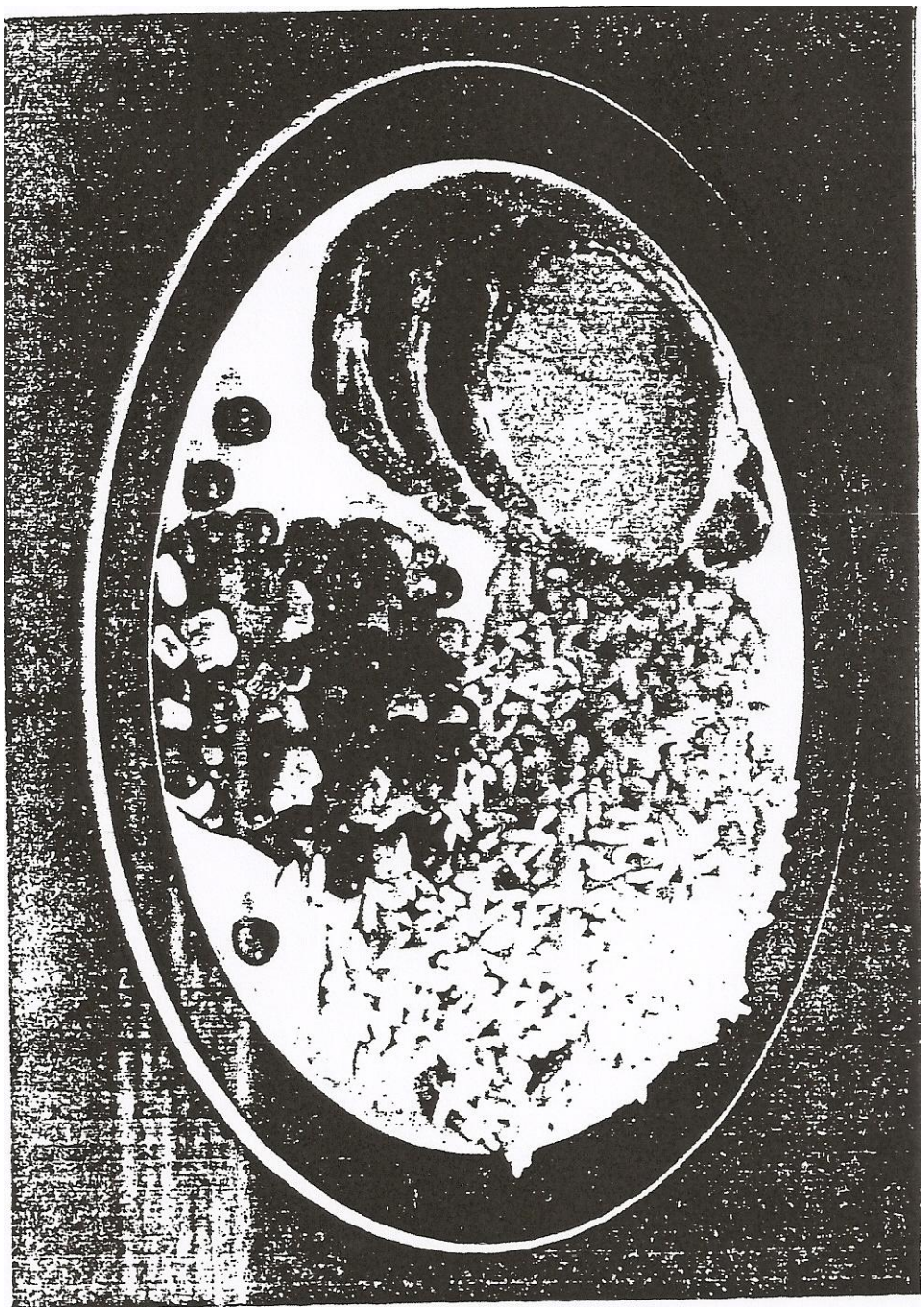
How much butter/fat do you usually spread on each slice of bread? Please look at the picture before you answer.

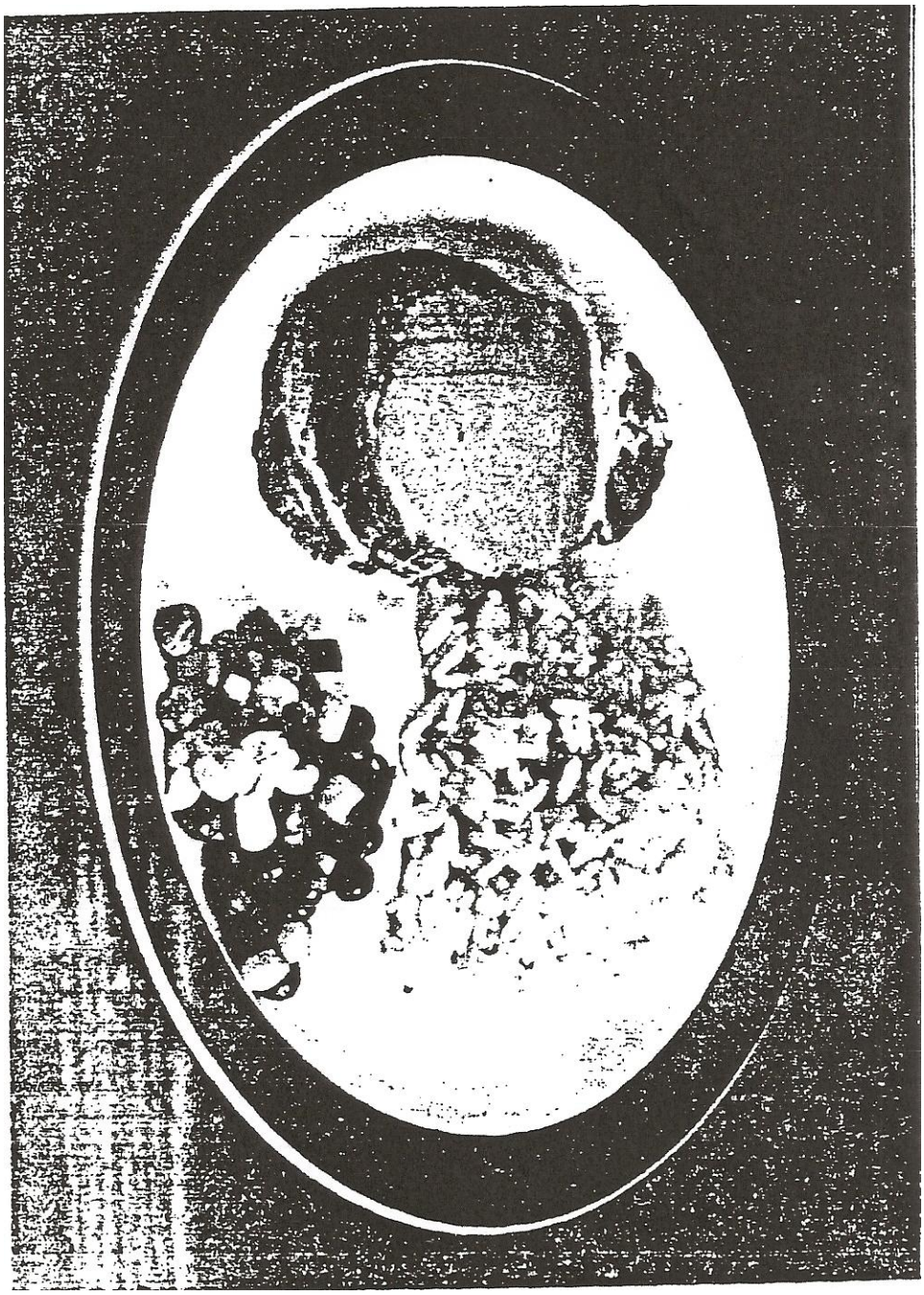
THIKFAT

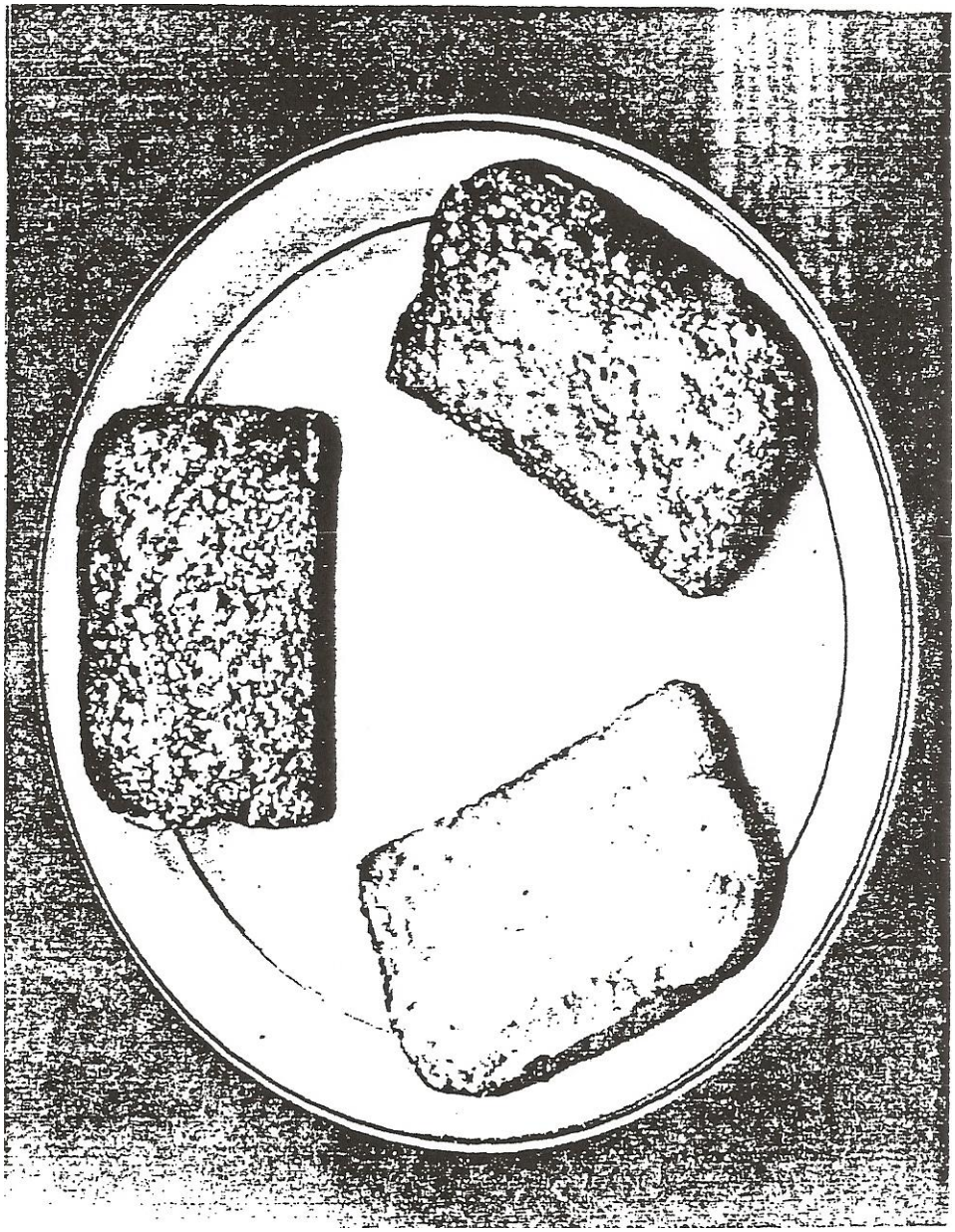
Slice of bread and butter:

Thin	Thick	Scraped	No fat
1	2	3	4









10 Butter/"Bregott"
20 Standard margarine, e.g. "Milda", "Hushållseve", "Melba", "Tre Ess".
30 Table margarine e.g. "Flora", "BordsEve"
40 Minarin, e.g. "Lätt och Lagom", "Lättmargarin", "Lätta"
50 Other, please specify. _____

WHCHFAT

	Weekdays glass/day	Weekends glass/day
How much milk with reduced fat do you drink altogether in one day? (e.g. light milk, light sour milk, light yoghurt)	LTMILK1 __ glass	LTMILK2 __ glass
How much standard milk do you drink altogether in one day? (e.g. milk, sour milk, yoghurt, "Kefir" etc)	RGMILK1 __ glass	RGMILK2 __glass
How many glasses of soft drinks, nectar and sweetened juices do you drink per day?	NEKTAR1 __ glass	NEKTAR2 __ glass
How many glasses of fruit juice do you drink per day?	JUICE1 __ glass	JUICE2 __ glass

Now we would like you to describe how much you normally eat of the following foodstuffs. Diets often vary during the year, but we are interested in how much you normally eat during the greater part of the year.
(Please note! If you have changed your diet due to illness, then describe your diet before you became ill)

	More than 4 times/ week	1-4 times/ week	1-3 times/ month	Less than once/month	Never	
How often do you eat?	1	2	3	4	5	
Vegetables:						
Tomatoes	o	o	o	o	o	TOMATO
Green cabbage + spinach	o	o	o	o	o	SPINACH
White cabbage	o	o	o	o	o	CABBAGE
Cauliflower + sprouts + Broccoli	o	o	o	o	o	CAULIF
Pepper: green, red	o	o	o	o	o	BELLPEP
Lettuce	o	o	o	o	o	SALAD
Green beans, peas	o	o	o	o	o	BEANPEA
Root Vegetables	o	o	o	o	o	CARROT
Carrots	o	o	o	o	o	
Potatoes, boiled	o	o	o	o	o	POTBOIL
Potatoes, fried	o	o	o	o	o	POTFRY
French fries or chips	o	o	o	o	o	CHIPS
Fruits						
Bananas	o	o	o	o	o	BANANA
Oranges, mandarin	o	o	o	o	o	
Grapefruit or other citrusfruit.	o	o	o	o	o	CITRUS
Apples, Pears.	o	o	o	o	o	APPLE
Cheese						
Cheese, not cottage cheese	o	o	o	o	o	CHEESE
Ice cream						
Ice Cream	o	o	o	o	o	ICECREAM

	week	week	month	month	
How often do you usually eat?					
Kött, fisk, ägg:					
Bacon, "Bayonne Ham", smoked pork, smoked ham	1 o	2 o	3 o	4 o	5 o - BACON
Beef or pork:					
Fried in frying pan	o	o	o	o	o - HEATFRY
Cooked in the oven	o	o	o	o	o - HEATOVN
Boiled	o	o	o	o	o - MEAT BOL
Frankfurter sausage as a dish:					
Fried in frying pan	o	o	o	o	o - KORVFRY
Cooked in the oven	o	o	o	o	o - KORVOVN
Boiled	o	o	o	o	o - KORV BOL
Liver	o	o	o	o	o - LIVER
Liver paté	o	o	o	o	o LIVERSG
Mackerel or salmon:					
Fried in frying pan	o	o	o	o	o LAXFRY
Boiled or cooked some other way	o	o	o	o	o LAX BOIL
Other kinds of fish:					
Fried in frying pan	o	o	o	o	o FISHFRY
Boiled or cooked in oven	o	o	o	o	o FISHBOL
Shell fish, mussels, shrimps	o	o	o	o	o SHELFSH
Tinned sardines or tuna fish	o	o	o	o	o SARDIN
Smoked fish e.g. Baltic herring "böckling"	o	o	o	o	o FISHSMK
Food which is grilled or cooked over open fire	o	o	o	o	o GRILL
Meat juice or gravy	o	o	o	o	o GRAVY
Eggs, boiled	o	o	o	o	o EGGBOIL
Eggs, fried, omelette, pancakes etc.	o	o	o	o	o EGGFRY
Pasta, rice					
Macaroni, spagetti or other types of pasta	o	o	o	o	o PASTA
Rice	o	o	o	o	o RICE
Baked cakes and biscuits					
Coffee cakes and biscuits	o	o	o	o	o ROLLS
Pastries and gateaux	o	o	o	o	o CAKES

How many cups of tea do you normally drink per day? __cups/day CUPTEA

How many sugar lumps or teaspoons sugar do you normally use?

__ number of lumps or spoons in a cup of coffee. SUGRCOF

__ number of lumps or spoons in a cup of tea. SUGRTEA

Do you use other sorts of sweeteners (sacharin, honey etc.)?

1 o No <——— FAKSUGR

2 o Yes ----> What sort? _____ FAKWHCH 0=not specified 1=specified

When you eat fried meat how do you prefer the surface to be?

1 o Lightly fried

2 o Medium fried

3 o Crispy CRISPY

How do you prefer your fried meat to be prepared?

1 o On the highest heat (the whole time or part of the time) HARDFRY

2 o Never on the highest heat

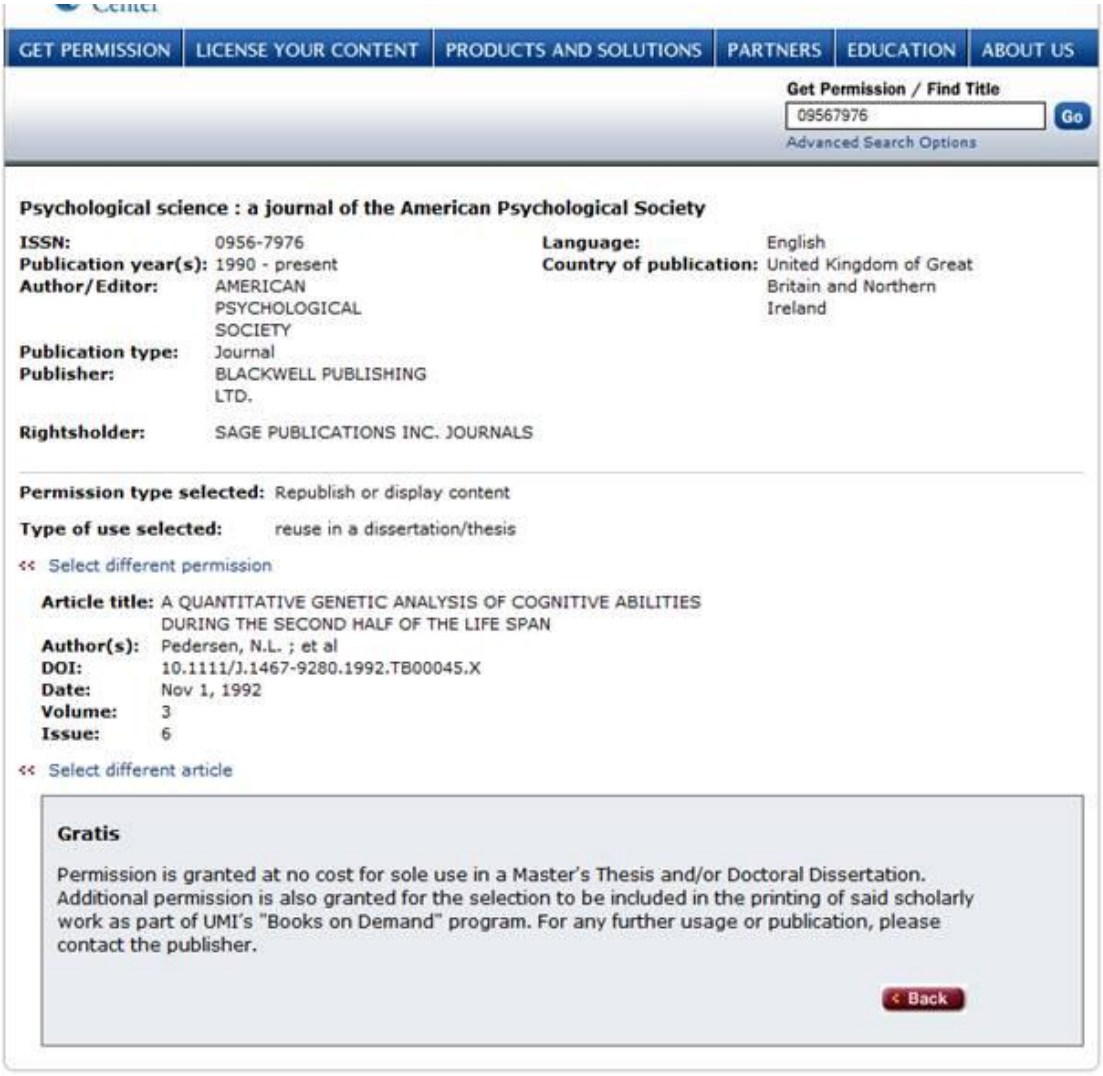
What do you do if you get a piece of bread with mould on it?

1 o I eat it anyway

2 o I cut away the mould, then eat the rest

3 o I throw away the whole piece of bread MOLDY

Appendix B: Copyright Release for Table 3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